ABSTRACT

The thesis entitled **"Stereoselective formal synthesis of Pseudopterosin aglycone, bio-active natural Styryl-lactones and development of novel synthetic methodologies using prins-cyclization"** has been divided into three chapters.

Chapter I: This chapter deals with an introduction to styryl lactones and previous synthetic approaches to (+)-goniodiol and leiocarpin C, which has been divided into two sections:

***Section* A:** This section describes the introduction and biological activity of styryl lactones and earlier synthetic approaches to (+)-goniodiol and leiocarpin C.

***Section* B:** This section describes Stereoselective total synthesis of (+)-goniodiol and leiocarpin C.

Chapter II: This chapter deals with an introduction to inflammation and biological activity of pseudopterosins and previous synthetic approaches and stereoselective formal synthesis of pseudopterosin aglycone and (+)-curcuphenol, which has been divided into two sections:

***Section* A**: This section describes an introduction to inflammation and biological activity of pseudopterosins and previous synthetic approaches to pseudopterosin aglycone and (+)-curcuphenol.

***Section* B:** This section describes stereoselective formal synthesis of pseudopterosin aglycone.

Chapter III: This chapter describes the introduction and stereoselective total synthesis of goniothalesdiol A.

Chapter IV: This chapter describes the introduction to prins cyclization and syntheses of 4-substituted tetrahydropyran and dihydro-*2H*-pyran derivatives *via.* prins cyclization.

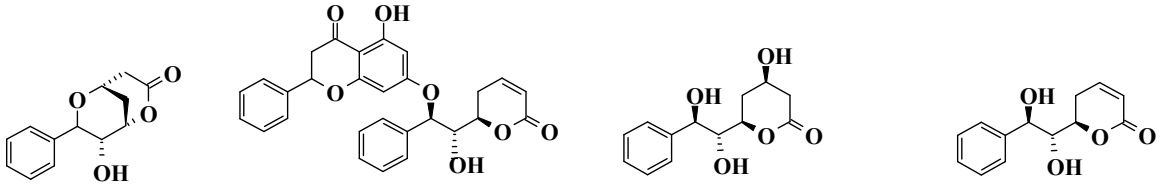
CHAPTER-I: **This chapter deals with an introduction to Styryl lactones and previous synthetic approaches to (+)-goniodiol and Leiocarpin C, which has been divided into two sections:**

Section A: Introduction and biological activity of Styryl lactones:

Styryl lactones are natural heterocyclic compounds with potential cytotoxicity including excellent antitumor, antifungal, and antibiotic behavior.[3] Up to now; more than twenty styryl lactones have been isolated from plants and fungi. Most of the styryl-lactones are isolated from the genus *Goniothalamus* (Annonaceae), which are widely distributed throughout Malaysia. A number of these species were used by Malays as traditional medicine to treat various ailments and had been claimed to have connection with an antifertility effects such as procurement of abortion, undefined post-natal treatments and low birth rate. Styryl lactones possess interesting biological properties, in particular antiproliferative activity against cancer cells. In general, the cytotoxicity of styryl lactones is specific against cancer cells.

Section B: Stereoselective total synthesis of (+)-goniodiol and Leiocarpin C:

Leiocarpin C was isolated from the seeds of *Goniothalamus leiocarpus* (Annonaceae), a tropical plant found in the south of the Yunnan Province in China. Leiocarpins A–C (Figure 1) were found to possess cytotoxic activity against several human tumor cell lines. (+)-goniodiol was isolated from the leaves and twigs of *Goniothalamus sesquipedalis* (Annonaceae) and from the stem bark of *Goniothalamus gigantus* (Annonaceae). This is a potent and selective cytotoxic compound against human lung carcinoma A-549 (ED_{50}= 0.12 mg/mL and p-388 murine leukemia cells (IC_{50}= 4.56 mL).



Leiocarpin A **Leiocarpin B** **Leiocarpin C** **(+)-goniodiol**

Figure 1

In continuation of our interest in the synthesis of lactone containing natural products, we herein report a facile and modular synthetic approach towards the total synthesis of Leiocarpin C and also the synthesis of (+)-goniodiol utilizing Sharpless asymmetric dihydroxylation, Horner–Wadsworth–Emmons olefination and intramolecular lactonization as key steps.

The retrosynthetic analysis of (+)-goniodiol and Leiocarpin C have been dispicted in **Figure 1**. Here we planned to achieve the both targets through a key intermediate, which is shaped from different starting materials with diverse approaches.

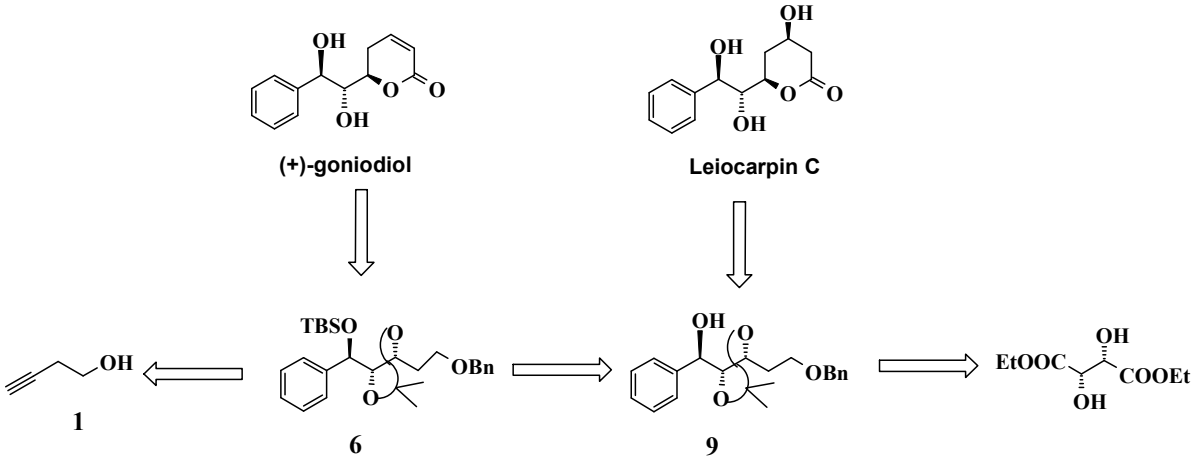
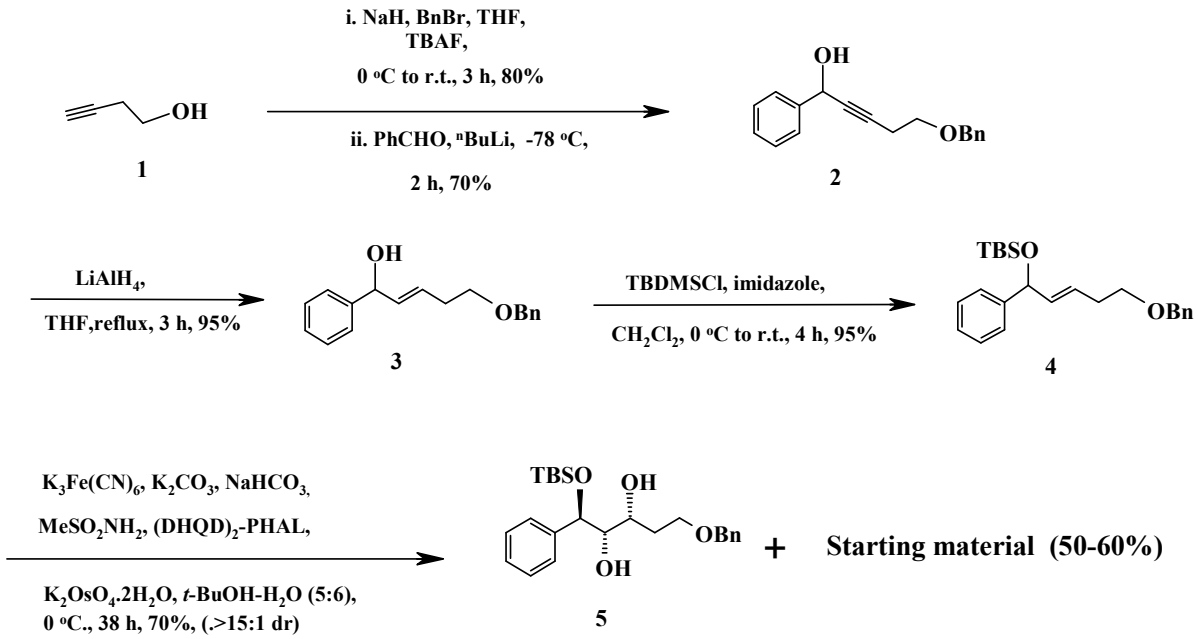


Figure 2: Retrosynthetic plan for total synthesis of (+)-goniodiol and Leiocarpin C.

