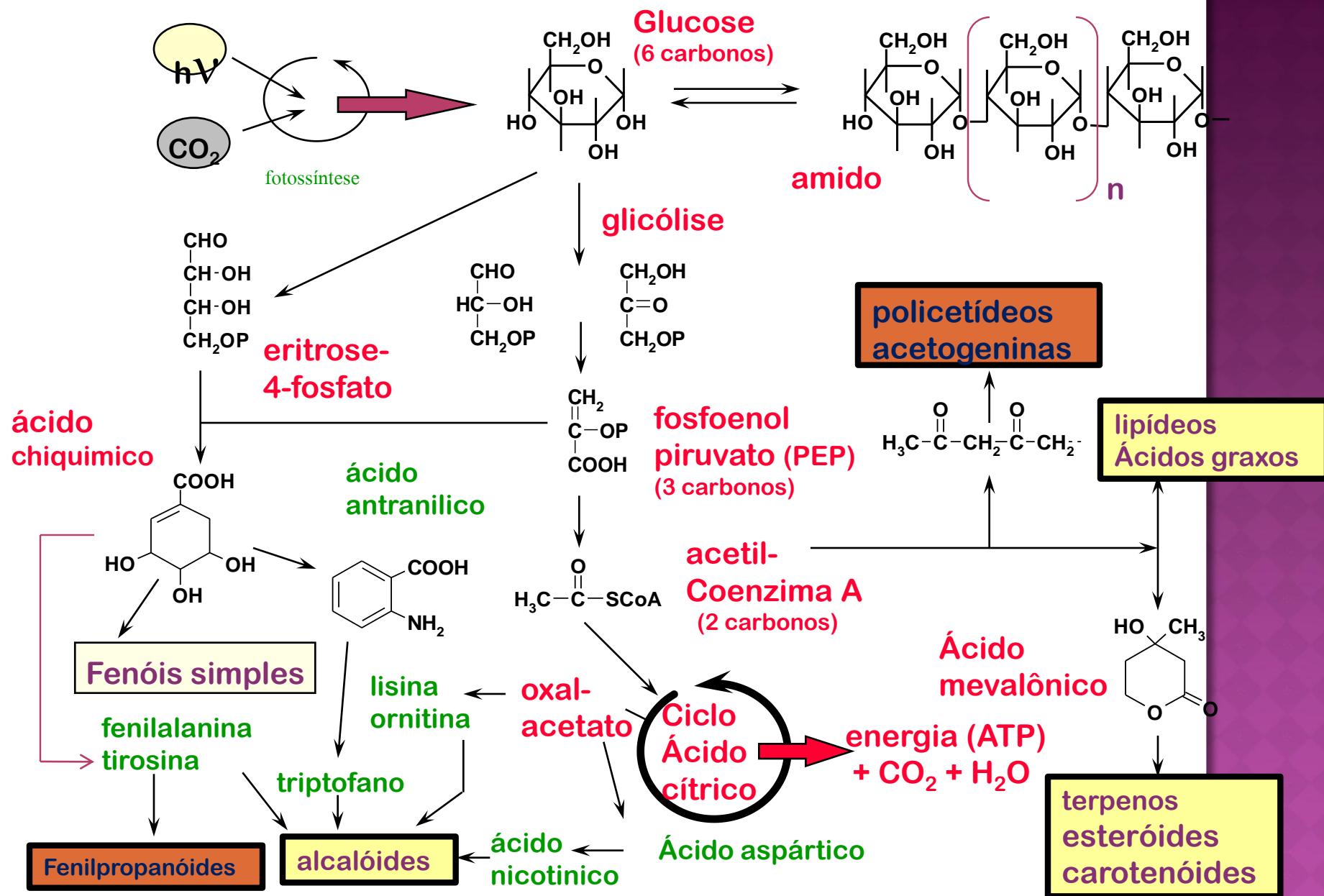


COMPOSTOS FENÓLICOS

COMPOSTOS FENÓLICOS

- Origem Química: Policetídeos; Ácido Chiquímico
- Distribuição Taxonômica: ampla (ex. ácido caféico é um dos compostos fenólicos mais comuns em plantas)
- Fontes comuns: Uva-Ursi, Salgueiro, Tomilho, Rosmarino, Lúpulo, cebolas, etc.
- Propriedades Terapêuticas: antisépticos & antimicrobianos; antiinflamatórios & analgésicos; antispasmódicos; antipréticos; diuréticos; irritantes tópicos.



Origem dos compostos aromáticos



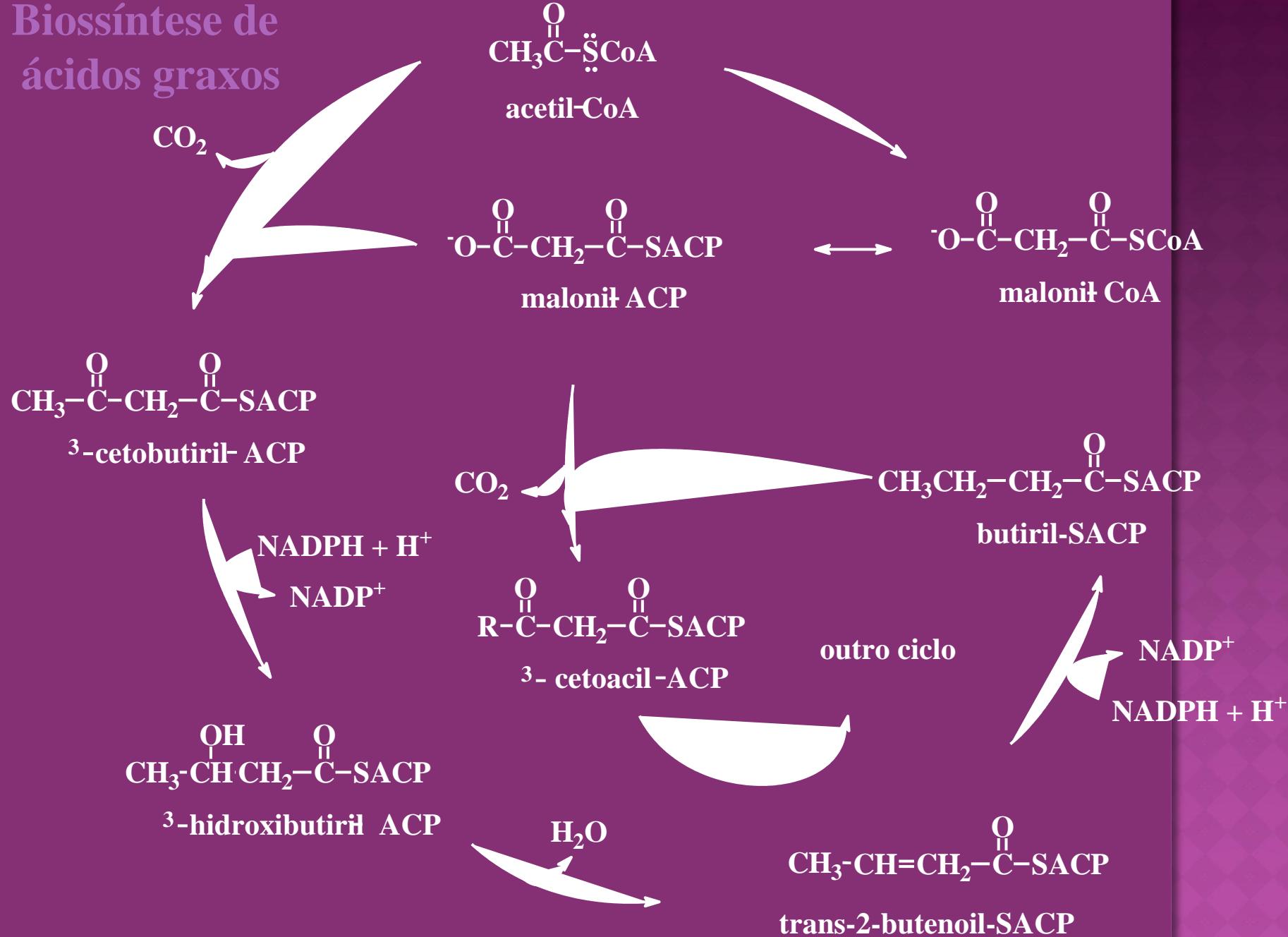
ÁCIDO
CHIQUÍMICO



POLICETÍDEOS

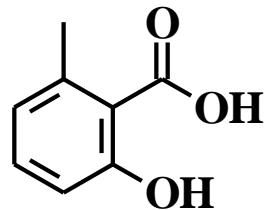
POLICETÍDEOS

Biossíntese de ácidos graxos

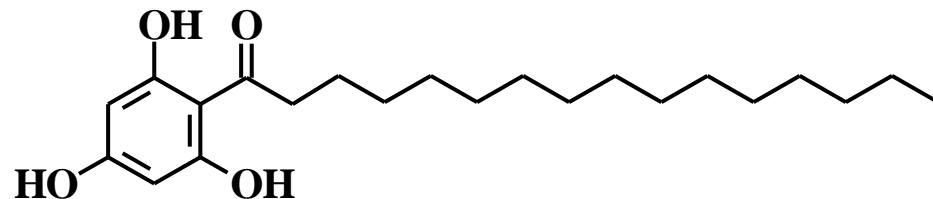


Policetídeos Aromáticos:

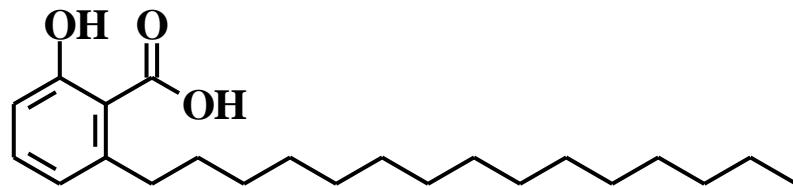
Envolvem condensação de Claisen em compostos β -policetometilênicos.



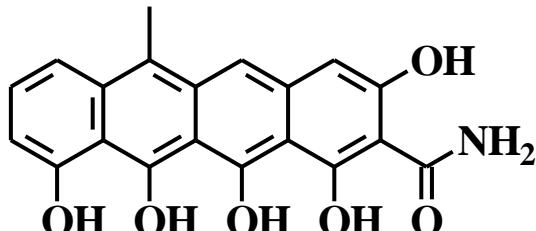
ácido 6-metilsalicílico



produto de algas (*Zonaria* - Dictyotales)

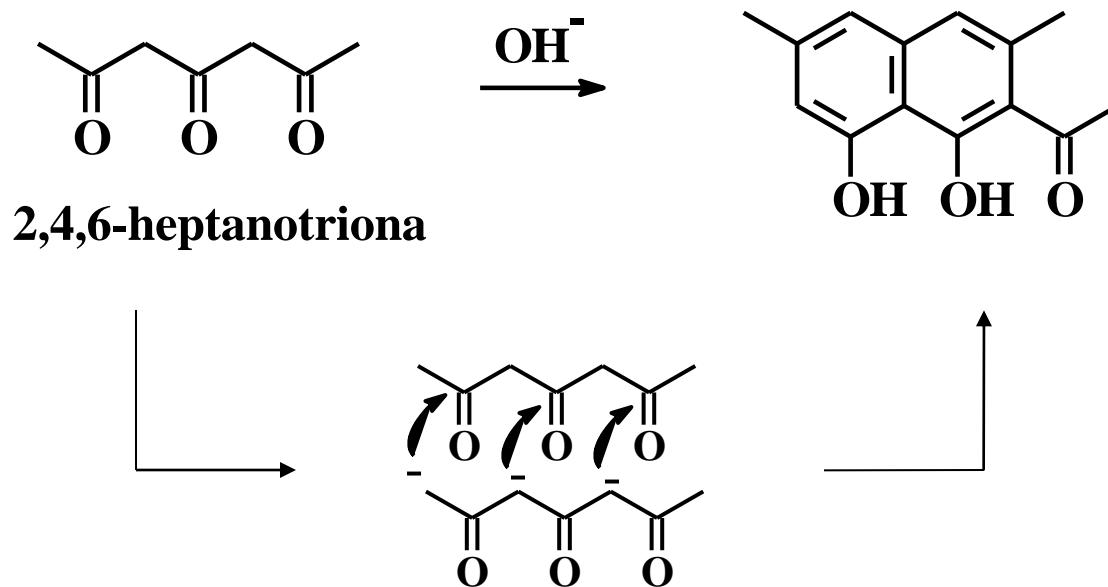


Ácido anacárdico
(*Pistacia vera* - Anacardiaceae)

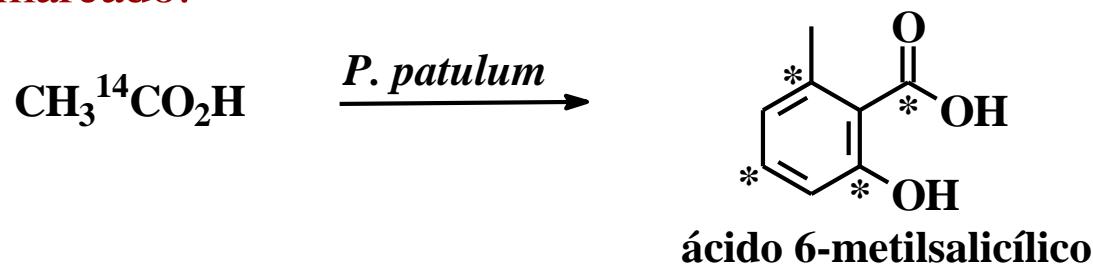


6-metiltetraciclina

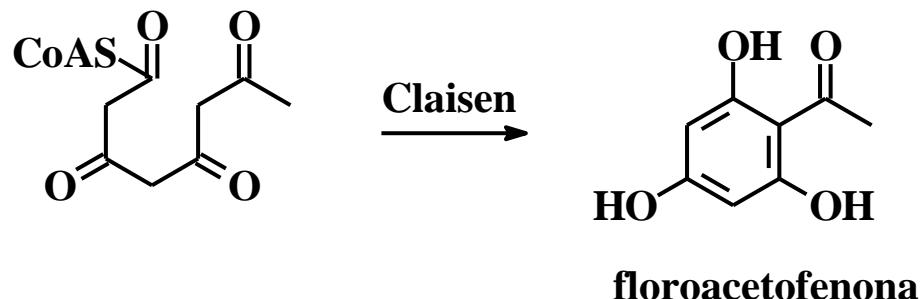
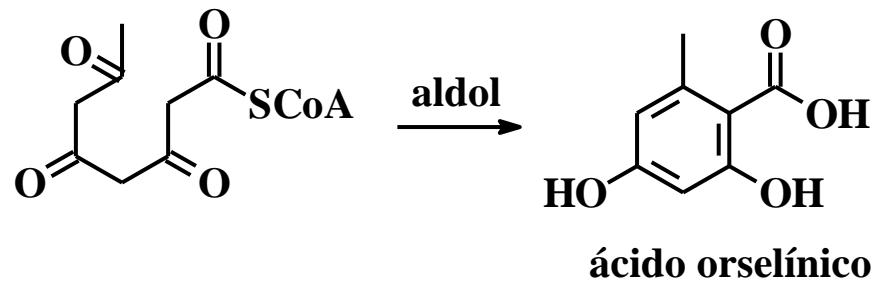
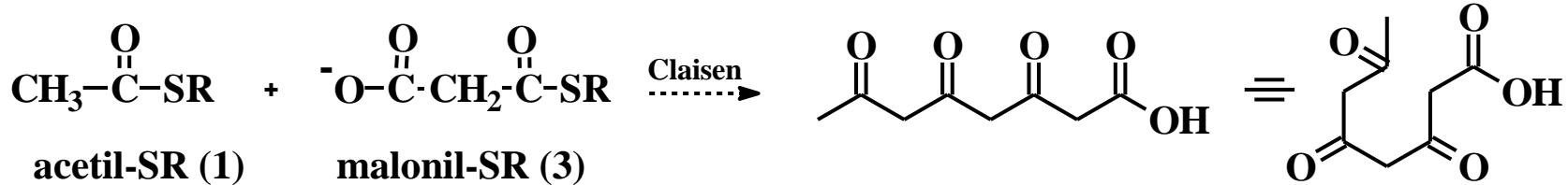
Collie (1907): Síntese biomimética que gerou a hipótese da biossíntese policetídica de moléculas aromáticas.



Birch (1950): Confirmou a hipótese através da incorporação de acetato marcado.

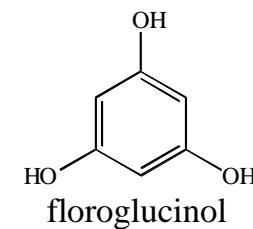
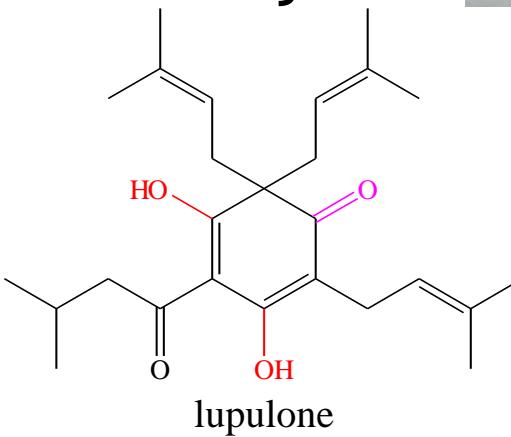
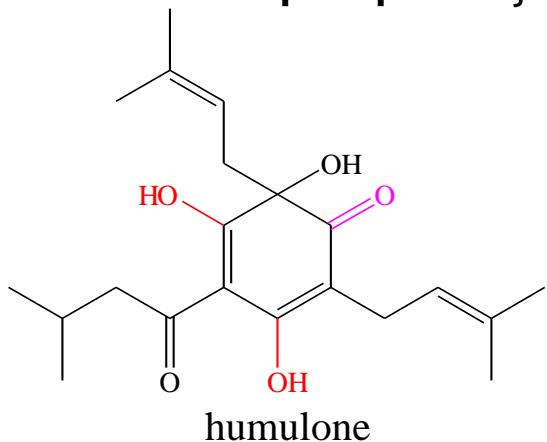


Dois modos diferentes de ciclização em cadeias policetometilênicas



LÚPULO (ESTRÓBILOS)

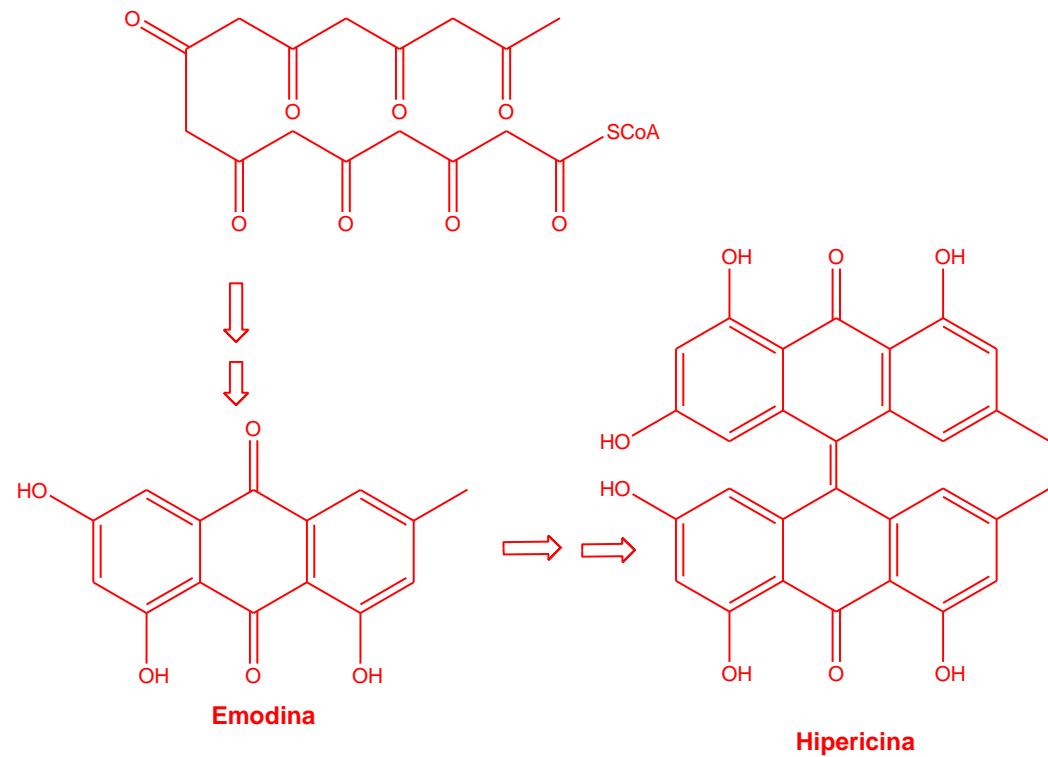
- *Humulus lupulus* L.
(Cannabaceae)
- humulona, lupulona (derivados do floroglucinol)
- Usados na preparação da cerveja

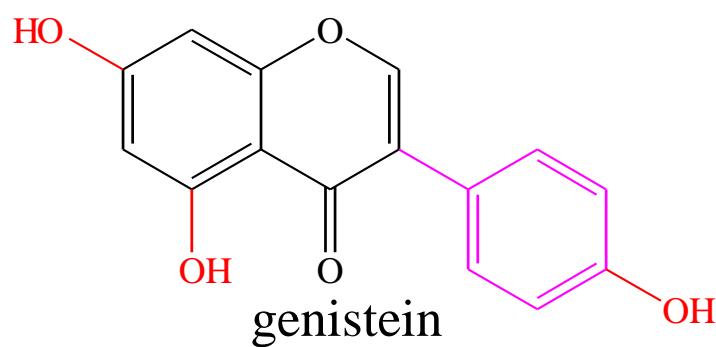
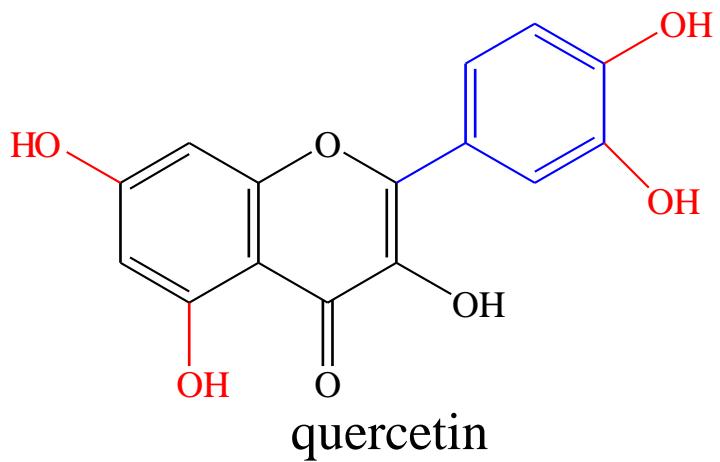
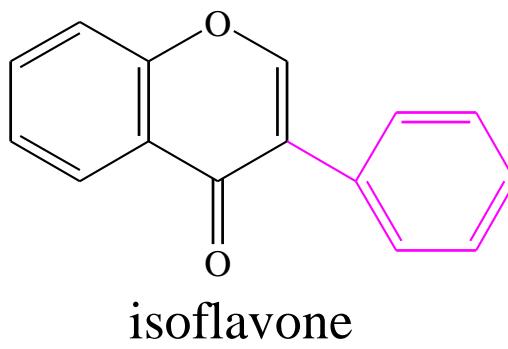
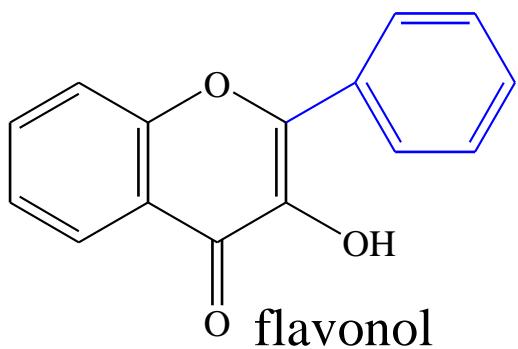


HYPERICUM PERFORATUM L.



