CHAPTER II

Section A

Introduction to olefin metathesis reaction and previous approaches for Amphidinilactone A
2.1. Introduction:

Ever since the first isolation of Exaltolide in 1927 by Kerschbaum, interest in macrocyclic lactones, defined as lactones with more than 8 atoms in the ring, has been increasing. Indeed, natural macrocyclic lactones, the term macrolide has been for years a synonym for “macrolactone glycoside antibiotics” and thus will not be used herein, present a large spectrum of interesting properties from perfume, to pheromone or insecticide activity, to medicinal (antibiotic, cytotoxic, antiangiogenesis) properties and a wide range of structures from 8-membered ones such as octalactins to the 60-membered quinolidomicins. From their first isolation in the 50s, macrolide antibiotics, such as erythromycin were widely used for treatment of bacterial infections, and because of their safety and efficacy, they are still the preferred therapeutic agents for treatment of respiratory infections. Another important class of macrolactones with a wide range of biological activities is the cyclodepsipeptides.

The term “macrolide” is used to describe natural products with a macrocyclic lactone ring of 12 or more elements. The term macrolide was introduced in 1957 by Woodward to denote the class of substances produced by Streptomyces species containing a macrocyclic lactone ring. The macrolide class is large and structurally diverse. Macrolides are produced by the fermentation of microorganisms and/or are found in marine invertebrates, such as sponges, bryozoa, or marine cyanobacteria, and in dinoflagellate species belonging to the genera Amphidinium, Gambierdiscus, Prymnesium, and Protoceratium. The polyether and macrolide antibiotics have been the focus of a great deal of attention since the 1950’s, when the first of these metabolites were isolated. Around 80 polyethers and 100 macrolides have now been characterized. Among several macrolides, most of them are polymethylated, polyhydroxy(methoxy)lated, or polyether compounds, whilst a few embed contiguous isoxazole units. In general, such compounds exhibit potent biological activities. The synthesis of macrolides has received considerable attention in pharmaceutical industry. The introduction of macrolide rings onto organic molecule often increases the stability, bioactivities and also alters the lipophilicity. Natural macrolides having odd number of ring atoms are comparatively less abundant than even numbers. Recently, cytotoxic Irimotiolide (15-membered macrolide), Amphidinolide Y (17-
membered macrolide), Amphidinolide T\textsuperscript{12} (19-membered macrolide) has been isolated. Before the isolation of Amphidinolactone A, only two 13-membered macrolides, bartanol 9 and bartallol 10 were known.\textsuperscript{13} These were isolated\textsuperscript{13a} from a Cytospora sp. and their structures established by a detailed study of their high field \textsuperscript{1}H and \textsuperscript{13}C NMR spectra. Unlike the other 14-membered ring macrolides isolated from this source, bartanol and bartallol have a novel rearranged 13-membered macrocyclic ring.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Figure 1}
\end{figure}

In 2007, Kobayashi \textit{et al.} isolated amphidinolactone A (1), a cytotoxic 13-membered macrolide isolated from a symbiotic dinoflagellate \textit{Amphidinium} sp. (Y-25) separated from an Okinawa marine acoel flatworm Amphiscolops sp.\textsuperscript{14}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{Fig. 2 Structure of amphidinolactone A (3)}
\end{figure}

Construction of lactone through the formation of C-C bond and particularly by intramolecular ring-closing metathesis\textsuperscript{15} reaction stands as a promising tool for the synthesis of macrolides and heterocycles. As per literature review, to make 13 membered macrolide by utilizing ring closing metathesis reaction was proven difficult. In this article, the influence of protecting groups and the substrate specific nature of the ring-closing metathesis reaction was studied.
2.2. Olefin metathesis reaction:

Ever since the birth of the art of organic synthesis, as marked by Wohler’s synthesis of urea in 1828, progress in this field has, to a large degree, been dependent on our ability to construct carbon frameworks through carbon–carbon bond forming reactions. Olefin metathesis is an organic reaction that entails the union of fragments of alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds. Carbon-carbon bond forming reactions are among the most important family of reactions in organic synthesis. Olefin metathesis is now become a strong and potent synthetic technique and is a powerful method for the clean construction of innumerable classes of chemical architectures. The wide use of this reaction successively in the total synthesis of natural product led to the awarding of Nobel Prize in Chemistry to the pioneers in olefin metathesis: Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock in the 2005. The functional group tolerance of these catalysts and their ability to be handled without the use of glove box or Schlenk techniques have propelled this synthetic methodology in to the forefront of carbon–carbon bond forming techniques in total synthesis. Therefore herein, we have discussed briefly about the ruthenium alkylidenes participation in olefin metathesis reaction.

![Figure 3](image)

Metathesis reaction represents a bimolecular process involving the exchange of bonds between the two reacting chemical species and in the olefin metathesis is a reaction which involves the redistribution of olefin bond. The term metathesis was first introduced by Colderon in 1967 although this reaction was initially observed in 1950s during the study on Ziegler-Natta polymerization process. The first report of the processes involving olefin metathesis was reported by Eleuterio. Traditional catalysts are prepared by a reaction of the metal halides with alkylation agents. Historically, olefin metathesis has been studied both from a mechanistic standpoint and in the context of polymer synthesis. The traditional, industrial catalysts are ill-defined and used mainly for petroleum products.
Modern catalysts are well-defined organometallic compounds that come in two main categories, commonly known as Schrock catalysts and Grubbs' catalysts. Schrock catalysts are molybdenum(VI)- and tungsten(VI)-based, and are examples of Schrock alkylidenes. Schrock entered the olefin metathesis field in 1979 as an extension of work on tantalum alkylidenes.20 Schrock in 1990, prepared the alkylidenes for olefin metathesis and in 1993, prepared the asymmetric catalyst in which the saturated part was replaced with a binol ligand.21(figure 4)

On the other hand, Grubbs' catalysts are ruthenium(II) carbenoid complexes.22

By utilization the so called catalyst in different type of metathesis reactions, resulted several types of olefin metathesis processes. Some important classes of olefin metathesis include:

- Cross Metathesis (CM)
- Ring-Opening Metathesis (ROM)
- Ring-closing metathesis (RCM)
- Ring opening metathesis polymerisation (ROMP)
- Acyclic diene metathesis (ADMET)
- Ethenolysis
Cross-metathesis (CM) and Ring closing metathesis (RCM) reactions are widely used in total synthesis of a lot of complex bioactive natural products. Herein, a brief discussion about CM and RCM reactions has been given.

2.2.1. Cross-Metathesis (CM):

Carbon-carbon bond construction is an interesting part of organic research. Numbers of procedures are there to construct c-c bond, olefin metathesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily handled catalysts. Consequently, olefin metathesis is now widely considered as one of the most powerful synthetic tools in organic chemistry. Until recently the intermolecular variant of this reaction, cross-metathesis, had been neglected despite its potential. With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction have improved to a level that was unimaginable just a few years ago. These advances, together with a better understanding of the mechanism and catalyst–substrate interactions, have brought us to a stage where more and more researchers are employing cross-metathesis reactions in multistep procedures and in the synthesis of natural products. The recent inclusion of alkynes and hindered bi cyclic olefins as viable substrates for bimolecular metathesis coupling, the discovery of enantioselective cross-metathesis and cross-metathesis in water, and the successful marriage of metathesis and solid-phase organic synthesis has further widened the scope of this versatile reaction. Progress in the development of the metathesis reaction has been directly correlated to improvements in the functional group compatibility and the reactivity of the catalysts. Cross metathesis reactions have numerous advantages typical of modern olefin-metathesis reactions i.e. to carry out this reaction 1–5 mol% of catalyst required and high yields can obtain under mild conditions in relatively short reaction times, a wide range of functional groups are tolerated, with minimal substrate protection necessary, this is a well adoptable process for industrial applications due its reversibility character and relatively atom-economic and ethylene is usually the only by-product which is a gas, the olefin substrates are generally easier and less expensive to prepare than those associated with other common catalytic C-C bond-forming reactions (e.g. unsaturated boranes, stannanes, halides, triflates), the olefinic products are suitable for further structural elaboration (e.g. hydrogenation, epoxidation,
halogenation, cycloaddition), high levels of chemo-regio and stereoselectivity can be attained.

Cross-metathesis between two acyclic olefins offers interesting possibilities for synthesizing higher-substituted alkenes. The use of highly substituted asymmetric olefins is not practical because of the expected complex spectrum of products. Use of terminal olefins in the formation of volatile ethylene as a byproduct provides the driving force for the reaction. The volume of work reported in the areas of RCM, ROMP, and novel combinations thereof has dramatically overshadowed that reported for olefin cross-metathesis (CM). This unique method for the intermolecular formation of carbon-carbon double bonds has not yet found widespread application in organic synthesis because general reaction conditions that give high product and trans/cis selectivity have not been developed. The simplified CM reaction between two terminal olefins is depicted below.

