STUDIES TOWARD THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE MARTINELLA ALKALOIDS

by

VIVEK BADARINARAYANA

Presented to the Faculty of the Graduate School of The University of Texas at Arlington in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS AT ARLINGTON

August 2006
Copyright © by Vivek Badarinarayana 2006
All Rights Reserved
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Professor Carl Lovely for his patience, guidance and encouragement throughout my graduate studies. His technical and editorial skills were essential in completing this dissertation. His sound knowledge in chemistry helped me overcome the different obstacles that I encountered during my research. In addition, I would like to thank the members of my committee, Professors Martin Pomerantz, Rasika Dias, Dmitry Rudkevich, Frederick MacDonnell and Subhrangsu Mandal for their time and valuable advice during the course of my research.

I would also like to thank the past and present members of the Lovely group, Dr. Hossen Mahmud, Dr. Hema Seshadri, Dr. Yingzhong Chen, Dr. Greg Browning, Dr. Hongwang Du, Dr. Yong He, Ms Helen Wu, Mr. Brian Wayland, Mr. Christian Madu, Ms. Lesley Schmid, Dr. Sivappa Rasapalli, Dr. Pasupathy Krishnamoorthy, Mr. Sabuj Mukherjee, Mr. Panduka Koswatta, Vindana Ekanayake, Heather Fenton, Karuna Koda, and Manoj Bhandari. Additional thanks go to Dr. Shreeyukta Singh, and Mr. Chuck Savage for their assistance. Very special thanks to Ganeshram Iyer and Rama Konduri for their help, and support.
Financial support from the Robert A. Welch Foundation and The University of Texas at Arlington are gratefully acknowledged. I owe a debt of gratitude to my parents, and brother for their continued guidance and encouragement. Finally, I would like to thank my wife, Mallika, for her support, patience and encouragement during the last 4 years; none of this would have been possible without her.

March 13, 2006
ABSTRACT

STUDIES TOWARD THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE MARTINELLA ALKALOIDS

Publication No. ______

Vivek Badarinarayana, PhD.

The University of Texas at Arlington, 2006

Supervising Professor: Dr. Carl J. Lovely

This dissertation consists of two parts. The first part describes the enantioselective total synthesis of martinellic acid. The Martinella alkaloids have attracted considerable attention in the synthetic community over the past few years. This interest is due in large part to their unique structure and useful biological activity (bradykinin receptor antagonist). In model systems we have successfully used the [3+2] azomethine ylide-alkene cycloaddition to construct the heterocyclic core of these alkaloids. The enantioselective approach described herein also involves the azomethine ylide-alkene cycloaddition as a key step in the total synthesis. The pyrrolo[3,2-
c]quinoline core of this alkaloid was constructed in an enantioselective fashion by the elaboration of an N-aryl pyrrolidinone, which was obtained via Pd-catalyzed aryl amination reaction using a non-racemic lactam. Pirkle’s chiral solvating agent was successfully used to demonstrate the stereochemical integrity of not only the N-aryl lactam (obtained by Pd-catalyzed cross-coupling) but also the cycloaddition precursor and the cycloaddition product (tetracyclic pyrroloquinoline core). The tetracyclic compound obtained via the azomethine ylide-alkene cycloaddition was elaborated to (-)-martinellic acid in 11 steps and 6% overall yield.

The second part of this dissertation describes application of several novel organometallic complexes for carrying out various organic transformations. A fluorinated tris(pyrazolyl)borato silver(I) complex catalyzes the addition of ethyl diazoacetate to benzene rings, providing norcaradienes, which undergo electrocyclization to provide the corresponding cycloheptatriene (the Büchner reaction). These reactions are surprisingly selective for addition to the aromatic moiety rather than C–H insertion. A copper complex containing a fluorinated triazapentadienyl ligand has been used to catalyze some carbene and nitrène addition and insertion chemistry. Nitrène addition occurs rapidly and with both aryl and alkyl substituted olefins providing the corresponding aziridine. The carbene transfer reactions that were attempted include C-H insertion, O-H insertion and N-H insertion, of which the latter two were very efficient.
# TABLE OF CONTENTS

ACKNOWLEDGEMENTS........................................................................................................ iii

ABSTRACT ................................................................................................................................ v

LIST OF ILLUSTRATIONS.................................................................................................. xiii

LIST OF TABLES................................................................................................................ xv

PART I – STUDY TOWARD THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE MARTINELL ALKALOIDS ......................................................... 1

1. INTRODUCTION ........................................................................................................... 2

1.1 Martinella alkaloids .......................................................... 2

1.2 Synthetic efforts toward construction of pyrrolo[3,2-c]quinoline core... 3

1.2.1 Earliest reports on pyrrolo[3,2-c]quinoline synthesis .............. 3

1.2.2 More recent approaches .................................................... 4

1.3 Total synthesis of (±)-martinellic acid.............................................. 29

1.4 Enantioselective total synthesis of (-)-martinellic acid .............. 35

2. RESULTS AND DISCUSSION................................................................................... 38

2.1 Initial efforts......................................................................................... 38

2.2 Pd-catalyzed coupling of a chiral lactam with aryl bromides........ 40

2.3 Proposed synthetic route toward the synthesis of pyrroloquinoline core ................................................................................................................. 43
2.4 Demonstrating the enantiomeric purity of the substrates ........................ 64

3.  EXPERIMENTAL DETAILS ....................................................................... 71
3.1 General procedures .............................................................................. 71

PART II – METAL CATALYZED ORGANIC TRANSFORMATIONS ............... 97

4.  INTRODUCTION ......................................................................................... 98
4.1 Carbene and nitrene chemistry ............................................................ 98
4.2 Catalysts for metal carbene transformation ........................................ 98
4.3 Tris(pyrazolyl)borates ......................................................................... 101
4.4 Application of tris(pyrazolyl)borates in catalysis ............................... 104

5.  RESULTS AND DISCUSSION ................................................................. 110
5.1 Silver-catalyzed Bűchner reactions ..................................................... 110
5.2 Copper-catalyzed nitrene insertion ..................................................... 115
5.3 Copper-catalyzed cyclopropanation .................................................... 116
5.4 Copper-catalyzed N-H and O-H insertion .......................................... 117

6.  EXPERIMENTAL DETAILS ....................................................................... 119

APPENDIX

1. $^1$H NMR AND $^{13}$C NMR SPECTRA OF
   2-[(5S)-5-TERT-BUTYLDIMETHYLSILYLOXYMETHYL]-2-OXO-1-PYRROLIDINYL BENZONITRILE 170a ......................................................... 121

2. $^1$HNMR AND $^{13}$C NMR SPECTRA OF
   (5S)-5-TERT-BUTYLDIMETHYL-1-(2-NITROPHENYL)-2-PYRROLIDINONE 170b .......................................................... 125

3. $^1$H AND $^{13}$C NMR SPECTRA OF
METHYL 5-NITRO-2-[(5S)-5-\{[(TERT-BUTYL)DIMETHYLSILOXY]}-2-OXO-1-PYRROLIDINONE] BENZOATE 174 ................................................................................................................. 129

4. $^1$H AND $^{13}$C NMR SPECTRA OF METHYL 5-AMINO-2-[(5S)-5-\{[(TERT-BUTYL)DIMETHYLSILOXY]}-2-OXO-1-PYRROLIDINONE] BENZOATE 175 ................................................................................................................. 133

5. $^1$H AND $^{13}$C NMR SPECTRA OF METHYL 5-AMINO-2-[(5S)-5-\{[(TERT-BUTYL)DIMETHYLSILOXY]}-2-OXO-1-PYRROLIDINONE] BENZOATE 176b .................. 137

6. $^1$H AND $^{13}$C NMR SPECTRA OF (5S)-5-(HYDROXYETHYL)-2-PYRROLIDINONE ........................................................................................................ 141

7. $^1$H AND $^{13}$C NMR SPECTRA OF (5S)-5-[(TERT-BUTYL)DIMETHYLSILYLOXY]-2-PYRROLIDINONE 184 ................................................................................................................. 144

8. $^1$H AND $^{13}$C NMR SPECTRA OF 4-[(5S)-5-CYANOMETHYL-2-OXO-1-PYRROLIDINYL]BENZONITRILE 185a ......................................................... 147

9. $^1$H AND $^{13}$C NMR SPECTRA OF 4-[(5S)-5-(CARBOXYMETHYL)METHYL-2-OXO-1-PYRROLIDINYL]BENZONITRILE 185b ................................................. 151

10. $^1$H AND $^{13}$C NMR SPECTRA OF 4-[(5S)-5-[(TERT-BUTYL)DIMETHYLSILYLOXY]-2-OXO-1-PYRROLIDINYL]BENZONITRILE 185c .. 155

11. $^1$H AND $^{13}$C NMR SPECTRA OF 4-[(5S)-5-CYANOMETHYL-2-OXO-1-PYRROLIDINYL]BENZONITRILE 185d ......................................................... 159

12. $^1$H AND $^{13}$C NMR SPECTRA OF 2-(CARBOMETHOXY)METHYL 5-NITRO-2-[(5S)-5-\{[(TERT-BUTYL)DIMETHYLSILYLOXY]}-2-OXO-1-PYRROLIDINYL] BENZOATE 185e ......................................................... 163

13. $^1$H AND $^{13}$C NMR SPECTRA OF 2-(CARBOMETHOXY)METHYL 5-AMINO-2-[(5S)-5-\{[(TERT-BUTYL)DIMETHYLSILYLOXY]}-2-OXO-1-PYRROLIDINYL]
<table>
<thead>
<tr>
<th></th>
<th>Chemical Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF METHYL 5-IODO-2-[(5S)-5-(HYDROXYETHYL)-2-OXO-1-PYRROLIDINYL] BENZOATE</td>
</tr>
<tr>
<td>15</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF METHYL 5-IODO-2-[(5S)-5-(ETHYNYL)-2-OXO-1-PYRROLIDINYL] BENZOATE</td>
</tr>
<tr>
<td>16</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF METHYL 5-IODO-2-[(5S)-5-(ETHYNYL)-2-OXO-1-PYRROLIDINYL] BENZOIC ACID</td>
</tr>
<tr>
<td>17</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF (5S)-5-(ETHYNYL)-1-[4-IODO-2-(HYDROXYMETHYL)PHENYL-2-PYRROLIDINONE</td>
</tr>
<tr>
<td>18</td>
<td>$^1$H NMR SPECTRUM OF 4-IODO-2-(HYDROXYMETHYL)-1-[(2S)-5-HYDROXY-1-BUTYLAMINO]BENZENE</td>
</tr>
<tr>
<td>19</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF ETHYL-4-METHOXY-4-IODO-2-(HYDROXYMETHYL)-1-[(2S)-5-HYDROXY-1-BUTYLAMINO]BENZENE</td>
</tr>
<tr>
<td>20</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF (5S)-5-ETHENYL-1-[4-IODO-2-FORMYLPHENYL]-2-PYRROLIDINONE</td>
</tr>
<tr>
<td>21</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF (3aS, 3bS, 11bS)-10-IODO-1,2,3,3a,4,5,11b-OCTAHYDRO-1-(PHENYL METHYL)-6H-DIPYRROLO[1,2-a:3',2'-c]QUINOLINE-6-ONE</td>
</tr>
<tr>
<td>22</td>
<td>$^1$H AND $^{13}$C NMR SPECTRA OF ETHYL-(3/4)-(3aS, 4S, 9bS)-8-IODO-2,3,3a,4,5,9b-HEXAHYDRO-1-(PHENYL METHYL)-1H-PYRROLO[3,2-c]QUINOLINE-4-PROPANOL</td>
</tr>
<tr>
<td>23</td>
<td>$^1$H NMR AND $^{13}$C NMR SPECTRUM OF (3aS, 3bS, 11bS)-10-CARBOXYMETHYL-1,2,3,3a,4,5,11b-OCTAHYDRO-1-(PHENYL METHYL)-6H-DIPYRROLO[1,2-a:3',2'-c]QUINOLINE-6-ONE</td>
</tr>
</tbody>
</table>
24. $^1$H AND $^{13}$C NMR SPECTRA OF ETHYL-2,3,3,3-
(3aS, 4S, 9bS)-8-iodo-2,3,3a, 4,5,9b-hexahydro-5-(3-
oxabutanoyl)-1-(phenylmethyl)-1H-pyrrole[3,2-c]
quinoline-4-propyl acetate 198 .......................... 210

25. $^1$H AND $^{13}$C NMR SPECTRA OF ETHYL-2,3-
methyl (3aS, 4S, 9bS)-2,3,3a, 4,5,9b-hexahydro-5-(3-
oxabutonyl)-1-(phenylmethyl)-1H-pyrrole[3,2-c]
quinoline-8-carboxylate 199 .............................. 214

26. $^1$H AND $^{13}$C NMR SPECTRA OF ETHYL-2,3,3-
methyl (3aS, 4S, 9bS)-2,3,3a, 4,5,9b-hexahydro-5-(3-
oxabutonyl)-1-(phenylmethyl)-5-(trifluoromethyl)
-1H-pyrrole[3,2-c]quinoline-8-carboxylate 200 .......... 218

27. $^1$H AND $^{13}$C NMR SPECTRA OF ETHYL-2,3,3,3-
methyl (3aS, 4S, 9bS)-4-(3-azidopropyl)-2,3,3a, 4,5,9b-
hexahydro-5-(3-oxabutanoyl)-1-(phenylmethyl)-1H-
pyrrole[3,2-c]quinoline-8-carboxylate 202 .............. 221

28. $^1$H AND $^{13}$C NMR SPECTRA OF METHYL (3aS, 4S, 9bS)-4-(3-
aminopropyl)-2,3,3a, 4,5,9b-hexahydro-5-
(3-oxabutanoyl)-1-(phenylmethyl)-1H-pyrrole[3,2-c]
quinoline-8-carboxylate hydrochloride salt 132 ........ 225

29. $^1$H AND $^{13}$C NMR SPECTRA OF METHYL MARTINELLATE 142 228

30. $^1$H AND $^{13}$C NMR SPECTRA OF MARTINELLIC ACID 2 .......... 232

REFERENCES .................................................. 234

BIOGRAPHICAL INFORMATION .................................. 244
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Structure of martinelline and martinellic acid</td>
<td>3</td>
</tr>
<tr>
<td>1.2</td>
<td>Summary of the various routes used by different groups to synthesize the</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>pyrrolo[3,2-c]quinoline core of the <em>Martinella</em> alkaloids</td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>Pirkle’s chiral solvating agent 171</td>
<td>42</td>
</tr>
<tr>
<td>2.2</td>
<td>Expanded $^1$H NMR spectrum of (±)-170 + 4 eq 171 ($t$-butyl signal)</td>
<td>43</td>
</tr>
<tr>
<td>2.3</td>
<td>Expanded $^1$H NMR spectrum of (-)-170 + 4 eq 171 ($t$-butyl signal)</td>
<td>43</td>
</tr>
<tr>
<td>2.4</td>
<td>Proposed synthetic route toward the synthesis of the pyrroloquinoline</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>core of the <em>Martinella</em> alkaloids</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>Alternate synthetic route toward the synthesis of tricyclic triamine 132</td>
<td>47</td>
</tr>
<tr>
<td>2.6</td>
<td>New synthetic route toward the formation of the olefin</td>
<td>51</td>
</tr>
<tr>
<td>2.7</td>
<td>X-ray structure of the pyrroloquinoline core 194</td>
<td>58</td>
</tr>
<tr>
<td>2.8</td>
<td>Racemic and non-racemic substrates for enantiomeric purity analysis</td>
<td>65</td>
</tr>
<tr>
<td>2.9</td>
<td>Expanded $^1$H NMR spectrum of (-) and (±)-193 (aldehyde signal)</td>
<td>66</td>
</tr>
<tr>
<td>2.10</td>
<td>Expanded $^1$H NMR spectrum of (-) and (±)-193 (aromatic signal)</td>
<td>67</td>
</tr>
<tr>
<td>2.11</td>
<td>Formation of diastereomeric solvates of (±)-193 in the presence of 171</td>
<td>68</td>
</tr>
<tr>
<td>2.12</td>
<td>Expanded $^1$H NMR spectrum of (-) and (±)-194 (aromatic signal)</td>
<td>69</td>
</tr>
<tr>
<td>2.13</td>
<td>Expanded $^1$H NMR spectrum of (-) and (±)-194 (benzylic proton signal)</td>
<td>69</td>
</tr>
<tr>
<td>4.1</td>
<td>Examples of chiral copper complex</td>
<td>100</td>
</tr>
</tbody>
</table>
4.2 Comparing pyrazolyl borates to common ligands................................. 102
4.3 First examples of fluorinated scorpionate metal complexes............... 103
4.4 Comparison bis(pyrazolyl)borate 234 and triazapentadienyl ligand 235…… 107
5.1 C-H insertion products from toluene and mesitylene......................... 114
5.2 Fluorinated ligands used for carbene and nitrene insertion
  reactions................................................................. 115
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Ratio of different products formed during radical cyclization</td>
<td>6</td>
</tr>
<tr>
<td>1.2 Yield for cycloaddition precursor and cycloaddition reaction</td>
<td>9</td>
</tr>
<tr>
<td>1.3 Ratio of products $30c$ and $30b$</td>
<td>10</td>
</tr>
<tr>
<td>1.4 Ratio of diastereomers of $53$</td>
<td>15</td>
</tr>
<tr>
<td>2.1 Results of Pd-catalyzed aryl-amidation using lactam $169$</td>
<td>42</td>
</tr>
<tr>
<td>2.2 Results of cross-coupling chemistry with series of lactams</td>
<td>53</td>
</tr>
<tr>
<td>2.3 Summary of optical rotation studies</td>
<td>63</td>
</tr>
<tr>
<td>5.1 Yields and isomer ratio of the silver catalyzed Büchner reaction of benzene derivatives with EDA</td>
<td>113</td>
</tr>
</tbody>
</table>
PART I STUDY TOWARD THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE MARTINELLA ALKALOIDS
CHAPTER 1

INTRODUCTION

1.1 Martinella alkaloids

Martinelline 1 and martinellic acid 2 were isolated from the root of *Martinella iquitosensis* by Witherup and co-workers from Merck Laboratories.¹ Earlier reports show that the root extract of this plant was used by 13 ethnolinguistic groups from eight different South American countries to cure eye ailments.² Further investigations by the Merck group showed that both these alkaloids function as bradykinin receptor antagonist (B₁ active at 6400 nM, B₂ active at 250 nM). Our interest in developing synthetic approaches towards these molecules is twofold – (a) these alkaloids are the only naturally occurring nonpeptidic bradykinin receptor antagonist and (b) the partially reduced pyrrolo[3,2-c]quinoline ring system inherent in these heterocycles is not found in any other naturally occurring alkaloid.
1.2 Synthetic efforts toward construction of pyrrolo[3,2-c]quinoline core

1.2.1 Earliest reports on pyrrolo[3,2-c]quinoline synthesis

There were only limited reports on the synthesis of pyrrolo[3,2-c]quinolines prior to the appearance of these alkaloids in the literature. The synthesis of 1H-pyrrolo[3,2-c]quinoline was first reported in 1934 and was obtained by decarboxylation of 1H-pyrrolo[3,2-c]quinoline-2,3-dicarboxylic acid. The dicarboxylic acid was obtained by oxidation of indolo[3,2-c]quinoline, which was a byproduct of alkali fusion of an indigo dye “Ciba yellow”. Grundon and McCorkindale synthesized the dihydro pyrrolo[3,2-c]quinolone core from diethyl (2-ethoxyethyl)malonate (3) and aniline in boiling diphenyl ether (Scheme 1.1).
The pyrrolo[3,2-c]quinoline 6 was prepared by dehydrogenation of the tricyclic lactam 5 with palladium on charcoal at high temperature. The carbonyl of lactam 5 was converted to chloride by treatment with POCl₃ and the resulting chloride was treated with a range of amines to form 7 (Scheme 1.2). The carbonyl in 5 can be converted to the corresponding chloride 8, which undergoes reduction on catalytic hydrogenation.

