CHEMISTRY OF NATURAL PRODUCTS

CHEM 445
Credit (2+1)

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Quick LOOK!

- Introduction to Natural Products.
- Terpenoids
- Steroids
- Alkaloids
- Flavones

List Required Textbooks

- ✓ **Chemistry of Natural Products.**
  Sujata V. Bhat, Bhimsen A. Nagasampagi, Meenakshi Sivakumar, First Edition - 2005
  ISBN: 3-540-40669-7; Springer, Berlin.
- ✓ **Chemistry of Natural Products.** (Prof. Hassan El Hazmi, **Arabic Edition**).
- ✓ **Natural products Isolation**. Richard J. P. Cannell. Springer. 2002.
- ✓ **Total Synthesis of Natural Products.** Jie Jack Li, E.J. Corey, First Edition 2012.

Schedule of Assessment Tasks for Students During the Semester

	Assessment task (i.e., essay, test, quizzes, group project, examination, speech, oral presentation, etc.)	Week Due	Proportion of Total Assessment
1	**Major exam I**	Week 6	20%
2	**Major exam II**	Week 12	20%
3	**Quiz and activities**	Week 1-15	20%
4	**Final Exam**	Week 16	40%

- Naturally occurring from plants and microorganisms having small organic compounds:
  - including heterocyclic compounds, and peptides.
  - does not include proteins, carbohydrates, and nucleic acids.
- MW: ~150 ~ <800 amu ("small molecule").

What are "Natural Products"?

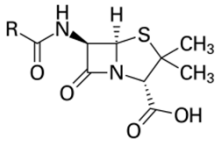
Chemical characteristics

Why study Natural Products?

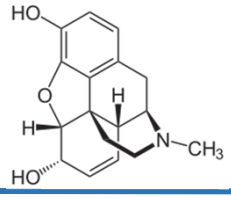
- Natural products are the source of the most complex and fascinating chemical structures.
- Natural products represent ***biological diversity***.
- Natural products are expressions of the ***genome***.
- Natural products represent natural biological activity, whether as ***single*** compounds or as ***complex*** mixtures.
- Natural products are part of the natural wealth of the country, and can be an important source of *livelihood, from agriculture and food, pharmaceuticals, fine chemicals industry*.
- Natural products can be an effective bridge from tradition to modern scientific developments, including *genetics, molecular biology, biotechnology, and pharmaceutical science*.

Range of products from natural products

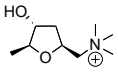
The antibiotic penicillin is a natural product derived from the fungus *Penicillium chrysogenum*



The opioid analgesic drug morphine is a natural product derived from the plant *Papaver somniferum*

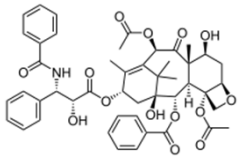


Source Amanita muscaria

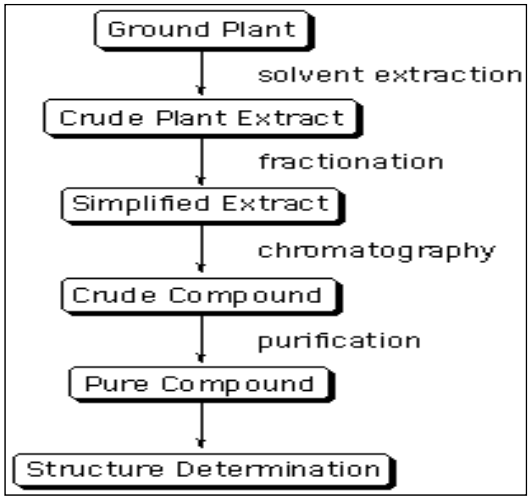


(+) Muscarine

Paclitaxel (Taxol) is a natural product derived from the yew tree



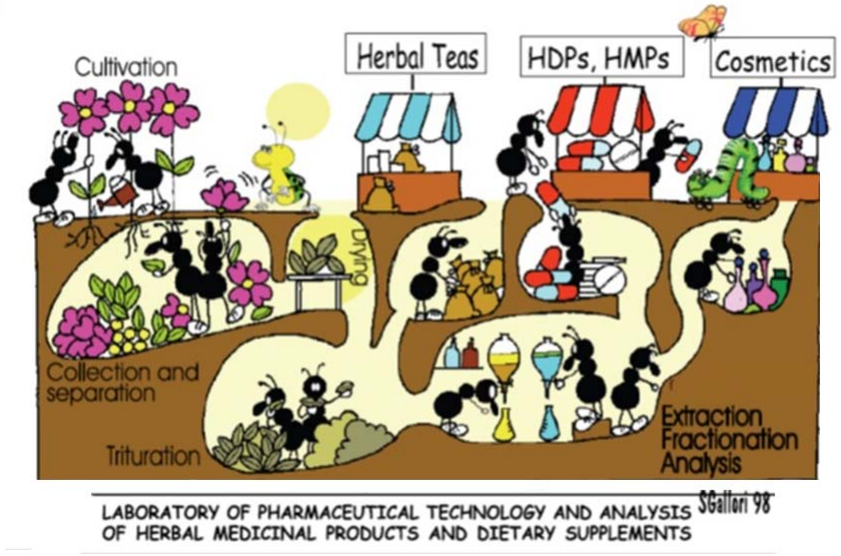
General isolation strategy of natural products



- Extract the ***dried and ground*** plant material with a ***suitable solvent***.
- Concentrate the extract.
- Separate and purify each component.
- Since the concentrate contains an enormous variety of compounds, early isolations involved *selective crystallization* of the most dominant component in the mixture.
- Liquid natural products were *distilled*.
- Natural organic acids were isolated by aqueous basic extraction and natural organic bases (alkaloids) were isolated by aqueous acidic extraction.

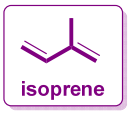
Classical structural elucidation is done by

- Determination of *functional groups*.
- Determination of the *carbon skeleton* and the location of the functional groups.
- Degradation to smaller fragments (A-B-C ------> A + B + C)
- Elemental analysis (**CHN**).
- Reactivity (leading to new reactions)
- ***Stereochemistry***.
- Synthesis of the smaller fragments (A, B, C) and the entire molecule (A-B-C).
- Classification of the compound into a biogenetic family of compounds
  - More modern structural elucidation and characterization by spectroscopy including NMR, MS, ESR, IR, X-ray, UV



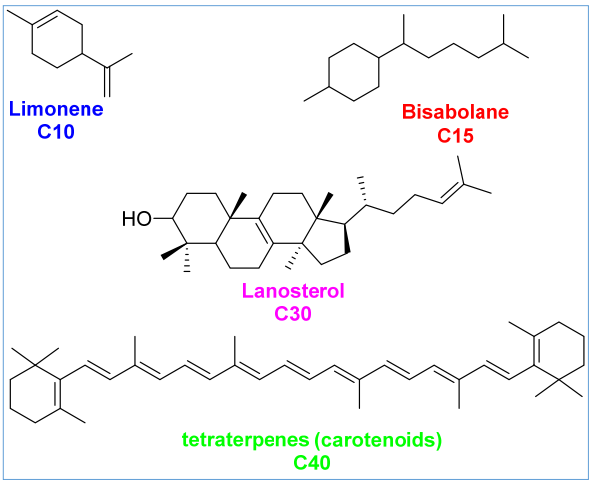
Terpenes: The isoprene rule!

- Terpenes form a group of compounds, the majority of which occur in the ***plant of kingdom***.
- A few terpenes have been obtained from other sources.
- The simpler monoterpoenoids are chief constituents of the ***essential oils***; these are the volatile oils obtained from the tissues of certain ***plant*** and ***trees***.
- Most natural terpenoids are hydrocarbons have the molecular formula **$(C_5H_8)n$; n ≥1**.
- Naturally occurring terpenoids can be built up of ***isoprene units***.

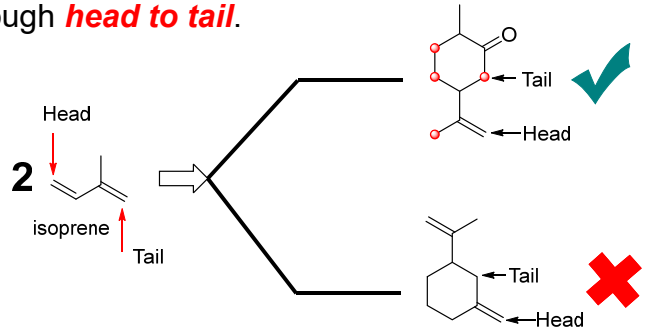


The Isoprene Rule

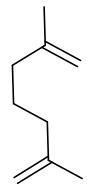
n	Class	No. of Carbons
2	Monoterpene	C10
3	Sesquiterpene	C15
4	Diterpene	C20
5	Sesterpene	C25
6	Triterpene	C30
8	tetraterpene	C40



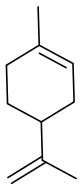
- The thermal decomposition of most of terpenes provide isoprene unit as one of the product and this is led to the suggestion that the skeleton structures of the all
- Naturally occurring terpenes can be built up of isoprene unit.
- The isoprene units may joined ***head to tail***; ***tail to tail***; or ***head to head***.
- All terpenes joined through ***head to tail***.



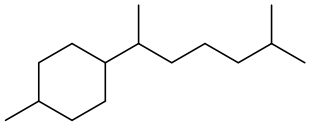
Examples



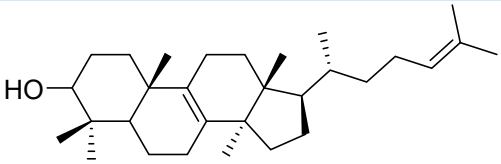
Acyclic



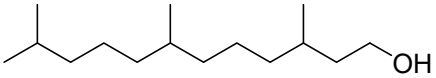
Limonene
C10



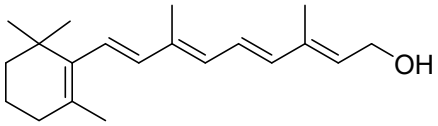
Bisabolane
C15



Lanosterol
C30



Phytol
C15



Vitamin A
C20

Classification of Terpenoids

- Most natural terpenoid hydrocarbon have the general formula $(C_5H_8)_n$. They can be classified on the basis of value of n or number of carbon atoms present in the structure.

S.No.	Number of carbon atoms	Value of n	Class
1.	10	2	Monoterpenoids($C_{10}H_{16}$)
2.	15	3	Sesquiterpenoinds($C_{15}H_{24}$)
3.	20	4	Diterpenoids($C_{20}H_{32}$)
4.	25	5	Sesterpenoids($C_{25}H_{40}$)
5.	30	6	Triterpenoids($C_{30}H_{48}$)
6.	40	8	Tetraterpenoids($C_{40}H_{64}$)
7.	>40	>8	Polyterpenoids(C_5H_8)n

- Each class can be further subdivided into subclasses according to the number of rings present in the structure:

i) Acyclic Terpenoids: They contain open structure.

ii) Monocyclic Terpenoids: They contain one ring in the structure.

iii) Bicyclic Terpenoids: They contain two rings in the structure.

iv) Tricyclic Terpenoids: They contain three rings in the structure.

v) Tetracyclic Terpenoids: They contain four rings in the structure.

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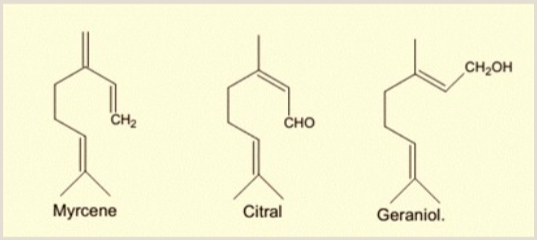
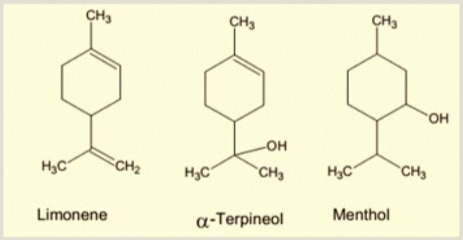
:A) Mono Terpenoids

i) Acyclic Monoterpenoids



ii) Monocyclic monoterpenoid



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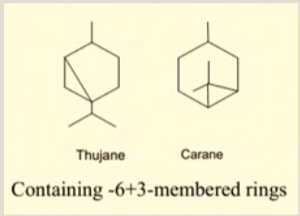
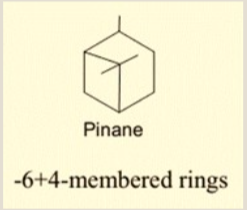
:A) Mono Terpenoids

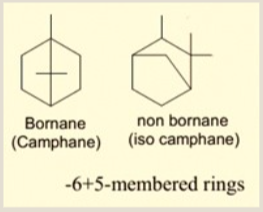
- iii)Bicyclic monoterpenoids: These are further divided into three classes.



a) Containing -6+3-membered rings



b) Containing -6+4-membered rings.



c) Containing -6+5-membered rings.

