

تفريغ عقاقير



اسم الموضوع: Mevalonic acid pathway

إعداد الصيدلاني / أ.ع: Alaa Otoum

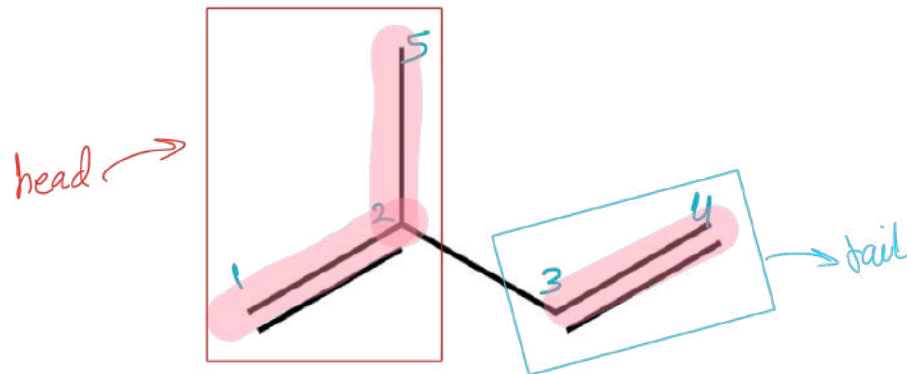


لجان الدفوعات

Terpenes:

الها يتجيبے من
Isoprene unit

- Large structurally diverse family of natural products >370000
- Limited medicinal uses
- Most important: plants which contain volatile oils
- Formed from C5 isoprene units joined together: the fundamental building block for terpenes.
- C4 chain with methyl-substituted C2 (C5).
- - Double bonds between C1=C2 and C3=C4



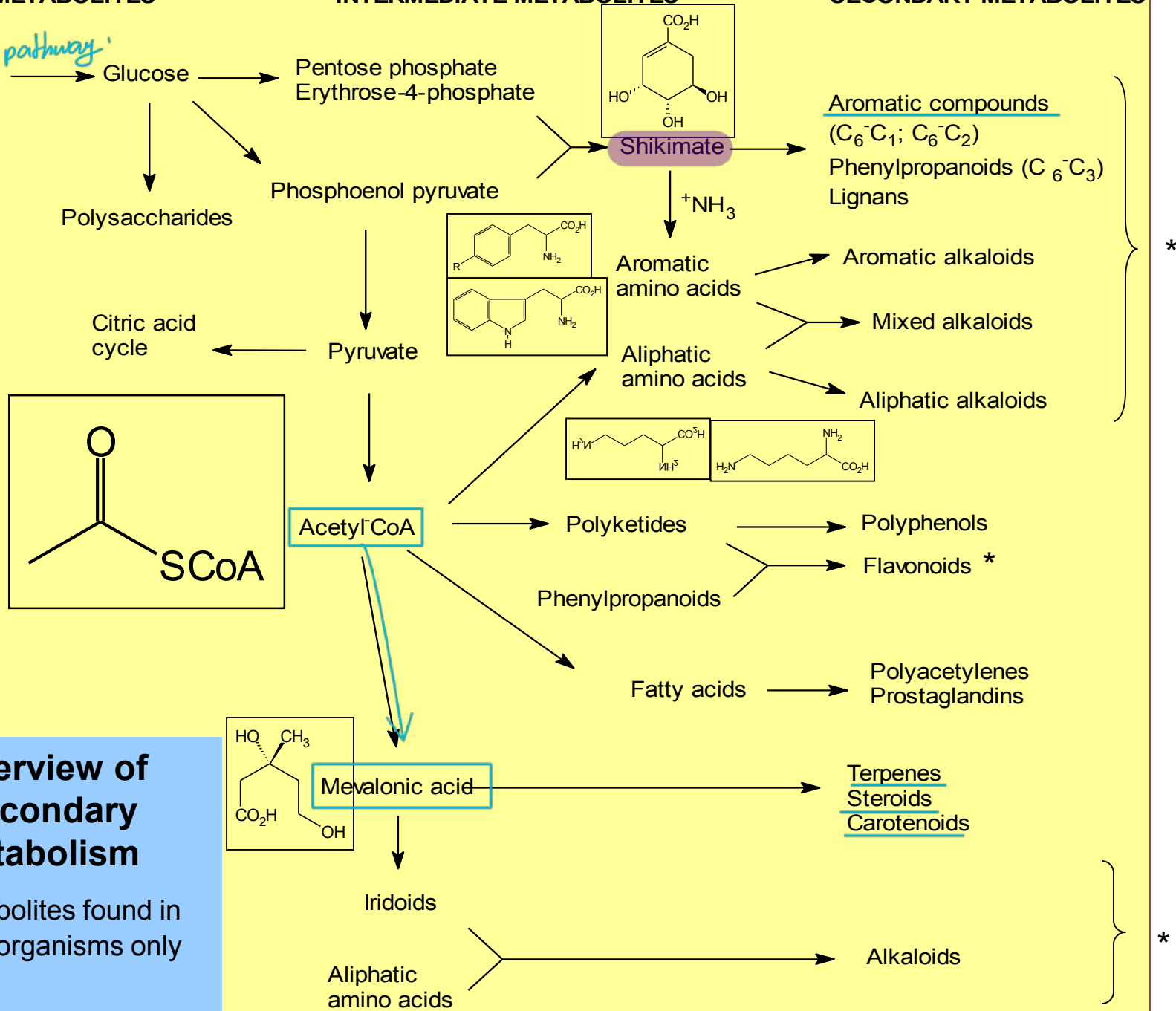
C5 isoprene

PRIMARY METABOLITES

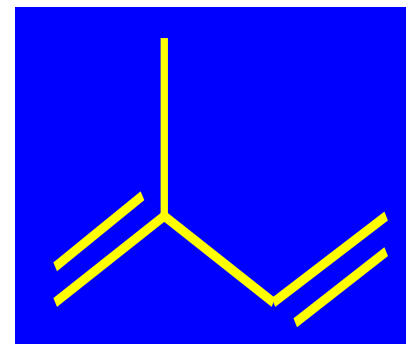
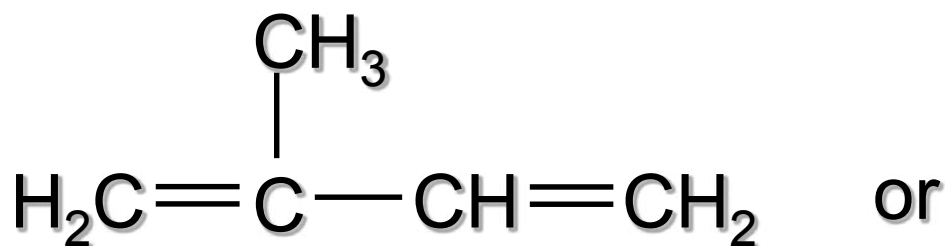
INTERMEDIATE METABOLITES

SECONDARY METABOLITES

shikimic acid pathway
 $\text{CO}_2 + \text{H}_2\text{O} \rightarrow$



Terpenes are natural products that are structurally related to isoprene.



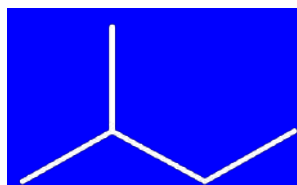
Isoprene

الاسم العلمي فقط

(2-methyl-1,3-butadiene)

The Isoprene Unit

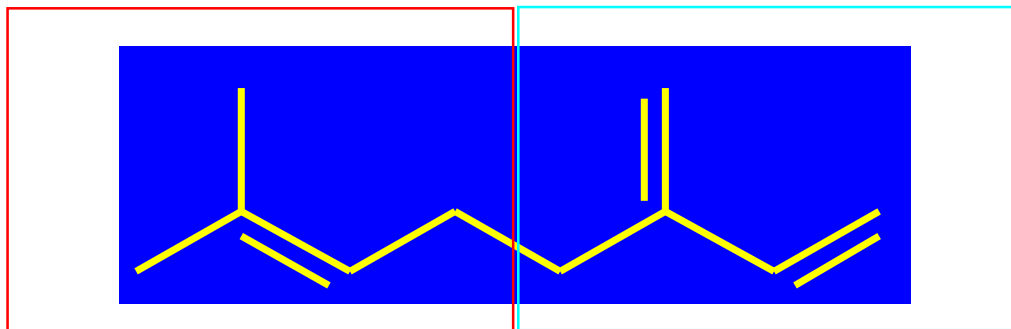
An isoprene unit is the carbon skeleton of isoprene (ignoring the double bonds)



Myrcene contains two isoprene units.

isoprene + isoprene.

معروف بـ حمزة الطيب .

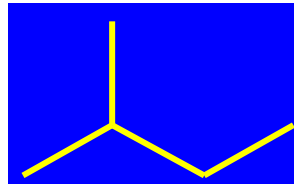


The Isoprene Unit

The isoprene units of myrcene are joined "head-to-tail."

رأس السلسلة الأولى، ح يرتبط مع ذيل السلسلة الثانية أو رأس السلسلة الثانية مع ذيل السلسلة الأولى
ما يعني أنه من 10 carbons

Head



Tail

Tail

Head



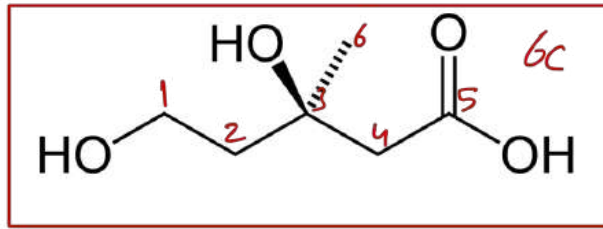
Terpenoidal compounds

- **Terpenoidal compounds** , a wide diverse group of compounds that shares the presence of the isoprene C₅ unit , upon this rule classifications are based , these classifications are:
- 1. Hemiterpenes C₅
- 2. Monoterpenes C₁₀ (also called terpenoids) 2 isoprene units
- 3. Sesquiterpenes C₁₅ 3 isoprene units
- 4. Diterpenes C₂₀
- 5. Sesterterpenes C₂₅
- 6. Triterpenes C₃₀ (steroids)
- 7. Tetraterpenes C₄₀ موصوفة باللون الأحمر في السندرة واللون البرتقالي في الجوز - مازيفرات -
- 8. Polyisoprenes
- The C₅ is present as a C₄ chain of carbons and hydrogens and the fifth carbon is present as a substituent or a group on carbon number 2.

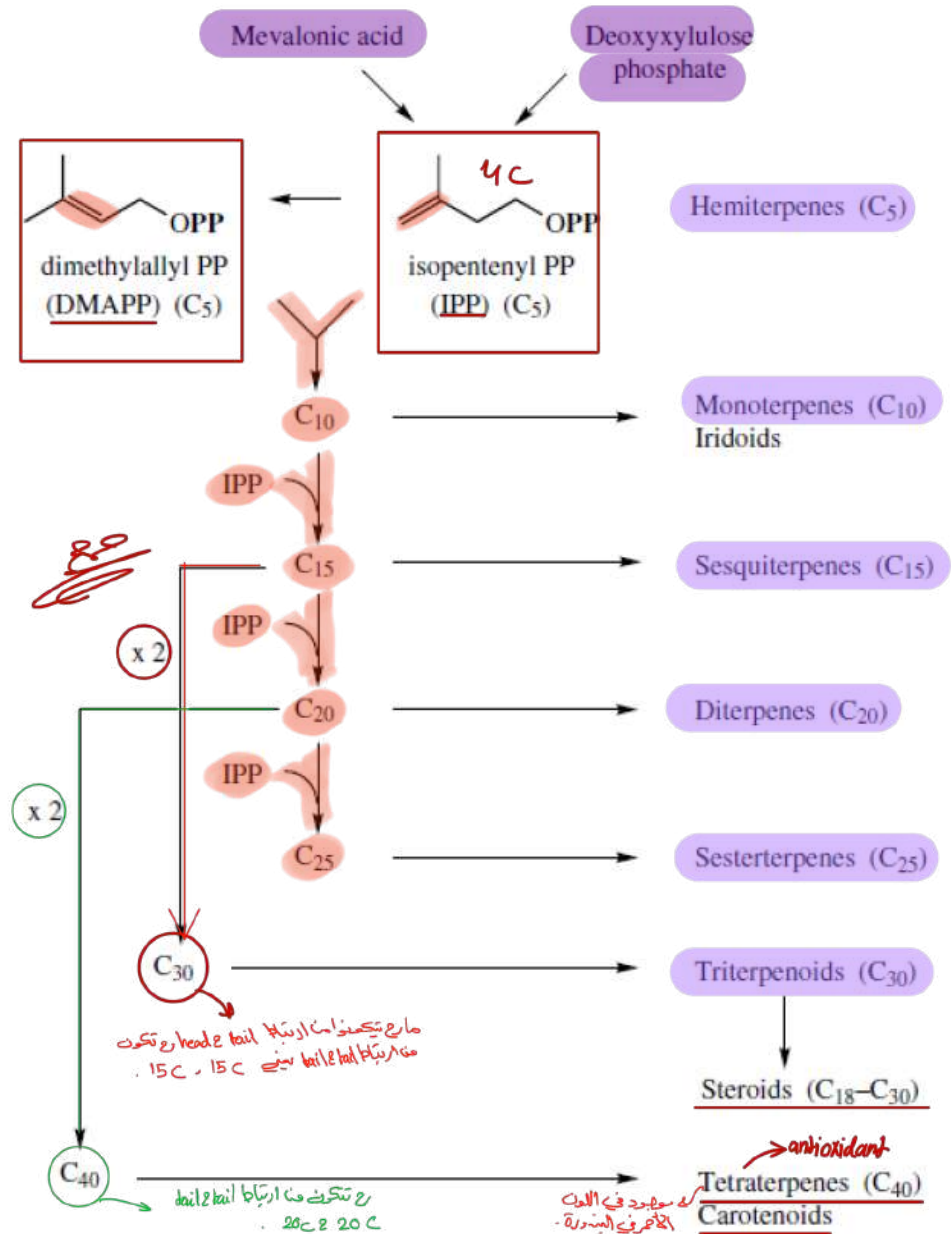
→ acetate mevalonic pathway
 من بين موجود في النبات هو أرضيا
 موجود في جسم الإنسان يصنع
 جسيما VD و cholesterol
 و cortisol

