KJM5230 - Biologisk aktive molekyler (Bioactive Molecules)

The cource discuss the

of important classes of drugs and bioactive natural products.

Synthesis / biosynthesis, mode of action,

bioavailability and stability for chosen drug classes.

Structure activity and structure optimalisation

Book

T. L. Lemke; D. A. Williams; V. F. Roche; S. W. Zito: *Foye's Principles of Medicinal Chemisrty*, 2008. Wolters Kluver/Lippincott Williams&Wilkins. ISBN: ISBN 978-0-78176879-5

Pensum / required reading

Part l:

Part l: Chapters 1-2; 4-5; 10

- **Natural Products**
- **Drug Design**
- **Reseptors - Drug Action**
- **Drug Metabolism**

Part II.

Part III. Sect. 5 Chemotherapeutical Agents: chapters 38-43.

- **Antibiotics/Antimicrobial Agents**
- **Antiparasitic Agents**
- **Antifungal Agents**
- **Antimycobacterial Agents**
- **Anticancer Agents**
- **Antiviral Agents**

Lecture notes

Origin of Drugs / Bioactive Compounds

- **Natural Products / Natural Product Derivatives**
- **Random testing, serendipity***
- **Screening of Libraries**
- **(Rational) Drug Design** (1. mentioned SciFinder 1970, most papers after 1990)

- **Screening/Design/Serendipity**
- **Lead compound**
- **Design/Structure Optimisation**
- **Actual Drug**

⟹

- **Activity**
- **Toxicity**
- **Bioavailability**
- **Metabolism**

in vitro
in vivo animals
in vivo humans

Why new drugs?

- **Resistance**
- **New diseases (Aging, life style)**
- **Less tollerance for side effects**

***Fortunate discovery by accident**
"The three princes of Serendip" Persian Fairy tail
Serendip=Sri Lanka

Origin of Drugs / Bioactive Compounds: History

Before 1800: Plants, plant extracts, inorganic material

1805: Morphine isolated from opium (structure proposed 1935, prooved by synth. 1952)

1828: First organic synthesis (urea)

1840-1850: First synthesized org. compds used in medicine: $CHCl_3$, Et_2O anestechia)

Ex of early synthetic drugs:

- **Choral hydrate (sleeping pill) 1869**
- **Acetyl salicylic acid synth. 1853, clin. trials 1893**
- **Phenazone synth. 1884**
- **Benzocaine 1902**
- **Prontocil 1932**

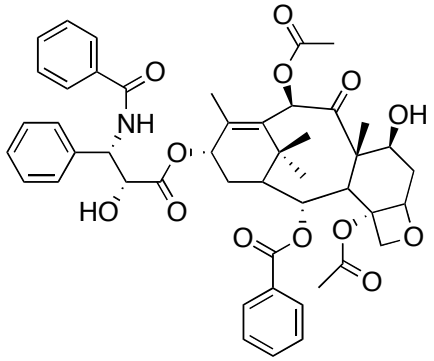
Ex of early isolated nat. prod.

- **Quinine ca 1825**
- **Digitoxin 1841 (structure 1928)**
- **Salicylic acid, antipyretic 1875**
- **Cocaine isol. 1860, local anestethic 1884**
- **Benzylpenicillin 1941**

Traditional medicine
Screening
Serendipity

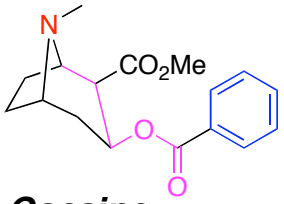
Natural Products

- **Only source of drugs before last part of 19th century**
- **Antibiotics 1940 - 1960**
- **Cyclosporin (immunomodulator) isolated from soil fungus Hardangervidda 1971**
- **Taxol isolated 1960s, approved drug USA 1992**

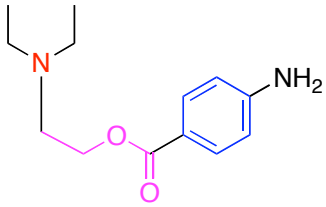


- **Lead compounds**

Hydrophilic Aminogroup (can be protonated) — **Spacer** $-C_n-X-$ X: $-CO_2-$ -CONH- -NHCO- — **Lipophilic (Aryl)**

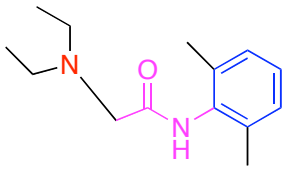


Cocaine



Procaine
(1905)

Acid labile ester

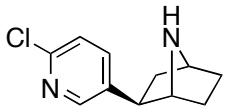


Lidocaine/Xylocaine
(1946)

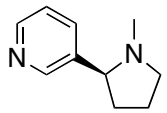
Natural Products

Sources

- **Microorganisms (bacteria, fungi) - Antibiotics**
- **Higher plants, ex. morphine, quinine, taxol**
- **Sponges (polycellular "animals", no real organs or cell tissue) ex. agelasines**
- **Higher animals, fewer examples, epibatidine from South American tree frog**



Epibatidine
painkiller, toxic!
potent inhibitor of certain nicotinic reseptors



Nicotine

Microorganisms, sponges, plants

- **No immune system, produce their own antibiotics as defence**
- **Secondary metabolites with great structural diversity, stereochemistry!**
- **Secondary metabolites have no known metabolic role in cells**
- **Three main classes: alkaloids, terpenoids, phenolics**

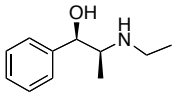
Alkaloid Natural Products

- **Largets class of secondary metabolites*, >6500 compds known**
- **Contains N, most compds basic (alkaline)**
- **Often highly toxic**
- **Found in certain higher plants (seldom in bacteria)**
- **Little is known regarding why alkaloides are produced - defence**
- **Biosynthesis from amino acids**

*** Not directly involved in growth, development, reproduction**

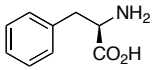
Alkaloid Natural Products

Amino alkaloids: N as amine / amide (not in heterocycle)

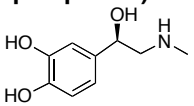


(-)Efedrin

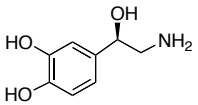
Biosynth from phenylalanine



Bioactivity ≈ Adrenaline (Epinephrine) only weaker

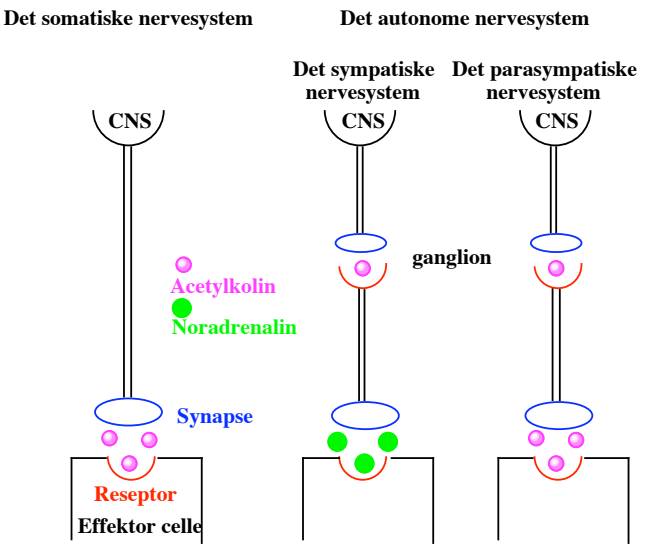


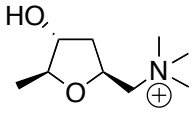
Adrenalin - Hormone



Noradrenalin - Neurotransmittor

Source *Ephedra sinica*





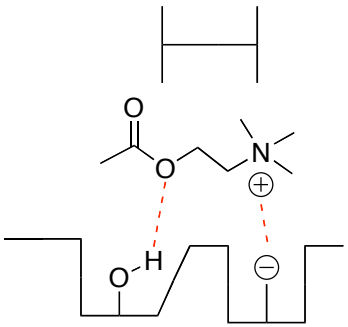
(+) Muscarine

Source *Amanita muscaria*

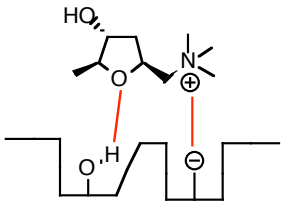
Sub types cholinerge reseptors

Acetylcholine

ca. 5Å

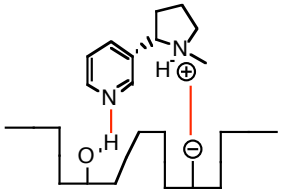


Muscarinerge



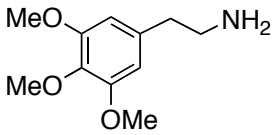
Nicotinerge

Nicotine from *Nicotiana tabacum*



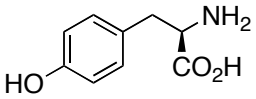
Alkaloid Natural Products

Amino alkaloids



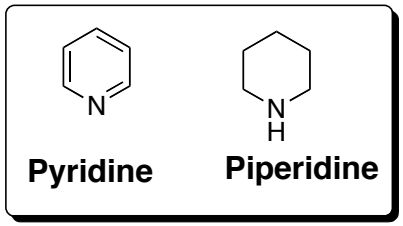
Mescaline

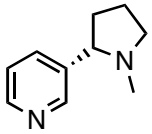
Biosynth from thyrosine



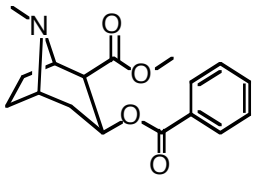
Source
Lophophora williamsi

Pyridine / piperidine alkaloids



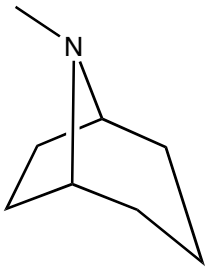


Nicotine



Cocaine

Source
Erythroxylon coca



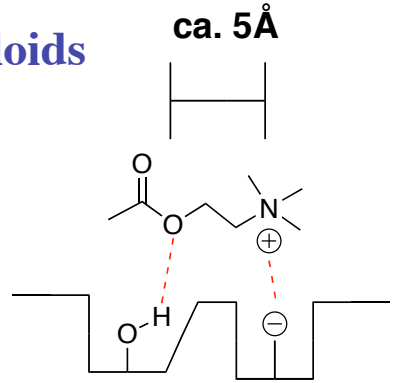
tropane

(8-methyl- 8-azabicyclo[3.2.1]octane)

