

**Ring-closing metathesis: Synthesis Relgro,10'-Oxorelgro, (3*R*,4*S*)-4-Hydroxylasiodiplodin, (3*R*,4*R*)-4-Hydroxy-de-*O*-methyl-lasiodiplodin, 8,9- Dihydrogreensporone D, Dechlorogreensporone F and Greensporone F.**

**Chapter I: This chapter is further divided into two sections.**

**Section A:** Importance of natural product synthesis and a brief introduction to Resorecylic acid lactones.

**Section B:** Brief Introduction of Ring Closing Metathesis Reaction .

**Chapter II:** First total syntheses of proposed structures of Relgro and 10'-Oxorelgro

**Chapter-III: This chapter is further divided into two sections.**

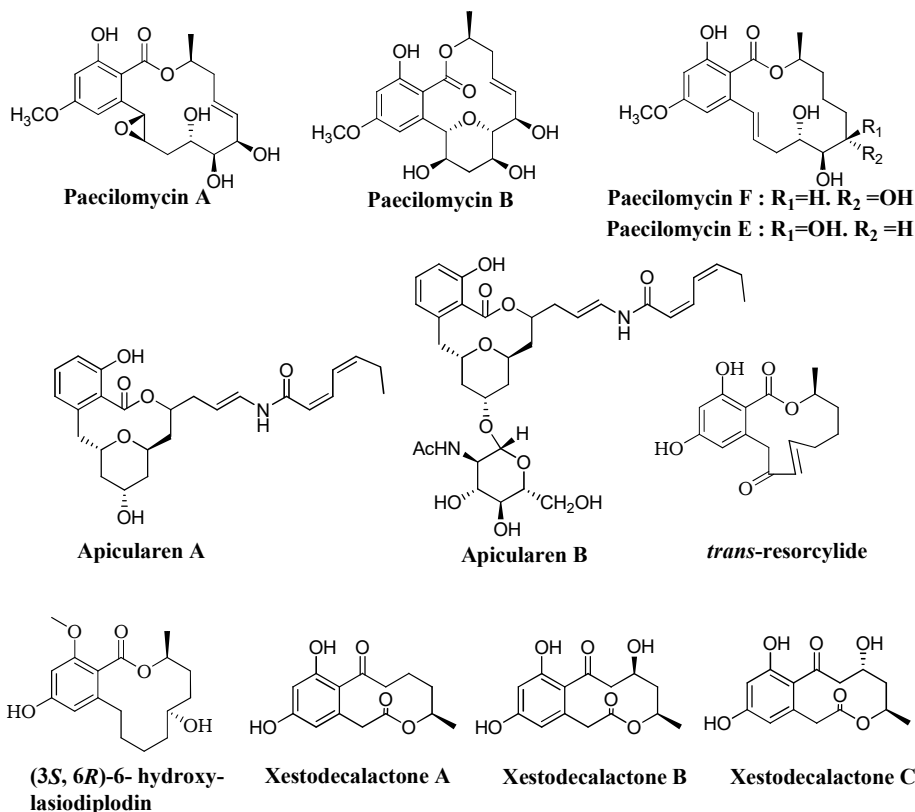
**Section A:** Biological background of lasiodiplodins including its isolation and previous synthetic approaches.

**Section B:** Stereo selective total Syntheses of (3*R*,4*S*)-4-hydroxylasiodiplodin and (3*R*,4*R*)-4-hydroxy-de-*O*-methyl-lasiodiplodin.

**Chapter-IV:** First Stereoselective total Syntheses of 8,9- Dihydrogreen sporone D, Dechlorogreensporone F and Greensporone F.

## CHAPTER I:

**Statement of problem:** Importance of natural product synthesis and a brief introduction to Resorcylic acid lactones.



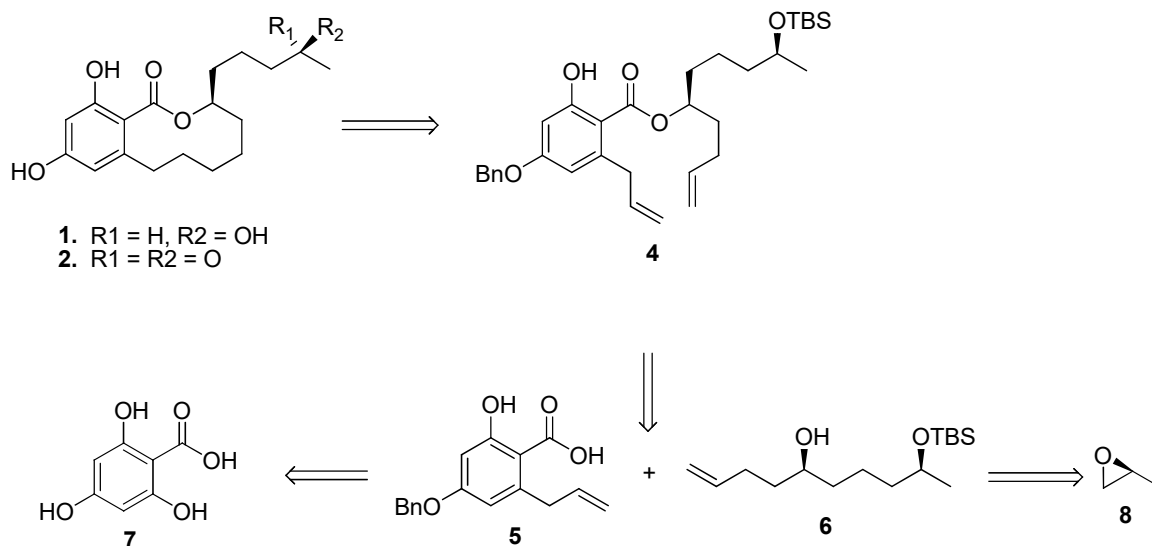
## CHAPTER II

## Introduction:

- A 10-membered β-resorcylic macrolide, relgro was isolated along with other metabolites by panichlert et al., from the seagrass-derived fungus *Fusarium* sp. PSU -ES73. The fungus obtained from the leaves of *T.hemprichiiseagrass* found in Trang Province, Thailand. P.Saetang and co-workers established absolute configuration of relgro and 10'-Oxorelgro in 2016.
- Structurally, relgro has two stereogeniccenters at C-6' and C-10' whereas 10'-Oxorelgro has only one stereogeniccenters at C-6' and carbonyl functionality at C-10'. The absolute configuration at C-6' was assigned by comparing the Cotton effect at 266 nm in CD spectrum with that of 3R, 5S-Sonnerlactone and the absolute configuration of the secondary alcohol at C-10 was determined on the basis of Mosher ester analysis.

