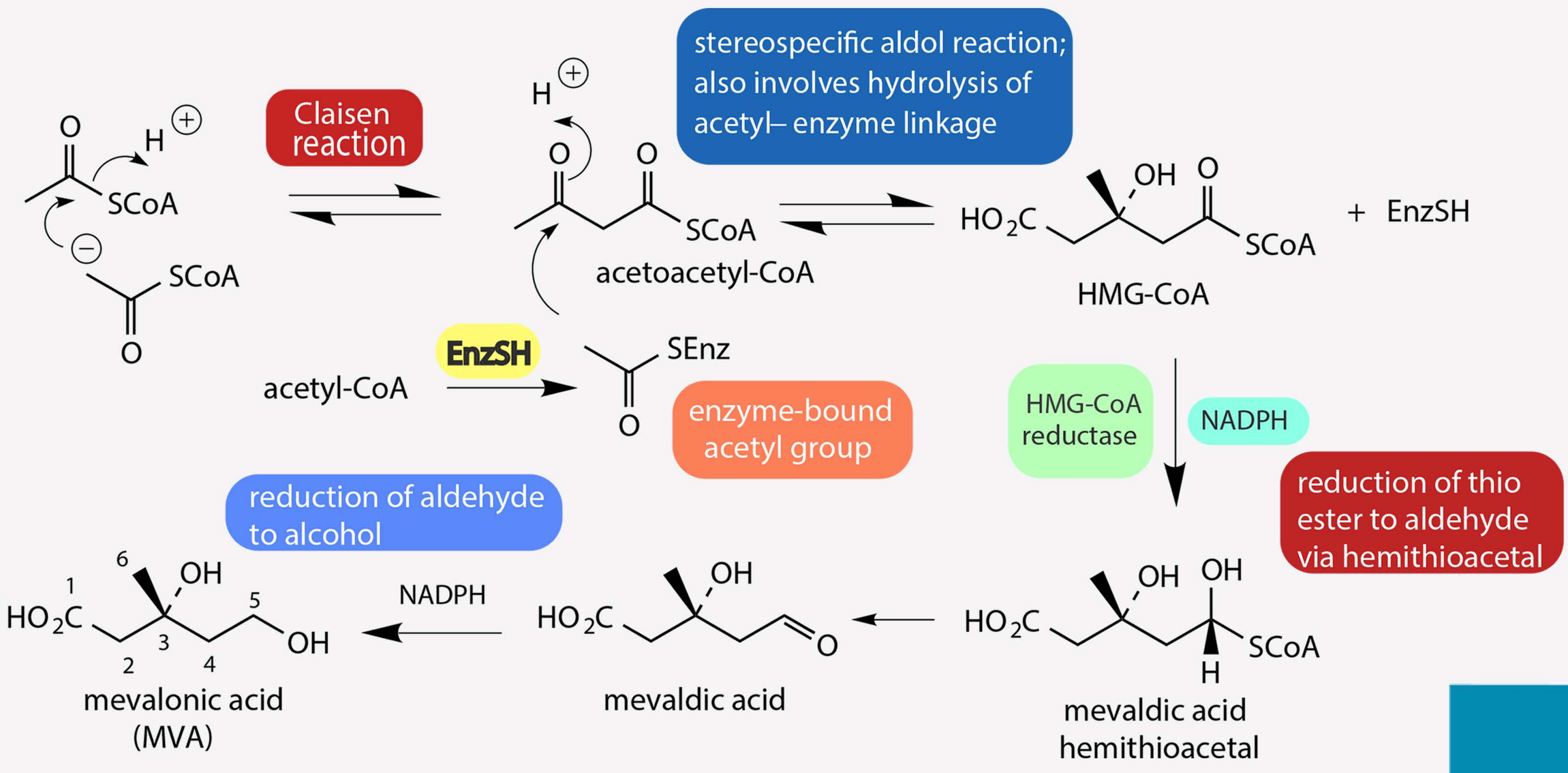
THE MEVALONATE PATHWAYS
" Mevalonic acid formation "

The mevalonate pathway was discovered in the 1950's,
The mevalonate pathway was long believed to be the only mechanism to prepare isoprene.
Mevalonic acid, itself - a product of acetate metabolism- , had been established as a precursor of the animal sterol cholesterol

