# CHAPTER – II

## Towards the Synthesis of the Macrocyclic Core of Pladienolides A and B

# CHAPTER-2 Towards the Synthesis of the Macrocyclic Core of Pladienolides A and B.

## 2.1. INTRODUCTION

Macrolides are products of actinomycetes (soil bacteria) or semi-synthetic derivatives of them. Erythromycin, a polyketide macrolide, is an orally effextive antibiotic discovered in 1952 in the metabolic products of a strain of *Streptomyces erythreus*, originally obtained from a soil sample. The term polyketide or polypropionate was coined to refer to natural products containing multiple carbonyl and hydroxyl groups, each separated by a methylene spacer unit. Polyketides are generally non essential molecules that are synthesized as secondary metabolites following the onset of stationary or unfavorable circumstances in the life cycle of a microorganism. Micro organisims make a wealth of unusual metabolites that have a secondary role in the organism's ontogeny, such as self-defence, aggression, or even communication, as the need arises. Polyketides are such a group of secondary metabolites, exhibiting remarkable diversity both in terms of their structure and function. Polyketide natural products are known to possess a wealth of pharmacologically important activities, including antimicrobial, antifungal, antiparasitic, antitumor and agrochemical properties. These metabolites are ubiquitous in distribution and have been reported from organisms as diverse as bacteria, fungi, plants, insects, dinoflagellates, mollusks and sponges. The wide spectrum of activity of polyketides make them economically, clinically and industrially the most sought after molecules. Many polyketide products are well known compounds such as erythromycin A, a broad spectrum macrolide antibiotic, Oxytetracycline and Reserveratrol are also antibiotic in nature, Laulimalide and Epothilone B (anticancer agent), Avermectin (antihelmintic agnet), or the immunosuppresants FK506, Pironetin and Rapamycin. Oleandomycin,

Methymycin, Rifamycin S, Amphotericin (antifungal and antibiotic), lovastatin and compactin (cardiovascular agent), are a few more of the thousands of polyketides discovered so far (Figure 1). Polyketides are usually categorized on the basis of their chemical structures.

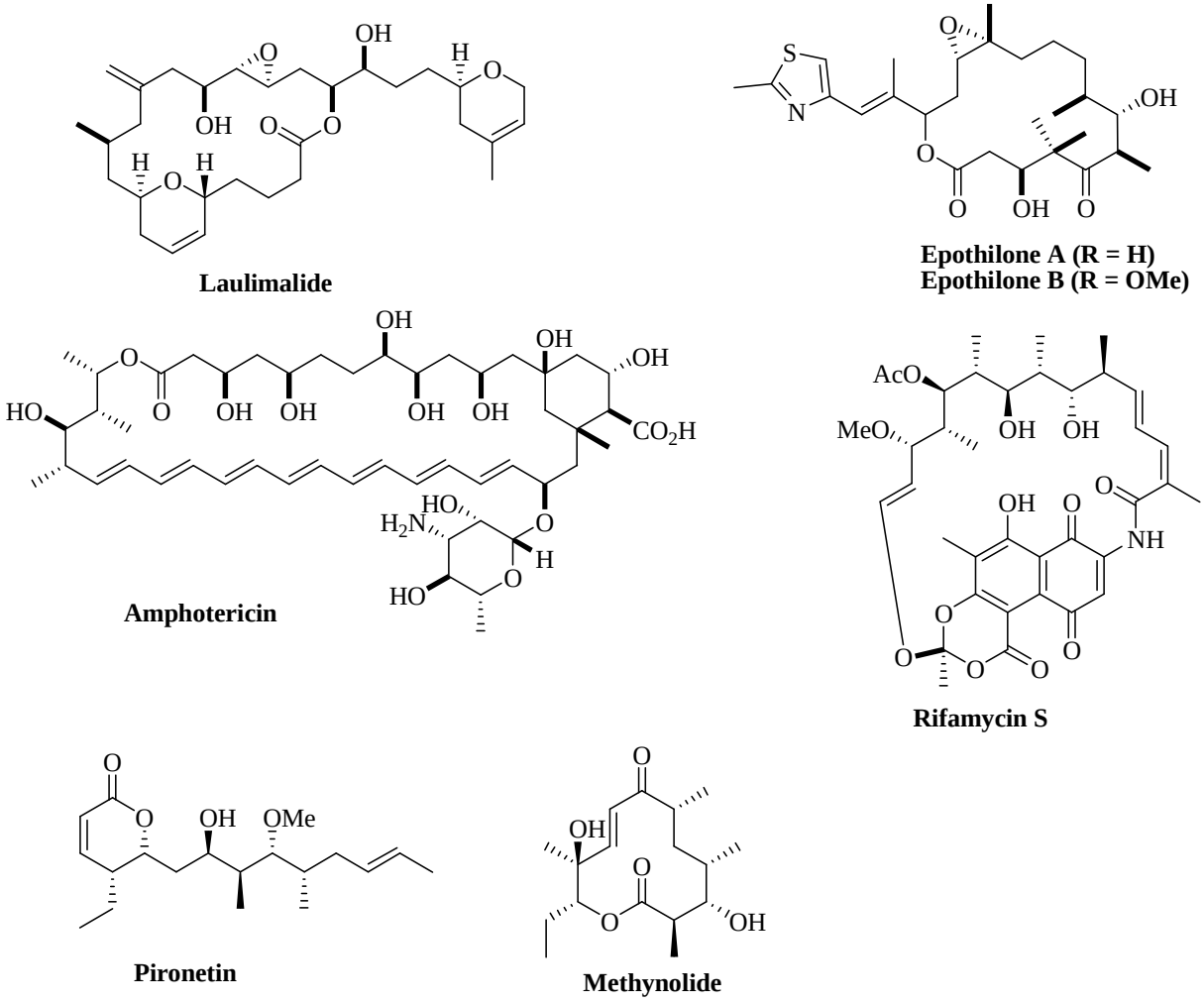



**Figure1. Some of the representative examples of polyketide natural products.**

The stereochemical and hetero functional complexity of the polypropionate derived macolide antibiotics possess a formidable challenge for stereoselective synthesis, and

these structures have provided the stimulus for the development of a host of new enantio- and diastereoselective bond constructions.

## Location of the macrolide binding site in the ribosome and the mechanism of action.

The macrolide antibiotics inhibit protein synthesis by binding to the 23S Rrna molecule (in the 50S subunit) of the bacterial ribosome blocking the exit of the growing peptide chain of sensitive microorganisms. (Human do not have 50S ribosomal subunits, but have ribosomes composed of 40S and 60S subunits). Certain resistant microorganisms with mutational changes in components of this subunit of the ribsome fail to bind the drug. The association between erythromycin and the ribosome is reversible and takes place only when the 50S subunit is free from tRNA molecules bearing nascent peptide chains. Grampositive bacteria accumulate about 100 times more erythromycin than do gramnegative microorganisms. The non-ionized form of the drug is considerably more permeable to cells, and this probably explains the increased antimicrobial activity that is observed in alkaline pH.

The precise mechanism of protein synthesis inhibition by macrolides depends on the specific chemical structure of the drug molecule. Ths affects its interaction with the ribsome as well as the mode of the inhibitory action. Four modes of inhibition of portein synthesis have been ascribed to macrolides: 1). Inhibition of the progression of the nascent peptide chain during early rounds of translation.[1, 2] . 2). Promotion of peptidyl tRNA dissociation from the ribosome.[3]. 3). Inhibition of peptide bond formation.[4]. 4). Interference with 50S subunit assembly.[5] All of these mechanisms have some correlation with the location of the macrolide binding site on the ribsome. The macrolide binding site is located on the large ribosomal subunit inside the nascent peptide exit tunnel near the

peptidyl transferase center. Its proximity to the peptidyl transferase center explains the inhibitory effect of some macrolides on peptide bond formation. The sugar residues at the $C_5$ position of the lactone ring protrude towards the peptidyl transferase center. The long disaccharide mycaminosemycarose side chains of the 16-memebered ring drug tylosin, spiramycin and carbomycin A stretch far enough towards the active site of the peptidyl transferase to directly interfere with the catalysis of peptide bond formation.[6] The shorter desosamine monosaccharide residues of the 14-membered ring macrolides do not reach the peptidyl transferase, which explains the lack of inhibitory effects of these drugs on the reaction of transpeptidation.[7] The main mechanism of inhibition of protein synthesis by macrolides is related to their binding in the nascent peptide exit tunnel. Several studies showed that interactions between the ribosome and the nascent peptide that take place inside the exit tunnel affect the progression of protein synthesis as well as the reactions catalyzed by the ribosomal peptidyl transferase.[8] The inhibition of peptide progression eventually results in the dissociation of peptidyl tRNA from the ribsome.

## THE POLYOXO-MACROLIDES.

The polyoxo-macrolides, produced by *Streptomyces* microorganisms, are a clinically important group of polketide antibiotics. They are characterized structurally by a 12- (e. g. methymycin), 14- (e. g. erythromycin A), or 16- membered (e. g. tylosin) lactone ring with one or more deoxy-sugars attached and with up to 12 asymmetric centers systematically incorporated into the aglycone.

Synthetic efforts directed towards the polyoxo-macrolides began in the mid 1970's with the discovery and development of new methods for constructing large-ring lactones. In particular, the introduction of efficient methods for the macrolactonization of long-chain hydroxy acids, i. e. seco-acids, by the internal esterfication of a secondary hydroxyl

group with a suitablyactivated carboxyl group meant that the synthetic problem was reduced to one of stero chemical control. Note, however, that the effectiveness of this standard deso-acid approach to poly-macrolide synthesis is critically dependent on having a seco-acid derivative which can adopt a low-energy conformation, resembling the preferred diamond-lattice of the maccrolide ring, in order to facilitate efficient cyclization by one of these methods. As a result macrolactonization yields are generally a function of seco-acid substitution pattern, stereochemistry, and protecting groups. In comparison, there are only few examples of macolide total synthesis where macrocyclization is carried out by carbon-carbon bond formation, and these are mainly in the 16 membered ring series. Further developments in this area, therefore, are anticipated.

## The biosynthesis of Polyketides.

A vast number of polyketides have been isolated, exhibiting a huge structural diversity. Inspite of the wide variety of stereochemical and oxidation state permutations represebted in these molecules, they all share their common origin fromhighly functionalized carbon chains whose assemblage is controlled by multi enzyme systems called polyketide synthases (PKSs) polyketides are synthesized by sequential reactions catalysed by a collection of enzyme activites called polyketide synthases (PKSs).[9] These are large multi enzyme protein complexes that contain a coordinated group of active sites. The biosynthesis occurs in a stepwise manner from simple 2-, 3-, 4-carbon building blocks such as acetyl-CoA, propionyl CoA, butyryl-CoA and their activated derivatives, malonylmethylmalonyl and ethylmalonyl-CoA. The key chain-building step of polyketide biosynthesis is a decarboxylative condensation analogous to the chain elongation step of classical fatty acid biosynthesis which occurs in the following well-

understood way: Unlike fatty acid biosynthesis, however, in which each successive chain elongation step is followed by a fixed sequence of keto reduction, dehydration and enoyl reduction as shown in Figure 2, the individual chain elongation intermediates of polyketide biosynthesis undergo all, some, or none of these functional group modifications, resulting in a stiking level of chemical complexity in the products. Additional degress of complexity arise from the use of different starter units and chain elongation units as well as the generation of new stereo-isomers.

