Chapter 1
Synthesis of Antibacterial Natural Products

Section A
Synthesis of Antibacterial 1,4-Benzoquinone Primin and its Analogs

This study deals with the synthesis of antibacterial natural product; Primin and its water soluble analog, Primin acid. It also discusses previous literature protocols and advancements about the synthesis of 1,4-benzoquinone derivatives. It involves utilization of well known synthetic protocols for example Grignard reaction and Johnson’s Claisen rearrangement for synthesizing this class of compounds.
1.1 Introduction

Nature, produces hundreds of compounds through a variety of biogenetic pathways and quite a few of them have attracted the synthetic organic chemist’s attention due to their remarkable structural features and/or the conferred specific bioactivity. Synthesis of bioactive molecules is in the forefront of synthetic organic chemistry. Most of such biologically active compounds were isolated from plants, animals, fungi, and microorganisms like bacteria. Total synthesis is playing a pivotal role in the drug discovery process because it allows exploration and development of chemical biology through molecular design and mechanistic study.

Quinones, mainly terpenoid benzoquinones are abundant in nature, and play a crucial role in many life processes. Natural pigments are coloured due to presence of the quinone skeleton. Quinones exhibit major role in various redox processes. For example, the ubiquinones are important electron transfer agents in the respiratory chain and pyrroloquinolinequinone (PQQ) is a redox cofactor. 1,4-Benzocquinone scaffolds have gained prominence recently owing to their excellent biological properties. This unit is present in several biologically important natural products, for example, doxorubicin (Figure 1) which is used in front-line cancer chemotherapy treatment. Quinone motif is interesting fundamental π-electron system having two interesting qualities of high electron affinity and photoreactivity.

Lettowiquinone (Figure 2) was isolated from ripe and unripe fruits of Lettowianthus stellatus by Nkunya and co-workers in 2010. This natural product belongs to the class of geranylbenzoquinoid and exhibits mild in vitro activity against Plasmodium falciparam, malarial parasite ($IC_{50} = 20 \mu g \text{ mL}^{-1}$).
Belamcandaquinones (J) 3a, belamcandaquinones (K) 3b, belamcandaquinones (L) 3c, belamcandaquinones (M) 3d (Figure 3) are novel 1,4-benzoquinones, which were isolated from the rhizome of Ardisia gigantifolia. These compounds were tested for their anticancer activity against cancer cell lines PC-3, EMT6, A549, Hela, RM-1 and SGC7901. However, they did not exhibit any cytotoxic activity.\(^7\)
Taiwaniaquinones (A) 4a, Taiwaniaquinones (D) 4b, Taiwaniaquinones (H) 4c and dichroanal (B) 4d (Figure 4) were isolated from *Taiwania cryptomeria*. Compound 4a and 4b have shown potent cytotoxic activity against KB epidermoid carcinoma cancer cells.

![Figure 4. Structure of Taiwaniaquinones A (4a), D (4b), H (4c) and dichroanal (4d).](image)

3-Hydroxythymoquinone 511 (Figure 5) was isolated from the leaves of the plant *Laggera durrens* (vahl.) and shown phytotoxic activity. Compound 5 inhibited growth and germination of the grass weed *Agrostis capillaris* utilizing 250 μM concentration. The mode of action of compound has not yet been deciphered.

![Figure 5. Structure of 3-Hydroxythymoquinone 5.](image)

These 1,4-benzoquinone derivatives possess a wide variety of biological activities. These compounds act as agricultural fungal pathogen control against *Collectotrichum sp.*12 antibacterial activities against *Staphylococcus aureus* and *Streptococcus pyogenes*13 subtermite activity against *Coptotermes formosanus*.14

2-Methoxy-6-propyl-1,4-benzoquinone 6 and 2-methoxy-6-methyl-1,4-benzoquinone 7, antibiotic compounds, have been isolated from the fungus *Carmarops microspora*.15 Compound 7 was first synthesized by Gras *et al.*16 on protected guaiacol albeit in low yield. Compound 6 was first synthesized by Claisen *et al.*17 followed by Dean *et al.*18, and by König *et al.*19 Primin (2-methoxy-6-pentyl-1,4-benzoquinone) 8 was isolated by Bloch *et al.* in 1927 from plant *Primula obconica*.20 Primin, 2-methoxy-6-pentylbenzoquinone 8 (Figure 6), has been reported to occur in 2013 PhD thesis: *T. Kaur*, University of Pune
a variety of plants including *Primula obconica* (primrose), *Miconia* (*M. eriodonta DC*) (Melastomaceae)\(^1\) and *Iris* (*I. sibirica, I. pseudacorus, I. missourensis*) (Iridaceae) *species*.\(^2\)

![Structure of Primin and its analogues](image)

**Figure 6.** Structure of Primin 8 and its analogues.

Interestingly, it has also been isolated from the broth extract of endophytic fungus, *Botryosphaeria mamane* PSU-M76\(^3\) and has shown antibacterial activity against *Staphylococcus aureus* ATCC 25923 and methicillin-resistant *S. aureus* SK1 with equal MIC values of 8 µg/mL.

Primin has exhibited potential anticancer activity against M109 tumor cell lines (IC\(_{50}\) 10 µg/mL) and A2780 cell lines (IC\(_{50}\) 10 µg/mL).\(^4\) It has also been shown potent antiprotozoal activity against *Trypanosoma brucei rhodesiense* (IC\(_{50}\) 0.14 µM) and *Leishmania donovani* (IC\(_{50}\) 0.71 µM).\(^5\) To increase the water solubility of primin (LogP 2.99), its water soluble analog primin acid, 9 (LogP 0.96, *i.e.* about 100 times more hydrophilic) has been designed.\(^6\) The allergenic effect of these *p*-benzoquinones is believed to be mediated from the Michael addition of the nucleophilic protein residues.

### 1.1.1 Previous reports

**1.1.1a Schildknecht’s approach (1967)**

First total synthesis of 8 was reported by H. Schildknecht and co-workers in 1967.\(^7\) Compound 8 was prepared in a five step sequence and in 23% overall yield, starting from *o*-vanillin (Scheme 1).
Scheme 1. Synthesis of Primin using Schildknecht’s approach; **Reagents and conditions:** (a) Fremy’s salt (potassium nitrosodisulfonate), aq. acetone, 21%.

1.1.1b Bieber’s approach (1990)

Bieber *et al.*²⁸ reported the improved synthesis of primin 8 (Scheme 2). In their synthetic protocol, they have used protected guaiacol 12 as a starting material, further treatment with *n*-butyl lithium and quenching with pentyl bromide yielded the phenolic derivative 11. Subsequently, oxidation of phenolic derivative 11 using salcomine furnished primin 8.

Scheme 2. Synthesis of Primin using Bieber’s approach; **Reagents and conditions:** (a) *n*-BuLi, pentylbromide, THF, 80%; (b) *N,N’*-Bis(salicyclidene)ethylenediaminocobalt (II) (Salcomine), DMF, O₂, 86%.

1.1.1c Mabic’s approach (1999)

Mabic’s *et al.*²⁶ started the synthesis of 8 (Scheme 3) using acetate protected bromo guaiacol 13 which was treated with alkenes 14, 15, respectively under Heck reaction conditions to get the olefins 16, 17. The double bonds of alkenes 16, 17 were reduced and protecting group was removed to get 18 and 11, respectively. Both phenols 17 and 11 were oxidized to quinones 8 and 9, respectively.

Scheme 3. Synthesis of Primin using Mabic’s approach; **Reagents and conditions:** (a) Pd(OAc)₂, P(o-tol)₃, TEA, 51%; (b) (i) H₂, Pd/C, EtOAc; (ii) Ba(OH)₂, H₂O, THF, 94%; (c) *N,N’*-Bis(salicyclidene)ethylenediaminocobalt (II) (Salcomine), DMF, O₂, 70%.

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1.1.1d Kingston’s approach (2001)

Kingston’s et al.\textsuperscript{24} started the synthesis of primin 8 (Scheme 4) using o-
vanillin 19, which was treated with pentyl magnesium bromide to furnish the alcohol
20. The alcohol 20 was reduced to compound 11 and further oxidized to primin 8
using Fremy’s salt.

\textbf{Scheme 4.} Synthesis of Primin using Kingston’s approach; \textit{Reagents and conditions}: (a)
Pentylmagnesiumbromide, THF; (b) H\textsubscript{2}, Pd/C, 2-5 days, MeOH; (c) Fremy’s salt (potassium
nitrosodisulfonate), aq. acetone, 21%.

1.1.1e Moody’s approach (2005)

Moody’s et al.\textsuperscript{29} started the synthesis of primin 8 (Scheme 5) using 2-
methoxyphenol 21 which was treated with allyl alcohol under Mitsunobu reaction
conditions to isolate intermediate ether 22. The ether 22 was subjected to Claisen
rearrangement conditions to furnish the compound 23. The double bond of compound
23 was reduced and was oxidized to primin 8.

\textbf{Scheme 5.} Synthesis of Primin using Moody’s approach; \textit{Reagents and conditions}: (a) TPP,
DIAD, allylic alcohol, toluene; (b) DMF, µW (300), 25-60 min; (c) H\textsubscript{2}, Pd/C, EtOAc; (d)
Fremy’s salt (potassium nitrosodisulfonate), aq. acetone, 43%.

1.2 Present work: Objective and Rationale

Our own interest in synthesizing antibacterial bio-active compounds,
prompted us to have a look for an efficient synthetic strategy for 1,4-benzoquinones.
Due to their diverse biological activities the synthesis of 2-methoxy-6-alkyl-1,4-
benzoquinones has been planned. In continuation of our research\textsuperscript{30} we were interested
in the synthesis of 6, 7 and 8 and its water-soluble analogue 9. Flexible scheme was
devised and outlined in retrosynthetic plan (Scheme 6).

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1.3 Results and Discussion

The synthetic approach for the synthesis of primin 8 and its analogs 6, 7, and 9 was envisioned via the retrosynthetic route as shown in Scheme 6. All the 1,4-substituted-benzoquinones 6, 7, 8, and 9 were visualized from common precursor o-vanillin. For the synthesis of primin 8 and primin acid 9, compound 24 could be visualized as a common intermediate. This intermediate 25, could be obtained from Johnson-Claisen rearrangement of the homoallylic alcohols. Synthesis of 1,4-benzoquinones 6 and 7 were also obtained from o-vanillin.

The commercially available material, o-vanillin 19 was converted to common intermediate 25, as illustrated in Scheme 7. Thus, the phenolic group was protected as its TBS ether, using tert-butyldimethylsilyl chloride in DMF. The formation of product 26 was confirmed by its spectral analysis. In $^1$H NMR spectrum, the TBS proton signals were observed at δ 0.79 and 0.00 ppm. In $^{13}$C NMR spectrum, the TBS carbon signals were observed at δ -4.2, 18.9 and 25.8 ppm. The protected aldehyde 26 was subjected to Grignard reaction conditions using vinylmagnesium bromide (1.0 M in THF) to furnish allylic alcohol 24 in 92% yield. The formation of product 24 was confirmed by its spectral analysis. In $^1$H NMR spectrum, the olefinic proton multiplet signals were observed at δ 6.18-6.01 and 5.40-5.17 ppm. In $^{13}$C NMR spectrum, the terminal olefinic carbon signals were observed at δ 139.3 and 114.3.
ppm. The fully saturated analogue 27 was obtained by the hydrogenation of the olefin 23 at 60 psi in 80% yield.

![Scheme 7](image)

**Scheme 7.** Synthesis of 2-methoxy-6-propyl-1,4-benzoquinone, 6.

In the product 27, absence of olefinic protons in the NMR spectra and appearance of new peaks in $^1$H NMR spectrum, signals at $\delta$ 0.95 (t, $J$ = 7.3 Hz), 1.66-1.55 (m) and 2.60 (t, $J$ = 7.9 Hz) ppm were observed. In $^{13}$C NMR spectrum, the new peaks were appeared at $\delta$ 14.1, 23.3 and 32.6 ppm further confirmed the formation of the saturated analogue 26. The TBS group was deprotected$^{32}$ in compound 27 using LiOH/DMF to furnish the compound 28 which on oxidation with salcomine afforded the title compound, 7 in 75% yield. In $^1$H NMR spectrum, signals of compound 7 at $\delta$ 6.46 (dt, $J$ = 2.3 Hz, 1H) and 5.85 (d, $J$ = 2.3 Hz, 1H) and in $^{13}$C NMR spectrum, signals at $\delta$ 187.6 and 182.1 (C=O) and 107.1 and 133.0 (olefinic bond) ppm characteristic peaks for 1,4-benzoquinone were observed. Compound 6 was crystallized from ethanol/dichloromethane (1:9) and its single crystal X-ray analysis proved the structure (Figure 7).

![Figure 7](image)

**Figure 7.** ORTEP diagram of 2-methoxy-6-propyl-1,4-benzoquinone, 6.

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The protected aldehyde 26 was reduced to alcohol 29 in 90% yield. The formation of product 29 was confirmed by NMR analysis. In $^1$H NMR spectrum, signals for the methylene proton at δ 4.70 ppm and in $^{13}$C NMR spectrum, at δ 61.8 ppm were observed. The primary alcohol was protected as its tosyl derivative 30 in 75% yield. The formation of product 30 was confirmed by its spectral analysis. In $^1$H NMR spectrum, additional characteristic resonance for the tosyl group were observed as two doublets at δ 7.92 (d, $J = 8.5$ Hz), 7.45 (d, $J = 8.1$ Hz), while the aromatic methyl group appeared as a singlet at δ 2.48 ppm. In $^{13}$C NMR spectrum, signal for tosyl group (methyl group) resonates at δ 26.0 ppm. Rest of the spectral data was in full agreement with the assigned structure. The tosylate 30 after reductive removal afforded the compound 31 in 85% yield. The TBS group was deprotected in compound 31 using LiOH/DMF to furnish the compound 32 which on oxidation with salcomine afforded 2-methoxy-6-methyl-1,4-benzoquinone, 7 in 80% yield (Scheme 8). In $^1$H NMR spectrum, signals of compound 7 at δ 6.51 (dt, $J = 2.4$ Hz, 1H) and 5.85 (d, $J = 2.4$ Hz, 1H) and $^{13}$C NMR spectrum, signals at δ 187.4 and 182.4 ppm (carbonyls) and 107.3 and 133.8 ppm (olefinic bond) characteristics for 1,4-benzoquinone was observed.

Scheme 8. Synthesis of 2-methoxy-6-methyl-1,4-benzoquinone, 7.

The protected aldehyde 26 under Grignard reaction condition using vinylmagnesium bromide furnished allylic alcohol 24 in 92% yield. In $^1$H NMR spectrum, signals for the olefinic proton were observed at δ 6.18-6.01 and 5.40-5.17 ppm. In $^{13}$C NMR spectrum, signals for the terminal olefinic carbon were observed at
The allylic alcohol 24 was subjected to Johnson-Claisen rearrangement\textsuperscript{34} using trimethyl-\textsc{o}-acetate, xylene and propionic acid in catalytic amount to furnish the product 25 in 90% yield. In \textsuperscript{1}H NMR spectrum, signals for the olefinic protons at δ 6.26-6.13 ppm, aliphatic group protons at δ 2.75-2.34 ppm and aliphatic ester group protons at δ 3.75 ppm were observed (Scheme 9). Hydrogenation of the olefinic compound 25 resulted in the formation of compound 33. The absence of olefinic protons in the NMR confirmed the formation of the product 33. Compound 32 was reduced with lithium aluminum hydride in THF to furnish the alcohol 34 in 91% yield.

\textbf{Scheme 9.} Synthesis of 2-methoxy-6-pentyl-1,4-benzoquinone, Primin 8.

This compound 34 was confirmed by absence of ester group protons and presence of methylene protons at δ 3.6 (t, J = 6.4 Hz) ppm in \textsuperscript{1}H NMR and at δ 62.8 ppm in \textsuperscript{13}C NMR spectra. Compound 34 was crystallized from methanol/dichloromethane (1:9) and its single crystal X-ray analysis proved the structure (Figure 8).

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The primary alcohol was protected as its tosyl derivative 35, 93% yield. The formation of product 35 was confirmed by spectral analysis. In $^1$H NMR spectrum, additional characteristic resonance for the tosyl group were observed as two doublets at $\delta$ 7.79 (d, $J = 8.2$ Hz), 7.68 (d, $J = 8.0$ Hz) ppm, while the aromatic methyl group appeared as a singlet at $\delta$ 2.36 ppm. In $^{13}$C NMR spectrum, signals for the tosyl group (methyl) resonates at $\delta$ 21.6 ppm. Compound 35 was subjected to lithium aluminum hydride reduction conditions to furnish compound 36. In $^1$H NMR spectrum, absence of aromatic ring of tosyl and presence of peak at 0.88 (t, $J = 8.0$ Hz) confirmed the formation of product 36. The TBS group was deprotected in compound 36 using LiOH/DMF to furnish the compound 37, which on oxidation with salcomine afforded the title compound, primin 8 in 81% yield (Scheme 8). In $^1$H NMR spectrum, of compound 8 signals at $\delta$ 6.49 (dt, $J = 2.3$ Hz, 1H) and 5.88 (d, $J = 2.3$ Hz, 1H) and $^{13}$C NMR spectrum, signals at $\delta$ 187.7 and 182.1 (carbonyls) and 107.1 and 132.9 (olefinic bond) characteristics for 1,4-benzoquinone were observed.

