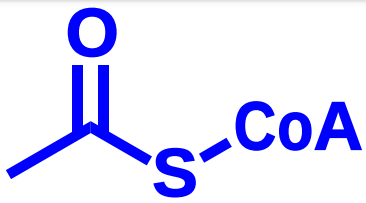
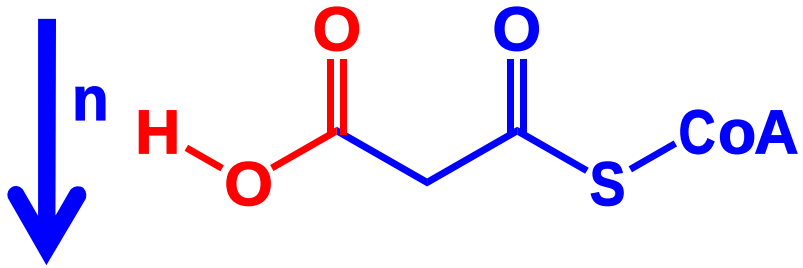
Biosynthesis of Fatty Acids

Source
- β-oxidation of FA
- Glycolysis of glucose

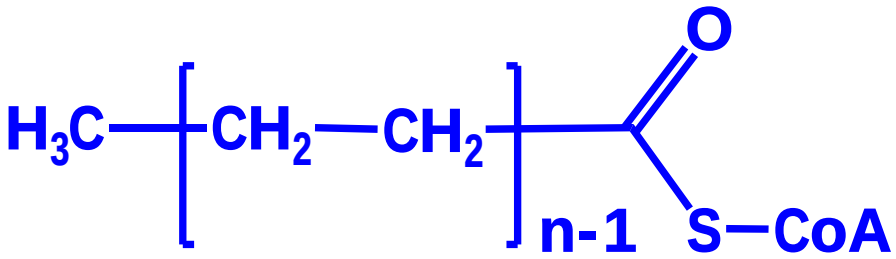


Acetyl CoA



Malonyl CoA

Carboxylation of acetyl CoA



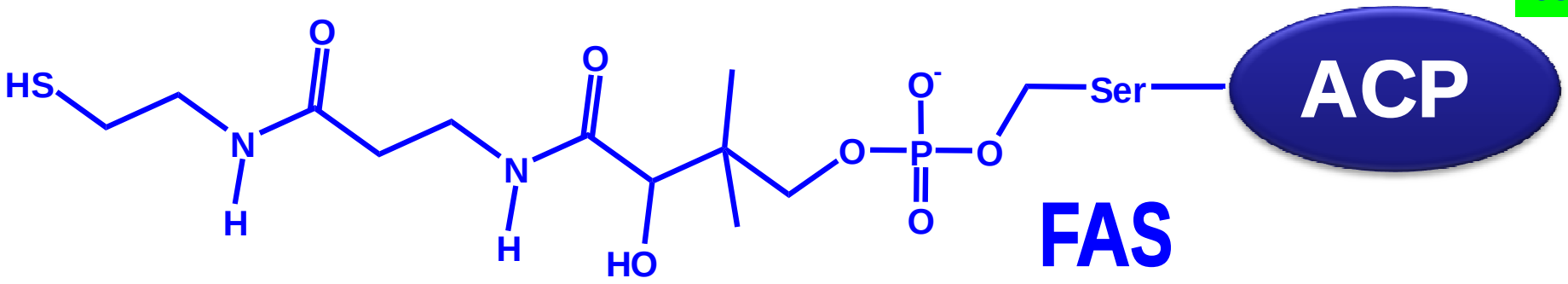
Saturated thioesters

↓

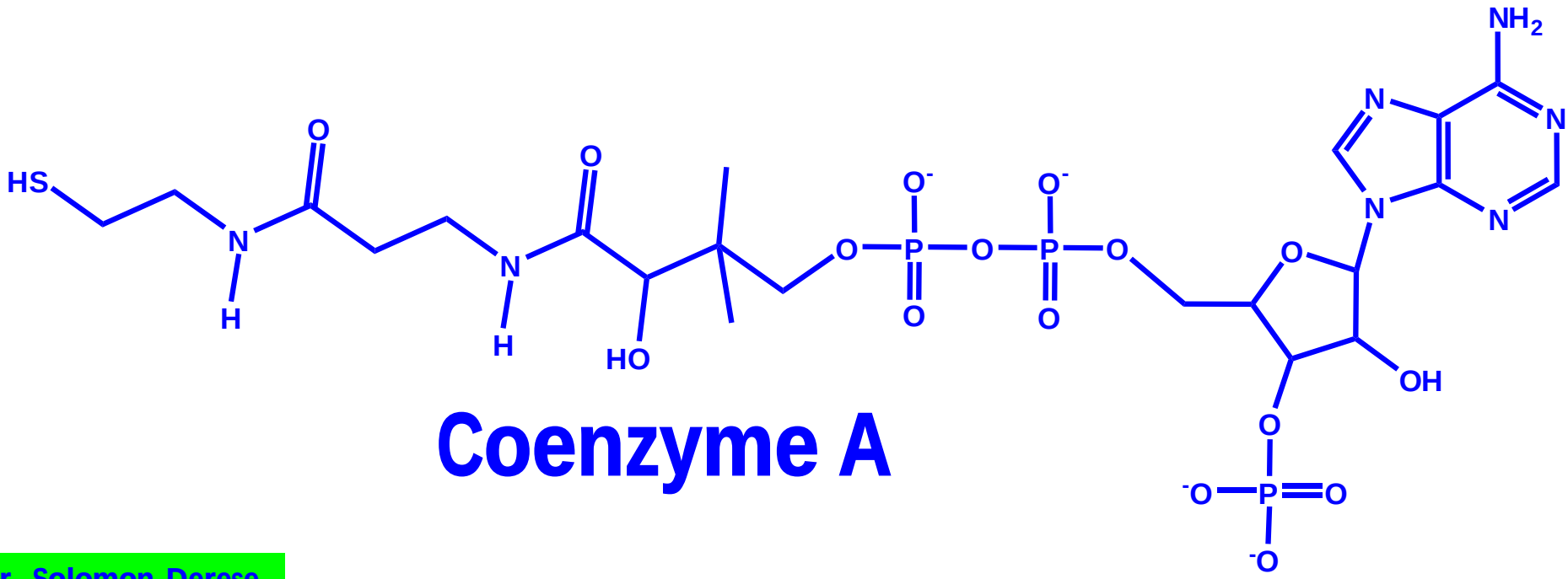
Saturated fatty acids

The processes of fatty acid biosynthesis are known to be catalyzed by a multienzyme complex known as **Fatty Acid Synthase (FAS).**

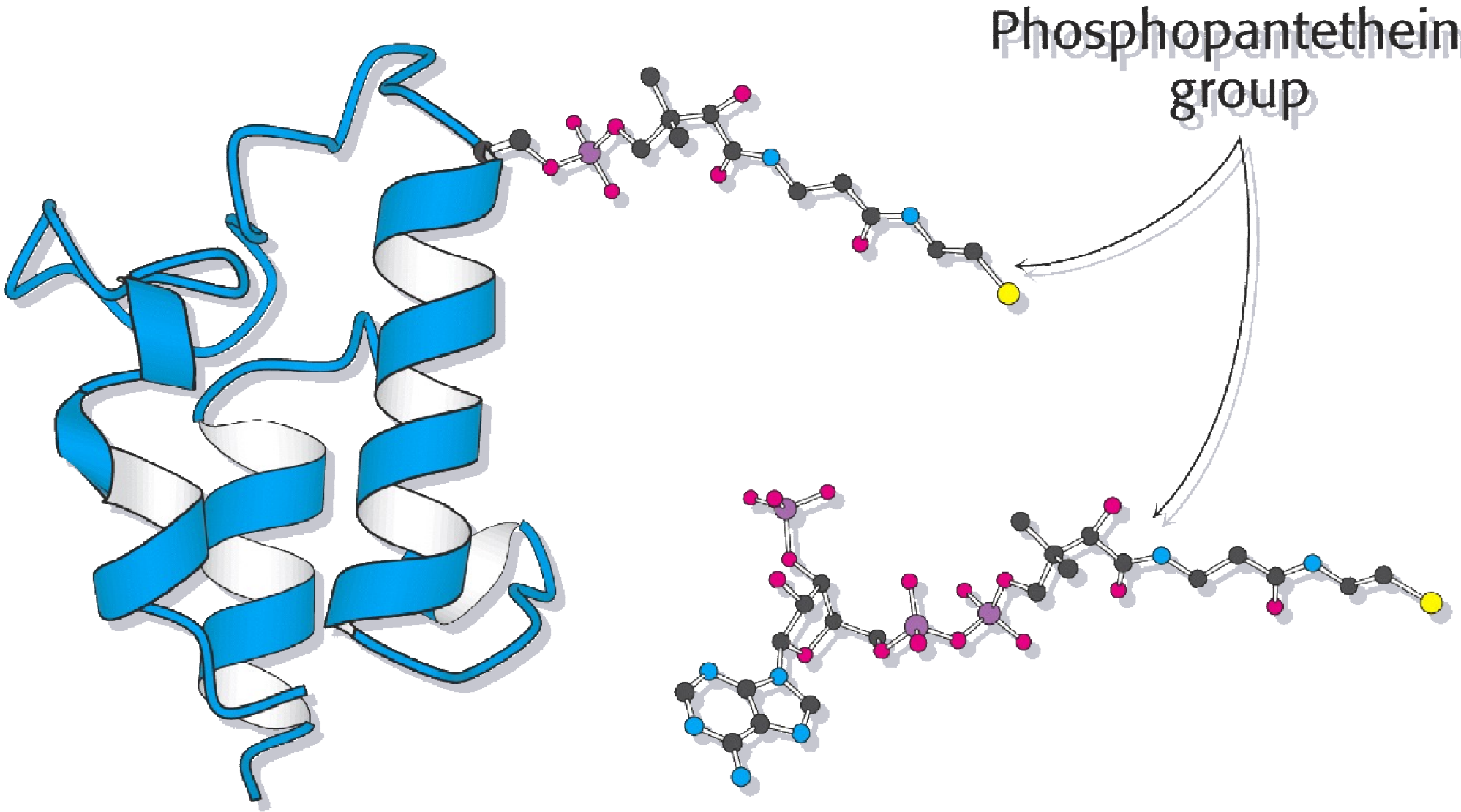
Fatty acid synthase is arranged around a central **Acyl Carrier Protein** (ACP), which contains a protein bound **pantetheine chain** [Condensing Enzyme ($HSE_{condensing}$)] similar to the long chain of Coenzyme A, with **six** distinct catalytic centers.



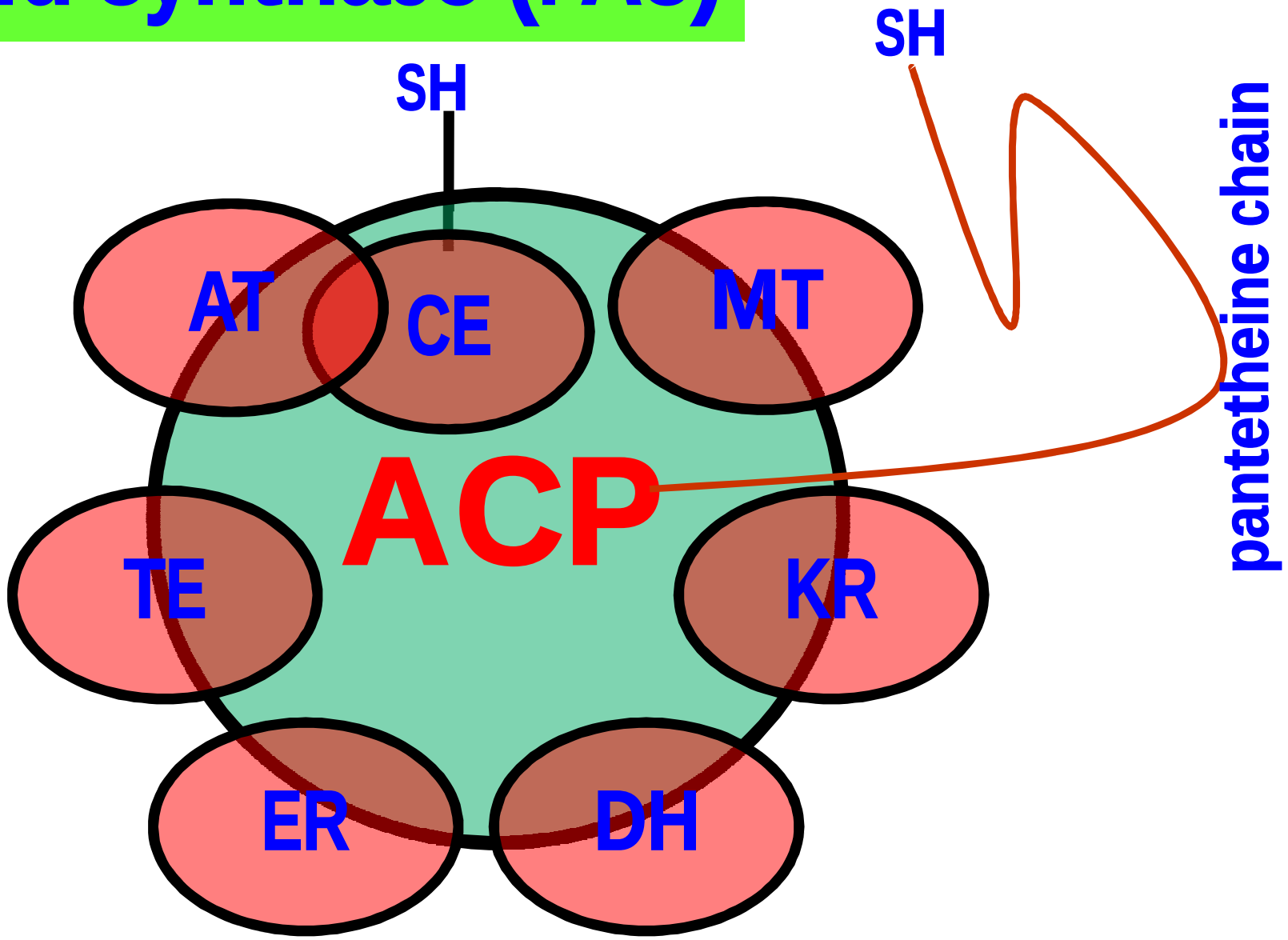
FAS



Coenzyme A


Phosphopantetheine group
Acyl carrier protein
Coenzyme A

Fatty Acid Synthase (FAS)



AT= Acetyl transferase
MT= Malonyl transferase
CE= Condensing enzyme

ACP= Acyl Carrier Protein
KR= Keto Reductase
ER= Enoyl Reductase

DH= DeHydratase
TE= ThioEsterase

Before acetyl CoA and malonyl CoA can be used in biosynthetic reactions, they have to be attached to the fatty acid synthase .

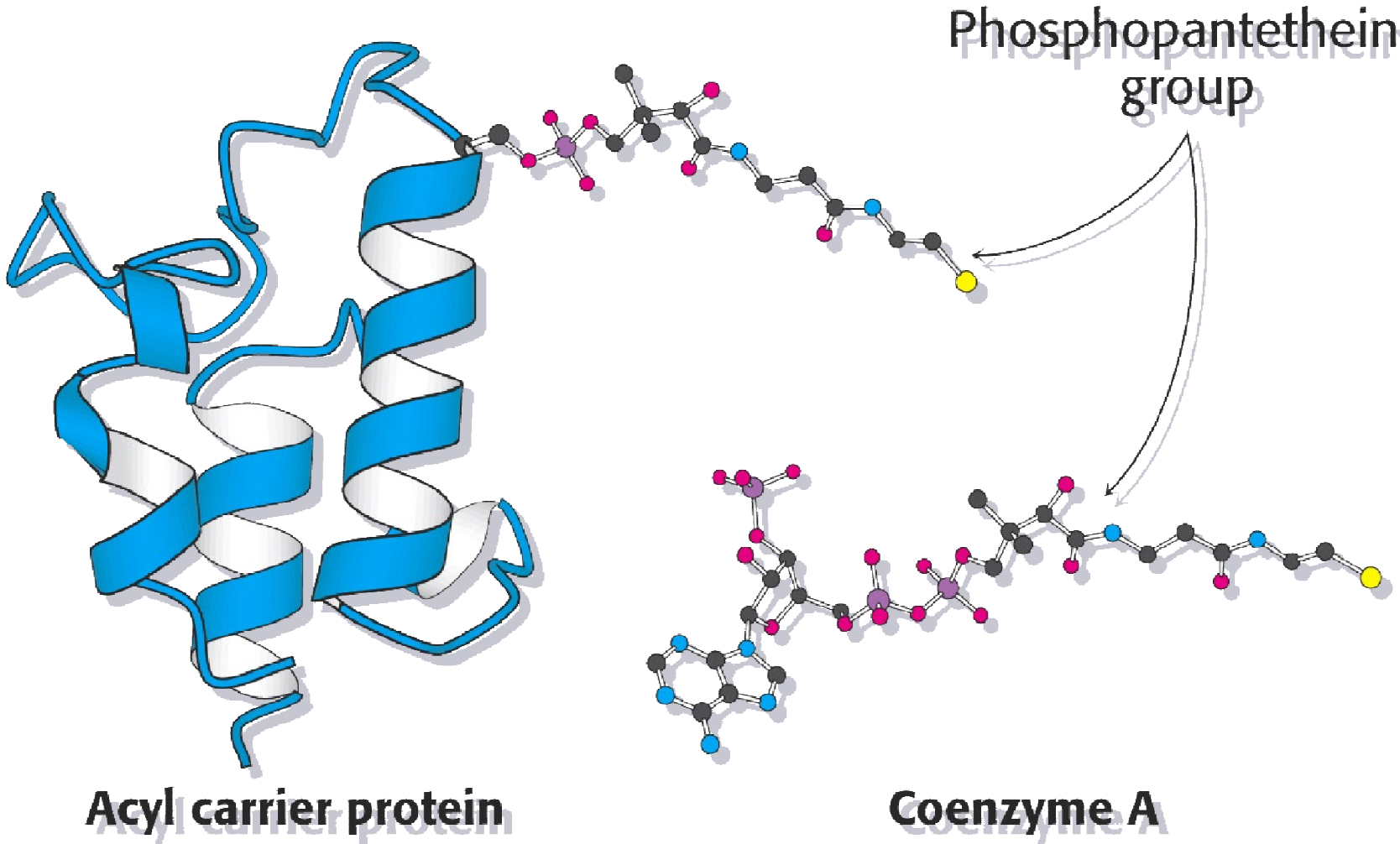
In this reaction the – SCoA group of acetyl CoA and malonyl CoA are substituted by the thiol groups (SH) of $HSE_{condensing}$ and ACP, respectively, of FAS.