## The various domains making up the polyketide synthase

*CHEMISTRY OF POLYKETIDE SYNTHASES: ROLES OF VARIOUS DOMAINS*

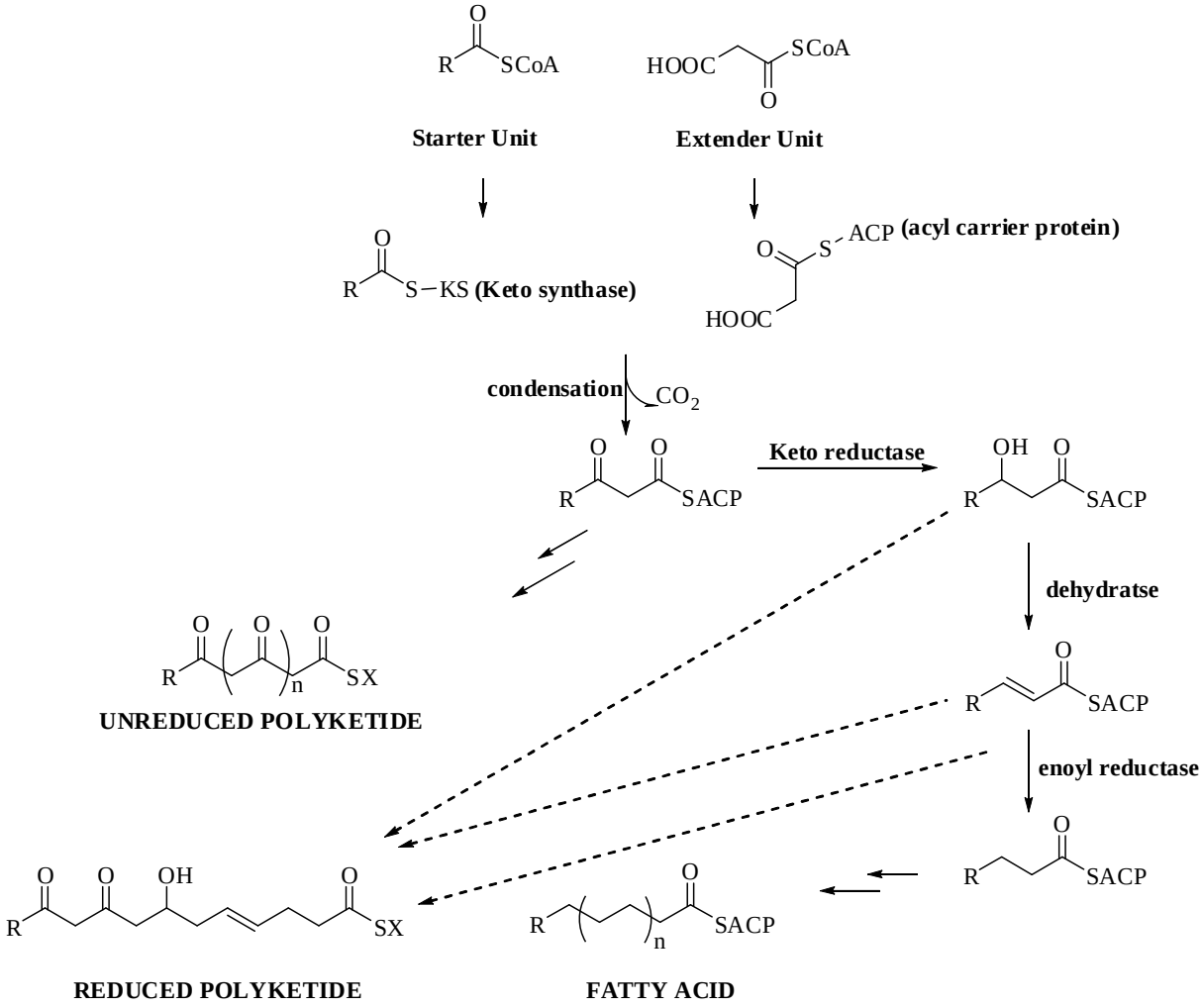



**Figure 2: Biosynthesis of polyketide units.**

Component domains of polyketides consist of acyl-transferases (AT) for the loading of starter, extender and intermediate acyl units; acyl carrier proteins (ACP) which hold the growing macrolide as a thiol ester; β-keto-acyl synthases (KS) which catalyse chain extension; β-keto reductases (KR) responsible for the first reduction to an alcohol. Dehydratases that eliminate water to give an unsaturated thiolester; enoyl reductases (ER)

which catalyse the final reduction to full saturation; and finally a thiolesterase (TE) to catalyse macrolide release and cyclisation.

## Construction of poly propionate macrolide antibiotics.

These groups of macrocyclic lactone and lactam natural products with their multiple asymmetric centres and arry of substituents and functional groups, together with their important biological activities, have been the centre of much recent synthetic interest. Four general approaches to controlling the critical $sp^3$ stereochemistry of macrolides have been developed:

(i) *ring-cleavage*, where the appropriate (*cis / trans*) relationship of asymmetric centres is first secured using the conformational bias of a small or medium ring, which is then opened to give an acyclic fragment with the stereo centers correctly related;

(ii) *Carbohydrate*,where the existing asymmetric centers and functionality of an enantiomerically-pure sugar are manipulated, often on a pyranoside or furanoside ring, which can then be easily opened (related then to (i));

(iii) *acyclic*, where new asymmetric centers are stereoselectively introduced on acylic precursor;

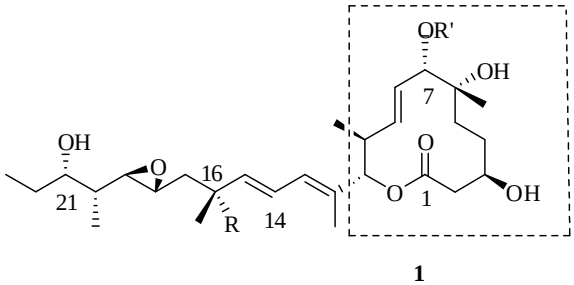
(iv) *macrocyclic*, where new asymmetric centers are stereoselectively introduced on to an intact macrolide, or other large ring, using the conformational bias of the large ring.

These conceptually different approaches all feature in the various macrolide syntheses which have so far been accomplished. Combinations of these approaches are often adopted. The intriguing stereochemical architecture present in the polyketides has attracted the imagination and thrown up a challenge to the intellect of chemists in designing new methods with increasing ease with which these skeletons can be made. Their sterecontrolled, asymmetric total synthesis has stimulated the development of new

methodologies and concepts for C-C bond formation in the context of acyclic stereocontrol. A brief and summarized survey of the metods available in the literature for the construction of polyketide skeletons is appropriate to place our efforts in context. To begin with they include: (a) *aldol* additions[10-18]; (b*) allylation and crotylation* reactions[19-22]; (c) *nitrileoxide cycloadditions*[23,24]; (d) *Hetero-Diels-alder* reactions[25] and (e) *Desymmetrization method* [26].

## 2.2. ISOLATION AND BIOLOGICAL ACTIVITY OF PLADIENOLIDES A AND B

In 2004 Sakai et al. reported the identification of seven 12-membered macrolides (pladienolide A-G), from *Streptomyces platensis* Mer-11107 by way of a cell-based assy that evaluated the suppression of hypoxia-induced gene expression controlled by the human VEGF promoter.[27] They also inhibit the growth of a variety of cancer cell lines in vitro with low nanomolar $IC_{50}$ values. COMPARE analysis with panel screening of 39 human cancer cell lines indicated that the compounds have a unique mode of antitumor action unlike those of anticancer drugs currently in clinical use. Pladienolides also cause in vivo tumor regression in several human cancer xenograft models. Intravenous treatment of several tumor xenograft models with E7107 for five consecutive days has led to completer remission as well as tumor shrinkage in a variety of tumor xenografts.




**1**

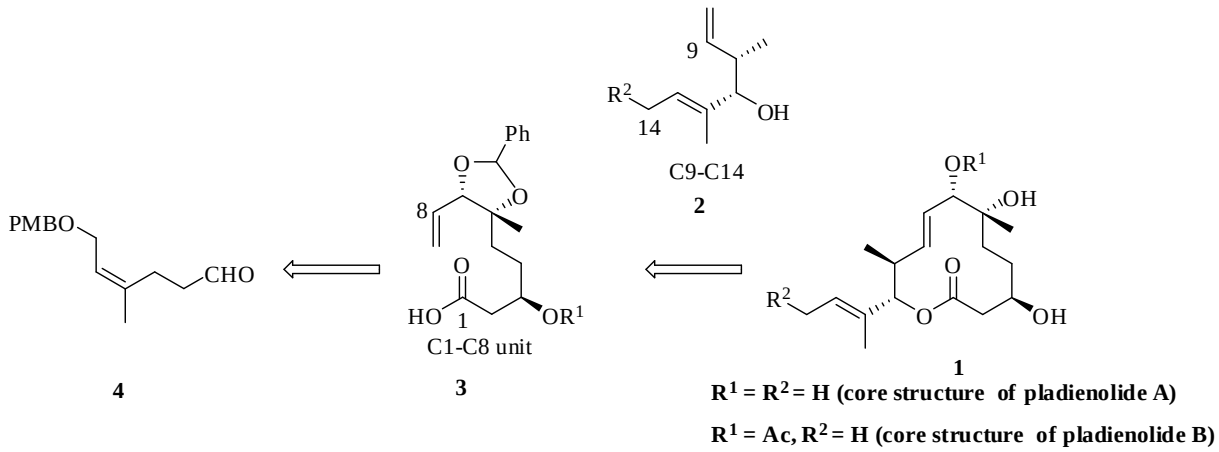
**Pladienolide A : R' = H**
**Pladienolide B : R' = Ac**

**Figure 4**

## 2.3. PREVIOUS APPROACHES FOR THE SYNTHESIS OF CORE STRUCTURE OF PLADIENOLIDE A AND B.

### 2. 3. 1. Kotake approach [28]

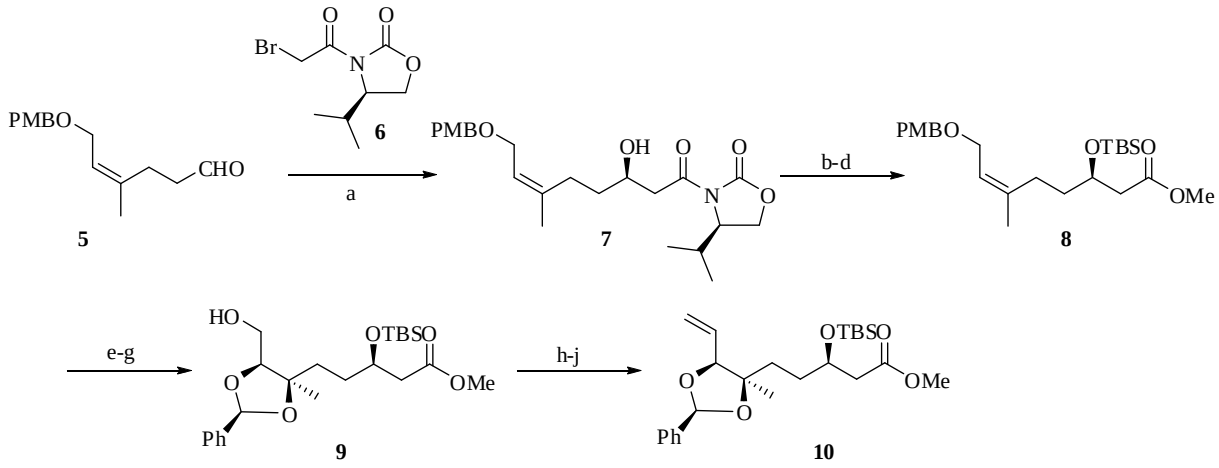
The first synthesis of pladienolide A and pladienolide B was reported in 2007. As a scheme was designed involves condensation of two fragments between a C1-C8 unit and a C9-C14 unit. The retrosynthetic analysis of these natural products pladienolide A and pladienolide B based on this strategy is shown in Scheme 1.




**Scheme 1**

The preparation of C1-C8 began with the construction of the macrolide moiety (Scheme 2). Aldehyde **5**, prepared from nerol by protection with a PMB group and regioselective ozonolysis, was subjected to the $Sm^{II}$ mediated asymmetric Reformatsky reaction described by Fukuzawa et al. using bromoacetyloxazolidinone **6** as a chiral auxiliary to afford β-hydroxyamide **7** with good diastereoselectivity. After removal of the chiral auxiliary, protection of the hydroxyl group, and methylation, ester **8** was obtained in good yield 85%. A second asymmetric reaction, the asymmetric dihydroxylation of **8**, proceeded in 76% *de*. Protection of the diastereomeric mixture of *syn*-diols with a benzylidene acetal group and subsequent removal of the terminal PMB group afforded

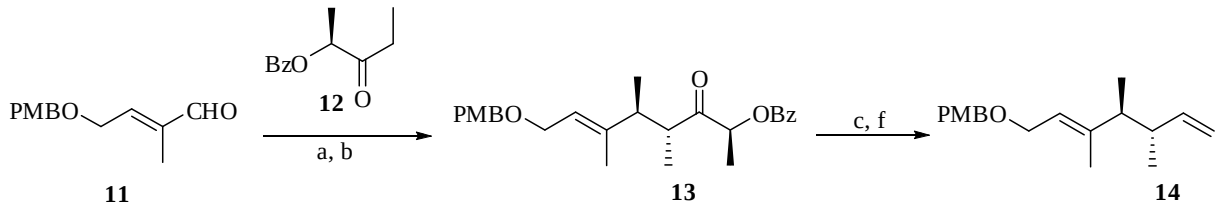
primary alcohol **9**. Recrystallization afforded **9** as a single diastereomer. Sequential oxidation, Wittig olefination, and hydrolysis gave the desired C1-C8 unit **10** in 64% yield.




