CHAPTER 1

Total synthesis of Achaetolide
INTRODUCTION

The term macrocycle refers to medium and large-ring compounds which have 7–12 or more atoms in the ring. Macrocyclic structures that have one or more ester linkages are generally referred as macrolides or macrocyclic ring lactones. Ever since their first discovery in 1952, erythromycin and oleandomycin macrolides have been an important class of antibiotics.\(^1\) It was generally believed that large ring compounds could not be synthesized or isolated because they could not adopt a tetrahedral geometry (by Bayer’s strain theory).\(^2\) However, in 1926, Ruzicka et al., elucidated the structures of two macrocyclic musk compounds civetone (1, 17 membered) and muscone (2, 15 membered) and has put an end to the concept. It has been proposed that large rings adopt non-planar conformations, which are flexible and almost strain free.\(^3\)

![Figure 1](image1.png)

Figure 1

In 1927, Kerschbaum, isolated the first macrocyclic lactones namely exaltolide 3 and ambrettolide 4 from *Angelica* root and *Ambrette* seed oil respectively.\(^4\) A great breakthrough in macrolide chemistry came in 1950 when Brockmann and Henkel\(^5\) isolated the first macrolide antibiotic picromycin 5 from an *Actinomyces* culture (Figure 2).

![Figure 2](image2.png)

Figure 2
Chapter I

Nomenclature

According to IUPAC rules, macrolides formed from aliphatic acids should be named by adding “olide” as a suffix to the name of the hydrocarbon with the same number of carbon atoms. The numbering starts from the ester carbonyl carbon. An alternative way of naming lactones by IUPAC rules is based on the nomenclature of heterocycles. According to this rule lactones are named as oxacyclo ketones and the numbering starts from the ring oxygen. However, trivial names are extensively used to represent macrolides.

![Chemical Structures](image)

**Figure 3**

Biological activity

The lactone functionality is most abundant among the natural products that have medium-sized-ring systems. The medium-sized lactones are secondary metabolites biosynthesized mainly by fungi, bacteria and marine organisms, with only a few being produced by plants or insects. Macrolides are an important class of antibiotic drugs used to treat infections caused by gram-positive bacteria and certain gram-negative bacteria; they are also used as an alternative drug to penicillin. Macrolide antibiotics play therapeutically important role, they are well established class of anti-microbial agents and play a significant role in the chemotherapy of infectious diseases. New findings in the field of anti-tumour and antibiotic properties, together with pheromones and plant growth regulators with macrolactone framework, are an inspiration for the chemists to study macrolides.

Ten-Membered ring lactones

The isolation, structural elucidation and synthetic studies of the known ten-membered lactones are rather new. Jasmine ketolactone, isolated from Italian jasmine oil, was the only decalactone known before 1975. In the last three decades several new ten-membered lactones have been isolated and synthesized. According to their structures
and/or biosynthesis, they are classified in monocyclic polyketides, monocyclic oxylipins, aliphatic bicyclic and aromatic bicyclic lactones. A few important ten-membered lactones and its biological activity are discussed below.

**Monocyclic Ten-Membered-Ring Lactones**

**Polyketides**

Polyketides are a class of natural products synthesized by bacteria, fungi, and plants through successive condensation of acetyl coenzyme A, as well as the compounds derived from them by further condensations.

Diplodialides (8-11) are the first described group of monocyclic ten-membered lactones. Diplodialide A shows inhibitory activity against steroid hydroxylase (Figure 4).

\[ (+) \text{ Diplodialide A (8)} \quad (-) \text{ Diplodialide B (9)} \quad (-) \text{ Diplodialide C (10)} \quad \text{Diplodialide D (11)} \]

**Figure 4**

Pyrenolides (12, 13, 14) were isolated in 1980, by Nukina et al. They inhibit growth and morphogenic activities of fungi (Figure 5).

\[ (-) \text{ Pyrenolide A (12)} \quad (-) \text{ Pyrenolide B (13)} \quad (-) \text{ Pyrenolide C (14)} \]

**Figure 5**

Decarestrictines, are a series of metabolites produced by different strains of the *Pencillium* species. Majority of molecules are ten-membered ring lactones, which differ in the oxygenation pattern. The most biologically active among these natural products is decarestrictine D 15. *In vitro* and *in vivo* studies show these compounds are inhibitors of cholesterol biosynthesis (Figure 6)
Herbarums (16, 17, 18 - Figure 7) were isolated from fungus Phoma (P. herbarum), by Rivero-Cruz et al. These lactones exhibit significant phytotoxic effects against the seedlings of Amaranthus hypochondriacus at very low concentrations and these metabolites interact with the bovine brain calmodulin, inhibiting activation of the enzyme cAMP phosphodiesterase.

Microcarpalide 19 was isolated from an endophytic fungus growing on the bark of the tropical tree Ficus microcarpa L. It shows a weak cytotoxic effect against KB cells, human LoVo cells (human colon adenocarcinoma cells) and also acts as a micro-filament disrupting agent (Figure 8).

Oxylipins

Ten-membered-ring lactones which are metabolites of fatty acid are called oxylipins. Didemnilactones A-20, B-21, C-22, ascidiatrienolides A 23, neodidemnilactone and muegglone 24 belong to this class of compounds (Figure 9).
Chapter I

Figure 9

Bicyclic Ten-Membered-Ring Lactones

Aliphatic

Sch 642305

Sch 642305 25 (Figure 10) was isolated from Penicillium verrucosum, and inhibits bacterial DNA primase with an EC$_{50}$ value of 70 μM.$^{11}$ The same molecule was isolated from fungus Septofusidium sp. in 2005 and was found to inhibit HIV-1 Tat transactivation.$^{12}$

Aromatic

Xestodecalactones A–C

Sporostatin 26 and xestodecalactones A–C (27, 28, and 29) are ten-membered ring keto-lactones that bear a fused 1,3-dihydroxybenzene ring. Sporostatin was isolated from the fungus of Sporormiella sp. M5032.$^{13}$ It was shown to be an inhibitor of cyclic
adenosine 3,5’-monophosphate phosphodiesterase (cAMP-PDE) and a specific inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase (Figure 11).\textsuperscript{14} Xestadecalactones were first isolated in 2002, from the fungus \textit{Penicillium cf. montanense}, which were obtained from marine sponge \textit{Xestospongia exigua}.\textsuperscript{15} Xestadecalactone B 28 was found to be active against \textit{Candida albicans} and used as active ingredient for the treatment of carcinosis.\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure11.png}
\caption{Complex Ten-Membered-Ring lactones}
\end{figure}

\textbf{Complex Ten-Membered-Ring lactones}

Apicularens A 30 and B 31 were isolated from the myxobacterial genus \textit{Chondromyces}. Unlike other benzolactones, the lactone functionality is directly bonded at the aromatic ring, ortho to the hydroxyl group.\textsuperscript{17} These lactones can be considered as cyclic salicylic acid derivatives that bear a bridged tetrahydropyran system and an \textit{N}-acyl enamine side chain. Apicularen A suppresses the proliferation of human promyelocytic leukemia cells (HL-60 cells) and induces apoptosis (Figure 12).\textsuperscript{18}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12.png}
\caption{Figure 12}
\end{figure}
General strategy for the construction of macrolides

The key step in macrolide synthesis is the formation of macrocyclic ring.\textsuperscript{19} Cyclization reaction to form 9 to 11 membered-ring system is a disfavoured process due to loss of entropy associated with the formation of more rigid ring structure; also macrolactonization reaction is a competition between intra and intermolecular reaction leading to the formation of diolide and oligomers.\textsuperscript{20} However, by using high dilution, slow addition and immobilisation techniques, the intermolecular reaction can be suppressed. Ten-membered lactone rings can be generated by cyclization of a corresponding acyclic precursor, direct C-C bond formation, ring contraction and ring expansion reactions.

a. Ring closure by lactonization

Direct esterification of long chain hydroxy acids is usually an inefficient way to prepare macrolides, as very dilute solutions of starting materials are required. However, this method can be useful, if the acyclic precursor can adopt a conformation, easy for the interacting sites to reach each other to form a macrolactone. Two methods are frequently used to realise the macrolactonization