The deprotection of TBS group and methyl ester of the key intermediate 33 (Scheme 10) which under the similar oxidation conditions employed for the synthesis of primin 8 afforded the water-soluble analog, primin acid 9 in 71% yield. In $^{13}$C NMR spectrum, signals at $\delta$ 187.6 and 182.2 (carbonyls) and 107.2 and 133.3 (olefinic bond) characteristics for 1,4-benzoquinone were observed.
1.4 Conclusion

In conclusion, an efficient syntheses of antibacterial benzoquinones, 6, 7, 8, 9 has been achieved from o-vanillin in 47, 39, 34, and 25% overall yields, respectively. The key steps were Grignard reaction and Johnson-Claisen rearrangement.

Scheme 10. Schematic representation of synthesis of Primin acid, 9.
1.5 Experimental

2-(tert-Butyldimethylsilyloxy)-3-methoxybenzaldehyde (26)

![Chemical structure of 2-(tert-Butyldimethylsilyloxy)-3-methoxybenzaldehyde (26)]

To a stirred solution of o-vanillin (5.0 g, 32.0 mmol) in anhydrous DMF (10 mL) under nitrogen atmosphere, imidazole (3.3 g, 49.0 mmol) and TBSCl (7.4 g, 49.0 mmol) were added. The reaction was stirred at room temperature for 7 h, water was added and was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 8:2) to afford product 26 (8.3 g).

**Yield** 8.3 g, 95%; colorless oil; Rₜ = 0.66 (PE/EA, 7:3).

**Mol. Formula** C₁₄H₂₂O₃Si

**IR (CHCl₃)** νₓₜ (cm⁻¹) = 3034, 2957, 1584, 1481, 1216, 1071.

**¹H NMR** (CDCl₃, 200 MHz) δ (ppm) = 10.30 (s, 1H, CHO), 7.16 (dd, J = 7.7, 7.7 Hz, 1H, CH), 6.85-6.70 (m, 2H, CH), 3.61 (s, 3H, OCH₃), 0.79 (s, 9H, CH₃), 0.00 (s, 6H, SiCH₃).

**¹³C NMR** (CDCl₃, 50 MHz) δ (ppm) = 190.3 (CHO), 150.8 (C), 149.2(C), 127.9 (C), 121.2 (CH), 119.1 (CH), 116.9 (CH), 55.1 (OCH₃), 25.9 (CH₃), 19.0 (C), -4.1(SiCH₃).

**Elemental analysis** Calcd for C₁₄H₂₂O₃Si: C, 63.12; H, 8.32

**Elemental analysis** Found: C, 63.20; H, 8.40.

1-[2-(tert-Butyldimethylsilyloxy)-3-methoxyphenyl] prop-2-en-1-ol (24)

![Chemical structure of 1-[2-(tert-Butyldimethylsilyloxy)-3-methoxyphenyl] prop-2-en-1-ol (24)]

To a 0-5 °C cooled solution of compound 26 (3.9 g, 15.0 mmol) in anhydrous THF (10 mL) vinyl magnesium bromide (15 mL, 15.0 mmol, 1.0 M in THF) was slowly

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added. After stirring for 5 h, reaction mixture was quenched with aqueous NH₄Cl solution (2 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to give allylic alcohol 24 (4.05 g).

**Yield**
4.0 g, 95%; colorless oil; \( R_f = 0.52 \) (PE/EA, 7:3).

**Mol. Formula**
C₁₄H₂₂O₃Si

**IR (CHCl₃)**
\( \nu_{\text{max}} \text{ (cm}^{-1}) = 3034, 2957, 1584, 1481, 1216, 1071. \)

**¹H NMR**
(CDCl₃, 200 MHz)
\( \delta_H \text{ (ppm)} = 6.94-6.77 \text{ (m, 3H, } CH) \), 6.18-6.01 (m, 1H, CH), 5.94-5.64 (m, 1H, CH), 5.40-5.17 (m, 2H, CH), 3.79 (s, 3H, OCH₃), 1.00 (s, 9H, CH₃), 0.21 (s, 6H, SiCH₃).

**¹³C NMR**
(CDCl₃, 50 MHz)
\( \delta_C \text{ (ppm)} = 149.7 \text{ (C)}, 139.3 \text{ (CH)}, 133.7 \text{ (C)}, 121.2 \text{ (CH)}, 118.9 \text{ (CH)}, 114.3 \text{ (CH₂)}, 110.7 \text{ (CH)}, 68.9 \text{ (CH)}, 60.4 \text{ (CHOH)}, 54.7 \text{ (OCH₃)}, 26.1 \text{ (CH₃)}, 18.9 \text{ (C)}, -3.8 \text{ (SiCH₃)}. \)

**Elemental analysis**
Calcd for C₁₄H₂₂O₃Si: C, 63.12; H, 8.32
Found: C, 63.20; H, 8.40

**tert-Butyl-(2-methoxy-6-propylphenoxy)-dimethylsilane (27)**

![Image of tert-Butyl-(2-methoxy-6-propylphenoxy)-dimethylsilane (27)]

To a solution of compound 24 (3.1 g, 10.5 mmol) in anhydrous MeOH (10 mL), 10% Pd/C (0.1 g) was added. The resulting heterogeneous solution was stirred vigorously under H₂ atm at 60 psi. After stirring for 4 h, the mixture was filtered over celite. The filtrate was evaporated and purified by silica gel column chromatography (PE/EA, 8:2) to furnish pure product 27 (2.36 g).

**Yield**
2.36 g, 80%; colorless oil; \( R_f = 0.70 \) (PE/EA, 8:2).

**Mol. Formula**
C₁₆H₂₈O₂Si

**IR (CHCl₃)**
\( \nu_{\text{max}} \text{ (cm}^{-1}) = 2957, 2931, 2858, 1583, 1481, 1279, 1251, 1228, 1086. \)
To a 0-5 °C cooled solution of compound 27 (0.78 g, 2.74 mmol) in anhydrous DMF (2 mL), LiOH (197 mg, 9.6 mmol) was added. The reaction mixture was stirred at room temperature for 4 h under an argon atmosphere. After completion of reaction, it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 8:2) to furnish phenol 28 (0.41 g).

**Yield**

0.41 g, 90%; colorless viscous oil; $R_f = 0.48$ (PE/EA, 8:2).

**Mol. Formula**

C$_{10}$H$_{14}$O$_2$

**IR (CHCl$_3$)**

$\nu_{\text{max}}$ (cm$^{-1}$) = 3544, 2960, 2870, 1618, 1591, 1478, 1442, 1358, 1268, 1220, 1185, 1080.

**$^1$H NMR**

$\delta_H$ (ppm) = 6.78-6.71 (m, 3H, CH), 5.69 (s, 1H, OH), 3.86 (s, 3H, OCH$_3$), 2.61 (t, $J$ = 7.5 Hz, 3H, CH$_2$), 1.74-1.59 (m, 2H, CH$_2$), 0.96 (t, $J$ = 7.3 Hz, 3H, CH$_3$).

**$^{13}$C NMR**

$\delta_C$ (ppm) = 146.3 (C), 143.3 (C), 128.5 (C), 122.4

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

$\delta_H$ (ppm) = 6.79-6.72 (m, 3H, CH), 3.78 (s, 3H, OCH$_3$), 2.60 (t, $J$ = 7.9 Hz, 3H, CH$_2$), 1.66-1.55 (m, 2H, CH$_2$), 1.01 (s, 9H, CH$_3$), 0.95 (t, $J$ = 7.3 Hz, 3H, CH$_3$), 0.19 (s, 6H, SiCH$_3$).

**Elemental analysis**

Calcd for C$_{16}$H$_{28}$O$_2$Si: C, 68.52; H, 10.06

Found: C, 72.38; H, 10.09.
To a solution of compound 28 (0.3 g, 1.8 mmol) in anhydrous DMF (3 mL), salcomine (59.0 mg, 0.18 mmol) was added. The resulting reaction mixture was stirred vigorously for 6 h. After completion of the reaction, it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to furnish 6 (0.24 g).

Yield
0.24 g, 75%; yellow solid; $R_f = 0.34$ (PE/EA, 7:3).

Melting point
76-78°C

Mol. Formula
C₁₀H₁₂O₃

IR (CHCl₃)
$\nu_{\text{max}}$ (cm⁻¹) = 3022, 2966, 2937, 2876, 2847, 1681, 1651, 1603, 1628, 1458, 1317, 1232, 1216.

$^1$H NMR
(CDCl₃, 200 MHz)
$\delta_H$ (ppm) = 6.46 (dt, $J = 2.3$ Hz, 1H, CH), 5.85 (d, $J = 2.3$ Hz, 1H, CH), 3.79 (s, 3H, OCH₃), 2.39 (t, $J = 6.6$ Hz, 3H, CH₂), 1.58-1.46 (m, 2H, CH₂), 0.94 (t, $J = 7.2$ Hz, 3H, CH₃).

$^{13}$C NMR
(CDCl₃, 50 MHz)
$\delta_C$ (ppm) = 187.6 (C), 182.1 (C), 158.8 (C), 147.2 (C), 133.0 (CH), 107.1 (CH), 56.2 (OCH₃), 30.6 (CH₂), 21.0 (CH₂), 13.7 (CH₃).

Elemental analysis
Calcd for C₁₀H₁₂O₃: C, 66.65; H, 6.71
Found: C, 66.72; H, 6.79.
(2-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)methanol (29)

To a cooled solution of compound 26 (2.0 g, 7.49 mmol in anhydrous MeOH (10 mL), sodium borohydride (277 mg, 7.49 mmol) was added. The solution was stirred at room temperature for 2 h under a N₂ atmosphere. After completion of the reaction, methanol was evaporated and was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to give product 29 (1.81 g).

**Yield**

1.81 g, 90%; colorless viscous oil; \( R_f = 0.62 \) (PE/EA, 8:2).

**Mol. Formula**

\( \text{C}_{14}\text{H}_{24}\text{O}_{3}\text{Si} \)

**IR (CHCl₃)**

\( \nu_{\text{max}} (\text{cm}^{-1}) = 3398, 2929, 1585, 1483, 1277, 1083, 1042. \)

**\(^1\text{H NMR}\)**

\( \delta_{\text{H}} (\text{ppm}) = 6.92-6.78 (\text{m, 3H, CH}), 4.70 (\text{s, 2H, CH₂}), 3.79 (\text{s, 3H, OCH₃}), 1.01 (\text{s, 9H, CH₃}), 0.20 (\text{s, 6H, SiCH₃}). \)

**\(^{13}\text{C NMR}\)**

\( \delta_{\text{C}} (\text{ppm}) = 149.7 (\text{C}), 142.6 (\text{C}), 132.2 (\text{C}), 121.2 (\text{CH}), 120.5 (\text{CH}), 111.0 (\text{CH}), 61.8 (\text{CH₂OH}), 54.8 (\text{OCH₃}), 26.0 (\text{CH₃}), 18.8 (\text{C}), -4.0 (\text{SiCH₃}). \)

**Elemental analysis**

Calcd for \( \text{C}_{14}\text{H}_{24}\text{O}_{3}\text{Si} \): C, 62.64; H, 9.01

Found: C, 62.72; H, 9.09

2-((tert-Butyldimethylsilyl)oxy)-3-methoxybenzyl 4-methylbenzenesulfonate (30)

To a solution of compound 29 (1.76 g, 6.56 mmol) in anhydrous CH₂Cl₂ (10 mL), Et₃N (912 µL), TsCl (1.24 g, 6.56 mmol) and DMAP (cat.) was added. The resulting

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mixture was stirred at room temperature for 2 h. After completion of the reaction (TLC), it was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na$_2$SO$_4$ and solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 9:1) to furnish product 30 (2.07 g).

Yield

2.07 g, 75%; colorless viscous oil; $R_f = 0.70$ (PE/EA, 9:1).

Mol. Formula

C$_{21}$H$_{30}$O$_5$Si

IR (CHCl$_3$)

ν$_{max}$ (cm$^{-1}$) = 3019, 2957, 2931, 2858, 1586, 1595, 1484, 1378, 1288, 1254, 1216, 1174, 1082.

$^1$H NMR

(CDCl$_3$, 200 MHz)

δ$_H$ (ppm) = 7.92 (d, $J =$ 8.5 Hz, 2H, CH), 7.45 (d, $J =$ 8.1 Hz, 2H, CH), 7.00-6.79 (m, 3H, CH), 4.66 (s, 2H, CH$_2$), 3.79 (s, 3H, OCH$_3$), 2.48 (s, 3H, CH$_3$), 1.03 (s, 9H, CH$_3$), 0.22 (s, 6H, SiCH$_3$).

$^{13}$C NMR

(CDCl$_3$, 50 MHz)

δ$_C$ (ppm) = 149.8 (C), 146.8 (C), 143.1 (C), 141.7 (C) 130.2 (CH), 128.7 (C), 127.0 (CH), 122.3 (C), 121.0 (CH), 111.6 (CH), 54.8 (OCH$_3$), 41.7 (CH$_2$OH), 26.0 (CH$_3$), 21.8 (C), 18.9 (C), -3.9 (SiCH$_3$).

Elemental analysis

Calcd for C$_{21}$H$_{30}$O$_5$Si: C, 59.68; H, 7.16

Found: C, 59.73; H, 7.10

tert-Butyl (2-methoxy-6-methylphenoxy)dimethylsilane (31)

To a 0-5 °C cooled solution of compound 30 (2.76 g, 6.56 mmol) in anhydrous THF (10 mL) LAH (0.24 g, 6.56 mmol) was slowly added. The reaction mixture was stirred at room temperature for 4 h under an argon atmosphere. After completion of the reaction (TLC), it quenched with 1N NaOH (10 mL). The resulting white precipitate was filtered through Celite and the filtrate was dried over anhydrous.
Na₂SO₄ and solvent was evaporated to give crude residue which was purified by silica gel column chromatography (PE/EA, 7:3) to furnish product 31 (1.56 g).

**Yield**
1.56 g, 87%; colorless viscous oil; \( R_f = 0.61 \) (PE/EA, 9:1).

**Mol. Formula**
\( \text{C}_{14}\text{H}_{24}\text{O}_{2}\text{Si} \)

**IR (CHCl₃)**
\( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3018, 2958, 2931, 2858, 1585, 1487, 1438, 1314, 1279, 1252, 1217, 1085.

**\(^1\)H NMR**
- \( \delta_H \) (ppm) = 6.65-6.52 (m, 3H, CH), 3.62 (s, 3H, OCH₃), 2.09 (s, 3H, CH₃), 0.86 (s, 9H, CH₃), 0.02 (s, 6H, SiCH₃).

**\(^13\)C NMR**
- \( \delta_C \) (ppm) = 149.9 (C), 143.1 (C), 129.8 (C), 129.6 (C), 123.7 (CH), 122.8 (C), 120.5 (CH), 109.1 (CH), 54.8 (OCH₃), 26.1 (CH₃), 18.8 (C), 17.1 (CH₃), -3.9 (SiCH₃).

**Elemental analysis**
Calcd for C\(_{14}\)H\(_{24}\)O\(_2\)Si: C, 66.61; H, 9.58
Found: C, 66.71; H, 9.62.

**2-Methoxy-6-methylphenol (32)**

To a cooled solution of compound 31 (0.46 g, 2.0 mmol) in anhydrous DMF (2 mL), LiOH (172 mg, 6.0 mmol) was slowly added. The reaction mixture was stirred at room temperature for 4 h under an argon atmosphere. After completion of the reaction (TLC), it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 9:1) to furnish phenol 32 (0.225 g).

**Yield**
0.23 g, 90%; colorless viscous oil; \( R_f = 0.56 \) (PE/EA, 9:1).

**Mol. Formula**
\( \text{C}_8\text{H}_{10}\text{O}_2 \)

**IR (CHCl₃)**
\( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3543, 3020, 2928, 1722, 1602, 1485,
In a flame-dried flask, phenol 32 (0.214 g, 1.55 mmol) was taken and dissolved in anhydrous DMF (3 mL) and salcomine (50 mg, 0.15 mmol) was added. The resulting reaction mixture was stirred vigorously for 6 h. After completion of the reaction (TLC), it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 9:1) to furnish compound 7 (0.19 g).

**Yield** 0.19 g, 80%; yellow solid; \( R_f = 0.13 \) (PE/EA, 9:1).

**Melting Point** 144-6°C

**Mol. Formula** C₈H₁₀O₂

**IR (CHCl₃)** \( v_{\max} (\text{cm}^{-1}) = 3423, 3020, 2976, 2927, 2400, 1681, 1652, 1605, 1524, 1457, 1426, 1314, 1215, 1073. \)

**¹H NMR**

\[
\begin{align*}
\delta_H (\text{ppm}) & = 6.73 (\text{m}, 3\text{H}, CH), 5.68 (\text{s}, 2\text{H}, OH), \ \\
3.87 (\text{s}, 3\text{H}, OCH₃), 2.25 (\text{s}, 3\text{H}, CH₃).
\end{align*}
\]

**¹³C NMR**

\[
\begin{align*}
\delta_C (\text{ppm}) & = 146.2 (C), 143.7 (C), 123.9 (C), 123.1 (CH), 119.1 (CH), 108.2 (CH), 56.0 (OCH₃), 15.4 (CH₃).
\end{align*}
\]

**Elemental analysis**

Caled for C₈H₁₀O₂: C, 69.54; H, 7.30

Found: C, 69.50; H, 7.25.

