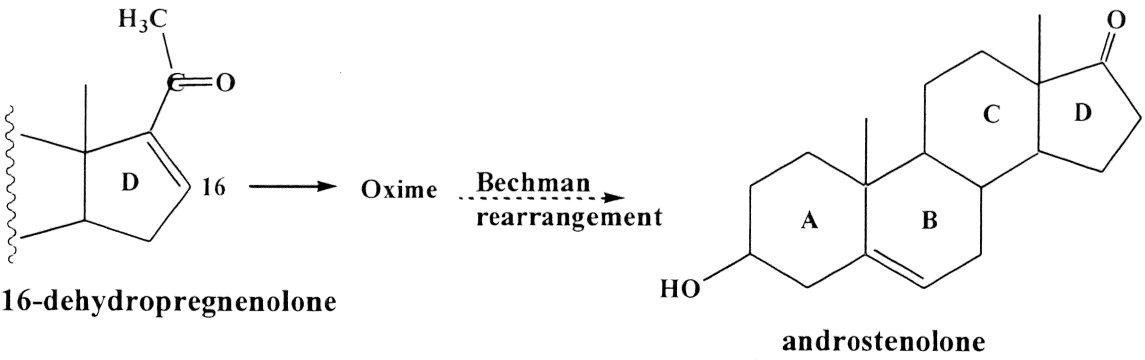
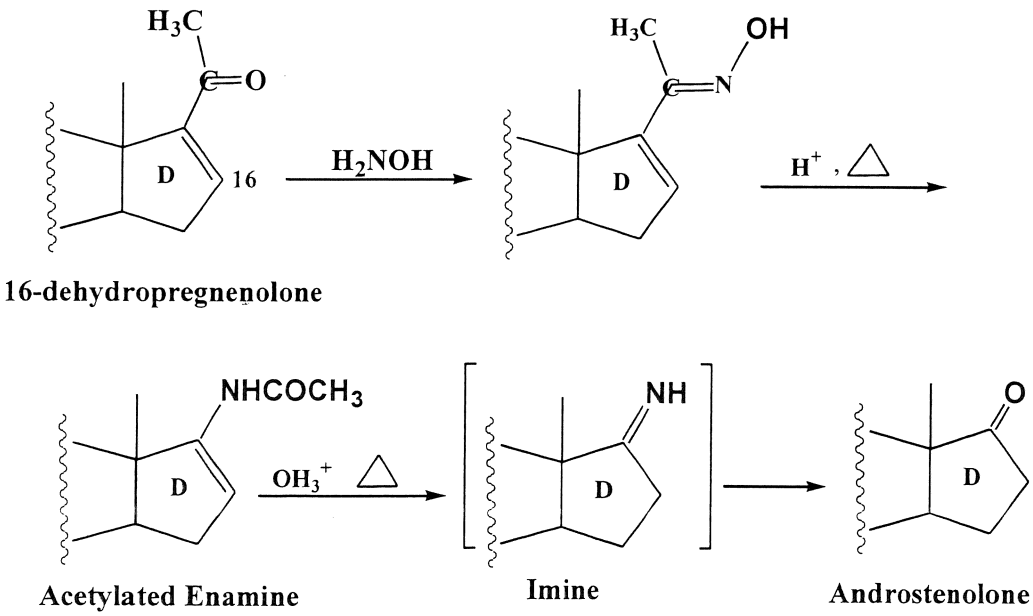
Beckmann rearrangement: synthesis of androstenolone

Androstenolone is an important chemical intermediate for the synthesis of sex hormones (testosterone, estrone..)

