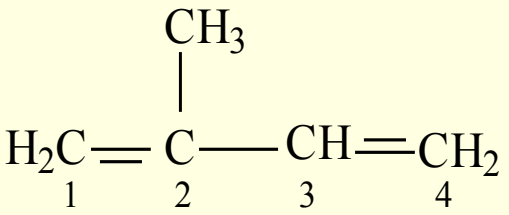
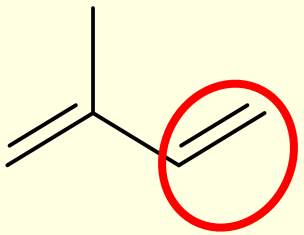
Chemistry of Essential oils

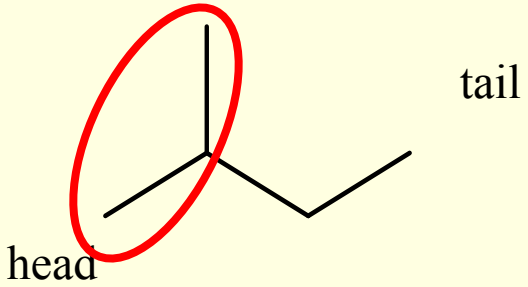
Terpens

Form a large and structurally diverse family of natural products derived from C_5 isoprene units joined in a head to tail fashion





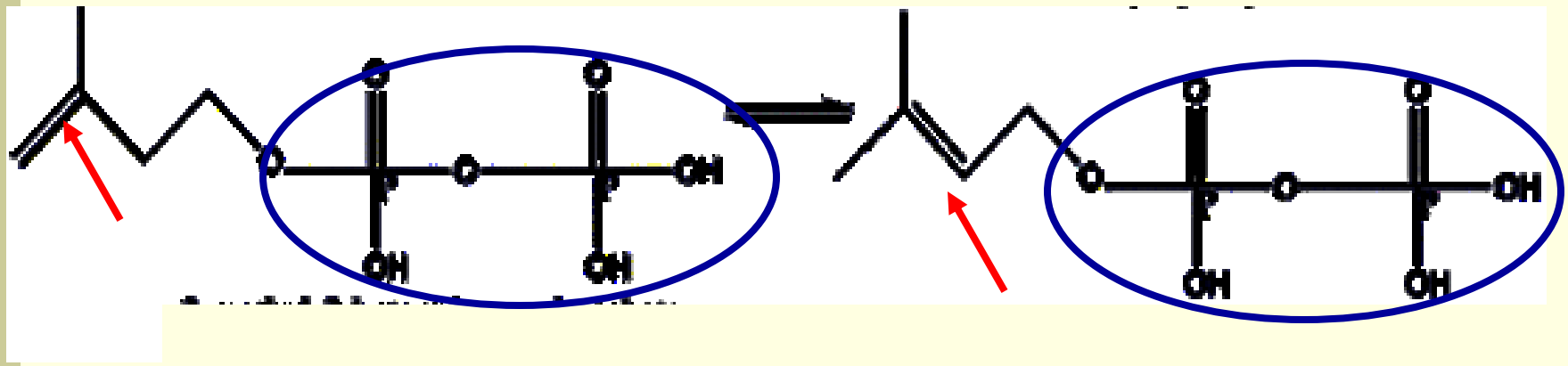
Isoprene



Isoprene unit

C_5

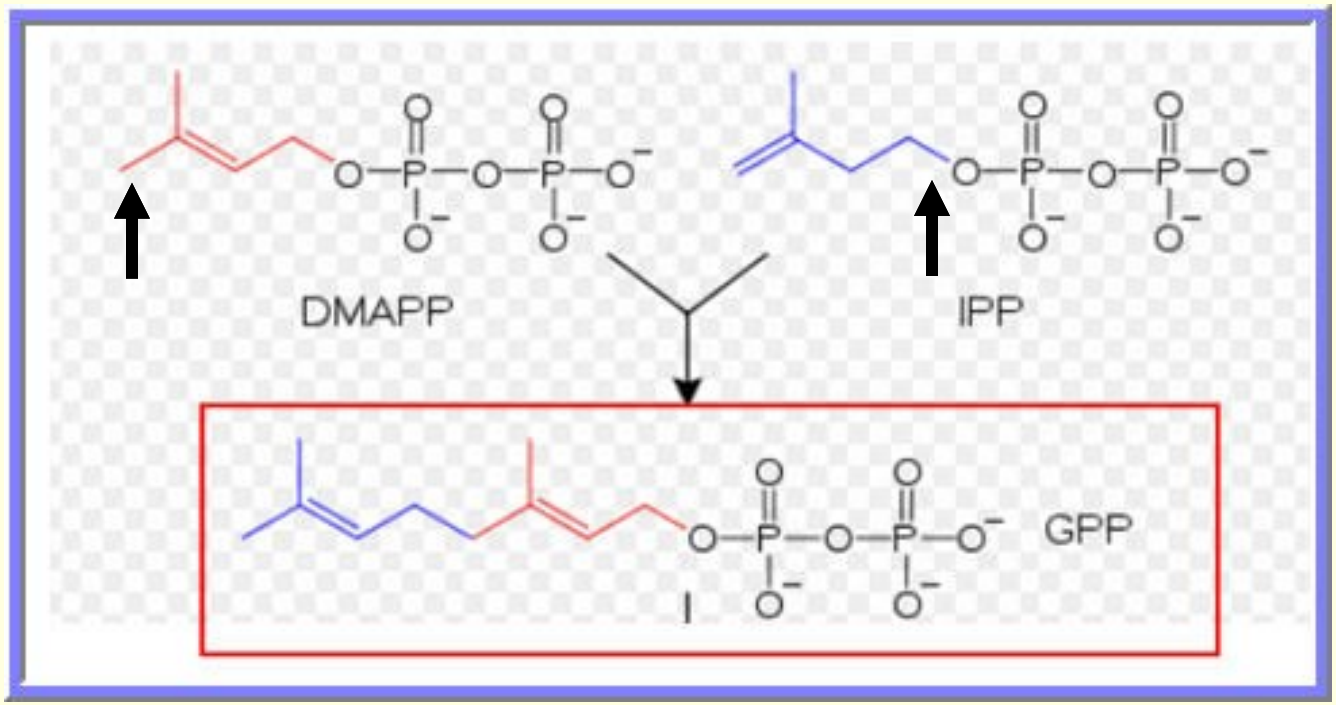
The biologically active isoprene units were identified as the pyrophosphate esters IPP (Isopentenyl pyrophosphate) And DMAPP (Dimethylallyl pyrophosphate)



Isopentenyl pyrophosphate
IPP

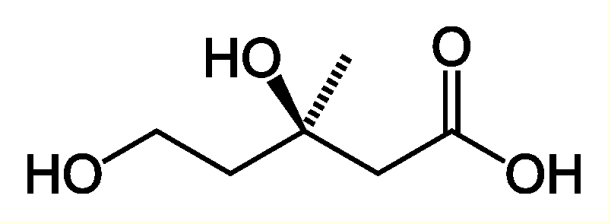
Dimethylallyl
pyrophpsphate DMAPP

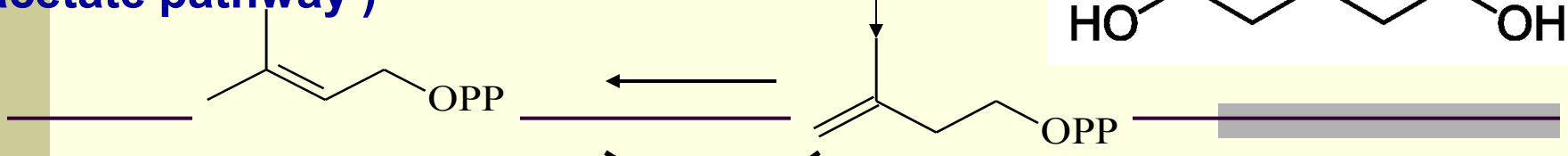
Prenyl transferase



Origin of terpenes (acetate pathway)

Mevalonic acid

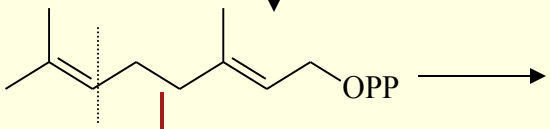




DMAPP (C_5) IPP (C_5) Hemiterpenes (C_5)

Prenyl transferase

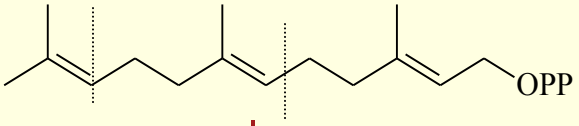
GPP (C_{10})



→ Monoterpens & Iridoids (C_{10})

IPP

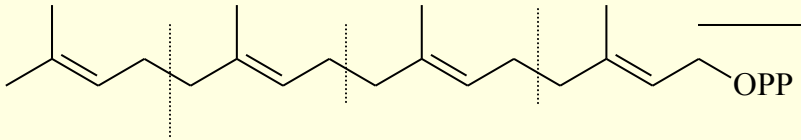
FPP (C_{15})



→ Sesquiterpenes (C_{15})

IPP

GGPP (C_{20})



→ Diterpenes (C_{20})

2 x FPP → squalene → Triterpenes (C_{30})

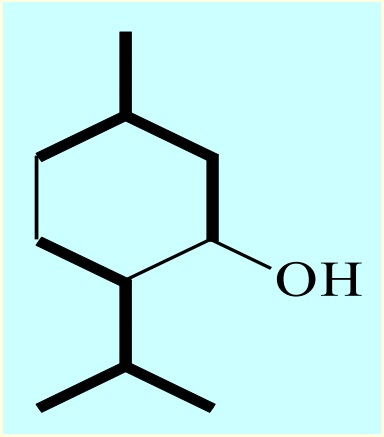
2 x GGPP → Tetraterpens (C_{40})

→ Steroids (C_{18}-C_{30})

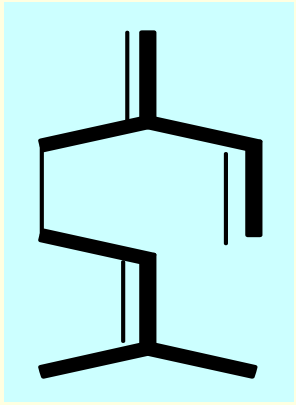
Terpenoids

- **C10-Monoterpenes**
  - Regular monoterpenes (essential oils, oleoresins, iridoids)
  - Irregular monoterpenes (pyrethrins)
- **C15-Sesquiterpenes (essential oils, sesquiterpenoid lactons)**
- **C20-Diterpens (e.g. retinol)**
- **C30-Triterpens & steroids (saponins, cardiac glycosides)**
- **C40-tetraterpenes (e.g. β-carotenes)**

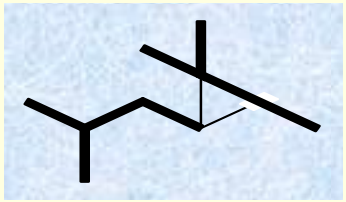
Regular monoterpene skeleton

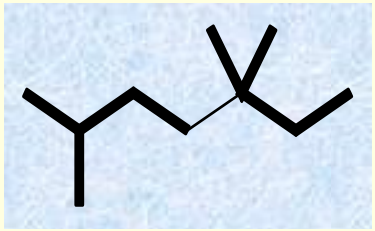


Menthol



myrcene

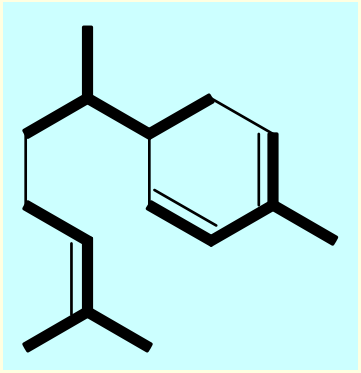




Irregular monoterpene skeletons
Pyrethrins

Sesquiterpenes
(C15)

Zingiberine

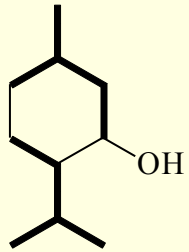


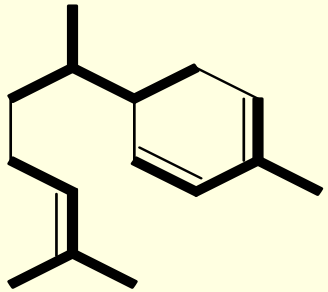
Chemistry of Essential oils

- **Essential oils are complex and highly variable mixtures of constituents.**

although few contain only single constituent as bitter almond, winter green and mustard oils

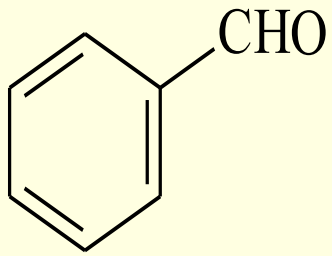
- **Terpenoids**





The odor and the taste of volatile oils is due to the oxygenated comp.