The thiol groups are behaving as nucleophiles and the SCoA group as a leaving group in a nucleophilic acyl substitution reaction.

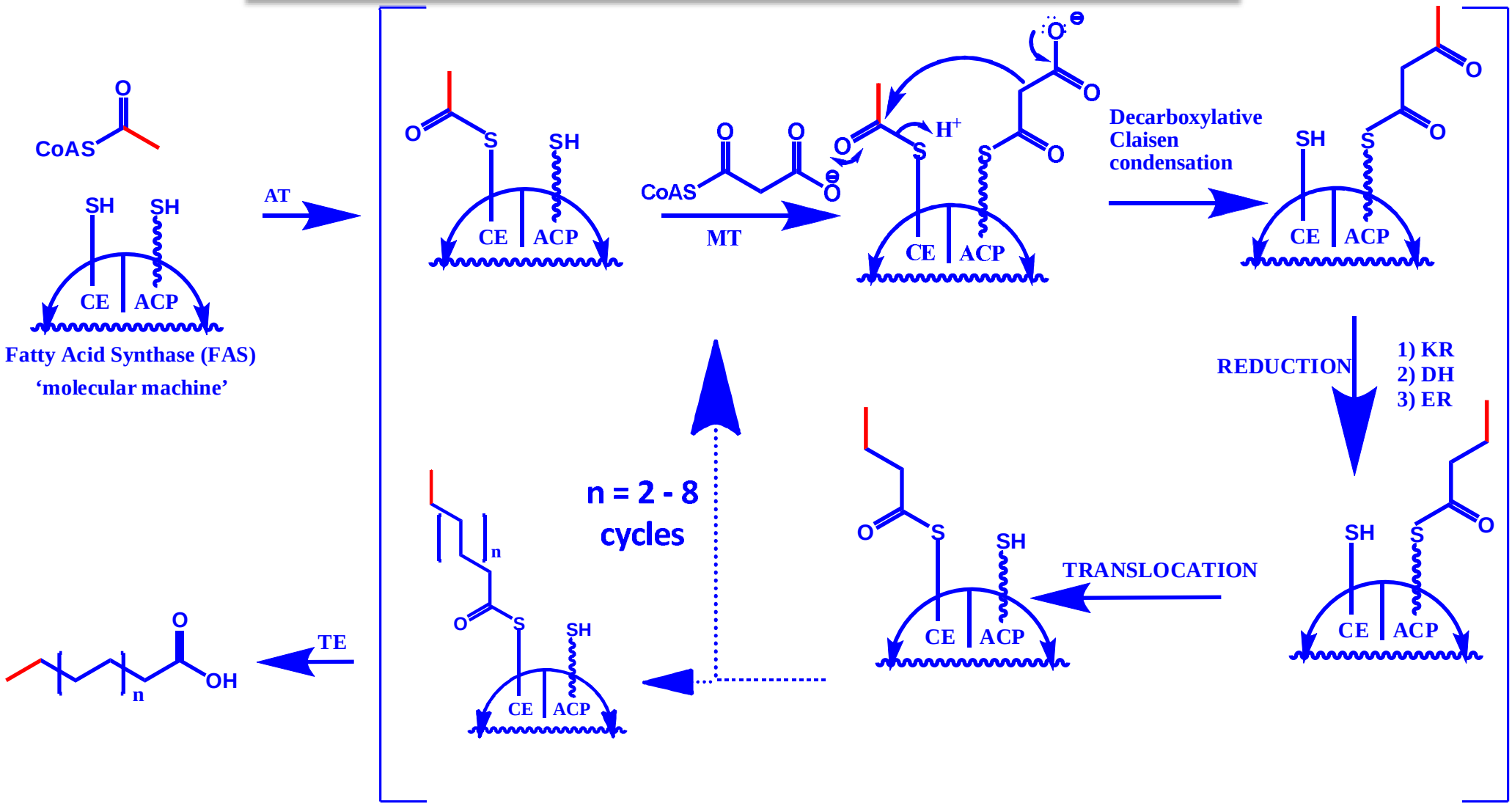
Once they are anchored to the fatty acid synthase, a carbon-carbon bond formation reaction occurs.

Acetyl-CoA and malonyl-CoA themselves are not involved in the condensation step: they are converted into enzyme-bound thioesters, Acetyl-$SE_{condensing}$ and Malonyl S-ACP, respectively.

The intermediates in fatty acid synthesis are covalently linked to the Acyl Carrier Protein (ACP).



Biosynthesis of Fatty Acids



AT= Acetyl transferase **ACP= Acyl Carrier Protein**

MT= Malonyl transferase **KR = Keto Reductase**

CE= Condensing enzyme **ER = Enoyl Reductase**

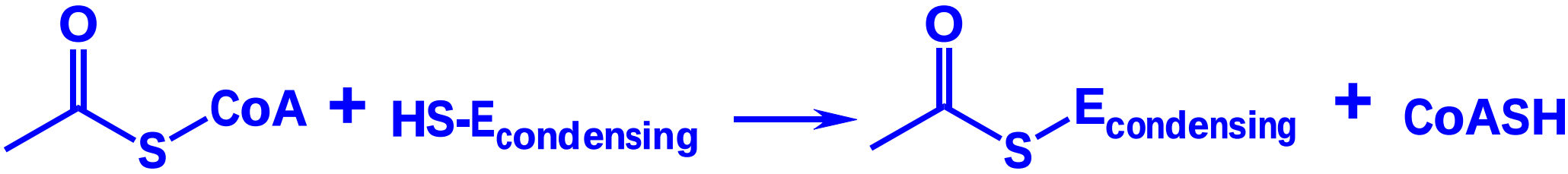
DH= Dehydratase

TE= Thioesterase

Steps in the Biosynthesis of Fatty Acids

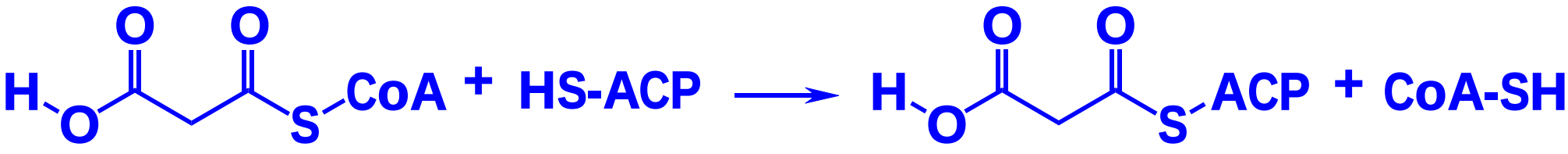
Step I

Transfer of the acetyl group of acetyl CoA to the Condensing Enzyme (HS-$E_{condensing}$).



Step II

Transformation of Malonyl CoA into Malonyl SACP.

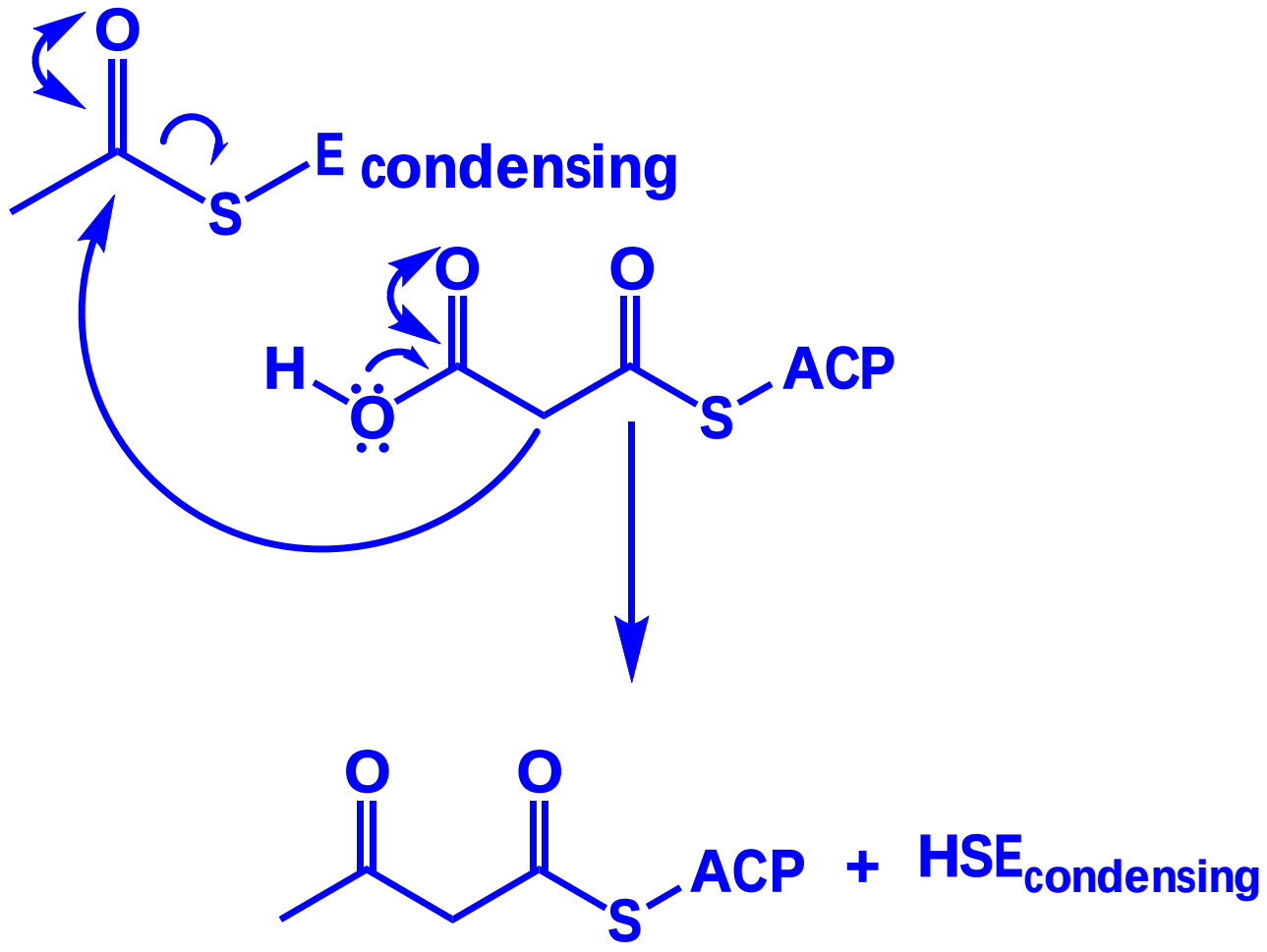


Malonyl CoA

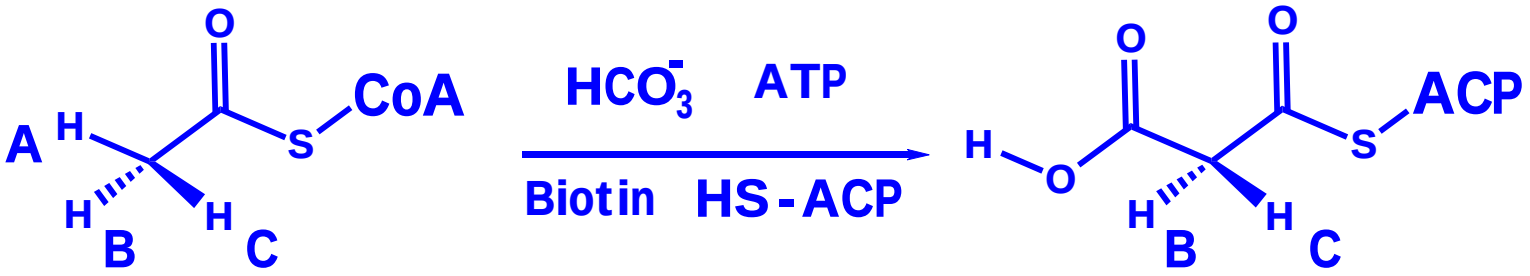
Malonyl SACP

Step III

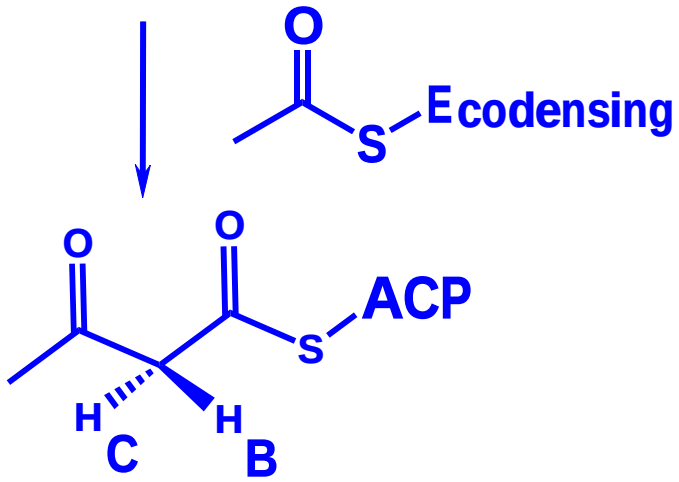
Condensation of acetyl $E_{condensing}$ with Malonyl SACP.



It has been shown that the carboxylation of acetyl CoA goes with retention of configuration but the condensation with Malonyl SACP goes with inversion of configuration.



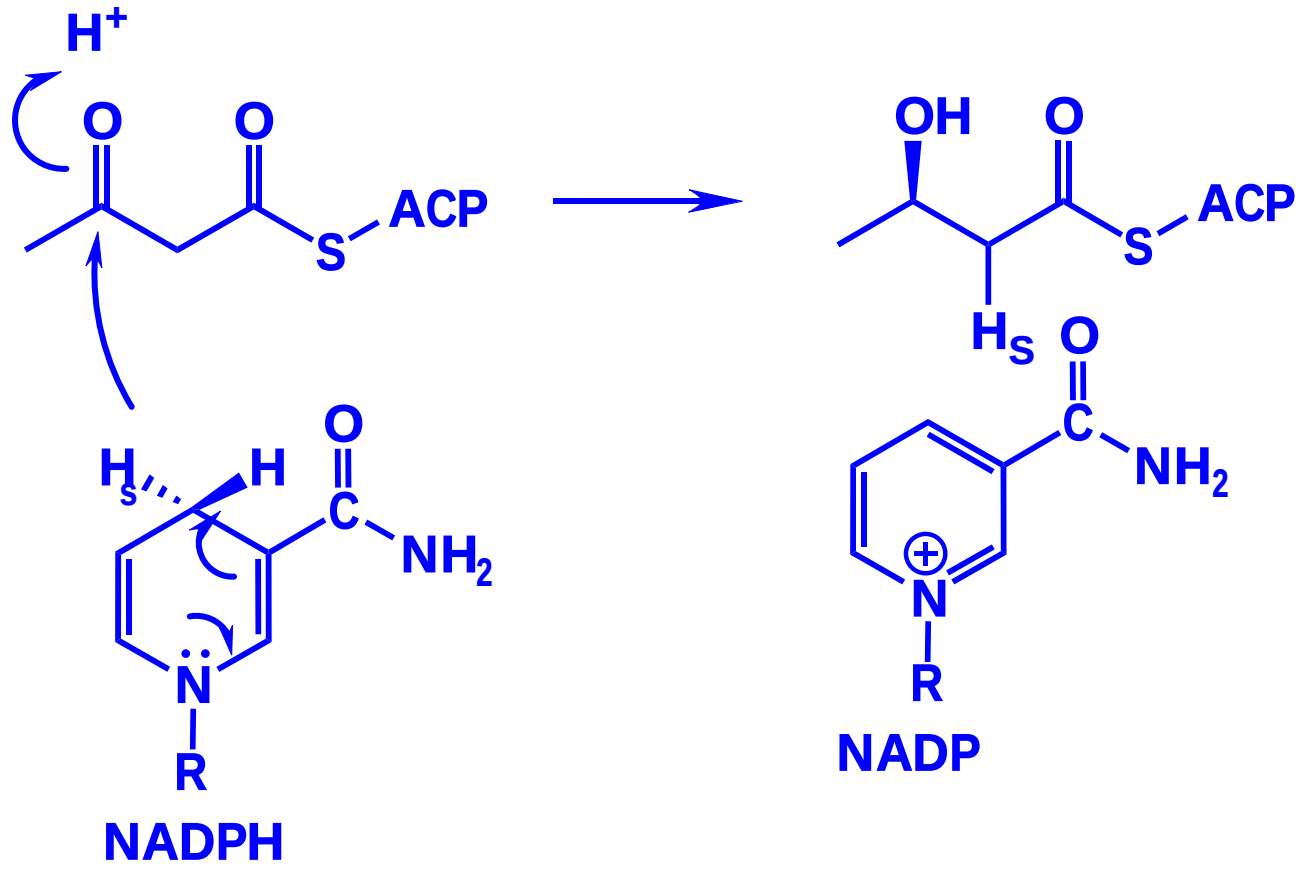
(Retention of configuration)



(Inversion of configuration)

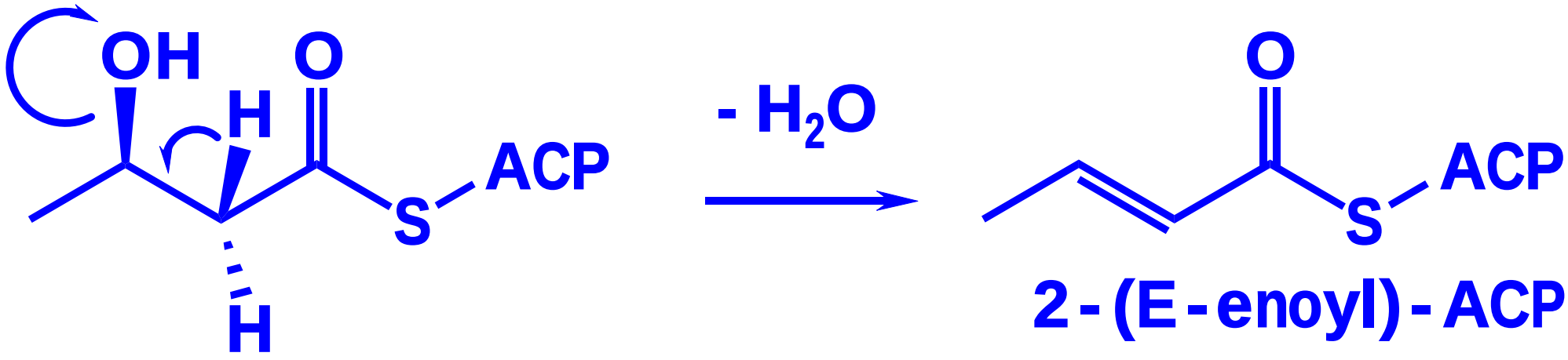
Step IV

Stereospecific reduction mediated by NADPH producing 3-(R)-hydroxy intermediate exclusively.



