2. BISELYNGBYASIDE

2.1. INTRODUCTION:

Ocean continues to be most important source of pharmacologically active compounds. Marine natural products belonging to the genus *Lyngbya* (family-Bacteria, phylum- Cyanobacteria) have proved to be particularly rich sources of biologically potent secondary metabolites. Macrolides containing glycosidic linkage also showed promising biological activities. Biselyngbyaside 1 (figure 1) is a remarkable marine natural metabolite, isolated recently from a marine cyanobacterium *Lyngbya* species collected from the Okinawa Prefecture in Japan, by Suenaga and co-workers. Biselyngbyaside, is a densely olefinated 18 membered macrolide glycoside with unique structure and interesting biological activity. It possesses high degree of structural diversity and exhibits broad spectrum cytotoxicity against human cancer cell line panel. Biselyngbyaside 1 exhibited cytotoxicity against HeLaS3 cells with an IC$_{50}$ value 0.1 μg/mL. The limited resource of biselyngbyaside from Nature could not allow the biologists for extensive screening of its biological activity. Thus a total synthesis is necessary to study the biological activities in detail, unfortunately no total syntheses of biselyngbyaside is reported in literature till date.

![Image of Biselyngbyaside 1](image1.png)

**Figure 1**

ISOLATION:

Various species of the genus *Lyngbya* are prolific producers of secondary metabolites, many of which possess a wide range of biological activities such as
biselyngbyaside,\textsuperscript{3} bisebromoamide,\textsuperscript{4} ulongapeptin\textsuperscript{5} and palauamide.\textsuperscript{6} Suenaga \textit{et al.} collected the marine cyanobacterium \textit{Lyngbya sp.} in Okinawa prefecture which was extracted with methanol. The concentrated extract was partitioned between ethyl acetate and water. Ethyl acetate layer was concentrated and partitioned between \textit{n}-hexanes and 90\% aqueous methanol. The concentrated methanol layer was subjected to bio-assay guided fractionation by cytotoxicity against HeLa S3 cells with column chromatography (ODS silica gel, methanol-water) and reverse-phase HPLC to give 1 as a colorless oil. Complete structure of 1 was confirmed by studying all the data from \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, mass, IR and 2D NMR spectroscopy including \textsuperscript{1}H-\textsuperscript{1}H COSY, NOESY and HMBC correlations.

\textbf{Structural elucidation:}

The \textsuperscript{1}H NMR spectrum of 1 showed the presence of six methyl groups at \(\delta\) 3.62, 3.15, 1.67, 1.64, 1.55 and 1.02. The molecular formula of 1 was determined to be \(\text{C}_{34}\text{H}_{52}\text{O}_{9}\) by ESIMS showed (M+Na\textsuperscript{+}) peak at \(m/z\) 627.3487. The IR spectrum of 1 showed absorption bands at 3589, 3502 (broad) and 1725 cm\textsuperscript{-1} which clearly indicated the presence of hydroxyl and ester groups. In the \textsuperscript{13}C NMR spectrum, 34 carbon signals were observed, including one carbonyl carbon at \(\delta\) 172.1 ppm, 12 olefin carbons (\(\delta\) 140.1, 138.4, 135.3, 133.3, 133.0, 132.7, 132.1, 131.9, 129.3, 127.9, 127.4 and 124.9) and six methyl carbons at \(\delta\) 61.0, 55.6, 23.6, 22.5, 18.1, and 10.2. Remaining carbon signals were assigned to six methylenes and nine methines, based on the results of HMQC experiment. The absolute stereochemistry of C3, C17 and the 3-\textit{O}-methylglucoside moiety was determined by the modified Mosher’s method\textsuperscript{7} and with synthetic degradation products. The geometries of the two trisubstituted olefins were clarified to be \textit{8E} and \textit{18Z}, based on the NOESY correlations. The \textit{trans}-geometry of the olefins at C4, C12, C14 and C21 positions was confirmed by their coupling constants in \textsuperscript{1}HNMR spectra and NOESY correlations.

\textbf{Biological activity:}

Biselyngbyaside 1, exhibited cytotoxicity against HeLaS3 cells with an IC\textsubscript{50} value 0.1 \textmu g/mL. It was evaluated against a disease-oriented panel composed of 39
human cancer cell lines (HCC panel) at the Japanese Foundation for Cancer Research. The average GI\textsubscript{50} value across all of the cell lines tested was 0.60 μM and biselyngbyaside exhibited differential cytotoxicities: the central nervous system cancer SNB-78 (GI\textsubscript{50} 0.036 μM) and lung cancer NCI H522 (GI\textsubscript{50} 0.067 μM) were especially sensitive. Biselyngbyaside was COMPARE negative, indicating that it likely inhibits cancer cell proliferation through a novel mechanism.

2.2. PRESENT WORK:

As a part of our ongoing research program towards the synthesis of bio-active marine natural products and in view of structural features as well as potent cytotoxic properties of biselyngbyaside, we were attracted towards the synthesis of biselyngbyaside 1.

The identification of strategic bonds and functional group transformation which go into their construction in arriving at key synthons, play a vital role in sketching a feasible scheme for the synthesis, generally containing a pathway of synthetic intermediates connected by possible reactions for the required interconversion. In the present context, as it is apparent from the structure, the molecule is a densely olefinated macrolide having six olefin bonds with the other active functional groups appended to it. Careful insight into the structure led us to be choosier about starting material, either commercially available or prepared with some operationally simple protocols.

Reterosynthesis:

The retrosynthetic analysis of biselyngbyaside 1 is shown in scheme 1. The 18-membered macrolide 1 may be constructed by the ring-closing metathesis (RCM) of diene 2. The RCM precursor 2 in turn could be derived from Yamaguchi esterification of C5-C23 and C1-C4 fragments 3 and 4, respectively. The C5-C23 segment may be prepared from Julia–Kocienski olefination with the fragments 5 and 6. The fragments 4 and 6 could be prepared from the common intermediate allyl alcohol 7, which could be conveniently prepared from 1, 3-propane diol as starting
material. The crucial reactions involved in the synthesis of the individual fragments were copper catalyzed crotylation, regioselective opening with Me₃Al, Barbier’s allylation and E-Selective MeLi addition. Sharpless asymmetric epoxidation and Crimmin’s acetate aldol reactions are successfully used to install the required chirality at C10 and C17 stereocentres. Julia–Kocienski olefination, Yamaguchi esterification and Ring-Closing metathesis are the other crucial key steps for the construction of biselyngbyaside 1.

![Scheme 1](image)

**Results and discussion:**

Our synthesis commenced with known common intermediate allyl alcohol 7, which was conveniently prepared by well-known documented procedure using commercially available 1, 3-propane diol as starting material as depicted in scheme 1. The allyl alcohol 7 can be used for the synthesis of both C1-C4 and C5-C12 fragments 4 and 6 respectively.
Synthesis of common intermediate allyl alcohol 7:

Selective mono-protection of 1, 3-propane diol as its tert-butyl diphenylsilyl ether 9 was achieved by using TBDPSCI and imidazole in the presence of CH₂Cl₂ with 90% yield. The ¹H NMR spectrum of compound 9 revealed the presence of two multiplets at δ 7.83-7.64 and δ 7.54-7.32 corresponding to aromatic protons suggested the conversion of etherification reaction. Oxidation of primary hydroxyl functionality in 9 using pyridinium dichromate (PDC) in dichloromethane provided the corresponding aldehyde, which was subsequently subjected to two carbon homologation through Wittig olefination using (ethoxycarbonylmethylene) triphenyl phosphorane in anhydrous dichloromethane to give α, β-unsaturated ester 10 in 88% yield for two steps (scheme 2) with E-selectivity.

![Diagram](image)

**Scheme 2**

¹H NMR spectrum of 10 showed a multiplet at δ 6.97-6.83 ppm and a doublet at δ 5.78 ppm with a coupling constant $J_{CH=CH} = 15.6$ Hz clearly indicating the presence of olefin bond with trans- geometry corresponding to α, β-unsaturated ester 10. The IR spectrum of 10 showed a strong absorption peak at 1722 cm⁻¹ further confirmed the presence of ester functionality. The ¹³C NMR spectrum of 10 showed a peak at 166.3 ppm belonging to the carbonyl carbon of the ester and olefin carbons resonated at δ 145.7 and δ 129.6 ppm, which clearly indicated the presence of α, β-unsaturated ester. Reduction of ester functionality in 10 was achieved with DIBAL-H in dichloromethane as solvent under anhydrous conditions at -78 °C to room
temperature to afford the corresponding allyl alcohol 7 in 88% yield. The compound 7 was characterized by its ESI MS which showed [M+Na]^+ peak at m/z 363 indicated the reduction of ester to alcohol.

**Stereoselective synthesis of acid fragment (4):**

Stereoselective synthesis of fragment 4 was achieved by using allylalcohol 7 as depicted in scheme 3. The well known Sharpless asymmetric epoxidation using (+)-DET was explored to incorporate the stereogenic centres at olefin functionality. The compound 7 was exposed to Sharpless asymmetric epoxidation\(^9\) using (+)-DET, titanium (IV) isopropoxide and tert-butyl hydroperoxide in dichloromethane as solvent under anhydrous conditions to give epoxy alcohol 11 in 82% yield. It can be seen from the results that the expected chiral epoxide 11 was obtained in good yield and enantioselectivity (9:1). The product was confirmed by its \(^1\)H NMR spectrum which suggested the presence of oxirane protons at \(\delta\) 3.61 as a doublet of doublet and \(\delta\) 3.15 ppm as a doublet of triplet. The compound 11 was further confirmed by its ESIIMS which showed [M+Na]^+ peak at m/z 379. Epoxy alcohol 11 was converted into its corresponding iodide using triphenylphosphine, imidazole and I\(_2\) in dry THF at room temperature. The resultant iodo derivative was subjected to reductive elimination, followed by the opening of epoxide in the presence of activated zinc dust in refluxing ethanol to afford the desired chiral allyl alcohol 12 in over 70% yield.\(^{10a}\) The product 12 was confirmed by its \(^1\)H NMR spectrum which revealed the presence of olefin protons resonating at \(\delta\) 5.94-5.81 as a multiplet for 1H, a doublet of triplet at \(\delta\) 5.30 for 1H and 5.12 ppm as a doublet of triplet for 1H. The product was further confirmed by its \(^{13}\)C NMR spectrum which showed all the representative peaks for olefin as well as aliphatic and aromatic carbons. This transformation was further confirmed by its mass spectrum which showed [M+Na]^+ peak at m/z 363.
The secondary hydroxyl group in 12 was protected as PMB ether 13 by using p-methoxybenzyl bromide and NaH at 0 °C to room temperature for two hours in 90% yield. The compound 13 on desilylation with NH₄F in MeOH provided the desired alcohol 14 in 87% yield. Disappearance of tert-butyl protons as a singlet at δ 1.03 ppm in the ¹H NMR of compound 14 clearly indicated the desilylation of TBDPS group. This was further confirmed by its mass spectrum which showed [M+Na]⁺ peak at m/z 245. Oxidation of primary hydroxyl group in 14 was achieved using IBX in DMSO/THF to afford the corresponding aldehyde, which without further purification was oxidized into acid 4 under Pinnick oxidation conditions¹⁰b (NaClO₂, NaH₂PO₄,2H₂O and 2-methyl-2-butene) in dichloromethane with 78% yield for two steps. The ¹H NMR spectrum of 4 showed the absence of CH₂OH protons and ESIMS spectra of 4 showed [M+Na]⁺ peak at m/z 259 clearly indicated the conversion of alcohol into acid functionality. The compound, thus obtained was in agreement with the reported data.¹¹

