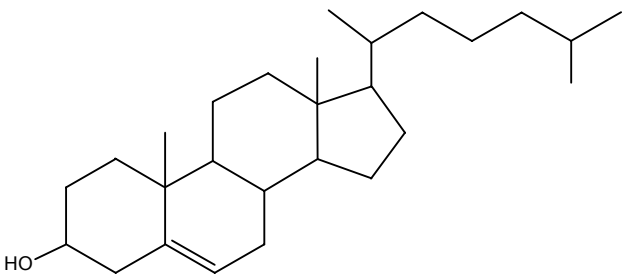
Cholesterol

April 2, 2003

Bryant Miles

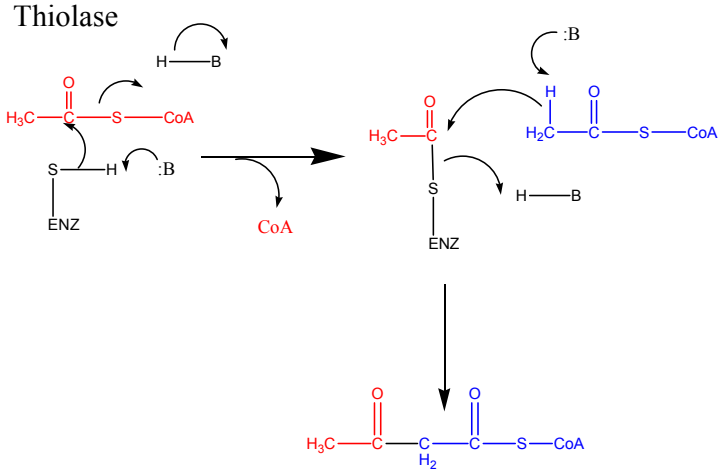


Cholesterol

- Cholesterol is most prevalent steroid in animal cells.
- Cholesterol is an important component of mammalian membranes.
- Cholesterol is also a precursor for steroidal hormones and bile salts. H
- Cholesterol is synthesized in the liver.
- Cholesterol biosynthesis is under hormonal regulation.

Stage I: Acetyl CoA → Isopentenyl pyrophosphate

Thiolase

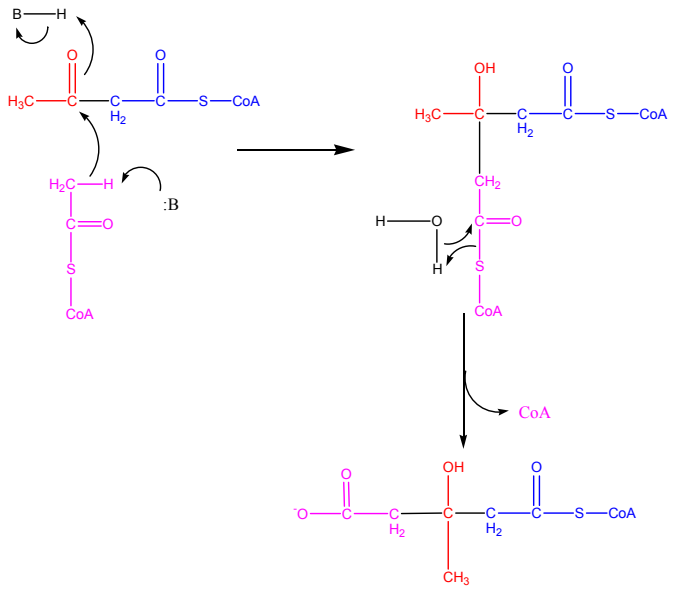


Cholesterol biosynthesis begins in the cytosol of liver cells. In the first step of cholesterol biosynthesis 3-hydroxy-3-methylglutaryl CoA is produced from 3 molecules of acetyl-CoA. Note that this is exactly the same as ketobody biosynthesis.