* يعني الاستخدام الذي يكون تصنيع الـ "acetate mevalonic pathway" عالي في جسمهم
 مع يكون الكوليسترول عالي عندهم

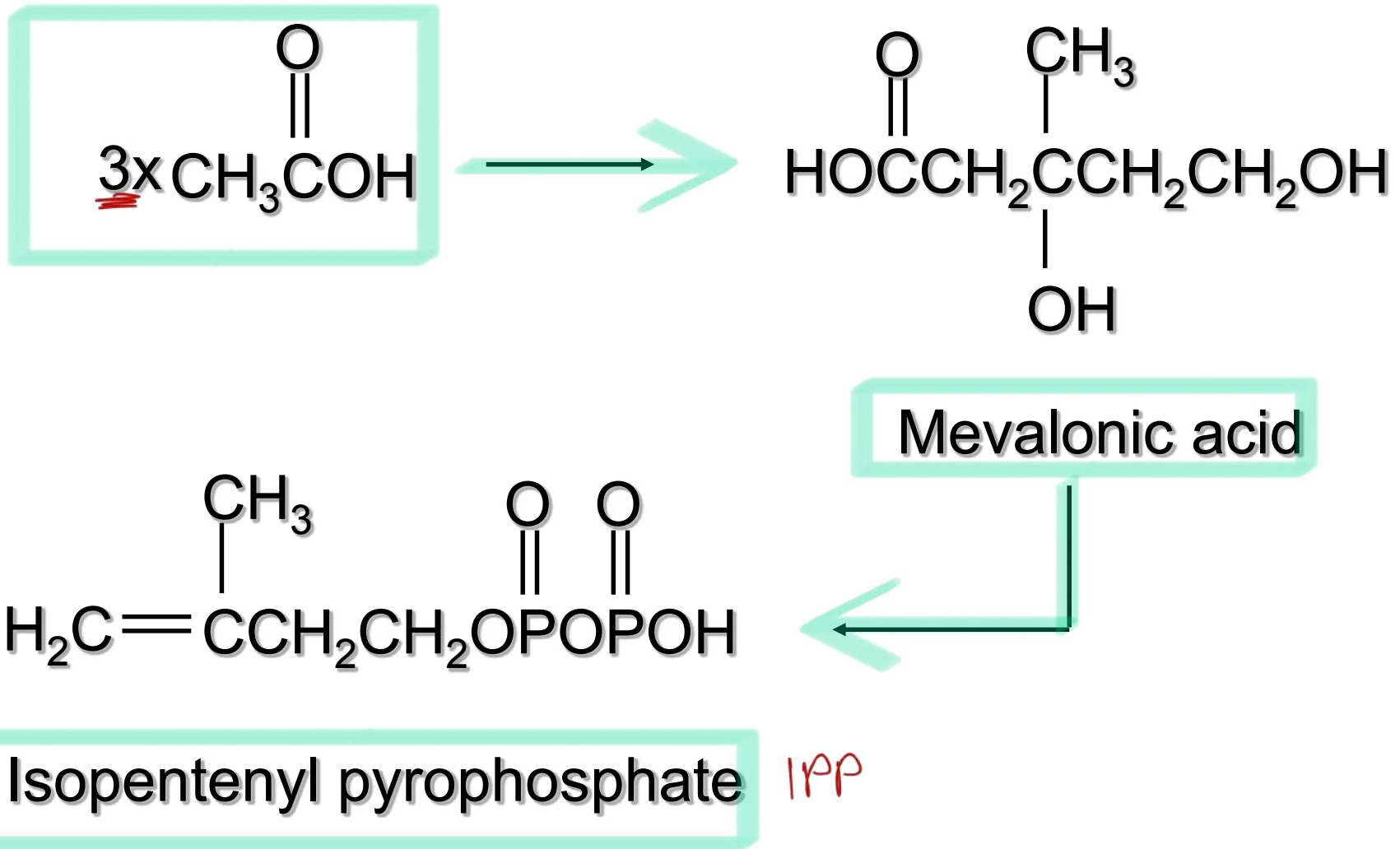
Mevalonic acid is an intermediate for isoprene units.
It is a product of acetate metabolism (in all living tissues cytosol)



لے لیں انہیں عنیدی نوعین سے ال isoprene لانے
لازم ہوں غنیہ بالی لکٹروناتے مردادہ فقیر بالی لکٹروناتے
- electrophile and nucleophile

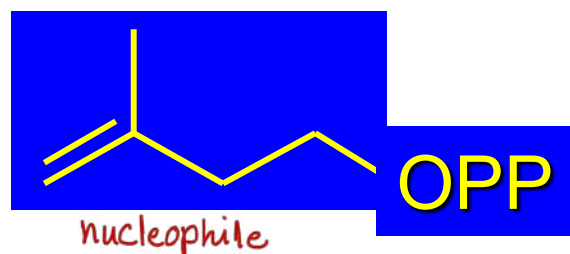


The Biological Isoprene Unit

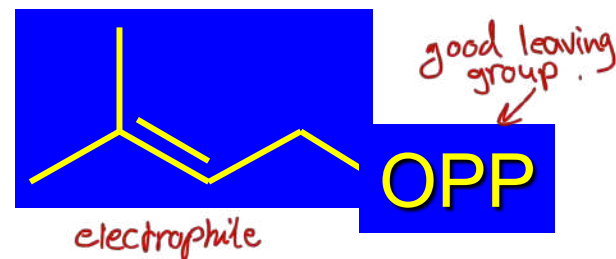
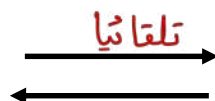


Isopentenyl and Dimethylallyl Pyrophosphate

Isopentenyl pyrophosphate is interconvertible with 2-methylallyl pyrophosphate.



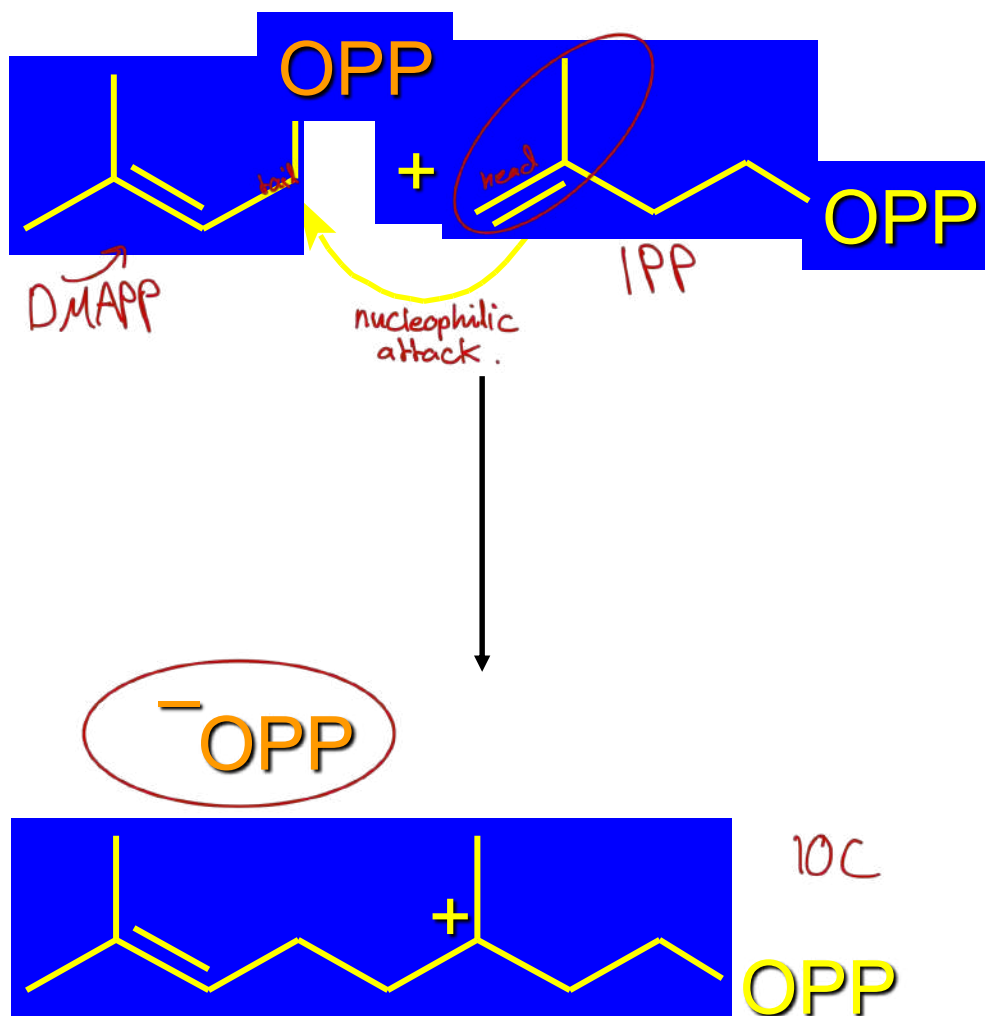
Isopentenyl pyrophosphate



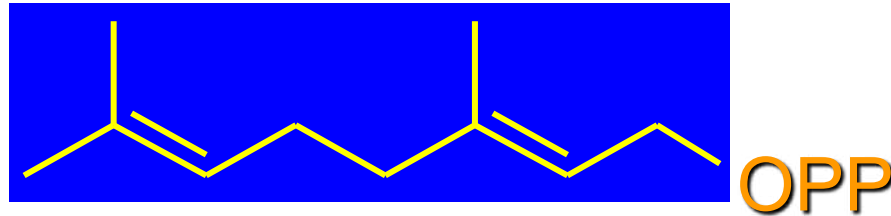
Dimethylallyl pyrophosphate

Dimethylallyl pyrophosphate has a leaving group (pyrophosphate) at an allylic carbon; it is reactive toward nucleophilic substitution at this position.

Carbon-Carbon Bond Formation



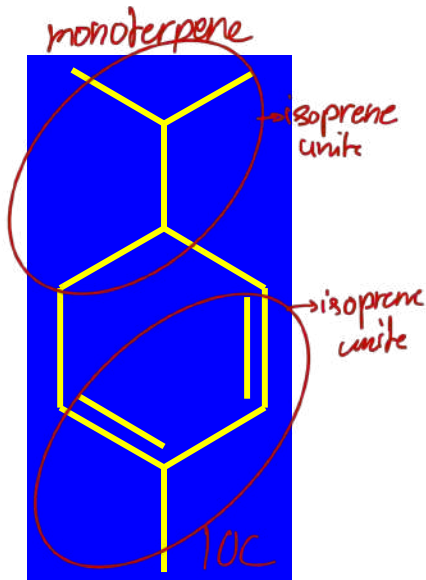
After C—C Bond Formation...



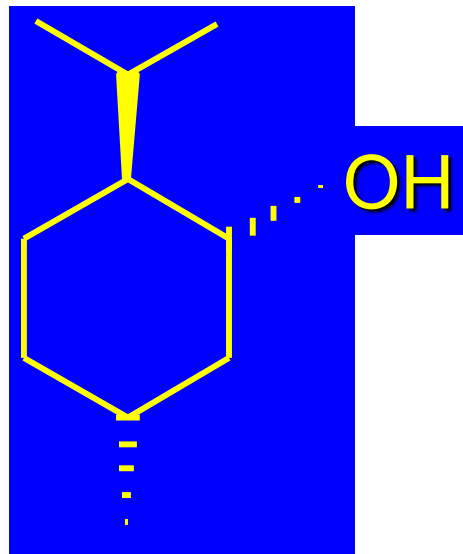
This compound is called geranyl pyrophosphate. It can undergo hydrolysis of its pyrophosphate to give

geraniol (rose oil). → acetate mevalonic pathway
التي يعطي الرائحة المميزة للورد .