Commercially available homopropargyl alcohol **1** was converted into its benzyl ether and then this treated with butyllithium in tetrahydrofuran to give the lithium acetylide which was further reacted with benzaldehyde to afford propargyl alcohol **2** in 56% yield

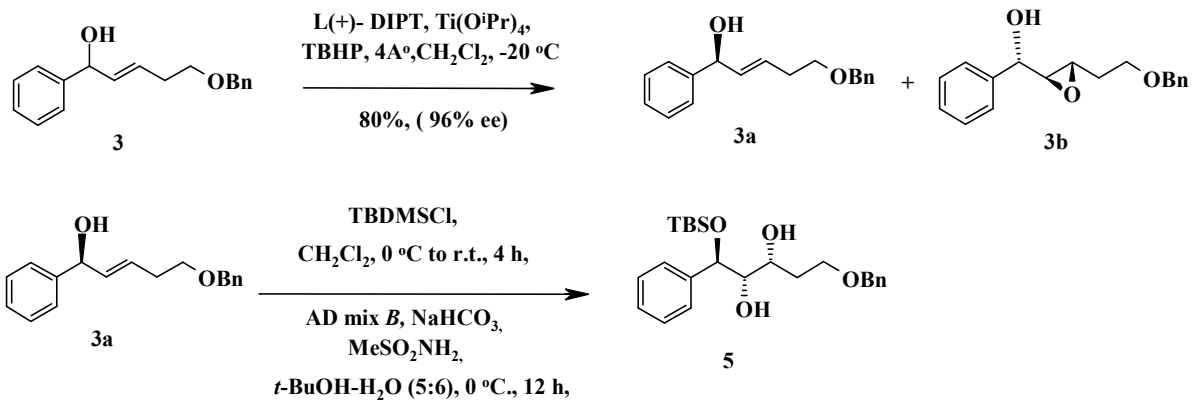
Reduction of propargyl alcohol **2** with lithium aluminum hydride in refluxing tetrahydrofuran gave the allylic alcohol **3** with *trans* configuration in 95% yield. Protection of **3** with tert-butyldimethylsilyl chloride in the presence of imidazole afforded compound **4** in 95% yield. The key intermediate, diol **5** was prepared in 70% (>15:1 dr, 30%overall yield) by stereoselective Sharpless dihydroxylation of allylic alcohol **4** using $(DHQD)_2$-PHAL,

methane sulfonamide, potassium osmate(VI) dihydrate, potassium hexacyanoferrate(III), potassium carbonate in *tert*-butyl alcohol–water (with >15:1 dr), which was confirmed by chiral HPLC analysis **(Scheme 1)**.



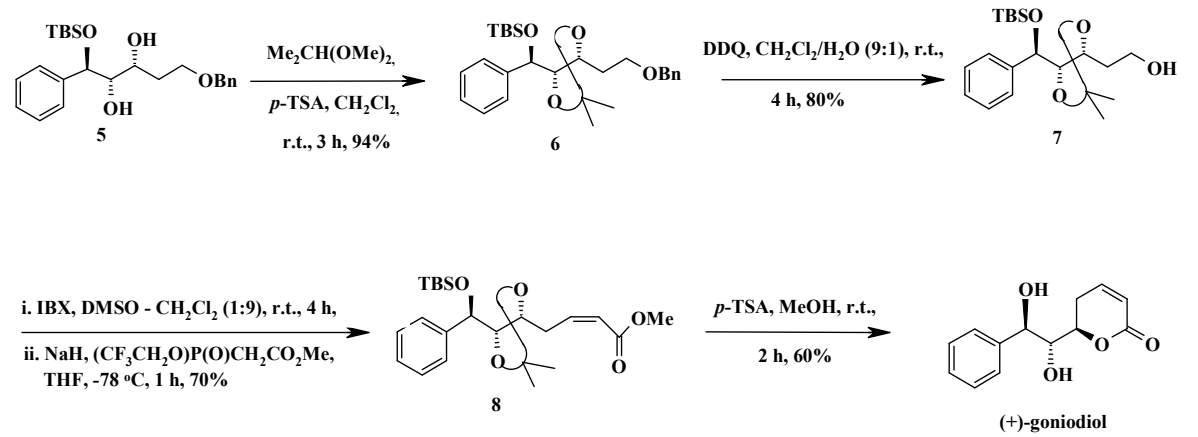
Scheme - 1

We were also achieved the same diol **5** from the allylic alcohol **3** using an alternative method. Wherein, the enantiomerically pure alcohol **3a** was obtained from racemic alcohol **3** by the kinetic resolution of Sharpless asymmetric epoxidation using L (+)-DIPT, Ti $(O^iPr)_4$ and TBHP with 80% yield (96% *ee*). The chiral alcohol **3a** underwent silyl protection nicely with TBDMSCl in dry dichloromethane followed by Sharpless dihydroxylation with AD mix *β*, methane sulfonamide and sodium bicarbonate in *tert*-butyl alcohol–water (9:1) to afford diol **5** in 80% yield **(scheme 2)**.



Scheme 2

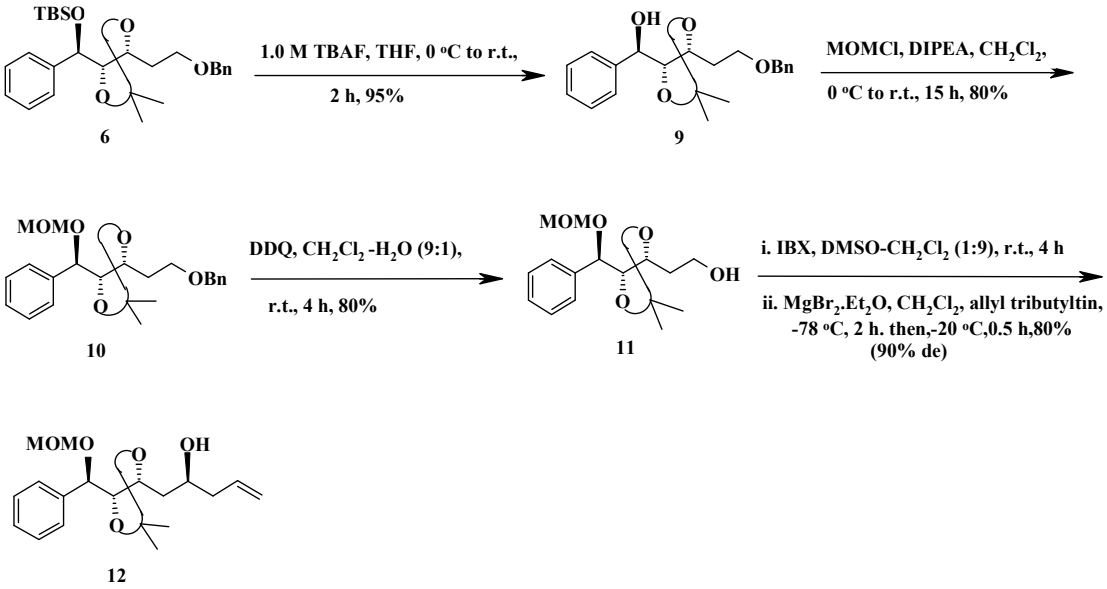
The diol **5** was protected as the acetonide with 2,2-dimethoxypropane using a catalytic amount of *p*-toluene sulfonic acid in dry dichloromethane to afford acetonide **6**. Debenzylation of the acetonide **6** was achieved by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)–water[11] to give the primary alcohol **7**. The alcohol **7** was then treated with 2-iodoxybenzoic acid (IBX)/dimethyl sulfoxide in dichloromethane to furnish the corresponding aldehyde in good yield, which was further subjected to modified Horner–Wadsworth–Emmons olefination[12] using sodium hydride and bis(2,2,2-trifluoroethyl) (methoxycarbonyl)methylphosphonate in tetrahydrofuran at –78 °C to afford *α,β*- unsaturated ester **8**, predominantly as the (Z)-isomer in 70% yield (Z/E, 70:30).



Scheme 3

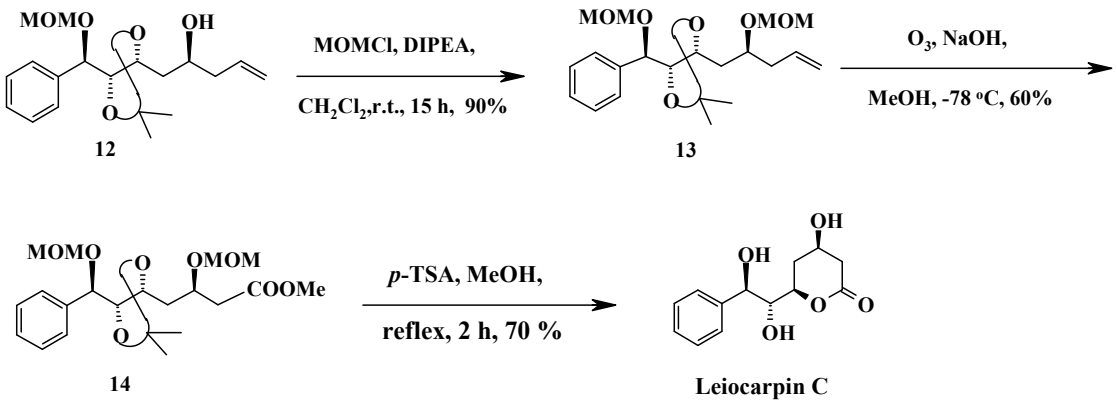
The cyclization of *cis*- *α,β*- unsaturated ester **8** was achieved *via* intramolecular lactonization to afford (+)-goniodiol in 60% yield after sequential removal of silyl and acetonide protecting groups using a catalytic amount of *p*-toluene sulfonic acid in methanol **(scheme-3).**

Deprotection of TBDMS ether of acetonide **6** was achieved by using 1.0 M tetra butyl ammonium fluoride solution afforded as the secondary alcohol **9** in 95% yield. Methoxymethyl protection of secondary alcohol **9** was achieved with methoxymethyl chloride under basic medium using DIPEA to afford MOM product **10** in 80% yield.