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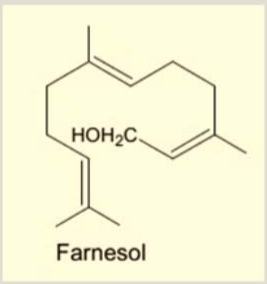
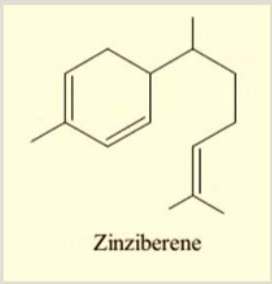
B) Sesquiterpenoids:

- i) Acyclic sesquiterpenoids



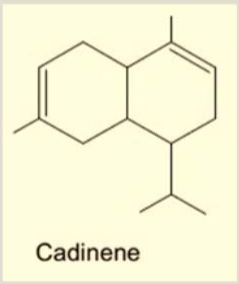
Farnesol

ii) Monocyclic sesquiterpenoids



Zinziberene

iii) Bicyclic sesquiterpenoids.



Cadinene

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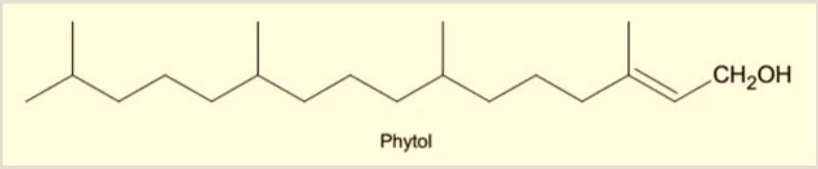
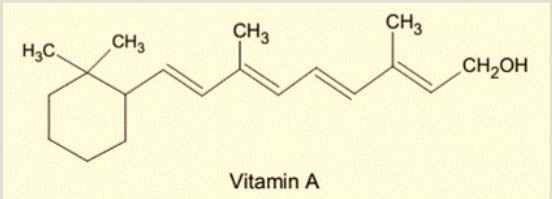
C) Diterpenoids:

i) Acyclic diterpenoids



Phytol

ii) Mono cyclic diterpenoids:



Vitamin A

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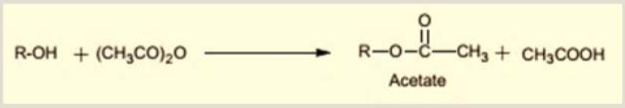
General Methods of structure elucidation

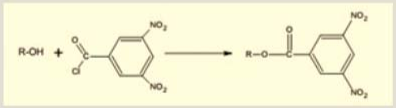
Terpenoids

i) **Molecular formula:** molecular formula is determined by usual quantitative analysis and mol.wt determination methods and by means of mass spectrometry. If terpenoid is optically active, its specific rotation can be measured.

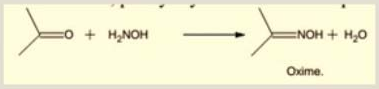
ii) **Nature of oxygen atom present:** If oxygen is present in terpenoids its functional nature is generally as alcohol aledhyde, ketone or carboxylic groups.

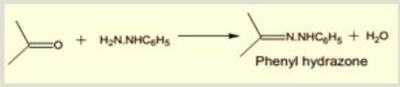
a) **Presence of oxygen atom present:** presence of –OH group can be determined by the formation of acetates with acetic anhydride and benzoyate with 3,5-dinitirobenzoyl chloride.

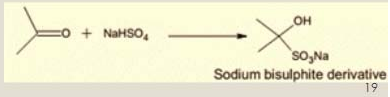




b) **Presence of >C=O group:** Terpenoids containing carbonyl function form crystalline addition products like oxime, phenyl hydrazone and bisulphite etc.







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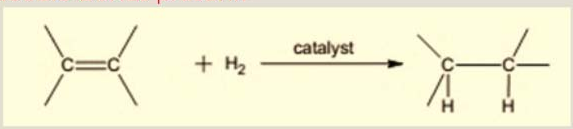
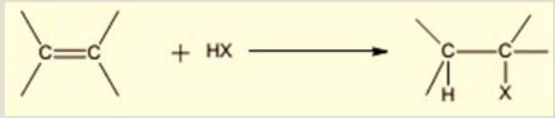
General Methods of structure elucidation

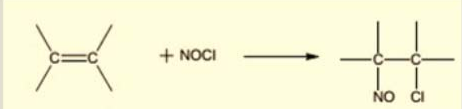
iii) Unsaturation:

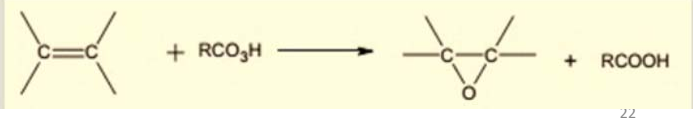
The presence of olefinic double bond is confirmed by means of bromine, and number of double bond determination by analysis of the bromide or by quantitative hydrogenation or by titration with monoperpthalic acid. Presence of double bond also confirmed by means of catalytic hydrogenation or addition of halogen acids. Number of moles of HX absorbed by one molecule is equal to number of double bonds present.





Addition of nitrosyl chloride(NOCl) (**Tilden's reagent**) and epoxide formation with peracid also gives idea about double bonds present in terpenoid molecule.





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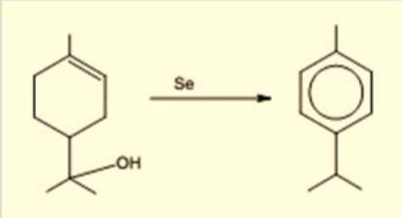
General Methods of structure elucidation

iv) Dehydrogenation:

- On dehydrogenation with Sulphur or selenium, terpenoids converted to aromatic compounds. Examination of these products the skelton structure and position of side chain in the original terpenoids can be determined. For example **α-terpineol** on Se-dehydrogenation yields **para-cymene**.



v) Oxidative degradation:

- Oxidative degradation has been the parallel tool for elucidating the structure of terpenoids. Reagents for degradative oxidation are **ozone**, acid, neutral or alkaline potassium permanganate, chromic acid, sodium hypobromide, osmium tetroxide, nitric acid, lead **tetra acetate** and **peroxy acids**. Since oxidizing agents are selective, depending on a particular group to be oxidized, the oxidizing agent is chosen with the help of structure of degradation products.

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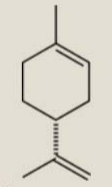
General Methods of structure elucidation

vi) Relation between general formula of compound and type of compounds:

For example limonene (mol. formula. $C_{10}H_{16}$) absorbs 2 moles of hydrogen to give tetrahydro limonene (mol. Formula $C_{10}H_{20}$) corresponding to the general formula. C_nH_{2n}. It means limonoene has monocyclic structure.

General formula of parent saturated Hydrocarbon	Type of structure
C_nH_{2n+2}	Acyclic
C_nH_{2n}	Monocyclic
C_nH_{2n-2}	Bicyclic
C_nH_{2n-4}	Tricyclic
C_nH_{2n-6}	Tetracyclic



limonene

vii) Spectroscopic studies:

UV Spectroscopy: In terpenes containing conjugated dienes or a,β-unsaturated ketones, UV spectroscopy is very useful tool, **IR Spectroscopy:** IR spectroscopy is useful in detecting group such as hydroxyl group (~3400cm^{-1}) or an oxo group (saturated 1750-1700cm^{-1}), **NMR Spectroscopy, Mass Spectroscopy, and X-ray analysis**

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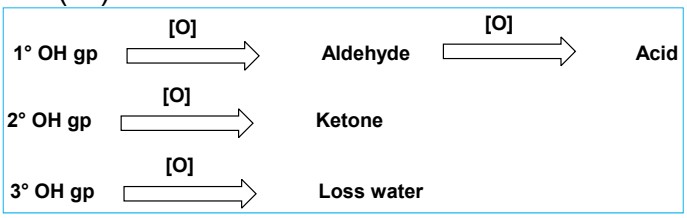
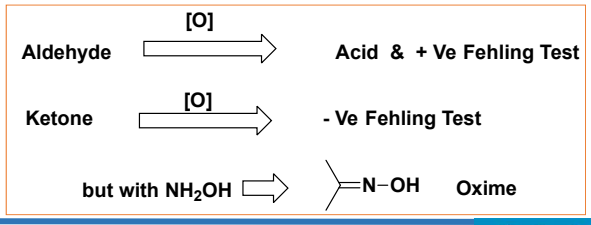
General Method for Structure Determination

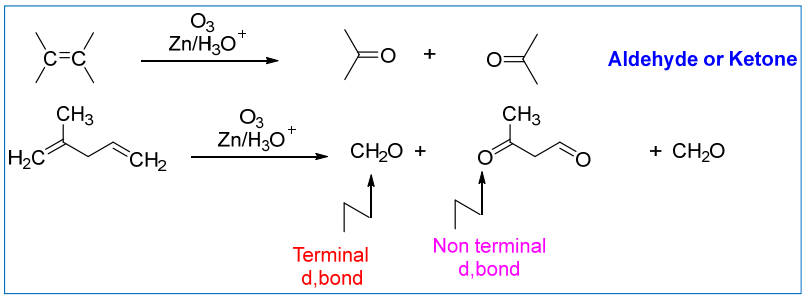
- **Molecular weight** (No of isoprene unit)
- **Oxygen** present as OH, CHO, COR (IR).



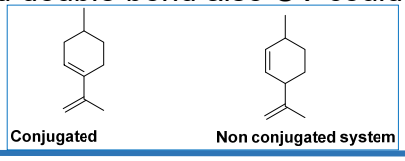
- **Carbonyl Compounds**:



- The olefinic double bond can be detected by H_2; Br_2; ……etc.
- If it absorb one mole of H_2 or Br_2 ……..>> one double bond.
- Ozonolysis:

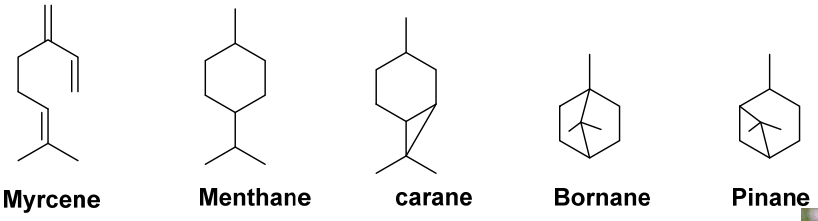


- **Diel's Alder reaction**: conjugated double bond also UV could be used to determine the conjugation.



Monoterpenes

- A class of terpenoids which has two isoprene unit isolated from bayberry, oil.
- It can be cyclic or open chain and the cyclic can be mono or bicyclic.



Myrcene Menthane carane Bornane Pinane

Verbena

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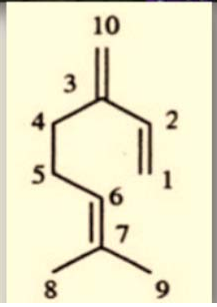
Myrcene

- Chemical formula: $C_{10}H_{16}$, b.p. 166-168°C. η^{20}_D 1.4692
  Myrcene is an acyclic monoterpene hydrocarbon occurring in Verbena oil. is a colorless, liquid with a pleasant odor.



UV: λ_{max} 225 nm.
IR: υ_{max} , 1672, 1634, 1597, 997. 900, 893 cm^{-1}.
^{1}H NMR: δ 1.56, 1.63 (6H, C-7 methyls), 4.83-5.07 (m, 5H, H-1a, H-1b, H-10a, H-10b and H-6), 6.19 (dd. 1H. H-2).
^{13}C NMR: δ 15.5 (C- 1), 139.0 (C-2), 145.9 (C-3), 30.8 (C-4), 26.1 (C-5), 124.4 (C-6), 131.0(C-7), 17.1 (C-8). 25.1 (C-9). 112.6 (C-10).

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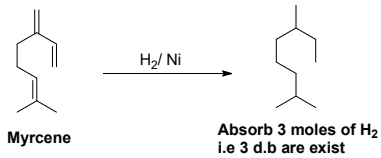
Reactions

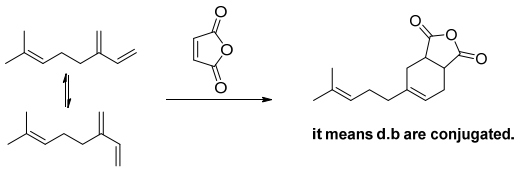
- **Hydrogenation**



Myrcene

Absorb 3 moles of H_2
i.e 3 d.b are exist

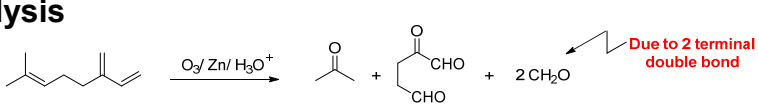
- **Diels Alder Reaction**



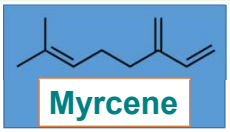
Myrcene

it means d.b are conjugated.