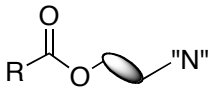
Pyridine / piperidine alkaloids

Parasympatolytika (Antikolinergika)

Tropanalkaloids



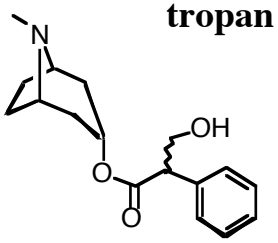
Antagonist:



R>Me
"N": Quart. or tert (protonated. *in vivo*)
distance as in AcCh

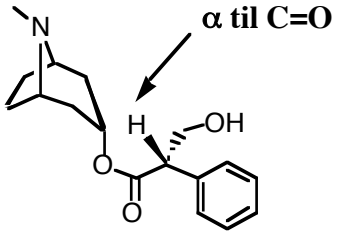
tropan

Source *Atropa belladonna* og *Hyoscamus niger*



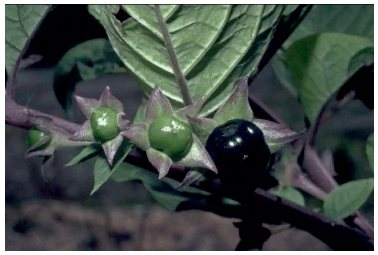
(±) ***Atropin***

Base



(-) Hyoscyamin

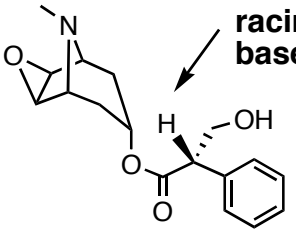
Muscle relax (guts, eye)



Atropa belladonna

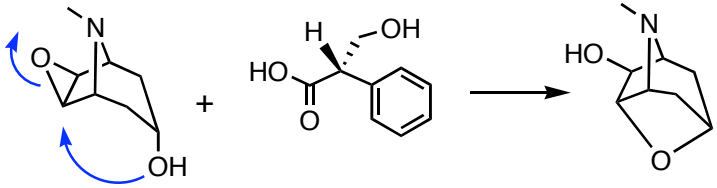
Hyoscamus niger (bulmeurt)

Scopolamin



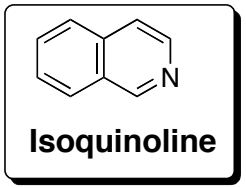
racimisation base

Ester hydrol.

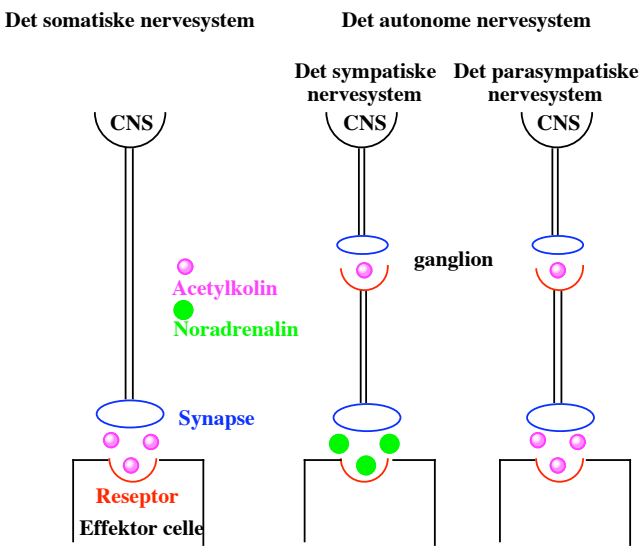


Skopin + ***Tropasyre*** → ***Skopolin***

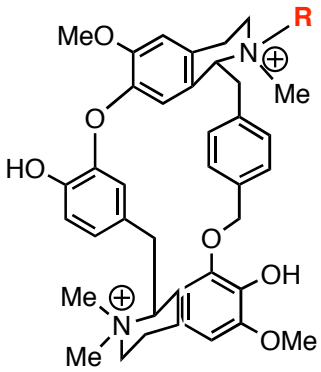
Alkaloid Natural Products



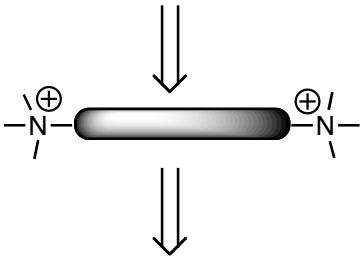
Isoquinoline alkaloids



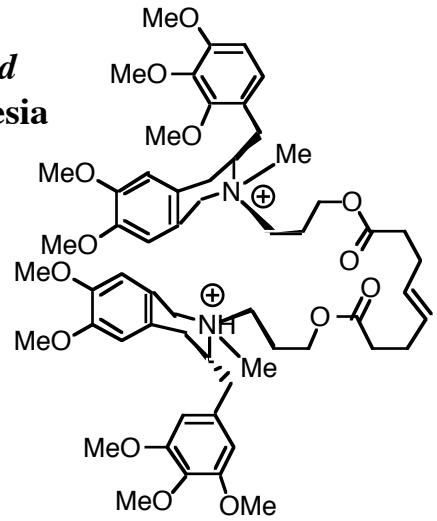
Curare - Poison - Southamerican indians
Mixt. of alkaloids
Several sources *i.e.* *Chondodendron tomentosum*



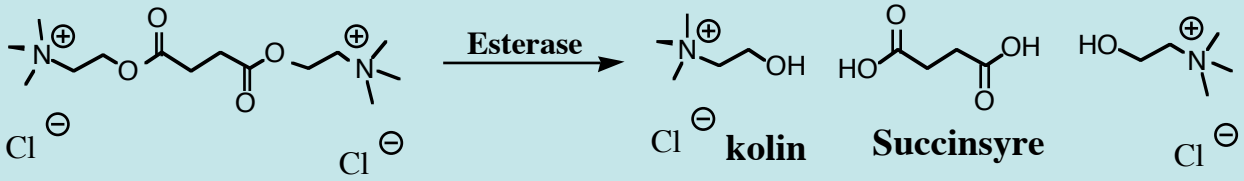
R=H: *Tubocurarin*
R=Me: Wrong struct.



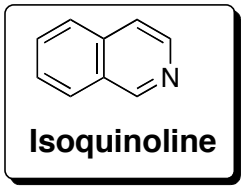
Ex. *Mivacurium klorid*
Muscle relax, anesthesia



***Suksametonium*, Curacit® "Nesset"**

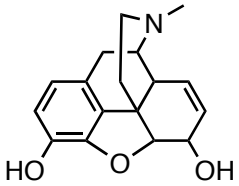


Alkaloid Natural Products

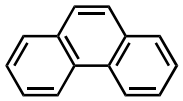


Isoquinoline alkaloids

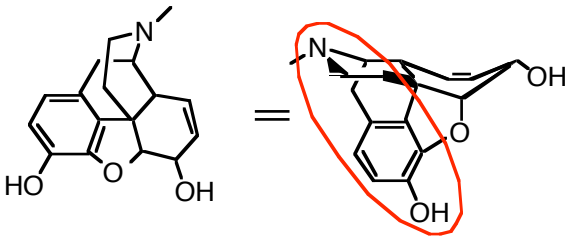
Morfin isolert fra opium 1803 (Morpheus: gresk søvngud)



