The thesis entitled **"STEREOSELECTIVE TOTAL SYNTHESIS OF FUNGAL METABOLITE HERBARUMIN-I, PLANT NATURAL PRODUCT LEIOCARPIN A AND DEVELOPMENT OF SYNTHETIC METHODOLOGIES"** is divided into three chapters.

Chapter I: Describes stereo chemical total synthesis fungal metabolite of Herbarumin-I by using L-Ascorbic acid involving the barbier type reaction, swern oxidation, grigard reaction, and macrocyclization reactions.

Chapter II: Divided into two sections *i.e* Section A and Section B.

Section A: Deal the stereoselective synthesis of leiocarpin A by using D-mannitol involving barbier type reaction, grigard reaction, ring closing metethesis, oxamicheal addition reactions.

Section B: Deals the phospomolybdicacid-catalyzed synthesis of tetrhydro pyrano and furano quinolines.

Chapter III: Divided into two sections *i.e* Section A and Section B

Section A: Deals with ring opening of epoxide with amines with $NbCl_5$ as a Lewis acid.

Section B: Deals the Niobium (V) chloride catalyzed tetrahydropyranylation of alcohols.

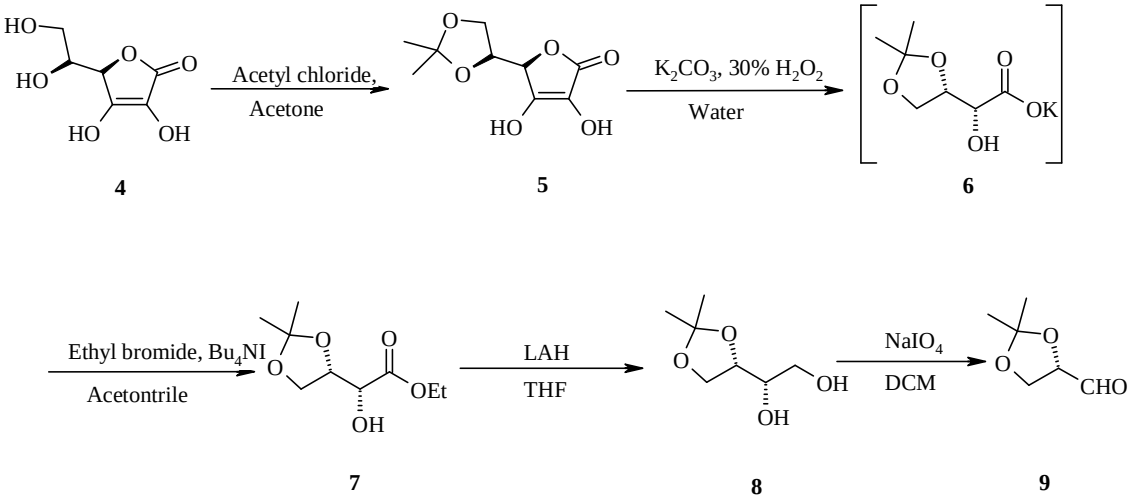
Chapter I:

Stereoselective total synthesis of fungal metabolite Herbarumin I a ten membered lactone:

Bioassay guided fractionation of a culture broth and mycelium of the fungus *Phoma herbarum* Westend (Sphaeropsidaceae) led to the discovery of three novel nonenolides named herbarumin-I (**1**), II (**2**) and III (**3**) (**Figure 1**) These lactones

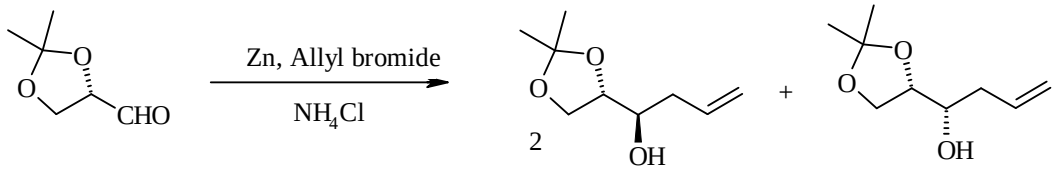
exhibited significant phytotoxic effects when tested against the seedlings of Amaranthus hypochondriacus at very low concentrations using a Petri dish bioassay. Amongst these lactones herbarumin-I (**1**) shows promising phytotoxic effects with IC_{50} values as low as 5.43 X 10^{-5}. Enzyme-inhibition studies of compounds **1–3** also suggested an interesting behaviour superior to chlorpromazine, as calmodulin-dependent enzyme cyclic nucleotide (cAMP) phosphodiesterase calmodulin inhibitors without interfering with the basal activity or the independent form of the enzyme.

