Chapter 2

Synthesis and characterization of dehydroabietylamine and abietic acid derivatives
2.1.1 Introduction

A natural chemical entity plays a major role in the drug discovery programme and constitutes approximately 30% drugs. In this contribution, a collection of naturally-occurring abietane-type diterpenes and their derivatives have significant place. Abietane diterpenoids are widely occured in plants, which exhibited a variety of industrial uses as well as pharmacological properties. The natural abietanoids and their derivatives possess various biological activities such as antimicrobial, anti-inflammatory,\(^1\) antiulcer, cardiovascular, allergenic, antiallergic,\(^2\) antipenetrant activities, filmogenic, surfactant, antifeedant, etc.\(^3\)

Among various abietanoids, tricyclic diterpenoid, dehydroabietylamine and abietic acid are more interesting for thier special structures and properties. Abietic acid (3) is a major constituent in rosin. Rosin is a natural extract obtained from pine trees and its total output is 2-3 millions of ton annually.\(^4\)–\(^9\) Rosin is mainly a mixture of C\(_{20}\) monocarboxylic diterpenic resins including abietic-type acids and pymaric type acids. The rosins are transformed into the disproportionated rosin at 200 to 240 °C, in which the percentage of dehydroabietic acid is more than 50%.\(^5\),\(^8\),\(^10\)

Dehydroabietylamine (DHA) (1) is derived from abietic acid. Dehydroabietylamine posses weak affinity for the human central cannabinoid (CB\(_1\)) and peripheral cannabinoid (CB\(_2\)) receptors. Dehydroabietylamine (1) is a eco-friendly chemical with diversified applications including in synthesis of pesticides and pharmaceuticals, preparation of surfactants and corrosion inhibitor, manufacture of epoxy resins, paper-making, and so on.\(^11\)–\(^13\) Among these applications, the most important is in the preparation of cationic surfactants that used DHA (1).
2.1.2 Literature Review

Abietane type diterpenoid derivatives as antimicrobial agents

Antimicrobial agents composed of a diverse class of chemical entities acting against different kinds of microbes such as bacteria, fungi, viruses, protozoa, helminthous, etc. Bob Goodson, et al. reported the N-substituted glycine trimer of dehydroabietylamine with antibacterial activity using various assays.\(^{14}\)

Wen Gu, et al. synthesized a series of N-substituted-1H-dibenzo\[a,c\]Carbazole derivatives of dehydroabietic acid and found that these are moderate antimicrobial agent against *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli* and *Pseudomonas fluorescens* and also they act as anti-fungal agents against *Candida albicans*, *Candida tropicalis* and *Aspergillus niger*.\(^{15}\)

Adyary Fallarero et al. reported (+)-dehydroabietic acid, an abietane-type diterpene was potentially inhibits the *Staphylococcus aureus*.\(^{16}\)

Abietane type diterpenoid derivatives as anti-inflammatory agents

The inflammation is associated with various diseases such as Alzheimer’s disease, asthama, multiple sclerosis, arthritis, diabetes mellitus, carcinoma, viral infections etc. which leads chronic inflammation.\(^{17,18}\) Hence, the control of inflammation is required. It can be done by controlling the mediators such as plasma proteases, prostaglandins, leukotrienes, histamine, nitric oxide etc.\(^{19,20}\) through various process including COX, LOX, Capseses, Kinases etc.\(^{21,22}\)
Nobuyuki Takahashi et al. described that abietic acid suppresses the inflammation effect through the control of tumour necrosis factor-K and inhibiting cycloxygenase 2.23 Wendell, W. W. et al. synthesized some derivatives of dehydroabietylamine, which are potential inhibitors of phospholipase-A$_2$ (PLA$_2$) and topical anti-inflammatory agents.13

**Abietane diterpenoid derivatives as anticonvulsant agents**

Alan Talevi et al. described that the anticonvulsant activity of abietic acid and it is potent one with concentration of 30 and 100 mg/kg was confirmed in the Maximal Electroshock Test, both orally and intraperitoneally.24