Scheme 4

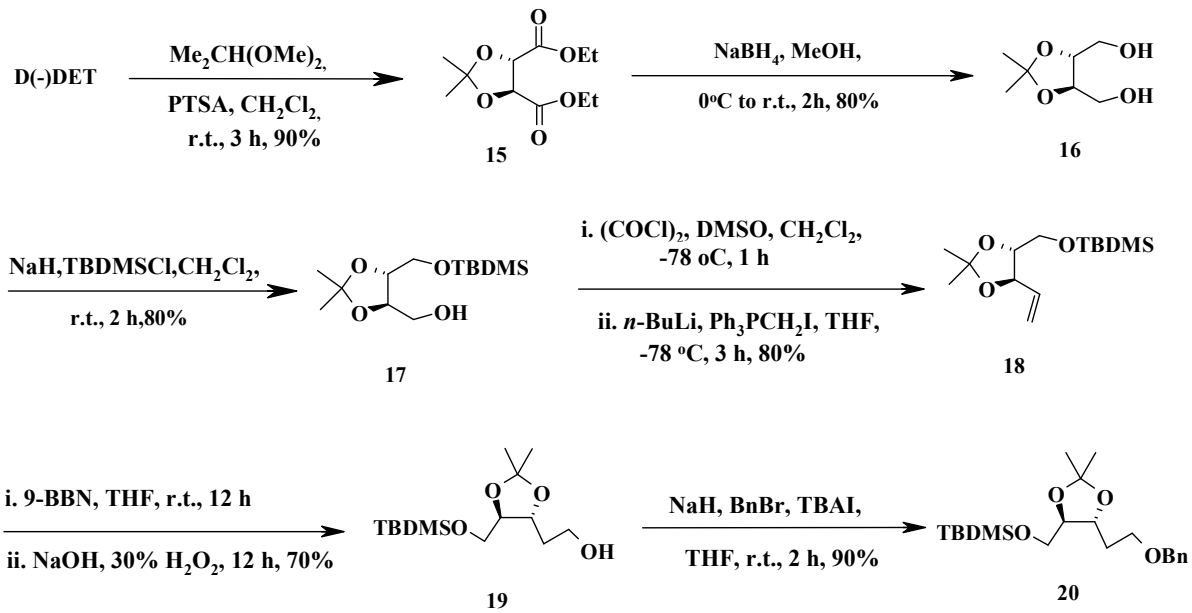
After that, debenzylation of the MOM product **10** was achieved by using 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)–water[11] to give the primary alcohol **11**, which was further oxidized to afford an aldehyde using IBX/DMSO. Highly diastereoselective allylation of the aldehyde was achieved with allyltributyltin using magnesium bromide– diethyl ether complex in dichloromethane at –78 °C to give the *β*-hydroxy allyl derivative **12** in 80% yield and 90% ee (*anti*/*syn*, 95:5) **(scheme-4).**



Scheme 5

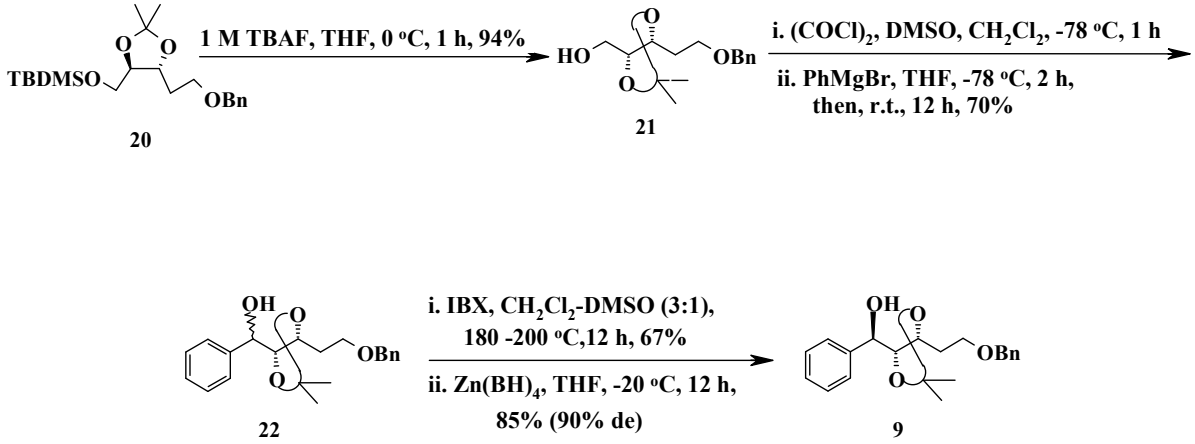
The *β*-hydroxy group **12** was protected to give MOM ether **13**, which was then subjected to ozonolysis followed by treatment with potassium hydroxide in methanol to furnish methyl ester **14**. The resulted methyl ester **14** was cyclized through an intramolecular lactonization in a single step using a catalytic amount of *p*-toluene sulfonic acid in methanol to afford Leiocarpin C in 70% yield **(Scheme 5).**

The fragment **9** was prepared from a chiral C_2-asymmetrical diol which in turn was derived from readily available (–)-diethyl D-tartarate **(Scheme 4)**. Monoprotection of the diol was achieved with *tert*-butyldimethylsilyl chloride in the presence of sodium hydride to give the TBDMS ether **17** in 80% yield. Swern oxidation of **17** gave the unstable aldehyde, which was immediately subjected to one-carbon Wittig olefination with triphenylphosphonium iodide using butyllithium in tetrahydrofuran at 0°C to room temperature to afford olefin **18** in 80% yield. The olefin derivative **18** was converted into the corresponding primary alcohol **19** in 70% yield by hydroboration with 9-BBN dimer in dry tetrahydrofuran followed by oxidation with hydrogen peroxide in the presence of sodium hydroxide. The protection of primary alcohol **19** with benzyl bromide in the presence of sodium hydride afforded benzyl ether **20** in 90% yield **(Scheme 6).**



Scheme 6

Deprotection of the TBDMS ether **20** using tetrabutylammonium fluoride gave the primary alcohol **21** in 94% yield. Swern oxidation of the resulting primary alcohol **21** with oxalyl chloride, dimethyl sulfoxide in dichloromethane at –78 °C gave the aldehyde, which was subsequently treated with phenylmagnesium bromide to afford the secondary alcohol **22** in 70% yield as an inseparable mixture of diastereoisomers.



Scheme 7

To obtain the required diastereomer as the major product, the racemic mixture of alcohol **22** was oxidized with IBX (DMSO–CH_2Cl_2, 1:3) under reflux conditions to give the ketone, which was subsequently subjected to stereoselective alkoxy-directed 1,2- *anti* keto-reduction with zinc borohydride in tetrahydrofuran at –20°C to afford the secondary alcohol **9** as the major isomer in 85% yield in two steps.

In conclusion, a concise and efficient synthesis of leiocarpin C has been achieved in a highly stereoselective manner. The synthesis involves Chan alkyne reduction, Sharpless asymmetric dihydroxylation, Horner–Wadsworth–Emmons olefination, aryl Grignard reaction, hydroboration, stereoselective alkoxy-directed keto reduction, and intra molecular lactonization. This synthetic sequence provides an easy access to the preparation of styryl lactones of biological importance.

CHAPTER-II: This chapter deals with an introduction to Inflammation and previous synthetic approaches and Stereoselective formal synthesis of Pseudopterosin aglycone and (+)-curcuphenol, which has been divided into two sections:

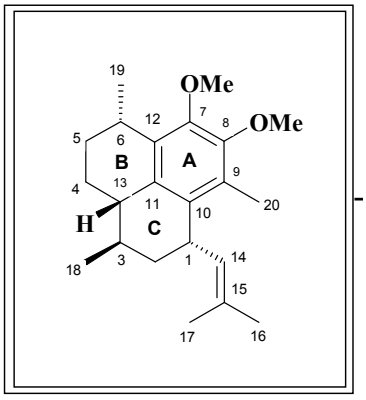
***Section* A: Introduction to inflammation and biological activity of Pseudopterosins:**

In the recent years, the most troublesome complication is inflammation, which is occurring in 15% to 32% of cases. The cause of the inflammation may be due to viral infection or may be a consequence of coronary artery bypass grafting. The process inflammation can be explained "using which the body's white blood cells and chemicals protect us from infection and foreign substances such as bacteria and viruses". When inflammation occurs, chemicals from the body's white blood cells are released into the blood or affected tissues in an attempt to rid the body of foreign substances. This release of chemicals increases the blood flow to the area and may result in redness and warmth. Some of the chemicals cause leakage of fluid into the tissues, resulting in swelling. The inflammatory process may stimulate nerves and cause pain. In some diseases, when there are no foreign substances to fight off, the body's protective immune system would like to damage its own tissues.