In our strategy, the synthesis of the Herbarumin I started with readily available L-ascorbic acid (**4**), which converted into (*S*)- 2,3-*O*-isopropylidene glyceraldehyde **9** by known procedures in the literature (scheme1).



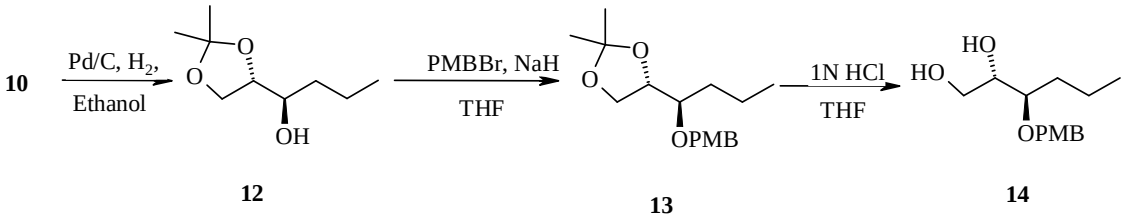
Scheme 1

The treatment of (*S*)- 2,3-*O*-isopropylidene glyceraldehyde with allyl bromide, activated Zn and sat. NH_4Cl, which give mixture of homo allylic alcohol **10** and **11** in the ratio 95:5 (anti:syn) (scheme 2).



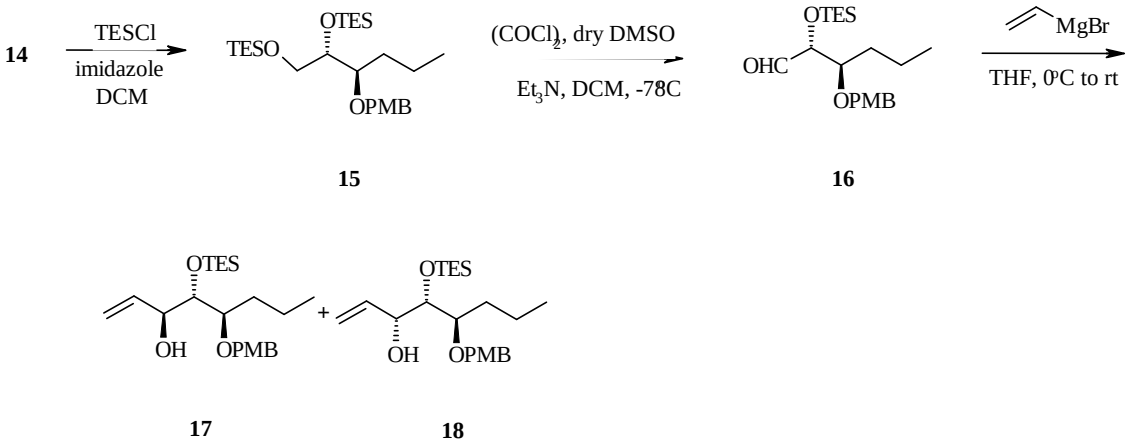
Scheme 2

The required anti isomer **10** was reduced with PD/C and hydrogen gas followed by alcohol **12** was protected with 4-methoxy benyl bromide in presence of NaH at 0 ^{o}C to rt for 4h afforded compound **13,** then the acetonide group was deprotected in presence of 1N HCl in THF at room temperature provided diol **14** (scheme 3).