**Abietane diterpenoid derivatives as antitumor agents**

Now-a-days cancer is one of the most common diseases and affects the majority of people. A number of anticancer agents were reported for the treatment of various kind of cancer. But, the main disadvantage of these agents is their side effects such as cytotoxicity towards to healthy cells and lack of selectivity and specificity for cancer cells. Therefore there is a lot of research is going on to investigate the anti cancer drugs with high specificity and less cytotoxicity from many years. From this point of view chemists are actively synthesized dehydroabietylamine derivatives and reported the potential one. Xiaoping Rao et al. reported that α-aminophosphonates of Dehydroabietylamine were potential anticancer agents against *SMMC7721 liver cancer cells*.25

Miguel A. González et al. were synthesized dehydroabietic acid derivatives and screened them for cytotoxic, antimycotic and antiviral activities; the results revealed that they are moderate agents as cytotoxic but neither antimycotic nor antiviral agents.26
Miguel A. González et al. were synthesized dehydroabietic acid derivatives and screened them for cytotoxic and antimycotic activities, the results revealed that they are moderate agents.\textsuperscript{10}

Bibiana Zapata et al. were synthesized 14-hydroxyabietane derivatives and found that they are moderate to good agents for cytotoxic and antimycotic activities.\textsuperscript{27}

**Abietane diterpenoid derivatives as antioxidant agents**

Antioxidants are the substances present at low concentrations and significantly prevent oxidation caused by “Reactive oxygen species”. Wang et al. were reported the antioxidant activity of diterpenes from taiwania cryptomerioides and majorly the abietane diterpenoids are good antioxidants compared other active principle present in it.\textsuperscript{28}

**Abietane diterpenoid derivatives as antimalarial agents**

Ramzi A. Mothana et al. were isolated five abietane-type diterpenes; screened them for \textit{in vitro} antiprotozoal activity against erythrocytic schizonts of \textit{Plasmodium} falciparum, intracellular amastigotes of leishmania infantum and trypanosoma cruzi and free trypomastigotes of \textit{T. brucei}. Among them 5,6-didehydro-7-hydroxy-taxodone showed remarkable activity.\textsuperscript{29}

**2.2 Synthesis of dehydroabietyl amine and abietic acid derivatives**

The required dehydroabietylamine and abietic acid were purchased from chemical firms. The derivatives of dehydroabietylamine were synthesized according to the Scheme 2.1. Here we synthesized the derivatives by either condensing the aliphatic ester with dehydroabietylamine or alklyting the dehydroabietylamine with aliphatic halide or by reacting acid chloride with dehydroabietylamine to afford the desired products.
Scheme 2.1

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>$R_1-X$</th>
<th>2(a-f)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>$\text{F}_3\text{C}O\text{O}$</td>
<td>2a</td>
<td>58</td>
</tr>
<tr>
<td>2.</td>
<td>$\text{Br}_3\text{C}O\text{O}$</td>
<td>2b</td>
<td>59</td>
</tr>
<tr>
<td>3.</td>
<td>$\text{Cl}$</td>
<td>2c</td>
<td>60</td>
</tr>
<tr>
<td>4.</td>
<td>$\text{Br}$</td>
<td>2d</td>
<td>34</td>
</tr>
<tr>
<td>5.</td>
<td>$\text{Cl}$</td>
<td>2e</td>
<td>63</td>
</tr>
<tr>
<td>6.</td>
<td>$\text{Cl}$</td>
<td>2f</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 2.1 Dehydroabietylamine derivative
The derivatives of abietic acid were synthesized according to the \textbf{Scheme 2.2} and \textbf{Scheme 2.3}. First we convert the acid (3) into its acid chloride (4) by reacting with oxylyl chloride in dichloromethane at 0 °C – RT. Then, the acid chloride (4) is treated with various amines to afford the desired amides. Further, these amides were reduced to get amines. And also the abietic acid (3) was reduced to corresponding alcohol using Lithium aluminium hydride in dry tetrahydrofuran under nitrogen atmosphere.

\begin{center}
\includegraphics[width=\textwidth]{scheme2.png}
\end{center}

\textbf{Reagents and Reaction Conditions:} \textbf{Step 1:} oxylyl chloride (1.2 eq.)/dichloromethane, 0 °C–RT. \textbf{Step 2:} aliphatic amines (1.2 eq.)/dry tetrahydrofuran, under N\textsubscript{2} atmosphere.

