The Total Synthesis of Some Natural Products

Islamabad

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in

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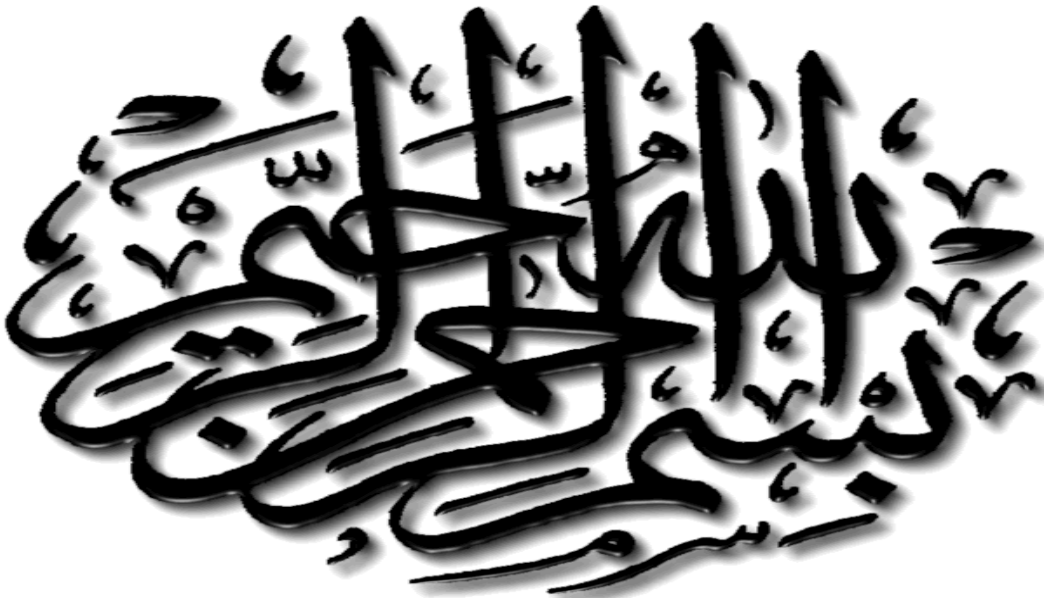

IN THE NAME OF ALLAH, THE MOST BENEFICENT THE MOST MERCIFUL

This is to certify that this dissertation entitled ***"The Total Synthesis of some Natural Products"*** *submitted by MUHAMMAD QASIM is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University, Islamabad, as satisfying the dissertation requirements for the degree of* ***Master of Philosophy*** *in* ***Organic Chemistry****.*

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Dated:……..

Dedicated to
my loving parents,
sisters and brothers

Allah will exalt those who believe among
you and those
who have knowledge to high ranks.

(The Holy Quran)

ABSTRACT

The work presented in this thesis consists of Total synthesis of Desmethyldiaportinol and Trilepisumic acid which are naturally occurring isocoumarin and derivative of caffeic acid respectively.

Desmethyldiaportinol was synthesized in 17 steps. 3,5-Dimethoxyhomopthalic acid was synthesized starting from commercially available 3,5-Dihydroxybenzoic acid and then it was condensed with 3,4-Dibromobutanoyl chloride which was itself synthesized starting from allyl bromide to yield 3-(2,3-Dibromopropyl)-6,8-dimethoxyisocoumarin. The conversion of bromides into hydroxyl groups were carried out by refluxing in a mixture of acetone and water. Finally demethylation was achieved by refluxing in 33% HBr to yield the required compound.

Trilepisumic acid was synthesized in 4 steps starting from the condensation of 3,4-Dimethoxybenzaldehyde with malonic acid to yield 3,4-Dimethoxycinnamic acid. Esterification was carried out by treatment with vanillin and then the formyl group was oxidized into acid by using one equivalent of $KMnO_4$ in acidic medium. Finally demethylation was achieved by refluxing in 33% HBr to yield the required compound.

The structures of all the compounds were confirmed by FTIR, ^{1}HNMR and ^{13}CNMR spectroscopy.

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Chapter 1 Introduction

In nature there are two types of metabolites which are commonly known as primary and secondary metabolites. Primary metabolites are such compounds which are directly involved in development and reproduction of an organism while secondary metabolites are such compounds that are not directly involved in development and reproduction of an organism that's why these are also called as **extrolites**. In fact the term natural product is also used for these secondary metabolites. Taking into account the immense importance of secondary metabolites because of their diverse biological and pharmacological roles, scientists have shown their interest in these metabolites for long time.

1.1 Classification of Secondary Metabolites

On the basis of their origin, secondary metabolites have broadly divided into these major classes.

1. Polyphenolic compounds

2. Terpenoids

3. Alkaloids

4. Polyketide

1.1.2 Polyphenolic compounds

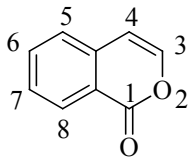
The polyphenolic compounds are such substances that possess an aromatic ring having more than one hydroxyl groups. Hydroxycinnamic acids, phenylpropenes, coumarins, isocoumarins, flavonoids and stilbenes etc., are the most common members of the polyphenolic compounds.

Keeping in view the immense biological activities I have focused my research work on the total synthesis of (1) Desmethyldiaportinol and (2) Trilipisumic acid which are in nature isocoumarin and polyhydroxycinnamic acid derivative respectively.

PART 1

1.2 Isocoumarin

Isocoumarins are positional isomer of coumarins with inverted lactone moiety. Natural sources of isocoumarins are fungi, molds, lichens, bacteria, higher plants and insects[1]. The IUPAC name for isocoumarin is 1*H*-isochromen-1-one, structure with numbering is as shown.



In literature many reviews have been published on synthetic methods and pharmaceutical applications of isocoumarin such as by Dighe, N. S *et al.* [2] (2010), Musa, M. A *et al.* [3] (2008), E. Napolitano *et al.*[4] (1997), R. A. Hill[5] (1986), V.Yamato[6] (1983), W. B. Turner and Aldridge[7] (1983) and R. D. Barry[8] (1964).

Like other classes of natural products most of the isocoumarins are known by their trivial names which are derived either from the generic or the specific name of the source organisms. Examples of the name derived from genera are artemidin (*Artemicia Glauca*), bergenin (*Bergenia Crassfolia*), kigelin (*Kigelia Pinata*) etc.,

Species derived names are mellein (*Aspergillus mellus*), duclauxin (*P. duclauxi*) etc.

1.2.1 Structural Diversity

In nature majority of the isocoumarins have large structural diversity in accordance to different alkyl or aryl substituents at C-3 position. Isocoumarins biogenetically derived from acetate pathway were oxygenated at C-8 position while some also have retained C-6 position oxygenated. Isocoumarins with deoxygenated C-6 position were not acetate derived and are

generally found in plants such as hydrangenol, phyllodulicin etc. C-4 and C-5 substituted isocoumarins are relatively less common in nature.

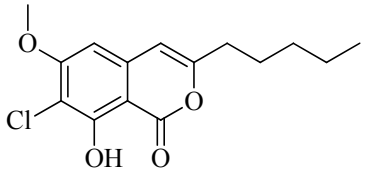
Halogenated isocoumarins are also present in nature but less common. Dichlorodiaportin is a chlorine containing isocoumarin isolated from *Penicillium nalgiovense*[9].

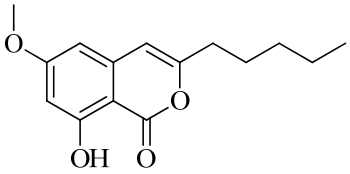
1.3 Biological Activities

These secondary metabolites have a wide spectrum of biological activities such as antimalarial, antidiabatic, anticancer and anti-angiogenic[10-14].

i) Antimosquito

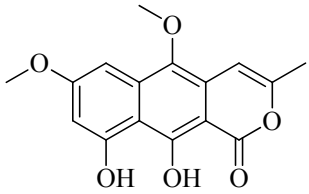
7-Chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin and 8-Hydroxy-6-methoxy-3-pentylisocoumarin were isolated from the *Tessmannia densiflora* Harms (Caesalpiniaceae) that showed mosquito larvicidal activity[15].





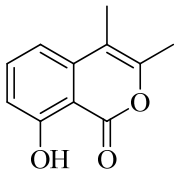
ii) Antioxidant

Paepalantine was isolated from Paepalanthus bromelioides showed antioxidant activity on rat liver mitochondria[16].



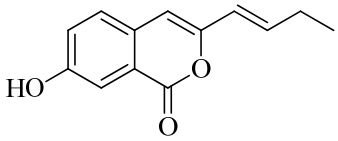
iii) Antifungal

Antifungal oospolactone was isolated from *Gleophyllum Sepiarium*. It has been reported to have remarkable action against different strains of asexual ascomycetes *Alternaria*[17].



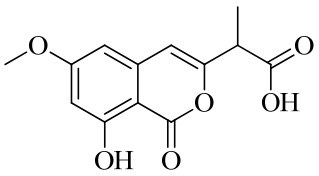
iv) Headache and dilution of blood

7-Hydroxyartemidin was isolated from the leaves of *Artemisia drucunculus* L. It has free hydroxyl group at C-7 position and also reported for the treatment of headache, dizziness and for dilution of blood[18].



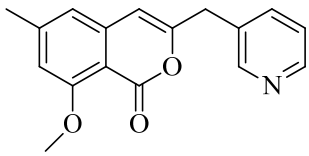
v) Angiogenesis Inhibitor NM-3

Tumor cells release such chemicals which are responsible for the growth of new blood vessels that supply nutrients to tumor cells for their development. NM-3 has inhibitory effects against the growth and development of these blood vessels. In other words, it prevents the growth of cancer cells[19].



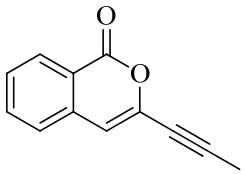
vi) Microtubules Assembly Inhibitor

Pyridyl-isocoumarin derivative also known by a no.185322 was reported to inhibit the cell division of human multiple myeloma cells[20].



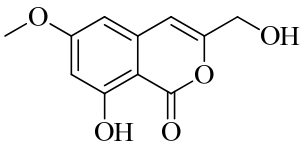
vii) Antifeedant

Capillarin, an isocoumarin isolated from the buds of Artemisia capillaries was found to be efficient as antifeedants towards the larvae of cabbage butterfly [21].



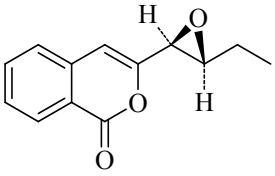
viii) Cytotoxic Activity

Cytogenin was isolated from *streptoverticillium eurocidicum*. It was reported to exhibit anticancer activity against IMC carcinomia in mice. The compound was also considered as effective immunological regulator [22].

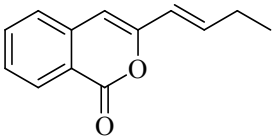


ix) Antimalarial Activities

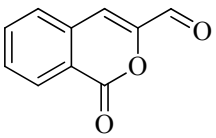
Artemidinal, Epoxiartimidin and artemidin were isolated from a shrub artemisia campestris. The extract of this shrub in water commonly known as taguq in highlands of Algeria was used as a diuretic. It is in successful clinical trials[23].



(+)-Epoxyartemidin



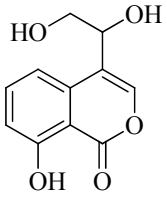
Artemidin



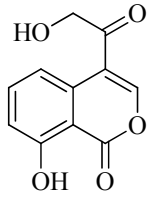
Artemidinal

x) Antibacterial

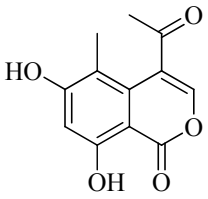
Oospoglycol, Oosponol[24], 4-Acetyl-6,8-dihydroxy-5-methylisocoumarin[25], (-) sescandelin[26] and AGI-7[27] are naturally occurring isocoumarins that have been reported as antibacterial especially for plant cells, bacteria and plant-pathogenic bacteria. AGI-7 also showed root promoting activity[28].



