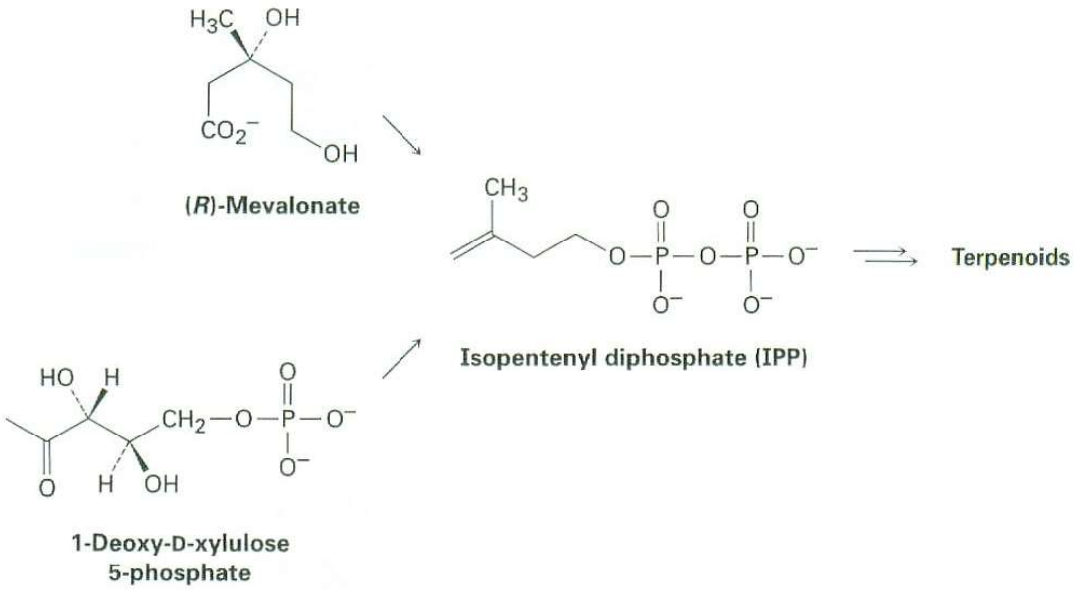
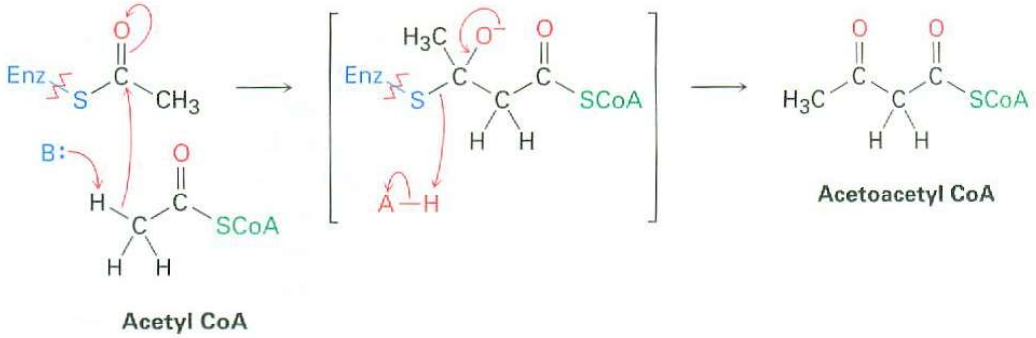
both pathways are used. We'll look only at the mevalonate pathway, which is more common and better understood at present.