\textbf{Scheme 2.2}
Reagents and Reaction Conditions: LiAlH₄ (1.5 eq.)/Dry Tetrahydrofuran; Under N₂ atmosphere

Scheme 2.3

Table 2.2 Derivatives of abietic acid

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>R₂—X</th>
<th>5(a-d) &amp; 6(a-c)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NH₃</td>
<td>5a</td>
<td>48</td>
</tr>
<tr>
<td>2.</td>
<td>—NH₂</td>
<td>5b</td>
<td>50</td>
</tr>
<tr>
<td>3.</td>
<td>NH</td>
<td>5c</td>
<td>58</td>
</tr>
<tr>
<td>4.</td>
<td>OH</td>
<td>5d</td>
<td>48</td>
</tr>
<tr>
<td>5.</td>
<td>Reduction of 5a</td>
<td>6a</td>
<td>48</td>
</tr>
<tr>
<td>6.</td>
<td>Reduction of 5b</td>
<td>6b</td>
<td>30</td>
</tr>
<tr>
<td>7.</td>
<td>Reduction of 5c</td>
<td>6c</td>
<td>35</td>
</tr>
<tr>
<td>8.</td>
<td>Reduction of 3</td>
<td>7</td>
<td>58</td>
</tr>
</tbody>
</table>
2.3 Experimental section

2.3.1 Materials and methods

All starting synthetic reagents were purchased from Sigma-Aldrich, Merck and S D fine chemicals and used without purification. All reactions in anhydrous solvents were performed in flame-dried glassware under an inert atmosphere of dry nitrogen. The progress of chemical reactions was monitored by thin-layer chromatography on silica gel 60- F254 plates E. Merck silica gel aluminium plates and visualized with UV light. The following mobile phases were employed for TLC, chloroform and methanol mixture or hexane and ethyl acetate mixture with appropriate ratios. The instrumental techniques used for the characterization of the newly synthesized compounds include $^1$H and $^{13}$C NMR and mass spectroscopy. $^1$H and $^{13}$C NMR spectra were recorded on a (400 and 75 MHz) Fourier transform spectrophotometer in CDCl₃ or DMSO-d₆ solution using tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in ppm relative to TMS. The melting points were determined on Selaco melting point apparatus and are uncorrected.

2.3.2 Protocols followed to synthesize the derivatives

2.3.2.1 Procedure followed for the synthesis of Dehydroabietylamine (DHA) derivatives:

**Synthesis of N- [{[(1R, 4aS)-1, 2a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl]methyl]-2, 2, 2-trifluoroacetamide (2a):** To a solution of dehydroabietylamine (1.0 eq. 6.23 mmol) in dry tetrahydrofuran (25 mL) was added triethylamine (2.0 eq. 12.46 mmol) at 0 °C under N₂ atmosphere followed
by trifluoroethyl acetate (1.1 eq. 6.85 mmol). The resultant reaction mixture was heated at 65 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with dilute HCl (20 mL). Then the reaction mass was diluted with ethyl acetate (40 mL) and organic layer was separated and washed with water (2*20 mL), brine (2*20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to get a pale yellow oil. The crude was purified over neutral silica gel of mesh 60-120 and eluted the desired product with 10% to 20% ethyl acetate in n-hexane to afford the pure amide (1.37 g, 58%).

**Synthesis of N- [{(1R, 4aS)-1, 2a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl]methyl}-2, 2, 2-tribromoacetamide (2b):** To a solution of dehydroabietylamine (1.0 eq. 6.23 mmol) in dry tetrahydrofuran (25 mL) was added triethylamine (2.0 eq. 12.46 mmol) at 0 °C under N₂ atmosphere followed by tribromoethyl acetate (1.1 eq. 6.85 mmol). The resultant reaction mixture was heated at 65 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with dilute HCl (20 mL). Then the reaction mass was diluted with ethyl acetate (40 mL) and organic layer was separated and washed with water (2*20 mL), brine (2*20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to get yellow oil. The crude was purified over neutral silica gel of mesh size 60-120 and eluted the desired product with 10% to 20% ethyl acetate in n-hexane to afford the pure amide (1.37 g, 58%).