Activation of one or both interacting sites of a hydroxy acid precursor greatly improves lactonization

\begin{center}
\textbf{Scheme 1}
\end{center}

Acid activation

\begin{center}
\textbf{Acid activation}
\end{center}

\begin{center}
\textbf{Alcohol activation}
\end{center}

This method involves activating both the carboxyl and hydroxyl groups simultaneously (scheme 2).\textsuperscript{21} Mechanism involves formation of a 2-pyridine thioester \textsuperscript{34} of the hydroxyl acid. Usually 2,2'-dipyridyl disulfide is the activating reagent, but also other nitrogen-containing disulfides have also been used. Internal proton transfer then affords an intermediate in which both the carbonyl and the hydroxyl group have been activated.
Proton gets transferred from the hydroxy group to the carboxylic oxygen, leading to the formation of the polar intermediate 35, which undergoes electrostatic cyclization to form lactone 36 (Scheme 2). Gerlach modification uses silver salts (AgClO₄, AgBF₄, AgOTf) to create a chelation between the sulfur and the alcohol, which allows the reaction to be carried out at room temperature.²²

![Scheme 2](image)

Mukaiyama developed a method to activate the hydroxy acid using 1-methyl-2-chloropyridinium iodide 37.²³ The mechanism of this reaction is similar to that of the Corey’s double activation method (Scheme 3).

![Scheme 3](image)

ii. **The Yamaguchi lactonization reaction**

The mixed anhydride is prepared by using 2,4,6-trichlorobenzoyl chloride and the seco acid in THF under basic conditions.²⁴ After the formation of the mixed anhydride 40, it is added very slowly to a very highly diluted solution of DMAP in toluene to form the macrolactone 36 (Scheme 4).
iii. Miscellaneous mixed anhydride method

A very common way to activate the carboxyl group of a long chain hydroxy acid is to convert it to a mixed anhydride. The mixed anhydride is prepared to accelerate the reaction and overcome the unfavourable entropy factors leading to the formation of polymeric products. The anhydride then reacts intramolecularly with the hydroxyl group under basic reaction conditions, to form a macrolactone. Pivaloyl chloride, trifluoroacetic anhydride, \( p \)-toluenesulfonyl chloride and di-\textit{tert}-butyl dicarbonate, NMBA (2-methyl-6-nitrobenzoic anhydride) are used to prepare the mixed anhydride.

**Alcohol activation**

Mitsunobu lactonization involves activation of the alcohol by forming a dipolar alkoxy phosphonium salt \( \text{43} \) from the hydroxy acid \( \text{42} \), \( \text{PPh}_3 \) and diethyl azodicarboxylate (DEAD).\textsuperscript{25} This activated intermediate reacts by an \( S_N 2 \) displacement gives the lactone \( \text{45} \), with the inversion of configuration of the alcohol (Scheme 5).
b. **Ring closure by C–C and C=C bond formation**

i. **NHK reaction:**

The reaction between organochromium reagents and aldehydes or ketones is known as Nozaki-Hiyama-Kishi (NHK) reaction (Scheme 7). Organochromiums reagents are generated *in situ* by the reaction of organohalides with CrCl$_2$ in the presence of traces of Ni salts. The intramolecular version of this reaction is frequently used for the construction of macrocyclic rings. Due to their low basicity, the organochromium reagents are compatible to a wide variety of functional groups and the reactions are highly selective.

![Scheme 7](image)

ii. **Ring closing metathesis**

Construction of macrocycles by ring-closing metathesis (RCM) is often used as a key step in the synthesis of natural products containing large rings. The corner-stone of the RCM reaction is the development of well defined metathesis catalysts, which are tolerant to many functional groups as well as reactive towards a diverse range of substrates. The most common RCM catalysts are shown in figure 13. Grubbs’ 1$^{\text{st}}$ generation catalyst 48, Furstner’s catalyst 49, Grubbs’ 2$^{\text{nd}}$ generation catalyst 50 & 51, and Hoveyda-Grubbs’ catalyst 52.

![Figure 13](image)
Generally accepted mechanism of metathesis reactions (Chauvin mechanism) consist of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkenes, metal carbenes, and metallocyclobutane intermediates (Scheme 8). Since all the individual steps are reversible, an equilibrium mixture of olefins are obtained. However, the forward reaction is favoured as the liberation of highly volatile ethylene gas.

![Scheme 8]

**Figure 14**

A major drawback of the RCM reaction is the lack of stereocontrol, mixtures of (E) and (Z) cycloalkenes are formed. 8-11 membered rings are sensitive to the reverse process (ROM or ROMP) because of their intrinsic ring strain. Outcome of the RCM reaction depends on the nature of the substrate, reaction temperature, solvent, strain of the ring being formed and catalyst.
Structural determination of achaetolide

In 1983, Bodo et al., reported the isolation of achaetolide (53, Figure 15) from the culture broth of Achaetomium crisalliferum. In 2009, Takada and co-workers extracted the same compound from the culture broth of Ophiobolus sp. isolated from dead stem of Achillea alpina ssp. pulchra and determined the absolute stereochemistry of the compound.

Structure of achaetolide 53 was determined by using a combination of mass spectrometry, infrared spectroscopy and largely by 1D and 2D NMR spectroscopy. The ESI-MS spectrum provided a signal at \( m/z = 301.2033 \), thus establishing its molecular formula (C\(_{16}\)H\(_{28}\)O\(_{5}\)). The IR spectrum peaks at 1630, 1718, and 3450 cm\(^{-1}\) showed the presence of double bond, ester carbonyl and alcohol functionalities respectively. Achaetolide exist as a mixture of conformers in the \(^1\)H NMR spectrum, most of the resonances were observed as pair of signals and the ratios of signals changed on varying the solvent (9:1 in CDCl\(_3\), 2:1 in CD\(_3\)OD and 5:3 in acetone-d\(_6\)), so the absolute stereochemistry was determined for 6-O-7-O-isopropylidene derivative of achaetolide 54, which exists as a single enantiomer.
The relative stereochemistry of the macroline moiety was assigned by using $^1$H NMR spectra. The NOE between H$_6$ and H$_7$ protons reveals a *cis*-relationship on the dioxolane ring (Figure 16). Large coupling constants for $J_{H7-Ha8}$ (10.2 Hz) and $J_{Ha8-H9}$ (9.7 Hz) indicate pseudo-*anti* orientations for H$_7$/Ha$_8$ and Ha$_8$/H$_9$. H$_\beta$8 appeared as a doublet (15.8 Hz), suggesting that it couples only with Ha$_8$, and is perpendicular to H$_7$ and H$_9$. The NOESY spectrum shows correlation peaks for H$_5$/Ha$_8$, H$_6$/H$_7$, H$_6$/H$_9$, and H$_7$/H$_9$, confirming the stereo-chemical relationship for the C6–C9 moiety. Coupling constants for H$_3$/H$_4$ and H$_5$/H$_6$ (8.3 and 9.0 Hz, respectively) and strong NOESY signals H$_3$/H$_5$ and H$_4$/H$_6$ disclosed the C3–C6 plane. Absolute stereochemistry was also found by Mosher ester analysis and through chemical transformations. The absolute configuration of achaetolide was found to be 3S, 6R, 7S, and 9R.

Nonetheless, a total synthesis of the molecule would ultimately prove the absolute configuration of the molecule and would allow evaluating its biological activity. The structural features of achaetolide combined with our interest on the synthesis of macrolides prompted us to attempt the synthesis of achaetolide.$^{33}$
PRESENT WORK

Retrosynthesis

Our retrosynthetic plan was to construct the macrolide by ring-closing (RCM) reaction. Acyclic precursor could be obtained by coupling the secondary alcohol 65 and acid 74 through a Mitsunobu esterification. The fragment 65 was envisioned from epichlorohydrin 55 using Jacobson hydrolytic kinetic resolution and dihydroxylation of the lactone 61. The acid fragment could be obtained from the known epoxy alcohol 70 which in turn is prepared from 1,3-propane diol.