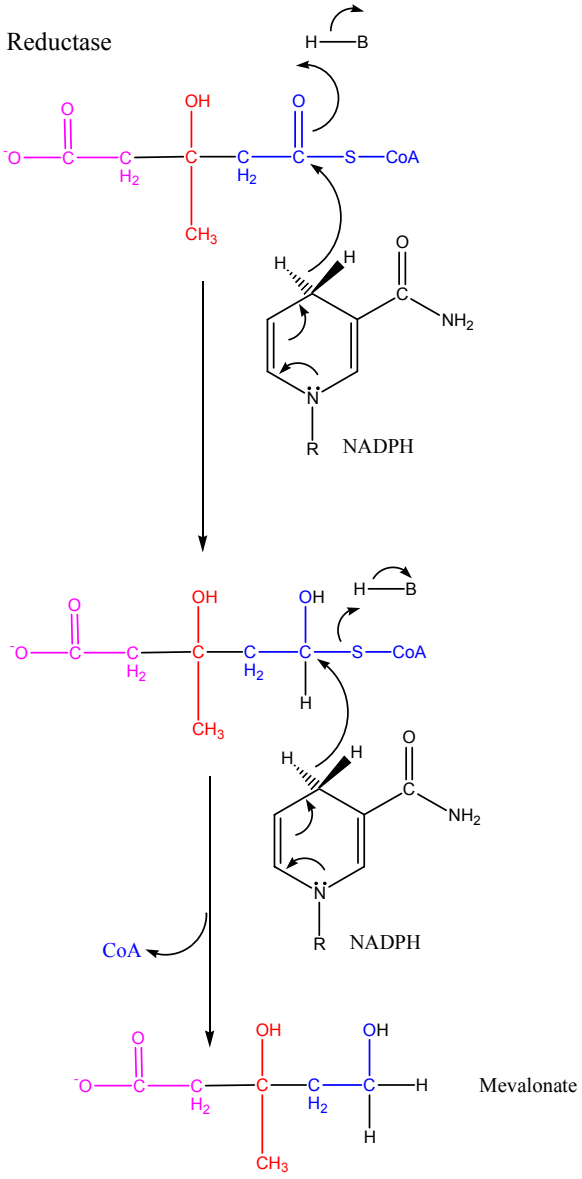
The first step is catalyzed by the familiar thiolase enzyme which in this case is catalyzing the claisen condensations of 2 acetyl CoA molecules to form acetoacetyl CoA.

The next step is catalyzed by HMG-CoA synthase. This reaction is a second Claisen condensation. The product is 3-hydroxy 3-methylglutaryl CoA which is abbreviated HMG-CoA.

HMG-CoA Synthase



HMG-CoA Reductase



The third step of cholesterol biosynthesis is the reduction of HMG-CoA to mevalonate. The enzyme that catalyzes this 4 electron reduction is HMG-CoA Reductase. This is an integral membrane protein transversing the endoplasmic reticulum membrane. The active site of this enzyme is facing the cytosol.

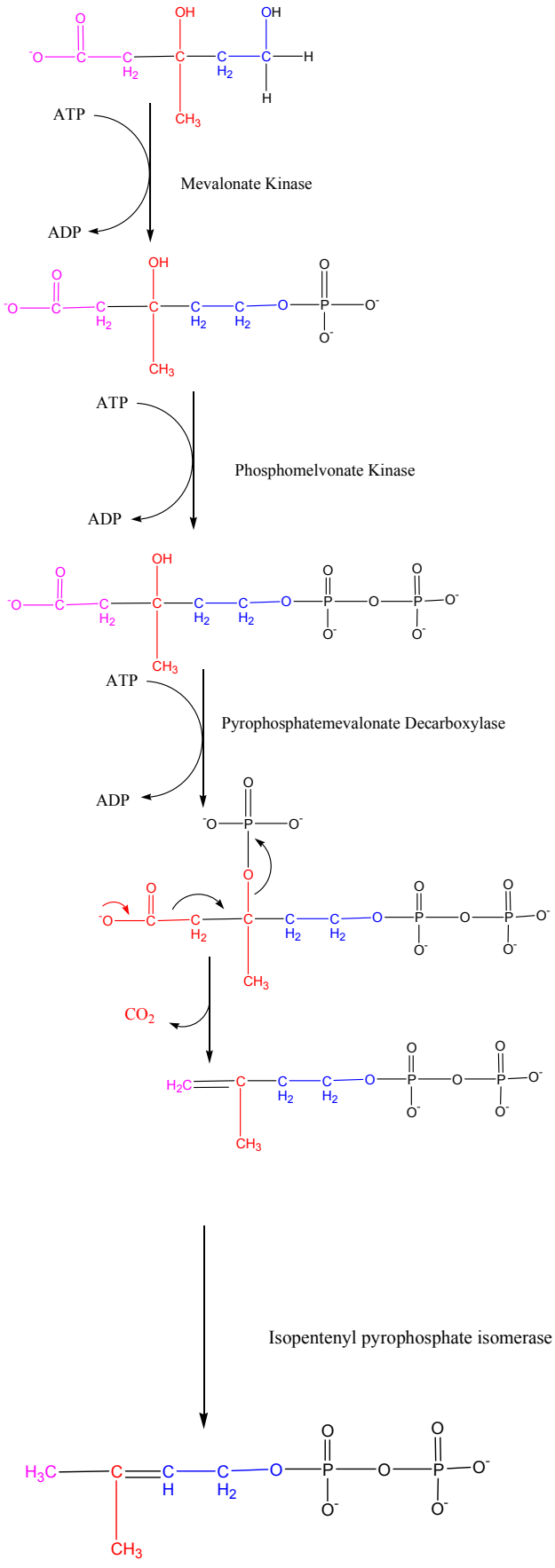
This is the rate determining step of cholesterol biosynthesis. HMG-CoA reductase is the principle site of allosteric regulation of cholesterol biosynthesis.