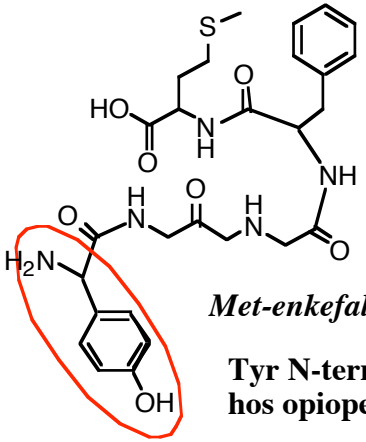
Derivative of phenantrene



Morfinanalogs, binds to opiopeptide (endorfin / enkefalin) reseptors



Morfin

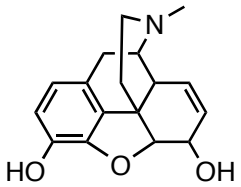


Met-enkefalin

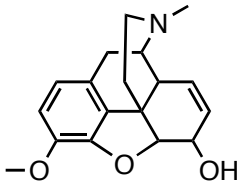
Tyr N-terminal hos opiopeptider

Naturally occuring and semisynth analgetic opioides

Morphine

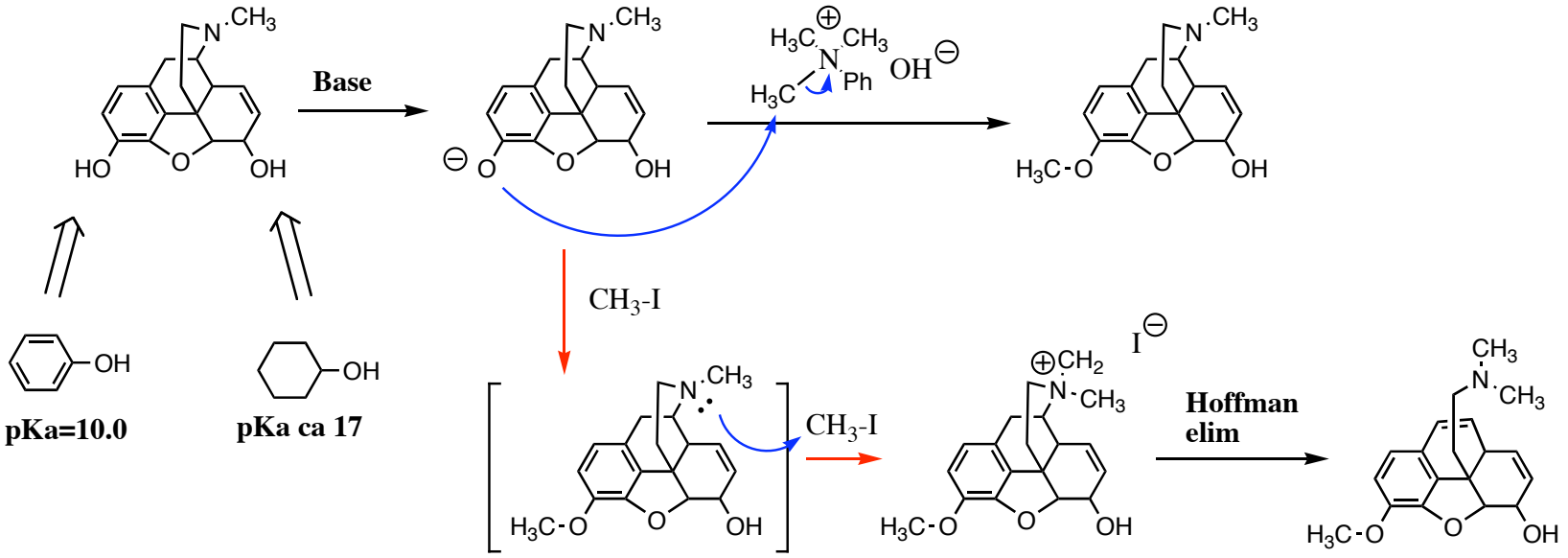


Codeine



also against cough
slow metabol. to morphine

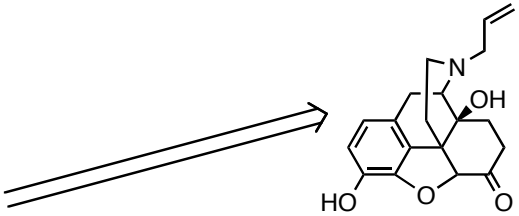
Small amounts in opium, semisynth from morphine



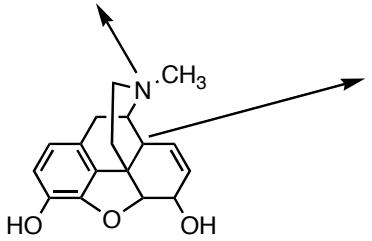
Total synthetic analgetic opioides

SAR - morphine

Must be tert N.
N-CH_3: agonist
N-R (3-4 C, unsat. or ring): antagonist
N-R (large): agonist: Ph-CH_2CH_2 10X more active enn -CH_3

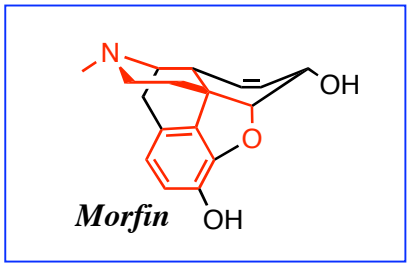


Nalokson
Antidote

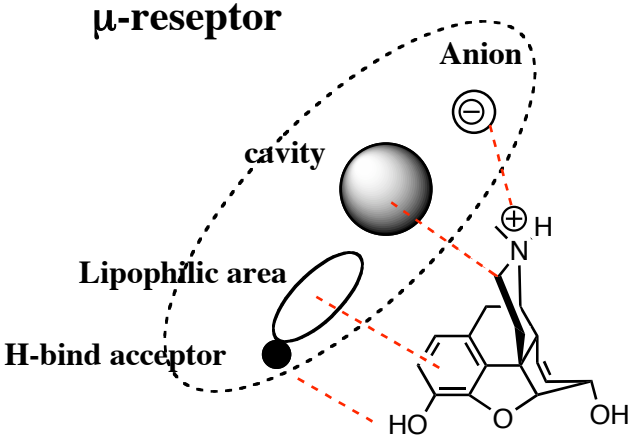


OH increase (often)activity

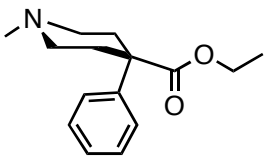
Ether bridge not neccesary



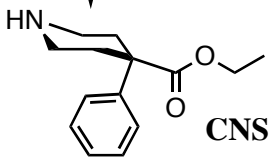
Model of morphine bound to μ-reseptor



Petidin (Meperidin)
Ketodur®,Ketorax®

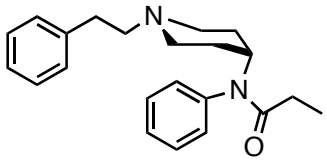


in vivo



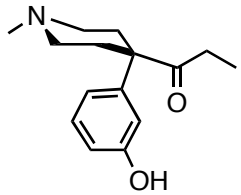
CNS eksitering

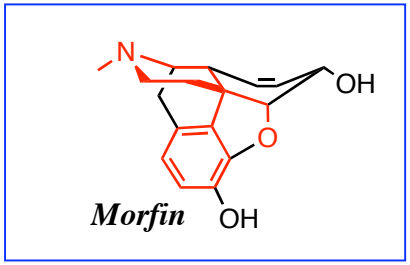
Fenantyl
Fenantyl®, Leptanal®
(anestetica)



Moscow theatre

Ketobemidon
Ketodur®,Ketorax®
Ketogan ®

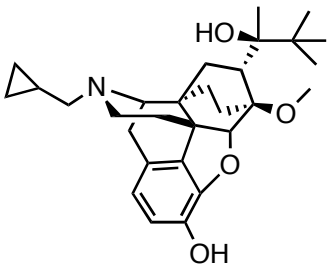




Morfin

Buprenorfin

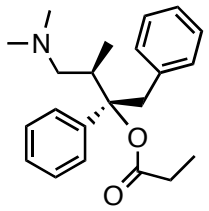
Temgesic®, Subutex®



More potent than M. (pain)
Partiell μ-agonist:
Antagonister **high doses**
Naloxon effects (dysfori etc)

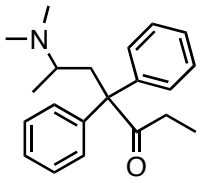
Dekstropropoksyfen

Aporex®



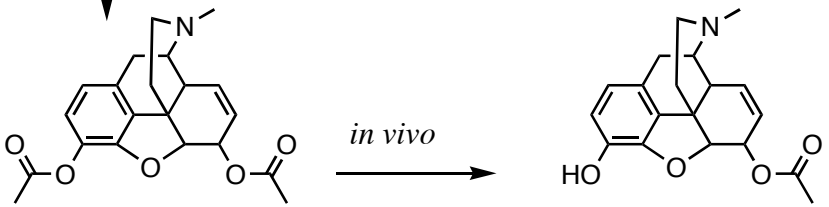
(+) most active
less adict. than M.

Metadon



μ-Agonist
analgetc, not euphoria,
Long duration
Good oral availabil.