**2-Methoxy-6-methylcyclohexa-2, 5-diene-1, 4-dione (7)**

\[
\begin{align*}
\text{MeO} & \\
O & \\
\text{7}
\end{align*}
\]

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To a solution of compound 24 (4.0 g, 13.6 mmol) in xylene (5 mL), trimethyl-o-acetate (9.79 g, 10.2 mL, 8.1 mmol), propionic acid (40 μL) was added in catalytic amount. The resulting mixture was refluxed at 140 °C for 6 h. After completion of the reaction (TLC), the xylene was evaporated under reduced pressure. The crude reaction residue was purified by silica gel column chromatography (PE/EA, 8:2) to afford pure product 25 (4.28 g).

**Yield**
4.28 g, 90%; colorless oil; \( R_f = 0.60 \) (PE/EA, 7:3).

**Mol. Formula**
\( \text{C}_{19}\text{H}_{30}\text{O}_{4}\text{Si} \)

**IR (CHCl₃)**
\( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3021, 2955, 1738, 1480, 1252, 1086.

**\(^1\text{H NMR}\)**
(CDC\(_3\), 200 MHz)
\( \delta_H \) (ppm) = 7.32-6.75 (m, 3H, CH), 6.26-6.13 (m, 1H, CH), 3.82 (s, 3H, OCH\(_3\)), 3.75 (s, 3H, OCH\(_3\)), 2.75-2.34 (m, 4H, CH\(_2\)), 1.15 (s, 9H, CH\(_3\)), 0.28 (s, 6H, SiCH\(_3\)).

**\(^{13}\text{C NMR}\)**
(CDC\(_3\), 50 MHz)
\( \delta_C \) (ppm) = 173.3 (C), 150.6 (C), 142.1(C), 129.5 (C), 128.3 (CH), 126.4 (CH), 121.0 (CH), 118.0 (CH), 110.1 (CH), 54.8 (OCH\(_3\)), 51.5 (OCH\(_3\)), 33.8 (CH\(_2\)), 28.7 (CH\(_3\)), 26.1 (CH\(_2\)), 18.9 (C), -4.0 (SiCH\(_3\)).

**Elemental analysis**
Calcd for C\(_{19}\)H\(_{30}\)O\(_4\)Si: C, 65.10; H, 8.63
Found: C, 65.20; H 8.72.
To a solution of compound 25 (4.5 g, 12.8 mmol) in dry MeOH (10 mL), 10% Pd/C (100 mg) was added. The heterogeneous solution was vigorously stirred for 12 h under H$_2$ atmosphere. After completion of the reaction (TLC), methanol was evaporated and filtered over celite. The solvent was evaporated and the crude product was purified by silica gel column chromatography (PE/EA, 8:2) to furnish pure product 33 (4.24 g).

**Yield**

4.24 g, 94%; colorless oil; $R_f = 0.51$ (PE/EA, 7:3).

**Mol. Formula**

C$_{14}$H$_{22}$O$_3$Si

**IR (CHCl$_3$)**

$\nu_{\text{max}}$ (cm$^{-1}$) = 3033, 2937, 1735, 1475, 1234, 1088.

**$^1$H NMR**

(CDCl$_3$, 200 MHz)

$\delta_H$ (ppm) = 6.83-6.72 (m, 3H, CH$_3$), 3.77 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 2.65 (t, $J = 6.9$ Hz, 2H, CH$_2$), 2.65 (t, $J = 6.9$ Hz, 2H, CH$_2$), 2.33-2.27 (m, 2H, CH$_2$), 1.74-1.60 (m, 3H, CH$_2$), 1.01 (s, 9H, CH$_3$), 0.19 (s, 6H, SiCH$_3$).

**$^{13}$C NMR**

(CDCl$_3$, 50 MHz)

$\delta_C$ (ppm) = 174.1 (C), 149.8 (C), 142.6 (C), 133.3 (C), 121.8 (CH), 120.6 (CH), 109.0 (CH), 54.6 (OCH$_3$), 51.4 (OCH$_3$), 34.0 (CH$_2$), 30.1 (CH$_2$), 29.5 (CH$_2$), 26.1 (CH$_3$), 24.8 (CH$_2$), 18.9 (C), -3.9 (SiCH$_3$).

**Elemental analysis**

Calcd for C$_{14}$H$_{22}$O$_3$Si: C, 64.73; H, 9.15.

Found: C, 64.81; H, 9.22.

5-[2-(tert-Butyldimethylsilyloxy)-3-methoxyphenyl]pentan-1-ol (34)

To a cooled solution of compound 33 (4.0 g, 11.0 mmol) in anhydrous THF (10 mL), LAH (0.4 g, 11.0 mmol) was slowly added. The reaction mixture stirred at room
temperature for 4 h under an argon atmosphere. After completion of the reaction (TLC), it was cooled to 0-5°C and quenched with 1N NaOH (10 mL). The resulting white precipitate was filtered through celite and the filtrate was dried over anhydrous Na₂SO₄ and evaporated. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to afford product 34 (3.35 g).

**Yield** 3.35 g, 91%; colorless viscous oil; \( R_f = 0.31 \) (PE/EA, 7:3).

**Mol. Formula** \( \text{C}_{18}\text{H}_{32}\text{O}_3\text{Si} \)

**IR (CHCl₃)** \( \nu_{\text{max}} \text{ (cm}^{-1}) = 2953, 2930, 1720, 1465, 1250, 1082. \)

**\(^1\text{H NMR}\)** (CDCl₃, 200 MHz) \( \delta_H \text{ (ppm)} = 6.87-6.68 \text{ (m, 3H, } CH) , 3.77 \text{ (s, 3H, OCH}_3), 3.61 \text{ (t, } J = 6.4 \text{ Hz, } 2H, CH_2OH), 2.64 \text{ (t, } J = 7.3 \text{ Hz, } 2H, CH_2), 1.62-1.33 \text{ (m, 6H, } CH_2), 1.01 \text{ (s, 9H, } CH_3), 0.19 \text{ (s, 6H, } SiCH_3). \)

**\(^{13}\text{C NMR}\)** (CDCl₃, 50 MHz) \( \delta_C \text{ (ppm)} = 149.8 \text{ (C), 142.6 \text{ (C), 133.7 \text{ (C), 121.8 \text{ (CH), 120.5 \text{ (CH), 109.0 \text{ (CH), 62.8 \text{ (CH}_2OH), 54.6 \text{ (OCH}_3), 32.7 \text{ (CH}_2), 30.4 \text{ (CH}_2), 29.8 \text{ (CH}_2), 26.0 \text{ (CH}_3), 25.7 \text{ (CH}_2), 18.8 \text{ (C), -3.9 \text{ (SiCH}_3).} \)

**Elemental analysis** Calcd for \( \text{C}_{18}\text{H}_{32}\text{O}_3\text{Si} \): C, 66.62; H, 9.94. Found: C, 66.73; H, 9.88.

5-[2-(tert-Butyldimethyldimethyloxyl)-3-methoxyphenyl]pentyl-4-methylbenzene sulfonate (35)

![Structure of product 35](image)

To a solution of compound 34 (3.0 g, 9.2 mmol) in anhydrous CH₂Cl₂ (10 mL), Et₃N (1.0 mL), TsCl (1.74 g, 9.2 mmol) and DMAP (cat.) was added. The resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (TLC), it was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 9:1) to furnish product 35 (4.11 g).
tert-Butyl-(2-methoxy-6-pentylphenoxy)dimethylsilane (36)

To a cooled solution of compound 35 (4.0 g, 8.3 mmol) in anhydrous THF (10 mL), LAH (0.3 g, 8.3 mmol) was slowly added. The reaction mixture was stirred at room temperature for 4 h under an argon atmosphere. After completion of the reaction (TLC), it was quenched with 1N NaOH (10 mL). The resulting white precipitate was filtered over celite and filtrate was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to furnish pure product 36 (2.40 g).

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To a cooled solution of compound 36 (1.0 g, 3.2 mmol) in anhydrous DMF (2 mL), LiOH (220 mg, 9.6 mmol) was added and the reaction mixture was stirred at room temperature for 4 h under an argon atmosphere. After completion of the reaction (TLC), it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to furnish phenol 37 (0.5 g).

**Yield**

2.40 g, 95%; colorless viscous oil; \( R_f = 0.83 \) (PE/EA, 7:3).

**Mol. Formula**

C₁₈H₃₂O₂Si

**IR (CHCl₃)**

\[ \nu_{\text{max}} \left( \text{cm}^{-1} \right) = \text{3019, 2839, 1585, 1486, 1261, 1099.} \]

**¹H NMR**

\( \delta_H \) (ppm) = 6.86-6.71 (m, 3H, CH₃), 3.76 (s, 3H, OCH₃), 2.60 (t, \( J = 7.8 \) Hz, 3H, CH₂), 1.61-1.55 (m, 2H, CH₂), 1.35-1.32 (m, 2H, CH₂), 1.00 (s, 9H, CH₃), 0.88 (t, \( J = 6.7 \) Hz, 3H, CH₃), 0.18 (s, 6H SiCH₃).

**¹³C NMR**

\( \delta_C \) (ppm) = 149.8 (C), 142.6 (C), 134.2 (C), 129.8 (CH), 121.8 (CH), 120.5 (CH), 108.9 (CH), 54.7 (OCH₃), 32.0 (CH₂), 29.9 (CH₂), 26.1 (CH₃), 22.7 (CH₂), 19.0 (C), 14.1 (CH₃), -3.9 (SiCH₃).

**Elemental analysis**

Calcd for C₁₈H₃₂O₂Si: C, 70.07; H, 10.45. Found: C, 70.18; H, 10.58.

**2-Methoxy-6-pentylphenol (37)**

![Chemical Structure](image)

To a cooled solution of compound 36 (1.0 g, 3.2 mmol) in anhydrous DMF (2 mL), LiOH (220 mg, 9.6 mmol) was added and the reaction mixture was stirred at room temperature for 4 h under an argon atmosphere. After completion of the reaction (TLC), it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to furnish phenol 37 (0.5 g).

**Yield**

0.5 g, 80%; colorless viscous oil; \( R_f = 0.45 \) (PE/EA, 7:3).

**Mol. Formula**

C₁₂H₁₈O₂

**IR (CHCl₃)**

\( \nu_{\text{max}} \left( \text{cm}^{-1} \right) = \text{3500, 2835, 1580, 1483, 1254, 1092.} \)
To a solution of phenol 37 (0.388 g, 2 mmol) in anhydrous DMF (3 mL), salcomine (64.4 mg, 0.2 mmol) was added. The resulting reaction mixture was stirred vigorously for 6 h. After completion of the reaction (TLC), it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 6:4) to afford title compound primin 8 (0.33 g).

Yield: 0.33 g, 81%; yellow solid; $R_f = 0.30$ (PE/EA, 7:3).

Melting point: 62-64°C.

Mol. Formula: C₁₂H₁₈O₂

IR (CHCl₃): $ν_{max}$ (cm⁻¹) = 3034, 2912, 1685, 1604, 1432, 1250.

¹H NMR

(CDCl₃, 200 MHz) δH (ppm) = 6.60-6.53 (m, 3H, CH), 5.51 (s, 1H, OH), 3.68 (s, 3H, OCH₃), 2.49-2.41 (m, 2H, CH₂), 1.44-1.40 (m, 2H, CH₂), 1.19-1.08 (m, 3H, CH₂), 0.71 (t, J = 6.7 Hz, 3H, CH₃).

¹³C NMR

(CDCl₃, 50 MHz) δC (ppm) = 146.2 (C), 143.4 (C), 128.7 (C), 122.4 (CH), 122.3 (CH), 119.1 (CH), 108.9 (CH), 56.0 (OCH₃) 31.8 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 26.1 (CH₂), 22.6 (CH₂), 14.0 (CH₃).

Elemental analysis: Calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 74.23; H, 9.33.
To a solution of ester 37 (0.704 g, 2 mmol) in MeOH (2 mL), 5% KOH in MeOH-H$_2$O (12 mL, 3:1) was added and the resulting reaction mixture was heated under reflux for 3 h. The reaction mixture was acidified with 1N HCl (10 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 6:4) to furnish acid 38 (0.25 g).

Yield 0.25 g, 55%; white solid; $R_f$ = 0.20 (PE/EA, 7:3).

Mol. Formula C$_{12}$H$_{16}$O$_4$

IR (CHCl$_3$) $\nu_{\text{max}}$ (cm$^{-1}$) = 3400, 2923, 1725, 1338, 1250.

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$H (ppm) = 6.47-6.72 (m, 3H, CH), 4.74 (s, 1H, OH), 3.87 (s, 3H, OCH$_3$), 2.65 (t, $J$ = 7.0 Hz, 2H, CH$_2$), 2.38 (t, $J$ = 7.0 Hz, 2H, CH$_2$), 1.68-1.65 (m, 4H, CH$_2$).

$^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$C (ppm) = 179.2 (C), 146.3 (C), 143.4 (C), 127.8 (C), 122.3 (CH), 119.2 (CH), 108.3 (CH), 55.9 (OCH$_3$), 33.8 (CH$_2$), 29.2 (CH$_2$), 29.1 (CH$_2$), 24.4 (CH$_2$).

Elemental analysis Calcd for C$_{12}$H$_{16}$O$_4$: C, 69.21; H, 7.74. Found: C, 69.26; H, 7.73.

5-(5-Methoxy-3,6-dioxocyclohexa-1,4-dienyl)-pentanoic acid (Primin acid) (9)
In a flame-dried flask, phenol 38 (0.224 g, 1 mmol) was taken and dissolved in anhydrous DMF (3 mL) and stirred for 15 min. Then salcomine (32 mg, 0.1 mmol) was added, and the reaction mixture was stirred vigorously for 7 h (TLC). After completion of the reaction (TLC), it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 6:4) gave primin acid 9 (0.17 g).

**Yield**
0.17 g, 71%; yellow solid; R₇ = 0.14 (PE/EA, 7:3).

**Melting point**
97-98°C

**Mol. Formula**
C₁₂H₁₄O₅

**IR** (CHCl₃)
νmax (cm⁻¹) = 3390, 1730, 1654, 1602, 1432, 1249.

**¹H NMR**
(CDCl₃, 200 MHz)
δH (ppm) = 6.47 (dt, J = 5.7 Hz, 1H, CH), 5.85 (d, J = 7.3 Hz, 2H, CH₂), 3.77 (s, 3H, OCH₃), 3.65 (d, J = 6.2 Hz, 1H, CH), 2.54-2.30 (m, 2H, CH₂), 1.77-1.55 (m, 4H, CH₂).

**¹³C NMR**
(CDCl₃, 50 MHz)
δC (ppm) = 187.6 (C), 182.2 (C), 182.0 (C), 177.5 (C), 158.9 (C), 147.0 (C), 133.3 (CH), 107.2 (CH), 56.4 (OCH₃), 30.9 (CH₂), 28.4 (CH₂), 27.0 (CH₂), 25.3 (CH₂).

**Elemental analysis**
Calcd for C₁₂H₁₄O₅: C, 60.50; H, 5.92.
Found: C, 60.47; H, 5.89.

**X-ray crystal structure determination**
X-ray diffraction data for all the crystallized compounds were collected at T = 296 K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. Crystal to detector distance was 6.05 cm, 512 x 512 pixels / frame and other conditions used are oscillation / frame (-0.3°),
maximum detector swing angle (–30.0°), beam center (260.2, 252.5) and in plane spot width (1.24). SAINT integration and SADABS correction were also applied. The structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)\textsuperscript{61} was used for structure solution and full matrix least squares refinement on F2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97.

2-Methoxy-6-propylcyclohexa-2, 5-diene-1,4-dione (6)

Single crystals of the compound were found to grow best in solution mixture of ethanol and dichloromethane by slow evaporation. Colorless needle like crystal of approximate size 320 x 160 x 20 mm\(^3\), was used for data collection. Multirun data acquisition, total scans (3), total frames (17946), exposure / frame (15.0 sec), \(\theta\) range (2.15 to 29.37°) and completeness to \(\theta\) of 29.37° (98.6 %) were registered. The compound has molecular formula C\(_{10}\) H\(_{12}\) O\(_3\) and \(M = 180.20\). Crystals belong to Triclinic system with P-1 space group with unit cell dimensions as a = 10.0123(17), b = 10.2107(18), c = 11.190(3) Å. Other parameters like volume 931.3(3) Å\(^3\), \(Z = 4\), \(D_c = 1.285\) Mg/m\(^3\), absorption coefficient \(\mu (Mo-K\alpha) = 0.094\) mm\(^{-1}\) were also recorded. 11542 reflections measured of which 2874 are unique. The final R indices \([I>2\sigma(I)]\) are R1 = 0.0764, wR2 = 0.1930.

