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UMI
THE TOTAL SYNTHESIS OF XESTOMANZAMINE A

By

Francis Bartholomew Panosyan

A thesis submitted in conformity with the requirements
for the degree of Master of Science, Graduate Department of Chemistry, in the
University of Toronto

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The Total Synthesis of Xestomanzamine A

Francis Bartholomew Panosyan
M.Sc. 2000
Department of Chemistry, University of Toronto

Abstract:

The first efficient and practical route to C-5 functionalized N-methylated imidazole is reported. 5-Iodo-1-methylimidazole was synthesized in four steps from imidazole with complete regiospecificity in 73% overall yield. The synthesis of xestomanzamine A, a marine natural product isolated in 1995 from an Okinawan sponge of Xestospongia sp., was achieved using 5-iodo-1-methylimidazole as a precursor to a modified Grignard reaction with a β-carboline moiety. The total synthesis of xestomanzamine A was achieved in 59% yield based upon imidazole and 53% based upon tryptamine. Two pathways were investigated for the synthesis of the closely related xestomanzamine B from 5-iodo-1-methylimidazole. Although unsuccessful, these attempts offer practical alternatives for the preparation of precursors, which can be used to complete this synthesis in the future.
Dedicated to my parents
Acknowledgments

I would like to thank my family for being supportive of my dreams and believing in me. Although physically absent, I was always foremost in their thoughts.

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<td>Acetyl</td>
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<td>AFA</td>
<td>Acetic formic anhydride</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2’-Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butoxycarbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
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<td>DBDMH</td>
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<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<td>Diisopropylethylamine</td>
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<td>Dimethyl sulfoxide</td>
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<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric acid</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase transfer catalyst</td>
</tr>
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<td>TEOF</td>
<td>Triethyl orthoformate</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>Thin layer chromatography</td>
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<td>Tol</td>
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I. Introduction

Nitrogen-containing marine natural products have become increasingly important for their biological activities. Marine alkaloids represent about 25% of all reported marine natural products and 54% of these alkaloids are extracted from sponges.\(^1\)

Among these marine alkaloids, β-carboline (I) alkaloids have been receiving tremendous interest due to their biological activities.\(^2\) Although secondary marine metabolites often have no terrestrial counterpart, β-carbolines are unique in being the most commonly encountered type of alkaloid in the terrestrial environment.\(^3\)

![β-carboline](image)

Manzamines are unique β-carboline alkaloids from marine sponges with structures that are often characterized by having intricate nitrogen-containing polycyclic systems. A wide variety of manzamines and other compounds, thought to be their biogenetic precursors, have been reported from a total of nine different marine sponge genera.\(^3\)
In 1995 Kobayashi and coworkers reported the isolation of two new β-carboline alkaloids as cytotoxic constituents of the Okinawan marine sponge *Xestospongia* sp.¹ These two natural products contain a heteroaroyl substituent at C-1 of the β-carboline. Xestomanzamine B (3) is the 3,4-dihydro analogue of xestomanzamine A (2).

The prototype of the manzamine family, manzamine A (4)⁵, is perhaps the most well known manzamine. Manzamine A displays significant *in vitro* activity (IC₅₀ of 0.07µg/mL on P388 mouse leukaemia cells), and has recently been shown to have excellent antimalarial activity⁶.
The heteroaroyl substituent at C-1 of xestomanzamine A (2) and B (3) has an imidazole (5) substructure.

![imidazole](image)

Imidazole-containing marine alkaloids are beginning to attract increasing attention. Some of these alkaloids, which have been isolated from sponges, have been shown to have antitumour and antibacterial activities\(^7\) (Fig. 1).

![Figure 1: Some examples of imidazole containing marine alkaloids](image)

Although xestomanzamines A (2) and B (3) combine the substructures of \(\beta\)-carboline (1) and imidazole (5), their biological activities have not matched those of manzamine A (4) and some of the other imidazole (5) containing marine natural products. Xestomanzamine B (3), however, was shown to exhibit weak cytotoxicity against KB human epidermoid carcinoma cells (IC\(_{50}\) 14.0 \(\mu\)g/mL)\(^2\). We felt that xestomanzamines A (2) and B (3), with their unique combination of the \(\beta\)-carboline (1) and imidazole (5) substructures, offered exciting targets for total synthesis.
1.1 Biogenetic Pathway

Like most β-carboline structures, one can envisage the β-carboline (1) structure to be derived from a tryptophan residue condensed with a second amino acid\(^8\) (Scheme 1).

\[
\begin{array}{c}
\text{X}=	ext{H, OH} \\
R=\text{Amino acid side chain}
\end{array}
\]

*Scheme 1: General biosynthetic pathway to β-carbolines*

The biogenetic pathway towards xestomanzamine A (2) and B (3) is presumed to be from an \(N\)-methylated histidine residue, followed by a sequence of oxidation steps\(^4\) (Scheme 2).

*Scheme 2: Biogenetic pathway to xestomanzamines A and B*
1.2 Synthesis of β-carbolines

1.2.1 Classical approaches

The traditional methods for the synthesis of the β-carboline (1) ring systems are similar to those used for the isoquinoline (6) ring systems, the key step being the closure of the ring, while the C-1 substituent is introduced at earlier stages.

1.2.1.1 The Bischler-Napieralski synthesis

In the Bischler-Napieralski approach to isoquinolines, cyclodehydration of β-phenethylamides (7) to 3,4-dihydroisoquinoline (8) derivatives can be achieved by means of condensing agents such as phosphorus pentoxide or zinc chloride (Scheme 3).

Scheme 3: The Bischler-Napieralski cyclodehydration

Under the original conditions described by the discoverers the yields are often very poor, but many modifications to the reaction conditions, using lower temperatures and milder condensing agents, have since improved the reaction.
The mechanism of the Bischler-Napieralski cyclodehydration has been shown to involve the loss of the carbonyl oxygen prior to the cyclization to give the imidoyl phosphate [7-I], which in turn is rapidly converted into a nitrilium salt [7-II]. Subsequent cyclization leads to the 3,4-dihydroisoquinoline (8)\textsuperscript{12} (Scheme 4).

Scheme 4: The Mechanism of the Bischler-Napieralski cyclodehydration

The Bischler-Napieralski approach to the synthesis of 3,4-dihydro-β-carbolines was first reported by Spaeth and Lederer\textsuperscript{13} in 1930 (Scheme 5).

