

# Tema N° 6

# Metabolismo secundario

Universidad Central de Venezuela  
Facultad de Farmacia  
Farmacognosia y Medicamentos Herbarios

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Año 2013-2014

METABOLISMO

Reacciones  
químicas

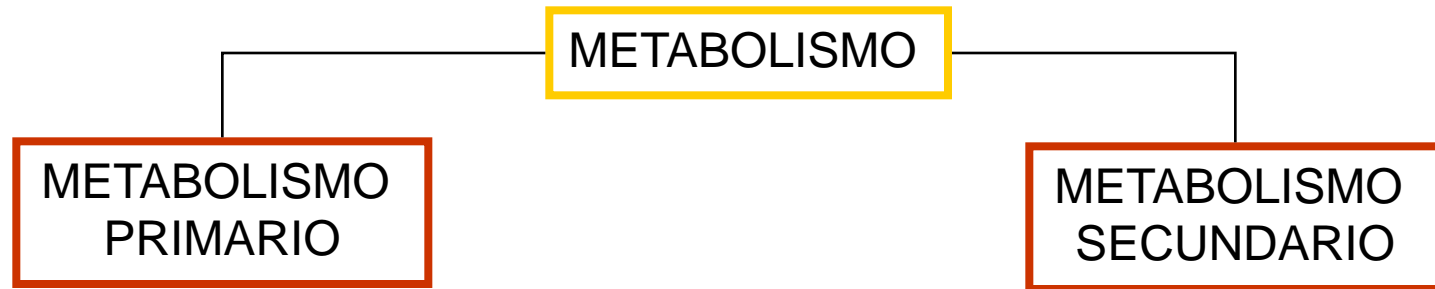
Enzimas,  
cofactores

Síntesis  
(Anabolismo)

Degradación  
(Catabolismo)

METABOLITOS

METABOLITOS



Procesos metabólicos **esenciales** que poseen la **mayoría** de los seres vivos:

- Fotosíntesis
- Glucólisis
- Ciclo de las pentosas
- Ciclo de Krebs, etc.

Utilizan y sintetizan sustancias **esenciales** para la vida, llamadas **metabolitos primarios** o productos bioquímicos:

- Carbohidratos (polisacáridos)
- Aminoácidos (proteínas)
- Ácidos grasos comunes (lípidos)

Procesos metabólicos **especiales** que poseen **ciertos** organismos vivos:

- Ruta del ácido siquímico
- Ruta del acetato polimalonato
- Ruta DOXP ó MEP
- Condensación de aminoácidos alifáticos

Utilizan y sintetizan sustancias **especiales** para ciertos organismos, llamadas **metabolitos secundarios** o productos naturales:

- Fenoles (flavonoides, cumarinas, lignanos, quinonas, taninos, etc.)
- Alcaloides
- Terpenos

# METABOLISMO PRIMARIO



+ Agua + CO<sub>2</sub>

↓ *Fotosíntesis*

*Ciclo de las pentosas*

Glucosa

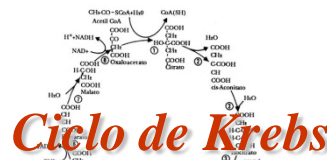
*Glucólisis*

Eritrosa-4-fosfato

Fosfoenolpiruvato

Gliceraldehido-3-fosfato

Piruvato



Acetil~CoA

Aminoácidos alifáticos

Ruta

Ácido siquímico

Ruta

Acetato polimalonato

Ruta

Ácido mevalónico

Ruta

DOXP/MEP

Aminoácidos aromáticos

**ALCALOIDES**

**TERPENOS**

**COMPUESTOS FENÓLICOS**

# METABOLISMO SECUNDARIO



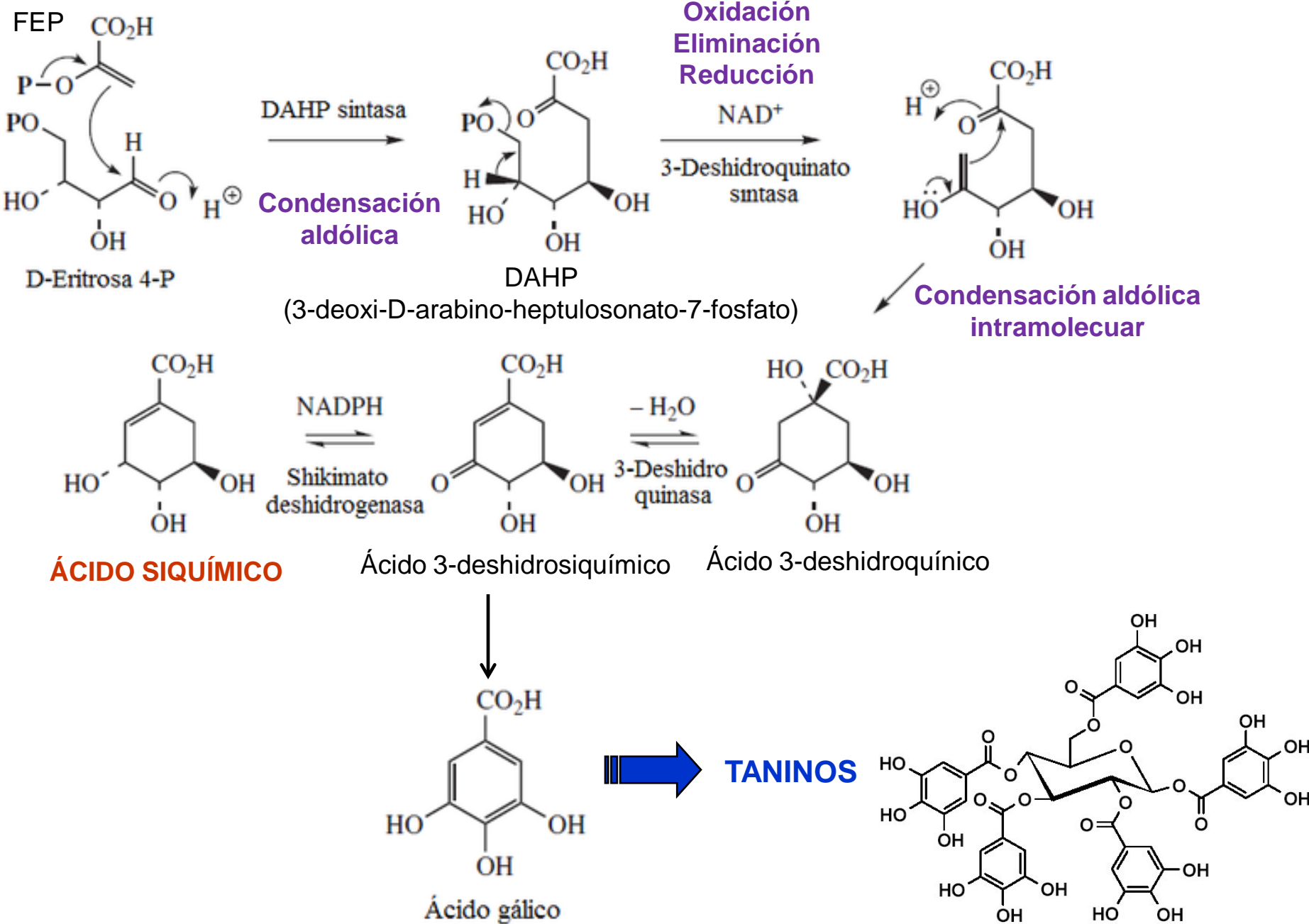
# Metabolitos secundarios

- Se originan de productos del metabolismo primario (precursores biosintéticos).
- Se les atribuyen una variedad de funciones en el organismo que los contienen.
- Muchos poseen propiedades farmacológicas muy específicas.

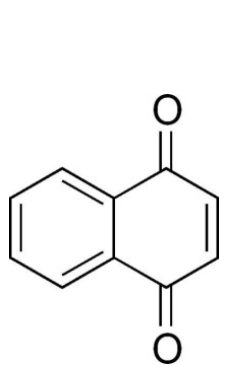
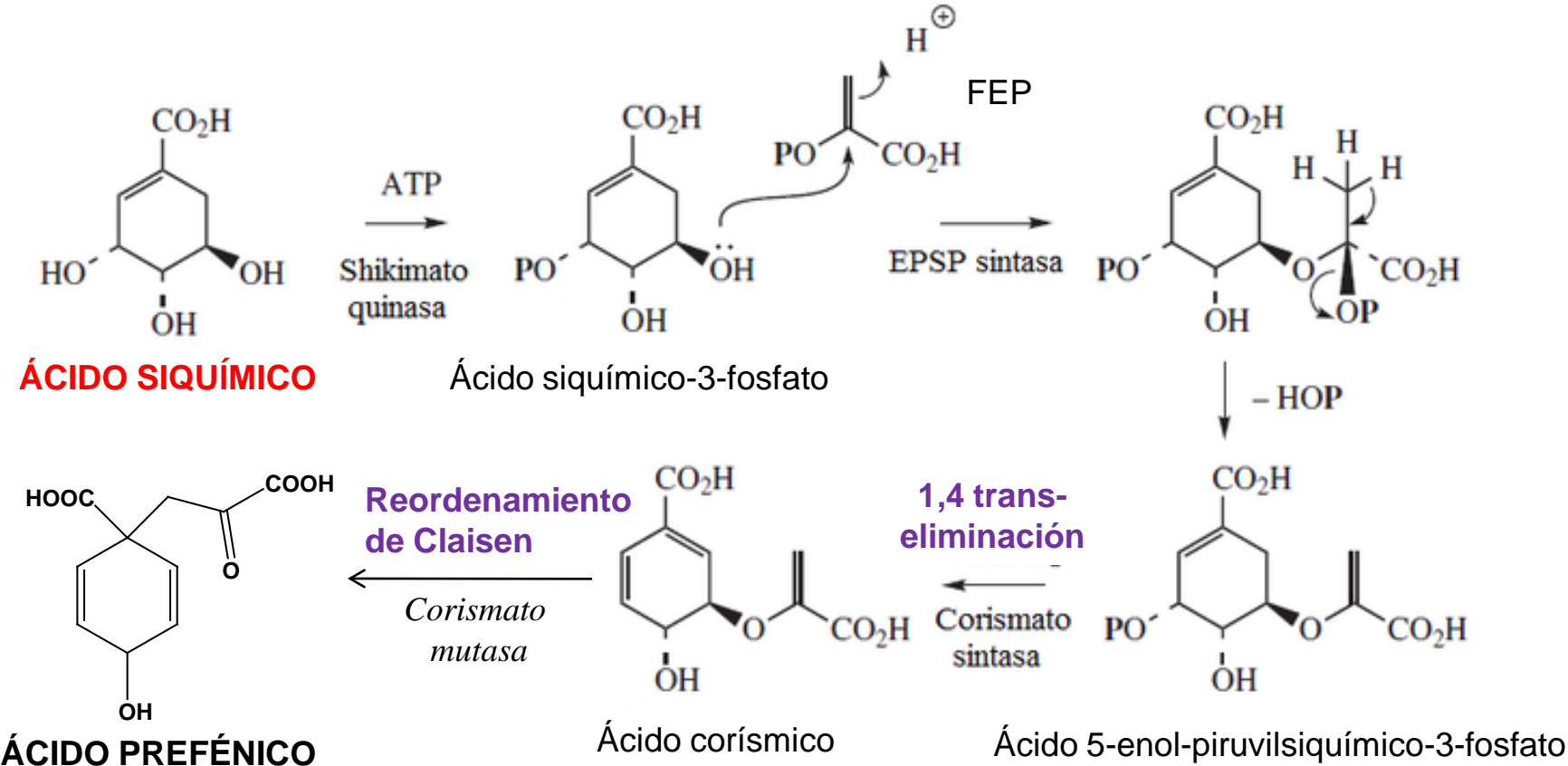
# Metabolismo secundario

- ❑ Ruta del ácido siquímico
- ❑ Ruta del acetato polimalonato
- ❑ Ruta 1-desoxi-D-xilulosa-5-fosfato (DOXP) ó 2-C-metil-D-eritritol-4-fosfato (MEP)
- ❑ Condensación de aminoácidos alifáticos

