CHAPTER I

Stereoselective total synthesis of (+)-strictifolione and (6R)-6[(E, 4R, 6R)-4, 6-dihydro-10-phenyl-1-decenyl]-5, 6-dihydro-2H-2-pyrone

- Introduction to α, β-unsaturated δ-lactones
- Stereoselective total synthesis of (+)-strictifolione
- Stereoselective total synthesis (6R)-6[(E, 4R, 6R)-4, 6-dihydro-10-phenyl-1-decenyl]-5, 6-dihydro-2H-2-pyrone
SECTION – A

Introduction to $\alpha, \beta$-unsaturated $\delta$-lactones
INTRODUCTION

6-Substituted-5,6-dihydro-2H-pyran-2-one (α, β-unsaturated δ-lactone) is an integral structural subunit of an ever increasing number of biologically promising natural products. This unit is valuable for a wide variety of biological activities, such as insect growth inhibition and insect antifeedent, antifungal, and antitumor properties. The pyrone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) including leaves, stems, flowers, and fruits. Various kinds of substitutions have been found at the C-6 position of the ring such as polyacetoxy alkane, polyhydroxy alkane, a combination of both, or even a simple alkane. Biological activity of these types of molecules, their structural complexities, and the challenge to synthesize them in optically pure form made them an attractive target for many total syntheses. Isolation and biological activities of some of these natural products are discussed below.

1. α, β-unsaturated δ-lactone

Tarchonanthus lactone (2)

Tarchonanthus lactone 2 was isolated by Bohlmann et al. from Tarchonanthustrilobus compositae. Hsu et al. have reported that tarchonanthus lactone lowers plasma glucose in diabetic rats.²

2. Tarchonanthus lactone
Passifloricin A (3)

Passifloricin A 3, was isolated from the resin of *Passiflora foetida var. hispida*[^4], a species from the family Passifloraceae that grows in tropical zones of America and was found to be active in the *Artemia salina* test. Passifloricin was found to be active in the *Artemia salina* test.

![Passifloricin A](image)

3. Passifloricin A \( n = 12 \)

(+)–Boronolide (4)

(+)–Boronolide was isolated from the bark and branches of *Tetradenia fruticosa* and from the leaves of *Tetradenia barbera*,[^5] which have been used as local folk medicine in Madagascar and southern Africa. (+)–Deacetylboronolide and (+)–dideacetylboronolide were obtained from *Tetradenia riparia*,[^6] a central African species widely used as a tribal medicine. Medicinal properties of boronolides have been exploited for a long time in crude form. Zulu used roots of these plants as an emetic, and infusion of leaves has been reported to be effective against malaria.[^7]

![Boronolide](image)

\( R = R^1 = \text{Ac (}+)\text{-Boronolide} \)
\( R = R^1 = \text{H (}+)\text{-Deacetylboronolide} \)
\( R = \text{H, } R^1 = \text{Ac (}+)\text{-Dideacetylboronolide} \)

Argentilactone (5) and Massoialactone (6)

In 1977, Ruveda and co-workers reported the isolation of argentilactone 5[^8] from *Aristolochia argentina* (Aristolochiaceae). Later, this natural pyranone was also isolated from *Chorisia crispflora* and *Annona haematantha*. Argentilactone 5 was shown to have

antileishmanial and cytotoxic activities. Massoialactone 6 was first isolated from the bark oil of *Cryptocarya massoia* by Abe in 1937. This lactone has been used for many centuries as a constituent of native medicines.

![Massoialactone](image1)

 ![Massoialactone](image2)

**Kurzilactone (7)**

Kurzilactone 7, a new α,β-unsaturated-δ-lactone, has been isolated from the leaves of *Cryptocarya kurzii*. The structure of kurzilactone was determined by spectroscopic methods. Kurzilactone exhibits marked cytotoxicity against KB cells with IC$_{50}$ = 1 μg/mL.

![Kurzilactone](image3)

**(-)-Ratjadone (8)**

In 1994, the polyketide ratjadone 8 was isolated from cultures of *Sorangium cellulosum* strain Soce 360. Ratjadone displays potent in vitro antifungal activity with MIC values in the range from 0.004 to 0.6 μg/mL for *Mucor hiemalis*, *Phythophthora drechsleri*, *Ceratocystis ulmi*, and *Monilia brunnea*. Additionally, significant cytotoxicity in mammalian L929 cell lines (IC$_{50}$ = 0.05 mg/mL) and HeLa cell line KB3.1 (IC$_{50}$ = 0.04 ng/mL) has been demonstrated.

![Ratjadone](image4)
Fostriecin (9)

Fostriecin 9 was isolated in 1983 from *Streptomyces pulveraceus*. This compound displayed potent *in vitro* activity against a broad range of cancer cell lines and its inhibitory activity against protein serine/threonine phosphatases.

(-)-Callystatin A (10)

(-)-Callystatin A 10 is a polyketide-based natural product isolated in 1997 by Kobayashi et al from the marine sponge *Callyspongia truncata*. It exhibits remarkable cytotoxicity with an IC$_{50}$ value of 10 pg/mL against KB cell lines and 20 pg/mL against L1210 cells.

Spicigerolide and related lactones

$\alpha,\beta$-Unsaturated $\delta$-lactones (+)-spicigerolide 11, (+)-hyptolide 12, (-)-synrotolide 13 and (+)-anamarine 14 have been isolated from several *Hyptis* species and other botanically related genera. Synparvolide B 15 is another related member of this group isolated from the leaves of *Syncolostemon parviflorus*. These compounds contain a polyoxygenated chain connected with an $\alpha,\beta$-unsaturated six membered lactone and have been found to show a range of pharmacological properties, such as cytotoxicity against human tumor cells, antimicrobial and antifungal activity, etc. (+)-Spicigerolide, for instance, has been found to exhibit cytotoxicity with ED$_{50}$ = 1.5 $\mu$g/mL in the human
nasopharyngeal carcinoma (KB) assay system. Other structurally similar lactones 'Synrolide', 'Hypotolide' and 'Anamarine' from Hyptis and taxonomically related species have been found to be antimicrobial.\textsuperscript{19} (+)-Hypotolide and synparvolide B were found to exhibit anti-inflammatory properties.

\textbf{Cryptocarya lactones}

Cryptocarya diacetate 16 and Cryptocarya triacetate 17 were isolated from the bark of Cryptocarya latifolia.\textsuperscript{20} These compounds exhibit significant cytotoxic activity.
(6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one (18)

(6S)-5,6-Dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one (18), was isolated from Ravensara crassifolia DANGUY (Lauraceae) (syn. Cryptocarya crassifolia Baker), tree growing up to 18-20m long in the eastern region of Madagascar and displayed antifungal activity against the phytopathogenic fungus Cladosporium cucumerinum.

![Chemical structure of (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one (18)](structure18.png)

18. (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one

Rugalactone (19)

Rugalactone 19 was isolated by Meragelman et al. from the species of Cryptocarya rugulosa. These trees are widely distributed in tropic and subtropics and grow upto 18-20m height. Rugalactone exhibits anticancer activity against NF-kB in human lymphoma cell lines.

![Chemical structure of Rugalactone (19)](structure19.png)

19. Rugalactone

(+)-Strictifolione (20) and (6R)-6-[(E, 4R, 6R)-4,6-dihydro-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrone (21)

(+)-Strictifolione 20 was isolated by Aimi et al. from the stem bark of Cryptocarya strictifolia that grows in Indonesia. It was found to exhibit antifungal activity. The absolute configuration of (+)-strictifolione 20 was confirmed by its first stereoselective synthesis and was found to be (6R,4'S,6'S). (6R)-6-[(E, 4R, 6R)-4,6-Dihydro-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrone 21 was isolated by Hostetmann et al. from Ravensara.
crassifolia\textsuperscript{21} along with compound 18. The absolute configuration of compounds 21 and 18 was determined by LC-NMR.

\begin{center}
\includegraphics[width=0.2\textwidth]{strictifollone.png}
\end{center}

20. (\textit{+})-Strictifollone

\begin{center}
\includegraphics[width=0.2\textwidth]{compound21.png}
\end{center}

21. (6\textit{R})-6\{(E, 4\textit{R}, 6\textit{R})-4,6-dihydro-10-phenyl-1-decenyl\)-5,6-dihydro-2\textit{H}-2-pyrone
Stereoselective total synthesis of (+)-strictifolione
SYNTHESIS OF (+)-STRICTIFOLIONE

Because of important biological activity, we have synthesized (+)-strictifolione 20 with an alternative approach. Initially, we have outlined the previous synthetic approaches of compound 20.

PREVIOUS SYNTHETIC APPROACHES:

Cossey’s approach:

Janine Cossey et al.\textsuperscript{25} completed the synthesis of (+)-strictifolione 20 starting from 3-phenylpropionaldehyde 22 (Scheme 1) by using enantioselective allyltitanations (using catalysts (R,R)-I & (S,S)-I) to control the stereogenic centers at C6, C4', and C6' and a cross-metathesis to control the configuration of the double bond at C1'-C2'.
Ramana’s approach:

Ramana et al.\textsuperscript{26} approach involves synthesis of fragment 37 from D-glucose 30 (Scheme 2) and coupling of this fragment 37 with compound 40 (Scheme 3). The alkyne 41 thus produced was reduced to diol 42 using red-Al. The diol 42 was protected with 2,2'-DMP and later reacted with DDQ and produced primary alcohol 44. After oxidation and Z-selective Horner-Wadsworth-Emmons reaction of alcohol 44 produced the Z-ester 45. Lactonization of 45 produced (+)-strictifolione 20.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {D-Glucose};
\node at (1.5,-0.5) {30};
\node at (2.2,0) {ref. 35, \textit{O}};
\node at (2.2,-0.5) {\textit{O}};
\node at (3.5,0) {a-c, \textit{O}};
\node at (3.5,-0.5) {\textit{O}};
\node at (5,0) {a-c, \textit{O}};
\node at (5,-0.5) {\textit{O}};
\node at (6.5,0) {d, \textit{Ph}};
\node at (6.5,-0.5) {\textit{Ph}};
\node at (8,0) {e,f, \textit{Ph}};
\node at (8,-0.5) {\textit{Ph}};
\node at (9.5,0) {g, \textit{Ph}};
\node at (9.5,-0.5) {\textit{Ph}};
\node at (11,0) {i,k, \textit{Ph}};
\node at (11,-0.5) {\textit{Ph}};
\node at (12.5,0) {h,l, \textit{Ph}};
\node at (12.5,-0.5) {\textit{Ph}};
\node at (14,0) {35};
\node at (14,-0.5) {36};
\node at (15.5,0) {34};
\node at (15.5,-0.5) {31};
\node at (17,0) {32};
\node at (17,-0.5) {33};
\node at (18.5,0) {37};
\end{tikzpicture}
\end{center}

Scheme 2

Reagents and conditions: (a) 30\% AcOH, r.t., 75\%; (b) NaIO\textsubscript{4} on silica gel, CH\textsubscript{2}Cl\textsubscript{2}, 96\%; (c) C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}P'\textsubscript{Ph}\textsubscript{3}Br', n-BuLi, THF, 0 °C, r.t., 67\%; (d) Raney-Ni, ethanol, 60 psi, 98\%; (e) 30\% AcOH, reflux, 72\%; (f) LiAlH\textsubscript{4}, THF, r.t., 92\%; (g) 3-pentanone, CSA, 85\%; (h) DEAD, TPP, benzoic acid, THF, 91\%; (i) PTSA, methanol, 74\%; (j) TsCl, Bu\textsubscript{2}SnO, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 89\%; (k) NaH, THF, 0 °C, 94\%. 
Reagents and Conditions: (a) TPP, CCl₄, reflux, 87%; (b) n-BuLi, THF, -40 °C, 79%; (c) TBSCI, imidazole, CH₂Cl₂, r.t., 81%; (d) n-BuLi, BF₃·Et₂O, THF, -78 °C, 85%; (e) red-Al, ether, -20 °C, 73%; (f) 2,4-DMP, CSA, acetone, 95%; (g) DDQ, DCM-water (9:1), 86%; (h) (i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C; (ii) ethyl (di-o-tolylphosphono)acetate, NaH, THF, 0 to -78 °C, overall 81%; (i) PPTS, ethanol, 55 °C, 67%.

