POLITECNICO DI MILANO

School of Industrial and Information Engineering

Course 096125 (095857)

Introduction to Green and Sustainable Chemistry





Secondary Metabolites from Plants

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Dipartimento CMIC “Giulio Natta”

https://iscamapweb.chem.polimi.it/citterio/education/course-topics/

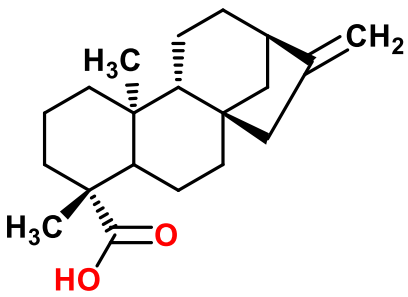
Biosynthesis and Biogenesis: Primary Metabolism.

- The sequence of enzymatic steps in the synthesis of a specific end product in a living organism is called Biosynthesis, whereas production or generation of living organisms from other living organisms is called Biogenesis. Organisms vary widely in their capacity to synthesize and transform chemicals.
- The pathways for general modifying and synthesizing carbohydrates, proteins, fats, and nucleic acids are found to be essentially the same in all organisms, apart from minor variations. These processes are collectively described as primary metabolism, with the compounds involved in the pathways being termed primary metabolites.
- **Primary metabolites** are compounds that are commonly produced by all plants and that are directly used in plant growth and development. The main primary metabolites are **carbohydrates, proteins, nucleic acids, and lipids**. The starting materials are CO_2, H_2O and NH_3. All organisms possess similar primary metabolic pathways and use similar primary metabolites.

Secondary Metabolism.

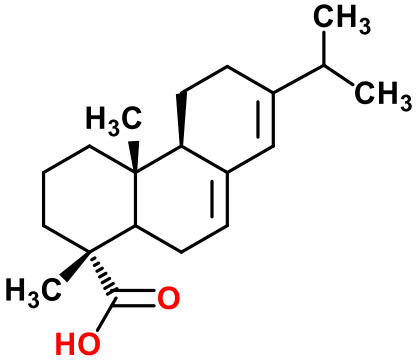
- The products of **secondary metabolism** are substances often present only in a few specialized/differentiated cell types, and are not necessary for the cells themselves, but they are useful to the body as a whole.

Primary metabolite

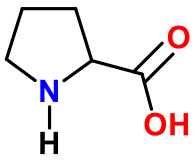


Kaurenoic acid

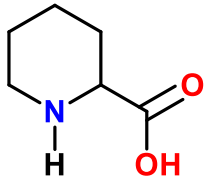
Secondary metabolite



Abietic acid



Proline

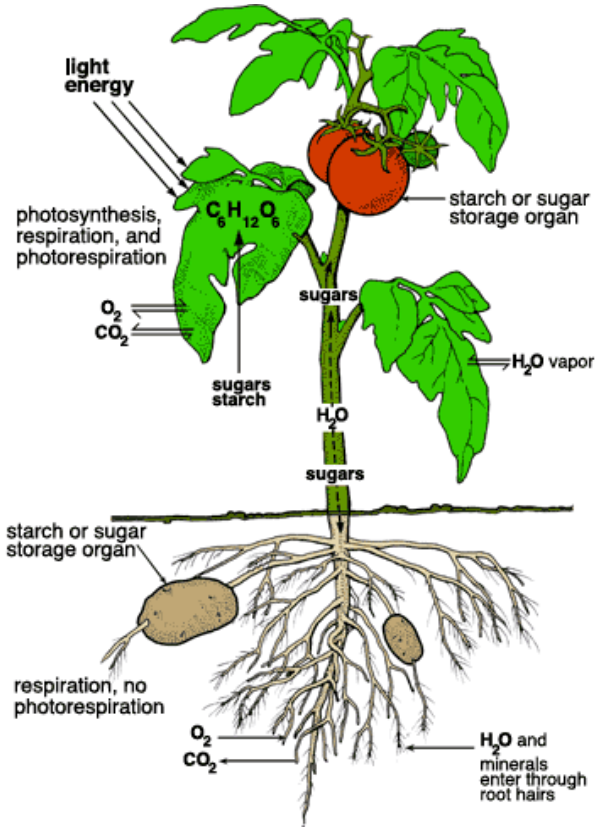


Pipecolic acid

The secondary metabolites are grouped into classes based on similar structures, biosynthetic pathways, or types of plants that produce them. The largest such classes are the terpenoids, phenolics, and alkaloids. Secondary compounds often occur in combination with one or more sugars. These combination molecules are known as glycosides. Usually the sugar is glucose, galactose or rhamnose.

Plant Secondary Metabolites.

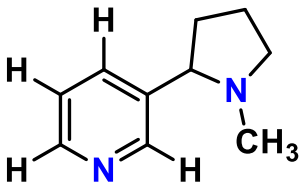
- Plants make a variety of less widely distributed compounds such as morphine, caffeine, nicotine, menthol, and rubber. These compounds are the products of secondary metabolism, which is the metabolism of chemicals that occurs irregularly or rarely among plants, and that have no known general metabolic role.
- In secondary metabolism, the biosynthetic steps, substrates and products are characteristic of families and species. Species which are taxonomically close display greater similarities; those which are distant have greater differences.
- Most plants have not been examined for secondary compounds and new compounds are discovered almost daily.



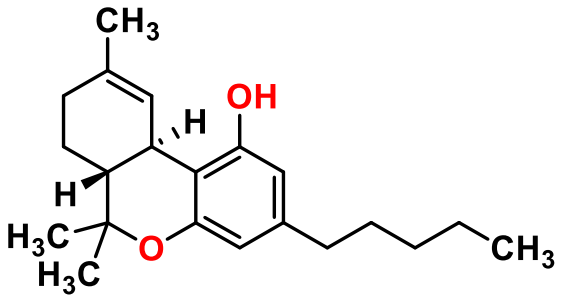
Photosynthesis, respiration, leaf water exchange, and translocation of sugar (photosynthate) in a plant.

Functions of Secondary Compounds in Plants.

- The most common roles for secondary compounds in plants are **ecological roles** that govern interactions between plants and other organisms.
- Many secondary compounds are brightly colored pigments like anthocyanin that color flowers red and blue. These attract pollinators and fruit and seed dispersers.
- Nicotine and other toxic compounds may protect the plant from herbivores and microbes.
- Other secondary compounds like rubber and tetrahydrocannabinol (THC) from cannabis plants have no well known function in plants.



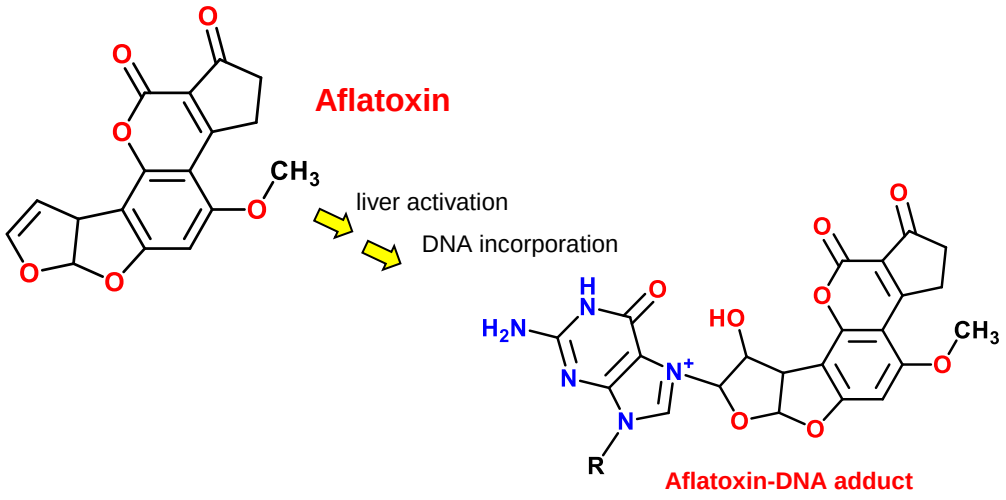
nicotine



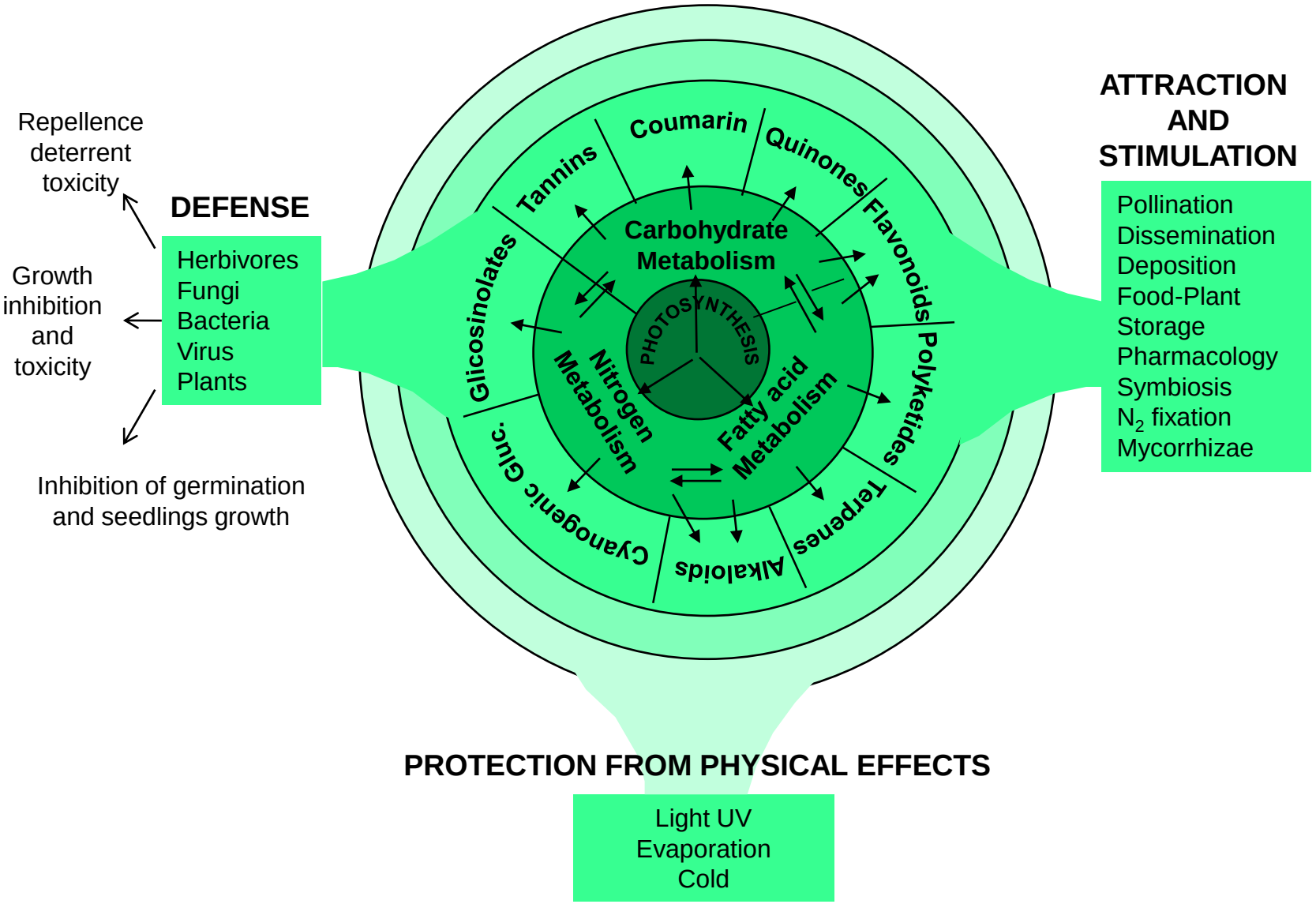
THC

Mycotoxin from Mold and Fungi.

- **Aflatoxin** is a naturally occurring mycotoxin produced by two types of mold: *Aspergillus flavus* and *A. parasiticus*, plus related species, *A. nomius* and *A. niger*. *A. flavus* is common and widespread in nature and is most often found when certain grains are grown under stressful conditions such as drought. At least 13 different types of aflatoxins are produced in nature with aflatoxin B1 considered as the most liver toxic. (cause cancer in animals!)
- Aflatoxins mainly occur in contaminated crops like corn, peanuts, and other seed. Occasionally can be found in milk, cheese and milk products through contaminated animal feed. Other nuts, figs and spices can be contaminated.



Functions of Secondary Metabolites in Plants.



Interest in Secondary Metabolites.

- Aroma substances
- Dyes
- Pharmacological and nutraceutical substances

BIODIVERSITY

More than 275,000 known species of angiosperms

> 100000 known compounds.

UN Conference on Environment
in Rio de Janeiro, 1992

↓

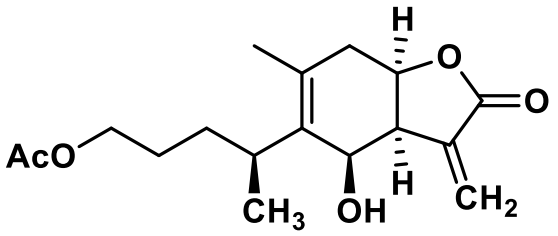
Convention on Biological Diversity

Sustainable use of components of biological diversity in ways and at times that do not lead to the depletion of biodiversity.

PROTECTION.

- **Plant strategies:**
  - Induction of defense molecules in response to attack by herbivores or pathogens (**phytoalexins**)
  - Pro-toxins harmless activated by an enzyme triggered as a result of an attack
  - Buildup of constitutive defense products
  - Production of food substances deterrents (tannins; toxic subst.)
  - Production of substances that mimic animal hormones (plant sterols produced by mimicking the hormone of the set)
  - Production of compounds that attract predators of the herbivores.

Inula britannica,

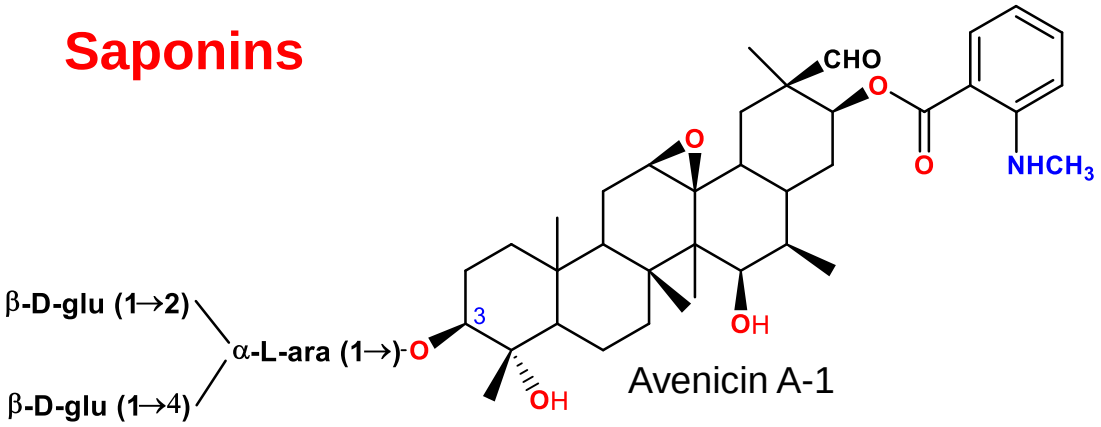


1-O-acetylbritannilactone

antifungal and anti-cancer activities

Examples of Defense Metabolites.

Saponins



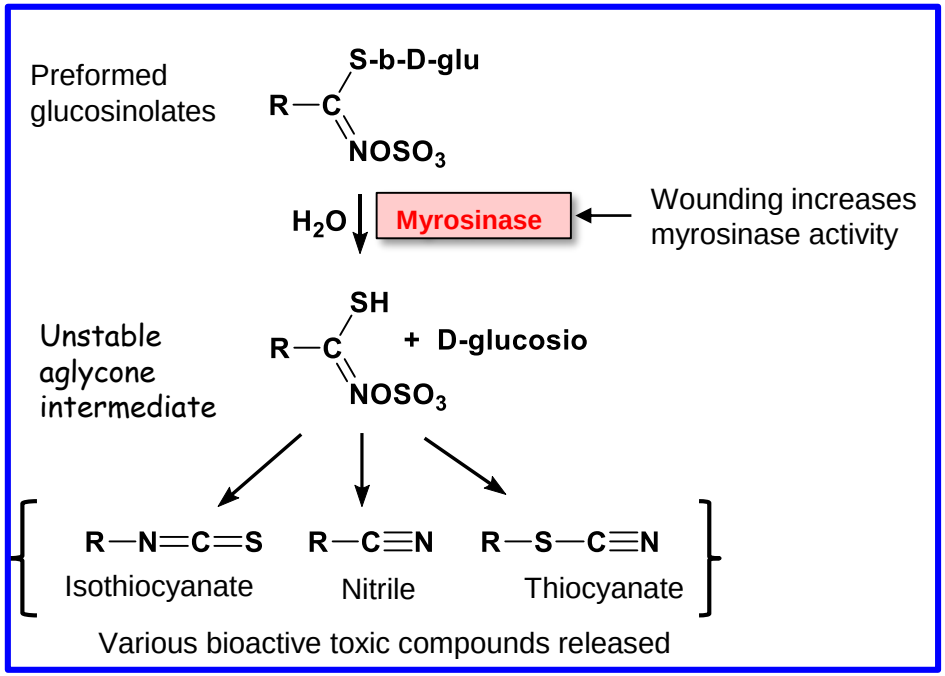
Avenicin A-1

Produced in rots of oat (defense from fungi).

Glucosinolates breakdown products:

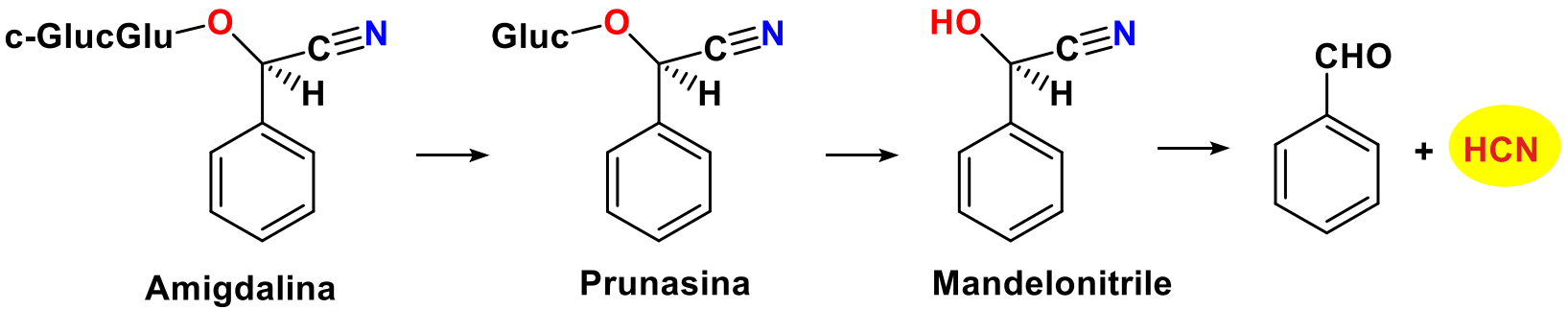
1-isothiocyanates
2-nitriles and elemental sulphur
3-thiocyanates
4-oxazolidine—thiones
5-epithionitriles

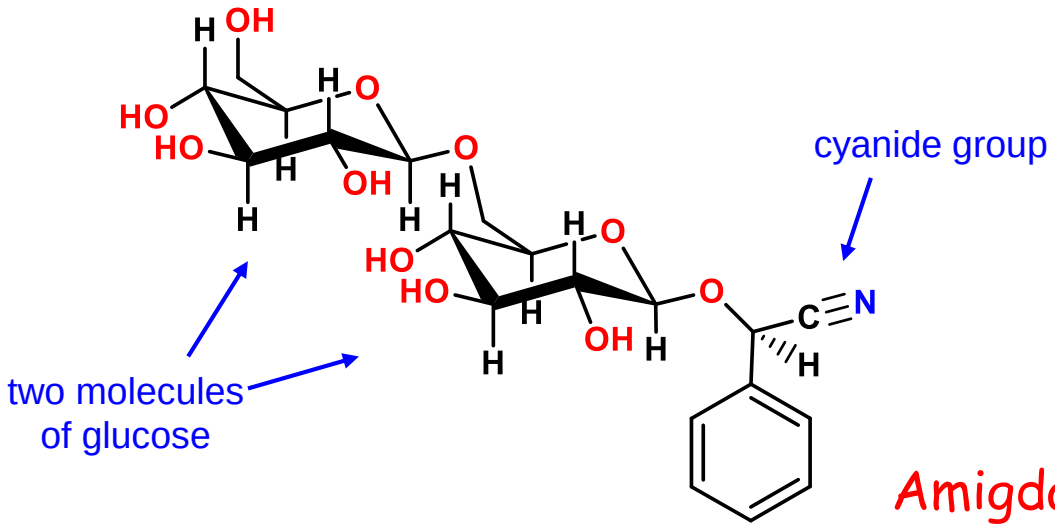
Glucosinolates



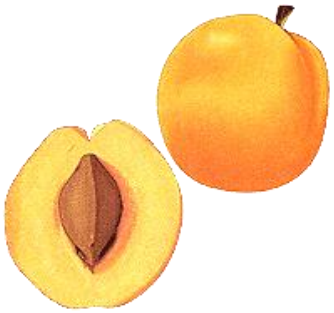
Grubb and Abel, TIPS, 2006

Examples of Defense Metabolites: Cyanogenic Glycosides.





Amigdaline



Plant – Plant.

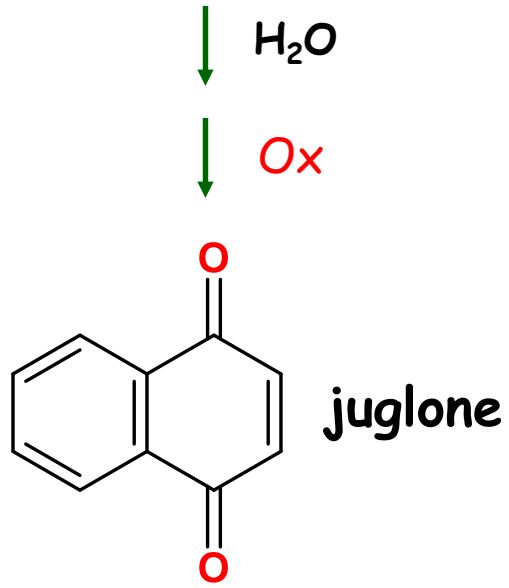
ALLELOPATHY

mutual influence between plants through the secretion of specific substances.

Tomato plants evidence diseases and die if grown up near a walnut tree (*Juglans Nigra*).
The toxicity area is defined by the tree canopy size.

➡ a glycosylated molecule that, when hydrolyzed and oxidized, in soil becomes a potent toxin.

Pro-toxin:
1,4-dihydroxy-2-naphthoate glycoside

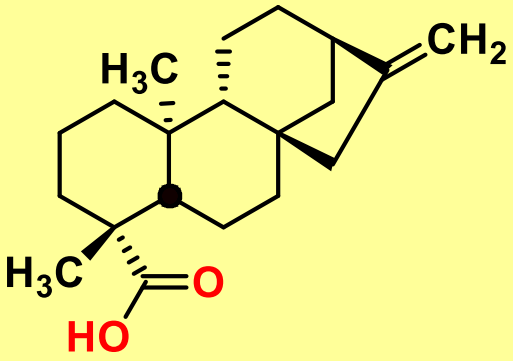


Primary-Secondary Metabolites Boundary??

