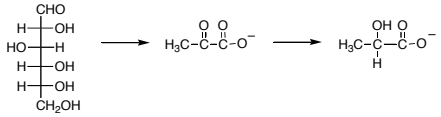
Chapter 26: Lipids. Hydrophobic (non-polar, soluble in organic solvent), typically of low molecular compound or organic origin

- fatty acids and waxes
- essential oils
- many vitamins
- hormones (non-peptide)
- components of cell membranes (non-peptide)

Share a common biosynthesis that ultimately derives their carbon source from glucose (glycolysis)

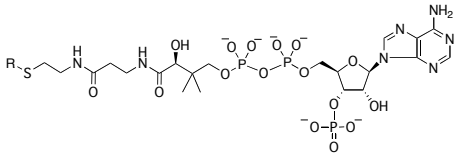
Glucose → pyruvate → lactate



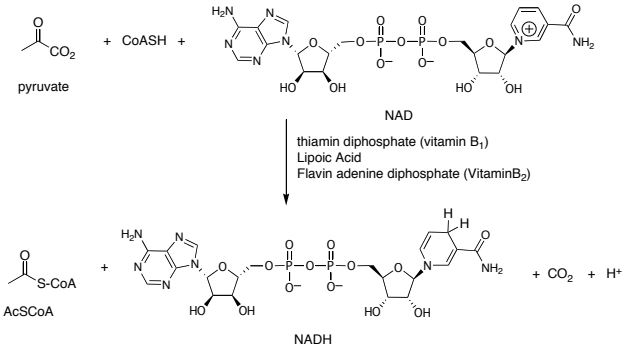
280

26.1: Acetyl Coenzyme A. AcSCoA is a *thioester*.

R= H, CoASH
R= acetyl, AcSCoA



Pyruvate dehydrogenase: Multi-enzyme complex that converts pyruvate to AcSCoA.



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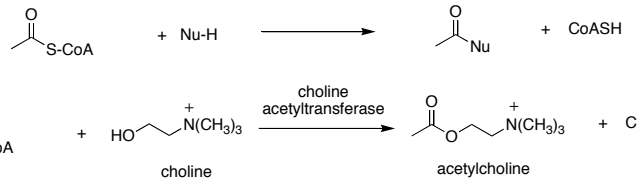
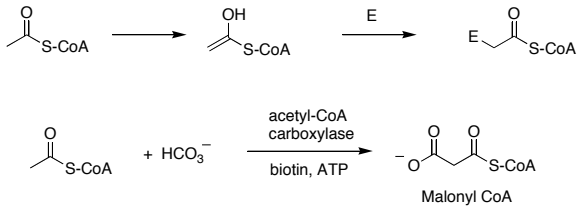
Acetyl CoA is a thioester. Thioesters are more reactive toward nucleophilic acyl substitution than esters, but considerably less reactive than acid chlorides and anhydrides.



Thioester enolize more readily than esters. The enol can react with electrophile to afford α-substitution products



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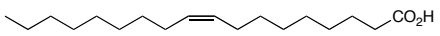
26.2: Fats, Oils, and Fatty Acids. *Fatty acids*: refers to long, straight-chain saturated and unsaturated acids, typically from C_{12} - C_{20} (Table 26.1, p. 1069).

saturated fatty acids:

$CH_3(CH_2)_nCO_2H$

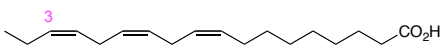
n=10, lauric acid (C_{12})
n=12, myristic acid (C_{14})
n=14, palmitic acid (C_{16})
n=16, steric acid (C_{18})

unsaturated fatty acid

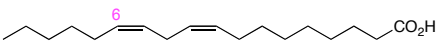


C_{18}, oleic acid

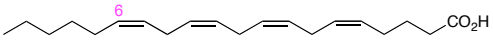
polyunsaturated fatty acids (PUFA)



C_{18}, linolenic acid (18:3)



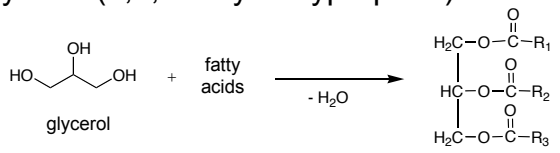
C_{18}, linoleic acid (18:4)



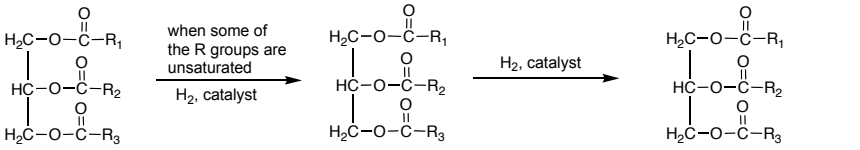
C_{20}, arachidonic acid (20:4)

283

Fats and Oils: *Triglycerides* (triaceylglycerols) are tri-esters of glycerol (1,2,3-trihydroxypropane) and fatty acids.