The marine pseudopterosins are members of a family of diterpene pentose glycosides, which are formed by gorgonian soft corals during photo syntheses. Gorgonian soft corals are commonly known as sea feathers, sea whips and sea fans. Many research groups have successfully isolated a variety of pseudopterosins from these organisms that have confirmed as extremely potent anti-inflammatory and analgesic agents that reduce swelling and skin irritation and accelerate wound healing; acts as inhibitor of phospholipase A, a key enzyme in inflammatory response. Hence, the pseudopterosins have demonstrated commercial value, as the original compounds; have been successfully incorporated into cosmetics to inhibit inflammation experienced during mild allergic reactions. The anti-inflammatory and analgesic activity of the pseudopterosins has been ascribed to the inhibition of eicosanoid release. This potency and the fact that their biological mode of action appear to be novel have made these substances and their analogues are attractive targets for synthetic as well as biochemical research.

***Section* B: Stereoselective formal synthesis of pseudopterosin aglycone:**

A distinguished feature of the pseudopterosin family is the stereochemical variation in the hexahydro-1H-phenalene core. In addition that, the glycosidic linkage on aglycone at either C-7 or C-8 along with the identity of the sugar and the degree of acetylation account for the additional structural variation of this family of diterpenes.



Pseudopterosins G-J Aglycone
dimethyl ether enantiomer **1.**

Figure 1

The biological activity and commercial potential of the pseudopterosins encouraged a number of approaches to their synthesis. Total syntheses of pseudopterosin A and E have been described. In most of syntheses, the bulk of the synthetic effort has focused on the aglycone. In addition several approaches to the tricyclic ring system in varying degrees of elaboration have been published.

We here in report a facile and flexible new synthetic route of a typical A→AB→ABC strategy based annulation sequence towards pseudopterosin aglycone dimethyl ether **1** beginning with an acyclic 1, 5-pentandiol **3**.

As a part of ongoing synthetic plan towards the flexible stereoselective synthesis of pseudopterosin aglycone, here an intermediary synthetic route has designed to accomplish (S)-(+)-curcuphenol **2**, a natural product belongs to phenolic sesquiterpenes of the bisabolane family, have been isolated from the marine sponge *Didiscus flarus*, shows potent antifungal and antitumor activity, Inhibits strongly the activity of gastric H, K-ATPase.

The retrosynthetic analysis shows that the pseudopterosin aglycone **1** and also the (S)-(+)-curcuphenol **2** can be synthesized from compound **17** and this could be synthesized from the inexpensive and commercially available 1, 5-pentandiol **3 (figure 2)**.

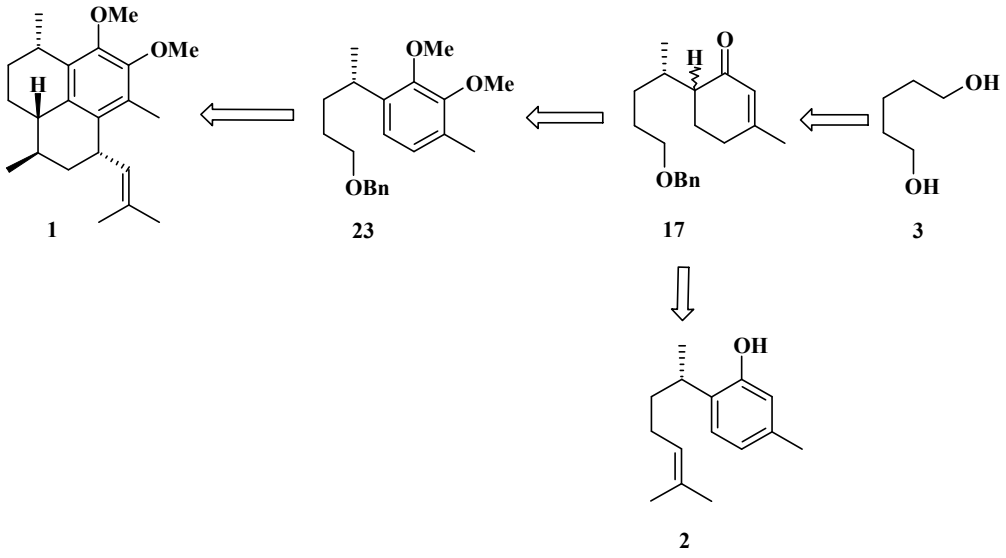
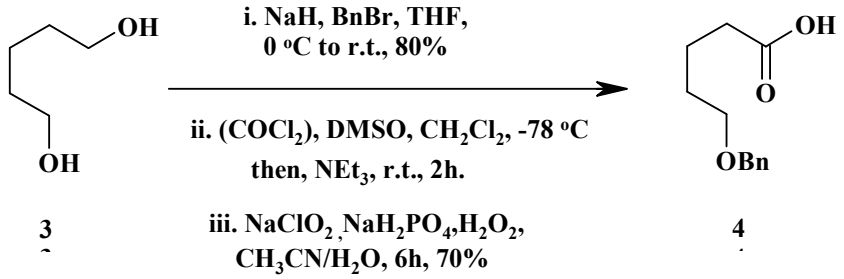


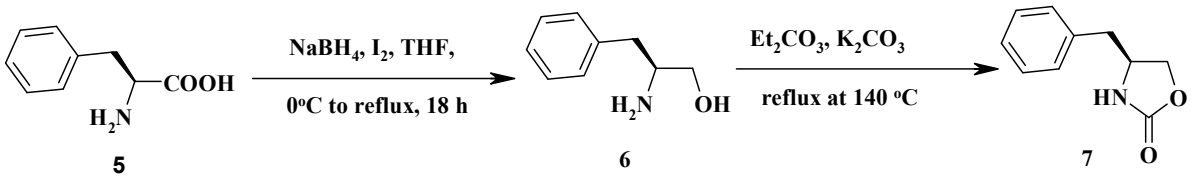
Figure 2: Retrosynthetic analysis of pseudopterosin aglycone **1** and S-(+)-curcuphenol **2.**

The synthesis of Pseudopterosin aglycone was initiated by 1,5- pentandiol **3**. Mono protection of the pentandiol **3** was achieved with benzyl bromide in presence of sodium hydride to afford the benzyl ether in 80% yield. Swern oxidation of alcohol derivative gave the unstable aldehyde, which was immediately subjected to oxidation with $NaClO_2$ and $NaH_2PO_4.2H_2O$ using 35% H_2O_2 in CH_3CN at 0 °C at room temperature to afford acid derivative **4** in 70 % yield **(scheme 1)**.



Scheme 1

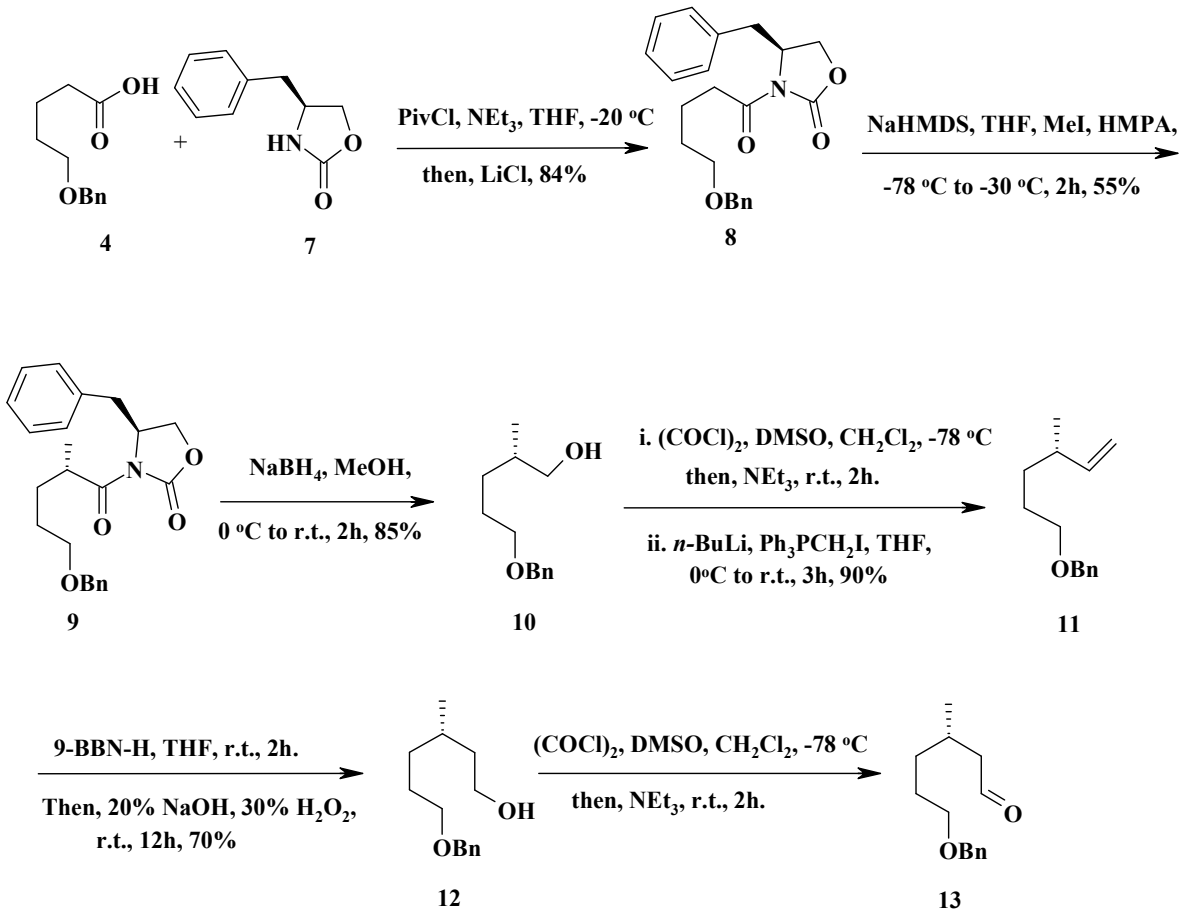
The auxiliary **7** prepared from natural L-phenyl alanine, was used to control absolute stereo induction through possible subsequent methylation step. L-phenyl alanine **5** was converted into the resultant alcohol **6** in good yield by reduction with $NaBH_4$ and iodine under reflux condition, which was later on shaped to chiral auxiliary **7** under reflux with Ethyl carbonate and potassium carbonate afford with good yield.