There are 3 mechanisms for the regulation of HMG-CoA reductase.

1. Phosphorylation by cAMP dependent kinase which inactivates the enzyme. This phosphorylation is reversed by the phosphatase activity of specific phosphatases.
2. Degradation of HMG-CoA reductase. This reductase has a very short half life of 3 hours. The stability of this enzyme depends on the cholesterol concentration. High concentrations of cholesterol result in a short life time for the reductase.
3. Gene expression. Cholesterol concentrations control the expression of mRNA for the reductase. Cholesterol high, level of expression reduced. Cholesterol low, level of expression increased.

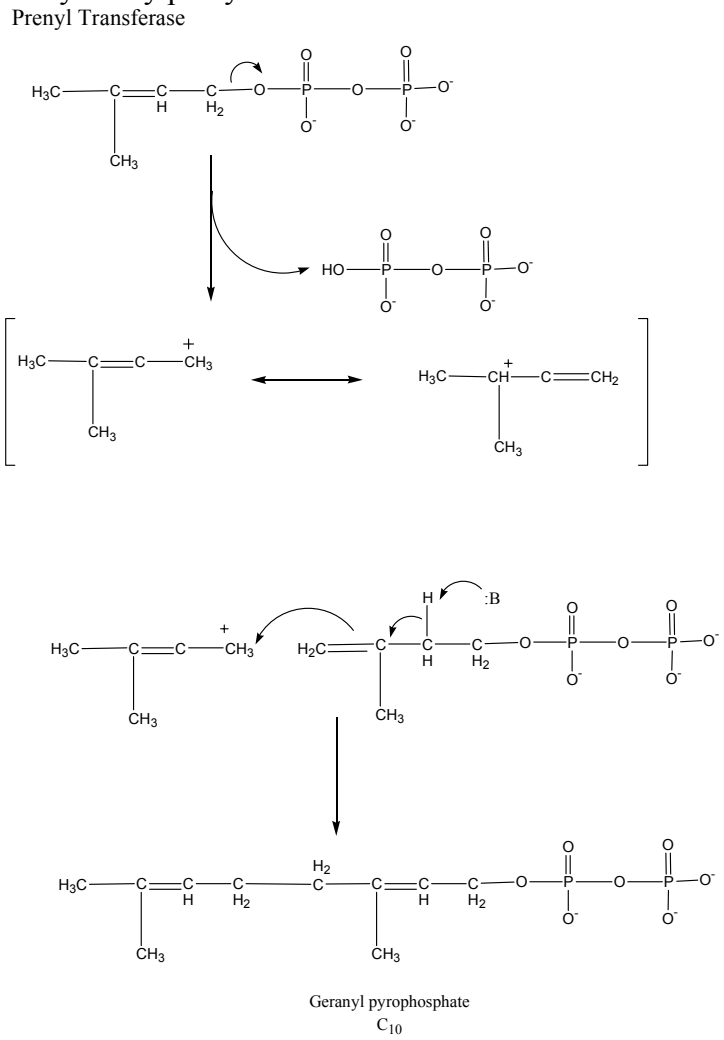
The mevalonate is converted into isopentenyl pyrophosphate and dimethylallyl pyrophosphate. This requires a series of four reactions shown on the following page.