Scheme 5: Bischler-Napieralski approach to β-carbolines

1.2.1.2 The Pictet-Spengler condensation

The Pictet-Spengler reaction involves the condensation of β-arylethylamines (11) with carbonyl compounds to form C-1 substituted tetrahydroisoquinolines (12)\textsuperscript{14} (Scheme 6).
Scheme 6: The Pictet-Spengler cyclization

The reaction of an amine with an aldehyde gives an intermediate imine (Schiff base) [11-I], or iminium salt [11-III], which cyclizes to form a tetrahydroisoquinoline (12) (Scheme 7).

Scheme 7: Mechanism of Pictet-Spengler cyclization

In 1934 Hahn and Ludwig\textsuperscript{15} reported the first synthesis of a \(\beta\)-carboline through a Pictet-Spengler cyclization (Scheme 8). This 1,2,3,4-tetrahydro-\(\beta\)-carboline (15) was C-1 substituted with a benzyl functionality.

Scheme 8: \(\beta\)-carboline synthesis through Pictet-Spengler
1.2.2 Recent approaches

Though the Bischler-Napieralski and the Pictet-Spengler reactions are those most commonly adopted for preparing β-carbolines, other methods have also been used\textsuperscript{16} and these will be briefly surveyed here.

1.2.2.1 The Livinghouse cyclization

This direct approach to 1-acyl substituted β-carbolines was developed by Livinghouse and coworkers in 1986\textsuperscript{17} and has been used by others\textsuperscript{18} to obtain the 3,4-dihydro-β-carboline skeleton. This approach closely resembles the Bischler-Napieralski cyclization in proceeding via the α-ketoimidoyl chloride. The isonitrile (16) is acylated with phenacyl chloride (17), which is then treated with silver tetrafluoroborate to give the 3,4-dihydro-β-carboline (18) (Scheme 9).

![Scheme 9: The Livinghouse approach to 3,4-dihydro-β-carbolines](image-url)
1.2.2.2 Construction of the pyridine ring

Gribble and Johnson\textsuperscript{19} reported the synthesis of the β-carboline skeleton through the construction of the pyridine substructure. Love's modification\textsuperscript{20}, which avoids the use of acid during all steps of the synthesis, starts with the indole derivative (19) (Scheme 10).

![Scheme 10: Intramolecular cyclization to form the β-carboline skeleton](image)

Murakami\textsuperscript{21} developed a synthesis of the β-carboline system through a novel cyclization effected with polyphosphoric acid (PPA). The formamide group of the tetrahydro-β-carboline skeleton (24) is then hydrolyzed, followed by dehydrogenation with palladium and alkylation with dimethyl sulfate to give the β-carboline (25) (Scheme 11).
Scheme 11: The Murakami approach to β-carbolines

A modification of the Murakami synthesis by Dekhane and Dodd\textsuperscript{22} utilizes titanium tetrachloride as the reagent effecting the intramolecular alkylation at C-3 (Scheme 12).

Scheme 12: The Dodd modification to the Murakami synthesis

The use of vinyl azide (30) as a precursor to the β-carboline skeleton (31) was reported by Moody and Ward\textsuperscript{23} although this method proved to be a poor route to C-1 substituted β-carbolines (Scheme 13).
Hibino and coworkers\textsuperscript{24} have shown that the thermal electrocyclization of 1-azahexatriene (32) is another route to the pyridine ring system. This method was shown to be a versatile method for the synthesis of \( \beta \)-carboline containing natural products (Scheme 14).

1.2.2.3 \textit{Construction of the indole ring}

Boger\textsuperscript{25} was the first to show the possibility of forming the \( \beta \)-carboline ring system through an intramolecular substitution reaction. Quéguiner and coworkers\textsuperscript{26} have since shown the versatility of this approach (Scheme 15).
In the Quéguiner method\textsuperscript{26}, 2-aminophenylboronic acid (36) is coupled with 3-fluoro-4-iodopyridine (37) to give an intermediate (35) which can be cyclized to form the β-carboline skeleton (Scheme 16).

\textbf{1.3 Functionalization of Imidazoles}

Imidazoles (5) with free N-hydrogen are subject to tautomerism.

This facile tautomeric interconversion by prototropic rearrangement becomes evident when an imidazole is unsymmetrically substituted (38) (Scheme 17). The convention used to cover this phenomenon is to include both positions in the nomenclature\textsuperscript{27}. 

\begin{center}
\textbf{Scheme 15: Intramolecular substitution of fluoropyridine}
\end{center}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{image15.png}};
\end{tikzpicture}
\end{center}

\begin{center}
\textbf{Scheme 16: The precursors of the Quéguiner method}
\end{center}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{image16.png}};
\end{tikzpicture}
\end{center}

\begin{center}
\textbf{Scheme 17: Tautomerism in 4(5)-methylimidazole}
\end{center}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{image17.png}};
\end{tikzpicture}
\end{center}
1.3.1 Construction of the imidazole ring

Jones\textsuperscript{28} reported the synthesis of 5-imidazolecarboxylates from $N$-acyl-substituted glycine derivatives (Scheme 18). The $N$-substituted glycine (39) was formylated and the sodium enolate (40) subsequently cyclized with thiocyanate in acidic conditions to yield 2-mercapto-5-imidazolecarboxylate (41). The mercaptoimidazole is then oxidized with nitric acid to yield the 5-imidazolecarboxylate (42).

\[ R' \text{CONH} \text{COOMe} \xrightarrow{\text{HCOOMe}} R' \text{CONH} \text{CHONa} \]

\[ \text{NaOMe} \xrightarrow{\text{KSCN}} \text{H}^+ \]

\[ \text{MeOOCC} \text{N} \text{R} \xrightarrow{\text{HNO}_3} \text{MeOOCC} \text{N} \text{SH} \]

Scheme 18: The Jones method for construction of the imidazole ring

An improved procedure was later reported by Rapoport and coworkers\textsuperscript{29} for producing 1-methyl-4-imidazolecarboxylate (46) (Scheme 19) and 1-methyl-5-imidazolecarboxylate utilizing the ring construction approach.

\[ \text{HOOC-NH}_2 \text{HCl} \xrightarrow{\text{TEOF} \text{HCl}} \text{HO}_2 \text{C-N} \text{NH} \xrightarrow{\text{MeOH} \text{H}^+} \text{MeO}_2 \text{C-N} \xrightarrow{\text{MnO}_2} \]

\[ \text{TEOF} = \text{H} \text{OEt} \text{EtO} \text{OEt} \]

