Chapter II, Section A, Introduction

\[ \text{THPO} \xrightarrow{n-\text{BuLi, dry THF, -78 °C to 10 °C}} \text{THPO} \xrightarrow{-\text{CICOOMe}} \text{THPO} \xrightarrow{\text{Me}_2\text{CuLi, dry THF, -78 °C, 90%}} \]

\[ \text{DIBAL, dry toluene, 0 °C, 84%} \]

\[ p-\text{iiodophenol, DEAD, PPh}_3, \text{ dry toluene, 90%} \]

\[ 1) \text{50% aq. AcOH, 40 °C} \]

\[ 2) \text{Acryloyl chloride, Et}_3\text{N, CH}_2\text{Cl}_2, 91\% \]

Scheme 4
Present Work

Pondaplin 1, a novel cyclic prenylated phenylpropanoid was recently isolated from *Annona glabra* L. (Annonaceae). It shows selective cytotoxicities against six human solid tumor cell lines and particularly potent activity against MCF-7 breast and PC-3 prostate cancer cell lines. Many related phenylpropanoids exhibit a broad range of biological activities such as antimicrobial, anticancer and hypotensive properties. Moreover, phenyl propanoid derivatives are known to inhibit enzymes such as cAMP phosphodiesterase and prostaglandin synthetase.\(^8\)\(^{-10}\)

\[\text{Retro synthetic route for Pondaplin}\]

Synthetic strategy for Pondaplin is outlined below in Fig. 4.

We chose a strategy for the synthesis of Pondaplin 1 starting from \(p\)-hydroxybenzaldehyde. Propargyl alcohol was protected as trityl ether 21 by treating with triphenylmethyl chloride and triethyl amine. The compound 21 was subjected to methoxycarbonylation to afford 22 in 86% yield. The conjugate addition of lithium dimethylcuprate to 22 in dry THF at -100 to -85 °C provided Z-ester 23 as the sole product in 90% yield. The structure of 23 was characterized from its PMR, IR and mass spectral properties. The PMR of compound 23 clearly showed a singlet at δ 5.59 for olefinic hydrogen (Scheme 5). The reduction of 23 with LAH/AlCl\(_3\) in dry ether at 0 °C afforded the corresponding Z-allylic alcohol 24 in 74% yield. Standard bromination conditions furnished bromide 25 in 62% yield.\(^13\)
Bromide 25 was used in an alkylation reaction with \( p \)-hydroxybenzaldehyde 26 to give \( O \)-alkylated compound 27 in 63% yield. Modified Wadsworth-Emmons condensation\textsuperscript{14} on 4-substituted benzaldehyde 27 using \( \text{NaH}, \text{bis(2,2,2-trifluoroethyl)}(\text{methoxycarbonyl)methyl)phosphonate in THF at -78 °C afforded Z-ethyl ester 28 in 88% yield. The PMR of compound 28 clearly showed peaks at \( \delta \) 6.83 (d, \( J = 12.6 \text{ Hz}, 1\text{H} \)), \( \delta \) 5.80 (d, 1H, \( J = 12.6 \text{ Hz} \)). Removal of the trityl group to afforded...
Z-hydroxy ester 29 followed by saponification to give the corresponding Z-hydroxy acid 30 in 99% yield. The olefinic protons in 28-30 (H-7 and H-8) showed coupling constants of 12.6 Hz. Subjecting hydroxy acid 30 to intramolecular Keck coupling conditions in the presence of 1,3-dicyclohexylcarbodiimide and DMAP in CH₂Cl₂ at 0 °C did not give the expected product 1, instead a dimer 15 was formed. The PMR spectrum of the dimer 15 showed the olefinic protons (H-7 and H-8) at δ 6.50 (J = 14.8 Hz) and δ 7.60 (J = 15.6 Hz) respectively indicating a trans double bond. Our ¹H NMR data matches the dimer reported by Joullie et al.