### Scheme 1.2

1.2.2 More recent approaches

In a large part motivated by the desire to develop approaches to the *Martinella* alkaloids, a number of groups have developed a variety of strategies to access the pyrrolo[3,2-c]quinoline heterocycles of this natural product. A discussion of these approaches is presented below:

#### i Radical cyclizations

Jones synthesized the pyrrolo[3,2-c]quinoline core of the *Martinella* alkaloids through the radical cyclization of the *N-(2′-iodophenyl)*pyrroles 12. The tertiary amide
was obtained by treating 2-iodoaniline with acryloyl chloride followed by alkylation with methyl iodide. The radical cyclization precursor 12 was obtained by treatment of 11 with tosylmethyl isocyanide and the resulting pyrrole was subjected to standard reductive radical cyclization conditions. The N-H pyrrole derivative 12, was a poor substrate, however, the incorporation of an N-Boc group substantially increased the yield of the cyclization. The higher yield with 15 can be attributed to the electron-withdrawing effect of the Boc group which effectively stabilizes the radical intermediate (Scheme 1.3).\(^{6a, b}\)

**Scheme 1.3**

\[
\begin{align*}
10 & \xrightarrow{i. CH_2=CHCOCl, Et_2O, 0^\circ C, 96\%} 11 \\
 & \xrightarrow{ii. MeI, NaH, THF, r. t., 81\%} 12 \\
12 & \xrightarrow{Boc_2O, Et_3N, THF, r. t., 99\%} 13 \\
12 & \xrightarrow{Bu_3SnH, AIBN, Toluene, reflux, 17\%} 14 \\
14 & \xrightarrow{Bu_3SnH, AIBN, Toluene, reflux, 57\%} 15 
\end{align*}
\]

A subsequent study of substituent effects was conducted by the same group with the related substrates. Along with the 6-endo-trig products 17, the formation of 6- exo 18 or 5- exo 19, was also observed in almost every case. In one example (Table 1.1, entry 5), the pyrrolo[3,2-c]quinoline 17e, was the only product in fair yield (Scheme 1.4).\(^{6b}\)
**Scheme 1.4**

![Scheme 1.4](image)

**Table 1.1 Ratio of different products formed during radical cyclization**

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>17 (%)</th>
<th>18 (%)</th>
<th>19 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Me</td>
<td>H</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>SEM</td>
<td>H</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>Me</td>
<td>Boc</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>SEM</td>
<td>CO$_2$Me</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>SEM</td>
<td>Me</td>
<td>43</td>
<td>-</td>
</tr>
</tbody>
</table>

**ii. 1,3-Dipolar cycloadditions of azomethine ylides**

There are two types of 1,3-dipolar cycloaddition of azomethine ylides and an olefin that have been used to construct the heterocyclic core of the *Martinella* alkaloids:

a) Intermolecular cycloaddition of azomethine ylides and b) Intramolecular cycloaddition of azomethine ylides.

a) Intermolecular cycloaddition of azomethine ylides

Hadden and Stevenson used an intermolecular cycloaddition of stabilized azomethine ylides to an electron deficient olefin to form suitably substituted pyrrolidine derivatives. The azomethine ylide was obtained from the imine (20, $R = Me$, $R_1 = R_2 =$...
H) derived from methyl glycinate and 2-nitrobenzaldehyde, using silver acetate at room temperature. The all-cis trisubstituted pyrrolidine 21, did not give the expected pyrrolo[3,2-c]quinoline 22 upon reduction with hydrogen and palladium, but gave an $\alpha$-amino acid ester (Scheme 1.5). A similar observation was also made by Nyerges when attempting a similar reaction between ethyl glycinate and various 2-nitrobenzaldehydes. Quinoline 24 is thought to be formed by the aromatization and elimination of an amino moiety from the $\beta$-amino imine 23. Although this approach was unsuccessful for construction of pyrrolo[3,2-c]quinoline, Hadden and Stevenson were able to develop methodology to synthesize chiral quinoline containing amino acids. In order to avoid the formation of the undesired quinoline 25, Nyerges and co-workers generated the azomethine ylides from 26, in the presence of ethyl acrylate as the dipolarophile. The resulting all-cis cycloadduct 27 was reduced with sodium sulfite to give the cis-fused pyrrolo[3,2-c]quinolines 28 in good yields (Scheme 1.6, Table 1.2).
Scheme 1.5

\[
\begin{align*}
R_1^\text{NO}_2 & \xrightarrow{\text{AgOAc, Toluene, DBU, r. t.}} R_2^\text{NO}_2 \\
R_1^\text{NH}_2 & \xrightarrow{10\% \text{ Pd/C, H}_2, \text{EtOH, r. t., 1 atm}} R_2^\text{NH}_2
\end{align*}
\]

Scheme 1.6

\[
\begin{align*}
R_1^\text{COOEt} & \xrightarrow{\text{AgOAc, Toluene, Et}_3\text{N, r. t.}} R_2^\text{COOEt} \\
R_1^\text{COOEt} & \xrightarrow{\text{Na}_2\text{S}_2\text{O}_4, \text{EtOH, H}_2\text{O, 55-60°C}} R_2^\text{COOEt}
\end{align*}
\]
Table 1.2 Yield for cycloaddition precursor and cycloaddition reaction

<table>
<thead>
<tr>
<th>R_1</th>
<th>R_2</th>
<th>Yield</th>
<th>Yield</th>
<th>Yield</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>76</td>
<td>79</td>
<td>72</td>
<td>98</td>
</tr>
<tr>
<td>MeO</td>
<td>MeO</td>
<td>82</td>
<td>85</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>OCH_2O</td>
<td>70</td>
<td>81</td>
<td>71</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>H</td>
<td>-</td>
<td>-</td>
<td>77</td>
<td>86</td>
</tr>
</tbody>
</table>

R = Me

b) Intramolecular cycloaddition of azomethine ylides

There were two independent communications in 1999,\textsuperscript{10,11} that described the synthesis of (tricyclic) pyrrolo[3,2-c]quinoline core by intramolecular 1,3-dipolar cycloadditions of non-stabilized azomethine ylides, using the same general strategy reported by Martin and Cheavens during their synthesis of tricyclic compounds \textsuperscript{30} (Scheme 1.7, Table 1.3).\textsuperscript{12} Our group evaluated an approach starting from anthranilic acid derivatives (\textsuperscript{31}).\textsuperscript{10}
Mahmud synthesized the unsaturated benzaldehyde derivative 32 by allylation of the sulfonamide 31, which was followed by a two step conversion of the carboxymethyl group to the aldehyde 32. This unsaturated benzaldehyde derivative 32 was then condensed with various N-alkylglycines, to provide the non-stabilized
azomethine ylide in situ, that undergoes cycloaddition with the alkene to form the expected cycloadduct 33 in good yield (Scheme 1.8).

The carboxymethyl group that is present at the C-7 position was incorporated via a Pd-catalyzed carboxylation reaction of the aryl bromide. The resulting tricyclic compound 34a underwent chemoselective hydrogenation removing the pyrrole nitrogen benzyl group. In a similar approach, He was able to synthesize the pyrrolo[3,2-c]quinoline core with a carbonyl moiety at the C-2 position through the cyclization of the acrylamide derivative 38 (Scheme 1.9). The carboxylation, as well as the deprotection of the benzyl group, was carried out in a similar fashion to that previously reported by this group. During these studies, it was found that nitrogen protection is required for the cycloaddition to occur. The acrylamide derivative 41 does not provide
the desired cycloadduct, but undergoes a decarboxylative Michael addition to form 42 (Scheme 1.10).\textsuperscript{14}

**Scheme 1.9**

\[
\begin{align*}
&\text{i. BzCl, NaHCO}_3, \\
&\text{CH}_2\text{Cl}_2, 95\% \\
&\text{ii. LiAlH}_4, \text{THF}, \\
&0\, ^\circ\text{C}, 93\% \\
&\text{iii. CH}_2\text{=CHCOCl,} \\
&\text{NaHCO}_3, \text{CH}_2\text{Cl}_2, 89\%
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \text{N} \\
& \text{OH} \\
& \text{Br} & \text{N} \\
36 & \text{37} & \text{38}
\end{align*}
\]

**Scheme 1.10**

Control experiments between the cycloaddition adduct, with various amines have helped establish, the mechanism of the decarboxylative Michael addition.\textsuperscript{13b}

Snider and co-workers\textsuperscript{11} developed a stereoselective eight step route, from 2-hydroxymethylaniline (43), to the tricyclic triamine core of the martinellic acid. The 2-hydroxymethylaniline was treated with vinylcyclopropane 44 to provide the \(N\)-arylprrrolidinone 45 which was oxidized using \(\text{MnO}_2\) to give the pyrrolidinone.
aldehyde 46. The intramolecular azomethine ylide cycloaddition was carried out by the condensation of N-benzylglycine with aldehyde 47 giving a 9:1 mixture of the \textit{exo}-46 and \textit{endo}-46 heterocycles. The major isomer was reduced with LiBH$_4$ to provide the amino alcohol 48, which was then elaborated to the tricyclic triamine 49 in five steps (Scheme 1.11).

\textbf{Scheme 1.11}

\begin{center}
\begin{tikzpicture}
  \node (43) at (0,0) {\ce{\text{NH}_2\text{OH}}};
  \node (44) at (2,0) {\ce{O\_\_O\_\_O\_\_Toluene, 65 \text{o}C, 2 d, 56\%}};
  \node (45) at (4,0) {\ce{\text{HO}N\_\_\_\_\_\_Toluene, reflux, 12 h}};
  \node (46) at (6,0) {\ce{\text{O}N\_\_\_\_\_\_MnO}_2, \text{CH}_2\text{Cl}_2, r. t., 12 h, 96\%}};
  \node (47) at (8,0) {\ce{\text{BnNHCH}_2\text{COOH}}};
  \node (48) at (10,0) {\ce{\text{exO-47 (68\%)}}};
  \node (49) at (12,0) {\ce{\text{xHCl}}};
  \node (50) at (14,0) {\ce{\text{BnNH}_2\text{COOH}}};
  \node (51) at (16,0) {\ce{\text{LiBH}_4, THF, MeOH, reflux, 6 d, 67\%}}};
\end{tikzpicture}
\end{center}

\textit{iii. Hetero Diels-Alder approach}

Batey and co-workers$^{15}$ reported a novel one-pot synthesis of substituted hexahydropyrrolo[3,2-c]quinolines, using a Lewis acid promoted three component coupling reaction of anilines 50, benzaldehydes 51 and an N-substituted 2-pyrroline
(52). The imine which is formed \textit{in situ} acts as a diene in a hetero Diels-Alder reaction, with the electron rich dienophile – the endocyclic enamine. The diastereoisomeric ratio was strongly solvent dependent, but, the selective preparation of the required \textit{exo}-adduct was not possible (Scheme 1.12, Table 1.4).

\textbf{Scheme 1.12}
Table 1.4 Ratio of diastereoisomers of 53

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
<th>R₇</th>
<th>Yield (%)</th>
<th>endo:exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>91</td>
<td>51:49</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>Cl</td>
<td>93</td>
<td>57:43</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>84</td>
<td>50:50</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>96</td>
<td>42:58</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>NO₂</td>
<td>96</td>
<td>53:47</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>CO₂Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>61</td>
<td>50:50</td>
</tr>
<tr>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>Cl</td>
<td>47</td>
<td>40:60</td>
</tr>
<tr>
<td>H</td>
<td>NO₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>Cl</td>
<td>65</td>
<td>55:45</td>
</tr>
</tbody>
</table>

In the absence of an aldehyde, an adduct formed, by the coupling of the anilines with two equivalents of pyrroline and was structurally similar to martinelline but the required exo-isomer (exo-55) was a minor component in a 5.6:1 mixture of the diastereoisomers (Scheme 1.13).
In order to improve the diastereoselectivity, changing the N-substituent on the 2-pyrroline component was investigated.\textsuperscript{16} Since ultimately a guanidine side chain had to be incorporated on the pyrrole nitrogen, and thioureas are useful guanidine precursors, an $\textit{N}$-thioamoyl group was considered as an $\textit{N}$-protecting group. The lanthanide triflate catalyzed hetero Diels-Alder reaction provided the pyrrolo[3,2-\textit{c}]quinolines (\textit{exo}-58, \textit{endo}-58) as a 7:3 mixture. The major isomer \textit{exo}-58, was transformed into a highly functionalized derivative of martinelline, containing two of the three guanidine side chains and an aryl group in place of the C-2 side chain (Scheme 1.14). Binding affinity studies of 60 against human bradykinin B\textsubscript{1} and human and rat B\textsubscript{2} receptors, suggests that the guanidine containing C-7 ester side chain, is of greater importance for B2 receptor antagonist activity than the C-2 aliphatic guanine side chain, similar to increased affinity of martinelline over martinellic acid.\textsuperscript{16}
Independently, Stevenson’s group studied this three component coupling and found anhydrous indium trichloride to be the most effective Lewis acid catalyst. This group focused on obtaining a cycloadduct with an alkyl side chain attached to the C-2 position and a protecting group on nitrogen that can be easily removed. Initial examples with imines derived from aliphatic aldehydes did not work well and reaction with imines obtained from methyl glyoxalate, gave poor yields of mixtures of *endo* and *exo* isomers (2:1).\(^{17,18}\) The reaction of \(52\) with imine \(61\), which was derived from cinnamaldehyde, gave a 1.1:1 mixture of the *exo* and *endo* stereoisomers of \(62\) (Scheme 1.15),\(^{19}\) which after separation of the *exo* isomer was suitable for further elaboration.
The side chain at the C-2 position was elaborated by first converting the alkene portion to aldehyde 63 via ozonolysis of the corresponding trifluoroacetamide. The resulting aldehyde was then subjected to Wittig reaction with a nitrile stabilized ylide to give a 2:1 mixture of (Z) and (E)-unsaturated nitrile (64). The reduction of the nitrile, followed by selective deprotection of the nitrogen group provided 65, which contains the central core of the Martinella alkaloids (Scheme 1.16). The same group also described the synthesis of the parent C-2 truncated hexahydropyrrolo[3,2-c]quinoline (67) from 66 and 52 in 43% yield. Neither Lewis, nor protic acids, were required to effect this transformation. Hurvois and co-workers reported a similar transformation using BF₃.OEt as a catalyst. The cycloadduct obtained, was further functionalized at C-2 position, via a diastereoselective anodic cyanation (Scheme 1.17).
Hetero Diels-Alder chemistry was used to synthesize a potent antibacterial agent \( \text{72} \) starting from \( \text{69} \), \( \text{70} \) and \( \text{71} \) in one step. This molecule \( \text{72} \), is effective against methicillin-resistant \textit{Staphylococcus Aureus in vitro}. The pyrrolo[3,2-\text{c}]quinolines coupled to an indole ring were obtained in a 2:1 ratio of \textit{cis} to \textit{trans}-isomers (Scheme 1.18).\(^{21} \) Two total syntheses of martinelline were reported which utilized the imino-Diels Alder strategy to assemble the pyrrolo[3,2-\text{c}]quinoline core, these will be discussed later.
Gurjar and co-workers used a Heck strategy to construct hexahydropyrrolo[3,2-c]quinoline ring system. The reaction between iodobenzene (73) with 4,5-dihydropyrrole (prepared from 2-aminoethenol in 5 steps) gave the tricyclic compound 75 in 1 step. The Heck reaction was accompanied by the tandem cyclization between the amine and the carbethoxy group. The hexahydropyrrolo[3,2-c]quinoline 76 was obtained by the catalytic reduction of the double bond in the pyrrole ring (Scheme 1.19). 22

An alternate example of a palladium catalyzed Heck reaction, was used to synthesize 3-alkyl-1-arylpyrrolo[3,2-c]quinoline 79, which were investigated for anti-ulcer activities. One approach was based on the intramolecular cyclization of 4-(N-allyl-N-aryl)amino-3-iodoquinolines (77). The same derivatives were obtained by the palladium-catalyzed
heteroannulation with 1-trimethylsilylalkynes and sequential desilylation (Scheme 1.20).\textsuperscript{22, 23}

\textbf{Scheme 1.20}

\[ \text{Heteroannulation with 1-trimethylsilylalkynes and sequential desilylation} \]

\begin{align*}
\text{R}_1 & \quad \text{Me} \\
\text{R}_2 & \quad \text{Me} \\
\text{R}_3 & \quad \text{Me} \\
\text{R}_4 & \quad \text{Me} \\
\text{Allyl halide} & \quad \text{NaH, THF, r.t.} \\
\text{Pd(OAc)}_2 & \quad \text{LiCl, KOAc, DMF, 120 °C, 60-85\%} \\
\text{Pd(OAc)}_2 & \quad \text{LiCl, KOAc, DMF, 120 °C, 60-85\%} \\
\text{NaOH} & \quad \text{MeOH, reflux, 1 h} \\
\text{R}_1 = \text{H, OAc, OH} \\
\text{R}_2 = \text{Me, Et, i-Pr, CH}_2\text{OH, CH}_2\text{CH}_2\text{OH} \\
\text{R}_3 = \text{H, Me} \\
\text{R}_4 = \text{OH, OMe, OCF}_3
\end{align*}

\textit{Cyclization of substituted benzylidene-3-alkenylamines}

During the investigation of an intramolecular hetero Diels-Alder route to the construction of the heterocyclic core of the \textit{Martinella} alkaloids, Aubé discovered an alternative Lewis acid-mediated cyclization of benzylidene-3-alkenylamines (Scheme 1.21). The urea 83 was obtained in 80\% yield from imine 82, was seen as a useful intermediate in martinelline synthesis, due to the \textit{cis} relationship of the pyrrolidine substituents. Tosylation of 83 gave sulfonamide 84, which was subjected to basic hydrolysis. Hydrolysis of the ester occurred concomitantly with cleavage of the urea, thus, re-esterification was required prior to the iodoamination reaction which gave pyrroloquinoline 86 (Scheme 1.21).\textsuperscript{24}
**Scheme 1.21**

Hara and co-workers synthesized the pyrroloquinoline moiety of martinelline from a 1,2-dihydroquinoline 80 which was prepared by using a tandem Michael-Aldol reaction as a key step. Their synthesis started with the preparation of Michael acceptor 88. Michael donor 87 was synthesized from commercially available 5-hydroxyanthranilic acid in 5 steps. Michael reaction of 87 and 88 (4 steps from 2-pyrrolidinone), in the presence of benzyltriethylammonium chloride and sodium carbonate proceeded, followed by an intramolecular Aldol cyclization to afford dihydroquinoline 89 in 83% yield. Aldehyde 89, was transformed to α,β-unsaturated carbonyl compound 90, with exo-methylene in 69% yield and 5 steps. Cyanation of 90, using potassium cyanide, proceeded smoothly to provide cyanomethyl ketone 91 in 88% yield. 91 was converted to pyrroloquinoline 92 in 3 steps and 58% overall yield from 91 (Scheme 1.22).
vii Enantioselective synthesis of the pyrroloquinoline core

The first enantioselective synthesis of the martinelline core was reported by Ennis and co-workers, using (R)-(−)-phenylglycinol as the source of asymmetry. The quinoline derivative used in the synthesis was prepared via a Pd-catalyzed carbonylative cyclization procedure starting from the protected N-allyl-2-iodoaniline. The tetracyclic lactam, was obtained by the condensation of γ-keto ester with (R)-(−)-phenylglycinol, which was treated with triethylsilane in the presence of titanium tetrachloride, to give the pyrrolo[3,2-c]quinoline core of the Martinella alkaloids. Complete deprotection was achieved in 2 steps and the resulting lactam was finally reduced with lithium aluminumhydride to give the heterocycle (Scheme 1.23).
The pyrrolo[3,2-c]quinoline core was synthesized by Hara and co-workers using a silicon-tethered ring closing metathesis reaction and intramolecular allylic amination as key steps.\(^{27}\) They first attempted the preparation of the substrate 100, by introducing the side chain unit to aldehyde 99, using allylmagnesium bromide followed by silylation with chlorodiphenyl allyl silane. The resulting silicon compound was subjected to ring closing metathesis to give 101. The silicon tether was removed and the free hydroxy groups were converted to the acetate 102. The allyl ester bearing a hindered acetate group was treated with Pd(dba)\(_2\) and Bu\(_3\)P in THF at room temperature, to provide the desired tetrahydroquinoline 103. A two step approach, which included the Mannich reaction and 1,4-conjugate addition was carried out, for synthesizing 104. Finally, the synthesis of pyrroloquinoline was achieved in 2 steps, in 58% yield (Scheme 1.24).\(^{27}\)
Scheme 1.24

\[
\begin{align*}
\text{CHO} & \xrightarrow{i. \text{ allylMgBr, ether, } -10^\circ\text{C}} \text{NHTs} \\
\text{BnO} & \xrightarrow{ii. \text{ Et}_3\text{N, CH}_2\text{Cl}_2, \text{ r. t., } 5 \text{ min, } 97\%} \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{O}_3\text{Si} \text{O}_3\text{Cl}} \text{NHTs} \\
\text{BnO} & \xrightarrow{\text{Cl}_2\text{P(Ph)P(Ph)}_2\text{Ru=CHPh, CH}_2\text{Cl}_2 \text{ reflux}} \text{NHTs} \\
\end{align*}
\]

\[
\begin{align*}
\text{NHTs} & \xrightarrow{i. \text{ TBAF, THF, r. t., } 84\%} \text{OAc} \\
\text{BnO} & \xrightarrow{ii. \text{ Ac}_2\text{O, TsOH, CH}_2\text{Cl}_2, 0^\circ\text{C, } 3 \text{ h, } 97\%} \text{NHTs} \\
\end{align*}
\]

ix Miscellaneous methods

The Fischer indolization method, is a general route for the synthesis of fully aromatic pyrrolo[3,2-c]quinolines, from the 4-hyrazinoquinolines (107). A range of 1H-pyrrolo[3,2-c]quinoline derivatives were obtained in excellent yields via cyclization under thermal conditions (Scheme 1.25).\textsuperscript{28} Henichart and co-workers, synthesized some pyrrolo[3,2-c]quinoline esters starting from, 1,4-dihydro-6,7-dimethoxy-4-oxaquinoline (110) (Scheme 1.26a).\textsuperscript{29}
Schenley Industries patented the synthesis of some dihydropyrrolo[3,2-c]quinolines in 1952. It was found that these compounds were potent amoebicides on animals in vivo. Ozawa and Nagaoka used similar chemistry to synthesize several 1-phenyl-4-methylpyrrolo[3,2-c]quinolines and evaluated them for their antibacterial activity. A similar strategy was followed by Wright and co-workers during their investigation of the hypotensive properties of new 4-aminoquinolines. Brown and co-workers, were searching for conformationally restrained analogues of 4-(arylamino)quinolines as reversible inhibitors of the gastric (H⁺/K⁺)-ATPase. The condensation reaction between 2-acetylbutyrolactone and anilines provided 1-arylated-4-methyl-2, 3-dihydropyrrolo[3,2-c]quinolines. The mixture of (E-) and (Z-) enamines, was converted to the reactive dichloroquinoline derivatives, by treatment with POCl₃. The final product was obtained by the reaction of with...
substituted anilines. Badawey and Kappe also used a similar sequence of reactions to prepare the \(N\)-unsubstituted pyrrolo[3,2-c]quinolines (Scheme 1.26b).\(^{34}\)