Takayama's approach:

Takayama et al.²⁷ completed the total synthesis and determined the absolute configuration of (+)-strictifolione 20 starting from (S)-malic acid 46 and (S)-glycidol 53. This approach involves synthesis of alcohol 52 from (S)-malic acid (Scheme 4) and aldehyde 57 from (S)-glycidol (Scheme 5). The alcohol 52 was converted later into sulfone 59 which underwent Kocienski-modified Julia olefination with aldehyde 57 produced a mixture (4:1) of isomeric E- and Z- alkenes 60 which was difficult to separate (Scheme 6). Deprotection of acetonide and acetal function at C₂ in compound 60, followed by MnO₂ oxidation of resulting allylic alcohol moiety gave the 5,6-dihydro-α-pyrone, which was recrystallized from n-Hexane/CHCl₃ to afford the pure E-isomer of (+)-strictifolione 20 in 30% overall yield.
Chapter-I: Section-B  
Stereoselective total synthesis of (+)-strictifolione

Reagents and conditions: (a) conc. H$_2$SO$_4$, EtOH, reflux, 4 h, 93%; (b) Ph$_3$CCl, DBU, CH$_2$Cl$_2$, r.t., 25 h, 71%; (c) LiAlH$_4$, Et$_2$O, reflux, 1.5 h, 88%; (d) TBDPSCI, Et$_3$N, DMAP, CH$_2$Cl$_2$, -10 °C, 72%; (e) MsCl, CH$_2$Cl$_2$, r.t., 12 h, quant.; (f) BCl$_3$, CH$_2$Cl$_2$, -10 °C, quant.; (g) K$_2$CO$_3$, MeOH, 0 °C, 88%; (h) n-BuLi, THF, rt, 98%; (i) NaHCO$_3$, I$_2$, aq. acetone, 0 °C, 77%; (j) Me$_3$NHB(OAc)$_3$, MeCN--AcOH (1:1), -20 °C, 25 h, 95%; (k) 2,2'-dimethoxypropane, PTSA, CH$_2$Cl$_2$, r.t., 3 h, 82%; (l) TBAF, 4 °A MS, THF, r.t., 2 h, 100%.

Reagents and conditions: (a) TBDPSCI, imidazole, CH$_2$Cl$_2$, r.t., 3 h, 67%; (b) vinylmagnesium bromide, Cul, THF, -25 °C, 1 h, 88%; (c) acrolein disopropylacetal, PPTS, 40-60 °C, 32 h, 74% (diastereomeric mixture 1:1); (d) RuCl$_2$(CHPh)(PCy$_3$)$_2$, CH$_2$Cl$_2$, reflux, 2 h, quant. (transcisis 1:1, isolated trans-isomer 44%); (e) TBAF, THF, r.t., 1 h, 87%; (f) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, -78 °C, 10 min, 90%.

Scheme 4

Scheme 5
Chapter-I: Section-B  
Stereoselective total synthesis of (+)-strictifolione

Reagents and conditions: (a) MsCl, 2,6-lutidine, CH₂Cl₂, r.t., 10 h, quant.; (b) LiBr, DMF, r.t., 5 days, 86%; (c) 1-phenyl-5-mercaptotetrazole, NaH, DMF, r.t.-70 °C, 96%; (d) m-CPBA, CH₂Cl₂, r.t., 24 h, 96%; (e) 57, NaHMDS, THF, -60 °C, 1.5 h, 34% (E-, Z-isomer 4:1); (f) PPTS, acetone-H₂O (6:1), r.t., 1.5 h, 80%; (g) MnO₂, pyridine, CH₂Cl₂, 24 h, 50%.

Sabitha's approach:

Scheme 6

Scheme 7
Reagents and Conditions: (a) \((R, R)\)-Jacobson's catalyst, \(H_2O, AcOH, 0 \degree C\text{-}rt., 1 h, 46\%\); (b) vinyl magnesium bromide, \(CuCN, -78 \degree C\) to \(-40 \degree C, 4 h, 92\%\); (c) (i) \(PhCHO, TFA, CH_2Cl_2, K_2CO_3, MeOH, r.t., 0.5 h, 59\%\); (ii) \(MOMCl, Hunig's base, 0 \degree C\text{-}r.t., 2 h, 90\%\); (d) (i) \(Li\text{-}liq NH}_3, dry THF, -78 \degree C, 60\%; (ii) \(LiC_2H, DMSO, 0 \degree C\text{-}r.t., 4 h, 80\%\); (e) \(NaH, THF, r.t., 1 h, 85\%\); (f) \(Pd/C, H_2, CaCO_3, EtOAc, Quinoline, r.t., 85\%\); (g) \(CeCl_3.7H_2O, CH_3CN:MeOH, reflux, 12 h, 60\%\).

Sabitha et al.\(^{28}\) achieved the total synthesis of \((+)-strictifolione\) \(20\) using Prins cyclisation and olefin cross-metathesis as the key steps. The \(anti\)-diol fragment \(69\) was synthesized from homo allylic alcohol \(63\) and benzaldehyde using Prins protocol as a key reaction (Scheme 7) and the lactone \(78\) was synthesized from the allylic alcohol \(75\) using Still-Gennari-Wittig reaction as a key reaction (Scheme 8). Finally both the fragments \(69\) and \(78\) were coupled by using olefin cross-metathesis reaction to yield \((+)-strictifolione\) \(20\).

![Scheme 8](image-url)
Enders approach:

In this approach\textsuperscript{29} the total synthesis of (+)-strictifolione 20 was described using Julia-Kocienski olefination reaction as a key step to produce \textit{E}-configured alkene (Scheme 11). The stereocenter of lactone moiety was created by enzymatic reduction of ester 84 with baker’s yeast (Scheme 11). The \textit{anti}-configuration of 1,3 diol in compound 80 was achieved by applying a SAMP-hydrazone \textit{a,\textit{a}’}-bisalkylation/deoxygenation protocol (Scheme 10).

Scheme 10

\textbf{Reagents and conditions:} (a) \textit{t}-BuLi, THF, -78 °C, Br(\textit{CH}_2)_2OTBS, -100 °C-r.t.; (b) \textit{t}-BuLi, THF, -78 °C; Ph(\textit{CH}_2)_2I, -100 °C-r.t., 71\% over two steps; (c) sat. aq oxalic acid, Et\textsubscript{3}O, r.t., 96\%; (d) NaBH\textsubscript{4}, MeOH, 0 °C; (e) NaH, THF, 0 °C, then CS\textsubscript{2} and Mel, 0 °C-r.t., 99\%; (f) Bu\textsubscript{3}SnH, AIBN (cat), toluene, reflux; (g) TBAF, THF, r.t., 93\% over two steps; (h) Ph\textsubscript{3}P, imidazole, I\textsubscript{2}, Et\textsubscript{3}O-CH\textsubscript{3}CN, 0 °C, 84\%; (i) 1-1-Phenyl-1H-tetrazole-5-thiol, NaH, THF-DMF, 0 °C, then 82, 0 °C-r.t., 99\%; (j) m-CPBA, NaHCO\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 87\%.
Reagents and conditions: (a) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, -78 °C then Et$_3$N, -78 °C-r.t.; (b) 83, DME, -(65-60) °C, KHMDS, -(65-60) °C-r.t., E/Z = 8.5:1, 61%; (c) PPTS, acetone-H$_2$O, r.t.; (d) MnO$_2$, CH$_2$Cl$_2$, r.t., 69% over two steps.
PRESENT WORK

(+)-Strictifolione (20), a 6-substituted 5, 6-dihydro-2H-pyran-2-one or α, β-unsaturated δ-lactone was isolated by Aimi et al.\textsuperscript{23} from the stem bark of Cryptocarya strictifolia that grows in Indonasia. The compound exhibited antifungal property. The structure was proposed based on spectroscopic data. The absolute stereochemistry of was determined as (6R,4'S,6'S) by its first total synthesis\textsuperscript{27} (Fig. 1).

Due to its interesting structural pattern and impressive activity, we have synthesized 20 from the two fragments 69 and 78 by olefin cross-metathesis using Grubbs’ II generation catalyst. The fragment 69 was prepared by readily available 3-phenyl propanol using Swern oxidation, Wittig homologation, Zn mediated Barbier-type allylation and Sharpless kinetic resolution as key steps. The fragment 78 was prepared from compound 94 which was prepared from L-ascorbic acid 93 (Scheme 19). The retro synthetic analysis for (+)-strictifolione is represented in Scheme 12.
Our synthesis was started from commercially available 3-phenyl propan-1-ol 87, which was converted to 3-phenyl propanal 88 under Swern reaction conditions (Scheme 13).

![Scheme 13](image)

The aldehyde 88 was reacted with (carboethylmethylene) triphenyl phosphorane in CH$_2$Cl$_2$ at room temperature to afford the (E)-$\alpha$, $\beta$-unsaturated ester in 84% yield (Scheme 14). Formation of product 89 was ascertained from $^1$H NMR spectrum (Fig. 1B. 1), which revealed the presence of olefin protons at $\delta$ 6.94 (1H, m) and $\delta$ 5.81 (1H, d, $J = 14.0$ Hz), ethyl group protons at $\delta$ 4.15 (2H, q, $J = 7.0$ Hz) and $\delta$ 1.27 (3H, t, $J = 7.0$ Hz) along with other required protons. In the $^{13}$C NMR spectrum of the compound (Fig. 1B. 2), chemical shift values at $\delta$ 166.9 and $\delta$ 60.2 indicated the presence of ester.

![Scheme 14](image)

The IR spectrum of 89 (Fig. 1B. 3) showed a sharp band at 1721 cm$^{-1}$ indicating the presence of carbonyl functional group. The structure of compound 89 was also confirmed by ESIMS signal at $m/z$ 205 [M+H]$^+$ (Fig. 1B. 4).

