Subject	Chemistry
Paper No and Title	14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)
Module No and Title	16: Total synthesis of complex organic compounds using disconnection approaches
Module Tag	CHE_P14_M16

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CHEMISTRY	Paper No. 14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)
	Module No. 16: Total synthesis of complex organic compounds using disconnection approaches

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1. Learning Outcomes

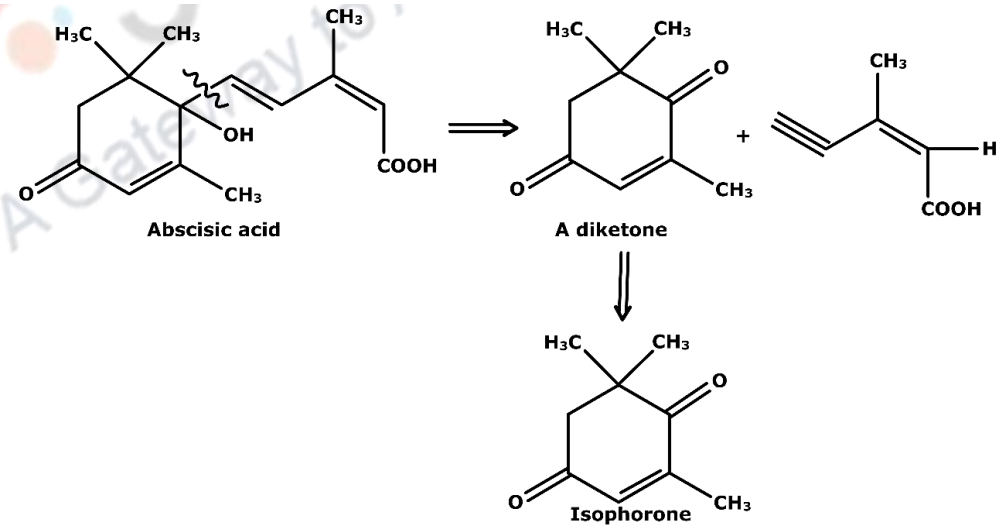
After studying this module, you shall be able to

- Know about the total synthesis of complex organic molecules
- Design the synthetic steps of complex organic molecules
- Understand the synthetic pathways of complex organic molecules.

2. Total synthesis of Abscisic acid

Abscisic acid or ABA is an inhibitory rather than stimulatory hormone for plants. It is involved in the closure of stomata, bud and seed dormancy and is known to inhibit other hormonal actions. It helps plants to survive under adverse environmental conditions.

Retrosynthetic pathway:



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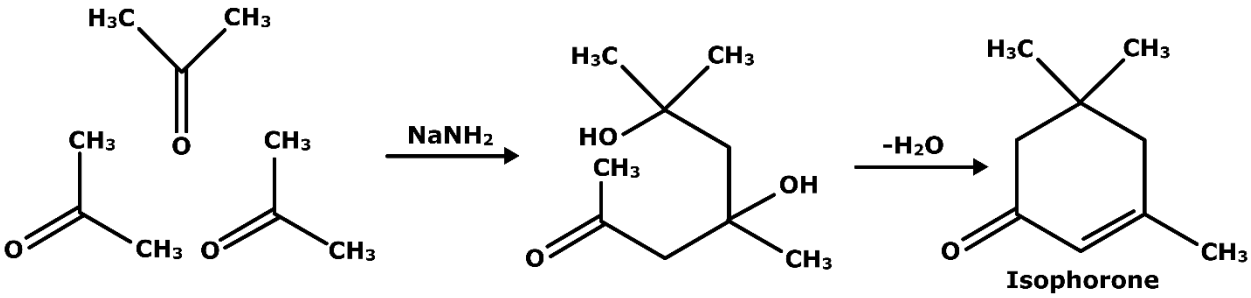
Synthesis: Isophorone is synthesized by the aldol condensation of acetone in the presence of sodamide ($NaNH_2$) followed by dehydration as shown below:



Three molecules of acetone have been utilized for the reaction.

Step1: Ketone group present in isophorone is protected by the reaction between isophorone and ethylene glycol under acidic conditions. After protection, mixture of two isomeric ketals is formed in 70:30 ratio. These are two double-bond isomers, which are separated by fractional distillation.

Step2: Ketal which is formed in 70% yield on reaction with potassium permanganate ($KMnO_4$) under basic conditions form *cis*-diol. Here on hydroxyl group is secondary hydroxyl group while other is tertiary hydroxyl group.

Step3: Secondary hydroxyl group in *cis*-diol on further oxidation with potassium permanganate ($KMnO_4$) under basic conditions is oxidized to ketone.

Step4: Tertiary alcohol was dehydrated using methanesulphonyl chloride under basic conditions. Ketal is not cleaved under basic conditions.