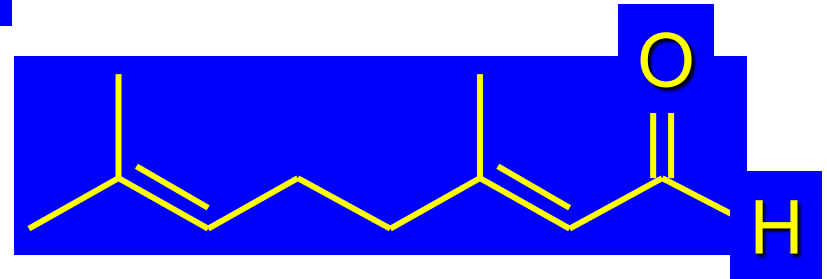
Representative Monoterpenes



α -Phellandrene
(eucalyptus)

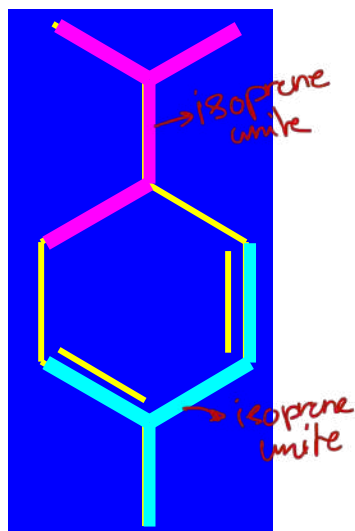


الرائحة المميزة في النعناع .
Menthol
(peppermint)

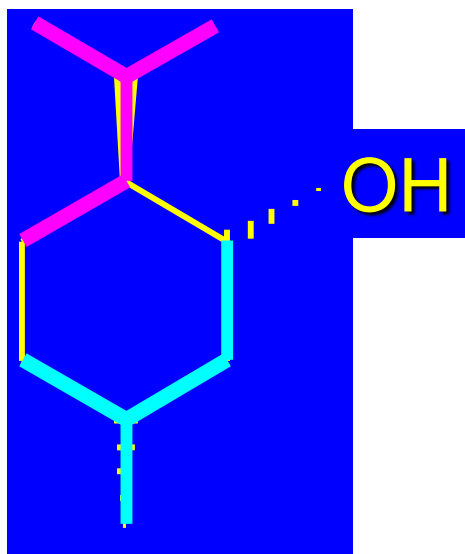


Citral $\rightarrow$ aldehyde
(lemon grass)

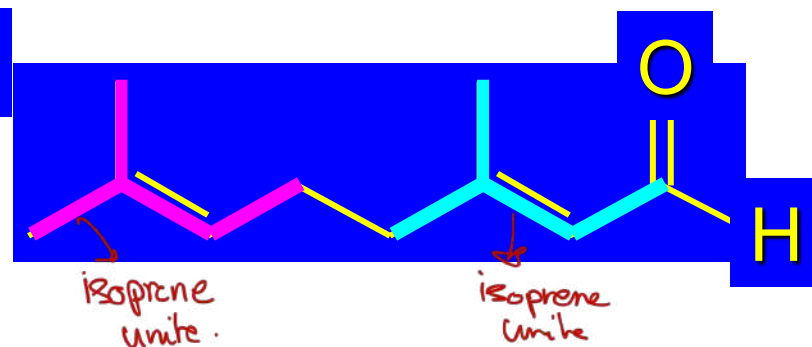
Representative Monoterpenes



α -Phellandrene
(eucalyptus)



Menthol
(peppermint)



Citral
(lemon grass)

Representative Monoterpenes



α -Phellandrene
(eucalyptus)



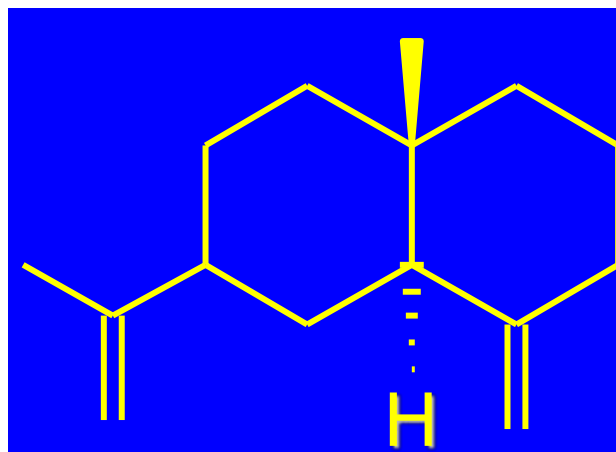
Menthol
(peppermint)



Citral
(lemon grass)

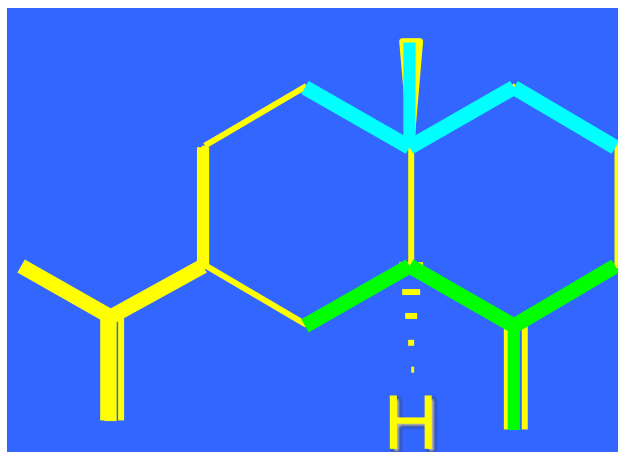
Representative Sesquiterpenes

↳ third isoprene unit.



α -Selinene
(celery)

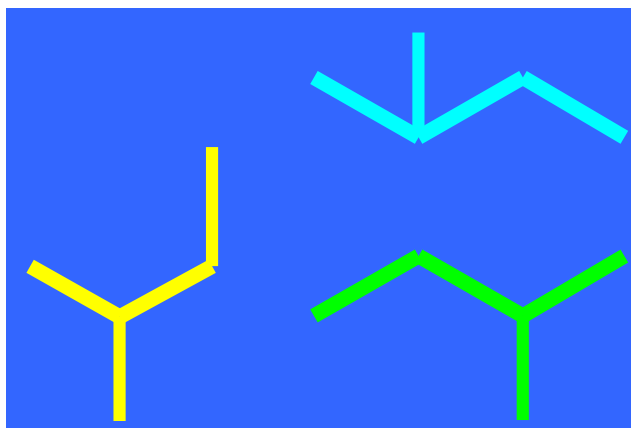
Representative Sesquiterpenes



α -Selinene

صعبدوني الشومر (celery)

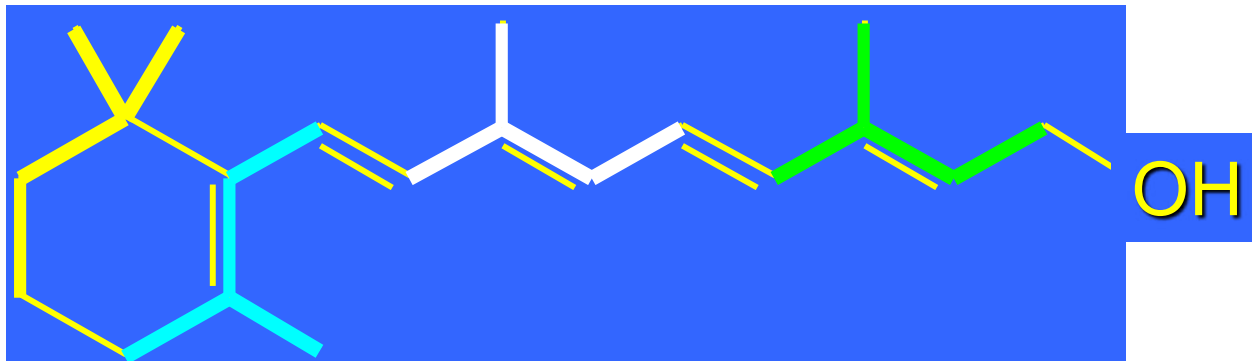
Representative Sesquiterpenes



α -Selinene
(celery)

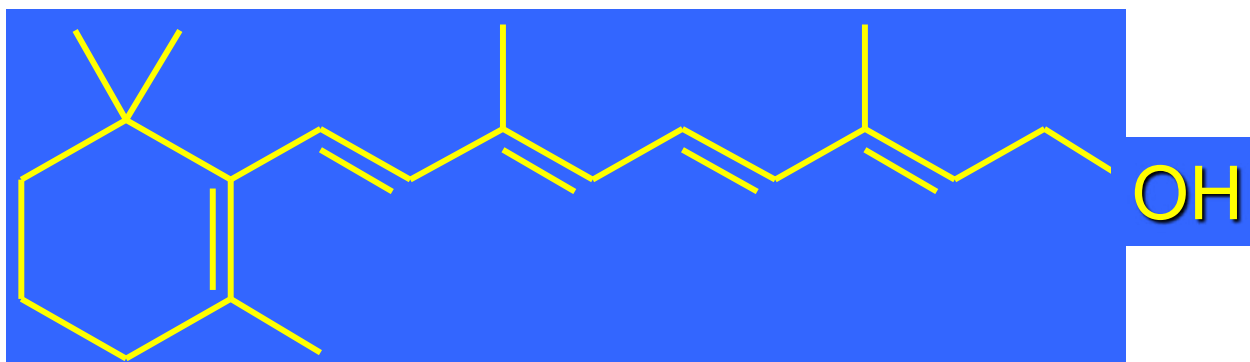
Representative Diterpenes

↳ 4 isoprene units.



Vitamin A

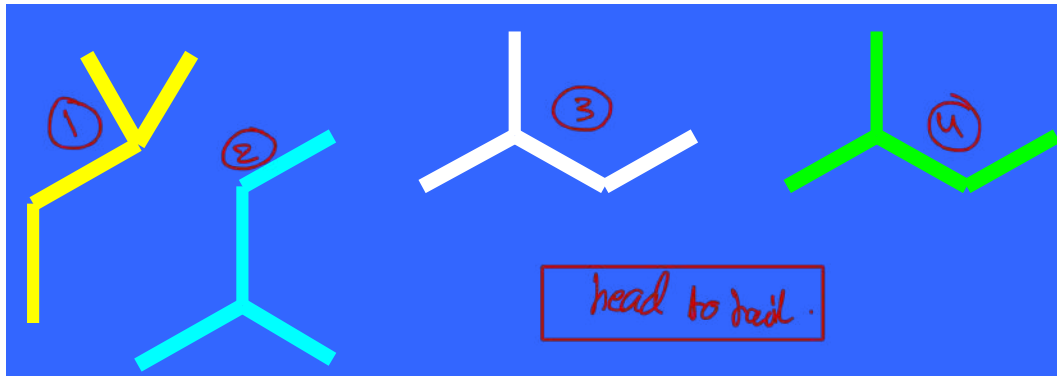
Representative Diterpenes



Vitamin A

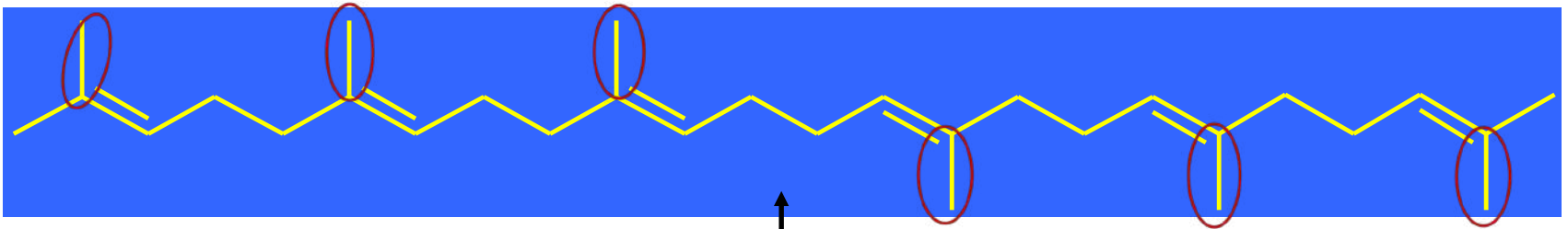
Representative Diterpenes $\rightarrow 20\text{C}$

سؤال سنوات Vitamin A diterpenes. ← من الأمثلة على

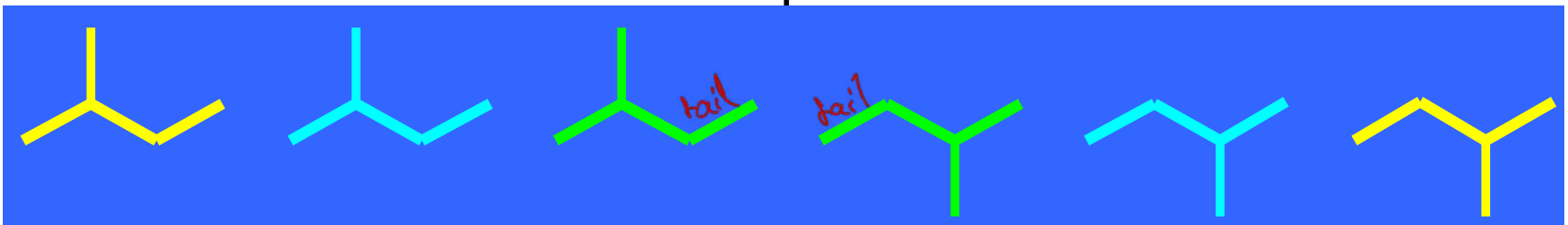


Vitamin A

Representative Triterpene



Tail-to-Tail linkage of isoprene units

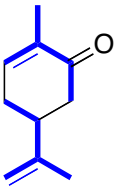


Squalene
(shark liver oil)

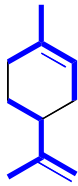
Terpenes: The Isoprene Rule. Isoprenoids- C_{10} (*terpenes*), C_{15} (*sesquiterpenes*) and C_{20} (*diterpenes*) plant; essential oils

C_{40} : terpenoids are derived from “isoprene units” (C_5)

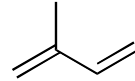
أصغر وحدة
التي تتكون منها
monoterpene



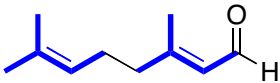
(+)-Carvone (caraway seeds)
(-)-Carvone (spearmint)



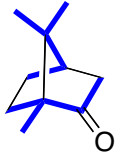
(+)-limonene (oranges)
(-)-limonene (lemons)



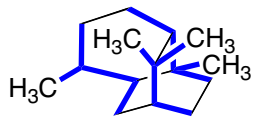
isoprene
(2-methyl-1,3-butadiene)



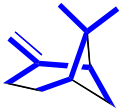
Citral
(lemon grass)



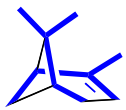
Camphor



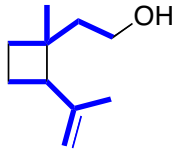
patchouli alcohol
(patchouli oil)



β -pinene



α -pinene



Grandisol

Joining of the isoprene units

- The joining of the isoprene units is either through head to tail or tail to tail fashion.
- If we have an N or O atom joining the units, it is no longer a terpenoid.
- In case of terpenoidal alkaloids or terpenoidal indole alkaloids, we call them terpenoidal because of presence of units of terpenes but we cannot classify them as terpenes.

