CHAPTER I

Section A

Introduction to pyran containing bioactive natural products and previous approaches for the macrolide core of Leucascandrolide A
1.1. Introduction to Natural Products Containing Pyran Rings:

Natural products have attracted the attention of biologists and chemists the world over for the last five decades as it continues to be one of the most important sources of pharmacologically active compounds\(^1\) in the quest for drugs against life threatening diseases such as microbial infections, diseases of the heart and the circulatory system, cancer and others.\(^2\) Marine sources are considered as the potent source for highly bioactive natural products containing pyran ring. Marine natural products have been isolated from marine organisms and reported in approximately 6,800 publications. In addition to these publications there are approximately another 9,000 publications which cover syntheses, reviews, biological activity studies, ecological studies etc. on the subject of marine natural products.\(^3\) Several of the compounds isolated from marine source exhibit biological activity. The ocean is considered to be a source of potential drugs. Marine organisms not only elaborate pharmaceutically useful compounds but also produce toxic substances. Most marine natural products, especially polyketides, possess polyhydroxy and polyoxy substituents in their structures. Polyketide macrolides continue to show promising biological activities. One of the most important societal contributions of marine natural products chemists have been the isolation and identification of toxins responsible for sea food poisoning. Outbreaks of seafood poisoning are usually sporadic and unpredictable because toxic fish or shellfish does not produce the toxins themselves, but concentrate them from organisms that they are eating. Most marine toxins are produced by microorganisms such as dinoflagellate or marine bacteria and may be passed through several levels of the food chain. The identification of marine toxins has been one of the most challenging areas of marine natural products chemistry. The major occupation of marine natural products chemists for the past two decades have been the search for potential pharmaceuticals. It is difficult to single out a particular bioactive molecule that is destined to find a place in a particular medicine. However, many compounds have shown promise. The marine organisms are produced some of the most cytotoxic compounds ever discovered, but their abundance in nature are very small for further studies.
The biological activities of an extract of marine organisms or isolated compounds could be assessed in several ways. Due to limited amount of the material availability and high cost of biological testing, it is impossible in any laboratory to examine all permutations of drug-animal interaction, to unmask the drug potential of materials. Besides, the candidate drugs have to pass through rigorous toxicological evaluation and clinical trials before they reach the clinician’s armamentarium. A fair understanding of biological, toxicological and clinical evaluation is essential to those interested in searching potential drugs from marine organisms. Marine organisms produce some of the most cytotoxic compounds ever discovered, but the yields of these compounds are invariably so small that natural sources are unlikely to provide enough material for drug development studies. It’s worthwhile at this juncture to discuss few pyran ring containing marine natural products such as which have been of paramount importance to the mankind and also to the researchers who have been actively involved in the synthesis and isolation of these natural products.

1.1.1. Bistramide A

Kozmin and co-workers\(^4^c\) have reported the first total synthesis of bistramide A (1), thus confirming Wipf’s prediction of the stereochemical assignment of bistramide C which was isolated from the marine ascidian *Lissoclinum bistratum* by Gouiffes and co-workers (Figure 1).\(^4^a\) The bistramides demonstrate significant neuro- and cytotoxic properties as well as profound effects on cell cycle regulation. In particular, bistramide A has an IC\(_{50}\) of 0.03-0.32 \(\mu\)g/mL for the P388/dox, B16, HT29, and NSCLC-N6 cell lines.\(^4^b\) From the time of their original isolation, the bistramides have presented a challenging stereochemical conundrum. Synthetic efforts toward the bistramides were hampered by the lack of information regarding their relative and absolute configuration prior to Wipf’s theoretical and synthetic studies.

![Figure 1. Bistramide A (1)](image-url)
1.1.2. Zampanolide

In 1996 Tanaka and Higa have disclosed the isolation, partial structure elucidation, and biological activity of the architecturally novel macrolide (+)-zampanolide (2), obtained from *Fasciospongia rimosa*, an Okinawan sponge, which was associated with anticancer as well as antitumor cell growth inhibitory activities. The extreme scarcity and the impressive cytotoxicity displayed by these macrolides led to their synthesis in laboratory. The first total synthesis of (+)-zampanolide has been achieved by A. B Smith et al.5b

![Figure 2. (+)-Zampanolide (2)](image)

1.1.3. Spongistatins

The first members of the spongipyran family of antimitotic marine macrolides were reported independently by three research groups in 1993 (Pettit and coworkers, 

![Figure 3. Spongistatins](image)

**Spongistatin 3 :** \( X = Cl \)  
(Altohyrtyin A)  
**Spongistatin 4 :** \( X = H \)  
(Altohyrtyin C)

**Figure 3. Spongistatins**
Kitagawa/kobayashi group and Fusetani group). The spongistatins (althohyrtin A 3 and althohyrtin B 4) have been found to be extraordinarily effective against a variety of chemoresistant tumor types, which comprise the NCI panel of 60 human cancer cell lines. Their structural novelties, limited availability, activity against a broad range of human cancer cell lines and microtubule assembly inhibitions, antifungal properties combined, led to make the spongistatins as important and challenging synthetic targets. Spongistatin possesses extraordinary activity compared to other members of the family (Figure 3).

1.1.4. Bryostatins

One potent antitumoral compounds, bryostatin (5) was isolated and characterized by Pettit et al., in 1982 from the marine animal the bryozoan Bugulu neritina (Figure 4) which are highly oxygenated macrolides with a unique polyacetate backbones. Bryostatin (5) has been found to cause differentiation of B-chronic lymphocytic leukemia in an unprecedented fashion, and be capable of converting leukemia cells in vitro to those typical of hairy cell leukemia which is curable. Successful extension of these experiments to the clinic may results in the first really curative techniques for human chronic lymphocytic leukemia. The potential for treating chronic myelogenous leukemia patients is also very promising. Bryostatin (5) was found capable of inducing macrophage-like differentiation in maturing CML cells. Most importantly, bryostatin was dramatically effective against cells that taken from patients in the CML blast phase. Against a line of acute lymphoblastic leukemia, bryostatin (5) was found to capable of inducing further differentiation along the B-cell lineage.
Interestingly, bryostatin has been found to potentiate ARA-C apoptosis or programmed cell death, and this combination looks very promising for clinical evaluation.\textsuperscript{18} Another facet of the activity of bryostatin against lymphomas is involved its ability to convert a high-grade lymphoma cell line 20 an intermediate grade, again offering clinical potential.\textsuperscript{22}

1.1.5. Spirastrellolides

Spirastrellolide A and B (7 and 8, Figure 5) are two closely related polyketides that were isolated by Anderson and coworkers recently from the marine sponge \textit{Spirastrella coccinea}.\textsuperscript{8a} As part of ongoing examination of the \textit{S. coccinea} extract, the same research group also identified the five new spirastrellolides C (9) to G (13).\textsuperscript{8b} Spirastrellolides have a 47-carbon linear polyketide backbone incorporated into a highly functionalized 38-membered lactone containing a tetrahydropyran ring, a bicyclic spiroacetal ring system and a tricyclic bis-spiroacetal ring system, embedded in the macrocycle. Their structural novelty, limited availability, a potent inhibitory activity against protein phosphatase 2A combined, made the spirastrellolides as important and challenging synthetic target.

In addition to its ability to initiate premature entry into mitosis and untimely mitotic arrest in cells, spirastrellolides exhibit a potent inhibitory activity against protein phosphatase 2A (IC\textsubscript{50} = 1 nM) with an excellent selectivity for PP2A over PP1 (ratio of IC\textsubscript{50} values 1:50),\textsuperscript{8c} and it does not inhibit PP2C. Its biological activities, therefore, resemble other known Ser/Thr phosphatase inhibitors fostriecin and okadaic acid. Developments of protein phosphatase inhibitors have lagged behind interest in kinase inhibitors because of the perceived notion that kinases are much more highly regulated and specific. However, there has been a renewed interest in recent years because reversible protein phosphorylation is critical “as the other half” of checkpoints in cell cycles, and protein phosphatases assume an equally important role in regulating cellular signal transductions and should not be ignored. Designing phosphatase inhibitor can lead to a new paradigm in developing cancer therapeutics.\textsuperscript{8d}
1.1.6. Laulimalide and Isolaulimalide

Laulimalide (14) and Isolaulimalide (15) are 18-membered macrocyclic lactones isolated from the marine sponge 
*Cacspongia mycofijuensis*\(^9a\) which are a new class of microtubule stabilizing agents having high therapeutic utility. They are Coincident with the microtubule change these two compounds induce nuclear convolution and the formation of multiple micronuclei. They promote elongating activity readily than paclitaxel.\(^9b\) Several syntheses for laulimalide and isolaulimalide have been reported so far (Figure 6).\(^9c,d\)
1.1.7. Attenuols

Attenuols A (16) and B (17), isolated from the EtOH extract of the Chinese bivalve Pinna attenuata by Uemura et al.,\textsuperscript{10a} exhibited cytotoxicity against P388 cells (IC\textsubscript{50} values of 24 and 12 µg/mL, respectively) (Figure 7). These compounds are unique isomeric triols: attenol A has a 1,5-dioxaspiro[4.5]decane core and attenol B has a 6,8-dioxabicyclo[3.2.1]octane framework, and equilibrium under acidic conditions is 16/17 = 3 : 1. They determined their relative structures by 2D NMR and absolute configurations by the modified Mosher method, however, those of the spiroacetal carbon of 16 were assumed by considering the anomeric effect. Uemura’s group first synthesized these compounds to confirm the stereochemistry.\textsuperscript{10b,10c}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{attenol.png}};
\end{tikzpicture}
\end{center}

\textbf{Figure 7. Attanol A and Attanol B}

1.1.8. Halistatin

Halistatin (18) was found to be exceptionally potent antineoplastic constituents of two different marine sponges located in The Republic of Comoros.\textsuperscript{11} Against the NCI human cancer cell lines panel, the negative log\textsubscript{10} GI\textsubscript{50} values range to over nine and represent an excellent selection of human cancer types. Briefly stated, the halistatins offer considerable promise for improving future human cancer treatment(Figure 8).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{halistatin.png}};
\end{tikzpicture}
\end{center}

\textbf{Figure 8. Halistatin (18)}
1.1.9. Dactylolide

(+)-Dactylolide (19), a new cytotoxic natural product which was derived from a marine sponge of the genus *Dactylospongia*, collected off the coast of the Vanuatu islands\textsuperscript{12} as a tumor cell growth inhibitory macrolides (Figure 9). The less abundance and the impressive biological activities displayed by this macrolide led to their laboratory synthesis. The first asymmetric total syntheses of (+)-dactylolide, has been achieved by A. B Smith *et al.*\textsuperscript{12b}

![Figure 9. (+)-Dactylolide (19)](image)

1.1.10. Scytophycins

One polyketides with *trans*-2,6-disubstituted dihydropyrans named scytophycins (isolated from the cultured terrestrial blue-green algae *Scytonema pseudohofmanni*) were first reported by Moore *et al.*, in 1986.\textsuperscript{13a} Along with scytophycin C (20, Figure 10), four related polyketide-derived macrolides scytophycins A, B, D and E were also isolated from same algae. These are novel series of polyoxygenated 22 membered macrolide, differing in substitution at C\textsubscript{16} and C\textsubscript{27}, with a C\textsubscript{21} side chain terminating in an N-methyl vinyl formamide group. These are exhibiting potent cytotoxicity against a variety of human carcinoma cell lines, as well as broad-spectrum antifungal activity.\textsuperscript{13b} The first total synthesis was described by Paterson\textsuperscript{13c} followed by many other syntheses.\textsuperscript{13d}

![Figure 10. Scytophycin C (20)](image)
1.1.11. Phorboxazole A

Isolation of phorboxazole A (21) by Molinski and Searle in 1995,\textsuperscript{14a} the structurally complex and potent biological activity (Figure 11) had sparked a flurry of interest from the synthetic community. Comprising 15 asymmetric centers, four diversely substituted hydropyran rings, a 21-membered macrolactone, two oxazole rings, and a variety of unsaturations, the phorboxazoles present a considerable challenge for synthetic organic chemist. A total of six research groups have reported synthesis of the phorboxazole, beginning with Forsyth’s synthesis of phorboxazole A (21) in 1998,\textsuperscript{14b} followed by Evans’s synthesis of phorboxazole B in 2000.\textsuperscript{14c} Subsequent synthesis of phorboxazole A has been completed by the research groups led by Smith (2001,\textsuperscript{14d} 2005\textsuperscript{14e}), In addition, numerous other formal and total synthetic efforts have been described.\textsuperscript{14e} The phorboxazole is among the most potent cytostatic agents yet discovered, exhibiting a mean \( \text{GI}_{50} < 1.58 \) against the NCI panel of 60 tumor cell lines.\textsuperscript{14h} While it is known that the phorboxazole is induce S-phase cell cycle arrest without interference of the microtubules, the exact mode of activity is not fully understood. Recently, Forsyth, La Clair et al. have shown that fluorescently labeled phorboxazole derivatives induced association of cell-cycle-dependent kinase 4 (cdk4) with extranuclear cytokeratin intermediate filaments (KRT10),\textsuperscript{14i} and perturbation of cdk4 is known to inhibit cells cycle progression at the G1/S phase.\textsuperscript{14j} In addition, new, potent analogues are beginning to shed some light on the phorboxazole pharmacophore.\textsuperscript{14k,l}

![Figure 11. (+)-Phorboxazole A (21)](image_url)

1.1.12. (‒)-Lasonolide A

One potent anticancer activity containing compound, Lasonolide A (22, Figure 12) was isolated from shallow water Caribbean sponge; species of Forcepia.\textsuperscript{15} It shows a
potent activity against A-549 human lung carcinoma. Lee’s seminal synthetic work included a correction of the structure and a reassignment of the absolute configuration.\textsuperscript{16} Lee prepared the tetrahydropyran scaffold of lasonolide through a cyclisation with silyl ether. Later, several groups have synthesized the tetrahydropyran core of lasonolide A.\textsuperscript{17} Interesting structure of lasonolide A, potent anticancer activity and natural scarcity have made it an attractive target for synthetic organic chemists. As a result lots of syntheses were resulted by applying a variety of key reactions.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12.png}
\caption{(-)-Lasonolide A (22)}
\end{figure}

1.1.13. (–)-Kendomycin

(–)-Kendomycin (23), a novel macrocyclic polyketide was first isolated in 1996 from \textit{Streptomyces violaceoruber}, possesses potent activity as both an endothelin receptor antagonist and an antiosteoporotic agent.\textsuperscript{18} Reisolation by the Zeeck’s group\textsuperscript{19} revealed, in addition, significant antibacterial activities against multiresistant bacteria, including vancomycin–resistant strains and remarkable cytotoxicity against a series of human tumor cell lines ($\text{GI}_{50} < 0.1 \text{ M}$). The impressive biological profiles, in conjunction with the challenging architecture, defined by X-ray and Mosher ester analysis, triggered considerable synthetic efforts,\textsuperscript{20} culminating in 2004 with the first total synthesis (Figure 13).\textsuperscript{21}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure13.png}
\caption{(–)-Kendomycin (23)}
\end{figure}
1.1.14. (+)-SCH 351448

SCH 351448 (24, Figure 14) is a hexane soluble material purified from a *Micromonospora* sp. fermentation broth. The reported ability of natural SCH 351448 to activate transcription from the low-density lipoprotein (LDL) receptor promoter is of mechanistic and biomedical importance. The single-crystal X-ray structure of SCH 351448 shows a remarkable topology. The ionized and un-ionized carboxyl groups are intramolecularly hydrogen-bonded and together with the phenol and hydroxyl groups to accommodate a heptacoordinate sodium ion in interior cavity of a hydrophobic globular structure. At this point, it is remained unclear whether SCH 351448 functions by mediating sodium or other ion transport across membranes or whether the role of the chelated sodium ion is structural i.e., does SCH 351448 behave as a hydrophobic small molecule ligand for a cellular receptor. To answer all related questions, synthetic program was started to provide materials for future structural, physicochemical and biological studies.