**Stereoselective synthesis of C5-C12 segment (6):**

The journey towards the synthesis of segment 6 commenced with the known allyl alcohol 7. Allyl alcohol 7 was subjected to Sharpless asymmetric epoxidation⁹
using (-)-DET, titanium (IV) isopropoxide and tert-butyl hydroperoxide in dichloromethane under anhydrous conditions to afford epoxy alcohol 15 in 80% yield (Scheme 4).

\[ \text{HO-C} = \text{C-OH} \quad \xrightarrow{(-)-DET, Ti(O'Pr)_4, TBHP, CH}_2\text{Cl}_2, 4 \text{ A}^\circ\text{ MS} \quad \xrightarrow{-30 ^\circ\text{C}, 8 \text{ h}, 80\%} \quad \text{HO-C} = \text{C-O} \prescript{}{\text{OTBDPS}} \]

\[ \text{Me}_3\text{Al, CH}_2\text{Cl}_2, 0 ^\circ\text{C, 12 h, 75\%} \]

\[ \text{HO-C} = \text{C-OH} \quad \xrightarrow{1. \text{NaIO}_4, \text{THF}: \text{H}_2\text{O} (1:1) \quad \xrightarrow{2. \text{Ph}_3\text{P} = \text{C(Me)COOEt}, \text{CH}_2\text{Cl}_2, \text{rt, 3 h}, 82\%} \quad \text{C} = \text{C-O} \prescript{}{\text{EtO}}\text{C} = \text{C-O} \prescript{}{\text{OTBDPS}} \]

**Scheme 4**

The compound 15 was confirmed by its \(^1\)H NMR spectrum which showed the presence of oxirane protons at \(\delta 3.61\) as doublet of doublet and \(\delta 3.15\) ppm as doublet of triplet. The compound 15 was further confirmed by its ESI MS which showed \([\text{M+Na}]^+\) peak at \(m/z\) 379. The regioselective opening of epoxy alcohol 15 was achieved using Me\(_3\)Al in dry CH\(_2\)Cl\(_2\) under anhydrous conditions to furnish the 1, 2-diyl 16 as a sole product in 75% yield.\(^{12}\) Oxidative cleavage of the diol 16 into corresponding aldehyde was achieved by treatment of 16 with NaIO\(_4\) in THF/H\(_2\)O system. The resultant aldehyde was subsequently subjected to two carbon homologation through Wittig olefination using ethyl-2-(triphenyl phosphoranylidene) propanoate in benzene to give \(\alpha, \beta\)-unsaturated ester 17 as a single isomer (\(E\)-isomer) in over 82% yield (scheme 4). The \(^1\)H NMR spectrum of 17 revealed the presence of a doublet at \(\delta 6.49\) for 1H with a coupling constant \(J_{CH=CH} = 10\) Hz suggested the presence of substituted \(\alpha, \beta\)-unsaturated ester. The IR spectrum of 17 showed a strong absorption peak at 1710 cm\(^{-1}\) suggested the presence of carbonyl functionality of ester group. The \(^{13}\)C NMR spectrum of 17 clearly showed a peak at 168.3 ppm corresponding to carbonyl (C=O) carbon of \(\alpha, \beta\)-unsaturated ester. The compound 17 was further confirmed by its ESIMS which showed \([\text{M+Na}]^+\) peak at \(m/z\) 447.
The reduction of ester functionality in 17 was achieved using DIBAL-H in dichloromethane under anhydrous conditions at -78 °C to afford the corresponding α, β-unsaturated aldehyde, which without further purification was directly used for the next step (scheme 5). Aldehyde was subjected under Barbier allylation conditions (Zn, allyl bromide and sat. NH₄Cl) in dry THF at 0 °C to room temperature for 3 h to furnish the mixture of allyl alcohols 18 and 19 in 9:11 ratio with 92% overall yield. The diastereomeric ratio of the mixture was determined by HPLC. These compounds were confirmed by its ESIMS which showed (M+Na)⁺ peak at m/z 351 and IR spectrum which showed a characteristic absorption at 3321 cm⁻¹ clearly suggested the presence of alcohol functionality. The mixture of diastereomers was separated by silica gel column chromatography. The absolute stereochemistry of the newly generated hydroxyl group during the allylation was confirmed by modified Mosher’s analysis and NMR studies.

**Modified Mosher’s analysis.**

Mosher’s analysis is the most commonly used nuclear magnetic resonance (NMR) based method for the determination of absolute configuration of newly generated chiral alcohols and amines. The Mosher’s analysis relies on the fact that the protons in diastereomeric R and S Mosher esters display different arrays of chemical shifts (δ) in their Proton NMR spectra. For this analysis, we have to prepare one set of esters with R and S Mosher’s acid (α-methoxy-β-trifluoromethylphenylacetic acid) and the alcohol moiety whose stereo center is to be determined. By calculating the
sign of the difference in chemical shifts ($\Delta \delta$) for a number of analogous pairs of protons (the set of $\Delta \delta^{SR}$ values) in the diastereomeric esters, we can easily predict the absolute configuration of the carbinol stereo center.

The major diastereomer 19 was subjected to esterification with $R$ and $S$ Mosher’s acids individually in the presence of DCC, DMAP in dry CH$_2$Cl$_2$ at room temperature to afford each of diastereomeric $R$- and $S$-MTPA esters $M_1$ and $M_2$, respectively in good yields (figure 2).

**Confirmation of stereochemistry at new stereogenic centre:**

According to the following formula, we calculated the $\Delta \delta$ values of the particular proton of the each compound $M_1$ and $M_2$, respectively and arrange them in a basic model (figure 3) of Mosher’s ester analysis for the confirmation of stereogenic centre.

$$\Delta \delta^{SR} = (\delta^S - \delta^R) \times 10^3$$
Calculation:

\[ \Delta \delta_{_{\text{SR}}}^{_{\text{a}}} = (\delta_{S} - \delta_{R}) \times 10^3 \]
\[ = 2.41 - 2.45 \times 10^3 \]
\[ = -0.04 \times 10^3 \]
\[ = -40 \]

\[ \Delta \delta_{_{\text{SR}}}^{_{\text{b}}} = (\delta_{S} - \delta_{R}) \times 10^3 \]
\[ = 2.28 - 2.32 \times 10^3 \]
\[ = -0.04 \times 10^3 \]
\[ = -40 \]

\[ \Delta \delta_{_{\text{SR}}}^{_{\text{c}}} = (\delta_{S} - \delta_{R}) \times 10^3 \]
\[ = 2.64 - 2.58 \times 10^3 \]
\[ = 0.06 \times 10^3 \]
\[ = +60 \]

According to the Mosher’s analysis and NMR studies, we concluded that the new stereogenic centre at secondary hydroxyl is \( S \) in the major homo allylalcohol 19.

The minor diasteromer 18 was subjected to Mitsunobu conditions (TPP, DIAD, \( p \)-nitrobenzoic acid) in dry THF under anhydrous conditions at 0 °C to room temperature for 16 h to afford the corresponding \( p \)-nitrobenzoate (scheme 6). Immediate hydrolysis of freshly prepared benzoate under basic conditions using \( \text{K}_2\text{CO}_3 \) in methanol at room temperature afforded allyl alcohol 19 with complete inversion of stereochemistry (\( S \)) at C7 alcoholic position in quantitative yields (scheme 6).
The alcohol functionality in 19 was protected as methyl ether using NaH and MeI in anhydrous THF at 0 °C to afford the product 20 in 90% yield (scheme 7). The 1H NMR spectrum of 20 showed a singlet at δ 3.05 clearly indicated the presence of OCH₃ and product was further confirmed by its mass spectrum, which showed (M+Na)⁺ peak at m/z 459. The primary TBDPS group in 20 was desilylated using NH₄F in methanol to provide the primary alcohol 21 in 87% yield. The 1H NMR spectrum of 21 revealed the diminished aromatic protons and its mass spectrum showed (M+Na)⁺ peak at m/z 215 confirmed the product. Now the stage was set for the introduction of tetrazole ring to prepare the desired PT-sulfone 6 employed for Julia-Kocienski olefination. Alcohol 21 was subjected under Mitsunobu conditions using 1-Phenyl-1H-tetrazole-5-thiol (PTSH), TPP and DIAD in dry THF under anhydrous conditions at room temperature to afford the corresponding thioether which was subsequently subjected with hexa-ammonium heptamolybdate tetrahydrate and H₂O₂ in ethanol at room temperature for 12 h to afford the title compound sulfone 6 in 87% yield for two steps (scheme 6).

Synthesis of α, β-unsaturated aldehyde (5):

Synthesis of aldehyde fragment 5 was achieved by copper catalyzed regioselective coupling 15 between crotyl bromide 22 and ethyl propiolate 8 as depicted in Scheme 7. Copper (I) mediated allylation of ethyl propiolate 8 in presence
of weak inorganic base K$_2$CO$_3$ provided the inseparable regioisomers 23a and 23b in 85% yield and 4:1 ratio, respectively. The ratio of the isomers was determined by chiral HPLC. The IR spectrum showed a strong absorption peak at 1710 cm$^{-1}$ belonging to the carbonyl (C=O) function of ethyl ester. The $^{13}$C NMR spectroscopy clearly showed a peak at 153.6 ppm for carbonyl carbon of alkynoate and two other peaks resonating at 128.5 and 122.3 ppm represented the olefin carbons.

