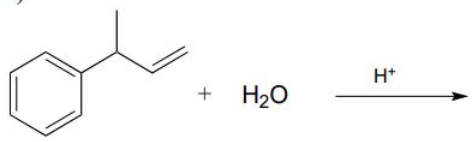
14.E: Electrophilic Reactions (Exercises)

P14.1: Draw the major product(s) (including all stereoisomers) that would be expected to result from the nonenzymatic electrophilic addition reactions below. Your product(s) should result from the most stable possible carbocation intermediate. ***Hint***: consider the possibility of thermodynamically favorable rearrangement steps.

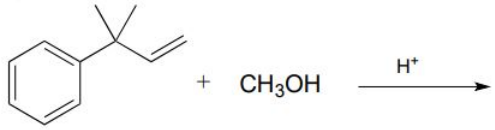
a)

b)

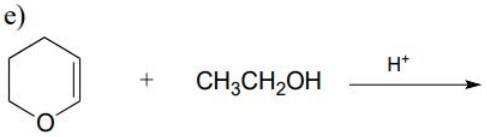
c)



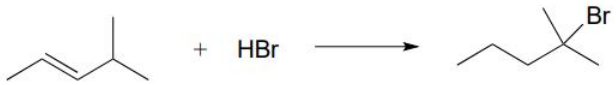
d)



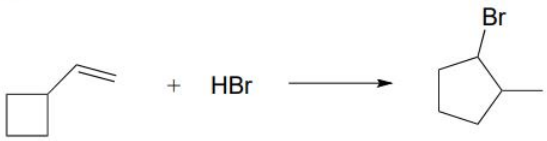
e)



P14.2: Draw likely mechanisms for the nonenzymatic reactions below. Products shown are not necessarily the most abundant for the reaction.



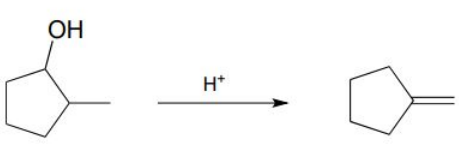
c)



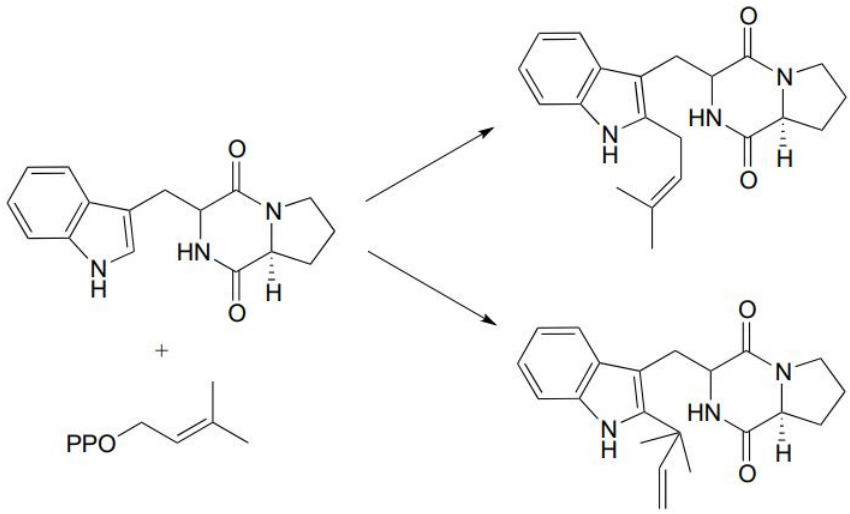
d)

a)

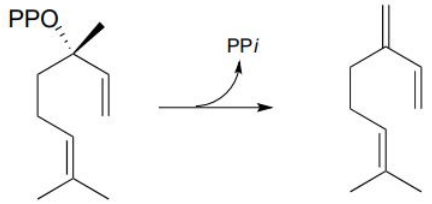
b)