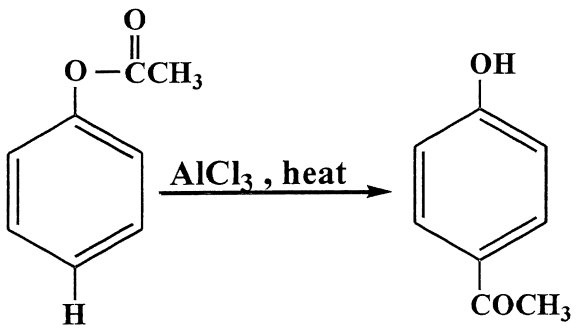


Beckmann rearrangement: synthesis of androstenolone



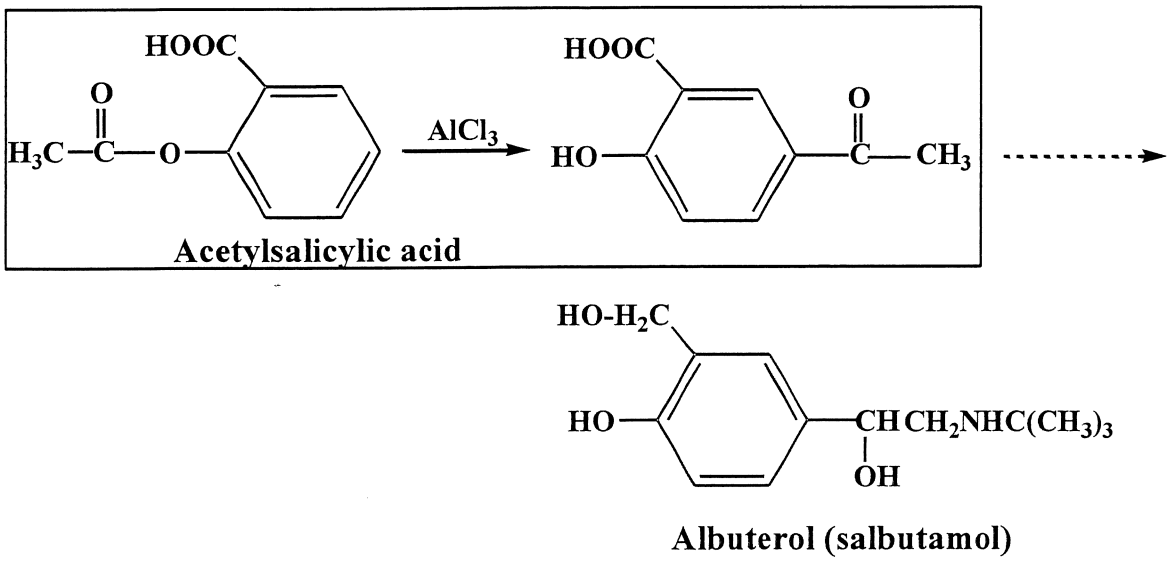
Fries rearangement

- The migration of acetyl group at para position; it is an intra-molecular acylation reaction (an electrophilic aromatic substitution



Phenyl acetate p-hydroxyacetophenone

Fries rearangement, Synthesis of β_2 agonist albuterol



Albuterol (salbutamol)