**Mecanism of cross-metathesis:**

Hérisson and Chauvin first proposed the widely accepted mechanism of transition metal alkene metathesis. The direct [2 + 2] cycloaddition of two alkenes is formally symmetry forbidden and thus has a high activation energy. The Chauvin mechanism involves the [2 + 2] cycloaddition of an alkene double bond to a transition metal alkylidene to form a metallacyclobutane intermediate. The metallacyclobutane produced can then cyclorevert to give either the original species or a new alkene and alkylidene. Interaction with the d-orbitals on the metal catalyst lowers the activation energy enough that the reaction can proceed rapidly at modest temperatures.

![Figure 6](image-url)
Commonly employed alkene metathesis reactions
Cross-metathesis is a powerful method for the rapid synthesis of simple and complex olefinic building blocks. Grubbs catalyst and Hoveyda-Grubbs catalyst are generally used for this reaction to lead high yield of desired product. Some examples by using grubbs II generation catalyst were shown in Scheme 1.

**Scheme 1**

### 2.2.2. Ring-closing metathesis (RCM)

The olefin metathesis reaction has been known since the 1960s, but it was not until the early 1990s that this transformation became an important tool in synthetic organic chemistry. It was thus in 1992 that Grubbs and Fu published two seminal papers describing the application of ring-closing metathesis (RCM) to the synthesis of simple five-, six-, and seven-membered monocyclic systems containing oxygen and nitrogen atoms using a molybdenum catalyst that had been first prepared by Schrock. From onwards RCM became an interesting and exciting protocol for total synthesis of number of natural products. Ruthenium and the molybdenum catalysts are very reactive and well tolerance behaviors towards all types of functional groups, but the Mo-based complexes
suffer the potential disadvantage of being more air and moisture sensitive. Therefore ruthenium-based catalysts were treated as ideal catalyst worldwide.

Recently modified, highly efficient, ruthenium-based catalysts

**Figure 7**

The high selectivity and reactivity of all ruthenium catalyst for carbon-carbon π-bonds minimizes protecting group manipulations while enabling the use of RCM as an excellent alternative to other ring-forming reactions for the efficient construction of complex cyclic targets having a variety of ring sizes. The Ring-Closing Metathesis (RCM) allows synthesis of 5- up to 30-membered cyclic alkenes. The E/Z-selectivity depends on the ring strain.

**Chauvin's Mechanism for RCM:**

Chauvin had suggested the following mechanism which was universally accepted.

Initiation:
Catalytic Cycle:

Figure 8

It is now generally accepted that the mechanism of both cyclic and acyclic olefin metathesis proceeds through a series of metalla cyclobutanes and carbene complexes. Although the relative stabilities of the carbenes and metalla cyclobutanes can change with reaction conditions, catalyst composition and alkene substitution, the mechanism of olefin metathesis (Figure 8) appears to be the same for all catalysts. The key intermediate is a metallacyclobutane, which can undergo cycloreversion either towards products or back to

Scheme 2

(Diagram for most commonly employed different types of alkene metathesis reactions.)
starting materials. When the olefins of the substrate are terminal, the driving force for RCM is the removal of ethene from the reaction mixture.

As with any other cyclization method, the synthetic efficiency of RCM is limited by the competition between intramolecular ring-closing and intermolecular oligomerization reactions. Olefin metathesis is represented as a fully reversible set of [2 + 2] cycloaddition-cycloreversion equilibria, implying a thermodynamic distribution of “living” metathesis products. The emergence of metathesis reactions in chemical synthesis over the last few years has been dramatic. It has been delightful to review the field and highlight some of its most exciting applications in total synthesis. Some excellent use of ring closing metathesis had been demonstrated below.

Olefin ring closing metathesis and hydrosilylation reaction in aqueous medium by Grubbs second generation ruthenium catalyst was demonstrated in 2008 by Verma et al (scheme 3).

The total synthesis of (−)-muricatacin had been achieved via highly regioselective and stereoselective tandem ring-closing/cross metathesis reaction in which both lactone formation (scheme 4).

The first total synthesis of elatol which is a halogenated sesquiterpene in the chamigrene natural product family had been achieved a ring-closing olefin metathesis to concomitantly form the spirocyclic core as well as the fully substituted chlorinated olefin (scheme 5).
A straightforward total synthesis of the cyclooctenoid sesquiterpene dactylol has been achieved via ring-closing metathesis (RCM) of the resulting dienes to form the cyclooctene ring using Schrock's molybdenum carbene as a precatalyst (scheme 6).\textsuperscript{28}

![Scheme 6](image)

The total synthesis of the novel lactone natural product octalactin A was done. The key step involves the facile construction of the eight-membered lactone core via ring-closing metathesis (RCM) (scheme 7).\textsuperscript{29}

![Scheme 7](image)

Racemic and enantiopure targets containing the 6,8-dioxabicyclo[3.2.1]octane skeleton, was conveniently synthesized from monocyclic diene precursors using an intramolecular ruthenium-catalyzed ring-closing metathesis reaction as the key step (scheme 8).\textsuperscript{30}

![Scheme 8](image)

The ring closing reaction was widely demonstrated in 10-membered lactones. In this context, we are going to discuss about some similar lactones. The total syntheses of stagonolide B and its 4-epimer were carried out to probe into how the relative stereochemistry of allylic hydroxy groups and their protecting groups influence the efficiency of the ring closing metathesis (scheme 9).\textsuperscript{31}
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Scheme 9

Ring-closing metathesis to form a diene system in the total synthesis of pochonin C was completed by Winssinger and co-workers in 2004 (scheme 10).\(^\text{32}\)

Scheme 10

Wood and co-workers in 2004 had reported the total synthesis of ingenol via ring-closing-metathesis reaction (scheme 11).\(^\text{33}\)

Scheme 11

Ring-closing-metathesis reactions in the total synthesis of amphidinolide A and its stereoisomers was successfully demonstrated by Maleczka and co-workers (scheme 12).\(^\text{34}\)

Scheme 12
Hirama and co-workers in 2002 published the total synthesis of ciguatoxin CTX3C by using multiple use of ring-closing-metathesis reaction (scheme 13).\cite{35}

\begin{center}
\includegraphics[width=\textwidth]{scheme13.png}
\end{center}

\textbf{Scheme 13}

\section*{2.3. Previous approaches:}

Herein, a brief account of the previous works carried out the total synthesis of amphidinolactone A has been reviewed.

\subsection*{2.3.1 Kobayashi’s Approach:}\cite{36}

Kobayashi et al. reported first total synthesis Amphidinolactone A and thus they confirmed that the absolute stereochemistry was identical with the proposed one.\cite{20}

\subsection*{2.2.2a. Retrosynthesis:}
Scheme 14: Retrosynthetic analysis

2.3.1b. Synthesis:

The synthesis of the C-6–C-13 segment 5 of 3 is summarized in Scheme 5. 2,3-Di-O-cyclohexylidene-(R)-(+)glyceraldehyde 9 was treated with vinylmagnesium bromide to give 10 as an inseparable 5:3 diastereomeric mixture. Protection of the hydroxy group at C-11 in 10 as benzyl ether yielded 11, which was subjected to oxidative cleavage of terminal olefin followed by Wittig reaction to provide a 4:1 (E:Z) mixture of ester 13. Reduction of ester 13 with DIBAL-H gave alcohol, which was oxidized with Dess–Martin periodinane and then subjected to Yamamoto’s silver-catalyzed asymmetric allylation to give a 5:3:2 mixture of 14, 15 and Z isomers, respectively. At this stage, alcohols 14 and 15 were separated by silica gel column chromatography. Removal of benzyl group in 14 followed by protection of hydroxy groups provided MOM ether, which was treated with p-TsOH.H2O to afford diol 16. Selective mesylation of diol 16 followed by treatment with K2CO3 in MeOH provided the C-6–C-13 segment 5 (scheme 15).

Scheme 15

Reagents and conditions: a) THF,0 °C, 40 min, 60%, b) BnBr, NaH, DMF, 50 °C, 1 h, c) OsO4, dioxane:H2O/ 3:1, d) CH2Cl2, rt, e) DIBAL-H, CH2Cl2, –40 °C, f) DMP, CH2Cl2, rt, g) Allyltrimethoxy silane, AgF, h) (R)-p-Tol-BINAP, MeOH, –20 °C, i) Na, Liq-NH3, –78 °C, j) MOMCl, iPr2NEt, CH2Cl2, rt, k) p-TSOH.H2O, MeOH, l) MsCl, pyridine, 0 °C, m) K2CO3, MeOH.
The synthesis of the C-1–C-5 segment 8 is summarized in Scheme 16. Commercially available alcohol 17 was treated with PDC in DMF to provide the C-1–C-5 segment 8. Known acetylene 7 and the C-6–C-13 segment 5 in hand, they turned to alkynylation of oxirane under Yamaguchi condition (Scheme 17). Coupling of 25 with known acetylene 16 using n-BuLi and BF\(_3\).OEt\(_2\) provided the alcohol 6. Reduction of 6 with hydrogen and Lindlar’s catalyst followed by esterification with the resulted alcohol and acid 8 using 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDC) gave ester 4.