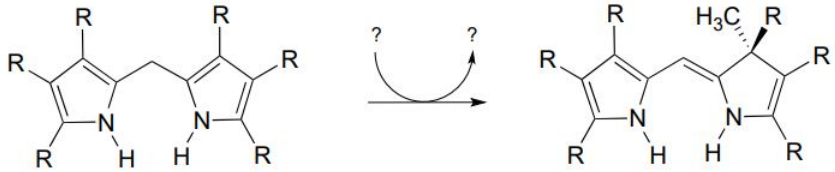
P14.3: Provide mechanisms for the following reactions, both of which are part of an alkaloid synthesis pathway in fungi. (Microbiol. 2005, 151, 2199)



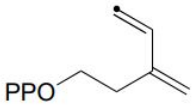
P14.4: Draw a likely mechanism for the reaction below. The product is myrcene, a compound produced by fir trees as a defense against insects. (J. Biol. Chem 1997, 272, 21784)



P14.5: Provide a mechanism for the following reaction from the vitamin B_{12} biosynthetic pathway, and identify the missing participants indicated by questions marks in the figure.



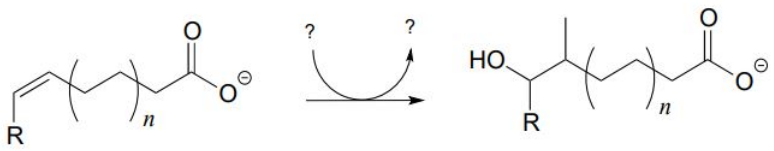
P14.6: A diene molecule synthesized in the laboratory was found to irreversibly inhibit the action of isopentenyl diphosphate isomerase (section 14.3) when the carbon indicated with a dot becomes covalently bonded to a cysteine residue in the enzyme's active site. Propose a mechanism showing how this could happen. (J. Am. Chem. Soc. 2005, 127, 17433)



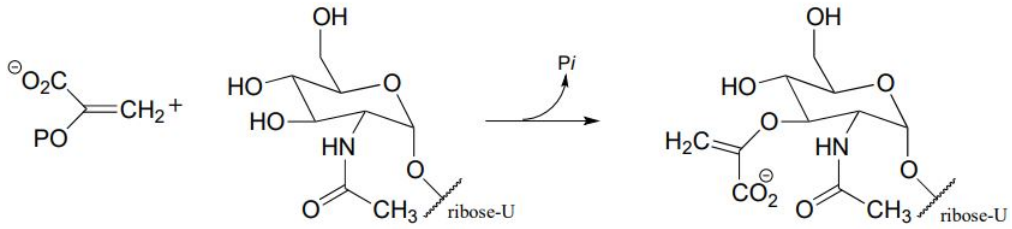
inhibitor

P14.7: Nonenzymatic electrophilic addition of water to alkynes results in the formation of a ketone or an aldehyde, depending on the starting alkyne. A vinylic carbocation is a key intermediate, and the reaction is accelerated with the use of a catalytic amount of strong acid. Predict the product the addition of water to propyne, and draw a mechanism for the reaction.

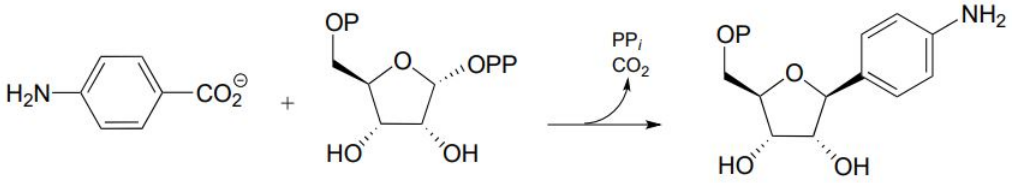
P14.8: The reaction below is part the pathway by which some bacteria -including the species which cause tuberculosis and leprosy - form distinctive branched-chain fatty acids for incorporation into their cell walls. This enzyme is of interest to scientists as possible targets for new antibiotic drugs. Propose a likely mechanism, and identify the missing participants denoted by questions marks. (J. Biol. Chem. 2006, 281, 4434)