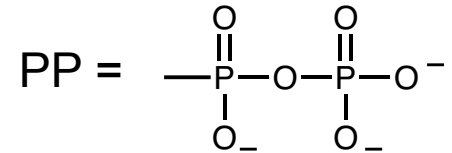
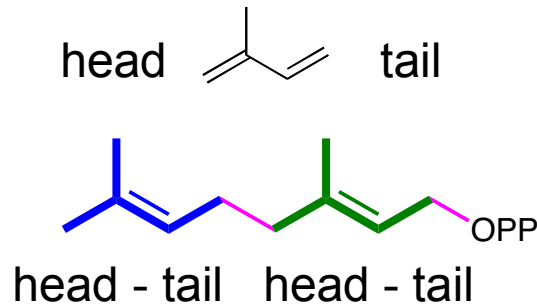
Head to tail:

- smaller compounds 25 C ↩
- joining of C4 to C1 or C2
- very limited number of compounds, 3 or 4
units, not larger

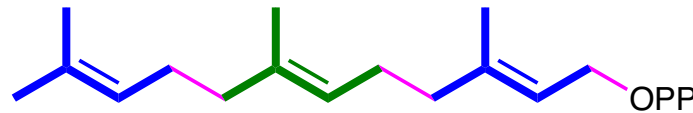
Tail to tail:

- larger compounds (due to huge steric hindrance), joining of C4 to C4 or to C3

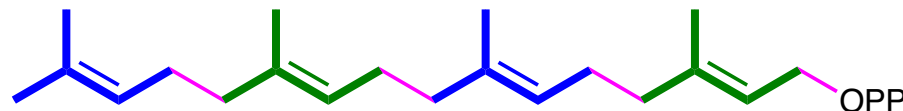
The precursor to C₁₀ terpenoids (*monoterpenes*) is **geraniol** diphosphate (diphosphate), which consists of two C₅ “isoprene units” that are joined “head-to-tail”



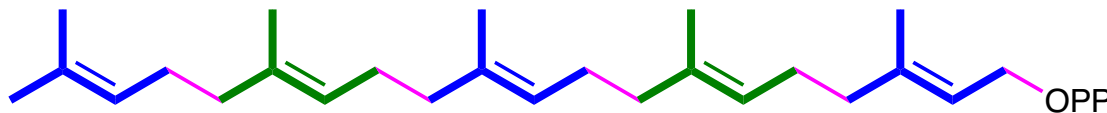
C₁₅ *sesquiterpenoids* are derived from **farnesyl diphosphate**, which consists of three C₅ “isoprene units” that are joined “head-to-tail”



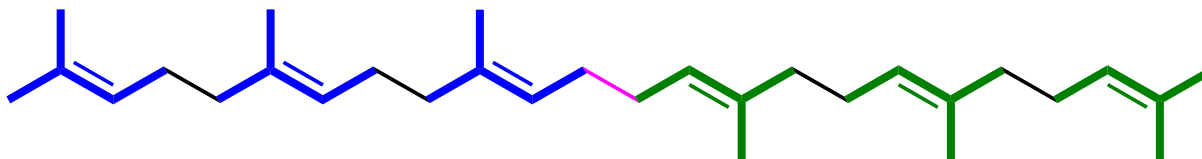
C₂₀ *diterpenoids* are derived from **geranylgeranyl diphosphate**, which consists of four C₅ “isoprene units” that are joined “head-to-tail”



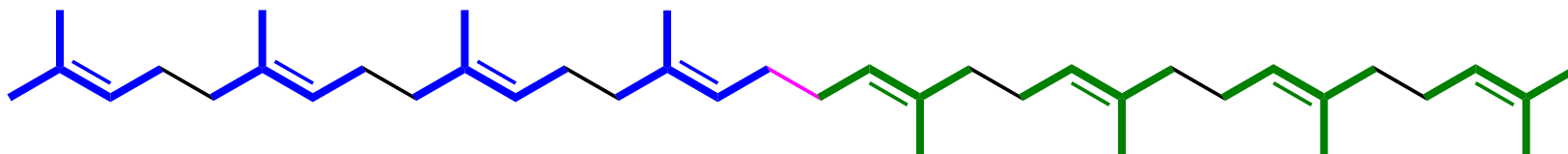
C_{25} *sesterpenoids* are derived from **geranyl****farnesyl****diphosphate**, which consists of five C_5 “isoprene units” that are joined “head-to-tail”

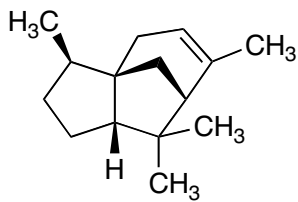


triterpenoids and *steroids* are derived from **squalene**, which consists of two C_{15} farnesyl units” that are joined “tail-to-tail”

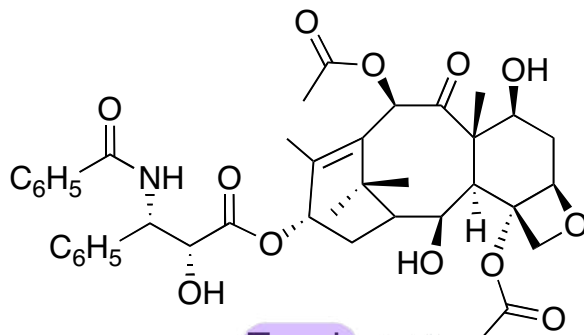


C_{40} *tetraterpenoids* are derived from **phytocene**, which consists of two C_{20} geranylgeranyl units” that are joined “tail-to-tail”

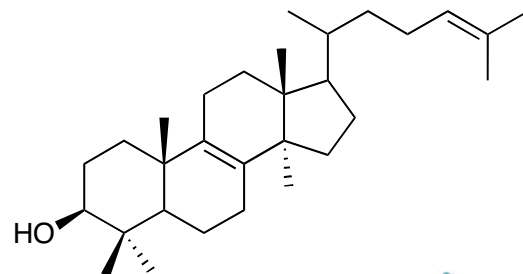




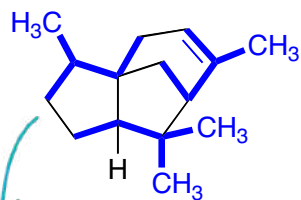
cedrane



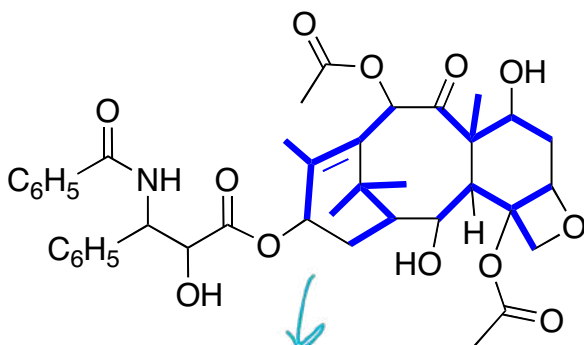
Taxol → diterpene



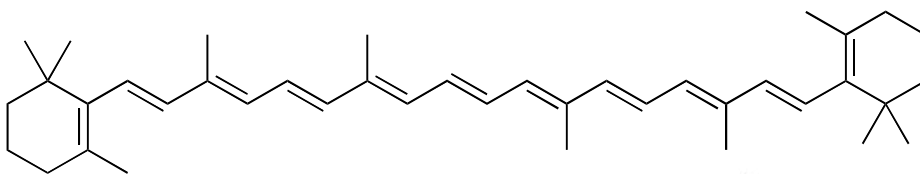
Lanosterol → steroidal triterpene.



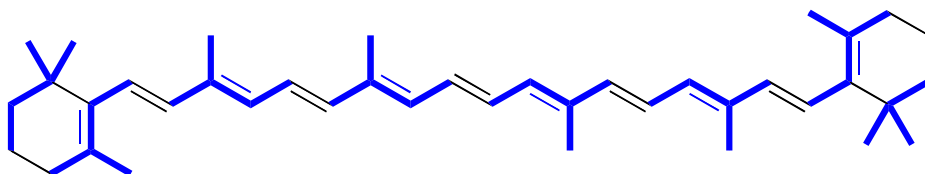
sesquiterpenoids



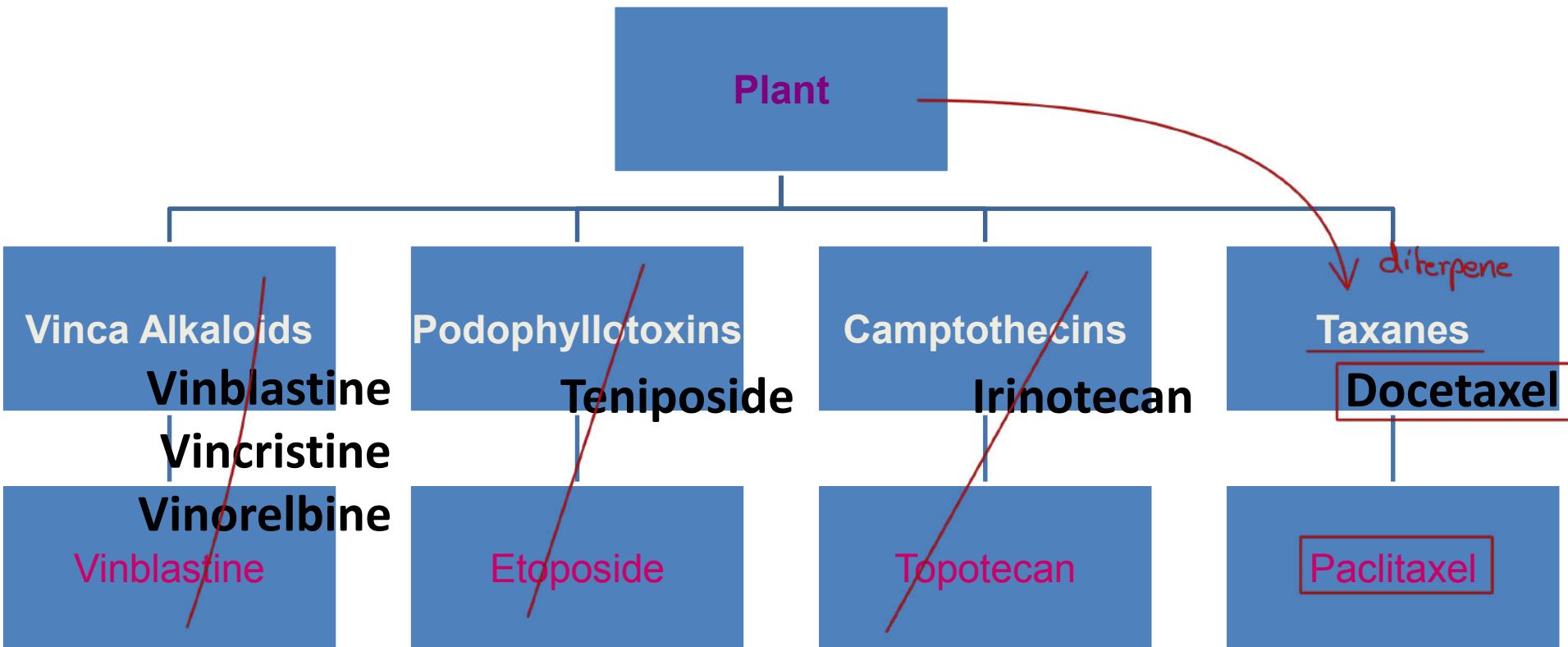
diterpene.



β-carotene → tetraterpene.



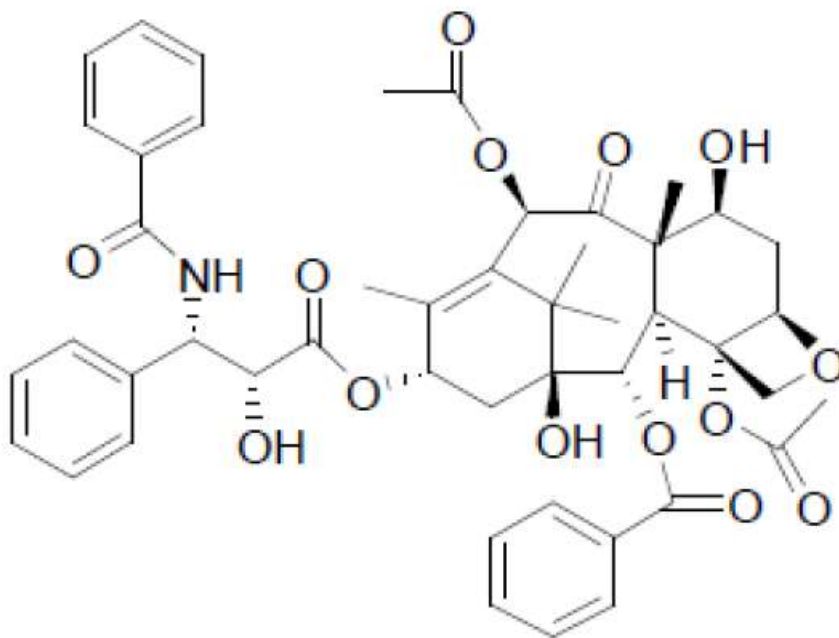
Anti-Cancer from Plant



Source of Taxol

Taxol occurs naturally and can be isolated from the bark of Pacific Yew (*Taxus brevifolia*) and from the leaves of European Yew (*Taxus baccata*).

