Chapter 2

Section A

Total synthesis of Granulatamide A
Introduction

Indole skeleton is a key structural unit in many natural products and pharmaceutical compounds. Moreover, tryptamine based molecules are generally considered as esteemed structures with drug-like qualities and expectant effects for different types of diseases. The best selling drugs rizatriptan\(^1\) and eletriptan\(^2\) are tryptamine based structures. Among the tryptamine-based polycyclic scaffolds, LE300 analogues\(^3\) have been synthesized widely and exhibit quite potent affinities on drug targets such as dopamine receptors (DRs), serotonin receptors (5-HTRs), and \(\alpha\)-\(1\)-adrenergic receptor (\(\alpha\)-1-AR).

Voltage-gated sodium channels are responsible for action potential initiation and propagation in excitable cells, including nerve, muscle and neuroendocrine cell types. The human voltage-gated sodium channels\(^4\) (hNav) play critical physiological roles in the body and hence important targets in medicine. Several lipopeptidic secondary metabolites isolated, have shown hNaV activity. For example, the cyclic lipopetides antillatoxin\(^5\) and antillatoxin-B\(^6\) are sodium channel activators with potencies comparable to the brevetoxins.\(^7\) The mixed polyketide–peptide kalkitoxin\(^8\) (1) is a potent sodium channel blocking agent (Figure 1). Recently, jamaicamides A, B and C (2–4) were isolated at Hector’s Bay in Jamaica and blocked\(^9\) sodium channel activity in a cell-based screening assay which involves measuring the end-point of mitochondrial dehydrogenase activity in neuroblastoma cells.

![Figure 1](image-url)

The metabolites, hermitamides A, 5 and B, 6 (Figure 2) exhibited\(^10\) LD\(_{50}\) values of 5 \(\mu\)M and 18 \(\mu\)M in the brine shrimp bioassay and IC\(_{50}\) values of 2.2 \(\mu\)M and 5.5 \(\mu\)M to Neuro-
2a neuroblastoma cells in tissue culture respectively. It was found that bacillamide 7 showed\textsuperscript{11} algicidal activity against C. polykrikoides with LC\textsubscript{50} of 3.2 g/mL.

![Chemical structures of Hermitamide A, Hermitamide B, and Bacillamide](image)

Granulatamides A (8) and B (9) (Figure 3) were isolated\textsuperscript{12} from the 2-propanol extract of the soft coral Eunicella granulata collected in Senegal.

![Chemical structures of Granulatamide A and Granulatamide B](image)

Granulatamide A showed moderate in vitro cytotoxicity against a panel of human tumour cells as shown in Table 1.

**Table 1.** GI\textsubscript{50} (µM) values of granulatamide A against Tumor Cell Lines

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>GI\textsubscript{50} (µM)</th>
<th>Cell Line</th>
<th>GI\textsubscript{50} (µM)</th>
<th>Cell Line</th>
<th>GI\textsubscript{50} (µM)</th>
</tr>
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<tr>
<td>DU-145</td>
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<td>SK-BR3</td>
<td>2.7</td>
<td>PANC1</td>
<td>10.4</td>
</tr>
<tr>
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<td>4.7</td>
<td>SK-MEL-28</td>
<td>3.9</td>
<td>HT29</td>
<td>2.2</td>
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<tr>
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<td>11.6</td>
<td>HMEC1</td>
<td>6.2</td>
<td>LOVO</td>
<td>10.5</td>
</tr>
<tr>
<td>IGROV</td>
<td>6.7</td>
<td>A549</td>
<td>6.7</td>
<td>LOVO-DOX</td>
<td>12.0</td>
</tr>
<tr>
<td>IGROV-ET</td>
<td>12.7</td>
<td>K-562</td>
<td>6.8</td>
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</tr>
</tbody>
</table>
There is no literature report available for the synthesis of granulatamide A. Taking into account the biological importance of granulatamide A, it was planned to synthesize it by a route involving use of Horner–Wadsworth–Emmons (HWE) olefination reaction as a key step.

**Horner–Wadsworth–Emmons olefination**

The fundamental part of organic synthesis is the formation of carbon-carbon bonds. In 1950, George Wittig developed a pioneering new reaction for preparing alkenes from aldehydes or ketones using phosphonium salts. The utility of the Wittig reaction\(^{13}\) was expanded by Horner\(^{14}\) through the use of phosphine oxide anions instead of phosphonium salts, resulting in a simplified workup. This work was further developed by Wadsworth and Emmons\(^{15}\) using phosphonate anions as nucleophiles, which have full potential as a reliable and general method for the olefination of aldehydes and ketones with excellent geometric selectivity. The reaction is hence known as the Horner-Wadsworth-Emmons (HWE) reaction. Unlike the Wittig reaction however, a stabilized ylide is used in HWE reaction (Figure 4) to form predominantly a *trans* olefin.

\[
\begin{align*}
\text{H} & \quad \text{R} = \quad \text{(EtO)}_2\text{P} & \quad \text{O} \\
\text{O} & \quad \text{OEt} \quad \text{Base} \quad \text{R} \quad \text{O} & \quad \text{OEt}
\end{align*}
\]

**Figure 4. Representative Horner-Wadsworth-Emmons olefination reaction**

After deprotonation of the phosphonate with base, the nucleophilic carbanion attacks a carbonyl group in a stepwise manner to form the initial C-C bond (Figure 5). The thermodynamic *threo* adduct is favored and believed to be in equilibrium with the oxaphosphetane which assist in formation of the mainly *trans* products. The use of the phosphonate moiety leads to certain advantages of the HWE methodology over the Wittig reaction\(^{16}\). The phosphonate stabilized carbanions are more nucleophilic and basic than the corresponding phosphonium ylides. In addition to this, the water soluble phosphate salt which is a by-product from HWE reaction also allows more facile purifications over the triphenylphosphine oxide as a by-product in Wittig reaction.
Another advantage of the HWE protocol is its versatility and receptiveness to diverse reaction conditions. By adjusting the reaction conditions, kinetically favored $Z$ olefin can be isolated. There are further modifications to produce $cis$ olefin by Breuer\textsuperscript{17}, Patois and Savignac\textsuperscript{18} who utilized phosphonates 10 and 11 respectively with bulky 5-membered heterocyclic ring systems. Still and Gennari\textsuperscript{19} used trifluoroethyl phosphonate (12) and most recently Ando\textsuperscript{20} used phosphonate 13 to get $Z$ olefin.

![Figure 5. Proposed HWE mechanism](image)

While in the reactions with phosphonate 12 using low temperatures and crown ether additive, good yields are obtained from a variety of aromatic and aliphatic aldehydes. The phosphonates 13 employed by Ando often can be used at warmer temperature and without the hygroscopic crown ether. Many bases, solvents and temperatures have been explored in an effort to increase the $Z$ selectivity of these modified protocols. For
example, it has been found that potassium counter ions will often lead to a higher ratio of 
cis products, but this can also be highly dependent upon the substrate.

From both the experimental results and molecular orbital calculations\textsuperscript{21}, HWE reaction
occurs by a mechanism shown in Figure 7. The phosphonate A and 13 reacts with an
aldehyde to form the intermediate B\textsubscript{1} and B\textsubscript{2}, in which the stereochemistry of the
developing double bond is established. This is followed by formation of \textit{threo} and
\textit{erythro} oxaphosphetane C\textsubscript{1} and C\textsubscript{2} respectively. Due to the steric effect of two phenyl
rings, \textit{erythro} conformation is preferred in C\textsubscript{2}. Further, \textit{threo} and \textit{erythro}
oxaphosphetanes produce \textit{E} and \textit{Z}-olefins respectively. This reveals the \textit{E} and \textit{Z}
selectivity of phosphonate A and 13 respectively.

![Mechanistic routes for E and Z selective HWE reactions](image)

\textbf{Figure 7. Mechanistic routes for E and Z selective HWE reactions}

Overall, variety of these phosphonates allow C-C bond formation which is applied widely
in synthetic chemistry. The utilization of Horner-Wadsworth-Emmons olefination
reaction in construction of complex molecules can be seen from some of the examples as
shown below.