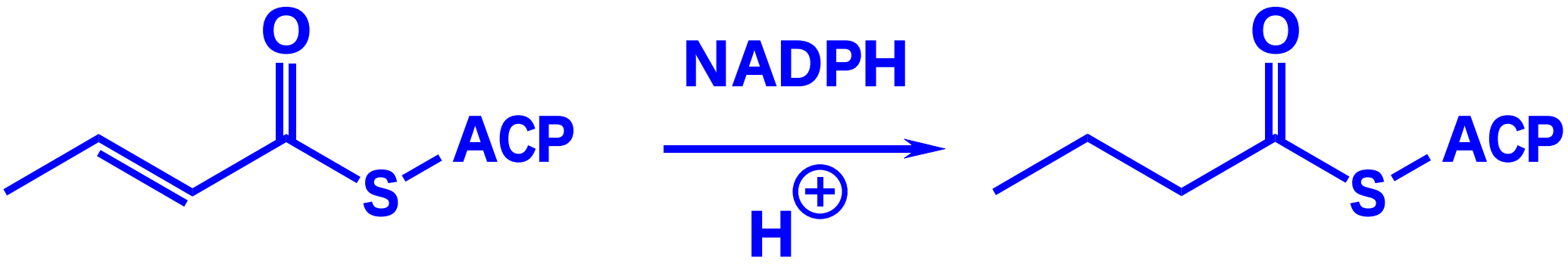
Step V

Syn elimination produces a 2-(E-enoyl)-ACP derivative, a trans-alkene.



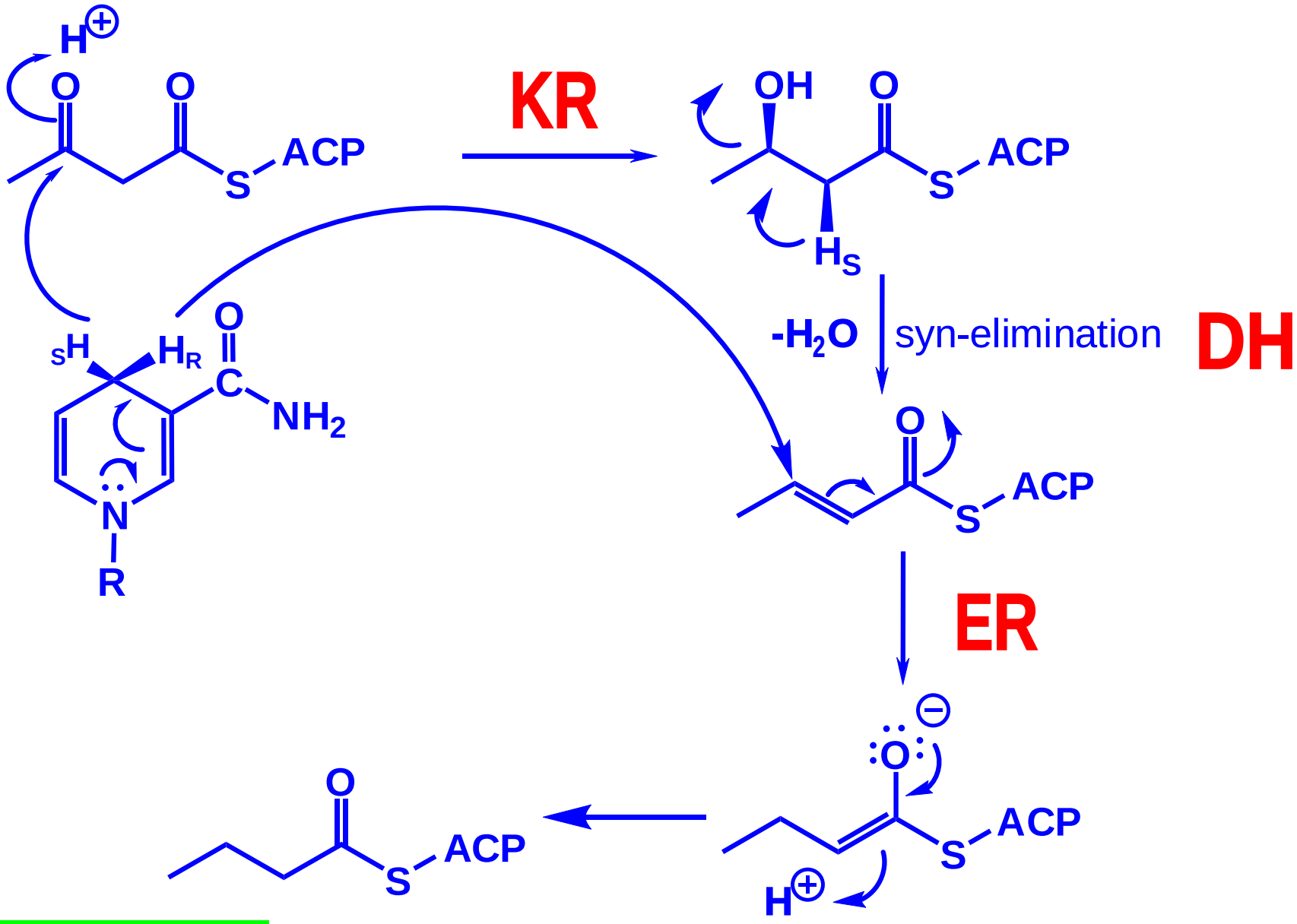
Step VI

The cycle is completed by further reduction mediated by NADPH to produce a saturated acyl-SACP.



Ketone → Methylene - *Reduction*

Achieved in 3 steps:



Repetition of this cycle (steps II to VI) utilizing the newly formed acyl intermediate in place of acetyl SCoA, leads to the lengthening of the carbon chain by two carbon atoms every cycle, to yield acyl-species of the general formula $Me(CH_2CH_2)_nCH_2COSACP$.

This process terminates when the chain reaches C_{16} or C_{18}, yielding palmitic or stearic acid, or their thiol esters.

It is probable that as the chain length approaches C_{16} - C_{18}, the active site thiol of the condensing enzyme has greater affinity for an acetyl-SACP species.

That is, steric or electronic effects hinder access acyl substrates bigger than C_{16} - C_{18} to the active site, and termination of the chain results.

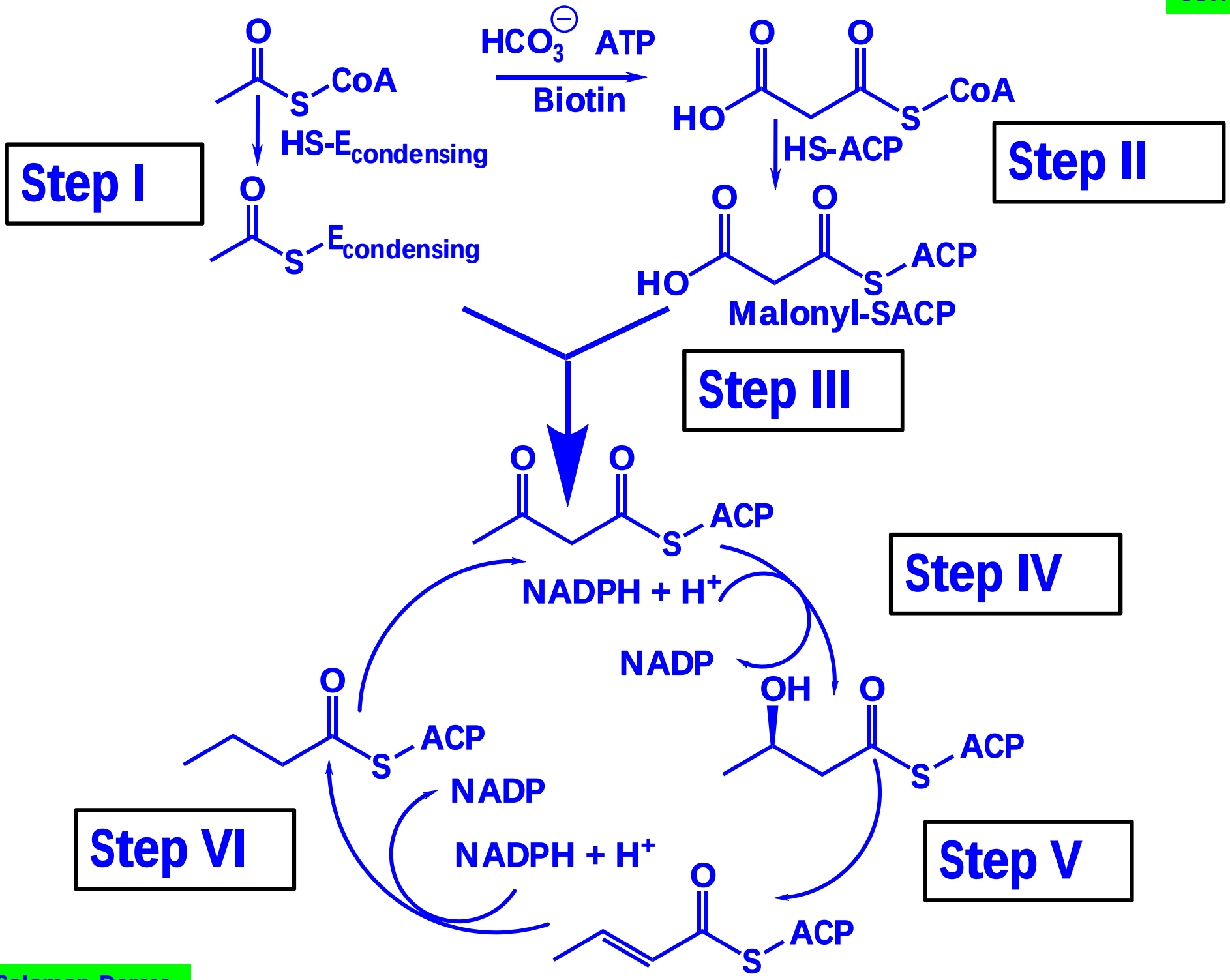
$$Me(CH_2CH_2)_nCH_2COSE_{condensing} \xrightarrow{H_2O} Me(CH_2CH_2)_nCH_2CO_2H$$

Extension of the chain beyond C_{18} does occur but the ultimate chain length is rarely greater than C_{22}-C_{24}, except in higher plants where the chain of up to C_{30} are encountered.

The combination of one acetate starter unit with seven malonates would give the C_{16} fatty acid, palmitic acid, and with eight malonates the C_{18} fatty acid, stearic acid.

Note that the two carbons at the head of the chain (methyl end) are provided by acetate, not malonate, whilst the remainder are derived from malonate, which itself is produced by carboxylation of acetate.

This means that all carbons in the fatty acid originate from acetate, but malonate will only provide the C_2 chain extension units and not the C_2 starter group.


Step I
HS-E condensing
E condensing
CoA
HCO3⊖ ATP
Biotin
Step II
HS-ACP
Malonyl-SACP
ACP
Step III
Step IV
NADPH + H+
NADP
Step V
Step VI
NADP
NADPH + H+

The pathway can be visualized as a cyclic process in which the acetyl primer undergoes a series of Claisen condensation reactions with seven malonyl extender molecules and, following each condensation, the [β-carbon of the β-3-ketoacyl moiety formed is completely reduced by a three-step ketoreduction-dehydration-enoyl-reduction process.

The saturated acyl chain product of one cycle becomes the primer substrate for the following cycle, so that two saturated carbon atoms are added to the primer with each turn of the cycle.

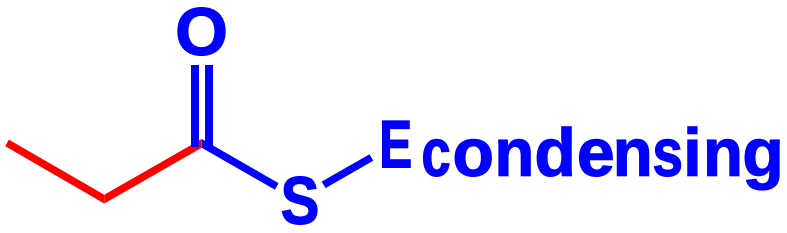
Odd numbered fatty acids

The linear combination of acetate C_2 units explains why the common fatty acids are straight chained and possess an even number of carbon atoms.

Other acyl CoA moieties (e.g. proinoyl SCOA, with three carbons) may also function as starter units in place of the usual starter acetyl SCoA.

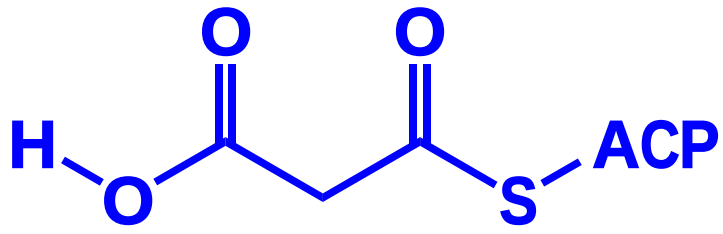
The biosynthesis of fatty acids that possesses an odd number of carbon atoms is essentially similar to the biosynthesis of their even numbered counter parts.

The synthesis of odd numbered fatty acids involve the use of the same extender unit, malonyl SACP, with an odd numbered starter unit.



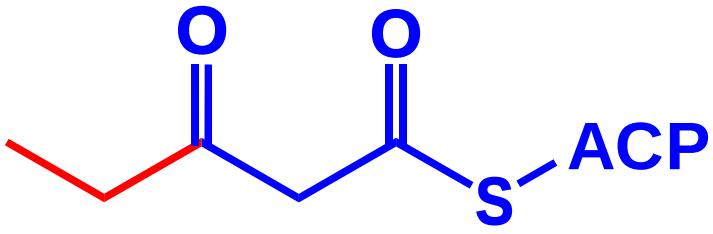
Starter unit

Proinoyl SE condensing

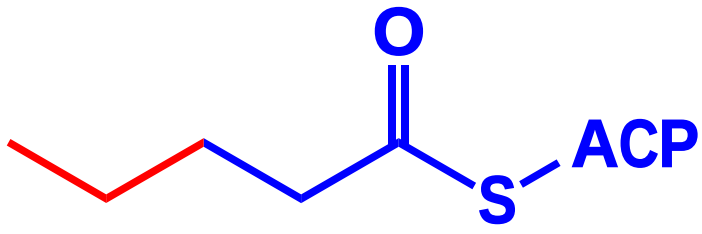


Malonyl SACP

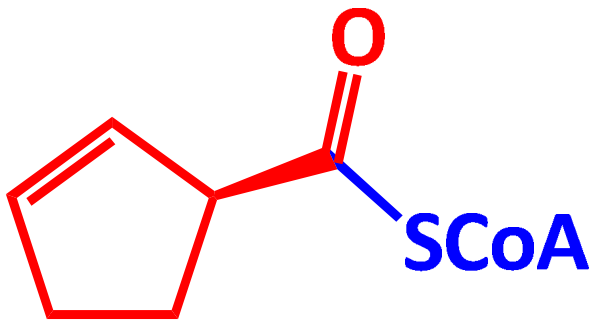
Extender unit



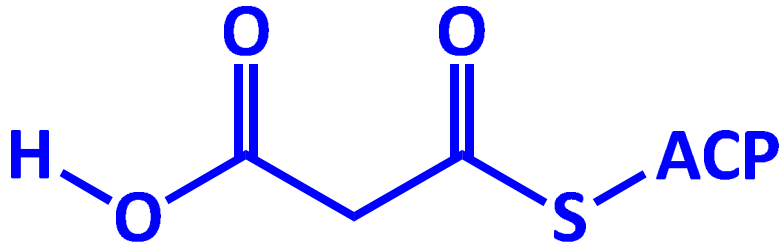
Reduction



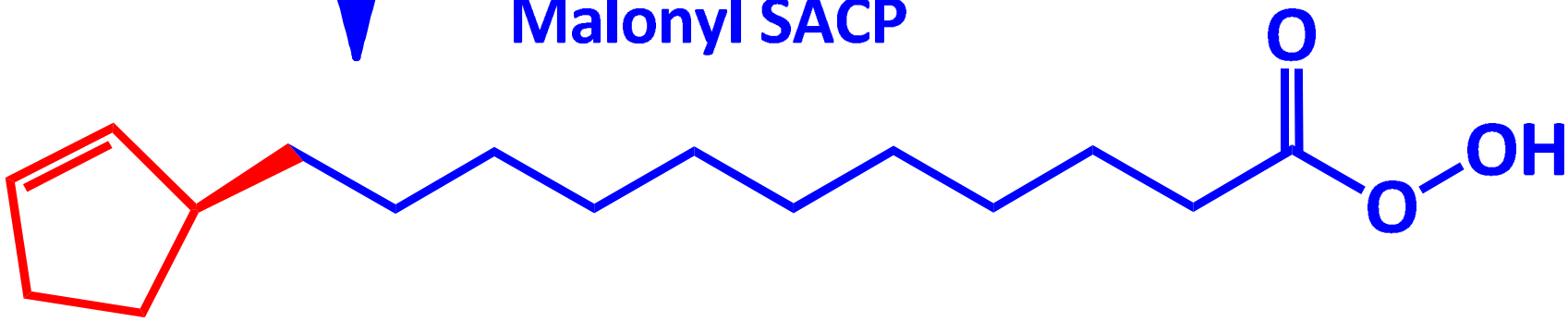
It would appear that it is the availability of unusual starters that determines whether normal or abnormal fatty acids are produced, rather than a requirement for special enzymes.



