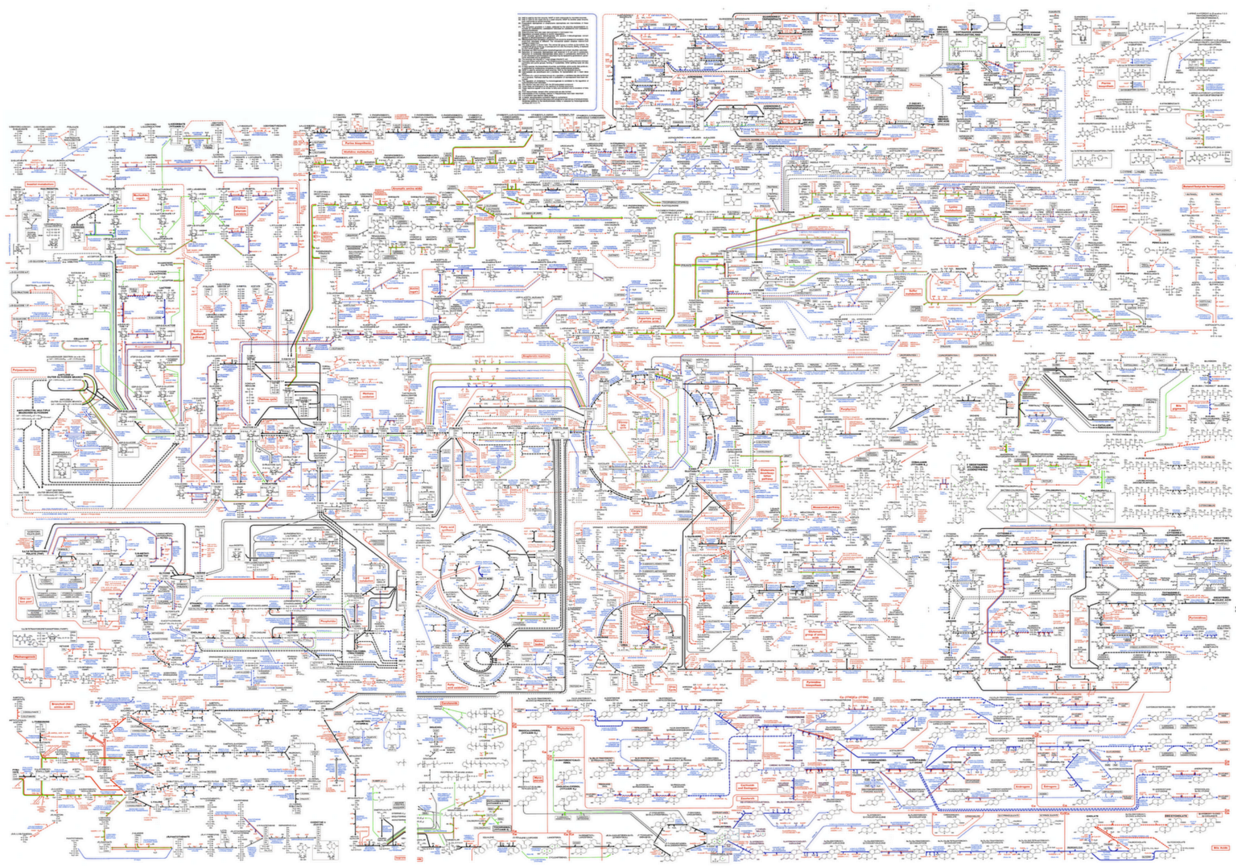
Week 6 July 31, 2014

The Organic Chemistry of Life

The famous poster “Biochemical Pathways” by G. Michal:

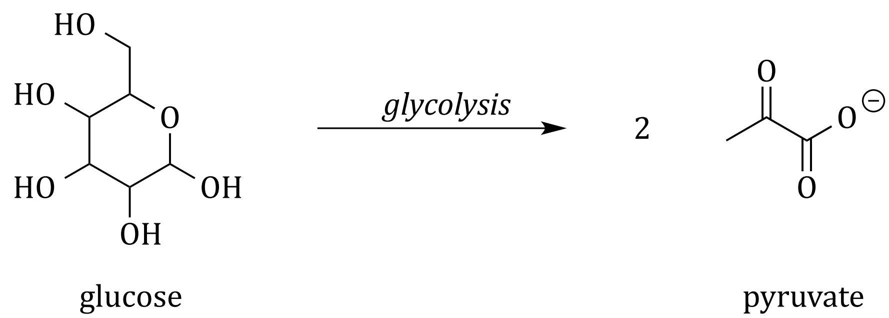


Every biological process involves the making and breaking of chemical bonds; these are *chemical transformations* (mostly organic chemistry)!