1. Harvey J. E. et al (2003)\textsuperscript{22}

![Oximidine I](image)
2. **Li G. et al (2009)**\(^{23}\)

![Chemical structure of (-)-5,6-Dihydrocineromycin B](image1)

3. **Kumar P. et al (2012)**\(^{24}\)

![Chemical structure of (±)-bis-homosarkomycin ethyl ester](image2)

**Present Plan**

Thus, considering the biological importance of granulatamide A and presence of Z olefin in its structure, it was planned to synthesize granulatamide A (8) by a strategy which involves Z-selective Horner-Wadsworth-Emmons (HWE) olefination. Using E selective HWE olefination, it was envisioned to get the unreported E-isomer (16) of granulatamide A. It was also decided to synthesise tryptamine derived amide 18 which can be used for the synthesis of prebalamide\(^{25}\) and amide 19 which is already used as an intermediate for the synthesis of hermitamide B. The retrosynthetic plan was as shown in Scheme 1.
Results and Discussion

According to the retrosynthetic scheme, the synthesis started with readily available starting material tryptamine (Scheme 2) which was treated with bromoacetyl bromide in presence of diisoproylethylamine in anhydrous tetrahydrofuran to give N-(2-(1H-indol-3-yl)ethyl)-2-bromoacetamide 14. $^1$H NMR (Figure 9) showed singlet at $\delta$ 3.79 and $^{13}$C NMR (Figure 10) displayed singlet at $\delta$ 21.29 for methylene group adjacent to carbonyl carbon of amide. Both the NMR spectral data were consistent with the reported$^{26}$ values.
As the target molecule 8 is having Z double bond, new phosphonate 15 was envisioned for this synthesis using the analogy with Z selective phosphonate 13. Thus, phosphonate 15 was obtained by Arbuzov reaction of compound 14 with diphenyl phosphite in presence of NaH in anhydrous THF at 0 °C (Scheme 2). The formation of product 15 was confirmed by presence of additional signals in the aromatic region in $^1$H and $^{13}$C NMR. In a different observation, the protons of methylene group showed a doublet at δ 3.02 -3.10 with a coupling constant of 20 Hz indicating the coupling with adjacent phosphorous in $^1$H NMR spectrum (Figure 11). The methylene carbon also displayed a doublet at δ 35.42-34.36 with a coupling constant of 133.56 Hz due to coupling with P. This observed heteronuclear coupling with phosphorous was justified by analogy with similar observation reported for other phosphonates. By carefully interpreting the $^{13}$C NMR (Figure 12), it was noticed that there is a possibility of aromatic carbons showing long range coupling with P. All other protons and carbons in structure 15 were seen at appropriate places.
After having phosphonate 15 in hand, Z selective Horner–Wadsworth–Emmons olefination reaction was carried out. Thus, phosphonate 15 was treated with commercially available 2-undecanone at -78 °C using K'OBu as a base in anhydrous tetrahydrofuran. After workup, the reaction mixture was separated by column chromatography to furnish two products in 80% yield. The major product was in 90% and the minor was in 10%. From the spectral data, the major product was shown to be granulatamide A (8) having Z double bond and the minor was its E isomer 16.

$^1$H NMR spectrum (Figure 13) for compound 8 showed, triplet at $\delta$ 2.60 with coupling constant 7.5 Hz for the allylic methylene protons, a doublet at $\delta$ 1.78 with coupling constant 1.5 Hz for allylic methyl protons and triplet at $\delta$ 0.88 with coupling constant 7 Hz for methyl protons. A broad singlet at $\delta$ 5.44 for two protons, namely one olefinic proton and other D$_2$O exchangeable NH was also seen. All other protons were resonating at appropriate places. $^{13}$C NMR (Figure 14) displayed singlet at $\delta$ 13.86 for methyl carbon, at $\delta$ 24.42 for allylic methyl carbon, and at $\delta$ 32.75 for allylic methylene carbon. All aromatic carbons were seen as eleven singlets from $\delta$ 110.93 to 166.46. Twelve singlets were observed in the aliphatic region approving the presence of all aliphatic carbons. From all the above spectral data and comparison with reported$^{11}$ values, the structure 8 was confirmed for granulatamide A.

$^1$H NMR (Figure 19) for compound 16 showed a triplet at $\delta$ 2.06 with coupling constant 6.75 Hz for the allylic methylene protons, a doublet at $\delta$ 2.15 with coupling constant 0.92 Hz for allylic methyl protons, a doublet at $\delta$ 5.47 with coupling constant 0.92 Hz for one olefinic proton, a broad triplet at $\delta$ 5.50 for one D$_2$O exchangeable -NH and a triplet at $\delta$ 0.90 with coupling constant 6.87 Hz for methyl protons. All the other protons were resonating at appropriate places. $^{13}$C NMR (Figure 20) displayed a singlet at $\delta$ 14.15 for
methyl carbon, a singlet at $\delta$ 18.24 for allylic methyl carbon and a singlet at $\delta$ 40.80 for allylic methylene carbon along with signals for all other aromatic and aliphatic carbons.

The allylic methyl protons for granulatamide A (8) and its $E$-isomer 16 showed triplet at $\delta$ 1.78 and $\delta$ 2.15 respectively. The downfield shift of these protons in $E$ isomer can be explained by anisotropic effect of the carbonyl group.

In addition, both isomers were characterized using NOE experiment. For granulatamide A (8), olefinic proton showed NOE with methylene (1.18%) and methyl protons (2.12%) (Figure 8) which confirmed Z geometry of the double bond. Interestingly, in the $E$ isomer (16), olefinic proton showed NOE with four methylene protons (0.7%, 3.2%, 1.16%, and 0.62%) confirming the $E$ geometry of double bond. Thus, new phosphonate 15 has been used for the first time for the synthesis of granulatamide A (8) in good yield. This constitutes the first synthesis of biologically active natural product granulatamide A.

The $E$ isomer 16 is not reported in the literature. It was formed in minor amount in the above Z selective HWE reaction. Thus, it was envisaged to use $E$ selective HWE reaction to synthesize compound 16 in major amount as shown in Scheme 3.
As, the target molecule 16 has E double bond, use of a phosphonate 17 was envisioned considering the analogy with E selective phosphonate A (Figure 17). The phosphonate 17 was synthesized by reacting compound 14 with neat triethylphosphite at 80 °C. After work up and purification by column chromatography an oily product was obtained which was shown to be compound 17 from the spectral data. Thus, $^1$H NMR (Figure 17) showed all the protons at the expected positions along with a doublet for methylene protons at $\delta$ 2.76-2.82 with a coupling constant of 20 Hz, which can be attributed to coupling with phosphorous. In $^{13}$C NMR spectrum (Figure 18) the coupling (131.04 Hz) of C and P was seen for the methylene carbon adjacent to phosphorous which resonated at $\delta$ 34.50-35.54 as a doublet. Similarly, coupling of P with $-\text{OCH}_{2}$ and $-\text{OCH}_{2}\text{CH}_{3}$ was seen from the doublets resonating at $\delta$ 62.69-62.64 and at $\delta$ 16.22-16.17 with $J = 6.3$ Hz each.

Further, phosphonate 17 was reacted with 2-undecanone at room temperature in presence of K$'\text{OBu}$ as a base in anhydrous THF which furnished E-olefin (16) in 92% and Z-olefin (8) in 8%. The yield of the reaction was 85%. Both the compounds were confirmed by NMR data which was identical as discussed in the earlier reaction.
In order to find the synthetic utility of phosphonate 17, amides 18 and 19 were selected as target molecules. As mentioned earlier these two amides are useful as intermediates for the synthesis of other biologically active molecules. Compound 18 was prepared (Scheme 4) by treating phosphonate 17 with benzaldehyde (prewashed with aqueous NaHCO$_3$ solution to remove benzoic acid). After workup and purification with column chromatography a solid product was obtained which showed a doublet for olefinic proton adjacent to amide carbonyl at $\delta$ 6.28 with coupling constant of 15 Hz indicating presence of trans coupled proton in $^1$H NMR (Figure 23). The other olefinic proton was overlapped on the aromatic protons. Two methylene groups were resonating as triplet at $\delta$ 3.02 with $J = 6.7$ Hz and as quartet at $\delta$ 3.71 with $J = 6.7$ Hz.

The $^{13}$C NMR (Figure 24) showed presence of additional carbons in aromatic region along with two methylene carbons. All this spectral data together established structure 18 for this product which was also confirmed by comparing the data with the literature$^{28}$ spectral values.

In the next experiment, phosphonate 17 was treated with paraformaldehyde at room temperature using NaH as a base which gave compound 19 in good yield. $^1$H NMR (Figure 26) showed two doublets for terminal olefinic protons at $\delta$ 5.57-5.59 ($J = 10$ Hz) and at $\delta$ 6.08-6.12 ($J = 16.5$ Hz). All carbons were resonating at appropriate positions in $^{13}$C NMR spectrum (Figure 27). The terminal olefinic carbon was identified by DEPT experiment (Figure 28) which showed the inverted singlet for methylene carbon at $\delta$ 125.35.