**Synthesis of N- [{(1R, 4aS)-1, 4a-dimethyl-7-(propan-2-yl)-1,2,3,4,4a, 9, 10, 10a-octahydrophenanthren-1-yl] methyl} acetamide (2c):** To a solution of dehydroabietylamine (1.0 eq. 6.23 mmol) in tetrahydrofuran (20 mL) was added triethylamine (2.0 eq. 12.46 mmol) at 0 °C under N₂ atmosphere followed by acetyl
chloride (1.1 eq. 6.85 mmol). The resultant reaction mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with dilute HCl (20 mL). Then the reaction mass was diluted with ethyl acetate (40 mL) and organic layer was separated and washed with water (2*20 mL), brine (2*20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to get a yellow oil. The crude was purified over neutral silica gel of mesh size 60-120 and the desired product was eluted with 10% to 20% ethyl acetate in n-hexane to get pure amide (2.07 g, 60%).

Synthesis of N-benzyl-1-((1R, 4aS)-7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl)methanamine (2d): To a solution of dehydroabietylamine (1.0 eq. 6.23 mmol) in tetrahydrofuran (25 mL) was added triethylamine(2.0 eq. 12.46 mmol) at 0 °C followed by benzyl bromide (1.1 eq. 6.85 mmol). The resultant reaction mixture was heated at 65 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with dilute HCl (20 mL). Then the reaction mass was diluted with ethyl acetate (40 mL) and organic layer was separated and washed with water (2*20 mL), brine (2*20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to get yellow oil. Then it is triturated with dry ether yields a white precipitate. Ether was decanted; precipitate was washed with ether several times to get of pure amine (0.93 g, 34%).

Synthesis of [(1R, 4aS)-1,4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl] methyl](triphenylmethyl)amine (2e): To a solution of dehydroabietylamine (1.0 eq. 6.23 mmol) in tetrahydrofuran (25 mL) was added triethylamine(2.0 eq. 12.46 mmol) at 0 °C followed by triphenylmethyl chloride (1.1 eq. 6.85 mmol). The resultant reaction mixture was stirred at room temperature. After
completion of the reaction (monitored by TLC), the reaction mixture was quenched with dilute HCl (20 mL). Then the reaction mass was diluted with ethyl acetate (40 mL) and organic layer was separated and washed with water (2*20 mL), brine (2*20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to get yellow oil. Then it is trititated with dry ether yields a white precipitate. Ether was decanted; precipitate was washed with ether several times to get of pure amine (2.1 g, 63%).

**Synthesis of N-(((1R, 4aS)-7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl)methyl)benzamide (2f):** To a solution of dehydroabietylamine (1.0 eq. 6.23 mmol) in tetrahydrofuran (20 mL) was added triethylamine (2.0 eq. 12.46 mmol) at 0 °C under N₂ atmosphere followed by benzoyl chloride (1.1 eq. 6.85 mmol). The resultant reaction mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with dilute HCl (20 mL). Then the reaction mass was diluted with ethyl acetate (40 mL) and organic layer was separated and washed with water (2*20 mL), brine (2*20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to get a yellow oil. The crude was purified over neutral silica gel of mesh size 60-120 and the desired product was eluted with 10% to 20% ethyl acetate in n-hexane to get pure amide (2.07 g, 60%).

2.3.2.2 Procedure followed for the synthesize abietic acid derivatives

**Synthesis of (1R, 4aR)-1, 4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 7, 10a-decahydrophenanthrene-1-carbonyl chloride (4):** To a solution of dihydroabiatic acid (1.0 eq. 9.95 mmol), in dichloromethane (30 mL) at 0 °C under N₂ atmosphere, oxyl chloride (2.5 eq. 24.88 mmol) was added followed by DMF (0.1 mL). The resultant reaction mixture was heated at 60 °C. After completion of the
reaction (monitored by TLC), the reaction mixture was concentrated under vacuum in
under N₂ atmosphere to remove the excess of oxlyl chloride and to afford yellow oil
(2.98 g, 93%). The product (acid chloride) was used immediately for the next step
without any purification.