![Figure 14. (+)-SCH 351448 (24)](image)

1.1.15. Latrunculin A

Among the most prolific sponges in the Red Sea is the red colored *Latrunculia magnifica* that enjoys immunity from attack by fish. Two toxins, latrunculin A (25) and latrunculin B (26), were isolated from this sponge, known to be particularly toxic to fish (Figure 15). They are the first marine macrolides known to contain 16- and 14-membered rings and are also further characterized by the rare natural occurrence of the thiazolidinone
Studies of their mode of action indicates that both compounds are able to disrupt microfilament organization in cultured cells.\textsuperscript{24b} The stereochemistry of the 8-methyl group in latrunculin B is presently unknown.

\textbf{Figure 15. Latrunculin A and Latrunculin B}

\textbf{1.1.16. Sorangicin A}

Ho¨fle and co-workers had reported the isolation of members of another family of architecturally complex macrolides from the \textit{cellulosum} strain So ce 90,\textsuperscript{25a} were termed as sorangicins.\textsuperscript{25b} Importantly, (+)-sorangicin A (27), the most potent and prevalent congener, is demonstrated remarkable antibiotic activity against a broad spectrum of both Gram-positive [minimum inhibitory concentration (MIC) 0.01-0.3 \(\mu g/mL\)] and Gram-negative bacteria (MIC 3-25 \(\mu g/mL\)).\textsuperscript{25c}

\textbf{Figure 16. (+)-Sorangicin A (27)}
1.1.17. Apoptolidin

First reported by Hayakawa and co-workers,$^{26a}$ apoptolidin (28) is a cytotoxic agent found during the course of a screening programs directed towards the discovery of novel apoptosis inducers. Isolated from the cultivation broth of an actinomycete identified as *Nocardiopsis* sp., apoptolidin was found to selectively induce cell death via apoptosis in rat glia cells transformed with adenovirus E1A and E1A/E1B19K oncogenes with considerable potency (Figure 17). Using a series of molecular and cell-based tools and techniques, Khosla and co-workers later had identified the mitochondrial F0F1-ATPase as the cellular target of apoptolidin.$^{26b}$

![Figure 17. Apoptolidin (28)](image)

1.2. Synthesis of Dihydropyrans

Several approaches have been reported for the preparation of dihydropyrans and some of the more varied methodologies include electrophile-initiated alkylation of glycals, hetero-Diels–Alder cycloadditions, bis(oxazoline)-copper-catalyzed asymmetric hetero-Diels-Alder reaction, olefin metathesis, intramolecular Wadsworth-Emmons, Ireland-Claisen rearrangement, and an intramolecular silyl-modified Sakurai reaction.

The condensation of vinylsilanes with aldehydes or acetals is resulted dihydropyrans with a good yield. An oxonium ion intermediate is involved in this stereoselective reaction (Scheme 1).$^{27}$
For the first time, Steinhuebel et al. showed that arylzinc couplings with 1,2-dihydropyran that had given high $\alpha/\beta$ anomeric stereocontrol dihydropyran. Nucleophilic addition of organozincs to 1,2-dihydropyryl acetates represent a new, broadly defined method for the stereocontrolled synthesis of $\alpha$-substituted pyrans (Scheme 2).\(^{28}\)

An olefin metathesis or a double bond migration sequence of allyl ethers to cyclic enol ethers was catalyzed by first and second generation Grubbs' catalysts. These ruthenium carbene complexes were activated to catalyze the double bond migration by implementation of hydride sources such as NaH or NaBH\(_4\) (Scheme 3).\(^{29}\)

Hydrophobic ionic liquid such as [Bmim]PF\(_6\) are powerful media for bis(oxazoline)-copper-catalyzed asymmetric hetero-Diels-Alder reactions, that allow a convenient catalyst recycling. The reactivities and stereoselectivities were comparable to those of corresponding homogeneous reactions. Furthermore, the reaction was remarkably accelerated in [Bmim]PF\(_6\) compared to dichloromethane (Scheme 4).\(^{30}\)
Propenyl ether undergo a 6-endo cyclization by using SmI$_2$ as catalyst to afford the dihydropyran as 2:1 mixture of the E and Z isomers (Scheme 5).\textsuperscript{31}

\textbf{Scheme 5}

First report of a hetero Diels-Alder (HDA) reaction was appeared in literature in 1951 by Gresham and Steadman (Scheme 6).\textsuperscript{32}

\textbf{Scheme 6}

In presence of Lewis acid catalyst, reaction proceeded smoothly at room temperature with better yield and selectivity (Scheme 7).\textsuperscript{33}

\textbf{Scheme 7}

An Ireland-Claisen rearrangement of the 1,4-dioxanone gave the substituted dihydropyran carboxylic acid (Scheme 8) for use in a macrolide synthesis.\textsuperscript{34}
An intramolecular Wadsworth-Emmons reaction features in a conversion of phosphonates to dihydropyran (Scheme 9).\(^{35}\)

Intramolecular Sakurai Cyclization (IMSC) of aldehydes was an efficient procedure for the preparation of a variety of diastereometrically pure \textit{exo}-methylene tetrahydropyrans (Scheme 10).\(^{36}\)

Phosphoromolybdic acid (PMA-SiO\(_2\)) catalysed Ferrier type rearrangement of glucals for synthesis of 2,3-unsaturated glycopyranosides (Scheme 11).\(^{37}\)

The diastereoselective synthesis of 6-trifluoromethyl-5,6-dihydropyrans was realized by the triphenyl phosphine-catalyzed [4 + 2] annulation of ethyl \(\alpha\)-benzylallenoates and trifluoromethyl ketone (Scheme 12).\(^{38}\)
1.2.1. Iodocyclization and applications in Natural Product:

Among all the heterocycle, 2,6-disubstituted dihydropyrans are probably one of the most common structural motifs spread across various natural products, from simple glucose to structurally complex secondary metabolites such as luminaolide, leucascandrolide A, aspergillide A, B and C, misakinolides, phorboxazole, laulimalide, swinholides, scytophycins, and even more elaborated architectures present in polytoxins, maitotoxins, and other marine derived natural products.

Many of the methods were discussed previously require long reaction times, stoichiometric use of expensive reagents, harsh reaction conditions, and some time gives poor yield and selectivity. To avoid the above limitations, in our group we have searched for a catalyst with high catalytic activity, easy availability, short reaction time, environment friendly and simple work-up procedure. Molecular iodine attracted our attention, as recently it has attained considerable importance in organic synthesis because of low cost, nontoxic nature, ready availability, environment friendly, easy handling, high efficiency for various organic transformations to the corresponding products in excellent yields with excellent diastereoselectivity. Since it has been used as a mild Lewis acid catalyst for the activation of carbonyl compounds, including acetalization reactions, we envisaged that iodine could catalyze the reaction for the formation of 2,6-di-substituted-3,4-dihydropyrans starting from δ-hydroxy α,β-unsaturated aldehydes (Scheme 13).\textsuperscript{40}

\[
\begin{align*}
\text{Scheme 13} & \\
\text{The formation of the trans-2,6-disubstituted-3,4-dihydropyrany from δ-hydroxy α,β-unsaturated aldehydes by using molecular iodine was explained bellow (Scheme 14).} & \\
\text{Our recent developed methodology,} & \\
\text{Iodocyclization is going to be a potent protocol for synthesis of pyran rings by using low cost reagents with a quantitative yield. In our group, Iodocyclization reaction has been successfully implemented for synthesis of a number of natural products such as (+)-Sorangicin A, Polyrhacitide A, epi-Cryptocaryolone}
\end{align*}
\]
Scheme 14: Proposed mechanism

(+)-Sorangicin A (27) was disconnected into three major fragments and the iodocyclization protocol was initially applied for the synthesis of the Bicyclic Core.⁴⁰

(+)-Sorangicin A
The highlights of the synthesis of the Bicyclic Core of (+)-Sorangicin A (45) was described in Scheme 15.

Scheme 15

Successively, the total synthesis of Polyrhacitide A and epi-Cryptocaryolone had been achieved by our group.\(^41\)

The total synthesis of Polyrhacitide A (29) and epi-Cryptocaryolone (30) was highlighted below (Scheme 16).

Scheme 16

1.3. Synthesis of Tetrahydropyrans:

The platinum-catalyzed hydroalkoxylation of \(\gamma\)- and \(\delta\)-hydroxy olefins tolerated various substitution pattern and a number of functional group including pivaloate and acetate esters, amides, silyl and benzyl ethers, and pendant hydroxyl and olefinic groups.\(^42\)
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Scheme 17

The reaction of tertiary 1,4-diols and 1,5-diols with cerium ammonium nitrate at room temperature gave tetrahydrofuran and tetrahydropyran derivatives in high yield and stereoselectivity. Various fragrant compounds have been synthesized using this method.\(^{43}\)

\[
\text{HO-R=CHR} \xrightarrow{2 \text{ mol-}\% \left[\text{PtCl}_2\left(\text{H}_2\text{C} = \text{CH}_2\right)\right]_2}
\]

\[
4 \text{ mol-}\% \text{ P(4-CH}_3\text{C}_6\text{H}_4\text{CF}_3)_3}
\]

\[
\text{Cl}_2\text{CHCHCl}_2, 70 \degree\text{C, 64 h}
\]

\[\text{Scheme 17}\]

Scheme 18

Key step of an eco-friendly, commercially cheap and highly diastereoselective synthesis of substituted \textit{cis}-2,6-piperidines and \textit{cis}-2,6-tetrahydropyrans is an iron-catalyzed thermodynamic equilibration of 2-alkenyl 6-substituted piperidines and 2-alkenyl 6-substituted tetrahydropyrans allowing the isolation of enriched mixtures of the most stable \textit{cis}-isomers (Scheme 19).\(^{44}\)

\[
\text{HO-HO-R}_1\text{R}_2 \xrightarrow{1,2 \text{ eq. CAN}} \text{CH}_3\text{CN, rt, 16 h}
\]

\[\text{Scheme 18}\]

Scheme 19

The gold(I)-catalyzed cyclization of chiral monoallylic diols to form tetrahydropyrans is highly stereoselective. Substrates that differ only in olefin geometry are provided enantiomeric products from formal \textit{S}_\text{N}2' reactions in high yields with excellent chirality transfer. In the presence of additional stereocenters the allylic alcohol stereochemistry efficiently controls the facial selectivity (Scheme 20).\(^{45}\)

\[
\text{HO-R-OAc} \xrightarrow{2 \text{ mol-}\% \text{ FeCl}_3.6\text{H}_2\text{O}} \text{CH}_2\text{Cl}_2, \text{rt, 2 h}
\]

\[\text{Scheme 19}\]

Scheme 20

\[
\text{HO-R} \xrightarrow{1 \text{ mol-}\% \text{ PPh}_3\text{AuCl}} \text{CH}_2\text{Cl}_2, \text{MS, rt, 3 h}
\]

\[\text{Scheme 20}\]
The ruthenium(VII) complex $\text{O}_3\text{ReOSiPh}_3$ is a particularly effective catalyst for Prins cyclizations using aromatic and $\alpha,\beta$-unsaturated aldehydes. The reaction conditions are mild, and the highly substituted 4-hydroxytetrahydropyran products were formed stereoselectively (Scheme 21).\(^\text{46}\)

![Scheme 21]

Cyclization of $\delta$-halocarbanions to cyclobutanes is a very slow process, thus formation of tetrahydropyran derivatives via addition to aldehydes and subsequent cyclization is possible in excellent yield. A simple mechanistic discussion, optimization of the reaction conditions, and the scope of the reaction are discussed (Scheme 22).\(^\text{47}\)

![Scheme 22]

An efficient method allow the construction of 2,6-cis-4,5-dibromo-tetrasubstituted tetrahydropyran rings with well-controlled stereochemistry by using InBr$_3$ in good yields.\(^\text{48}\)

![Scheme 23]

A Pd-catalyzed arylation reaction for the intramolecular formation of biaryl compounds using a novel phosphine ligand offers enhanced catalytic activity for transformations of previously unreactive substrates (Scheme 24).\(^\text{49}\)
Scheme 24

Recently, Marko and co-workers have reported that the tandem Ene reaction-Intra Molecular Sakurai Cyclisation (IMSC) of aldehydes was a particularly efficient procedure for the synthesis of a variety of diastereometrically pure exo-methylene tetrahydropyrans (Scheme 25).\(^{50}\)

```
R\(\rightarrow\)O + OTBS \(\rightarrow\) Et\(_2\)AlCl \(\rightarrow\) R\(\rightarrow\)O
CH\(_2\)Cl\(_2\)
```

Scheme 25

Intramolecular palladium catalyzed cyclization of alkenols allows additional functionalization of the tetrahydropyran through the trapping of an intermediate palladium species. Thus, methoxy-carbonylation\(^{51a,b}\), vinylation\(^{51c}\), and hydride elimination\(^{51d}\) lead to 2-functionalized tetra-hydropyrans (Scheme 26).

```
R\(\rightarrow\)OH + \(\rightarrow\) R\(\rightarrow\)O
```

Scheme 26

A significant variation on the alkenol theme is the stereo- and regio- selective ring opening of hydroxyepoxides (Scheme 27).\(^{52}\) 5-exo-Cyclization compete with the 6-endo mode but the latter is dominant when an electron-rich unsaturated function is present \(\alpha\)-position to the epoxide carbon atom.

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Scheme 27

22
1.3.1. Prins-cyclization and Prins-Type Macrocyclization:

1.3.1a. Introduction to Prins cyclization:

The Prins reaction is an organic reaction consisting of an electrophilic addition of an aldehyde or ketone to an alkene or alkyne followed by capture of a nucleophile or the acid catalyzed condensation of olefins with aldehydes. A variety of Lewis acids have been used to mediate such a cyclization. In 1919, Prins reported the condensation of formaldehyde with styrene in the presence of an acid catalyst to form a diol product. This reaction afforded a mixture of compounds; the major products of classical Prins reaction are normally 1,3-glycols, unsaturated alcohols and the products obtained from acid-catalyzed polymerization of the olefins (Scheme 28).

The Prins reaction has become a powerful tool for constructing carbocyclic and heterocyclic compounds. The Prins cyclization has wide applications including, among others, the synthesis of polyether antibiotics and other complex natural products that contain tetrahydropyran backbones are significant.

\[
\begin{align*}
\text{RCH}_2\text{OH} + \text{R'C} &= \xrightarrow{\text{H}^+} \text{RCH}_2\text{OH} + \text{R'C} \\
\end{align*}
\]

Scheme 28

In the late 1960s, Stapp briefly examined the direct synthesis of tetrahydropyran derivatives via the Prins cyclization (Scheme 29).

\[
\begin{align*}
\text{R'CHR} + \text{CH}_2\text{O} &\xrightarrow{\text{HX}} \text{X} \\
\end{align*}
\]

Scheme 29

1-\text{n}-Butyl-3-methylimidazolium chloroaluminate [bmin]Cl\text{AlCl}_3 was successfully employed as a reaction medium for Prins cyclizations, to produce 4-chlorotetrahydropyran derivatives in short reaction times with good yield (Scheme 30).
Chan$^{57}$ as well as Coppi reported that the coupling between allylsilanes and aldehydes could be used to prepare 2,6-disubstituted-4-halotetrahydropyrans. Coppi and co-workers$^{58}$ found that an analogous condensation could be achieved by directly mixing aldehydes and unsaturated alcohols at 0 °C in the presence of Lewis acid (Scheme 31).

![Scheme 31](image)

A variety of Lewis acids have been used to mediate such a cyclization. In most cases, the cyclization products are 2,6-disubstituted dihydropyran or 2,4,6-trisubstituted tetrahydropyran derivatives.