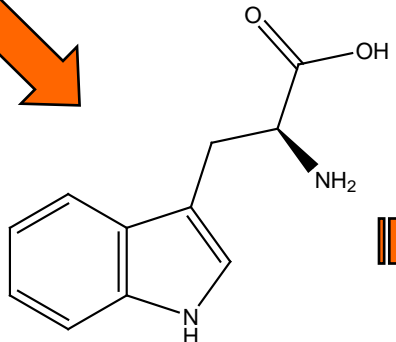
# Ruta del ácido siquímico



# Ruta del ácido siquímico



**NAFTOQUINONAS**

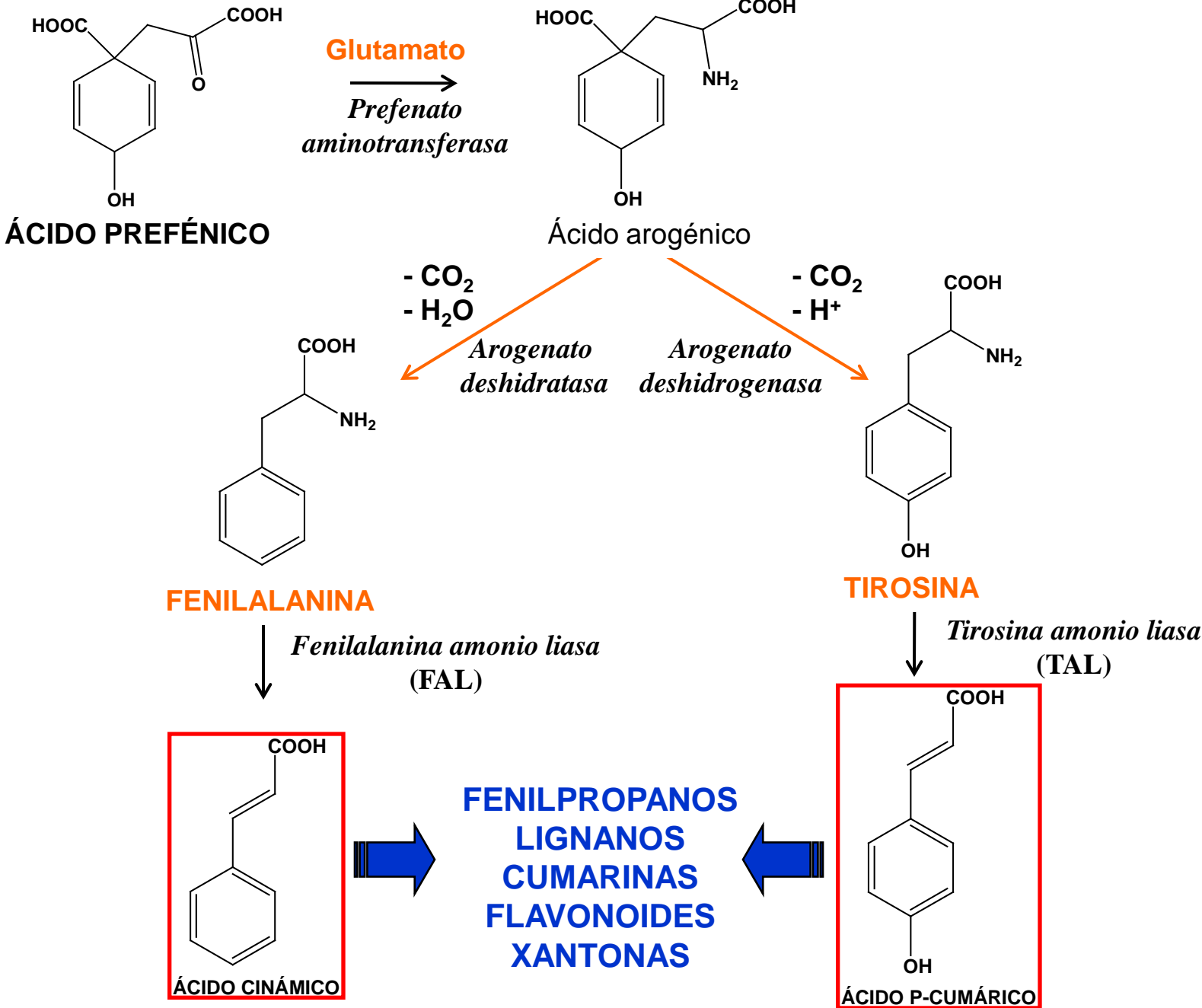


**TRIPTÓFANO**

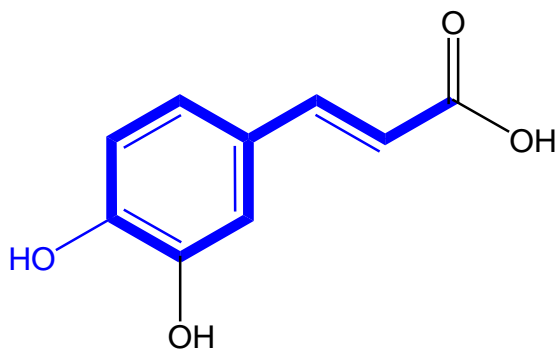
**ALCALOIDES INDÓLICOS**



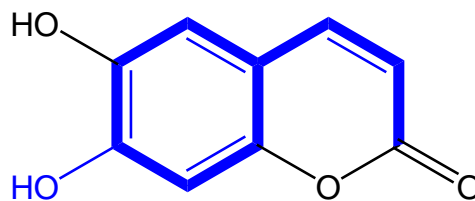
# Ruta del ácido siquímico



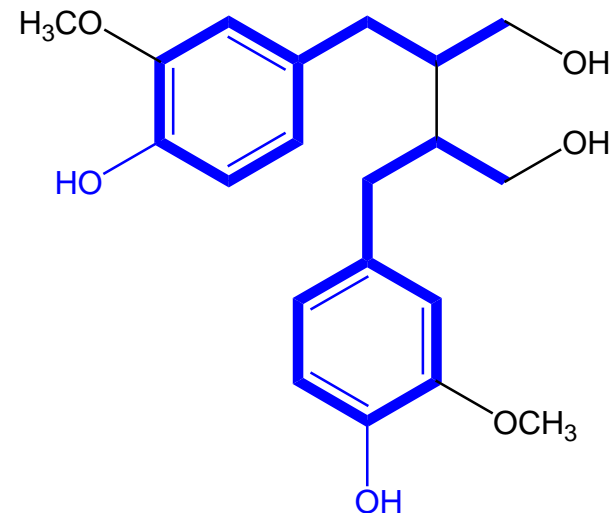
# COMPUESTOS FENÓLICOS DERIVADOS DE LA RUTA DEL ÁCIDO SIQUÍMICO



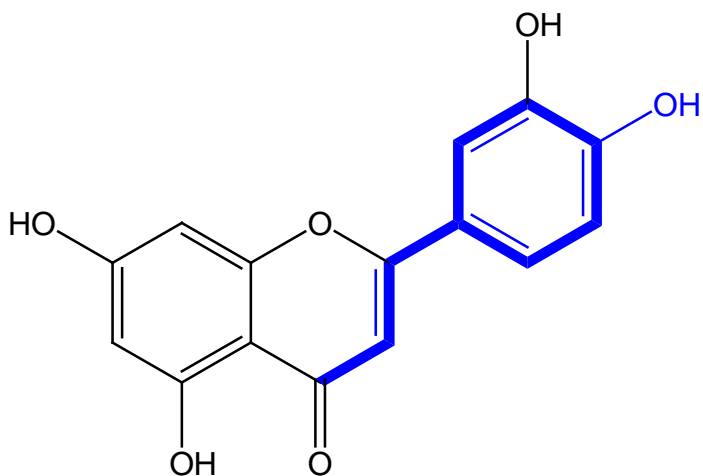
**FENILPROPANOS**



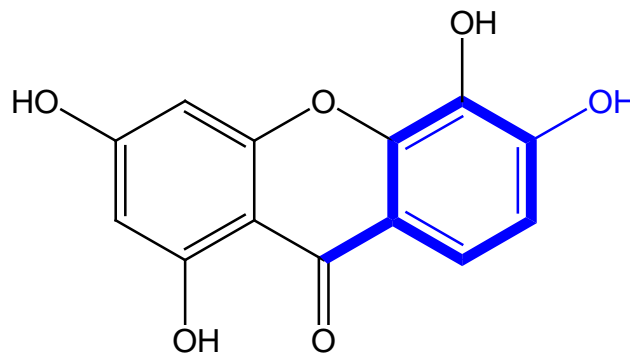
**CUMARINAS**



**LIGNANOS**

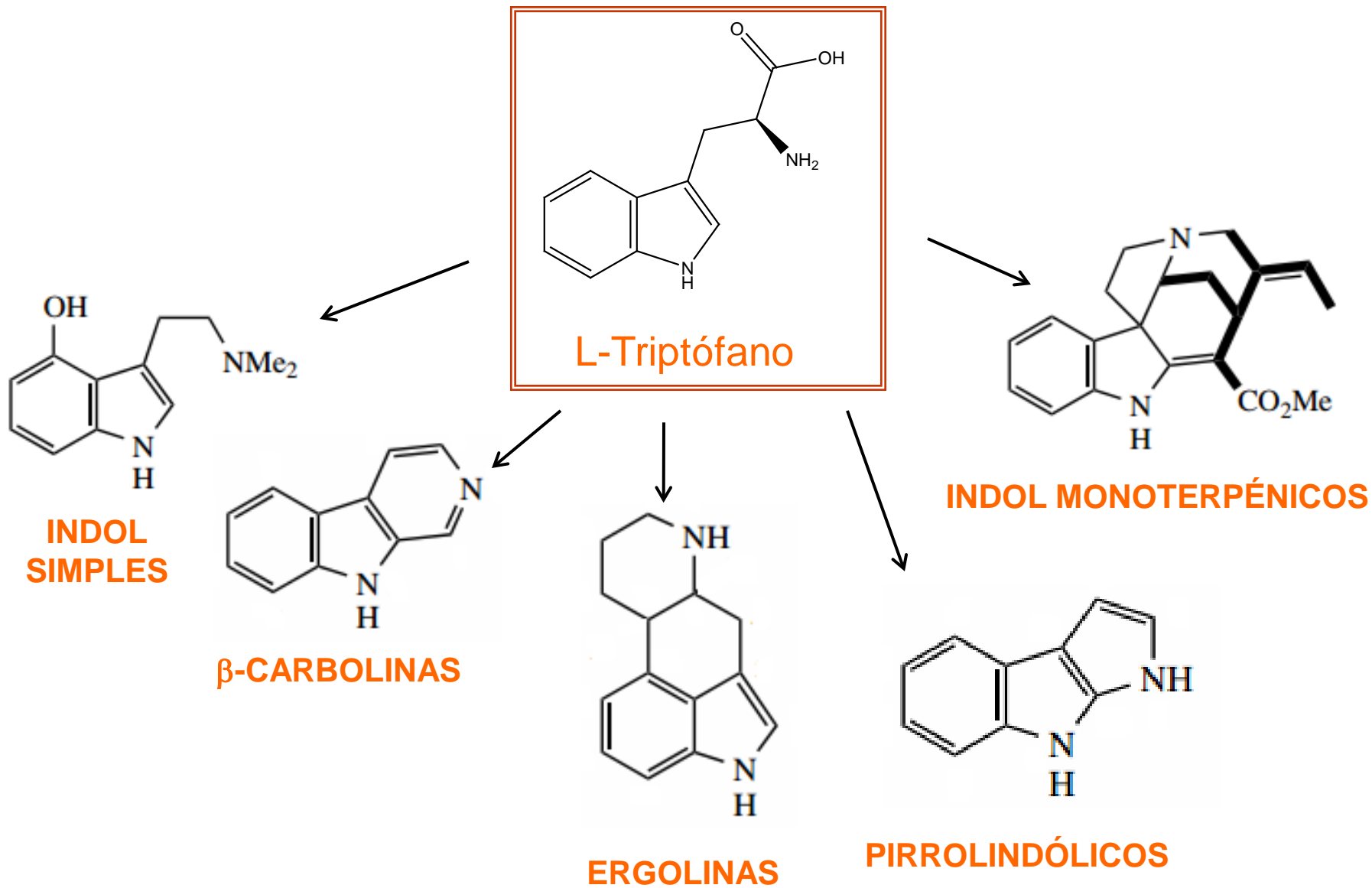


**FLAVONOIDES**

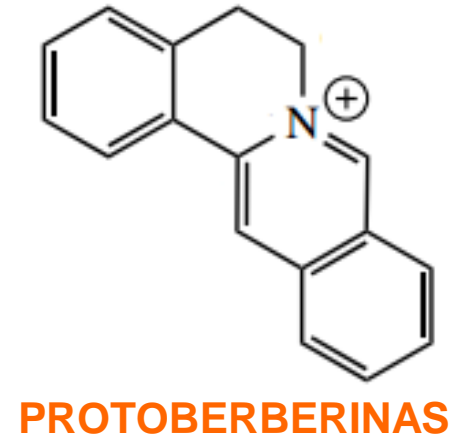
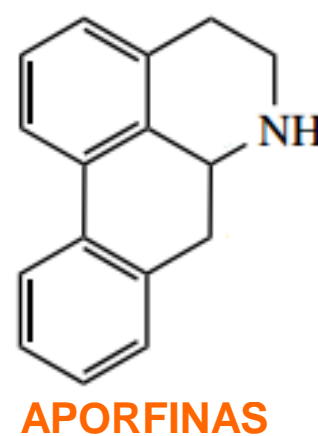
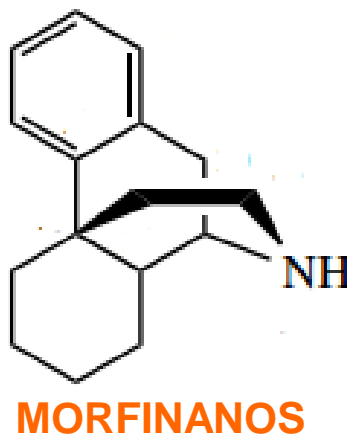
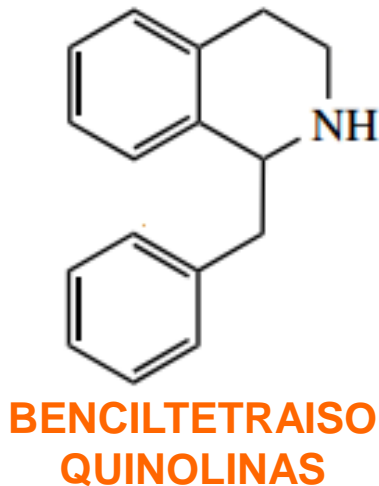
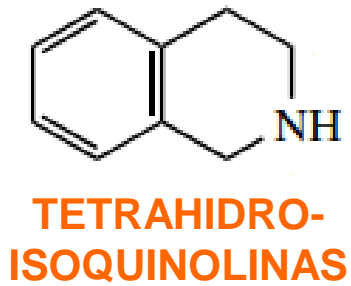
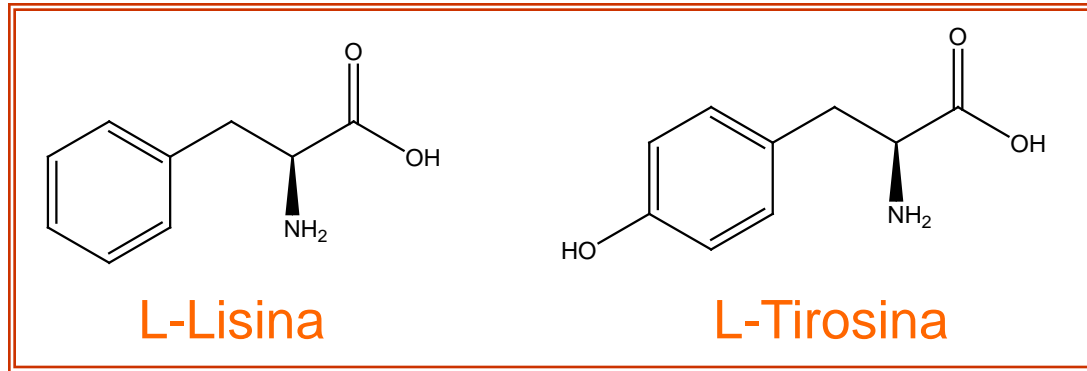


**XANTONAS**

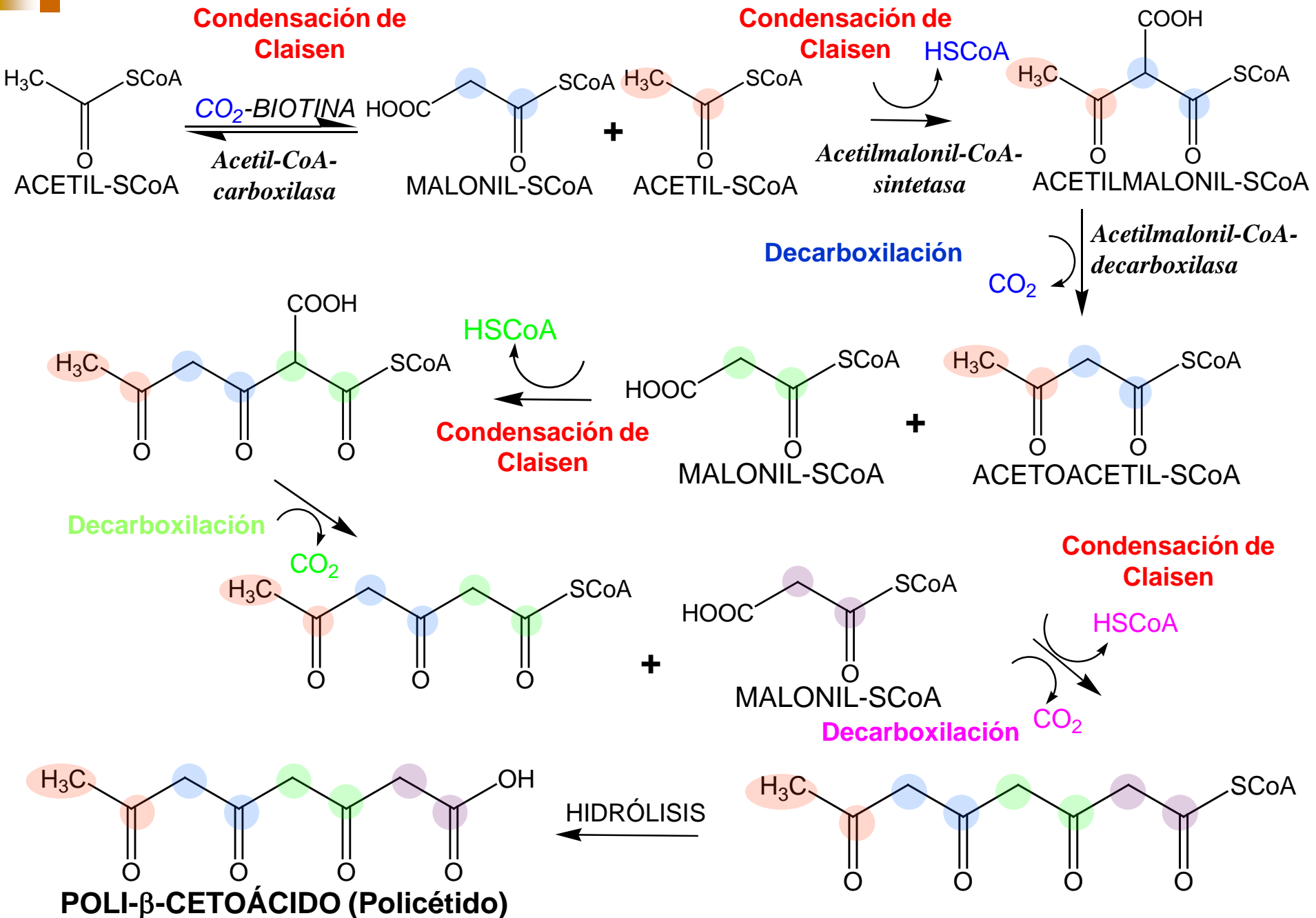
## ALCALOIDES INDÓLICOS derivados del aminoácido aromático triptófano



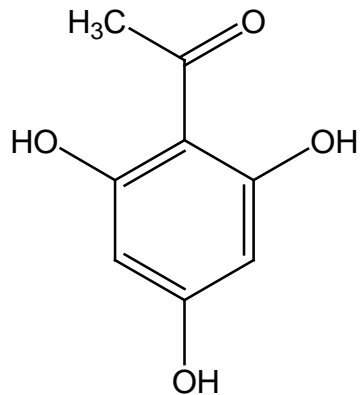
# ALCALOIDES derivados de aminoácidos aromáticos



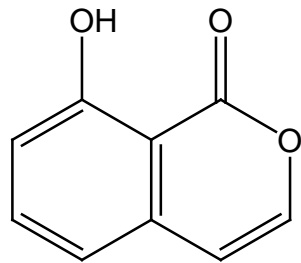
# Ruta del acetato polimalonato



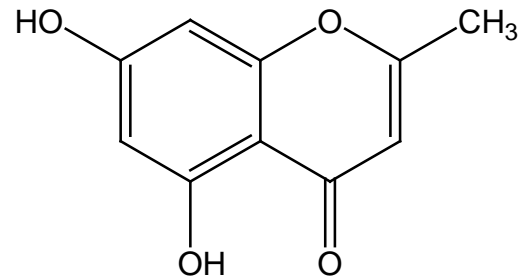
# COMPUESTOS FENÓLICOS DERIVADOS DE LA RUTA ACETATO-POLIMALONATO