The Mevalonate Pathway to Isopentenyl Diphosphate

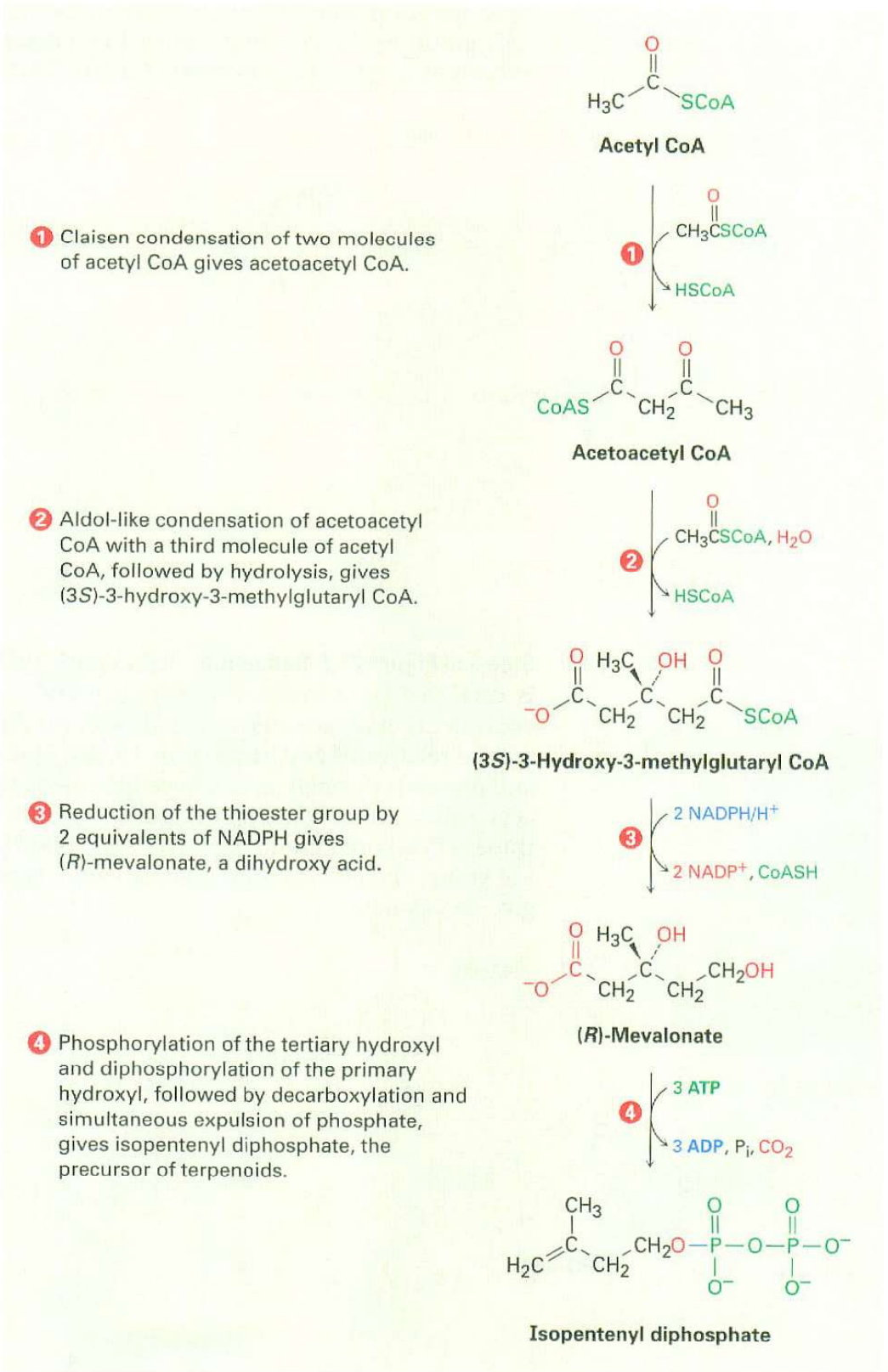
As summarized in Figure 27.7, the mevalonate pathway begins with the conversion of acetate to acetyl CoA, followed by Claisen condensation to yield acetoacetyl CoA. A second carbonyl condensation reaction with a third molecule of acetyl CoA, this one an aldol-like process, then yields the six-carbon compound 3-hydroxy-3-methylglutaryl CoA, which is reduced to give mevalonate. Phosphorylation, followed by loss of CO_2 and phosphate ion, completes the process.

Step 1 of Figure 27.7: Claisen Condensation The first step in mevalonate biosynthesis is a Claisen condensation (Section 23.7) to yield acetoacetyl CoA, a reaction catalyzed by acetoacetyl-CoA acetyltransferase. An acetyl group is first bound to the enzyme by a nucleophilic acyl substitution reaction with a cysteine –SH group. Formation of an enolate ion from a second molecule of acetyl CoA, followed by Claisen condensation, then yields the product.