All this spectral data together established structure of this product as 19 which was also confirmed by comparing with the literature$^{10}$ spectral values.
Conclusion

The Z and E selective phosphonates 15 and 17 were prepared for the first time. The total synthesis of biologically active natural product granulatamides A (8) has been successfully achieved in 68% overall yield, using phosphonates 15 in Z selective Horner–Wadsworth–Emmons olefination. Also the trans isomer (16) of granulatamides A was synthesized in 73% overall yield using phosphonates 17 in E selective Horner–Wadsworth–Emmons olefination. The phosphonates 17 was also used for the synthesis of amides 18 and 19 which act as intermediates in the synthesis of hermitamide B and prebalamide.
Chapter 2: Section A

Experimental Section

Preparation of 2-bromo-N-[2-(1H-indol-3-yl)ethyl]acetamide (14)

To a stirring solution of tryptamine (7.51g, 21.36 mmol) in anhydrous tetrahydrofuran (100 mL) under a nitrogen atmosphere at 0 °C were added diisopropylethyl amine (4.1 mL, 23.53 mmol) and bromoacetyl bromide (2.05 ml, 23.53 mmol) and stirred at rt. After 2 hours, ethyl acetate was added and the reaction mixture washed with water twice, 1N hydrochloric acid and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator. Further purification by column chromatography on silica using pet ether-ethyl acetate as eluent, yielded compound 14 as an off-white solid in 95% yield. M.p 82°C.

$^1$H NMR (200 MHz, CDCl$_3$): δ 8.28 (br. s., 1H); 7.55-7.63 (m, 1H), 7.31-7.40 (m, 1H), 7.07-7.26 (m, 2H), 7.01-7.02 (d, $J = 2$ Hz, 1H), 6.58 (brs, 1H), 3.79 (s, 2H), 3.55-3.64 (q, $J = 6$ Hz, 2H), 2.99 (t, $J = 6$ Hz, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 165.45, 136.34, 127.03, 122.19, 122.15, 119.41, 118.53, 112.22, 111.29, 40.30, 29.21, 24.90

HRMS (ESI): m/z calcd for C$_{12}$H$_{13}$BrN$_2$NaO (M+Na)$^+$, 303.0103; found, 303.0099.

Preparation of Diphenyl (2-(1H-indol-3-yl)ethylcarbamoyl)methylphosphonate (15)

To a suspension of NaH (60% in mineral oil, 0.085g, 2.13 mmol) in THF (100 mL) was added diphenyl phosphite (0.59 g, 2.13 mmol) drop wise at 0 °C during a period of 20 min. After half an hour, the gas evolution had ceased and bromoacetamide 14 (0.5 g, 2.13 mmol) was added drop wise over a period of 20 min. The cooling bath was removed and the reaction mixture was stirred at rt for 12 h. A saturated aqueous solution of NH$_4$Cl (200 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers
were dried (Na$_2$SO$_4$) and the solvents were removed under reduced pressure. The residue was purified by column chromatography using pet ether and ethyl acetate as eluent to give product as a pale yellow solid in 90% yield. M.p 109 °C.

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.24-8.42 (m, 1H), 7.52-7.53 (d, $J = 15$ Hz, 1H), 7.23-7.30 (m, 5H), 7.04-7.18 (m, 8H), 6.87 (brs., 1H), 6.77 (m, 1H), 3.52 (q, $J = 5$ Hz, 2H), 3.02-3.10 (d, 20 Hz, 2H), 2.85 (t, $J = 5$ Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.65, 149.72, 149.72, 149.65, 136.29, 129.83, 127.05, 125.64, 122.34, 121.87, 120.58, 120.54, 119.17, 118.45, 112.07, 111.27, 40.02, 35.42-34.36 (d, $J = 133.56$ Hz), 24.86.

HRMS (ESI): m/z calcd for C$_{48}$H$_{46}$N$_4$NaO$_8$P$_2$ (2M+Na)$^+$, 891.2689; found, 891.2670.

**Preparation of granulatamides A (8)**

1M potassium tert-butoxide in THF solution (0.39 g, 2.3 mmol) was added to a solution of phosphonate 15 (0.5 g, 1.15 mmol) in 15 mL of THF at room temperature. After stirring for 1 h, cooled to -78 °C then a solution of 2-undecanone (0.29 g, 0.35 mL, 1.7 mmol) in THF was added and stirring was continued for another 15 min. The reaction mixture warmed up to room temperature, the stirring was continued for 24 h. Next, a saturated aqueous NH$_4$Cl solution was added extracted with DCM, and the combined organic extracts were washed with Na$_2$S$_2$O$_3$ solution and water, dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo* after filtration. The column chromatographic separation on silica gel (pet ether-ethyl acetate) provided 8 in 90% and 16 in 10% (both as pale yellow oil) Yield 80%.

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.16 (s, 1H, D$_2$O exchangeable), 7.61-7.63 (d, $J = 7.63$ Hz, 1H), 7.36-7.39 (m, 1H), 7.20-7.23 (td, $J = 7.55$, 1.07 Hz, 1H), 7.11-7.14 (m, 1H), 7.04-7.05 (d, $J= 2.14$ Hz, 1H), 5.40-5.45 (br. s, 2H, 1 H is D$_2$O exchangeable), 3.63-3.67
(q, \( J = 6.71 \text{ Hz}, 2\text{H} \)), 3.0 (t, \( J = 6.71 \text{ Hz}, 2\text{H} \)), 2.61 (t, \( J = 7.5 \text{ Hz}, 2\text{H} \)), 1.79 (d, \( J = 1.53 \text{ Hz}, 3\text{H} \)), 1.38-1.48 (m, 2H), 1.25-1.30 (m, 12H), 0.88 (t, \( J = 7 \text{ Hz}, 3\text{H} \)).

\(^{13}\text{C NMR (125 MHz, CDCl}_3\)): \( \delta \) 166.46, 154.64, 136.11, 127.07, 121.89, 121.75, 119.17, 118.52, 118.27, 112.92, 110.93, 38.99, 32.75, 31.64, 29.55, 29.43, 29.34, 29.07, 28.08, 25.14, 24.42, 22.41, 13.86

HRMS (ESI): m/z calcd for C\(_{23}\)H\(_{34}\)N\(_2\)O\(_4\)Na (M+Na\(^+\)), 377.2567; found, 377.2563.

**Preparation of diethyl (2-[[2-(1H-indol-3-yl)ethyl]amino]-2-oxoethyl)phosphonate (17)**

A slurry of bromoacetamide 14 (0.5 g, 12.0 g, 1.78 mmol) in triethyl phosphite (0.32 mL, 0.3 g, 1.8 mmol) was heated under N\(_2\) atmosphere at 80 °C for 3 h. The residue was purified by column chromatography using pet ether and ethyl acetate as eluents to get product as brownish oil in 90% yield.

\(^1\text{H NMR (500 MHz, CDCl}_3\)): \( \delta \) 8.4-8.6 (br.d., 1H, D\(_2\)O exchangeable), 7.58-7.60 (d, \( J = 7.93 \text{ Hz}, 1\text{H} \)), 7.34-7.35 (d, \( J = 8.24 \text{ Hz}, 1\text{H} \)), 7.17 (t, \( J = 7.63 \text{ Hz}, 1\text{H} \)), 7.08-7.12 (m, 1H), 7.06 (brs., 1H), 6.79 (brs., 1H), 4.00-4.08 (m, 4H), 3.58-3.62 (q, \( J = 6.51 \text{ Hz}, 2\text{H} \)), 2.98 (t, \( J = 6.87 \text{ Hz}, 2\text{H} \)), 2.76-2.82 (d, \( J = 20 \text{ Hz}, 2\text{H} \)), 1.26 (t, \( J = 7.02 \text{ Hz}, 6\text{H} \)).

\(^{13}\text{C NMR (125 MHz, CDCl}_3\)): \( \delta \) 163.89, 136.34, 127.15, 122.30, 121.91, 119.20, 118.53, 112.38, 111.20, 62.69-62.64 (d, \( J = 6.3 \text{ Hz} \)), 40.00, 35.54-34.50 (d, \( J = 131.04 \text{ Hz} \)), 25.00, 16.22-16.17 (d, \( J=6.3 \text{ Hz} \))

HRMS (ESI): m/z calcd for C\(_{16}\)H\(_{23}\)N\(_2\)NaO\(_4\)P (M+Na\(^+\)), 361.1288; found, 361.1291.
Preparation of *trans* isomer of granulatamide A (16)

1M potassium *tert*-butoxide in THF solution (0.33 g, 2.95 mmol) was added to a solution of phosphonate 17 (0.5 g, 1.44 mmol) in 10 mL of THF at room temperature. After stirring for 10 min, a solution of 2-undecanone (0.45 mL, 0.37 g, 0.88 mmol) in THF was added and stirring was continued for 5 h. Then saturated aqueous NH₄Cl solution was added and then organic layer was separated and aqueous layer was extracted ethyl acetate and the combined organic extracts were washed with water, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* after filtration. Silica gel column chromatography (pet ether-ethyl acetate) provided 16 in 92% and 8 in 8% (both as pale yellow oil) Yield 85%.