Synthesis {[(1R, 4aR)-1,4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 10, 10a-decahydrophenanthren-1-yl] methyl} amine (5a): Excess of ammonia gas was
purged into stirred a solution of dihydroabietic acid chloride (1.0 eq. 9.28 mmol) in
dichloromethane at 0 °C under N₂ atmosphere for 3 hours and continued stirring for
overnight. After completion of the reaction (monitored by TLC), it is quenched with
3N hydrochloric acid and extracted with dichloromethane (2*25 mL). Then the
combined dichloromethane layer was washed successively with dilute HCl (2*25
mL), saturated sodium bicarbonate solution (2*25 mL), brine solution (2*25 mL), and
with water (2*25 mL). Finally the dichloromethane layer was dried over anhydrous
sodium sulfate and concentrated under vacuum to get a pale yellow solid. The crude
was purified over neutral silica gel of mesh size 60-120 and the desired product was
eluted with 20% to 35% ethyl acetate in n-hexane to get pure amide (1.35 g, 48%).

Synthesis of (1R, 4aR)-N, N-diethyl-1, 4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 10a-decahydro-phenanthrene-1-carboxamide (5b): To a solution of
Dihydroabietic acid chloride (4) (1.0 eq., 6.23 mmol) in dichloromethane (30 mL) at 0
°C under N₂ atmosphere was added diethyl amine (1.1 eq. 6.85 mmol). The resultant
reaction mixture was stirred at room temperature overnight. After completion of the
reaction (monitored by TLC), the reaction mixture was extracted with
dichloromethane (2*25 mL), then the combined organic layer was washed with
NaHCO₃ solution (2*25 mL), water (2*25 mL), and brine (2*25 mL). Finally the
organic layer was dried over anhydrous sodium sulfate and concentrated under

72
Chapter 2

vacuum to get colorless oil. The crude was purified over neutral silica gel of mesh size 60-120 and the desired product was eluted with 20% to 35% ethyl acetate in n-hexane to get pure amide (1.02 g, 50%).

**Synthesis of (1R, 4aR)-N, 1, 4a-trimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 10, 10a-decahydrophenanthrene-1-carboxamide (5c):** To a solution of Dihydroabietic acid chloride (4) (1.0 eq., 6.23 mmol) in dichloromethane (30 mL) at 0 °C under N₂ atmosphere was added methylamine solution (1.1 eq. 6.85 mmol, 2M in THF). The resultant reaction mixture was stirred at room temperature overnight. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with dichloromethane (2*25 mL), then the combined organic layer was washed with NaHCO₃ solution (2*25 mL), water (2*25 mL), and brine (2*25 mL). Finally the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to get colorless oil. The crude was purified over neutral silica gel of mesh size 60-120 and the desired product was eluted with 20% to 35% ethyl acetate in n-hexane to get pure amide (1.15 g, 58%).

**Synthesis of {(1R, 4aR)-1-(ethoxymethyl)-1,4a-dimethyl-7-(propan-2-yl)-1,2,3,4,4a, 4b, 5, 6, 7,10a-decahydrophenanthrene (5d):** To a solution of Dihydroabietic acid chloride (4) (1.0 eq., 6.23 mmol) in dichloromethane (30 mL) at 0 °C under N₂ atmosphere was added excess of ethanol. The resultant reaction mixture was stirred at room temperature overnight. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with dichloromethane (2*25 mL), then the combined organic layer was washed with NaHCO₃ solution (2*25 mL), water (2*25 mL), and brine (2*25 mL). Finally the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to get crude. The crude was purified over neutral silica gel of mesh size 60-120 and the desired product was eluted
with 10% to 15% ethyl acetate in n-hexane to get pure amide (0.49 g, 48%).

**General Protocol for the reduction of amide to corresponding amine [6(a-c)]**

To a suspension of LiAlH$_4$ in tetrahydrofuran (4.0 eq. 1.33 mmol) in dry THF at 0-5 °C under N$_2$ atmosphere, amides (1.0 eq. 0.33 mmol) in dry tetrahydrofuran (20 mL) was added in drop wise over the period of 5 minutes. The resultant reaction mixture was stirred for 4 hrs (gradually allowing the temperature to rise to room temperature). After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated ammonium chloride solution and acidified with 3N hydrochloric acid. Then the reaction mixture was extracted ethyl acetate (3*25 mL), washed with water (3*25 mL), and then with brine (3*25 mL). Finally the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to get crude amine. The crude amine on treating with 2M hydrogen chloride in dry ether at 0 °C under N$_2$ atmosphere and then kept overnight at room temperature, solvent removed under vacuum and triturated with dry ether to get corresponding hydrochlorides salts of amine.
2.4 Characterization data