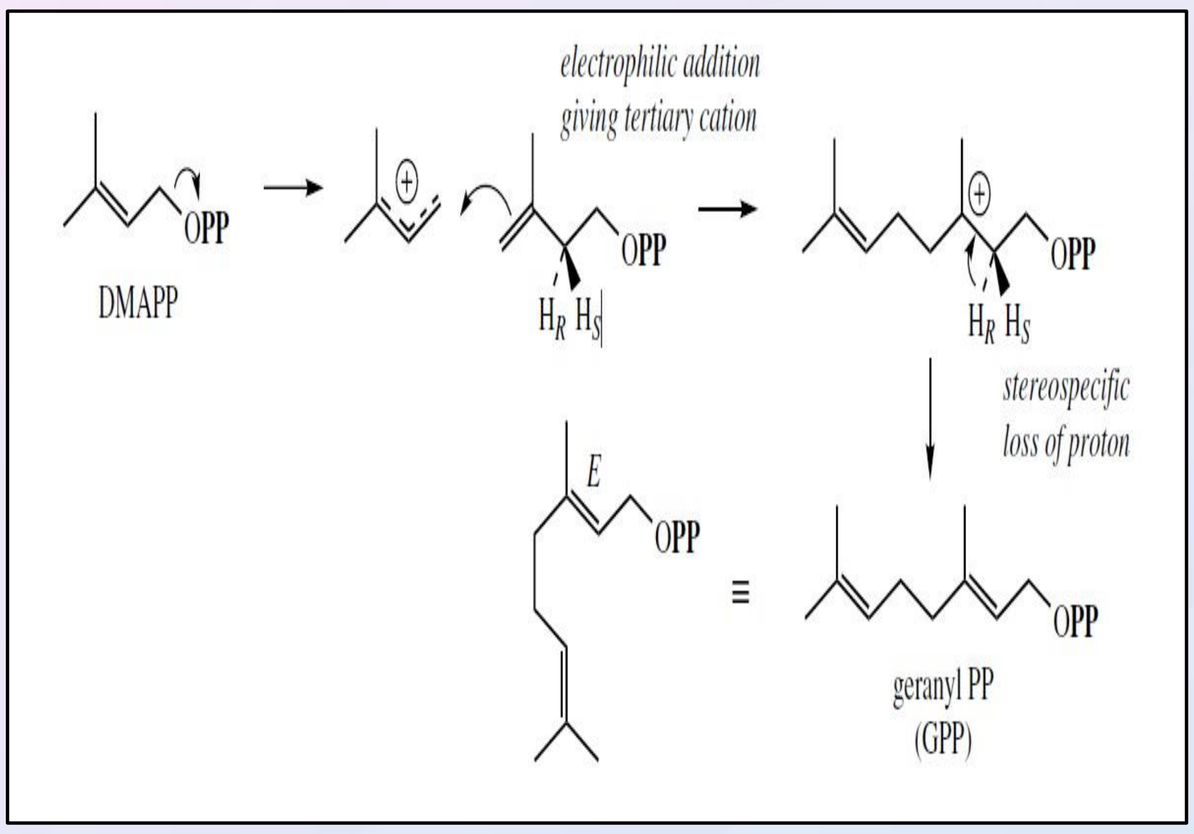


- ☑ Two molecules of acetyl-coenzyme A combine initially in a Claisen condensation to give acetoacetyl-CoA then a a third molecule is incorporated via a stereospecific aldol addition giving branched-chain ester (HMG-CoA).
- ☑ Acetoacetyl-CoA is the more acidic substrate, and might be expected to act asthe 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 two-step reduction of the thioester group to a primary alcohol, and provides an essentially irreversible and ratelimiting transformation.

Reference: Dewick, P. M. (2002). Medicinal natural products: a biosynthetic approach. John Wiley & Sons.

Prepared by: Mark Hosny Amin
Under supervision of: Staff members of 4th Year, Pharmacognosy department.

