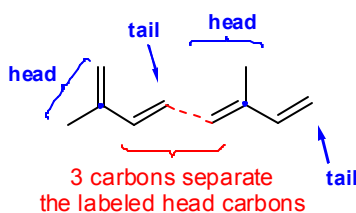


Biosynthesis of Terpenes

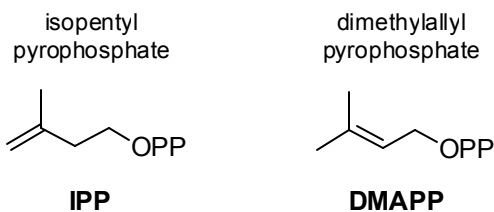
Structure

- Terpenes are natural products that can be viewed as oligomers of five carbon isoprene subunits

Isoprene Rule – Isoprene units are typically linked in a head-to-tail fashion in terpenes



- Instead of isoprene, terpenes are actually formed from IPP and DMAPP, which are synthesized from acetyl-CoA



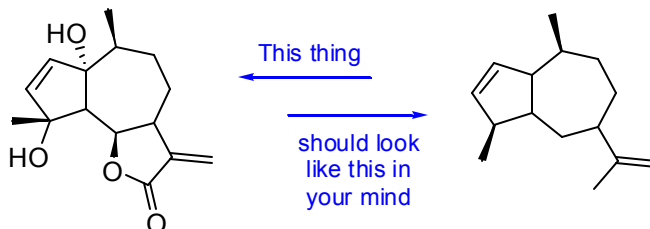
Nomenclature

Hemiterpenes – 5 carbons	(1 isoprene unit)
Monoterpenes – 10 carbons	(2 isoprene units)
Sesquiterpenes – 15 carbons	(3 isoprene units)
Diterpenes – 20 carbons (e.g. retinals)	(4 isoprene units)
Sesterpenes – 25 carbons	(5 isoprene units)
Triterpenes – 30 carbons (e.g. steroids)	(6 isoprene units)

Identifying Isoprene Units in a Terpene

For many terpenes, it is possible to look at the structure and identify the isoprene monomers on inspection without having to work through a mechanism. Here's a method to go about doing it:

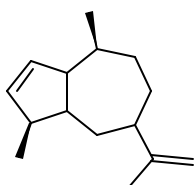
1) Forget about the Functional Groups



- Most terpene biosyntheses work by assembling the complex hydrocarbon core and then using other enzymes to oxidize the framework to add functionality. These processes are unlikely to oxidize C-C bonds, so the first thing you do is simplify matters by ignoring the functional groups.
- Don't get hung up on looking for the double bonds that are present in isoprene, IPP, and DMAPP. Those bonds are reactive and thus are often masked with functionality in the final product.

2) Classify the Terpene and Determine How Many Isoprenes are Present

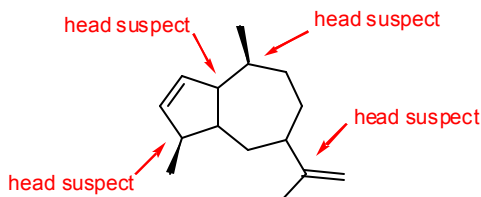
- Count the number of carbons in the structure. This number should be divisible by five, and the quotient is the number of isoprene units present in your compound.



There are 15 carbons present, so there are 3 isoprene subunits that we must find

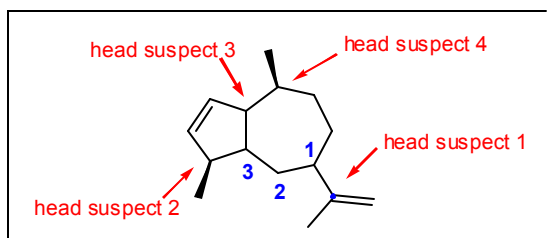
3) Identify Possible Locations of Isoprene Heads

- You have to start somewhere, so start by identifying the most obvious positions for heads.
- These are typically 3° or 4° carbons with one or more methyl groups.
- Especially look for unsaturated carbons bonded only to carbon atoms, particularly a methyl group.