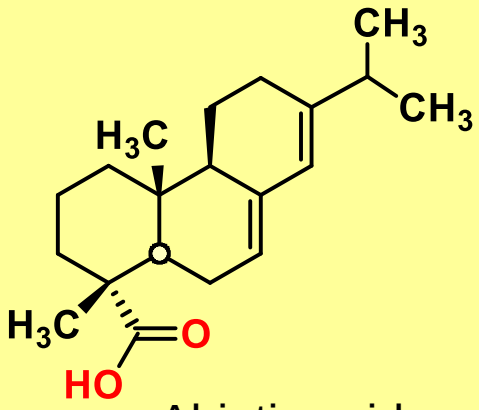
Primary metabolite

Secondary metabolite

Gibberellin biosynthesis



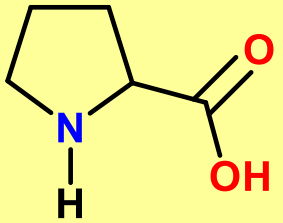
Kaurenoic acid



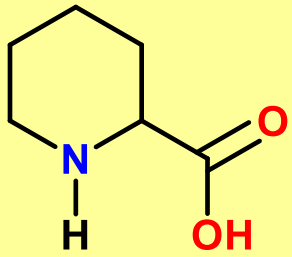
Abietic acid

Resin component

Essential amino acid



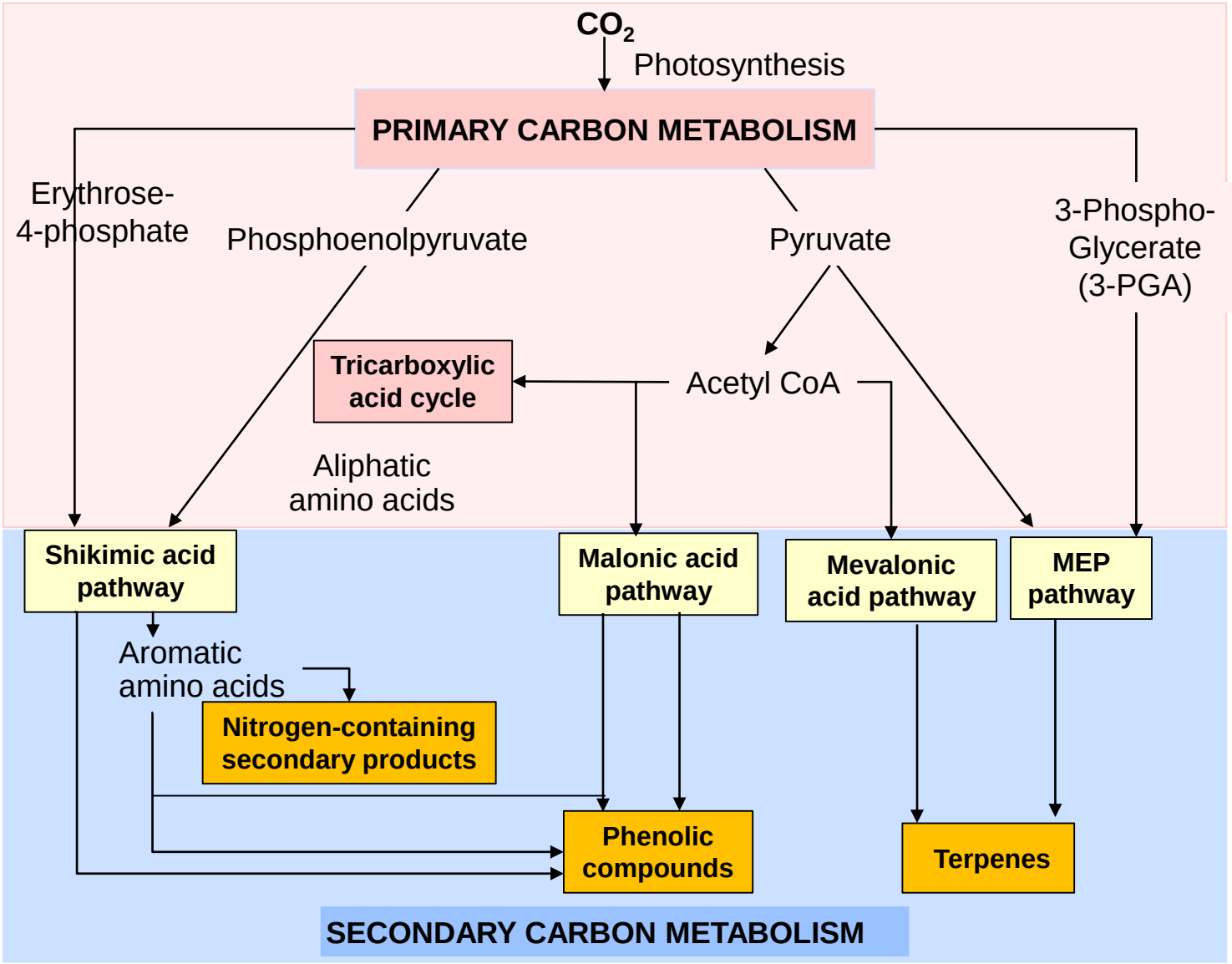
Proline



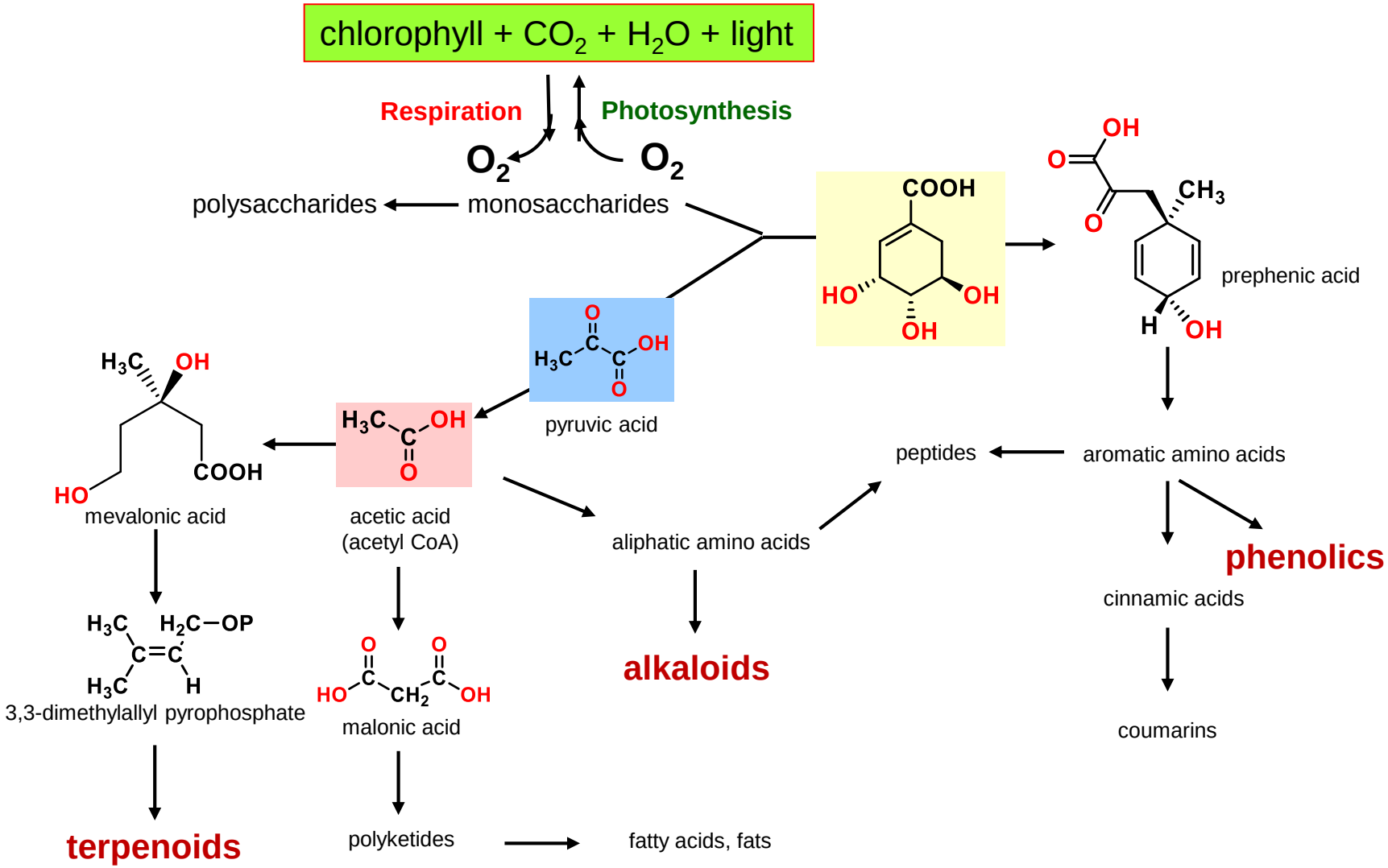
Pipecolic acid

Alkaloid

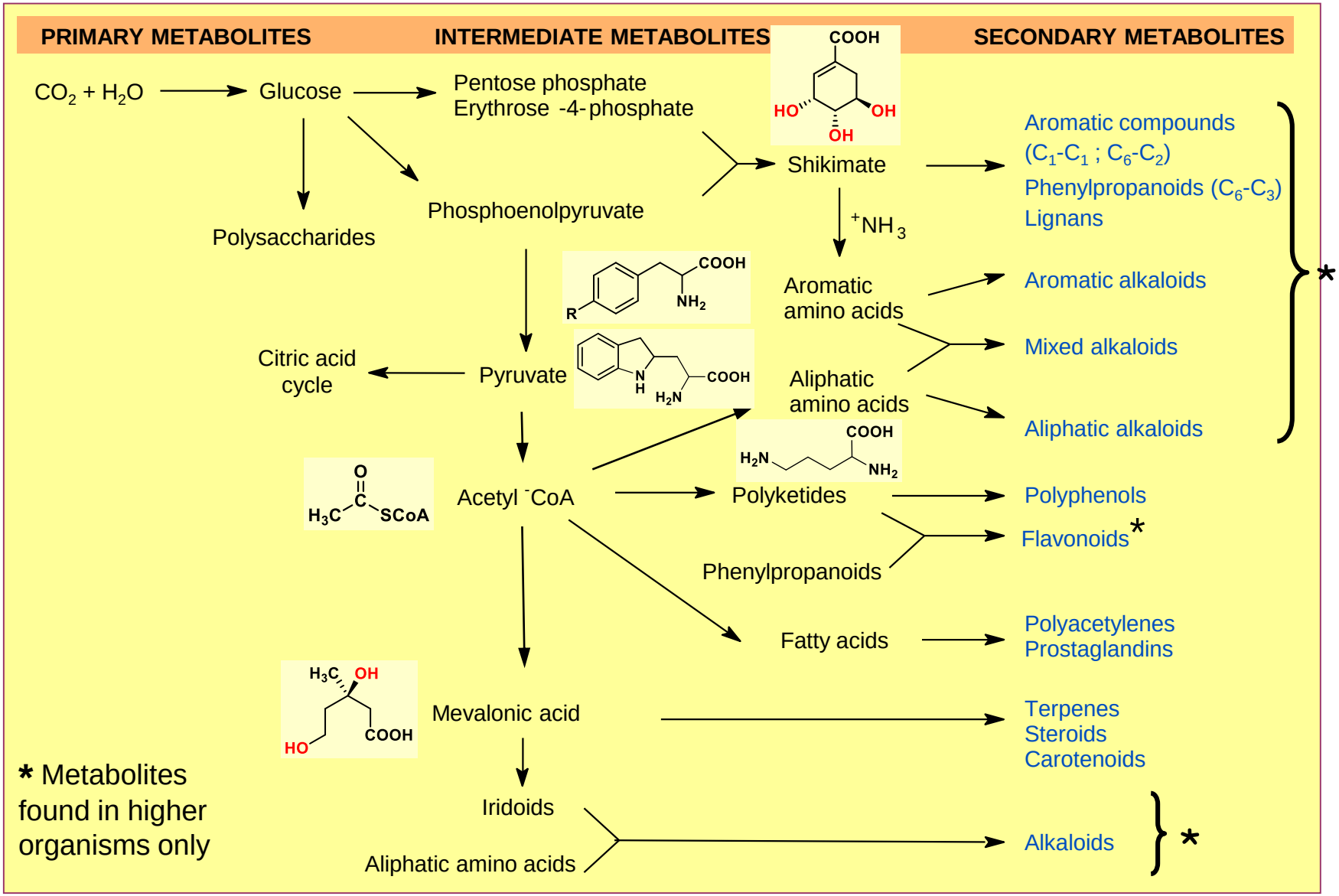
General View of Plant Metabolism.



Main Pathways to Secondary Metabolites.



Overview of Secondary Metabolism.



Secondary Metabolites - Three Main Groups:

- Terpenes
- Phenolic Compounds
- Alkaloids

They are synthesized from primary metabolites.

Main Secondary Metabolites (SM).

Nitrogen containing:

- Alkaloids (20,000)
- Non protein amino acids (600)
- Amines (100)
- Cyanogenic glycosides (100)
- Glucosinolates (100)

Main Secondary Metabolites (SM) (2).

Without nitrogen:

- Terpenoids (29,000):

  Mono-1000

  Sesquiterpene-3000

  Diterpenes-1000

  Triterpenes, steroids, saponines-4,000

- Phenolics (8,000):

  Flavonoids-2000

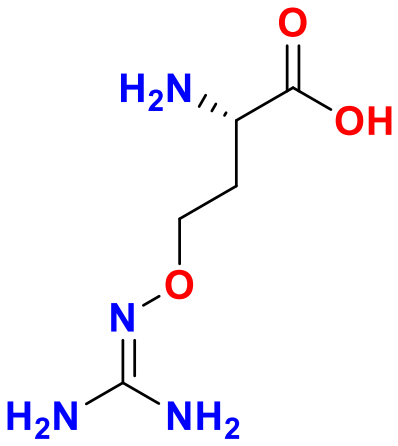
  Polyacetylens-1000

  Polyketides-750

  Phenylpropanoids-500

Co-evolution in Plant SMs - Natural Enemy.

Plant defence	Plant taxon	Natural enemy	Counter resistant
Toxic amino acids	Various Leguminosae	Bruchid weevil (tonchio)	Modified tRNA synthase



Dioclea seed

L-canavanine
(similar to arginine, no protein amino acid)

Curculionide (Weevil)

Co-evolution in Plant SMs - Natural Enemy (2).

- Canavanine is toxic due to its incorporation into proteins that rise to functionally aberrant polypeptides
- The tRNA-Arginine in insects uses also Canavanine
- The insect mutated its tRNA and will not incorporate Canavanine instead of Arginine

Adaptations of specialist herbivores & pathogens:

The process of co-evolution between plants and their natural enemies is believed to have generated much of the earth's biological diversity.

This includes chemical diversity!!

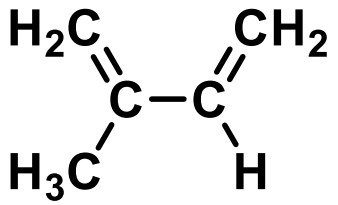
TERPENES.

- 30.000 known compounds.

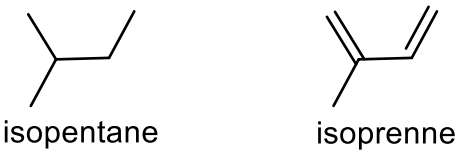
Wallach (1910) Isoprene rule

Terpenes can be hypothetically build from repetitive 5-units of isoprene molecules

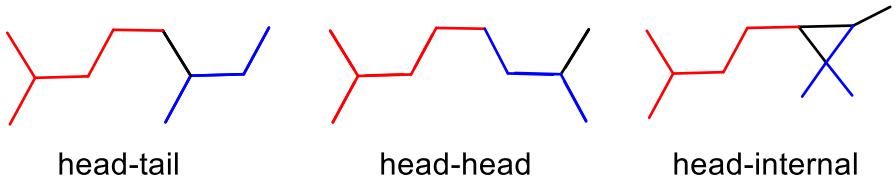
C_5 Unit



Isoprene C_5H_8

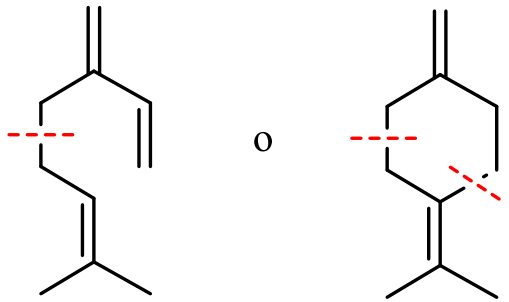


Firstly isolated from turpentine [the distillate from tree (e.g. pine) resins]



Recognition of Isoprene Unit in Terpenes.

- Recognition of the isoprene unit as a component of the structure of terpenes has been a great aid in elucidating their structures
- Many terpenes also have isoprene units linked in rings, and others (terpenoids) contain oxygen.



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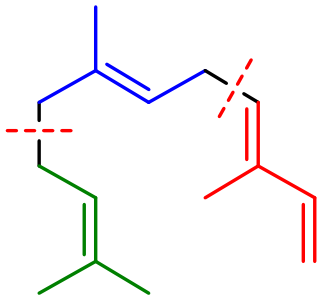
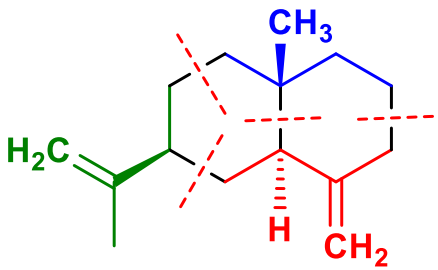
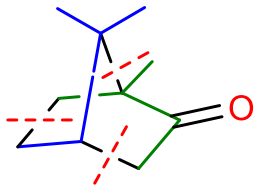
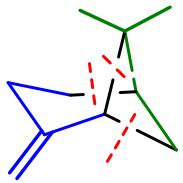




α-Selinene



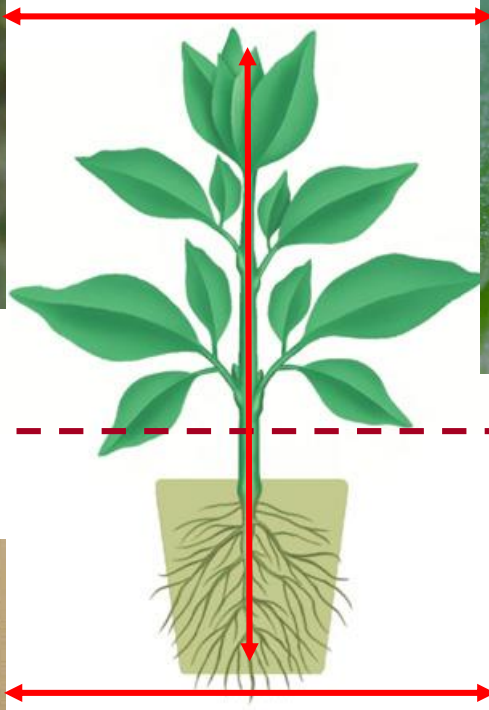


The Terpenoids of Plant Origin.

Biological Role (volatile and non volatile):

- Flavour, fragrance, scent
- Antibiotics
- Hormones
- Membrane lipids
- Insect attractants
- Insect antifeedants
- Mediate the electron transport processes (in respiration and photosynthesis)

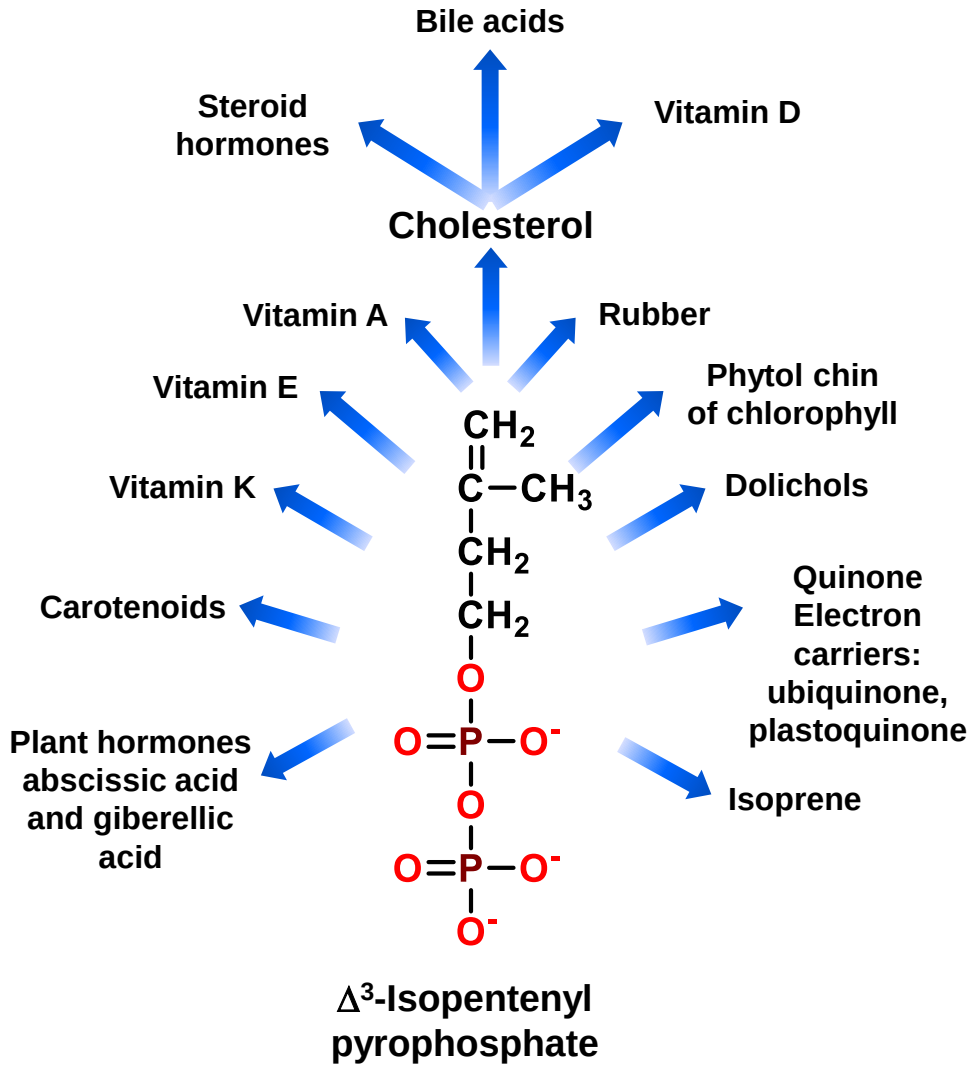
Terpenoids and Communication.



Key Intermediate: Isopentenylpyrophosphate.

Over 40,000 compounds derived from isopentenyl pyrophosphate (IPP) have been characterized.*

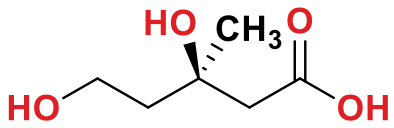
In mammals, these include: cholesterol, bile acids, steroid hormones, dolichol, coenzyme Q, and prenylated proteins. In plants, the isoprenoid pathway generates a wide variety of compounds including rubber, isoprene gas, carotenoids and some vitamins.



*Sacchettini, James C.; Poulter, C. Dale 1997 Creating Isoprenoid Diversity. Science 277(5333) 1788-1789
Peñuelas J, Munné-Bosch S 2005 Isoprenoids: an evolutionary pool for photoprotection. Trends Plant Sci. Apr;10(4):166-9..

Mevalonic Acid as Source of IPP.

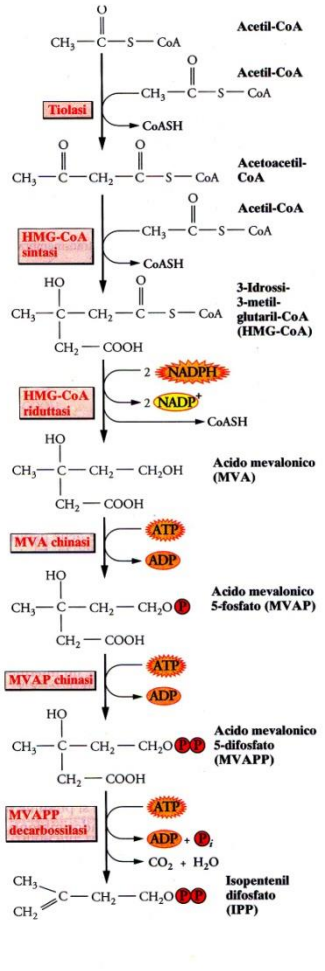
The biological precursor of all terpenes is the isopentenyl diphosphate (IPP) synthesized or from MEVALONIC ACID (cytosol ER) or from glyceraldehyde phosphate / pyruvate (plastids)



mevalonic acid

3,5-dihydroxy-3-methylpentanoic acid

mevalonic acid route



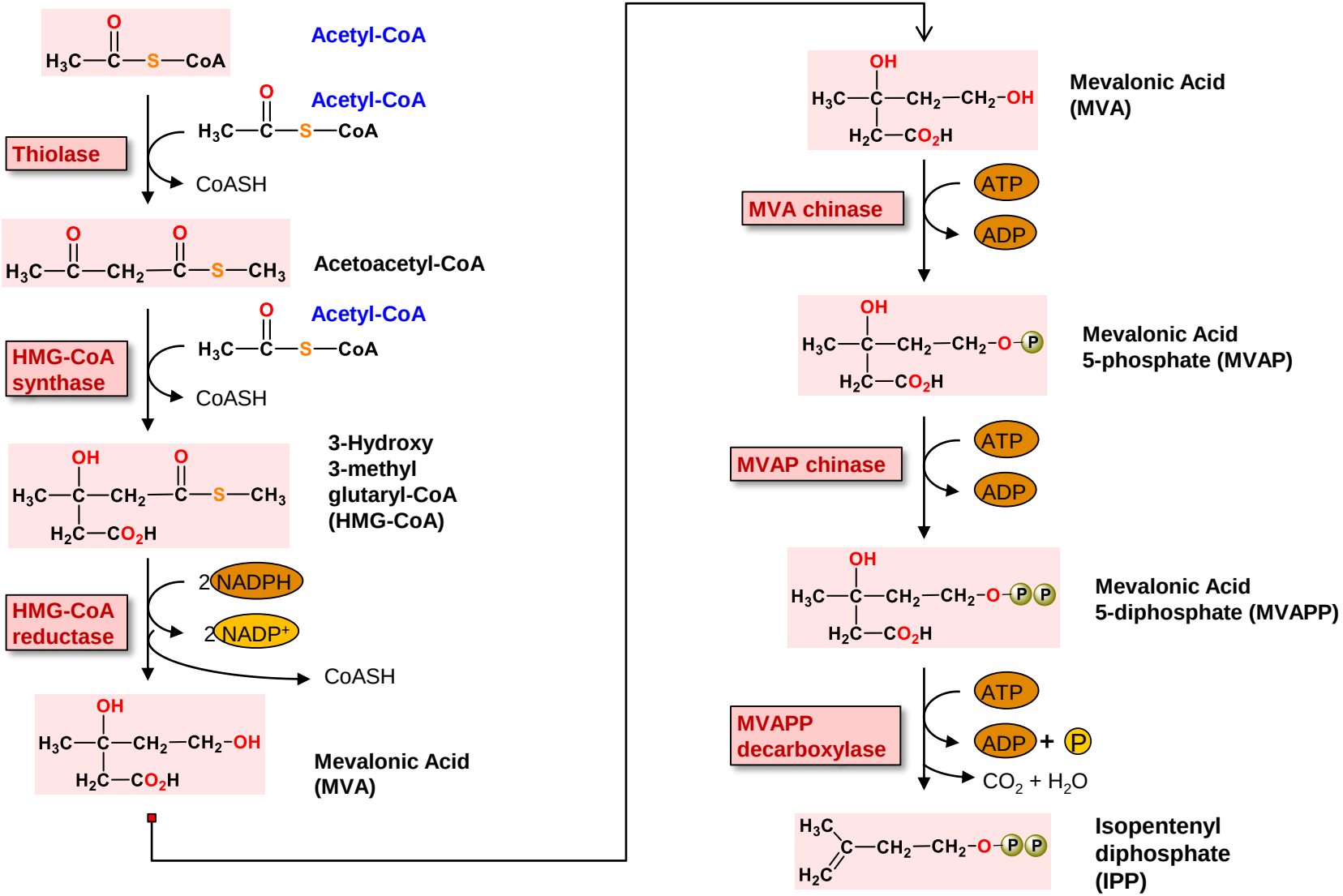
3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR)

HMG-CoA REDUCTASE

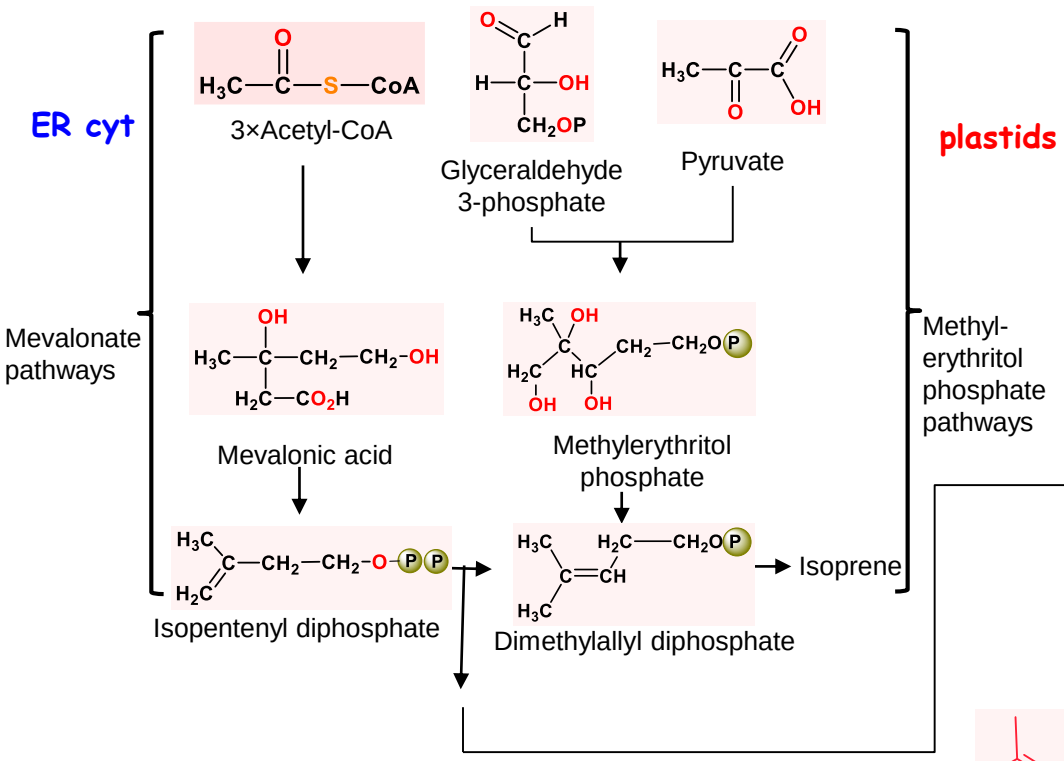
IN ANIMALS RULES THE CHOLESTEROL BIOSYNTHESIS

IN PLANTS IS INDUCIBLE BY PATHOGENS

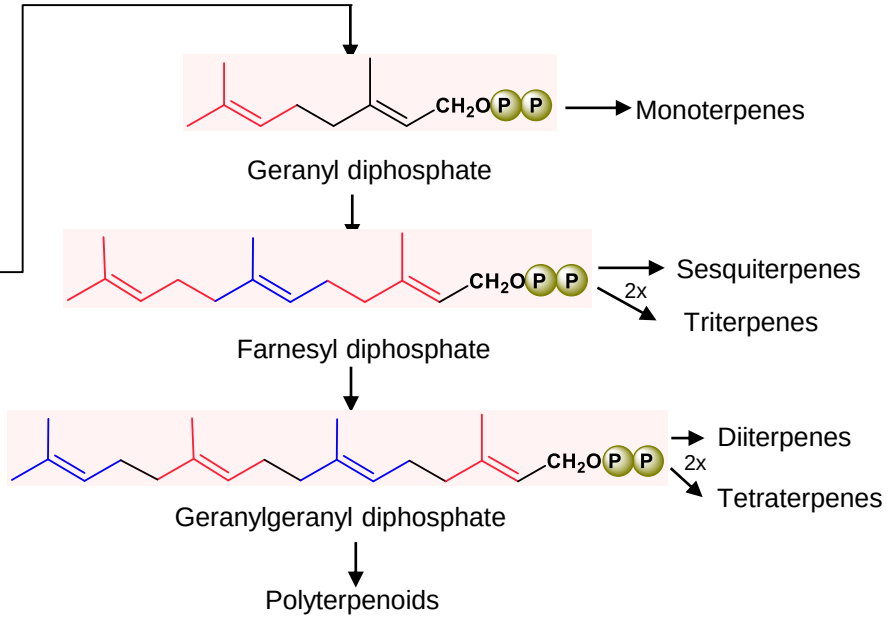
Pyruvic Acid as Source of IPP.



Biosynthetic Pathways to Terpenes.