Scheme 2

The acid derivative **4** was coupled with lithiated Evan's auxiliary **7,** which was lithiated at -20 °C using *n*-BuLi in anhydrous THF under mixed anhydride conditions furnishing imide **8** in 84 % yield. Evans Diastereoselective Alkylation of the Lithium enolate of imide **8**, achieved by treatment with NaHMDS in THF at -78 °C followed by the addition

of MeI delivered the compound **9** in moderate yield with high diastereoselectivity (> 99%). After introduction of Methyl stereogenic centre, imide **9** was eliminated by reduction with $NaBH_4$ in MeOH at room temperature furnish alcohol **10** in 85% yield along with the auxiliary **7,** which was recycled for preparation of imide **8.** The chiral alcohol **10** was oxidized to respective aldehyde with quantitative yield under Swern conditions, which was immediately subjected to single carbon Wittig olefination with triphenylphosphonium iodide using *n*-butyl lithium in THF at 0 °C to room temperature to afford olefin **11** in 90% yield.



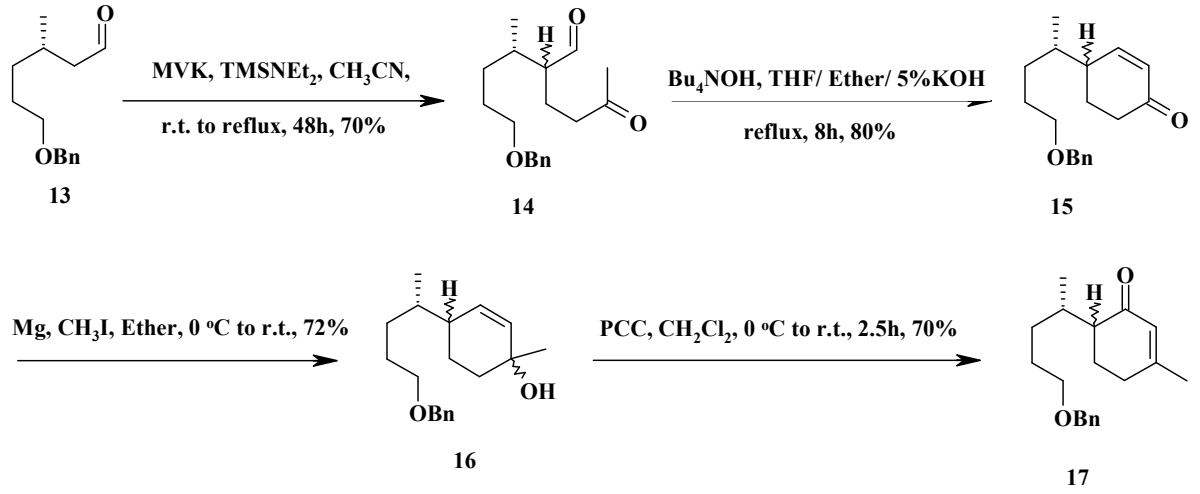
Scheme 3

The olefin derivative **11** was converted into the corresponding primary alcohol **12** in 70% yield by hydroboration with 9-BBN dimer in dry THF followed by oxidation with hydrogen peroxide in the presence of sodium hydroxide. Swern oxidation of the resulting

primary alcohol **12** with oxalyl chloride and dimethyl sulfoxide in dichloromethane at -78 °C gave the chiral aldehyde **13** with quantitative yield **(scheme 3)**.

The diastereomeric mixture of Michael addition product **13** was obtained as a result of diethyl amine trimethyl silane (DEATMS) mediated conjugate addition of the chiral aldehyde **14** with buten-3-one (MVK) in CH_3CN under refluxing condition, wherein the inseparable diastereoisomers were obtained with 70% yield.

The cyclization of the keto-aldehyde compound **14** was achieved *via* aldol condensation under phase transfer reaction conditions. When the compound **14** was vigorously refluxed with the solvent mixture of 5% potassium hydroxide solution, tetrabutylammoniumhydroxide, diethyl ether and THF delivered the desired Robinson annulated enone product **15** in 80% yield as a mixture of diastereomeric isomers.

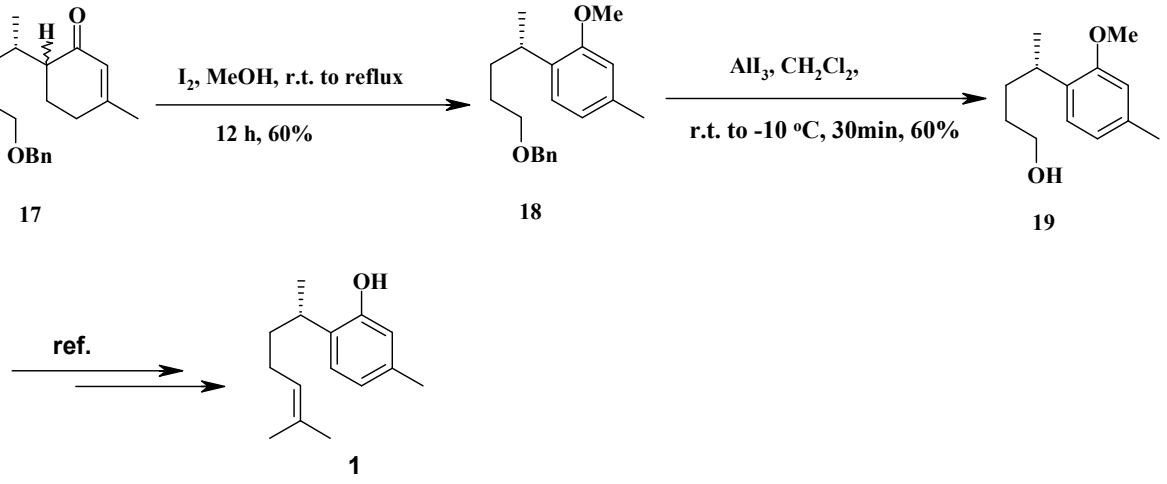


13 14 15 16 17

Scheme 4

Later the diastereomeric mixture of enone compound **15** treated with *in situ* CH_3MgI to afford the diastereomeric mixture of **16** in 72% isolated yield, where in the methyl Grignard generated by addition of MeI to the activated Mg turnings in dry ether under inert atmosphere in cold condition. Oxidation of diastereomeric mixture of Grignard compound **16** was achieved by pyridinium chloro chromate (PCC) enabled [1, 3]- oxidative rearrangement and produced enone **17** as diastereoisomeric mixture in 70% yield. **(Scheme 4)**.

The diastereomeric mixture of compound **17** containing enone moiety was under goes oxidative aromatization and converts into methyl phenyl ether under drastic reflux condition of molecular iodine and methanol mixture, furnishes compound **18** with 60% yield. For the selective deprotection of benzyl ether belongs to compound **18**, we were chosen AlI_3, which was generated by Al powder and molecular I_2 under inert conditions. At -10 °C under inert atmosphere, the compound **18** was reacted with AlI_3 provides only benzyl deprotected alcohol **19** in 60% yield without disturbing the methyl ether protection. This debenzylation reaction was completed with in 30 min **(scheme 5)**.

