Chimica Farmaceutica e Tossicologica 2

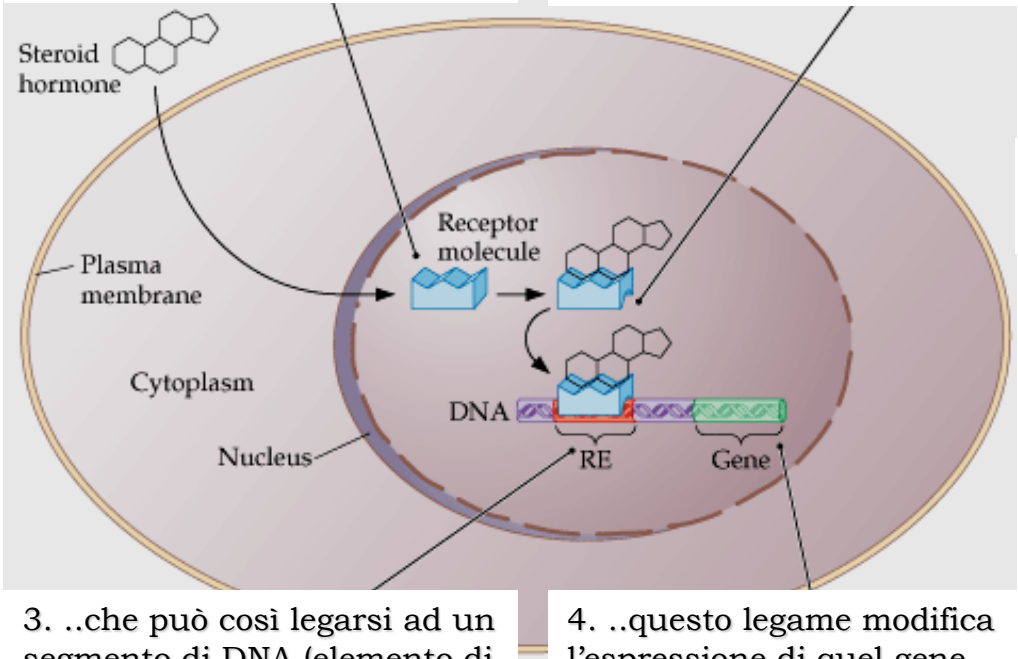
Ormoni steroidei

- recettori nucleari;
- nomenclatura;
- biogenesi.

Ormoni steroidei: modulazione recettoriale

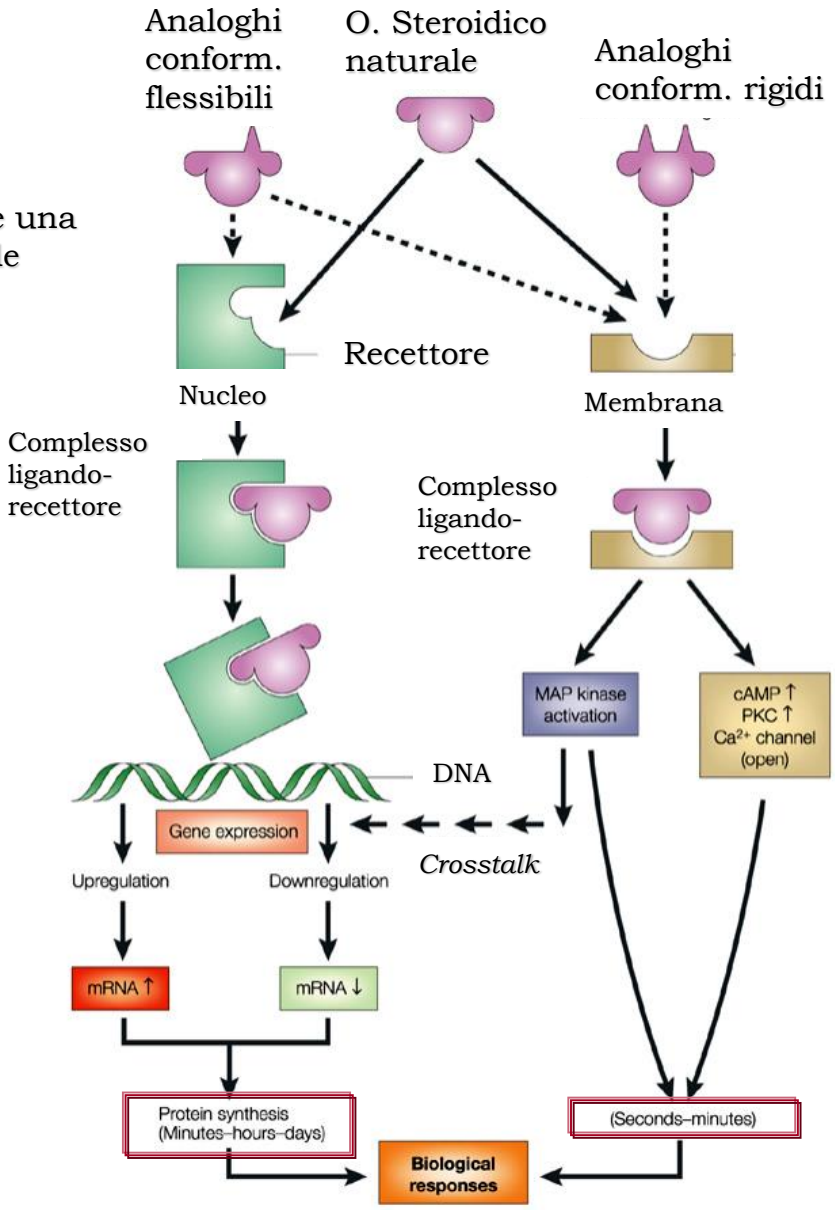
1. O. steroideo diffonde nella cellula e si lega al recettore

2. Il recettore attivato subisce una modificazione conformazionale



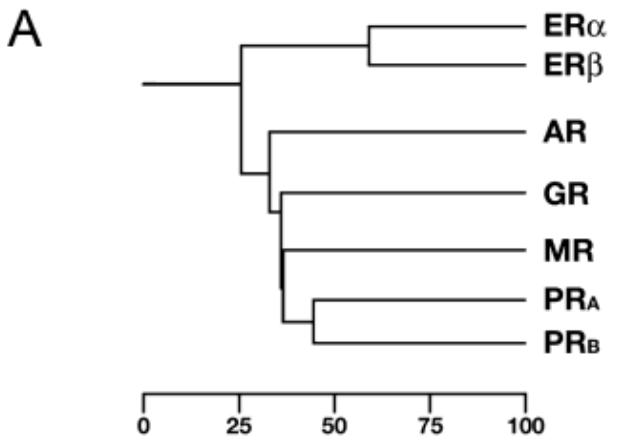
3. ..che può così legarsi ad un segmento di DNA (elemento di risposta, RE) parte di un gene

4. ..questo legame modifica l'espressione di quel gene

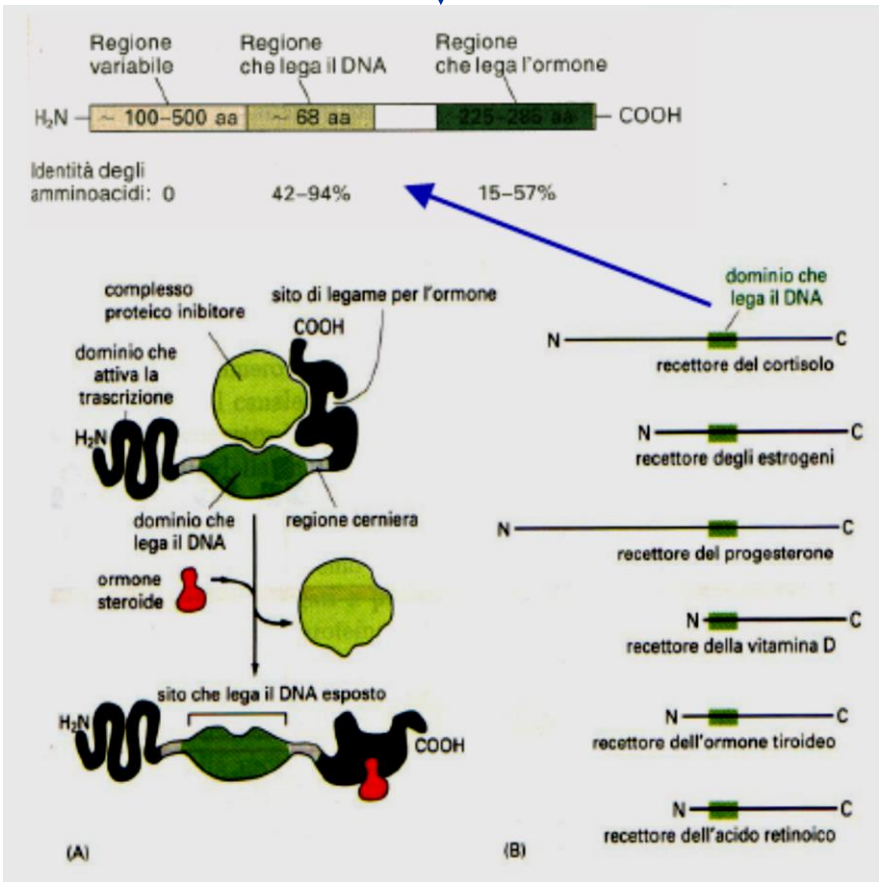


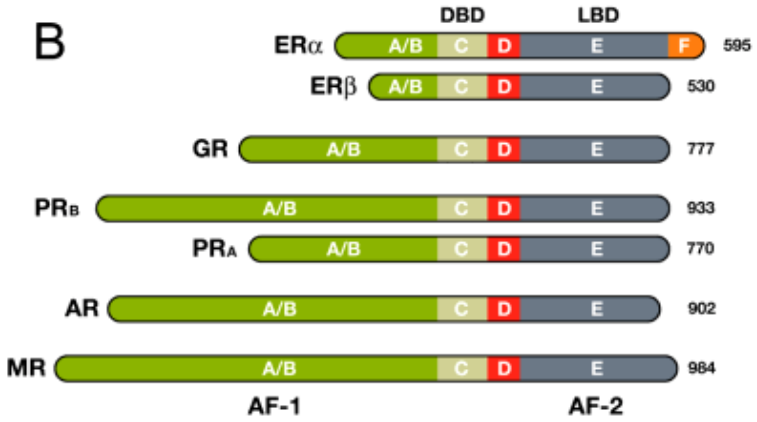
1128-Nature Reviews Drug Discovery 3, 27-41 (January 2004)

Ormoni steroidei: recettori nucleari (azione lenta)

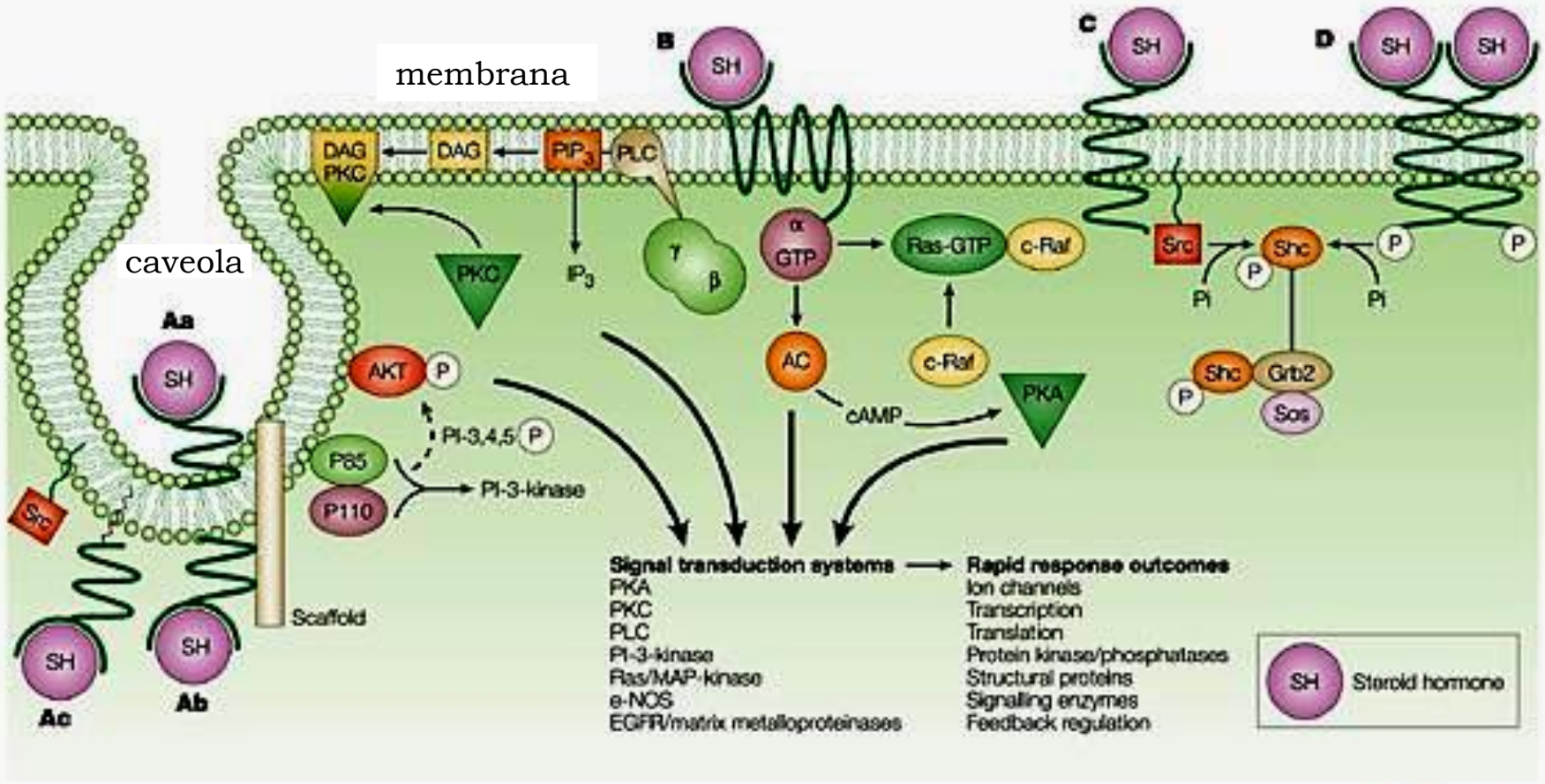


albero filogenetico





Ormoni steroidei: recettori di membrana (azione rapida)