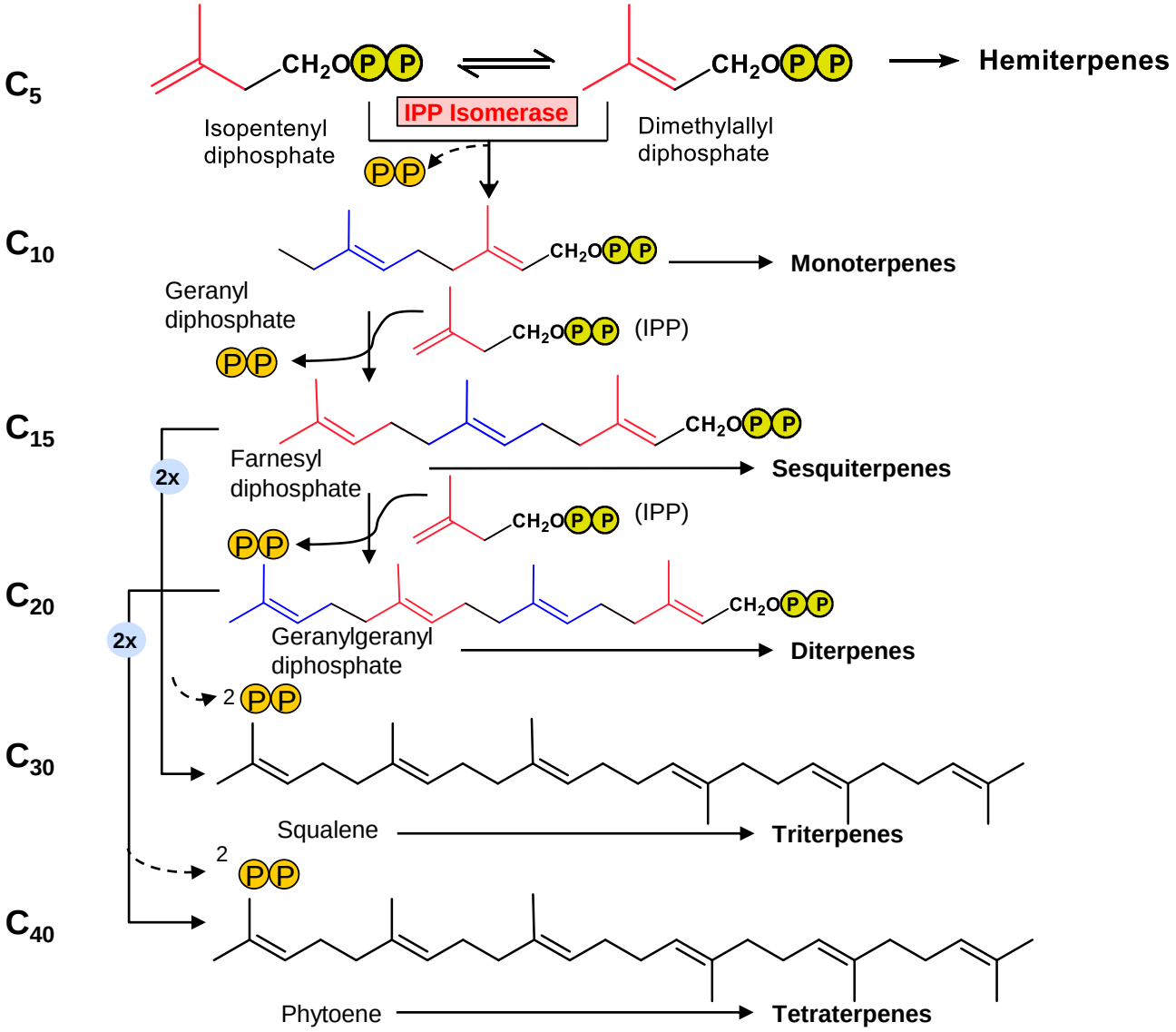


PRENYL TRANSFERASE: determine the chain extension: produce geranyl pyrophosphate (GPP; C10), farnesyl pyrophosphate (FPP; C15), geranylgeranyl pyrophosphate (GGPP; C20)



TERPENE SYNTHASES: modify the products of prenyl transferase (cyclizations) producing a great variety of terpenes. (monoterpene synthase, sesquiterpene synthase, diterpene synthase)

Terpene Synthesis from IPP Basic Unit.



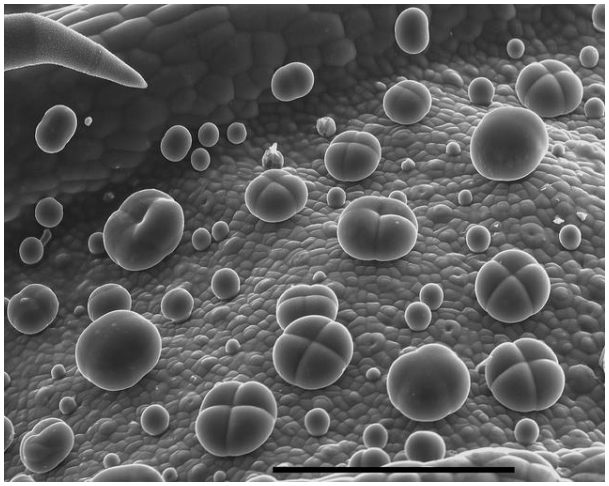
Sites of Production of Terpenes.

Monoterpenes C_{10}
Diterpenes C_{20}
Tetraterpenes C_{40}

plastids

Sesquiterpenes C_{15}
Triterpenes C_{30}

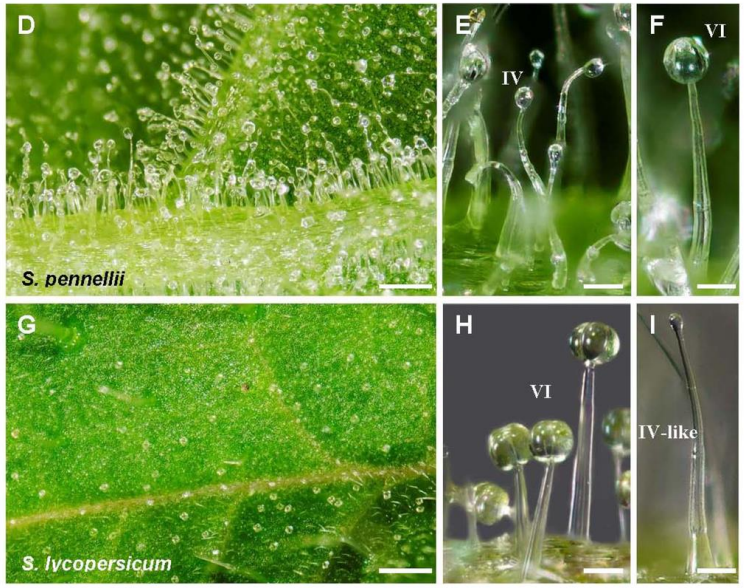
cytosol
ER



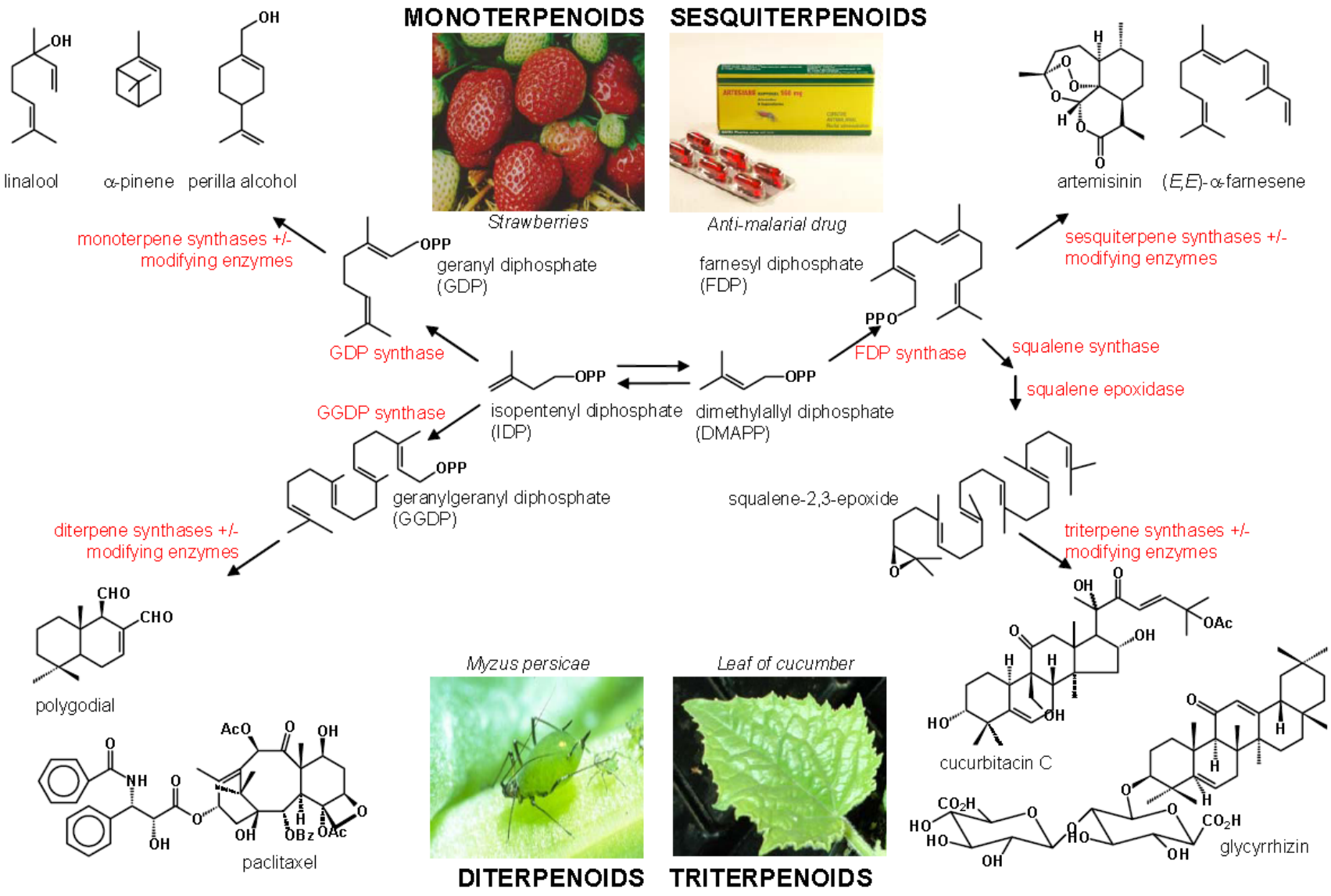
Glandular trichomes

present on the leaf surface, they accumulate and secrete terpenes

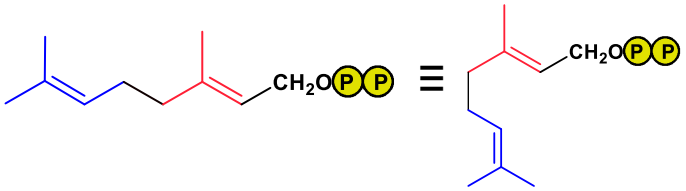
(mint, thyme, lemon)



Common Precursor of Terpenoids.



MONOTERPENES C10.



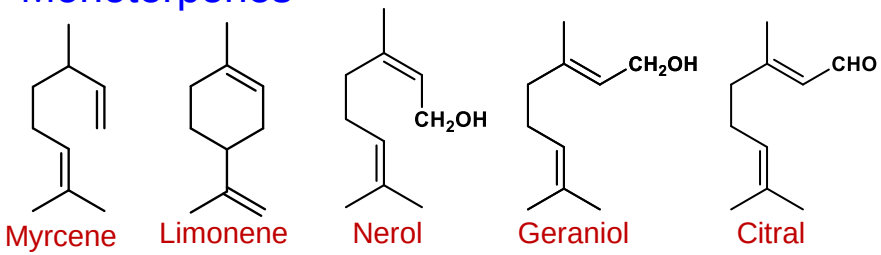
DMAPP + IPP ⟶ GPP

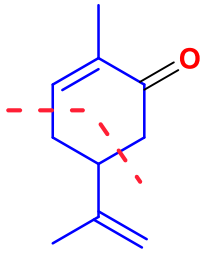
Geranyl-PP

VOLATILE SUBSTANCES

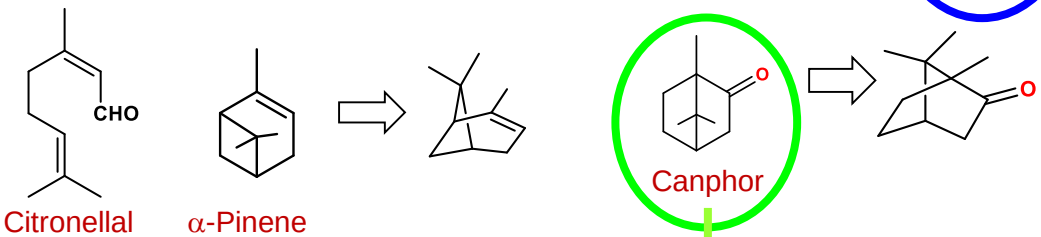
- **pollinator attraction**
- **insect repellent**

Monoterpenes





(R)-Carvone; Spearmint aroma



Peppermint aroma

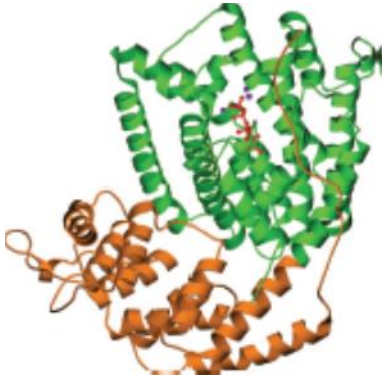
deterrent food for herbivores - allelopathy

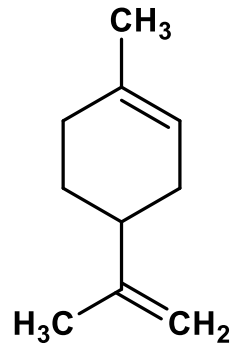
Source: Taiz L., Zeiger E. (2010): Plant Physiology. p. 373.

MONOTERPENE SYNTHASE.

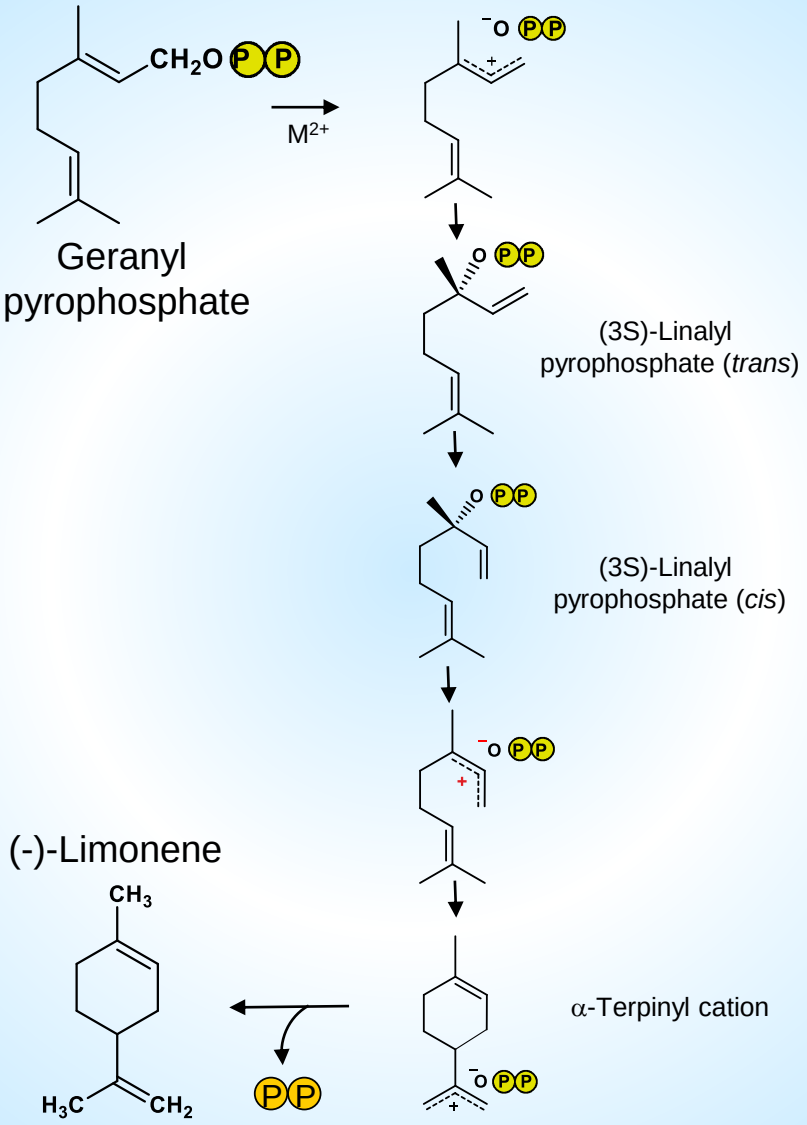
- LIMONENE SYNTHASE

Catalyzes the simplest of cyclization reactions of terpenoids and serves as model for this type of reactions.



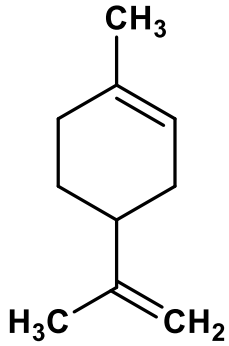


Limonene

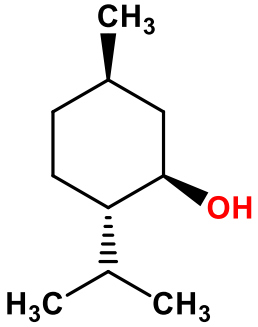


Pinenes.

Pinenes are among the most common monoterpenes and are the main components of turpentine produced from pine and fir trees: they are toxic to fungi and insects



Limonene



Menthol

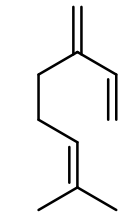
Attack of beetles
to the stem of a pine

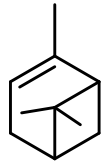
Monoterpenes.

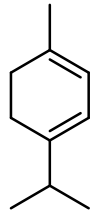
Insecticides: pinenes piretrins

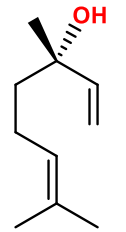
Attraction of pollinators: Linalool, cineole

Leaves deterrents: camphor, cineole

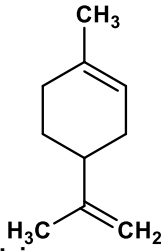

Myrcene


α-Pinene

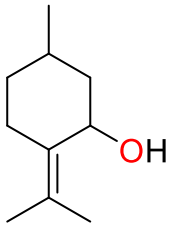

Terpinene



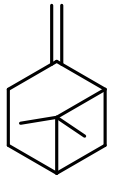
Linalool

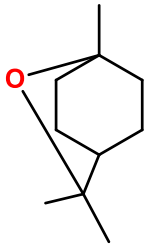


Limonene

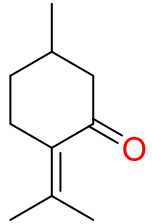


Mentol

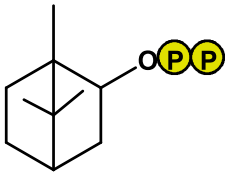

β-Pinene



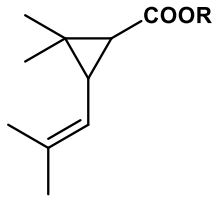
1,8-Cineole



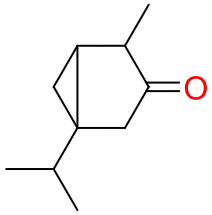
Mentone



Bornyl diphosphate

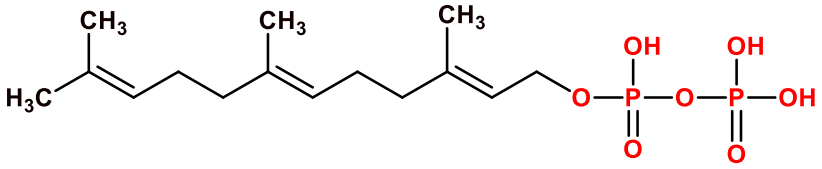


Pyrethrin I



Thujone

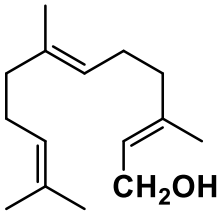
SESQUITERPENES C15.



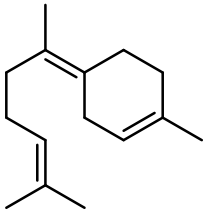
Farnesyl-pyrophosphate

GPP + IPP ⟶ FPP
Farnesyl-PP

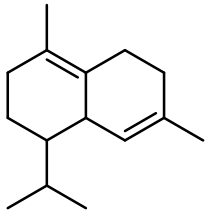
Sesquiterpenes



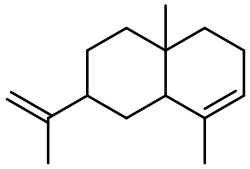
Farnesol



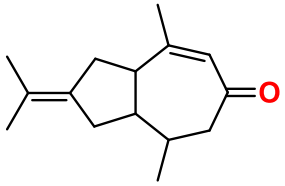
Bisabolene



Cadinene

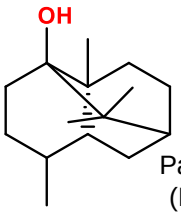


Selinene

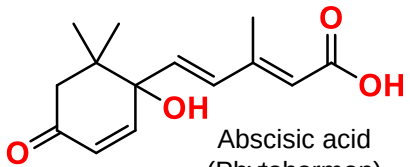


Vetivone

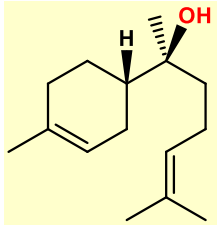
used as anti-inflammatory



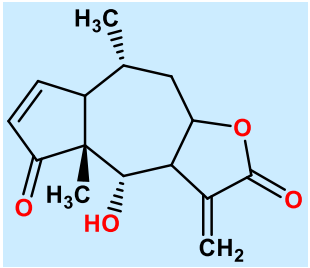
Patchoulol
(Partum)



Abscisic acid
(Phytohormon)



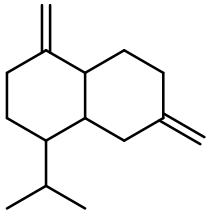
(-)-α-Bisabolol



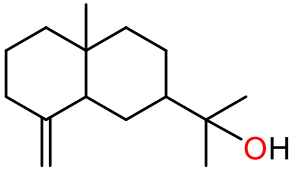
sesquiterpene lactones (chicory, artichoke, endive, etc.)
deterrents food (bitter taste) used to flavor bitters.

→ Helenalin from ARNICA

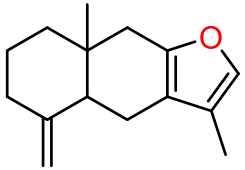
Other Representative Sesquiterpenes



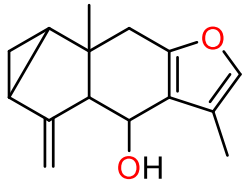
Bulgarene



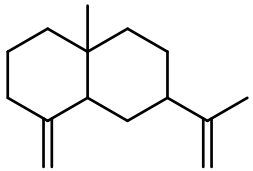
Eudesmol



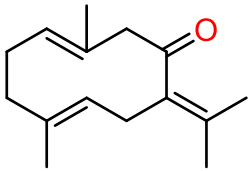
Atractylone



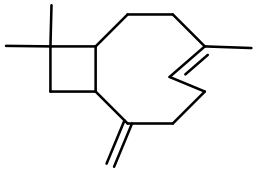
Linderene



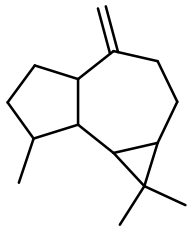
β-Salinene



Germacrone

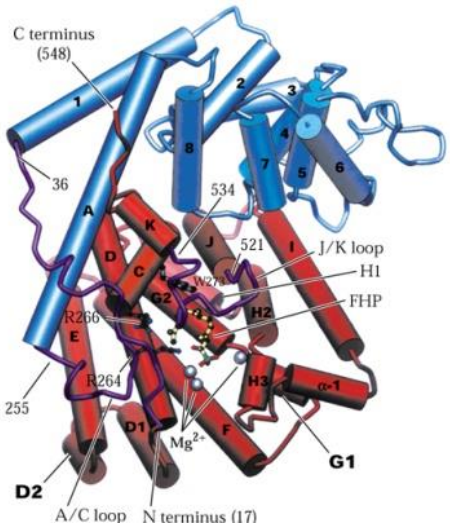


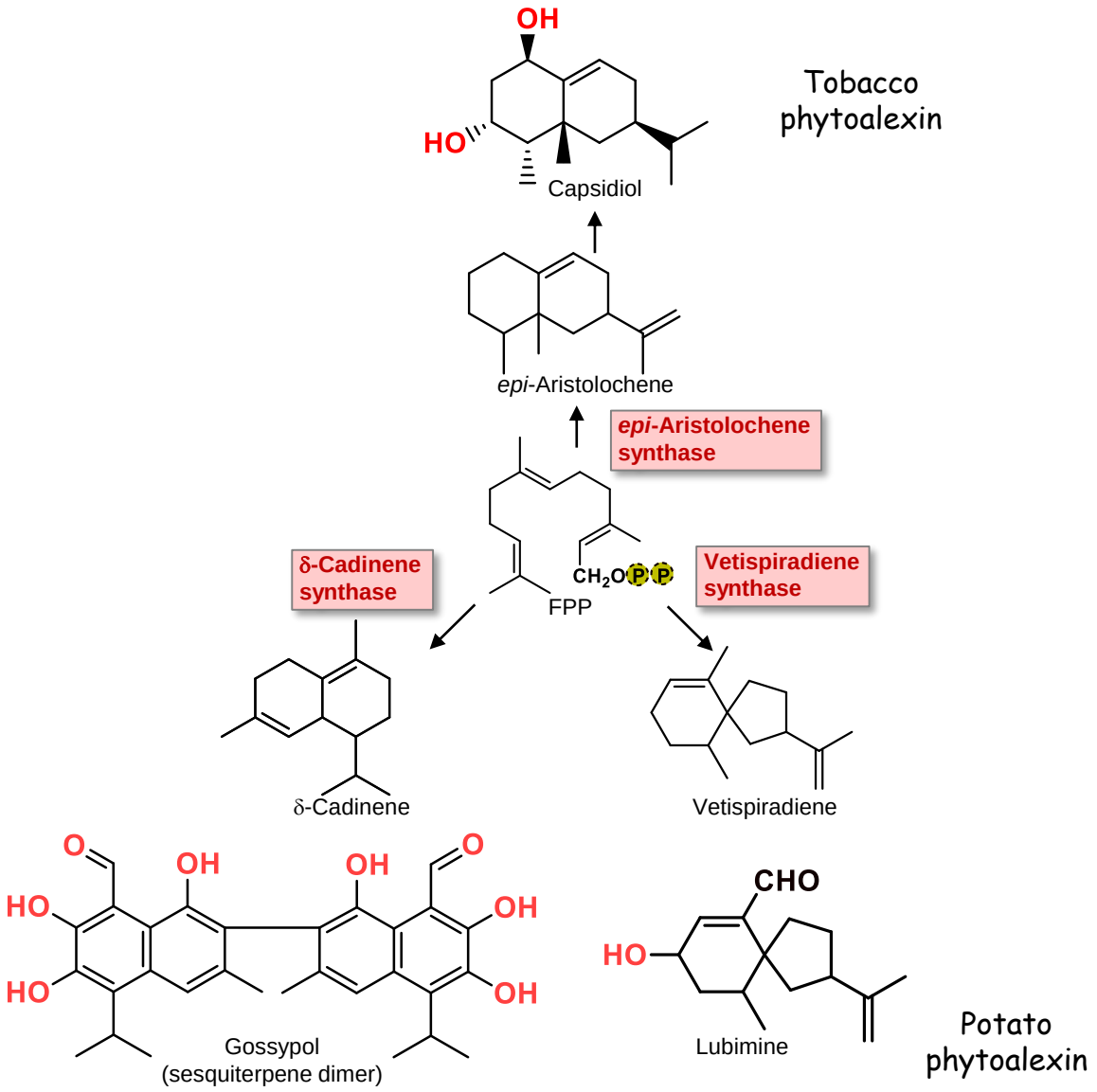
Caryophyllene



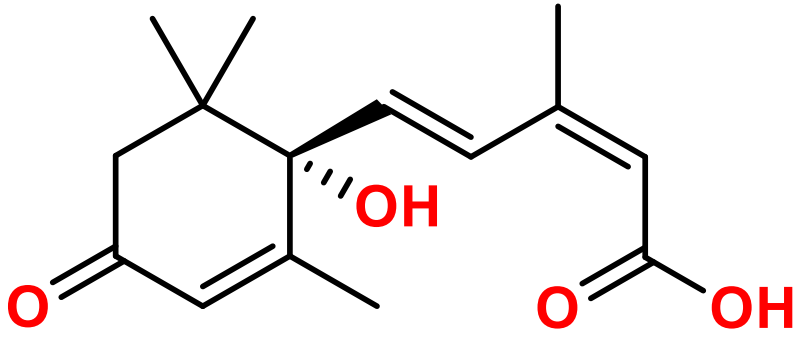
Aromadendrene

Sesquiterpene Synthases Produce Several Phytoalexins.

