Vitamins

Paper-302

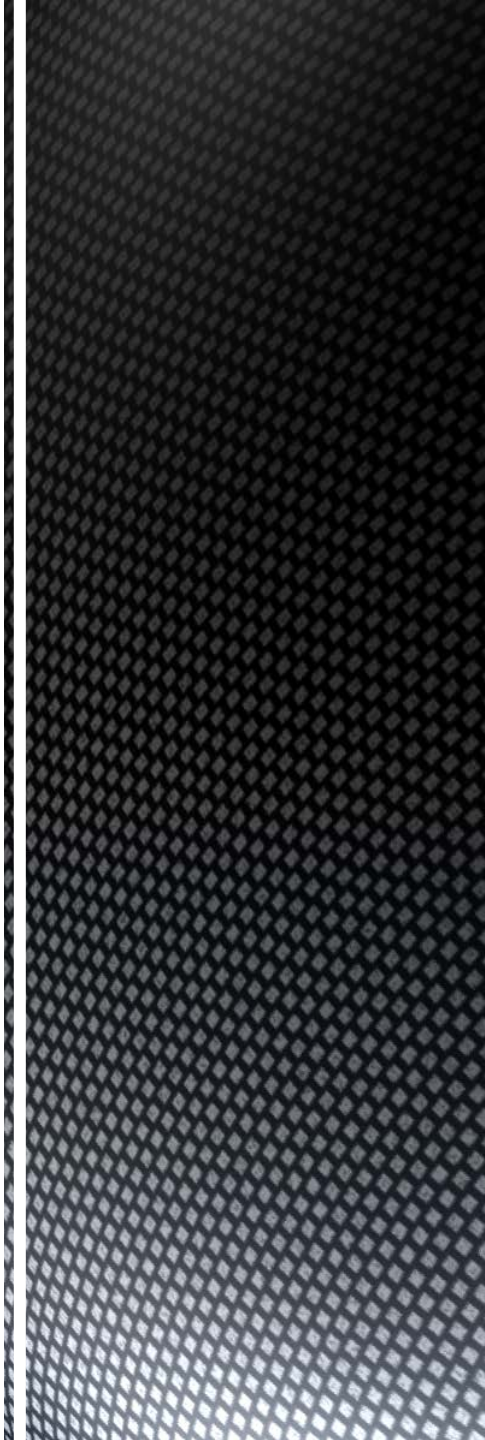
Chemistry of Natural Products

Oragano pharmaceutical Chemistry,

Sem-III

Saurashtra University

rajkot

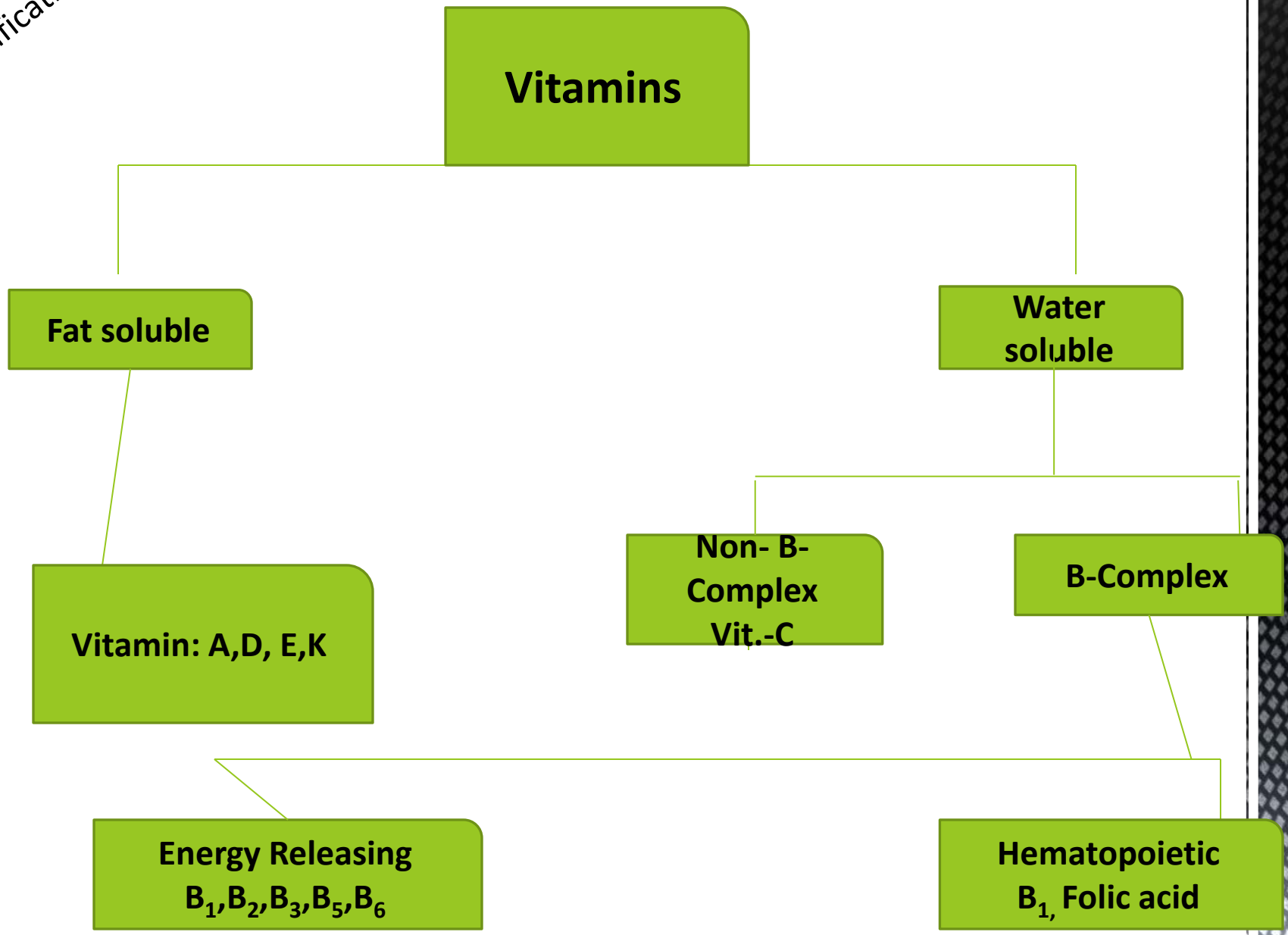


Introduction

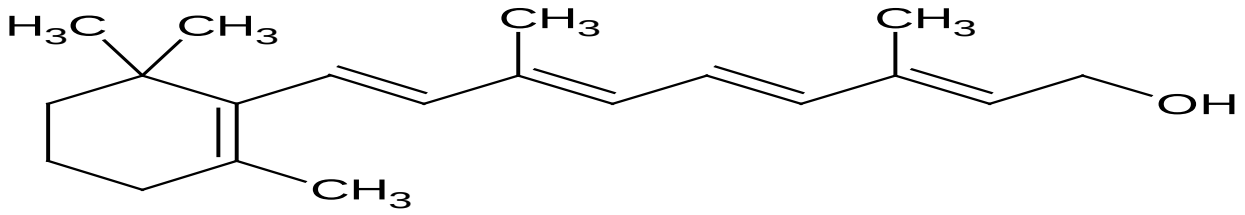
- Vitamins are naturally occurring compounds which is essential for plant and animals for growth.
- Vitamins cannot be synthesized by them selves(Vitamin-D).
- Deficiency of Vitamins causes the disease and it can be cured by administration of that vitamin (Rich diet).
- Vitamine denoting an amine required for life.
- Unfortunately all vitamin does not contain N, so ‘e’ dropped out.
- Vitamine ⟶ Vitamin.
- All vitamins are not work alone it require Co-enzymes.
- They possess marked physiological activity and high specificity of function.
- They require in small quantities but regular catalytically nature.

Year	Discovery	Scientist
1921-31	Vitamin D2 was synthesized from ergosterol	Windows Robension, Rereink & Van Wijk
1927-28	Ascorbic acid was isolated from adrenal glands	Szent, Gyorg & Zilva
1923	Ascorbic acid was synthesized	Reichstein & Hawoth
1935	Thiamine was synthesized	Willians Andersay & Westphal
1936	Tocopherol was discovered, isolated & Synthesized	Evans, Fernholz Karrer & Smith Todd
1936	Synthesis of Riboflavin	Kahn & Karrer
1937	Vitamin-A	Kuhn
1939	Pyridoxine structure	Kuhn, Harris & Forkers
1939	Structure of Pantothenic acid & synthesis	R.J. William folks, Kuhn Reieshstein
1939	Vitamin K- discovery	Dam & Karre Doisy & Almquist Fieser, Ansbacher Ferhn holf
1942	Biotin-synthesis	Du Vignard
1949	Vit.B12-isolated	Smith parker Folikers

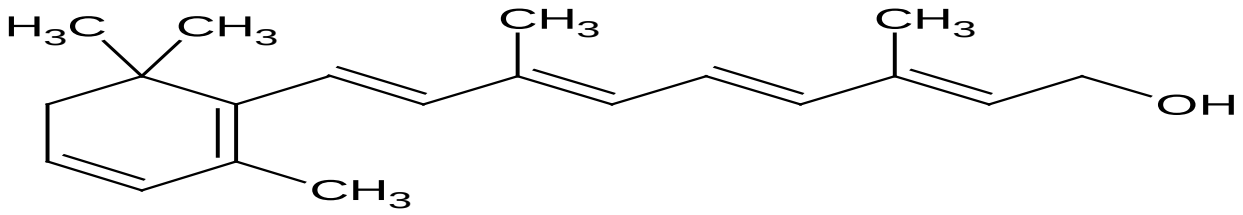
Classification



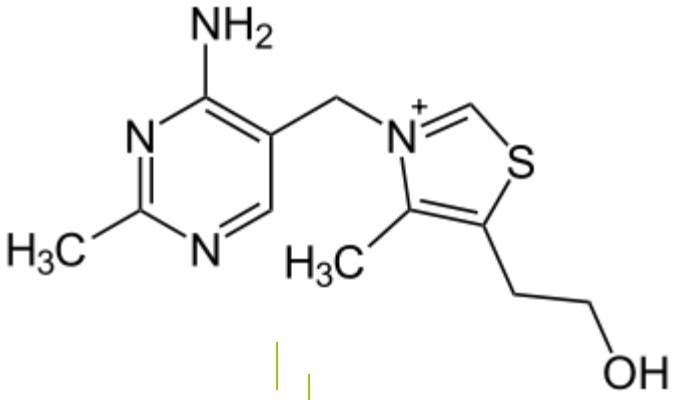
Structure of Vitamins



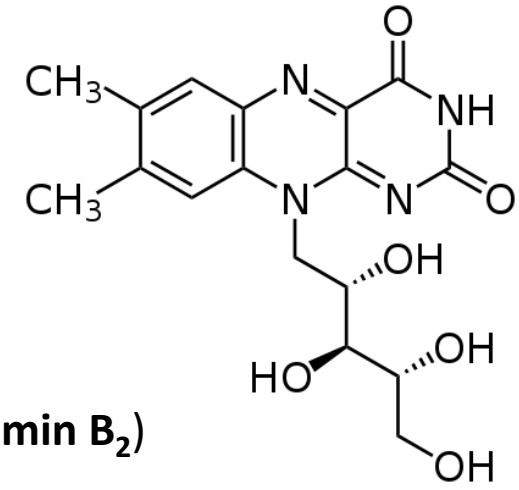
Vitamin-A-1: Retinol



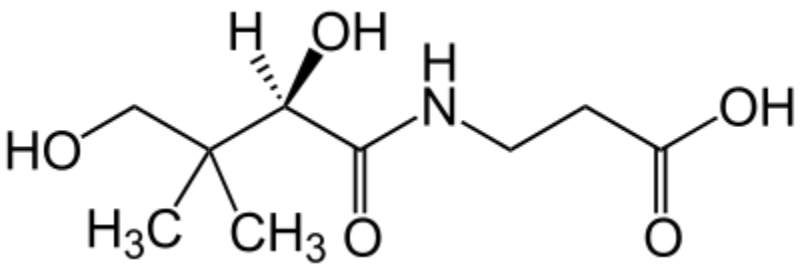
Vitamin-A-2: 3-Dehydroretinol



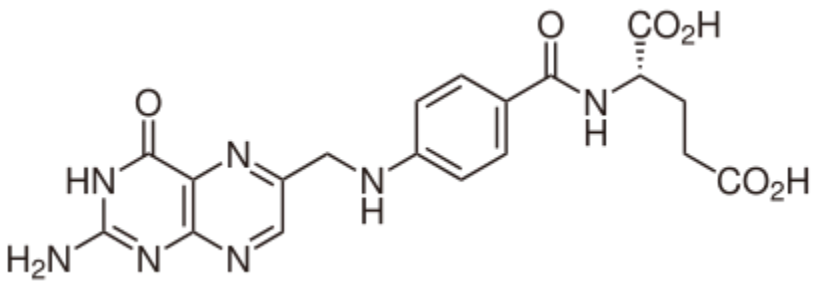
Thiamin-**vitamin B_1**



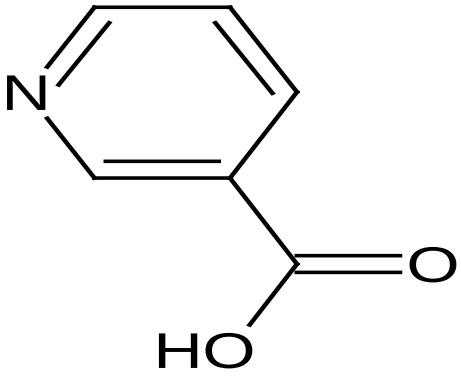
Riboflavin (vitamin B_2)



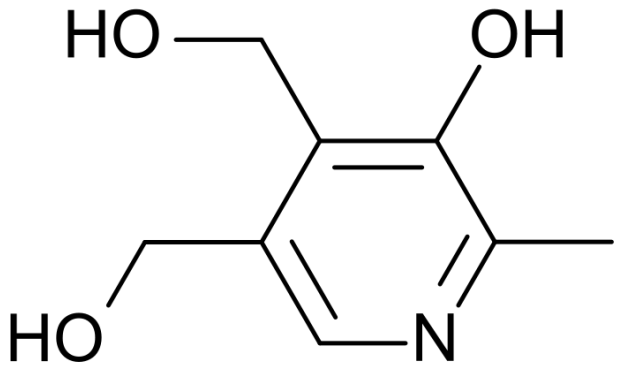
Pantothenic acid-Vitamin B_5



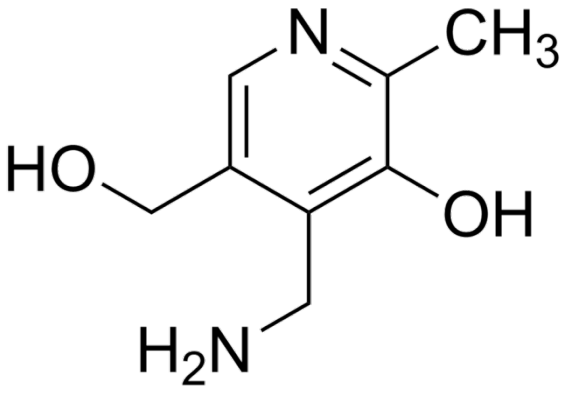
Folic acid-B vitamin



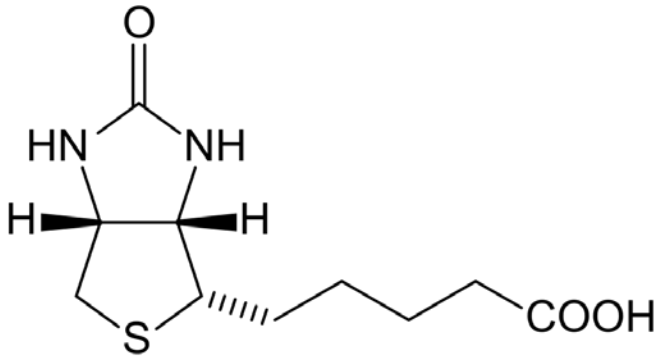
Vitamin-B_3 (Nicotinic acid)



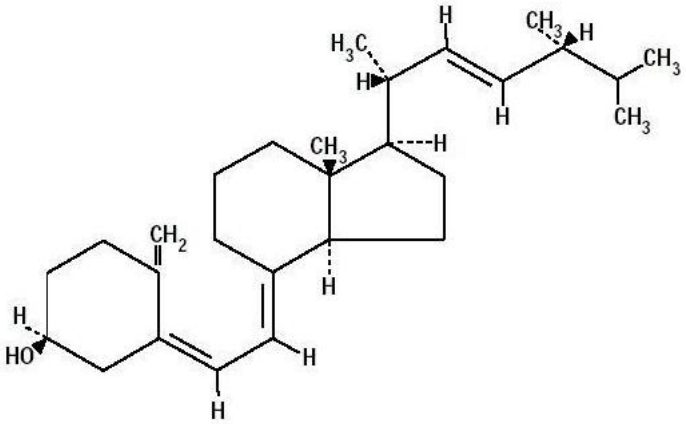
Vitamin-B_6 (pyridoxine)



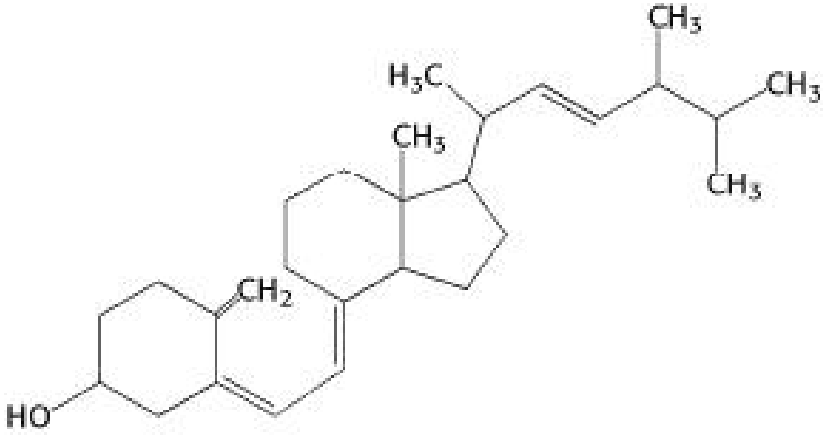
pyridoxamine



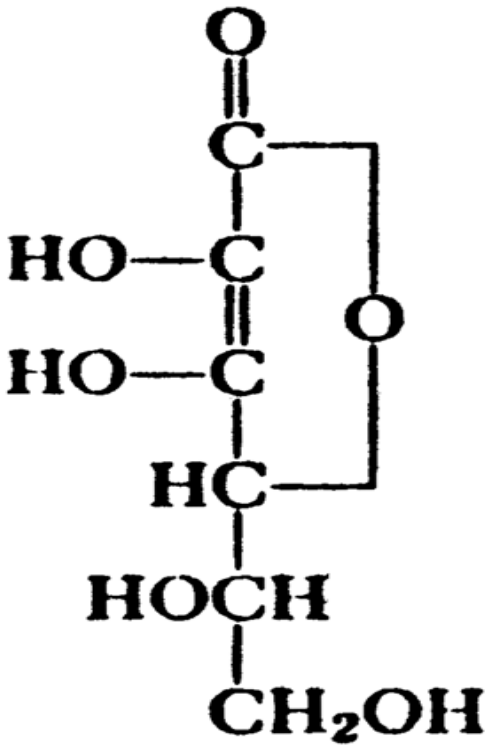
β-Biotin



Vitamin D (Ergosterol)

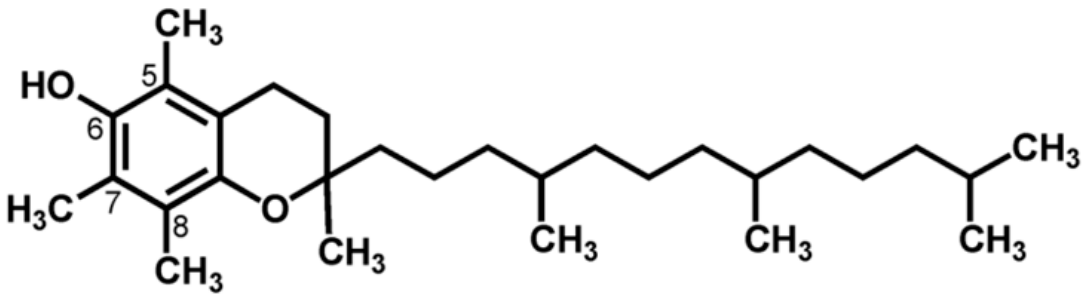


Calciferol (Ergocalciferol)