The R groups can be saturated or unsaturated, the same or different



Partially hydrogenated: some cis double bond are isomerized to trans double bonds

Hydrogenated- only saturated fatty acids

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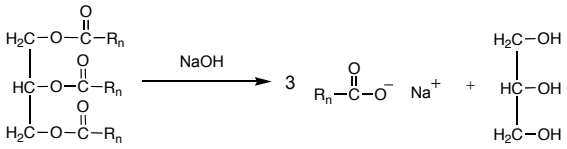
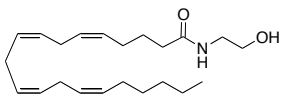
Soaps: sodium & potassium salts of fatty acid produced from the saponification (base hydrolysis) of animal fats (glycerides)

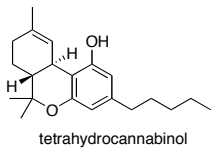


Soaps have a hydrophilic, polar "head group" (carboxylate salt) and a hydrophobic, non-polar "tail."

Fatty acid amides (FAA):



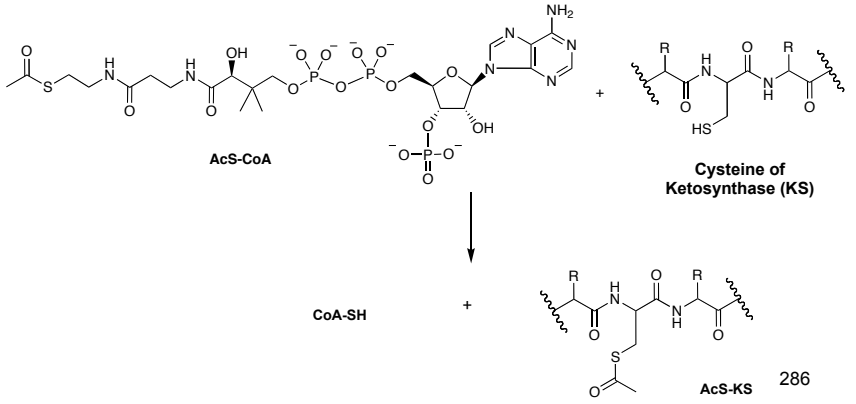
Anandamide
an ethanolamine amide of arachidonic Acid (C_{20})



tetrahydrocannabinol

285

26.3: Fatty Acid Biosynthesis. Fatty acid biosynthesis is performed by a cluster of discrete enzymes in bacteria, and a very large multi-protein assembly in animals (*fatty acid synthase*, FAS). The fatty acid is attached to an *acyl carrier protein* (ACP), while other proteins perform an iterative two-carbon chain extension reaction that will yield the fatty acid.



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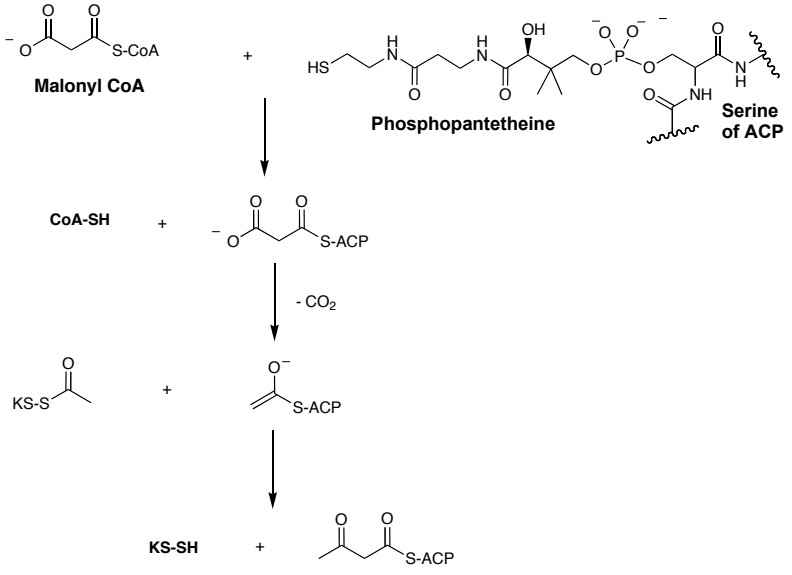
FAS chain extension reaction: Ketosynthase (KR)