Step5: Tertiary alcohol was dehydrated using methanesulphonyl chloride under basic conditions. Ketal is not cleaved under basic conditions.

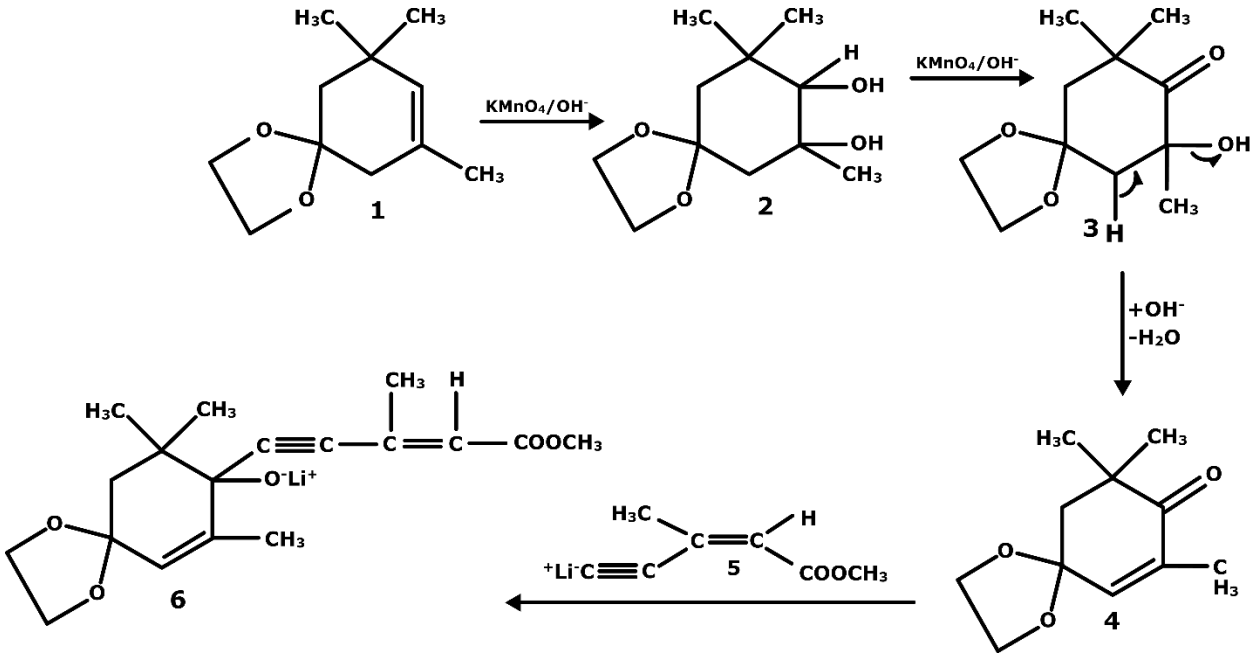
Step6: Reaction of (**4**) with (*Z*)-3-methyl-2-penten-4-ynoate (**5**) in the presence of lithium diisopropylamide (LDA), at -78^{o}C forms the corresponding (**6**).

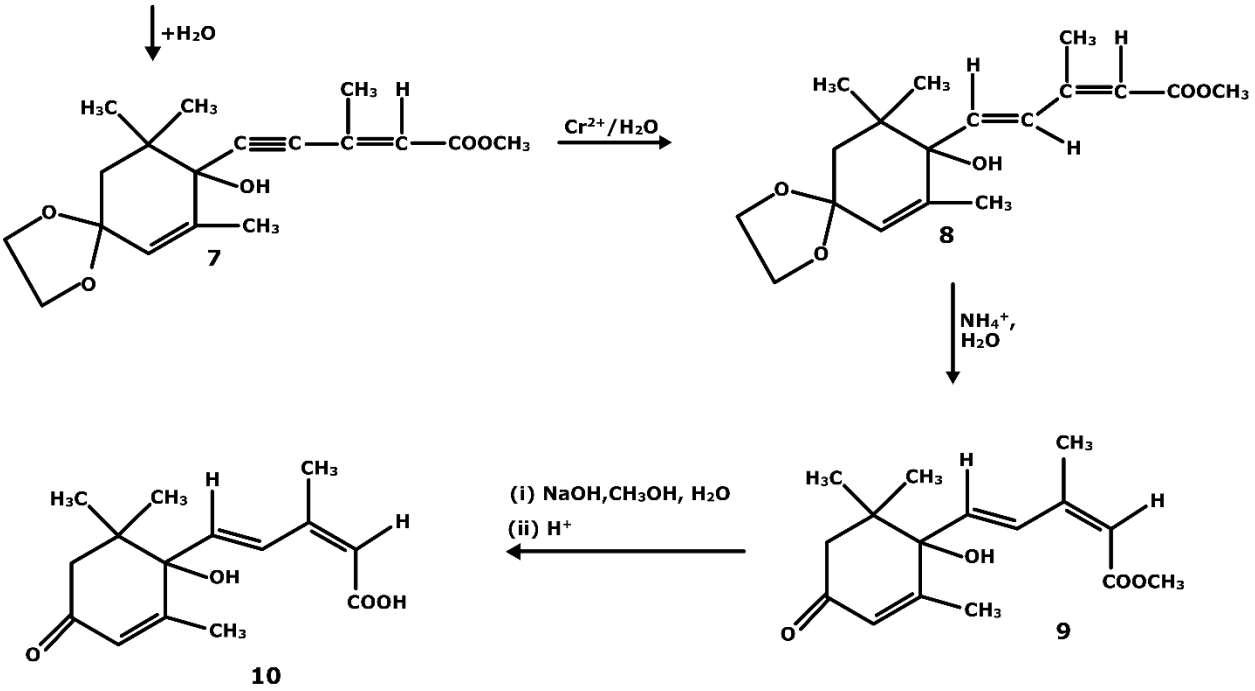
Step7: Lithium salt (**6**) on hydrolysis form the alcohol (**7**).