Michael addition of lithium dimethylcuprate (Me$_2$CuLi) to the alkynoate was achieved via the procedure of Corey et al.$^{16}$ to give the expected enoate with requisite olefin geometry. In situ preparation of Gilman reagent (Me$_2$CuLi) from MeLi and freshly dried CuI, followed by treatment with mixture of esters 23a and 23b in dry THF under anhydrous conditions at -78 °C gave the corresponding $\alpha, \beta$-unsaturated ester 24 as a sole product in 70% yield (scheme 8). Fortunately, ester 24 possessed the requisite trans-geometry needed for the preparation of aldehyde fragment 5. The $^1$H NMR spectrum of 24 showed a singlet at $\delta$ 1.85 for 3H corresponding to methyl (CH$_3$C=CH-) and a singlet at $\delta$ 5.65 belonging to olefin proton (CH$_3$C=CH-) of mono substituted $\alpha, \beta$-unsaturated ester. The controlled reduction of ester functionality in 24 was achieved using DIBAL-H in dry CH$_2$Cl$_2$ at -78 °C under inert atmosphere to furnish the corresponding aldehyde 25 in 65% yield. The $^1$H NMR spectrum of 25 showed a doublet at $\delta$ 9.95 for one proton clearly indicated the presence of aldehyde. The product was further confirmed by the diminished quartet peak at $\delta$ 4.10 ppm and triplet at $\delta$ 1.27 ppm. Aldehyde 25 proved to be labile and was therefore used immediately, without further purification. Aldehyde was subjected to Crimmin’s assymmetric aldol conditions$^{17}$ to install the requisite stereo center at C-17 hydroxyl function. Aldehyde 25 was treated with the known chiral auxiliary (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl) ethanone 26$^{18}$ in the presence of one equiv. of titanium (IV)
chloride and little excess of Hunig’s base (1.2 equiv) in dichloromethane under anhydrous conditions. The reaction was progressed successfully to furnish the diastereomers of β-hydroxy amide (dr 88:12) having the required stereochemistry for the major syn-product 27 (53%) along with the undesired minor anti-product (12%). The diastereomeric ratio of the crude product was determined by HPLC (Scheme 8). The mixture of diastereomeric products was easily separated by column chromatography.

Disappearance of aldehyde proton at 9.95 ppm and presence of five protons at δ 7.36-7.31 in the 1H NMR spectrum of the compound 27 clearly indicated the addition of chiral auxiliary. The 13C NMR spectrum of 27 showed a peak at δ 202.2 belonging to the carbonyl carbon (NH-C=O) of amide functionality and another peak at 172.0 ppm belonging to thiocarbonyl (NH-C=S) carbon of aldol adduct. The product was further confirmed by its ESIMS showed (M+Na)+ peak at m/z 395 and IR absorption showed a characteristic band at 3445 cm⁻¹ indicates the alcohol functionality. Secondary hydroxyl in 27 was protected as its silyl-ether 28 using TBSOTf in presence of 2, 6-Lutidine in dichloromethane at -78 °C under inert atmosphere in quantitative yields. The 1H NMR spectrum of 28 showed a singlet at δ 0.84 ppm for nine protons and two more singlets at δ 0.05, δ 0.03 suggested the presence of TBS group. 13C NMR spectrum of 28 showed two peaks resonating at δ -4.2, δ -4.8 ppm suggested the silyl attached carbons. The product was further confirmed by its mass spectrum which showed (M+Na)+ peak at m/z 511. The reductive cleavage of chiral auxiliary in compound 28 was achieved by using DIBAL-H at -78 °C in dichloromethane under anhydrous conditions gave the desired aldehyde 29 in 65% yield. The product was confirmed by disappearance of the aromatic protons.
at δ 7.36-7.31 and presence of doublet at δ 9.78 (aldehydic proton) in the $^1$H NMR spectrum of 29 and further confirmed by observing the disappearance of carbonyl derivative signals at δ 202.2 and 177.2 in its $^{13}$C NMR spectrum. Aldehyde 29 was subjected to two carbon homologation through Wittig olefination using triphenyl phosphoranylidene acetaldehyde (Ph$_3$PCHCHO) in dry CH$_2$Cl$_2$ under reflux conditions to afford the desired $\alpha$, $\beta$-unsaturated aldehyde 5 in quantitative yields\textsuperscript{19} (Scheme 9).

\[
\text{TBSO} \quad \text{R} \quad \text{O} \quad \text{28} \quad \xrightarrow{\text{DIBAL-H, -78°C}} \quad \text{OTBS} \quad \text{29} \quad \xrightarrow{\text{PPh$_3$CH=CHO, benzene, reflux, 2h, 90%}} \quad \text{5}
\]

**Scheme 9**

The $^1$H NMR spectrum of 5 revealed the presence of multiplet at δ 6.90-6.77 and another multiplet at δ 6.18-6.06 with a coupling constant $J_{\text{CH=CH}} = 15.1$ Hz providing the trans-geometry of double bond corresponding to $\alpha$, $\beta$-unsaturated aldehyde 5. The $^{13}$C NMR spectrum of compound 5 showed a peak at 166.3 ppm belongs to carbonyl carbon of $\alpha$, $\beta$-unsaturated aldehyde and olefin carbons resonated at 145.7 and 129.6 ppm respectively. IR spectrum showed a strong absorption band at 1697 cm$^{-1}$ corresponding to the carbonyl function of aldehyde. The product was further confirmed by its ESI MS which showed [M+K]$^+$ peak at m/z 347.0

**Construction of C5-C23 segment from 5 and 6:**

The synthesis of C5-C23 segment 3 was achieved by coupling of two partners, 5 and 6 under Julia–Kocienski olefination conditions\textsuperscript{20} which gave highly (E)-selective central diene unit of the fragment 30. Initially, sulfone 6 was deprotonated under anhydrous conditions using potassium hexamethyldisilazane (KHMDS) in dry THF followed by trapping of anion by treatment with $\alpha$, $\beta$-unsaturated aldehyde 5 at -78 °C for 3 h provided 95:5 mixture of (E, Z) coupling products in 88% yield (Scheme 10).
Diastereomers were easily separated by column chromatography using silica gel eluting with 4% EtOAc/hexanes. The major product separated from the column was concluded to be desired trans-hexadiene 30. The product was well characterized by collective information of all the spectral data including $^1$H, $^{13}$C NMR, mass, HRMS and IR spectroscopy. The $^1$H NMR spectrum of 30 showed the absence of aldehyde proton at 9.48 ppm and presence of 11 protons in the olefin region between $\delta$ 6.08-4.98 ppm provided the structural confirmation. The $^{13}$C NMR spectra of 30 showed 12 peaks at olefin region confirmed the presence of six double bonds. The product was further confirmed by its HRMS, which showed $[M+Na]^+$ peak cacl for C$_{30}$H$_{52}$NaO$_2$ is 495.3629 and found to be 495.3669.

The tert-butyl silyl group in 30 was cleaved in the presence of 2 equiv. of tetra-$n$-butyl ammonium fluoride (TBAF) in dry THF at 0 °C under anhydrous conditions provided the allyl alcohol 3 in 86% yield (Scheme 11). The $^1$H NMR of compound 3 revealed the absence of TBS protons suggested the cleavage of silyl group. The product was further confirmed by its mass spectrum which showed $[M+Na]^+$ peak at $m/z$ 381.
Construction of diene 2 from C5-C23 fragment and acid fragment 3:

Our efforts towards the synthesis of biselyngbyaside comes to end by construction of diene 2 from (S)-3-(4-methoxybenzyloxy) pent-4-enoic acid 4 and alcohol fragment 3 under Yamaguchi esterification conditions. The reaction was proceeded smoothly and gave the ester product without loss of stereochemistry at C17 hydroxyl function. The compound 2 was well characterized by its \(^1\)H NMR, \(^{13}\)C NMR, IR and HRMS spectral data. The \(^1\)H NMR of diene compound 2 revealed the presence of couple of doublet peaks at aromatic region and a singlet peak at \(\delta 3.76\) (s, 3H) clearly indicated the presence of PMB group. Huge no of multiplets with integration of 12 protons in the olefin region in \(^1\)H NMR spectra of 3 suggested the presence of olefin protons and a sharp singlet at \(\delta 3.14\) (s, 3H) belongs to the methyl protons (OCH\(_3\)) further confirmed the formation of ester. The \(^{13}\)C NMR spectrum of 2, which showed a peak at \(\delta 170.0\) ppm corresponding to the carbonyl carbon of the ester (C=O) and 14 peaks appeared at olefin region suggested the presence of seven double bonds. The product was further confirmed by its HRMS (ESI) calcd. for C\(_{36}\)H\(_{48}\)NaO\(_6\) [M+Na]\(^+\) at \(m/z\) 599.3343 and found to be at \(m/z\) 599.3320.
2.3 Experimental Section

3-((tert-Butyldiphenylsilyloxy)propan-1-ol (9).

![Diagram of 3-((tert-Butyldiphenylsilyloxy)propan-1-ol (9).]

Imidazole (27 g, 394 mmol) was added slowly to a stirred solution of 1, 3-propane diol (15 g, 197 mmol) in CH$_2$Cl$_2$ (150 mL) at 0 °C. After being stirred for 30 min, TBDPS-Cl (54 g, 197 mmol) in CH$_2$Cl$_2$ (50 mL) was added dropwise and allowed to stir for 4 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (150 mL). Two layers were separated and aqueous layer was extracted with CH$_2$Cl$_2$ (2x 50 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated on rotary evaporator. The residue was purified by column chromatography using silicagel (24% EtOAc in hexanes) to provide the monosilylated compound 9 (56 g, 90%) as a colorless liquid.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta_H$ (ppm) 7.83-7.64 (m, 4H), 7.54-7.32 (m, 6H), 3.97-9.79 (m, 4H), 2.55 (brs, 1H), 1.92-1.76 (m, 2H), 1.08 (s, 9H).

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

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

MS (ESI) : $m/z$ 315 [M+H]$^+$

HRMS (ESI) : calcd for C$_{19}$H$_{26}$O$_2$Si [M+H]$^+$ 315.1775. Found. 315.1774.

(E)-Ethyl 5-((tert-Butyldiphenylsilyloxy)pent-2-enoate (10).

![Diagram of (E)-Ethyl 5-((tert-Butyldiphenylsilyloxy)pent-2-enoate (10).]
PDC (Pyridinium dichromate) (26.8 g, 72 mmol) was added portion wise to the stirred solution of mono silylated compound 9 (15 g, 48 mmol) in CH$_2$Cl$_2$ (200 mL) at 0 °C and allowed to stir for 4 h at room temperature. After completion of the reaction (monitored by TLC), excess solvent was removed under reduced pressure below 45 °C and residue was purified by column chromatography using SiO$_2$ (10% EtOAc in hexanes) to provide the corresponding aldehyde, which without further purification was directly used for the next step. The freshly prepared aldehyde was dissolved in dichloromethane (100 mL) and was added two carbon stable ylides ethoxy carbonylmethylene triphenylphosphorane (Ph$_3$P=CHCOOEt) (20 g, 57.6 mmol) at room temperature and allowed to stir for 2 h at same temperature. After completion of the reaction (monitored by TLC), excess solvent was concentrated under reduced pressure and the residue was purified with column chromatography using silica gel (3% EtOAc in hexanes) to afford the corresponding $\alpha$, $\beta$-unsaturated ester 10 (13.8 g, 88% overall) as a colorless liquid.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta_H$ (ppm) 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).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta_C$ (ppm) 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.