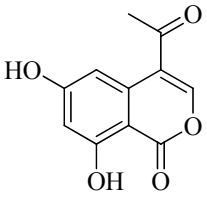
Oospoglycol



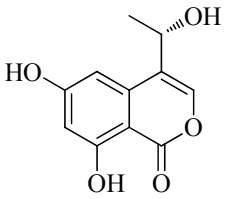
Oosponol



4-Acetyl-6,8-dihydroxy-5-methyl-1H-isochromen-1-one



AGI-7

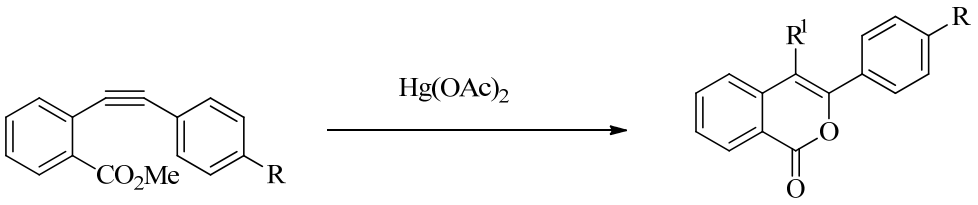


(-)-Sescandelin

1.4 Synthetic Approaches

There were many methods reported in literature for the synthesis of isocoumarin nucleus. Some of the most imported, reliable and high yield methods which were also reported in recent literature are mentioned here.

In this method diaryl alkyne ester was treated with mercuric acetate to yield isocoumarin. The method was best for the preparation of 3-substituted isocoumarins[29].

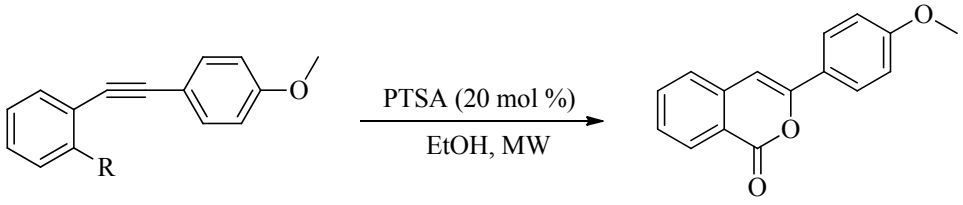


R= H, Br, Cl, I, Ac

R_1= H, CH_3, Cl, Br

Scheme 1.1

p-Toluene sulfonic acid was used as a catalyst for the cyclization of different ortho-functionalized diaryl alkynes under microwave irradiation using ethanol solvent to generate isocoumarins. Reaction was performed both under reflux and microwave irradiation and the best results were obtained under microwave irradiation. Carboxylic acid group at ortho position gave the 98% yield[30].

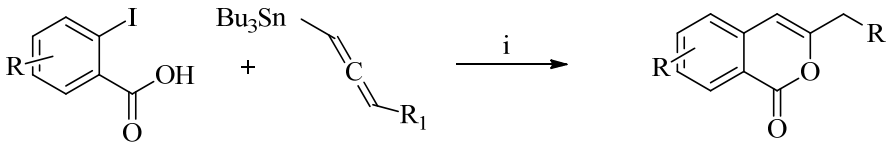


R= CN, COOR, $CONH_2$, COOH

Scheme 1.2

Tandem Stille Reaction

Many 3-substituted isocoumarins have been synthsized by treating *o*-iodobenzoic acid with allenyltributyltin using palladium acetate, triphenylphosphine and tetrabutyl ammoniumbromide in *N, N*-dimethylformamide as a solvent at 80°C[31].

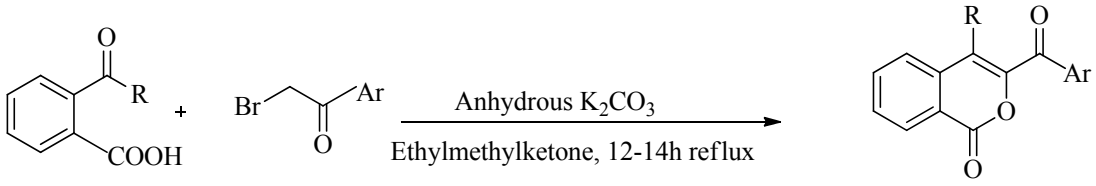


i = $Pd(OAc)_2$ (5%), PPh_3 (10%)

n-Bu_4NBr (1 eq) , DMF 25-80^{0}C

Scheme 1.3

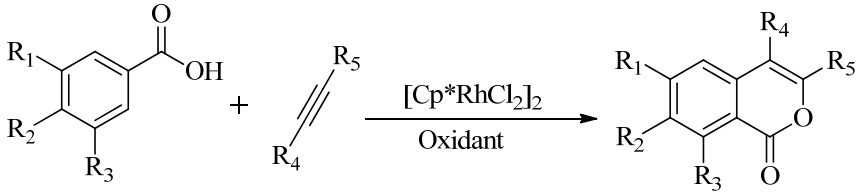
o-Acylbenzoic acid and alpha halo acetophenone were refluxed in ethylmethyl ketone by using potassium carbonate as a mild base to generate 3-Acylisocoumarins in good yield[32].



R= alkyl, aryl

Scheme 1.4

Polyoxygenated benzoic acids showed rapidly oxidative coupling with alkynes by regioselective C-H bond breakage. The process was catalyzed by rhodium to yield polysubstituted isocoumarins in excellent yield[33].



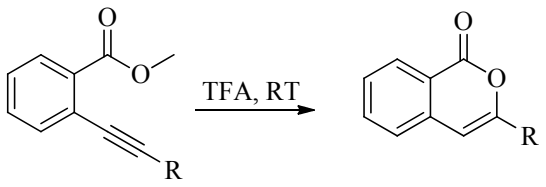
R_1,R_2, R_3 = -OMe, Me

R_4, R_5 = H, Me, Et

Scheme 1.5

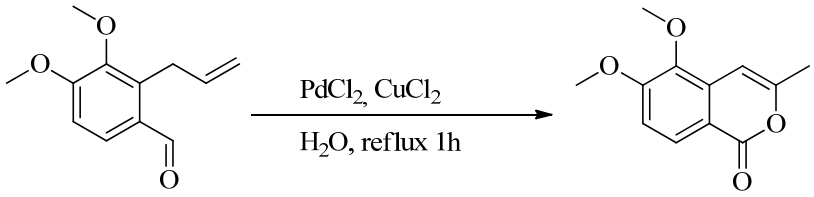
Acid catalyzed cyclization

Methyl 2-(2-arylethynyl) benzoate was cyclized to corresponding isocoumarin in high yield under acidic conditions at room temperature. This type of reaction is called 6-endo-dig cyclization here 6 represents to six member ring, endo means the bond broken during cyclization is inside and dig represents the electrophilic carbon on which nucleophile attacks is diagonal meaning sp hybridized[34].



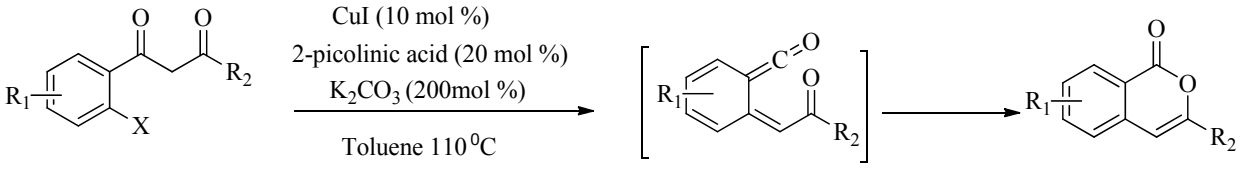
Scheme 1.6

o-Allylbenzaldehydes were mediated by $PdCl_2$-$CuCl_2$ in water to undergo a domino reaction (a series of intramolecular reactions which involves a reactive intermediate), including 6-exo-trig cyclization, addation of water, the elimination of PdHCl, the isomerization of C-C double bond, the oxidation of hemiacetals with the elimination of PdHCl and regeneration of $PdCl_2$ in situ to yield new substituted isocoumarins in one pot with high yield[35].



Scheme 1.7

Cu(I) catalyzed reaction of 1-(2-Halophenyl)-1,3-diones has been developed for the synthesis of 3-substituted isocoumarins. It based on a cascade Cu-catalyze intramolecular Ullmann-type C-arylation and rearrangement. This methodology is not only simple but also best for the synthesis of 3-substituted isocoumarins[36].

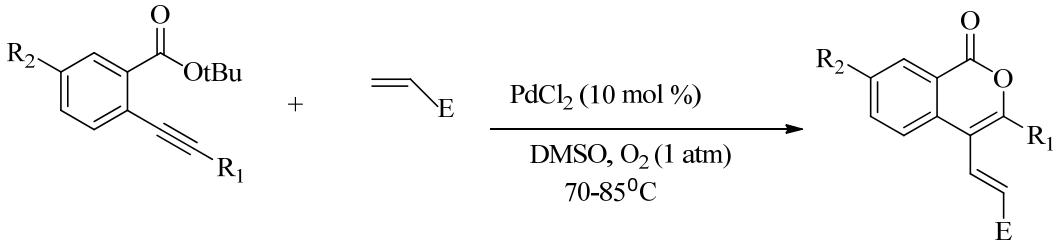


R_2= OH, OMe , NHPh

X= Cl, Br, I

Scheme 1.8

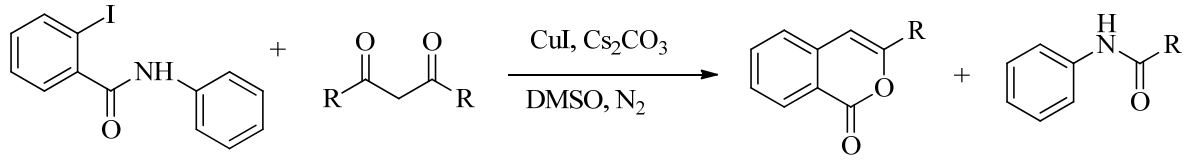
Oxidative coupling of t-Butyl 2-alkynylbenzoates with activated olefins such as acrylates and styrenes catalyzed by palladium (II) chloride yielded 3,4-disubstituted isocoumarins. Reaction was carried out at 70-85°C in DMSO under aerobic conditions[37].



E = electron withdrawing group

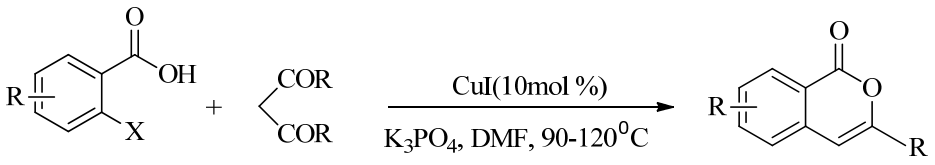
Scheme 1.9

This is a copper (I) iodide catalyzed domino reaction of 2-Iodo-*N*-phenylbenzamide with 1,3-dicarbonyl compound using cesium carbonate as a base to yield 3-substituted isocoumarins. This is a copper catalyzed C-C and C-O tandem coupling[38].



Scheme 1.10

o-Halo benzoic acids were treated with 1,3-Dicabonylcompounds in the presence of copper iodide as a catalyst by using DMF as a solvent under the action of potassium phosphate at 90-120°C to yield 3-substituted isocoumarin derivatives in good to excellent yields.1,3-Dicarbonyl compounds could be alkyl or aryl substituted[39].



X= I, Br, Cl

Scheme 1.11

Part II

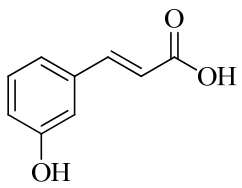
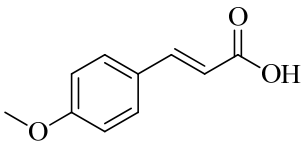
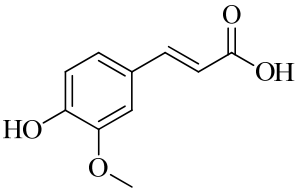
Polyhydroxyaromatic acids are an important class of secondary metabolites in which cinnamic acids and its derivatives have a valuable scope not only due to pharmacological applications but also due to their industrial applications. In nature cinnamic acids have vast structural diversity not only in accordance to different substitution pattern on aromatic ring but also due to different derivatives of acid moiety.

1.5 Biological Activities of Cinnamic Acids and Its Derivatives

Cinnamic acids and its derivatives have a broad spectrum of biological activities such as anti-TB, antidiabatic, antimicrobial, antimalarial and cytotoxic etc., some of bioactive compounds are given below.

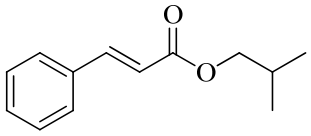
i) Antidiabetic

m-Hydroxy and *p*-Methoxy cinnamic acids were effective insulin releasers in both in-vivo and in-vitro. Among cinnamic acids derivatives ferculic acid has been reported the most effective insulin releasing agent[40].