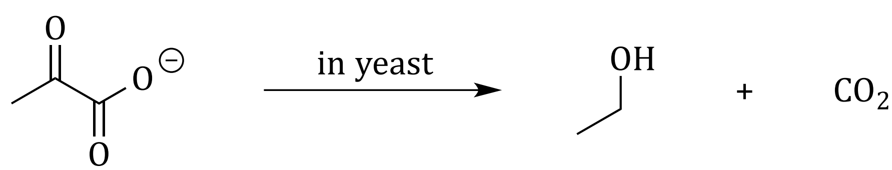
How is organic chemistry in the cell different from organic chemistry in the lab?

The Organic Chemistry of Life:
Bread and Beer

Nearly all organisms get energy from *glycolysis*, the transformation of glucose into pyruvate:



In yeast, pyruvate is converted to ethanol and carbon dioxide:



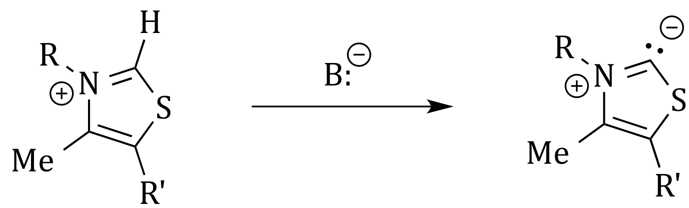
What use does the yeast have for ethanol and CO_2?

What use do *we* have for ethanol and CO_2?

How might the yeast accomplish this transformation?

The Organic Chemistry of Life:
Bread and Beer: CO_2

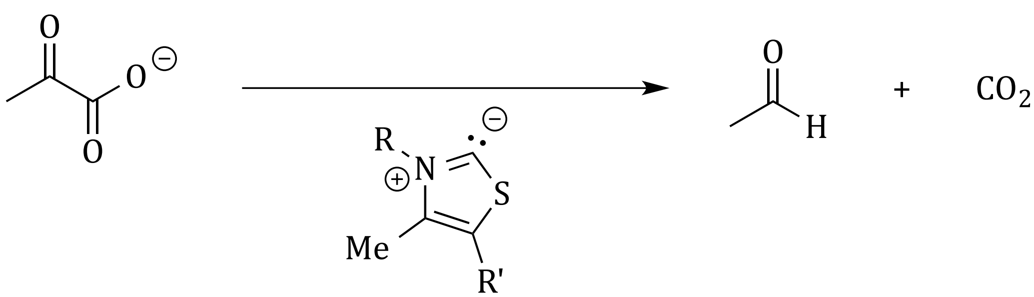
The decarboxylation of pyruvate requires thiamine as a *cofactor*, in the form of a thiamine diphosphate (TPP) ylide:



TPP
(thiamine diphosphate)

TPP ylide

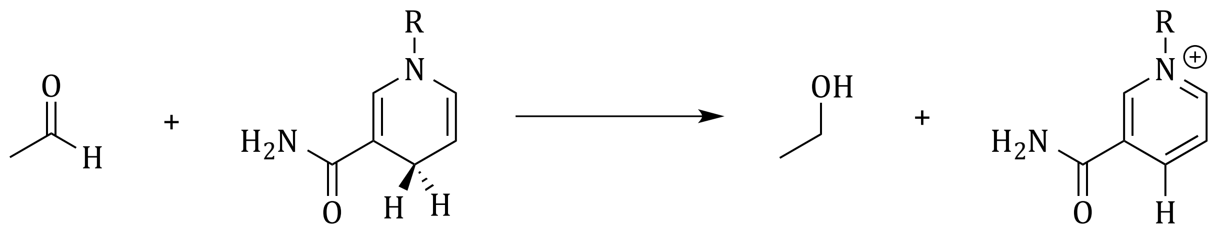
Show how the TPP ylide can catalyze the decarboxylation of pyruvate. This reaction is the source of the CO_2 that makes bread rise and makes beer bubbly.



