Part A

Synthesis of 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol

Introduction and Literature Review

A prenylated hydroquinone, 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol (85), has been isolated from the root bark of *Cordia alliodora*, also known as *Cerdana alliodora* Ruiz and Pavon. It is a tall tree frequently encountered in Central America, South America and the Caribbean island. In Panama, *Cordia alliodora* is the most widespread species. A decoction of the leaves is used as a tonic for pulmonary diseases in traditional Mexican medicine and is applied on bruises and swelling in Salvador. An ointment made of the plant seeds is employed to treat skin diseases. The compound (85) also showed anti fungal properties against the pythogenic mold *Cladosporium cucumerinum*.

![OH](image)

2-(1Z)-(3-Hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4- benzenediol (85)

Results and Discussion

Literature does not record any synthesis of the title compound. Keeping in mind the medicinal value of the compound, the synthesis of (85) has been undertaken. Aldol condensation in aqueous media and Grignard reaction in the presence of CeCl3, as the key steps have been employed in the novel synthesis of title compound. Diagrammatic representation of the different steps used in this multi-step synthesis is given in *Scheme XV* below:
Salicylaldehyde (86) was oxidised using K$_2$S$_2$O$_8$ under aqueous condition to get 2,5-dihydroxybenzaldehyde (87) as a yellow colored crystalline compound having m.p 100-103° in 30% yield. IR spectrum exhibited the absorption band at 3450 (O-H), 3032 (Ar-C-H), 1710 (0=0), 1660 (C=C). $^1$H NMR showed the main peaks at 4.91 (br s, 1H, O-H), 3.63 (br s, 1H, O-H), 6.77-6.98 (m, 3H, Ar-H).

2,5-Dihydroxybenzaldehyde (87) was subjected to methylation using dimethylsulphate under MW irradiation to get white crystals of (88) having m.p 49-50°, with 80% yield, after purification by silica gel column chromatography using pure n-hexane. IR showed peaks at 3030 (Ar-C-H), 1715 (O=O), 1660 (C=C), 1240
(OCH₃) and disappearance of band at 3450 (OH). ¹H NMR peaks were observed at 6.81-7.22 (m, 3H, Ar-H), 3.83 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃).

Aldol condensation³⁴ of 2,5-Dimethoxybenzaldehyde (88) with 6-Methylhept-5-en-2-one using aq. NaOH under MW was carried out to yield a transparent liquid (89) in 84% yield after purification by silica gel column chromatography using 3% ethylacetate in n-hexane as eluant. IR peaks were observed at 3030 (ArC-H), 1680 (C=O), 1240 (OCH₃). Some important NMR peaks are 7.34 (d, 1H, J=7.2, ArCH=C), 6.50 (d, 1H, J=7.2, ArCH=CH), 2.62 (t, 2H, J=1.8, COCH₂) which confirmed the formation of ‘Z’ isomer in 42% yield.

MeMgl in THF on Grignard reaction³⁴² in the presence of CeCl₃ with 2-(1Z)-(7-methyl-3-oxoocta-1,6-dienyl)-1,4-dimethoxybenzene (89) gave 1,2-addition product (90) in 87% yield after purification by silica gel, column chromatography using 10% ethylacetate in n-hexane as eluant. CeCl₃ was used to get exclusively 1,2 addition product instead of 1,4 addition in the Grignard reaction. IR peaks were observed at 3450 (O-H), 3030 (ArC-H), 1660 (C=C), 1240 (OCH₃). The IR peak at 1680 was missing which indicated that addition product (90) was formed. The characteristic peaks in NMR were at 6.25 (d, 1H, J=7.2, Ar-CH=C), 5.41(d, 1H, J=7.2, ArCH=CH), 1.81(t, 2H, J=2.1, (OH)C-CH₂).

Deprotection³⁴³ of (89) using BBr₃ in DCM at -78° furnished the title compound (85) as a yellow viscous liquid in 85% yield. The IR peak at 1240 (OCH₃) as well as ¹H NMR at 3.86 and 3.73 were missing, which implied that deprotection had occurred successfully.¹H NMR spectral peaks of the title compound were observed at δ 6.64-6.48 (m, 3H, Ar-H), 6.25 (d, 1H, J=7.2, ArCH=C), 5.41 (d, 1H, J=7.2, ArCH=CH), 5.08 (m, 1H, (CH₂)₂C=CH), 2.09 (m, 2H, -CH₂CH=C(CH₃)₂), 1.81 (t, 2H, (OH)C-CH₂), 1.61 (s, 6H, -CH₂CH=C(CH₃)₂), 1.36 (s, 3H, (OH)C-CH₃). The spectral data of the title compound matched well with that reported in the literature.³³⁸ The title compound has been obtained in 13.4% overall yield.