- **Ozonolysis**

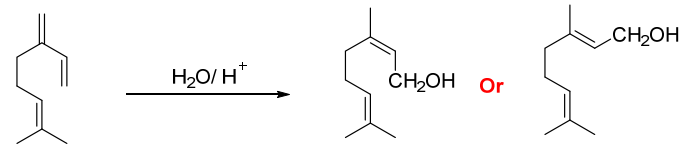


Acetone Ketoaldehyde formaldehyde



Myrcene is a significant component of the essential oil of several plants including bay, cannabis, ylang-ylang, wild thyme, parsley, cardamom, and hops.

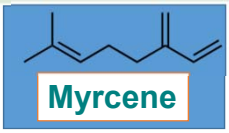
- **Hydration (1,4-addition)**



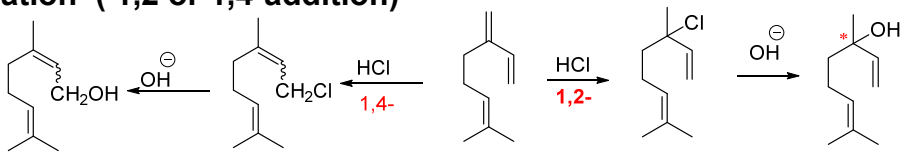
Myrcene

Nerol
"Z"

Geraniol
"E"



- **Hydrohalodgenation (1,2 or 1,4-addition)**

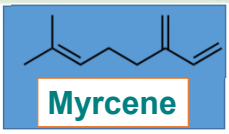


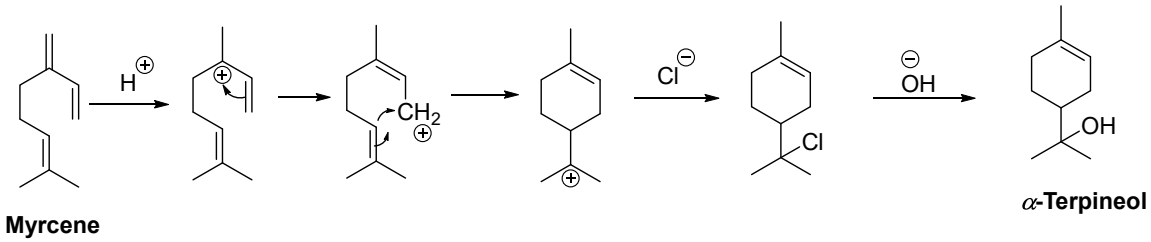
Nerol or Geraniol
"Z/E"

Myrcene

Linalool
(R, S)

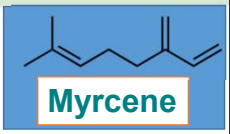
Synthesis of terpineol

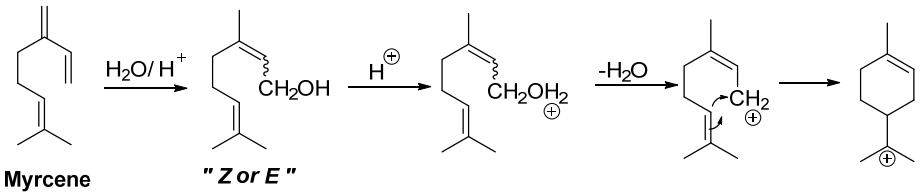




Myrcene

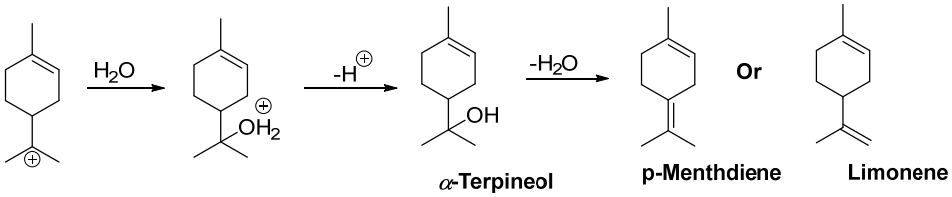
α-Terpineol





Myrcene

" Z or E "



α-Terpineol

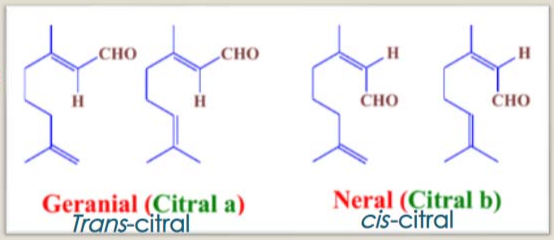
p-Menthdiene

Limonene

Citral

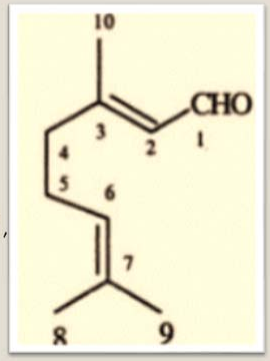
- Chemical formula: $C_{10}H_{16}$, b.p. 77 °C. η^{20}_D 1.4898
- **Citral** is one of the major constituents of lemon grass oil.

Mixture of at least 4 geometrical isomers of di-olefinic aldehyde



Geranial (Citral a) *Trans*-citral

Neral (Citral b) *cis*-citral



UV: λ_{max} 236 nm.
IR: υ_{max} , 1665, 1625. 1603, 1398. 1190, 1117 cm^{-1}.
^{1}H NMR: δ 1.65 (6H, d, C-7 methyls), 2.15 (3H, s, C-3 Me), 5.0 (1H, t, H-6), 5.8 (1H, d, H-2), 9.84 (1H, d, H-1).
^{13}C NMR: δ 190 (C-1). 127-5 (C-2), 162.1 (C-3).405 (C-4), 265 (C-5), 123.5 (C-6). 132.3 (C-7). 25.3 (C-8), 17.4 (C-9), 17.0 (C-10).
MS: m/z 69 (100), 41, 84. 94, 109, 67. 83. 81.

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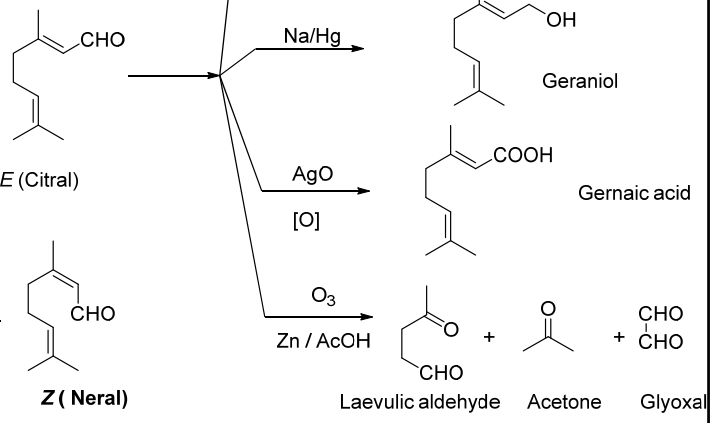
Citral

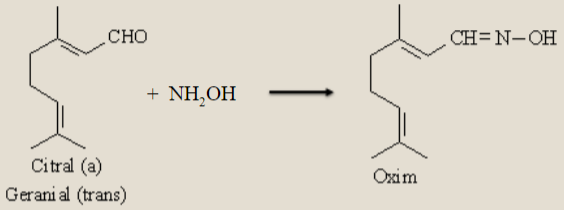
Present in lemon myrtle, grass oil, liquid.

Lemon myrtle

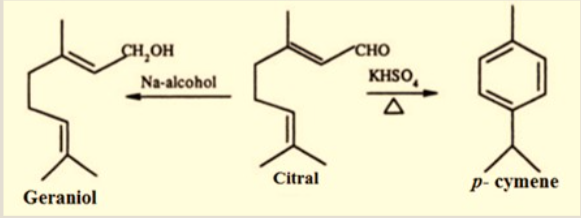


Structure elucidation

- Formation of an oxime of citral indicated the presence of an oxo group in citral.



- Citral when heated with potassium hydrogen sulphate afforded the known aromatic hydrocarbon, p-cymene, which fixed the position of methyl and isopropyl groups in citral.



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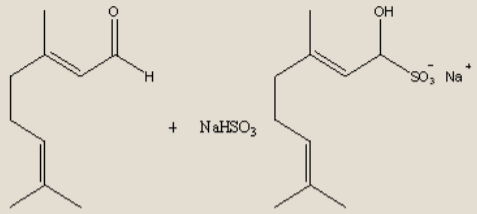
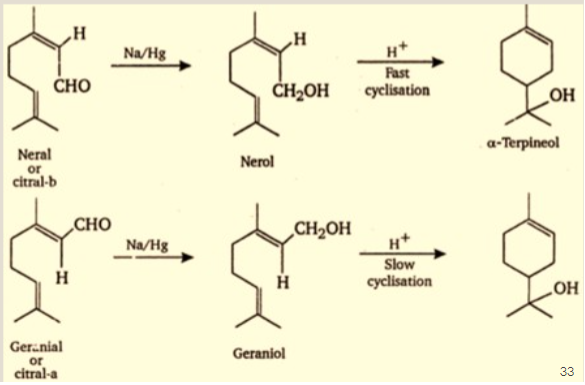
Structure elucidation

- **Citral** formed both mono- and di- bisulphites by the addition of sodium bisulfite to reveal the presence of a **conjugated aldehyde** group. Its UV spectrum displayed a band at 238 nm to confirm this.



- **Citral** on reduction with **sodium-amalgam** citral gave an alcohol, **geraniol,** $C_{10}H_{18}O$.



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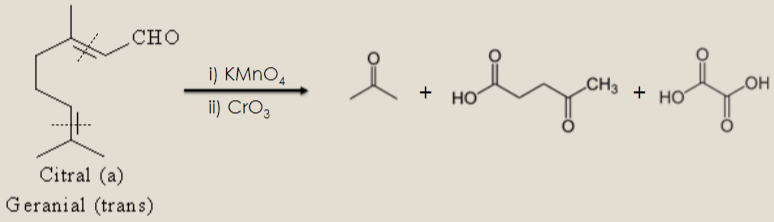
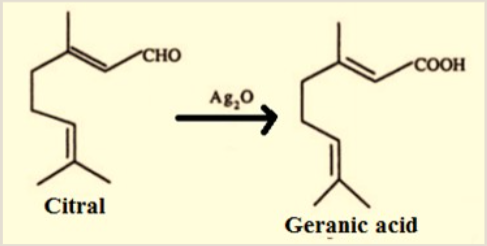
Structure elucidation

- **Citral** on oxidation with alkaline permanganate, yielded **acetone**, **oxalic** and **levulenic acid**.



Citral (a)
Geranial (trans)

- Citral oxidation with silver oxide afforded an acid **geranic acid**, $C_{10}H_{16}O_2$ containing the same number of carbon atoms suggesting that citral had an aldehyde group.



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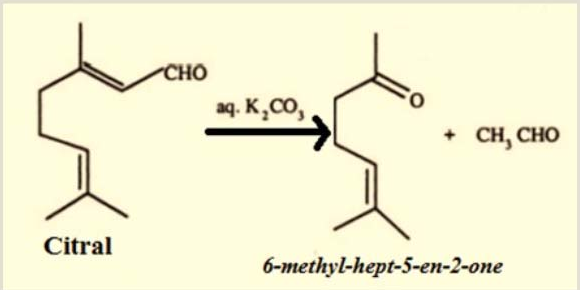
Structure elucidation

Based on the above data and coupled with the biogenetic considerations that **citral** is formed by the joining of **two isoprene** units in the head to tail fashion, structure of **citral** was assigned tentatively.

This structure was further supported by the degradation of **citral** on treatment with aqueous **potassium carbonate** when **6-methyl-hept-5-en-2-one** and **acetaldehyde** were obtained. The structure of **citral** was finally confirmed by its synthesis.