Less active μ-agonist

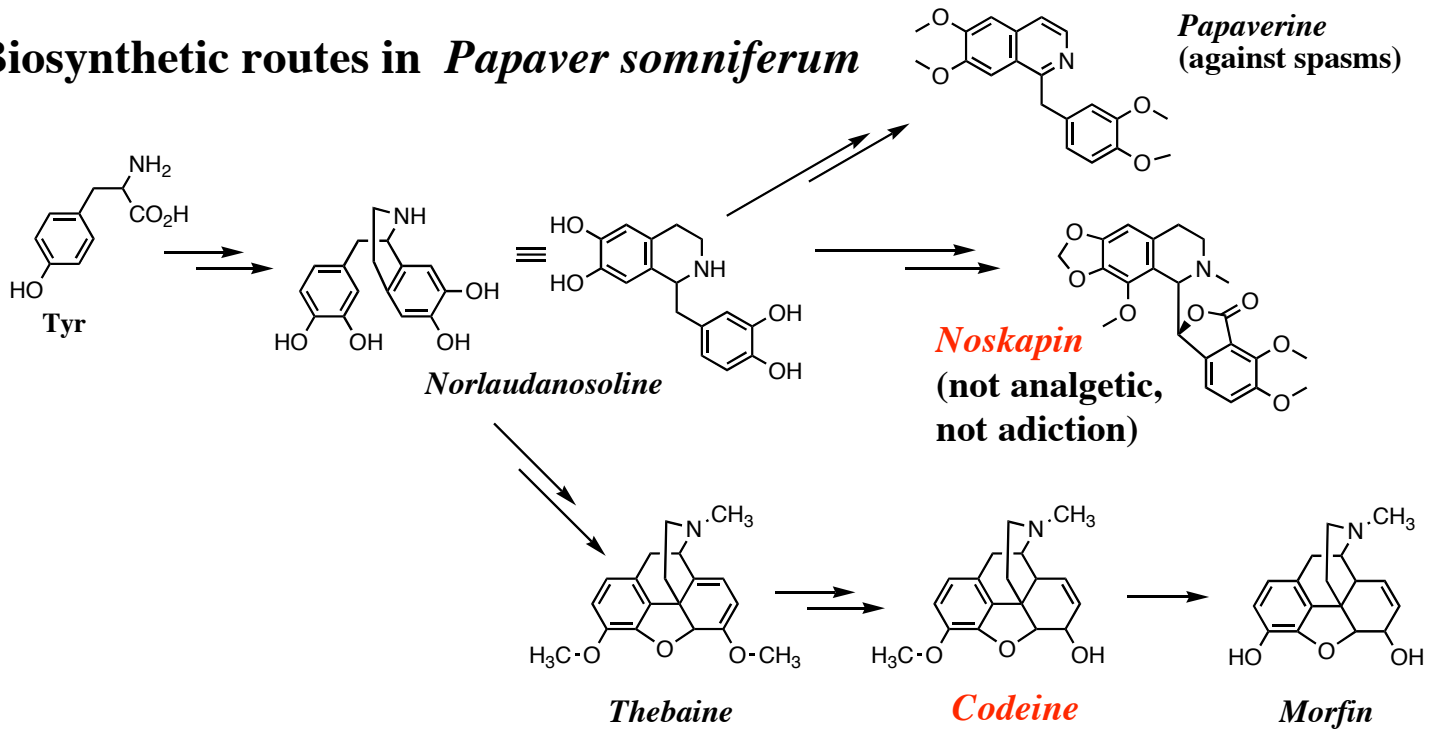


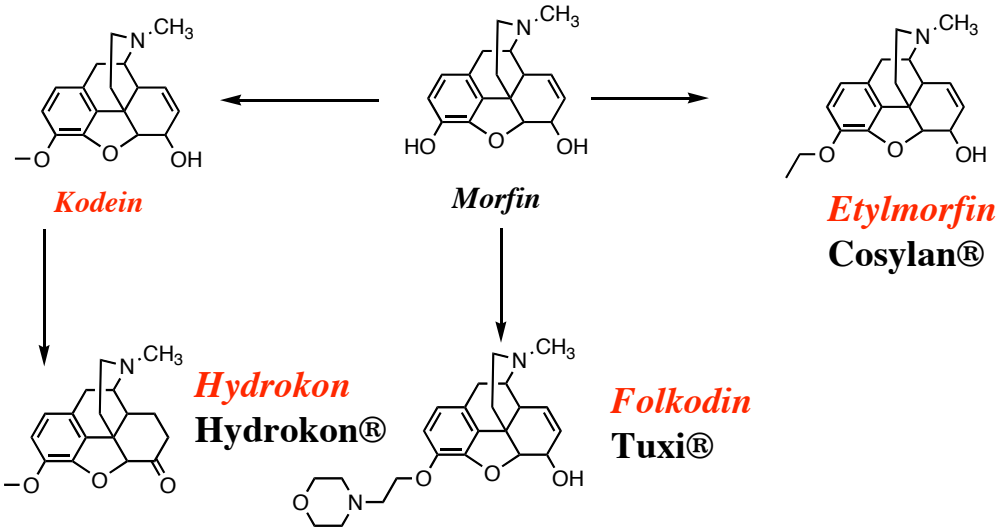
Heroin
increased BBB penetration
bad μ-agonist

bether μ-agonist than morphine

Naturally occuring and antitussiva opioides

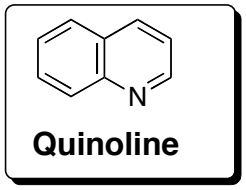
Biosynthetic routes in *Papaver somniferum*



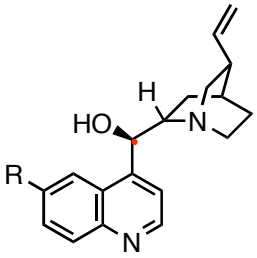


Alkaloid Natural Products

Quinoline alkaloids



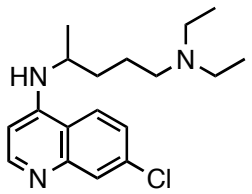
Cinchona pubescens (Kinatre) from South America



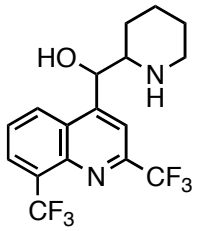
R=OMe: Quinine (Cinchonidine epimer at C-9)

R=H: Quinidine (Cinchonine epimer at C-9)

Quinidine: Antiarytmic
Quinine: Antimalaria



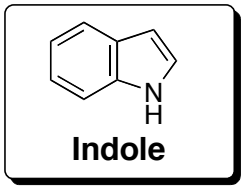
Chloroquine



Mefloquine

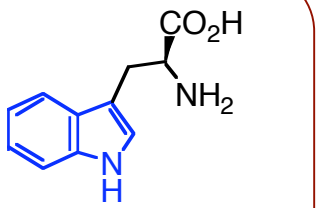
Dihydroquini(di)ne and der.
Chiral ligands
Asym. dihydroxylation (Sharpless)

Alkaloid Natural Products

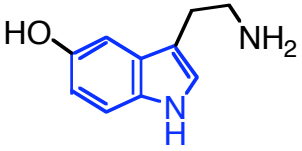


Indole

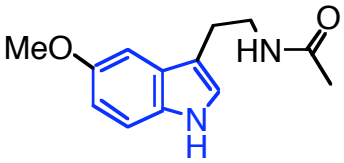
Indole natural products



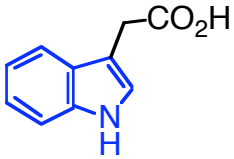
Tryptophan
Essential amino acid



Serotonin
Neurotransmitter

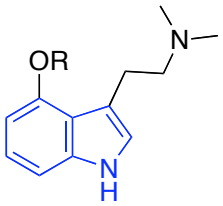


Melatonin
Hormone



Auxine
Plant growth hormone

Indole alkaloids



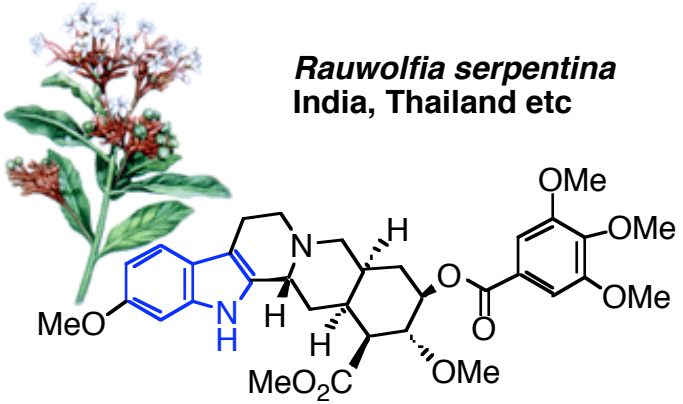
Halucinogens from *Psilocybe* mushroms

R=H: *Psilocin* ← *in vivo*
R=PO_3H: Psilocybin

Serotoninagonists,
not broken down in the body
strong, continuos nerve impulse

Psilocybe semilanceata
(Spiss fleinsopp)

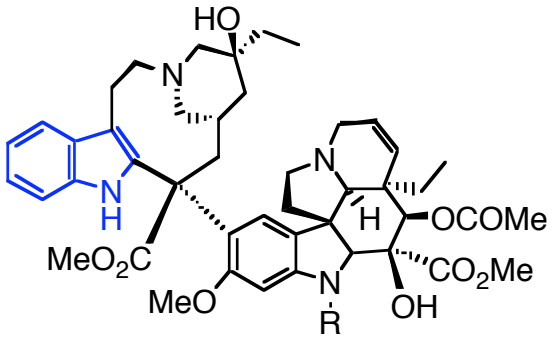
Psilocybe Mexicana



Rauwolfia serpentina
India, Thailand etc

Reserpine
from Rauwolfia sp.
Reduce blood pressure

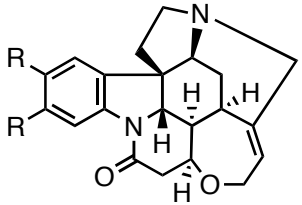
Vinca alkaloids
from *Vinca rosea*
Anticancer comp.



R=-Me: *Vinblastin, Oncovin®*
R=-CHO: *Vinkristin, Velbe®*

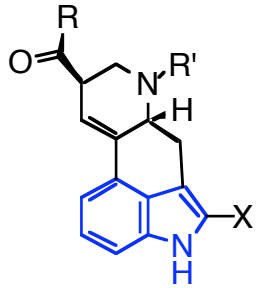
Vinca rosea
(Catharantus roseus)
From Madagaskar
Perivinkle

Strychnos alkaloids - from *Strychnos nux vomica*



R= H; *Strycnine*
R=OMe; *Brucine* (1/50 of S. activity)

Muscle spasms

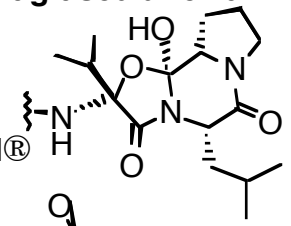


Secale alkaloids and derivatives
from *Claviceps purpurea* (meldrøye)

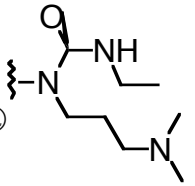
X=H, R'=Me, R=OH: *Lysergic acid*
X=H, R'=Me, R=NEt_2: *LSD*

X=H, R'=Me, R=-NHCH(Et)CH_2OH: Metylergometrin,
Uterus contractions, drug used after birth

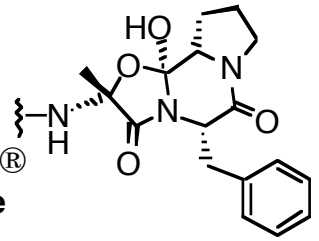
X=Br, R'=Me, R=
Bromokriptin, Parlodel®
Prolactine inhibitor