Step8: Alcohol (**7**) is reduced to *trans*-alkene (**8**) using aqueous dimethyl-formamide solution of chromous sulphate.

Step9: Ketal group in *trans*-alkene (**8**) is deprotected to the corresponding ketone (**9**) using ammonium ions.

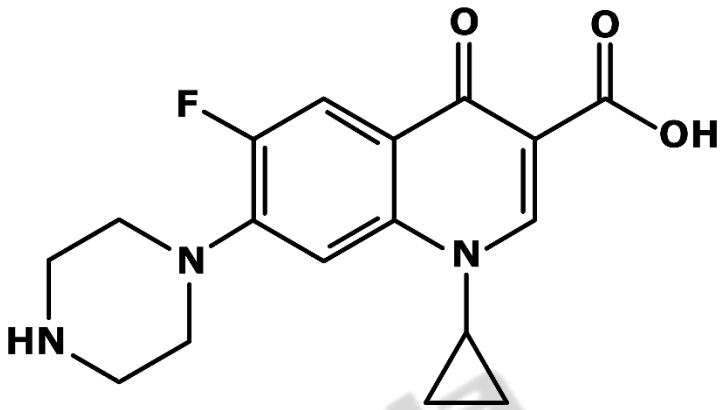
Step10: Saponification of (**9**) followed by acidification form the target molecule absicisic acid (**10**).