Scheme 19: The Rapoport method of obtaining C-4 functionalized imidazole
The \( \alpha \)-amino-\( \beta \)-methylaminopropionic acid hydrochloride (43) is cyclized with triethyl orthoformate using a hydrogen chloride catalyst. After esterification the ring is dehydrogenated to give the C-4 substituted imidazole (46). The same method can be used to effect the synthesis of methyl 1-methyl-5-imidazolecarboxylate. 29

1.3.2 Substitution at nitrogen

1.3.2.1 Alkylation at nitrogen

The immediate product of alkylating imidazole (5) is the protonated \( N \)-alkylimidazole (47); with loss of a proton to another imidazole (5) molecule a second alkylation occurs. The reaction of imidazole with alkyl halides gives a mixture of imidazolium, 1-alkylimidazolium (47) and 1,3-dialkylimidazolium (49) salts 27 (Scheme 20).

![Scheme 20: Alkylation of imidazole with iodomethane](image)

1.3.2.2 Acylation at nitrogen

Acylation of imidazole (5) initially forms the \( N \)-3-acylimidazolium salt [50-I] which, on loss of a proton, produces the \( N \)-acylimidazoles (50) 30 (Scheme 21).

![Scheme 21: Acylation of imidazole with acetic anhydride](image)
1.3.3 Substitution at carbon

1.3.2.1 Protonation/Deprotonation

Imidazole (5) (pKₐ of 7.1) undergoes hydrogen exchange in acidic medium through a sequence of proton-addition/proton-loss. Hydrogen at the C-5 position exchanges twice as rapidly as at C-4 and more than hundred times faster than at C-2 \(^{31}\). A much faster exchange in neutral or weakly basic medium takes place at room temperature, which leads to a regioselective C-2 exchange. This special regioselectivity is due to the process where the protonic salt (51) is formed first, then C-2 deprotonation of the salt produces the transient ylid (52), the carbene (53) being an important resonance contributor\(^{27}\) (Scheme 22).

![Scheme 22: Mechanism of regioselective C-2 exchange](image)

Comparison of the decarboxylation of the 2-imidazolecarboxylic acid and 5-imidazolecarboxylic acid shows the 2-substituted acid to lose carbon dioxide \(10^6\) times faster than the C-5 acid. This is an indication of the low stability of the C-5 ylide, since the decarboxylation is thought to be influenced by the ylide stability\(^{32}\). Contrary to some earlier literature\(^{33}\), it is now well proven that, in the absence of blocking groups at C-2 of imidazole (5), there is a rapid equilibration of the imidazol-4-yl and imidazol-5-yl anions to give preferentially the imidazol-2-yl anion\(^{34,35}\).
1.3.2.2  **Halogenation**

Halogenation of imidazole (5) has been the topic of extensive studies. Chlorination with hypochlorite in alkaline solution substitutes only at the C-4 and C-5 positions\(^3\). Imidazole (5) is brominated with ease at all free carbon positions\(^3\). (Scheme 23). The bromination of 1-methylimidazole (48) has also been reported to proceed with ease\(^3\). Iodination of imidazoles also gives the fully halogenated product\(^3\).

![Scheme 23: Bromination of imidazole](image)

1.3.2.3  **Halogen-Metal exchange**

The sequential formation of imidazole anions and their subsequent reactions with electrophiles is potentially a very attractive approach for the synthesis of functionalised imidazoles\(^4\). This route is complicated, however, by the aforementioned equilibration to the imidazol-2-yl anion, the apparent solution being functionalising/blocking of the C-2 position. There is ample precedent in the literature for the sequential functionalisation of imidazole in the order C-2\(\rightarrow\)C-5\(\rightarrow\)C-4\(^3\). The method employed commonly involves a series of metal-halogen exchange reactions, where there is a successive replacement of a halogen in the \(N\)-protected trihaloimidazoles.

El Borai and Hassanein\(^4\) reported a positionally stable imidazolylmagnesium halide. This stability was utilized for sequential functionalisation of the imidazole
ring in the order C-5 → C-4 → C-2 \(^{40}\) (Scheme 24).

1.4 Previous synthesis of xestomanzamine A

The total synthesis of xestomanzamine A has been reported by Molina and coworkers\(^ {43}\) in 1996.

The \(\beta\)-carboline moiety was synthesized via a "tandem aza-Wittig/electrocyclic ring closure". The iminophosphorane (57) is prepared through the sequential treatment of \(N\)-methoxymethylindole-3-carboxaldehyde (55) with ethyl azidoacetate (56) and triphenylphosphine (Scheme 25).

The iminophosphorane (57) reacted with acetaldehyde in \(o\)-xylene at 160°C in the presence of palladium on charcoal to give the 1-methyl-\(\beta\)-carboline (58) (Scheme 26).
Scheme 26: 1-Methyl-β-carboline from the iminophosphorane

Although the imine [57-I] was not isolated, this cyclization presumably occurs through the imine intermediate [57-I] analogous to those employed in Pictet-Spengler reactions\textsuperscript{16}. The 1-methyl-β-carboline ester was hydrolyzed and decarboxylated at the C-3 position to provide the N-protected 1-methyl-β-carboline (59) (Scheme 27).

Scheme 27: Decarboxylation at the C-3 position

The methyl substituent on C-1 was then oxidized with selenium oxide to the corresponding aldehyde (60) (Scheme 28).
The β-carboline-1-carbaidehyde (60) was coupled with 5-lithio-1-methyl-2-triethylsilylimidazole (61) (Scheme 29).

Oxidation with Jones’ reagent oxidizes the secondary alcohol at C-10, bridging the imidazole to the β-carboline, to yield the ketone (63) (Scheme 30).

Deprotection of the ketone (63) in refluxing formic acid produces xestomanzamine A (2) (Scheme 31).
1.5 Retrosynthetic analysis

In our first synthetic strategy (Scheme 32), which was geared towards the direct synthesis of xestomanzamine A (2), the main focus was to eliminate the need for protecting the indole nitrogen and most notably the C-2 of the imidazole.

The classical approach to the β-carboline skeleton using the Pictet-Spengler condensation seemed to offer an immediate solution to forming the β-carboline skeleton without the need for protection of the indole nitrogen. Moreover, this route would allow the synthesis of xestomanzamine A (2) from the readily available tryptamine (13), thus closely mimicking the proposed biogenetic pathway (Scheme 2).