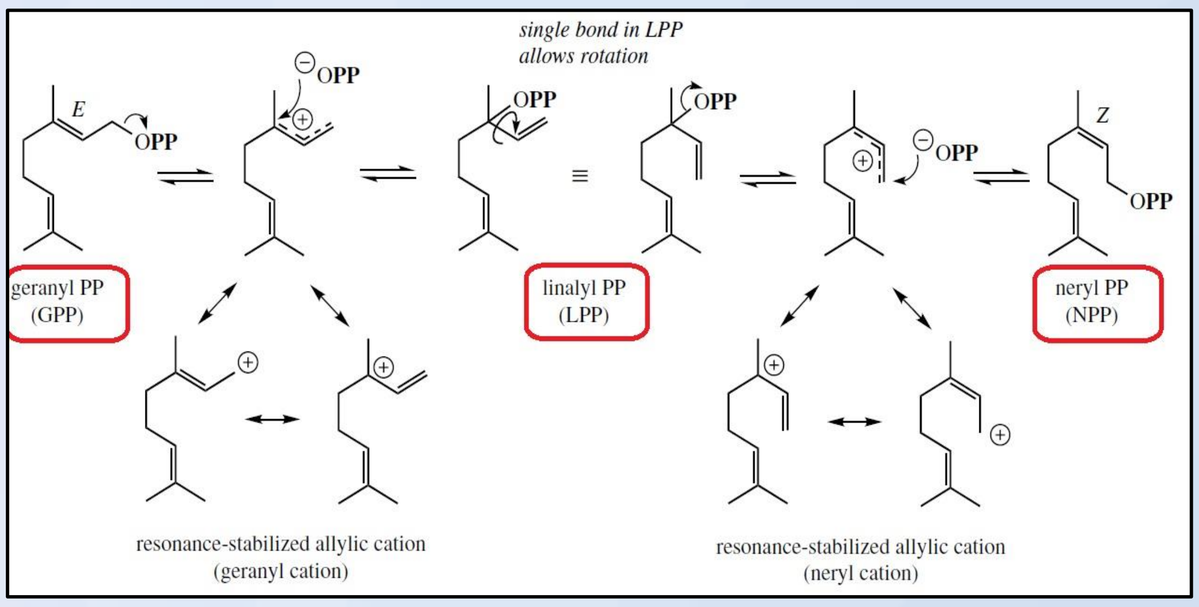
Monoterpenes biosynthesis



Combination ofdimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP) through **prenyl transferase** enzyme yields **geranyl diphosphate (GPP)** .