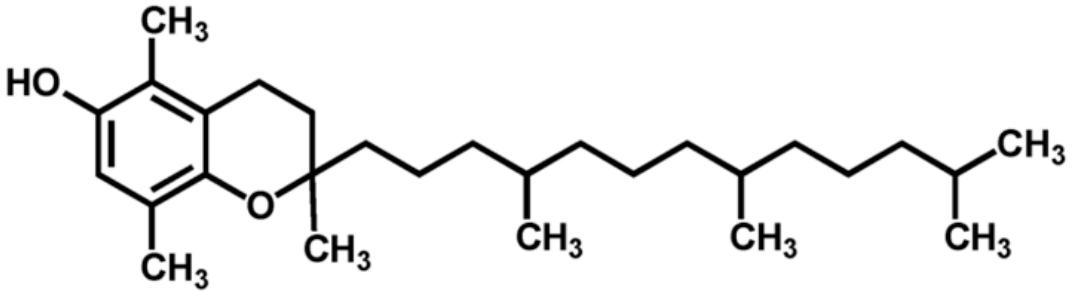


Vitamin C (Ascorbic Acid)

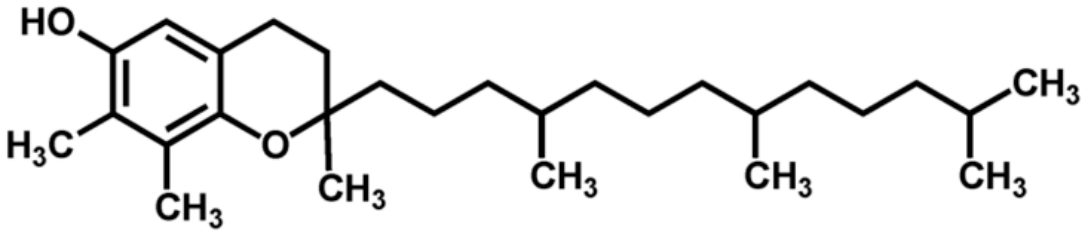
α-Tocopherol



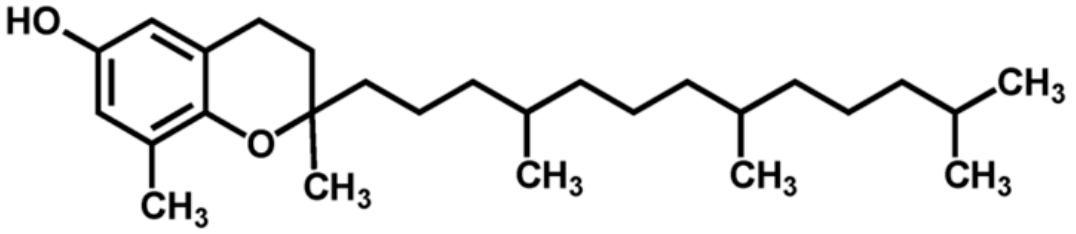
β-Tocopherol



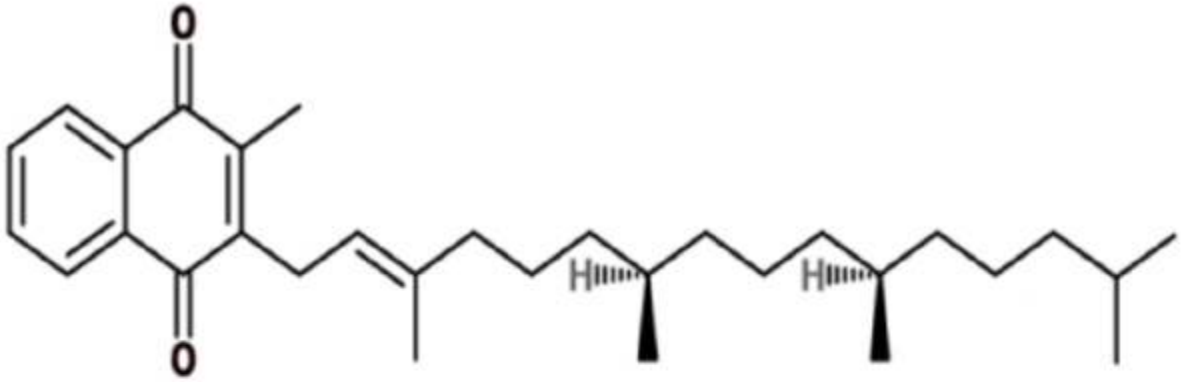
γ-Tocopherol



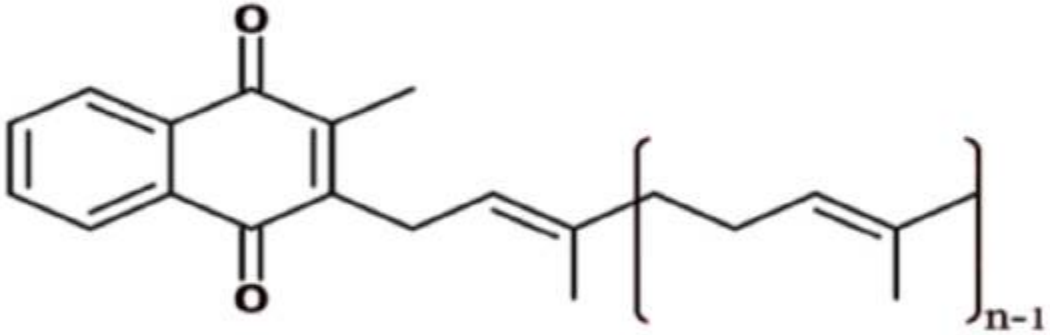
δ-Tocopherol



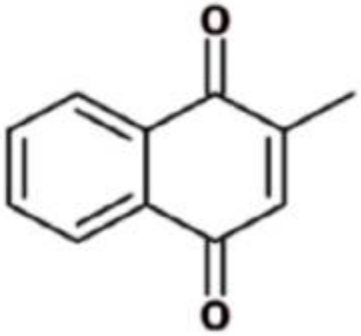
Vitamin K1
(phylloquinone)



Vitamin K2
(menaquinone)



Vitamin K3
(menadione)



Source of various vitamin and their deficiency diseases.

Name of vitamin	Source	Deficiency and Diseases
Retinol (Axeropthol) – A_1	Fish liver oil, sea & Fresh water fish	Night blindness, xeropthalmia, Dryness of skin
3, 4, Dihydro Retinol- A_2	Liver of fresh water fishes	Loss of appetite weakness
Thiamnie – B_1	Milk, Eggs, Yeast, Rice, Wheat, Liver etc.	Crocking of lips, Corneal opacity cheilosis
Panthothenic Acid – B_3	Liver, Kid green plants etc.	Chick, Dermatitis
Alfafa – K	Cabbage, Cereals, leafs	Hemorrhagic conditions
Nicotinic acid(Niacin) – B_5	Rice, Wheat, Adrenal gland etc.	Pellagra
Pyridoxime(Adermine)– B_6	Milk, Eggs, Yeast, Rice, Wheat, Liver, Meat etc.	Dermatitis
Cyanocobalamin – B_{12}	Liver of all animals	megaloblast immature RBC Degradation of spinal Cord

Source of various vitamin and their deficiency diseases.

Name of vitamin	Source	Deficiency and Diseases
Para-amino benzoic acid (PABA)	grains, eggs, milk, and meat.	Retardation of growth
Folic Acid – B_9	Liver, Kidney, Banana, Strawberry, Lemon etc.	
Ascorbic Acid – C	Citrus fruits, Green Vegetables etc.	Scurvy brightness of bones , loose teeth
Ergosterol – D	Fish liver oil	Rickets
Tocopherol – E	Liver of Horses, Cotton seed oil etc.	Fertility, nerve impulses, muscle weakness and degeneration of the retina

Physiological Activity of all Vitamins(B-complex)

Name	Co-enzyme	Type of reaction
Thiamine HCl (B_1)	Thiamine pyrophosphate	Decarboxylation of α-keto acids
Riboflavin (B_2)	Flavin mononucleotide(FMN) Flavin adenine dinucleotide(FAD)	Oxidation, Reduction reaction
Pantothenic acid (B_3)	Co-enzyme A	Transference of Acetyl group
Nicotinic acid – B_5	Diphosphopyridine nucleotide, Triphosphopyridine nucleotide	Oxidation, Reduction reaction
Pyridoxime – B_6	Pyridoxal phosphate	Transamination of amino acids

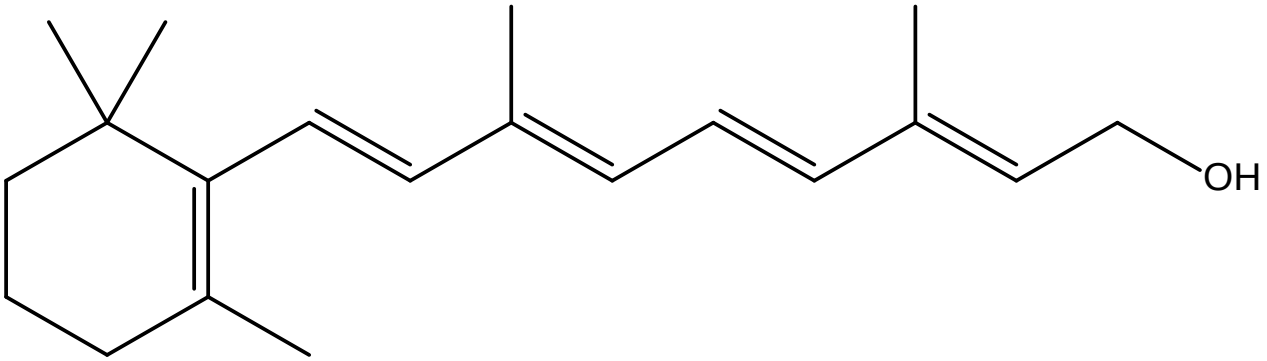
Physiological Activity of all Vitamins(B-complex)

Name	Co-enzyme	Type of reaction
Cyanocobal amine – B_{12}	Cobamide co-enzyme	Carbon-chain isomerization
Biotin	Biotin	CO_2 fixation reaction
Folic acid	Tetra hydro folic acid	Various reaction involving single carbon reaction

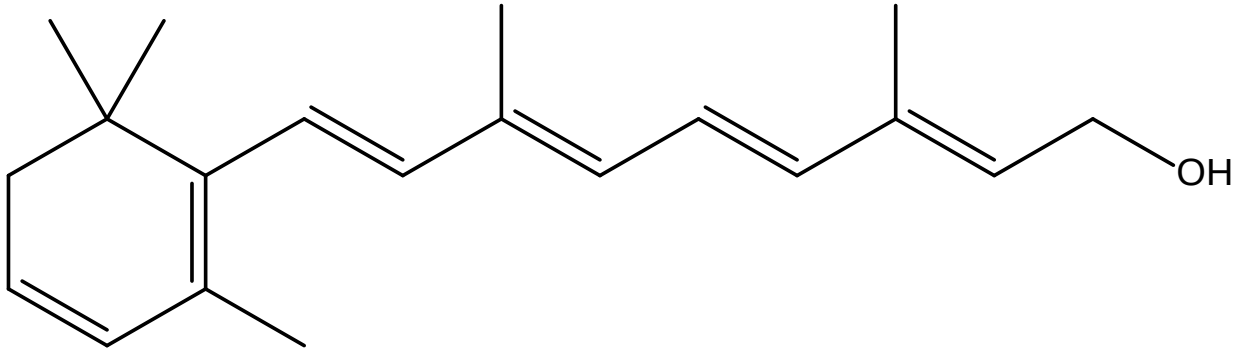
Common properties:-

- All vitamins are complex in nature generally. (Exception:- Vit. B_5 (Nicotinic acid) PABA(p-amino benzoic acid))
- They do not provide source of energy
- They act as catalytic in nature
- They can not be synthesized from amino acid
- They are required in a very small amount
- Every vitamin possesses a specific physiological activity
- Deficiency of any vitamin causes a ,particular disease which are cured by the administration of only that vitamin
- They can’t be synthesized in body

Vitamin A



(2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraen-1-ol



(2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)nona-2,4,6,8-tetraen-1-ol

Vitamin A

- Properties:-
  - Crystalline solid, M.P. 63-64 °C
  - Optically inactive
  - Resistance to heat
  - Sensitive to air & light
  - Destroyed by U.V. light
  - When isolated-yellow oil

- Sea water fishes → only vit.- A_1
- Fresh water fishes → Vit. A_1 and A_2 both
- It is insoluble in water & glycerin but soluble in absolute alcohol, $CHCl_3$, ether, Liq. Paraffin.

Detection and Estimation:

[A] Carr-price method:

2% solution of vit. A_1 in $CHCl_3$ + 20-25 % solution of $SbCl_3$ in $CHCl_3$

↓

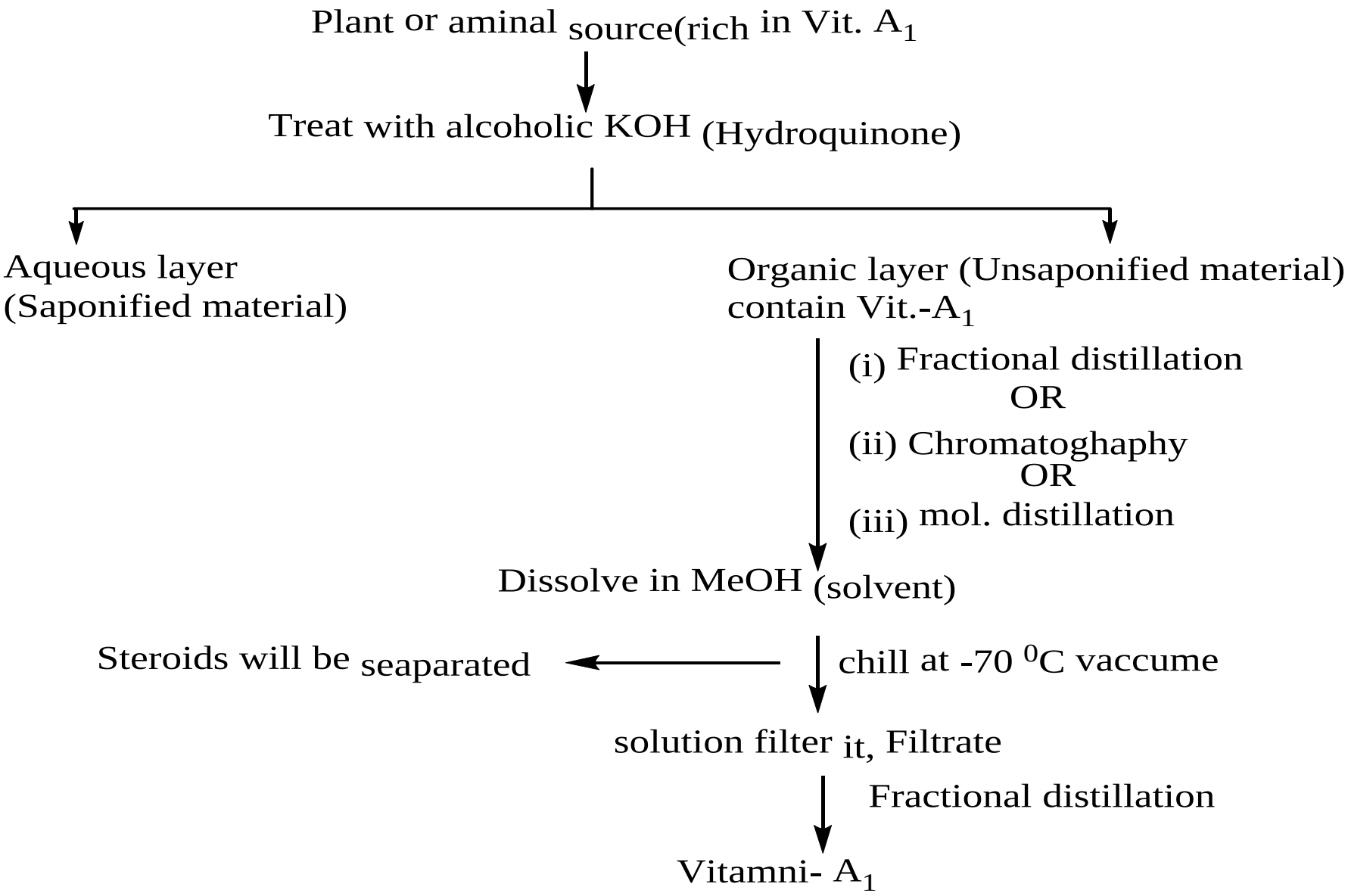
- blue colour, max intensity for 10 sec measured by lovibond tintometer → result expressed as CLO

- It proves the presence of vit-A_1
- Then immediately disappearing

[B] U.V. Method (Martin) :-

Vitamain A_1 in Cyclohexane/ Ethyl Acetate/ Isopropyl alcohol $\xrightarrow[\text{band}]{\text{absorption}}$ λ: 325-428 mμ in U.V.

Isolation:


Plant or aminal source(rich in Vit. A_1
Treat with alcoholic KOH (Hydroquinone)
Aqueous layer
(Saponified material)
Organic layer (Unsaponified material)
contain Vit.-A_1
(i) Fractional distillation
OR
(ii) Chromatoghaphy
OR
(iii) mol. distillation
Dissolve in MeOH (solvent)
chill at -70 ^{0}C vaccume
Steroids will be seaparated
solution filter it, Filtrate
Fractional distillation
Vitamni- A_1

Structure elucidation of vitamin A_1 [Karrer & Heilborn]

1) From mass spectroscopy and elemental analysis the M.F. of V it. A_1 (Retinol) is $C_{20}H_{30}O$
2) **1 º -OH group:-**

Acetylation:-

$$C_{20}H_{30}O \xrightarrow[-CH_3COOH]{(CH_3CO)_2O} \text{Mono acetyl derivative.}$$

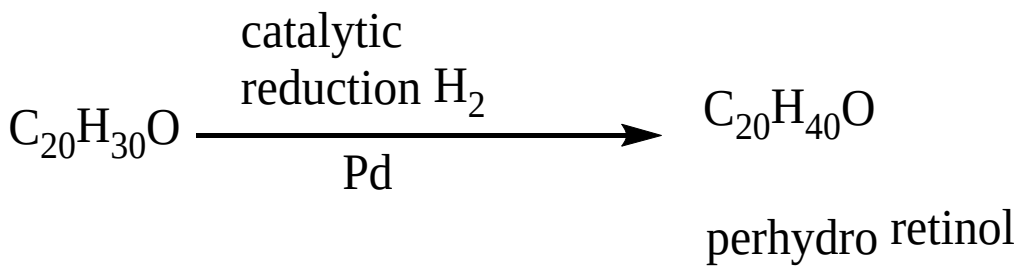
∴ one -OH group present

Oxidation:-

$$C_{20}H_{30}O \xrightarrow{[O]} \text{Aldehyde}$$

∴ 1º –OH group present

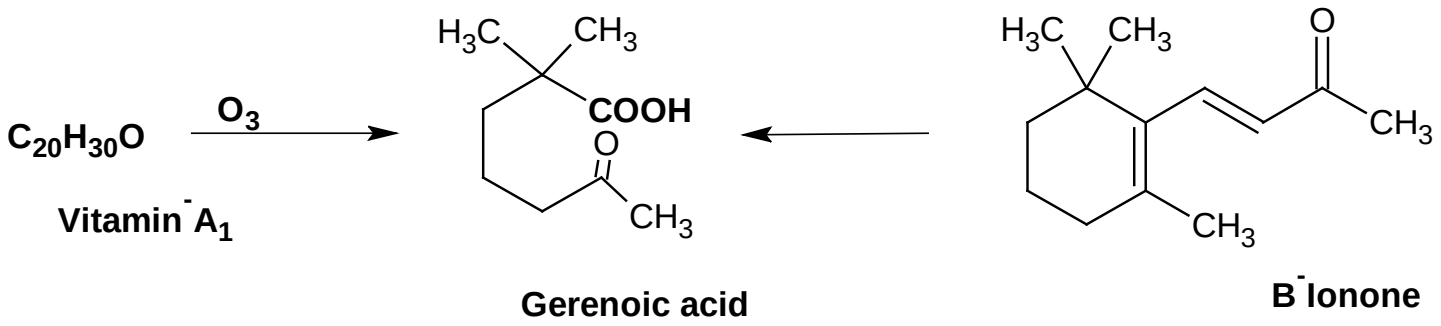
3. Double bond present:-



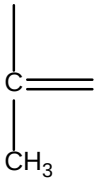
∴ 5 double bonds present

4.Presence of β-ionone ring (Ozonolysis):

Vitamin –A_1 on ozonolysis gives geronic acid per mole of Vitamin-A_1 and same compound is obtained by ozonolysis of β-ionone .