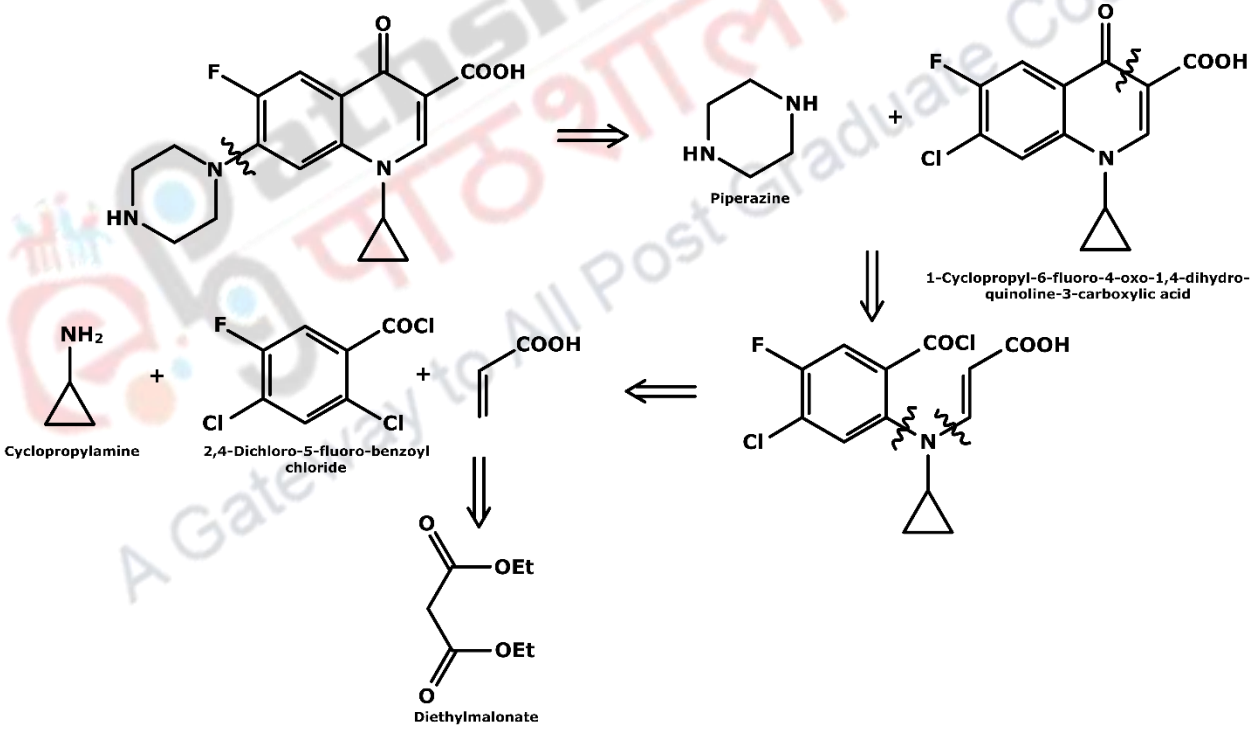


3. Total synthesis of Ciprofloxacin

Ciprofloxacin is an antibiotic used to treat a number of bacterial infections. Some of them are bone and joint infections, diarrhea, respiratory tract infections etc. It can be taken by mouth or used intravenously.



Retrosynthetic analysis:



CHEMISTRY	Paper No. 14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)
	Module No. 16: Total synthesis of complex organic compounds using disconnection approaches

Synthesis:

Step1: 2,4-dichloro-5-fluorobenzoyl chloride condenses with diethyl malonate in the presence of magnesium ethoxide in ether to form diethyl 2,4-dichloro-5-fluorobenzoylmalonate.

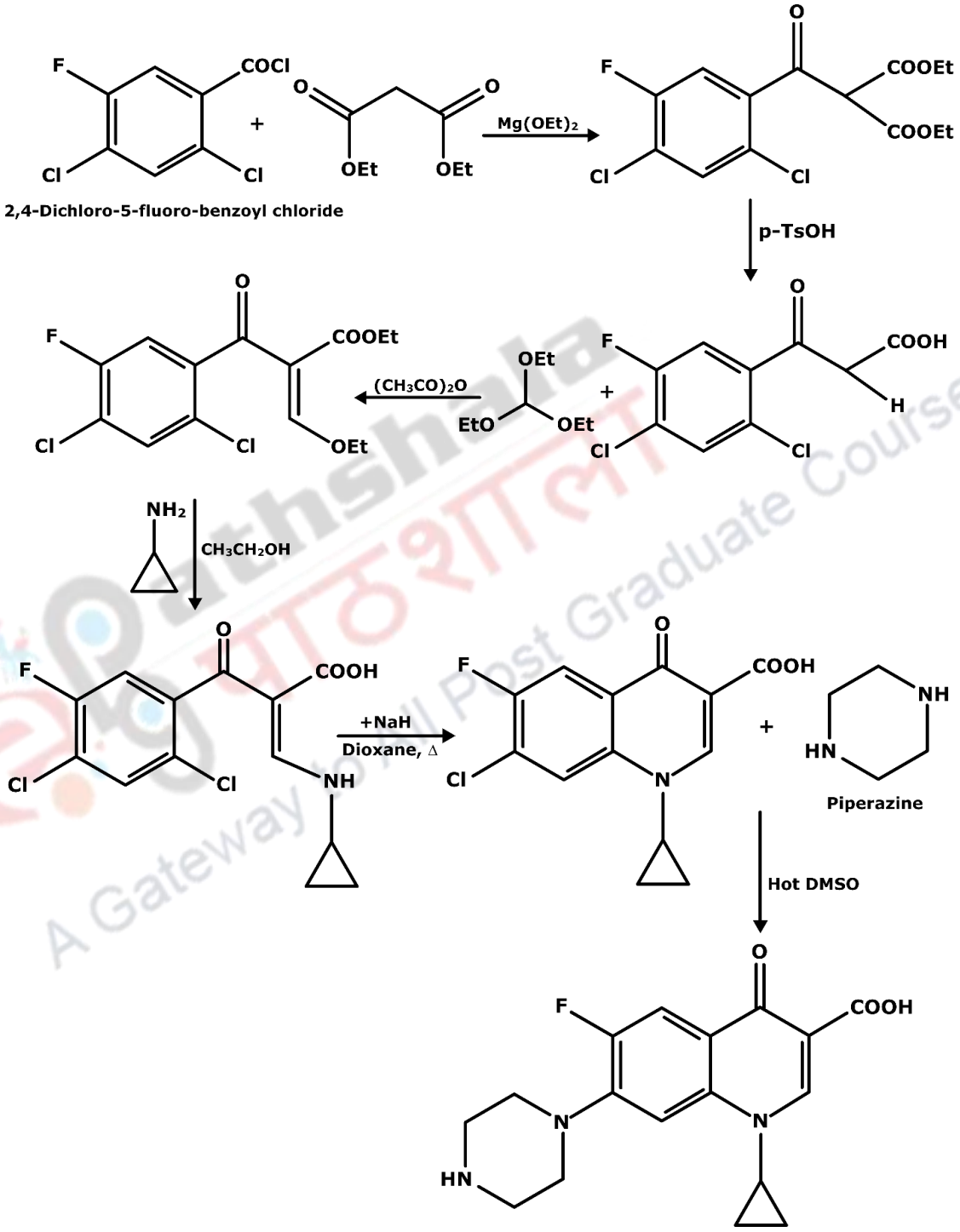
Step2: Diethyl 2,4-dichloro-5-fluorobenzoylmalonate is partially hydrolyzed and decarboxylated with *p*-toluenesulfonic acid in water forming ethyl 2,4-dichloro-5-fluorobenzoylacetate.