IR (KBr) : $\nu_{max}$ 2957, 1722, 1110, 703, 505 cm$^{-1}$.

MS (ESI) : $m/z$ (100) 405 [M+Na]$^+$. 

$(E)$-5-(tert-Butyldiphenylsilyloxy) pent-2-en-1-ol (7).
DIBAL-H (5.95 g, 24 mL, 41.8 mmol, 25% in toluene) was added dropwise to the stirred solution of ester 10 (8 g, 20.9 mmol) in dichloromethane (100 mL) under 
N₂ atmosphere at -78 °C. The reaction mixture was allowed to stir for 20 min at same 
temperature and then allowed to stir for 2 h at room temperature. After completion of 
the reaction (monitored by TLC), it was quenched by adding 2 mL of cold methanol 
and allowed to stir for 10 min; then saturated aq. solution of sodium potassium tartarate (50 mL) was added. The reaction mixture was allowed to stir for 2 h at room 
temperature. Two layers were separated and aqueous layer was extracted with 
dichloromethane (2 x 30 mL). The combined organic layers were washed with brine 
(40mL), dried over anhydrous Na₂SO₄ and concentrated on rotary evaporator. The 
residue was purified by column chromatography using silicagel (20% EtOAc in 
hexanes) to provide the allyl alcohol 7 (7.0 g, 87.5% yield) as a colorless liquid.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3) : \delta_H (\text{ppm}) \]

- 7.70 (d, \( J = 6.5 \text{ Hz}, 4\text{H} \)), 7.40 
- (m, 6H), 5.67 (m, 2H), 4.07 (bs, 2H), 3.76 
- (t, \( J = 5.3\text{Hz}, 2\text{H} \)), 2.30 (m, 2H), 1.93 (bs, 
- 1H), 1.09 (s, 9H).

\[ ^13C \text{ NMR (75 MHz, CDCl}_3) : \delta_C (\text{ppm}) \]

- 135.4, 133.7, 130.9, 129.4, 
- 129.0, 127.5, 63.4, 35.4, 26.7, 19.1.

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

MS (ESI) : \( m/z \) (100) 363 [M+Na]⁺.

HRMS (ESI) : calcd for \( \text{C}_{21}\text{H}_{28}\text{NaO}_2\text{Si} \) \( [\text{M+H}]^+ \) : 363.1751, found : 363.1752.

\((2S, 3S)-3-(\text{2-}(\text{tert-Butyldiphenylsilyloxy}) \text{ ethyl} \) oxiran-2-yl) methanol (11).
To a freshly flame dried double necked round bottom flask equipped with activated 4 A\(^0\) molecular sieves (6 g) and dry CH\(_2\)Cl\(_2\) (50 mL) at -20 °C was added Ti (O\(^{i}\)Pr\(_4\)) (0.84 g, 0.87 mL, 2.9 mmol) dropwise and allowed to stir for 10 min, then it was added D-(+) diethyl tartrate (0.75 g, 0.62 mL, 3.67 mmol) and the mixture was allowed to stir for 30 min at same temperature. To this reaction mixture was added allyl alcohol 7 (5 g, 14.7 mmol) in an interval of 30 min. and TBHP (5.25 g, 14.6 mL, 58.8 mmol, 4M in toluene) was added and stirring was continued till completion of the reaction (8h). The reaction mixture was warmed to 0 °C, filtered through the pad of celite. The filtrate was quenched with water (8.7 mL), 20% aq.NaOH (1.45 mL) and vigorously stirred for 1h. The biphasic solution was separated and aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 50 mL). The combined organic extracts were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was purified by column chromatography to afford the pure epoxide 11 as a colorless oil (4.1 g, 80% yield).

\(^{1}\)H NMR (300 MHz, CDCl\(_3\)) : \(\delta_h\) (ppm) 7.74-7.30 (m, 10H), 3.92 (dd, \(J = 2.2, 12.6\) Hz, 1H), 3.86-3.79 (m, 2H), 3.61 (dd, \(J = 4.5, 12.6\) Hz, 1H), 3.15 (dt, \(J = 5.8, 2.2\) Hz, 1H), 2.16 (bs, 1H), 1.83 (q, \(J = 5.8\) Hz, 2H), 1.08 (s, 9H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : \(\delta_c\) (ppm) 135.4, 133.5, 129.6, 127.6, 61.6, 60.6, 58.6, 53.7, 44.7, 26.7, 19.1.

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

MS (ESI) : \(m/z\) (100) 379.0 [M+Na]\(^+\).

HRMS (ESI) : calc'd for C\(_{21}\)H\(_{28}\)NaO\(_3\)Si [M+Na]\(^+\) : 379.170, found : 379.1701.

\([\alpha]_{D}^{20}\) : -16.9 (c 2.5, CHCl\(_3\)).
(S)-5-(tert-Butyldiphenylsilyloxy) pent-1-en-3-ol (12).

To a solution of epoxy alcohol (1.6 g, 3.7 mmol) in THF (30 mL) were added slowly TPP (1.18 g, 4.5 mmol), iodine (1.15 g, 4.5 mmol) and imidazole (0.31 g, 4.6 mmol) in portion wise at 0 °C under nitrogen atmosphere and stirred for 1 h. After completion of the reaction (monitored by TLC), the excess solvent was removed on rotary evaporator and the reaction mass was quenched by adding aq. saturated hypo solution (10 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. A mixture of crude epoxy iodide and Zinc dust (0.9 g, 13.0 mmol) were refluxed in ethanol (30 mL) for 3 h. It was quenched with aqueous. Sat.NH₄Cl (15 mL), extracted with diethyl ether. The organic layer was separated and washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc in hexanes) afforded allyl alcohol 12 as pale yellow oil (8.3 g, 70%).

\[
\begin{align*}
\text{1H NMR (300 MHz, CDCl}_3) & : \delta_H (ppm) 7.73-7.63 (m, 1H), 7.47-7.33 (m, 6H), 5.94-5.81 (m, 1H), 5.30 (dt, J = 11.3, 17.1 Hz, 1H), 5.12 (dt, J = 1.8, 10.3 Hz, 1H), 4.42 (q, J = 5.4, 11.3 Hz, 1H), 3.94-3.78 (m, 2H), 3.05 (bs, 1H), 1.83-1.73 (m, 2H), 1.07 (s, 9H). \\
\text{13C NMR (75 MHz, CDCl}_3) & : \delta_C (ppm) 140.5, 135.4, 133.0, 129.7, 127.7, 114.2, 71.9, 62.4, 38.3, 26.7, 19.0. \\
\text{IR (KBr)} & : \nu_{max} 3437, 2083, 1638, 1106, 702 \text{ cm}^{-1}. \\
\text{MS (ESI)} & : m/z (100) 363.0 [M+Na]^+.
\end{align*}
\]
HRMS (ESI) : calcd for C_{21}H_{26}NaO_{2}Si [M+Na]^+ : 363.1751, found : 363.1751.

\[ [\alpha]^{20}_D \] : -5.2 (c 1.0, CHCl_3).

(S)-tert-Butyl(3-(4-methoxybenzyloxy)pent-4-enyloxy)diphenylsilane (13).

To a stirred suspension of NaH (0.53 g, 22 mmol) in dry THF (5 mL) was added allyl alcohol 12 (3 g, 8.82 mmol) at 0 °C. After being stirred for 20 min, PMB-Br (2.66 g, 13.23 mmol) in THF (5 mL) was added dropwise at 0 °C and stirring was continued for 3h. After completion of the reaction (monitored by TLC), it was quenched by adding water (25 mL) at 0 °C. Two layers were separated and the organic layer was washed with brine (20 mL). Combined organic layers were dried over Na_2SO_4 and excess solvent was concentrated on rotary evaporator. The residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to obtain the PMB protected compound 13 (3.7 g, 92.5% yield) as colorless oil.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] : \[ \delta_H \text{ (ppm)} \]

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>7.70-7.26 (m, 10 H)</td>
<td>7.15 (d, J = 8.3 Hz, 2H), 6.77 (d, J = 8.3 Hz, 2H), 5.78-5.63 (m, 1H), 5.20 (d, J = 6.0 Hz, 1H), 5.15 (s, 1H), 4.48 (d, J = 11.3 Hz, 1H), 4.22 (d, J = 11.3 Hz, 1H), 4.04-3.94 (m, 1H), 3.75 (s, 3H), 3.83-3.63 (m, 2H), 1.89-1.63 (m, 2H), 1.03 (s, 9H).</td>
</tr>
</tbody>
</table>

\[ ^13C \text{ NMR (75 MHz, CDCl}_3 \] : \[ \delta_C \text{ (ppm)} \]

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>159.0, 139.0, 135.5, 129.5, 127.6, 113.7, 77.0, 60.1, 55.2, 38.5, 26.8.</td>
<td></td>
</tr>
</tbody>
</table>

MS (ESI) : m/z (100) 483 [M+Na]^+.
HRMS (ESI) : \text{calcd for } \text{C}_{29}\text{H}_{36}\text{NaO}_3\text{Si} \quad \text{[M+Na]}^+ : 483.2326, \text{found } 483.2324.
\[ \alpha \]$_D^{20}$ : - 6.4 (c 1.0, CHCl$_3$).

**(S)-3-(4-methoxybenzyloxy) pent-4-en-1-ol (14).**

Ammonium fluoride (2.41 g, 65.2 mmol) was added portion wise to a stirred solution of PMB protected compound 13 (3g, 6.52 mmol) in MeOH (30 mL) at room temperature and the reaction mixture was allowed to stir for 12 h at same temperature. After completion of the reaction (monitored by TLC), concentrate the excess methanol on rotary evaporator and residue was purified by silica gel column chromatography using petroleum ether/ EtOAc (80:20) as eluents to give pure alcohol product 14 (0.395 g, 87% yield) as colorless oil.

$^1$H NMR (300 MHz, CDCl$_3$) : \( \delta_H \) (ppm) 7.27-7.24 (m, 2H), 6.90-6.87 (m, 2H), 5.84-5.74 (m, 1H), 5.27 (d, \( J = 5.8 \) Hz, 1H), 5.25 (s, 1H), 4.56 (d, \( J = 11.6 \) Hz, 1H), 4.30 (d, \( J = 11.6 \) Hz, 1H), 4.04-3.97 (m, 1H), 3.80 (s, 3H), 3.78-3.69 (m, 2H), 2.50 (bs, 1H), 1.93-1.72 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : \( \delta_C \) (ppm) 159.2, 138.1, 129.5, 129.4, 117.4, 113.8, 79.6, 69.9, 60.6, 55.2, 37.7.

IR (KBr) : \( \nu_{\text{max}} \) 3412, 1624, 1513, 1248, 1039, 827 cm$^{-1}$.

MS (ESI) : \( m/z 245(100) \ [\text{M+Na}]^+ \).