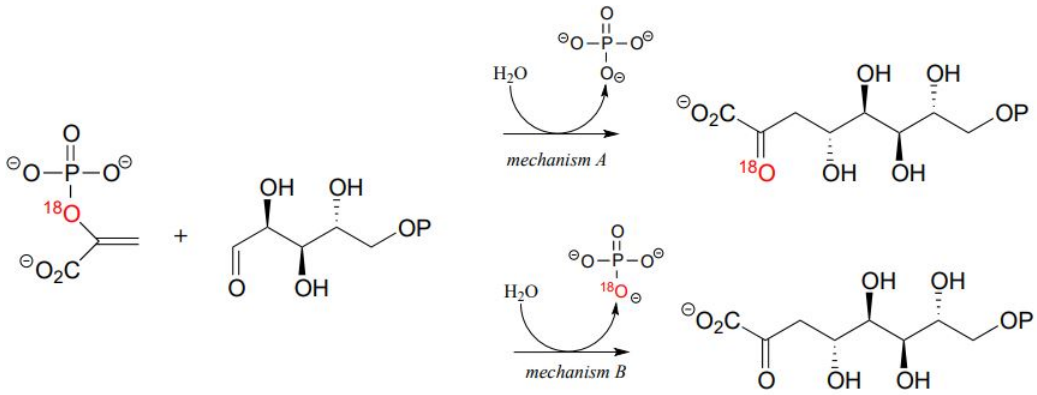
P14.9: Suggest a likely mechanism for this reaction, which is a key step in the synthesis of bacterial cell walls. Your mechanism should show an electrophilic addition, followed by an E1 elimination.



P14.10: Suggest a mechanism for the following reaction, which is part of the pathway by which many microbes synthesize methanopterin, a derivative of the vitamin folic acid. ***Hint***: the mechanism can be described as an electrophilic aromatic substitution with a final decarboxylation step in place of the usual deprotonation step. (J. Biol. Chem. 2004, 279, 39389.

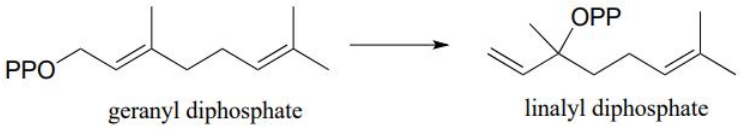


P14.11: Researchers investigated the mechanism of the enzyme 3-deoxy-D-manno-octulosonate-8-phosphate synthase by running the reaction with one of the substrates labeled with the 18O isotope (colored red in the scheme below). Consider the two hypothetical results shown below, each pointing to a different mechanism. Both mechanisms involve a carbocation intermediate. (Biochem. Biophys. Res. Commun. 1988, 157, 816)



a. Propose a mechanism that is consistent with result A, in which the \(^1$8O$ \) label ends up in the ketone group of the organic product.
b. Propose a mechanism that is consistent with result B, in which the \(^$18O$ \) label ends up in the inorganic phosphate by-product

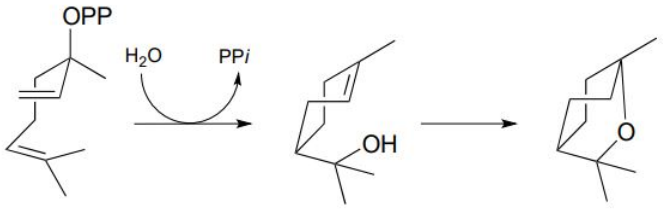
P14.12: Consider the following isomerization reaction (J. Biol. Chem. 1989, 264, 2075):



