INTRODUCTION

Enamides are recognised as an important structures. They are often used as reactive intermediates for a number of different reactions and are also present in many natural products and pharmaceutical leads. Enamide is the key side chain in many bioactive natural products. E.g; Salicylihalamides, Lobatamide, Oximidines, Palmerolide, Lituarines, Salarins, Poecillastrins etc. Genus piper is the rich source of enamides.

The most well known amide Piperine 1 was the first amide to be isolated from *piper* species in 1818. In bioassays it displayed central nervous system depressant, antipyretic, analgesic and antiinflammatory activities. Kiuchi et al. isolated seven amides 2-8 from *piper nigrum* which showed larvicidal activity against second stage larvae of *Toxocara canis*.

Waterman et al. isolated five isobutylamides 9-13 from *Dinosperma erythrococca* (Rutaceae). These isobutylamides were tested for Insecticidal activity. Erythrococcamide 9 showed lethal activity against the housefly (Musca domestica) and the tobacco budworm (Heliothis virescens). Compound 12 showed lethal activity against Heliothis virescens at 500 ppm, and Compound 13 showed lethal activity against Musca domestica at 500 ppm.
Shaheen Siddiqui et al. isolated three amides pipilyasine (14), pipzubedine (15) and pipyaqubine (16) from the seeds extract of *Piper nigrum* Linn. These amides exhibited a larvicidal activity against 4th instar larvae of Aedes aegypti L., a Dengue vector mosquito and a carrier of yellow fever.\(^5\)

Jia Li et al. isolated eight amide alkaloids (17-24) from *Piper boehmeriaefolium* in 2011. These amides exhibited significant cytotoxic activity against human cervical carcinoma HeLa cells.\(^6\)
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Scutifoliamide A (25) and B (26), hoffmannseggiamide A (27) and B (28) isobutylamides isolated from the leaves of *Piper scutifolium* have been reported to inhibitory activity against the growth of the fungi *Cladosporium sphaerospermum* and *C. cladosporioides*.  

![Chemical structures of Scutifoliamide A (25), B (26), Hoffmannseggiamide A (27), and B (28).](image)

Jih-Jung Chen et al. isolated three amides 29-31 from the stem bark of *Zanthoxylum ailanthoides*. Compounds 29, 31 exhibited inhibitory activity on superoxide generation and elastase release by neutrophils.

![Chemical structures of amides 29-31 isolated from Zanthoxylum ailanthoides.](image)

Piperchabamides A-D (32-35), retrofractamides A-C (36-38), pipernonaline 39 and dehydropipernonaline 40 were isolated from the fruits of *Piper chaba*. These amides were tested for adipogenesis of 3T3-L1 cells. Retrofractamide A (36) was significantly increased the amount of adiponectin released into the medium and the uptake of 2-deoxyglucose into the cells. Retrofractamide A also increased mRNA levels of adiponectin, peroxisome proliferator-activated receptor γ2 (PPARγ2), glucose transporter 4 (GLUT4), and insulin receptor substrate 1 (IRS-1), but did not act as a PPARγ agonist different from troglitazone. Retrofractamide B (37) showed insecticidal activity.
Curvularides A–E (41-45) were isolated by Kittakoop et al. in 2010, from the endophytic fungus *Curvularia geniculata*. The structures of Curvularides A and E was confirmed by single-crystal X-ray crystallography. Curvularide B (42) exhibited antifungal activity against *Candida albicans*.\(^\text{12}\)

**PRESENT WORK**

(-)-Kunstleramide 53 is a dienamide natural product was recently isolated by Hamid *et al.* from dichloromethane extract of bark of *Beilschmiedia kunstleri* Gamble, along with six known compounds.\(^\text{13}\) (-)-Kunstleramide was found to exhibit moderate cytotoxic activity against five cancer cell lines. The structure and stereochemistry of 53 were established on the basis of spectral data as (2E,4E)-7-
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

(3',4'-dimethoxyphenyl)-N-ethyl-6-(R)-hydroxyhepta-2,4-dienamide (Fig 1). This is the first ethyl dienamide from natural source.

In continuation of our interest on the total synthesis of bio-active natural products, herein we report the first total synthesis of (-)-Kunstleramide and its analogues 53 utilizing the MacMillan α-hydroxylation, Horner-Wardsworth-Emmons (HWE) olefination and Wittig reaction as key steps. The retrosynthetic analysis for (-)-Kunstleramide 53 is described in Scheme 1.

![Scheme 1](image)

Initially, the synthesis of (-)-Kunstleramide 53 started from 3,4-dimethoxyphenylpropanol which was oxidized to aldehyde using IBX, DMSO and CH₂Cl₂. Following MacMillan α-hydroxylation using nitrosobenzene (PhNO) and 40% of L-proline in DMSO, followed by rapid in situ Horner–Wadsworth–Emmons olefination using DBU as base resulted in the formation of anilinoxyolefinic ester, which was further treated with 20 mol% of CuSO₄·5H₂O in methanol at room temperature to cleave the O–N bond providing γ-hydroxy α,β-unsaturated ester 47 in a 60% yield.

The formation of compound 47 was revealed from ¹H NMR spectrum (Fig. 2.02), which displays signals for two olefinic protons at δ 7.0 (dd, J = 15.6, 4.5 Hz, 1H), 6.05 (d, J = 15.6 Hz, 1H) and one hydroxy proton at δ 4.44 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H) and 1.28 (t, J = 7.1 Hz, 3H) for ethyl ester. In ¹³C NMR spectrum (Fig. 2.03) the carbonyl carbon in ester showed signal at δ 166.4, The IR spectrum (Fig. 2.04) showed
absorption band at 1713 cm\(^{-1}\) due to carbonyl functional group and the mass spectrum (Fig. 2.05) showed a peak at \(m/z\) 303 \([\text{M+Na}]^+\).

**Scheme 2**

The absolute stereochemistry of the newly generated center in compound 47 bearing the hydroxyl group was determined by preparing MTPA esters by modified Mosher’s method,\(^{15}\) and found to be in \(R\)-configuration (Fig. 2.01). The newly generated allylic alcohol was reacted with \((S)-\alpha\)-methoxy-\(\alpha\)-trifluoromethyl phenylacetic acid, \((R)-\alpha\)-methoxy-\(\alpha\)-trifluoromethyl phenylacetic acid respectively to form \(S\) and \(R\)-MTPA ester derivatives of 47a and 47b (Scheme 3). The formation of compound \(S\)-MTPA ester derivatives of 47a established by \(^1\)H NMR spectrum (Fig. 2.06), which displayed signals for allylic carbon bearing proton at \(\delta\ 5.78\) (m, 1H), for aromatic protons 7.27 (m, 5H). Further its mass spectrum confirmed the formation of 47a by showing a molecular ion at \(m/z\) 519 \([\text{M+Na}]^+\). The formation of compound \(R\)-MTPA ester derivatives of 47b established by \(^1\)H NMR spectrum (Fig. 2.07), which displayed signals due to allylic carbon bearing proton at \(\delta\ 5.83\) (m, 1H), for aromatic protons 7.34 (m, 5H). Further its mass spectrum confirmed the formation of 47b by showing a molecular ion at \(m/z\) 519 \([\text{M+Na}]^+\). Tabulated the \(^1\)H NMR spectral data of each of the two diastereomeric MTPA esters as \(\delta_S, \delta_R\), determined chemical shift difference \(\Delta\delta = \delta_S - \delta_R\) were given in table 1.
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

![Scheme 3](image)

### Table 1: Calculation of Chemical shift difference (Δδ) values for S, R -MTPA derivatives of compound 47.

<table>
<thead>
<tr>
<th>Protons</th>
<th>δₘ</th>
<th>δᵣ</th>
<th>Δδ = δₘ−δᵣ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5.86</td>
<td>5.98</td>
<td>-0.12</td>
</tr>
<tr>
<td>3</td>
<td>6.85</td>
<td>6.88</td>
<td>-0.03</td>
</tr>
<tr>
<td>4</td>
<td>5.78</td>
<td>5.83</td>
<td>-0.05</td>
</tr>
<tr>
<td>5</td>
<td>2.97</td>
<td>2.94</td>
<td>0.03</td>
</tr>
<tr>
<td>1¹</td>
<td>4.17</td>
<td>4.19</td>
<td>-0.02</td>
</tr>
<tr>
<td>2¹</td>
<td>1.26</td>
<td>1.28</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

The negative chemical shift difference to the left side of MTPA plane and positive chemical shift differences to the right side of MTPA plane determined that hydroxyl stereochemistry is in R configuration (Fig. 2.01).

![Figure 2.01](image)

Figure 2.01: Determination of absolute configuration and Δδ values for the S and R-MTPA ester derivatives of 47 (Δδ =δₘ−δᵣ).

Protection of hydroxy group of compound 47 with tertiarybutyldimethylsilyl group formed TBS ether 48 in 96% yield. ¹H NMR spectrum (Fig. 2.08), which displays signals at δ 0.86 (s, 9H), -0.07 (s, 3H) and -0.20 (s, 3H) for the TBS protons and the
mass spectrum showed a peak at \( m/z \ 417 \ [\text{M+Na}]^+ \) (Fig. 2.10) further confirmed the formation of product 48 (Scheme 4).

![Scheme 4](image)

The resulting ester 48 was reduced with DIBAL-H in \( \text{CH}_2\text{Cl}_2 \) to give the allylic alcohol 49 in 96% yield (Scheme 5). The formation of the product was confirmed by \(^1\text{H}\) NMR spectrum (Fig. 2.11) which displays signal at \( \delta \ 4.16-4.07 \ (\text{m, 2H}) \) for primary alcohol protons and disappearance of ester protons in compound 49. The IR spectrum (Fig. 2.13) showed absorption band at 3481 cm\(^{-1}\) due to alcohol functional group and the mass spectrum (Fig. 2.14) showed a molecular ion peak at \( m/z \ 375 \ [\text{M+Na}]^+ \).

![Scheme 5](image)

Alcohol 49 oxidized to aldehyde using IBX, DMSO and \( \text{CH}_2\text{Cl}_2 \). The crude aldehyde was subjected to Wittig reaction with (ethoxycarbonylmethylene) triphenylphosphorane in dry benzene to furnish \( E, E \) ester 50 in 85% (along with 3% \( Z, E \) ester, which was easily separated by column chromatography). The formation of compound 50 was established by \(^1\text{H}\) NMR spectrum (Fig. 2.15), which displayed four signals for olefinic protons appeared at \( \delta \ 7.25 \ (\text{dd, } J = 15.3, 10.9 \text{ Hz, 1H}), 6.29 \ (\text{dd, } J = 15.3, 10.9 \text{ Hz, 1H}), 6.11 \ (\text{dd, } J = 15.3, 5.4 \text{ Hz, 1H}) \) and 5.84 (d, \( J = 15.3, 1 \text{ H} \)). In \(^{13}\text{C}\) NMR spectrum (Fig. 2.16) the carbonyl carbon in ester showed signal at \( \delta \ 167.0 \). The IR spectrum (Fig. 2.17) showed absorption band at 1715 cm\(^{-1}\) due to carbonyl functional group and the mass spectrum (Fig. 2.18) showed a peak at \( m/z \ 443 \ [\text{M+Na}]^+ \) (Scheme 6).
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Scheme 6

The ester compound 50 was hydrolyzed with LiOH.H2O to give diene acid 51 in 90% yield. The formation of acid was established by disappearance of ethyl group proton signals in 1H NMR spectrum (Fig. 2.19) of compound 51. In 13C NMR spectrum (Fig. 2.20) the acid carbonyl carbon showed a signal at δ 172.1, the IR spectrum (Fig. 2.21) showed absorption band at 1685 cm\(^{-1}\) due to acid carbonyl group and the mass spectrum showed a peak at m/z 415 [M+Na]\(^+\) further confirmed the formation of product 51 (Scheme 7).

Scheme 7

The diene acid 51 was converted to ethylamide 52 in 93% yield using HATU, DIPEA and ethylanine.\(^\text{16}\) The formation of amide was established by 1H NMR spectrum (Fig. 2.22), which displayed signals at δ 5.59 (br s, 1H), 3.37 (q, J = 7.5 Hz, 2H) and 1.17 (t, J = 7.5 Hz, 3H). In 13C NMR spectrum (Fig. 2.23) the amide carbonyl carbon showed signal at δ 165.9. The IR spectrum (Fig. 2.24) showed absorption band at 1661 cm\(^{-1}\) due to amide carbonyl functional group and the mass spectrum (Fig. 2.25) showed a peak at m/z 442 [M+Na]\(^+\) (Scheme 8).

Scheme 8

51
Finally deprotection of TBS ether in compound 52 with PTSA in MeOH afforded the target molecule 53 in 95% yield (Scheme 9). The formation of product 53 was established by the study of their $^1$H (Fig. 2.26), $^{13}$C NMR (Fig. 2.27), IR (Fig. 2.28) and HRMS (ESI) (Fig. 2.29) spectral data and found to be identical in all respects for the natural product.

![Scheme 9](image)

The key acid 51 prepared above was used for the synthesis of several analogues of (-)-Kunstleramide 54-68 discussed below.

Accordingly, the acid 51 was reacted with benzylamine using HATU, DIPEA gave 54a in 89% yield. The formation of compound 54a was established by $^1$H NMR spectrum, which displayed signals for phenyl ring protons appeared at $\delta$ 7.36-7.27 (m, 5H) and benzylic protons at $\delta$ 4.52 (d, $J = 5.6$ Hz, 2H). In $^{13}$C NMR spectrum the carbonyl carbon in amide showed signal at $\delta$ 165.9. The IR spectrum showed absorption band at 1661 cm$^{-1}$ due to amide carbonyl functional group and the mass spectrum showed a peak at $m/z$ 504 [M+Na]$^+$. Deprotection of TBS group in compound 54a with PTSA in MeOH gave 54 in 92% yield (Scheme 10). The formation of product 54 was confirmed from its spectral data by disappearance of TBS proton signals in $^1$H NMR (Fig. 2.30), $^{13}$C NMR (Fig. 2.31) spectrum. Further confirmed by IR and HRMS (ESI) (Fig. 2.32).
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

The acid group of compound 51 was transformed into an amide group by using HATU, DIPEA to give 55a in 86% yield. The $^1$H NMR spectrum showed two doublets resonated at $\delta$ 7.22 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), for aromatic protons and at $\delta$ 3.80 (s, 3H) for methoxy protons corresponding to the compound 55a. The mass spectrum showed molecular ion peak at $m/z$ 534 [M+Na]$^+$ further confirmed the product 55a (Scheme 11). In the next step TBS group of compound 55a was deprotected using catalytic amount of PTSA in MeOH gave 55 in 89% yield. The formation of the compound 55 was confirmed by $^1$H NMR (Fig. 2.33) spectrum, in which disappearance of signals corresponding to TBS group, IR absorption at 3311 cm$^{-1}$ clearly indicated the presence of hydroxyl functional group and the mass spectrum HRMS (ESI) (Fig. 2.35) showed a molecular ion peak at $m/z$ 398.1963 [M+H]$^+$ further confirmed the structure 55 (Scheme 11).
The diene acid 51 was treated with 3,4,5-trimethoxy benzylamine and HATU, DIPEA in DMF to result the amide 56a in 88% yield. The formation of compound 56a was confirmed by $^1$H NMR spectrum which showed signals at $\delta$ 6.71-6.67 (m, 2H) for the aromatic protons and two singlets at $\delta$ 3.84 (s, 6H), 3.82 (s, 3H) for methoxy protons. The molecular ion peak at $m/z$ 594 [M+Na]$^+$ in its mass spectrum confirms the formation of product 56a (Scheme 12). Deprotection of TBS ether group in compound 56a using catalytic amount of PTSA in MeOH gave 56 in 83% yield, which was characterized from its $^1$H NMR spectrum (Fig. 2.36) which showed disappearance of signals corresponding to TBS group. All other protons resonated at the expected chemical shift values. The IR spectrum showed absorption at 3442 cm$^{-1}$ for the hydroxyl group and HRMS (ESI) (Fig. 2.38) showed a molecular ion at $m/z$ 458.2175 [M+H]$^+$ for the compound 56 (Scheme 12).