Drug Synthesis
الاصطناع (التخليق) الدوائي

Synthesis of Some Drugs,Chemical Curriculum

Faculty of Pharmacy
Drug Synthesis

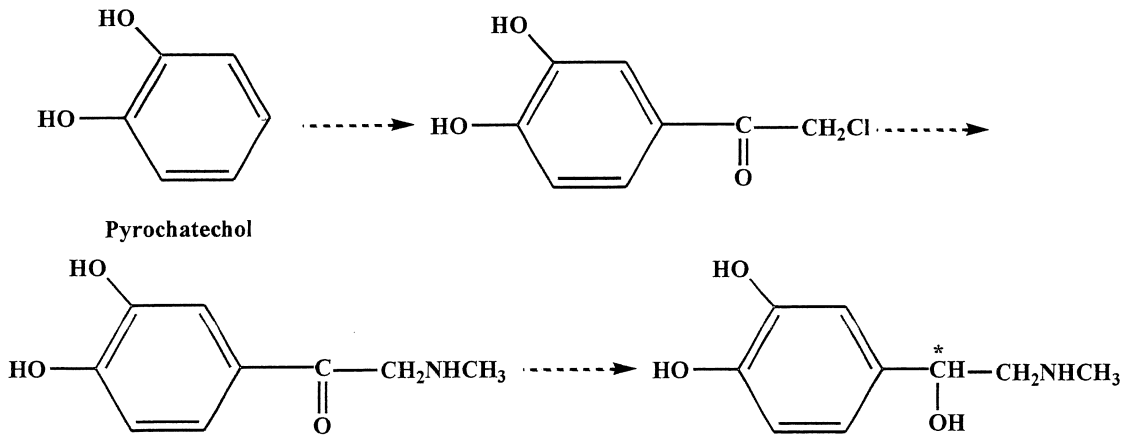
11. Arylalkylamines

A. Synthesis of Adrenergic, Sympathomimetic Drugs

Epinephrine and Norepinephrine
Albuterol (Salbutamol)
Dopamine
Ephedrine

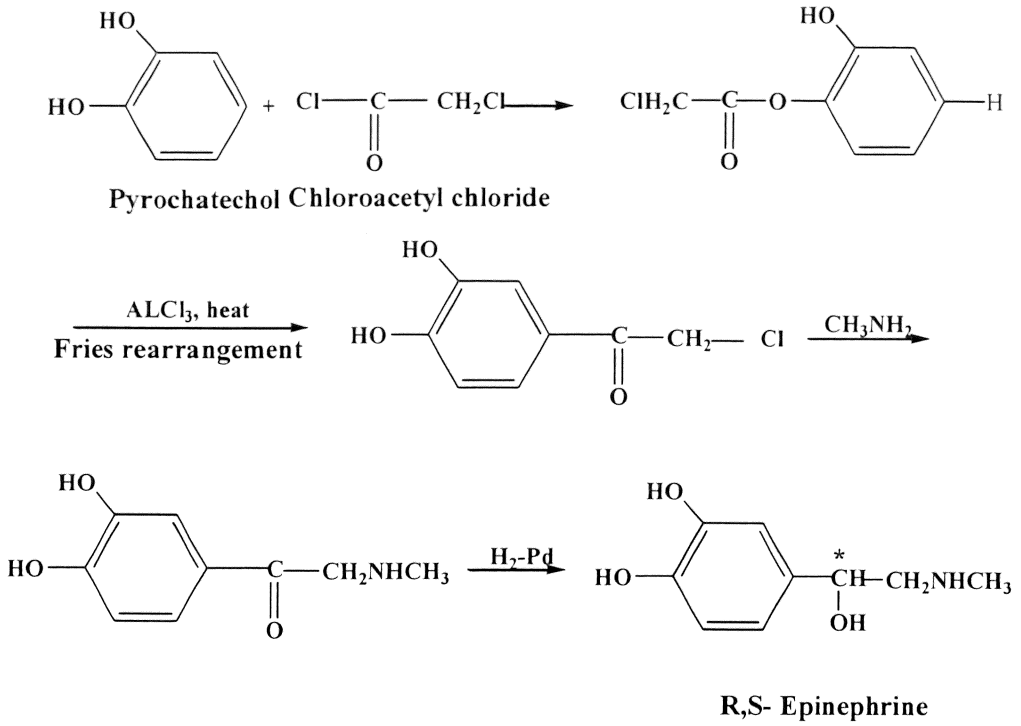
Synthesis of Epinephrine Through acylation reaction (Fries rearrangement)

- Epinephrine is obtained by synthesis which starts with pyrocatechol by acylation with Chloroacetyl chloride $ClCOCH_2Cl$.



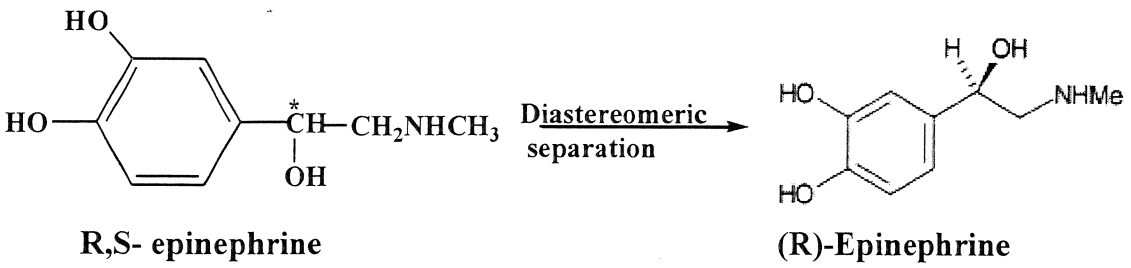
R,S- Epinephrine

Synthesis of Epinephrine through acylation reaction(Fries rearrangement)



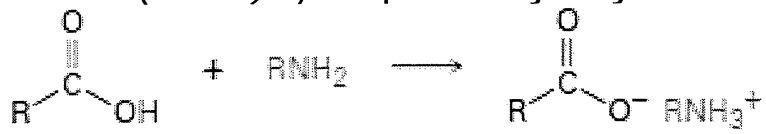
Resolution of the Epinephrine racemate

- Chemical synthesis in general, yields racemic mixture.
- Resolution is effected by diastereomeric separation using (+) tartaric acid.
- Natural epinephrine is R(-) configuration is 50 times more active than the S(+) isomer.