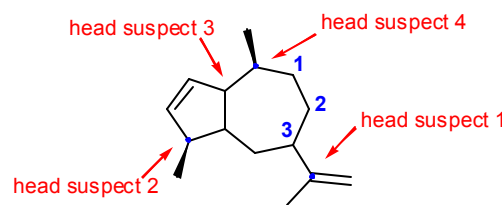
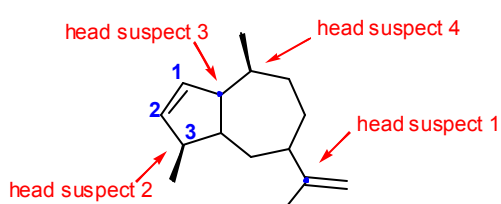
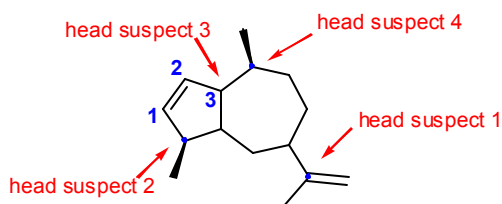
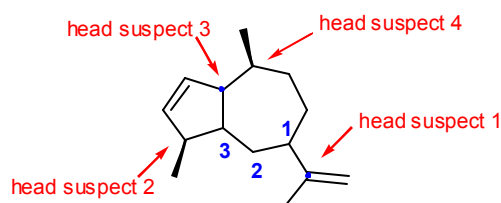
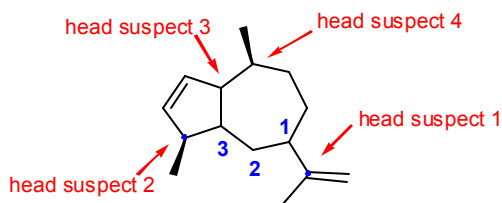


4) Begin Assigning Isoprenes

- Start with your #1 suspect: hopefully something with methyls hanging off
- Isoprenes bond head-to-tail, and as a result, head carbons will have 3 “non-head” carbons between them
- Starting from suspect #1, begin numbering along the chain



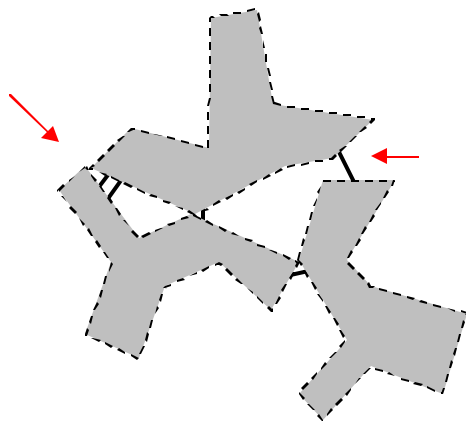
if you number starting from your prime head suspect, there are two other suspects three carbons away



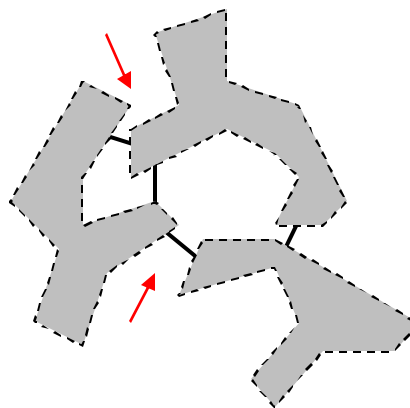
you cannot find another head suspect three carbons away if you assign a head carbon to suspect 3

- Isopropyl groups and methyl vinyl groups (unsaturated isopropyl) are dead giveaways for head groups, since it is impossible to break them down into being parts of two isoprenes (it would leave one methyl group uncircled and isolated)
- As shown in this example, sometimes when you number you get into “dead ends” (right side above). If this happens, choose a new direction. If everything is a dead end, start over from a new head suspect.

5) Confirm Your Assignment



Good

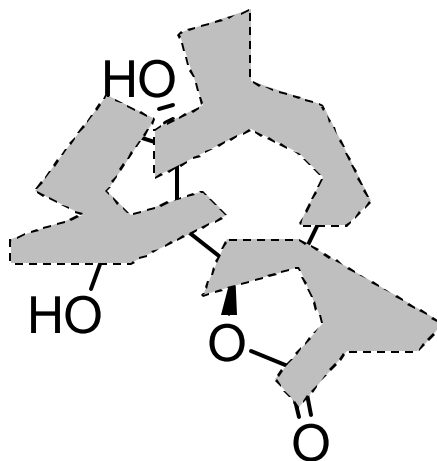


Also good

Arrows indicate a proper "head-to-tail" linkage

- Circle your isoprenes
- While *all* of the head carbons might not be separated by three carbons, you usually want at least one path where each subunit is connected to the next in true head-to-tail fashion.
- Don't worry about finding other linkages that are not head-to-tail, so long as you have that one path that is head-to-tail (in the case above, the left and upper heads are also separated by a two carbon path).
- Often, especially for larger terpenes, there exists more than one correct way to circle isoprene units.