The Prins-cyclization of homoallyl mercaptans with aldehydes in the presence of indium trichloride afforded 2,4,6–trisubstituted thiacyclohexanes$^{59}$ as an 8:1 mixture of diastereomers (Scheme 32).

![Scheme 32](image)

The reaction of cis-mercaptan gave a mixture of cis-cis-cis and cis-trans-cis-thiacyclohexane derivatives with the latter as the predominant product whereas trans-mercaptan generated exclusively a cis-trans-cis thiacyclohexane derivative (Scheme 33).

![Scheme 33](image)
The aldol-Prins reactions of enol allylsilanes in the presence of camphorsulphonic acid afforded the tetrahydropyran derivative with cis-diastereo-selectivity.\textsuperscript{60} The aldol-Prins reactions of enol allylsilanes with aldehydes led to the formation of cis-2,6-disubstituted tetrahydropyran derivatives (Scheme 34).

\[
\begin{align*}
\text{Ph-} & \quad \text{O} \quad \text{O} \\
\text{Si Me}_3 & \quad + \quad \text{R-CHO} \\
\text{BF}_3\cdot\text{OEt}_2 & \quad \rightarrow \\
\text{Ph-} & \quad \text{OH} \quad \text{O} \quad \text{R}' \\
\end{align*}
\]

\textbf{Scheme 34}

Recently, the segment-coupling Prins-cyclization has been reported\textsuperscript{61} involving esterification, reductive acetylation and Lewis acid promoted cyclization (Scheme 35).

\[
\begin{align*}
\text{OH} \quad \text{R} & \quad \xrightarrow{\text{R}^1\text{COOH}, \text{DCC, DMAP}} \quad \text{OAc} \\
\text{O} \quad \text{R} & \quad \xrightarrow{1) \text{DIBAL-H}, 2) \text{Ac}_2\text{O, Py, DMAP}, 3) \text{Lewis acid}} \quad \text{R}' \\
\end{align*}
\]

\textbf{Scheme 35}

1.3.1b. Prins-Type Macrocyclization and applications in Natural Product Synthesis:

Prins-type macrocyclizations have recently emerged as a successful strategy in the synthesis of polyketide-derived natural products. This reaction provides a concise and selective means to form tetrahydropyran containing macrocyclic ring of varying size. A high degree of functionality within the macrocycle is tolerated and the yields for these transformations are typically good to excellent. Since the initial report of a Prins macrocyclization reaction in 1979, examples of this approach did not re-emerge until 2008. However, the use of this method in natural product synthesis has rapidly gained momentum in the synthetic community, with multiple examples of this macrocyclization tactic reported in the recent literature such as synthetic strategies toward neopeltolide by Lee,\textsuperscript{62a} Formal synthetic strategy toward neopeltolide by Yadav and Kumar,\textsuperscript{62b} Synthetic strategy toward bryostatin analogues by Wender,\textsuperscript{62c} formal synthetic strategy toward kendomycin by Rychnovsky and Bahnck,\textsuperscript{62d} synthetic studies toward clavosolide A by Rychnovsky\textsuperscript{62e} and synthetic strategy toward polycavernoside A by Lee and Woo.\textsuperscript{62f} The general strategy for Prins macrocyclization is given below in Scheme 36.
Lee and co-workers reported the total synthesis of neopeltolide (31) utilizing a Prins macrocyclization in March 2008. The applications of this macrocyclisation in neopeltolide of two different macrocyclization precursors from a common advanced intermediate are given below (Scheme 37).
In November 2009, Yadav and Kumar reported a formal synthesis of neopeltolide,\textsuperscript{62b} in which the macrolactonisation was achieved by a Prins macrocyclization in a similar manner to Lee’s strategy.

By utilizing the above macrocyclisation, we have successfully prepared the core of leucasandrolide A with good yield and high diastereoselectivity which is described briefly in this article.

1.4. Previous Approaches:

In 1996, Pietra and co-workers identified a new genus of calcareous sponges \textit{Leucasandra caveolata} obtained from the northeastern coast of New Calendonia Coral Sea, which resulted in the discovery of a highly complex natural product designated as leucasandrolide A. This macrolide exhibits high in vitro cytotoxicity against human KB and P388 tumor cell lines displaying IC\textsubscript{50} values of 0.05 and 0.25 µg/mL, respectively. The natural product also possesses potent antifungal ability against \textit{Candida albicans}, pathogenic yeast that attacks AIDS patients and other immunocompromised individuals. Additionally, following hydrolysis of the C5 ester linkage, biological testing of the 18-membered macrocyclic core and the separated side chain demonstrated that the macrocyclic domain is solely responsible for the cytotoxicity, while the oxazole-containing unsaturated side chain appears to be responsible for the antifungal activity. The highly oxygenated 18-membered macrolide has eight stereogenic centers and three alkenes and also features two trisubstituted tetrahydropyran rings, one of these having an unusual oxazole-containing side chain axially appended at C5. A subsequent report indicates that leucasandrolide A is no longer available from its initial natural source. It has been proposed that leucasandrolide A and its cometabolite leucasandrolide B are products of opportunistic microbial colonization of the sponge, as evidenced by the large amounts of dead tissue in the initial harvest of \textit{Leucasandra caveolata}. Currently, there is no natural source of leucasandrolide A. Based on its impressive biological activity, inaccessibility from natural sources, and structural complexity associated with ample synthetic challenges, the construction of leucasandrolide A has spurred considerable synthetic interest, resulting in several total and formal syntheses.
1.4.1. Rychnovsky’s approach: Williams and co-workers published the total synthesis of leucascandrolide A macrolide (50) by aldol-Prins reaction that developed by the same group for the synthesis of some natural products which was shown in Scheme 38.

1.4.1a. Retrosynthesis:

\[
\begin{align*}
\text{Scheme 38: Retrosynthetic analysis}
\end{align*}
\]

1.4.1b. Discussion:

Synthesis of the optically pure aldehyde 35 was prepared by using some well established reactions from the known compound 37. The first stereogenic center of 37 was introduced by Noyori reaction followed by TBS protection, DIBAL-\(H\) reduction and iodination gave the iodo compound 39. Myers’ pseudoephedrine auxiliary was used to introduce the C12 stereocenter by alkylation of iodide 39 and acid treatment gave the lactone 40. Reductive acetylation axial allylation and ozonolysis completed the synthesis of 35. The synthesis of fragment 36 was commenced from the known aldehyde 38. Noyori hydrogenation of a \(\alpha\)-keto ester generated the only stereogenic center in the target 36. Bunnelle’s method was used to convert the ester 41 to the 2-substituted allylsilane 42. The sensitive enol ether was introduced using esterification with chloroacetyl chloride, reductive acetylation and elimination of the acetate and chloride groups by Li/\(\text{NH}_3\) reduction to isolate the enol ether 36 (Scheme 39).
Scheme 39

Reagents and conditions: a) (R)-BINAP-RuCl(C₆H₆), 80 atm H₂, EtOH, 96%, 94% ee; b) TBSCCl, imidazole, DMF, 86%; c) DIBAL-H, THF, –25 °C, 88%; d) PPh₃, I₂, imidazole, CH₂Cl₂, quant; e) combine LDA, (–)-pseudoephedrine propionamide, LiCl, then add 15, THF, –78 °C, 98%, >20:1 dr; f) 2N H₂SO₄, dioxane, 95 °C, 77%; g) i. DIBAL-H, CH₂Cl₂, –78 °C, ii. Ac₂O, DMAP, pyridine, 95%; h) Allyl-trimethylsilane, BF₃.OEt₂, CH₂Cl₂, –78 °C, 97%, >20:1 dr; i) O₃, CH₂Cl₂, –78 °C, then PPh₃, 95%; j) N₂CHCO₂Et, SnCl₂, CH₂Cl₂, 72%; k) (S)-BINAP-RuCl(C₆H₆), 4 atm H₂, EtOH, 100 °C, 51%, >95%ee; l) TMSI, Et₃N, CH₂Cl₂, 91%; m) i. CeCl₃, TMSCH₂MgCl, THF/Et₂O, –78 °C to 23 °C, ii. SiO₂ gel, CH₂Cl₂, 87% n) ClCH₂COCl, pyridine, CH₂Cl₂, 95%; o) i. DIBAL-H, CH₂Cl₂, –78 °C, ii.Ac₂O, DMAP, pyridine, CH₂Cl₂, 95%; p) Li , NH₃, THF, –78 °C, 65%

Aldehyde 35 and enol ether 36 were coupled using the same conditions BF₃.OEt₂ and 2,6-di-tertbutylpyridine at –78 °C, to give the product 43 as a 5.5:1 mixture of epimers at

Scheme 40

Reagents and conditions: a) i. BF₃.Et₂O, 2,6-di-tert-butylpyridine, CH₂Cl₂, –78 °C, ii. NaBH₄, EtOH, 78%, 5,5:1 dr at C9; b) MeO.BF₄⁻, proton Sponge, 4 A° M.S., CH₂Cl₂, 79% (single epimer) plus C9 epimer (15%); c) i. OsO₄, NMO, ii. NaIO₄, 80%; d) L-Selectride, THF, –90 to –60 °C, 82% (single epimer) plus C5 epimer (10%); e) TBAF,
THF, 92%; f) TBSOTf, 2,6-lutidine, CH₂Cl₂, 89%; g) H₂, Pd(OH)₂, EtOAc, 96%; h) Swern, 94%; i) Me₂AlCl, Me₃SnCCCH₂CH(CH₃)₂, PhCH₃, -78 °C, 80%, 3.5:1 dr at C17; j) Red-Al, Et₂O, 60% (Single epimer) plus recovered SM and C17 epimer; k) Ac₂O, DMAP, pyridine, CH₂Cl₂, 89%; l) Neutral Al₂O₃, hexanes, 96%; m) Swern, 97%; n) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, 71%; o) K₂CO₃, MeOH, ii. Cl₃C₆H₂COCl, Et₃N, DMAP, C₆H₆, 23 °C, 56%; p) HF-Pyridine, THF, 96%.

C9. The crucial methylation of C9 was carried out with trimethyloxonium tetrafluoroborate and proton sponge and the C9 epimers were separated at this stage. Oxidative cleavage of the alkene and L-Selectride reduction introduced the axial C5 alcohol and reprotection gave 44 (Scheme 40). The C17 substituent was introduced by a chelation-controlled alkynylstannane addition to the corresponding aldehyde. Red-Al reduction gave the (E)-alkene 34 and deprotection of TBS and oxidation of the C1 alcohol gave the seco acid ester 45. Hydrolysis, Yamaguchi-type cyclization and desilylation completed the synthesis of the leucascandrolide A macrolide 33.

1.4.2. Paterson’s approach.⁶⁴

Paterson and co-workers published the total synthesis of core of leucascandrolide A (50) by utilizing Jacobsen asymmetric hetero Diels-Alder and 1,5-anti aldol coupling reaction.

1.4.2a. Retrosynthesis:

The retrosynthetic analysis of this compound was shown in Scheme 41.

![Scheme 41: Retrosynthetic analysis](https://example.com/scheme41.png)
1.4.2b. Discussion:

The synthesis of the trisubstituted tetrahydropyran 49 began with a Jacobsen asymmetric hetero Diels-Alder reaction of aldehyde 51 and readily available 2-siloxydiene 52, promoted by the chromium tridentate catalyst 53. Installation of the equatorial C5 hydroxy group was achieved by treatment with NaBH₄ in MeOH to give secondary alcohol following TIPS ether formation, selective acidic removal of the TBS group gave primary alcohol 55. Homologation to the methyl ketone involved activation of alcohol 55 as its triflate derivative, displacement with lithium trimethylsilyl acetylide and basic methanolysis to give alkyne. Subsequent Hg(II)-mediated hydration gave the methyl ketone 49 cleanly. Thus, treatment of 49 with cHex₂BCl and Et₃N in Et₂O generated the corresponding less substituted enolate, which on addition of aldehyde 48 provided, after oxidative workup, aldol adduct was obtained and 1,3-anti reduction of b-hydroxy ketone 56 with Me₄NBH( OAc)₃ provided diol. Next, acidic removal of the TBS group gave triol 57, which was oxidized selectively at the primary hydroxy group by using catalytic TEMPO and iodobenzene diacetate to give d-lactone. Methylation of the isolated C9 hydroxy group with Me₃OBF₄ and proton sponge gave advanced intermediate 58. Suitable activation of the anomeric position was achieved by treating d-lactone 58.
Scheme 42
Reagents and conditions: a) 4 A° M.S, 20 °C, 20 h; acidified CHCl₃, 20 °C, 4 h, 80%; b) NaBH₄, MeOH, 20 °C, 2 h, 99%; c) TIPSOTf, lut, CH₂Cl₂, −78 °C, 2 h, d) CSA, 2:1 MeOH/ CH₂Cl₂, 20 °C, 1 h, 82% (over two steps); e) Tf₂O, pyr, CH₂Cl₂, −10 °C, 1 h; f) LDA, TMSC, HMPA, −78° to 20 °C, 1 h; K₂CO₃, MeOH, 20 °C, 12 h, 84% (over two steps); g) cat. Hg(OAc)₂, PPTS, wet THF, 40 °C, 1 h, 86%; h) cHex₂BCl, NEt₃, Et₂O, O °C, 30 min; −78 °C, 2 h; −78° to −30 °C, 24 h, 99%; i) Me₄NBH(OAc)₃, 3:1 MeCN/AcOH, −40 to −20 °C, 24 h, 99%; j) CSA, 2:1 MeOH/ CH₂Cl₂, 25 °C, 1 h; k) TEMPO, Phl(OAc)₂, CH₂Cl₂, −20 °C, 12 h, 99% (over two steps); l) Me₃OBF₄, proton sponge, CH₂Cl₂, 0 to 20 °C, 1 h, 84%.

with DIBAL- H followed by in situ acetylation to afford acetate 59. Treatment of 59 with an excess of silyl enol ether 50 in the presence of catalytic ZnBr₂ afforded ketone 60 cleanly. Next, a 1,3-syn reduction was achieved by using LiAlH(OtBu)₃ alone gave allylic alcohol. Acetylation of the resultant (17S)-hydroxy group followed by oxidative removal of the PMB group gave alcohol followed by oxidation to the corresponding acid and saponification afforded seco-acid 46 which set the stage for the Mitsunobu macro-lactonization with treatment of 46 with DEAD and Ph₃P in degassed benzene for 5 min proceeded to give the desired macrocycle (Scheme 43). Cleavage of the equatorial C5 TIPS ether was achieved by HF.pyr in THF to furnish macrocycle 61 for the introduction of the axially oriented side chain at C5.
Scheme 43
Reagents and conditions: a) DIBAL-H, CH₂Cl₂, then Ac₂O, pyr, DMAP, –78 to –20 °C, 15 h; b) ZnBr₂, CH₂Cl₂, 20 °C, 4 h; c) LiAlH(OtBu)₃, CH₂Cl₂, –78 to –10 °C, 1.5 h; d) Ac₂O, pyr, DMAP, CH₂Cl₂, 0 to 20 °C, 15 h; e) DDQ, 10:1 CH₂Cl₂/pH 7 buffer, 20 °C, 1 h; f) TEMPO, Ph(OAc)₂, CH₂Cl₂, 20 °C, 1 h; NaClO₂, NaHPO₄, 2-methyl-2-butene, aq. t-BuOH, 0 to 20 °C, 1 h; g) K₂CO₃, MeOH, 20 °C, 18 h; h) DEAD, PPh₃, PhH, 20 °C, 5 min; i) HF.pyr, THF, 0 to 20 °C, 5 h.

In summary, a highly stereocontrolled synthesis of the potent cytotoxic macrolide core of leucascandrolide A was proceeded in 23 steps from 8 (longest linear sequence) and 5.3% overall yield.