geranyl diphosphate linalyl diphosphate

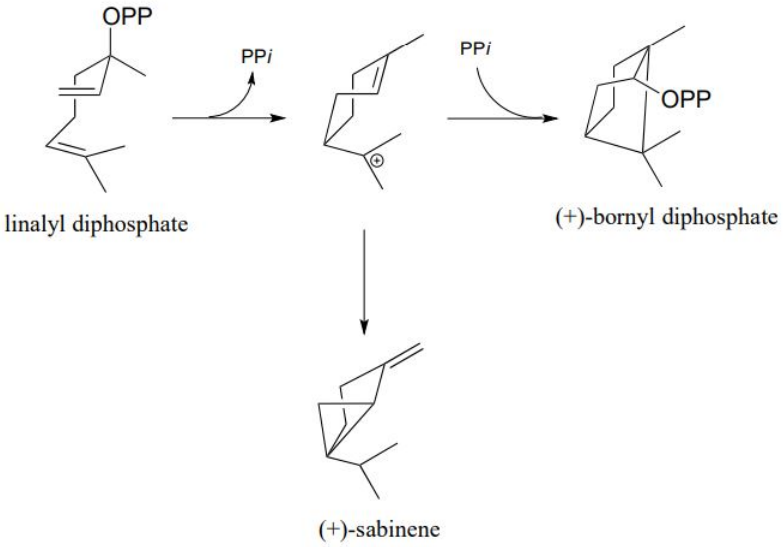
(JBC264, 2075)

a. Suggest a likely mechanism involving a carbocation intermediate.
b. Suggest an isotopic labeling experiment (using substrate labeled with $^{1}8O$) that could confirm or rule out a alternative, concerted isomerization mechanism (ie. one without formation of a carbocation intermediate). Explain your reasoning.
c. Propose a mechanism for the following reaction (notice that the starting compound is linalyl diphosphate from part (a), drawn in a different conformation). (Arch Biochem Biophys 2003, 417, 203)



linalyl diphosphate 1,8-cineole

For parts d-f, refer to the figure below:

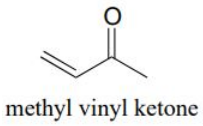


linalyl diphosphate (+)-bornyl diphosphate

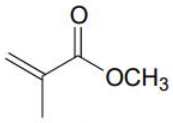
(+)-sabinene

d. Provide mechanisms for the conversion of linalyl diphosphate to (+)-bornyl diphosphate.
e. Provide mechanisms for the conversion of linalyl diphosphate to (+)-sabinene.
f. Is the second step in the (+)-bornyl diphosphate pathway (addition of phosphate) a Markovnikov or anti-Markovnikov addition? Explain the regiochemistry of this step in terms of carbocation stability.

P14.13: The two compounds shown below were each treated with HBr, and the products isolated and analyzed by $^{1}HNMR$. Use the NMR data provided to determine the structure of both products, then explain the observed regiochemistry of the addition reaction.



methyl vinyl ketone



methyl methacrylate

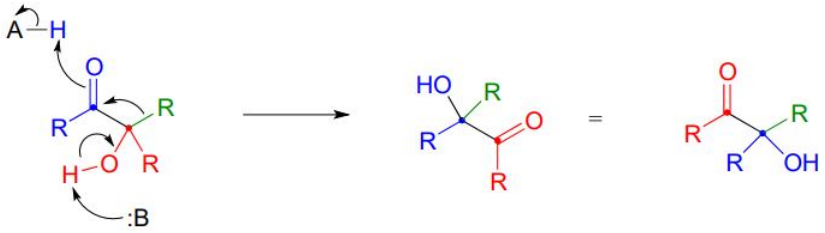
^1H-NMR data for product of HBr addition to methyl vinyl ketone:

δ□□□□□	Integration	Splitting
2.2	1.5	s
3.0	1	t
3.5	1	t

^1H-NMR data for product of HBr addition to methyl methacrylate:

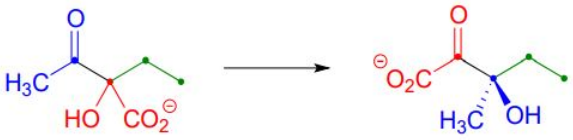
δ□□□□□	Integration	Splitting
1.3	3	d
2.3	1	sextet
3.5	2	d
3.7	3	s

P14.14: Ketones and aldehydes with a hydroxy group in the □ position are known to undergo an isomerization reaction known as an acyloin rearrangement:

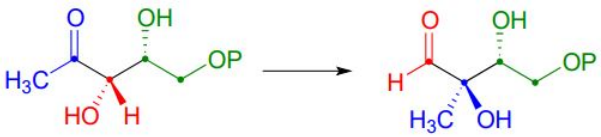


Notice in the general acyloin rearragnement mechanism below, the green alkyl group is shifting from the □ carbon (red) to the carbonyl carbon (blue). Notice also that this shift does not involve a carbocation intermediate, although a resonance contributor can be drawn in which the carbonyl carbon has a positive charge.

a. Draw a mechanism for this acyloin rearrangement step in the biosynthetic pathway for the amino acid leucine:

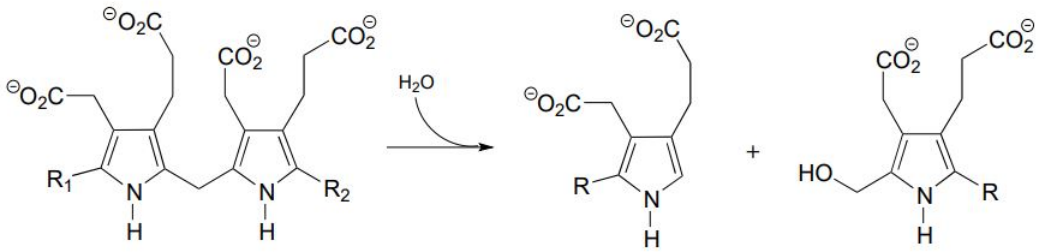


b. Draw a mechanism for this acyloin rearrangement step in the isoprenoid biosynthetic pathway in bacteria:

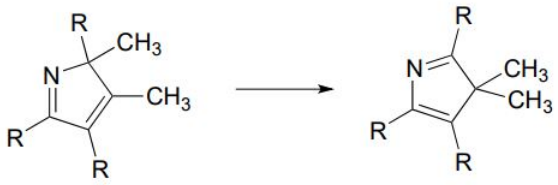


P14.15: Propose mechanisms for these reactions in the vitamin B_{12} biosynthetic pathway:

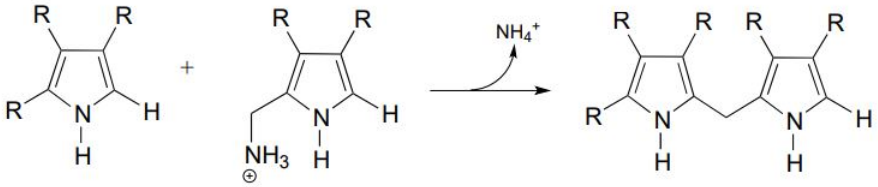
a)



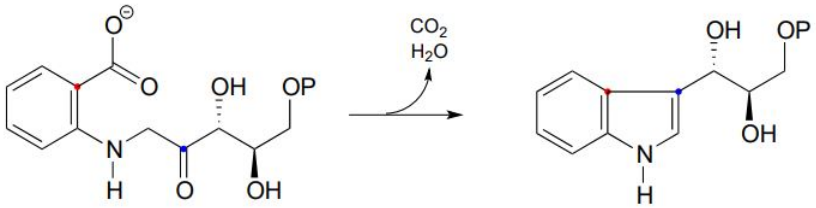
b)



c)

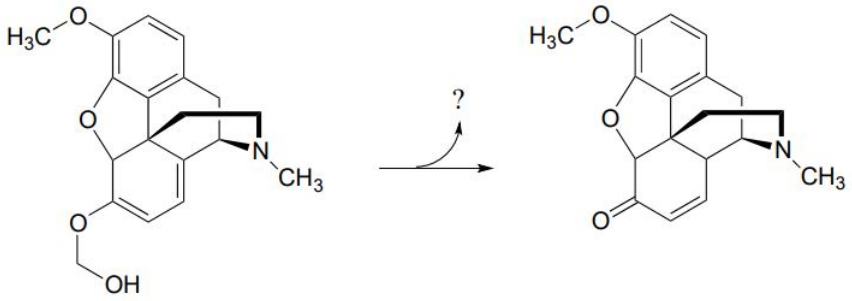


P14.16: An early reaction in the biosynthesis of tryptophan can be described as an intramolecular electrophilic aromatic substitution/decarboxylation hybrid, followed by an E1 dehydration (EC 4.1.1.48).