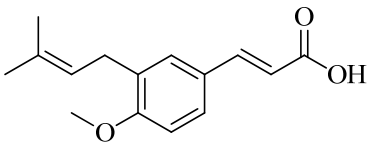
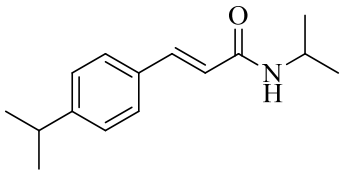
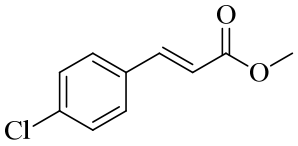
ii) Antimicrobial

Anti-microbial activity of cinnamic acid derivative was due to the presence of amide and ester moiety. Isobutyl cinnamate exhibited strong anti-bacterial and also very good antifungal properties[41].



iii) Antifungal activity

3-Isoprenyl-4-methoxycinnamic acid has been reported to have highest anti-fungal activity against *A. niger*. Ester derivative of cinnamic acid such as Methyl-4-chlorocinnamate also has highest cytotoxic activity against *C. rolfsii*. While in amide derivatives (E)-*N*-isopropyl-3-(4-isopropylphenyl)acrylamide showed the highest fungi toxic activity [42].

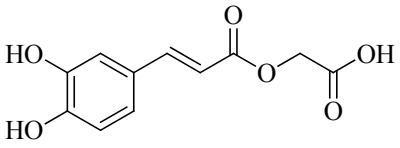




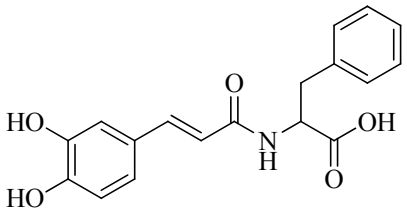
iv) In cosmetics as a fragrance

Cinnamic acid and its derivatives are used as a fragrance in many cosmetics materials. Cinnamic acid itself is not considered as an odorant but its ester derivatives serves as a precursor with long lasting aroma. Methyl cinnamates are also used in flavores[43].

v) HIV-1 integrase inhibitors

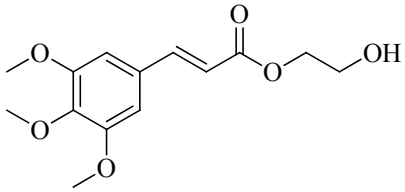
Human immunodeficiency virus (HIV) integrase (IN) is an enzyme which catalyzes the production of HIV DNA copy into the host cell DNA. So 3-(3,4-Dihydroxy-phenyl)-acrylic acid carboxymethyl ester and 3-(3,4-Dihydroxy-phenyl)-2-[3-(3,4-dihydroxyphenyl)-acryloylamino]-propionic acid have been reported to inhibit the activity of this enzyme. These compounds have equal or slightly higher HIV-1 IN inhibitory activity compared to parent compound L-chicoric acid[44].





vi) Anti-Oxidant

Cinnamic acids derivatives also exhibited a strong antioxidant activity. This activity makes the compounds as a potential drug for the treatment of pathologies. The compound (*E*)-2-Hydroxyethyl-3-(3,4,5-trimethoxyphenyl)acrylate also exhibited the antioxidative activity[45] both in NBT and DPPH free radical inhibition models with $IC_{50} = 11$.



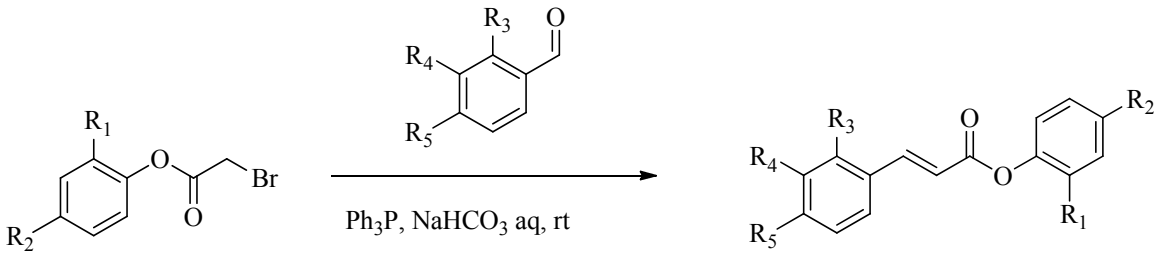
1.6 Synthetic Strategies

Many methods have been reported in literature for the synthesis of cinnamic acids and their derivatives. Some of the most imported, reliable and high yield methods which are also reported in recent literature are being mentioned here.

Water mediated Wittig approach.

Wittig reaction is a very important reaction in organic synthesis to make a C-C double bond. To a stirred solution of triphenylphosphine in saturated aqueous sodium bicarbonate,

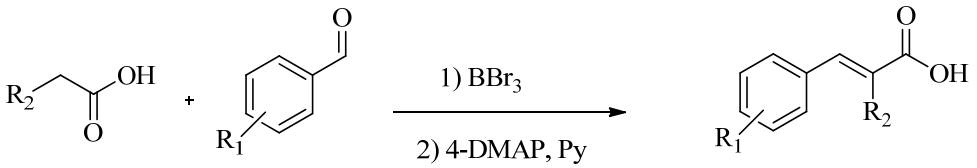
α-bromoester and aldehyde was added at pH 5.5 to yield aryl and Benzyl (E) cinnamate derivatives[46].



R_1=OMe, H, R_2= OMe, Br, NO_2 R_3, R_4, R_5=OMe, H

Scheme 1.12

Cinnamic acids have been synthesized in good yield by using aliphatic carboxylic acids and aromatic aldehydes , in the presence of boron tribromide as a reagent, pyridine and 4-Dimethylaminopyridine as bases and N-methyl-2-pyrolidone as a solvent. The reaction mixture was refluxed at 180-190 ˚C for 10-12 hours[47].

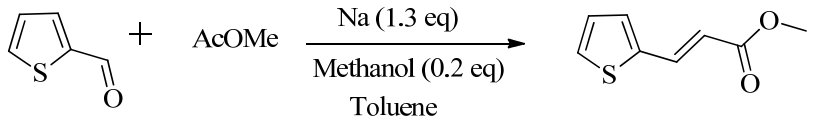


R_1=Cl, OMe, NO_2 R_2=H, CH_3

Scheme 1.13

Claisen-Shmidt condensation.

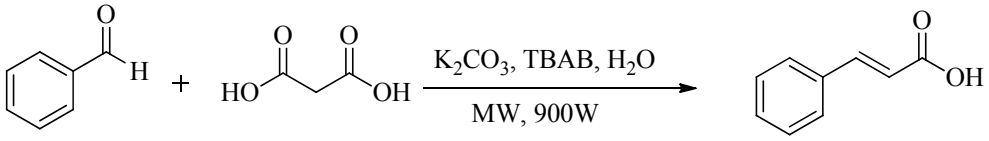
A number of cinnamic acids derivatives have been prepared by a Claisen-Shmidt condensation. In which sodium metal was suspended in toluene and the mixture was refluxed for 10 minutes. After removing the solvents methyl acetate and p-Anisaldehyde were added. The mixture was stirred at room temperature and acetic acid was added drop wise to yield cinnamic acids derivatives in good yield[48].



Scheme 1.14

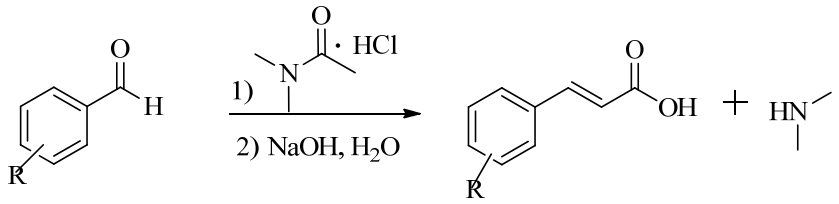
TBAB mediated Knovenogel condensation in water

This is a best, mild and environment-friendly method for the synthesis of cinnamic acids. Aromatic aldehydes and ketones were condensed in water with potassium carbonate as a mild base and tetrabutylammoniumbromide (TBAB) was used as a phase transfer catalyst under micro-wave irradiation to yield cinnamic acids in good yield[49].



Scheme 1.15

Cinnamic acids[50] have been synthesized in good yield by refluxing aromatic aldehydes in *N*,*N*-Dimethylacetamide hydrochloride which act both as a reagent and solvent at 190-200 °C for 8-10h.

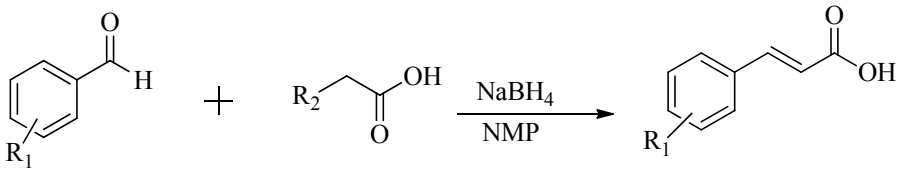


R= Cl, -OMe, $-NO_2$

Scheme 1.16

Cinnamic acids[51] have been synthesized by the direct reaction of aromatic aldehydes with aliphatic carboxylic acid by refluxing in *N*-methyl-2-pyrolidone with sodium borohydride at

190 ˚C. The yield obtained in this reaction is also good. Like Dobner and Knovenogel there is no need of decarboxylation.



R_1= Cl, -NO_2, -OMe

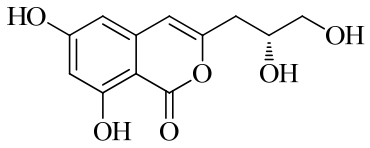
R_2= H, - CH_3

Scheme 1.17

1.7 Plan of Work

An exhuastic literature survey reveals that among polyphenolic compounds, isocoumarins and cinnamic acids derivatives show a wide range of synthetic applications not only of biological significance but also to industrial point of view.

Desmethyldiaportinol[52] is an isocoumarin and was isolated from an endophytic fungus *ampelomyces* sp. in 2008.



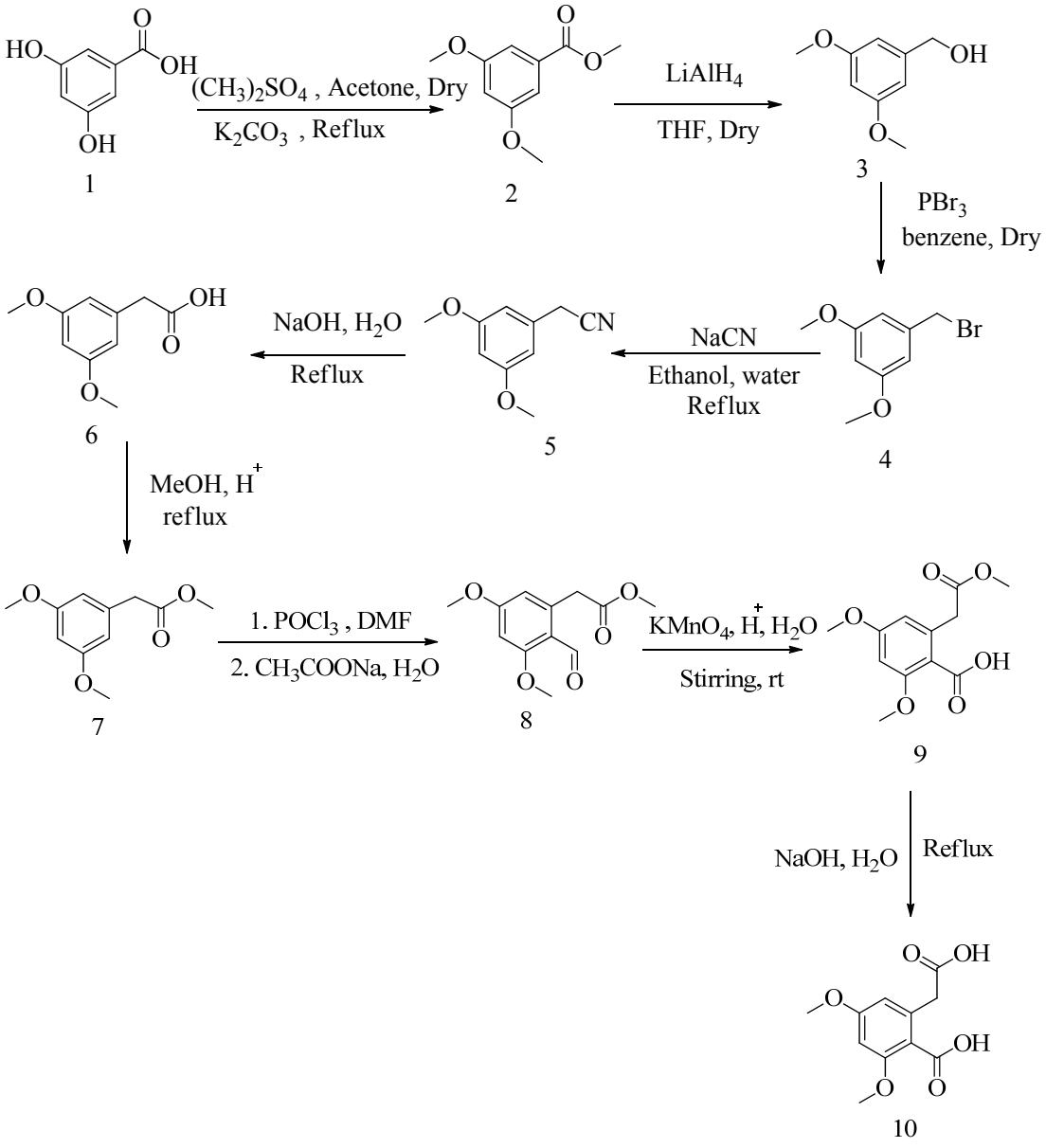
(*R*)-3-(2,3-dihydroxypropyl)-6,8-dihydroxy-1*H*-isochromen-1-one