**Statement of problem:** First total syntheses of Relgro, 10'-Oxorelgro and its structural elucidation.

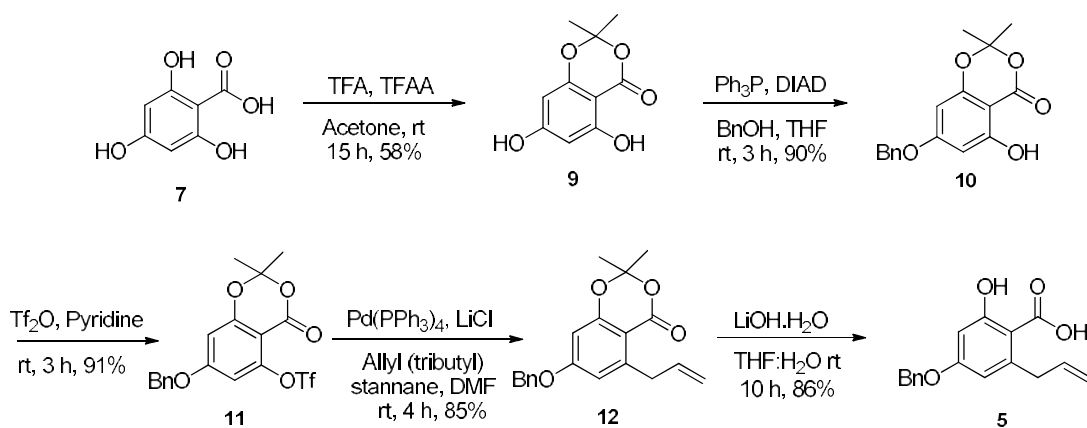
### Retrosynthetic analysis of Relgro and 10'-Oxorelgro



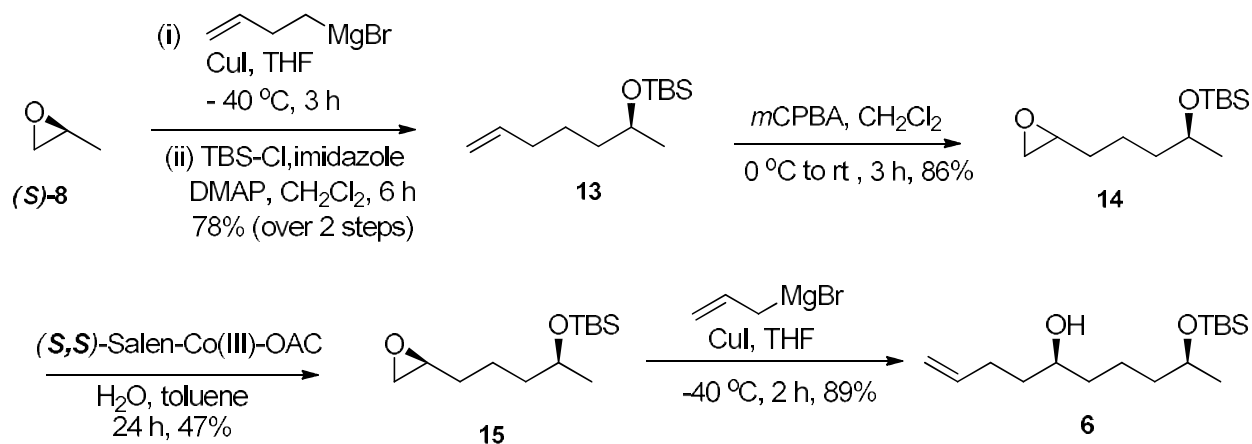
### Results and discussion:

The total synthesis of **Relgro** and **10'-Oxorelgro** commenced with commercially available 2,4,6-trihydroxybenzoic acid **7**. This synthesis has been achieved using following key reactions: Stille coupling to obtain aromatic acid **5** and chiral epoxide **8**, Jacobsen kinetic resolution to yield alcohol **6**, the coupling reaction of fragments by utilising EDC promoted coupling and RCM reaction.