Scheme 12

The acid group of compound 51 was converted to amide 57a in 81% yield using HATU, DIPEA and $p$-chlorobenzylamine. The protons in which characteristic signals resonated at their expected chemical shifts. $^1$H and $^{13}$C NMR spectra showed the required 28 carbon framework while mass data showed peak at $m/z$ 538 [M+Na]$^+$ to confirm the structure of 57a (Scheme 13). In the next step TBS group of compound 57a was deprotected using catalytic amount of PTSA in MeOH gave 57 in 85% yield. The formation of compound 57 was confirmed by $^1$H NMR (Fig. 2.39) and $^{13}$C NMR (Fig. 2.40) spectrum, in which disappearance of signals corresponding to TBS group. In its IR spectrum showed absorption band at 3418 cm$^{-1}$ clearly indicated the presence of
hydroxyl functional group and its mass spectrum HRMS (ESI) (Fig. 2.41) showed a molecular ion peak at \( m/z \) 424 \([\text{M+Na}]^+\) further confirmed the structure 57 (Scheme 13).

Scheme 13

The acid 51 was reacted with pyrrolidine using HATU, DIPEA gave 58a in 86% yield (Scheme 14). The formation of compound 58a was established by \(^1\)H NMR spectrum, which displayed signals for four methylene protons appeared at \( \delta \) 3.58-3.48 (m, 4H), 2.00-1.92 (m, 2H), 1.90-1.82 (m, 2H). In \(^{13}\)C NMR spectrum the carbonyl carbon in amide showed signal at \( \delta \) 164.8. The IR spectrum showed an absorption band at 1625 cm\(^{-1}\) due to amide carbonyl functional group and The mass spectrum showed a peak at \( m/z \) 468 \([\text{M+Na}]^+\). Deprotection of TBS group in compound 58a with PTSA in MeOH gave 58 in 90% yield. The formation of product 58 was confirmed from its spectral data by disappearance of TBS group signals in \(^1\)H NMR (Fig. 2.42), \(^{13}\)C NMR (Fig. 2.43) spectrum. Further confirmed by IR and EI-MS (Fig. 2.44).

Scheme 14
The diene acid 51 was treated with piperidine and HATU, DIPEA in DMF to result the amide 59a in 92% yield. The formation of product 59a was confirmed from its spectral data. The $^1$H NMR spectrum of 59a showed signals at δ 3.57 (br s, 2H), 3.44 (br s, 2H), 1.64-1.47 (m, 6H) for five methylene protons and its mass spectrum showed molecular ion peak at $m/z$ 482 [M+Na]$^+$. TBS group in compound 59a was removed using catalytic amount of PTSA in MeOH gave 59 in 94% yield, which was characterized from its $^1$H NMR (Fig. 2.45) and $^{13}$C NMR (Fig. 2.46) spectrum which showed disappearance of signals corresponding to TBS group. All other protons resonated at the expected chemical shift values. The IR spectrum showed absorption at 3334 cm$^{-1}$ for the hydroxyl group and its mass spectrum (Fig. 2.47) showed a molecular ion at $m/z$ 368 [M+NH$_4$$]^+$ for the compound 59 (Scheme 15).

Scheme 15

The acid 51 was reacted with morpholine and HATU, DIPEA in DMF to afford the amide 60a in 87% yield. The formation of compound 60a was established by $^1$H NMR spectrum which displayed signals at δ 3.73-3.65 (m, 4H), 3.64-3.55 (br s, 4H) for four -CH$_2$ protons protons. IR spectrum showed an absorption at 1649 cm$^{-1}$ for the amide carbonyl group and its mass spectrum showed a molecular ion peak at $m/z$ 484 [M+Na]$^+$ which confirmed the required product 60a (Scheme 16). Deprotection of TBS ether group in compound 60a using catalytic amount of PTSA in MeOH gave 60 in 93% yield. The formation of product was confirmed from its $^1$H NMR spectrum (Fig. 2.48) which showed disappearance of signals corresponding to TBS. The IR spectrum
showed absorption at 3410 cm\(^{-1}\) for the hydroxyl group and further its HRMS (ESI) (Fig. 2.50) confirmed the formation of product 60 (Scheme 16).

**Scheme 16**

The acid group of compound 51 was transformed into an amide by using HATU, DIPEA and thiomorpholine gave 61\textsubscript{a} in 84\% yield. The \(^1\)H NMR spectrum showed signals at \(\delta\) 3.88 (br s, 2H), 3.80 (br s, 2H), 2.65-2.59 (m, 4H) for four \(-\text{CH}_2\) protons corresponding to the compound 61\textsubscript{a}. The mass spectrum showed a molecular ion peak at \(m/z\) 500 [M+Na]\(^+\) further confirmed the product 61\textsubscript{a} (Scheme 17). In the next step TBS group of compound 61\textsubscript{a} was removed using catalytic amount of PTSA in MeOH gave 61 in 88\% yield. The formation of amide 61 was confirmed by \(^1\)H NMR spectrum (Fig. 2.51), in which disappearance of signals corresponding to TBS group, IR absorption at 3359 cm\(^{-1}\) clearly indicated the presence of hydroxyl functional group and its mass spectrum (Fig. 2.53) showed a molecular ion peak at \(m/z\) 386 [M+Na]\(^+\) further confirmed the structure 61 (Scheme 17).
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Scheme 17

The diene acid 51 was treated with 1-methylpiperazine and HATU, DIPEA in DMF to result the amide 62a in 81% yield. The formation of compound 62a was confirmed by $^1$H NMR spectrum which showed signals at δ 3.72 (br s, 2H), 3.58 (br s, 2H), 2.76-2.70 (m, 2H), 2.43 (br s, 4H) for four -CH$_2$ protons and a singlet at δ 2.32 (s, 3H) for N-methyl protons. The molecular ion peak at m/z 497 [M+Na]$^+$ in its mass spectrum confirms the formation of product 62a (Scheme 18). Deprotection of TBS ether group in compound 62a using catalytic amount of PTSA in MeOH gave 62 in 79% yield, which was characterized from its $^1$H NMR spectrum (Fig. 2.54) which displayed absence of signals corresponding to TBS group. All other protons resonated at the expected chemical shift values. The IR spectrum showed absorption at 3405 cm$^{-1}$ for the hydroxyl group and its mass spectrum HRMS (ESI) (Fig. 2.56) showed a molecular ion at m/z 383 [M+Na]$^+$ for the compound 62 (Scheme 18).
Scheme 18

The acid 51 was reacted with 1-ethylpiperazine using HATU, DIPEA gave 63a in 88% yield. The formation of product 63a was established by $^1$H NMR spectrum, which displayed signals corresponding to the compound 63a. In $^{13}$C NMR spectrum the carbonyl carbon in amide showed signal at $\delta$ 165.4. The IR spectrum showed absorption band at 1652 cm$^{-1}$ due to amide carbonyl functional group and the mass spectrum showed a peak at $m/z$ 511 [M+Na]$^+$. The TBS protecting group in compound 63a was removed using PTSA in MeOH to give 63 in 82% yield. The formation of the compound 63 was established from its $^1$H (Fig. 2.57) and $^{13}$C NMR (Fig. 2.58) spectrum with the conspicuous disappearance of signals due to TBS group. Further confirmed by IR and HRMS (ESI) (Fig. 2.59) (Scheme 19).

Scheme 19

The acid group of compound 51 was converted to amide 64a in 93% yield using HATU, DIPEA and 1-phenylpiperazine. The protons in which characteristic signals resonated at their expected chemical shipfts. $^1$H and $^{13}$C NMR spectrum showed the required 25 carbon framework, while its mass data showed peak at $m/z$ 559 [M+Na]$^+$ to confirm the structure. (Scheme 20). The deprotection of TBS group in amide 64a was achieved using PTSA in MeOH to give compound 64 in 91% yield. The formation of product 64 was confirmed from its spectral data by disappearence of TBS group signals in $^1$H NMR (Fig. 2.60), $^{13}$C NMR (Fig. 2.61) spectrum. The IR spectrum showed absorption at 3370 cm$^{-1}$ for the hydroxyl group and further confirmed by HRMS (ESI) (Fig. 2.62).
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Scheme 20

The acid group of compound 51 was converted to amide 65a in 86% yield using HATU, DIPEA and 1-(pyridin-2-yl)piperazine. The protons in which characteristic signals resonated at their expected chemical shifts. $^1$H and $^{13}$C NMR spectrum showed the required 24 carbon framework while its mass spectrum data showed peak at $m/z$ 560 [M+Na]$^+$ to confirm the structure (Scheme 21). The TBS ether group in compound 65a was removed using PTSA in MeOH to give 65 in 95% yield, which was characterized from its $^1$H NMR spectrum (Fig. 2.63) which showed disappearance of signals corresponding to TBS group. All other protons resonated at the expected chemical shift values. The IR spectrum showed absorption band for hydroxyl group at 3276 cm$^{-1}$ and its mass spectrum HRMS (ESI) (Fig. 2.65) showed a molecular ion at $m/z$ 424.2228 [M+H]$^+$ further confirmed the compound 65 (Scheme 21).

Scheme 21
The acid group of compound 51 was transformed into an amide group by using HATU, DIPEA and 2-(piperazin-1-yl)pyrimidine gave 66a in 83% yield. The $^1$H NMR spectrum showed signals at $\delta$ 8.36 (d, $J = 4.9$ Hz, 2H), 6.58 (t, $J = 4.9$ Hz, 1H) for aromatic protons corresponding to the compound 66a. Its mass spectrum showed molecular ion peak at $m/z$ 561 [M+Na]$^+$ further confirmed the product 66a (Scheme 22).

In the next step TBS group of compound 66a was deprotected using catalytic amount of PTSA in MeOH gave 66 in 89% yield. The formation of the compound 66 was confirmed by $^1$H NMR (Fig. 2.66) and $^{13}$C NMR (Fig. 2.67) spectrum, in which disappearance of signals corresponding to TBS group, IR absorption at 3418 cm$^{-1}$ clearly indicated the presence of hydroxyl functional group and its mass spectrum HRMS (ESI) (Fig. 2.68) showed a molecular ion peak at $m/z$ 425.2183 [M+H]$^+$ further confirmed the structure 66 (Scheme 22).

![Scheme 22](image)

The acid group of compound 51 was converted to amide 67a in 91% yield using HATU, DIPEA and 1-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine. The protons in which characteristic signals resonated at their expected chemical shifts. $^1$H, $^{13}$C NMR spectrum showed the required 33 carbon framework while its mass spectral data showed peak at $m/z$ 619 [M+Na]$^+$ to confirm the structure 67a (Scheme 23). The deprotection of TBS group in amide 67a was achieved using PTSA in MeOH to give compound 67 in 91% yield. The formation of product 67 was confirmed from its
spectral data by disappearance of TBS group signals in $^1$H NMR (Fig. 2.69), $^{13}$C NMR (Fig. 2.70) spectrum. Further confirmed by IR and mass (ESI) (Fig. 2.71).

Scheme 23

The acid group of compound 51 was reacted with 1-benzhydrylpiperazine using HATU, DIPEA gave 68a in 90% yield. The protons in which characteristic signals resonated at their expected chemical shifts. $^1$H, $^{13}$C NMR spectrum showed the required 38 carbon framework while its mass spectral data showed peak at m/z 649 [M+Na]$^+$ to confirm the structure 68a (Scheme 24). The TBS ether group in compound 68a was removed using PTSA in MeOH to give 68 in 92% yield. The formation of product 68 was confirmed from its spectral data by disappearance of TBS group signals in $^1$H NMR (Fig. 2.72), $^{13}$C NMR (Fig. 2.73) spectrum. Further confirmed by IR and HRMS (ESI) (Fig. 2.7491).

Scheme 24
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

**BIOLOGICAL ACTIVITIES**

Antiproliferative activities of kunstleramide 53 and its derivatives 54-68 were evaluated in the following human cancer cell lines: human lung carcinoma epithelial (A549), human epithelial cervical cancer (HeLa), human breast adenocarcinoma (MCF7) and human neuroblastoma (IMR32).