There is a one chiral center in molecule with configuration is *R* .The aliphatic portion of molecule contain free hydroxyl groups which makes this portion of molecule hydrophilic in nature. These free hydroxyl groups are also very important for further derivatization

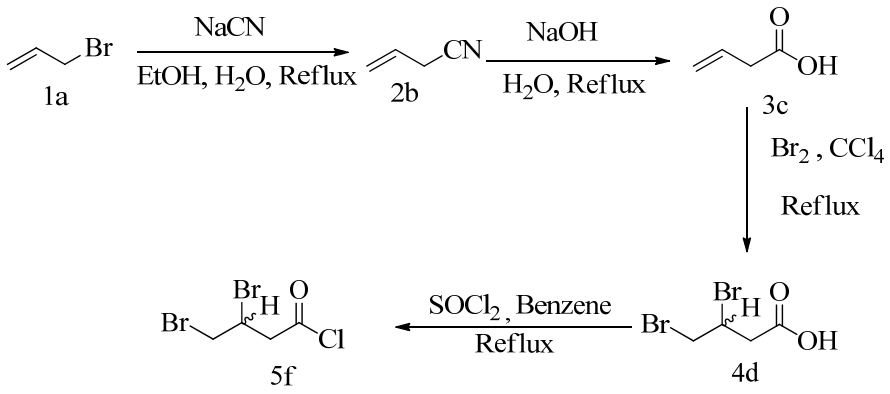
Desmethyldiaportinol was also reported as cytotoxic when tested *in vitro* against L5178Y cells of mouse[52]. This activity of molecule makes it very attractive for total synthetic chemists and that´s why we made a plan for its synthesis. It has been proved that the condensation of homopthalic acid with acid chlorides is a best way for isocoumarin synthesis.

Following this protocol 3,5-Dimethoxyhomopthalic acid and 3,4-Dibromobutanoyl choride will be synthesized and then these two precursors will be condensed with each other to yield required isocoumarin.

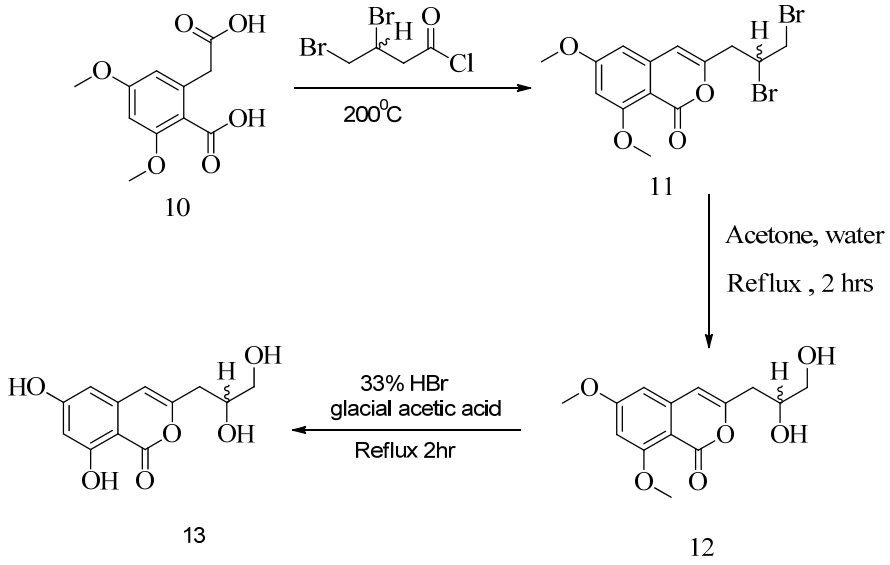
a) Synthesis of 3,5-Dimethoxyhomopthalic acid



b) Synthesis of (±)-3,4-Dibromo butanoyl chloride



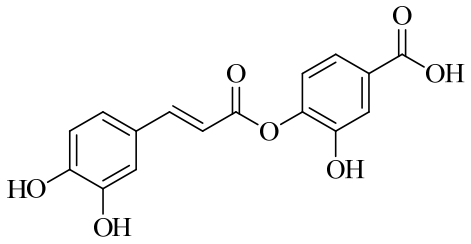
c) Condensation of 5f & 10



Proposed scheme for (±)-Desmethyldiaportiol

Total synthesis of Trilepisumic acid

It was isolated from Trilepisium madagascariense[53] in 2012.

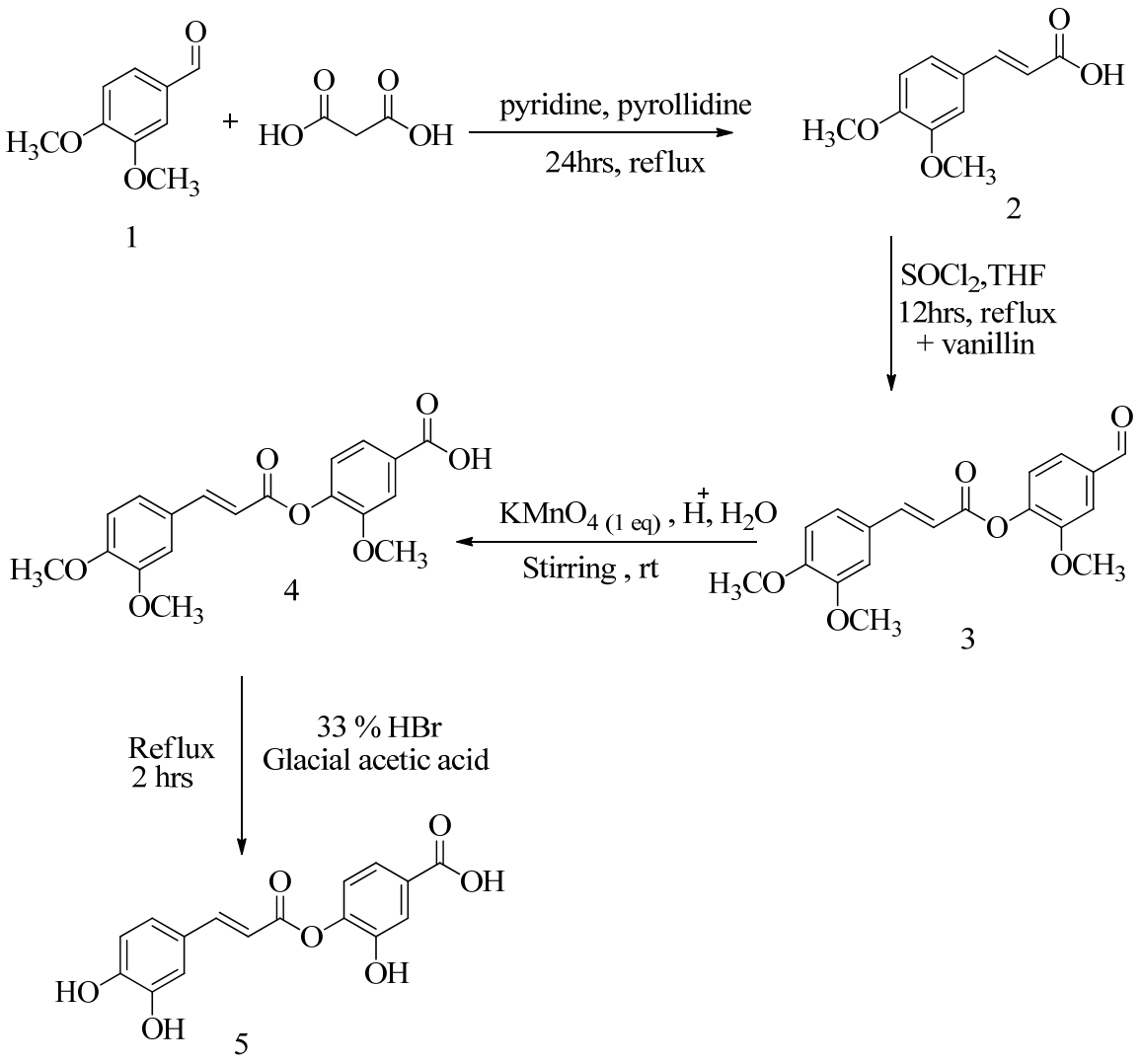


(*E*)-4-((3-(3,4-Dihydroxyphenyl)acryloyl)oxy)-3-hydroxybenzoic acid.

The free hydroxyl groups can make the molecule antioxidant and can also be used for further derivatization.

This molecule has been reported as anti microbial[53] which makes the molecule attractive for synthesis and that´s why we have also selected it for total synthesis. Actually the molecule is an ester of caffeic acid and caffeic acid is a derivative of cinnamic acid. Dobner condensation is a well known synthetic way for cinnamic acid synthesis.

In first step 3,4-Dimethoxycinnamic acid will be synthesized, then it will be converted into acid chloride for treatment with vanillin, then the formyl group will be oxidized into acid and finally demethylation will be achieved by refluxing in HBr. The proposed scheme is given below,



Proposed scheme for Trilepisumic acid

Chapter-2 EXPERIMENTAL

2.1.1 Purification and drying of solvents

Purification and drying of solvents were carried out according to standard procedures. All the Dried solvents were stored over 4°A type molecular sieves except THF and benzene. A brief note about the purification procedure is given below.

1) Acetone

One liter acetone with oven dried calcium oxide (200g) was refluxed for 6-8 hours. Then pure acetone was distilled at 56 °C.

2) Methanol

One liter methanol with activated calcium oxide (200g) was refluxed for 7-9 hours. Then it was distilled out. After it methanol was refluxed with 6g magnesium turnings and few crystals of iodine, when white color was appeared then it was distilled out at 65 °C.

3) THF

One liter THF was refluxed with 5-6g of sodium wire and 10g benzophenone. When dark blue colure was appeared which is the indication of ketyl formation then it was distilled out at 65 °C and stored over sodium wires.

4) Benzene

Benzene was kept with activated calcium oxide overnight then it was distilled out. After it one liter benzene was refluxed with 6g sodium wire and 10g of benzophenone when dark blue color was appeared then it was distilled out at 80°C and stored over sodium wire.

2.1.2 Instrumentation

Melting points were determined on a digital Gallenkamp melting point apparatus model (MP-D) BM 3.5 and are uncorrected. FTIR spectra were recorded on a Bio-Rad-Excalibur Series Model No. FTS 300 MX spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$, DMSO-d_6, MeOD solutions at 300 MHz and 75 MHz on a Bruker AM-300 spectrophotometer respectively.

2.1.3 Chromatographic techniques

1) Thin Layer Chromatography (TLC)

All the reactions were monitored through thin layer chromatography by using precoated silica gel aluminum plates (layer thickness 0.2mm, HF_{254}, Reidal-de-Haen from Merck)

Solvent systems used for the development of chromatograms were,

A) *n*-Hexane: Ethyl acetate (4:1)

B) Methanol: Chloroform (1:9)

All the chromatograms were analyzed under ultraviolet light at λ_{max} 365nm and 254nm.