¹H NMR (500 MHz, CDCl₃): δ 8.21 (brs., 1H, D₂O exchangeable), 7.63-7.65 (d, J = 7.93 Hz, 1H), 7.39-7.41 (d, J = 8.24 Hz, 1H), 7.21-7.25 (m, 1H), 7.13-7.17 (m, 1H), 7.07 (d, J = 2.14 Hz, 1H), 5.48-5.52 (br. t, 1H, D₂O exchangeable), 5.47 (d, J = 0.92 Hz, 1H), 3.67 (q, J = 6.41 Hz, 2H), 3.02 (t, J = 6.71 Hz, 2H), 2.15 (d, J = 0.92 Hz, 3H), 2.04-2.08 (t, J = 6.75 Hz, 2H), 1.40-1.47 (m, 2H), 1.27-1.33 (m, 12H), 0.90 (t, J = 6.87 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃): δ 167.24, 154.68, 136.41, 127.40, 122.18, 122.08, 119.47, 118.84, 117.91, 113.23, 111.24, 40.80, 39.42, 31.91, 29.54, 29.50, 29.34, 29.28, 27.49, 25.46, 22.71, 18.24, 14.15

HRMS (ESI): m/z calcd for C₂₃H₃₅N₂O (M+H)⁺, 355.2749; found, 355.2747.
Chapter 2: Section A

Preparation of \(N\)\-[2-(1H-indol-3-yl)ethyl]prop-2-enamide (19)

A solution of phosphonate 17 (0.34 g, 1.0 mmol) in 10 mL THF was NaH (0.08 g, 2 mmol) under an \(N\_2\) atmosphere at 0 °C. The reaction mixture was stirred at this temperature for 30 min. Then the paraformaldehyde (0.03 g, 1.0 mmol) was added in one portion and the reaction mixture was stirred at rt for 5 h. Before adding water (10 mL), reaction was cooled to 0 °C. Then solvent was removed under reduced pressure and the residue extracted with \(\text{CH}_2\text{Cl}_2\) (3× 15 mL). Combined organic layers were dried and evaporated under reduced pressure, affording the crude product which was purified by column chromatography (Pet ether- ethyl acetate) to get product as yellow oil in 80%.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 10.82 (brs., 1H), 8.23 (t, \(J = 5.04\) Hz, 1H), 7.53-7.55 (d, \(J = 7.93\) Hz, 1H), 7.33-7.35 (d, \(J = 7.93\) Hz, 1H), 7.15 (s, 1H), 7.07 (t, \(J = 7.48\) Hz, 1H), 6.96-7.00 (m, 1H), 6.1-6.25 (dd, \(J = 10\) Hz, 17 Hz, 1H), 6.05-6.15 (d, \(J = 16.5\) Hz 1H), 5.57-5.59 (d, \(J = 10\) Hz, 1H), 3.41-3.45 (q, \(J = 6.92\) Hz, 2H), 2.86 (t, \(J = 7.32\) Hz, 2H)

\(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta\) 164.50, 136.18, 131.89, 127.15, 124.83, 122.59, 120.88, 118.19, 111.72, 111.33, 39.46, 25.10.

HRMS (ESI): m/z calcd for \(\text{C}_{13}\text{H}_{14}\text{N}_2\text{NaO} \text{(M+Na)}^+\), 237.0998; found, 237.0998.

Preparation of \(N\)\-[2-(1H-indol-3-yl)ethyl]cinnamamide (18)

A solution of phosphonate 17 (0.5 g, 1.44 mmol) in 20 mL THF was added 1M potassium tert-butoxide (0.33 g, 2.95 mmol) in THF under an \(N\_2\) atmosphere at 0 °C. The reaction mixture was stirred at this temperature for 30 min. Then the benzaldehyde (0.18 g, 1.72 mmol) in THF (5 mL) was added slowly and the reaction mixture was stirred at rt for 4 h. Then water (10 mL) was added, the solvent was removed under reduced pressure and the residue extracted with \(\text{CH}_2\text{Cl}_2\) (3× 15 mL). Combined organic
layers were dried and evaporated under reduced pressure, affording the crude product which was purified by column chromatography (pet ether: ethyl acetate) to get product as brownish solid in 85%. M.p. 115 °C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.37 (brs., 1H), 7.57-7.63 (m, 2H), 7.40-7.45 (m, 2H), 7.34-7.37 (d, $J = 8$ Hz, 1H) 7.29-7.33 (m, 3H), 7.19 (t, $J = 7.32$ Hz, 1H), 7.11 (t, $J = 7$ Hz, 1H), 7.00-7.01 (d, $J = 1.65$ Hz, 1H), 6.27-6.30 (d, $J = 15$ Hz, 1H), 5.88 (br. t, $J = 5.34$ Hz, 1H), 3.69-3.73 (q, $J = 6.7$ Hz, 2H), 3.02 (t, $J = 6.7$ Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 165.96, 140.81, 136.39, 134.73, 129.58, 128.73, 127.71, 127.27, 122.20, 122.10, 120.74, 119.40, 118.67, 112.74, 111.31, 39.94, 25.26.

HRMS (ESI): m/z calcd for C$_{19}$H$_{18}$N$_2$NaO (M+Na)$^+$, 313.1313; found, 313.1311.
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$^1$H and $^{13}$C NMR spectra of products

Figure 9. $^1$H-NMR spectrum of 14 (500MHz, CDCl$_3$)

![HN-CO-Br](image)

Figure 10. $^{13}$C-NMR spectrum of 14 (125MHz, CDCl$_3$)

![13C-NMR spectrum of 14](image)
Figure 11. $^1$H-NMR spectrum of 15 (500MHz, CDCl₃)

Figure 12. $^{13}$C-NMR spectrum of 15 (125MHz, CDCl₃)
Figure 13. $^1$H-NMR spectrum of 8 (500MHz, CDCl$_3$)

Figure 14. $^{13}$C-NMR spectrum of 8 (125MHz, CDCl$_3$)
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**Figure 15.** DEPT spectrum of 8 (125MHz, CDCl$_3$)

**Figure 16.** NOE spectrum of 8 (500MHz, CDCl$_3$)
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Figure 17. $^1$H spectrum of 17 (500MHz, CDCl$_3$)

Figure 18. $^{13}$C-NMR spectrum of 17 (125MHz, CDCl$_3$)
Figure 19. $^1$H-NMR spectrum of 16 (500MHz, CDCl$_3$)

Figure 20. $^{13}$C-NMR spectrum of 16 (125MHz, CDCl$_3$)
Figure 21. DEPT spectrum of 16 (125MHz, CDCl₃)

Figure 22. NOE spectrum of 16 (500MHz, CDCl₃)
Figure 23. $^1H$ spectrum of 18 (500MHz, CDCl$_3$)

Figure 24. $^{13}C$ spectrum of 18 (125MHz, CDCl$_3$)
Figure 25. DEPT spectrum of 18 (125MHz, CDCl₃)

Figure 26. ¹H spectrum of 19 (500MHz, DMSO-d₆)
Figure 27. $^{13}$C spectrum of 19 (125MHz, DMSO-$d_6$)

Figure 28. DEPT spectrum of 19 (125MHz, DMSO-$d_6$)
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Section B

Formal synthesis of Balasubramide
Introduction

Alkaloids having lactam rings showed diverse pharmacological activities and hence motivated chemists to develop new synthetic strategies. The fruits and leaves of Rutaceae Clausena lansium (Lour.) Skeels (a fruit tree widely distributed in southern China) are used for the treatment of influenza, gastrointestinal disorders, viral hepatitis, and dermatological diseases in folk medicine. The hot-water extract of the leaves led to isolation of eight membered lactam namely, (±)-ξ-Clausenamide (1) (Figure 1) showing effective liver-protecting and anti-anemia effects.

(+) Balasubramide (2) was isolated from Clausena indica which grows in the central montane rainforests in Sri Lanka. It was named in memory of late Prof. S. Balasubramanian of the University of Peradeniya and in appreciation of his valuable help in collecting and identifying the plant material. Some of the compounds containing eight membered lactam are (−) Balasubramide (3) and (±) Norbalasubramide (4).