Table 1. Crystal data and structure refinement for compound 6.
Empirical formula | C₁₀H₁₂O₃  
Formula weight | 180.20  
Temperature | 296(2) K  
Wavelength | 0.71073 Å  
Crystal system | Triclinic  
Space group | P-1  
Unit cell dimensions | a = 10.0123 (17) Å  
| b = 10.2107(18) Å  
| c = 11.190(3) Å  
| α = 98.807(4)°  
| β = 116.387(3)°  
| γ = 106.241(3)°  
Volume | 931.3(3) Å³  
Z | 4  
Density (Calcd) | 1.285 Mg/m³  
Absorption coefficient | 0.094 mm⁻¹  
F(000) | 384  
Crystal size | 320 x 160 x 20 mm³  
Theta range for data collection | 2.15 to 29.37°  
Index ranges | -13 <= h <= 13, -14 <= k <= 13, -15 <= l <= 15  
Reflections collected | 17946  
Independent reflections | 5058 [R(int) = 0.0571]  
Completeness to theta = 28.28° | 98.6 %  
Absorption correction | Semi-empirical from equivalents  
Refinement method | Full-matrix least-squares on F²  
Data / restraints / parameters | 5058 / 0 / 239  
Goodness-of-fit on F² | 0.966  
Final R indices [I > 2σ(I)] | R1 = 0.0764, wR2 = 0.1930  
R indices (all data) | R1 = 0.1839, wR2 = 0.2587  
Largest diff. peak and hole | 0.650 and -0.230 e. Å⁻³

5-[2-(tert-Butyldimethylsilyloxy)-3-methoxyphenyl] pentan-1-ol (34)

Single crystals of the compound were found to grow best in solution mixture of methanol and dichloromethane by slow evaporation. Colorless needle like crystal of approximate size 568 x 223 x 68 mm³, was used for data collection. Multirun data acquisition, total scans (3), total frames (40024), exposure / frame (15.0 sec), θ range (0.58 to 28.41°) and completeness to θ of 28.41° (89.6 %) were registered. The compound has molecular formula C₁₈H₃₂O₃Si
and $M = 324.53$. Crystals belong to Triclinic system with P-1 space group with unit cell dimensions as $a = 7.846(3)$, $b = 14.427(5)$, $c = 35.046(12)$ Å. Other parameters like volume $3962(2)$ Å³, $Z = 8$, $D_c = 1.088$ Mg/m³, absorption coefficient $\mu$ (Mo–Kα) = 0.128 mm⁻¹ were also recorded. 11542 reflections measured of which 2874 are unique. The final R indices [I>2$\sigma$(I)] are $R1 = 0.1706$, $wR2 = 0.4320$.

**Table 2. Crystal data and structure refinement for compound 34.**

<table>
<thead>
<tr>
<th><strong>Empirical formula</strong></th>
<th>C₁₈H₃₂O₃Si</th>
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<tr>
<td><strong>Formula weight</strong></td>
<td>324.53</td>
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<td><strong>Temperature</strong></td>
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<tr>
<td><strong>Wavelength</strong></td>
<td>0.71073 Å</td>
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<tr>
<td><strong>Crystal system</strong></td>
<td>Triclinic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P-1</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td></td>
</tr>
<tr>
<td>$a = 7.846(3)$ Å</td>
<td>$\alpha = 90.044(6)^\circ$</td>
</tr>
<tr>
<td>$b = 14.427(5)$ Å</td>
<td>$\beta = 93.070(7)^\circ$</td>
</tr>
<tr>
<td>$c = 35.046(12)$ Å</td>
<td>$\gamma = 89.989(7)^\circ$</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>3962(2) Å³</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>8</td>
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<tr>
<td><strong>Density (Calcd)</strong></td>
<td>1.088 Mg/m³</td>
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<tr>
<td><strong>Absorption coefficient</strong></td>
<td>0.128 mm⁻¹</td>
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<tr>
<td><strong>F(000)</strong></td>
<td>1424</td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
<td>568 x 223 x 68 mm³</td>
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<tr>
<td><strong>Theta range for data collection</strong></td>
<td>0.58 to 28.41°</td>
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<tr>
<td><strong>Index ranges</strong></td>
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<tr>
<td>Reflections collected</td>
<td>17856 ( [R(\text{int}) = 0.1131] )</td>
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<tr>
<td>-----------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>5058 ( [R(\text{int}) = 0.0571] )</td>
</tr>
<tr>
<td>Completeness to theta = 28.41°</td>
<td>89.6 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on ( F^2 )</td>
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<tr>
<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on ( F^2 )</td>
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<tr>
<td>Final R indices ([I&gt;2\sigma(I)])</td>
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</tr>
<tr>
<td>R indices (all data)</td>
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<td>0.981 and -0.591 e. Å(^{-3})</td>
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1.6 References


Chapter 1


### 1.7 Appendix A: Characterization data of synthesized compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
<th>Page No.</th>
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</thead>
<tbody>
<tr>
<td>Compound 26</td>
<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
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<td>Compound 28</td>
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<td>Compound 6</td>
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<td>Compound 29</td>
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<td>Compound 30</td>
<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
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<td>Compound 31</td>
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<td>Compound 34</td>
<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
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<td>Compound 35</td>
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<td>Compound 36</td>
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<tr>
<td>Compound 8</td>
<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
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</tr>
<tr>
<td>Compound 9</td>
<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
<td>52</td>
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</table>
2-(tert-Butyldimethylsilyloxy)-3-methoxybenzaldehyde (26)
$^1$H NMR

![1H NMR spectrum](image)

$^1$C NMR

![13C NMR spectrum](image)

DEPT

![DEPT spectrum](image)

1-[2-(tert-Butyldimethylsilyloxy)-3-methoxyphenyl]prop-2-en-1-ol (24)
Chapter 1

**1H NMR**

![1H NMR spectra](image)

**13C NMR**

![13C NMR spectra](image)

**DEPT**

![DEPT spectra](image)

*tert*-Butyl-(2-methoxy-6-propylphenoxy)-dimethylsilane (27)

2013 PhD thesis: T. Kaur, University of Pune
2-Methoxy-6-propylphenol (28)
2-Methoxy-6-propylcyclohexa-2,5-diene-1,4-dione (6)
(2-((tert-Butyldimethylsilyl)oxy)-3-methoxyphenyl)methanol (29)
2-(((tert-Butyldimethylsilyl)oxy)-3-methoxybenzyl-4-methylbenzenesulfonate (30)
Chapter 1

**1H NMR**

![1H NMR Spectrum](image)

**13C NMR**

![13C NMR Spectrum](image)

**DEPT**

![DEPT Spectrum](image)

*tert*-Butyl-(2-methoxy-6-methylphenoxy)dimethylsilane (31)
2-Methoxy-6-methylcyclohexa-2,5-diene-1,4-dione (7)
Methyl 5-(2-((tert-butyldimethylsilyloxy)-3-methoxyphenyl)pentanoate (33)
**Chapter 1**

**1H NMR**

![1H NMR spectrum](image)

**13C NMR**

![13C NMR spectrum](image)

**DEPT**

![DEPT spectrum](image)

5-[2-(tert-Butyldimethylsilyloxy)-3-methoxyphenyl]pentan-1-ol (34)

2013 PhD thesis: T. Kaur, University of Pune
**Chapter 1**

**1H NMR**

![1H NMR Spectrum](image)

**13C NMR**

![13C NMR Spectrum](image)

**DEPT**

![DEPT Spectrum](image)

5-[2-(tert-Butyldimethylsilyloxy)-3-methoxyphenyl]pentyl-4-methylbenzenesulfonate (35)
Chapter 1

**$^1$H NMR**

![$^1$H NMR spectrum](image1)

**$^{13}$C NMR**

![$^{13}$C NMR spectrum](image2)

**DEPT**

![DEPT spectrum](image3)

*tert*-Butyl-(2-methoxy-6-pentylphenoxy)dimethylsilane (36)

2013 PhD thesis: T. Kaur, University of Pune
2-Methoxy-6-pentylcyclohexa-2,5-diene-1,4-dione (Primin) (8)
5-(5-Methoxy-3,6-dioxocyclohexa-1,4-dienyl)-pentanoic acid (Primin acid) (9)
This section deals with the synthetic efforts tried towards the first total synthesis of antibacterial natural product, Oenostacin. It also discusses previous literature protocols utilized in the synthesis. It involves utilization of synthetic protocols for example extended Heck reaction and Chelation control selective reduction for synthesizing this natural product.
1.1 Introduction

Selman Waksman in 1942 coined the term antibiotic (from Greek αντί - anti, "against" + βιοτικός - biotikos, "fit for life") to describe any substance produced by a micro-organism that is antagonistic to the growth of other micro-organisms in high dilution. The strict definition of "antibiotic" therefore excludes synthetic compounds such as the sulphonamides (which are antimicrobial agents). In modern usage, the term "antibiotic" is more precisely used to refer to any chemotherapeutic or antimicrobial agent with activity against micro-organisms such as bacteria, fungi, or protozoa. Many antibiotic compounds used in modern medicine are produced and isolated from living organisms, such as the penicillin class produced by fungi in the genus penicillin, or streptomycin from bacteria of the genus Streptomyces. Although, a plethora of bioactive compounds have been shown to be promising agents against a wide range of micro-organisms, however there is still a strong need felt to develop newer antibiotics since these organisms have been developing resistance against even newly introduced antibiotics.

The plant Oenothera biennis (Family: Onagraceae) commonly known as Evening Primrose is a genus of herbs and shrubs; its species are widely distributed in temperate America along with some species found in tropics. Few species of this genus O. biennis have been introduced as ornamental plants in India. The seeds contain high γ-linolenic acid content and are useful for the formation of prostaglandins and related hormones. The seeds possess fatty acids and sterols while the leaves show high content of flavonoids and oenothein A. The plant possess several bio-active properties e.g. antiarthritic, antitumor and antithrombic properties. The bioactive component oenostacin 1 was isolated from the roots of the plant O. biennis in the year 1999 (Figure 1).

![Figure 1. Structure of antibacterial agent Oenostacin, 1.](image-url)
It has shown to be potent antibacterial agent against *Staphylococcus aureus* and *Staphylococcus epidermidis* having EC$_{50}$ 0.12 μM activity. It is known that *S. aureus*, one of the most successful opportunistic human Gram positive pathogens, is responsible for postoperative wound infections, bacteraemia, pneumonia, osteomyelitis, mastitis, acute endocarditis, and deep abscesses in various organs. In contrast to *S. aureus*, infections caused by *S. epidermidis* are less acute in nature. However, *S. epidermidis* is an important human pathogen and is the predominant cause of many nosocomial infections.\(^1\)

Considering, its potent biological activities and low yield from natural sources, it is highly desirable to synthesize this potent antibacterial compound 1. Oenostacin 1 shows potent activity against *S. aureus* and *S. epidermidis*, respectively and the latter strains has often been found to be resistant to antibiotics such as penicillin, amoxicillin and methicillin.

1.2 Present work: Objective and Rationale

However, the bioactive compound 1 is not abundant in nature and no other methods are reported in literature, therefore, synthesis of compound 1 and its analogues for further structural activity relationship (SAR) is highly desirable. The retrosynthetic plan was designed for the antibacterial agent, oenostacin 1. Flexible scheme was devised and outlined in retrosynthetic plan (Scheme 1).

![Scheme 1](image)

**Scheme 1.** Retrosynthetic strategy for the synthesis of antibacterial agent, Oenostacin 1.

2013 PhD thesis: *T. Kaur*, University of Pune
1.3 Results and Discussion

Retrosynthetic analysis of oenostacin 1 suggested it could be assessed from the fully methylated analog 2. This fully protected analog 2 in turn could be synthesized by selective reduction of \(\alpha,\beta\)-double bond of \(\alpha,\beta,\gamma,\delta\)-conjugated diene ester 3.\(^7\) This diene could be synthesized from the Heck cross-coupling reaction of protected analog 4 and diene 5. Compound 4 could be easily synthesized by protecting phenolic and carboxylic groups of 4-bromo-3,5-dihydroxy benzoic acid (Scheme 1).

Initially, Heck reaction was tried on 4-bromo-3,5-dihydroxy benzoic acid 6 with \((E)\)-methyl-penta-2,4-dienoate 5 using conventional reaction conditions (Table 1).\(^7\) However, unreacted starting materials were recovered. It was then visualized that due to presence of free phenolic and carboxylic acid groups, the coupling reaction was failed to furnish the desired product. So it was mandatory to protect the phenolic and carboxylic acid groups of 4-bromo-3,5-dihydroxy benzoic acid 6. In order to accomplish this, various protecting groups were screened. To achieve the array of derivatives, 4-bromo-3,5-dihydroxy benzoic acid 6 was treated with benzyl bromide to furnish benzyl derivative 7, methoxyl methyl bromide to furnish methoxy methyl (MOM) derivative 8, \(p\)-methoxy benzyl bromide to furnish \(p\)-methoxybenzyl (PMB) derivative 9, and acetyl chloride to furnish acetate derivative 10, respectively (Table 1). However, Heck reaction of protected 4-bromo-3,5-dihydroxy benzoic acid derivatives 7, 8, 9, 10 with diene compound 5 respectively, did not furnish the desired product.

| Table 1. Standardization of Heck cross-coupling reaction conditions |
|---|---|---|
| **Substrates** | \(\alpha, \beta, \gamma, \delta\)-conjugated-diene |
| Product |
| ![Structure 6](image) | ![Structure 5](image) | No reaction |

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We came to know through literature search that substrates bearing free carboxylic acid group furnishes Heck reaction product in good yields. Hence, we tried our reaction with substrate 11, however no product formation was observed.  

It was then decided to protect the phenolic and carboxylic group of 4-bromo-3,5-dihydroxy benzoic acid 6 as methoxy and methyl ester, respectively and investigate the Heck reaction again. The formation of product 12 was delineated by its
spectral analysis. In $^1$H NMR spectrum, the methoxy proton signals were observed at $\delta$ 3.94 (s) and 3.92 (s) ppm. In $^{13}$C NMR spectrum, the methoxy carbon signals were observed at $\delta$ 56.5 and 52.4 ppm. The classical Heck reaction on the 4-bromo-3,5-dihydroxy benzoic acid 6 with (E)-methyl penta-2,4-dienoate 5 and palladium acetate as a catalyst and dicyclohexyl-N-methylamine as a base furnished the desired $\alpha,\beta,\gamma,\delta$-conjugated diene ester 3 in 37% yield (Scheme 2). The formation of product 3 was confirmed by its spectral analysis. In $^1$H NMR spectrum, the olefinic proton signals were observed at $\delta$ 6.75-6.55 (m) and 7.47-7.32 (m) ppm. In $^{13}$C NMR spectrum, the olefinic carbon signals were observed at $\delta$ 147.3, 131.9, 131.3 and 120.4 ppm.

Scheme 2. Successful Heck reaction conditions on the analog 12.

Afterwards, regioselective reduction of $\alpha,\beta$-double bond of $\alpha,\beta,\gamma,\delta$-conjugated diene ester 3 was attempted under various reduction conditions reported in the literature.\textsuperscript{9} Initial attempts for the reduction of 3 with Wilkinson’s catalyst or H$_2$/Pd-C (10%) furnished the tetrahydro compound 13.\textsuperscript{10} The formation of product 13 was confirmed by its spectral analysis. In $^1$H NMR spectrum, the olefinic proton signals were observed at $\delta$ 1.69-1.63 (m) and $\delta$ 2.68 (t, $J$ = 7.5 Hz, 2H) and 2.34 (t, $J$ = 7.8 Hz, 2H) ppm. In $^{13}$C NMR spectrum, the olefinic carbon signals were observed at $\delta$ 33.9, 30.9, 24.8 and 22.6 ppm (Scheme 3).

Scheme 3. Optimized conditions for the selective hydrogenation on derivative 3.

Hence, it was decided to carry out chelation control reduction method using sodium borohydride and cobalt chloride hexahydrate as a catalyst.\textsuperscript{11} The formation of product 2 was confirmed by its spectral analysis. In $^1$H NMR spectrum, the olefinic proton signals were observed at $\delta$ 6.18-6.01 (m) and 5.40-5.17 (m) ppm. In $^{13}$C NMR
spectrum, the olefinic carbon signals were observed at δ 139.3 and 114.3 ppm. The desired product 2 was obtained in 85% yield which was fully characterized by its spectroscopic methods (IR, $^1$H, $^{13}$C NMR and EI-MS) (Scheme 4).

**Scheme 4.** Optimized reduction reaction conditions on the analog 3.

To achieve the title compound 1, protected analogue 2 was first subjected to methyl ester hydrolysis. Afterwards, methoxy groups of compound 14 were deprotected using TMS-Cl/NaI in acetonitrile to furnish deprotected analogue 15 (Scheme 5).

**Scheme 5.** Synthetic efforts towards the synthesis of antibacterial agent Oenostacin, 1.

The formation of product 15 was confirmed by its spectral analysis. In $^1$H NMR and $^{13}$C NMR spectrum, absence of proton signals at δ 3.94 (s), 3.92 (s) and 56.5, 52.4 ppm, respectively confirmed deprotection of all the protecting groups to furnish compound 15.
There are many reports in the literature to protect aliphatic carboxylic acid group in the presence of aromatic carboxylic group. Few methods reported in the literature were tried for this selective esterification as discussed in Table 2. However, none of the methods could furnish the desired product.