**Scheme 1.26b**

\[
\begin{align*}
\text{R}_2\text{NH}_2 + \text{R}_1\text{O} & \xrightarrow{\text{Toluene, reflux}} \text{R}_2\text{N} & \xrightarrow{\text{POCl}_3, 80-90^\circ\text{C}} \text{Cl} \\
\text{R}_1\text{O} & \xrightarrow{\text{NaN}_3, \text{acetone, reflux}} \text{R}_2\text{N} & \xrightarrow{\text{Ph}_3\text{P, acetone, reflux \(X = H\)}} \text{N}_3 \\
\end{align*}
\]

Nagaoka prepared fully aromatic 1-phenyl-pyrrolo[3,2-c]quinolines (121) by a minor variation of this method from 4-chloro-3-vinylquinolines 119 in 2 steps (Scheme 1.27).\(^{35}\)

**Scheme 1.27**

\[
\begin{align*}
\text{R}_2\text{Cl} + \text{Br}_2 & \xrightarrow{\text{CCl}_4, \text{r. t.}} \text{R}_2\text{Br} & \xrightarrow{\text{PhNH}_2, \text{EtOH, reflux}} \text{Ph}_2\text{N} \\
\text{R} = \text{H} & 77\% & \text{R} = \text{OMe} 70\% \\
\end{align*}
\]

Mekheimer described the synthesis of methyl-3-amino-4-chloropyrrolo[3,2-c]quinoline-2-carboxylate.\(^{36}\) The 2,4-dichloroquinoline-3-carbonitrile, was reacted with an excess of methyl glycinate in the presence of triethylamine, to give the 4-aminoquinoline. Cyclization in refluxing methanol with sodium methoxide as the catalyst provided the
target tricycle. The preparation of 7-chloro-2-methyl-1H-pyrrolo[3,2-c]quinoline derivatives, was achieved in 2 steps from, 4,7-dichloroquinoline. The reaction of 122 with 2-chloro-allylamine, followed by the treatment of chloroalkene 123 with polyphosphoric acid, resulting in the formation of 124 in 30-40% yield (Scheme 1.28).\(^{37}\)

**Scheme 1.28**

\[
\begin{align*}
\text{Cl} & \quad \text{NH} \quad \text{Cl} \\
\text{Cl} & \quad \text{EtOH, r. t.} & \quad \text{Cl} & \quad \text{PPA, 90 - 94 °C} & \quad \text{Me} \\
122 & \quad 123 & \quad \text{R} & = \text{Et} & \quad 42\% \\
& \quad & \quad \text{R} & = \text{Ph} & \quad 30\%
\end{align*}
\]

In another approach, 4-nitroquinoline N-oxide, was reacted with the carbanion derived from malonic ester. The 2,3-dihydro-3-methyl-2-oxo-1H-pyrrolo[3,2-c]quinoline-3-carboxylate N-oxide was obtained by alkylation and reduction (Scheme 1.29).\(^{38}\)

**Scheme 1.29**

\[
\begin{align*}
\text{NO}_2 & \quad \text{CH}_3(\text{CO}_2\text{Et})_2, \text{NaOEt, EtOH, r. t., 36\%} \\
\text{N} & \quad \text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} & \quad \text{H}_2, 10\% \text{Pd/C, EtOH, r. t., 50\%} \\
125 & \quad 126 & \quad 127
\end{align*}
\]

The above section covers the synthetic details of the various routes, that a number of groups have followed to synthesize the pyrrolo[3,2-c]quinoline core of the *Martinella* alkaloids in addition to approaches to the parent heterocycle. A schematic summary of these routes is illustrated in figure 1.2. As can be seen, several innovative approaches have been developed to synthesize the heterocyclic core of these alkaloids, however, only four groups have successfully used their approach to complete the total synthesis.
There have been three total synthesis of (±)-martinellic acid, one formal total synthesis. There are two groups including our group, who have carried out the enantioselective total synthesis of (-)-martinellic acid.

Figure 1.2 Summary of the various routes used by different groups to synthesize the pyrrolo[3,2-c]quinoline core of the Martinella alkaloids

1.3 Total synthesis of (±)-martinellic acid

Snider and co-workers synthesized (±)-martinellic acid based on the intramolecular cycloaddition of azomethine ylides, which was discussed in section 1.2.2. The tricyclic intermediate 129 was prepared by the elaboration of the N-
arylpyrrolidinone 128 in a similar manner to that of 48 (Scheme 1.11 45→48). The tricyclic triamine 132, which is the common intermediate in all martinelline (1) and martinellic acid (2) total syntheses, was obtained from 129 in 7 steps. The introduction of the guanidine moiety on to the hindered secondary amine was carried out in a unique fashion developed by this group. The amine 131 was converted to the bis cyanamide 133 by treatment with cyanogen bromide and NaHCO₃. The reaction with prenylamine in hexafluoro-2-propanol at 120 °C, provides the methyl martinellate, which was hydrolyzed with aqueous NaOH in methanol. Pure (±)-martinellic acid was obtained after reverse phase chromatography in 14 steps and 3% overall yield (Scheme 1.30).

Scheme 1.30

[Diagram of the synthetic route from 128 to 133 with the main steps and yields shown, followed by the formation of martinellic acid (64% yield from 131).]
The first total synthesis of martinelline (1) was published by Powell and Batey in 2002.\textsuperscript{41} They used the hetero Diels-Alder strategy, to construct the heterocyclic core of these alkaloids. They found that the reaction of methyl 4-aminobenzoate (54) with benzylxycarbonyl protected 2-pyrroline (52), in presence of 5\% camphorsulphonic acid in anhydrous THF, gives the tricyclic amine (Scheme 1.13, \textit{exo-56}) with the correct stereochemistry. The tricyclic triamine 132 was obtained after deprotection with Pearlman’s catalyst, followed by acidification with HCl. This key intermediate was synthesized in 2 steps and 58\% overall yield, which a vast improvement to Snider’s\textsuperscript{40} and Ma’s\textsuperscript{42} approach. The introduction of the isoprenylguanidine group, at the pyrrolidine nitrogen and the propyl amine nitrogen, was carried out in 2 steps. The substituted guanidine was first introduced at the pyrrolidine nitrogen of 134. Functional group manipulation, followed by guanylation of the amine present on the C-2 side chain with isothiourea provided 135. Hydrolysis of the methyl ester and global deprotection of all the protected nitrogen provided (±)-martinellic acid. The allylic alcohol side chain present in martinelline (1), was synthesized through a 5 step sequence. The coupling of the allylic alcohol side chain with martinelllic acid was achieved using BOP-Cl and Hünig’s base, which provided (±)-martinelline in 9 steps (from the longest linear sequence) and 10\% overall yield (Scheme 1.31).
Ma and co-workers, synthesized racemic martinelline, using a similar approach to that of Powell and Batey. They took advantage of the hetero Diels-Alder reaction that Batey and Powell had developed for the synthesis of the heterocyclic core of these alkaloids, however, the hetero Diels-Alder reaction was not diastereoselective. Squaric acid was used to catalyze the Diels-Alder cycloaddition of methyl 4-aminobenzoate (54), ethyl glyoxalate and the enamine 52 in acetonitrile, to providing the exo- and endo-cycloaddition products in a 1:2 ratio and 92% yield. The chemoselective reduction of diester 137 was carried out using NaBH₄/LiCl. The N-1 nitrogen was protected and the resulting acetamide subjected to Swern-oxidation to give the corresponding aldehyde as a (2:1) mixture of trans- and cis-isomers, which showed the isomerization at the 2-position had occurred. The aldehyde was converted to the diester 139 via Wittig chemistry and there was a very small amount of the 2-epimer found. In this way they were able to alter the stereochemistry of the major isomer from
the imino Diels-Alder reaction to that required for the synthesis of martinellines. The tricyclic triamine 132 was obtained in 13 steps from 4-aminobenzoate (54). The introduction of the guanidine side chains was accomplished by treatment Boc protected 3-methyl-2-butenyl-S-methylisothiourea (141) in the presence of AgNO₃ (Scheme 1.32). Hydrolysis of the ester followed by deprotection of the Boc sidechains provided martinelllic acid after converting it to a TFA salt. Martinelline was synthesized by coupling of the allylic alcohol side chain, mediated with EDCI, followed by the deprotection of the Boc-groups using TFA in the presence of anisole.

Recently our group has successfully carried out a concise formal total synthesis of martinellic acid.⁴⁴,⁴⁵ The synthesis was achieved from a pyrroloquinol-2-one that was
constructed via an azomethine ylide alkene cycloaddition discussed in section 1.2.2 (Scheme 1.9). The first task in the elaboration of 39 was to convert the carbonyl function at the C-2 position to an \( \alpha \)-methoxy amine that would serve as a handle to incorporate the side chain through iminium ion chemistry. After some experimentation with various reducing agents, it was found that the lactam 39 could be reduced to the aminal 144 with DIBAL-H, which in turn was converted to the corresponding methoxy derivative 145 by simply treating the aminal in a 4:1 mixture of methanol and chloroform at reflux (Scheme 1.33). It was planned to generate an \( N \)-acyl iminium ion which would then undergo nucleophilic addition with a copper acetylide. Treatment of \( \alpha \)-methoxy amine 146 with protected propargyl amine 147 in presence of CuBr, with sonication under aqueous conditions gave the desired product 148 in fair yield.

**Scheme 1.33**

Reduction of the alkyne along with global deprotection of the benzyl groups, Cbz and Boc group was achieved using \( \text{Pd(OH)}_2 \) in the presence of HCl, providing the tricyclic
triamine 132 in 90% yield. In this manner our group was able to synthesize a key intermediate 132) that has been successfully elaborated to the Martinella alkaloids.

1.4 Enantioselective total synthesis of (-)-martinellic acid

The first total synthesis of (-)-martinellic acid was carried out by Ma and co-workers in 2001. Strategically the quinoline derivative 153 was prepared first which was annulated to construct the pyrrolidine ring and the resulting tricyclic system 156 was elaborated to the tricyclic triamine 132. This approach started with a non-racemic N,N-disubstituted β-amino ester 149 (prepared in 4 steps from 1,4-butandiol) and assembled the 2-substituted 4-oxoquinoline 153 via, an Ullman type aryl amination reaction of 149 with 1,4-diodobenzene. This was followed by an intramolecular Friedel-Crafts acylation of 151 mediated by AlCl₃. The resulting iodoquinoline was carbonylated and protective group exchange gave 153 (Scheme 1.34). The alkylation of 4-oxoquinoline 153 was carried out using TfOCH₂CH₂Br. The resulting intermediate was immediately converted into the azide 154. Cyclization with Ph₃P/H₂O, provided the tricyclic imine 155, which was reduced stereoselectively with NaBH₄ after the removal of the silyl protecting group. This hexahydropyrrolo[3,2-c]quinoline, was converted to the tricyclic triamine 132, via a series of standard functional group transformation. The tricyclic triamine was elaborated to martinelllic acid using the sequence of reactions as discussed earlier (Scheme 1.32). The spectroscopic data was identical to those reported by Merck chemists,¹ however, the specific rotation was substantially different by order of a magnitude, which was attributed to non-linear effects (although not confirmed experimentally), as the concentrations employed in the rotation determinations, were
different. There has been no other enantioselective total synthesis of martinelllic acid and there has been no clear explanation on the discrepancy with the optical rotation measurements.

Scheme 1.34

Our group had begun working on the enantioselective approach toward the total synthesis of these alkaloids. Details of the synthesis will be discussed in the subsequent chapter of this dissertation. The second chapter will describes our endeavors which
include initial approaches as well as the route that was successfully used to complete the total synthesis of martinellic acid.
CHAPTER 2
RESULTS AND DISCUSSION

2.1 Initial efforts

After the development of a concise and stereoselective route for the construction of the hexahydropyrrolo[3,2-c]quinoline core of the martinelline and martinellic acid, synthetic efforts were directed toward an enantioselective synthesis of 1 and 2. The relative stereochemistry of the three chiral centers at C-2, C-2a and C-5a was assigned based on spectral data, although their absolute configurations were unknown. The stereospecific synthesis of the Martinella alkaloids using a chiral template of known configuration would allow the determination of absolute configurations of all three stereogenic centers. The initial retrosynthetic (Scheme 2.1) analysis that had been considered to construct the heterocyclic core 132 of these alkaloids clearly indicates that L-5-methyl glutamate would serve as a suitable block to introduce the absolute stereochemistry in the synthesis. The tricyclic triamine 132 would be obtained from 157 by functional group interchange, which, in turn, would be obtained by the azomethine ylide-alkene cycloaddition of unsaturated benzaldehyde derivative 158. The precursor for the cycloaddition would be obtained by functional group interchange of 159, which would be synthesized by Pd-catalyzed coupling of aryl halides with the glutamate derivate.
This analysis suggested that the side chain of L-glutamate would provide the C-2 guanidine containing side chain of martinelline and martinellic acid. The allyl amine 160 was synthesized by Mahmud in five steps starting from 5-methyl-L-glutamate.\textsuperscript{14} Several attempts were made to couple the allyl amine 160 with an aryl halide 162 or aryl triflate 163 using the Buchwald-Hartwig aryl amination reaction (Scheme 2.2).\textsuperscript{48, 49}

Unfortunately, all attempts to carry out this cross-coupling reaction failed. There are two possible reasons that make the allylamine unreactive toward the cross-coupling reaction—i) the steric encumbrance imposed by both the conformationally flexible three
carbon ester side chain of 160 and the ortho substituents on the aryl halide/triflate; ii) the intramolecular self condensation between the amine and the ester functionalities to afford a vinyl lactam.

2.2 Pd-catalyzed coupling of a chiral lactam with aryl bromides

During the course of these experiments, Shakespeare demonstrated the intermolecular cross-coupling reaction between four, five, six and seven membered ring lactams and a variety of aryl bromides (Scheme 2.3). This result suggested that it might be possible to carry out cross-coupling of suitably protected lactams derived from pyrroglutamic acid with aryl bromides.

Scheme 2.3

Initially attempts were made to couple (S)-(+)-5-(hydroxymethyl)-2-pyrrolidinone to an aryl iodide through an intramolecular variant of the reaction using Shakespeare’s conditions (Pd(OAc)$_2$, DPPF, NaOBu-$_t$, toluene, 120 °C). However this intramolecular aryl-amidation failed, so our attention turned to the intermolecular variant. The TBS-protected hydroxymethyl pyrrolidinone was prepared starting from commercially available $S$-$(+)$-glutamic acid using the sequence of reactions developed by Ackerman and co-workers. The corresponding alcohol is commercially available, but is rather expensive. The intermolecular cross-coupling reaction between the pyrrolidinone 169
with aryl bromides using Shakeaspeare’s condition, generally gave poor yields of the desired N-arylpyrrolidinone (Scheme 2.4), although higher yields were obtained with highly electron deficient aryl bromides. However when the alternative Buchwald’s conditions (Pd$_2$(dba)$_3$, Xantphos, Cs$_2$CO$_3$, toluene, 100-105 °C) for the cross-coupling between the lactam 169 with o-bromobenzonitrile were employed, we were delighted to find that the reaction gave 74% yield of 170 (Scheme 2.5). It was demonstrated that this reaction was quite general for a number of arylbromides, including some ortho substituted systems. (Table 2.1). However, an aldehyde or ester moiety in the ortho position, did give appreciable yields of the cross-coupling product.

Scheme 2.4

Scheme 2.5
Table 2.1 Results of Pd-catalyzed aryl-amidation using lactam 169

<table>
<thead>
<tr>
<th>Aryl Bromide</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="168a" /></td>
<td><img src="image" alt="170a" /></td>
<td>74</td>
<td>48</td>
</tr>
<tr>
<td><img src="image" alt="168b" /></td>
<td><img src="image" alt="170b" /></td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>

The products from aryl-amidation reactions with both non-racemic as well as racemic lactam 169 were obtained, in order to demonstrate that there was no compromise of the stereochemical integrity during these transformations. The cross-coupled products from both the racemic and non-racemic lactams were studied by $^1$H NMR spectroscopy in the presence of Pirkle’s chiral solvating agent 171.\(^{53}\)

![171](image)

**Figure 2.1 Pirkle’s chiral solvating agent 171**

When 4 equivalents of 171 were added to CDCl$_3$ solutions of the racemic $N$-aryl lactam (±)-170, the $t$-butyl signals of the TBS-moiety were well resolved (figure 2.3). Under otherwise identical conditions, only one $t$-butyl signal was found in the spectra of the cross-coupling products 170 derived from lactam (S)-169 (figure 2.2).
Doping experiments showed that >2% of the other stereoisomer could be detected under the conditions used to determine the optical purity and therefore the products were obtained in >95% ee.

2.3 Proposed synthetic route toward the synthesis of pyrroloquinoline core

Now that $^1$H NMR experiments had demonstrated that these reactions take place with no compromise on the stereochemical integrity, the following synthetic route was considered to synthesize the heterocyclic core of the *Martinella* alkaloids (Figure 2.4).
Figure 2.4 Proposed synthetic route toward the synthesis of the pyrroloquinoline core of the *Martinella* alkaloids

Several attempts were made to halogenate benzonitrile (170a), however, none of the reactions gave the desired halide. Some of the halogenation reactions that were attempted are summarized in (Scheme 2.6).  

Scheme 2.6
Even conditions that Aubé had used to halogenate a related substrate, (condition iv, Scheme 2.6)\textsuperscript{24} failed to give the desired product using N-aryl pyrrolidinone $170a$. A further challenge that we encountered in this route was adjusting the oxidation state of the nitrile moiety in $170a$. Acidic hydrolysis as well as basic hydrolysis of the nitrile did not give the desired carboxymethyl ester. A literature search revealed that benzonitrile itself required conc. phosphoric and sulfuric acid mixture under reflux to undergo hydrolysis.\textsuperscript{55a} It was assumed that $170a$ would not be sufficiently robust to withstand these harsh conditions. Another approach would be to reduce the nitrile to the aldehyde and we did investigate several conditions to carry out this transformation. DIBAL reduction of the aldehyde group did give the benzaldehyde derivative however there was concomitant reduction of the pyrrolidinone to pyrrolidine. An alternate method of reduction involved the use of Raney Ni (Scheme 2.7),\textsuperscript{55b} unfortunately, these conditions failed to reduce the nitrile to the benzoaldehyde derivative $172$ in our hands.

**Scheme 2.7**

Attempts to prepare the corresponding anthranilate derivative through cross-coupling reaction of methyl 2-bromobenzoate and $169$ were not successful. Since the elaboration of the benzonitrile $170a$ did not work we decided to follow a different approach.

During these endeavors toward elaborating $170a$, it became apparent that it would be more advantageous to use a substrate that already contained appropriate
substituents, in the correct positions. Methyl 2-bromo-5-nitrobenzoate appeared to satisfy these criteria and so was investigated in the cross-coupling reaction with the non-racemic lactam 169. Our first task was to optimize the conditions for the cross-coupling reaction, since the standard conditions established for other substrates (Scheme 2.5)52 gave poor yields (30-35%) of 174. Instead of using 2.5 mol% of the Pd-catalyst and 7.5 mol% xantphos, the catalyst as well as ligand loading, were increased by double. To our delight the reaction gave 65% of the desired product 174. The yield was good even for large scale reactions (on a 10 mmol scale provided 60% yield of 174). It was planned to incorporate the halo group (X = Br, I) via the corresponding amine, which meant that, the nitro-group had to be reduced. The initial approach to reduce the nitro-group in 174 involved the use of Pd/C (10%) with NaBH₄ and methanol as the hydrogen source. This resulted in only partial reduction of the nitro-group. Later (10%) Pd/C with hydrogen balloon (1 atm) was used to carry out the reduction and it worked well giving quantitative yields of the desired amine 175 (Scheme 2.8)
The next step involved the conversion of the amine to an appropriate halide. It was decided to utilize iodide since it would be more reactive to Pd-catalyzed cross-coupling thus, easier to incorporate the carboxy methyl group, which is present as free acid at the C-7 position in martinelllic acid. Standard Sandmeyer conditions (H$_2$SO$_4$, NaNO$_2$, CuI)$^{56}$ for iodination was too harsh for this substrate; the reaction gave only 25% of the iodide. More neutral conditions were employed involving the use of $n$-amyl nitrite,$^{57}$ initially providing the diazonium compound which, in the presence diiodomethane, formed the aryl iodide 176 (Scheme 2.9).$^{58}$ The reaction gave a mixture of both the protected 176a as well as the desilylated alcohol 176b the relative amounts
were scale dependent. However, further investigations on this result were not pursued, as we needed the deprotected alcohol was required and so, the mixture of 176a/176b was treated with a THF solution of tetrabutylammonium fluoride (TBAF) to afford the alcohol 176b.59

Next, adjustment of oxidation state of the hydroxymethyl group of the pyrrolidinone derivative 176b to the aldehyde, was investigated. Several oxidizing agents were evaluated to carry out this transformation; however none of them provided good yields of the aldehyde required to carry out further elaboration (Scheme 2.10).60 The first oxidizing agent that was investigated was TPAP (tetralkyl ammonium perruthenate, Pr4N+RuO4−), which provided only 11% of the desired aldehyde 177.60a PCC oxidation did not work either.60b Two reports by Smith and co-workers, described the successful oxidation of 5-hydroxymethyl pyrrolidinone derivatives, using a Moffat type of oxidation (DCC, pyridine, TFA, DMSO, r. t.).60c,d The Moffat oxidation of 176b was successful, but resulted in only ~33% of the desired aldehyde. The next oxidizing agent that was tried was the Dess Martin periodinane, which was prepared according to the procedure developed by Martin and co-workers.61 The periodinane obtained was used for oxidation of alcohol 176b,60c unfortunately however, it did not work. When the
oxidation was carried out using commercially available periodinane, the aldehyde was obtained. Complete consumption of starting material took place within 2 h and two new components were observed by TLC analysis, however, after work up only 30% of the aldehyde was obtained. Later runs were allowed to go for 6 h but each time only 30% of the product was obtained after work up. The oxidation was also carried out using IBX (iodoxy benzoic acid 178a) in DMSO.\textsuperscript{60f} TLC analysis showed encouraging results with complete consumption of starting material, but \textsuperscript{1}H NMR spectroscopy showed only a small percentage of the desired product. The maximum conversion to the desired aldehyde using IBX was about 25%. The crude aldehyde obtained from the oxidation with IBX, periodinane and DCC/DMSO was subjected to Wittig olefination directly (Scheme 2.11),\textsuperscript{60c,d} however, the olefin 179 was not obtained. Several other oxidizing agents screened including TCT/DMSO\textsuperscript{60g} and TEMPO/NaOCl\textsuperscript{60h} (Scheme 2.10), but these reactions were unsuccessful. Presumably, the aldehyde 177 was not obtained in good yield, because by analogy to Smith’s observations with a related system, this aldehyde is not very stable.\textsuperscript{60c,d}
Since elaboration of the alcohol 176b to the olefin 179 was unsuccessful, an alternate approach to obtain the olefin was considered.