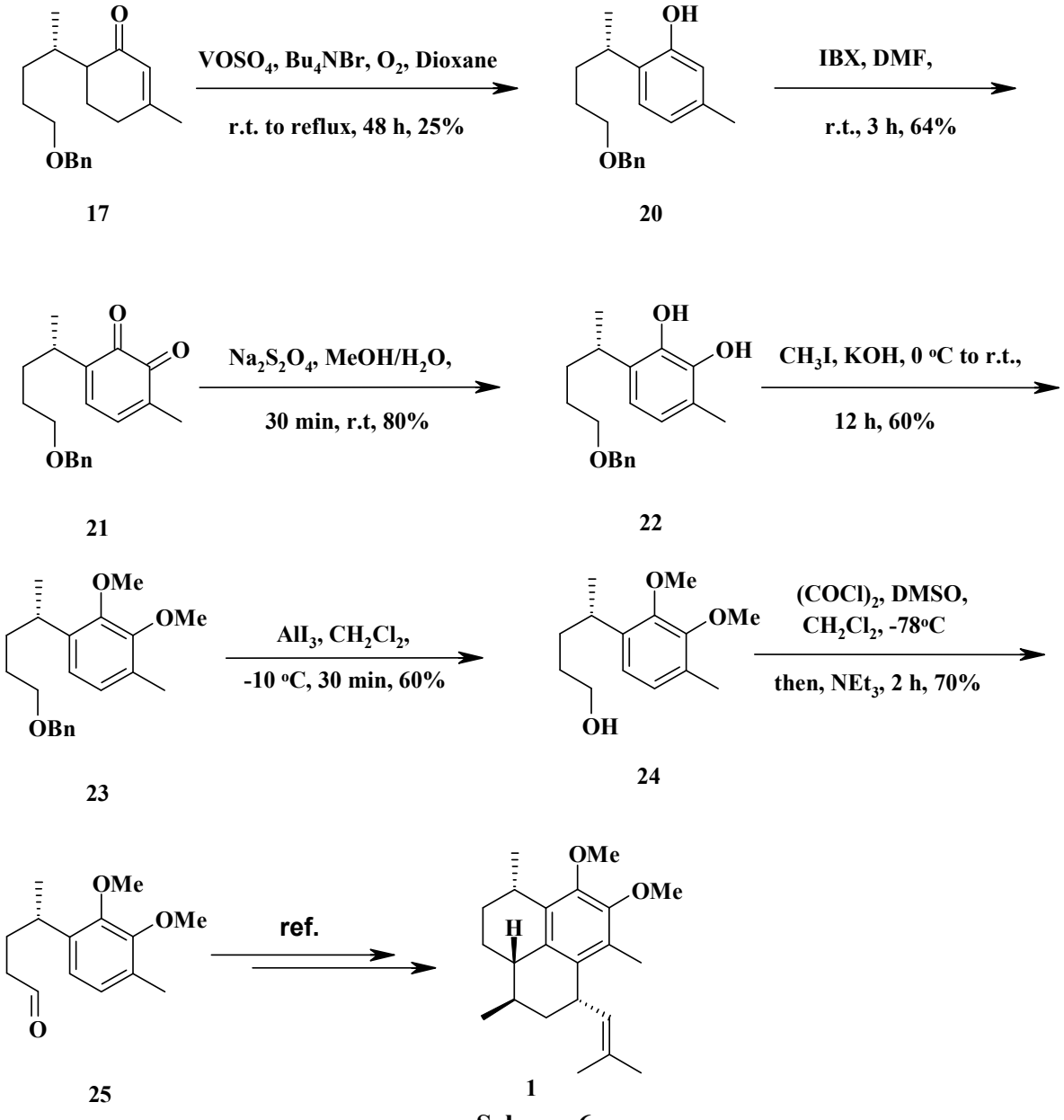


Scheme 5

The synthesized chiral compound **19** is reported to convert into (S)-(+)-curcuphenol in the literature. Thus we accomplish the stereoselective formal synthesis of (S)-(+)-curcuphenol.

The reaction of 2–cyclohexenone derivative **17** with the combination of a commercially available a ligand free vanadium catalyst ($VOSO_4$), a bromide source (Bu_4NBr), and an acid (TFA) in minimum amount of 1, 2-dioxane solvent under 48 hours of refluxed condition in presence of atmospheric oxygen undergoes into catalytic oxidative aromatization to give the corresponding phenol derivative **20,** where in the isolated yield of phenolic product was only 25%. The resulted phenol derivative **20** with IBX underwent regioselective oxidation to accomplish the *o*-quinone **21** in 64% yield. The unstable *o*-

quinone **21** with sodium dithionate by reductive aromatization to provide the desired catachol product **22** with 80% yield. Hereafter, the catachol compound **22** was treated with pulverized KOH and MeI in anhydrous DMSO, in the process the desired Catachol dimethylether **23** was produced with 60% yield.



Scheme 6

The derived dimethoxy catachol derivative **23** was subjected to strong Lewis acid mediated debenzylation process using AlI_3 at -10 °C under inert atmosphere, which was leads to formation of the alcoholic product **24** with 60% yield. The primary alcohol **24** was subjected to Swern oxidation to afford the corresponding aldehyde **25** with quantitative yield **(scheme 6)**. The target chiral synthon (S)-4-(2,3-dimethoxy-4-methylphenyl)pentanal **25** was reported to convert into pseudopterosin dimethyl ether aglycone (Putative enantiomer of PsG-PsJ) **1** in the literature.[24] More over, this target key intermediate **25** also act as key precursor, which could be constructive towards the total synthesis of various aglycones corresponding to Pseudopterosins (A-F) and (P-Z).

In summary, we have accomplished a stereoselective formal synthesis of Pseudopterosin aglycone dimethylether. The synthesis of (S)-4-(2,3-dimethoxy-4-methylphenyl)pentanal **25** was obtained from 1,5- pentandiol utilizing Evan's diastereo-selective alkylation, Robinson annulation, [1,3]- oxidative rearrangement, Oxidative aromatization, regioselective *o*-quinone formation reactions as key steps.

CHAPTER-III: This chapter deals with Asymmetric synthesis of pyran moieties and which has been divided into two sections:

Introduction:

Natural products with 2,6- disubstituted tetrahydropyran scaffolds have gained prominence recently owing to their excellent biological properties. Several natural products have the substituted pyran moiety with *cis* stereo connectivity at the 2,6- positions.[1] Some recent examples, which fall into this class, include leucascandrolides, phorboxazoles, (+)-SCH 351448. The synthesis of these compounds has attracted attention owing to their interesting biological properties and challenges posed by the substitution pattern. In continuing our interest in synthesizing natural products possessing pyran moiety, herein we report an efficient synthetic route to goniothalesdiol A.

Stereoselective total synthesis of goniothalesdiol A:

Goniothalesdiol A **1** and goniothalesacetate **2**, a new class of styryl lactones, were isolated from the stems of a southern Taiwan tree *Goniothalamus amuyon* **(Figure 1).** The styryl lactones and acetogenins are two major types of bioactive compounds isolated from the *Goniothalamus* (Annonaceae) species.

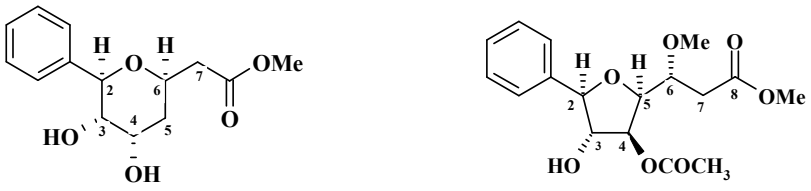


Figure 1

The structure and relative configuration of goniothalesdiol A **1** were determined on the basis of NMR spectroscopy, and the absolute configuration was predicted by biosynthesis. The retrosynthetic analysis of goniothalesdiol A **1** have been depicted in **Figure2**. Here we planned to achieve the target through a key intermediate **7**, which is shaped from commercially available starting material homopropargyl alcohol **3**.

