Cholesterol Synthesis

Thomas Dayspring, MD, FACP

Clinical Assistant Professor of Medicine

University of Medicine and Dentistry of New Jersey,
New Jersey Medical School

Diplomate of the American Board of Clinical Lipidology

Certified Menopause Practitioner: North American Menopause Society

North Jersey Institute of Menopausal Lipidology
Wayne, New Jersey

St Joseph's Regional Medical Center Paterson, NJ

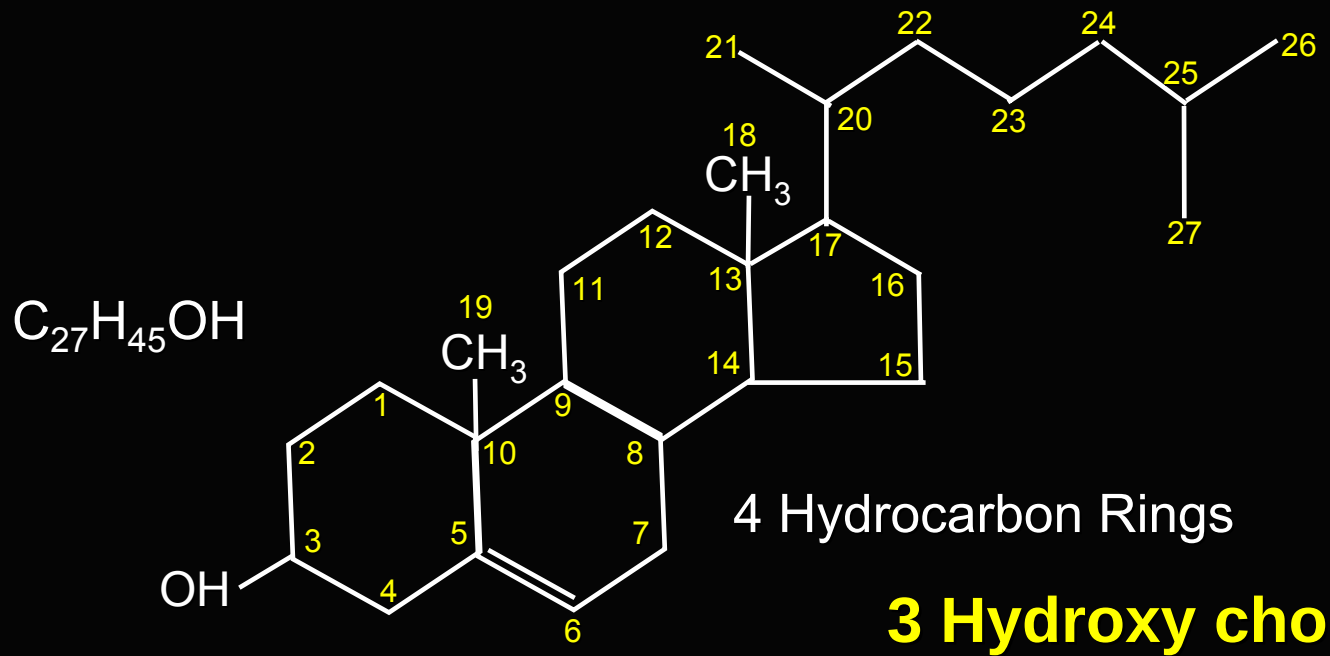
1964 Nobel Prize Physiology & Medicine

Cholesterol Synthesis Pathway

Konrad Bloch

Feodor Lynen

A sterol with 27 carbon molecules with an -OH group at the # 3 position

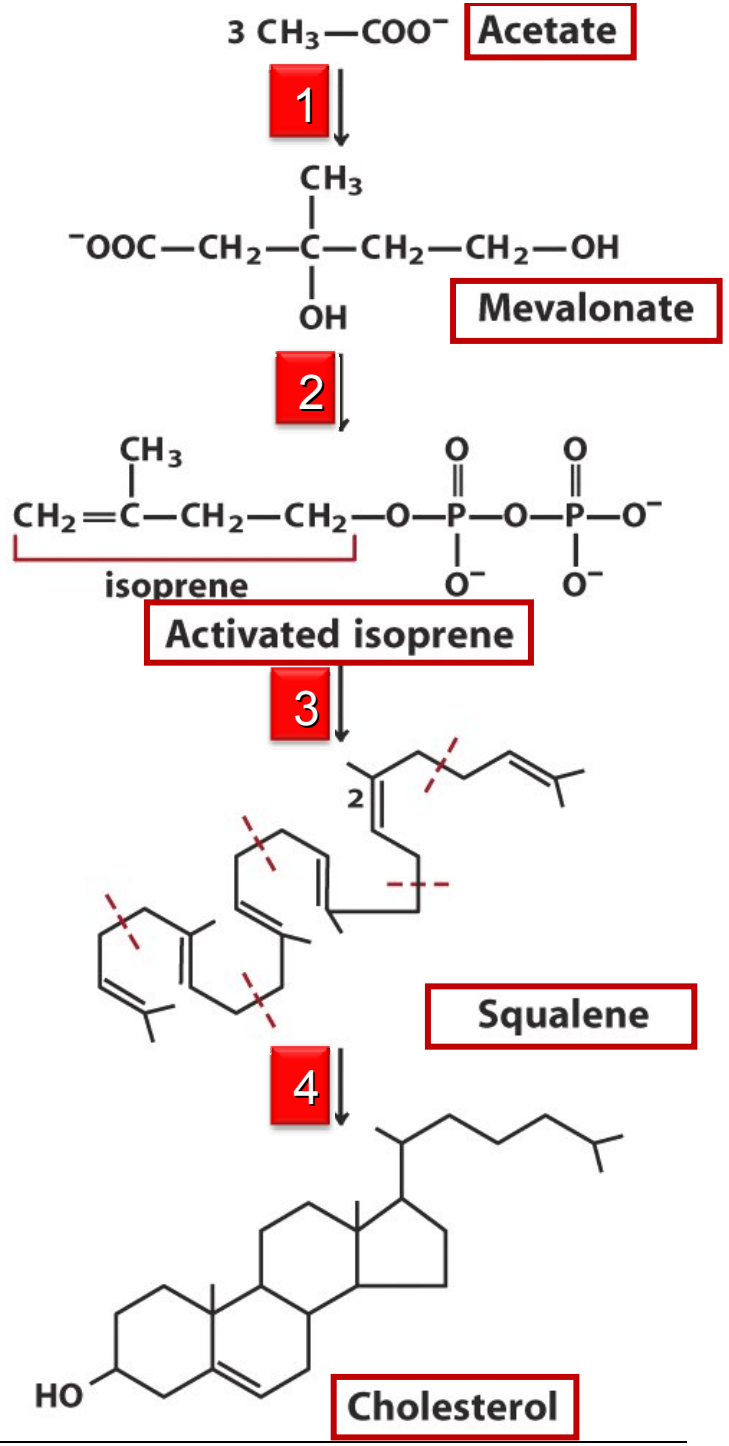