Note how the TPP ylide turns a tough α-decarboxylation into an easy β-decarboxylation!

The Organic Chemistry of Life:
Bread and Beer: Ethanol

The transformation of acetaldehyde into ethanol requires the cofactor NADH. Propose a mechanism:

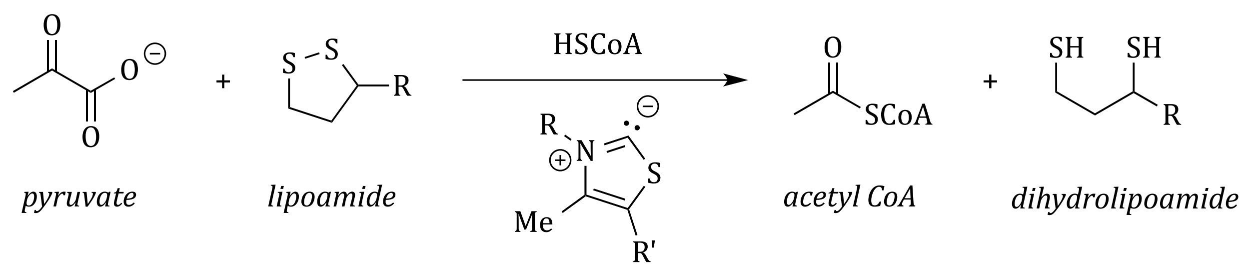


What is the "orgo lab" equivalent of NADH?

The *reverse* process – oxidation of ethanol to acetaldehyde – is catalyzed by an enzyme in your liver, *liver alcohol dehydrogenase* (LADH). This enzyme requires the cofactor NAD^+. Why? What is the "orgo lab" equivalent of NAD^+?

The Organic Chemistry of Life:
Biosynthesis of Acetyl CoA

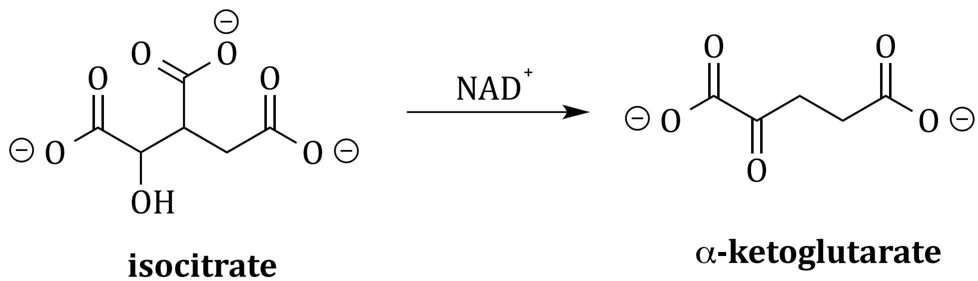
Pyruvate is also the source of *acetyl coenzyme A*, a thioester that is the crucial building block for a huge number of biomolecules. The overall transformation involves the TPP ylide and a *disulfide* that is known as *lipoamide*. Let's propose a mechanism:

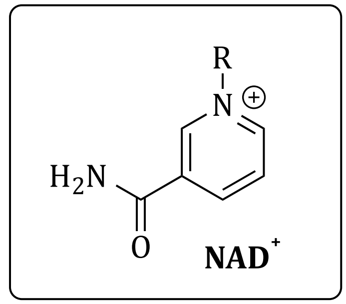


Why are thioesters like acetyl CoA so useful in biological systems?

The Organic Chemistry of Life:
Test Yourself Now!

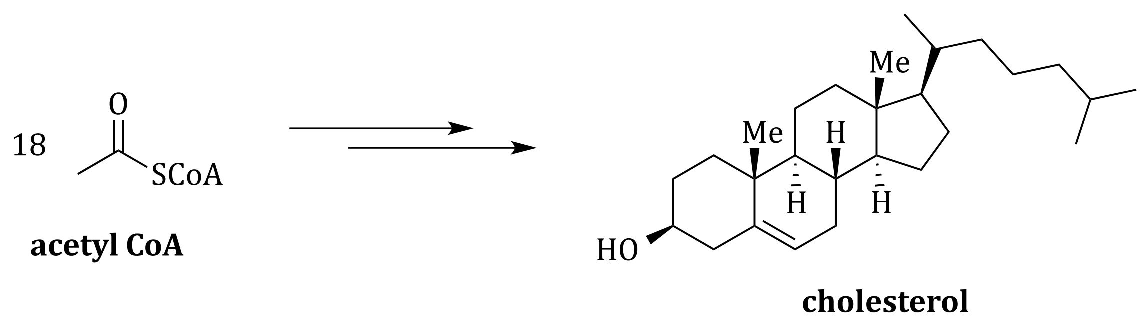
Provide a complete curved-arrow mechanism for the following biochemical transformation, which is part of the citric acid (Krebs) cycle. Structures of cofactors are shown at the right.