Scheme 6

Since this approach gave unsatisfactory results in the final step, we next investigated an alternative strategy as shown in Scheme 6. Trityl ether 27 was deprotected to give alcohol 31, which was acylated with bromoacetyl bromide to give the bromo ester 32 in nearly quantitative yield. Further treatment of bromide 32 with P(OEt)₃ and an in situ Horner-Wadsworth-Emmons reaction in the presence of NaH in dry THF at reflux conditions did not give the required product 1 but instead gave a trans α,β-unsaturated ester 33. The coupling constants of the newly formed double bond in compound 33 at 15.8 Hz (H-7 and H-8), indicating the trans nature of the olefinic double bond. PMR, CMR and mass spectroscopy supported the assigned structure. Yet another alternative approach was employed on bromide 20, but treatment with Samarium(II) iodide in dry THF failed to afford the natural product 1.
We considered that the double bond reduction of the \( \alpha,\beta \)-unsaturated ester might favor the cyclization. To examine this, the hydroxy ester 36 was prepared from \( p \)-hydroxybenzaldehyde 26 in two steps. The two carbon Wittig olefination, followed by \( \alpha,\beta \) unsaturated ester double bond reduced with \( \text{Mg}/\text{MeOH} \) afforded 36 in 90% overall yield for the two steps. The structure of 36 was characterized from its PMR, IR and mass spectral properties. The PMR of compound 36 clearly showed two triplets at \( \delta \) 2.82 and \( \delta \) 2.53 indicating the reduction of ester double bond. O-Alkylation of 36 with \( \text{NaH} \) and bromide compound 25 afforded compound 37. Deprotection of trityl group was achieved using PPTS in methanol to afford allyl alcohol 38 in 67% yield. Ester hydrolysis of 38 followed by intramolecular cyclization using Keck coupling conditions allowed macrolactonization to give the saturated analogue 40 of pondaplin in 55% yield (Scheme 7). The structure of saturated analogue 40 was characterized from its PMR, CMR, IR and mass spectral properties.

\[
\text{OHC-} \quad \begin{array}{c}
\text{26} \\
\text{Ph,P=CHCOOME} \\
\text{dry MeOH, 98%}
\end{array}
\quad \text{Mg/ dry MeOH} \quad \text{35} \quad \text{90%}
\]

\[
\begin{array}{c}
\text{OH} \\
\text{36} \\
\text{NaH, dry THF, (25), 60%}
\end{array}
\quad \text{PPTS, MeOH, rt., 67%}
\]

\[
\begin{array}{c}
\text{OMe} \\
\text{38} \\
\text{sq. LiOH, MeOH, rt., 96%}
\end{array}
\quad \text{40}
\]

\[
\text{DCC, DMAP, dryCH}_2\text{Cl}_2, 55\%
\]

\textit{Scheme 7}
Another pondaplin analogue 45 was synthesized from saturated ester 36. Compound 36 was subjected to alkylation with NaH and prenyl bromide to afford O-prenyl ester 41 in 92% yield. Allylic oxidation of 41 was achieved using SeO₂ to afford E-aldehyde 42. The structure of compound 42 was characterized from its PMR, IR and mass spectral properties. The PMR of compound 42 clearly showed a singlet at δ 9.47. The aldehyde was reduced with NaBH₄ in MeOH to give the corresponding E-allylic alcohol 43 in 83% yield (Scheme 8). Hydrolysis of compound 43 to afford hydroxy acid 44 followed by intramolecular cyclization with DCC/DMAP in CH₂Cl₂ at 0 °C gave the saturated analogue 45. The structure of saturated analogue 45 was characterized from its PMR, CMR, IR and mass spectral properties.

Scheme 8
In conclusion our efforts to synthesize pondaplin 1 ended up in the preparation of its analogues as illustrated briefly in the following figure.

Figure 5
EXPERIMENTAL

2-Propynyl trityl ether (21)

To a stirred solution of triphenylmethylchloride (49.2 g, 176.7 mmol) in 100 mL dry CH₂Cl₂ were added at 0 °C triethylamine (26.8 mL, 192.8 mmol) and 2-propyn-1-ol (9.0 g, 160.7 mmol). After 2 hours stirring at room temperature, water was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were washed with saturated brine solution, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with 15:1 and then 12:1 hexane-ethylacetate to afford 21 as colorless crystals (43.1 g, 90%).

¹H NMR (CDCl₃, 300 MHz): δ 7.46 - 7.37 and 7.19 - 7.30 (each m, 6H and 9H, Ar-H), 3.76 (s, 2H), 1.42 (s, 1H).

Methyl 4-(trityloxy)-2-butynoate (22)

To a suspension of Mg (3.6 g, 151 mmol) in dry THF (50 mL) ethyl bromide (11.7 mL, 151 mmol) was added drop wise under nitrogen atmosphere at 0 °C. It is allowed to stir for 30 minutes at room temperature. To this Grignard reagent, compound 21 (30.0 g, 100.6 mmol) in dry THF (75 mL) was added at 0 °C. After stirring for 2 hours, methylchloroformate (9.3 mL, 120.7 mmol) in THF was added to the reaction mixture at 0 °C. The reaction mixture was stirred for another 5-6 hours. The reaction mixture was quenched with saturated NH₄Cl solution and filtered over celite. The filtrate was washed with saturated brine solution and dried over anhydrous Na₂SO₄. The organic layer was concentrated to give crude material, which after column chromatography provided the pure product 22 (30.8 g, 86%) as a liquid.

¹H NMR (CDCl₃, 300 MHz): δ 7.46 - 7.37 and 7.19 - 7.30 (each m, 6H and 9H, Ar-H), 3.89 (s, 2H), 3.78 (s, 3H).