**Scheme 2**

a). $Sm^0$, $CH_2I_2$, 6, THF, -78 ºC to RT, 90% (>98 *de*); b). LiOH, $H_2O_2$, THF/$H_2O$ (4:1), RT; c). TMS diazomethane, THF/MeOH (10:1), RT; d). TBSCl, imidazole, DMF, RT, 85% (3 steps); e). AD-mix-alpha, methanesulfonamide, tBuOH/$H_2$0 (1:1), 0 ºC, 92% (76 % *de*), f). benzaldehyde dimethyl acetal, PPTS, $CH_2Cl_2$, RT, 98%; g). DDQ, $CH_2Cl_2$/$H_2O$ (10:1), 0 ºC, recrytallization, 65%; h). DMP, $CH_2Cl_2$, RT, 78% (2 steps); j). LiOH, THF/MeOH/$H_2O$ (2:2:1), RT, 82%

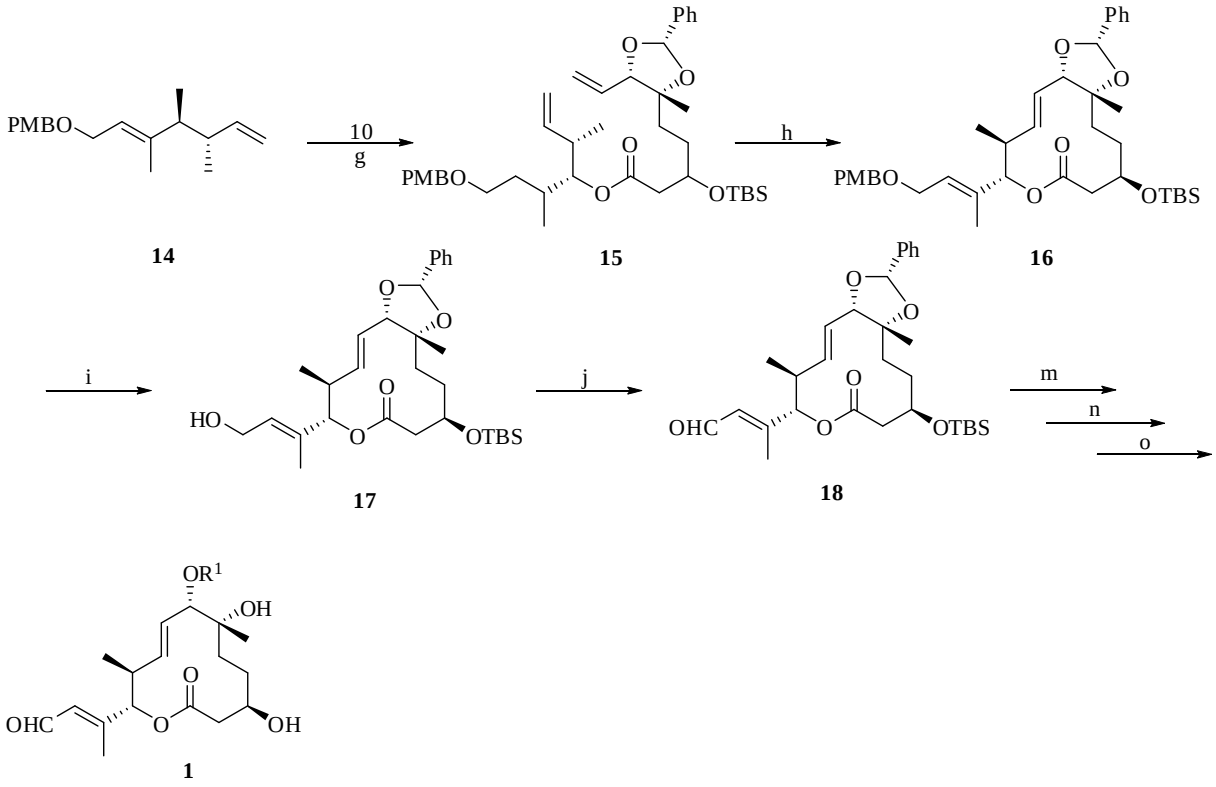
Synthesis of the C9-C14 unit began with construction of C10 and C11 stereogenic centers by an *anti*-aldol reaction developed by Paterson et al. by using aldehyde **11** and lactate derived chiral ketone **12** (Scheme 3). This reaction proceeded with excellent diastereoselectivity (98 % *de*), and the desired *anti*-aldol product **13** was obtained in pure form after recrytallization and protection with a TBS group. An additional four steps, including oxidative cleavage of the α-benzoyloxy ketone, gave desired C9-C14 unit **14**.




**Scheme 3**

a) **10**, $Cy_2BCl$, $Me_2NEt$, Diethyl ether, -78 °C to -26 °C, recrystallization, 81% (>99% *de*); b) TBSOTf, 2, 6-lutidine, $CH_2Cl_2$, -78 °C , quant.; c) $LiBH_4$, THF, -78 °C to RT; d) $NaIO_4$, THF/$H_2O$ (4:1), RT; e) methyltriphenylphosphonium iodide, *n*BuLi, THF, -15 °C, 73% (3steps); f) 1 N HCl, MeCN, RT, 99%

An esterfication reaction between C1-C8 unit **10** and C9-C14 unit **14** by means of the method described by Yamaguchi and co-workers afforded bis-terminal olefin **15** (Scheme 4). Next the key RCM reaction to construct the macrolide moiety by using Hoveyda-Grubbs catalyst in refluxing toluene afforded the desired macrolide **16** was obtained 46% yield. Removal of the PMB group and subsequent oxidation with DMP gave macrolide **18**.



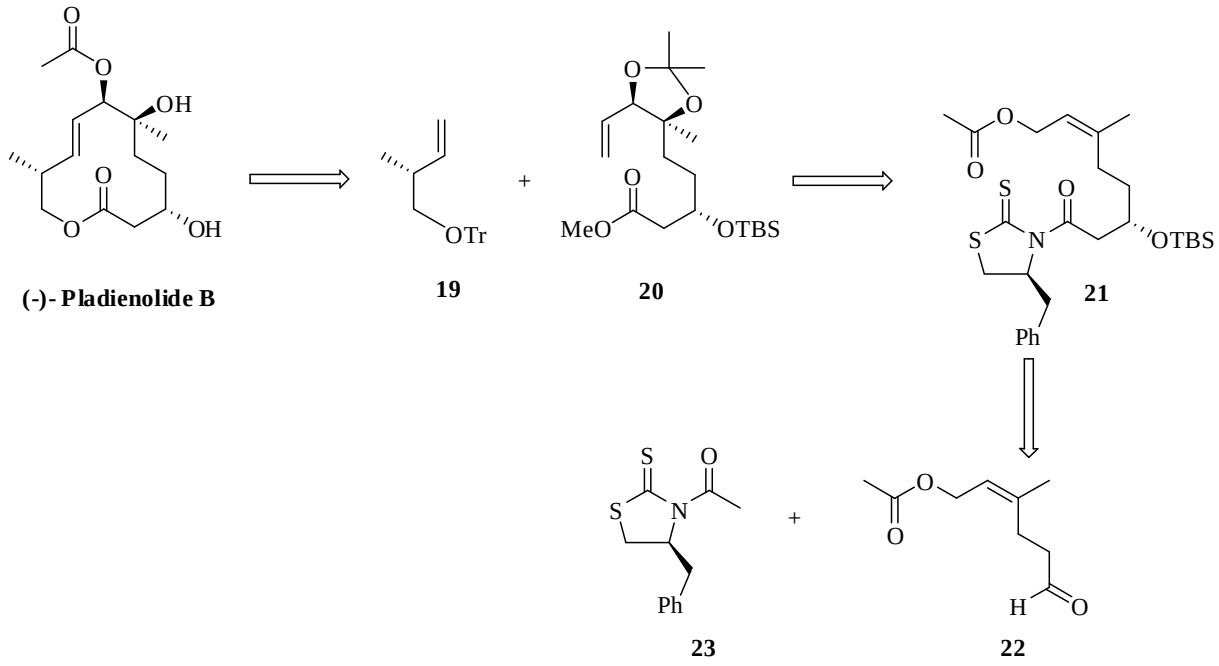

**Scheme 4**

a) **8,** 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF, 0 °C to RT, then **13**, DMAP, toluene, RT, 93%; h) 2nd generation Hoveyda-Grubbs catalyst, toluene, reflux, 46%; i) DDQ, $CH_2Cl_2$ / pH 7 buffer (10:1), RT, 80%; j) DMP, $CH_2Cl_2$, RT, quant,; k) TBAF, THF, RT, quant.; l) dichloroacetic anhydride, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C, quant.; m) PPTS, MeOH, RT, 64%; n) $K_2CO_3$, MeOH, RT, 96%; o) aceticanhydride, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C, 82%

The two silyl groups (one is at macrolide moiety and another is at side chain moiety) were removed before the benzylidene group, and the resulting hydroxyl group at the C21-position opened the neighboring epoxide to form a tetrahydrofurn ring. Therefore, the two silyl groups were converted into acid-stable dichloroacetyl groups, the benzylidene group was removed by treatment with PPTS in MeOH over 46 h to afford 6,7-diol. Methanolysis of gave macroclic core of pladienolide A (**1**). The final regioselective acetylation proceeded as expected, and macocyclic core of pladienolide B (**2**) was obtained in good yield.

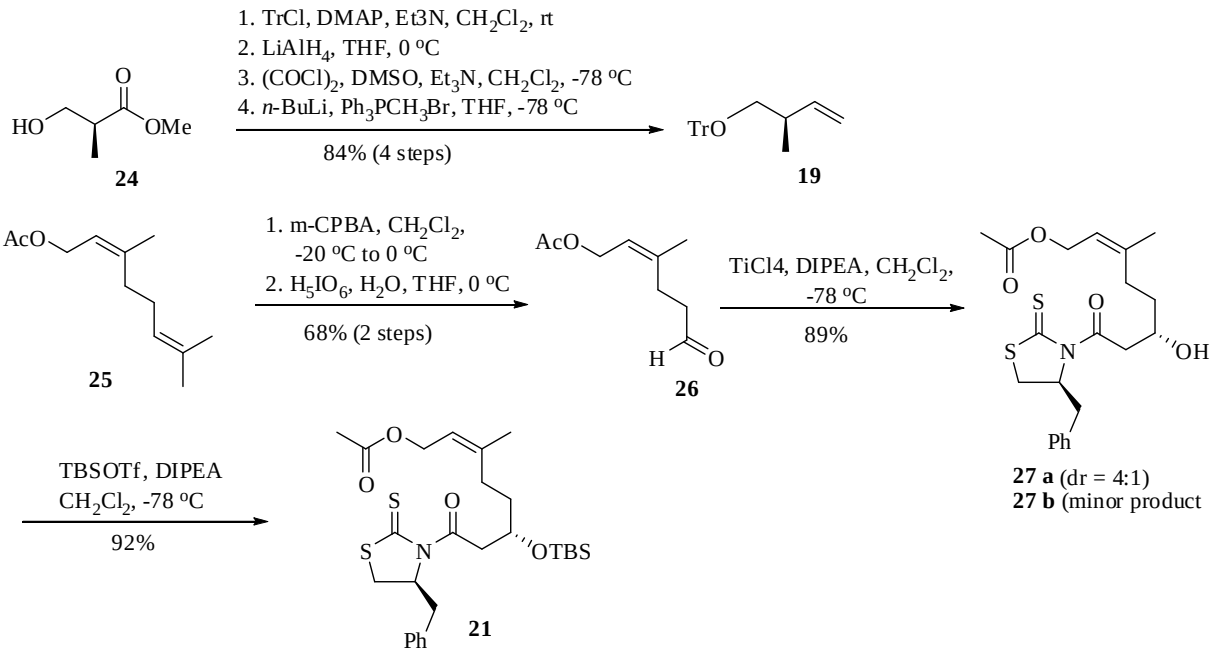
### 2.3.2. Skaanderup approach [29]

Skaanderup and co-workers also synthesized the macrocyclic Core of (-) - Pladienolide B using chiral auxiliary-mediated asymmetric aldol addition and an osmium-catalyzed asymmetric dihydroxylation. The retrosynthetic analysis of this natural product (-) - Pladienolide B based on this strategy is shown in (Scheme 5). Macrolactonization and (*E*) - selective cross metathesis between olefin **19** and **20** could construct the 12-membered lactone. **19** would in turn be available from commercial (*S*)-Roche ester and **21** was anticipated to arrive from sequential olefination and osmium catalyzed asymmetric dihydroxylation thereby installing the vicinal oxygen-substituted stereocenters of the macrocycle. Finally, key intermediate **21** would result from chiral auxiliary mediated asymmetric aldol addition of known acetylthiazolidine-thione **23** and aldehyde **22**.