Resolution of the Epinephrine racemate by diastereomeric separation

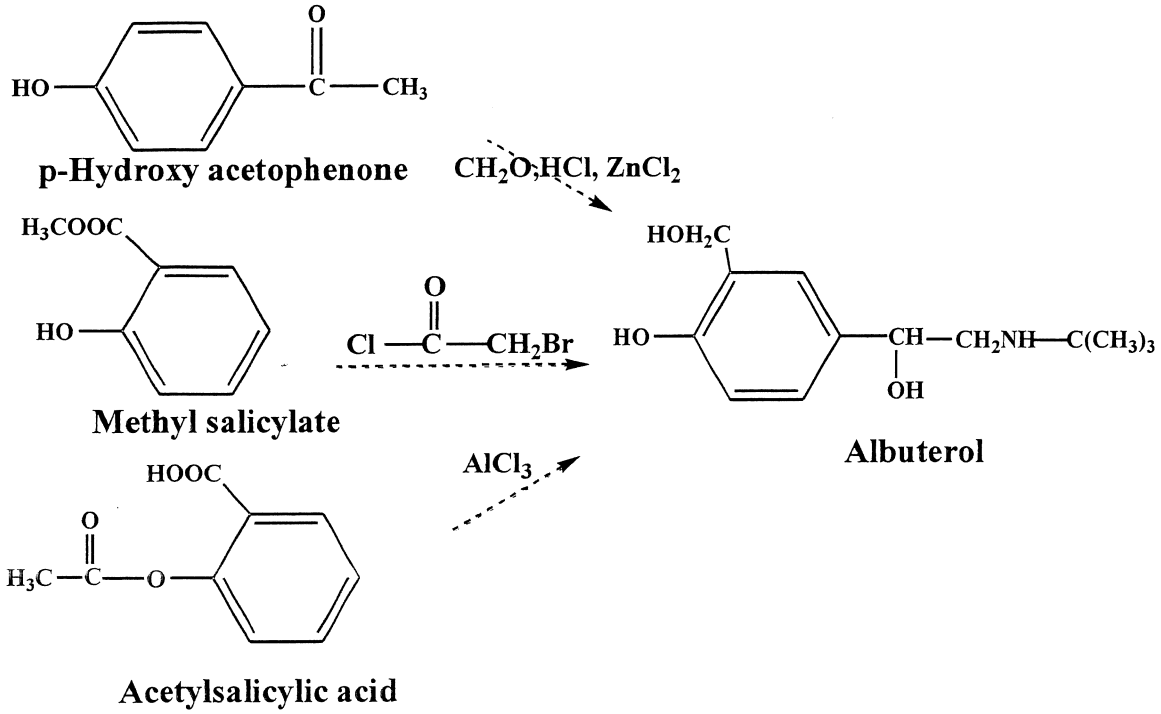
• The most common method of resolution uses an acid–base reaction between the racemate of a chiral carboxylic acid (RCO_2H) or chiral amine base (RNH_2) and an amine base (RNH_2) or carboxylic acid (RCO_2H) respectively to yield an ammonium salt:



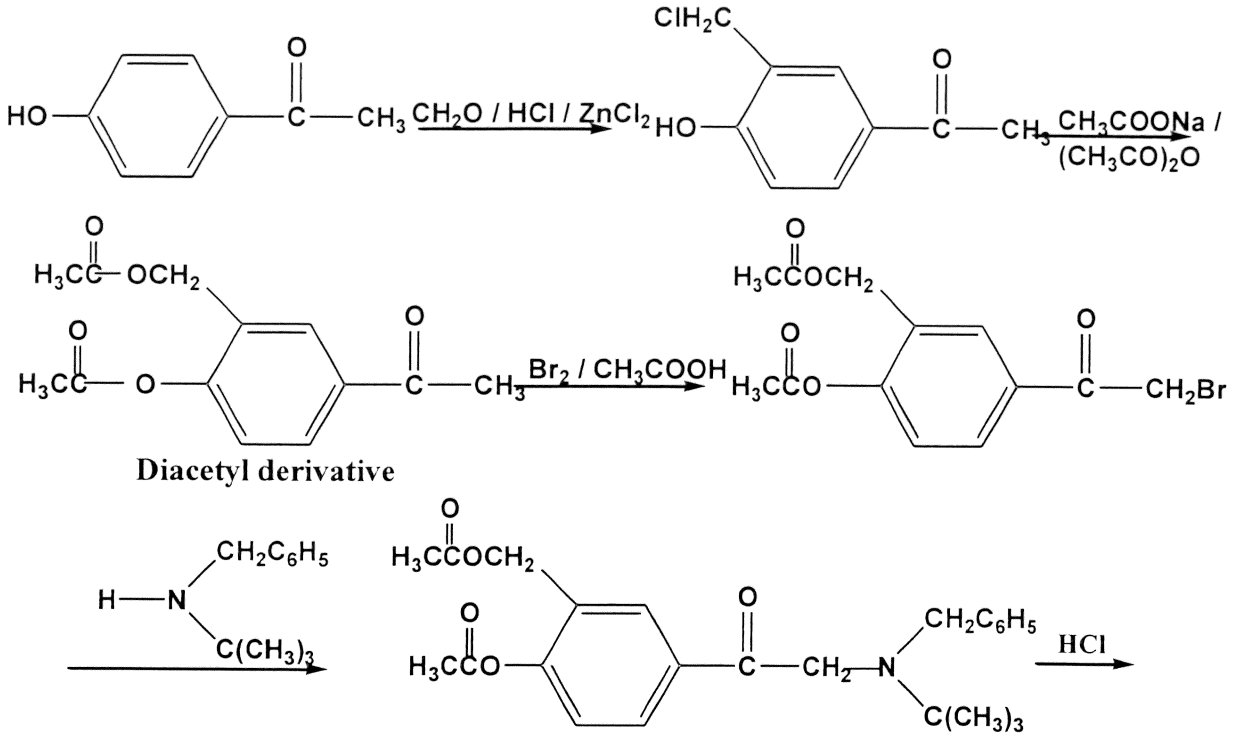
Carboxylic acid | Amine base | Ammonium salt