Methyl (Z)-3-methyl-4-(trityloxy)-3-butynoate (23)

To a suspension of Cul (20.9 g, 105.3 mmol) in dry THF was added at 0 °C 1 M MeLi in ether (105.3 mL, 105.3 mmol) and the mixture was stirred at 0 °C for 45 minutes. To this was added at -100 to -85 °C a precooled solution of 22 in dry ether; the mixture was stirred at -90 °C for 3 hours. Saturated aqueous NH₄Cl was added and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated aqueous NH₄Cl,
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saturated brine solution, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue 23 (18.8 g, 90%) was used without any purification.

$^1$H NMR (CDCl$_3$, 200 MHz) : δ 7.46 - 7.37 and 7.19 - 7.30 (each m, 6H and 9H, Ar-H), 5.59 (s, 1H), 4.32 (s, 2H), 3.54 (s, 3H), 2.09 (s, 3H).

(Z)-3-Methyl-4-(trityloxy)-2-buten-1-ol (24)

To a stirred suspension of LiAlH$_4$ (2.9 g, 80.6 mmol) in dry ether (40 mL) at 0 °C was added drop wise a solution of AlCl$_3$ (3.5 g, 26.8 mmol) in dry ether (20 mL) and allowed it to stir for 30 minutes. To this was added at 0 °C a solution of 23 (20.0 g, 152 mmol) in dry ether (50 mL). The reaction mixture was allowed to warm at room temperature and stirred for 4 hours. It was then cooled to 0 °C, diluted with ether and quenched with drop wise addition of saturated aqueous Na$_2$SO$_4$ (20 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na$_2$SO$_4$. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography to afford the compound 24 (13.6 g, 74%) as a viscous liquid.

$^1$H NMR (CDCl$_3$, 200MHz): δ 7.46 - 7.37 and 7.19 - 7.30 (each m, 6H and 9H, Ar-H), 5.55 (t, $J = 6.8$ Hz, 1H), 3.92 (d, $J = 6.8$ Hz, 2H), 3.62 (s, 2H), 1.87 (s, 3H).

(Z)-4-Bromo-2-methyl-2-butenyl trityl ether (25)

To a stirred solution of 24 (10.0 g, 29.0 mmol) in dry acetonitrile, were added at room temperature LiBr (15.1 g, 174.4 mmol) and triethylamine (8.5 mL, 60.9 mmol). To this was added at 0 °C methanesulfonyl chloride (3.1 mL, 58.0 mmol), this mixture was then stirred at 0 °C for 4 hours. The reaction mixture was poured into water; this mixture was extracted with hexane and the extracts were washed with saturated brine solution, dried over anhydrous Na$_2$SO$_4$, and concentrated. The residue was chromatographed on silica gel with 15:1 and then 12:1 hexane-ethylacetate to afford 25 (7.3 g, 62%) as colorless syrup.

$^1$H NMR (CDCl$_3$, 200Hz): δ 7.46 - 7.37 and 7.19 - 7.30 (each m, 6H and 9H, Ar-H), 5.60 (t, $J = 7.6$ Hz, 1H), 3.79 (d, $J = 7.6$ Hz, 2H), 3.62 (s, 2H), 1.88 (s, 3H).
4-[[Z]-3-Methyl-4-(trityloxy)-2-butenylox]benzaldehyde (27)

To a stirred suspension of freshly activated NaH (590 mg, 24.5 mmol) in dry THF (10 mL) under N₂ atmosphere was added p-hydroxy benzaldehyde 26 (1.5 g, 12.29 mmol) in dry THF (10 mL) in a dropwise manner at 0 °C. After stirring for 30 minutes at 0 °C, compound 25 (5.9 g, 14.7 mmol) in THF was added dropwise. The reaction mixture was stirred for 6 hours at 0 °C and quenched with saturated KBr solution. The layers were separated and aqueous layer extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with saturated brine solution and then dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford 27 (3.4 g, 63% yield) as viscous liquid.

\[ ^1H \text{NMR (CDCl}_3, 200\text{Hz)} \]
<table>
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<tr>
<th>Chemical Shifts</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Protons</th>
<th>Assignments</th>
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<tr>
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<td>J = 8.9 Hz</td>
<td>2H</td>
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<td>6H and 9H</td>
<td>Ar-H</td>
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<tr>
<td>1.88 (s)</td>
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<td>3H</td>
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Methyl-(Z)-3-[[Z]-3-methyl-4-(trityloxy)-2-butenyloxy]phenyl-2-propenoate (28)