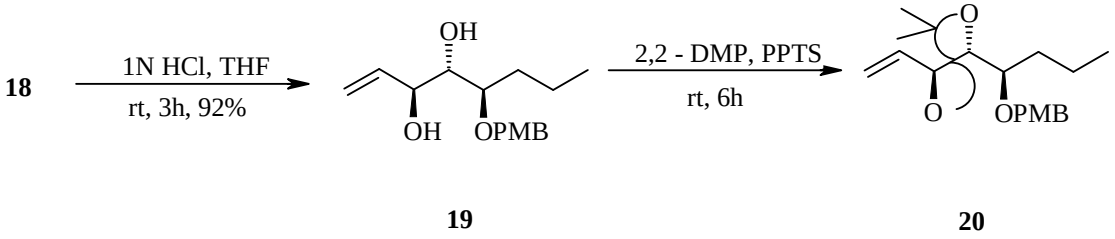
Scheme 3

Thus the diol **14** was protected with as TES ether by using TESCl, in the presence of imidazol, in DCM afforded TES ether compound **15**. The compound **15** was oxidized under swern conditions furnished aldehyde **16,** via domino deprotection of the primary O-TES group and subsequent oxidation of the primary alcohol to aldehyde moved for next step without further purification it was subjected to vinylation reaction with vinyl magnesium bromide, which was *insitu* generation of grignard reagent by activated magnesium turnings and vinyl bromide in THF at room temperature afforded to the corresponding allylic alcohols as mixture of **17** and **18** *anti : syn* (9 : 1).



Scheme 4

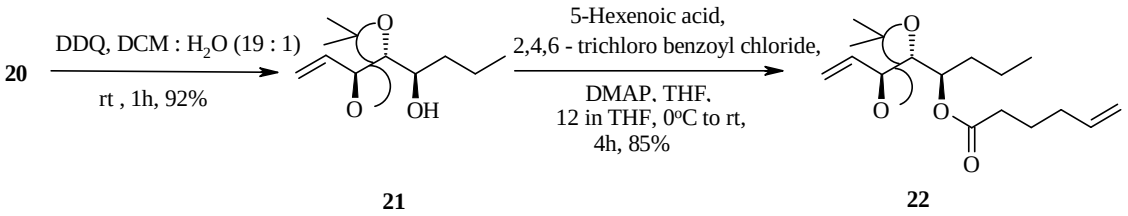
The subsequent deprotection of **17** was the presence of 1N HCl in THF gave diol **19**, which on subsequent protection of acetonide in the presence of 2,2 dimethoxy propane and catalytic amount of PPTS provided compound **20**.



Scheme 5

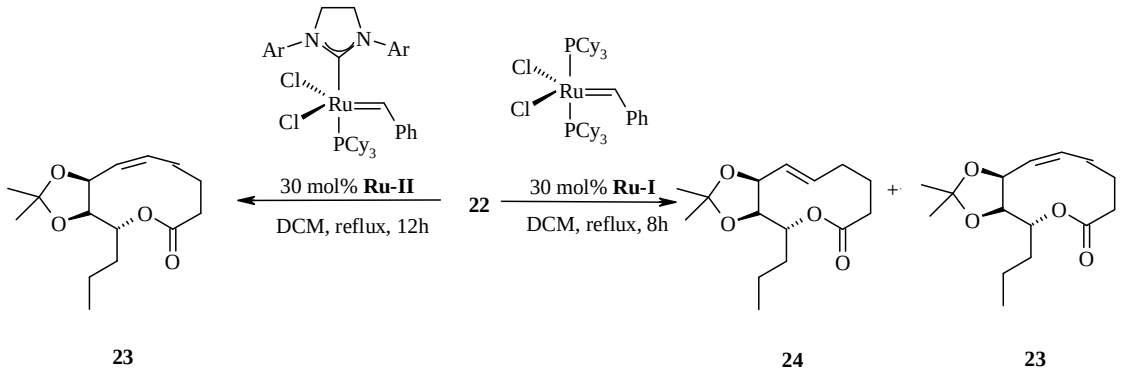
The oxidative cleavage of PMB ether of compound **20** in the presence of DDQ in DCM at 0 ^{o}C afforded alcohol **21**. The alcohol **21** was esterification with hexenoic acid in the presence of 2,4,6 tri chloro benzoyl chloride afforded di olefinic ester **22**.