Synthesis of \(N\)\{-[(1R, 4aS)-1, 2a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl]methyl\}-2, 2-trifluoroacetamide (2a)

\[
\text{HNMR (CDCl}_3, \delta \text{ ppm): 7.19-7.21 (d, 1H), 7.03-7.05 (dd, 1H), 6.934-6.935 (d, 1H), 6.28 (bs, 1H), 3.30-3.32 (m, 2H), 2.94-2.99 (m, 1H), 2.82-2.89 (m, 2H), 2.33-2.36 (m, 1H), 1.78-1.87 (m, 4H), 1.42-1.52 (m, 3H), 1.29-1.30 (m, 1H), 1.25-1.28 (m, 6H), 1.01 (s, 3H), 0.87-0.90 (s, 3H).} \]

\[^{13}\text{C NMR (CDCl}_3, \delta \text{ ppm) 14.12, 18.6, 22.26, 23.96, 25.33, 30.14, 31.60, 33.35, 36.18, 37.42, 38.20, 45.93, 50.42, 112.3, 114.82, 117.2, 119.40, 124.0, 126.96, 134.44, 145.80, 146.60, 157.64; Mass=}396.42 (M+1), 358.40, 381.47.\]

Synthesis of \(N\)\{-[(1R, 4aS)-1, 2a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl]methyl\}-2, 2-tribromoacetamide (2b)

\[
\text{HNMR (CDCl}_3, \delta \text{ ppm): 7.21-7.23 (d, 1H), 7.05-7.07 (dd, 1H), 6.94-6.95 (d, 1H), 6.31 (bs, 1H), 3.31-3.32 (m, 2H), 2.96-2.98 (m, 1H), 2.81-2.88 (m, 2H), 2.31-2.37 (m, 1H), 1.81-1.87 (m, 4H), 1.43-1.52 (m, 3H), 1.29-1.32 (m, 1H), 1.27-1.29 (m, 6H),} \]
1.01 (s, 3H), 0.89-0.90 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), δ ppm) 14.14, 18.8, 22.32, 23.94, 25.36, 30.18, 31.68, 33.41, 36.18, 37.46, 38.18, 45.98, 50.52, 112.38, 114.92, 117.2, 119.45, 124.12, 126.91, 134.46, 145.88, 146.68, 157.65; LCMS=561.98 (M+1), 563.95(M+3), 565.97 (M+5).

Synthesis of \(N\)-\{[(1R, 4aS)-1, 4a-dimethyl-7-(propan-2-yl)-1,2,3,4,4a, 9, 10, 10a-octahydrophenanthren-1-yl] methyl\} acetamide (2c)

\[\begin{align*}
\text{2c}
\end{align*}\]

\(^1\)H NMR (CDCl\(_3\), δ ppm): 7.17-7.18 (d, 1H), 6.99-7.01 (dd, 1H), 6.90 (s, 1H), 5.51 (bs, 1H), 3.22-3.25 (m, 1H), 3.08-3.12 (m, 1H), 2.90-2.95 (m, 1H), 2.79-2.86 (m, 2H), 2.28-2.31 (dt, 1H), 1.98 (s, 3H), 1.65-1.91 (m, 5H), 1.36-1.43 (m, 3H), 1.26 (s, 3H), 1.22-1.25 (m, 6H), 0.94 (s, 3H); LCMS=327.60, 369.40 (corresponding to potassium adduct and 655.61 corresponding to dimer).

Synthesis of \(N\)-benzyl-1-\{[(1R, 4aS)-1, 4a-dimethyl-7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl]methanamine (2d)

\[\begin{align*}
\text{2d}
\end{align*}\]
1H NMR (CDCl₃, δ ppm): 7.54-7.55 (d, 2H), 7.32-7.34 (d, 3H), 6.97-6.99 (d, 1H), 6.78-6.85 (dd, 1H), 6.71 (s, 1H), 4.07 (s, 2H), 2.73-2.78 (m, 1H), 2.63-2.67 (m, 2H), 2.43-2.46 (d, 1H), 1.67-1.70 (m, 1H), 1.58-1.61 (m, 3H), 1.48 (s, 3H), 1.30-1.36 (m, 3H), 1.17 (m, 4H), 1.06-1.10 (m, 6H), 0.97 (s, 3H); Mass=376.73 (M+1).