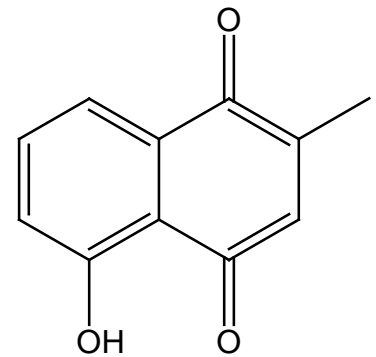
**FENOLES  
SIMPLES**



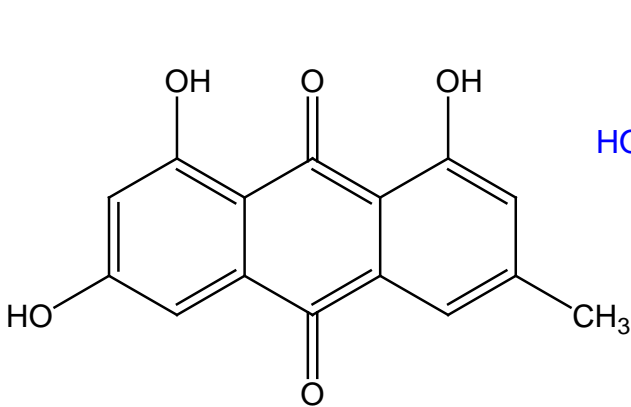
**ISOCUMARINAS**



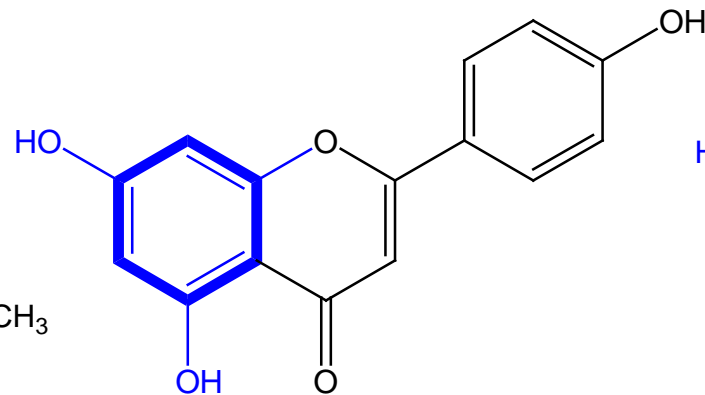
**CROMONAS**



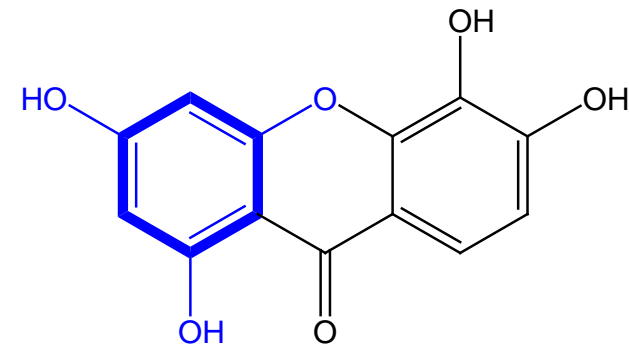
**NAFTOQUINONAS**



**ANTRAQUINONAS**

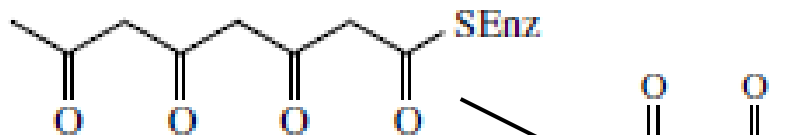


**FLAVONOIDES**

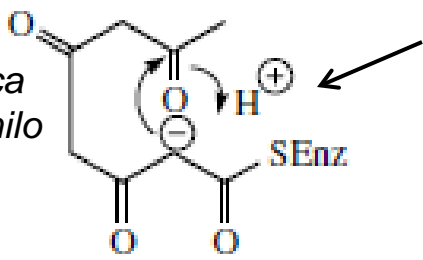


**XANTONAS**

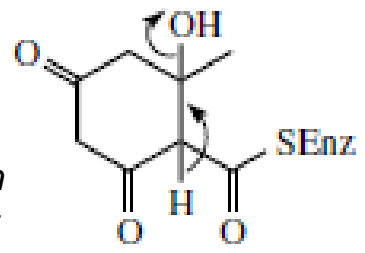
# Reacciones intramoleculares de los policétidos



Adición aldólica sobre el carbonilo

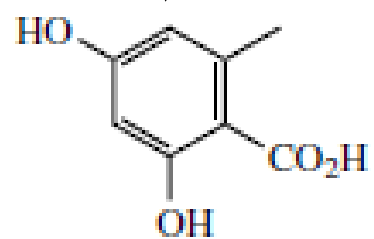


**Condensación aldólica**



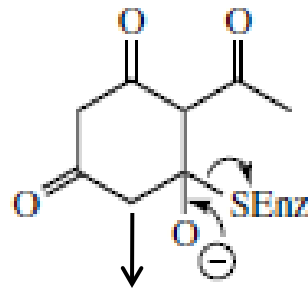
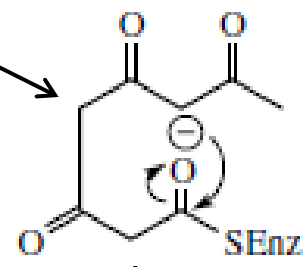
Deshidratación favorecida por formación de un sistema conjugado

•Enolización  
•Hidrólisis



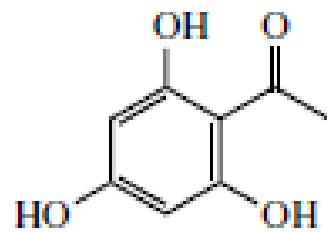
Enolización favorecida por formación de un anillo aromático

**Condensación de Claisen**

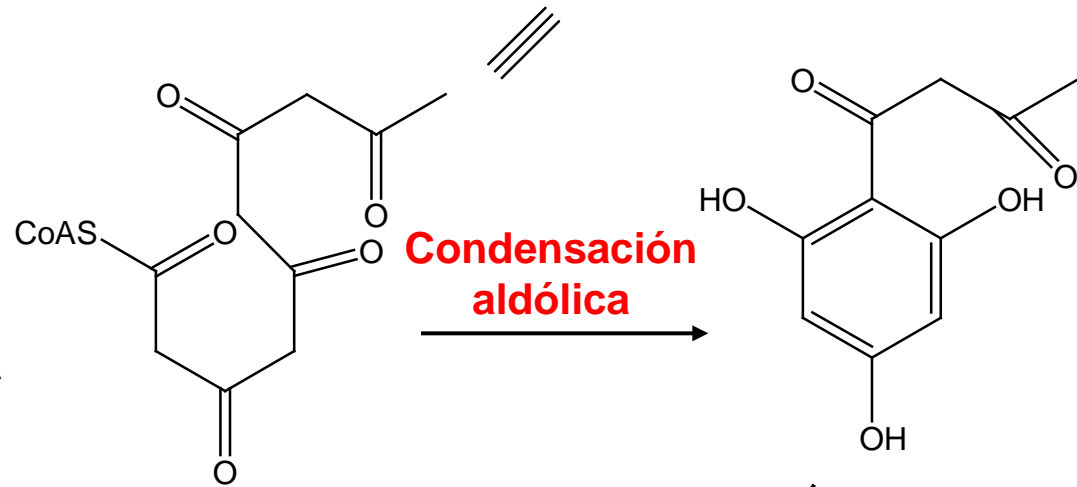
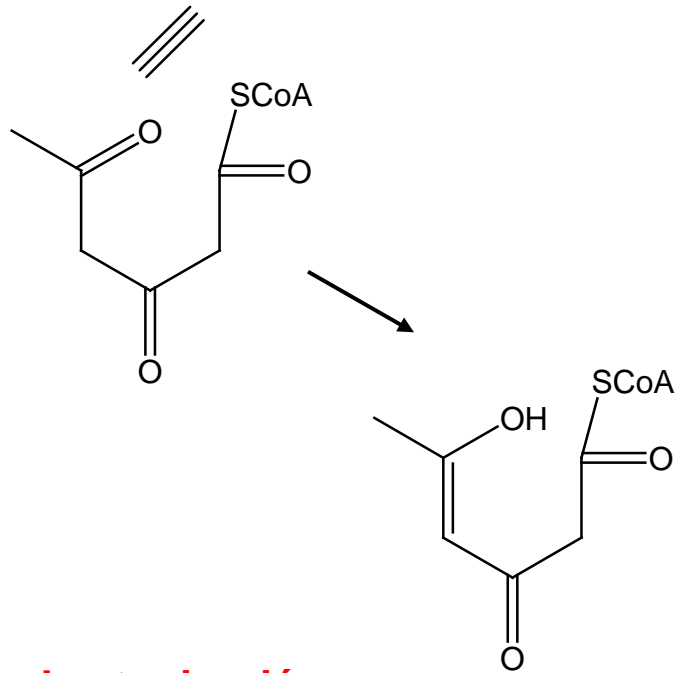
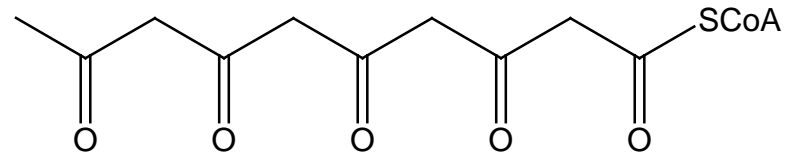
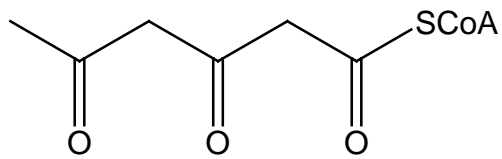


Reformación de carbonilo posible por expulsión de grupo saliente

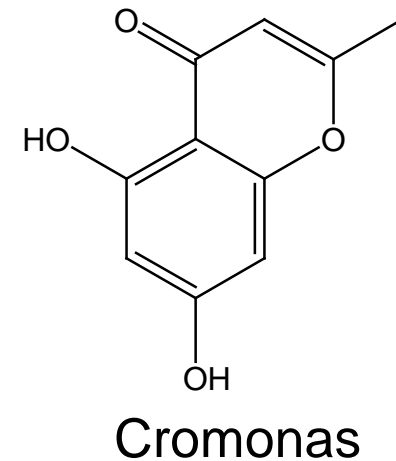
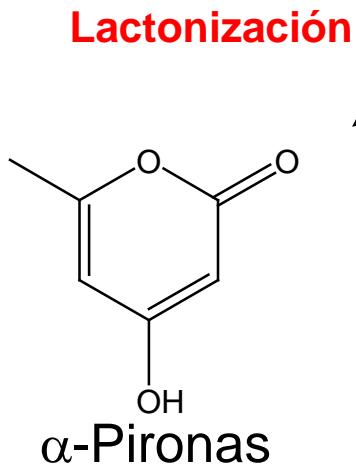
**Enolización**



# Reacciones intramoleculares de los policétidos

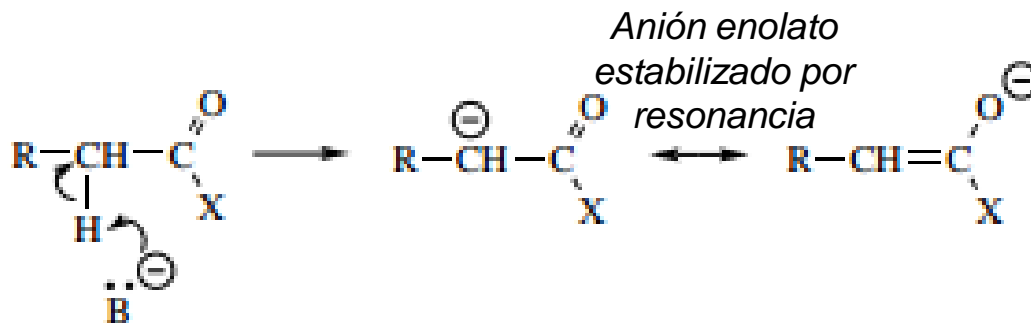


**Lactonización**

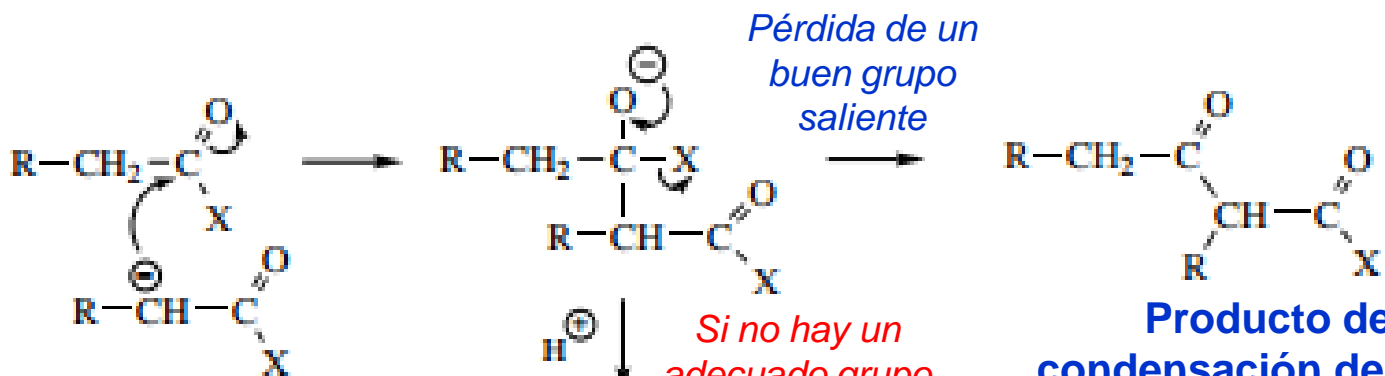




## Condensación Aldólica y Condensación de Claisen



*Adición  
nucleofílica  
sobre el  
carbonilo*



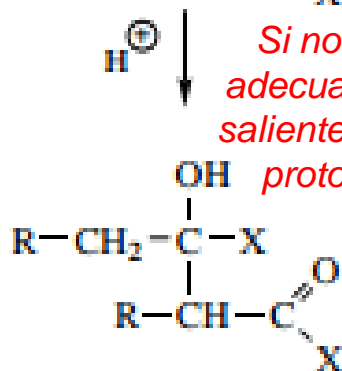
*Pérdida de un  
buen grupo  
saliente*

**Producto de la  
condensación de Claisen**

R = X = H, acetaldehído  
R = H, X = OEt, acetato de etilo

R = H, X = OEt, aceto acetato de etilo

*Si no hay un  
adecuado grupo  
saliente ocurre la  
protonación*



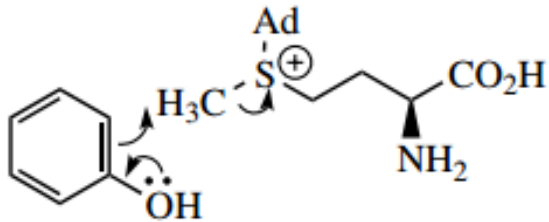
**Producto de la  
condensación aldólica**

R = X = H, aldol

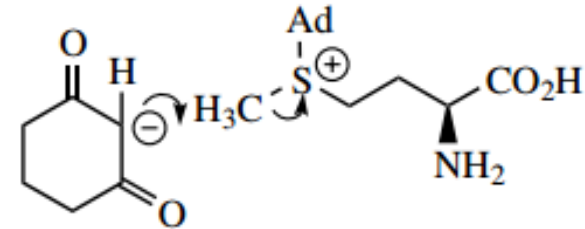
## C-Metilaciones usando SAM

(*S*-adenosilmetionina)

Posiciones orto y para son activadas por OH

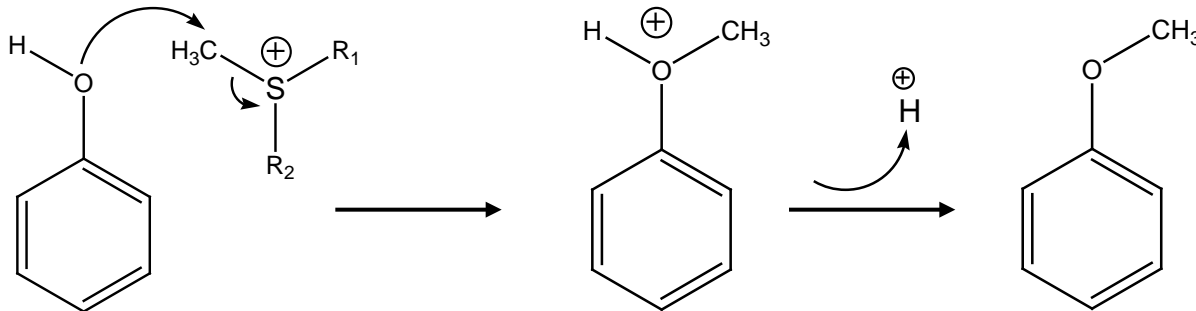


grupos carbonilos incrementan la acidez y formación del anión enolato

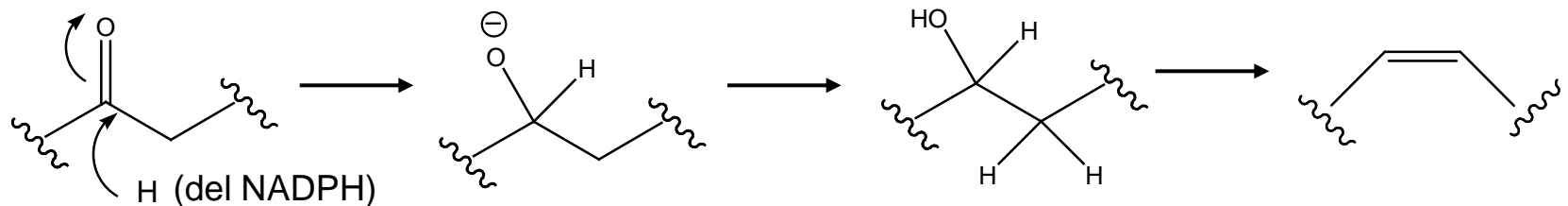


## O-Metilaciones usando SAM

(*S*-adenosilmetionina)

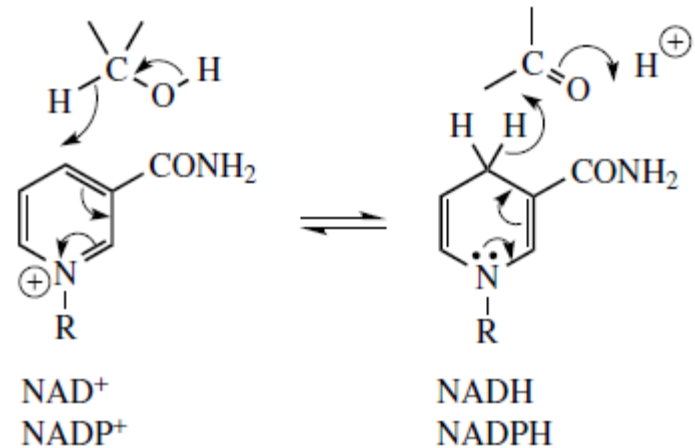
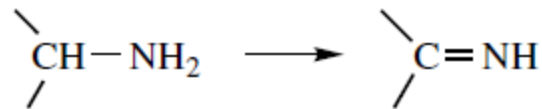
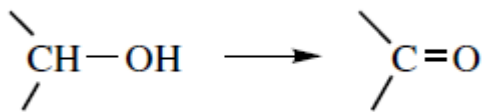