* The details of the removal of the protecting group from the C-2 of imidazole were not discussed by Molina.43
We then imagined a Fischer-type esterification of the 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (64) to the methyl ester (65). Dehydrogenation of the tetrahydro-β-carboline (65) to the methyl β-carboline-1-carboxylate (66) could be achieved with methods developed by others as well as in our laboratory. We envisaged a coupling of the C-5 substituted N-methylimidazole (67) through a procedure developed in our laboratory, where the Grignard addition to the methyl β-carboline-1-carboxylate (66) in the presence of excess lithium salt would produce the ketone, xestomanzamine A (2) (Scheme 33), rather than the normal tertiary alcohol.

![Scheme 33: Grignard addition to the β-carboline-1-carboxylic ester](image)

Our second synthetic plan, which was inspired by the Livinghouse approach to 3,4-dihydro-β-carbolines, was directed towards the synthesis of xestomanzamine B (3) (Scheme 34).

![Scheme 34: Retrosynthetic plan towards xestomanzamine B](image)
The synthetic approach towards xestomanzamine B (3) relies again on tryptamine (13) as the starting material. Amines can be converted to isonitriles with a variety of methods, the most common being the sequential formylation/dehydration. The isonitrile (68) can be protected on the indole nitrogen with a carbamate functionality\textsuperscript{17}. The protected isonitrile (69) can be cyclized with 1-methyl-5-imidazolecarbonyl chloride (71) to give the N-protected xestomanzamine B (70) (Scheme 35).

\begin{center}
\begin{tabular}{c|c|c}
70 & & 69 & 71 \\
MeO\textsubscript{2}C & & MeO\textsubscript{2}C & Cl
\end{tabular}
\end{center}

Scheme 35: Cyclization of the isonitrile with imidazole-5-carbonyl chloride

The indole nitrogen can be deprotected to give xestomanzamine B (3), which in turn could be dehydrogenated to unveil yet another route to xestomanzamine A (2) (Scheme 36).

\begin{center}
\begin{tabular}{c|c}
2 & 3 \\
\end{tabular}
\end{center}

Scheme 36: Xestomanzamine A through the synthesis of xestomanzamine B
II Results and Discussion

2.1 Grignard Approach (xestomanzamine A)

2.1.1 Synthesis of the β-carboline substructure

2.1.1.1 Pictet-Spengler condensation

The β-carboline skeleton was obtained through a Pictet-Spengler condensation of tryptamine hydrochloride (72) with glyoxylic acid to form the salt of 1,2,3,4-tetrahydro-β-carboline (73) as a white solid. The yield of this reaction was 80%. The Pictet-Spengler reaction is a weakly acid-catalyzed reaction. The reaction was initiated with addition of a concentrated solution of potassium hydroxide to solubilize the reagents, but then the pH was brought down with glacial acetic acid to a pH of 4 (Scheme 37).

![Scheme 37: Pictet-Spengler condensation of tryptamine hydrochloride](image)

The Pictet-Spengler reaction belongs to the Mannich-Knoevenagel mechanistic class, except that in this case the nucleophilic attack is intramolecular (Scheme 38).
The condensation of tryptamine (13), which was generated from tryptamine hydrochloride (72) in the presence of potassium hydroxide, with glyoxylic acid produced the iminium species [13-I], which underwent an intramolecular electrophilic aromatic substitution. The imine [13-I] was attacked first by the more nucleophilic C-3 site of the indole to give the spiro intermediate [13-II]. The initial preferential substitution at C-3 of the indole is consistent with various molecular orbital calculations which find the highest electron density and highest concentration of the HOMO at C-3. Intermediate [13-II] then underwent a 1,2-alkyl shift to form a 6-membered ring [13-III], which on loss of a proton gave the 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid hydrochloride (73). The product (73), which was in its salt form, was purified by stirring in methanol at 0°C and subsequently filtered to give a white solid. The tetrahydro-β-carboline-1-carboxylic acid (73) could not be dissolved in common
organic solvents and showed a peak at 3343 cm$^{-1}$ under IR analysis, which corresponds to the secondary amine, and a peak at 1616 cm$^{-1}$ for the carbonyl stretch.

2.1.1.2 *Fischer esterification*

Esterification of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (73) with methanol gave the methyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate hydrochloride (74) (Scheme 39).

![Scheme 39: Fischer esterification of tetrahydro-β-carboline-1-carboxylic acid](image)

The reaction was performed in methanol saturated with dry hydrogen chloride gas and the refluxing solvent was passed through activated 3Å molecular sieves in a Soxhlet extraction thimble. The Fischer esterification reaction is an equilibrium process. The reaction was driven to completion by using methanol as the solvent and by removing water as it was formed, utilizing molecular sieves. The $^1$H-NMR spectrum of the product (74) showed the protons of the methyl group at δ 3.88 in DMSO-$d_6$. The IR spectrum of (74) showed a peak at 1756 cm$^{-1}$ for the carbonyl stretch. The yield of the reaction was 94%.
2.1.1.3 Dehydrogenation of the tetrahydro-β-carboline

Numerous methods exist to effect the dehydrogenation of the β-carboline substructures. Nickel sulfate*, FeCl₃, K₂FeCN₆, DDQ, NBS, and H₂O₂ are some of the oxidants examined in the literature*. The use of palladium on charcoal has also been a popular method since its first use. The dehydrogenation of the tetrahydro-β-carboline (74) was carried out with the use of elemental sulfur in refluxing xylenes (Scheme 40).