- Hipericina: ação antibiótica, inibidora da dopamina β -hidroxilase (aumentando níveis de dopamina).
- Atividade fotossensibilizadora, acumulando em células cancerosas, sendo testada em terapia fotodinâmica





Flavonoid

C6

-

C3

-

C6

FENILPROPANÓIDES

Síntese de Aminoácidos
Aromáticos



PLANTAS/
MICRORGANISMOS

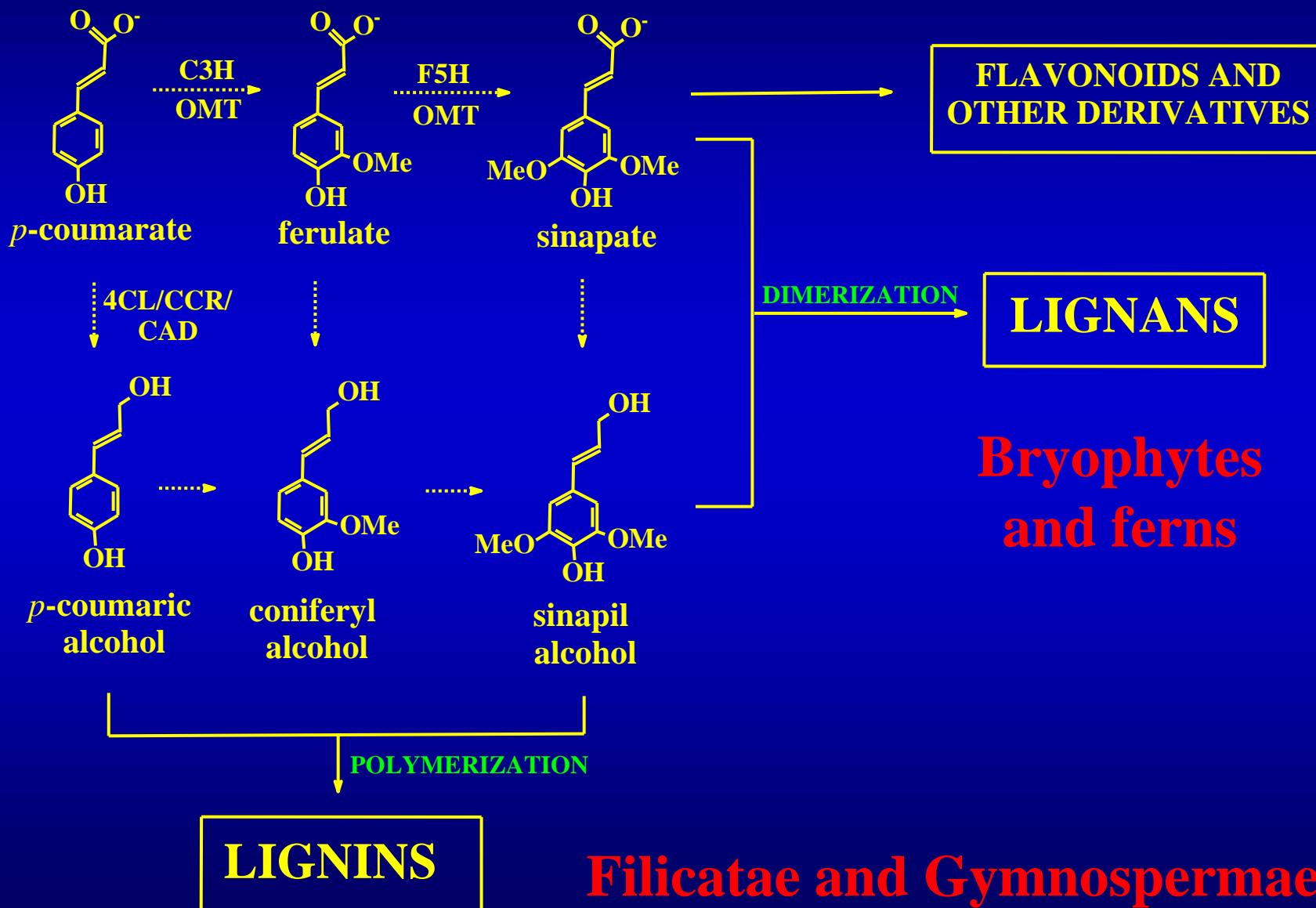


ANIMAIS

Evolution of phenylpropanoid pathway in plants

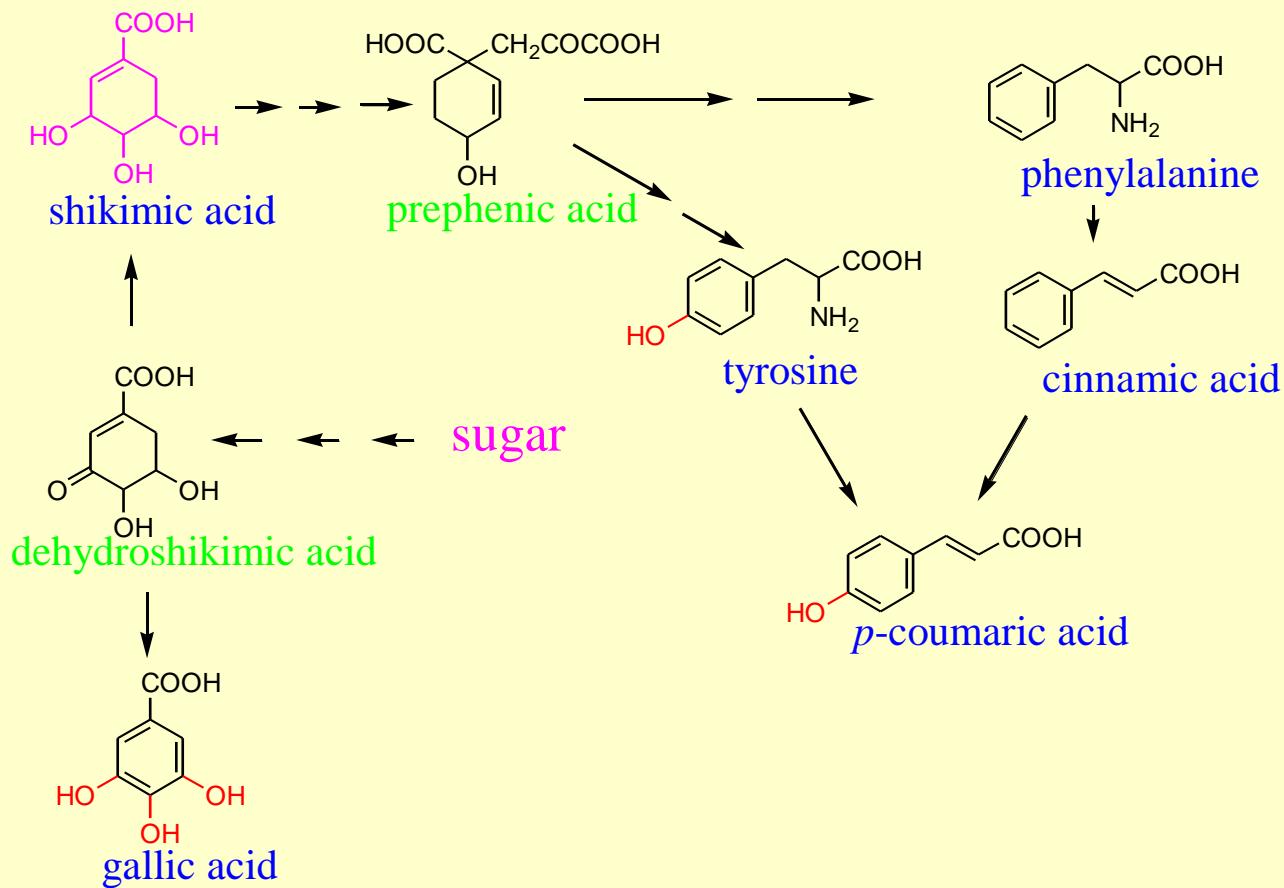
	Probable age 10^6 yr BP	Primary metabolites	Secondary metabolites
Algae	1500	phenylalanine/tyrosine	
Bryophyta	380	cinnamic acids	flavones flavonols anthocyanidins
Lycopodiatae	350		
Equisetatae	300		procyanidins
Filicatae	300	cinnamyl alcohols	lignins
Gymnospermae	280	propenyl/allylphenols	lignans
Angiospermae	135		neolignans

General phenylpropanoid metabolism



ÁCIDO CHIQUÍMICO

BIOSYNTHESIS OF PHENYLPROPANOID COMPOUNDS



JOHAN FREDERIK EYKMAN (1851-1915)

1881 - Faculty of Medicine of University of Tokyo

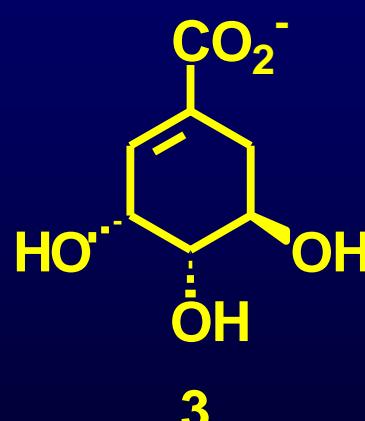
**“Sur les principes constituents
de *I'llicium religiosum* (Seib)**

***Recueil Travaux Chimique des Pays-Bas* 4, 32-54 (1885)**

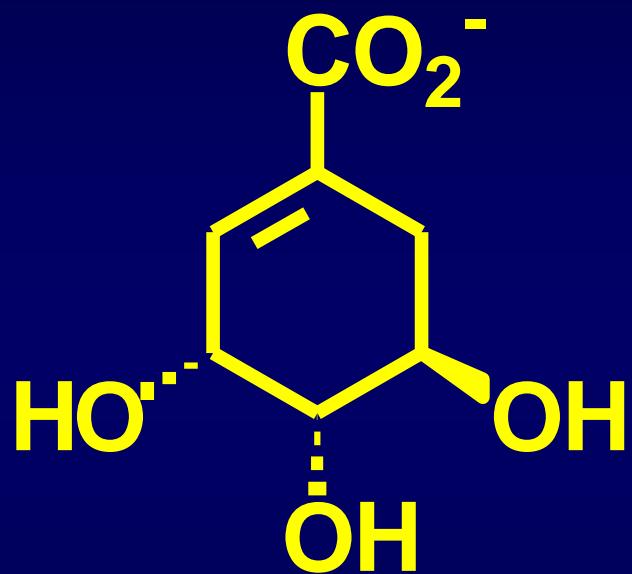
Shikimic acid

(“shikimi-no-ki” - *Illicium religiosum*)

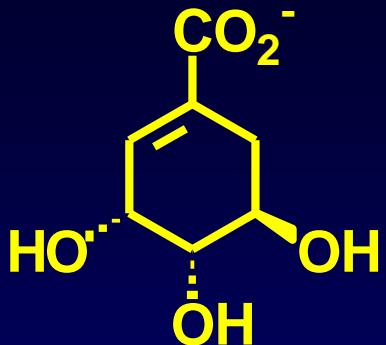
$C_7H_{10}O_5$;
mp 184°C;
 $[\alpha]_D - 176^\circ$ EtOH;
 $[\alpha]_D - 246^\circ$ water



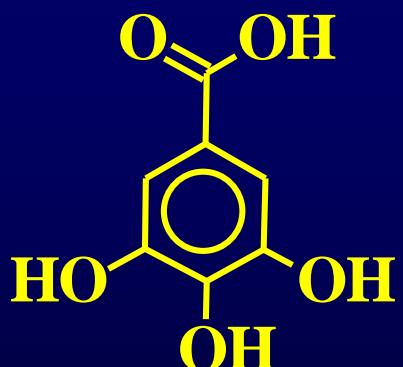
H.O. L. Fischer (1930)



(-)shikimic acid



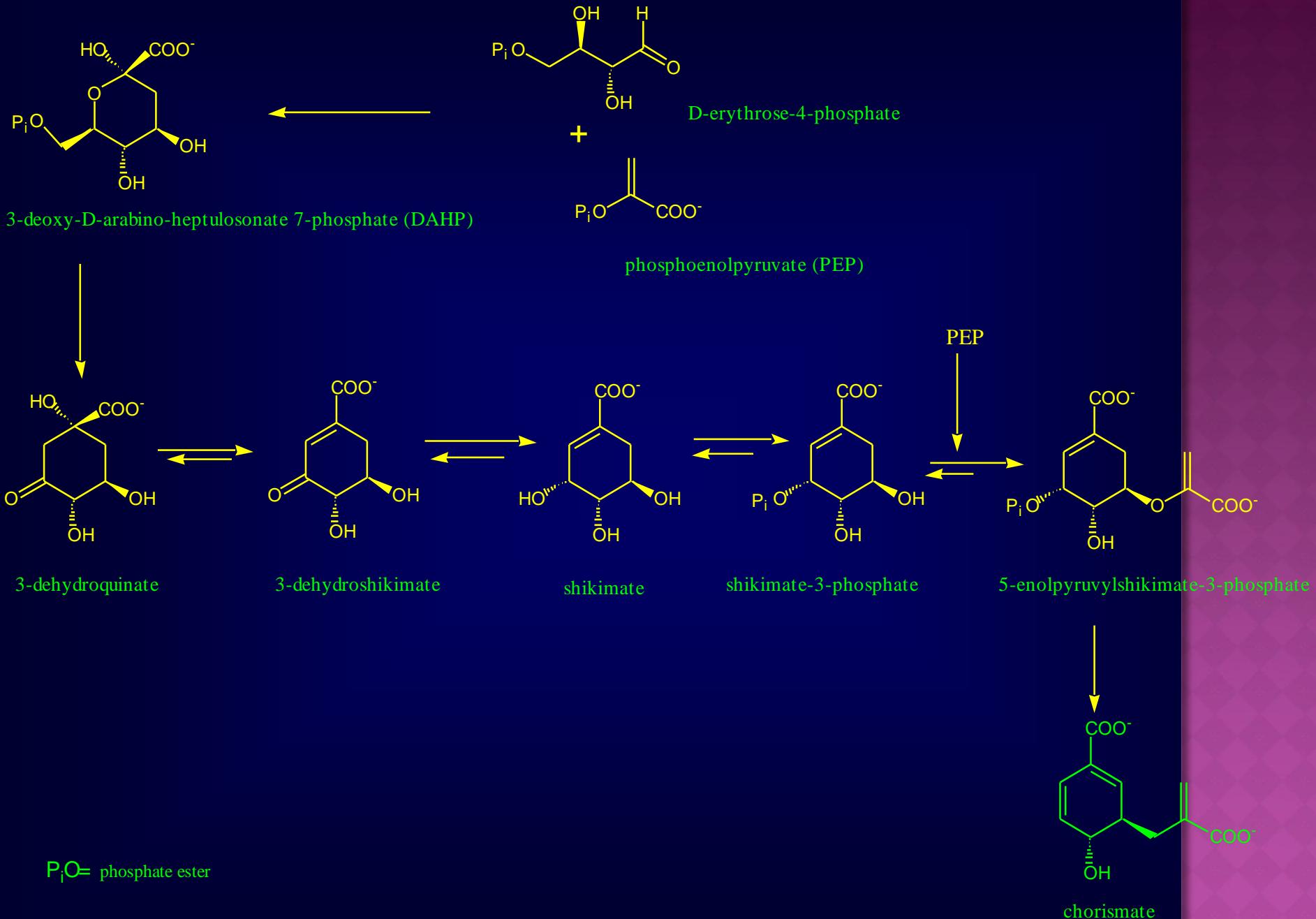
Ácido (-)-chiquimico



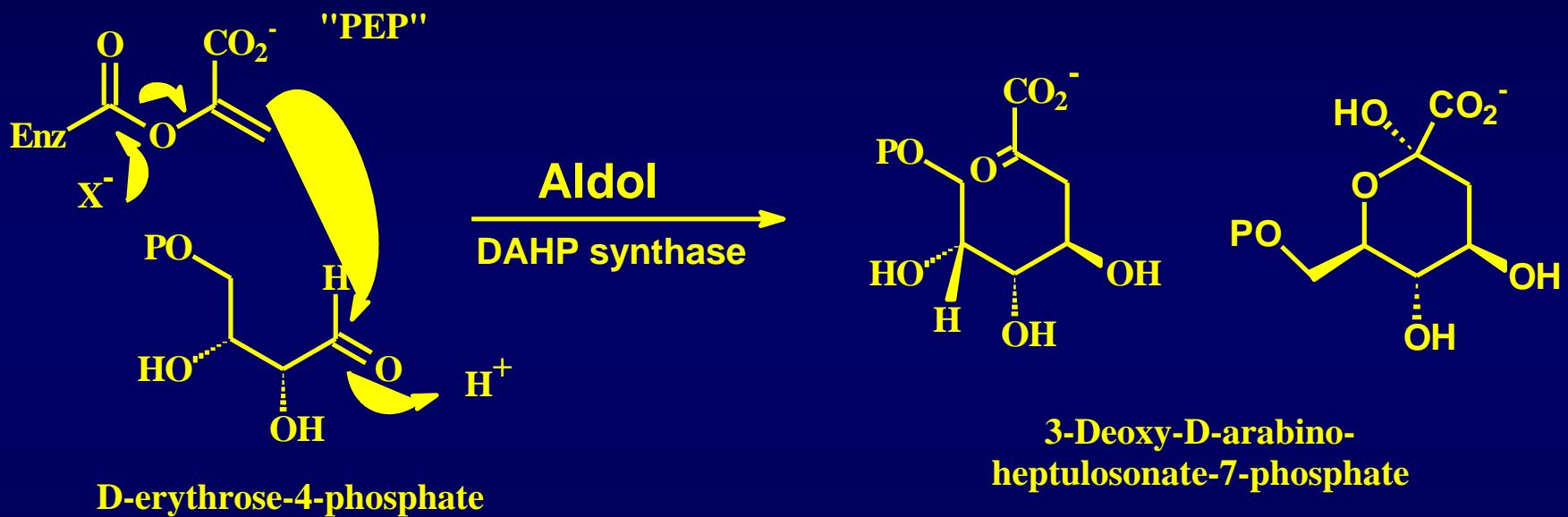
ácido gálico



ácido clorogênico



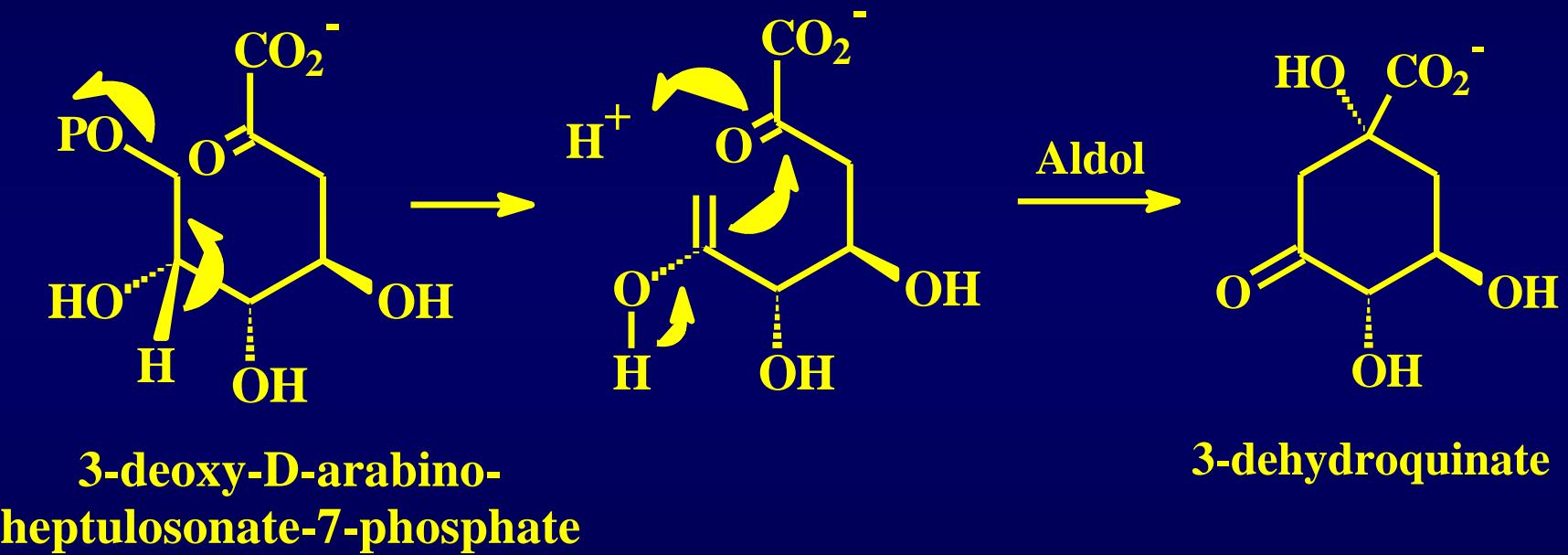
3-Deoxy-D-arabino-heptulosonate 7-phosphate (DAHP) synthase