In short, we have carried out a novel synthesis of title compound (85) known to exhibit antifungal activity, by making use of easily available starting material, acceleration by MW irradiation and use of water as green solvent in the key steps.
**Part-B**

**Synthesis of 1-(3’-methoxypropanoyl)-2,4,5-trimethoxybenzene**

**Introduction and Literature Review**

1-(3’-Methoxypropanoyl)-2,4,5-trimethoxybenzene (91) has been isolated from *Cordia alliodora* by Hostettmann *et al.* The title compound is reported to have antifungal and larvicidal activity against the phytopathogenic mold *Calosporium cucumerinum* and larvae of yellow fever transmitting mosquito *Aedes aegypti*, respectively.

![Chemical structure of 1-(3’-Methoxypropanoyl)-2,4,5-trimethoxybenzene (91)](attachment:image)

Traditionally, the fruits of *Cordia alliodora* are eaten and both seeds and leaves are used to treat various health disorders like pulmonary diseases, skin diseases, swellings and bruises. Several synthesis of the title compound have been reported in literature.

In the first reported synthesis, Sinha *et al.* have converted β-asarone, from *Acros calamus* to 1-(3’-methoxypropanoyl)-2,4,5-trimethoxybenzene by SeO₂ mediated allylic oxidation and finally selective reduction of the double bond. The scheme is outlined below:

![Synthesis scheme of 1-(3’-methoxypropanoyl)-2,4,5-trimethoxybenzene](attachment:image)

(a) SeO₂, Dioxane.
Chapter IV

(b) PCC, DCM
(c) NaCN, MnO₂, AcOH, MeOH
(d) H₂, 10% Pd-C

In another attempt Sinha et al. employed microwave irradiation for the synthesis of the title compound as given in the scheme below:

![Chemical Structure]

(a) Piperidine, AcOH, MW, 3min.
(b) PdCl₂, HCOOH, aq. NaOH.
(c) MeOH, H⁺, MW.

Later Tamariz et al. synthesized the title compound by Friedal-Craft reaction as outlined below:

![Chemical Structure]

(i) AlCl₃, CHCl₃CHCl₂, 80°, 168 h.
(ii) AlCl₃, CHCl₃CHCl₂, MW, 80°, 8 h.

Results and Discussion

We herein report a simple, inexpensive and short synthesis of 1-(3'-methoxypropanoyl)-2,4,5-trimethoxybenzene (91) from readily available starting
Chapter IV

materials using Heck reaction of the unactivated ring and appropriate alkene as the key step. The reaction sequence employed is as given in Scheme XVI below:

**Scheme XVI**

Oxidation of hydroquinone (92) with sodium dichromate led to the formation of yellow coloured quinone (93) crystals which on treatment with excess of acetic anhydride gave 1,2,4-triacetoxybenzene (94) in quantitative yield. Formation of the product was confirmed through its $^1$H NMR data which showed a peak at $\delta$ 2.25 for $-\text{CH}_3$ protons of acetate.

a) $\text{Na}_2\text{Cr}_2\text{O}_7$, $\text{H}_2\text{SO}_4$, $\text{H}_2\text{O}$
b) (CH$_3$CO)$_2$O
c) $\text{HCl}$, C$_2$H$_5$OH
d) DMS, $\text{NaOH}$, $\text{H}_2\text{O}$
e) $\text{K}_2\text{S}_2\text{O}_8$, CH$_3$CN, I$_2$, MW
f) $\text{Pd(OAc)}_2$ (1 mol %), $\text{NaOAc}$, (Bmim)Br
g) ZnCl$_2$, Mg, $\text{H}_2\text{O}$
1,2,4-Trihydroxybenzene (95) was obtained through acid hydrolysis of 1,2,4-triacetoxybenzene and further subjected to methylation to get 1,2,4-trimethoxybenzene (96) after treatment with dimethyl sulphate in aqueous NaOH.\textsuperscript{352} The characteristic peaks in PMR are at 6.69 (d, 1H, J=9.0, Ar-H), 6.42 (d, 1H, J=3.0, Ar-H), 6.29 (dd, 1H, J=9.0, J=3.0, Ar-H), 3.81 (s, 3H, -OCH\textsubscript{3}), 3.75 (s, 3H, -OCH\textsubscript{3}), 3.67 (s, 3H, -OCH\textsubscript{3}).