1.4.3. Cossy’s approach:⁶⁵

In 2007, Cossy and co-workers published the total synthesis of the macrolide ol leucascandrolide A. A chemoselective synthesis of the macrocyclic core of leucascandrolide A has been achieved, utilizing highly enantioselective allylmetalations, an enantioselective Noyori reduction of a propargylic ketone and olefin metatheses as the key steps.

1.4.3a. Retrosynthesis:

Scheme 44: Retrosynthetic analysis
1.4.3b. Discussion:

The synthesis of fragment C9-C15 started with the transformation of but-3-en-1-ol to aldehyde 68 which was obtained after protection of the alcohol (TBDMSCl, imidazole) and ozonolysis (O₃, −78 °C, then Et₃N). The addition of the highly face selective titanium complex Ti(R,R)-I 71 to aldehyde 68 (Et₂O, −78 °C) allowed us to control the stereogenic centers at C11 and C12, producing the desired homoallylic alcohol 69. After transformation of 69 to the unsaturated ester 66 by using acryloyl chloride, Et₃N and CH₂Cl₂. The first one-pot reaction involved a tandem RCM/hydrogenation10 (Ru-I, 3 mol %, then H₂, Pd/C) forming lactone 70. The second one-pot reaction was the transformation to 64 followed by acylation of the alkoxy aluminum intermediate. Silyl enol ether 65 was prepared in two steps from the commercially available 4-methyl pent-1-yne. The starting alkyne was acylated via an organozinc intermediate (n-BuLi, ZnBr₂ and AcCl) providing the propargylic ketone which was treated with LiHMDS to furnish the corresponding lithium enolate which was trapped with TMSCl gave the silyl enol ether 65 (Scheme 45).

![Scheme 45](image)

Reagents and conditions: a) TBSCl, imidazole, DMF; b) O₃, CH₂Cl₂, −78 °C, then Et₃N, 76% (2 steps); c) Ti(R,R)-I, Et₂O, -78 °C, 86%; d) Et₃N, CH₂Cl₂, 92%; e) Ru-I, CH₂Cl₂, 40 °C, 48 h, then Pd/C, 5%, H₂, 1 atm, rt, 70%; f) DIBAL-H, CH₂Cl₂, −78 °C, then Ac₂O, Py, DMAP, 98%.

Fragment 65 was then coupled with the C9-C15 fragment 64 by using a Mukaiyama-type reaction by treatment with ZnCl₂ at −78 °C to afford tetrahydropyran. After reduction of ketone by using Noyori catalyst Ru(R,R)-II (78) under phase transfer conditions (HCO₂Na, n-Bu₄NCl, H₂O/CH₂Cl₂), the desired propargylic alcohol 72 was isolated. The propargyl alcohol was reduced with Red-Al to the (E)-allylic alcohol, the crude material
Scheme 46

Reagents and conditions: a) ZnCl₂, CH₂Cl₂, −78 °C to rt, 89%; b) HCOONa, n-Bu₄NCl cat Ru(R,R)-II (3mol %), H₂O/CH₂Cl₂ (1/1), 4 days, rt; c) Red Al, 30 °C, THF, 24 h; d) TBSOTf, 2,6 Lutidine, 0 °C, 92% (over two steps); e) NH₄F, MeOH 60 °C, 4h; f) DMP, CH₂Cl₂, g) Ti(R,R)-II, Et₂O, −78 °C, 80% (over 2 steps); h) Ag₂O, Mel, rt, Drierite, Et₂O, 96%; i) OsO₄ 5 mol %, NMO 1 equiv, 24 h, 0 °C, t-BuOH/H₂O (2/1), j) NaI₂O₄, THF/H₂O, n-Bu₄NCl, 30 min, rt, k) Ti(R,R)-II, Et₂O, −78 °C, 78% (2 steps); l) OsO₄ 5 mol %, NMO 1 equiv, 24 h, 0 °C, t-BuOH/H₂O (2/1), 66%; m) NaI₂O₄, THF/H₂O, n-Bu₄NCl, 30 min, rt; n) AllylTMS, SnCl₄, CH₂Cl₂, −78 °C, 74% (2 steps).

was directly treated with TBSOTf to give TBS protected compound. The primary alcohol was chemoselectively deprotected (NH₄F, MeOH) to afford alcohol 73. The primary alcohol 73 was oxidized to an aldehyde (Dess-Martin periodinane) which was directly treated with the highly face-selective titanium complex Ti(R,R)-II, (77) to produce homoallylic alcohol. The hydroxy group in compound, was then transformed to a methyl
ether compound 74 had to be converted to an aldehyde by selective oxidative cleavage of the terminal double bond furnish the desired aldehyde. This aldehyde was directly subjected to a stereoselective allylation using Ti(R,R)-II to produce homoallylic alcohol 76. At first, triol was obtained by dihydroxylation (OsO₄ cat, NMO) and its subsequent oxidative cleavage with NaIO₄ generated the corresponding aldehyde. The obtained hydroxy-aldehyde was then directly treated with a premixed solution of allyltrimethylsilane and SnCl₄ at −78 °C producing syn-1,3-diol (Scheme 46). Compound 63 was treated with methyl acrylate in the presence of Hoveyda-Grubbs catalyst Ru-III (15 mol %) to provide chemoselectively the unsaturated ester 62. The elaboration of cis-tetrahydroxy-2,3-diol 62 was realized under basic conditions by using a catalytic amount of t-BuOK (20 mol %) which afforded 79. After treatment with TBAF in THF, diol cis- was isolated as a single diastereoisomer. At first, a mild saponification of the methyl ester with TMSOK in Et₂O afforded the hydroxyl acid, the cyclization of which provided selectively the macrocyclic core of leucascandrolide A (33) under the Yonemitsu-modified Yamaguchi protocol.

Scheme 47
Reagents and conditions: a) Ru-III (15 mol %), CH\textsubscript{2}Cl\textsubscript{2}, 84%; b) \textit{t}-BuOK (20 mol %), THF, 0 °C, (\textit{cis}/\textit{trans}=3/1); c) TBAF, THF, rt, 38% (2 steps); d) TMSOK, Et\textsubscript{2}O, e) 2,4,6-trichlorobenzoyl chloride, Et\textsubscript{3}N, DMAP, Toluene, 75%.

Thus, macrolide was synthesized in 25 steps and 1.2% overall yield from but-3-en-1-ol. Synthetic highlights include highly stereoselective allylmetalations, an enantioselective Noyori reduction, a cross-metathesis followed by an intramolecular 1,4-addition to build up the \textit{cis}-tetrahydropyran.

1.4.4. Williams’s approach:

Williams and co-workers published the formal total synthesis of leucascandrolide A macrolide by asymmetric allylation as a key reaction.

1.4.4a. Retrosynthesis:

\[ \text{Scheme 48: Retrosynthetic analysis} \]

1.4.4b. Discussion:

The preparation of the C1–C9 aldehyde 80 commenced with the conversion of the known epoxide 83 into the allyl silane 85 through the copper-catalyzed addition of the Grignard reagent prepared from 2-bromo-3 trimethylsilylpropene (Scheme 49). Subsequent protection of the resulting homoallylic alcohol gave the TBS ether. Treatment of 85 with freshly recrystallized NBS at −78 °C led to the immediate formation of the
labile corresponding allylic bromide which was displaced directly with a tributylstannylcuprate to give the allyl stannane 86 and subsequent asymmetric allylation was effected following the tin-boron transmetalation of the allylstannane by using the boron bromide reagent 88 developed by Corey et al. Nucleophilic addition to the aldehyde 87 provided the S homoallylic alcohol 89 and ring closure of resulted alcohol to afford the 2,6-cis-tetrahydropyranyl moiety of 80. The homoallyl alcohol 90 was prepared by using some well known reaction. Methylation of the homoallylic alcohol at 90 was followed by oxidative cleavage (OsO₄, NMO; NaIO₄) to provide the corresponding diketone 91.

Scheme 49

Reagents and conditions: a) Mg, THF, (2-bromoallyl)trimethylsilane; then epoxide, CuI, −50 °C to −10 °C, 2 h; 79%; b) TBSCI, imidazole, DMF; 100%; c) NBS, propylene oxide, CH₂Cl₂/DMF (2:3), −78 °C; d) Bu₃SnLi, CuBr·DMS, THF, −78 °C to −40 °C; 77% (2 steps); e) the (S,S)-1,2-diphenylethane bis (sulfonamide), BBr₃, CH₂Cl₂, 0 °C, 1 h; then
comp, rt, 10 h; then aldehyde, −78 °C, 1.5 h; 100%, d.r. 11:1; f) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 100%; g) HF.pyr, CH$_3$CN, 99%; h) NaH, PhH, 90 °C, 75%; i) MeI, CaCO$_3$, CH$_3$CN/H$_2$O (9:1), 16 h, 100%; j) the (R,R)-1,2-diphenylethane bis (sulfonamide), BBr$_3$, CH$_2$Cl$_2$, 0 °C, 1 h; then comp, rt, 10 h, then aldehyde, −78 °C, 1.5 h, 96%, d.r., 8.5:1; k) Me$_3$OBF$_4$, proton sponge, 4-A° M.S., CH$_2$Cl$_2$, 96%; l) OsO$_4$, NMO, acetone/H$_2$O (2:1), 16 h, m) NaIO$_4$, THF/phosphate buffer (pH 7: 1:1), 16 h, 80%, (2 steps), n) L-Selectride, THF, −78 °C., 1.5 h, 84%; o) TBDPSCl, imidazole, DMF, 40 h; 73%; p) LiAlH$_4$ (2 equiv), (-)-N-methylephedrine (2 equiv), N-ethylaniline (4 equiv), Et$_2$O, −78 °C, 2 h, 95%; q) Ts$_2$O, pyridine, THF, 84%; r) NaH, PhH, 60 °C, 16 h, 73%; s) Dess–Martin periodinane, NaHCO$_3$, CH$_2$Cl$_2$, 95%.

$L$-Selectride promoted selective reduction at C5 of the tetrahydropyranone, which led to the corresponding axial alcohol and this alcohol was protected as its TBDPS ether. The asymmetric reduction of the ketone at C11 and formation of the 2,6-trans-tetrahydropyran was done and followed by selective removal of the TBS groups and treatment with sodium hydride. The Dess–Martin oxidation of the primary alcohol yielded the aldehyde 93. The hydrozirconation of 4-methyl-1-pentyne with the Schwartz reagent was followed by transmetalation with dimethylzinc to give allylic alcohols which was oxidized directly to the enone which was allowed for Corey–Bakshi–Shibata (CBS) borohydride reduction and subsequent acetylation to give 94 was followed by oxidative deprotection of the alcohol at C1 and the acid was obtained by oxidation of the resulting primary alcohol to the carboxylic acid and subsequent basic methanolation of the acetate at C17. The crude product was subjected to the Yonemitsu-modified Yamaguchi protocol to give the macrolide. Finally, deprotection of the alcohol at C5 by treatment with fluoride provided the leucascandrolide A macrolactone 33.
CH₂Cl₂, 75%; c) (S)-2-methyloxazaborolidine, BH₃·THF, –10 °C, 89%, d.r. 5:1; d) Ac₂O, pyridine, DMAP, CH₂Cl₂, 97%; e) DDQ, CH₂Cl₂/phosphate buffer (pH 7) / t-BuOH (40:10:1), 1.5 h; quant; f) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂; g) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, aqueous t-BuOH, 0 °C, 45 min, 56% (2 steps); h) K₂CO₃, MeOH, 16 h; i) 2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP, benzene, 63%, (2 steps); j) TBAF, THF, 67%.

In summary, investigations into asymmetric allylation methodology have extended this fundamental technique to the efficient, convergent construction of leucascandrolide A macrolactone.
CHAPTER I

Section B

Total synthesis of the macrolide core of

Leucascandrolide A
1.5. PRESENT WORK

We achieved a unique synthetic solution for the synthesis of leucascandrolide featuring a concise, convergent, and highly stereoselective approach to this complex natural product. Our interest for macrolactone core of leucascandrolide A arose from studies in which we demonstrated that the critical trans-2,6-disubstituted tetrahydropyran relevant to the C11-C15 fragment would be prepared following a recently developed iodocyclization of δ-hydroxy α,β-unsaturated aldehyde with allyltrimethylsilane in the presence of molecular iodine (Scheme 51). The second most important reaction was to apply a Prins-type macrocyclization which has recently emerged as a successful strategy in the synthesis of polyketide derived complex natural products. Here we disclose an effective and concise formal total synthesis of leucascandrolide A by utilizing some recent protocols like iodocyclization and intramolecular Prins-macrocyclization.

1.5.1. Retrosynthesis:

Scheme 51: Retrosynthetic analysis of the leucascandrolide A
Chapter I, Section B

The retrosynthetic analysis of leucascandrolide A was shown in Scheme 51. From the retrosynthetic perspective, disconnection of Leucascandrolide A at the macrolactone core 61 and the oxazole containing side chain at the C5 hydroxyl yield two fragment 47. The macrolactone core 61 could be obtained from aldehyde 95 through a late stage Prins-cyclization. The alcohol fragment 96 could be prepared from the C11-C15 pyran of 98 which could be obtained following our recently reported protocol. The δ-hydroxy α,β-unsaturated aldehyde 99 precursor for the iodocyclization reaction as well as the acid fragment 97 could be obtained starting from a known chiral epoxide 100.

The crucial reactions involved in the synthesis of the core of leucascandrolide A are Jacobsen’s hydrolytic kinetic resolution, cross-metathesis, Jørgensen’s asymmetric epoxidation, iodine-catalyzed cyclization, CBS-reduction, Yamaguchi esterification and intramolecular Prins-macrocyclization.

1.5.2. Synthesis of the alcohol fragment (96):

The journey towards the synthesis of subtarget 96 began with the kinetic resolution of 2-(p-methoxybenzylloxyethyl)oxirane 103 (obtained from 3-butenol 101 in two steps as shown in Scheme 52). The commercially available homoallyl alcohol 101 was converted to its p-methoxybenzyl ether 102 by treating with sodium hydride (60% w/v dispersion in oil) and benzyl bromide in dry THF at 0 °C in 95% yield. p-Methoxybenzyl ether 102 was confirmed by its 1H NMR spectrum, which showed resonances at their corresponding chemical shift as a singlet for two benzylic protons and a multiplet for aromatic protons. Absence of hydroxyl functionality was also confirmed by IR spectrum, which showed no absorption band for hydroxyl functionality. Treatment of 102 with m-CPBA in dichloromethane at 0 °C afforded the racemic epoxide 103 in 92% yield. Compound 103 in 1H NMR spectrum showed the absence of olefinic protons at their respective chemical shifts and the appearance of three oxirane protons at 2.98, 2.71 and 2.45 ppm as multiplets manifested the formation of epoxide.

The racemic terminal epoxide 103 was converted to the chiral epoxide 100 in 45% yield along with chiral diol 104 by 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-butyalsicylidene)-1,2-cyclohexanediamino-cobalt (II) (Scheme 52). The optical rotation of the compound 100 was found to be $[^\alpha]_{D}^{25} -10.8$ (c 2, CHCl$_3$) which was correlated with that of the earlier
reported value. Chiral epoxide 116 was confirmed by its $^1$H NMR studies, which exhibited the resonance at the respective chemical shifts.