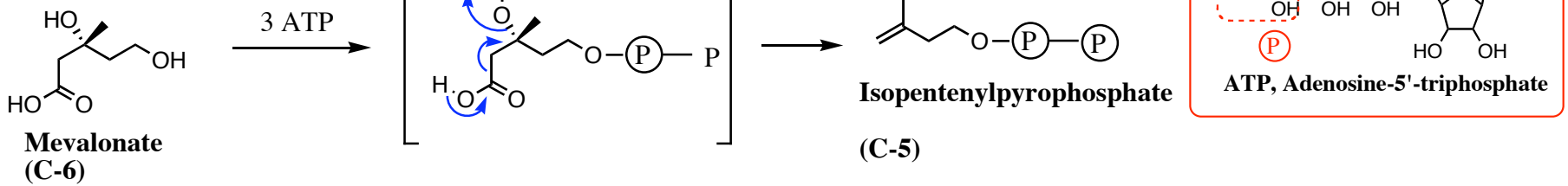
X=H, R'=Allyl, R=
Kabergolin, Dostinexl®
Prolactine inhibitor



X=H, R'=Me, R=
Ergotamin, Anervanel®
Drug against migraine



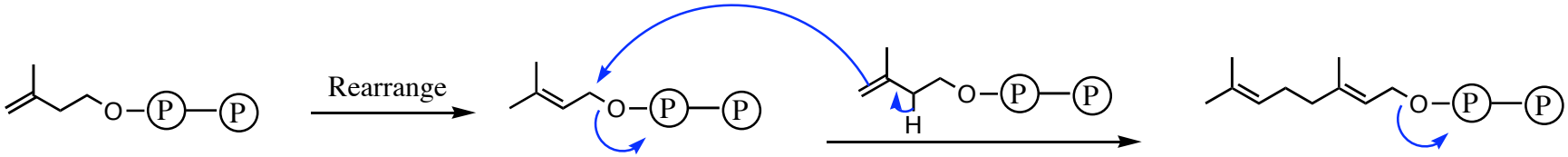
Terpenoide Natural Products



Mevalonate (C-6)

Isopentenylpyrophosphate (C-5)

ATP, Adenosine-5'-triphosphate



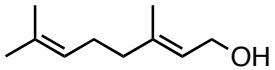
Isopentenylpyrophosphate (C-5)

Dimethylallylpyrophosphate (C-5)

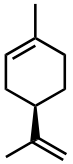
***trans*-Geranylpyrophosphate (C-10)**

C-10: Monoterpenes
C-15: Sesquiterpenes
C-20: Diterpenes
C-25: Sesterterpenes
C-30: Triterpenes

Monoterpenes (C-10) Ex.



Geraniol

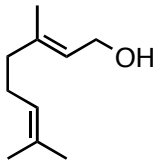


(+) Limonene

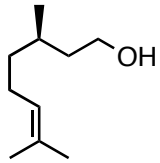
Natures leaving group

Monoterpenes

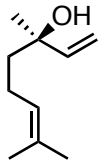
Voilatile compds, smell, taste etc.



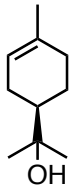
trans-Geraniol



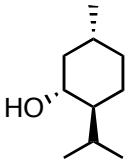
(-)–β-citronellol



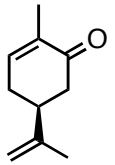
(-) Linalool



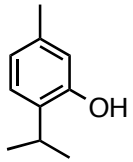
(+)-α-Terpineol



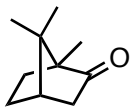
(-)-Menthol



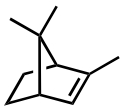
(+)-Carvone



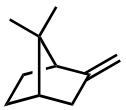
Thymol



(+) Camphor

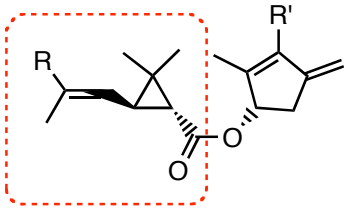


α-Pinene

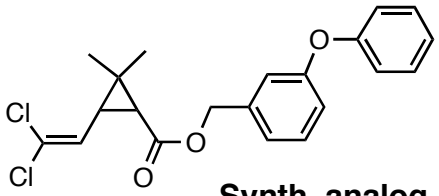


β-Pinene

Pyrethrines
Insecticides from *Chrysanthemum cinerariifolium*



C-10

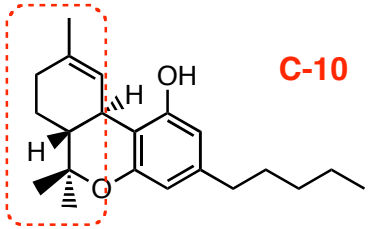


Synth. analog
more stable
mixt of isomers

***Permetrin*, Nix®**

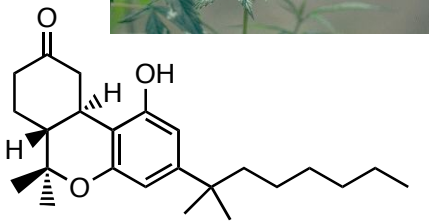
Shampoo, Lice, scabies

Cannabinoids,
from *Cannabis sativa* (Hemp)



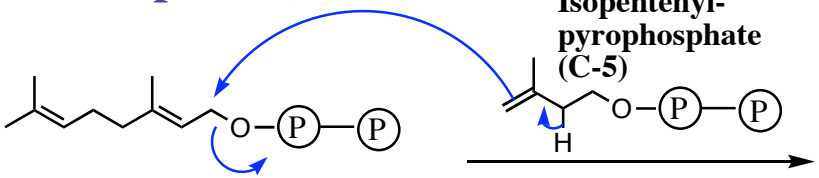
C-10

Tetrahydrocanabinol



Nabilone
Antiemetic (not reg N.)

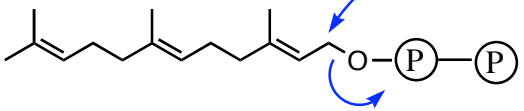
Diterpenes (C-20)



Isopentenyl-pyrophosphate (C-5)

***trans*-Geranylpyrophosphate**

(C-10)

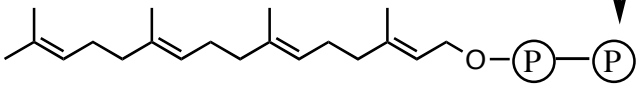


Isopentenyl-pyrophosphate (C-5)

***trans, trans*-Farnesylpyrophosphate**
(C-15)

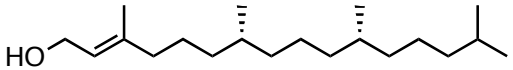
Sesquiterpenes

Head to tail coupling

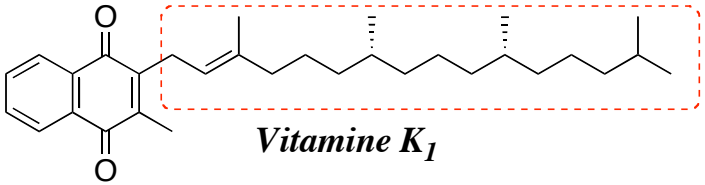


***all trans*-Geranylgeranylpyrophosphate**
(C-20)

Diterpenes

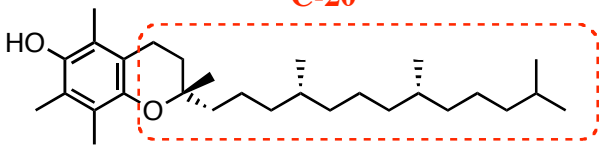


Phytol

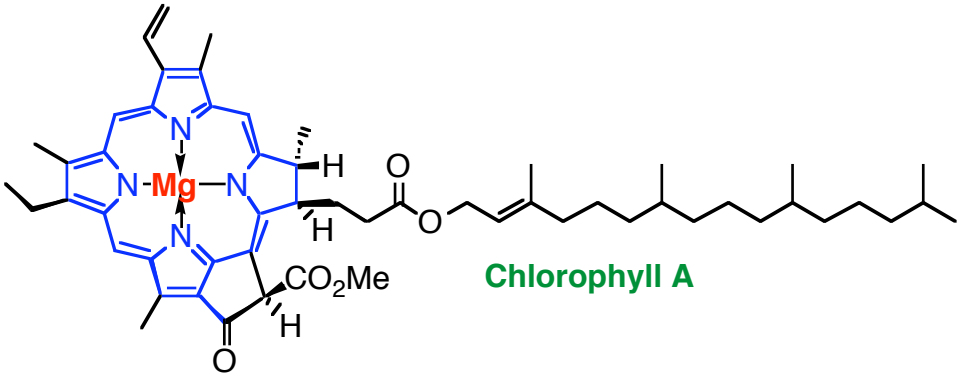


Vitamine K_1

C-20

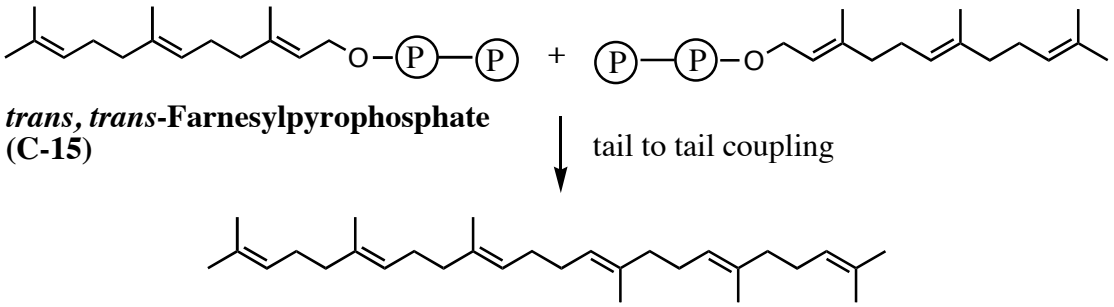


Vitaminee E (α-Tocopherol)