Iodination of 1,2,4-trimethoxybenzene (96) was done using I\textsubscript{2} and K\textsubscript{2}S\textsubscript{2}CV\textsubscript{3} in acetonitrile under microwave irradiation. The absence of double doublet at d 6.69 in the \textsuperscript{1}H NMR spectra and the presence of peak at 73.0 for C-I bond in \textsuperscript{13}C NMR confirmed the formation of 1-iodo-2,4,5-trimethoxybenzene (97).

The Heck reaction\textsuperscript{354} of 1-iodo-2,4,5-trimethoxybenzene (97) using Pd(OAc)\textsubscript{2} as catalyst and (Bmim)Br as solvent, with methyl acrylate led to the formation of methyl 2,4,5-trimethoxy cinnamate (98). The product formation was characterized by \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopy wherein the peaks for C=C at 7.51 and 6.30 and 145.1 and 115.3 respectively were observed.

The Mg/Zn\textsubscript{2} mediated selective reduction\textsuperscript{355} of C=C in aqueous media led to the formation of the final compound (91) in 52.6% overall yield. \textsuperscript{1}H NMR spectral peaks of the title compound (91) were observed at 6.77 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H), 3.88 (s, 3H, -OCH\textsubscript{3}), 3.83 (s, 3H, -OCH\textsubscript{3}), 3.79 (s, 3H, -OCH\textsubscript{3}), 3.67 (s, 3H, -OCH\textsubscript{3}), 2.89 (t, 2H, J=7.6, Ar-CH\textsubscript{2}--), 2.59 (t, 2H, J=7.6, -CH\textsubscript{2}-COOH\textsubscript{3}). It’s \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and IR spectra were found to be in agreement to the ones reported for the original compound.\textsuperscript{344}

In conclusion, synthesis of the title compound (91) has been achieved through rate acceleration by microwave irradiation and the use of aqueous media in the key steps.
Chapter IV

Part-C

Synthesis of 1,2,4-trihydroxynonadecane and its chiral analogue

(2R,4R)-nonadec-1,2,4-triol

Introduction and Literature Review

Persea americana is grown all over the tropics of the world for its edible fruit, the avocado. 1,2,4-trihydroxynonadecane (99) has been isolated by Oberlies et al.,\textsuperscript{357} for the first time, along with two other constituents 1,2,4 trihydroxyheptadec-16-ene (100) and 1,2,4-trihydroxyheptadec-16-yne (101), after activity directed fractionalization of unripe fruits of Persea americana. There structures were elucidated through IR, $^1$H, $^{13}$C and mass spectroscopy. Compound (99) was isolated as a white powder. All these compounds showed activity against six human tumor cell lines in culture and showed selectivity for prostate adenocarcinoma cells.

![Chemical Structures]

Later, Abe et al.,\textsuperscript{358} screened the Mexican medicinal plant for trypanocidal activity against Trypanosoma cruzi and isolated compound (99) along with two more long chain trihydroxy compounds (102) and (103), which have stereocenter at C-2 and C-4. Compound (99) showed moderate activity against epimastigotes and trypomastigotes. In both reports for the isolation of compound (99), the isolated yields from the natural sources were very less (0.0010% and 0.0004% respectively). Due to substantial biological activity of 1,2,4-trihydroxynonadecane ((99)), its synthesis through chemical methods, in good yields, would be useful.
Chapter IV

Results and Discussion

Literature does not record any synthesis of the title compound (99). Synthesis of compound (99) has been carried out in good yield using known reactions. Various steps employed in the synthesis of compound (99) are given below in Scheme XVII.