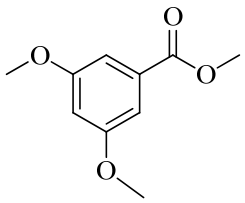
2) Preparative Thin Layer Chromatography (PTLC)

Glass plates (20.20cm) coated with silica gel (HF_{254} Merck) of 1mm layer thickness were used for the purification of desired synthesized compounds.

2.2 Total synthesis of (±)-Desmethyldiaportinol

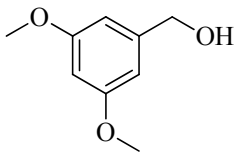
2.2.1 Synthesis of 3,5-Dimethoxyhomopthalic acid (10)

Methyl 3,5-Dimethoxybenzoate



3,5-Dihydroxybenzoic acid (30g, 0.16 mol) was refluxed with dimethylsulfate (40g, 0.32 mol) in dry acetone by using anhydrous potassium carbonate (38.4g, 0.48 mol) as a mild base for 10h. The reaction mixture was filtered when hot and the filter cake washed with dry hot acetone. The combined filtrate and washings were rotary evaporated to leave a light brown crystalline substance. Light yellow crystalline solid. Yield 85 %. R_f 0.8. m.p 42°C; IR (neat) ύ (cm^{-1}); 1732 (ester C=O).

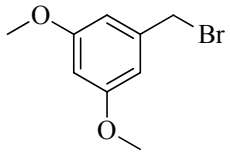
3,5-Dimethoxybenzyl alcohol



To a stirred suspension of lithium aluminum hydride (3.2g, 0.08 mol) in sodium dried tetrahydrofuran (50 ml) was added, at such a rate to maintain a gentle reflux a solution of Methyl 3,5-Dimethoxybenzoate (15g, 0.7 mol) in dry tetrahydrofuran (30 ml). The reaction mixture was refluxed for 3h and then stirred overnight, ethyl acetate was added cautiously after the completion of reaction. The reaction mixture was poured onto ice, acidified with aqueous acid and extracted with ethyl acetate (2x75ml). The extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was rotary evaporated to leave oil which solidified on standing. Recrystallization with petroleum ether afforded 3,5-Dimethoxy benzyl alcohol. White crystalline solid. Yield 70%. R_f 0.3. m.p 43-45°C; IR(neat) ύ (cm^{-1}); 3550 (alcoholic OH), ^1H NMR ($CDCl_3$, δ ppm); 3.06 (1H, s, -OH), 3.7 (6H, s, -OMe), 4.45 (2H, s, $-CH_2$), 6.48 (2H, d, *J*=

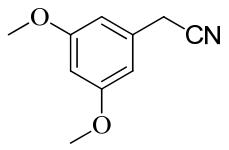
2.1 Hz, Ar-H), 6.35 (1H, t, *J*= 2.4 Hz, Ar-H), ^{13}C NMR ($CDCl_3$, δ ppm); 65 ($-CH_2$), 55 (-OMe), 99-160 (Ar-C).

3,5-Dimethoxybenzyl bromide



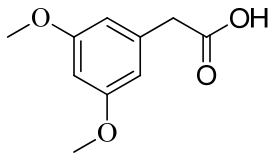
3,5-Dimethoxybenzyl alcohol (11.0g, 0.059 mol) was stirred with phosphorous tribromide (8 ml, 0.06 mol) in dry benzene (75 ml) for 4h. The reaction mixture was poured onto ice, organic layer was separated, washed with aqueous sodium carbonate (10%) then with water and finally dried over anhydrous sodium sulfate. Removal of solvent gives solid 3,5-Dimethoxybenzyl bromide. Light yellow solid. Yield 70%. R_f 0.65. m.p 68-69°C. IR(neat) ύ (cm^{-1}) ; 855 (C-Br) ,^{1}H NMR ($CDCl_3$, δ ppm); 3.8 (6H, s, -OMe) ,4.45 (2H, s, $-CH_2$) ,6.56 (2H, d, *J*= 2.1 Hz, Ar-H), 6.41 (1H, t, *J*= 2.4 Hz, Ar-H), ^{13}C NMR ($CDCl_3$, δ ppm); 33.7 ($-CH_2$) ,55 (-OMe) ,100-160 (Ar-C).

3,5-Dimethoxybenzyl cyanide



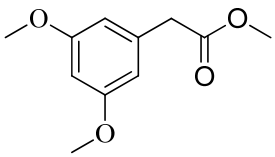
3,5-Dimethoxybenzyl bromide (10g, 0.045 mol) was refluxed with potassium cyannide (4.5g, 0.05 mol) in ethanol (45ml) and water (60ml) for 6h. After completion, the reaction mixture was poured onto ice cold water and extracted with ethyl acetate (2x50ml).The extract was dried over anhydrous sodium sulfate, evaporated to afford the 3,5-Dimethoxybenzyl cyanide as prisms. Light yellow solid. Yield 75%. R_f 0.55. m.p 48-49°C. IR(neat) ύ (cm^{-1}); 2268 (CN).

3,5-Dimethoxyphenyl acetic acid



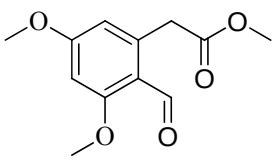
3,5-Dimethoxybenzyl cyanide (10g, 0.0084 mol) was dissolved in ethanol and refluxed with 100ml solution of 20% NaOH for 48h. The reaction mixture was poured onto ice cold water and acidified with dilute acid until pH became to 7 and then extracted with ethyl acetate (3x45ml). The organic solvent was evaporated to afford 3,5-Dimethoxyphenyl acetic acid as crystalline substance. White solid. Yield 70%. R_f 0.2. m.p 101-102°C. IR(neat) ύ (cm^{-1}); 1722 (C=O acid), 3290 (-OH).

Methyl 2-(3,5-dimethoxyphenyl)acetate



3,5-Dimethoxyphenyl acetic acid (10.0g, 0.05 mol) was refluxed in methanol (150 ml) with few drops of conc.H_2SO_4 as a catalyst for 8-10h. After completion of reaction the reaction mixture was concentrated to 50ml and then extracted with ethyl acetate. The extract was washed with saturated brine and then dried over anhydrous Na_2SO_4. Solvent was evaporated to give Methyl 2-(3,5-dimethoxyphenyl)acetate as viscous oil. White solid. Yield 88%. R_f 0.75. m.p 46-48°C. IR(neat) ύ (cm^{-1}); 1722 (C=O ester).

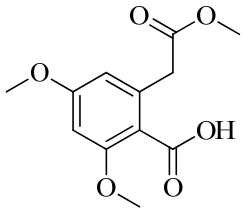
Methyl 2-(2-formyl-3,5-dimethoxyphenyl)acetate



Distilled phosphorous oxychloride (7ml, 0.058 mol) was added drop wise into a stirred solution of Methyl 2-(3,5-dimethoxyphenyl)acetate in dry DMF (9ml) at 55°C. The temperature

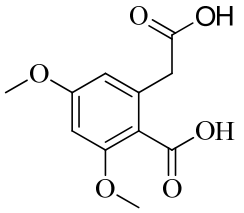
was then increased from 55°C to 100°C for 2.5h and stirred overnight at room temperature. Then reaction mixture was poured cautiously into aqueous solution of sodium acetate (8 %) and Methyl 2-(2-formyl-3,5-dimethoxyphenyl)acetate was precipitated out. White crystalline solid. Yield. 70%; R_f 0.58. m.p 98-99°C. IR(neat) ύ (cm^{-1}); 1722 (C=O ester), 1718 (C=O formyl gp.), ^1H NMR ($CDCl_3$, δ ppm); 10.4 (1H, s, -CHO) 3.7 (6H, s, -OMe), 3.90 (3H, s, ester-OMe), 3.94 (2H, s, $-CH_2$), 6.33 (1H, s, Ar-H), 6.44 (1H, s, Ar-H), ^{13}C NMR ($CDCl_3$, δ ppm); 190 (aldehyde C=O), 171.59 (ester C=O), 55.85 ($-CH_2$), 40-51(-OMe) 55.56 (ester-OMe), 97-165 (Ar-C).

2,4-Dimethoxy-6-(2-methoxy-2-oxoethyl)benzoic acid



Methyl 2-(2-formyl-3,5-dimethoxyphenyl)acetate (5g, 0.0052 mol) was dissolved in acetone (30 ml) and then was stirred with acidic $KMnO_4$ at 0°C for 30 minutes. The reaction mixture was then stirred over night at room temperature. After completion of reaction, it was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to leave 2,4-Dimethoxy-6-(2-methoxy-2-oxoethyl)benzoic acid. yellow solid. Yield. 78%. R_f 0.2. m.p 120-122°C. IR(neat) ύ (cm^{-1}); 1720 (C=O ester), 1695 (C=O acid),3320 (-OH acid).

3,5-Dimethoxyhomopthalic acid

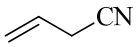


2,4-Dimethoxy-6-(2-methoxy-2-oxoethyl)benzoic acid (4g, 0.0045 mol) was dissolved in ethanol (50 ml). Then it was refluxed with 5% NaOH (50ml) for 3h and the ethanol was rotary

evaporated. The aqoues layer was acidified with dilute hydrochloric acid and the light yellow precipitates of 3,5-Dimethoxyhomothalic acid were filtered out. White crystalline solid.[54] Yield.70%. R_f 0.12. m.p 174-176°C. IR(neat) ύ (cm^{-1}); 1700 (C=O acid), 3286 (-OH acid) ^1H NMR ($CDCl_3$, δ ppm); 12.5 (2H, s, -OH), 3.7 (6H, s, -OMe), 3.5 (2H, s, $-CH_2$), 6.5 (1H, s, Ar-H), 6.443 (1H, s, Ar-H).

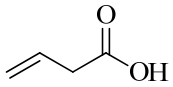
2.2.2 Synthesis of (±)- 3,4-Dibromobutanoyl chloride (5f)

Allyl Cyanide



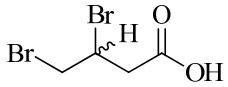
Allyl bromide (10ml, 0.05 mol) was dissolved in ethanol (55 ml) and then was refluxed with sodium cyanide (3.5g 0.055 mol) in water (100 ml).The solvent was rotary evaporated then it was extracted with ethyl acetate (2x 50ml). The organic layer was dried over anhydrous sodium sulphate and then was rotary evaporated to leave yellow oil. Yield 70%. R_f 0.65. IR(neat) ύ (cm^{-1}); 2275 (CN).

3-Butenoic Acid



Allyl cyanide (7ml, 0.003 mol) was dissolved in ethanol and was refluxed with 10% NaOH for 10 hrs. After the completion of reaction the dilute HCl was added in reaction mixture. The product was extracted with ethyl acetate and the organic layer was rotary evaporated to leave a yellow oil of 3-butenoic acid. Yield 70%. R_f 0.35. IR (neat) ύ (cm^{-1}); 1722(C=O acid), 3254 (-OH).

(±)-3,4-Dibromobutanoic acid

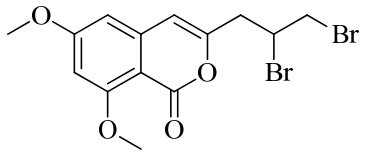


3-Butenoic acid (6 ml, 0.0025 mol) was refluxed in dry CCl_4 (35 ml) and bromine (4.5 ml) was added drop wise. The reaction mixture was rotary evaporated and then was extracted

with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and then was rotary evaporated to yield (±)-3,4-Dibromobutanoic acid. Viscous brown oil. Yield 72%. R_f 0.35. IR (neat) ύ (cm^{-1}); 1722 (C=O acid), 875 (-Br).