• Reaction of racemic amine (R ,S) such as racemic epinephrine, with single enantiomer (R) of carboxylic acid will give diasteriomeric mixture of ammonium salts: RR and RS that are separated by their differing solubility. The carboxylic acid is then removed from each diastereomer by reaction with strong base

Synthesis of Albuterol

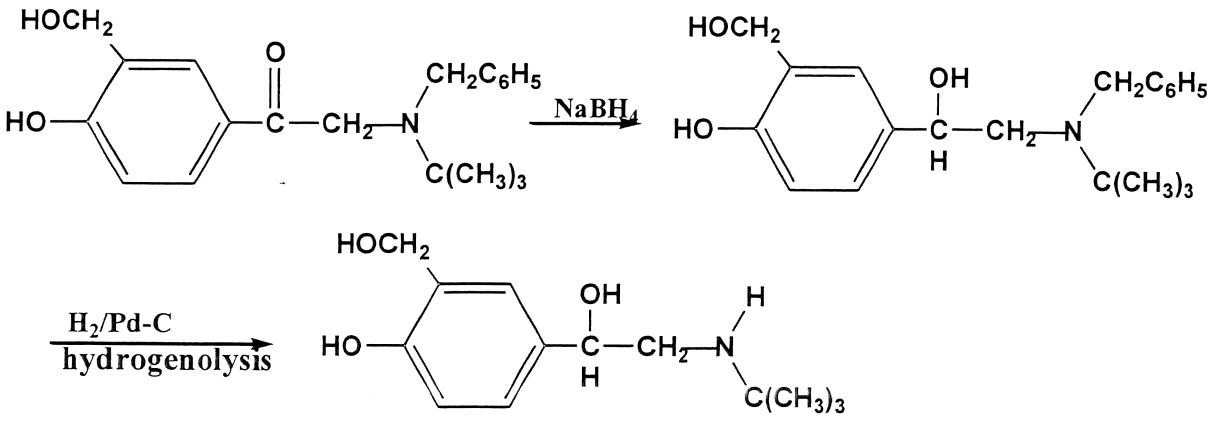


Synthesis of Albuterol through chloromethylation reaction, method 1

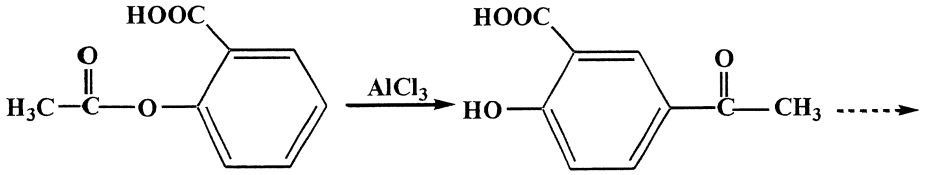


Continue

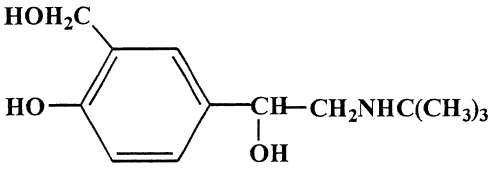
Synthesis of Albuterol (chloromethylation reaction) method 1