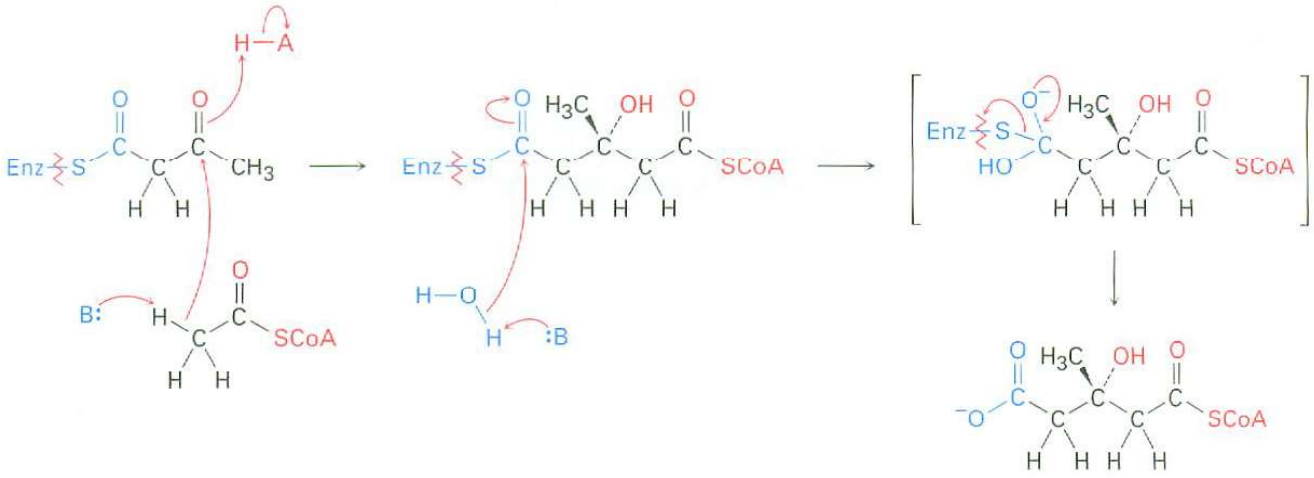


Step 2 of Figure 27.7: Aldol Condensation Acetoacetyl CoA next undergoes an aldol-like addition (Section 23.1) of an acetyl CoA enolate ion in a reaction catalyzed by 3-hydroxy-3-methylglutaryl-CoA synthase. The reaction again occurs

Figure 27.7 MECHANISM: *The mevalonate pathway for the biosynthesis of isopentenyl diphosphate from three molecules of acetyl CoA. Individual steps are explained in the text.*