**Biological assay**

Since it is known that different cell lines display different sensitivities towards a cytotoxic compound, the use of more than one cell line is therefore considered necessary in the detection of cytotoxic compounds. Bearing this in mind different cell lines human lung carcinoma epithelial (A549), human epithelial cervical cancer (HeLa), human breast adenocarcinoma (MCF7) and human neuroblastoma (IMR32) were used in the present study. Human tumor cell lines were were obtained from American Type culture collection. All the cells were maintained in Dulbecco’s modified Eagle’s medium (DMEM), supplemented with 10% fetal calf serum and 100 µg/ml Penicillin and 100 µg/ml streptomycin sulfate (Sigma), sodium pyruvate, non-essential amino acids. Cell lines were maintained at pH 7.2 to 7.5 and 37 °C in a humidified atmosphere containing 5% CO₂ in the incubator. The viability was checked using Phase Contrast Microscope. The live cells appear phase bright. The cells form projections when they attach to growth surface. Cells were trypsinized when subconfluent from T75 flasks / 90mm dishes and seeded in 96 well plates at a concentration of 0.5×10⁴ cells/100µl in complete medium. The cells were treated with different test concentrations (10, 20, 40, 60, 80 and 100 µg/mL) of compounds 53-68 and their cytotoxicities were compared with the activity of a positive control, Combretastatin (CA4) at identical conditions with five replicates each. Cytotoxicity was measured using the SRB assay. Briefly: The cells (0.5×10⁴) were seeded in each well containing 0.1mL of RPMI medium or DMEM in 96 well plates. After 24h; different test concentrations were added and cell viability was assessed after 2days. The cell growth was stopped by gently layering trichloroacetic acid (50%, 50 µL) on top of the medium in all the wells. The plates were incubated at 4 °C for 1 h to fix the cells attached to the
bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water and air-dried. The plates were stained with SRB dye (0.4% in 1% acetic acid, 100 µL) for 30 min. The plates were washed five times with 1% acetic acid and then air-dried. The adsorbed dye was dissolved in Tris base solution (150 µL, 10 mM, pH 10.4) and plates were gently shaken for 1 h on an orbital shaker. The optical density (OD) was recorded on a Enspire, Perkin Elmer (USA) microplate reader at 510 nm. All experiments were conducted under the standard laboratory illumination. The cell growth was determined by subtracting mean OD value of respective blank from the mean OD value of experimental set. Percent growth in presence of test compounds was calculated considering the growth in absence of any test compounds as 100% and in turn percent growth inhibition in presence of test compounds was calculated. The data was subjected to linear regression analysis and the regression lines were plotted for the best straight-line fit. The IC\textsubscript{50} concentrations were calculated using the respective regression analysis. All data are average values from triplicate samples, and the experiments were repeated at least two times.

**Results**

All the sixteen compounds evaluated displayed antiproliferative activity against the cancer cell lines tested in a concentration-dependent way. The IC\textsubscript{50} values (µM) for 53-68 and Combretastatin (CA4) (a positive drug control) are summarized in Table 1. Compound 67 is more potent on all test cell lines. While the compounds 65, 66 and 68 was more potent for lung carcinoma cell line (A549), compounds 55, 64 was more potent for cervical cancer cell line (HeLa), compound 53, 64 was more potent for neuroblastoma cell line (IMR-32). Overall, these results indicate that compounds 66, 67 and 68 having higher antiproliferative activity on tumor cells than natural product 53.
Table 1. IC\textsubscript{50} values for antiproliferative activities of compounds 53-68 against cancer cell lines\textsuperscript{a}

<table>
<thead>
<tr>
<th>Compound</th>
<th>A-549 (µM)</th>
<th>Hela (µM)</th>
<th>MCF-7 (µM)</th>
<th>IMR-32 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>13.83 ± 0.27</td>
<td>14.58 ± 0.13</td>
<td>12.87 ± 0.71</td>
<td>9.43 ± 0.12</td>
</tr>
<tr>
<td>31</td>
<td>17.12 ± 0.63</td>
<td>12.93 ± 0.94</td>
<td>33.56 ± 0.1</td>
<td>16.59 ± 0.97</td>
</tr>
<tr>
<td>32</td>
<td>16.81 ± 0.74</td>
<td>9.45 ± 0.61</td>
<td>26.61 ± 0.83</td>
<td>17.35 ± 0.26</td>
</tr>
<tr>
<td>33</td>
<td>19.19 ± 0.15</td>
<td>10.72 ± 0.1</td>
<td>15.33 ± 0.91</td>
<td>13.41 ± 0.78</td>
</tr>
<tr>
<td>34</td>
<td>16.46 ± 0.2</td>
<td>13.36 ± 0.1</td>
<td>18.05 ± 0.16</td>
<td>15.66 ± 0.93</td>
</tr>
<tr>
<td>35</td>
<td>24.36 ± 0.92</td>
<td>14.14 ± 0.94</td>
<td>26.23 ± 0.91</td>
<td>12.01 ± 0.58</td>
</tr>
<tr>
<td>36</td>
<td>16.67 ± 0.49</td>
<td>14.09 ± 0.64</td>
<td>39.47 ± 0.83</td>
<td>11.02 ± 0.22</td>
</tr>
<tr>
<td>37</td>
<td>17.9 ± 0.65</td>
<td>16.41 ± 0.73</td>
<td>16.18 ± 0.96</td>
<td>20.36 ± 0.74</td>
</tr>
<tr>
<td>38</td>
<td>18.03 ± 0.49</td>
<td>20.59 ± 0.93</td>
<td>20.15 ± 0.83</td>
<td>16.09 ± 0.24</td>
</tr>
<tr>
<td>39</td>
<td>22.17 ± 0.54</td>
<td>16.49 ± 0.71</td>
<td>17.13 ± 0.96</td>
<td>18.87 ± 0.42</td>
</tr>
<tr>
<td>40</td>
<td>15.68 ± 0.33</td>
<td>11.68 ± 0.48</td>
<td>11.51 ± 0.52</td>
<td>10.79 ± 0.4</td>
</tr>
<tr>
<td>41</td>
<td>14.17 ± 0.67</td>
<td>9.75 ± 0.17</td>
<td>11.97 ± 0.1</td>
<td>9.43 ± 0.29</td>
</tr>
<tr>
<td>42</td>
<td>8.93 ± 0.73</td>
<td>23.57 ± 0.9</td>
<td>23.57 ± 0.9</td>
<td>11.06 ± 0.95</td>
</tr>
<tr>
<td>43</td>
<td>9.92 ± 0.98</td>
<td>12.61 ± 0.42</td>
<td>14.66 ± 0.58</td>
<td>10.79 ± 0.45</td>
</tr>
<tr>
<td>44</td>
<td>8.58 ± 0.11</td>
<td>8.75 ± 0.54</td>
<td>12.3 ± 0.36</td>
<td>9.23 ± 0.34</td>
</tr>
<tr>
<td>45</td>
<td>10.6 ± 0.31</td>
<td>10.48 ± 0.15</td>
<td>12.54 ± 0.23</td>
<td>11.86 ± 0.44</td>
</tr>
<tr>
<td>Piperine</td>
<td>11.89 ± 0.18</td>
<td>19.21 ± 0.73</td>
<td>12.96 ± 0.49</td>
<td>10.19 ± 0.38</td>
</tr>
<tr>
<td>Cambretastatin\textsuperscript{b}</td>
<td>6.45 ± 0.41</td>
<td>5.36 ± 0.12</td>
<td>4.63 ± 0.47</td>
<td>5.72 ± 0.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a} IC\textsubscript{50} is defined as the concentration, which results in a 50\% decrease in cell number as compared with that of the control cultures in the absence of an inhibitor and were calculated using the respective regression analysis. The values represent the mean ± SE of three individual observations.

\textsuperscript{b} Cambretastatin was employed as positive control.
**EXPERIMENTAL**

**EXPERIMENTAL DATA:**

(R,E)-ethyl 5-(3,4-dimethoxyphenyl)-4-hydroxypent-2-enoate (47):

![Chemical Structure](image)

To a stirred solution of IBX (7.1 g, 25.51 mmol) in dry DMSO (7 mL) was added a solution of 46 (2.5 g, 12.75 mmol) in dry CH₂Cl₂ (20 mL) at room temperature and stirred for 3 h at room temperature. After completion of the reaction, the mixture was filtered and diluted with ice cold water (10 mL) and extracted into CH₂Cl₂ (2 x 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄ and evaporated to give crude aldehyde (2.27 g, Yield 92%), which was used for further reaction. To a solution of thus obtained aldehyde (2.0 g, 10.30 mmol) was added nitrosobenzene (1.10 g, 10.30 mmol) and L-proline (0.474 g, 4.12 mmol) in anhydrous DMSO (30 mL) at 20 °C. The reaction mixture was vigorously stirred for 25 min under nitrogen and then cooled to 0 °C. Thereafter a cooled (0 °C) and a premixed solution of triethyl phosphonoacetate (6.13 mL, 30.92 mmol), DBU (4.62 mL, 30.92 mmol) and anhydrous LiCl (1.314 g, 30.92 mmol) in CH₃CN (30 mL) was added quickly (1-2 min). The resulting mixture was allowed to warm to room temperature over 1 h, and reaction was quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum and reaction mixture was diluted with water (100 mL) and extracted into Et₂O (3 x 100 mL). The combined organic layers was washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give crude product, which was dissolved in methanol (20 mL) and reacted with CuSO₄·5H₂O (0.514 g, 2.061 mmol) and the reaction mixture was stirred at r.t. for overnight and quenched with a cold saturated NH₄Cl solution (20 mL). The mixture was filtered on a Celite pad and washed thoroughly with ethyl acetate (100 mL) concentrated and extracted into ethyl acetate (3 x 75 mL). The combined organic layer was washed with brine, dried over anh. Na₂SO₄,
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

filtered and concentrated in vacuo. The crude product was then purified over silica gel column using Hexanes/EtOAc (75:25) as eluent to give compound 47 as a brown color liquid (1.88 g, Yield 60%). The enantiomeric excess was determined by chiral HPLC column: (CHIRAL PAK OJ-H: 250 x 4.6mm, 5µ) mobile phase: 20% IPA in Hexane, Flow rate: 0.75 mL/min, detection: 210 nm

$\text{[}\alpha\text{]}_b^{25} \quad : +5 \ (c \ 0.4, \text{CHCl}_3)$.

$^1\text{H NMR (300 MHz, CDCl}_3) \quad : \delta 7.0 \ (dd, \ J = 15.6, 4.5 \text{ Hz, 1H}), 6.85-6.71 \ (m, 3 \text{ H}), 6.05 \ (d, \ J = 15.6 \text{ Hz, 1H}), 4.55-4.44 \ (m, 1\text{H}), 4.20 \ (q, \ J = 7.1 \text{ Hz, 2H}), 3.86 \ (s, 6\text{H}), 2.91 \ (dd, \ J = 13.6, 4.9 \text{ Hz, 1H}), 2.72 \ (dd, \ J = 13.6, 8.1 \text{ Hz, 1H}), 1.28 \ (t, \ J = 7.1 \text{ Hz, 3H}).$

$^{13}\text{C NMR (75 MHz, CDCl}_3) \quad : \delta 166.4, 148.9, 148.8, 147.8, 129.1, 121.4, 120.4, 112.5, 111.2, 71.6, 60.3, 55.8, 55.7, 42.7, 14.1.$

IR (neat) cm$^{-1}$

: $3492, 2938, 2837, 1713, 1656, 1515, 1462, 1264, 1238, 1158, 1030, 767.$

ESIMS (m/z)  
: $303 \ [\text{M + Na}]^+.$

Molecular formula  
: $\text{C}_{15}\text{H}_{20}\text{O}_5.$

(R,E)-ethyl 5-(3,4-dimethoxyphenyl)-4-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)pent-2-enoate (47a):

\[
\text{MeO} \quad \text{MeO} \\
\begin{array}{c}
\text{OSMTPA} \\
\text{47a}
\end{array}
\]

$\text{N,N'-Dicyclohexylcarbodiimide (DCC) (14.7 mg, 0.071 mmol), a catalytic amount of 4-dimethylaminopyridine (DMAP), and CH}_2\text{Cl}_2 \ (2 \text{ mL})$ taken under a nitrogen atmosphere were allowed to cool at $0 \text{°C}$ for 10 min after which a solution of alcohol 47 (20 mg, 0.071 mmol) in CH$_2$Cl$_2$ (2 mL) was added. This was allowed to stir for an additional 10 min, followed by the dropwise addition of (S)-α-methoxy-α-trifluoromethyl phenylacetic acid (16.7 mg, 0.071 mmol) in CH$_2$Cl$_2$ (2 mL). This
reaction mixture was then stirred at 0 °C for 1 h and then at room temperature for 12 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over anhydrous Na₂SO₄, and evaporated to give crude ester, which was purified over silica gel column chromatography using Hexanes/EtOAc (95:5) as eluent to afford colorless oil (S)-Mosher’s ester of 47a (24.8 mg, 70%)

**1H NMR (300 MHz, CDCl₃)**: δ 7.42-7.16 (m, 5H), 6.85 (dd, J = 15.8, 6.0 Hz, 1H), 6.92-6.64 (m, 3H), 5.86 (d, J = 15.8 Hz, 1H), 5.92-5.71 (m, 1H), 4.17 (q, J = 6.7 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.37 (s, 3H), 3.06-2.85 (m, 2H), 1.26 (t, J = 6.7 Hz, 3H).

**ESIMS (m/z)**: 519 [M+Na]⁺.

**Molecular formula**: C₂₅H₂₇F₃O₇.

(R,E)-ethyl 5-(3,4-dimethoxyphenyl)-4-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)pent-2-enoate (47b):

![Chemical structure of 47b]

**1H NMR (300 MHz, CDCl₃)**: δ 7.44-7.31 (m, 5H), 6.88 (dd, J = 15.8, 6.0 Hz, 1H), 6.76-6.59 (m, 3H), 5.98 (d, J = 15.8 Hz, 1H), 5.89-5.79 (m, 1H), 4.19 (q, J = 6.7 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.43 (s, 3H), 3.00-2.90 (m, 2H), 1.28 (t, J = 6.7 Hz, 3H).

**ESIMS (m/z)**: 519 [M+Na]⁺.

**Molecular formula**: C₂₅H₂₇F₃O₇.
(R,E)-ethyl 4-((tert-butyldimethylsilyl)oxy)-5-(3,4-dimethoxyphenyl)pent-2-enoate (48):

To a solution of the alcohol 47 (1.8 g, 6.42 mmol) in dry CH₂Cl₂ (30 mL) was added imidazole (0.875 g, 12.85 mmol) and the mixture was stirred for 10 min at 0 °C. To this solution tert-butyldimethylsilyl chloride (1.157 g, 7.714 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 6 h. After completion of the reaction, the mixture was diluted with water and extracted into CH₂Cl₂ (3 x 75 mL). The combined extract was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by column chromatography using Hexanes/EtOAc (97:3) as eluent to give pure compound 48 (2.43 g, 96%) as a colorless liquid.

[\alpha]_D^{25} : +0.6 (c 1, CHCl₃).

¹H NMR (300 MHz, CDCl₃) : δ 6.96 (dd, J = 15.1, 4.5 Hz, 1H), 6.81-6.68 (m, 3H), 5.96 (d, J = 15.1 Hz, 1H), 4.46-4.37 (m, 1H), 4.18 (q, J = 7.5 Hz, 2H), 3.86 (s, 6H), 2.83-2.65 (m, 2H), 1.28 (t, J = 7.5 Hz, 3H), 0.86 (s, 9H), -0.07 (s, 3H), -0.20 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) : δ 166.5, 150.2, 148.5, 147.7, 130.1, 121.8, 120.0, 113.2, 111.1, 73.1, 60.2, 55.9, 55.7, 43.8, 25.7, 18.1, 14.2, -4.9, -5.3.