Conversion of epoxide 100 into a homoallyl alcohol 106 through the copper(I)-catalyzed addition of a vinyl Grignard reagent at $-20\,^\circ\mathrm{C}$ in 85% yield. The $^1$H NMR spectrum of compound 106 revealed two methylene protons adjacent to the double bond at $\delta$ 2.23 ppm and characteristic terminal olefin protons at $\delta$ 5.83 ppm and 5.10 ppm. IR absorption showed characteristic band at 3434 cm$^{-1}$ for hydroxyl functionality. The hydroxyl group of alcohol 106 was converted to its methyl ether 107 using MeI and sodium hydride in 94% yield and it revealed by the appearance of characteristic protons at $\delta$ 3.32 ppm as singlet and disappearance of broad singlet for hydroxyl protons at 2.94 ppm and $^{13}$C NMR spectrum also showed appearance of one peaks at $\delta$ 56.7 ppm. Then one carbon homologation of the methyl protected homoallylic alcohol 107 was performed by a cross-metathesis (CM) between the alcohol and acrolein using a Hoveyda-Grubbs catalyst ($10\,\text{mol\%}$) in CH$_2$Cl$_2$ at room temperature to afford a $\alpha,\beta$-unsaturated aldehyde 108 in 92% yield. $^1$H NMR revealed a downfield shift for olefinic protons. The characteristic $\alpha,\beta$-unsaturated olefinic protons resonated at $\delta$ 6.81ppm as multiplate and $\delta$ 6.12 ppm as doublet. A doublet at $\delta$ 9.48 ppm appeared for aldehyde proton and similarly a peak at $\delta$ 193.7 ppm appeared in $^{13}$C NMR spectrum for aldehyde carbon. IR spectrum showed a peak at 1690 cm$^{-1}$ and, ESI-HRMS also showed (M+Na)$^+$ peak at $m/z$ 301.1407 which proved the presence of conjugated aldehyde.
The aldehyde 108 was then subjected to asymmetric epoxidation under Jørgensen’s conditions with H$_2$O$_2$ in the presence of a proline-derived catalyst to furnish an epoxy aldehyde, which on condensation with Ph$_3$P=CHCO$_2$Et afforded an epoxy ester 109 in 80% yield. The structure was confirmed by its $^1$H NMR study which showed the appearance of ester protons at δ 1.18 ppm as quartet and 1.29 ppm as triplet and the oxepoxide protons at δ 3.17 and 2.97 ppm. The epoxy ester 109 was also confirmed by $^{13}$C NMR spectrum on the appearance of carbonyl group of ester peak at δ 165.6 and all eight oxirane carbons at their corresponding positions and a new peak at δ 14.2. IR absorption spectrum revealed a sharp peak at 1720 cm$^{-1}$ which unambiguously proved the formation of epoxy ester. A peak at m/z [M + Na]$^+$ 387.1791 in ESI-HRMS spectrum was helped us to confirm product formation.

The regioselective opening of epoxide of 109 was taken place by using trimethyl aluminum (TMA) followed by slow addition of water in CH$_2$Cl$_2$ at −40 °C to afford δ-hydroxy compound 110 in 92% yield. The structure was confirmed by its $^1$H NMR study which showed the absence of oxirane protons and the presence of three methyl protons at δ 1.06 ppm as doublet while the IR spectrum disclosed the absorption band at 3472 cm$^{-1}$ indicating the presence of –OH functionality. The ester functionality in 109 was reduced to hydroxyl functionality using DIBAL-H at −78 °C to afford the diol 111 in 88% yield (Scheme 54). The diol was characterized by ESI-HRMS which showed [M + Na]$^+$ peak at m/z 361.1982 and $^1$H NMR spectrum showed the disappearance of characteristic peaks at δ 4.17 ppm and δ 1.29 ppm. IR absorption showed characteristic broad band at 3408 cm$^{-1}$.
which indicate the presence of hydroxyl functionalities. The product was characterized by ESI-HRMS which showed [M + Na]$^+$ peak at m/z 361.1982. This diol 111, on selective oxidation in the presence of bis(acetoxy)iodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidine-N-oxide (TEMPO) afforded the desired δ-hydroxy α,β-unsaturated aldehyde 99 in 90% yield.\(^\text{73}\) \(^1\)HNMR revealed a downfield shift for olefinic protons. The characteristic α,β-unsaturated olefinic protons resonated at δ 7.09 ppm as multiplet and δ 6.08 ppm as double doublet, a doublet at δ 9.49 ppm appeared for aldehyde proton in \(^1\)H NMR and similarly a peak at δ 194.1 ppm appeared in \(^{13}\)C NMR spectrum for aldehyde carbon. IR spectrum also showed a peak at 1689 cm$^{-1}$ which proved the presence of conjugated aldehyde. Thus with a sizable amount δ-hydroxy α,β-unsaturated aldehyde in hand, we turned our attention to the most crucial cyclizations step where we tried various reaction conditions to get the desired 2,6-disubstituted-3,4-dihydropyran ring systems.

Initially, we investigated the effect of 5 mol% iodine on the conversion of 99, with allyltrimethyl silane in CH$_2$CN at room temperature to obtain 98. After 12 h at room temperature, the reaction afforded the expected trans-2,6-disubstituted-3,4-dihydropyran 98 in 38% yield (Scheme 55). The reaction was incomplete even after 48 h of stirring at
room temperature. We had employed 10 mol% iodine for completion of the reaction. Even though, increasing the iodine concentrations did not help in improving the yield and reduction of reaction time expectedly. However, no reaction was observed in absence of iodine even after a long time (48 h). To optimize the reaction conditions, screening was performed on several parameters, such as solvents, temperature, and catalyst concentration. Initially, the reaction was performed in different solvent systems (CH$_2$Cl$_2$, TBME, THF) at room temperature with 5 mol% of iodine; THF was found to be superior to other solvents. Next, the reaction was examined carefully under reflux conditions which led to an intractable mixture of products. The experiment was also conducted carefully under the influence of different concentrations of the catalyst at room temperature with THF as solvent. The use of 10 mol% molecular iodine (based on δ-hydroxy α,β-unsaturated aldehyde) gave the best result with a yield of 96% after 45 min of reaction. The $^1$H and $^{13}$C NMR of the product revealed a single diastereomer which was supported by HPLC analysis data (de >99%). $^1$H NMR spectrum showed extra olefin protons at δ 5.86 (m, 1H), δ 5.16-5.0 (m, 2H) and disappearance of aldehyde peak resonated at δ 9.49 ppm in compound 99.

Then, selective oxidation of the terminal olefin in presence internal olefin of 98 was carried out under different conditions. First, we tried two step process- dihydroxylation and then chopping of diol to aldehyde by NaIO$_4$. When OsO$_4$, NMO was employed for dihydroxylation, both internal and terminal olefin took part in reaction and thus we got mixture of products with moderate yield of the desired product. Next, dihydroxylation reaction under Sharpless asymmetric dihydroxylation (SAD) condition using K$_3$Fe(CN)$_6$, OsO$_4$ and (DHQD)$_2$- PHAL was performed. Although reaction was selective for terminal olefin, it was slow and never went to completion. Finally, recently developed one step dihydroxylation-oxidation protocol was applied where OsO$_4$, 2,6 lutidine, NaIO$_4$ were used as reagents and 1,4 dioxane-H$_2$O (3:1) mixture used as solvent system. Fortunately, reaction went to completion in 1 h and the desired aldehyde was produced in 92% yield. The aldehyde thus obtained was unstable in nature, passed through a bed of silica gel and immediately used for the next step without further characterization. Subsequent oxidation of aldehyde 112 under Pinnick conditions using NaClO$_2$, 

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NaH$_2$PO$_4$·H$_2$O, 2-methyl-2-butene (Scheme 56) afforded a carboxylic acid 113 in 90% yield. A very broad absorption trough at 3029 cm$^{-1}$ and another at 1732 cm$^{-1}$ in IR spectra indicating the presence of acid group. It’s $^1$H NMR revealed absence of peaks for terminal olefinic protons whereas other spectral data were in complete agreement with the product. The carboxylic acid 113 which on treatment with diazomethane in ether at 0 °C gave the ester 114 in 94% yield. The $^1$H NMR spectrum of 114 showed a singlet at δ 3.32 ppm for three protons corresponding to the methyl ester and $^{13}$C NMR spectrum also showed appearance of one peaks at δ 51.6 ppm. IR spectrum also revealed a peak at 1737 cm$^{-1}$, a characteristic peak of ester moiety. The saturation of olefinic functionality using Pd-CaCO$_3$/H$_2$ smoothly delivered the corresponding saturated ester 115 in 93% yield. The compound 115 was characterized by ESI-HRMS which showed (M + Na)$^+$ peak at m/z 417.2240 and $^{13}$C NMR spectrum shows absence of olefinic carbons at δ 132.1 and 127.0 ppm. The absence of characteristic olefinic protons in $^1$H NMR confirmed the reduction of double bond in 114.

The saturated ester 115 was allowed for a nucleophilic addition of the lithiated derivative of dimethyl methyl phosphonate furnished the β-keto phosphonate 116 in 92% yield. The β-keto phosphonate thus obtained was unstable to column chromatography in nature, passed through a bed of silia gel and immediately used for the next step without
Further characterization. The $\beta$-keto phosphonate 116 on treatment with 3-methylbutanal 117 in the presence of NaHMDS gave $\alpha,\beta$-unsaturated ketone 118 in 81% yield. The $^1$H NMR spectrum of compound 118 showed characteristic olefinic resonances for $\alpha,\beta$-unsaturated ketone at $\delta$ 6.81 as double doublet and $\delta$ 6.11 as doublets corresponding to two adjacent olefinic protons with a coupling constant $J_{CH=CH} = 15.6$ Hz providing the trans geometry of the double bond and the $^{13}$C NMR spectrum showed a peak at 198.4 ppm which corresponds to keto carbon. IR absorption showed characteristic band at 1717 cm$^{-1}$ for ketone functionality. The product was further confirmed by ESI-HRMS showed (M + Na)$^+$ peak at $m/z$ 469.2940. The crucial Corey-Bakshi-Shibata$^{78}$ (CBS) reduction of $\alpha,\beta$-unsaturated ketone 118 was done by applying the reagent [(S)-2-methyloxazaborolidine at $-20$ $^\circ$C in the presence of borane-dimethylsulfide complex installed the C17 stereogenic center present in 96 with a 12:1 diastereomeric ratio (by HPLC) in 82% yield as a separable mixture (Scheme 57). The product 96 was confirmed by $^1$H NMR, $^{13}$CNMR, IR, HRMS spectra. The $^1$H NMR spectrum shows absence of $\alpha,\beta$-unsaturated protons of ketone and appearance of olefinic protons as multiplet at $\delta$ 5.62 ppm as multiplet and double doublet at $\delta$ 5.46 ppm with $J = 15.3$ Hz and also disappearance of peak at 6.81 ppm and 6.11 ppm. The $^{13}$C NMR showed the absence of ketone carbon which was situated at 198.4 ppm. IR spectrum of compound 96 disclosed
the absorption band at 3454 cm\(^{-1}\) corresponding to hydroxyl functional group and HRMS showed (M + Na\(^+\)) peak at m/z 471.3069.

### 1.5.3. Synthesis of the acid fragment (97):

Having the required alcohol fragment 96 in hand, our next target was to synthesize acid fragment 97. The synthesis commenced with the copper(I)-catalyzed addition of the Grignard reagent vinyl magnesium bromide to the chiral epoxide 100 to afford the homoallyl alcohol 106 in 85% yield. The characterization of the chiral epoxide 100 and homoallyl alcohol 106 was described in Scheme 58. The resultant secondary hydroxyl group which was obtained by opening of epoxide 100, was protected as its TBS-ether using TBSOTf and 2,6-lutidine in anhydrous CH\(_2\)Cl\(_2\) to obtain 119 in 93% yield. The \(^{13}\)C NMR spectra of compounds 119 was revealed the presence of silyl methyl protons at δ \(-4.4\) and \(-4.8\) ppm and ESI-HRMS showed (M + Na\(^+\)) peak at m/z 373.2181. PMB deprotection was achieved by the treatment of DDQ\(^{79}\) in CH\(_2\)Cl\(_2\)/H\(_2\)O (9:1) and the desired primary alcohol 120 was produced with 94% yield. Its \(^1\)H NMR revealed the absence of a set of two doublets at δ 7.19, 6.81 ppm, and a quartet at δ 4.36 ppm for two benzylic protons and a singlet at δ 3.78 ppm for three methoxy protons of PMB group. A peak at m/z 231.1775 [M + Na\(^+\)] in ESI-HRMS spectrum was an additional proof in this favor. The primary alcohol 120 when subjected to Dess-Martin-Periodinane\(^{80}\) oxidation, it afforded smoothly the aldehyde 121 which was immediately used for further oxidation under Pinnick conditions\(^{77}\) using NaClO\(_2\), NaH\(_2\)PO\(_4\), t-BuOH, H\(_2\)O and 2-methyl-2-butene gave acid 97 in 90% yield (scheme 58). The acid functionality showed a peak at 1713
cm\(^{-1}\) in IR whereas the corresponding peak for carbonyl carbon appeared at \(\delta 177.6\) ppm in \(^{13}\)C NMR spectrum. Along with above data, a peak at \(m/z\ 267.1385\ [M + Na]^+\) in ESI-HRMS spectrum was given additional support in this favor.

1.5.4. Synthesis of the macrolide (61):

With alcohol 96 and acid fragment 97 in hand, our next task was to couple both of the fragments and verify the Prins-type macrocyclization on an 18-membered macrolactone. The coupling of C1-C6 acid fragment 96 and C7-C23 alcohol fragment 97 was performed in different conditions to optimize the yield. Initially, the reaction was performed in employing dicyclohexyl carbodiimide (DCC) and a catalytic amount of DMAP in CH\(_2\)Cl\(_2\) to afford ester 122 in 42% yield.\(^81\) To improve the yield, again the coupling was examined with EDCI and DMAP in CH\(_2\)Cl\(_2\) furnished the ester in 57% yield.\(^82\) However, a better result was achieved under Yamaguchi conditions\(^83\) by employing 2,4,6-Trichloro benzoyl chloride, Et\(_3\)N and DMAP in toluene to obtain the ester 122 in 93% yield, which contains all 23 carbons of the target molecule (Scheme 59). The \(^1\)H NMR and \(^{13}\)C NMR spectra were in full accord with the product where TBS, 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 \(m/z\ 692.4883\ [M + NH_4]^+\) in ESI-HRMS spectrum was confirmed the formation of ester. Deprotection of the PMB ether in 122 upon treatment with DDQ\(^79\) afforded the desired primary alcohol 123 in 95% yield. \(^1\)H NMR revealed the absence of a set of two doublets at \(\delta 7.21, 6.81\) ppm, a quartet at \(\delta 4.39\) ppm for two benzylic protons and a singlet at \(\delta 3.36\) ppm for three methoxy protons of PMB group and also \(^{13}\)C NMR spectra revealed the absence of characteristic peaks for PMB group. A peak at 3466 cm\(^{-1}\) appeared in IR spectreum further confirmed the introduction of a hydroxyl group. The resulting primary alcohol 123 was oxidized to aldehyde 95 with Dess-Martin periodinane\(^80\) reagent which was unstable in nature and quickly purified by a short flash column chromatography and directly used for the next step without further characterization.
The next important task was to perform the Prins macrocyclization. As expected, the construction of 18-membered macrocycle 61 by intramolecular Prins-cyclization\(^{84}\) of aldehyde 95 was a significant challenge. Initially, macrocyclization was taken place by using 10 equiv of TESOTf and 15 equiv of TMSOAc in 0.01M solution of AcOH and subsequent hydrolysis afforded the macrolide 61 with very low yield. After extensive investigations, we eventually found that treatment of the aldehyde 95 with >30 equiv of TMSOAc and TESOTf in 0.01M solution of AcOH resulted in the Prins adduct and hydrolysis with K\(_2\)CO\(_3\) in MeOH furnished macrolide 61 in 72% yield over three steps. This macrocyclization with high diastereoselectivity (dr > 97:3) and good yield provides an additional example of the powerful and versatile nature of the Prins-macrocyclization strategy. The final target was characterized by \(^1\)H NMR, \(^{13}\)C NMR, IR, ESI-HRMS spectra which were in good agreement with the data mentioned by Kozmin and co-workers and also the analytical data \textit{i.e.} optical rotation value was in complete agreement with the reported values.\(^{85}\)
In conclusion, our investigations into the allylation of a δ-hydroxy α,β-unsaturated aldehyde with an allyltrimethyl silane in the presence of a catalytic amount of molecular iodine as a protocol combined with the intramolecular Prins-macrocyclization has led to a concise formal total synthesis of leucascandrolide A, which proceeded in only a 20-step longest linear sequence with a 11.5% overall yield starting from a known epoxide.
Experimental Section
1.6. EXPERIMENTAL SECTION

1.6.1. 1-((but-3-enyloxy)methyl)-4-methoxybenzene (102)

To a suspension of NaH (10.0 g, 417 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (400 mL) was added dropwise a solution of 3-buten-1-ol 101 (15.0 g, 208 mmol) at 0 °C. To this reaction mixture TBAI (0.05 g) and PMB bromide (30 mL, 250 mmol) were added subsequently and stirring was continued for 2 h at the same temperature and overnight at room temperature. The reaction mixture was quenched by small crushed ice flakes until a clear solution (biphasic) has formed. The reaction mixture was extracted with EtOAc (2 x 200 mL). The organic extracts were washed with water (1 x 100 mL), brine (1 x 100 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvents followed by column chromatography afforded the pure product 102 (32.06 g, 95% yield) as a colorless liquid.