Scheme 16

The ester was subjected to RCM by using Grubbs’ first-generation catalyst followed by removal of MOM groups to furnish Amphidinolactone A (3). The synthetic material was spectroscopically (IR, \(^1\)H and \(^{13}\)C NMR, HRMS) identical with natural product. Thus, the absolute stereochemistry of Amphidinolactone A (3) was established as 8\(R\), 11\(S\) and 12\(R\).

Scheme 17

Reagents and conditions: a) \(n\)-BuLi, BF\(_3\).OEt\(_2\), \(-78^\circ\)C, 20 min, b) \(H_2\), Lindlar's Pd-cat, quinoline, c) 4, EDC, CH\(_2\)Cl\(_2\), rt, d) Grubbs 1st generation catalyst, e) \(p\)-TsOH.H\(_2\)O, MeOH, 0 \(^\circ\)C.
2.3.2. Mohapatra’s Approach:

Mohapatra et al. reported a concise and efficient total synthesis Amphidinolactone via a protecting group directed stereoselective intramolecular Nozaki-Hiyama-Kishi (NHK) reaction for macrocyclization.

2.3.2a. Retrosynthesis:

![Scheme 18]

2.3.2b. Synthesis:

Synthesis of fragment 22 was initiated starting from a known chiral epoxide 25 which was prepared by using Jacobsen’s hydrolytic kinetic resolution protocol. The epoxide 25 underwent clean addition of lithium acetylide prepared from TBS-protected alkyne by treatment with \( n \)-BuLi in THF at \(-78 \, ^{\circ}C\) and the resulting secondary hydroxyl group was protected as its benzyl ether with NaH and benzyl bromide at \( 0 \, ^{\circ}C \) to afford 27 followed by deprotection of the silyl group with \( p \)-TsOH in MeOH at room temperature followed by Lindlar-catalyzed partial hydrogenation\(^6\) afforded the Z-olefin derivative 28 (Scheme 19). Oxidation of the resulting hydroxyl group with TEMPO and BAIB followed by further Pinnick oxidation with NaClO\(_2\) in presence of 2-methyl-2-butene afforded acid which on treatment with \( \text{CH}_2\text{N}_2\) in ether at \( 0 \, ^{\circ}C \) gave ester 29. Deprotection of the PMB
group with DDQ in CH₂Cl₂:H₂O (19:1) at room temperature gave alcohol 30 which on Dess-Martin periodinane oxidation followed by Takai olefination afforded the trans-vinyl iodide 31 as the only product. Saponification of the ester functionality with LiOH in THF:H₂O (3:2) afforded the required acid fragment 22.

The chiral epoxide 25 on treatment with lithium acetylide followed by deprotection of the TBS-ether linkage with p-TsOH in MeOH afforded 33. The primary hydroxyl group of 33 was converted to iodide 35 via tosylation and treatment of the tosylate derivative with NaI in acetone. The Wittig salt 36 was prepared by treating 35 with triphenylphosphine in acetonitrile under reflux conditions (Scheme 20). Cis-geometry at C17-C18 was then introduced by performing Wittig reaction of 36 with n-propanal by generating in situ ylide with n-BuLi at −78 °C to obtain 37 as the only product followed by partial hydrogenation using Lindlar’s catalyst (Pd on CaCO₃) in presence of quinoline (catalytic) afforded alcohol 24.
Scheme 20

Reagents and conditions: (a) n-BuLi, BF$_3$(OEt)$_2$, alkyne derive., $-78 \, ^\circ\mathrm{C}$, 1 h, 86%; (b) p-TsOH, MeOH, 0 °C-rt, 1 h, 94%; (c) TsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 6 h, 80%; (d) NaI, acetone, reflux, 3 h, 90%; (e) TPP, CH$_3$CN, 100 °C, 12 h, 94%; (f) n-BuLi, propionaldehyde, $-78 \, ^\circ\mathrm{C}$, 4 h, 83%; (g) H$_2$, Pd/C on CaCO$_3$, quinoline (catalytic), benzene, rt, 3 h, 91%.

The coupling of fragment 22 and fragment 24 was achieved under Yamaguchi conditions to obtain the ester 20, which contains all 20-carbons of the target molecule (Scheme 20). Deprotection of the PMB ether in 20 upon treatment with DDQ afforded alcohol 38 and a subsequent Dess-Martin periodinane oxidation of 38 gave the required aldehyde 18. The critical macrocyclization of 18 via Nozaki-Hiyama-Kishi coupling reaction was performed in DMSO and THF (3:1) mixture, high yield was obtained although the reaction took about 24 h to completely consume the starting material to afford a 2:1 mixture of inseparable diastereomeric allylic alcohols 39 and 40.

To obtain a single isomer, the OBn protecting group was replaced by OTBDPS group and followed same sequence of reactions as illustrated above. Then, the critical macrocyclization of 19 via Nozaki-Hiyama-Kishi coupling reaction was performed to afford the required isomer as a only product as 41. Finally, deprotection of the TBDPS ether linkage with TBAF and acetic acid afforded the target natural product amphidinolactone A (3).
Scheme 21
Reagents and conditions: (a) (i) DCC, DMAP, CH$_2$Cl$_2$, 0 °C-rt, 12 h, 58%; (ii) EDCI, DMAP, CH$_2$Cl$_2$, 0 °C-rt, 12 h, 70%; (iii) 2,4,6-trichlorobenzoyl chloride, DMAP, THF, toluene, rt, 6 h, 89%; (b) DDQ, CH$_2$Cl$_2$;H$_2$O (9:1), rt, 3 h, 91%; (c) DMP, CH$_2$Cl$_2$, rt, 4 h; (d) CrCl$_2$, NiCl$_2$, DMSO:THF (3:1), rt, 24 h, 81% over two steps.

Scheme 22
Reagents and conditions: (a) CrCl$_2$, NiCl$_2$, DMSO, rt, 24 h, 85% over two steps; (b) TBAF, AcOH, THF, 0 °C-rt, 18 h, 87%.

A convergent total synthesis of amphidinolactone A is described in 13 longest linear steps in 22% overall yield involving macrolactonization using intramolecular Nozaki- Hiyama-Kishi (NHK) reaction for the construction of 13-membered lactone ring.
CHAPTER II

Section B

Synthesis of the macrolactone Core of Amphidinolactone A
2.4. Present Work:

The interesting biological profile as well as the structural complexity of amphidinolactone A (3) has attracted the attention of synthetic organic chemists worldwide. Herein, we provide a complete account of our synthetic studies. We envisioned a convergent synthesis of macrolactone core of amphidinolactone A and we expected that this synthetic strategy would provide a highly stereoselective route to amphidinolactone A (3). Moreover, the synthetic protocol could sort out all the selectivity problems faced by Kobayashi et al. during the total synthesis.

2.4.1. Retrosynthesis

Scheme 23
According to our retrosynthetic analysis of amphinolactone A (3) shown in Scheme 23, 43 could be achieved through ring-closing metathesis reaction of 45 which in turn could be obtained by coupling of acid fragment 46 and alcohol fragment 47. Acid fragment 46 and alcohol fragment 47 could be obtained from (R)-epichlorohydrin 48 and (R)-2,3-O-isopropylidene glyceraldehyde 49, respectively. The crucial reactions involved in the synthesis of the individual fragments are Jocobsen’s hydrolytic kinetic resolution, Sharpless asymmetric epoxidation, Lindlar’s hydrogenation, Ring closing metathesis and Yamaguchi esterification.

2.4.2 Results and Discussions:
Synthesis of the fragment 46:

Chiral epoxide 48 prepared by following Jacobsen’s hydrolytic kinetic resolution protocol, was taken as the starting material for the synthesis of acid fragment 46. The racemic epoxide was subjected to solvent free hydrolytic kinetic resolution employing 0.55 eq of water in the presence of 0.005 mol% of (S,S’)-(−)-N-N’-bis-(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino-cobalt(II) to afford the chiral epoxide 48 in 45% yield along with the chiral diol. The epoxide 48 was opened with lithium acetylide prepared from TBS-protected alkyne 50 using n-BuLi, BF<sub>3</sub>.OEt<sub>2</sub> in THF at −78 °C to afford the secondary hydroxyl compound 51 in 92% yield (Scheme 24). The product 51 formation was confirmed by <sup>1</sup>H NMR which showed two singlet at δ 9.1 and 0.05 ppm, characteristics of TBS group. <sup>13</sup>C NMR also showed resonance characteristics

![Scheme 24](image-url)
peak for triple bond carbons at δ 83.6 and 74.6 ppm. Product formation was further confirmed by its ESI-HRMS which showed a peak at m/z 327.1509 [M + Na]^+ and a broad peak at 3416 cm\(^{-1}\) due to the presence of hydroxyl group in IR. The epoxidation of the resulting homopropargyl alcohol 51 proceeded smoothly with NaH in THF at 0 °C to obtain the epoxy compound 52 in 91% yield. The epoxy compound 52 was confirmed by its \(^1\)H NMR spectrum, which showed resonance at δ 3.62, 3.07, 2.78 ppm as multiplets for three oxirane protons. Absence of hydroxyl functionality was also confirmed by IR spectrum, which showed no absorption band for hydroxyl functionality. Partial hydrogenation was taken place by treating with Lindlar’s catalyst\(^{40}\) in presence of catalytic amount of quinoline under hydrogen atmosphere to afford 53 with the required Z olefin in 96% yield. The appearance of two multiplet for double bond at δ 5.53 and 5.41 ppm in \(^1\)H NMR and two new peaks at δ 132.9, 123.2 ppm and disappearance of two alkyne peaks at δ 83.6 and 74.6 ppm in \(^{13}\)C NMR confirmed the transformation to a Z-olefin. The compound was characterized by ESI-HRMS which showed (M + Na)^+ peak at m/z 293.1893.