![Figure 1](image_url)

There are only three synthetic reports for balasubramide, which are shown below along with synthetic routes for norbalasubramide.

\[ \text{Ph-O-C(=NH)NH}_2 + \text{Br} \rightarrow \text{Ts} \]

\[ \text{Ts} \]

\[ \text{Ts} \rightarrow \text{Ts} \]

\[ \text{Ts} \rightarrow \text{Ts} \]

\[ \text{(-)-(5R,6S)-balasubramide} \]


\[ \text{Ph-O-C(=OK)} \rightarrow \text{A} \rightarrow \text{R=N} \]

\[ R=\text{H, norbalasubramide} \]

\[ R=\text{Me, (±)-balasubramide} \]


\[ \text{Ph-O-CCl}_3 \rightarrow \text{A} \rightarrow \text{R=N} \]

\[ R=\text{H, (-)-(5R,6S)-norbalasubramide} \]

\[ R=\text{Me, (-)-(5R,6S)-balasubramide} \]

\[ \text{trans epoxide} \]

By reviewing the literature reports 2 and 3 mentioned above, it was found that in the last step balasubramide was synthesized from epoxyamide (5). According to both the reports, during the synthesis, epoxyamide produced was inseparable mixture which


...
was used as such without purification and characterization for further transformation to get balasubramide as shown below (Scheme 1).

**Present Plan**

It was planned to synthesize epoxyamide (5) by a new route and to characterize it by spectral and analytical methods. This would be then, a formal synthesis of (±) balasubramide. The retrosynthetic plan is shown in Scheme 2.

**Results and Discussion**

According to the plan, synthesis started with Boc substituted tryptamine. The Boc substitution was planned purposely since -N-Boc group can be converted to -N-methyl using LAH which is the requirement of the target molecule. The Boc
substituted tryptamine 7 was already synthesized and characterized earlier in Chapter 1 (page no. 41). Further it was refluxed with LAH in anhydrous tetrahydrofuran (Scheme 3). The formation of monomethylated tryptamine 8 was confirmed by comparing the melting point (81 °C) with the reported value (82 °C). It was also supported by disappearance of signals of Boc group and presence of singlet for methyl group at δ 2.28 in $^1$H NMR and at δ 35.77 in $^{13}$C NMR spectra. All other protons were resonating at appropriate positions.

Further, 2-(1H-indol-3-yl)-N-methylethanamine 8 was treated with bromoacetyl bromide in the presence of diisoproylethylamine as a base, in anhydrous tetrahydrofuran to furnish 2-bromo-N-[2-(1H-indol-3-yl)ethyl]-N-methylacetamide 9 as shown in Scheme 4. The molecular ion peak observed at 317.0270, in HRMS confirmed the molecular formula $\text{C}_{13}\text{H}_{15}\text{BrN}_{2}\text{O}$ (M+Na).

$^1$H NMR spectrum of compound 9 showed doubling of all signals indicating the presence of rotamers (Figure 2). The presence of rotamers can be explained by the hindered rotations about the amide bond present in compound 9.

![Figure 2. Depiction of rotation about amide bond](image-url)
Thus, $^1$H NMR spectrum exhibited two singlets each of two protons at $\delta$ 3.87 and 3.44 for CH$_2$-Br and two triplets at $\delta$ 3.71 and 3.65 each of two protons with coupling constant 6.9 Hz for CH$_2$-N. Additional two triplets of benzylic methylene protons were seen at $\delta$ 3.04 and 3.09 of which the later was overlapping on the singlet of methyl group. The singlet for methyl of the other rotamer was observed at $\delta$ 2.97. All the other aromatic protons were also showing double signals at appropriate positions (Figure 3). From the integration, the ratio of the rotamers was 1:1. The $^1$H NMR and its expanded NMR are depicted below clearly showing the presence of mixture of two rotamers.
Figure 3

The structure of compound 9 was confirmed by $^{13}$C NMR and DEPT experiment which also showed two sets of signals for the two rotamers as shown in Figure 4.

Figure 4

In order to get trans epoxide, our attention was to synthesize trans olefin. Thus, it was planned to synthesize trans-selective phosphonate 10 by reacting compound 9 with
neat triethylphosphite as shown in Scheme 5. After usual work up and purification by column chromatography an oily product was obtained. This phosphonate 10 was characterized using analytical and spectral data. The molecular ion peak observed at 375.1449, in HRMS, confirmed the molecular formula as C_{17}H_{25}N_{2}NaO_{4}P (M+Na).

![Scheme 5](image_url)

{\textsuperscript{1}H} NMR spectra of product 10 showed doubling of the signals confirming the presence of rotamers similar to the starting compound 9. In addition to this, a hetero nuclear coupling of proton and phosphorous was also observed. Thus, two distinct doublets corresponding to CH_{2}-P of two rotamers were seen at δ 3.06-3.11 and 2.69-2.64 with coupling constant of 30 Hz which was due to H-P hetero nuclear coupling. Two triplets for six protons each, at δ 1.26 and 1.35 for 2x -OCH_{2}CH_{3} and two multiplates for four protons each at 4.00-4.09 and δ 4.17-4.23 for 2x -OCH_{2}CH_{3} were also observed. All other protons showed a similar doubling pattern. From the integration values in {\textsuperscript{1}H} NMR, the two rotamers were found to be present in the ratio of 1:1. The {\textsuperscript{1}H} NMR and its expanded parts are shown below in Figure 5.
Figure 5

$^{13}$C NMR also showed two sets of signals for the two rotamers (Figure 6). DEPT experiment showed three signals for methyl groups and twelve inverted signals for methylene groups. The NMR showed the possibility of coupling of carbon with phosphorous. Amongst the inverted signals in DEPT, the four singlets at $\delta$ 31.84, 32.91, 33.04, and 34.10 were due to -P-CH$_2$ having two rotamers as well as coupling with P. Similarly four singlets at $\delta$ 62.45, 62.50, 62.59, and 62.64 were due to two carbons of 2x-OCH$_2$CH$_3$ having two rotamers as well as coupling with P. Due to the large distance the remaining two methylene carbons were not showing coupling with P but showed only doubling pattern due to rotamers. The four singlets at $\delta$ 16.18, 16.23, 16.26, and 16.31 were due to two methyl carbons of 2X–OCH$_2$CH$_3$ having rotamers as well as coupling with P. The remaining two singlets for one N-CH$_3$ at $\delta$ 33.78 and 37.22 were due to rotamers. The carbonyl carbon of amide showed four
singlets at δ 164.61, 164.66, 165.06, and 165.10 which were also due to rotamers as well as coupling with P. All the other aromatic carbons were also showing double signals at appropriate positions. Thus, all this spectral data confirmed the structure of the new phosphonate 10.
Further, Horner–Wadsworth–Emmons olefination of benzaldehyde with phosphonate 10 in the presence of \( t \)-BuOK as a base in anhydrous tetrahydrofuran was carried out, which gave exclusively trans olefinic compound 11 in 92% yield as shown in Scheme 6. The formation of the product was confirmed by HRMS, which showed molecular ion peak at 305.1648 for the molecular formula \( C_{20}H_{21}N_2O \) (M+H).

\[
\text{Scheme 6}
\]

Similar to the starting compound 10, \(^1\)H NMR of product 11 also showed two rotamers in the ratio of 7:3 which was calculated by integration of two distinct triplets for \( \text{CH}_3-N \) at \( \delta \) 3.67 and 3.77. The remaining methylene and methyl protons were overlapped on each other and two trans coupled doublets for olefinic protons were resonating at \( \delta \) 6.14-6.17 and 7.40-7.43 with coupling constant of 15.3 and 15.6 Hz respectively. \(^1\)H NMR and its expanded parts are shown in Figure 7.
Figure 7

$^{13}$C NMR and DEPT experiments also elucidated the structure of the product 11 (figure 8). $^{13}$C NMR showed presence of six singlets in the aliphatic region out of which, four singlets at $\delta$ 23.21, 24.35, 49.41, and 50.09 were due to methylene carbons and other at $\delta$ 33.97 and 36.09 were for methyl carbons of both the rotamers. All the spectral data confirmed the trans structure of the product 11.
The next target was to get the \textit{trans} epoxide. From the literature survey, it was noticed that in the epoxidation\textsuperscript{10} using \textit{m}-CPBA, the stereochemistry of olefin is retained. Thus, having \textit{trans} olefin \textit{11} in hand, \textit{m}-CPBA was selected as a reagent for the epoxidation. \textit{m}-CPBA is a strong oxidizing agent which is used for the oxidation of aldehydes and ketones to esters (Bayer Villiger oxidation), olefines to epoxides, sulfides to sulfoxides and sulfones, amines to nitroalkanes. In many reactions due to an outstanding reactivity, \textit{m}-CPBA is used more selectively than hydrogen peroxide and other peracids. The mechanism for epoxidation using \textit{m}-CPBA, involving a butterfly transition state is shown in Figure 9.