[\( \alpha \)]$_D^{20}$ : - 48.3 (c 1.2, CHCl$_3$).
(S)-3-(4-methoxybenzylxyloxy) pent-4-enoic acid (4).

![Chemical Structure](image)

To a stirred solution of IBX (2.54 g, 9 mmol) in DMSO (2 mL) under N₂ atmosphere was added alcohol 14 (1 g, 4.54 mmol) in anhydrous THF (5 mL) at room temperature. The reaction mixture was allowed to stir for 1 h and then diluted with Et₂O (20 mL). The white precipitate was filtered through a pad of Celite and the filtrate was washed with saturated aqueous NaHCO₃ (20 mL), dried over anhydrous Na₂SO₄ and volatiles were removed under reduced pressure and the crude product, which without further purification was used to next step.

The crude aldehyde was dissolved in mixture of tBuOH: H₂O (1:1, 5 mL) and cooled to 0 °C. 2-methyl-2-butene (1.2 mL, 3.4 mmol, 2M solution in THF) was added and stirring was continued for 10 min at same temperature. Sodium perchlorate (32 mg, 3.4 mmol) and sodium dihydrogenphosphate (53 mg, 3.4 mmol) in water (1 mL) was added with an interval of 10 min at 0 °C and reaction mixture was stirred vigorously for 4h at room temperature. After completion of the reaction (monitored by TLC), it was partitioned between EtOAc and water. Organic layer was separated and aqs.layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography using silica gel (50% EtOAc in hexanes) to obtain the acid compound 4 (0.51 g, 87 % yield for two steps) as colorless liquid.

\[ \text{1H NMR (200 MHz, CDCl₃)} \quad \delta_H (\text{ppm}) \]

\[
\begin{align*}
7.24 & \text{ (d, } J = 8.7 \text{ Hz, 2H),} \\
6.86 & \text{ (d, } J = 8.7 \text{ Hz, 2H),} \\
5.78 & \text{ (m, 1H),} \\
5.37-5.27 & \text{ (m, 2H),} \\
4.55 & \text{ (d, } J = 11.6 \text{ Hz, 1H),} \\
4.35 & \text{ (d, } J = 11.6 \text{ Hz, 1H },) \\
4.23 & \text{ (m, 1H),} \\
3.79 & \text{ (s, 3H),} \\
2.69 & \text{ (dd, } J = 7.7, 15.5 \text{ Hz, 1H),} \\
2.56 & \text{ (dd, } J = 4.8, 15.5 \text{ Hz, 1H).}
\end{align*}
\]
\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) : \( \delta_c \) (ppm) 175.8, 159.2, 136.7, 129.5, 118.5, 113.8, 76.2, 70.2, 55.2, 40.8.  

IR (KBr) : \( \nu_{max} \) 3410, 2923, 2362, 1713, 1612, 1513 cm\(^{-1}\).  

MS (ESI) : \( m/z \) 236 (100) [M-H]\(^+\).  


\([\alpha]_{D}^{20}\) : -33.1 (c 1.2, CHCl\(_3\)).

\(((2R, 3R)-3-(2-(tert-Butyldiphenylsilyloxy) ethyl) oxiran-2-yl) methanol (15).\)

To a freshly flame dried double necked round bottom flask equipped with activated 4 A\(^0\) molecular sieves (12 g) and dry CH\(_2\)Cl\(_2\) (100 mL) at -20 °C were added Ti(O\(^i\)Pr\(_4\)) (1.75 mL, 5.88 mmol) and allowed to stir for 10 min. D-(−) diethyl tartarate (1.25 mL, 7.35 mmol) was added to the mixture and allowed to stir for 30 min. To this reaction mixture allyl alcohol 11 (10 g, 296.4 mmol) was added in an interval of 30 min. TBHP (29.1 mL, 117.6 mmol, 4M in toluene) was added to the above reaction mass and stirring was continued till completion of the reaction (8h). The reaction mixture was warmed to 0 °C and filtered through a pad of celite. The filtrate was quenched with water (17.4 mL), 15% aq. NaOH (2.9 mL) and stirred vigorously for 1h. The biphasic solution was separated and aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 50 mL). The combined organic extracts were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the pure epoxide 15 as colorless oil (8.6 g, 80% yield).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \( \delta_h \) (ppm) 7.74-7.30 (m, 10H), 3.92 (dd, \( J = 2.2, 12.6 \) Hz, 1H), 3.86-3.79 (m, 2H), 3.61
\[ \delta_C \text{ (ppm) } 135.4, 133.5, 129.6, 127.6, 61.6, 60.6, 58.6, 53.7, 44.7, 26.7, 19.1. \]

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

MS (ESI) : \( m/z \) 379.0 (100) [M+Na]\(^+\).

HRMS (ESI) : calcd for \( \text{C}_{21}\text{H}_{28}\text{NaO}_3\text{Si} \) [M+Na]\(^+\) : 379.170, found : 379.1701.

\([\alpha]^{20}_D\) : +17.6 (c 2.0, CHCl\(_3\)).

(2S, 3S)-5-(\text{tert}-\text{Butyldiphenylsilyloxy})-3-methylpentane-1, 2-diol (16).

Trimethylaluminium (1.16 g, 16 mmol, 2M in toluene) was added dropwise to a stirred solution of epoxy alchol 15 (2 g, 5 mmol) in dry CH\(_2\)Cl\(_2\) (25 mL) at 0 °C and stirring was continued for 1 h at same temperature. After completion of the reaction (monitored by TLC), it was diluted with water (30 mL) and allowed stir for 30 min at room temperature. Two layers were separated and aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated on rotary evaporator. The residue was purified by silica gel column chromatography (30% EtOAc in hexanes) to provide the 1, 2 diol compound 16 (1.6 g, 75% yield) as a colorless liquid.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \( \delta \) (ppm) 7.65-7.52 (m, 4H), 7.41-7.23 (m, 6H), 3.75-3.65 (m, 2H), 3.45 (d, \( J = 6.7 \))
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OTBDPS

1H, 1.78-1.58 (m, 2H), 1.58-1.45 (m, 1H), 0.98 (s, 9H), 0.81 (t, J = 6.7 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : δ (ppm) 135.5, 133.0, 129.7, 127.7, 76.0, 64.9, 62.1, 35.7, 34.0, 26.7, 19.0, 16.5.

IR (KBr) : $\nu_{\text{max}}$ 3384, 2958, 2931, 2858, 1427, 1111, 823, 737, 702, 505 cm$^{-1}$.

MS (ESI) : m/z 395 (100) [M+Na]$^+$.


$[\alpha]_{D}^{30}$ : + 3.0 (c 1.8, CHCl$_3$).

(S, E)-Ethyl 6-(tert- butyldiphenylsilyloxy) - 2, 4-dimethylhex-2-enoate (17).

A solution of diol (2.4 g, 6.2 mmol) in methanol (20 mL) was treated with NaIO$_4$ (4.18 g, 18.6 mmol) portion wise at 0 °C and allowed to stir for 2 h at room temperature. Reaction mixture was filtered through pad of celite and filtrate was concentrated in vacuo. Residue was dissolved in water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, excess solvent was concentrated in vacuo to afford the corresponding aldehyde, which without purification was used for next reaction.

To the crude aldehyde in benzene (25 mL) was added ethyl-2-(triphenyl phosphoranylidene) propanoate (4.12 g, 1.8 mmol) at room temperature and allowed to stir for 2 h. The reaction mixture was concentrated in vacuo and residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to give compound 17 (2.45 g, 82% overall yield) as a colorless oil.
$^1$H NMR (300 MHz, CDCl$_3$) : $\delta_H$ 7.67-7.56 (m, 4H), 7.42-7.30 (m, 6H), 6.49 (d, $J = 10.0$ Hz, 1H), 4.17 (q, $J = 7.17$ Hz, 2H), 3.61 (t, $J = 5.8$ Hz, 2H), 2.86-2.73 (m, 1H), 1.84 (s, 3H), 1.69-1.48 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.04 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta_C$ (ppm) 168.3, 147.3, 135.4, 129.5, 127.5, 61.6, 60.3, 39.3, 29.6, 26.7, 19.8, 19.1, 14.2, 12.4.

IR (KBr) : $\nu_{\text{max}}$ 2958, 2858, 1710, 1266, 1109, 702, 504 cm$^{-1}$.

MS (ESI) : $m/z$ (100) 447 [M+Na]$^+$. HRMS (ESI) : calcd for C$_{26}$H$_{40}$NO$_3$Si [M+NH$_4$]$^+$ : 442.2772, found : 442.2773.

$[\alpha]^{30}_D$ : + 15.9 (c 2.2, CHCl$_3$).

$(7S, E)$-9-$(\text{tert-Butyldiphenylsilyloxy})$-5, 7-dimethylnona-1, 5-dien-4-ol (18+19).

DIBAL-H (0.5 g, 3.53 mmol, 25% solution in Toluene) was slowly added to the stirred solution of ester (1.5 g, 3.53 mmol) in dry CH$_2$Cl$_2$ (30 mL) under nitrogen atmosphere at -78 °C and allowed to stir for 20 min at same temperature and then allowed to stir for 2 h at room temperature. After completion of the reaction (monitored by TLC), reaction mixture was quenched by adding 30 mL aq. solution of sodium potassium tartrate. The reaction mixture was allowed to room temperature for 2 h. Two layers were separated and the aqueous layer was extracted with diethyl ether (2x 20 mL). The organic layers were combined, washed with brine (20mL), dried over anhydrous Na$_2$SO$_4$ and concentrated on rotary evaporator. The residue was
purified by chromatography using silica gel (4% EtOAc in hexanes) to provide the aldehyde (1.2 g, 80%) as a colorless liquid which without purification was immediately used for further reaction.

Freshly prepared aldehyde was dissolved in THF (15 mL) and cooled to 0 °C. After being stirred for 10 min, Zn dust (1.23 g, 18.8 mmol) and allyl bromide (1.7 g, 14.1 mmol) were added to the reaction mass at the same temperature. It was added a saturated aqueous solution of NH₄Cl (10 mL) dropwise over a period of 5 min. The reaction mixture was allowed to stir for 1h at same temperature until the total aldehyde was consumed in the reaction (monitored by TLC). The mixture was filtered and precipitate was thoroughly washed with EtOAc (30 mL). The aqueous layer was separated and the organic layer was washed successively with saturated aqueous NH₄Cl (10 mL) and brine (10 mL) and dried over Na₂SO₄. After solvent removal under reduced pressure an oily residue that was purified with silica gel column chromatography (3% EtOAc in hexanes) to provide 55:45 mixture of 18 and 19 (1.8 g, 92 %yield) as a colorless oil.