To a stirred suspension of NaH (120.5 mg, 5.02 mmol) in dry THF (5 mL) at 0 °C under nitrogen was added bis(2,2,2-trifluoroethyl)(methoxy)carbonylmethyl)-phosphonate (730 mg, 4.01 mmol) in dry THF (10 mL). After the mixture was stirred for 30 minutes at 0 °C, the reaction mixture was cooled to -78 °C and then a solution of aldehyde 27 (1.5 g, 3.34 mmol) in dry THF (5 mL) was added dropwise. After stirring for 1 hour, the reaction mixture was diluted with 5 mL of Et₂O and quenched by the slow addition of 4 mL of H₂O. The layers were separated and the aqueous phase was extracted with two 10 mL portions of Et₂O. The organic extract was washed with brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give α, β-unsaturated ester 28 (1.4 g, 88%) as a viscous liquid.

\[ ^1H \text{NMR (CDCl}_3, 200\text{MHz)} \]
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<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Protons</th>
<th>Assignments</th>
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<td>J = 8.9 Hz</td>
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<tr>
<td>7.46 - 7.37</td>
<td>(each m)</td>
<td>6H and 9H</td>
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<tr>
<td>6.72 (d)</td>
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<tr>
<td>5.80 (d)</td>
<td>J = 12.6 Hz</td>
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<tr>
<td>5.55 (t)</td>
<td></td>
<td></td>
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</tbody>
</table>
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\[ J = 7.6 \text{ Hz}, 1\text{H}, \ \text{4.38 (d, J = 7.6 Hz, 2H), 3.72 (s, 3H)}, \ \text{3.63 (s, 2H), 1.88 (s, 3H)}. \]

\textbf{Methyl-(Z)-3-[(Z)-3-methyl-4-hydroxy-3-methyl-2-butenyl]oxy}phenyl-2-propenoate (29)

To a stirred solution of 28 (1.0 g, 1.98 mmol) in methanol (10 mL) was added catalytic amount of PPTS. The reaction mixture was stirred at room temperature for about 2 hours. Methanol was removed under reduced pressure. The crude residue was purified by silica gel column chromatography to afford 29 (348 mg, 67%) as a viscous liquid.

\[ ^1\text{H NMR (CDCl}_3, 300\text{MHz)}: \delta 7.78 (d, J = 8.9 \text{ Hz, 2H, Ar-H}), 6.83 (d, J = 12.6 \text{ Hz, 1H}), 6.72 (d, J = 8.9 \text{ Hz, 2H, Ar-H}), 5.80 (d, J = 12.6 \text{ Hz, 1H}), 5.55 (t, J = 7.6 \text{ Hz, 1H}), 4.58 (d, J = 7.6 \text{ Hz, 2H}), 4.18 (s, 2H), 3.72 (s, 3H), 1.88 (s, 3H). \]

\textbf{(Z)-3-[(Z)-4-Hydroxy-3-methyl-2-butenyl]oxy}phenyl-2-propenoate (30)

To a stirred solution of 29 (300 mg, 1.14 mmol) in methanol (3 mL) and water (2 mL) was added LiOH.H\textsubscript{2}O (82.4 mg, 3.43 mmol) at room temperature. After stirring for 6 hours, the mixture was acidified by addition of 0.5 M solution of HCl to pH 3 and then extracted with ethylacetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give \( \alpha, \beta \)-unsaturated acid 30 (281 mg, 99%) as a colourless solid.

\[ ^1\text{H NMR (CDCl}_3, 200\text{MHz)}: \delta 7.66 (d, J = 8.9 \text{ Hz, 2H, Ar-H}), 6.92 (d, J = 12.6 \text{ Hz, 1H}), 6.82 (d, J = 8.9 \text{ Hz, 2H, Ar-H}), 5.82 (d, 1H, J = 12.6 \text{ Hz}), 5.65 (t, J = 7.6 \text{ Hz, 1H}), 4.58 (d, J = 7.6 \text{ Hz, 2H}), 4.18 (s, 2H), 1.88 (s, 3H). \]

\textbf{Dimer (15)}

To a stirred solution of \( N, N' \)-dicyclohexylcarbodiimide (DCC) (166 mg, 0.8 mmol) and \( N,N' \)-dimethylaminopyridine (DMAP) (97 mg, 0.8 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} at 0 \text{°C} was added a solution of 30 (200 mg, 0.8 mmol) in CH\textsubscript{2}Cl\textsubscript{2} slowly and the mixture allowed to stir at room temperature for 12 hours. Precipitated urea was then filtered off and the filtrate was washed twice with 0.5 N HCl and with saturated
NaHCO₃ solution and dried over anhydrous Na₂SO₄. The solvent was removed by evaporation and the residue was purified by silica gel column chromatography (hexane/ethylacetate, 8:2) to afford dimer 15 (102 g, 55%) as colorless crystals.

\[ ^{1}H \text{ NMR (200 MHz, CDCl}_3 \] : δ 7.60 (d, J = 15.6 Hz, 1H, H-7), 7.39 (d, J = 8.9 Hz, 2H, ArH), 6.8 (d, J = 8.8 Hz, 2H, ArH), 6.5 (d, J = 14.8 Hz, 1H, H-8), 5.62 (t, J = 6.8 Hz, 1H), 4.6 (brs, 4H, -OCH₂), 1.8 (s, 3H, -CH₃).