\textbf{Figure 8}

The next target was to get the \textit{trans} epoxide. From the literature survey, it was noticed that in the epoxidation\textsuperscript{10} using \textit{m}-CPBA, the stereochemistry of olefin is retained. Thus, having \textit{trans} olefin \textit{11} in hand, \textit{m}-CPBA was selected as a reagent for the epoxidation. \textit{m}-CPBA is a strong oxidizing agent which is used for the oxidation of aldehydes and ketones to esters (Bayer Villiger oxidation), olefines to epoxides, sulfides to sulfoxides and sulfones, amines to nitroalkanes. In many reactions due to an outstanding reactivity, \textit{m}-CPBA is used more selectively than hydrogen peroxide and other peracids. The mechanism for epoxidation using \textit{m}-CPBA, involving a butterfly transition state is shown in Figure 9.
\( m \)-CPBA is also used as an epoxidizing agent for \( \alpha-\beta \)-unsaturated amides. Some of the examples illustrating the use of \( m \)-CPBA for epoxidation of \( \alpha-\beta \)-unsaturated amides are shown below.


\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{O} & \quad \text{OH} & \quad \text{HN} & \quad \text{OR} & \quad \text{R}\_2 \quad \text{m-CPBA, DCM, 80\%} \quad \text{Ph} & \quad \text{O} & \quad \text{O} & \quad \text{OH} & \quad \text{HN} & \quad \text{OR} & \quad \text{R}\_2 \quad \text{R}\_1
\end{align*}
\]

2. Masanori, B. et al (2003)\(^ {12} \)

\[
\begin{align*}
\text{OR}\_1 & \quad \text{HN} & \quad \text{OR}\_2 & \quad \text{Ph} & \quad \text{m-CPBA, DCM, -78\degree C; 1\,h} & \quad \text{OR}\_1 & \quad \text{HN} & \quad \text{OR}\_2 & \quad \text{Ph}
\end{align*}
\]

3. Han, Y. T. et. al. (2014)\(^ {13} \)

\[
\begin{align*}
\text{Ph} & \quad \text{OR}\_2 & \quad \text{HN} & \quad \text{OR}\_1 & \quad \text{m-CPBA, NaHCO}_3, \quad \text{DCM, 58\%;} & \quad \text{Ph} & \quad \text{OR}\_2 & \quad \text{HN} & \quad \text{OR}\_1
\end{align*}
\]
From the above literature reports of epoxidations on $\alpha$-$\beta$-unsaturated amides, it was decided to synthesize epoxyamide 5 using $m$-CPBA. Therefore compound 11 was treated with $m$-CPBA in DCM at 0 °C. After disappearance of starting material and appearance of a new spot on TLC, reaction mixture was worked up by usual procedure. The attempts to purify the epoxide by column chromatography resulted into decomposition of the product.

\[ \text{Scheme 7} \]

$^1$H NMR of the crude compound showed disappearance of doublet for olefinic proton which was present at $\delta$ 6.14-6.17 in the $^1$H NMR of the starting compound, suggesting the complete conversion into the product 5 (Figure 10).
Chapter 2: Section B

Figure 10

On expanding the aliphatic region (Figure 11), it was found that the doublets at δ 3.56 and 4.0 were due to the protons on the epoxide ring. Rest of the ^1H NMR spectra was complex and difficult to analyze due to the overlapping of the signals. The possibility of rotamers also could not be denied.

Figure 11

Due to the presence of rotamers and overlapping of signals, the ^13C NMR of crude epoxide 5 (Figure 12) was complex and difficult to analyze. From the DEPT experiment, it was shown that four singlets at δ 29.72, 37.83, 44.33, and 45.20 were due to two methylene carbons and four singlets at δ 36.11, 57.19, 57.77, and 58.05 were belonging to one methyl and two methine carbons of rotamers of expected epoxide 5.
HRMS of crude compound showed one peak at 343.1417 which matched with the molecular formula C$_{20}$H$_{20}$N$_2$O$_2$+Na of the epoxide 5. This data also suggested the presence of expected epoxide 5. Further purification and final confirmation is in progress. Considering the difficulty in purifying the epoxide, attempt to synthesize (±)-balasubramide directly from the crude epoxide 5 is also ongoing.
Figure 12
Conclusion

Epoxide 5 was synthesized in a crude form using a new route in which trans selective Horner–Wadsworth–Emmons olefination and trans epoxidation using m-CPBA, were the key steps. The spectral analysis of the crude compound supported the formation of epoxide 5. This constitutes a formal synthesis of (±)-balasubramide.
Experimental Section

Preparation of 2-(1H-indol-3-yl)-N-methylethanamine (8)

To a suspension of LAH (0.29 g, 7.64 mmol) in THF (8 mL) at 0 °C was added a solution of N-(t-butoxycarbonyl)tryptamine (0.5 g, 1.92 mmol) in THF (20 mL). The reaction mixture was stirred for 30 min at room temperature and then refluxed for 3 h. The reaction was then cooled to 0 °C and the excess of LAH was hydrolyzed by adding successively and very carefully, water (15 mL), 15% aqueous solution of NaOH (15 mL). During these steps it was necessary to add THF (100 mL) to avoid the mixture becoming very thick. The suspension was filtered and the white solid, made up of LiOH and Al(OH)₃, was washed with THF (30 mL). The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure to give product 8 as beige solid in 95%. M. p. 82 °C.

¹H NMR (500 MHz, CDCl₃): δ ppm 2.28 (s, 3H), 2.48 (brs. 1H), 2.79 (t, J = 6.41 Hz, 2H), 2.86 (t, J = 6.71 Hz, 2H), 6.79 (s, 1H), 6.96-7.01 (m, 1H), 7.03-7.09 (m, 1H), 7.17-7.19 (d, J = 8.24 Hz, 1H), 7.48-7.50 (d, J = 7.63 Hz, 1H) 9.07 (brs., 1H).

¹³C NMR (125 MHz, CDCl₃): δ ppm 25.16, 35.77, 51.59, 111.21, 112.87, 118.56, 118.88, 121.61, 122.29, 127.19, 136.39.
Figure 13. $^1$H-NMR spectrum of 8 (500MHz, CDCl$_3$)

Figure 14. $^{13}$C-NMR spectrum of 8 (125MHz, CDCl$_3$)
Preparation of 2-bromo-N-[2-(1H-indol-3-yl)ethyl]-N-methylacetamide (9)

To a stirring solution of N-methyl tryptamine (0.4 g, 2.5 mmol) in anhydrous tetrahydrofuran (20 mL) under a nitrogen atmosphere at 0 °C, were added diisopropylethyl amine (2.4 mL, 0.56 g, 2.78 mmol) and bromoacetyl bromide (0.49 mL, 0.36 g, 2.78 mmol). After 2 hours, ethyl acetate was added and the reaction mixture washed with water twice, 1N hydrochloric acid (2x15) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator and separated by column chromatography to give the product (95%) as a yellow film.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ conformer mixture

8.56 (br. s., 1 H), 8.42 (br. s., 1 H), 7.66-7.68 (d, $J = 7.93$ Hz, 1H), 7.58-7.60 (d, $J = 7.93$ Hz, 1H), 7.36-7.41 (m, 2H), 7.12-7.25 (m, 4H), 7.03 (d, $J = 1.83$ Hz, 1H), 6.96-6.67 (d, $J = 2.14$ Hz, 1H), 3.87 (s, 2H), 3.71 (t, $J = 6.90$ Hz, 2H), 3.65 (t, $J = 6.87$ Hz, 2H), 3.44 (s, 2H), 3.09 (t, $J = 6.87$ Hz, 2H), 3.03-3.07 (m, 5H), 2.97 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ conformer mixture

167.39, 166.75, 136.39, 136.38, 127.39, 126.82, 122.75, 122.37, 122.35, 122.01, 119.80, 119.36, 118.63, 118.01, 112.49, 111.70, 111.38, 111.36, 51.50, 49.54, 36.90, 34.02, 26.75, 26.61, 25.91, 24.12, 22.92

Preparation of diethyl (2-[[2-(1H-indol-3-yl)ethyl](methyl)amino]-2-oxoethyl)phosphonate (10)

A slurry of bromoacetamide 9 (1.4 g, 4.74 mmol) in triethyl phosphite (0.9 mL, 5.22 mmol) was heated under N$_2$ atmosphere at 80 °C for 6 h. The residue was purified by column chromatography using ethyl acetate and methanol as eluent to get the oily product (85%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ conformer mixture
8.77 (br. s., 2 H), 8.61 (br. s., 1 H), 7.65-7.66 (d, \( J = 7.93 \) Hz, 2 H), 7.58-7.61 (m, 2 H), 7.38 (m, 3 H), 7.19 (m, \( J = 8.05, 6.98, 4.96, 1.07 \) Hz, 3 H), 7.10-7.15 (m, 3 H), 7.05 (d, \( J = 2.44 \) Hz, 1 H), 6.97 (d, \( J = 2.44 \) Hz, 2 H), 4.17-4.23 (m, 7 H), 4.00-4.09 (m, 7 H), 3.71 (m, 7 H), 3.06 (s, 2 H), 3.00-3.05 (m, 6 H), 2.59-2.65 (m, 2 H), 1.33-1.37 (m, 6 H), 1.24-1.28 (m, 6 H).