## Reducciones

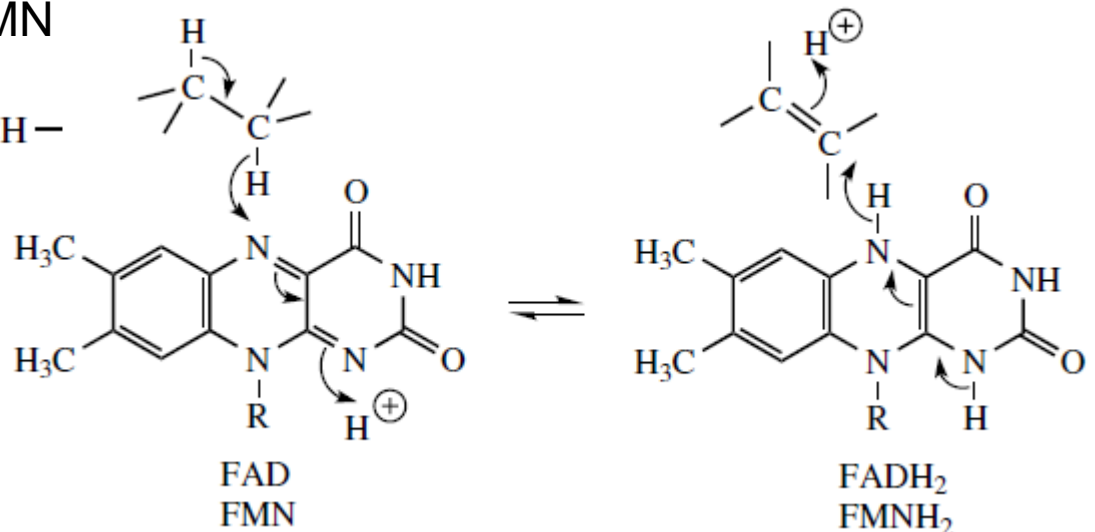


## Reacciones de oxidación y reducción

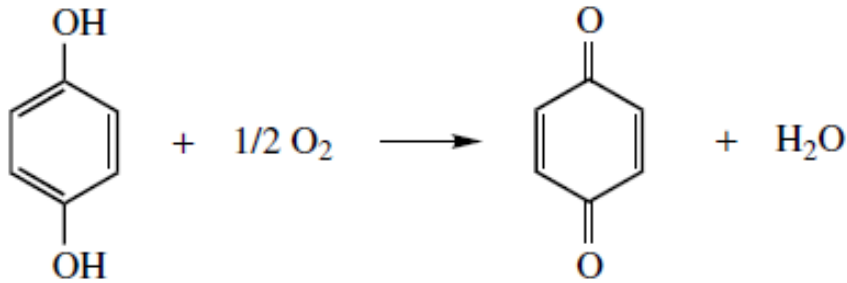
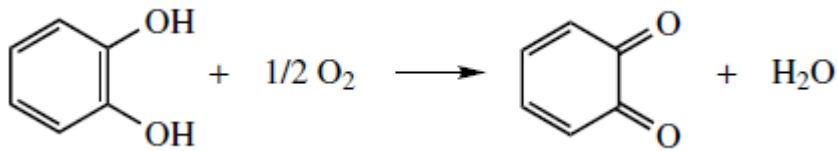
Deshidrogenasas:  $\text{NAD}^+$  y  $\text{NADP}^+$



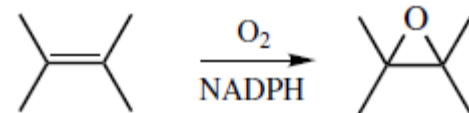
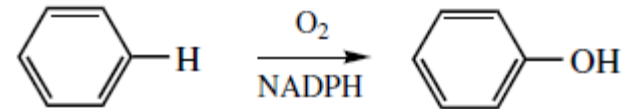
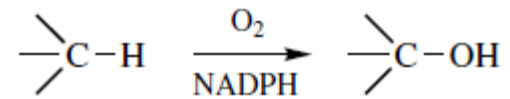
Deshidrogenasas:  $\text{FAD}$  y  $\text{FMN}$



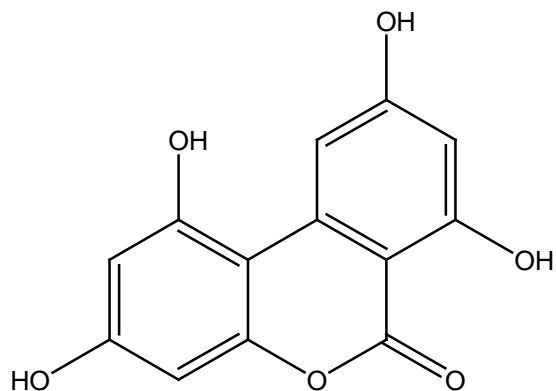
## Oxidasas



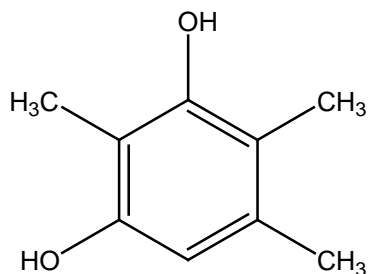
## Mono-oxigenasas



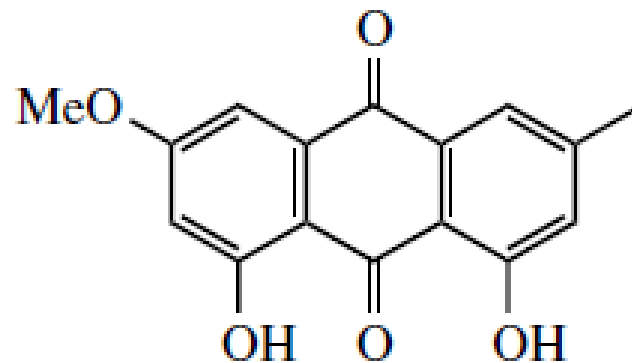
Sugiera una ruta biosintética razonable para los compuestos 1-4.



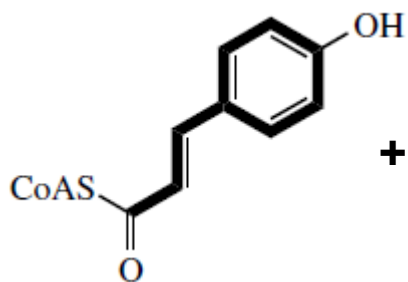
1



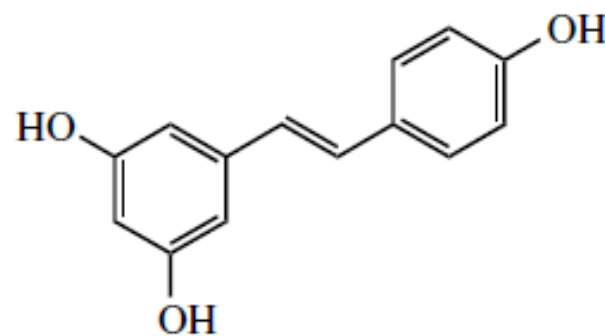
2



3

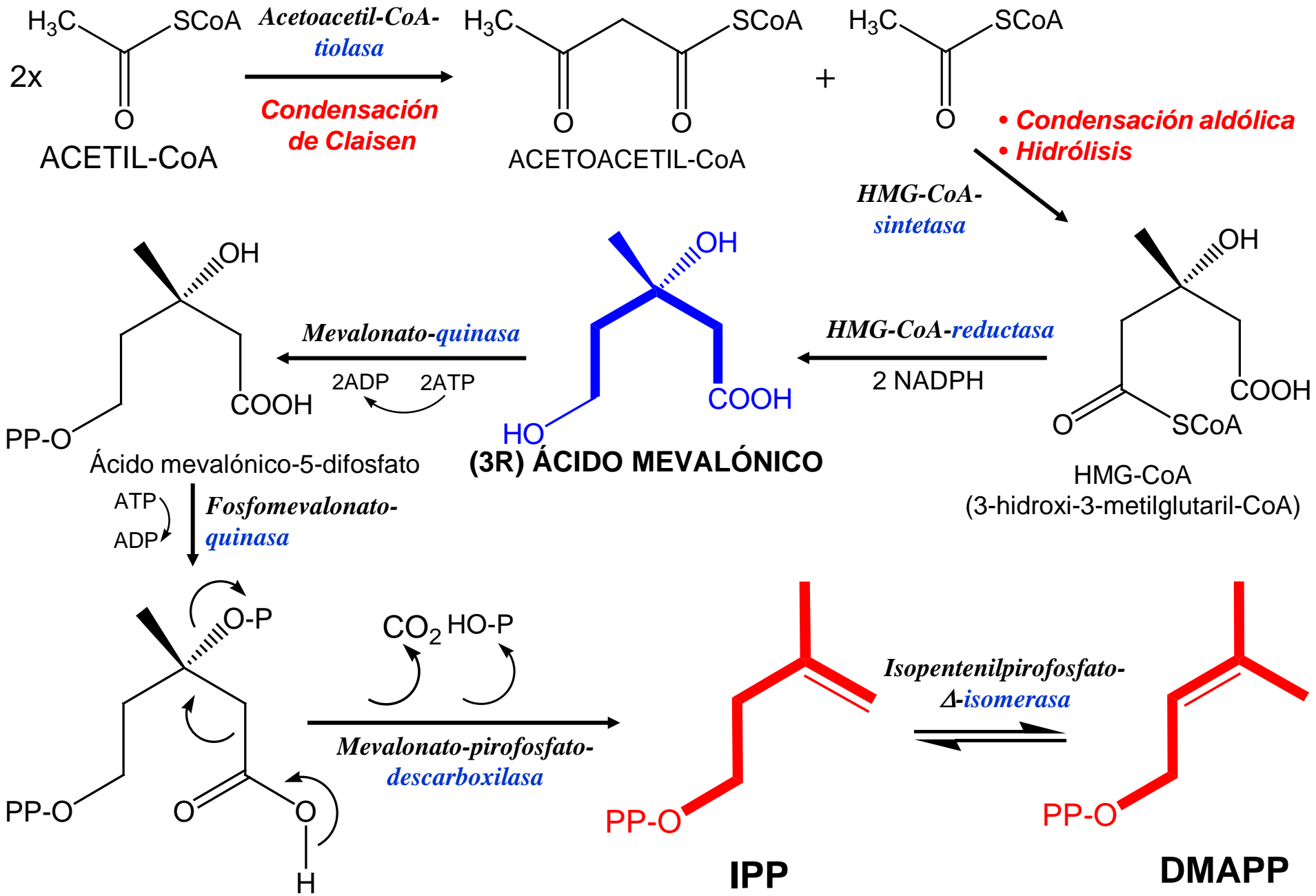


+ 3 malonil-S-CoA  $\dashrightarrow$

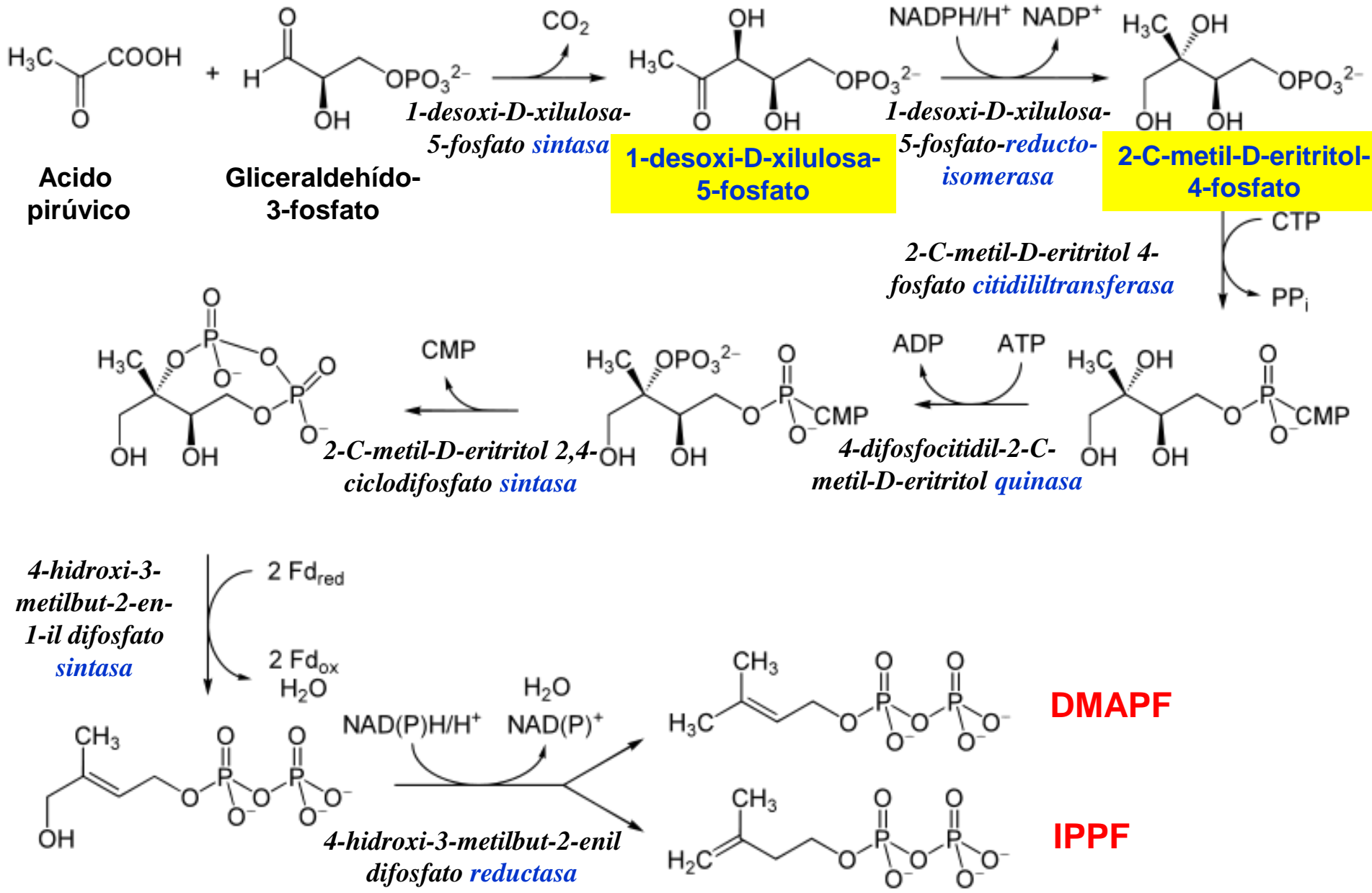


4

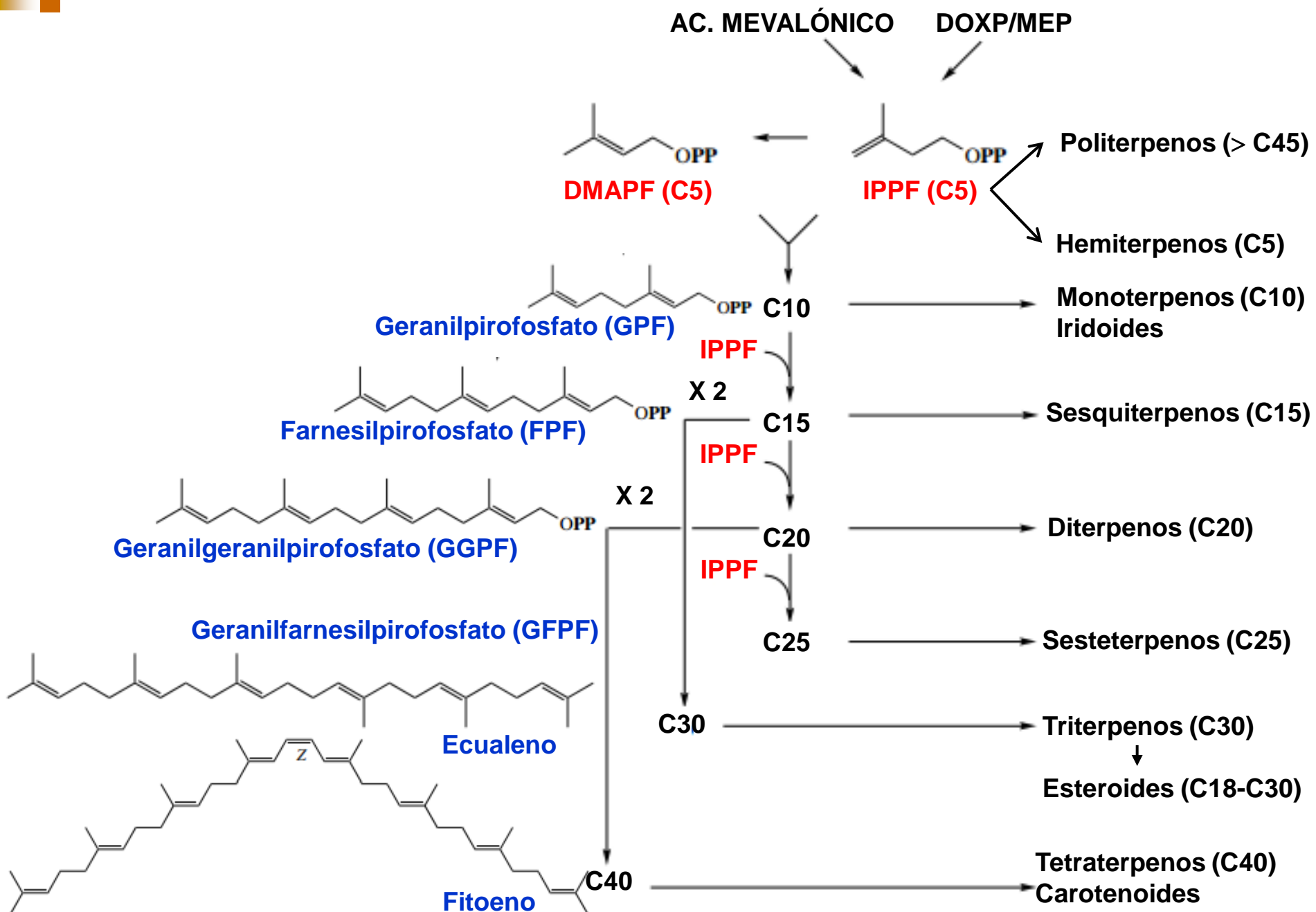
# Ruta del ácido mevalónico



Ruta 1-desoxi-D-xilulosa-5-fosfato (DOXP) / 2-C-metil-D-eritritol-4-fosfato (MEP)