Melting Point : 142-146 °C.

4-[(Z)-4-Hydroxy-3-methyl-2-butenyloxy]benzaldehyde (31)

Employing same procedure as mentioned for 29, compound 31 was made from 27 (2.0 g, 4.46 mmol) in 90% yield (825 mg) as a viscous liquid.

\[ ^{1}H \text{ NMR (200 MHz, CDCl}_3 \] : δ 9.84 (s, 1H), 7.78 (d, J = 8.9 Hz, 2H, Ar-H), 6.72 (d, J = 8.9 Hz, 2H, Ar-H), 5.55 (t, J = 7.6 Hz, 1H), 4.58 (d, J = 7.6 Hz, 2H), 4.18 (s, 2H), 3.72 (s, 3H), 1.88 (s, 3H).

(Z)-4-(4-Formylphenoxy)-2-methyl-2-butenyl bromoacetate (32)

To a stirred solution of 31 (500 mg, 2.42 mmol) in dry CH₂Cl₂ were added at 0 °C 2,6-lutidine (0.56 mL, 4.84 mmol). To this was added at 0 °C bromoacetyl-bromide (0.31 mL, 3.63 mmol); this mixture was then stirred at 0 °C for 4 hours. The reaction mixture was poured into water; this mixture was extracted with CH₂Cl₂, and the extracts were washed with saturated NaHCO₃ solution, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was chromatographed on silica gel with 15:1 and then 12:1 hexane-ethylacetate to afford 32 (780 mg, 99%) as colorless liquid.

\[ ^{1}H \text{ NMR (200 MHz, CDCl}_3 \] : δ 9.89 (s, 1H, -CHO), 7.82 (d, J = 8.9 Hz, 2H, ArH), 6.98 (d, J = 8.9 Hz, 2H, ArH), 5.72 (t, J = 6.8 Hz, 1H), 4.78 (s, 2H), 4.72 (d, J = 6.7 Hz, 2H), 3.81 (s, 2H), 1.88 (s, 3H).

Ethyl(E)-3-(4-[(Z)-4-hydroxy-3-methyl-2-butenyloxy]phenyl)-2-propenoate (33)

To a stirred suspension of freshly activated NaH (30 mg, 1.21 mmol) in dry THF (5 mL) under nitrogen atmosphere was added 32 (500 mg, 6.09 mmol) in dry THF (5 mL) in a dropwise manner at 0 °C. After stirring for 30 minutes at 0 °C,
triethylphosphine \([\text{P(OEt)}_3]\) (101 mg, 6.09 mmol) was added dropwise. The resulting mixture was vigorously refluxed for 4 hours and then quenched with saturated aqueous \(\text{NH}_4\text{Cl}\). The layers were separated and aqueous layer extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine solution and then dried over anhydrous \(\text{Na}_2\text{SO}_4\). Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford 33 (104 mg, 62% yield) as colorless crystals.

\[ ^1\text{H NMR (200 MHz, CDCl}_3\text{)}: \delta 7.60 (d, J = 15.8 \text{ Hz}, 1\text{H}), 7.42 (d, J = 8.7 \text{ Hz}, 2\text{H}, \text{ArH}), 6.80 (d, J = 8.7 \text{ Hz}, 2\text{H}, \text{ArH}), 6.25 (d, J = 15.8 \text{ Hz}, 1\text{H}), 5.6 (t, J = 6.8 \text{ Hz}, 1\text{H}, \text{olefinic}), 4.60 (d, J = 6.7 \text{ Hz}, 2\text{H}), 4.26 (q, J = 7.1, 14.2 \text{ Hz}, 2\text{H}), 4.21 (s, 2\text{H}), 1.88 (s, 3\text{H}), 1.33 (t, J = 7.1 \text{ Hz}, 3\text{H}). \]

\[ ^13\text{C NMR (75 MHz, CDCl}_3\text{)}: \delta 167.29, 160.3, 144.1, 140.9, 129.6, 127.4, 122.2, 115.9, 115.0, 64.0, 61.9, 60.3, 21.3, 14.3. \]

IR (KBr) : 1709 cm\(^{-1}\).

FAB Mass : \(m/z\) 277 (M+1).

Melting Point : 67-70 °C.