Mevalonate kinase phosphorylates mevalonate with ATP to form phosphomevalonate. Phosphomevalonate kinase phosphorylates phosphomevalonate with a second molecule of ATP to form pyrophosphomevalonate. Pyrophosphomevalonate decarboxylase phosphorylates the 3-hydroxyl group of mevalonate with a 3rd molecule of ATP. This is followed by a transelimination of the phosphate group and the carboxylate group to form the double bound of isopentenyl pyrophosphate. Isopentenyl pyrophosphate is isomerized into dimethylallyl pyrophosphate by isopentenyl pyrophosphate isomerase.



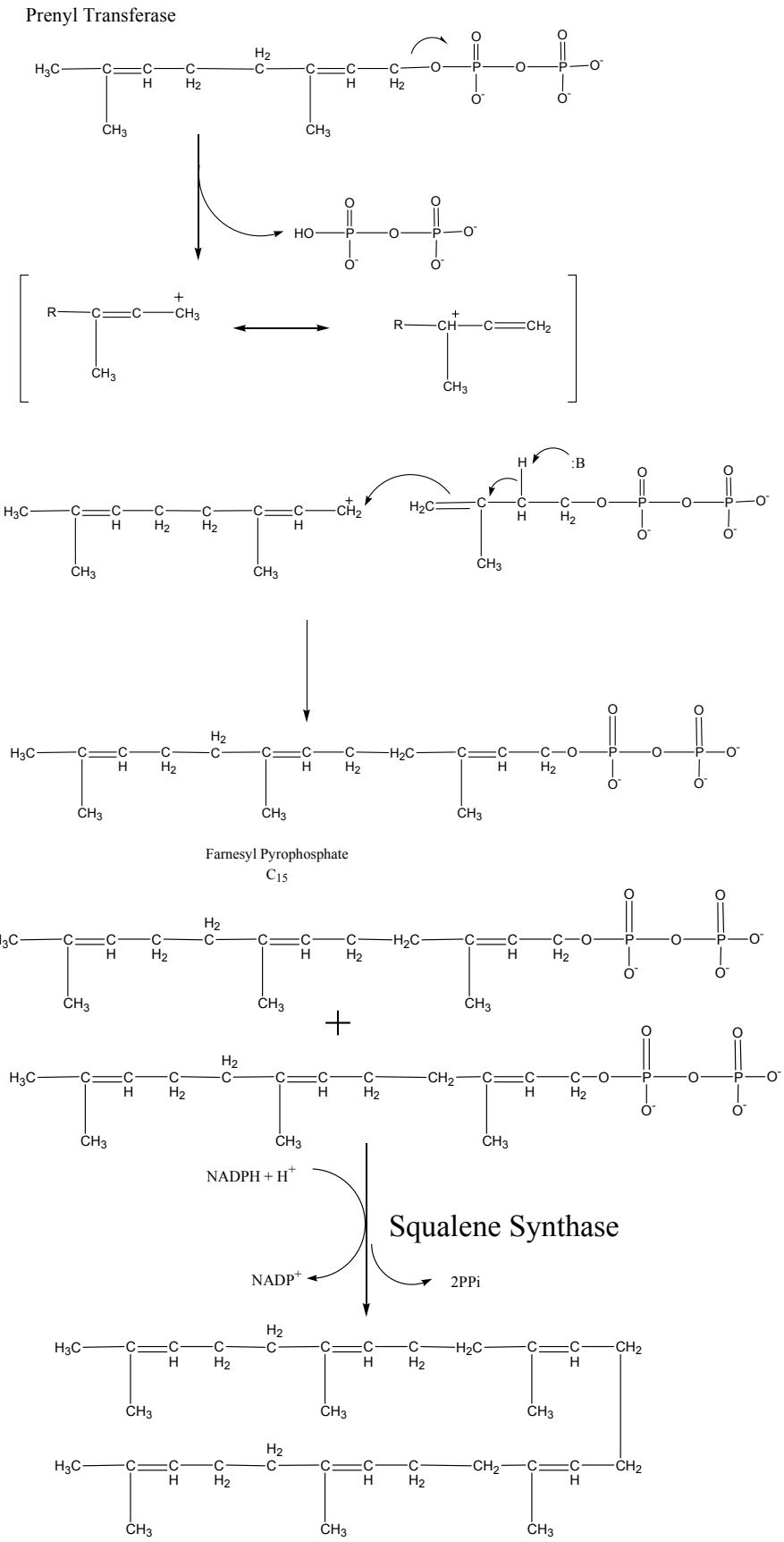
Stage 2: Isopentenyl Pyrophosphate to Squalene