Synthesis of [(1R, 4aS)-1,4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl] methyl](triphenylmethyl)amine (2e)

![Image of 2e]

1H NMR (CDCl₃, δ ppm): 7.54-7.55 (d, 2H), 7.32-7.34 (d, 3H), 6.97-6.99 (d, 1H), 6.78-6.85 (dd, 1H), 6.71 (s, 1H), 4.07 (s, 2H), 2.73-2.78 (m, 1H), 2.63-2.67 (m, 2H), 2.43-2.46 (d, 1H), 1.67-1.70 (m, 1H), 1.58-1.61 (m, 3H), 1.48 (s, 3H), 1.30-1.36 (m, 3H), 1.17 (m, 4H), 1.06-1.10 (m, 6H), 0.97 (s, 3H); HPLC purity=100%; LCMS=286.50 (M⁺) (minus the trityl group).

Synthesis of N-(((1R, 4aS)-7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl)methyl)benzamide (2f)

![Image of 2f]
\( ^1 \text{H NMR (CDCl}_3, \delta \text{ ppm): 7.72-7.73 (d, 2H), 7.47-7.50 (t, 1H), 7.40-7.43 (t, 2H), 7.18-7.23 (d, 1H), 6.98-6.99 (dd, 1H), 6.89 (s, 1H), 6.22 (s, 1H), 2.29-2.32 (d, 1H), 1.96-2.01 (m, 1H), 1.68-1.82 (m, 4H), 1.49-1.56 (m, 4H), 1.33-1.49 (m, 2H), 1.21-1.26 (m, 10H), 1.02 (s, 3H) LCMS=390.51.} \)

**Synthesis** \{[(1R, 4aR)-1,4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 10, 10a-decahydrophenanthren-1-yl] methyl\} amine (5a)

\[ \text{5a} \]

\( ^1 \text{H NMR (CDCl}_3, \delta \text{ ppm): 5.78 (s, 1H), 5.37-5.38 (t, 1H), 2.20-2.28 (m, 1H), 2.10-2.11 (m, 3H), 2.02 (s, 1H), 1.63-1.82 (m, 3H), 1.59-1.63 (m, 3H), 1.28-1.31 (m, 5H), 1.23-1.25 (m, 4H), 1.01-1.04 (m, 6H), 0.86 (s, 3H); Mass=301.67.} \)

**Synthesis of (1R, 4aR)-N, N-diethyl-1, 4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 10, 10a-decahydro-phenanthrene-1-carboxamide (5b)\)

\[ \text{5b} \]

\( ^1 \text{H NMR (CDCl}_3, \delta \text{ ppm): 5.77 (s, 1H), 5.38-5.39 (t, 1H), 3.47-3.51 (m, 2H), 3.33-3.72 (m, 2H), 2.17-2.23 (m, 3H), 2.06-2.08 (m, 3H), 1.80-1.90 (m, 2H), 1.61-1.63 (m, 2H), 1.32 (s, 3H), 1.21-1.26 (m, 6H), 1.12-1.14 (m, 6H), 1.00-1.03 (m, 6H), 0.85-0.98 (s, 5H); LCMS=357.90.} \)
Synthesis of (1R, 4aR)-N, 1, 4a-trimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 10, 10a-decahydrophenanthrene-1-carboxamide (5c)

\[
\text{5c}
\]

\(^1\)H NMR (CDCl \(_3\), \(\delta\) ppm): 5.78 (s, 1H), 5.37-5.38 (t, 1H), 2.20-2.28 (m, 1H), 2.26 (s, 3H), 2.10-2.11 (m, 3H), 2.02 (s, 1H), 1.63-1.82 (m, 3H), 1.59-1.63 (m, 3H), 1.28-1.31 (m, 5H), 1.23-1.25 (m, 3H), 1.01-1.04 (m, 6H), 0.86 (s, 3H); LCMS= 327.60.