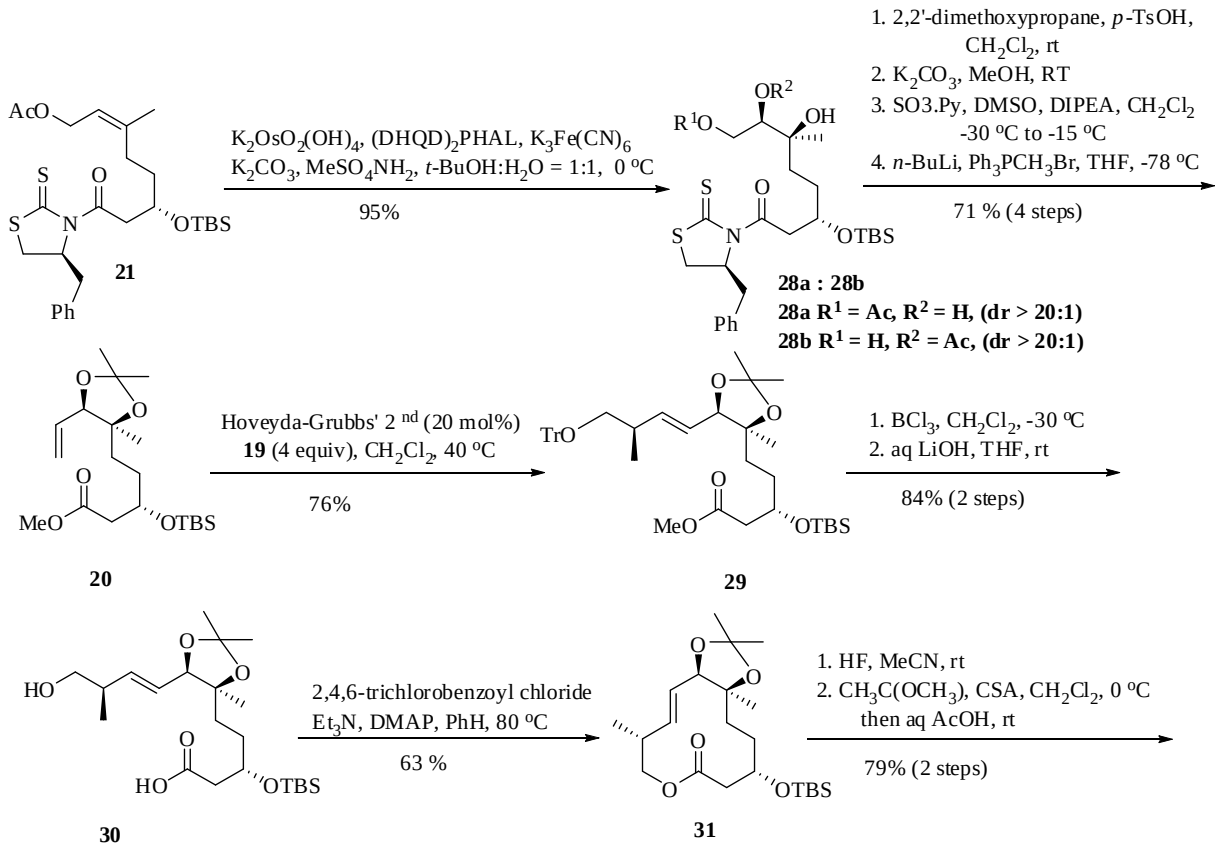

**Scheme 5**

Tritylation of (*S*)-Roche ester followed by LAH reduction, Swern oxidation, and Wiitig methylenation afforded alkene **19** smoothly over this four-step sequence (Scheme 6). Prilezhaev epoxidation of commercial acetate (*Z*)-3,7-dimethyloct-2,6-dienyl acetate and subsequent epoxide cleavage using periodic acid provided aldehyde **22**. Secondary alcohol **27a** was available *via* an asymmetric aldol reaction of aldehyde **22** with a chiral acetylthiazolidinethione enolate generated from **23** using Vilarrasa's conditions. The selectivity of the aldol reaction could be tuned to give **27a** or **27b** as the major product even when the same acetylthiazolidinethione was employed. The titanium enolate generated with titanium tetrachloride and Hunig's base gave predominantly the desired isomer **27a** in excellent yield. If the enolate was generated from dichlorophenylborane and (-)-sparteine, **27b** was fromed as the major product. The aldol product was then protected as the TBS ether to give **21** in 92% yield.




**Scheme 6**

From the well-defined olefin geometry of the substrate, which relates back to nerol and using the $(DHQD)_2PHAL$ ligand, diol **28a** was produced in good yield and selectivity greater than 20:1 at the newly formed stereocenters (Scheme 7). Acetate **28b** was also formed in equal diastereomeric ratio and is the likely product of intramolecular acetyl migration. The key alkene fragment **20** was prepared from **28a** in a four-step sequence initially aetonide formation and treatment with $K_2CO_3$ in methanol to concomitantly cleave the acetate and convert the chiral auxiliary into a methyl ester. Parikh-Doering oxidation followed by Wittig methylation provided alkene **20** in 71% yield over these four steps.




**(-)-pladienolide B**

**Scheme 7**

The (*E*)-alkene **29** was formed efficiently by the cross-metathesis reaction between **20** and **19** with 10 mol% Hoveyda-Grubbs' second-generation catalyst by adding **19** in two portions gave the desired alkene. Selective deprotection of the trityl ether using a solution of $BCl_3$ followed by methyl ester hydrolysis successfully gave *seco*-acid **30**. Attempts to close the macrocycle under modified Yamaguchi conditions at 80 °C afforded **31**. The TBS and acetonide groups were then effectively removed through the action of aqueous HF in MeCN. Finally, the secondary allylic alcohol was acetylated selectively by treating

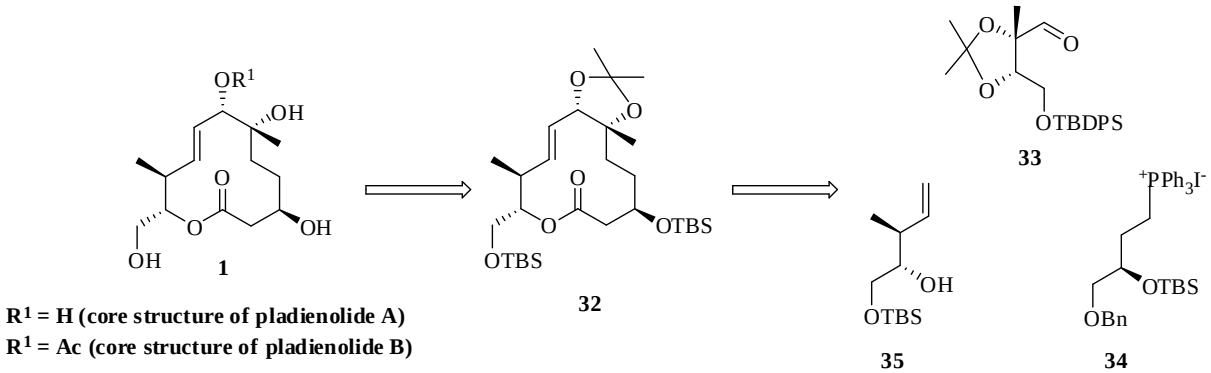
the diol with trimethyl orthoacetate and CSA followed by cleavage of the resulting orthoester with aqueous AcOH to give the macrocyclic core of **(–)-Pladienolide B**.

## 2.4. PRESENT WORK

In continuation of our efforts towards the synthesis of biologically active natural products,[30] we initiated a program towards the synthesis of macrocyclic core of pladienolide A and pladienolide B (Fig. 4). Because of their attractive biological activities, in particular the potent and selective inhibition of the growth of a variety of cancer cell lines in vitro with low nanomolar $IC_{50}$ values, this group of natural products has provoked much interest.

### 2.4.1. Retrosynthetic analysis:

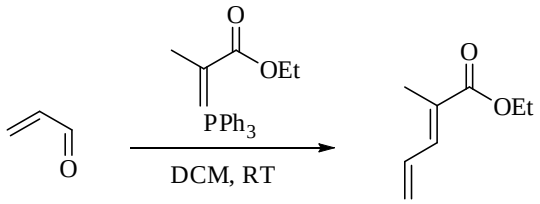
Having a general interest in total synthesis of bioactive natural products, the synthesis of macrocyclic core of pladienolide A and pladienolide B were approached using Sharpless asymmetric epoxidation, [31] Wittig installation, Cross-metathesis[32] and Yamaguchi esterfication.[33] The retrosynthetic analysis of this natural products based on this strategy is shown in (Scheme 8).




**Scheme 8**

### 2.4.2. Synthesis of fragment of 33:

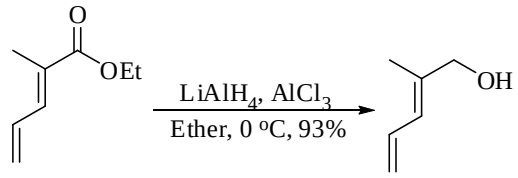
Synthesis of fragment **33** began with the Wittig olefination of ethyl-2-(triphenylphosphoranylidene) propanoate, the **ylide** with acrylaldehyde **36** in THF resulting exclusively in *cis* trisubstituted olefin **37** (Scheme 9). The $^1$H NMR spectrum with resonance at δ 6.87, 6.30, 5.11 and ESIMS peak at an *m/z* 141 $[M+H]^+$ confirmed the formation of ester.




**36** **37**

**Scheme 9**

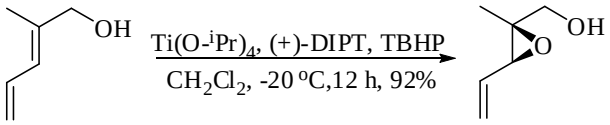
The pure ester **37** so obtained in 90% yield was subjected to chemoselective reduction using the alane [34] generated *in situ* by premixing LAH with $AlCl_3$ in 3:1 ratio in dry ether at -15 $^oC$ to 0 $^oC$ yielding allyl alcohol **38** (Scheme 10). Absence of -O-$CH_2$ protons and $CH_3$ protons suggested the formation of allyl alcohol.




**37** **38**

**Scheme 10**

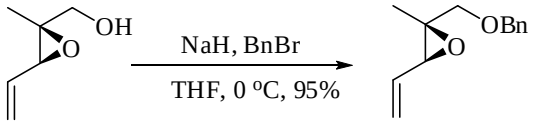
Allyl alcohol **38** was then subjected to Sharpless asymmetric epoxidation protocol using (+)-DIPT leading to the chiral epoxide **39** in high enantiomeric purity in 92% yield (Scheme 11). The epoxide was confirmed by its $^1$H NMR spectrum with resonance at δ 3.79-3.51for one proton attached to the carbon bearing the oxirane **39**.




**38** **39**

**Scheme 11**

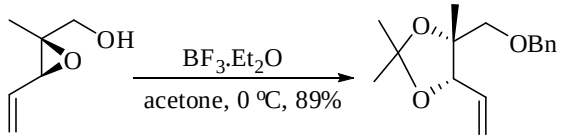
The hydroxyl group was then protected as corresponding benzyl ether **40** in 95% yield on treatment with NaH and benzyl bromide in THF at 0 $^{o}$C (Scheme 12). The benzyl ether **40** was characterized by the $^{1}$H NMR spectrum with the signals of the aromatic protons at δ 7.34-7.18 as a multiplet for 5 protons for $-C_6H_5$ and a characteristic resonance at δ 4.50 as singlet for 2 benzylic protons Ph-$CH_2$. In addition the IR spectrum revealed the disappearance of the absorption due to free hydroxyl group at 3450 cm$^{-1}$.




**39** **40**

**Scheme 12**

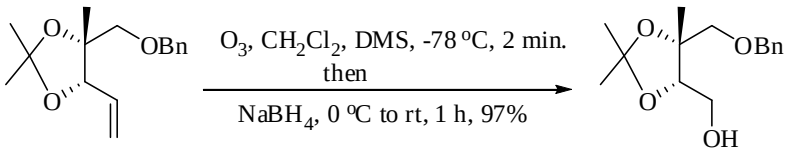
Regioselectiv opening of the benzylic epoxide was affected using $BF_3$-$Et_2O$ in excess of acetone yielding an acetonide **41** in 89% yield (Scheme 13). The acetonide was confirmed by $^{1}$H NMR spectrum with resonance at δ 1.40 for six protons of the isopropylidene **41.**




**40** **41**

**Scheme 13**

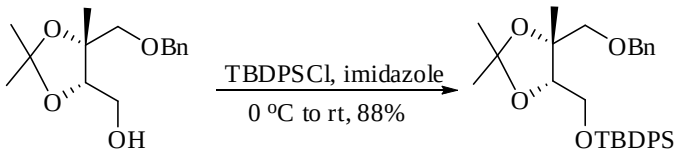
Ozonolysis of the double bond, followed by the the reduction of aldehyde with $NaBH_4$ provided **42** in 97% yield over 2 steps (Scheme 14). Absence of olefinic protons in $^1H$ NMR spectrum confirmed the formation of **42**. IR absorption showed characteristic band for hydroxyl functionality.




**41** **42**

**Scheme 14**

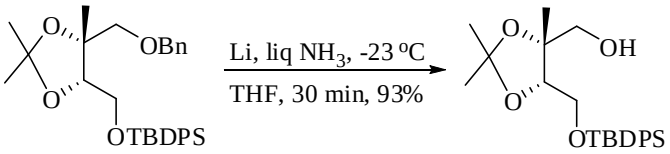
The hydroxyl group was then protected as corresponding *tert*-butyldiphenylsilyl ether **43** in 88% yield on treatment with TBDPSCl and imidazole at room temperature (Scheme 15). Absence of hydroxyl functionality in **43** was also confirmed by its IR spectrum, which showed no absorption band for hydroxyl functionality at 3450 $cm^{-1}$.




**42** **43**

**Scheme 15**

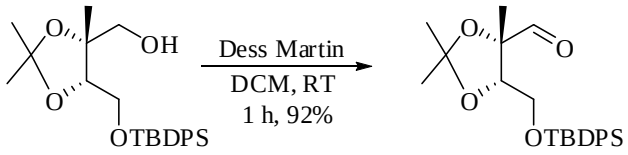
Deprotection of the benzyl group under Birch reduction conditions resulted in a primary alcohol **44** in 93% yield (Scheme 16), which was characterized by its $^1H$ NMR spectrum which revealed the absence of 2 benzylic protons Ph-$CH_2$ confirming the formation of **44.**




**43** **44**

**Scheme 16**

The alcohol **44** was oxidized to aldehyde **33** using Dess-Martin periodinane resulted key fragment aldehyde **33** in 92% yield (Scheme 17). The $^1$H NMR spectrum which revealed aldehyde proton resonance at δ 9.72, absence of hydroxyl functionality in **33** was also confirmed by its IR spectrum, which showed no absorption band for hydroxyl functionality. ESIMS peak at *m/z* 435 $[M+Na]^+$ confirmed the formation of aldehyde **33**.