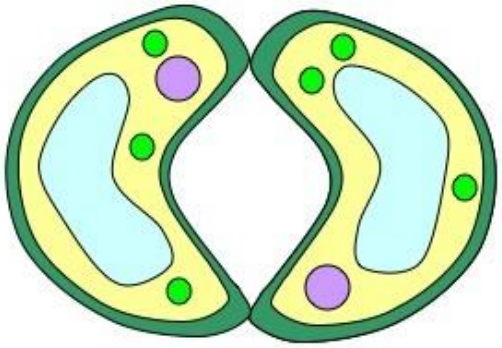




Abscisic Acid.

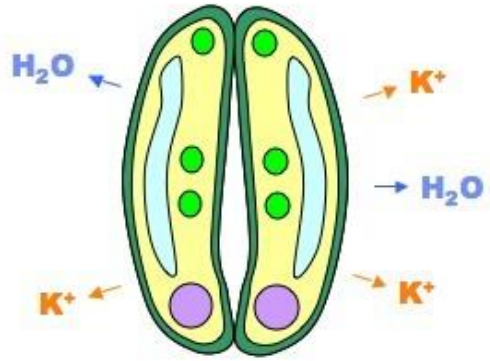


Cells turgid / Stoma open



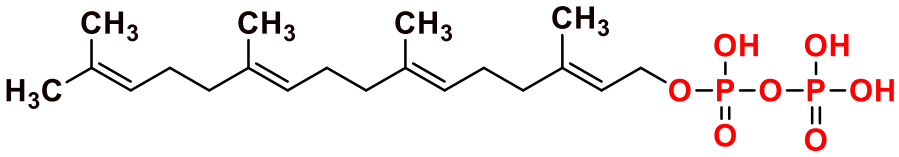
ABA
(Abscisic acid)

Cells flaccid / Stoma closed



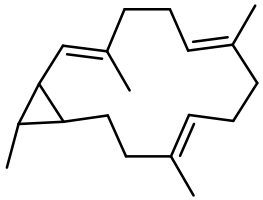
ABA is the major player in mediating the adaptation of the plant to stress

DITERPENES C20.

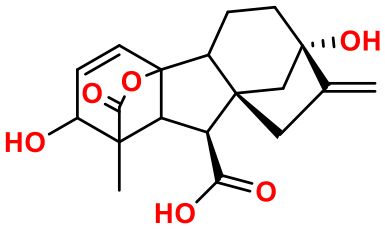


FPP + IPP ⟶ GGPP
Geranylgeranyl-PP

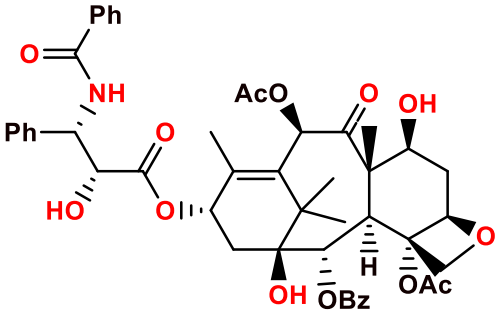
Diterpenes



Casbene
(Phytoalexin)

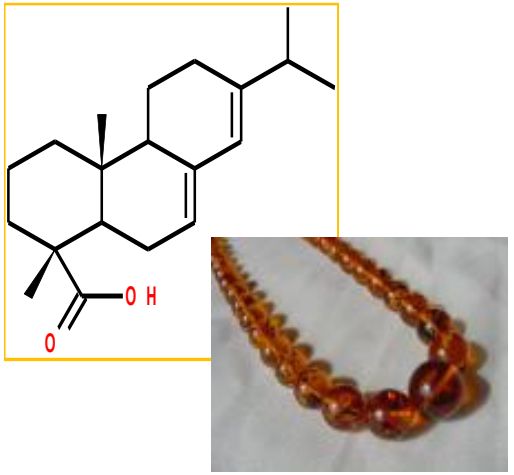


Giberellic acid
(Phytoalexin)



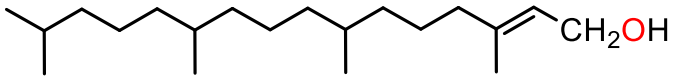
Taxol (anti-cancer)

Abietic acid (amber)

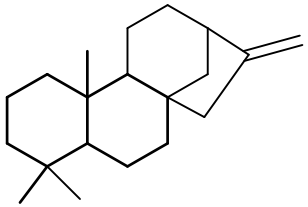


This acid is used as a component of adhesives for food packaging, transporting or holding food.

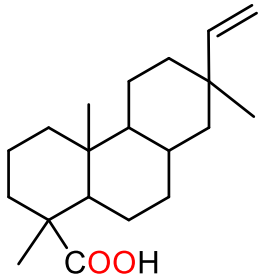
Other Representative Diterpenes



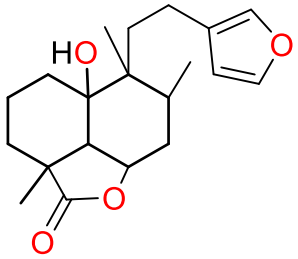
Phytol



Kaurene



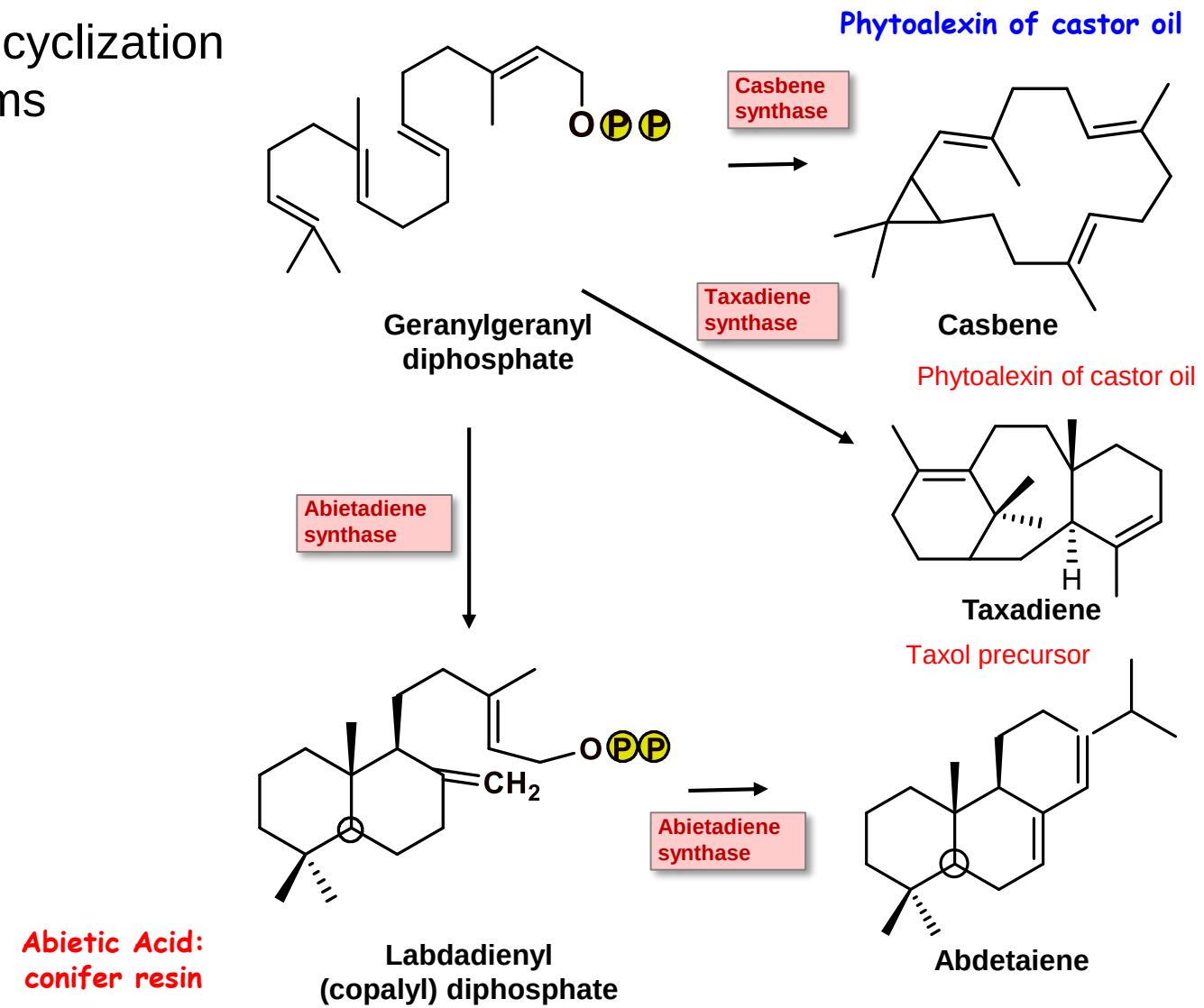
Pimeric acid



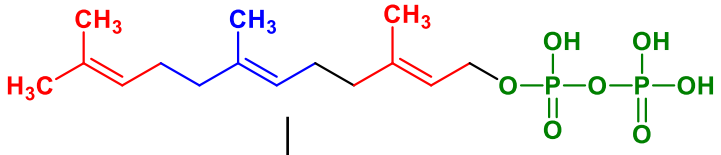
Marrubin

Diterpene Synthases.

- 2 different cyclization mechanisms

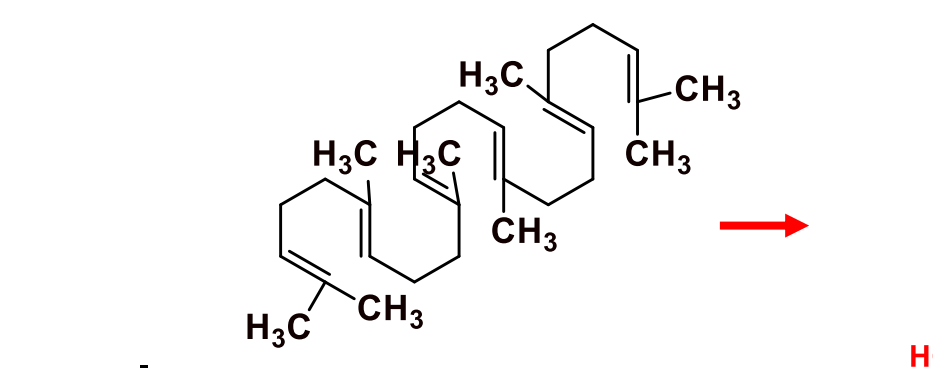


TRITERTERPENES C30.

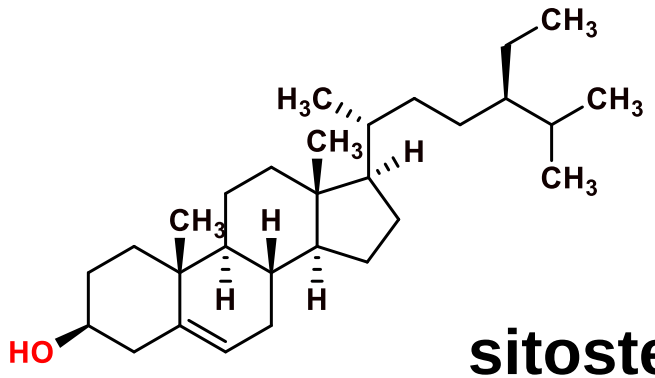


FPP + FPP ⟶ SQUALENE

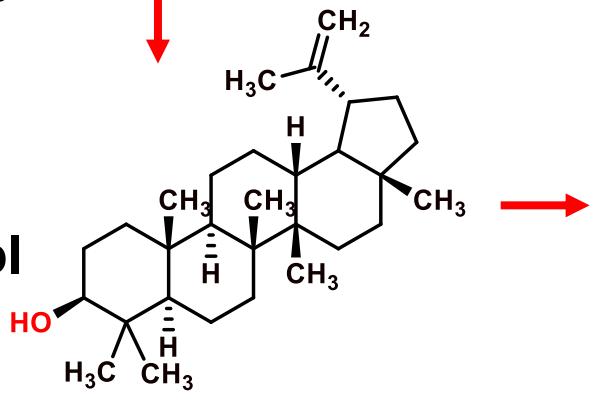
Head to head linkage



squalene



sitosterol



lupeol

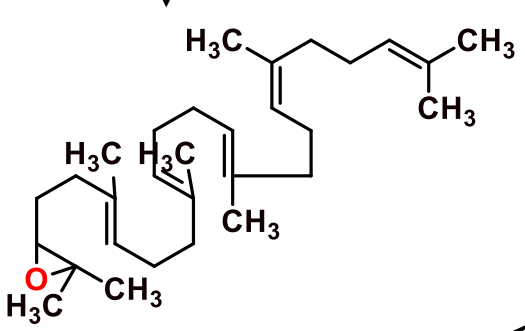
Saponins

glycosylated toxic substances produced by the roots and stems of many species

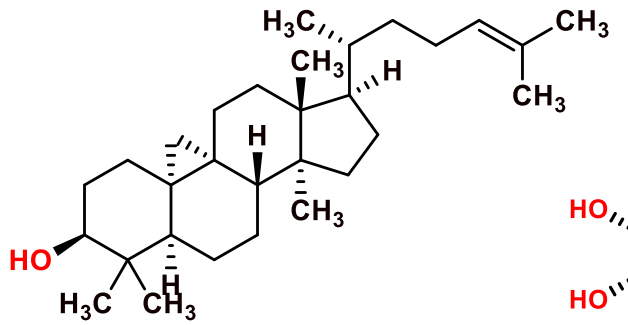
Triterpene Structures.

All arise from squalene, generate growth regulators (brassinosteroids) and compounds of surface waxes.

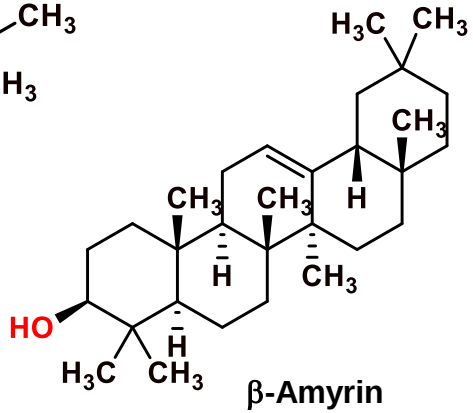
SQUALENE



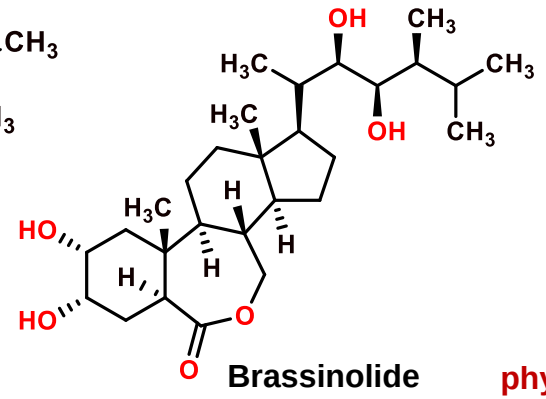
Oxidosqualene



Cycloartenol

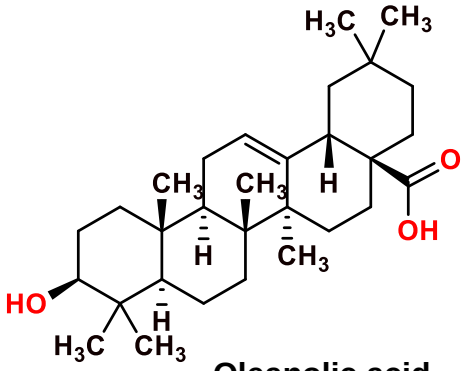


β-Amyrin



Brassinolide

and phytosterols

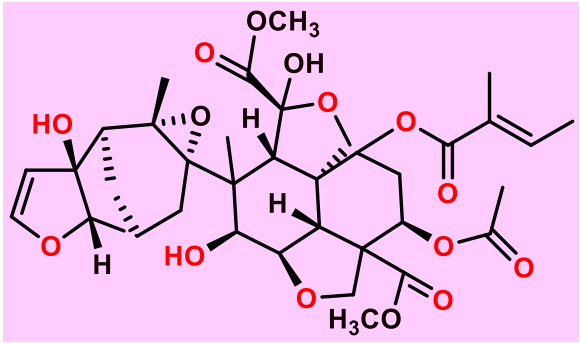


Oleanolic acid

Found in fruit waxes

Triterpene Structures (2).

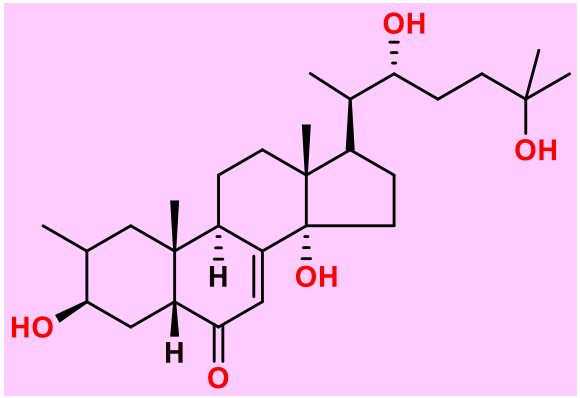
(A) Azadirachtin, a limonoid



Limonoids: Triterpenes responsible of bitter taste in lemons;
deterrents for herbivores;

azadiractina powerful deterrent to insects, low toxicity for mammals: insecticide sold in Africa and Asia.

(B) α-Ecdysone, an insect molting hormone



isolated from ferns: plant steroids hormone-like suit of insects when ingested by insects interfere with the molting process.

TETRATERPENES C40.

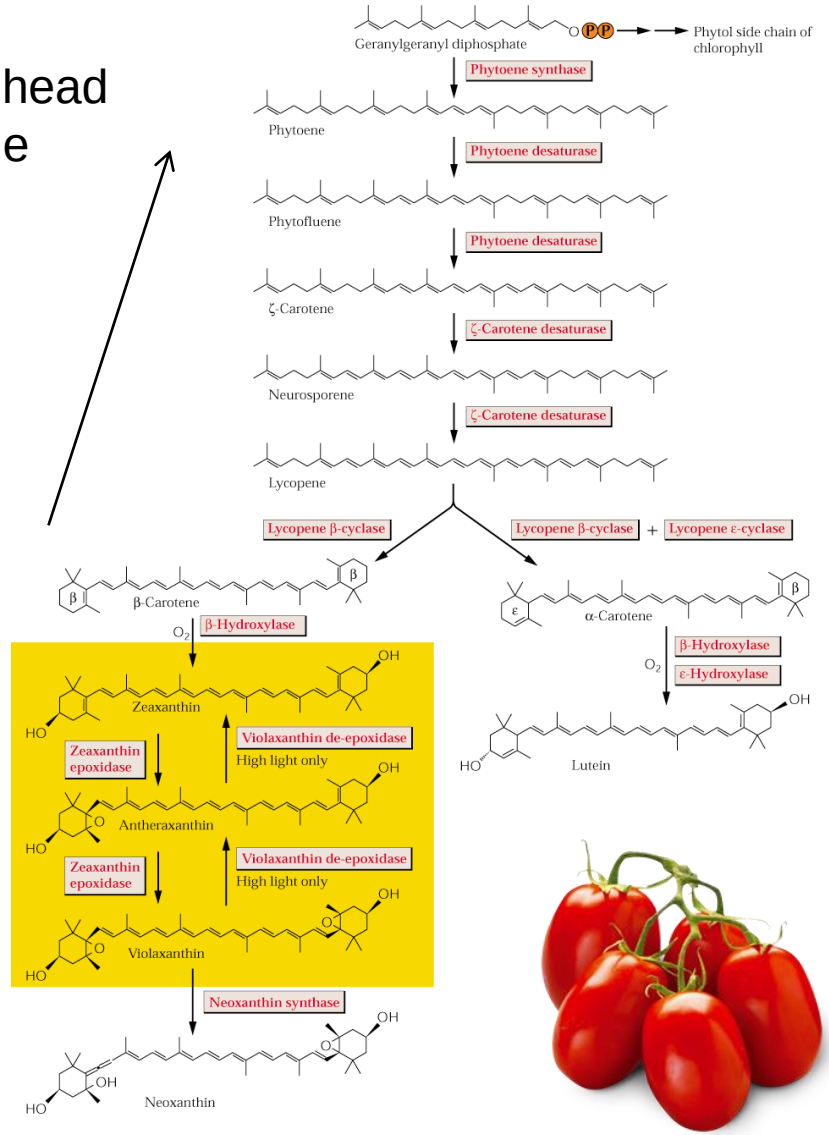
Products formed by condensation head to head of two GGP molecules to form the phytoene

Phytoene synthase: mechanism similar to the one of squalene synthase

PHYTOENE:

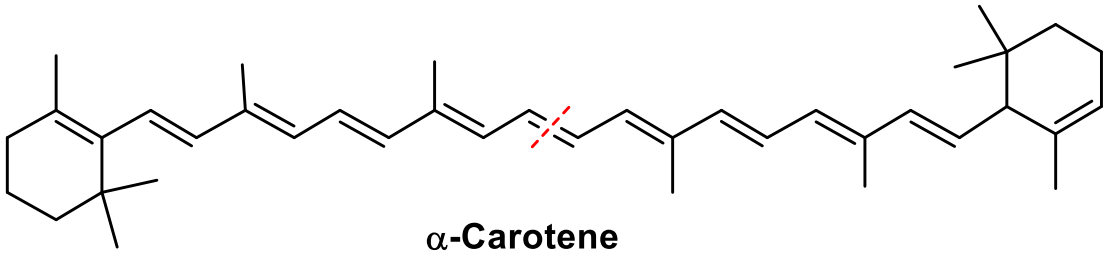
- Desaturations
- Cyclizations

CAROTENOIDS

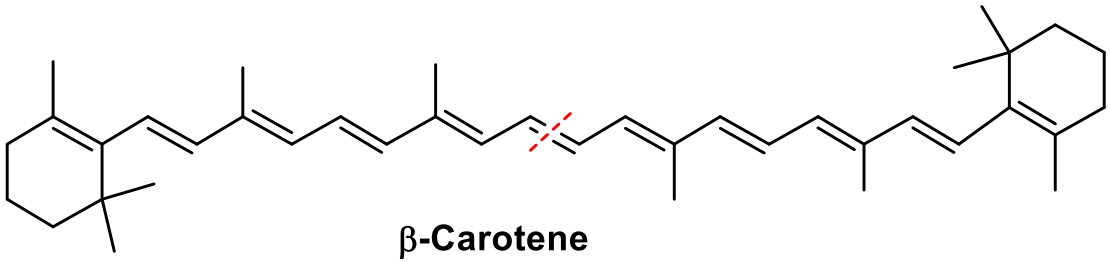


Carotenoids.

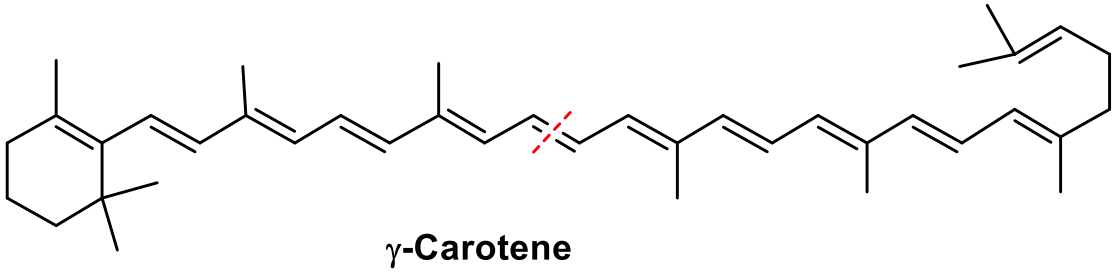
The carotenes are tetraterpenes. They can be thought of as two diterpenes linked in tail-to-tail fashion. The carotenes all can be converted to vitamin A by enzymes in the liver.



α-Carotene



β-Carotene



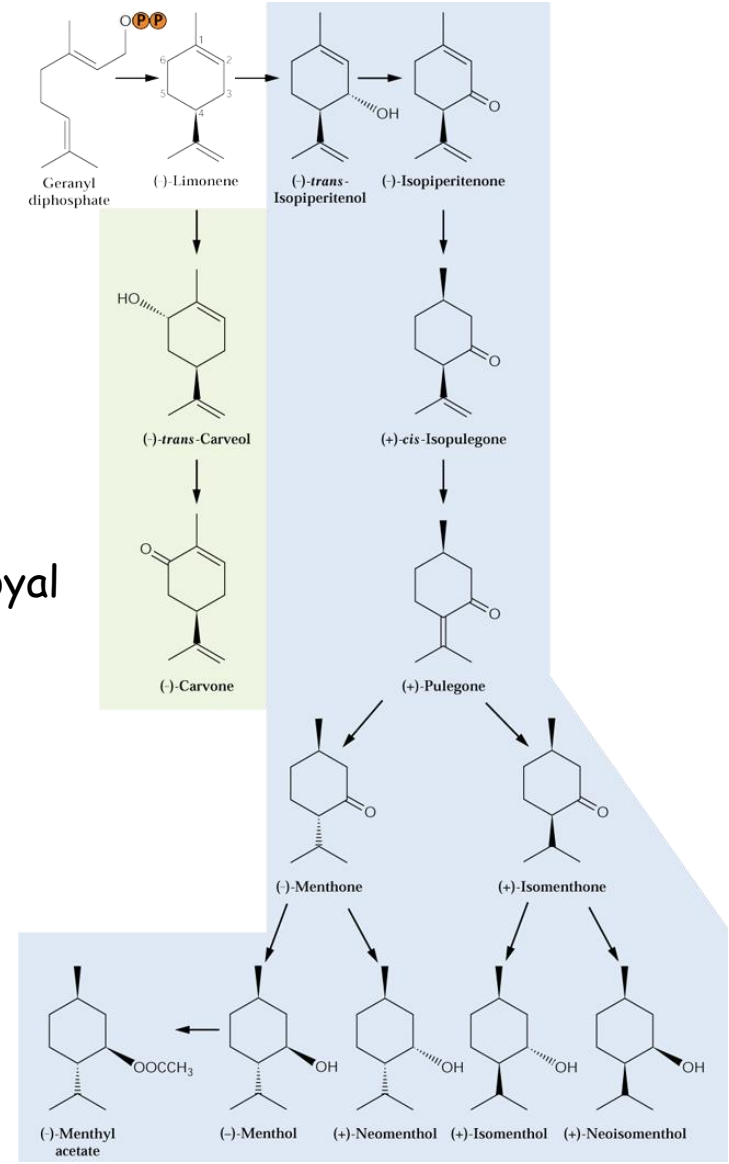
γ-Carotene

Subsequent Modifications.

- Modifications of the base skeletons, as oxidation, reduction, isomerization, conjugation, produce thousands of different terpenoids with a variety of biological activities in plants and animals.

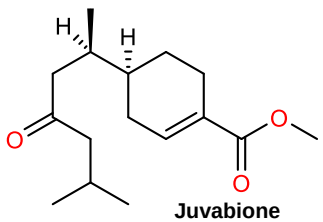
Example:

- Components of mint essential oil derived from modifications of limonene.

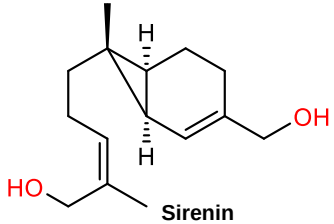


Compounds of Biological and Pharmaceutical Interest.

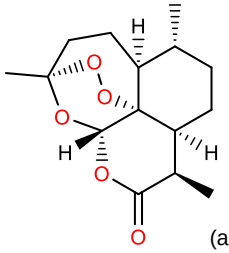
Reactions similar to those responsible for the production of essential oils generate thousands of compounds of biological and pharmaceutical interest.