- Aromatic compounds
- Other compounds



$CH_2=CH.CH_2N=C=S$

Terpeneless volatile oils

Oils from which terpenes have been removed in part or entirely.

Since terpenes deteriorate rapidly through oxidation and resinification

Terpeneless volatile oil is characterized by :

- More alcohol soluble
- More stable against oxidation and resinification
- Have much stronger odor

Preparation of terpeneless volatile oils

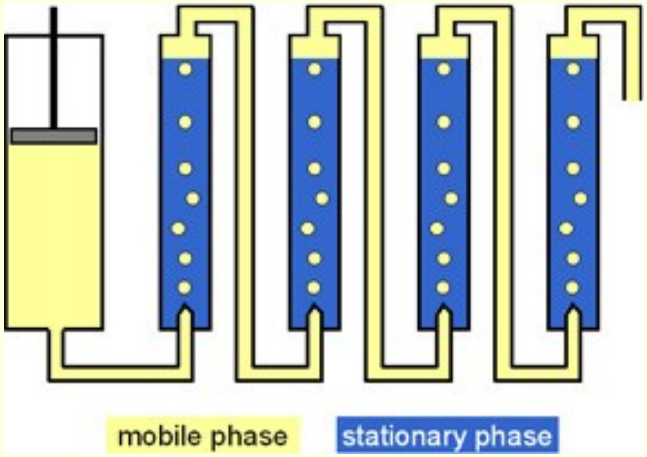
- Repeated fractional distillation in vacuum.

the boiling point of terpene < B.p. of terpenoids

The B.P. of sesquiterpenes > B.p. of terpenoides

Extraction of more oxygenated compounds.

- Using counter-current chromatography.



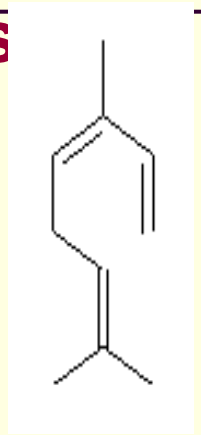
Classification of essential oils

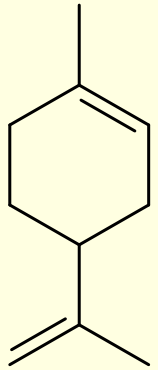
- According to biogenetic origin

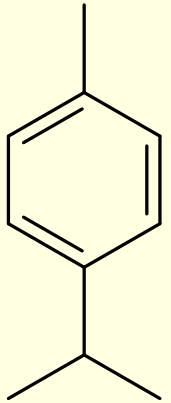
A-Terpenes &Terpenoids

Monoterpenes:

a) Acyclic
b) Alicyclic → Monocyclic / Bicyclic
c) Aromatic

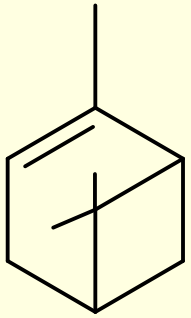




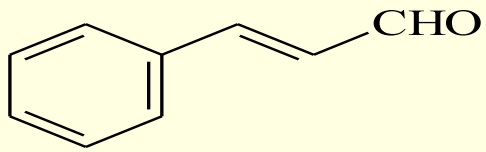


Sesquiterpenes

a) Acyclic
b) Alicyclic → Monocyclic / Bicyclic or tricyclic
c) Aromatic (azulenes)



B-Phenylpropanoid (C6-C3) derived aromatics



According to functional groups

I- Hydrocarbons **II- Alcohols**

III- Phenols **IV- Esters**

V- Aldehydes **VI- Ketones**

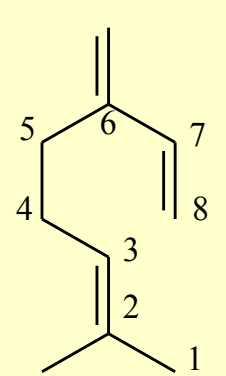
VII- Oxides **VIII- Peroxides**

IX-Sulfur compounds **X-Nitrogen compounds**

Hydrocarbons

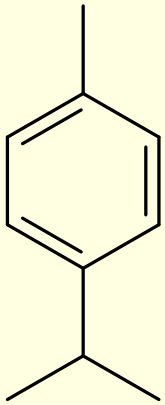
(Monoterpenes)

Acyclic | Aromatic | Alicyclic



Myrcene

Oils of hops & turpentine



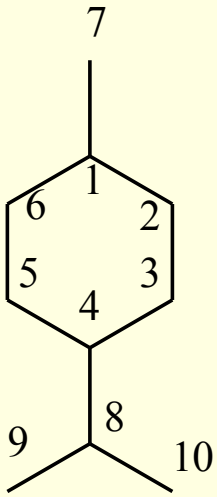
p-Cymene

Oils of Thyme & Eucalyptus

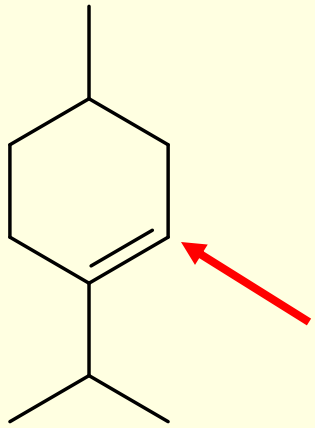
p-isopropyl methyl-benzene

Alicyclic → Monocyclic | Bicyclic

Monocyclic → Saturated | Unsaturated



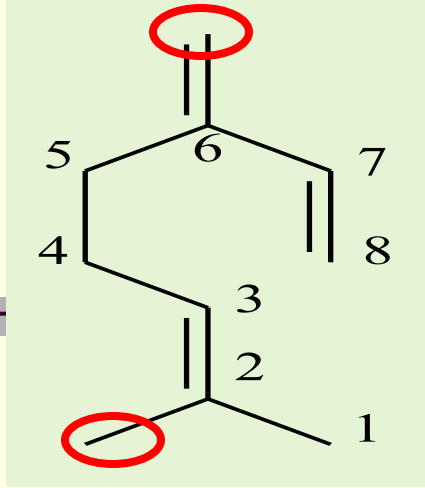
p-Menthane



Δ^3 p-Menthene

Myrcene

2 methyl, 6 methylene $\Delta^{2:7}$ octadiene



Source :obtained from oil of hops

Identification:

-Myrcene +2Na + 2ROH ⟶ dihydromyrcene

- $2Na + 2ROH \longrightarrow 2RO^{-}Na^{+} + H_2$

Br_2 ↓

Tetrabromodihydromyrcene (m.p. 88 ° C)

-Oil + lead salt⟶ needle crystal

-Heat the oil in sealed tube ⟶ diterpene

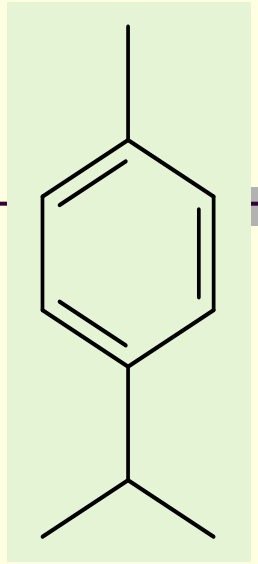
- oil + KMnO4 ⟶ succinic acid

inhibitor of gastric and duodenal ulcers

Aromatic hydrocarbons

e.g. p-cymene

p-isopropyl methyl benzene



Source : Thyme and eucalyptus oils

Properties: colorless, optically inactive

Identification:

- with $KMnO_4$ (hot & conc. → p-hydroxy isopropyl benzene m.p. 155°C

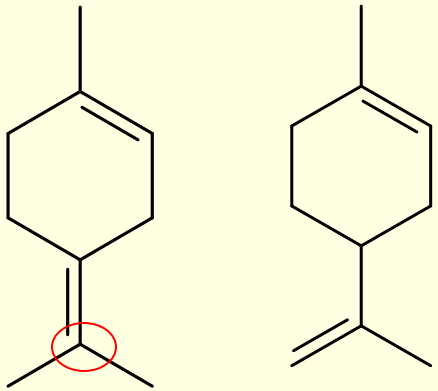
Uses:-Cymene is used in flavoring of beverages, cakes and confectionery as well as in fragrances.

eugenol , carvacrol , thymol**, p-cymene** and γ-terpinene cause inhibition of drug resistance and biofilm formation of oral bacteria

Alicyclic hydrocarbons
Monocyclic, Monoterpenes, Unsaturated

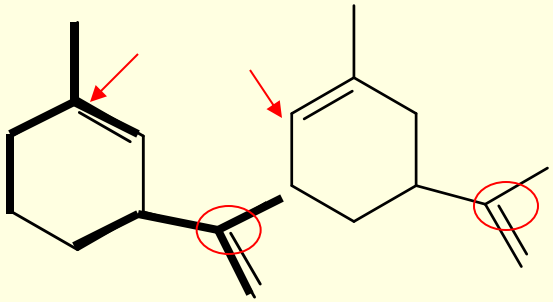
p-menthadiene

m-menthadiene



Terpinolene $\Delta^{1:8}$

Limonene



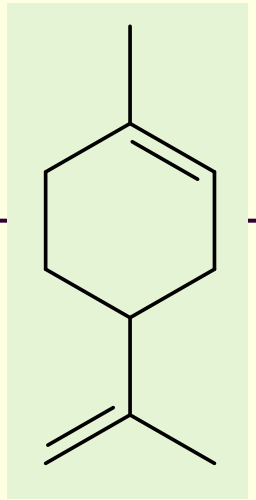
Sylvestrene

Mixture of two hydrocarbons

$\Delta^{1:8(9)}$, $\Delta^{6:8(9)}$

Oil +acetic anhydride +conc.H_2SO_4 + conc. HNO_3 → blue color

Limonene



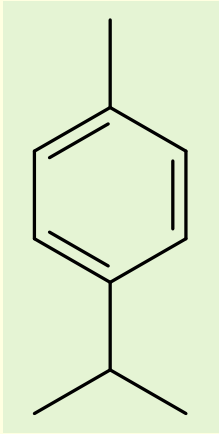
$\Delta^{1:8(9)}$ p-menthadiene

d-Form: oils of lemon, bitter orange & caraway

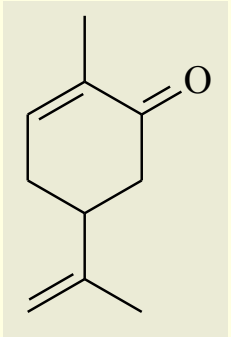
l-Form: oil of *Pinus sylvestris*

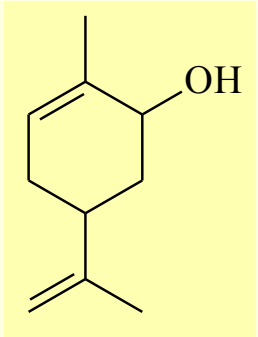
dl-Form (dipentene):oils of lemongrass, nutmeg & fennel.

(dehydrogenation)sulfur → **p-cymene**



Limonene → **auto-oxidation** → **carvone + carveol**





Limonene

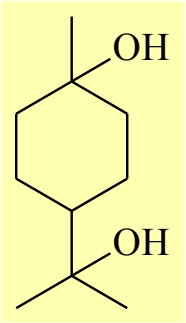
Acid

Cold

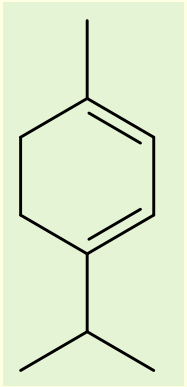
Heat

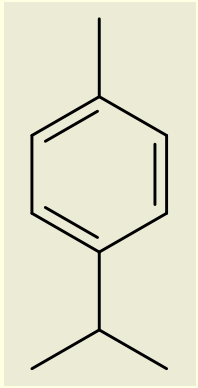
terpin hydrate

α- terpinene + p-cymene



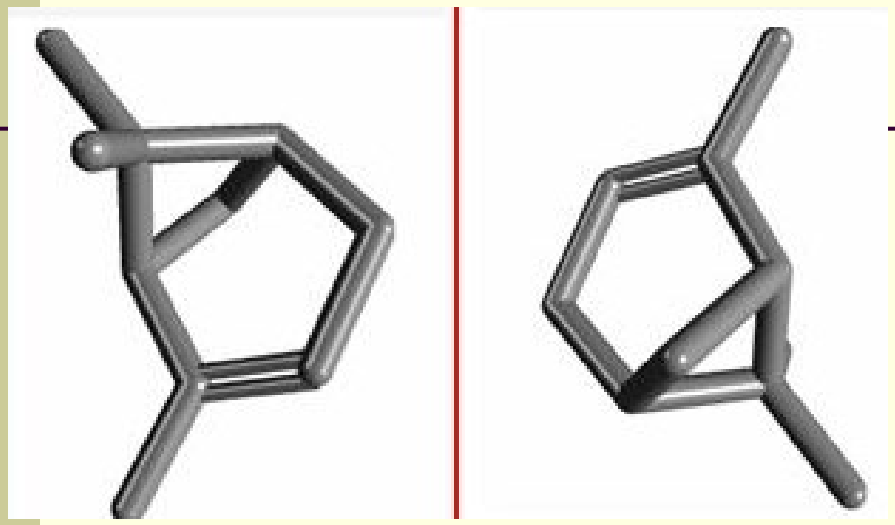
. H_2O

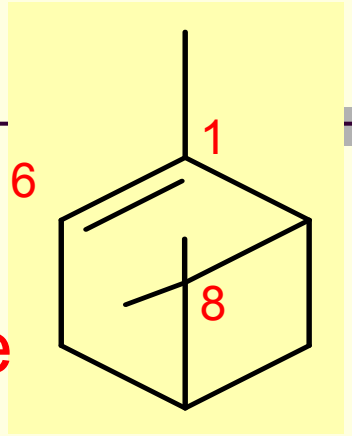




d-limonene has chemopreventive activity against many types of cancer.

Bicyclic Monoterpenes





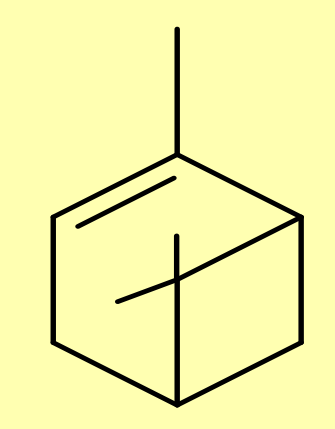
α-Pinene

1,8,8-trimethyl bicyclo 2,4 $\Delta^{1(6)}$ heptene

- **Oil of Terpentine & coniferae plants**
- Isolation by fractional distillation
- Purified by forming crystalline nitrosochloride
- Liberated by aniline

α-Pinene

α-pinene and β-pinene inhibit the growth of infectious endocarditis causing gram-positive bacteria.



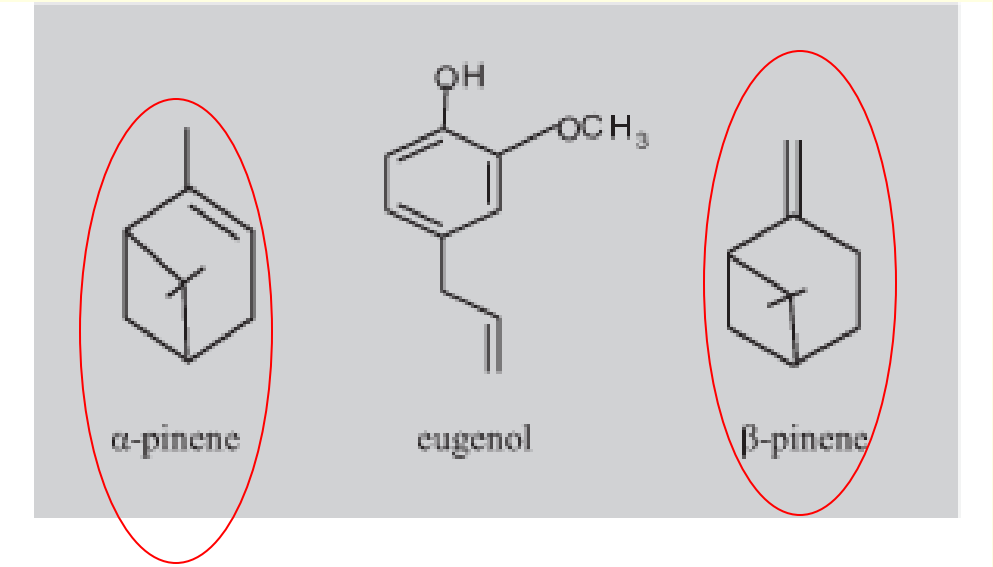
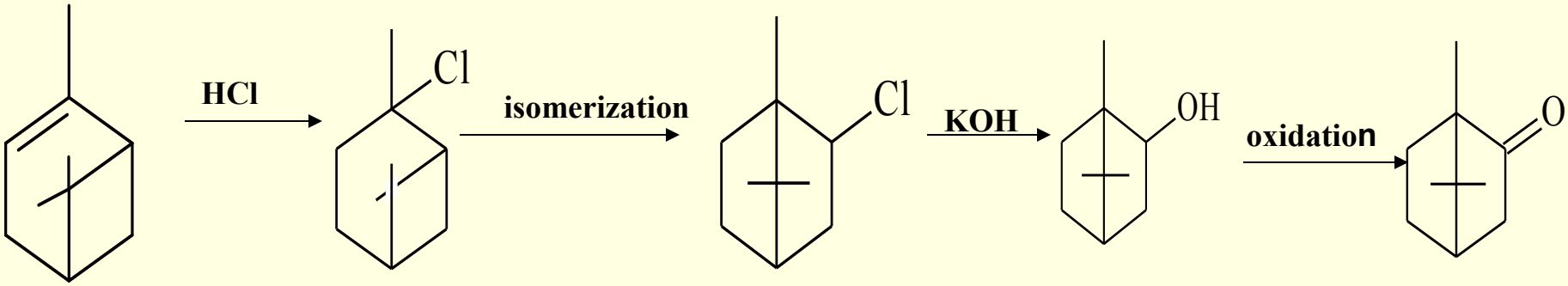


FIGURE 1 - Molecular structures of phytochemicals used in the antimicrobial assays.

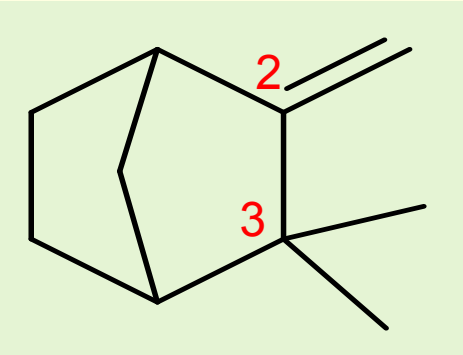
Preparation of synthetic camphor



α-pinene | pinene HCl | bornyl chloride | bornyl alcohol | camphor

Terpenes having camphane structure

Camphene



2-methylene 3,3-dimethyl bicyclo1,4-heptane

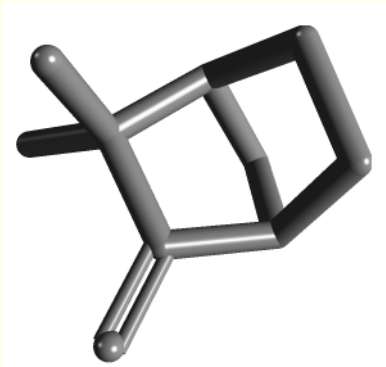
Oil of Terpentine

d-Form in oils of nutmeg & ginger

l-Form in oils of valeriana & citronella

dl-Form in oil of rosemary

Colorless to white solid with **camphor like odor**.

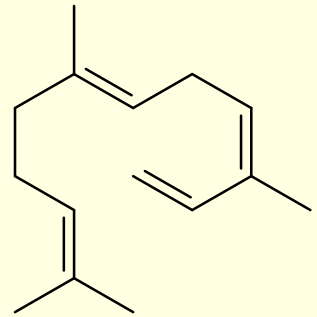


- **Camphene,** a Plant-Derived Monoterpene, Reduces Plasma **Cholesterol** and **Triglycerides** in Hyperlipidemic Rats, (Nov., 2011)

camphene exerted antitumor activity *in vivo* by inhibiting growth of melanoma cells (by apoptosis), 2015.

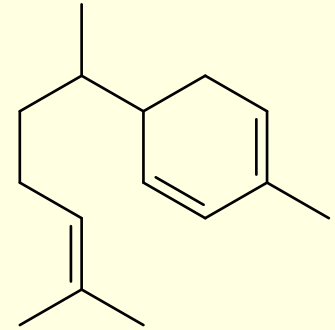
Sesquiterpenes

- Acyclic
- Monocyclic
- Bicyclic
- Tricyclic



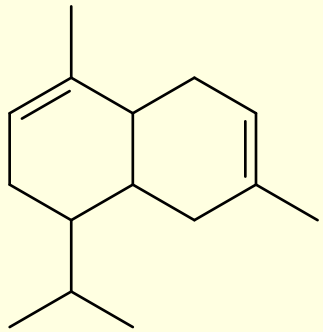
Sesquicitronellene

Oil of Citronella



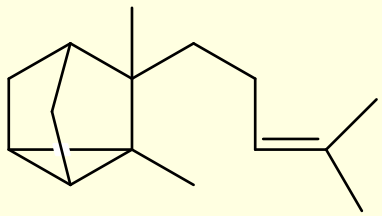
Zingiberine

Oil of Ginger



Cadinene

Oil of Savin

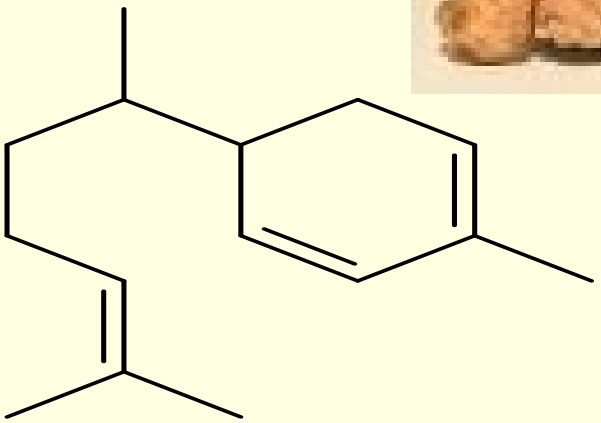


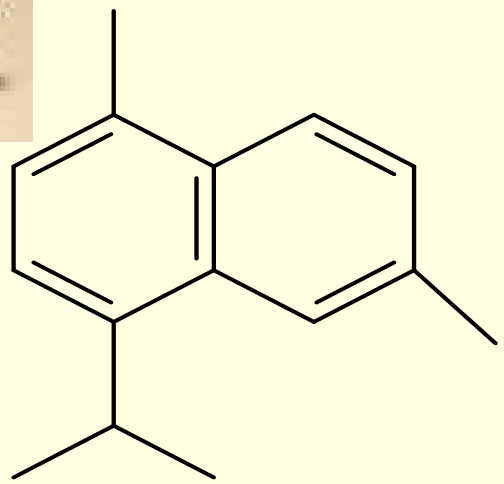
α-Santalene

Oil of Sandal wood

Forms nitrosochloride derivative.

Zingiberine





- Zingiberine + Sulphur $\xrightarrow{\text{Dehydrogenation}}$ Cadalene (colorless liquid)
- Cadalene **+ HCl gas** $\longrightarrow$ **dihydrochloride**

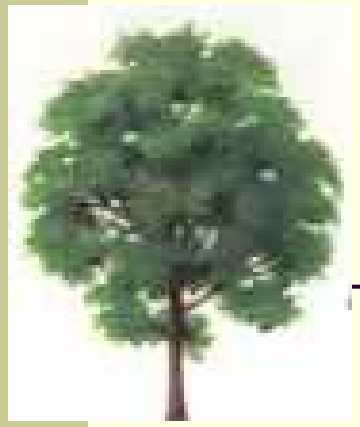
  (m.p.)

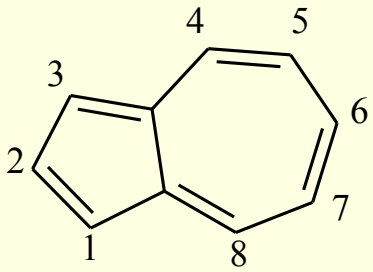
- **Zingiberine** can be used as a novel and natural potential therapeutic in counteracting oxidative damages in the field of **neurodegenerative disorders** [Alzheimer's and dementias, Parkinson's Disease, Multiple Sclerosis,….]

(**Neuroprotective**).

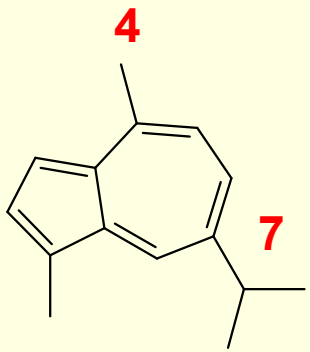
-Natural **anticancer** agent.

Azulene Derivatives

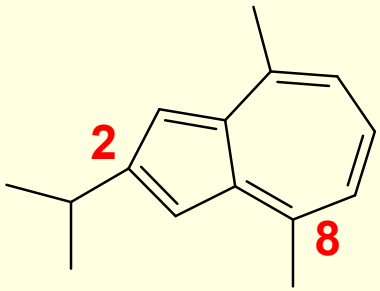




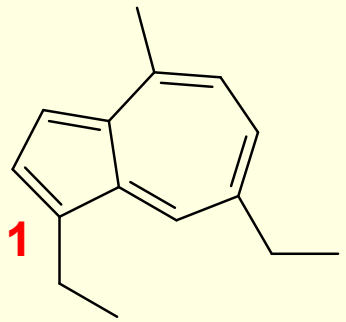
- They are colored hydrocarbons included under sesquiterpenes, but partially aromatic.
- Azulenes are usually named after the names of the plants in which they occur



Guaiazulene
Oil of Guaiacum



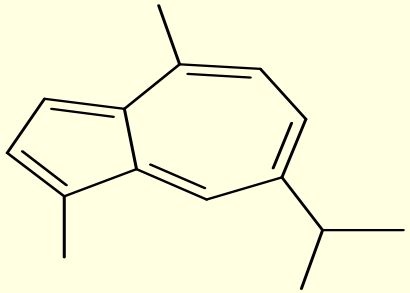
Vetivazulene
Oil of Vetiver

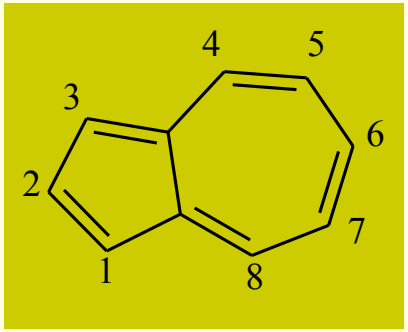


Chamazulene
Oil of Chamomile

Isolation of Azulene Derivatives

- Through formation of additive compounds with phosphoric, sulphuric or ferrocyanic acids ($H_4Fe(CN)_6$), regenerated by decomposition with water.





Guaiazulene

1,4-dimethyl,7-isopropyl azulene

- Obtained by dehydrogenation of oil of Guaiacum, it forms blue needles.

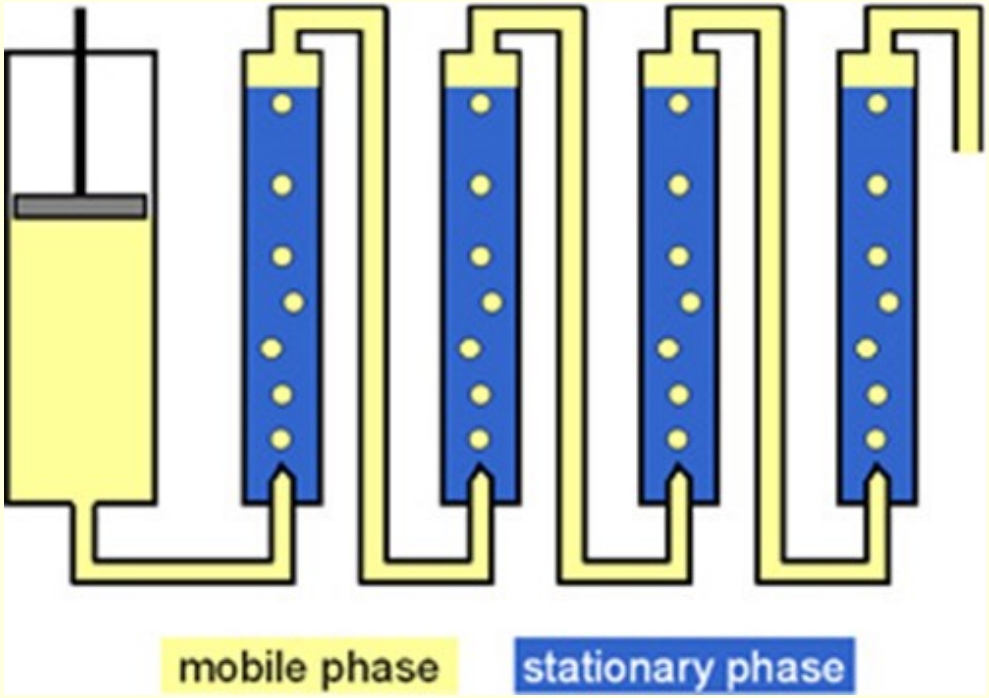
Uses:

- Azulene and guaiazulene are **popular** ingredients in beauty, cosmetic, **skin**, and body **care products.**
- Azulene and guaiazulene are **phototoxic** when exposed to sunlight.
- Therefore, extreme care must be taken when using cosmetic products with azulene/guaiazulene.

General methods of isolation of terpene hydrocarbons

- Fractional distillation under reduced pressure or in atmosphere of inert gas.
- Through formation of crystalline additive compounds e.g:
  - **α-pinene** as nitrosochloride, liberated by treatment with aniline.

- Camphene as hydrochloride, regenerated by treatment with alkali.
- Chromatographic methods specially gas chromatography
- Counter current extraction (Automatic liquid / liquid extraction system).

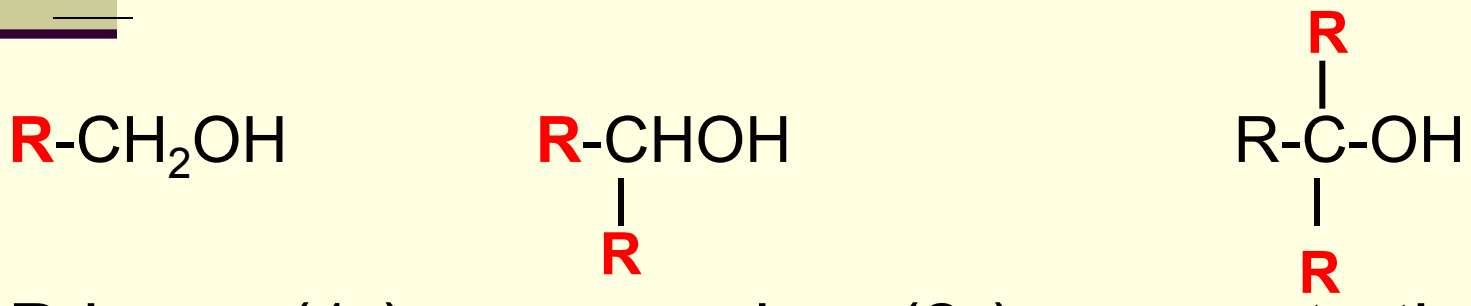

mobile phase
stationary phase

Alcohols and Phenols

Alcohols and Phenols

- Alcohols have general formula **R–OH**, structurally similar to water but with one of the hydrogens replaced by an alkyl group. Their functional group is the hydroxyl group,–OH.
- Phenols have the same functional group, but it is attached to an aromatic ring.

H–O–H	R–O–H	Ar–O–H
Water	an alcohol	a phenol



Primary (1°) secondary (2°) tertiary (3°)

General methods of isolation of alcohols.

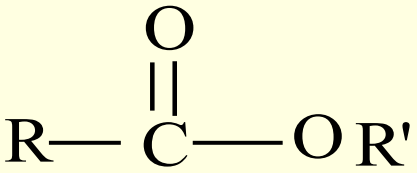
- Fractional distillation
- Chromatographic methods
- Formation of crystalline derivatives
- Products of dehydration $\xrightarrow[-H_2O]{}$ hydrocarbons

The ease of alcohol dehydration is $3^o > 2^o > 1^o$

Geraniol is exception of 1ry. Alc. which dehydrate readily

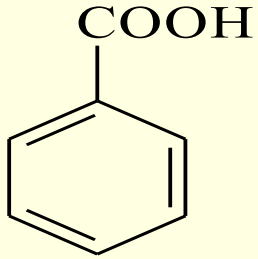
- Additive compounds with $CaCl_2$
- Esters

Esters



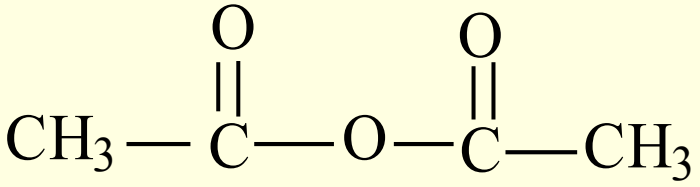
- **Borates** (H_3BO_3) 1º >2º (3º not)

- **Benzoates**

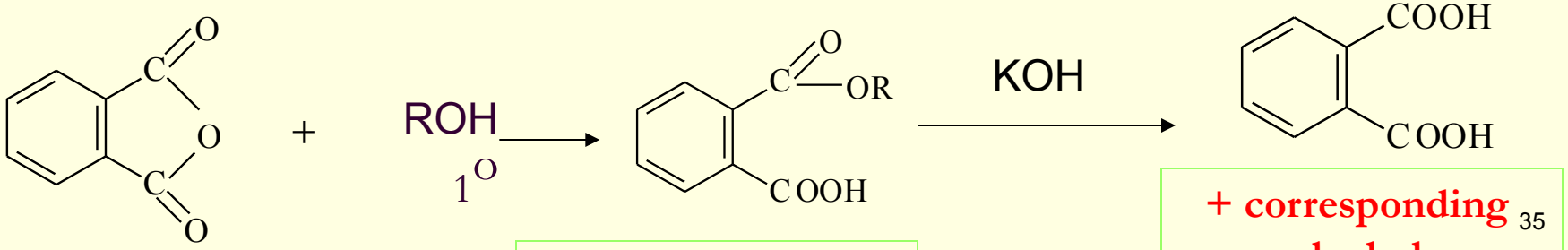


(3°not)

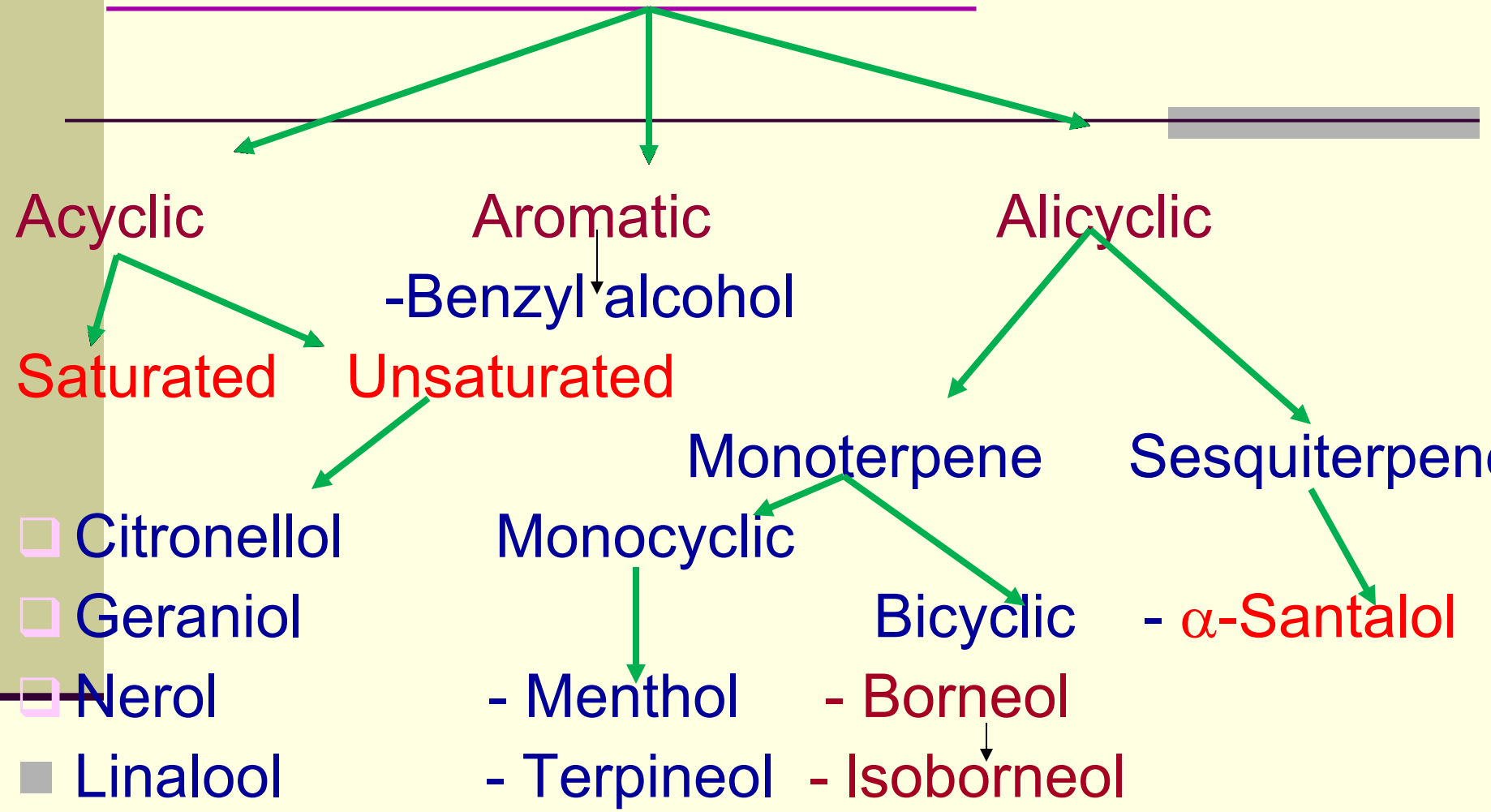
- **With anhydrides**
  - Acetic anhydride 1º >2º > 3º



  - Phthalic anhydride (**1º alc. Only**)

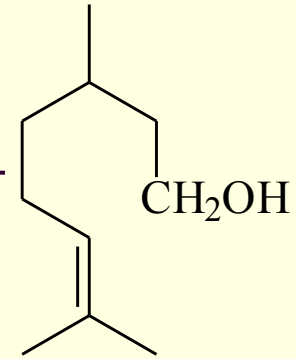


Alcohols in volatile oils

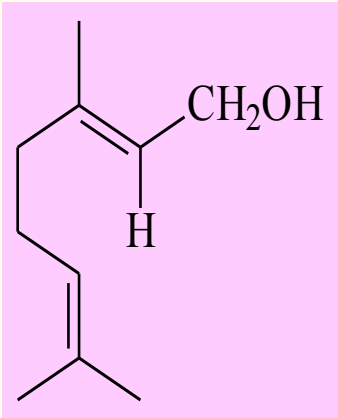


Alcohols are amongst the strongest antimicrobial compounds in essential oils but lack the irritant properties of other **antimicrobial** constituents like phenols.

Citronellol



- Oil of **Citronella** (d-form)
- Oil of **Geranium** and Rose (l-form)
- Isolation:
- Fractional distillation
- Separated from geraniol and other terpene alcohols through the **acid phthalate.**

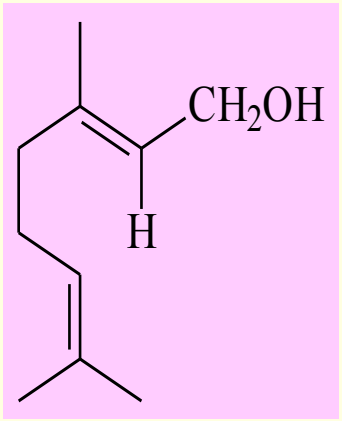


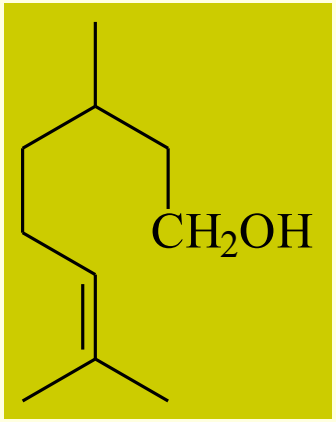
Separation of citronellol from geraniol

With phthalic anhydride at 200°C

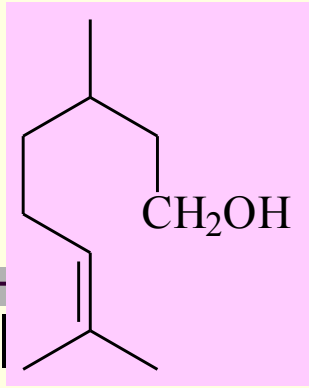
Geraniol → decomposes to hydrocarbone

Citronellol → phthalate ester which is taken and regenerated by alkali

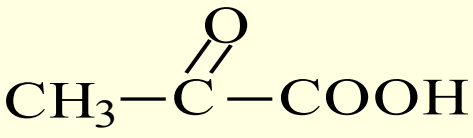




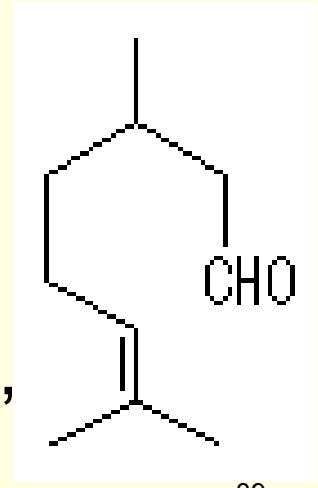
Citronellol



- Properties:
  - Lighter than water, More **stable** than geraniol
  - Toward the action of formic acid and alkalies
- Identification:
- - Conversion to citronellyl ester of pyruvic acid (keto acid),

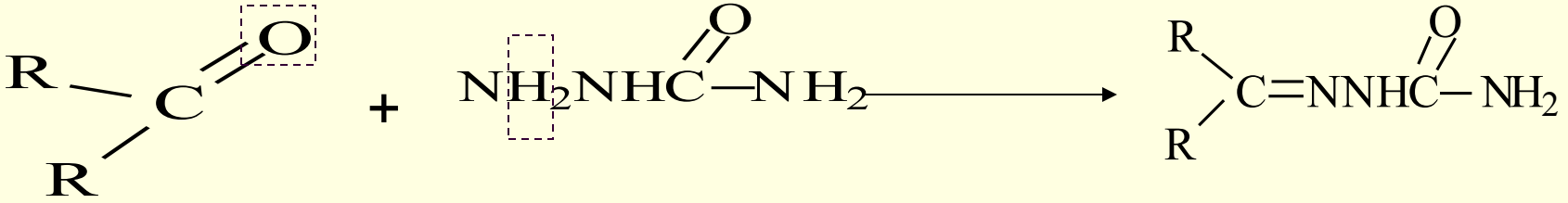


- the semicarbazone of which melts at 110-111°C. (geraniol not)
- On oxidation with chromic acid → citronellal,



Semicarbazone

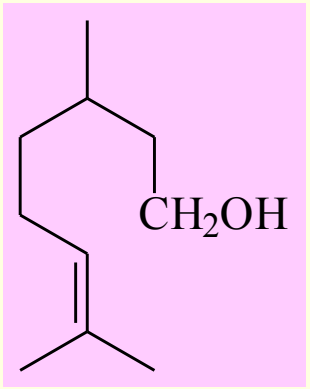
- Formed from addition elimination reaction between ketones or aldehydes and semicarbazide
- Semicarbazones are crystalline compounds with definite M.P.



Semicarbazide Semicarbazone

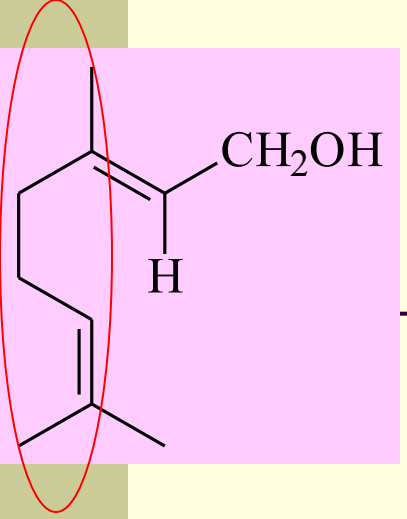
Determination of Citronellol by Formylation:

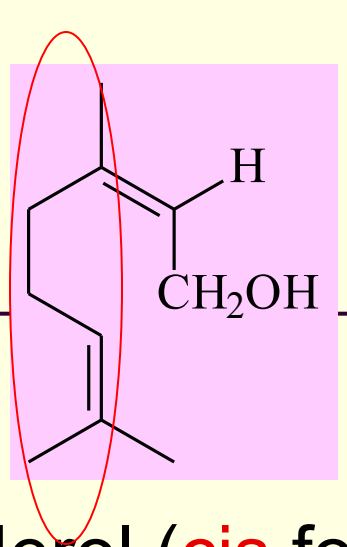
- Citronellol (very stable) can be determined by forming ester with 100% formic acid where as other alcohols usually dehydrate by this concentration of formic acid.



Researches demonstrated the anticonvulsant activity of the citronellol

Citronellol inhibited P-gp (mediates the development of resistance to anticancer drugs).





Geraniol (trans form) Nerol (cis form)

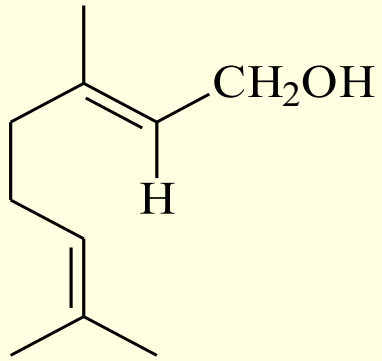
Oils of Palmerosa, rose **Neroli (Orange flower)**

Citronella and **geranium** Oil of Petit grains

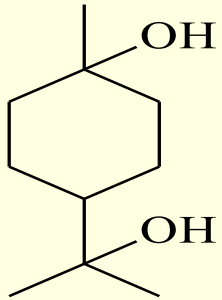
Isolation: of geraniol from nerol

Geraniol forms a crystalline derivative with **anhydrous** **$CaCl_2$**, which is decomposed with water while nerol does not form such compound.

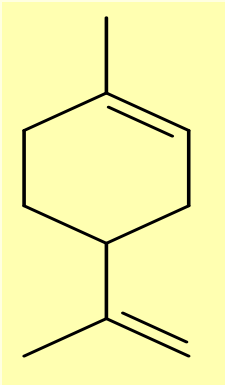
Geraniol



- **Properties:**
- **Geraniol is a colorless liquid, lighter than water, optically inactive, when exposed to air, it becomes, colored and less fragrant.**

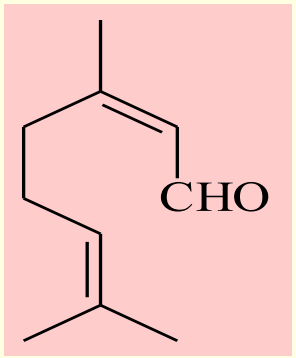


- **With 5% H_2SO_4, → terpin hydrate.**
- **With H_3PO_4 or HCl gas, → dipentene**



O2

- **Geraniol oxidation → citral**



Identification:

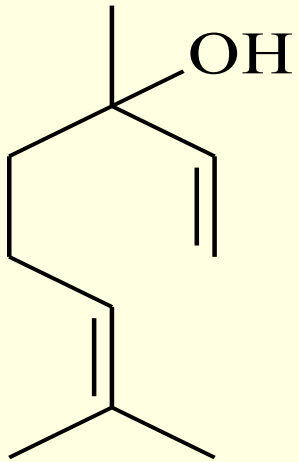
- To 1 ml of Geraniol, add 1 ml of **acetic anhydride** and 1 drop of phosphoric acid, keep warm for 10 minutes, add 1 ml of water, and shake in warm water for 5 minutes. Cool and make slightly alkaline with anhydrous sodium carbonate solution. An odor of **geranyl acetate** is evolved.

sweet fruity floral rose lavender odor

Recently:

- Geraniol is known to exhibit **insecticidal** and **repellent** properties with low toxicity.
- Geraniol has been suggested to represent a new class of **chemoprevention** agents for cancer.
- Antimicrobial, anti-oxidant, anti-inflammatory.
- The effect of geraniol as a **penetration enhancer** for transdermal drug delivery has also attracted the attention of researchers and formulation scientists.

Linalool



Oil of **Coriander** and oil of Nutmeg (d-form)

Oils of Bergamot, **Lemon**, lavender (l-form)

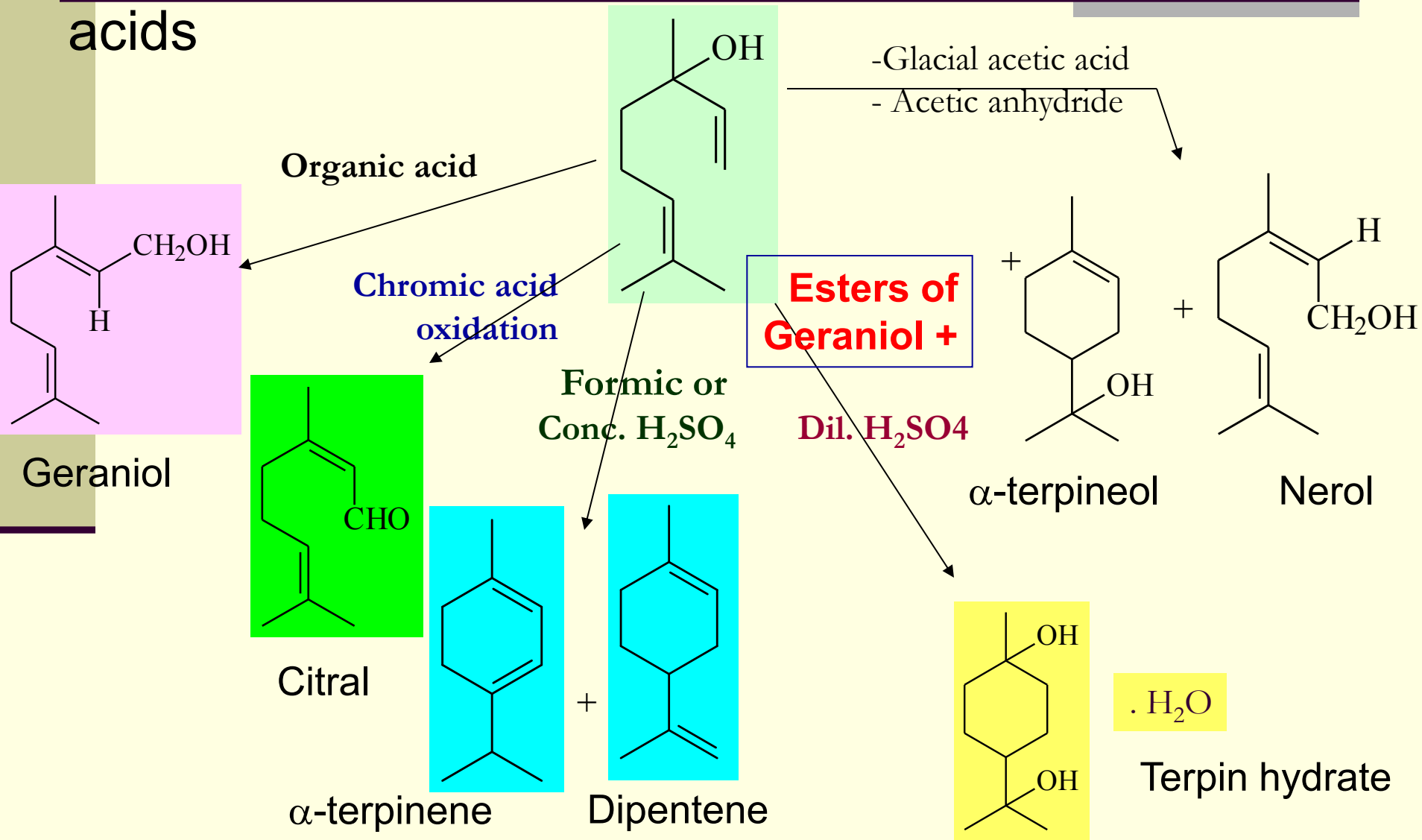
Present free or as acetate ester (linalyl acetate)

- Isolation:

- Fractional distillation (no definite crystalline derivative)

Properties of Linalool

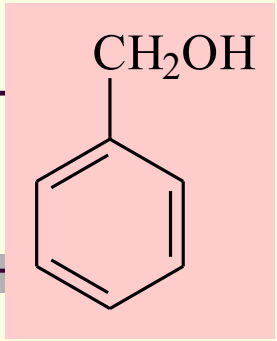
- Being a tertiary alcohol, it is very sensitive to organic acids



Recently

- **Linalool, a natural compound of the essential oils, has been shown to have antinociceptive, antimicrobial, and anti-inflammatory properties.**
- **Liver protective effect. (2014)**

Aromatic Alcohols (source + str. +use



Benzyl alcohol

Free or as ester of benzoic and cinnamic acids in balsams as Peru and Tolu, as ester of acetic acid as in oil of Jasmine.

- Isolation:
- Fractional distillation of original or saponified oils, or by the formation of complex addition product with anhydrous $CaCl_2$.
- Properties:
- Colorless liquid with a faint aromatic odor, sparingly volatile with steam.
- - Soluble in ethanol; sparingly soluble in water.
- On exposure to air ⟶ benzaldehyde ⟶ benzoic acid.

Benzyl alcohol

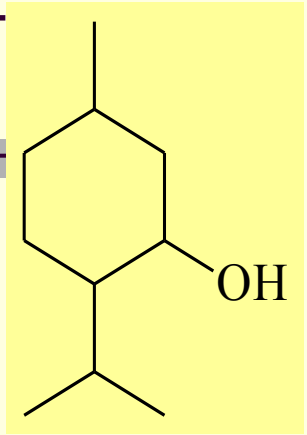
- **Identification:**

- **Through preparation of derivatives as acid phthalate, p-nitrobenzoate.**
- **Oxidation with chromic oxide and H_2SO_4 or $KMnO_4 \rightarrow$ benzoic acid.**
- **Uses:**
- **In perfume; cosmetic and soap industries**
- **Synthesis of flower oils as Jasmine & gardenia.**
- **Fixative and a diluents in perfume mixtures.**

Other aromatic alcohols are phenyl ethyl alcohol and cinnamyl alcohol

Monocyclic terpene Alcohols

Menthol (*p*.menthane, 3-ol)

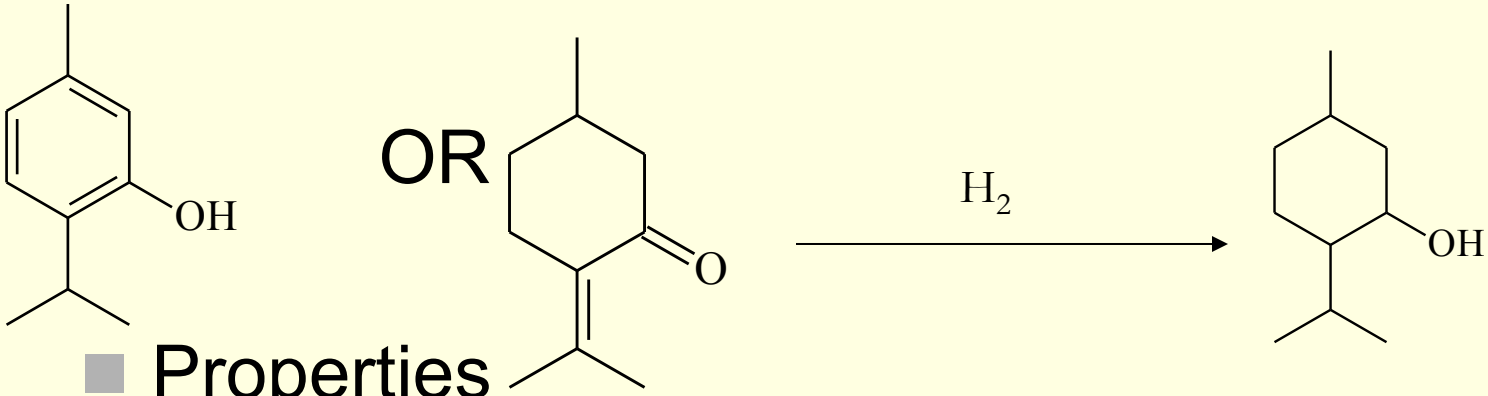


Occurs in l-form in various Peppermint oils

- **(*Mentha piperita*) 50-65% menthol.**
- ***Mentha arvensis* (Japanese mint) the oil is called Cornmint oil 75-90% menthol.**
- **Isolation:**
- **Crystals of menthol is precipitated by a very slow cooling of the corn-mint oil ,**

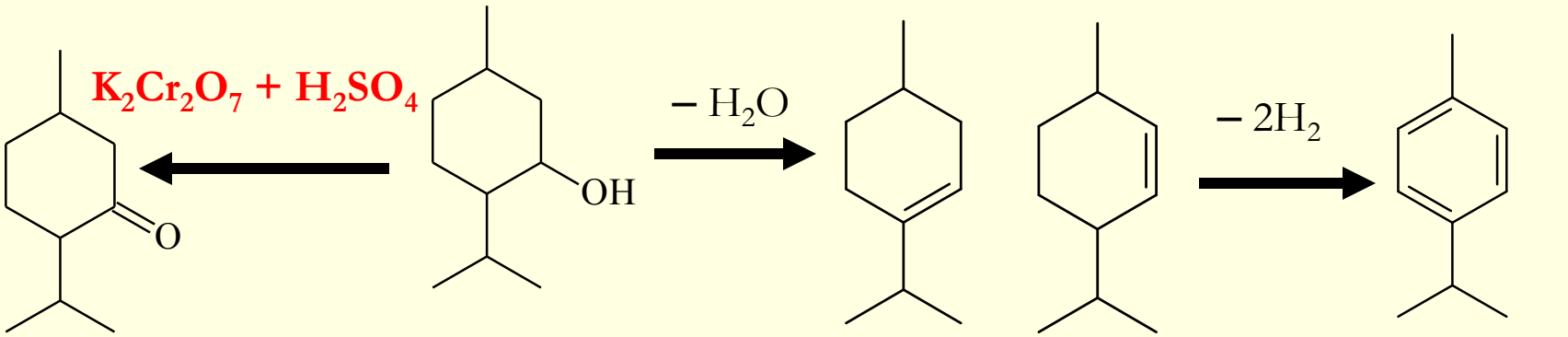
Menthol

- Menthol can be also synthesized by hydrogenation of thymol or pulegone:



- Properties
- White needle-shapes crystals with mint odor and a cooling taste.

Menthol



Menthone

p-Menthene

P-Cymene

Menthol

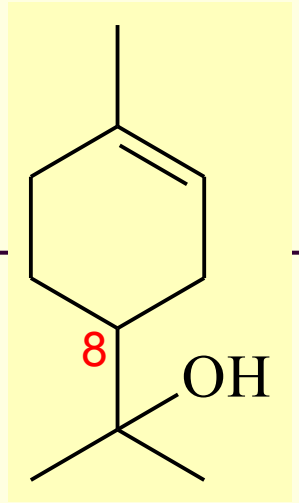
- Identification:
- Through preparation of derivatives as acid phthalate, p-nitrobenzoate.
- **Color test:** Solution of menthol in H_2SO_4 + a drop of vanillin sulphuric acid reagent → **orange yellow** color, changing to **violet** on addition of water drops.
- Uses:
- An ingredient of itch-relieving creams
- In preparations used to decongest the upper respiratory tract in case of rhinitis.
- In oral hygiene products and shaving products.
- In food technology.
- kills the germs responsible for the bad breath. Therefore, instead of simply being a cover up for bad breath, it helps to eliminate the cause altogether.

Menthol recently:

- Used as a penetration enhancer in topical transdermal formulations.
- Menthol decrease nicotine-induced psychostimulation.
- Menthol, the active ingredient in several topically applied analgesics.

Geraniol

α-terpineol



Δ^1 p-menthene-8-ol

- Oil of Neroli (d-form)
- Oils of camphor & lemon (l-form)
- Oils of geranium (dl-form)
- Identification:
- Through the preparation of several compounds e.g nitrosochloride.

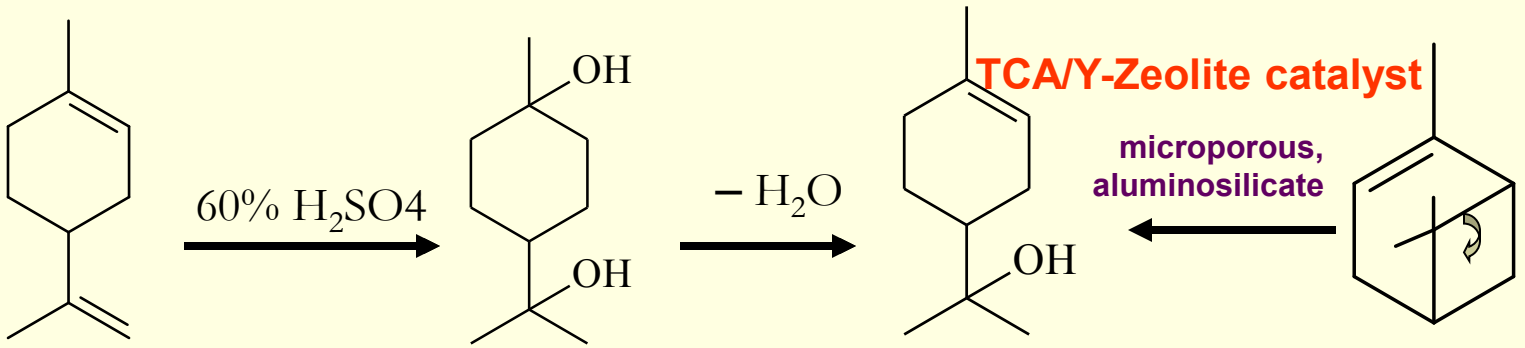
α-terpineol

- Isolation:

* Fractional distillation.

*Formation of crystalline derivatives as phthalates.

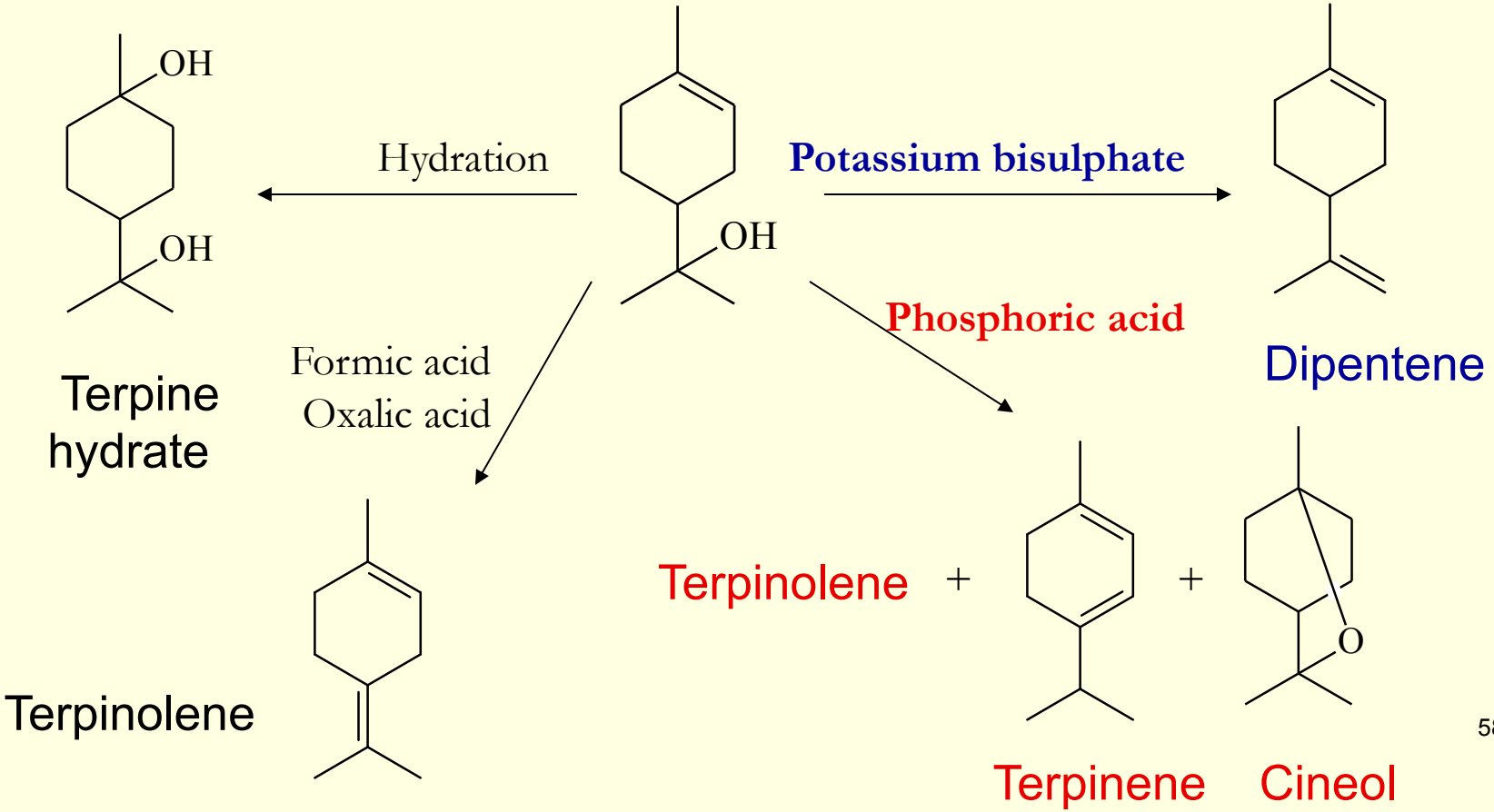
*Synthetically from various pine oils which contain dipentene and α-pinene (commercial method):



Dipentene | Terpine hydrate | α-Terpineol | α-Pinene

α-terpineol

- Properties:
- Crystalline compound, sparingly soluble in water. With bromine → oily dibromide.



α-terpineol

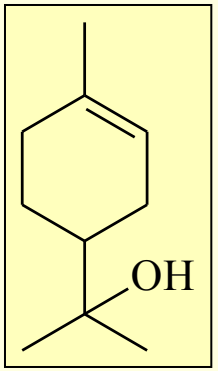
- Uses:

  It is one of the most important compounds used in perfume, cosmetic, and soap industries because of its lilac-like odor and the low price of the synthetic product.

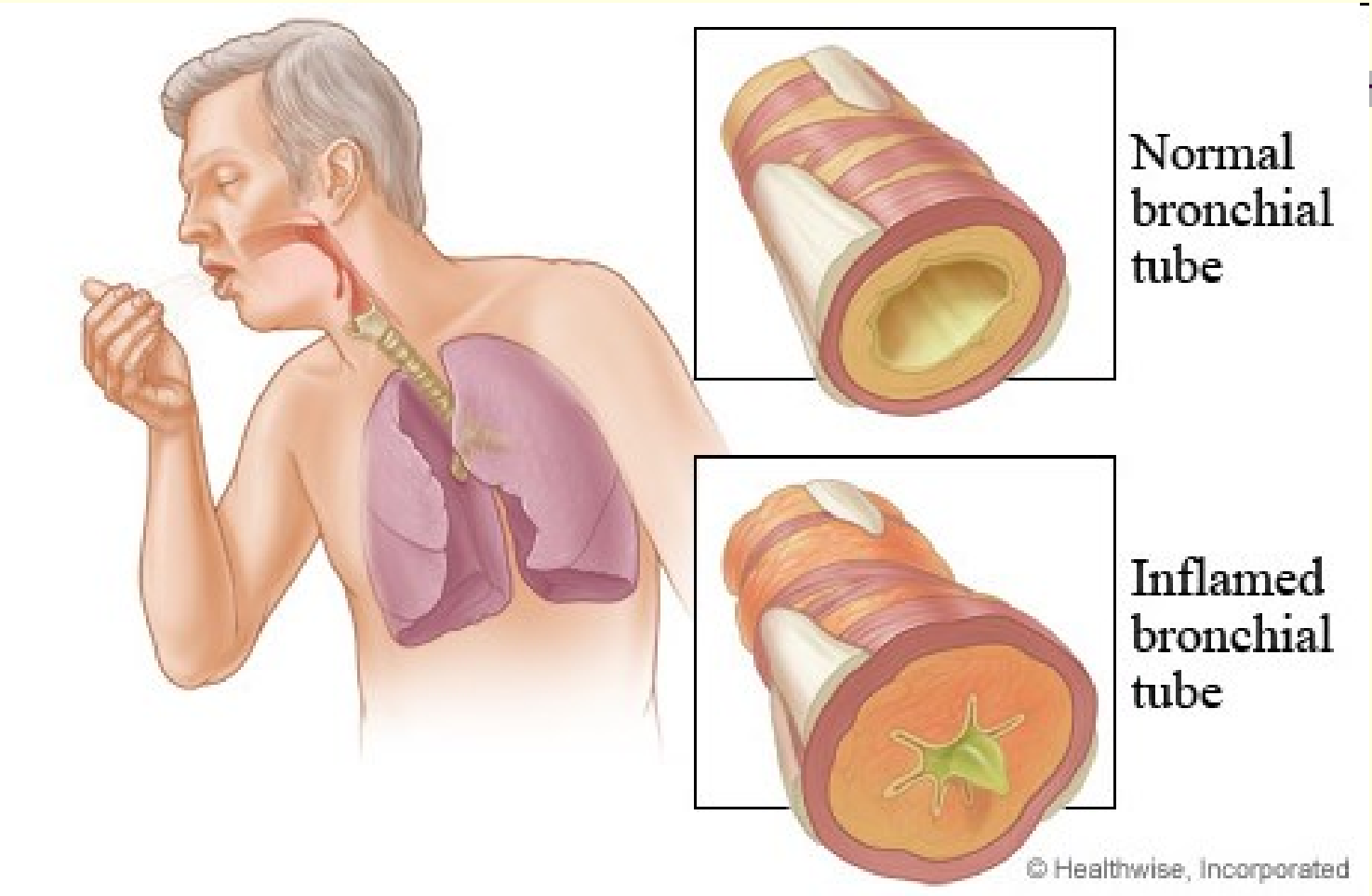
Recently, Linalool and α-terpineol exhibited strong antimicrobial activity against periodontopathic and cariogenic bacteria. However, their concentration should be kept below 0.4 mg/ml.

In 2017,

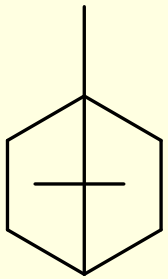
- Discovery of a novel series of α-terpineol derivatives as promising anti-asthmatic agents

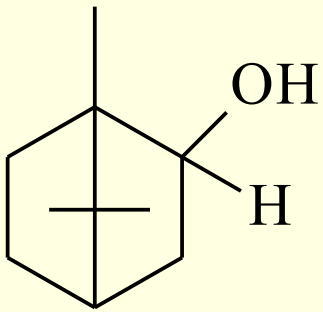


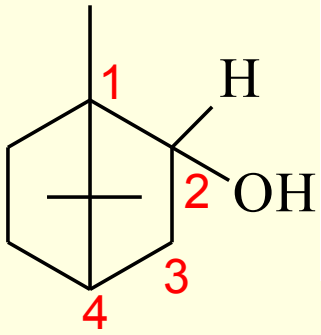
- A series of novel α-terpineol derivatives were designed and synthesized through structural derivatization of the tertiary hydroxyl moiety or reduction of the double bond.

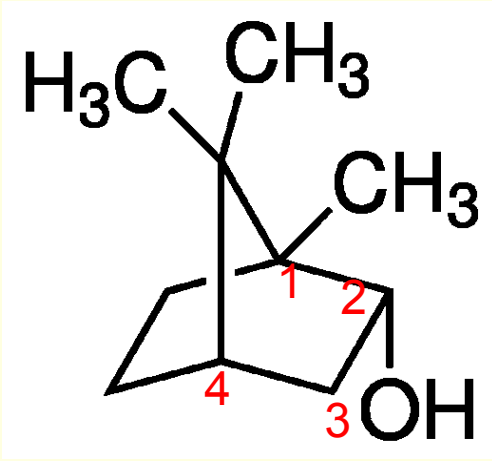

Normal bronchial tube
Inflamed bronchial tube
© Healthwise, Incorporated

Bicyclic monoterpene alcohols



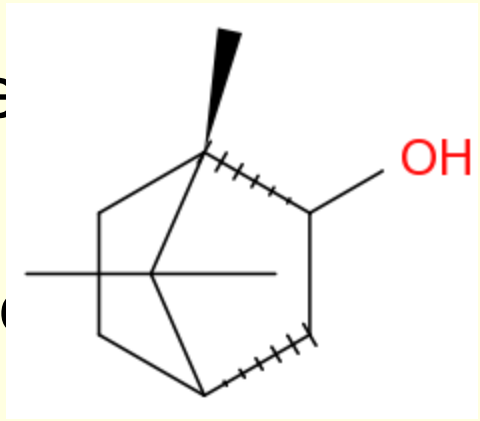






Camphane Borneol isoborne

bornane type 2-hydroxy camphane



- d-Borneol(Borneo-camphor): oils of ros
  lavender
- **l-borneol (Ngai-camphor):**
- Oils **of citronella**, coriander

and valerian roots.

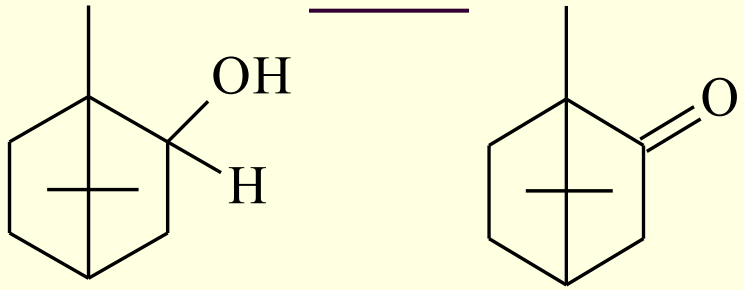
Borneol

- Isolation:

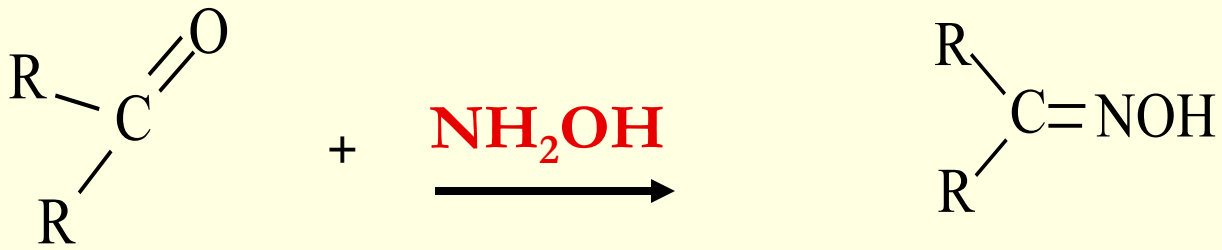
- Borneol crystals can be precipitated from cooling the distillate of the *Dryobalanops* tree trunk (Dipterocarpaceae).
- Saponification of pine needle oil, removal of hydrocarbons by distillation, cooling → borneol

Methods for Separation of borneol from camphor :

- Through formation of ester with phthalic or succinic acid.

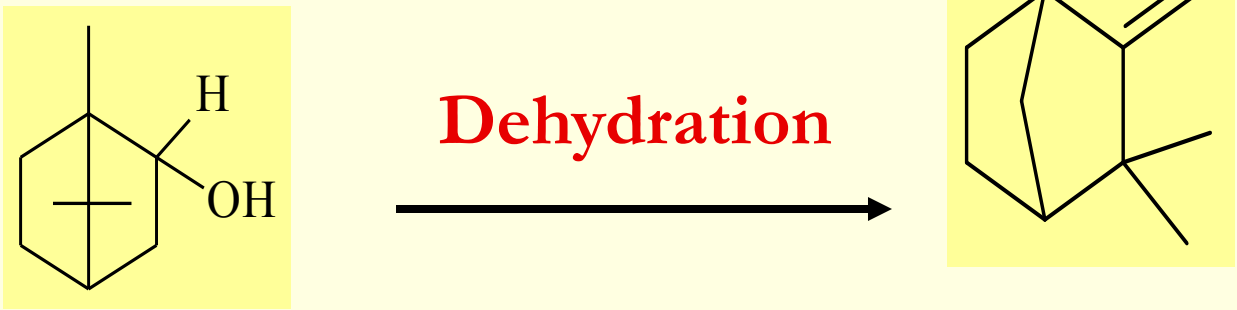


- Through forming non-volatile esters with benzoic or stearic anhydride and removing camphor by distillation.
- Converting camphor to its oxime which is soluble in 25% H_2SO_4.



Borneol

- Separation of borneol from isoborneol:
- By heating with zinc chloride in benzene, isoborneol (unstable) ⟶ the solid terpene hydrocarbon camphene.



Isoborneol camphene

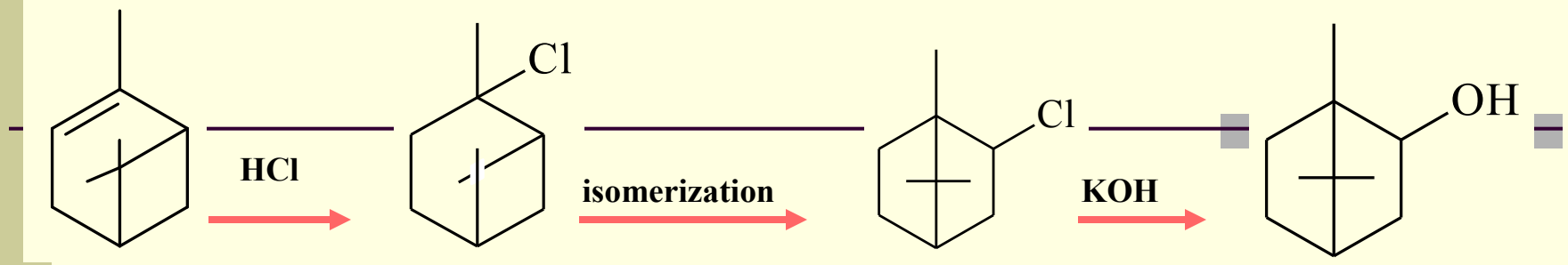
Borneol is purified through its crystalline acid phthalate.

Borneol

- **Properties:**
- **Crystalline compound with camphor like odor.**
- **Soluble in alcohol, ether, sparingly soluble in benzene.**
- **Volatile at ordinary temperature.**
- **Readily oxidized to camphor by (CuO, Cl_2).**

- **Reduction of camphor by sodium and alcohol $\rightarrow$ a mixture of borneol and isoborneol.**

Borneol



α-pinene pinene HCl bornyl chloride Borneol

- Identification:

Through the preparation of derivatives as nitrobenzoates

- Uses:

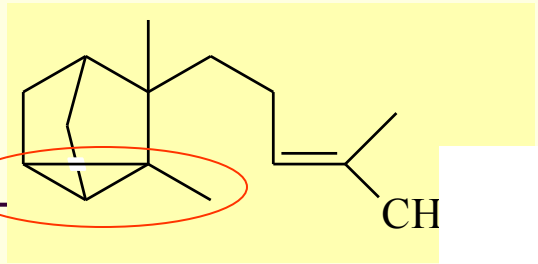
Borneol is used for scenting certain preparations.

Borneol specifically inhibits the nAChR **(Nicotinic acetylcholine receptor)** -mediated effects.

Other recent uses:

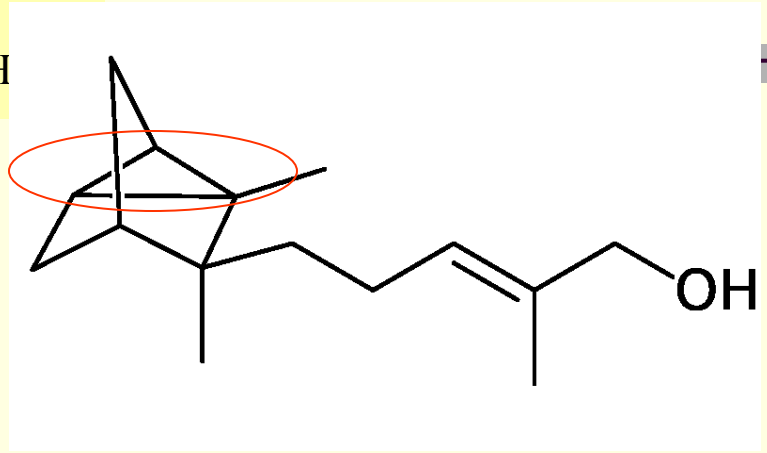
- Isoborneol, showed dual **viricidal** activity against herpes simplex virus 1 (HSV-1). First, it **inactivated HSV-1** within 30 min of exposure, and second, isoborneol at a concentration of 0.06% completely **inhibited viral replication.**

Sesquiterpene Alcohols



α- santalol

3 D conformer

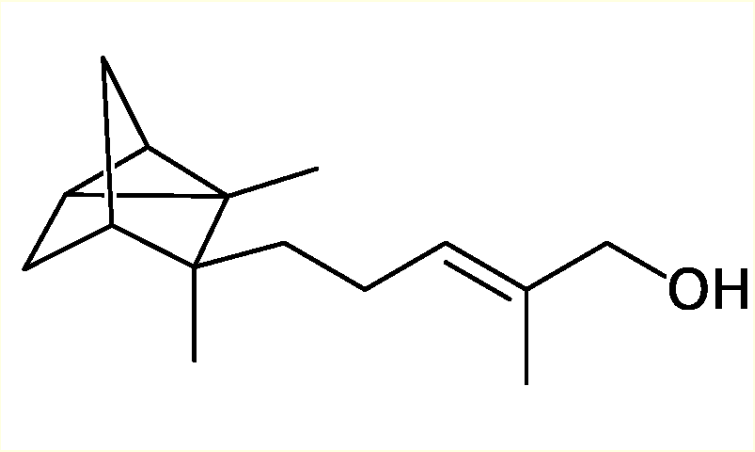


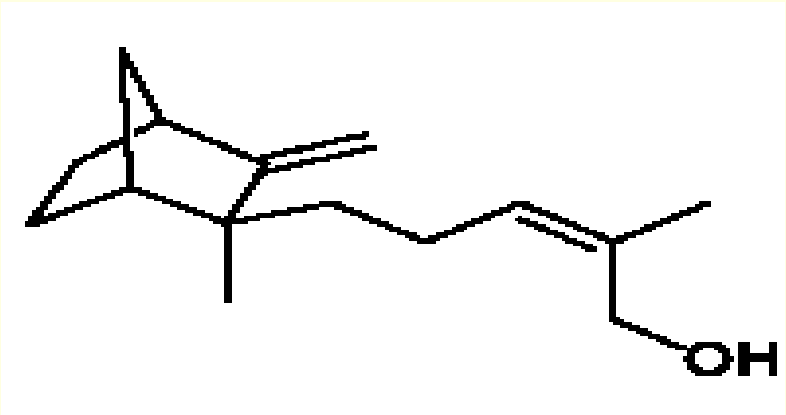
- Isolation:
- Fractional distillation
- Properties:
- Viscous yellowish liquid with a sandalwood-like odor.
- Identification:
- Oxidation with chromic oxide ⟶ santalal,
- the semicarbazone of which melts at 230 °C.
- Uses:
- Perfumes, urinary disorders (diuretic and antiseptic)

- β-Santalol exhibited anti-influenza A/HK (H3N2) virus activity. Swine

- α-Santalol, a major component of sandalwood oil showed **anti-cancer** activity in prostate cancer cells by inducing apoptosis and activation of caspase-3 activity (central role in cell apoptosis.).

- α- and β-santalols could be considered as **neuroleptic** by resemblance to the pharmacological activities of **chlorpromazine**
- *in vivo* anti-hyperglycemic and antioxidant.





Determination of alcohol content in volatile oils

- **Through esterifying** the alcohols with acetic anhydried and estimation of the resulting acetate by hydrolysis with alcoholic KOH.
- This method is not suitable for tertiary alcohols, other methods can be used.
- **Dehydration method:** Some tertiary alcohols dehydrate quantitatively under the influence of certain reagents. The amount of resulting water is determined from which the percentage of alcohol can be calculated.