From the above reaction it is cleared that β-Ionone ring present in Vitamin-A_1

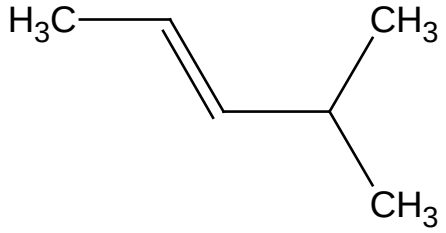
- Presence of  Groups (Isoprene Units)

Vitamin-A_1 $\xrightarrow{\text{Oxidized with Alkline } KMnO_4}$ 2 CH3COOH + Geronoc acid

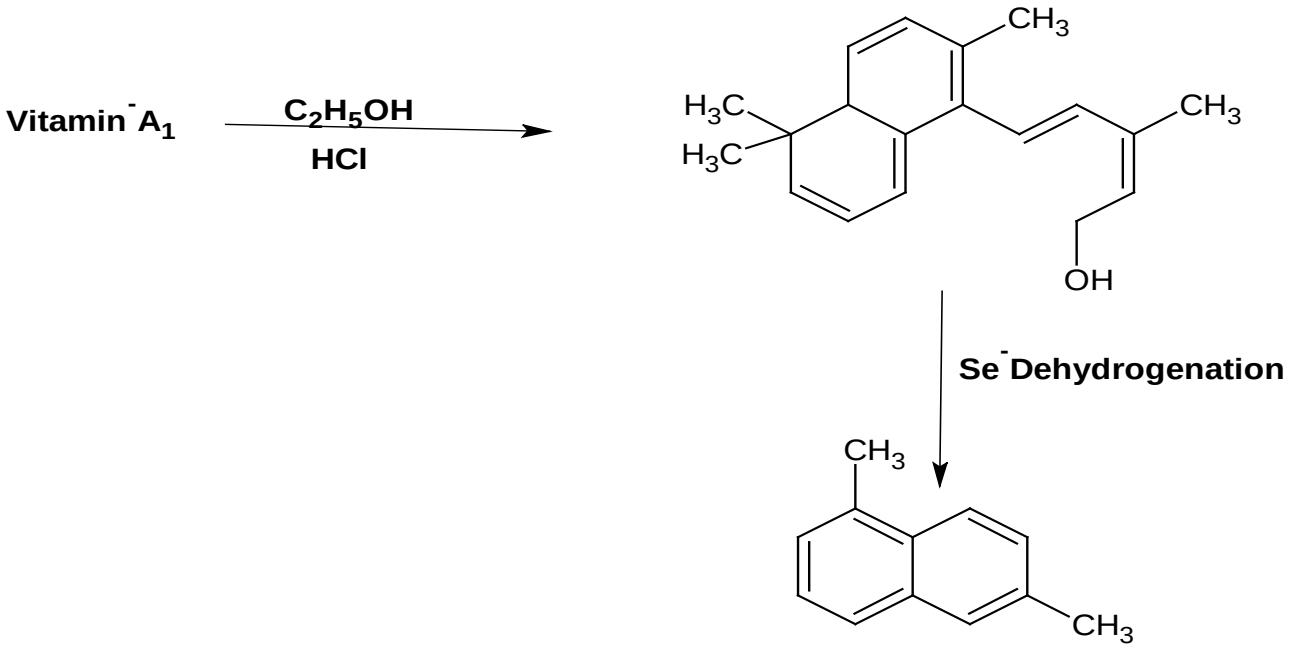
2- Isoprene unit present as a side chain.

- But if Vitamin-A_1 oxidized by hot CrO_3 , it furnished three moles of acetic acid.

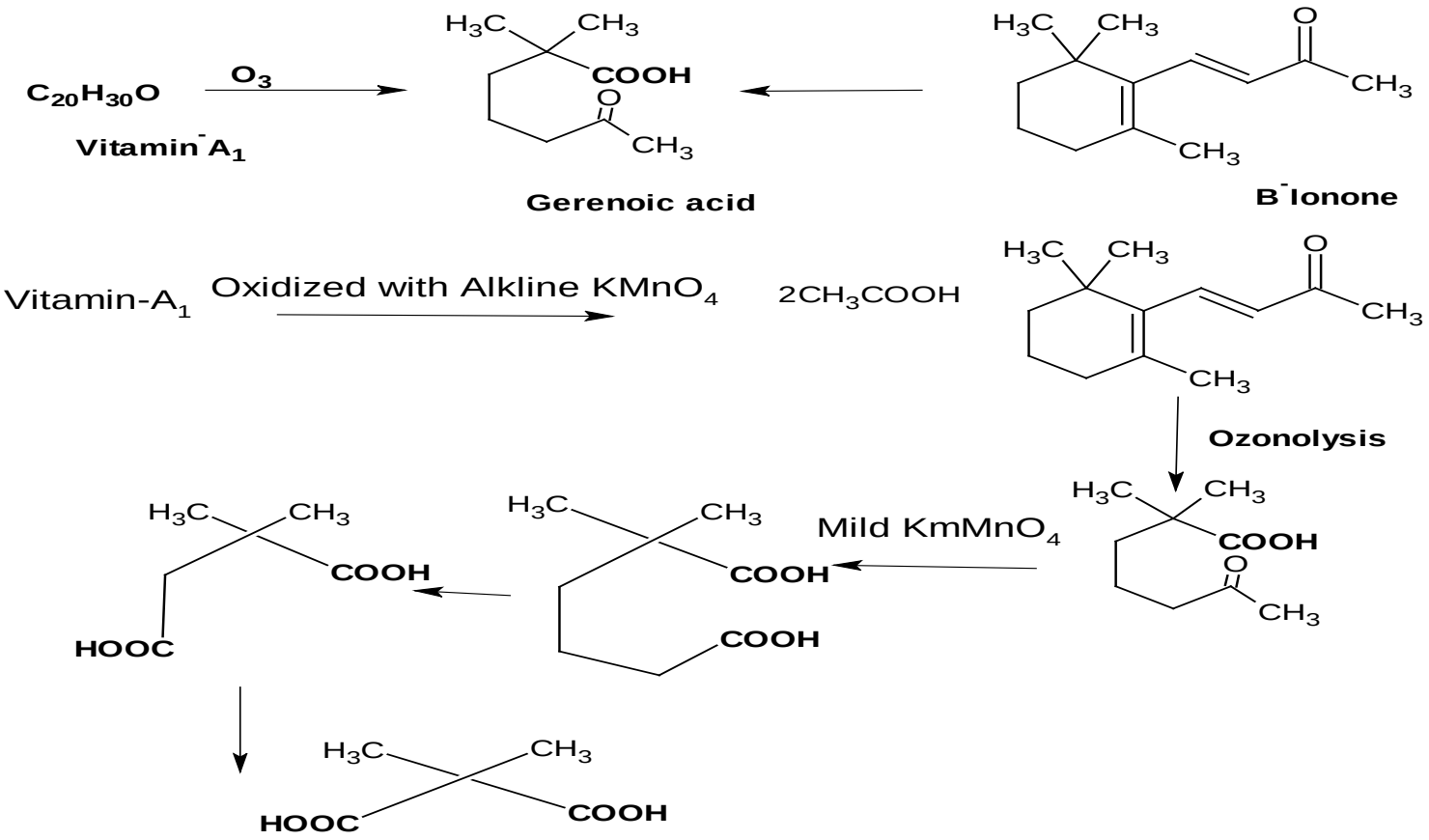
Vitamin-A_1 $\xrightarrow{\text{Oxidized with Hot } CrO_3}$ $3CH_3COOH$

So, this reaction tells us that third unit of Isoprene must be present in cycle.
Three methyl group in the form of : 

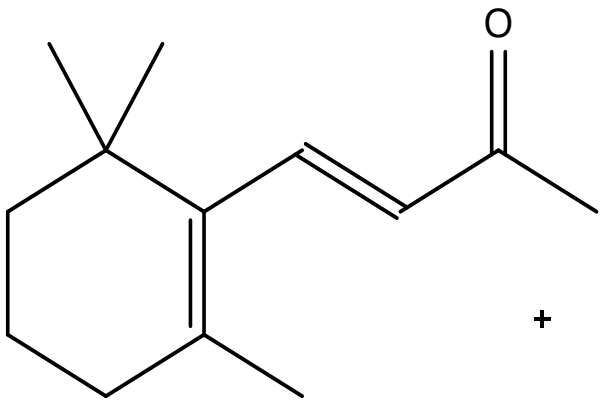
Vitamin-A_1 on heating with ethanolic HCl is converted into some compounds which on dehydrogenation with Se forms 1,6 dimethyl naphthalene.
Formation of this product can only be explained it there are two isoprene units.