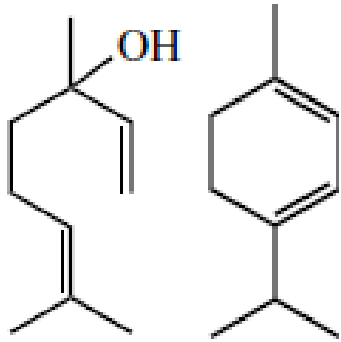


# Biosíntesis de terpenos

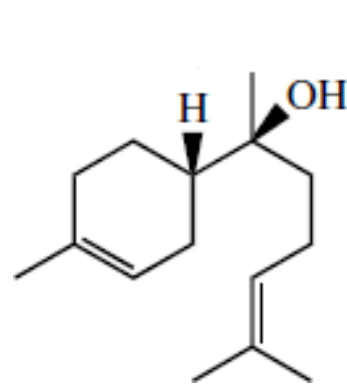




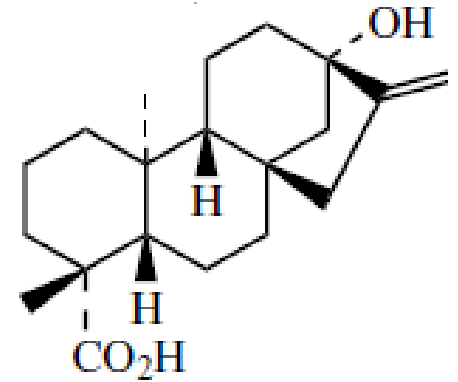
# Terpenos derivados de la ruta del ácido mevalónico y ruta DOXP/MEP



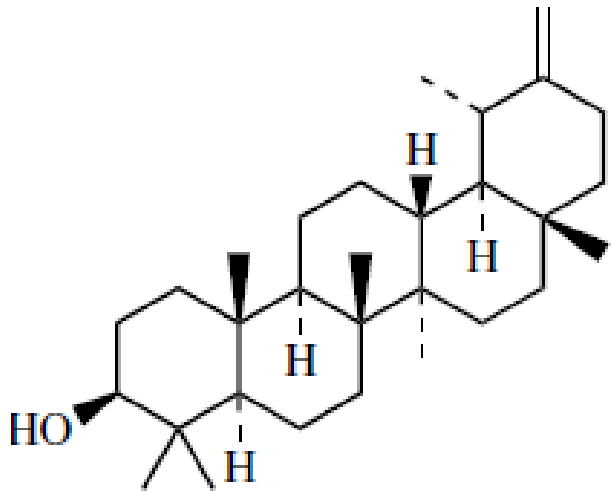
**MONOTERPENOS**



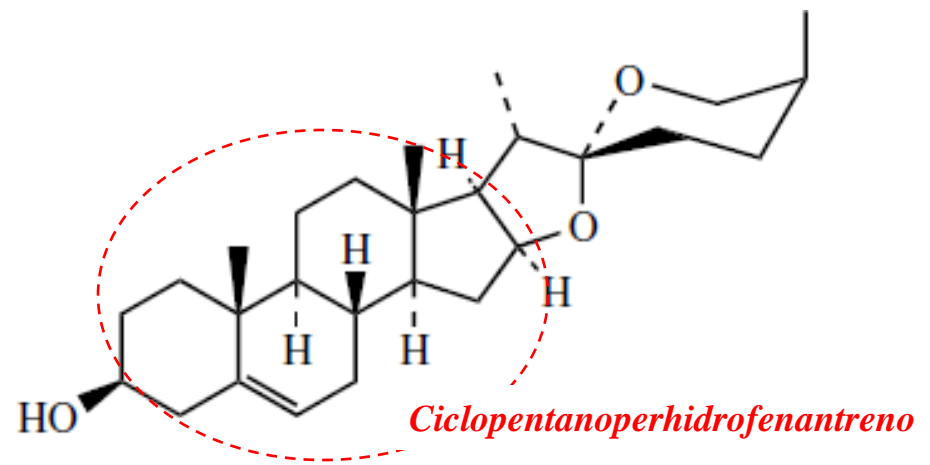
**SESQUITERPENOS**



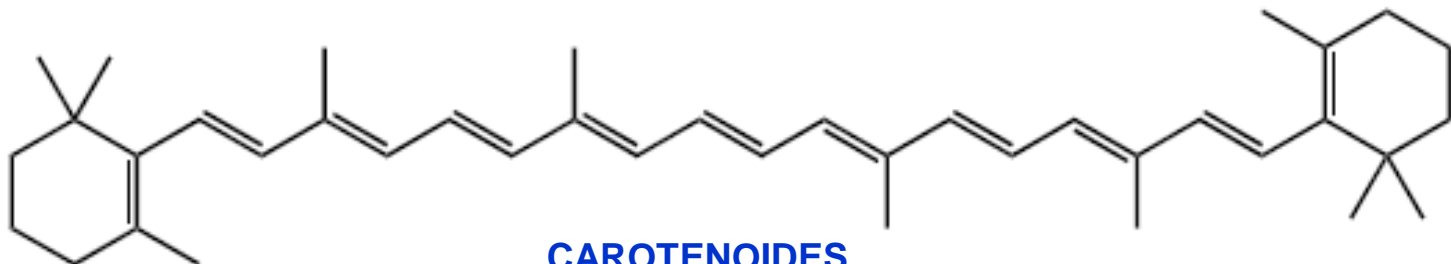
**DITERPENOS**



**TRITERPENOS**



**ESTEROIDES**

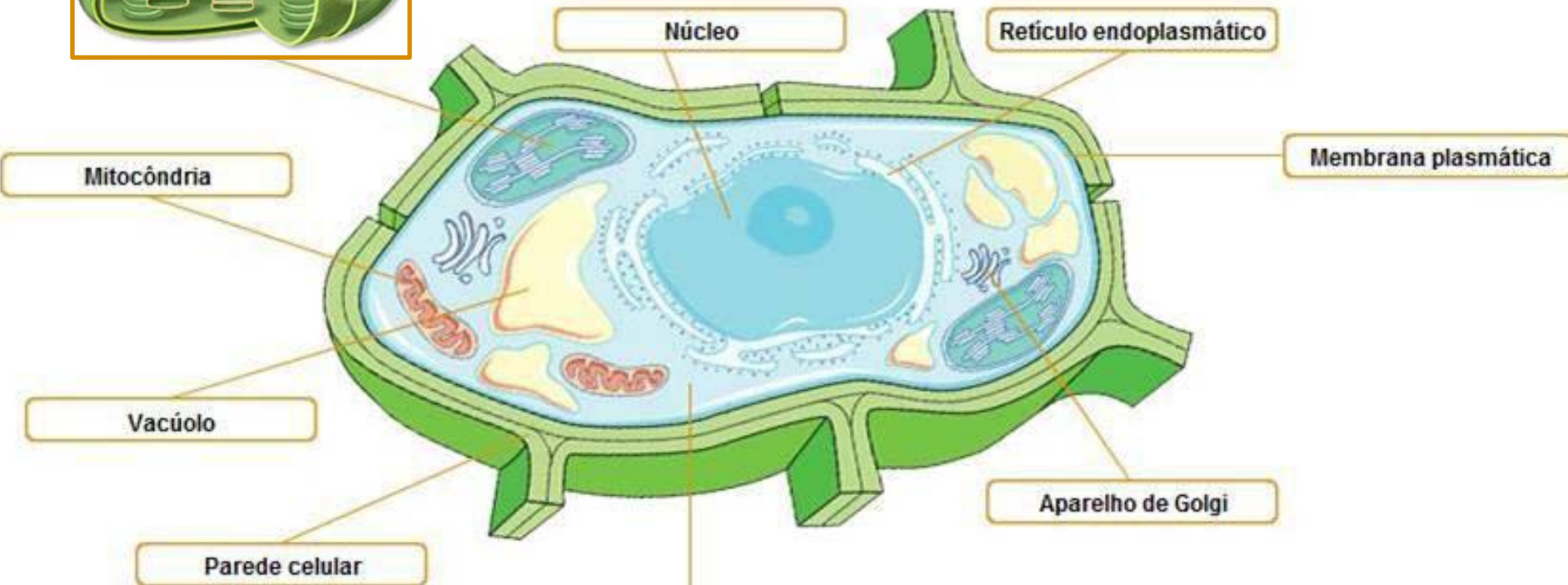


**CAROTENOIDES**

**RUTA DOXP/MEP**  
(Monoterpenos,  
diterpenos,  
carotenoides)



**CÉLULA VEGETAL**

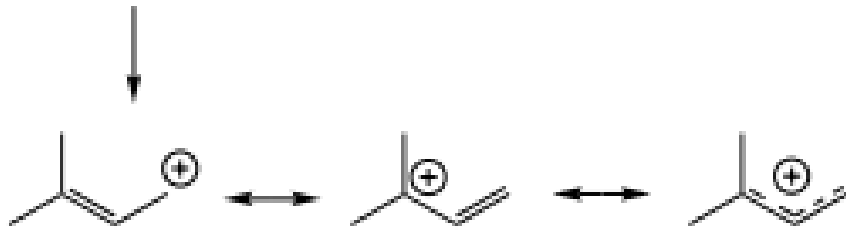


**CITOPLASMA**  
**RUTA MEV**  
(Triterpenos,  
politerpenos)

COLA

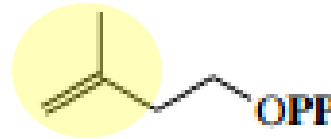


DMAPP

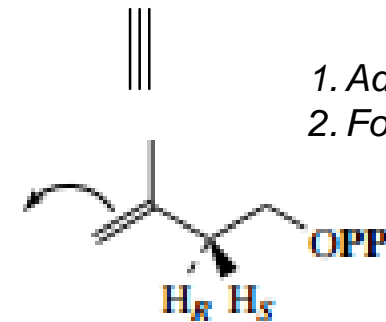


Catión alílico estabilizado por resonancia

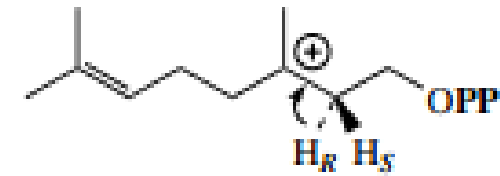
CABEZA



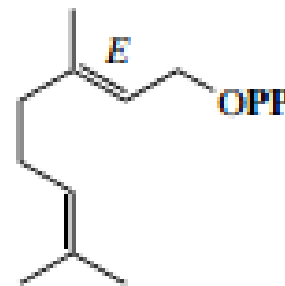
IPP



1. Adición electrofílica
2. Formación del catión terciario



Pérdida estereoespecífica de un protón

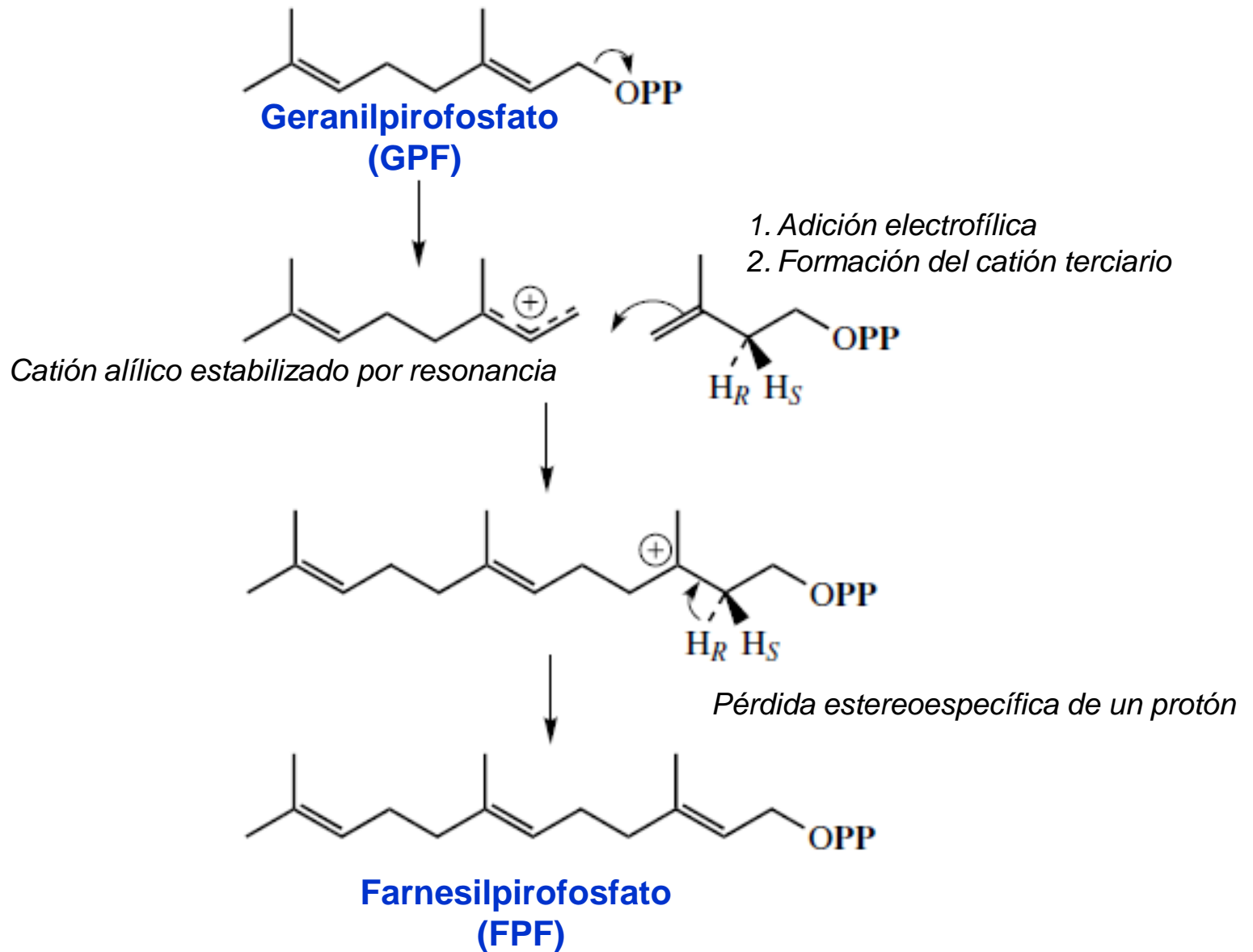


≡



Geranilpirofosfato (GPF)

Monoterpenos  
Sesquiterpenos  
Diterpenos  
Sesteterpenos  
Politerpenos



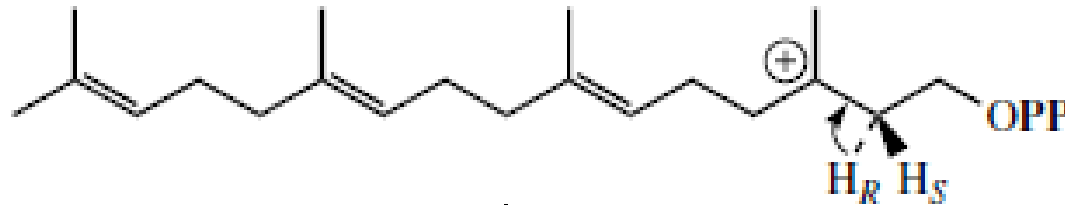


**Farnesilpirofosfato  
(FPF)**

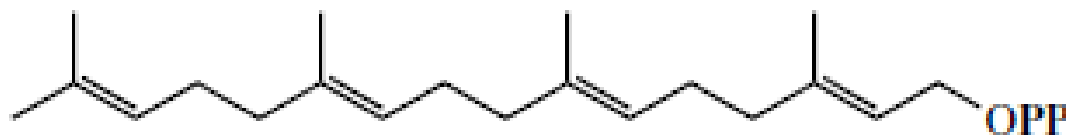


1. Adición electrofílica
2. Formación del catión terciario

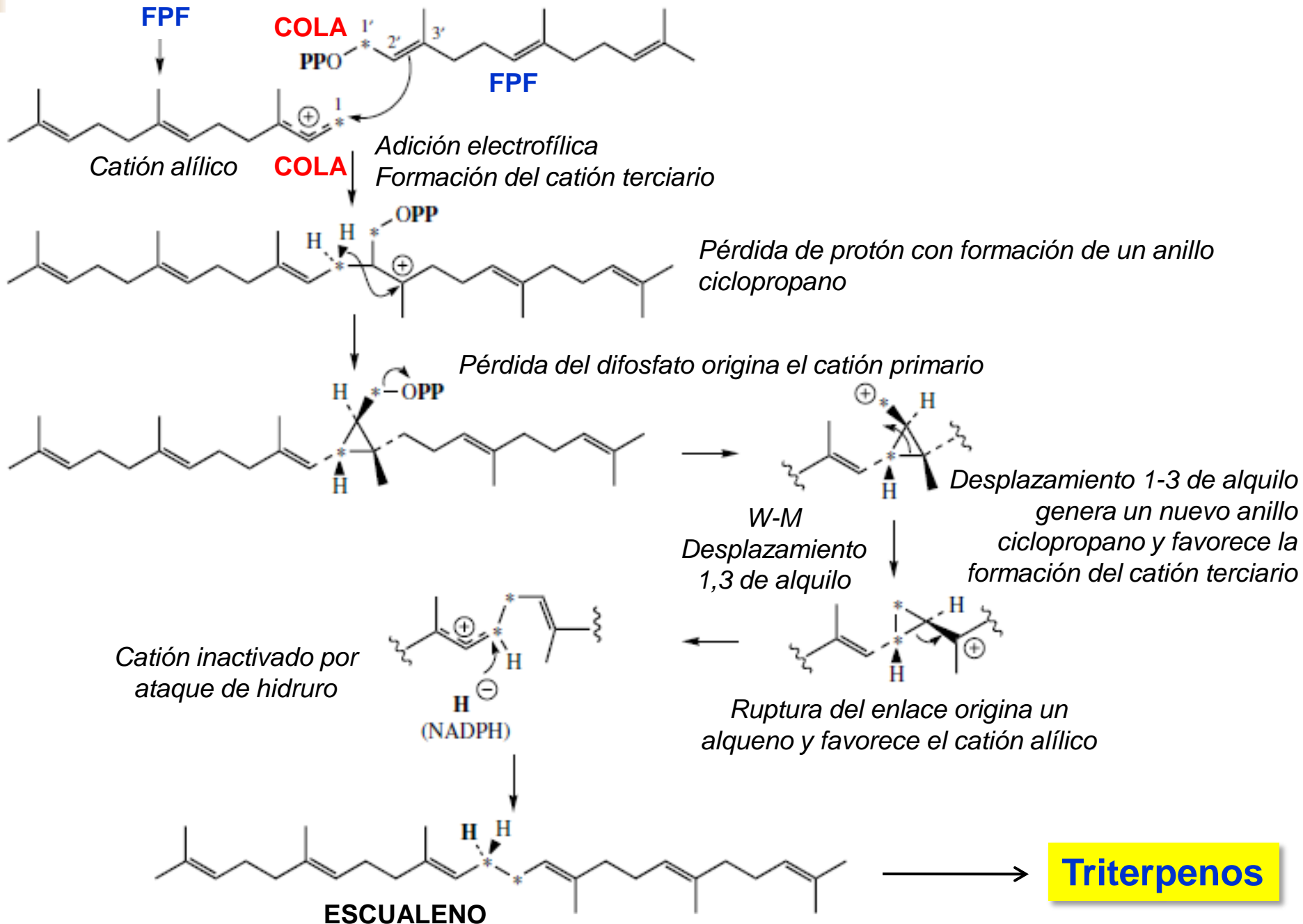
*Catión alílico estabilizado por resonancia*