Since the major stumbling block in the route described in figure 2.5 involved the homologation of the cross-coupled product, it was decided to investigate homologation prior to cross-coupling (Figure 2.6). An extensive literature search provided an approach for homologation, involving the conversion of 5-hydroxymethyl pyrrol-2-one to the corresponding cyanide in two steps. Hydrolysis of the nitrile and reduction would then provide the required alcohol.
The first step was sulfonylation with tosyl chloride in the presence of Et$_3$N and DMAP and this was followed by cyanation with KCN in refluxing acetonitrile. The tosylation proceeds very effectively and does not require chromatographic purification, as recrystallization can be used. This is advantageous as this reaction can be accomplished on a large scale (15-20 g starting alcohol). Cyanation is rather slow (50 h) but gives the product in quantitative yield and does not require purification (Scheme 2.12).

**Scheme 2.12**

Hydrolysis of the nitrile 182 was carried out initially by heating a solution of 182 in sulfuric acid, water and methanol at 120 °C in a sealed tube. This method did not give good yields (25-35%) of the ester and was not feasible for large scale synthesis. A modified method for the hydrolysis of the nitrile was developed, in which the reaction was carried out using a standard reflux set up and the reaction simply was heated at reflux for four days, providing 55-60% of ester 183 and does not require any purification. The methyl ester was reduced using NaBH$_4$ and the resulting alcohol is
protected as the TBS ether (Scheme 2.13). The overall yield for the synthesis of the TBS protected higher homologue lactam 184 is 25% starting from the lower homologue 180.

Scheme 2.13

The higher homologue lactam 184 was then used for the cross-coupling reaction with methyl-2-bromo-5-nitrobenzoate using the standard conditions developed for the synthesis of N-aryl pyrrolidinone 174. Gratifyingly it was found that the Pd-catalyzed cross-coupling reaction with the silyl-protected 5-hydroxyethyl-2-pyrrolidinone 184 provided 55% (85%, based on recovered starting material) of the N-aryl pyrrolidinone 185e. The unreacted lactam 184 was recovered after the reaction in 35% yield, this is useful especially when the cross-coupling was carried out in large scale (20 mmol). The pyrrolidinone derivatives (182, 183, 184) prepared en route to 184, were also subjected to cross-coupling with some highly electron deficient aryl bromides to check the versatility of the aryl-amidation chemistry (Table 2.1). As can be seen, these proceed uneventfully leading to the construction of highly functionalized adducts.
Table 2.2 Results of cross-coupling chemistry with series of lactams

<table>
<thead>
<tr>
<th>Aryl Bromide</th>
<th>Lactam</th>
<th>Product</th>
<th>Time h</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>168c</td>
<td>182</td>
<td>185a</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>168c</td>
<td>183</td>
<td>185b</td>
<td>16</td>
<td>55</td>
</tr>
<tr>
<td>168c</td>
<td>184</td>
<td>185c</td>
<td>6</td>
<td>91</td>
</tr>
<tr>
<td>168d</td>
<td>184</td>
<td>185d</td>
<td>6</td>
<td>82</td>
</tr>
</tbody>
</table>

It was found that there were no complications in applying similar chemistry for elaborating the aromatic moiety that had been previously developed (Scheme 2.8 and 2.9) to prepare N-aryl lactam 187 (Scheme 2.14).
After the successful elaboration to the N-aryl lactam 185e the next step was conversion of the primary alcohol into the corresponding olefin. It was planned to utilize selenylation followed by oxidative elimination to provide the olefin 179 in a one-pot two-step process. Initial experiments with N-(phenylseleno)phthalimide did not provide the desired selenide. Subsequently, o-nitrophenylselenocyanate was found to be the ideal selenylating agent to obtain the selenide which was immediately subjected to oxidative elimination using hydrogen peroxide to provide the desired olefin 179 in good yields (85% for two steps) (Scheme 2.15).

The last transformation prior to cycloaddition required manipulation of the oxidation level of the carboxymethyl group in 179 would give the unsaturated benzaldehyde derivative, which is the cycloaddition precursor for the azomethine ylide-alkene cyclization. The controlled reduction of the methyl benzoate 179 to the desired benzyl alcohol 188a turned out to be somewhat problematic. The reduction of the ester group in 179 with lithium borohydride occurred with concomitant reductive ring opening of the
pyrrolidinone leading to the formation of 188b. The poor material thoughput in the reduction step (Scheme 2.16), would make the total synthesis unfeasible. Therefore, efforts were focused on improving the yield of the simple reduction product. Two ways were considered as a solution to this problem: i) Convert the carboxymethyl group to an activated ester and then perform the reduction. ii) Find a more chemoselective reducing agent that would not lead to the concomitant reductive ring opening of the lactam. Both these approaches were investigated. In order to prepare the activated ester, the carboxymethyl group was hydrolyzed using aqueous LiOH. The resulting carboxylic acid 189 was subjected to reduction using NaBH₄ in the presence of iodine, however this reaction did not work. Therefore, the carboxylic acid 189 was esterified using N-hydroxysuccinimide providing the activated ester. The activated ester 190 was reduced using NaBH₄ to give the desired alcohol in reasonable yield (Scheme 2.17). Although this reaction sequence was reasonably serviceable, it involved more steps and thus, a more direct approach was sought. Subsequently it was found that a solution of LiBH₄ in THF can also be used for the reduction of the methyl ester, the key to success of this reaction, is to maintain the temperature at 0 °C throughout the reaction and the addition of the LiBH₄ (1.2-2.0 equivalents total) should be done over a period of time (20 - 24 h).
During the course of our investigation on improving the chemoselectivity of the reduction reaction (Scheme 2.16), we also attempted to elaborate the by-product 188b to the heterocyclic core of the Martinella alkaloids. The benzylic alcohol was selectively oxidized to the aldehyde 191, however further elaboration failed (Scheme 2.18). Attempts to protect the aniline nitrogen of in 192 with a Boc-group was unsuccessful, as was the cycloaddition of 192 failed. The failure of 191 to undergo cycloaddition was not surprising as it was known that protection of the free amine is
required for the cycloaddition to work.\textsuperscript{13, 14} The oxidative cyclization of 188b to 189 with PCC was also tried, but it did not give the desired product 189. We did not pursue further investigation on this substrate 188b, since the material throughput in the reduction of 179 was improved.

**Scheme 2.18**

![Scheme 2.18](image)

The oxidation of the benzyl alcohol 188a can be carried out using MnO\(_2\) (72 h, r. t.)\textsuperscript{14} or IBX (6 h, r. t.)\textsuperscript{60f} to give the unsaturated benzaldehyde derivative 193 in 90% yield. The resulting cycloaddition precursor 193 was subjected to the azomethine ylide-alkene cyclization reaction using conditions that our group had developed during model studies (Scheme 2.19).\textsuperscript{10} The cycloaddition reaction worked well giving 65% of the desired product and 9% (10:1 based on analysis of the \(^1\)H NMR spectrum of the crude product) of the diastereomer. The x-ray structure confirms the stereochemistry of the cis ring fusion of the pyrrolidine and trans junction of the pyrrolidinone (Figure 2.7).
With this synthetic strategy, we were not only able to construct the pyrroloquinoline core, but also had a three carbon handle that can be elaborated to the side chain, that is present at the C-2 position of martinellic acid. The tetracyclic compound 194 is similar to the one that Snider and co-workers had reported previously, however in this work, the cycloadduct is non-racemic and has a 7-iodo substituent instead of the bromo-moiety. The elaboration of the tetracycle 194 to the tricyclic triamine 132 has already
been carried out by Snider and co-workers using their racemic substrate, however it involved a few protection and deprotection chemistry, which not only increased the number of steps but also resulted in loss of material. Efforts were focused on developing a more efficient approach which would involve fewer steps, which in turn, might reduce material loss. The iodo-group in 193 was carbonylated using the conditions that were already well established in our lab. Attempts were made to open the pyrrolidinone using the Meerwein salt, however the desired product was not obtained (Scheme 2.21). Lactam opening with Schwartz reagent also did not work. After surveying with other reducing agents (LiEt₃BH, solid LiBH₄), none of which gave successful results, we opted to evaluate Snider’s procedure to open the lactam.

**Scheme 2.21**

The Snider approach involved reductive opening of the lactam (with 2M LiBH₄ in THF and methanol in refluxing THF). In contrast to the bromo derivative, the iodo compound 194, took only 4 – 5 days to form the propyl alcohol derivative 197 (rather than 8 days). The next important transformation involved carbonylation of the iodo
group, for this the procedure previously developed in our lab was employed.\textsuperscript{14} Before the carbonylation was carried out, the free alcohol and the amine in 196, had to be protected and they were protected as acetate using literature procedure (Scheme 2.22).\textsuperscript{40} Acetylation resulted in the formation of a 3:2 mixture of the keto/enol form of 198.

\textbf{Scheme 2.22}

\begin{center}
\includegraphics[width=\textwidth]{scheme_2.22}
\end{center}

During the carbonylation of the acetylated compound 198 the amine was deprotected after 24 hours (this observation was made by analyzing the $^1$H NMR spectrum of the crude carbonylated product). The acetylated alcohol was deprotected using NaOMe (Scheme 2.23).

\textbf{Scheme 2.23}

\begin{center}
\includegraphics[width=\textwidth]{scheme_2.23}
\end{center}

In order to elaborate 199 to the tricyclic triamine, the hydroxy group had to be converted to an amine and the benzyl group had to be removed. The free amine in 199 was protected as the trifluoroacetamide using trifluoroacetic anhydride and pyridine. This
reaction did not work very well, giving only 45-50% of the desired product, however, during one such transformation, 20% starting material was recovered. The resulting trifluoroacetamide 200, was first mesylated with, MsCl and the crude mesylate was treated with NaN₃ (Scheme 2.24). Deprotection of the trifluoroacetamide was achieved using NaOMe. The resulting azido compound 202 was reduced using Pearlman’s catalyst to give the tricyclic triamine 132 (Scheme 2.24). Thus, using this strategy, we had successfully synthesized 132 which is a common intermediate in all of the martinelllic acid total synthesis reported to date⁵³.

Scheme 2.24
With the central core of martinellic acid in hand, all that remained to be done was the incorporation of the guanidine moiety 141. Efforts were focused on elaborating the thiourea 203 derivative synthesized by Mahmud to the side chain intermediate 141. The thiourea intermediate 203, was methylated to give the methyl isothiourea, which was immediately subjected to Boc protection to give 141 (Scheme 2.26). The guanylation chemistry developed during the model studies conducted in our lab, was not very efficient to furnish the desired product.

Considering the similarity of the substrates developed by our group and Ma’s group, using their strategy for guanylation seemed to be feasible. The AgNO$_3$ catalyzed guanylation did not work that efficiently for us (40-45% of the desired product 142). In order to obtain better yields the reaction mixture was stirred for longer time (26 h instead of 16 h). It should be noted that the Ma groups’ reported yield was incorrect and our yields are comparable (62% with modified procedure). The optical rotation of the
methyl ester derivative 142 $[[\alpha]_D = -95.2 \ (c = 0.58 \text{ CHCl}_3)]$ matched Ma’s value $[[\alpha]_D = -94.2 \ (c = 0.6 \text{ CHCl}_3)]$

The methyl ester in 142 was hydrolyzed using NaOH and the resulting acid was subjected to Boc-deprotection using trifluoroacetic and anisole as a proton sponge to give martinellic acid (Scheme 2.27). The final product was purified using HPLC with the conditions used by Batey and co-workers for the purification of martinellic acid that they had synthesized. The $^1$H NMR and $^{13}$C NMR matched the ones reported by Witherup and co-workers$^1$ and those of synthetic material$^{41, 42}$ Optical rotation of the compound that we had synthesized $[[\alpha]_D = -20.5 \pm 4.0 \ (c = 0.20 \text{ methanol})]$, is different from those reported earlier.$^{1, 42}$ The value being slightly off from the natural product $[[\alpha]_D = -8.5 \ (c = 0.01 \text{ methanol})]$, does not come as a great surprise, and may simply be a function of the purity of the isolated natural product. Further since our values for the rotation were obtained at different concentrations, non-linear effects can be discounted.

These results are summarized table 2.3.

<table>
<thead>
<tr>
<th>Amount of material used (mg)</th>
<th>MeOH (ml)</th>
<th>c (gm/100ml)</th>
<th>$[\alpha]_{obs}$</th>
<th>$[\alpha]_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6</td>
<td>1.45</td>
<td>0.32</td>
<td>-0.092</td>
<td>-28.8</td>
</tr>
<tr>
<td>4.6</td>
<td>1.8</td>
<td>0.26</td>
<td>-0.082</td>
<td>-31.5</td>
</tr>
<tr>
<td>4.6</td>
<td>2.3</td>
<td>0.2</td>
<td>-0.053</td>
<td>-26.5</td>
</tr>
<tr>
<td>4.6</td>
<td>2.3 + TFA</td>
<td>0.2</td>
<td>-0.05</td>
<td>-25.0</td>
</tr>
</tbody>
</table>
2.4 Demonstrating the enantiomeric purity of the substrates

The significantly contrasting value from that reported by Ma {\([\alpha]_D = -122.5 (c = 0.31)\)} cannot be accounted for and the difference suggested that perhaps our material was partially racemic. Therefore the enantiomeric purity of our material had to be determined in order to check if any racemization had occurred during the synthesis. Once the tetracycle 194 is formed, racemization at any subsequent point would involve inverting the stereochemistry at three different centers and thus was deemed unlikely. Based on this analysis, it was thought that if racemization occurred it was the cycloaddition precursor during the cycloaddition was the most likely candidate. In order to make sure that (194) is completely non-racemic, we once again took advantage of the Pirkle’s chiral solvating agent. The racemic cycloaddition precursor was synthesized using Snider’s approach (Scheme 1.11), but with the 7-iodo substituent. The 2-hydroxymethyl-5-iodoaniline (205) was synthesized from anthranilic acid (206) in 3 steps (Scheme 2.27).
Once the racemic cycloaddition precursor [(±)-193] as well as racemic pyrroloquinoline [(±)-194] (Figure 2.8) were synthesized, they were used in $^1$H NMR analysis using Pirkle's chiral solvating agent.

When 2 equivalents of 171 were added to CDCl₃ solution of the racemic unsaturated benzaldehyde derivative (±)-193, the signal due to the aldehyde proton was well resolved (Figure 2.9). A signal for one of the aromatic protons ($J = 1.8$ Hz) was also resolved (Figure 2.10). Under otherwise identical conditions, only one signal was
found in the spectra of the non-racemic product (-)-193. (Pirkle’s chiral solvating agent, (R)-(+)\,-\,2,2,2-trifluoro-1-(9-anthryl)ethanol has been successfully used in the determination of the enantiomeric purity and in some cases the absolute configuration of various compounds such as sulfoxides, lactones, amines, sulfinate esters.\textsuperscript{53})

Figure 2.9 Expanded $^1$H NMR spectrum of (-) and (±)-193 (aldehyde signal), a) (±)-193 with 2eq Pirkle’s chiral solvating agent, b) (-)-193 with 2 eq Pirkle’s chiral solvating agent
Figure 2.10 Expanded $^1$H NMR spectrum of (-) and ($\pm$)-193 (aromatic signal), a) ($\pm$)-193 with 2eq Pirkle’s chiral solvating agent, b) (-)-193 with 2 eq Pirkle’s chiral solvating agent.

This appears to be the first example where an aldehyde peak has been resolved using Pirkle’s chiral solvating agent. It renders the $^1$H NMR spectra of enantiomers "nonequivalent" and this allows the determination of enantiomeric composition by the
observation of separate signals for each enantiomer. The spectral non-equivalence arises from the formation of diastereomeric solvates that ideally have non-identical spectra because of interactions between the chiral solvating agent and the enantiomers of the substrates. In the case of the racemic aldehyde (±)-**193** used in the analysis, possible hydrogen bonding interactions are shown in figure 2.11

![Diagram](image)

Figure 2.11 Formation of diastereomeric solvates of (±)**193** in the presence of **171**

Similar **1H** NMR experiments were carried out with the racemic and non-racemic tetracycle **194**. However, the amount of chiral solvating agent was increased to 4 equivalents, to see appreciable resolution of the peaks. Apart from broadening of the signals, there was separation of one of the aromatic signals (Figure 2.12, as well as, one of the benzylic signals (Figure 2.13). The spectrum was recorded in C₆D₆, since the dispersion was not as good in CDCl₃.
These $^1$H NMR experiments, clearly indicate that there is no compromise in the stereochemical integrity of these compounds and thus during the cycloaddition. From
here on racemization would require breaking of three bonds, *viz*, the *cis*-fused pyrrolidine and the C-H bond at the C-2 position, this is unlikely.

Thus with the help of $^1$H NMR spectroscopy we have clearly showed that there is no racemization occurring in our approach. The enantioselective total synthesis has been achieved in 0.7% overall yield and 17 steps (from the longest linear sequence). The optical rotation value that was obtained by our group is consistent over three different batches of martinelliac acid prepared. This validates not only the $[\alpha]_D$ value but also the chemistry that was developed to complete the total synthesis.
CHAPTER 3
EXPERIMENTAL DETAILS

3.1 General procedures

All reagents were purchased from commercial suppliers and were used as
received unless otherwise noted. Solvents were dried by distillation over appropriate
drying agents: tetrahydrofuran and diethyl ether were distilled from
sodium/benzophenone ketyl; benzene and dichloromethane were distilled over calcium
hydride or purified using Pure Solv SPS-400-5 solvent purification system. $^1$H and $^{13}$C
NMR ($\delta$ in ppm) spectra were recorded in CDCl$_3$ (unless otherwise noted) at 500 and
125.8 MHz, respectively; using a JEOL Eclipse+ 500 spectrometer unless otherwise
noted using residual CHCl$_3$ as reference ($^1$H NMR and carbon absorption of CDCl$_3$ for
$^{13}$C NMR). Infrared spectra were recorded either as neat films or as KBr pellets using a
Bruker Vector 22 spectrometer. Electron impact mass spectra (EI-MS) were obtained
with a Finnigan MAT-70 or Bear Instruments Kodiak spectrometer and electron spray
ionization (ESI-MS) was obtained from HT labs Inc, San Diego, CA. Elemental
analyses were performed using a Perkin-Elmer 2400 CHN analyzer. Optical rotation
was measured on a Perkin-Elmer 241MC polarimeter (c = g/100 mL) and the observed
value was an average of 2-3 runs. The solvent used for optical rotation is CHCl$_3$ unless
otherwise noted. High resolution mass spectra (HR-MS) were obtained from Dr. Powell’s lab in University of Florida, Gainesville, Florida.

**General procedure for the cross-couplings** A 10 mL Schlenk tube was charged with the lactam $^{169}$ (1.2 mmol), $\text{Pd}_2(\text{dba})_3$ (23 mg, 0.025 mmol), xantphos (44 mg, 0.075 mmol), and $\text{Cs}_2\text{CO}_3$ (0.456 g, 1.4 mmol) and alternately purged and backfilled with $\text{N}_2$. The aryl bromide $^{168}$ (1.00 mmol) and 1,4-dioxane (1 mL) were added and the stirred mixture was heated at 105 °C until the reaction was complete by TLC as evidenced by disappearance of the aryl bromide. The resulting mixture was cooled to room temperature, diluted with $\text{CH}_2\text{Cl}_2$ (~20 mL), filtered through Celite, and concentrated. The residue was purified by flash chromatography on $\text{SiO}_2$ with the specified ratio of hexanes and EtOAc as eluant.