- Taxol is classified as a taxane diterpenoid or taxoid.
- Diterpenoids are natural products that contain a C-20 carbon skeleton derived biogenetically from geranylgeraniol pyrophosphate.



Source of Taxol

Taxol was discovered due to its strong cytotoxicity and good activity in the P 388 mouse leukemia assay.

- In 1977, it was shown that Taxol's outstanding activity against solid tumors such as the B16 melanoma and the MX-1 mammary xenograft in nude mice.

Source of Taxol is **Pacific yew** الطقسوس : شجر دائم الخضرة من الفصيلة الصنوبرية

- *Taxus brevifolia* Nutt. Family: Taxaceae

- **Part harvested: Bark**

- **Harvest techniques: Bark peeled with knives in vertical** strips from cut stem or standing tree.

- If bark is peeled from circumference of trunk, tree will die.

- The *Taxus brevifolia* has an obvious ^{سبب}supply problem in obtaining a complex natural product from the bark of a scarce tree.

- Once the bark is removed from the tree, the tree dies.

- It is a slow growing tree and not a viable long term option for large scale of Taxol production

An alternative isolation from the leaves *Taxus baccata* (1g/kg) which is ten times greater than the amount of *Taxus brevifolia* (0.1g/kg).



Taxus brevifolia



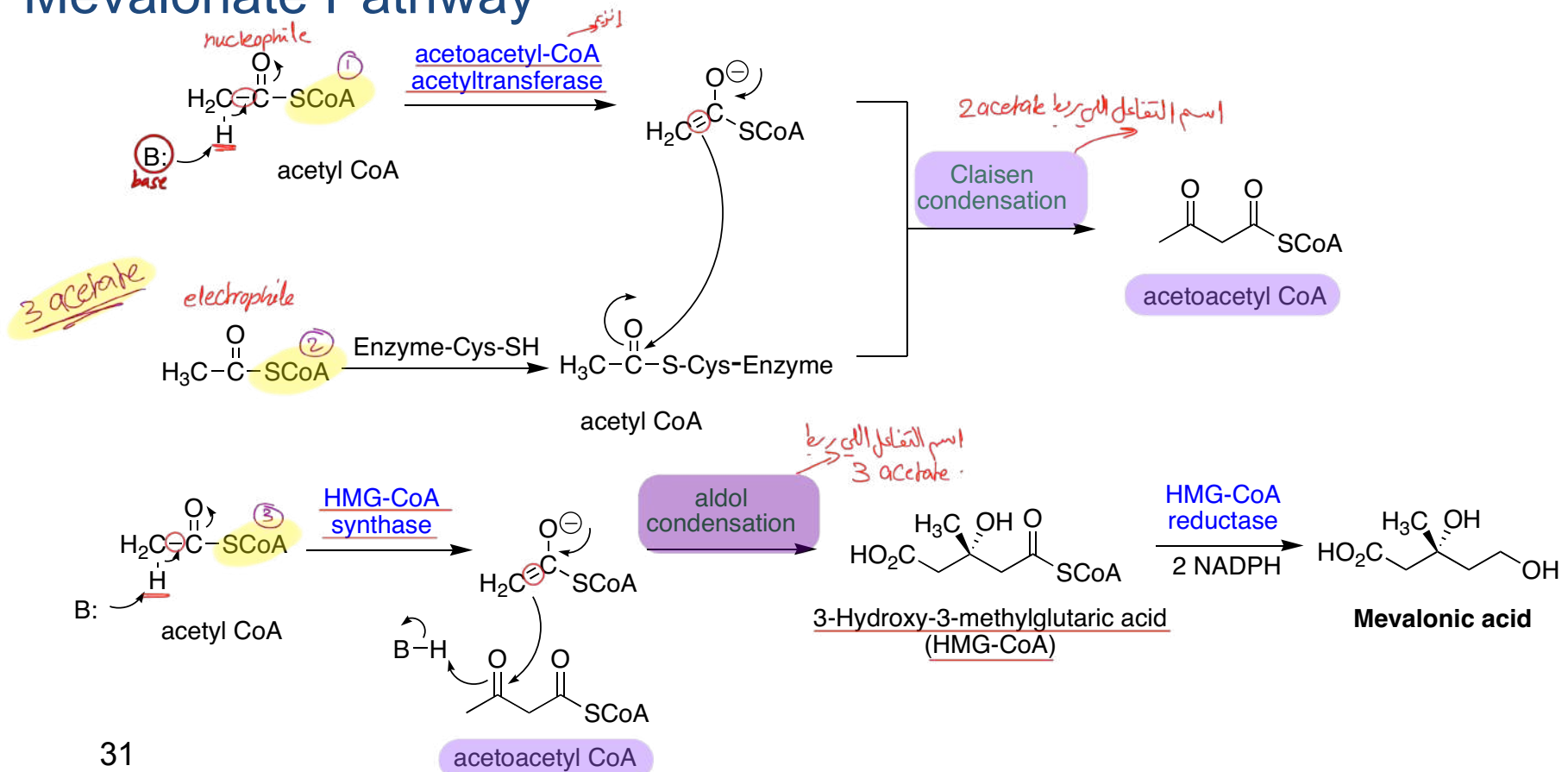
Taxus baccata

Isopentyl Diphosphate: The Biological Isoprene Unit.

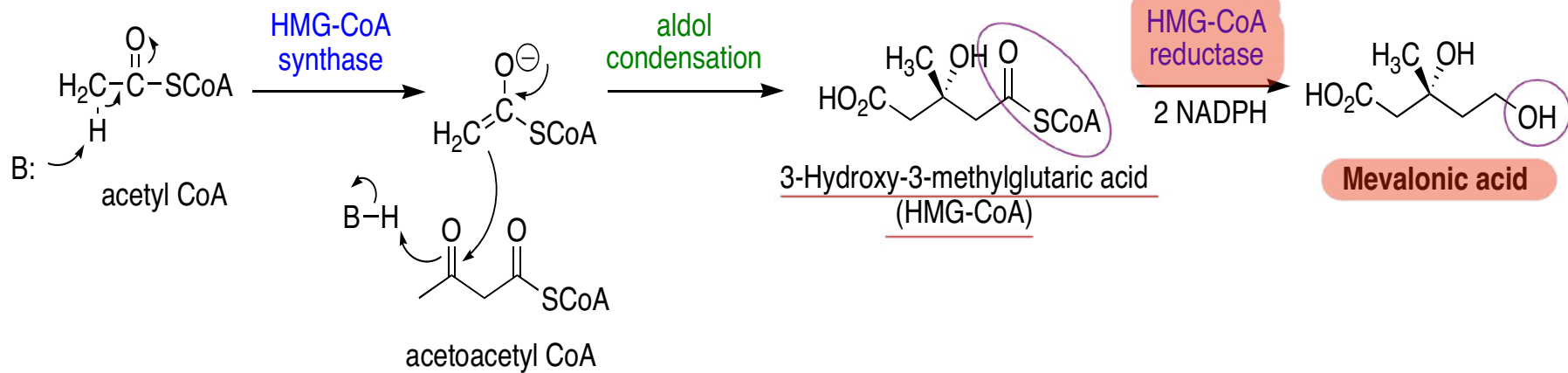
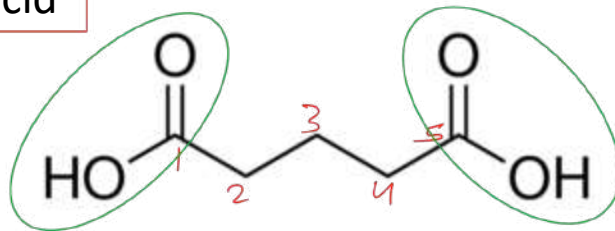
Mevalonic acid is the biosynthetic precursor to the actual C₅ “isoprene units,” which are isopentyl diphosphate (IPP, tail) and dimethylallyl diphosphate (DMAPP, head)

The Pathway from Acetate to Isopentenyl Diphosphate.

Mevalonate Pathway

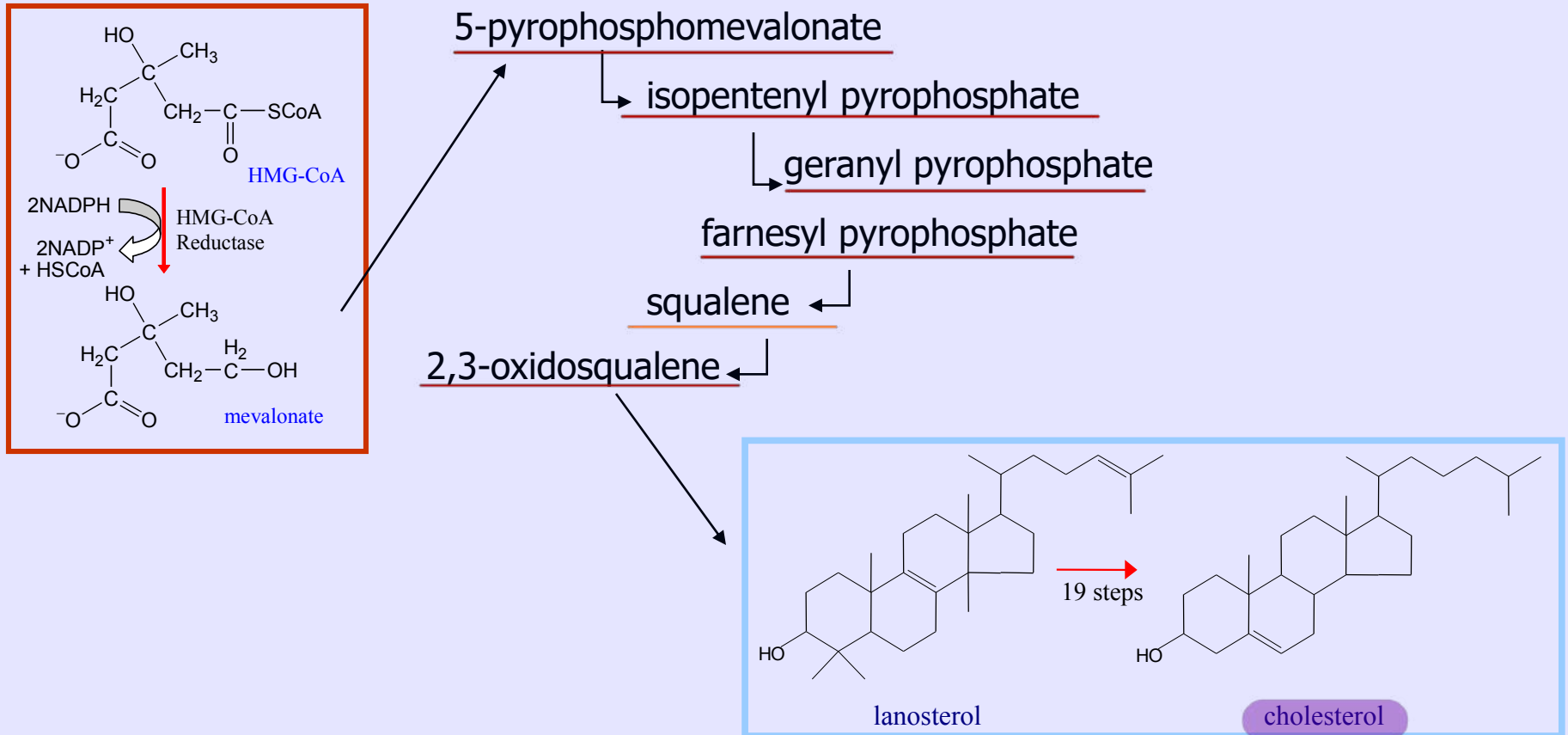


Glutaric acid



The Mevanolate Pathway²

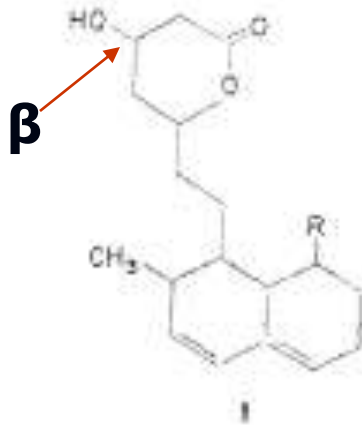
The biosynthesis of **cholesterol** and **isoprenoids** (a group of compounds responsible for cell fluidity and cell proliferation)



In 1976.....

- ML-236A, ML-236B, ML-236C: metabolites isolated from a fungus (*Penicillium citrinum*) were found to reduce serum cholesterol levels in rats.