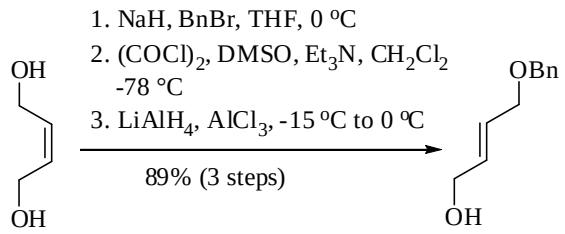



**44** **33**

**Scheme 17**

**2.4.3. Synthesis of fragment of 34:**

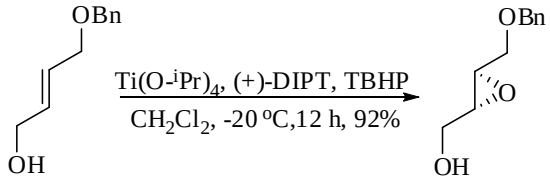
Synthesis of fragment **34** began with benzylation of (*Z*)-but-2-ene-1,4-diol **45** followed by Swern oxidation, and chemoselective reduction using $LiAlH_4$ to afford alkene **46** in 89% smoothly over this three-step sequence (Scheme 18). The $^1$H NMR spectrum resonances at δ 7.32-7.27 and 4.48 can be attributed to formation of **46.**




**45** **46**

**Scheme 18**

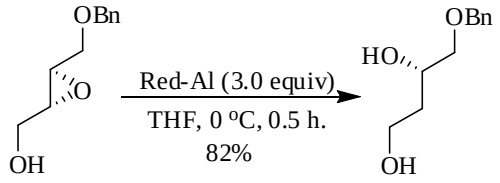
Compound **46** underwent Sharpless asymmetric epoxidation conditions using (-)-DIPT to give chiral epoxy alcohol **47** in 92% isolated yield (Scheme 19). The structure was confirmed by its $^{1}$H NMR spectrum which showed the absence of olefin protons and the presence of the two oxirane protons. ESIMS peak at *m/z* 217 $[M+Na]^{+}$ confirmed the formation of **47**.




**46** **47**

**Scheme 19**

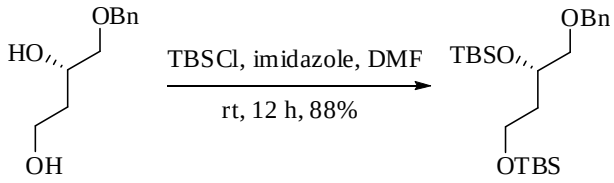
The reductive opening of epoxide **47** was achieved with Red-Al to realize the 1, 3-diol **48** (Scheme 20). Absence of oxirane protons at respective chemical shifts suggested the formation of diol **48**. In addition the IR spectrum revealed the absorption due to free hydroxyls group at 3450 $cm^{-1}$. ESIMS peak at /*z* 219 $[M+ Na]^{+}$ confirmed the formation of **48.**




**47** **48**

**Scheme 20**

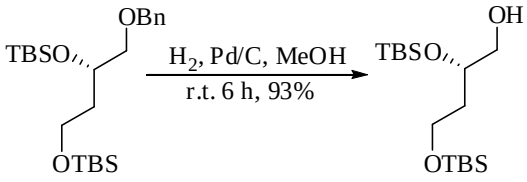
This diol **48** was converted into di–TBS ether **49** (Scheme 21) which was characterized by the $^1$H NMR spectrum with the signals for the silyl protons at δ 0.98, 0.29. Absence of hydroxyl functionality in **49** was also confirmed by its IR spectrum, which showed no absorption band for hydroxyl functionality.




**48** **49**

**Scheme 21**

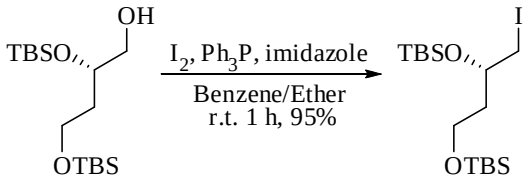
Compond di-TBS ether **49** was subjected to debenzylation resulting a primary alcohol **50** in 93% yield (Scheme 22). The $^1$H NMR spectrum which revealed the absence of aromatic nucleus confirmed the debenzylation. ESIMS peak at *m/z* 357 $[M+Na]^+$ confirmed the formation of **50**.




**49** **50**

**Scheme 22**

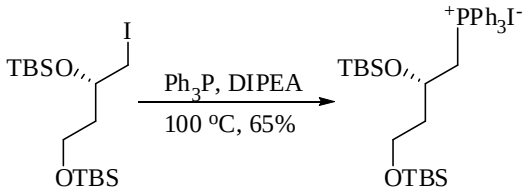
The primary alcohol was **50** was treated with $I_2$, $Ph_3P$ and imidazole afforded iodination at the primary hydroxyl group **51** in 95% yield (Scheme 23). The iodo compound **51** thus obtained was directly used after flash column chromatography for the next reaction.




**50** **51**

**Scheme 23**

The desired iodo compound **51** was then further elaborated to the corresponding Wittig salt **34** (Scheme 24). The compound **34** was characterized by ESIMS which showed [M-I] peak at *m/z* 579.

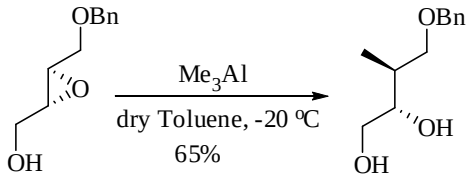



**51** **34**

**Scheme 24**

**2.4.4. Synthesis of fragment 35:**

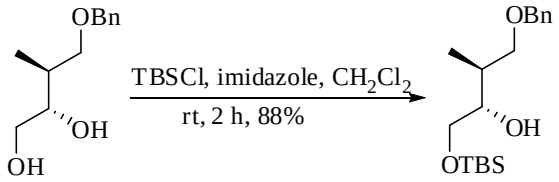
The regioselective opening of **47** with trimethyl aluminun ($Me_3Al$) [35] at -20 °C gave 1,2-diol **52** in 65% yield (Scheme 25). The structure was confirmed by its $^1H$ NMR spectrum which showed the absence of oxirane protons and the presence of three methyl protons at δ 0.82 as doublet. ESIMS peak at *m/z* 211 $[M+H]^+$ confirmed the formation of **52**.




**47** **52**

**Scheme 25**

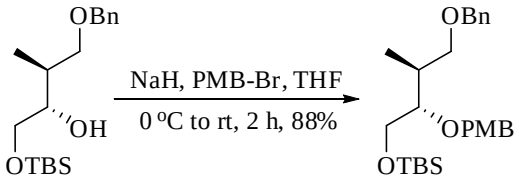
The 1,2-diol **52** was silylated using TBDMSCl , imidazole in dichloromethane provided the fully protected **53** in 88% yield (Scheme 26). The compound was characterized by ESIMS which showed $[M+H]^+$ peak at *m/z* 325.




**52** **53**

**Scheme 26**

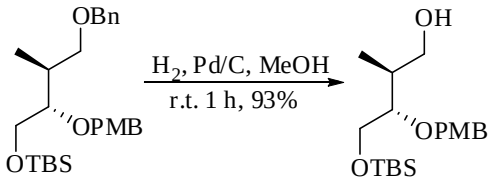
The compound **53** was converted into its PMB ether **54** by treating with sodium hydride (60% w/v dispersion in oil) and PMB-Br in dry THF at 0 °C in 88% yield (Scheme 27). PMB ether **54** was confirmed by its $^1$H NMR spectrum, which showed resonance at δ 4.64 as a singlet for four benzylic protons.




**53** **54**

**Scheme 27**

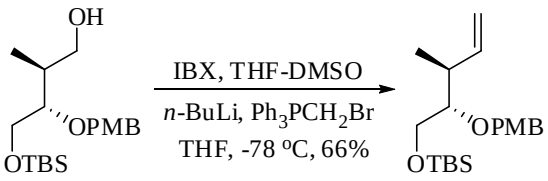
Catalytic reduction of **54** with Pd/C in MeOH at room temperature gave **55** in 93% yield (Scheme 28). The $^1$H NMR spectrum revealed the absence of one benzylic protons confirming the debenzylation. ESIMS peak at *m/z* 377 $[M+Na]^+$ which confirmed the formation of **55**.




**54** **55**

**Scheme 28**

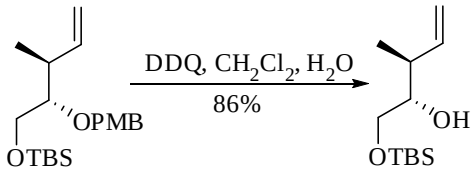
The primary alcohol **55** was oxidized to aldehyde in good yield using IBX and the aldehyde was subjected to Wittig methylenation to provide **56** in 66% yield (Scheme 29). The compound **56** was confirmed by its $^1$H NMR spectrum resonances at δ 5.91, 5.18-4.92 ppm which can be attributed to terminal alkene protons.




**55** **56**

**Scheme 29**

Removal of the PMB ether from **56** was successfully achieved with DDQ to afford compound **35** in 86% yield (Scheme 30). The compound **35** was confirmed by its $^1$H NMR spectrum resonances at their respective chemical shifts confirming the formation of **35.** ESIMS peak at *m/z* 231 $[M+H]^+$ confirmed the formation of **35**.

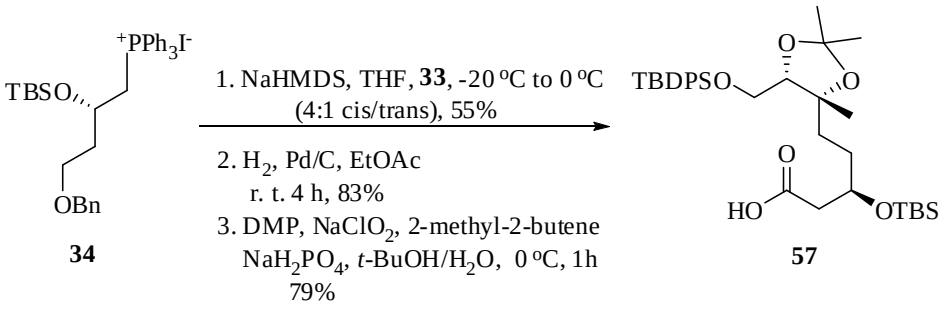



**56** **35**

**Scheme 30**

### 2.4.5. Coupling of fragments 33 and 34:

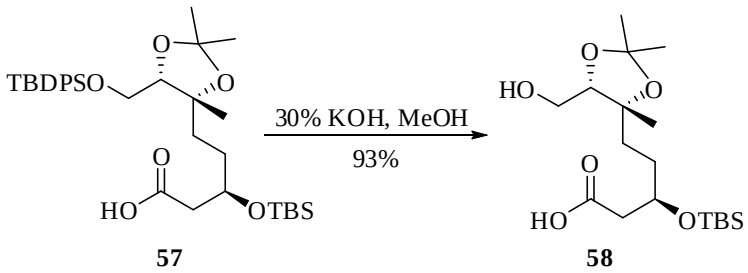
The satge was set for the chemoselective Wiitg coupling between **33** and **34**, followed by deprotection of benzyl group and reduction of double bond with Pd/C. The resulting primary alcohol was oxidized to acid **57** (Scheme 31). Compound **57** was characterized by ESIMS which showed $[M+H]^+$ peak at *m/z* 615.




**34** **57**

**Scheme 31**

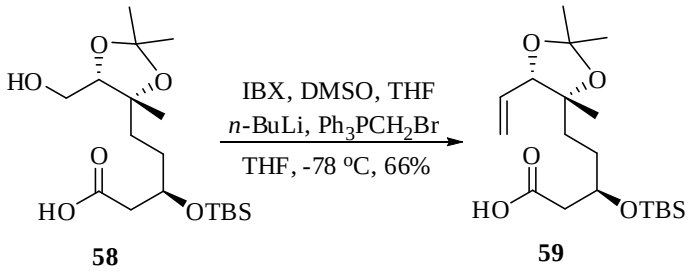
This acid **57** was further converted into corresponding primary alcohol **58** by treatment with 10% KOH /MeOH in 93% yield (Scheme 32). The $^1H$ NMR spectrum of **58** revealed the absence of tert-butyldiphenyl protons confirming the formation of **58**.




**57** **58**

**Scheme 32**

The alcohol **58** was oxidized to aldehyde followed by Wittig methylenation to provide **59** in 66% yield (Scheme 33). The compound **59** was confirmed by its $^{1}$H NMR spectrum resonances at δ 6.31-5.91, 5.18-4.92 which can be attributed to terminal alkene protons. ESIMS peak at *m/z* 395 $[M+Na]^{+}$ confirmed the formation of compound **59**.




**58** **59**

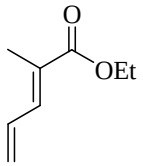
**Scheme 33**

**2.5. Conclusion:**

In conclusion, our efforts towards the synthesis of macrocyclic core of pladienolide A and pladienolide B have been described *via* Sharpless asymmetric epoxidation and Wittig installation,

# 2.6 EXPERIMENTAL SECTION

### 2.6.1. (*Z*)-ethyl 2-methylpenta-2, 4-dienoate (37):




To a stirred solution of NaH (2.05 g, 53.57 mmol) in THF (60 mL) was added ethyl 2-(diethoxyphosphoryl) propanoate (11.47 g, 48.21 mmol) slowly at 0 $^{o}$C. After stirring for 3 h acrylaldehyde **36** (3.57 mL, 53.57 mmol) in THF (40mL) was added dropwise over a period of 15 min and the reaction mixture was stirred for further 2 h at -78 °C. The reaction was quenched with sat. aq. $NH_4Cl$ added dropwise at 0 $^{o}$C and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (90:10) afforded compound **37** (6.7 g, 90%) as a viscous liquid.