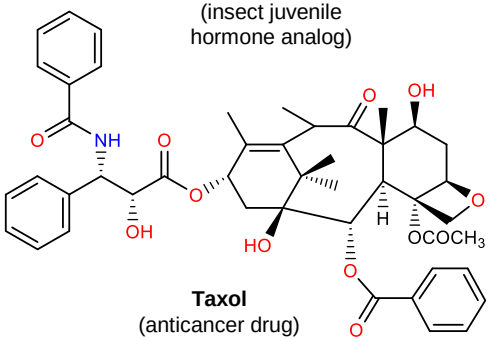
Juvabione
(insect juvenile hormone analog)



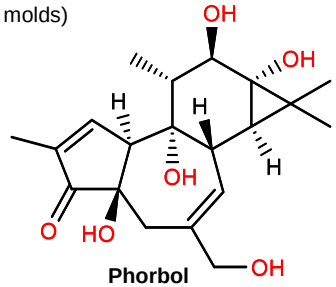
Sirenin
(sperm attractant in water molds)



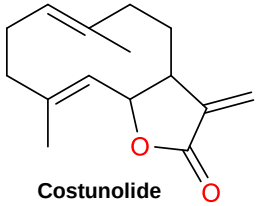
Artemisinin
(antimalarial drug)



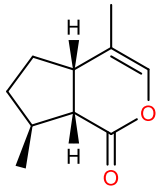
Taxol
(anticancer drug)



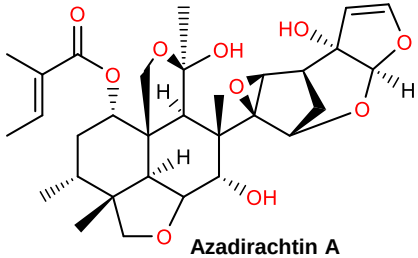
Phorbol
(irritant and co-carcinogen)



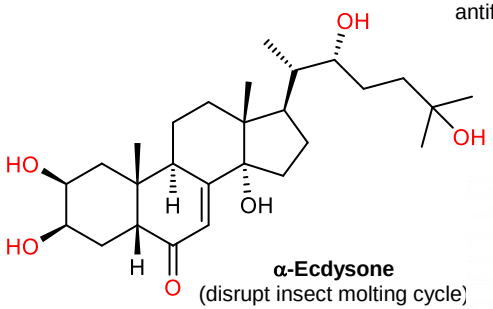
Costunolide
(repellente per insetti antifeedant di mammiferi)



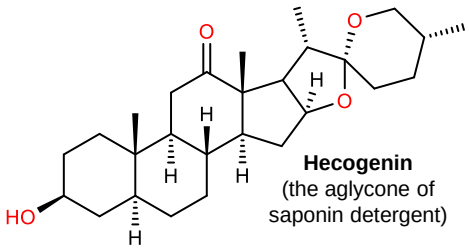
Nepetalactone
(active principle of catnip)



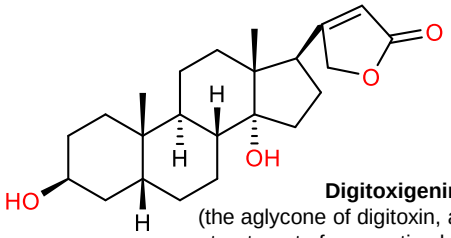
Azadirachtin A
(insect antifeedant)



α-Ecdysone
(disrupt insect molting cycle)



Hecogenin
(the aglycone of saponin detergent)



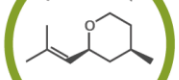
Digitoxigenin
(the aglycone of digitoxin, a cardiolide for treatment of congestive heart disease)

Aroma Compounds in Common Flowers.

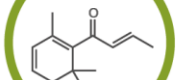
A wide range of compounds contribute to the scents of flowers. This graphic looks at a selection of major contributors for a number of common flowers. Note that volatile aroma compounds can vary significantly between species; this graphic represents a broad overview of common components, and is by no means definitive!

Roses

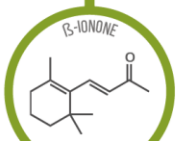
(-)-CIS-ROSE OXIDE



β-DAMASCENONE

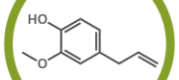


β-IONONE

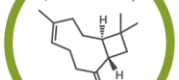


Carnations

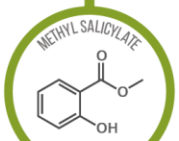
EUGENOL



β-CARYOPHYLLENE

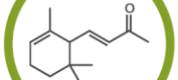


METHYL SALICYLATE

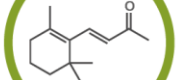


Violets

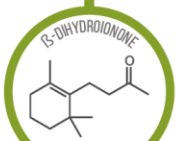
α-IONONE



β-IONONE

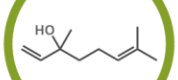


β-DIHYDROIONONE

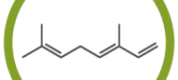


Lilies

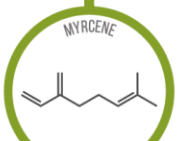
LINALOOL



(E)-β-OCIMENE

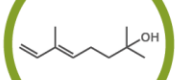


MYRCENE

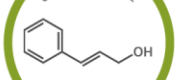


Hyacinth

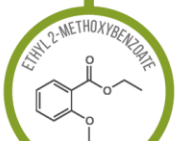
OCIMENOL



CINNAMYL ALCOHOL



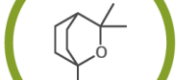
ETHYL 2-METHOXYBENZOATE



Chrysanthemums

α-PINENE

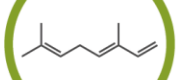
EUCALYPTOL



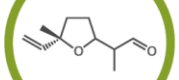
CHRYSANTHENONE

Lilacs

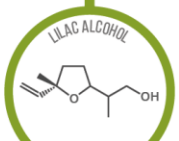
(E)-β-OCIMENE



LILAC ALDEHYDE

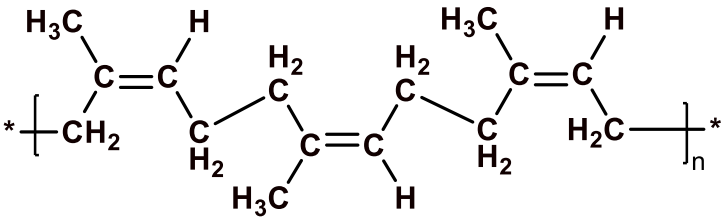


LILAC ALCOHOL



Latexes: NATURAL RUBBER.

Latex = mixture of organic compounds produced in laticifers
Laticifer = cells or groups of cells that form tubes, canals, or networks
Latex may be inelastic or elastic
Rubber – elastic latex composed of polymers



Natural rubber

The isoprene units of natural rubber are all linked in a head-to-tail fashion and all of the bonds are *cis*.

Pure rubber is soft and tacky, so it must be vulcanized by heating with sulphur. A reaction takes place that produces cross-links between the cis-polyisoprene chains and makes the robber much harder.

Rubber Latexes.

Well diffused in Euphorbiaceae plants – known for milky latex (“milky sap”) – in laticifers. Present also in the Asteraceae family (i.e. Guayule that grows in arid regions in the South America and Mexico) and in Compositae (i.e. Russian dandelion).

Brazilian (Para) rubber tree
(*Hevea brasiliensis*)

Russian dandelion
(*Taraxacum koksaghyz*)

Guayule
(*Parthenium argentatum*)

Other Latexes Chicle – Manilkara zapota.

Chicle – *Manilkara zapota*

New World – Sapotaceae

The latex of the chicle plant originally provided the base for chewing gum, a product that has become immensely popular. Today's chewing gums list "gum base" as the latex ingredient, and these may or may not contain any actual chicle.

Plant Resins.

Some plants produce resins, mixtures of compounds that are secreted into specialized canals or ducts within the plant. The **polymerized terpene structure** of plant resins has provided plenty of challenges to chemists seeking to determine their structures. Can contain volatile oils. They have also provided products that have been employed in a range of applications, from incenses to paints to sailing ships.

Uses of resins:

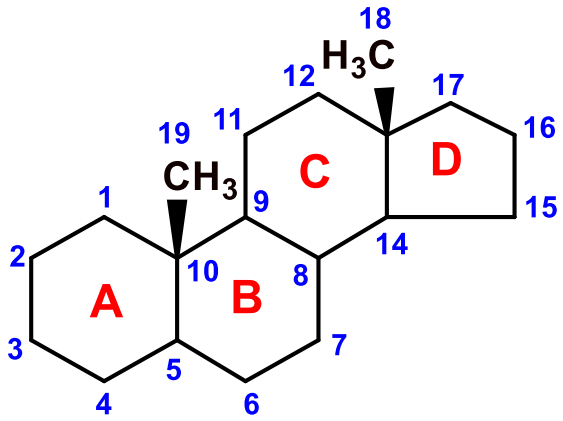
- incense (frankincense and myrrh) →
- embalming
- mastic
- lacquer
- artist's paints
- naval stores (pines)
- amber – jewel of plant origin →

STEROIDS.

Steroids are important “biological regulators” that nearly always show dramatic physiological effects when they are administered to living organisms.

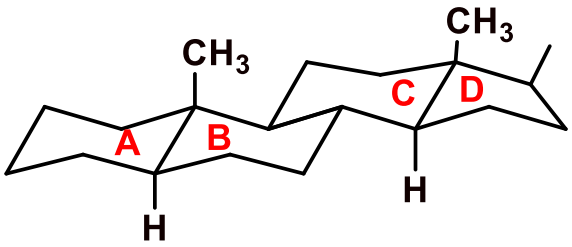
STRUCTURE AND SYSTEMATIC NOMENCLATURE

- Steroids are derivatives of the perhydrocyclopentanophenanthrene ring system

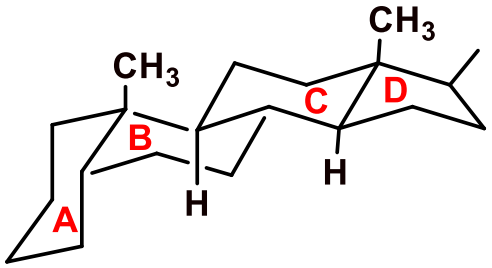


Steroids (2).

In most steroids the B, C and C, D ring junctions are *trans*. The A, B ring junction may be either *cis* or *trans*.



All ring junctions are *trans*



A, B ring junction is *cis*

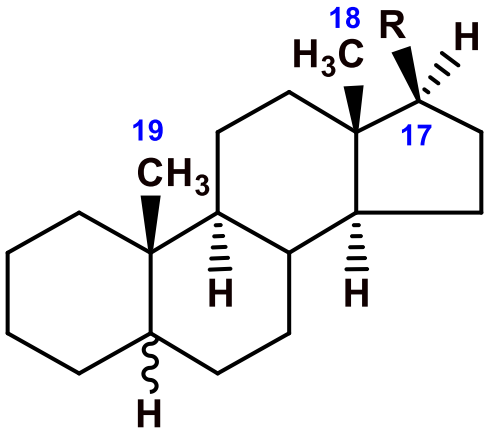
Angular methyl groups: The methyl groups that are attached at points of ring junction

β substituents: other groups that lie on the same general side of the molecule as the angular methyl groups.

α substituents: groups that lie on the bottom.

Steroids (3).

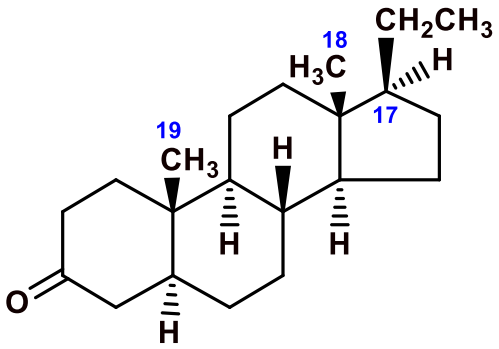
When α and β designation are applied to the hydrogen atom at position 5, the ring system in which the A, B ring junction is *trans* become the 5 α series; if the junction is *cis* becomes the 5 β series. In systematic nomenclature, the R group at position 17 determines the base name of an individual steroid.



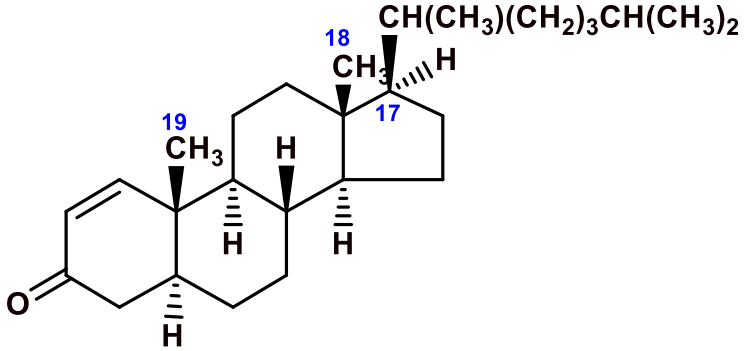
- H → **Androstane** - $^{20}CH_2{}^{21}CH_3$ → **Pregnane**

^{20} ^{21} ^{22} ^{23} ^{24}
$-CH(CH_3)CH_2CH_2CH_3$ → **Cholane**

Examples



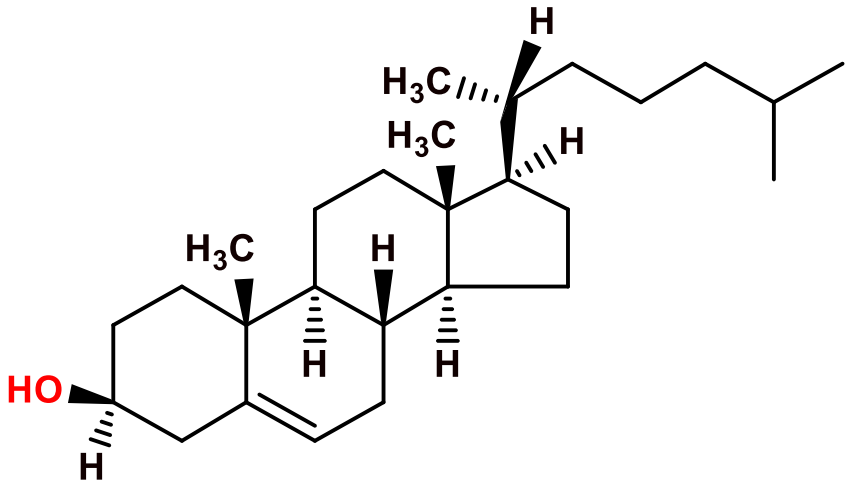
5α-Pregnan-3-one



5α-Colest-1-en-3-one

Cholesterol.

Cholesterol can be isolated by extraction of nearly all animal tissues. part of the difficulty in assigning an absolute structure to cholesterol is that cholesterol contains eight tetrahedral. For example:



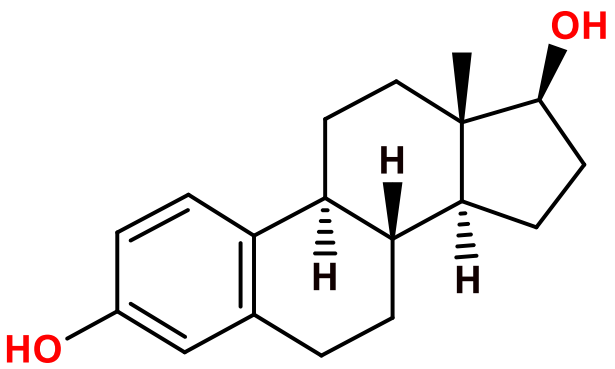
Cholesterol is known to serve as an intermediate in the biosynthesis of all of the steroids of the body.

Sex Hormones.

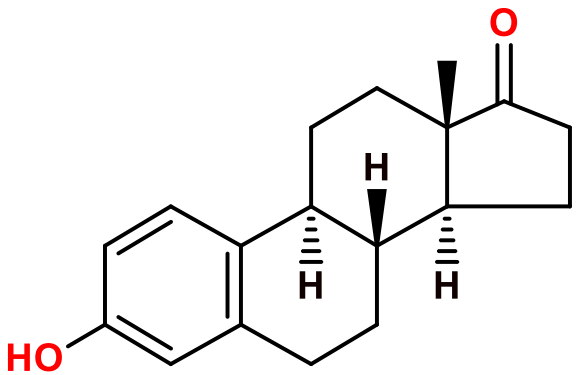
The sex hormones can be classified into three major groups:

(1) The female sex hormones, or oestrogens.
(2) The male sex hormones, or androgens.
(3) The pregnancy hormones, or progestin.

- The first sex hormone to be isolated was an estrogen, estrone.



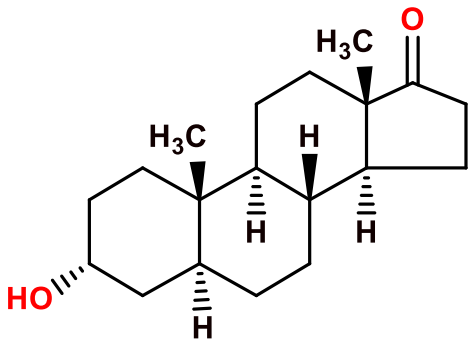
Estradiol



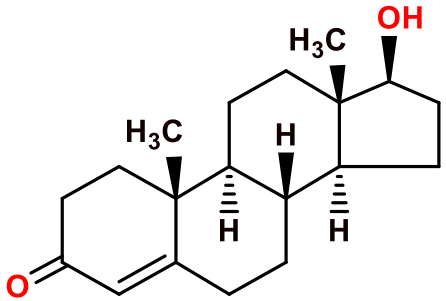
Estrone

Examples of the Second Sex Hormones.

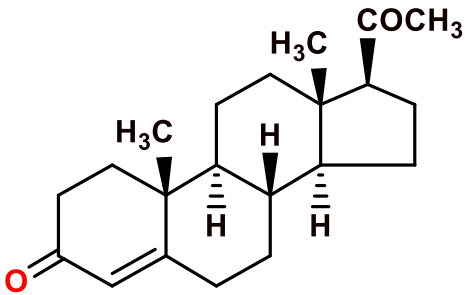
Testosterone and estradiol are the chemical compounds from which “maleness” and “femaleness” are derived. They differ slightly in their structure. Progesterone and norethindrone are important progestin.



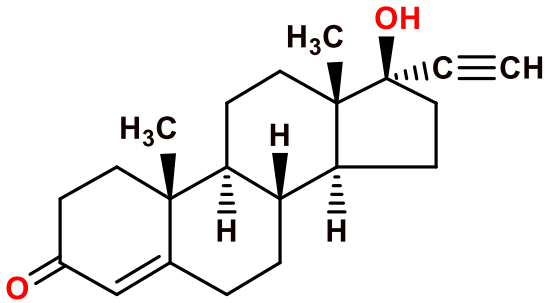
Androsterone



Testosterone



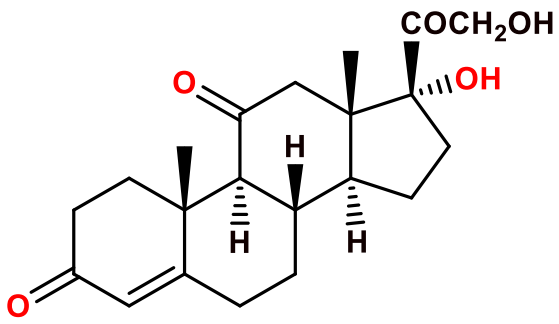
Progesterone



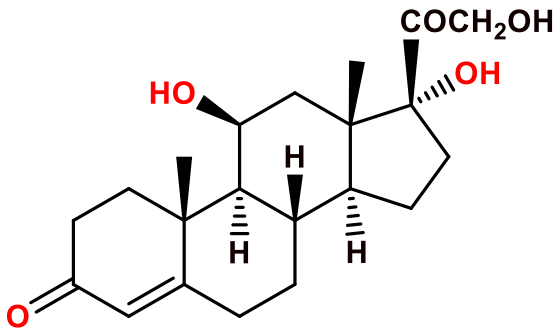
Norethindrone

Adrenocortical Hormones.

At least 28 different hormones were isolated from the adrenal cortex. Included in this group are the following two steroids:



Cortisone

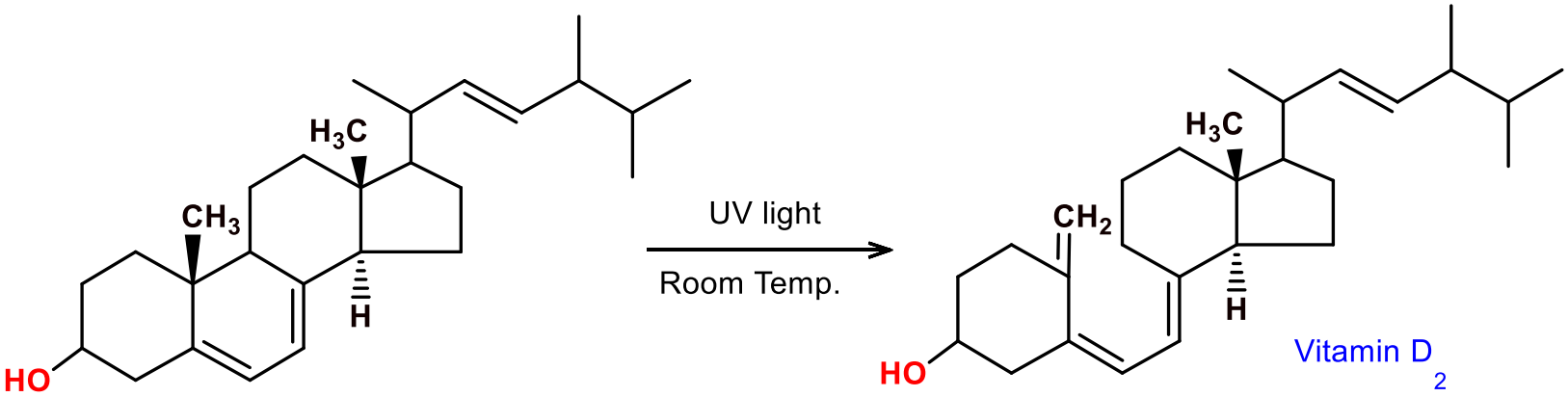


Cortisol

Most of adrenocortical steroids have an oxygen at position 11. Cortisol is the major hormone synthesized by the human adrenal cortex.

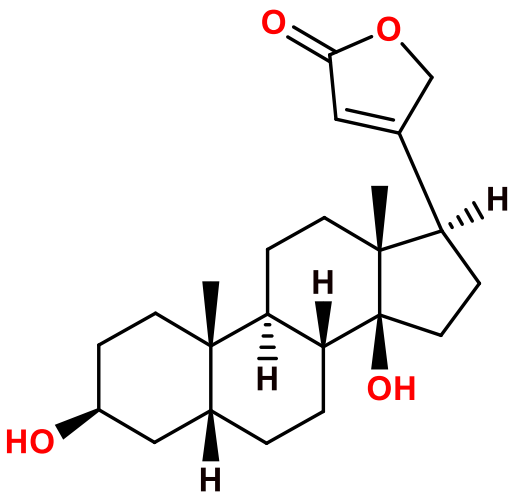
D Vitamins.

Vitamin D2 can be produced by photochemical reaction in which the dienoid ring B of ergosterol opens to produce a conjugated triene.

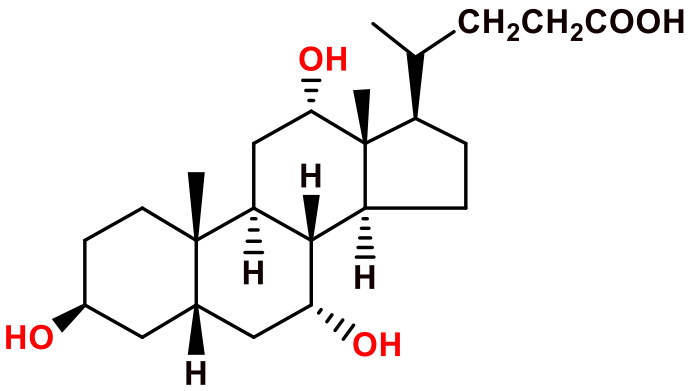


Other Structures.

- Digitoxigenin is a cardiac aglycone that can be isolated by hydrolysis of digitalis.
- Cholic acid is the most abundant acid obtained from the hydrolysis of human or ox-bile.



Digitoxygenine

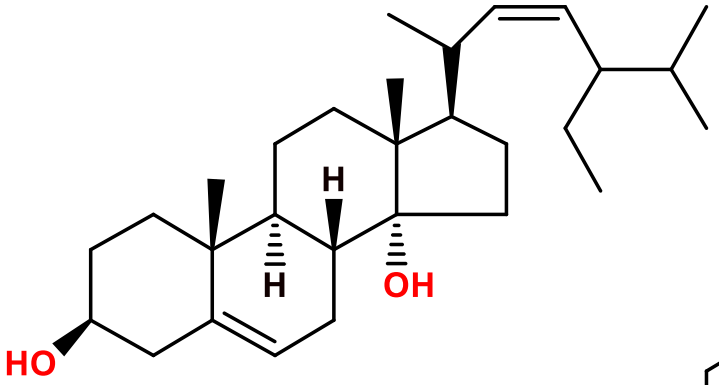


Cholic acid

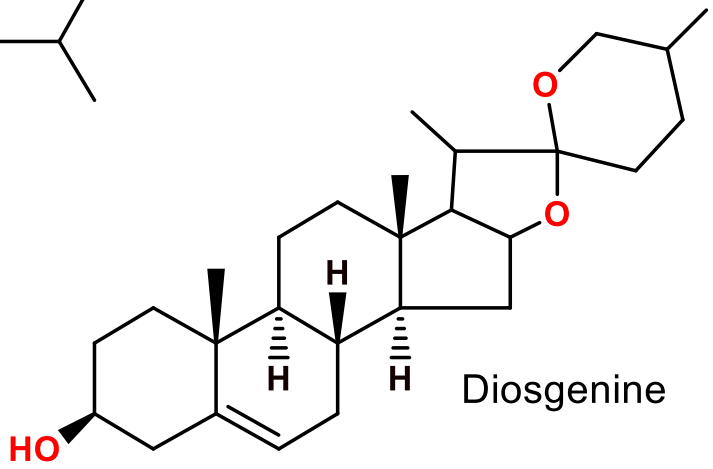
Vegetable Steroids.

Stigmasterol is a widely occurring plant steroid that is obeained commercially from soybean oil.

Diosgenin is obtained from a *Mexican vine*, *cabeza de negro*, Genus *Dioscorea*. It is used as the starting material for a commercial synthesis of cortisone and *sex* hormones.



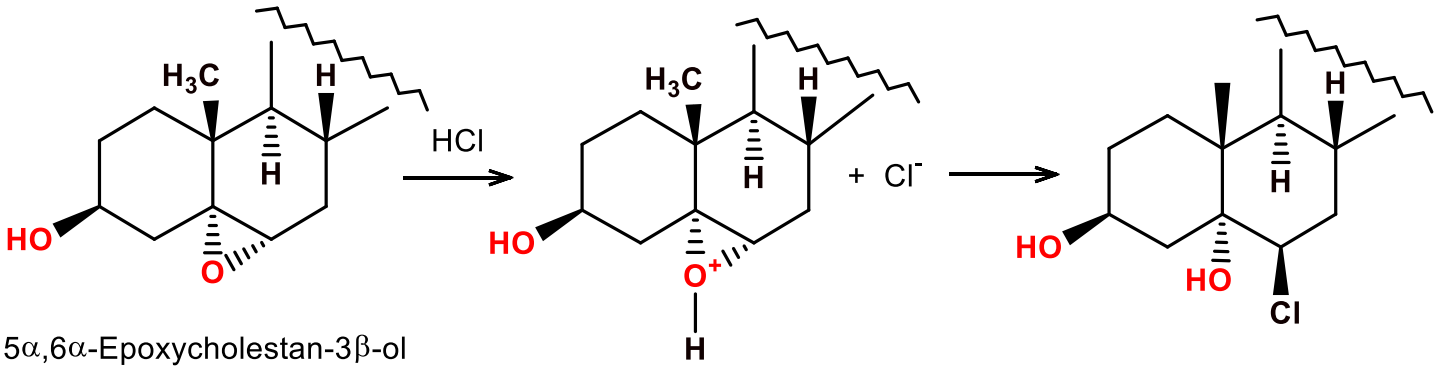
Stigmasterol



Diosgenine

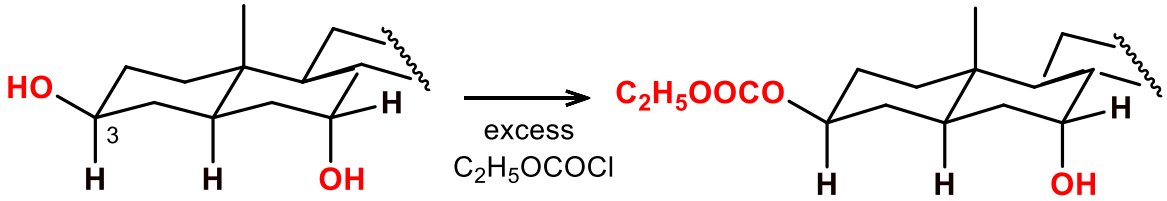
Reactions of Steroids.

The stereochemistry of steroid reactions is often quite complex. It is strongly influenced by the steric hindrance presented at the β face of the molecular methyl groups. So, when the epoxide ring of 5α,6α-Epoxycholestan-3β-ol is opened, attack by chloride ion must occur from the β face, but it takes place at the more open 6 position.



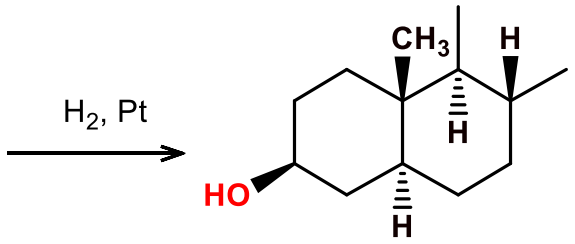
5α,6α-Epoxycholestan-3β-ol

The relative openness of equatorial groups also influences the stereochemical course of steroid reactions.