Treatment of compound 89 with DIBAL-H at -78 °C in toluene yielded aldehyde 90 in 78% yield (Scheme 15).
Scheme 15

The crude aldehyde 90 on Barbier-Type allylation with allyl bromide, Zinc metal and aqueous ammonium chloride in THF at 0 °C produced (E)-8-phenylocta-1,5-dien-4-ol 91 in 93% yield (Scheme 16).31

Scheme 16

The compound 91 was characterized from its 1H NMR, 13C NMR and ESIMS spectral data. The 1H NMR spectrum showed the five olefinic protons at $\delta$ 5.78-5.62 (2H, m), 5.45 (1H, m), 5.11-5.03 (2H, m), one oxygen attached allyl proton at $\delta$ 4.03 (1H, m) and one hydroxyl proton at $\delta$ 1.42 (1H, brs) (Fig. 1B. 5). The 13C NMR spectrum showed four olefin carbons at $\delta$ 134.3, 132.9, 130.8, 118.0 and one oxygenated carbon at $\delta$ 71.2 (Fig. 1B. 6). A peak at $m/z$ 225 $[M+Na]^+$ in ESIMS spectrum confirmed the formation of 91 (Fig.1B. 7).

The compound 91 on Sharpless kinetic resolution with Ti(OiPr)$_4$, (+)-DIPT and TBHP in CH$_2$Cl$_2$ at -20 °C produced the epoxy compound 92 in 45% yield (Scheme 17).32

Scheme 17
Chapter-I: Section-B  

Stereoselective total synthesis of (+)-strictifolione

Formation of the compound 92 was confirmed by its IR, $^1$H NMR, $^{13}$C NMR, ESIMS and HRESIMS data. The $^1$H NMR spectrum showed presence of three olefin protons at $\delta$ 5.77 (1H, m) and 5.16-5.02 (2H, m), one homoallylic proton at $\delta$ 3.69 (1H, m), two epoxy and two benzylic protons at $\delta$ 2.93 (1H, m), 2.87-2.62 (3H, m) (Fig. 1B. 8). The $^{13}$C NMR spectrum showed presence of two olefin carbons at $\delta$ 134.0, 118.0 and three oxygenated carbons at $\delta$ 68.2, 60.8, 54.7 (Fig. 1B. 9). The ESIMS of compound 92 showed a peak at $m/z$ 241 corresponds to [M+Na]$^+$ (Fig. 1B. 10). A peak at $m/z$ 241.1212 of [M+Na]$^+$ in HRESIMS confirmed the formation of epoxy compound 92 (Fig. 1B. 11).

The compound 92 showed optical rotation value of $[\alpha]_{D}^{25} = -11.2$ (c 1.0, CHCl$_3$).

The compound 92 was then treated with Red-Al at 0 °C in dry THF and was allowed to stir for 2 h at room temperature to form the intermediate 69 in 77% yield (Scheme 18).

![Scheme 18](image)

The formation of compound 69 was confirmed by its IR, $^1$H NMR, $^{13}$C NMR, ESIMS and HRESIMS data. The IR spectrum of 69 (Fig. 1B. 12) showed a broad band at 3370 cm$^{-1}$ indicating the presence of hydroxyl group. The $^1$H NMR spectrum showed presence of three olefin protons at $\delta$ 5.77 (1H, m) and 5.12-5.03 (2H, m) and two protons that were attached to oxygen bearing carbon atoms at $\delta$ 3.99-3.84 (2H, m) (Fig. 1B. 13). In $^{13}$C NMR spectrum of compound 69, the peaks at $\delta$ 134.6 and 118.0 represented two olefinic carbon atoms and the peaks at $\delta$ 68.2 and 68.0 confirmed the presence of to two oxygenated carbon atoms (Fig. 1B. 14). A peak at $m/z$ 243 [M+Na]$^+$ in ESIMS spectrum (Fig. 1B. 15) and a peak at $m/z$ 243.1363 [M+Na]$^+$ in HRESIMS (Fig. 1B. 16) confirmed formation of the product.

The $[\alpha]_{D}^{25}$ value of compound 69 was +4.1 (c 1.0, CHCl$_3$).
The compound 94 was prepared (Scheme 19) from commercially available L-ascorbic acid 93 through reported procedure.\textsuperscript{33}

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

\[ \text{ref. 33} \quad \text{HO} \quad \text{COOEt} \]

\textbf{Scheme 19}

The formation of compound 94 was confirmed from IR, \(^1\)H, \(^{13}\)C NMR and ESIMS spectra. The \(^1\)H NMR spectrum (Fig. 1B. 17), where presence of four protons that are attached to carbon atom bearing oxygen resonated at \(\delta 4.36\) (1H, d, \(J = 8.0\) Hz), 4.27- 4.12 (3H, m) and six acetonide protons at \(\delta 1.45\) (3H, s), 1.40 (3H, s) along with the other required protons confirmed the product. It was further confirmed by \(^{13}\)C NMR spectrum (Fig. 1B. 18), which showed signals at \(\delta 171.9, 109.8, 76.3, 70.2, 65.6, 61.8\) and 26.0 and 25.3 indicating presence of carbonyl group, acetonoid carbon, oxygen attached carbons and two methyl groups.

The hydroxyl group of 94 was converted into xanthate ester 95 by treating with NaH and CS\(_2\) in THF at 0 °C followed by the addition of MeI at 0 °C and warmed to room temperature. The xanthate ester was formed in 89% yield (Scheme 20).

\[ \text{OH} \quad \text{COOEt} \quad \text{1.NaH, CS\(_2\), THF, 0 °C, 30 min} \quad \text{2.Mel, 0 °C to r.t., 1 h, 89\%} \]

\textbf{Scheme 20}

The structure of the xanthate ester 95 was confirmed from its IR, \(^1\)H, \(^{13}\)C NMR and ESIMS spectra. In the \(^1\)H NMR spectrum (Fig. 1B. 19) of the compound 95, xanthate ester methyl protons resonated at \(\delta 2.62\) (3H, s). In the \(^{13}\)C NMR spectrum (Fig. 1B. 20) of compound 95, the peaks at \(\delta 215.5, 166.1\) indicating the presence of xanthate ester and ester carbonyl functions respectively. The ESIMS peak corresponding to \(m/z 295\) [M+H]\(^+\) supported the above transformation (Fig. 1B. 21).
The compound 95 showed optical rotation value of $[\alpha]_D^{25} = -15.2$ (c 1.0, CHCl$_3$).
The xanthate ester 95 was treated with $n$-Bu$_3$SnH and catalytic amount of AIBN in toluene under reflux condition to give ester 96 (Scheme 21) in 87% yield.

![Scheme 21](image)

The product 96 was confirmed from their IR, $^1$H, $^{13}$C NMR and ESIMS spectra. In IR spectrum of compound 96 showed a peak 1736 cm$^{-1}$ corresponding to ester carbonyl (Fig. 1B. 22). In the $^1$H NMR spectrum (Fig. 1B. 23), absence of signals at $\delta$ 2.62 (3H, s) indicated that removal of xanthate ester. In $^{13}$C NMR spectrum (Fig. 1B. 24), absence of signals at $\delta$ 215.5 indicated removal of xanthate ester. The molecular ion peak at $m/z$ 206 $[M+18]^+$ in its mass spectrum confirmed the above conversion (Fig. 1B. 25).
The optical rotation value of compound 96 was $[\alpha]_D^{25} = -11.4$ (c 1.0, CHCl$_3$). The ester compound 96 was converted into corresponding aldehyde using DIBAL-H in toluene at -78 °C for 15 minutes. Subsequently this aldehyde was converted into (Z)-$\alpha$, $\beta$-unsaturated ester 97 using the Still–Gennari–Wittig reaction at -78 °C for 1 h in 83% yield (Scheme 22).

![Scheme 22](image)

The formation of (Z)-$\alpha$, $\beta$-unsaturated ester 97 was explained by IR, $^1$H, $^{13}$C NMR and ESIMS spectra. In the $^1$H NMR spectrum (Fig. 1B. 26) of the compound 97, the alkene protons resonated at $\delta$ 6.34 (1H, m) and 5.90 (1H, d, $J = 9.0$ Hz) indicating cis-alkene compound formed. In the $^{13}$C NMR spectrum (Fig. 1B. 27) of compound 97, which showed carbon signal at $\delta$ 144.9, 121.2 indicated presence of alkene carbons in compound.
The molecular ion peak at $m/z$ 201 $[M+H]^+$ in its mass spectrum (Fig. 1B. 28) confirmed the formation of unsaturated ester product.

The optical rotation value of 97 was $[\alpha]_D^{25} = +1.66$ ($c$ 1.0, CHCl$_3$).

The $\alpha, \beta$-unsaturated ester 97 was cyclized with 2N HCl in MeOH at 0 °C to give corresponding lactone alcohol 98 using reported procedure in 83% yield (Scheme 23).

![Scheme 23](image)

The alcohol 98 was subjected to Swern oxidation to produce the corresponding aldehyde in 90% yield, which was converted into terminal vinyl lactone 78 using Wittig reaction with triphenyl phosphonium methyl iodide and $n$-BuLi in THF at -78 °C for 1 h in 75% yield (Scheme 24).

![Scheme 24](image)

The formation of vinyl lactone 78 was confirmed by its IR, $^1$H, $^{13}$C NMR and ESIMS spectra. In the $^1$H NMR spectrum (Fig. 1B. 29) the five olefin protons resonated at $\delta$ 6.89 (1H, m), 6.07 (1H, d, $J = 9.0$ Hz), 5.95 (1H, m) and 5.41-5.29 (2H, m) along with other required protons confirming the product. In $^{13}$C NMR spectrum (Fig. 1B. 30) the peak at $\delta$ 163.9 was observed corresponding to $\alpha, \beta$-unsaturated lactone carbonyl. The mass spectrum of 78 showed a peak at $m/z$ 125 $[M+H]^+$.

The compound showed the optical rotation value of $[\alpha]_D^{25} = +13.6$ ($c$ 0.8, CHCl$_3$). All these spectral and physical data of compound 78 were identical with those reported earlier.28
The olefin cross metathesis of compound 69 with vinyl lactone 78 using Grubbs' II generation catalyst\textsuperscript{35} in CH\textsubscript{2}Cl\textsubscript{2} yielded (+)-strictifolione 20 in 66\% yield (scheme 25).

![Scheme 25]

The compound (+)-strictifolione 20 was confirmed by its IR, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and ESIMS spectral data. The \textsuperscript{1}H NMR spectrum (Fig. 1B. 31) of compound 20 showed four olefinic protons at $\delta$ 6.84 (1H, m), 6.01 (1H, d, $J = 9.0$ Hz), 5.85 (1H, m), 5.64 (1H, dd, $J = 15.5$ Hz, 6.5 Hz) and three protons that are attached to carbons bearing oxygen atoms at $\delta$ 4.86 (1H, m), 4.03-3.89 (2H, m) along with other required protons confirmed the formation of 20. A peak at $\delta$ 163.8 corresponds to lactone carbonyl carbon in the \textsuperscript{13}C NMR spectrum (Fig. 1B. 32) of 20 along with peaks at $\delta$ 77.7, 68.7 and 68.2 corresponding to three oxygenated carbon atoms confirming the formation of compound 20. The mass spectrum showed $m/z$ value at 339 [M+Na]\textsuperscript{+} (Fig. 1B. 33).