The cyclization of **22** in the presence of Grubbs' second-generation catalyst led to the exclusive formation of the undesired (Z)-isomer **23** in 85% yield. In the ^{1}H NMR spectrum of **24** and **23**, whose spectral data compared well with that reported in the



Scheme 6

literature. However, compound **22**, in the presence of Grubbs' first generation catalyst yielded an E/Z mixture of cyclic olefins (***24:23*** = *E:Z* = 80:20) in 82% yield. The

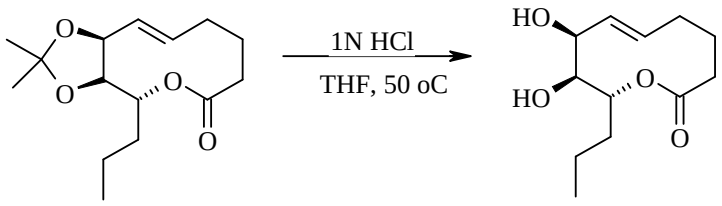


Scheme 7

diastereomers were separated by chromatography using an $AgNO_3$–silica gel column. These compounds are conformed by comparising the reported compounds.

Finally the deprotection of acetonide group of compound **24** with 1N HCl in THF under reflux conditions for 6h gave target compound **1** in 85% yield as white solid. The optical rotation is $[\alpha]_D^{25}$ +12.0^o (c 0.5, EtOH) were in good accordance previously reported $[\alpha]_D^{25}$ +10.8^o (c 0.51, EtOH), with those of natural product isolated $[\alpha]_D^{25}$

+28.0^{o} (c 0.1, EtOH). The IR, ^{1}H NMR, ^{13}C NMR and mass data of the synthetic herbarumin I **1** was in good accordance with those of the natural product.



24a **1**

Scheme 8

Chapter II:

Section-A: Stereoselective synthesis of Leocarpin-A a plant natural product:

The Leiocarpin A, leiocarpin B, leiocarpin C and 7-*epi*-goniodiol are four new styryllactones, recently isolated by Chaoming Li et al. from the ethanolic extract of stem bark of *Goniothalamus leiocarpus* (Annonaceae). Apart from interesting biological profile of these styryllactoes are attractive synthetic targets with structural complexity and biological activity. The leiocarpin A have the same structural relationship with 2,5-deoxygoniopypyrone except for the configurations at C_6 (figure1).

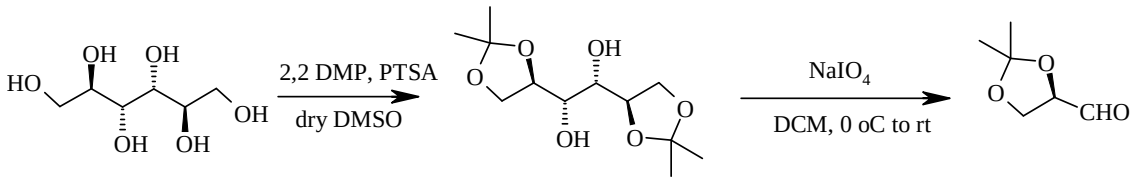
1 **2**

Leiocarpin-A **2,5-Deoxygoniopypyrone**

Figure 1

Owing to the importance of these styrylactones regarding cytotoxic activity and basic structural features, we encouraged to stereoselective synthesis of leiocarpin A starting from commercially available D-mannitol.

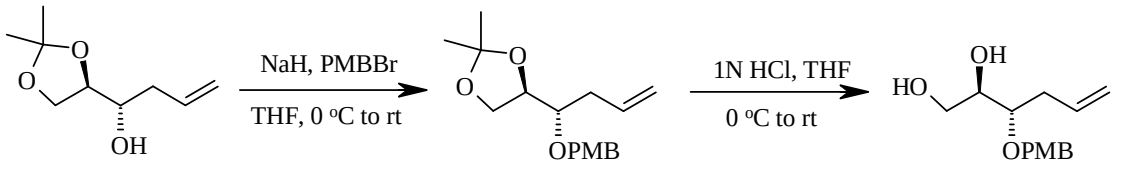
In direct reciprocation of retrosynthetic analysis, we commanced our synthesis from D-mannitol **3**. The cheap and commercially easy availability high enantiomeric purity and equivalence of double unit of C3-chiral building block because of C_2 symmetry were the strong incentives to start from D-mannitol. The foremost step was the conversion of D-mannitol into 1,2:5,6-di-*O*-isopropylidine-D-mannitol **4** using 2,2-dimethoxy propane and cat. PTSA in dry DMSO for 8h as shown in scheme 1. The treatment of diacetonide D-mannitol **4** with $NaIO_4$, and sat. $NaHCO_3$ in DCM at 0 ^oC for 8h afforded the (*R*)-2,3-*O*-isopropylidineglyceraldehyde **5** in quantitative yield