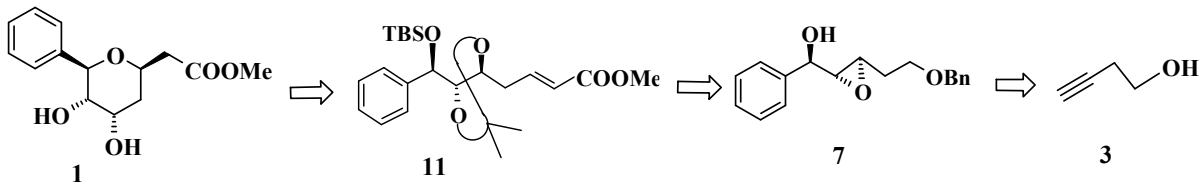
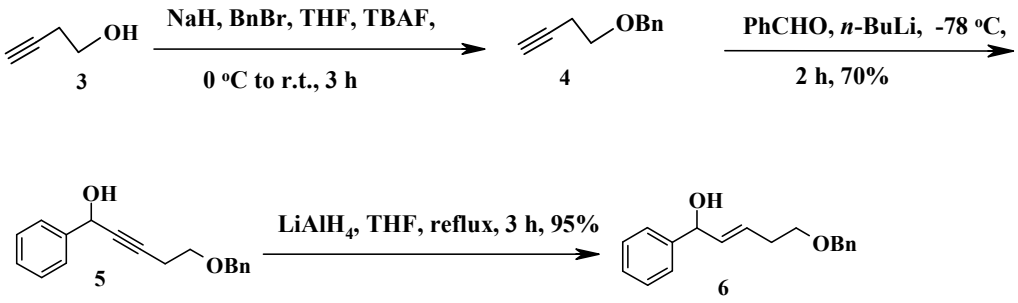


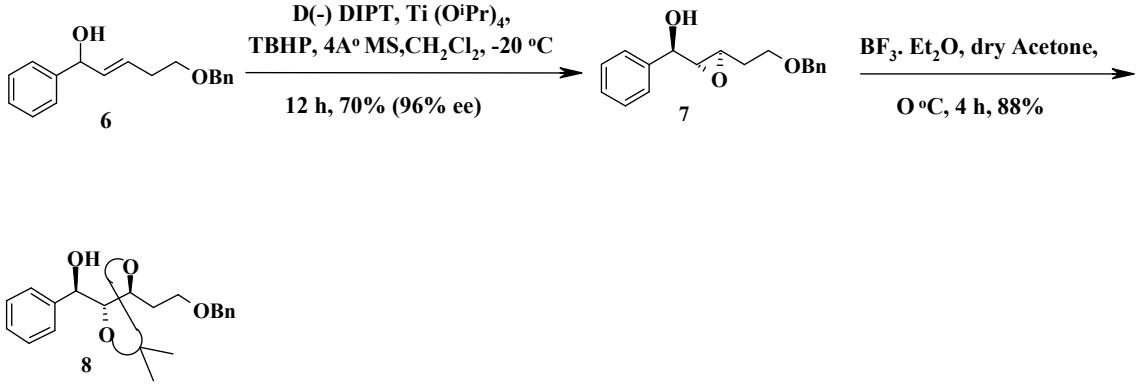
Figure 2: Retrosynthetic analysis of goniothalesdiol A **1**.

Our synthesis began with protection of homopropargyl alcohol **3** as its benzyl ether **4** by treating with NaH and benzyl bromide. The ether **4** was treated with *n*-BuLi in THF to generate the lithium acetylide, which was subsequently reacted with benzaldehyde to give propargyl alcohol **5**. The C-C triple bond of alcohol **5** was then reduced with $LiAlH_4$ in THF to afford allyl alcohol **6** with *trans* C-C double bond **(Scheme 1)**.



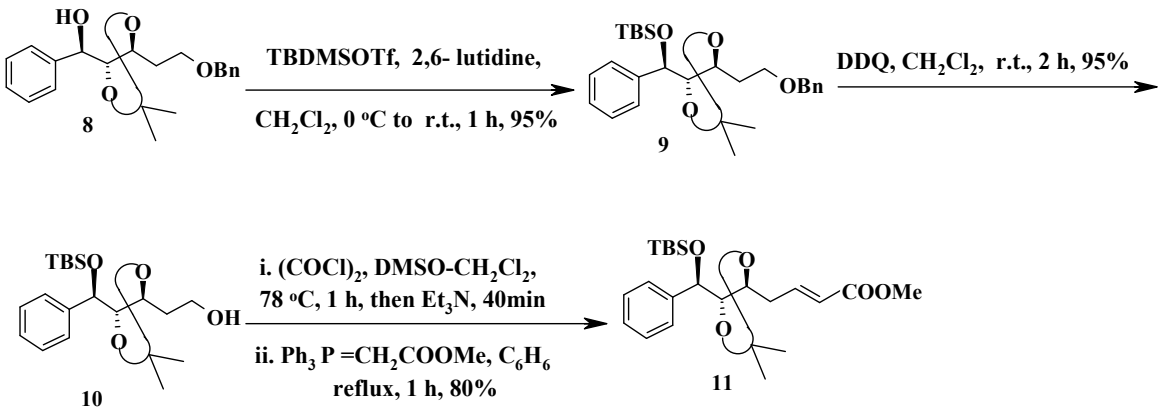
Scheme 1

The key intermediate epoxy alcohol **7** was prepared by the kinetic resolution of Sharpless asymmetric epoxidation of **6** using D(-)-DIPT, $Ti(O^iPr)_4$ and TBHP (80% yield, 96% *ee*). Compound **7** was treated with anhydrous acetone in the presence of $BF_3.Et_2O$ at 0 °C to furnish the acetonide **8** in 88% yield **(Scheme 2)**.



Scheme 2

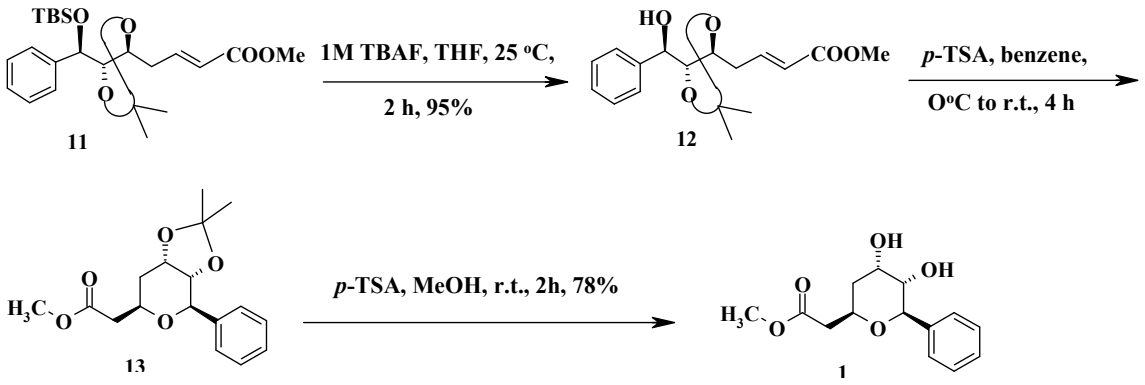
The chiral precursor **8** was protected as its TBS ether **9** in 95% yield using TBDMSOTf and 2,6- lutidine. Oxidative cleavage of ether **9** with DDQ gave the primary alcohol **10** in 95% yield.



Scheme 3

The swern oxidation of **10** gave the corresponding aldehyde in quantitative yield, which was further treated with stabilized two-carbon Wittig ylide (Ph_3PCH_2COOMe) in refluxing benzene to furnish the *α,β*- unsaturated ester **11** with *trans* configuration in 80% yield **(Scheme 3)**.

The TBDMS ether of *α,β*- unsaturated ester **11** was deprotected by treating with TBAF in dry tetra hydropyran at room temperature to afforded the hydroxy ester **12** in 95% yield. Compound **12** was treated with *p*-TSA in benzene at room temperature to form the pyran skeleton in **13** by means of intramolecular oxy-Michael addition[12] of -OH group at C(2) onto the (*E*)- configured C(6),C(7) double bond. Eventual deprotection of acetonide using *p*-TsOH in MeOH at room temperature accomplishes the target molecule goniothalesdiol A **1** in 78% yield **(Scheme 4).**



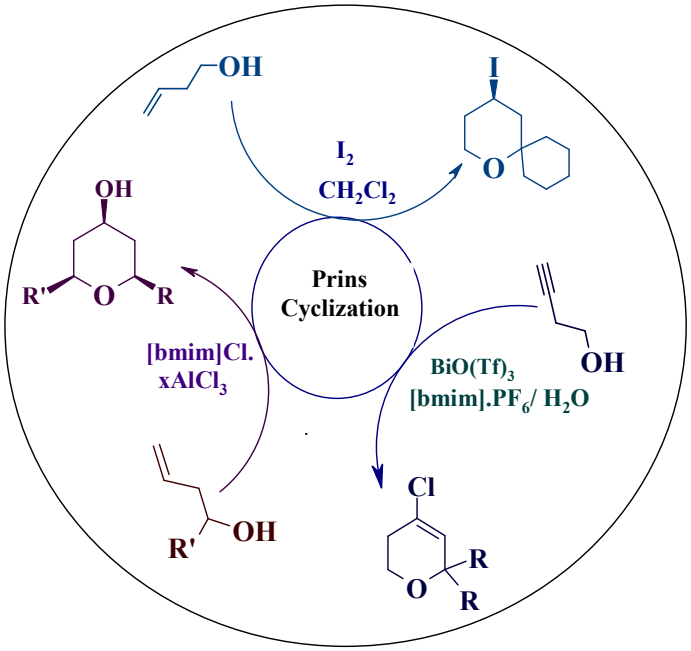
Scheme 4

In conclusion, we have described a concise stereoselective synthesis of goniothalesdiol A **1** in eleven steps from homopropargyl alcohol in a highly stereoselective manner using Chan alkyne reduction, Sharpless kinetic resolution, stereoselective epoxide opening and Wittig reaction and intramolecular oxy-Michael reaction as key steps.