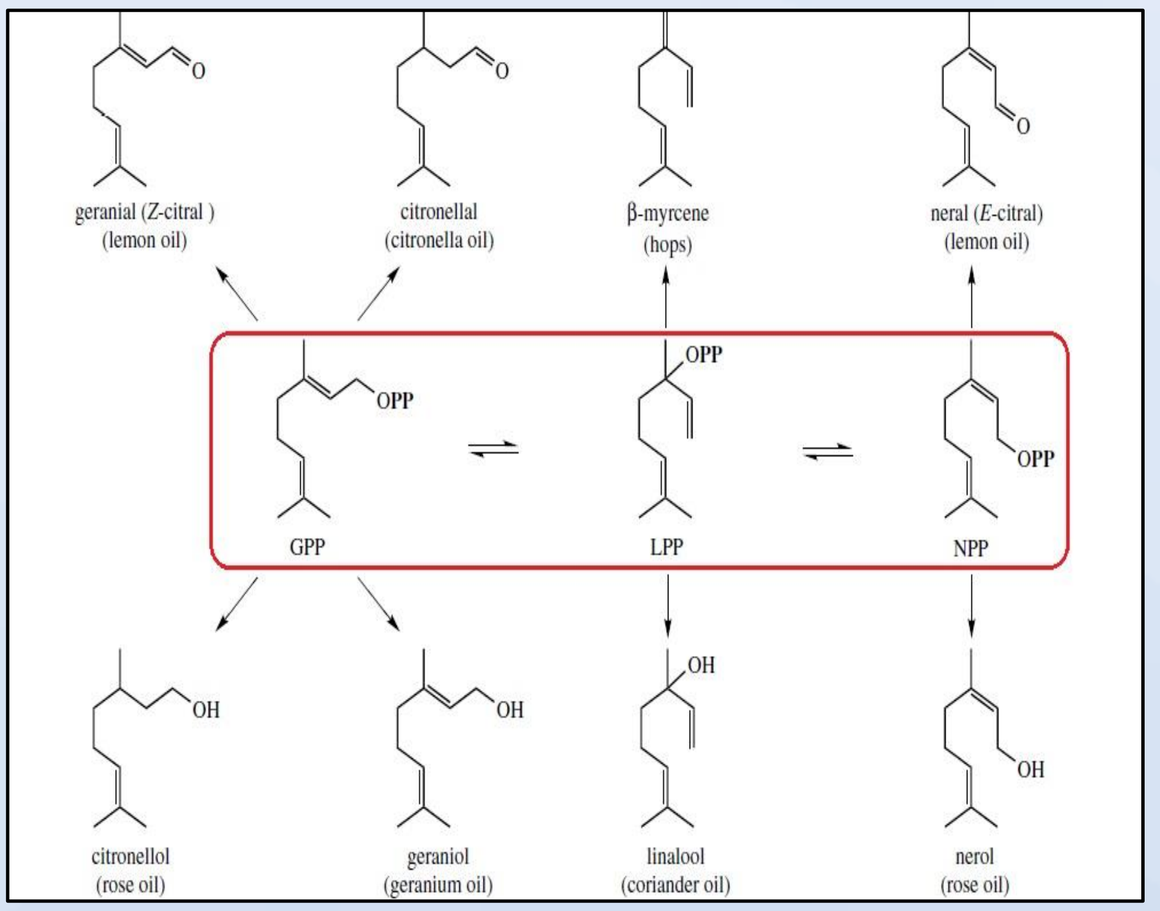
Steps

1-Ionization of (DMAPP) to the allylic cation .
2-Addition to the double bond of IPP.
3-Loss of a proton (the proton lost (H_R) is analogous to that lost on the isomerization of IPP to DMAPP) .



- **Linalyl PP** and **neryl PP** are isomers of geranyl PP .
- They are formed from geranyl PP by ionization to the allylic cation .

- If the attachment of diphosphate group is changed to tertiary carbon give **Linalyl PP**
- If sterochemestiry at the double bond is changed to Z give **Neryl PP**



- These three compounds, by relatively modest changes, can give rise to a range of linear monoterpenes found as components of volatile oils used in flavoring and perfumery.
- These Compounds may be hydrocarbons, alcohols, aldehydes, or perhaps esters, especially acetates.

Reference: Dewick, P. M. (2002). Medicinal natural products: a biosynthetic approach. John Wiley & Sons.

Prepared by /

Yasmin Nasr EL-Din Mohamed

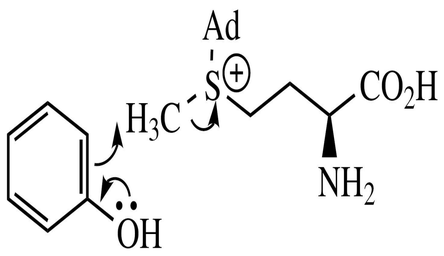
Under the supervision of : Staff members of 4th year applied pharmacognosy department .

Alkylation reactions

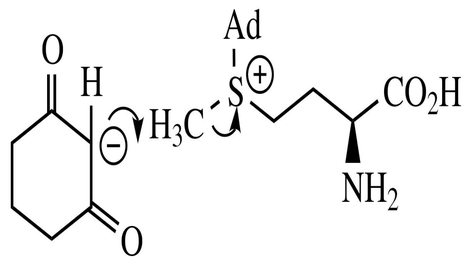
Nucleophilic Substitution

(A) *C-alkylation using SAM* :

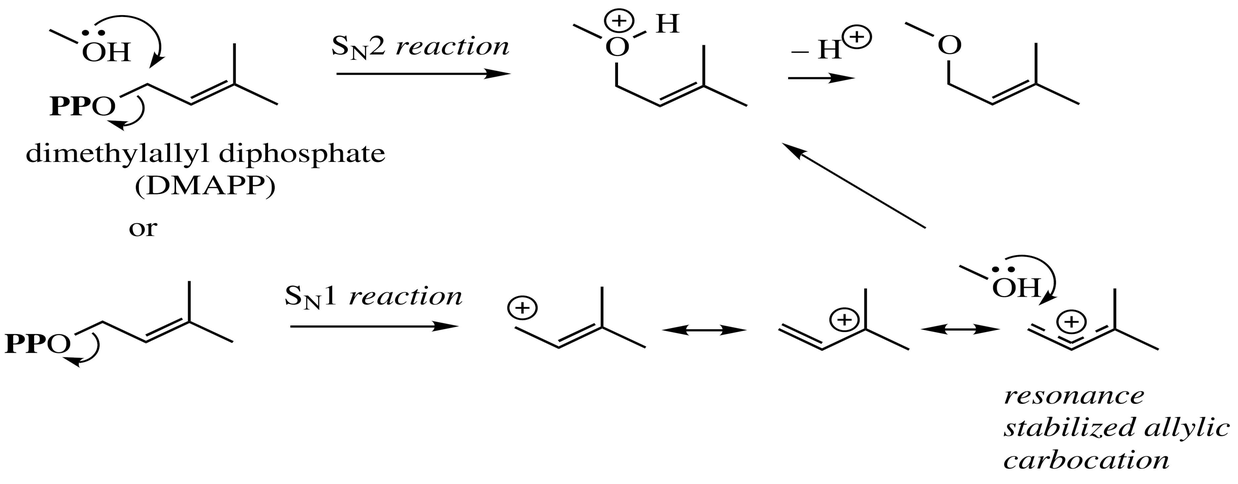
ortho *(and* para*)* *positions are activated by OH*