3 **4** **5**

Scheme 1

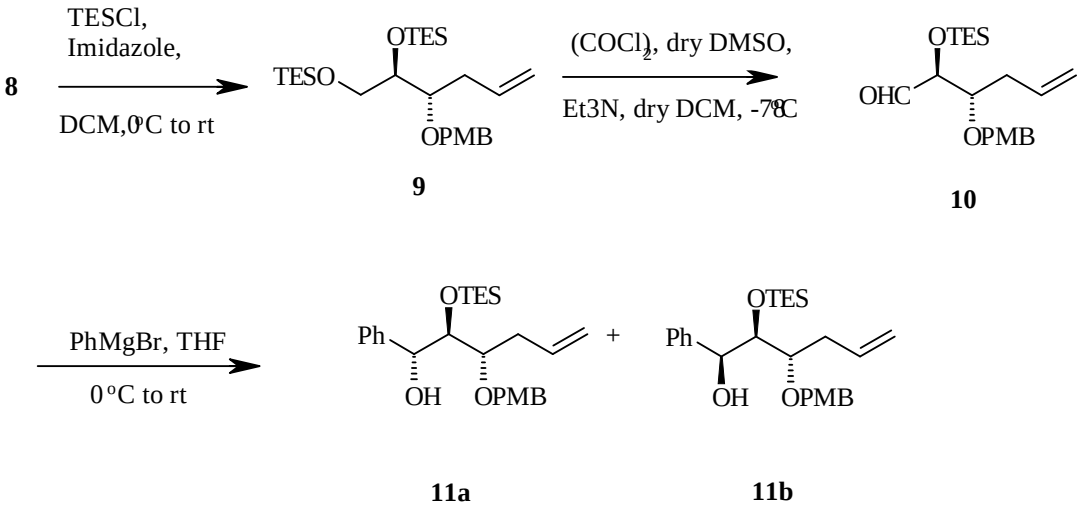
The next endeavor was the stereoselective allyl addition to the aldehyde **5.** Accordingly**,** the compound **5** was treated with allyl bromide, in presence of activated zinc dust and saturated NH_4Cl for 4h, which gave the mixture of diastereomers **6a** and **6b** in the ratio of the *95:5* (*anti : syn*) The required isomer of homo allylic alcohol **6a** was protection with 4-methoxy benzyl bromide in presence of NaH at 0^oC to room temperature for 4h afforded the product **7**. Acetonide deprotection of **7** was in 1N HCl in THF provided diol **8** in quantitative yield.



6a **7** **8**

Scheme 2

The diol **8** was silylated with tri ethyl silyl chloride in presence of imidazole in di chlromethane at 0 ^{o}C to room temperature furnish di TES compound **9**. The compound **9** was oxidized under swern conditions furnished aldehyde **10,** via domino



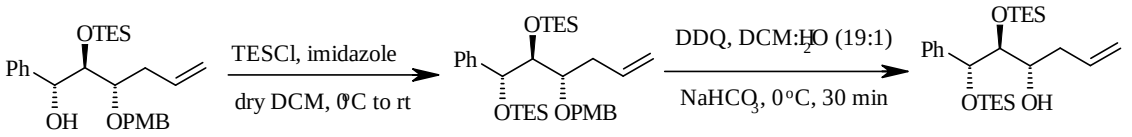
9 **10**

11a **11b**

Scheme 3

deprotection of the primary O-TES group and subsequent oxidation of the primary alcohol to aldehyde, and which on subsequent phenylation with phenyl magnesium bromide in THF at 0 ^{o}C to room temperature afforded to the corresponding benzylic alcohols as mixture of **11a** and **11b** (9: 1 *anti: syn*).