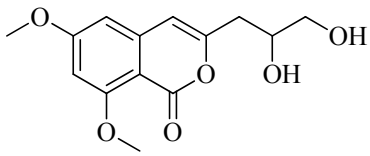
2.2.3 Condensation of 5f & 10

3-(2,3-Dibromopropyl)-6,8-dimethoxy-1H-isochromen-1-one



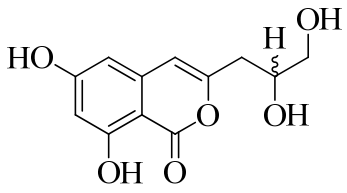
3,5-Dimethoxyhomothalic acid (1.9g, 0.0012 mol) and (±)-3,4-Dibromobutanoyl chloride (which itself prepared by refluxing 3,4-dibromobutanoic acid thionyl chloride) were heated at 200 ˚C for 4-5 h. After completion of reaction it was allowed to cool down. The reaction mixture was dissolved into ethyl acetate and 3-(2,3-Dibromopropyl)-6,8-dimethoxy-1H-isochromen-1-one was purified by preparative thin layer chromatography using petroleum ether and ethyl acetate (2:1) as a mobile phases. Brown solid. Yield 65%. R_f 0.32. m.p 118-120˚C. IR(neat) ύ (cm^{-1}); 1724 (C=O ester), 3126 (C=C-H), 835 (C-Br).

3-(2,3-Dihydroxypropyl)-6,8-dimethoxyisocoumarin



3-(2,3-Dibromopropyl)-6,8-dimethoxyisocoumarin (0.18g, 0.00032 mol) was refluxed with acetone and water mixture (1:5) for 3h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 5% sodium bicarbonate and then dried over anhydrous sodium sulfate. The organic layer was rotary evaporated to leave yellowish colored semisolid which was recrystallized by methanol. Light yellow solid. Yield 70%. R_f 0.22. m.p 130-133˚C. IR(neat) ύ (cm^{-1}); 1722 (C=O ester), 3145 (C=C-H), ^{1}H NMR ($CDCl_3$, δ ppm); 6.57 (1H, s, C=C-H), 3.95 (6H, s, -OMe), 4.39 (3H, m, - $\underline{CH_2}$-OH, $\underline{H}$-Carbinol carbon), 3.6 (2H, s, -OH), 1.9,2.0 (2H,dd, $^{1\text{-}2}J$= 9Hz, $^{1\text{-}3}J$= 12Hz-CH_2), 6.6-7.30 (2H, Ar-H).

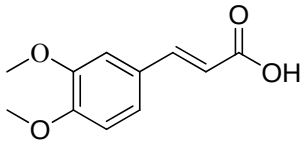
Desmethyldiaportinol



3-(2,3-Dihydroxypropyl)-6,8-dimethoxyisocoumarin (0.1g, 0.000034 mol) was refluxed with 33% HBr in glacial acetic acid (6 ml) for 2hr. The reaction mixture was poured into ice 50g and then solid sodium carbonate was added to attain pH 6.The compound was extracted with ethyl acetate and solvent was evaporated to afford Desmethyldiaportinol. Yellowish solid. Yield 70%. R_f 0.22. m.p 178°C. IR(neat) ύ (cm^{-1}); 1722 (C=O ester), 3145 (C=C-H), 3455 (-OH), ^{1}H NMR ($CDCl_3$, δ ppm); 6.57 (1H, s, C=C-H), 3.95 (6H, s, -OMe), 4.39 (3H, m, - $\underline{CH_2}$-OH, $\underline{H}$-Carbinol carbon), 3.6 (2H, s, -OH), 5.2 (2-OH-Ar), 1.9,2.0 (2H,dd, ^{1-2}J= 9Hz, ^{1-3}J= 12Hz-CH_2), 6.6-7.30 (2H, Ar-H).

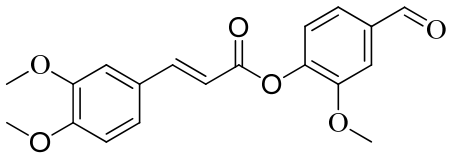
2.3 Total synthesis of Trilipisumic acid

3,4-Dimethoxycinnamic acid



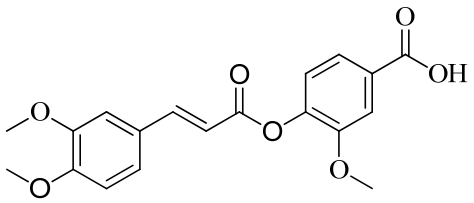
3,4-Dimethoxybenzaldehyde (5g, 0.02 mol) was refluxed with Malonic acid (8g, 0.06 mol) in pyridine (50ml) and few drops of pirolidine as a catalyst for 18-20h. The reaction mixture was acidified with dilute hydrochloric acid to attain pH 7. The precipitates of 3,4-Dimethoxycinnamic acid were settled down and were filtered. The precipitates were washed with cold water and then were dried. Light yellow solid. Yield 85%. R_f 0.22. m.p 130-133°C. IR(neat) ύ (cm^{-1}); 1650 (C=O acid), ^{1}H NMR (DMSO, δ ppm); 3.7-3.8 (6H, s, -OMe), 12.2 (1H, s, acid), 6.4 (1H, d, *J*=15.9Hz, α-H), 7.52 (1H, d, *J*= 15.9Hz, β-H), 6.9-7.31 (3H, m, Ar-H), ^{13}C NMR (DMSO, δ ppm); 168.3 (C=O acid), 55.97-56.01(-OMe), 110.66 (α-C) 151.2 (β -C), 111.9-151.2(Ar-C).

(E)-4-Formyl-2-methoxyphenyl 3-(3,4-dimethoxyphenyl)acrylate



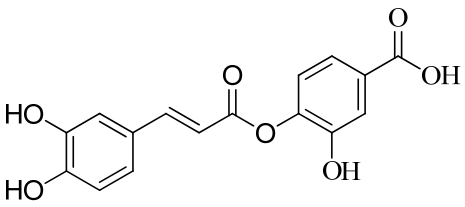
3,4-Dimethoxycinnamic acid (4.5g, 0.012 mol) was refluxed with $SOCl_2$ (8 ml) in dry benzene for 8h. The solvent was rotary evaporated to afford viscous yellow oil of 3,4-Dimethoxycinnamoyl chloride. Then this acid chloride was treated with vanillin (3.5g, 0.012 mol) using triethyl amine (5ml) in THF at room temperature for 12h. Then the reaction mixture was poured into ice cold water and precipitates were appeared after 30 minutes and filtered out. These precipitates were washed with 5% HCl and then with ice cold water to afford (E)-4-Formyl-2-methoxyphenyl 3-(3,4-dimethoxyphenyl)acrylate. White solid. Yield 75% R_f 0.89. m.p 130-133°C. IR(neat) ύ (cm^{-1}); 1710 (C=O ester), 1725 (C=O acid), ^{1}H NMR (DMSO, δ ppm); 3.9 (9H, s, -OMe), 9.98 (1H, s,-CHO), 6.5 (1H, d, *J*= 15.9Hz, α-H), 7.86 (1H, d, *J*=15.9Hz, β -H), 6.9-7.55 (6H, m, Ar-H), ^{13}C NMR (DMSO, δ ppm); 191 (C=O aldehyde), 164 (C=O ester), 55.91-56.14 (-OMe), 109.62 (α-C), 152.14 (β -C), 109.76-151.95 (Ar-C).

(E)-4-((3-(3,4-Dimethoxyphenyl)acryloyl)oxy)-3-methoxybenzoic acid



(E)-4-Formyl-2-methoxyphenyl 3-(3,4-dimethoxyphenyl)acrylate was dissolved in acetone (3g, 0.054 mol) and then was stirred with acidic $KMnO_4$ at 0°C for 30 minutes. The reaction mixture was then stirred over night at room temperature. Then was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to leave (E)-4-((3-(3,4-Dimethoxyphenyl)acryloyl)oxy)-3-methoxybenzoic acid as white solid. White solid. Yield 75%. R_f 0.42. m.p 130-133°C. IR(neat) ύ (cm^{-1}); 1710 (C=O ester), 1720 (C=O acid); ^{1}H NMR (DMSO, δ ppm); 3.9 (9H, s, -OMe), 12.95 (1H, s,-COOH) ,6.8 (1H, d, *J* =15.9Hz, α-H), 7.76 (1H, d, *J* =15.9Hz, β -H), 7.0-7.63 (6H, m, Ar-H).

Trilepisumic acid



(E)-4-((3-(3,4-Dimethoxyphenyl)acryloyl)oxy)-3-methoxybenzoic acid (1.2g, 0.000034 mol) was refluxed with 33% HBr in glacial acetic acid (6 ml) for 2hr. The reaction mixture was poured into ice 50g and then solid sodium carbonate was added to attain pH 6.The compound was extracted with ethyl acetate and solvent was evaporated to afford (E)-4-((3-(3,4-Dihydroxyphenyl)acryloyl)oxy)-3-hydroxybenzoic acid as colorless crystalline solid. Silvery solid. Yield 75%. R_f 0.22. m.p 130-133°C. IR(neat) ύ (cm^{-1}); 1712 (C=O ester), 1725 (C=O acid), 3450 (-OH), ^{1}H NMR (DMSO, δ ppm); ^{1}H NMR (DMSO, δ ppm); 5.35 (3H, s, -OH), 12.95 (1H, s,-COOH), 6.8 (1H, d, *J*= 15.9Hz, α-H), 7.76 (1H, d, *J*= 15.9Hz, β -H), 7.0-7.63 (6H, m, Ar-H).

Chapter-3

Results and Discussion

Total syntheses of naturally occurring isocoumarin (±)-Desmethyldiaportinol and naturally occurring Trilepisumic acid have been carried out.

3.1 Total synthesis of (±)-Desmethyldiaportinol

Its synthesis was accomplished in three parts,

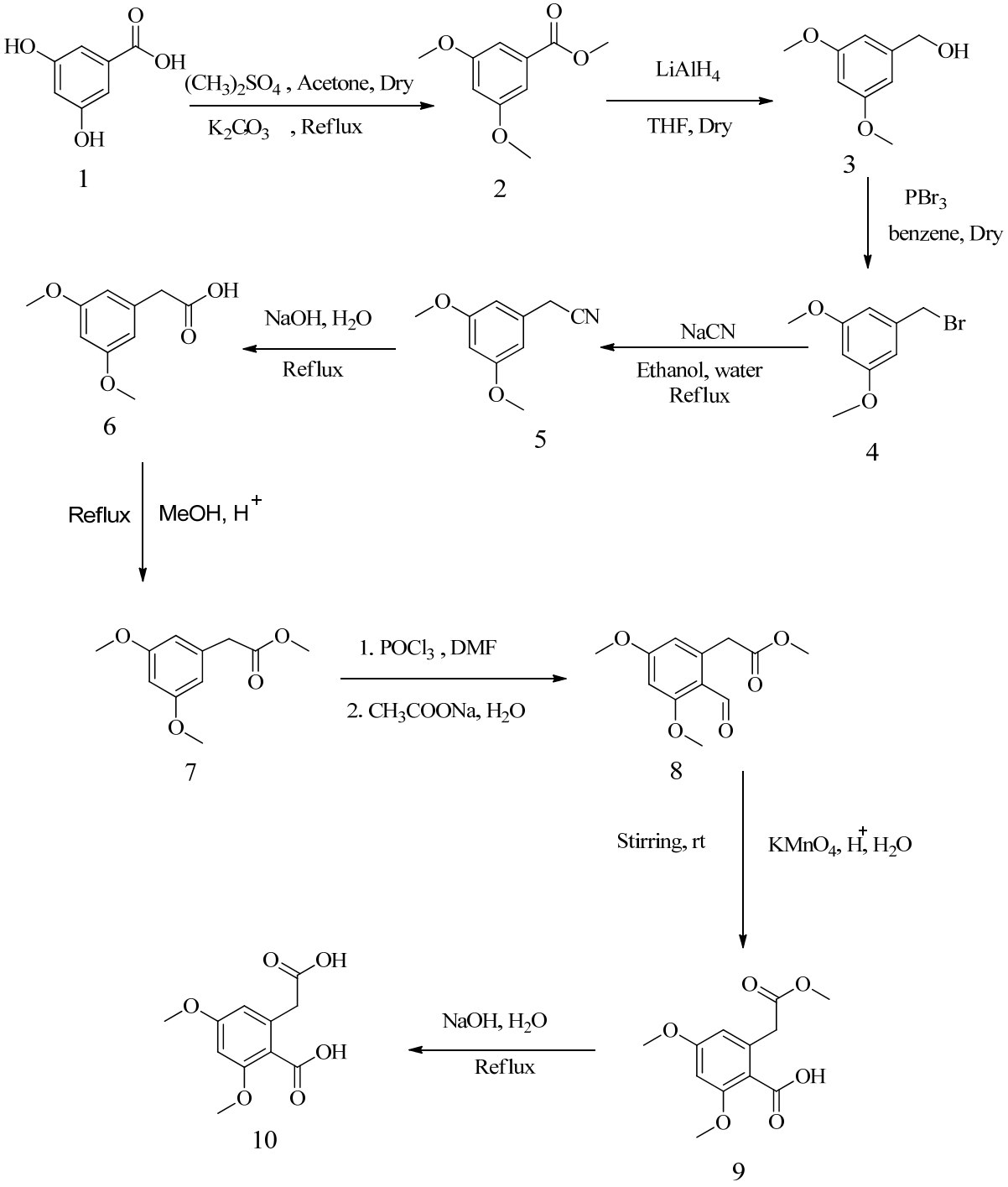
a) Synthesis of 3,5-dimethoxyhomopthalic acid

b) Synthesis of (±)-3,4-dibromobutanoyl chloride

c) Condensation of 5f &10.

a) Synthesis of 3,5-dimethoxyhomopthalic acid

Commercially available 3,5-Dihydroxybenzoic acid was converted into 3,5-Dimethoxymethylbenzoate by treating with dimethylsulfate in dry acetone and anhydrous potassium carbonate was used as a mild base. It showed a characteristic (C=O) stretching absorption in FTIR spectrum at 1732 cm^{-1}. The methyl ester was then reduced by lithium aluminum hydride in dry THF to yield 3,5-dimethoxybenzyl alcohol. The signal in ^{1}H NMR spectrum at 3.06 ppm was confirmed the presence of proton of hydroxyl group.