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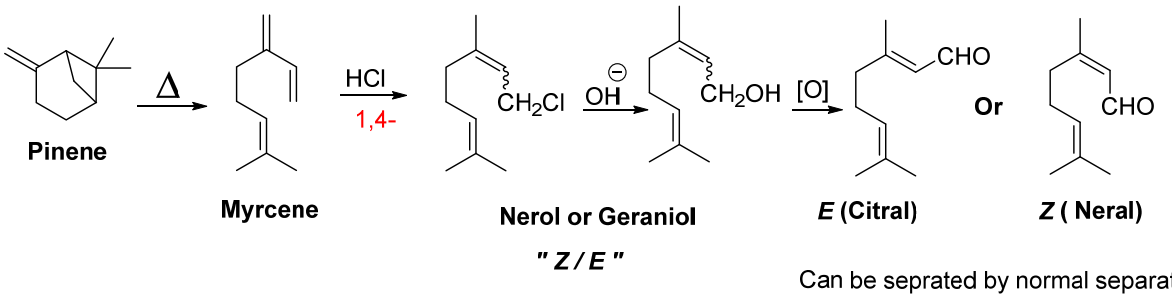
Synthesis of Citral



Pinene — Myrcene — Nerol or Geraniol — *" Z / E "* — *E* (Citral) — *Z* (Neral)

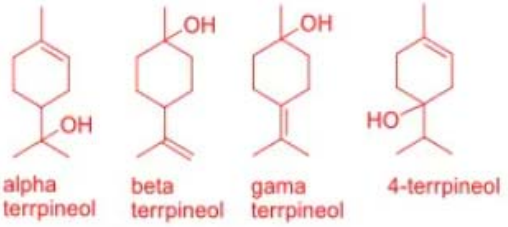
Can be seprated by normal separation

α-Terpinol

Physical properties of alpha Terpineol

Properties of alpha Terpineol	
Chemical formula	$C_{10}H_{18}O$
Molar mass ($g \cdot mol^{-1}$)	154.253
Appearance	Colorless liquid
Density(g/cm^3)	0.93
Melting point(°C)	−35.9 to −28.2
Boiling point(°C)	214–217
Solubility in water(g/L)	2.42

- ✓ Sources : Pine oils, cajuput oil, and petitgrain oil
- ✓ Terpineol is usually a mixture of isomers with alpha-terpineol as the major constituent.



alpha terrpineol | beta terrpineol | gama terrpineol | 4-terrpineol

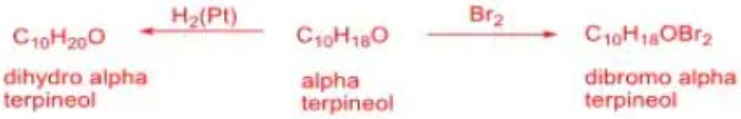
Uses:

- ✓ α-Terpineol has a pleasant odor similar to Lilac.
- ✓ α-Terpineol is a common ingredient in perfumes and soaps.
- ✓ Due to pleasant aroma, It is very relaxing.

Structural Elucidation of α-Terpineol (by Chemical method)

1. Molecular Formula of α-Terpineol

- ✓ Elemental analysis, % composition, Empherical Formula determinations reveals that the MF of α-terpineol = $C_{10}H_{18}O$
- ✓ α -Terpineol belongs to mono terpenoid class of terpenoids
- ✓ It contains two isoprene units joined head to tail

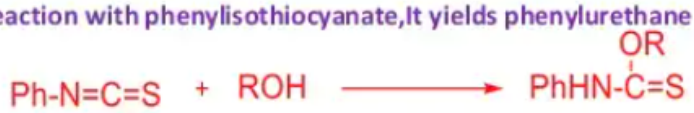


- ✓ α-terpineol adds to one molecule of H2 or Br2
- ✓ **Conclusion:** α-terpineol contains one double bond.

Structural Elucidation of α-Terpineol (Chemical method)

❖ **Nature of Oxygen atom**

- ✓ It does not undergo easy esterification …… ……. no alcohol group
- ✓ α-Terpineol does not undergoes oxidation with mild oxidizing agents to form aldehyde or ketone. …… no pri or sec alcoholic group
- √ It is not soluble in dil. NaOH …… ……..no phenolic group.
- ✓ with H_2SO_4, It readily undergoes dehydration……t alcoholic group.
- ✓ On reaction with phenylisothiocyanate,It yields phenylurethane



Conclusion: α-Terpineol contains a tertiary alcoholic group.

3. Ring Nature of α- Terpeniol

- ✓ From above discussion we know that MF is $C_{10}H_{18}O$
- ✓ α- Terpeniol contain 1 double bond ≈ 2H
- ✓ α- Terpeniol contain 1 –OH group ≈ 1H

Hence the saturated MF is $C_{10}H_{17}$ - OH

2H H

$C_{10}H_{20}$ ≈ C_nH_{2n}

We know that

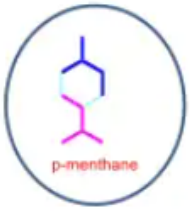
General Formula of Parent Hydrocarbon	Type of Structure
C_nH_{2n+2}	Acyclic
C_nH_{2n}	Monocyclic
C_nH_{2n-2}	Bicyclic
C_nH_{2n-4}	Tricyclic
C_nH_{2n-6}	Tetracyclic

Conclusion: α-Terpineol is a monocyclic terpinoid

Nature of Carbon skeleton in the molecule:

- ✓ when α-Terpineol is heated with sulphuric acid, it forms some p-cymene.

- ✓ P-cymene is a well known compound it contain methyl and isopropyl group at 1,4 position of benzene ring.
- ✓ As our molecule α-Terpineol contain only one double bond, hence α-Terpineol is a saturated p-cymene is p-methane.



A

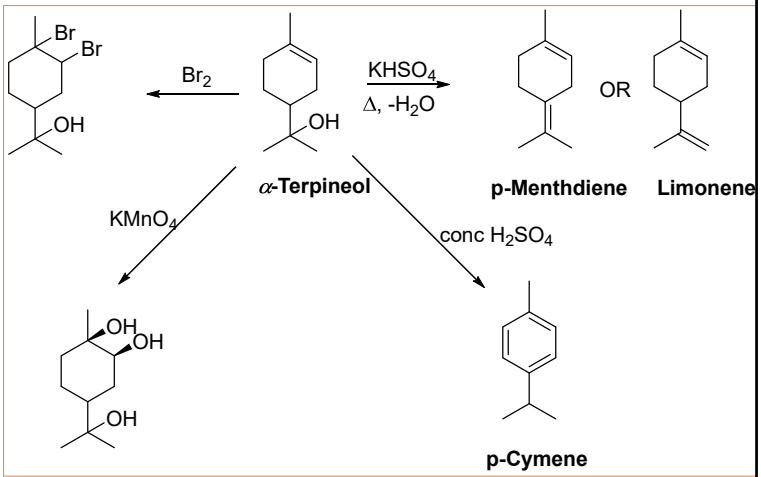
This assigned skeleton for α-Terpineol

- ✓ accounts for i) 2 isoprene units
  - ii) monoterpinoid nature
  - iii) Monocyclic in nature
  - iv) Special isoprene rule

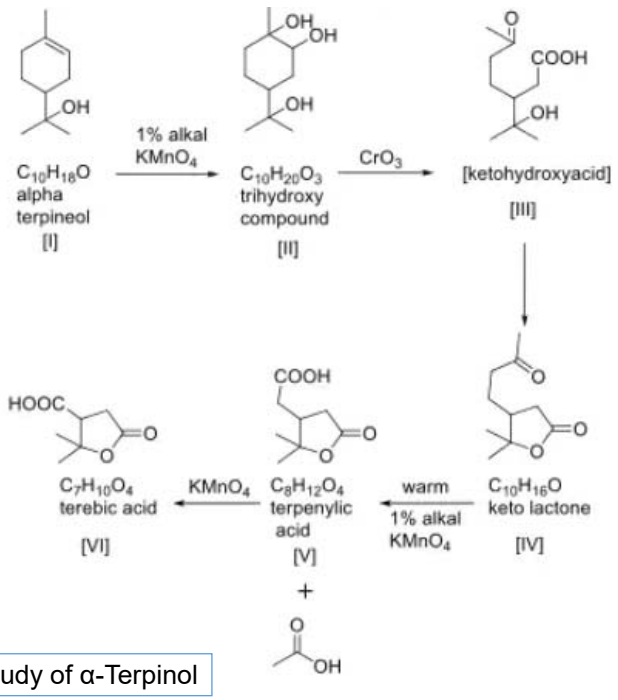
Monocyclicterpenes alpha-Terpineol

Solid; m.p: 55 ºC; optically active; 2 isoprene unit; cyclic.

Reactions



- Now in this p-menthane carbon skeleton, we have to fix the position of one double bond and a tertiary alcoholic group to get the structure of α-Terpinol

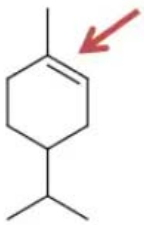


- Graded oxidation study of α-Terpinol

[II] is a trihydroxy compound ⟹ Originally one tertiary -OH was present
-2OH group's are added across double bond

[II] ketohydroxyacid ⟹ [IV] ketolactone (IR value 1775 cm^{-1})
No carbon loss therefore it is a γ-ketolactone

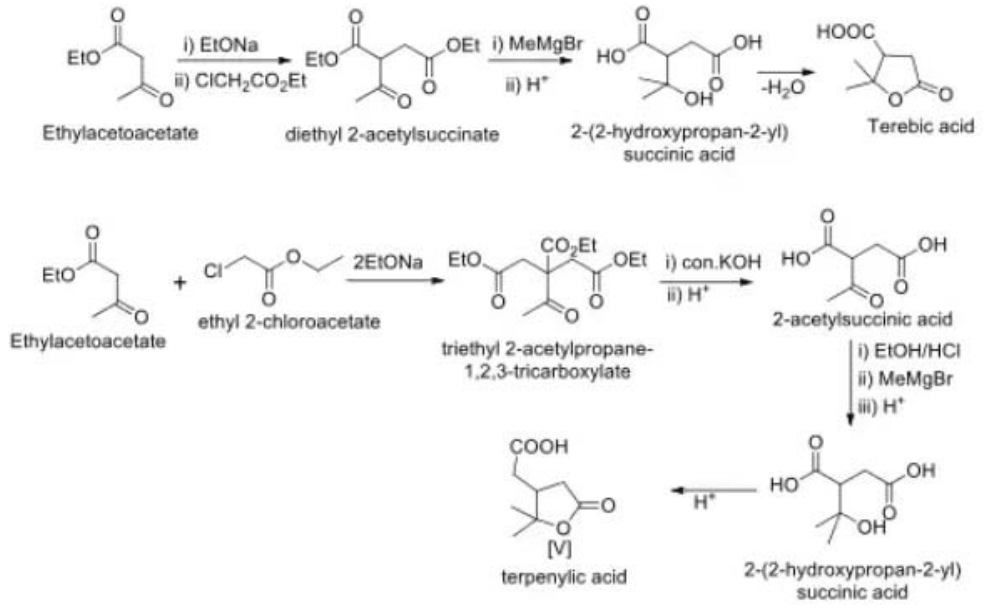
[IV] ⟹ [V] + CH_3COOH Formation of acetic acid indicates that double bond must be present next to $-CH_3$ group in p-cymene structure.



A

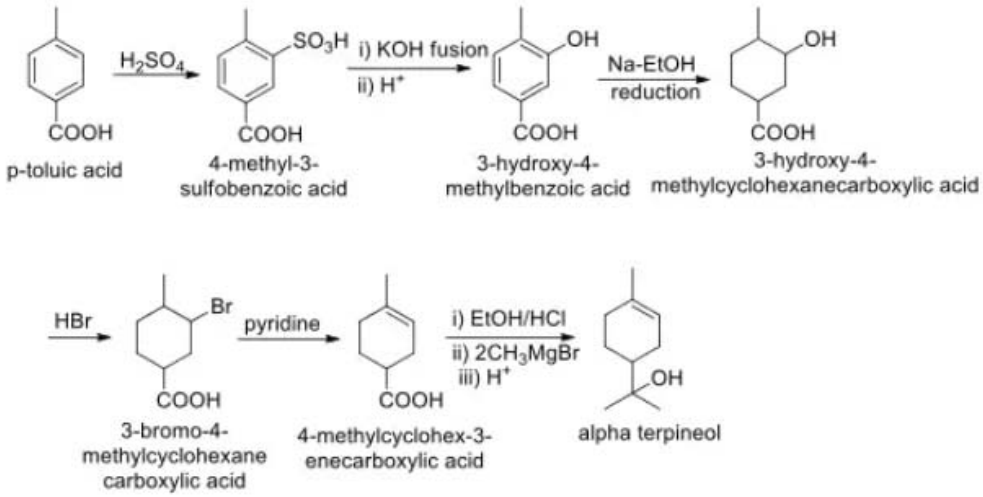
This double bond position clearly explain the formation of CH_3COOH in the reaction sequence

Synthesis of Terebic acid and Terpenylic acid further confirms an assigned structure.