Synthesis of (1R, 4aR)-1-(ethoxymethyl)-1,4a-dimethyl-7-(propan-2-yl)-1,2,3,4,4a, 4b, 5, 6, 7,10a-decahydrophenanthrene (5d)

\[
\text{5d}
\]

\(^1\)H NMR (CDCl \(_3\), \(\delta\) ppm): 5.78 (s, 1H), 5.37-5.38 (d, 1H), 4.04-4.75 (m, 2H), 2.81-2.93 (m, 1H), 2.20-2.33 (m, 1H), 2.04-2.12 (m, 2H), 1.70-1.85 (m, 4H), 1.45-1.65 (m, 6H), 1.20-1.30 (m, 12H), 0.97-1.03 (m, 3H).

Synthesis of [(1R, 4aR)-1,4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 10, 10a-decahydrophenanthren-1-yl] methyl] amine (6a)
1H NMR (CDCl, δ ppm): 5.78 (s, 1H), 5.37-5.38 (t, 1H), 2.20-2.28 (m, 1H), 2.10-2.11 (m, 3H), 2.02 (s, 1H), 1.63-1.82 (m, 3H), 1.59-1.63 (m, 3H), 1.28-1.31 (m, 5H), 1.23-1.25 (m, 4H), 1.01-1.04 (m, 6H), 0.86 (s, 3H); Mass=301.67.

Synthesis of [(1R, 4aR)-1,4a-dimethyl-7-(propan-2-yl)-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthren-1-yl]methanamine (6b)

1H NMR (CDCl, δ ppm): 5.78 (s, 1H), 5.37-5.38 (t, 1H), 2.67-2.69 (m, 1H), 2.42-2.44 (m, 1H), 2.20-2.28 (m, 1H), 2.10-2.11 (m, 3H), 2.02 (s, 1H), 1.63-1.82 (m, 3H), 1.59-1.63 (m, 3H), 1.28-1.31 (m, 5H), 1.23-1.25 (m, 4H), 1.01-1.04 (m, 6H), 0.86 (s, 3H); LCMS=288.2.

Synthesis of [(1R,4aR)-1,4a-dimethyl-7-(propan-2-yl)-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthren-1-yl]methyl]diethylamine (6c)
$^1$H NMR (CDCl$_3$, δ ppm): 5.77 (s, 1H), 5.38-5.39 (t, 1H), 3.47-3.51 (m, 2H), 3.33-3.72 (m, 2H), 2.39-2.40 (m, 1H), 2.12-2.15 (m, 1H), 2.17-2.23 (m, 3H), 2.06-2.08 (m, 3H), 1.80-1.90 (m, 2H), 1.61-1.63 (m, 2H), 1.32 (s, 3H), 1.21-1.26 (m, 6H), 1.12-1.14 (m, 6H), 1.00-1.03 (m, 6H), 0.85-0.98 (s, 5H); MS=345.

Synthesis of [(1R, 4aR)-1,4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 7,10a-decahydrophenanthren-1-yl] methanol (7)

\[ \text{Synthesis of [(1R, 4aR)-1,4a-dimethyl-7-(propan-2-yl)-1, 2, 3, 4, 4a, 4b, 5, 6, 7,10a-decahydrophenanthren-1-yl] methanol (7)} \]

$^1$H NMR (CDCl$_3$, δ ppm): 5.78 (s, 1H), 5.40-5.41 (t, 1H), 3.46-3.49 (m, 1H), 3.14-3.24 (m, 1H), 2.08-2.24 (m, 1H), 2.01-2.08 (m, 2H), 1.80-1.88 (m, 2H), 1.51-1.60 (m, 6H), 1.37-1.41 (m, 2H), 1.21-1.26 (m, 2H), 1.03-1.05 (m, 1H), 1.00-1.02 (m, 6H), 0.89 (s, 3H), 0.83 (s, 3H); Mass = 286.01 (found).
2.6 Bibliography


APPENDICES
Chapter 2

$^1$H NMR Spectra of compound 2a

$^{13}$C NMR Spectra of compound 2a
Chapter 2

Mass Spectra of compound 2a

$^1$H NMR Spectra of compound 2c
Chapter 2

Mass Spectra of compound 2c

$^1$H NMR Spectra of compound 2d
Chapter 2

Mass Spectra of compound 2d

'H NMR Spectra of compound 2e
Chapter 2

$^1$H NMR Spectra of compound 2f

Mass Spectra of compound 2f