**Table 2. Attempted reaction conditions tried for the selective esterification**

<table>
<thead>
<tr>
<th>Methods tried</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amberlite-IR 120, MeOH, reflux</td>
<td>Diesterified product</td>
</tr>
<tr>
<td>NiCl₂·6H₂O, MeOH, reflux</td>
<td>Diesterified product</td>
</tr>
<tr>
<td>2N H₂SO₄, MeOH, reflux</td>
<td>Decomposition</td>
</tr>
<tr>
<td>I₂/H₂O, MeOH, reflux</td>
<td>NR</td>
</tr>
</tbody>
</table>

In order to accomplish the synthesis of this natural product in good yield, we thought of alternative strategy (Scheme 6). Alternatively, we visualized that compound 1 could be synthesized by the oxidation of the benzylic acid derivative 16, which in turn could be obtained from allylic alcohol 17.

![Scheme 6](image)

Scheme 6. Retrosynthetic strategy for the synthesis of antibacterial agent, Oenostacin 1.

Compound 17 in turn could be obtained aldehydic compound 18, which could be easily accessible from bromo derivative 19. Compound 19 could be synthesized by the reduction of ester 12 and TBS protection of the benzylic alcohol.

First 3,5-dihydroxy-4-bromobenzoic acid 6 was fully protected to furnish compound 12 and further ester group was reduced with LAH/THF to alcohol 20 (Scheme 6). The formation of product 20 was confirmed by its spectral analysis. In ¹H NMR spectrum, the proton signal for benzylic group was observed at δ 4.64 (s) ppm.

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In $^{13}$C NMR spectrum, benzylic carbon signals were observed at $\delta$ 64.7 ppm, thus confirming the formation of the product. The primary alcohol group of compound 20 was then protected as $t$-butyl-dimethylsilyl ether derivative 19. In $^1$H NMR spectrum, of compound 19 the proton signals for $t$-butyl-dimethylsilyl were observed at $\delta$ 0.94 and 0.10 ppm. In $^{13}$C NMR spectrum, the $t$-butyl-dimethylsilyl carbon signals were observed at $\delta$ 25.89, 18.34 and -5.27 ppm. This bromo compound 19 was subjected to bromo to lithium exchange reaction and quenched with DMF as a nucleophile to furnish aldehydic compound 18. In $^1$H NMR spectrum, the proton signal for compound 18 aldehydic group was observed observed at $\delta$ 10.38 ppm. In $^{13}$C NMR spectrum, aldehydic carbon signal was observed at $\delta$ 188.8 ppm.

![Scheme 7](image)

Scheme 7. Synthetic efforts towards antibacterial agent, Oenostacin 1.

Compound 18 was treated with vinyl magnesium bromide (1.0M) to generate the allylic alcohol 17 in 75% yield. In $^1$H NMR spectrum, the proton signals for compound 17 allylic group were observed at $\delta$ 6.50-6.06 (m), 5.15-5.14 (m) and 4.99-4.94 (m) ppm. In $^{13}$C NMR spectrum, allylic carbon signals were observed at $\delta$ 140.2, 68.4 and 113.2 ppm. This allylic compound 17 was then subjected to Johnson-Claisen rearrangement to obtain the compound 21. TBDMS group was deprotected in compound 21 using pyridinium-$p$-toluenesulphonate (PPTS) in 87% yield to furnish alcohol 16.
First we have tried this with Oxone:iodobenzoic acid (1:2) in acetonitrile and water, but the reaction could not furnish the desired product. It results in the generation of complex mixture which was difficult to purify by silica gel column chromatography.

Scheme 8. Synthetic efforts carried out for the oxidation of benzylic alcohol 16.

Again, when the reaction was tried using IBX and HOBt combination, it was unsuccessful. Similarly, when we tried to oxidize alcohol 16 using trichloroisocyanuric acid, TEMPO, sodium bromide, and DCM as a solvent, decomposition of the starting material took place (Scheme 8). However, when we tried to oxidize alcohol 16 using iodoxybenzoic acid (IBX) and DMSO, we could get aldehyde 23 in 94% yield (Scheme 9).


We further tried to oxidize the aldehyde 23 into acid 22 by following methods: (a) CuBr, TBHP (b) Silver Oxide/NaOH. However, none of the methods led to the acid 22 (Scheme 10).
Scheme 10. Synthetic efforts for the oxidation of aldehyde 23 into acid 22.

1.4 Conclusion

In conclusion, two different synthetic routes were explored towards the synthesis of antibacterial agent oenostacin 1. Since, the synthesis of target compound 1 could not be accomplished. But we believe that some of the synthesized compounds being close analog of compound 1, could be useful in deducing valuable structure-activity-relationship (SAR) of bioactive molecules for further studies.
1.5 Experimental

Methyl-4-bromo-3,5-dimethoxybenzoate (12)

\[
\begin{array}{c}
\text{OCH}_3 \\
\text{H}_3\text{CO}_2\text{C} \\
\text{Br} \\
\text{OCH}_3 \\
12
\end{array}
\]

To a stirred suspension of K$_2$CO$_3$ (8.91 g, 64.9 mmol) in acetone (20 mL) at room temperature was added 3,5-dihydroxy-4-bromo-benzoic acid (5.0 g, 21.6 mmol). The mixture was stirred for 30 min and then dimethylsulphate (6.15 mL, 64.9 mmol) was added. The reaction mixture was refluxed for 3 h and then filtered through celite. The crude mixture was purified by silica gel column chromatography (PE/EA, 8:2) to isolate product 12 (5.73 g).

**Yield** 5.73 g, 97%; white solid; \( R_f = 0.5 \) (PE/EA, 7:3).

**Melting Point** 122-123°C

**Mol. Formula** C$_{10}$H$_{11}$BrO$_4$

**IR (CHCl$_3$)**

\[ \nu_{\text{max}} (\text{cm}^{-1}) = 3861, 3860, 3843, 3643, 2936, 2846, 2400, 1741, 1693, 1547, 1515, 1236, 1121. \]

**\(^1\)H NMR**

\[ \delta_H (\text{ppm}) = 7.23 (\text{s, } CH, 2H), 3.94 (\text{s, } OCH}_3, 3H), \]

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

\[ 3.92 (\text{s, } OCH}_3, 3H). \]

**\(^{13}\)C NMR**

\[ \delta_C (\text{ppm}) = 166.3 \text{ (C), 156.9 \text{ (C), 130.1 \text{ (CH),}}}, \]

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

\[ 106.5 \text{ (CH), 105.4 \text{ (CH), 58.5 \text{ (OCH}_3), 56.5 \text{ (OCH}_3), 52.4 \text{ (OCH}_3).} \]

**Elemental analysis**

Calcd for C$_{10}$H$_{11}$BrO$_4$: C, 43.66; H, 4.03

Found: C, 43.72; H, 4.10.

Methyl-3,5-dimethoxy-4-((1\(E\), 3\(E\))-5-methoxy-5-oxopenta-1, 3-dien-1-yl)benzoate (3)

\[
\begin{array}{c}
\text{OCH}_3 \\
\text{H}_3\text{CO}_2\text{C} \\
\text{CO}_2\text{CH}_3 \\
3
\end{array}
\]

To a solution of bromo derivative 12 (2.0 g, 7.32 mmol) in dry DMF (10 ml), potassium carbonate (2.02 g, 14.65 mmol) and palladium acetate (0.82 g, 0.3 mmol) were added and refluxed it at 160 °C for 3 h. The reaction was stirred for 3 h. After 2013 PhD thesis: T. Kaur, University of Pune
completion it was filtered over celite and filtrate was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 9:1) to afford product 3 (0.83 g).

**Yield** 0.83 g, 37%; yellow solid; R₇ = 0.55 (PE/EA, 7:3).

**Melting Point** 104-109°C

**Mol. Formula** C₁₆H₁₈O₆

**IR (CHCl₃)** νₘₐₓ (cm⁻¹) = 3893, 3860, 3843, 3829, 2948, 2400, 1718, 1238, 747.

**¹H NMR** (CDCl₃, 200 MHz) δₕ (ppm) = 7.40-7.21 (m, CH, 5H), 6.75-6.55 (m, CH, 1H), 5.96 (d, J =14.1 Hz, CH, 1H), 3.91 (s, OCH₃, 3H), 3.74 (s, OCH₃, 3H).

**¹³C NMR** (CDCl₃, 50 MHz) δₜ (ppm) = 167.6 (C), 166.6 (C), 158.7 (C), 147.3 (CH), 131.9 (CH), 131.3 (CH), 130.5 (CH), 120.4 (CH), 117.8 (CH), 104.8 (CH), 55.9 (OCH₃), 52.3 (OCH₃), 51.4 (OCH₃).

**Elemental analysis** Calcd for C₁₆H₁₈O₆: C, 62.74; H, 5.92

**Found:** C, 62.81; H, 5.81

*(E)-Methyl 3,5-dimethoxy-4-(5-methoxy-5-oxopent-1-en-1-yl) benzoate (2)*

To a solution of compound 3 (2.0 g, 6.53 mmol) in anhydrous MeOH (10 mL) and 10% cobalt chloride hexahydrate (190 mg) was added. The resulting solution was cooled at 0 °C for 30 min and slowly NaBH₄ (0.24 g, 6.53 mmol) for 6 h. After completion of the reaction (TLC), MeOH was evaporated and filtrate was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 8:2) to furnish pure product 26 (1.71 g).
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Yield 1.71 g, 85%; yellow syrupy solid; $R_f = 0.60$ (PE/EA, 8:2).

Mol. Formula $C_{16}H_{20}O_6$

IR (CHCl$_3$) $\nu_{\text{max}}$ (cm$^{-1}$) = 3861, 3843, 3744, 3017, 2950, 1723, 1646, 1578, 1547, 1515, 1458, 1413, 1322, 1238, 1216, 1122.

$^1$H NMR $\delta$H (ppm) = 7.23 (s, CH, 2H), 3.94 (s, OCH$_3$, 3H), 3.92 (s, OCH$_3$, 3H).

$^{13}$C NMR $\delta$C (ppm) = 166.3 (C), 156.9 (C), 130.1 (CH), 106.5 (CH), 105.4 (CH), 58.5 (OCH$_3$), 56.5 (OCH$_3$), 52.4 (OCH$_3$).

Elemental analysis Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54

Found: C, 62.41; H, 6.62.

Methyl-3,5-dimethoxy-4-(5-methoxy-5-oxopentyl) benzoate (13)

To a solution of compound 3 (0.5 g, 1.612 mmol) in anhydrous MeOH (10 mL), 10% Pd/C (50 mg) was added and the resulting heterogeneous solution was stirred vigorously under H$_2$ atm for 6 h. After completion of the reaction (TLC), the mixture was filtered over celite. The filtrate was evaporated and purified by silica gel column chromatography (PE/EA, 8:2) to furnish pure product 13 (0.41 mg).

Yield 0.41 g, 80%; syrupy solid; $R_f = 0.62$ (PE/EA, 8:2).

Mol. Formula $C_{16}H_{22}O_6$

IR (CHCl$_3$) $\nu_{\text{max}}$ (cm$^{-1}$) = 3861, 3843, 3019, 2954, 1725, 1582, 1248, 1221, 1130.

$^1$H NMR $\delta$H (ppm) = 7.23 (s, CH, 2H), 3.91 (s, OCH$_3$, 3H), 3.85 (s, OCH$_3$, 3H), 3.66 (s, OCH$_3$, 3H), 2.68 (t, $J = 7.5$ Hz, 2H), 2.34 (t, $J = 7.8$ Hz, 2H), 1.69-1.61 (m, CH$_2$, 2H), 1.53-1.49 (m, CH$_2$, 2H).

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To a solution of compound 2 (0.5 g, 1.61 mmol) in MeOH-H₂O (8 mL, 3:1) NaOH was added and the resulting solution was heated at reflux 3 h under an N₂ atmosphere. The reaction mixture was acidified with 1N HCl (10 mL) and then extracted with EtOAc (3 × 20 mL). The crude residue was purified by silica gel column chromatography (PE/EA, 6:4) to give acid 14 (0.30 g).

**(E)-4-(4-carboxybut-1-en-1-yl)-3,5-dimethoxybenzoic acid (14)**

To a solution of compound 2 (0.5 g, 1.61 mmol) in MeOH-H₂O (8 mL, 3:1) NaOH was added and the resulting solution was heated at reflux 3 h under an N₂ atmosphere. The reaction mixture was acidified with 1N HCl (10 mL) and then extracted with EtOAc (3 × 20 mL). The crude residue was purified by silica gel column chromatography (PE/EA, 6:4) to give acid 14 (0.30 g).

**Yield**

0.30 g, 67%; white solid; Rₛ = 0.20 (PE/EA, 7:3).

**Mol. Formula**

C₁₄H₁₆O₆

**IR (CHCl₃)**

νₘₐₓ (cm⁻¹) = 3861, 3843, 3019, 2954, 1725, 1582, 1248, 1221, 1130.

**¹H NMR**

δₕ (ppm) = 7.26-7.25 (s, CH, 3H), 6.73-6.66 (m, CH, 1H), 3.84 (s, OCH₃, 3H), 2.69 (t, J = 7.3 Hz, 2H), 2.30 (t, J = 7.8 Hz, 2H).

**¹³C NMR**

δₙ (ppm) = 177.9 (C), 170.1 (C), 159.5 (C), 136.5 (C), 130.7 (C), 125.4 (CH), 122.2 (C), 106.1 (CH), 56.3 (OCH₃), 34.9 (CH₂), 29.5 (CH₂).

**Elemental analysis**

Caled for C₁₄H₁₆O₆: C, 59.99; H, 5.75

Found: C, 60.01; H, 5.82.
To a solution of compound 14 (0.282 g, 1.0 mmol) in dry acetonitrile (3.0 mL), chlorotrimethylsilane (0.216 g, 2.0 mmol), sodium iodide (0.45 g, 3.0 mmol) was added and heated at 100 °C under reflux under N₂ atmosphere. The reaction was refluxed for 3 h and acetonitrile was evaporated, acidified with 1N HCl and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 8:2) to furnish pure product 26 (0.105 g).

**Yield**

0.105 g, 42%; yellow syrupy solid; $R_f = 0.2$

(PE/EA, 1:1).

**Mol. Formula**

C₁₂H₁₂O₆

**IR (CHCl₃)**

$\nu_{\text{max}}$ (cm⁻¹) = 3861, 3843, 3019, 2954, 1725, 1582, 1248, 1221, 1130.

**¹H NMR**

(Acetone-D₆, 200 MHz) $\delta_H$ (ppm) = 7.96-7.05 (m, CH, 4H), 3.26 (t, $J = 8.0$ Hz, 2H), 2.62 (t, $J = 7.5$ Hz, 2H).

**¹³C NMR**

(Acetone-D₆, 50 MHz) $\delta_C$ (ppm) = 172.6 (C), 171.8 (C), 151.1 (C), 134.1 (CH), 130.9 (CH), 126.4 (CH), 120.9 (CH), 119.4 (CH), 117.9 (CH), 117.9 (CH), 35.2 (CH₂), 33.7 (CH₂).

**Elemental analysis**

Calcd for C₁₂H₁₂O₆: C, 57.14; H, 4.80

Found: C, 57.23; H, 4.89.

**(4-Bromo-3,5-dimethoxyphenyl) methanol (20)**

To an ice-cold solution of compound 12 (2.0 g, 7.32 mmol) in anhydrous THF (10 mL), LAH (0.27 g, 7.32 mmol) was added slowly and stirred at room temperature for 4 h under an argon atmosphere. After completion of the reaction, it was cooled to 0-5 °C and quenched with 1N NaOH (10 mL). The resulting white precipitate was filtered through Celite and the filtrate was dried over anhydrous Na₂SO₄ and evaporated to

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give a crude residue which was purified by silica gel column chromatography (PE/EA, 7:3) to furnish product 20 (1.56 g).

**Yield** 1.56 g, 87%; colorless oil; $R_f = 0.61$ (PE/EA, 9:1).

**Melting Point** 98-100°C

**Mol. Formula** C$_9$H$_{11}$BrO$_3$

**IR (CHCl$_3$)** $\nu_{\text{max}}$ (cm$^{-1}$) = 3894, 3860, 3643, 2936, 2846, 2401, 1741, 1706, 1693, 1547, 1515, 1236, 1121.

**$^1$H NMR**

\[ \delta_H (\text{ppm}) = 6.57 (s, CH, 2H), 4.64 (s, CH$_2$, 2H), \]

(CDC$_3$, 200 MHz) 3.89 (s, OCH$_3$, 3H).

**$^{13}$C NMR**

\[ \delta_C (\text{ppm}) = 156.8 (C), 141.5 (CH), 102.8 (CH), \]

(CDC$_3$, 50 MHz) 99.4 (C), 64.7 (CH$_2$), 56.2 (OCH$_3$).

**Elemental analysis**

Calcd for C$_9$H$_{11}$BrO$_3$: C, 43.75; H, 4.49

Found: C, 43.82; H, 4.52.

((4-Bromo-3, 5-dimethoxybenzyl)oxy)(tert-butyl)dimethylsilane (19)

To a solution of compound 20 (3.92 g, 16.0 mmol), in anhydrous DMF (10 mL) imidazole (1.67 g, 24.5 mmol) and TBSCl (3.7 g, 24.5 mmol) was added. The reaction was stirred at room temperature for 7 h. After completion the precipitate, water was added and it was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 8:2) to afford product 19 (5.47 g).