Sterols are waxy insoluble substances or lipids synthesized from acetyl coenzyme A (CoA). They are steroid-based alcohols having a hydrocarbon (aliphatic) side chain of 8–10 carbons at the 17 position and a hydroxyl group (-OH) at the 3 position (making it an alcohol). Because of the hydrophilicity at the -OH end and hydrophobicity at the hydrocarbon side chain, sterols can be incorporated into the lipid bilayers of the cytoplasmic membrane.

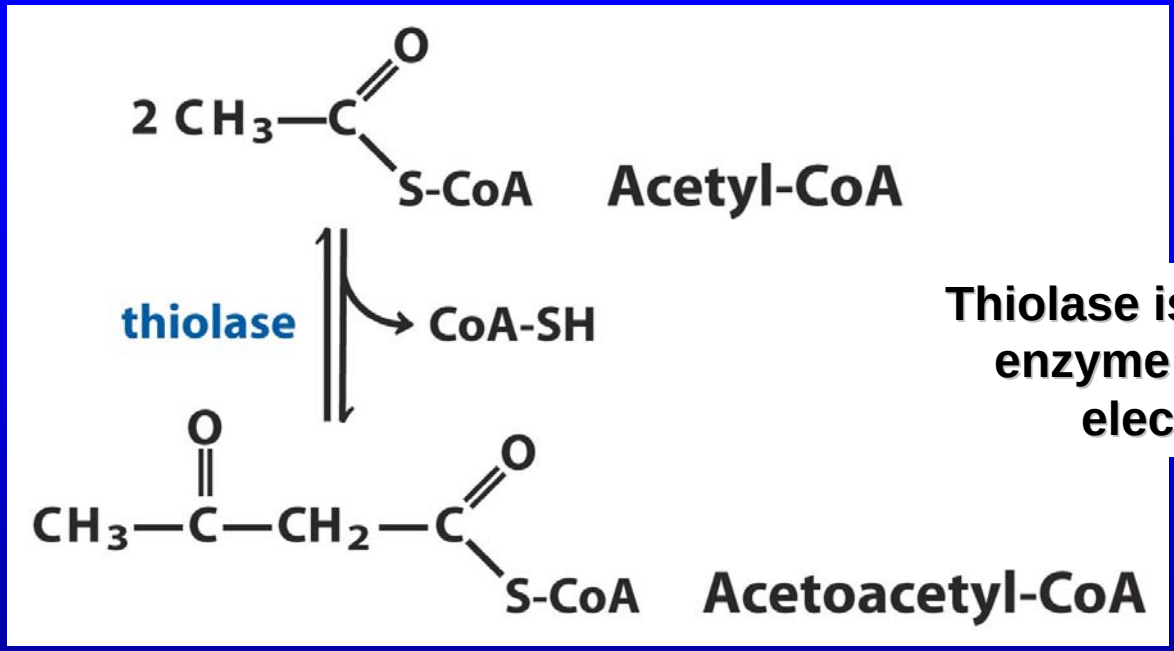
Four Stages of Cholesterol Biosynthesis

The liver is responsible for about 15% of cholesterol synthesis and the remainder is extrahepatic.