Step3: Ethyl 2,4-dichloro-5-fluorobenzoylacetate condenses with triethyl orthoformate in refluxing acetic anhydride to form ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-ethoxyacrylate.

Step4: Ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-ethoxyacrylate on reaction with cyclopropylamine in ethanol form ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-cyclopropylaminoacrylate.

Step5: Ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-cyclopropylaminoacrylate on cyclization with NaH in refluxing dioxane form 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid.

Step6: 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid condensed with piperazine in hot DMSO to form Ciprofloxacin.



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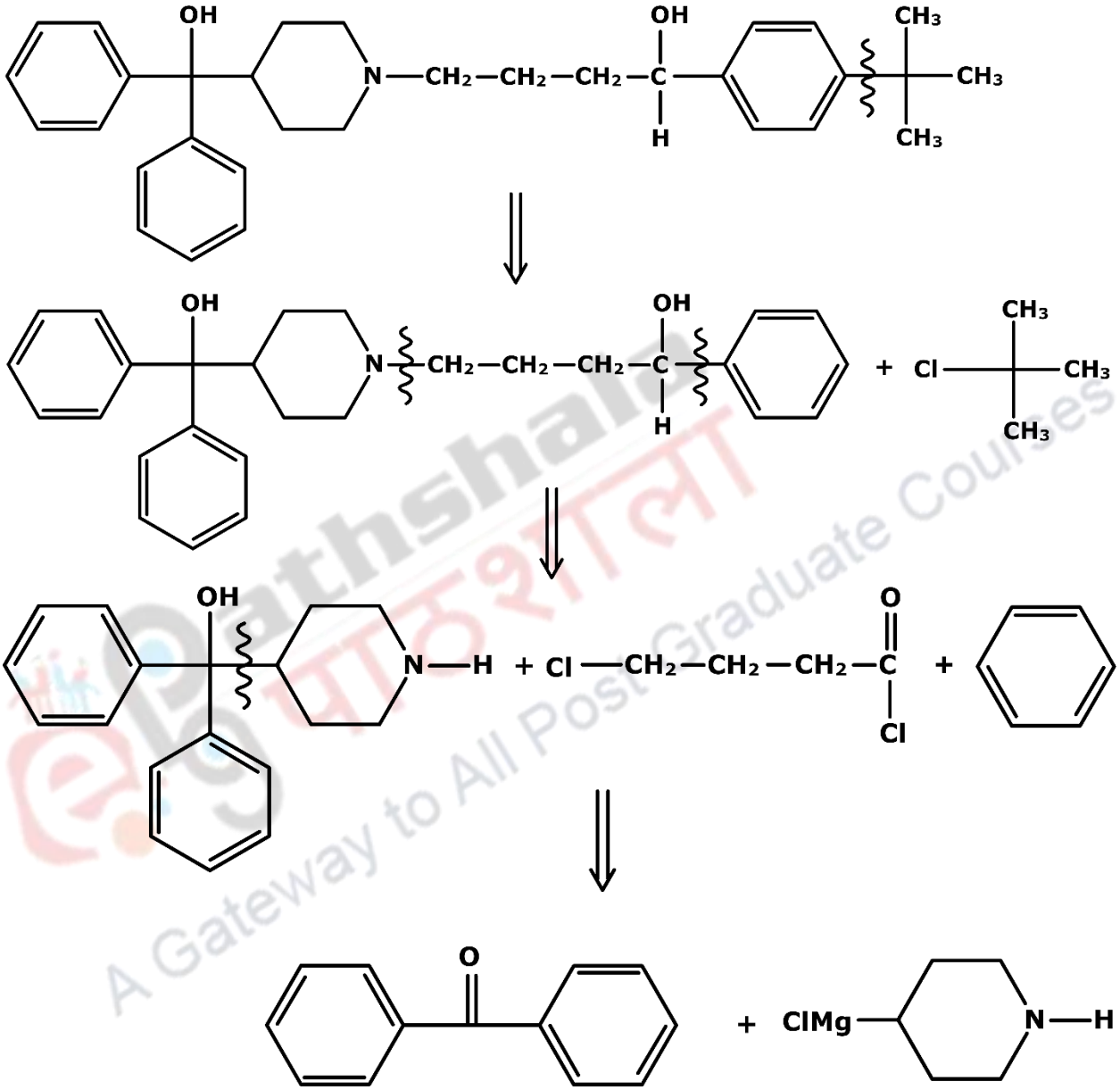
4. Total synthesis of Terfenadine