IR (neat) cm⁻¹ : 2954, 2932, 2856, 1719, 1657, 1515, 1465, 1262, 1159, 1115, 1032, 833, 774.

ESIMS (m/z) : 417 [M + Na]⁺.

Molecular formula : C₂₁H₃₄O₅Si.
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

(R,E)-4-((tert-butyldimethylsilyl)oxy)-5-(3,4-dimethoxyphenyl)pent-2-en-1-ol (49):

To a cooled (0 °C) solution of ester 48 (2.4 g, 6.09 mmol) in dry CH₂Cl₂ (50 mL) was added slowly DIBAL-H (1M in toluene, 9.08 mL, 9.13 mmol) for 1 h. The reaction mixture was stirred at room temperature for 2 h, cooled to 0 °C and quenched with methanol (2 mL) and sodium potassium tartarate solution (10 mL). The reaction mixture was passed through a short pad of Celite rinsing with CH₂Cl₂. The organic phase was separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL). Combined organic layer was concentrated and the residue was purified by column chromatography over silica gel using Hexanes/EtOAc (80:20) as eluent to afford 49 (1.95, 91%) as colorless liquid.

[α]D 25 : +2.5 (c 1.2, CHCl₃).

¹H NMR (300 MHz, CDCl₃) : δ 6.81-6.67 (m, 3H), 5.78-5.72 (m, 2H), 4.32-4.23 (m, 1H), 4.16-4.07 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.74-2.65 (m, 2H), 0.83 (s, 9H), -0.10 (s, 3H), -0.20 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) : δ 148.3, 147.3, 134.4, 131.1, 128.5, 121.7, 113.1, 110.8, 73.9, 62.8, 55.8, 55.6, 44.5, 25.7, 18.0, -4.7, -5.2.

IR (neat) cm⁻¹ : 3481, 2931, 2856, 1514, 1465, 1261, 1030, 834, 774.

ESIMS (m/z) : 375 [M + Na]⁺.

Molecular formula : C₉H₃₂O₄Si.
(R,2E,4E)-ethyl 6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dienoate (50):

To a stirred solution of IBX (2.1 g, 7.50 mmol) in dry DMSO (2 mL) was added a solution of 49 (1.32 g, 3.75 mmol) in dry CH$_2$Cl$_2$ (30 mL) at room temperature and stirred for 3 h at room temperature. After completion of the reaction, the mixture was filtered and diluted with ice cold water (10 mL) and extracted into CH$_2$Cl$_2$ (2 x 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na$_2$SO$_4$ and evaporated to give crude aldehyde 1.20 g, 91%), which was used directly for next step without purification.

To a solution of the aldehyde (1.2 g, 3.42 mmol) in dry benzene (30 mL) was added Ph$_3$P=CHCO$_2$Et (1.431 g, 4.114 mmol) and stirred at reflux temperature for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue purified by column chromatography, eluted with Hexanes/EtOAc (94:6) to afford 50 as colorless syrup as a mixture of geometrical isomers (E/Z 95:5). The mixture was separated by silica gel column chromatography to give pure E isomer (1.21 g, 85 %).

[$\alpha$]$_D^{25}$ : $-6.8$ (c 0.7, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.25 (dd, $J$ = 15.3, 10.9 Hz, 1H), 6.81-6.64 (m, 3 H), 6.29 (dd, $J$ = 15.3, 10.9 Hz, 1H), 6.11 (dd, $J$ = 15.3, 5.4 Hz, 1H), 5.84 (d, $J$ = 15.3 Hz, 1H), 4.41-4.31 (m, 1H), 4.20 (q, $J$ = 7.1 Hz, 2H), 3.85 (s, 6H), 2.77-2.67 (m, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H), 0.85 (s, 9H), -0.09 (s, 3H), -0.18 (s, 3H).
Chapter II
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 167.0, 148.4, 147.5, 145.2, 143.9, 130.4, 126.8, 121.7, 121.0, 113.1, 110.9, 73.9, 60.2, 55.8, 55.7, 44.3, 25.7, 18.1, 14.2, -4.9, -5.2.

IR (neat) cm$^{-1}$ : 2954, 2932, 2856, 1715, 1644, 1515, 1465, 1263, 1237, 1139, 1031, 835, 776.

ESIMS (m/z) : 443 [M + Na]$^+$. Molecular formula : C$_{23}$H$_{36}$O$_5$Si.

(R,2E,4E)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dienoic acid (51):

To a solution of ester compound 50 (1.2 g, 2.85 mmol) in THF (10 mL) and H$_2$O (10 mL) was added LiOH.H$_2$O (0.599 g, 14.28 mmol). This solution was allowed to stir for 6 h at room temperature. The reaction mixture was concentrated, the residue was diluted with H$_2$O (10 mL) and acidified with KHSO$_4$, the aqueous layer was extracted into EtOAc. The combined organic layer was washed with brine, dried over anh. Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel Hexanes/EtOAc (70:30) as eluent to give compound 51 (1.0 g, 90%) as a colorless viscous liquid.

$[\alpha]_D^{25}$ : $-50$ (c 0.4, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.34 (dd, $J = 15.1$, 10.5 Hz, 1H), 6.79 (d, $J = 8.1$ Hz, 1H), 6.73-6.67 (m, 2H), 6.34 (dd, $J = 15.1$, 10.5 Hz, 1H), 6.17 (dd, $J = 15.8$, 4.5 Hz, 1H), 5.85 (d, $J = 15.1$ Hz, 1H), 4.43-4.34 (m, 1H), 3.86 (s, 6H), 2.77-2.70 (m, 2H), 0.86 (s, 9H), -0.08 (s, 3H), -0.17 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 172.1, 148.6, 147.6, 146.5, 146.1, 130.3, 126.6,
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

121.8, 120.1, 113.3, 111.2, 73.8, 55.8, 55.7, 44.2, 25.7, 18.0, -4.9, -5.1.

IR (neat) cm\(^{-1}\):

3447, 2930, 2855, 1685, 1640, 1613, 1512, 1463, 1416, 1257, 1139, 1105, 1001, 831, 771.

ESIMS (m/z):

415 [M + Na]\(^{+}\).

Molecular formula:

C\(_{21}\)H\(_{32}\)O\(_{5}\)Si.

\((R,2E,4E)-6-((\text{tert-butyldimethylsilyl})\text{oxy})-7-(3,4-\text{dimethoxyphenyl})-\text{N-ethylhepta-2,4-dienamide} (52):\)

To a solution of 51 (50 mg, 0.127 mmol) in dry DMF (2 mL) was added HATU (25 mg, 0.127 mmol) and DIPEA (0.33 mL, 0.190 mmol) at 0 °C, stirred at same temperature for 5 min. Then temperature raised to r.t, then added ethylamine (1M in THF, 0.13 mL, 0.127 mmol). The mixture was stirred at r.t. for overnight. After completion of reaction, the mixture was diluted with EtOAc and washed with water. The organic layer was dried and concentrated, the residue was purified by column chromatography over silica gel using Hexanes/EtOAc (8:2) as eluent to afford 52 (49 mg, 93%) as light yellow liquid.

\([\alpha]_D^{25}\):

-18 (c 1, CHCl\(_3\)).

\(^1\)H NMR (300 MHz, CDCl\(_3\)):

\(\delta\) 7.19 (dd, \(J = 15.1, 11.3\) Hz, 1H), 6.79 (d, \(J = 8.3\) Hz, 1H), 6.70 (s, 2H), 6.23 (dd, \(J = 15.1, 11.3\) Hz, 1H), 6.06 (dd, \(J = 15.1, 5.2\) Hz, 1H), 5.79 (d, \(J = 15.8\) Hz, 1H), 5.59 (br s, 1H), 4.35 (m, 1H), 3.86 (s, 6H), 3.37 (q, \(J = 7.5\) Hz, 2H), 2.72 (m, 2H), 1.17 (t, \(J = 7.5\) Hz, 3H), 0.85 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)):

\(\delta\) 165.9, 148.4, 147.5, 143.7, 140.1, 130.6, 126.9,
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

123.5, 121.8, 113.2, 111.0, 74.0, 55.8, 55.7, 44.3, 34.4, 25.7, 18.1, 14.8, -4.8, -5.1.

IR (neat) cm\(^{-1}\): 2930, 2856, 1661, 1616, 1515, 1462, 1260, 1150, 834, 773.

ESIMS (m/z): 442 [M + Na]\(^+\).

Molecular formula: C\(_{23}\)H\(_{37}\)NO\(_4\)Si.

\((R,2E,4E)-7-(3,4\text{-dimethoxyphenyl})\text{-N-ethyl-6-hydroxyhepta-2,4-dienamide (53)}:\)

To a cooled (0 °C) solution of 52 (80 mg, 0.190 mmol) in MeOH (5 mL) was added catalytic amount of PTSA and stirred at same temperature for 0.5 h. After completion of the reaction, the mixture was quenched with solid sodium bicarbonate, filtered and MeOH was evaporated under reduced pressure to afford a crude product, which was purified by column chromatography on silica gel Hexanes/EtOAc (70:30) as eluent to give alcohol compound 53 (58 mg, 95%) as a white solid.

\([\alpha]_D^{25}\): −54.2 (c 0.042, MeOH).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.13 (dd, \(J = 14.3, 9.0\) Hz, 1H), 6.74 (d, \(J = 8.3\) Hz, 1H), 6.67 (d, \(J = 9.0\) Hz, 2H), 6.25 (dd, \(J = 14.3, 11.3\) Hz, 1H), 6.04 (dd, \(J = 14.3, 5.2\) Hz, 1H), 5.75 (d, \(J = 14.3\) Hz, 1H), 5.61 (br s, 1H), 4.36 (m, 1H), 3.79 (s, 6H), 3.30 (q, \(J = 7.5\) Hz, 2H), 2.79 (dd, \(J = 13.5, 4.5\) Hz, 1H), 2.66 (dd, \(J = 13.5, 4.5\) Hz, 1H), 2.03 (br s, 1H), 1.10 (t, \(J = 7.5\) Hz, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 165.9, 148.9, 147.8, 142.3, 139.9, 129.6, 127.6, 124.1, 121.5, 112.7, 111.3, 72.5, 55.8, 43.3, 34.5, 14.8.

IR (KBr) cm\(^{-1}\): 3432, 2922, 1649, 1593, 1536, 1258, 1148, 1027, 991, 805.
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

HRMS (ESI) (m/z) : calcd. for C\textsubscript{17}H\textsubscript{23}NO\textsubscript{4}Na [M + Na]\textsuperscript{+} 328.1519; found 328.1526.

Molecular formula : C\textsubscript{17}H\textsubscript{23}NO\textsubscript{4}.

**General experimental procedure for amide formation:**
To a solution of acid (1 mmol) in dry DMF (5 mL) was added HATU (1 mmol) and DIPEA (1.5 mmol) at 0 °C, stirred at same temperature for 5 min. Then temperature raised to r.t, and added amine (1 mmol). The mixture was stirred at r.t. for overnight. After completion of reaction, the mixture was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to give crude residue, which was purified on silica gel column chromatography using hexane/EtOAc as the eluent to give the product.

**General experimental procedure for TBS deprotection:**
To a cooled (0 °C) solution of TBS ether compound (1 mmol) in MeOH (5 mL) was added catalytic amount of PTSA and stirred at same temperature for 0.5 h. After completion of the reaction, the mixture was quenched with solid sodium bicarbonate and filtered and MeOH was evaporated under reduced pressure to afford a crude product, which was purified on silica gel column chromatography using hexane/EtOAc as the eluent to give the corresponding amide product.

The spectral (IR, \textsuperscript{1}H and \textsuperscript{13}C NMR and HRMS) data of the representative products are given below.

(R,2E,4E)-N-benzyl-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dienamide (54a):

\[ [\alpha]_D^{25} = -12.9 \ (c \ 0.2, \ CHCl_3). \]
Chapter II

First Stereoselective Total synthesis of (−)-Kunstleramide &
its analogues

1H NMR (600 MHz, CDCl3): δ 7.36-7.27 (m, 5H), 7.24 (dd, J = 15.0, 11.2 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.70 (d, J = 6.4 Hz, 1H), 6.69 (s, 1H), 6.24 (dd, J = 15.0, 11.2 Hz, 1H), 6.08 (dd, J = 15.0, 5.2 Hz, 1H), 5.81 (d, J = 15.0 Hz, 1H), 5.78-5.73 (m, 1H, NH), 4.52 (d, J = 5.6 Hz, 2H), 4.37-4.32 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.76-2.67 (m, 2H), 0.84 (s, 9H), -0.10 (s, 3H), -0.18 (s, 3H).

13C NMR (75 MHz, CDCl3): δ 165.9, 148.4, 147.4, 143.9, 140.4, 138.1, 130.5, 128.5, 127.6, 127.2, 126.8, 123.2, 121.7, 113.2, 111.0, 73.9, 55.7, 55.6, 44.3, 43.5, 25.7, 18.0, -4.8, -5.2.

IR (neat) cm⁻¹: 2929, 2855, 1661, 1613, 1515, 1461, 1260, 1150, 1029, 833, 773.

ESIMS (m/z): 504 [M+Na]+.

Molecular formula: C₂₈H₃₉NO₄Si.

(R,2E,4E)-N-benzyl-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dienamide (54):

[α]D²⁵: -17.3 (c 0.3, CHCl₃).

1H NMR (300 MHz, CDCl₃): δ 7.36-7.23 (m, 6H), 6.82 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.73 (s, 1H), 6.34 (dd, J = 15.1, 11.2 Hz, 1H), 6.13 (dd, J = 15.1, 5.1 Hz, 1H), 5.85 (d, J = 15.1 Hz, 1H), 5.83 (br s, 1H), 4.52 (d, J = 4.8 Hz, 2H), 4.47-4.41 (m, 1H), 3.86 (s, 6H), 2.86 (dd, J = 13.5, 5.0 Hz, 1H), 2.74 (dd, J = 13.5, 7.9 Hz, 1H), 1.82 (br s, 1H).
Chapter II  First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

\[ ^{13} \text{C NMR (125 MHz, CDCl}_3\text{)} \quad \delta 165.9, 148.8, 147.7, 142.7, 140.4, 138.0, 129.6, 128.6, 127.7, 127.5, 127.4, 123.7, 121.6, 112.6, 111.2, 72.4, 55.8, 43.6, 43.2. \]

IR (KBr) cm\(^{-1}\)  : 3426, 3303, 2922, 2853, 1649, 1594, 1540, 1516, 1259, 1235, 1141, 1025, 747, 699.