Cholesterol synthesis is a four-step process starting from its precursor acetate: CH3-COO−



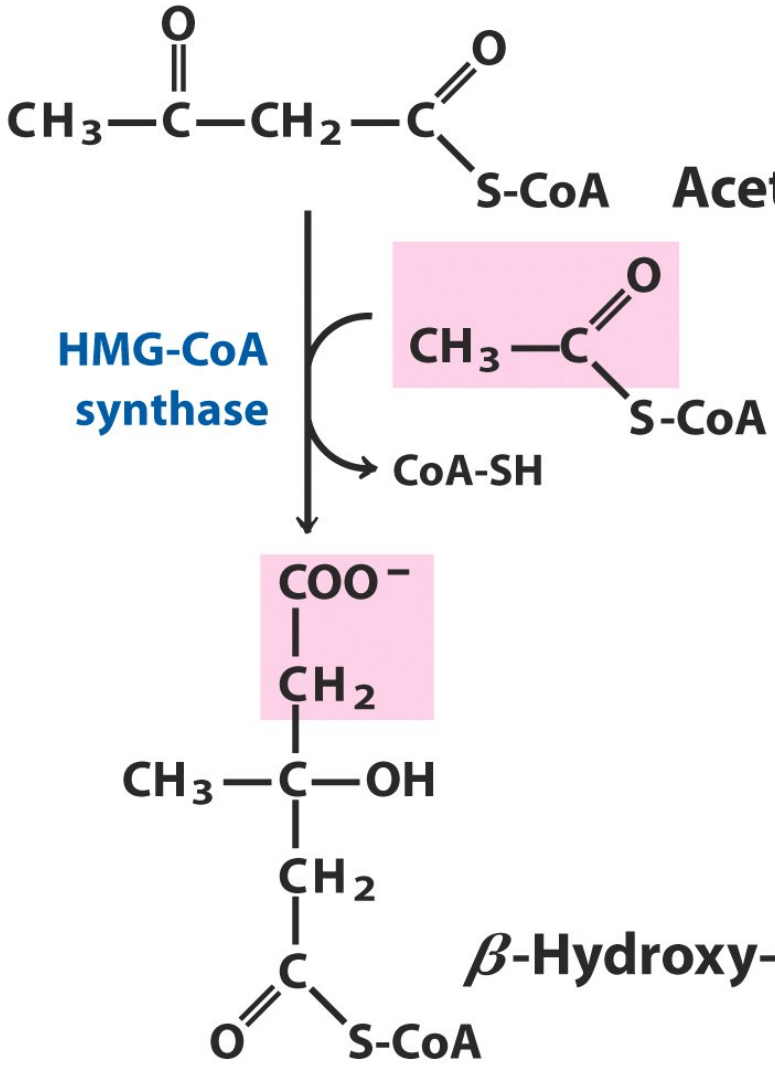
Cholesterol Synthesis: Stage 1



Thiolase is an oxidant enzyme (removes electrons)