1.7.2. 2-(2-(4-methoxybenzyloxy)ethyl)oxirane (103)

To an olefin 102 (31.75 g, 196 mmol) in dry CH₂Cl₂ (300 mL) at 0 °C was added slowly m-chloroperbenzoic acid (50.71 g, 294 mmol) as a solid and the reaction mixture was stirred for 1 h. The solution was washed thoroughly with cold aqueous NaOH solution (19.60 g, 490 mmol) and the organic layer was separated. Evaporation of the solvent after drying over anhydrous Na₂SO₄ yielded the crude epoxide, which was purified by column chromatography to afford 103 as a viscous liquid (32.09 g, 92% yield).

IR (Neat) : ν_max 3033, 2860, 1603, 1495, 1258, 1100, 1013, 911 cm⁻¹;

¹H NMR (CDCl₃, 300MHz) : δ 7.20 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.54 (m, 2H), 2.98 cm⁻¹;
1.6.3. (S)-2-(2-(4-methoxybenzoyloxy)ethyl)oxirane (100)

A mixture of (S,S)-(−)-N-N′-Bis(3,5-dimethyl salicylidene)-1,2-cyclohexanediamino-cobalt-II 105 (0.54 g, 0.89 mmol) toluene (4 mL) and acetic acid (0.1 mL, 1.78 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The oxirane 103 (31.68 g, 178 mmol) was added in one portion, and the stirred mixture was cooled in an ice water bath. Water (1.8 mL, 98 mmol) was slowly added and the temperature of the reaction mixture was maintained in such a way that it never rises more than 20 °C. After 1 h, addition was complete. The ice bath was removed and the reaction mixture was stirred for 36 h. The crude reaction mixture was purified by column chromatography to afford the chiral epoxide 100 (14.16, 45% yield) as colorless oil.

1H NMR and 13C NMR are similar to that of compound 103.

IR (KBr): ν_{max} 3032, 2860, 1603, 1495, 1258, 1101, 912 cm⁻¹.

EIMS: m/z Calcd for C₁₃H₂₀O₅Na [M+Na]^+: 231.0628, found 231.0631.

1.6.4. (R)-1-(4-Methoxybenzoyloxy)hex-5-en-3-ol (106):

A freshly prepared vinyl magnesium bromide (76.9 mL, 76.92 mmol) (1 M solution in THF) was added drop wise to a solution of Cul (0.73 g, 3.85 mmol) in THF (50 mL) at –20 °C. The mixture was stirred from 30 minutes and chiral epoxide 100 (8.0 g, 38.46
mmol) was added in THF (50 mL) dropwise to the above mixture. After 2 h, the reaction (monitored by TLC) was quenched with saturated solution of NH₄Cl (75 mL) and diluted with diethyl ether (50 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 75 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get the crude mass. Purification by flash column chromatography over silica gel (ethyl acetate: hexane = 1:9) afforded the desired homoallyl alcohol 106 (7.7 g, 85%) as a colorless oil.

[α]D²⁵ : +4.2 (c 1.1, CHCl₃);
IR (neat, KBr) : νmax 3434, 3074, 2933, 2862, 1613, 1513, 1464, 1302, 1249, 1174 cm⁻¹;
¹H NMR (300 MHz, CDCl₃) : δ 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.83 (m, 1H), 5.14-5.06 (m, 2H), 4.45 (s, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.76-3.57 (m, 2H), 2.94 (br s, 1H), 2.23 (t, J = 6.8 Hz, 2H), 1.81-1.71 (m, 2H) ppm;
¹³C NMR (75 MHz, CDCl₃) : δ 159.2, 134.8, 130.0, 129.3, 117.4, 113.8, 72.9, 70.4, 68.6, 55.2, 41.9, 35.8 ppm;
ESI-HRMS : m/z Calcd for C₁₃H₂₀O₅Na [M+Na]⁺: 259.1305, found 259.1306.

1.6.5. (R)-1-Methoxy-4-((3-methoxyhex-5-enyloxy)methyl)benzene (107):

To a suspension of NaH (1.38 g, 34.74 mmol, 60% in mineral oil) in dry THF (50 mL), homoallyl alcohol 106 (4.1 g, 17.37 mmol) dissolved in dry THF (100 mL), was slowly added at 0 °C under N₂ atmosphere. The suspension was stirred for 1 h at room temperature. Then, methyl iodide (2.35 mL, 34.74 mmol) was added slowly at 0 °C to the above reaction mixture and then it was allowed to stir at room temperature for 4 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of NH₄Cl (50 mL) at 0 °C and diluted with ethyl acetate (100 mL). The two layers were separated and the aqueous layer was
extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 75 mL), dried over anhydrous Na$_2$SO$_4$ and solvent was removed under reduced pressure to obtain the crude mass which on purification over silica gel column chromatography (ethyl acetate: hexane = 1:19) afforded methyl ether 107 (4.08 g, 94%) as a light yellow liquid.

\[ \alpha \]$_D^{25}$ : $-15.5$ (c 0.95, CHCl$_3$);  
IR (neat, KBr) : $\nu_{\text{max}}$ 3074, 2932, 2854, 2837, 1613, 1513, 1464, 1248, 1094, 1036, 915, 821 cm$^{-1}$;  
$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.21 (d, $J = 8.3$ Hz, 2H), 6.83 (d, $J = 9.1$ Hz, 2H), 5.77 (m, 1H), 5.09-5.00 (m, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.56-3.44 (m, 2H), 3.38 (m, 1H), 3.32 (s, 3H), 2.25 (t, $J = 6.3$ Hz, 2H), 1.8-1.63 (m, 2H) ppm;  
$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 159.0, 134.4, 130.5, 129.1, 116.9, 113.6, 77.3, 72.5, 66.4, 56.6, 55.1, 37.8, 33.8 ppm;  
ESI-HRMS : $m/z$ calcd. for C$_{15}$H$_{22}$NaO$_3$ [M + Na]$^+$: 273.1461, found 273.1455.

1.6.6. (R,E)-5-Methoxy-7-(4-methoxybenzyl)hept-2-enal (108):

\[
\begin{align*}
\text{OHC} & \quad \begin{array}{c}
\text{OMe} \\
\text{OPMB}
\end{array} \\
\end{align*}
\]

To a solution of methyl ether compound 107 (4.0 g, 16.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added Hoveyda-Grubbs catalyst (0.98 mg, 1.6 mmol) followed by acrolein (9.0 g, 160.0 mmol) at room temperature under nitrogen atmosphere and the resulting mixture was stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), it was concentrated to dryness under reduced pressure and the crude oil was directly purified by short flash column chromatography over silica gel (ethyl acetate: hexane = 1:7) furnished the desired \(\alpha,\beta\) unsaturated aldehyde 108 (4.1 g, 92%) as a colorless liquid.

\[ \alpha \]$_D^{25}$ : $-10.4$ (c 0.55, CHCl$_3$);
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IR (neat, KBr) : \( \nu_{\text{max}} \) 2935, 2861, 2837, 2740, 1690, 1513, 1248, 1093, 1034, 821 cm\(^{-1} \);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \( \delta \) 9.48 (d, \( J = 7.9 \) Hz, 1H), 7.20 (d, \( J = 8.5 \) Hz, 2H), 6.84 (d, \( J = 8.5 \) Hz, 2H), 6.78 (m, 1H), 6.12 (dd, \( J = 7.9, 15.9 \) Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.57-3.42 (m, 3H), 3.33 (s, 3H), 2.63-2.40 (m, 2H), 1.85-1.63 (m, 2H) ppm;

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : \( \delta \) 193.7, 159.1, 154.4, 134.8, 129.2, 113.7, 76.6, 72.6, 66.0, 56.9, 55.1, 36.7, 34.0 ppm;

ESI-HRMS : m/z calcd. for C\(_{16}\)H\(_{22}\)NaO\(_4\) [M+Na]\(^+\) : 301.1410, found 301.1407.

1.6.7. (E)-Ethy 3-((2R,3R)-3-((S)-2-methoxy-4-(4-methoxybenzyloxy)butyl)oxiran-2-yl)acrylate (109):

![Chemical Structure](image)

To a stirred solution of \( \alpha,\beta \) unsaturated aldehyde 108 (3.9 g, 14.03 mmol) in CH\(_2\)Cl\(_2\) (40 mL) at 0 °C was added TMS-protected diphenyl prolinol catalyst (0.46 g, 1.40 mmol) followed by H\(_2\)O\(_2\) (35 % aq., 1.23 mL, 18.23 mmol). The reaction mixture was stirred vigorously at room temperature until total consumption of the starting material (monitored by TLC). Then Ph\(_3\)P=CHCO\(_2\)Et (5.8 g, 16.83 mmol) was added in one portion at 0 °C and stirred for another 1 h at room temperature. After removal of the solvents under reduced pressure, the residue was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:8) to give the desired epoxy compound 109 (3.69 g, 80%) as a colorless oil.

\([\alpha]_D^{25}\) : +5.4 (c 1.25, CHCl3);

IR (neat, KBr) : \( \nu_{\text{max}} \) 2979, 2935, 2861, 1720, 1657, 1613, 1513, 1303, 1249, 1182, 1092, 1035, 853, 821 cm\(^{-1} \);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \( \delta \) 7.19 (d, \( J = 8.5 \) Hz, 2H), 6.82 (d, \( J = 8.5 \) Hz, 2H), 6.64 (dd, \( J = 6.8, 15.3 \) Hz, 1H), 6.07 (d, \( J = 15.9 \) Hz, 1H), 4.39 (s, 2H), 4.18 (q, \( J = 6.7 \) Hz, 2H),
3.79 (s, 3H), 3.55-3.41 (m, 3H), 3.34 (s, 3H), 3.17 (d, $J = 7.6$ Hz, 1H), 2.97 (dd, $J = 6.8, 15.4$ Hz, 1H), 1.86-1.64 (m, 4H), 1.29 (t, $J = 7.6$ Hz, 3H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 165.6, 159.2, 144.5, 130.4, 129.3, 123.8, 113.8, 75.9, 72.7, 66.1, 60.6, 58.6, 57.4, 56.7, 55.2, 37.0, 34.4, 14.2 ppm;

ESI-HRMS : $m/z$ calcd. C$_{20}$H$_{28}$NaO$_6$ for [M + Na]$^+$: 387.1778, found 387.1791.

1.6.8. (4$S$,5$R$,7$S$,E)-Ethyl 5-hydroxy-7-methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-enoate(110):

The epoxy compound 109 (3.5 g, 9.3 mmol) was taken in a 250 mL RB and to it, CH$_2$Cl$_2$ (70 mL) was added under nitrogen atmosphere. The reaction mixture was cooled to $-40$ °C. Trimethyl aluminium (46.6 mL, 93.1 mmol, 2M in toluene) was slowly added under nitrogen atmosphere at the same temperature. After 10 min, H$_2$O (1.0 mL, 55.9 mmol) was added very carefully and slowly so that the internal temperature did not change. After effervescence ceased, it was allowed to stir for further 3 h at $-40$ °C and TLC showed the complete consumption of the starting material. It was quenched very slowly with saturated NH$_4$Cl (50 mL) and diluted with CH$_2$Cl$_2$ (100 mL). HCl (1.0 N, 50 mL) was added and vigorously stirred until a clear separation of the two layers took place. The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (2 x 100 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na$_2$SO$_4$, evaporated to dryness and then purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) to get the desired product 110 (3.35 g, 92%) as a colorless oil.

$[\alpha]D^{25}$ : $-4.5$ (c 1.45, CHCl$_3$);

IR (neat, KBr) : $\nu_{max}$ 3472, 2936, 2874, 2836, 1713, 1651, 1613, 1513, 1301, 1250, 1180, 1092, 1036, 847, 821 cm$^{-1}$;
1H NMR (300 MHz, CDCl₃) : δ 7.18 (d, J = 8.3 Hz, 2H), 6.93 (dd, J = 7.5, 15.9 Hz, 1H), 6.82 (d, J = 8.3 Hz, 2H), 5.78 (d, J = 15.9 Hz, 1H), 4.38 (s, 2H), 4.17 (q, J = 6.8 Hz, 2H), 3.85 (m, 1H), 3.79 (s, 3H), 3.61 (m, 1H), 3.51-3.42 (m, 2H), 3.33 (s, 3H), 2.95 (br. s, 1H), 2.31 (m, 1H), 1.92 (m, 1H), 1.77-1.63 (m, 2H), 1.45 (m, 1H), 1.29 (t, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H) ppm;

13C NMR (75 MHz, CDCl₃) : δ 166.5, 159.1, 150.6, 130.3, 129.3, 121.8, 113.7, 76.8, 72.7, 71.4, 66.3, 60.2, 57.1, 55.2, 42.8, 36.6, 33.1, 15.5, 14.2 ppm;

ESI-HRMS : m/z calcd. for C₂₁H₃₂NaO₆ [M + Na]⁺: 403.2096, found 403.2083.

1.6.9. (4S,5R,7S,E)-7-Methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-ene-1,5-diol (111):

To a stirred solution of α,β-unsaturated ester 110 (3.2 g, 8.2 mmol) was dissolved in CH₂Cl₂ (60 mL) and cooled to −78 °C under nitrogen atmosphere. DIBAL-H (14.5 mL, 20.4 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 CH₂Cl₂ (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 CH₂Cl₂ (3 x 50 mL). The combined organic layer was washed with brine (2 x 75 mL), dried over anhydrous Na₂SO₄, evaporated to dryness under vacuum which on silica gel column chromatography (ethyl acetate: hexane = 2:3) produced the desired α,β-unsaturated alcohol 111 (2.43 g, 88%).