(170a). The product was purified by flash chromatography ($\text{SiO}_2$, 3:2 hexanes/EtOAc), yielding 170a as a yellow solid (244 mg, 74%). mp 54-56 °C. $[\alpha]_D = -50.8$ (c = 0.5). $^1\text{H}$ NMR: $\delta = 7.69$ (dd, $J = 7.8, 1.4$ Hz, 1H), 7.63 (td, $J = 7.8, 1.4$ Hz, 1H), 7.43 (d, $J = 7.8$ Hz), 7.39 (td, $J = 7.8, 1.4$ Hz, 1H), 4.39 (m, 1H), 3.54 (d, $J = 2.8$ Hz, 2H), 2.68-2.64 (m, 1H), 2.58-2.55 (m, 1H), 2.40-2.36 (m, 1H), 2.08-2.06 (m, 1H), 0.82 (s, 9H), -0.05 (s, 3H), -0.07 (s, 3H); $^{13}\text{C}$ NMR: $\delta = 175.7, 141.0, 133.6, 133.5, 129.7, 127.7, 116.7, 111.5, 63.7, 61.9, 30.9, 25.8, 21.9, 18.1, -5.6$; FT-IR (KBr, cm$^{-1}$): 3078, 2929, 2231, 1707, 840, 770. EI-MS ($m/z$): 331.1 (M+H$^+$, 22), 315.1 (5.3), 273.2 (100), 229 (5.6),
217 (10.4), 185.1 (21.8), 157.1 (6.3), 129.1 (7.9), 57 (12.1). Anal. Calcd. for 
C₁₈H₂₆N₂O₂Si: C, 65.41; H, 7.93; N, 8.48. Found: C, 65.20; H, 7.56; N, 8.41.

(5S)-5-tert-Butyldimethylsilyloxymethyl-1-(2-nitrophenyl)-2-pyrrolidinone (170b).

The product was purified by flash chromatography (SiO₂, 7:3 hexanes/EtOAc), yielding 170b as a yellow solid (182 mg, 52%). 
mp 87-89 °C. [α]D = -171.2 (c = 0.5). ^1H NMR: δ = 8.02 (dd, J = 7.8, 1.4 Hz, 1H), 7.63 (td, J = 7.8, 1.4 Hz, 1H), 7.45 (d, J = 7.8 Hz), 7.42 (d, J = 7.8 Hz, 1H), 4.16 (m, 1H), 3.63 (d, J = 2.4 Hz, 2H), 2.61-2.57 (m, 1H), 2.53-2.48 (m, 1H), 2.40-2.36 (m, 1H), 2.08-2.06 (m, 1H), 0.82 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H); ^13C NMR: δ = 175.6, 146.5, 133.7, 131.9, 128.1, 125.6, 64.0, 62.3, 30.6, 25.8, 22.1, 18.1, -5.5; FT-IR (KBr, cm⁻¹): 3078, 2929, 2231, 1707, 840, 770. EI-MS (m/z): 351.1 (M+H⁺, 31.7), 335.1 (5.3), 293 (100), 277 (35), 263 (9.6), 205.1 (54.3), 189.1 (17.6), 177.1 (32.6), 143.1 (66.6), 123.1 (20.7), 74.9 (36.3). Anal. Calcd. for 
C₁₇H₂₆N₂O₄Si: C, 58.26; H, 7.48; N, 7.99. Found: C, 58.04; H, 7.67; N, 8.29.


A 10 mL Schlenk tube containing lactam 169 (0.278 g, 1.2 mmol), Cs₂CO₃ (0.456 g, 1.4 mmol), xantphos (88 mg, 0.15 mmol), and Pd₂dba₃ (46 mg, 0.05 mmol) was alternately evacuated and backfilled with nitrogen. Dioxane (1.0 mL) and methyl 5-nitro-2-
bromobenzoate (0.26 g, 1.0 mmol) were introduced and then resulting mixture was heated at 105 °C for 10 h. The mixture was cooled, diluted with CH$_2$Cl$_2$ and then filtered through Celite. After concentration, the residue was purified by flash chromatography (SiO$_2$, 1:1 hexane/EtOAc) to give pale orange crystals of the N-aryl pyrrolidinone, (0.27 g, 66%). mp: 76-78 °C. [α]$_D$ = 0.00 (c = 0.66) $^1$H NMR δ = 8.77 (d, J = 2.7 Hz, 1H), 8.36 (dd, J = 8.7, 2.7 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 4.28 (m, 1H), 3.91 (s, 3H), 3.66 (dd, J = 11.0, 4.6 Hz, 1H), 3.61 (dd, J = 11.0, 4.1 Hz, 1H), 2.61 (m, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 2.03 (m, 1H), 0.78 (s, 9H), -0.059 (s, 3H), -0.06 (s, 3H); $^{13}$C NMR δ = 175.7, 164.4, 145.9, 143.8, 129.9, 129.6, 127.1, 126.6, 64.3, 62.8, 52.9, 30.9, 25.7, 21.9, 18.1, -5.6; FT-IR (KBr, cm$^{-1}$): 2918, 1773, 1762, 1347, 749. ESI-MS (m/z): 431 (M+Na$^+$, 100), 409 (M+H$^+$, 37), 377 (23). Anal. Calcd. for C$_{19}$H$_{28}$N$_2$O$_6$Si: C, 55.86; H, 6.91; N, 6.86. Found: C, 55.70; H, 7.05; N, 7.05.

Methyl 5-amino-2-[(5S)-5-[( tert-Butyl ) dimethylsilyloxy]-2-oxo-1-pyrrolidinyl]-2-oxo-1-pyrrolidinyl] benzoate (175). In a 25 mL round bottom flask were placed the N-aryl pyrrolidinone 174 (0.27 g, 0.66 mmol), and 10% palladium on charcoal (27 mg). The flask was alternatively evacuated and backfilled with hydrogen. Methanol (4.0 mL) was introduced and the mixture was stirred at room temperature under a balloon of hydrogen gas (1 atm) for 16 h. The mixture was filtered through Celite. After concentration, the residue was purified by flash chromatography (SiO$_2$, 1:4 hexane/EtOAc) to give pale yellow crystals of the amine 175, (0.24 g, 97%). mp: 137-
Methyl 5-iodo-2-[(5S)-5-{hydroxymethyl}-2-oxo-1-pyrrolidinyl] benzoate (176b).

The amine 175 (0.20 g, 0.54 mmol) was taken up in acetonitrile (1.8 mL) and diiodomethane (0.20 mL, 2.48 mmol) and n-pentyl nitrite (0.52 mL) were added. The solution was purged with nitrogen for 15 min and heated to 85-90 °C for 22 h under nitrogen. The reaction mixture was cooled to room temperature followed by the addition of tetrabutyl ammonium fluoride solution (1.0 M, 0.54 mL, 0.54 mmol) in THF. The resulting mixture was stirred at room temperature for 7 h, quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give a dark orange oil. The crude product was purified by flash chromatography (SiO$_2$, 0.5:9.5 methanol/EtOAc) to give pale yellow crystals of 176b (0.16 g, 81%). mp: 142-144 °C. [α]$_D$ = -149.1 (c = 0.61). $^1$H NMR δ = 8.11 (d, J = 1.8 Hz, 1H), 7.30 (s, 3H), 7.05 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 2.7 Hz, 1H), 3.91 (m, 1H), 3.87 (s, 3H), 3.56 (dd, J = 11.4, 4.1 Hz, 1H), 2.52 (m, 1H), 2.44 (m, 1H), 2.26 (m, 1H), 2.05 (m, 1H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR δ = 176.8, 165.6, 146.1, 128.9, 128.1, 119.1, 117.5, 63.2, 62.7, 52.2, 30.9, 25.9, 21.9, 18.2, -5.4, -5.5; FT-IR (KBr, cm$^{-1}$): 3457, 3355, 2953, 2856, 1719, 1670, 1328, 1233, 837, 775. ESI-MS (m/z): 401 (M+Na$^+$, 90), 379 (M+H$^+$, 100), 347 (59). Anal. Calcd. for C$_{19}$H$_{30}$N$_2$O$_4$Si: C, 60.29; H, 7.99; N, 7.40. Found: C, 59.98; H, 8.22; N, 7.54.
Hz, 1H), 7.85 (dd, J = 8.2, 1.8 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 4.31 (m, 1H), 3.90 (s, 3H), 3.75 (dt, J = 12.8, 2.3 Hz, 2H), 3.46 (td, J = 12.1, 1.8 Hz, 2H), 2.68 (m, 1H), 2.49 (m, 1H), 2.31 (m, 2H); $^{13}$C NMR $\delta$ = 175.0, 167.3, 141.6, 139.1, 135.6, 131.2, 127.1, 91.1, 62.7, 53.5, 31.9, 20.6; FT-IR (KBr, cm$^{-1}$): 3466, 3066, 2966, 2883, 2118, 1700, 1667, 832, 781, 561. ESI-MS ($m/z$): 398 (M+Na$^+$, 56), 376 (M+H$^+$, 16), 344 (100).

Anal. Calcd. for C$_{13}$H$_{14}$INO$_4$: C, 41.62; H, 3.76; N, 3.73. Found: C, 41.90; H, 4.08; N, 3.67.

**Methyl (S)-5-oxo-2-pyrrolidineacetate (183):** The nitrile 182$^{63}$ (8.50 g, 68.0 mmol) was dissolved in methanol (68 mL). Sulfuric acid (13.8 mL) was added slowly to the nitrile solution. Then the reaction mixture was heated at reflux for 96 h. The reaction mixture was cooled in an ice bath followed by addition of cold water (13.8 mL) and neutralized with solid K$_2$CO$_3$ with small portions of sat K$_2$CO$_3$ added to maintain a thick solution. Once the pH reached 7.0 the neutralized reaction mixture was filtered and extracted with CH$_2$Cl$_2$ (3 x 300 mL). The combined organic layer washed with brine and dried over anhydrous sodium sulfate. The dried organic layer was concentrated to provide 183 (5.9 g, 55%) as a colorless oil which was used directly in the next step. $^1$H NMR $\delta$ = 6.41 (br, 1H), 4.01-3.97(m, 1H), 3.69 (s, 3H), 2.60-2.56 (dd, J = 16.7, 4.0 Hz, 1H), 2.50-2.44 (dd, J = 16.7, 9.2 Hz, 1H) 2.35-2.29 (m, 3H), 1.74-1.68 (m, 1H); $^{13}$C NMR $\delta$ = 177.8, 171.8, 52.0, 51.7, 50.5, 40.9, 30.8, 297, 26.8.
(5S)-5-(tert-butyl dimethylsilyloxyethyl)-2-pyrrolidinone (184): Sodium borohydride (3.50 g, 92.0 mmol) was added portionwise to a solution of the ester 183 (5.90 g, 37.0 mmol) in dry ethanol (200 mL) at room temperature. After 50 h, acetone (10 mL) was added and the solution stirred for another 0.5 h. The mixture was acidified using concentrated hydrochloric acid with cooling, not permitting the pH to fall below 3.5. The solvent was evaporated and the residue was purified by flash chromatography (SiO\(_2\), 4:1 EtOAc/MeOH) to give (4.40 g, 92%) of the desired product as a clear oil. \([\alpha]\)\(_D\) = +32.7 (c = 0.33 MeOH). \(^1\)H NMR (D\(_2\)O) \(\delta = 3.84-3.80\) (quint, 6.9 Hz, 1H), 3.68-3.65 (t, \(J = 6.4\) Hz, 2H), 2.40-2.35 (ddd, 7.3, 2.8 Hz, 2H), 2.34-2.26 (m, 1H), 1.84-1.70 (m, 3H); \(^{13}\)C NMR \(\delta = 181.5, 58.7, 52.7, 37.7, 29.9, 26.4\); FT-IR (neat, cm\(^{-1}\)) : 3270, 2937, 1676. HR-MS: Calcd. for C\(_6\)H\(_{11}\)NO\(_2\)Na \((m/z)\): 152.0682 (M\(^{+}\)Na\(^{+}\)), found 152.0685.

Chlorosilane was added portionwise to a stirred solution of the above alcohol (4.40 g, 34.0 mmol) and imidazole (4.70 g, 74.0 mmol) in 22.8 mL DMF. The mixture was stirred for 16 h at which point. After 16 h at room temperature, 100 mL of EtOAc was added. The solution was washed with water and brine, dried with Na\(_2\)SO\(_4\) and evaporated. The product was purified via flash column chromatography (SiO\(_2\), 100% EtOAc) to give (7.60 g, 92%) of the desired product as a white solid. \([\alpha]\)\(_D\) = +26.2 (c = 1.1). \(^1\)H NMR \(\delta = 6.43\) (br, 1H), 3.72-3.70 (m, 3H), 2.27-2.20 (m, 3H), 1.67-1.64 (m, 3H), 0.82 (s, 9H), -0.01 (s, 6H); \(^{13}\)C NMR \(\delta = 171.9, 61.5, 53.6, 39.2, 30.1, 28.0, 26.0, 25.0, 18.3, -5.3, -5.4\); FT-IR (KBr, cm\(^{-1}\)) : 3104, 1731, 1604, 1348, 1251. HR-MS: Calcd. for C\(_{12}\)H\(_{26}\)NO\(_2\)Si \((m/z)\): 244.1727 (M\(^{+}\)H\(^{+}\)), found 244.1723.
General method for cross-coupling: The conditions for the cross-coupling with lactams 182, 183 and 184 was similar to the one that is described on page 68.

4-[(5S)-5-Cyanomethyl-2-oxo-1-pyrrolidinyl]benzonitrile (185a) The product was purified by flash chromatography (SiO$_2$, 1:9 hexanes/EtOAc), yielding 185a as a pale yellow solid (202 mg, 90%). mp 113-115°C. [α]$^D$ = +22.0 (c = 0.5). $^1$H NMR: δ = 7.70 (dd, J = 8.7, 1.4 Hz, 2H), 7.60 (td, J = 8.7, 1.4 Hz, 2H), 7.45 (d, J = 7.8 Hz), 4.60-4.56 (m, 1H), 2.86-2.80 (m, 1H), 2.72-2.52 (m, 4H), 2.16-2.11 (m, 1H); $^{13}$C NMR: δ = 173.9, 140.5, 133.5, 123.4, 118.5, 116.1, 109.3, 54.9, 53.8, 30.7, 24.4; FT-IR (KBr, cm$^{-1}$): 3110, 3066, 2963, 2250, 2227, 1699, 1602, 1507, 1460, 841. ESI-MS (m/z): 248 (M+Na$^+$, 9), 226 (M+H$^+$, 19), 185 (100). Anal. Calcd. for C$_{13}$H$_{11}$N$_3$O: C, 69.32; H, 4.92; N, 18.66. Found C, 69.45; H, 5.05; N, 18.64.

4-[(5S)-5-[(Carbomethoxy)methyl]-2-oxo-1-pyrrolidinyl]benzonitrile (185b). The product was purified by flash chromatography (SiO$_2$, 1:4 hexanes/EtOAc), yielding 185b as a white waxy solid (142 mg, 55%). [α]$^D$ = +31.0 (c = 0.5). $^1$H NMR: δ = 7.67-7.65 (m, 4H), 4.71-4.68 (m, 1H), 2.72-2.65 (m, 2H), 2.60-2.53 (m, 1H), 2.48-2.40 (m, 2H), 1.98-1.90 (m, 1H); $^{13}$C NMR: δ = 174.4, 170.7, 141.3, 133.2, 122.3, 118.7, 108.4, 55.6, 52.1, 37.6, 30.9, 24.1; FT-IR (neat, cm$^{-1}$): 2953, 2225, 1709,1707, 1602, 1508, 1435, 841, 731. HR-MS: Calcd. for C$_{14}$H$_{15}$N$_2$O$_3$ (m/z): 259.1077 (M+H$^+$), found 259.1073.

(185c). The product was purified by flash chromatography (SiO₂, 2:3 hexanes/EtOAc), yielding 185c as a colorless oil (313 mg, 91%). [α]D = +29.4 (c = 0.5). ¹H NMR: δ = 7.70 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 4.53-4.49 (m, 1H), 3.73-3.64 (m, 2H), 2.70-2.64 (m, 1H), 2.55-2.49 (m, 1H), 2.39-2.31 (m, 1H), 2.01-1.90 (m, 2H), 1.60-1.54 (m, 1H), 0.92 (s, 9H), 0.06 (s, 6H); ¹³C NMR: δ = 174.9, 141.9, 133.1, 122.1, 121.1, 118.9, 58.7, 56.4, 35.3, 31.4, 25.9, 23.8, 18.3, -5.4, -5.3; FT-IR (neat, cm⁻¹): 2951, 2226, 1697, 1602, 1587, 841, 734. HR-MS: Calcd. for C₁₉H₂₉N₂O₂Si (m/z): 345.1993 (M+H⁺), found 345.1994.

[(5S)-5-[(tert-butyl)dimethylsilyl]oxy]ethyl]-1-(4-nitrophenyl)-2-pyrrolidinone

(185d). The product was purified by flash chromatography (SiO₂, 1:1 hexanes/EtOAc), yielding 185d as a pale yellow solid (299 mg, 82%) mp: 88-90 °C. [α]D = +70.2 (c = 0.5). ¹H NMR: δ = 8.21 (d, J = 9.2 Hz, 2H), 7.87 (d, J = 9.2 Hz, 2H), 4.57-4.54 (m, 1H), 3.77-3.73 (m, 1H), 3.70-3.65 (m, 1H), 2.60-2.54 (m, 1H), 2.39-2.31 (m, 1H), 2.10-1.95 (m, 1H), 1.62-1.56 (m, 1H), 0.93 (s, 9H), 0.07 (s, 6H); ¹³C NMR: δ = 174.9, 143.9, 143.5, 124.7, 120.6, 59.3, 56.4, 35.2, 31.5, 25.9, 23.6, 8.3, -5.4, -5.3; FT-IR (neat, cm⁻¹): 2953, 2856, 1704, 1596, 1509, 1464, 835, 751. ESI-MS (m/z): 387 (M+Na⁺, 27), 365 (M+H⁺, 100), 233 (7), 205 (4), 187 (5). Anal. Calcd. for C₁₈H₂₈N₂O₄Si: C, 59.31; H, 7.74; N, 7.69. Found C, 59.01; H, 7.57; N, 7.68.
Methyl 5-nitro-2-[(5S)-5-{(tert-butyl)dimethylsilyloxyethyl}-2-oxo-1-pyrrolidinyl] benzoate (185e). A 10 mL Schlenk tube containing lactam 184 (2.92 g, 12.0 mmol), Cs₂CO₃ (4.56 g, 14.0 mmol), xantphos (0.88 g, 1.5 mmol), and Pd₂(dba)₃ (0.46 g, 0.5 mmol) was alternately evacuated and backfilled with nitrogen. Dioxane (10 mL) and methyl 5-nitro-2-bromobenzoate (2.60 g, 10.0 mmol) were introduced and then resulting mixture was heated at 105 °C for 10 h. The mixture was cooled, diluted with CH₂Cl₂ and then filtered through Celite. After concentration, the residue was purified by flash chromatography (SiO₂, 1:1 hexane/EtOAc) to give the N-aryl pyrrolidinone 185e (2.11 g, 55%) as a pale orange oil. The unreacted lactam (1.0 g, 35%) was recovered. [α]D = 0.00. ¹H NMR δ = 8.72 (d, J = 2.8 Hz, 1H), 8.36 (dd, J = 8.7, 2.8 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 4.48 (m, 1H), 3.90 (s, 3H), 3.64-3.60 (m, 2H), 2.58-2.53 (m, 2H), 2.47-2.43 (m, 1H), 1.99-1.97 (m, 1H), 1.91-1.89 (m, 1H), 1.71-1.65 (m, 1H), 0.86 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ¹³C NMR δ = 174.9, 164.9, 145.3, 142.6, 129.9, 127.1, 126.9, 126.4, 59.2, 58.4, 52.9, 36.9, 31.0, 25.9, 25.3, 18.3, -5.4; FT-IR (neat, cm⁻¹): 2951, 1733, 1528, 1343, 1102, 836. HR-MS: Calcd. for C₂₀H₃₂N₂O₆Si (m/z): 423.1946, (M+H⁺), found 423.1945.

Methyl 5-amino-2-[(5S)-5-{(tert-butyl)dimethylsilyloxyethyl}-2-oxo-1-pyrrolidinyl] benzoate (186). In a 25 mL round bottom flask were placed 185e (2.11 g, 5.40 mmol) and 10% palladium on charcoal (0.21 g). The flask was alternatively evacuated and backfilled with hydrogen. Methanol (40.0 mL) was introduced and the
mixture was stirred at room temperature under a balloon of hydrogen gas (1 atm) for 24 h. The mixture was filtered through Celite. After concentration, the residue was purified by flash chromatography (SiO$_2$, 100% EtOAc) to give pale yellow crystals of the amine (1.74 g, 89%). mp = 100-102 °C. [α]$_D$ = -39.3 (c = 0.65).

$^1$H NMR: δ = 7.26 (d, $J$ = 2.8 Hz, 1H), 6.94 (d, $J$ = 8.7 Hz, 1H), 6.80 (dd, $J$ = 8.7, 2.8 Hz, 1H), 4.11-4.09 (m, 1H), 3.82 (s, 3H), 3.58-3.57 (m, 2H), 2.51-2.48 (m, 2H), 2.38-2.34 (m, 1H), 1.87-1.83 (m, 2H), 1.61-1.56 (m, 1H), 0.84 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H); $^{13}$C NMR: δ = 175.8, 166.1, 145.9, 129.1, 127.9, 118.9, 117.5 (2C), 59.9, 59.8, 52.3, 37.2, 30.9, 25.9, 18.2, -5.4, -5.5; FT-IR (neat cm$^{-1}$): 3451, 3376, 2955, 1721, 1667, 1508, 1446, 1243, 1094. EI-MS ($m/z$): 392 (M$^+$, 21), 335 (100), 303 (26), 243 (34), 173 (24). HR-MS Calcd. for C$_{20}$H$_{32}$N$_2$O$_4$Si ($m/z$): 415.2024, (M+H$^+$), found 415.2012. Anal. Calcd. for C$_{20}$H$_{32}$N$_2$O$_4$Si: C, 61.19; H, 8.22; N, 7.14. Found: C, 60.79; H, 7.87; N, 7.20.