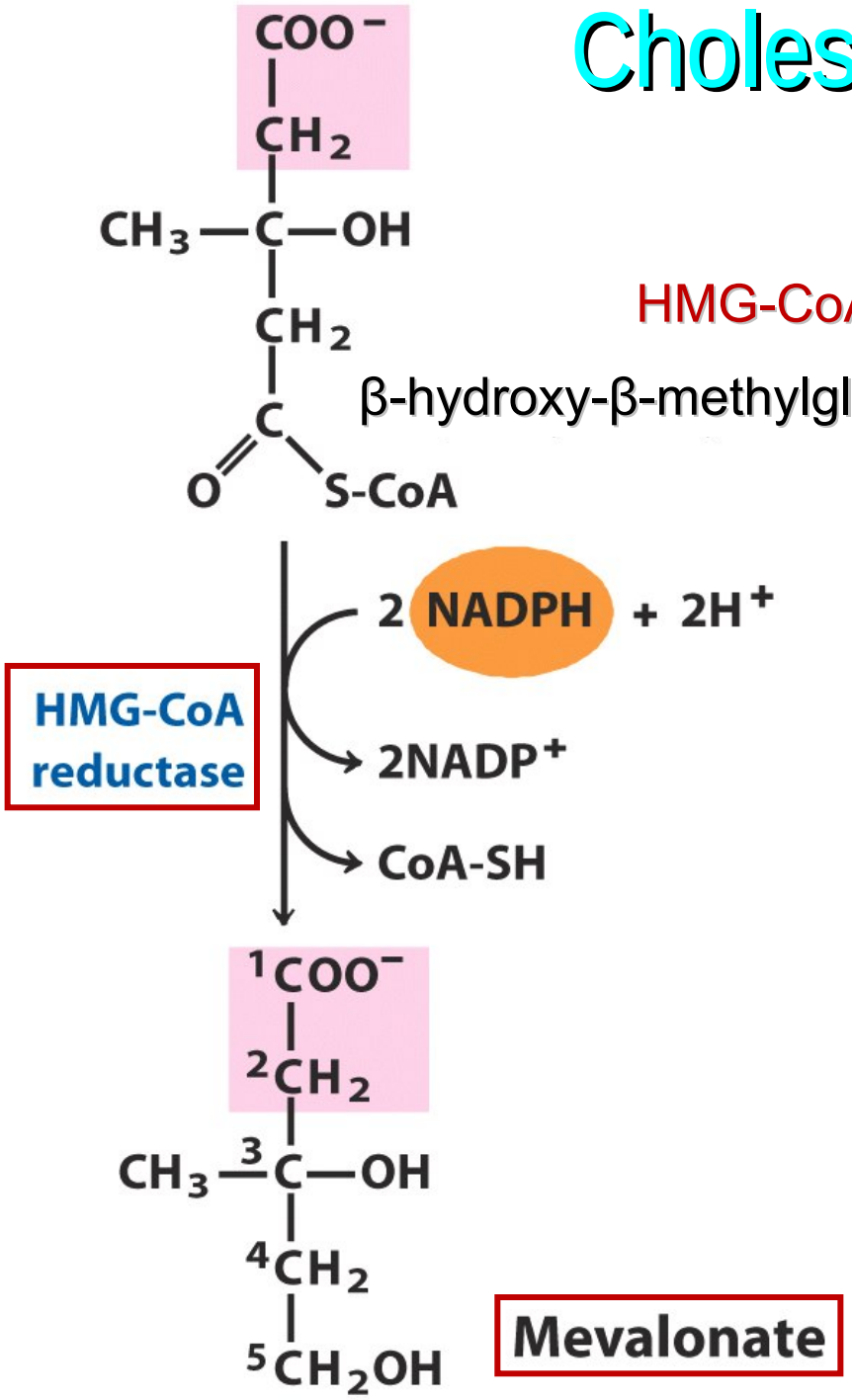
- In the first step, two molecules of acetyl-CoA upon the action of thiolase reversibly forms acetoacetyl-CoA

Cholesterol Synthesis: Stage 1



- Acetyl-CoA condenses with acetoacetyl-Co upon the action of cytosolic hydroxymethylglutaryl (HMG) synthase and becomes HMG-CoA.

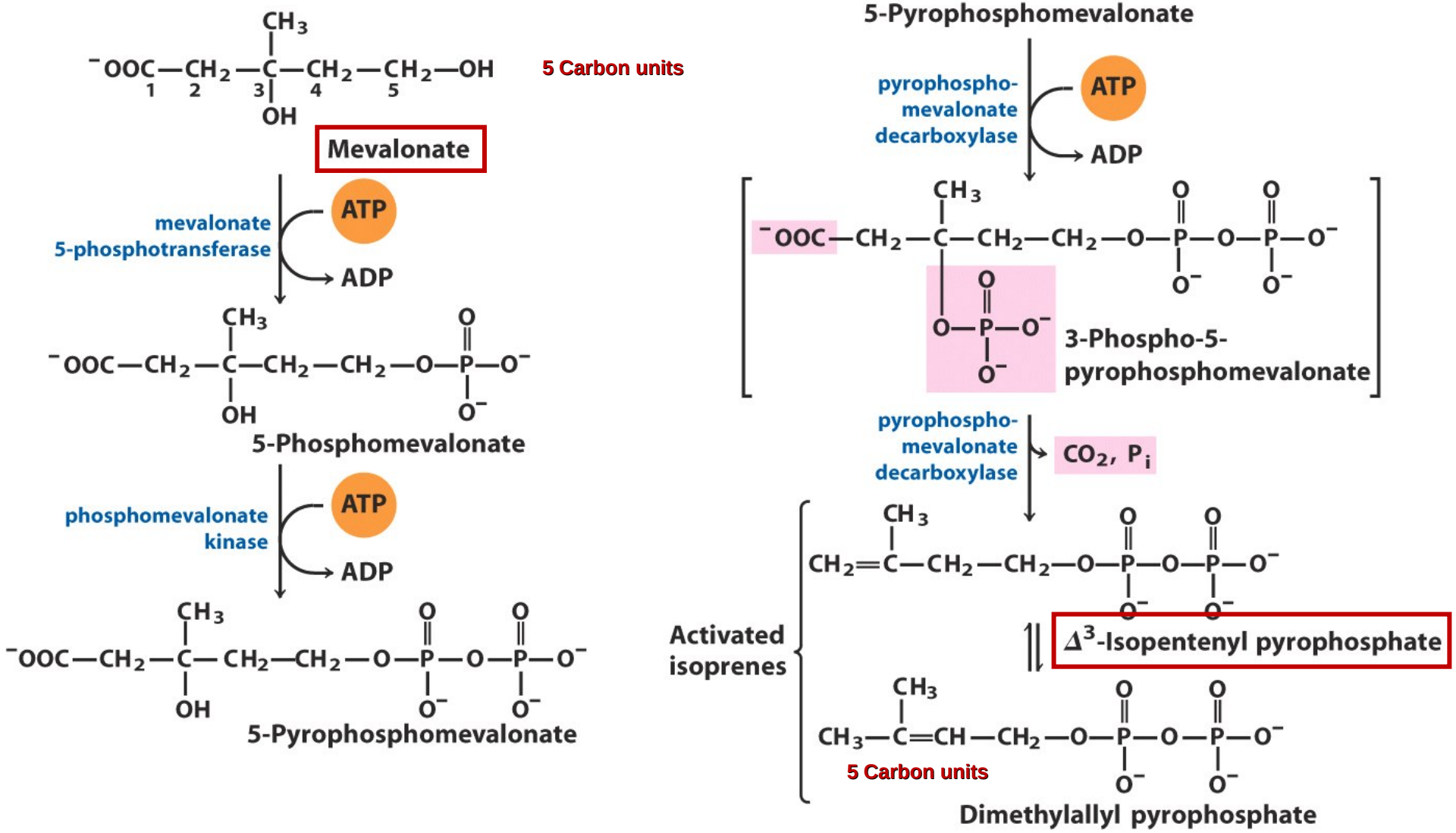
Cholesterol Synthesis: Stage 1



The catalytic action (rate-limiting state) of HMG-CoA reductase, an integral part of the smooth endoplasmic reticulum, irreversibly forms mevalonate (a five-carbon intermediate) with NADPH serving as the reductant. HMG-CoA reductase transcription is tightly regulated by a membrane-bound transcription factor designated as sterol regulatory element-binding protein-2 (SREBP-2)

Different from mitochondrial HMG-CoA which plays a role in ketosis

Cholesterol Synthesis: Stage 2



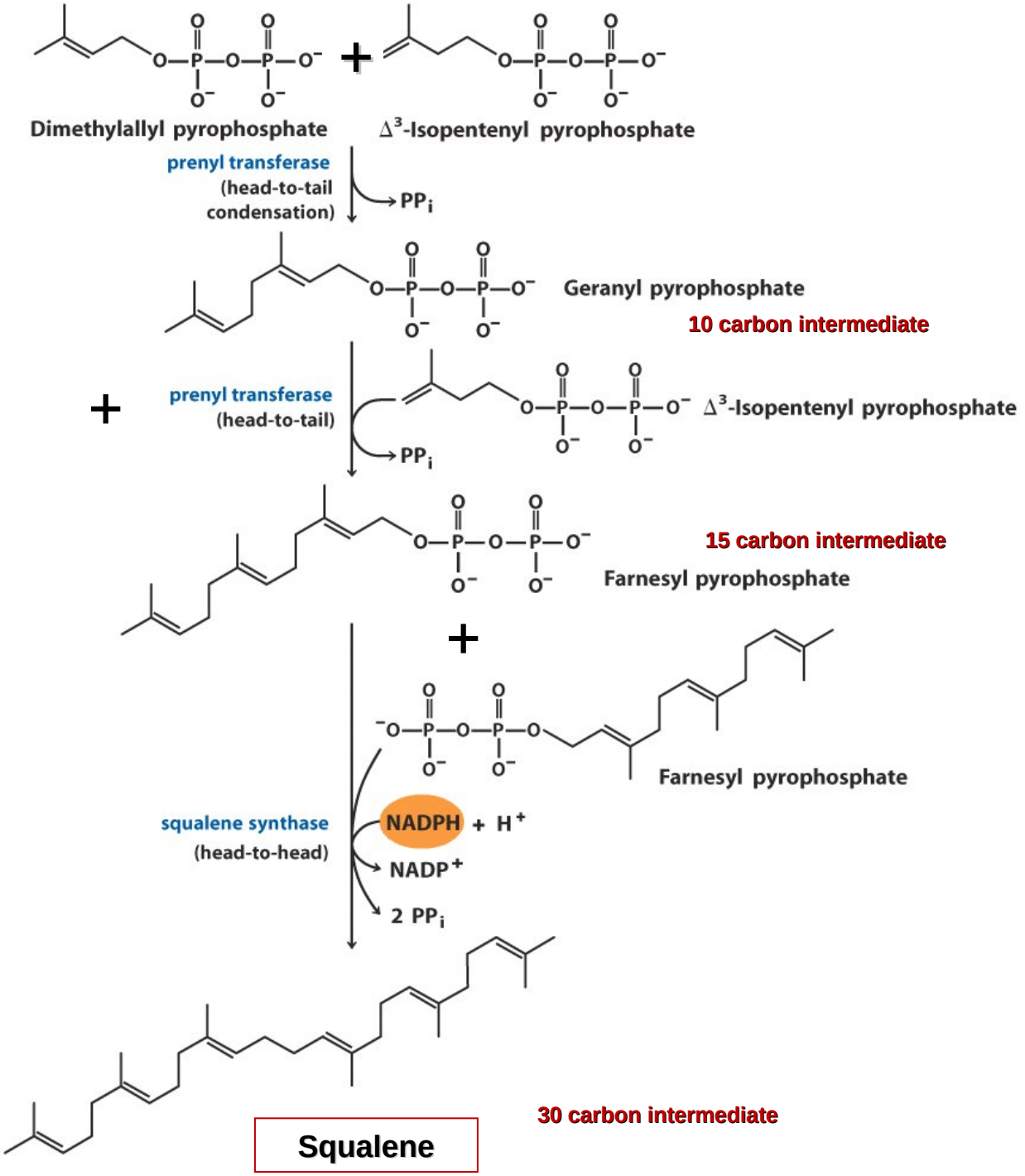
- In the second step, mevalonate is phosphorylated from ATP to isoprene units or isoprenoids, namely isopentyl pyrophosphate, which can isomerize or interconvert to dimethylallyl pyrophosphate

Cholesterol Synthesis: Stage 3

Isoprenoids react with each other to form geranyl pyrophosphate.

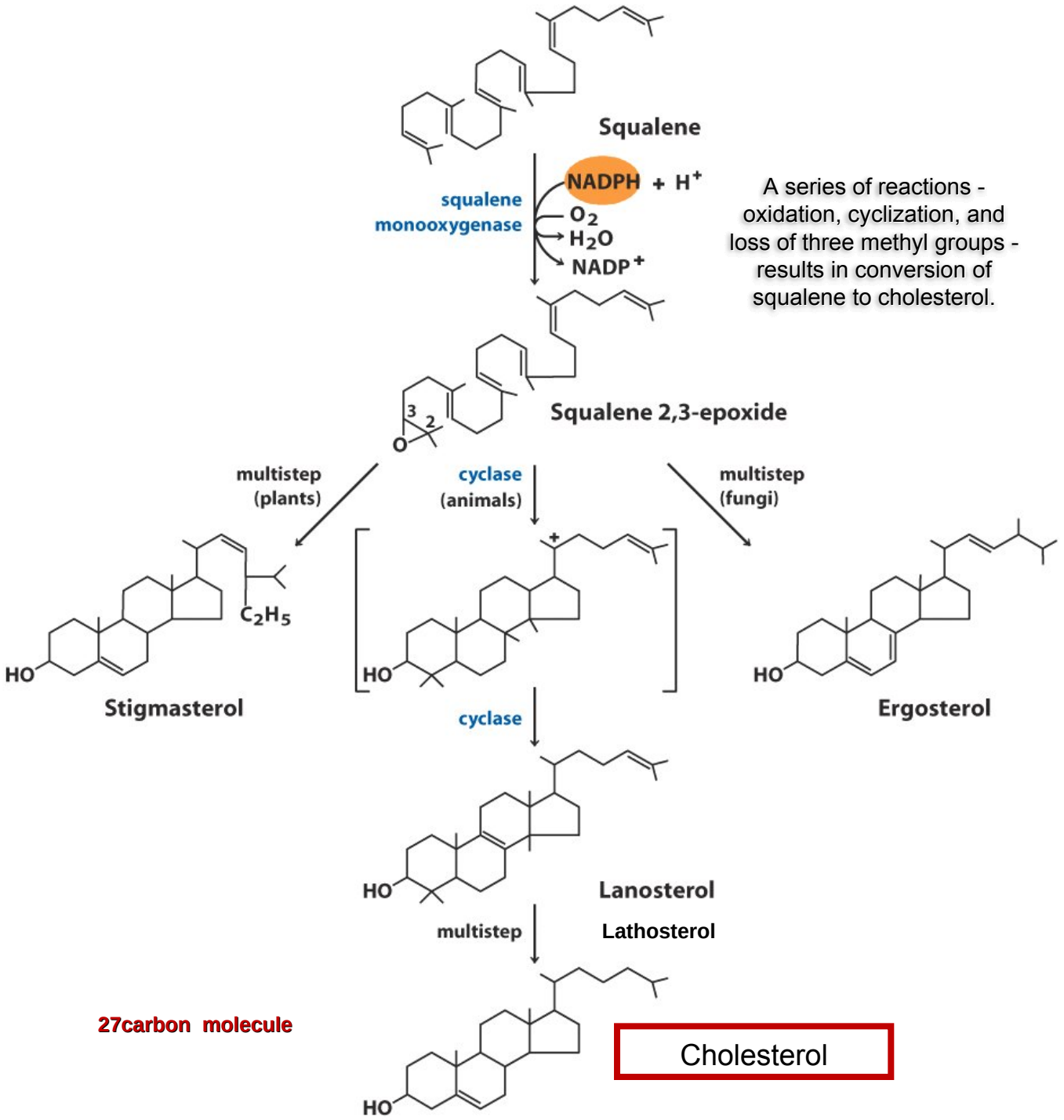
Condensation with another isopentyl-PP yields farnesyl pyrophosphate.

Squalene synthase catalyzes the condensation of two molecules of farnesyl-PP with reduction by NADPH to make squalene.



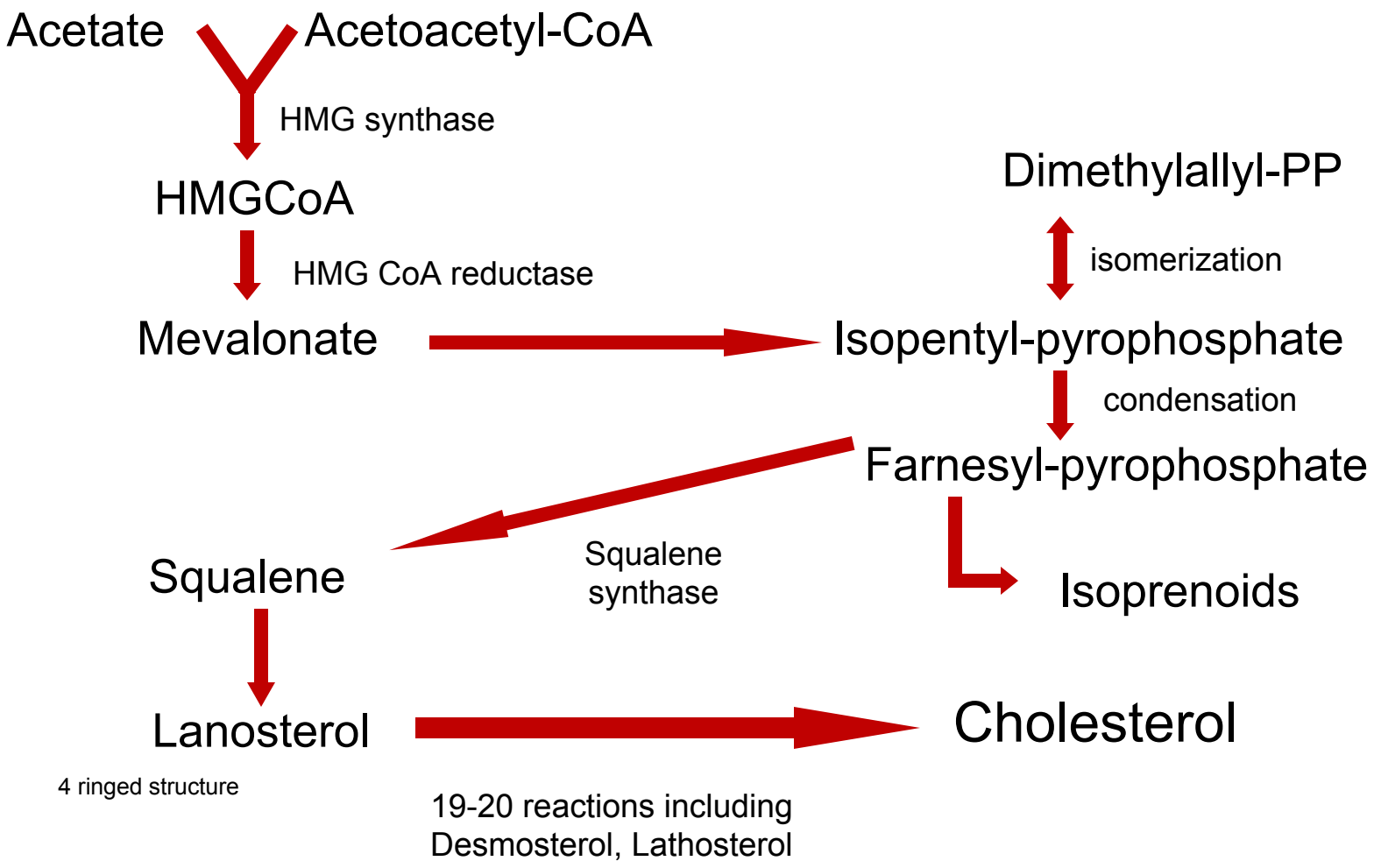
Cholesterol Synthesis: Stage 4

The fourth step involves conversion of the linear squalene molecule to the four-ringed steroid nucleus.