Scheme XVII

Hexadecanol (104) was oxidized to 1-hexadecanal using PCC doped on silica gel under microwave irradiation. Its IR spectrum showed absorption bands at 1740 (C=O) and disappearance of a broad band at 3350 cm⁻¹ (-OH) indicating the formation of aldehyde. The ¹H NMR spectrum showed peaks at 9.71 (t, 1H, J=1.5, -CHO), 2.32 (m, 2H, -CH₂-CHO), 1.55-1.19 (m, 26H, methylene protons) and 0.82 (t, 3H, -CH₃).
Grignard reaction of allylmagnesium bromide\textsuperscript{359} with 1-hexadecanal (105) gave crude nonadec-1-en-4-ol (106). This was purified through silica gel chromatography using 3\% ethyl acetate in n-hexane to afford pure nonadec-1-en-4-ol. Formation of the product was confirmed by IR spectrum which showed bands at 3300 (-OH), 1655 (C=C) and \textsuperscript{1}H NMR peaks at 5.72 (m, 1H, -CH=CH\textsubscript{2}), 5.02 (dd, 2H, -CH=CH\textsubscript{2}), 3.57 (m, 1H, -C(OH)H-), 2.18 (m, 2H, -CH(OH)-CH\textsubscript{2}-CH\textsubscript{2}-), 1.43-1.25 (m, 26H, methylene protons), 0.85 (t, 3H, -CH\textsubscript{3}).

Nonadec-1-en-4-ol (106) was subjected to KI\textsubscript{0}\textsubscript{3} catalyzed dihydroxylation of the double bond to obtain the title compound (99) after chromatographic purification in 23.9\% overall yield. The spectroscopic analysis of the compound (99) was done and it was found to be in agreement to that reported in the literature.\textsuperscript{356}

Development of synthetic strategy, for the introduction of enantioselectivity at C-2 and C-4, of compound (99) would be useful for the synthesis of compound (102) and (103). Therefore, stereoselective synthesis of analogues of compound (99) was also undertaken.

Microorganisms and enzyme catalyzed reaction are among the best methods for synthesis of enantiomerically pure compounds.\textsuperscript{357} Lipases and esterases are the most widely used enzymes which show broad substrate specificity. To bring about stereoselectivity in compound (99), lipase catalyzed esterification and asymmetric dihydroxylation has been employed in the key steps. Diagrammatic representation of various steps employed in the synthesis is given below:

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme_xviii.png}
\caption{Scheme XVIII}
\end{figure}

(a) \textit{Candida cylindracea}, diethyl ether,
(b) ADmix \textbeta, (Bmim)BF\textsubscript{4}/t-BuOH

Enzymatic resolution\textsuperscript{360} of racemic nonadec-1-ene-4-ol was done using \textit{Candida cylindracea} lipase. Lipase catalyzed esterification is a two step mechanism.
In the first step, the acyl group of the ester is transferred to the enzyme, forming an acyl-enzyme complex. In the second step, one of the competing enantiomers of the chiral alcohol will be preferentially esterified. Acetylation of racemic nonadec-1-en-4-ol (106), catalyzed by lipase, led to the formation of acetyl derivative (109) of one of the enantiomer while the other enantiomer was left unreacted (107). The products of enzymatic resolution were separated by column chromatography eluting with increasing gradient of ethyl acetate and n-hexane. HPLC analysis of nonadec-1-en-4-ol showed that an enantiomeric excess of 60.3% was obtained. Attempts to carry out lipase catalyzed enantioselective esterification, in ionic liquid as solvent and subsequent recycling were not successful as the product isolation from the reaction mixture could not be done.

Finally (R)-nonadec-1-en-4-ol (107) was subjected to asymmetric dihydroxylation by using the ADβ mixture using (Bmim)BF₄/t-butyl alcohol as solvents at -4°C. The asymmetric dihydroxylation of prochiral terminal C=C gave the title compound (108). Its characterization was done using IR, PMR and ¹³C NMR spectral analysis. IR bands were observed at 3350, 3321 (OH), 2920, 2850 and ¹H NMR peaks at 3.94 (m, 1H, -C(OH)H-C(OH)H₂), 3.83 (m, 1H, -CH₂-C(OH)H-), 3.56 (d, 1H, J=3.3, -CH(OH)H), 3.48 (d, 1H, J=6.9, -CH(OH)H), 1.49 (m, 2H, -CH₂-C(OH)H₂), 1.35-1.19 (m, 26H, methylene protons), 0.81 (t, 3H, -CH₃). The title compound (108) was obtained in 23.19% overall yield with an optical rotation of [α]₂⁰D=1.59 (c=5.56, CH₂Cl₂).

This methodology can be extended to the enantioselective total synthesis of compound (102) and (103) as has been demonstrated by the synthesis of the chiral analogue (108) of compound (99).