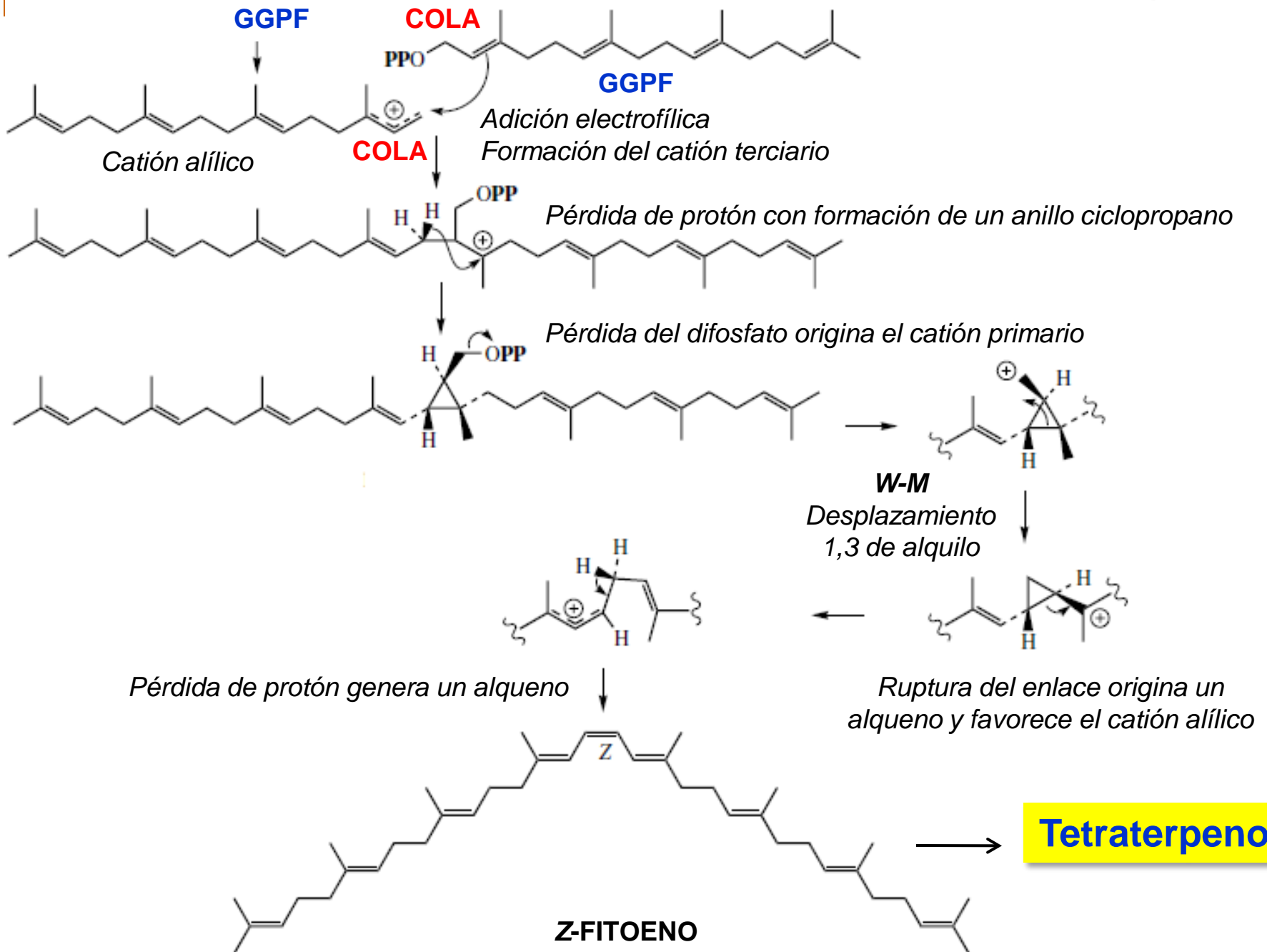


*Pérdida estereoespecífica de un protón*



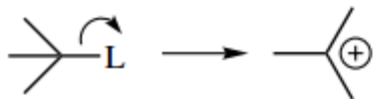
**Geranilgeranilpirofosfato  
(GGPF)**





# Reacciones características en la biosíntesis de terpenos

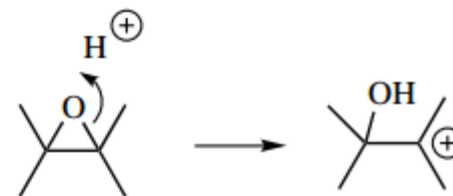
## Generación de carbocatión



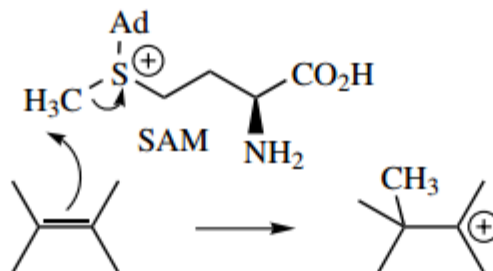
*Pérdida de un grupo saliente*



*Protonación de alquenos*

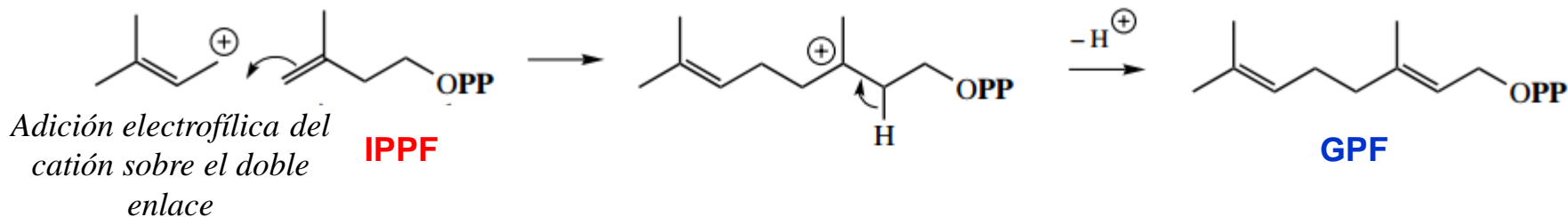


*Protonación y apertura del anillo del epóxido*



*Metilación de alqueno vía SAM*

## Adiciones inter- e intramolecular



*Intramolecular adición: ciclación*





# Reacciones características en la biosíntesis de terpenos

## Reordenamiento de Wagner- Meerwein

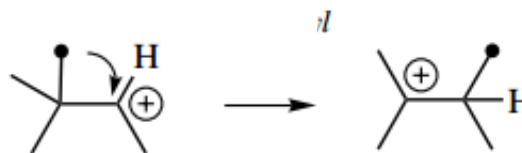
desplazamiento  
1,2- de hidruro



Carbocación  
secundario

Carbocación  
terciario

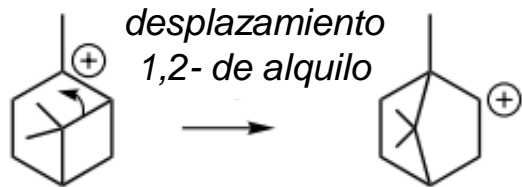
desplazamiento  
1,2- de metilo



Carbocación  
secundario

Carbocación  
terciario

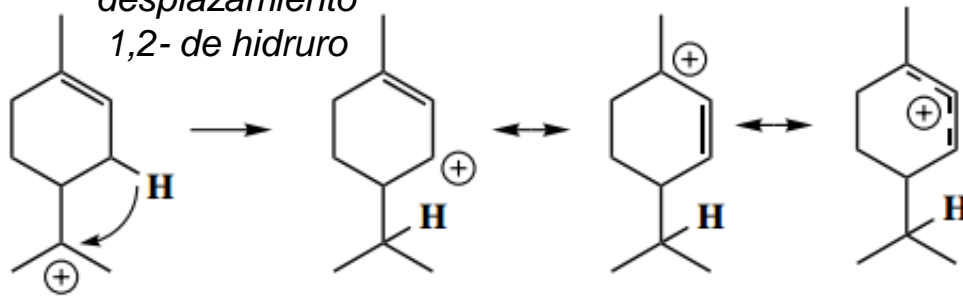
desplazamiento  
1,2- de alquilo



Carbocación terciario,  
pero anillo tenso de  
cuatro miembro

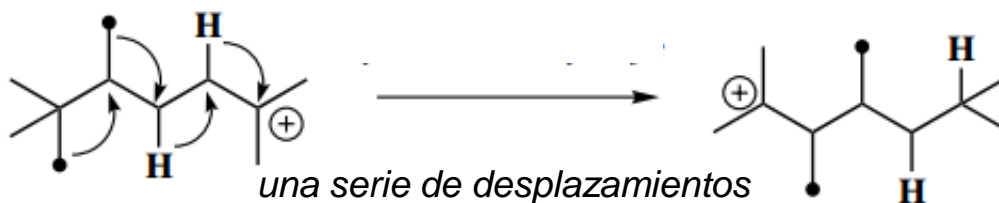
Carbocación secundario,  
pero la tensión del anillo  
reducida en el anillo de  
cinco miembro

desplazamiento  
1,2- de hidruro



Carbocación  
terciario

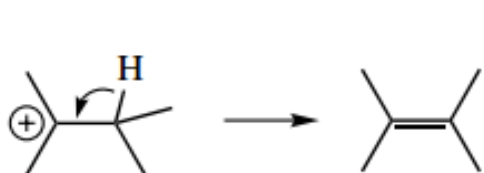
Cación alílico estabilizado  
por resonancia



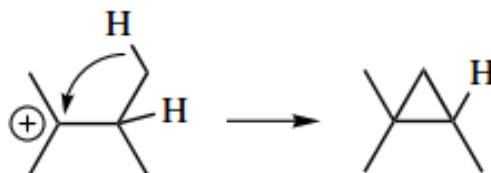
una serie de desplazamientos  
concertados 1,2 de hidruro y metilo

# Reacciones características en la biosíntesis de terpenos

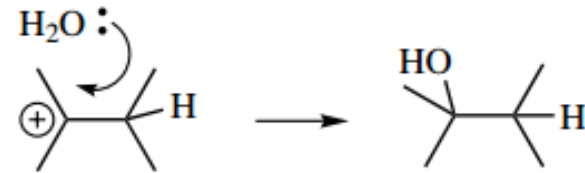
## Descarga del carbocatión



*Pérdida de protón*

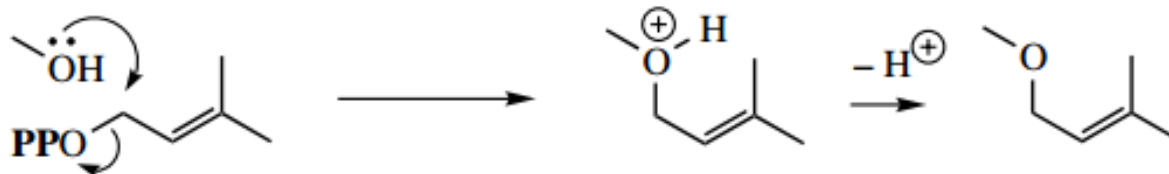


*Ciclación / Pérdida de protón*



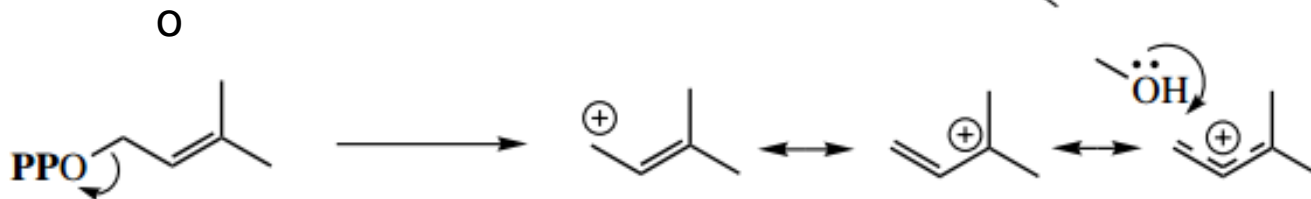
*Adición de agua,  
formación de alcoholes*

## O- Alquilación

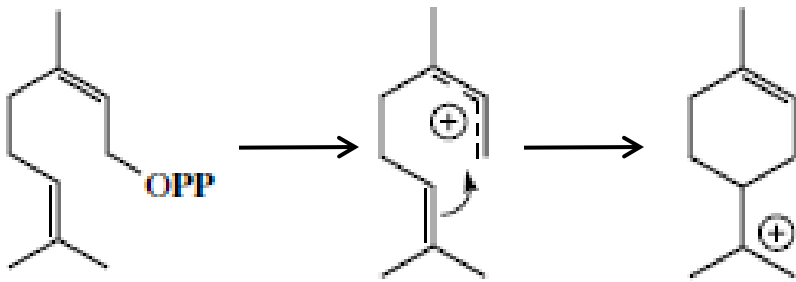


**DMAPF**

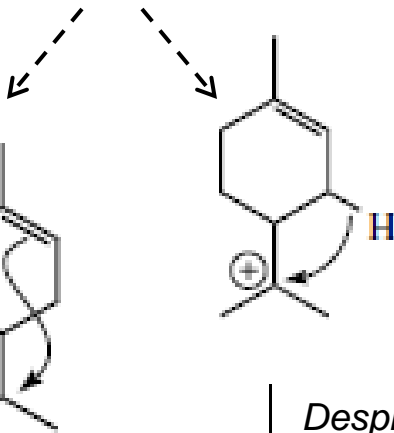
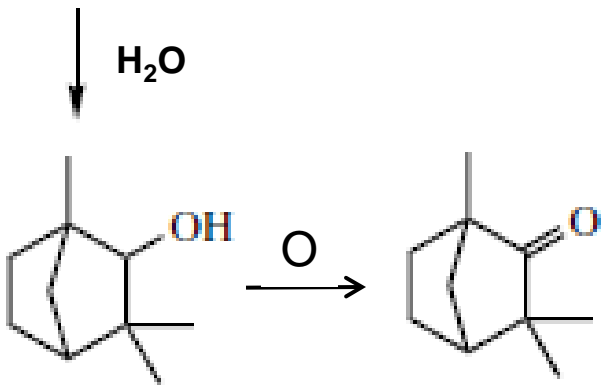
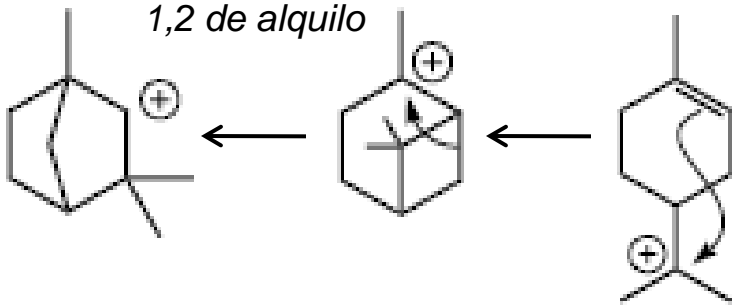
*difosfato es un  
buen grupo  
saliente*



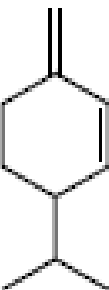
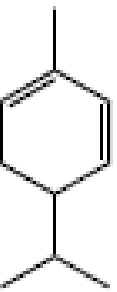
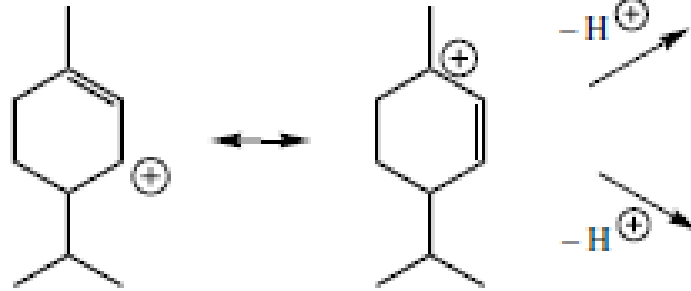
*Carbocatión  
estabilizado por  
resonancia*