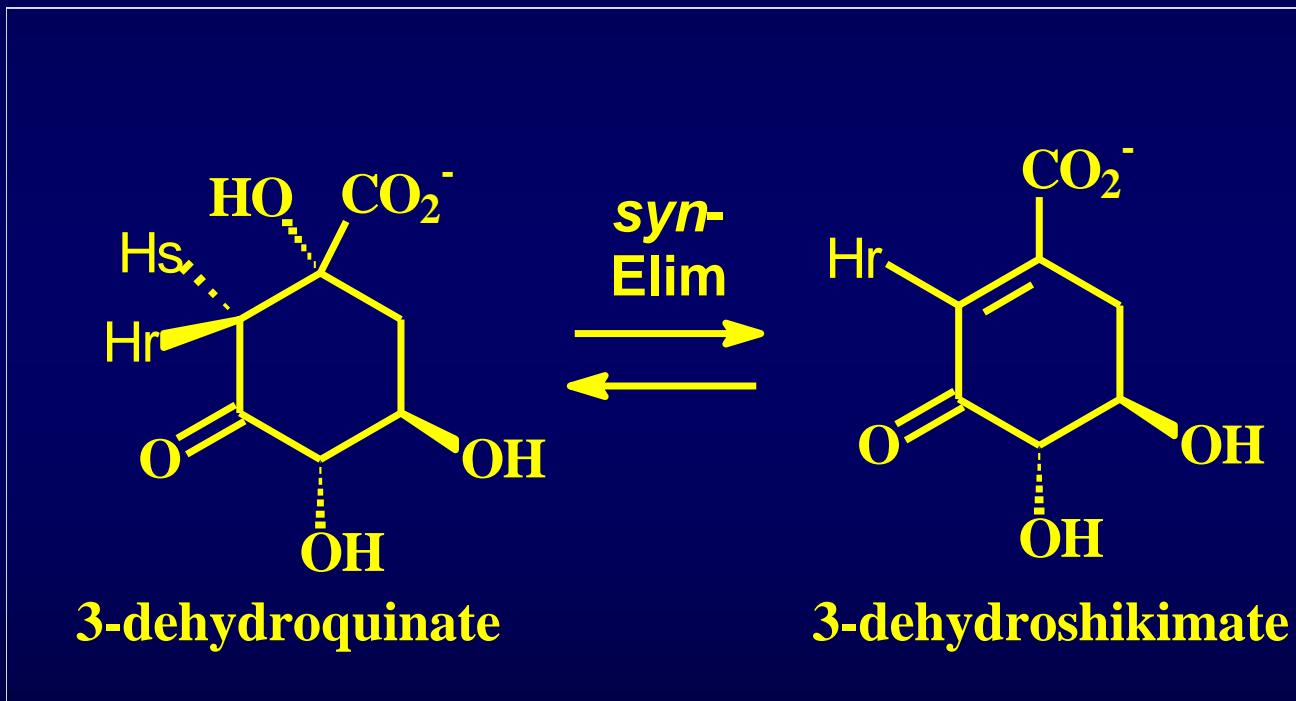
DAHP synthase is inducable upon wounding in potatoes and tomatoes

[Dyer at al. (1989) *Proc. Natl. Acad. Sci. USA* 86:7370-73].

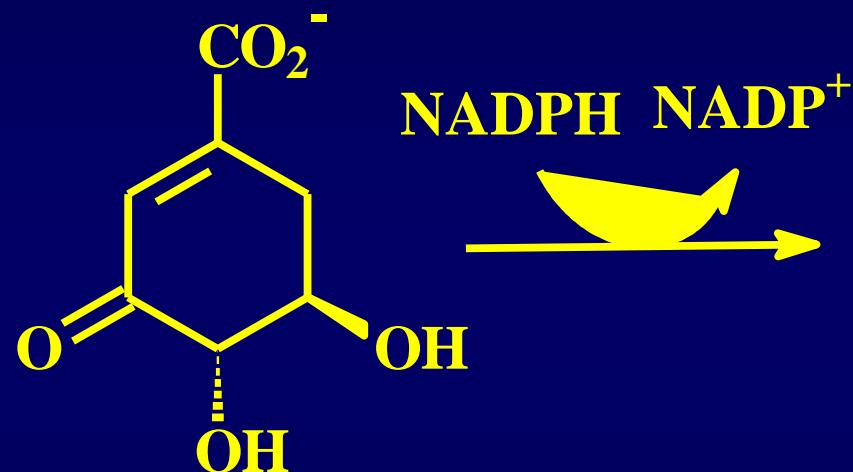
3-Dehydroquinate synthase



3-Dehydroquinate dehydratase (3-dehydroquinase)



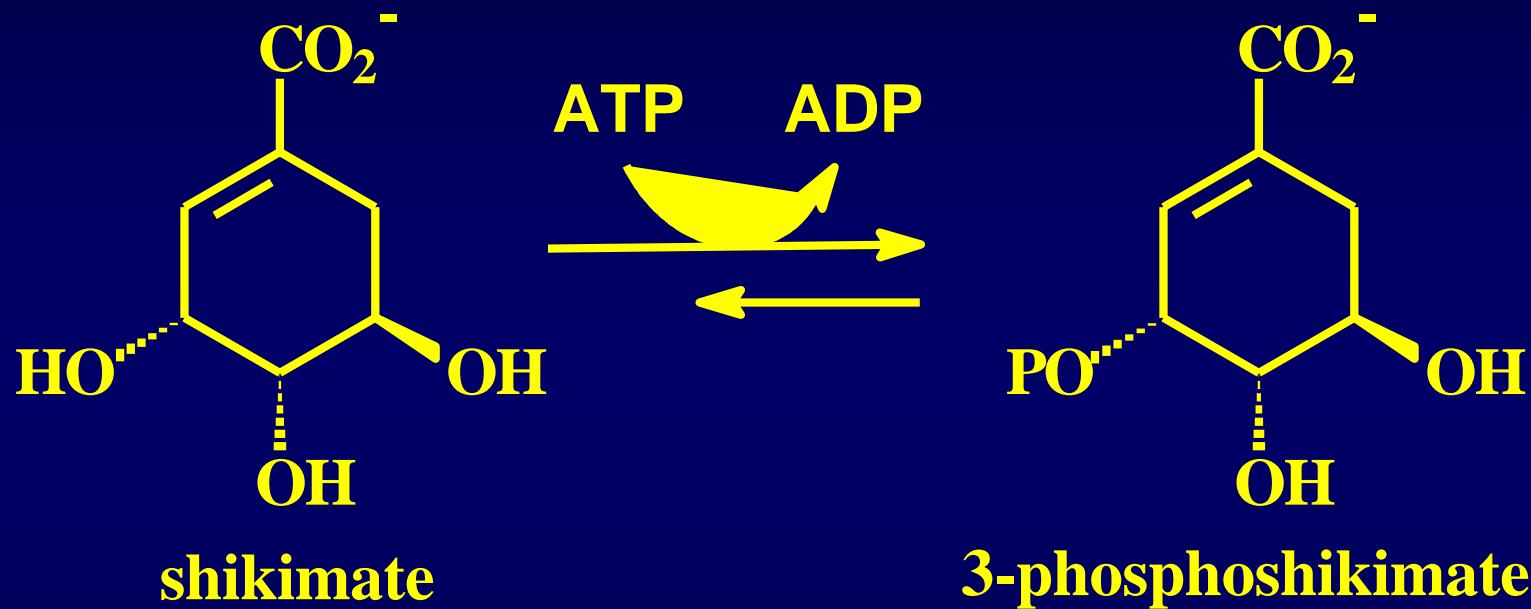
Shikimate dehydrogenase (shikimate oxido-reductase)



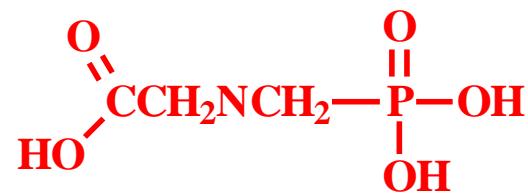
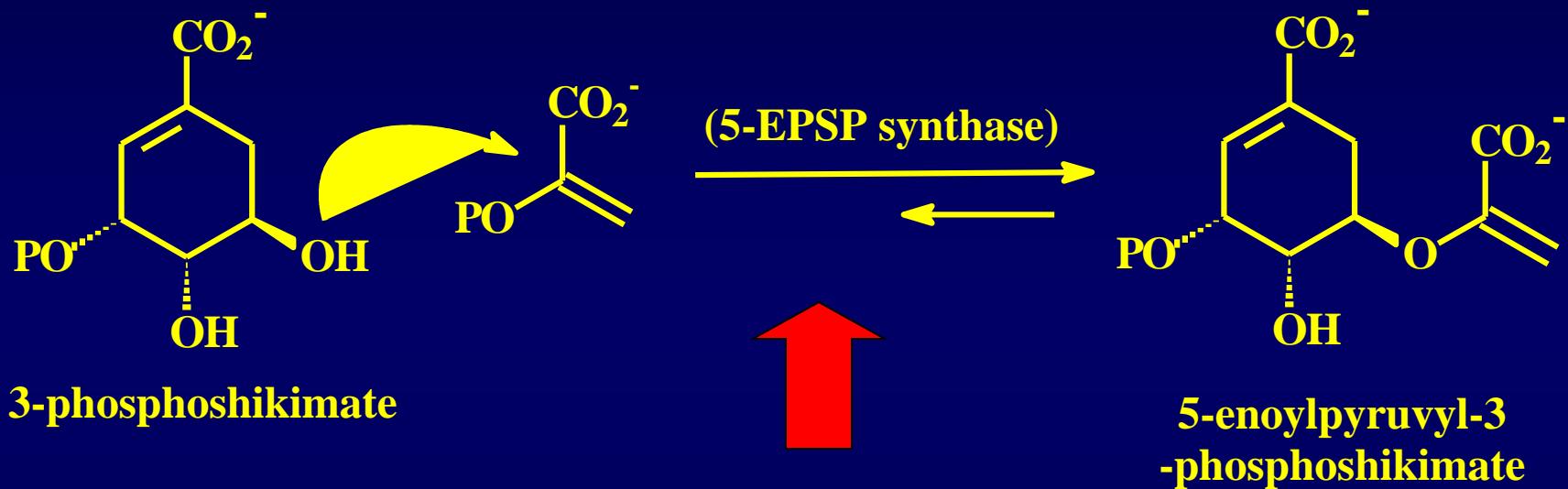
3-dehydroshikimate

shikimate

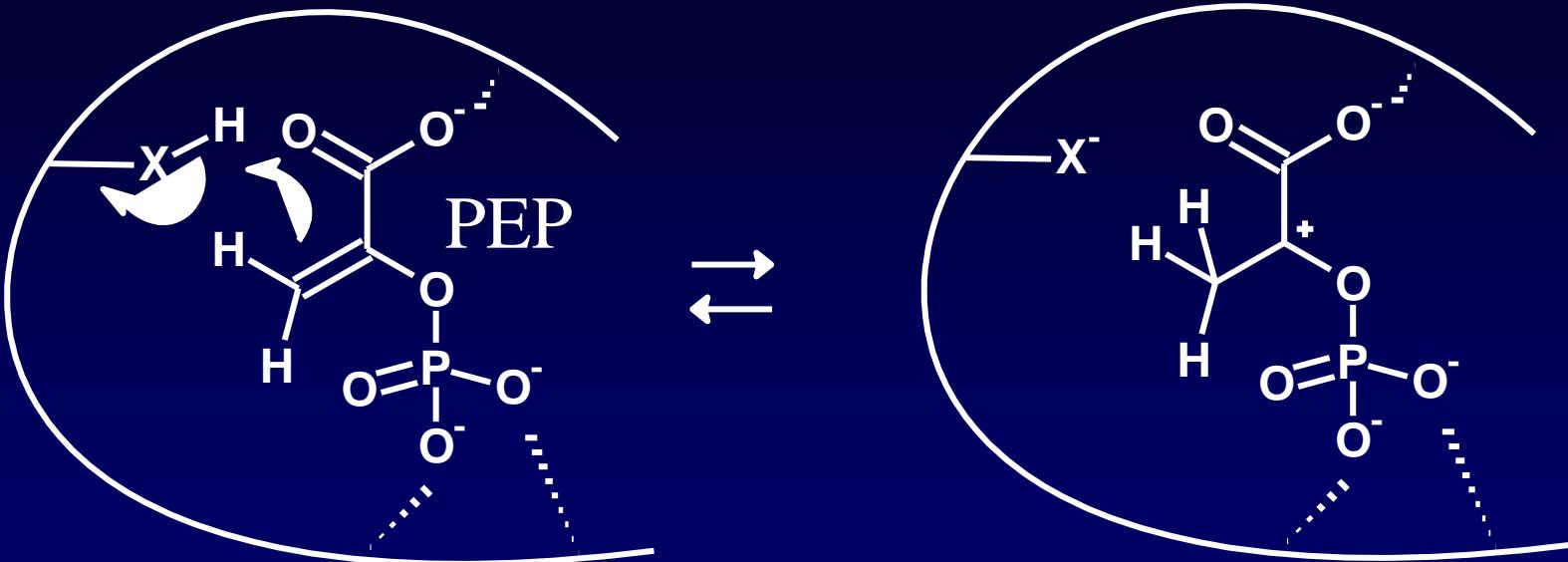
Shikimate kinase



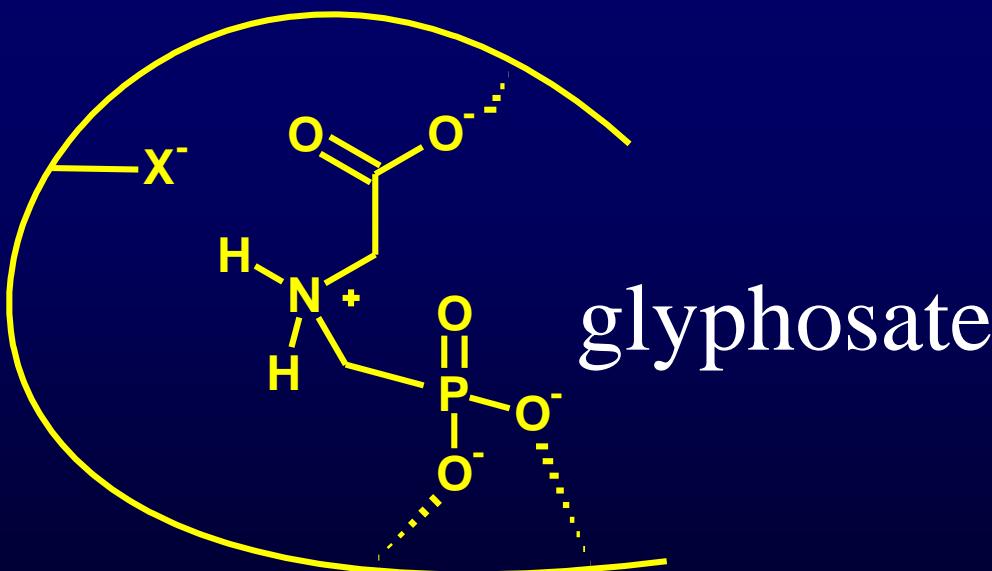
5-enolpyruvylshikimate -3-phosphate synthase



"glyphosate - Roundup"
(N-phosphonomethylglycine
inhibitor of EPSP)