Scheme 9

Synthesis of (S)-nonene oxide 57 by hydrolytic kinetic resolution

The synthesis commenced from the regioselective ring opening of commercially available epichlorohydrin 55 by n-hexylmagnesium bromide in anhydrous THF at -78 °C, in the presence of catalytic CuCN to give chlorohydrin, which on reaction with aqueous sodium hydroxide solution in THF gave nonene oxide 56 in 70 % yield (for 2 steps). The epoxide 56 was confirmed by using $^1$H NMR spectrum, resonances at $\delta$ 2.87-2.80 (multiplet), 2.69 (dd) and 2.40 (dd) each integrating to one proton represent protons on the oxirane ring. The racemic nonene oxide 56 was then subjected to Jacobsen hydrolytic kinetic resolution employing 0.55 eq. of water in the presence of 0.005 mol% of {($S,S'$)-$N,N'$-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexane diamino-Co(III)-acetate} to afford the chiral oxirane 57 in 43% yield along with the diol 58 in 45% yield (Scheme 10). The optical rotation of the oxirane 57 was found to be $[\alpha]_D^{25} = -16.8$ (c 1.0, CHCl$_3$) which was correlated with that of the earlier reported data $[\alpha]_D^{25} = -16.2$ (c 2.0, CHCl$_3$).
**Scheme 10**

**Synthesis of lactone 61**

The chiral nonene oxide 57 was then added to an anhydrous THF solution of lithiated ethyl propiolate at -78 °C (generated by the reaction of n-BuLi with ethyl propiolate), the alkynyl group was regioselectively added at the less hindered side of the epoxide,\(^\text{36}\) which was confirmed by \(^1\)H NMR spectrum, a peak at \(\delta\) 4.20, quartet, integrating to two hydrogens for the methylene group and peak at \(\delta\) 0.89 as triplet for the methyl group were observed. \(^1\)C NMR spectrum showed resonances at \(\delta\) 153.6 for the carbonyl group and at 85.9, 74.9 for the two alkyne carbons. IR absorptions at 3549 and 1709 cm\(^{-1}\) showed the presence of hydroxyl and carbonyl functional groups respectively. The homopropargylic alcohol 59 was then partially hydrogenated using Lindlar’s catalyst [Pd-CaCO\(_3\) (poisoned with lead)] in the presence of catalytic quinoline under hydrogen atmosphere to give the olefin 60. A new set of protons appeared in the \(^1\)H NMR spectrum at \(\delta\) 6.41-6.30 as a multiplet and at \(\delta\) 5.89 as doublet of triplet with \(J=11.3\) Hz confirming the Z-configuration of the newly formed olefin, \(^1\)C spectrum showed peaks at \(\delta\) 146.2 and 121.5 for the olefin carbons and in ESI-MS peak was observed at \(m/z\) 243 [M+H]\(^+\). The alcohol obtained was directly used for the next reaction without any further purification, thus 60 on exposure to catalytic p-TSA smoothly underwent lactonization at room temperature to afford the lactone 61 in 82% yield (for 2 steps). The \(^1\)H NMR and \(^1\)C spectrum showed the disappearance of methylene and methyl group peaks of the ester functionality, along with the presence of other required peaks. HRMS peak was found at \(m/z\) 219.1354 [M+ Na]\(^+\) (a decrease by 45 amu for the loss ethyl) with the characteristic carbonyl stretch at 1718 cm\(^{-1}\) in IR spectrum also proved the formation of \(\alpha, \beta\) unsaturated lactone 61 (Scheme 11).
The lactone 61 was then subjected to dihydroxylation using OsO₄ and NMO as re-oxidant in aqueous solution of acetone. The dihydroxylation reaction was highly diastereoselective, leading to the exclusive formation of diol 62 in 58% yield. In ¹H NMR spectrum, the peaks for the olefinic protons were absent and two new broad peaks at δ 3.43 and 2.7 for the hydroxyl protons were observed. ¹³C NMR spectrum showed two new peaks at δ 70.4, 65.9 for the two carbons attached to oxygen. The increase in IR absorption frequency ν =1728 cm⁻¹ for the carbonyl group and ESI-MS signal at m/z 253 [M+Na]⁺ also confirmed the diol 62. The diol was protected as its acetonide using 2,2 dimethoxy propane with catalytic PPTS in dichloromethane. ¹H NMR spectrum analysis of the product 63 showed disappearance of the two broad singlets at δ 3.43 and 2.7 observed for the hydroxyl protons and increase in the integration area in the upfield region due to the six protons of the isopropylidene unit. ¹³C NMR spectrum showed peaks at δ 110.5 for the new quarternary carbon and at 25.9, 23.9 for the two methyl groups in the isopropylidene unit. HRMS peak at m/z 293.1736 [M+Na]⁺ also supports the transformation (Scheme 12).

**Scheme 11**

**Scheme 12**

**Synthesis of alcohol 65**

Reduction of the lactone 63 to lactol 64 was achieved using DIBAL-H at -78 °C in anhydrous dichloromethane. The product was confirmed by IR spectrum, the characteristic carbonyl group peak was absent and also it showed a broad peak at 3522 cm⁻¹ for the
hydroxyl group. One carbon homologation of the lactol 64 was successfully carried out by using methyltriphosphonium ylide (generated by the reaction of n-BuLi with methyltriphosphonium bromide) to afford the alcohol 65 in 77% yield. The compound was ascertained by $^1$H NMR spectrum peaks at $\delta$ 5.76 (ddd) for the internal olefinic proton and a multiplet at $\delta$ 5.34-5.20 for the two terminal olefinic protons. In $^{13}$C NMR spectrum, peaks were observed at $\delta$ 133.8 and 118.6 for the terminal and internal olefin carbons respectively. HRMS signal was observed at m/z 293.2087 [M+Na] corresponding to the molecular formula C$_{16}$H$_{30}$O$_3$.

Scheme 13

Synthesis of allyl alcohol 69

1,3-Propane diol 66 was selectively mono protected as its silyl ether using TBDPSCl and imidazole in dichloromethane, the mono protected alcohol 67 was oxidized to aldehyde under Swern reaction conditions, [COCl$_2$, DMSO, NEt$_3$] at -78 $^\circ$C. The aldehyde was then converted to two carbon homologated $\alpha,\beta$-unsaturated ester 68 using Ph$_3$P=CHCOOEt in 88% yield. The product was characterised by its $^1$H NMR spectrum, which showed the peaks at $\delta$ 6.97-6.83 as a multiplet and at $\delta$ 5.78 as doublet of doublet for the two olefinic protons with a coupling constant $J$ =17.0 Hz confirming trans configuration, along with the characteristic peaks for the ethyl group. The ester 68 was reduced to the allylic alcohol 69 using DIBAL-H, absence of ester group peaks in the $^1$H and $^{13}$C NMR spectrum and a peak at m/z 363 [M+Na]$^+$ in the ESI-MS confirmed the product 69.$^{38}$

Scheme 14
Synthesis of Acid 74

Allylic alcohol 69 was subjected to Sharpless asymmetric epoxidation following the standard protocol using [(+)-DET, TBHP, Ti(ıt-O-Pr)₄] to afford the epoxy alcohol 70. The product was confirmed by its ¹H NMR study which showed the absence of olefin protons and presence of the two oxirane protons at δ 3.61 as doublet of doublet and δ 3.15 as doublet of triplet. Compound 70 was further confirmed by ESI-MS which showed peak at m/z 379 [M+Na]⁺. The epoxy alcohol was converted into its iodo compound using TPP, I₂ and imidazole, which on reductive elimination with activated Zn dust afforded the allylic alcohol 71 in 85% yield.₃⁹ In ¹³C NMR, peaks at δ 140 and 114.2 for the olefin carbons confirmed the product. Secondary allylic alcohol 71 was protected as its TBS ether using TBS-Cl to give the compound 72, which on selective deprotection of TBDPS ether using ammonium fluoride afforded the alcohol 73 in 80% yield. ¹H and ¹³C NMR spectrum showed the absence of TBDPS group peaks in the down field region. The alcohol was converted to its acid by two steps process; at first, the alcohol was converted to its aldehyde using IBX, which on further oxidation using NaClO₂ and NaH₂PO₄ (Pinnick conditions) afforded the acid 74 in 76 % yield.₄₀ The acid was confirmed by its ¹³C NMR spectrum which showed a peak at 176.3, ESI-MS peak at m/z 231 [M+H]⁺.