HO
OH
O
OH
1
(CH3)2SO4 , Acetone, Dry
K2CO3 , Reflux
2
LiAlH4
THF, Dry
3
PBr3
benzene, Dry
4
NaCN
Ethanol, water
Reflux
5
NaOH, H2O
Reflux
6
Reflux
MeOH, H+
7
1. POCl3 , DMF
2. CH3COONa, H2O
8
Stirring, rt
KMnO4, H+, H2O
9
NaOH, H2O
Reflux
10

Scheme 3.1

3,5-Dimethoxybenzyl alcohol was treated with phosphorous tribromide in dry benzene at room temperature to yield 3,5-Dimethoxybenzyl bromide. In ^{1}H NMR spectrum the absence of broad signal at 3.06 ppm confirms the conversion of alcohol into bromide. The benzyl bromide (**4**) was treated with sodium cyanide in ethanol and water to yield 3,5-Dimethoxybenzyl cyanide. The reaction was a nucleophilic substitution in which bromide was replaced by a cyanide nucleophile. The vibrational stretching frequency at 2285 cm^{-1}confirms the presence of nitrile moiety. Then the cyanide group was hydrolyzed in basic medium to yield 3,5-dimethoxyphenyl acetic acid. It was a white crystalline solid having melting point 102-103°C. The basic hydrolysis was a slow process which accomplished in 70 hours. The IR showed a strong absorption at 1710 cm^{-1} for carbonyl and broad band at 3260 cm^{-1} for hydroxyl group of acid. The phenyl acetic acid (**6)** was then refluxed into methanol which act as a nucleophile and solvent and few drops of sulphuric acid were used as a catalyst to convert acid into corresponding methyl ester (**7**). In IR the absence of broad band of hydroxyl group confirms the functional group interconversion. Then this nucleus was formylated by using $POCl_3$ and DMF. Actually the $POCl_3$ and DMF generates a reactive intermediate which is called chloroiminium ion and also known as Vilsmeier Haack reagent that´ s why the reaction is also called Vilsmeier Haack reaction. The compound **(8**) was a crystalline solid having melting point 98-100 °C. In ^{1}H NMR spectrum the signal at 10.42 ppm confirms the functional group addition. The formyl moiety was oxidized into acid by treating with $KMnO_4$ .The reaction was catalyzed by slow addition of few drops of acids which increase the electrophilic character of formyl group. The compound (**9**) was also obtained as a solid having melting point 130-133°C. Then the ester (**9**) was also hydrolyzed into acid to yield 3,5-Dimethoxyhomopthalic acid. Hydrolysis was also carried out in basic medium using 10% KOH in ethanol. In ^{1}H NMR spectrum the signal at 12.5 ppm confirms the presence of acidic protons.

Table 3.1: Physical data of all intermediates and Desmethyldiaportinol

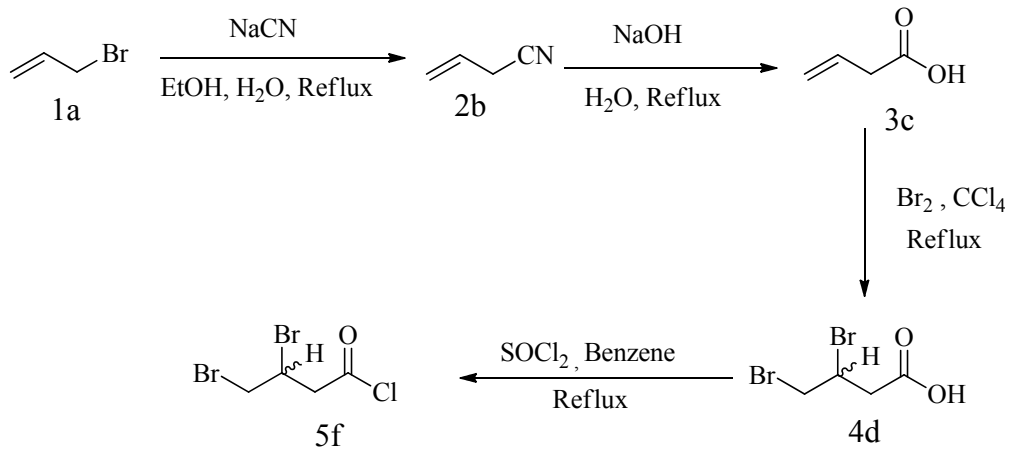
Comp#	Physical appearance	m.p. (°C) obs/(lit)[54]	R_f	Yield (%)
2	Light yellow Solid	42/(43-44)	0.8	85
3	White Solid	44-45/(46)	0.3	70
4	Yellow solid	68-69/(70)	0.65	75
5	White Solid	48-49/(49)	0.45	72
6	White Solid	103-102/(103)	0.2	68
7	Light yellow Solid	47-50	0.85	82
8	Pale yellow Solid	98-99	0.44	76
9	Pale yellow	120	0.2	78
10	White Solid	174-176	0.12	80
11	Brown Solid	118-120	0.35	65
12	Yellow Solid	130	0.25	79
13	Yellowish Solid	178	0.15	70

Mobile phase: pet ether: ethyl acetate (4:1)

b) Synthesis of (±)-3,4-Dibromobutanoyl chloride

Allyl bromide was converted into allyl cyanide by refluxing with aqueous sodium cyanide. It showed a characteristic (-CN) stretching absorption in FTIR spectrum at 2245 cm^{-1}.The compound was obtained as a yellow oil with garlic like smell. Then allyl cyanide was hydrolyzed in basic medium to yield 3-Butenoic acid. Hydrolysis in basic medium is a slow process. The vibrational stretching frequency at 3250 cm^{-1} confirms the presence of hydroxyl

group of acid. Then compound was refluxed in CCl_4 and addition of bromine was achieved by slow addition of bromine. Disappearance of dark red color of bromine was the indication of addition. In IR spectrum vibrational stretching frequency at 865 cm^{-1} confirms the presence C-Br bond.



Scheme 3.1 continued

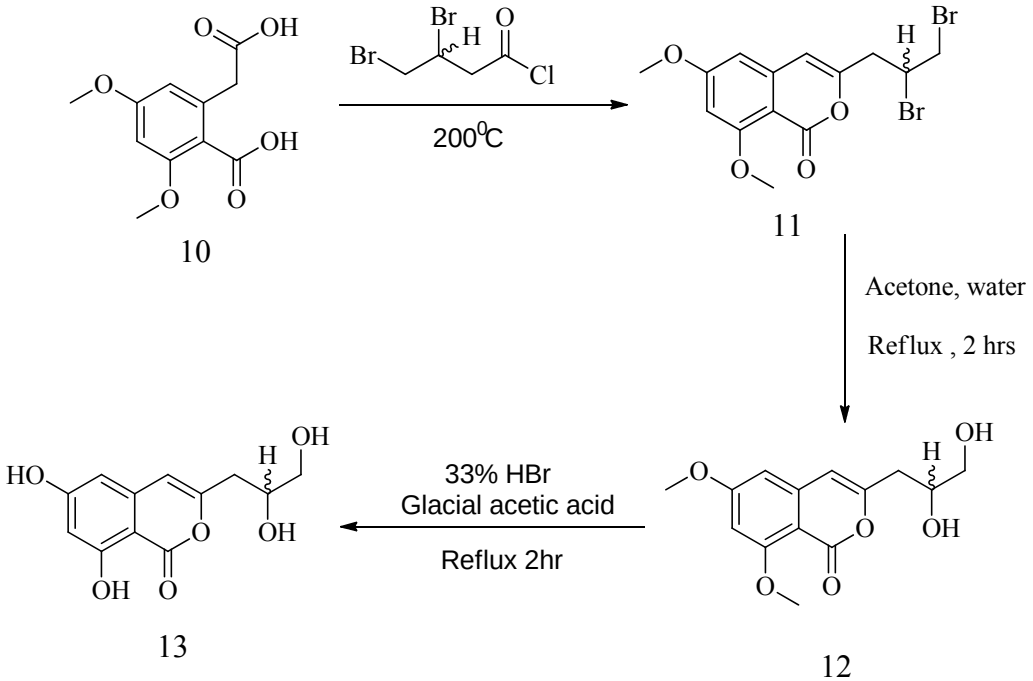
Table 3.2: FTIR spectral data of all intermediates and Desmethyldiaportinol

Comp#	ύ (cm^{-1})					
	(C=Oester)	**(C=Oacid)**	**CHO**	**-OH**	**-CN**	**-C-Br**
2	1735	-	-	-	-	-
3	-	-	-	3450	-	-
4	-	-	-	-	-	855
5	-	-	-	-	2245	-
6	-	1722	-	-	-	-
7	1732	-	-	-	-	-

8	1734	-	1718	-	-	-
9	-	1725	-	-	-	-
10	-	1720	-	-	-	-
11	-	-	-	-	-	875
12	-	-	-	3350	-	-
13	-	-	-	3455	-	-

3,4-Dibromobutenoic acid was then refluxed with thionyl chloride to yield 3,4-Dibromobutanoyl chloride as a viscous brown oil.

c) Condensation of 5f & 10.



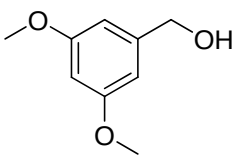
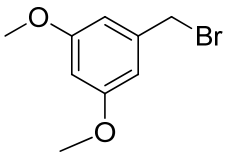
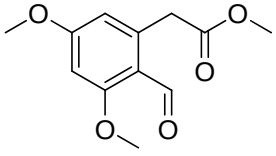
10 11 12 13

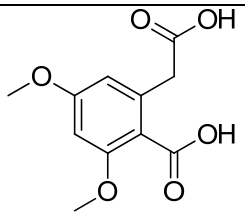
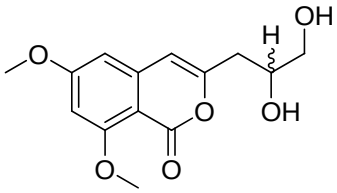
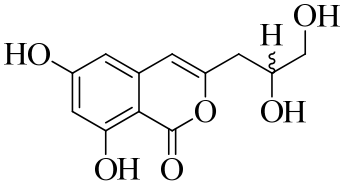
Scheme 3.1

Then this brown oil was condensed with 3,5-Dimethoxyhomopthalic acid to yield isocoumarin (**11**). The purity of the product was checked on TLC and there was a mixture of

products and our desired product was isolated by PTLC (Preparative Thin Layer Chromatography) with silica gel as a stationary phase and petroleum ether ethyl acetate in (2:1) ratio as a mobile phase. Isolated product was further purified by recrystallization in methanol. The IR showed a strong absorption at 1724 cm^{-1} for carbonyl, 3126 cm^{-1} for (C=C-H) and 1570 cm^{-1} for (C=C) moiety. The bromides groups were converted into hydroxyl groups by refluxing isocoumarin (**11**) into a mixture of acetone and water. In ^{1}H NMR spectrum the signal at 3.6 ppm confirms the presence of hydroxyl protons. For demethylation compound (**12**) was treated with 33% HBr in glacial acetic acid and ^{1}H NMR spectrum confirms the presence of broad signal for hydroxyl group at 5.2 ppm.