\[^{13}\text{C} \text{NMR (125 MHz, CDCl}_3\text{: } \delta \text{ conformer mixture}\]

165.19, 165.15, 164.75, 164.70, 136.41, 136.36, 127.37, 126.88, 122.80, 122.41, 122.12, 121.83, 119.52, 119.19, 118.57, 118.06, 111.64, 111.33, 62.73, 62.67, 62.60, 62.54, 51.37, 49.33, 37.31, 34.19, 33.87, 33.12, 33.00, 31.93, 24.03, 23.09, 16.40, 16.35, 16.32, 16.27

\textbf{Preparation of (2E)-N-[2-(1H-indol-3-yl)ethyl]-N-methyl-3-phenylprop-2-enamide (11)}

1M potassium tert-butoxide in THF solution (0.47 g, 4.1 mmol) was added to a solution of phosphonate 10 (0.6 g, 1.7 mmol) in 10 mL of THF at room temperature. After stirring for 10 min, a solution of benzaldehyde (0.25 mL, 0.27 g, 2.5 mmol) in THF was added and stirring was continued for 6 h. Then saturated aqueous \( \text{NH}_4\text{Cl} \) solution was added and then organic layer was separated and aqueous layer was extracted ethyl acetate and the combined organic extracts were washed with water, dried over anhydrous \( \text{Na}_2\text{SO}_4 \) and concentrated \textit{in vacuo} after filtration. Silica gel column chromatography (pet ether-ethyl acetate) provided 11 in 92%.

While interpreting NMR, the protons at 3.67 were considered as four for the sake of convenience, which were actually two protons.

\(^1\text{H} \text{NMR (500 MHz, CDCl}_3\text{: } \delta \text{ conformer mixture}\)

8.83 (brs., 2 H), 8.76 (brs., 1 H), 7.71-7.74 (d, \( J = 15.56 \) Hz, 1 H), 7.66-7.68 (d, \( J = 7.63 \) Hz, 1 H), 7.61-7.62 (d, \( J = 7.63 \) Hz, 2 H), 7.48-7.49 (d, \( J = 6.10 \) Hz, 2 H), 7.40-7.43 (d, \( J = 15.56 \) Hz, 2 H), 7.32 (t, \( J = 7.78 \) Hz, 3 H), 7.27-7.28 (d, \( J = 7.63 \) Hz, 2 H), 7.12-7.23 (m, 11 H), 6.95 (s, 1 H), 6.75-6.88 (m, 7 H), 6.14-6.17 (d, \( J = 15.26 \) Hz, 2 H), 3.77 (t, \( J = 7.32 \) Hz, 2 H), 3.67 (t, \( J = 6.26 \) Hz, 4 H), 2.97-3.10 (m, 15 H).
13C NMR (125 MHz, CDCl₃): δ conformer mixture

167.00, 166.09, 142.14, 141.16, 136.25, 136.01, 134.90, 134.71, 129.52, 129.23, 128.73, 128.41, 128.36, 128.14, 127.44, 127.36, 127.22, 127.06, 126.60, 122.89, 121.96, 121.62, 121.37, 119.12, 118.75, 118.26, 117.50, 117.35, 117.22, 112.29, 111.53, 111.03, 110.80, 49.83, 49.15, 35.83, 33.71, 24.09, 22.95

Preparation of (2S,3R)-N-[2-(1H-indol-3-yl)ethyl]-N-methyl-3-phenyloxirane-2-carboxamide (5)

0.095 g (1 equivalent) of the amide (11) from was dissolved in 30 ml of dichloromethane. Then 0.17 g (3.25 equivalents) of m-chloroperbenzoic acid (70-75%) was added. The reaction mixture was stirred for 2 days. The reaction was monitored with TLC. After completion of the reaction, the reaction mixture was washed successively with 2×20 mL of a sodium sulphite solution, 2×20 mL of saturated aqueous NaHCO₃ and 20 mL of brine. The organic layer was dried (Na₂SO₄), filtrated and evaporated under reduced pressure yielding the epoxide (5) in 50%.

13C NMR (125 MHz, CDCl₃): δ 29.67, 36.07, 37.79, 44.29, 45.16, 57.15, 57.73, 58.00, 121.48, 121.67, 121.87, 123.28, 124.4, 125.68, 125.7, 127.84, 128.62, 128.66, 128.83, 128.86, 130.49, 131.09, 135.42, 139.84, 139.96, 159.80, 166.79.
Chapter 2: Section B

References


Section C

Evaluation of energy barriers and chemical shifts of rotamers of amides
Introduction

The *cis*-trans isomerization of amides\(^1\) is an extensively investigated phenomenon. Most of the NMR studies of this class of compounds are concerned with the double-bond character of the amide bond arising due to the delocalization of lone pair of electrons on the nitrogen and restricted rotation around the amide bond. This rotation occurs via intermediate resonance structures as shown in Figure 1. These structures suggest an approximately planar amide framework and restricted rotations about \(C-N\) bond due to its double-bond character. This gives a barrier to rotation around the amide bond for interconverting \(R_2\) and \(R_3\) substituents.

![Figure 1. *Cis*-trans isomerism in amides](image)

The energy barrier for rotation of the \(C-N\) bond is relatively high as compared to the barriers about other covalent single bonds. This is due to the partial \(\pi\)-bond character between the carbonyl group and the nitrogen atom that forces the amide function to be planar (structures 2 and 4) as shown in no. in Figure 1.

The energy barrier for rotation is high enough to study this phenomenon by NMR spectroscopy at room temperature. However at higher temperature, molecules possess the energy sufficient to overcome the barrier to rotate. The rate of interconversion can be calculated at the coalescence temperature where the two signals are just merged. The activation parameters are calculated by coalescence temperature using DNMR (Dynamic NMR) spectroscopy. It is also known that the rotation rate of amides is affected by the solvent and by the interaction of the oxygen of the carbonyl group with Lewis acids.
The hindered rotations arise due to the double-bond character which leads to the geometrically and magnetically nonequivalent nitrogen substituents even when $R_2$ and $R_3$ are same e.g. $N,N$-dimethyl formamide (DMF). $^1$H NMR spectrum of DMF near room temperature exhibit one broad singlet for aldehydic proton and two resonances for the nonequivalent $N$-methyl groups. The protons of the $N$-methyl group cis to carbonyl resonate at higher field than those of trans (Figure 2). Thus the cis-methyl protonsexperience greater shielding. This observation is consistent with the model given by Paulsen and Todt.

![Figure 2. Nonequivalence of $N$-methyl groups in DMF](image)

DMF is a classic example of a fluxional molecules (that undergoes dynamics such that some of the atoms interchange between symmetry-equivalent positions). At temperatures near 120 °C, the $^1$H NMR spectrum of DMF shows only one signal for the methyl groups. This is due to more energy available at higher temperature which is used for fast rotations. The "coalescence temperature" for DMF is 120 °C as shown below in Figure 3.

![Figure 3](image)

The similar nonequivalence of protons is observed for formamide (Figure 4).
Following are some of the literature reports showing cis-trans isomerism of amide due to C-N bond rotations.


In the present work, restricted rotations about amide bond were observed for compounds 9, 10 and 11 (Figure 5). The synthesis of these compounds was described in section II of this Chapter.
GIAO/DFT (gauge-including atomic orbital/Density functional theory) is a most widely used method to calculate NMR values. The continuous sets of gauge transformation are performed to obtain accurate density and from that density tensors for NMR are calculated. The GIAO method with different levels of theory were employed to interpret NMR data (chemical shifts, coupling constants, H-bonding), to optimize minimum energy structures. It is also used to predict the energy for rotational barrier about amide bond.

**Present Plan**

Theoretical calculations were carried out using the B3LYP/6-31+G(d) methodology in an attempt to predict minimum energy structures and the energy for rotational barrier about amide bond for the compounds 9, 10, and 11.

**Results and Discussion**

The minimum energy structures obtained are shown below in Figure 6.
Figure 6. Optimized structures for rotamers of 9 (9a, 9b), 10 (10a, 10b), and 11 (11a, 11b)
The energies for rotational barrier about amide bond for the compounds 9, 10, and 11 were calculated using B3LYP/6-31+G(d) level of theory using Self Consistent Reaction Field theory of adding chloroform solvent (Table 1).