One-carbon homologation\(^{41}\) with trimethyl sulfonium iodide and \(n\)-BuLi in THF at −10 °C afforded the allylic alcohol 54 in 85% yield. The terminal three olefinic protons of the product resonated as a multiplet at δ 5.85, 5.22, 5.09 ppm where as the allylic oxygen attached proton resonated at δ 4.11 ppm as a quartet in \(^1\)H NMR. \(^{13}\)C NMR revealed two new peaks at δ 140.5, 114.5 ppm for olefinic carbons whereas peak at m/z 307.2051 [M + Na]^+ in ESI-HRMS spectrum further confirmed this transformation. The newly formed secondary hydroxyl group was protected as its PMB ether 55 by treating with NaH, PMBBr in 91% yield. The \(^1\)H NMR of 55 revealed two new peaks as doublet at δ 7.21, 6.82 ppm for aromatic group and ABq pattern at δ 4.37 (\(J = 11.3\) Hz) ppm for the two benzylic protons. Next, TBS group was deprotected using p-TsOH (cat.) in MeOH to afford the primary alcohol 56 with 89% yield (scheme 25). The structure was confirmed by its \(^1\)H NMR study which showed the absence of TBS protons and carbon peaks at δ 5.3 for TBS in \(^{13}\)C NMR. IR spectrum of compound 56 disclosed the absorption band at 3406 cm\(^{-1}\) and ESIMS showed (M + H)^+ peak at m/z 313.1794 clearly indicating the absence TBS ether. Treatment of the resulted primary hydroxyl compound 56 with BAIB and TEMPO\(^{42}\) in DCM produced aldehyde 57 which was quickly purified by flash column
chromatography and directly subjected to Pinnick oxidation\textsuperscript{43} by NaClO\textsubscript{2}, NaH\textsubscript{2}PO\textsubscript{4}, 2-methyl-2-butene in \textit{t}-BuOH:H\textsubscript{2}O to convert to acid 46 in 89\% yield (over two steps). The disappearance of two protons in \textsuperscript{1}H NMR at \(\delta\) 3.58 ppm region and appearance of two extra protons (\(\alpha\) to the acid) at \(\delta\) 2.31 ppm as multiplet confirmed the conversion. The mass spectroscopy showed (M + Na)\textsuperscript{+} peak at \(m/z\) 327.1182.

![Scheme 25](image)

Its 1710 cm\textsuperscript{-1} peak in IR spectrum and \(\delta\) 179.3 ppm peak in \textsuperscript{13}C NMR spectrum provided additional proof in favor of acid formation.

**Synthesis of the alcohol fragment 4:**

Synthesis of fragment 47 was commenced with two-carbon homologation of the known aldehyde \((R)-2, 3-\text{O}-\text{isopropylidene glyceraldehyde (49)}\) to give \(\alpha,\beta\)-unsaturated ester 58 in 85\% yield. The ester was converted to the corresponding \(E\)-allylic alcohol 59 by using DIBAL-\(H\) set the platform for introducing two more chiral centers via Sharpless
asymmetric epoxidation. Thus the allyl alcohol 59 on treatment with (−)-DET, titanium(IV)isopropoxide and tert-butyl hydroperoxide in dichloromethane in anhydrous condition at −20 °C to yield epoxy alcohol 60 in 92% yield (94:6 ratio with the required isomer as the major product) (Scheme 26). The structure was confirmed by its 1H NMR study which showed the absence of olefinic protons and the presence of two oxirane protons at 3.14-3.07 ppm as multiplets and methylene protons adjacent to hydroxyl group with an upfield shift at 4.02-3.84 ppm as a multiplet (versus 4.14 ppm for allyl alcohol). The epoxy alcohol was transformed to its iodo derivative (Scheme 14) by standard I2, TPP, imidazole protocol and the iodo derivative immediately used for next step without further characterization. When the iodo derivative was treated with activated Zn dust and NaI in refluxing MeOH, reductive epoxide ring opening took place to produce the allyl alcohol 61. The geminal protons of the olefin resonated as a set of singlets at δ 5.0 and 4.83 ppm, while two olefinic carbons resonated at δ 110.7 and 145.5 ppm. A peak at m/z [M + H]+ 423 further confirmed the product. The resulting secondary hydroxyl group of 61 was protected as its PMB ether by using PBB bromide and sodium hydride in THF at 0 °C to obtain 62 in 92% yield. Its 1H NMR revealed two doublets at δ 7.21 (J = 8.7 Hz), 6.80 (J = 8.7 Hz) ppm for aromatic protons of PMB group along with the other required protons. 13C NMR revealed two new peaks at δ 133.1, 123.9 for olefinic carbons and three new peaks at δ 20.4, 17.0, 13.9 ppm for aliphatic carbons.
whereas peak at $m/z$ 311.1628 [M + Na]$^+$ in HRMS spectrum further confirmed this transformation. Then, deprotection of the isopropylidene group with $p$-TsOH in MeOH at room temperature afforded diol 63 in 87% yield. Its $^1$H NMR revealed the absence of a set of two doublets at $\delta$ 1.36, 1.31 ppm, and a broad singlet at $\delta$ 4.36 ppm for two hydroxyl protons. In IR spectroscopy a broad peak at 3409 cm$^{-1}$ and a peak at $m/z$ 261.1115 [M+Na]$^+$ in ESI-HRMS spectrum was an additional proof in the favor of formation of diol. The primary hydroxyl group of the diol 63 (Scheme 27) was selectively protected as its TBDPS ether 47 by TBDPSCI, imidazole in DCM at 0 °C with 89%

![Diagram of reaction](attachment:image.png)

**Scheme 27**

yield. In $^1$H NMR, the two phenyl group of TBDPS resonated as a set of two multiplets at $\delta$ 7.68-7.61 ppm integrating for four protons and $\delta$ 7.46-7.32 ppm integrating for six protons where as the nine protons of $t$-Butyl group resonated as a singlet at $\delta$ 1.05 ppm and the $^{13}$C NMR spectra were in full accord with the incorporation of TBDPS group. A peak at $m/z$ [M + H]$^+$ 499.2275 thus confirmed the formation of the alcohol fragment 47.

**Coupling of fragment 46 and 47:**

Our next target was to couple both the fragments and investigate the critical ring-closing metathesis reaction. As per our investigation in chapter I, we had followed the Yamaguchi conditions for the esterification reaction. In this case, the yield was only 30-35% with complete destruction of the starting materials. However, a better result was achieved by uniting both the coupling partners with EDCI and DMAP in CH$_2$Cl$_2$ to afford the triene ester 44 in 90% yield (Scheme 4). The $^1$H NMR and $^{13}$C NMR spectra were in full accord with the product where PMB, olefins and other functionalities resonated at
their respective positions. IR absorption showed the absence of characteristic band for
hydroxyl functionality whereas a peak at \( m/z \ 785.3847 \ [M + NH_4]^+ \) in ESI-HRMS
spectrum was confirmed the formation of ester. Now the stage was ready to perform the
crucial RCM reaction. The ester 44 was refluxed with Grubbs II generation\(^{49}\) catalyst in
\( \text{CH}_2\text{Cl}_2 \) under high dilution conditions (0.001 M) for 5 h. The reaction was failed to
provide the lactone 42. Again this RCM reaction was kept in different solvent
concentrations and exending the time, this attempt also proven unsuccess. The extent of
bias if any conferred by the protecting groups on the outcome of the ring-closing
metathesis reaction could not be predicted with certainty. We envisaged that PMB-
protecting groups around the reacting centers might act as a temporary constraint to
adequately come closer for the reaction to happen. This prediction was also supported by
computational analysis (Fig. 9) as well as further experimental studies. In order to unravel
the observed experimental trends quantum chemical

\[ \text{Fig. 9 Minimum energy calculated for di-PMB protected lactone core 2 (44.18 kcal/mol) and diol-lactone 3 (24.71 kcal/mol) of amphidinolactone A.} \]
calculations are carried out on the PMB protected lactone and PMB deprotected lactone. This trends quantum chemical calculation were revealed that Minimum energy calculation for di-PMB protected lactone core 42 was found 44.18 kcal/mol and diol-lactone 43 was found 24.71 kcal/mol of amphidinolactone A (3). To further prove our predictions, di-PMB protected ester 44 was treated with DDQ in CH$_2$Cl$_2$:H$_2$O (9:1) to obtain diol -- in 93% yield (Scheme 28). Its $^1$H NMR revealed the absence of a set of two doublets at $\delta$ 7.20, 6.83 ppm, a peak at $\delta$ 4.43 ppm for two benzylic protons and a singlet at $\delta$ 3.79 ppm for three methoxy protons of PMB group. A peak at $m/z$ 723.2354 [M + Na]$^+$ in ESI-HRMS spectrum and a very big peak at 3445 cm$^{-1}$ revealed the deprotection of PMB group. Treatment of diol 45 with Grubbs II generation catalyst in refluxing CH$_2$Cl$_2$ under high dilution (0.001 M) conditions smoothly furnished the required 13-membered lactone ring system 43 present in amphidinolactone A (3) in 76% yield. Geometry (trans) of the newly formed double bond was established by its coupling constant, while one of the olefinic proton signals appeared at $\delta$ 5.66 ppm as a doublet of a doublet ($J_{\text{trans}}$ coupling constant 15.7 Hz) and other olefinic proton signals appeared at their respective chemical shifts. The $^{13}$C NMR data were in good agreement with the constitution and configuration of the assigned structure for 43. Along with above data, a peak at $m/z$ 517.2400 [M + Na]$^+$ in ESI-HRMS spectrum was given additional support for the formation of 13 membered lactone (scheme 29).