2-Cyclopentylcarboxyl CoA



Malonyl SACP



Hydnocarpic acid

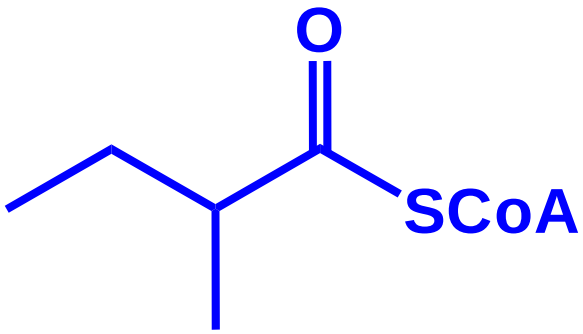
***Hydnocarpus wightiana* (Flacourtiaceae)**

Branched-chain Fatty acids

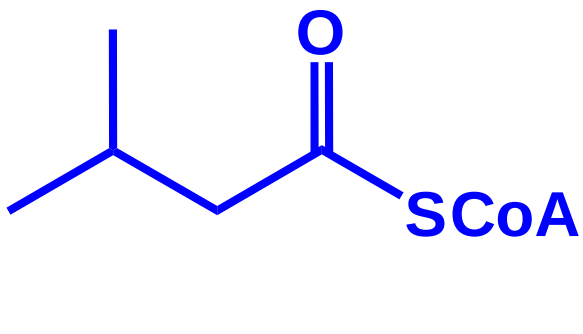
While straight chain fatty acids are the most common, branched chain fatty acids have been found to occur in mammalian systems.

Branched fatty acids are formed either

I. By priming the reaction with a branched starter (e.g 3-Methylbutyric SCoA or 2-methylbutyl SCoA)

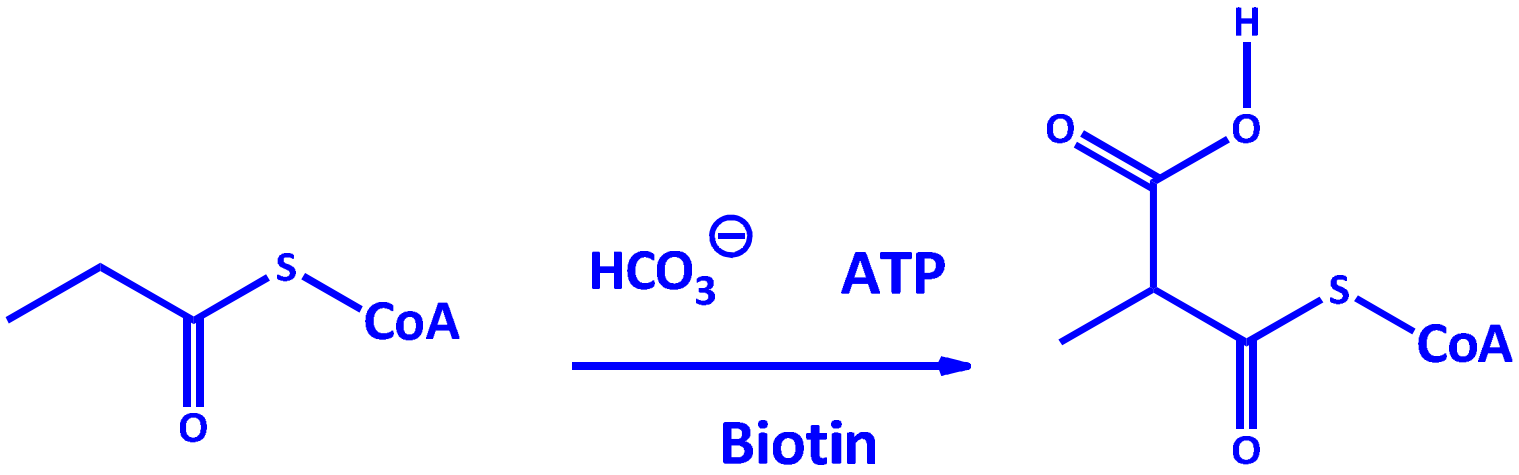


2-Methylbutyric acid



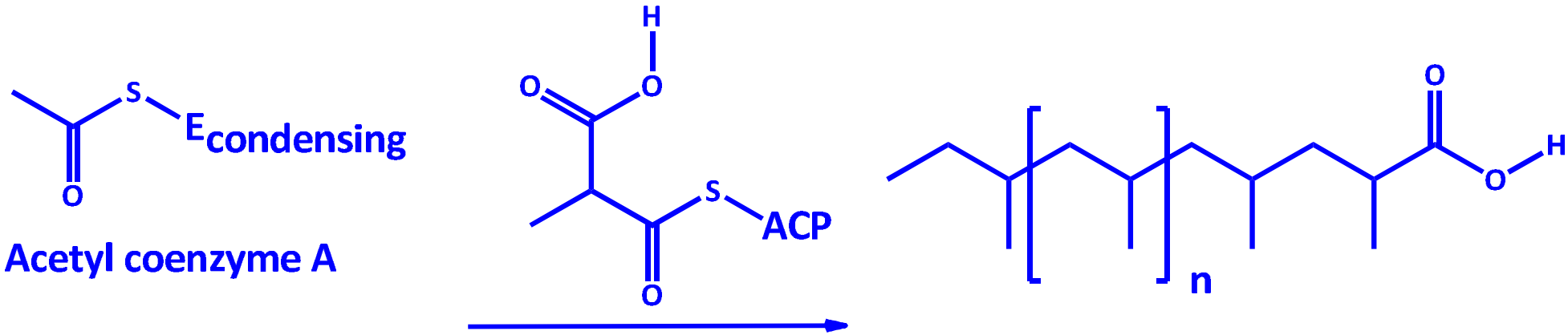
3-Methylbutyric acid

II. By using an alkylated malonyl SCoA extender unit.



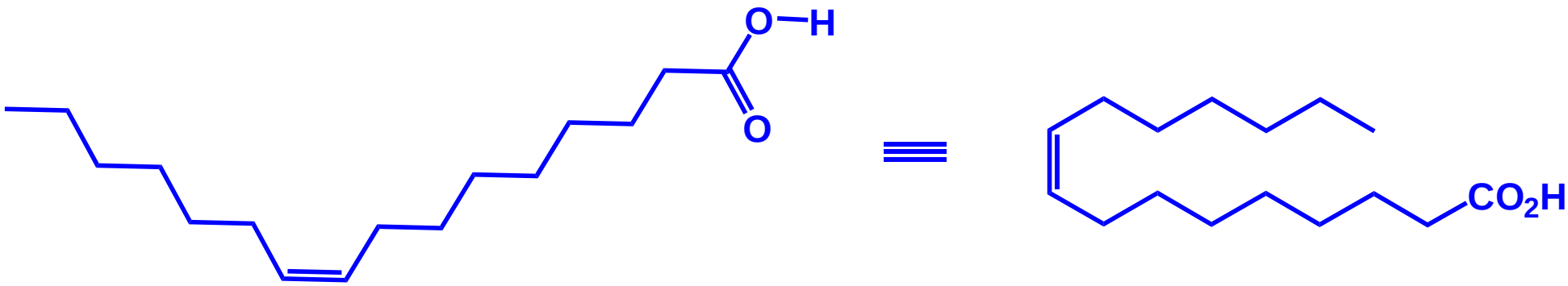
Propinoyl coenzyme A

Methylmalonyl-SCoA

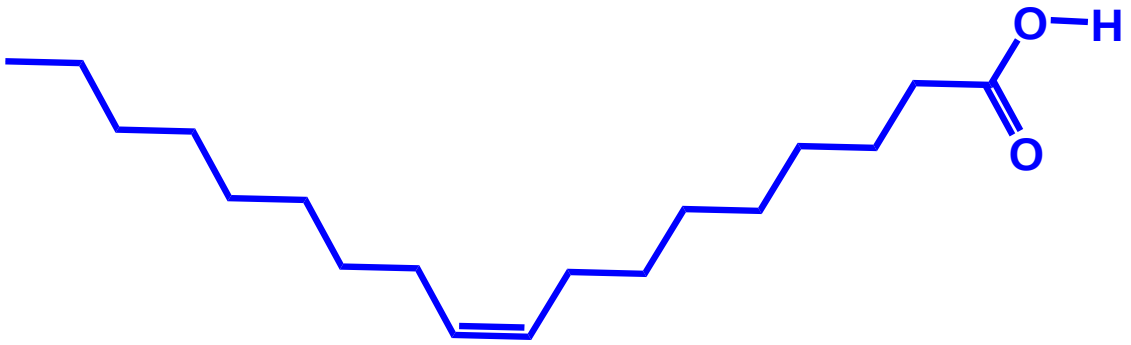


Unsaturated fatty acids

The majority of naturally occurring unsaturated fatty acids are in the C18 series. Acids shorter than C14, or higher than C22, are rare. Some representative examples are:



Palmitoleic acid



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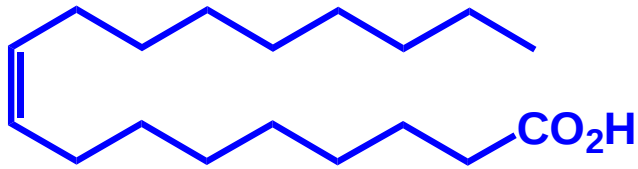
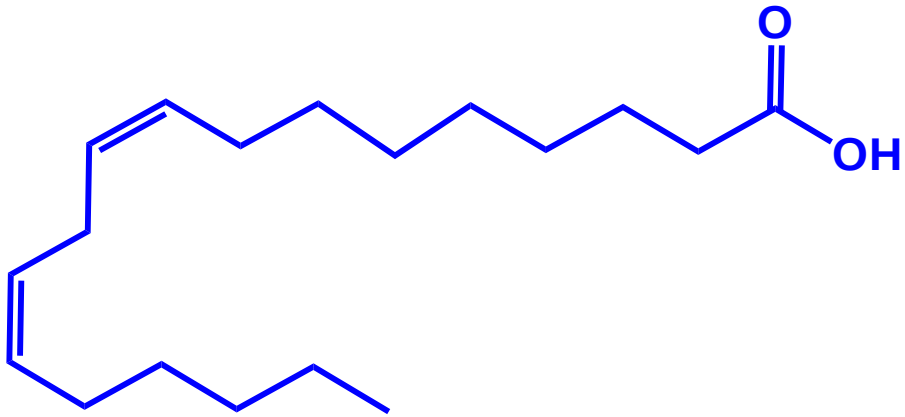
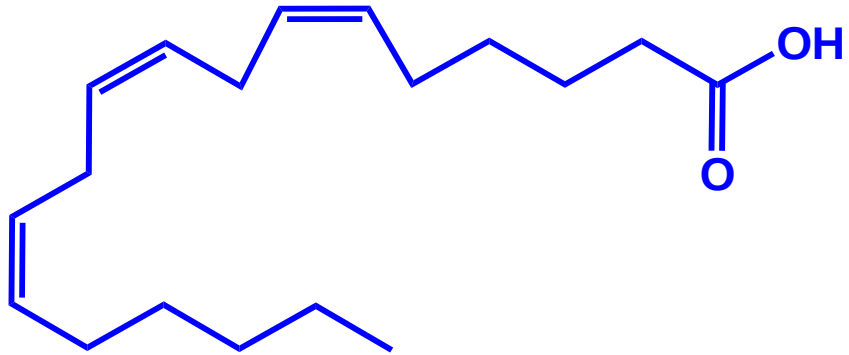


Oleic acid (>80% of oil in olive oil)



Linoleic acid



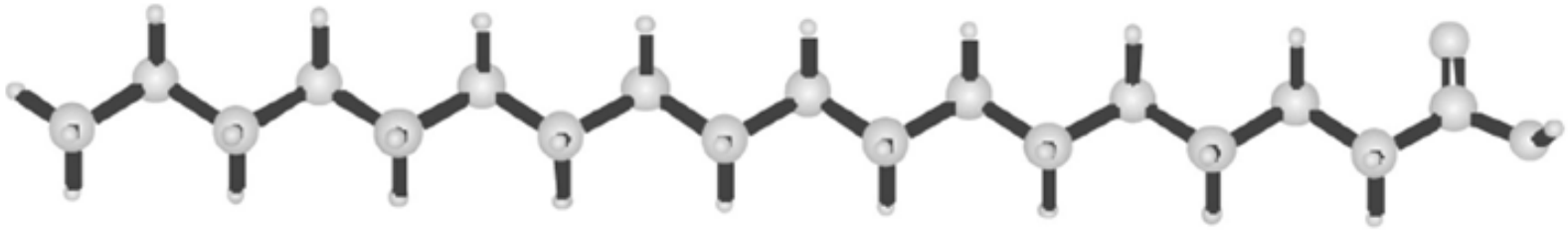
γ-Linoleic acid

Eladic acid

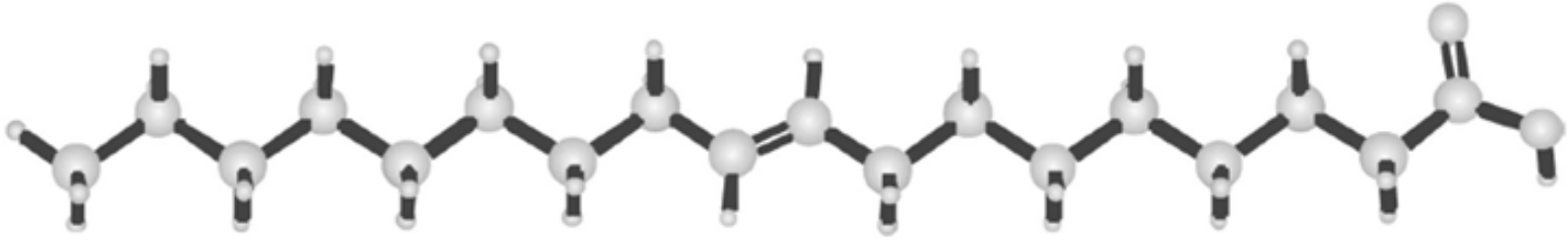
Geometry of double bonds

It will be noted that most of the double bonds in the examples given possess the *cis* (Z) - stereochemistry while trans double bonds are found in fatty acids, they occur more rarely.

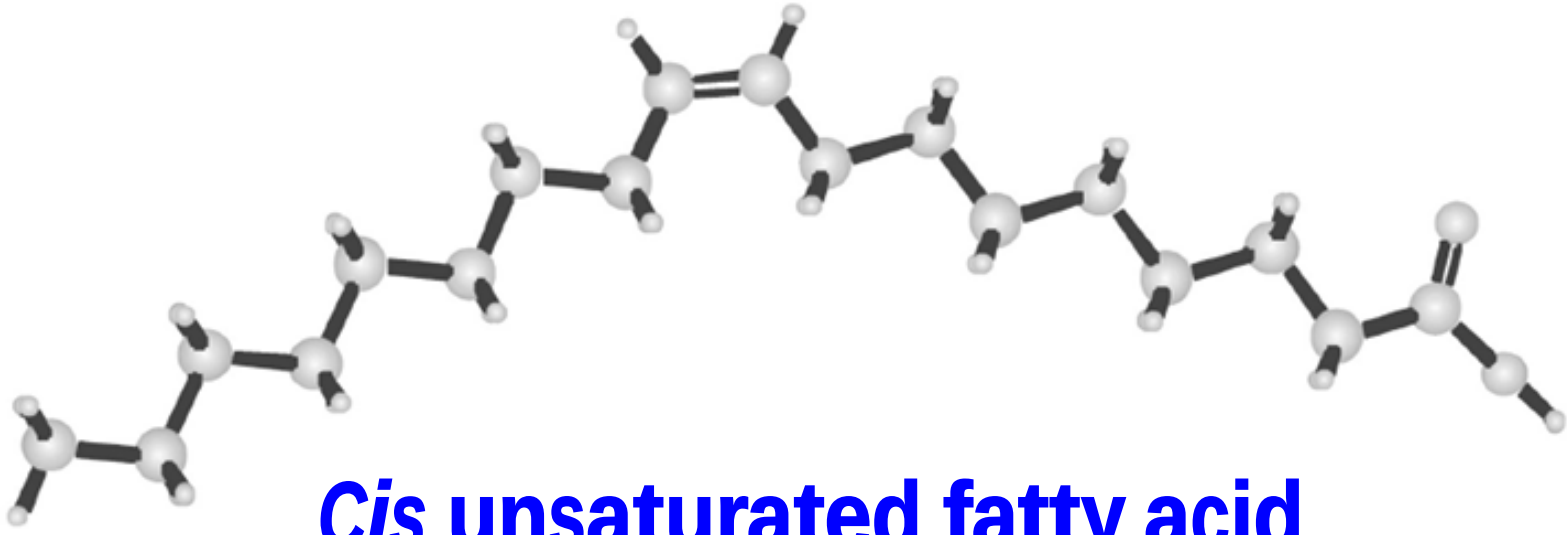
The *cis* double bond has an important biological significance: by introducing a "bend" in the alkyl chain it prevents the hydrophobic chains of the acyl groups in fats, phosphoglycerides form compact aggregates maintaining the fluidity of fat depot and cell membranes.