[α]D²⁵ : +3.9 (c 0.73, CHCl₃);

IR (neat, KBr) : νmax 3408, 2933, 2871, 1612, 1513, 1302, 1248,
Chapter I, Experimental Section

1H NMR (300 MHz, CDCl₃) : \( \delta 7.19 \) (d, \( J = 8.9 \) Hz, 2H), \( 6.82 \) (d, \( J = 8.3 \) Hz, 2H), \( 5.60 \) (d, \( J = 5.3 \) Hz, 2H), \( 4.39 \) (s, 2H), \( 4.02 \) (d, \( J = 3.8 \) Hz, 2H), \( 3.78 \) (s, 3H), \( 3.67-3.55 \) (m, 2H), \( 3.52-3.41 \) (m, 2H), \( 3.34 \) (s, 3H), \( 2.13 \) (m, 1H), \( 1.94-1.63 \) (m, 2H), \( 1.61-1.46 \) (m, 2H), \( 0.98 \) (d, \( J = 6.8 \) Hz, 3H) ppm;

13C NMR (75 MHz, CDCl₃) : \( \delta 159.1, 134.3, 130.0, 129.3, 113.7, 76.6, 72.3, 71.9, 66.4, 63.4, 57.1, 55.2, 42.7, 37.1, 33.4, 16.3 \) ppm;


1.6.10. (4S,5R,7S,E)-5-Hydroxy-7-methoxy-9-(4-methoxybenzoyloxy)-4-methylnon-2-enal (99):

To a stirred solution of diol 111 (2.35 g, 6.95 mmol) in CH₂Cl₂ (40 mL) at 0 °C, iodobenzenediaacetate (2.46 g, 7.65 mmol) followed by TEMPO (0.217 g, 1.39 mmol) was added and allowed to stir at ambient temperature for 3 h. After conversion of the primary alcohol completely to aldehyde (monitored by TLC), the reaction mixture was quenched with saturated solution of Na₂S₂O₅ (20 mL) and extracted with CH₂Cl₂ (3 x 40 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporation of solvent led to crude aldehyde which on purification by short flash chromatography over silica gel (ethyl acetate: hexane = 3:7) afforded aldehyde 99 (2.1 g, 90%) as a thick viscous liquid and used immediately for the next reaction.

\( [\alpha]_D^{25} \) : +2.1 (c 1.0, CHCl₃);

IR (neat, KBr) : \( \nu_{max} \), 3459, 2936, 2874, 2837, 1689, 1613, 1513, 1302, 1248, 1089, 1034, 821 cm⁻¹;
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\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] : $\delta$ 9.49 (d, $J = 8.3$ Hz, 1H), 7.20 (d, $J = 9.1$ Hz, 2H), 6.94 (m, 1H), 6.84 (d, $J = 9.1$ Hz, 2H), 6.08 (m, 1H), 4.40 (s, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 3.64 (m, 1H), 3.52-3.43 (m, 2H), 3.34 (s, 3H), 2.43 (m, 1H), 1.95 (m, 1H), 1.80-1.67 (m, 2H), 1.55-1.44 (m, 2H), 1.10 (d, $J = 6.8$ Hz, 2H) ppm;

\[ ^13C \text{NMR (75 MHz, CDCl}_3 \] : $\delta$ 194.1, 160.4, 159.2, 132.9, 130.2, 129.3, 113.7, 80.1, 72.7, 71.6, 66.2, 57.1, 55.2, 43.3, 36.7, 32.9, 15.6 ppm;

ESI-HRMS : m/z calcd. for C_{19}H_{28}NaO_5 [M + Na]^+ : 359.1829, found 359.1830.

1.6.11. (2R,3S,6R)-6-Allyl-2-((S)-2-methoxy-4-(4-methoxybenzyl)oxy)butyl)-3-methyl-3,6-dihydro-2H-pyran (98):

![Diagram of the molecule]

To a stirred solution of $\delta$-hydroxy $\alpha,\beta$-unsaturated aldehyde 99 (2.0 g, 5.95 mmol), and allyltrimethyl silane (1.45 mL, 8.93 mmol) in THF (30 mL) was added iodine (0.15 g, 0.59 mmol) at 0 °C and allowed to come to room temperature. After completion of the reaction (as indicated by TLC), it was quenched with saturated solution of Na$_2$S$_2$O$_3$ (10 mL) and diluted with tert-butyl methyl ether (20 mL). The organic layer was separated and the aqueous layer extracted with tert-butyl methyl ether (TBME) (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to give pale yellow oil. This was finally purified by column chromatography over silica gel (ethyl acetate: hexane = 1:19) to obtain the cyclized product 98 (2.1 g, 96%).

$[\alpha]_D^{25}$ : +14.2 (c 0.8, CHCl$_3$);

IR (neat, KBr) : $\nu_{max}$ 3482, 2925, 2857, 1729, 1612, 1513, 1459, 1367, 1300, 1247, 1178, 1091, 1037, 914, 820, 723
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$^1$H NMR (300 MHz, CDCl$_3$) : \(\delta\) 7.27 (d, \(J = 8.5\) Hz, 2H), 6.87 (d, \(J = 8.5\) Hz, 2H), 5.86 (m, 1H), 5.70-5.59 (m, 2H), 5.16-5.00 (m, 2H), 4.45-4.38 (m, 2H), 4.16 (m, 1H), 3.81-3.74 (m, 3H), 3.62 (m, 1H), 3.57-3.46 (m, 3H), 3.36-3.26 (m, 3H), 2.41 (m, 1H), 2.26 (m, 1H), 2.00-1.66 (m, 4H), 1.53 (m, 1H), 0.97 (d, \(J = 7.2\) Hz, 3H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : \(\delta\) 159.0, 135.2, 131, 130.6, 129.2, 127.9, 116.7, 113.7, 74.8, 72.6, 71.5, 71.0, 66.5, 57.0, 55.2, 38.8, 38.8, 34.2, 34.0, 18.0 ppm;

ESI-HRMS : \(m/z\) calcd. for C$_{22}$H$_{32}$NaO$_4$ [M + Na]$^+$: 383.2198, found 383.2195.

1.6.12. 2-((2$^R$,5$^S$,6$^R$)-6-((S)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro -2$^H$-pyran-2-yl)acetaldehyde (112):

To a stirred solution of the compound 98 (1.8 g, 5.0 mmol) in 1,4-dioxane (25 mL) was added 2,6-lutidine (2.33 mL, 20.0 mmol) at room temperature. NaIO$_4$ (4.28 g, 20.0 mmol) was dissolved in distilled water (10 mL) and then added to the above reaction mixture. Finally, OsO$_4$ (0.5 mL, 0.5 mmol, 1 M solution in toluene) was added and stirring was continued for 3 h under dark at room temperature. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with saturated aq. NaHSO$_3$ (30 mL) solution. Organic solvent was removed under reduced pressure and the residual aqueous layer was extracted with $t$-butyl methyl ether (3 x 50 mL). The combined organic layer was washed with 1 N HCl (3 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to obtain the crude mass which was passed through a small pad of
silica gel (ethyl acetate: hexane = 1:3) to afford aldehyde 112 as a colorless liquid which was immediately used for the next step.

1.6.13. 2-((2R,5S,6R)-6-((S)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro-2H-pyran-2-yl)acetic acid (129):

To a solution of aldehyde 112 (1.78 g, 4.92 mmol) in tert-butyl alcohol (25 mL), 2-methyl-2-butene (5.8 mL, 5.8 mmol, 1 M solution in THF) was added at room temperature. NaH$_2$PO$_4$ (1.8 g, 11.6 mmol) and sodium chlorite (0.59 g, 7.38 mmol) were dissolved in water (10 mL) to make a clear solution which subsequently added to the reaction mixture at 0 °C. It was then allowed to stir for further 3 h at room temperature. The reaction mixture was diluted with water (15 mL). The organic solvent was removed under reduced pressure and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate: hexane = 2:5) to afford the acid 113 (1.53 g, 81% over two steps) as a colorless oil.

$[^\alpha]_D^{25}$: +28.9 (c 1.16, CHCl$_3$);

IR (neat, KBr): $\nu_{max}$ 3029, 2931, 2876, 1732, 1713, 1612, 1513, 1301, 1248, 1094, 847, 821 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.24 (d, $J = 8.3$ Hz, 2H), 6.84 (d, $J = 8.3$ Hz, 2H), 5.66 (s, 2H), 4.60 (m, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.36-3.41 (m, 4H), 3.31 (s, 3H), 2.64 (dd, $J = 9.1, 15.1$ Hz, 1H), 2.45 (dd, $J = 4.5, 15.1$ Hz, 1H), 1.98 (t, $J = 6.8$ Hz, 1H), 1.81 (q, $J = 6.0$ Hz, 1H), 1.72 (m, 1H), 1.52 (dt, $J = 1.5, 9.0$ Hz, 1H), 0.96 (d, $J = 6.8$ Hz, 1H) ppm;
13C NMR (75 MHz, CDCl3) : δ 174.8, 159.1, 132.1, 130.3, 129.3, 126.6, 113.7, 75.1, 72.7, 71.5, 68.7, 66.6, 56.6, 55.2, 39.0, 38.0, 34.1, 34.0, 17.7 ppm;


To a stirred solution of acid 113 (1.3 g, 3.44 mmol) in ether at 0 °C, was added freshly prepared diazomethane solution in ether (25 mL). It was stirred for 10 min at the same temperature and then quenched with saturated solution of Na2S2O3 (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h to evaporate excess diazomethane. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na2SO4 and evaporated under reduced pressure to get the crude mass. The crude mass was purified by silica gel column chromatography (ethyl acetate: hexane = 1:8) to afford methyl ester 114 (1.29 g, 96%) as a light yellow liquid.

[α]D 25 : +25.1 (c 2.0, CHCl3);

IR (neat, KBr) : νmax 3027, 2951, 2875, 1737, 1612, 1513, 1458, 1301, 1248, 1197, 1095, 1036, 847, 821 cm⁻¹;

1H NMR (300 MHz, CDCl3) : δ 7.20 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 2.64 (s, 2H), 4.58 (m, 1H), 4.39 (s, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.55-3.36 (m, 4H), 3.32 (s, 3H), 2.61 (dd, J = 9.1, 15.1 Hz, 1H), 2.41 (dd, J = 4.5, 15.1 Hz, 1H), 1.98-1.42 (m, 5H), 0.97 (d, J = 6.8 Hz, 3H) ppm;
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$^1$C NMR (75 MHz, CDCl$_3$) : $\delta$ 171.5, 159.1, 132.1, 131.9, 129.2, 127.0, 113.7, 74.8, 72.6, 71.3, 68.7, 66.6, 57.0, 55.2, 51.6, 39.1, 38.8, 36.7, 34.1, 17.8 ppm;

ESI-HRMS: $m/z$ calcd. for C$_{22}$H$_{32}$NaO$_6$ [M + Na]$^+$: 415.2096, found 415.2087.


![Chemical Structure](image)

Pd/C (10%) (50 mg) was added to a stirred solution of the compound 114 (1.2 g, 3.06 mmol) in toluene (20 mL) followed by catalytic amount of triethylamine at room temperature under hydrogen atmosphere. The mixture was stirred for 1 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 and then thoroughly washed with ethyl acetate (3 x 15 mL). The filtrate was concentrated under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate: hexane = 1:7) furnished the desired product 115 (1.12 g, 93%) as a colorless liquid.

$[\alpha]_{D}^{25}$ : +30.4 (c 1.9, CHCl$_3$);

IR (neat, KBr) : $\nu_{max}$ 2933, 2873, 1740, 1612, 1513, 1460, 1301, 1248, 1171, 1092, 1036, 846, 821 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.29 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 4.47 (s, 2H), 4.26 (m, 1H), 3.86 (m, 3H), 3.60-3.42 (m, 4H), 3.37 (s, 3H), 2.70 (dd, $J = 8.1$, 14.9 Hz, 1H), 2.50 (dd, $J = 5.8$, 14.9 Hz, 1H), 1.89-1.32 (m, 7H), 1.03 (d, $J = 6.2$ Hz, 3H) ppm;

65
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.9, 159.1, 130.7, 129.2, 113.7, 74.9, 73.3, 72.6, 68.0, 66.7, 57.2, 55.2, 51.5, 38.3, 38.2, 34.3, 33.6, 27.5, 26.3, 18.3 ppm;

ESI-HRMS: $m/z$ calcd. for C$_{22}$H$_{34}$NaO$_6$ [M + Na]$^+$: 417.2248, found 417.2240.


![Structure of the molecular formula](image)

To a stirred solution of the dimethyl methyl phosphonate (1.26 g, 10.15 mmol) in THF (30 mL), n-BuLi (4.1 mL, 10.15 mmol, 2.5 M in hexane) was slowly added at $-78$ °C under nitrogen atmosphere and allowed to slowly warm to 0 °C. After 1 h, the reaction mixture was again cooled to $-78$ °C and to it, ester 115 (1.0 g, 2.54 mmol) dissolved in THF (15 mL) was slowly added and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH$_4$Cl (30 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (100 mL) and dried over Na$_2$SO$_4$. The organic layer was concentrated under reduced pressure to obtain the crude mass which on purification by silica gel column chromatography (ethyl acetate: hexane = 5:1) afforded the desired keto phosphonate 116 (1.12 g, 92%) as a colorless liquid which was immediately used for next step without further characterization.
1.6.17. \((E)-1-((2S,5S,6R)-6-((S)-2-Methoxy-4-(4-methoxybenzyl)oxy)butyl)-5-methyl-tetra-hydro-2H-pyran-2-yl)-6-methylhept-3-en-2-one \((118)\):

To a stirred solution of the keto phosphonate \(116\) (1.0 g, 2.06 mmol) in THF (20 mL) was added NaHMDS (2.67 mL, 2.67 mmol, 1M in THF) at \(-78^\circ\)C under nitrogen atmosphere and allowed to come to 0 °C. After 1 h, the reaction mixture was again cooled to \(-78^\circ\)C and isovaleraldehyde \(117\) (0.354 g, 4.12 mmol) was slowly added to it and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH\(_4\)Cl (20 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL) and dried over anhydrous Na\(_2\)SO\(_4\). The organic layer was concentrated to dryness under reduced pressure to get the crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:6) furnished the desired keto \(118\) (0.74 g, 81%) as a colorless liquid.

\([\alpha]_D^{25}\) : +19.1 (c 1.4, CHCl\(_3\));

IR (neat, KBr) : \(v_{max}\) 2956, 2927, 2854, 1717, 1606, 1513, 1463, 1256, 1169, 1091, 1034, 848, 821 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \(\delta\) 7.27 (d, \(J = 8.3\) Hz, 2H), 6.87 (d, \(J = 8.3\) Hz, 2H), 6.81 (dd, \(J = 8.3, 15.9\) Hz, 1H), 6.11 (d, \(J = 15.9\) Hz, 1H), 4.43 (s, 2H), 4.30 (m, 1H), 3.80 (s, 3H), 3.56-3.46 (m, 4H), 3.30 (s, 3H), 2.90 (dd, \(J = 6.8, 15.9\) Hz, 1H), 2.70 (dd, \(J = 6.8, 15.9\) Hz, 1H), 2.09 (t, \(J = 6.8\) Hz, 2H), 1.85-1.24 (m, 10H), 0.96 (d,
$J = 6.0 \text{ Hz, } 3\text{H}$, 0.92 (dd, $J = 6.8, 15.9 \text{ Hz, } 6\text{H}$) ppm;

$^{13}\text{C NMR (75 MHz, CDCl}_3$) : $\delta 198.4, 159.0, 146.6, 131.6, 130.6, 129.2, 113.6, 74.8, 73.2, 72.6, 67.6, 66.6, 57.1, 55.2, 43.5, 41.6, 38.2, 36.2, 34.0, 33.6, 27.8, 27.6, 26.4, 22.3, 18.3 ppm;

ESI-HRMS : $m/z$ calcd. for C$_{27}$H$_{42}$NaO$_5$ [M + Na]$^+$: 469.2924, found 469.2940.


To a 50 mL round bottom flask charged with a magnetic stir bar was added S-CBS catalyst (0.087 g, 0.314 mmol) in THF (15 mL) under argon. The reaction was cooled to –20 °C and BH$_3$•Me$_2$S (1.57 mL, 3.14 mmol, 2M in THF) was added. To this reaction mixture, a solution of ketone 118 (0.71 g, 1.57 mmol) dissolved in THF (8 mL) was added dropwise. The reaction was stirred for 8 h at –20 °C and TLC checked which showed complete consumption of the starting material. MeOH (5 mL) was carefully added to quench excess BH$_3$. The reaction was diluted with saturated aqueous NH$_4$Cl (20 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried with anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) giving the desired alcohol 96 (0.576 g, 82%) as a colorless liquid.