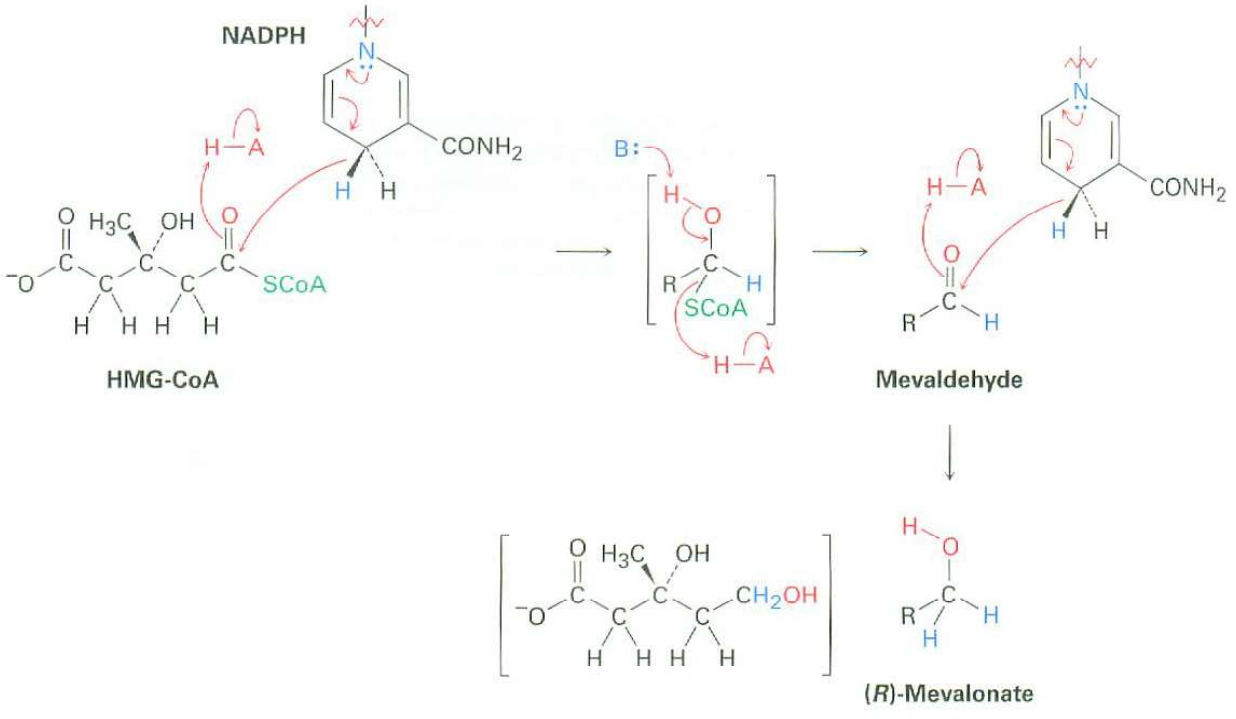


by initial formation of a thioester bond between the substrate and a cysteine –SH group in the enzyme, followed by enolate-ion addition and subsequent hydrolysis to give (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).

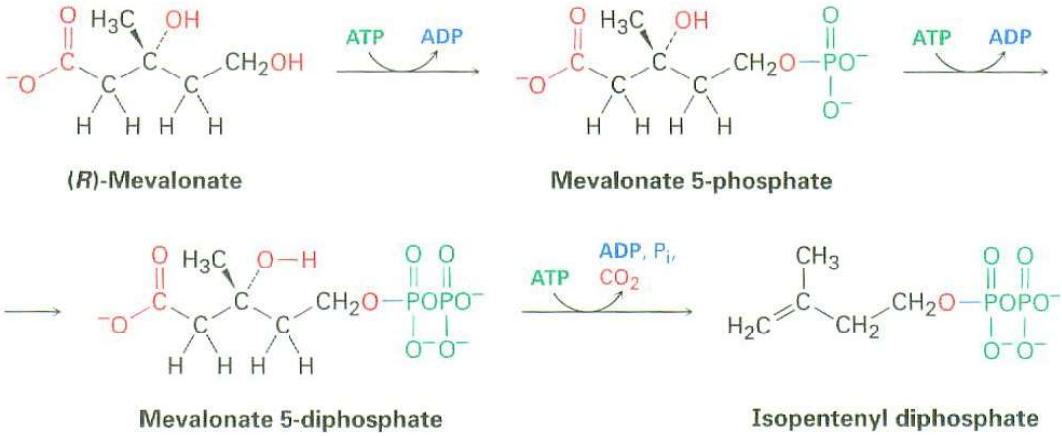


(3*S*)-3-Hydroxy-3-methylglutaryl CoA (HMG-CoA)

Step 3 of Figure 27.7: Reduction Reduction of HMG-CoA to give (*R*)-mevalonate is catalyzed by 3-hydroxy-3-methylglutaryl-CoA reductase and requires two equivalents of reduced nicotinamide adenine dinucleotide phosphate (NADPH), a close relative of NADH (Section 19.12). The reaction occurs in several steps and proceeds through an aldehyde intermediate. The first step is a nucleophilic acyl substitution reaction involving hydride transfer from NADPH to the thioester carbonyl group of HMG-CoA. Following expulsion of HSCoA as leaving group, the aldehyde intermediate undergoes a second hydride addition to give mevalonate.