Scheme 28
Thus, a convergent synthesis of macrolactone core of amphidinolactone A has been achieved through ring-closing metathesis reaction as the macrolactonization step. The RCM precursor was obtained by the union of acid and alcohol fragments derived from \((R)\)-epichlorohydrin and \((R)\)-2,3-\(O\)-isopropylidene glyceraldehyde, respectively.
Experimental Section
2.5. EXPERIMENTAL SECTION

2.5.1. ((R)-9-(tert-Butyldimethylsilyloxy)-1-chloronon-4-yn-2-ol (51).

A flame-dried 250 mL two necked round bottom flask was charged with TBS protected 5-hexyne 1-ol 50 (3.0 g, 14.12 mmol) in THF (100 mL) and cooled to −78 °C. To this solution, n-BuLi (2.5M in hexanes, 5.64 mL, 14.12 mmol) was added drop-wise via syringe, warmed slowly to 0 °C. During this period, the reaction mixture turned to dark red in color. After 30 min, (R)-epichlorohydrin 48 (1.1 g, 11.29 mmol) was slowly added followed by BF₃.OEt₂ (1.43 mL, 11.29 mmol) at −78 °C and stirred for an additional 30 min. The reaction was then quenched with saturated NaHCO₃ (50 mL), diluted with ethyl acetate (50 mL), and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 60 mL). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/hexane = 1:19) provided the desired secondary alcohol 51 (3.96 g, 92%) as a colorless oil.

[α]D²⁵: −5.0 (c 0.9, CHCl₃);
IR (neat, KBr) : ν max 3074, 2932, 2854, 2837, 1613, 1513, 1464, 1248, 1094, 915, 821 cm⁻¹;
¹H NMR (300 MHz, CDCl₃) : δ 3.93 (m, 1 H), 3.73-3.56 (m, 4 H), 2.55-2.48 (m, 2H), 2.32-2.15 (m, 2 H), 1.65-1.50 (m, 4 H), 0.91 (s, 9 H), 0.05 (s, 6 H) ppm;
¹³C NMR (75 MHz, CDCl₃) : δ 83.6, 74.6, 70.0, 62.6, 48.3, 31.9, 25.9, 25.3, 24.7, 18.5, 18.3, −5.3 ppm;
ESI-HRMS : m/z calcd for C₁₅H₂₉ClNaO₂Si [M + Na]+ 327.1518; found 327.1509.

2.5.2. (R)-tert-Butyldimethyl-(7-(oxiran-2-yl)hept-5-ynloxy)silane (52).
Chapter II, Experimental Section

To a suspension of NaH (0.69 g, 28.78 mmol, 60% w/v dispersion in mineral oil) in dry THF (25 mL), was added dropwise a solution of chlorohydrins 51 (3.5 g, 11.51 mmol) in dry THF (50 mL) under N\textsubscript{2} atmosphere at 0 °C. The reaction mixture was allowed to stir at room temperature for 30 min. After completion of the reaction (monitored by TLC), it was quenched with ice cold water (50 mL) at 0 °C. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and the solvent evaporated under reduced pressure. The crude mass was purified by silica gel chromatography (ethyl acetate/hexane = 1:49) to afford the epoxide 52 (2.70 g, 91%) as a light yellow liquid.

[\alpha]_{D}^{25} : -9.2 (c 0.8, CHCl\textsubscript{3});

IR (neat, KBr) : ν\textsubscript{max} 3051, 2933, 2859, 1741, 1613, 1467, 1392, 1252, 1102, 996, 838, 776 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) : δ 3.62 (t, J = 5.8 Hz, 2 H), 3.07 (m, 1 H), 2.78 (t, J = 4.7 Hz, 1 H), 2.65 (m, 1 H), 2.57 (m, 1 H), 2.44 (m, 1 H), 2.23-2.14 (m, 2 H), 1.70-1.48 (m, 4 H), 0.9 (s, 9 H), 0.05 (s, H) ppm;

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) : δ 82.5, 74.2, 62.7, 50.3, 46.4, 31.9, 25.9, 25.2, 22.5, 18.5, 18.3, -5.3 ppm;

ESI-HRMS : m/z calcd for C\textsubscript{15}H\textsubscript{28}NaO\textsubscript{2}Si [M + Na]+ 291.1751; found 291.1739.

2.5.3. (R,Z)-tert-Butyldimethyl-(7-(oxiran-2-yl)hept-5-enyloxy)silane (53).

Lindlar catalyst (Pd/C on CaCO\textsubscript{3}) (10 mol%) was added to a stirred solution of alkyne 52 (2.5 g, 9.32 mmol) in benzene (10 mL) followed by catalytic amount of quinoline (0.02 mL, 0.093 mmol) at room temperature under hydrogen atmosphere. The mixture
was vigorously stirred for 3 h at room temperature. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:49) to yield the desired Zolefin 53 (2.41 g, 96%).

$[\alpha]_D^{25}$: $-5.5$ (c 1.35, CHCl$_3$);

IR (neat, KBr) : $\nu_{max}$ 2932, 2858, 1742, 1467, 1389, 1253, 1101, 836, 775 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 5.53 (m, 1 H), 5.41 (m, 1 H), 3.62 (t, $J$ = 6.4 Hz, 2 H), 2.95 (m, 1 H), 2.74 (t, $J$ = 4.5 Hz, 1 H), 2.51 (m, 1 H), 2.38 (m, 1 H), 2.26 (m, 1H), 2.06 (q, $J$ = 7.2 Hz, 2 H), 1.58-1.47 (m, 2 H), 1.46-1.35 (m, 2 H), 0.89 (s, 9 H), 0.05(s, 6 H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 132.9, 123.2, 63.0, 51.6, 46.5, 32.4, 30.1, 27.1, 25.9, 25.8, 18.3, $-5.3$ ppm;

ESI-HRMS : m/z calcd for C$_{15}$H$_{30}$NaO$_2$Si [M + Na]$^+$ 293.1907; found 293.1893.

2.5.4. $(R,Z)$-10-$(\text{tert-Butyldimethylsilyloxy})$deca-1,5-dien-3-ol (54).

To a stirred solution of trimethylsulfonium iodide (predried by azeotropic method using dry toluene) (4.53 g, 22.2 mmol) in THF (30 mL) was cooled to −20 °C, added $n$-BuLi (7.4 mL, 2.5M in hexane, 18.5 mmol) and stirred for 30 min. After stirring the reaction mixture for 30 min at −20 °C, the epoxide 53 (2.0 g, 7.4 mmol) in THF (20 mL) was added via syringe over 20 min at the same temperature. After complete addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 30 min. After stirring at room temperature for 2 h, the reaction was quenched with saturated ammonium chloride (40 mL) water and diluted with diethyl ether (60 mL). The organic layer was separated and the aqueous layer extracted with diethyl
ether (2x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:19) to obtain the secondary allylic alcohol 54 (1.79 g, 85%) as colorless syrup.

$[\alpha]_D^{25}$ : +9.7 (c 0.8, CHCl$_3$);
IR (neat, KBr) : $\nu_{\text{max}}$ 3410, 3011, 2932, 2858, 1466, 1389, 1253, 1101, 837, 775 cm$^{-1}$;
$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 5.85 (m, 1 H), 5.53 (m, 1 H), 5.37 (m, 1H), 5.22 (d, $J = 16.8$ Hz, 1 H ), 5.09 (d, $J = 10.3$ Hz, 1 H ), 4.11 (q, $J = 6.0$, 12.2 Hz, 1 H), 3.58 (t, $J = 6.2$ Hz, 2 H), 2.28 (t, $J = 6.7$ Hz, 2 H), 2.12 (q, $J = 6.9$, 13.9 Hz, 2 H), 1.57-1.35 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm;
$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 140.5, 133.0, 124.5, 114.5, 72.4, 63.0, 35.0, 32.3, 27.1, 25.9, 18.3, -5.3 ppm;
ESI-HRMS : m/z calcd for C$_{16}$H$_{32}$NaO$_2$Si [M + Na]$^+$ 307.2064; found 307.2051.