**W-M**  
Desplazamiento  
1,2 de alquilo



**W-M**  
Desplazamiento  
1,3 de hidruro

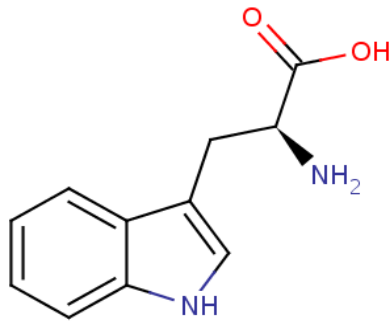


# Biosíntesis de Alcaloides

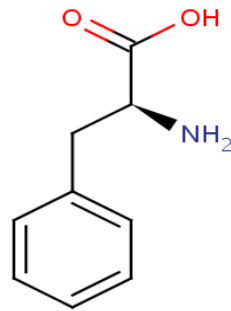
## Aminoácidos precursores

- L-Triptófano
  - L-Tirosina
  - L-Lisina
  - Ácido antranílico
  - L-Histidina
  - L-Ornitina
  - L-Lisina
  - Ácido nicotínico
- Aminoácidos aromáticos
- (Aminoácido básico)
- Aminoácidos alifáticos básicos

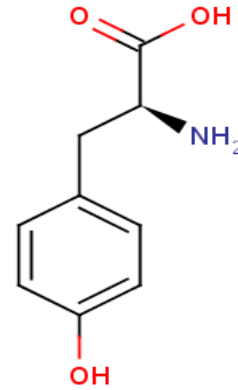
# Aminoácidos precursores de los alcaloides



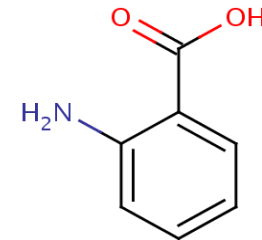
**L-Triptófano**



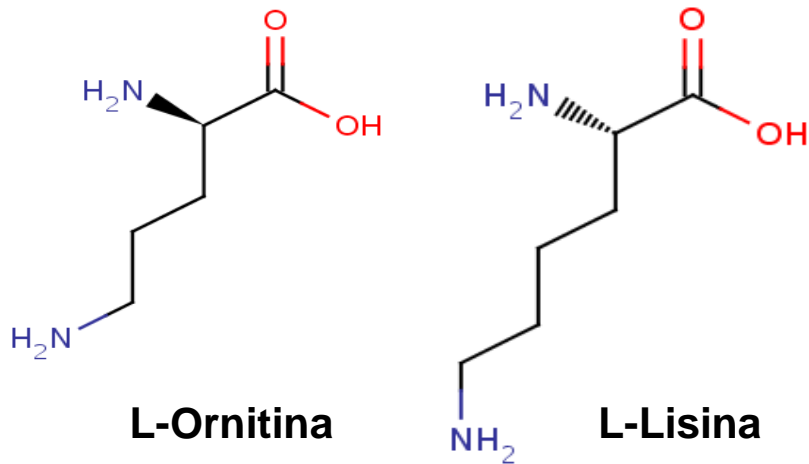
**L-Fenilalanina**



**L-Tirosina**

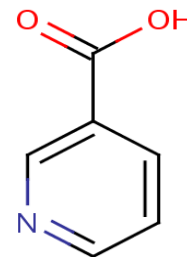


**Ácido antranílico**

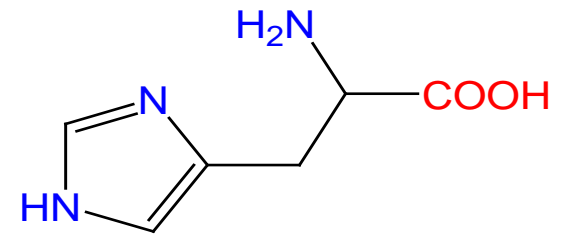


**L-Ornitina**

**L-Lisina**



**Ácido nicotínico**



**Histidina**

Triptófano

Tirosina

Fenilalanina

Antranilato

Ácido nicotínico

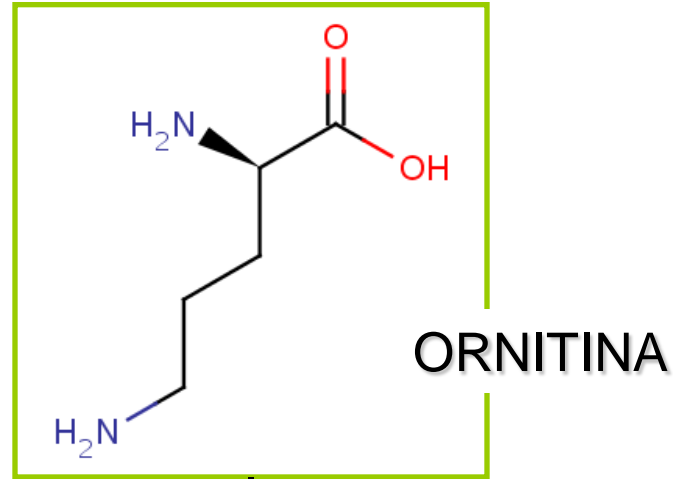
Ornitina

Lisina

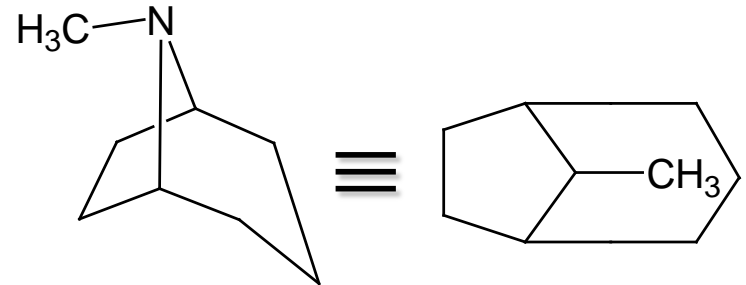
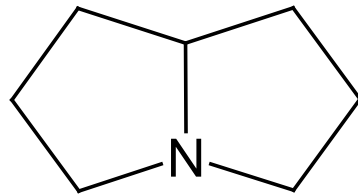
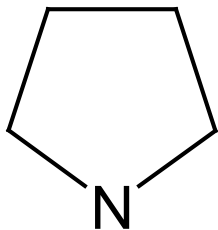
Condensación de  
aminoácidos alifáticos

Histidina

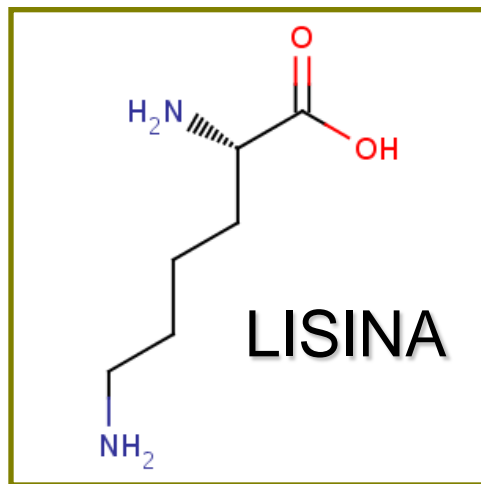
# Alcaloides derivados de la L-Ornitina



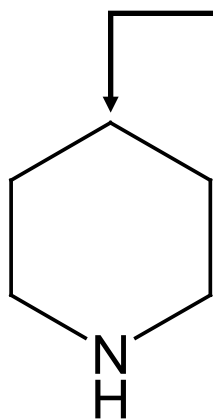
## NÚCLEOS BÁSICOS



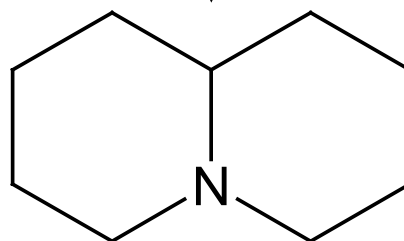
# Alcaloides derivados de la L-Lisina



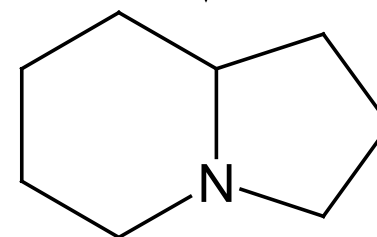
## NÚCLEOS BÁSICOS



PIPERIDINA



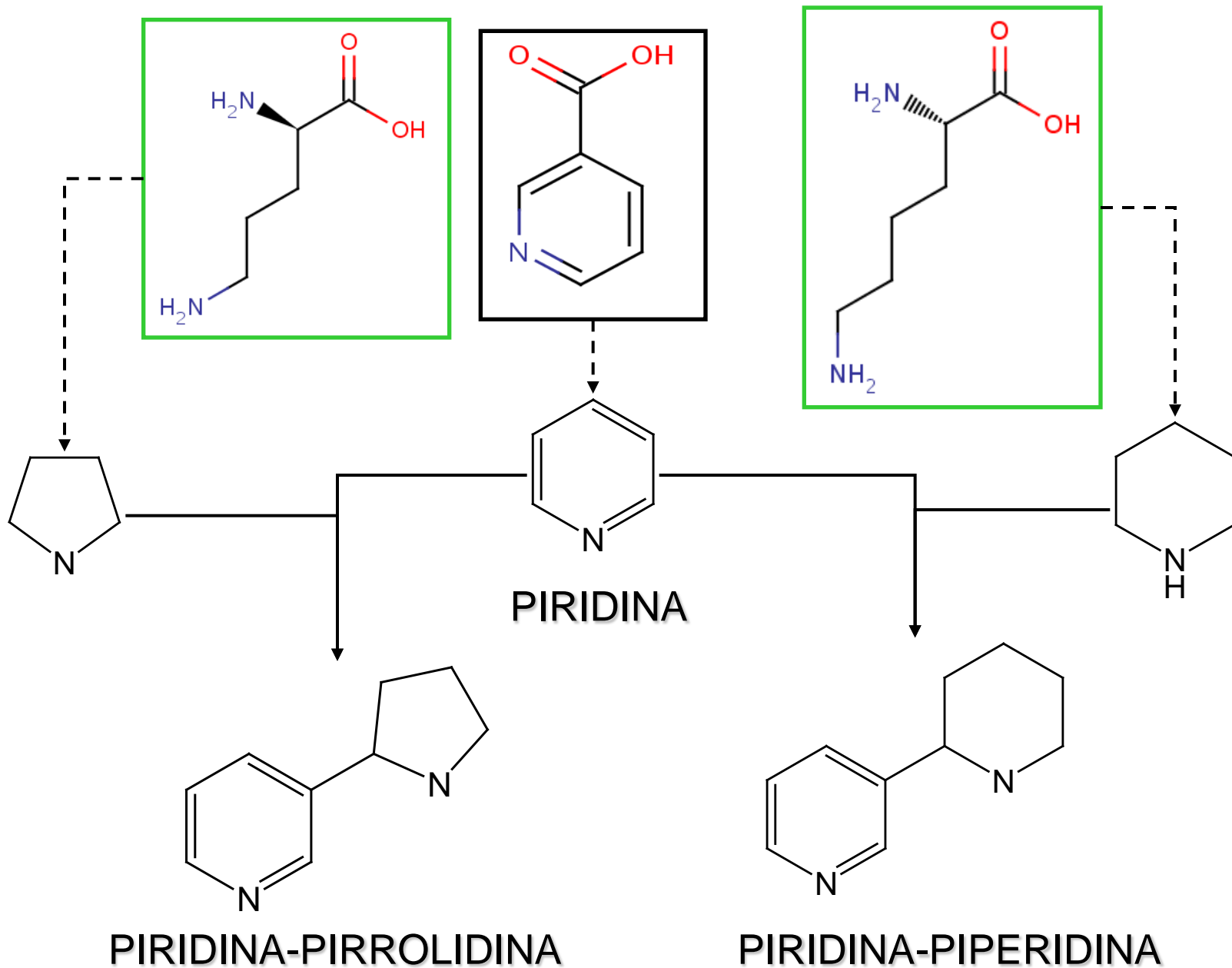
QUINOLIZIDINA



INDOLIZIDINA



# Alcaloides derivados del Ácido Nicotínico-L-Ornitina/-L-Lisina





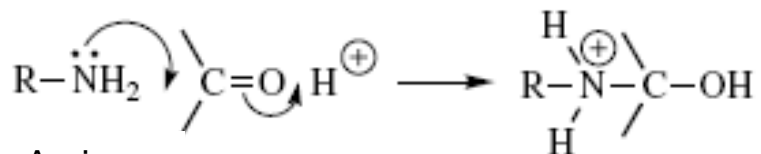
# Reacciones características de la biosíntesis de alcaloides

- Formación de Base de Schiff
- Condensación de Mannich
- Condensación aldólica entre grupos iminos

# Reacciones características de la biosíntesis de alcaloides

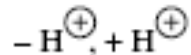
## Formación de Base de Schiff

*Ataque nucleofílico sobre el carbonilo*

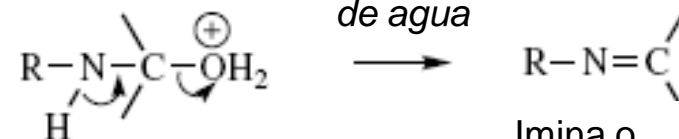


Amina primaria

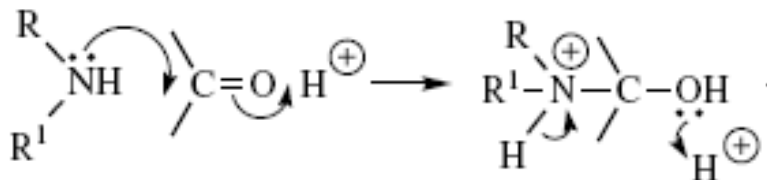
*Equilibrio entre especies, protón puede estar sobre el N ó sobre el O*



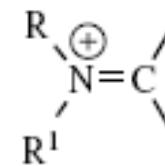
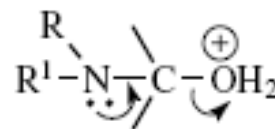
*Eliminación de agua*



Imina o Base de Schiff



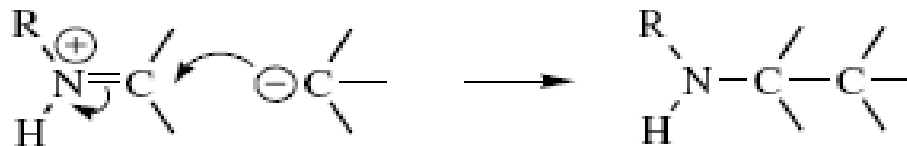
Amina secundaria



Base de Schiff cuaternaria

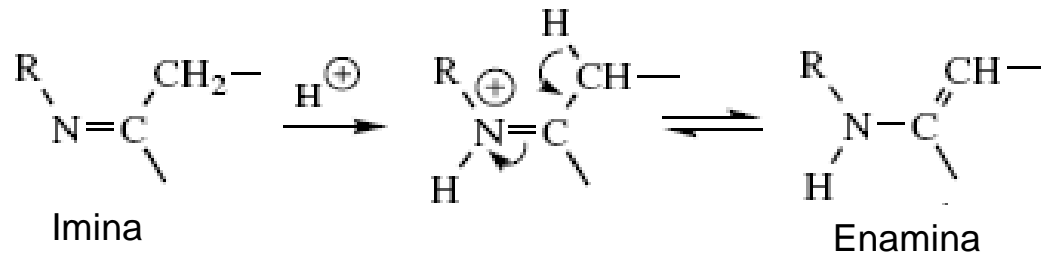
## Condensación de Mannich

*Adición nucleofílica sobre el ion iminium*

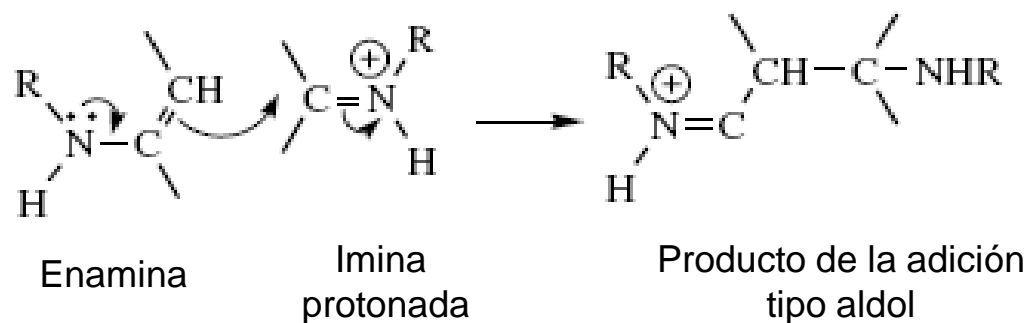


Ion iminium Nucleófilo tipo carbanión (ion enolato)