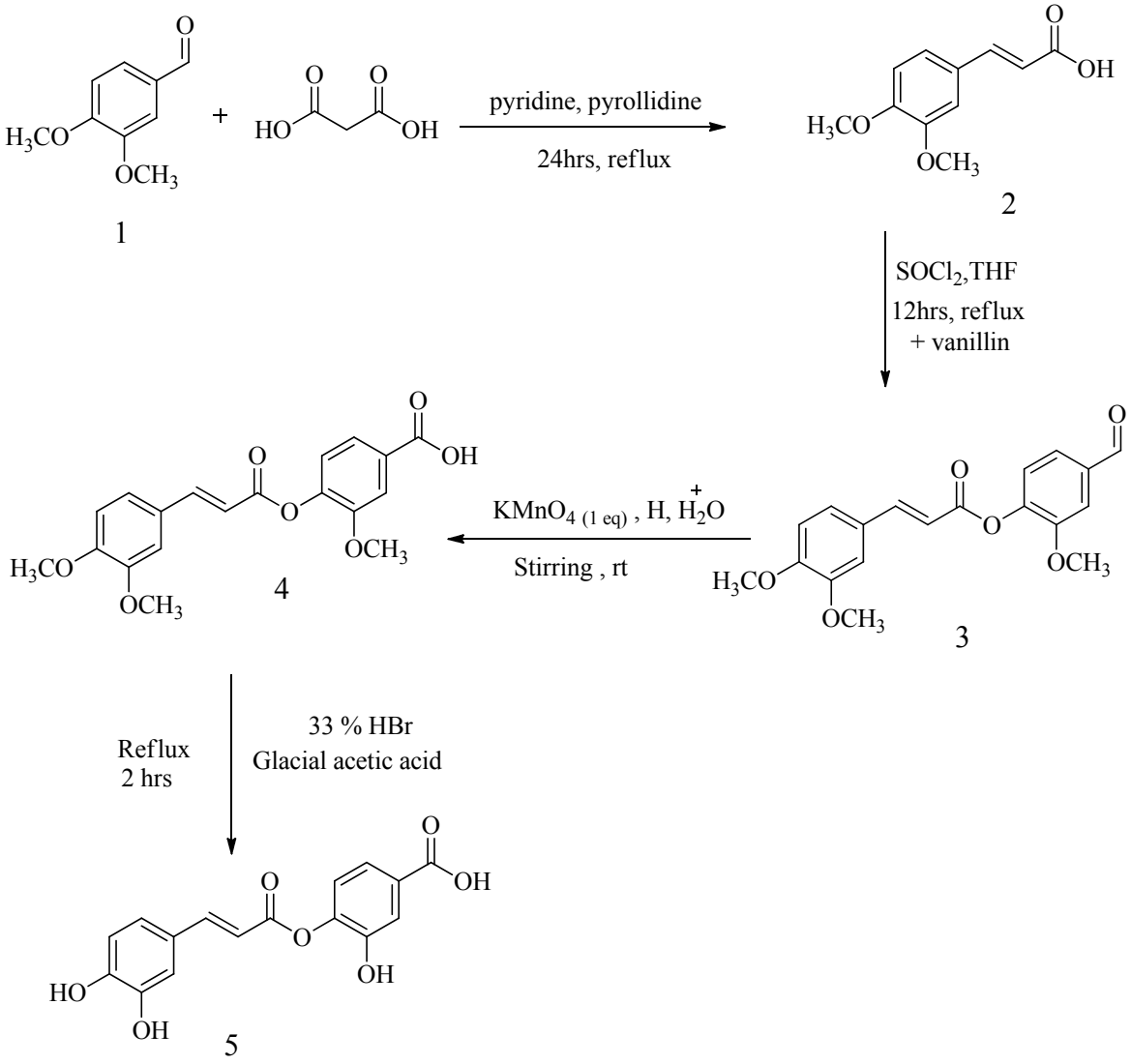
Table 3.3: ^{1}H and ^{13}C NMR spectral data of intermediates and Desmethyldiaportinol

Comp#	Structures	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
3		3.06 (1H, s, -OH), 3.7 (6H, s, -OMe), 4.45 (2H, s, $-CH_2$), 6.48 (2H, d, *J*= 2.1 Hz, Ar-H), 6.35 (1H, t, *J*= 2.4 Hz, Ar-H),	65 ($-CH_2$), 55 (-OMe), 99-160 (Ar-C).
4		3.8 (6H, s, -OMe), 4.45 (2H, s, $-CH_2$), 6.56 (2H, d, *J*= 2.1 Hz, Ar-H), 6.41 (1H, t, *J*=2.4 Hz, Ar-H),	33.7 ($-CH_2$), 55 (-OMe), 100-160 (Ar-C).
8		10.4 (1H, s, -CHO), 3.7 (6H, s, -OMe), 3.90 (3H, s, ester-OMe), 3.94 (2H, s, $-CH_2$), 6.33 (1H, s, Ar-H), 6.44 (1H, s, Ar-H),	190 (aldehyde C=O), 171.59 (ester C=O), 55.85 ($-CH_2$), 40-51(-OMe) 55.56 (ester-OMe), 97-165 (Ar-C).

10		12.5 (2H, s, -OH), 3.7 (6H, s, -OMe), 3.5 (2H, s, -CH_2), 6.5 (1H, s, Ar-H), 6.443 (1H, s, Ar-H).	-
12		6.57 (1H, s, C=C-H), 3.95 (6H, s, -OMe), 4.39 (3H, m, - $\underline{CH_2}$-OH, $\underline{H}$-Carbinol carbon), 3.6 (2H, s, -OH), 1.9,2.0 (2H,dd,2H,dd,$^{1\text{-}2}J$= 9Hz, $^{1\text{-}3}J$= 12Hz-CH_2 -CH_2), 6.6-7.30 (2H, Ar-H).	-
13		6.57 (1H, s, C=C-H), 3.95 (6H, s, -OMe), 4.39 (3H, m, - $\underline{CH_2}$-OH, $\underline{H}$-Carbinol carbon), 3.6 (2H, s, -OH), 5.2 (2-OH-Ar) 1.9,2.0 (2H,dd,2H,dd,$^{1\text{-}2}J$= 9Hz, $^{1\text{-}3}J$= 12Hz-CH_2 -CH_2), 6.6-7.30 (2H, Ar-H).	-

3.2 Total synthesis of Trilepisumic acid

It was synthesized starting from 3,4-Dimethoxybenzaldehyde. This benzaldehyde was condensed with malonic acid in pyridine and pyrollidine was used as a catalyst at 200 °C. The condensation called Dobner condensation which is a modification of Knovenogel condensation. In Knovenogel condensation one of the reactant used is diethylmalonate which after the coupling with benzaldehyde hydrolysed into acid and then decarboxylation takes place to give cinnamic acid while Dobner condensation has a short route with providing efficient yield. The product was a white crystalline solid having m.p 182-184°C. In ^{1}H NMR spectrum the signal at 12.25 ppm confirms the presence of acidic protons and signal at 6.4 ppm as a doublet with *J*=15.9Hz was and signal at 7.52 ppm as a doublet with *J* =15.9Hz was assigned to alpha and beta protons respectively.



The cinnamic acid (**2**) was refluxed in thionyl chloride with few drops of DMF as a catalyst to yield acid chloride. The acid chloride was treated with 4-Hydroxy-3-methoxybenzaldehyde (vanillin) to yield the ester of 3,4-Dimethoxycinnamic acid. The ^{1}H NMR spectrum confirms the presense of aldehydic proton at 9.98 ppm and absence of acidic proton. ^{13}C NMR spectrum also confirms the presence of carbonyl carbon of aldehyde and ester at 191 ppm and 164 ppm respectively. The product was a white crystalline solid having m.p. 99-102°C.

Table 3.4: Physical data of intermediates and Trilipesumic acid

Comp#	Physical appearance	m.p. (°C)	R_f	Yield (%)
2	White Solid	181-182	0.8	85
3	White Solid	128	0.3	70
4	White Solid	152	0.65	75
5	White Solid	160	0.45	72

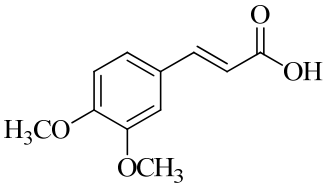
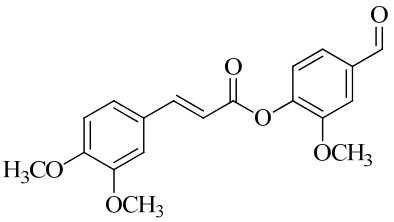
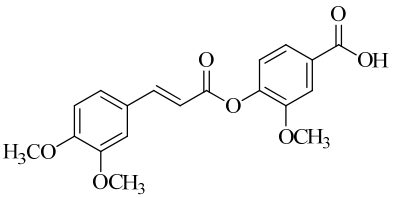
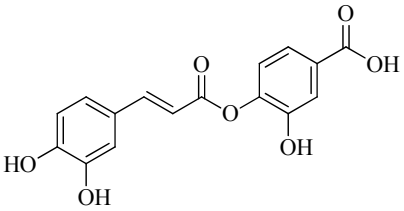
Mobile phase: Chloroform: Methanol (9:1)

The vibrational stretching frequency of carbonyl group of ester was 1708 cm^{-1} which is less than the normal range this is due to the extended conjugation. The formyl group was oxidized into acid by treating with one equivalent of $KMnO_4$ in acidic medium. The reaction was carried out at room temperature. The acid was used to increase the electrophilic character of formyl group. The product was also a white crystalline solid having m.p 130-133°C and solubility was in DMSO. ^1H NMR spectrum confirms the presence of acidic proton at 12.95 ppm. The compound (**4**) was demethylated by refluxing in 33% HBr in Glacial acetic to yield the Trilepisumic acid. HBr is a very harsh reagent for demethylation. In IR spectrum the presence of strong band at 3450 cm^{-1} confirms the presence of hydroxyl groups. The compound was a silvery solid with m.p at 180°C.

Table 3.5: FTIR spectral data of intermediates and Trilipesumic acid

Comp#	ύ (cm^{-1})			
	(C=O ester)	**(C=O acid)**	**CHO**	**-OH**
2	-	1650	-	-
3	1710	-	1725	-
4	-	1720	-	-
5	-	1722	-	3490

Table 3.6: ^{1}H and ^{13}C NMR spectral data of intermediates and Trilipesumic acid

Comp#	Structures	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
2		3.7-3.8 (6H, s, -OMe), 12.2 (1H, s, -COOH), 6.4 (1H, d, *J*= 15.9Hz, α-H), 7.52 (1H, d, *J*=15.9Hz, β -H), 6.9-7.31 (3H, m, Ar-H),	168.3 (C=O acid), 55.97-56.01 (-OMe), 110.66 (α-C), 151.2 (β -C), 111.9-151.2 (Ar-C).
3		3.9 (9H, s, -OMe), 9.98 (1H, s,-CHO), 6.5 (1H, d, *J*= 15.9Hz, α-H), 7.86 (1H, d, *J*= 15.9Hz, β -H), 6.9-7.55 (6H, m, Ar-H).	191 (C=O aldehyde), 164 (C=O ester), 55.91-56.14 (-OMe), 109.62 (α-C), 152.14 (β -C), 109.76-151.95 (Ar-C).
4		3.9 (9H, s, -OMe), 12.95 (1H, s, -COOH), 6.8 (1H, d, *J*= 15.9Hz, α-H), 7.76 (1H, d, *J* = 15.9Hz, β -H), 7.0-7.63 (6H, m, Ar-H).	-
5		5.35 (3H, s, -OH), 12.95 (1H, s,-COOH), 6.8 (1H, d, *J*= 15.9Hz, α-H), 7.76 (1H, d, *J*= 15.9Hz, β -H), 7.0-7.63 (6H, m, Ar-H).	-

Conclusion

Total synthesis of Desmethyldiaportinol and Trilepisumic acid have been carried out successfully for first time.

Synthesis of Desmethyldiaportinol was carried out in 17 steps and synthesis of Trilepisumic acid was carried out in 4 steps.

All the compounds were characterized by FTIR, ^{1}HNMR and ^{13}CNMR spectroscopy.

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