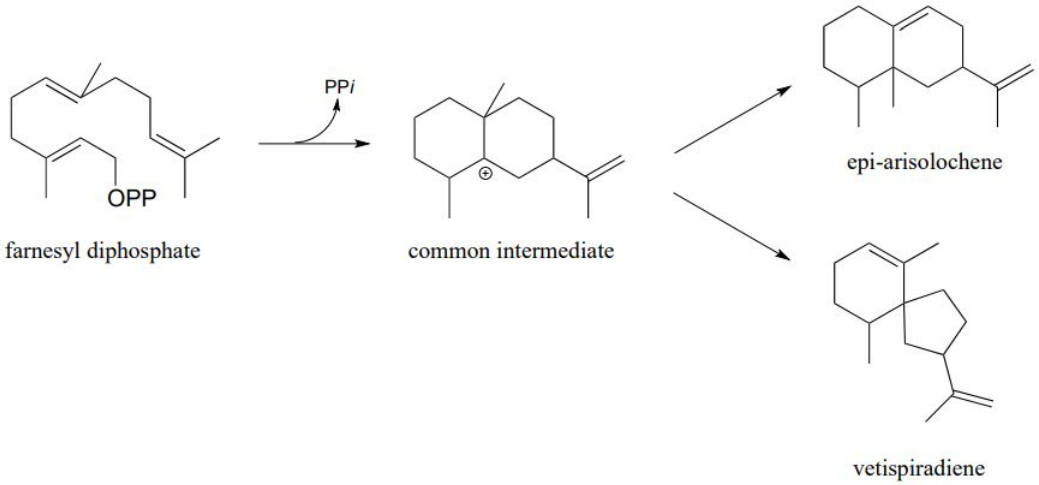
a. Draw a mechanism that corresponds to the verbal description given above. Use resonance structures to show how the nitrogen atom helps to stabilize the carbocation intermediate. ***Hint***: the electrophilic carbon in this case is a ketone rather than a carbocation.
b. What aspect of this reaction do you think helps to compensate for the energetic disadvantage of not having a powerful carbocation electrophile?
c. Again thinking in terms of energetics, what is the 'driving force' for the dehydration step?

P14.17: Propose a likely carbocation-intermediate mechanism for the following reaction in the biosynthesis of morphine, being sure to identify the structure of the organic compound released in the reaction.



P14.18: Propose mechanisms for these three electrophilic cyclization reactions. Carbocation rearrangement steps are involved.

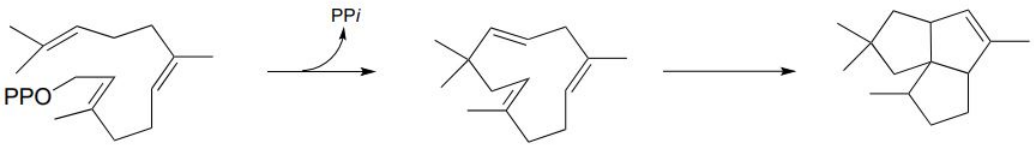
a. epi-arisolochene
b. vetispiradiene (Science 1997, 277, 1815)



farnesyl diphosphate

common intermediate

c. pentalenene (Science 1997, 277, 1820)

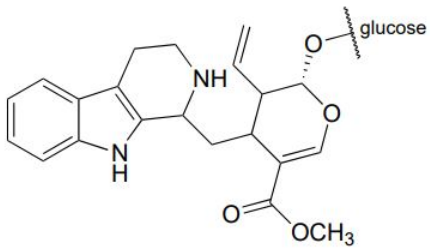


farnesyl diphosphate

intermediate

pentalenene

P14.19: Strictosinide, an intermediate in the biosynthesis of the deadly poison strychnine, is formed from two steps: a) intermolecular imine formation, and b) an intramolecular, ring-forming electrophilic aromatic substitution with the imine carbon from step (a) as the electrophile.