HRMS (ESI) (m/z)  : calcd. for C\(_{22}\)H\(_{26}\)O\(_4\)N [M+H]\(^+\) 368.1856; found 368.1858.

Molecular formula  : C\(_{22}\)H\(_{25}\)NO\(_4\).

(R,2E,4E)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-N-(4-methoxybenzyl)hepta-2,4-dienamide (55a):

[\([\alpha]\)\(\text{D}\)]\(_{25}\)  : \(-19.3\) (c 0.4, CHCl\(_3\)).

\(^1\text{H NMR (300 MHz, CDCl}_3\text{)} \quad \delta 7.24 (dd, J = 14.9, 10.7 \text{ Hz, 1H}), 7.22 (d, J = 8.6 \text{ Hz, 2H}), 6.86 (d, J = 8.6 \text{ Hz, 2H}), 6.78 (d, J = 8.6 \text{ Hz, 2H}), 6.72 (m, 2H), 6.24 (dd, J = 15.2, 11.1 \text{ Hz, 1H}), 6.07 (dd, J = 15.2, 5.2 \text{ Hz, 1H}), 5.79 (d, J = 14.9 \text{ Hz, 1H}), 5.70-5.61 (m, 1H), 4.46 (d, J = 5.6 \text{ Hz, 2H}), 4.39-4.30 (m, 1H), 3.86 (s, 6H), 3.80 (s, 3H), 2.75-2.70 (m, 2H), 0.84 (s, 9H), -0.09 (s, 3H), -0.17 (s, 3H).

\[^{13}\text{C NMR (125 MHz, CDCl}_3\text{)} \quad \delta 165.8, 158.8, 148.3, 147.3, 143.9, 140.4, 130.5, 130.2, 129.0, 126.8, 123.2, 121.7, 113.8, 113.0, 110.9, 73.9, 55.6, 55.1, 44.2, 43.0, 25.6, 18.0, -4.9, -5.2. \]

IR (neat) cm\(^{-1}\)  : 2930, 2855, 1661, 1612, 1513, 1252, 1031, 833, 775.
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

ESIMS (m/z) : 534 [M+Na]+.
Molecular formula : C_{20}H_{41}NO_{5}Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-N-(4-methoxybenzyl)hepta-2,4-dienamide (55):

\[
\text{[\alpha]_D^{25}} : -30.0 \ (c \ 0.1, \text{CHCl}_3).
\]

$^1$H NMR (300 MHz, CDCl$_3$) :
\[
\delta \ 7.22 \ (dd, J = 14.8, 11.1 \text{ Hz}, 1\text{H}), 7.19 \ (d, J = 8.3 \text{ Hz}, 2\text{H}), 6.79 \ (d, J = 7.9 \text{ Hz}, 1\text{H}), 6.72 \ (m, 2\text{H}), 6.28 \ (dd, J = 14.9, 11.1 \text{ Hz}, 1\text{H}), 6.09 \ (dd, J = 14.9, 5.3 \text{ Hz}, 1\text{H}), 6.09-6.05 \ (m, 1\text{H}, \text{NH}), 5.82 \ (d, J = 14.9 \text{ Hz}, 1\text{H}), 4.43-4.37 \ (m, 1\text{H}), 4.40 \ (d, J = 5.1 \text{ Hz}, 2\text{H}), 3.84 \ (s, 6\text{H}), 3.77 \ (s, 3\text{H}), 2.82 \ (dd, J = 13.5, 5.0 \text{ Hz}, 1\text{H}), \ (dd, J = 13.5, 7.7 \text{ Hz}, 1\text{H}), 2.23 \ (br \ s, 1\text{H}, \text{OH}).
\]

$^{13}$C NMR (75 MHz, CDCl$_3$) :
\[
\delta \ 165.8, \ 158.8, \ 148.6, \ 147.6, \ 142.7, \ 140.2, \ 130.1, 129.6, \ 129.1, \ 127.4, \ 123.8, \ 121.4, \ 113.9, \ 112.5, \ 111.1, \ 72.4, \ 55.7, \ 55.1, \ 43.1, \ 43.0.
\]

IR (KBr) cm$^{-1}$ :
\[
3311, \ 2932, \ 2837, \ 1650, \ 1618, \ 1590, \ 1516, \ 1253, \ 1156, \ 1026, \ 991, \ 805.
\]

HRMS (ESI) (m/z) :
calcd. for C$_{23}$H$_{28}$O$_5$N [M+H]$^+$ 398.1962;
found 398.1963.

Molecular formula : C$_{23}$H$_{27}$NO$_5$.

(R,2E,4E)-6-((tert-butylidimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-N-(3,4,5-trimethoxybenzyl)hepta-2,4-dienamide (56a):
Chapter II
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

\[ \alpha_D^{25} \quad : -29.1 \, (c \, 0.2, \text{CHCl}_3). \]

\( ^1 \text{H} \) NMR (500 MHz, CDCl\(_3\))
\[ \delta \, 7.25 \, (dd, \, J = 14.9, 11.2 \text{ Hz}, \, 1H), \, 6.77 \, (d, \, J = 8.5 \text{ Hz}, \, 1H), \, 6.71-6.67 \, (m, \, 2H), \, 6.50 \, (s, \, 2H), \, 6.25 \, (dd, \, J = 14.9, 11.2 \text{ Hz}, \, 1H), \, 6.09 \, (dd, \, J = 14.9, 5.1 \text{ Hz}, \, 1H), \, 5.83 \, (d, \, J = 14.9 \text{ Hz}, \, 1H), \, 5.83-5.79 \, (m, \, 1H, \, \text{NH}), \, 4.44 \, (d, \, J = 5.1 \text{ Hz}, \, 2H), \, 4.38-4.33 \, (m, \, 1H), \, 3.85 \, (s, \, 6H), \, 3.84 \, (s, \, 6H), \, 3.82 \, (s, \, 3H), \, 2.77-2.69 \, (m, \, 2H), \, 0.84 \, (s, \, 9H), \, -0.10 \, (s, \, 3H), \, -0.17 \, (s, \, 3H). \]

\( ^{13} \text{C} \) NMR (75 MHz, CDCl\(_3\))
\[ \delta \, 165.8, \, 152.9, \, 148.2, \, 147.2, \, 143.9, \, 140.3, \, 136.6, \, 133.9, \, 130.4, \, 126.7, \, 123.2, \, 121.6, \, 112.9, \, 110.8, \, 104.5, \, 73.7, \, 60.5, \, 55.7, \, 55.6, \, 55.5, \, 44.1, \, 43.7, \, 25.5, \, 17.9, \, -5.0, \, -5.3. \]

IR (neat) cm\(^{-1}\)
\[ : 2931, \, 2854, \, 1661, \, 1593, \, 1512, \, 1462, \, 1260, \, 1236, \, 1128, \, 1003, \, 833, \, 774. \]

EIMS (m/z)
\[ : 594 \, [\text{M+Na}]^+. \]

Molecular formula
\[ : \text{C}_{31}\text{H}_{45}\text{NO}_{7}\text{Si}. \]

\( (R,2E,4E)-7-(3,4\text{-dimethoxyphenyl})-6\text{-hydroxy-N-(3,4,5\text{-trimethoxybenzyl})hepta-2,4-dienamide} \) (56):

\[ \alpha_D^{25} \quad : -32.6 \, (c \, 0.15, \text{CHCl}_3). \]

\( ^1 \text{H} \) NMR (300 MHz, CDCl\(_3\))
\[ \delta \, 7.24 \, (dd, \, J = 14.9, 10.9 \text{ Hz}, \, 1H), \, 6.80 \, (d, \, J = 8.0 \text{ Hz}, \, 1H), \, 6.68 \, (d, \, J = 6.5 \text{ Hz}, \, 1H), \, 6.51 \, (s, \, 2H), \, 5.79 \, (d, \, J = 10.9 \text{ Hz}, \, 1H), \, 5.75 \, (d, \, J = 10.9 \text{ Hz}, \, 1H), \, 5.10 \, (s, \, 2H), \, 3.85 \, (s, \, 6H), \, 3.84 \, (s, \, 6H), \, 3.82 \, (s, \, 3H), \, 2.77-2.69 \, (m, \, 2H), \, 0.84 \, (s, \, 9H), \, -0.10 \, (s, \, 3H), \, -0.17 \, (s, \, 3H). \]
Chapter II  First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Hz, 1H), 6.74-6.70 (m, 2H), 6.48 (s, 2H), 6.30 (dd, J = 15.1, 11.1 Hz, 1H), 6.16-6.12 (m, 1H, NH), 6.10 (dd, J = 15.1, 5.3 Hz, 1H), 5.85 (d, J = 15.1 Hz, 1H), 4.43-4.38 (m, 1H), 4.41 (d, J = 5.3 Hz, 2H), 3.84 (s, 6H), 3.81 (s, 6H), 3.79 (s, 3H), 2.84 (dd, J = 13.7, 5.0 Hz, 1H), 2.72 (dd, J = 13.7, 7.7 Hz, 1H), 2.10 (brs, 1H, OH).

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \]: \delta 165.7, 153.3, 148.8, 147.8, 142.7, 140.5, 133.8, 129.5, 127.5, 123.6, 121.4, 112.5, 111.2, 104.8, 72.4, 60.7, 56.0, 55.8, 44.0, 43.2.

IR (KBr) cm\(^{-1}\): 3442, 2925, 2853, 1597, 1511, 1454, 1236, 1122, 1023.

HRMS (ESI) (m/z): calcd. for C\(_{25}\)H\(_{32}\)O\(_7\)N [M+H]\(^+\) 458.2173;
found 458.2175.

Molecular formula: C\(_{25}\)H\(_{31}\)NO\(_7\).

\((R,2E,4E)-6-((\text{tert-butyldimethylsilyl})\text{oxy})-\text{N-}(4-\text{chlorobenzyl})-7-(3,4-\text{dimethoxyphenyl})\text{hepta-2,4-dienamide (57a):}\)

\([\alpha]_D^{25}\): \(-13.4\) (c 0.2, CHCl\(_3\)).

\(^1H\text{ NMR (300 MHz, CDCl}_3 \): \delta 7.38-7.18 (m, 5H), 6.82-6.65 (m, 3H), 6.24 (dd, J = 14.9, 11.3 Hz, 1H), 6.09 (dd, J = 14.9, 4.1 Hz, 1H), 5.82 (d, J = 14.3 Hz, 1H), 5.79 (br s, 1H), 4.49 (s, 2H), 4.40-4.31 (m, 1H), 3.85 (s, 6H), 2.73 (d, J = 4.3 Hz, 2H), 0.85 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H).

\[^{13}C\text{ NMR (75 MHz, CDCl}_3 \]: \delta 166.0, 148.3, 147.4, 144.2, 140.7, 136.8, 133.0,
Chapter II  

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

130.5, 128.9, 128.5, 126.7, 122.9, 121.7, 113.1, 110.9, 73.8, 55.7, 55.6, 44.2, 42.7, 25.7, 18.0, -4.8, -5.2.

IR (neat) cm\(^{-1}\): 2928, 2855, 1661, 1613, 1514, 1463, 1259, 1149, 1029, 834, 772.

EIMS (m/z): 538 [M+Na]\(^+\).

Molecular formula: C\(_{28}\)H\(_{38}\)ClNO\(_4\)Si.

\((R,2E,4E)-N-(4-chlorobenzyl)-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dienamide (57):\)

\([\alpha]_D^{25}\): \(-15.7\) (c 0.35, CHCl\(_3\)).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.29 (d, \(J = 8.2\) Hz, 2H), 7.24 (dd, \(J = 15.0, 4.1\) Hz, 1H), 7.22 (d, \(J = 8.2\) Hz, 2H), 6.81 (d, \(J = 8.2\) Hz, 1H), 6.74 (d, \(J = 8.2\) Hz, 1H), 6.72 (s, 1H), 6.33 (dd, \(J = 15.0, 11.2\) Hz, 1H), 6.13 (dd, \(J = 15.0, 5.2\) Hz, 1H), 5.98-5.94 (m, 1H), 5.84 (d, \(J = 15.0\) Hz, 1H), 4.47 (d, \(J = 6.0\) Hz, 2H), 4.45-4.41 (m, 1H), 3.86 (s, 6H), 2.86 (dd, \(J = 13.5, 4.8\) Hz, 1H), 2.73 (dd, \(J = 13.5, 7.9\) Hz, 1H), 1.79 (br s, 1H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 166.0, 148.7, 147.6, 143.0, 140.6, 136.6, 133.0, 129.5, 129.0, 128.6, 127.3, 123.4, 121.4, 112.5, 111.1, 72.4, 55.7, 43.1, 42.7.

IR (KBr) cm\(^{-1}\): 3286, 2925, 1659, 1609, 1555, 1513, 1265, 1233,
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

1138, 1035, 800, 743.

HRMS (ESI) (m/z): calcd. for C_{22}H_{25}O_{3}NCl [M+H]^+ 402.1466; found 402.1466.

Molecular formula: C_{22}H_{24}ClNO_{4}.

\((R,2E,4E)\)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(pyrrolidin-1-yl)hepta-2,4-dien-1-one (58a):

![Chemical Structure of 58a](image)

\([\alpha]_D^{25}\) : −4.2 (c 0.22, CHCl₃).

\(^1\)H NMR (500 MHz, CDCl₃): δ 7.27 (dd, J = 15.2, 11.7 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.72-6.67 (m, 2H), 6.26 (dd, J = 15.2, 11.7 Hz, 1H), 6.12 (d, J = 14.8 Hz, 1H), 6.07 (dd, J = 15.2, 5.4 Hz, 1H), 4.38-4.31 (m, 1H), 3.85 (s, 6H), 3.58-3.48 (m, 4H), 2.77-2.67 (m, 2H), 2.00-1.92 (m, 2H), 1.90-1.82 (m, 2H), 0.84 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H).

\(^{13}\)C NMR (125 MHz, CDCl₃): δ 164.8, 148.3, 147.3, 143.8, 141.1, 130.5, 127.2, 121.7, 121.4, 113.0, 110.8, 74.0, 55.7, 55.6, 46.4, 45.8, 44.3, 25.9, 25.7, 24.1, 18.0, -4.8, -5.2.

IR (neat) cm\(^{-1}\): 2953, 2856, 1625, 1514, 1445, 1261, 1152, 1029, 834, 769.

EIMS (m/z): 468 [M+Na]^+.

Molecular formula: C_{25}H_{39}NO_{4}Si.