**Ethyl(E)-3-(4-hydroxy phenyl)-2-propenoate (35)**

To a solution of \(p\)-hydroxy benzaldehyde 26 (10.0 g, 81.9 mmol) in 30 mL dry methanol were added ethoxycarbonyl methylene triphenyl phosphine (34.2 g, 98.3 mmol) at 0 °C and allow it to stir for 5 hours at room temperature. Methanol solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford 35 (14.2 g, 98% yield) as colorless liquid.

\[ ^1\text{H NMR (200 MHz, CDCl}_3\text{)}: \delta 7.60 (d, J = 15.8 \text{ Hz}, 1\text{H}), 7.42 (d, J = 8.7 \text{ Hz}, 2\text{H}, \text{ArH}), 6.80 (d, J = 8.7 \text{ Hz}, 2\text{H}, \text{ArH}), 6.25 (d, J = 15.8 \text{ Hz}, 1\text{H}, \text{ArH}), 4.26 (q, J = 7.1, 14.2 \text{ Hz}, 2\text{H}), 1.33 (t, J = 7.1 \text{ Hz}, 3\text{H}). \]

**Methyl-3-(4-hydroxy phenyl)propanoate (36)**

To a solution of 35 (10.0 g, 56.17 mmol) in 50 mL methanol were added Mg turnings (13.0 g, 562.7 mmol) through reflux condenser. After short time an exothermic reaction occurred, this results a short time boiling of the reaction mixture. After all the Mg had been consumed, the mixture was cooled to room temperature.
and then diluted with CH₂Cl₂ (50 mL) and poured into ice-cold brine solution (50 mL). The organic layer was separated and dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford 36 (9.1 g, 90%) as colourless liquid.

**¹H NMR (200 MHz, CDCl₃)**

\[ \delta 7.05 \text{ (d, } J = 8.9 \text{ Hz, 2H, ArH)} , \]
\[ 6.68 \text{ (d, } J = 8.9 \text{ Hz, 2H, ArH)} , \]
\[ 3.65 \text{ (s, 3H)} , \]
\[ 2.85 \text{ (t, } J = 8.3 \text{ Hz, 2H)} , \]
\[ 2.56 \text{ (t, } J = 7.5 \text{ Hz, 2H)} . \]

**Methyl-3-((Z)-3-methyl-4-(trityloxy)-2-butenyl)oxy)phenylpropanoate (37)**

To a stirred suspension of freshly activated NaH (66 mg, 16.6 mmol) in dry THF (10 mL) under nitrogen atmosphere was added 36 (1.5 g, 8.3 mmol) in dry THF (10 mL) in a dropwise manner at 0 °C. After stirring for 30 minutes at 0 °C, 25 (4.04 g, 9.96 mmol) in THF was added dropwise. The reaction mixture was stirred for 6 hours at 0 °C and quenched with saturated KBr solution. The layers were separated and aqueous layer eluted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with saturated brine solution and then dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford 37 (2.53 g, 60%) as viscous liquid.

**¹H NMR (300 MHz, CDCl₃)**

\[ \delta 7.46 - 7.37 \text{ and 7.19 - 7.30 (each m, 6H and 9H, Ar-H)} , \]
\[ 7.05 \text{ (d, } J = 8.9 \text{ Hz, 2H, ArH)} , \]
\[ 6.68 \text{ (d, } J = 8.9 \text{ Hz, 2H, ArH)} , \]
\[ 5.62 \text{ (t, } J = 5.7 \text{ Hz, 1H)} , \]
\[ 4.31 \text{ (d, } J = 6.7 \text{ Hz, 2H)} , \]
\[ 3.59 \text{ (s, 2H)} , \]
\[ 2.82 \text{ (t, } J = 8.3 \text{ Hz, 2H)} , \]
\[ 2.53 \text{ (t, } J = 7.5 \text{ Hz, 2H)} , \]
\[ 1.89 \text{ (s, 3H)} . \]

**Methyl-3-((Z)-4-hydroxy-3-methyl-2-butenyl)oxy)phenylpropanoate (38)**

Employing same procedure as mentioned for 29, compound 38 was made from 37 (2.0 g, 3.95 mmol) in 67% yield (690 mg) as a viscous liquid.