Terfenadine is an antihistamine drug used for the treatment of allergic conditions. It was sold in the market by various brand names, like Seldane, Triludan and Teldane.

Retrosynthetic analysis:



CHEMISTRY	Paper No. 14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)
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Synthesis:

Step1: Friedel-carft acylation of benzene with 4-hydroxyl-butyryl chloride in the presence of $AlCl_3$ as catalyst results in the formation of 4-hydroxyl-1-phenyl-butan-1-one.

Step2: 4-Hydroxyl-1-phenyl-butan-1-one on reaction with thionyl chloride ($SOCl_2$) results in the formation of 4-chloro-1-phenyl-butan-1-one.

Step3: 4-Chloro-1-phenyl-butan-1-one is reduced to 4-chloro-1-phenyl-butan-1-ol using sodium borohydride ($NaBH_4$).

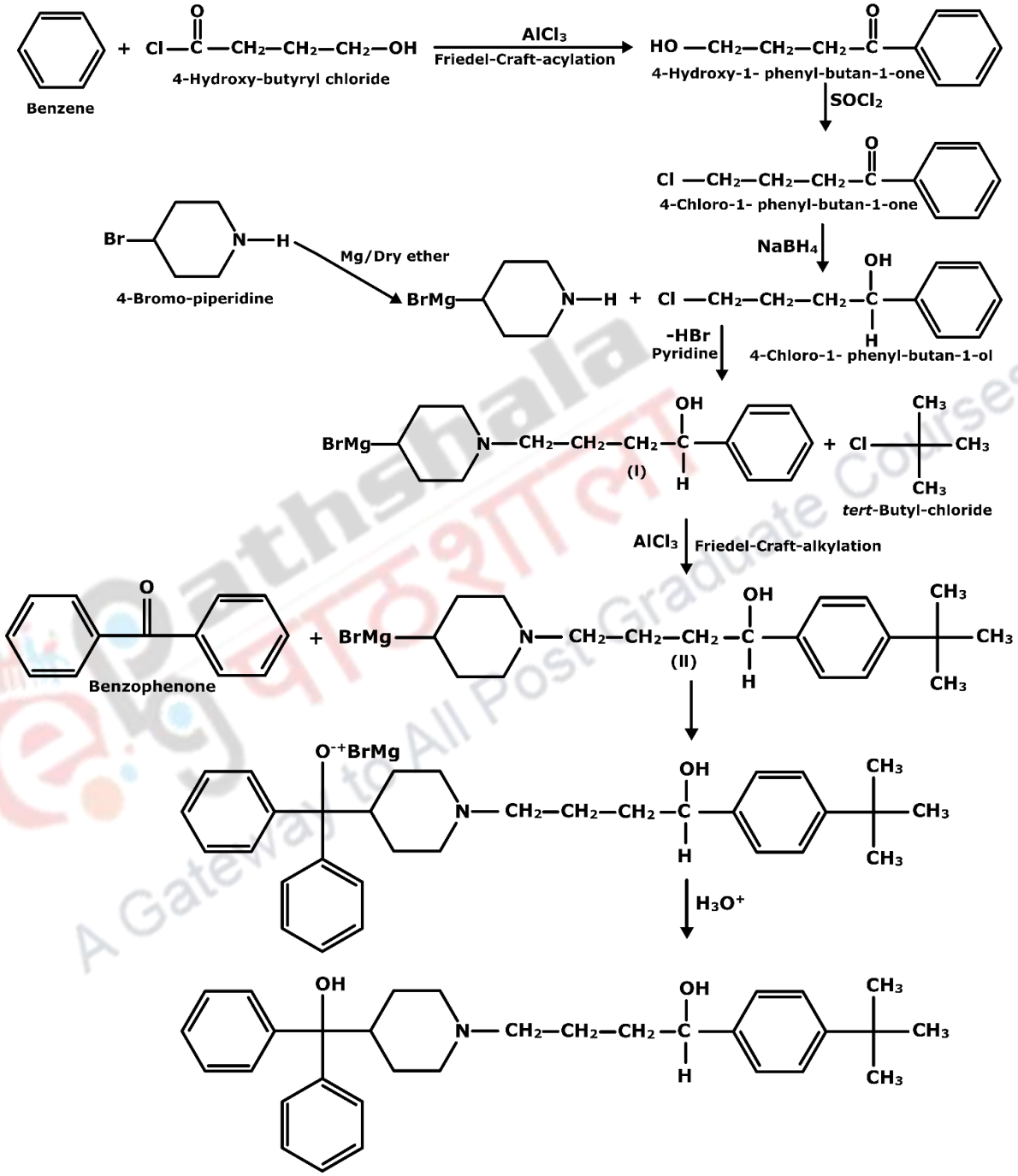
Step4: 4-Bromo-piperidine on reaction with magnesium in dry ether form piperidine-magnesium bromide.