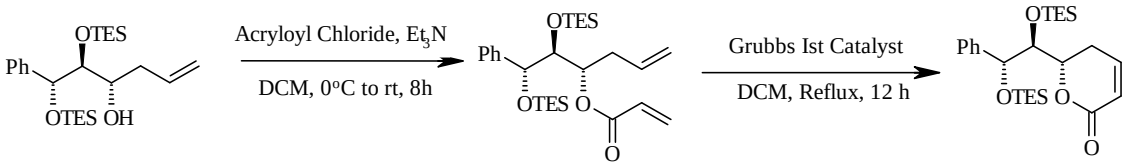
The required anti isomer of benzylic alcohol **11a** was protected with TESCl in the presence of imidazole in dry dichloromethane afforded the compound **12**,



11a **12** **13**

Scheme 4

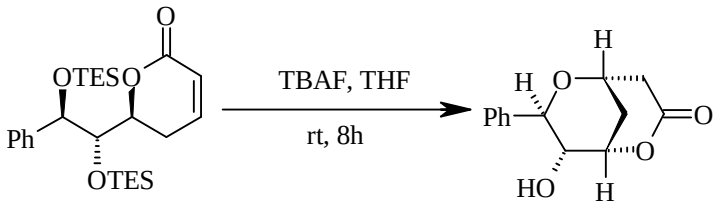
which on sub sequent DDQ mediated oxidative cleavage of PMB group in DCM:warer 19:1 ratio provided homoallylic alcohol **13**.



13 **14** **15**

Scheme 5

The homo allylic alcohol **13** was acryloylated with acryloyl chloride afforded compound **14**, the dien was cyclized by ring closing metathesis in the presence of Grubbs, first generation catalyst provided lactone **15**, finally deprotection of TES group target as colorless solid leiocarpin A with $[\alpha]_D^{25}$ +94.9 (c = 0.4, $CHCl_3$) were in good



15 **1**

Scheme 6

with TBAF in dry THF, followed by cyclization through oxamicheal addition afforded accordance with those of natural product. Pleasingly, the IR, ^{1}H NMR, ^{13}C NMR and

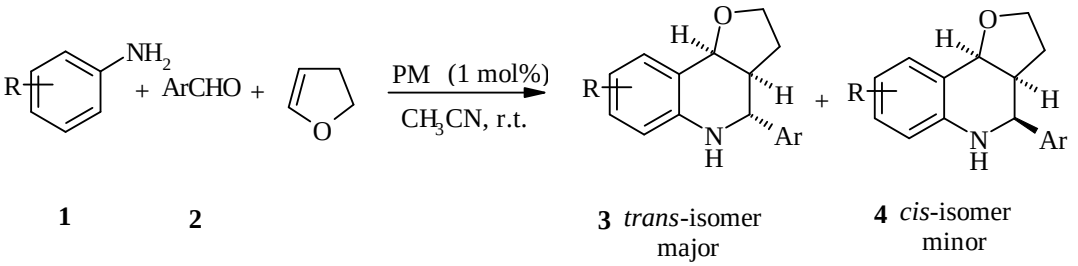
mass data of the synthetic leiocarpin A **1** was in good accordance with those of the natural product.

Section B:

Development of new synthetic methodologies is an important subject in organic chemistry. Synthesis involves expensive reagents and catalysts, which are not easily available. To replace all such reagents and catalysts different improved processes have now been discovered to carry out the reactions efficiently and conveniently with readily available inexpensive materials. Modern methodologies are also concerned with the yield and selectivity of the product. In this chapter we describe phospomolybdic acid catalyzed synthesis of tetrhydro pyrano and furano quinolines.

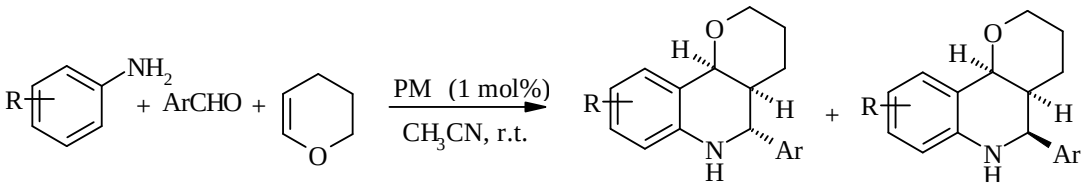
Phospomolybdicacid (PMA, $H_3PMo_{12}O_{40}$) catalyzed synthesis of tetrhydro pyrano and furano quinolines:

Pyrano- and furanoquinoline derivatives belongs to an important class of natural products and exhibit a wide spectrum of biological activities such as antiallergic, antib inflammatory, antipyretic, analgesic, antiplatelet, psychotropic and estrogenic activity. Many biologically active alkaloids contain pyranoquinoline and furanoquinoline moiety. Hence, the synthesis of pyranoquinoline and furanoquinoline derivatives is of much current importance. Generally the pyranoquinoline and furanoquinoline derivatives are prepared by aza-Diels-Alder. The treatment of anilines **1** and benzaldehydes **2** with 2,3-dihydrofuran (DHF) in the presence of 1 mol% of phosphomolybdic acid in acetonitrile afforded the corresponding furanoquinolines **3** and **4** in high yields (scheme 1).