Saturated fatty acid



Trans unsaturated fatty acid



Cis unsaturated fatty acid

The typical pattern in polyunsaturated fatty acids is to have methylene groups flanked by two double bonds "a methylene – interrupted" pattern of unsaturation.

Biosynthesis of unsaturated fatty acids

There are two common routes towards the biosynthesis of unsaturated fatty acids depending on the organism:

I. Anaerobic route (occurs in some bacteria)

- Proceed in the absence of oxygen

II. Aerobic route (in animals and plants)

- An absolute requirement for oxygen

The aerobic process is by far the most common, and operates in yeasts, certain bacteria, algae, higher plants and vertebrates.

The aerobic route directly introduces a double bond into a fatty acid precursor by a process known as **oxidative desaturation**, which is regulated by **desaturase enzymes**.

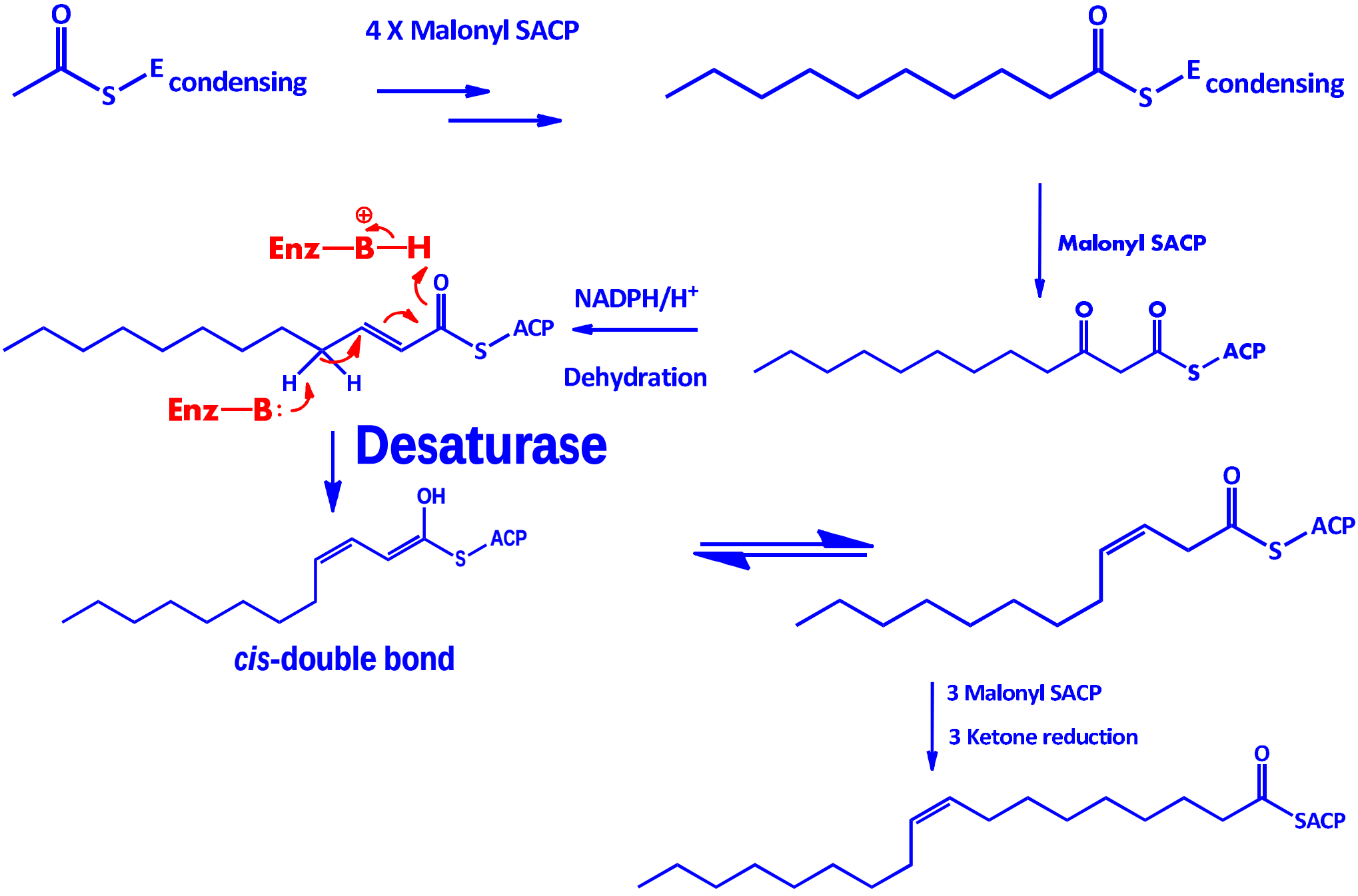
The anaerobic pathway is mainly confined to anaerobic bacteria.

I. Anaerobic route

The fact that unsaturated fatty acids are synthesized in the absence of oxygen is apparent from their wide spread occurrence in anaerobic bacteria. However, only monounsaturated fatty acids are synthesized.

Dehydrogenation occurs during chain elongation.

Anaerobic route to oleic acid

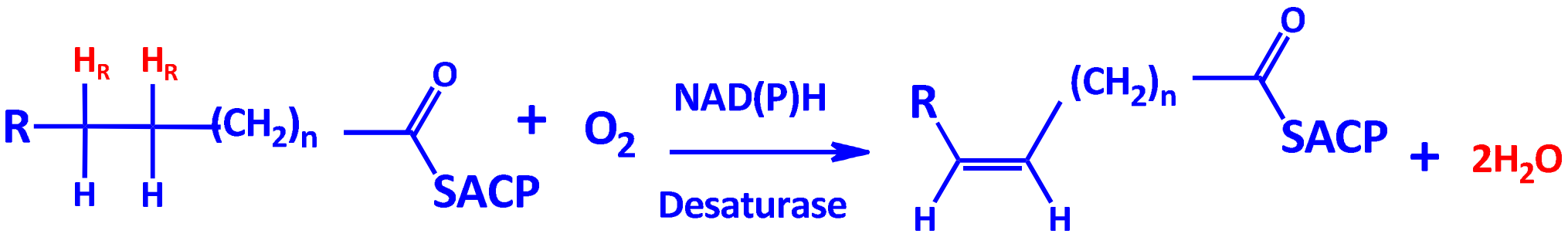


This is an anaerobic route as no oxidation is required (the double bond is already there — it just has to be moved) and is used by prokaryotes such as bacteria.

II. Aerobic route

Production of unsaturated fatty acids (insertion of double bonds) requires molecular oxygen. In an oxidation step, hydrogen is removed and combined with O_2 to form water.

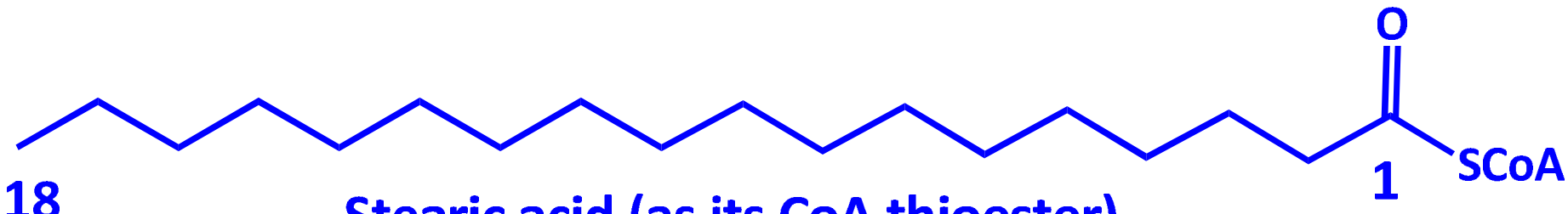
Dehydration occurs after the required chain length of fatty acid is formed leading to mono- and poly-unsaturated fatty acids.



This is apparently accomplished by syn elimination of a *vicinal* pair of pro-R hydrogen atoms, resulting in the formation of a *cis*-double bond exclusively.

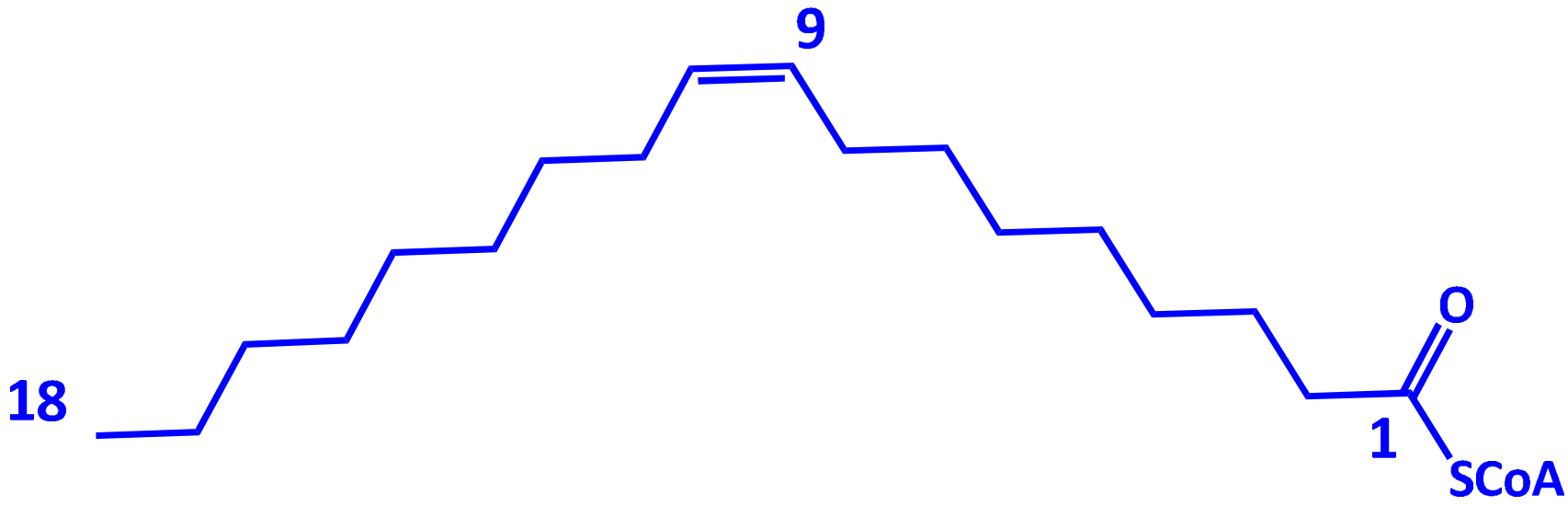
The double bond is usually introduced between C-9 and C-10.

Example



Stearic acid (as its CoA thioester)

Oxidative desaturation

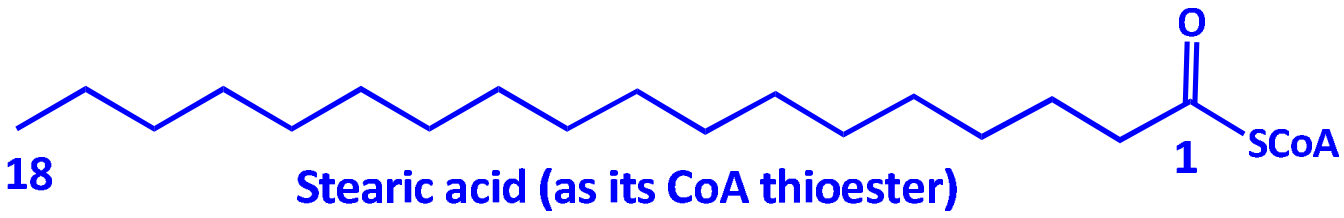


Most organisms possess a Δ9-desaturase enzyme that introduces a *cis* double bond into a saturated fatty acid at C-9.

The position of further desaturation then depends very much on the organism.

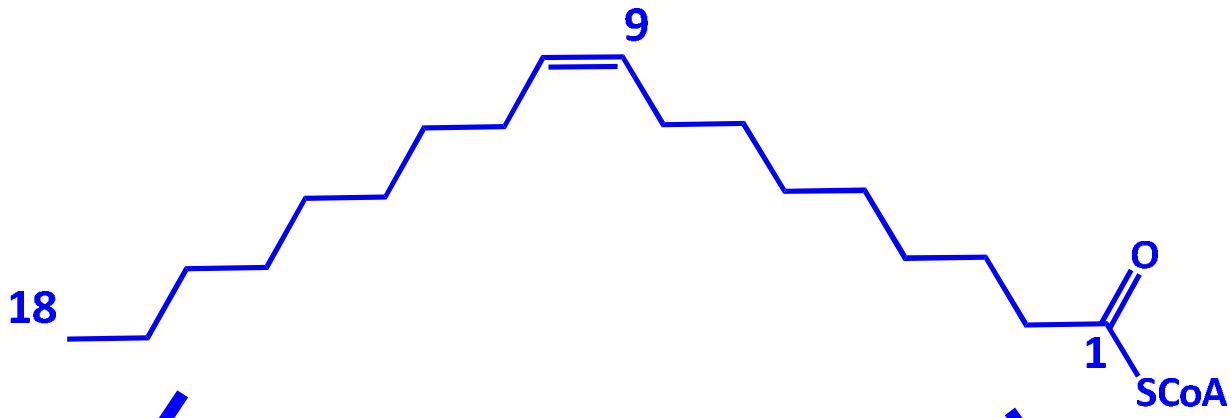
Non-mamalian enzymes tend to introduce additional double bonds between the existing double bond and the methyl terminus.

Animals always introduce new double bonds towards the carboxyl group.



Stearic acid (as its CoA thioester)

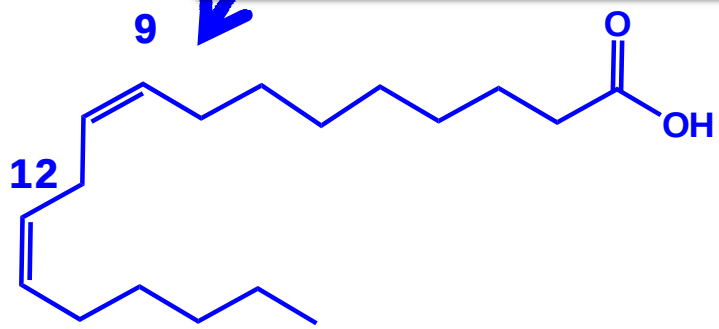
Oxidative desaturation



In plants

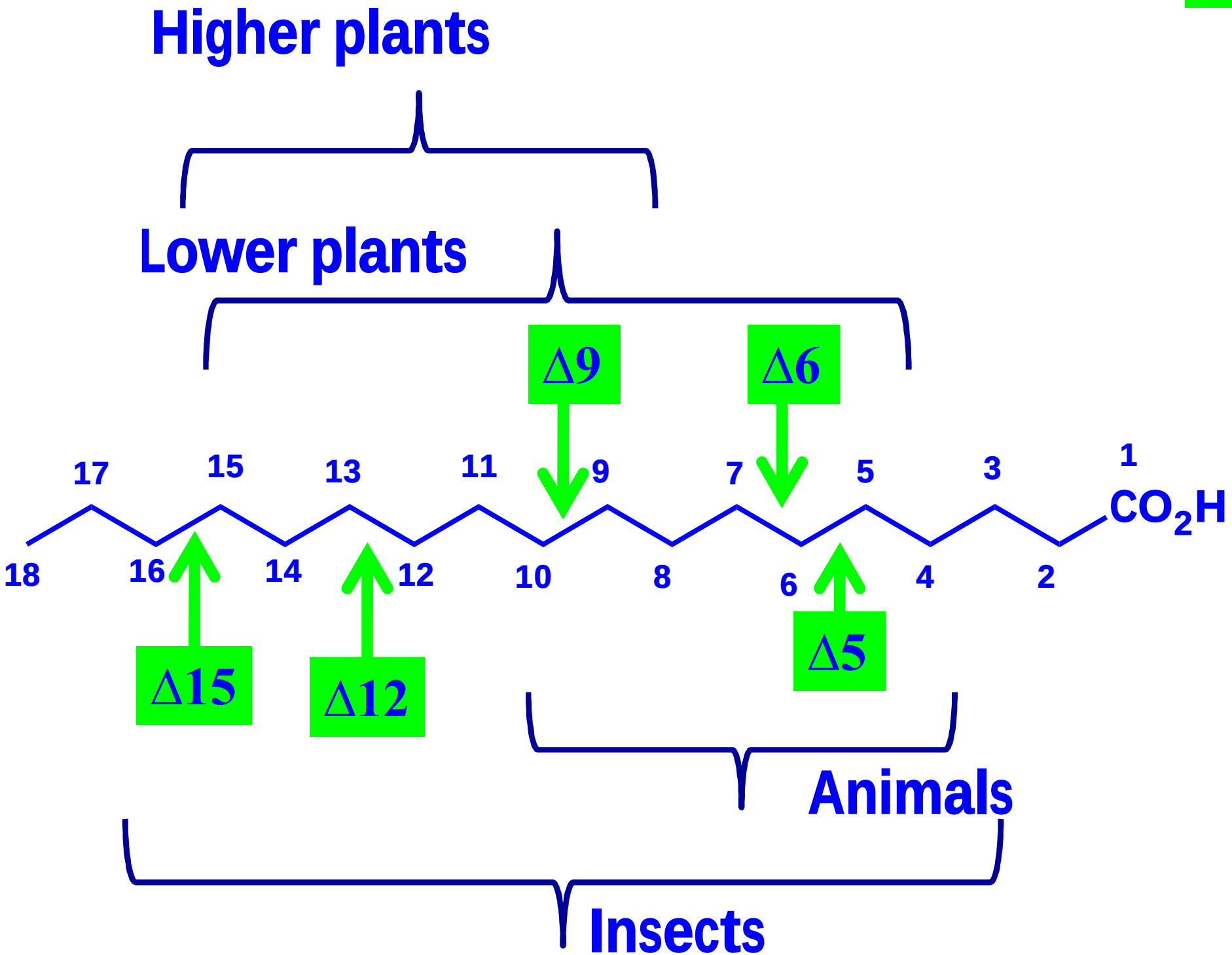
Oxidative Desaturation

In animals



Linoleic acid

γ-Linoleic acid


Higher plants
Lower plants
Δ9
Δ6
17
15
13
11
9
7
5
3
1
CO2H
18
16
14
12
10
8
6
4
2
Δ15
Δ12
Δ5
Animals
Insects

The first double bond introduced into a saturated acyl chain is generally in the Δ9 position so that substrates for further desaturation contain either a Δ9 double bond or one derived from the Δ9 position by chain elongation.