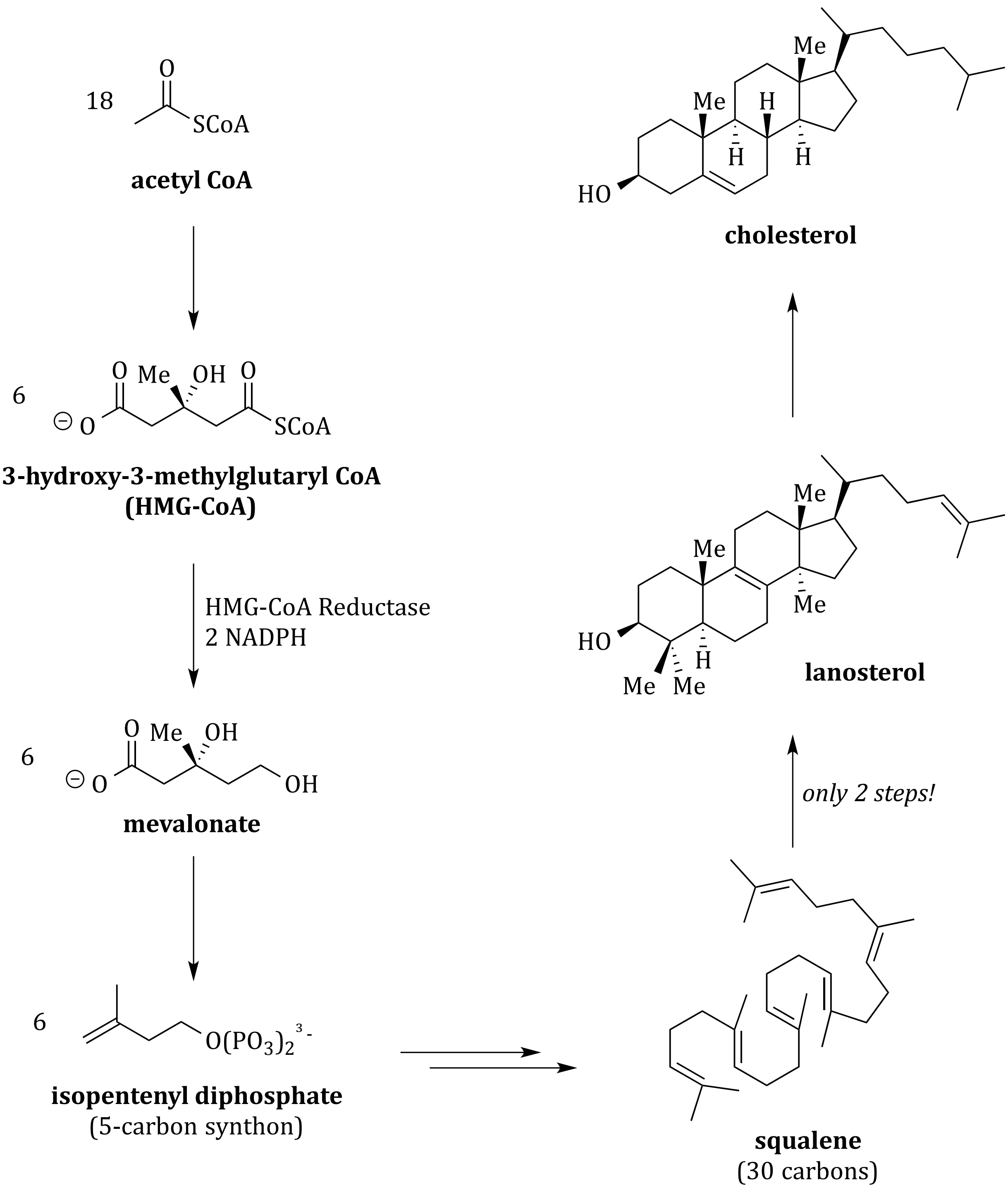
The Organic Chemistry of Life:
Cholesterol Biosynthesis