Isopentenyl pyrophosphate isomerase converts isopentenyl pyrophosphate into dimethylallyl pyrophosphate as shown on the bottom left. In the next reaction shown below, dimethylallyl pyrophosphate is condensed head to tail with isopentenyl pyrophosphate to generate geranyl pyrophosphate. This reaction is catalyzed by prenyl transferase.

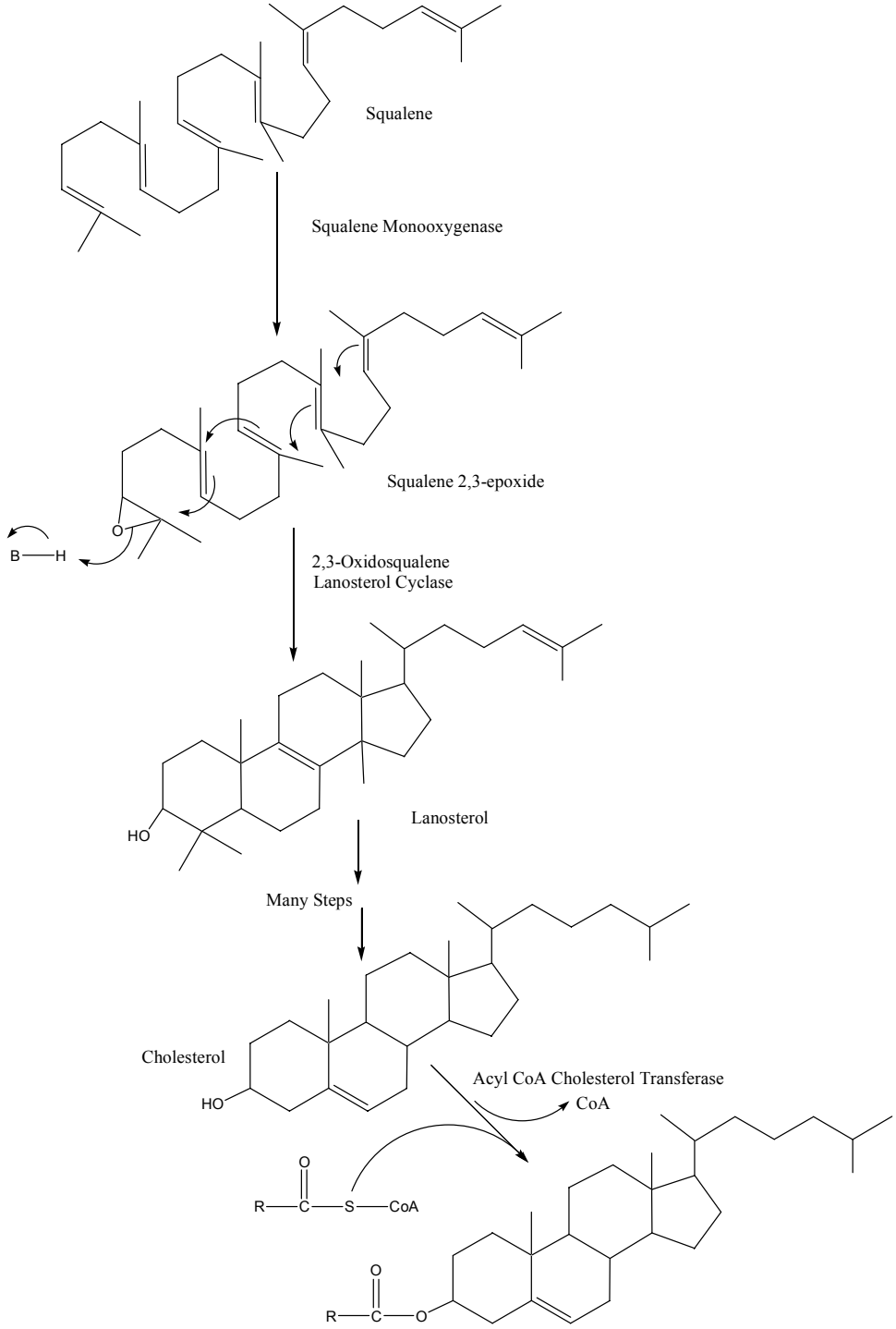


The reaction mechanism is a Sn1 nuclear substitution reaction. The pyrophosphate group of dimethylallyl pyrophosphate leaves generating a resonance stabilized carbocation which is attacked by the isopentenyl pyrophosphate as shown above to produce geranylpyrophosphate.