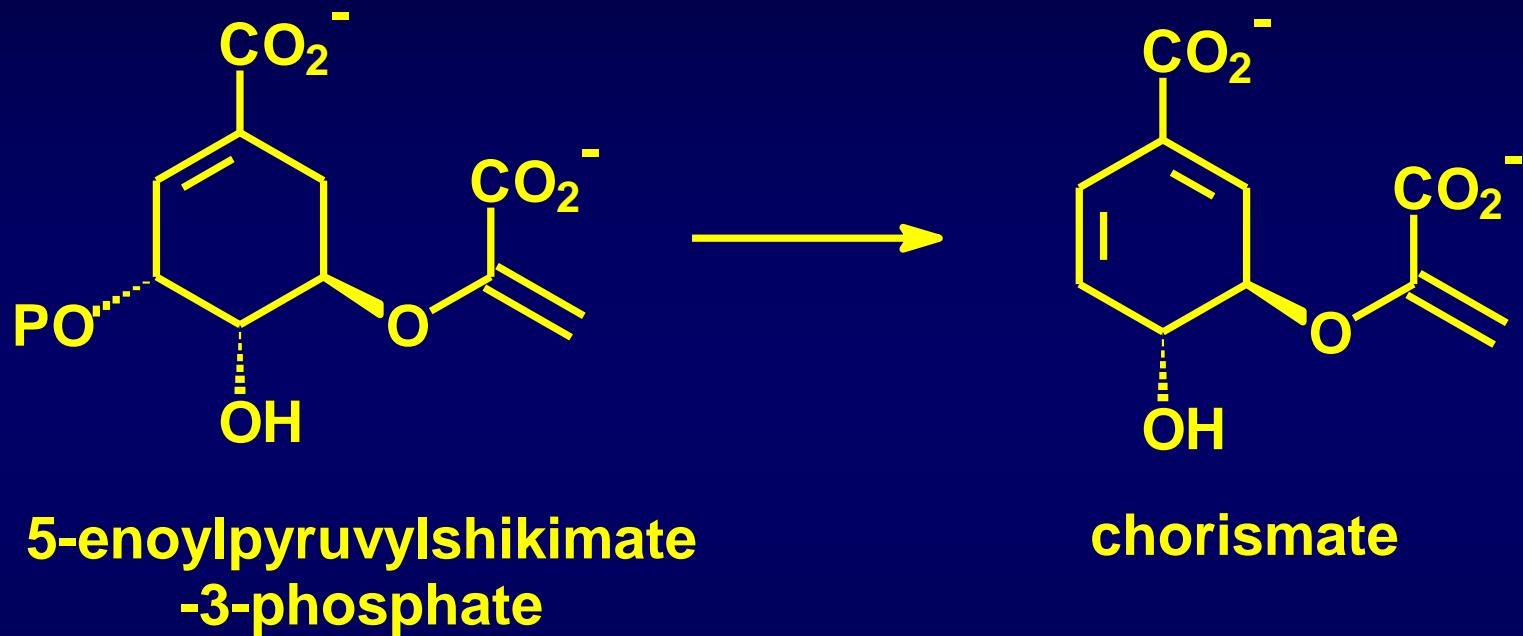


5-enolpyruvylshikimate
-3-phosphate synthase



glyphosate

Chorismate synthase



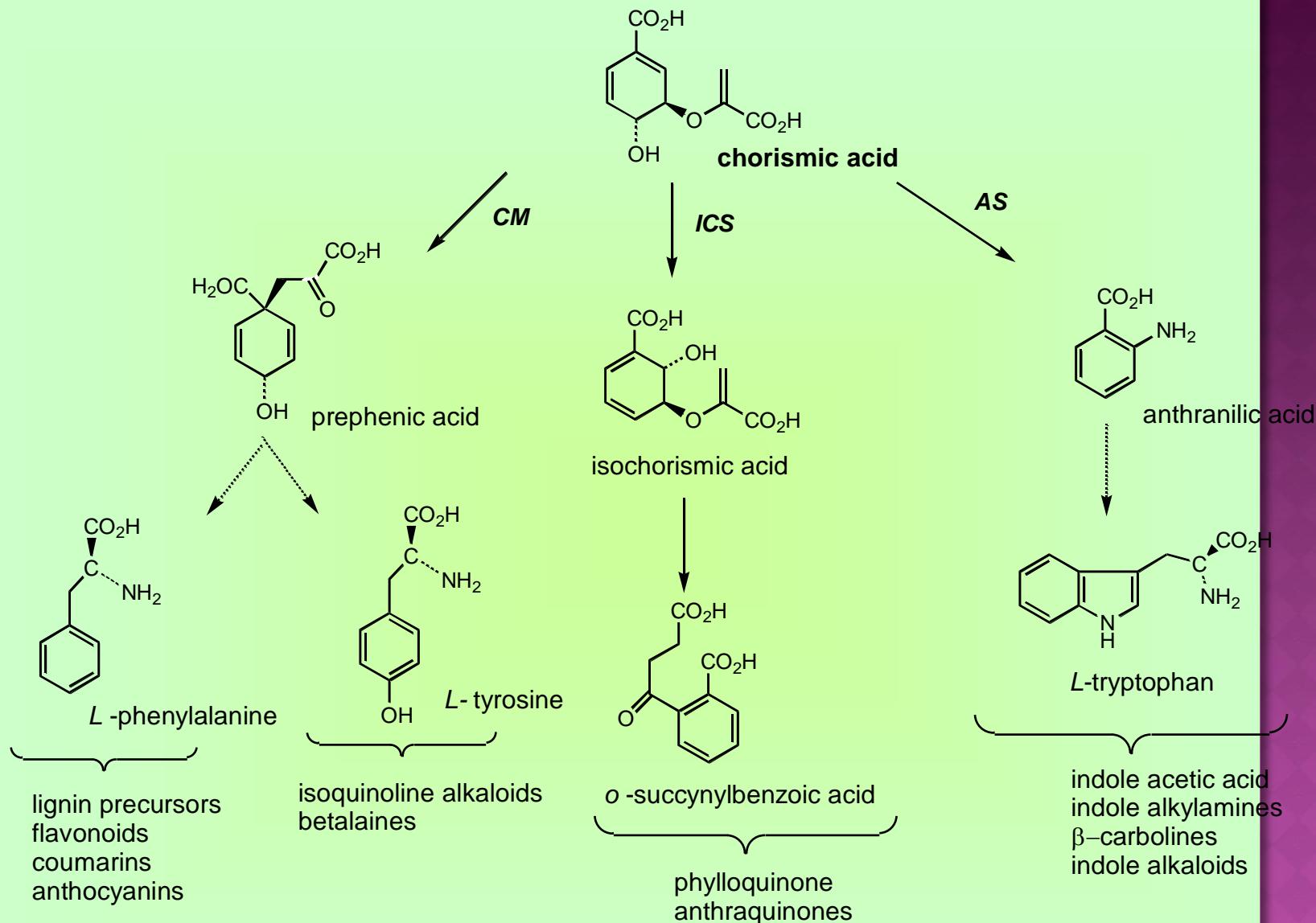
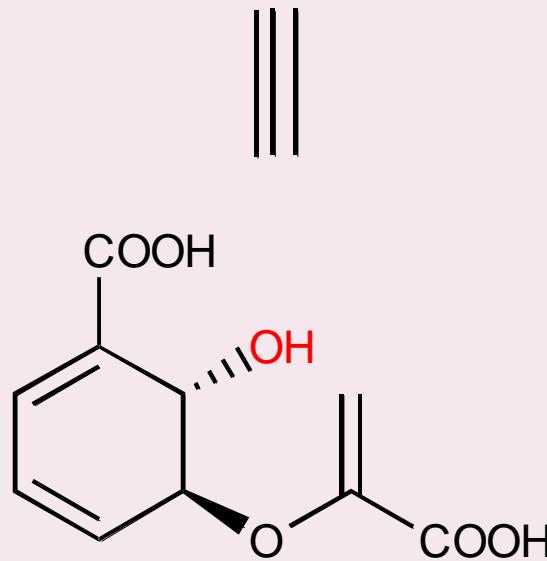
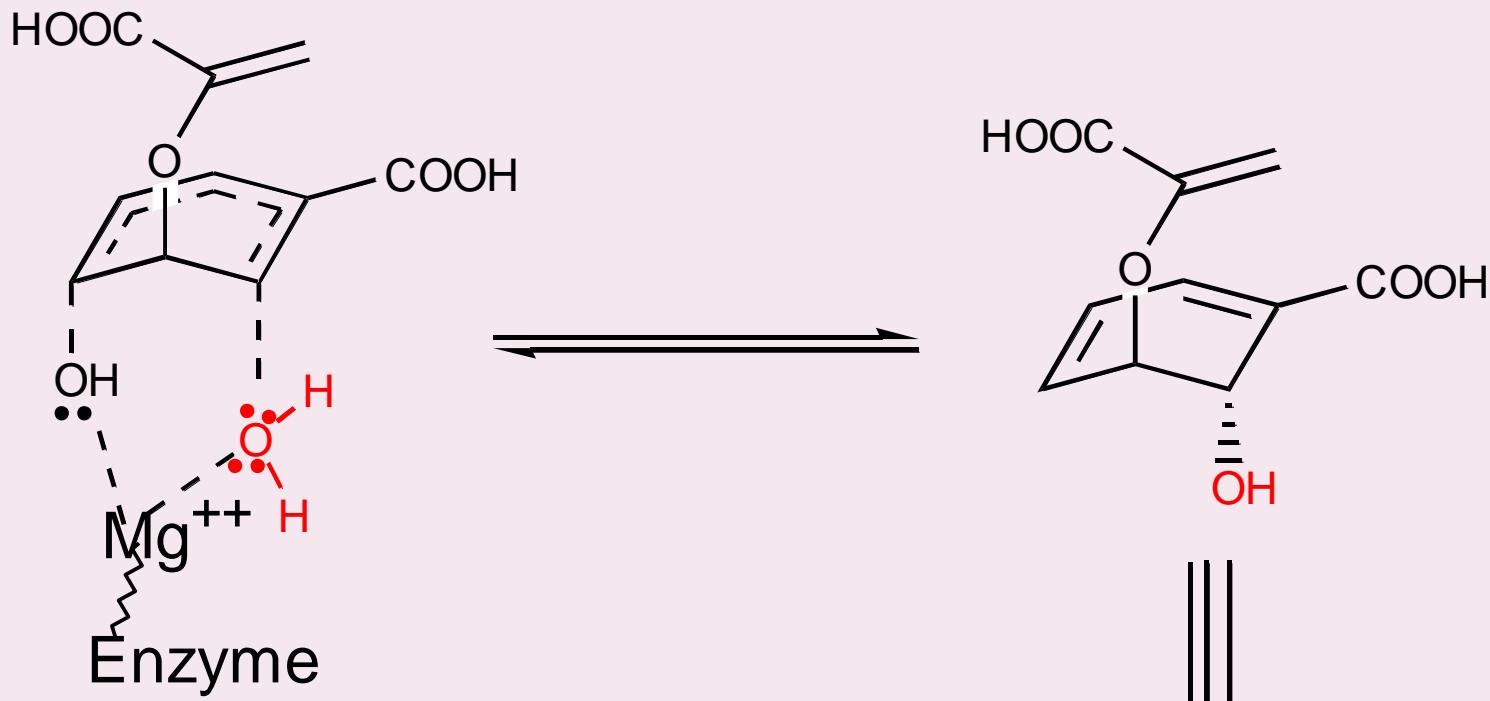
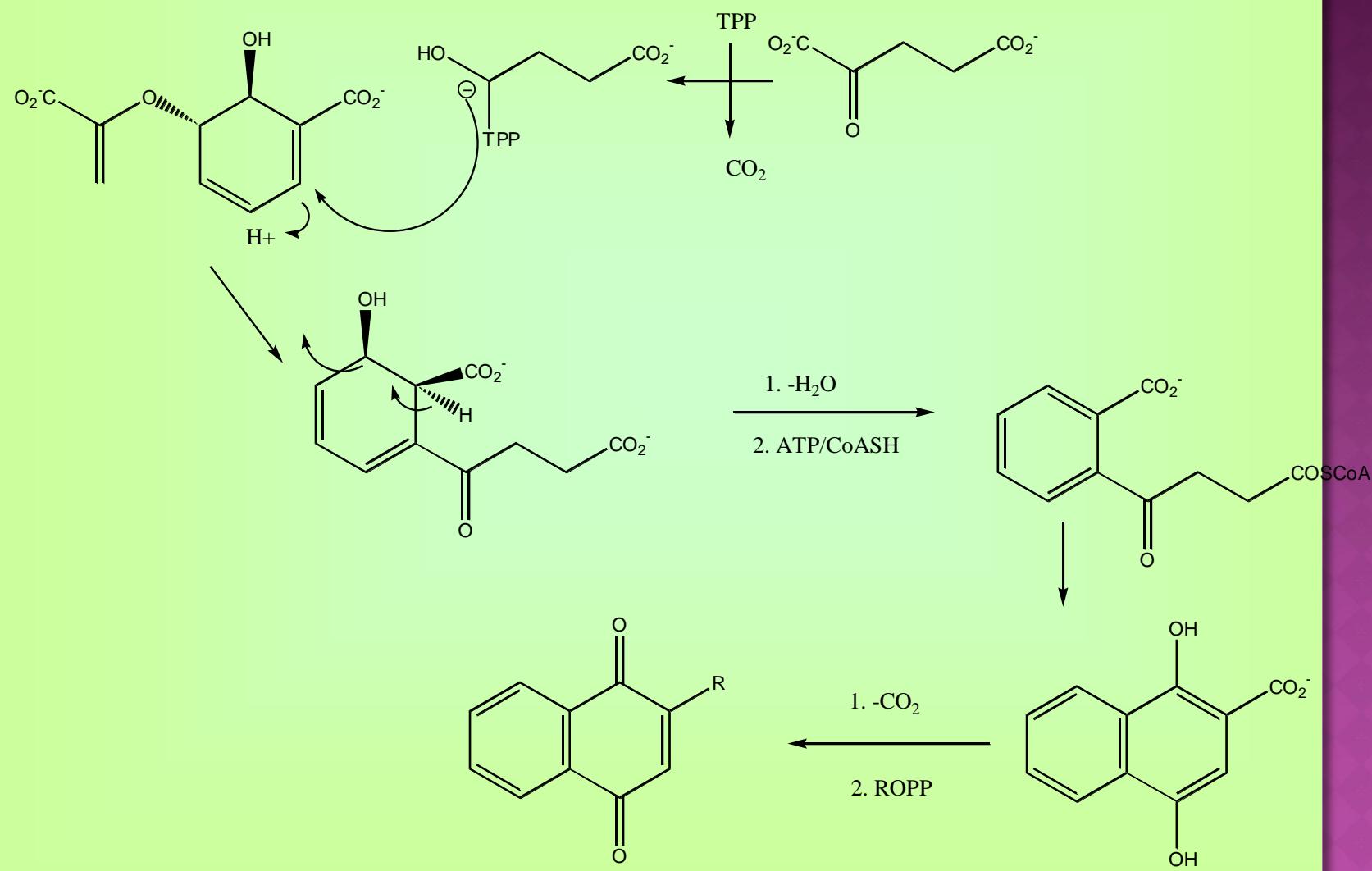


Figure 1- Diversion of chorismic acid into the secondary metabolism by the enzymes anthranilate synthase (AS), chorismate mutase and isochorismate synthase (ICS)



Mecanismo da ICS

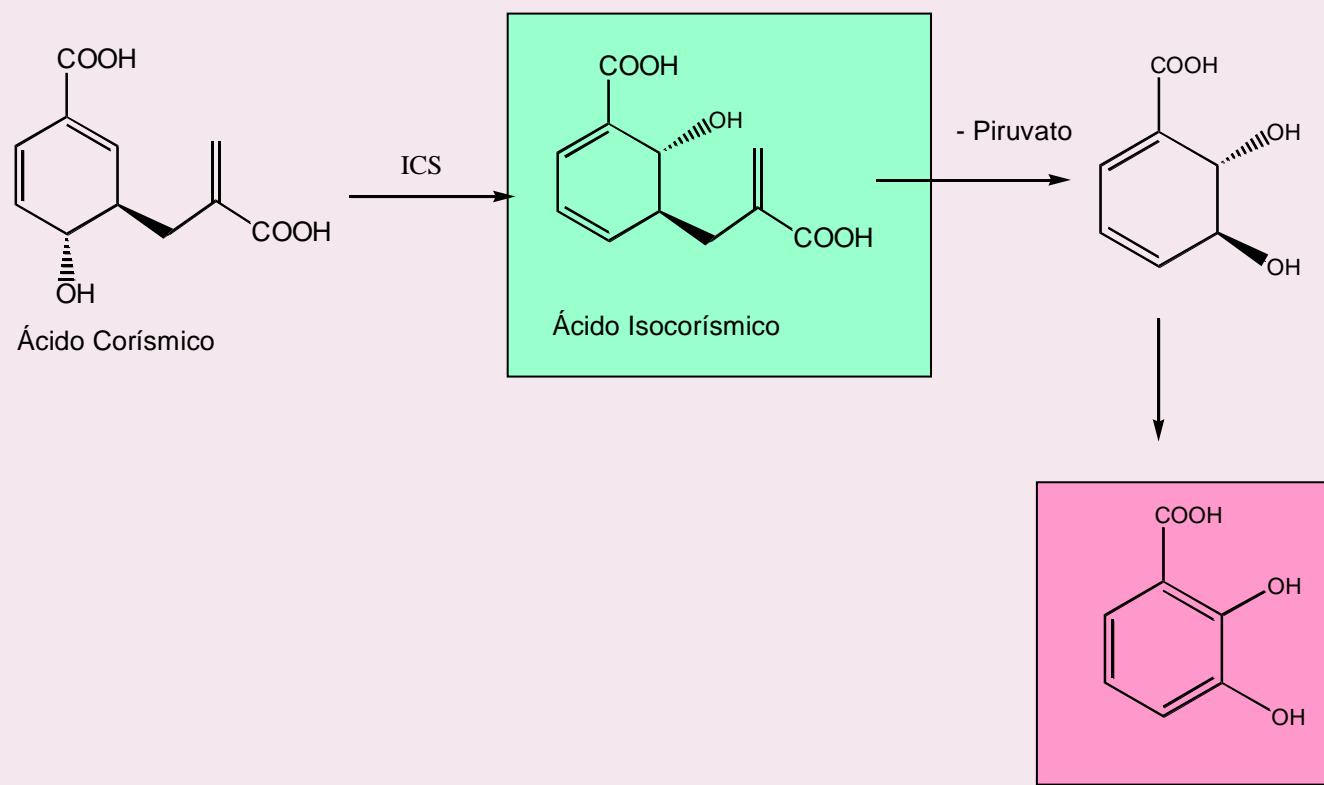
Formação de Naftoquinonas a partir do Isocorismato



Ácido Salicílico

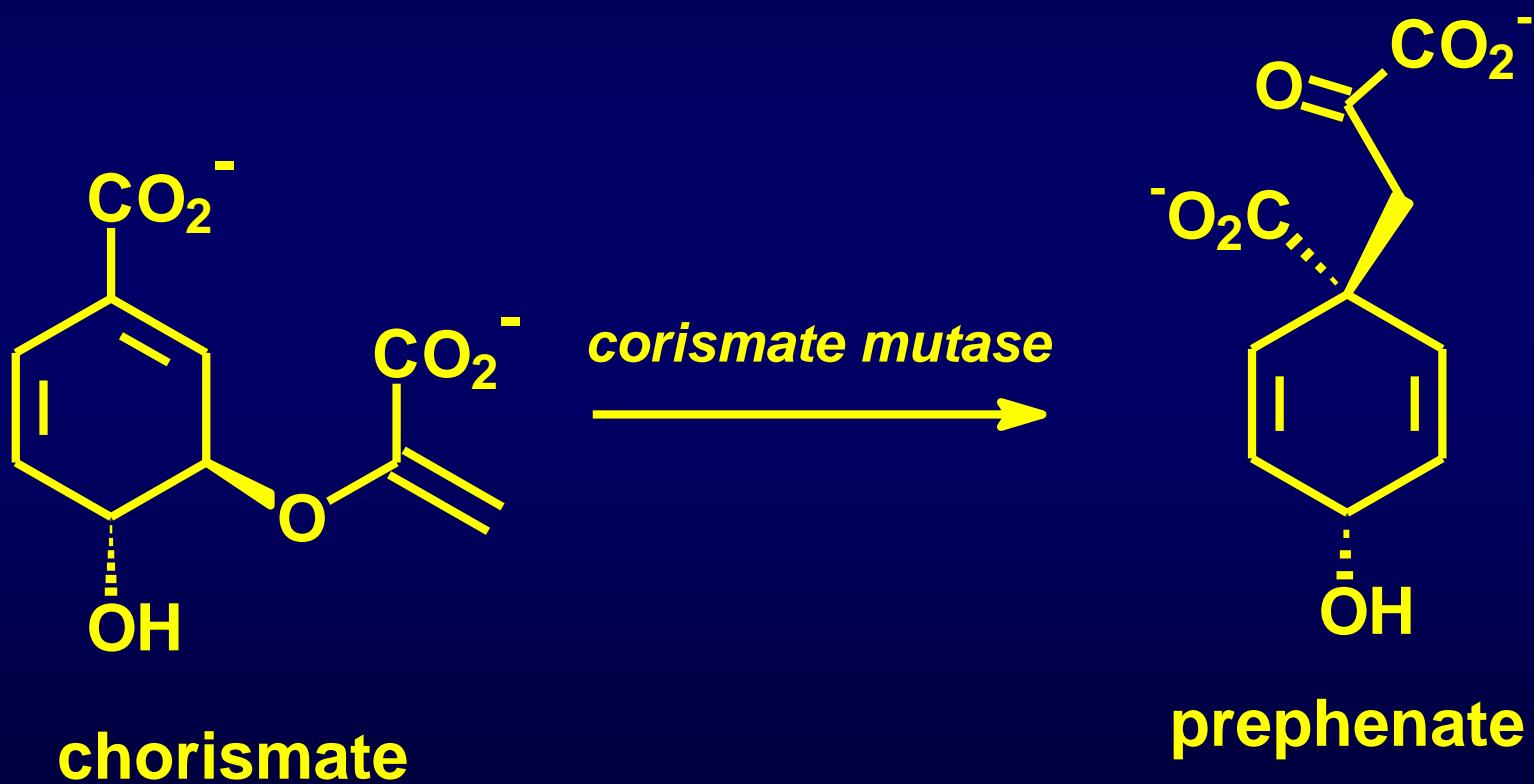
Formação de compostos

C₆-C₁ a partir do Isocorismato



Corismate mutase

The only example in the primary/intermediate metabolism of a 3,3-sigmatropic rearrangement of the Claisen type

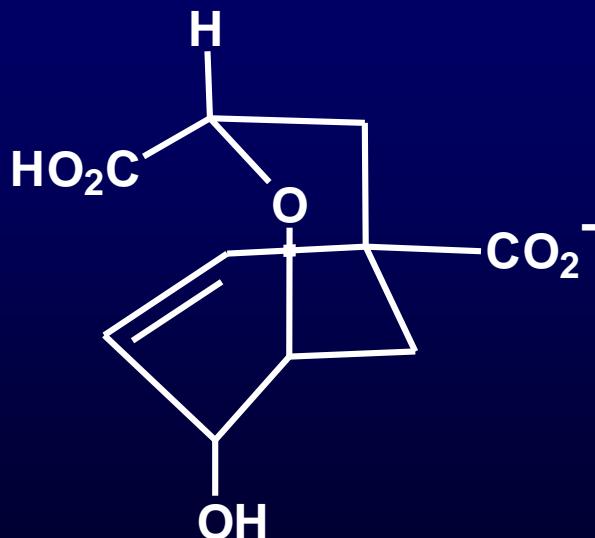
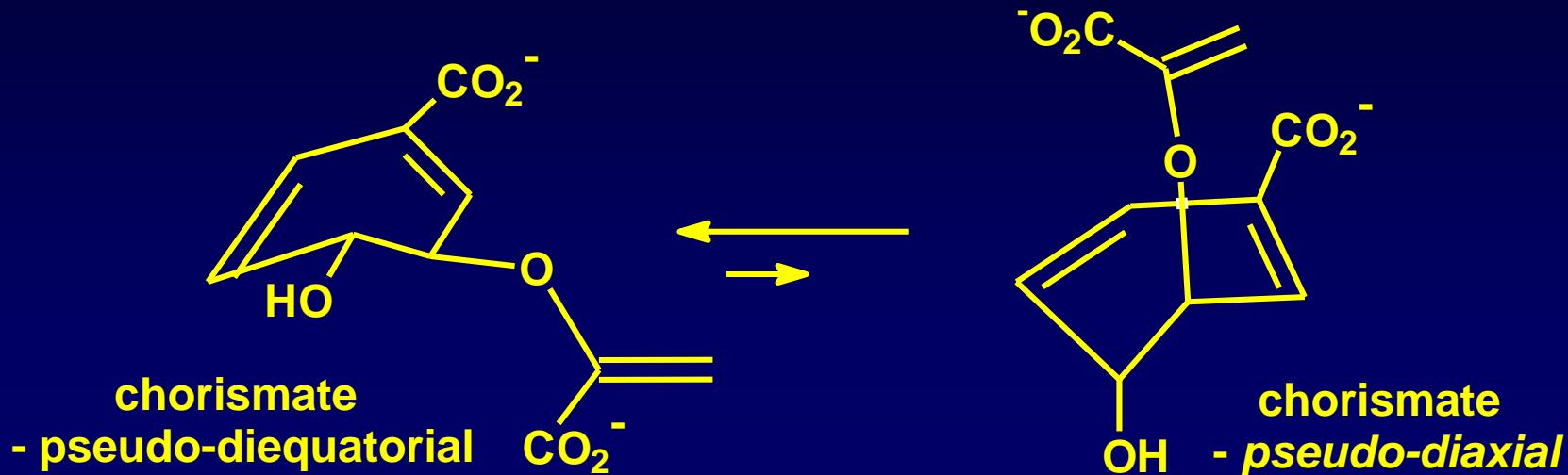