Chlorophyll A

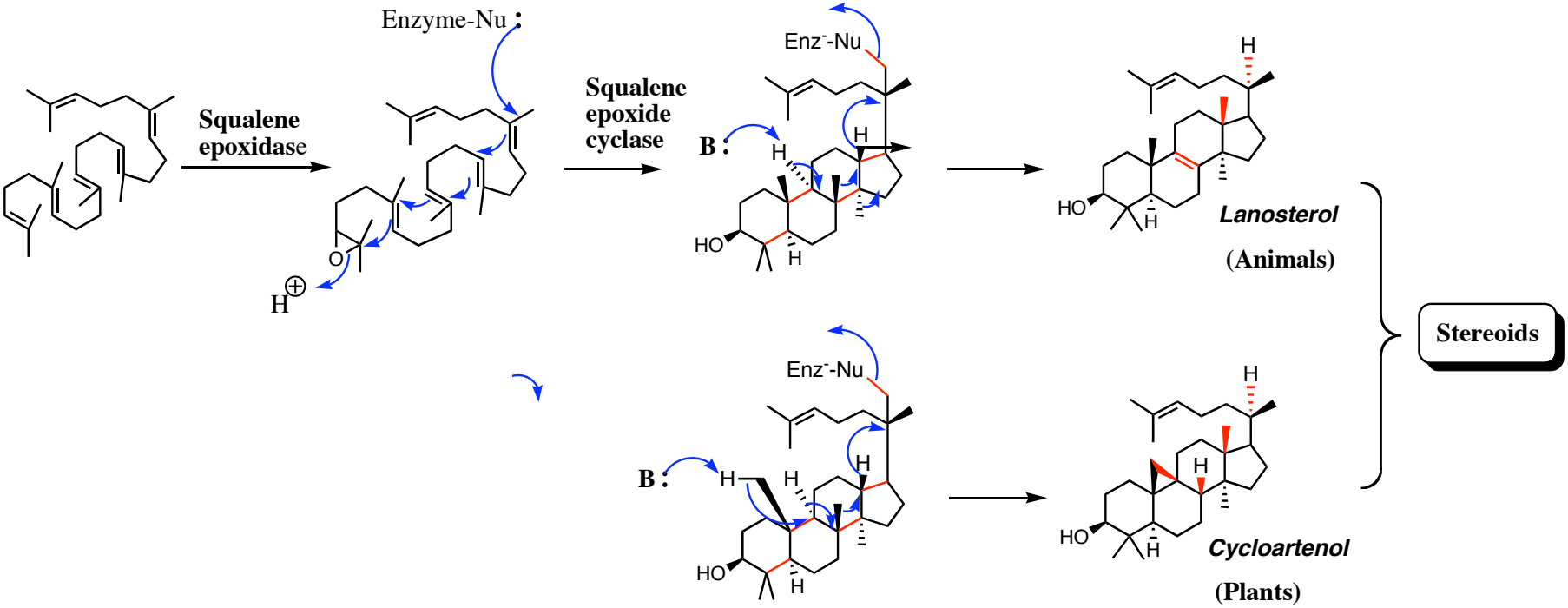
Triterpenes (C-20)



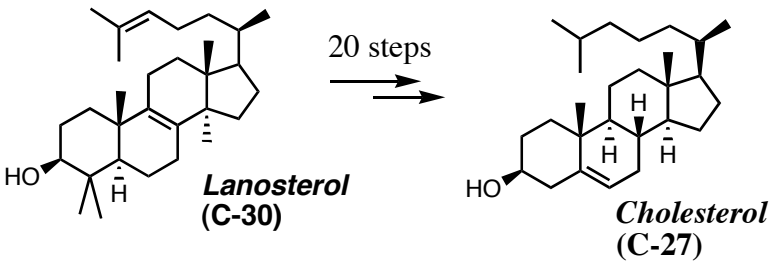
***trans, trans*-Farnesylpyrophosphate (C-15)**

tail to tail coupling

Squalene (C-30)



Stereoids



Lanosterol
(C-30)

Cholesterol
(C-27)

Cholesterol

Sex hormones

- **Estrogens**
- **Progesterones**
- **Testosteron and anabolic stereoids**

Corticoids

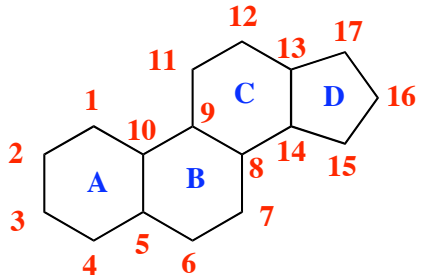
- **Glucocorticostereoids**
  - **Cortison etc. etc.**
- **Mineralcorticostereoidsr**
  - **Aldosterone**

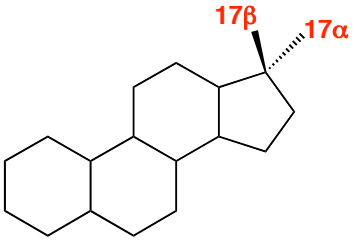
Digitalis glycosides

Fucidinic acid (antibiotic)

Brassinostereoids (Plant growth hormones)

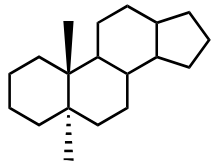
etc. etc.

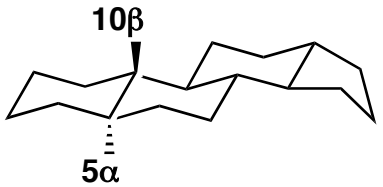




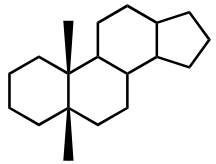
B / C og C / D always *trans* (animals)

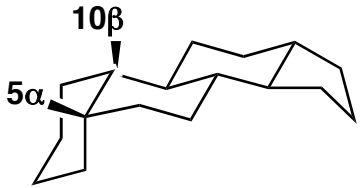
A / B *trans* fused



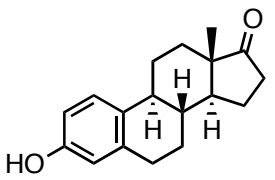


A / B *cis* fused



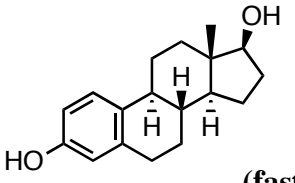


Sex hormones - Estrogenes



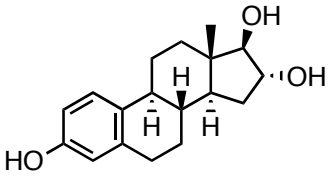
Estrone
(low activity)

in vivo



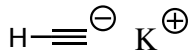
Estradiol

in vivo
(fast metabol)

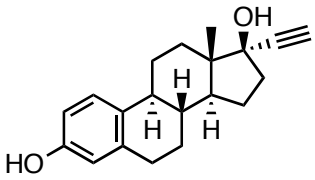


Estriol
(low activity)

Used in drugs

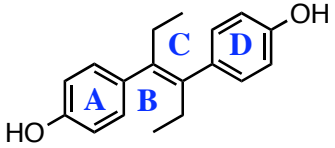


2 ekviv.

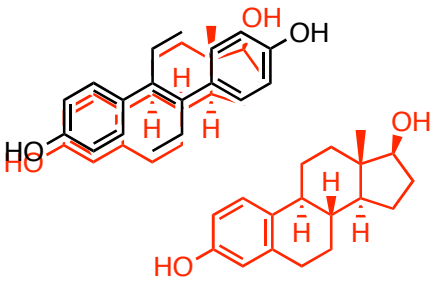


Ethinyl estradiol
(only estrogen im P-pills)

Estrogene agonists (mimics)

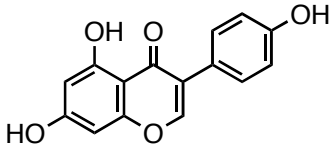


Dietylstilbøstrol
Estrogene agonist, drug before



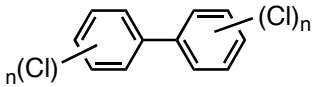
Estradiol

Phytoestrogen (in soya)

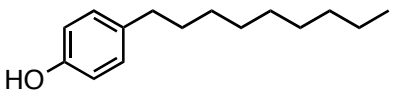


Genistein
(isoflavonoid)

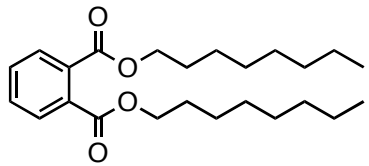
PCB



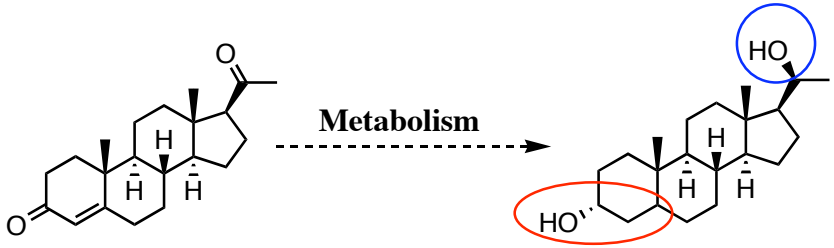
Alkylphenols



Phtalates

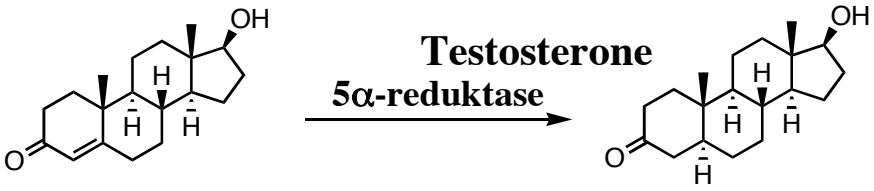


Sex hormones - Progesterones (gestagenes, progestrines)



Progesterone

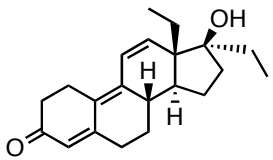
Many semisynth drugs in use (better bioavalabil.)