1 **2** **3** *trans*-isomer major **4** *cis*-isomer minor

Scheme 1

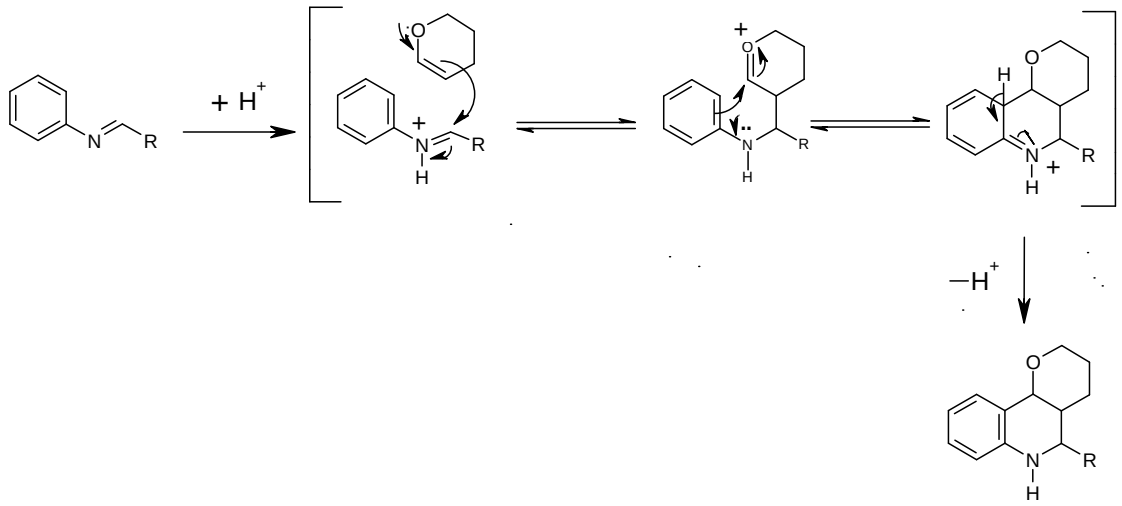


1 **2** **5** trans-isomer major **6** Cis-isomer minor

Scheme 2

In a similar manner, treatment of anilines **1** and benzaldehydes **2** with 3,4-dihydro-2*H*-pyran (DHP) in the presence of 1 mol% of phosphomolybdic acid in acetonitrile afforded the corresponding pyranoquinolines **5** and **6** in high yield (Scheme 2).

Proposed mechanism for the synthesis of pyrano- and furanoquinoline:



Scheme 3:

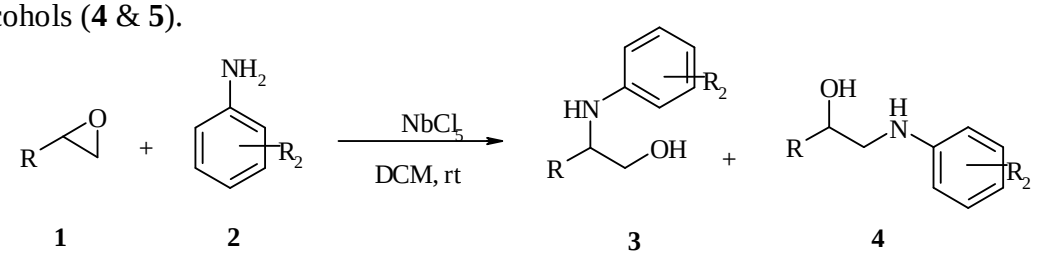
Chapter III:

Niobium (V) chloride: A new and efficient reagent for development of new synthetic methodologies:

In this chapter we described Niobium penta chloride catalyzed synthetic methods. In the view of the recent surge in the activity of Niobium reagents as mild and vater-tolerent Lewis acid. We wish to disclose a new protocol for the rapid synthesis of variety of methodologies.