**Methyl 5-iodo-2-[(5S)-5-(hydroxyethyl)-2-oxo-1-pyrrolidinyl] benzoate (187).** The above amine (1.65 g, 4.15 mmol) was taken up in acetonitrile (29 mL). Diiodomethane (3.20 mL, 2.48 mmol) and n-pentyl nitrite (7.7 mL) were added. The solution was purged with nitrogen for 15 min and heated to 85-90 °C for 22 h under nitrogen. The reaction mixture is cooled to room temperature followed by addition of 1.0 M TBAF (10 mL) in THF. The reaction was stirred at room temperature for 7 h, quenched with water, and extracted with ethyl acetate. The organic phase was washed
with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give dark orange oil. The crude product was purified by flash chromatography (SiO$_2$, 0.5:9.5 methanol/EtOAc) to give pale yellow crystals (1.11 g, 68%) of 187. mp = 135-137 °C. [α]$_D$ = -67.3 (c = 0.81). $^1$H NMR δ = 8.22 (d, $J$ = 2.3 Hz, 1H), 7.84 (dd, $J$ = 8.3, 2.3 Hz, 1H), 6.94 (d, $J$ = 8.3 Hz, 1H), 4.32-4.29 (m, 1H), 3.84 (s, 3H), 3.63-3.58 (m, 2H), 2.52-2.45 (m, 2H), 2.41-2.38 (m, 1H), 1.93-1.87 (m, 2H), 1.74-1.69 (m, 1H); $^{13}$C NMR δ = 175.2, 165.2, 141.6, 140.0, 136.9, 130.5, 129.3, 91.6, 58.9, 58.4, 52.7, 36.4, 30.9, 25.3; FT-IR (neat cm$^{-1}$): 3466, 2945, 1730, 1664, 1580, 1480, 1438. EIMS (m/z): 389 (M$^+$, 68), 357 (53), 344 (100), 312 (84), 243 (39). Anal. Calcd. for C$_{14}$H$_{16}$INO$_4$: C, 43.21; H, 4.14; N, 3.60. Found: C, 43.47; H, 4.10; N, 3.54.

**Methyl 5-iodo-2-[(5$S$)-5-(ethynyl)-2-oxo-1-pyrrolidinyl]benzoate (179).** Alcohol 186 (1.1 g, 2.8 mmol) and o-nitrophenyl selenocyanate (1.2 g, 5.4 mmol) is taken in THF (8.45 mL). PBu$_3$ (2.4 mL, 9.5 mmol) was added dropwise. TLC showed no starting material after 1 h. At which point the reaction mixture was cooled to 0 °C and 30% H$_2$O$_2$ (1.5 mL 5.0 eq) was added dropwise. TLC showed no change for 5 min at 0 °C. 30% H$_2$O$_2$ (1.5 mL, 5.0 eq) was added and the reaction was stirred at room temperature for 7 h. EtOAc added and the organic layer was washed with saturated sodium bicarbonate. The aqueous phase was then extracted twice with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate followed by
concentration. The crude product was purified via flash column chromatography (SiO₂, 100% EtOAc) to give 179 (0.89 g, 85%) as a pale yellow solid. mp = 99-101 °C. [α]D = +12.7 (c = 0.65). ¹H NMR δ = 8.23 (d, J = 1.8 Hz, 1H), 7.81 (dd, J = 8.7, 2.3 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 5.80-5.76 (m, 1H), 5.13-5.07 (dd, J = 17.0, 4.5 Hz, 2H), 4.52 (q, J = 8.7 Hz, 1H), 3.86 (s, 3H), 2.56-2.52 (m, 2H), 2.47-2.42 (m, 1H), 1.98-1.94 (m, 1H); ¹³C NMR δ = 175.4, 164.9, 141.4, 140, 137.7, 137.2, 130.4, 118.9, 91.8, 64.7, 52.6, 30.9, 26.7; FT-IR (KBr cm⁻¹): 3065, 2947, 1729, 1695, 1581, 1556, 1481, 1456. ESI-MS (m/z): 394 (M+Na⁺, 84), 372 (M+H⁺, 13), 340 (100). Anal. Calcd. for C₁₄H₁₄INO₃: C, 45.30; H, 3.80; N, 3.77. Found: C, 45.29; H, 3.69; N, 3.70.

5-iodo-2-[(5S)-5-(ethynyl)-2-oxo-1-pyrrolidinyl]benzoic acid (189). Methyl ester 179 (0.70 g, 1.88 mmol) is dissolved in THF (4.5 mL) followed by addition of aqueous solution of 1 M LiOH (7.0 mL). The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The aqueous layer was then acidified with 1 N HCl till the pH reached 7.0. The acidified solution was extracted with ethyl acetate (3 x 30 mL), dried over anhydrous sodium sulfate and concentrated to give 189 (1.0 g, 99%) as a pale yellow oil which was used in the next step. ¹H NMR δ = 8.29 (d, J = 1.8 Hz, 1H), 7.82 (dd, J = 8.7, 1.8 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.81-5.78 (m, 1H), 5.09 (dd, J = 17.0, 4.5 Hz, 2H), 4.53 (q, J = 7.8 Hz, 1H), 2.64 (t, J = 9.2 Hz, 2H), 2.01-1.94
(m, 1H); $^{13}$C NMR $\delta = 177.2, 167, 141.7, 140.5, 137.4, 136.9, 130.4, 119.3, 65.4, 31.0, 26.7$; FT-IR (neat cm$^{-1}$): 3000, 2918, 2850, 1708, 1649, 1481, 1415.

Acid (189) (1.00 g, 2.90 mmol) was dissolved in ethyl acetate (13.3 mL) and cooled in an ice bath. $N$-hydroxysuccinimide (0.40 g, 3.48 mmol) was added followed by addition of DCC (0.71 g, 3.44 mmol). The reaction mixture was stirred at 0 °C for 10-15 min and at room temperature for 12 h. After 12 h the white precipitate was filtered through Celite and washed with ethyl acetate (100 mL). The combined organic extract was washed with saturated sodium bicarbonate (2 x 30 mL) followed by saturated sodium chloride (2 x 30 mL). The organic layer was dried and concentrated to give yellow oil (1.21 g, 95%). To a stirred solution of (190) (1.21 g, 2.76 mmol) in THF (5.5 mL) was added NaBH$_4$ (0.13 g, 3.43 mmol) at 0 °C. After 5 min ethanol (1.5 mL) was added to the reaction mixture and then stirred for 11 h at room temperature. The reaction mixture was then quenched by addition of saturated ammonium chloride and diluted with water. The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic extract was dried over sodium sulfate and concentrated to give yellow oil (SiO$_2$, 4:1 EtOAc/hexane) to give (188a) (0.69 g, 73%) of the product as colorless oil. (Spectral and analytical data given below)

(5S)-5-ethynyl-1-[4-iodo-2-(hydroxymethyl)phenyl]-2-pyrrolidinone (187a). $N$-aryl pyrrolidinone (186) (0.62 g, 1.70 mmol) was dissolved in dry THF (6.2 mL). This solution was purged with nitrogen and cooled in an ice bath to 0 °C followed by addition of anhydrous methanol (0.1 mL, 1.5 mmol). LiBH$_4$ (1.0 mL, 2 M in THF) was
added to this mixture dropwise and the resulting mixture is stirred at 0 °C. The reaction was closely monitored by TLC (3:2 EtOAc/CH₂Cl₂) and another portion LiBH₄ (1.0 mL) was added after 16 h. After 20 h from the start of the reaction, it was quenched by the addition of saturated ammonium chloride (20 mL) and the resultant solution was extracted with EtOAc (3 x 50 mL). The organic layer was washed once with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated. The resulting yellow oil was purified via flash column chromatography (SiO₂, 4:1 EtOAc/hexane) to give 188a (0.43 g, 70%) of the product as colorless oil. [α]D = +32.6 (c = 0.30). ¹H NMR δ = 7.87 (d, J = 1.8 Hz, 1H), 7.63 (dd, J = 8.3, 1.8 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 5.62-5.55 (m, 1H), 5.08 (dd, J = 17.9, 10.5 Hz, 2H), 4.51-4.46 (m, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.31 (d, J = 12.0 Hz, 1H), 2.65-2.57 (m, 2H), 2.48-2.44 (m, 1H), 2.01-1.97 (m, 1H); ¹³C NMR 176.2, 140.9, 139.9, 137.8, 136.5, 135.1, 119.6, 93.5, 65.1, 61.2, 30.9, 26.6; FT-IR (neat cm⁻¹) 3389, 2981, 1683, 1559, 1405. ESI-MS (m/z): 366 (M+Na⁺, 100), 326 (M+H⁺, 50), 268 (12), 214 (13). Anal. Calcd. for C₁₃H₁₄INO₂: C, 45.5; H, 4.11; N, 4.08. Found: C, 45.62; H, 4.36; N, 4.10.

The byproduct (188b) (87 mg, 15%) was isolated as yellow oil. [α]D = +0.12 (c = 1.0). ¹H NMR δ = 7.41-7.39 (dd, J = 8.7, 2.3 Hz, 1H), 7.30 (d, J = 2.3 Hz, 1H), 6.40 (d, J = 8.7 Hz, 1H), 5.75-5.7 (dq, J = 10.5, 6.0 Hz, 1H), 5.19 (d, J = 17.0 Hz, 1H), 5.12 (d, J = 10.5 Hz, 1H), 4.57 (d, J = 3.7 Hz, 2H), 3.82-3.80 (m, 1H), 3.65-3.63 (dd, J = 6.0, 5.5 Hz, 2H), 1.75-1.65 (m, 4H); ¹³C NMR δ = 146.6, 139.4,
137.9, 137.4, 126.7, 115.4, 114.1, 64.2, 62.6, 55.4, 32.1, 29.1; FT-IR (neat cm\(^{-1}\)) 3376, 2938, 1575, 1504, 1405. HR-MS: Calcd. for C\(_{13}\)H\(_{19}\)INO\(_2\) (m/z): 348.0455 (M+H\(^+\)), Found 348.0447.

**5-iodo-2-[(2S)-vinyl-5-hydroxy-1-butylamino]benzaldehyde (192).** 188b (80 mg, 0.23 mmol) was dissolved in CH\(_2\)Cl\(_2\) (2.5 mL) and 85% activated MnO\(_2\) (129 mg, 1.26 mmol, 5.5 eq) was added to this solution. The slurry was stirred at room temperature for 24 h at which point another portion of MnO\(_2\) (129 mg, 1.26 mmol, 5.5 eq) was added. The reaction mixture was stirred for another 24 h, followed by filtration through Celite. The Celite pad was washed with methanol and the filtrate was concentrated. The crude was purified by flash column chromatography (SiO\(_2\), 4:1 EtOAc/hexane) to give 191 (79 mg, 90%) as a yellow oil. 

\[\alpha\]\(D\) = +59.3 (c = 1.2). \(^1\)H NMR \(\delta = 9.70\) (s, 1H), 8.4 (brd, 1H), 7.70 (d, \(J = 2.3\) Hz, 1H), 7.53 (dd, \(J = 9.2, 2.3\) Hz, 1H), 6.48 (d, \(J = 9.2\) Hz, 1H), 5.76-5.71 (dq, \(J = 10.5, 6.0\) Hz, 1H), 5.18 (td, \(J = 11.0, 1.4\) Hz 1H), 5.15 (td, \(J = 4.5, 1.4, 0.90\) Hz, 1H), 3.97-3.95 (m, 1H), 3.69-3.67 (dd, \(J = 6.4\) Hz, 2H), 1.79-1.66 (m, 4H); \(^{13}\)C NMR \(\delta = 193.0, 149.5, 144.5, 143.7, 138.2, 120.7, 115.9, 114.6, 62.5, 55.0, 31.7, 28.9; FT-IR (neat cm\(^{-1}\)) 3371, 2941, 1655, 1571, 1503, 1428. HR-MS: Calcd. for C\(_{13}\)H\(_{17}\)INO\(_2\) (m/z): 346.0298 (M+H\(^+\)), Found 346.0294.

(5S)-5-ethynyl-1-[4-iodo-2-formylphenyl]-2-pyrrolidinol (192). A slurry of the alcohol 187a (0.44 g, 1.28 mmol) and 70% activated MnO\(_2\) (0.86 g 5.4 eq) in CH\(_2\)Cl\(_2\)
(12.0 mL) was stirred at 25 °C under N₂ for 24 h. Another portion of MnO₂ (0.86 g, 5.4 mmol) was added and the reaction mixture was allowed to stir for another 24 h. The solution was filtered through celite, which was washed with MeOH (2 x 20 mL). The combined filtrates were concentrated. The product was purified via flash column chromatography (SiO₂, 4:1 EtOAc/hexane) to give 193 (0.39 g, 90%) as a colorless oil. [α]D = -53.0 (c = 0.41). \(^1\)H NMR δ = 9.83 (s, 1H), 8.21 (d, \(J = 1.8\) Hz, 1H), 7.90 (dd, \(J = 8.3, 1.8\) Hz, 1H), 6.9 (d, \(J = 8.3\) Hz, 1H), 5.7-5.4 (m, 1H), 5.18 (d, \(J = 10.0\) Hz, 1H), 2.65-2.48 (m, 2H); FT-IR (neat cm\(^{-1}\)): 2872, 1701, 1581, 1477, 1397. ESI-MS (m/z): 364 (M+Na\(^+\), 100), 342 (M+H\(^+\), 72), 314 (37), 248 (35), 187 (11). Anal. Calcd. for C\(_{13}\)H\(_{12}\)INO\(_2\): C, 45.77; H, 3.55; N, 4.11. Found: C, 45.54; H, 3.78; N, 4.11.

(3aS, 3bS, 11bS)-10-iodo-1,2,3,3a,4,5,11b-octahydro-1-(phenylmethyl)-6H-dipyrrrolo[1,2-a:3',2'-c]quinolin-6-one (194).

Compound (192) (0.24 g, 0.70 mmol) and N-benzylglycine hydrochloride (0.25 g, 1.26 mmol, 1.8 eq) was dried under the pump for 15 min and then purged with nitrogen. Dry toluene (23 mL) was added followed by addition of Et\(_3\)N (0.27 mL, 2.1 mmol, 3 eq). The reaction mixture was heated in oil bath at 120 °C for 23 h. After completion of the reaction the toluene was removed by evaporation and the resulting
green solid was partitioned between water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers were washed with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated. The brown solid was purified via flash column chromatography (SiO$_2$, 1:1 EtOAc/hexane) and the resulting solid was recrystallized (3:2 EtOAc/CH$_2$Cl$_2$) to provide 194 (0.22 g, 71%) of as an off white crystalline solid. mp = 191-193 °C. $[\alpha]_D$ = -80.9 (c = 0.44). $^1$H NMR $\delta$ = 8.62 (d, $J$ = 9.2 Hz, 1H), 7.61-7.59 (dd, $J$ = 9.2, 2.0 Hz, 1H), 7.56 (d, $J$ = 2.0 Hz, 1H), 7.25-7.21 (m, 5H), 4.28 (d, $J$ = 12.4 Hz, 1H), 4.05 (ddd, $J$ = 17.0, 9.6, 8.0 Hz, 1H), 3.16 (d, $J$ = 3.7 Hz, 1H), 3.12 (d, $J$ = 12.4 Hz, 1H), 2.92 (ddd, $J$ = 9.7, 7.0, 3.7 Hz, 1H), 2.65-2.59 (m, 1H), 2.56-2.52 (m, 1H), 2.36-2.34 (m, 1H), 2.22-2.17 (m, 1H), 2.06-2.0 (m, 1H), 1.69-1.57 (m, 3H); $^{13}$C NMR $\delta$ = 174.2, 140.2, 139.6, 137.4, 136.9, 128.4 (2C), 128.3, 127, 126.7 (2C), 121, 85.9, 64, 58.2, 57.2, 51.3, 41.5, 32.3, 24.1, 23.8; FT-IR (KBr, cm$^{-1}$): 2928, 2785, 1693, 1481, 1367. ESI-MS ($m/z$): 467 (M$^+$Na$^+$, 100), 445 (M$^+$H$^+$, 89), 366 (53), 338 (66), 301 (14), 288 (13), 274 (8). Anal. Calcd. for C$_{21}$H$_{21}$IN$_2$O: C, 56.77; H, 4.76; N, 6.30 Found: C, 56.60; H, 4.80; N, 6.42.

The diastereomer (28 mg, 5%) was isolated. $[\alpha]_D$ = -64.2 (c = 0.33). $^1$H NMR $\delta$ = 8.18 (d, $J$ = 8.9 Hz, 1H), 7.61 (d, $J$ = 2.0 Hz, 1H), 7.54-7.48 (ddd, $J$ = 8.9, 2.0 Hz, 1H), 7.37-7.28 (m, 5H), 4.11-4.09 (ddd, $J$ = 7.7, 3.1 Hz 1H); 4.00 (d, $J$ = 8.3 Hz, 1H), 3.96 (d, $J$ = 12.8 Hz, 1H), 3.74 (d, $J$ = 12.8 Hz, 1H), 2.84-2.82 (m, 2H), 2.61-2.54 (m, 3H0, 2.23-2.19 (m, 1H), 1.98-1.93 (m, 1H), 1.91-1.85 (m, 1H), 1.65-1.61 (m, 1H); $^{13}$C NMR $\delta$ =
The pyrroloquinoline (0.18 g, 0.41 mmol) was dissolved in dry THF (150 mL) followed by addition of MeOH (0.03 mL, 2 eq). The solution was degassed with nitrogen and a solution of LiBH₄ (0.19 mL, 2 M in THF) was added dropwise. The reaction mixture was heated in an oil bath at 85-90 °C for 2 days. Additional LiBH₄ (0.19 mL 2 M in THF) and MeOH (0.03 mL) were added to the refluxing solution every 24 h. After 4 days the reaction mixture was cooled in an ice bath and acidified to pH 4-5 with 1N hydrochloric acid followed by neutralization with 2 N sodium hydroxide. The THF was removed under vacuum. The resulting mixture was dissolved in water and extracted three times with ethyl acetate. The combined organic layers was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated in vacuo. The brown oil was purified via flash column chromatography (SiO₂, 3:2 EtOAc/hexane) to give 197 (0.15 g, 85%) as a off white solid. mp = 39-41 °C [α]D = -84.7 (c = 0.53). ¹H NMR δ =  7.36 (s, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.29-7.18 (m, 5H), 6.38 (d, J = 8.3 Hz, 1H) 4.28 (d, J = 12.0 Hz, 1H), 3.70(d, J = 6.4, Hz, 1H), 3.69 (d, J = 5.5 Hz, 1H) 3.22 (t, J = 8.0 Hz, 1H), 3.14 (d, J = 12.0 Hz, 2H), 2.87 (td, J = 9.0, 3.2 Hz, 1H), 2.18-2.08 (m, 1H), 2.02-1.89 (m, 2H), 1.77-1.66 (m, 3H), 1.61-1.55 (m, 1H), 1.52-
1.47 (m, 1H); $^{13}$C NMR $\delta = 144.6, 140.0, 136.9, 128.7, 128.2, 126.9, 116.5, 63.6, 62.9,$
57.8, 52.5, 51.5, 39.2, 29.9, 28.6, 25.8; FT-IR (neat cm$^{-1}$): 3337, 3025, 2932, 2784,
1595, 1490. HR-MS: Calcd. for C$_{21}$H$_{26}$IN$_2$O ($m/z$): 449.1084 (M+H$^+$), Found 449.1070.

(3a$S$, 4$S$, 9b$S$)-8-iodo-2,3,3a,4,5,9b-hexahydro-5-(3-oxobutanoyl)-1-(phenylmethyl)-
$1H$-pyrrolo[3,2-c]quinoline-4-propyl acetate (198). 83 mg (0.19 mmol) amino alcohol (196)
was dissolved in CH$_2$Cl$_2$ (20 mL) and cooled in an ice bath (0 °C). Et$_3$N (0.52 mL, 3.8 mmol, 20
eq) was added followed by dropwise addition of 0.13 mL (1.9 mmol, 10 eq) acetyl chloride. The resulting yellow solution is stirred at 0 °C for 5 min and then at room
temperature for 5 h under nitrogen. After 5 h the reaction mixture was diluted with
CH$_2$Cl$_2$ (20 mL) and washed with saturated sodium bicarbonate (15 mL), the organic
layer was dried over anhydrous sodium sulfate and Et$_3$N was removed by azeotropic
distillation with CH$_2$Cl$_2$. The brown oil was purified via flash column chromatography
(SiO$_2$, 1:1 EtOAc/hexane) to give 198 (0.13 g, 75%) (3:2 keto/enol mixture) as a yellow
semi solid. $^1$H NMR $\delta = 7.65-7.63$ (dd, $J = 8.3$, 1.8 Hz, 0.6H), 7.62-7.60 (dd, $J = 8.3$,
1.8 Hz, 0.4H), 7.55 (d, $J = 1.8$ Hz, 0.6H), 7.5 (d, $J = 1.8$ Hz, 0.4H), 7.22-7.17 (m, 3H),
7.13 (d, $J = 7.3$ Hz, 1H), 7.08 (d, $J = 7.3$ Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 0.4H), 6.90 (d, $J$
= 8.3, 0.6H), 5.26 (s, 0.4H), 4.93-4.91 (dd, $J = 11.0$, 4.6 Hz, 0.6H), 4.9 (brd $J = 11.0$ Hz,
0.4H), 3.94-3.89 (m, 3H), 3.63 (d, $J = 15.5$ Hz, 0.6H), 3.58 (d, $J = 15.5$ Hz, 0.6H), 2.90-
2.84 (m, 1H), 2.56-2.50 (m, 1H), 2.45 (d, $J = 11.0$ Hz, 0.4H), 2.30 (d, $J = 11.0$ Hz,
0.4H), 2.22 (s, 0.6 X 3H), 2.19-2.13 (m, 0.4 X 3H), 2.04-1.99 (m, 1H), 1.96 (s, 0.6 X 3H), 1.94 (s, 0.4 X 3H), 1.86-1.81 (m, 1H), 1.57-1.54 (m, 1H), 1.47-1.46 (m, 1H), 1.28-1.25 (m, 1H), 1.04-0.96 (m, 1H); $^{13}$C NMR $\delta = 203, 175, 171.7, 171.1, 166.9, 139.4, 139.1, 137.5, 128.3, 128.2, 128.1, 128.0, 91.0, 89.9, 89.2, 64.2, 63.8, 57.7, 57.6, 52.9, 50.3, 46.6, 46.5, 31.0, 30.5, 29.8, 25.3, 25.2, 21.0. FT-IR (neat cm$^{-1}$) 2961, 1733, 1643, 1484.