Step5: Piperidine magnesium bromide on reaction with 4-chloro-1-phenyl-butan-1-ol in the presence of pyridine as a base forms (I).

Step6: Reaction between (I) and *tert*-butyl bromide in the presence of $AlCl_3$ as catalyst (Friedel-Craft-acylation) forms (II).

Step7: Reaction between (II) and benzophenone forms (III).

Step8: (III) on hydrolysis forms tef *tert*-butyl bromide in the presence of $AlCl_3$ as catalyst (Friedel-Craft-acylation) forms Terfenadine.



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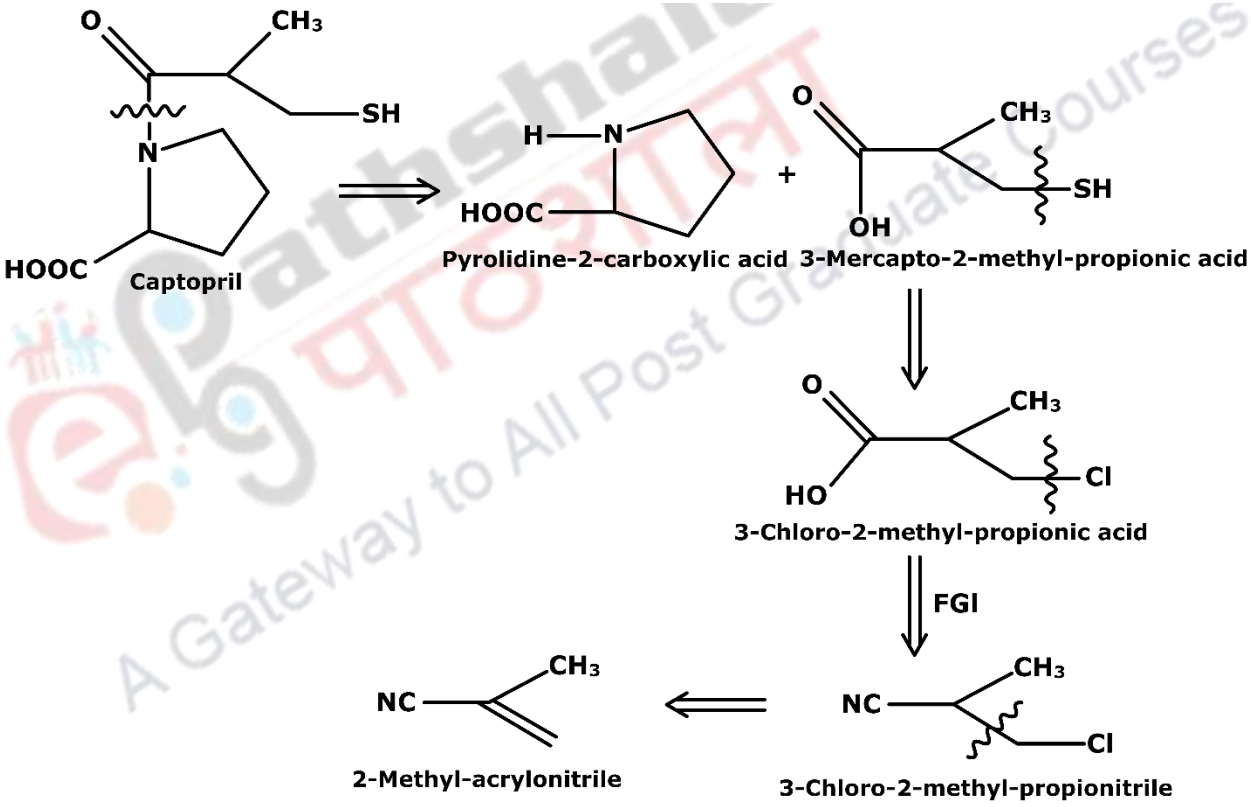
5. Total synthesis of Captopril

Captopril is an angiotensin-converting enzyme (ACE) inhibitor. This was discovered in 1977. This is used for the treatment of hypertension, some types of congestive heart failure and preservation of kidney function in diabetic nephropathy. It also shows mood-elevating properties in some patients.