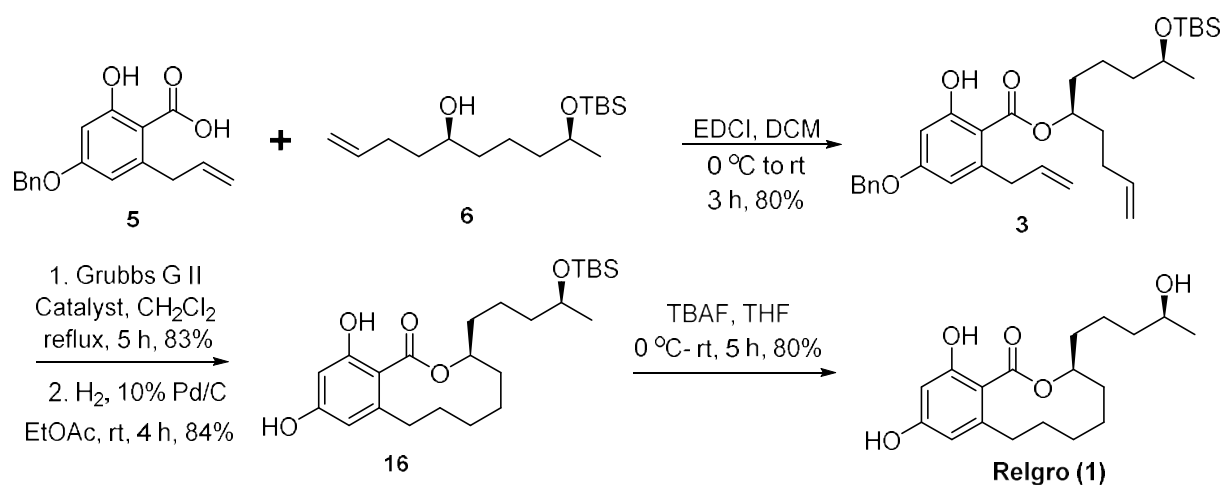
### Scheme 1. Synthesis of fragment 5



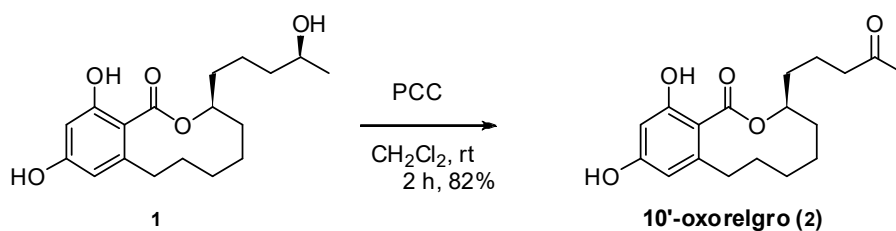
## Scheme 2. Synthesis of Fragment 6



## Scheme 3. Coupling of the fragments 5 and 6:



## Scheme 4. Total Synthesis of the 10'-Oxorelgro (2):



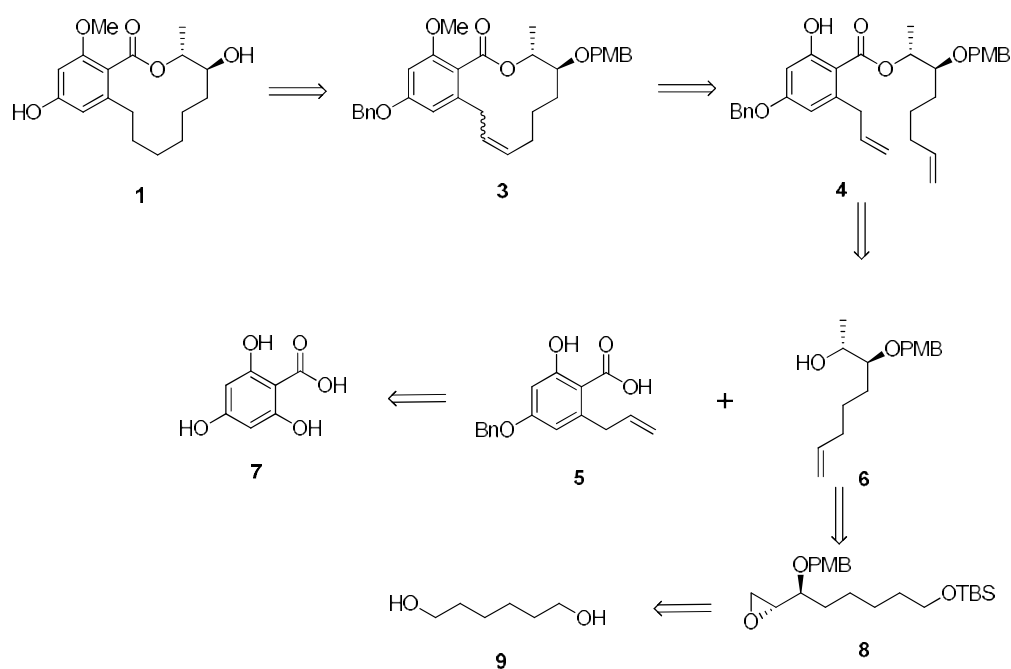
## Conclusion:

In summary, we have successfully accomplished the first total synthesis of proposed relgro (**1**) and 10'-oxorelgr (**2**) with good overall yield. Our synthetic investigations revealed that the reported structure of relgro (**1**) and 10'-oxorelgr (**2**) needs revision. We hereby suggesting the structure of relgro might be with 6'*S*, 10'*S* configuration. The real structure of 10'-oxorelgr (**2**) might be with 6'*S* configuration. The synthetic strategy delineated here includes Stille coupling, EDCI promoted coupling reaction, Jacobsen hydrolytic kinetic resolution and ring-closing metathesis. The synthetic strategy explored here may also be useful to synthesize a number of related RALs. Further, synthetic efforts towards structural verification of relgro and 10'-oxorelgr under investigation in our laboratory.

## CHAPTER III:

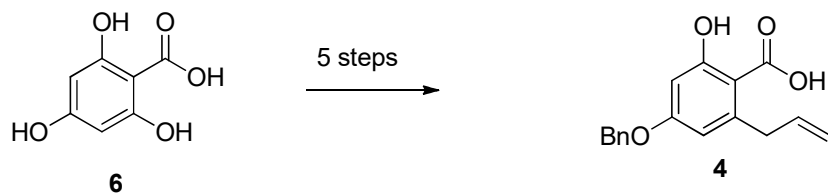
**Statement of problem:** Stereoselective total Syntheses of (3*R*,4*S*)-4-hydroxylasiodiplodin, (3*R*,4*R*)-4-hydroxy-de-O-methyl-lasiodiplodin.