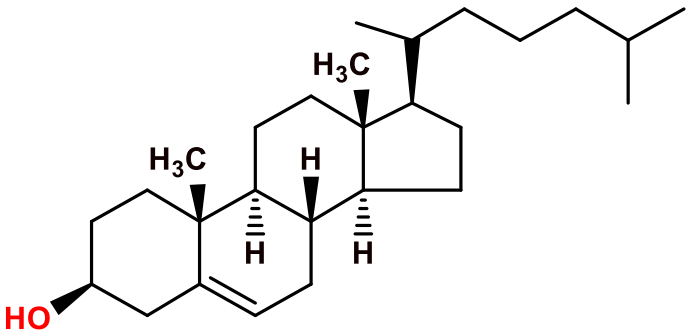


Reactions of Steroids (2).

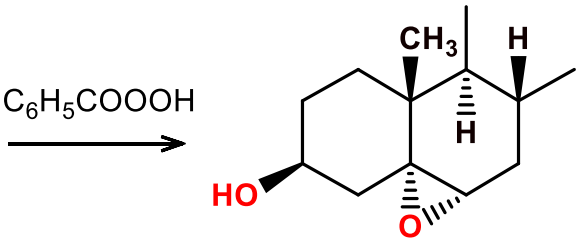
But many reagent react preferentially relatively at the α face.



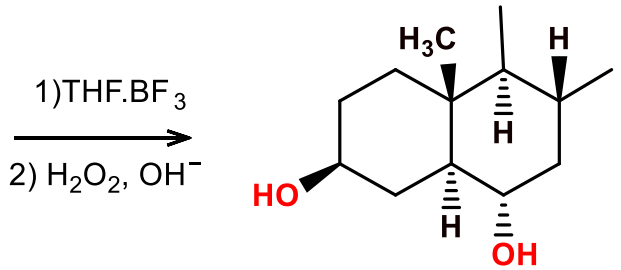
5α-Colestan-3β-ol (85-95%)



Colesterol



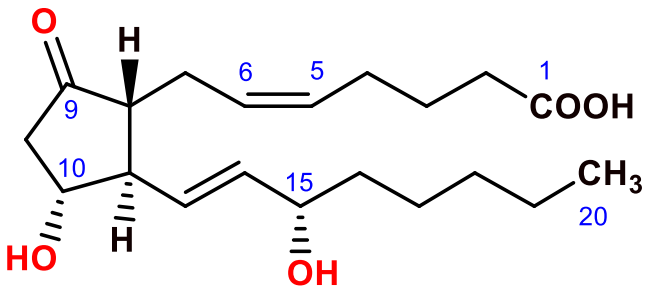
5α,6α-Epossicolestan-3β-olo (100%)



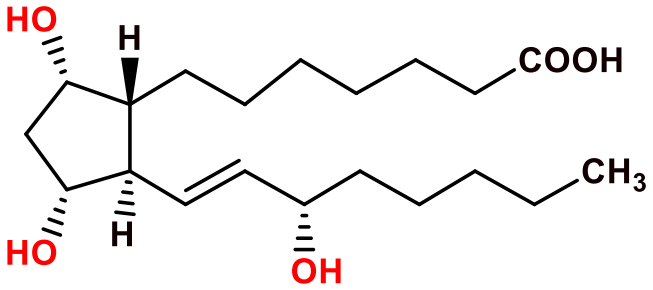
5α-Colestan-3β,6α-diol (78%)

Prostaglandins.

Prostaglandins are C**20**-carboxylic acids that contain a five-membered ring, at least one double bond, and several oxygen-containing functional groups. Two of the active prostaglandins are prostaglandin E**2** and prostaglandin F**1α**.

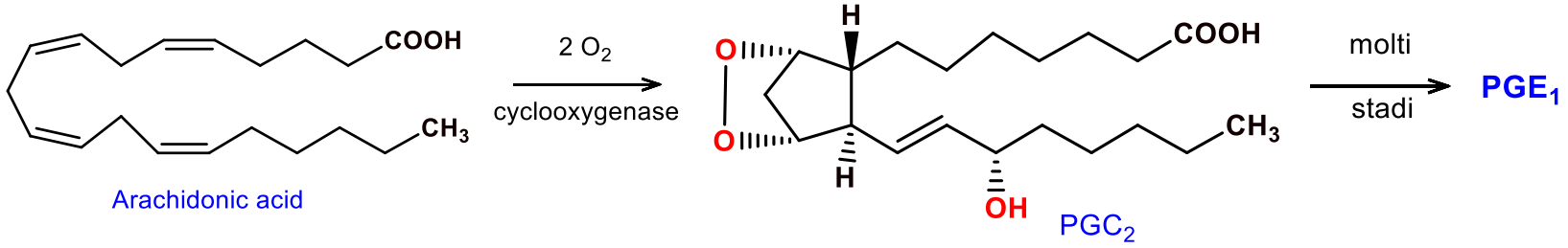


Prostaglandin E_2



Prostaglandin $F_{1\alpha}$

The biosynthesis of prostaglandins of the 2 series begins with a C**20** polyenoic acid, arachidonic acid.

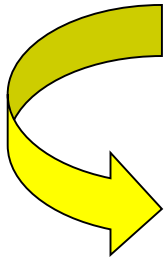


Arachidonic acid

PGC_2

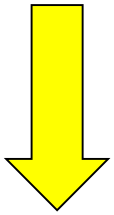
PHENOLIC COMPOUNDS.

- Plant colonization of terrestrial environments: the need for mechanical support and waterproofing



CELL WALL

LIGNIN



PHENOLIC COMPOUNDS

More than 8,000 phenolics formed through shikimate pathway or malonate/acetate pathway. They have structural and adaptive role.

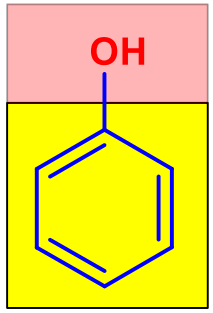
Functions of Phenolic Compounds.

- defense against herbivores & pathogens
- mechanical support (lignin)
- pollinator attraction
- absorption of harmful UV radiation
- allelopathic substances

Structural Units of Phenolic Compounds.

MOST OF PHENOLIC COMPOUNDS RESULT FROM 2 PATHWAYS:

1) FROM PHENYLPROPANOID **C6C3**

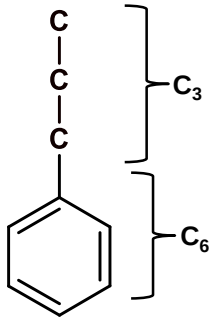


or

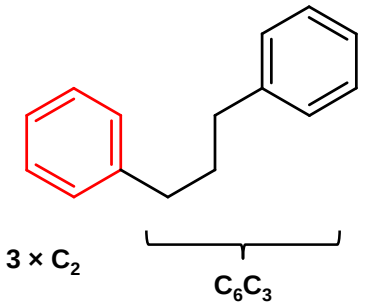
2. FROM PHENYLPROPANOID – ACETATE **C6C3-C3**

(derivatives of benzoic acids **C6C1** are also phenolic compounds)

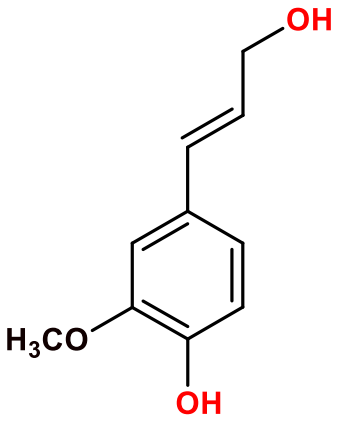
Structural Units of Phenolic Compounds (2).



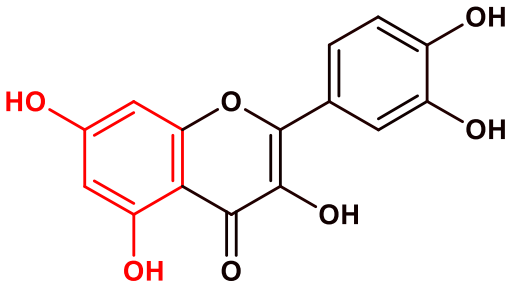
Phenylpropanoid Skeleton (C_6C_3)



Phenylpropanoid-acetate skeleton (C_6C_3-C_6), with phenylpropanoid-derived (C_6C_3) and acetate-derived (3 × C_2) rings



Caniferyl alcohol, a component of lignin and many lignans

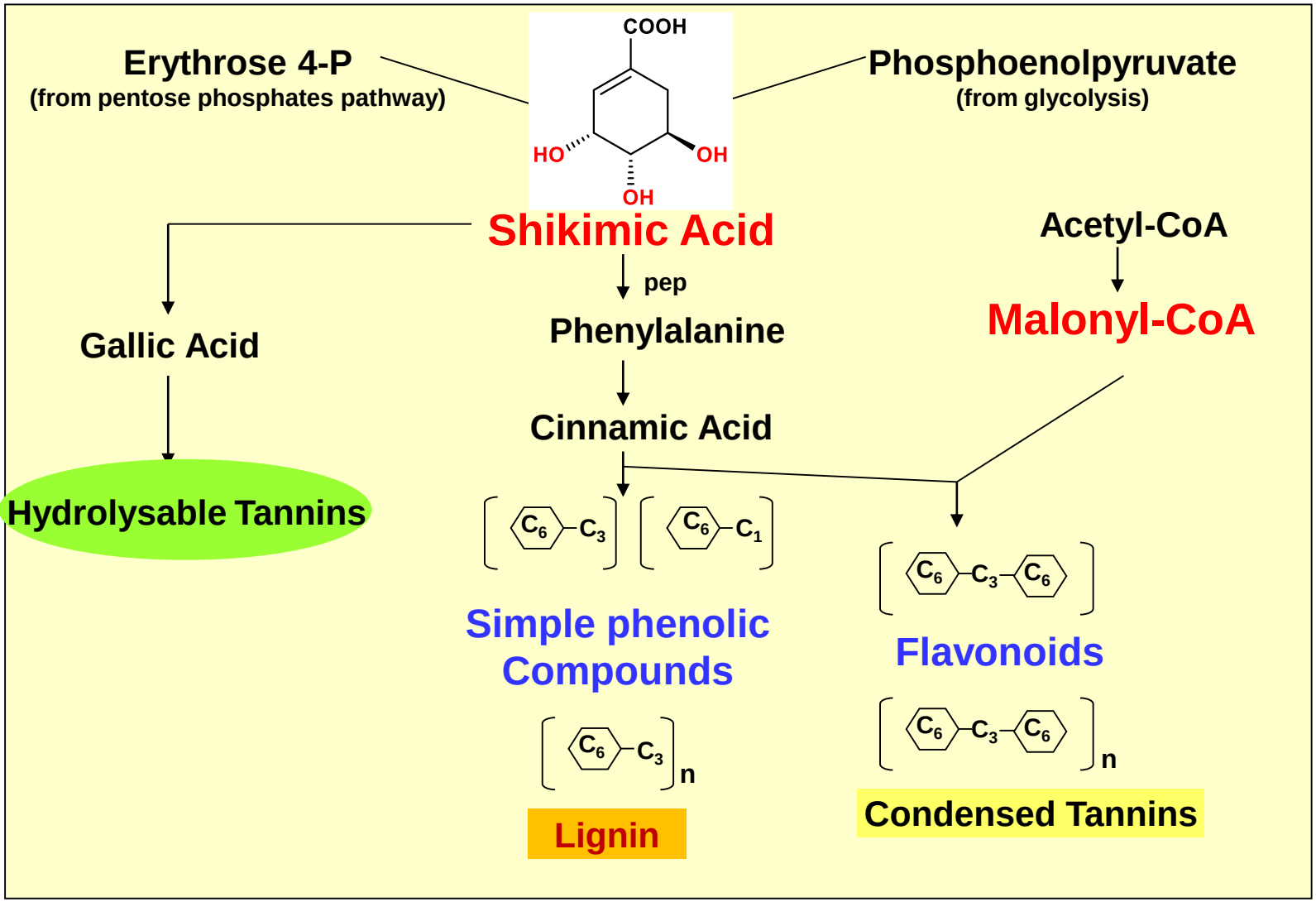


Quercetin, a flavonoid (C_6C_3-C_6)

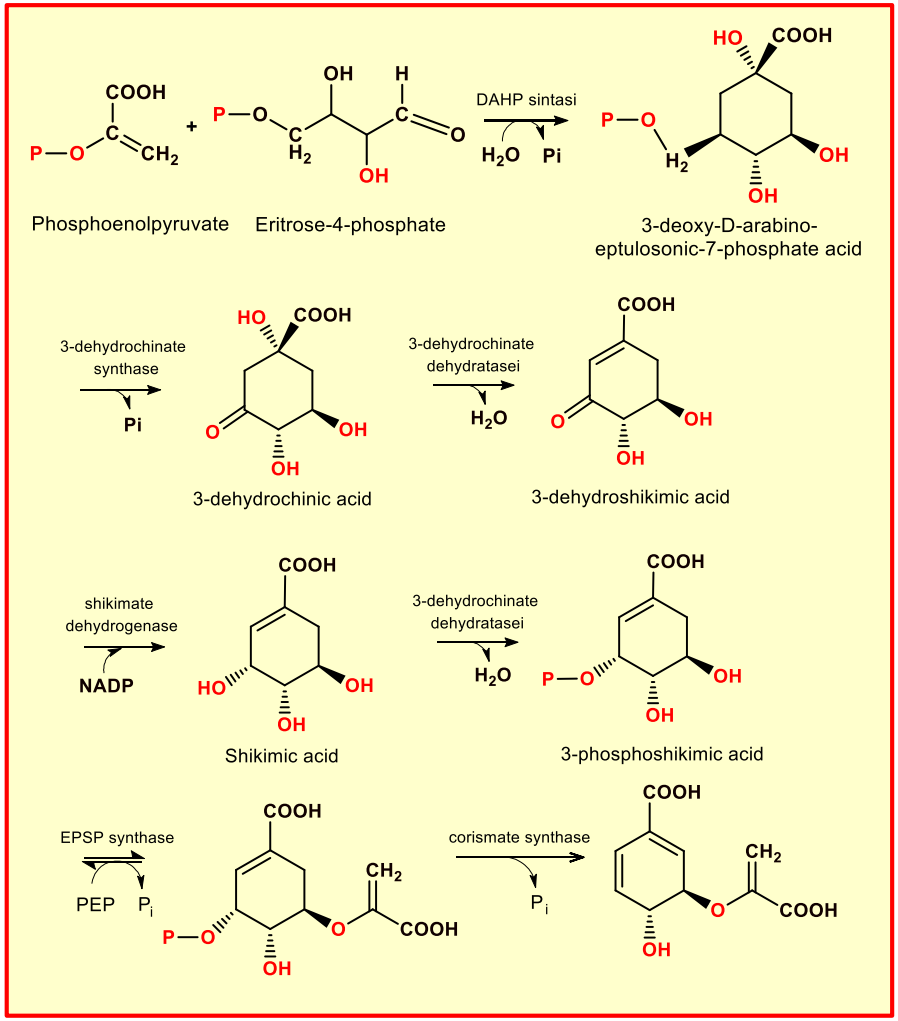
Phenylpropanoid skeleton

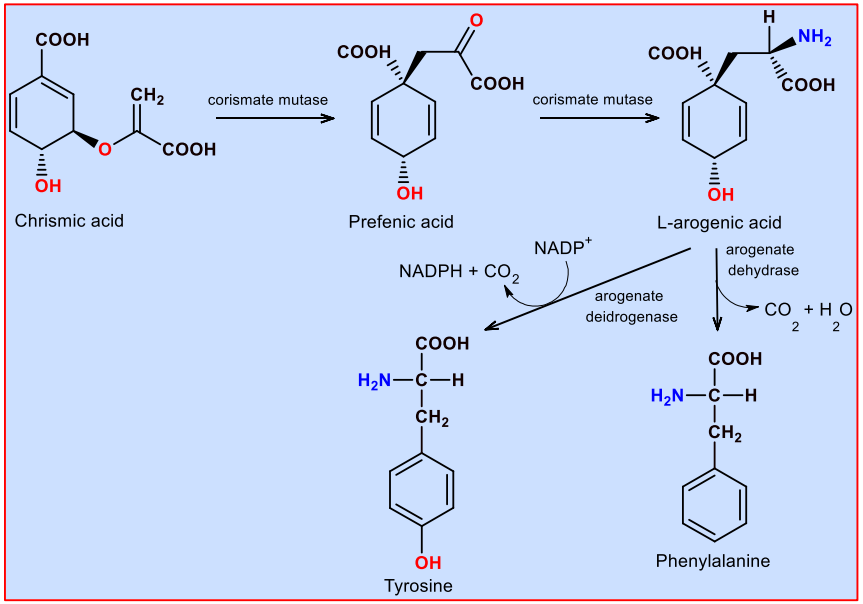
Acetate-derived rings

Metabolism of Phenolic Compounds.

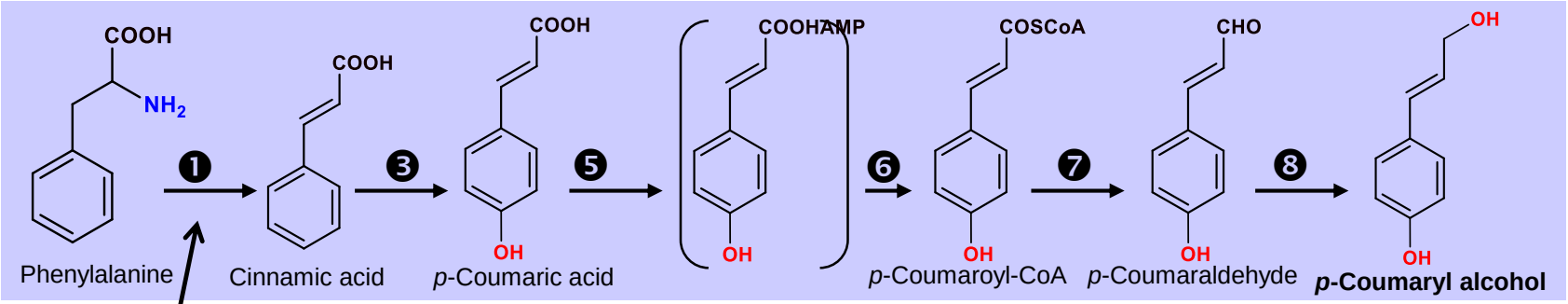


Shikimic Acid Pathway or Aromatic Amino Acids Pathway.



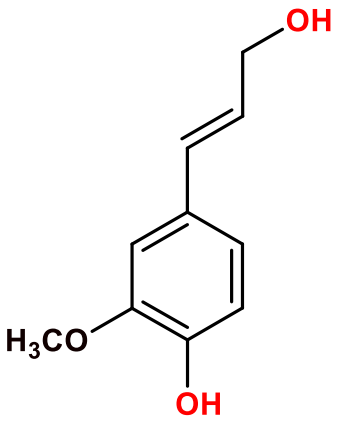


Structural Units of Lignin.

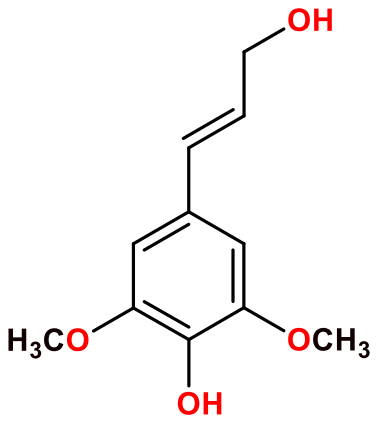


LIGNIN IS FORMED FROM 3 DIFFERENT PHENYLPROPANOID ALCOOLS: CONIFERYL, COUMARYL AND SINAPYL.

THESE ARE FORMED FROM PHENYLALANINE VIA DIFFERENT DERIVATIVES



Coniferyl alcohol



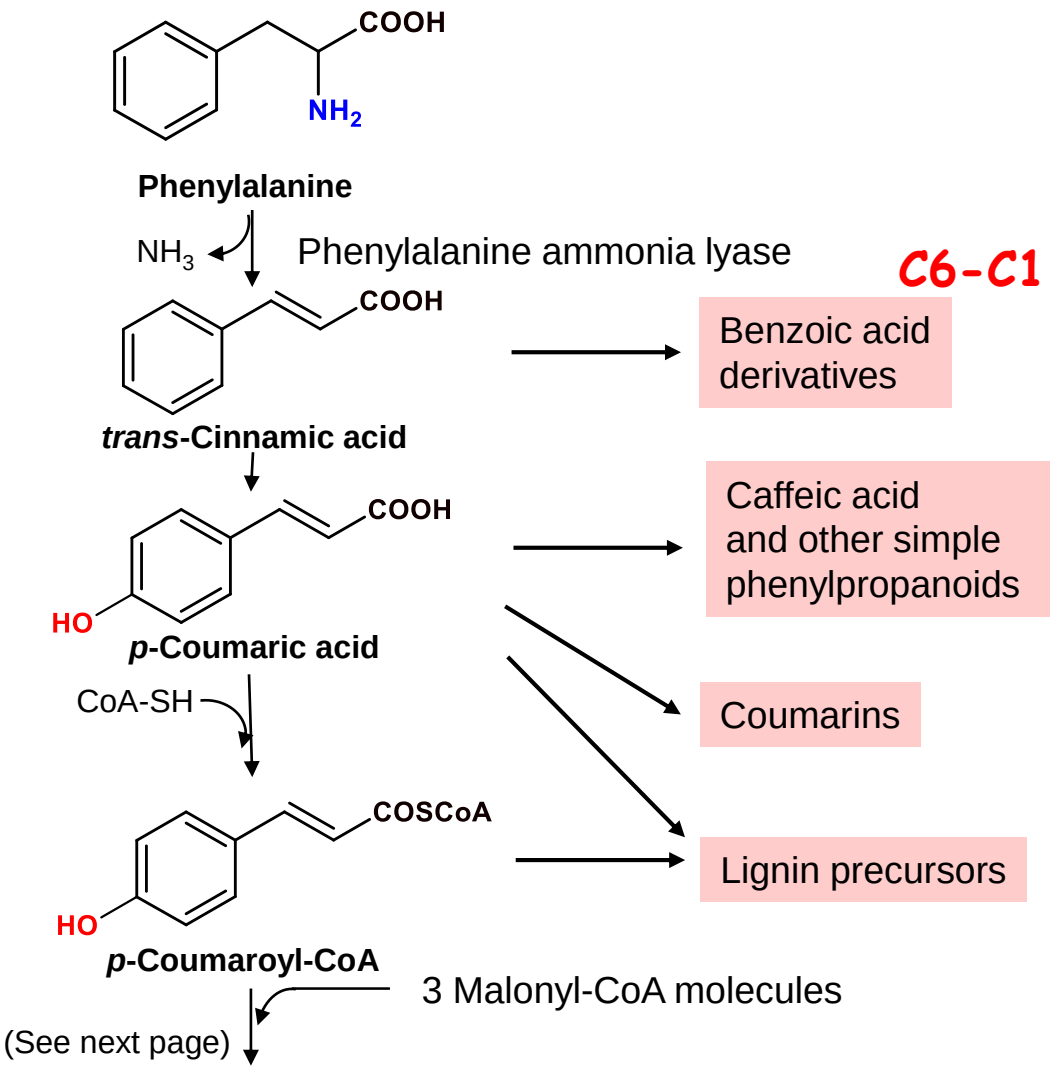
Sinapyl alcohol

Enzymatic Catalysis in the Biosynthesis of Phenolic Compounds.

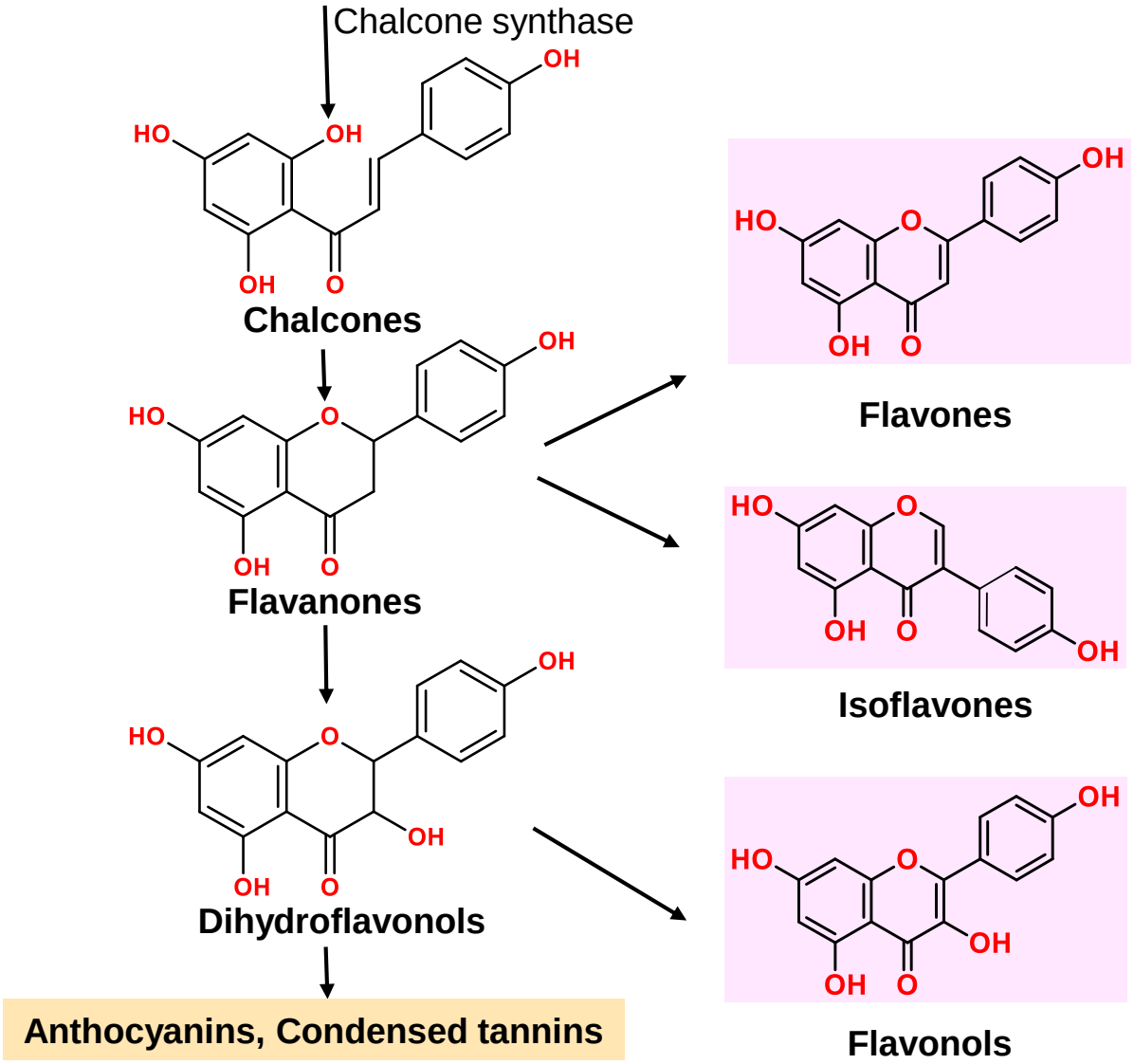
The biochemical pathways that lead to the biosynthesis of various classes of phenolic compounds have many characteristics in common

PAL enzyme:

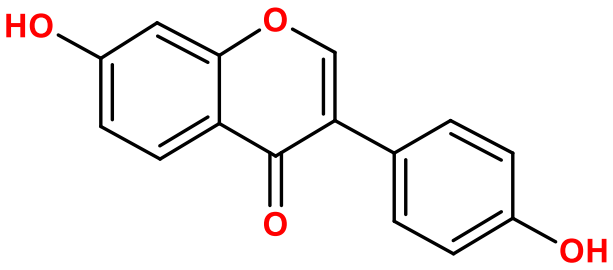
Phenylalanine ammonia lyase is the key enzyme in the synthesis of phenolic compounds



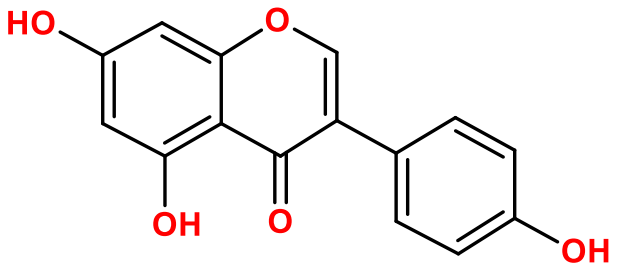
Antocyans and Flavonoids.