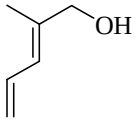
IR (KBr) : $\nu_{max}$, 3300, 3100, 2000, 1710, 1040 cm$^{-1}$.

$^{1}$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.18 (1H, s), 6.69 (1H, m), 5.62-5.57 (2 H, m), 4.25 (2 H, q, $J$ = 7.0 Hz), 1.48 (3H, s), 1.27 (3H, t, $J$ = 7.0 Hz)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 167.2, 141.8, 132.2, 130.1, 119.5, 61.7, 14.2, 11.8.

ESIMS : *m/z* 141 $[M+H]^+$

### 2.6.2. (*Z*)-2-methylpenta-2, 4-dien-1-ol (38):



To a stirred solution of $LiAlH_4$ (2.72 g, 71.78 mmol) in THF (30 mL) was added $AlCl_3$ (3.19 g, 23.92 mmol) slowly at 0 $^oC$. After stirring for 1 h compound 37 (6.7g, 14.64 mmol) in THF (30mL) was added dropwise and the reaction mixture was stirred for further 1 h at 0 $^oC$ .The reaction was quenched by the addition of moistened $Na_2SO_4$ at 0 $^oC$. After stirring overnight at room temperature, the mixture was filtered over a small pad of Celite to afford the crude allyl alcohol that was purified by column chromatography using hexane/EtOAc (70:30) afforded pure 38 (1.33 g, 93% yield) as a colorless liquid.

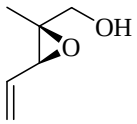
IR (KBr) : $\nu_{max}$, 3580, 3300, 3100, 2850, 2000 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 5.91-5.83 (2H, m), 5.54-5.32 (2 H, m), 3.33-3.48 (2 H, m), 1.21 (3H, s)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 143.3, 141.3, 125.7, 118.7, 61.3, 29.8, 22.4, 13.4.

ESIMS : *m/z* 121 $[M+Na]^+$

**2.6.3. ((2*S*, 3*R*)--2-methyl-vniyloxiran-2-yl) methanol (39):**




To a suspension of the powder of activated $4A^0$ (0.266 g) molecular sieves in dry $CH_2Cl_2$ (10 mL) $Ti(O^iPr)_4$ (4.0 mL, 13.57 mmol) and (+)-DIPT (3.1 mL, 14.92 mmol) were added sequentially at -20 $^oC$. After stirring for 30 min. allylic alcohol **38** (1.33g, 13.57 mmol) in dry $CH_2Cl_2$ (10 mL) was added to it and the stirring was continued for another 30 min at the same temperature. Then TBHP (7.3 mL) was added to it and stirred for another 3 h at the same temperature. The reaction was quenched by addition of water (40 mL) it was allowed to keep at room temperature by stirring for 30 min. After recooling at 0 $^oC$ an aq. solution of NaOH (30% W/V, 6.7 mL, saturated with brine) was added to it and the

mixture was stirred at 0 $^{o}$C for 1h. Solvent was removed under reduced pressure and the residue was extracted with ether (2 x 50 mL).The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography using hexane/EtOAc (60:40) afforded pure **39** (1.42 g, 92%) as a viscous liquid.

IR (KBr) : $\nu_{max}$, 3450, 3020, 2850, 1239 cm$^{-1}$.

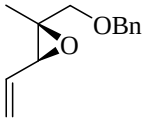
$^{1}$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 5.83 (1H, m), 5.41-5.35 (2 H, m), 4.32 (1H, m), 3.79-3.51 (2 H, m), 1.33 (3H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 136.2, 115.8, 67.0, 61.1, 58.4, 17.1

ESIMS : *m/z* 137 $[M+Na]^+$

$[\alpha]_D^{25}$ : +23.0 (*c* 0.96, $CHCl_3$)

**2.6.4. (2*S*, 3*R*)--2-(benzyloxymethyl)- 2-methyl-3-vniyloxirane (40):**




To a stirred suspension of NaH (954 mg, 24.91 mmol) in THF (10 mL) was added a solution of **39** (1.42 g, 12.45 mmol) in THF (10 mL) dropwise at 0 $^{o}$C under nitrogen atmosphere. After stirring for 15 min, benzyl bromide (1.62 mL, 13.70 mmol) was added and the reaction mixture was stirred over night. The reaction was quenched with saturated aq. $NH_4Cl$ (25 mL) at 0 $^{o}$C and extracted with ethylacetate (2 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (70:30) afforded pure **40** (2.41g, 95%) as a colorless liquid.

IR (KBr) : $\nu_{max}$, 3100, 3030, 2850, 1250, 1040 cm$^{-1}$.

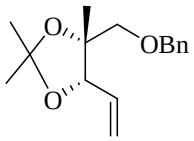
$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.34-7.18 (5H, m), 5.84 (1H, m), 5.42-5.16 (2 H, m), 4.46 (2H, s), 4.19 (1H, m), 3.32-3.27 (2H, m), 1.28 (3H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 138.2, 132.9, 127.9, 126.2, 118.8, 84.9, 81.7, 73.8, 73.6, 69.8, 29.7, 28.3, 21.9.

ESIMS : *m/z* 227 $[M+Na]^+$

$[\alpha]_D^{25}$ : +16.2 (*c* 0.15, $CHCl_3$)

**2.6.5. (4*R*, 2*S*)-4-(benzyloxymethyl)-2, 2, 4-trimethyl-5-vniyl-1.3-dioxirane (41):**




To a solution of the compound **40** (2.41 g, 11.81mmol) in a slight excess of actone was added $BF_3.Et_2O$ (1.48 mL, 11.81mmol) at 0 $^oC$ and the reaction mixture was stirred at 0 $^oC$ for three h. After completion of the reaction, the reaction mixture was quenched by the addition of solid $NaHCO_3$ at 0 $^oC$ and the solvent was evaporated under reduced pressure to yield a residue which was again extracted with EtOAc (2 x 50 mL) sequentially using a saturated bicarbonate solution. The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (90:10) afforded pure **41** (2.75 g, 89%) as colorless liquid.

IR (KBr) : $\nu_{max}$, 3020, 3000, 1250, 1210, 1500, 1300 $cm^{-1}$.

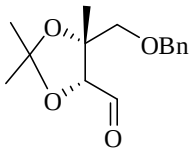
$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.41-7.38 (5H, m), 5.83 (1H, m), 5.21-5.19 (2 H, m), 4.61 (2H, s), 4.15 (1H, d, *J* = 12.0 Hz), 3.30-3.19 (2H, m), 1.41 (3H, s), 1.39 (3H, s), 1.32 (3H, s).

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 136.9, 136.2, 130.3, 128.6, 115.1, 111.2, 86.9, 84.3, 81.7, 74.3, 30.8, 26.7, 23.1, 19.3, 14.1.

ESIMS : *m/z* 285 $[M+Na]^+$

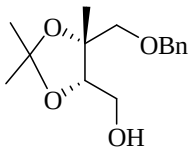
$[\alpha]_D^{25}$ : +26.0 (*c* 0.50, $CHCl_3$)

**2.6.6. (4*R*, 5*R*)-5-(benzyloxymethyl)-2, 2, 5-trimethyl-1, 3-dioxolane-4-carbaldehyde:**




To a stirred solution containing **44** (2.75 g, 10.49 mmol) in $CH_2Cl_2$ (30 mL), ozone enriched was gently bubbled at -78 $^oC$ until a blue coloration persisted. While still at -78 $^oC$ DMS (5 mL) was added. The temperature was then allowed to warm to room temperature, the solvent was evaporated under reduced pressure to yield a residue. The residue was purified by flash column chromatography to afforded aldehyde (2.58 g, 93%).This aldehyde was immediately used for the subsequent reaction.

**2.6.7. ((4*S*, 5*R*)-5-(benzyloxymethyl)-2, 2, 5-trimethyl-1, 3-dioxolane-4-yl) methanol (42):**




$NaBH_4$ (1.11g, 29.31mmol) was added to the solution of aldehyde (2.58g, 9.77 mmol) in MeOH. After stirring 1 h, the reaction mixture was diluted with DCM (50 mL) and saturated $NH_4Cl$ (10 mL) was added. The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (70:30) to afforded pure **42** (2.52 g, 97%) as a yellow liquid.

IR (KBr) : $\nu_{max}$, 3450, 3000, 1250, 1210, 1100 $cm^{-1}$.

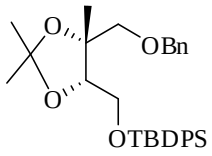
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.39-7.21 (5H, m), 4.45 (2H, s), 3.99 (1H, t, $J$ = 12.0 Hz), 3.81-3.13 (4H, m), 1.41 (3H, s), 1.29 (6H, s)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 137.6, 128.7, 127.6, 108.4, 82.8, 73.7, 72.9, 6.12, 28.6, 27.8, 23.3.

ESIMS : *m/z* 289 $[M+Na]^+$

$[\alpha]_D^{25}$ : +8.0 (*c* 0.42, $CHCl_3$)

**2.6.8. (((4*S*, 5*R*)-5-(benzyloxymethyl)-2, 2, 5-trimethyl-1, 3-dioxolan-4-yl) methoxy) (*tert*- butyl) diphenylsilane (43):**




Imidazole (902 mg, 13.26 mmol) and TBDPS-Cl (2.46mL, 9.47 mmol) were added sequentially to a solution of **42** (2.52g, 9.47 mmol) in dry $CH_2Cl_2$ (20 mL) at 0 $^oC$. After stirring 1 h at room temperature, the reaction was quenched with saturated aq. $NH_4Cl$ solution (10 mL) and extracted with DCM (2 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (90:10) afforded pure TBDPS compound **43** (4.21 g, 88%) as a viscous solid.

IR (KBr) : $\nu_{max}$, 3030, 3000, 2900, 1250, 1150, 1100 $cm^{-1}$.

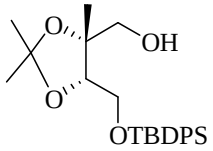
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.67-7.14 (15H, m), 4.35 (2H, s), 3.42-3.73 (3H, m), 3.34 (1H, d, $J$ = 9.0 Hz), 3.18 (1H, d, $J$ = 9.0 Hz), 1.38 (6H, s), 1.29 (3H, s), 1.05 (9H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 137.4, 135.6, 132.2, 131.3, 129.7, 129.3, 127.4, 108.6, 85.2, 74.3, 73.2, 65.1, 27.8, 26.9, 26.1, 17.9.

ESIMS : *m/z* 527 $[M+Na]^+$

$[\alpha]_D^{25}$ : +6.5 (*c* 0.42, $CHCl_3$)

**2.6.9. (((4*R*, 5*S*)-5-((*tert*-butyldiphenylsilyloxy) methyl)-2, 2, 4-trimethyl-1, 3-dioxolan-4-yl) methanol (44):**




To a solution of compound **43** (1 g, 1.98 mmol) in THF (10 mL), with a septum was fitted ammonia condenser and about 1.34 mL of ammonia was collected in the flask. To this clear solution at -23 $^oC$ was added portion wise lithium metal (23 mg, 3.96 mmol). A deep blue color appeared and the reaction mixture was stirred at the same temperature for half an hour. After the reaction was completed, the reaction mixture was quenched by adding solid $NH_4Cl$ till the blue color of the reaction mixture disappeared and the ammonia was allowed to evaporate. The reaction mixture was then extracted with ether (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (80:20) to afford pure **44** (0.763 g, 93%) as a yellow liquid.

IR (KBr) : $\nu_{max}$, 3580, 2950, 1260, 1200, 1100, 1040 $cm^{-1}$.

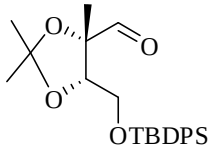
$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.78-763 (4H, m), 7.44-7.39 (6H, m), 4.05 (2H, m), 3.76 (3H, m), 1.62 (6H, s), 1.26 (3H, s), 1.09 (9H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 134.0, 130.0, 129.5, 108.5, 81.9, 78.8, 65.4, 59.4, 26.8, 19.2

ESIMS : *m/z* 436 $[M+Na]^+$

$[\alpha]_D^{25}$ : +11.9 (*c* 0.50, $CHCl_3$)

**2.6.10. (((4*S*, 5*S*)-5-((*tert*-butyldiphenylsilyloxy) methyl)-2, 2, 4-trimethyl-1, 3-dioxolane-4- Carbaldehyde (33):**

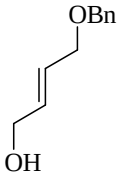



To a solution of the alcohol **44** (763 mg, 1.84 mmol) in $CH_2Cl_2$ (10 mL) at 0 $^oC$ was added Dess-Martin periodinane reagent (937 mg, 2.21 mmol). The reaction mixture was stireed at room temperature, after the completion of the reaction hexanes (15 mL) was added at 0 $^oC$ where upon solids were separated. After filtration, the filtrate was concentrated to give residue. Purification of the residue by column chromatography using hexane/EtOAc (95:5) afforded pure aldehyde **33** (699 mg, 92%) as a viscous liquid.