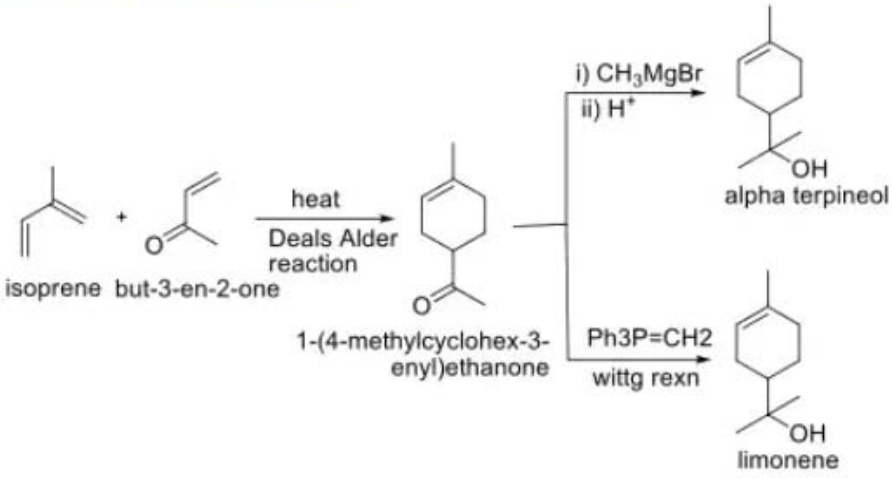
Synthesis of α-Terpineol

a) From p-Toluic acid

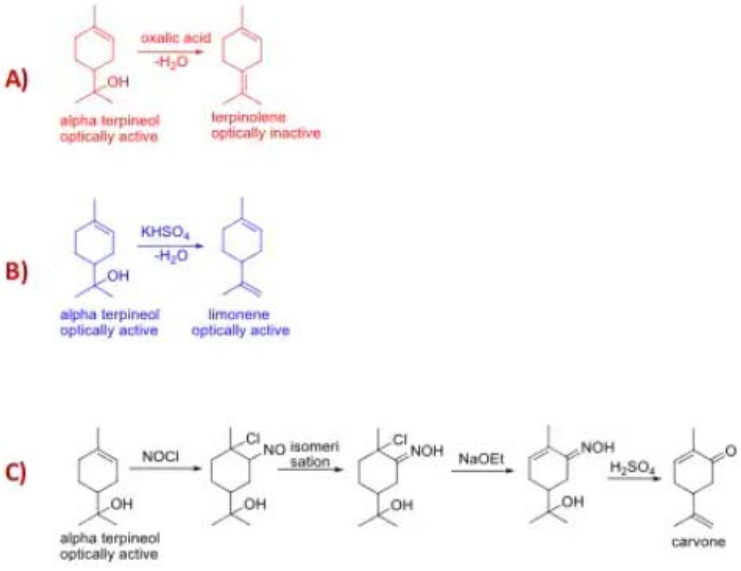


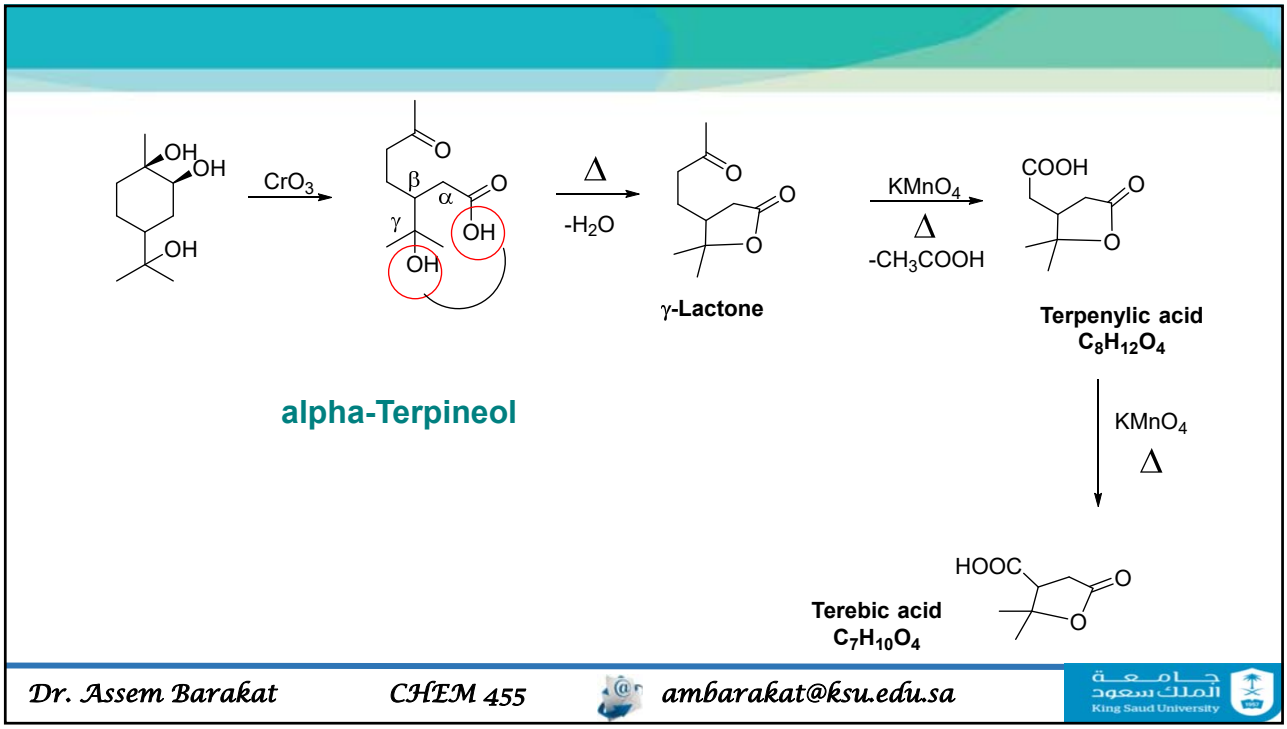
Short synthesis of alpha terpeniol

b) From Diels-Alder reaction



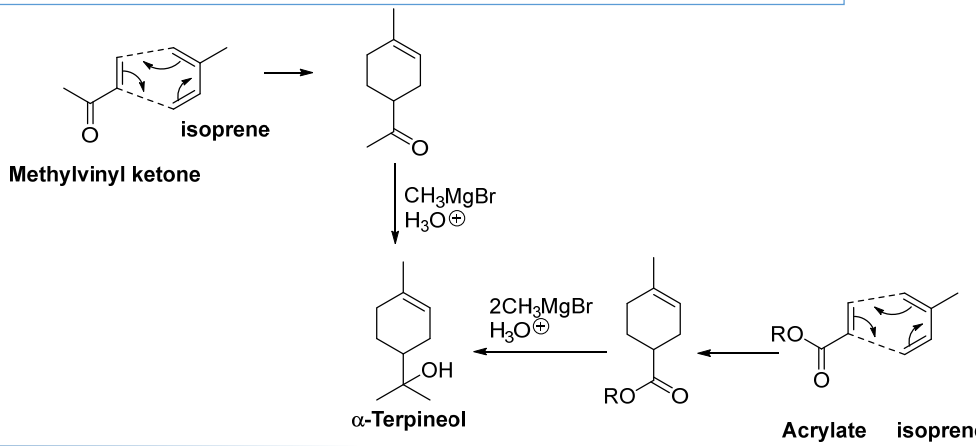
Synthesis of other terpenoids from alpha terpineol



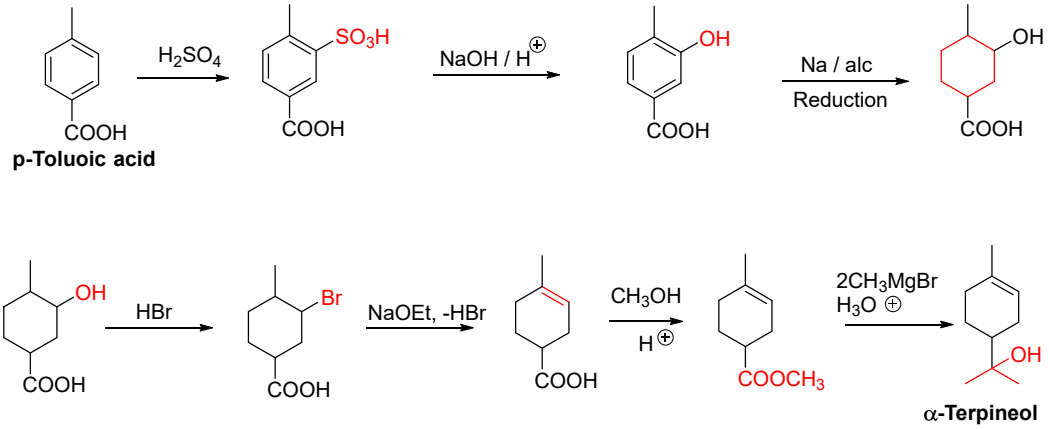


Synthesis of α- Terpineol

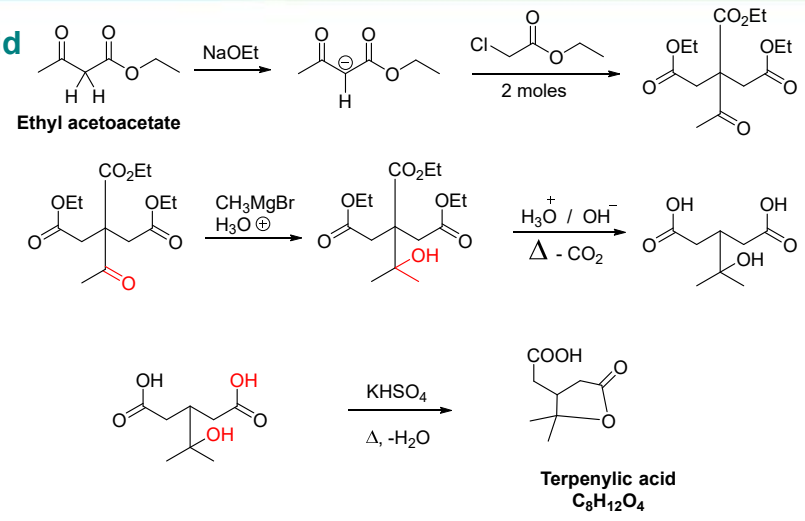
- α-Terpineol could be prepared from myrcene as mention in myrcene.
- Diel's Alder reaction



Synthesis of α- Terpineol from *p*-Toluoic acid

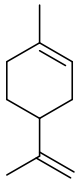


Synthesis of Terpenylic acid

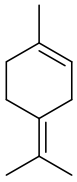


HOME WORK

- What is the difference between these two monocyclic terpenes?
- What is the difference between them in the reaction with:
  - O_3/Zn/AcOH
  - $KMnO_4$ (dil)
  - $KMnO_4$ (conc) /Heat
- How to prepare from α-terpineol?



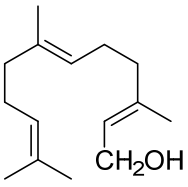
Limonene



p-Menthdiene

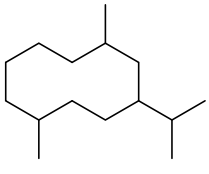
Sesquiterpeneoids

A class of terpenes which have ***three isoprene*** units (C15) ; can be **cyclic** or **acyclic**.