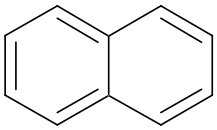


AC, adenylyl cyclase; DAG, diacylglycerol; EGFR, epidermal growth factor receptor; e-NOS, endothelial nitric oxide synthase; IP3, inositol triphosphate; MAP, mitogen-activated protein; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol triphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

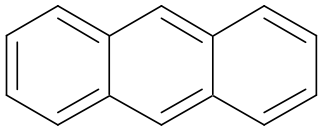
Nature Reviews Drug Discovery 3, 27-41 (January 2004)

ORMONI STEROIDICI

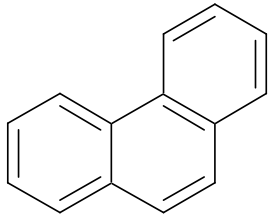
- Colesterolo → dal termine greco *cole* = bile e *steros* = solido; Ippocrate → calcoli biliari;
- Aristotele: effetti castrazione negli uccelli e nell'uomo;
- La pratica della castrazione << aggressività, >> peso negli animali domestici; (eunuchi,cori medioevali);
- Arnolph A. BERTHOLD (1803-1861): impianta testicolo nella cavità addominale di galletti castrati dell'altro → conservazione caratteri sessuali secondari e comportamento simile ai galli normali
- Thomas ADDISON (1793-1860): relazione tra ghiandole surrenali e particolare patologia dal colorito bronzeo dell'epidermide (morbo di Addison);
- C-É Brown-Sequard (1817-1894): prepara un estratto testicolare testandolo su se stesso, rinnovato vigore;
- Adolf O. Windaus (Nobel Prize in 1928) identificazione strutture steroidee;
- Heinrich O. Wieland (Monaco) (Nobel Prize in 1928), acidi biliari;
- Adolf F. Butenandt e Edward A. Doisy (1929), isolano indipendentemente un ormone steroidico sessuale attivo dalle urine di donne incinte (estrone);
- Adolf F. Butenandt, Tadeusz Reichstein (1930), strutture del progesterone e dei corticosteroidi;
- Bachmann, Woodward, Robinson, and Cornforth (1951), prime sintesi di strutture steroidiche;
- 1950-1960, primi studi biochimici, dimostrazione biogenesi da unità acetato;
- Hench et al. (Mayo Clinic) (1949) dimostrano un significativo miglioramento in pazienti affetti da artrite reumatoide in seguito a trattamento con cortisone;
- Gregory G.Pincus et al. (1965) usano formulazioni di estrogeni e progestinici per la contraccezione.



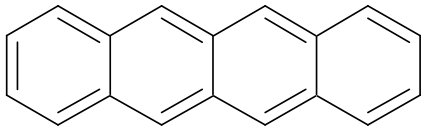
naftalene



antracene

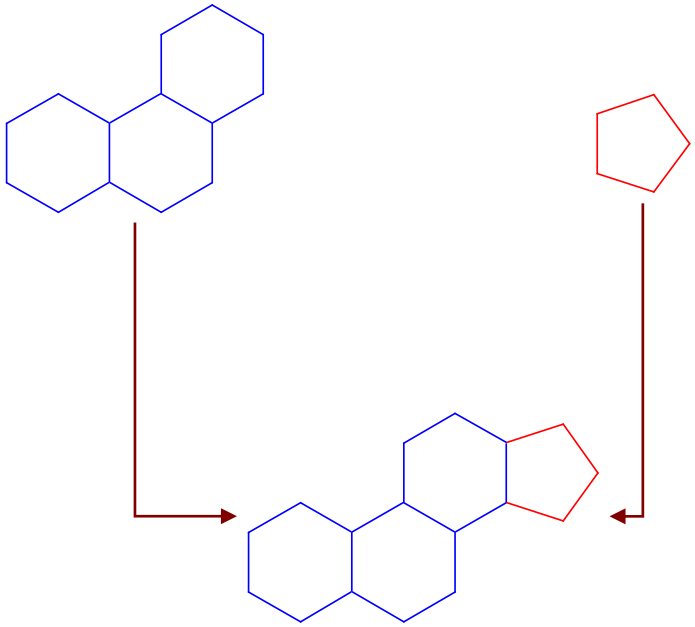


fenantrene



tetracene

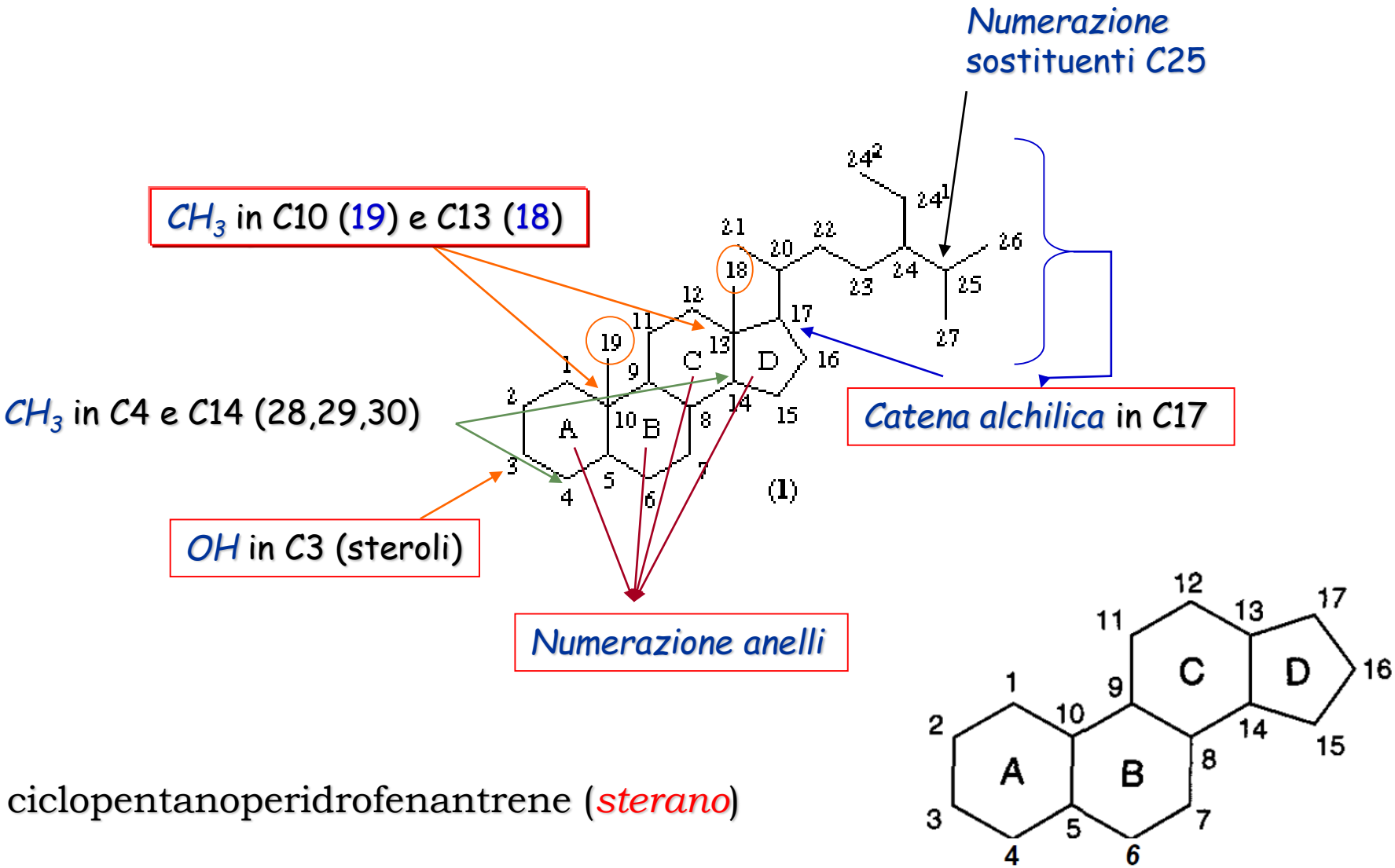
peridrofenantrene



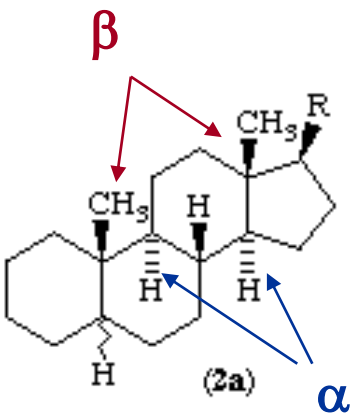
ciclopentano

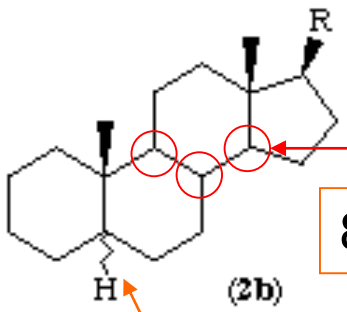
ciclopentanoperidrofenantrene

Nomenclatura steroidi

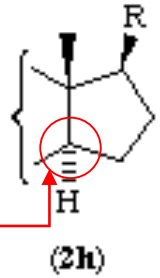


ciclopentanoperidrofenantrene (*sterano*)



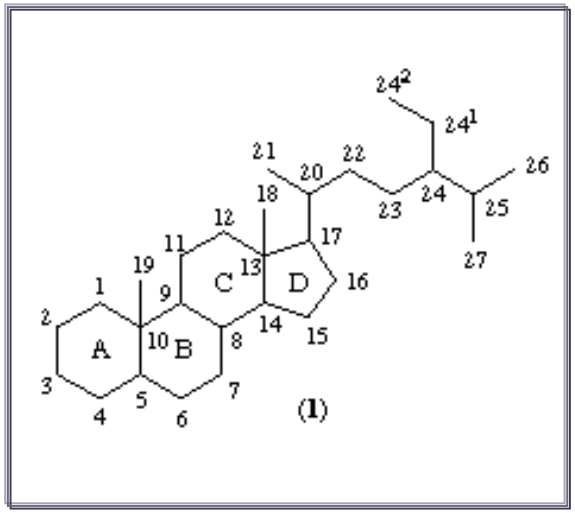


14α

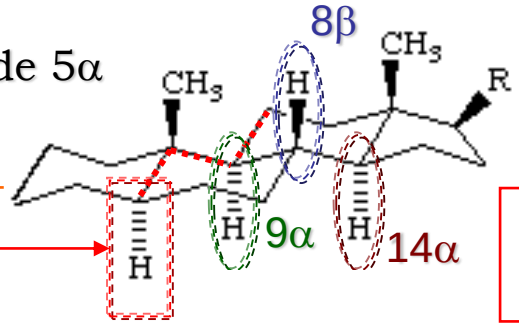


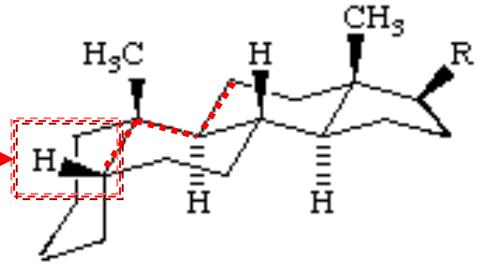
8β ,9α ,14α

ξ (xi)