Corismate mutase

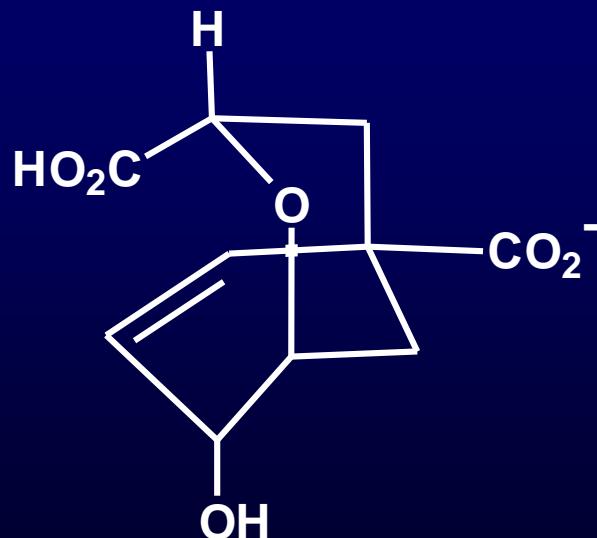
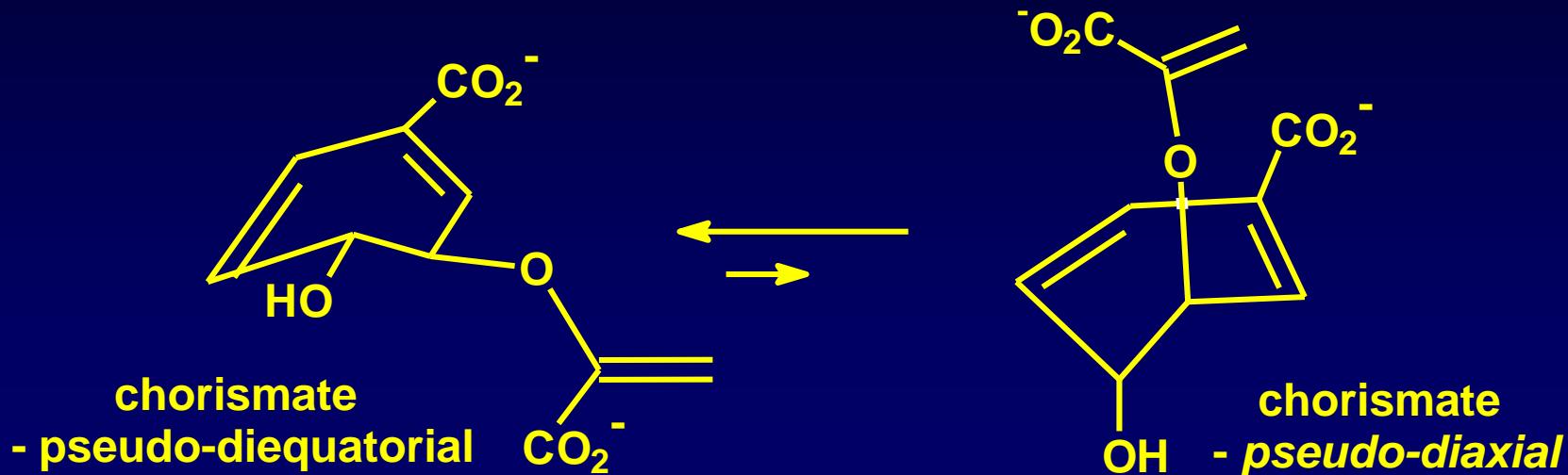
2×10^6 fold rate enhancement over the uncatalysed process

Only 127 amino acids residues (3 sub-unities)

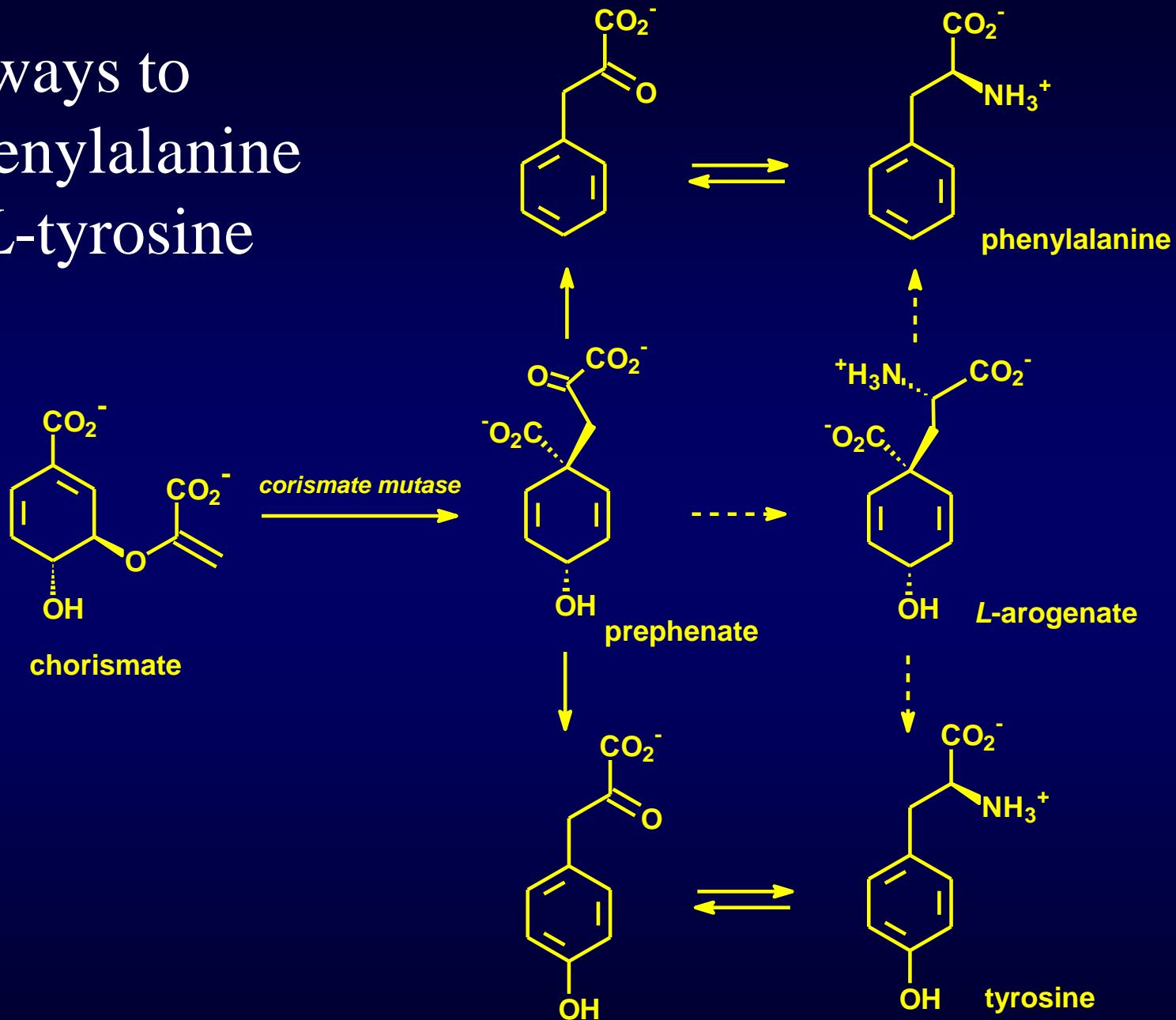
Corismate mutase inhibitor



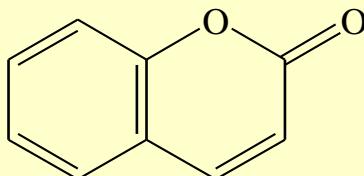
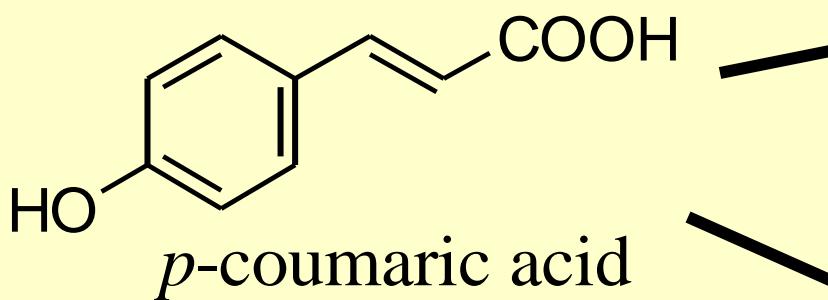
Corismate mutase inhibitor



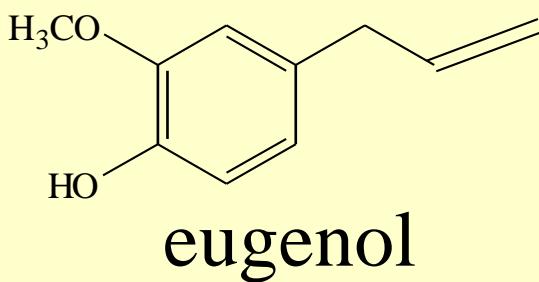
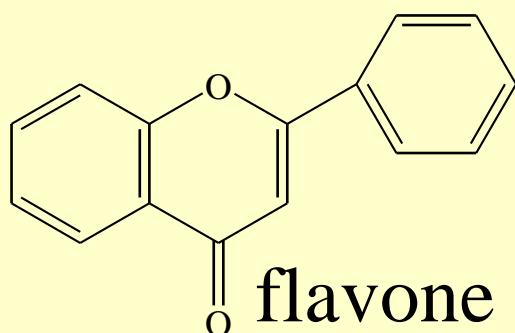
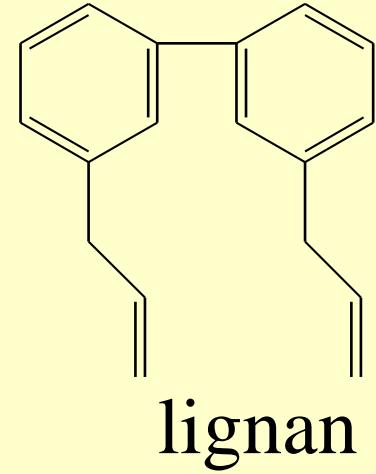
Pathways to *L*-phenylalanine and *L*-tyrosine

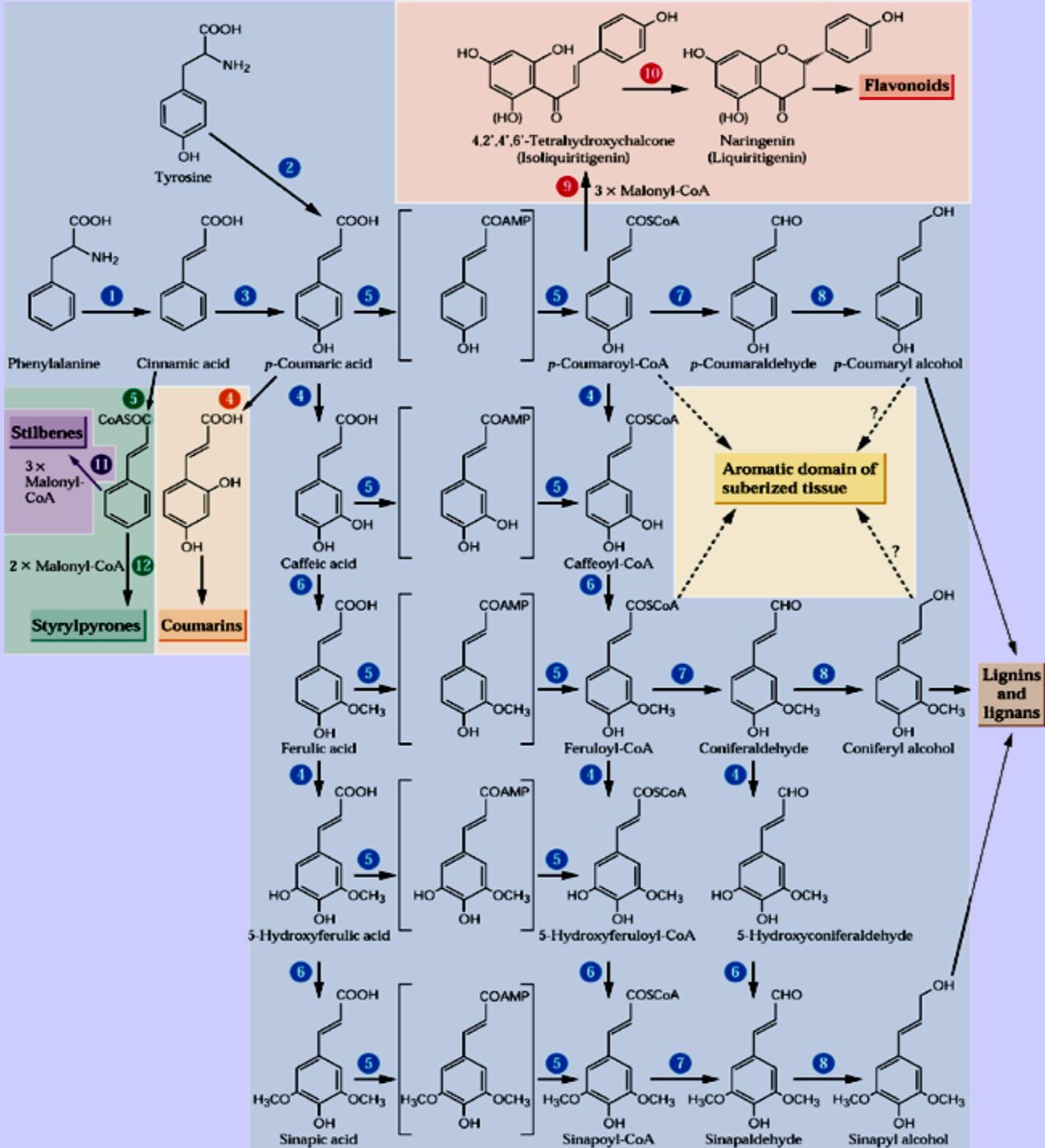


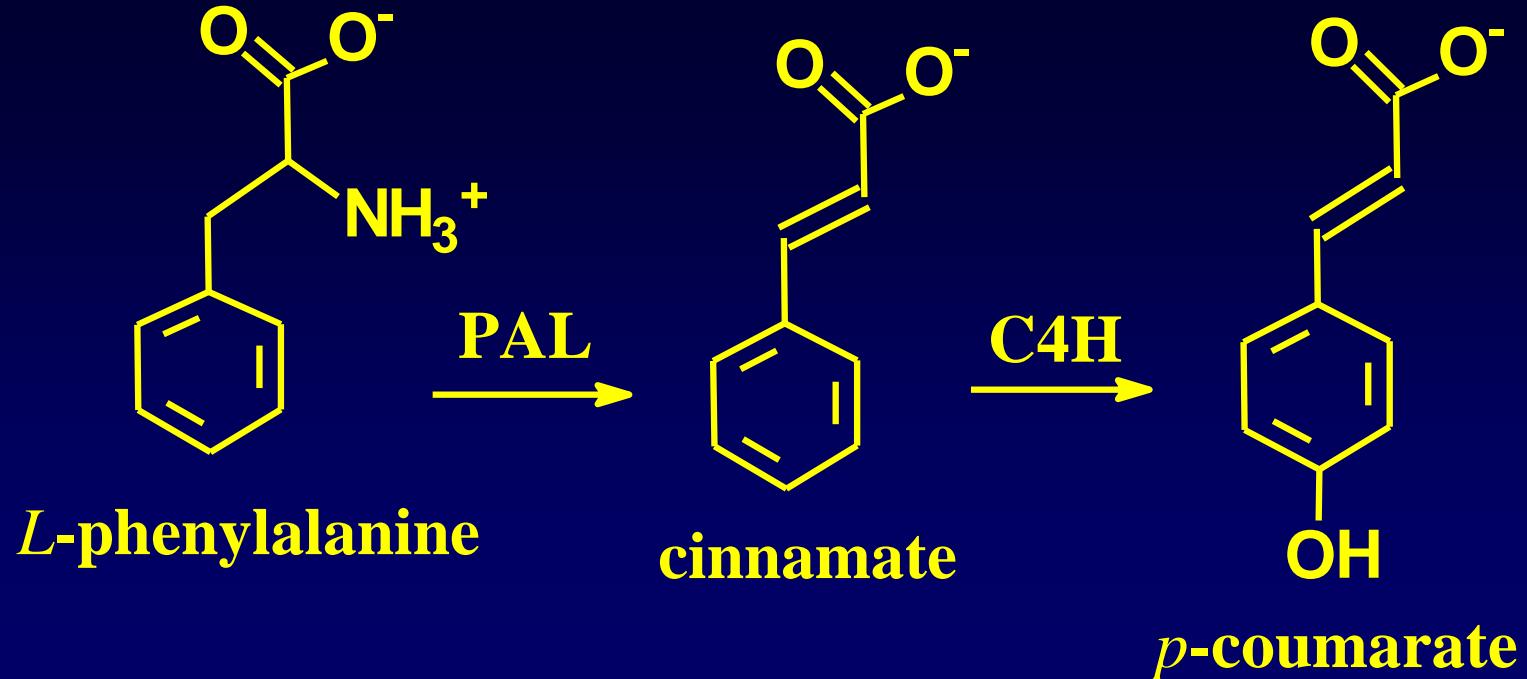
Phenylpropanoid metabolism



Lignin



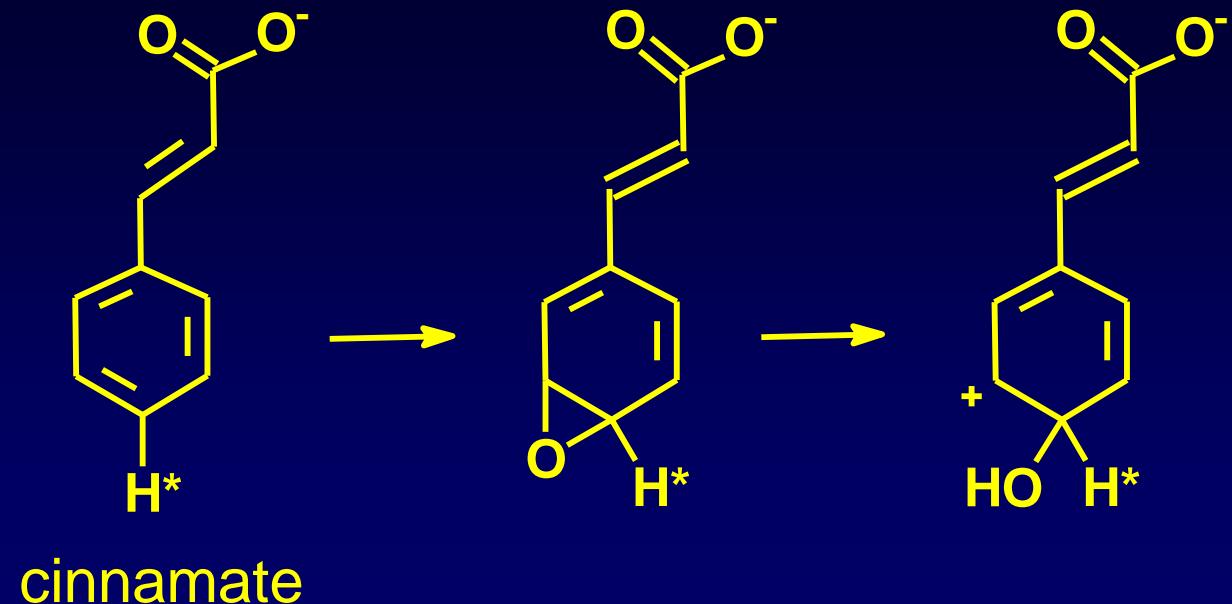




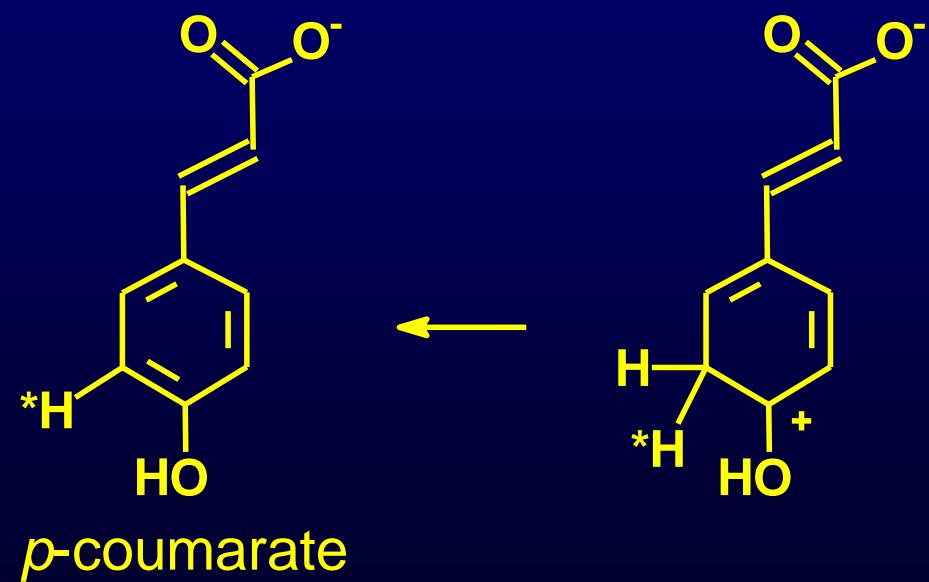
Hydroxylases (monooxygenases, mixed-function oxidases):