Acetyl CoA is the starting material for the biosynthesis of cholesterol. Propose a complete curved-arrow mechanism for this transformation:



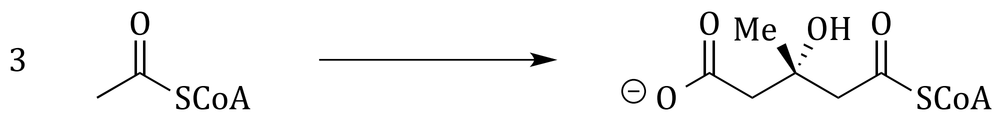
Cholesterol Biosynthesis:
Overview

Here are the **big steps** involved in cholesterol biosynthesis:



Cholesterol Biosynthesis:
1) Synthesis of HMG-CoA

Provide a complete curved-arrow mechanism for the synthesis of HMG-CoA from three molecules of acetyl CoA. How does the enzyme "hold onto" the molecules while they react?

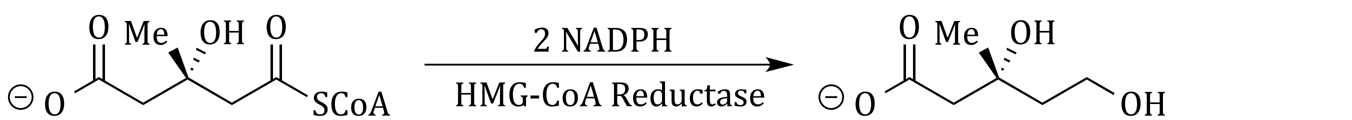


acetyl CoA

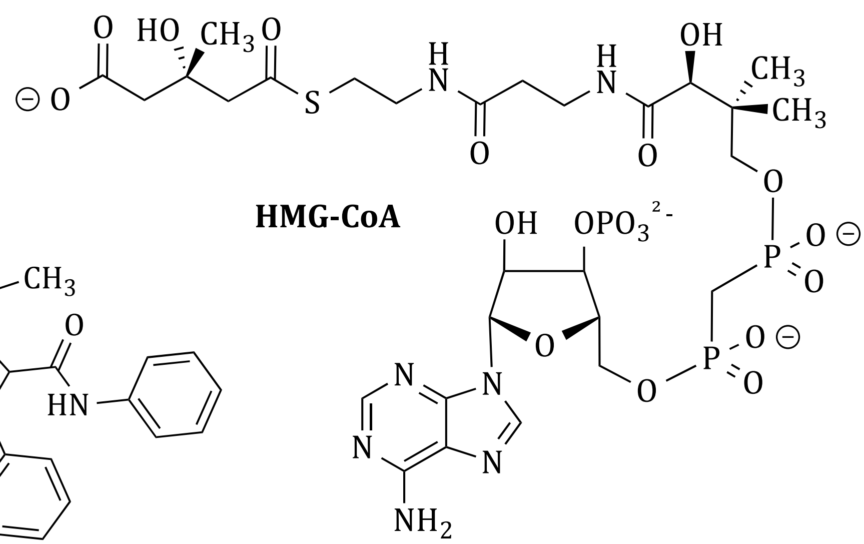
3-hydroxy-3-methylglutaryl CoA (HMG-CoA)

Cholesterol Biosynthesis:
2) HMG-CoA Reductase: Targeted by Statins

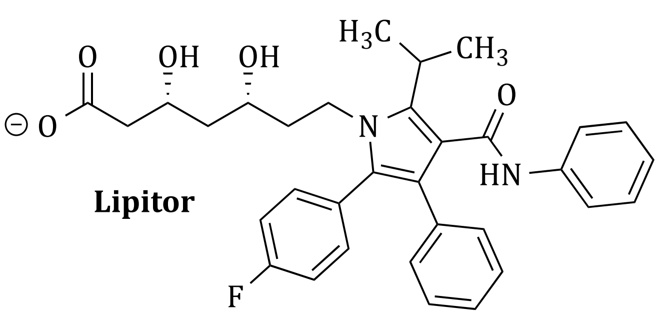
The remarkable anti-cholesterol drugs known as *statins* target the next step of cholesterol biosynthesis: the reduction of HMG-CoA to mevalonate. Provide a mechanism for this reaction. Are there any *cofactors* involved in this reaction?