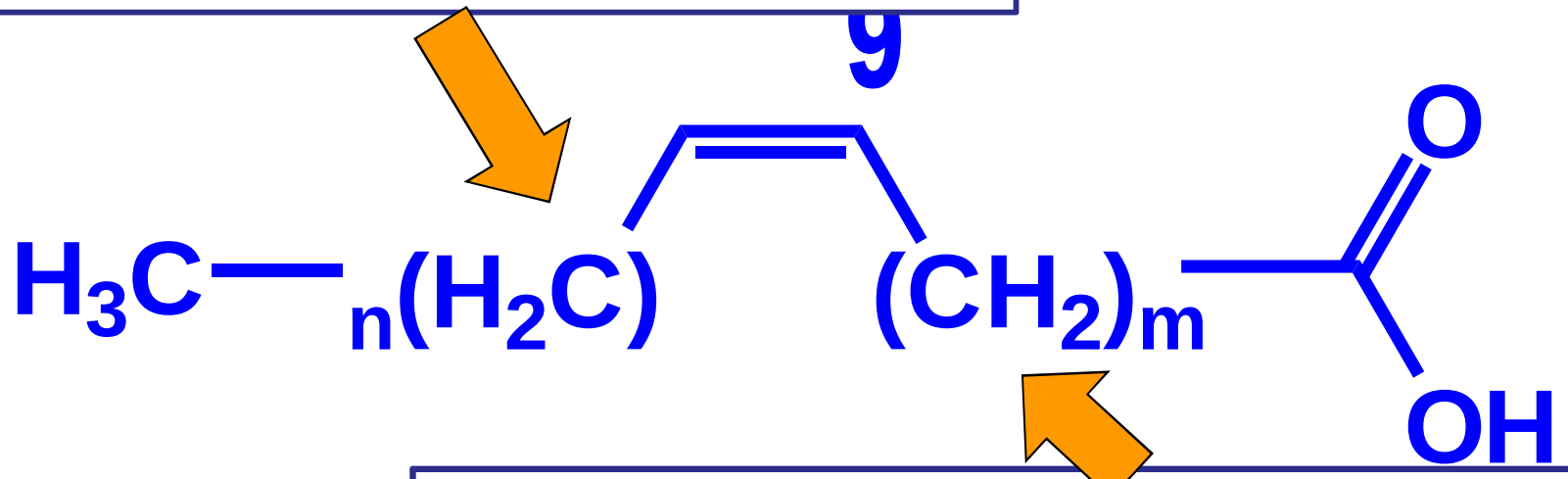
Just like Δ9 desaturation that inserts the first double bond, further desaturation is an oxidative process requiring molecular oxygen.

Animal systems cannot introduce double bonds beyond the C-9 position. Thus, second and subsequent double bonds are always inserted between an existing bond and the carboxyl end of the acyl chain, never on the methyl side.

Plants, on the other hand, introduce second and third double bonds between the existing double bond and the terminal methyl group.

Consequently, double bonds are found at the C-9, C-6, and C-5 positions as a result of desaturation in animals, at the C-9, C-12 and C-15 positions in plants, and at the C-5, C-6, C-9, C-12 and C-15 positions in insects and other invertebrates.

Plants: Further unsaturation occurs primarily in this region



Animals: Further unsaturation occurs primarily in this region

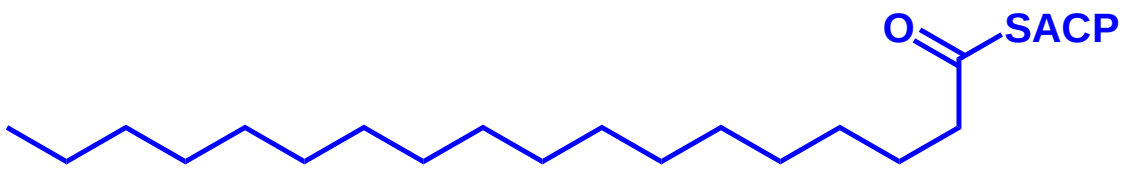
Fatty Acid Modifications

The biosynthesis of fatty acids mainly yield straight chain saturated fatty acids with sixteen and/or eighteen carbons. Other fatty acids are obtained by structural modifications of these straight chain saturated acids.

These modifications include:

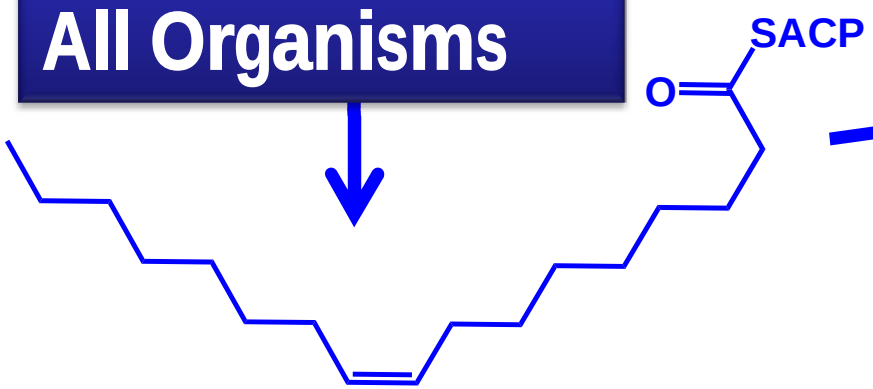
I. Chain elongation to give longer fatty acids.

II. Desaturation, giving unsaturated fatty acids.



STEARIC ACID

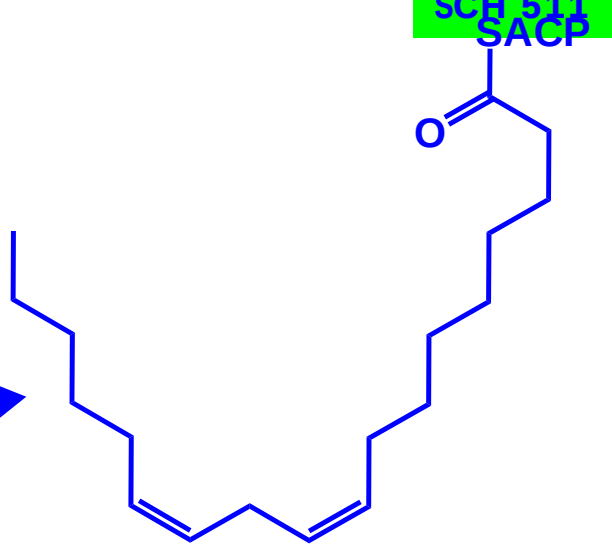
All Organisms



OLEIC ACID 18:1 (9c)

Desaturation towards methyl terminus

Plants Fungi

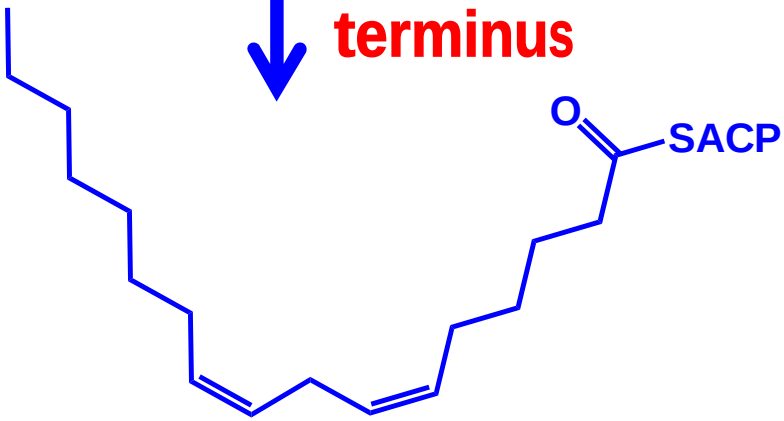


LINOLEIC ACID 18:2 (9c, 12c)

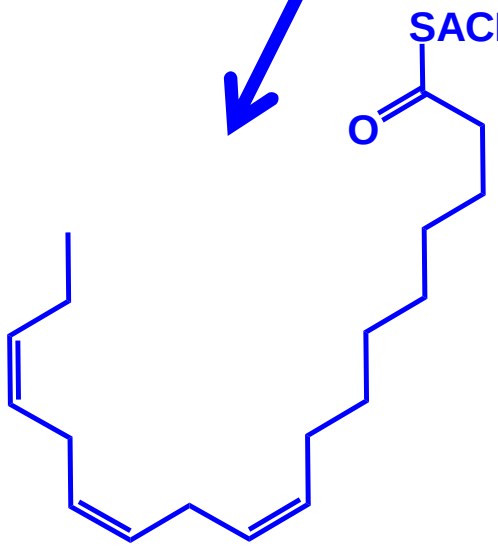
Plants Fungi

Animals

Desaturation towards carboxyl terminus



18:2 (9c, 6c)



α-LINOLENIC ACID 18:2 (9c, 12c, 15c)

The most common mono unsaturated FA in animals are oleic acid (18:1(9c)) and palmitoleic acid (16:1(9c)). Fatty Acid Desaturase enzymes in animals can only introduce double bond up to C-9.

Thus the important unsaturated fatty acids Linoleic (with C-9 and C-12 double bonds) and Linolenic acids (with C-9, C-12 and C-15 double bonds) can not be biosynthesized in animals including humans.

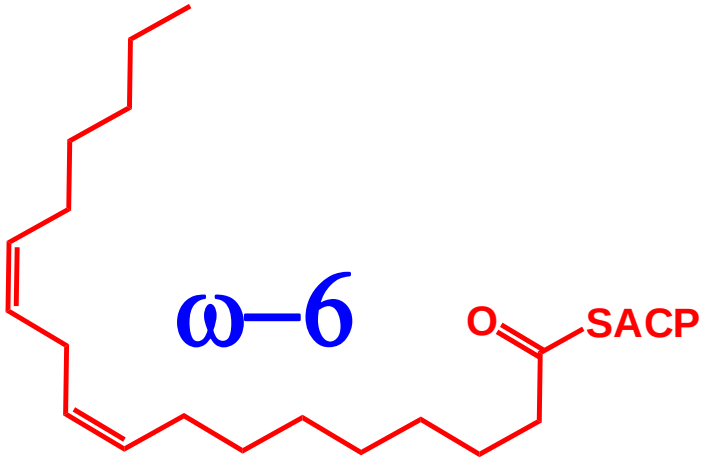
They must be obtained from the diet. Plants have the enzymes necessary to synthesize these acids. Such fatty acids are described as **Essential Fatty Acids (EFA).**

Linolenic acid, an omega-3 fatty acid, and linoleic acid, an omega-6 fatty acid are both found in soybean oil and other types of plant oils.

Omega 3
1000 mg, 180 cap - $58.65

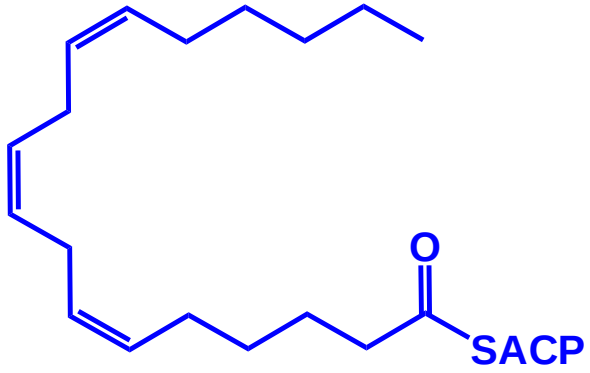
Animals can metabolize these two fatty acids obtained from the diet to form longer and more unsaturated PUFAs to meet their metabolic needs. Since these two fatty acids must be obtained from the diet, they are considered to be essential fatty acids.

Linoleic acid is the starting material from which the body makes arachidonic acid, the precursor for prostaglandins, the hormone like substance that regulates a wide range of body functions, including growth, wound healing and epidermal health.



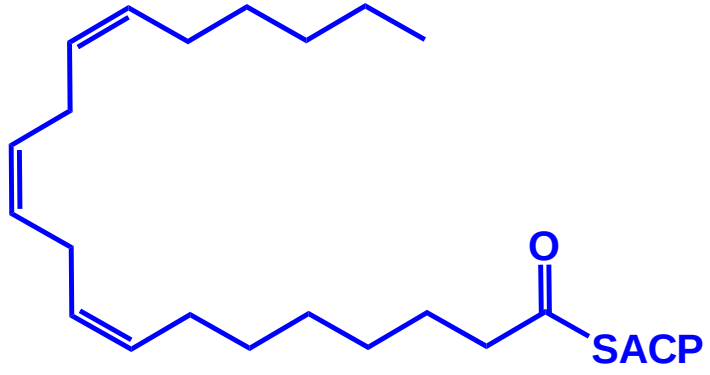
LINOLEIC ACID 18:2 (9c, 12c)

ANIMALS



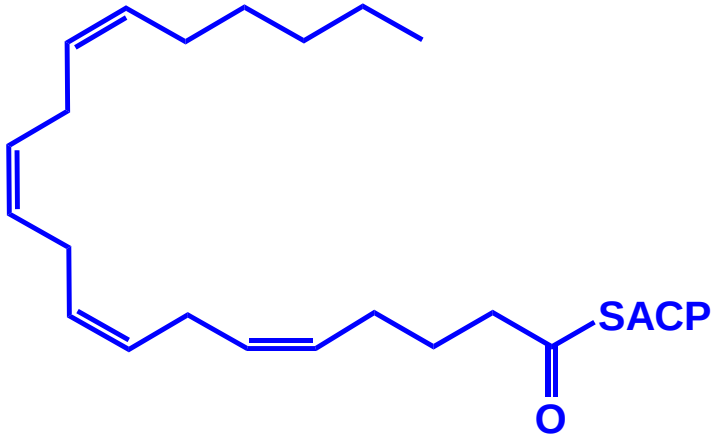
γ-LINOLEIC ACID 18:3 (6c, 9c, 12c)

Chain extension by reaction with malonate

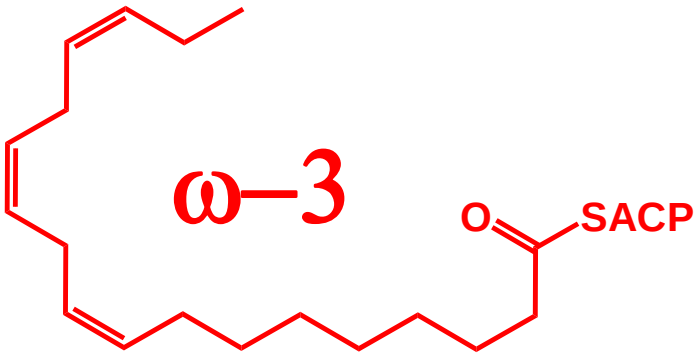


DIHOMO–γ-LINOLEIC ACID 20:3 (8c, 11c, 14c)

ANIMALS



ARACHIDONIC ACID 20:4 (5c, 8c, 11c, 14c)

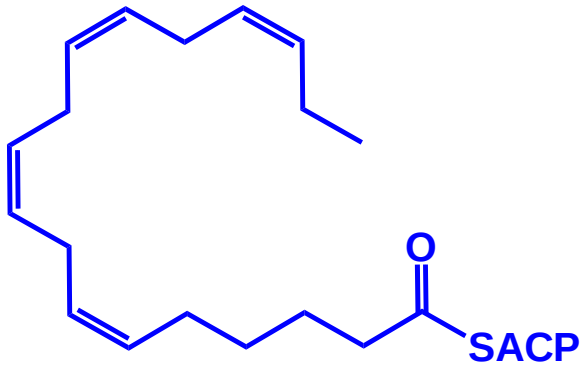


18:3 (9c, 12c, 15c)