2.5.5.$(R,Z)$-tert-Butyl(8-(4-methoxybenzyloxy)deca-5,9-dienyloxy)dimethylsilane (55):

To a suspension of NaH (0.28 g, 7.04 mmol, 60% w/v dispersion in mineral oil) in dry THF (25 mL) was added dropwise a solution of resulting allylic alcohol 54 (1.0 g, 3.52 mmol) at 0 °C and continued the stirring for the next 45 min at room temperature. At 0 oC, freshly prepared $p$-methoxy benzyl bromide (0.71 g, 3.52 mmol) was added and stirred further for 4 h at room temperature with frequent monitoring of the progress of the reaction by TLC. The reaction mixture was quenched with crushed ice flakes until a clear solution (biphasic) was formed. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (2 x 70 mL), brine (100 mL), and dried over anhydrous Na$_2$SO$_4$. Solvent was
removed under reduced pressure and the crude was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:49) to afford the PMB-ether 55 (1.29 g, 91%) as a colorless liquid.

\[ \left[ \alpha \right]_{D}^{25} \] : +11.7 (c 1.1, CHCl$_3$);

IR (neat, KBr) : $\nu_{max}$ 2933, 2857, 1613, 1513, 1464, 1301, 1249, 1174, 1099, 835, 775 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.21 (d, $J$ = 9.0 Hz, 2 H), 6.82 (d, $J$ = 9.0 Hz, 2 H), 5.73 (m, 1 H), 5.48-5.32 (m, 2 H), 5.24-5.14 (m, 2 H), 4.51 (d, $J$ = 11.3 Hz, 1 H), 4.47 (d, $J$ = 11.3 Hz, 1 H), 3.79 (s, 3 H), 3.71 (q, $J$ = 6.9, 14.5 Hz, 1 H), 3.58 (t, $J$ = 6.0 Hz, 2 H), 2.43-2.19 (m, 2 H), 2.08-2.01 (m, 2 H), 1.54-1.30 (m, 4 H), 0.90 (s, 9 H), 0.04 (s, 6 H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 158.9, 138.6, 131.6, 130.7, 129.1, 125.0, 117.1, 113.6, 80.0, 69.6, 63.0, 55.1, 33.4, 32.4, 27.1, 25.9, -5.3 ppm;

ESI-HRMS : m/z calcd for C$_{24}$H$_{40}$NaO$_5$Si [M + Na]$^+$ 427.2639; found 427.2623.

2.5.6. (R,Z)-8-(4-Methoxybenzyloxy)deca-5,9-dien-1-ol (56).

To a stirred solution of TBS ether 55 (1.0 g, 2.47 mmol) in MeOH (20 mL) was added $p$-TsOH (catalytic) at 0 °C and the resulting solution was stirred for 1 h at ambient temperature. The reaction mixture was quenched with aqueous NaHCO$_3$ (20 mL). MeOH was removed under reduced pressure, the residue extracted with EtOAc (3 x 50 mL), the combined organic layer washed with brine (50 mL), dried over Na$_2$SO$_4$, and evaporated to dryness which on silica gel column chromatography (EtOAc/hexane: 1/7) furnished the desired primary alcohol 56 (0.64 g, 89%) as a viscous colorless liquid.

\[ \left[ \alpha \right]_{D}^{25} \] : +19.3 (c 0.9, CHCl$_3$);
IR (neat, KBr) : $\nu_{\text{max}}$ 3406, 3074, 2933, 2861, 1612, 1513, 1459, 1301, 1247, 1175, 1037, 821, 774 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.21 (d, $J = 8.3$ Hz, 2 H), 6.81 (d, $J = 8.3$ Hz, 2 H), 5.72 (m, 1 H), 5.47-5.3 (m, 2 H), 5.24-5.12 (m, 2 H), 4.50 (d, $J = 11.5$ Hz, 1 H), 4.25 (d, $J = 11.5$ Hz, 1 H), 3.78 (s, 3 H), 3.69 (q, $J = 6.9$, 13.9 Hz, 1 H), 3.53 (t, $J = 6.2$ Hz, 2 H), 2.36 (m, 1 H), 2.22 (m, 1 H), 2.08-1.97 (m, 2 H), 1.56-1.32 (m, 4 H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 158.9, 138.5, 131.4, 130.6, 129.2, 125.3, 117.2, 113.6, 79.9, 69.7, 62.7, 55.2, 33.4, 32.2, 27.0, 25.6 ppm;

ESI-HRMS : $m/z$ calcd for C$_{18}$H$_{26}$NaO$_3$ [M + Na]$^+$ 313.1774; found 313.1794.

2.5.7. ($R,Z$)-8-(4-Methloxy)deca-5,9-dieniooxybenzyc acid (46):

![Diagram]

To a stirred solution of primary alcohol 56 (0.35 g, 1.21 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C, were added iodobenzenediacetate (0.43 g, 1.33 mmol) followed by TEMPO (0.04 g, 0.24 mmol) and allowed to stir at ambient temperature for 30 min. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated solution of Na$_2$S$_2$O$_3$ (20 mL). The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (3 x 25 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporation of solvent led to crude aldehyde which was passed through a small pad of silica gel (ethyl acetate/hexane = 1:4) to afford the corresponding aldehyde 57 (0.32 g, 94%) as a thick viscous liquid and used immediately for the next reaction.
To a solution of resulting aldehyde 57 (0.32 g, 1.04 mmol) in tert-butyl alcohol (10 mL), 2- methyl-2-butene (0.5 mL, 1.04 mmol, 2M solution in THF) was added at room temperature. Sodium dihydrogenphosphate (0.49 g, 3.12 mmol) and sodium chlorite (0.14 g, 1.56 mmol) were dissolved in water (5 mL) to make a clear solution which was subsequently added to the above mentioned reaction mixture at 0 °C. It was allowed to stir for further 3 h at room temperature. The reaction mixture was extracted with EtOAc (3 x 20 mL), the combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexane: 3/7) to afford the corresponding acid 46 (0.29 g, 93%) as a colorless oil.

\[ \alpha \]D

IR (neat, KBr) : \( \nu_{max} \) 3450, 3007, 2932, 2857,1741, 1613, 1513, 1420, 1248, 1172, 1034, 821 cm⁻¹;

\(^1\)H NMR (300 MHz, CDCl₃) : δ 7.19 (d, J = 8.5 Hz, 2 H), 6.8 (d, J = 8.7 Hz, 2 H), 5.72 (m, 1 H), 5.47-5.33 (m, 2 H), 5.24-5.12 (m, 2 H), 4.49 (d, J = 11.7 Hz, 1 H), 4.25 (d, J = 11.7, 1 H), 3.77 (s, 3 H), 3.69 (q, J = 6.6, 13.9 Hz, 1 H), 2.45-2.17 (m, 4 H), 2.07 (m, 1 H), 1.73-1.61 (m, 2 H) ppm;

\(^{13}\)C NMR (75 MHz, CDCl₃) : δ 178.5, 158.9, 138.4, 130.3, 129.2, 126.1, 117.2, 113.6, 79.8, 69.6, 55.1, 33.4, 33.3, 26.6, 24.6 ppm;

ESI-HRMS : m/z calcd for C₁₈H₂₄NaO₄ [M + Na]+ 327.1203; found 327.1182.
2.5.8. (S,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (58):

![Chemical Structure](image1)

To the crude aldehyde 49 in benzene (50 mL) was added ethoxycarbonylmethylene triphenylphosphorane (19.49 g) at room temperature and stirred for 2 h. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography using petroleum ether/EtOAc (95:5) to give pure product 58 (6.80 g, 95% yield).

$[\alpha]_D^{25}$: $+82.3$ (c 0.7, CHCl$_3$).

IR (KBr): $\nu_{\text{max}}$ 2983, 2925, 2851, 1718, 1306, 1267, 1175, 1032, 980, 774 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): 6.84 (dd, $J = 5.4$ Hz, 15.7 Hz, 1 H), 6.06 (d, $J = 15.8$ Hz, 1 H), 4.62 (q, $J = 6.0$ Hz, 1H), 4.24-4.12 (m, 3H), 3.64 (t, $J = 7.5$ Hz, 1H), 1.42 (s, 3H), 1.38 (m, 3H), 1.3 (t, $J = 6.8$ Hz, 3H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.0, 144.5, 122.4, 110.1, 74.9, 68.7, 60.5, 26.4, 25.7, 14.1 ppm;

ESI-HRMS: Calcd for C$_{10}$H$_{16}$O$_4$Na [M+Na]$^+$: 223.0939.

2.5.9. (S,E)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (59):

![Chemical Structure](image2)

To an stirred solution of $\alpha,\beta$-unsaturated ester 58 (6.2 g, 23.2 mmol) was dissolved in CH$_2$Cl$_2$ (60 mL) and cooled to $-78$ °C under nitrogen atmosphere. DIBAL-$H$ (34.5 mL, 42.4 mmol) was slowly added to it over a period of 5 min. After 30 min of stirring at the same temperature, TLC was checked which showed complete consumption of starting material. It was quenched by slow addition of saturated solution of sodium potassium tartrate (50 mL), diluted with CH$_2$Cl$_2$ (40 mL) and allowed to stir at room temperature for another 2 h to get a clear two separated layers. The organic layer was separated and the
aqueous layer extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layer was washed with brine (2 x 75 mL), dried over anhydrous Na$_2$SO$_4$, evaporated to dryness under vacuum which on silica gel column chromatography (ethyl acetate: hexane = 2:3) produced the desired $\alpha,\beta$-unsaturated alcohol 59 (5.8 g, 88%).