**Yield** 5.47 g, 95%; colorless oil; $R_f = 0.76$ (PE/EA, 7:3).

**Mol. Formula** C$_9$H$_{11}$BrO$_3$Si

**IR (CHCl$_3$)** $\nu_{\text{max}}$ (cm$^{-1}$) = 3744, 2931, 2890, 2854, 1693, 1547, 1514, 1460, 1415, 1367, 1329, 1255, 1229, 1158.

**$^1$H NMR**

\[ \delta_H (\text{ppm}) = 6.56 (s, CH, 2H), 4.70 (s, CH$_2$, 2H), \]

(CDC$_3$, 200 MHz) 3.87 (s, OCH$_3$, 3H), 0.94 (s, CH$_3$, 9H), 0.10 (s, Si(CH$_3$)$_2$, 6H).
4-((tert-Butyldimethylsilyl)oxy)methyl)-2,6-dimethoxybenzaldehyde (17)

To a -78 °C cooled solution of compound 19 (2.0 g, 5.55 mmol) in anhydrous THF (10 mL) n-butyl lithium (5.21 mL, 8.33 mmol, 1.6 M in hexane) was slowly added. The reaction mixture was warmed at 0-5 °C for 0.5 h, again cooled at -78 °C and dimethyl formamide (DMF) (0.65 mL, 8.33 mmol, 1.6 M in hexane) was slowly added at and stirring was continued for another 0.5 h. The reaction mixture was stirred for 1 h, it was quenched with aqueous NH₄Cl solution (2 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 8:2) to give aldehyde 17 (1.12 g).

**Yield**
1.12 g, 65%; colorless oil; \( R_f = 0.30 \) (PE/EA, 7:3).

**Mol. Formula**
C_{10}H_{26}O_{4}Si

**IR** (CHCl₃)
\( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3743, 3441, 2933, 2855, 1676, 1608, 1576, 1514, 1461, 1409, 1366, 1320, 1229, 1124, 1070.

**\(^1\)H NMR**
(\( \text{CDCl}_3", 200 \text{ MHz} \)) \( \delta_H \) (ppm) = 10.38 (s, CHO, 1H), 6.50 (s, CH, 2H), 4.67 (s, \( \text{CH}_2 \), 2H), 3.81 (s, OCH₃, 3H), 0.89 (s, \( \text{CH}_3 \), 9H), 0.05 (s, Si\( \text{CH}_3 \), 6H).

**\(^{13}\)C NMR**
(\( \text{CDCl}_3", 50 \text{ MHz} \)) \( \delta_C \) (ppm) = 188.8 (CHO), 162.1 (C), 150.8 (C), 100.5 (CH), 105.4 (CH), 64.4 (CH₂), 55.7 (OCH₃), 25.7 (CH₃), 18.1 (C), -5.5 (SiCH₃).

**Elemental analysis**
Calcd for C_{10}H_{26}O_{4}Si: C, 61.90; H, 8.44

Found: C, 63.81; H, 8.86.
1-(4-(((tert-Butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)prop-2-en-1-ol (18)

To a 0-5 °C cooled solution of compound 17 (1.0 g, 3.22 mmol) in anhydrous THF (10 mL), vinyl magnesium bromide (3.22 mL, 3.22 mmol, 1.0 M in THF) was slowly added and stirring was continued for 5 h. After completion of the reaction (TLC), it was quenched with aqueous NH₄Cl solution (2 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (PE/EA, 7:3) to give allylic alcohol 18 (0.82 g).

**Yield**

0.82 g, 75%; yellowish oil; $R_f = 0.25$ (PE/EA, 7:3).

**Mol. Formula**

C₁₈H₃₀O₄Si

**IR (CHCl₃)**

$\nu_{max}$ (cm⁻¹) = 3843, 3744, 3678, 3648, 3619, 3564, 3014, 2932, 2855, 1740, 1693, 1646, 1586, 1515, 1461, 1420, 1367, 1314, 1253, 1216, 1110.

**¹H NMR**

(CDCl₃, 200 MHz) $\delta_H$ (ppm) = 6.50 (s, CH₂, 2H), 6.18-6.01 (m, CH, 1H), 5.61-5.52 (m, CH, 1H), 5.15-4.93 (m, CH₂, 2H), 4.65 (s, CH₂, 2H), 3.75 (s, OCH₃, 3H), 0.89 (s, CH₃, 9H), 0.04 (s, SiCH₃, 6H).

**¹³C NMR**

(CDCl₃, 50 MHz) $\delta_C$ (ppm) = 157.5 (C), 142.7 (C), 140.2 (C), 116.6 (CH₂), 113.1 (CH), 101.8 (CH), 105.4 (CH), 68.3 (CH₂), 64.8 (CH), 55.7 (OCH₃), 25.8 (CH₃), 18.3 (C), -5.3 (SiCH₃).

**Elemental analysis**

Calcd for C₁₈H₃₀O₄Si: C, 62.74; H, 5.92

Found: C, 62.81; H, 5.81.
(E)-Methyl-5-((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)pent-4-enoate (21)

To a solution of compound 18 (4.0 g, 11.8 mmol) in xylene (5 mL), trimethyl-o-acetate (20.2 mL, 16.2 mmol) and propionic acid (40 μL) was added in catalytic amount. The resulting mixture was refluxed at 140 °C for 6 h. After completion of the reaction (TLC), the xylene was evaporated under reduced pressure. The crude reaction residue was purified by silica gel column chromatography (PE/EA, 8:2) to give pure product 21 (3.5 g).

Yield 3.5 g, 75%; colorless oil; Rf = 0.40 (PE/EA, 7:3).

Mol. Formula C_{21}H_{34}O_{5}Si

IR (CHCl_3) \nu_{max} (cm^{-1}) = 3861, 3843, 3743, 3678, 3648, 3618, 3589, 3557, 3501, 2936, 2850, 1727, 1647, 1609, 1579, 1547, 1514, 1460, 1418, 1366, 1317, 1220, 1124.

H NMR

(CDCl_3, 200 MHz) \delta_H (ppm) = 6.94 (d, J = 16.3 Hz, CH, 1H), 6.72-6.64 (m, CH, 2H), 6.53 (d, J = 12.0 Hz, CH, 1H), 4.71 (s, CH_2, 2H), 3.85 (s, OCH_3, 3H), 3.83 (s, OCH_3, 3H), 2.37 (t, J = 7.8 Hz, CH_2, 2H), 1.15 (t, J = 7.5 Hz, CH_2, 2H), 0.09 (s, CH_3, 9H), -0.02 (s, SiCH_3, 6H).

C NMR

(CDCl_3, 50 MHz) \delta_C (ppm) = 174.5 (C), 158.5 (C), 142.62 (C), 126.2 (CH), 124.6 (CH), 102.2 (CH), 67.0 (CH_2), 55.7 (OCH_3), 55.6 (OCH_3), 34.5 (CH_2), 27.7 (CH_2), 25.9 (CH_3), 18.4 (C), 9.2 (SiCH_3).

Elemental analysis Caled for C_{21}H_{34}O_{5}Si: C, 63.92; H, 8.69

Found: C, 63.98; H, 8.75.

(E)-Methyl 5-(4-(hydroxymethyl)-2,6-dimethoxyphenyl)pent-4-enoate (22)
To a 0 °C cooled solution of compound \(21\) (1.0 g, 2.54 mmol) in absolute ethanol (10 mL), pyridinium-\(p\)-toluene sulphonate (0.64 g, 2.54 mmol) was added and stirred for 6 h. After completion of the reaction, ethanol was evaporated under reduced pressure. The crude reaction residue was purified by silica gel column chromatography (PE/EA, 7:3) to give pure product \(22\) (0.61 g).

**Yield**
0.61 g, 87%; colorless oil; \(R_f = 0.30\) (PE/EA, 7:3).

**Mol. Formula**
\(C_{15}H_{20}O_5\)

**IR (CHCl\(_3\))**
\(v_{\text{max}} (\text{cm}^{-1}) = 3843, 3743, 3678, 3648, 3619, 2932, 2846, 1726, 1647, 1581, 1547, 1515, 1459, 1419, 1314, 1214, 1122.\)

**\(^1\)H NMR**
\((\text{CDCl}_3, 200 \text{ MHz})\)
\(\delta_H (\text{ppm}) = 6.92 (\text{d, } J = 16.2 \text{ Hz, } CH, 1\text{H}), 6.73-6.62 (\text{m, } CH, 2\text{H}), 6.51 (\text{s, } CH, 1\text{H}), 4.60 (\text{s, } CH_2, 2\text{H}), 3.80 (\text{s, } OCH_3, 3\text{H}), 3.79 (\text{s, } OCH_3, 3\text{H}), 2.32 (t, J = 7.8 \text{ Hz, } CH_2, 2\text{H}), 1.13 (t, J = 7.6 \text{ Hz, } CH_2, 2\text{H}).\)

**\(^{13}\)C NMR**
\((\text{CDCl}_3, 50 \text{ MHz})\)
\(\delta_C (\text{ppm}) = 174.5 (C), 158.5 (C), 141.9 (C), 126.4 (CH), 124.6 (CH), 112.5 (CH), 101.8 (CH), 64.9 (CH_2), 55.5 (OCH_3), 55.1 (OCH_3), 30.7 (CH_2), 29.8 (CH_2).\)

**Elemental analysis**
Calcd for \(C_{15}H_{20}O_5\): C, 64.27; H, 7.19
Found: C, 64.32; H, 7.27.
1.6 References


### 1.7 Appendix B: Characterization data of synthesized compounds

<table>
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<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
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Ethyl-4-bromo-3,5-dimethoxybenzoate (12)

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Ethyl-4-bromo-3,5-dimethoxybenzoate (12)
Methyl-3,5-dimethoxy-4-((1E,3E)-5-methoxy-5-oxopenta-1,3-dien-1-yl) benzoate (3)

1H NMR

13C NMR

DEPT
Methyl-3,5-dimethoxy-4-((1E,3E)-5-methoxy-5-oxopenta-1,3-dien-1-yl) benzoate (3)
Chapter 1

\textbf{1}^H NMR

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

\textbf{13}C NMR

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

\textbf{DEPT}

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

\textit{(E)-Methyl-3,5-dimethoxy-4-\((5\text{-methoxy-5-oxopent-1-en-1-yl})\)benzoate (2)}
Chapter 1

FT-IR

(E)-Methyl-3,5-dimethoxy-4-(5-methoxy-5-oxopent-1-en-1-yl)benzoate (2)
(E)-4-(4-Carboxybut-1-en-1-yl)-3,5-dimethoxybenzoic acid (14)
Methyl-3,5-dimethoxy-4-(5-methoxy-5-oxopentyl)benzoate (13)
(E)-4-(4-Carboxybut-1-en-1-yl)-3,5-dihydroxybenzoic acid (15)
(4-Bromo-3,5-dimethoxyphenyl)methanol (20)
(4-Bromo-3,5-dimethoxyphenyl)methanol (20)
Chapter 1

$^1$H NMR

$^1$C NMR

DEPT

$((4\text{-Bromo-3,5-dimethoxybenzyl} \text{oxy})(\text{tert-butyl})\text{dimethylsilane (19)}}$
1H NMR

13C NMR

DEPT

4-(((tert-Butyldimethylsilyl)oxy)methyl)-2,6-dimethoxybenzaldehyde (17)

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Chapter 1

FT-IR

4-(((tert-Butyldimethylsilyl)oxy)methyl)-2,6-dimethoxybenzaldehyde (17)
FT-IR

\[ 1-(4-(((\text{tert-Butyldimethylsilyl})\text{oxy})\text{methyl})-2,6-\text{dimethoxyphenyl})\text{prop-2-en-1-ol} \] (18)
(E)-Methyl-5-(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl) pent-4-enoate (21)
(E)-Methyl-5-(4-(hydroxymethyl)-2,6-dimethoxyphenyl)pent-4-enoate (22)
Chapter 1
Synthesis of Antibacterial Natural Products

Section C
Formal Synthesis of (-)-Centrolobine

This section deals with the formal synthesis of antibacterial natural product, (-)-Centrolobine. It also discusses previous literature protocols utilized in the synthesis. It involves utilization of well known synthetic protocols for example extended Oxidative Kinetic Resolution (OKR) and Barbier reaction towards formal synthesis of this natural product.
1.1 Introduction

(-)-Centrolobine 1 is a crystalline substance isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile* growing in the Amazon forest (Figure 3). In 2002, Colobert group accomplished asymmetric total synthesis of compound 1, confirming its absolute configuration. Three further, asymmetric syntheses followed from the groups of Rychnovsky, Evans and Cossy, respectively.

![Figure 1. Structure of (-)-Centrolobine, 1.](image_url)

(-)-Centrolobine 1, has been reported to be an antibiotic having strong antileishmanial activity with Calculated LD$_{50}$ values of 77 nM.

1.1.1 Previous reports

Various approaches leading to (-)-centrolobine 1 have been reported. First asymmetric total synthesis of 1 was done by Solladie and co-workers in 2002, which also established the absolute configuration of 1. Since then, a number of groups have synthesized of 1 in both racemic and optically active forms. A variety of approaches including chiral pool method have been devised to provide access to the cis-2,6-disubstituted tetrahydropyran rings. These include Prins and related cyclizations, reductive etherification, one-pot cross metathesis–hydrogenation–lactonization procedure, radical cyclization, nucleophilic addition–stereoselective reduction protocol, intramolecular oxy-Michael reaction, diastereoselective ring rearrangement metathesis–isomerization sequence, FeCl$_3$-mediated cyclization of 1,5-diol, and hetero-Diels-Alder reaction.

1.1.1a Solladie’s approach (2002)

Solladie *et al.* reported the first enantioselective total synthesis of (-)-centrolobine 1 (Scheme 1). The key reaction was the synthesis of the cis-disubstituted tetrahydropyran framework by intramolecular cyclization of the enantiopure...
hydroxyketone 5 with Et$_3$SiH and TMSOTf resulted in the generation of compound 6 which after deprotection of auxiliary and the Wittig reaction on resulting aldehyde, reduction of double bond furnished the compound 1 in 93% yield.$^2$

Scheme 1. Synthesis of (-)-Centrolobine using Solladie’s approach; Reagents and conditions: (a) i) LDA, THF, -78 °C; ii) K$_2$CO$_3$, rt, acetone; iii) Me$_2$SO$_4$, reflux, 82%; (b) i) DIBAL-H/ZnBr$_2$, THF, 80%; ii) HCl.NH(OMe)$_2$, AlMe$_3$, CH$_2$Cl$_2$, reflux, 93%; iii) p-(OMe)C$_6$H$_4$MgBr, ether/THF, reflux, 71%; (c) TMSOTf, Et$_3$SiH, CH$_2$Cl$_2$, 0 °C, 81%; (d) i) TFAA, 2,4,6-collidine, MeCN, 0 °C, 82%; ii) 4 benzyloxybenzyltriphenylphosphonium salt, n-BuLi, 0 °C, 96%; iii) H$_2$, Pd/Al$_2$O$_3$, 50 bar, rt, 93%.

1.1.1b Rychnovsky’s approach (2002)

The synthesis of (-)-centrolobine 1 commenced with a Keck enantioselective allylation of aldehyde 7 to give the homoallylic alcohol (Scheme 2), followed by esterification and reductive acetylation led to the (R)-acetoxy ether 8. The resulting ether derivative 8 was subjected to SnBr$_4$ promoted cyclization furnished tetrahydropyran 9. The tosylate protecting group of compound 9 was transformed to methyl ether by basic hydrolysis and alkylation. Compound 9 was subjected to reduction conditions to furnish (-)-centrolobine 1.$^3$

Scheme 2. Synthesis of (-)-Centrolobine using Rychnovsky’s approach; Reagents and conditions: (a) i) (S)-BINOL, Ti(O-iPr)$_4$, allyl-SnBu$_3$, 79%, 94% ee; ii) DCC, DMAP, 4-(OBn)C$_6$H$_4$CH$_2$CH$_2$CO$_2$H, 94%; iii) i) DIBAL-H, -78 °C, 96%; ii) Ac$_2$O, DMAP, pyridine, 2013 PhD thesis: T. Kaur, University of Pune
93%; (b) SnBr₄, CH₂Cl₂, -78 °C, 84%; (c) i) K₂CO₃, MeOH, reflux; ii) Mel, K₂CO₃, acetone, 85%; (d) i) Bu₃SnH, AIBN (cat.), PhCH₃, reflux, 86%; ii) H₂, 10% Pd/C, 72%.

1.1.1c Evans’s approach (2003)

The stereoselective intramolecular reductive etherification of δ-trialkylsilyloxy substituted ketones with catalytic bismuth tribromide and triethylsilane was the key step for the synthesis of (-)-centrolobine 1 (Scheme 3). Enantioselective allylation of aldehyde 11 and protection of the resulting secondary alcohol furnished the triethysilyl ether 12. The olefinic ether was subjected to cross-metathesis by using the Grubb’s 2nd generation catalyst to afford the corresponding α,β-unsaturated ketone. Selective hydrogenation of the alkene with Wilkinson’s catalyst furnished the aryl ketone 13. Treatment of the δ-triethylsilyloxy aryl ketone 13 with bismuth tribromide and triethylsilane at room temperature followed by in situ removal of the tert-butyldimethylsilyl group afforded the (-)-centrolobine 1.⁴

![Scheme 3. Synthesis of (-)-Centrolobine using Evan’s approach; Reagents and conditions:](image)

1.1.1d Boulard’s approach (2004)

Boulard et al. employed the protection on the commercially available alcohol 14, then protection of free hydroxyl as its benzyl ether 15 and then asymmetric allylation on aldehyde derived from compound 15 by PCC oxidation (Scheme 4).