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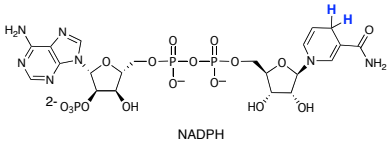
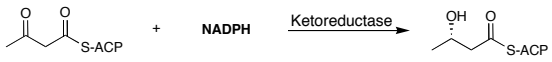
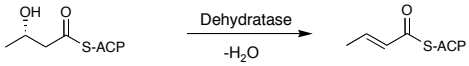
Ketoreductase: NADPH (nicotinamide adenine diphosphate phosphate) is a nucleophilic hydride (H^-) donor (reducing agent)

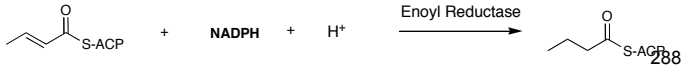




Dehydratase (DH):



Enoyl Reductase (ER)



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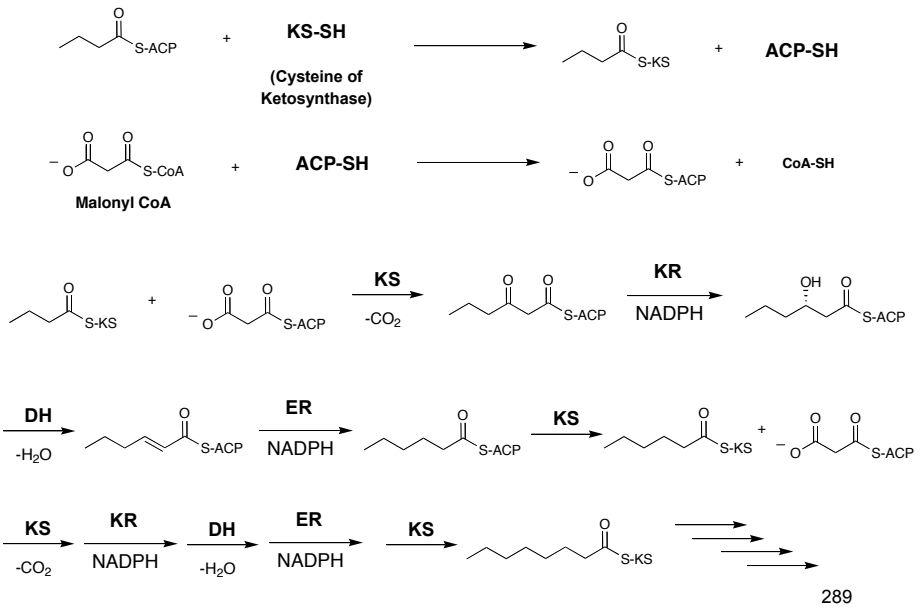
Iterative two-carbon chain extension



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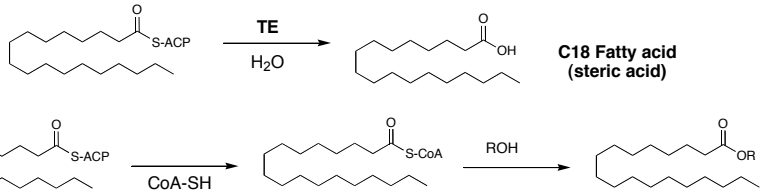
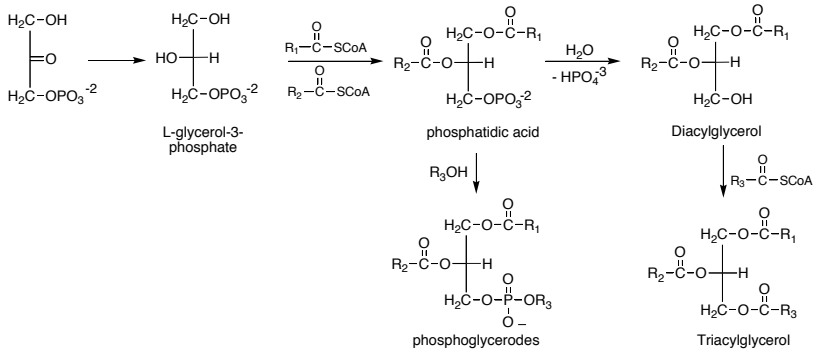
Thioesterase