Here are the complete structures of HMG-CoA and the drug Lipitor®. What step in the reduction of HMG-CoA is blocked by the binding of Lipitor®? How can you tell?



HMG-CoA



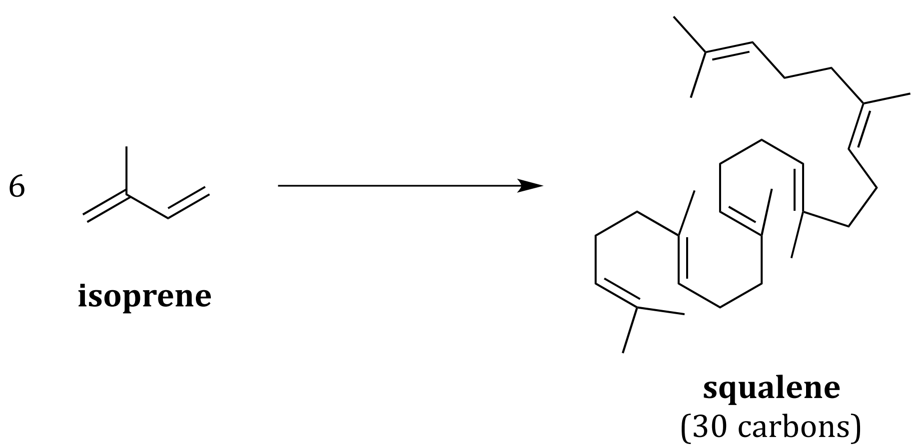
Lipitor

Cholesterol Biosynthesis:
3) From Mevalonate to IPP to Squalene

Provide a complete curved-arrow mechanism for the reaction of mevalonate with three equivalents of ATP to yield isopentenyl diphosphate

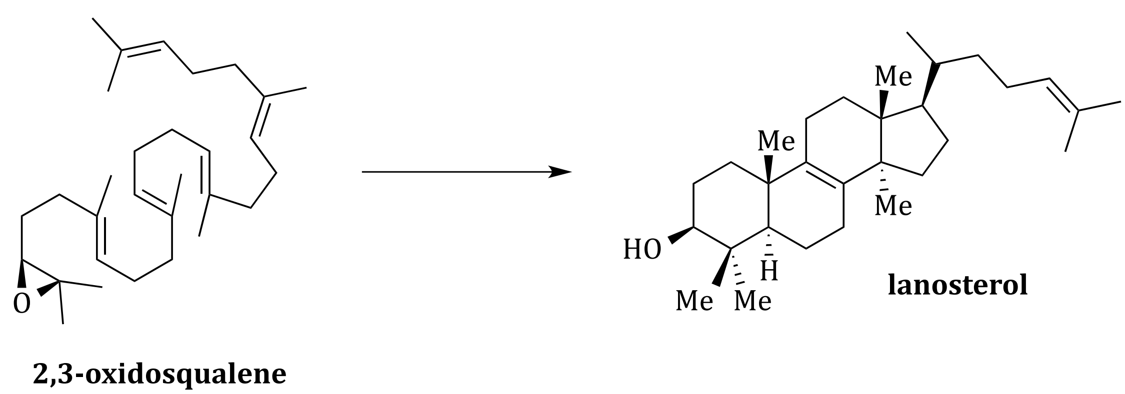
What is the “orgo-lab” equivalent of ATP?

Isopentenyl diphosphate contains a 5-carbon unit known as an *isoprene* unit. Can you see how six of these isoprene units can be joined together to form squalene?



Cholesterol Biosynthesis:
4) From Squalene to Cholesterol

Squalene is then converted to *lanosterol*. The first step is an oxidation that proceeds through a mechanism much like that of the laboratory synthesis of epoxides by peracids. Then the epoxide is opened with acid and a remarkable cascade, followed by several carbocation rearrangements, yields lanosterol in a single enzymatic step. This reaction is one of the most remarkable enzyme-catalyzed biosynthetic transformations:



Finally, lanosterol is converted into cholesterol in several further enzymatic steps….