carbonyl groups increase acidity and allow formation of enolate anion



(B) *O-alkylation using DMAPP* :



diphosphate is good leaving group

resonance stabilized allylic carbocation

1. **O-methyl and N-methyl linkages may be obtained using hydroxyl and amino functions as nucleophiles**
2. **The generation of C-methyl linkages requires participation of nucleophilic carbon.**
3. **positions ortho or para to a phenol group, or positions adjacent to one or more carbonyl group, are thus candidates for C-methylation**
4. **C5 isoprene unit in the form of dimethylallyl diphosphate (DMAPP) may also act as an alkylating agent, and a similar SN2 nucleophilic displacement can be proposed, the diphosphate making a good leaving group**

Reference: Dewick, P. M. (2002). *Medicinal natural products: a biosynthetic approach*. John Wiley & Sons.

Prepared by: **Mirna Shahier Shawky .**

Under supervision of: **Staff members of 4th Year, Pharmacognosy department.**

Hybridization as a factor for drug activity variation

Introduction:

In plant breeding hybridization forms a possible means of combining in a single variety the desirable characters of two or more lines, varieties or species, and occasionally of producing new and desirable characters not found in either parent.

Several methods of breeding crops by the use of sexual hybridization are available in addition to intervarietal hybridization, interspecific hybridization in which hybrid vigour is also apparent.

Hybridization of Opium:

The inheritance of the opium alkaloids (morphine, codeine, thebaine, narcotine and papaverine) has been studied in the cross Papaver somniferum × P. setigerum.

A heterotic increase in codeine and thebaine was found in different F1 plants, and in the F2 plants, with the exception of codeine, some increase in alkaloid content was noted. An absence of narcotine was generally dominant over its presence. A continuation of this work to the F8 generation resulted in a population that was completely diploid but which showed considerable diversity with regard to the opium contents of morphine, narcotine and papaverine. The pattern of alkaloids was closer to that of P. somniferum than to that of P. Setigerum with morphine contents ranging from 8.0 to 30.0%. The authors envisaged That a suitable Breeding programme could result in opium with a higher level of morphine than that normally encountered.

References:

- Evans, William Charles. Trease and evans' pharmacognosy E-book. Elsevier Health Sciences, 2009.
- Khanna et al., Planta Med., 1986, p. 157.
- Shukla et al., Int. J. Pharmacognosy, 1995, 33, 228.

Prepared by: Kareem Rashad Adly

Under supervision of: Staff members of 4th Year, Pharmacognosy department.

Glycosylation reactions

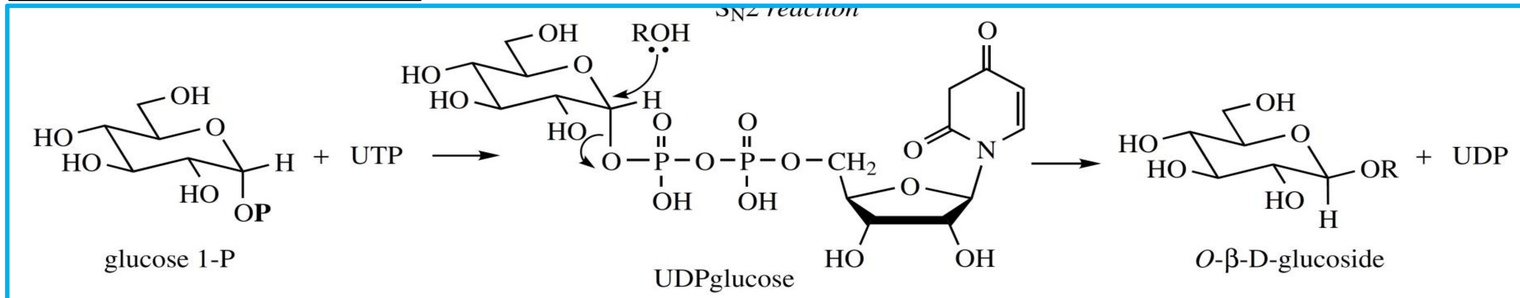
- Sugar + aglycone=glycoside
- Sugar + Sugar =polysaccharide.
- Linkage may be (O , N , C)
- The agent for glycosylation is a uridine diphosphosugar, e.g. UDPglucose.
- The hydrolysis of glycosides is achieved by specific hydrolytic enzymes, e.g. β-glucosidase for β-glucosides and β-galactosidase for β-galactosides .