\((R,2E,4E)\)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(pyrrolidin-1-yl)hepta-2,4-dien-1-one (58):
Chapter II
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

![Chemical Structure](image)

**[α]_D^{25}** : $-12.6$ (c 0.3, CHCl₃).

**¹H NMR (300 MHz, CDCl₃)**

$\delta$ 7.29 (dd, $J = 14.9, 11.1$ Hz, 1H), 6.81 (d, $J = 7.9$ Hz, 1H), 6.77-6.69 (m, 2H), 6.37 (dd, $J = 15.1, 11.1$ Hz, 1H), 6.16 (d, $J = 15.1$ Hz, 1H), 6.13 (dd, $J = 15.1, 5.4$ Hz, 1H), 4.48-4.38 (m, 1H), 3.86 (s, 6H), 3.52 (br s, 4H), 2.86 (dd, $J = 13.5, 5.2$ Hz, 1H), 2.74 (dd, $J = 13.5, 7.7$ Hz, 1H), 2.04 (br s, 2H), 1.91 (br s, 2H).

**¹³C NMR (75 MHz, CDCl₃)**

$\delta$ 164.8, 148.7, 147.6, 142.5, 140.9, 129.7, 127.9, 122.0, 121.4, 112.5, 111.1, 72.5, 55.8, 55.7, 46.4, 45.9, 43.2, 25.9, 24.2.

**IR (KBr) cm⁻¹**

3402, 2924, 1720, 1623, 1591, 1514, 1445, 1623, 1234, 1025, 808, 729.

**EIMS (m/z)**

454 [M+Na]$^+$.  

Molecular formula: $C_{19}H_{25}NO_4$.

(R,2E,4E)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(piperidin-1-yl)hepta-2,4-dien-1-one (59a):

![Chemical Structure](image)

**[α]_D^{25}** : $-8.7$ (c 0.3, CHCl₃).

**¹H NMR (500 MHz, CDCl₃)**

$\delta$ 7.19 (dd, $J = 14.8, 11.1$ Hz, 1H), 6.76-6.71 (m, 1H), 6.68-6.63 (m, 2H), 6.30-6.18 (m, 2H), 6.01 (dd, $J = 15.1, 5.3$ Hz, 1H), 4.34-4.27 (m, 1H), 3.81
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

\((s, 6H), 3.57 \text{ (br s, 2H)}, 3.44 \text{ (br s, 2H)}, 2.73-2.63 \text{ (m, 2H)}, 1.64-1.47 \text{ (m, 6H)}, 0.81 \text{ (s, 9H)}, -0.13 \text{ (s, 3H)}, -0.21 \text{ (s, 3H)}.\)

\[^{13}\text{C} \text{NMR} \text{ (125 MHz, CDCl}_3\text{)}\]: \(\delta 165.1, 148.2, 147.2, 143.1, 141.6, 130.4, 127.2, 121.6, 120.0, 112.9, 110.7, 73.8, 55.6, 55.5, 46.6, 44.2, 42.9, 26.4, 25.5, 25.3, 24.3, 17.9, -4.9, -5.3.\)

IR (neat) cm\(^{-1}\): 2932, 2855, 1649, 1623, 1514, 1442, 1259, 1137, 1026, 834, 774.

EIMS \((m/z)\): 482 [M+Na].

Molecular formula: \(\text{C}_{26}\text{H}_{41}\text{NO}_4\text{Si}').

\((R,2E,4E)-7-(3,4\text{-dimethoxyphenyl})-6\text{-hydroxy-1-}(\text{piperidin-1-yl})\text{hepta-2,4-dien-1-one} \text{ (59):}\)

\([\alpha]_d^{25}\): \(-14.3 \text{ (c 0.28, CHCl}_3\text{)}.\)

\(^1\text{H} \text{NMR} \text{ (300 MHz, CDCl}_3\text{)}\): \(\delta 7.24 \text{ (dd, } J = 14.3, 11.3 \text{ Hz, 1H}), 6.82 \text{ (d, } J = 8.3 \text{ Hz, 1H}), 6.75 \text{ (d, } J = 8.3 \text{ Hz, 1H}), 6.74 \text{ (s, 1H), 6.43-6.30 \text{ (m, 2H)}, 6.10 \text{ (dd, } J = 15.1, 5.2 \text{ Hz, 1H), 4.47-4.38 \text{ (m, 1H), 3.87 \text{ (s, 6H)}, 3.54 \text{ (br s, 4H), 2.86 \text{ (dd, } J = 13.5, 5.2 \text{ Hz, 1H), 2.75 \text{ (dd, } J = 13.5, 8.3 \text{ Hz, 1H), 1.71-1.51 \text{ (m, 6H)}.}\)

\(^{13}\text{C} \text{NMR} \text{ (75 MHz, CDCl}_3\text{)}\): \(\delta 165.2, 148.5, 147.4, 142.1, 141.5, 129.7, 127.9, 121.3, 120.5, 112.4, 111.0, 72.4, 55.7, 55.6, 46.7, 43.2, 43.0, 26.4, 25.4, 24.3.\)

IR (KBr) cm\(^{-1}\): 3334, 2931, 2849, 1644, 1614, 1568, 1514, 1464,
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

1258, 1232, 1138, 1002, 803, 763.

EIMS (m/z) : 368 [M+NH₄]⁺.
Molecular formula : C₂₀H₂₇NO₄.

(R,2E,4E)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-morpholinohepta-2,4-dien-1-one (60a):

\[
\begin{align*}
\text{MeO} & \quad \begin{array}{c}
\text{MeO} \\
\text{OTBS} \\
60a
\end{array} \\
\end{align*}
\]

\[\alpha \text{D}^{25} \quad : -9.3 \quad (c 0.3, \text{CHCl₃}).\]

\(^{1}H\) NMR (300 MHz, CDCl₃) : \(\delta 7.28 \text{ (dd, } J = 15.1, 11.3 \text{ Hz, 1H}), 6.77 \text{ (d, } J = 9.0 \text{ Hz, 1H}), 6.71-6.65 \text{ (m, 2H), 6.27 \text{ (dd, } J = 15.1, 11.3 \text{ Hz, 1H}), 6.22 \text{ (d, } J = 15.1 \text{ Hz, 1H}), 6.09 \text{ (dd, } J = 15.1, 5.2 \text{ Hz, 1H}), 4.40-4.31 \text{ (m, 1H), 3.85 (s, 6 H), 3.73-3.65 \text{ (m, 4H), 3.64-3.55 (br s, 4H), 2.76-2.70 \text{ (m, 2H), 0.85 (s, 9H), -0.08 (s, 3H), -0.16 (s, 3H).}}\]

\(^{13}C\) NMR (75 MHz, CDCl₃) : \(\delta 165.9, 148.4, 147.4, 143.9, 140.4, 138.1, 130.5, 128.5, 127.6, 127.2, 126.8, 123.2, 121.7, 113.2, 111.0, 73.9, 55.7, 55.6, 44.3, 43.5, 25.7, 18.0, -4.8, -5.2.\]

IR (neat) cm⁻¹ : 2928, 2855, 1649, 1621, 1594, 1514, 1460, 1263, 1238, 1114, 1032, 837, 770.

EIMS (m/z) : 484 [M+Na]⁺.
Molecular formula : C₂₅H₃₉NO₅Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-morpholinohepta-2,4-dien-1-one (60):

85
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

\[\text{[\alpha]}_D^{25} : -12.9 \ (c \ 0.24, \text{CHCl}_3).\]

\[^1\text{H} \ NMR \ (300 \text{ MHz, CDCl}_3) : \delta \ 7.29 \ (dd, \ J = 14.7, \ 11.1 \text{ Hz, 1H}), \ 6.81 \ (d, \ J = 7.9 \text{ Hz, 1H}), \ 6.78-6.70 \ (m, \ 2H), \ 6.38 \ (dd, \ J = 15.2, \ 10.9 \text{ Hz, 1H}), \ 6.28 \ (d, \ J = 14.7 \text{ Hz, 1H}), \ 6.14 \ (dd, \ J = 15.2, \ 5.0 \text{ Hz, 1H}), \ 4.49-4.39 \ (m, \ 1H), \ 3.86 \ (s, \ 6H), \ 3.68 \ (br \ s, \ 4H), \ 3.61 \ (br \ s, \ 4H), \ 2.87 \ (dd, \ J = 13.7, \ 5.0 \text{ Hz, 1H}), \ 2.73 \ (dd, \ J = 13.7, \ 7.9 \text{ Hz, 1H}).\]

\[^{13}\text{C} \ NMR \ (75 \text{ MHz, CDCl}_3) : \delta \ 165.4, \ 148.7, \ 147.6, \ 142.7, \ 142.4, \ 129.5, \ 127.7, \ 121.4, \ 119.5, \ 112.4, \ 111.1, \ 72.4, \ 66.6, \ 55.7, \ 45.9, \ 43.2, \ 42.2.\]

\(\text{IR (neat) cm}^{-1} : 3410, \ 2922, \ 2854, \ 1649, \ 1620, \ 1592, \ 1514, \ 1441, \ 1263, \ 1238, \ 1114, \ 1028, \ 850, \ 760.\)

\(\text{HRMS (ESI) (m/z) : calcd. for C}_{19}\text{H}_{26}\text{O}_5\text{N} \ [\text{M+H}]^+ \ 348.1805; \text{ found 348.1809.}\)

\(\text{Molecular formula : C}_{19}\text{H}_{25}\text{NO}_5.\)

\((R,2E,4E)-6-((\text{tert-butyldimethylsilyl})\text{oxy})-7-(3,4-\text{dimethoxyphenyl})-1-\text{thiomorpholinohepta-2,4-dien}-1\text{-one (61a)}.\)

\[\text{[\alpha]}_D^{25} : -17 \ (c \ 0.2, \text{CHCl}_3).\]

\[^1\text{H} \ NMR \ (500 \text{ MHz, CDCl}_3) : \delta \ 7.25 \ (dd, \ J = 14.8, \ 11.1 \text{ Hz, 1H}), \ 6.77 \ (d, \ J = 8.5 \text{ Hz, 1H}), \ 6.70-6.66 \ (m, \ 2H), \ 6.26 \ (dd, \ J = 15.1, \ 10.9 \text{ Hz, 1H}), \ 6.23 \ (d, \ J = 14.8 \text{ Hz, 1H}), \ 6.07 \ (dd, \ J = 15.1, \ 5.3 \text{ Hz, 1H}), \ 4.37-4.32 \ (m, \ 1H), \ 3.88 \ (br \ s,\]

86
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

\[ \text{1H NMR (500 MHz, CDCl}_3\] : \( \delta 7.28 (dd, J = 15.1, 11.1 \text{ Hz, 1H}), 6.83 (d, J = 8.0 \text{ Hz, 1H}), 6.77-6.72 (m, 2H), 6.39 (dd, J = 15.1, 11.1 \text{ Hz, 1H}), 6.29 (d, J = 14.6 \text{ Hz, 1H}), 6.14 (dd, J = 15.1, 5.3 \text{ Hz, 1H}), 4.47-4.42 (m, 1H), 3.94 (br s, 2H), 3.87 (s, 6H), 3.83 (br s, 2H), 2.87 (dd, J = 13.7, 5.0 \text{ Hz, 1H}), 2.74 (dd, J = 13.7, 7.9 \text{ Hz, 1H}), 2.64 (br s, 4H), 1.74 (br s, 1H, OH).

\[ \text{13C NMR (75 MHz, CDCl}_3\] : \( \delta 165.2, 148.5, 147.4, 142.1, 141.5, 129.7, 127.9, 121.3, 120.5, 112.4, 111.0, 72.4, 55.6, 46.7, 43.2, 43.0, 26.4, 25.4.

IR (KBr) cm\(^{-1}\) : 3359, 2925, 2840, 1643, 1612, 1567, 1514, 1461, 1252, 1148, 1028, 807, 765.

\( \text{EIMS (m/z)} \) : 500 [M+Na]⁺.

Molecular formula : \( \text{C}_{25}\text{H}_{39}\text{NO}_{4}\text{SSi} \).

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-thiomorpholinohepta-2,4-dien-1-one (61):

\([\alpha]_D^{25}\) : -21.6 (c 0.24, CHCl\(_3\)).
Chapter II  First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

EIMS (m/z) : 386 [M+Na]^+.
Molecular formula : C_{19}H_{25}NO_4S.

(R,2E,4E)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (62a):

![Structure of 62a]

$[^{13}\text{C}]$ NMR (75 MHz, CDCl$_3$) : δ 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6, 119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5, 25.6, 17.9, -4.9, -5.3.

IR (neat) cm$^{-1}$ : 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773.

EIMS (m/z) : 497 [M+Na]^+.
Molecular formula : C_{26}H_{42}N_{2}O_{4}Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (62):

![Structure of 62]

$[^{13}\text{C}]$ NMR (75 MHz, CDCl$_3$) : δ 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6, 119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5, 25.6, 17.9, -4.9, -5.3.

IR (neat) cm$^{-1}$ : 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773.

EIMS (m/z) : 497 [M+Na]^+.
Molecular formula : C_{26}H_{42}N_{2}O_{4}Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (62):

$[^{13}\text{C}]$ NMR (75 MHz, CDCl$_3$) : δ 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6, 119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5, 25.6, 17.9, -4.9, -5.3.

IR (neat) cm$^{-1}$ : 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773.

EIMS (m/z) : 497 [M+Na]^+.
Molecular formula : C_{26}H_{42}N_{2}O_{4}Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (62):

$[^{13}\text{C}]$ NMR (75 MHz, CDCl$_3$) : δ 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6, 119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5, 25.6, 17.9, -4.9, -5.3.

IR (neat) cm$^{-1}$ : 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773.

EIMS (m/z) : 497 [M+Na]^+.
Molecular formula : C_{26}H_{42}N_{2}O_{4}Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (62):

$[^{13}\text{C}]$ NMR (75 MHz, CDCl$_3$) : δ 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6, 119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5, 25.6, 17.9, -4.9, -5.3.

IR (neat) cm$^{-1}$ : 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773.

EIMS (m/z) : 497 [M+Na]^+.
Molecular formula : C_{26}H_{42}N_{2}O_{4}Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (62):

$[^{13}\text{C}]$ NMR (75 MHz, CDCl$_3$) : δ 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6, 119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5, 25.6, 17.9, -4.9, -5.3.

IR (neat) cm$^{-1}$ : 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773.

EIMS (m/z) : 497 [M+Na]^+.
Molecular formula : C_{26}H_{42}N_{2}O_{4}Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (62):

$[^{13}\text{C}]$ NMR (75 MHz, CDCl$_3$) : δ 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6, 119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5, 25.6, 17.9, -4.9, -5.3.

IR (neat) cm$^{-1}$ : 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773.