The compound showed the optical rotation value of $[\alpha]_{D}^{25} = +62.1$ (c 0.6, CHCl\textsubscript{3}). The spectral data of the compound 20 are in good agreement with the data reported earlier.\textsuperscript{5}
EXPERIMENTAL SECTION

General
Commercial reagents were used without further purification. All solvents were purified by standard techniques. Column chromatographic (CC) separations were carried out on silica gel (SiO₂; 60-120 mesh). Optical rotation: Jasco Dip 360 digital polarimeter at 25 °C. NMR spectra: in CDCl₃: Varian Gemini 200, Brucker 300, or Varian Unity 400 NMR spectrometers; chemical shifts (δ) are given in ppm and are referenced to Me₄Si as internal standard; coupling constants (J) are given in Hz. MS: Finnigan MAT 1020B or micro mass VG 70-70H (70 eV), ESIMS: LC-MSD-Trap-SL and HRMS: QSTAR XL, Hybrid MS system(Applied Biosystems) spectrometers operating at 70 eV using a direct inlet system.

3-Phenyl propanal (88):

\[
\text{88}
\]

To a stirred solution of oxalyl chloride (3.15 mL, 36.76 mmol), in dry dichloromethane (90 mL), DMSO (3.26 mL, 45.95 mmol) was added at -78 °C and stirred at the same temperature for 0.5 h. A solution of 3-phenyl propan-1-ol 87 (2.5 g, 18.38 mmol) in dichloromethane (20 mL) was added at -78 °C and stirred for 1.5 h at the same temperature. Et₃N (12.8 mL, 91.9 mmol) was added at 0 °C and stirred for an additional 30 min. The reaction mixture was diluted with water (70 mL) and extracted with dichloromethane (2 x 80 mL). The combined organic layers were washed with brine (40 mL), dried (over Na₂SO₄) and concentrated to give 88 (2.03 g, 82%) as colorless liquid. The crude aldehyde thus obtained was utilized immediately for further step.
(E)-Ethyl-5-phenylpent-2-enoate (89)

![Chemical Structure](image)

To a stirred solution of phenyl propanal 88 (2.0 g, 14.92 mmol) in dry CH₂Cl₂ (20 mL) ethyl (triphenyl phosphorylidene) acetate (6.23 g, 17.91 mmol) was added and the mixture was stirred at ambient temperature for 8 h. It was then concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure (E)-ethyl-5-phenylpent-2-enoate 89 (2.55 g, 84%) as a colorless oil.

**Molecular formula**: C₁₃H₁₆O₂

**Physical state**: Colorless oil

**Elemental analysis**

<table>
<thead>
<tr>
<th>Element</th>
<th>Found (%)</th>
<th>Calcd (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>76.41</td>
<td>76.44</td>
</tr>
<tr>
<td>H</td>
<td>7.94</td>
<td>7.90</td>
</tr>
</tbody>
</table>

**IR spectrum**: ν_max 1721, 1655, 1454, 1317, 1267 cm⁻¹ (Fig. IB. 3)

**¹H-NMR spectrum**: δ 7.28-7.11 (5H, m), 6.94 (1H, m), 5.81 (1H, d, J = 14.0 Hz), 4.15 (2H, q, J = 7.0 Hz), 2.74 (2H, t, J = 7.0 Hz), 2.55-2.46 (2H, m), 1.27 (3H, t, J = 7.0 Hz) (Fig. IB. 1)

**¹³C-NMR spectrum**: δ 166.9, 148.1, 140.8, 128.7, 128.5, 126.1, 121.9, 60.2, 34.0, 33.7, 14.1 (Fig. IB. 2).

**ESI-Mass spectrum**: m/z 205 [M+H]^+; 227 [M+Na]^+ (Fig. IB. 4)

**HRMS-spectrum**: m/z 205.1221 (Calcd for C₁₃H₁₇O₂ m/z 205.1201).
To a stirred solution of compound 89 (2.5 g, 12.25 mmol) in dry toluene (25 mL) at -78°C DIBAL-H (1.0 M, 14.70 mL, 14.70 mmol) was added dropwise and the mixture was stirred at that temperature for 30 min. The reaction mixture was then quenched by slow addition of dry methanol (10 mL) and was brought to room temperature. Saturated sodium potassium tartrate (10 mL) was added and stirred for 1 h. Then the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (2x50 mL). The organic layer was separated and dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude aldehyde 90 (1.52 g, 78%) thus obtained was used further without purification.

The crude aldehyde 90 (1.40 g, 8.75 mmol) was dissolved in THF (15 mL). Activated Zn (2.84 g, 43.75 mmol) and allyl bromide (2.22 mL, 26.25 mmol) were added at 0 °C and stirred for 10 min. To this mixture saturated NH₄Cl solution (10 mL) was added dropwise at 0 °C and the solution was stirred for 3 h at ambient temperature. Then the reaction mixture was extracted with EtOAc (2x15 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 3:7) afforded pure (E)-8-phenyl octa-1,5-diene-4-ol 91 (1.64 g, 93%) as a colorless liquid.

**Molecular formula**: C₁₄H₁₈O

**Physical state**: Colorless liquid

**Elemental analysis**: Found: C, 83.18; H, 8.93%.

Calcd: C, 83.12; H, 8.97%.

**IR spectrum**: νₑₓₘₐₓ 3422, 1610, 1556, 1450 cm⁻¹.

**¹H-NMR spectrum**: (200 MHz, CDCl₃):

δ 7.24-7.11 (5H, m), 5.78-5.62 (2H, m), 5.45 (1H, m), 5.11-5.03 (2H, m), 4.03 (1H, m), 2.67 (2H, t, J = 7.0 Hz), 2.39-
2.31 (2H, m), 2.28-2.17 (2H, m), 1.42 (1H, brs) (Fig. 1B, 5).

$^{13}$C-NMR spectrum : (50 MHz, CDCl$_3$)

$\delta$  141.7, 134.3, 132.9, 130.8, 128.3, 128.2,125.9, 118.0, 71.2, 42.0, 35.5, 33.9 (Fig. 1B. 6).

ESI-Mass spectrum : $m/z$ 225 [M+Na]$^+$ (Fig. 1B. 7).

HRMS-spectrum : 225.1247 (Calcd for C$_{14}$H$_{18}$ONa: $m/z$ 225.1255).

(S)-1-((2S,3S)-3-Phenethyloxiran-2yl) but-3-en-1-ol (92)

![Chemical Structure](image)

To a suspension of powered molecular sieves (4 °A, 200 mg) in dry CH$_2$Cl$_2$ (15 mL) Ti(OiPr)$_4$ (1.1 mL, 3.71 mmol) and (+)- DIPT (0.931 mL, 4.45 mmol) were added sequentially at -20 °C. After stirring for 30 min allyl alcohol 91 (1.5 g, 7.42 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added and stirring was continued for another 30 min at the same temperature. Then TBHP (0.89 mL, 3.56 mmol) was added and after stirring for another 5 h at the same temperature, the reaction mixture was quenched by addition of water (15 mL). It was allowed remain at room temperature by stirring for 30 min. After re-cooling at 0 °C, an aqueous solution of NaOH (30% w/v, 10 mL saturated with brine) was added to it and the mixture was stirred at 0 °C for 1h. The reaction mixture was extracted with ether (2x40 mL). The combined organic extracts were washed with brine (2x20 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 4:6) afforded pure (S)-1-((2S,3S)-3-phenethyloxiran-2-yl)but-3-en-1-ol 92 (0.72 g, 45%) as a colorless liquid.
Molecular formula: $\text{C}_{14}\text{H}_{18}\text{O}_2$

Optical Rotation: $[\alpha]_D^{25} = -11.2$ (c 1.0, CHCl$_3$).

Elemental analysis: Found: C, 77.08; H, 8.35%.
Calcd: C, 77.03; H, 8.31%.

IR spectrum: $\nu_{\text{max}}$ 3447, 1640, 1503, 1454 cm$^{-1}$.

$^1$H-NMR spectrum: (200 MHz, CDCl$_3$)
$\delta$ 7.30-7.10 (5H, m), 5.77 (1H, m), 5.16-5.02 (2H, m), 3.69 (1H, m), 2.93 (1H, m), 2.87-2.62 (3H, m), 2.31-2.13 (2H, m), 1.90-1.79 (3H, m) (Fig. 1B. 8).

$^{13}$C-NMR spectrum: (50 MHz, CDCl$_3$)
$\delta$ 141.1, 134.0, 129.9, 129.7, 126.2, 118.0, 68.2, 60.8, 54.7, 38.0, 33.2, 32.3 (Fig. 1B. 9).

ESI-Mass spectrum: $m/z$ 241 [M+Na]$^+$ (Fig. 1B. 10).

HRESIMS-spectrum: $m/z$ 241.1212 (Calcd for C$_{14}$H$_{18}$O$_2$Na: $m/z$ 241.1204) (Fig. 1B. 11).

(3$S$, 5$S$)-1-Phenyloct-7-ene-3,5-diol (69)

To a stirred solution of 92 (0.650 g, 2.98 mmol) in dry THF (15 mL) under N$_2$ atmosphere at 0 °C was added Red-Al solution in toluene (65% w/v, 2.78 mL, 8.94 mmol) and reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated NH$_4$Cl solution (15 mL) and then extracted with EtOAc (2x30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 5:5) afforded pure (3$S$, 5$S$)-1-phenyloct-7-ene-3, 5-diol 69 (0.5 g, 77%) as a colorless oil.
<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>$\text{C}<em>{14}\text{H}</em>{20}\text{O}_2$</td>
</tr>
<tr>
<td>Physical state</td>
<td>Colorless oil</td>
</tr>
<tr>
<td>Optical rotation</td>
<td>$[\alpha]_D^{25} = +4.1 \ (c \ 1.0, \ \text{CHCl}_3)$</td>
</tr>
<tr>
<td>Elemental analysis</td>
<td>Found: C, 76.38; H, 9.11%. Calcd: C, 76.33 H, 9.15%</td>
</tr>
<tr>
<td>IR spectrum</td>
<td>$\nu_{\text{max}}$ 3370, 1641, 1496, 1454 cm$^{-1}$. (Fig. 1B. 12).</td>
</tr>
<tr>
<td>$^1$H-NMR spectrum</td>
<td>$(200 \text{ MHz, CDCl}_3)$</td>
</tr>
<tr>
<td></td>
<td>$\delta$ 7.28-7.10 (5H, m), 5.77 (1H, m), 5.12-5.03 (2H, m), 3.99-3.84 (2H, m), 2.97 (2H, m), 2.78 (1H, m), 2.61 (1H, m), 2.21 (2H, t, $J = 7.0 \text{ Hz}$), 1.81 (1H, m), 1.72 (1H, m), 1.58 (2H, t, $J = 7.0 \text{ Hz}$) (Fig. 1B. 13).</td>
</tr>
<tr>
<td>$^{13}$C-NMR spectrum</td>
<td>$(50 \text{ MHz, CDCl}_3)$</td>
</tr>
<tr>
<td></td>
<td>$\delta$ 142.1, 134.6, 128.2, 125.5, 118.0, 68.2, 68.0, 41.5, 38.8, 32.0, 29.3 (Fig. 1B. 14).</td>
</tr>
<tr>
<td>ESI-Mass spectrum</td>
<td>$m/z$ 243 $[\text{M+Na}]^+$ (Fig. 1B. 15).</td>
</tr>
<tr>
<td>HRESIMS</td>
<td>$m/z$ 243.1363 (Calcd for $\text{C}<em>{14}\text{H}</em>{20}\text{O}_2\text{Na}$: $m/z$ 243.1360 $[\text{M+Na}]^+$) (Fig. 1B. 16).</td>
</tr>
</tbody>
</table>
Chapter-I: Section-B  
Stereoselective total synthesis of (+)-strictifolione

(R)-ethyl-2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(methylthiocarboxothioyloxy)acetate (95)

To a stirred suspension of NaH (60%, 0.431 g, 10.78 mmol) in THF (10 mL) a solution of 94 (2.0 g, 9.8 mmol) in THF (10 mL) was added dropwise at 0 °C under N₂ atmosphere. After stirring for 20 min, CS₂ (2.07 mL, 29.41 mmol) was added and the reaction mixture was stirred for 30 min. Then iodo methane (3.86 mL, 58.52 mmol) was added and stirring is continued for 1 h at the same temperature, the reaction mixture was quenched with ice and saturated NH₄Cl (20 mL) at 0 °C and extracted with EtOAc (2×40 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure (R)-ethyl-2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(methylthiocarboxothioyloxy)acetate 95 (2.56 g, 89%) as a colorless liquid.