(R) Mosher’s ester of major allyl alcohol (M₁)

To a solution of major allyl alcohol (25 mg, 0.06 mmol) in CH₂Cl₂ (1 mL) were added (S)-α-Methoxy-α-trifluoromethylphenylacetaciacid [(R)-MTPA] (14 mg, 0.06 mmol), DCC (60 mg, 0.3 mmol) and DMAP (35 mg, 0.3 mmol) at 0 °C under inert atmosphere. The solution was warmed up to room temperature and stirred for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 1% EtOAc in hexanes to provide (R)-Mosher’s ester of major allyl alcohol M₁ as colorless oil (23.6 mg, 95% yield).

¹H NMR (300 MHz, CDCl₃) : \( \delta_H (ppm) \) 7.69-7.55 (m, 4H), 7.53-7.42 (m, 1H), 7.41-7.27 (m, 10H), 5.72-5.42 (m,
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1H), 5.41-5.24 (m, 1H), 5.20 (d, J = 9.2 Hz, 1H), 5.12-4.85 (m, 2H), 3.63-3.45 (m, 2H), 3.53 (s, 3H), 2.72-2.53 (m, 1H), 2.52-2.36 (m, 1H), 2.36-2.19 (m, 1H), 1.42 (s, 3H), 1.30-1.19 (m, 2H), 1.03(s, 9H), 0.93 (d, J = 6.4 Hz, 3H).

(S) Mosher's ester of major allyl alcohol (M₂).

(4S, 7S, E)-9-(tert-butyldiphenylsilyloxy)-5, 7-dimethylnona-1, 5-dien-4-ol (19).
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$^1$H NMR (300 MHz, CDCl$_3$) : $\delta_H$ (ppm) 7.52-7.36 (m, 4H), 7.42-7.10 (m, 6H), 5.59-5.36 (m, 1H), 4.96-4.82 (m, 2H), 4.79 (d, $J = 10.9$ Hz, 1H), 3.79-3.69 (m, 1H), 3.87 (t, $J = 6.6$ Hz 1H), 3.50 (t, $J = 6.4$ Hz, 2H), 2.64-2.48 (m, 1H), 2.21-2.10 (m, 2H), 1.52 (s, 3H), 1.44-1.28 (m, 2H), 0.97 (s, 9H), 0.87 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta_C$ (ppm) 135.5, 134.8, 132.2, 129.6, 129.5, 127.5, 117.4, 76.2, 62.0, 40.1, 39.8, 28.3, 26.8, 20.9, 19.1, 11.9.

IR (KBr) : $\nu_{max}$ 3321, 2931, 2858, 1111,702, 504 cm$^{-1}$.

MS (ESI) : $m/z$ 445 (100) [M+Na]$^+$. 


$[\alpha]^{20}_D$ : +3.5 (c 0.6, CHCl$_3$).

$((E, 3S, 6S)$-6-Methoxy-3, 5-dimethylnona-4, 8-dienyloxy$(tert-butyl)$ diphenylsilane (20).

To a well stirred suspension of freshly activated NaH (0.114 mg, 4.72 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (15 mL), a solution of alcohol (1 g, 2.36 mmol) in dry THF (5mL) was added drop wise at 0 °C. After being stirred for 30 min, Methyl iodide (1 g, 7.08 mmol) was added and the reaction mixture was brought to room temperature and stirred for 1 h. Ice pieces were added to quench the
reaction and allowed to stir for 10 min. Organic layer was separated and aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. Excess solvent was concentrated in vacuo and residue was purified by silica gel column chromatography (4% EtOAc in hexanes) to give pure product 20 (0.92 g, 90%) as a colorless oil.

\[1\text{H NMR (300 MHz, CDCl}_3\text{) : } \delta 7.67-7.48 \text{ (m, 4H), 7.42-7.19 (m, 6H), 5.69-5.43 (m, 1H), 5.01-4.86 (m, 2H), 4.81 (d, } J = 10.2 \text{ Hz, 1H), 3.51 (t, } J = 5.6 \text{ Hz, 2H), 3.33 (t, } J = 6.9 \text{ Hz, 1H), 3.05 (s, 3H), 2.66-2.49 \text{ (m, 1H), 2.32-1.97 (m, 2H), 1.62-1.26 \text{ (m, 2H), 1.43 (s, 3H), 0.96 (s, 9H), 0.87 (d, } J = 6.7 \text{ Hz, 3H).} \]

\[13\text{C NMR (75 MHz, CDCl}_3\text{) : } \delta 135.5, 135.3, 135.0, 134.0, 132.4, 129.4, 127.5, 116.1, 86.9, 62.1, 55.7, 40.1, 38.2, 28.5, 26.8, 21.2, 19.1, 10.5. \]

IR (KBr) : \( \nu_{max} 2956, 2929, 2857, 1110, 702, 504 \text{ cm}^{-1}. \)

MS (ESI) : \( m/z 459 \text{ (100) [M+Na]}^+. \)


\[ [\alpha]^{20}_D : +4.9 \text{ (c 1.4, CHCl}_3\text{).} \]

\( (3S, 6S, E) \text{-6-Methoxy-3, 5-dimethylnona-4, 8-dien-1-ol (21).} \)

NH₄F was added to a stirred solution of methyl ether compound (1g, 2.3 mmol) in MeOH (20 mL) at room temperature and allowed to stir for 12 h at same
temperature. After completion of the reaction (monitored by TLC), purified by column chromatography using petroleum ether/ EtOAc (80:20) to give a pure alcohol product 21 (0.395 g, 85% yield) as colorless oil.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \]: \] \[ \delta 5.79-5.62 \text{ (m, 1H), 5.2-5.06 \text{ (m, 2H), 5.01 \text{ (d, } J = 10.9 \text{ Hz, 1H), 3.65-3.54 \text{ (m, 2H), 3.48 \text{ (t, } J = 6.9 \text{ Hz, 1H), 3.18 \text{ (s, 3H), 2.67-2.54 \text{ (m, 1H), 2.45-2.16 \text{ (m, 2H), 1.69-1.39 \text{ (m, 2H), 1.55 \text{ (s, 3H), 1.01 \text{ (d, } J = 6.6 \text{ Hz, 3H).}}}}}} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \]: \] \[ \delta 135.2, \text{ 134.9, 116.4, 86.9, 61.4, 55.6, 40.1, 38.2, 29.0, 21.3, 10.5.}} \]

IR (KBr) : \[ \nu_{\text{max}} 3382, 2956, 2858, 1449, 1092, 703, 506 \text{ cm}^{-1}. \]

MS (ESI) : \[ m/z 215 \text{ (100) [M+Na]}. \]

\[ [\alpha]^{30}_D : + 4.46 \text{ (c 0.56, CHCl}_3). \]

5-((3S, 6S, E)-6-Methoxy-3, 5-dimethylnona-4, 8-dienylsulfonyl)-1-phenyl-1H-tetrazole (6).

DIAD (0.612 g, 0.6 mL, 3.0 mmol, 40% toluene solution) was added to dropwise to a stirred solution of 5-mercapto-1-phenyltetrazole (0.5 g, 3.0 mmol), PPh\textsubscript{3} (800 mg, 3.0 mmol), and alcohol (0.5 g, 2.52 mmol) in THF (10 mL) at 0 °C, then allowed to stir at room temperature for 3 h. The mixture was diluted with EtOAc (15 mL), washed with water (20 mL), brine (20 mL) sequentially, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified with column chromatography (SiO\textsubscript{2}, hexane:EtOAc = 98:2) afforded the thioether compound (0.85 g, 95% yield).
The above purified thioether compound was dissolved in EtOH (10 mL), was added a solution of Hexaammonium heptamolybdate tetrahydrate (0.31 g, 0.238 mmol) in 30% H$_2$O$_2$ (5mL), at rt and allow to stir for 24 hr. The reaction mixture was diluted with EtOAc (20 mL) washed with water and brine sequentially, dried (anh.Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified with column chromatography by using hexane: EtOAc (97:3) to afford the title compound tetrazole 6 (0.8 g, 87% yield) as colorless gummy liquid.

$^{1}$H NMR (500 MHz, CDCl$_3$) : $\delta_{H}$ (ppm) 7.70-7.66 (m, 2H), 7.62-7.56 (m, 3H), 5.74-5.64 (m, 1H), 5.10 (d, $J = 9.5$ Hz, 1H), 5.04 (d, $J = 17.0$Hz, 1H), 4.99 (d, $J = 10.5$ Hz, 1H), 3.70 (t, $J = 7.6$ Hz, 1H), 3.60 (dt, $J = 4.7$, 10.5 Hz, 1H), 3.52 (t, $J = 7.6$ Hz, 1H), 3.17 (s, 3H), 2.67-2.57 (m, 1H), 2.44-2.35 (m, 1H), 2.26-2.18 (m, 1H), 2.06-1.94 (m, 1H), 1.8-1.7 (m, 1H), 1.54 (s, 3H), 1.05 (d, $J = 6.6$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta_{C}$ (ppm) 134.6, 132.5, 131.3, 129.6, 124.9, 116.8, 86.5, 57.4, 54.5, 38.0, 31.2, 29.0, 21.1, 12.7.

IR (KBr) : $\nu_{max}$ 2934, 1640, 1497, 1338, 1152, 1092, 919, 763, 690, 543 cm$^{-1}$.

MS (ESI) : $m/z$ 413(100) [M+Na]$^+$. 

HRMS (ESI) : calcd for C$_{19}$H$_{26}$NaN$_4$OS [M+Na]$^+$: 413.2682, found: 413.2688.

$[^{[\alpha]}]_D^{30}$ : -6.9 (c 1.75, CHCl$_3$).
(E)-Ethyl hept-5-en-2-ynoate (23a).

![Chemical structure of (E)-Ethyl hept-5-en-2-ynoate](image)

To a stirred solution of ethyl propiolate 8 (10 g, 102 mmol) in DMF (250 mL), K$_2$CO$_3$ (14 g, 102 mmol), Na$_2$SO$_3$ (0.65 g, 51 mmol), Cul (0.38 g, 2 mmol), DBU (cat) were added at room temperature under N$_2$ atmosphere. After being stirred for 10 min at 30 °C, crotyl bromide (20 g, 153 mmol) were added and allowed to stir for 12 h at same temperature. After completion of the reaction, reaction mass was filtered through celite pad and the filtrate was diluted with diethyl ether (150 mL), washed with saturated aqueous NH$_4$Cl (100 mL), brine (100 mL) and dried over Na$_2$SO$_4$. Excess solvent was concentrated under reduced pressure and residue was purified by silica gel column chromatography (3% EtOAc in hexanes) to afford the title compound 23a along with its regioisomer 23b (16 g, 88% yield) in 80:20 (the ratio of isomers were confirmed by HPLC) as pale thick yellow liquid.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta_H$ (ppm) 5.80-5.30 (m, 2H), 4.27-4.16 (q, $J = 6.7$ Hz, 2H), 3.06 (d, $J = 6.7$ Hz, 2H), 1.74-1.72 (m, 2H), 1.33 (t, $J = 6.0$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta_C$ (ppm) 153.6, 128.5, 122.3, 86.5, 74.2, 61.7, 21.7, 17.5, 13.9;

IR (KBr) : $\nu_{max}$ 3028, 2984, 2212, 1710, 1257, 751 cm$^{-1}$.