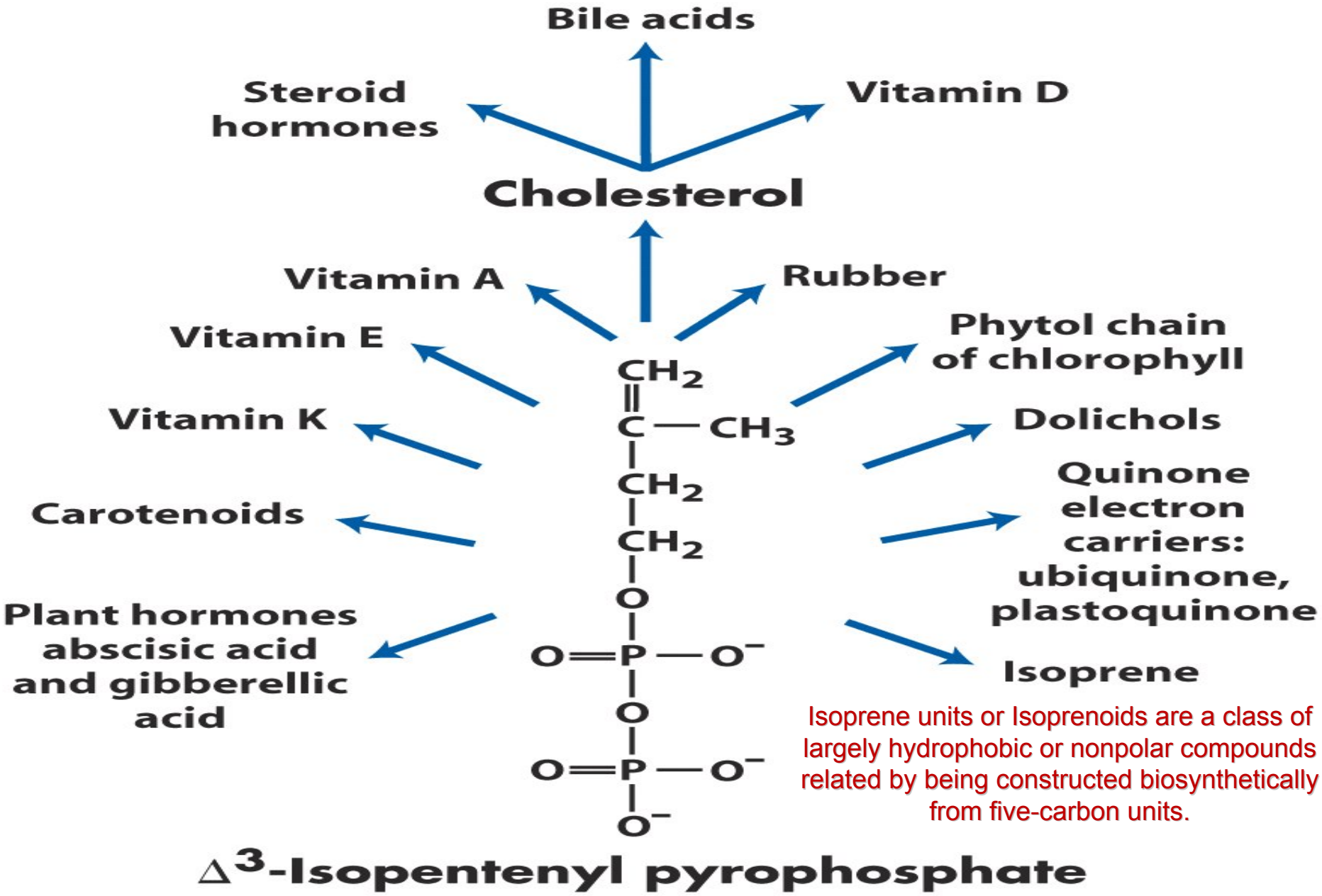
A series of reactions - oxidation, cyclization, and loss of three methyl groups - results in conversion of squalene to cholesterol.

Cholesterol Synthesis



Dayspring T in Chap 14 Davidson, Toth, Maki Therapeutic Lipidology 2008

Natural Products Derived from Activated Isoprene Units



Isoprene units or Isoprenoids are a class of largely hydrophobic or nonpolar compounds related by being constructed biosynthetically from five-carbon units.