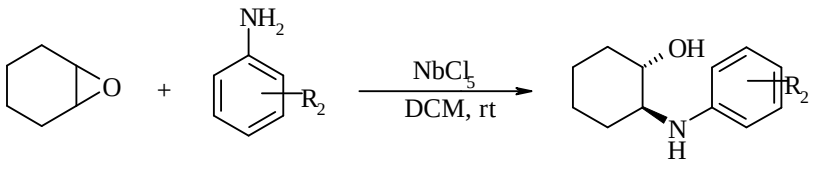
Section A: Niobium (V) chloride is a new catalyst for the synthesis of amino alcohol:

In this chapter synthesis of variety of biologically significant amino alcohols using catalytic amount of Niobium (V) chloride under mild conditions were described. The treatment of styrene oxide **1** with aromatic amine **2** in DCM in the presence of 10% of Niobium penta chloride for appropriate time s at room temperature afforded amino alcohols (**4** & **5**).



1 **2** **3** **4**

Scheme 1



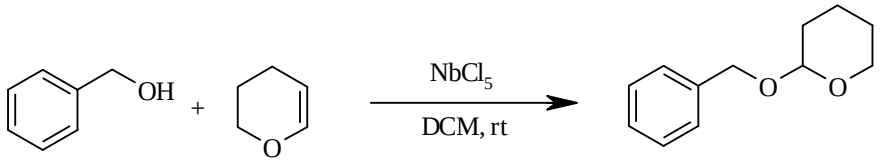
5 **2** **6**

Scheme 2

Similarly, various epoxides like cyclohexane oxide, epi chlorohydrin with aromatic amine under similar conditions to gave corresponding amino alcohols in high yields.

Section B: Niobium (V) Chloride as a acid catalyzed tetrahydropyranylation of alcohols:

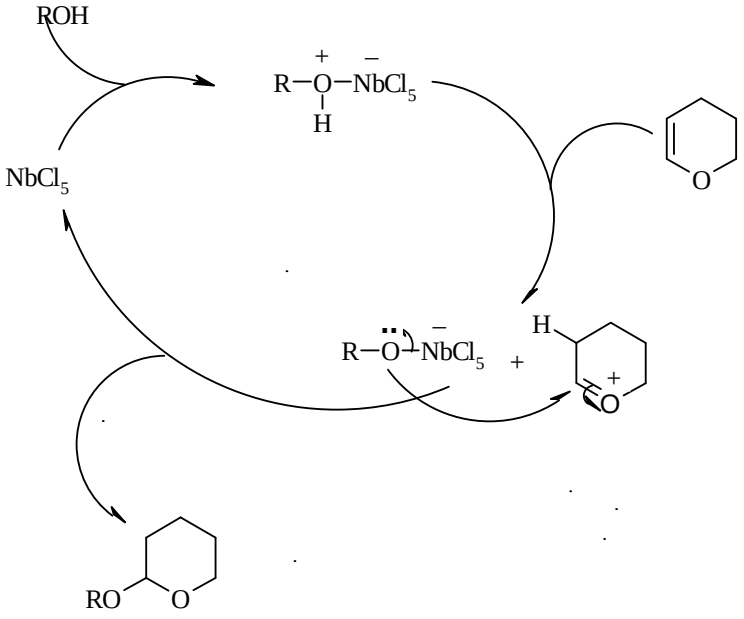
During endeavors of the total synthesis of biologically active natural products, which involves the protection and deprotection of a variety of functional groups were involved. Among the various functional groups, hydroxy is very familiar and its protection as



1 **2** **3**

Scheme 1

Proposed mechanism for tetrahydropyranylation of alcohols:



Scheme 2

tetrahydropyranyl ether (THP) is a common and widely used transformation in organic synthesis. The tetrahydropyran derivatives are attractive for the reason that they are less expensive, easily deprotected and stable under variety of reaction conditions that they are less expensive, easily deprotected and stable under variety of reaction conditions such as strongly basic media, metal hydrides, metal triflates, Grignard reagents, acylating agents, oxidative reagents and alkylating agents. THP groups are also the protective groups of choice in peptide, nucleotide, carbohydrate and steroid chemistry.

According to scheme 1, treatment of benzyl alcohol **1** with dihydropyran **2** in the presence of Niobium (V) chloride in DCM at room temperature afforded corresponding THP ethers **3** in high yields. The reactions were clean and products were high yields in shorter times. The crude products were purified by column chromatography.