### Scheme 1. Retrosynthetic Analysis of (3*R*,4*S*)-4-hydroxylasiodiplodin (**1**)

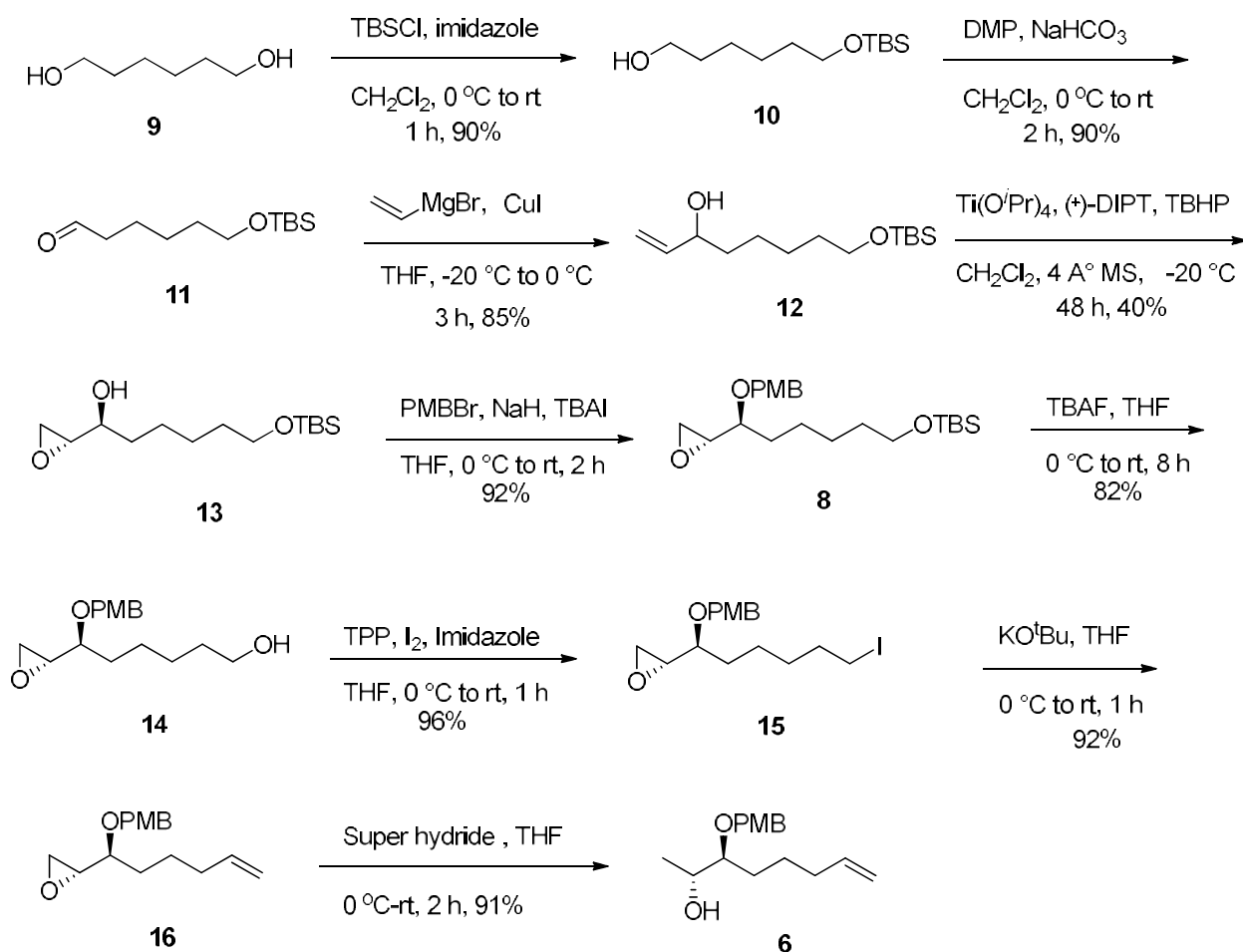


## Results and discussion:

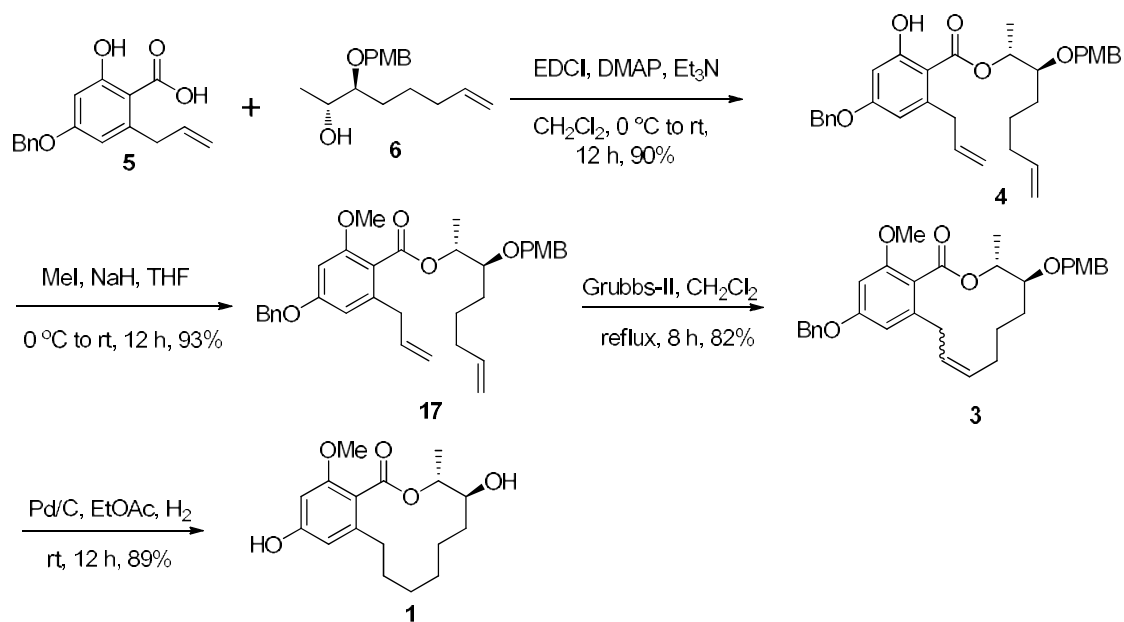
## Scheme 2. Synthesis of epoxide fragment 4