Scheme 40: Dehydrogenation of the tetrahydro-β-carboline

This method has been used successfully in our laboratory for the dehydrogenation of other β-carbolines and, in addition to its tolerance to a wide range of functionalities, such as esters, alkenes, epoxides and ethers, it has the added advantage of cheapness and simplicity. The methyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (74) obtained was in its hydrochloride salt form, which is inert towards dehydrogenation. 2,2,6,6-Tetramethylpiperidine was used to neutralize the hydrogen chloride present and allow the free base of methyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (74), to react with the sulfur. The susceptibility of the ester carbonyl site to nucleophilic attack required the use of the bulky non-nucleophilic base 2,2,6,6-tetramethylpiperidine. The evolution of hydrogen sulfide was detected when a paper wetted with a solution of aqueous lead (II) acetate turned black. The excess
sulfur was removed from the fully aromatic β-carboline methyl ester (66) by washing the crude product with acetone. The acetone dissolved the β-carboline ester (66) selectively, while leaving sulfur and the insoluble 2,2,6,6-tetramethylpiperidine hydrochloride behind. The yield of this reaction was 87%. The IR spectrum of the product (66) showed the carbonyl stretch at 1677 cm\(^{-1}\). The low frequency of the carbonyl absorption can be attributed to the linear geometry of the aromatic β-carboline methyl ester (66) which brings the carbonyl oxygen closer and in a geometrically more favourable position for hydrogen bonding to the hydrogen of the indole ring. The conjugation of the carbonyl group with the aromatic ring provides yet another reason for the low frequency of the carbonyl absorption (Scheme 41).

Scheme 41: H-bonding and conjugation of the carbonyl

With the synthesis of the β-carboline ester (66) in hand, the synthesis of the imidazole substructure next focused our attention.
2.1.2 Synthesis of the imidazole substructure

The commercially available 5-chloro-1-methylimidazole (75) was tested in our laboratory for magnesium insertion without success\(^3\) (Scheme 42).

![Scheme 42: Insertion of magnesium in 5-chloro-1-methylimidazole](image)

We felt that this insertion might be more successful with the bromo-substituted imidazole. 5-Bromo-1-methylimidazole (77) was not available commercially and had to be synthesized.

2.1.2.1 Bromination of 1-methylimidazole

The bromination of 1-methylimidazole (48) through the successive reaction with butyllithium (BuLi), followed by addition of bromine, is not effective in producing 5-bromo-1-methylimidazole (77). This is due to the aforementioned equilibration of the imidazol-5-yl anion to give preferentially the imidazol-2-yl anion.
We have investigated the regiospecific bromination of the commercially available 1-methylimidazole (48) with a variety of known brominating agents (Fig. 2).

![Figure 2: Brominating agents tested for regioselectivity on 1-methylimidazole](image)

We discovered that unlike the other brominating agents, which gave a variety of C-2, C-4 and C-5 brominated derivatives of 1-methylimidazole, bromination of 1-methylimidazole (48) with 1,3-dibromo-5,5-dimethylhydantoin (84) produced the 5-bromo-1-methylimidazole (77) regiospecifically (Scheme 43).

![Scheme 43: Regiospecific bromination of 1-methylimidazole](image)

In our efforts to optimize the yields of the reaction, we investigated the reaction at different temperatures and conditions (Table 1).
Table 1: Variation of the reaction conditions for the regiospecific bromination of 1-methylimidazole using DBDMH to produce 5-bromo-1-methylimidazole.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>DBDMH (eq) (84)</th>
<th>Additive</th>
<th>Yield (%) (77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.5</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>1.0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0.5</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0.5</td>
<td>AIBN</td>
<td>20</td>
</tr>
<tr>
<td>-18</td>
<td>1.0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>-41</td>
<td>1.0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>-78</td>
<td>0.5</td>
<td>AIBN</td>
<td>0</td>
</tr>
</tbody>
</table>

5-Bromo-1-methylimidazole (77) could be obtained selectively in only 20% yield. Increasing the temperature and the equivalents of the brominating agent decreased the selectivity for the desired product (77). Introducing AIBN to catalyze the reaction had no effect on the yield or the selectivity of the bromination. The ineffectiveness of AIBN to stimulate higher bromination rates suggests a non-radical mechanism for this reaction. A possible mechanism for this reaction is shown (Scheme 44).

![Scheme 44: An electrophilic substitution mechanism for the bromination](image)

The difficulties we encountered in selectively brominating 1-methylimidazole (48) led us to investigate an alternative route to 5-bromo-1-methylimidazole (77).
2.1.2.2  *Bromination/Debromination/Methylation*

The possibility of selectively methylating the C-4(5) functionalized imidazole was to be explored (Scheme 45), in essence mimicking the proposed biogenetic pathway to xestomanzamine A (Scheme 2).

![Scheme 45: Selective methylation as a route to 5-bromo-1-methylimidazole](image)

The selective debromination of 2,4,5-tribromoimidazole (54) to 4(5)-bromomimidazole (85) has been reported\(^5\) using sodium sulfite as the reducing agent (Scheme 46).

![Scheme 46: Selective debromination of 2,4,5-tribromoimidazole](image)

This approach is unfortunately unsuccessful for the debromination of 2,4,5-tribromo-1-methylimidazole (86) to give 5-bromo-1-methylimidazole (77)\(^5\) (Scheme 47).

![Scheme 47: Resistance of tribromo-1-methylimidazole to reduction by sodium sulfite](image)
The synthesis of 5-bromo-1-methylimidazole (77) was therefore envisaged to proceed through tribromination, selective debromination and selective methylation starting from imidazole (5) (Scheme 48).

![Scheme 48: Retrosynthesis of 5-bromo-1-methylimidazole from imidazole](image)

The bromination of imidazole (5) was effected with the use of bromine, in 56% yield\(^{56,58}\). 2,4,5-Tribromoimidazole (54) is insoluble in refluxing water, and can therefore be isolated readily from the reaction mixture. The product (54) was purified by dissolving in a basic solution and fractionally precipitating with an acid (Scheme 49). The solubility of 2,4,5-tribromoimidazole (54) in aqueous basic solutions is due to the increased acidity of the hydrogen on the nitrogen because of the electron withdrawing effect of the three bromine atoms. The melting point of 2,4,5-tribromoimidazole (54), m.p. 219-222 °C, was in accordance with literature values.\(^{56,58}\)

![Scheme 49: The solubility of 2,4,5-tribromoimidazole in aqueous solutions](image)
The selective debromination of 2,4,5-tribromoimidazole (54) to 4(5)-bromoimidazole (85) was affected with the aforementioned simple procedure reported by Balaban and Pyman, where sodium sulfite acted as the reducing agent (Scheme 46). The yield of the reaction was 53% and the $^1$H-NMR spectrum of the product (85) showed two peaks at δ7.60 and 7.06 in CDCl$_3$ indicative of H-2 and H-4(5) respectively.

A mechanism for this reaction has not been proposed. The conversion of 4,5-dibromoimidazole (87) to 4(5)-bromoimidazole (85) has also been reported by the same authors (Scheme 50).