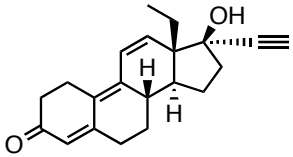
Testosterone

5α-Dihydrotestosterone (5DHT)
More active A-B ring *trans*
***Cis* isomer inaktive**

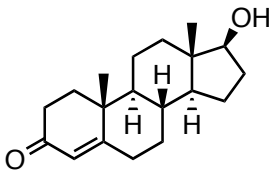
Doping - Anabolic stereoids



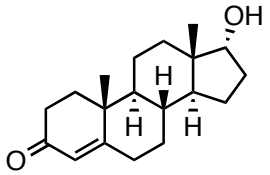
THG (tetrahydrogestrinon)



Gestrinon



Testosterone

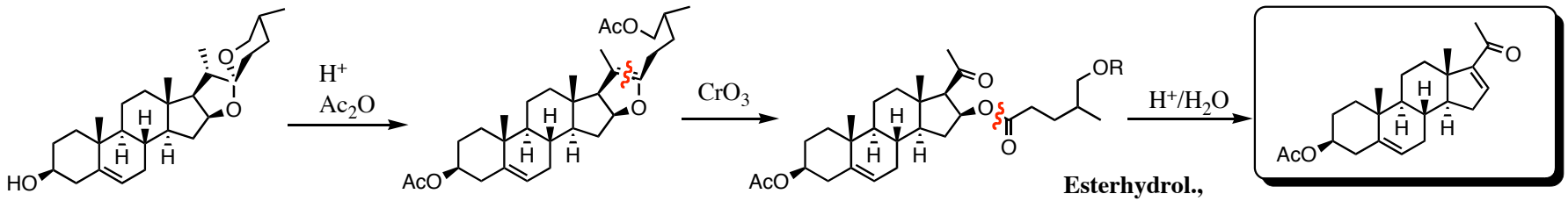


Epi-testosteron
Only small androgene / anabole activity
Different biosynt. pathway than T

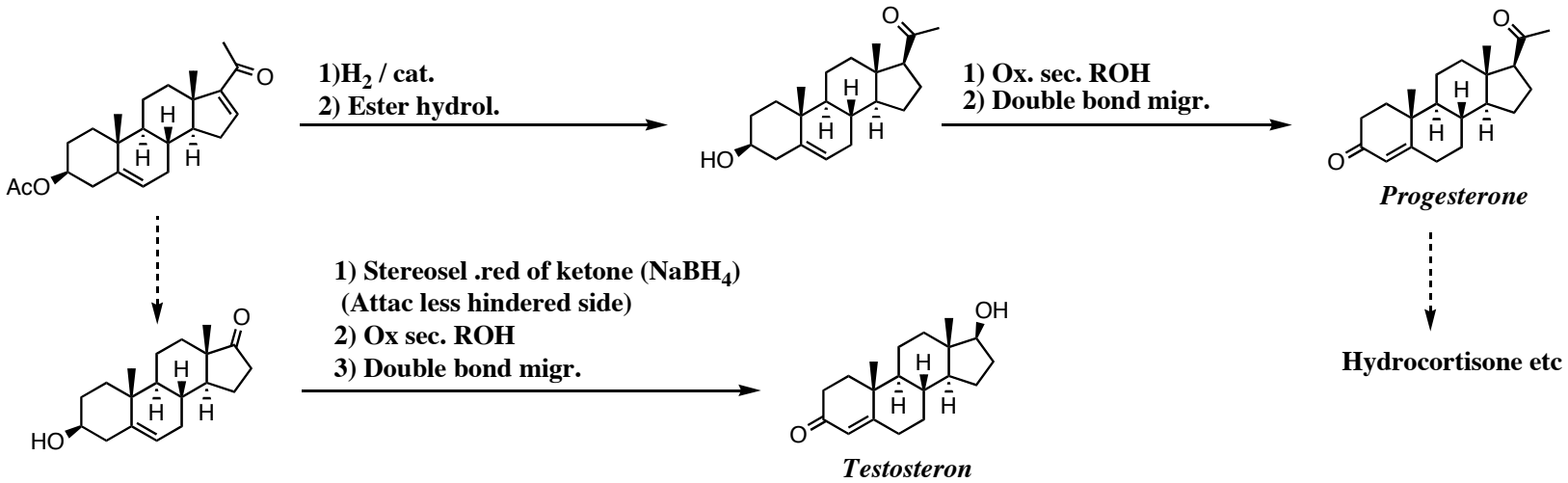
Normal: T : E ratio ca 6 : 1
Doping T: E increases

E added to hide signs of doping

Semisynthesis sex hormones

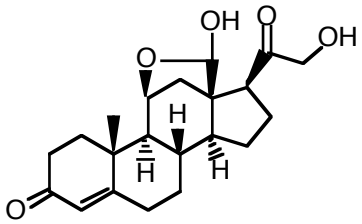


Diosgenine
(6% in Yam roots, *Dioscorea sp*)



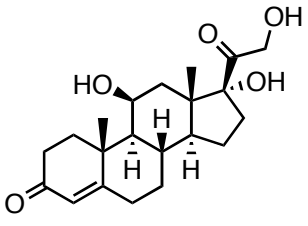
Corticostereoids

Mineralcorticoid



Aldosterone
Regulation of elektrolyttic ballance
increase re-uptake of Na (and hence H_20)

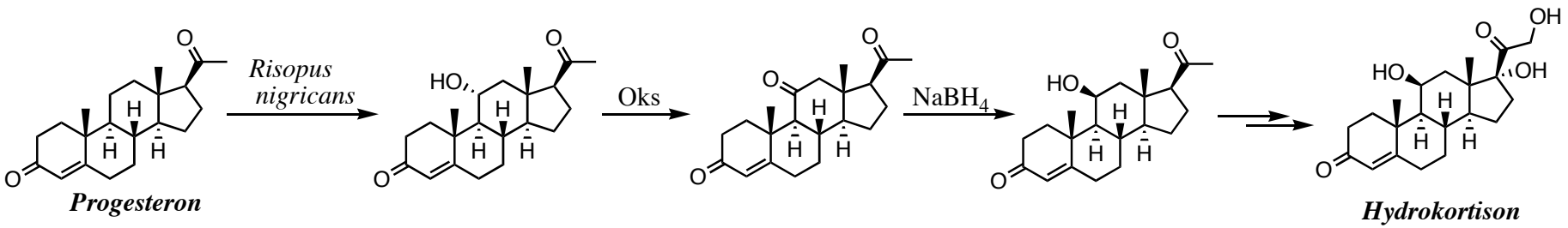
Glucocorticoid



Hydrokortison

Effect on metabolism (karbohydrates, lipids, proteins)
Antiinflammatoric

Numerous semisynth. analogs as drugs
Various antiinflam. activity, mineralcorticoid side effects

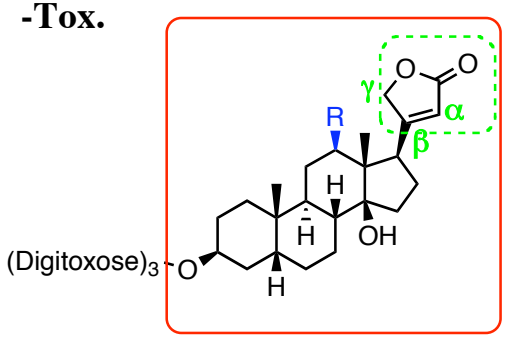


Progesteron ***Hydrokortison***

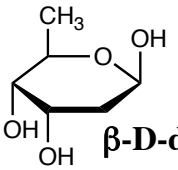
Digitalis purpurea
(foxglowe, revebjelle)

Digitalis glycosides (cardenolides)

-Treatment of hart disease 1500 BC (Egypt)
-Increase hart contraction
-Tox.



Aglycone: Biolog. activity
(KH part; solubility etc..)
γ-lactone



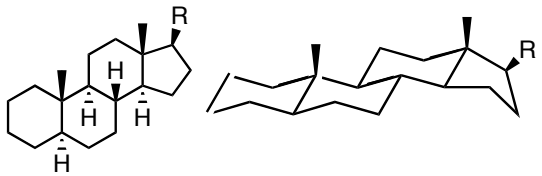
β-D-digitoxose

Digitoxin
Digitoxin® R= H

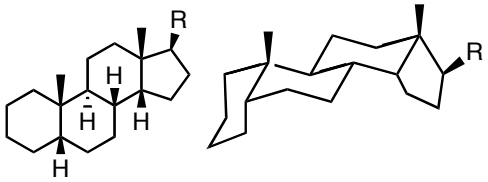
Digoxin
Lanoxin® R= OH

A-B and C-D *cis* condens.