α-LINOLENIC ACID

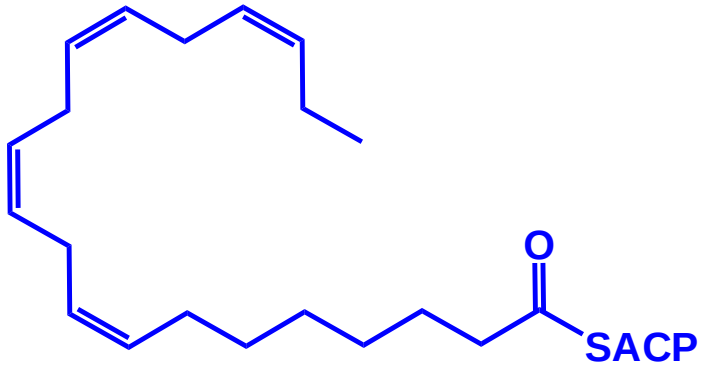
ANIMALS

DEASTURASE



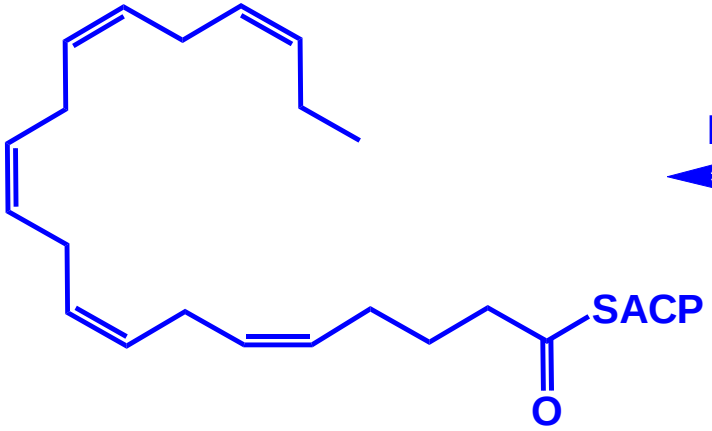
STEARIDONIC ACID 18:4 (6c, 9c, 12c, 15c)

Chain extension by reaction with malonate



EICOSATETRAENOIC ACID 20:4 (8c, 11c, 14c, 17c)

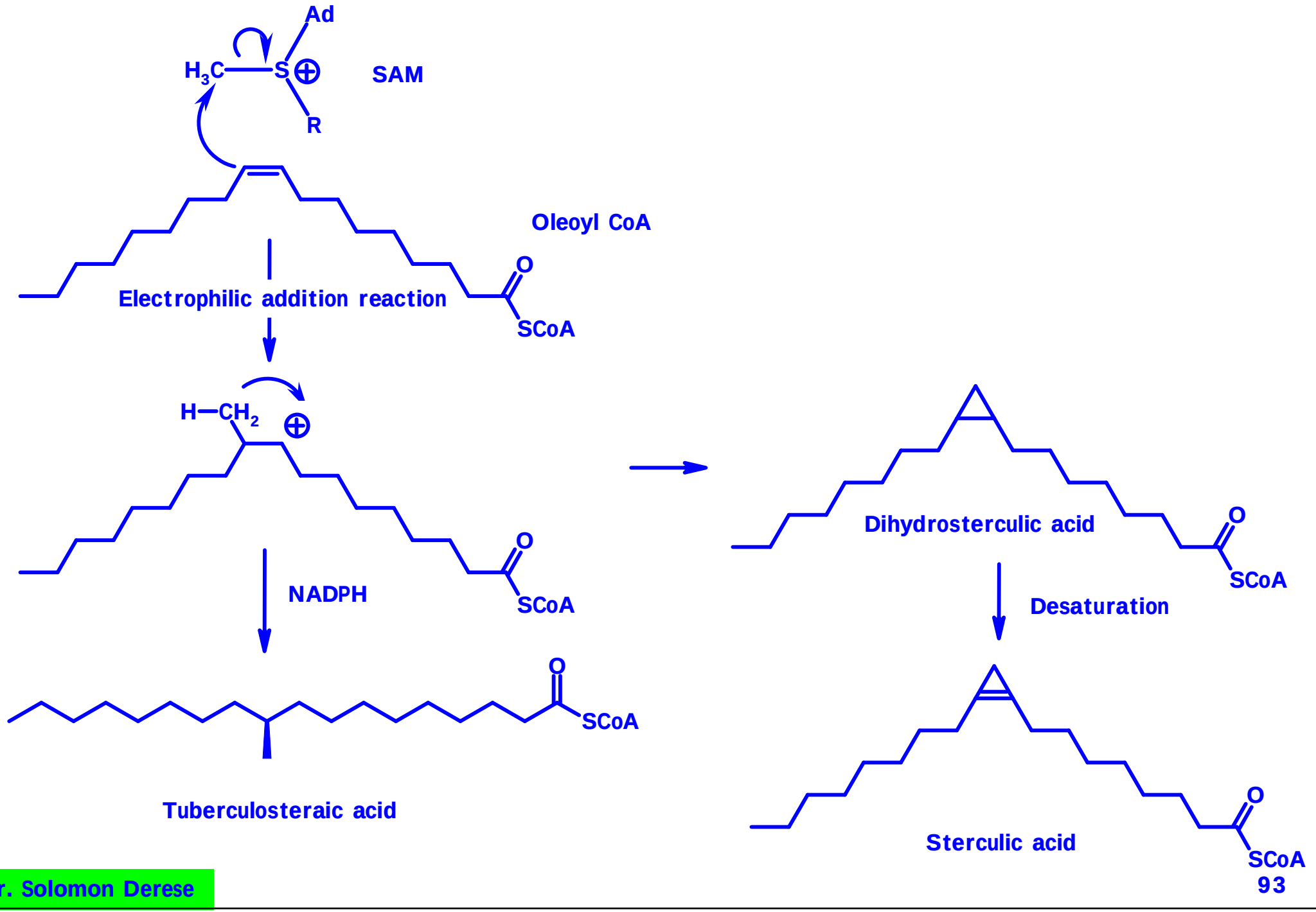
DEASTURASE



EICOSAPENTAENOIC ACID (EPA)

20:5 (5c, 8c, 11c, 14c, 17c)

Further Structure Modification



Prostaglandins

The prostaglandins are a group of modified C20 fatty acids first isolated from human semen and it was recognized that they were synthesized in the prostate gland (hence the name).

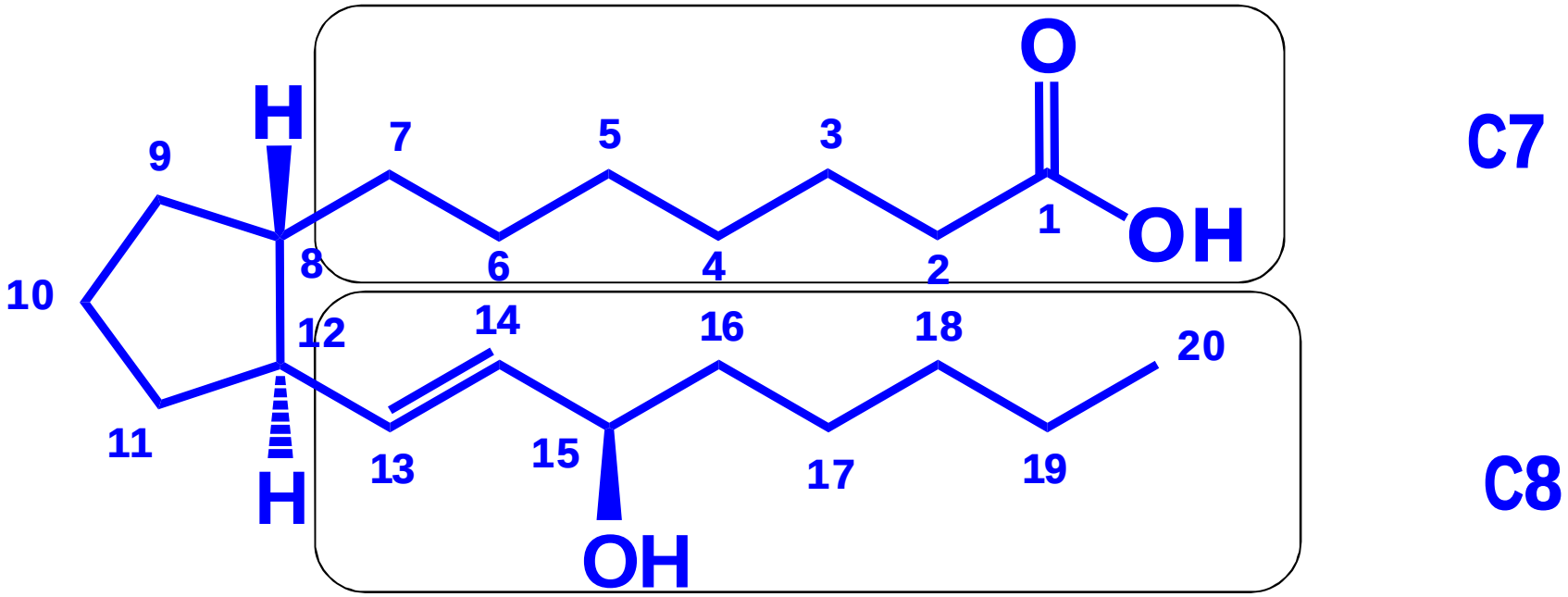
They are now known to occur widely in animal tissues, but only in tiny amounts, and they have been found to exert a wide variety of pharmacological effects on humans and animals.

It is thought that they are moderators of hormone activity in the body, a theory that explains their far reaching biological effects.

They are active at very low, hormone-like concentrations and can regulate blood pressure, contractions of smooth muscle, gastric secretion, and platelet aggregation.

Imbalances in prostaglandins can lead to nausea, diarrhea, inflammation, pain, fever, menstrual disorders, asthma, ulcers, hypertension, drowsiness or blood clots.

The basic prostaglandin skeleton is that of a cyclized C20 fatty acid containing a cyclopentane ring, a C7 side-chain with the carboxyl function, and a C8 side-chain with the methyl terminus.



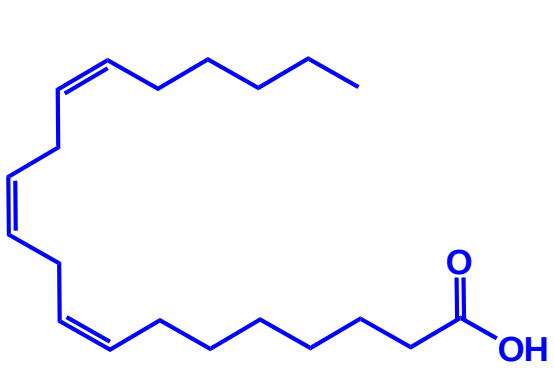
Basic skeleton of Prostaglandin

Naturally occurring prostaglandins contain a cyclopentane ring, a trans double bond between C-13 and C-14, and a hydroxyl group at C-15.

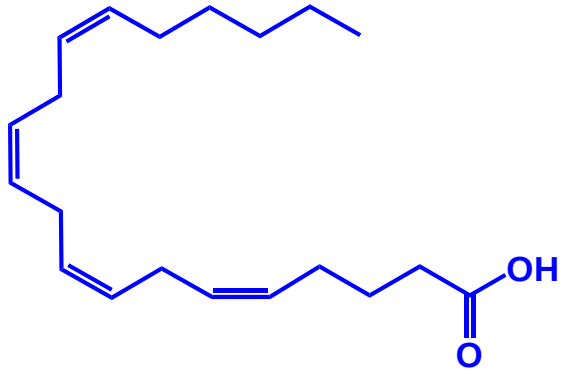
The prostaglandins are produced by most mammalian cells.

Prostaglandins are biosynthesized from three fatty acids, dihomo-γ-linolenic (20:3 (8c,11c,14c)), arachidonic (20:4 (5c,8c,11c,14c)), and eicosapentaenoic (20:5 (5c,8c,11c,14c,17c)) acid, which yield prostaglandins of the 1-, 2-, and 3-series, respectively.

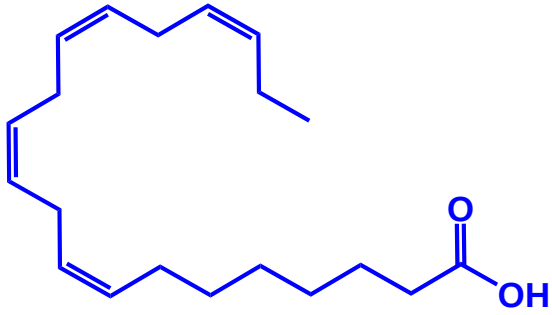
These three fatty acids are obtained from the essential fatty acids linoleic and linolenic acid.



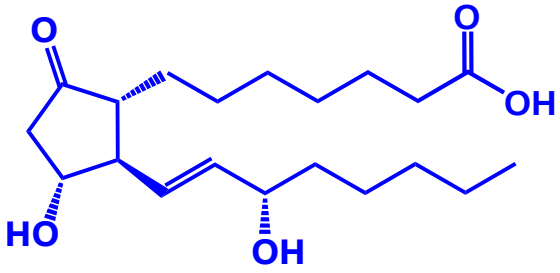
DIHOMO–γ-LINOLEIC ACID



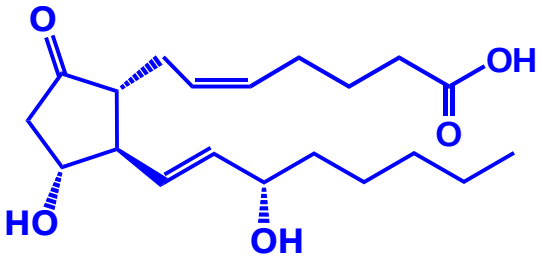
ARACHIDONIC ACID



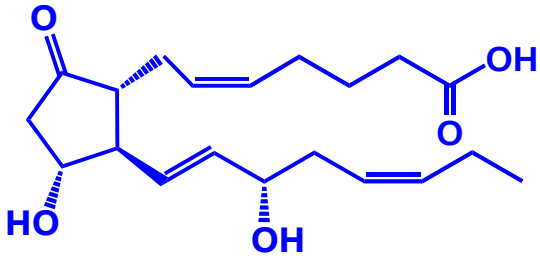
EICOSATETRAENOIC ACID



PGE_1



PGE_2

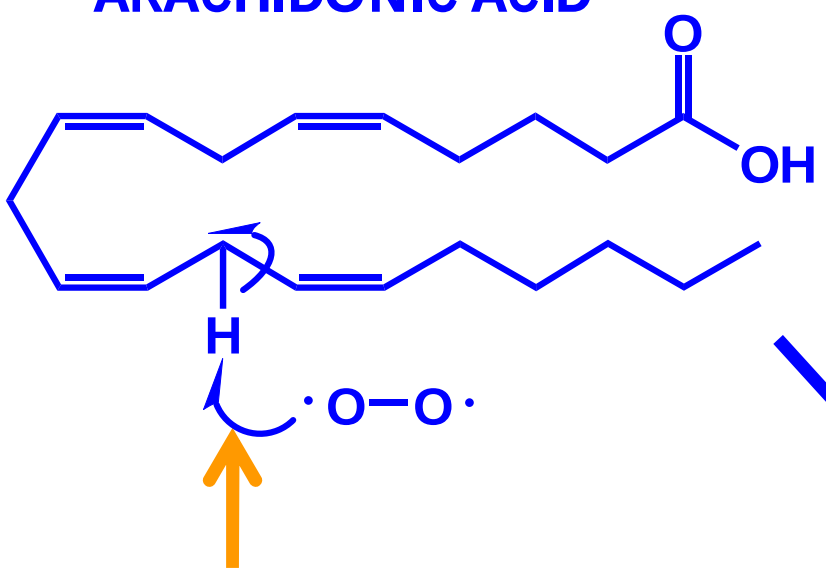


PGE_3

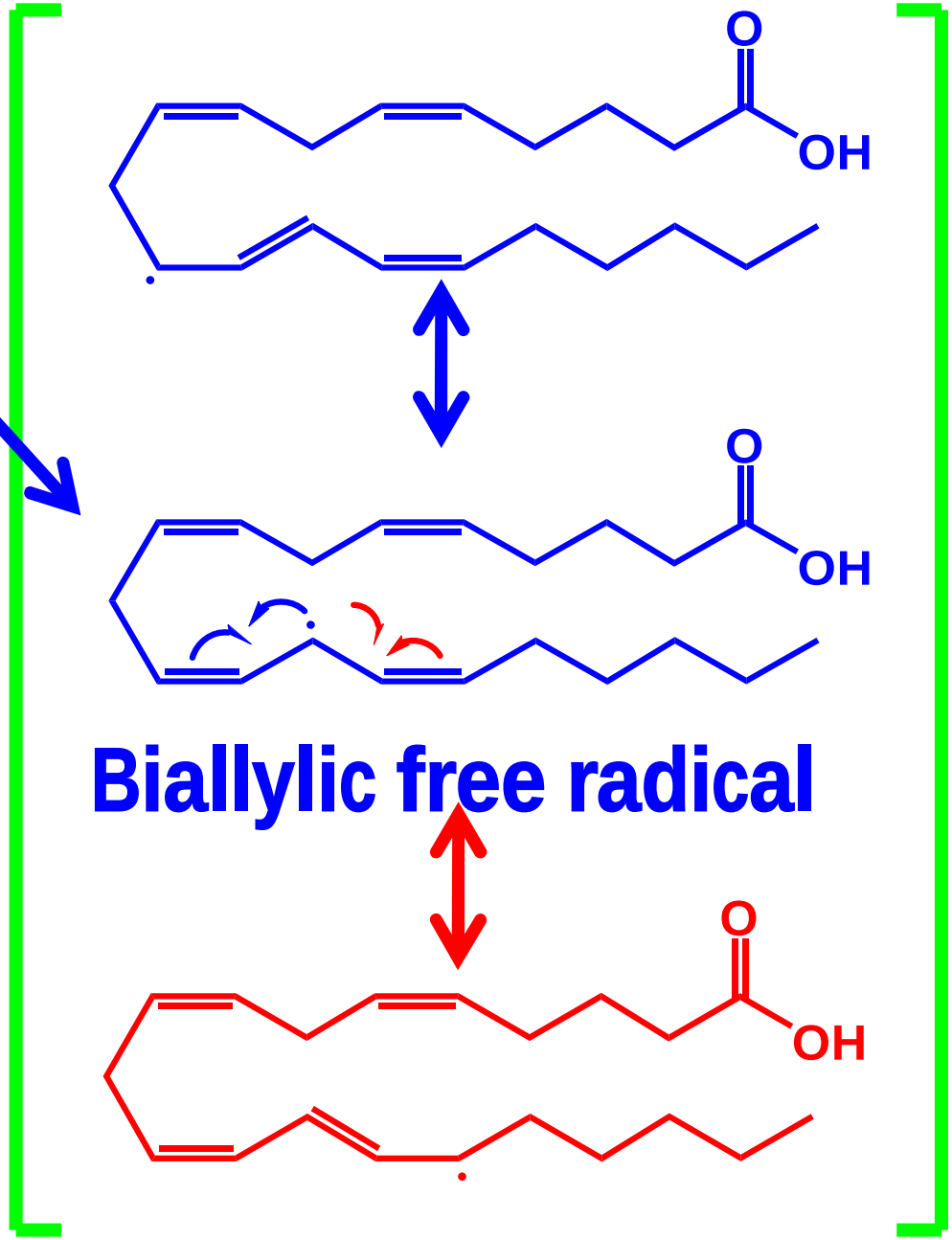
The numerical subscripts indicate the number of carbon-carbon double bonds in the side chains.