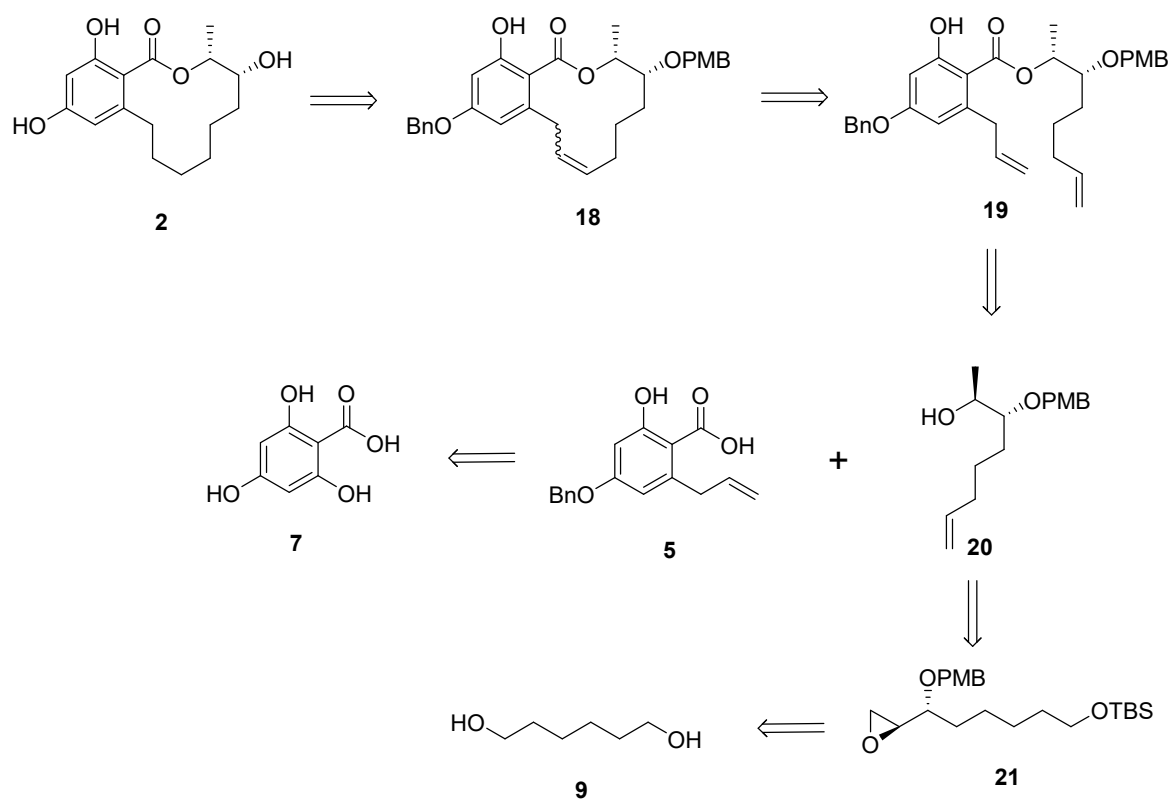
## Scheme 3. Synthesis fragment 6



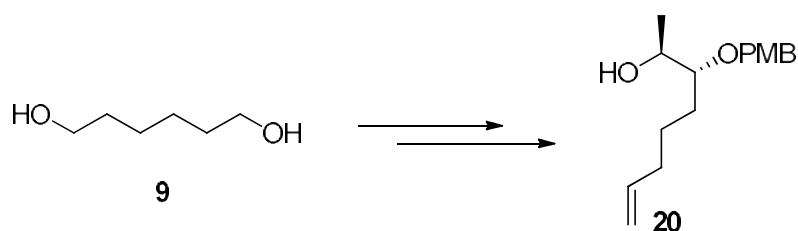
## Scheme 4. Total Synthesis (3R,4S)-4-hydroxylasiodiplodin (1)



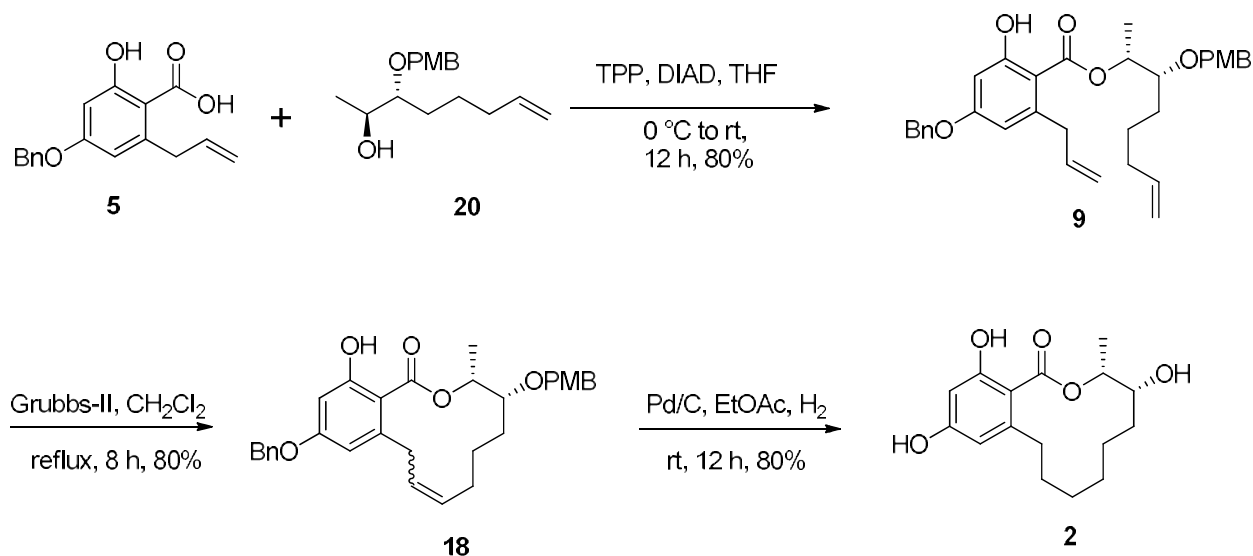
## Retrosynthesis of (3R,4R)-4-hydroxy-de-O-methyl-lasiodiplodin (2)



## Scheme 3. Synthesis fragment 20



## Scheme 3. Total synthesis of (3R,4R)-4-hydroxy-de-O-methyl-lasiodiplodin (2)



## Conclusion:

We have demonstrated an efficient, highly stereoselective approach to accomplish the first total synthesis of (3R,4R)-4-hydroxy-de-O-methyl-lasiodiplodin from commercially available 1,6-hexanediol. The total synthesis of (3R,4S)-4-hydroxylasiodiplodin has been accomplished by employing palladium catalyzed Stille coupling, EDC promoted coupling and ring-closing metathesis as the key steps. This method can be conveniently utilized for the synthesis of different other resorcylic macrolides towards the development of such class of compounds.