- (i) Membrane-bound (microsomal) cytochrome P₄₅₀ dependent oxygenases;
- (ii) Soluble phenolase(introduce the second OH)

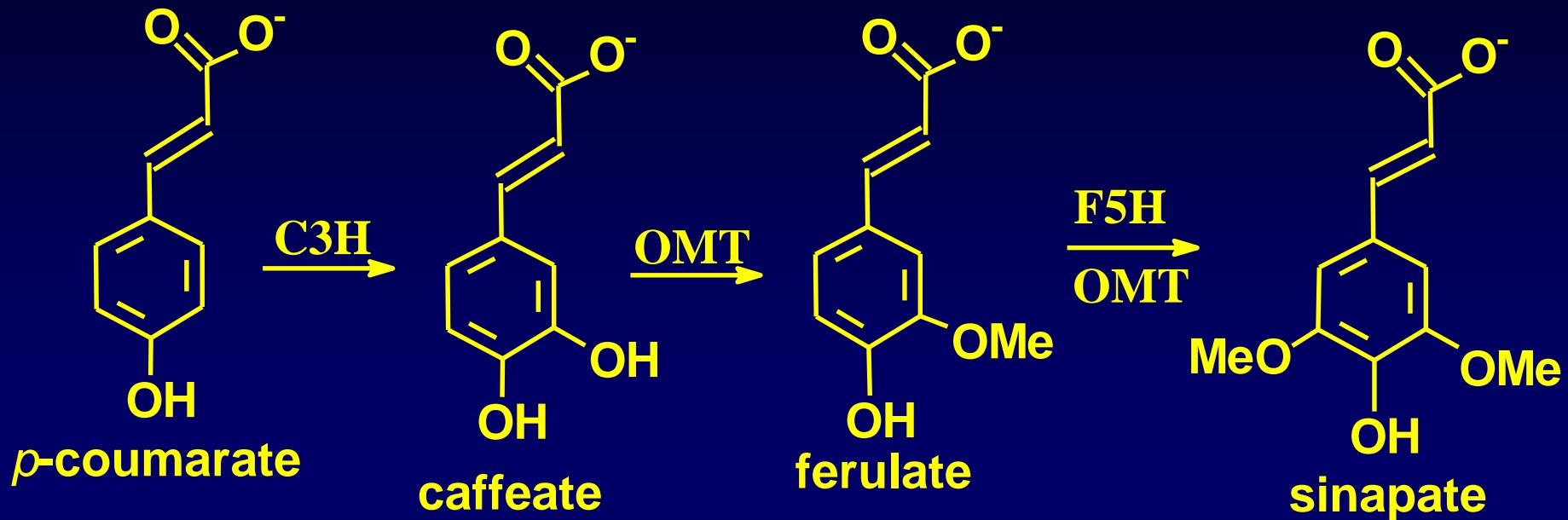
NIH
SHIFT



cinnamate

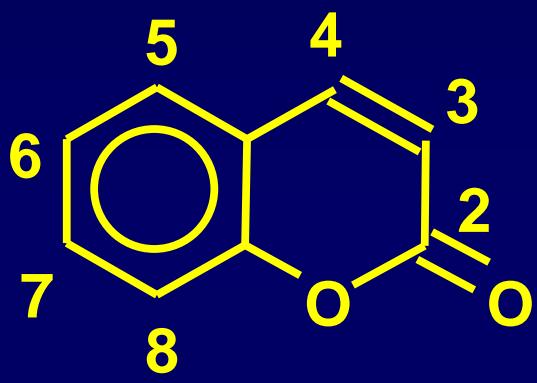


p-coumarate



OMT methylation:
requires SAM (S-adenosyl-L-methionine)

Coumarins



coumarin

(benzo- α -pyrone)

Coumarona odorata (1820)

Occurrence of coumarins

Up to 1990:

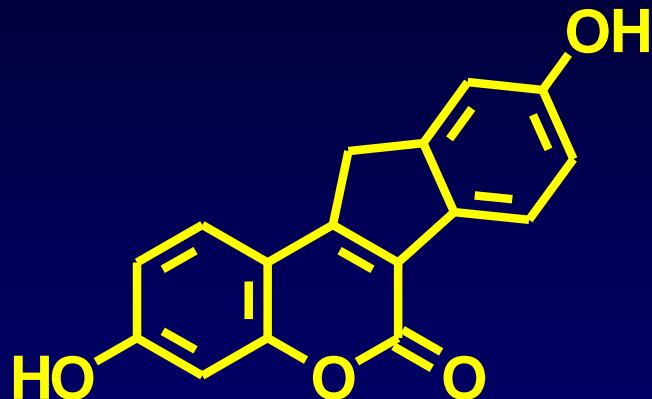
1000 coumarins

(especially from Rutaceae and
Umbelliferae species).

Biological activities of coumarins



cumarina
(aromatizante)



cumestrol
(estrogênico)



aflatoxina B₁
(hepatotóxica e
carcinogênica)



dicumarol
(antibacteriano,
coagulante)

Furanocoumarins

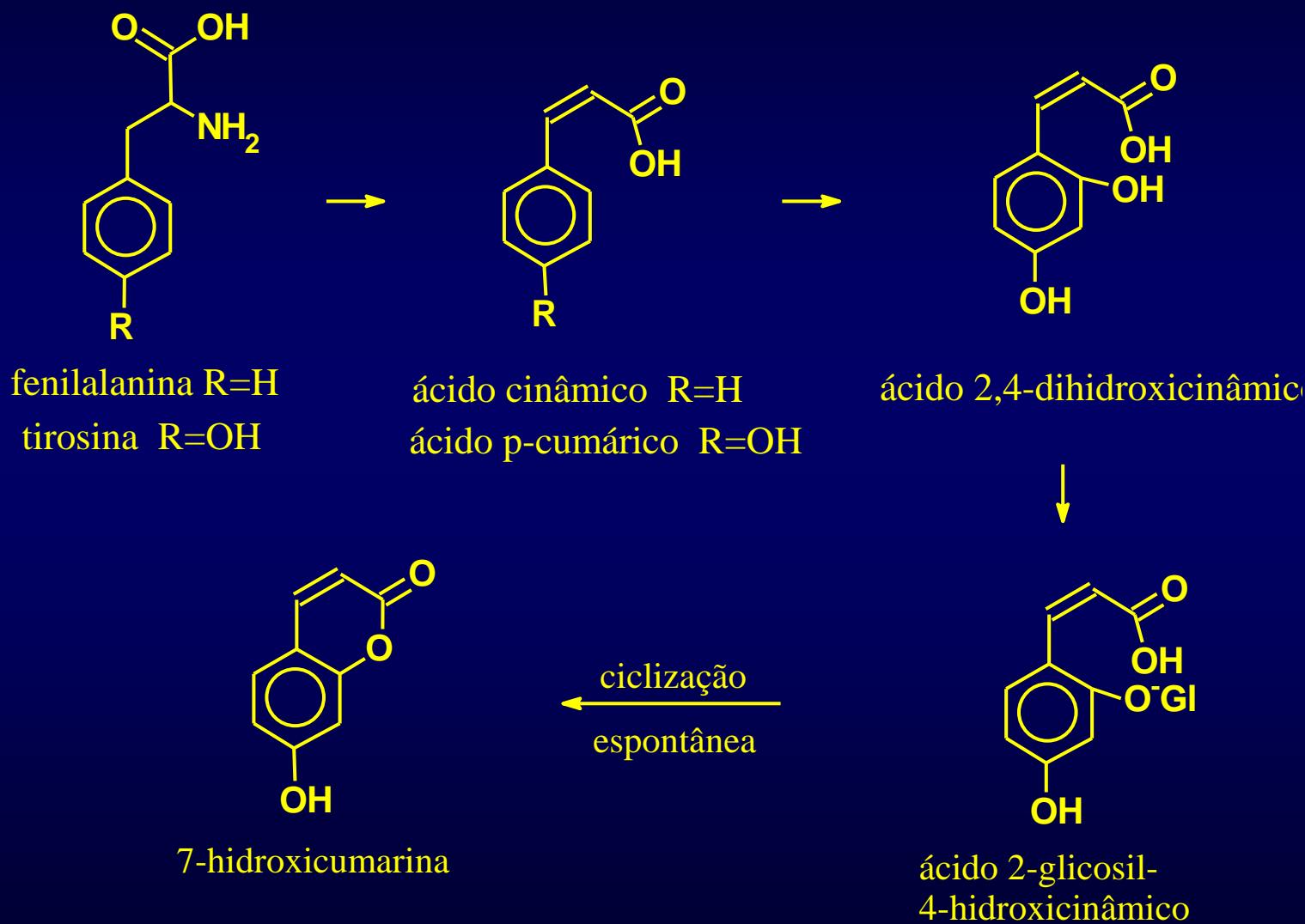


bergapten

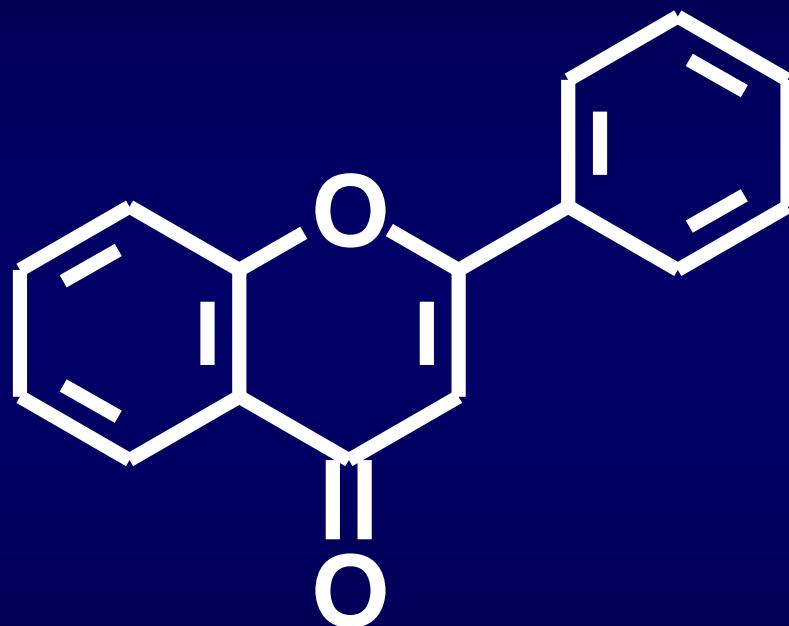


pimpinelin

Biosynthesis of coumarins

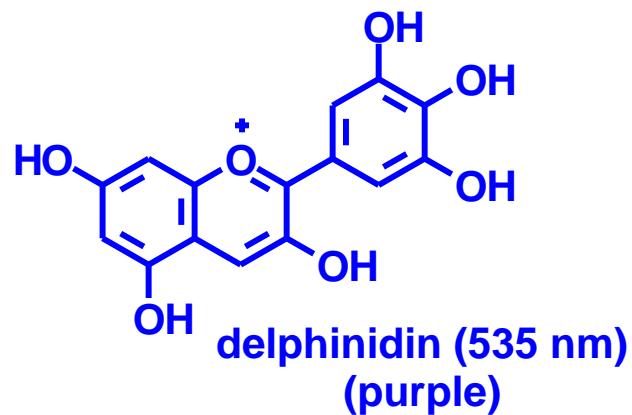
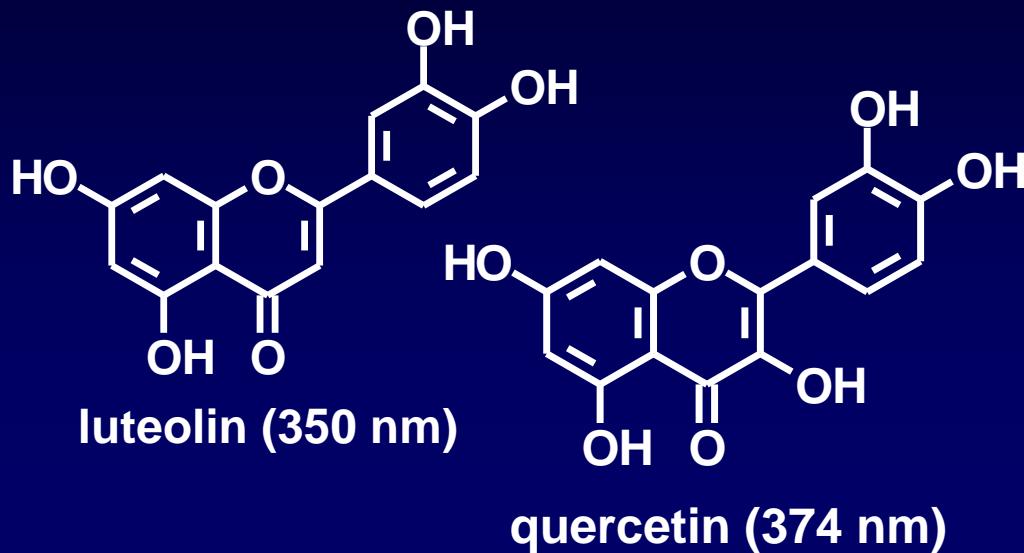


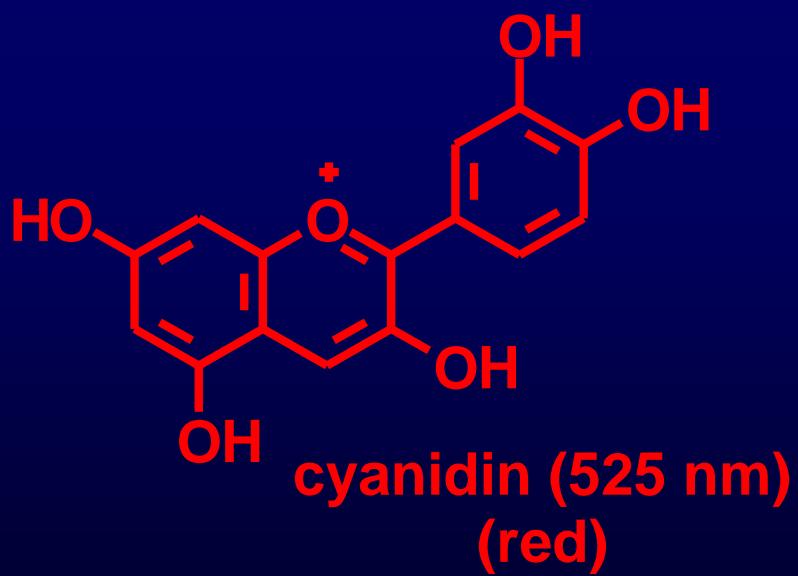
Flavonóides



5000 isolados e caracterizados

Flavonóides







isosalipurposide

(399 nm)



aureusidin

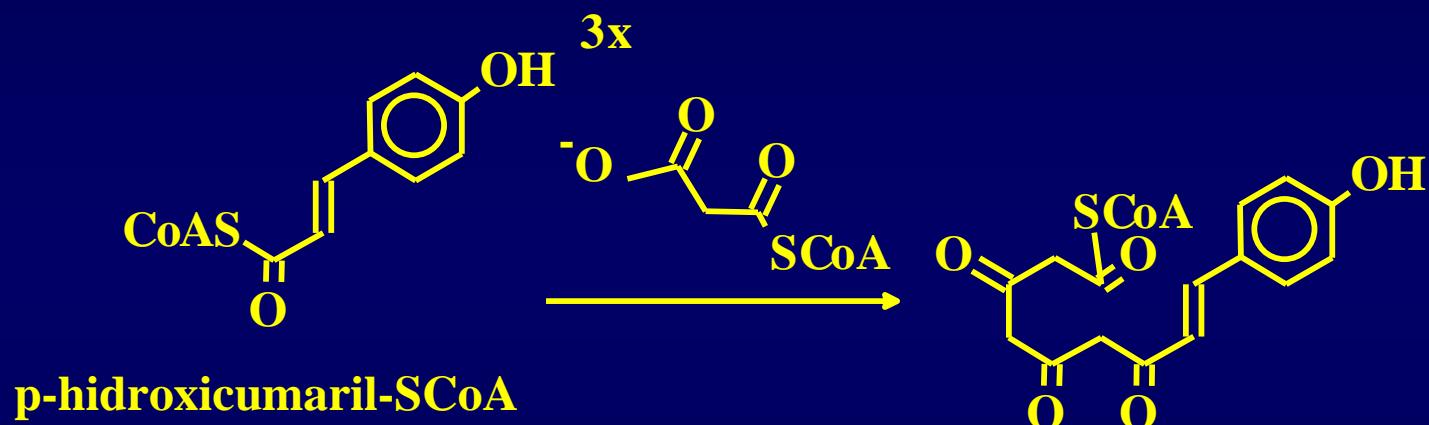
Biflavonoids



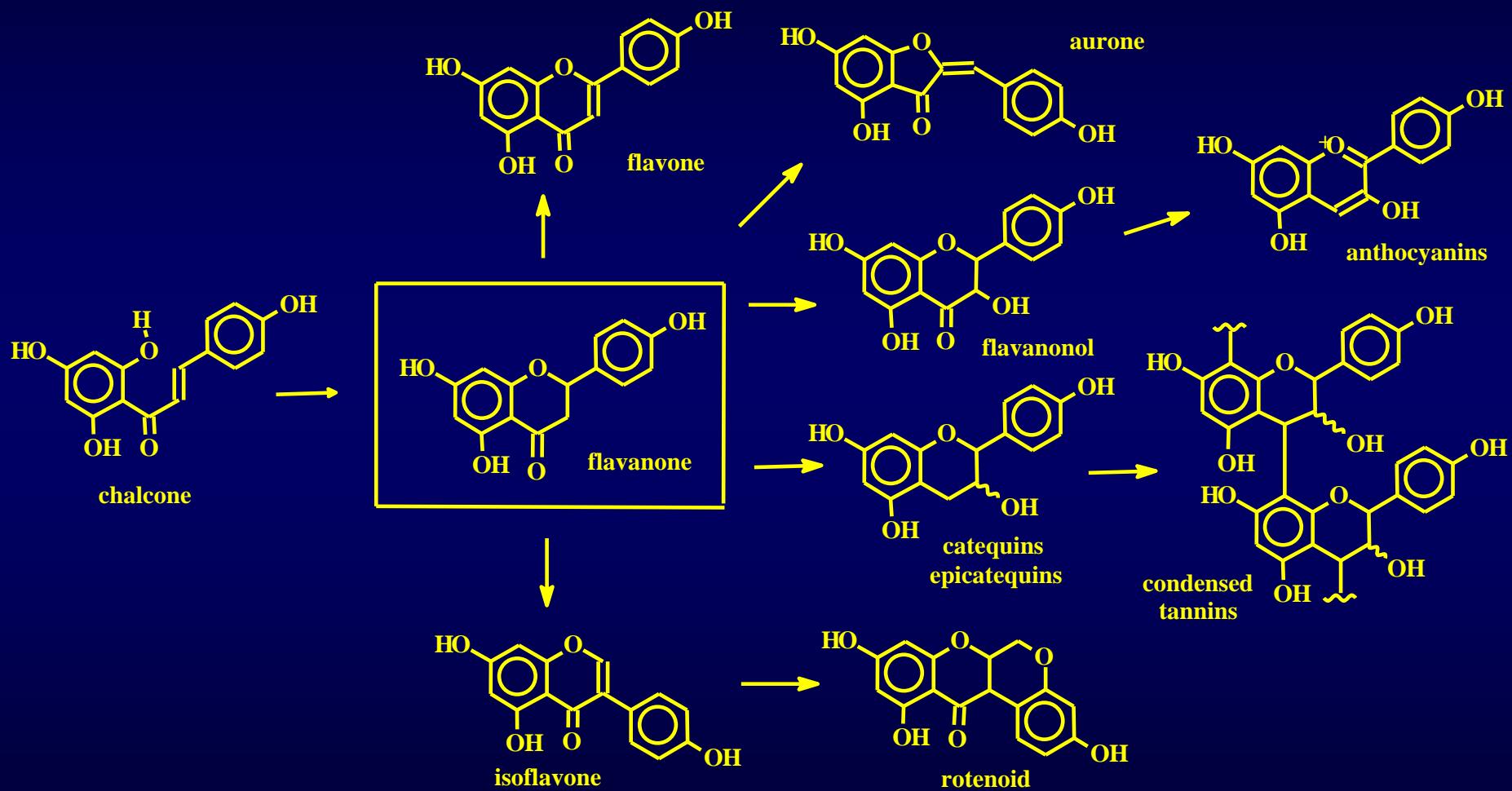
Amentoflavone (*Gingko biloba*)