Synthesis of albuterol from Aspirin (Fries rearrangement), method 3



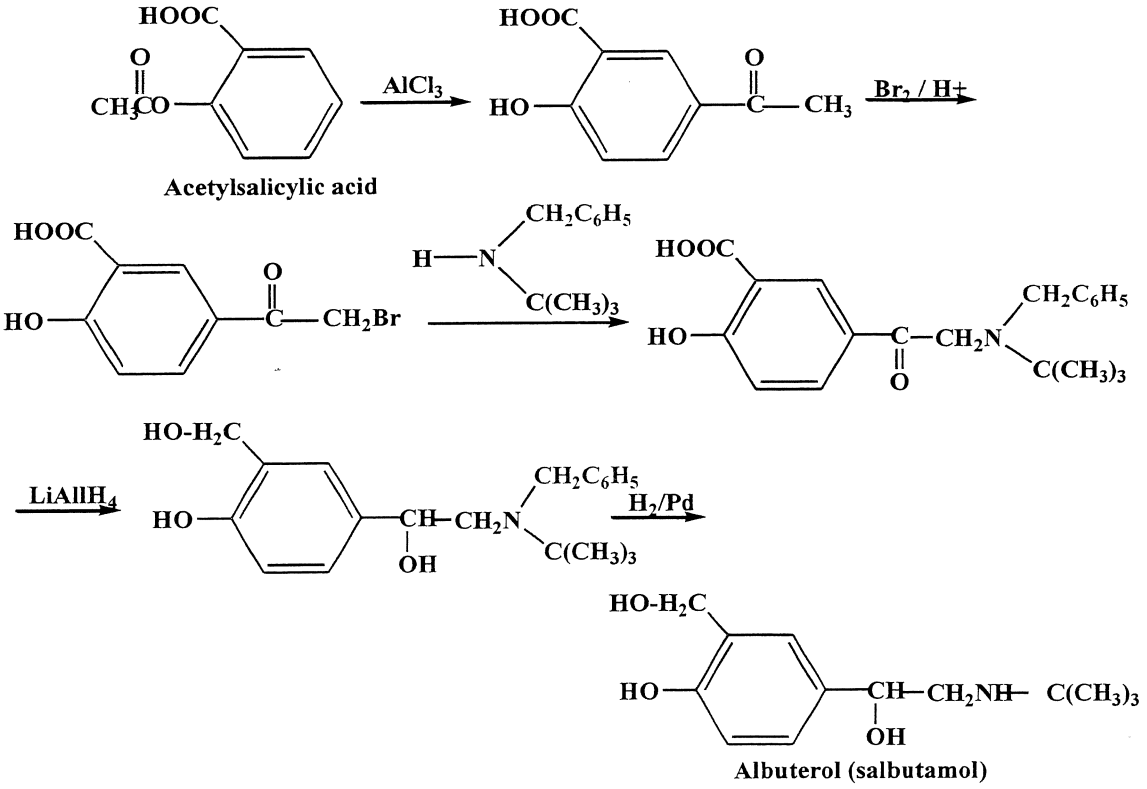
Acetylsalicylic acid 5-acetyl-2-hydroxybenzoic acid



Albuterol

(*RS*)-4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol

Synthesis of albuterol from Aspirin (Fries rearrangement), method 3



Acetylsalicylic acid

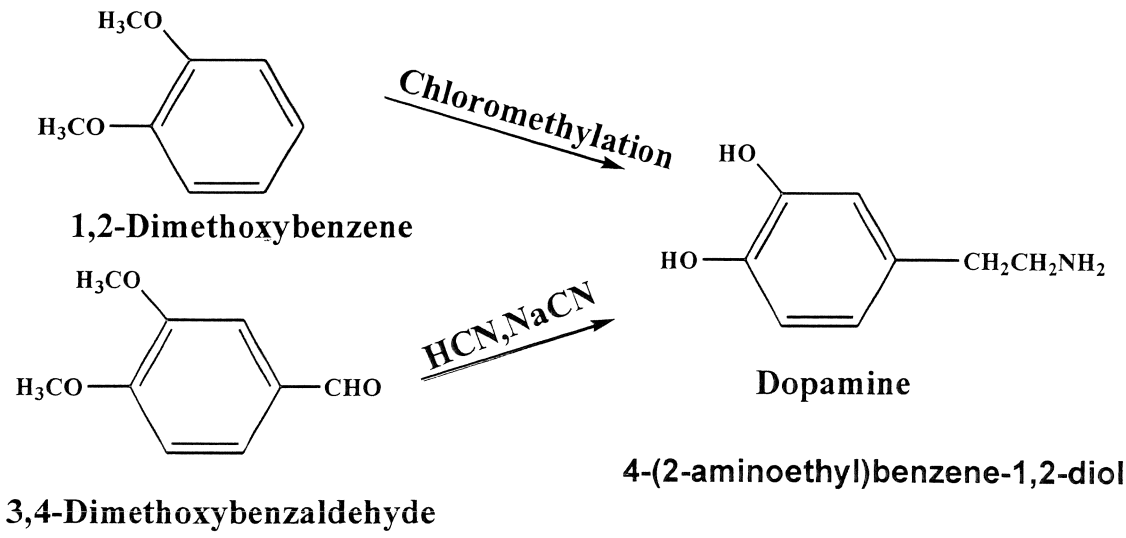
Albuterol (salbutamol)