$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 9.72 (1H, s), 7.59-7.37 (10H, m), 3.91-4.04 (3H, m), 1.32 (6H, s), 1.26 (3H, s), 0.98 (9H, s)

ESIMS : *m/z* 435 $[M+Na]^+$

**2.6.11. (*E*)-4-(benzyloxy) but-2-en-1-ol (46):**




To a stirred solution of $LiAlH_4$ (647 g, 17.04 mmol) in THF (10 mL) was added $AlCl_3$ (757 mg, 5.68 mmol) slowly at 0 $^oC$. After stirring for 1 h compound (*Z*)-4-(benzyloxy) but-2-enal 45 (2 g, 11.36 mmol) in THF (10 mL) was added dropwise and the reaction

mixture was stirred for further 1 h at 0 $^{o}$C .The reaction was quenched by the addition of moistened $Na_2SO_4$ at 0 $^{o}$C. After stirring over night at room temperature, the mixture was filtered over a small pad of Celite to afford the crude allyl alcohol that was purified by column chromatography using hexane/EtOAc (70:30) afforded pure 46 (1.88 g, 89% yield) as a yellow liquid.

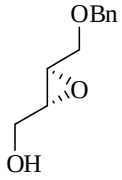
IR (KBr) : $\nu_{max}$, 3400, 3100, 3030, 1600, 1250 $cm^{-1}$.

$^{1}$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.32-7.27 (5H, m), 5.91-5.70 (2H, m), 4.48 (2H, s), 4.09-3.92 (4H, m)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 137.4, 135.3, 128.6, 127.8, 127.4, 72.4, 64.2

ESIMS : *m/z* 201 $[M+Na]^{+}$

**2.6.12. ((2*S*, 3*S*)-3-(benzyloxy methyl) oxiran-2-yl) methanol (47):**




To a suspension of the powder of activated 4 $A^{0}$ (0.376 g) molecular sieves in dry $CH_2Cl_2$ (10 mL), $Ti(O^{i}Pr)_4$ (0.62 mL, 2.11mmol) and (-)-DIPT (0.66 mL, 3.16 mmol) were added sequentially at -20 $^{o}$C. After stirring for 30 min. allylic alcohol **46** (1.88g, 10.56 mmol) in dry $CH_2Cl_2$ (10 mL) was added to it and the stirring was continued for another 30 min at the same temperature. Then TBHP (5.73 mL, 26.40 mmol) was added to it and stirred for another 3 h at the same temperature. The reaction was quenched by addition of water (6.33 mL). It was allowed to keep at room temperature by stirring for 30 min. After recooling at 0 $^{o}$C an aq. solution of NaOH (30% W/V, 1.0 mL, saturated with brine) was added to it and the mixture was stirred at 0 $^{o}$C for 1h. Solvent was removed under reduced pressure and the residue was extracted with $CH_2Cl_2$ (2 x 50 mL).The combined

organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography using hexane/EtOAc (60:40) afforded pure **47** (1.88 g, 92%) as a viscous liquid.

IR (KBr) : $\nu_{max}$, 3600, 3200, 3.30, 2850, 1600 $cm^{-1}$.

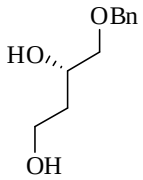
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.32 (5H, m), 4.52 (2H, s), 3.96-3.78 (3H, m), 3.26 (1H, m), 2.25 (1H, m), 1.89 (1H, m)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 136.7, 128.6, 127.4, 73.6, 69.0, 61.2, 55.2, 54.3

ESIMS : *m/z* 217 $[M+Na]^+$

$[\alpha]_D^{25}$ : +21.6 (*c* 0.30, $CHCl_3$)

**2.6.13. (*R*)-4-(benzyloxy) butane-1, 3-diol (48):**




To a stirred solution of **47** (1.88 g, 9.69 mmol) in dry THF (20 mL) under $N_2$ atmosphere at 0 $^oC$ was added Red-Al solution in toluene (8.39 mL, 29.07 mmol of 70% w/w) and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aq. $NH_4Cl$ (10 mL) solution then extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography using hexane/EtOAc (50:50) afforded pure **48** (1.55 g, 82%) as a colourless liquid.

IR (KBr) : $\nu_{max}$, 3450, 3200, 2950, 1600, 1500, 1250 $cm^{-1}$.

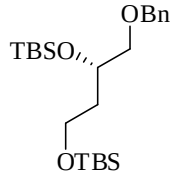
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.47-7.37 (5H, m), 4.50 (2H, s), 3.80 (2H, m), 3.63-3.40 (2H, m), 3.54 (1H, m), 1.91-1.72 (2H, m)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 137.8, 128.6, 127.8, 127.6, 73.7, 73.2, 70.9, 61.7, 34.3.

ESIMS : *m/z* 219 $[M+Na]^+$

$[\alpha]_D^{25}$ : +23.7 (*c* 0.15, $CHCl_3$)

**2.6.14. (*R*)-5-(benzyloxy methyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (49):**




Imidazole (2.16 g, 31.78 mmol) and TBDMS-Cl (2.38 g, 15.81 mmol) were added sequentially to a solution of **48** (1.55 g, 7.94 mmol) in dry DMF (20 mL) at 0 $^oC$. After stirring for 5 min DMAP (catalytic amount) was added to the reaction mixture and the stirring was continued for 12 h at room temperature. The reaction was quenched with saturated aq. $NH_4Cl$ solution (5 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (95:5) afforded pure di-TBS compound **49** (2.9 g, 88%) as a viscous liquid.

IR (KBr) : $\nu_{max}$, 3000, 1600, 1500, 1250, 1210 $cm^{-1}$.

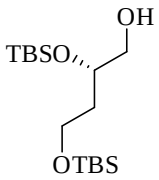
$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.32-7.19 (5H, m), 4.53 (2H, s), 4.09-3.90 (1H, m), 3.73-3.69 (2H, m), 3.43-3.39 (2H, m), 1.81-1.72 (1H, m), 1.69-1.62 (1H, m), 0.98 (18H, s), 0.23 (12H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 139.1, 128.3, 127.4, 127.3, 75.9, 73.2, 69.1, 59.8, 38.1, 26.2, 18.3, -5.7, -5.4

ESIMS : *m/z* 447 $[M+Na]^+$

$[\alpha]_D^{25}$ : -17.3 (*c* 0.50, $CHCl_3$)

**2.6.15. (*R*)-2, 4-bis (*tert*-butyldimethylsilyloxy) butan-1-ol (50):**




To a solution of **49** (1 g, 2.35mmol) in MeOH (10mL) was added 50 mg of 10% Pd-C and the mixture was stirred under a hydrogen atmosphere for 6 h. After completion of the reaction the solution was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/EtOAc (80:20) to afford pure **50** (732 mg, 93%) as a colorless liquid.

IR (KBr) : $\nu_{max}$, 3650, 2950, 1250, 1110 $cm^{-1}$.

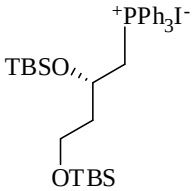
$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 3.91 (1H, m), 3.79-3.61 (3H, m), 1.82-1.69 (2H, m), 0.98 (18H, s), 0.29 (12H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 74.8, 69.9, 67.5, 59.4, 38.2, 25.7, 21.4, 18.4, -5.7, -5.4

ESIMS : *m/z* 357 $[M+Na]^+$

$[\alpha]_D^{25}$ : -11.9 (*c* 0.35, $CHCl_3$)

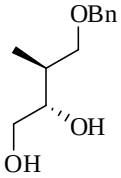
**2.6.16. Phosphonium Wittig salt (34):**



Iodine (831 Mg, 3.28 mmol) was added in one portion to a vigorously stirred solutiol of alcohol **50** (732 mg, 2.19 mmol), $PPh_3$ (689 mg, 2.62 mmol) and imidazole (268 mg, 3.94 mmol) in benzne/ether (1:2, 20mL) at room temperature. After 40 min, the mixture was diluted with ether (100 mL), washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and brine (100 mL), dried over $Na_2SO_4$ filtered and concentrated. Flash chromatography (hexanes) provided Iodo compound **51** (924 mg, 95%) as a colorless oil. This material was treated with *i* -$Pr_2NEt$ (1.0 mL, 6.24 mmol) and $PPh_3$ (8.18 g, 31.21 mmol) and heated at 80 $^oC$ without solvent for 13 h. The mixture was cooled and extracted with hexane (3 x 100 mL). Flash chromatography of the hexane-insoluble residue (10% $MeCN/CHCl_3$) provided **34** (1.5 g, 65%) as a pale yellow foam.

ESIMS : *m/z* 579 $[M\text{-}I]^-$

**2.6.17. (2*R*, 3*R*)-4-(benzyloxy)-3-methylbutane-1, 2-diol (52):**




To a cold (-23 $^oC$) suspension of **47** (1 g, 5.15 mmol) in hexane (15 mL), $Me_3Al$ (7.73 mL, 15.46 mmol, 2.0 M) in hexane was added dropwise until it become clear solution. After 30 min at this temperature the solution was cooled to 0 $^oC$, the raction mixture was quenched with 1 N HCl (5 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography using hexane/EtOAc (50:50) afforded pure **52** (703 mg, 65%) as a colorless solid.

IR (KBr) : $\nu_{max}$, 3500, 3200, 2950, 1600, 1250, 970 $cm^{-1}$.

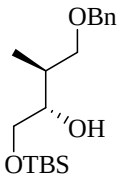
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.39-7.25 (5H, m), 4.54 (2H, s), 3.92 (1H, m), 3.74-3.44 (4H, m), 3.18 (1H, m), 3.04 (IH, brs), 1.26 (1H, m), 0.82 (3H, d, $J$ = 7.0 Hz)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 137.5, 128.6, 127.8, 127.4, 74.7, 74.1, 73.3, 64.8, 35.2, 12.5

ESIMS : *m/z* 223 $[M+Na]^+$

$[\alpha]_D^{25}$ : +28.1 (*c* 0.96, $CHCl_3$)

**2.6.18. (2*R*, 3*R*)-4-(benzyloxy)-1(*tert*-butyldimethylsilyloxy)-3-methylbutane 2-ol (53):**




Imidazole (455 mg, 6.69 mmol) and TBDMS-Cl (554 mg, 3.68 mmol) were added sequentially to a solution of **52** (703 mg, 3.34 mmol) in $CH_2Cl_2$ (10 mL) at 0 $^oC$. After stirring for 1 h at room temperature. The reaction was quenched with saturated aq. $NH_4Cl$ solution (5 mL) and extracted with $CH_2Cl_2$ (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (80:20) afforded pure TBS compound **53** (954 mg, 88%) as a viscous liquid.

IR (KBr) : $\nu_{max}$, 3400, 3030, 2900, 1600, 1250, 970 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.48-7.29 (5H, m), 4.69 (2H, s), 4.15-4.09 (1H, m), 3.89-3.81 (2H, m), 3.75-3.69 (1H, m), 3.68-

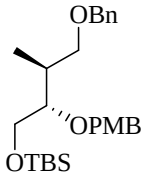
3.59 (1H, m), 3.53 (1H, m), 1.86 (1H, m), 0.98 (9H, s), 0.96 (3H, s), 0.21 (6H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 137.5, 128.6, 127.8, 127.4, 75.7, 74.1, 73.3, 54.4, 35.2, 25.9, 18.1, 12.5, -5.7, -5.4

ESIMS : *m/z* 325 $[M+H]^+$

$[\alpha]_D^{25}$ : +17.9 (*c* 0.15, $CHCl_3$)

**2.6.19. ((2*R*, 3*R*)-4-(benzyloxy)-2-(4-methoxy benzyloxy)-3-methylbutoxy) (*tert*-butyl) dimethylsilane 2-ol (54):**




(2*R*, 3*R*)-4-(Benzyloxy)-1(*tert*-butyldimethylsilyloxy)-3-methylbutane 2-ol **53** (954 mg, 2.94 mmol) was taken in 10 mL of dry THF, Then, NaH (60% dispersion in mineral oil, 124 mg, 3.23 mmol) was added to it portionwise at 0 $^oC$. The reaction mixture was stirred at 0 $^oC$ for 1 h followed by the addition of 4-methoxybenzylbromide. The reaction mixture was stirred for a further 2 h at room temperature. Water was added carefully to the reaction mixture to quench any excess of NaH. The reaction mixture was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatogray hexane/EtOAc (90:10) to afford **54** (1.15 g, 88%) as a viscous liquid.