CHAPTER IV: **This chapter describes the introduction to prins cyclization and syntheses of 4-substituted tetrahydropyran and dihydro-*2H*-pyran derivatives *via.* Prins cyclization.**

Introduction:-

The Prins cyclization reaction has been shown to be a very useful reaction for the construction of oxygen containing heterocyclic units that appear in many natural products. The acid catalyzed condensation of olefins with carbonyl compounds, known as the Prins reaction, is an important reaction for carbon–carbon bond formation. The Prins cyclization reaction itself proceeds largely through a chair-like transition state that allows for control of stereoisomers in the course of the reaction. The relevance of this reaction as a carbon-carbon bond forming reaction has led to the study and application of many variations. One of the most important variation is the use of Lewis acids to promote the Prins reaction (such as $BF_3{\cdot}Et_2O$, $SnCl_4$, $TiCl_4$, $TiBr_4$, $FeCl_3$, $InCl_3$). The halo-Prins reaction is one such modification with replacement of protic acids and water by lewis acids. This is the reason we desired to study Prins cyclization as a key reaction during the synthetic preparation of 4-substituted tetrahydropyrans and dihydropyrans using various lewis acidic mediums shown in following synthetic methods.



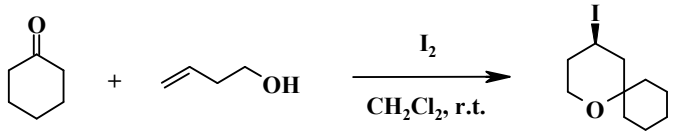
Iodine-promoted Prins-Cyclization of ketones: a facile synthesis of spirocyclic-4-iodotetrahydropyrans and 5, 6-dihydro-2H-pyrans.

The tetrahydropyran ring system is a core unit in a number of natural products. In particular, spirocyclic-4-tetrahydropyran derivatives are found in various biologically active molecules. Generally, tetrahydropyran derivatives are prepared via Prins-cyclization using acid catalysis. Although a large number of methods are available for the Prins-cyclization of aldehydes, only a few procedures are reported for ketones. Therefore, the development of a simple and convenient method involving inexpensive and readily available reagents would extend the scope of the Prins-cyclization in natural product synthesis.

Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products with high selectivity in excellent yields. Owing to advantages associated with this eco-friendly catalyst, the mild lewis acidity associated with molecular iodine has been explored as a powerful reagent for various organic transformations.

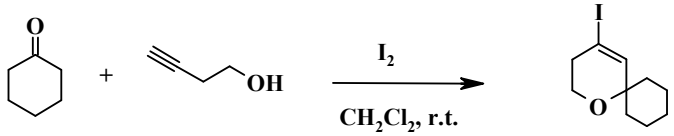
In this article, we report an efficient and metal catalyst free Prins-cyclization for the rapid synthesis of spirocyclic tetrahydropyrans from homoallylic alcohols and ketones using

molecular iodine under neutral conditions. Accordingly, treatment of 3-buten-1-ol with cyclohexanone in the presence of molecular iodine at ambient temperature for 30 min gave the corresponding 4-iodotetrahydropyran in 96% yield **(Scheme 1).**



Scheme- 1

Similarly, various ketones to give the respective spirocyclic-4-iodotetrahydro-pyrans in excellent yield. Encouraged by the results obtained with 3-buten-1-ol, we turned our attention to various substituted homoallylic alcohols. Furthermore, simple homopropargylic alcohol underwent smooth coupling with cyclohexanone to produce spirocyclic dihydropyran derivative **(Scheme 2).**



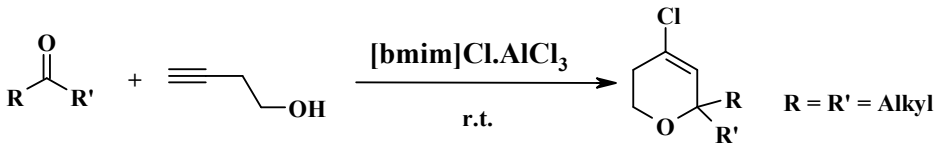
Scheme-2

Likewise, 3-pentyn-1-ol also reacted well with several ketones to generate 2,3,4-trisubstituted pyran derivatives in high yields under similar conditions. As solvent, dichloromethane appeared to give the best result. In all cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and the products were obtained in excellent yields with high diastereoselectivity and only a single isomer was obtained in each reaction, the structure of which was confirmed by ^{1}H NMR and also by comparison with authentic samples. The scope and generality of this Prins-cyclization process is illustrated with respect to various ketones and homoallylic and homopropargylic alcohols.

Chloroaluminate ionic liquid promoted Prins type cyclization: a facile synthesis of 4-chloro -5, 6- dihydro-*2H*-pyran derivatives.

The chloro vinyl group in the moiety is responsible for the activity exerted by diverse marine natural products such as aplysiapyranoids A-D and furoplocamioids A-C, are halogenated monoterpenes oxacyclic skeletons. Accordingly, we synthesize diverse aliphatic, aromatic analogues containing 4-chlorodihydropyrans and spirocyclic 2-alkyl-4-chloro dihydropyran. In this respect, ionic liquids are attracting growing interest as alternative reaction media for various chemical and biotransformations. In particular, chloroaluminate ionic liquids are having Lewis acidity, which can be varied over a wide range, and their intrinsic ability to solvate a variety of substances. These ionic liquids are easily prepared from $AlCl_3$ and 1-butyl-3-methylimidazolium chloride. These chloroaluminate ionic liquids have negligible vapour pressures, making them useful alternatives to conventional molecular organic solvents for various synthetically useful transformations. Furthermore, chloroaluminate ionic liquids play dual roles both as Lewis acid catalyst and as solvent.

In view of the emerging importance of the use of Ionic liquids as cost-effective and environmentally benign catalysts, we herein describe a simple and efficient protocol for the cyclization reactions of aldehydes and ketones with homopropargylic alcohols to produce dihydropyrans using 1-n-butyl-3-methylimidazolium chloroaluminate [bmim]Cl·$AlCl_3$ (N = 0.56-0.67) ionic liquid under mild reaction conditions **(Scheme 3)**.



Scheme 3

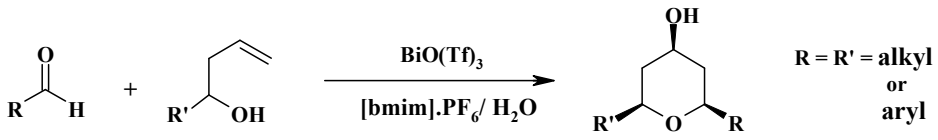
In this article, we report an efficient chloroaluminate ionic liquid mediated Prins-cyclization for the rapid synthesis of spirocyclic dihydropyrans from homopropargylic alcohols along with symmetrical ketones using 1-n-butyl-3-methylimidazolium chloroaluminate. Accordingly, treatment of 3-buten-1-ol with cyclohexanone in the presence of [bmim]Cl·$AlCl_3$

ionic liquid at ambient temperature within 5-10 min gave the corresponding spirocyclic 2-alkyl-4-chloro-5,6-hydropyran in good yield and in this case the formation of single product was observed.

In a similar manner, various aromatic and aliphatic aldehydes underwent smooth cyclization reaction with homopropargylic alcohols to give the corresponding dihydropyran derivatives in high yields with mixture of the isomers were observed by TLC and ^{1}HNMR spectrum. This is due to the formation of the diastereomers in the later case.

Bismuth triflate catalyzed Prins-type cyclization in ionic liquid: synthesis of 4-tetrahydro pyranol derivatives

The acid catalyzed olefin-aldehyde condensation, known as the Prins reaction, is an important carbon-carbon bond forming reaction in organic synthesis. Especially, tetrahydropyrans hydroxylated at the 4-position are having more synthetic value. Although many synthetic methods have been reported, there is still the scope to find potential alternate approaches and the development of ecofriendly and good yield procedures would be more useful. In recent years, bismuth compounds have been attracted as ecofriendly reagents in organic synthesis. In this report, we describe the synthesis of tetrahydropyranol derivatives through the Prins-type cyclization reaction of homoallylic alcohols with aldehydes using bismuth triflate in [bmim]PF_6 solvent system.



Scheme 4

The reaction was carried out by adding benzaldehyde and 3-buten-1-ol to a mixture of bismuth triflate and [bmim]PF_6. After that, water was added to the reaction mixture at room temperature and stirring was continued for 15 min, the TLC observation showed the disappearance of starting materials. Then, the crude product was extracted with diethyl ether

and purified over silica gel, providing the product in 80% yield. As per spectral studies, the product was confirmed as *cis*- diastereoisomer and compared the literature data **(Scheme 4).** Similarly, various aldehydes reacted smoothly with homoallylic alcohols to give the corresponding tetrahydropyranol derivatives in good yield.

In summary, we have described a green protocol for the preparation of tetrahydropyranol derivatives through the Prins-type cyclization using bismuth triflate and [bmim] PF_6. The attractive features of this process are the recyclability, mild reaction conditions, ecofriendly reagent, and cleaner reactions with good yields, which make it a useful process for the synthesis of tetrahydropyran core structure.

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***** Experimental at the end of each chapter provides detailed experimental procedures, tabulated spectral data and spectra of all new compounds

Note:- ***Compound numbers in the synopsis are different from those present in the thesis.***