Methyl (3a$S$, 4$S$, 9b$S$)-2,3,3a,4,5,9b-hexahydro-5-(3-oxobutanoyl)-1-(phenylmethyl)-1$H$-pyrrolo[3,2-c]quinoline-8-carboxylate (199).

A slurry of NaOAc (106 mg 1.29 mmol), Ph$_3$P (47.0 mg 0.18 mmol), 197 (248 mg 0.43 mmol) and Pd(OAc)$_2$ (27 mg, 0.12 mmol) in dry MeOH (2.5 mL) and DMF (2.5 mL) was placed in a pressure vessel. The vessel was purged with nitrogen for 10 min and then with CO. The reaction mixture was stirred under CO (75 psi) at 120 $^\circ$C. After 24 h the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was evaporated and the residue was taken up in CH$_2$Cl$_2$ (22.0 mL) and 0.5 M NaOMe (0.94 mL) and stirred overnight at room temperature. After the reaction was complete it was diluted with CH$_2$Cl$_2$ and washed twice with saturate sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude was purified via flash column chromatography (SiO$_2$, gradient elution 100% CHCl$_3$ – 99:1 CHCl$_3$/MeOH) to give 199 (156 mg, 96%) as a yellow solid. mp = 42-44 $^\circ$C. $[\alpha]$$_D$ = -132.7 (c = 0.49). $^1$H NMR $\delta =$
7.8 (d, J = 1.8 Hz, 1H), 7.75 (dd, J = 8.7, 1.8 Hz, 1H), 7.24-7.23 (m, 4H), 7.21-7.17 (m, 1H), 6.53 (d, J = 8.7 Hz, 1H), 4.8 (brs, 1H), 4.31 (d, J = 12.4 Hz, 1H), 3.83 (s, 3H), 3.75-3.69 (m, 2H), 3.31-3.28 (t, J = 16.5, 8.5 Hz), 3.2 (brd, J = 3.7 Hz, 1H), 3.14 (d, J = 12.4 Hz, 1H), 2.92-2.88 (td, J = 10.5, 3.2 Hz, 1H), 2.22-2.12 (m, 1H), 1.91-1.79 (m, 3H), 1.75-1.68 (m, 3H), 1.58-1.47 (m, 2H); 13C NMR δ = 167.5, 149.2, 139.9, 134.3, 130.6, 128.6, 128.1, 126.8, 117.8, 116.9, 113.2, 64.0, 62.8, 57.5, 52.4, 51.6, 51.4, 38.8, 29.7, 28.6, 25.8; FT-IR (neat cm⁻¹) 3369, 2947, 1698, 1613, 1521, 1436. HR-MS: Calcd. for C_{23}H_{28}N_{2}O_{3} (m/z): 381.2173 (M+H^+), Found 381.2163.

**Methyl (3aS, 4S, 9bS)-2,3,3a,4,5,9b-hexahydro-5-(3-oxobutanoyl)-1-(phenylmethyl)-5-(trifluoroacetyl)-1H-pyrrolo[3,2-c]quinoline-8-carboxylate (200).**

TFAA (0.52 mL, 3.7 mmol, 10 eq) was added dropwise to a solution of 198 (139 mg, 0.37 mmol) and pyridine (0.8 mL, 3.7 mmol, 10 eq) in dry CH_{2}Cl_{2} (13.0 mL) at 0 °C. The solution was allowed to stir for 30 min and at room temperature for 12h. becoming dark brown. Dry MeOH (13.0 mL) was added to the solution, which was stirred for 30 min. The solution was concentrated by blowing nitrogen through the flask. The solution was diluted with CH_{2}Cl_{2} (40 mL) and washed with saturated sodium bicarbonate (10 mL). The organic layer was separated and dried over saturated sodium sulfate and concentrated to obtain crude as brown oil. The crude was purified via flash column chromatography (SiO_{2}, gradient elution 100% CHCl_{3} – 99:1 CHCl_{3}/MeOH) to give 200 (87 mg, 50%) as a
yellow oil. $^1$H NMR $\delta = 8.34$ (d, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 2.7$ Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 1H), 7.21-7.15 (m, 6), 3.95 (s, 3H), 3.82-3.85 (m, 2H), 3.51 (m, 1H), 3.36 (d, $J = 10$ Hz, 1H), 3.05 (d, $J = 10$, 1H), 2.87 (dd, $J = 8.4$, 7.5 Hz, 1H), 2.56 (m, 1H), 2.21 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H), 1.51 m, 1H), 1.43-1.37 (m, 3H), 1.0 (m, 1H); HR-MS: Calcd. for C$_{25}$H$_{27}$F$_3$N$_2$O$_4$ ($m$/z): 477.1996 (M+H$^+$), Found 477.1990.

**Methyl (3a$S$, 4$S$, 9b$S$)-4-(3-azidopropyl)-2,3,3a,4,5,9b-hexahydro-1-(phenylmethyl)-1H-pyrrolo[3,2-c]quinoline-8-carboxylate (202).**

MsCl (0.07 mL, 0.91 mmol, 10 eq) was added dropwise to a stirred solution containing of 199 (46 mg, 0.09 mmol) and pyridine (0.15 mL, 1.42 mmol, 15 eq) in dry CH$_2$Cl$_2$ (47 mL) at 0 °C under nitrogen. The solution was stirred at 0 °C for 10 min and 24 h at room temperature. The solution was diluted with CH$_2$Cl$_2$ (80 mL) and washed with water (4 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 52 mg of the crude mesylate as an off white oil. The crude mesylate was dissolved in DMF (2 mL) and sodium azide (58 mg, 0.9 mmol, 10 eq) was added to the solution. The solution was stirred at room temperature for 36 h. The solution was diluted with CH$_2$Cl$_2$ (20 mL) and washed with water (4 x 6 mL) and saturated sodium chloride (4 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 26 mg of the crude trifluoroacetamide azide as an oil. The crude trifluoroacetamide azide was dissolved in dry CH$_2$Cl$_2$ (10 mL) and NaOMe (0.31 mL, 0.5
M in MeOH) was added. The solution was stirred for 1 h, diluted with CH₂Cl₂ (10 mL) and washed with saturated sodium chloride (4 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The crude was purified by flash column chromatography (SiO₂ gradient elution 100% CHCl₃ – 99:1 CHCl₃/MeOH) to give 202 (20.0 mg, 51%) as a yellow oil. [α]₅ = -134.8 (c = 0.66). ¹H NMR δ = 7.81 (s, 1H), 7.76 (dd, J = 8.7, 1.8 Hz, 1H), 7.24-7.16 (m, 5H), 6.56 (d, J = 8.7 Hz, 1H), 4.55 (s, 1H), 4.3 (brd J = 12.5 Hz, 1H), 3.84 (s, 3H), 3.37 (t, J = 6.4 Hz, 2H), 3.33 (t, J = 8.7 Hz 1H), 3.21 (brd, J = 4.6 Hz, 1H), 3.13 (d, J = 12.5 Hz, 1H) 2.90 (td, J = 8.9, 2.8 Hz, 1H), 2.16-2.12 (m, 1H), 2.04-1.98 (m, 1H), 1.96-1.88 (m, 1H), 1.80-1.66 (m, 3H), 1.62-1.50 (m, 3H), 1.57-1.52; ¹³C NMR δ = 167.4, 148.9, 134.3, 130.6, 128.6, 128.1, 126.8, 117.4, 113.3, 68.1, 63.9, 57.4, 53.5, 52.1, 51.6, 51.3, 38.5, 30.3, 25.7; FT-IR (neat cm⁻¹) : 2957, 2095, 1704, 1610, 1517, 1437. HR-MS: Calcd. for C₃₈H₂₈N₅O₂ (m/z): 406.2236 (M+H⁺), Found 406.2238.

Methyl (3α, 4α, 9bS)-4-(3-aminopropyl)-2,3,3a,4,5,9b-hexahydro-1H-phenylmethyl-1H-pyrrolo[3,2-c]quinoline-8-carboxylate hydrochloride salt (132).

A slurry containing of 20% Pd(OH)$_₂$ (116 mg) on carbon and 201 (39.0 mg) in of 20:1 MeOH/HCl (20 mL) was stirred under a balloon of H₂ gas (1 atm) for 3 h. The solution was filtered through Celite and washed with MeOH (2 x 100 mL). The combined filtrate was concentrated to
give 38 mg of crude oil. The oil was dried by azeotropic distillation with MeOH to give
132 (25 mg, 89%) as a yellow oil. $^1$H NMR (CD$_3$OD): $\delta = 8.0$ (s, 1H), 7.71 (s, 1H),
6.86 (s, 1H), 4.7 (s, 1H), 3.8 (s, 3H), 3.2 (s, 1H), 3.1 (s, 2H), 3.05 (s, 2H), 2.48-2.27 (m,
1H), 2.02 (s, 3H), 1.97 (s, 1H), 1.29 (m, 1H); $^{13}$C NMR: $\delta = 167.1, 149.8, 132.7, 131.4,
117.9, 114.5, 112, 49.6, 48.6, 48.3, 48.1, 47.9, 47.8, 47.6, 47.4, 47.3, 38.2, 29.2, 22.7.

**Methyl Martinellate (142):** To a solution of 132 (20 mg, 0.07 mmol), 141 (64 mg, 0.25
mmol), and Et$_3$N (0.08 mL, 0.6 mmol) in CH$_3$CN (2 mL) and MeOH (1 mL) were
added dropwise a solution of AgNO$_3$ (60 mg, 0.35 mmol) in 0.5 mL CH$_3$CN over 0.5 h
period. After the reaction mixture was stirred 16 h at 40 °C in the dark, it was filtered
and the filtrate concentrated to dryness. The residue was dissolved in CHCl$_3$ and
washed with water once. The aqueous layer was extracted with CHCl$_3$ twice and the
combined organic layer was dried and concentrated. The residue was purified by flash
column chromatography (SiO$_2$, 9:1 CH$_2$Cl$_2$/MeOH) to give 13.0 mg (38%) of the
product as yellow oil. $[\alpha]_D = -95.2$ (c = 0.58). $^1$H NMR $\delta = 7.95$ (s, 1H), 7.66 (d, $J =
8.0$ Hz, 1H), 6.60 (d, $J = 8.0$ Hz, 1H), 5.29-5.23 (m, 1H), 5.21-5.20 (m, 2H), 3.89 (dd, $J$
= Hz, 1H), 3.79 (s, 3H), 3.77-3.74 (m, 2H), 3.43-3.34 (m, 6H), 3.20-3.10 (m, 1H), 2.40-
2.32 (m, 1H), 2.08-2.04 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H),
1.63-1.66 (m, 2H), 1.51 (s, 9H), 1.47 (s, 9H), 1.47-1.40 (m, 4H); $^{13}$C NMR $\delta = 167.4,
162.2, 159.7, 159.5, 146.5, 137.5, 137.4, 137.2, 131.7, 130.2, 120.2, 119.5, 118.1,
113.9, 82, 78, 53.8, 51.5, 50.6, 46.9, 43.6, 43.1, 42.6, 39.7, 39.5, 32.0, 30.1, 29.8, 29.5,
28.5, 28.1, 27.9, 26.5, 25.7, 18.1, 14.2, 13.9, 13.3. HR-MS: Calcd. for C$_{38}$H$_{60}$N$_7$O$_6$
($m/z$): 710.4600 (M+H$^+$), Found 710.4609
**Martinellie acid (2)** to a solution of 142 (10 mg, 0.01 mmol) in methanol (1.5 mL) and water (0.5 mL) was added 0.15 M NaOH (0.5 mL). The reaction mixture was refluxed for 10 h and then neutralized with 0.1 N HCl cautiously. MeOH was removed under reduced pressure and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried and concentrated. The residue was purified by column chromatography (SiO$_2$, 9:1 CH$_2$Cl$_2$/MeOH) to give 6 mg of the corresponding acid, which was confirmed by NMR. $^1$H NMR $\delta$ = This acid was dissolved in 1 mL of CH$_2$Cl$_2$ before 0.03 mL of anisole and 0.05 mL of anhydrous trifluoroacetic acid were added. The mixture was stirred at room temperature for 14 h and then concentrated. The residue was purified by using Baker Bond (C$_{18}$) 40 µm Prep LC packing (Gradient elution 100% H$_2$O to 100% MeOH in 20% increments with 0.05% TFA in MeOH.) to yield 4.6 mg (38%)

$[\alpha]_D = -25.0$ (c = 2.0 MeOH please view page 59 for detailed results) $^1$H NMR (CD$_3$OD) $\delta$ = 7.83 (s, 1H), 7.65 (dd, $J$ = 2.0, 10.0 Hz, 1H), 6.57 (d, $J$ = 10 Hz, 1H), 5.38 (brt, 1H), 5.3 (d, $J$ = 5.0 Hz, 1H), 5.23 (brt, 1H), 3.98 (d, $J$ = 5.0 Hz, 1H), 3.95 (d, $J$ = 5 Hz, 1H), 3.77 (d, $J$ = 5 Hz, 2H), 1.79 (s, 3H), 1.75 (s, 6H), 1.70 (s, 3H), 1.67-1.61 (m, 2H).
PART II METAL CATALYZED ORGANIC TRANSFORMATIONS
CHAPTER 4
INTRODUCTION

4.1 Carbene and nitrene chemistry

Interest in carbenes and nitrenes as highly reactive intermediates in organic chemistry dates back to the last century. There has been significant progress in the reactions of carbenes and nitrenes in the last decade. The earliest work in this field was carried out predominantly with under thermal or photolytic activation, often giving rise to a highly reactive intermediate, which reacts with any component present in the reaction mixture. Unless they are carried out under carefully controlled conditions, reactions of carbenes and nitrenes can lead to a majority of undesired side products. Recently there has been growing interest in this field due to the advent of catalytic methods for generation of the carbene and their metallio congeners, which allows much greater control over the course of their reactions.

4.2 Catalysts for metal carbene transformation

Diazo compounds are inherently unstable to acid-promoted decomposition, and it is this instability that models their effectiveness for catalytic reactions with transition metal compounds. Transition metal complexes that are effective catalyst for diazo decomposition are Lewis acids. Their activity depends on coordinative unsaturation at the metal center, which allows them to react as electrophiles with diazo compounds. In
the generally accepted mechanism for catalytic decomposition of diazo compounds depicted in Scheme 4.1,\textsuperscript{73,74} electrophilic addition causes the loss of dinitrogen and production of a metal-stabilized metallocarbene (IV). Transfer of the electrophilic carbene entity to an electron-rich substrate (S:) regenerates the catalytically active L\textsubscript{n}M. The earliest work in catalytic carbene transfer was limited to heterogeneous catalysis with insoluble copper and copper compounds.\textsuperscript{71,72,77} Introduction of homogeneous copper catalysts 40 years\textsuperscript{75} ago has not only resulted in decrease in the use of heterogeneous catalyst but also in an exponential growth in the field of catalyst design and application.

**Scheme 4.1**
Copper(II) complexes were initially favored over those of air-sensitive copper(I) because of their stabilities and general ease of preparation. Apart from the achiral copper compounds that have extensive uses as catalysts for carbene transformations, a number of chiral ligands (Figure 4.1) have developed to effect asymmetric carbine transfer in cyclopropanation and other transformations. The chiral complexes shown in figure 4.2 are among the most effective catalysts for enantioselective intermolecular cyclopropanation reactions.

![Figure 4.1 Examples of chiral copper complex](image)

Palladium(II) chloride and palladium(II) acetate have been used effectively for cyclopropanation reactions with diazomethane. Palladium(II) is not a very good catalyst for reactions involving diazocarbonyl compounds probably because carbene dimer formation is a common outcome, whereby subsequent reactions of these dimers increases the formation of complex mixtures (Scheme 4.2).
Scheme 4.2

Rhodium complexes have been most effective in a variety of reactions involving carbene transformations. Apart from dirhodium(II) catalyst,\(^{74,77}\) other rhodium complexes, such as iodorhodium porphyrins\(^ {78}\) and hexarhodium hexadecacarbonyl\(^ {81}\) have been used as catalysts for carbene transfer. Other transition metals that have been successfully used for carrying out carbene transfer include osmium, iron, platinum and nickel.\(^ {73}\) These have been used in catalytic as well as stoichiometric amounts.

4.3 Tris(pyrazolyl)borates

Trofimenko first introduced poly(pyrazolyl)borates in 1960 and since then these systems have been employed in numerous occasions in coordination chemistry.\(^ {80}\) Scorpionate complexes of almost every transition metal and metalloid have been prepared,\(^ {81}\) as well as several lanthanoids and actinoids, a statement that can not be made for few other ligands.
For a long time poly(pyrazolyl)borates have been compared to $\beta$-diketones, when bidendate $[R_2B-(Pz)_2 = \text{VII}]$, or to Cp, Cp*, when tridendate $[RB(Pz)_3 = \text{IX}]$, as shown in figure 4.2. Even though such comparisons had some value in describing poly(pyrazolyl)borates, they were not helpful in underscoring the unusual and specific features of this ligand system. These comparisons failed to explain the close relationship of the bis- and tris-(pyrazolyl)borates. The term “scorpionate ligands” was coined by Trofimenko in order to comprehensively describe this class of ligands.

Several groups have successfully synthesized and used complexes of pyrazolyl borates in organic synthesis. The pyrazole derivatives are usually prepared by condensation of $\beta$-diketones with hydrazine and the resulting pyrazoles are then reacted at high temperature with an alkali borohydride to give the alkali scorpionate salt. The desired transition metal complex can be obtained by treating this borohydride complex with metal salts. There have been several reviews on this area$^{81,82}$ as well as a book by Trofimenko has been published.$^{83}$ The main drawback of some of these scorpionate
complexes is their thermal and air instability, particularly in complexes with no substituent or a small alkyl group (e.g. methyl) in the 3-position. A greater degree of stabilization can be achieved by introduction of a large substituent (e.g. phenyl or t-butyl) in the 3-position, or by electron-withdrawing groups to one or multiple positions of the pyrazole rings.\textsuperscript{83-85}

Figure 4.3 First examples of fluorinated scorpionate metal complexes

Graham and co-workers\textsuperscript{84} have shown that hydridovinyliridium carbonyl complex (Figure 4.3) could be isolated as an air-stable solid by using hydro(3-trifluoromethyl)-5-methylpyrazolyl)borate as a ligand. Later Dias published the synthesis and crystal structure of the complex hydrotris(3,5-bis(trifluoromethyl)pyrazolyl)borate (Tp(CF\textsubscript{3})\textsubscript{2}) as the potassium salt (Figure 4.4).\textsuperscript{85a} This publication was followed by several additional publications by Dias group in which the Tp(CF\textsubscript{3})\textsubscript{2} ligand was used.\textsuperscript{85b-d} The stabilizing ability of the Tp(CF\textsubscript{3})\textsubscript{2} moiety is most dramatic in low-valent complexes of the late transition metals. Dias has reported the isolation of the Tp(CF\textsubscript{3})\textsubscript{2} adducts of the carbonyl complexes of copper(I),\textsuperscript{85b} silver(I),\textsuperscript{85c} and gold(I).\textsuperscript{85d} Each of these coinage metal carbonyls can be classified as nonclassical metal carbonyls, showing evidence by IR spectroscopy of very little backbonding from the filled metal $d$ orbitals into the $\pi$ orbitals of CO ($\nu_{\text{CO}} = 2137, 2162,$
and 2144 cm$^{-1}$ for the complexes of Cu, Ag, and Au respectively compared to 2143 cm$^{-1}$ for gas gas phase CO molecule.$^{17b, c, d}$

4.4 Application of tris(pyrazolyl)borates in catalysis

The earliest example of Tp complex that was used for catalysis was hydrotris(3,5-dimethylpyrazolyl)borato copper(I) (Tp*Cu(C$_2$H$_4$)). This complex was used by Perez, Brookhart and Templeton for catalytic aziridination and cyclopropanation of alkenes, and the cyclopropenation of alkynes.$^{86}$ Good yields were obtained for cyclopropanation and aziridination of styrene and cis-cyclooctene, and lower yields were seen with 1-hexene (Scheme 4.3).