Scheme 50: Debromination of 4,5-dibromoimidazole

The formation of 4(5)-bromoimidazole (85) from 2,4,5-tribromoimidazole (54) may consequently be presumed to go through 4,5-dibromoimidazole (87) (Scheme 51).

Scheme 51: The presumed sequence of the debromination reaction

The bromine on the 4(5)-bromoimidazole (85) is attached to an imidazole ring which is comparatively richer electronically. It is conceivable that the reducing power of sodium sulfite is not enough to remove the last bromine atom due its greater stability in an electron-rich environment.
With 4(5)bromoimidazole (85) at hand, we attempted a simple methylation in the presence of potassium carbonate as a base, using iodomethane as the methylating agent and acetone as the solvent (Scheme 52).

![Scheme 52: Methylation of 4(5)-bromoimidazole](image)

Methylation of 4(5)-bromoimidazole (85) using different equivalents of iodomethane was investigated (Table 2).

**Table 2: Methylation of 4(5)-bromoimidazole under various conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>CH₃I (eq)</th>
<th>Temperature (°C)</th>
<th>Base</th>
<th>Reaction Time (hr)</th>
<th>Yield % (77)</th>
<th>Yield % (88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>25</td>
<td>K₂CO₃</td>
<td>24</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>25</td>
<td>K₂CO₃</td>
<td>24</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>25</td>
<td>K₂CO₃</td>
<td>6</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>25</td>
<td>-</td>
<td>6</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>56</td>
<td>-</td>
<td>6</td>
<td>39</td>
<td>21</td>
</tr>
</tbody>
</table>

(a) *Product compositions were determined by ¹H-NMR spectroscopy.*

It became apparent that in the presence of a base, the major product in the methylation of 4(5)-bromoimidazole (85) was 4-bromo-1-methylimidazole (88) rather than the desired 5-bromo-1-methylimidazole (77). These experimental observations are in agreement with the results of methylation of 4(5)-bromoimidazole (85) reported by Fujii and coworkers.¹⁹ The solvent and the base used by Fujii were ethanol and sodium hydroxide respectively. In the absence of a base, the selectivity for the C-5 substituted regioisomer (77) was slightly enhanced as apparent in entries 4 and 5 (Table 2).
Fujii, Ohba and Mukaihira reported a similar result in the absence of a base although they used dimethylformamide as the solvent. In our hands, the methylation reaction of 4(5)-bromoimidazole (85) did not yield the reported 66% of 5-bromo-1-methylimidazole (77).

The optimum condition for obtaining the desired 5-bromo-1-methylimidazole (77) through methylation of 4(5)-bromoimidazole (85) was found to be in the absence of base and using acetone as the solvent as indicated in entry 5 (Table 2). The isolated yield of the reaction after column chromatography was 35%. The $^1$H-NMR of the product (77) matched the literature values$^{60}$.

In addition to the difficulties involved in the regiospecific methylation of 4(5)-bromoimidazole (85), we were dismayed by the low conversion of the reaction. The combined yield of the methylation products (77) and (88) was never more than 69%, even in the presence of excess methylaing reagent, as shown in entry 3 (Table 2).

The methylation reaction of imidazole (5) using excess iodomethane was followed through $^1$H-NMR to investigate the conversion ratio of the reaction. Imidazole (5) was used as a model molecule for our investigation, to eliminate the regioselectivity problem (Scheme 53).

Scheme 53: Methylation products of imidazole
Imidazole (5) was mixed with one equivalent of sodium methoxide in deuterated methanol (Fig. 3).

On addition of iodomethane to the NMR tube, a peak characteristic of the methyl group appeared instantaneously at 63.73. The appearance of a second peak characteristic of the second methyl group at 63.93 occurred after only 15 min at room temperature. A comparison of the integration indicates that the yield of the 1-methylimidazole (48) at that moment was around 30%. With this information in hand, it is prudent to argue that the product of the methylation, 1-methylimidazole (48), underwent another methylation at the second nitrogen atom, to give the ionic \(N,N^\prime\)-dimethylimidazolium iodide (49).

The competition of the second imidazole nitrogen in the methylation reaction to give the 1,3-dimethylimidazolium salt (49) made the regiospecific methylation of 4(5)-bromoimidazole (85) critical for obtaining high yields of the 5-bromo-1-methylimidazole (77).
Although the procedure at hand for the synthesis of 5-bromo-1-methylimidazole (77) was not completely satisfactory, the magnesium insertion was to be tested before optimizing the reaction conditions for the methylation of 4(5)-bromoimidazole (85). The formation of the Grignard reagent (90) was tested using Michler’s ketone (91). The test for the formation of the Grignard reagent (90) failed to produce the anticipated greenish-blue colour (Scheme 54).

![Scheme 54: Testing the presence of Grignard formation with Michler’s ketone](image)

The failure to insert magnesium at the C-5 of 5-bromo-1-methylimidazole (77) is in agreement with a report by Katritzky and coworkers\(^\text{61}\), where the failure to react magnesium with a mixture of 5-bromo-1-methylimidazole (77) and 4-bromo-1-methylimidazole (88) was mentioned.

The inability of magnesium to insert between the bromine and carbon (90), compounded with our inability to synthesize 5-bromo-1-methylimidazole (77) in a regiospecific manner in high yields, directed our focus towards the synthesis of the corresponding iodo-substituted imidazole.
2.1.2.3 *Iodination/Deiiodination/Methylation*

The synthesis of 5-iodo-1-methylimidazole (92) was attempted using a similar strategy. Imidazole (5) was iodinated at all three carbons, selectively deiodinated and then regiospecifically methylated to afford 5-iodo-1-methylimidazole (92).

(Scheme 55).

\[ \begin{align*}
\text{5} & \quad \Rightarrow \quad \text{92} \quad \Rightarrow \quad \text{94} \quad \Rightarrow \quad \text{93} \quad \Rightarrow \quad \text{5} \\
\text{Scheme 55: Retrosynthetic plan towards 5-iodo-1-methylimidazole} 
\end{align*} \]

The synthesis of 2.4.5-triiodoimidazole (93) has been reported through the action of iodine on imidazole (5) in basic solutions\(^ {62} \). A more recent method uses iodine in the presence of bis-(trifluoroacetoxy)iodobenzene (95) for the iodination\(^ {63} \).