## Condensación aldólica entre grupos iminos

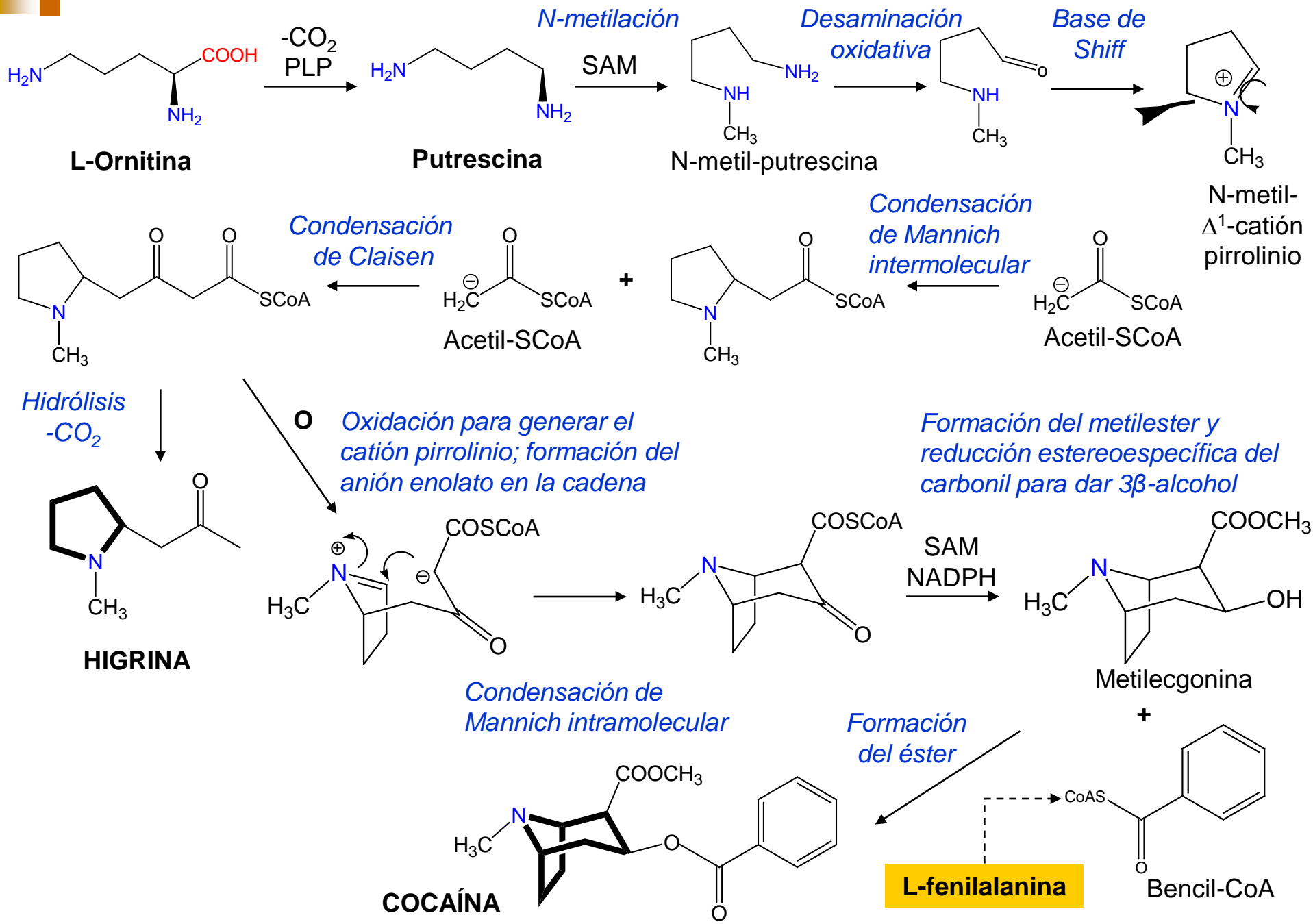


*Tautamerismo imina-enamina*

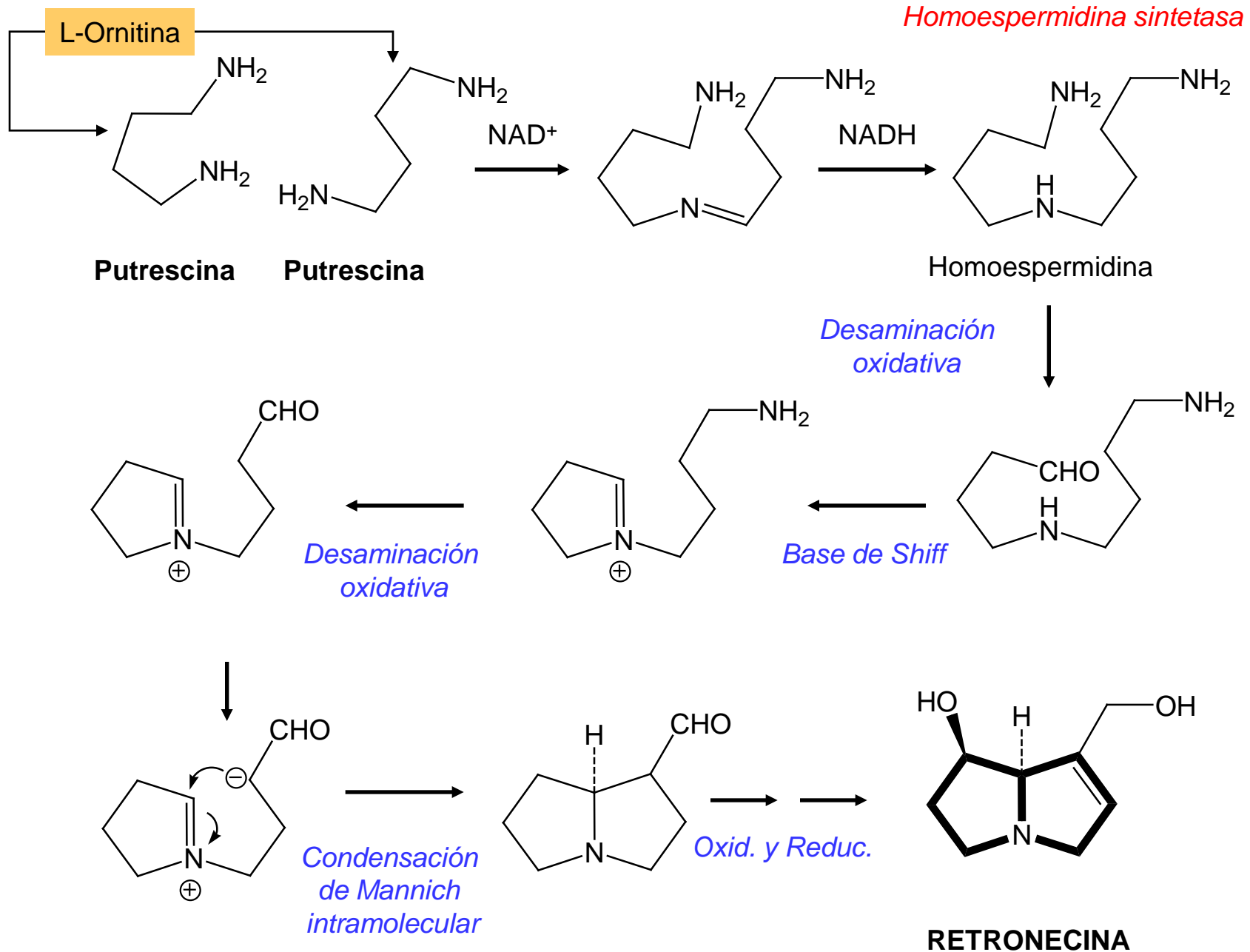


*Reacción tipo aldol entre dos sistemas de iminas*

# Alcaloides derivados de la L-ornitina

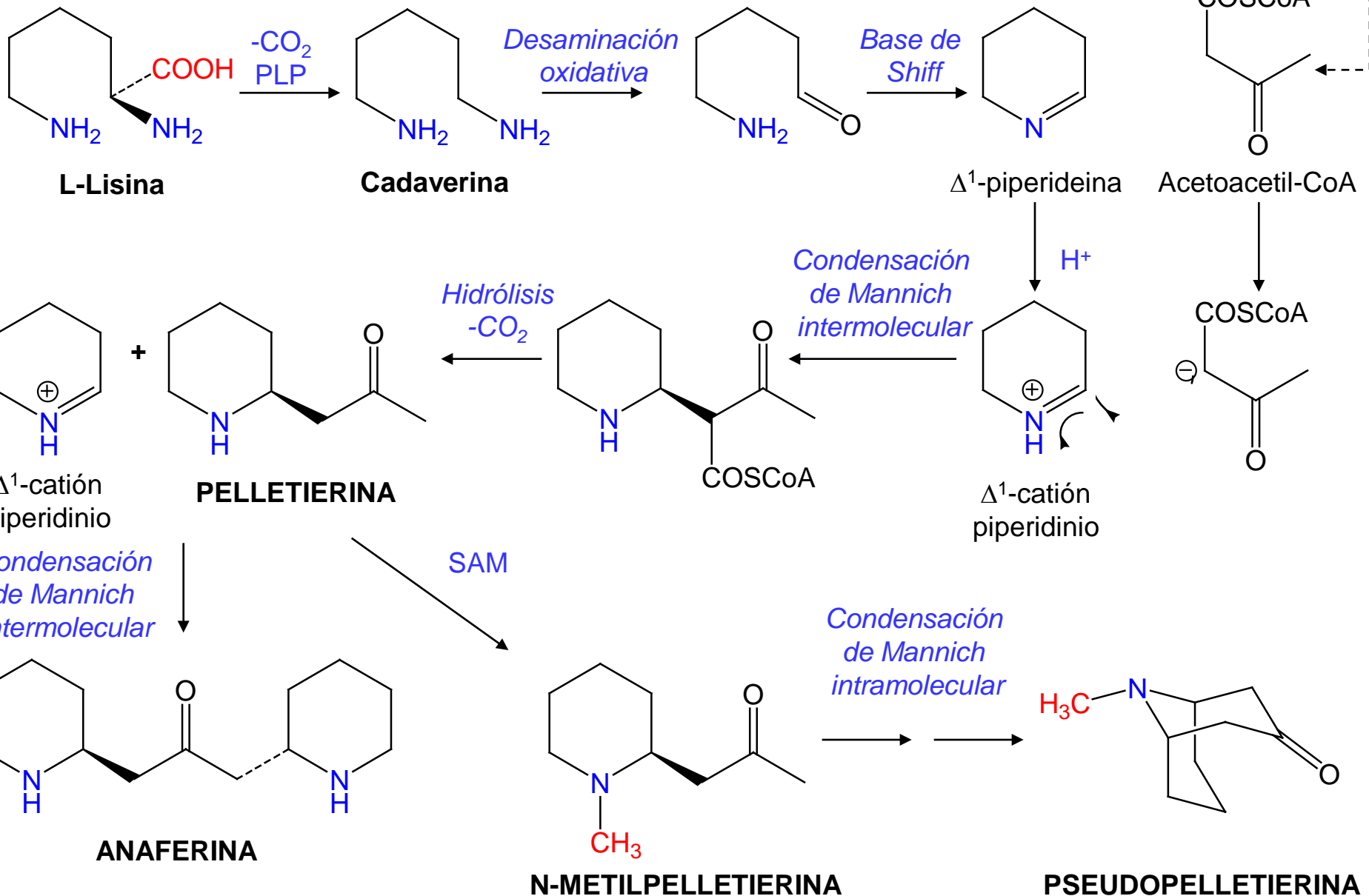


# Alcaloides derivados de la L-ornitina

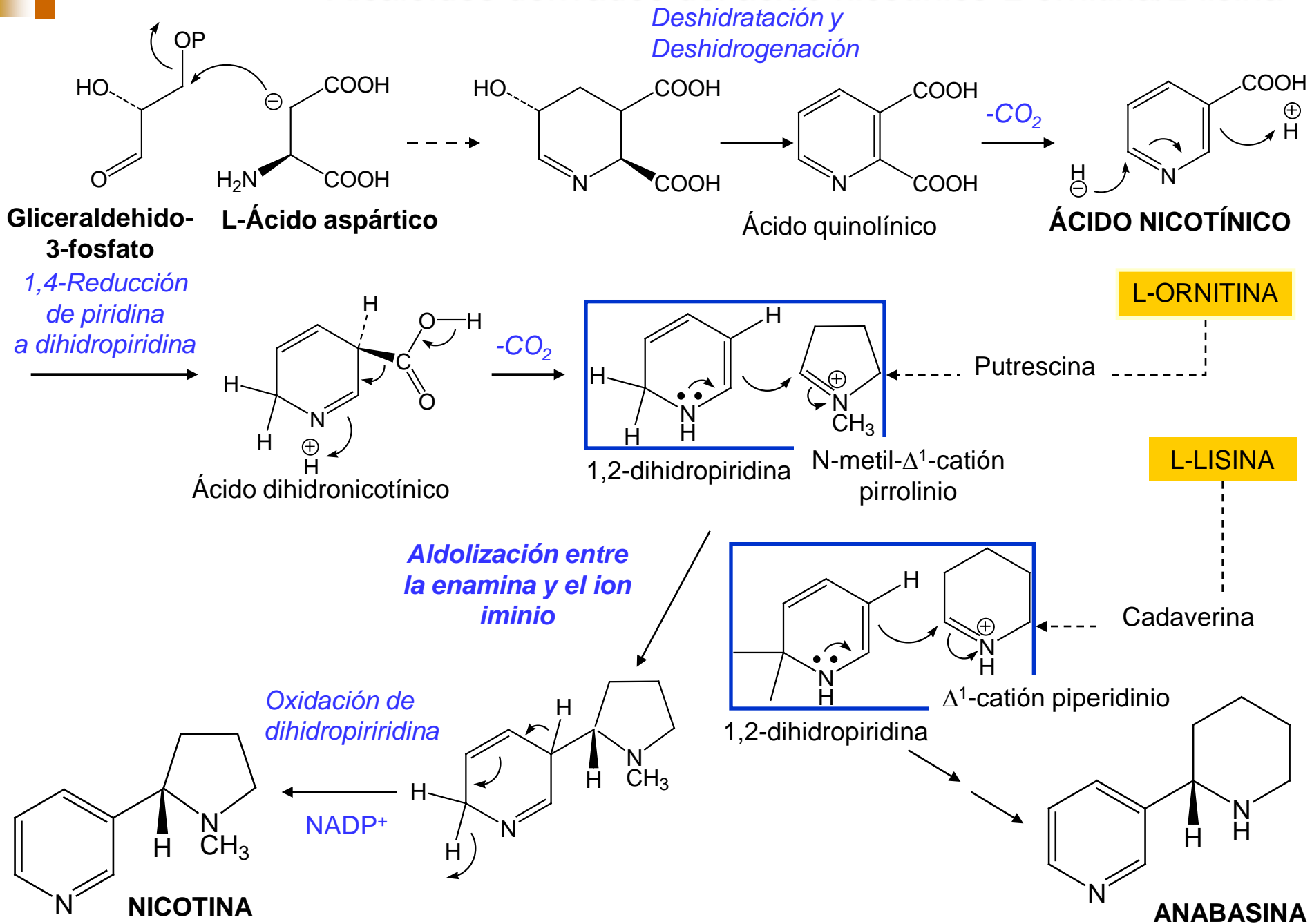


# Alcaloides derivados de la L-lisina

2 x Acetil-CoA

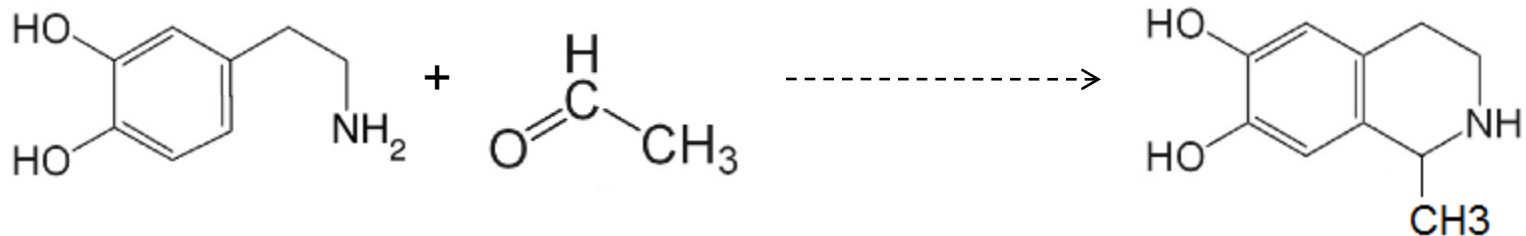


# Alcaloides derivados del ácido nicotínico-L-ornitina/L-lisina

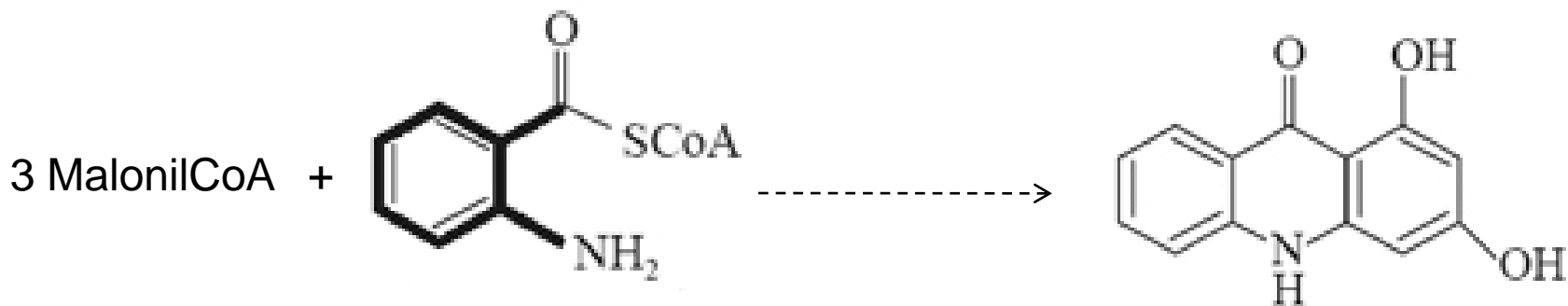




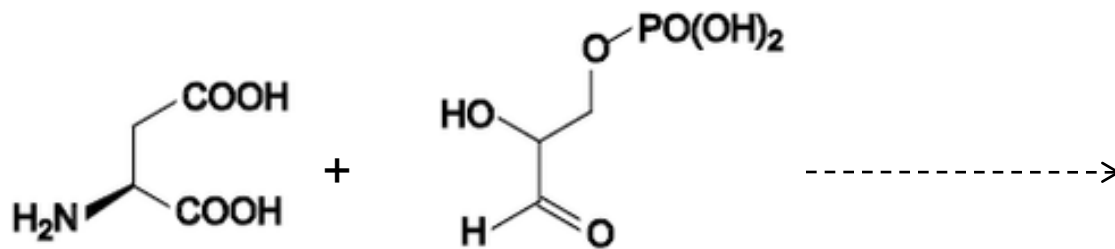
Sugiera una ruta biosintética razonable para los compuestos 1-3 a partir de sus precursores inmediatos.



1



2



3