Molecular formula : C₁₁H₁₈O₅S₂  
Physical state : Colorless liquid  
Optical Rotation : -15.2 (c 1.0, CHCl₃).

Elemental analysis : Found: C, 44.81; H, 6.13%.  
Calcd: C, 44.88; H, 6.16%.

IR spectrum : ν_max 1742, 1589, 1458, 1372, 1202 cm⁻¹.  
¹H-NMR spectrum : (300 MHz, CDCl₃)  
δ 5.75 (1H, d, J = 6.0 Hz), 4.58 (1H, q, J = 6.0 Hz), 4.23
Stereoselective total synthesis of (+)-strictifolione

(2H, q, \(J = 7.0\) Hz), 4.07 (1H, m), 3.92 (1H, m), 2.62 (3H, s), 1.41 (3H, s), 1.32 (3H, s), 1.28 (3H, t, \(J = 7.0\) Hz) (Fig. 1B. 19).

\(^{13}\)C-NMR spectrum: (75 MHz, CDCl\(_3\))
\[\delta 215.5, 166.1, 110.4, 79.4, 74.7, 65.4, 61.6, 26.3, 25.6, 19.3, 14.3 (\text{Fig. 1B. 20}).\]

ESI-Mass spectrum: \(m/z 295\) [M+H]+ (Fig. 1B. 21).

\((R)\)-ethyl-2(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (96)

\[
\text{\begin{align*}
\text{O} & \quad \text{C} \\
& \quad \text{OEt}
\end{align*}}
\]

96

To a solution of 95 (2.5 g, 8.50 mmol) in dry toluene was added catalytic amount of AIBN and tributyltin hydride (2.97 mL, 11.05 mmol) at ambient temperature and then refluxed for 1 h. Then it was allowed to cool at room temperature, diluted with water (10 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure \((R)\)-ethyl-2(2,2-dimethyl-1,3-dioxolan-4-yl)acetate 96 (1.38 g, 87%) as a colorless liquid.

Molecular formula: \(C_9H_{16}O_4\)
Physical state: Colorless liquid
Optical rotation: \(-11.4\) (\(c 1.0\), CHCl\(_3\)).
Elemental analysis:
- Found: C, 57.47; H, 8.51%.
- Calcd: C, 57.43; H, 8.57%.

IR spectrum: \(\nu_{\text{max}} 1736, 1457, 1371, 1255\) cm\(^{-1}\) (Fig. 1B. 22).

\(^{1}\)H-NMR spectrum: (300 MHz, CDCl\(_3\))
Chapter-I: Section-B Stereoselective total synthesis of (+)-strictifolione

$\delta$ 4.41 (1H, m), 4.19-4.08 (3H, m), 3.60 (1H, m), 2.68 (1H, dd, $J = 12.0$, 5.0 Hz), 2.43 (1H, dd, $J = 12.0$, 7.0 Hz), 1.39 (3H, s), 1.32 (3H, s), 1.27 (3H, t, $J = 7.0$ Hz) (Fig. 1B.23).

$^{13}$C-NMR spectrum : (75 MHz, CDCl$_3$)

$\delta$ 170.5, 109.1, 72.0, 69.1, 60.6, 38.9, 26.8, 25.4, 14.1 (Fig. 1B.24).

ESI-Mass spectrum : $m/z$ 206 [M+18]$^+$ (Fig. 1B.25).

(R, Z)-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (97)

To a stirred solution of compound 96 (1.2 g, 6.38 mmol) in dry toluene (15 mL) at -78 °C DIBAL-H (1.2M, 6.38mL, 7.65 mmol) was added dropwise and the mixture was stirred at that temperature for 15 min. The reaction mixture was then quenched by slow addition of dry methanol (10 mL) and was brought to room temperature. Saturated sodium potassium tartrate (10 mL) was added and stirred for 1 h. Then the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (2x30 mL). The organic layer was separated and dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude aldehyde (0.72 g, 79%) thus obtained was used further without purification.

To a suspension of NaH (60%, 0.213 g, 5.34 mmol) under N$_2$ atmosphere in dry THF (10 mL) was added bis-(2,2,2-trifluoroethyl)(methoxy-carbonyl methyl) phosphonate (1.23 mL, 5.83 mmol) at 0 °C. After the mixture was stirred for 30 min at the same temperature, the reaction mixture was cooled to -78 °C, and then a solution of crude aldehyde (0.7 g, 4.86 mmol) in dry THF (10 mL) was added dropwise. After stirring for 1 h, the reaction mixture was diluted with 5 mL of ether and quenched by slow addition of 4 mL of water. The reaction mixture was extracted with ether (2x30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The
residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure \((R, Z)\)-methyl-4-(2,2-dimethyl-1,3-dioxaan-4yl)but-2-enoate 97 (0.806 g, 83%) as a colorless oil.

<table>
<thead>
<tr>
<th>Molecular formula</th>
<th>C(<em>{10})H(</em>{16})O(_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>Colorless oil</td>
</tr>
<tr>
<td>Optical rotation</td>
<td>([\alpha]_{D}^{25} = +1.66) (c = 1.0, CHCl(_3)).</td>
</tr>
<tr>
<td>Elemental analysis</td>
<td>Found: C, 59.95; H, 8.08%. Calcd: C, 59.98; H, 8.05%.</td>
</tr>
</tbody>
</table>
| \(^1\)H-NMR spectrum | (300 MHz, CDCl\(_3\))  
\(\delta 6.34 (1H, m), 5.90 (1H, d, J = 9.0 \text{ Hz}), 4.21 (1H, m), 4.02 (1H, m), 3.72 (3H, s), 3.58 (1H, m), 3.02 (1H, m), 2.89 (1H, m), 1.42 (3H, s), 1.34 (3H, s)\) (Fig. 1B. 26). |
| \(^{13}\)C-NMR spectrum | (50 MHz, CDCl\(_3\)): \(\delta 166.4, 144.9, 121.2, 109.2, 74.7, 68.6, 50.9, 32.6, 26.6, 25.4\) (Fig. 1B. 27). |
| ESI-Mass spectrum | m/z 201 [M+H]\(^+\) (Fig. 1B. 28). |

\((R)\)-6-(hydroxymethyl)-5, 6-dihydro-2\(H\)-pyran-2-one (98):

To a stirred solution of compound 97 (0.75 g, 3.75 mmol) in MeOH, 2N HCl was added at 0 °C and stirred for 3h. After completion the reaction was quenched with NaHCO\(_3\) and extracted with EtOAc (20 mL). The combined organic layer was washed with brine and concentrated in vaccuo. The residue was subjected to column chromatography to afford pure compound 98 (0.39 g, 83%) as colourless liquid. The spectral data of this compound were identical with those reported earlier.\(^\text{11}\)

| Molecular formula | C\(_6\)H\(_8\)O\(_3\) |
Chapter-I: Section-B Stereoselective total synthesis of (+)-strictifolione

Physical state : Colourless oil

Optical rotation : $[\alpha]_D^{25} = +170.9 \ (c = 1.0, \ CHCl_3)$.

Elemental analysis : Found: C, 56.29; H, 6.23%.
Calcd: C, 56.24; H, 6.29%.

IR Spectrum : $\nu_{\text{max}}$ 1747, 1534, 1332, 1179 cm$^{-1}$

$^1$H-NMR spectrum : (300 MHz, CDCl$_3$):

$\delta$ 6.98 (1H, m), 6.03 (1H, d, $J = 10.0$ Hz), 4.43 (1H, m),
3.91 (1H, dd, $J =12.0, 3.5$ Hz), 3.75 (1H, dd, $J =12.0, 4.5$
Hz), 2.61 (1H, m), 2.31 (1H, m), 2.05 (1H, brs).


(R)-5, 6-Dihydro-6-vinylpyran-2-one (78)

To a solution of oxalyl chloride (0.16 mL, 1.87 mmol) in dry CH$_2$Cl$_2$ (4 mL) at -78 °C, DMSO (0.28 mL, 4.0 mmol) was added dropwise with stirring under N$_2$ atmosphere. After 15 min. compound 98 (0.16 g, 1.25 mmol) dissolved in dry CH$_2$Cl$_2$ (3 mL) was added into the reaction mixture and subsequently after stirring for 0.5 h at -78 °C, Et$_3$N (0.9 mL, 6.25 mmol) was added and the mixture was stirred for another 0.5 h at 0 °C. The reaction mixture was quenched with saturated NH$_4$Cl solution (8 mL) at 0 °C and extracted with diethyl ether (2x10 mL). The combined organic extracts were washed with brine (2x10 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The aldehyde, thus obtained (0.142 g, 90%) was used directly after flash chromatography for the next reaction.

To a stirred suspension of triphenyl phosphonium methyl iodode (0.678 g, 1.68 mmol) in dry THF (3 mL) at -78 °C, n-BuLi in hexane (1.6 M, 0.98 mL, 1.57 mmol) was added dropwise under N$_2$ atmosphere and was allowed to keep at room temperature. After 45 min
the reaction mixture was again cooled to -78 °C and the aldehyde obtained above, dissolved in dry THF (3 mL) was added dropwise and stirred for another 45 min. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL) at 0 °C and extracted with diethyl ether (2x10 mL). The combined organic extracts were washed with brine (2x10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure (R)-5, 6-dihydro-6-vinylpyran-2-one 78 (0.104 g, 75%) as a pale yellow liquid.

**Molecular formula**: C₇H₈O₂

**Physical state**: pale yellow liquid

**Optical rotation**: [α]D²⁵ = +91.2 (c = 0.8, CHCl₃).

**Elemental analysis**: Found: C, 67.65; H, 6.52%.
Calcd: C, 67.73; H, 6.50%.

**IR spectrum**: v_max 1719, 1605, 1421, 1385, 1251 cm⁻¹.

**¹H-NMR spectrum**: (300 MHz, CDCl₃)
δ 6.89 (1H, m), 6.07 (1H, d, J = 9.0 Hz), 5.95 (1H, m), 5.41-5.29 (2H, m), 4.92 (1H, m), 2.51-2.38 (2H, m) (Fig. 1B. 29).