26.4 Phospholipids.



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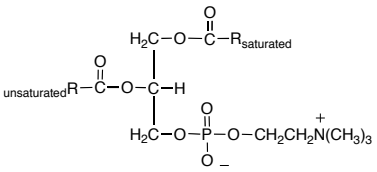
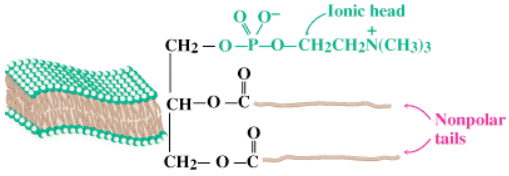
Glycerophospholipids are important components of cell membranes. Nonpolar tails aggregate in the center of a bilayer ionic head is exposed to solvent Cell membranes are ~5 nm thick



Phosphatidylcholine (lechtins)



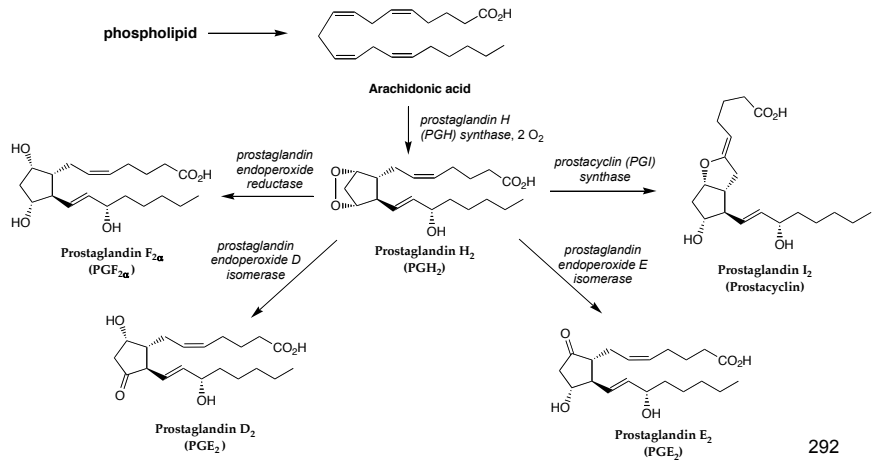
26.6: Waxes. esters of long chain fatty acids (C_{16} - C_{36}) with long chain alcohols (C_{24} - C_{36})

$$CH_3(CH_2)_nCO_2–(CH_2)_nCH_3$$

291

26.6: Prostaglandins. (eicosanoids) C_{20} compounds derived from arachidonic acid and related fatty acids

hormone: (Greek, *horman*, to set in motion) chemical messengers from one cell to another, that acts as a signal for a biochemical event.



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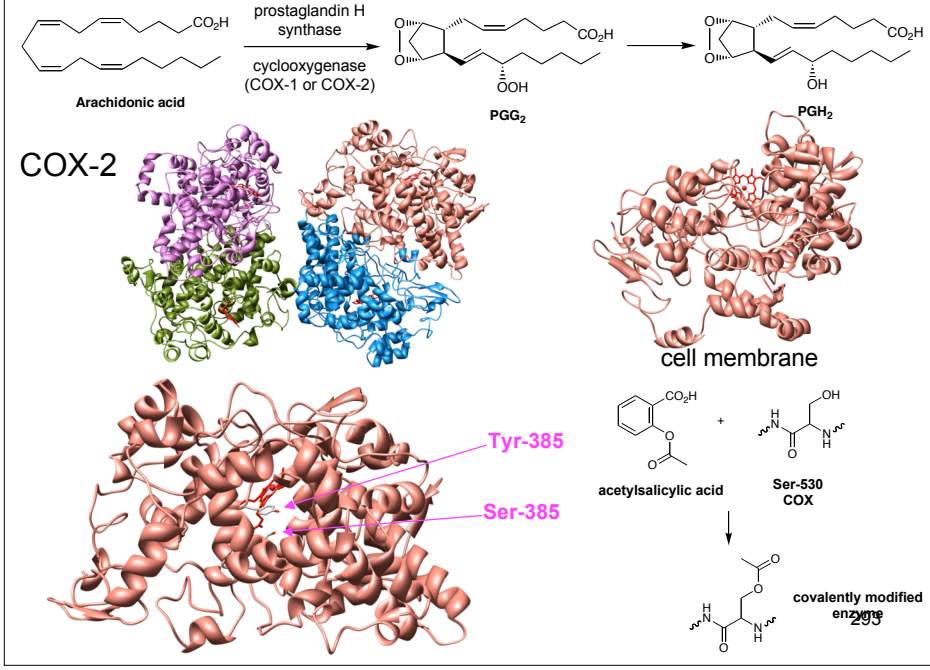
Prostaglandin biosynthesis