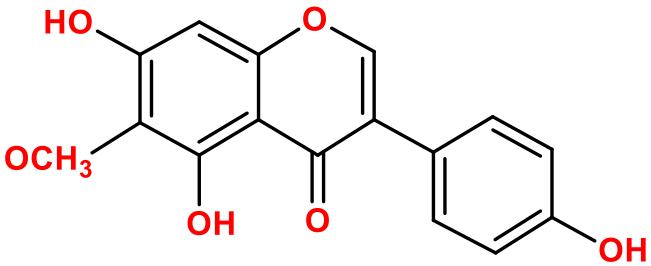
Typical Isoflavones.



Daidzein



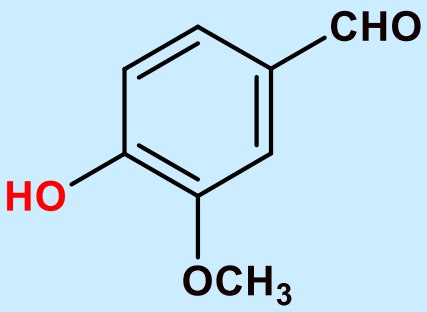
Genistein



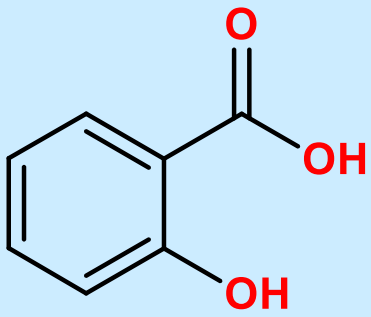
Glicitein

Benzoic Acid Derivatives C6C1.

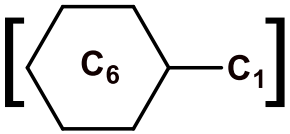
(C)



Vanillin

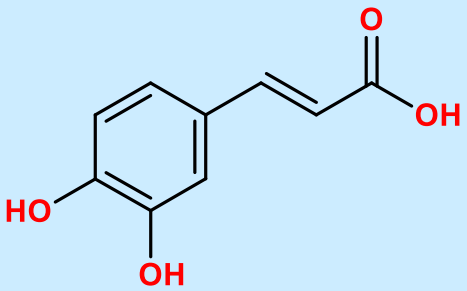


Salicylic acid

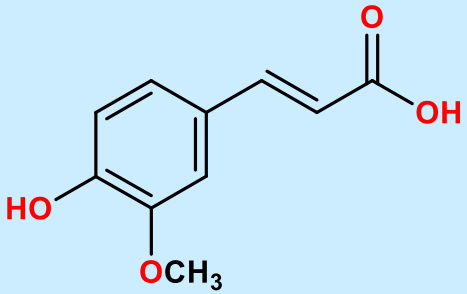
Benzoic acid derivatives 

Simple Phenolic Compounds C6C3.

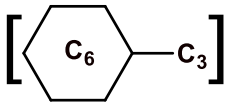
(A)



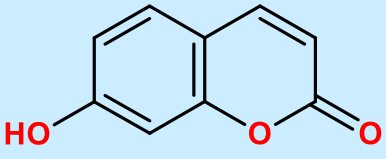
Caffeic acid



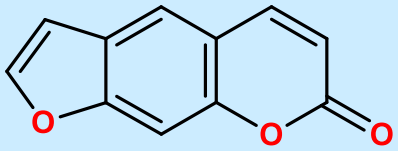
Ferulic acid

Simple phenylpropanoids 

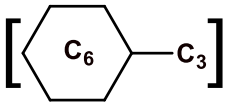
(B)



Umbelliferone,
a simple coumarin

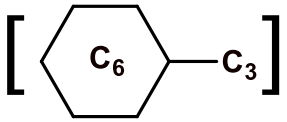


Psoralen,
a furanocoumarin

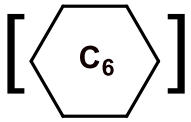
Coumarins 

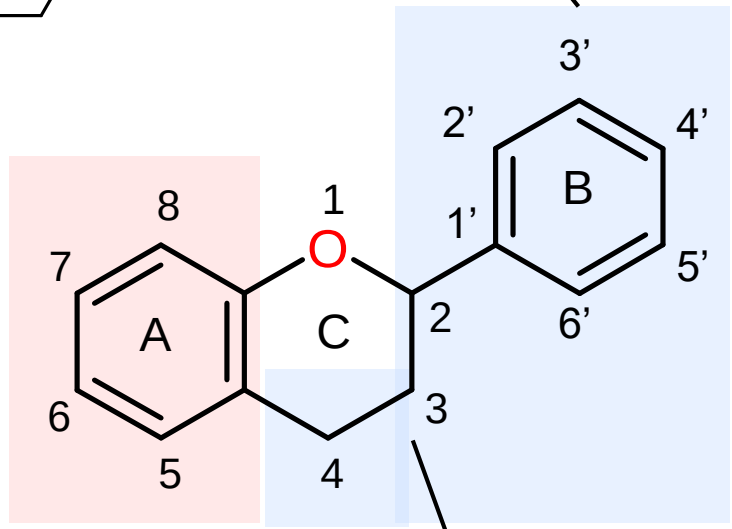
Flavonoids C6C3-C6.

From shikimic acid pathway via phenylalanine



From malonic acid pathway

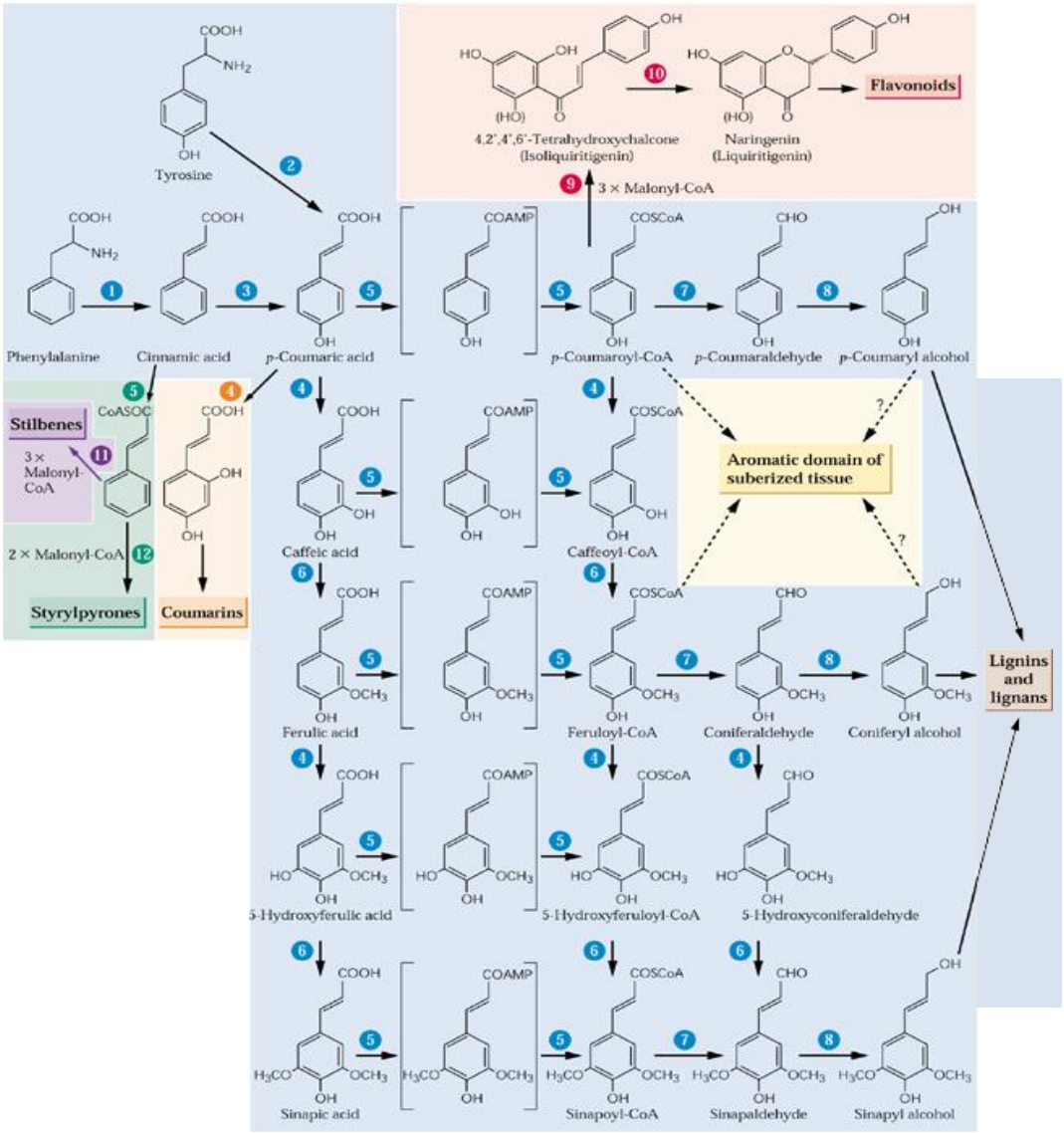




The three-carbon bridge

Basic flavonoid skeleton

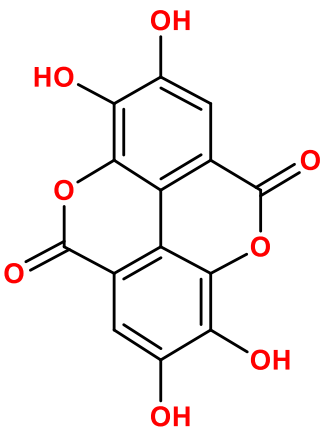
The Complex Tree of Flavonoids.



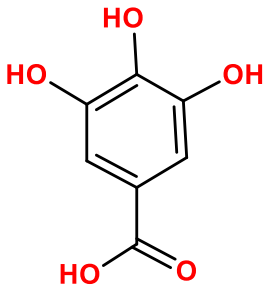
Tannins, Polyphenols and Flavonoids.

Hydrolysable tannins

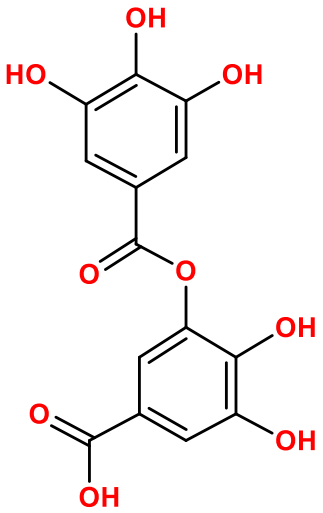
(leather water proofing)



Ellagic acid



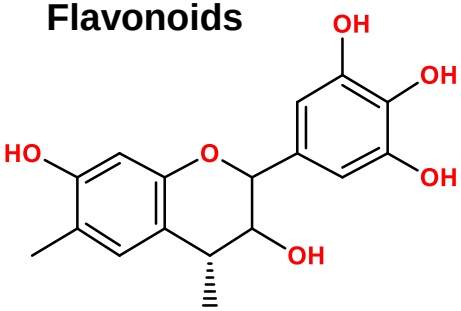
Gallic acid



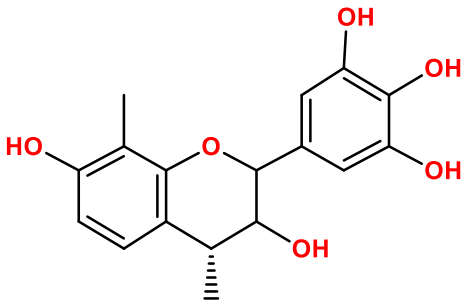
Digallic acid

Condensed tannins

Flavonoids



Mimose



Pine

+ formaldehyde = adhesives

High Levels of Polyphenols and Antioxidants Include Fruits and Vegetables.








Green tea-catechin

Bean-isoflavon

wine-resveratrol

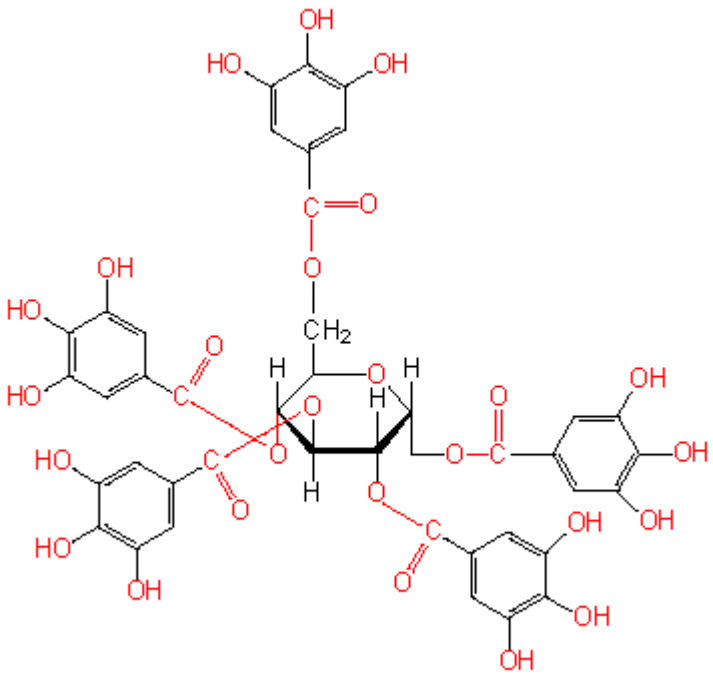
fruits- flavonoids

apple&onion-quesetin

black tea- polyphenols

Tannins.

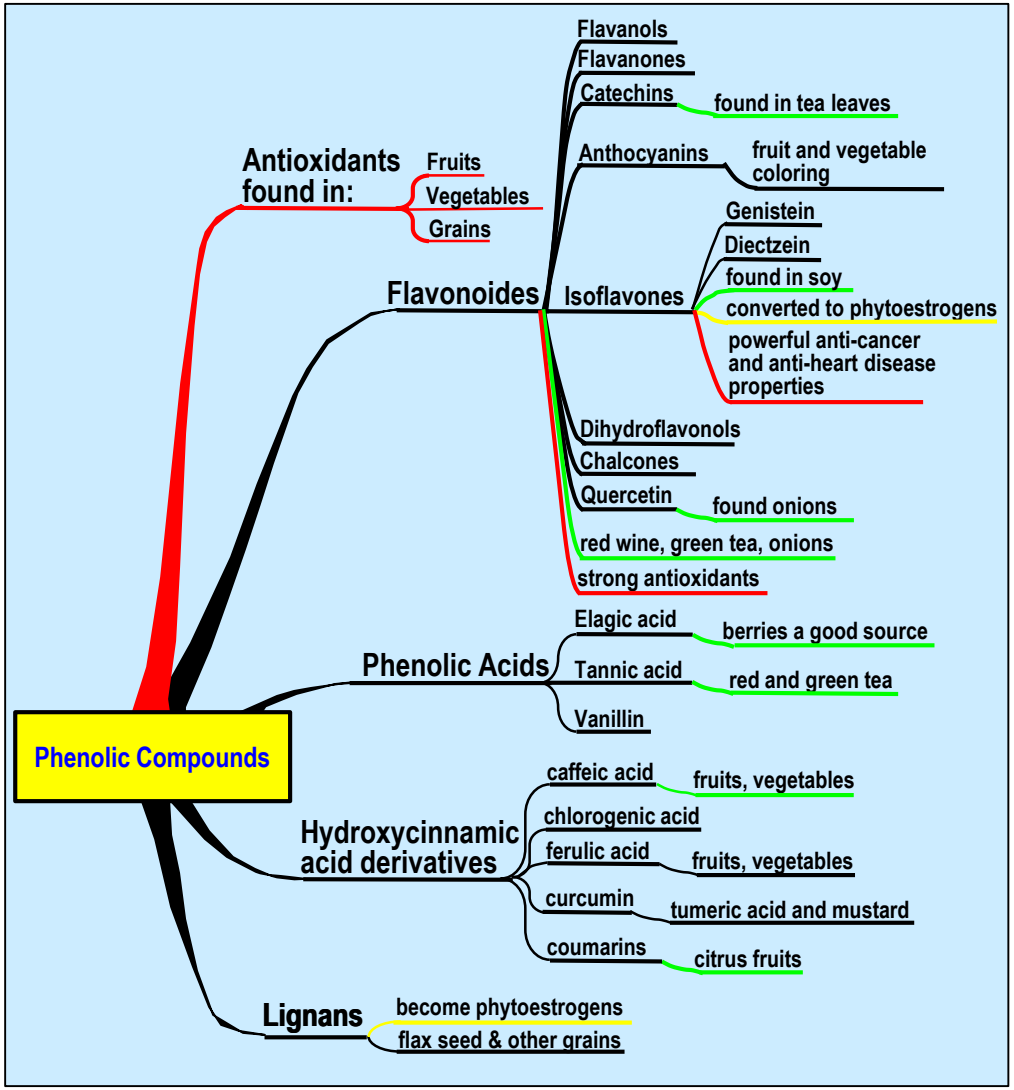
- Not carbohydrate – do not contain sugar
- Polyphenolic compounds of different nat
  1. Hydrolysable tannins
     Residues of gallic acid that are linked to glucose *via* glycosidic bonds
  2. Condensed tannins (non hydrolyzable)
     Biphenyl condensates of phenols



- Anti-nutrient effects
  - Combine with proteins, cellulose, hemicellulose, pectin and minerals
  - Can inhibit microorganisms and enzymes
- In plants
  - Most domesticated plants have been selectively bred for low concentrations of tannins – bird resistant milo exception
  - Many warm season legumes and browses contain tannins
  - Colored seed coats indicative of tannins - Acorns

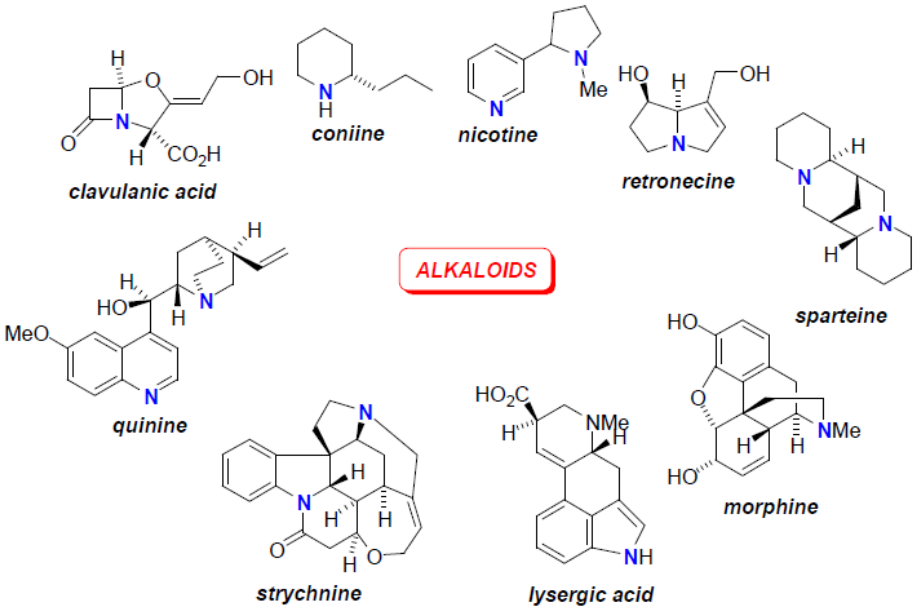
Biomass as Alternative Source of Phenols.

- Phenols are present in nature in plants and in ferns whereas they are nearly absent in animals.
- Phenols are characteristic and specific to each type of biomass.
- **3 –8 % by weight of biomass**



ALKALOIDS.

- Alkaloids generally include alkaline substances that have nitrogen as part of the structure and originate from amino acids. More than 20,000 alkaloids are known and are the largest and differentiated class of secondary compounds.. They are very common in certain plant families, especially:
  - *Fabaceae* – peas and beans
  - *Asteraceae* - sunflowers
  - *Papaveraceae* - poppies
  - *Solanaceae* – tomato
  - *Apocynaceae* - dogbanes
  - *Asclepiadaceae* - milkweeds
  - *Rutaceae* – citrus



- Any non-peptidic & non-nucleotide nitrogen containing compounds, basis of 25% of drugs on the market.

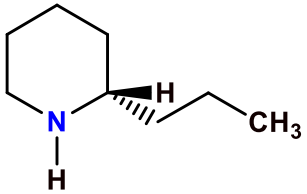
ALKALOIDS: Overview.

- Most commonly isolated from plants but known in most other orders of organisms from fungi to mammals
- Selected alkaloids have been used as
  - Poisons (hunting, murder, euthanasia)
  - Euphoriants, psychedelics, and stimulants (morphine, cocaine)
  - Medicines (ephedrine)
- Many of our modern drugs contain alkaloids or synthetic analogs
- Originally defined as nitrogenous compounds from plants of complex molecular structure and significant pharmacological activity.
- More recently defined as cyclic, nitrogen containing compounds which are true secondary metabolites
- Most compounds in this class derive part of their structure from amino acids or their derivatives.
- Being basic, they protonate and form salts in acid media, so can be extracted out of alkaline but not acidic water.

Biological Properties of Alkaloids.

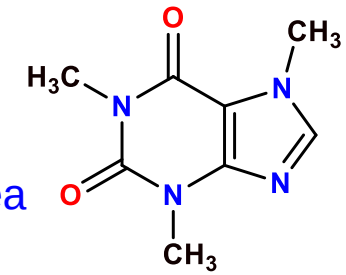
- Alkaloids can act as poisons

Coniine
Hemlock



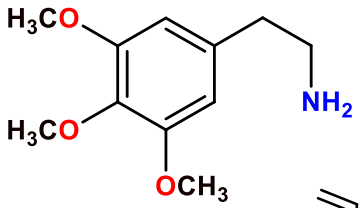
- Alkaloids can act as stimulants

Caffeine
coffee and tea



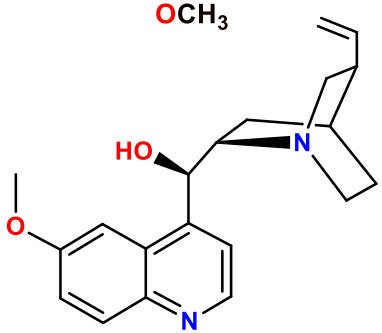
- Alkaloids can act as hallucinogens

Mescaline
Peyote cactus



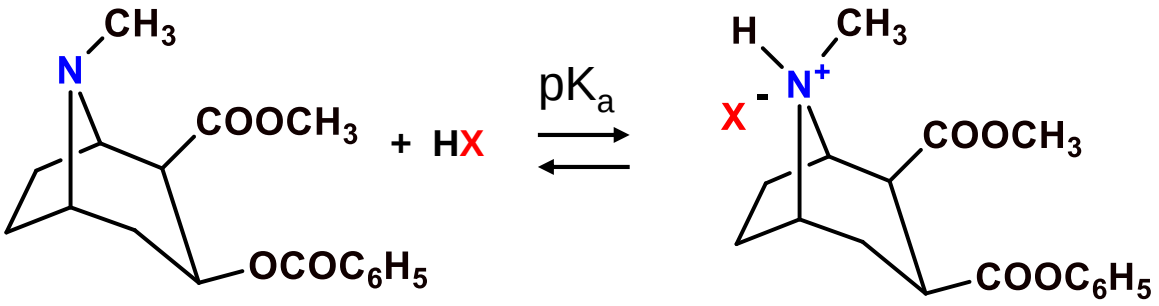
- Alkaloids can act as medicines

Quinine
Anti-malaria



Basicity of Alkaloids.

- As the name implies alkaloids are basic in nature (pK_a >7)*
- Medicinally important alkaloids are usually administered as the ammonium salts



Cocaine
smokable

Cocaine hydrochloride
not smokable but water soluble
(i.e. snortable)

- The hydrochloride salt is what is sold as “Coke”
- Basification of the hydrochloride leads to the “Free Base” which is known as “Crack”

*Warhurst et al. Malaria Journal 2003 2, 26.

Functions of Alkaloids in Plants.

- They may act as **protective** against insects and herbivores due to their bitterness and toxicity.
- They are, in certain cases, the final **products of detoxification** (waste products).
- **Source of nitrogen** in case of nitrogen deficiency.
- They, sometimes, act as **growth regulators** in certain metabolic systems.
- They may be utilized as a **source of energy** in case of deficiency in carbon dioxide assimilation.

Classification of Alkaloids.

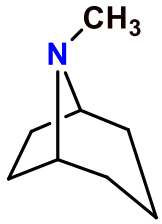
Hagnauer system of classification:

- True alkaloids (nitrogen in a heterocyclic ring. e.g. Atropine).
- Proto alkaloids (amphetamine, aconitine, ..., no heterocyclic ring)
- Pseudo alkaloids (caffeine, theobromine, … not from amino acids)

- Other classifications:
  - Biogenetic.
    - Based on the biogenetic pathway that form the alkaloids.
  - Botanical Source.
    - According to the plant source of alkaloids.
  - Type of Amines.
    - Primary, Secondary, Tertiary alkaloids.
  - Basic Chemical Skeleton

Classification by Basic Chemical Backbone.

- Main structural motif in true alkaloids:

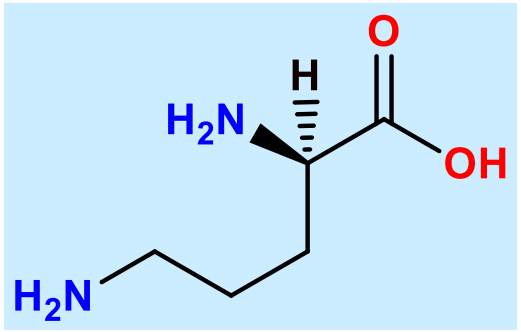


Starting amino acid

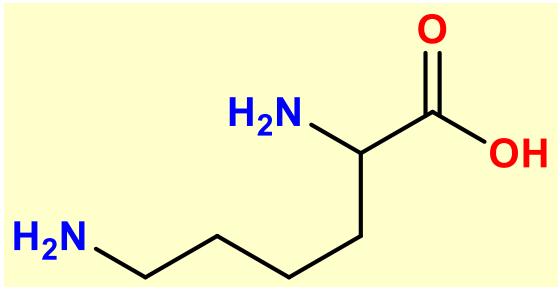
- Tropane alkaloids → ornithine
- Quinoline alkaloids → tryptophan
- Pyridine, piperidine alkaloids → [pyridine] / lysine
- Imidazole alkaloids → histidine
- Indole alkaloids → tryptophan
- Isoquinoline alkaloids → tyrosine

Classification of Alkaloids. Alkaloids from Ornithine and Lysine.

- Classified according to amino acid from which they were formed

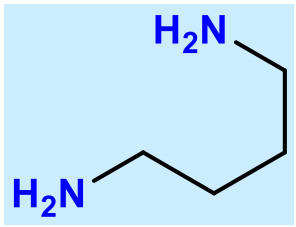


Ornithine

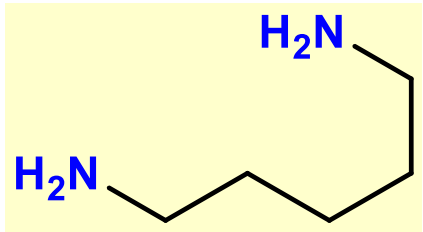


Lysine

- Biosynthesis through symmetrical diamines



Putrescine

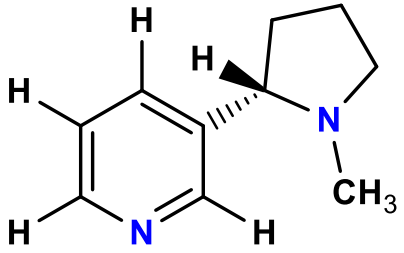


Cadaverine

- Alkaloids: generally aliphatic in nature

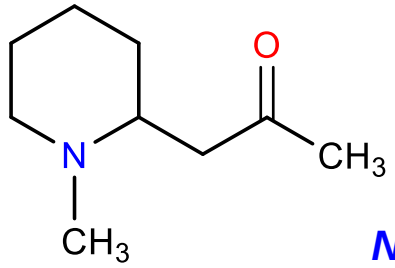
Examples of Alkaloids from Ornithine and Lysine.