IR (KBr) : $\nu_{max}$, 3030, 3000, 1600, 1500, 1250, 1210, 1040 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.23-6.73 (9H, m), 4.64 (4H, s), 3.92 (3H, s), 3.81 (1H, m), 3.32 (1H, m), 3.22 (2H, m), 3.01 (1H,

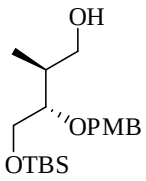
m), 2.31 (1H, m), 0.98 (9H, s), 0.96 (3H, s), 0.21 (6H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 159.7, 137.5, 129.8, 129.6, 127.4, 114.2, 79.8, 74.4, 73.3, 62.6, 55.8, 33.0, 25.9, 18.1, 12.5, -5.7, -5.4

ESIMS : *m/z* 444 $[M]^+$

$[\alpha]_D^{25}$ : +54.0 (*c* 1.1, $CHCl_3$)

**2.6.20. (2*R*, 3*R*)-4-(*tert*-butyldimethylsilyloy)-3-(4-methoxybenzyloxy)-2-methylbutan-1-ol (55):**




To a solution of **54** (1.15 g, 2.59mmol) in MeOH (20mL) was added 150 mg of 10% Pd-C and the mixture was stirred under a hydrogen atmosphere for 6 h. After completion of the reaction the solution was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/EtOAc (70:30) afforded pure **55** (852 mg, 93%) as a colorless liquid.

IR (KBr) : $\nu_{max}$, 3450, 3030, 2950, 1500, 1250, 970 $cm^{-1}$.

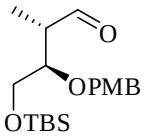
$^1$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.42 (1H, d, *J* = 8.0 Hz) 6.93 (1H, d, *J* = 8.0 Hz), 4.74 (2H, s), 3.81 (3H, s), 3.68 (1H, m), 3.28 (2H, s), 3.22 (1H, m), 3.01 (1H, m), 2.41 (1H, m), (9H, s), 0.21 (6H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 159.7, 129.8, 129.6, 114.2, 79.5, 73.0, 67.1, 62.6, 55.8, 35.2, 25.9, 18.1, 12.5, -5.7, -5.4

ESIMS : *m/z* 377 $[M+Na]^+$

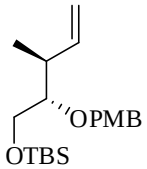
$[\alpha]_D^{25}$ : +36.3 (*c* 0.96 $CHCl_3$)

**2.6.21. (2*S*, 3*R*)-4-(*tert*-butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2-methylbutanal:**




To a stirred solution of IBX (1.36 g, 4.81 mmol) in DMSO (1 mL) under nitrogen atmosphere was added compound **55** (852 mg, 2.40 mmol) in anhydrous THF (20 mL) at room temperature and the mixture was stirred for 4 h. Then it was diluted with $Et_2O$ (5 mL). The mixture was filtered through a pad of Celite and the filtrate was washed with saturated aqueous $NaHCO_3$, dried over anhdrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by flash column chromatography afforded pure aldehyde (813 g, 96%) as a yellow liquid. This aldehyde was immediately used for the subsequent reaction.

**2.6.22. (*tert*-butyl ((2*R*,3*R*)-2-(4-methoxybenzyloxy)-3-methylpent-4-enyloxy)dimethylsilane (56):**




*n*-BuLi (2.88 mL, 1.6 M sol in hexane, 4.61 mmol) was added drop wise to the -78 °C solution of triphenylmethylphosphonium iodide (1.76 g, 5.77 mmol) in THF (5 mL) and stirred for 0.5 h to generate triphenylphosphoniumylide. After that, aldehyde (813 mg,

2.30 mmol) in THF (5 mL) was added dropwise over a period of 15 min and the reaction mixture was stirred for further 2 h at -78 °C. The reaction was quenched with sat. aq. $NH_4Cl$ added dropwise at 0 $^oC$ and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (95:5) afforded compound **56** (533 mg, 66%) as a viscous liquid.

IR (KBr) : $\nu_{max}$, 3100, 3030, 2950, 1680, 1600, 1500, 1250 $cm^{-1}$.

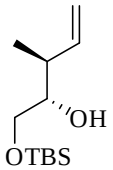
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 7.49 (1H, d, $J$ = 8.0 Hz), 7.09 (1H, d, $J$ = 8.0 Hz), 5.94-5.81 (1H, m), 5.18-4.92 (2H, m), 4.61 (2H, s), 3.98 (3H, s), 3.89-3.81 (1H, m), 3.39 (1H, m), 3.29-3.19 (2H, m), 3.19-2.95 (1H, m), 2.23 (3H, d, $J$ = 7.0 Hz), 0.98 (9H, s), 0.21 (6H, s)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 159.7, 129.8, 129.6, 114.2, 79.5, 73.0, 67.1, 62.6, 55.8, 35.2, 25.9, 18.1, 12.5, -5.7, -5.4

ESIMS : *m/z* 373 $[M+Na]^+$

$[\alpha]_D^{25}$ : +11.6 (*c* 0.15, $CHCl_3$)

**2.6.23. (2*R*, 3*R*)-1-(*tert*-butyldimethylsilyloxy)-3-methylpent-4-en-2-ol (35):**




Compound **56** (533 mg, 1.52mmol) was taken in 5 mL of $CH_2Cl_2/H_2O$ (9:1), DDQ (518 mg, 2.28 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered off, and the filtrate was washed

with 5% $NaHCO_3$ solution, water and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (90:10) to afforded compound **35** (30 mg, 86%) as a viscous liquid.

IR (KBr) : $\nu_{max}$, 3650, 3300, 3020, 1680, 1250 $cm^{-1}$.

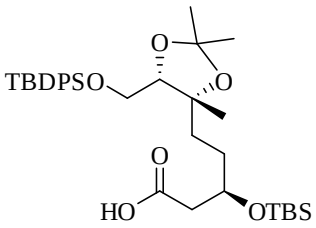
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 5.91 (1H, m), 5.16-4.94 (2H, m), 3.81 (1H, m), 3.35 (1H, m), 3.32 (2H, m), 3.1 (1H, m), 2.22 (3H, d, $J$ = 6.8 Hz), 0.98 (9H, s), 0.21 (6H, s)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 142.9, 111.3, 81.4, 69.3, 43.2, 21.7, 14.7, 13.8, -5.7, -5.4

ESIMS : *m/z* 231$[M+H]^+$

$[\alpha]_D^{25}$ : +28.3 (*c* 0.50, $CHCl_3$)

**2.6.24. (*R*)-3-(*tert*-butyldimethylsilyloxy)-5-((4*R*, 5*S*)-5-((*tert*-butyldiphenylsilyloxy) methyl- 2, 2, 4-trimethyl-1, 3-dioxolan-4-yl) pentanoic acid (57):**




Wittig coupling between **33** and **34** followed by the reduction of the double bond and benzyl group afforded the primary alchol. To this primary alcohol (196 mg, 0.326 mmol) dissolved in $CH_2Cl_2$ (10 mL) were added $NaHCO_3$ (54 mg, 0.653 mmol) and Dess-Martin periodinane (277 mg, 0.653 mmol). The mixture was stirred at room temperature for 1 h and quenched with a saturated $NaHCO_3$ solution (1 mL) and a saturated aqueous sodium thiosulfate solution (1 mL). The mixture was stirred until the two layers became

clear. The aqueous layer was extracted with $CH_2Cl_2$ (2 x 20 mL), and the combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*, and the crude aldehyde was used for the next step without purification.

The crude aldehyde from the above was dissolved in *t*-BuOH (5 mL) and $H_2O$ (2 mL). To this solution was added 2-methyl-2-butene (2 mL) followed by sodium chlorite (46 mg) and sodium phosphate monobasic monohydrate (190 mg) in $H_2O$ (2.2 mL) dropwise. The mixture was stirred at room temperature for 25 min. Then, ethylacetate (2 x 25 mL) was added, and the organic layer was washed with brine and dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. The crude acid was passed through a short column to afford the crude acid **57** (158 mg, 79%) as a colorless liquid.

IR (KBr) : $\nu_{max}$, 3300, 2954, 2850, 2500, 1739, 1720, 1472, 1463, 1378, 1217, 1054 $cm^{-1}$.

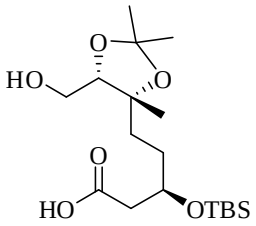
$^1H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 12.1 (1H, brs), 7.62 -7.09 (10H, m), 3.98 (2H, m), 3.42-3.12 (2H, m), 2.51 (2H, m), 1.98 (4H, m), 1.29 (3H, s), 1.27 (6H, s), 0.98 (9H, s), 0,21 (6H, s)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 176.2, 134.0, 130.0, 129.5, 108.5, 85.9, 84.8, 66.4, 59.4, 45.2, 32.2, 30.1, 26.8, 25.9, 19.5, 19.2, 18.4, -5.4

ESIMS : *m/z* 615 $[M+H]^+$

$[\alpha]_D^{25}$ : +5.9 (*c* 0.32, $CHCl_3$)

**2.6.25. (*R*)-3-(*tert*-butyldimethylsilyloxy)-5-((4*R*, 5*S*)-5-(hydroxymethyl)-2, 2, 4-trimethyl-1, 3-dioxolan-4-yl) pentanoic acid (58):**




The crude acid from the above **57** (158 mg, 0.257mmol) was dissolved in MeOH (3 mL). To this 30% KOH (1 mL) was added at 0 $^{o}$C. The mixture was stirred at room temperature for 3 h. Then ethylacetate (2 x 25 mL) was added, and the organic layer was washed with brine and dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (30:70) afforded compound **58** (89 mg, 93%) as a yellow liquid.

IR (KBr) : $\nu_{max}$, 3473, 3300, 2954, 2858, 1739, 1472, 1463, 1436, 378, 1217, 1054, 1005 $cm^{-1}$.

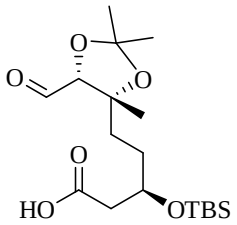
$^{1}$H NMR ($CDCl_3$, 200 MHz) : $\delta$ 3.96 (1H, m), 3.36 (1H, m), 3.24 (2H, m), 2.44 (1H, m), 1.98 (1H, m), 1.44-138 (4H, m), 1.29 (3H, s), 1.27 (6H, s), 0.98 (9H, s), 0.21 (6H, s)

$^{13}$C NMR ($CDCl_3$, 50 MHz) : $\delta$ 177.6, 114.2, 86.1, 85.7, 67.9, 60.3, 48.1, 40.2, 31.4, 25.7, 21.9, 18.5, -5.4

ESIMS : *m/z* 377 $[M+H]^+$

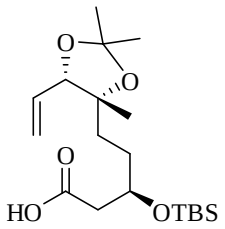
$[\alpha]_D^{25}$ : -4.2 (*c* 0.15, $CHCl_3$)

**2.6.26. (*R*)-3-(*tert*-butyldimethylsilyloxy)-5-((4*R*, 5*S*)-5-formyl-2, 2, 4-trimethyl-1, 3-dioxolan-4-yl) pentanoic acid :**



To a stirred solution of IBX (135 mg, 0.478 mmol) in DMSO (0.1 mL) under nitrogen atmosphere was added compound **58** (89 mg, 0.239 mmol) in anhydrous THF (3 mL) at room temperature and the mixture was stirred for 4 h. Then it was diluted with $Et_2O$ (1 mL). The mixture was filtered through a pad of Celite and the filtrate was washed with saturated aqueous $NaHCO_3$, dried over anhdrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by flash column chromatography afforded pure aldehyde (71 mg, 81%) as a viscous liquid. This aldehyde was immediately used for the subsequent reaction.

**2.6.27. (*R*)-3-(*tert*-butyldimethylsilyloxy)-5-((4*R*, 5*S*)-2, 2, 4-trimethyl-5-vinyl-1, 3-dioxolan- 4-yl) pentanoic acid (59):**




*n*- BuLi (0.23 mL, 1.6 M sol in hexane, 0.379 mmol) was added to drop wise to the -78 °C solution of triphenylmethylphosphonium iodide (145 mg, 0.474 mmol) in THF (2 mL) and stirred ½ h to generate triphenylphosphoniumylide. After that, aldehyde (71 mg, 0.189 mmol) in THF (2 mL) was added dropwise over a period of 15 min and the reaction mixture was stirred for further 2 h at -78 °C. The reaction was quenched with sat. aq. $NH_4Cl$ was added dropwise at 0 $^oC$ and extract with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in *vacuo*. Purification of the residue by column chromatography using hexane/EtOAc (95:5) afforded compound **59** (46 mg, 66%) as a yellow liquid.

IR (KBr) : $\nu_{max}$, 3025, 2928, 2856, 1739, 1559, 1472, 1436, 1377, 1257, 1059 $cm^{-1}$.

$^{1}H$ NMR ($CDCl_3$, 200 MHz) : $\delta$ 5.80 (1H, m), 5.41-5.16 (2H, m), 4.56 (1H, m), 3.54 (1H, m), 2.52 (1H, m), 2.27 (1H, m), 1.44-138 (4H, m), 1.29 (3H, s), 1.27 (6H, s), 0.98 (9H, s), 0.21 (6H, s)

$^{13}C$ NMR ($CDCl_3$, 50 MHz) : $\delta$ 177.3, 143.1, 115.4, 109.1, 88.3, 84.7, 62.2, 45.3, 35.1, 34.8, 29.3, 28.4, 14.9, 14.3, -5.4

ESIMS : *m/z* 395 $[M+Na]^+$

$[\alpha]_D^{25}$ : +7.3 (*c* 0.96, $CHCl_3$)

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