Complete oxidation of Vitamin-A_1



Synthesis of perhydro Retinol

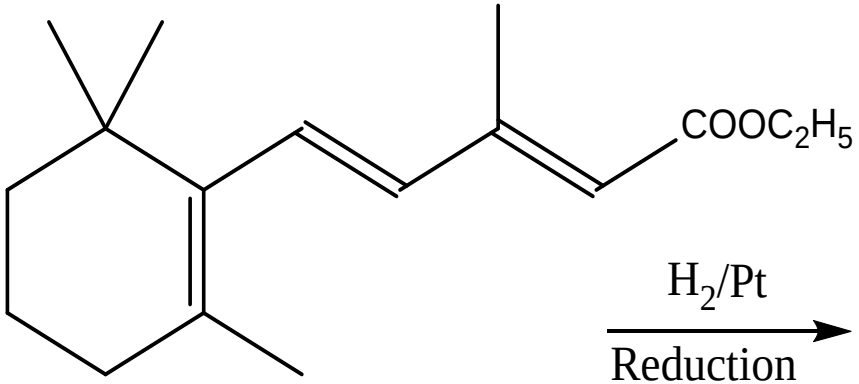


+ Zn + $BrCH_2COOC_2H_5$

Ethyl bromo acetate

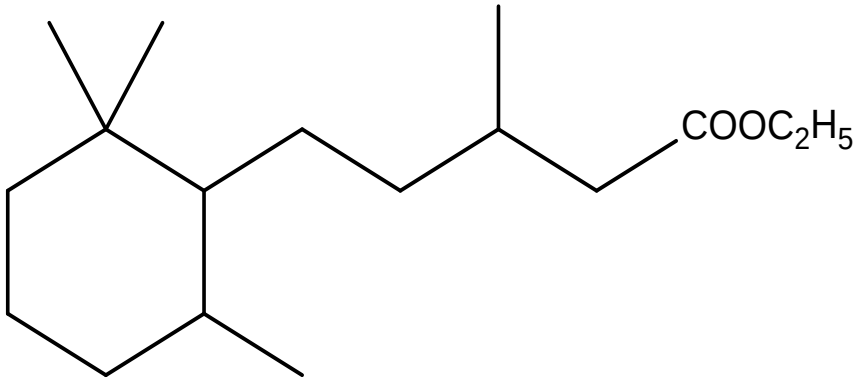
β-ionone

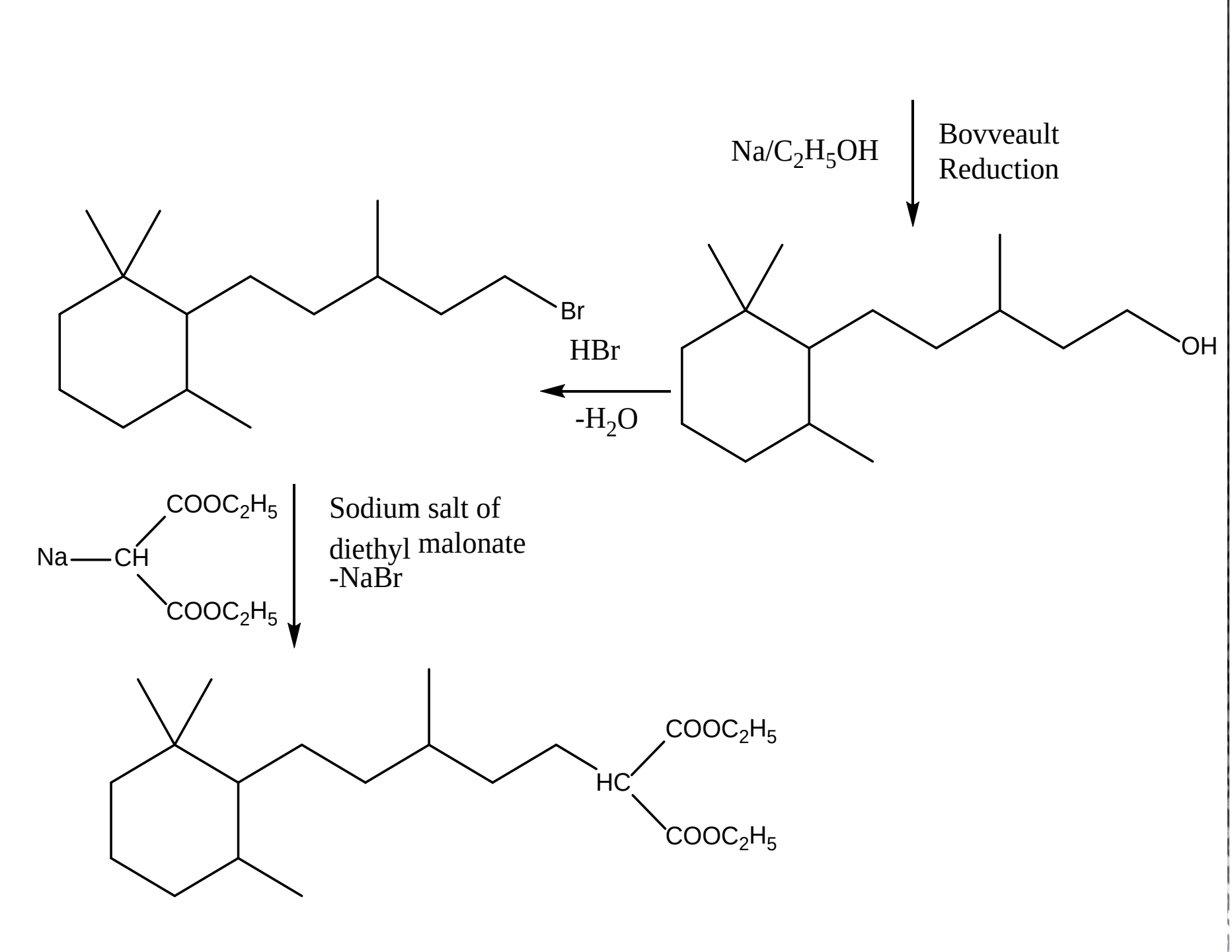
Reformatsky reaction

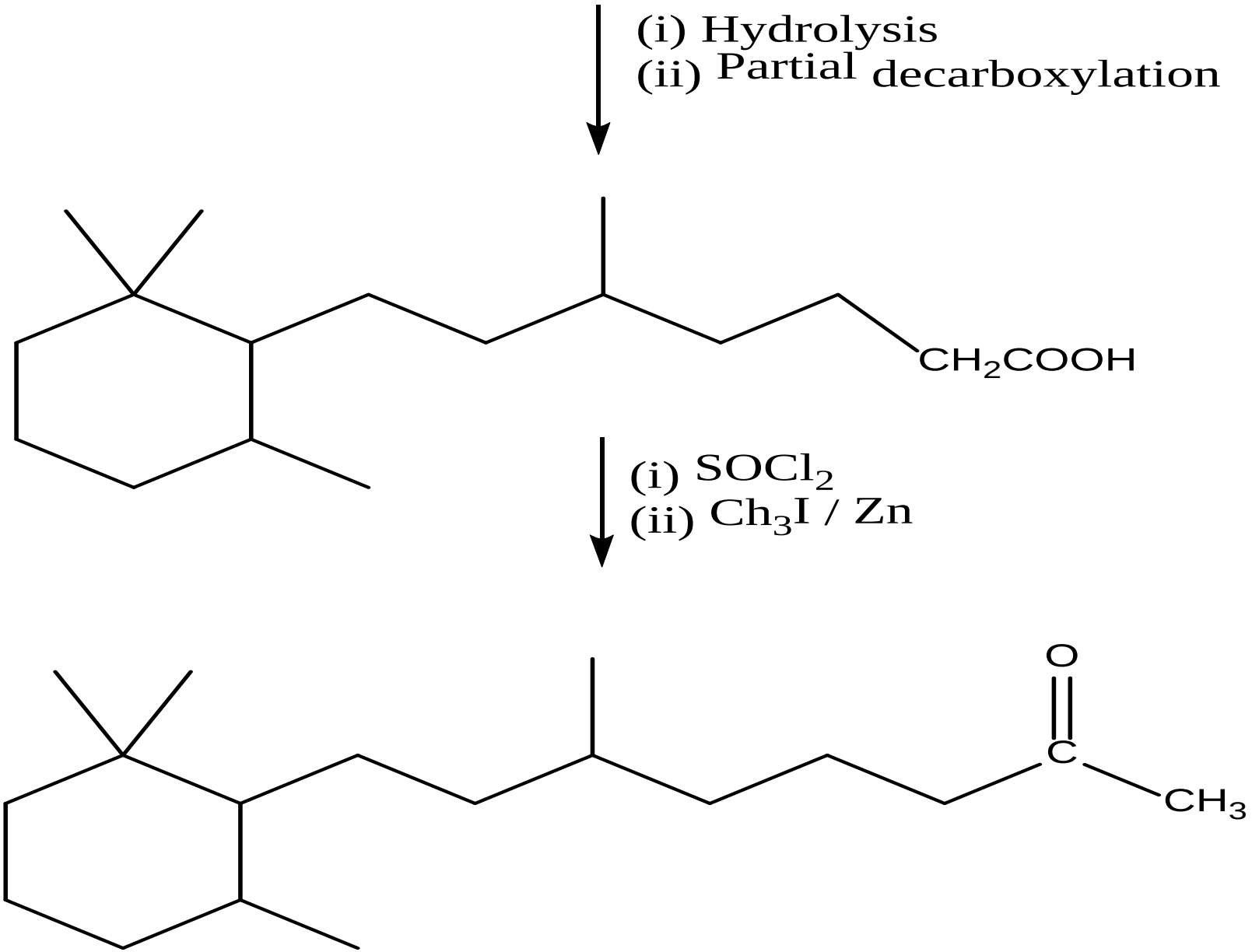


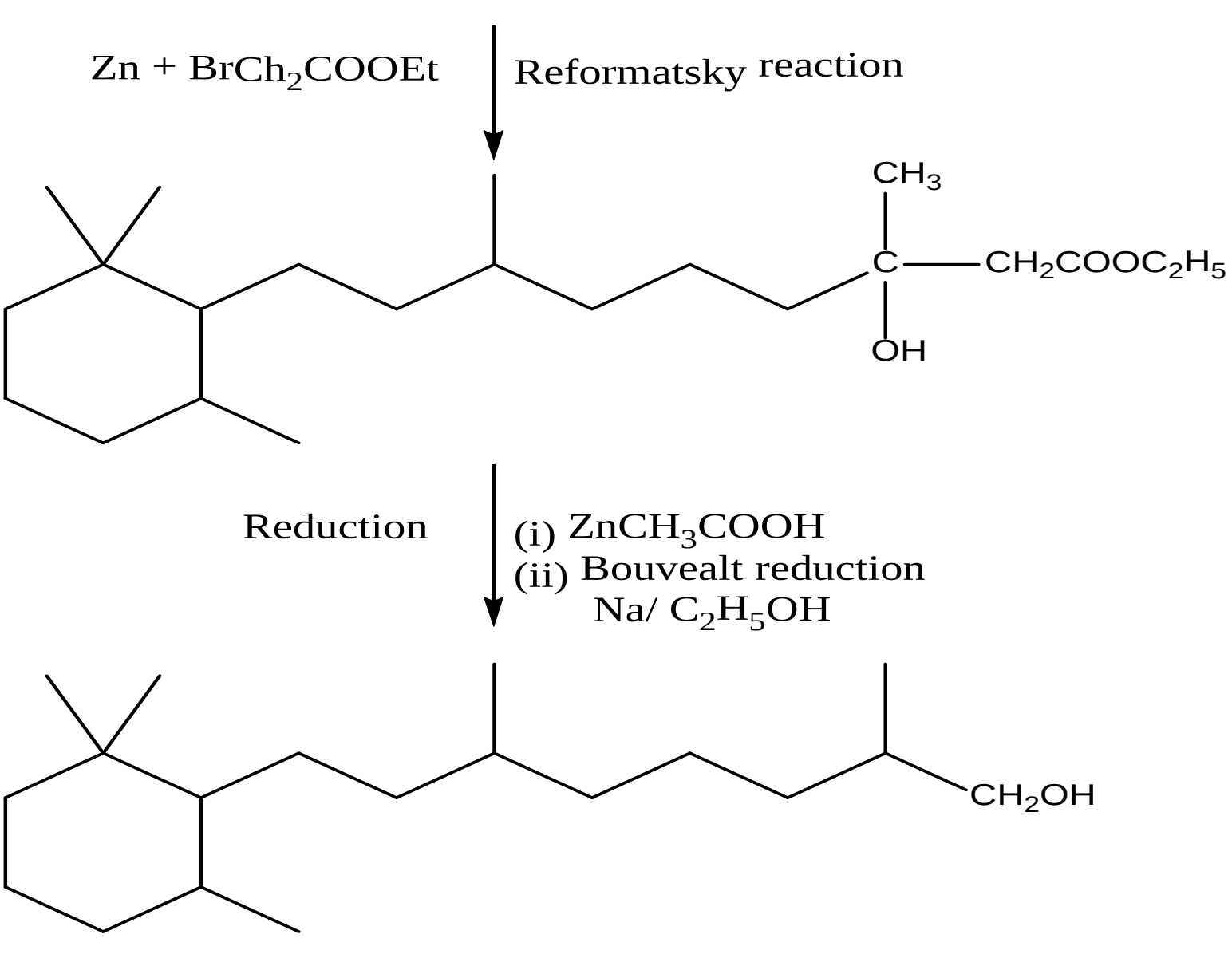
H_2/Pt

Reduction



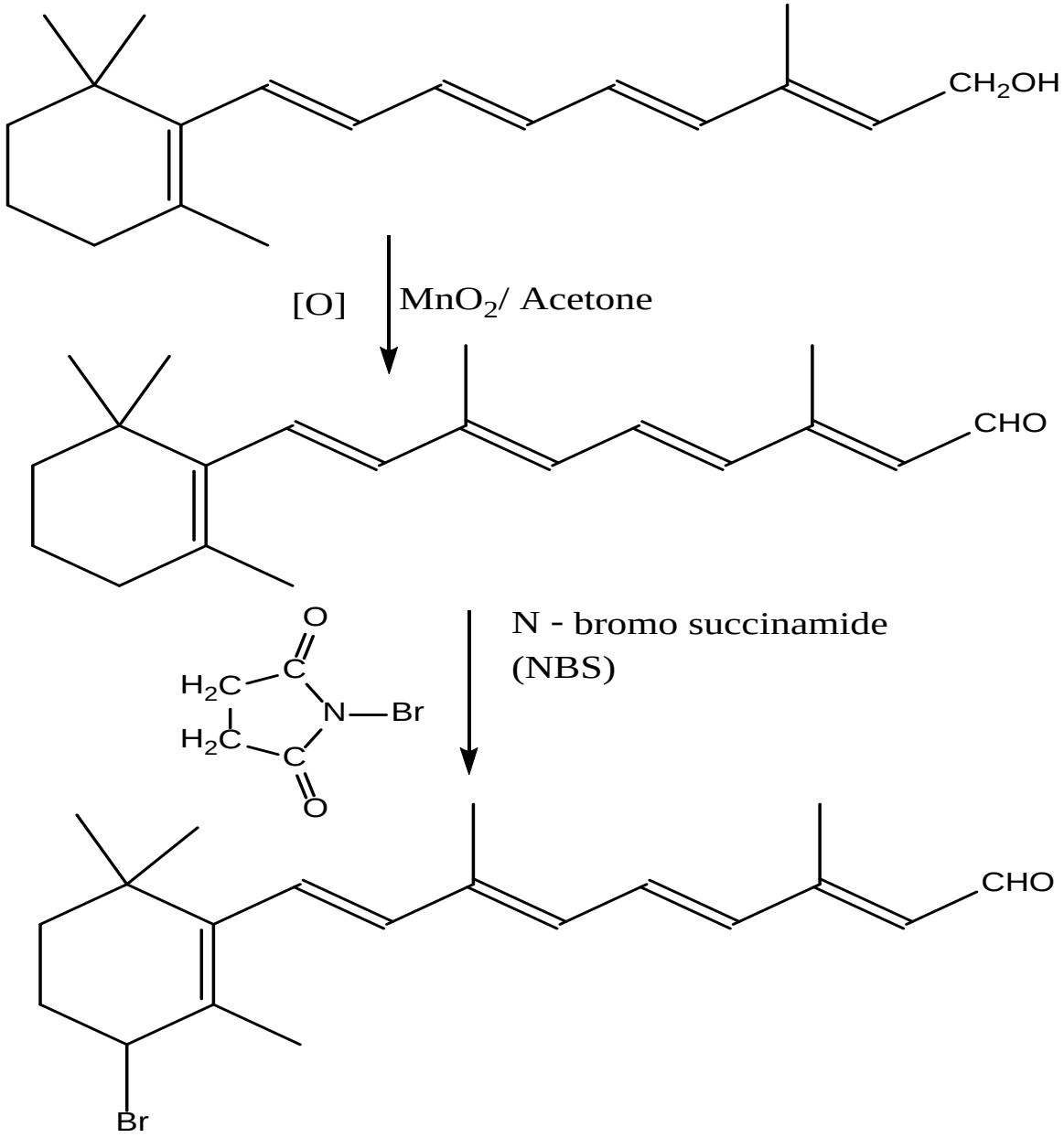

Na/C2H5OH
Bovveault
Reduction
OH
HBr
-H2O
Br
COOC2H5
Na
CH
COOC2H5
Sodium salt of
diethyl malonate
-NaBr
COOC2H5
HC
COOC2H5

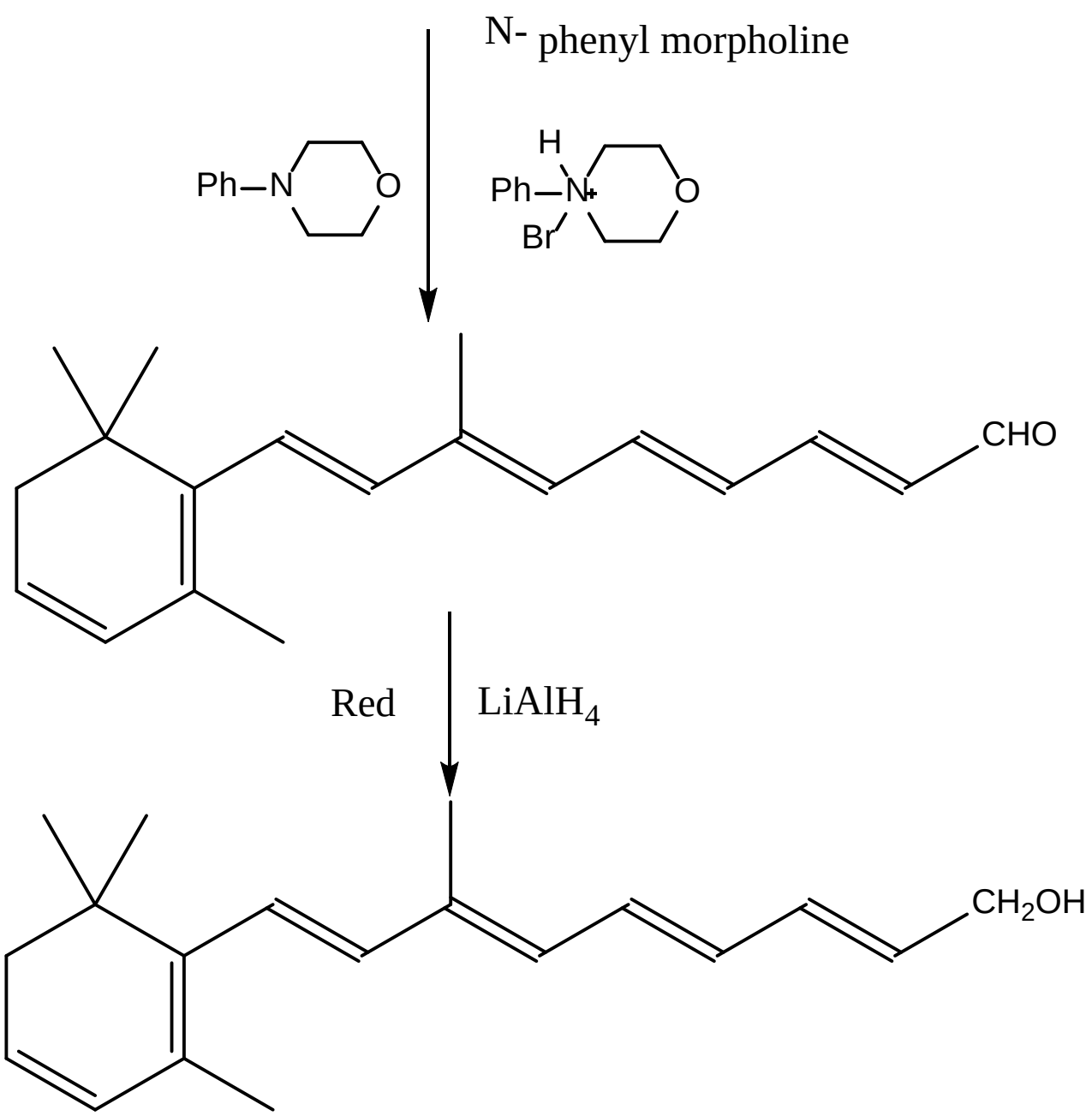

(i) Hydrolysis
(ii) Partial decarboxylation
CH2COOH
(i) SOCl2
(ii) Ch3I / Zn
O
C
CH3



perhydro Retinol
(Reduced Vit. A_1)