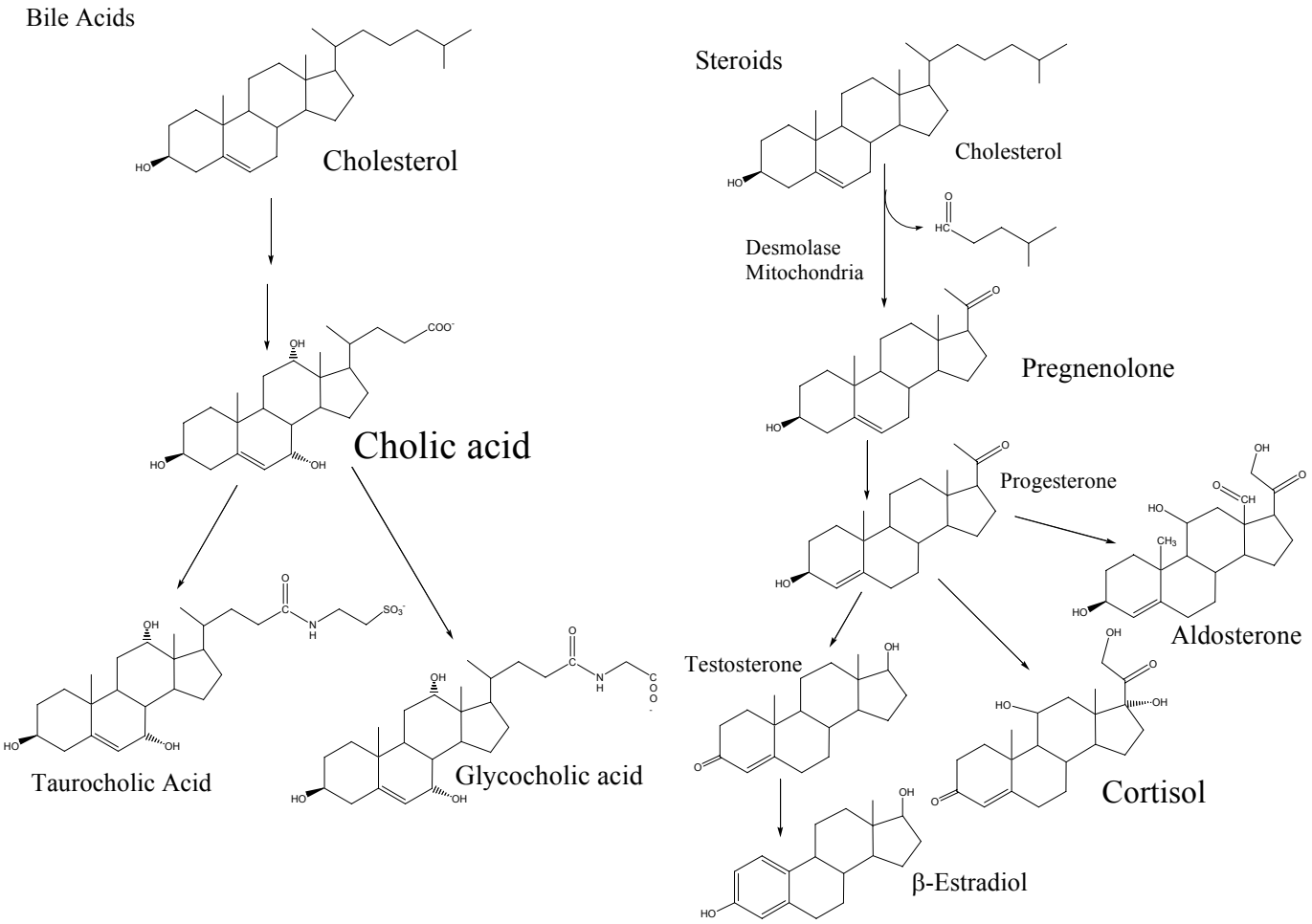
This reaction is repeated. The pyrophosphate group of geranyl pyrophosphate leaves generating a resonance stabilized carbocation which is attacked by a second isopentyl pyrophosphate in a head to tail fashion to from the 15C farnesyl pyrophosphate as shown on the next page. The last reaction is catalyzed by squalene synthase which condenses 2 farnesyl pyrophosphates in a head to head fashion.