**¹H NMR (200 MHz, CDCl₃)**

\[ \delta 7.05 \text{ (d, } J = 8.9 \text{ Hz, 2H, ArH)} , \]
\[ 6.76 \text{ (d, } J = 8.9 \text{ Hz, 2H, ArH)} , \]
\[ 5.62 \text{ (t, } J = 5.7 \text{ Hz, 1H)} , \]
\[ 4.51 \text{ (d, } J = 6.7 \text{ Hz, 2H)} , \]
\[ 4.16 \text{ (s, 2H)} , \]
\[ 3.67 \text{ (s, 3H)} , \]
\[ 2.89 \text{ (t, } J = 8.3 \text{ Hz, 2H)} , \]
\[ 2.58 \text{ (t, } J = 7.5 \text{ Hz, 2H)} , \]
\[ 1.89 \text{ (s, 3H)} . \]
Chapter II, Experimental Section

3-(4-[(Z)-4-Hydroxy-3-methyl-2-butenyl]oxy)phenyl) propanoic acid (39)

Employing same procedure as mentioned for 30, compound 39 was made from 38 (400 mg, 1.52 mmol) in 96% yield (370 mg) as a viscous liquid.

\[ \text{H NMR (200 MHz, CDCl}_3\text{): } \delta 7.05 (d, J = 8.9 \text{ Hz}, 2H, ArH), \]
\[ 6.78 (d, J = 8.9 \text{ Hz}, 2H, ArH), 5.71 (t, J = 5.7 \text{ Hz}, 1H), \]
\[ 4.51 (d, J = 6.7 \text{ Hz}, 2H), 4.18 (s, 2H), 2.89 (t, J = 8.3 \text{ Hz}, 2H), 2.61 (t, J = 7.5 \text{ Hz}, 2H), 1.80 (s, 3H). \]

Saturated analogue 40

Employing same procedure as mentioned for dimer 15, compound 40 was made from 39 (200 mg, 0.8 mmol) in 55% yield (102 mg) as crystals.

\[ \text{H NMR (200 MHz, CDCl}_3\text{): } \delta 7.08 (d, J = 8.9 \text{ Hz}, 2H, ArH), \]
\[ 6.78 (d, J = 8.9 \text{ Hz}, 2H, ArH), 5.65 (t, J = 5.7 \text{ Hz}, 1H, olefinic), \]
\[ 4.60 (s, 2H), 4.51 (d, J = 6.6 \text{ Hz}, 2H), 2.90 (t, J = 8.3 \text{ Hz}, 2H), 2.61 (t, J = 7.5 \text{ Hz}, 2H), 1.80 (s, 3H). \]

\[ \text{C NMR (75 MHz, CDCl}_3\text{): } \delta 173.2, 157.0, 139.7, 132.5, 129.0, 119.8, \]
\[ 114.5, 70.8, 67.4, 35.7, 29.9, 19.3. \]

\[ \text{IR (KBr): } 1733 \text{ cm}^{-1}. \]

\[ \text{FAB Mass: } 233 (M+1). \]

\[ \text{Melting Point: } 123-125^\circ \text{C}. \]

Methyl 3-[(3-methyl-2-butenyl)oxy] phenyl propanoate (41)

To a stirred solution of 36 (4.0 g, 22.2 mmol) in 20 mL of dry acetone was added K$_2$CO$_3$ (9.2 g, 66.6 mmol) and prenyl bromide (3.1 mL, 26.6 mmol). The resulting mixture was vigorously refluxed for 4 hours. The reaction mixture were filtered and washed with ether. The solvent was removed under reduced pressure and purified by silica gel column chromatography eluted with hexane-ethyl acetate (9:1) to afford 41 as a viscous liquid (5.0 g, 92%).

\[ \text{H NMR (200 MHz, CDCl}_3\text{): } \delta 7.08 (d, J = 8.9 \text{ Hz}, 2H, ArH), 6.76 (d, J = 8.9 \text{ Hz}, 2H, ArH), 5.48 (t, J = 5.2 \text{ Hz}, 1H, olefinic), 4.45 (s, 2H), 3.65 (s, 3H), 2.89 (t, J = 8.3 \text{ Hz}, 2H), 2.59 (t, J = 7.5 \text{ Hz}, 2H), 1.79 (s, 3H). \]
Methyl 3-(4-[(E)-3-methyl-4-oxo-2-butenyl]oxy) phenyl propanoate (42)

To a stirred solution of 41 (2.0 g, 8.13 mmol) in 20 mL of dry ethanol was added selenium dioxide (SeO₂) (900 mg, 8.13 mmol). The resulting mixture was vigorously refluxed for 4 hours. Ethanol solvent was removed under reduced pressure and the residue was filtered and washed with ether. The organic layer was washed with saturated brine solution and then dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography eluted with hexane-ethyl acetate (8:2) to afford 42 as a viscous liquid (1.1 g, 50%).

\[
\begin{align*}
\text{\textit{H} NMR (200 MHz, CDCl₃)}: & \delta 9.47 (s, 1H, CHO), 7.06 (d, J = 8.9 \text{ Hz, 2H, ArH}), 6.76 (d, J = 8.9 \text{ Hz, 2H, ArH}), 6.62 (t, J = 5.2 \text{ Hz, 1H, olefinic}), 4.82 (s, 2H), 3.62 (s, 3H), 2.89 (t, J = 8.3 \text{ Hz, 2H}), 2.59 (t, J = 7.5 \text{ Hz, 2H}), 1.82 (s, 3H).
\end{align*}
\]