## CHAPTER IV

## Introduction:

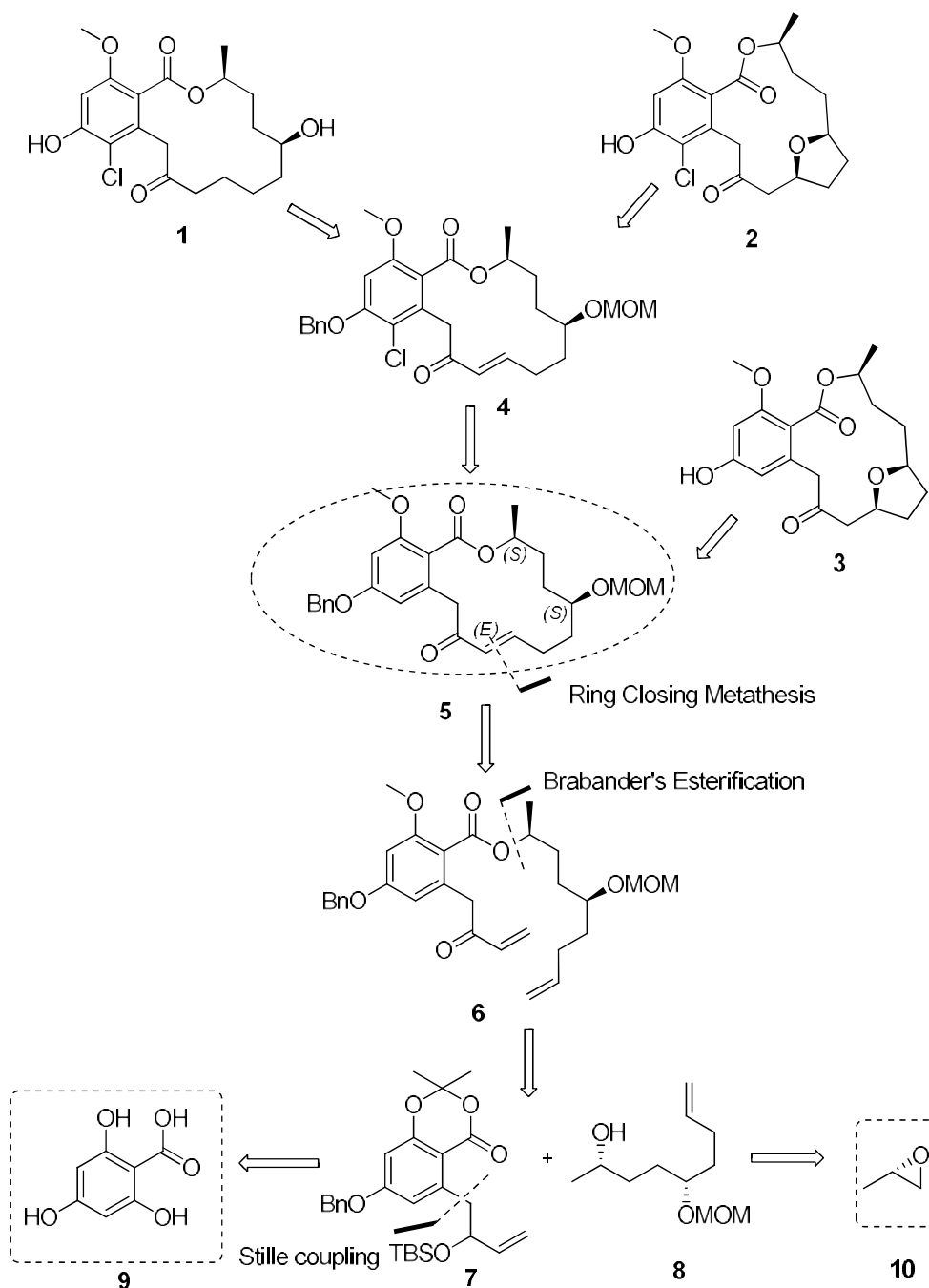
In 2014 Nicholas H. oberlier reported the isolation of 14 new 14-membered resorcylicacid lactones from fresh water aquatic fungus *Halenospora* sp. collected in North Carolina. All these structures were elucidated through spectrometric and



spectroscopic techniques. Except 8 and 12, all isolated compounds were tested against 2 cancer cell lines that are HT-9(Colon) and MDA-MB-435(Melanoma).