$[\alpha]_D^{25}$ : $+28.1$ (c 0.5, CHCl$_3$).

IR (KBr) : $\nu_{\text{max}}$ 3414, 2987, 2873, 1374, 1245, 1218, 1058, 1009, 856, 770 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 5.92 (m, 1H), 5.68 (dd, $J$ = 7.9 Hz, 11.3 Hz, 1H), 4.49 (m, 1H), 4.14 (s, 2H), 4.05 (t, $J$ = 6.8 Hz, 1H), 3.55 (t, $J$ = 6.8 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 133.5, 128.3, 109.3, 76.4, 69.3, 62.6, 26.6, 25.8 ppm;

EI-MS : Calcd for C$_8$H$_{14}$O$_3$Na [M+Na]$^+$: 181.

2.5.10. ($R$)-4-((S)-1-(4-Methoxybenzyloxy)allyl)-2,2-dimethyl-1,3-dioxolane (60):

To a freshly flame dried double necked round bottom flask equipped with activated 4 A° molecular sieves (~15 g) and dry CH$_2$Cl$_2$ (200 mL) at $-20$ °C were added Ti(O$i$Pr)$_4$ (2.3 mL, 1.9 mmol), (−)-diethyl tartrate (1.4 mL, 1.3 mmol) and the mixture was stirred for 30 min. To this reaction mixture it was added allyl alcohol 59 (5.25 g, 21.1 mmol) in an interval of 30 min. and TBHP (26 mL, 104 mmol, 4 M solution in toluene) were added and stirring was continued till completion of the reaction (8 h). The reaction mixture was warmed to 0 °C, filtered through Celite. The filtrate was quenched with water (34 mL), 15% aq. NaOH solution (5.6 mL) and stirred vigorously for 1 h. The biphasic solution was separated and aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude residue was purified by column chromatography to afford the pure epoxide 60 as colorless oil (4.8 g, 95% yield).

$[\alpha]_D^{25}$ : $+11.0$ (c 0.5, CHCl$_3$).
$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 4.17-4.06 (m, 2H), 4.02-3.84 (m, 3H), 3.69 (bs, 1H), 3.14-3.07 (m, 2H), 1.45 (s, 3H), 1.43 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 110.0, 75.1, 65.9, 60.7, 55.3, 54.9, 26.3, 25.5 ppm;

ESI-MS : Calcd for C$_8$H$_{14}$O$_4$Na [M+Na]$^+$: 197.

2.5.11. (S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (61):

To a stirred solution of epoxy alcohol 60 (6.5 g, 14.84 mmol) in dry THF (75 mL), TPP (5.83 g, 22.26 mmol) followed by imidazole (3.02 g, 44.52 mmol) was added under nitrogen atmosphere and stirred for 5 min to dissolve it completely. It was cooled to 0 °C and then iodine (5.65 g, 22.26 mmol) was added portionwise to it. After completion of reaction (monitored by TLC), it was quenched with saturated solution of hypo (50 mL). The organic layer was diluted with Ethyl acetate (100 mL), washed with brine (2 x 50 mL), dried over Na$_2$SO$_4$, concentrated and then purified rapidly by short silica gel flash column chromatography (Ethyl acetate: hexane = 1: 49) to get red colored iodo product which was immediately used for the next step.

The iodo compound after column purification was immediately dissolved in MeOH (50 mL) and to it, activated Zn dust (2.9 g, 44.52 mmol) and NaI (6.67 g, 68 mmol) was successively added. It was refluxed for 3 h. After completion of the reaction, excess Zn dust was filtered out and the filtrate was removed under reduced pressure to get a semisolid. It was diluted with Ethyl acetate (100 mL), washed with saturated NH$_4$Cl (2 x 50 mL), brine (2 x 30 mL), dried over Na$_2$SO$_4$, evaporated under reduced pressure and purified by silicagel column chromatography (Ethyl acetate: hexane = 5: 95) to get colorless liquid 61 (5.13 g, 82% over two steps) as a colorless liquid.
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$[\alpha]_D^{25}$: $+8.4 (c 0.6, CHCl_3)$;

IR (KBr) : $\nu_{max}$, 3452, 2988, 2936, 2889, 1375, 1247, 1218, 1157, 1067, 848, 772 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 5.77 (m, 1H), 5.28 (d, $J = 17.3$ Hz, 1H), 5.14 (d, $J = 10.5$ Hz, 1H), 1.14 (m, 1H), 4.0 (m, 1H), 3.93-3.76 (m, 2H), 2.83 (bs, 1H), 1.35 (s, 3H), 1.32 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 136.0, 116.5, 109.2, 78.0, 71.9, 64.9, 26.2, 25.0 ppm;

ESI-MS : Calcd for C$_8$H$_{14}$O$_3$Na [M+Na]$^+$: 181.

2.5.12. $(R)$-4-((S)-1-(4-Methoxybenzyloxy)allyl)-2,2-dimethyl-1,3-dioxolane (62):

![Structure](image)

To a suspension of NaH (0.8 g, 21.56 mmol, 60% w/v dispersion in mineral oil) in dry THF (125 mL) was added dropwise a solution of secondary allylic alcohol 61 (3.2 g, 17.56 mmol) at 0 °C and continued the stirring for the next 45 min at room temperature. At 0 °C, freshly prepared $p$-methoxy benzyl bromide (1.53 g, 7.56 mmol) was added and stirred further for 4 h at room temperature with frequent monitoring of the progress of reaction by TLC. The reaction mixture was quenched by small crushed ice flakes until a clear solution (biphasic) had formed. The combined organic layers were washed with water, brine and dried over anhydrous Na$_2$SO$_4$. After removing the volatiles under reduced pressure, crude $p$-methoxy benzyl ether was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:49) to afford the pure product 62 (3.6 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$: $+12.5 (c 1.0, CHCl_3)$;

IR (neat, KBr) : $\nu_{max}$, 3070, 2985, 2926, 1727, 1639, 1427, 1249, 1115, 1066, 821 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.18 (d, $J = 8.6$ Hz, 2 H), 6.81 (d, $J = 8.6$Hz, 2 H), 5.77 (m, 1 H), 5.40-5.27 (m, 2 H), 4.54 (d, $J = 11.5$ Hz, 1 H), 4.30 (d, $J = 11.3$Hz, 1 H ), 4.4-3.6 (m,
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2 H), 3.79 (s, 3 H), 3.76 (m, 1 H), 3.67 (m, 1 H),
1.36 (s, 3 H) 1.31 (s, 3 H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : δ 159.1, 135.2, 130.1, 129.4, 119.6, 113.7, 109.4,
80.6, 77.5, 70.1, 66.8, 55.2, 26.5, 25.2 ppm;

ESI-MS : m/z calcld (C$_{16}$H$_{22}$O$_4$): m/z 301 [M + Na]$^+$.  

2.5.13. (2R,3S)-3-(4-Methoxybenzyloxy)pent-4-ene-1,2-diol (63):

\[
\text{HO} \quad \text{OH} \\
\text{OPMB} \\
\text{OPMB}
\]

To a solution of 62 (1.5 g, 5.39 mmol) in methanol (50 mL), CSA (cat.) was added at 0
° C and stirred at room temperature for 2 h after which it was quenched with Et3N (3 mL),
and the solvent evaporated under reduced pressure. The residue was purified by column
chromatography (Silica gel, ethyl acetate/hexane = 2:3) to give 63 (1.1 g, 87%).

$[\alpha]_D^{25}$ : +25.4 (c 0.42, CHCl$_3$);

IR (neat, KBr) : $\nu_{ma}$, 3408, 2924, 1612, 1513, 1301, 1248, 1176,
1035, 932, 821 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : δ 7.18 (d, $J = 8.5$ Hz, 2 H), 6.82 (d, $J = 8.5$ Hz, 2
H), 5.79 (m, 1 H), 5.39-5.27 (m, 2 H), 4.53 (d, $J =
11.3$ Hz, 1 H), 4.27 (d, $J = 11.3$ Hz, 1 H), 3.84 (m, 1
H), 3.78 (s, 3 H), 3.66-3.57 (m, 3 H) 2.89 (br s, 2 H)
ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : δ 159.2, 134.9, 129.8, 129.4, 120.0, 113.8, 81.6,
73.1, 70.2, 63.2, 55.2 ppm;

ESI-HRMS : m/z calcld for C$_{13}$H$_{18}$NaO$_4$ [M + Na]$^+$ 261.1097;
found 261.1115.