![Scheme 4. Synthesis of (-)-Centrolobine using Boulard’s approach; Reagents and conditions:](image)
(a) NaH, BnBr, DMF, reflux, 90%; (b) i) PCC, CH₂Cl₂, rt, quantitative; ii) S,S-(I), ether, -78 °C, 61%; (c) i) Acrylic acid, (II), CH₂Cl₂, 2 days, ii) Pd/C, H₂, 4 days, 56%; (d) i) 4-(OMe)-C₆H₄MgBr, THF, -78 °C; ii) TMSOTf, Et₃SiH, -78 °C to rt, 23%.

The homoallylic alcohol 16 was subjected to following reactions i.e. cross metathesis (CM), hydrogenation, lactonization and debenzylation, respectively to furnish lactone 17. A one-pot transformation from 17 to 1 was achieved by addition of 4-methoxyphenylmagnesium bromide followed by TMSOTf and Et₃SiH.

1.1.1e Clark’s approach (2004)

In the synthesis of centrolobine 1 (Scheme 5), Clark et al. carried out one pot three-component Maitland–Japp reaction using Chan’s diene 18 and aldehyde 11, further addition of anisaldehyde furnished tetrahydropyran-4-one 19. Compound 19 was subjected to ester hydrolysis and subsequent decarboxylation provided keto compound 20. Finally, reduction of keto group of 20 furnished (-)-centrolobine 1.

1.1.1f Loh’s approach (2005)

Loh’s approach based on an asymmetric allylation of aldehyde 21 using (R)-BINOL indium complex and allyltri-n-butyltin as allylating agent. The formation of 4-Bromo THP ring 22 was accomplished via catalytic Prin’s cyclization using InBr₃.
in presence of TMSBr. Finally, dehalogenation and catalytic hydrogenation provided (-)-centrolobine 1 (Scheme 6).\(^7\)

![Scheme 6. Synthesis of (-)-Centrolobine using Loh’s approach; Reagents and conditions: (a) InCl\(_3\), (R)-BINOL, allyl-SnBu\(_3\), CH\(_2\)Cl\(_2\), -78 °C to rt, 24 h, 68%, 84% ee; (b) InBr\(_3\), TMSBr, p-anisaldehyde, CH\(_2\)Cl\(_2\), -78 °C, 83%; (c) Bu\(_3\)SnH, 1,1’-azobis(cyclohexane)carbonitrile, reflux, 24 h, 98%; ii) Pd/C, H\(_2\), MeOH/EA, 7 h, 71%, 84% ee."

1.1.1g Chandarshekhar’s approach (2005)

Chandarshekhar et al. efficiently utilized Keck allylation on aldehyde 23 (Scheme 7), furnished allylic alcohol 24. The protection of hydroxyl with TBSCl resulted in compound 25, which was subjected to the set of functional group manipulations: oxidation, Wittig olefination, reduction of ester as well as double bond, followed by oxidation to aldehyde, then Wittig-Horner olefination with phosphonate (III) provided the key intermediate 26. Compound 26 on exposure to HF-pyridine triggered \textit{in situ} silyl cleavage followed by intramolecular oxy-anion Michael addition to provide substituted pyran, and subsequently benzyl ether cleavage and keto group reduction provided (-)-centrolobine 1.\(^8\)

![Scheme 7. Synthesis of (-)-Centrolobine using Chandarshekhar’s approach; Reagents and conditions: (a) (R)-BINOL, allyl-SnBu\(_3\), Ti(O-iPr)\(_4\), CH\(_2\)Cl\(_2\), -20 °C, 70 h, 73%, 97% ee; (b) i) TBSCl, CH\(_2\)Cl\(_2\), 0 °C, 87%; (c) i) Mg/MeOH, rt, 3 h, 85%; ii) K\(_2\)CO\(_3\), MeI, acetone, 0 °C, 4 h, 73%; iii) O\(_3\), CH\(_2\)Cl\(_2\), 1 h, -20 °C; iv) Ph\(_2\)PCHCO\(_2\)Et, CH\(_2\)Cl\(_2\), 2 h, 84%; v) Mg/MeOH, rt.]

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Chapter 1

81%; vi) LAH, THF, 0 °C to rt, 76%; vii) IBX, DMSO, rt, 4 h, 80%; viii) (I), Ba(OH)₂·8H₂O, THF/H₂O (4:1), rt, 5 h, 81%; ix) HF-Py, THF, 0 °C to reflux, 4 h, 80%; x) Pd/C, H₂, EtOH/EA/H₂O (5:1:1), 10 h, 70%.

1.1.1h M. P. Jennings’s approach (2005)

This approach utilized asymmetric allylation of aldehyde 21 to get homoallylic alcohol 16. Esterification of 16 with acryloyl chloride and subsequent ring closing olefin metathesis with Grubbs’ second-generation catalyst (IV) provided compound 27. Compound 27 was subjected to hydrogenation conditions to furnish compound 28, which by Grignard reaction and dehydration furnished (-)-centrolobine 1 (Scheme 8).⁹

![Scheme 8. Synthesis of (-)-Centrolobine using Jenning’s approach; Reagents and conditions: (a) Allyl-MgBr, THF, -20 °C, 1 h, 84%; (b) acryloyl chloride, Et₃N, DMAP, CH₂Cl₂, 0 °C, 4 h, 86%; ii) Grubb’s catalyst (IV), CH₂Cl₂, reflux, 5 h, 87%; (c) Pd/C, H₂, EtOH, rt, 40 h, 84%; ii) TESCl, imidazole, DMF, rt, 87%; (d) p-(OMe)-C₆H₄MgBr, THF, -78 °C, Et₃SiH, MeCN, -40 °C, 96%.](image)

1.1.1i Blechert’s approach (2006)

In Blechert’s approach, reductive opening of epoxide 29 with LiAlH₄ (Scheme 9) afforded the alcohol 30.
Scheme 9. Synthesis of (-)-Centrolobine using Blechert’s approach; Reagents and conditions: (a) LAH, Et$_2$O, -20 °C, 94%; (b) n-BuLi, Cul, [Ir(COD)Cl]$_2$, (V), THF, -20 °C to rt, 87%, 98% ee; (c) Grubb’s catalyst (V), toluene, 50 °C, 6 h; (d) NaBH$_4$, 55%; (e) Styrene, Grubb’s catalyst, 5 mol% Pd/C, H$_2$, 50%.

Transition metal catalyzed asymmetric allylation on 31, provided ether 32. Compound 32 was treated with Grubbs’ catalyst to furnish compound 33, which undergoes rearrangement to afford 34. Compound 34 was subjected to cross metathesis conditions to furnish styrene derivative, which on hydrogenation completed the synthesis of 1.$^{10}$

1.1.1j Prasad’s approach (2007)

Prasad et al. started with bis-weinreb amide 35 derived from L-(+)-tartaric acid (Scheme 10). Bis-Weinreb amide 35 was treated with 4-pentenylmagnesium bromide to furnish 1,4-diketone 36. Stereoselective reduction of diketo with L-selectride, followed by protection with silyl group furnished diene 37. Ozonolysis followed by Grignard reaction afforded racemic diol, which on desilylation provided compound 38. FeCl$_3$ mediated cyclization provided 39, which on oxidative cleavage was converted to aldehyde 40, thus completing the formal synthesis of (-)-centrolobine 1.$^{11}$

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Scheme 10. Synthesis of (-)-Centrolobine using Prasad’s approach; *Reagents and conditions*: (a) C_5H_9MgBr, THF, 0 °C, 1 h, 96%; (b) i) L-selectride, THF, -78 °C, 3 h, 94%; ii) TBSCl, imidazole, DMAP, DMF, 80 °C, 3 h, 94%; (c) i) O_3/O_2, Me_2S, NaHCO_3, CH_2Cl_2, MeOH, 0 °C, 1 h; ii) p-(OMe)C_6H_4MgBr, THF, 0 °C, 1 h, 90%; iii) TBAF, THF, rt, 8 h, 89%; (d) FeCl_3, rt, 30 min, 70%; (e) Pb(OAc)_4, benzene, rt, 2 h, quantitative yield.

1.1.1k Hasimoto’s approach (2007)

In this synthetic approach, hetero-Diels–Alder (HDA) reaction between 4-aryl-2-silyloxy-1,3-butadiene 41 and phenyl propargyl aldehyde 42 derivative played a key step (Scheme 11). The HDA reaction between 41 and 42 occurred in presence of Rh_2(R-BPTPI)_4, as a chiral Lewis acid catalyst to provide exclusively cis-2,6-disubstituted tetrahydropyran-4-one 43. The triple bond was reduced by catalytic hydrogenation provided 44. Keto group reduction and some protecting group manipulation afforded (-)-centrolobine 1.\(^\text{12}\)
Scheme 11. Synthesis of (-)-Centrolobine using Hasimoto’s approach; Reagents and conditions: (a) Rh$_2$(R-BPTP)$_4$, CH$_2$Cl$_2$, 87%; (b) H$_2$, 10% Pd/C, EtOAc, 2 h, 94%; (c) i) TsNHNH$_2$, MeOH, reflux, 2 h; ii) NaBH$_3$CN, TsOH, DMF-sulfolane (1:1), 110 °C, 1 h; ii) K$_2$CO$_3$, MeOH, reflux.

1.1.1l Furman’s approach (2008)

Lewis acid catalyzed intramolecular reactions of oxocarbenium ions with vinylstannanes for the stereoselective construction of 2,6-disubstituted dihydropyrans was used as the key reaction sequence in this current approach (Scheme 12). The starting material epoxide 46 was synthesized from the corresponding olefin 45 via Sharpless asymmetric dihydroxylation followed by tosylation of the primary hydroxyl group and NaOH treatment. The ring opening of epoxide 46 with lithium acetylide–ethylenediamine complex and subsequent hydrostannylation afforded alcohol 47. The Prin’s cyclization of 47 with 4-tosyloxybenzaldehyde in presence of TMSOTf yielded dihydropyran 48, which on further standard functional group manipulation furnished (-)-centrolobine 1.\(^{13}\)

![Scheme 12. Synthesis of (-)-Centrolobine using Furman’s approach; Reagents and conditions:](image)

1.1.1m Spilling’s approach (2009)

Synthesis of cis-tetrahydropyran ring was achieved by cross metathesis reaction of two fragments (R)-phosphonate 49 and (R)-alkenol 50, yielding the phosphono-carbonate 51.
Scheme 13. Synthesis of (-)-Centrolobine using Spilling’s approach; Reagents and conditions: (a) i) Grubb’s catalyst, CuI, CH$_2$Cl$_2$, 0 °C, 60%; (b) Pd$_2$(dba)$_3$, dppe, i-Pr$_2$NEt, THF, 60 °C, 85%; (c) O$_3$, MeOH, CH$_2$Cl$_2$, 71%.

The stereospecific palladium catalyzed cyclization furnished cis-tetrahydropyran-vinyl phosphonate 52 which after ozonolysis yielded the aldehyde 40. This aldehyde 40 could be transformed into natural product 1 in two steps (Scheme 13).

1.2 Present work: Objective and Rationale

Reretrosynthetically, synthesis of 1 was visualized from key intermediate homoallylic alcohol 16 (Scheme 14). Compound 16 could be obtained by the Barbier allylation reaction of aldehyde 53, the resulting racemic homo-allylic alcohol 16 could be resolved by the oxidative kinetic resolution (OKR). This aldehyde 53 in turn could be obtained from (E)-ethyl 3-(4-(benzyloxy)phenyl)acrylate 54, by nickel boride and lithium aluminum hydride (LAH) reduction of double bond and saturated ester, respectively and finally the oxidation of the saturated alcohol with pyridinium dichromate (PDC).
1.3 Oxidative Kinetic Resolution (OKR)

The oxidative kinetic resolution (OKR) of racemic secondary alcohols plays an important role in the synthesis of various natural products. The enantio-riched alcohols are integral part of several important transformations. Adam et al. reported the use of [Cr(salen)] complexes in the presence of iodosobenzene and PhI(OAc)$_2$ as an oxidant for the resolution of racemic secondary alcohols to ketones. Several groups utilized vanadium, cobalt, iridium, palladium catalyzed aerobic oxidative resolution protocols for the resolution of racemic secondary alcohols. Further Xia et al. reported the use of [Mn(salen)] complexes for the resolution of racemic alcohols to optically pure secondary alcohols and ketones. Xia et al. modified the protocol, using chiral [Mn(salen)] complexes as a catalyst, potassium bromide as a phase transfer catalyst and PhI(OAc)$_2$ as a co-oxidant (Figure 2).
1.3a Mechanism for Oxidative Kinetic Resolution (OKR)

First step is the formation of reactive intermediate A, which is generated by reaction of iodosobenzenediacetate (IBDA) and Mn(III) complex. This reactive intermediate A, reacts selectively with one isomer to form complex B. Further electronic reorganization of complex eliminates acetic acid, CH\(_3\)(O)C\(^-\) radical and high-valent Mn(V) species C. This intermediate C, in the presence of KBr/H\(_2\)O generates the complex D, which results in the generation of ketone and catalyst is generated for next catalytic cycle. This hypothesis has been further corroborated by UV-visible experiments and ESI-MS analysis (Scheme 15).

![Scheme 15. Postulated mechanism for the oxidative kinetic resolution (OKR).](image)

1.4 Results and Discussion

Initially, 4-hydroxybenzaldehyde \(55\) was taken as a starting material and Wittig reaction was performed on it without protecting phenolic hydroxyl group. \(\alpha,\beta\)-2013 PhD thesis: T. Kaur, University of Pune
Unsaturated product 57 was obtained albeit in low yield (Scheme 16). It was assumed that presence of free phenolic group would be responsible for low yield.

![Scheme 16. Synthesis of compound 57 utilizing Wittig reaction.](image)

Then phenolic hydroxyl group of compound 55 was protected as tosyl 58, and then Wittig reaction resulted in the generation of α,β-unsaturated ester, 59. Compound 59 was subjected to lithium aluminum hydride reduction conditions, to furnish the saturated alcohol. This reaction failed to give the desired alcohol and resulting in the generation of complex reaction mixture (Scheme 17).

![Scheme 17. Synthesis of compound 59 utilizing Wittig reaction.](image)

In the next scheme, phenolic group of 4-hydroxybenzaldehyde 55 was protected as benzyl ether to furnish compound 60 (Scheme 18). The protected aldehyde 60 was treated with Wittig salt to form α,β-unsaturated ester 54. The formation of product 54 was confirmed by its spectral analysis. In $^1$H NMR spectrum, the olefinic proton multiplet signals were observed at δ 7.64 (d, $J = 15.9$ Hz, 1H) and 6.30 (d, $J = 15.9$ Hz, 1H) ppm. In $^{13}$C NMR spectrum, olefinic carbon signals were observed at δ 144.2 and 115.2 ppm. The double bond reduction was carried out using nickel chloride hexahydrate and sodium borohydride to furnish saturated ester 61. The formation of product 61 was confirmed by its spectral analysis. In $^1$H NMR spectrum, the olefinic proton multiplet signals were disappeared and new peaks were observed at δ 2.87 (t, $J = 8.1$ Hz, 1H) and 2.56 (t, $J = 7.9$ Hz, 1H) ppm. In $^{13}$C NMR spectrum, carbon signals were observed at δ 36.1 and 30.0 ppm. Reduction of the

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methyl ester 61 with lithium aluminium hydride furnished the alcohol 62 in 70% yield. In $^1$H NMR spectrum, new peak was observed at $\delta$ 3.65 (t, $J = 6.4$ Hz) in $^1$H and 70.0 ppm in $^{13}$C NMR. The saturated alcohol 62 was oxidized to aldehydic compound 53. In $^1$H NMR spectrum, the aldehydic proton signals were observed at $\delta$ 9.69 (m) ppm. In $^{13}$C NMR spectrum, carbon signal was observed at $\delta$ 201.4 ppm and in IR spectrum peaks at 2865 and 1720 cm$^{-1}$, characteristic of aldehyde were observed. Aldehyde 53 was subjected to Barbier allylation$^{23}$ conditions to afford the homoallylic alcohol 54. In $^1$H NMR spectrum, the olefinic proton signals were appeared at $\delta$ 5.87-5.69 (m, 1H), 5.18-5.14 (m, 1H), 5.11-5.06 (m, 1H), 2.77-2.48 (m, 2H), 2.48-2.11 (m, 2H) ppm. This homoallylic alcohol 63 was oxidized to keto compound 64 and further treated with $R$-alpine borane. The reaction did not yield the desired product. So, we decided to employ Jacobsen’s-oxidative kinetic resolution (OKR) method on the racemic homoallylic alcohol 63.