![Scheme 15](image_url)

**Scheme 15**

**Coupling of the alcohol 65 and acid 74 fragments**

Alcohol 65 and acid 74 were coupled under Mitsunobu conditions using triphenylphosphine and DIAD to afford the diene 75 in 62% yield, with the inversion of configuration at the hydroxyl carbon (Scheme 16).²⁵ The characteristic changes that proved
the coupling has happened was six vinyllic protons in the \textsuperscript{1}H NMR spectrum which were found at $\delta$ 5.90-5.67 (m, 2H), 5.23-5.17 (m, 3H), 5.09 (m, 1H) and a peak at $\delta$ 170.4 for the carbonyl group in the \textsuperscript{13}C NMR spectrum, further in ESI-MS a peak was observed at 503.0[M+Na]$^+$ which confirmed the product 75.

\textbf{Scheme 16}

\textbf{Completion of the synthesis}

Diene 75 was subjected to ring closing metathesis (RCM) reaction, using 10 mol\% of Grubbs’-II generation catalyst in CH$_2$Cl$_2$ in refluxing conditions, but to our dismay, an array of spots were observed in TLC. Performing the same reaction using toluene as a solvent at higher temperature or using Grubbs’-I generation catalyst were also not fruitful. Reviewing the literature, it has been documented that there have been some hurdles in the RCM for similar substrates. Having failed to construct the macrocycle, we thought the bulkiness of the TBS ether and the isopropylidene group around the reaction centre would play a role in the reaction, so the TBS group was deprotected using 1M TBAF to realize the diene 76 with a free allylic hydroxy group. The product was identified by the obvious loss of peaks for the TBS group in both the \textsuperscript{1}H and \textsuperscript{13}C spectra. HRMS peak at m/z 391.2444 also support the compound 76 (Scheme 17).
Alcohol 76 on exposure to Grubbs'-II catalyst underwent the RCM reaction smoothly in refluxing CH₂Cl₂, but two spots were observed on TLC. The two compounds were separated by silica gel column chromatography and were characterised by spectral data. The non-polar isomer was found to be E-isomer 77. ¹H NMR analysis of the compound showed a peak at δ 5.71 (dd, J =15.8, 9.2 Hz) and at 5.57 (dd, J =15.8, 7.9 Hz) confirming the trans geometry of the newly formed double bond. The polar isomer was found to be Z isomer 78. ¹H NMR showed peaks at δ 5.65-5.59 (dd, J = 11.8, 10.5 Hz) and at δ 5.56-5.50 as a multiplet for the olefinic protons, with coupling constant 11.8 Hz confirmed the cis geometry of the double bond. These peaks, along with the other required peaks supported the transformation. The trans isomer 77 was further confirmed by its HRMS, which showed a peak at m/z 363.2155 [M+Na]⁺ corresponding to molecular formula C₁₉H₄₅O₅. Specific rotation of the compound 77 [α]D⁰₃₀ = - 35.0 (c 0.15, CHCl₃) was in good agreement with the data reported in the literature.³²

Scheme 18

Completion of the total synthesis would require deprotection of the isopropylidene unit. Accordingly, compound 77 was treated with trifluoroacetic acid in dichloromethane to afford the achaetolide 53 in 65% yield as a white solid (Scheme 19). The product had all the spectral properties in perfect agreement with the literature for the naturally occurring achaetolide.³²

Scheme 19
**EXPERIMENTAL SECTION**

**2-Heptyloxirane (56)**

![Structure of 2-Heptyloxirane](image)

In a dry two neck RB flask, n-hexyl bromide (13.4 g, 81.2 mmol) was added to a suspension of magnesium (2.9 g, 12.1 mmol) in anhydrous THF (60 mL) under nitrogen atmosphere and stirred for 30 min. Grignard reagent thus prepared was added slowly over 30 min. to a solution of epichlorohydrin (5.0 g, 54.0 mmol) in anhydrous THF (40 mL) containing CuCN (0.48 g, 5 mmol) at -78 °C and stirred for 3 h. Saturated NH₄Cl solution was added to the reaction and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL), the combined organic extracts were washed with water, brine, dried over Na₂SO₄ and concentrated under vacuum to give chlorohydrin (7.5 g). The crude reaction mass was dissolved in THF/Water (8:2) solution (75 mL) and NaOH (5.0 g, 12.6 mmol) was added and stirred at 0 °C for 8 h. The reaction mass was filtered through a pad of celite and water (25 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL), the combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated at 25 °C on rota evaporator. Purification of the residue on silica gel (hexane: diethylether - 9:1) afforded the nonene oxide 56 (5.4 g, 70%).

1H NMR (300 MHz, CDCl₃) : δ 2.87-2.80 (m, 1H), 2.69 (dd, J = 5.2, 3.7 Hz, 1H), 2.40 (dd, J = 5.2, 3.0 Hz, 1H), 1.55-1.22 (m, 12H), 0.89 (t, J = 6.79 Hz, 3H)

13C NMR (75 MHz, CDCl₃) : δ 52.1, 46.8, 32.3, 31.6, 29.2, 29.1, 25.8, 22.5, 13.9

**(S)-2-Heptyloxirane (57)**

![Structure of (S)-2-Heptyloxirane](image)

In a 100 mL round bottom flask was charged (S)-1 (133 mg, 0.22 mmol) and 3 ml of toluene. To this acetic acid (55 µL, 0.9 mmol) was added and stirred at room temperature open to air for 30 min. The solution was then concentrated under vacuum. The resulting brown residue was dissolved in racemic epoxide 56 (6.3 g, 43.3 mmol), cooled to
0 °C and water (0.44 mL, 0.24 mmol) was added dropwise for 5 min. The reaction was allowed to stir at room temperature for 16 h, purification of the crude reaction mass over silica gel column chromatography (hexane:diethyl ether-95:5) afforded the enantiopure epoxide 57 (2.7 g, 43%) along with the diol 58 (2.8 g, 45%)

\[ \alpha \]D^25 : -16.8 (c 1.0, CHCl₃)

(S)-ethyl 5-hydroxydodec-2-ynoate (59)

To a solution of ethyl propiolate (2.8 mL, 27.4 mmol) in anhydrous THF (50 mL) at -78 °C was added n-BuLi (11 mL, 2.5 M in hexane, 27.4 mmol) and stirred for 15 min. BF₃.OEt₂ (3.38 mL, 27.4 mmol) was added followed by a solution of epoxide 57 (2.6 g, 18.3 mmol) in THF (15 mL) and the stirring was continued for 4 h at the same temperature. The reaction was quenched by adding saturated NH₄Cl solution and brought to room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 30 mL), the combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude was purified by silica gel column chromatography (hexane:ethyl acetate - 97:3) to give alkyne 59 (3.66 g, 80%).

IR (KBr) : \( \nu_{\text{max}} \) 3549, 2929, 2859, 2236, 1709, 1258, 1073, 759 cm⁻¹

\(^1\)H NMR (300 MHz, CDCl₃) : δ 4.20 (q, \( J = 7.0 \) Hz, 2H), 3.0 (p, \( J = 3.8 \) Hz, 1H), 2.52 (dd, \( J = 16.9, 5.1 \) Hz, 1H), 2.44 (dd, \( J = 16.9, 5.1 \) Hz, 1H), 2.3 (br.s, 1H), 1.58-1.2 (m, 15H), 0.89 (t, \( J = 6.7 \) Hz, 3H)

\(^{13}\)C NMR (75 MHz, CDCl₃) : δ 153.6, 85.9, 74.9, 69.4, 61.9, 36.4, 31.7, 29.3, 29.1, 27.6, 25.5, 22.6, 14.0, 13.9

ESI-MS : \( m/z \) 263 [M+Na]+

HRMS : Calcd for C₁₄H₂₄NaO₃ [M+Na]+: 263.1618, found: 263.1625

\([\alpha]_D^{30} \) : + 3.7 (c 0.605, CHCl₃)

22
2Z-5S-Hydroxydodec-2-enoate (60)

Lindlar catalyst (Pd-CaCO₃, poisons with lead, 500 mg) and quinoline (0.02 mL) were added to a solution of alkyne 59 (3.0 g, 12.3 mmol) in benzene (25 mL). The resulting suspension was stirred at room temperature for 1 h under hydrogen atmosphere. After complete consumption of starting material, as indicated by TLC, the mixture was filtered through a pad of celite and washed with ethyl acetate (10 mL). The filtrate was concentrated in vacuo to afford the alkene 60 (2.95 g) as a pale yellow liquid, which was used for the next step without any further purification.