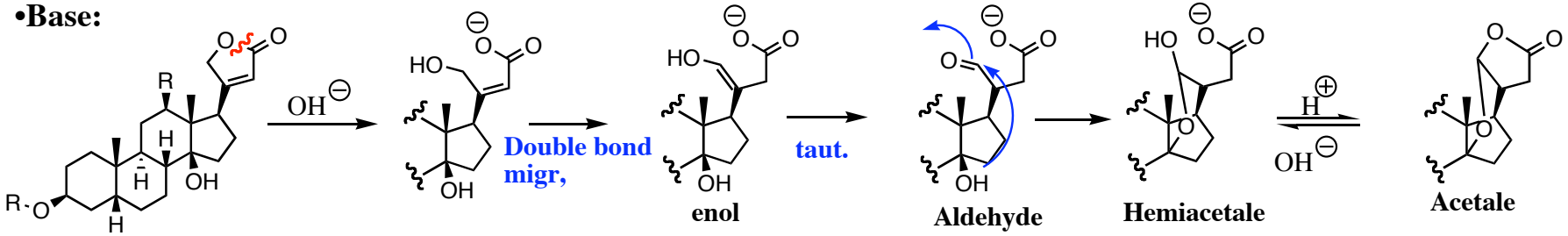
All *trans*



A-B cis, B-C trans. C-D cis

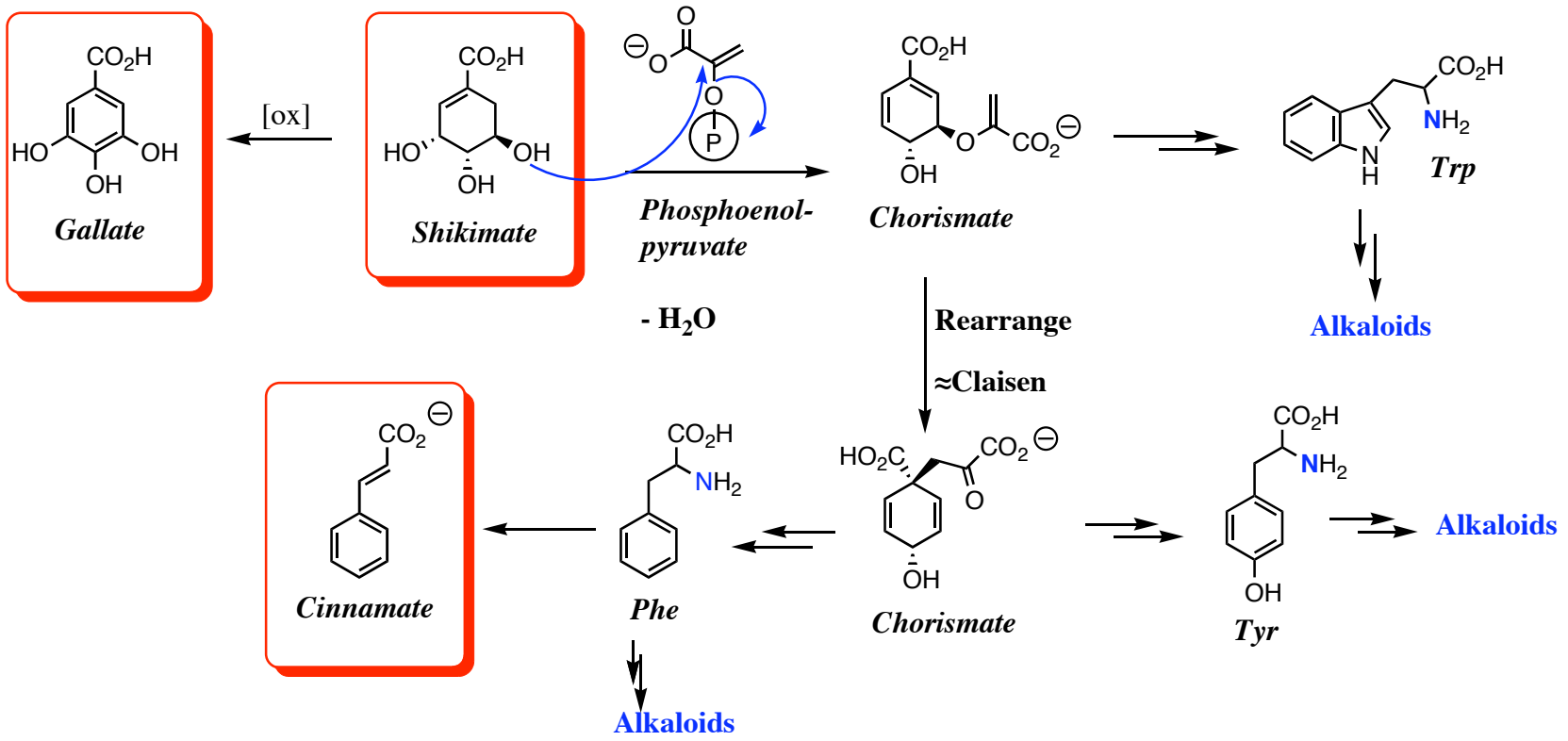


Stability
•Acid: Cleavage of sugars (acidic hydro acetals)
•Base:

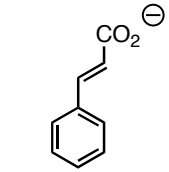


Phenolic Natural Products

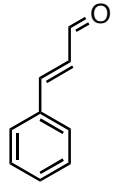
Biosynthesis from shikimate (- alkaloids)



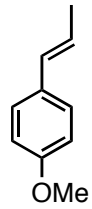
From cinnamate



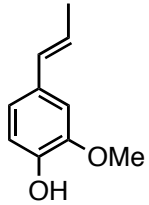
Cinnamate



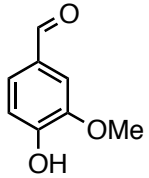
Cinnemal



Anetol



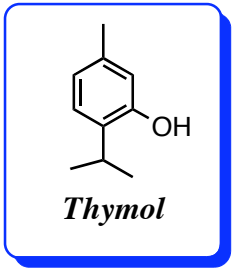
Eugenol



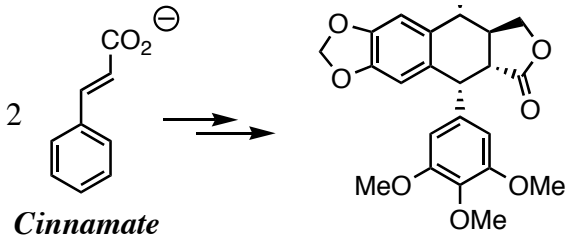
Vaniline

Voilatile compds, smell, taste etc., Not monoterpenes

Monoterpene



Thymol

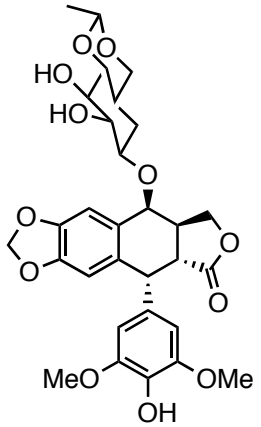


Cinnamate *Podophyllotoxin*

From *Podophyllum peltarum*
May apple

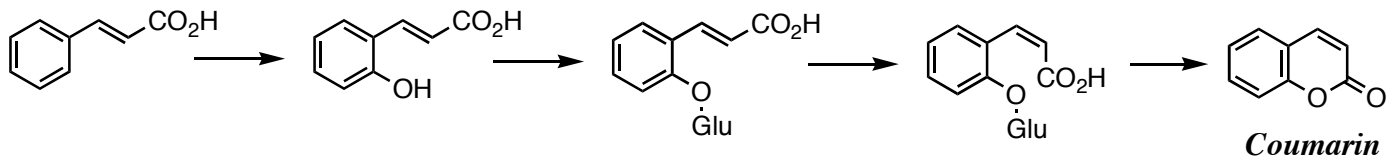
Antiviral, veneric warts

Toxic - lead for anticancer drugs

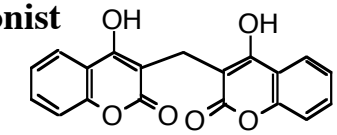


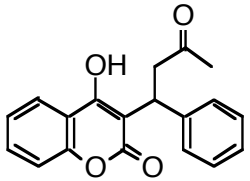
Etoposide

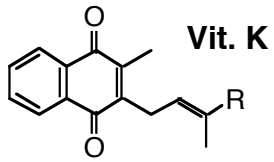
From cinnamate



Dicoumarol
-Anticoagulant - Vit K antagonist
-Sweet clower disease

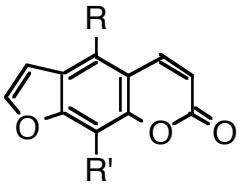




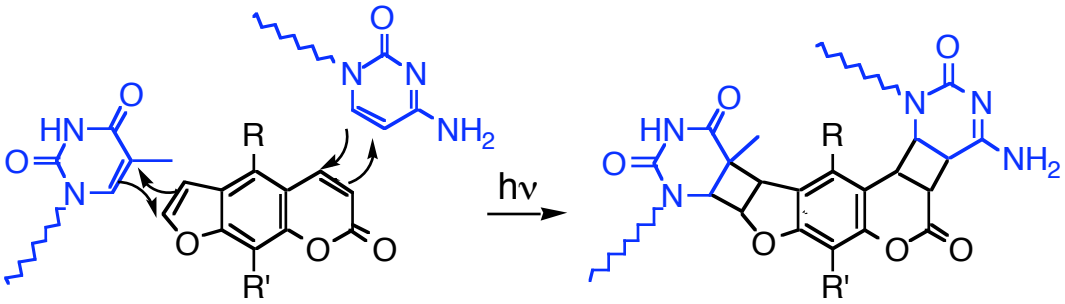


Warfarin - Marevan®

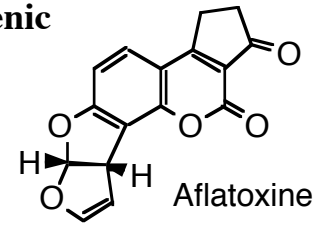
Psoralenes
-Isolated from various plants
-Photochemotherapy against psoriasis
-[2+2] cycloadd. With cytocin / thymin in DNA



R=R'=H: Psoralen
R=H, R'=OMe: Xantotoxin (8-MOP) -
Metoksalen - Geroxalen(R)



Aflatoxines
-From *Aspergillus flavus* (fungus)
-Attacks nuts etc.
-Carcinogenic



Aflatoxine B_1