Finally, we resolved racemic alcohol 63 employing oxidative kinetic resolution (OKR) conditions into enantiomeric pure product 16 and keto derivative 64. The enantiomeric excess ($ee$) of the resolution was calculated based on the Moscher’s ester method and found to be 85%.
In order to improve the yield of the key intermediate, we started with 4-iodophenol 56 for the synthesis of 1. The phenolic group of compound 56 was protected as benzyl ether to furnish compound 65 (Scheme 19). The protected iodo-compound 65 was treated with allylic alcohol, in the presence of palladium acetate to afford aldehyde 53. In earlier scheme, the yield of the desired aldehyde 53 was only 29.8% and was synthesized in 5 steps. To improve the yield of desired aldehyde 53 and reduce the number of steps this new method was applied. In this present standardized method we could isolate the aldehyde 53 in 69% yield and in two steps. This aldehyde 53 could be used for Barbier reaction conditions to furnish homoallylic alcohol 63 in 85% yield.
Scheme 19. Alternative route towards the formal synthesis of (-)-centrolobine, 1.

The optical purity of the enantiomeric pure product 16 has been determined using $^{19}$F-NMR spectroscopy. The alcohol 16 coupled with a chiral shift reagent, (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid in the presence of HBTU and DCM as a solvent, to furnish the optically pure ester 66 in 60% yield (Scheme 20). The enantiomeric excess (ee) of the resolution was calculated based on the Moscher’s ester method and found to be 85%.

Scheme 20. Derivatization of alcohol to ester using Moscher’s method.

Mechanism for the conversion of iodo-65 to aldehyde-53

It has been reported in the literature that in the first step palladium (0), subsequently reacts with aromatic halides via oxidative addition to give intermediate (E), followed by co-ordination to the π-electron of the allylic alcohol at the β-position to form σ-complex H intermediate. Sometimes co-ordination to the π-electron of the allylic alcohol at the α-position also occurs to form σ-complex G intermediate (Scheme 21). Both the intermediates G and H after syn-elimination yields the α/β-subsituted carbonyl compounds.
1.5 Conclusion

We have accomplished synthesis of the key intermediate, homo-allylic alcohol 16, by following oxidative kinetic resolution (OKR). Our synthetic route following scheme 18 resulted compound 16 in 8.3% (8 steps). The other route (Scheme 19) furnished compound 16 in 22% overall yields (4 steps). The compound 16 could be transformed into the title compound 1 by following reported methods.\textsuperscript{7, 25} In conclusion, we have accomplished a formal synthesis of (-)-centrolobine 1.
1.6 Experimental

4-(Benzyloxy)benzaldehyde (60)

To a stirred suspension of K₂CO₃ (10.35 g, 75.0 mmol) in dry DMF (20 mL) at room temperature was added 4-hydroxybenzaldehyde (6.10 g, 50.0 mmol) and TBAI (cat). The mixture was stirred for 30 min and then benzyl bromide (8.96 mL, 75.0 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then quenched with water and extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and evaporated to give a crude mixture that was purified by silica gel column chromatography (PE/EA, 8:2) to isolate product 60 (10.0 g).

**Yield**
10.0 g, 95%; white solid; Rfb = 0.5 (PE/EAlA), 7:3).

**Melting Point**
78-79°C

**Mol. Formula**
C₁₄H₁₂O₂

**IR (CHCl₃)**
νmax (cm⁻¹) = 3019, 2725, 1694, 1600, 1509, 1215.

**1H NMR**
(CDCl₃, 200 MHz)
δH (ppm) = 9.9 (s, 1H, CHO), 7.83 (d, J = 8.8 Hz, 2H, CH), 7.45-7.37 (m, 5H, CH), 7.07 (d, J = 8.7 Hz, 2H, CH), 5.14 (s, 2H, CH₂).

**13C NMR**
(CDCl₃, 50 MHz)
δC (ppm) = 190.8 (CHO), 164.0 (C), 136.0 (C), 132.0 (CH), 130.1 (C), 129.0 (CH), 128.3 (CH), 127.5 (CH), 115.1 (CH), 70.2 (CH₂).

**Elemental analysis**
Caled for C₁₄H₁₂O₂: C, 79.22; H, 5.70
Found: C, 79.29; H, 5.78

**GC/MS (EI)**
213 [M]⁺

(E)-Ethyl-3-(4-(benzyloxy)phenyl)acrylate (54)

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In the solution of (ethoxycarbonylmethylene)triphenyl phosphorane (17.4 g, 50.0 mmol) in anhydrous THF (30 mL) was slowly added to a solution of aldehyde 60 (9.54 g, 45.0 mmol) in anhydrous THF (20 mL) and then stirred it at room temperature for 24 h. THF was evaporated and purified by silica gel column chromatography (PE/EA, 8:2) to isolate product 54 (11.4 g).

**Yield**
11.4 g, 90%; white solid; $R_f = 0.38$ (PE/EA, 8:2).

**Melting Point**
58.7-58.9°C

**Mol. Formula**
$C_{18}H_{18}O_3$

**IR (CHCl₃)**
$\nu_{\max} (\text{cm}^{-1}) = 3019, 2725, 2401, 1698, 1635, 1510, 1216$. 

**$^1$H NMR**

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**$^{13}$C NMR**

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**Elemental analysis**
Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43

**Found:** C, 76.50; H, 6.49.

**GC/MS (EI)**

282 [M]⁺

**Ethyl 3-(4-(benzyloxy)phenyl)propanoate (61)**

To a cooled solution of compound 54 (5.64 g, 20.0 mmol) in anhydrous MeOH (30 mL), NiCl$_2$·6H$_2$O (4.74 g, 20 mmol) was added. To this slowly sodium borohydride (740 mg, 20 mmol) was added and stirred it at room temperature for 4 h. After completion of the reaction, methanol was evaporated, aqueous NH$_4$Cl was added (2 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, and evaporated to furnish a crude mixture that
was purified by silica gel column chromatography (PE/EA, 8:2) to isolate product 61 (5.05 g).

**Yield**
5.05 g, 89%; colorless oil; $R_f = 0.4$ (PE/EA, 8:2).

**Mol. Formula**
$C_{18}H_{20}O_3$

**IR (CHCl$_3$)**

$\nu_{\text{max}}$ (cm$^{-1}$) = 3363, 3020, 2400, 1725, 1605, 1511, 1454.

**$^1$H NMR**

$\delta$ (ppm) = 7.43-7.28 (m, 5H, CH), 7.09 (d, $J = 8.6$ Hz, 2H, CH), 6.88 (d, $J = 8.7$ Hz, 2H, CH), 5.00 (s, 2H, CH$_2$), 4.09 (q, $J = 7.1$ Hz, 2H, CH$_2$), 2.87 (t, $J = 8.1$ Hz, 2H, CH$_2$), 2.56 (t, $J = 7.9$ Hz, 2H, CH$_2$), 1.21 (t, $J = 7.1$ Hz, 3H, CH$_3$).

**$^{13}$C NMR**

$\delta$ (ppm) = 172.8 (C), 157.2 (C), 137.0 (C), 132.8 (C), 129.2 (CH), 128.4 (CH), 127.8 (CH), 127.3 (CH), 114.7 (CH), 69.9 (CH$_2$), 60.2 (CH$_2$), 36.1 (CH$_2$), 30.0 (CH$_2$), 14.3 (CH$_3$).

**Elemental analysis**
Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09

Found: C, 76.10; H, 7.16

3-(4-(Benzyloxy)phenyl)propan-1-ol (62)

To a cooled solution of compound 61 (2.84 g, 10.0 mmol) in dry THF (10 mL), LAH (370 mg, 10.0 mmol) was slowly added and stirred at room temperature for 4 h under an atmosphere of argon. After completion of the reactio, it was cooled and quenched with 1N NaOH (10 mL). The white precipitate formed during the reaction was filtered through celite bed and filtrate was dried over anhydrous Na$_2$SO$_4$ and the solvent was evaporated to under reduced pressure. The crude was purified by silica gel column chromatography (PE/EA, 7:3) to give product 62 (2.05 g).

**Yield**
2.05 g, 85%; white solid; $R_f = 0.28$ (PE/EA, 6:4).

**Melting Point**
46.7-47.9°C

**Mol. Formula**
$C_{16}H_{18}O_2$

**IR (CHCl$_3$)**

$\nu_{\text{max}}$ (cm$^{-1}$) = 3616, 3434, 3018, 2874, 2402, 1611,
3-(4-(Benzyloxy)phenyl)propanal (53)

To a solution of the alcohol 62 (2.42 g, 10.0 mmol) in CH₂Cl₂ (20 mL), trichloroisocyanuric acid (2.32 g, 10.0 mmol) was added and the solution was stirred and maintained at 0°C, followed by addition of TEMPO (0.015 g, 0.1 mmol). After completion of the reaction (TLC), warmed to room temperature and stirred for 15 min and then filtered on Celite, and the organic phase was washed with 15 mL of a saturated solution of Na₂CO₃, followed by 1 N HCl and brine, dried over anhydrous Na₂SO₄, and evaporated to furnish a crude mixture that was purified by silica gel column chromatography (PE/EA, 7:3) to isolate product 53 (2.20 g).

Method II: In a Flame dried RB flask, having magnetic needle was charged with 2.0 g of TBAB, it was refluxed at 130°C until the formation of ionic liquid. Pd(OAc)₂ (5.3 mg, 0.024 mmol), allyl alcohol (272 µL, 4.0 mmol), sodium hydrogen carbonate (236 mg, 4.0 mmol) and iodide (620 mg, 2.0 mmol) were refluxed for 3 h. After completion of the reaction (TLC), warmed to room temperature and stirred for 15 min and then filtered on celite, and the organic phase was washed with 1N HCl and brine,
dried over anhydrous Na$_2$SO$_4$, and column purified (PE/EA, 7:3) to isolate product 53 (0.33 g, 69%).

**Yield**

2.2 g, 92%; colorless oil; $R_f = 0.41$ (PE/EA, 8:2).

**Mol. Formula**

C$_{16}$H$_{16}$O$_2$

**IR (CHCl$_3$)**

$\nu_{\text{max}}$ (cm$^{-1}$) = 3063, 3032, 2865, 1954, 1721, 1601.

**$^1$H NMR**

(CDCl$_3$, 200 MHz)

$\delta$ (ppm) = 9.69 (m, 1H, CHO), 7.40-7.27 (m, 5H, CH), 7.03 (d, $J = 8.7$ Hz, 2H, CH$_2$), 6.86 (d, $J = 8.6$ Hz, 2H, CH), 4.95 (s, 2H, CH$_2$), 2.82 (t, $J = 7.1$ Hz, 2H, CH$_2$), 2.62 (t, $J = 7.9$ Hz, 2H, CH$_2$).

**$^{13}$C NMR**

(CDCl$_3$, 50 MHz)

$\delta$ (ppm) = 201.4 (CHO), 156.9 (C), 136.8 (C), 132.4 (C), 131.7 (CH), 129.0 (CH), 128.3 (CH), 127.6 (CH), 127.2 (CH), 114.6 (CH), 69.6 (CH$_2$), 45.1 (CH$_2$), 26.9 (CH$_2$).

**Elemental analysis**

Calcd for C$_{16}$H$_{16}$O$_2$: C, 79.97; H, 6.71

Found: C, 79.89; H, 6.65

1-(4-(Benzyloxy)phenyl)hex-5-en-3-ol (63)

To a solution of the allyl bromide (1.71 mL, 20 mmol) in THF (10 mL), aldehyde 53 (2.40 g, 10 mmol), saturated aqueous NH$_4$Cl (5 mL) and zinc metal (3.25 g, 20 mmol) was added. The mixture was stirred at room temperature for 3 h and after completion of the reaction it was filtered to remove excess zinc and precipitated salts, and the organic layer separated. It was extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, and evaporated to furnish a crude mixture that was purified by silica gel column chromatography (PE/EA, 7:3) to isolate product 63 (2.50 g).

**Yield**

2.50 g, 89%; white solid; $R_f = 0.3$ (PE/EA, 7:3).

**Melting Point**

98-100°C

**Mol. Formula**

C$_{19}$H$_{22}$O$_2$

**IR (CHCl$_3$)**

$\nu_{\text{max}}$ (cm$^{-1}$) = 3367, 3019, 2935, 2401, 1716, 1610,
To a solution of substrate 64 (2.39 g, 8.50 mmol) in CH₂Cl₂ (5 mL), and water (10 mL) catalyst (S,S)-Salen-Mn\textsuperscript{III}Cl (0.107 g, 0.16 mmol), additive KBr (0.808 g, 6.80 mmol), was added and stirred for a few minutes at room temperature. The oxidant PhI(OAc)\textsubscript{2} (1.91 g, 5.94 mmol) was added and the mixture was stirred for 30 min until the completion of reaction. The products were extracted by using diethyl ether and purified on silica gel column chromatography giving yields as 43% for (S)-1.02 g, \( R_f = 0.3 \), PE/EA, 7:3) as colorless oil and 46% for 65 (1.30 g).

1-(Benzyloxy)-4-iodobenzene (65)

To a stirred suspension of K\textsubscript{2}CO\textsubscript{3} (1.88 g, 13.6 mmol) in anhydrous DMF (5 mL) at room temperature was added 4-iodophenol 65 (2.0 g, 9.09 mmol) and TBAI (cat). The mixture was stirred for 20 min and then benzyl bromide (1.3 mL, 10.9 mmol) was added and stirred for a few minutes at room temperature.
added. The reaction mixture was stirred at room temperature for 10 h and then quenched with water and extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine, dried (anhydrous Na₂SO₄) and evaporated to give a crude mixture that was purified by silica gel column chromatography (PE/EA, 8:2) to isolate product 65 (2.62 g).

Yield 2.62 g, 93%; white solid; \( R_f = 0.5 \) (PE/EA, 6:4).
Melting Point 56.5-58.6°C
Mol. Formula \( \text{C}_{13}\text{H}_{11}\text{IO} \)
IR (CHCl₃) \( \nu_{\text{max}} \text{ (cm}^{-1}) = 3362, 3019, 1725, 1614, 1541, 1485, 1454, 1349. \)

\(^1\text{H} \text{ NMR} \)
\( \delta_H \text{ (ppm)} = 7.53 \text{ (d, } J = 9.1 \text{ Hz, 2H, CH}), \)
\( 7.32 \text{ (m, 5H, CH}), \)
\( 6.75 \text{ (d, } J = 9.0 \text{ Hz, 2H, CH}), \)
\( 5.04 \text{ (s, 2H, CH).} \)

\(^{13}\text{C} \text{ NMR} \)
\( \delta_C \text{ (ppm)} = 158.6 \text{ (C), 138.2 (CH), 136.5 (C),} \)
\( 128.6 \text{ (CH), 128.1 (CH), 127.4 (CH), 117.3 (CH),} \)
\( 83.0 \text{ (C), 70.0 (CH).} \)

Elemental analysis Calcd for \( \text{C}_{13}\text{H}_{11}\text{IO}: \) C, 50.35; H, 3.58
Found: C, 50.41; H, 3.65

\((S)-1-(4-(Benzyloxy)phenyl)hex-5-en-3-yl \text{ (R)-3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (66)}\)

To a \(0^\circ\) C cooled solution of substrate 16 (71 mg, 0.25 mmol) in CH₂Cl₂ (1 mL) and \((R)-(+)\text{-}\alpha\text{-methoxy-}\alpha\text{-}(trifluoromethyl)phenylacetic acid (58.5 mg, 0.25 mmol), and HBTU (95 mg, 0.25 mmol) was added and stirred for 4 h at that temperature. The products were extracted by using DCM and purified on silica gel column chromatography to furnish product 66 (75.2 mg, 60%).

Yield 75.2 mg, 60%; white solid; \( R_f = 0.3 \) (PE/EA, 2:8).
Mol. Formula \( \text{C}_{29}\text{H}_{29}\text{F}_{3}\text{O}_{4} \)

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$^{19}$F NMR

$\delta_F$ (ppm) = 70.05 (major), 70.02 (minor)

(CDCl$_3$, 200 MHz)
1.7 References

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   1723; (b) Carreño, M. C.; Mazery, R. D.; Urbano, A.; Colobert, F.; Solladie, 

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    **2008**, *47*, 3755.
### 1.8 Appendix C: Characterization data of synthesized compounds

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<td>Compound 66</td>
<td>$^{19}$F NMR</td>
<td>130</td>
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Chapter 1

**1H NMR**

![1H NMR spectrum](image)

**13C NMR**

![13C NMR spectrum](image)

**DEPT**

![DEPT spectrum](image)

4-(Benzyloxy)benzaldehyde (60)

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**Chapter 1**

1H NMR

![1H NMR spectrum](image)

13C NMR

![13C NMR spectrum](image)

DEPT

![DEPT spectrum](image)

*(E)-Ethyl-3-(4-(benzyloxy)phenyl)acrylate (54)*

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Chapter 1

1H NMR

13C NMR

DEPT

Ethyl 3-(4-(benzyloxy)phenyl)propanoate (61)

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Chapter 1

1H NMR

13C NMR

DEPT

3-(4-(Benzylxy)phenyl)propan-1-ol (62)

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Chapter 1

1H NMR

13C NMR

DEPT

3-(4-(Benzyloxy)phenyl)propanal (53)

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$^1$H NMR

$^1$C NMR

DEPT

1-(4-(Benzyloxy)phenyl)hex-5-en-3-ol (63)

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Chapter 1

**1H NMR**

![1H NMR spectrum](image)

**13C NMR**

![13C NMR spectrum](image)

**DEPT**

![DEPT spectrum](image)

1-(Benzyloxy)-4-iodobenzene (65)

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$(S)$-1-(4-(benzyloxy)phenyl)hex-5-en-3-yl $(R)$-3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (66)