Action and use of Albuterol

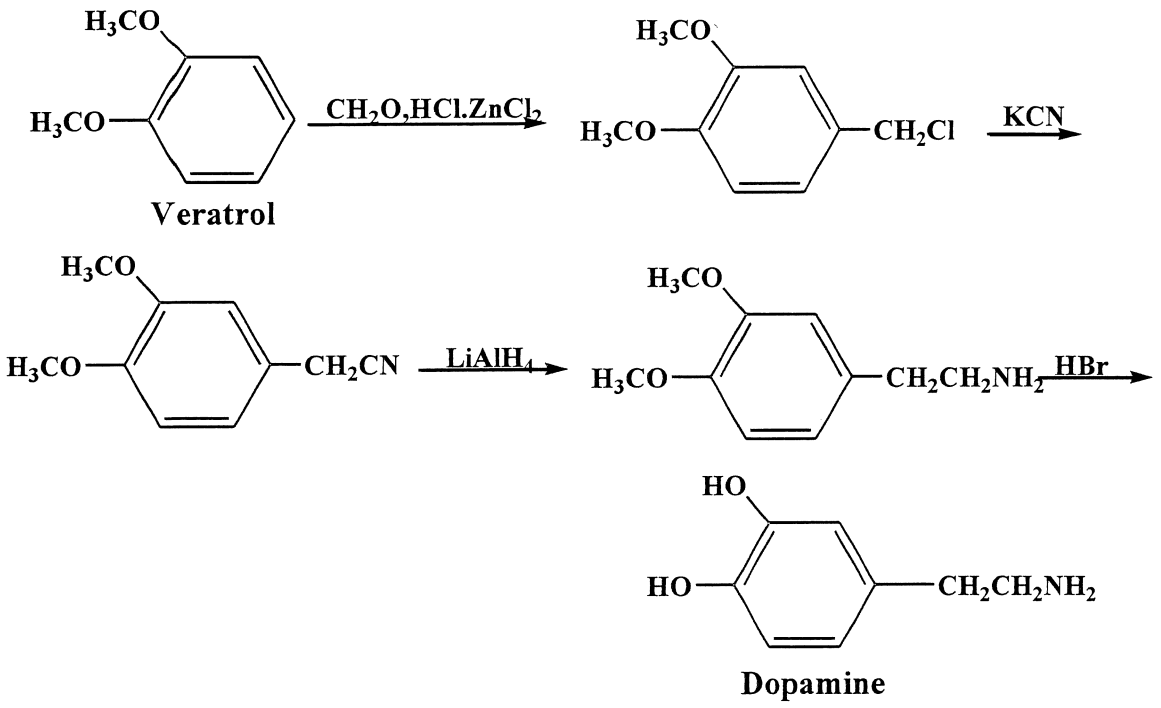
- β_2-adrenergic sympathomimetic agent.
- it has little effect on β_1 adrenoreceptors of the heart.
- Widely used for severe and chronic bronchial asthma

Synonyms are salbutamol, ventolin and others

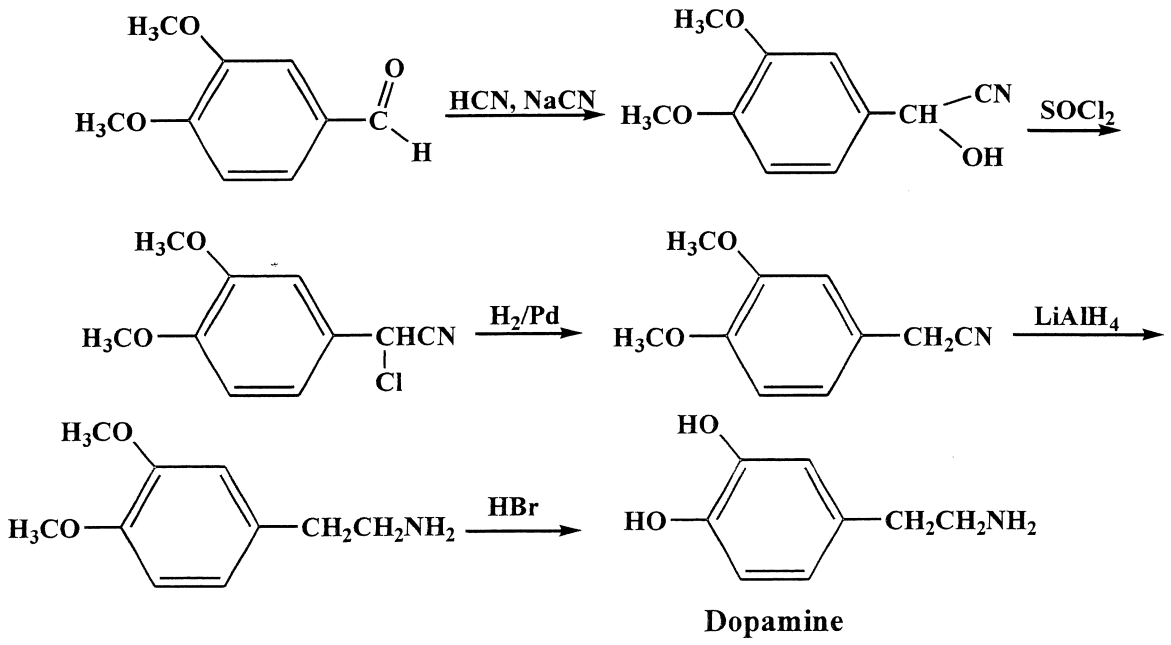
Synthesis of Dopamine



Synthesis of Dopamine (chloromethylation) Method 1



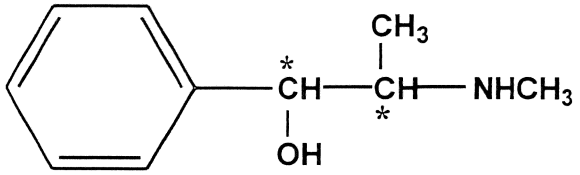
Synthesis of Dopamine through cyanohydrine Method 2