This work was done by Akira Endo, Masao Kuroda and Yoshio Tsujita at the Fermentation Research Laboratories, Tokyo, Japan.³



ML-236A R = -OH
ML-236B R = -OCOCH(CH₃)CH₂CH₃
ML-236C R = -H

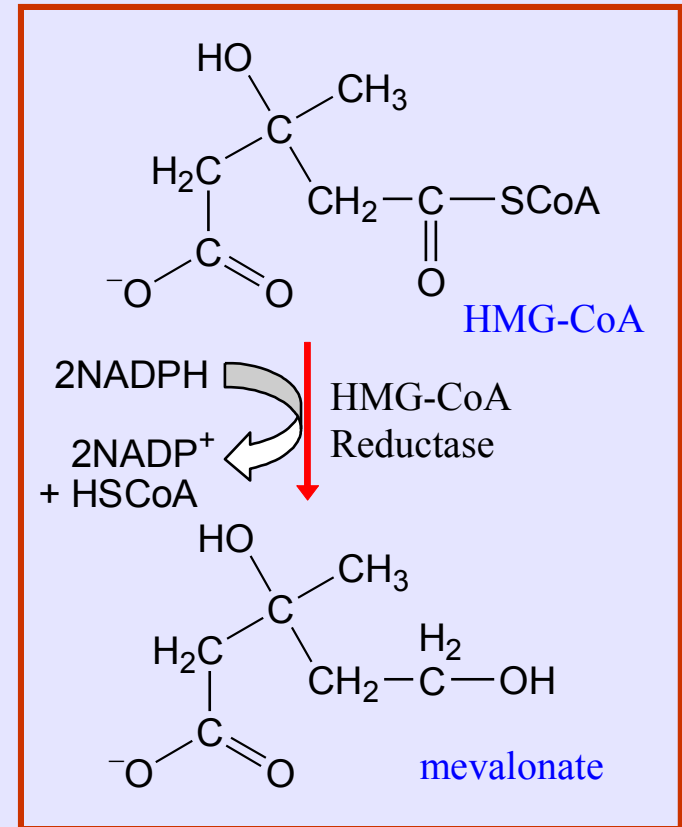
Preliminary experiments showed that these fungal metabolites had no effect on mevanolate or other steps in the biosynthetic pathway.

This led to the speculation that their action was somewhere between the mevanolate and the HMG-CoA

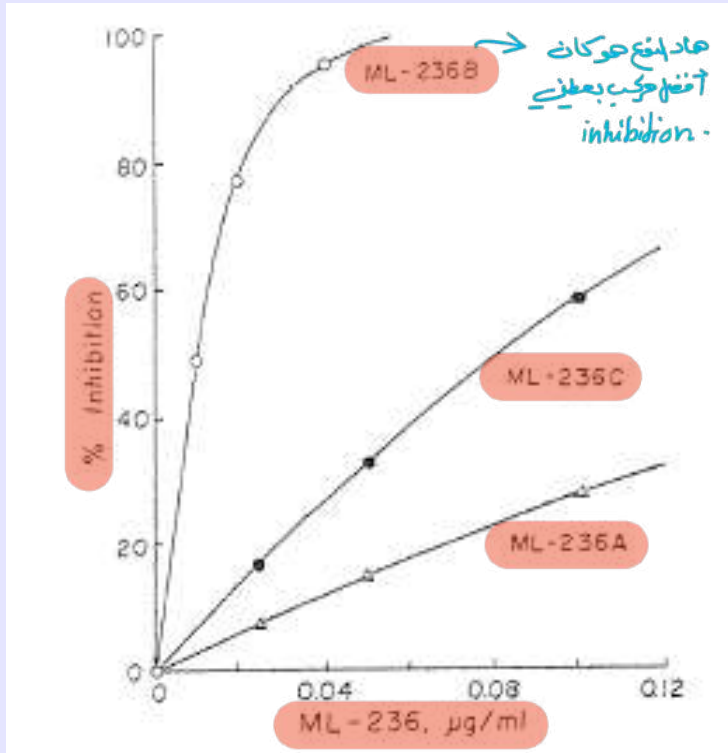
Target: HMG-CoA Reductase (HMGR)

- The enzyme that catalyzes the conversion of HMG-CoA to mevalonate.
- This reaction is the rate-determining step in the synthetic pathway.

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)



RESULTS



- Rats received oral dose of test compounds (5 mg/kg suspended in 0.5 mL of saline)
- Control group received 0.5 mL of saline
- Of the 3 substances tested, **ML-236B** had the highest level of hypocholesterolemic activity.

Amounts required for 50% inhibition

ML-236A 0.18 µg/mL

ML-236B 0.01 µg/mL

ML-236C 0.08 µg/mL

Handwritten Urdu notes:

- آہستہ سے نفع لانا (Benefit slowly)
- احتیاطاً کمزور قلیل لہجہ (Caution, weak, low tone)
- احتیاطاً کمزور قلیل لہجہ - inhibition (Caution, weak, low tone - inhibition)

Statins

هي أدوية بتمنع تصنيع الكوليستيرول بالجسم عن طريق تثبيط
انزيم HMG-CoA reductase

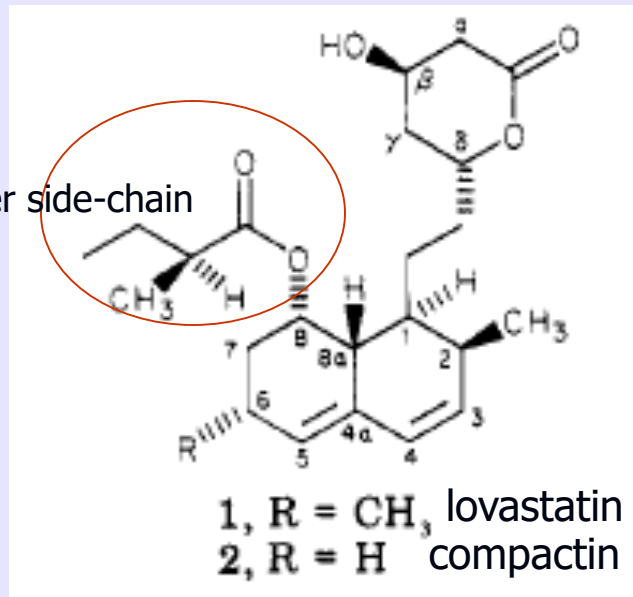
- ML-236B was later called **compactin** (6-demethylmevinolin or mevastatin). A related fungal metabolite called **lovastatin** (mevinolin) was also found to be another **good inhibitor of HMG-CoA reductase**. Lovastatin was isolated from *Aspergillus terreus*.

Today, there are two classes of statins:

Natural Statins: Lovastatin (mevacor), Compactin, Pravastatin (pravachol), Simvastatin (Zocor).

Synthetic Statins: Atorvastatin (Lipitor), Fluvastatin (Lescol).

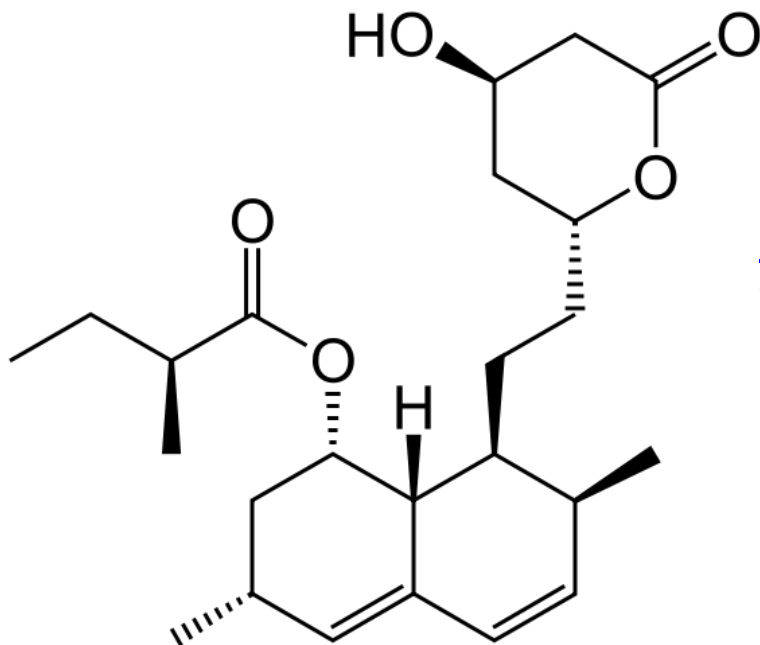
Statins are competitive inhibitors of HMG-CoA reductase. They are bulky and literally get “stuck” in the active site. This prevents the enzyme from binding with its substrate, HMG-CoA.



Statins (or HMG-CoA reductase inhibitors)

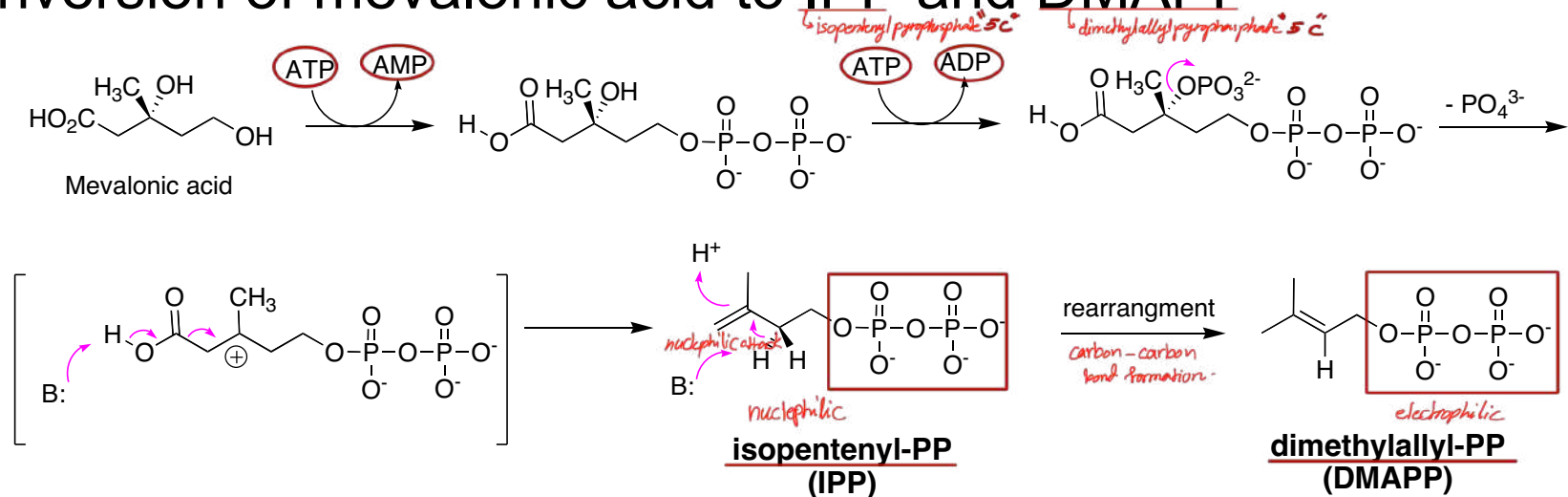
Statins (or **HMG-CoA reductase inhibitors**) are a class of lipid-lowering medications that inhibit the enzyme HMG-CoA reductase which plays a central role in the production of cholesterol. High cholesterol levels have been associated with cardiovascular disease (CVD).^[1] Statins have been found to reduce cardiovascular disease and mortality in those who are at high risk. The evidence is strong that statins are effective for treating CVD in the early stages of a disease (secondary prevention) and in those at elevated risk but without CVD (primary prevention).^{[2][3]} Side effects of statins include muscle pain, increased risk of diabetes mellitus, and abnormalities in liver enzyme tests. Additionally, they have rare but severe adverse effects, particularly muscle damage.^{معظم في العضلات}

As of 2010, a number of statins are on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.^[6] Several combination preparations of a statin and another agent, such as ezetimibe/simvastatin, are also available. In 2005 sales were estimated at \$18.7 billion in the United States.^[7] The best-selling statin is atorvastatin, which in 2003 became the best-selling pharmaceutical in history. The manufacturer Pfizer reported sales of US\$12.4 billion in 2008. Due to patent expirations, several statins are now available as less expensive generics.



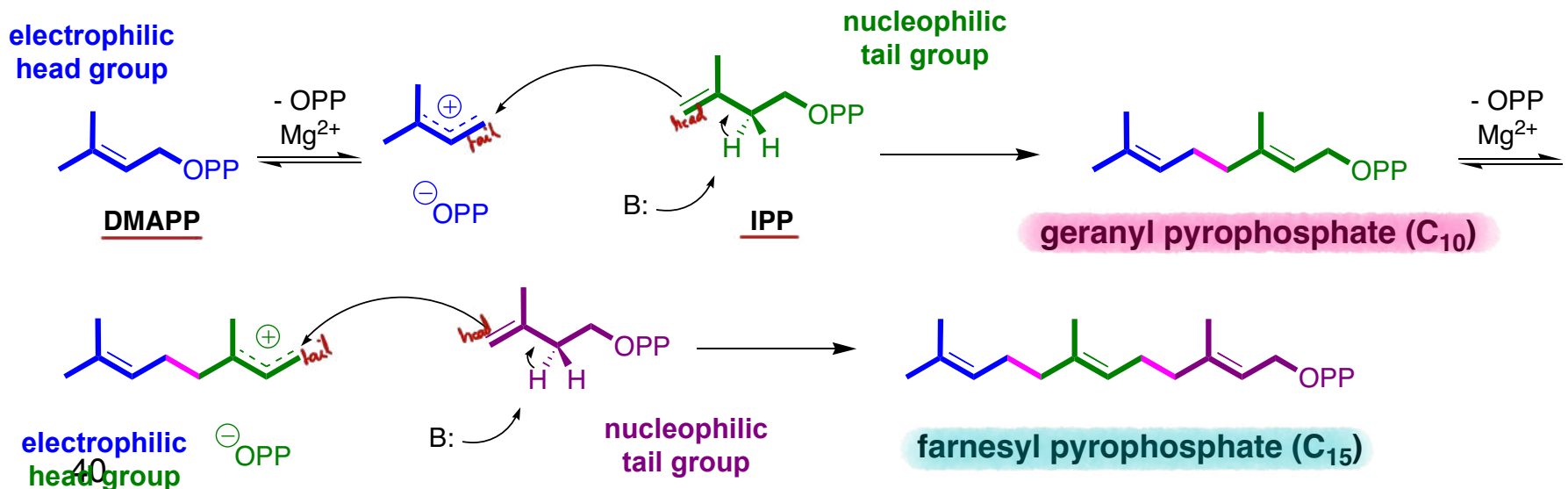
[Lovastatin](#), a compound isolated from [*Aspergillus terreus*](#), was the first statin to be marketed.