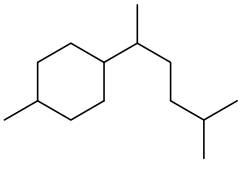
Farnesol

Vachellia farnesiana



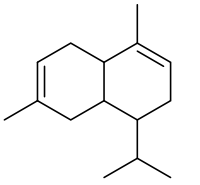
Germacrane

Red dead-nettle



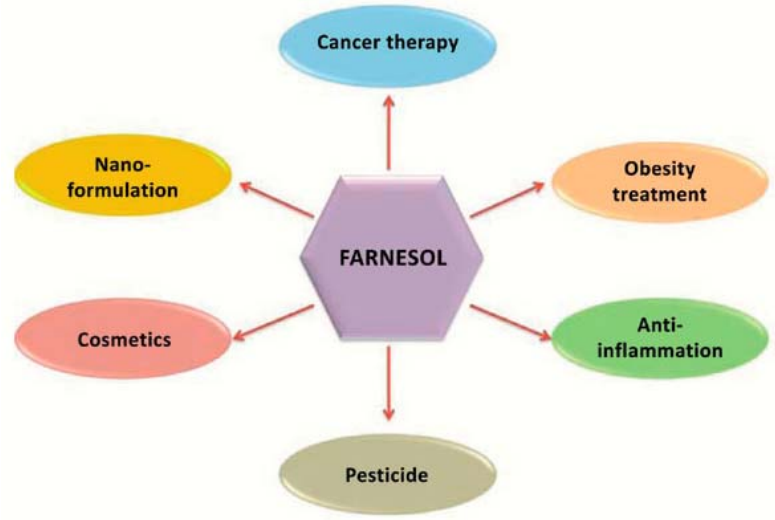
Bisbolane

Cubeb

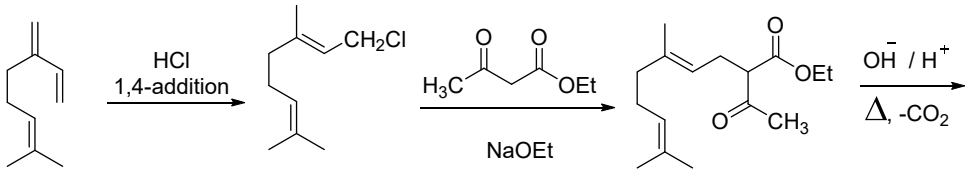


Cadenine

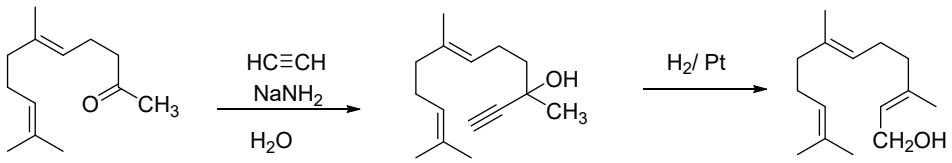
Cade



Farnesol

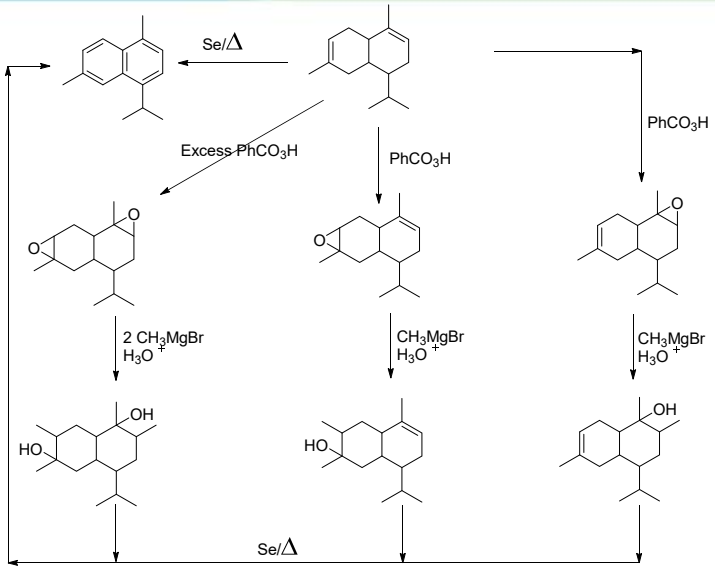


Myrcene



Farnesol

Cadenine



Stereoids

Cholesterol

Sex hormones
- Estrogens
- Progesterones
- Testosteron and anabolic stereoids

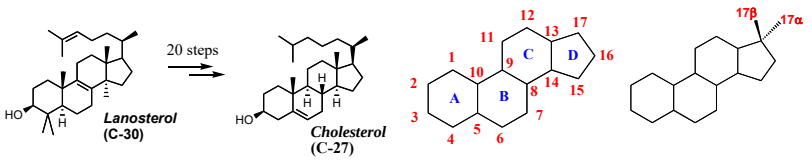
Corticoids
- Glucocorticostereoids
  - Cortison etc. etc.
- Mineralcorticostereoidsr
  - Aldosterone

Digitalis glycosides

Fucidinic acid (antibiotic)

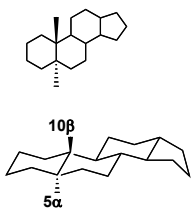
Brassinostereoids (Plant growth hormones)

etc. etc.

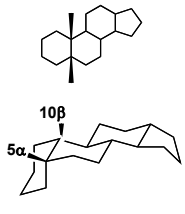


B / C og C / D always *trans* (animals)

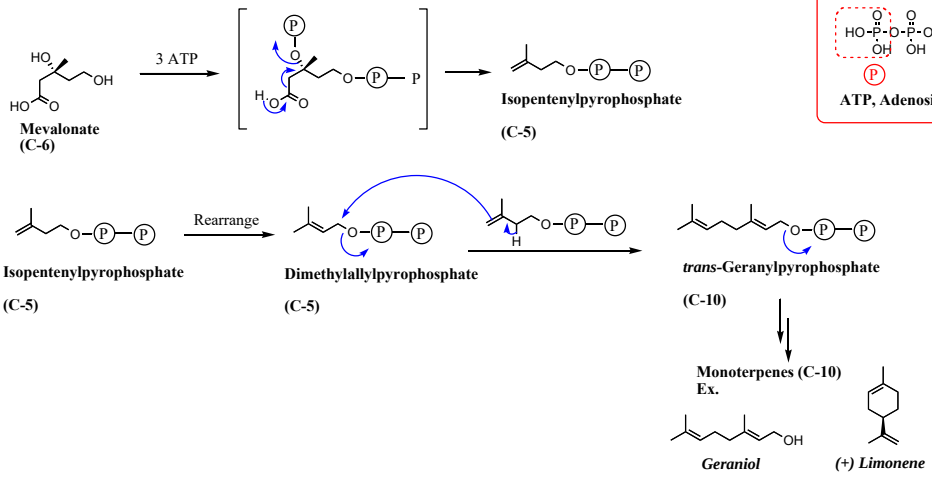
A / B *trans* fused



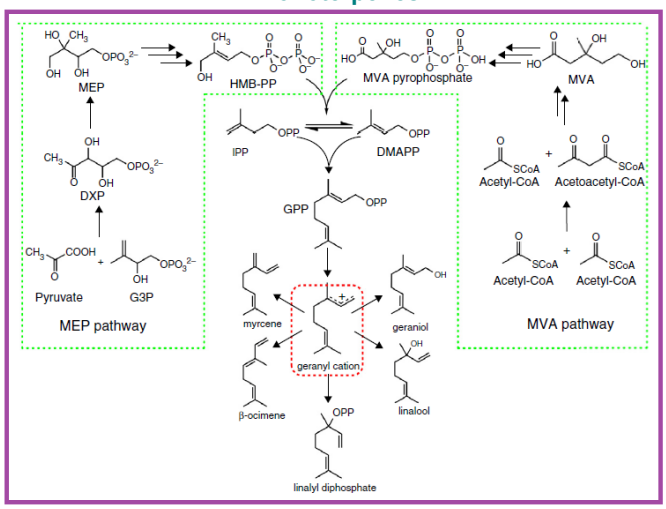
A / B *cis* fused

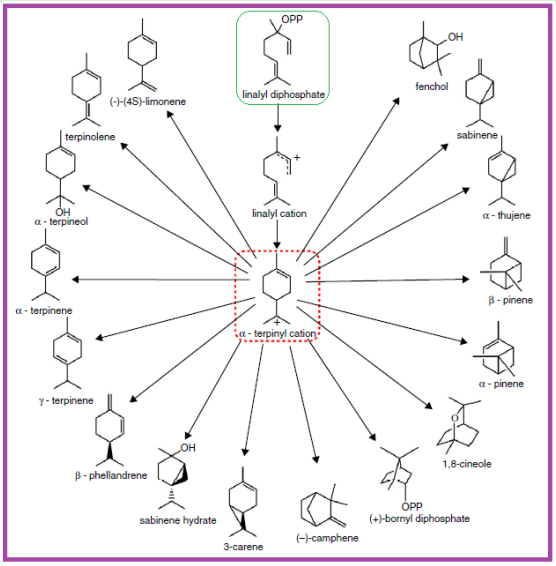


Biosynthetic Pathways for Terpenoids



Monoterpenes





Current Opinion in Chemical Biology **2016**, *34*:37–43

DITERPENOIDS

Definition:-

- **Diterpenes** are a class of chemical compounds composed of two terpene units, often with the molecular formula $C_{20}H_{32}$.
- Diterpenes consist of four isoprene subunits.
- They are biosynthesized by plants, animals and fungi via the HMG-CoA reductase pathway, with geranylgeranyl pyrophosphate being a primary intermediate.
- Diterpenes form the basis for biologically important compounds such as retinol, retinal, phytol and taxanes.
- Diterpenes can be classified as linear, bicyclic, tricyclic or tetracyclic, pentacyclic, and macrocyclic diterpenes depending on their skeletal core.
- In nature, they are commonly found in a polyoxygenated form with keto and hydroxyl groups, these last often esterified by small-sized aliphatic or aromatic acids.

Acyclic: Phytol

Monocyclic: Vitamin A(retinol)

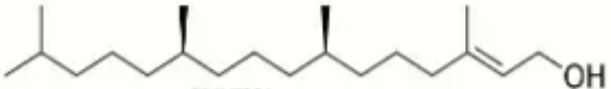
Bicyclic: Manool

Tricyclic: Abietic acid, Podocarpic acid

Tetracyclic: Gibberellic acid

PHYTOL

- **Introduction:-**
- It is a kind of diterpene which comes under the "acyclic diterpene" category.
- Phytol is an acyclic diterpene alcohol and a constituent of chlorophyll.
- It is obtained from alkaline hydrolysis of chlorophyll, which is then converted to phytanic acid and stored in fats.
- It is commonly used as a precursor for the manufacture of synthetic forms of vitamin E and vitamin K1.
- It is an optically active compound which boils at 145°C at 0.03mm pressure.
- **Molecular Formula:** $C_{20}H_{40}O$
- **Melting Point:** < 25 °C



PHYTOL

STRUCTURAL ELUCIDATION-

- **Molecular formula:** $C_{20}H_{40}O$
- **Presence of double bond :**

When it is catalytically hydrogenated, it adds on one mole of hydrogen to form dihydrophytol indicating that phytol contains one double bond.

$$\underset{\text{Phytol}}{C_{20}H_{40}O} + H_2 \xrightarrow{Pt} \underset{\text{Dihydrophytol}}{C_{20}H_{42}O}$$

- **Presence of primary alcoholic group :**

Phytol on oxidation with chromic acid yields monocarboxylic acid called phytenic acid which has same no. of C- atom indicating the presence of primary alcoholic group.

- **Ozonolysis of phytol :**

on ozonolysis it yields glycoaldehyde and a saturated ketone

$$\underset{\text{Phytol}}{C_{17}H_{33}C = CH.\,CH_2OH} \xrightarrow{O_3} \underset{\text{Ketone (I)}}{C_{17}H_{33}CO} + \underset{\text{Glycolaldehyde}}{OHC.\,CH_2OH}$$

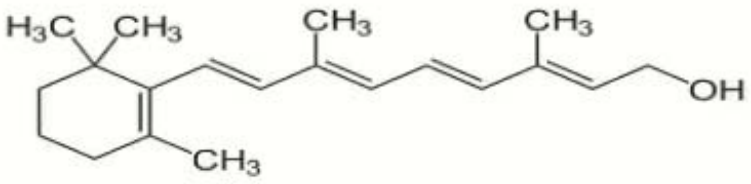
- **Structure of saturated ketone may be written as follows :**

$$CH_3CH.CH_2.CH_2\left|CH_2.\overset{CH_3}{CH}.CH_2CH_2\right|CH_2\overset{CH_3}{CH}.CH_2CH_2\left|CH_2.\overset{CH_3}{C}=O\right.$$

(I)

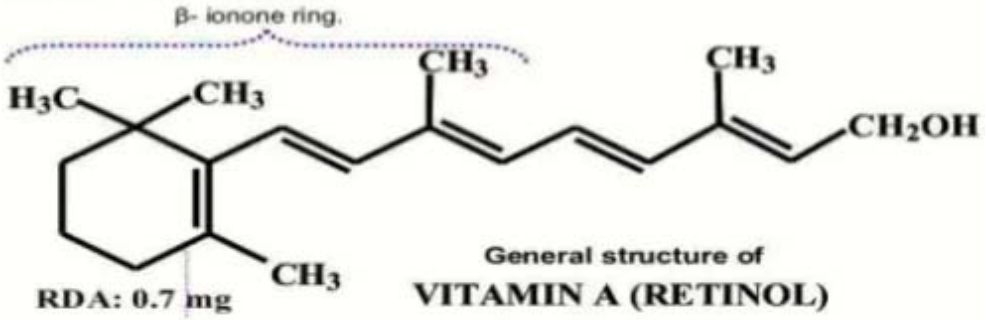
RETINOL

- It is a kind of diterpene which comes under the "Monocyclic diterpene" category.
- It is also called Vitamin A
- **Vitamin A** is the fat soluble vitamin, is a group of unsaturated nutritional organic compounds that includes retinol, retinal, retinoic acid, and several provitamin A carotenoids (most notably beta-carotene).
- All forms of vitamin A have a beta-ionone ring to which an isoprenoid chain is attached, called a *retinyl group*.
- **Molecular Formula:** $C_{20}H_{30}O$



Chemistry of vitamin A.

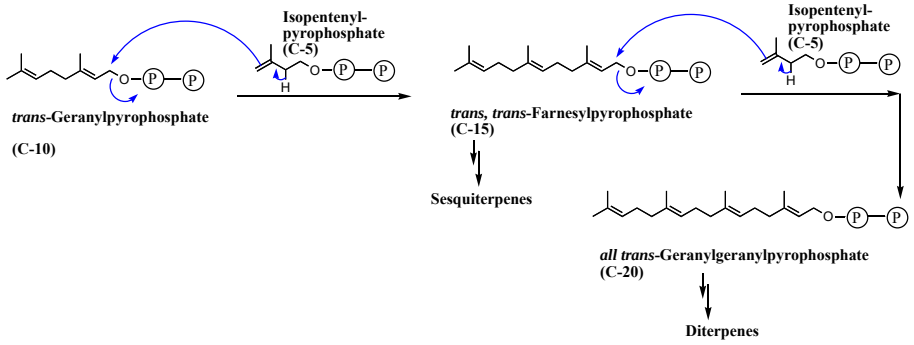
- Vitamin A (Retinol) is a cyclic polyene alcohol which resembles the structure of Diterpenoid.
- The structre of vitamin A constiture of a β- ionone ring.
- four conjugated double bonds in the side chain of vitaminA.
- They are in trans arrangement.
- Synthetic retinol is a trans isomer. It exists in 8 stereoisomeric forms.
- β- ionone ring and conjugated double bonds are essential for the biological activity of vitaminA.

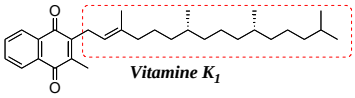


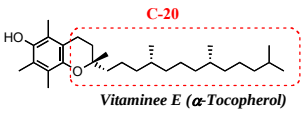
RDA: 0.7 mg

General structure of
VITAMIN A (RETINOL)

Diterpenes (C-20)







TRITERPENOID

- Compounds with carbon skeleton based on 6 isoprene units
- Derived biosynthetically from the acyclic C_{30} hydrocarbon
- Relatively complex cyclic structure
- Most either alcohols, aldehydes or carboxylic acids.
- Colourless, crystalline, often melting, optically active substance which generally difficult to characterize because lack of chemical reactivity
- Widely used test – Liebermann-Burchard reaction (acetic anhydride-conc H_2SO_4) – produces a blue-green colour with most triterpenes and sterols

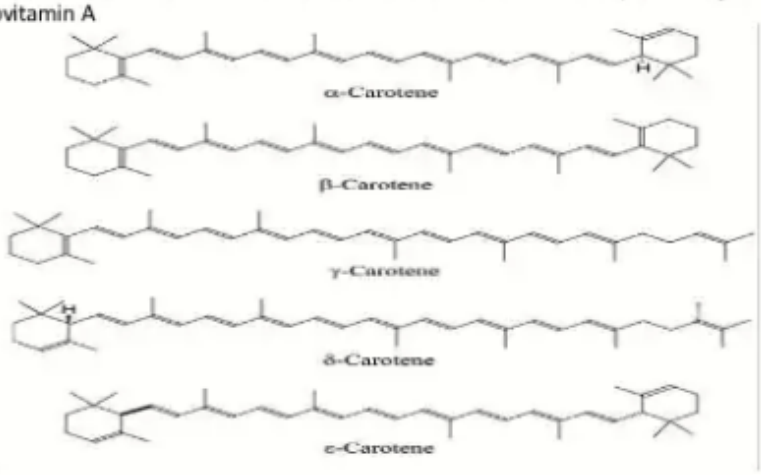
CAROTENOIDS

- Carotenoids are the group of non-nitrogenous , yellow , red or orange pigments that are universally distributed in living things.
- These are also called **tetraterpenoids** , that are produced by plants and algae as well as several bacteria and fungi.
- There are over 600 known carotenoids
- They split into 2 classes xanthophyll and carotenes
- Tetraterpenoids contain 40 C atoms
- General structure of carotenoid is a polyene chain consisting of 9-11 double bonds and possibly terminating in rings

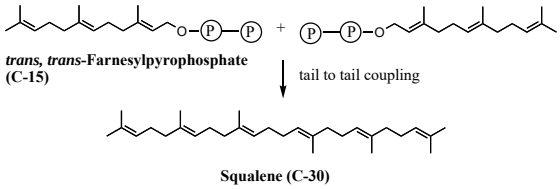
general structure of carotenoids

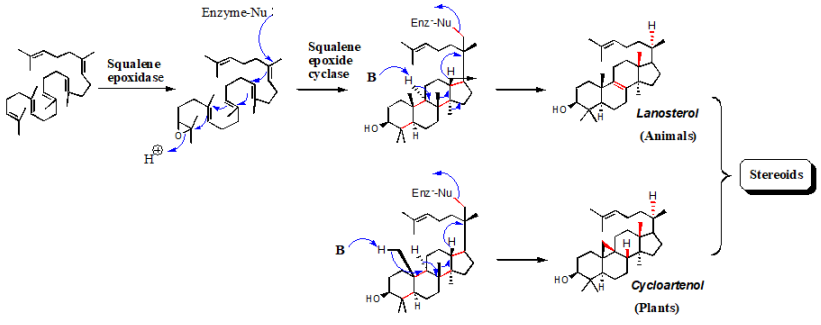
ALPHA & BETA CAROTENOIDS

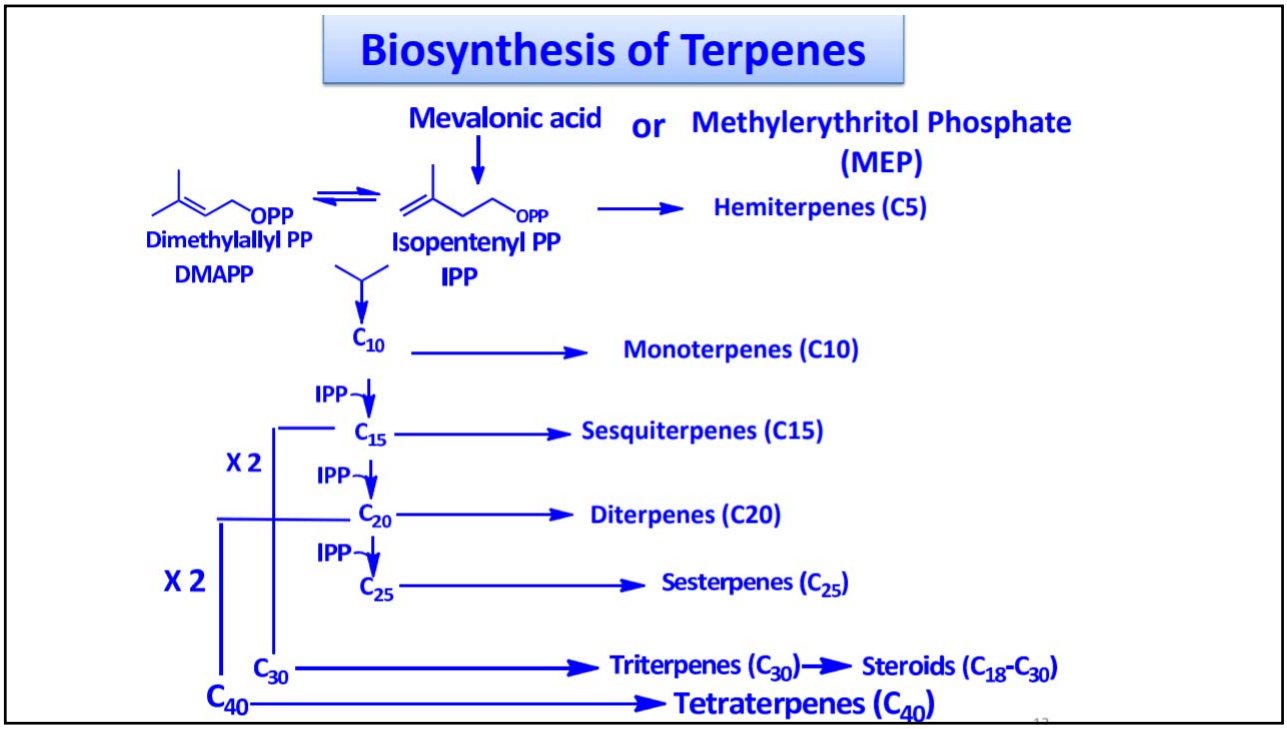
- About 600- 700 different carotenoids are known of which α & β carotene are the most prominent
- B carotene is the most known carotenoid and the most often naturally occurring carotene also known as provitamin A



Triterpenes (C-30)

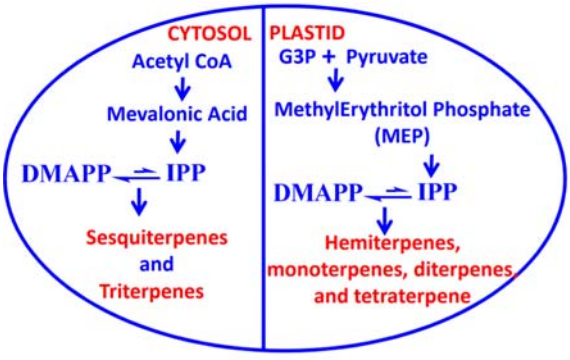




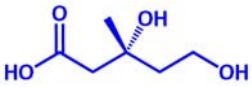


The five-carbon building blocks of all terpenoids, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), are derived from two independent pathways localized in different cellular compartments.

- The **cytosol localized Mevalonate pathway** provides C5 units for sesquiterpene and triterpene biosynthesis.
- The **methylerythritol phosphate (MEP or nonmevalonate) pathway**, localized in the plastids, is thought to provide IPP and dimethylallyl diphosphate for hemiterpene, monoterpene, and diterpene and tetraterpene biosynthesis.

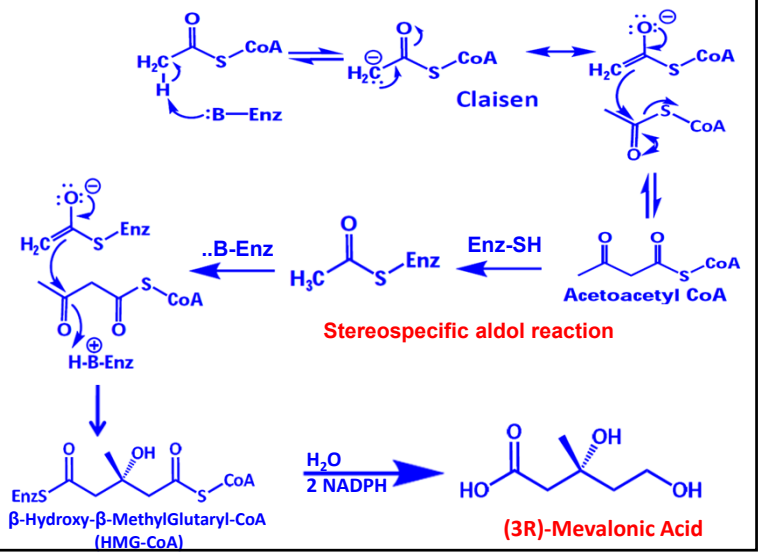


The Mevalonic Acid Pathway



(3R)-Mevalonic Acid

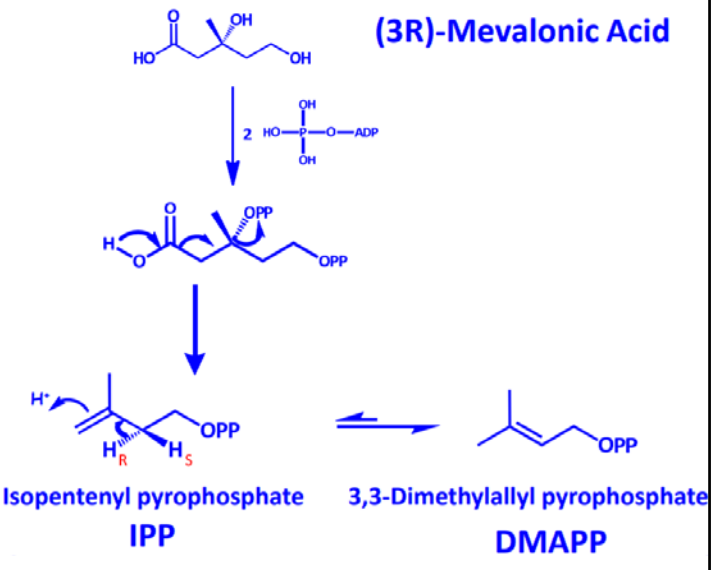
- Three molecules of acetyl-coenzyme A are used to form mevalonic acid.
- Two molecules combine initially in a Claisen condensation to give acetoacetyl-CoA, and a third is incorporated via a stereospecific aldol addition giving the branched-chain ester β-Hydroxy-β-MethylGlutaryl-CoA (HMG-CoA).
- In the second step, it should be noted that, on purely chemical grounds, acetoacetyl-CoA is the more acidic substrate, and might be expected to act as the nucleophile rather than the third acetyl-CoA molecule. The enzyme thus achieves what is a less favourable reaction.
- The conversion of HMGCoA into (3R)-MVA involves a twostep reduction of the thioester group to a primary alcohol.



The Mevalonic Acid Pathway

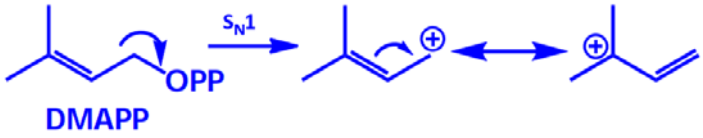
The six-carbon compound MVA is transformed into the five-carbon phosphorylated isoprene units in a series of reactions:

- phosphorylation of the primary alcohol group.
- Decarboxylation / dehydration
- then give IPP.
- IPP is isomerized to the other isoprene unit, DMAPP, by an isomerase enzyme which stereospecifically removes the pro-R proton (HR) from C-2, and incorporates a protonfrom water on to C-4.

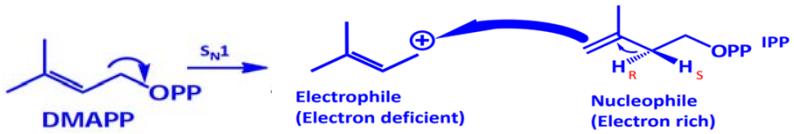


- *Whilst the isomerization is reversible, the equilibrium lies heavily on the side of DMAPP.*

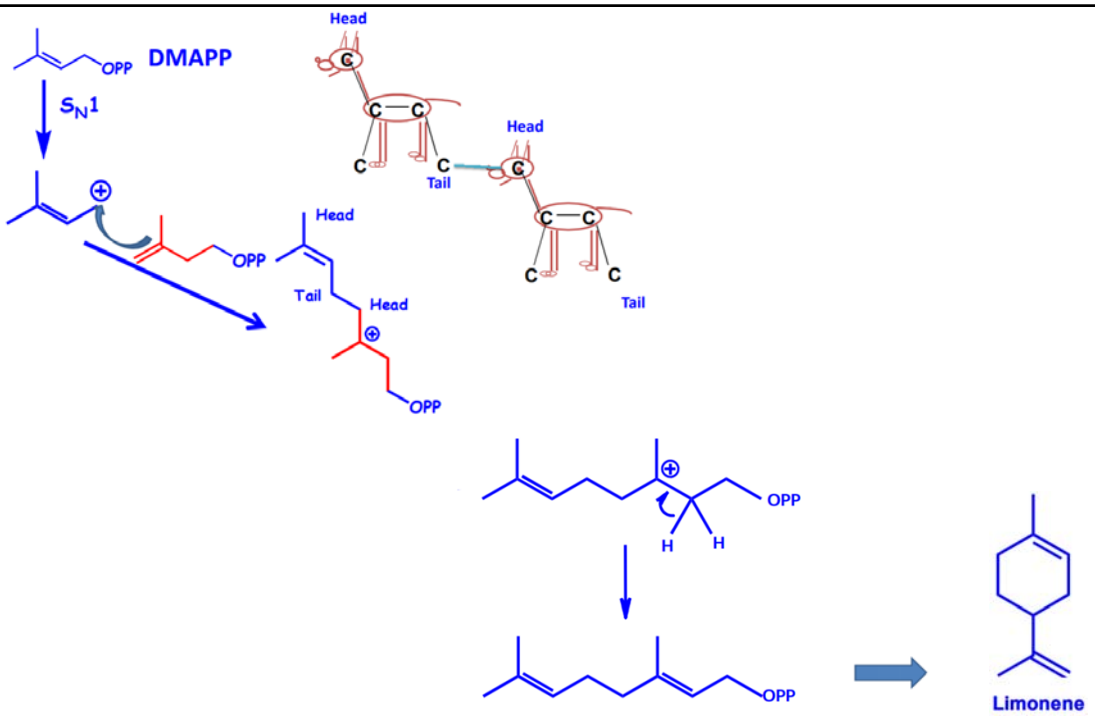
- DMAPP possesses a good leaving group, the diphosphate, and can yield via an S_N1 process an allylic carbocation which is stabilized by charge delocalization.
- This generates a reactive electrophile and therefore a good alkylating agent, DMAPP reacts as an electrophile.



- In contrast, IPP with its terminal double bond is more likely to act as a nucleophile, especially towards the electrophilic DMAPP

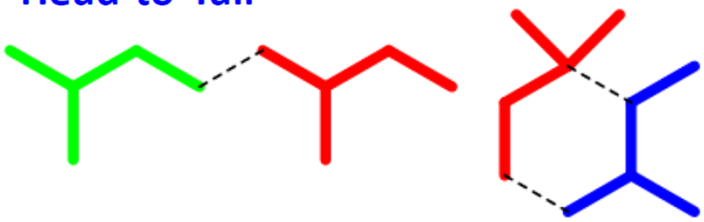


Therefore, terpenoids are synthesized by joining IPP (a nucleophile) and DMAPP (an electrophile) in a head to tail manner.

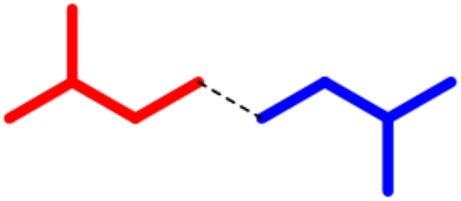


Joining Isoprene Units

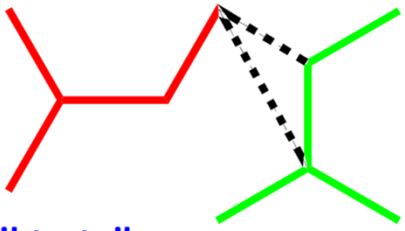
Head-to-Tail



Tail-to-Tail



Tail to Middle



Larger terpenoid units dimerize tail-to-tail.

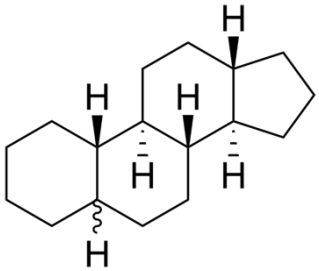
Steroids

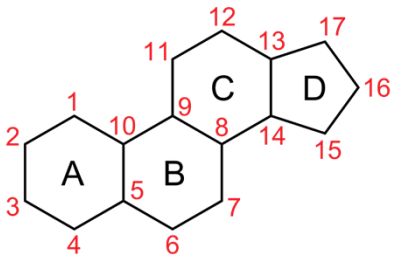
Steroid, any of a class of natural or synthetic organic compounds characterized by a molecular structure of 17 carbon atoms arranged in four rings.

Steroids are important in biology, chemistry, and medicine.

The **steroid group includes** all the sex hormones, adrenal cortical hormones, bile acids, and sterols of vertebrates, as well as the molting hormones of insects and many other physiologically active substances of animals and plants.

Steroids vary from one another in the nature of attached groups, the position of the groups, and the configuration of **the steroid nucleus (or gonane).**





Steroids

Cholesterol

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

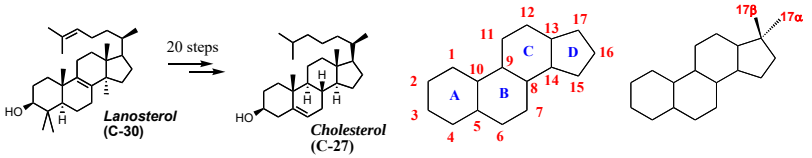
Corticoids
- **Glucocorticostereoids**
  - **Cortison etc. etc.**
- **Mineralcorticostereoidsr**
  - **Aldosterone**

Digitalis glycosides

Fucidinic acid (antibiotic)

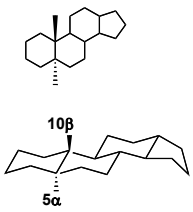
Brassinostereoids (Plant growth hormones)

etc. etc.

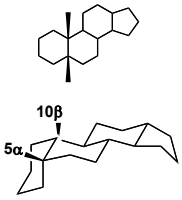


B / C og C / D always *trans* (animals)

A / B *trans* fused



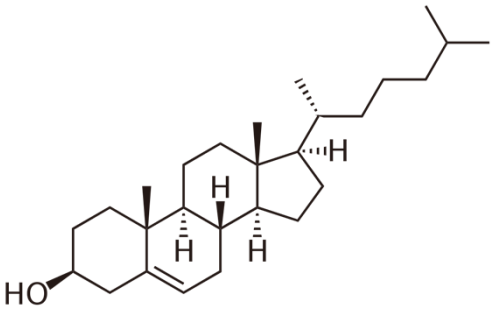
A / B *cis* fused



Sterol

Cholesterol

Cholesterol is a sterol (or modified steroid), a type of lipid.
Cholesterol is biosynthesized by all animal cells and is an essential structural component of animal cell membranes. It is a yellowish crystalline solid.

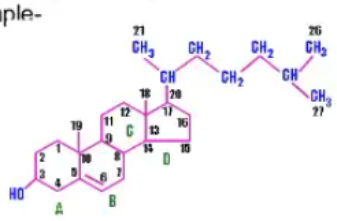


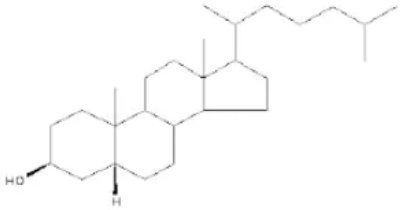
Sterol

The sterol may be further sub divided into the following three categories , namely:-

(a)Zoosterols:- such sterols those are obtained from of plants are obtained from the animal kingdom only.

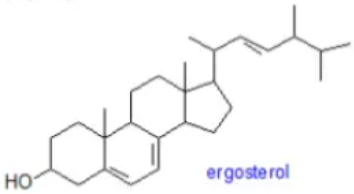
Example-

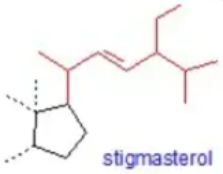


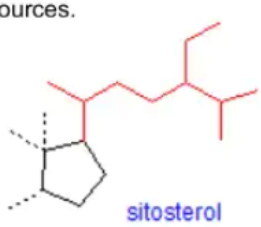


(i)Cholesterol, (ii)coprostanol.etc.

(b)Phytosterols:-such sterols those are derived from the plant sources.





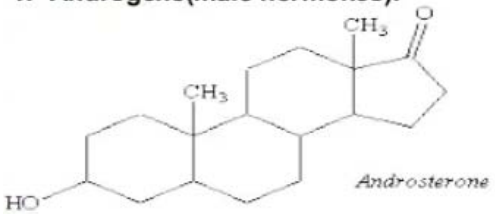


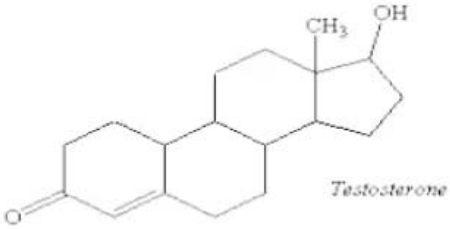
(c) Mycosterols :- such sterols those are obtained from either yeast or fungi.

Sex Hormones

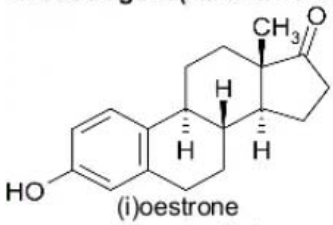
Sex hormone are usually classified under the following three heads ,namely:-

1. Androgens(male hormones):-



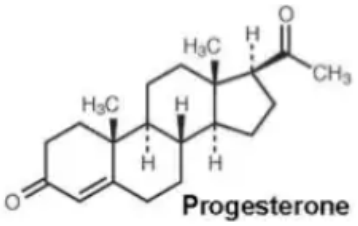


2.Oestrogens(female hormones):-



(i)oestrone
(ii)oestradiol
(iii)stilbesterol
(iv)hexesterol etc.

3.Gestogens(the carpus Luteum hormones):-

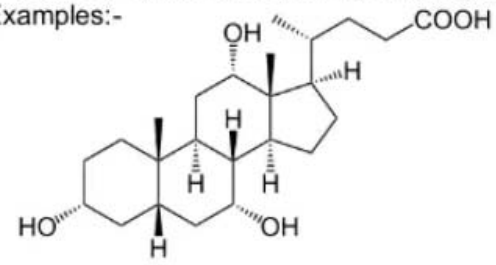


Progesterone

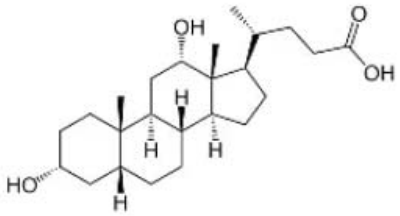
Bile salt

The liver secretion a clear, golden yellow viscous liquid known as 'bile' .It is stored in gall bladder and is useful for digestive system.

Examples:-



Cholic acid



deoxycholic acid

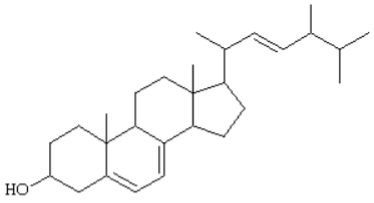
Biological significance of steroids

Cholesterol & vitamin D3

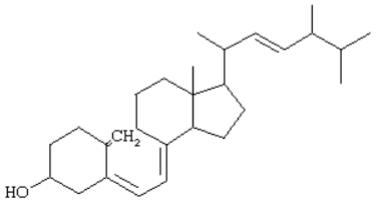
occur in all tissues of animals, green plants, and fungi such as yeasts.

In mammalian skin one precursor of cholesterol, 7-dehydrocholesterol, is converted by solar ultraviolet light to cholecalciferol, vitamin D3, which controls calcification of bone by regulating intestinal absorption of calcium.

The disease rickets, which results from lack of exposure to sunlight or lack of intake of vitamin D, can be treated by administration of the vitamin or of the corresponding derivative of ergosterol, ergocalciferol (vitamin D2).



ergosterol (8)



ergocalciferol (9)

Cholesterol & atherosclerosis

Sterols are present in tissues both in the nonesterified (free) form and as esters of aliphatic fatty acids.

In the disease atherosclerosis, fatty materials containing cholesterol form deposits (plaques), especially in the walls of the major blood vessels, and vascular function may be fatally impaired.

The disease has many contributory factors but typically is associated with elevated concentrations of cholesterol in the blood plasma. One aim of medical treatment is to lower the plasma cholesterol level.