Biosynthesis of flavonoids





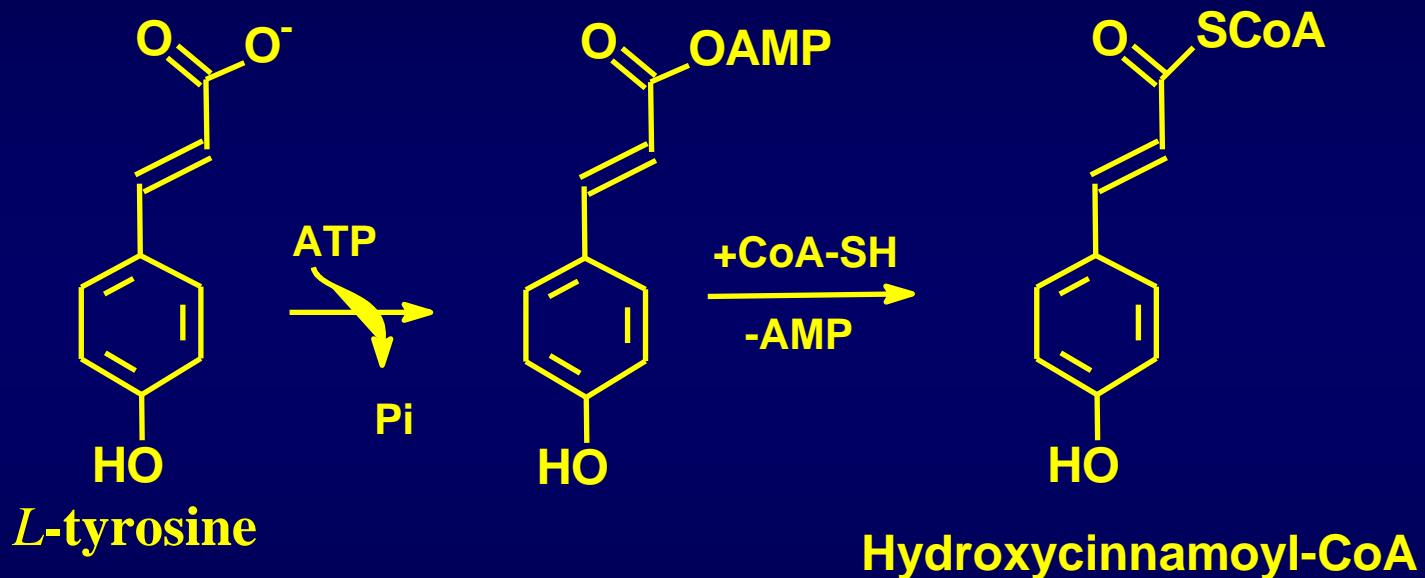
Biosynthesis of flavonoids

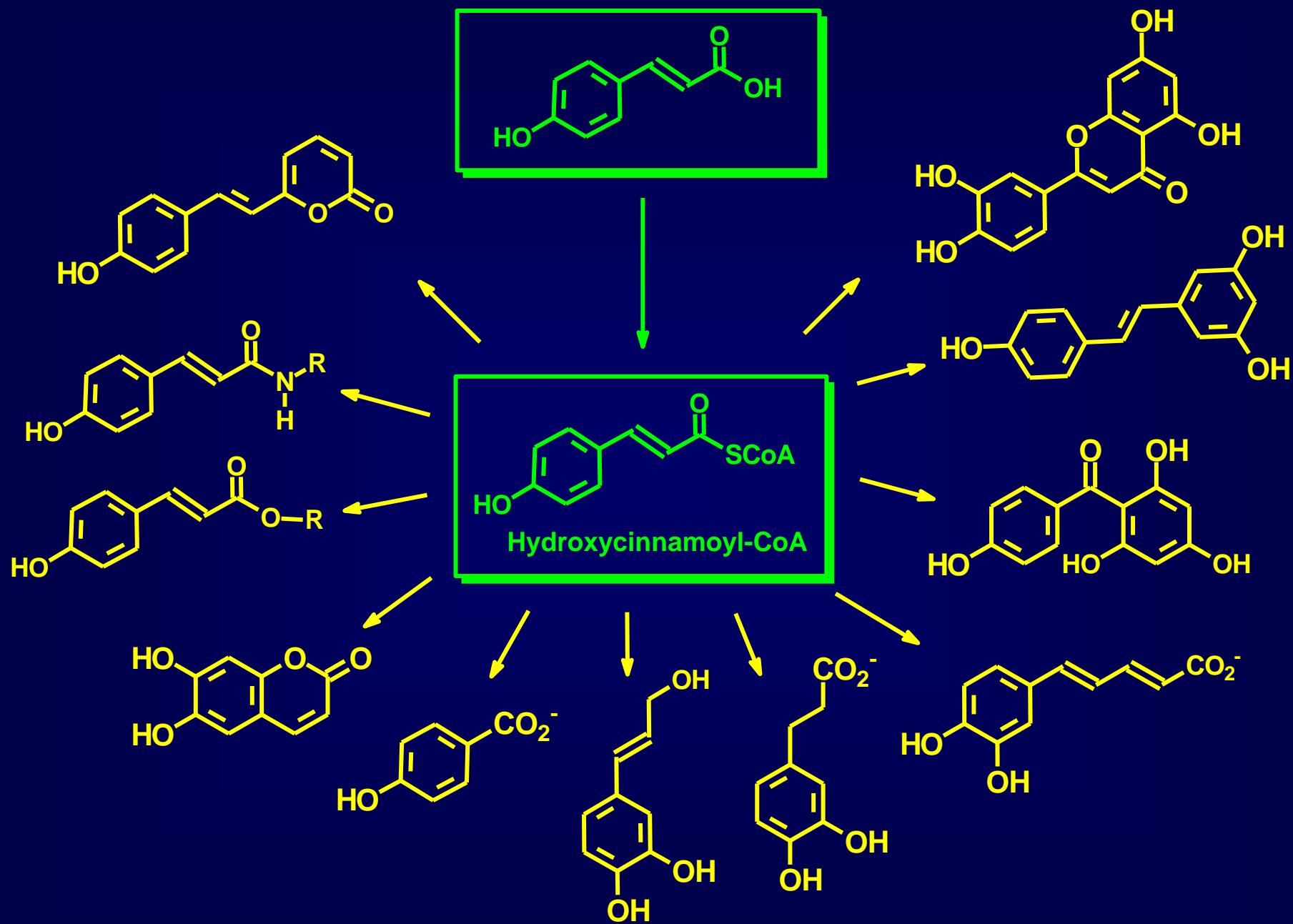


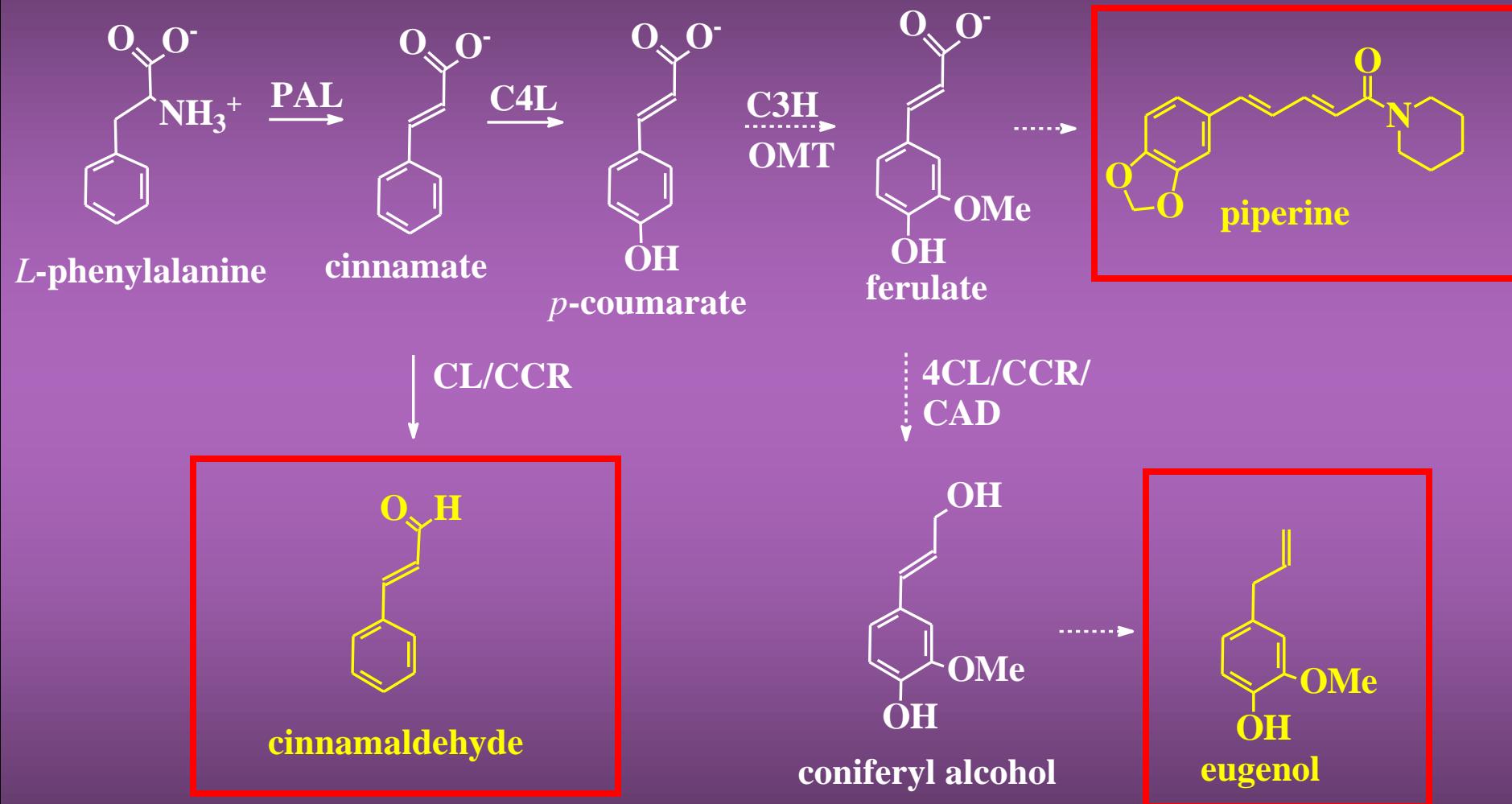
Distribution of flavonoids in the leaf fraction of the *Pisum sativum* cv. Argentum mutant

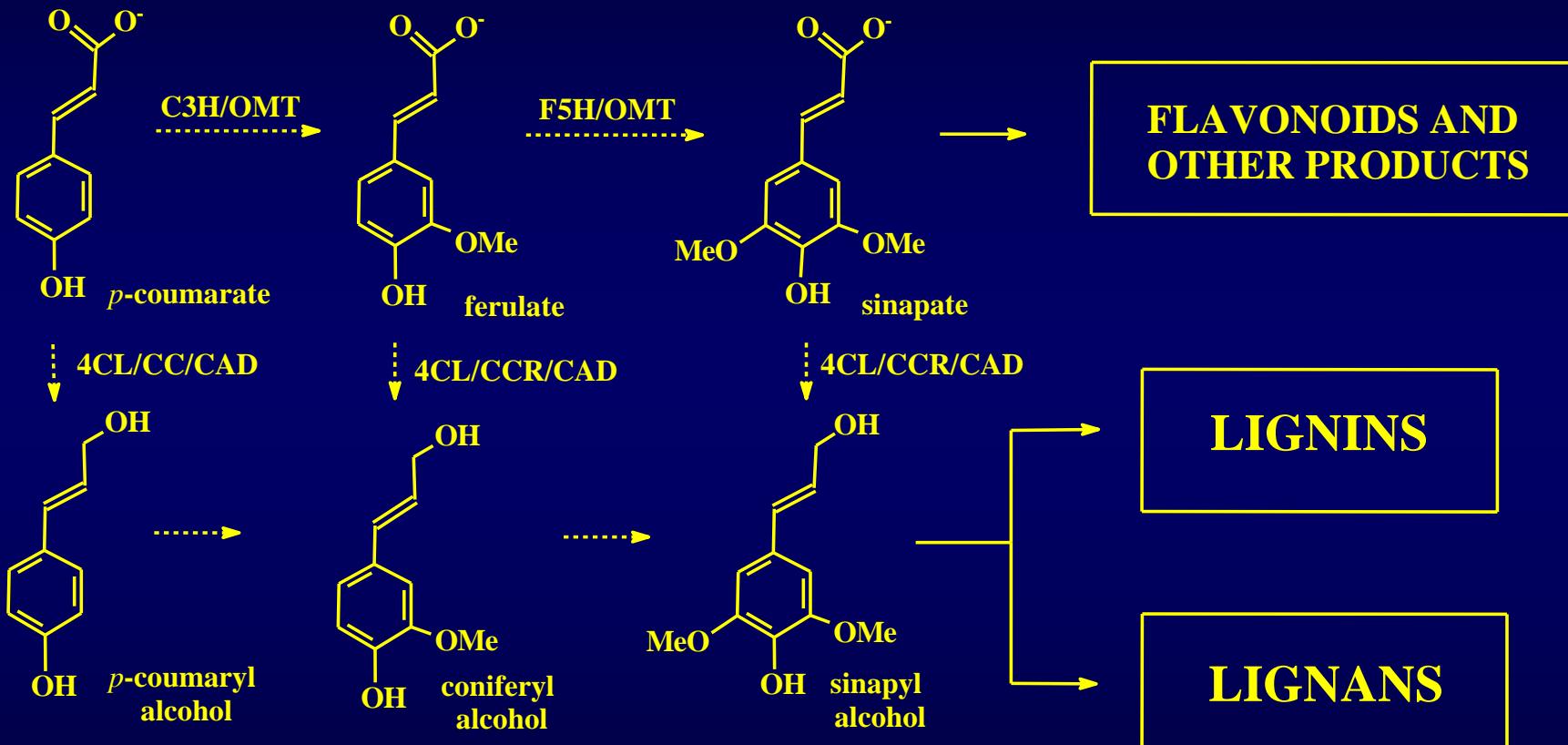
Compound	Upper epidermis	Mesophyll-vascular layer	Lower epidermis
anthocyanin	70.3	0	29.7
Flavonol glycoside	68.7	0	31.3

Activation step for cinnamoyl moiety

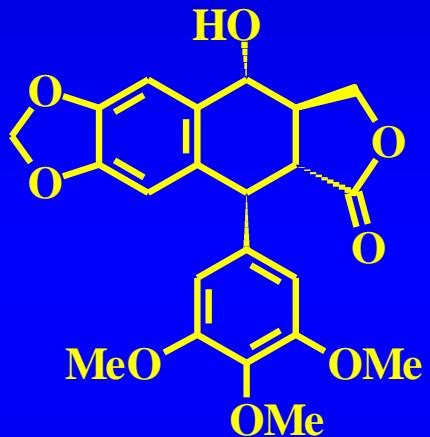




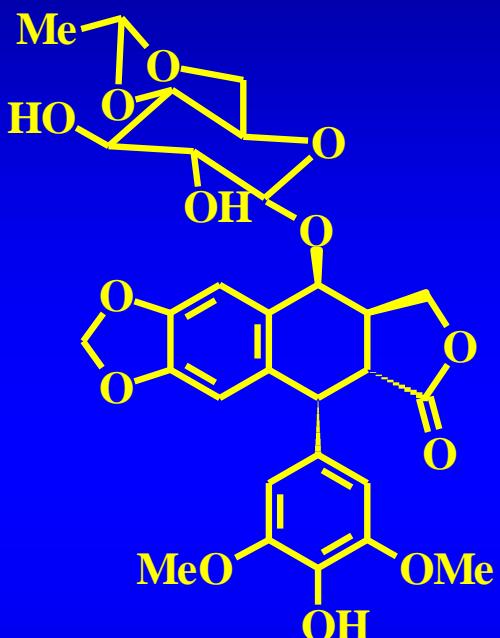




Antitumoral lignans from *Podophyllum hexandrum*



podophyllotoxin



etoposide

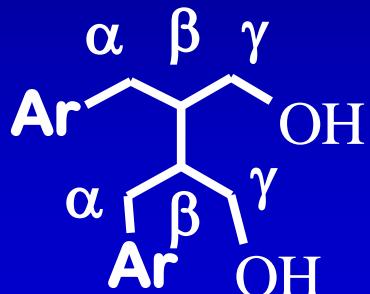


teniposide

Clinically used for treatment of testicular/lung cancer,
and certain form of leukemia.

Ross *et al.* (1984) *Cancer Res.* 44, 5857.

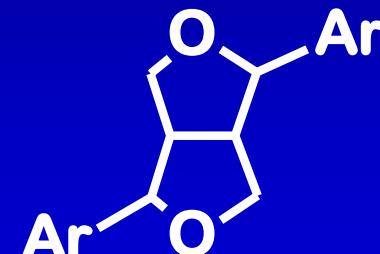
Lignans are dimers of coniferyl alcohol regardless the position of linkage (Gottlieb 1974)