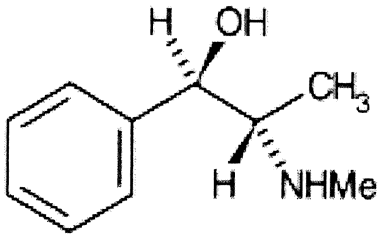


Action and use of Dopamine

- Dopamine is found in sympathetic neurons and ganglions in CNS
- It stimulates dopaminergic receptors
- It stimulates indirectly α- and β- adrenergic receptors
- It causes the release of norepinephrine.
- It is used in treating hypotension (trauma , myocardial shock, anaphylactic reaction

Ephedrine stereoisomers





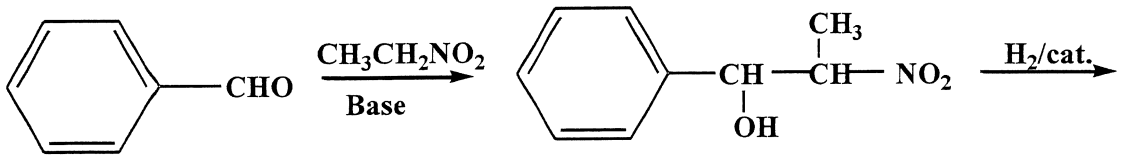
1*R*,2*S* (-) Ephedrine

- Because of the presence of two assymetric centers there are four stereoisomers:

- Racemic Erythro mixture: 1R,2S and 1S,2R which are called Ephedrine
- Racemic Threo mixture: 1S,2S and 1R,2R which are called Pseudoephedrine.

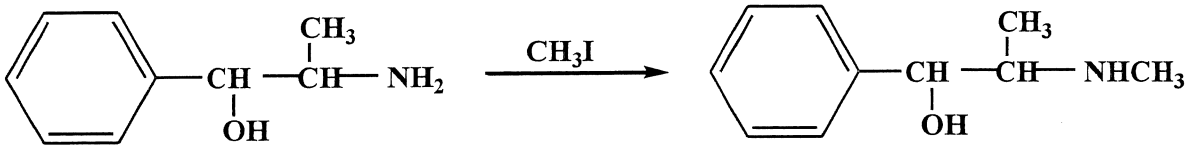
- *1R,2S* (-) Ephedrine is the most active as a pressor amine; the natural isomer which is still extracted from Ephedra sinica and Ephedra Equisetina.

Synthesis of (-) Ephedrine (aldol - like condensation



Benzaldehyde

2-nitro-1-phenylpropanol

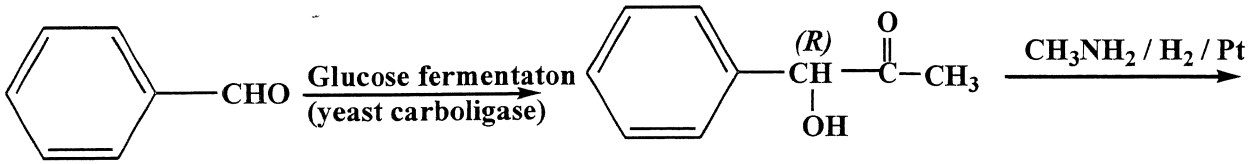


2-amino-1-phenylpropanol
separation of 1R,2S stereoisomer

(1*R*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol
(-) Ephedrine

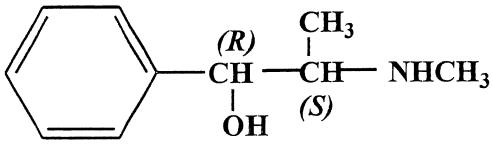
Assymetric synthesis of (-) Ephedrine (Fermentation method)

- Fermentation of glucose by yeast carboligase in the presence of benzaldehyde yields 1*R* (-)1-hydroxy-1-phenylpropanone.
- Catalytic hydrogenation of the latter in the presence of methylamine (reductive amination) yields selectively the desired ephedrine *1R,2S* (-) Ephedrine.



Benzaldehyde

(1R)-1-hydroxy-1-phenylpropan-2-one



The desired 1R,2S(-) Ephedrine