(2Z, 5E)-Ethyl 3-methylhepta-2, 5-dienoate (24).

![Chemical structure of (2Z, 5E)-Ethyl 3-methylhepta-2, 5-dienoate](image)
To a stirred suspension of freshly dried copper (I) iodide (17.5 g, 94.7 mmol) in dry THF (200 mL), MeLi (4.16 g, 189.4 mmol, 1.6M in ether) was added dropwise at 0 °C until it become clear solution. After being stirred for 30 min at this temperature the solution was cooled up to -78 °C then ester 23a (12 g, 78.9 mmol) in dry THF (50 mL) was added dropwise and allowed to stir for 2h at same temperature and for 30 min at -10 °C. The reaction mixture was poured into saturated aqueous NH₄Cl (250 mL) solution and the blue color aqueous layer was thoroughly extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (100 mL) and dried over Na₂SO₄. Excess solvent was concentrated under reduced pressure and crude reaction mass was chromatographed with silica gel using petroleum ether/ EtOAc (96:4) to give the pure product 24 (11 g, 83.4% yield) as pale yellow liquid.

\[
\begin{align*}
\text{1H NMR (300 MHz, CDCl₃)} & : & \delta_H (ppm) & 5.65 (s, 1H), 5.61-5.34 (m, 2H), 4.19-4.08 (q, J = 6.9 Hz, 2H), 3.31 (d, J = 6.2 Hz, 2H), 1.85 (s, 3H), 1.66 (d, J = 6.0 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H). \\
\text{13C NMR (75 MHz, CDCl₃)} & : & \delta_C (ppm) & 166.3, 158.3, 127.2, 115.9, 59.4, 36.6, 24.7, 17.8, 14.2. \\
\text{IR (KBr)} & : & \nu_{max} & 2925, 1726, 1377, 1223, 764 \text{ cm}^{-1}.
\end{align*}
\]

(2Z, 5E)-3-Methylhepta-2, 5-dienal (25).

DIBAL-H (4.23 g, 29.7 mmol, 25% in toluene) was added dropwise to the stirred solution of ester 24 (5 g, 29.7 mmol) in dry CH₂Cl₂ (100 mL) under N₂ atmosphere at -78 °C and allowed to stir for 20 min at same temperature. After completion of the reaction (monitored by TLC), it was quenched by adding 100 mL
of aqueous solution of sodium potassium tartrate. The reaction mixture was allowed to stir for 2 h at room temperature. Two layers were separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated on rotary evaporator below 45 °C. The residue was purified by silica-gel column chromatography (3% EtOAc in hexanes) to provide the compound 25 (2.4 g, 65%) as a pale yellow liquid with pungent smell.

$^1$H NMR (300 MHz, CDCl$_3$) : \[ \delta 9.95 \text{ (d, } J = 7.9 \text{ Hz, 1H), 5.87 \text{ (d, } J = 7.9 \text{ Hz, 1H), 5.64-5.31 \text{ (m, 2H), 3.24 \text{ (d, } J = 6.0 \text{ Hz, 2H), 1.96 \text{ (s, 3H), 1.70 \text{ (d, } J = 4.9 \text{ Hz, 3H).}} \]

$^{13}$C NMR (75 MHz, CDCl$_3$) : \[ \delta 191.3, 162.9, 129.3, 127.4, 125.7, 37.8, 22.1, 17.9. \]

IR (KBr) : \[ \nu_{max} 2925, 1713, 1695, 1378, 1144, 971 \text{ cm}^{-1}. \]

$(R, 4Z, 7E)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-5-methylnona-4, 7-dien-1-one (27).$

To a freshly flame dried 50 mL two neck round-bottom flask was dissolved N-acetyl thiazolidinethione 1-[(S)-4-benzyl-2-thioxothiazolidin-3-yl) ethanone] 26 (1.01 g, 4 mmol) in 20 mL of anhydrous CH$_2$Cl$_2$ under N$_2$ atmosphere and cooled to 0 °C. TiCl$_4$ (0.76 g, 4 mmol, 1M in CH$_2$Cl$_2$) was added to the above bright yellow solution at 0 °C and the suspension was allowed to stir for 15 min at same temperature. To the resulting homogeneous orange solution, was added DIPEA (0.62 g, 4.8 mmol) at 0 °C. The brick-red color solution was allowed to stir for 30 min at same temperature.
This titanium enolate solution was recooled to −78 °C and the aldehyde (0.5 g, 4 mmol) was transferred via cannula with rapid stirring. After being stirred for 2 h, the reaction was quenched by pouring into 15 mL of half saturated aq. NH₄Cl solution. The organic layer was separated and aqueous portion was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine solution (25 mL), dried over Na₂SO₄ and concentrated in vacuo to afford the desired aldol adduct 27 as pale yellow liquid (0.97 g, 65% yield). The diastereomeric ratio of the crude product (88:12) was determined by HPLC (using Waters Atlantis dC18 column and acetonitrile/water (6:4) as eluents). The mixture of diastereomers, which without further purification was directly used for the next step.

$^1$H NMR (300 MHz, CDCl₃) : δ 7.36-7.31 (m, 2H), 7.31-7.24 (m, 3H), 5.51-5.43 (m, 1H), 5.42-5.34 (m, 2H), 5.30 (d, J = 7.8 Hz, 1H), 4.93 (dt, J = 2.9, 8.8 Hz, 1H), 3.52 (dd, J = 2.9, 17.6 Hz, 1H), 3.44-3.37 (m, 1H), 3.31 (q, J = 8.8 Hz, 1H), 3.05 (m, 1H), 2.90 (d, J =10.7 Hz, 1H) 2.79 (dq, J = 14.7, 5.8 Hz, 2H), 2.54 (bs, 1H), 1.73 (s, 3H), 1.67 (d, J = 7.8 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl₃) : δ 201.2, 172.7, 136.3, 129.4, 129.1, 128.9, 128.8, 127.4, 127.2, 68.3, 65.0, 40.1, 38.3, 36.7, 32.0, 17.8, 16.7.

IR (KBr) : $\nu_{max}$ 3445, 2924, 1681, 1494, 1260, 1041, 744, 701 cm$^{-1}$.

MS (ESI) : $m/z$ 398 (100) [M+Na]$^+$.


$[\alpha]_{D}^{20}$ : +88.2 (c 2.0, CHCl₃).
(R, 4Z, 7E)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-(tert-butyldimethylsilyloxy)-5-methylnona-4, 7-dien-1-one (28).

To a stirred solution of the freshly prepared aldol adduct 27 (0.5 g, 1.33 mmol) in CH$_2$Cl$_2$ (5 mL), was added 2, 6-lutidine (0.28 g, 0.31 mL, 2.66 mmol) at 0 °C under inert atmosphere. After being stirred for 5 min, TBSOTf (0.45 g, 0.4 mL, 1.73 mmol) was added to the above reaction mass and allowed to stir for 15 min at same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (10 mL) and allowed to stir for 10 min at same temperature. Organic layer was separated and aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by the silica gel column chromatography (1% EtOAc in hexanes) to afford the silylated compound 28 (0.51 g, 80%) as a yellow color liquid.

$^1$H NMR (300 MHz, CDCl$_3$) : δ 7.40-7.27 (m, 5H), 5.54-5.29 (m, 2H), 5.26-5.13 (m, 2H), 5.03 (dt, $J = 3.4$, 9.0 Hz, 1H), 3.83-3.69 (m,1H), 3.38-3.31 (m, 1H), 3.31-3.22 ( m, 1H), 3.1-3.01 (m, 1H), 3.01-2.92 (m, 1H), 2.88 (d, $J = 11.3$ Hz, 1H), 2.62 (d, $J = 6.2$ Hz, 2H), 1.7-1.63 (m, 6H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : δ 201.0, 171.8, 136.6, 135.4, 129.4, 128.9, 128.4, 127.9, 127.1, 126.9, 68.8, 67.1, 46.5, 42.6, 36.5, 32.2, 25.7, 18.0, 16.6, -4.2, -4.8.
IR (KBr) : $v_{max}$ 2926, 2854, 1698, 1456, 1254, 1034, 834, 777, 701 cm$^{-1}$.

MS (ESI) : $m/z$ 511.8 (100) [M+Na]$^+$. 

HRMS (ESI) : calcd for C$_{26}$H$_{39}$NaNO$_2$Si [M+Na]$^+$: 512.2087, found: 512.2084.

$[\alpha]_{D}^{28}$ : +121.7 ($c$ 2.0, CHCl$_3$).

(R, 4Z, 7E)-3-(tert-Butyldimethylsilyloxy)-5-methylnona-4, 7-dienal (29).

To a stirred solution of silyl compound 28 (0.4 g, 0.81 mmol) in dry CH$_2$Cl$_2$ under N$_2$ atmosphere at -78 °C, DIBAL-H (0.128 g, 0.51 mL, 0.89 mmol, 25% in toluene) was added drop wise until the disappearance of the yellow colour and allowed to stir for 5min at same temperature. After completion of the reaction (monitored by TLC), reaction mixture was quenched by adding 5 mL of aq. solution of sodium potassium tartrate and allowed to stir for 30 min at room temperature. Two layers were separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated on rotary evaporator. The residue was purified by silica gel column chromatography (4% EtOAc in hexanes) to provide the compound 29 (0.21 g, 90%) as a pale yellow liquid with pungent smell.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta_H$ (ppm) 9.78 (s, 1H), 5.55-5.27 (m, 2H), 5.20 (d, $J = 6.7$ Hz, 1H), 4.96-4.82 (m, 1H), 2.72-2.50 (m, 2H), 2.49 -2.30 (m, 2H), 1.72-1.58 (m, 6H), 0.85 (s, 9H), 0.02 (d, 6H).
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$(ppm) 202.0, 128.3, 128.2, 127.7, 127.0, 65.4, 51.7, 42.5, 25.6, 23.3, 17.8, 16.5, -4.1, -5.0.

IR (KBr): $\nu_{max}$ 2976, 2925, 1713, 1378, 1144 cm$^{-1}$.

MS (ESI): $m/z$ 305(M+Na)$^+$.  
$\nu_{max}$ 2932, 2858, 1727, 1254, 1075, 835, 774 cm$^{-1}$.

$[\alpha]_D^{28}$ 4.1 (c 0.9, CHCl$_3$)  
(c 2.0, CHCl$_3$);

$(R, 2E, 6Z, 9E)$-5-(tert-Butyldimethylsilyloxy)-7-methylundeca-2, 6, 9-trienal (5).