**¹³C-NMR spectrum**: (50 MHz, CDCl₃)
δ 163.9, 144.7, 134.8, 121.6, 117.9, 77.8, 29.1 (Fig. 1B. 30).

**ESI-Mass spectrum**: m/z 125 [M+H]⁺.

(R)-5, 6-Dihydro-6-((E, 4S, 6S)-4, 6-dihydroxy-8-phenyloct-1-enyl) pyran-2-one (20):

![Structure of 20]

A solution of compound 69 (0.399 g, 1.81 mmol) and compound 78 (0.045 g, 0.36 mmol) in dry CH₂Cl₂ (50 mL) was first bubbled with N₂ flow, after which Grubbs second generation catalyst (0.045 g, 0.054 mmol) was added at once and the resulting mixture was
heated under N$_2$ at 50 °C for 4 h. After cooling the solvent was evaporated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 5:5) afforded pure (R)-5, 6-dihydro-6-((E, 4S, 6S)-4, 6-dihydroxy-8-phenyloct-1-enyl) pyran-2-one 20 (0.052g, 66%) as a white solid.

<table>
<thead>
<tr>
<th>Molecular formula</th>
<th>C$<em>{19}$H$</em>{24}$O$_{4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>White solid</td>
</tr>
<tr>
<td>Melting point</td>
<td>110-113 °C</td>
</tr>
<tr>
<td>Optical rotation</td>
<td>[α]$_{D}^{25}$ = +62.1 (c = 0.6, CHCl$_3$)</td>
</tr>
</tbody>
</table>
| Elemental analysis      | Found: C, 72.18; H, 7.61%.  
Calcld: C, 72.13; H, 7.65% |
| $^1$H-NMR spectrum      | (300 MHz, CDCl$_3$)      |
|                         | δ 7.29-7.07 (5H, m), 6.84 (1H, m), 6.01 (1H, d, J = 9.0 Hz), 5.85 (1H, m), 5.64 (1H, dd, J = 15.5 Hz, 6.5 Hz), 4.86 (1H, m), 4.03-3.89 (2H, m), 2.81-2.57 (2H, m), 2.44-2.38 (2H, m), 2.28-2.23 (2H, m), 1.90-1.71 (2H, m), 1.62 (2H, t, J = 5.5 Hz) (Fig. 1B. 31). |
| $^{13}$C-NMR spectrum   | (75 MHz, CDCl$_3$)       |
|                         | δ 163.8, 144.7, 141.8, 131.1, 129.9, 128.4, 128.3, 125.8, 121.5, 77.7, 68.7, 68.2, 42.1, 40.3, 38.9, 38.1, 29.8 (Fig. 1B. 32). |
| ESI-Mass spectrum       | m/z 339 [M+Na]$^+$ (Fig. 1B. 33). |
Selected IR, $^1$H NMR, $^{13}$C NMR and Mass spectra of compounds described in this section
Fig. 1B. 1\textsuperscript{H} NMR Spectrum of compound 89

Fig. 1H. 1\textsuperscript{3}C NMR Spectrum of compound 89
Sample code:
Comments: KBr(DCM) Pellet
Analyzed by:
Date: Monday, May 31, 2010

Fig. 1B.3: IR Spectrum of compound 89

Fig. 1B.4: ESI-Mass Spectrum of compound 89
Fig. 1B. 5: $^1$H NMR Spectrum of compound 91

Fig. 1B. 6: $^{13}$C NMR Spectrum of compound 91
Fig. 1B. 8: $^1$H NMR Spectrum of compound 92

Fig. 1B. 7: ESI-Mass Spectrum of compound 91

Fig. 1B. 8: $^1$H NMR Spectrum of compound 92
Fig. IB. 9: 13C NMR Spectrum of compound 92

Fig. IB. 10: ESI-Mass Spectrum of compound 92
Fig. 1B. 11: HRESI-Mass Spectrum of compound 92
Fig. 1B. 12: IR spectrum of compound 69

Fig. 1B. 13: $^1$H NMR spectrum of compound 69
Fig. IB. 14: $^{13}$C NMR spectrum of compound 69

Fig. IB. 15: ESI-Mass spectrum of compound 69
Fig. 1B. 16: HRESI-Mass Spectrum of compound 69
Fig. 1B. 17: $^1$H NMR spectrum of compound 94

Fig. 1B. 18: $^{13}$C NMR spectrum of compound 94
Fig. 1B. 19: $^1$H NMR spectrum of compound 95

Fig. 1B. 20: $^{13}$C NMR spectrum of compound 95
Sample Name: BDS-DEXN [NEAT]
Sample Preparation:
Collection time: Mon Aug 23 11:13:19 2010 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4 cm⁻¹

Fig. 1B. 21: ESI-Mass spectrum of compound 95
Fig. 1B. 23: $^1$H NMR spectrum of compound 96

Fig. 1B. 24: $^{13}$C NMR Spectrum of compound 96
Fig. 1B. 25: ESI-Mass spectrum of compound 96

Fig. 1B. 26: $^1$H NMR spectrum of compound 97
Fig. IB. 27: $^{13}$CNMR spectrum of compound 97

Fig. IB. 28: ESI-Mass spectrum of compound 97
Fig. IB. 29: $^1$H NMR spectrum of compound 78

Fig. IB. 30: $^{13}$C NMR spectrum of compound 78
Fig. 1B. 31: $^1$H NMR spectrum of compound 20

Fig. 1B. 32: $^{13}$C NMR spectrum of compound 20
SECTION – C

Stereoselective total synthesis (6R)-6[(E, 4R, 6R)-4, 6-dihydro-10-phenyl-1-decenyl]-5, 6-dihydro-2H-2-pyrone
SYNTHESIS OF (6R)-6[(E, 4R, 6R)-4, 6-DIHYDRO-10-PHENYL-1-DECENYL]-5, 6-DIHYDRO-2H-2-PYRONE (21)

(6R)-6[(E, 4R, 6R)-4, 6-Dihydro-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrone 21 was isolated by Hostetmann et al. from *Ravensara crassifolia* along with compound 18. Because of its interesting structural similarity with strictifoliolene 20 we have synthesized 21 in an alternative approach. The previous synthetic approaches of compound 21 were outlined below.

PREVIOUS SYNTHETIC APPROACHES:
Radha Krishna’s approach:
This approach involves synthesis of fragment 105 from commercially available 5-phenylpentan-1-ol 99 using Jacobsen’s hydrolytic kinetic resolution as a key reaction (Scheme 26). Nucleophilic ring opening of epoxide 105 with chiral propargylic alcohol 40 and deprotection of TBS function yielded the triol compound 106 (Scheme 27). The compound 106 on protection with 2,2'-DMP and reduction with LiAlH₄ afforded compound 107, which on subsequent protection with TBDMSCl and deprotection of PMB function yielded primary alcohol 108. The alcohol 108 on oxidation and Wittig reaction produced Z-(α, β)-unsaturated ester 109 which was reacted with PTSA in benzene to afford the compound 21.
Reagents and conditions: (a) (i) (COCl)$_2$, DMSO, Et$_3$N, -78 °C, 92%; (ii) CH$_3$PPh$_3$Br', n-BuLi, 0 °C, 55%; (iii) m-CPBA, CH$_2$Cl$_2$, r.t., 95%; (b) (R,R)-I, 0.55 equiv H$_2$O, 42%; (c) (i) PhCOCl, Et$_3$N, CH$_2$Cl$_2$, r.t., (ii) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, r.t., (iii) K$_2$CO$_3$, MeOH, r.t.; (d) (i) vinylmagnesium bromide, Cul, THF, r.t., 71%; (ii) TBSCl, imidazole, CH$_2$Cl$_2$, r.t., 92%; (e) m-CPBA, CH$_2$Cl$_2$, r.t., 96%; (f) (S,S)-I, 0.55 equiv H$_2$O, 41%.

Scheme 27

Reagents and conditions: (a) (i) n-BuLi, BF$_3$.OEt$_2$, THF, -78 °C, 72%, (ii) TBAF, THF, r.t., 87%; (b) (i) 2,2-DMP, CH$_2$Cl$_2$, PTSA, r.t., 95%, (ii) LAH, THF, r.t., 85%; (c) (i) TBSCl, imidazole, CH$_2$Cl$_2$, r.t., 98%, (ii) DDQ, CH$_2$Cl$_2$:H$_2$O, r.t., 79%; (d) (i) IBX, DMSO, r.t., (ii) (F$_3$CCH$_2$O)$_2$POCH$_2$COOMe, KHMDS, 18-Crown-6, THF, 76% (over two steps); (e) PTSA, C$_6$H$_6$, r.t., 65%.
Sabitha's approach:

Sabitha et al.\(^{28}\) completed the total synthesis of compound 21 starting from 5-phenylpentanal 110 using Prins cyclization as a key reaction. The compound 110 was reacted with homoallylic alcohol 63 under Prins reaction conditions and produced cyclic ether 111 (Scheme 28). Deprotection of the benzyl group and iodination of the resulted alcohol with TPP/I\(_2\) afforded the compound 112, which on reduction with Zn dust produced compound 113. Cross metathesis reaction between the compounds 113 and 75 with Grubbs' II generation catalyst produced the compound 114. Protection of the alcoholic function with MOMCl and deprotection of the silyl function in compound 114 produced compound 115. Later, the compound 115 was oxidized to corresponding aldehyde with IBX and the aldehyde thus produced was transformed into Z-(\(\alpha, \beta\))-unsaturated ester 116. The ester 116 was reacted with CeCl\(_3\).7H\(_2\)O and produced the target compound 21.

---

**Scheme 28**

Reagents and conditions: (a) (i) TFA, CH\(_2\)Cl\(_2\), r.t., 4 h, later \(\text{K}_2\text{CO}_3\), MeOH, r.t., 1 h, 65%; (ii) MOMCl, Hunig's base, CH\(_2\)Cl\(_2\), 0 °C-rt., 4 h, 95%; (b) (i) Li in liq NH\(_3\), 91%; (ii) TPP, I\(_2\), imidazole, Et\(_2\)O/CH\(_2\)Cl\(_2\), (3:1), 0 °C-rt.; (c) Zn dust, EtOH, 0 °C, 2 h, 92%; (d) 75, Grubbs' II generation catalyst, CH\(_2\)Cl\(_2\), reflux, 70%; (e) (i) MOMCl, Hunig's base, CH\(_2\)Cl\(_2\), 4 h, 86%; (ii) PPTS, MeOH, 12 h, 81%; (f) (i) IBX, DMSO, CH\(_2\)Cl\(_2\), 80%, (ii) (F\(_3\)CCCH\(_2\))\(_2\)POCH\(_2\)COO\(_2\)Me, NaH, THF, -78 °C-rt., 1 h, 85%; (g) CeCl\(_3\).7H\(_2\)O, CH\(_3\)CN-MeOH (1:1), 12 h, rt, 73%.
PRESENT WORK

(6R)-6[(E,4R,6R)-4,6-Dihydro-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrone (21), a $\alpha,\beta$-unsaturated $\delta$-lactone was isolated by Hostetmann et al. from *Ravensara crassifolia*.\(^{21}\) The structure was proposed based on spectroscopic data (Fig. 2). The absolute stereochemistry of 21 was determined as (6R,4'R,6'R) by its first total synthesis.\(^{36}\)

Due to its interesting structural similarity with (+)-strictifolione 20 we have taken up the synthesis of compound 21 from the common intermediate 78. We have synthesized 21 from two fragments 123 and 78 by olefin cross-metathesis using Grubbs’ II generation catalyst. The fragment 123 was prepared by readily available 5-phenyl propan-3-ol 117 using Swern oxidation, Wittig homologation, Zn mediated Barbier-type allylation and Sharpless kinetic resolution as key steps. The fragment 78 was prepared from compound 94 which was prepared from L-ascorbic acid 93 (Scheme 19). The retro synthetic analysis for (6R)-6[(E,4R,6R)-4,6-dihydro-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrone 21 is represented in Scheme 29.
The synthesis of 21 has started from readily available 5-phenylpentan-3-ol 117. The compound 117 was converted into 5-phenylpentanal 118 under Swern reaction conditions (Scheme 30).