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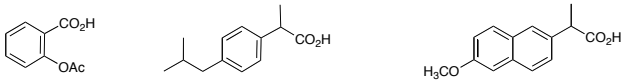
COX-1 is a constitutive enzyme that is expressed in virtually all mammalian cells

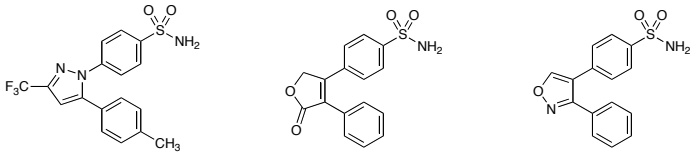
COX-2 is an inducible enzyme that is expressed as a results of a biochemical response; expressed in phagocytes (macrophages) as part of an inflammation response.

NSAIDs: non-steroidal anti-inflammatory drugs

Aspirin, ibuprofren, and naproxen are non-selective inhibitors of COX



Celebrex, vioxx, and brextra are selective inhibitors of COX-2 (coxibs)



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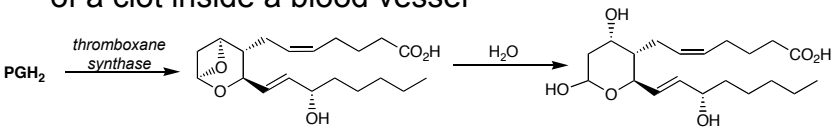
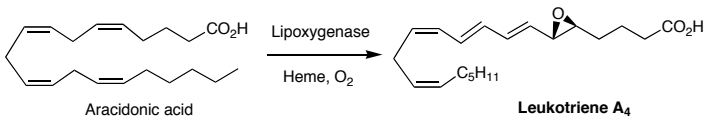
Thromboxanes: named for their role in thrombosis, the formation of a clot inside a blood vessel

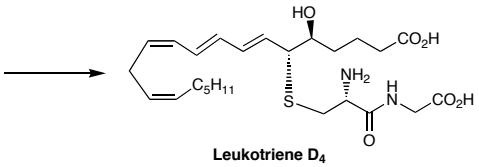


Thromboxane A_2 Thromboxane B_2

Leukotrienes



Aracidonic acid Leukotriene A_4



Leukotriene D_4

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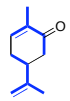
26.7: Terpenes: The Isoprene Rule. Isoprenoids- C_{10} (*terpenes*), C_{15} (*sesquiterpenes*) and C_{20} (*diterpenes*) plant; essential oils

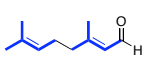
Ruzicka isoprene rule: terpenoids are derived from "isoprene units" (C_5)

isoprene
(2-methyl-1,3-butadiene)



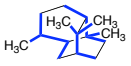
(+)-Carvone (caraway seeds)
(-)-Carvone (spearmint)

(+)-limonene (oranges)
(-)-limonene (lemons)



Citral
(lempon grass)

Camphour



patchouli alcohol
(patchouli oil)

β-pinene

α-pinene

Grandisol

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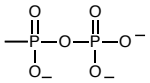
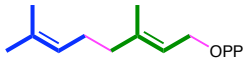
The precursor to C_{10} terpenoids (*monoterpenes*) is geraniol diphosphate (diphosphate), which consists of two C_5 "isoprene units" that are joined "head-to-tail"