(Scheme 56).

\[ \begin{align*}
\text{5} & \quad \Rightarrow \quad \text{92} \quad \Rightarrow \quad \text{94} \quad \Rightarrow \quad \text{93} \quad \Rightarrow \quad \text{5} \\
\text{Scheme 56: Iodination of imidazole} 
\end{align*} \]

A modification of a method for iodination of 4-hydroxyquinoline (96)\(^ {64} \) (Scheme 57), was reported for the iodination of imidazole (5)\(^ {60} \).

(Scheme 57).
Imidazole (5) was iodinated with iodine in an aqueous solution of sodium hydroxide in the presence of potassium iodide (Scheme 58). 2,4,5-Triiodoimidazole (93) separated from the solution upon neutralization with acetic acid. The yield of the reaction was 76% and the melting point was in agreement with literature reports 60, 63.

This reaction afforded the product 2,4,5-triiodoimidazole (93) in a simple and efficient manner. The purification of the product (93) did not suffer from the impracticality of using column chromatography as when bis-(trifluoroacetoxy)iodobenzene (95) is used.

The next step was the selective deiodination of 2,4,5-triiodoimidazole (93) to 4(5)-iodoimidazole (94). The use of sodium sulfite had been extended to the selective deiodination reaction of 2,4,5-triiodoimidazole (93)65. The deiodination of 2,4,5-triiodoimidazole (93) was effected in 50% yield 65a. The reaction in our hands afforded 4(5)-iodoimidazole (94) in 99% yield, with a simple modification in the workup procedure (Scheme 59).
Refluxing the triiodoimidazole (93) at 100°C reduced all the iodine atoms, and the product of the reaction was imidazole (5). The solvent used for the deiodination was therefore 30% ethanol in water to allow for a lower reflux temperature. The 1H-NMR spectrum of the reduction product 4(5)iodoimidazole (94) showed two peaks at 87.62 and 7.18 in CDCl3, indicative of H-2 and H-4(5) respectively.

The regiospecific methylation of 4(5)-iodoimidazole (94) to 5-iodo-1-methylimidazole (92) was next attempted using iodomethane and dimethyl sulfate. The iodine atom in 4(5)-iodoimidazole (94) was thought to affect the regioselectivity of the reaction, in one way or another, better than a bromine atom would in 4(5)-bromoimidazole (85). The methylation was investigated using different bases (NaH, K2CO3, NaOMe). It was found that, in the presence of a base, iodine affected the regioselectivity of the reaction in a negative manner, and the dominant product was 4-iodo-1-methylimidazole (98) (Scheme 60). 5-Iodo-1-methylimidazole (92) was isolated in only 30% yield in the absence of a base, with excess methylating agent.

Regiospecific methylation was thus yet again not achieved using this strategy.

Scheme 60: Methylation of 4(5)-iodoimidazole

The next strategy towards obtaining 5-iodo-1-methylimidazole (92) in a regiospecific manner is to introduce a methyl group to the 4(5)-iodoimidazole (94) after protonating the ring. The methylation was not envisaged to proceed in an acidic medium, but it was hoped that in a slightly acidic buffer solution, where both nitrogens
would be protonated, regiospecific methylation could be achieved to afford the desired product: namely, 5-iodo-1-methylimidazole (92) (Scheme 61).

![Scheme 61: Resonance contributors in protonated 4(5)-iodoimidazole](image)

On the basis of electronegativity and adjacent charge effects, and bearing in mind that iodine would be in a richer electron environment, one can imagine the resonance form of 4(5)-iodoimidazole [94-I] to be more stable than [94-II]. The methylation of 4(5)-iodoimidazole in this resonance form [94-I] would afford the desired 5-iodo-1-methylimidazole (92). The protonation of 4(5)-iodoimidazole (94) was tested using different mixtures of Tris buffer (pH 6.5) and acetone using TLC. After finding the proper ratio of buffer/acetone where all the 4(5)-iodoimidazole (94) was protonated, the methylation was attempted using excess iodomethane. The attempted methylation of the protonated species of 4(5)-iodoimidazole [94-I] was unsuccessful, and the starting material was recovered (Scheme 62).

![Scheme 62: Regiospecific methylation of the protonated species](image)

Having tested the pseudo protection of one of the nitrogens, the regiospecific protection of N-3 of 4(5)-iodo-1H-imidazole (94) was next considered. Cliff and
Pyne$^{66}$ have recently reported the regiospecific tosylation of 4(5)-idoimidazole (94) to afford 4-ido-1-p-tosylimidazole (99) in 78% yield (Scheme 63).

\[
\begin{array}{c}
\text{Scheme 63: Regiospecific tosylation of 4(5)-idoimidazole} \\
\text{This reaction was performed next, and the product 4-ido-1-p-tosylimidazole (99) was isolated in 98% yield with complete selectivity. The }^{1}H\text{-NMR of the tosylated product (99) showed the peaks of H-5 and H-2 at } \delta \text{ 7.37 and 7.88 respectively. The yield of the reaction was improved by adding a slight excess of } p\text{-toluenesulfonyl chloride.}
\]

Although it is tempting to argue that the large iodine atom interacts sterically with the electrophilic } p\text{-toluenesulfonyl chloride in a negative manner, and the more favourable 4-ido-1-p-tosylimidazole (99) is produced, it has very recently been shown$^{67}$ that the 5-iodosulfonamide (100) undergoes a conversion to the 4-iodosulfonamide (101) in the presence of } N,N\text{-dimethylsulfamoyl chloride (Scheme 64).}
Scheme 64: Rearrangement of N-protected 5-iodoimidazole to the 4-iodo regioisomer

Based on this observation, it is reasonable to assume that the ability of 5-iodo-1-p-tosylimidazole (102) to rearrange to the 4-iodo regioisomer (99) might be the reason for the regiospecificity of the reaction. The possibility of formation of both regioisomers: 4-iodo-1-p-tosylimidazole (99) and the sterically less favourable 5-iodo-1-p-tosylimidazole (102), cannot be excluded. Thus, the addition of excess p-toluenesulfonyl chloride in our reaction did not affect the regiospecificity of the tosylation but increased the yield of the 4-iodo product (99) (Scheme 65).