IR (KBr)  \( \nu_{\text{max}} \) 3426, 2927, 2858, 1715, 1644, 1459, 1417, 1177, 1035 cm\(^{-1}\)

\(^1\)H NMR (300 MHz, CDCl\(_3\))  \( \delta \) 6.41-6.30 (m, 1H), 5.89 (dt, \( J = 11.3,1.5 \) Hz, 1H), 4.16 (q, \( J = 6.7 \) Hz, 2H), 3.79-3.66 (m, 1H), 2.76 (m, 2H), 1.98 (broad d, \( J = 4.5 \) Hz, 1H), 1.52-1.20 (m, 15H), 0.85 (t, \( J = 6.7 \), 3H)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\))  \( \delta \) 166.8, 146.2, 121.5, 71.1, 60.0, 37.4, 36.4, 31.7, 29.5, 29.1, 25.5, 22.5, 14.1, 13.9

ESI-MS  \( m/z \) 243 [M+H]\(^+\)

\([\alpha]_D^{30}\)  + 4.7 (c 0.69, MeOH)

(6S)-6-Heptyl-5,6-dihydro-2H-pyran-2-one (61)

To a solution of alkene 60 (2.8 g, 11.6 mmol) in benzene (25 mL) was added catalytic \( p \)-TSA (25 mg,) and stirred at room temperature for 4 h, triethylamine was added and the mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane:ethyl acetate - 95:5) afforded the lactone 61 as a light yellow liquid (2.0 g, 82 % for two steps)
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IR (KBr) : \( \nu_{\text{max}} \) 2926, 2857, 1718, 1638 cm\(^{-1}\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \( \delta \) 6.86-6.76 (m, 1H), 6.02-5.97 (m, 1H), 4.43-4.33 (m, 1H), 2.34-2.28 (m, 2H), 1.86-1.73 (m, 1H), 1.68-1.22 (m, 11H), 0.89 (t, \( J = 6.7 \) Hz, 3H)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : \( \delta \) 164.6, 145.0, 121.4, 78.0, 34.8, 31.7, 29.4, 29.3, 29.1, 24.8, 22.6, 14.0, 33.8, 31.6, 29.2, 29.0, 24.7, 22.5, 14.0

ESI-MS : \( m/z \) 197 [M+H]\(^+\)

HRMS : Calcd for C\(_{12}\)H\(_{20}\)NaO\(_2\) [M+Na]\(^+\):219.1356, found: 219.1354

\([\alpha]^{30}_D\) : + 88.5 (c 0.515, CHCl\(_3\))

(3S,4S,6S)-6-heptyl-3,4-dihydroxytetrahydro-2H-pyran-2-one (62)

OsO\(_4\) [4.0 ml, 0.2 % in toluene, 6 mol %] was added to a solution of lactone 61 (1.4 g, 7.14 mmol) in acetone:water - 7:3 (40 mL) followed by NMO (2.0 g, 17.6 mmol). The reaction was stirred for 12 h at room temperature. After the completion of reaction (by TLC), a saturated solution of NaHSO\(_3\) (5 mL) was added followed by ethyl acetate (25 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated to afford the diol 62 as a white solid. (0.98 g, 58% yield).

M.P : 90-92 °C
IR (KBr) : \( \nu_{\text{max}} \) 3390, 3287, 2920, 2851, 1728, 1229, 1109 cm\(^{-1}\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \( \delta \) 4.78-4.67 (m, 1H), 4.31-4.27 (m, 1H), 4.0 (m, 1H), 3.43 (br.s, 1H), 2.7 (br.s, 1H) 2.2 (dt, \( J = 14.3, 3.7 \) Hz, 1H), 1.85-1.2 (m, 13H), 0.89 (t, \( J = 6.7 \) Hz, 3H)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : \( \delta \) 174.2, 78.3, 70.4, 65.9, 35.5, 33.8, 31.6, 29.2, 29.0, 24.7, 22.5, 14.0

ESI-MS : \( m/z \) 253 [M+Na]\(^+\)

24
[α]²⁵\text{D} : -32.0 (c 0.18, CHCl₃)

\((3aS,6S,7aS)-6-\text{Heptyl}-2,2-\text{dimethyldihydro}-3aH-[1,3]\text{dioxolo}[4,5-c]\text{pyran}-4(6H)-\text{one (63)}\)

To a solution of diol 62 (0.95 g, 4.1 mmol) in CH₂Cl₂ (15 mL) was added 2,2-DMP and cat. PPTS. The solution was stirred for 2 h at room temperature. After the completion of reaction (by TLC), the reaction was neutralized with NEt₃. The reaction was concentrated under reduced pressure to remove the volatiles and purified by silica gel column chromatography (hexane:ethyl acetate - 95:5) to give the compound 63 (0.73 g, 72%) as a thick liquid.

IR (KBr) : ν_{\text{max}} 2927, 1751, 1377, 1269, 1044 cm⁻¹

\(^1\text{H NMR (300 MHz, CDCl₃)} : \delta 4.49-4.62 (m, 3H), 1.97 (ddd, J = 15.1, 2.2, 1.5 Hz, 1H), 1.24-1.77 (m, 19H), 0.89 (t, J = 6.7 Hz, 3H)

\(^{13}\text{C NMR (75 MHz, CDCl₃)} : \delta 168.3, 110.5, 75.1, 72.8, 71.8, 34.8, 33.9, 31.7, 29.2, 29.0, 25.9, 24.7, 23.9, 22.6, 14.0

ESI-MS : m/z 271 [M+H]⁺

HRMS : Calcd for C₁₅H₂₆NaO₄ [M+Na]⁺: 293.1723, found: 293.1736

[α]²⁵\text{D} : 41.6 (c 1.25, CHCl₃)

\((3aS,6S,7aS)-6-\text{Heptyl}-2,2-\text{dimethyl-hexahydro-[1,3]}\text{dioxolo}[4,5-c]\text{pyran}-4-\text{ol (64)}\)

DIBAL-H (2.27 mL, 0.4 mmol, 25% wt. in toluene) was added to a solution of lactone 63 (0.540 g, 0.2 mmol) in anhydrous CH₂Cl₂ (15 mL) at -78 °C and stirred for 30 min under N₂ atmosphere. After the completion of reaction (by TLC), saturated sodium
potassium tartarate solution (5 mL) was added and the reaction was brought to room temperature and stirred for 3 h. After the clear separation of layers, the organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Purification by silica gel column chromatography (hexane:ethyl acetate - 9:1) afforded the lactol 64 (0.42 g, 78 % yield).

IR (KBr) : $\nu_{\text{max}}$ 3422, 2926, 2856, 1375, 1051 cm$^{-1}$

1H NMR (300 MHz, CDCl$_3$) : 4.7 (d, $J$ = 5.8 Hz, 1H), 4.33–4.29 (m, 1H), 3.67 (t, $J$ = 5.8 Hz,1H), 3.64–3.57 (m, 1H), 2.9 (br.s, 1H), 1.93–1.88 (m, 1H), 1.64 (ddd, $J$ = 14.6, 10.9, 3.9 Hz, 1H), 1.57–1.22 (m, 18H), 0.82 (t, $J$ = 6.8 Hz, 3H)

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 109.1, 96.4, 76.6, 72.8, 70.6, 35.4, 32.6, 31.7, 29.5, 29.1, 27.9, 25.8, 25.4, 22.6, 14.0

ESI-MS : $m/z$ 295 [M+Na]$^+$

HRMS : Calcd for C$_{15}$H$_{28}$NaO$_4$[M+Na]$^+$: 295.188, found: 286.1877

$[\alpha]_{D}^{30}$ : + 45.3 (c 0.91, CHCl$_3$)

(S)-1-((4R,5R)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)nonan-2-ol (65)

To a suspension of triphenylmethylphosphonium bromide (2.50 g, 7.32 mmol) in anhydrous THF (15 mL) at 0 °C was added n-BuLi (2.6 mL, 6.5 mmol, 2.5M in hexane) under nitrogen atmosphere and stirred for 30 min. A solution of lactol 64 (0.50 g, 1.83 mmol) in THF (5 mL) and was added to the ylide solution at 0 °C and stirring was continued for 4 h at room temperature. The reaction was quenched with saturated NH$_4$Cl solution (10 mL) and the organic and aqueous layers were separated. Aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with brine and dried over Na$_2$SO$_4$ and concentrated. The residue was purified by silica gel chromatography (hexane:ethyl acetate - 9:1) to afford the alkene 65 (0.380g, 77 %) as colourless thick liquid.
IR (KBr) : $\nu_{\text{max}}$ 3463, 2926, 2858, 1374, 1216, 1045, 927 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 5.76 (ddd, $J = 17.3$, 9.8, 7.5 Hz, 1H), 5.34-5.20 (m, 2H) 4.52 (td, $J = 7.5$, 0.8 Hz, 1H), 4.31 (ddd, $J = 9.8$, 6.0, 3.7 Hz, 1H), 3.79-3.69 (m, 1H), 3.0 (br.s, 1H), 1.53-1.23 (m, 20 H) 0.89 (t, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 133.9, 118.6, 108.8, 79.8, 78.4, 71.8, 37.5, 37.2, 31.7, 29.5, 29.2, 28.0, 25.5, 22.6, 14.0.

ESI-MS : m/z 293 [M+H]$^+$

HRMS : Calcd for C$_{16}$H$_{30}$NaO$_3$: 293.2089 [M+Na]$^+$, found: 293.2087

$[\alpha]_D^{32}$ : -14.0 ($c$ 0.205, CHCl$_3$)

3-(tert-Butyldiphenylsilyloxy)propan-1-ol (67)

Imidazole (17.3 g, 262.2 mmol) was added slowly to a solution of 1,3-propane diol (10.0 g, 131 mmol) in CH$_2$Cl$_2$ (150 mL) at 0 °C and stirred. After 30 min, TBDPS-Cl (36.0 g, 87.3 mmol) in CH$_2$Cl$_2$ (50 mL) was added slowly for a period of 30 min and allowed to stir for 4 h at room temperature. Water (150 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2x 50 mL) and the combined organic extracts was washed with brine (100 mL), dried over Na$_2$SO$_4$ and concentrated on rotary evaporator. The residue on purification by column chromatography using silica gel (hexane:ethyl acetate -75:25) afforded the mono silylated compound 67 (37.3 g, 90 %) as a colourless liquid.

IR (KBr) : 3354, 3074, 2930, 2858, 1428, 1111, 823, 702 cm$^{-1}$

$^1$H NMR (300 MHz, CDCl$_3$) : 7.83-7.64 (m, 4H), 7.54-7.32 (m, 6H), 3.97-3.79 (m, 4H), 2.55 (br.s, 1H), 1.92-1.76 (m, 2H), 1.08 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : 135.4, 133.2, 129.7, 127.6, 63.0, 61.7, 34.2, 26.7, 19.0

ESI-MS : 315 [M+H]$^+$

HRMS : Calcd for C$_{19}$H$_{26}$O$_3$Si: 315.1775 [M+H]$^+$, found: 315.1774
(E)-ethyl 5-(tert-butyldiphenylsilyloxy)pent-2-enoate (68)

A solution of oxalyl chloroide (9.1 mL, 100 mmol) in CH₂Cl₂ (100 mL) was cooled to -78 °C and DMSO (14.2 mL, 200 mmol) was slowly added. After 15 min, a solution of mono silylated alcohol 67 (15.4 g, 50 mmol) in CH₂Cl₂ (50 mL) was added and stirred for 1 h. NEt₃ was added to the reaction mixture, after 15 min the reaction was brought to room temperature and quenched by adding water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts was dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel (hexane:ethyl acetate - 9:1) to afford the aldehyde (14.0 g). The purified aldehyde was dissolved in CH₂Cl₂ (120 mL) and added ethoxycarbonylmethylene triphenylphosphorane (Ph₃P=CHCOOEt) (18.0 g, 52.6 mmol) at room temperature and allowed to stir for 2 h at same temperature. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure which gave a solid residue. The residue was triturated with diethylether (2 x 25 mL) to remove the insoluble triphenyl phosphine oxide and the ether solution was concentrated. Purification of the residue on silica gel column chromatography using (hexane:ethyl acetate - 95:5) afforded the α,β-unsaturated ester 68 (13.8 g, 88%, for 2 steps) as colourless liquid.

IR (KBr) : 2957, 1722, 1110, 703, 505 cm⁻¹

¹H NMR (CDCl₃, 200 MHz) : δ 7.63-7.53 (m, 4H), 7.40-7.23 (m, 6H), 6.97-6.83 (m, 1H), 5.78 (d, J = 15.6 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 6.4 Hz, 2H), 2.42-2.29 (m, 2H), 1.20 (t, J = 6.9 Hz, 3H), 0.97 (s, 9H)

¹³C NMR (CDCl₃, 75 MHz) : 166.3, 145.7, 135.5, 133.5, 129.6, 127.6, 123.0, 62.2, 60.1, 35.4, 26.7, 19.1, 14.2

ESI-MS : m/z 405 [M+Na]^+}

(2E)-5-[(tert-butyldiphenylsilyl)oxy]pent-2-en-1-ol (69)
DIBAL-H (5.95 g, 24 mL, 25% wt. in toluene, 41.8 mmol) was slowly added to the stirred solution of ester 68 (8.0 g, 20.9 mmol) in anhydrous CH$_2$Cl$_2$ (100 mL) under nitrogen atmosphere at -78 °C. The solution was allowed to stir for 20 min. at the same temperature and then at room temperature for 2 h. The reaction was quenched by adding saturated sodium potassium tartrate solution (50 mL). The reaction mixture was allowed to reach room temperature and then the layers were separated. The aqueous layer was extracted with ethyl acetate (2x 30 mL). The organic layers were combined, washed with water, dried over anhydrous Na$_2$SO$_4$ and concentrated on rotary evaporator. The residue was purified by chromatography using silica gel (hexane:ethyl acetate - 8:2) to provide the allylic alcohol 69 (7.0 g, 87%) as a colourless liquid.

IR (KBr) : ν$_{\text{max}}$ 3446, 2930, 1638, 1109, 702 cm$^{-1}$

$^1$H NMR (300 MHz, CDCl$_3$) : δ 7.70 (d, $J = 6.5$ Hz, 4H), 7.40 (m, 6H), 5.67 (m, 2H), 4.07 (br.s, 2H), 3.76 (t, $J = 5.3$ Hz, 2H), 2.30 (m, 2H), 1.93 (br.s, 1H), 1.09 (s, 9H)

$^{13}$C NMR (75 MHz, CDCl$_3$) : δ 135.4, 133.7, 130.9, 129.4, 129.0, 127.5, 63.4, 35.4, 26.7, 19.1

HRMS : Calcd for C$_{21}$H$_{28}$NaO$_2$Si: 363.1751 [M+Na]$^+$, found: 363.1752

[(2S,3S)-3-[2-[(tert-Butyldiphenylsilyl)oxy]ethyl]oxiran-2-yl]methanol (70)

![TBDPSO-OH](image)

To a flame dried double necked round bottom flask with activated 4A° molecular sieves (6.0 g) and dry CH$_2$Cl$_2$ (50 mL) at -20 °C was added Ti(OiPr)$_4$ (0.84g, 0.87 mL, 2.9 mmol). After 10 minutes, L-(+) diethyl tartarate (0.75 g, 0.62 mL, 3.67 mmol) was added to the reaction mixture and stirred for 30 min. To this reaction mixture allylic alcohol 69 (5.0 g, 14.7 mmol) was added over 30 min. followed by TBHP (5.25 g, 14.6 mL, 58.8 mmol, 4M solution in toluene) and the stirring was continued till completion of the reaction (8 h). The mixture was warmed to room temperature and filtered through celite pad. The filtrate was quenched with water (8.7 mL), 20% aq.NaOH (1.45 mL) and stirred vigorously for 1 h. The biphasic solution was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic extracts were dried over
anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the epoxide 70 as colourless oil (4.6 g, 88 % yield)

IR (KBr) : \( \nu_{\text{max}} \) 3437, 3075, 2931, 2856, 1469, 1431, 1094, 694 cm\(^{-1}\)

\(^1\)H NMR (300 MHz, CDCl₃) : \( \delta \) 7.70-7.60 (m, 4H), 7.46-7.30 (m, 6H), 3.92 (dd, \( J = \) 12.6, 2.2 Hz, 1H), 3.86-3.79 (m, 2H), 3.61 (dd, \( J = \) 12.6, 4.5 Hz, 1H), 3.15 (dt, \( J = 5.8, 2.2 \) Hz, 1H), 3.02-2.96 (m, 1H), 2.16 (br.s, 1H), 1.83 (q, \( J = 5.8 \) Hz, 2H), 1.08 (s, 9H)

\(^{13}\)C NMR (75 MHz, CDCl₃) : \( \delta \) 135.4, 133.5, 129.6, 127.6, 61.6, 60.6, 58.6, 53.7, 44.7, 26.7, 19.1

ESI-MS : \( m/z \) 379.0 [M+Na]\(^+\)

[\( \alpha \)]\(^{25}\) \text{D} - 16.9 (c 2.5, CHCl₃)

(3S)-5-[1-tert-Butyl-1,1-diphenylsilyl]oxy-1-penten-3-ol (71)

To a solution of epoxy alcohol 70 (2.1 g, 5.8 mmol) in diethyl ether:acetonitrile (3:1) (30 mL) were added TPP (2.3 g, 8.8 mmol), iodine (2.25 g, 8.8 mmol) and imidazole (0.74 g, 11.6 mmol) sequentially at 0 °C under nitrogen atmosphere and stirred for 30 min. After the completion of reaction (monitored by TLC), saturated sodium thiosulfate (10 mL) solution was added and extracted with ethyl acetate (2x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give the iodoepoxide. Activated Zn dust (0.9 g, 13.0 mmol) was added to the crude iodoepoxy compound in ethanol (20 mL) and stirred at refluxing temperature for 2 h. The mixture was passed through a short pad of celite. The filtrate was concentrated and the residue was purified by column chromatography (hexane:ethyl acetate - 8:2) to afford the allyl alcohol 71 as pale yellow oil (1.7 g, 85%)

\(^1\)H NMR (300 MHz, CDCl₃) : \( \delta \) 7.69-7.63 (m, 4H), 7.44-7.33 (m, 6H), 5.91-5.80 (m, 1H), 5.30 (dt, \( J = 11.3, 17.1 \) Hz, 1H), 5.12 (dt, \( J = 1.8, 1094, 694 \) cm\(^{-1}\)
To a solution of allylic alcohol (1.5 g, 11.3 mmol) in CH$_2$Cl$_2$ (15 mL) was added imidazole (0.84 g, 13.3 mmol) and cooled to 0°C. After 10 min, TBS-Cl (1.0 g, 6.42 mmol) was added to the reaction and stirred for 3 h at room temperature. The reaction was diluted with water (5 mL) and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL) and the combined organic extracts was dried over Na$_2$SO$_4$ and concentrated under vacuo. Purification of the residue on silica gel column chromatography (hexane:ethyl acetate - 95:5) afforded the compound 72 as thick liquid (1.9 g, 95%).
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(S)-3-(tert-Butyldimethylsilyloxy)pent-4-en-1-ol (73)

Ammonium fluoride (1.4 g, 39.0 mmol) was added to a stirred solution of compound 72 (1.8 g, 3.9 mmol) in methanol (30 mL) and stirred for 10 h at room temperature. The mixture was filtered through Buchner funnel and washed with ethyl acetate (10 mL). The filtrate was concentrated under vacuum and water (20 mL) was added and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts was washed with brine and dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue over silica gel column chromatography (hexane:ethyl acetate-9:1) afforded the alcohol 73 (0.7 g, 80%).

\[ \text{1H NMR (300 MHz, CDCl}_3\text{)}: \delta 5.88-5.74 (m, 1H), 5.17 (d, J = 17.2 Hz, 1H), 5.05 (d, J = 10.7 Hz, 1H), 4.41-4.32 (m, 1H), 3.81-3.60 (m, 2H), 2.76 (br.s, 1H), 1.86-1.61 (m, 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H) \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{)}: \delta 140.6, 114.1, 72.7, 59.7, 39.2, 25.7, 18.0, -5.1, -4.2 \]

\[ \text{ESI-MS: m/z 477 [M+Na]}
\]

(S)-3-(tert-Butyl-dimethyl-silanyloxy)-pent-4-enoic acid (74)

To a stirred solution of IBX (1.78 g, 6.35 mmol) in DMSO (2 mL) under nitrogen atmosphere was added compound 73 (0.7 g, 1.5 mmol) in anhydrous THF (10 mL) at room temperature and the mixture was stirred for 1 h. The reaction was then diluted with ether (10 mL) and filtered through a pad of celite. The filtrate was washed with aq. NaHCO₃ solution, and the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. This crude aldehyde was immediately used for the further reaction without additional purification. NaClO₂ (0.58 g, 6.40 mmol), NaH₂PO₄ (1.0 g, 6.40 mmol) and 2-methyl-2-butene (3.2 mL, 6.40 mmol, 2M solution in toluene) were added to a stirred solution of the aldehyde in t-BuOH (7.5 mL) and water (2.5 mL) and stirred at room
temperature for 6 h. The solvents were removed under reduced pressure and extracted with ethyl acetate (2 x 25 mL), the combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane:ethyl acetate - 8:2) to give the acid 74 (0.54 g, 76% for two steps) as a colourless liquid.

IR (KBr) : \( \nu_{\text{max}} \) 3365, 2826, 1715 cm⁻¹

\(^1\)H NMR (300 MHz, CDCl₃) : \( \delta \) 5.91-5.78 (m, 1H), 5.25 (dt, \( J = 17.1, 1.5 \) Hz, 1H), 5.07 (dt, \( J = 10.7, 1.5 \) Hz, 1H), 4.61-4.54 (m, 1H), 2.47 (dd, \( J = 15.1, 5.2 \) Hz, 1H), 2.47 (dd, \( J = 15.1, 5.2 \) Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H)

\(^13\)C NMR (75 MHz, CDCl₃) : \( \delta \) 176.3, 139.5, 115.2, 70.5, 43.3, 25.7, -5.2, -4.4

ESI-MS : m/z 231[M+H]⁺

\([\alpha]_D^{32}\) : 2.1, (c = 0.8, CHCl₃)

(2R)-1-[(4S,5R)-5-Ethenyl-2-methyl-1,3-dioxolan-4-yl]nonan-2-yl (3S)-3-[(tert-butyldimethylsilyl)oxy]pent-4-enoate (75)

To a solution of alcohol 65 (0.30 g, 1.11 mmol), PPh₃ (0.58g, 2.22 mmol), DIAD (0.414 mL, 2.22 mmol) and acid 74 (0.255g, 1.11 mmol) were added in dry benzene (5 mL) at 0 °C and stirred at room temperature for 6 h. The reaction was concentrated under reduced pressure to remove the volatile components and the residue was purified by silica gel column chromatography (hexane:ethyl acetate - 9:1) to give diene (0.35 g, 62%).

IR (KBr) : \( \nu_{\text{max}} \) 2925, 2855, 17377, 1253, 1084 cm⁻¹

\(^1\)H NMR (300 MHz, CDCl₃) : \( \delta \) 5.90-5.67 (m, 2H), 5.23-5.17 (m, 3H), 5.0-4.92 (m, 2H), 4.56 (m, 1H), 4.48-4.41 (m, 1H), 2.50 (dd, \( J = 15.8, 7.1 \) Hz, 1H), 2.38 (dd, \( J = 15.8, 5.6, 1H \), 1.6-
1.51 (m, 4H), 1.45 (s, 3H), 1.33-1.20 (m, 13H), 0.91-0.85 (m, 12H), 0.04-0.07 (2 s, 6H)

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 170.4, 140.2, 134.1, 118.4, 114.6, 108.3, 79.5, 74.8, 72.2, 70.5, 43.6, 35.2, 34.7, 31.7, 29.4, 29.1, 28.2, 25.8, 25.6, 25.0, 22.6, 18.1, 14.0, -4.4, -4.9

ESI-MS: $m/z$ 505 [M+Na]$^+$.  

HRMS: Calcd for C$_{27}$H$_{50}$NaO$_5$Si [M+Na]$^+$: 505.322, found: 505.3322

$[\alpha]^{32}_D$: -9.2, ($c$ = 1.4, CHCl$_3$)

(2R)-1-[(4S,5R)-5-ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]nonan-2-yl(3S)-3-hydroxypent-4-enoate (76)

TBAF (0.74 mL, 0.74 mmol) was added to a stirred solution of diene 75 (0.30 g, 0.62 mmol) in THF (10 mL) at 0 °C and stirred for 1 h at room temperature. The reaction was then quenched with saturated NH$_4$Cl, the phases were separated and the aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine, dried Na$_2$SO$_4$ and concentrated in vacuo. The residue upon purification by silica gel column chromatography (hexane:ethyl acetate-85:15) afforded 76 (0.183 g, 87%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.91-5.67 (m, 2H), 5.35-5.31 (m, 1H), 5.29-5.25 (m, 1H), 5.25-5.19 (m, 1H), 5.16-5.09 (m, 1H), 5.09-5.01 (m, 1H), 4.54-4.43 (m, 2H), 4.19-4.10 (m, 1H), 3.05 (br.s, 1H) 2.54(dd, $J$ = 3.7, 15.8, 1H), 2.45 (dd, $J$ = 15.8, 8.3 Hz, 1H) 1.70-1.46 (m, 4H), 1.45 (s, 3H), 1.34-1.24 (m, 13H), 0.89 (t, $J$ = 6.9 Hz, 3H)
\( ^{13}C \) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 171.8, 138.7, 134.0, 118.5, 115.3, 108.4, 79.4, 74.4, 72.5, 68.9, 41.4, 34.9, 34.6, 31.7, 29.3, 29.1, 28.1, 25.6, 25.1, 22.6, 14.0

ESI-MS: \( m/z \) 391 [M+Na]\(^+\)

HRMS: Calcd for C\(_{21}\)H\(_{36}\)NaO\(_5\)[M+Na]\(^+\): 391.2455, found: 391.2444

\([\alpha]_D^{30}\): -19.8 (c 0.535, CHCl\(_3\))

\( E-(3aS,5R,9S,11aR)-5\)-Heptyl-9-hydroxy-2,2-dimethyl-4,5,8,9-tetrahydro-3aH-[1,3]dioxolo[4,5-d]oxecin-7(11aH)-one (77)

To a solution of diene 76 (0.050 g, 0.136 mmol) in degassed CH\(_2\)Cl\(_2\) (120 mL) was added Grubbs’ second generation catalyst (0.012 g, 10 mol\%) and heated to reflux for 3 h under argon atmosphere. The reaction was concentrated under \textit{vacuo} and the residue was purified by silica gel column chromatography (hexane:ethyl acetate- 85:15) to give a mixture of \textit{trans} (0.024 g, 47%) and \textit{cis} (0.011 g, 23%) compounds.

\( ^1H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 5.71 (dd, \( J = 15.8, 9.2 \) Hz, 1H), 5.57 (dd, \( J = 15.8, 7.9 \) Hz, 1H), 4.82-4.75 (m, 1H), 4.54 (dd, \( J = 9.2, 5.2 \) Hz, 1H), 4.42-4.36 (m, 1H), 4.07 (dd, \( J = 10.5, 6.5 \) Hz, 1H), 2.79 (dd, \( J = 13.1, 7.9 \) Hz,1H), 2.31 (dd, \( J = 13.1,7.9 \) Hz, 1H), 2.28-2.24 (m, 1H), 1.71-1.63 (m, 1H), 1.61-1.56 (d, \( J = 15.8, 1H \)), 1.5 (s,1H), 1.48-1.41(m, 1H), 1.38-1.25 (m, 15H), 0.96 (t, \( J = 6.5 \) Hz, 3H)

\( ^{13}C \) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 170.0, 129.6, 108.6, 80.8, 74.9, 70.02, 74.4, 43.8, 38.0, 31.7, 29.2, 29.29, 29.7, 28.0 ,25.3,25.6 22.6, 14.0

ESI-MS: \( m/z \) 363 [M+Na]\(^+\)
HRMS: Calcd for C_{19}H_{45}NaO_{5} [M+Na]^+ : 363.2147, found: 363.2155

$[\alpha]_D^{30}$: -35.0 (c 0.15, CHCl₃)

Z-(3aS,5R,9S,11aR)-5-heptyl-9-hydroxy-2,2-dimethyl-4,5,8,9-tetrahydro-3aH-[1,3]dioxolo[4,5-d]oxecin-7(11aH)-one (78)

$^1$H NMR (500 MHz, CDCl₃: C₆D₆, 1:1): δ 5.65-5.59 (dd, J = 11.8, 10.5 Hz, 1H), 5.56-5.50 (m, 2H), 5.12-5.05 (m, 1H), 4.59-4.54 (m, 1H), 4.25-4.20 (m, 1H), 2.53 (dd, J = 11.8, 5.2 Hz, 1H), 2.35-2.31 (m, 1H), 2.29 (br.s, 1H), 1.96-1.88 (m, 2H), 1.60-1.51 (m, 1H), 1.49-1.46 (m, 4H), 1.33-1.20 (m, 13H), 0.88 (t, J = 6.5 Hz, 3H)

$^{13}$C NMR (125 MHz, CDCl₃: C₆D₆, 1:1): δ 169.0, 131.5, 130.3, 106.8, 76.1, 73.6, 67.9, 71.4, 40.7, 35.1, 35.0, 31.0, 28.8, 28.6, 28.0, 25.2, 22.1, 24.8, 13.0

ESI-MS: m/z 363 [M+Na]^+

$[\alpha]_D^{30}$: +13.5 (c 0.25, CHCl₃)

(E)-(4S,7R,8S,10R)-10-Heptyl-4,7,8-trihydroxy-3,4,7,8,9,10-hexahydro-oxecin-2-one (53)

To a solution 77 (0.020 g, 0.055 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added TFA (0.05 mL) and stirred for 1 h at room temperature. The mixture was concentrated under
vacuum and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate - 75:25) to give achaetolide (0.012 g, 65%) as a white solid.

Mp : 122-124 °C
IR (KBr) : νmax 3455, 2927, 2857, 1713, 1171 cm⁻¹

¹H NMR (300 MHz, CDCl₃) : δ 6.02 (dd, J = 15.6, 2.9 Hz, 1H), 5.68 (d, J = 5.6 Hz, 1H), 4.82 (dt, J = 7.8, 6.8 Hz, 1H), 4.76 (m, 1H), 4.57 (m, 1H), 3.6 (d, J = 9.7 Hz, 1H), 2.62 (dd, J = 11.7, 3.9 Hz, 1H), 2.58 (dd, J = 11.7, 3.9 Hz, 1H), 2.34 (m, 1H), 2.25 (br.s, 1H), 1.63 (br.s, 2H), 1.55 (m, 2H), 1.48 (d, J = 15.6 Hz, 1H), 1.26 (m, 10H), 0.88 (t, J = 7.8 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃) : δ 171.0, 130.8, 125.1, 75.3, 73.3, 67.2, 43.8, 36.9, 36.8, 31.7, 29.7, 29.4, 29.1, 25.0, 22.6, 14.1

ESI-MS : m/z 323 [M+Na]⁺
HRMS : Calcd. for C₁₆H₂₈O₄Na [M+Na]⁺, found: 323.1830.

[α]D²⁷ : - 24.0 (c 0.23, MeOH)
REFERENCES