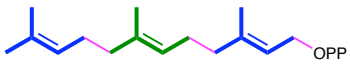
head  tail

PP = 

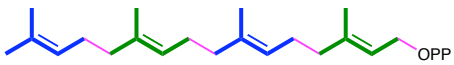


head - tail head - tail

C_{15} *sesquiterpenoids* are derived from farnesyl diphosphate, which consists of three C_5 "isoprene units" that are joined "head-to-tail"



C_{20} *diterpenoids* are derived from geranylgeranyl diphosphate, which consists of four C_5 "isoprene units" that are joined "head-to-tail"



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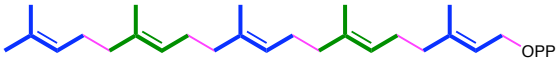
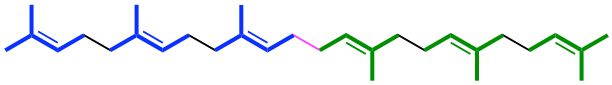
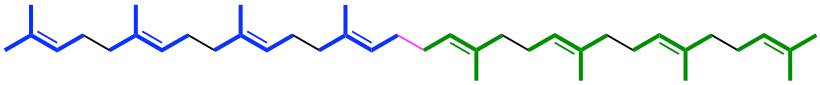
C_{25} *sesterpenoids* are derived from geranylfarnesyl diphosphate, which consists of five C_5 "isoprene units" that are joined "head-to-tail"



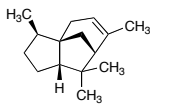
C_{30} *triterpenoids* and *steroids* are derived from squalene, which consists of two C_{15} farnesyl units" that are joined "tail-to-tail"

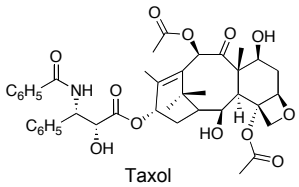


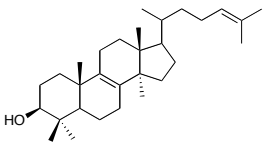
C_{40} *tetraterpenoids* are derived from phytocene, which consists of two C_{20} geranylgeranyl units" that are joined "tail-to-tail"

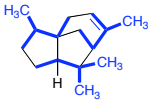


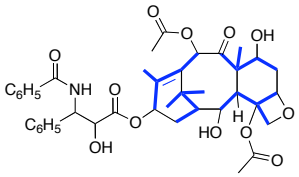
298

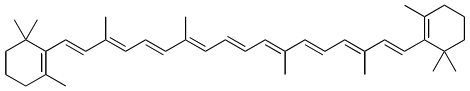

cedrane

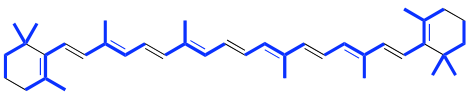

Taxol


Lanosterol






β-carotene



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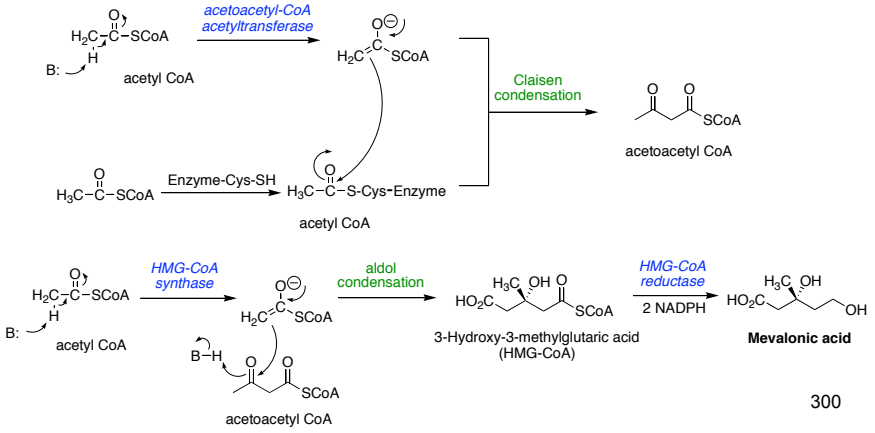
26.8: Isopentyl Diphosphate: The Biological Isoprene Unit.
Mevalonic acid is the biosynthetic precursor to the actual C_5 "isoprene units," which are isopentyl diphosphate (IPP, tail) and dimethylallyl diphosphate (DMAPP, head)