Conversion of mevalonic acid to IPP and DMAPP

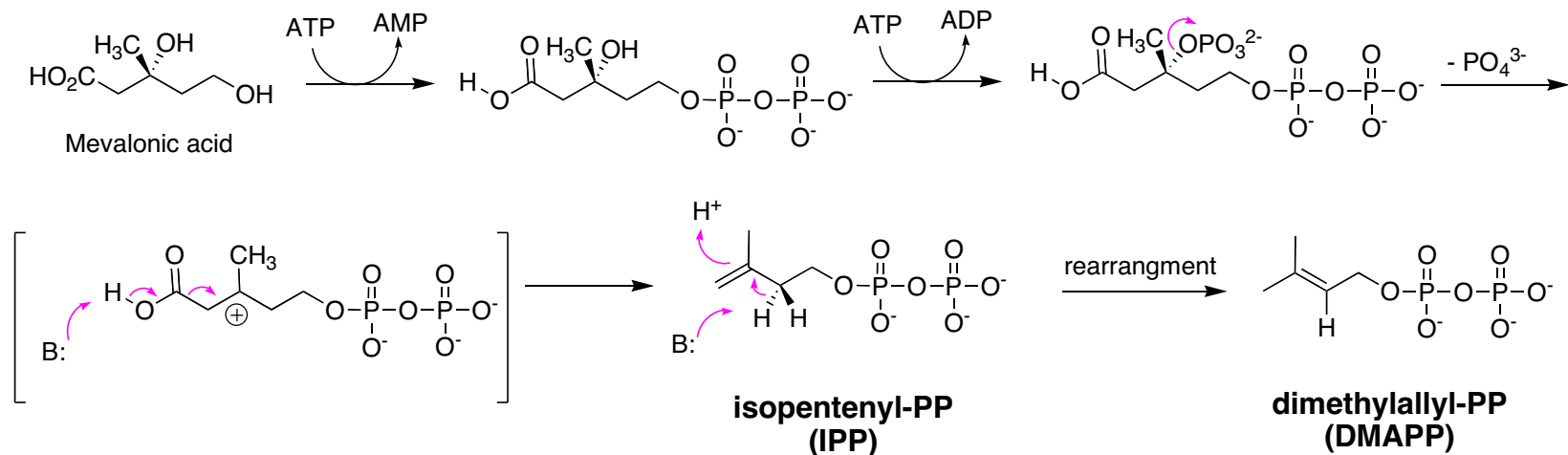


Carbon-Carbon Bond Formation in Terpene Biosynthesis.

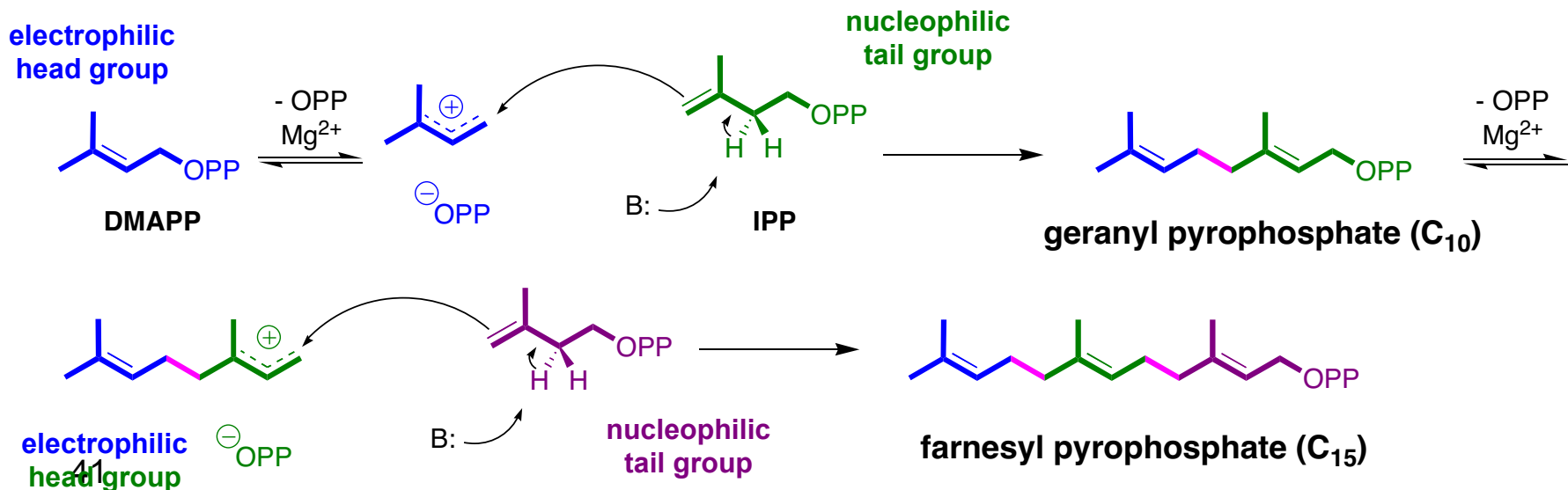
Conversion of IPP and DMAPP to geraniol-PP and farnesyl-PP

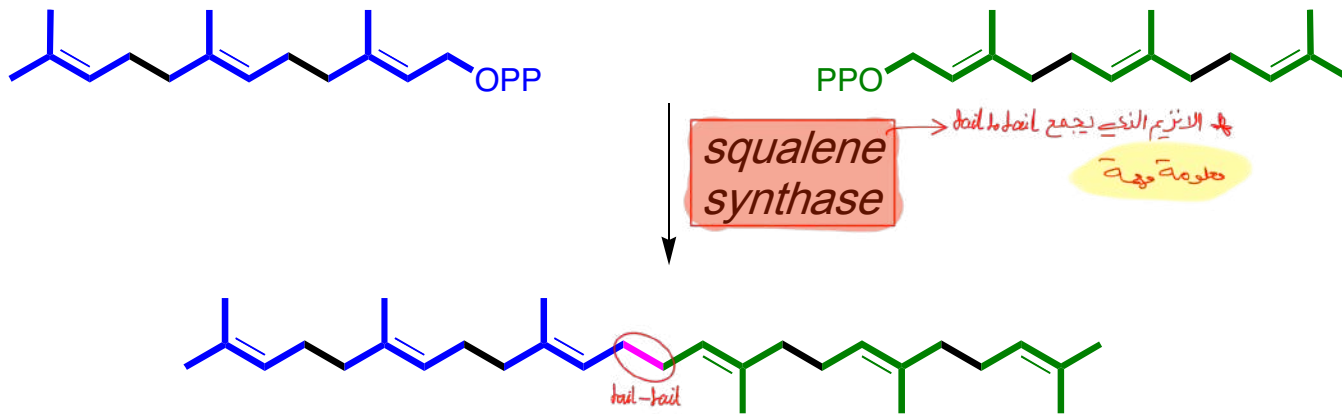


Conversion of mevalonic acid to IPP and DMAPP



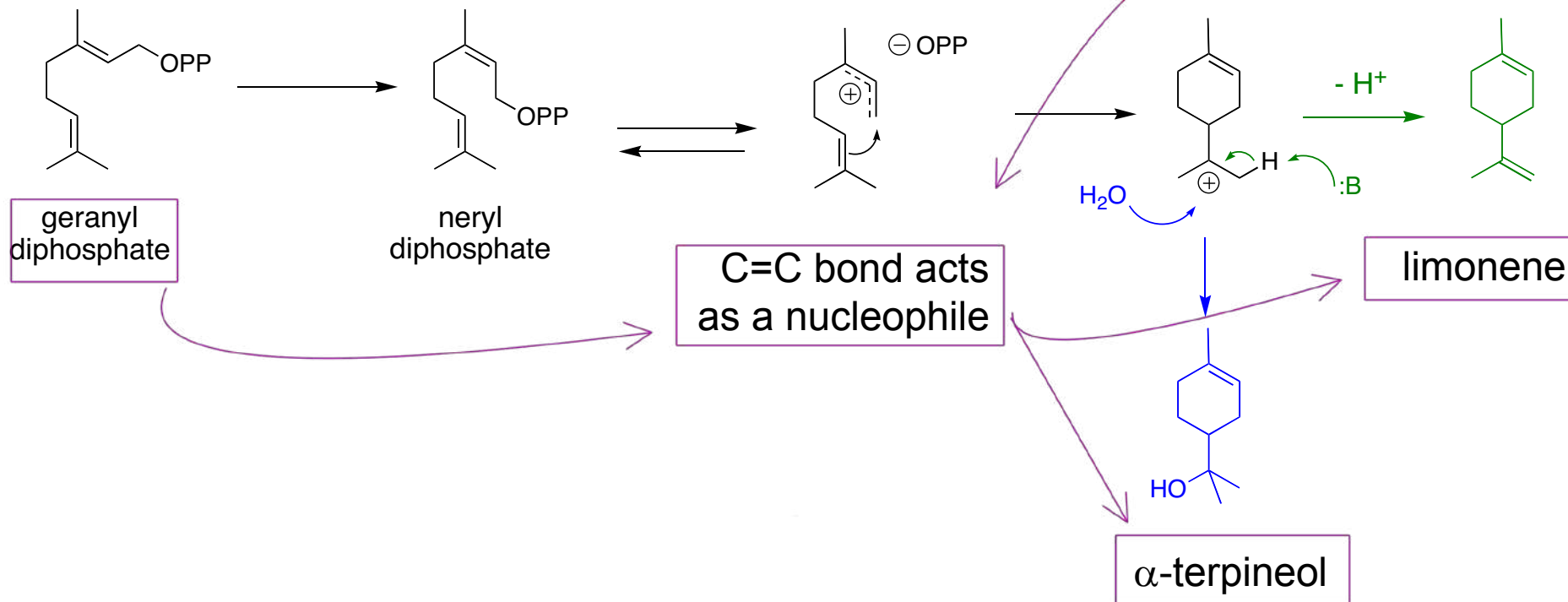
Carbon-Carbon Bond Formation in Terpene Biosynthesis. Conversion of IPP and DMAPP to geraniol-PP and farnesyl-PP

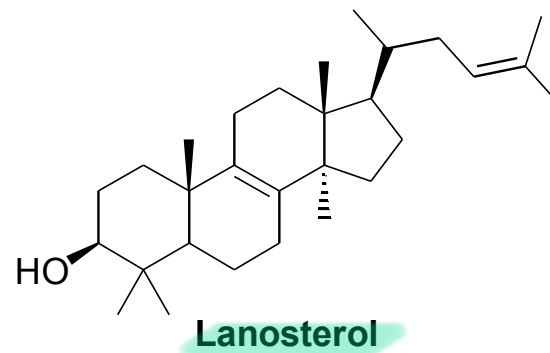
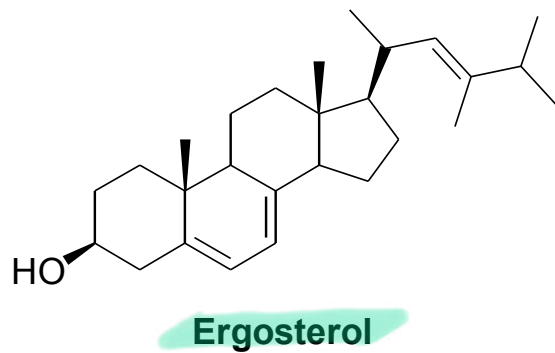
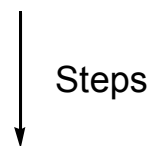
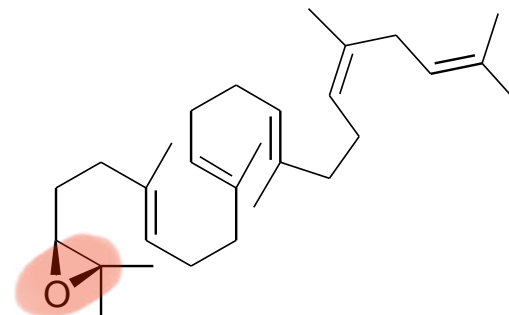
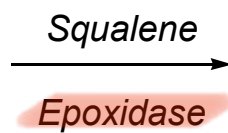
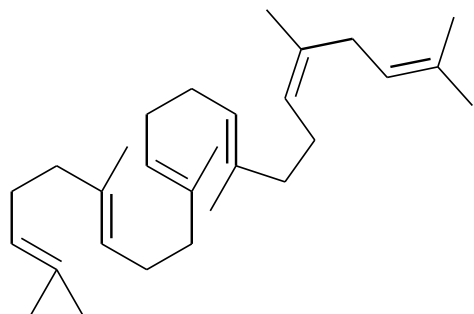




Conversion of geranyl-PP to monoterpenes

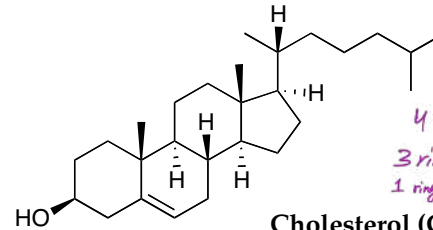
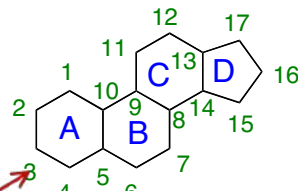
e.g. **Limonene & α -Terpineol**





Steroids.