EIMS (m/z) : 497 [M+Na]^+.
Molecular formula : C_{26}H_{42}N_{2}O_{4}Si.
**Chapter II**

*First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues*

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Spectral Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$^1$H NMR (500 MHz, CDCl$_3$)</strong></td>
<td>$\delta$ 7.26 (dd, $J = 14.8, 11.1$ Hz, 1H), 6.82 (d, $J = 7.9$ Hz, 1H), 6.75 (d, $J = 8.5$ Hz, 1H), 6.73 (s, 1H), 6.37 (dd, $J = 15.1, 11.2$ Hz, 1H), 6.30 (d, $J = 14.8$ Hz, 1H), 6.12 (dd, $J = 15.1, 5.4$ Hz, 1H); 4.46-4.39 (m, 1H), 3.86 (s, 6H), 3.56 (br s, 2H), 2.85 (dd, $J = 13.5, 5.1$ Hz, 1H), 2.75 (dd, $J = 13.5, 7.7$ Hz, 1H), 2.42 (br s, 4H), 2.31 (s, 3H).</td>
</tr>
<tr>
<td><strong>$^{13}$C NMR (75 MHz, CDCl$_3$)</strong></td>
<td>$\delta$ 165.2, 148.6, 147.5, 142.7, 142.1, 129.8, 127.7, 121.3, 119.9, 112.5, 111.1, 72.3, 55.8, 54.8, 54.3, 45.6, 43.2, 41.5.</td>
</tr>
<tr>
<td><strong>IR (neat) cm$^{-1}$</strong></td>
<td>3405, 2933, 2851, 1649, 1619, 1591, 1513, 1446, 1259, 1139, 1000, 771.</td>
</tr>
<tr>
<td><strong>HRMS (ESI) (m/z)</strong></td>
<td>calcd. for C$<em>{20}$H$</em>{30}$O$<em>{4}$N$</em>{2}$ [M+H]$^+$ 361.2121; found 361.2122.</td>
</tr>
<tr>
<td><strong>Molecular formula</strong></td>
<td>C$<em>{20}$H$</em>{28}$N$<em>{2}$O$</em>{4}$.</td>
</tr>
</tbody>
</table>

(R,2E,4E)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(4-ethyipiperazin-1-yl)hepta-2,4-dien-1-one (63a):

![Chemical Structure](image)

$[^{25}$D$]_{D}^{25} \quad -16.5$ (c 0.28, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.26 (dd, $J = 14.9, 11.2$ Hz, 1H), 6.77 (d, $J = 8.5$ Hz, 1H), 6.70-6.67 (m, 2H), 6.26 (dd, $J = 15.1, 11.1$ Hz, 1H), 6.24 (d, $J = 14.9$ Hz, 1H), 6.08 (dd, $J = 15.1, 5.4$ Hz, 1H), 4.38-4.32 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (br s, 2H), 3.68 (br s, 2H), 2.74-2.70 (m, 2H), 2.63-2.52 (m, 6H), 1.16 (t, $J = 7.1$ Hz, 3H), 0.85 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H).
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : δ 165.4, 148.3, 147.4, 143.9, 142.5, 130.5, 127.2, 121.8, 119.4, 113.1, 110.9, 73.9, 55.8, 55.7, 52.7, 52.0, 45.1, 44.3, 41.5, 29.2, 25.7, 18.1, 11.4, -4.8, -5.1.

IR (neat) cm\(^{-1}\) : 2929, 2855, 1652, 1625, 1514, 1439, 1262, 1155, 1027, 834, 775.

EIMS (m/z) : 511 [M+Na]\(^+\).

Molecular formula : C\(_{27}\)H\(_{44}\)N\(_2\)O\(_4\)Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)-6-hydroxyhepta-2,4-dien-1-one (63):

\([\alpha]_D^{25}\) : −21.3 (c 0.3, CHCl\(_3\)).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : δ 7.27 (dd, J = 15.1, 10.5 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.79-6.71 (m, 2H), 6.38 (dd, J = 15.1, 11.1 Hz, 1H), 6.31 (d, J = 14.3 Hz, 1H), 6.12 (dd, J = 15.1, 5.2 Hz, 1H), 4.48-4.38 (m, 1H), 3.87 (s, 6H), 3.73 (br s, 2H), 3.59 (br s, 2H), 2.86 (dd, J = 13.5, 5.2 Hz, 1H), 2.75 (dd, J = 13.5, 7.5 Hz, 1H), 2.57-2.40 (m, 6H), 1.11 (t, J = 7.5 Hz, 3H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : δ 165.2, 148.6, 147.5, 142.7, 142.1, 129.9, 127.7, 121.3, 119.9, 112.5, 111.0, 72.3, 55.6, 52.7, 51.9, 45.2, 43.2, 41.6, 11.5.

IR (neat) cm\(^{-1}\) : 3410, 2924, 2850, 1649, 1619, 1592, 1513, 1449, 1261, 1146, 1026, 762.

HRMS (ESI) (m/z) : calcd. for C\(_{21}\)H\(_{31}\)O\(_4\)N\(_2\) [M+H]\(^+\) 375.2278;
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

found 375.2283.

Molecular formula : \( \text{C}_{21}\text{H}_{30}\text{N}_{2}\text{O}_{4} \).

\((R,2E,4E)-6-((\text{tert-butyl(dimethyl)silyl})\text{oxy})-7-(3,4-\text{dimethoxyphenyl})-1-(4-phenylpiperazin-1-yl)\text{hepta}-2,4-\text{dien}-1\text{-one} (64a):\)

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{OTBS} & \quad \text{64a}
\end{align*}
\]

\[\alpha\]_D

\( \left[ \alpha \right]_{D}^{25} \) : -14.1 (c 0.22, \( \text{CHCl}_3 \)).

\( ^1\text{H NMR} \ (300 \text{ MHz,} \ \text{CDCl}_3)\) : \( \delta \) 7.42-7.22 (m 6H), 6.83-6.65 (m, 3H), 6.38-6.23 (m, 2H), 6.10 (dd, \( J = 15.1, 4.5 \text{ Hz} \), 1H), 4.44 (m, 1H), 3.86 (s, 6H), 3.85 (br s, 2H), 3.24 (br s, 4H), 2.74 (br s, 2H), 2.56-2.44 (m, 1H), 2.34-2.22 (m, 1H), 0.87 (s, 9H), -0.07 (s, 3H), -0.15 (s, 3H).

\( ^{13}\text{C NMR} \ (75 \text{ MHz,} \ \text{CDCl}_3)\) : \( \delta \) 165.3, 150.7, 148.4, 147.4, 143.9, 142.4, 130.4, 129.0, 127.1, 121.7, 120.3, 119.3, 116.4, 113.1, 111.0, 73.8, 55.7, 55.6, 49.5, 49.3, 45.4, 44.2, 41.7, 25.7, 18.0, -4.8, -5.2.

\( \text{IR (neat) cm}^{-1} \) : 2927, 2855, 1599, 1510, 1456, 1229, 1151, 1032, 833, 770.

\( \text{EIMS (m/z)} \) : 559 [\( \text{M+Na} \)]^+.

Molecular formula : \( \text{C}_{31}\text{H}_{44}\text{N}_{2}\text{O}_{4}\text{Si} \).

\((R,2E,4E)-7-(3,4-\text{dimethoxyphenyl})-6-\text{hydroxy}-1-(4-\text{phenylpiperazin-1-yl})\text{hepta-2,4-dien-1-one} (64):\)
Chapter II
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

\[
\begin{align*}
[\alpha]_D^{25} & : -19.0 \ (c \ 0.2, \ \text{CHCl}_3) . \\
^1\text{H} \text{ NMR (300 MHz, CDCl}_3) & : \delta 7.31 \ (dd, J = 14.3, 11.4 \ Hz, \ 1H), \ 7.30-7.27 \ (m, \ 2H), \ 7.01-6.89 \ (m, \ 3H), \ 6.82 \ (d, \ J = 8.0 \ Hz, \ 1H), \ 6.78-6.72 \ (m, \ 2H), \ 6.41 \ (dd, \ J = 15.2, 11.3 \ Hz, \ 1H), \ 6.36 \ (d, \ J = 15.2 \ Hz, \ 1H), \ 6.15 \ (dd, \ J = 15.2, 5.3 \ Hz, \ 1H), \ 4.48-4.42 \ (m, \ 1H), \ 3.87 \ (s, \ 6H), \ 3.85 \ (br \ s, \ 2H), \ 3.73 \ (br \ s, \ 2H), \ 3.20 \ (br \ s, \ 4H), \ 2.87 \ (dd, \ J = 13.7, 5.0 \ Hz, \ 1H), \ 2.75 \ (dd, \ J = 13.7, 5.0 \ Hz, \ 1H). \\
^{13}\text{C} \text{ NMR (75 MHz, CDCl}_3) & : \delta 165.3, \ 150.7, \ 148.8, \ 147.7, \ 142.5, \ 142.3, \ 129.5, \ 129.1, \ 127.9, \ 121.4, \ 120.5, \ 120.0, \ 116.5, \ 112.5, \ 111.1, \ 72.5, \ 55.8, \ 49.8, \ 49.3, \ 45.5, \ 43.3, \ 41.8. \\
\text{IR (KBr) cm}^{-1} & : 3370, \ 2924, \ 2854, \ 1642, \ 1607, \ 1564, \ 1463, \ 1231, \ 1142, \ 1027, \ 762. \\
\text{HRMS (ESI) (m/z)} & : \text{calcd. for C}_{25}\text{H}_{30}\text{N}_2\text{O}_4 [M+H]^+ 423.2278; \ \text{found} \ 423.2287. \\
\text{Molecular formula} & : \text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_4. \\
(R,2E,4E)-6-((\text{tert-butylidimethylsilyl})\text{oxy})-7-(3,4-\text{dimethoxyphenyl})-1-(4-(\text{pyridin-2-yl})\text{piperazin-1-yl})\text{hepta-2,4-dien-1-one (65a)}: \\
\begin{align*}
[\alpha]_D^{25} & : -14.2 \ (c \ 0.2, \ \text{CHCl}_3) . \\
^1\text{H} \text{ NMR (300 MHz, CDCl}_3) & : \delta 8.13 \ (d, \ J = 3.3 \ Hz, \ 1H), \ 7.45 \ (t, \ J = 6.7 \ Hz, \ 1H), \\
\end{align*}
\end{align*}
\]
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

7.23 (dd, J = 14.3, 11.0 Hz, 1H), 6.74-6.54 (m, 5H), 6.25 (d, J = 15.2 Hz, 1H), 6.22 (d, J = 14.3 Hz, 1H), 6.03 (dd, J = 15.2, 5.9 Hz, 1H), 4.33-4.26 (m, 1H), 3.79 (s, 6H), 3.75 (br s, 4H), 3.60 (br s, 2H), 3.47 (br s, 2H), 2.71-2.60 (m, 2H), 0.79 (s, 9H), -0.14 (s, 3H), -0.22 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 165.5, 158.7, 148.3, 147.6, 144.0, 142.5, 137.6, 130.4, 127.1, 121.7, 119.3, 113.6, 113.1, 110.9, 107.0, 73.9, 55.7, 55.6, 45.0, 44.3, 41.4, 25.7, 18.0, -4.8, -5.2.

IR (neat) cm$^{-1}$ : 2927, 2854, 1651, 1624, 1594, 1513, 1433, 1236, 1153, 1031, 833, 773.

EIMS (m/z) : 560 [M+Na]$^+$. Molecular formula : C$_{30}$H$_{43}$N$_3$O$_4$Si.

(R,2E,4E)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-(pyridin-2-yl)piperazin-1-y1)hepta-2,4-dien-1-one (65):

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{OH} & \quad \text{65} \\
\end{align*}
\]

$[^{\alpha}]_{D}^{25}$ : -17 (c 0.3, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 8.20 (d, J = 4.8 Hz, 1H), 7.54-7.49 (m, 1H), 7.32 (dd, J = 14.6, 10.9 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.78-6.73 (m, 2H), 6.69-6.64 (m, 2H), 6.42 (dd, J = 15.2, 11.2 Hz, 1H), 6.37 (d, J = 14.8 Hz, 1H), 6.15 (dd, J = 15.2, 5.4 Hz, 1H), 4.48-4.43 (m, 1H), 3.87 (s, 6H), 3.83 (br s, 2H), 3.67 (br s, 2H), 3.64 (br s, 2H), 3.54 (br s, 2H), 2.88 (dd, J = 13.5, 5.0 Hz, 1H), 2.75 (dd, J = 13.5, 7.9 Hz, 1H).
**Chapter II**  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

\[^{13}\text{C}\text{ NMR (75 MHz, CDCl}_3\text{)}\]: $\delta$ 165.4, 158.7, 148.6, 147.6, 147.5, 142.9, 142.3, 137.6, 129.7, 127.7, 121.3, 119.8, 113.7, 112.5, 111.0, 107.1, 72.4, 55.7, 44.9, 43.2, 41.4.

**IR (KBr) cm\(^{-1}\):** 3276, 2922, 2844, 1652, 1598, 1518, 1437, 1237, 1157, 1032, 994, 770.

**HRMS (ESI) (m/z):** calcd. for C\(_{24}\)H\(_{30}\)O\(_4\)N\(_3\) [M+H]\(^+\) 424.2230; found 424.2228.

**Molecular formula:** C\(_{24}\)H\(_{29}\)N\(_3\)O\(_4\).

\((R,2E,4E)-6-((\text{tert-butyldimethylsilyl})\text{oxy})-7-(3,4-\text{dimethoxyphenyl})-1-(4-(\text{pyrimidin}-2-yl)piperazin-1-yl)hepta-2,4-dien-1-one (66a):**

\[\alpha\]\(^{25}\)_D: $-6.4$ (c 0.26, CHCl\(_3\)).

\(^1\text{H NMR (300 MHz, CDCl}_3\text{)}\): $\delta$ 8.36 (d, $J = 4.9$ Hz, 2H), 7.31 (dd, $J = 14.7$, 10.9 Hz, 1H), 6.79 (d, $J = 8.6$ Hz, 1H), 6.74-6.67 (m, 2H), 6.58 (t, $J = 4.9$ Hz, 1H), 6.37-6.24 (m, 2H), 6.10 (dd, $J = 15.2$, 5.2 Hz, 1H), 4.42-4.32 (m, 1H), 3.90 (br s, 4H), 3.86 (s, 6H), 3.78 (br s, 2H), 3.67 (br s, 2H), 2.77-2.70 (m, 2H), 0.86 (s, 9H), -0.07 (s, 3H), -0.15 (s, 3H).

\[^{13}\text{C}\text{ NMR (75 MHz, CDCl}_3\text{)}\): $\delta$ 165.5, 161.2, 157.5, 148.3, 147.4, 143.9, 142.5, 130.4, 127.1, 121.7, 119.3, 113.1, 110.9, 110.2, 73.8, 55.7, 55.6, 45.2, 44.2, 43.5, 41.6, 25.6, 18.0, -4.9, -5.2.