Reference: Dewick, P. M. (2002). *Medicinal natural products: a biosynthetic approach*. John Wiley & Sons.

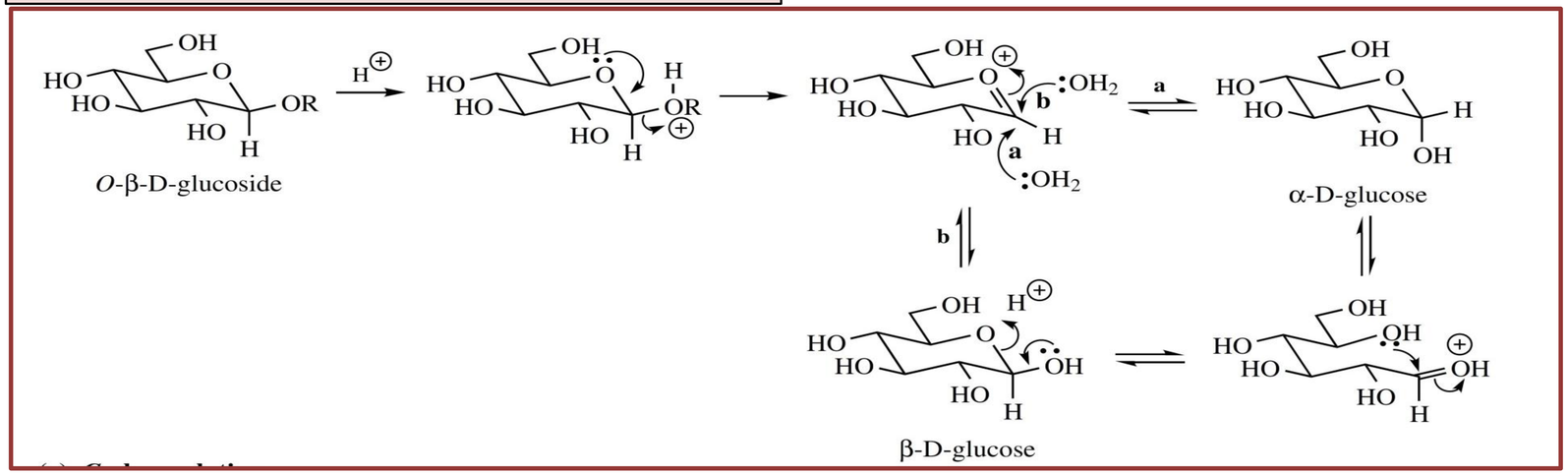
Prepared by: Noha Gamal abdel-hafez

Under supervision of: Staff members of 4th Year, Pharmacognosy department.