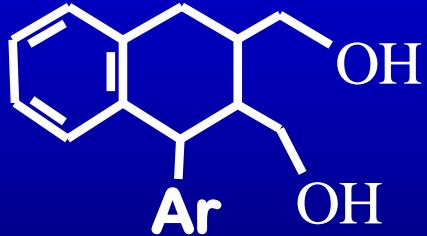
diarylbutane



dibenzylbutyrolactone



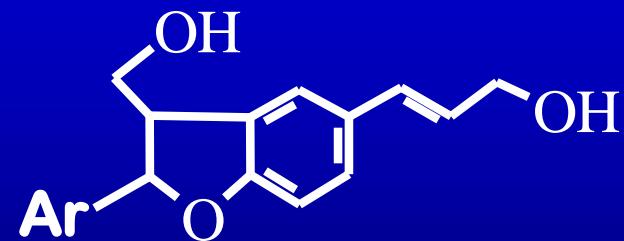
furofuran



aryltetralin



dibenzocyclooctaene

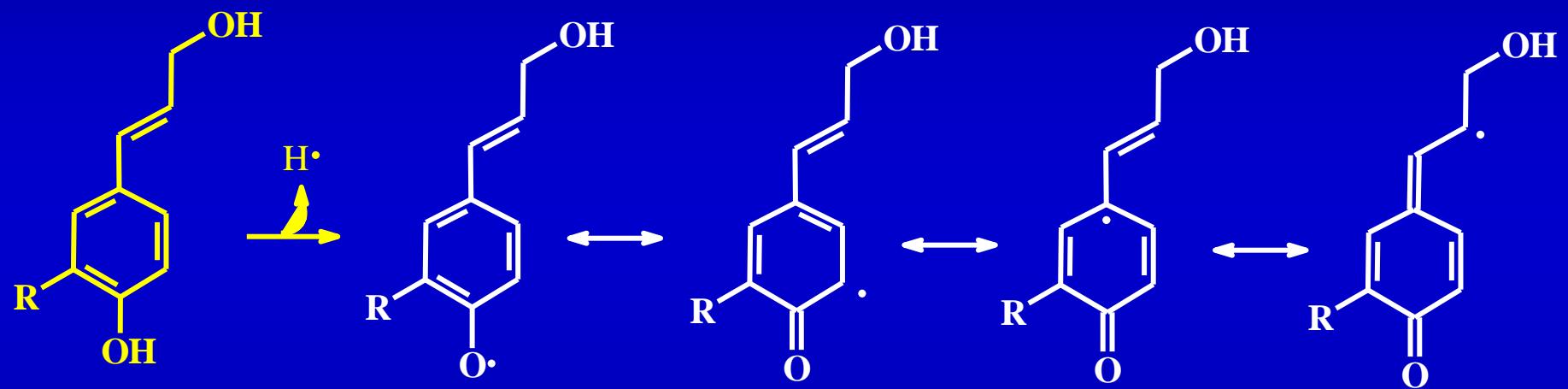


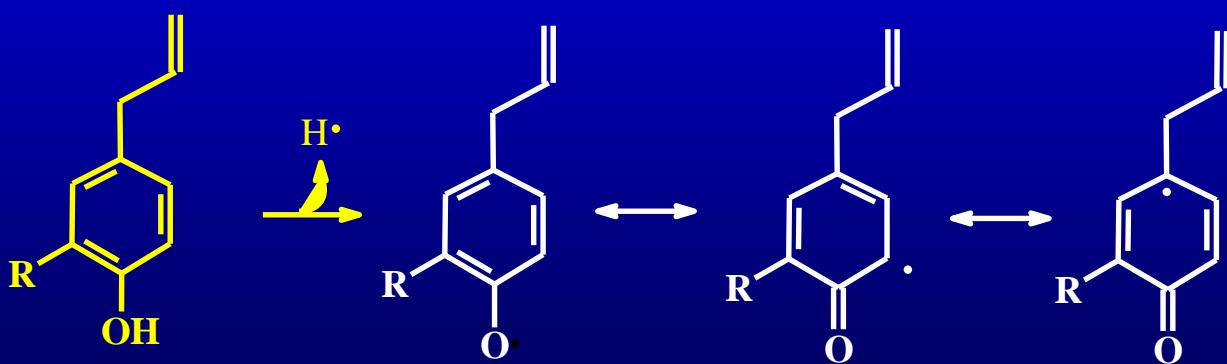
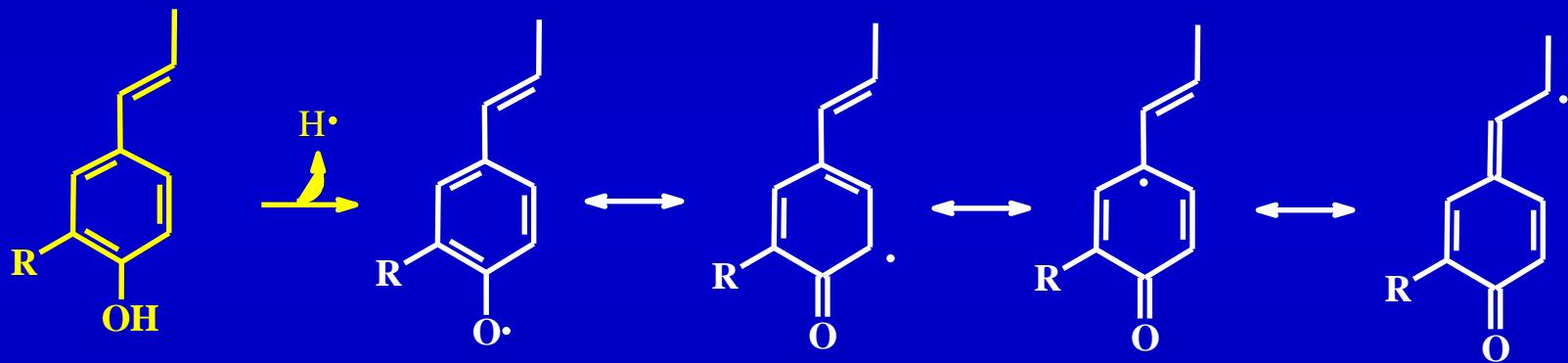
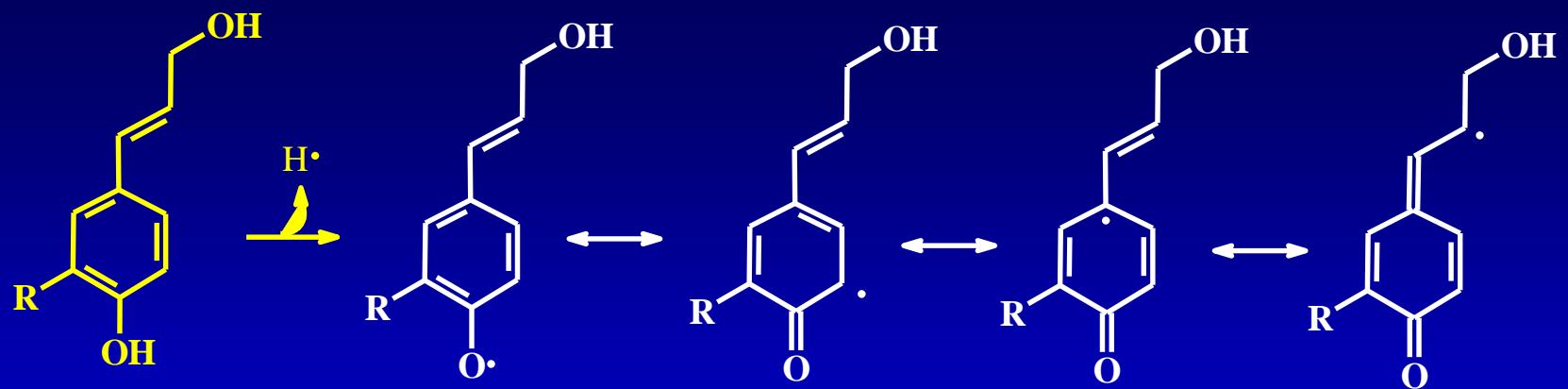
dihydrobenzofuran

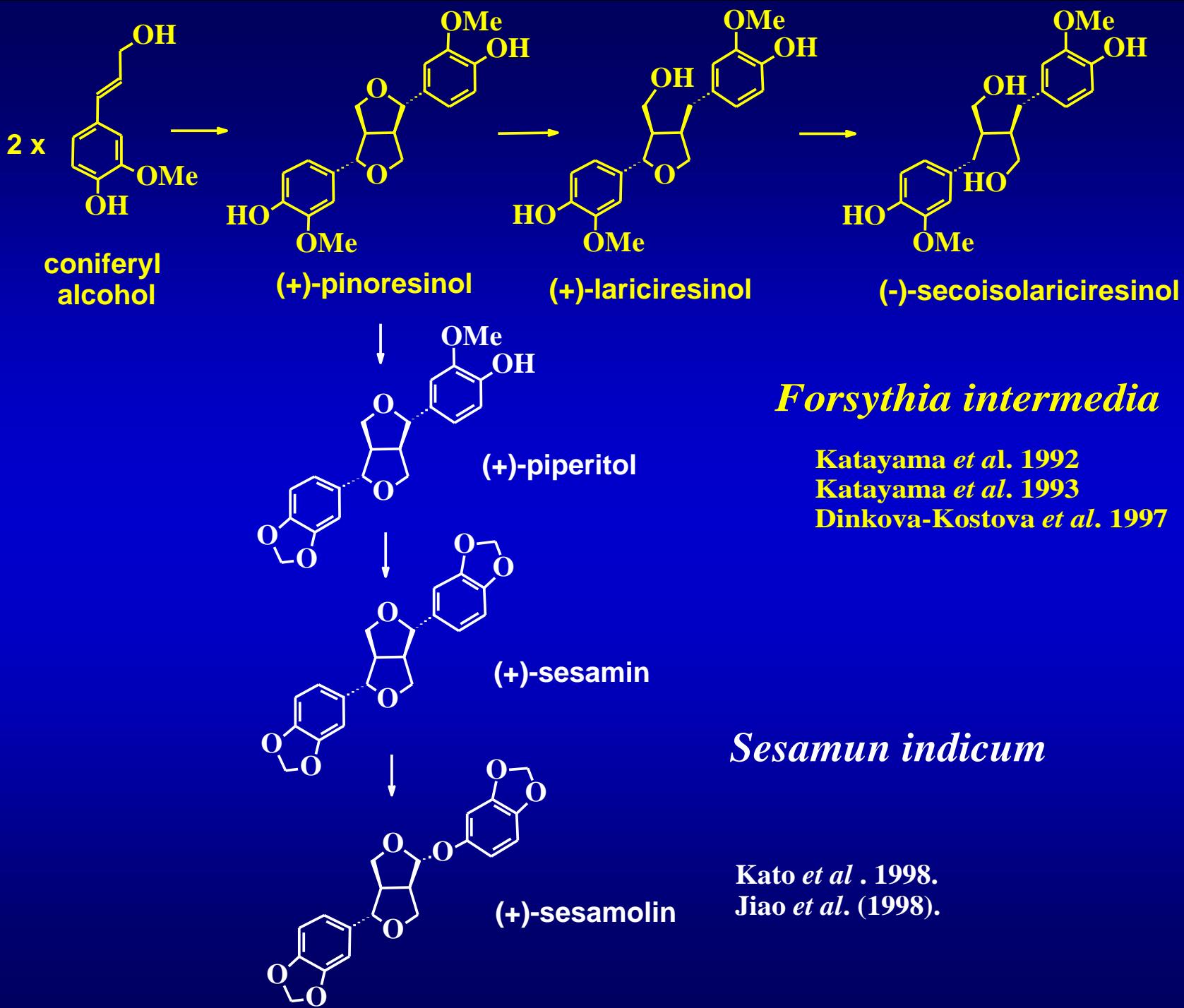
Tabela 1. Atividades biológicas observadas para lignóides (McRae & Towers, 1984)

atividade antitumoral	efeito catártico
atividade antimitótica	ação alergênica
atividade antiviral	ação hipotensiva
citotoxicidade	atividade inseticida
proteção hepática	atividade piscicida
ação no S.N.C.	inibidor de germinação
atividade cardiovascular	atividade fungistática
ação antifertilidade	influência sobre ácidos nucleicos
proteção ao estresse/ antifadiga	influência sobre atividades enzimáticas

Radical oxidation of cinnamyl alcohols



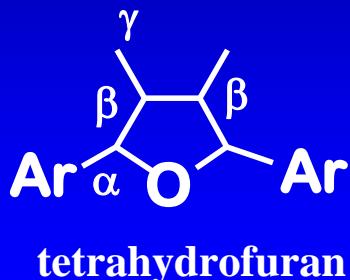




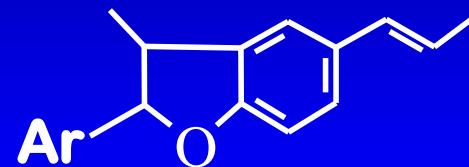
Examples of Neolignans (*sensu* Gottlieb 1974)



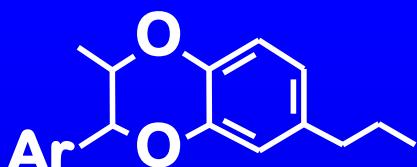
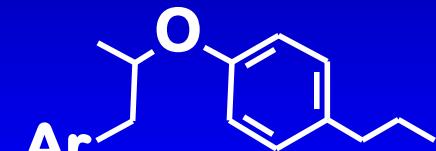
diarylbutane



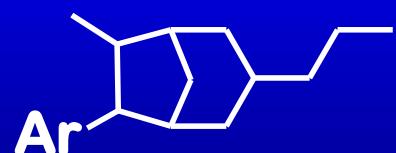
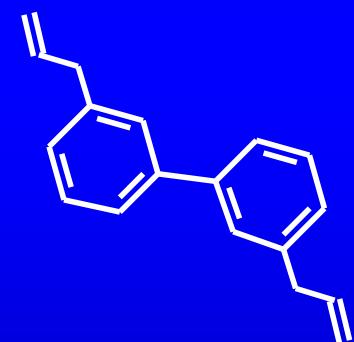
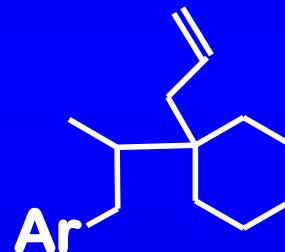
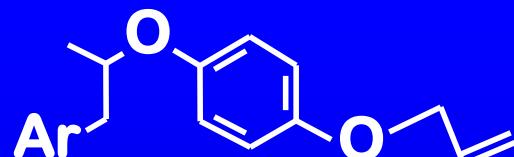
tetrahydrofuran



dihydrobenzofuran



benzodioxane



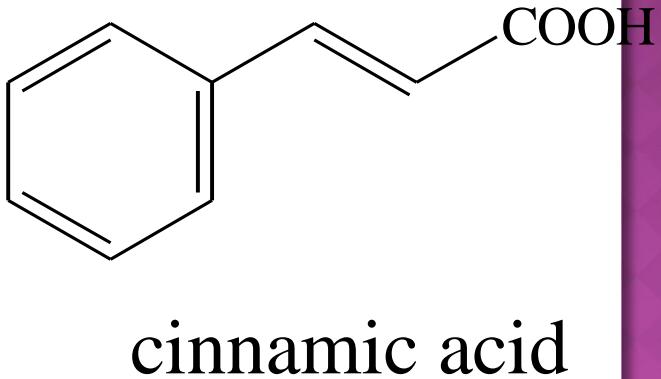
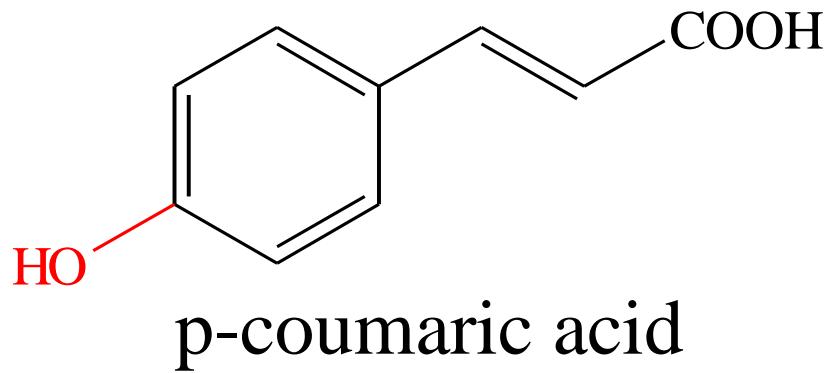
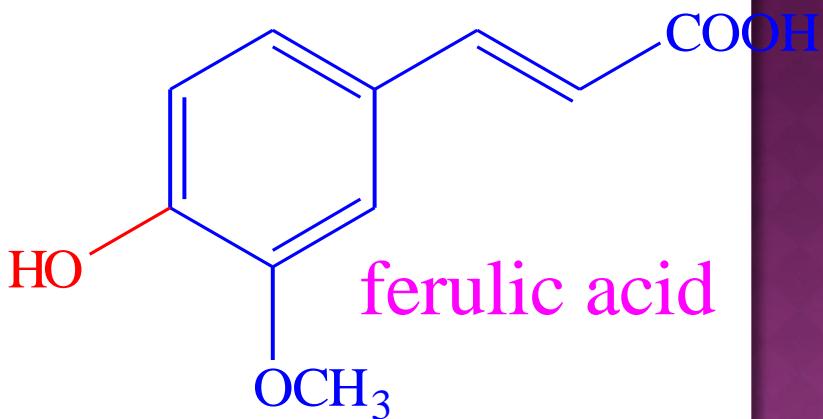
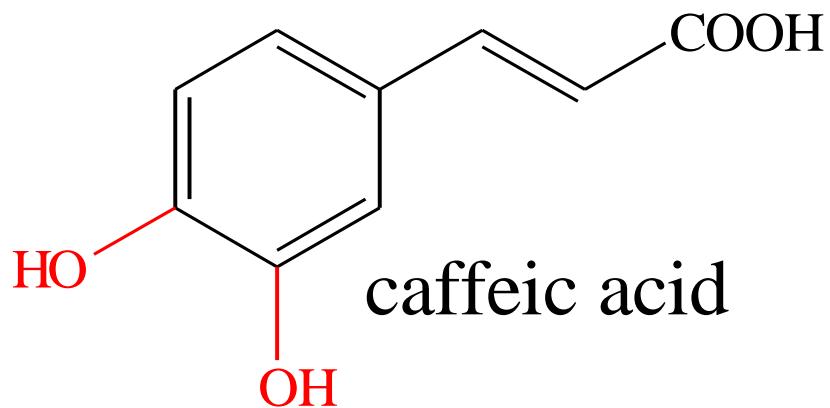
bicyclooctane



spiro

ASAFOETIDA

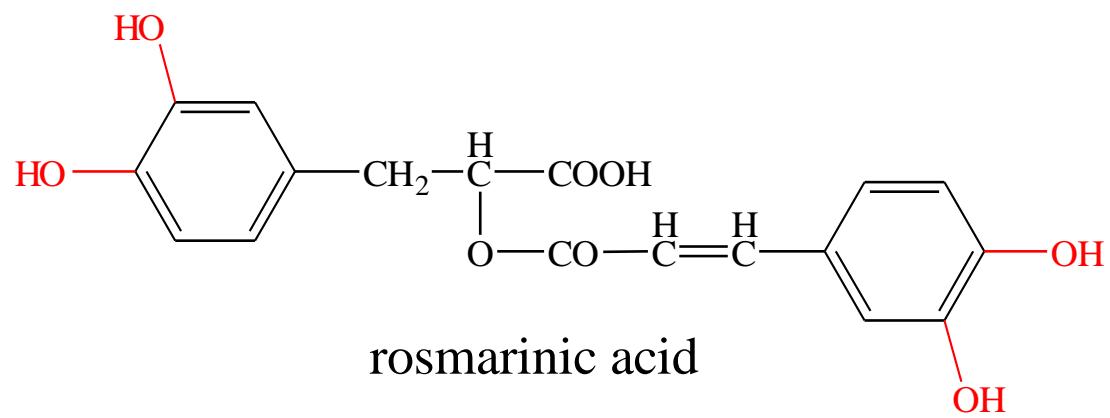
- *Ferula assa-foetida* L.
- Umbelliferae (Apiaceae)
- Oleo-gum-resin : resin 40-64% (Ferulic acid etc)
- Feulic acid inhibit platelet aggregation
- carminative, expectorant, antispasmodic properties, fixative
- export: Iran, Pakistan, Afghanistan





MELISSA LEAF, LEMON BALM

- *Melissa officinalis*
- Labiate (Lamiaceae)
- volatile oil 0.06-0.35% (rosmarinic acid > 4%)
- sedative, spasmolytic, antibacterial, nervous tension etc
- export: Bulgaria, Roumania, Spain
- Adulterant : Lemon oil



A close-up photograph of a lemon balm plant. The leaves are deeply lobed and serrated, with a bright green color. They are arranged in whorls along thin, upright stems. The background is plain white, making the green leaves stand out.

Lemon balm

THYME

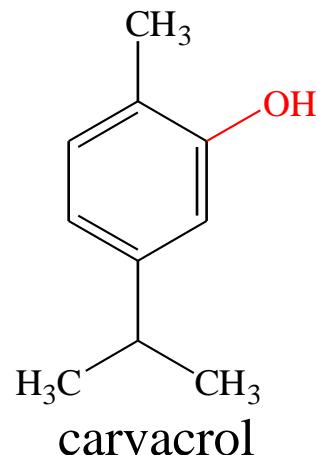
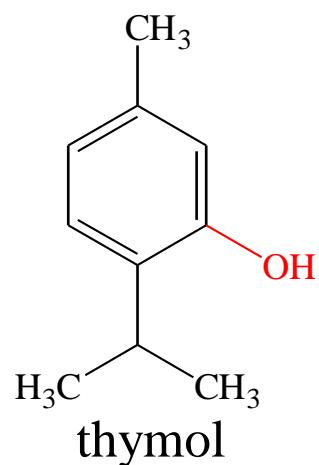
- *Thymus vulgaris, T. zygis*

- Labiateae

- volatile oil 1.2% (thymol 36-55%, carvacrol 1-4%)

- antiseptic, antitussive, expectorant

- export : Spain



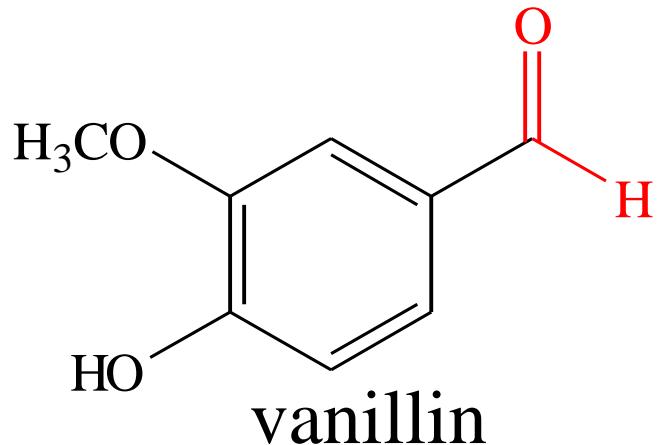
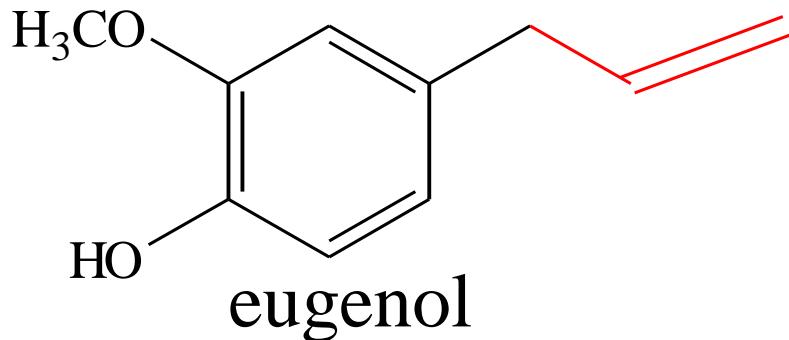


กานพลู

CLOVE

- *Syzygium aromaticum (Eugenia caryophyllus)*
- Myrtaceae
- volatile oil 14-21% (eugenol 84-95%)
- flavouring agent, stimulant, antiseptic
- Flower bud : Madagascar, Indonesia, Brazil
- Stem : Madagascar, Tanzania
- Leaves : Madagascar, Tanzania, Indonesia

Medicinol (clove) oil has a phenol content 85 - 90%



Deterioration

Opt : phenol content low, use in pharmacy

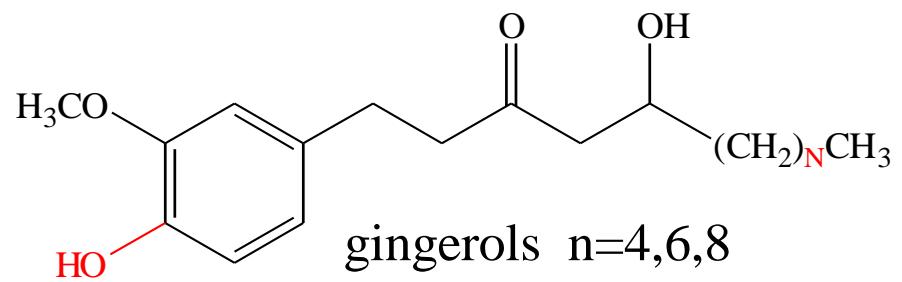
Strong : phenol content high, use in the manufacture
of vanillin





GINGER

- ◎ *Zingiber officinale*
- ◎ Zingiberaceae
- ◎ gingerol(an oily liquid consisting of homologous phenols)
- ◎ pungency of ginger
- ◎ inhibit prostaglandin synthetase (Anti-inflammatory)
- ◎ antiplatelet aggregation







HOP STROBIOLE

- ◎ *Humulus lupulus*
- ◎ Cannabaceae
- ◎ humulone, lupulone
(phloroglucinol derivative)
- ◎ use in preparation of beer
- ◎ England, Germany, Belgium, France, Russia, California