Biosynthesis of Prostaglandins

ARACHIDONIC ACID



Biallylic hydrogen



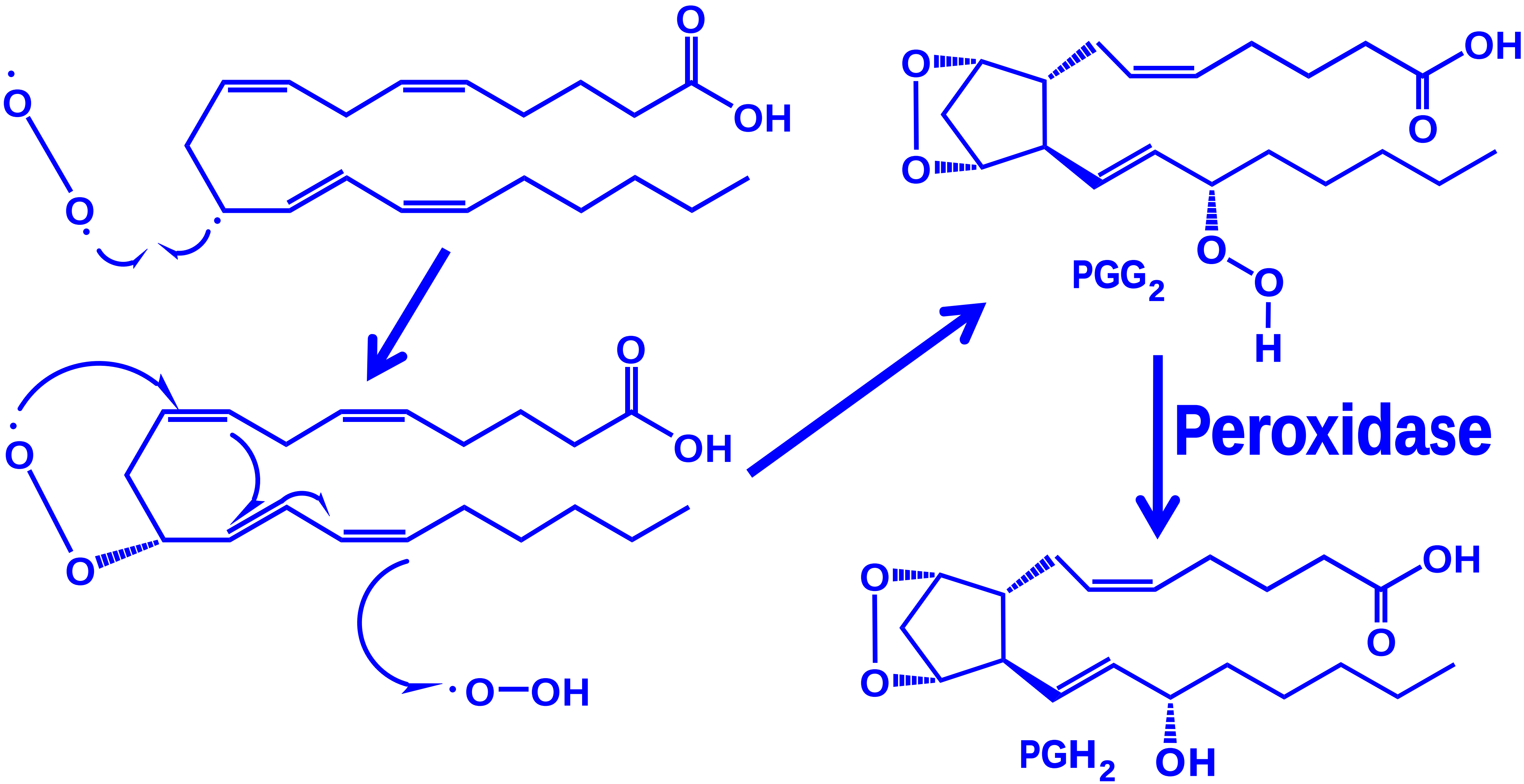
Biallylic free radical

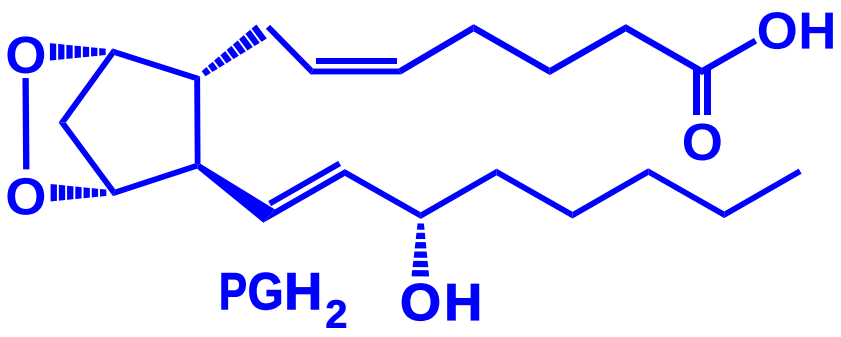
Resonance Stabilized

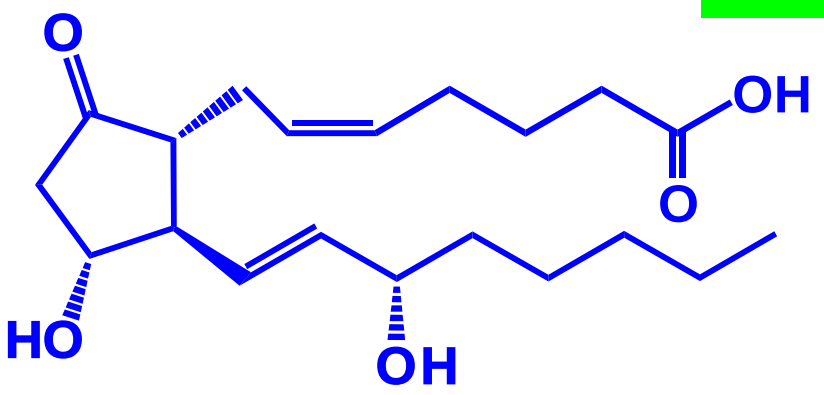
Oxygen is a diradical

HO–O·

A methylene flanked by double bonds on both sides is susceptible to free radical oxidation; free radical reaction allows addition of O_2 and formation of peroxide radical.


PGG2
Peroxidase
PGH2
O–OH

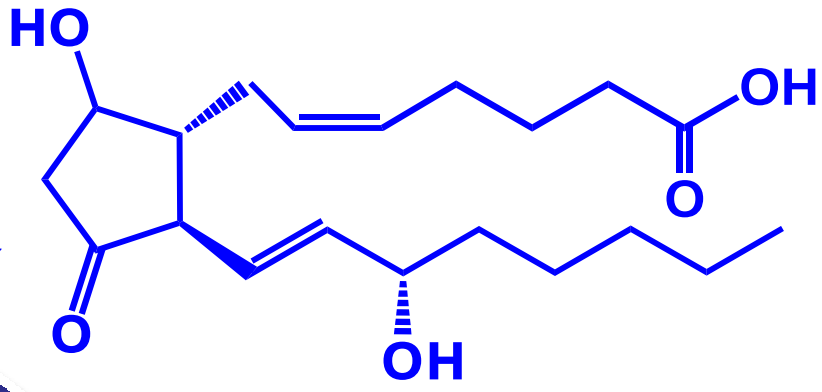




PGE2

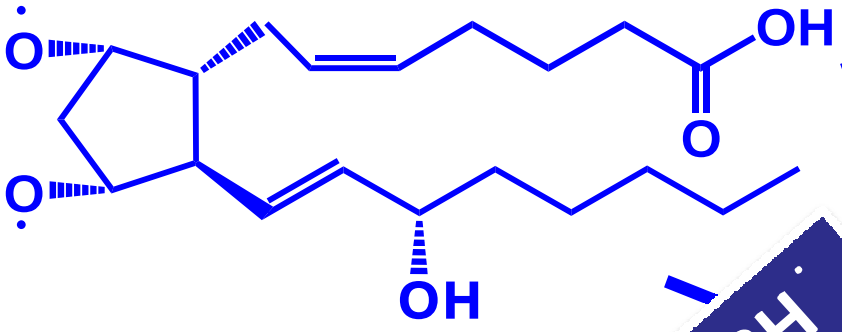
Radical cleavage of cyclic epoxide

+H·,- H·

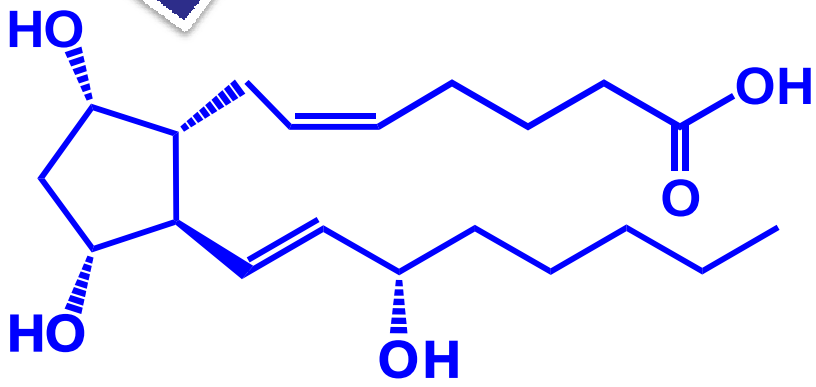


PGD2

+H·,- H·

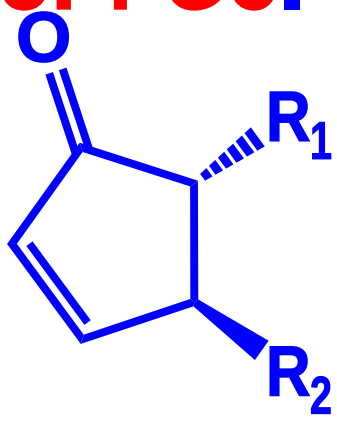


+2H·

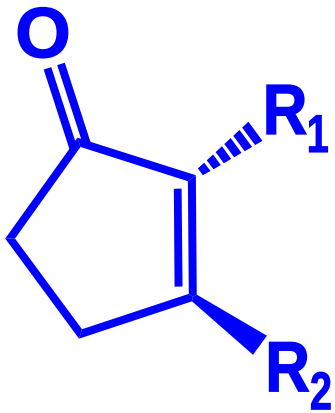


PGF2α

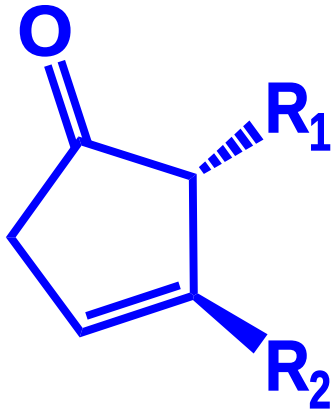
Prostaglandins are named in accordance with the format PGX, where X designates the functional groups of the five-membered ring. PGAs, PGBs, and PGCs all contain a carbonyl group and a double bond in the five-membered ring. The location of the double bond determines whether a prostaglandin is a PGA, PGB, or PGC.



PGA



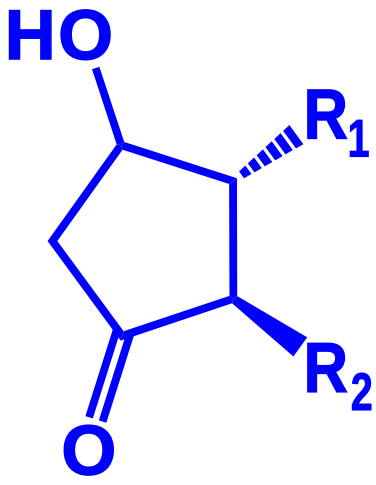
PGB



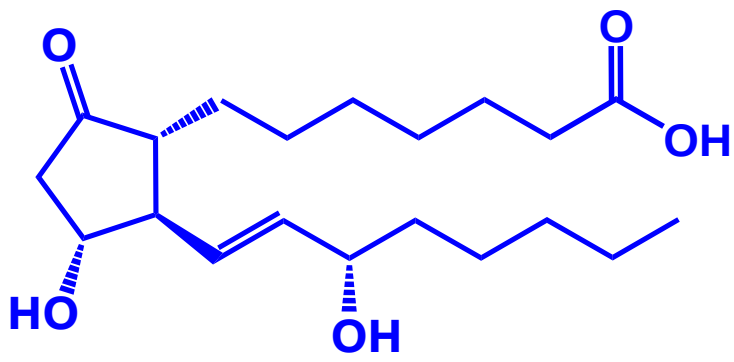
PGC

The letters following the abbreviation PG indicate the nature and location of the oxygen-containing substituents present in the cyclopentane ring.

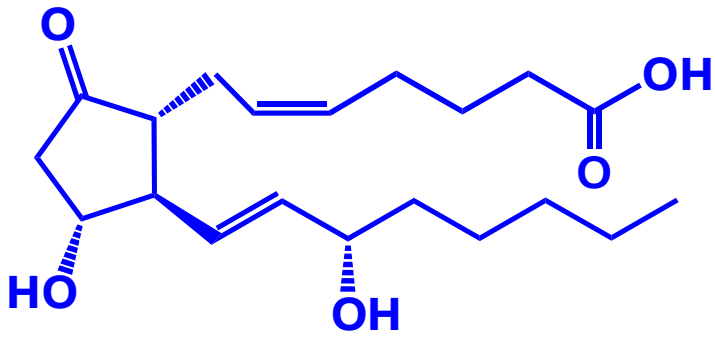
PGDs and PGEs are β-hydroxyketones, and PGFs are 1,3-diols. A subscript indicates the total number of double bonds in the side chains, and α and β indicate the configuration of the two OH groups in a PGF: "α" indicates a cis diol and "β" indicates a trans *diol.*



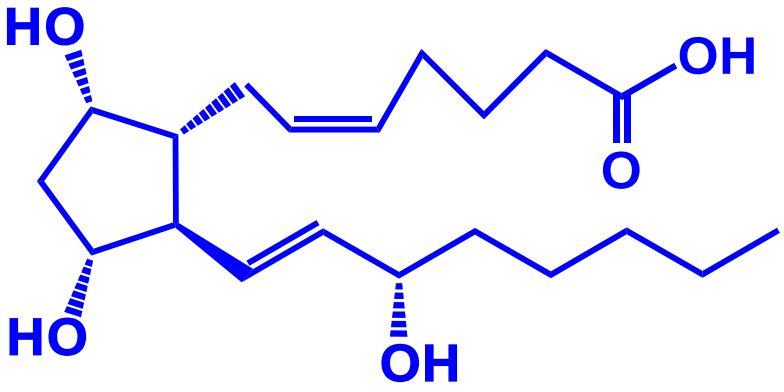
PGD



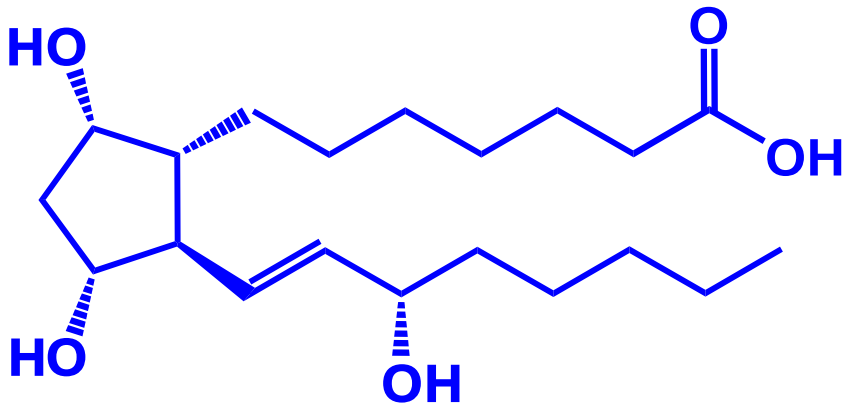
PGE_1



PGE_2



$PGF_{2\alpha}$



$PGF_{1\alpha}$