Prenyl Transferase
Farnesyl Pyrophosphate
C_{15}
NADPH + H^+
Squalene Synthase
$NADP^+$
2PPi
Squalene
C_{30}

Stage 3: Squalene to Cholesterol.



Squalene monooxygenase is an enzyme found in the endoplasmic reticulum membrane. This enzyme converts squalene into squalene 2,3-epoxide. A second enzyme found in the endoplasmic reticulum membrane 2,3-oxidosqualene lanosterol cyclase catalyzes a concerted series of cyclizations, 1,2 hydride hydride shifts, 1,2 methyl group shifts to produce lanosterol. The conversion of lanosterol into cholesterol involves over 20 steps. Circulating cholesterol is in the form of cholesterol esters which are synthesized by acyl-CoA:cholesterol acyltransferase.
Cholesterol is a precursor for bile acids and steroids.



Bile Salts are synthesized in the liver and then stored and concentrated in the gall bladder until you eat a fat rich meal and then they are secreted into your lower intestine. Bile salts are important for the digestion of food because they solubilize ingested fats. Glycocholic acid and taurocholic acid are 2 principle bile salts.

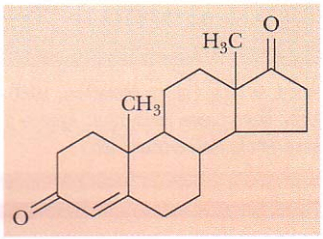
Steroid Hormones are crucial signal molecules in animals. We will explore them in greater detail (time permitting) latter in the semester. The biosynthesis of steroids begins with the desmolase reaction which converts cholesterol into pregnenolone. This enzyme is found in the mitochondria of the tissues that synthesize steroids (the adrenal gland and the gonads). Pregnenolone is transported from the mitochondria to the ER where it undergoes an oxidation and a double bond migration to form progesterone. Progesterone is a steroid that regulates the mestrual cycle in women and insures successful pregnancies. Progesterone is also a precursor for other steroid hormones such as the sex hormone steroids and the corticosteroids. The male sex hormones are called androgens. The female sex hormones are called estrogens. Testosterone is the most popular androgen which is produced in the testes of men. Androgens are necessary for sperm maturation. Women also produce testosterone in the ovaries in much smaller amounts. Testosterone is a precursor for the estrogens. One of the most important estrogens is β-estradiol.

The Corticosteroids are synthesized in the adrenal glands. Cortisol is a glucocorticoid which stimulates gluconeogenesis and glycogen synthesis in the liver. It activates PEPCK, Fructose 1-6 bisphosphatase, glucose 6-phosphatase, glycogen synthase and promotes protein degradation while inhibiting protein synthesis. Aldosterone is a mineralocorticoid which regulates the sodium and potassium balances in the

tissues. Aldosterone increases the kidney's capacity to absorb sodium, chloride and water form the kidney tubules.

Steroids Modulate Transcription in the Nucleus.
Steroid hormones act in a different manner than the hormones such as glucagon, insulin and epinephrine that we have discussed before. In most cases the steroid does not bind to cell receptors on the plasma membrane. Steroids pass easily across the plasma membrane and through the nuclear envelope. Steroids bind directly to receptors in the nucleus. The steroid receptors in the nucleus complex directly to specific sequences of DNA, increasing or decreasing the transcription of DNA to RNA for a particular gene.

Anabolic steroids enhance athletic performance in the short term but irreversibly damage the kidneys, liver and the heart. Sterility is also a common side effect. Anabolic steroids have dramatic effects on protein biosynthesis and building muscle mass. There is a growing list of All Star Major League Baseball players who have enhanced their athletic abilities by using the juice (anabolic steroids). Ken Caminti, Jose Canseco, Marc Mcguire, ect. Marc took Andro (4-Androstene-3-17-dione) which is metabolized into testosterone, an anabolic steroid.



4-Androstene-3,17-dione