6) Reinsert the Functional Groups



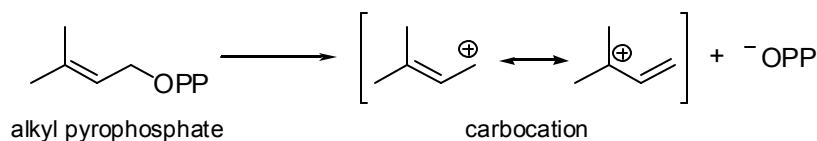
Terpenoid/Carbocation Rearrangement Mechanisms

General Notes

- I took this from a Chem 27 handout. Some of the material you don't know (yet). But, a fair amount of this stuff is applicable to this week's problem set.
- Enzymes often control the stereochemistry of these steps in a way that cannot be predicted "on paper."
- If faced with two plausible mechanisms, choose the alternative with the most stable intermediates and the fewest steps

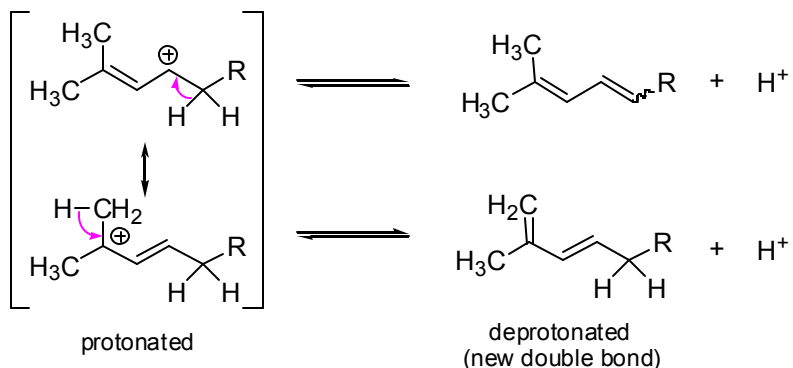
Common Mechanistic Steps

1) Ionization



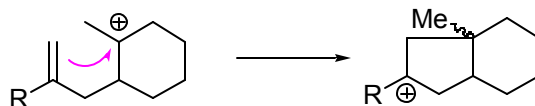
- Pyrophosphate (^-OPP) is a good leaving group
- Loss of ^-OPP results in the formation of a reactive carbocation

2) Deprotonation



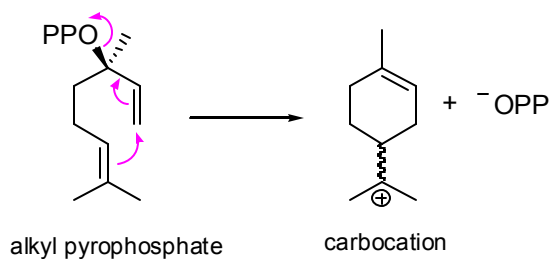
- Loss of a proton adjacent to a carbocation generates a double bond
- Always show protons being removed by a base (unlike the example above).

3) Olefin Attack of a Carbocation



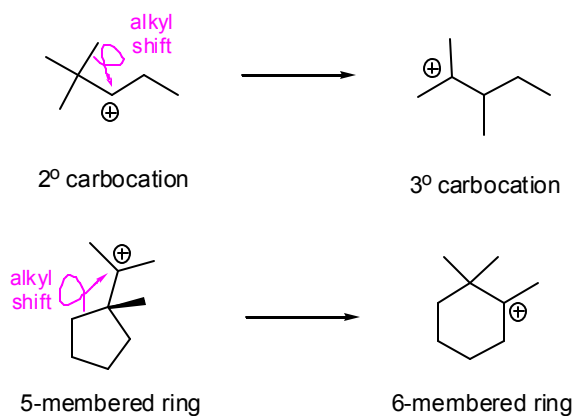
- The π bond is the nucleophile, while the carbocation (empty p orbital) is the electrophile
- Note that you are left with a new carbocation; the charge is conserved
- More often than not you attack with the less substituted carbon so that you generate the more substituted/stable carbocation

4) S_N2' Reaction



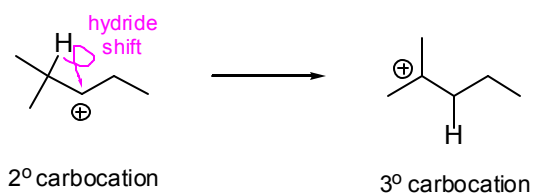
- The bottom π bond is the nucleophile, while the 3-carbon allyl system is the electrophile

5) Alkyl Shift



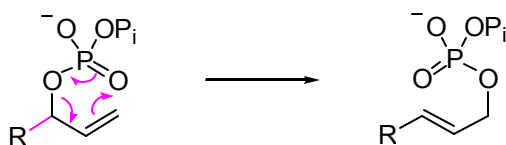
- Alkyl shifts are typically driven by the formation of a more stable cation
- Recall, carbocations are stabilized by greater alkyl substitution
- There is less ring strain in a six membered ring vs. a five membered ring

6) Hydride Shifts



- Hydride shifts are also driven by the formation of a more stable cation

7) Allyl-Phosphate Rearrangement



- This is a [3,3] sigmatropic shift, just like the Claisen rearrangement
- This is a key step in cases where, prior to phosphate rearrangement, the double bond is not positioned correctly to lead to a stable product (e.g., *trans* geometry)