The aldehyde 118 was allowed to react with (carboethylmethylene) triphenyl phosphorane in CH₂Cl₂ at room temperature to afford the (E)-α, β-unsaturated ester in 86% yield (Scheme 31). The formation of the compound 119 was confirmed by its IR, ¹H NMR, ¹³C NMR and MS data. The ¹H NMR spectrum of compound 119 showed presence of two the olefin protons at δ 6.90 (1H, m) and δ 5.76 (1H, d, J = 14.0 Hz), ethyl group...
protons at $\delta$ 4.12 (2H, q, $J = 7.0$ Hz) and $\delta$ 1.26 (3H, t, $J = 7.0$ Hz) along with other required protons (Fig.1C. 34). In the $^{13}$C NMR spectrum of the compound (Fig.1C. 35), chemical shift value at $\delta$ 166.9 indicated the presence of carbonyl group in ester and oxygen attached carbon at $\delta$ 60.2.

![Scheme 31](image1)

The IR spectrum of 119 (Fig. 1C. 36) showed sharp band at 1719 cm$^{-1}$ indicating the presence of carbonyl functional group. The compound 119 was also confirmed by showing ESIMS signal at 233 [M+H]$^+$ (Fig. 1C. 37).

Treatment of compound 119 with DIBAL-H at -78 °C in toluene yielded aldehyde 120 in 78% yield (Scheme 32).30

![Scheme 32](image2)

The aldehyde 120 on Barbier allylation with allyl bromide, Zinc metal and aqueous ammonium chloride in THF at 0 °C produced (E)-10-phenyldeca-1, 5-dien-4-ol 121 in 92% yield (Scheme 33).31

![Scheme 33](image3)
The compound 121 was characterized from its $^1$H NMR, $^{13}$C NMR and ESIMS spectral data. $^1$H NMR showed the presence of five olefinic protons at $\delta$ 5.82-5.56 (2H, m), 5.43 (1H, dd, $J = 12.0, 7.0$ Hz), 5.12-5.04 (2H, m) and one oxygenated allyl proton at $\delta$ 4.03 (1H, q, $J = 7.0$ Hz) along with other required protons (Fig. 1C. 38). The $^{13}$C NMR spectrum showed four olefin carbons at $\delta$ 134.2, 132.2, 132.0, 118.1 and one oxygenated carbon at $\delta$ 71.9 (Fig. 1C. 39).

The allylic alcohol 121 on Sharpless kinetic resolution with Ti(O\textsuperscript{OPr})\textsubscript{4}, (-)-DIPT and TBHP in CH\textsubscript{2}Cl\textsubscript{2} at -20 °C produced the epoxy compound 122 in 46% yield (Scheme 34).\textsuperscript{32}

The allylic alcohol 121 on Sharpless kinetic resolution with Ti(O\textsuperscript{OPr})\textsubscript{4}, (-)-DIPT and TBHP in CH\textsubscript{2}Cl\textsubscript{2} at -20 °C produced the epoxy compound 122 in 46% yield (Scheme 34).\textsuperscript{32}

Formation of the compound 122 was confirmed by its IR, $^1$H NMR, $^{13}$C NMR, ESIMS and HRESIMS data. The $^1$H NMR spectrum showed presence of three olefin protons at $\delta$ 5.88-5.75 (1H, m) and 5.16-5.04 (2H, m), one homoallylic proton at $\delta$ 3.75 (1H, m), two epoxy and two benzylic protons at $\delta$ 2.70-2.58 (3H, m), 2.40-2.21 (2H, m) (Fig. 1C. 40). The $^{13}$C NMR spectrum showed presence of two olefin carbons at $\delta$ 133.5, 118.0 and three oxygenated carbons at $\delta$ 68.1, 60.1, 55.0 (Fig. 1C. 41). ESIMS of compound 122 showed a peak at $m/z$ 269 corresponds to [M+Na]$^+$ (Fig. 1C. 42). A peak at $m/z$ 269.1514 of [M+Na]$^+$ in HRESIMS confirmed the formation of epoxy compound 122 (Fig. 1C. 43). It showed optical rotation value of $[\alpha]_D^{25} = +4.8$ (c 1.0, CHCl\textsubscript{3}).

The epoxide 122 was then treated with Red-Al at 0 °C in dry THF and was allowed to stir for 3 h at room temperature to form the intermediate 123 in 74% yield (Scheme 35).
The formation of the diol compound 123 was confirmed by its IR, $^1$H NMR, $^{13}$C NMR, ESIMS and HRESIMS data. The IR spectrum of 123 (Fig. 1C. 44) showed a broad band at 3368 cm$^{-1}$ indicating the presence of hydroxyl group. The $^1$H NMR spectrum showed presence of three olefin protons at $\delta$ 5.75 (1H, m) and 5.15-5.03 (2H, m) and two protons that were attached to oxygen bearing carbon atoms at $\delta$ 3.98-3.81 (2H, m) along with other protons (Fig. 1C. 45). In $^{13}$C NMR spectrum of compound 123, the peaks at $\delta$ 134.9 and 118.2 represented two olefinic carbon atoms and the peaks at $\delta$ 69.1 and 68.0 confirmed the presence of two oxygenated carbon atoms (Fig. 1C. 46). A peak at $m/z$ 271 [M+Na]$^+$ in ESIMS spectrum (Fig. 1C. 47) and a peak at $m/z$ 271.1671 [M+Na]$^+$ in HRESIMS (Fig. 1C. 48) confirmed the formation of the product.

The optical rotation value of compound 123 $[\alpha]_D$ was $-5.75$ (c 1.0, CHCl$_3$).

Synthesis of the lactone fragment 78 from L-ascorbic acid 93 was depicted in Chapter-I, Section-B.

The olefin cross-metathesis of diol compound 123 with vinyl lactone 78 using Grubbs’ II generation catalyst$^{15}$ in CH$_2$Cl$_2$ yielded (6R)-6[(E,4R,6R)-4,6-dihydro-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyron 21 in 68% yield (Scheme 36).
The compound 21 was confirmed by its IR, $^1$H NMR, $^{13}$C NMR and ESIMS spectral data. The $^1$H NMR spectrum (Fig. 1C. 49) of compound 21 showed four olefinic protons at $\delta$ 6.82 (1H, m), 6.01 (1H, d, $J$ = 9.8 Hz), 5.85 (1H, m), 5.64 (1H, dd, $J$ = 6.0, 15.1 Hz) and three protons that are attached to carbons bearing oxygen atoms at $\delta$ 4.86 (1H, q, $J$=7.5, 14.3 Hz), 4.05-3.78 (2H, m) along with other required protons confirmed the formation of 21. A peak at $\delta$ 164.1 corresponds to lactone carbonyl carbon in $^{13}$C NMR spectrum (Fig. 1C. 50) of 21 along with peaks at $\delta$ 77.8, 69.2 and 68.2 corresponding to three oxygenated carbon atoms confirmed the formation of compound 21. The mass spectrum showed $m/z$ value at 367 [M+Na]$^+$ (Fig. 1C. 51).

The compound showed the optical rotation value of $[\alpha]_D^{25} = +50.1$ (c 0.25, CHCl$_3$). The spectral data of the compound 21 are in good agreement with the data reported earlier. 1
EXPERIMENTAL SECTION

5-phenylpentanal (118):

![5-phenylpentanal](image)

To a stirred solution of oxalyl chloride (2.61 mL, 30.48 mmol), in dry dichloromethane (70 mL), DMSO (5.4 mL, 76.2 mmol) was added at -78 °C and stirred at the same temperature for 0.5 h. A solution of 5-phenylpropan-1-ol 117 (2.5 g, 15.24 mmol) in dichloromethane (30 mL) was added at -78 °C and stirred for 1.5 h at the same temperature. Et$_3$N (10.63 mL, 76.2 mmol) was added at 0 °C and stirred for an additional 30 min. The reaction mixture was diluted with water (60 mL) and extracted with dichloromethane (2 x 75 mL). The combined organic layers were washed with brine (40 mL), dried (over Na$_2$SO$_4$) and concentrated to give 118 (2.04 g, 83%) as colorless liquid. The crude aldehyde thus obtained was utilized immediately for further step.

(E)-ethyl-7-phenylhept-2-enoate (119)

![E-ethyl-7-phenylhept-2-enoate](image)

To a stirred solution of phenyl pentanal 118 (2.0 g, 12.34 mmol) in dry CH$_2$Cl$_2$ (20 ml) ethyl (triphenyl phosphoranylidene) acetate (5.15 g, 14.81 mmol) was added and the mixture was stirred at ambient temperature for 8 h. It was then concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure (E)-ethyl-7-phenylhept-2-enoate 119 (2.46 g, 86%) as a colorless oil.
Molecular formula : C\textsubscript{15}H\textsubscript{20}O\textsubscript{2}

Physical state : Colorless oil.

Elemental analysis : Found: C, 77.51; H, 8.70%.
Calcd: C, 77.55; H, 8.68%.

IR spectrum : \(\nu_{\text{max}}\) 1720, 1655, 1592, 1496, 1368, 1263 cm\(^{-1}\) (Fig. 1C. 36).

\(^1\text{H}-\text{NMR spectrum}\) : (200 MHz, CDCl\textsubscript{3}):
\(\delta\) 7.28-7.07 (5H, m), 6.90 (1H, m), 5.76 (1H, d, \(J = 14.0\) Hz), 4.12 (2H, q, \(J = 7.0\) Hz), 2.61 (2H, t, \(J = 7.0\) Hz), 2.21 (2H, q, \(J = 7.0\) Hz), 1.71-1.60 (2H, m), 1.56-1.42 (2H, m), 1.26 (3H, t, \(J = 7.0\) Hz) (Fig. 1C. 34).

\(^{13}\text{C}-\text{NMR spectrum}\) : (50 MHz, CDCl\textsubscript{3})
\(\delta\) 166.9, 149.1, 142.2, 128.7, 128.6, 125.9, 121.2, 60.1, 36.0, 32.1, 31.0, 27.3, 14.0 (Fig. 1C. 35).