من عطرين جفنا
ال structure ال steroid
ما عناه والباقى كا



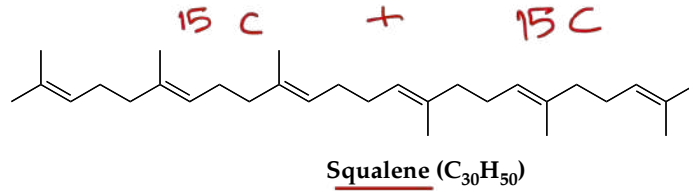
Cholesterol ($C_{27}H_{46}O$)

4 rings
3 rings
1 ring

كلهم اترنوه
ال cholesterol
فيه 27 C

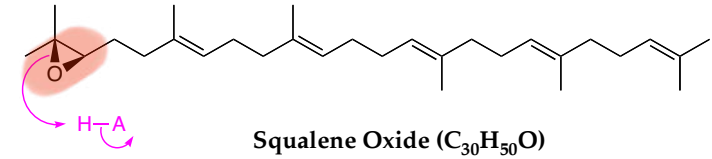
(mechanism 26.3, p. 1089) Cholesterol biosynthesis

part a: the cyclization

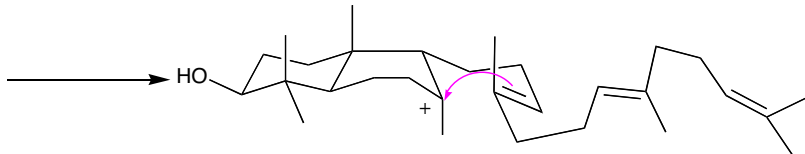
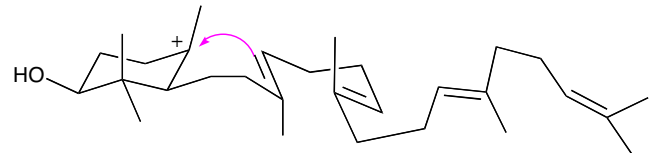
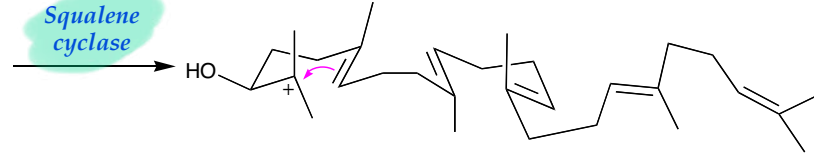


Squalene
epoxidase

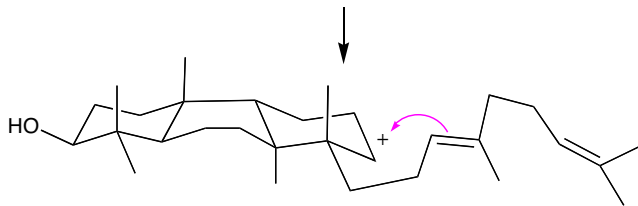
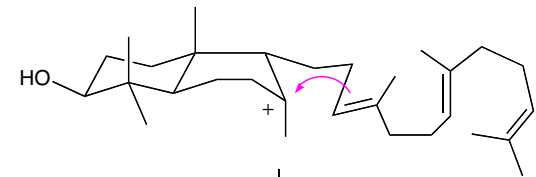
Heme, O_2



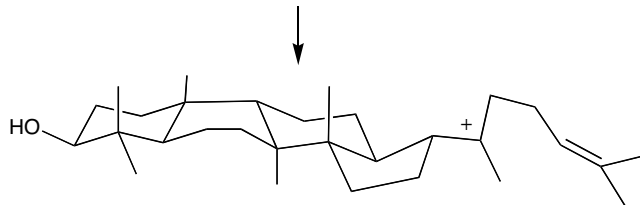
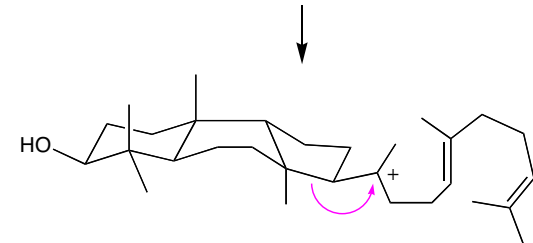
Squalene
cyclase



≡

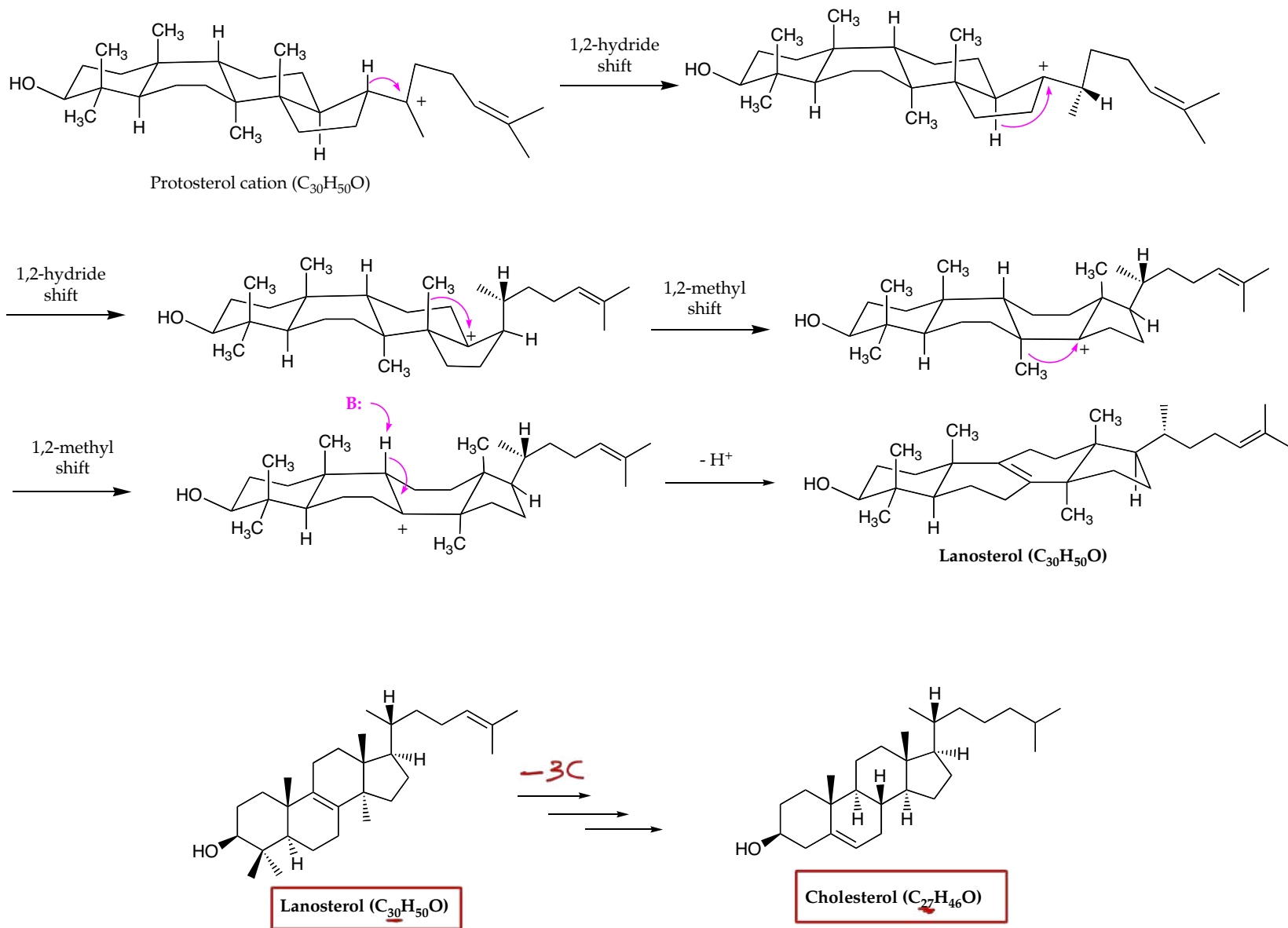


←



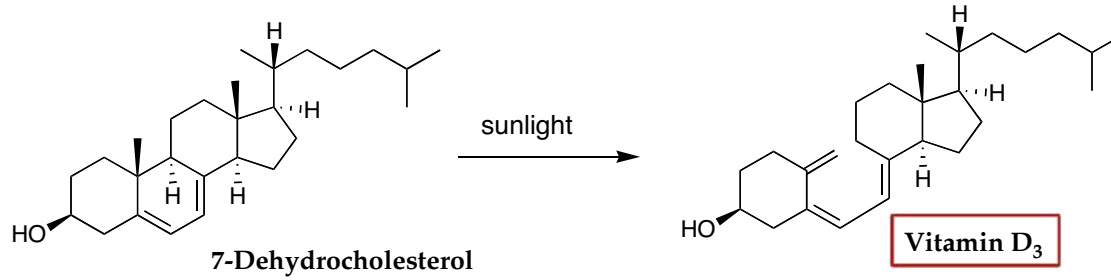
Protosterol cation

Cholesterol biosynthesis, part b: the 1,2-shifts



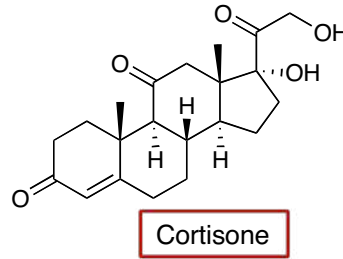
Vitamin D.

أهميته على السيترويدات



2 Bile Acids.

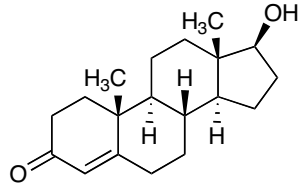
3 Corticosteroids.



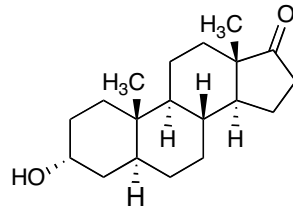
← هرمون تفرزه الغدة الكظرية يساعد في عمليات الأيض في جسم الإنسان
 هذا أستيروئيد anti-inflammatory ويعالج التهاب المفاصل.
 ↓
 adrenal medulla.

4 Sex hormones. androgens (male)

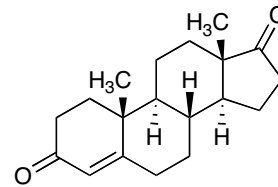
ال structure في مظهره .



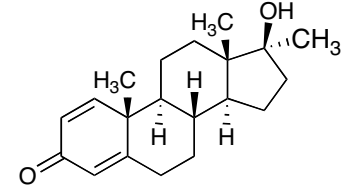
Testosterone



Androsterone

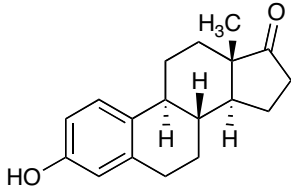


Androstenedione

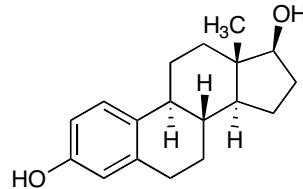


dianabol

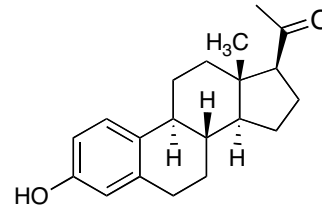
estrogens (female)



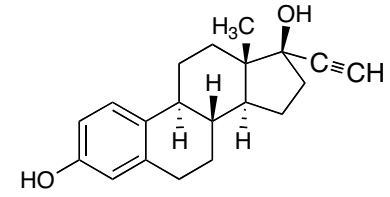
Estrone



Estradiol



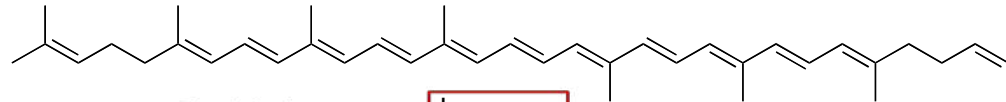
Progesterone



Ethynylestradiol

Carotenoids. derived from phytoene (C₄₀)

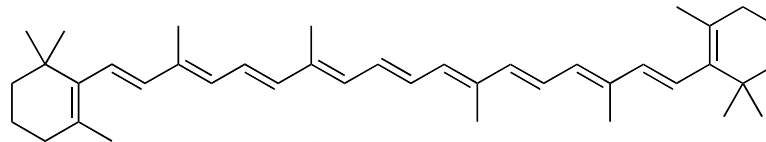
ليست ال steroid
لا تهم C₄₀



Lycopene

موجود في البندورة .

double-sing
في بطني لونه الأحمر
أو البرتقالي .



β-carotene

Reference

- 1) Paul, M. Dewick (1997). Medicinal natural products a biosynthetic approach, 152-216.
- 2) Lihong Hu, Zhongliang Chen,² Xiaofang Cheng and Yuyuan Xie., Chemistry of ginkgolides: structure±activity relationship as PAF antagonists. Pure Appl. Chem., Vol. 71, No. 6, pp. 1153±1156, 1999.
- 3) W.-S. Fang* and X.-T. LiangRecent Progress in Structure Activity Relationship and Mechanistic Studiesof Taxol Analogues. *Mini-Reviews in Medicinal Chemistry*, 2005, 5, 1-12