$[\alpha]_D^{25}$ : +17.9 ($c$ 0.9, CHCl$_3$);

IR (neat, KBr) : $\nu_{\text{max}}$ 3454, 2951, 2929, 2869, 1613, 1513, 1302,
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1H NMR (300 MHz, CDCl₃) : δ 7.26 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 5.62 (m, 1H), 5.46 (dd, J = 6.0, 15.3 Hz, 1H), 4.44 (s, 2H), 4.33 (m, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.67-3.57 (m, 2H), 3.57-3.50 (m, 2H), 3.35 (s, 3H), 1.94-1.32 (m, 14H), 1.01 (d, J = 6.2 Hz, 3H), 0.87 (d, J = 6.6 Hz, 6H) ppm;

13C NMR (75 MHz, CDCl₃) : δ 159.1, 134.2, 133.8, 130.3, 129.4, 113.7, 74.9, 73.6, 72.6, 68.7, 66.9, 66.5, 57.2, 55.2, 41.6, 40.8, 37.3, 34.0, 32.9, 28.2, 27.5, 26.0, 22.3, 22.2, 18.5 ppm;

ESI-HRMS : m/z calcd. for C_{27}H_{44}NaO_5 [M + Na]^+: 471.3081, found 471.3069.

1.6.19. (R)-tert-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (119):

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\begin{center}
\includegraphics[width=0.2\textwidth]{119.png}
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To a stirred solution of alcohol 106 (0.5 g, 2.12 mmol) in CH₂Cl₂ (30 mL) under nitrogen atmosphere, was added 2,6-lutidine (0.6 mL, 5.29 mmol) followed by TBSOTf (0.97 mL, 4.24 mmol) at 0 °C and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and diluted with CH₂Cl₂ (50 mL). The organic layer was separated and quickly washed with 1 N HCl (2 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄, evaporated to dryness under vacuum to obtain the crude product which on purification by silica gel column chromatography purification (ethyl acetate: hexane produced = 1:19) furnished the desired TBS ether 119 (0.69 g, 93%).

[α]₀²⁵ : −8.1 (c 0.33, CHCl₃);

IR (neat, KBr) : νmax 3075, 2999, 2953, 2930, 2857, 1613, 1513, 1463, 1249, 1093, 1040, 912, 836 cm⁻¹;
1H NMR (300 MHz, CDCl3) : δ 7.19 (d, J = 9.1 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 5.77 (m, 1H), 5.04-4.96 (m, 2H), 4.36 (q, J = 7.5, 18.8 Hz, 2H), 3.87 (m, 1H), 3.78 (s, 3H), 3.45 (m, 2H), 2.19 (m, 2H), 1.68 (m, 2H), 0.87 (s, 9H), 0.03 (d, J = 3.7 Hz, 6H) ppm;

13C NMR (75 MHz, CDCl3) : δ 159.0, 134.9, 130.6, 129.2, 116.9, 113.6, 72.5, 68.9, 66.6, 55.1, 42.2, 36.6, 25.8, 18.0, −4.4, −4.8 ppm;

ESI-HRMS : m/z calcd. for C26H34NaO3Si [M + Na]+: 373.2169, found 373.2181.

1.6.20. (R)-3-(tert-Butyldimethylsilyloxy)hex-5-en-1-ol (120):

To a solution of PMB protected compound 119 (0.55 g, 1.57 mmol) in CH2Cl2 (20 mL) and water (2 mL) was added DDQ (0.535 g, 2.36 mmol) at room temperature and allowed to stir for 2 h at the same temperature. After completion of the reaction, it was quenched with saturated NaHCO3 (20 mL) solution. The two layers were separated and the aqueous layer extracted with CH2Cl2 (2 x 30 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na2SO4 and evaporated to dryness to give red colored crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:7) to afford the desired primary alcohol 120 (0.34 g, 94%) as a colorless liquid.

[α]D^25 : −26.0 (c 0.46, CHCl3);

IR (neat, KBr) : νmax 3350, 3078, 2953, 2930, 2858, 1641, 1463, 1255, 1071 cm⁻¹;

1H NMR (300 MHz, CDCl3) : δ 5.74 (m, 1H), 5.09-4.99 (m, 2H), 3.95 (m, 1H), 3.83-3.62 (m, 2H), 2.28 (t, J = 6.6 Hz, 2H), 2.16 (br s, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 0.89 (s, 9H), 0.09 (d, J = 2.4 Hz, 6H) ppm;
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$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 134.5, 117.2, 71.0, 59.9, 41.6, 25.7, 35.7, 17.9, $-4.5$, $-4.9$ ppm;

ESI-HRMS: $m/z$ calcd. for C$_{12}$H$_{26}$NaO$_2$Si [M + H]$^+$: 231.1780, found 231.1775.

1.6.21. (R)-3-(tert-Butyldimethylsilyloxy)hex-5-enal (121):

![Chemical Structure of (R)-3-(tert-Butyldimethylsilyloxy)hex-5-enal (121)]

To a stirred solution of primary alcohol 120 (0.25 g, 1.09 mmol) and solid anhydrous NaHCO$_3$ (1.0 g) in CH$_2$Cl$_2$ (25 mL) at 0 °C, was added Dess-Martin periodinane (0.69 g, 1.63 mmol). The reaction mixture was stirred at 0 °C for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and washed with CH$_2$Cl$_2$ (50 mL). The filtrate was washed with saturated NaHCO$_3$ (2 x 30 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 40 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and solvent removed under reduced pressure to get crude aldehyde 121 (0.24 g) as a pale yellow liquid which was directly used in the next step.

1.6.22. (R)-3-(tert-Butyldimethylsilyloxy)hex-5-enoic acid (97):

![Chemical Structure of (R)-3-(tert-Butyldimethylsilyloxy)hex-5-enoic acid (97)]

To a solution of aldehyde 121 (0.24 g, 1.05 mmol) in tert-butyl alcohol (15 mL), 2-methyl-2-butene (1.59 mL, 1.56 mmol, 1M solution in THF) was added at room temperature. Sodium dihydrogen phosphate (0.49 g, 3.15 mmol) and sodium chlorite (0.14 g, 1.56 mmol) were dissolved in water (5 mL) to make a clear solution which subsequently added to the reaction mixture at 0 °C. It was allowed to stir for further 3 h at room temperature. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (30 mL). The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated to dryness under reduced pressure.
The crude product was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:9) to afford the desired acid 97 (0.22 g, 86% over two steps) as a colorless oil.

$[\alpha]_D^{25}$: $-18.9$ (c 0.7, CHCl$_3$);

IR (neat, KBr) : $\nu_{\text{max}}$ 3079, 2956, 2930, 2858, 1713, 1642, 1463, 1256, 1089 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 5.78 (m, 1H), 5.12-5.02 (m, 2H), 4.18 (m, 1H), 2.52-2.37 (m, 2H), 2.28 (t, $J = 6.8$ Hz, 2H), 0.86 (s, 9H), 0.06 (d, $J = 6.6$ Hz, 6H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 177.6, 133.7, 118.1, 68.8, 41.9, 41.7, 25.7, 17.9, -4.5, -5.0 ppm;

ESI-HRMS : $m/z$ calcd. for C$_{12}$H$_{24}$NaO$_3$ [M + Na]$^+$: 267.1387, found 267.1385.


To a stirred solution of the acid 97 (0.49 g, 2.01 mmol) in dry toluene (10 mL) at 0 oC, Et$_3$N (0.31 mL, 4.02 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.63 mL, 4.02 mmol) was added and stirred for 30 min at room temperature. DMAP (1.22, 10.04 mmol) and alcohol 96 (0.45 g, 1.004 mmol) was dissolved in dry toluene (10 mL) and this was added to the above mentioned solution at 0 °C and allowed to stir at room temperature for 6 h. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (50 mL) and water (25 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 40 mL). The combined organic layer was washed
with Na₂CO₃ (2 x 250 mL), brine (2 x 50 mL), dried over anhydrous Na₂SO₄ and solvent evaporated under reduced pressure to give a colorless oil which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:12) furnished the desired coupled product 122 (0.63 g, 93%, based on the starting alcohol) as a colorless liquid.

\[ \alpha \]D²⁵ : +14.3 (c 0.7, CHCl₃);  
IR (neat, KBr) :  \nu \text{max} 3076, 2953, 2928, 2856, 1734, 1613, 1513, 1463, 1302, 1249, 1171, 1091, 1037, 836 cm⁻¹;  
\(^1\)H NMR (300 MHz, CDCl₃) : δ 7.21 (d, \( J = 8.5 \) Hz, 2H), 6.81 (d, \( J = 8.9 \) Hz, 2H), 5.83-5.62 (m, 2H), 5.40-5.19 (m, 2H), 5.07-4.99 (m, 2H), 4.39 (s, 2H), 4.16 (m, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 3.60-3.42 (m, 3H), 3.36 (s, 3H), 2.41-2.35 (m, 2H), 2.31-2.18 (m, 2H), 2.01-1.23 (m, 14H), 0.92-0.83 (m, 18H), 0.03 (d, \( J = 15.8 \) Hz, 6H) ppm;  
\(^13\)C NMR (75 MHz, CDCl₃) : δ 170.7, 159.0, 134.3, 132.9, 129.7, 129.2, 128.2, 117.6, 113.7, 74.3, 72.6, 71.8, 68.7, 67.7, 66.5, 56.8, 55.2, 42.3, 41.9, 41.5, 38.8, 36.5, 34.7, 33.5, 28.2, 28.0, 26.9, 25.8, 22.3, 22.2, 18.2, 18.0, −4.6, −4.8 ppm;  
ESI-HRMS : m/z calcd. for C₃₀H₇₀NO₇Si [M + NH₄]⁺: 692.4916, found 692.4883.

1.6.24. \((R)\)-(((\(R,E\))-1-((2S,5S,6R)-6-((S)-4-Hydroxy-2-methoxybutyl)-5-methyl-tetrahydro-2-pyran-2-yl)-6-methylhept-3-en-2-yl) \(3-\)\(\text{tert-butyldimethylsilyloxy}\)hex-5-enoate (123):

To a solution of the compound 122 (0.31 g, 0.445 mmol) in CH₂Cl₂ (15 mL) and water (1 mL) at 0 °C, was added DDQ (0.152 g, 0.667 mmol) and allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated NaHCO₃ solution (10 mL) and diluted with CH₂Cl₂ (15 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na₂SO₄ and evaporated to give red colored
crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:5) afforded the desired primary alcohol 123 (0.23 g, 95%) as a colorless liquid.

\[ \alpha_D^{25} : +23.0 \text{ (c 0.52, CHCl}_3) \];

IR (neat, KBr) : \( \nu_{\text{max}} \) 3466, 3077, 2953, 2930, 1734, 1641, 1462, 1253, 1171, 1087, 836 cm\(^{-1}\);

\(^1\text{H NMR (300 MHz, CDCl}_3\) : \( \delta 5.87-5.62 \text{ (m, 2H)}, \delta 5.43-5.26 \text{ (m, 2H)}, \delta 5.08-4.99 \text{ (m, 2H)}, \delta 4.17 \text{ (m, 1H)}, \delta 3.87-3.72 \text{ (m, 2H)}, \delta 3.72-3.60 \text{ (m, 2H)}, \delta 3.42 \text{ (s, 3H)}, \delta 3.6 (m, 2H), 2.41 \text{ (d, } J = 5.5 \text{ Hz, 2H)}, 2.34-2.15 \text{ (m, 2H)}, 2.06-1.24 \text{ (m, 14H)}, 0.94 \text{ (d, } J = 5.7 \text{ Hz, 3H)}, 0.9-0.8 \text{ (m, 15H)}, 0.04 \text{ (d, } J = 11.9 \text{ Hz, 6H)} \text{ ppm};

\(^13\text{C NMR (75 MHz, CDCl}_3\) : \( \delta 171.1, 134.3, 133.0, 129.5, 117.6, 76.4, 72.9, 71.7, 68.7, 67.5, 59.8, 56.8, 42.2, 41.9, 41.5, 38.0, 36.6, 36.1, 35.1, 34.7, 28.4, 28.2, 28.0, 26.9, 25.8, 22.2, 18.3, -4.6, -4.8 \text{ ppm};

ESI-HRMS : \( m/z \) calcd. for C\(_{31}\)H\(_{58}\)NaO\(_6\)Si [M + Na]\(^+\) : 577.3895, found 577.3916.

1.6.25. \((R,E)-((2S,5S,6R)-6-((R)-2-Methoxy-4-oxobutyl)-5-methyl-tetrahydro-2H-pyran-2-yl)-6-methylhept-3-en-2-yl) 3-(tert-butyldimethylsilyloxy)hex-5-enoate (95):

To a stirred solution of primary alcohol 123 (0.15 g, 0.271 mmol) and solid anhydrous NaHCO\(_3\) (0.2 g) in CH\(_2\)Cl\(_2\) (10 mL), Dess-Martin periodinane (0.173 g, 4.062 mmol) was added at 0 oC under nitrogen atmosphere. The reaction mixture was stirred at
0 °C for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and thoroughly washed with CH₂Cl₂ (50 mL). The filtrate was washed with saturated NaHCO₃ (30 mL) solution. The aqueous layer was again extracted with CH₂Cl₂ (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get the crude aldehyde 95 (0.16 g) which was immediately used for next step without further purification and characterization.

1.6.26. Macrolide (61):

TMSOAc (1.71 mL, 11.21 mmol) was added to a solution of aldehyde 95 (0.16 mg, 0.28 mmol) in AcOH (15.0 mL) at room temperature. TESOTf (1.23 mL, 7.02 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into diethyl ether (100 mL) and washed with NaHCO₃ (4 x 100 mL). The aqueous layer was again extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to obtain the crude product which was dissolved in MeOH (10 mL) and then treated with K₂CO₃ (0.37 g, 2.89 mmol) at room
temperature. The reaction mixture was stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), it was concentrated under reduced pressure. The residue was dissolved in water (10 mL) and diethyl ether (20 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine (2 x 25 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was finally purified by flash column chromatography over silica gel (ethyl acetate: hexane = 1:2) to afford the macrolide 61 (0.104 g, 72% over three steps).

$\left[\alpha\right]_{D}^{25} : +54.7$ (c 1.18, EtOH);

IR (neat, KBr) : $\nu_{\text{max}}$ 3452, 2954, 2925, 2854, 1736, 1643, 1261, 1083, 1034 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 5.71 (m, 1H), 5.41-5.32 (m, 2H), 3.91 (m, 1H), 3.87 (m, 1H), 3.77-3.66 (m, 1H), 3.59-3.47 (m, 2H), 3.36 (s, 3H), 3.22 (m, 1H), 2.57 (dd, $J = 4.5, 13.6$ Hz, 1H), 2.44-2.30 (m, 3H), 2.09-1.96 (m, 3H), 1.95-1.83 (m, 4H), 1.36-1.23 (m, 8H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.03 (m, 1H), 0.85 (d, $J = 6.8$ Hz, 6H) ppm;

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 169.3, 132.4, 130.0, 73.6, 73.5, 73.0, 72.2, 70.8, 68.0, 63.0, 57.3, 43.0, 42.8, 41.6, 41.0, 40.8, 39.1, 35.4, 30.9, 28.1, 27.1, 24.1, 22.2, 18.2 ppm;

ESI-HRMS : $m/z$ calcd. for C$_{25}$H$_{42}$NaO$_6$ [M + Na]$^+$: 461.2874, found 461.2876.
References
1.7. REFERENCES


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