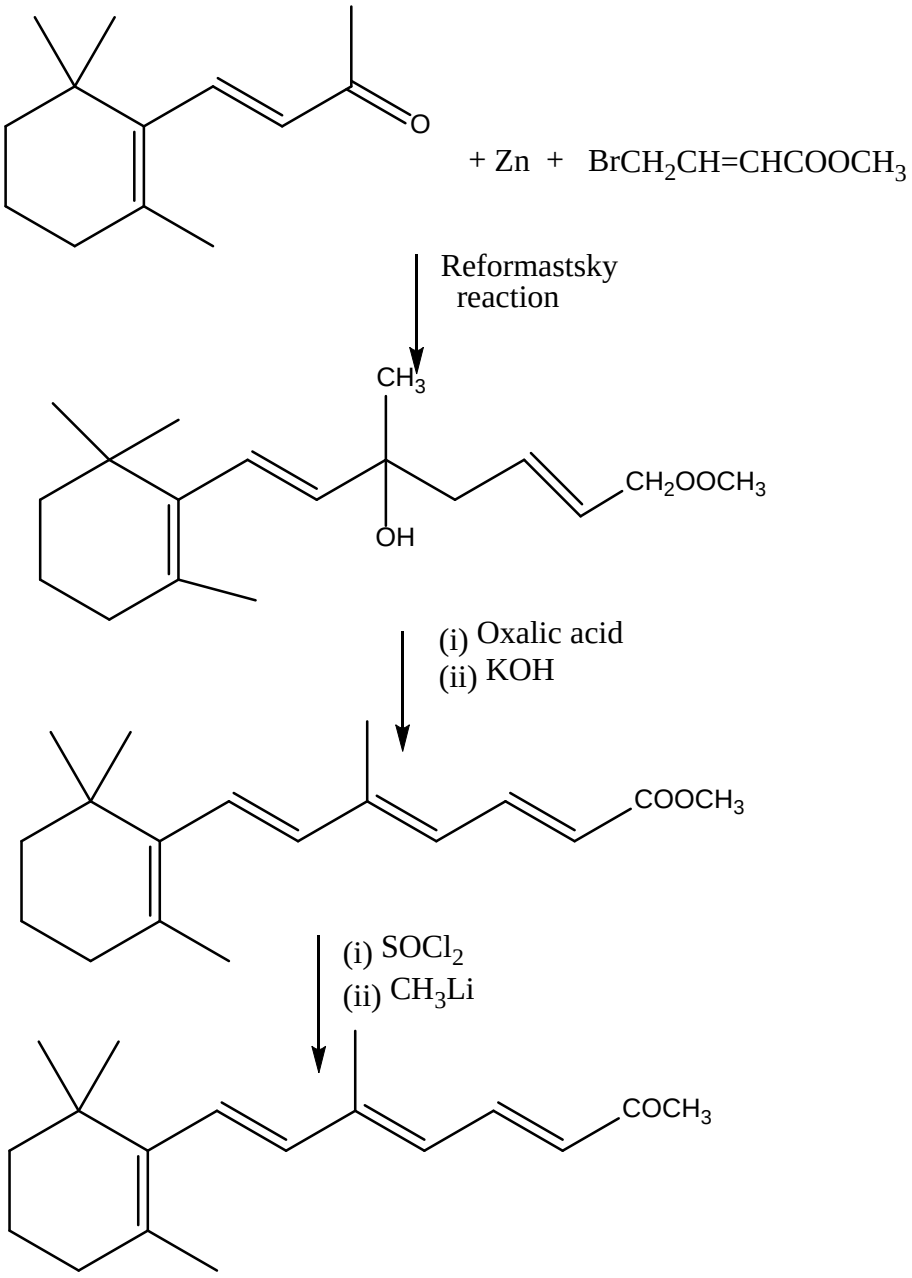
Conversion of Vit. A_1 to vit. A_2

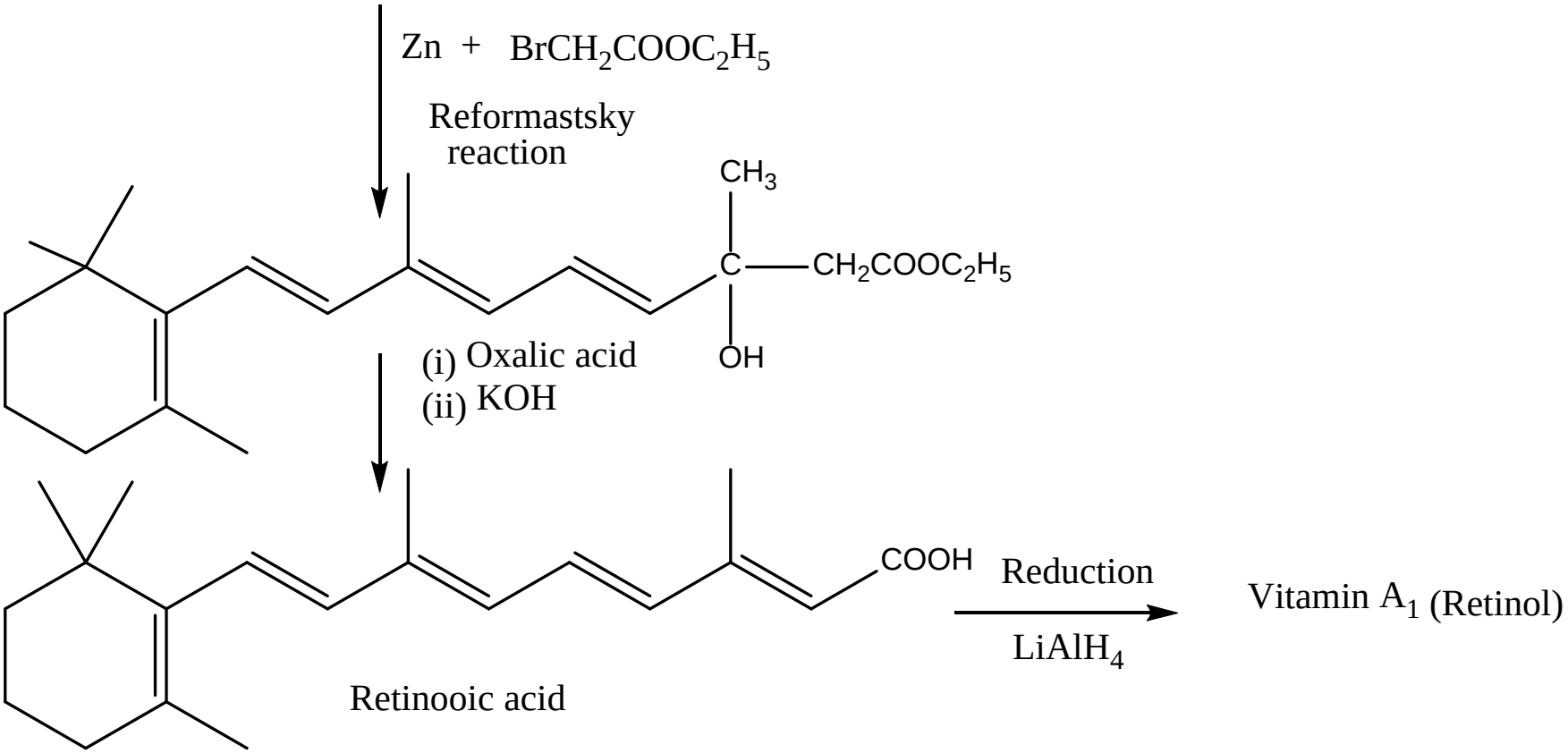



N- phenyl morpholine
Ph—N
O
H
Ph—N+
O
Br
CHO
Red
LiAlH4
CH2OH

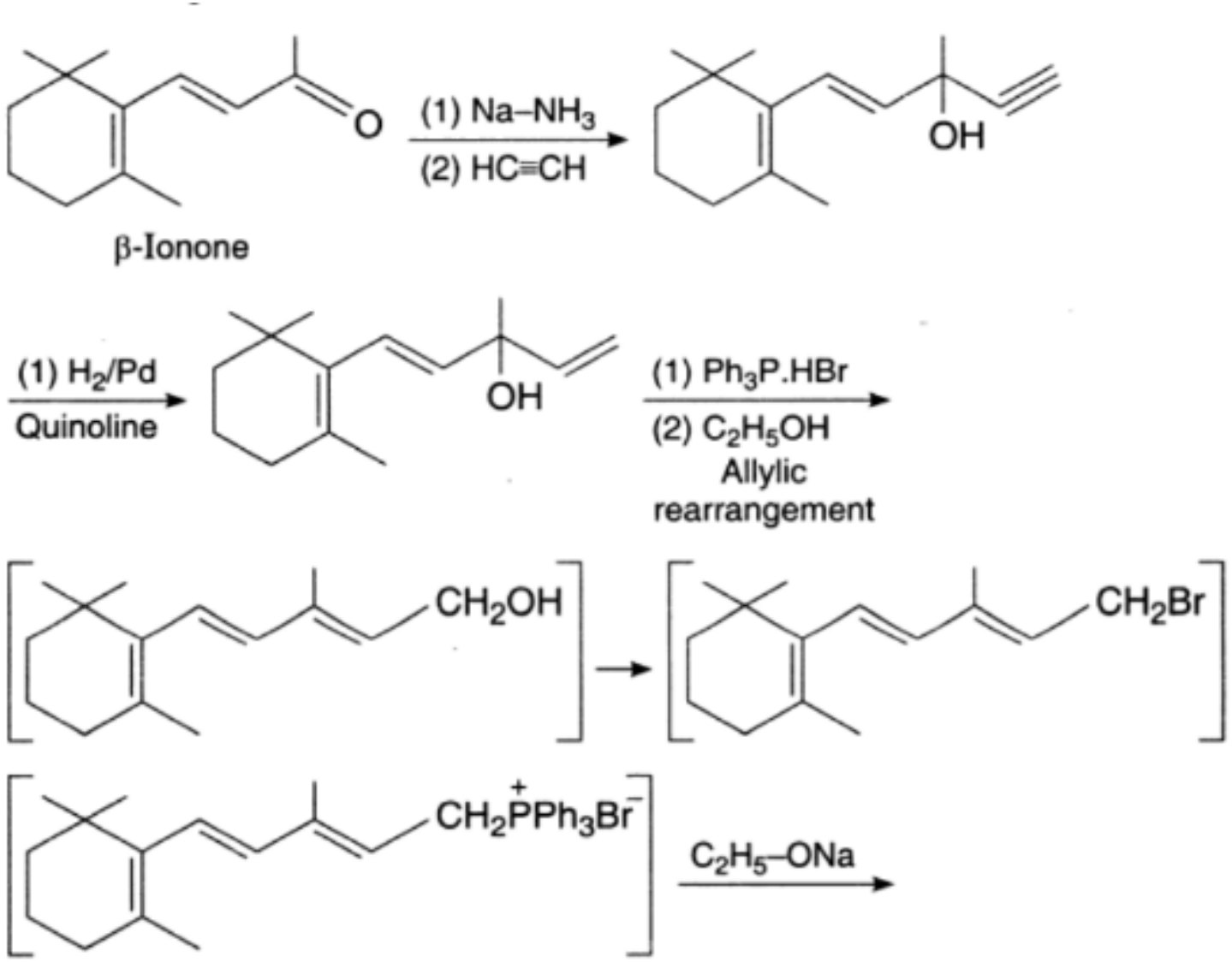
Synthesis of Vitamin A_1

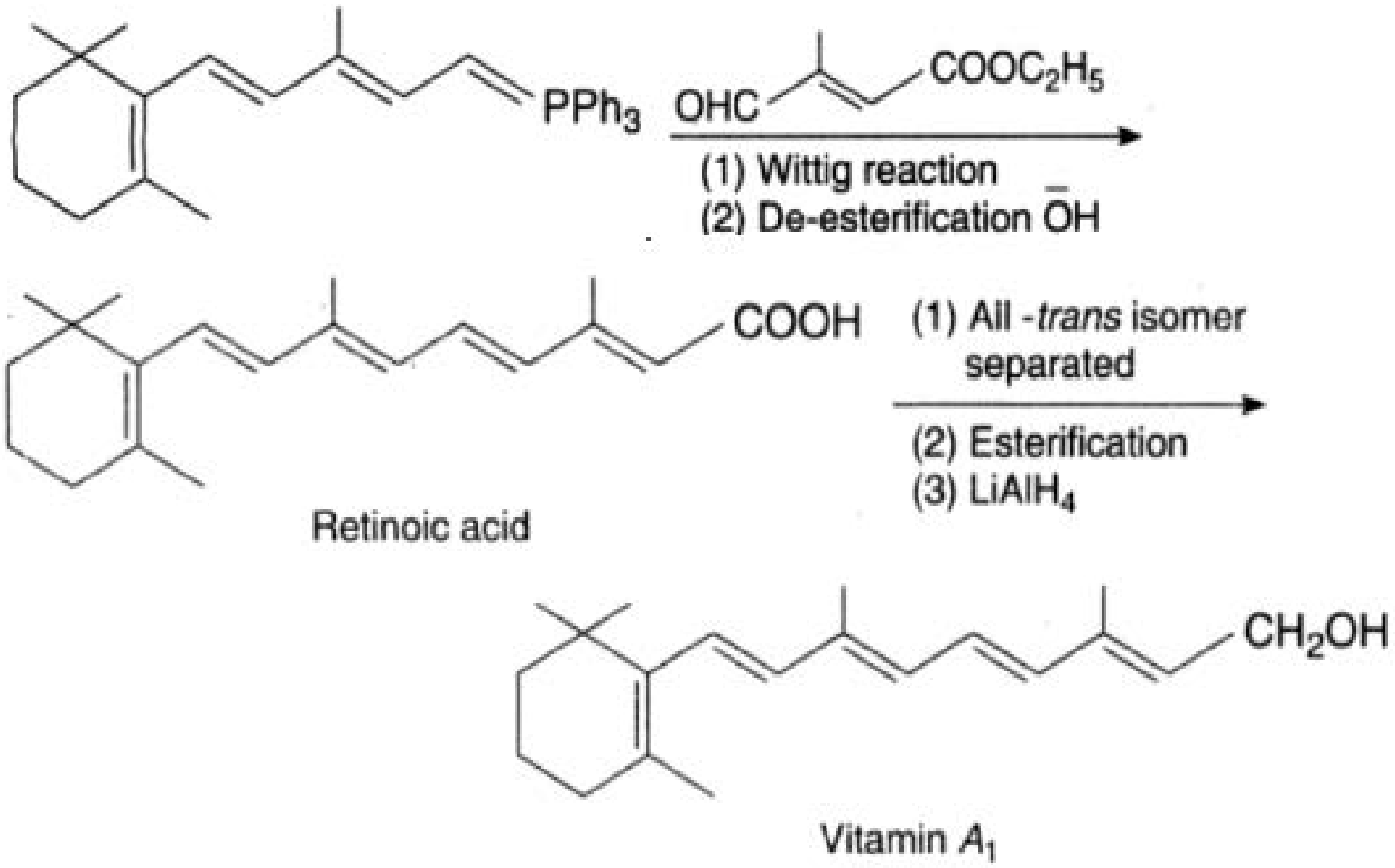
1) Van- Drop & Tischler Method:-




Zn + $BrCH_2COOC_2H_5$
Reformastsky reaction
CH_3
C
$CH_2COOC_2H_5$
OH
(i) Oxalic acid
(ii) KOH
COOH
Retinooic acid
Reduction
$LiAlH_4$
Vitamin A_1 (Retinol)

2) Pommer's synthesis:-

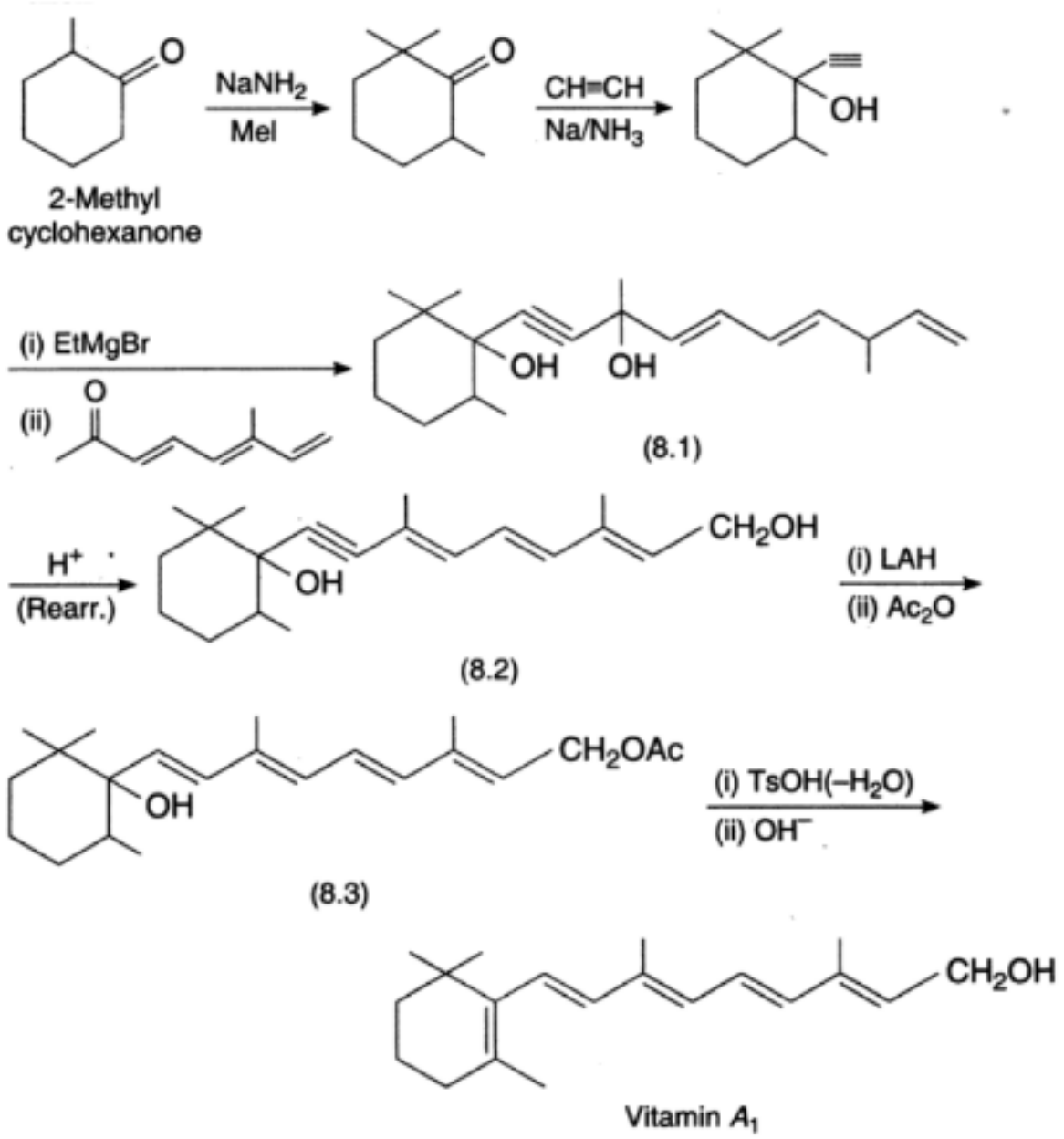




Retinoic acid

Vitamin A_1

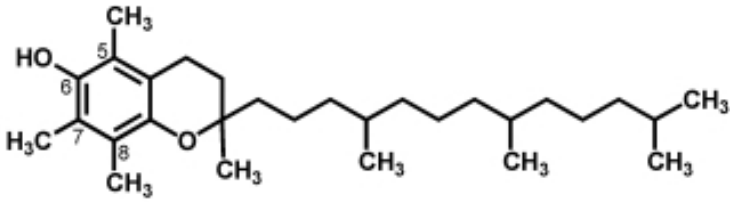
Attenburrow Synthesis:-



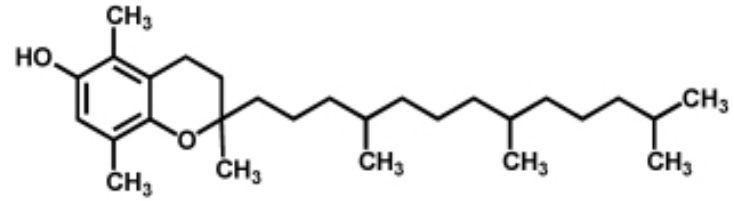
Vitamin – E (Tocopherol) :-

Structure:

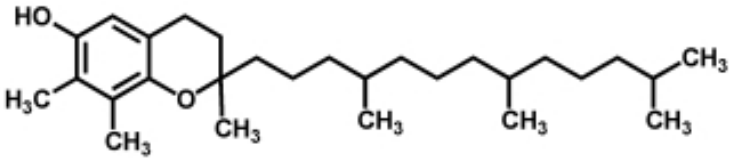
α-Tocopherol



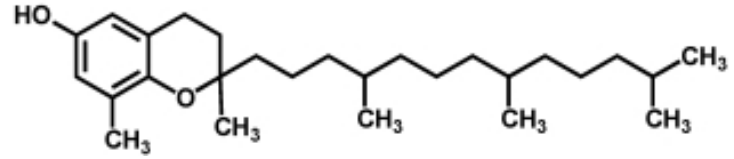
β-Tocopherol



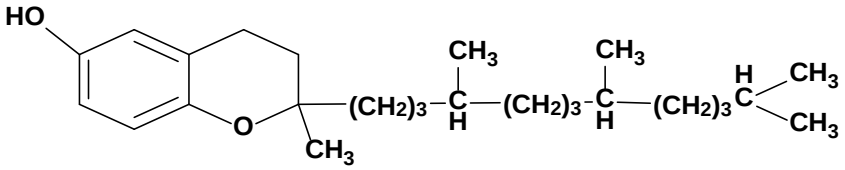
γ-Tocopherol



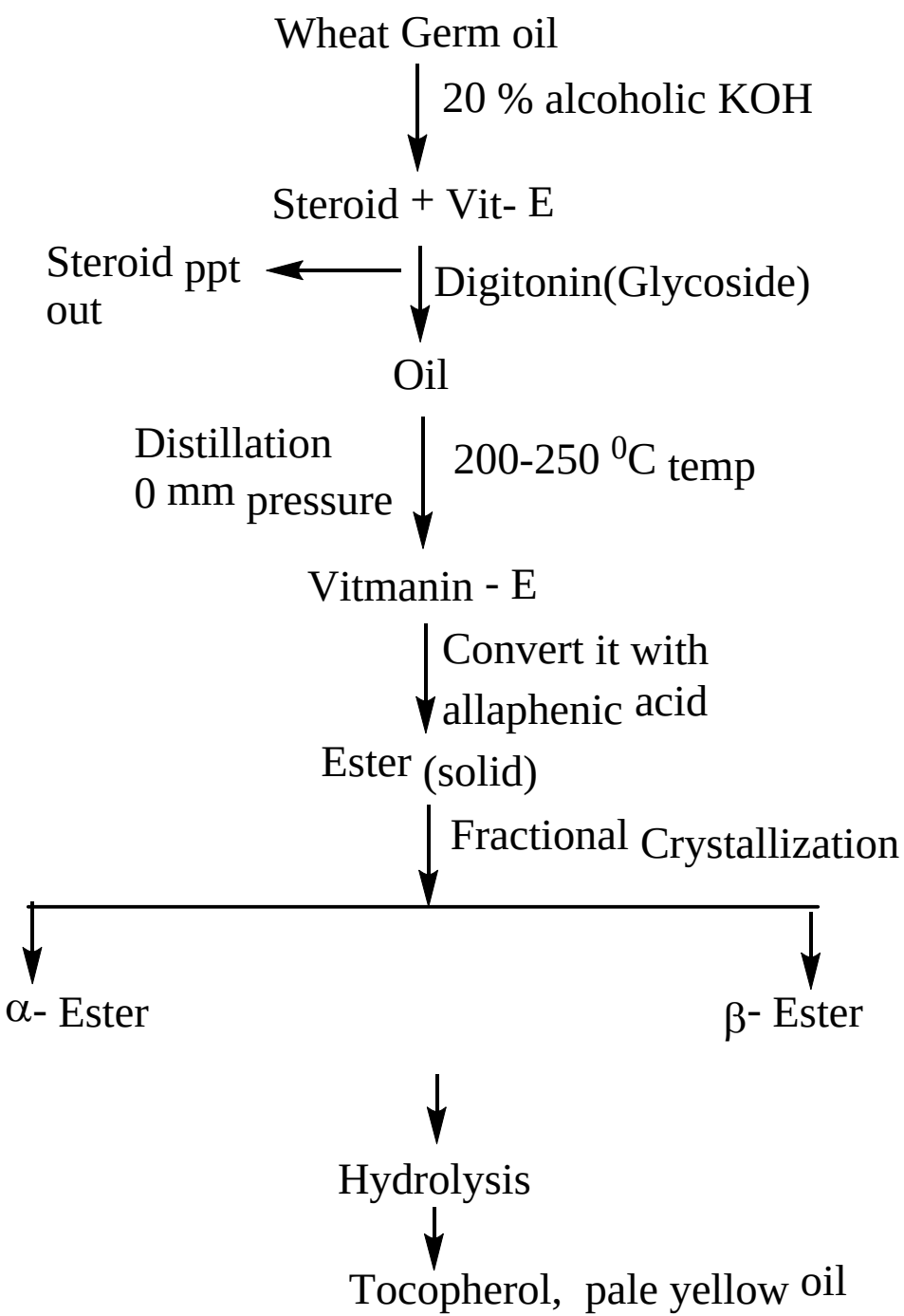
δ-Tocopherol



Tocol



Isolation:


Wheat Germ oil
20 % alcoholic KOH
Steroid + Vit- E
Steroid ppt out
Digitonin(Glycoside)
Oil
Distillation 0 mm pressure
200-250 ^{0}C temp
Vitmanin - E
Convert it with allaphenic acid
Ester (solid)
Fractional Crystallization
α- Ester
β- Ester
Hydrolysis
Tocopherol, pale yellow oil

Isolation(Adsorption Method):

Wheat Germ oil

↓

Dissolved in light petroleum

↓

This absorbed on Alumina to remove sterols

↓

Convert with Cyanic acid gas or
with Allophanic acid into esters

↓

α,β -tocopherol respectally separated

↓

Gives respective Tocopherol

Properties:

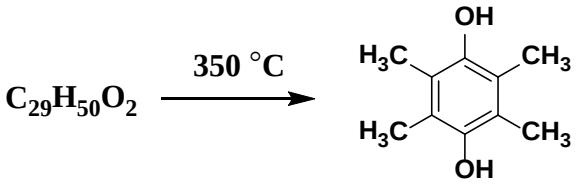
- Oily liq. : light yellowish & has characteristic taste
- Solution in alcohol, ether, $CHCl_3$, and fixed oil, insoluble in water
- Slowly oxidized in air, also affected by UV light & deactivated
- Tocol is parent compound of all tocopherols.

Constitution of Vitamin E:

1. M.F. : $C_{29}H_{50}O_2$
2. Nature of one Oxygen atom:
   - One of the oxygen is present Hydroxy group from Tocopherol forms mono-acetate, monoester and monoether.
   - It shown by an examination of UV spectra of α-Tocopherol and its acetate so it phenolic in nature
   - Color within $FeCl_3$ also present phenolic group

   $\therefore$ -OH group is phenolic and inn aromatic ring

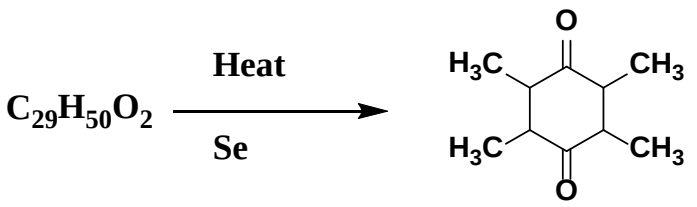
3. Nature of second Oxygen:
   - It is inactive oxygen and it is not taking part in reactivity that is cyclic ether.
4. Pyrolysis:-
   - α- Tocopherol when heated at 350 ^{0}C



Duroquinol

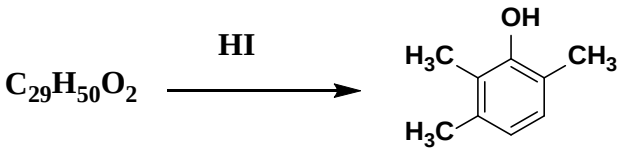
   - So position of second oxygen will be in para position.

- When heated with selenium:



α-tocopherol — Duroquinone

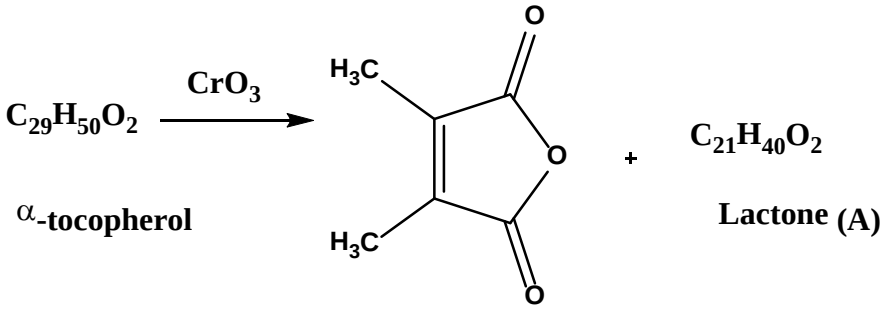
- When heated with HI :-



α-tocopherol — δ- cumenol

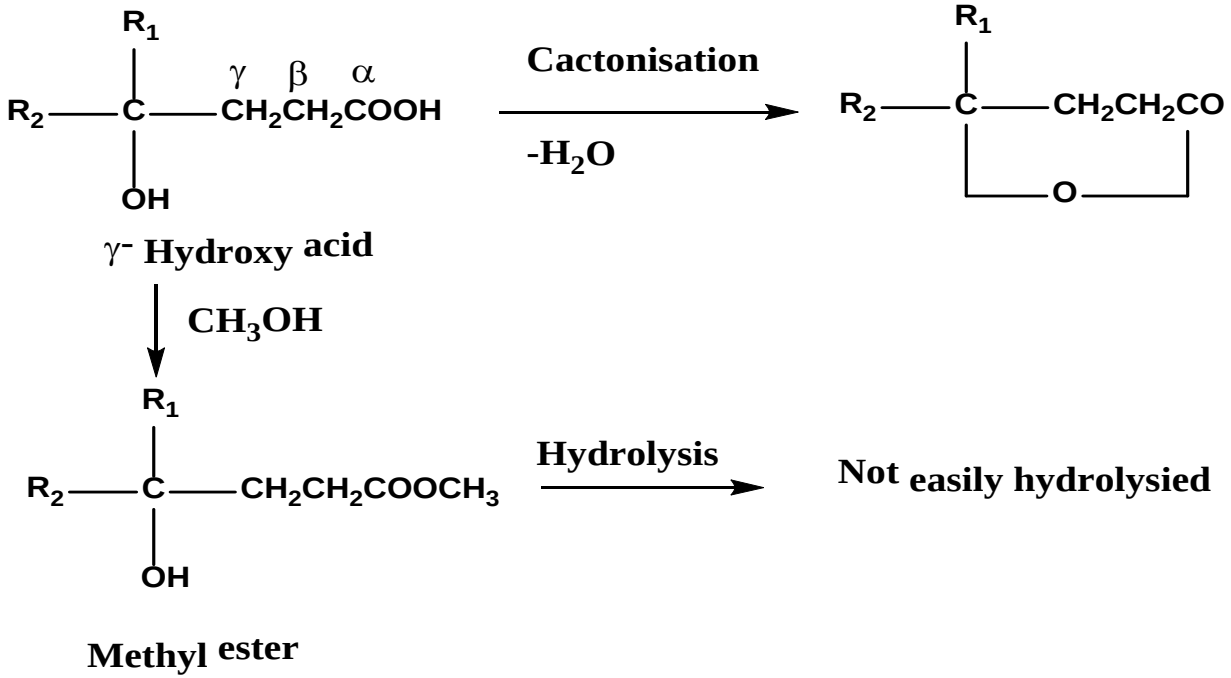
- From formation of the above product it was concluded that α-Tocopherol is the monomer of duroquinol but no the di-ether of duroquinol
- The possibility of α-Tocopherol as di-ether was ruled out by the fact that α-Tocopherol yields an allophanate which confirms the presence of one free hydroxy group
- Also UV spectrum of α-Tocopherol exhibited the band due to presence of free hydroxyl group so It is phenolic

5. Oxidation of α-Tocopherol :-



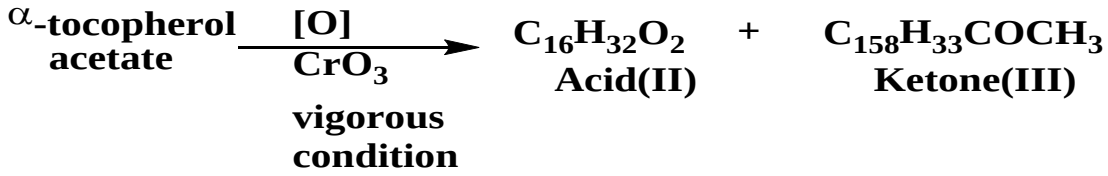
Comp was optically active & sat. lactone

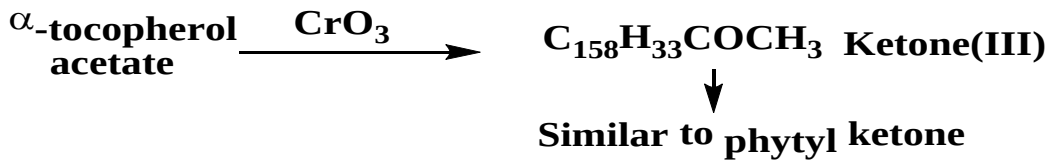
the structure of this lactone may be written as under(derived from γ-hydroxy acid)



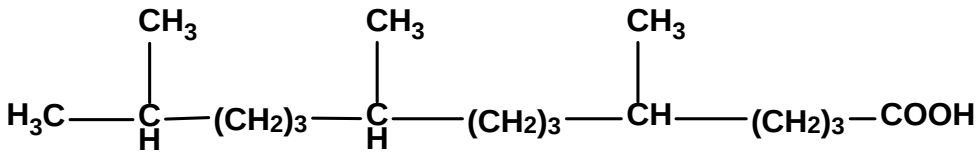
- Methyl ester of the hydroxy acid can't be hydrolyses
- Hydroxy acid resistance to oxidation & also could not be oxidized to a keto acid.
- All above facts that –OH group in γ- hydroxy acid and it is 3° in nature.

➢ When α- Tocopherol acetate is oxidized with chromic acid under more vigorous condition, it yield a mixture of an acid $C_{16}H_{32}O_2$(II) & a ketone $C_{18}H_{36}O$ (III)



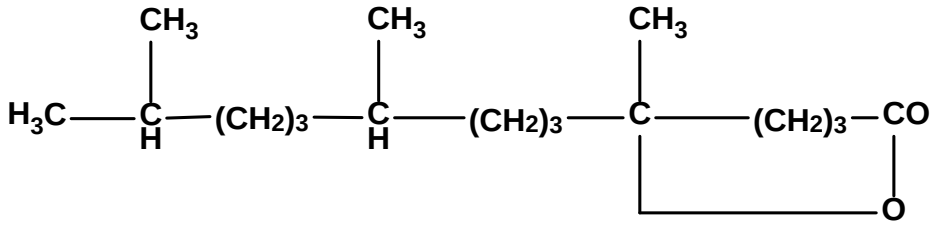


Fernholz further showed that acid(II) contain 3-CH_3 groups by using Kuhn-Roth method, most of naturally compound occurring isoprene units, this led Ferhhlz to following structure of the acid(II)



Str. of acid(II)

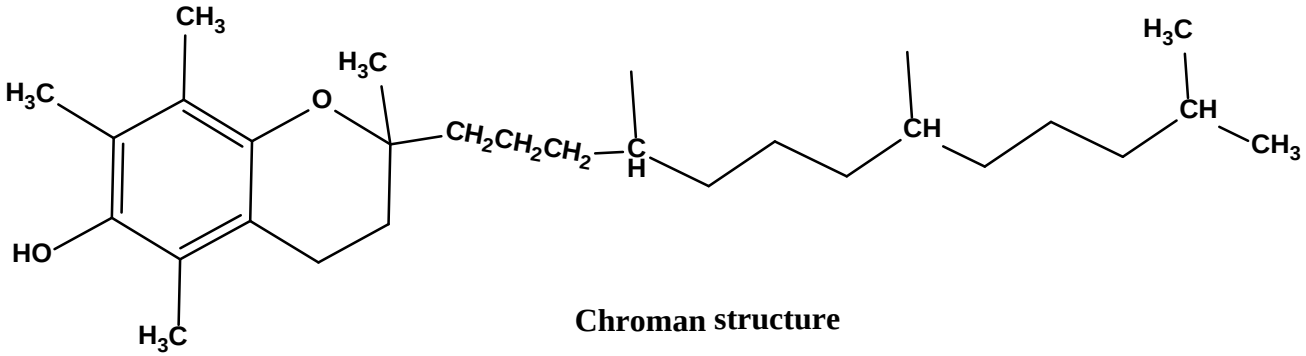
- As per acid(II) is degraded product of the lactone(I) the γ-lactone may be written as follow:



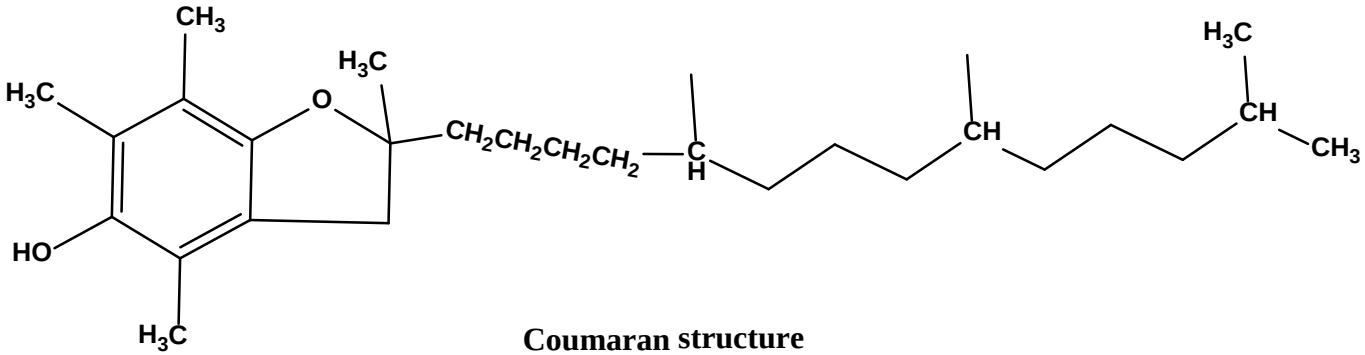
γ- lactone

6. Structure of α-Tocopherol:

- from the above evidences, it fellows that α-Tocopherol having a substituted benzene ring and long side chain also α-Tocopherol may be either chroman or coumarone structure



Chroman structure

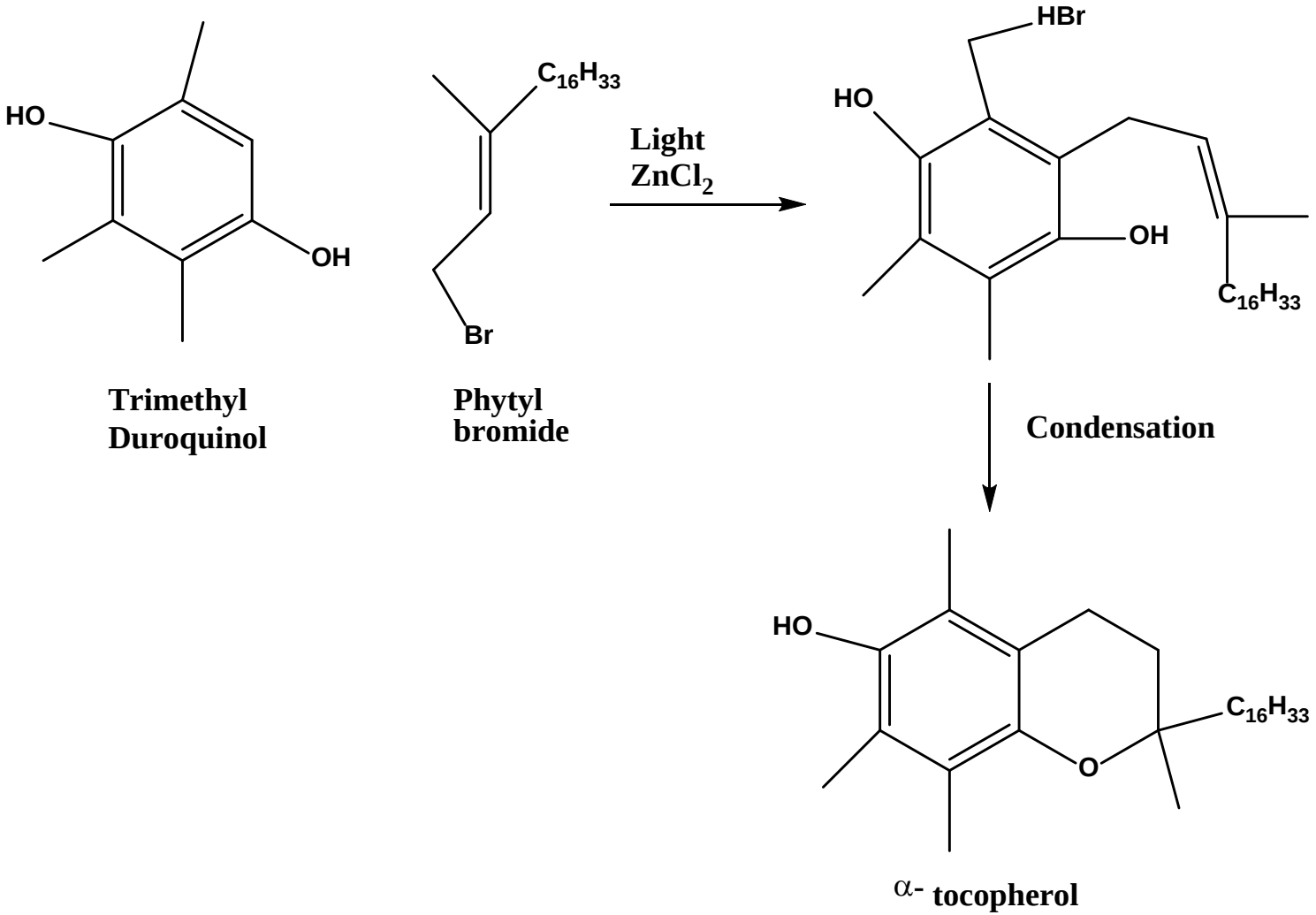


Coumaran structure

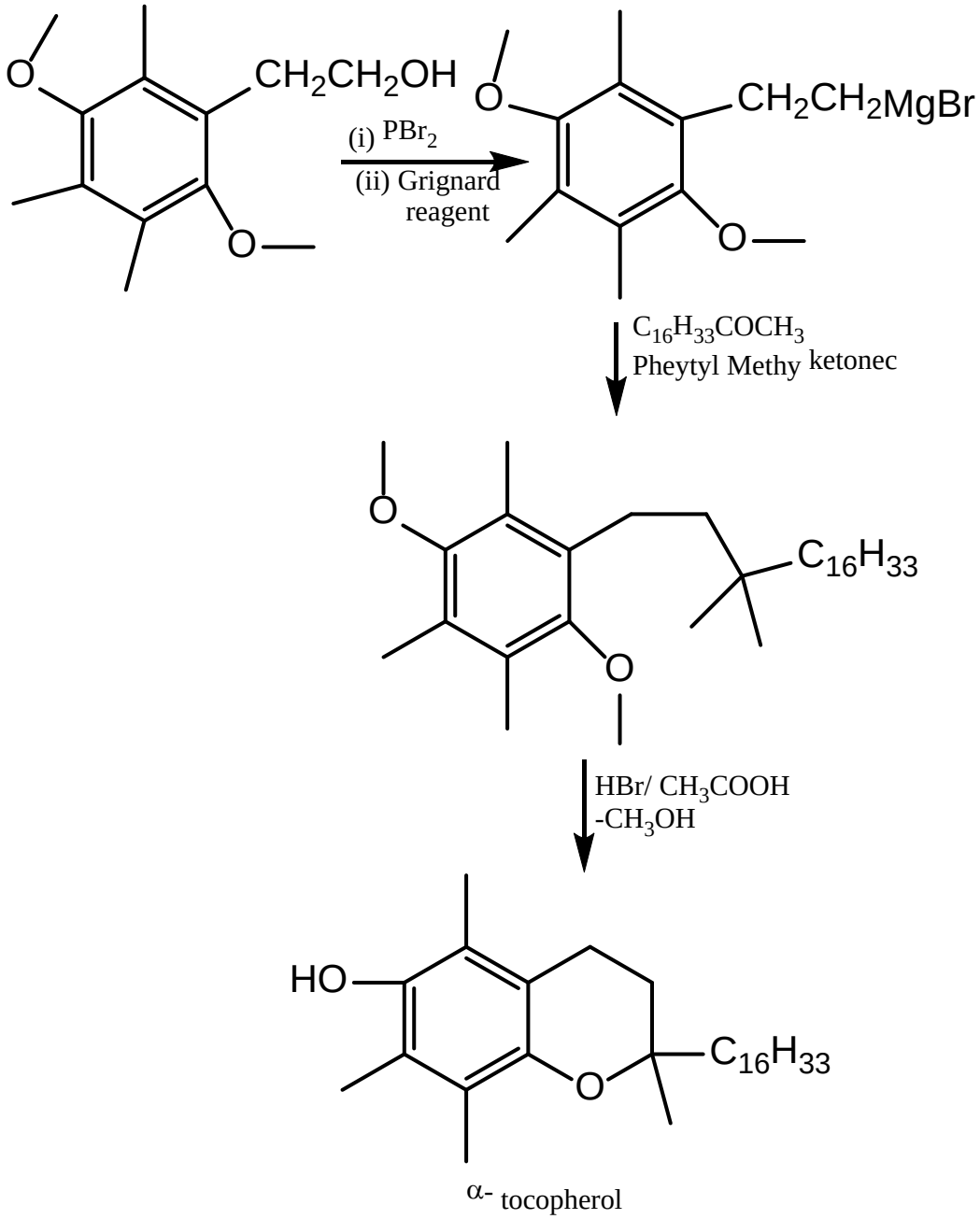
- The chroman str. Is more acceptable because chroman are formed from phenol γ, γ di-substituted allyl bromides while Coumarins are formed from phenols and un-substituted ally bromide
- α-Tocopherol can be synthesized from a hydroquinone(phenol) and Phytyl bromide γ, γ di-substituted allyl bromide.

Synthesis:-

(i) Karrer synthesis:-

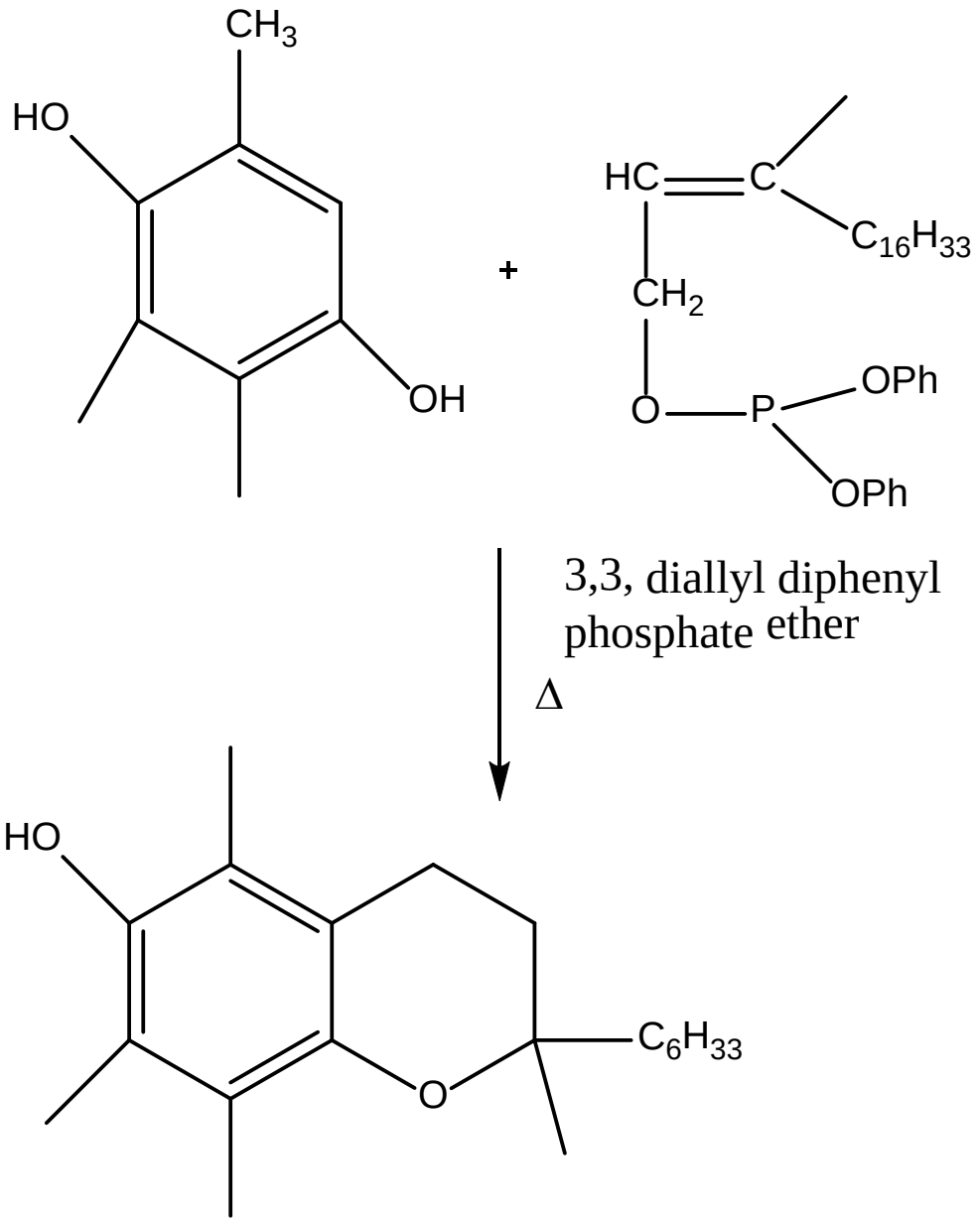


(2) Smith Reaction:-

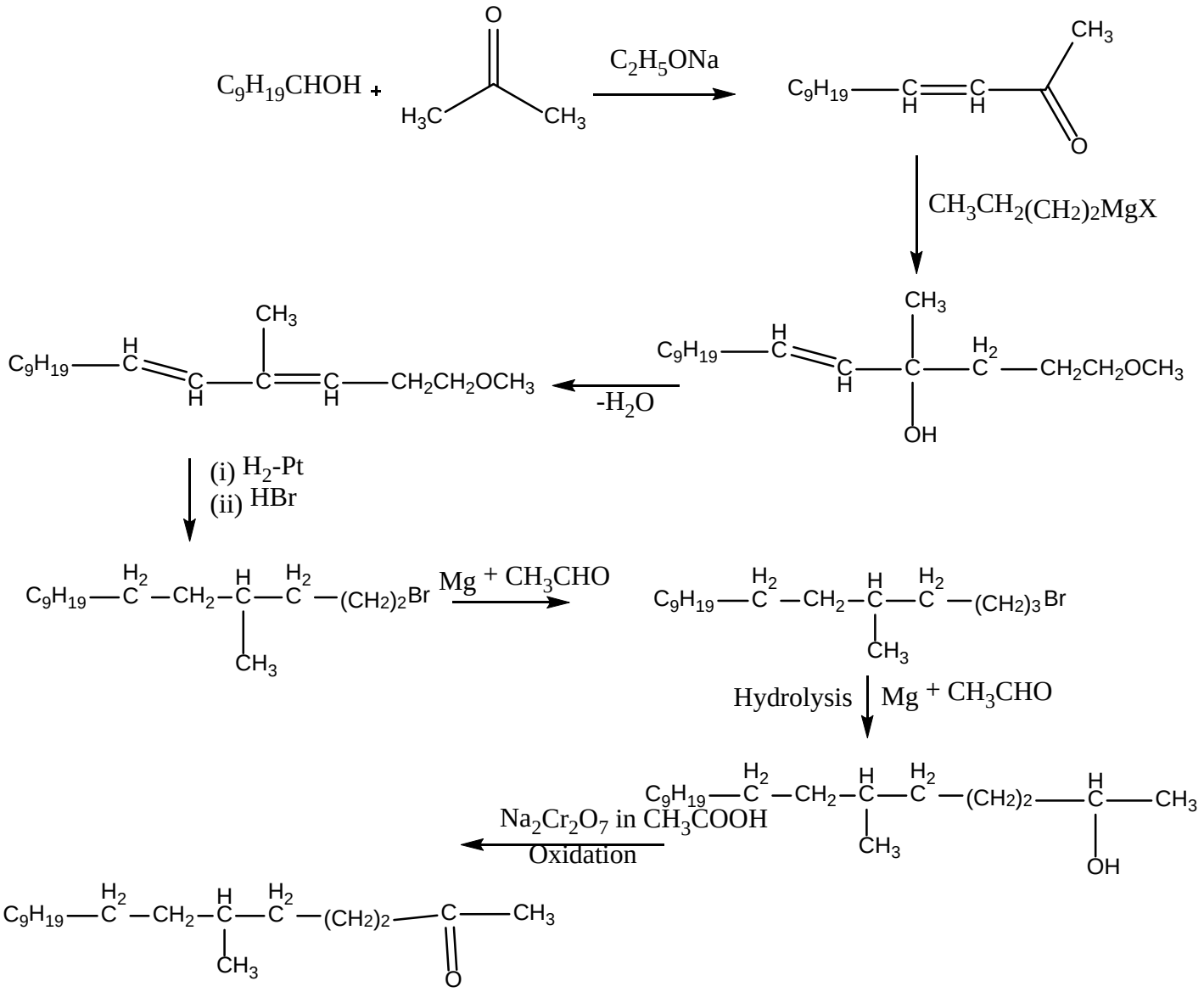


α- tocopherol

3) Miller Synthesis

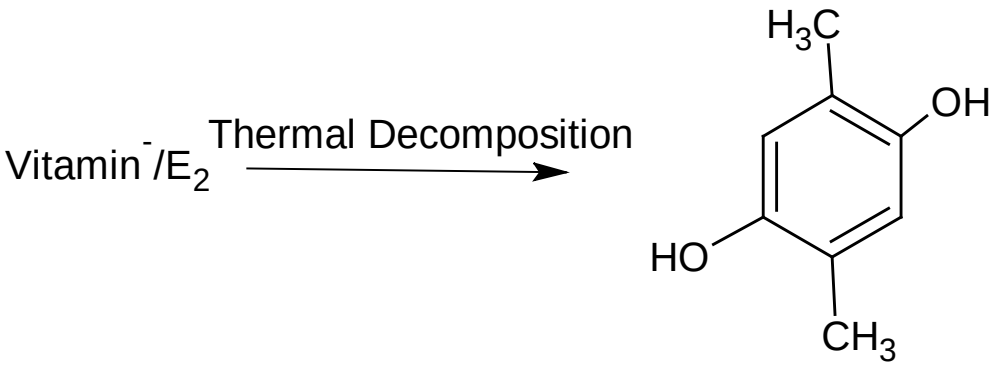


4) Phytyl ketone Synthesis:



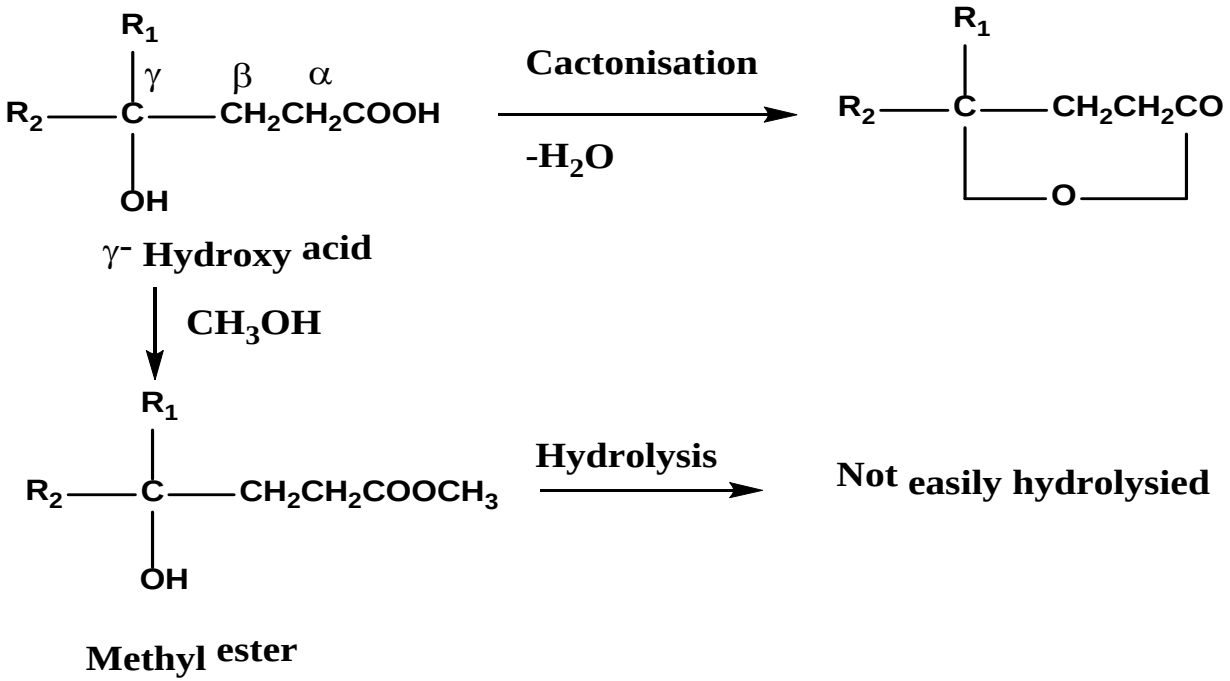
β-Tocopherol

- Molecular formula: $C_{28}H_{48}O_2$
- It shows UV absorption at 297 nm.
- From the above point it is cleat that it possess one less methylene group from the Vitamin-E1.
- On thermal decomposition β-Tocopherol furnished trimethyl quinol.

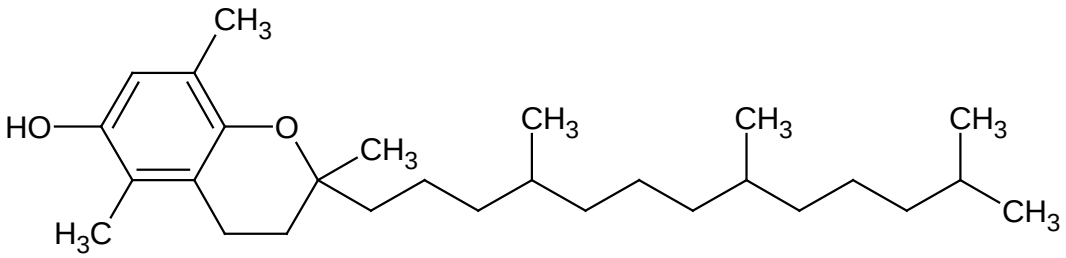


Result of thermal decomposition of Vitamin-E_1; it contain one more methyl group.

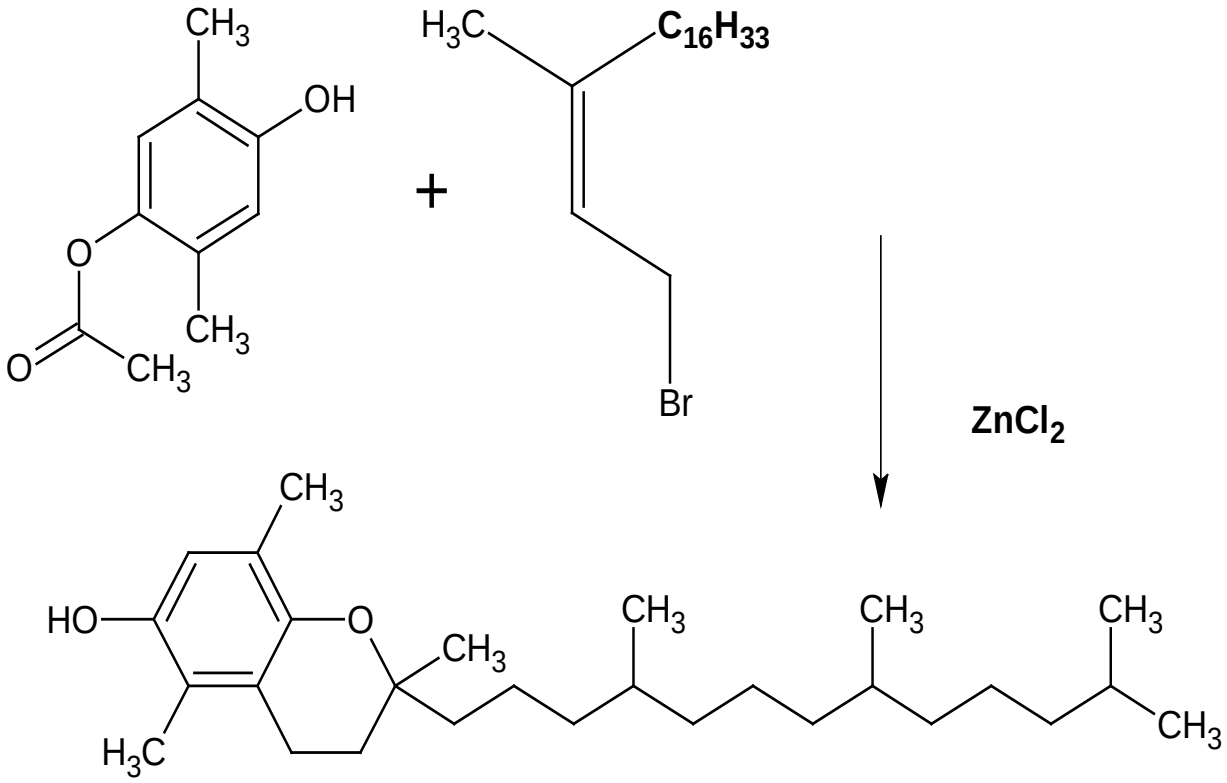
On oxidation with CrO_3 it gives same lactone as per Vitamin_E1



Thus only differ one methyl group in benzene ring substitution hence structure of Vitamin-E2

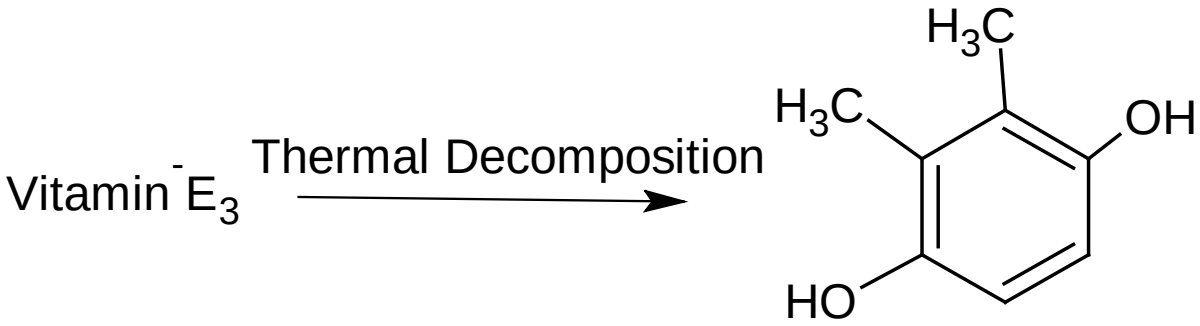


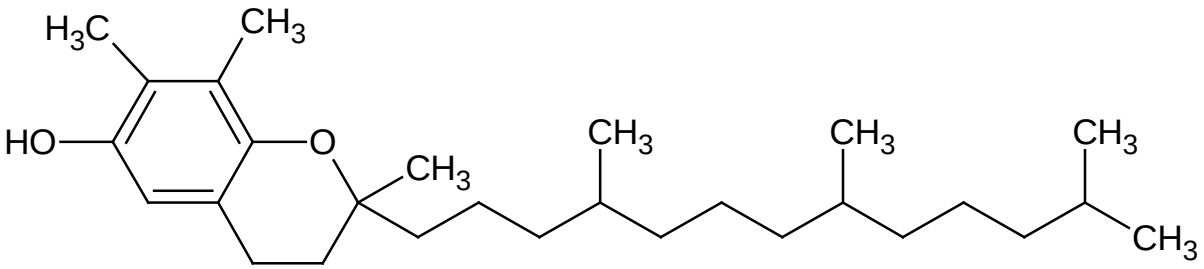
Synthesis of Vitamin-E_2



γ-Tocopherol

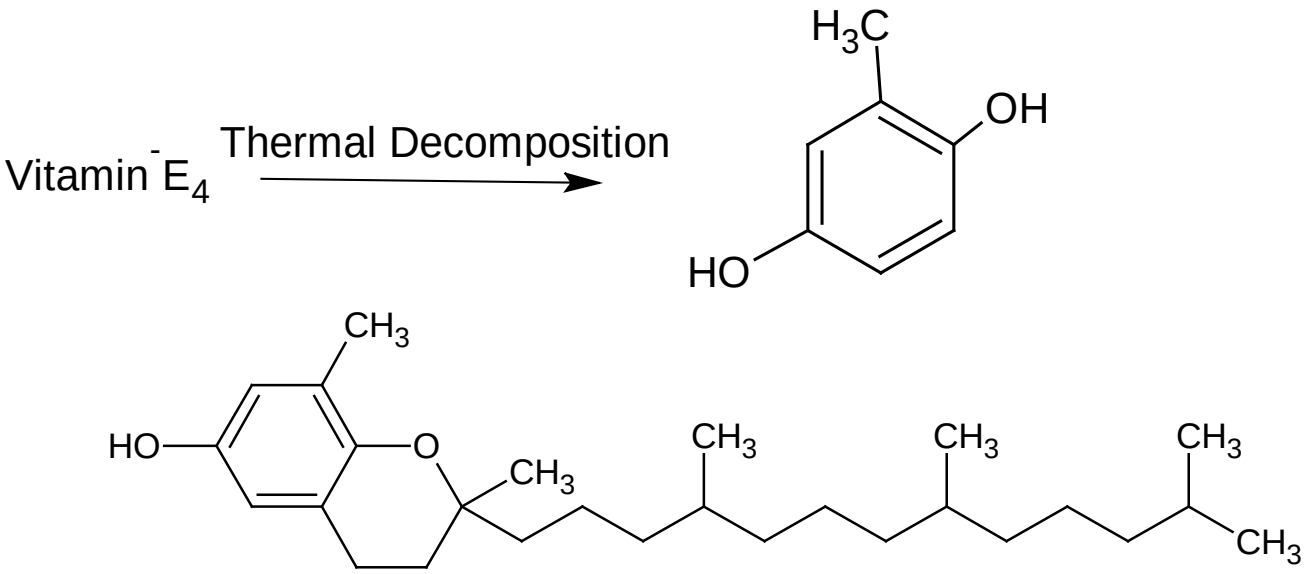
- Molecular Formula: $C_{28}H_{48}O_2$
- UV absorption : 298 nm
- This is isomeric with β-Tocopherol.
- The only difference is the position of two methyl group.





δ-Tocopherol

- Molecular Formula: $C_{27}H_{46}O_2$
- UV absorption : 298 nm
- This is isomeric with β-Tocopherol.
- The only difference is the position of two methyl group.