A flask containing Ph$_3$PCHCHO (260 mg, 0.84 mmol, 1.1 equiv) was added a solution of $(R, 4Z, 7E)$-3-(tert-Butyldimethylsilyloxy)-5-methylnona-4, 7-dienal 29 (0.2 g, 0.70 mmol, 1.0 eq) in dry CH$_2$Cl$_2$ (10 mL). The reaction mixture was stirred for 2h under refluxed conditions. After completion of the reaction (monitored by TLC), it was cooled to room temperature and excess solvent was removed under reduced pressure. The residue was purified directly by flash chromatography using silica gel (0.5% EtOAc in hexanes) to afford the title product $\alpha$, $\beta$-unsaturated aldehyde 5 (160 mg, 90% yield) as a pale yellow liquid.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.48 (d, $J = 7.9$ Hz, 1H), 6.90-6.77 (m, 1H), 6.18-6.06 (m, 1H), 5.51-5.24 (m, 2H), 5.16 (d, $J = 8.4$ Hz, 1H) 4.57-4.44 (m, 1H), 2.81-2.57 (m, 2H), 2.56-2.34 (m,
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2H), 1.66 (d, $J = 6.6$ Hz, 3H), 1.59 (s, 3H), 0.85 (s, 9H), 0.01 (s, 3H), 0.0 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : \( \delta 193.9, 155.4, 134.5, 128.7, 128.3, 126.9, 126.5, 68.6, 42.5, 35.6, 25.7, 23.3, 18.0, 17.8, -4.2, -4.9. \)

IR (KBr) : \( \nu_{\text{max}} 2926, 2855, 1697, 1462, 1251, 1071, 967, 834, 775 $\text{cm}^{-1}. \)

MS (ESI) : \( m/z 347 [\text{M+K}]^+. \)

: \( m/z (100) [\text{M+H}]^+. \)

\( [\alpha]_D^{30} \) : +10.0 (c 2.0, CHCl$_3$).

\((2E, 5Z, 7R, 9E, 11E, 14S, 15E, 17S)-17\text{-}\text{Methoxy\text{-}5, 14, 16\text{-}trimethylidicosa\text{-}2, 5, 9, 11, 15, 19\text{-}hexaen\text{-}7\text{-}yloxy})(\text{tert\text{-}butyl})\text{ dimethylsilane (30).} \)

KHMD (0.258 g, 0.65 mmol, 0.5 % in toluene) was added dropwise to a stirred solution of sulfone \( 6 \) (0.12 g, 0.325 mmol) in dry THF (5 mL, freshly distilled from LAH before use) at -78 °C and allowed to stir for 1 h at same temperature. Subsequently, a solution of aldehyde (0.2 g, 0.65 mmol) in dry THF (1 mL) was added dropwise to the thick brown colour reaction mixture at -78 °C and stirring was continued for 1 h at same temperature. The reaction mixture was warmed to room temperature and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), it was quenched by adding appropriate amount of saturated aq. NH$_4$Cl solution and the mixture was extracted with EtOAc. The organic layer was washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced
pressure. The residue was purified by column chromatography using silicagel (4% EtOAc in hexanes) to provide the trans-olefinated compound 30 (0.21 g, 88%) as colorless oil.

\[ \text{H NMR (500 MHz, CDCl}_3) \quad : \quad \delta \quad 6.08-5.94 \text{ (m, 2H), 5.83-5.65 \text{ (m, 1H), 5.63-5.49 \text{ (m, 2H), 5.48-5.28 \text{ (m, 2H), 5.25-5.13 \text{ (m, 2H), 5.13-4.98 \text{ (m, 2H), 4.44-4.32 \text{ (m, 1H), 3.49 \text{ (t, } J = 6.8\text{Hz,1H), 3.21 \text{ (s, 3H), 2.84-2.60 \text{ (m, 2H), 2.59-2.48 \text{ (m, 1H), 2.49-2.36 \text{ (m, 1H), 2.35-2.21 \text{ (m, 2H), 2.21-214 \text{ (m, 1H), 2.14-2.0 \text{ (m, 2H), 1.73-1.63 \text{ (m, 3H), 1.61 \text{ (s, 3H), 1.56 \text{ (s, 3H), 1.01 \text{ (d, } J = 6.8\text{ Hz, 3H), 0.90 \text{ (s, 9H), 0.05 \text{ (s, 3H), 0.04 \text{ (s, 3H).}}}}}

\[ \text{C NMR (75 MHz, CDCl}_3) \quad : \quad \delta \quad 135.2, 134.0, 132.2, 131.6, 130.5, 129.6, 129.2, 128.8, 128.6, 128.2, 126.5, 126.2, 116.1, 86.9, 70.0, 55.5, 42.6, 41.9, 40.3, 38.3, 32.6, 25.8, 20.7, 18.2, 17.8, 16.6, 10.7, -4.2, -4.7.}

\[ \text{IR (KBr) : } \nu_{\max} 2957, 2929, 2857, 1641, 1458, 1252, 1072, 988, 835, 776 \text{ cm}^{-1}. \]

\[ \text{MS (ESI): } m/z \quad 495 \text{ (100) } [\text{M+Na}]^+. \]

\[ \text{HRMS (ESI) : } \text{cacld for } C_{30}H_{52}NaO_2 [\text{M+Na}]^+: 495.3629, \text{ found: 495.3669.} \]

\[ [\alpha]_{D}^{20} : -1.1 \text{ (c 1.0, CHCl}_3). \]

\[ (c 2.0, \text{CHCl}_3); \]
Chapter II

(2E, 5Z, 7R, 9E, 11E, 14S, 15E, 17S) - 17-Methoxy-5, 14, 16-trimethyllicosanoic-2, 5, 9, 11, 15, 19-hexaen-7-ol (3).

A solution of the TBS ether 30 (0.2 g, 0.4 mmol) in dry THF (5 mL) was treated with 3 equiv of tert-butyl ammonium fluoride (TBAF) (0.33 g, 1.2 mmol) at 0 °C and stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), excess solvent was concentrated in vacuo and purified by silica gel column chromatography (12% EtOAc in hexanes) to provide the pure product alcohol 3 as colorless liquid (0.13 g, 86% yield).

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta$ $^1$H (ppm) $\delta$ 6.10-5.91 (m, 2H), 5.74-5.63 (m, 1H), 5.56-5.46 (m, 2H), 5.46-5.30 (m, 2H), 5.21 (d, $J$ = 8.0 Hz, 1H), 5.14 (d, $J$ = 10 Hz, 1H), 5.04 (d, $J$ = 18 Hz, 1H), 4.99 (d, $J$ = 10 Hz, 1H), 4.41-4.31 (m, 1H), 3.43 (t, $J$ = 6.8 Hz, 1H), 3.14 (s, 3H), 2.78-2.58 (m, 2H), 2.52-2.40 (m,1H), 2.38-2.29 (m, 1H), 2.28-2.22 (m, 2H), 2.22-2.14 (m, 1H), 2.08-1.92 (m, 2H), 1.65-1.61 (m, 3H), 1.53 (s, 3H), 1.50 (s, 3H), 0.95 (d, $J$ = 6.7 Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 135.1, 133.6, 131.6, 131.3, 131.1, 129.1, 128.5, 128.1, 127.3, 126.8, 126.6, 116.1, 86.9, 68.1, 54.5, 42.6, 41.0, 38.2, 35.6, 29.6, 17.9, 17.8, 16.6, 10.7.
IR (KBr) : \( \nu_{\text{max}} \) 3436, 2956, 2925, 2851, 1642, 1437, 
1218, 1092, 968, 910, 772 \text{ cm}^{-1}.

MS (ESI) : \( m/z \) 381 [M+Na]⁺.

HRMS (ESI) : cacld for C\(_{24}\)H\(_{38}\)NaO\(_2\) [M+Na]⁺: 381.2764, 
found: 381.2764.

\([\alpha]\)\(_D\) : +11.4 (c 1.0, CHCl\(_3\)).

(3S)-(2E, 5Z, 7R, 9E, 11E, 14S, 15E, 17S)-17-Methoxy-5,14,16-trimethylcicosa-2, 5,9,11,15,19-hexaen-7-yl 3-(4-methoxybenzyloxy) pent-4-enoate (2).

![Chemical Structure](image)

To a stirred solution of carboxylic acid 4 (46 mg, 0.196 mmol) in dry THF (1 mL) at room temperature were added triethylamine (0.017 g, 0.168 mmol) and 2, 4, 6-trichlorobenzoylchloride (0.040 g, 0.168 mmol). The reaction mixture was allowed to stir for 3 h at room temperature. The solids were filtered off through a pad of celite and washed with diethyl ether (5 mL). Filterate was concentrated under reduced pressure and residue was dissolved in dry benzene (3 mL). Alcohol 3 (0.05 g, 0.14 mmol) and DMAP (22 mg, 0.182 mmol) in benzene (3 mL) were added to the reaction mixture and allowed to stir at room temperature. After being stirred for 13 h, it was diluted with ether (5 mL) and washed with saturated NaHCO\(_3\) (5 mL). Organic layer was washed with brine (10 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (4% EtOAc in hexanes) to provide the title compound 2 (72 mg, 90%) as colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) : \( \delta \) 7.22-7.14 (m, 2H), 6.86-6.76 (m, 2H), 
6.04-5.83 (m,2H), 5.81-5.60 (m, 2H),
5.55-5.43 (m, 1H), 5.43-5.35 (m, 1H), 5.34-5.26 (m, 2H), 5.25-5.17 (m, 2H), 5.16-5.05 (m, 2H), 5.05-4.91 (m, 2H), 4.46 (d, $J = 11.6$ Hz, 1H), 4.30 (d, $J = 11.6$ Hz, 1H), 4.26-4.06 (m, 2H), 3.76 (s, 3H), 3.43 (t, $J = 6.7$ Hz, 1H), 3.14 (s, 3H), 2.68-2.57 (m, 2H), 2.53-2.39 (m, 2H), 2.38-2.29 (m, 2H), 2.29-2.22 (m, 1H), 2.22-2.12 (m, 2H), 2.05-1.93 (m, 2H), 1.67-1.59 (m, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 0.94 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta_C$ (ppm) 170.0, 159.1, 137.4, 137.2, 135.1, 135.0, 133.2, 132.2, 131.4, 131.2, 130.4, 129.3, 129.2, 128.3, 126.9, 126.2, 123.2, 117.7, 116.1, 113.7, 86.9, 77.1, 70.2, 55.5, 55.2, 42.6, 41.3, 40.3, 38.2, 31.5, 29.6, 22.6, 20.7, 17.8, 10.7.

MS (ESI) : $m/z$ 381 (M+Na)$^+$.  

HRMS (ESI) : caeld for C$_{36}$H$_{49}$NaO$_5$ [M+Na]$^+ : 599.3343$, found: $599.3320$.  

$[\alpha]^{28D}_D$ : $+4.7$ (C 0.8, CHCl$_3$)
2.4 REFERENCES:


