Chapter 4

An organocatalytic approach to asymmetric synthesis of Hagen's gland lactones and (-)-Colletallol
A stereocontrolled synthesis of Hagen’s gland lactones via iterative proline catalyzed α-aminoxylation and oxa-Michael addition reactions

4.1.1 Introduction

Hagen’s glands (Fig. 1) earlier known as pygidial glands (located near the abdominal tips) of the braconid wasps, D. Longicaudata (Ashmead), D. Tryoni (Cameron) and Fopius (Biosteres) arisanus, are found to contain fragrance rich lactones. This was first observed by Hagen (1953) and Buckingham (1975) who also put in efforts to study the significance of these secretions in the pest management of fruit fly population control in Hawaii and eastern Queensland, especially against the Queensland fruit fly Bactroceratrayon.i which is known to be an aggressive pest with a wide host range.1

Williams et al. suggested the presence of two bicyclic lactones and experimentally characterized these bicyclic lactones by NMR studies using Karplus based calculations.1c Kitching et al. have determined the absolute stereochemistry of these lactones through synthesis which employs an interesting route that uses 1,3-diol approach followed by PdCl2-catalyzed oxycarbonylation-lactonization reaction.2a

Figure 1. Hagen’s gland lactones and their epimers
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4.1.2. Review of Literature

Considering their possible role in pest management strategies, several authors have reported the synthesis of these lactones either targeting the natural isomer or its epimer. A detailed report of recent syntheses is described below.

Fernandes et al. (2012) ^7a

Fernandes and coworkers synthesized the Hagen’s gland lactone starting from sugar derivative. D-Glucono-δ-lactone 5 was converted to γ-lactone 6 which on cross metathesis catalyzed by Grubbs second-generation (Grubbs-II) catalyst furnished the lactone 7. Lactone 7 on iodolactonization followed by cycloetherification gave iodo lactone 9. This reaction goes via formation of plausible iodonium ion intermediate 8. Reductive radical-mediated removal of iodine from iodo lactone 9 using n-Bu3SnH and AIBN provided the Hagen’s gland lactone 2.

Gharpure et al. (2011) ^8

Gharpure and coworkers synthesized the Hagen’s gland lactone starting from aldehyde hexanal 10 which on enantioselective organocatalytic α-oxyamination in the presence of L-proline followed by reduction gave oxyamino product 11. Oxyamino compound 11 was treated with CuSO4·5H2O to obtain diol 12. Diol 12 on regioselective protection of the

\[
\begin{align*}
\text{(i) TBSCI, imidazole, } & \text{CH₂Cl₂, r.t., overnight} \\
\text{(ii) DABCO, ethyl propiolate } & \text{CH₂Cl₂, r.t., 4 h} \\
\text{(COCl)₂, benzene} & \text{r.t., 2 h, CH₃N₂} \\
\end{align*}
\]

\[
\begin{align*}
\text{r.t., 2 h, CH₃N₂} & \text{ether, 0 °C, 2 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{(i) TBSCI, imidazole, } & \text{CH₂Cl₂, r.t., overnight} \\
\text{OH} & \text{OTBS} \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \text{CuSO₄·5H₂O, MeOH} \\
\text{4 °C, overnight 48%} & \text{CO₂Et} \\
\end{align*}
\]

\[
\begin{align*}
\text{(i) TBSCI, imidazole, } & \text{CH₂Cl₂, r.t., overnight} \\
\text{(ii) DABCO, ethyl propiolate } & \text{CH₂Cl₂, r.t., 4 h} \\
\text{(COCl)₂, benzene} & \text{r.t., 2 h, CH₃N₂} \\
\text{r.t., 2 h, CH₃N₂} & \text{ether, 0 °C, 2 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{(i) TBSCI, imidazole, } & \text{CH₂Cl₂, r.t., overnight} \\
\text{(ii) DABCO, ethyl propiolate } & \text{CH₂Cl₂, r.t., 4 h} \\
\text{(COCl)₂, benzene} & \text{r.t., 2 h, CH₃N₂} \\
\end{align*}
\]

\[
\begin{align*}
\text{r.t., 2 h, CH₃N₂} & \text{ether, 0 °C, 2 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{(i) TBSCI, imidazole, } & \text{CH₂Cl₂, r.t., overnight} \\
\text{(ii) DABCO, ethyl propiolate } & \text{CH₂Cl₂, r.t., 4 h} \\
\text{(COCl)₂, benzene} & \text{r.t., 2 h, CH₃N₂} \\
\end{align*}
\]

\[
\begin{align*}
\text{r.t., 2 h, CH₃N₂} & \text{ether, 0 °C, 2 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{(i) TBSCI, imidazole, } & \text{CH₂Cl₂, r.t., overnight} \\
\text{(ii) DABCO, ethyl propiolate } & \text{CH₂Cl₂, r.t., 4 h} \\
\text{(COCl)₂, benzene} & \text{r.t., 2 h, CH₃N₂} \\
\end{align*}
\]

\[
\begin{align*}
\text{r.t., 2 h, CH₃N₂} & \text{ether, 0 °C, 2 h} \\
\end{align*}
\]

Scheme 2: Synthesis of Hagen’s gland lactone (Gharpure’s method)

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Sartillo-Piscil et al. (2009)\textsuperscript{4}

Sartillo-Piscil and coworkers synthesized the Hagen’s gland lactone starting from sugar derivative. Xylofuranose derivative 20 on selective tosylation of the primary hydroxyl group gave tosyl product 21. The tosyl group of compound 21 was substituted by Grignard reagent in the presence of Cul to get compound 22. Secondary hydroxyl group of 22 was removed by the use of the Barton–McCombie deoxygenation method affording compound 23. Compound 23 on C-glycosylation reaction with allyltrimethylsilane gave a distereoisomeric mixture of tetrahydrofurans 24 and 25 in which the 1,4-trans stereoisomer 24 was major product. Finally, on sequential dihydroxylation–dehomologation–oxidation procedure, Hagen’s gland lactone 2 was obtained.

Scheme 3: Synthesis of Hagen’s gland lactone (Sartillo-Piscil’s method)

2.1.3. Present work

Objective

During last decade, there has been growing interest in the use of small organic molecules to catalyze reactions in a stereoselective manner in organic synthesis. Proline is among the most successful secondary amine based organocatalyst which has been widely employed in several organic transformations.\textsuperscript{9}
As a part of our research interest in developing new methodologies and their subsequent application to bioactive compounds,\textsuperscript{10} we have recently developed an iterative approach to enantiopure synthesis of \textit{syn} and \textit{anti}-1,3-polyols based on proline catalyzed sequential $\alpha$-aminoxylation, followed by Horner-Wadsworth-Emmons olefination of aldehydes at ambient temperature.\textsuperscript{11a} This method has several advantages over the most widely used method to prepare 1,3-polyols in an iterative fashion. We have earlier reported the synthesis of various lactones using 1,3-polyol approach.\textsuperscript{11b,c} However the construction of bridged frameworks containing THF ring systems using the same remains unexplored. We therefore considered application of this methodology along with a highly diastereoselective oxa-Michael addition reaction in the efficient synthesis of substituted tetrahydrofuro[3,2-b]furan-2(3H)-one derivatives (Hagen’s gland lactones).

4.1.4 Results and discussion

As per the retrosynthetic scheme as delineated in scheme 4, the Hagen’s gland lactones could be synthesized from the skipped 1,3-diol fragment A. We envisioned that A could be derived from $\gamma$-hydroxy ester moiety B, a common intermediate which in turn could be obtained via iterative sequential $\alpha$-aminoxylation and Horner-Wadsworth-Emmons olefination of aldehyde C.

Scheme 4. Retrosynthetic route to the synthesis of Hagen’s gland lactones

As shown in scheme 5, the synthesis of the target lactones commenced with the commercially available hexanal 10a which on sequential $\alpha$-aminoxylation using nitroso
benzene as the oxygen source and L-proline as catalyst and subsequent HWE olefination using triethylphosphonoacetate, followed by hydrogenation using a catalytic amount of Pd/C, furnished the γ-hydroxy ester 25a. Thus, in two steps and one column purification 25a was obtained in 65% yield and 94% ee. Protection of the free hydroxyl group as its TBS ether gave 26a in 92% yield. Disappearance of peak at 3432 cm⁻¹ in IR spectrum confirmed the formation of 26a. The TBS protected hydroxyester 26a was then reduced using DIBAL-H in toluene (1.0 M) in CH₂Cl₂ as a solvent at -78 °C to furnish an aldehyde. Crude aldehyde was further subjected to α-aminoxylation reaction using L-proline as a catalyst followed by HWE-olefination to yield compound 27a in good diastereomeric excess (dr ratio 95:5) determined using HPLC. The IR spectrum of 27a showed the ester carbonyl absorption at 1712 cm⁻¹. With syn-1,3-diol 27a in hand we proceeded to the synthesis of Hagen’s gland lactone using oxa-Michael addition which was triggered through the fluoride-mediated cleavage of a silyl protecting group using TBAF in THF followed by lactonisation with catalytic amount of HCl (pH~3 in toluene). At this stage we could observe the formation of two products 1 & 2 (ratio 5:1). The stereochemistry of both the products was confirmed using detailed 1D and 2D-NMR techniques.

Scheme 5. Synthesis of Hagen’s gland Lactones

Taking into consideration this observation we considered it worthwhile to study the stereochemistry of both the products which was confirmed using detailed 1D and 2D-NMR techniques.
In NOESY analysis of the compound 1, proton H₃α shows nOe correlation with proton H₆α, indicating syn stereochemistry at the bridgehead of the substituted tetrahydrofuro[3,2-b]furan-2(3H)-one. H₃α also shows nOe correlation with proton H₅, which confirms the syn relative stereochemistry between these three protons. Since the methylene protons H₆α and H₆β resonated at different chemical shifts; the above results are also confirmed from the nOe of the H₆α and H₆β with the H₅ and H₆α. The H₆α resonating at δ 2.41 ppm showed nOe correlations with H₅ as well as with H₆α confirming the syn relative stereochemistry between these three protons. While the other methylene proton (H₆β) does not show nOe correlations either to H₅ or with H₆α confirming the syn relative stereochemistry between these three protons. While the other methylene proton (H₆β) does not show nOe correlations either to H₅ or with H₆α, indicating anti relative orientation with the H₅ and H₆α (Figure 2).

Figure 2: ¹H-¹H NOESY spectra of the compound 1 (400 MHz, CDCl₃, 298 °K)

Although the spectra of both the compounds 1 & 2 were quite similar, they showed significant differences in the chemical shift values especially of the methine protons. In case of compound 2 among the two methylene groups of the substituted tetrahydrofuro[3.2-b]furan-2(3H)-one, both the methylene show different chemical shifts for the individual proton. The methylene (H₆α) resonating at δ 2.37 and 1.66 ppm shows...
COSY correlation with two methine protons resonating at $\delta$ 4.07 and $\delta$ 5.11 ppm indicating that this methylene is from the furyl ring.

**Figure 3:** $^1$H-$^1$H NOESY spectra of the compound 2 (700 MHz, CDCl$_3$, 298 °K)

As it can be seen from **Figure 3**, the H$_5$ proton shows nOe correlation with $\delta$ 2.37 ppm (H$_{6a}'$) while H$_{6a}$ shows nOe correlation with $\delta$ 1.66 ppm (H$_{6a}'$). These results show that the H$_{6a}$ and H$_5$ methine protons show nOe correlation with different protons of the furyl methylene indicating anti relative stereochemistry between H$_5$ and H$_{6a}$. In addition, H$_{6a}$ also shows nOe correlation with H$_{3a}$ indicating syn stereochemistry at the bridgehead of the substituted tetrahydrofuro[3.2-b]furan-2(3H)-one. The above results are also evaluated from the fact that none of the protons among H$_{3a}$ and H$_{6a}$ shows nOe correlation with H$_5$ confirming the anti-relative stereochemistry of H$_5$ with the H$_{6a}$ and H$_{3a}$ as shown in the pictorial representation in **Figure 4**.

**Figure 4:** Pictorial representation of both cis and trans nOe correlations
This result motivated us to study the stereoselection of both oxa-Michael and cyclization reactions very closely. The reproducibility of the strategy and high yielding steps efficiently allowed us to quickly synthesize 1,3-syn diol compound 27a which was subjected to simultaneous desilylation/oxa-Michael reaction. Instead of going further for cyclization at this stage, we quenched the reaction mixture using saturated ammonium chloride solution to get the oxa-Michael product 28 (scheme 3). Preliminary examination using Thin Layer chromatography showed the presence of only one product. $^1$H and $^{13}$C NMR did not show the formation of other diastereomer and revealed that the oxa-Michael addition reaction proceeded in a highly diastereoselective manner. The stereochemistry of compound 28 was confirmed using detailed 1D and 2D NMR techniques.

![Scheme 6: Diastereoselective oxa-Michael addition reaction of 27a](image)

It was observed that in compound 28, H$_4$ and H$_1$ show nOe correlations indicating syn relative stereochemistry$^{14}$ while none of them shows nOe correlations with H$_3$ indicating anti relative stereochemistry with H$_3$ as shown in Figure 5. The relative stereochemistry among H$_1$ with H$_3$ was further confirmed by their nOe correlations with methylene protons (H$_2$ & H$_5$). It was found that H$_1$ shows nOe correlations only with H$_2$ while H$_3$ shows nOe correlations only with H$_5$ indicating anti relative stereochemistry between H$_1$ and H$_3$ as shown in the pictorial representation in Figure 7.
To check the feasibility of cyclization of 28 without epimerization, we carried out reaction using \( p \)-TSA in toluene both at room temperature and under reflux conditions. As anticipated, the cyclization reaction proved to be a total failure as it gave only the starting material back (Scheme 7). However, when compound 28 was treated with catalytic amount of HCl, it afforded the diastereomeric mixture of bicyclic compounds 1 & 2 in the ratio 5:1 respectively.

**Scheme 7**: Lactonization reaction

The possible reason for the formation of mixture of diastereomers in the cyclization step could be attributed to the racemization of either of the two protons (\( H_3 \) or \( H_4 \)) in the presence of HCl (pH 3) under reflux conditions, leading to cyclized products 1 & 2 with both the bridged protons syn to each other.
The formation of both the products may be explained individually on the basis of the acidic medium present. Compound 2 is found to be a major compound and compound 1 as a minor product in the ratio 5:1 respectively. The major product 2 i.e., epimer of Hagen’s gland lactone can be visualized to have formed via a retro-Michael reaction where a consequent ring opening occurs as a result of protonation of the oxygen atom of the THF ring leading to the formation of an open chain product. This open chain product now contains a planar sp² olefin where the free hydroxyl group is now free to attack the double bond from either the top of the plane which may give back starting material or may approach from the bottom of the sp² plane to give compound 28a that could easily undergo lactonisation to give 2.

**Plausible mechanism for the formation of 2:**

Whereas in case of compound 1 the reaction proceeds via a carbocation intermediate that is formed through the protonation of the free hydroxyl group. The carbonyl group of the ester could then approach the carbocation in a way that the cis fusion of the five membered ring is maintained, leading to the formation of 1. However since compound 1 is obtained as minor product, it can be concluded that the reaction proceeds predominantly via a retro Michael approach (*Scheme 9*).
In order to rationalise our findings, we planned to test the devised strategy by synthesizing 1,3-anti diol as an intermediate. For this purpose, we started with previously synthesized protected γ-hydroxy ester 26a which was reduced using DIBAL-H in toluene at -78 °C to furnish corresponding aldehyde. Crude aldehyde was further subjected to α-aminoxylation/HWE olefination reaction using D-proline as a catalyst to obtain 1,3-anti diol 27c with an excellent dr ratio (97:3).\(^\text{13}\) To test the formation of diastereomeric mixture, one-pot oxa-Michael/ lactonisation was performed on the diol 27c. In this case we observed the formation of only one product 1 as characterised by \(^{13}\)C NMR which was an entirely different result when compared to the syn-diol product (Scheme 8).

**Scheme 8: Synthesis of epi-Hagen’s gland Lactone**

This observation was further substantiated and proved by isolating the oxa-Michael adduct 29. Towards this end, compound 27c was submitted to a concomitant desilylation/oxa-Michael reaction with TBAF in THF for 3h to get 29 in 85% yield as shown in scheme 9. Characterisation of the oxa-Michael adduct 29 was carried out by 1D and 2D NMR techniques. Initially, nOe studies at 400 MHz were a little difficult to decipher as the peaks of both methine and methylene protons resonated at \(\delta\) 4.04 ppm. However, this issue was resolved by analyzing the spectra at higher field strength (700MHz) which showed a slight difference in chemical shifts for protons \(H_1\) and \(H_4\).
Scheme 9: Synthesis of compound 29

As shown in Figure 6, H₃ proton shows nOe correlation with both methine protons H₁ and H₄ indicating syn stereochemistry among them. The relative stereochemistry was also confirmed with the help of methylene group which shows two different signals for two protons (H₂ and H₃). The H₁ and H₃ methine protons show nOe correlations only with H₂ proton, but it does not show any correlation with H₄ proton indicating all the three methine protons (H₁, H₃ and H₄) being syn to each other as shown in the pictorial representation in Figure 7.

Figure 6: ¹H-¹H NOESY spectra of the compound 29 (700 MHz, CDCl₃, 298 °K)

After confirming the stereochemistry of compound 29, it was initially subjected to cyclization using p-TSA at rt to give compound 1 as a sole product. Even under reflux conditions, there was no racemisation and reaction led to the only product 1. We then examined the possibility of racemisation under strong acidic conditions by using conc. HCl both at rt and under reflux conditions. Interestingly, no racemisation was observed and cyclization was smooth leading to the desired product 1 in excellent yield. The
stereochemistry of 1 was confirmed simply by comparing the $^1$H-NMR and optical rotation (scheme 10).

\[
\begin{align*}
R - O - C - H &\xrightarrow{P-TSA, Toluene} R - O - C - \text{Et}
\end{align*}
\]

Scheme 10: Lactonization reaction

This could be due to the syn stereochemistry of the intermediate making cyclisation more facile than the racemization. To check the reproducibility and improve the confidence in the stereochemical outcome by the above methods, we thought of extrapolating the strategy to the synthesis of 3 and 4 isolated from D.krausii. Both the compound could easily be synthesized as a separable mixture of cis and trans isomers from the corresponding aldehyde octanal 24b by subjecting it to similar set of reaction conditions as described in scheme 5.

![Figure 7: nOe correlations for compounds 9 and 10](image)

4.1.5 Conclusion

In conclusion, we have developed a new, efficient and organocatalytic protocol to Hagens gland lactones using a proline catalyzed $\alpha$-aminoxylation and consequent oxa-Michael reaction. Desirable stereocenters can be obtained by using the suitable catalyst and this approach could further be extended to the synthesis of other stereoisomers and synthetic analogues.
4.1.6. Experimental section

**Ethyl (R)-4-hydroxydecanoate (25b):**

![Chemical Structure](image)

**General procedure for α-aminoxylation:** To a solution of octanal 10b (2.0 g, 15.62 mmol) and nitroso benzene (1.6 g, 15.62 mmol) in anhydrous DMSO (29 mL) was added L-proline (0.72 g, 6.2 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (6.22 mL, 31.25 mmol), DBU (4.29 mL, 31.25 mmol) and LiCl (1.32 g, 31.25 mmol) in CH₃CN (29 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et₂O (5×100 mL). The combined organic layers were washed with water, brine, dried (Na₂SO₄) and concentrated in vacuo to give crude product which was directly subjected to next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. On completion of reaction (until ¹H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give γ-alcohol. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (85:15) as eluent to give ethyl (R)-4-hydroxydecanoate 25b as a colourless liquid.

**Yield:** 2.19 g, 65%

**Mol. Formula:** C₁₂H₂₄O₃

**[α]₂⁰:** +1.17 (c 1.5, CHCl₃)

**IR (CHCl₃, cm⁻¹):** \( v_{\text{max}} \): 3432, 2934, 1718.
\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta 4.13 (q, J = 7.2\) Hz, 2H), 3.67-3.52 (m, 1H), 2.50-2.39 (m, 2H), 1.99-1.61 (m, 4H), 1.56-1.29 (m, 8H), 1.29-1.22 (m, 3H), 0.92 (d, \(J = 4.8\) Hz, 3H) ppm.

\(^13\)C NMR (126 MHz, CDCl\(_3\)): \(\delta 174.1, 80.9, 71.0, 60.2, 37.4, 32.1, 30.7, 29.5, 25.5, 22.5, 14.0, 13.9\) ppm.

MS (ESI): \(m/z\ 239.12\)

HRMS (ESI) \(m/z\): [M + Na]\(^+\) Calcd for C\(_{12}\)H\(_{24}\)O\(_3\)Na 239.1618; Found 239.1614

HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2-propanol : petroleum ether = 10:90. flow rate 0.5ml/min, \(\lambda = 220\) nm). Retention time (min):78.48 (minor) and 80.70 (major). The racemic standard was prepared in the same way using \(\alpha\)/-proline as a catalyst. ee>98%.

\((R)\)-Ethyl 4-hydroxyoctanoate (25a):

\[
\begin{align*}
\text{OH} & \\
\text{COOEt} & 
\end{align*}
\]

Hexanal 10a (2.0 g, 20 mmol) was subjected to the above condition to furnish crude product to give \((R)\)-ethyl 4-hydroxyoctanoate 25a as colorless liquid.

Yield: 2.44 g. 65 %

Mol. Formula: C\(_{10}\)H\(_{20}\)O\(_3\)

[\(\alpha\)]\(^{25}\) : -0.93 (c 2.24, CHCl\(_3\))

IR (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\ 3430, 2934, 1718, 1465, 1177.\)

\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta 0.86-0.93\) (m, 3H), 1.25 (t, \(J = 7.2\) Hz, 3H), 1.32-1.36 (m, 3H), 1.41-1.45 (m, 2H), 1.62-1.93 (m, 4H), 2.44 (t, \(J = 7.2\) Hz, 2H), 3.55-3.67 (m, 1H), 4.11 (q, \(J = 7.2\) Hz, 2H) ppm.

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 13.7, 13.8, 22.4, 27.5, 30.4, 31.9, 36.9, 60.1, 70.5, 174.0\) ppm.

MS (ESI): \(m/z\ 211.2468\) (M\(^+\)+Na).

Ethyl \((R)\)-4-((tert-butyldimethylsilyl)oxy)decanoate (26b):
General procedure for TBS protection: To an ice-cold stirred solution of 25b (1.70 g, 7.87 mmol) in DMF (10 mL) were added imidazole (1.00 g, 15.74 mmol) and TBSCl (1.77 g, 11.80 mmol) at 0 °C. The resulting mixture was stirred for 1 h at rt before H2O (20 mL) was added. The aqueous layer was extracted with Et2O (3 x 20 mL). The combined organic layers were washed with brine, dried (Na2SO4), and concentrated under reduced pressure. Silica gel column chromatography of crude product using petroleum ether: ethyl acetate: (95:05) as eluent gave TBS ether 26b as a colourless liquid.

Yield: 2.39 g, 92%

Mol. Formula: C18H38O3Si

[a]D25: -7.08 (c 1.6, CHCl3)

IR (CHCl3, cm⁻¹): νmax 2856, 1726.

1H NMR (200 MHz, CDCl3): δ 4.12 (q, J = 7.1 Hz, 2H), 3.75-3.59 (m, 1H), 2.40-2.29 (m, 2H), 1.82-1.63 (m, 2H), 1.47-1.34 (m, 2H), 1.30-1.22 (m, 11H), 0.88 (m, 12H), 0.04 (s, 6H) ppm.

13C NMR (101 MHz, CDCl3): δ 174.0, 71.2, 60.2, 37.0, 31.8, 31.7, 30.1, 29.5, 25.9, 25.1, 22.6, 18.1, 14.2, 14.1, -4.4, -4.6 ppm.

MS (ESI): m/z 353.20

HRMS (ESI) m/z: [M + Na]⁺ Calcd for C18H38O3NaSi 353.2482; Found 353.2472

(R)-Ethyl 4-(tert-butyldimethylsilyloxy)octanoate (25b):

Following the procedure as described above 25b was obtained from compound (1g, 5.3 mmol) as a crude product which was purified by column chromatography using petroleum ether: EtOAc (95:5) to give (R)-ethyl 4-(tert-butyldimethylsilyloxy)octanoate 25b as a colorless liquid.
Yield: 1.48 g, 92%

Mol. Formula: C_{16}H_{34}O_{3}Si

[α]_D^{25}: +9.96 (c 1.78, CHCl_3).

IR (CHCl_3, cm\(^{-1}\)): \(\nu_{\text{max}}\) 2858, 1726, 1463, 1256.

\(^1\)H NMR (400 MHz, CDCl_3): \(\delta\) -0.04 (s, 6H), 0.89 (s, 12H), 1.24-1.30 (m, 7H), 1.41-1.46 (m, 2H), 1.65-1.72 (m, 1H), 1.77-1.85 (m, 1H), 2.33-2.38 (m, 2H), 3.66-3.72 (m, 1H), 4.12 (q, \(J = 7.2\) Hz, 2H) ppm.

\(^{13}\)C NMR (100 MHz, CDCl_3): \(\delta\) -4.9, -4.7, 13.9, 14.0, 17.8, 22.6, 25.7, 27.2, 29.8, 31.5, 36.6, 59.9, 70.9, 173.5 ppm.

MS (ESI): \(m/z\) 325.4028 (M\(^{+}\)+Na).

Ethyl (4\(R\),6\(R\),\(E\))-(tert-butyl(dimethyl)silyl)oxy)-4-hydroxydec-2-enoate (27a):

![Structure](image)

**General procedure for iterative aminooxylation:** To a solution of ethyl ester 26a (1.0 g, 4.63 mmol) in CH_2Cl_2 (6 mL), was added DIBAL-H (2.5 mL, 2.3 M solution in toluene, 5.09 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then a solution of tartaric acid (2.5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colourless liquid, which was directly used in the next step without further purification. Following the general procedure for \(\alpha\)-aminooxylation (L-proline as a catalyst) 27a was obtained as a crude product (~95% diastereomeric excess) and was purified by flash column chromatography using petroleum ether: ethyl acetate (9:1) to furnish pure diol 27a as a colorless liquid.

Yield: 0.80 g, 71%

Mol. Formula: C_{18}H_{36}O_{4}Si

[α]_D^{25}: -15.76 (c 0.6, CHCl_3)

IR (CHCl_3, cm\(^{-1}\)): \(\nu_{\text{max}}\) 3436, 2967, 1218.
Chapter 4: Section A

\[ ^1H \text{ NMR} \ (200 \text{ MHz, } \text{CDCl}_3): \delta \ 6.92 \ (dd, J = 4.4, 15.6 \text{ Hz, } 1\text{H}), \ 6.10 \ (dd, J= 1.8, 15.6 \text{ Hz, } 1\text{H}), \ 4.46 \ (m, 1\text{H}), \ 4.19 \ (q, J = 7.1 \text{ Hz, } 2\text{H}), \ 3.96 \ (m, 1\text{H}), \ 1.76-1.50 \ (m, 4\text{H}), \ 1.27-1.23 \ (m, 7\text{H}), \ 0.94-0.90 \ (m, 12\text{H}), \ 0.16-0.08 \ (m, 6\text{H}) \text{ ppm.} \]

\[ ^13 \text{C NMR} \ (126 \text{ MHz, } \text{CDCl}_3): \delta \ 166.7, \ 149.7, \ 119.8, \ 73.3, \ 70.4, \ 60.3, \ 41.9, \ 37.7, \ 26.8, \ 25.8, \ 22.8, \ 17.9, \ 14.2, \ 14.0, \ -4.0, \ -4.8 \text{ ppm.} \]

\[ \text{MS (ESI)}: m/z \ 367.18 \]

\[ \text{HRMS (ESI)} \ m/z: [M + Na]^+ \text{ Calcd for } C_{18}H_{36}O_4NaSi \ 367.2275; \text{ Found } 367.2275. \]

\[ \text{HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H}_2\text{O = 90:10), flow rate} \ 1.0\text{ml/min. (}\lambda = \ 210 \text{ nm). Retention time (min): 7.31 (major) and 7.89 (minor). (dr 95:5)} \]

Ethyl (4S,6R,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydodec-2-enoate (27c):

\[
\begin{array}{c}
\text{TBS} \\
\text{O} \\
\text{OH} \\
\text{COEt}
\end{array}
\]

Compound 27c was prepared using the general procedure for iterative aminooxylation starting from ethyl ester 26a and using D-proline as a catalyst.

\[ \text{Yield: } 0.79 \text{ g. } 70\% \]

\[ \text{Mol. Formula: } C_{18}H_{36}O_4Si \]

\[ [\alpha]_D^{25}: -7.5 (c 0.4, \text{CHCl}_3) \]

\[ \text{IR (CHCl}_3, \ cm^{-1}): \nu_{\text{max}} 3430, 2934, 1718 \]

\[ ^1H \text{ NMR} \ (200 \text{ MHz, } \text{CDCl}_3): \delta \ 6.92 \ (dd, J = 4.2, 15.6 \text{ Hz, } 1\text{H}), \ 6.11 \ (dd, J = 1.9, 15.5 \text{ Hz, } 1\text{H}), \ 4.64 \ (ddt, J = 1.8, 4.2, 8.2 \text{ Hz, } 1\text{H}), \ 4.20 \ (q, J = 7.1 \text{ Hz, } 2\text{H}), \ 4.05-3.94 \ (m, 1\text{H}), \ 1.74-1.65 \ (m, 2\text{H}), \ 1.29 \ (t, J = 7.1 \text{ Hz, } 9\text{H}), \ 0.90 \ (m, 12\text{H}), \ 0.09 \ (d, J = 1.4 \text{ Hz, } 6\text{H}) \text{ ppm.} \]

\[ ^13 \text{C NMR} \ (101 \text{ MHz, } \text{CDCl}_3): \delta \ 166.7, \ 150.4, \ 119.8, \ 71.5, \ 68.0, \ 60.3, \ 40.5, \ 35.7, \ 27.8, \ 25.8, \ 22.7, \ 17.9, \ 14.2, \ 14.0, \ -4.5, \ -4.8 \text{ ppm.} \]

\[ \text{MS (ESI)}: m/z \ 367.19 \]

\[ \text{HRMS (ESI)} \ m/z: [M + Na]^+ \text{ Calcd for } C_{18}H_{36}O_4NaSi \ 367.2273; \text{ Found 367.2275.} \]

\[ \text{HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H}_2\text{O = 90:10), flow rate} \ 1.0\text{ml/min. (}\lambda = \ 210 \text{ nm). Retention time (min): 6.91 (major) and 7.43 (minor). (dr 95:5)} \]

Ethyl (4R,6R,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydodec-2-enoate (27b):
Compound 27b was prepared using the general procedure for iterative aminoxylolation starting from ethyl ester 26b and using L-proline as a catalyst.

**Yield:** 0.80 g, 70%

**Mol. Formula:** C_{20}H_{40}O_{4}Si

**[α]_D^{25}**: -6.49 (c 1.8, CHCl₃)

**IR** (CHCl₃, cm⁻¹): νmax 3450, 2920.

**¹H NMR** (200 MHz, CDCl₃): δ 6.91 (dd, J = 4.4, 15.6 Hz, 1H), 6.10 (dd, J = 1.9, 15.5 Hz, 1H), 4.24 - 4.09 (m, 2H), 4.07-3.82 (m, 1H), 3.82-3.51 (m, 1H), 1.63-1.52 (m, 4H), 1.27 (d, J = 4.5 Hz, 11H), 0.92-0.88 (m, 12H), 0.12 (d, J = 2.5 Hz, 6H) ppm.

**¹³C NMR** (126 MHz, CDCl₃): δ 166.7, 149.7, 119.8, 73.3, 70.4, 60.3, 42.0, 38.0, 31.8, 29.4, 25.8, 22.5, 17.9, 14.2, 14.0, -4.0, -4.7 ppm.

**MS** (ESI): m/z 395.20

**HRMS (ESI)** m/z: [M + Na]+ Calcd for C_{20}H_{40}O_{4}NaSi 395.2588; Found 395.2578.

**HPLC:** Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H₂O = 90:10), flow rate 1.0 ml/min, (λ = 210 nm). Retention time (min): 10.61 (major) and 11.61 (minor), dr 96:4.

**Ethyl 2-((2S,3R,5R)-5-butyl-3-hydroxytetrahydrofuran-2-yl)acetate (28):**

**General procedure for oxa Michael addition:** The solution of 27a (0.25 g, 0.92 mmol) was treated with TBAF (0.5 mL, 1.8 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt and quenched with saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give a crude product. Silica gel column chromatography of the crude product using petroleum ether: ethyl acetate: (8:2) as eluent gave oxa-Michael product 28 as a colorless liquid.
Chapter 4: Section A

Yield: 0.14 g, 85%

**Mol. Formula:** C_{12}H_{22}O_{4}

[$\alpha$]_{D}^{25}: +1.3 (c 0.3, CHCl_{3})

**IR** (CHCl_{3}, cm$^{-1}$): $v_{\text{max}}$ 3463, 2931, 1764

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.18 (d, $J = 7.0$ Hz, 2H), 4.14-4.10 (m, 1H), 4.06 (dd, $J = 6.1$, 9.2 Hz, 1H), 3.95 (td, $J = 4.6$, 9.4 Hz, 1H), 2.80 (dd, $J = 5.0$, 16.3 Hz, 1H), 2.51 (dd, $J = 9.2$, 16.5 Hz, 1H), 2.35 (t, $J = 7.6$ Hz, 1H), 2.01-1.96 (m, 1H), 1.82-1.75 (m, 1H), 1.49-1.42 (m, 2H), 1.33-1.26 (m, 6H), 0.91-0.87 (m, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.2, 82.3, 78.4, 77.2, 60.9, 40.3, 38.8, 35.2, 28.1, 22.7, 14.1, 14.0 ppm.

**MS (ESI):** $m/z$ 253.12

**HRMS (ESI)** $m/z$: [M + Na]$^+$ Calcd for C$_{12}$H$_{22}$O$_{4}$Na 253.1410; Found 253.1411

**Ethyl 2-((2S,3S,5R)-5-hexyl-3-hydroxytetrahydrofuran-2-yl)acetate (29):**

![Chemical Structure](image)

Compound 29 was prepared using the general procedure for oxa Michael addition starting from ethyl ester 27c.

Yield: 0.14 g, 85%

**Mol. Formula:** C$_{12}$H$_{22}$O$_{4}$

[$\alpha$]$_{D}^{25}$: -8.4 (c 1.0, CHCl$_3$)

**IR** (CHCl$_3$, cm$^{-1}$): $v_{\text{max}}$ 3463, 2931, 1764

$^1$H NMR (700 MHz, CDCl$_3$): $\delta$ 4.13-4.05 (m, 3H), 3.98-3.93 (m, 1H), 3.93-3.88 (m, 1H), 2.66 (dd, $J = 5.3$, 16.3 Hz, 1H), 2.45-2.41 (m, 1H), 2.30 (td, $J = 6.7$, 13.0 Hz, 1H), 1.58 (dd, $J = 4.9$, 7.9 Hz, 1H), 1.44-1.41 (m, 2H), 1.30-1.18 (m, 7H), 0.82-0.78 (m, 3H) ppm.

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 172.4, 79.8, 77.7, 76.8, 60.9, 40.2, 38.6, 35.8, 28.0, 25.7, 22.6, 14.0 ppm.

**MS (ESI):** $m/z$ 253.10

**HRMS (ESI)** $m/z$: [M + Na]$^+$ Calcd for C$_{12}$H$_{22}$O$_{4}$Na 253.1410; Found 253.1411
(3aS,5R,6aS)-5-Butyltetrahydrofuro[3,2-b]furan-2(3H)-one (1):

**General procedure for lactonization reaction:** The solution of crude 28 (0.1 g, 0.368 mmol) was treated with catalytic amount of dil. HCl (pH~3) in dry toluene. The reaction mixture was refluxed for 12 h and concentrated under reduced pressure to give a crude product. Silica gel column chromatography of the crude product using pet ether: ethylacetate: (85:15) as eluent afforded 1 as a syrupy liquid.

**Yield:** 0.047 g, 61%

**Mol. Formula:** C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>

\[ \alpha \]<sub>DB</sub>: -53.39 (c 0.8, CHCl<sub>3</sub>)

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** \( \delta \) 5.03-5.00 (m, 1H), 4.53-4.50 (m, 1H), 3.97 - 3.91 (m, 1H), 2.73 (d, \( J = 3.3 \) Hz, 2H), 2.46 - 2.39 (m, 1H), 1.91-1.86 (m, 1H), 1.70-1.65 (m, 1H), 1.60-1.54 (m, 1H), 1.37-1.30 (m, 4H), 0.92-0.89 (m, 3H) ppm.

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):** \( \delta \) 175.5, 84.7, 80.3, 78.2, 38.3, 36.6, 35.2, 28.2, 22.6, 13.9 ppm.

**MS (ESI):** \( m/\epsilon \approx 207.08 \)

**HRMS (ESI) \( m/\epsilon \):** [M + Na]<sup>+</sup> Calcd for C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>Na 207.0991; Found 207.0992

(3aR,5R,6aR)-5-Butyltetrahydrofuro[3,2-b]furan-2(3H)-one (2):

Compound 2 was prepared using the general procedure for lactonization reaction starting from ethyl ester 28.

**Yield:** 0.009 g, 12.2%

**Mol. Formula:** C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>

\[ \alpha \]<sub>DB</sub>: +47.22 (c 0.3, CHCl<sub>3</sub>)
Chapter 4: Section A

$^1$H NMR (700 MHz, CDCl$_3$): $\delta$ 5.12 (t, $J = 4.7$ Hz, 1H), 4.83-4.79 (m, 1H), 4.07 (dt, $J = 6.0, 10.7$ Hz, 1H), 2.76 (dd, $J = 6.7, 18.7$ Hz, 1H), 2.65 (d, $J = 18.9$ Hz, 1H), 2.38 (dd, $J = 4.5, 13.9$ Hz, 1H), 1.69-1.65 (m, 1H), 1.56-1.43 (m, 2H), 1.39-1.28 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H) ppm.

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 176.0, 84.9, 78.3, 77.3, 38.8, 36.6, 34.4, 28.2, 22.6, 13.9 ppm.

MS (ESI): $m/z$ 207.06

HRMS (ESI) $m/z$: [M + Na]$^+$ Calcd for C$_{12}$H$_{20}$O$_3$Na 207.0991: Found 207.0991

(3aS,5R,6aS)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (3):

General procedure: The solution of 27b (0.25 g, 0.92 mmol) was treated with TBAF (0.5 mL, 1.8 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt and quenched with saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na$_2$SO$_4$ and concentrated under reduced pressure to give a crude product. The solution of crude product in toluene was treated with catalytic amount of dil. HCl (pH~3) in dry toluene. The reaction mixture was refluxed for 12 h and concentrated under reduced pressure to give a crude product. Silica gel column chromatography of the crude product using pet ether: ethylacetate: (85:15) as eluent afforded 3 as a syrupy liquid.

Yield: 0.046 g, 60%

Mol. Formula: C$_{12}$H$_{20}$O$_3$

$[\alpha]_D^{25}$: -39.62 (c 0.8, CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.01 (ddd, $J = 2.3, 4.6, 6.9$ Hz, 1H), 4.53-4.49 (m, 1H), 3.94 (td, $J = 7.0, 13.8$ Hz, 1H), 2.42 (td, $J = 7.2, 14.2$ Hz, 2H), 1.89 (ddd, $J = 2.3, 7.9, 14.2$ Hz, 2H), 1.60-1.50 (m, 4H), 1.37-1.30 (m, 6H), 0.90 (s, 3H) ppm.

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 175.5, 84.7, 80.4, 78.2, 38.3, 36.4, 35.2, 29.7, 29.6, 28.2, 22.6, 14.0 ppm.

MS (ESI): $m/z$ 235.10
Chapter 4: Section A

**HRMS (ESI) m/z:** [M + Na]+ Calcd for C₁₂H₂₀O₃Na 235.1302: Found 235.1302

(3aR,5R,6aR)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (4):

![Chemical Structure](image)

Compound 4 was prepared using the general procedure for oxa Michael addition followed by general procedure for lactonization starting from ethyl ester 27b.

**Yield:** 0.009 g, 12%

**Mol. Formula:** C₁₂H₂₀O₃

**[α]₀²⁵:** +42.78 (c 0.5, CHCl₃)

**¹H NMR (500 MHz, CDCl₃):** δ 5.12 (t, J = 4.8 Hz, 1H), 4.84-4.80 (m, 1H), 4.07 (td, J = 5.3, 10.7 Hz, 1H), 2.79-2.68 (m, 2H), 2.39 (dd, J = 4.6, 13.7 Hz, 2H), 1.68-1.61 (m, 4H), 1.56-1.50 (m, 2H), 1.34 (dd, J = 6.5, 12.2 Hz, 4H), 0.92-0.90 (m, 3H) ppm.

**¹³C NMR (126 MHz, CDCl₃):** δ 175.5, 84.7, 78.2, 77.3, 38.2, 36.3, 35.2, 31.9, 29.6, 29.3, 22.5, 13.9 ppm.

**MS (ESI):** m/z 235.10

**HRMS (ESI) m/z:** [M + Na]+ Calcd for C₁₂H₂₀O₃Na 235.1304: Found 235.1305

---

4.1.7. Spectra
Ethyl (R)-4-hydroxyoctanoate (25a):

**¹H NMR (CDCl₃, 200 MHz)**

**¹³C NMR (CDCl₃, 101 MHz)**
Ethyl (R)-4-hydroxydecanoate (25b):

\[ \text{CHLOROFORM-d} \]

\[ \text{OH} \]

\[ \text{COOEt} \]

\[ \text{^1H NMR (CDCl}_3, \text{ 200 MHz)} \]

\[ \text{^13C NMR (CDCl}_3, \text{ 101 MHz)} \]
Ethyl (R)-4-((tert-butyldimethylsilyl)oxy)decanoate (26b):

> $^1$H NMR (CDCl$_3$, 200 MHz)

> $^{13}$C NMR (CDCl$_3$, 101 MHz)
Ethyl (4R,6R,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (27a):

\[ 
\text{CHLOROFORM-d} \\
\begin{array}{c}
\text{OTBSOH} \\
\text{COOEt}
\end{array} \\
\text{WATER}
\]

\[ 
\begin{array}{c}
\text{1H NMR (CDCl}_3, 200 MHz) \\
\end{array}
\]

\[ 
\begin{array}{c}
\text{13C NMR (CDCl}_3, 126 MHz) \\
\end{array}
\]
Ethyl (4S,6R,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (27c):

- **$^1$H NMR (CDCl$_3$, 200 MHz)**

- **$^{13}$C NMR (CDCl$_3$, 101 MHz)**
chapter 4: Section A

Ethyl (4R,6R,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydodec-2-enoate (27b):

\[ \text{OTBSOH} \quad \text{COOEt} \]

\[ ^1H \text{ NMR (CDCl}_3, 200 \text{ MHz)} \]

\[ ^{13}C \text{ NMR (CDCl}_3, 126 \text{ MHz)} \]
Ethyl 2-((2S,3R,5R)-5-butyl-3-hydroxytetrahydrofuran-2-yl)acetate (28):

\[ \text{CHLOROFORM-d} \]

$\text{\^{1}H NMR (CDCl}_3, 400 \text{ MHz)}$

$\text{\^{13}C NMR (CDCl}_3, 101 \text{ MHz)}$
Ethyl 2-((2S,3S,5R)-5-hexyl-3-hydroxytetrahydrofuran-2-yl)acetate (10):

$^1$H NMR (CDCl$_3$, 700 MHz)

$^{13}$C NMR (CDCl$_3$, 176 MHz)
(3aR,5R,6aR)-5-Butyltetrahydrofuro[3,2-b]furan-2(3H)-one (2):

$^1$H NMR (CDCl$_3$, 700 MHz)

$^{13}$C NMR (CDCl$_3$, 176 MHz)
Ethyl 2-((2S,3S,5R)-5-Butyl-3-hydroxytetrahydrofuran-2-yl)acetate (1):

**$^1$H NMR (CDCl$_3$, 400 MHz)**

**$^{13}$C NMR (CDCl$_3$, 101 MHz)**
Chapter 4: Section A

(3aR,5R,6aR)-5Hexyltetrahydrofuro[3,2b]furan2(3H)one (4):

\[ \text{\textit{\textbf{CHLOROFORM-d}}\text{(\textit{\textbf{CDCI}_3, 500 MHz})}} \]

\[ \text{\textit{\textbf{1H NMR (CDCl}_3, 500 MHz})} \]

\[ \text{\textit{\textbf{13C NMR (CDCl}_3, 126 MHz})} \]
(3aS,5R,6aS)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (3):

\[ \text{CHLOROFORM-}d \]

$^1$H NMR (CDCl$_3$, 500 MHz)

$^{13}$C NMR (CDCl$_3$, 126 MHz)
Chrom Type: HPLC Channel: 1

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### Chrom Type: HPLC Channel 1

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4.1.8. References


12. Diastereomeric and enantiomeric excess were determined using HPLC (See experimental section).

In order to determine the chiral purity of (R)-ethyl-4-hydroxydecanoate 25b, it was converted into lactone 30 on treatment with p-TSA in methanol.
13. The ratio of the mixture was determined by $^1$H-NMR of crude mixture.

14. The protons H1, H2, H3, H4 and H5 were arbitrarily assigned to show the relative syn and anti-stereochemistry.
Total synthesis of (−)-(6R,11R,14S)-colletallol via proline catalyzed α-aminoxylation and Yamaguchi macrolactonization

4.2.1 Introduction

Macrolides are broadly classified into two categories, first class of compounds having C$_2$ symmetry in a 16 membered lactone ring and another class of 14-membered unsymmetrical bis-macrolactone to which (−)-colletallol 3, a macrolide belongs. It was isolated from the plant pathogen Collectotrichum capsici along with structurally related macrolides colletol 1, colletodiol 2 and colletoketol 4 (Fig. 1). More recently, two related 14-membered bis-lactones were isolated from the aerobic fermentation of cultures of Cytospora sp. ATCC 20502, these being the structurally isomeric grahamimycin A 4 and grahamimycin A$_1$ 5. It was later realized that the structures of colletoketol and grahamimycin A were identical. These macrolactones can result from a biosynthesis via the macrodiolide colletotriene 6. This class of macrolactone has been a synthetic target of considerable interest due to its promising biological activity and unique structure with an array of functionalities.

Figure 1. Some 14 membered bis-lactones
4.2.2. Review of Literature

Three synthesis of (-)-colletallol 3 is reported in literature\textsuperscript{5} out of which one is racemic synthesis. Synthesis of its 14-epimer is also reported in literature.\textsuperscript{6}

**Radha Krishna et al. (2009)\textsuperscript{5a}**

Radha Krishna and co-workers accomplished the enantioselective synthesis of (-)-colletallol 3 starting from epoxide. Chiral propylene oxide 7 was treated with 2-(2-propynyl)tetrahydro-2\textsuperscript{H}-pyran 8 in the presence of \textit{n}-BuLi to give alcohol 9 which on treatment with PMBBr afforded protected alcohol 10. Compound 10 was treated with cat. amount of PTSA to give compound 11 which on reduction with LiAlH\textsubscript{4} in THF afforded allylic alcohol 12. Swern oxidation of allylic alcohol 12 gave the corresponding aldehyde, which on further oxidation with NaClO\textsubscript{2}, NaH\textsubscript{2}P\textsubscript{2}O\textsubscript{4}, 2-methyl-2-butene afforded the acid fragment 13.

![Scheme 1: Synthesis of acid fragment](image)

Synthesis of alcohol fragment started with hexenol 14 which on Sharpless asymmetric dihydroxylation gave diol 15. Diol 15 was converted to epoxide 16 which on ring opening
reaction with trimethylsulfonium iodide gave allylic alcohol 17 which was protected as its MOM ether 18. TBS deprotection of compound 18 furnished the corresponding alcohol 19.

Scheme 2: Synthesis of alcohol fragment

Esterification of acid 13 and alcohol 19 using DCC gave compound 20. PMB deprotection of compound 20 gave corresponding alcohol which on reaction with acryloyl chloride furnished diester 21. 21 on ring closing metathesis using Grubbs II afforded diolide 22. Finally MOM deprotection resulted into target colletallol 3.
Scheme 3: Completion of synthesis of colletallol

Zwanenburg et al. (1991)\(^5\)

Zwanenburg and co-workers accomplished the enantioselective synthesis of \((-\)-colletallol 3 starting from allylic alcohol. Asymmetric Sharpless epoxidation of allylic alcohol 23 gave epoxy-alcohol 24, which was converted into diazoketone 25. Irradiation of this diazoketone 25 in methanol, followed by silylation gave compound 26. Acetate group of silyl compound 26 was replaced with ether protection and ester was hydrolysed to give acid 27. Carboxylic acid 27 was esterified with phenylsulfonly ethanol and EE protecting group was removed to provide alcohol 28.

\[
\begin{align*}
\text{OAc} & \quad \text{23} & \quad \text{(-)-DET, t-BuOOH} & \quad \text{H} \quad \text{OH} & \quad \text{24} & \quad \text{RuO}_4, \text{CH}_3\text{CN/CCl}_4/\text{H}_2\text{O} \\
& & & & & \text{CICO}-\text{Bu, NEt}_3, \text{CH}_2\text{Cl}_2 \\
\text{OAc} & \quad \text{H} \quad \text{25} & \quad \text{hv, MeOH, TBSCI} & \quad \text{H} \quad \text{Me} \quad \text{26} & \quad \text{(i) NaOMe, MeOH, 0 °C} & \quad \text{ethyln vinyl ether, PPTS} & \quad \text{(ii) LiOH, THF/H}_2\text{O} & \quad 80\% \text{ (over 3 steps)}
\end{align*}
\]

Scheme 4: Synthesis of alcohol fragment

Synthesis of acid fragment started with alcohol 29 which on oxidation and subsequent Wittig-Horner reaction gave ester 30. Ester 30 on saponification gave acid 31.

\[
\begin{align*}
\text{OEE} & \quad \text{29} & \quad \text{(i) (COCl)}_2, \text{DMSO, NEt}_3 & \quad \text{OEE} & \quad \text{NaOH, THF/H}_2\text{O} & \quad \text{OEE} \\
& & & & & \quad \text{COOEt} & \quad 97\% \\
& & \text{(ii) (EtO)}_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et, LiCl, iPr}_2\text{EtN, CH}_3\text{CN}} & \quad 64\% \\
\end{align*}
\]
Scheme 5: Synthesis of acid fragment

The coupling of acid 31 with the alcohol fragment 28 was successfully accomplished using DCC/DMAP as the condensing agent to get half lactone 32. The half lactone 32 was converted into seco-colletallol 33 by successive removal of the EE protecting group and hydrolysis of ester group. Seco-colletallol 33 was subjected to macrolactonization using Yamaguchi condition to get lactone 34 which on TBS deprotection gave colletallol 3.

\[
\begin{align*}
31 & \xrightarrow{\text{DCC, DMAP}} 32 \\
28 & \xrightarrow{\text{CH}_2\text{Cl}_2, 97\%} 31
\end{align*}
\]

Scheme 6: Completion of synthesis of colletallol (Zwanenburg’s method)

Floc’h et al. (1997)

Floc’h and co-workers have synthesized 14-epimer of colletallol starting from hydroxyl butanoate 35. They used double Wittig reaction to construct the lactone ring. The free hydroxyl group of compound 35 was protected to get compound 36 which was reduced to aldehyde 37 using DIBAL-H at -78 °C.

\[
\begin{align*}
35 & \xrightarrow{\text{TBDPSI, Imidazole, THF, rt, 96\%}} 36 \\
36 & \xrightarrow{\text{DIBAL-H, Et}_2\text{O, -78 °C, 87\%}} 37
\end{align*}
\]
Scheme 7: Synthesis of aldehyde fragment

The enantioselective reduction of enone 38 with CBS reagent afforded the allylic alcohol 39 which on hydrogenation condition gave saturated alcohol 40. The free hydroxyl group was subjected to Mitsunobu condition to get p-anisyl ether 41 via inversion of configuration. Ether 41 on TBDPS deprotection gave alcohol 42. The alcohol 42 was esterified using bromoacetyl bromide to give the bromo ester 43 which was converted into the phosphonium salt 44 by addition of triphenylphosphine.

Scheme 8: Synthesis of phosphonium salt fragment

The phosphonium salt 44 was treated with 0.8 equiv of TEA to generate in situ the corresponding phosphorane which was condensed with 1.5 equiv of the aldehyde 37 in CH₃CN to give (E)-enoate 45. The cleavage of the silyl ether of (E)-enoate 45 afforded alcohol 46. Esterification of alcohol 46 with bromoacetyl bromide afforded ester 47 which on deprotection of the aldehyde function in neat formic acid yielded free aldehyde 48. The addition of triphenylphosphine to aldehyde 48 generated the phosphonium salt which undergoes Wittig reaction in the presence of large excess of TEA to give Wittig product 49. Cleavage of the p-anisyl ether of Wittig product 48 with CAN afforded the 14-epimer of colletallol.
Scheme 9: Synthesis of 14-epi-colletallol (Floc’h’s method)

4.2.3. Present work

Objective:

The promising biological activity and the unique structure of the 14-membered unsymmetrical diolides make them attractive synthetic target and so far three syntheses of colletallol (3) including a racemic synthesis have been reported in the literature. However, the natural (6R,11R,14R) colletalol was found to be inactive, its 14-epimer was found to be a useful target for structure activity studies.

In recent years, there has been growing interest in the use of small organic molecules to catalyze reactions in organic synthesis. As a result, the area of organocatalysis has now emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis, thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.
Figure 2. Colletallol and its 14-S-epimer

Proline is among the most successful secondary amine based organocatalysts which has been widely employed in the asymmetric aldol, Mannich, Michael addition, and α-functionalization, viz. α-aminoxylation, α-amination, and α-aminoxylation directed tandem reactions, among many others, providing rapid, catalytic, and atom-economical access to enantiomerically pure products.

In continuation of our interest in organocatalysis and asymmetric synthesis of 1,3-polyol and naturally occurring lactones we considered undertaking the enantioselective total synthesis of (−)-(6R,11R,14S)-colletallol (3-epimer), employing sequential α-aminoxylation/HWE olefination catalyzed by proline.

4.2.4. Results and Discussion:

As per the retrosynthetic scheme as delineated in scheme 10, colletallol could be synthesized from the acid fragment 52 and alcohol fragment 56. Both the acid and alcohol fragment could be accessed independently from chiral propylene oxide, a commercially available starting material.
Scheme 10. Retrosynthetic route to colletallol

Synthesis of acid fragment 52

Synthesis of acid fragment started with (R)-propylene oxide 7, which was converted to TBS protected homoallylic alcohol 50 by literature procedure. The olefin of TBS protected homoallylic alcohol 50 was oxidized to aldehyde in the presence of OsO₄ and NaIO₄ and the aldehyde without purification was subjected to the HWE olefination reaction with triethylphosphonoacetate in dry THF at 0°C to furnish the trans-olefin 51 in 82% (two steps, E/Z 99:1) yield. The IR spectrum of 51 showed the ester carbonyl absorption at 1708 cm⁻¹ and olefin C=C stretching at 1664 cm⁻¹. The ¹H NMR spectrum gave olefin protons at δ 5.84 (doublet of triplet) with the coupling constant J = 1.34, 15.66 Hz and δ 6.88-7.03 (multiplet) indicating trans-olefin. The ester group of trans-olefin 51 was hydrolyzed with LiOH to afford the corresponding acid 52 in 84% yield (scheme 11).
The disappearance of ethyl protons in the range of δ 4.19 as quartet and 1.29 as doublet in \(^1\)H NMR spectrum confirmed the formation of the product.

\[
\text{(R)-7} \quad \text{Vinyl magnesium bromide} \quad \text{THF, -78 °C} \quad \text{OTBS} \quad \text{50}
\]

\[
i) \text{OsO}_4, \text{NaI}O_4, 2,6-\text{Lutidine} \quad \text{Dioxane:H}_2\text{O} (3:1) \quad \text{rt, 30min}
\]

\[
\text{ii) HWE, DBU, THF} \quad 0 \quad \text{°C, 3 h} \quad 82\% \quad \text{51}
\]

\[
\text{OTBS} \quad \text{COOEt} \quad \text{LiOH, THF/MeOH (2:1)} \quad \text{OTBS} \quad \text{52}
\]

\[
\text{rt, 1 h} \quad 84\%
\]

**Scheme 11: Synthesis of acid fragment**

**Synthesis of alcohol fragment 56**

Synthesis of alcohol fragment started with (S)-propylene oxide 7. The ring opening of (S)-propylene oxide 7 with 3-butenyl magnesium bromide using Cul as a catalyst gave the corresponding alkenol which on protection of free hydroxyl group as TBS ether gave olefin 53\(^{13}\) in 81% yield. The olefin 53 was oxidized to aldehyde in the presence of OsO\(_4\) and NaI0\(_4\) and the aldehyde was subjected to \(\alpha\)-aminoxylation\(^{14}\) reaction using L-proline as a catalyst followed by HWE-olefination to yield compound 54 in 73% (two steps) yield and good diastereomeric excess (dr ratio 98:2).\(^{15}\) The IR spectrum of 54 showed the ester carbonyl absorption at 1712 cm\(^{-1}\). The \(^1\)H NMR spectrum gave olefin protons at δ 6.94 (doublet of doublet) with the coupling constant \(J = 4.7, 15.7\) Hz, and δ 6.06 (doublet of doublet) with the coupling constant \(J = 1.8, 15.7\) Hz indicating \textit{trans}-olefin. Protection of the free hydroxyl group as its TBDPS ether gave 55 in 95% yield. Disappearance of peak at 3432 cm\(^{-1}\) in IR spectrum confirmed the formation of 55. The TBS group was deprotected using PPTS in ethanol for 8 h to give alcohol 56 in 90% yield. Prolonging the reaction resulted in some deprotection of TBDPS group also. The IR spectra of 56 showed presence of hydroxyl absorption at 3378 cm\(^{-1}\).
Scheme 12: Synthesis of alcohol fragment

Completion of synthesis of colletallol

Having obtained both the fragments alcohol 56 and acid 52 in substantial amount we required to couple them and achieve the synthesis of target molecule by synthetic manipulations. Thus, both the fragments were subjected to esterification under different conditions. Our first few attempts using Steglich condition, Shiina condition and Mitsunobu procedures were unsuccessful. We then proceeded with Yamaguchi protocol where after a few optimizations, we could observe the formation of 57 within 40 minutes (87% yield) when the reaction was performed at 0°C (scheme 13). The TBS ether of 57 was cleaved by PPTS in EtOH to afford alcohol 58 in 86% yield. The IR spectra of 58 showed presence of hydroxyl absorption at 3370 cm\(^{-1}\). Hydrolysis of ethyl ester 58 to seco acid 59 using LiOH\(^{16}\) failed despite several attempts with different solvent combinations, temperature and equivalents, instead we ended up hydrolyzing the ester and acid fragment. Using DBU in benzene\(^{15}\) also gave only a complex reaction mixture. Since basic conditions were not found suitable to our substrate, therefore we considered changing the conditions to neutral medium. Finally the desired seco-acid 59 was obtained in 90% yield using bis(tributyltin) oxide\(^{17}\) in toluene under reflux conditions (Table 1). The disappearance of ethyl protons in the range of δ 4.18 as quartet in \(^1\)H NMR spectrum confirmed the formation of the product.
NR* Hydrolysis of internal ester to give alcohol and acid fragments

**Table 1: Optimisation for hydrolysis of 58**

Macrolactonization of seco-acid 59 was achieved using Yamaguchi coupling condition to give corresponding macrocycle lactone 60. From our previous experiences we thought that prolonged reaction times using PPTS would cleave TBDPS but attempts under varied temperature and reaction conditions were unsuccessful. We then chose ammonium fluoride in methanol under reflux conditions to cleave TBDPS which afforded the target molecule epi-3 in 75% yield (scheme 13).
4.2.5. Conclusion

In conclusion, a new and efficient total synthesis of (-)-colletallol (epi-3) with high diastereoselectivity has been achieved using proline catalyzed α-aminoxylation and Yamaguchi macrolactonization reactions. The synthetic strategy described here has significant potential as we have achieved overall yield of 22% in 11 linear steps. The method is amenable for further extension to the synthesis of all the isomers of (-)-colletallol and other 14-membered unsymmetrical bis-macrolactones.
4.2.6. Experimental Section

(R)-tert-Butyldimethyl-(pent-4-en-2-yl-oxy)-silane (50):

A round bottomed flask was charged with copper (I) iodide (0.76 g, 4 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (5 mL) was added. This suspension was cooled to -20 °C and vigorously stirred, and vinylmagnesium bromide (1M in THF. 60 mL, 60 mmol) was injected to it. A solution of (R)-propylene oxide 7 (2.3 g, 4 mmol) in THF (3 mL) was added slowly to the above reagent, and the mixture was stirred at -20 °C for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated to afford the crude alcohol product.

To a stirred solution of crude alcohol in CH₂Cl₂ (10 mL), imidazole (0.425 g, 6 mmol) was added. To this solution t-butylchlorodimethyl silane (0.9 g, 6 mmol) was added at 0 °C and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂ (3 x 50 mL). The extract was washed with brine, dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (49:1) as eluent provided (R)-tert-Butyldimethyl-(pent-4-en-2-yl-oxy)-silane 50 as a colorless liquid.

Yield: 6.08 g, 76%

[α]D²⁵: -11.87 (c 1.00 CHCl₃) {lit.¹² [α]D²⁸ -14.46 (c = 1.8, CHCl₃)}

Mol. Formula: C₁₁H₂₄O₅Si

IR (CHCl₃, cm⁻¹): νmax 3088, 2929, 2896, 1642, 1255, 1129

¹H NMR (200 MHz, CDCl₃): δ 0.06 (s, 6H), 0.91 (s, 9H), 1.14 (d, J = 6.06 Hz, 3H), 2.19 (dq, J = 1.01, 5.81, 11.88 Hz, 1H), 3.21-3.37 (m, 1H), 3.92-4.04 (m, 1H), 5.00-5.10 (m, 2H), 5.82 (d, J = 8.1 Hz, 1H) ppm.

¹³C NMR (50 MHz, CDCl₃): δ -4.7, -4.5, 18.1, 23.4, 25.9, 44.3, 68.6, 116.5, 135.6 ppm.

Enantiomeric ratio was determined by HPLC analysis: 98% ee
HPLC: Chiralcel OJ-RH (150 X 4.6mm) (MeOH: H₂O = 90:10, flow rate 0.7 ml/min, λ = 254 nm). Retention time (min): 6.31 (major) and 7.48 (minor). The racemic standard was prepared in the same way using racemic propylene oxide, ee 98%.

(R,E)-Ethyl 5-(tert-butyldimethylsilyloxy)hex-2-enoate (51):

To a solution of compound 50 (2 g, 7.34 mmol) in dioxane-water (3:1, 20 mL) were added 2.6-lutidine (1.70 mL, 14.69 mmol), OsO₄ (0.1M solution in toluene, 0.4 mL, 0.20 mmol) and NaIO₄ (6.28 g, 29.39 mmol). The reaction was stirred at 25 °C for 30 min. After the reaction was complete, the reaction mixture was passed through a pad of celite. Water (5 mL) and CH₂Cl₂ (10 mL) were added. The organic layer was separated, and the water layer extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was washed with brine and dried (Na₂SO₄) to give crude aldehyde which was used as such for the next step without further purification.

To the solution of triethylphosphonoacetate (2.2 mL, 11.01 mmol) and DBU (1.7 mL, 11.01 mmol) in THF, crude aldehyde dissolved in THF was added and the whole mixture was stirred at 0 °C for 3h. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude product. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (94:06) as eluent to afford the (R,E)-ethyl 5-(tert-butyldimethylsilyloxy)hex-2-enoate 51 as a pale yellow liquid.

Yield: 2.24 g, 82%

Mol. Formula: C₁₄H₂₈O₃Si

[α]D²⁵: -9.2 (c 1, CHCl₃) (lit. ⁹α [α]D²⁵: -9.5 (c 1.00, CHCl₃)).

¹H NMR (200 MHz, CDCl₃): δ 6.88-7.03 (m, 1H), 5.84 (dt, J = 1.34, 15.66 Hz, 1H). 4.19 (q, J = 7.20 Hz, 2H), 3.85-4.0 (m, 1H), 2.32 (tt, J = 1.13, 7.20 Hz, 2H), 1.29 (t, J = 7.07 Hz, 3H), 1.17 (d, J = 6.06 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H) ppm.
**Chapter 4: Section B**

\[^{13}\text{C} \text{ NMR (50 MHz, CDCl}_3\text{):} \delta 166.4, 146.0, 123.1, 67.6, 60.1, 42.4, 25.7, 23.7, 18.0, 14.2, -4.9, -4.6 \text{ ppm.} \]

**MS (ESI):** \( m/z \) 295.20

\((R,E)-5-((\text{tert-Butyldimethylsilyl})\text{oxy})\text{hex-2-enoic acid (52):}\)

\[
\begin{align*}
\text{OTBS} & \quad \text{COOH}
\end{align*}
\]

**Procedure for ester hydrolysis:**

To the ester 51 (1.4 g, 5.14 mmol) dissolved in THF (10 mL) and MeOH (5 mL) was added LiOH.H2O (266 mg, 6.49 mmol) and stirred at 0 °C to room temperature for 1 h. The reaction mixture was further diluted with H2O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified with 1 M HCl (pH 3) and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na2SO4, filtered, evaporated and the crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (80:20) as eluent to afford \((R,E)-5-((\text{tert-butyldimethylsilyl})\text{oxy})\text{hex-2-enoic acid 52 as a pale yellow liquid.} \)

**Yield:** 1.05 g, 84%.

**Mol. Formula:** \( \text{C}_{12}\text{H}_{24}\text{O}_3\text{Si} \)

\([\text{\alpha}]_D^{25}: -7.0 \text{ (c 1, CHCl}_3\text{)} \text{)} \}

\([\text{\alpha}]_D^{25}: -7.6 \text{ (c 0.81, CHCl}_3\text{)} \text{)} \}

**IR (CHCl3, cm\(^{-1}\)):** \( \nu_{\text{max}} 2972, 1717, 1680, 1475, 1449 \)

**\(^1\text{H NMR (200 MHz, CDCl}_3\text{):}** \( \delta 7.20-6.96 \text{ (m, 1H)}, 5.85 \text{ (d, } J = 15.7 \text{ Hz, 1H)}, 3.95 \text{ (q, } J = 6.0 \text{ Hz, 1H)}, 2.36 \text{ (t, } J = 6.9 \text{ Hz, 2H)}, 1.18 \text{ (d, } J = 6.0 \text{ Hz, 3H)}, 0.89 \text{ (s, 9H)}, 0.05 \text{ (s, 6H)} \text{ ppm.} \)

**\(^{13}\text{C NMR (101 MHz, CDCl}_3\text{):}** \( \delta 171.8, 149.0, 122.6, 67.5, 42.5, 25.8, 23.8, 18.0, -4.6, -4.9 \text{ ppm.} \)

**MS (ESI):** \( m/z \) 267.12. **HRMS (ESI) \( m/z \):** \([\text{M + Na}]^+ \text{ Calcd for C}_{12}\text{H}_{24}\text{O}_3\text{SiNa} 267.1387; \text{ Found 267.1385} \)

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(S)-tert-butyl(hept-6-en-2-yloxy)dimethylsilane (53):

A round bottomed flask was charged with copper (I) iodide (2.63 g, 13.78 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to -78 °C and vigorously stirred. and 3-butenylmagnesium bromide (0.5 M in THF, 42 mL, 20.67 mmol) was injected to it. A solution of (S)-propylene oxide 7 (8 g, 13.78 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at -78 °C overnight. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated to afford the crude alcohol.

To a solution of crude alcohol in DMF (15 ml), imidazole (1.41 g, 20.67 mmol) was added. To this solution tert-butylchlorodimethyl silane (3.12 g, 31.92 mmol) was added at 0 °C and reaction was stirred at room temperature for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂ (3 x 50 mL). The extract was washed with brine, dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (49:1) as eluent provided (R)-tert-butyl(hept-6-en-2-yloxy)dimethylsilane 53 as a colorless liquid.

Yield: 8.37 g, 81%.

Mol. Formula: C₁₃H₂₈O₄Si

[α]D²⁵: -9.2 (c 1, CHCl₃) {lit.¹³ [α]D²⁵ -9.5 (c 1.00, CHCl₃)}

IR (CHCl₃, cm⁻¹): νmax 3090, 2925, 1640, 1261, 1120

¹H NMR (200 MHz, CDCl₃): δ 5.94 - 5.68 (m, 1 H), 5.09 - 4.89 (m, 2 H), 3.89 - 3.71 (m, 1 H), 2.13 - 1.98 (m, 2 H), 1.55 - 1.35 (m, 4 H), 1.13 (d, J = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H) ppm.

¹³C NMR (50 MHz, CDCl₃): δ 139.0, 114.3, 68.5, 39.2, 33.8, 25.9, 25.1, 23.8, 18.1, -4.4, -4.7

MS (ESI): m/z 251.18

Enantiomeric ratio was determined by HPLC analysis; 98% ee
HPLC: Chiralcel OJ-RH (150 X 4.6mm) (MeOH: H₂O = 90:10, flow rate 0.7 ml/min, λ = 230 nm). Retention time (min): 8.15 (major) and 8.79 (minor). The racemic standard was prepared in the same way using racemic propylene oxide, ee 98%.

Ethyl (4R,7R,E)-7-((tert-butyldimethylsilyl)oxy)-4-hydroxyoct-2-enoate (54):

To a solution of compound 53 (2 g, 8.76 mmol) in dioxane-water (3:1, 16 mL) were added 2.6-lutidine (2.0 mL, 17.53 mmol), OsO₄ (0.1 M solution in toluene, 0.4 mL, 0.20 mmol) and NaIO₄ (7.53 g, 35.06 mmol). The reaction mixture was stirred at 25 °C for 15 min. After the reaction was complete, water (5 mL) and CH₂Cl₂ (10 mL) were added. The organic layer was separated, and the water layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was washed with brine and dried (Na₂SO₄) to give crude aldehyde which was used as such for the next step without further purification.

To a solution of above aldehyde and nitroso benzene (0.9 g, 8.76 mmol) in anhydrous DMSO (16 mL) was added L-proline (0.42 g, 3.5 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (3.50 mL, 17.52 mmol), DBU (2.40 mL, 17.52 mmol) and LiCl (0.75 g, 17.52 mmol) in CH₃CN (16 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature for 45 min and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et₂O (5 x 100 mL). The combined organic layers were washed with water, brine, dried (Na₂SO₄) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using petroleum ether: EtOAc (80:20) as eluent to give ethyl-(4R,7R,E)-7-((tert-butyldimethylsilyl)oxy)-4-hydroxyoct-2-enoate 54 as a colorless liquid.

Yield: 2.02 g, 73%.

Mol. Formula: C₁₆H₃₂O₄Si

[α]₁₆₀°: -26.7 (c 1, CHCl₃).
**IR** (CHCl₃, cm⁻¹): ν max 3056, 3019, 2962, 2916, 1712, 1661, 1472, 1463

**¹H NMR (200 MHz, CDCl₃):** δ 6.94 (dd, J = 4.7, 15.7 Hz, 1H), 6.06 (dd, J = 1.8, 15.7 Hz, 1H), 4.33-4.25 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.00-3.82 (m, 1H), 1.81-1.49 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H) ppm.

**¹³C NMR (101 MHz, CDCl₃):** δ 166.7, 150.4, 119.9, 70.9, 68.3, 60.2, 35.2, 32.2, 25.7, 23.0, 18.0, 14.1, -4.6, -4.9 ppm.

**MS (ESI):** m/z 339.18. **HRMS (ESI) m/z:** [M + Na]⁺ Calcd for C₁₆H₂₀O₄SiNa 339.1962; Found 339.1960

**HPLC:** Kromasil RP-18 (150 X 4.6mm) (MeOH : H₂O = 75:25), flow rate 1.0 ml/min. (λ = 254 nm). Retention time (min): 5.85 (major) and 7.81 (minor). (dr 98:2)

**Ethyl (4R,7R,E)-7-((tert-butyldimethylsilyl)oxy)-4-((tert-butyldiphenylsilyl)oxy)oct-2-enoate (55):**

![Chemical structure](OTBS COOEt OTBDPS)

**General procedure for TBDPS protection:** To a stirred solution of alcohol 54 (1.5 g, 4.74 mmol) in dry DMF (10 mL) and imidazole (484 mg, 7.12 mmol) at 0 °C was added TBDPSCl (1.96 g, 1.85 mL, 7.12 mmol) dropwise and DMAP (cat.) and the reaction mixture was warmed to rt for 6 h. The reaction mixture was quenched with H₂O (20 mL) and extracted with CH₂Cl₂ (3 x 40 mL). The combined organic layer was washed with brine (2 x 40 mL) and dried over anhydrous Na₂SO₄. The solvent was concentrated under reduced pressure to give crude product. The crude product was then purified by flash column chromatography using pet ether: EtOAc (98:2) as eluent to give ethyl-(4R,7R,E)-7-((tert-butyldimethylsilyl)oxy)-4-((tert-butyldiphenylsilyl)oxy)oct-2-enoate 55 as a colorless liquid.

**Yield:** 2.50 g, 95%.

**Mol. Formula:** C₃₂H₅₀O₄Si₂

[α]₀²⁵: +16.18 (c 1.2, CHCl₃)

**IR** (CHCl₃, cm⁻¹): ν max 3019, 2962, 2916, 1712, 1661, 1472, 1463
**Chapter 4: Section B**

**H NMR (200 MHz, CDCl₃):** \( \delta 7.72-7.61 \) (m, 4H), 7.45-7.35 (m, 6H), 6.88 (dd, \( J = 5.2, 15.6 \) Hz, 1H), 5.92 (dd, \( J = 1.4, 15.5 \) Hz, 1H), 4.37 (q, \( J = 5.0 \) Hz, 1H), 4.20 (q, \( J = 7.1 \) Hz, 2H), 3.84-3.59 (m, 1H), 1.34-1.27 (m, 6H), 1.14-1.06 (m, 13H), 0.89 (s, 9H), 0.04 (d, \( J = 3.5 \) Hz, 6H) ppm.

**C NMR (50 MHz, CDCl₃):** \( \delta 166.6, 150.1, 135.8, 133.9, 133.5, 129.7, 127.6, 120.2, 72.4, 68.4, 60.2, 39.5, 36.8, 27.0, 25.9, 23.8, 19.3, 18.1, 14.2, -4.4, -4.7 \) ppm.

**MS (ESI):** \( m/z 577.30 \).

**HRMS (ESI) m/z:** [M + Na]+ Calcd for C₃₂H₆₀O₄Si₂Na 577.3140; Found 577.3137

Ethyl (4R,7R,E)-4-((tert-butylidiphenylsilyl)oxy)-7-hydroxyoct-2-enoate (56):

![Structural formula]

**General procedure for TBDMS deprotection:** To a stirred solution of \( \alpha, \beta \)-unsaturated ester 55 (2.4 g, 4.3 mmol) in ethanol at 0 °C, PPTS (161 mg, 0.65 mmol) was added in portions, and the reaction mixture was warmed to rt, stirred for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na₂SO₄) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (80:20) as eluent to give ethyl (4R,7R,E)-4-((tert-butylidiphenylsilyl)oxy)-7-hydroxyoct-2-enoate 56 as a colorless liquid

**Yield:** 1.30 g, 95%

**Mol. Formula:** C₂₆H₃₆O₄Si

[\( \alpha \)]ᵢ̂₀²₅ : +12.42 (c 0.85, CHCl₃).

**IR (CHCl₃, cm⁻¹):** \( \upsilon \text{max} \) 3371, 2975, 2932, 1713, 1638, 1583, 1422, 1375, 1227, 1129

**H NMR (200 MHz, CDCl₃):** \( \delta 7.72-7.61 \) (m, 4H), 7.45-7.35 (m, 6H), 6.88 (dd, \( J = 5.2, 15.6 \) Hz, 1H), 5.92 (dd, \( J = 1.4, 15.5 \) Hz, 1H), 4.37 (q, \( J = 5.0 \) Hz, 1H), 4.20 (q, \( J = 7.1 \) Hz, 2H), 3.84-3.59 (m, 1H), 1.31 (t, \( J = 7.1 \) Hz, 6H), 1.14-1.06 (m, 13H), 0.89 (s, 9H), 0.04 (d, \( J = 3.5 \) Hz, 6H) ppm.

**C NMR (50 MHz, CDCl₃):** \( \delta 166.6, 150.1, 135.8, 133.9, 133.4, 129.7, 127.6, 120.2, 72.3, 67.9, 60.3, 39.0, 36.7, 27.0, 23.4, 19.3, 14.2 \) ppm.
MS (ESI): m/z 463.21.

HRMS (ESI) m/z: [M + Na]+ Calcd for C_{26}H_{36}O_{4}SiNa 463.2275; Found 463.2271.

**Ethyl (4R,7R,E)-7-(((R,E)-5-((E)/7-butyldimethylsilyl)oxy)hex-2-enoyl)oxy)-4-((tert-butyldiphenylsilyl)oxy)oct-2-enoate (57):**

![Chemical Structure Image]

To a solution of acid 52 (200 mg, 0.82 mmol) in toluene (4mL), was added triethyl amine (0.37 mL, 1.64 mmol) and 2,4,6-trichlorobenzoyl chloride (0.45 mL, 0.98 mmol) under nitrogen atmosphere at 0 °C and the resulting mixture was stirred at room temperature for 30 min. To this, alcohol 56 (240 mg, 0.55 mmol) in toluene (10 mL) and 4-dimethylaminopyridine (DMAP) (1.0 g, 8.2 mmol) were added successively at 0 °C. Stirring was continued for additional 10 min. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were thoroughly washed with saturated sodium bicarbonate solution, brine, dried (Na_{2}SO_{4}). and concentrated to afford the crude product which was purified by silica gel column chromatography using pet ether: EtOAc (90:10) as eluent to give ethyl (4R,7R,E)-7-(((R,E)-5-((E)/7-butyldimethylsilyl)oxy)hex-2-enoyl)oxy)-4-((tert-butyldiphenylsilyl)oxy)oct-2-enoate 57 as a colorless syrupy liquid.

**Yield:** 316 mg, 87%.

**Mol. Formula:** C_{38}H_{58}O_{6}Si_{2}

[α]_{D}^{25} = -16.82 (c 0.55, CHCl_{3})

**IR (CHCl_{3}, cm^{-1}):** ν_{max} 2935, 1716, 1680, 1475, 1320, 1216, 1144, 1110

**^{1}H NMR (400 MHz, CDCl_{3}):** δ 7.73-7.61 (m, 4H), 7.43-7.36 (m, 6H), 6.97-6.81 (m, 2H), 5.89 (d, J = 15.7 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.91-4.77 (m, 1H), 4.35 (d, J = 5.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.97-3.85 (m, 1H), 2.38-2.24 (m, 2 H), 1.32-1.26 (m, 4H), 1.18-1.16 (m, 6H), 1.08 (s, 12H), 0.88 (s, 9H), 0.05 (d, J = 4.6 Hz, 6H) ppm.
**Chapter 4: Section B**

**13C NMR (101 MHz, CDCl3):** δ 166.6, 166.0, 150.0, 145.8, 135.8, 134.8, 133.9, 133.4, 129.8, 127.6, 123.6, 120.2, 72.3, 70.6, 67.6, 60.3, 42.4, 36.6, 35.8, 27.0, 25.8, 23.9, 20.0, 19.3, 14.2, -4.5, -4.8 ppm.

**MS (ESI):** \( m/z \) 689.34

**HRMS (ESI) \( m/z \):** [M + Na]+ Calcd for C38H58O6SiNa 689.3269; Found 689.3263

**Ethyl \((4R,7R,E)-4-((\text{tert-butyl}diphenyl)silyl)oxy)-7-(((R,E)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoate (58):**

![Chemical Structure](image)

To a stirred solution of TBS protected \( \alpha,\beta \)-unsaturated ester 57 (260 mg, 0.39 mmol) in ethanol at 0 °C, PPTS (108 mg, 0.43 mmol) was added in portions, and the reaction mixture was warmed to rt. stirred for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (70:30) as eluent to give ethyl \((4R,7R,E)-4-((\text{tert-butyl}diphenyl)silyl)oxy)-7-(((R,E)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoate 58\) as a colorless thick syrupy liquid.

**Yield:** 185 mg, 86%.

**Mol. Formula:** C32H44O6Si

[a]_D^{25} = -14.87 (c 0.6, CHCl₃)

**IR (CHCl₃, cm⁻¹):** \( \nu_{\text{max}} \) 3410, 2935, 1727, 1690, 1466, 1322, 1216

**1H NMR (400 MHz, CDCl₃):** δ 7.69-7.58 (m, 4H), 7.46-7.31 (m, 6H), 6.98-6.80 (m, 2H), 5.91 (d, \( J = 5.9 \text{ Hz} \), 1H), 5.87 (d, \( J = 6.1 \text{ Hz} \), 1H), 4.91-4.80 (m, 1H), 4.39-4.31 (m, 1H), 4.18 (q, \( J = 6.9 \text{ Hz} \), 2H), 4.03-3.92 (m, 1H), 2.41-2.31 (m, 2H), 1.31-1.24 (m, 9H), 1.19 (d, \( J = 6.1 \text{ Hz} \), 4H), 1.09 (s, 9H) ppm.

**13C NMR (101 MHz, CDCl₃):** δ 166.6, 165.9, 150.0, 144.5, 135.8, 134.0, 133.4, 129.7, 127.6, 124.4, 120.3, 72.3, 70.9, 66.7, 60.3, 41.8, 36.6, 35.8, 27.0, 25.3, 23.9, 23.3, 20.0, 19.3, 14.2 ppm.
To a stirred solution of α,β-unsaturated ester 58 (170 mg, 0.31 mmol) in dry toluene at rt. bis(tributyltin) oxide (0.8 ml. 1.50 mmol) was added drop wise. The reaction mixture was refluxed at 110 °C for 24 h. After completion of reaction, the reaction mixture was cooled to rt evaporated and dissolved in ethyl acetate. The mixture was acidified with 1 M HCl (pH 5) and was extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine (2 x 5 mL) and dried over anhydrous Na₂SO₄. filtered, evaporated and the crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (50:50) as eluent to afford (4R,7R,E)-4-((tert-butylidiphenylsilyl)oxy)-7-(((R,E)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoic acid 59 as a colorless thick syrupy liquid.

Yield: 145 mg, 90%.

Mol. Formula: C₃₀H₄₀O₆Si

[α]D²⁵:-19.79 (c 1.25, CHCl₃)

IR (CHCl₃, cm⁻¹): νmax 3468, 2971, 2832, 1727, 1654, 1589, 1462, 1370, 1108

¹H NMR (200 MHz, CDCl₃): δ 7.75-7.55 (m, 4H), 7.51-7.32 (m, 6H), 7.13-6.67 (m, 2H), 6.22-5.69 (m, 2H), 5.00-4.69 (m, 1H), 4.53-4.32 (m, 1H), 4.09-3.92 (m, 1H), 2.40-2.34 (m, 1H), 1.78 (brs., 2H), 1.67-1.35 (m, 6H), 1.34-1.14 (m, 6H), 1.09 (s, 9H) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 171.0, 165.8, 152.3, 144.7, 135.8, 133.6, 133.1, 129.9, 127.7, 124.2, 119.7, 71.8, 70.6, 66.8, 41.8, 33.4, 32.0, 30.0, 27.0, 23.2, 19.8, 19.3 ppm.

MS (ESI): m/z 547.21

HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₃₀H₄₀O₆SiNa 547.2486; Found 547.2489
(3E,6R,9E,11R,14S)-11-((tert-butyldiphenylsilyl)oxy)-6,14-dimethyl-1,7dioxacyclotetradeca-3,9-diene-2,8-dione (60):

To a solution of secco-acid 59 (0.086 g, 0.16 mmol) in THF (2 mL) were added Et₃N (0.726 mL, 0.32 mmol) and 2,4,6-trichlorobenzoyl chloride (0.56 mL, 0.17 mmol) and the reaction mixture was stirred for 6h at room temperature under argon atmosphere and then diluted using dry toluene (20 mL), and added dropwise to a refluxing solution of 4-dimethyl aminopyridine (DMAP) in toluene (100 mL) for over a period of 13h using syringe pump (1.7 mL/h). The reaction mixture was stirred for an additional 8h. After completion of reaction as indicated by TLC, the resulting reaction mixture was cooled, evaporated, dissolved in EtOAc (15 mL), the reaction mixture was washed with saturated aq. NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated in vacuo to give crude macrocyclic lactone. Crude macrocyclic lactone was purified by silica gel column chromatography using petroleum ether/EtOAc (90:10) as eluent to afford (3E,6R,9E,11R,14S)-11-((tert-butyldiphenylsilyl)oxy)-6,14-dimethyl-1,7dioxacyclotetradeca-3,9-diene-2,8-dione 60 as a colorless thick syrupy liquid.

Yield: 68 mg, 82%.

Mol. Formula: C₃₀H₄₀O₆Si

[α]D²⁵: -29.27 (c 0.1, CHCl₃)

IR (CHCl₃, cm⁻¹): νmax 2965, 2811, 1745, 1644, 1575, 1450, 1110

¹H NMR (200 MHz, CDCl₃): δ 7.65 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.44-7.34 (m, 6H), 6.81-6.69 (m, 2H), 5.74 (d, J = 15.6 Hz, 2H), 5.24-5.17 (m, 1H), 5.13 (dt, J = 2.7, 6.5 Hz, 1H), 4.28 (t, J = 6.8 Hz, 1H), 2.82 (td, J = 6.8, 13.7 Hz, 1H), 2.33-2.27 (m, 1H), 1.80-1.73 (m, 1H), 1.67-1.61 (m, 1H), 1.55-1.48 (m, 1H), 1.42 (d, J = 6.5 Hz, 3H), 1.35 (dd, J = 6.5, 13.4 Hz, 1H), 1.12 (d, J = 6.5 Hz, 3H), 1.05 (s, 9H) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 166.7, 166.0, 150.0, 142.9, 135.7, 133.8, 133.3, 129.8, 127.6, 125.7, 120.9, 72.0, 70.0, 69.2, 37.3, 30.9, 27.8, 26.9, 20.0, 19.2, 18.7 ppm

MS (ESI): m/z 529.20
HRMS (ESI) m/z: [M + Na]+ Calcd for C_{30}H_{38}O_5NaSi 529.2381; Found 529.2380

(−)-(6R,11R,14S)-colletallol (epi-3):

To a refluxing solution of macrocyclic lactone 60 (12.5 mg, 0.025 mmol) in methanol, ammonium fluoride (13.7 mg, 0.37) was added, and the reaction mixture stirred for 3 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (70:30) as eluent to give (−)-(6R, 11R, 14S)-colletallol (epi-3) as a solid.

Yield: 4.8 mg, 75%.

Mol. Formula: C$_{14}$H$_{20}$O$_5$

[$\alpha$]$_D^{25}$: -107.5 (c 0.4, CH$_2$Cl$_2$) {lit. [$\alpha$]$_D^{25}$ -99.0 (c 0.02, CH$_2$Cl$_2$)}.

IR (CHCl$_3$, cm$^{-1}$): $\nu_{max}$ 3410, 2940, 1716, 1630, 1347, 1282, 1075

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.81-6.66 (m, 2 H), 5.93 (d, $J = 15.6$ Hz, 1 H), 5.77 (d, $J = 15.6$ Hz, 1 H), 5.24 (d, $J = 5.7$ Hz, 1 H), 5.11 (m, 1 H), 4.27 (m, 1 H), 2.84-2.75 (m, 1 H), 2.33 (dd, $J = 6.3$, 13.2 Hz, 1 H), 1.95 (m, 1 H), 1.89-1.79 (m, 1 H), 1.74-1.60 (m, 2 H), 1.41 (d, $J = 5.7$ Hz, 3 H), 1.21 (d, $J = 5.3$ Hz, 3 H) ppm.

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.5, 165.8, 149.5, 143.0, 125.5, 122.0, 71.2, 70.5, 69.5, 37.6, 31.5, 28.5, 20.2, 19.5 ppm.

MS (ESI): m/z 291.12

HRMS (ESI) m/z: [M + H]+ Calcd for C$_{14}$H$_{21}$O$_5$ 269.1384; Found 269.1373

4.2.7. Spectra
Chapter 4: Section B

Ethyl \((R,E)\)-5-((tert-butyldimethylsilyl)oxy)hex-2-enoate (51):

> $^1$H NMR (CDCl$_3$, 200 MHz)

> $^{13}$C NMR (CDCl$_3$, 50 MHz)
(R,E)-5-((tert-butyldimethylsilyl)oxy)hex-2-enoic acid (52):

\[ \text{OTBS} \]

\[ \text{COOH} \]

**\( ^1\)H NMR (CDCl\textsubscript{3}, 200 MHz)**

**\( ^{13}\)C NMR (CDCl\textsubscript{3}, 101 MHz)**
(S)-tert-butyl(hept-6-en-2-yloxy)dimethyilsilane (53):

\[ \text{OTBS} \]

\[ \text{H NMR (CDCl}_3, 200 \text{ MHz)} \]

\[ \text{C NMR (CDCl}_3, 50 \text{ MHz)} \]
Ethyl (4R,7R,E)-7-((tert-butyldimethylsilyl)oxy)-4-hydroxyoct-2-enoate (54):

![Chemical Structure and NMR Spectra]

- **1H NMR** (CDCl₃, 200 MHz)

- **13C NMR** (CDCl₃, 101 MHz)
Ethyl (4R,7R,E)-7-((tert-butyldimethylsilyl)oxy)-4-((tert-butyldiphenylsilyl)oxy)oct-2-enoate (55):

[Diagram of chemical structure]

- **1H NMR (CDCl₃, 200 MHz)**

[Diagram of 1H NMR spectrum]

- **13C NMR (CDCl₃, 50 MHz)**

[Diagram of 13C NMR spectrum]
Ethyl (4R,7R,E)-4-((tert-butyldiphenylsilyl)oxy)-7-hydroxyoct-2-enoate (56):

\[
\text{H NMR (CDCl}_3, 200 \text{ MHz)}
\]

\[
\text{C NMR (CDCl}_3, 50 \text{ MHz)}
\]

![Chemical Structures]

{\H NMR (CDCl\textsubscript{3}, 400 MHz)

{\C NMR (CDCl\textsubscript{3}, 101 MHz)

227 | P a g e

> $^1$H NMR (CDCl$_3$, 400 MHz)

> $^{13}$C NMR (CDCl$_3$, 101 MHz)
Chapter 4: Section B

(3E,6R,9E,11R,14R)-11-((tert-butyldiphenylsilyl)oxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (60):

\[ \text{H NMR (CDCl}_3, 200 \text{ MHz)} \]

\[ \text{\^{13}C NMR (CDCl}_3, 101 \text{ MHz)} \]
(3E,6R,9E,11R,14R)-11-hydroxy-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (epi-3):

\[ \text{Chemical Shift (ppm)} \]

\[ \text{^1H NMR (CDCl}_3, 500 \text{ MHz)} \]

\[ \text{^13C NMR (CDCl}_3, 125 \text{ MHz)} \]
D-7000 HPLC System Manager Report

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Application: HPLC
Sample Name: 14diol -p
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(75:25:)

Reported: 03/20/17 02:02 PM
Processed: 03/20/17 02:01 PM
Series: 8823
Volume: 10.0 ul

Chrom Type: HPLC Channel: 1

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2 7.51 1540 19763 1.318

116655 1507886 100.000

Peak rejection level: 0

Group Leader: Dr. Tripathi P.K.
COLUMN: Kromasil Re-M(150 X 4.6mm)
MOBILE PHASE: MEOH:H2O(75:25)
WAVELENGTH: 254nm
FLOW RATE: 1.0ml/min (1680 psi)
SAMPLE CONC: 1mg/ml Injection vol: 20ul
D-7000 HPLC System Manager Report

Analyzed: 02/25/16 11:19 AM
Reported: 05/20/16 11:58 AM
Processed: 05/20/16 11:57 AM

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Processing Method: SANTOSH
System(acquisition): Sys 1
Application: HPLC
Sample Name: l4diol
Injection from this vial: 1 of 1
Sample Description: ME0H:H20(70:30:)

Chrom Type: HPLC Channel: 1

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Peak rejection level: 0

Group Leader :-Dr.Tripathi P.K.
COLUMN : Kromasil RP-8 (150 X 4.6mm)
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WAVELENGTH : 254nm
FLOW RATE : 1.0 ml/min (1680 psi)
SAMPLE CONC : 1 mg/ml Injection vol: 20ul
D-7000 HPLC System Manager Report

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Application: HPLC
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Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(90:10)

Chrom Type: HPLC Channel: 1

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Peak rejection level: 0

Group Leader: Dr. Tripathi P.K.
COLUMN: Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE: MEOH:H2O(90:10)
WAVELENGTH: 254nm
FLOW RATE: 0.7 ml/min (740 psi)
SAMPLE CONC: 1 mg/ml Injection vol: 2ul
Chrom Type: HPLC Channel: 1

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Peak rejection level: 0

Group Leader: Dr. Tripathi P.K.
COLUMN: Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE: MEOH:H2O(90:10)
WAVELENGTH: 254nm
FLOW RATE: 0.7 ml/min (740 psi)
SAMPLE CONC: 1 mg/ml Injection vol: 2 ul
D-7000 HPLC System Manager Report

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Reported: 05/27/16 02:07 PM
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System(acquisition): Sys 1
Application: HPLC
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Injection from this vial: 1 of 1
Sample Description: ACN:H2O (90:10)

Chrom Type: HPLC Channel: 1

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<td>7855972</td>
<td>50.329</td>
</tr>
<tr>
<td></td>
<td></td>
<td>948371</td>
<td>15609316</td>
<td>100.000</td>
</tr>
</tbody>
</table>

Peak rejection level: 0

Group Leader: Dr. Tripathi P.K.
COLUMN: Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE: MeOH:H2O (90:10)
WAVELENGTH: 230nm
FLOW RATE: 0.7 ml/min (740 psi)
SAMPLE CONC: X mg/ml Injection vol: 2ul
D-7000 HPLC System Manager Report

Analyzed: 05/27/16 01:48 PM
Reported: 05/27/16 02:09 PM
Processed: 05/27/16 02:08 PM
Data Path: C:\WIN32APP\HSM\HPLC\DATA\893i\Series: 893i
Processing Method: SANTOSH
System(acquisition): Sys 1
Application: HPLC
Sample Name: SVK-BUTANYL-CHIRAL
Injection from this vial: 1 of 1
Sample Description: ME OH:H2O(95:05)
Volume: 10.0 ul
Series: 893i

Chrom Type: HPLC Channel: 1

No.  RT  Height  Area       Area %
1   8.15  732649  12806862  98.749
2   8.79  13131   162284  1.251
   745780  12969146  100.000

Peak rejection level: 0

Group Leader: Dr. Tripathi P.K.
COLUMN: Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE: ME OH:H2O(90:10)
WAVELENGTH: 230nm
FLOW RATE: 0.7 ml/min (740 psi)
SAMPLE CONC: X mg/ml Injection vol: 2ul
4.2.8. References


15. Diastereomeric ratio was determined using HPLC.