**Table 1. Calculation of energies for rotational barrier for the compounds 9, 10, and 11**

<table>
<thead>
<tr>
<th>Compound</th>
<th>E (a.u.)</th>
<th>ΔE (a.u.)</th>
<th>ΔE (ev)</th>
<th>ΔE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isomer1 (a)</td>
<td>Isomer2 (b)</td>
<td>(a-b)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>-3260.9166369</td>
<td>-3260.9149470</td>
<td>0.001690</td>
<td>0.046</td>
</tr>
<tr>
<td>10</td>
<td>-1414.7584377</td>
<td>-1414.7569149</td>
<td>0.001523</td>
<td>0.041</td>
</tr>
<tr>
<td>11</td>
<td>-958.9529411</td>
<td>-958.9525713</td>
<td>0.000370</td>
<td>0.010</td>
</tr>
</tbody>
</table>

For the compound 9 and 10, the values of ΔE were found to be 1.06 and 0.96 kcal/mol respectively. As described in previous section, by experimental NMR, rotameric ratio for both the compounds are 4.8:5.2 and 4.9:5.1 respectively. For the compound 11, value of ΔE is found to be 0.23 kcal/mol which is lower than the earlier ones. This means that the energy required for amide bond rotation is less for compound 11.

For one of the rotamers 11a, there are two possible resonating structures 11a’ and 11a” (Figure 7). In the structure 11a”, partial double character of the amide bond is reduced due to another resonating structure 11a’. Hence the energy barrier for rotating the amide bond is lowered which is seen from the ΔE value of 0.23 kcal/mol.
Now, for another contributing rotamer 11b, there is a possibility of two resonating structure as 11b’ and 11b’’ as shown below in Figure 8. In the both structures 11b’ and 11b’’, the hydrogen bonding can be visualized through five membered ring formation and which gives more stabilization.

The chemical shifts were also calculated for compounds 9a, 9b, 10a, 10b, 11a, and 11b by B3LYP/6-31+G(d) theory using CHCl₃ as a solvent and TMS as a reference. One rotamer in each case is depicted below with the numbering to the all atoms. The
chemical shift values of $^1$H and $^{13}$C NMR for both the isomers are shown in tabular form.

![Chemical structure](image)

**Table 2.** $^1$H NMR chemical shifts in δ

<table>
<thead>
<tr>
<th>Proton number</th>
<th>Isomer 1 (9a)</th>
<th>Isomer 2 (9b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-H</td>
<td>7.13595</td>
<td>7.20085</td>
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<td>23-H</td>
<td>6.94585</td>
<td>6.98835</td>
</tr>
<tr>
<td>25-H</td>
<td>6.90695</td>
<td>6.98095</td>
</tr>
<tr>
<td>24-H</td>
<td>6.89325</td>
<td>6.96475</td>
</tr>
<tr>
<td>26-H</td>
<td>6.76305</td>
<td>6.85685</td>
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<td>22-H</td>
<td>6.40145</td>
<td>6.23495</td>
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<td>19-H</td>
<td>4.14385</td>
<td>3.30885</td>
</tr>
<tr>
<td>32-H</td>
<td>3.93565</td>
<td>3.77085</td>
</tr>
<tr>
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<td>3.75945</td>
<td>3.87355</td>
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<td>2.86725</td>
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<td>18-H</td>
<td>2.52365</td>
<td>3.22255</td>
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<td>21-H</td>
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### Table 3. $^{13}$C NMR chemical shifts in δ

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</thead>
<tbody>
<tr>
<td>14-C</td>
<td>37.65355</td>
<td>32.19285</td>
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<td>15-C</td>
<td>49.81505</td>
<td>50.46315</td>
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<tr>
<td>2-C</td>
<td>51.96495</td>
<td>49.83235</td>
</tr>
<tr>
<td>8-C</td>
<td>108.63465</td>
<td>109.32255</td>
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<tr>
<td>4-C</td>
<td>113.25035</td>
<td>114.63275</td>
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<tr>
<td>5-C</td>
<td>116.56255</td>
<td>116.30105</td>
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<tr>
<td>11-C</td>
<td>115.87125</td>
<td>116.69385</td>
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<td>10-C</td>
<td>117.60065</td>
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<td>9-C</td>
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<td>7-C</td>
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<td>132.45745</td>
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<td>13-C</td>
<td>161.52455</td>
<td>162.68435</td>
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<tr>
<td>3-C</td>
<td>28.14185</td>
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</table>

![Structure Image](#)

### Table 4. $^1$H NMR chemical shifts in δ

10a
### Table 5

<table>
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<tr>
<th>Proton number</th>
<th>Isomer 1 (10a)</th>
<th>Isomer 2 (10b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-H</td>
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<td>24-H</td>
<td>6.89895</td>
<td>6.90195</td>
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<td>25-H</td>
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<td>21-H</td>
<td>6.64465</td>
<td>6.41035</td>
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<td>18-H</td>
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<td>46-H</td>
<td>0.67795</td>
<td>0.64135</td>
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<td>42-H</td>
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<td>0.58005</td>
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</table>

<table>
<thead>
<tr>
<th>Carbon number</th>
<th>Isomer 1 (10a)</th>
<th>Isomer 2 (10b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-C</td>
<td>161.82705</td>
<td>161.59605</td>
</tr>
<tr>
<td>7-C</td>
<td>133.56235</td>
<td>133.05105</td>
</tr>
<tr>
<td>12-C</td>
<td>126.97315</td>
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</table>
### Table 6. $^1$H NMR chemical shifts in $\delta$

<table>
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<tr>
<th>Proton number</th>
<th>Isomer 1 (11a)</th>
<th>Isomer 2 (11b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>43-H</td>
<td>7.50825</td>
<td>7.62805</td>
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<tr>
<td>33-H</td>
<td>7.31255</td>
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<td>38-H</td>
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<td>29-H</td>
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<td>7.16605</td>
</tr>
<tr>
<td>40-H</td>
<td>7.08475</td>
<td>7.05885</td>
</tr>
<tr>
<td>42-H</td>
<td>7.06875</td>
<td>7.09385</td>
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</table>
Table 7. $^{13}$C NMR chemical shifts in $\delta$

<table>
<thead>
<tr>
<th>Carbon number</th>
<th>Isomer 1 (11a)</th>
<th>Isomer 2 (11b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-C</td>
<td>162.66235</td>
<td>162.35165</td>
</tr>
<tr>
<td>17-C</td>
<td>142.95715</td>
<td>146.35715</td>
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<td>7-C</td>
<td>133.56445</td>
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<td>18-C</td>
<td>133.28715</td>
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<td>19-C</td>
<td>131.92105</td>
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<td>125.55095</td>
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<tr>
<td>4-C</td>
<td>113.19515</td>
<td>112.45625</td>
</tr>
</tbody>
</table>
The contributing structures for 9a, 9b, 10a, and 10b are visualized as shown below in Figure 9 while the contributing structures for 11a, and 11b are discussed earlier.

![Diagram of contributing structures](image)

Figure 9.

We have calculated the chemical shifts by theoretical method, B3LYP/6-31+G(d) for the structures 9a, 9b, 10a, 10b, 11a, and 11b. Some of the values of chemical shifts are matching with those of experimental values, e.g. CH$_2$-Br expt. 3.87 δ and calc. 3.87355 δ (Table 2, 31-H), CH$_2$-N expt. 51.5 δ and calc. 51.96495 δ (Table 3, 2-C), CH$_3$-N expt. 51.28 δ and calc. 51.87205 δ (Table 5, 2-C), CH$_3$-N expt. 3.05 δ and
calc. 3.01675 δ (Table 6, 34-H). The values which are not matching with experimental values like \( \text{CH}-\text{CO} \) expt. 6.14 δ and calc. 6.47695 δ (Table 6, 37-H), \( \text{CH}_2\text{-P} \) expt. 34.10 δ and calc. 39.84985 δ (Table 5, 15-C) can be explained by the possibility of contribution of other resonance structures.
Conclusion

Theoretical calculations were carried out using the DFT(B3LYP)/6-31+G(d) theory to predict minimum energy structures and to find the energy for rotational barrier about amide bond and chemical shift values of $^1$H and $^{13}$C NMR for the compounds 9, 10, and 11.
Experimental Section

Theoretical Investigations

In order to substantiate the experimental observations the theoretical investigations were carried out on the molecules employing density functional theory. For this purpose, one of the most popular and widely used functional B3LYP with combination of 6-31+G(d) basis set is used which is available in Gaussian Program.\(^9\)\(^{12}\) B3LYP functional is known to work very well for covalently bonded systems. The effect of solvation was incorporated by self-consistent reaction field (SCRF) theory incorporating the polarizable continuum model (PCM) using chloroform as solvent.\(^{13}\)\(^{14}\) First the molecules were subjected to geometry optimization and subsequently the NMR spectra were calculated in solvent phase. For both \(^1\)H- and \(^13\)C-NMR tetramethysilane (TMS) is used as a reference in the calculations.
References