26.10: The Pathway from Acetate to Isopentenyl Diphosphate.
Mevalonate Pathway



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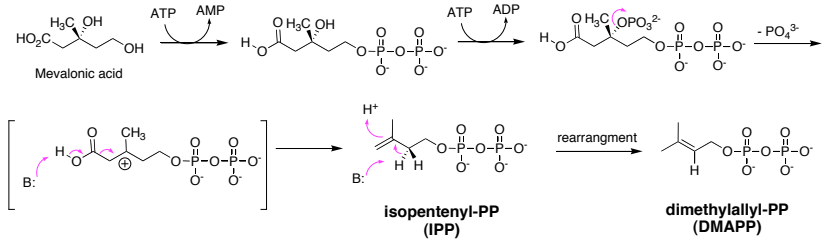
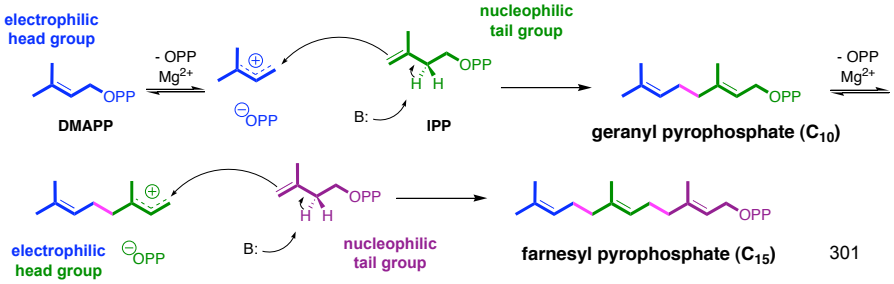
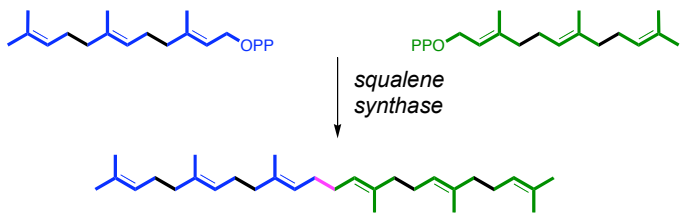
Conversion of mevalonic acid to IPP and DMAPP



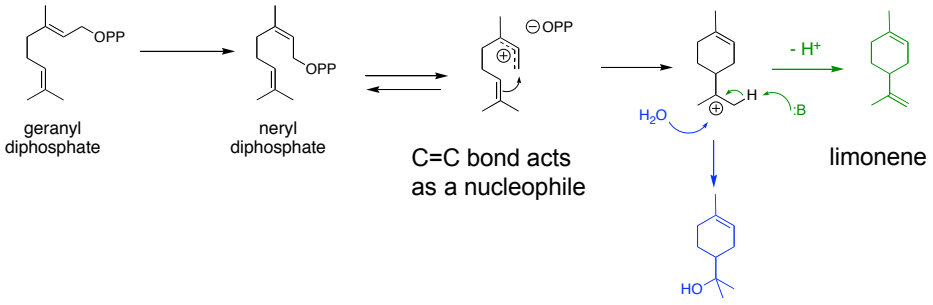
26.9: Carbon-Carbon Bond Formation in Terpene Biosynthesis.
Conversion of IPP and DMAPP to geraniol-PP and farnesyl-PP



301



Conversion of genanyl-PP to monoterpenes
Limonene & α-Terpineol



geranyl diphosphate

neryl diphosphate

C=C bond acts as a nucleophile

limonene

α-terpineol

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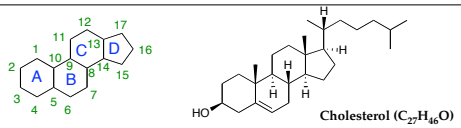
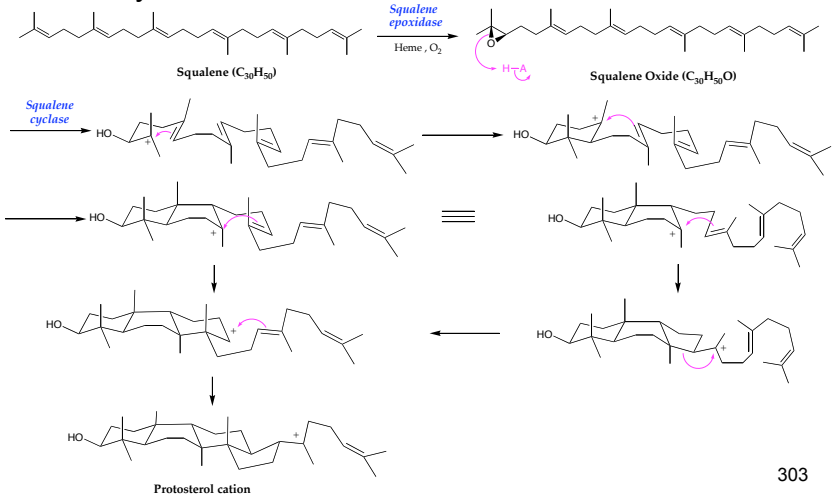
26.11: Steroids.