- Two examples of these alkaloids are:



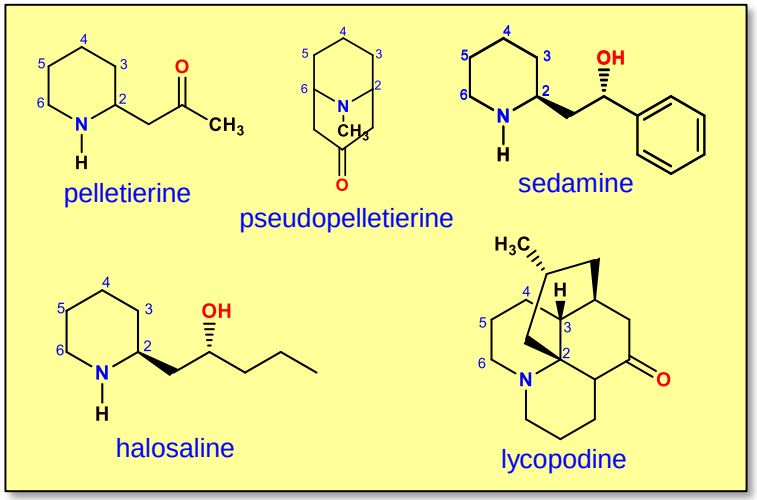
Nicotine
ex ornithine

Tobacco alkaloids

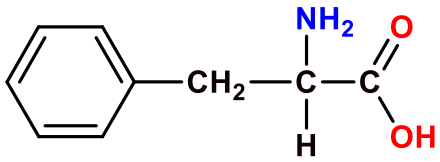


N-Methylpelletierine
ex lysine

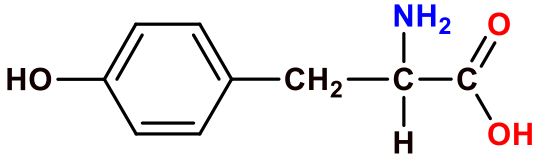
Piperidine alkaloids



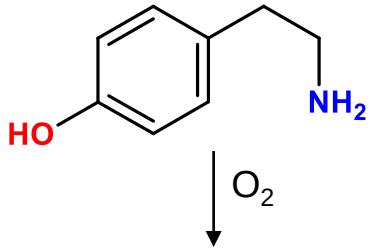
Alkaloids from Phenylalanine and Tyrosine.



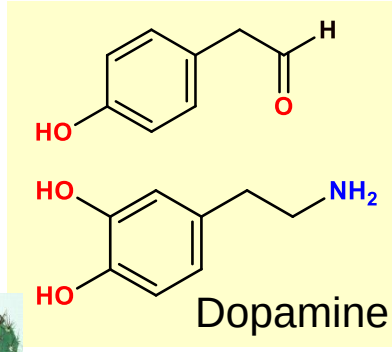
Phenylalanine



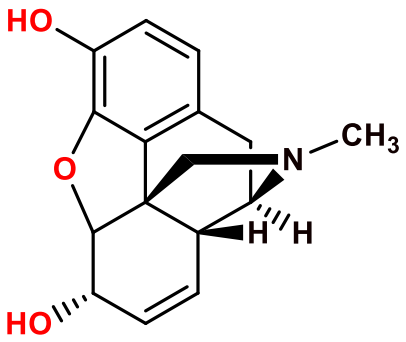
Tyrosine



- All these alkaloids possess Ar-C-C-N moiety
- Intermediates in biosynthesis:



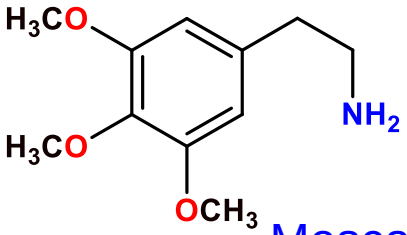
Esempi:



Morphine
ex tyrosine

Papaver somniferum L.

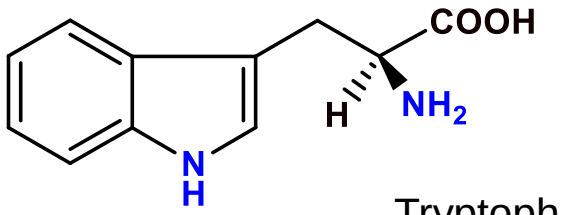
peyote cactus



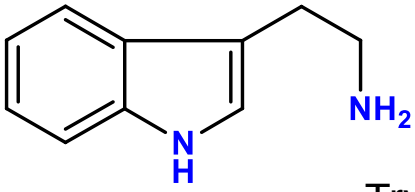
Mescaline

Alkaloids from Tryptophan.

- Alkaloids derived from Tryptophan have tryptamine as intermediate:

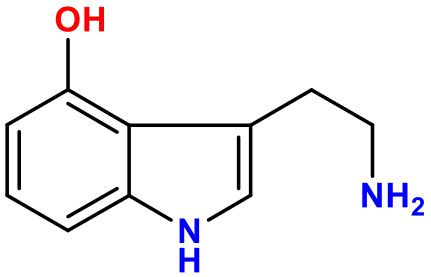


Tryptophan

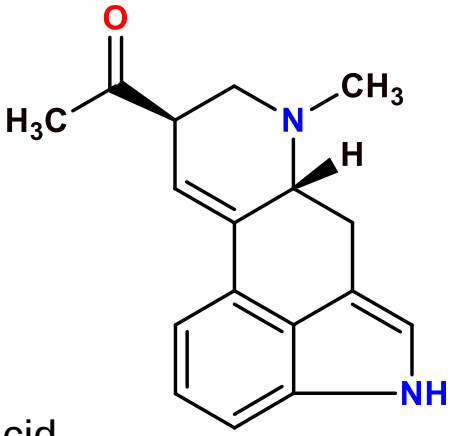


Tryptamine

- Two examples of these alkaloids are:



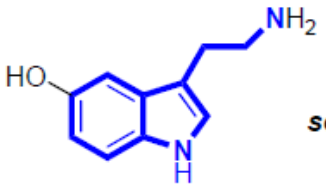
Pscilocin



Lysergic acid
diethylamide LSD

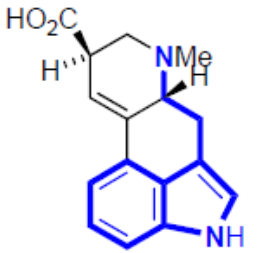
Tryptophan Derived Alkaloids.

- Alkaloids containing an indole subunit:
  - Skeleta built up by reductive amination, decarboxylation & hydroxylation)
  - Major classes:
  - simple derivatives (e.g. serotonin, bufotenine)

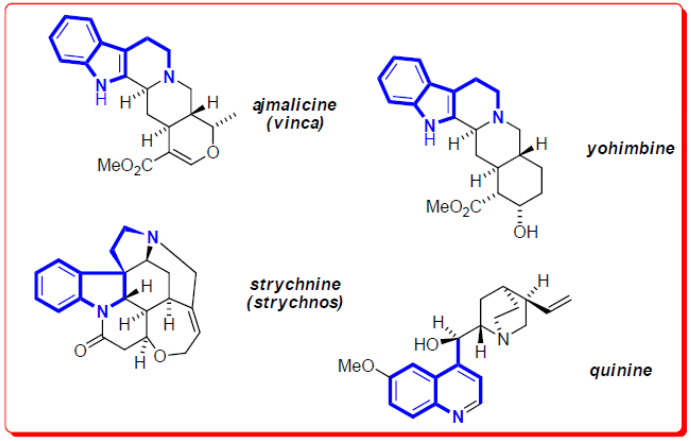


serotonin

  - mixed Trp/mevalonate alkaloids e.g.
    - ergot [DMAPP derived] (e.g. ergoline, lysergic acid)
    - vinca [secologanin derived]
    - yohombine [secologanin derived]
    - strychnos [secologanin derived]
    - quinine [secologanin derived]

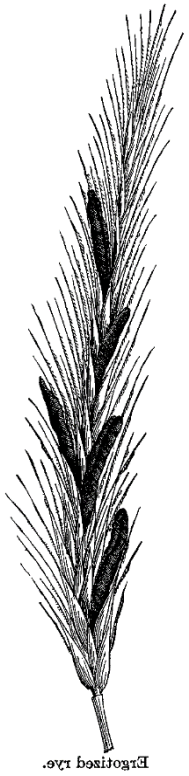


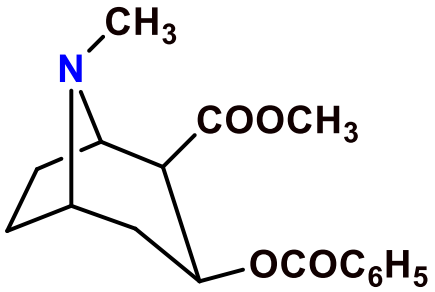
Lysergic acid (ergot)



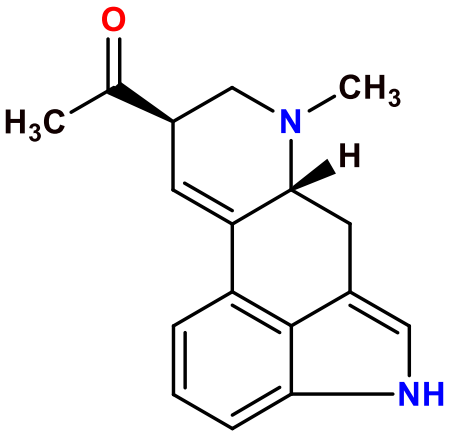
Psychoactive Alkaloids.

- Lysergic acid (precursor of **ergot alkaloids**) is an indole alkaloid isolated from a growth on rye called *Claviceps Purpurea*
- Cocaine is an alkaloid of tropane structure found in leaves of the South American shrub *Erythroxylon coca*.





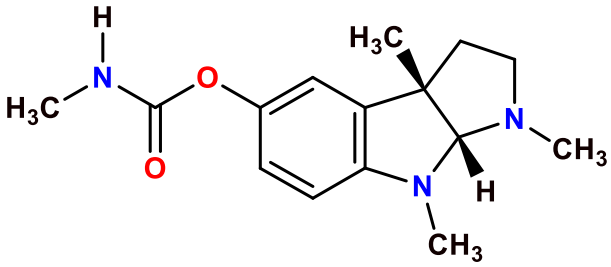
Cocaine



Lysergic acid diethylamide LSD

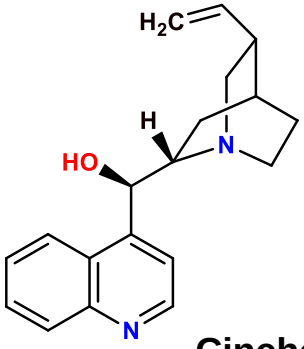
Other Examples of Alkaloids.

- The nerve toxin physostigmine (indole alkaloid) is isolated from the "bean of Calabar" *Physostigma venenosum*

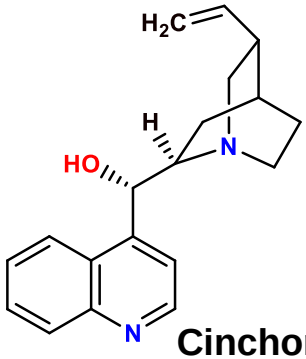


Physostigmine

- Cincona alkaloids (quinoline derivatives) are isolated from dried barks of *Cinchona succirubra* (Rubeaceae).



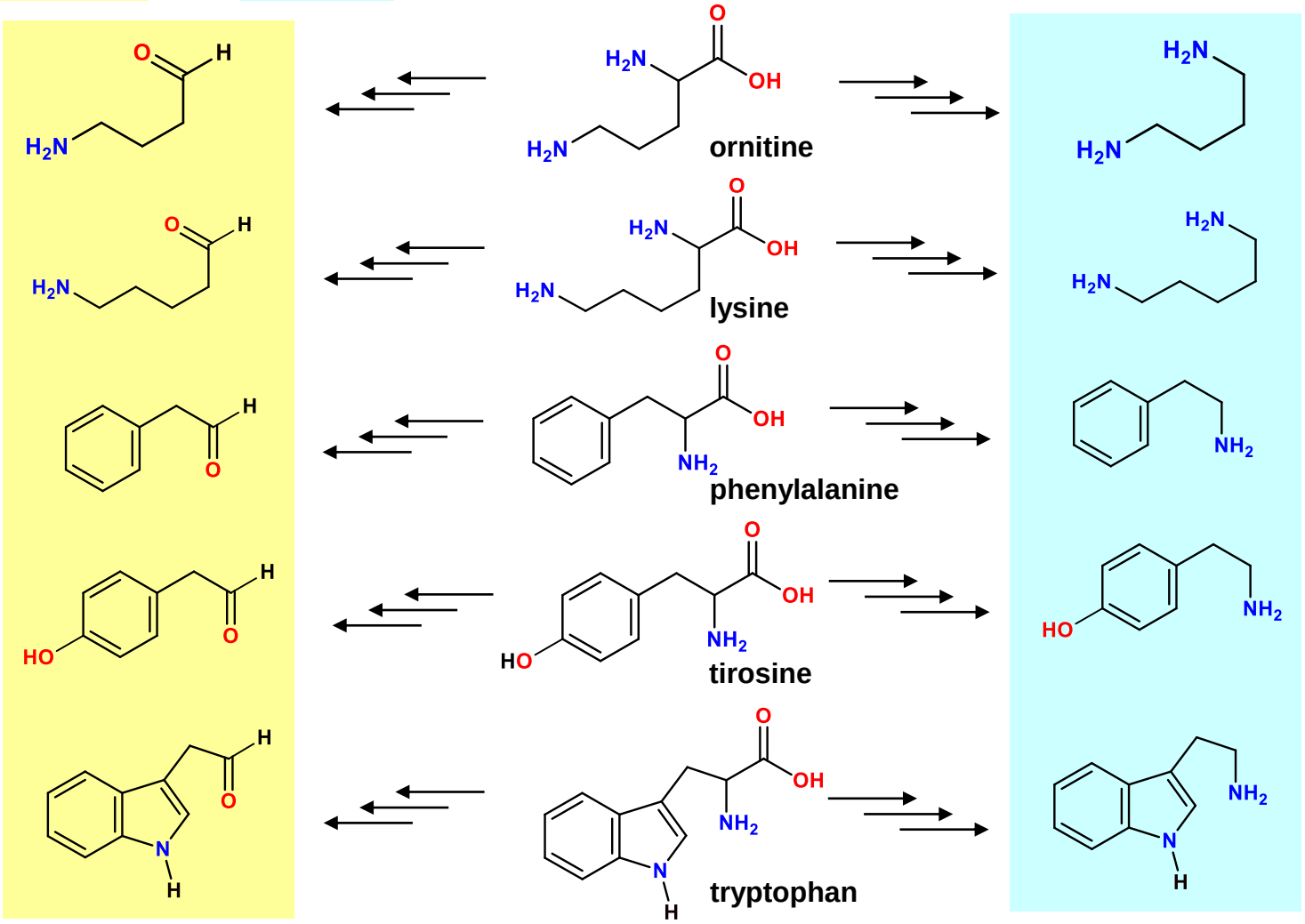
Cinchonidine



Cinchonine

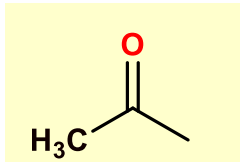
Biosynthesis of Alkaloids: The “Reagents”.

- Aldehydes and Amines are the common intermediates from amino acids

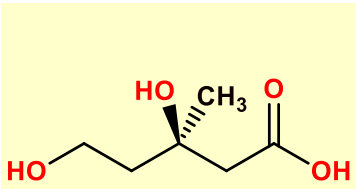


Other Biosynthetic Building Blocks.

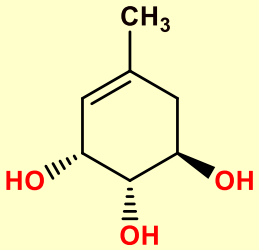
- Precise biosynthetic pathways: frequently not known
- Most use a small number of building blocks
- Amino acids (see previous) and:



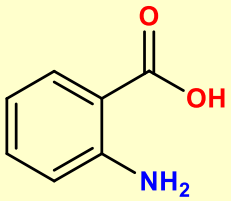
Unità acetato



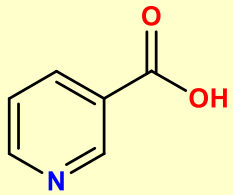
Acido mevalonico



Acido scichimico



Acido antranilico



Acido nicotinico

Biosynthetic Transformations

Major enzyme catalysed reactions:

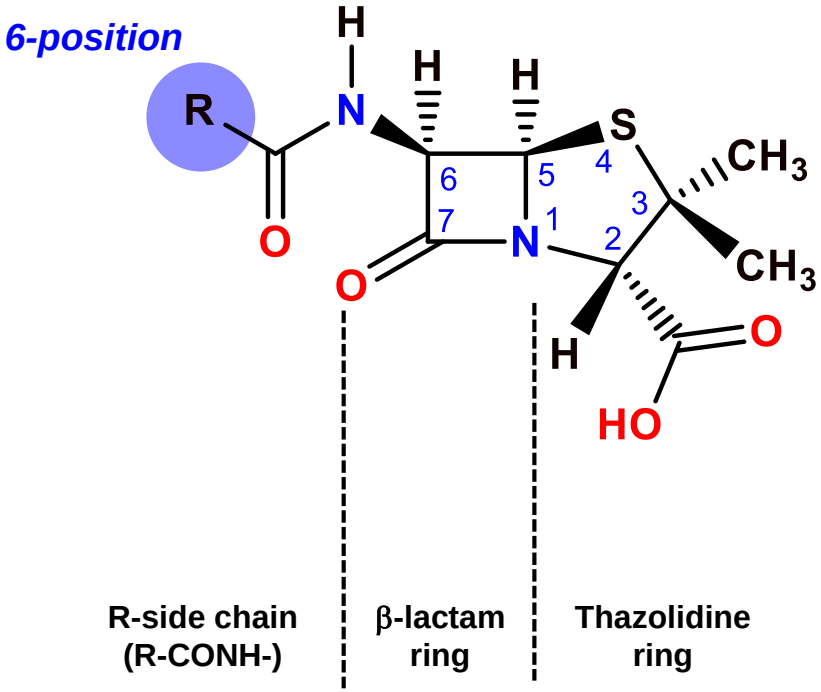
1) Decarboxylations
2) Transaminations
3) Methylations
4) Oxidations/Reductions
5) Carbon-carbon bond formation

Many, many other enzyme catalysed these reactions.

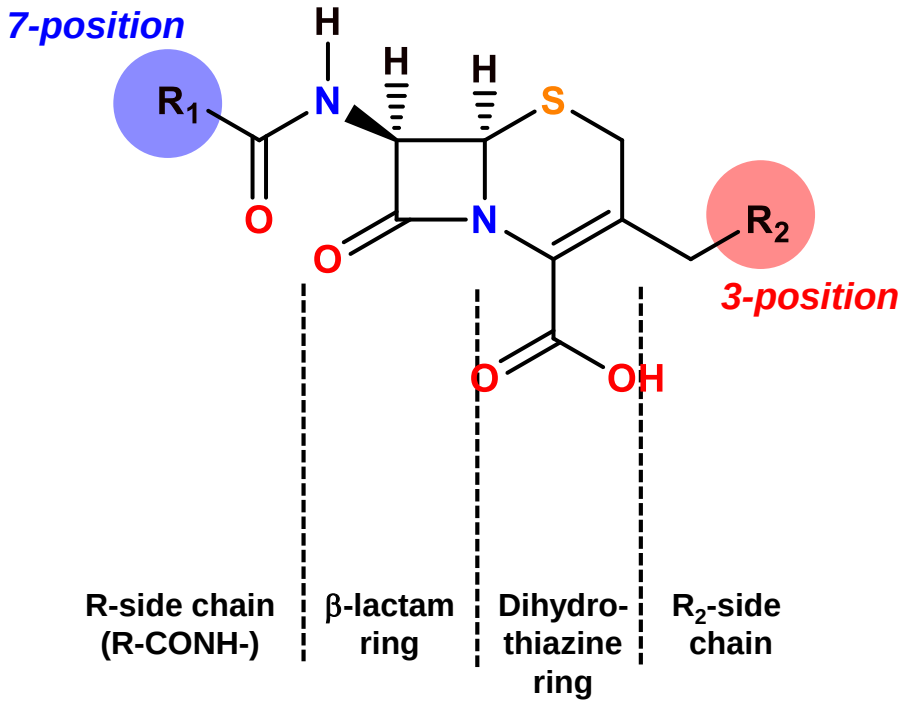
Pharmacological Activity.

1. Analgesics and narcotics: morphine and codeine.
2. CNS stimulants : caffeine and strychnine.
3. Anticancer: vincristine, vinblastine and taxol.
4. Mydriatics: atropine.
5. Anti-asthmatics : ephedrine.
6. Anti-tissue: codeine.
7. Expectorants: lobeline.
8. Anti- hypertensive: reserpine.
9. Smooth muscle relaxants: atropine and papaverine
10. Skeletal muscle relaxants: δ-tubocurarine.
11. Anthelmintic: pelletierine and arecoline.
12. Antiparasitics: quinine and emetine

Penicillin Antibiotics.



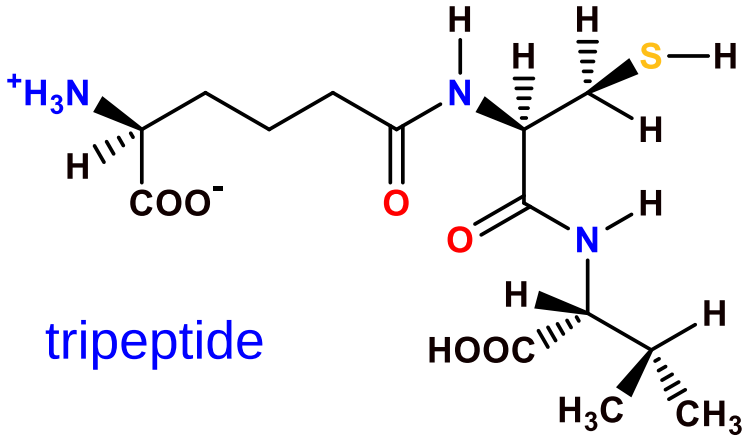
Penicillins



Cefalosporins

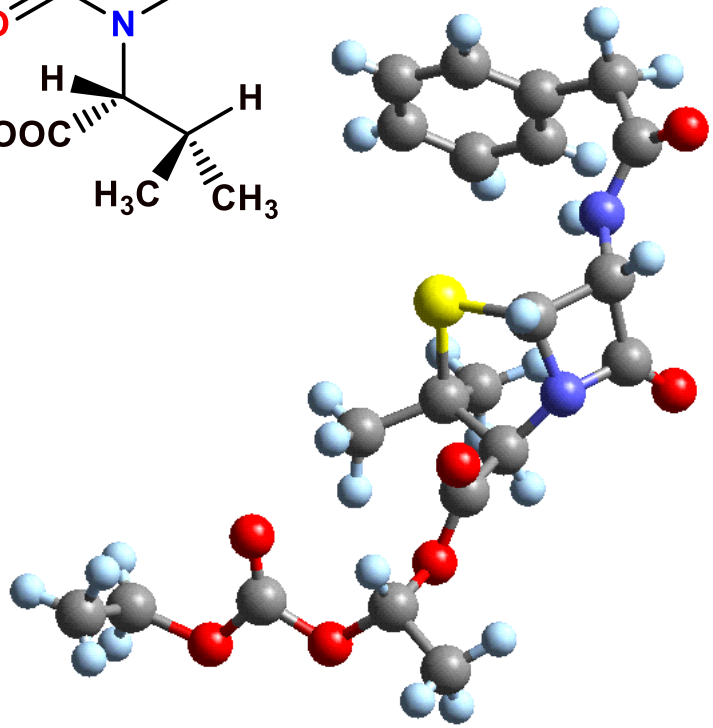
Penicillin Biosynthesis.

α-adipate
+
cysteine
+
valine



tripeptide

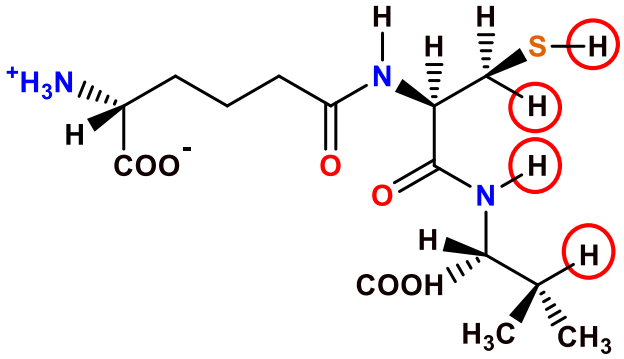
- start with peptide made of 3 amino acids (including a non-standard a.a., α-adipate)



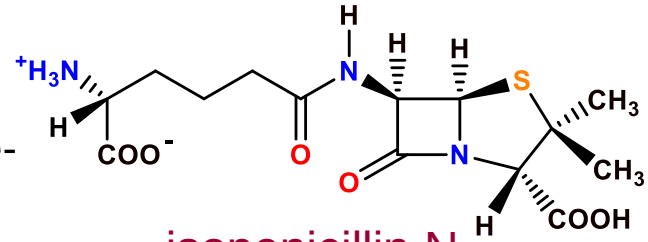
Penicillin Benzylpenicillin
(1'-Diethyl Carbonate Ester)

Penicillin Biosynthesis (2).

α-adipate
+
cysteine
+
valine

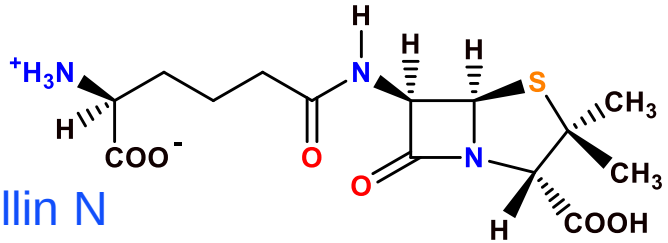


isopenicillin synthase

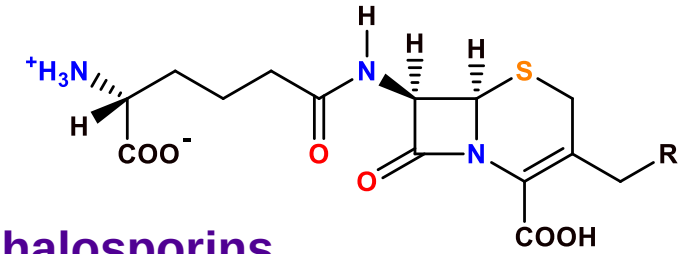


isopenicillin N

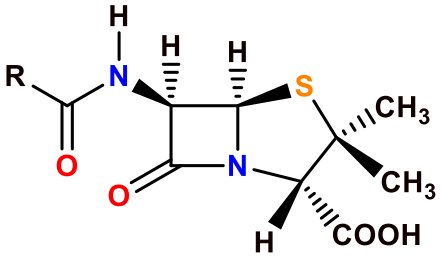
Epime-
rase



penicillin N



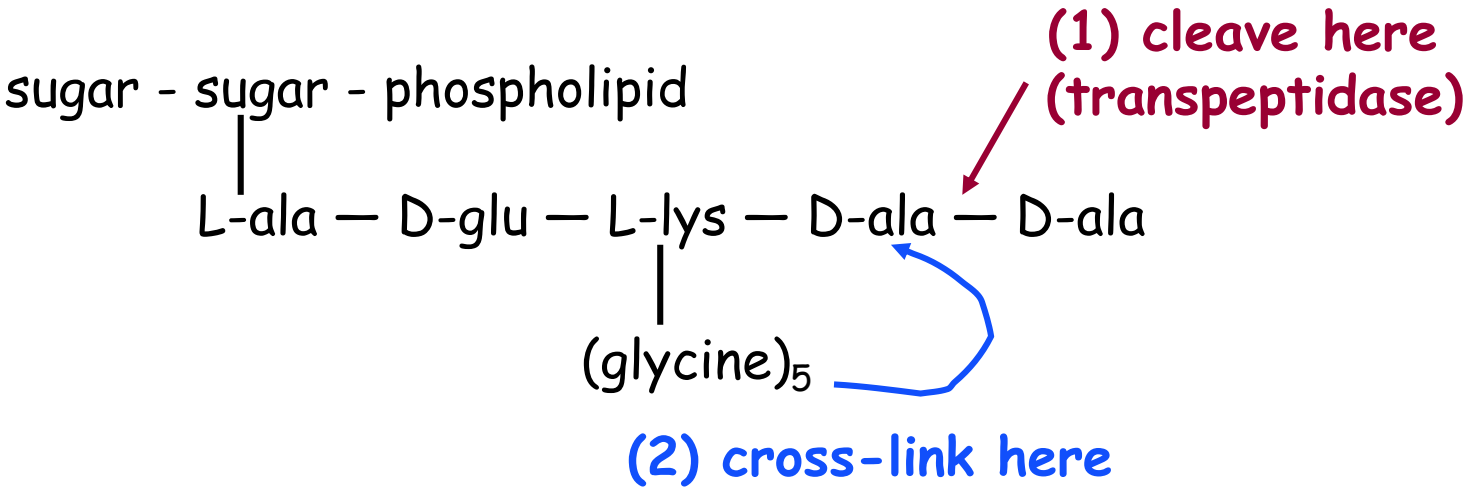
cephalosporins



penicillins

Penicillins: Mechanism of Action.

- This class of antibiotics interferes with synthesis of the cell wall of Gram-positive bacteria (Staphylococci, Streptococci)
- Cell wall is a repeating polymer of disaccharide, tetrapeptide repeats cross-linked into a 3D matrix



Penicillins inhibit the bacterial transpeptidase enzyme by **mimicking** its natural substrate, the terminal D-ala—D-ala

Transpeptidase attacks the β-lactam ring of penicillin, forms a covalent bond; enzyme is now out of business