**Scheme 4.3**

Perez also reported the addition of ethyl diazoacetate (EDA) to a variety of secondary and hindered primary amines in the presence of copper scorpionates to give N-H insertion products (Scheme 4.4).$^{87}$ Copper scorpionates have also been successfully used to catalyze carbene insertion into O-H bonds of primary and secondary alcohols (Scheme 4.4).$^{88}$

104
Copper complexes containing fully brominated Tp$_3^{Br}$ (hydrotris(3,4,5-tribromopyrazolyl)borate) ligand has been used to carry out C-H insertion for hydrocarbons. Insertion into C-H bonds of ethers occur selectively at the carbon atom $\alpha$ to the oxygen (Scheme 4.5)$^{89}$

Complexes of fluorinated trispyrazolylborates have also been used for catalytic carbene and nitrene insertion. The copper and silver scorpionate complexes developed by the Dias group have found application in various carbene and nitrene insertion chemistry (Scheme 4.6).$^{90}$
Scheme 4.6

Some general trends that have been observed for nearly all aziridination catalysts were: aromatic alkenes generally gave higher yields of aziridines than aliphatic alkenes, terminal alkenes gave higher yields than internal alkenes, and cis disubstituted alkenes gave higher yields than trans disubstituted alkenes. Catalysts 228 and 229, both function efficiently in cyclopropanation reactions, although the yields of the products obtained in these reactions are lower than those of the corresponding aziridinations. Fluorinated scorpionate catalysts gave a predominance of the cis products. The selectivity is reversed as compared to cyclopropanations carried out with more traditional catalysts. Fluorinated silver scorpionates 232 were also used, to carry out a few organic transformations. The silver systems were not viable nitrene transfer
catalysts as no aziridine products were formed. Both, the silver 232 as well as the copper 233 complexes, have been used for activation of C-H bonds (Scheme 4.7).\textsuperscript{90a,b}

Scheme 4.7

\[
\begin{align*}
R-H & \rightarrow \text{232/233} \text{EDA} \rightarrow R-CO_2Et \\
& \text{0 - 88\%}
\end{align*}
\]

Attempted cyclopropanation of styrene with silver complex 232 resulted in the formation of some unexpected products, the results of which will be discussed in the subsequent chapter.

More recently the Dias group synthesized a novel fluorinated triazapentadienyl ligand system.\textsuperscript{21} Fluorinated triazapentadienyl ([N{(C_{3}F_{7})C(Ph)N}]_{2}) can be compared to bis(pyrazolyl)borates ([H_{2}B(3,5-(CF_{3})_{2}Pz)_{2}]\textsuperscript{-}, Figure 4.4). Both these ligand systems are highly fluorinated, monoionic, nitrogen based donors and can form six-membered metalloccycles with metal ions and are analogous to the β-diketone ligands.

\[
\begin{align*}
\text{234} & \quad \text{235}
\end{align*}
\]

Figure 4.4 Comparison bis(pyrazolyl)borate 234 and triazapentadienyl ligand 235
Siedle has described the synthesis of these ligands starting from (C₄F₉)₃N. The other reports related to this area of interest involved the use of [N{(R)C(H)N}₂] (R = fluoroalkyl) as ligands for a few late transition metal ions and gallium. The Dias group synthesized fluoroalkyl substituted, triazapentadiene ligand [N{(C₃F₇)C(Dipp)N}₂]H (where Dipp = 2,6-diisopropylphenyl) from the reaction of 2,6-diisopropylaniline with the perfluoro-5-aza-4-nonene (C₃F₇-CF=N-C₄F₇) in ether (Scheme 4.8). The copper(I) acetonitrile complex is prepared by treating the free ligand with copper(I) oxide in acetonitrile. The organometallic complex has been completely characterized. We became interested in its reactivity and its potential utility as a catalyst in organic transformations. If this complex can act as a catalyst for carbene and nitrene insertion chemistry, then efforts could be focused on developing chiral catalyst (starting with chiral amines in Scheme 4.8). The chiral variants of these complexes can be compared to Pflatz’s 5-aza semicorins (Figure 4.2), which have demonstrated the highest stereocontrol in intermolecular cyclopropanation reactions.

Scheme 4.8
The results of some carbene and nitrene insertion chemistry catalyzed by 240 will be discussed in the next chapter.
CHAPTER 5
RESULTS AND DISCUSSION

5.1 Silver-catalyzed Büchner reactions

The silver(I) complex 232 has been shown to catalyze carbene insertion reactions into C-H and C-X (X = Cl, Br) bonds.\(^9\) We wanted to extend the chemistry of this complex by examining its utility in cyclopropanation by addition of a carbenoid to alkenes. A reaction took place when a dichloromethane solution of styrene was treated with ethyl diazoacetate (EDA) in presence of 5 mol\% of 232. Analysis of the complex \(^1\)H NMR spectrum of the crude reaction mixture indicated that the anticipated simple addition to the olefinic bond was not the major product. (Scheme 5.1) There were several unexpected signals, other than unreacted styrene, in the vinylic region of the spectrum that initially could not be accounted for. Further analysis of the spectrum clearly suggested that, addition to the aromatic moiety had occurred followed by a ring expansion, that is, a Büchner reaction had taken place.
The Büchner reaction is the thermal or photochemically induced carbene addition to an aromatic, forming a norcaradiene derivative followed by ring expansion to provide a cycloheptatriene. Typically under these conditions mixtures of conjugated and non-conjugated isomers are obtained.\textsuperscript{94} A search of the literature revealed that some rhodium complexes can catalyze the addition of a carbene to aromatic rings to give cycloheptatrienes (Scheme 5.2).\textsuperscript{95}

Transition metal catalyzed variants of the Büchner reactions are known, and tend to produce non-conjugated isomers due to the generally milder conditions employed.\textsuperscript{96} To determine if this reaction was occurring in the presence of the silver complex, a reaction of EDA and benzene was carried out using 232. Cycloheptatriene...
was formed in 74% yield, and none of the thermodynamically more stable conjugated isomers were observed. It should be noted that in addition to the ring expansion product, insertion of the carbene into the C-Cl bond of dichloromethane used as solvent had occurred (Scheme 5.3). As a small quantity of the C-Cl insertion product 244 was also obtained, the reaction was repeated in neat benzene (to prevent this competing reaction pathway), under these conditions the ring expansion product was obtained in a comparable 74% yield. This represented the first known example of a silver-catalyzed Büchner reaction and so we carried out a series of additions to substituted aromatics. Since these reaction conditions resulted in the addition and rearrangement with benzene, we decided to extend this observation with substituted derivatives (Table 5.1)

Scheme 5.3
Table 5.1 Yields and isomer ratio of the silver catalyzed Büchner reaction of benzene derivatives with EDA

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Reaction Conditions</th>
<th>Product Ratio by NMR</th>
<th>Isolated Yield (cycloheptatriene)</th>
</tr>
</thead>
<tbody>
<tr>
<td>247a</td>
<td>248a</td>
<td>Using CH$_2$Cl$_2$ as solvent</td>
<td>1:0.2 (25%) C-Cl insertion</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No solvent used</td>
<td>Not applicable</td>
<td>75%</td>
</tr>
<tr>
<td>247b</td>
<td>248b</td>
<td>Using CH$_2$Cl$_2$ as solvent</td>
<td>1.2:0.3 (20%) C-Cl insertion</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No solvent used</td>
<td>1.7:0.07 (4%) C-H insertion</td>
<td>62%</td>
</tr>
<tr>
<td>247c</td>
<td>248c</td>
<td>Using CH$_2$Cl$_2$ as solvent</td>
<td>1:0.55 (35%) C-Cl insertion</td>
<td>35%</td>
</tr>
</tbody>
</table>

With catalyst 232, no evidence of aryl C-H insertion was noted with benzene and only in the reaction with toluene was a small amount of benzylic C-H insertion (Figure 5.1, 250a) was observed in the $^1$H NMR spectrum of the crude reaction mixture. In a related study from our group it has been demonstrated that this complex is an
effective catalyst for C-H insertion and so the selectivity for the Büchner pathway is quite interesting.\textsuperscript{90a, 90b} Further investigation with mesitylene under these conditions clearly indicated the Büchner reaction was the major pathway, although C-H insertion \textbf{250b} did occur to an appreciable extent in this case.

![Figure 5.1 C-H insertion products from toluene and mesitylene](image)

Figure 5.1 C-H insertion products from toluene and mesitylene

Considering the number of reactive sites these results suggest that addition to C=C occurs 2-7 times faster than C-H insertion. Data obtained for some other benzene derivatives indicate that there is a preference for addition to electron-rich aromatics.\textsuperscript{99} Interpretation of the \textsuperscript{1}H NMR spectrum show that there are three regioisomeric products, which is consistent with previous reports\textsuperscript{97} and that the 4-isomer is predominant. The scorpionate systems appear to give rise to a greater proportion of the 3-isomer compared to the rhodium systems. Typically, rhodium(II) compounds are the most widely used catalysts for this important process.\textsuperscript{96} The yields of silver scorpionate \textbf{232} catalyzed process appear to be lower than with the rhodium-based systems, but this may be due to the slow decomposition of \textbf{232}. The presence of B-H moiety presumably leads to reduction of the Ag(I) to Ag (0), and attendant loss of activity.\textsuperscript{83}

In an effort to identifying a catalyst that retain the reactivity of \textbf{232}, but more stable we investigated the catalytic potential of \textbf{240} which as described in chapter 4 can be compared to fluorinated \textit{bis}(pyrazolyl)borates. Since the catalytic potential of copper
complexes 228, 229 and 233 (Figure 5.3) has already been well established,\textsuperscript{90a} the fluorinated pentadienyl complex 240 was used to carry out a series of carbene and nitrene insertion reactions.

![Figure 5.2 Fluorinated ligands used for carbene and nitrene insertion reactions](image)

5.2 Copper-catalyzed nitrene insertion

We attempted to carry out the aziridination of olefins. Copper(I) complex 240 was employed as the catalyst and $N$-tosyl iodinane was used as the nitrene source. The reaction with styrene worked very well giving very high yield of the desired product. The reaction was conducted with cyclooctene\textsuperscript{98} and the aziridine was obtained in high yields.
These examples indicate that the copper complex 240 can be used as a catalyst for nitrene insertion reactions. Some other olefins that were previously used were not subjected to aziridination because we wanted to check the versatility of these systems in carrying out various organic transformations.

5.3 Copper-catalyzed cyclopropanation

We attempted to carry out cyclopropanation using styrene as the alkene source. To our delight the reaction did proceed however, there was significant amount of the byproduct (homocoupling to give diethyl maleate/fumarate ratio (Scheme 5.5). Slowing the addition process of EDA resulted in significant amount unreacted starting material, but no homocoupling byproduct was observed. Using excess of the olefin also did not help.
No attempts were made to carry out the cyclopropanation with other olefins, since earlier results have shown that styrene is the most reactive alkene for carrying out cyclopropanation.

5.4 Copper-catalyzed N-H and O-H insertion

After having investigating carbene and nitrene addition reactions olefins and carbon-hydrogen bonds we wanted to apply this chemistry in system involving heteroatoms. 240 was used to catalyze carbene insertion across N-H bonds and to our delight the reaction worked very clean by giving the desired product in excellent conversions. The reaction was carried out with both a primary as well as secondary amine (Scheme 5.6)

Scheme 5.6

It was interesting to note that, although the C-H activation as well as cyclopropanation did not work well with 240, N-H insertion worked well and so O-H insertion reaction using EDA were investigated. It was gratifying to observe that the O-H insertion reaction also worked very well, again giving only the desired product. (Scheme 5.6)
These are all preliminary results on simple and reactive systems. Efforts are currently focused on extending these findings on more elaborate and complex systems. Once the chemistry using non-chiral ligands has been developed attempts will be made to construct chiral ligands for applications in asymmetric catalysis.

In conclusion, we have discovered a novel, silver-catalyzed carbene addition to aromatic rings that proceeds in good to moderate yields with good to high level of selectivity for a Büchner type pathway. We also report the application of a highly fluorinated triazapentadienyl ligands for carrying out a variety carbene and nitrene insertion reactions.
CHAPTER 6
EXPERIMENTAL DETAILS

All reactions involving silver complex 232 and copper complex 240 were carried out in glassware shielded from light by wrapping with aluminum foil.

General procedure for Büchner reactions: EDA (114 mg, 1.00 mmol) in CH₂Cl₂ or arene (247) (1.5 mL) was added by automatic syringe to a stirred solution of and 232 (40 mg, 0.05 mmol) in CH₂Cl₂ or arene 247 (5 mL) under nitrogen. The resulting solution was stirred overnight at room temperature under nitrogen, diluted with CH₂Cl₂ (~20 mL), filtered through Celite, and concentrated. The residue was then subjected to flash chromatography (SiO₂, 4:1 hexanes/ether, eluant system used for all Büchner products) to give the product 248 as a colorless fragrant oil. Spectral data for the products were identical to data previously reported by Greg Browning⁹⁰a and in the literature.⁹⁶b

General procedure for aziridination: A suspension of the alkene 210/252 (0.40 mmol), PhI=NTs 228 (224 mg, 0.60 mmol), and powdered 4Å molecular sieves (120 mg) in CH₃CN (1 mL) was stirred at room temperature while purging with nitrogen for 2 min. The copper complex 240 (16 mg, 0.02 mmol) was added, and the resulting mixture was stirred overnight under nitrogen. The reaction mixture was diluted with CH₂Cl₂ (~20 mL), filtered through Celite and concentrated. The residue was purified by
flash chromatography (SiO$_2$, 9:1 hexanes/EtOAc, eluant system used for all aziridine products), giving the desired product 251/253 as a colorless solid or oil. Spectral data for the products were identical to data reported by Greg Browning$^{90a}$ and in the literature.\textsuperscript{99,100}

**General procedure for N-H and O-H insertion:** A solution of the copper(I) complex 240 (16 mg, 0.02 mmol) in CH$_2$Cl$_2$ (1.0 mL) and the amine 214 or alcohol 216 (1.0 mmol) was purged under nitrogen. EDA (114 mg, 1.0 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added by automatic syringe pump over 45 min under nitrogen. The resulting solution was stirred overnight at ambient temperature under nitrogen. The solution was concentrated and the residue was purified by flash chromatography on SiO$_2$ (9:1 Hexanes/EtOAc), giving the desired product 215 (0.126 g, 80%), 256 (0.124 g, 85%) 217(0.119 g, 82%) as a colorless oil [241 (0.152 g, 85%)] is an off white solid). Spectral data for the products were identical to data reported in the literature.\textsuperscript{87,88,99}
APPENDIX 1

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
2-[(5S)-5-tert-Butyldimethylsilyloxyethyl-2-oxo-1-pyrrolidinyl]benzonitrile
(170a)
APPENDIX 2

$^1$HNMR AND $^{13}$C NMR SPECTRUM OF
(5S)-5-tert-Butyldimethylsilyloxyethyl-1-(2-nitrophenyl)-2-pyrrolidinone (170b)
APPENDIX 3

$^1$H AND $^{13}$C NMR SPECTRA OF
Methyl 5-nitro-2-[(5S)-5-[(tert-butyl)dimethylsilyloxy]-2-oxo-1-
pyrrolidinyl]benzoate (174)
APPENDIX 4

$^1$H AND $^{13}$C NMR SPECTRA OF

Methyl 5-amino-2-\{(5S)-5-\{[(tert-Butyl)dimethylsilyloxy]-2-oxo-1-pyrrolidinyl\}benzoate (175)
APPENDIX 5

$^1$H AND $^{13}$C NMR SPECTRA OF
Methyl 5-iodo-2-[(5S)-5-(hydroxymethyl) -2-oxo-1-pyrrolidinyl]benzoate (176b)
APPENDIX 6

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
(5$S$)-5-(hydroxyethyl)-2-pyrrolidinone
APPENDIX 7

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
(5S)-5-(tert-Butyl dimethylsilyloxy)-2-pyrrolidinone (184)
APPENDIX 8

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
4-[(5S)-5-Cyanomethyl-2-oxo-1-pyrrolidinyl]benzonitrile (185a)
APPENDIX 9

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF

4-[(5S)-5-[(Carboxymethyl)methyl]-2-oxo-1-pyrrolidinyl]benzonitrile (185b)
APPENDIX 10

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
4-[(5S)-5-[(tert-Butyl)dimethylsilyloxy]-2-oxo-1-pyrroolidiny]benzonitrile (185c)
APPENDIX 11

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
4-[(5S)-5-[(tert-Butyl)dimethylsilyloxy]-2-oxo-1-pyrrolidinyl]benzonitrile (185d)
APPENDIX 12

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF

Methyl 5-nitro-2-[(5S)-5-{{(tert-Butyl)dimethylsilyloxy}}-2-oxo-1-pyrroldinyl]benzoate (185e)
APPENDIX 13

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
Methyl 5-amino-2-\{(5S)-5-\{[\text{tert-Butyl} \text{dimethylsilyloxy}]\}-2-oxo-1-
pyrrolidinyl\}benzoate (186)
APPENDIX 14

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
Methyl 5-iodo-2-[(5S)-5-{(hydroxyethyl)-2-oxo-1-pyrrolidinyl]benzoate (187)
APPENDIX 15

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
Methyl 5-iodo-2-[(5S)-5-(ethynyl)-2-oxo-1-pyrrolidinyl]benzoate (179)
APPENDIX 16

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
5-iodo-2-[(5S)-5-(ethynyl)-2-oxo-1-pyrrolidinyl]benzoic acid (189)
APPENDIX 17

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF

$(5S)$-5-(ethynyl)-1[4-iodo-2-(hydroxymethyl)phenyl]-2-pyrrolidinone (188a)
APPENDIX 18

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
4-iodo-2-(hydroxymethyl)-1-[(2S)-vinyl-5-hydroxy-1-butylamino]benzene (188b)
APPENDIX 19

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF

4-iodo-2-(formyl)-1-[(2S)-vinyl-5-hydroxy-1-butylamino]benzene (192)
APPENDIX 20

$^1$H AND $^{13}$C NMR SPECTRA OF (5S)-5-ETHENYL-1-[4-IODO-2-FORMYLPHENYL]-2-PYRROLIDINONE 193
APPENDIX 21

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF

$(3aS, 3bS, 11bS)$-10-iodo-1,2,3,3a,4,5,11b-octahydro-1-(phenylmethyl)-6$H$-dipyrrrolo[1,2-a:3’,2’-c]quinoline-6-one (194)
APPENDIX 22

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
(3aS, 3bS, 11bS)-10-carboxymethyl-1,2,3,3a,4,5,11b-octahydro-1-(phenylmethyl)-
$6H$-dipyrrrolo[1,2-a:3',2'-c]quinoline-6-one (194)
APPENDIX 23
$^1$H NMR AND $^{13}$C NMR SPECTRUM OF (3aS, 4S, 9bS)-8-iodo-2,3,3a, 4,5,9b-hexahydro-1-(phenylmethyl)-1H-pyrrolo[3,2-c]quinoline-4-propanol (197)
APPENDIX 24

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF

(3a$S$, 4$S$, 9b$S$)-8-ido-2,3,3a, 4,5,9b-hexahydro-5-(3-oxabutanoyl)-1-(phenylmethyl)-1$H$-pyrrolo[3,2-c]quinoline-4-propyl acetate (198)
APPENDIX 25

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
Methyl (3aS, 4S, 9bS)-2,3,3a, 4,5,9b-hexahydro-5-(3-oxabutanoyl)-1-
(phenylmethyl)-1H-pyrrolo[3,2-c]quinoline-8-carboxylate (199)
APPENDIX 26

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
Methyl (3a$S$, 4$S$, 9b$S$)-2,3,3a, 4,5,9b-hexahydro-5-(3-oxabutanoyl)-1-
(phenylmethyl)-5-(trifluoromethyl)-1$H$-pyrrolo[3,2-c]quinoline-8-carboxylate (200)
APPENDIX 27

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
Methyl (3a$S$, 4$S$, 9b$S$)-4-(3-azidopropyl)-2,3,3a, 4,5,9b-hexahydro-5-(3-oxabutanoyl)-1-(phenylmethyl)-1$H$-pyrrolo[3,2-c]quinoline-8-carboxylate (202)
APPENDIX 28

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF
Methyl (3a$\text{S}$, 4$\text{S}$, 9b$\text{S}$)-4-(3-aminopropyl)-2,3,3a, 4,5,9b-hexahydro-5-(3-
oxabutanoyl)-1-(phenylmethyl)-1$H$-pyrrolo[3,2-c]quinoline-8-carboxylate
hydrochloride salt (132)
APPENDIX 29

$^{1}H$ NMR AND $^{13}C$ NMR SPECTRUM OF Methyl Martinellate (142)
APPENDIX 30

$^1$H NMR AND $^{13}$C NMR SPECTRUM OF

Martinelllic acid (2)
REFERENCES

2. Gentry, A.; Cook, K. J. Ethnopharmacol 1984, 11, 337.


86. Pérez, P. J.; Brookhart, M.; Templeton, J. L. Organometallics 1993, 12, 261.


98. Dr. Shreeyukta Singh carried out this transformation.


BIOGRAPHICAL INFORMATION

The author was born in India, having completed his primary, secondary and higher education there. He earned his Bachelor of Science degree in Chemistry from The University of Mumbai in 1997 and then went on to receive his Masters degree in Organic Chemistry from The University of Mumbai in 1999. He received his Ph. D. degree from the University of Texas at Arlington under the supervision of Dr. Carl Lovely.