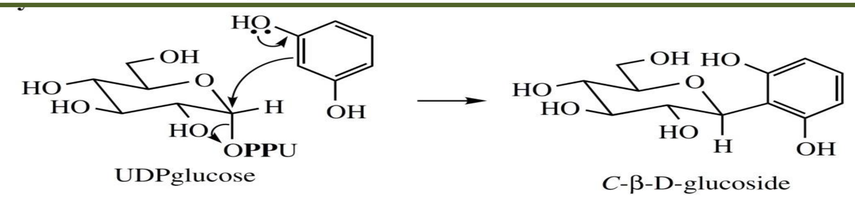
O-glycosylation



Hydrolysis of –O-glycosylation



C-glycosylation



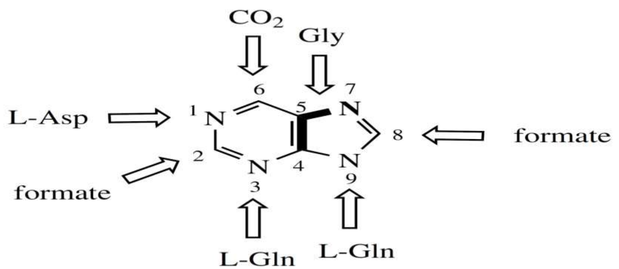
Purine Alkaloids Biosynthesis

Introduction

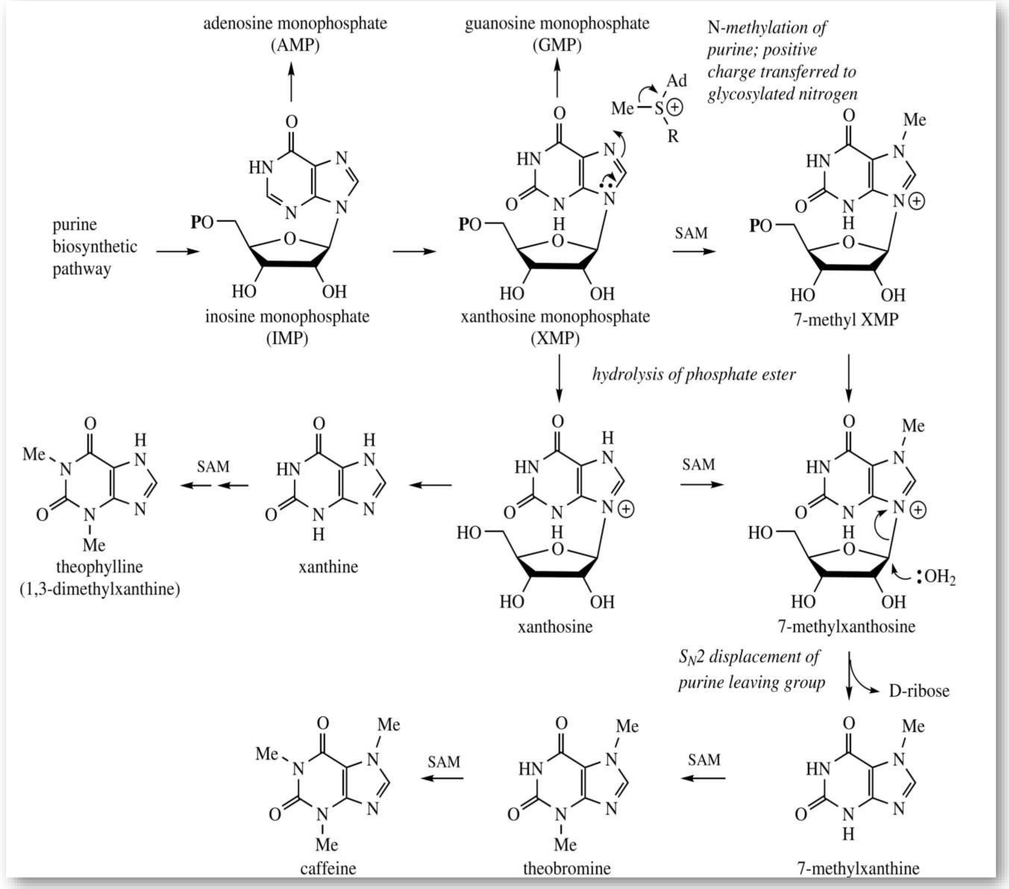
The purine derivatives caffeine, theobromine and theophylline are usually referred to as purine alkaloids.
Their origins are closely linked with those of the purine bases adenine and guanine.

Basic Structure

The purine ring is gradually elaborated by piecing together small components as glycine, glutamine and aspartic acid.