Methyl 3-(4-[(E)-4-hydroxy-3-methyl-2-butenyl]oxy) phenyl propanoate (43)

To a stirred solution of 42 (1.0 g, 3.84 mmol) in dry methanol (10 mL) under nitrogen atmosphere was added solid NaBH₄ (73 mg, 1.92 mmol) portionwise at 0 °C. After stirring for 30 minutes at 0 °C the reaction mixture was quenched with water. Methanol was removed under reduced pressure and the residue was extracted with ethyl acetate (2x30 mL). The organic layer was washed with saturated brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purified by silica gel column chromatography eluted with hexane-ethyl acetate (8:2) to afford 43 as a viscous liquid (850 mg, 83%).

\[
\begin{align*}
\text{\textit{H} NMR (200 MHz, CDCl₃)}: & \delta 7.06 (d, J = 8.9 \text{ Hz, 2H, ArH}), 6.76 (d, J = 8.9 \text{ Hz, 2H, ArH}), 5.72 (t, J = 5.2 \text{ Hz, 1H, olefinic}), 4.52 (d, J = 6.1 \text{ Hz, 2H}), 4.06 (s, 2H), 3.65 (s, 3H), 2.89 (t, J = 8.3 \text{ Hz, 2H}), 2.59 (t, J = 7.5 \text{ Hz, 2H}), 1.78 (s, 3H).
\end{align*}
\]

3-(4-[(E)-4-Hydroxy-3-methyl-2-butenyl]oxy) phenyl propanoic acid (44)

Employing same procedure as mentioned for 40, compound 44 was made from 43 (400 mg, 1.52 mmol) in 96% yield (374 mg).

\[
\begin{align*}
\text{\textit{H} NMR (200 MHz, CDCl₃)}: & \delta 7.06 (d, J = 8.9 \text{ Hz, 2H, ArH}), 6.80 (d, J = 8.9 \text{ Hz, 2H, ArH}), 5.72 (t, J = 5.2 \text{ Hz, 1H, olefinic}).
\end{align*}
\]
Saturated analogue 45

Employing same procedure as mentioned for dimer 15, compound 45 was made from 44 (200 mg, 0.8 mmol) in 55% yield (100 mg) as crystals.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.06 (d, $J = 8.9$ Hz, 2H, ArH), 6.78 (d, $J = 8.9$ Hz, 2H, ArH), 5.65 (t, $J = 5.2$ Hz, 1H, olefinic), 4.61 (s, 2H), 4.55 (d, $J = 6.0$ Hz, 2H), 2.90 (t, $J = 8.3$ Hz, 2H), 2.61 (t, $J = 7.5$ Hz, 2H), 1.80 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 173.2, 157.0, 137.7, 132.5, 129.0, 119.8, 114.5, 75.1, 67.4, 35.7, 29.9, 13.7.

IR (KBr): 1733 cm$^{-1}$.

FAB Mass: $m/z$ 233 (M+1).

Melting Point: 119-121 °C.
\textsuperscript{1}H NMR SPECTRUM OF COMPOUND 22
$^1$H NMR SPECTRUM OF COMPOUND 23
$^1$H NMR SPECTRUM OF COMPOUND 28
$^1$H NMR SPECTRUM OF COMPOUND 15
$^1$H NMR SPECTRUM OF COMPOUND 31
$^1$H NMR SPECTRUM OF COMPOUND 32
Current Data Parameters
NAME  29-279-M0010-259-p-7
EXPNO  1
PROCNO  1

FL - Acquisition Parameters
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Time  13:35
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POLARIZ  np30
TF  18562
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DS  2
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FIDRES  0.031376 Hz
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SI  0.000000 sec
NHMZ  0.000000 sec
NCAP  0.000000 sec

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GDD  10.02854 MHz

FL - Processing Parameters
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DB  0.5
PC  0.5

1H NMR SPECTRUM OF COMPOUND 33
$^{13}$C NMR SPECTRUM OF COMPOUND 33
MASS SPECTRUM OF COMPOUND 33
IR SPECTRUM OF COMPOUND 33
$^1$H NMR SPECTRUM OF COMPOUND 37
$^1$H NMR SPECTRUM OF COMPOUND 40
$^{13}$C NMR SPECTRUM OF COMPOUND 40
MASS SPECTRUM OF COMPOUND 40
$^1$H NMR SPECTRUM OF COMPOUND 42
$^1H$ NMR SPECTRUM OF COMPOUND 43
$\text{H NMR SPECTRUM OF COMPOUND 44}$
$^1$H NMR SPECTRUM OF COMPOUND 45
IR SPECTRUM OF COMPOUND 45
References