Vitamin K

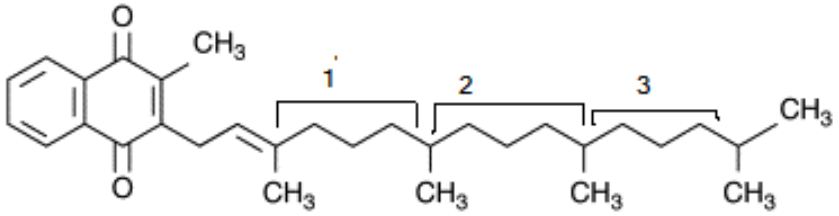
Two vitamins: K1 and K2

Source:

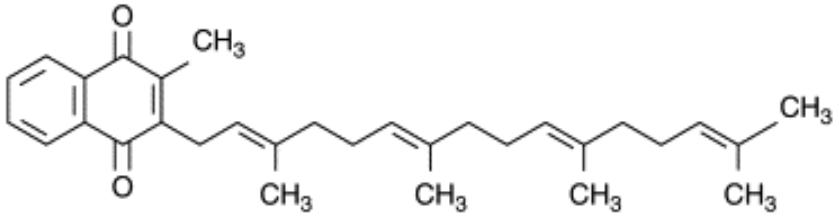
K1: green plant ,

K2: purified fish, meat, bacteria, soya bean oil

Structure:



Phylloquinone (vitamin K_1)



Menaquinone-4 (vitamin K_2)

Deficiency:

Blood coating time increase hence known as antihaemorrhagis vitamins

Hyper-vitamininosis K

Hemolytic anemia

jaundice

Increase breakdown of RBC

Role:

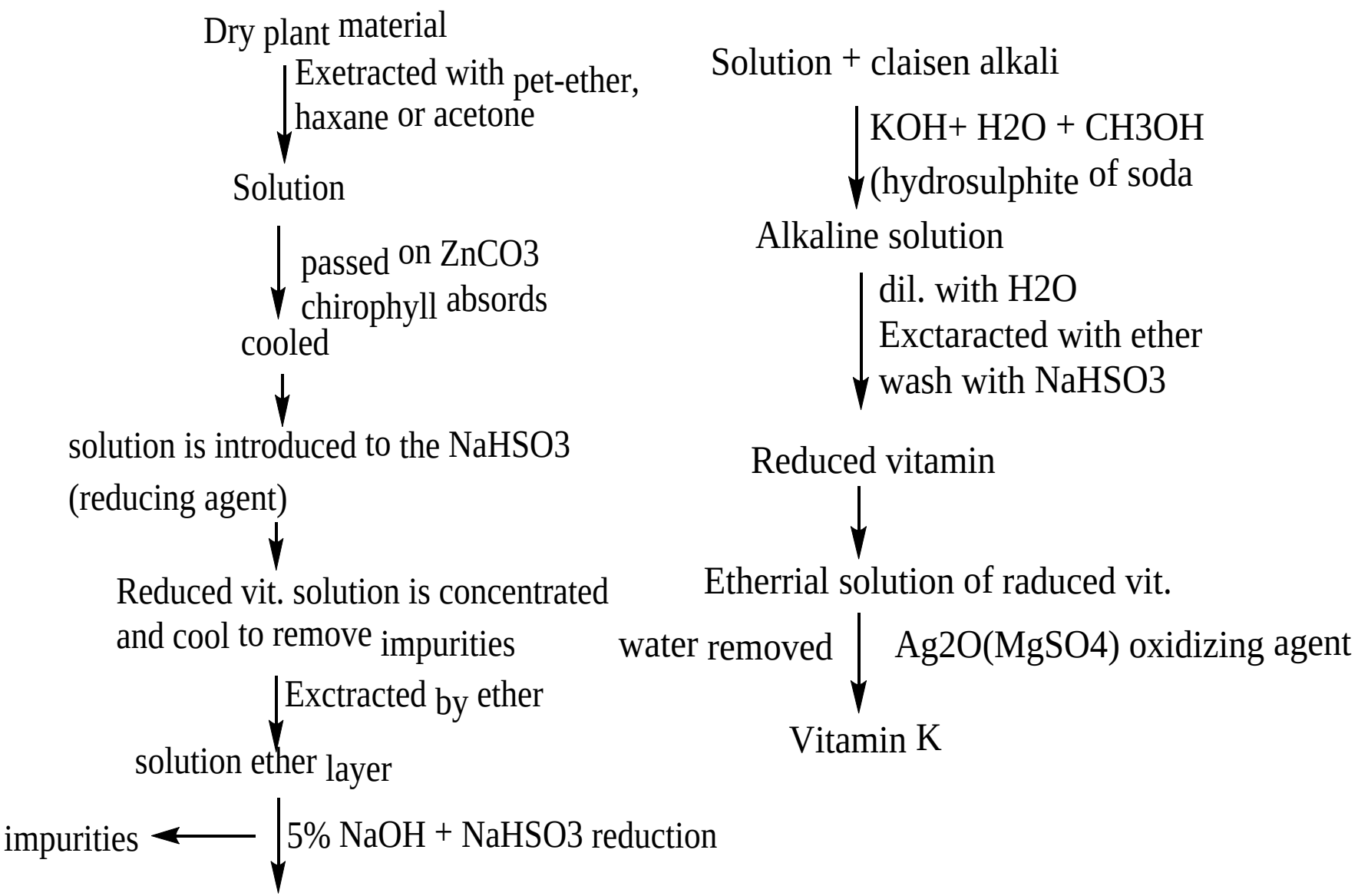
Coagulation of blood, antihaemorrhagis vit. Precursor of thrombin fibrinogen

They activate prothrombin $\rightarrow$Thrombin fibrinogen$\rightarrow$ fibrous materials

Properties:

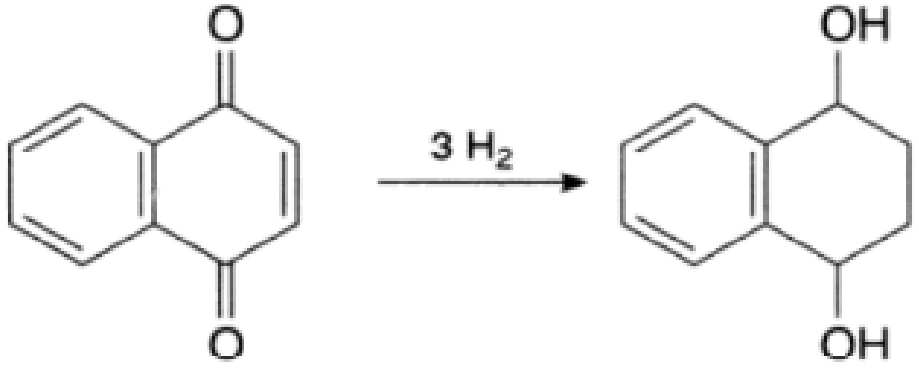
- K1: yellow oil
- **K2:** yellow: crystalline solid(mp= 54)
- Sensitive to light and alkali
- Heat resistance
- λ_{max}: 243,249,260,270nm
- Exhibit band due to presence of Chromophore

Isolation:


Dry plant material
Exetracted with pet-ether, haxane or acetone
Solution
passed on ZnCO3 chirophyll absords
cooled
solution is introduced to the NaHSO3 (reducing agent)
Reduced vit. solution is concentrated and cool to remove impurities
Exctracted by ether
solution ether layer
5% NaOH + NaHSO3 reduction
impurities
Solution + claisen alkali
KOH+ H2O + CH3OH (hydrosulphite of soda
Alkaline solution
dil. with H2O
Exctaracted with ether
wash with NaHSO3
Reduced vitamin
Etherrial solution of raduced vit.
water removed
Ag2O(MgSO4) oxidizing agent
Vitamin K

The molecular formula of vitamin K_1 was found to be $C_{31}H_{46}O_2$. Its redox potential is very similar to that of 1,4-quinone (Karrer et al., 1939). The UV spectra of vitamin K_1 is very similar to that of 2,3-disubstituted-1,4-naphthaquinones (McKee et al., 1939). On the basis of the above, vitamin K_1 appeared to be a 1,4-naphthaquinone derivative; this is supported by the fact that vitamin K_1 is very sensitive to light and alkalies.

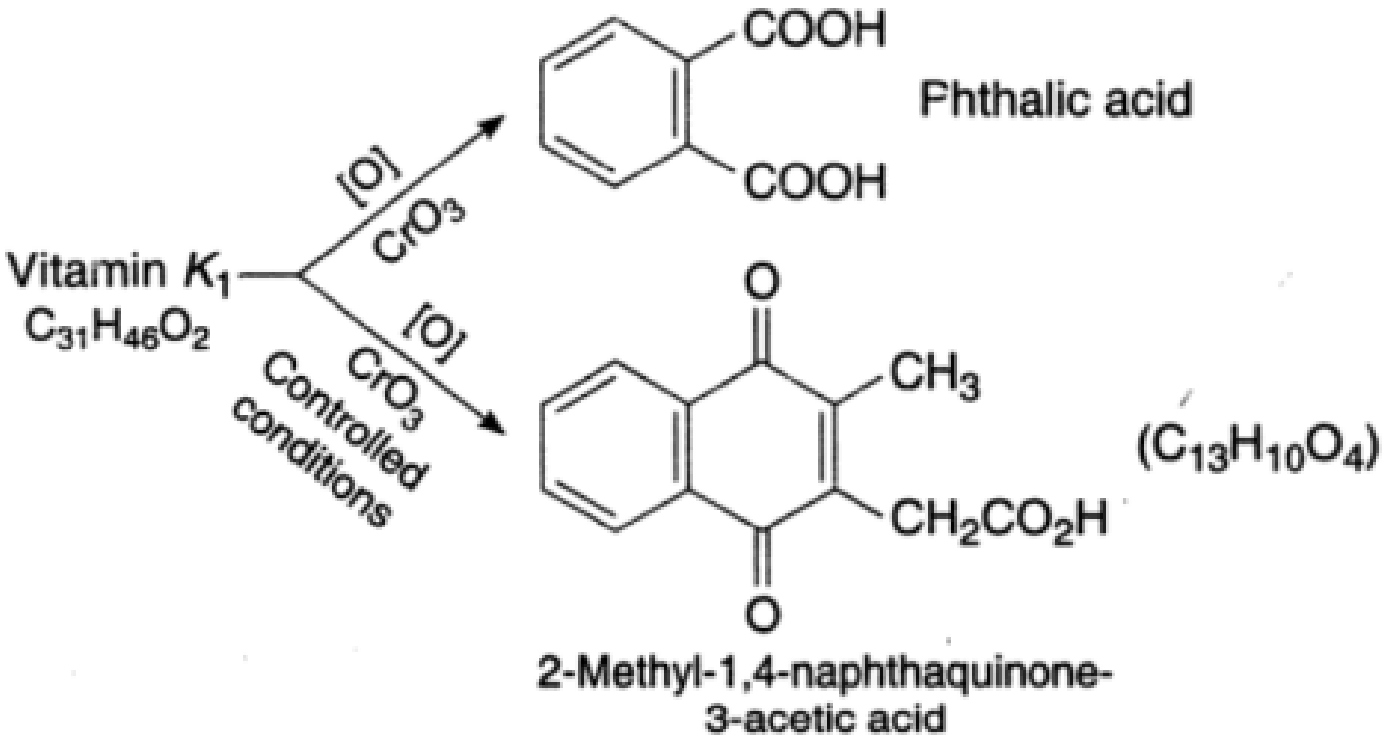
Catalytic hydrogenation of vitamin K_1 ($C_{31}H_{46}O_2$) gives a colourless octahydroderivative ($C_{31}H_{54}O_2$) by absorbing four molecules of hydrogen (McKee et al., 1939). It is known that three molecules of hydrogen are added when 1,4-naphthaquinone is reduced under these conditions (Scheme 73); thus the addition of a fourth mole of hydrogen to vitamin indicates the presence of an ethylenic double bond in a side chain.



1,4-Naphthaquinone

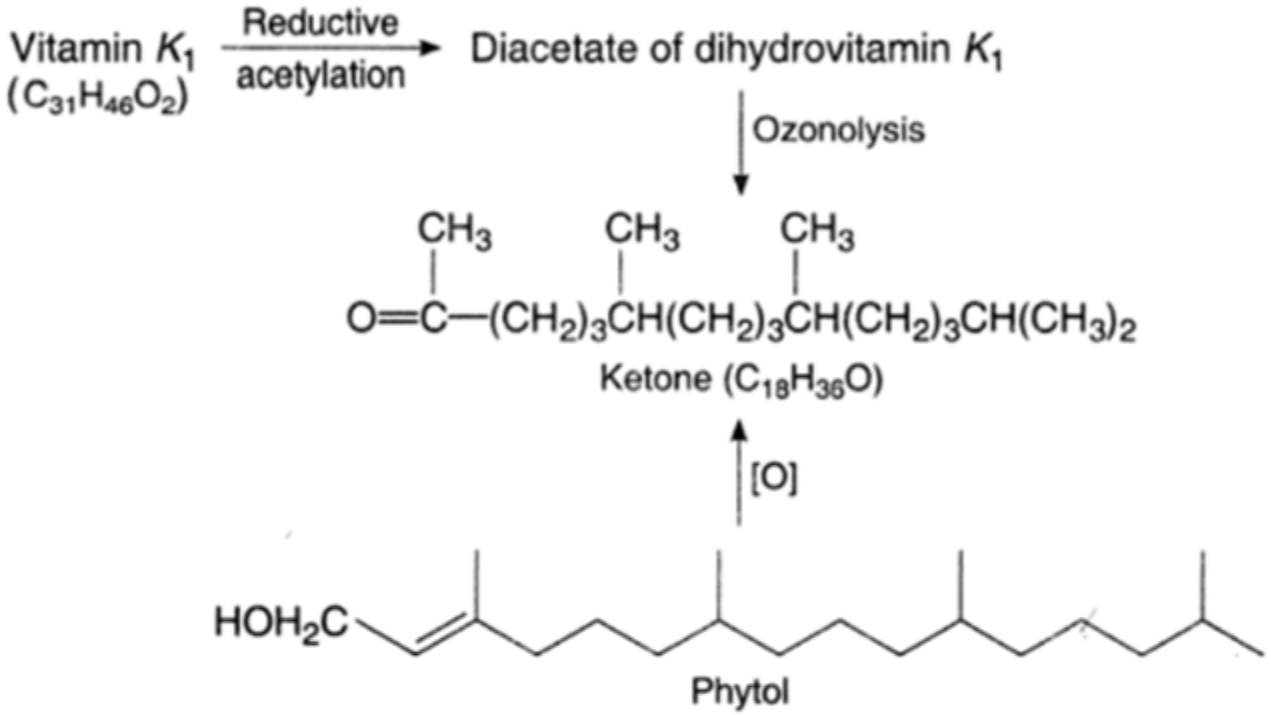
Vitamin K_1 when subjected to reductive acetylation gave diacetate of dihydrovitamin K_1 (Binkley et al., 1939). This diacetate is difficult to hydrolyse. This property is characteristic of 2,3-disubstituted-1,4-naphthaquinones.

Oxidation of vitamin K_1 with chromic acid gave phthalic acid. However, oxidation with chromic acid under controlled conditions gave a product, $C_{13}H_{10}O_4$, which was identified as 2-methyl-1,4-naphthaquinone-3-acetic acid (Binkly et al., 1939)

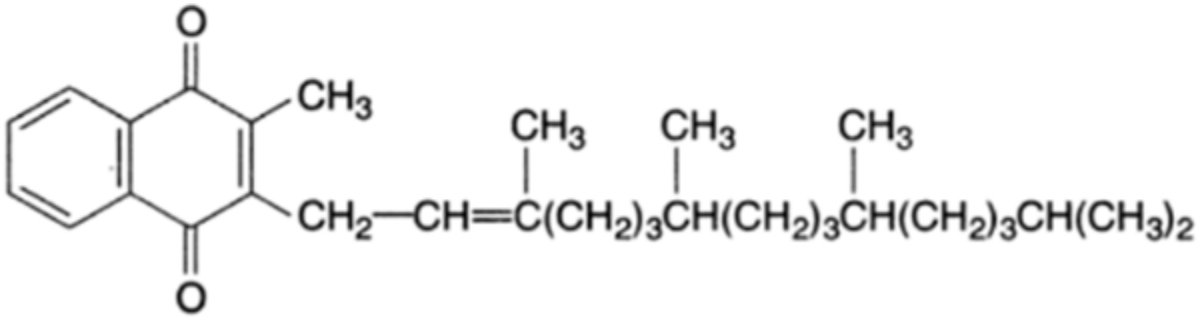


On the basis of the above findings, the presence of 1,4-naphthaquinone structure in vitamin K_1 is confirmed. It was also clear that in vitamin K_1 one ring is unsubstituted and that the other (quinoid ring) is substituted in positions 2 and 3. These conclusions find support in the fact that the UV spectrum of vitamin K_1 on comparison to the UV spectra of various substituted 1,4-naphthaquinone was found to be very closely similar only to 2,3-dialkyl derivatives of 1,4-naphthaquinones (Ewing et al., 1939).

It has already been stated that vitamin K_1 on subjecting to reductive acetylation gives diacetate of dihyrovitamin K_1. Ozonolysis of this diacetate gave a compound, $C_{18}H_{36}O$, which was found to be identical with the ketone produced by the oxidation of phytol (McKee et al., 1939)



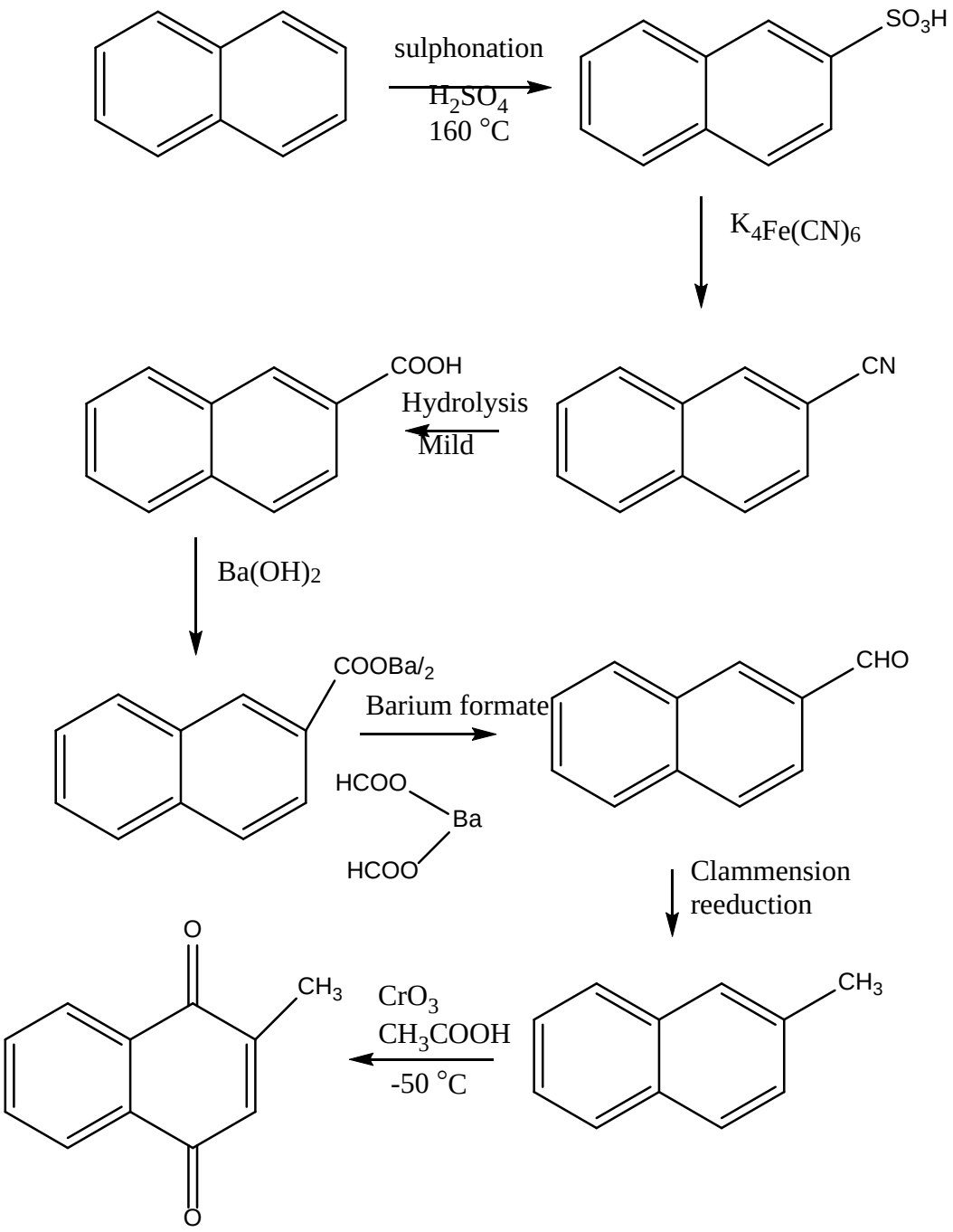
On the basis of the evidence obtained, vitamin K_1 is 2-methyl-3-phytyl-1,4-naphthaquinone.



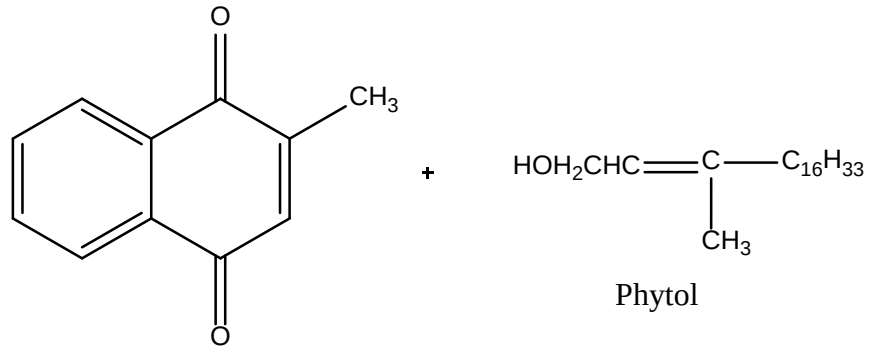
Vitamin K_1

Synthesis:

(i) From Naphthalene



Almquist Synthesis:



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Phytol

2-methylnaphthalene-1,4-dione

Reduction
ZnCl2/ Benzene