ESI-Mass spectrum : \(m/z\) 233 [M+H]\(^+\) (Fig. 1C. 37).

HRMS-spectrum : \(m/z\) 233.1539 (Calcd for C\textsubscript{15}H\textsubscript{21}O\textsubscript{2} \(m/z\) 205.1201).

\((E)-10\text{-phenyldeca-1, 5-dien-4-ol} (121)\)

\[
\begin{array}{c}
\text{OH} \\
\end{array}
\]

121

To a stirred solution of compound 119 (2.3 g, 9.91 mmol) in dry toluene (20 mL) at -78°C DIBAL-H (1.0M, 11.89mL, 11.89 mmol) was added dropwise and the mixture was stirred at that temperature for 30 min. The reaction mixture was then quenched by slow addition of dry methanol (10 mL) and was brought to room temperature. Saturated sodium potassium tartrate (10 mL) was added and stirred for 1 h. Then the reaction mixture was
diluted with water (10 mL) and extracted with diethyl ether (2x40 mL). The organic layer was separated and dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude aldehyde 120 (1.45g, 78%) thus obtained was used further without purification.

The crude aldehyde (1.45g, 7.73 mmol) was dissolved in THF (15 mL). Activated Zn (2.5g, 38.65 mmol) and allyl bromide (1.96 mL, 23.19 mmol) are added at 0 °C and stirred for 10 min. To this saturated NH₄Cl solution (10 mL) was added dropwise at 0 °C and the solution was stirred for 3 h at ambient temperature. Then the reaction mixture was extracted with EtOAc (2x15 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 3:7) afforded pure (E)-10-phenyldeca-1,5-dien-4-ol 121 (1.63 g, 92%) as a colorless liquid.

**Molecular formula**: C_{15}H_{22}O

**Physical state**: Colorless liquid

**Elemental analysis**: Found: C, 83.39; H, 9.69%. Calcd: C, 83.43; H, 9.63%.

**¹H-NMR spectrum**: (200 MHz, CDCl₃):

δ 7.28-7.07 (5H, m), 5.77 (1H, m), 5.60 (1H, m), 5.43 (1H, dd, J = 12.0, 7.0 Hz), 5.12-5.04 (2H, m), 4.03 (1H, q, J = 7.0 Hz), 2.60 (2H, t, J = 7.0 Hz), 2.30-2.21 (2H, m), 2.05 (2H, q, J = 7.0 Hz), 1.69-1.55 (2H, m), 1.50-1.36 (3H, m) (Fig. 1C. 38).

**¹³C-NMR spectrum**: (50 MHz, CDCl₃)

δ 142.8, 134.2, 132.2, 132.0, 128.2, 128.1, 125.3, 118.1, 71.9, 42.1, 36.0, 32.2, 31.0, 28.9 (Fig. 1C. 39).

**ESI-Mass spectrum**: m/z 231 [M+H]⁺.
(R)-1-((2R, 3R)-3-(4-phenylbutyl)oxiran-2-yl)but-3-en-1-ol (122)

To a suspension of powered molecular sieves (4 Å, 200 mg) in dry CH₂Cl₂ (15 mL) Ti(O\(^3\)Pr)\(_4\) (0.97 mL, 3.26 mmol) and (-)-DIPT (0.81 mL, 3.91 mmol) were added sequentially at -20 °C. After stirring for 30 min allyl alcohol 121 (1.5 g, 6.52 mmol) in dry CH₂Cl₂ (15 mL) was added and stirring was continued for another 30 min at the same temperature. Then TBHP (4M, 0.78 mL, 3.13 mmol) was added and after stirring for another 5 h at the same temperature, the reaction mixture was quenched by addition of water (15 mL). It was allowed remain at room temperature by stirring for 30 min. After re-cooling at 0 °C, an aqueous solution of NaOH (30% w/v, 10 mL saturated with brine) was added to it and the mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the residue was extracted with ether (3 x 40 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 4:6) afforded pure (R)-1-((2R, 3R)-3-(4-phenylbutyl)oxiran-2-yl)but-3-en-1-ol 122 (0.73 g, 46%) as a colorless oil.

Molecular formula : C\(_{16}\)H\(_{22}\)O\(_2\)
Physical state : Colorless liquid
Optical Rotaion : \([\alpha]_{D}^{25} = +4.8\) (c 1.0, CHCl₃)
Elemental analysis : Found: C, 78.05; H, 8.98%.
Calcd: C, 78.01; H, 9.00%.
IR spectrum : \(\nu_{\text{max}}\) 3423, 1642, 1453, 1200 cm\(^{-1}\).
\(^1\)H-NMR spectrum : (200 MHz, CDCl₃)
\(\delta\) 7.28-7.09 (5H, m), 5.81 (1H, m), 5.16-5.04 (2H, m), 3.75 (1H, m), 2.70-2.58 (3H, m), 2.40-2.21 (2H, m), 1.81(1H, brs), 1.71-1.61 (2H, m), 1.60-1.41 (4H, m) (Fig. 1C. 40).

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To a stirred solution of 122 (0.650 g, 2.64 mmol) in dry THF (15 mL) under N₂ atmosphere at 0 °C was added Red-Al solution in toluene (65% w/v, 2.46 mL, 7.92 mmol) and the reaction mixture was stirred at room temperature for 3 h. Then it was quenched with saturated NH₄Cl solution (15 mL) and then extracted with EtOAc (2x30 mL). The combined organic extracts were washed with brine (2x15 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 5:5) afforded pure (4R, 6R)-10-phenyldec-1-ene-4,6-diol 123 (0.48 g, 74%) as a colorless oil.

**Molecular formula**: C₁₆H₂₄O₂

**Physical state**: Colorless oil

**Optical rotation**: [α]D²⁵ = -5.75 (c 1.0, CHCl₃).

**Elemental analysis**: Found: C, 77.41; H, 9.71%.
Calcd: C, 77.38; H, 9.74%.

**IR spectrum**: νmax 3369, 1726, 1641, 1603, 1496, 1454, 1376 cm⁻¹. (Fig. 1C. 44).

**¹H-NMR spectrum**: (200 MHz, CDCl₃)
Stereoselective total synthesis (6R)-6[(E, 4R, 6R)-4, 6-dihydro-10-phenyl-1-decenyl]-5, 6-dihydro-2H-2-pyrene

δ 7.28-7.05 (5H, m), 5.75 (1H, m), 5.15-5.03 (2H, m), 3.98-3.81 (2H, m), 2.60 (2H, t, J = 7.0 Hz), 2.50 (1H, brs), 2.21 (2H, t, J = 7.0 Hz), 1.67-1.25 (9H, m) (Fig. 1C. 45).

\(^{13}\)C-NMR spectrum : (50 MHz, CDCl\(_3\))

δ 142.7, 134.9, 128.2, 128.1, 125.9, 118.2, 118.1, 69.1, 68.0, 42.0, 41.9, 37.1, 36.0, 31.4, 25.5 (Fig. 1C. 46).

ESI-Mass spectrum : \(m/z\) 271 [M+Na]\(^{+}\) (Fig. 1C. 47).

HRESIMS : \(m/z\) 271.1671 (Calcd for C\(_{16}\)H\(_{24}\)O\(_{2}\)Na: \(m/z\) 271.1669 [M+Na]\(^{+}\)) (Fig. 1C. 48).

(6R)-6[(E,4R,6R)-4, 6-dihydro-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrene (21):

A solution of compound 123 (0.449 g, 1.81 mmol) and compound 78 (0.045 g, 0.36 mmol) in dry CH\(_2\)Cl\(_2\) (50 mL) was first bubbled with N\(_2\) flow, after which Grubbs second generation catalyst (0.045 g, 0.054 mmol) was added at once and the resulting mixture was heated under N\(_2\) at 50 °C for 4 h. After cooling the solvent was evaporated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 5:5) afforded pure (R)-5, 6-dihydro-6-((E, 4S, 6S)-4, 6-dihydroxy-8-phenyloct-1-enyl) pyran-2-one 21 (0.052g, 66%) as a white solid.

Molecular formula : C\(_{21}\)H\(_{28}\)O\(_{4}\)

Physical state : White solid

Melting point : 64-66 °C

Elemental analysis : Found: C, 73.26; H, 8.14%.

Calcd: C, 73.23; H, 8.19%.
**Optical rotation**  
$[\alpha]_D^{25} = +50.1 \ (c \ 0.25, \ CHCl_3)$.

**$^1$H-NMR spectrum**  
$(300 \ MHz, \ CDCl_3)$  
$\delta$ 7.27-7.01 (5H, m), 6.82 (1H, m), 6.01 (1H, d, $J = 9.8 \ Hz$), 5.85 (1H, m), 5.64 (1H, dd, $J = 15.1, 6.0 \ Hz$), 4.86 (1H, q, $J = 14.3, 7.5 \ Hz$), 4.05-3.78 (2H, m), 3.0 (2H, brs), 2.60 (2H, t, $J = 7.5 \ Hz$), 2.45-2.36 (2H, m), 2.29-2.18 (2H, m), 2.10-1.85 (2H, m), 1.68-1.36 (6H, m) (Fig. 1C. 49).

**$^{13}$C-NMR spectrum**  
$(75 \ MHz, \ CDCl_3)$  
$\delta$ 164.1, 144.7, 142.4, 131.4, 129.7, 128.3, 128.2, 125.6, 121.4, 77.8, 69.2, 68.2, 42.0, 40.3, 37.3, 35.8, 31.3, 29.7, 25.4 (Fig. 1C. 50).

**ESI-Mass spectrum**  
$m/z$ 367 [M+Na]$^+$. (Fig. 1C. 51).
Selected IR, $^1$H NMR, $^{13}$C NMR and Mass spectra
of compounds described in this section
Fig. 1C. 34: ¹H NMR spectrum of compound 119

Fig. 1C. 35: ¹³C NMR spectrum of compound 119
Sample Name: BDS-ESTER (NEAT)
Sample Preparation:
Collection time: Fri Mar 26 11:26:01 2010 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4 cm⁻¹

Fig. 1C. 36: IR spectrum of compound 119

Fig. 1C. 37: ESI-Mass spectrum of compound 119
Fig. 1C. 38: $^1$H NMR spectrum of compound 121

Fig. 1C. 39: $^{13}$C NMR spectrum of compound 121
Fig. 1C. 40: $^1$H NMR spectrum of compound 122

Fig. 1C. 41: $^{13}$C NMR spectrum of compound 122
Sample code:

Comments: KBr(DCM) Pellet

Analyzed by:

Date: Monday, May 31, 2010

Fig. 1C. 44: IR spectrum of compound 123

Fig. 1C. 45: 1H NMR spectrum of compound 123
Fig. 1C. 46: $^{13}$C NMR spectrum of compound 123

Fig. 1C. 47: ESI-Mass spectrum of compound 123
Fig. 1C. 48: HRESI-Mass spectrum of compound 123
Fig. 1C. 49: $^1$H NMR spectrum of compound 21

Fig. 1C. 50: $^{13}$C NMR spectrum of compound 21
Fig. IC. S1: ESI-Mass spectrum of compound 21
REFERENCES