Biosynthetic Pathway



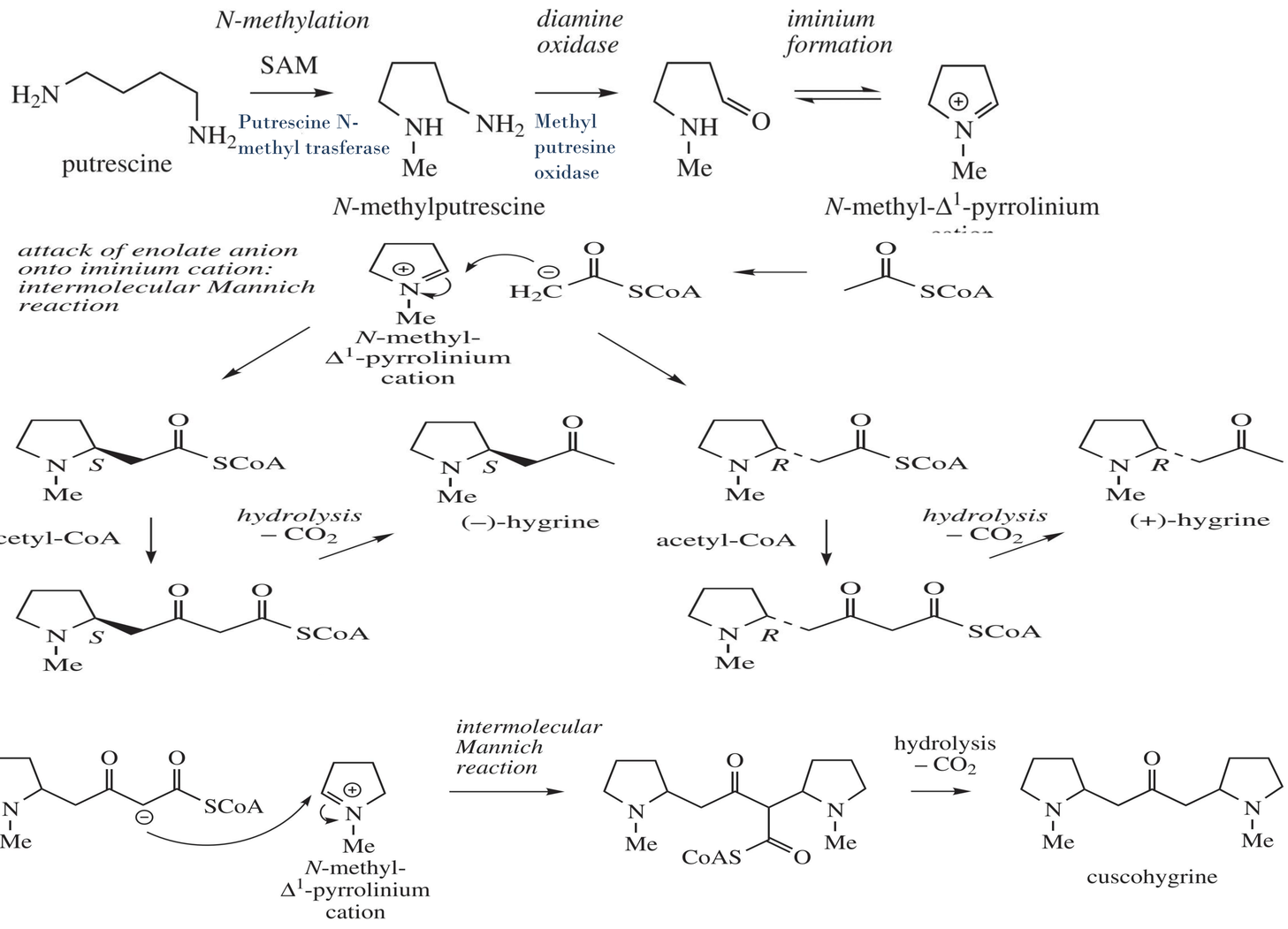
Reaction Steps

- Synthesis of Inosine 5 -monophosphate (IMP) and Xanthosine 5 -monophosphate (XMP).
- N-Methylation of Xanthosine 5 -monophosphate by S-adenosyl-methionine.
- Hydrolysis of phosphate ester generates the nucleoside 7-methylxanthosine.
- *SN2 displacement of D-ribose to give 7-methylxanthine.*
- Methylations on the nitrogens give **caffeine** by way of **theobromine**, whilst a different methylation sequence can account for the formation of **theophylline**.

Reference : Dewick, P. M. (2002). *Medicinal natural products: a biosynthetic approach*. John Wiley & Sons.

Prepared by: AHMED MOHAMED KAMEL
Under supervision of : Staff members of 4 th Year, Pharmacognosy department.

Pyrrolidine alkaloids(hygrine and cuscuohygrine)biosynthesis



pyrrolinium cation formation(shiff base formation).

The enolate anion from acetyl-CoA acts as nucleophile towards the pyrrolinium ion in a Mannich-like reaction

The second addition is a Claisen condensation extend-ing the side-chain, and the product is the 2-substituted pyrrolidine

The cuscohgrine arises by an intermolecular mannich reaction

Reference: Dewick, P. M. (2002). *Medicinal natural products: a biosynthetic approach*. John Wiley & Sons.

Prepared by: Salwa Abdellah Abdelaal

Under supervision of: Staff members of 4th Year, Pharmacognosy department.