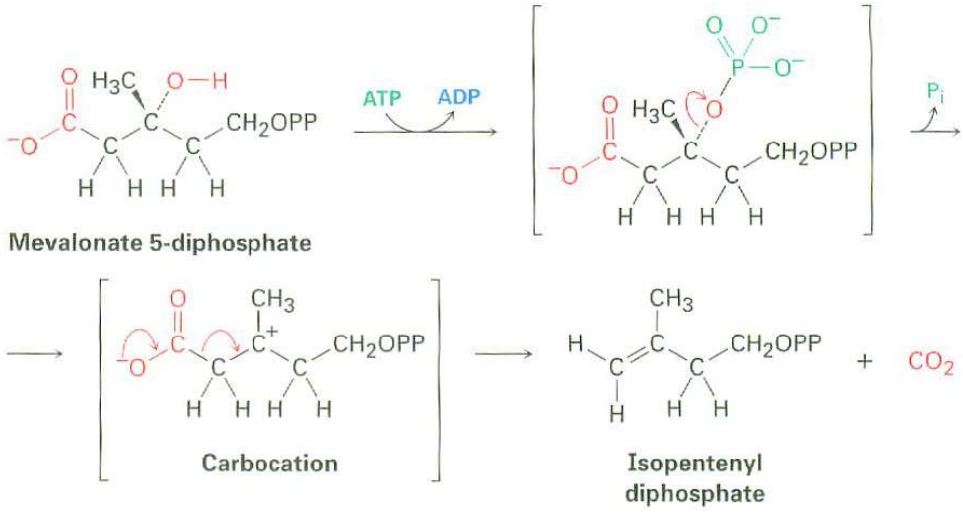


Step 4 of Figure 27.7: Phosphorylation and Decarboxylation Three additional reactions are needed to convert mevalonate to isopentenyl diphosphate. The first two are straightforward phosphorylations that occur by nucleophilic substitution reactions on the terminal phosphorus of ATP. Mevalonate is first converted to mevalonate 5-phosphate (phosphomevalonate) by reaction with ATP in a process catalyzed by mevalonate kinase. Mevalonate 5-phosphate then reacts with a second ATP to give mevalonate 5-diphosphate (diphosphomevalonate). The third reaction results in phosphorylation of the tertiary hydroxyl group, followed by decarboxylation and loss of phosphate ion.



The final decarboxylation of mevalonate 5-diphosphate appears unusual because decarboxylations of acids do not typically occur except in β-keto acids and malonic acids, in which the carboxylate group is two atoms away from an additional carbonyl group (Section 22.7). The function of this second carbonyl group is to act as an electron acceptor and stabilize the charge resulting from loss of CO_2. In fact, though, the decarboxylation of a β-keto acid and the decarboxylation of mevalonate 5-diphosphate are closely related.

Catalyzed by mevalonate-5-diphosphate decarboxylase, the substrate is first phosphorylated on the free –OH group by reaction with ATP to give a tertiary phosphate, which undergoes spontaneous dissociation to give a tertiary carbocation. The positive charge then acts as an electron acceptor to facilitate decarboxylation in exactly the same way a β carbonyl group does, giving isopentenyl diphosphate. (In the following structures, the diphosphate group is abbreviated OPP.)



Problem 27.6 Studies of the conversion of mevalonate 5-phosphate to isopentenyl diphosphate have shown the following result. Which hydrogen, *pro-R* or *pro-S*, ends up cis to the methyl group, and which ends up trans?

Mevalonate 5-diphosphate → **Isopentenyl diphosphate**

Conversion of Isopentenyl Diphosphate to Terpenoids

The conversion of isopentenyl diphosphate (IPP) to terpenoids begins with its isomerization to dimethylallyl diphosphate, abbreviated DMAPP and formerly called dimethylallyl pyrophosphate. These two C_5 building blocks then combine to give the C_{10} unit geranyl diphosphate (GPP). The corresponding alcohol, geraniol, is itself a fragrant terpenoid that occurs in rose oil.

Further combination of GPP with another IPP gives the C_{15} unit farnesyl diphosphate (FPP), and so on, up to C_{25}. Terpenoids with more than 25 carbons—that is, triterpenoids (C_{30}) and tetraterpenoids (C_{40})—are synthesized by dimerization of C_{15} and C_{20} units, respectively (Figure 27.8). Triterpenoids and

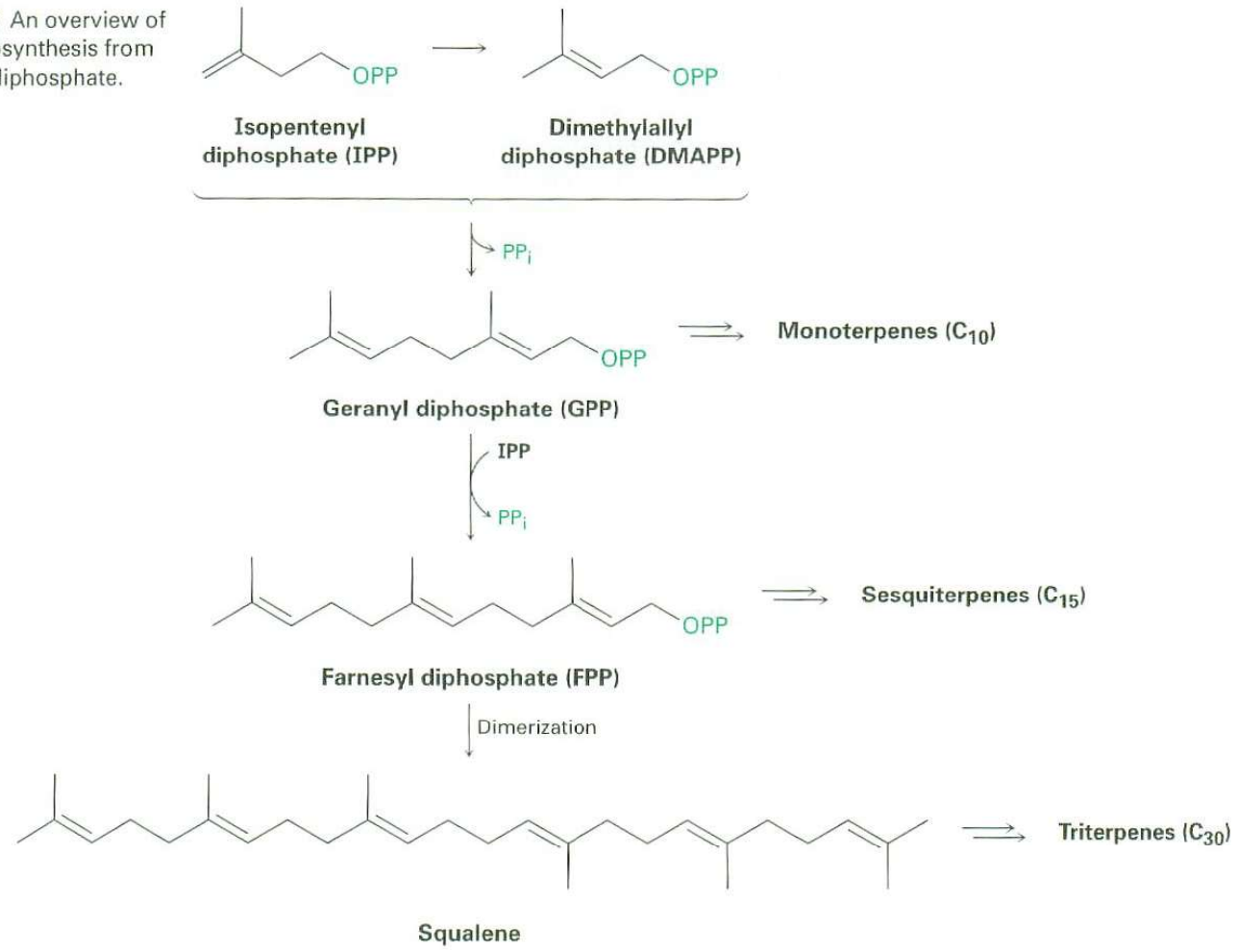


Figure 27.8 An overview of terpenoid biosynthesis from isopentenyl diphosphate.