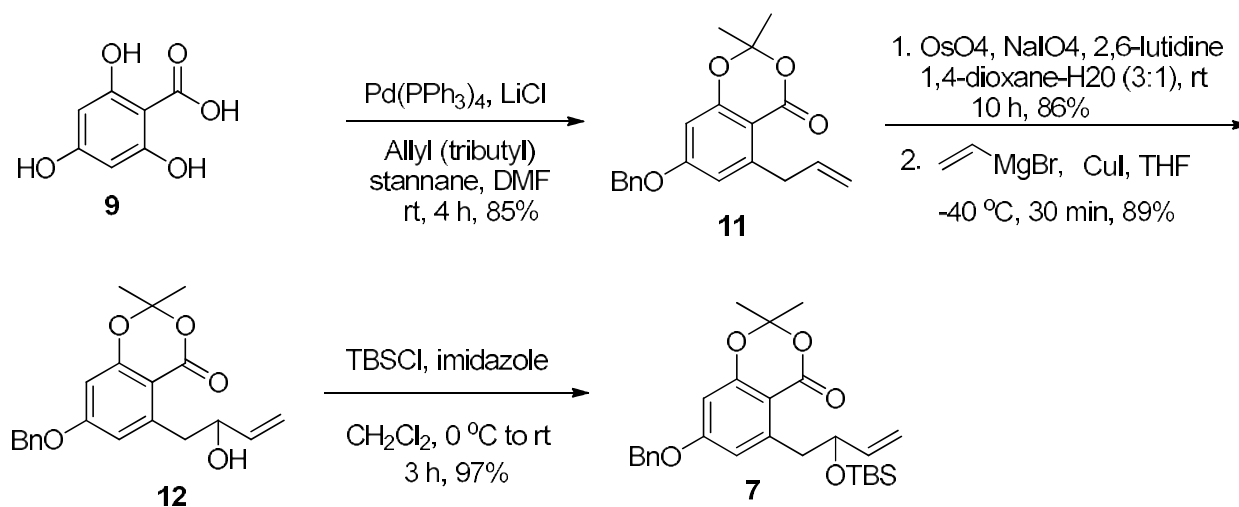
**Statement of problem:** First Stereoselective total Syntheses of 8,9-dihydrogreensporone D, Dechlorogreensporone F and Greensporone F.

### Scheme 1. Retrosynthetic analysis

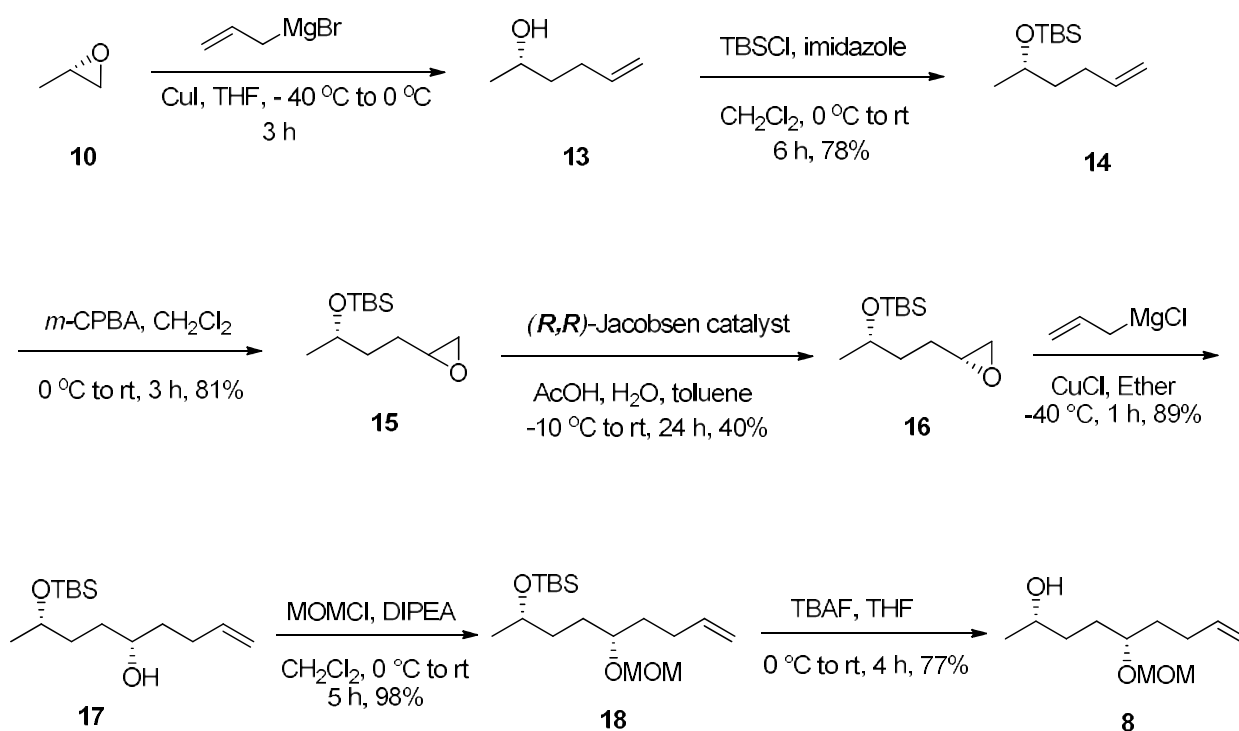


## Results and discussion:

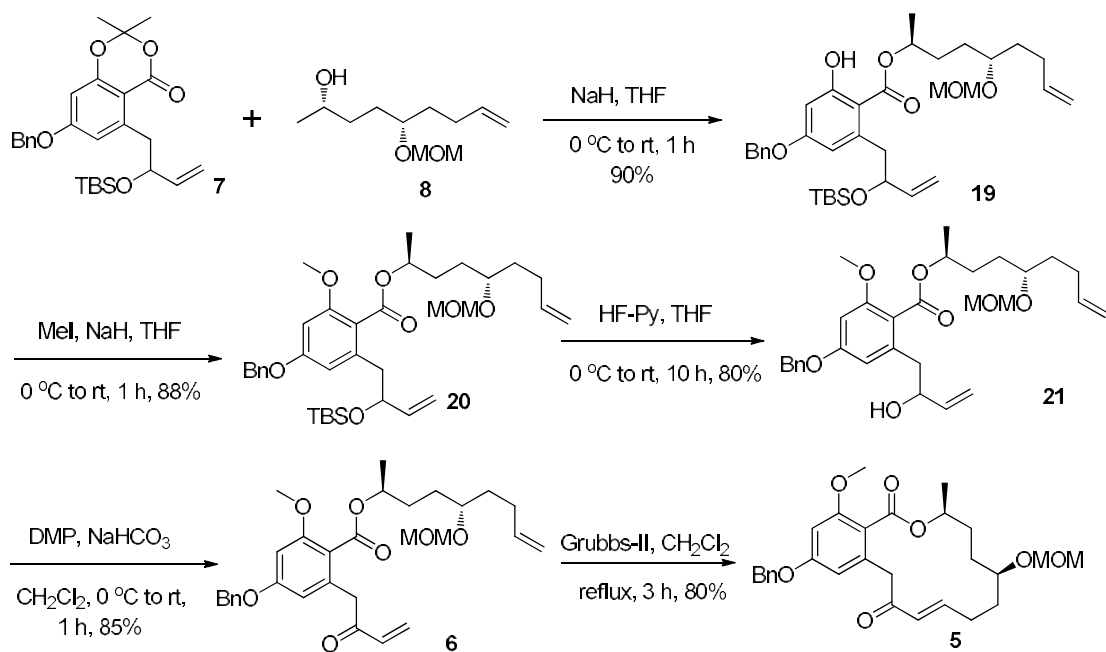
## Scheme 2. Synthesis of aldehyde fragment 7