**IR (neat) cm\(^{-1}\):** 2927, 2856, 1623, 1586, 1506, 1435, 1258, 1148, 1032, 834, 764.

**EIMS (m/z):** 561 [M+Na]\(^+\).
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Molecular formula : $\text{C}_{29}\text{H}_{42}\text{N}_{3}\text{O}_{4}\text{Si}$. 

$(R,2E,4E)$-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-(pyrimidin-2-yl)piperazin-1-yl)hepta-2,4-dien-1-one (66):

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

$[\alpha]_D^{25}$ : $-11.8 \ (c \ 0.28, \text{CHCl}_3)$.

$^1\text{H NMR (600 MHz, CDCl}_3)$ : $\delta$ 8.33 (d, $J = 4.5$ Hz, 2H), 7.32 (dd, $J = 14.6, 11.3$ Hz, 1H), 6.82 (d, $J = 8.2$ Hz, 1H), 6.77-6.72 (m, 2H), 6.55 (t, $J = 4.5$ Hz, 1H), 6.42 (dd, $J = 15.0, 11.3$ Hz, 1H), 6.37 (d, $J = 15.0$ Hz, 1H), 6.15 (dd, $J = 15.0, 5.2$ Hz, 1H), 4.48-4.43 (m, 1H), 3.87 (s, 6H), 3.86 (br s, 4H), 3.77 (br s, 2H), 3.63 (br s, 2H), 2.87 (dd, $J = 13.9, 5.2$ Hz, 1H), 2.75 (dd, $J = 13.9, 7.9$ Hz, 1H).

$^{13}\text{C NMR (75 MHz, CDCl}_3)$ : $\delta$ 165.5, 157.7, 148.8, 147.7, 142.6, 142.3, 129.5, 127.9, 121.4, 120.1, 112.4, 111.1, 110.4, 72.5, 55.7, 45.4, 43.6, 43.4, 43.2, 41.7.

$\text{IR (KBr) cm}^{-1}$ : 3418, 2924, 2854, 1651, 1591, 1513, 1443, 1236, 1154, 1030, 797, 768.

$\text{HRMS (ESI) (m/z)}$ : calcd. for $\text{C}_{23}\text{H}_{29}\text{O}_{4}\text{N}_{4} [\text{M+H}]^+ 425.2183$; found 425.2183.

Molecular formula : $\text{C}_{23}\text{H}_{28}\text{N}_{4}\text{O}_{4}$.

$(R,2E,4E)$-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-6-((tert-butyldimethylsilyloxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dien-1-one (67a):
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

\[
\text{\text{MeO}}\underline{\text{\text{O}}}
\]

\[\text{\text{MeO}}\underline{\text{\text{O}}}
\]

\[\text{\text{67a}}\]

\[
\begin{align*}
\text{[\alpha]_D^{25}} & : -11.3 \ (c 0.4, \text{CHCl}_3). \\
^{1}H \text{ NMR (300 MHz, CDCl}_3) & : \delta 7.25 \ (dd, J = 14.6, 11.2 \text{ Hz, 1H}), 6.85 \ (s, 1H), \\
& 6.78 \ (d, J = 8.2 \text{ Hz, 1H}), 6.76-6.72 \ (m, 2H), 6.71-6.68 \ (m, 2H), 6.29-6.23 \ (m, 2H), 6.06 \ (dd, J =15.4, 5.6 \text{ Hz, 1H}), 5.94 \ (s, 2H), 4.38-4.33 \ (m, 1H), 3.85 \ (s, 6H), 3.69 \ (br \ s, 2H), 3.55 \ (br \ s, 2H), 3.43 \ (br \ s, 2H), 2.78-2.67 \ (m, 2H), 2.43 \ (br \ s, 4H), 0.85 \ (s, 9H), -0.08 \ (s, 3H), -0.16 \ (s, 3H). \\
^{13}C \text{ NMR (75 MHz, CDCl}_3) & : \delta 165.2, 148.4, 147.5, 147.4, 146.6, 143.6, 142.1, 131.0, 130.4, 127.2, 122.1, 121.7, 119.6, 113.1, 111.0, 109.2, 107.7, 100.7, 73.9, 62.3, 55.7, 55.6, 52.9, 52.4, 45.4, 44.3, 41.8, 25.6, 18.0, -4.8, -5.2. \\
\text{IR (neat) cm}^{-1} & : 2928, 2855, 1652, 1624, 1512, 1441, 1241, 1149, 1036, 1000, 833, 772. \\
\text{EIMS (m/z)} & : 619 \ [M+Na]^+. \\
\text{Molecular formula} & : C_{33}H_{46}N_2O_6Si.
\end{align*}
\]

\[(R,2E,4E)-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dien-1-one (67):\]

\[
\begin{align*}
\text{[\alpha]_D^{25}} & : -16.0 \ (c 0.28, \text{CHCl}_3).
\end{align*}
\]
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

\(^1\)H NMR (600 MHz, CDCl\(_3\)) : δ 7.25 (dd, \(J = 14.3, 11.3\) Hz, 1H), 6.86 (s, 1H), 6.81 (d, \(J = 7.9\) Hz, 1H), 6.76-6.71 (m, 4H), 6.37 (dd, \(J = 15.4, 11.3\) Hz, 1H), 6.30 (d, \(J = 14.3\) Hz, 1H), 6.11 (dd, \(J = 15.4, 5.2\) Hz, 1H), 5.94 (s, 2H), 4.45-4.40 (m, 1H), 3.86 (s, 6H), 3.70 (br s, 2H), 3.55 (br s, 2H), 3.45 (s, 2H), 2.85 (dd, \(J = 13.5, 4.8\) Hz, 1H), 2.74 (dd, \(J = 13.5, 7.9\) Hz, 1H), 2.44 (br s, 4H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) : δ 165.2, 148.6, 147.6, 147.5, 142.4, 141.9, 131.1, 129.6, 127.9, 122.1 121.4, 120.1, 112.4, 111.0, 109.2, 107.7, 100.8, 72.4, 62.3, 55.7, 52.8, 52.3, 45.5, 43.2, 41.8.

IR (KBr) cm\(^{-1}\) : 3402, 2921, 1645, 1614, 1569, 1514, 1448, 1239, 1144, 1033, 1005, 798.

EIMS (m/z) : 481 [M+H]\(^+\).

Molecular formula : C\(_{27}\)H\(_{32}\)N\(_2\)O\(_6\).

(R,2E,4E)-1-(4-benzhydrylpiperazin-1-yl)-6-((tert-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dien-1-one (68a):

\([\alpha]_D^{25}\) : −4.9 (c 0.2, CHCl\(_3\)).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) : δ 7.41 (d, \(J = 7.4\) Hz, 4H), 7.29 (d, \(J = 7.4\) Hz, 4H), 7.24 (dd, \(J = 15.1, 11.3\) Hz, 1H), 7.19 (t, \(J = 7.4\) Hz, 2H), 6.77 (d, \(J = 8.5\) Hz, 1H), 6.70-6.67 (m, 2H), 6.28-6.20 (m, 2H), 6.05 (dd, \(J = 15.1, 5.4\) Hz, 1H), 4.37-4.31 (m, 1H), 4.23 (s, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.69 (br s, 2H), 3.54 (br s, 2H), 2.76-2.67.
### Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(m, 2H), 2.39 (br s, 4H), 0.84 (s, 9H), -0.10 (s, 3H), -0.17 (s, 3H).</strong></td>
<td></td>
</tr>
<tr>
<td><strong>13C NMR (125 MHz, CDCl₃)</strong></td>
<td>δ 165.9, 148.4, 147.4, 143.6, 142.1, 142.0, 130.5, 128.5, 127.8, 127.3, 127.0, 121.8, 119.7, 113.1, 110.9, 75.8, 74.0, 55.8, 55.7, 52.1, 51.5, 45.8, 44.4, 42.1, 25.7, 18.1, -4.8, -5.1.</td>
</tr>
<tr>
<td><strong>IR (neat) cm⁻¹</strong></td>
<td>2953, 2929, 2855, 1652, 1624, 1598, 1513, 1446, 1260, 1237, 1148, 999, 834, 754.</td>
</tr>
<tr>
<td><strong>EIMS (m/z)</strong></td>
<td>649 [M+Na]⁺.</td>
</tr>
<tr>
<td><strong>Molecular formula</strong></td>
<td>C₃₈H₅₀N₂O₄Si.</td>
</tr>
</tbody>
</table>

(R,2E,4E)-1-(4-benzhydrylpiperazin-1-yl)-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dien-1-one (68):

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>[α]D²⁵</strong></td>
<td>-6.2 (c 0.45, CHCl₃).</td>
</tr>
<tr>
<td><strong>1H NMR (300 MHz, CDCl₃)</strong></td>
<td>δ 7.41 (d, J = 7.4 Hz, 4H), 7.29 (d, J = 7.4 Hz, 4H), 7.23 (dd, J = 14.8, 11.1 Hz, 1H), 7.19 (t, J = 7.3 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.76-6.71 (m, 2H), 6.35 (dd, J = 15.2, 11.1 Hz, 1H), 6.28 (d, J = 14.8 Hz, 1H), 6.10 (dd, J = 15.2, 5.4 Hz, 1H), 4.45-4.39 (m, 1H), 4.24 (s, 1H), 3.86 (s, 6H), 3.69 (br s, 2H), 3.53 (br s, 2H), 2.85 (dd, J = 13.5, 5.0 Hz, 1H), 2.73 (dd, J = 13.5, 7.9 Hz, 1H), 2.39 (br s, 4H), 1.83 (br s, 1H, OH).</td>
</tr>
<tr>
<td><strong>13C NMR (75 MHz, CDCl₃)</strong></td>
<td>δ 165.2, 148.5, 147.5, 142.5, 141.9, 141.8, 129.6, 128.4, 127.8, 127.6, 126.9, 121.3, 119.9, 112.4, 111.0, 75.7, 72.4, 55.6, 51.9, 51.3, 45.6, 43.1, 42.0.</td>
</tr>
</tbody>
</table>
Chapter II

First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

IR (KBr) cm\(^{-1}\): 3386, 2924, 2853, 1648, 1618, 1591, 1513, 1450, 1236, 1146, 953, 753.

HRMS (ESI) (m/z): calcd. for C\(_{32}\)H\(_{37}\)O\(_4\)N\(_2\) [M+H]\(^+\) 513.2747; found 513.2743.

Molecular formula: C\(_{32}\)H\(_{36}\)N\(_2\)O\(_4\).

REFERENCES:

1. Tunmann, O. Apotheker Zeitung, 1918, 33, 353 (Chemical Abstracts, 19, 2940).
Chapter II
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues


Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.02: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 47

Fig. 2.03: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 47
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.04: IR spectrum of compound 47

Fig. 2.05: ESI-MS spectrum of compound 47
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.06: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 47a

Fig. 2.07: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 47b
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.08: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 48

Fig. 2.09: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 48
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.10: ESI-MS spectrum of compound 48

Fig. 2.11: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 49
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.12: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 49

Fig. 2.13: IR spectrum of compound 49
Chapter II
First Stereoselective Total synthesis of (-)-Kunstleramide &
its analogues

Fig. 2.14: ESI-MS spectrum of compound 49

Fig. 2.15: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 50
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.16: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 50

Fig. 2.17: IR spectrum of compound 50
Chapter II
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.18: ESI-MS spectrum of compound 50

Fig. 2.19: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 51
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

![Chemical Structure](image)

**Fig. 2.20:** $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 51

![NMR Spectrum](image)

**Fig. 2.21:** IR spectrum of compound 51

Indian Institute of Chemical Technology, Hyderabad
FTIR Analysis Report

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110
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.22: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 52

Fig. 2.23: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 52
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.24: IR spectrum of compound 52

Fig. 2.25: ESI-MS spectrum of compound 52
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.26: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 53

Fig. 2.27: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 53
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.28: IR spectrum of compound 53

Fig. 2.29: HRMS - ESI spectrum of compound 53
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.30: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 54

Fig. 2.31: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 54
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.32: HRMS-ESI spectrum of compound 54

Fig. 2.33: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 55
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.34: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 55

Fig. 2.35: HRMS-ESI spectrum of compound 55
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.36: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 56

Fig. 2.37: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 56
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.38: HRMS-ESI spectrum of compound 56

Fig. 2.39: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 57
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.40: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 57

Fig. 2.41: HRMS-ESI spectrum of compound 57
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.42: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 58

Fig. 2.43: $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of compound 58
Chapter II

First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.44: ESI-MS spectrum of compound 58

Fig. 2.45: \(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum of compound 59
Chapter II

First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.46: $^1$H NMR (75 MHz, CDCl$_3$) spectrum of compound 59

Fig. 2.47: ESI-MS spectrum of compound 59
Chapter II  
First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.48: $^1H$ NMR (300 MHz, CDCl$_3$) spectrum of compound 60

Fig. 2.49: $^{13}C$ NMR (75 MHz, CDCl$_3$) spectrum of compound 60
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.50: HRMS-ESI spectrum of compound 60

Fig. 2.51: $^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 61
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

![Chemical structure](image)

Fig. 2.52: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 61

![Chemical structure](image)

Fig. 2.53: ESI-MS spectrum of compound 61
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide &
its analogues

![Chemical Structure](image1)

**Fig. 2.54:** $^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 62

![Chemical Structure](image2)

**Fig. 2.55:** $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 62
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.56: HRMS-ESI spectrum of compound 62

Fig. 2.57: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 63
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.58: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 63

Fig. 2.59: HRMS-ESI spectrum of compound 63
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.60: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 64

Fig. 2.61: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 64
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.62: HRMS-ESI spectrum of compound 64

Fig. 2.63: $^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 65
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.64: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 65

Fig. 2.65: HRMS-ESI spectrum of compound 65
Chapter II

First Stereoselective Total synthesis of (−)-Kunstleramide &
its analogues

Fig. 2.66: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 66

Fig. 2.67: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 66
Chapter II  
First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.68: HRMS-ESI spectrum of compound 66

Fig. 2.69: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 67
Chapter II

First Stereoselective Total synthesis of (-)-Kunstleramide & its analogues

Fig. 2.70: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 67

Fig. 2.71: ESI-MS spectrum of compound 67
Chapter II  First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.72: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 68

Fig. 2.73: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 68
Chapter II

First Stereoselective Total synthesis of (−)-Kunstleramide & its analogues

Fig. 2.74: HRMS-ESI spectrum of compound 68