Cholesterol biosynthesis (mechanism 26.3, p. 1089)
part a: the cyclization



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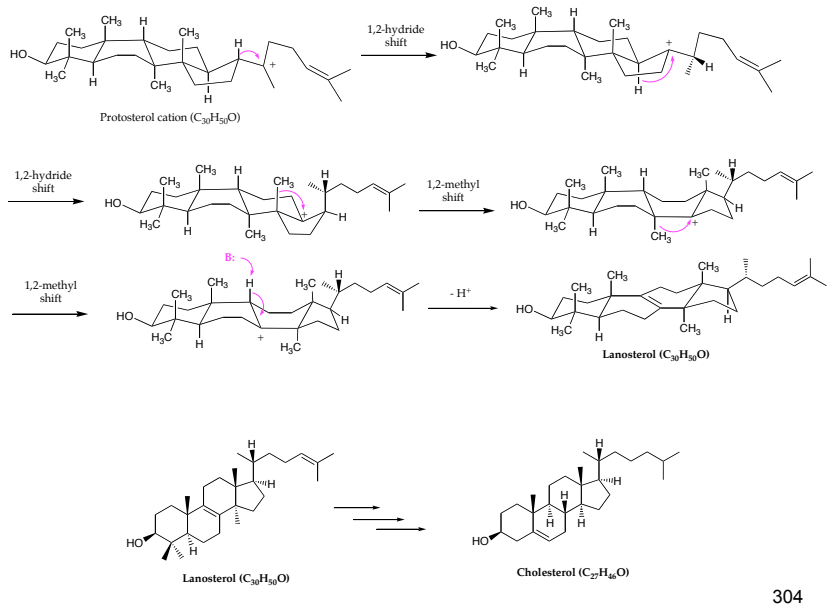
Cholesterol biosynthesis, part b: the 1,2-shifts



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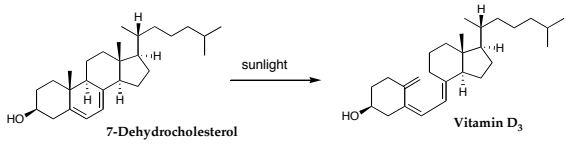
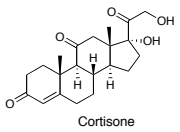
26.12: Vitamin D. (please read)



26.13: Bile Acids. (please read)

26.14: Corticosteroids. (please read)



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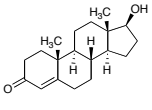
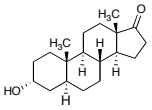
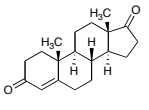
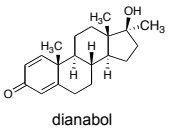
26.15: Sex hormones. (please read)

androgens (male)

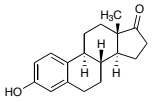

Testosterone

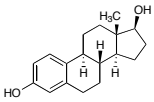

Androsterone

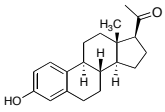

Androstenedione

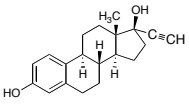

dianabol

estrogens (female)

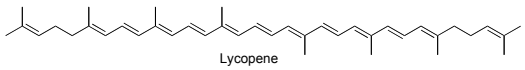

Estrone

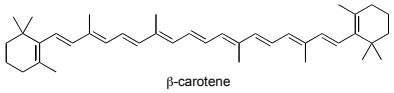

Estradiol


Progesterone


Ethynylestradiol

26.16: Carotenoids. (please read) derived from phytocene (C_{40})


Lycopene


β-carotene

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