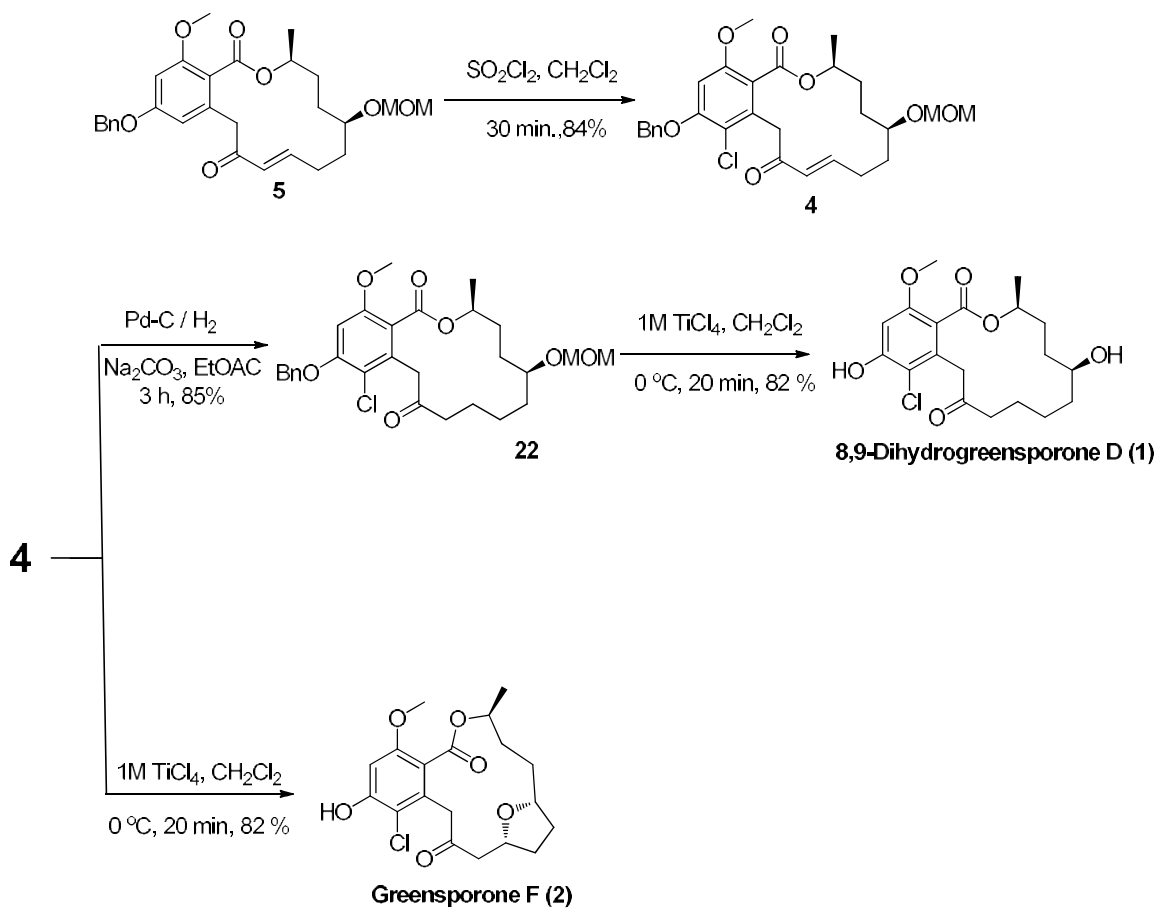
## Scheme 3. Synthesis of sulphone fragment 8



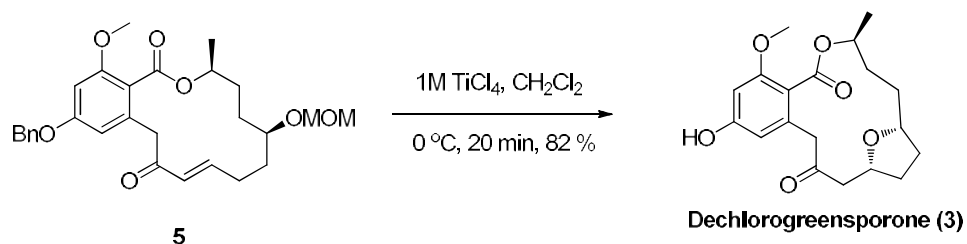
## Scheme 4. Coupling of fragments 7 and 8



**Scheme 5. Total synthesis 8,9- dihydrogreensporone D (1) and Greensporone F (2).**



**Scheme 6. Total synthesis of Dechlorogreensporone F (3)**

**Conclusion:**

The First total syntheses of 8,9-Dihydrogreensporone D (**1**), Greensporone F (**2**) and Dechlorogreensporone F (**3**) have been achieved in a concise manner following Danishefsky reaction, Mitsunobu reaction, Stille cross coupling, acid catalyzed transannularoxa-Michael cyclization, ring-closing metathesis (RCM) reaction, and De Brabander's esterification as key reactions. The strategy delineated here can be useful for the synthesis of other related RALs.