Retrosynthetic pathway:



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Synthesis:

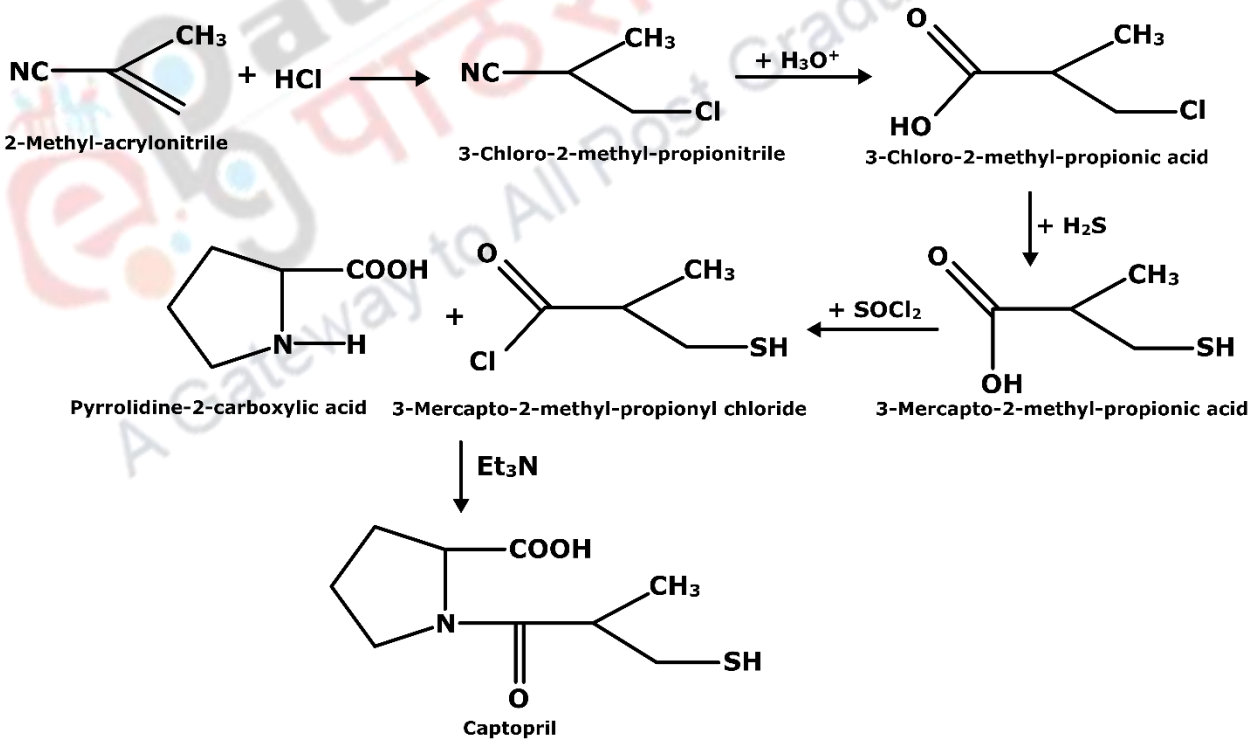
Step1: HCl is added to 2-methyl-acrylonitrile and form 3-chloro-2-methyl-propionitrile.

Step2: 3-Chloro-2-methyl-propionitrile on acidic hydrolysis forms 3-chloro-2-methyl-propionic acid.

Step3: 3-Chloro-2-methyl-propionic acid on reaction with hydrogen sulphide forms 3-mercapto-2-methyl-propionic acid.

Step4: Reaction of 3-mercapto-2-methyl-propionic acid with thionyl chloride ($SOCl_2$) results in the formation of 3-mercapto-2-methyl-propionyl chloride.

Step5: Condensation of 3-mercapto-2-methyl-propionyl chloride with pyrrolidine-2-carboxylic acid in the presence of base *tri*-ethylamine results in the formation of captopril.



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6. Summary

- Abscisic acid or ABA is an inhibitory rather than stimulatory hormone for plants.
- Retrosynthetic pathway and corresponding synthetic pathways of abscisic acid is given.
- Ciprofloxacin is an antibiotic used to treat a number of bacterial infections.
- The retrosynthetic analysis shows that the molecule, Ciprofloxacin can be synthesized from dimethylmalonate.
- The retrosynthetic pathway and total synthesis of Ciprofloxacin are explained with scheme.
- Terfenadine is an antihistamine drug used for the treatment of allergic conditions.
- The retrosynthetic pathway and total synthesis of Terfenadine are explained with scheme.
- Captopril is an angiotensin-converting enzyme (ACE) inhibitor and was discovered in 1977.
- The retrosynthetic pathway shows that Captopril can be synthesized from 2-methylacrylonitrile.

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