2.5.14. (2R,3S)-1-(tert-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)pent-4-en-2-ol
(47):

\[
\text{TBDPSO} \quad \text{OH} \\
\text{OPMB} \\
\text{OPMB}
\]
To a stirred solution of diol 63 (1.0 g, 4.2 mmol) in CH$_2$Cl$_2$ (50 mL) under nitrogen atmosphere at room temperature, was added TBDPSCl (1.12 mL, 4.2 mmol) and imidazole (0.57 g, 8.4 mmol). The reaction mixture was stirred at room temperature for 3 h. After completion (monitored by TLC), the reaction was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography to give 47 (1.78 g, 89%) as colorless viscous liquid.

$[\alpha]_D^{25}$ : +6.4 (c 0.5, CHCl$_3$);

IR (neat, KBr) : $\nu_{\text{max}}$ 3453, 2932, 2859, 1613, 1513, 1426, 1301, 1247, 1109, 1069, 930, 820, 703 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.68-7.61 (m, 4 H), 7.46-7.32 (m, 6 H), 7.16 (d, $J$ = 8.6 Hz, 2 H), 6.82 (d, $J$ = 8.6 Hz, 2 H), 5.84 (m, 1 H), 5.39-5.27 (m, 2 H), 4.52 (d, $J$ = 11.3 Hz, 1 H), 4.26 (d, $J$ = 11.3 Hz, 1 H), 3.79 (s, 3 H), 3.77-3.73 (m, 3 H) 2.45 (br s, 1 H), 1.05 (s, 9 H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 159.1, 135.5, 135.2, 133.2, 130.2, 129.7, 129.3, 127.7, 119.5, 113.7, 80.3, 73.5, 70.0, 64.4, 55.2, 26.8, 19.2 ppm;

ESI-MS : $m/z$ calcd for C$_{29}$H$_{36}$NaO$_4$Si [M + Na]$^+$ 499.2275; found 499.2252.

2.5.15. $^{(R,Z)}$-2-((2R,3S)-1-(tert-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)pent-4-en-2-yl)-8-(4-methoxybenzyloxy)deca-5,9-dienoate (44).

To a stirred solution of acid 46 (0.28 g, 0.92 mmol) in CH$_2$Cl$_2$ (15 mL) at 0 oC, Et$_3$N (0.30 mL, 1.68 mmol) followed by EDCI (0.24 g, 1.26 mmol) and DMAP (0.84 mmol,
0.09 g) were added and stirred for 30 min. Alcohol 47 (0.4 g, 0.84 mmol) was dissolved in CH₂Cl₂ (10 mL) and slowly added to the resulting reaction mixture at the same temperature and then allowed to stir for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layer was dried over Na₂SO₄ and the solvent evaporated under reduced pressure to give a colorless oil which on purification by silica gel column chromatography (ethyl acetate/hexane = 3:97) furnished the desired coupled product 44 (0.576 g, 90%, based on the starting alcohol) as a colorless liquid.

[α] D

IR (neat, KBr) : ν max 2923, 2855, 1738, 1612, 1512, 1462, 1381, 1245, 1107, 1069, 929, 819, 701 cm⁻¹;

1H NMR (300 MHz, CDCl₃) : δ 7.61 (d, J = 6.9 Hz, 4 H), 7.43-7.29 (m, 6 H), 7.20 (d, J = 8.7 Hz, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 8.5 Hz, 2 H), 5.78-5.64 (m, 2 H), 5.44-5.35 (m, 2 H), 5.31-5.14 (m, 4 H), 5.04 (q, J = 5.8, 9.6 Hz, 1 H), 4.5 (d, J = 11.5 Hz, 2 H), 4.26 (d, J = 11.7 Hz, 2 H), 3.98 (t, J = 6.9 Hz, 1 H), 3.85 (m, 1 H), 3.78 (s, 6 H), 3.71 (m, 2 H), 2.40-2.14 (m, 4 H), 2.08-1.98 (m, 2 H), 1.68-1.54 (m, 2 H), 1.02 (s, 9 H) ppm;

13C NMR (75 MHz, CDCl₃) : δ 172.7, 159.0, 138.6, 135.6, 135.5, 135.0, 130.5, 129.6, 129.2, 127.6, 126.0, 119.6, 117.3, 113.7, 79.9, 78.4, 74.7, 70.1, 69.7, 62.2, 55.2, 33.9, 33.4, 29.7, 26.7, 24.7, 19.2 ppm;

ESI-HRMS : m/z calcd for C₄₇H₅₈NaO₇Si [M + Na]+ 785.3844; found 785.3847.
2.5.16. \((R,Z)-(2R,3S)-1-(\text{tert-Butyldiphenylsilyloxy})-3\text{-hydroxypent-4-en-2-yl})-8\text{-hydroxy-deca-5,9-dienoate (45).}\)

To a stirred solution of di-PMB ether 44 (255 mg, 0.33 mmol) in CH\(_2\)Cl\(_2\) (15 mL), was added DDQ (227 mg, 1.0 mmol) at pH7 with phosphate buffer solution (1.6 mL) at 0 oC. The reaction mixture was allowed to stir for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated NaHCO\(_3\) (10 mL) solution. The organic layer was separated and the aqueous layer extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous Na\(_2\)SO\(_4\) and evaporated to give the crude product which on purification by silica gel column chromatography (ethyl acetate/hexane = 1:5) to afford the desired diol 45 (162 mg, 93%) as a colorless viscous liquid.

\([\alpha]_D^{25}\) : \(-7.5\) (c 1.4, CHCl\(_3\));

IR (neat, KBr) : \(\nu_{max} 3446, 2927, 2856, 1728, 1637, 1426, 1218, 1111, 768, 702\) cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \(\delta 7.70-7.61\) (m, 4 H), 7.46-7.34 (m, 6 H), 5.93-5.76 (m, 2 H), 5.60-5.34 (m, 3 H), 5.28-5.08 (m, 3 H), 4.93 (q, \(J = 4.5, 9.1\) Hz, 1 H), 4.42 (t, \(J = 4.5\) Hz, 2 H), 4.12 (q, \(J = 6.8, 12.1\) Hz, 1 H), 3.92 (dd, \(J = 5.3, 11.3\) Hz, 1 H), 3.77 (dd, \(J = 3.8, 11.3\) Hz, 1 H), 2.41-2.20 (m, 4 H), 2.17-2.15 (m, 3 H), 1.77-1.63 (m, 2H), 1.05 (s, 9 H) ppm;

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : 173.2, 140.3, 136.3, 135.6, 135.5, 132.6, 131.8, 129.9, 127.8, 125.8, 117.0, 114.8, 75.5, 73.1, 72.4, 63.1, 35.1, 33.6, 26.7, 26.6, 24.6, 19.1 ppm;
ESI-HRMS: m/z calcd for C₃₁H₄₂NaO₅Si [M + Na]+ 545.2694; found 545.2712.

2.5.17. (6Z,9R,10E,12S,13R)-13-((tert-Butyldiphenylsilyloxy)methyl) 9,12dihydroxyoxacyclotrideca-6,10-dien-2-one (43).

Grubbs second generation catalyst (16 mg, ca. 0.02 mmol) was dissolved in dry, deoxygenated CH₂Cl₂ (200 mL) under argon atmosphere. After the solution was heated to reflux, diene 45 (0.1 g, 0.2 mmol) was added slowly via syringe (30 min) in dry, deoxygenated CH₂Cl₂ (30 mL) to the reaction mixture. The reaction mixture was then stirred at reflux for an additional 8 h. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography (ethyl acetate/hexane = 3:7) afforded 43 (71 mg, 76%) (single stereoisomer) as a colorless viscous oil.

[α]₀²⁵ : −12.5 (c 0.8, CHCl₃);
IR (neat, KBr) : νmax 3421, 2926, 2855, 1733, 1463, 1428, 1379, 1110, 1035, 969, 767, 702 cm⁻¹;
¹H NMR (300 MHz, CDCl₃) : 7.69-7.62 (m, 4 H), 7.48-7.35(m, 6 H), 5.66 (dd, J = 7.7 Hz, 15.7 Hz, 1 H), 5.60-5.46 (m, 2 H), 5.23 (q, J = 6.2, 10.9Hz, 1 H), 4.8 (m, 1 H), 4.40-4.26 (m, 2 H), 3.99-3.78 (m, 2 H), 2.47-2.12 (m, 6 H), 2.20-1.82 (m, 2 H), 1.06 (s, 9 H) ppm;
¹³C NMR (75 MHz, CDCl₃) : δ 172.6, 135.9, 135.6, 131.3, 131.1, 130.4, 129.9, 127.8, 126.6, 124.4, 74.9, 73.6, 72.6, 63.9, 35.1, 32.5, 26.7, 25.7, 22.9, 19.2ppm;
ESI-HRMS: \( m/z \) calcd for \( \text{C}_{29}\text{H}_{38}\text{NaO}_5\text{Si} \ [\text{M} + \text{Na}]^+ \ 517.2381 \); found 517.2400.
References
2.6. REFERENCES


2. According to IUPAC (rule C-472.2), lactones formed from aliphatic acids are named by adding “-olide” to the name of the (nonhydroxylated) hydrocarbon with the same number of carbon atoms.