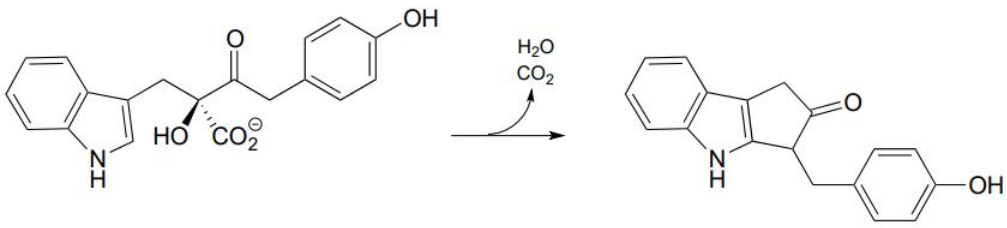


strictosinide

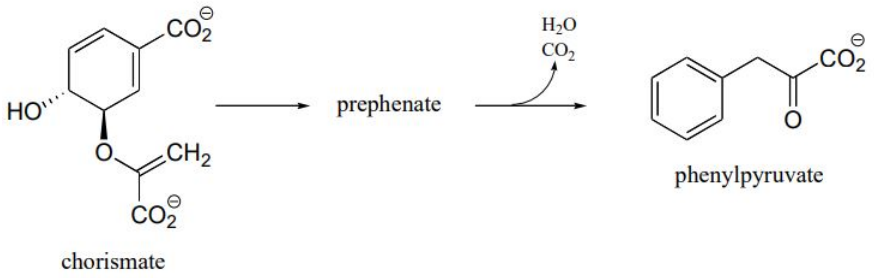
Given this information, predict the two precursors to strictosinide, and draw a mechanism for the reaction described. ***Hint***: use the 'retro' skills you developed in chapter 12 and chapter 13.

P14.20: In the introduction to chapter 8, we learned about reactions in which the cytosine and adenine bases in DNA are methylated. In the course of that chapter, we learned how adenine N-methylation occurs in bacteria, but we were not yet equipped to understand cytosine C-methylation, which was the more relevant reaction in terms of human health and development. Now we are: propose a reasonable mechanism for the C-methylation of cytosine.

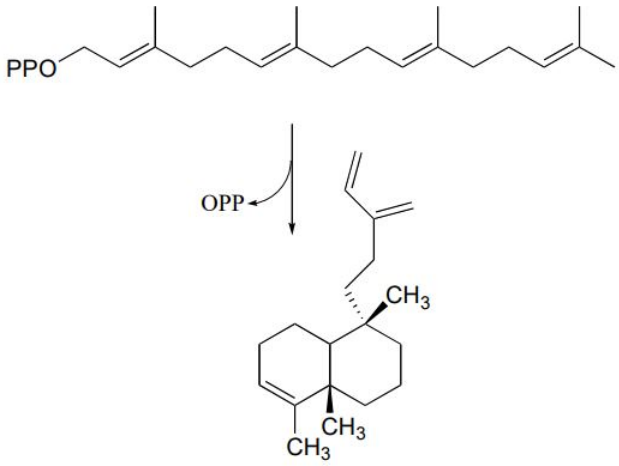
P14.21: The reaction below has been proposed to proceed via a cyclization step followed by an E1/decarboxylation step (in other words, an E1 mechanism where decarboxylation occurs instead of deprotonation). Draw a mechanism that fits this description, and show the most stable resonance contributors of the two key cationic intermediates.



P14.22: The conversion of chorismate to phenylpyruvate is a key transformation in the biosynthesis of phenylalanine. The first step is a concerted electrophilic rearrangement to form prephenate (this step involves a six-membered transition state). Deduce the structure of prephenate, and provide a complete mechanism for the transformation.



P14.23: Suggest likely a mechanism for the following reaction:



Contributors

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