steroide 5α





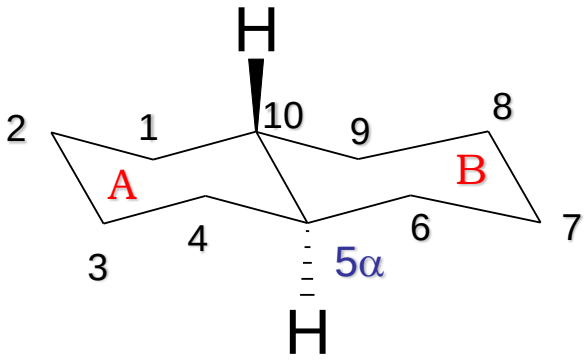
steroide 5β

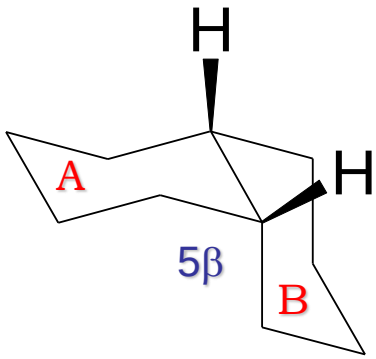
trans-anti-trans-anti-trans

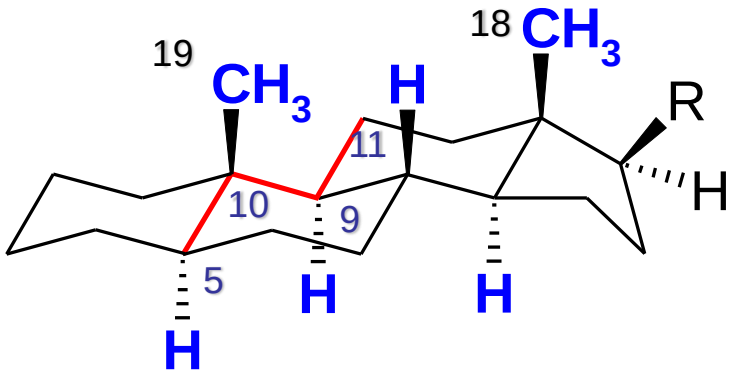
cis-anti-trans-anti-trans

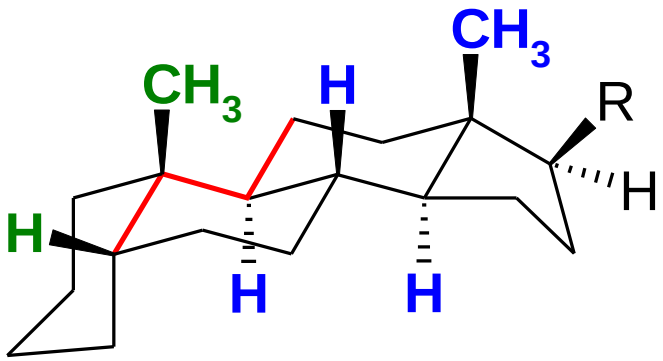
8β ,9α ,10β ,13β ,14α, 17β

2^7 = 128 possibili stereoisomeri





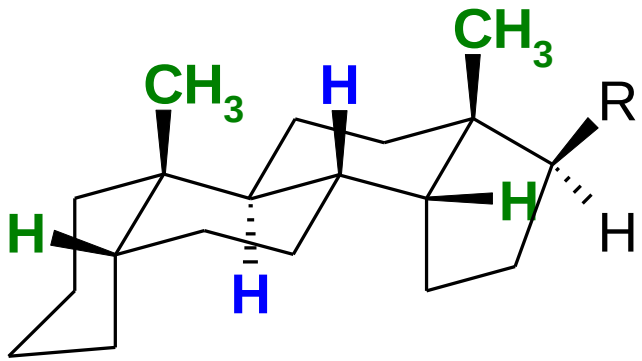




trans-anti (5-10, 9-11)-trans-trans

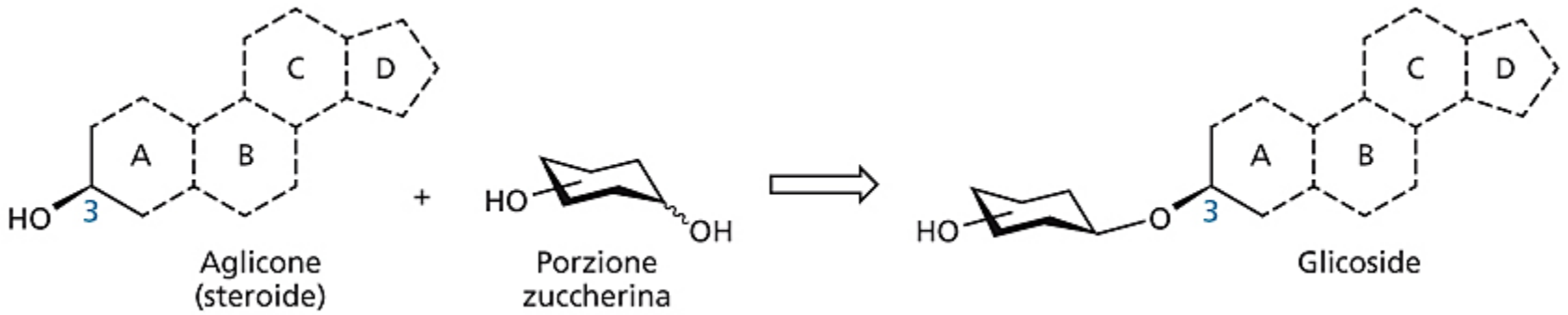
cis-anti-trans-trans

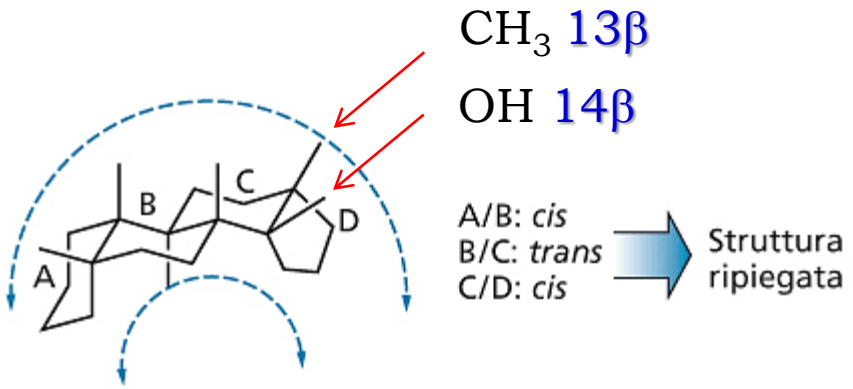
tutti gli anelli hanno fusione stereochimica trans diequatoriale



cis-anti-trans-cis

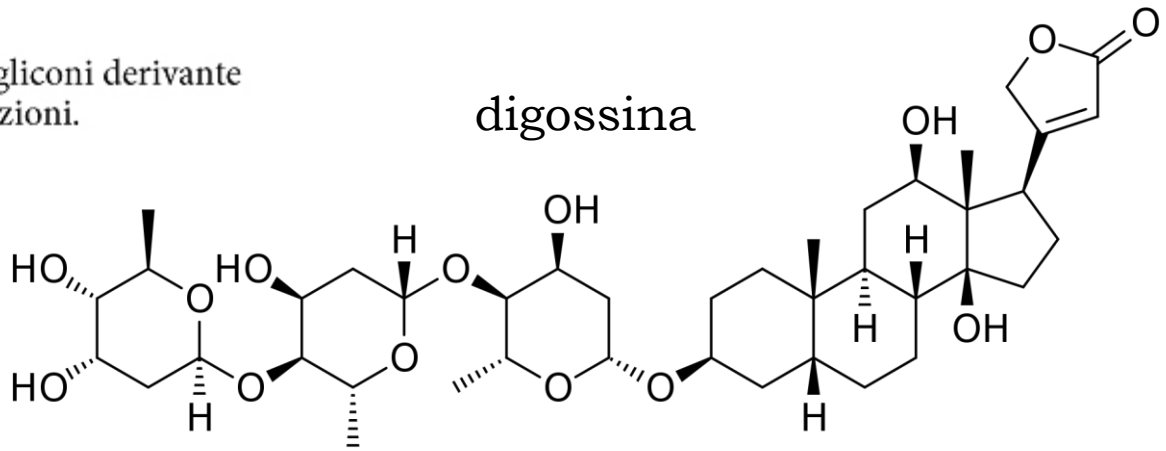
Glicosidi cardiaci (*forma e funzione*)



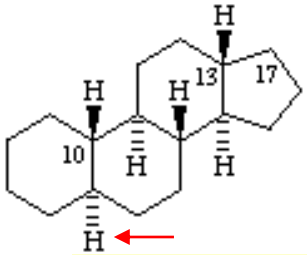


Struttura 'ripiegata' degli agliconi derivante dalla stereochimica delle giunzioni.

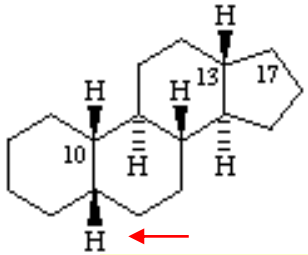
digossina



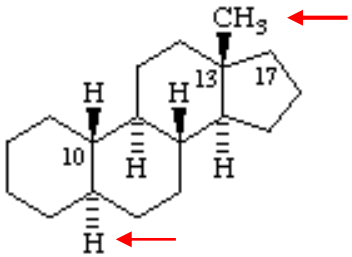
Carbocicli fondamentali, insaturazioni e sostituzioni alchiliche in C17



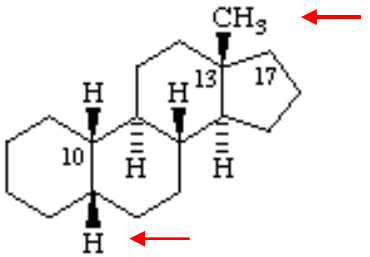
5α-Gonano



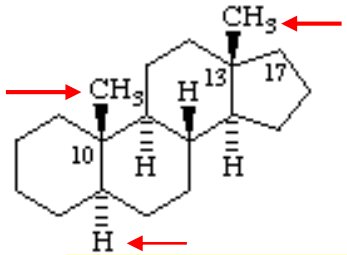
5β-Gonano



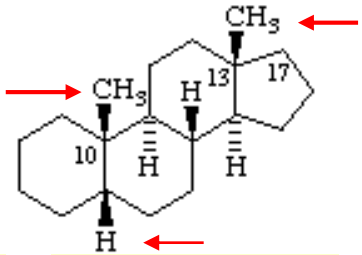
5α-Estrano



5β-Estrano



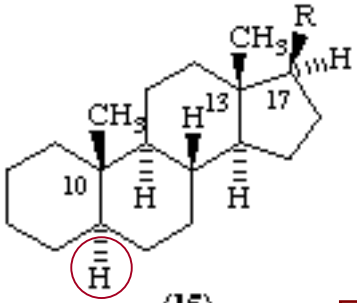
5α-Andostrano



5β-Andostrano

8β ,9α ,10β ,13β ,14α

Stereochimica dei sostituenti in catena laterale (I)



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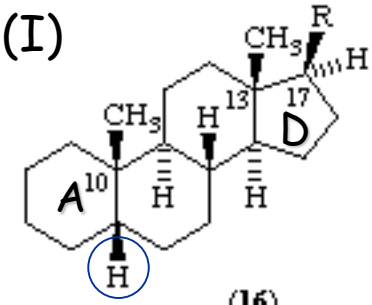
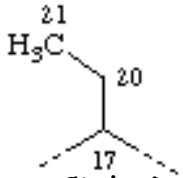
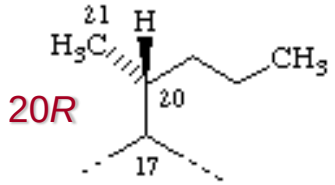
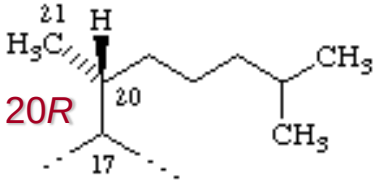
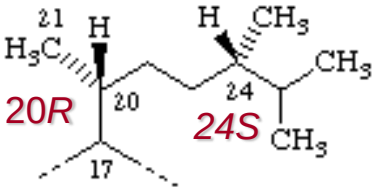
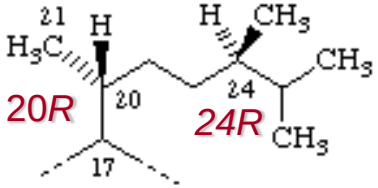


(16)

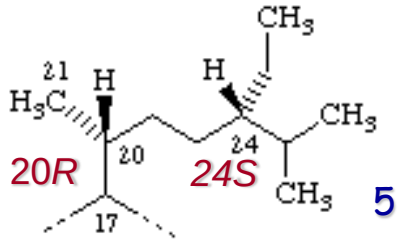
	Serie 5α	Ciclo D	Serie 5β
			
Progesterone	5 α-pregnano (non allopregnano) (2C)		5 β-pregnano
			
Acidi biliari	5 α-colano (non alloconano) (5C)	20R	5 β-colano (non coprostano)
			
Colesterolo	5 α-colestano (8C)	20R	5 β-colestano
			
Ergosterolo (22E) (provitamina D2)	5 α-ergostano (9C)	20R 24S	5 β-ergostano
			
Campesterolo (fitosterolo)	5 α-campestano (9C)	20R 24R	5 β-campestano

sterolo vegetale
(Brassica campestris)
Olio colza, lino, soia

Stereochimica dei sostituenti in catena laterale (II)

Serie 5α

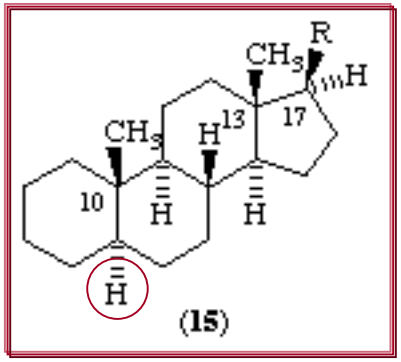
Serie 5β



5 α-poriferastano

5 β-poriferastano

Ciclo D



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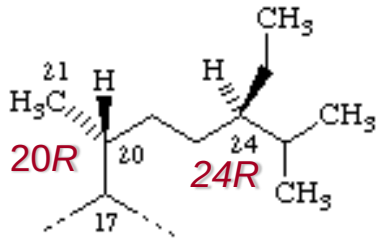
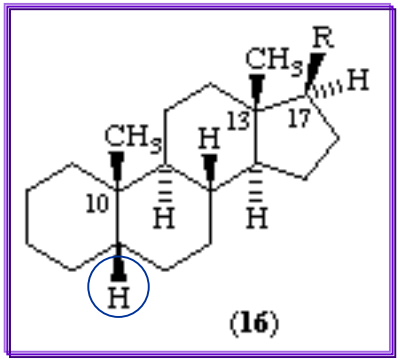


5 α-stigmastano

5 β-stigmastano



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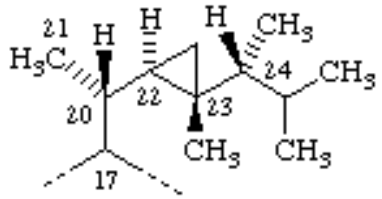


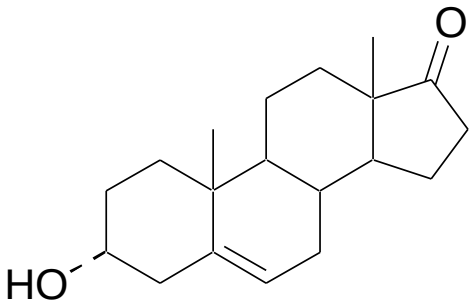
5 α-gorgostano

5 β-gorgostano

20S, 22R, 23R, 24R

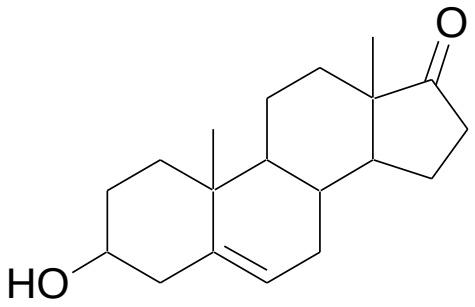
"ALLO" = prefisso che indica lo stereoisomero che presenta l'H in 5α

"EPI" = prefisso che indica l'inversione configurazionale di un –OH in uno steroide, rispetto all'isomero naturale o tipico



Deidroandrosterone

3α-idrossi-androst-5-ene-17-one



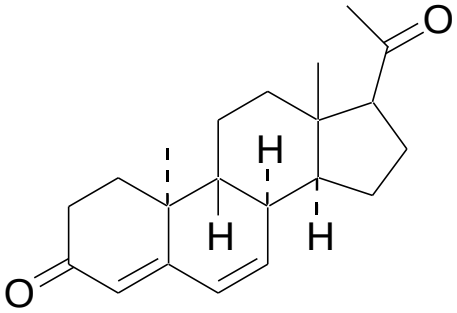
Deidroepiandrosterone

3β-idrossi-androst-5-ene-17-one

"ISO" = prefisso che indica l'inversione configurazionale di un centro chirale in uno steroide, rispetto all'isomero naturale o tipico

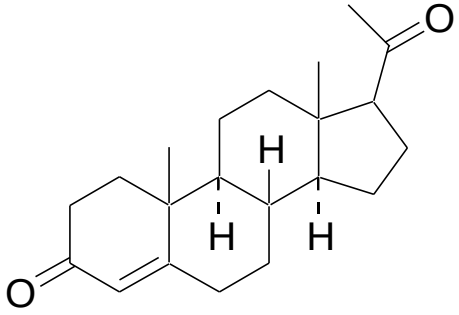
"SECO" = prefisso di struttura derivante dall'apertura di un ciclo della molecola di uno steroide (es. Vit. D)

Esempi di Nomenclatura I



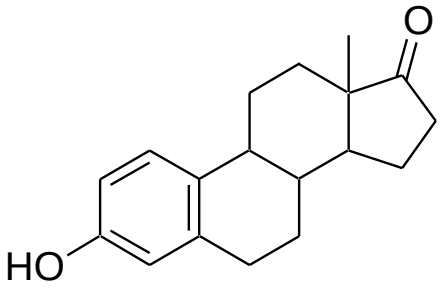
Didrogesterone

9β,10α-pregna-4,6-dien-3,20-dione



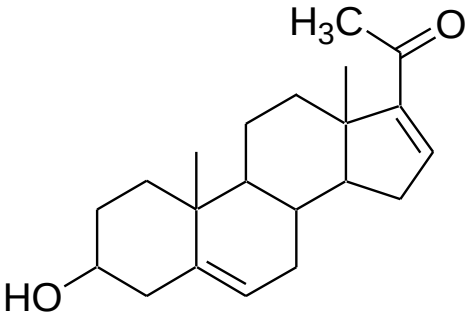
Progesterone

4-pregnen-3,20-dione



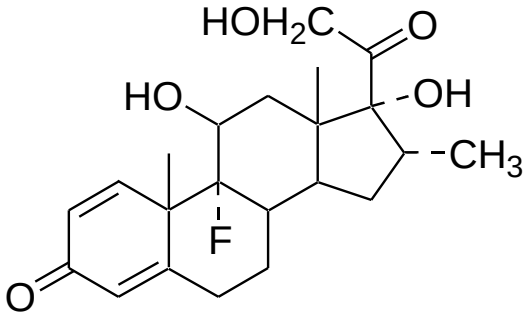
Estrone

3-Idrossiestra-1,3,5(10)-trien-17-one



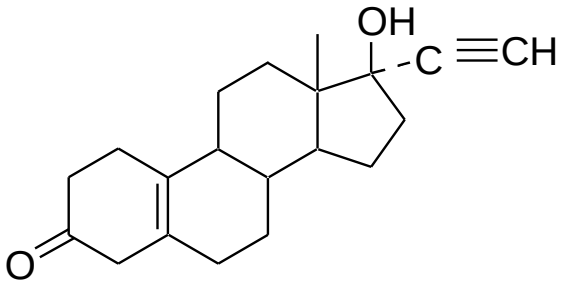
Pregna-5,16-dien-3β-ol-20-one

16-Deidropregnenolone



9α-Fluoro-16α-metil-11β,17α,21-triidrossipregna-1,4-dien-3,20-dione

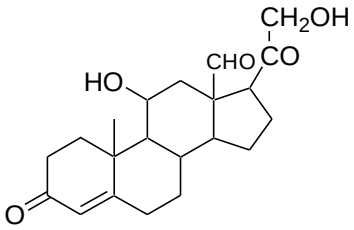
Desametasone



17-Idrossi-19-nor-17α-pregn-5(10)-en-20-in-3-one

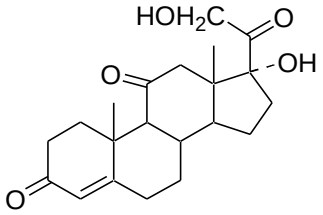
Noretinodrel

Esempi di Nomenclatura II



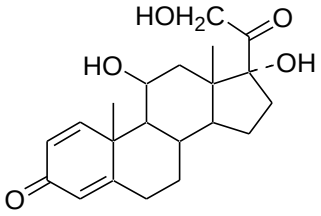
11β,21-diidrossipregn-4-en-3,18,20-trione

Aldosterone



17α,21-diidrossipregn-4-en-3,11,20-trione

Cortisone

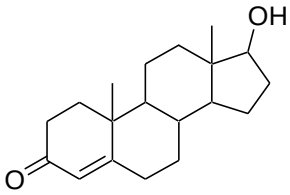


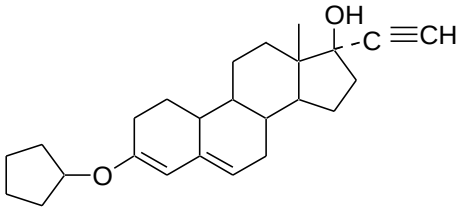
11β,17α,21-triidrossipregna-1,4-dien-3,20-dione

Prednisolone

17β-idrossiandrost-4-en-3-one

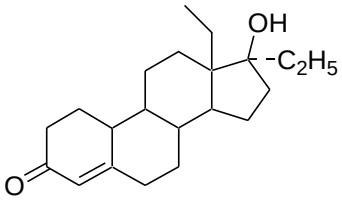
Testosterone





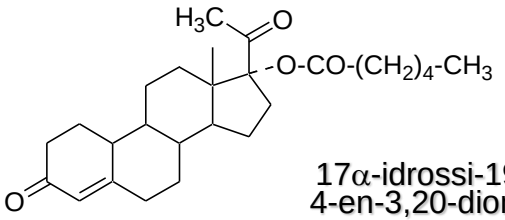
3-(ciclopentilossi)-19-nor-17α-pregna-3,5-dien-20-in-17-olo

Chingestanolo



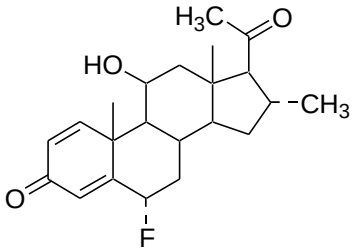
13β,17α-dietil-17β-idrossigon-4-en-3-one

Norboletone



17α-idrossi-19-norpregn-4-en-3,20-dione esanoato

Gestonorone caproato

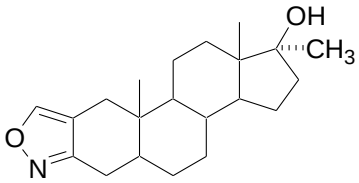


6α-fluoro-11β,21-diidrossi-16α-metilpregna-1,4-dien-3,20-dione

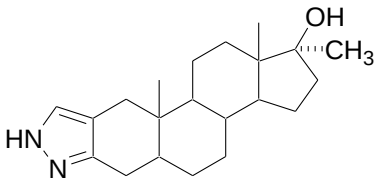
Fluorocortolone

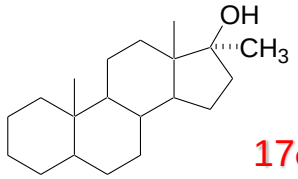
Esempi di Nomenclatura

Androisossazolo



Androstanazolo

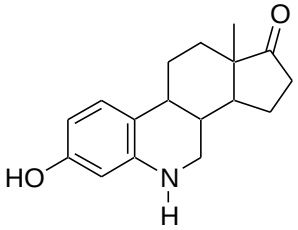




17α-metilandrostan-17-olo

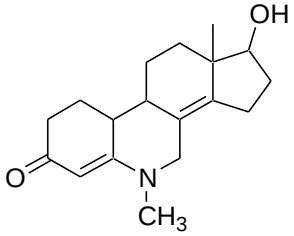
17α-metil-17β-idrossiandrostan[2,3-*c*]isossazolo (… pirazolo)

ETEROSTEROIDI

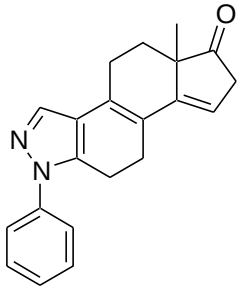


3-idrossi-6-azaestra-1,3,5(10)-trien-17-one

6-azaestrone

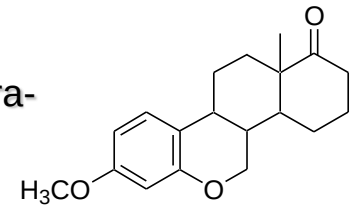


17β-idrossi-6-metil-6-azaestra-4,8(14)dien-3-one

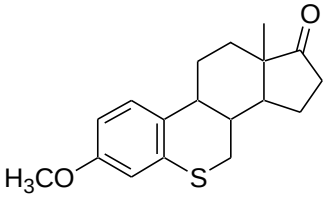


A-nor-3-fenil-2,3-diazaestra-1,5(10),8,14-tetraen-17-one

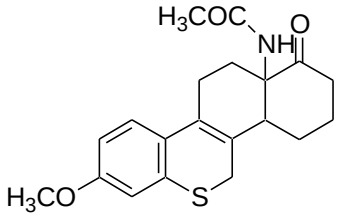
3-metossi-6-ossa-D-omoestra-1,3,5(10)-trien-17-one

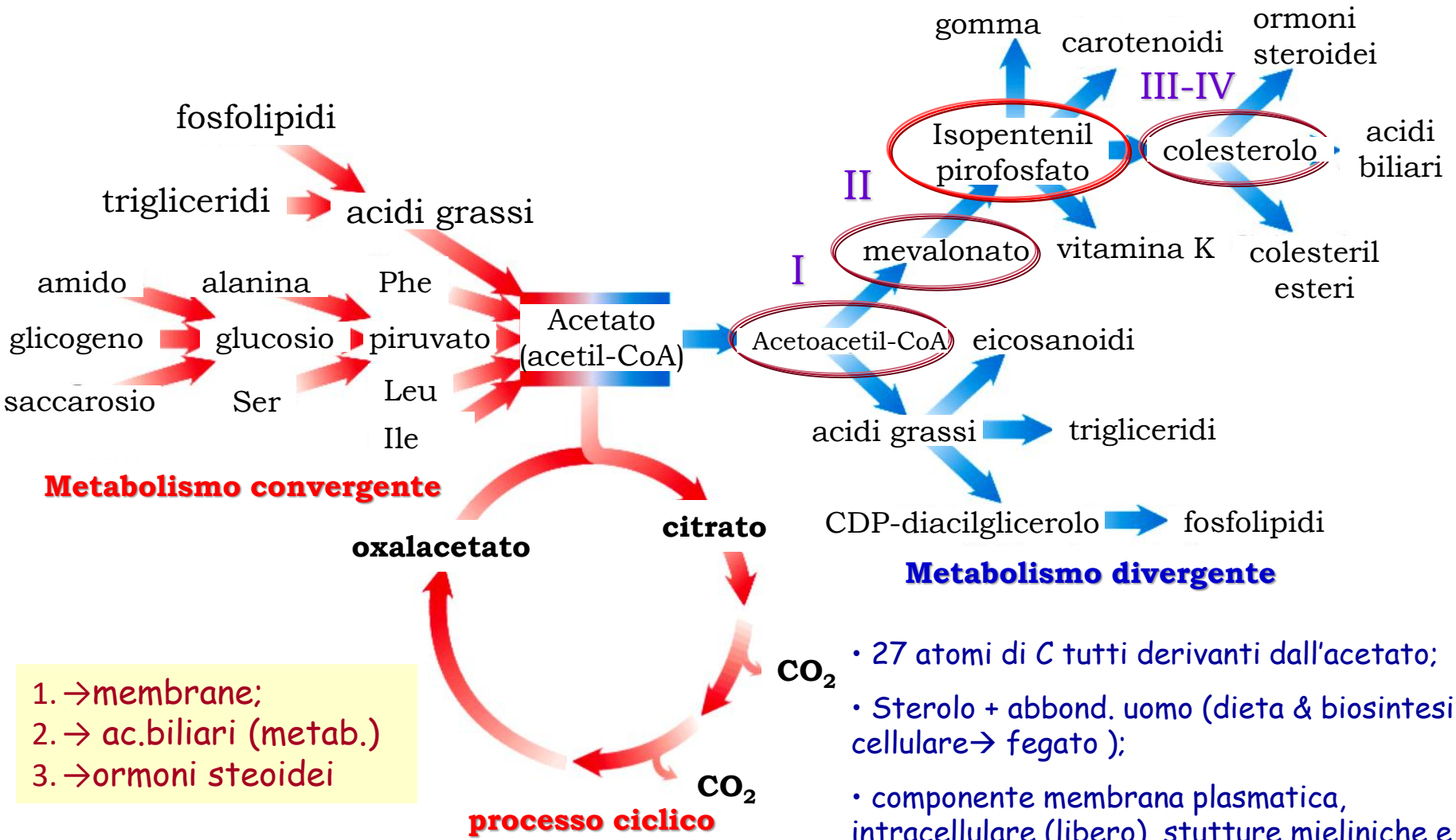


3-metossi-6-tiaestra-1,3,5(10)-trien-17-one

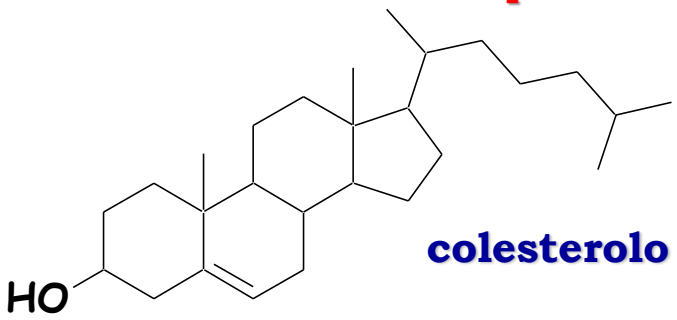


18-acetil-3-metossi-6-tia-18-aza-D-omoestra-1,3,5(10),8-tetraen-17-one





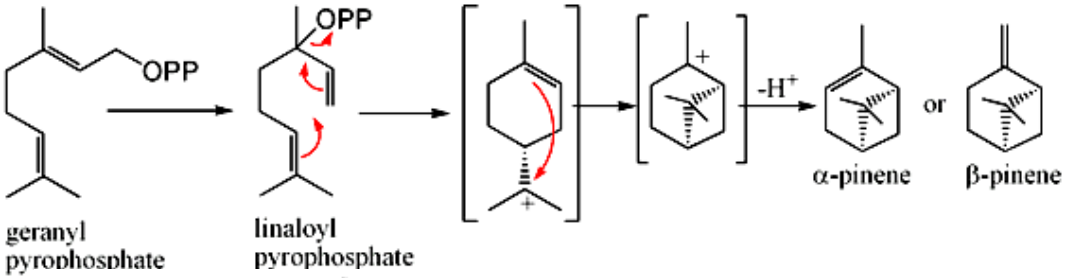
1. →membrane;
2. → ac.biliari (metab.)
3. →ormoni steoidei

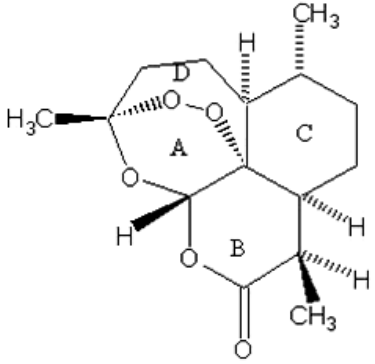


colesterolo

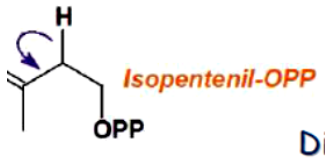
- 27 atomi di C tutti derivanti dall'acetato;
- Sterolo + abbond. uomo (dieta & biosintesi cellulare→ fegato);
- componente membrana plasmatica, intracellulare (libero), stutture mieliniche e SNC, esterificato nel plasma;
- precursore acidi biliari (fegato) e ormoni steroidei;
- la struttura ciclica del colesterolo non può essere metabolizzata a CO_2 e H_2O

B) Formazione delle catene poliisopreniche

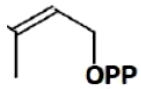




Tassoli

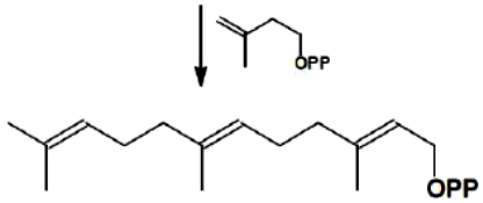


Dimethylallyltrans-transferase (geranyl pyrophosphate synthase)



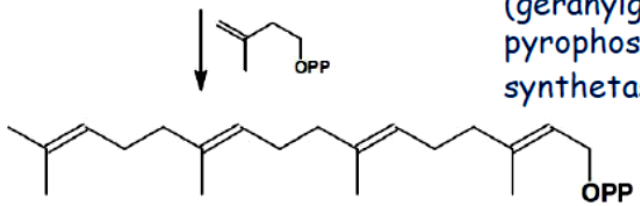
Geranil-OPP

Geranyltrans-transferase (farnesyl pyrophosphate synthetase)

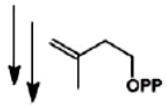


Farnesil-OPP

Farnesyltrans-transferase (geranylgeranyl pyrophosphate synthetase)



Geranilgeranil-OPP



SESQUITERPENI ← 15 C

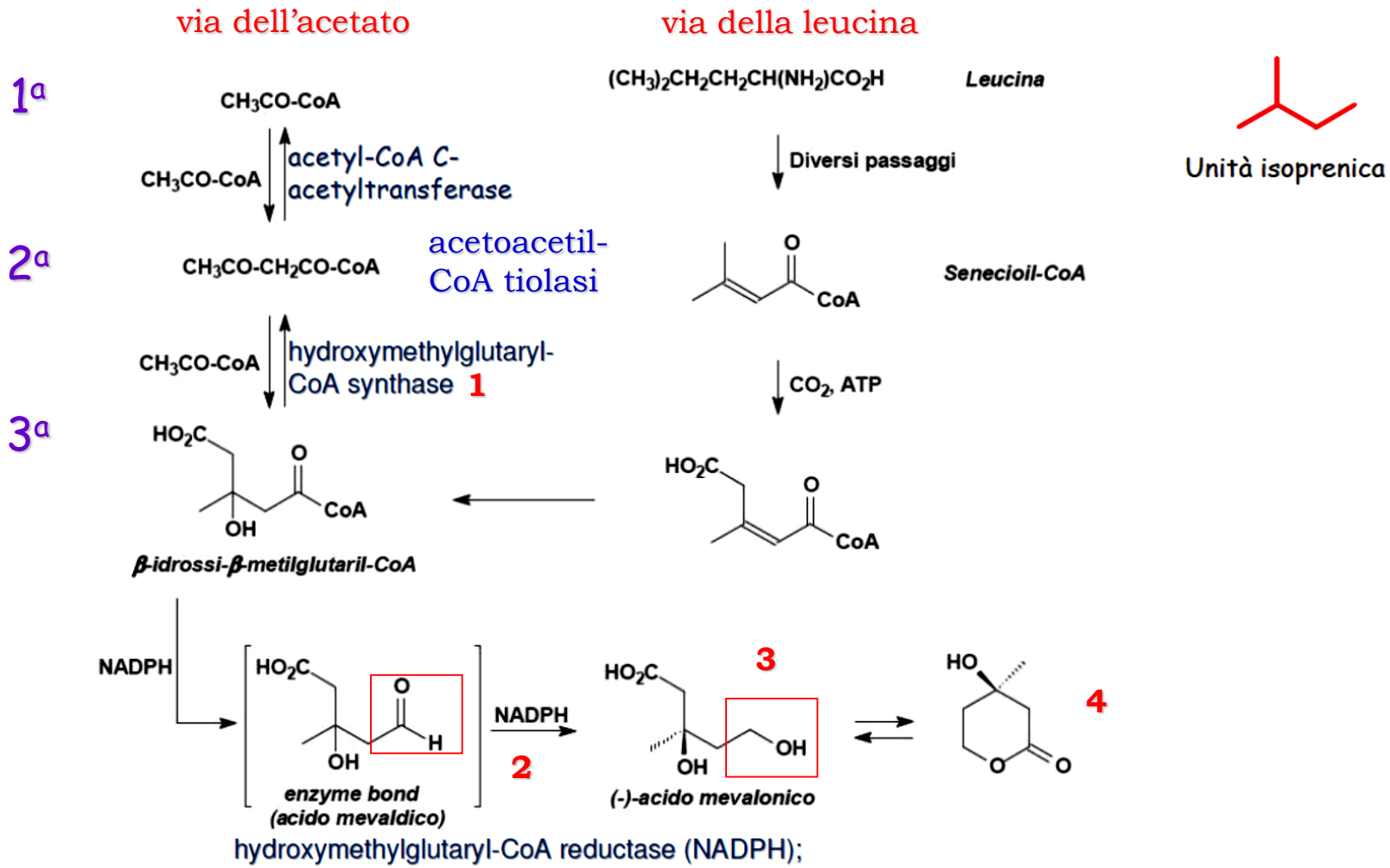
TRITERPENI ← 30 C (x 2)

DITERPENI ← 20 C

CAROTENOIDI ← 40 C (x 2)

POLIISOPRENOIDI

BIOGENESI DEL COLESTEROLO:
A1) FORMAZIONE DELL'UNITA' BASE ISOPRENICA

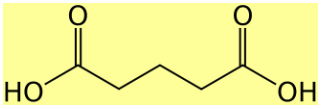


1 Due isoenzimi della HMG-CoA, una forma citoplasmatica l'altra mitocondriale (fegato).

2 In questa reazione si consumano due equivalenti di NADPH prodotte dal ciclo del pentoso fosfato.

3 acido (R)-3,5-diidrossi-3-metilpentanoico.

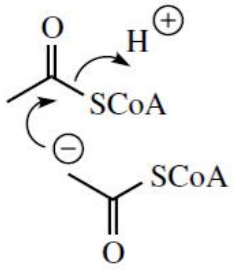
4 (R)-4-idrossi-4-metil-tetraidro-piran-2-one.

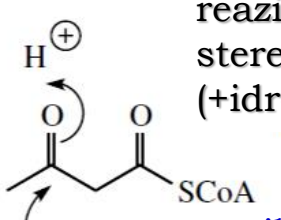


acido glutarico

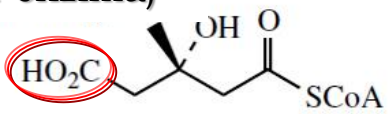
Claisen

reazione aldolica
stereospecifica
(+idrolisi acil-enzima)



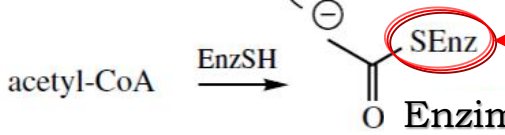


acetoacetil-CoA



+ EnzSH

HMG-CoA



idrossimetilglutaril-CoA sintasi

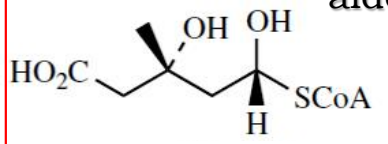
Enzima legato al gruppo acetile

Stadio lento irreversibile

HMG-CoA reductase

NADPH

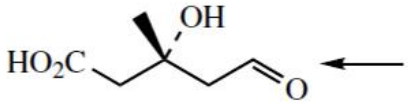
Riduzione tioestere a aldeide via emiacetale



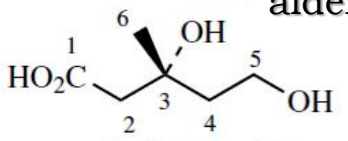
Emiacetale acido mevaldico

riduzione aldeide a OH

NADPH



acido mevaldico

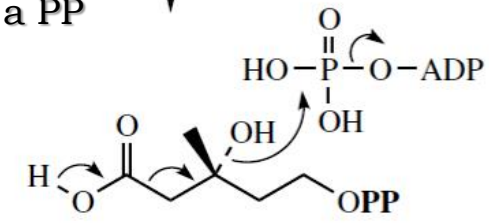


acido mevalonico

fosforilazione sequenziale di prim-OH a PP

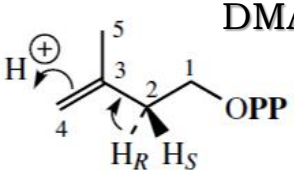
2 x ATP

1) Mevalonato kinasi
2) Fosfomevalonato kinasi



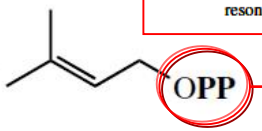
ATP facilita la decarbossilazione/ eliminazione

ATP
–CO2



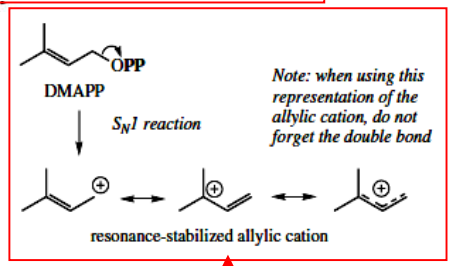
isopentenil PP (IPP)

isomerase



dimetilallil PP (DMAPP)

Isomerizzazione allilica stereospecifica: l'equilibrio favorisce DMAPP

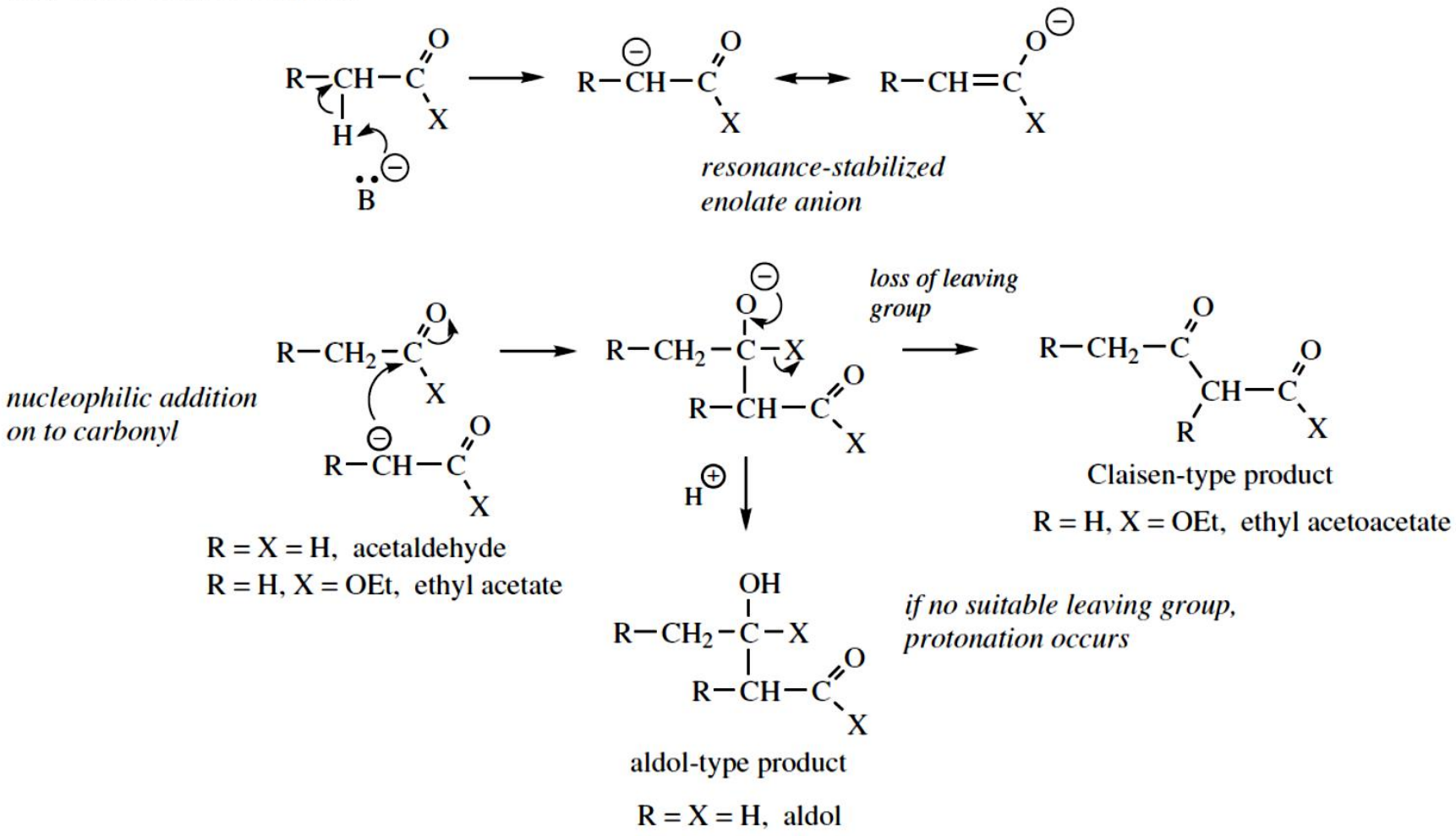


Rimuove stereospecificamente il protone *pro-R* (H*R*) da C-2, ed incorpora al C-4 un protone da H_2O.

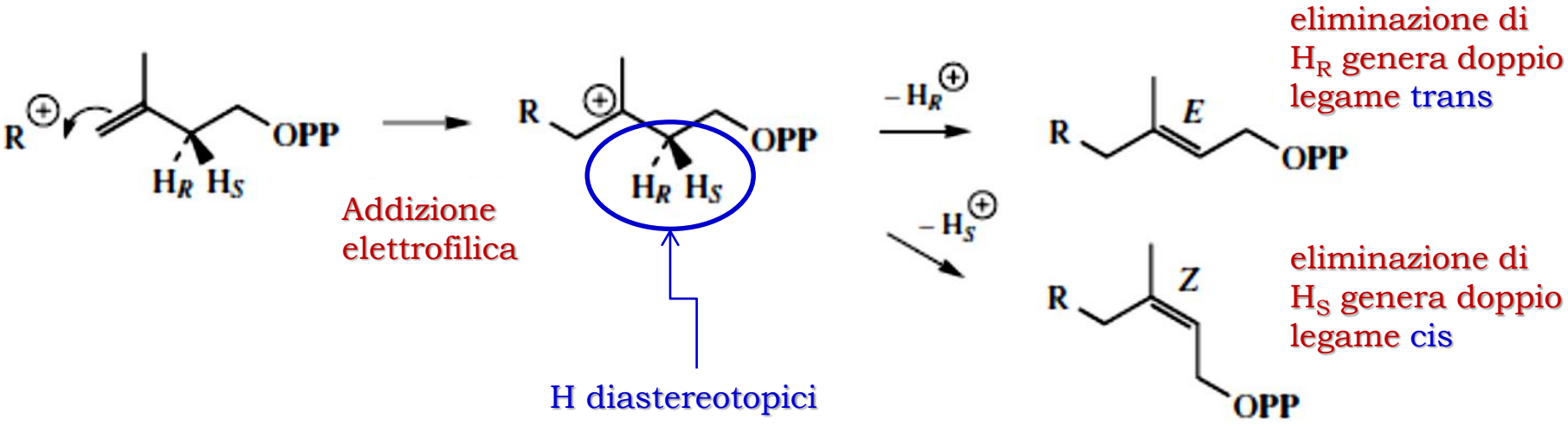
Isopentenil-difosfato D-isomerasi

decarbossilazione/disidratazione, Difosfomevalonato decarbossilasi

Aldol and Claisen reactions



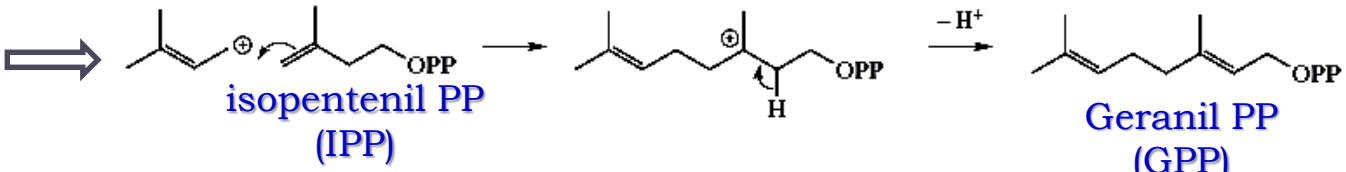
Il formarsi di un prodotto tipo Claisen o aldolico dipende soltanto dalla natura del gruppo uscente X. Due molecole di acetaldeide producono l'aldolo, mentre due molecole di etile acetato portano all'acetoacetato di etile.


R
OPP
H_R H_S
Addizione elettrofilica
$-H_R^{\oplus}$
$-H_S^{\oplus}$
E
Z
eliminazione di H_R genera doppio legame trans
eliminazione di H_S genera doppio legame cis
H diastereotopici

Reazioni di alchilazione-Addizioni inter- e intramolecolari

Addizione elettrofilica

Addizione elettrofilica (intermolecolare)



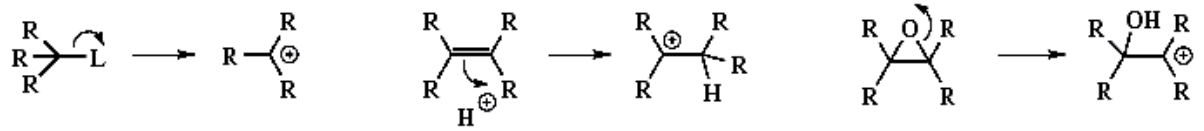
isopentenil PP (IPP)

Geranil PP (GPP)

Addizione elettrofilica (intramolecolare)

Formazione carbocatione

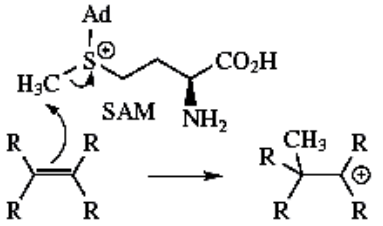
generazione carbocatione



perdita gruppo uscente

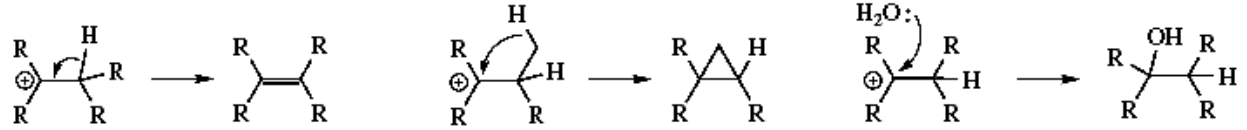
protonazione alchene

protonazione e apertura anello epossidico



metilazione alchene via SAM (S-adenosil metionina)

rimozione carbocatione

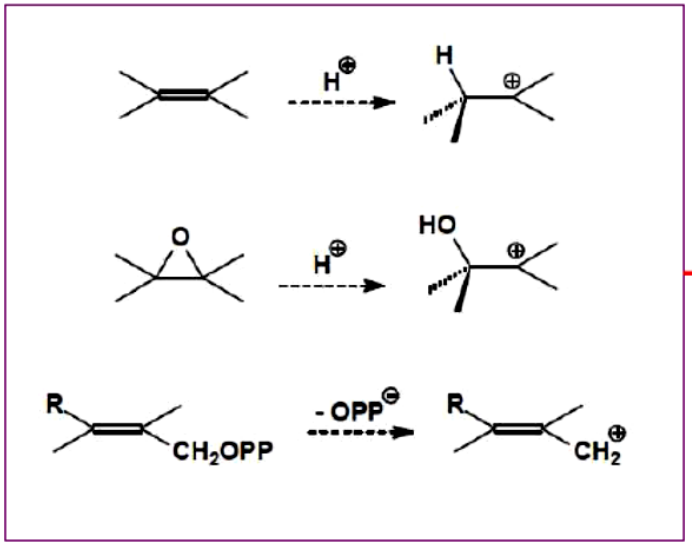


perdita protone

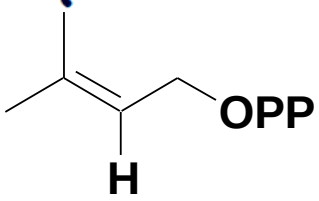
ciclizzazione/ perdita di protone

rimozione via nucleofilo (acqua)

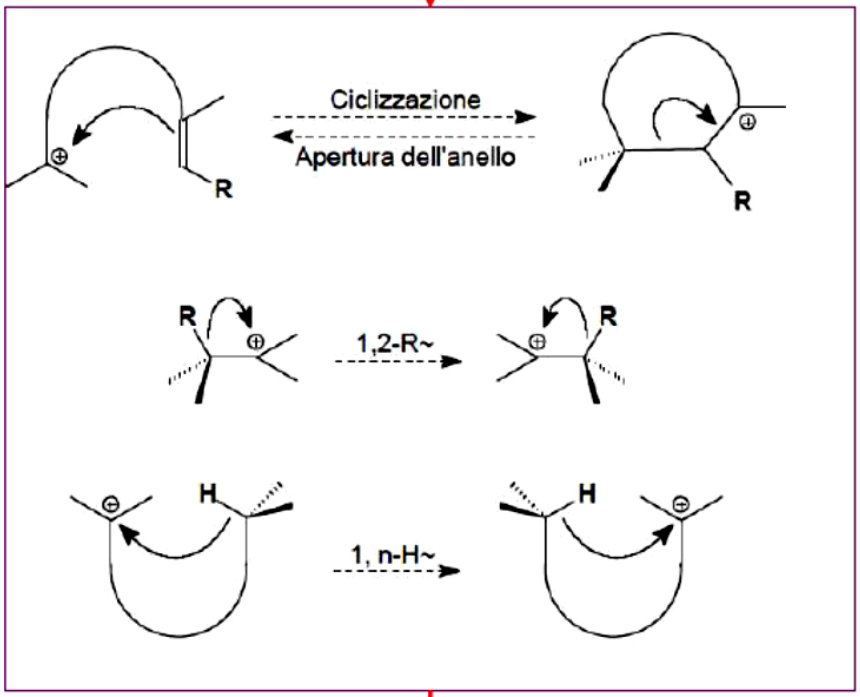
C) Ciclizzazione delle unità poliisopreniche (meccanismo)

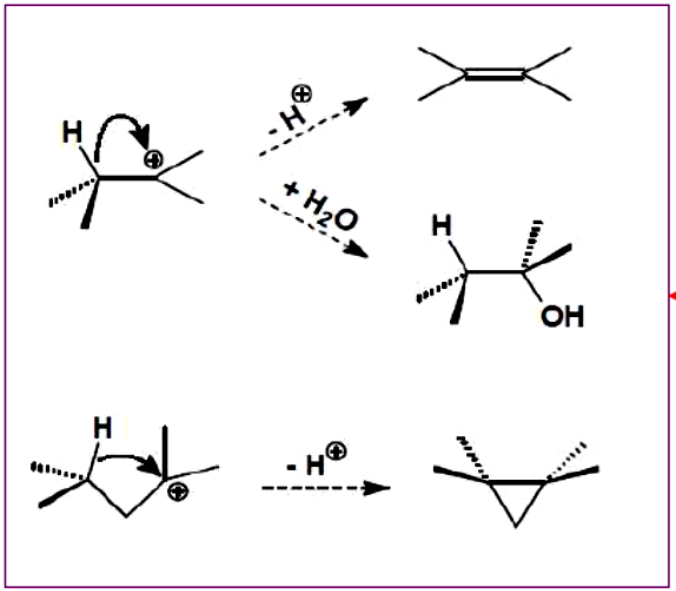


Iniziazione



Propagazione

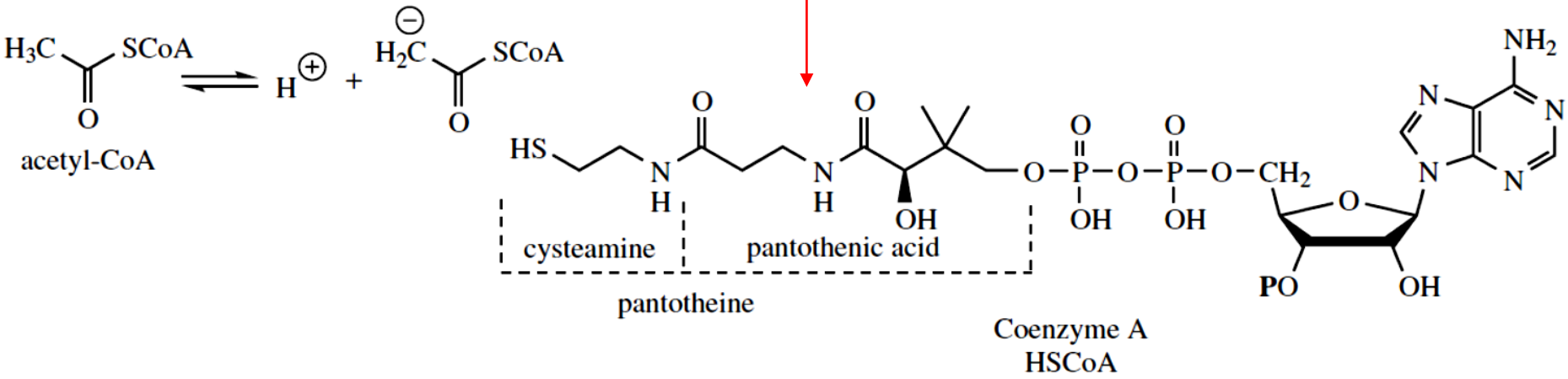




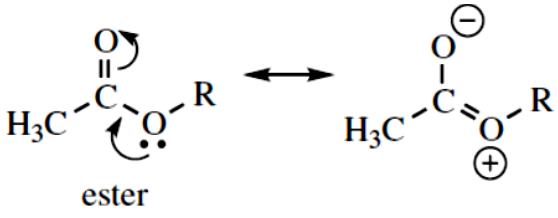
Terminazione

modo sincronizzato ed antiparallelo

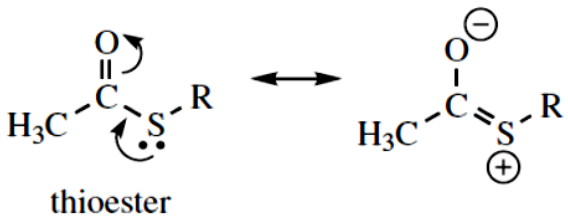
acido pantotenico (vitamina B5 o vitamina W)



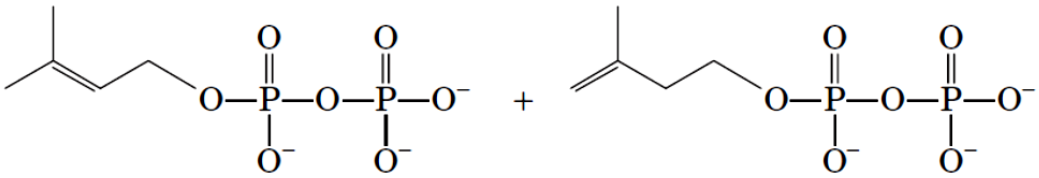
La risonanza riduce l'acidità degli α-H



La risonanza è meno favorevole nei tioesteri



Questo tipo di delocalizzazione è preminente negli esteri rispetto ai tioesteri; dimensione, elettronegatività, energia orbitali.

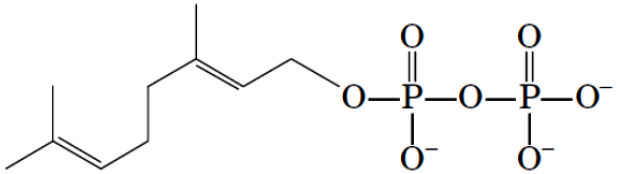


dimetilallil-PP

Δ^3-isopentenil-PP

prenil transferasi
(condensazione
testa-coda)

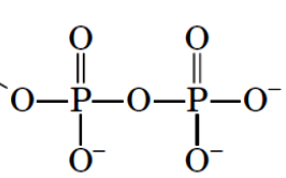
PP_i



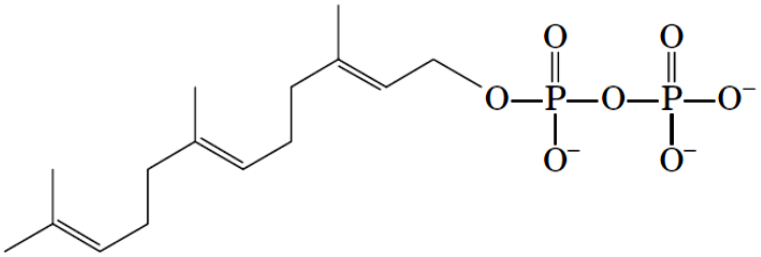
geranil-PP (10-C)

prenil transferasi
(condensazione
testa-coda)

PP_i

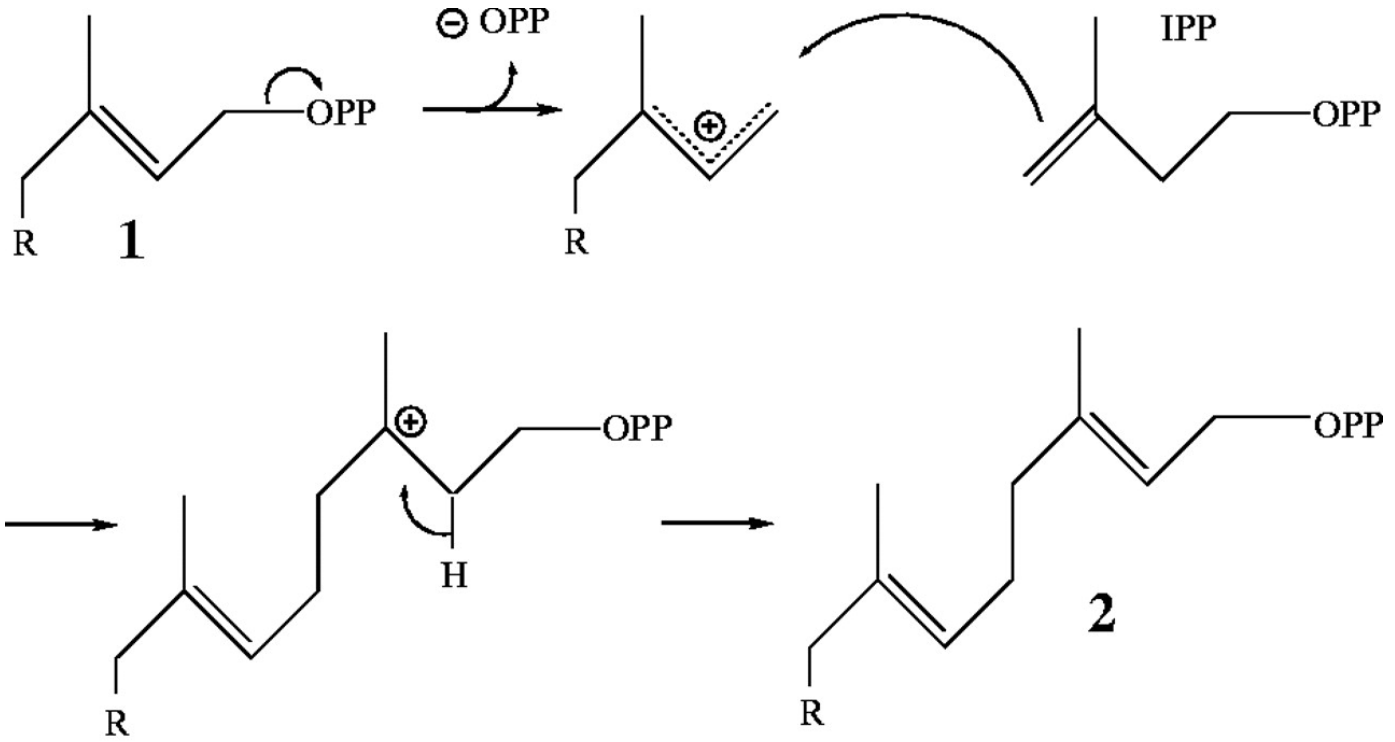


Δ^3-isopentenil-PP

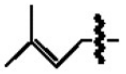


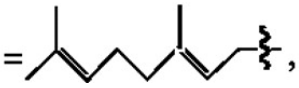
farnesil-PP (15-C)

Mechanism of the prenyltransferase reaction illustrating the condensations catalyzed by GPP synthase, FPP synthase, and GGPP synthase.

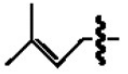


1: R = H, DMAPP

R =  , GPP

R =  , FPP

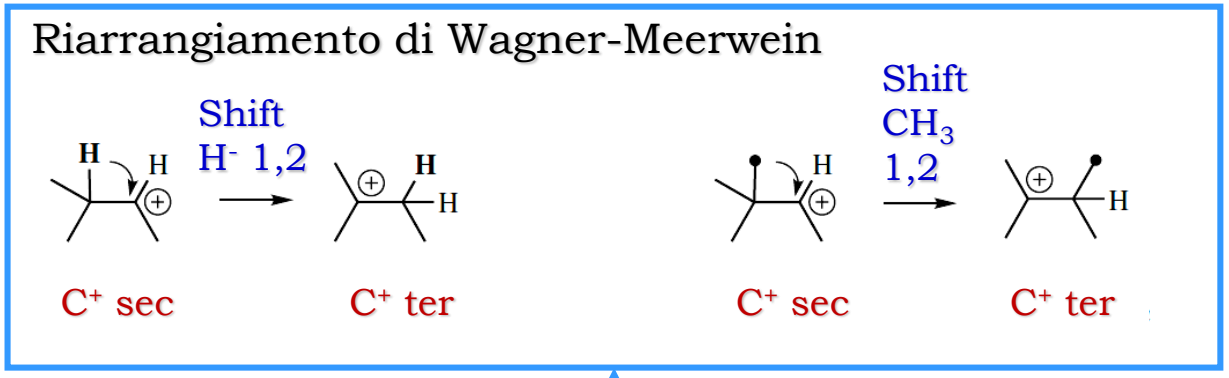
2: R = H, GPP

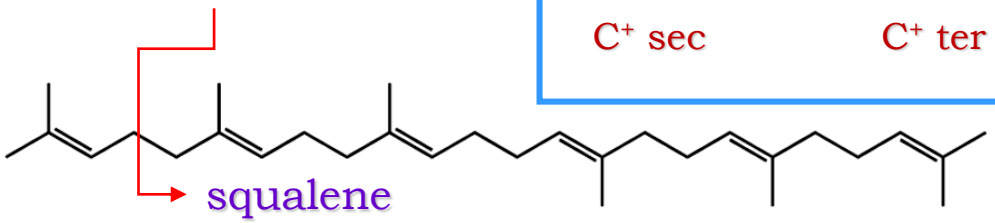
R =  , FPP

R =  , GGPP

Charles C. Burke et al. PNAS 1999;96:13062-13067

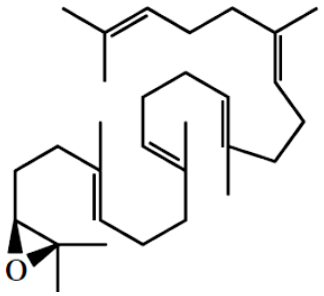
Polialchene (30C) presente in piante e animali e derivante da serie di SN_2 tra unità IPP





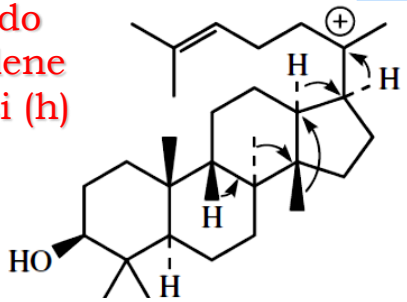
monoossigenasi O_2 NADPH

Sequenza di M-W



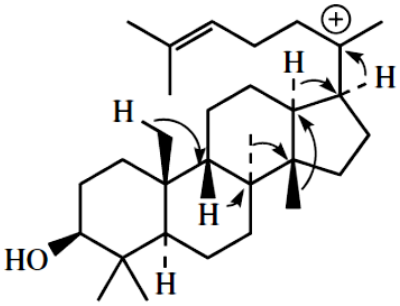
squalene ossido

ossido squalene ciclasi (h)



catione protosterilico

≡

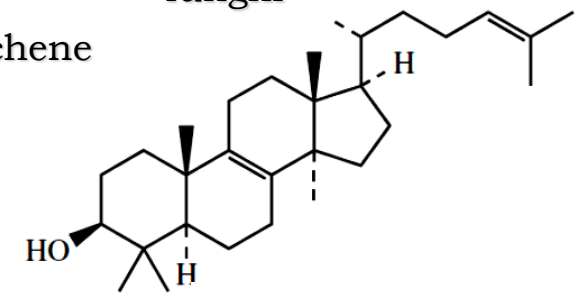


animali funghi

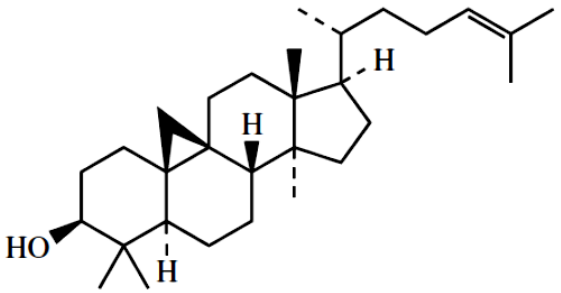
piante

- H^+ → ciclopropano

- H^+ → alchene

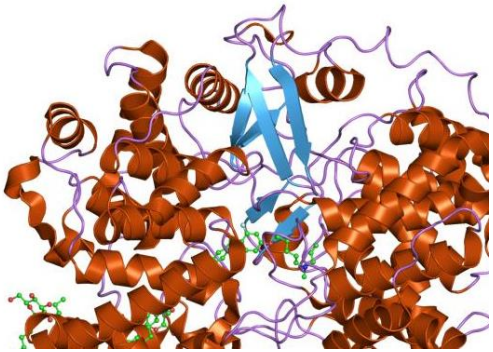


lanosterolo

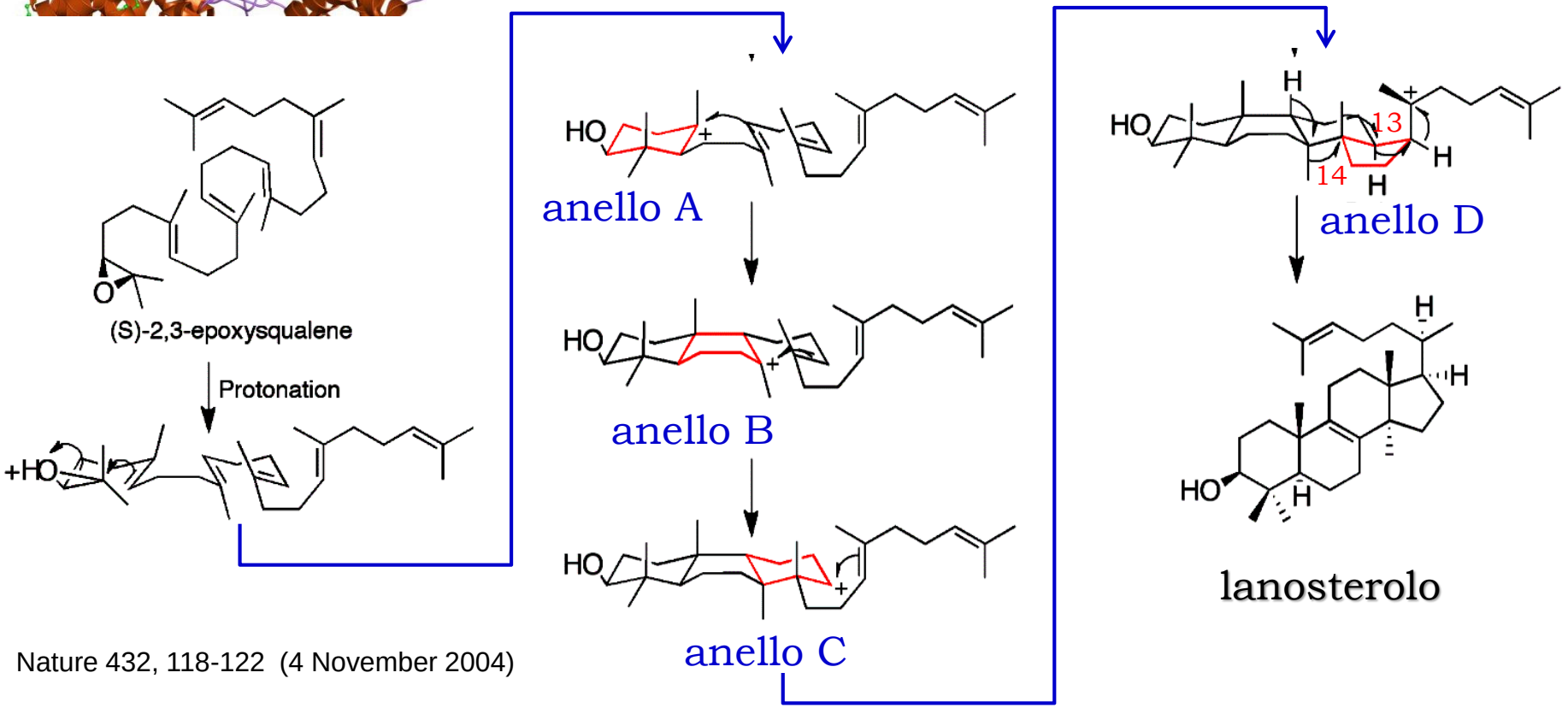


cicloartenolo

oxidosqualene ciclasi (OSC; lanosterolo sintasi, Pdb 1W6K)



Proteina monomerica di membrana composta di due domini (*barrel*) comunicanti e tre strutture *beta* più piccole. Il sito attivo, nel centro della proteina, è accessibile da un canale che il substrato (S)-2,3-epossidosqualene attraversa inducendo una modificazione conformazionale.

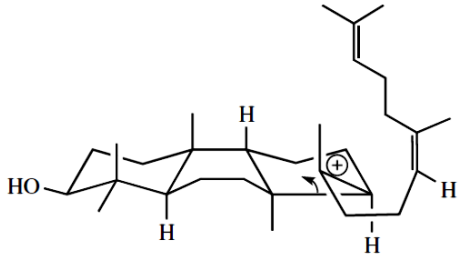


Nature 432, 118-122 (4 November 2004)

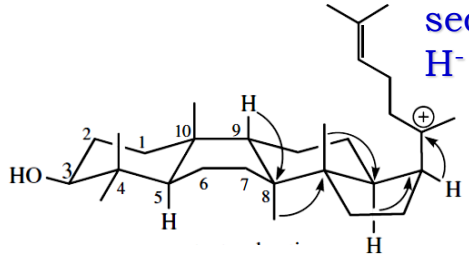
2,3-ossidosqualene

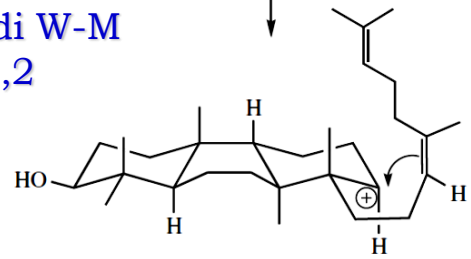
(sedia-barca-sedia-barca)

addizione Markovnikov



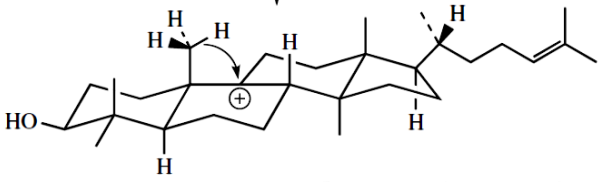
sequenza di W-M
H^- e CH_3 1,2

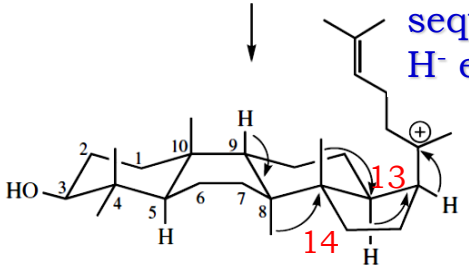




catione protostearilico
(sedia-barca-sedia-barca)

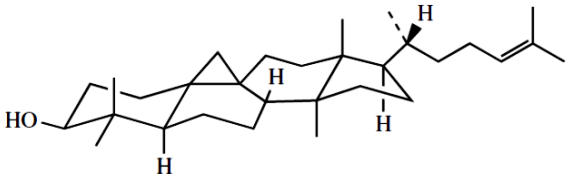
sequenza di W-M
H^- e CH_3 1,2

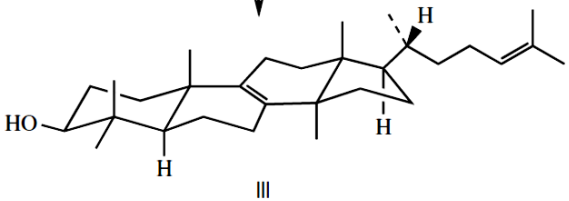


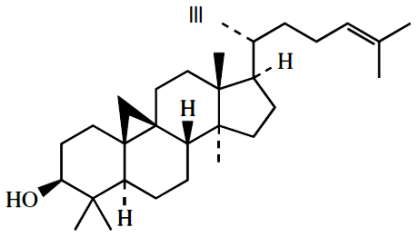


formazione △ e
$-H^+$ da CH_3 (10)

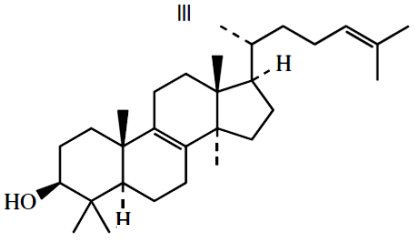
$-H^+$ (9) → C=C



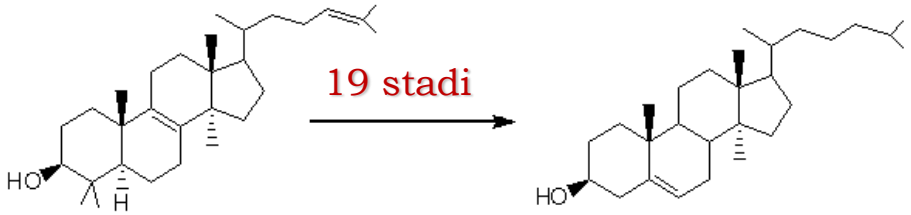




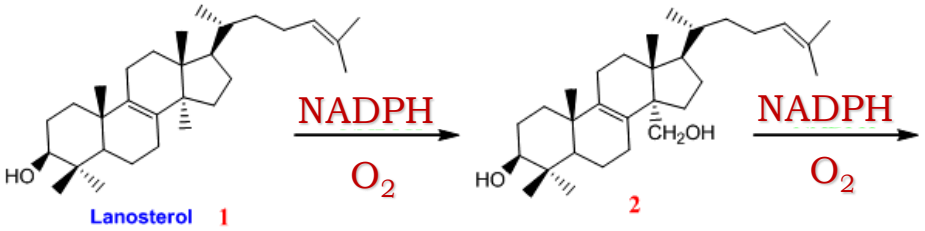
cicloartenolo



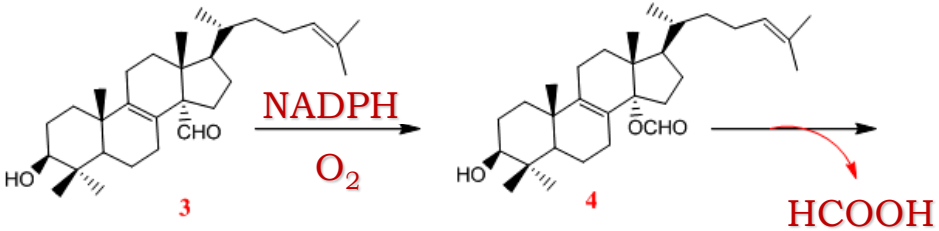
lanosterolo



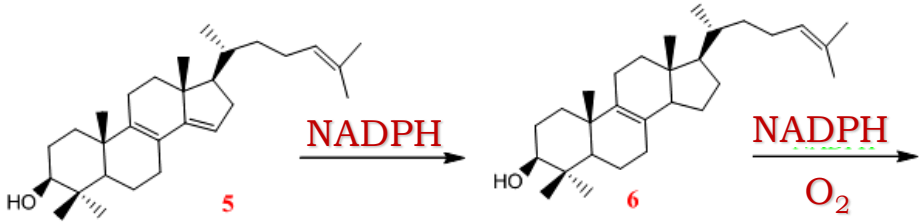
lanosterolo colesterolo



4,4-dimetil-14α-idrossimetil-5α-colesta-8-en-3β-olo

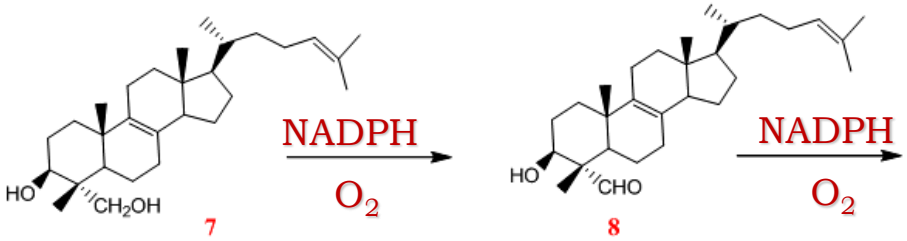


4,4-dimetil-14α-formil-5α-colesta-8-en-3β-olo



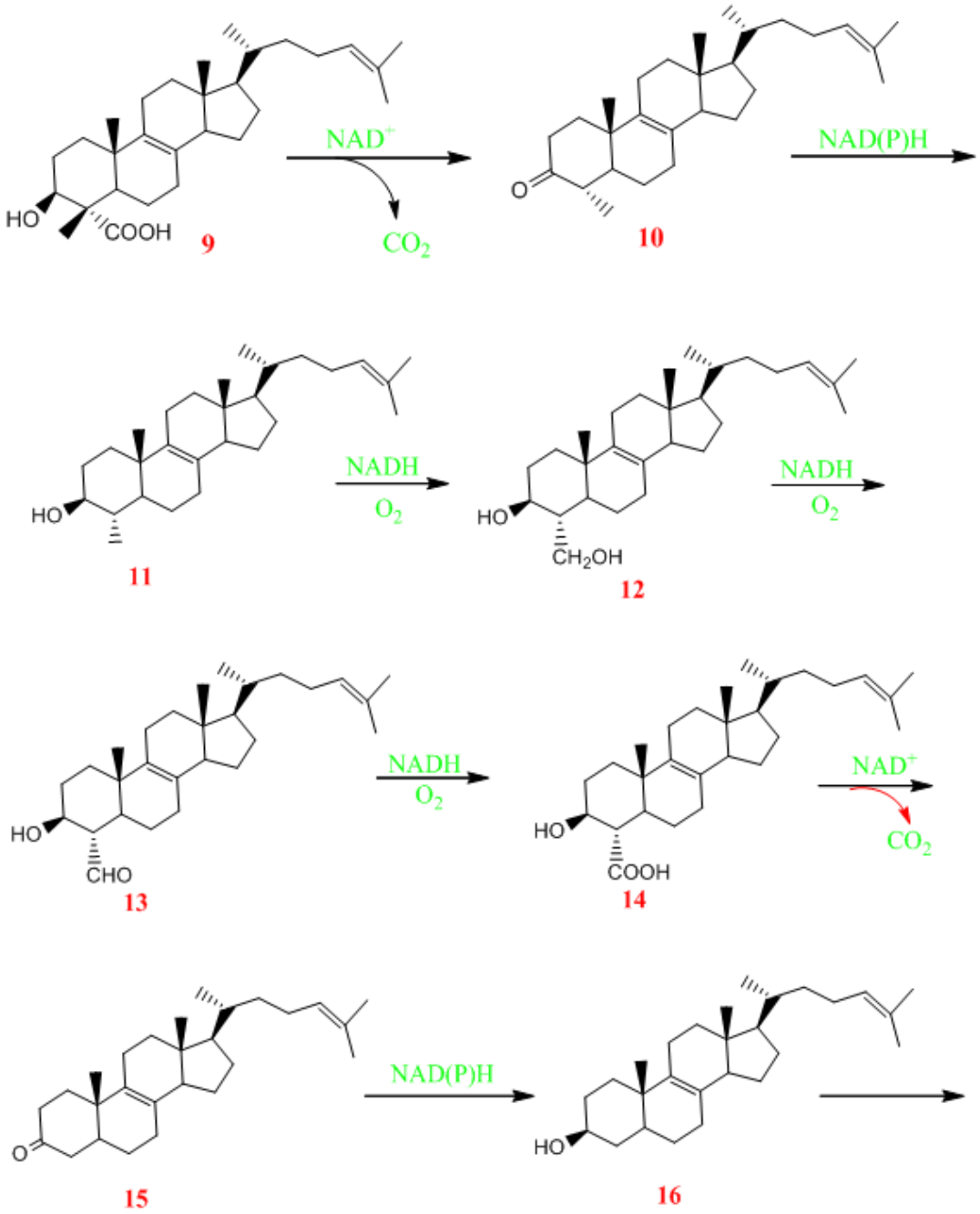
4,4-dimetil-5α-colesta-8,14-dien-3-β-olo

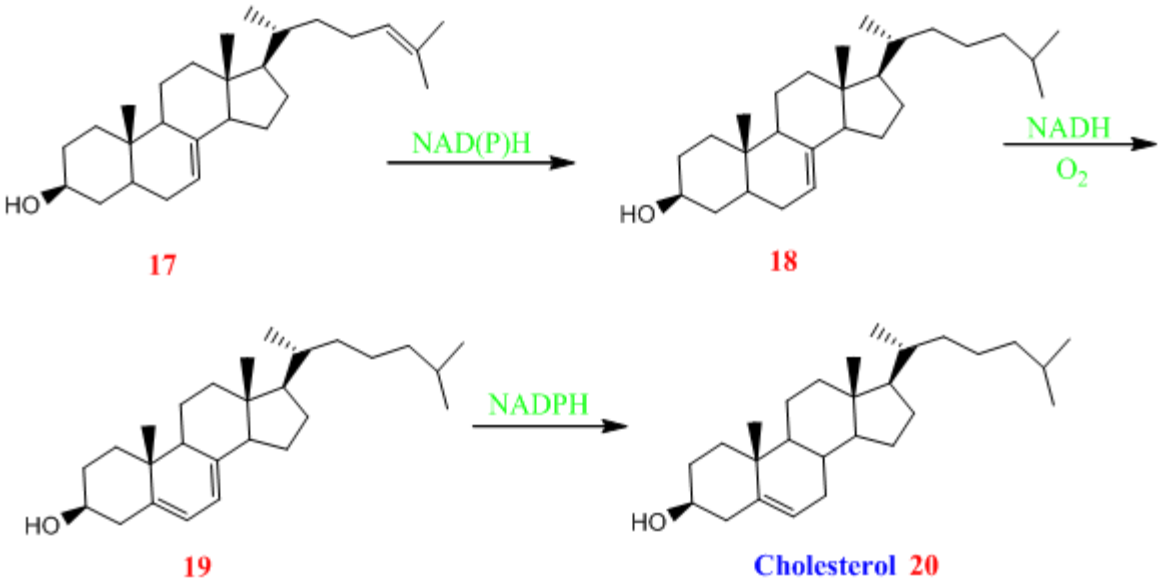
4,4-dimetl-5α-colesta-8-en-3-β-olo



4α-idrossimetil-4β-metil-5α-colesta-8-en-3β-olo

4α-formil-4β-metil-5α-colesta-8-en-3β-olo


HO
COOH
9
NAD+
CO2
O
10
NAD(P)H
HO
11
NADH
O2
HO
CH2OH
12
NADH
O2
HO
CHO
13
NADH
O2
HO
COOH
14
NAD+
CO2
O
15
NAD(P)H
HO
16



J. M. Risley, Cholesterol Biosynthesis: Lanosterol to Cholesterol, Journal of Chemical Education, 2002, 79, 377 – 384.