Scheme 65: Possible mechanism for the regiospecific tosylation of 4(5)-iodoimidazole

Lindel and Hochgürtel have very recently reported the methylation of the second nitrogen on a N-3 tosylated alkynylimidazole (103), using trimethyloxonium
tetrfluoroborate, to form the C-5 substituted alkynyl-1-methylimidazole (104) (Scheme 66).

\[ \text{Scheme 66: Methylation of C-4 substituted 1-tosylimidazole} \]

This strategy was examined for the methylation of the N-3 of 4-iodo-1-p-tosylimidazole (99) to afford 5-iodo-1-methylimidazole (92) (Scheme 67).

\[ \text{Scheme 67: Methylation of 4-iodo-1-p-tosylimidazole} \]

This reaction afforded the desired product (92) in 99% yield. The \(^1\)H-NMR spectrum had three singlet peaks at \( \delta \) 3.62, 7.13 and 7.62 for the methyl, H-4 and H-2 respectively. These values were in agreement with the reported literature values\(^{60}\) for 5-iodo-1-methylimidazole (92).

The methylation of N-3 of 4-iodo-1-p-tosylimidazole (99) using trimethyloxonium tetrafluoroborate produced 5-iodo-1-methyl-3-p-tosylimidazolium salt (105) which was not isolated (Scheme 68). The p-toluenesulfonyl functionality in
the salt (105) is an excellent electrophile and susceptible to nucleophilic attack. When the reaction mixture was quenched with methanol, the tosyl functionality was removed to produce the ester (106) and 5-iodo-1-methylimidazole (92).

Scheme 68: Mechanism of methylation and detosylation of 4-iodo-1-p-tosylimidazole

The desired product (92) was simply back-extracted from an acidic aqueous solution to separate the product (92) from the ester (106) and afford the pure white solid.

The sequence of reactions leading to 5-iodo-1-methylimidazole (92) from imidazole (5) (Scheme 69) does not carry the disadvantages associated with literature methods\(^{60,69}\) for the synthesis of 5-iodo-1-methylimidazole (92): namely, low yields, poor reproducibility and tedious purification methods. The overall yield for the synthesis of 5-iodo-1-methylimidazole (92) from imidazole (5) was 73%.

Scheme 69: Synthesis of 5-iodo-1-methylimidazole from imidazole
2.1.3 Synthesis of xestomanzamine A

The synthesis of xestomanzamine A was first attempted by addition of a solution of EtMgBr and 5-iodo-1-methylimidazole (92) in THF to a solution of the methyl β-carboline ester (66) in THF in the presence of excess lithium chloride. The indole nitrogen on the β-carboline ester (66) was deprotonated with the addition of one equivalent of EtMgBr prior to the addition of the 5-iodo-1-methylimidazole (92). Xestomanzamine A was obtained in low yields. Turner and Lindell \(^{70}\) reported a mild and simple procedure for the metal-halogen exchange with a N-protected 4-iodoimidazole (107), using EtMgBr in CH\(_2\)Cl\(_2\) (Scheme 70).

Repeating the reaction in CH\(_2\)Cl\(_2\) afforded xestomanzamine A in a better yield. Dichloromethane gave the Grignard organomagnesium intermediate a greater covalent character, which made the imidazol-5-yl carbanionoid less sensitive to equilibration to the imidazol-2-yl anion \(^{70}\) (Scheme 71).
It was noticed that the addition of EtMgBr to 5-iodo-1-methylimidazole (92) produced a white precipitate prior to the addition to the β-carboline ester (66). Grignard reagents exist in equilibrium with the corresponding binary organomagnesium compounds. At low temperatures and when there is a solvent-induced precipitation of the magnesium salt, there is a shift of the equilibrium towards the organomagnesium species [67-I] (Scheme 72).

Scheme 72: Grignard reagent in equilibrium with the organomagnesium species

The equilibrium was shifted towards the Grignard reagent (67) by heating EtMgBr and 5-iodo-1-methylimidazole (92) briefly prior to introduction to the methyl β-carboline ester (66). The yield of the xestomanzamine was in this way increased to 81%.

The role of lithium chloride was to stabilize the carbonyl oxygen and prevent the formation of the tertiary alcohol (Scheme 73). The physical data (m.p., \(^1\)H and \(^1^3\)C-NMR) obtained for xestomanzamine A (2) match those reported for the natural product\(^4\).

Scheme 73: Lithium cation stabilizes the carbonyl
2.2 Livinghouse Approach (xestomanzamine B)

2.2.1 Synthesis of 3-(2-isocyanatoethyl)indole

Dehydration of formamides is the most popular route for the preparation of isocyanides. This approach was discovered almost simultaneously by Hagedorn\textsuperscript{72}, Corey\textsuperscript{73}, and Ugi\textsuperscript{74}. 3-(2-Isocyanatoethyl)indole (68) can be prepared in this manner by first formylating tryptamine (13) and then dehydrating the N-formyltrypamine (109) (Scheme 74).

![Scheme 74: Retrosynthetic plan towards 3-(2-isocyanatoethyl)indole](image)

\textbf{2.2.1.1 Formylation of tryptamine}

The N-formylation of tryptamine (13) was effected in a refluxing solution of ethyl formate by Schöpf and Steuer\textsuperscript{75}. The product (109) was reported as a solid (Scheme 75).

![Scheme 75: Formylation using ethyl formate](image)
This reaction afforded the product (109) as a solid. The melting point of the solid was 74-76 °C. $^1$H-NMR shifts for the $N$-formyltryptamine (109) showed the formyl proton at δ 11.00 in CDCl$_3$. The yield of the reaction in our hands was 65%.

In an effort to improve the yield of this reaction, other methods were investigated for introducing the formyl functionality. Onda and Sasamoto$^{76}$ reported the synthesis of $N$-formyltryptamine (109) by heating tryptamine (13) in formic acid at 180 °C. A much milder procedure, first reported by Dalgliesch$^{77}$, was used by Tadao and coworkers$^{78}$ for the formylation of tryptamine (13) in 87% yield at room temperature. This method employed acetic formic anhydride (AFA) (110) for the formylation. Acetic formic anhydride (110) was made in situ and added to the tryptamine (13) (Scheme 76). This method has been used by others$^{79}$ for the formylation of tryptamine (13).

![Scheme 76: Acetic formic anhydride as a formylating agent](image)

A procedure reported by Krishamurthy$^{80}$ was used by us for the preparation of AFA (110) from formic acid and acetic anhydride. Formylation of tryptamine (13) with in situ generated AFA in the presence of 3Å molecular sieves afforded the $N$-formyltryptamine (109) in 97% yield. A trace amount of acetylation was also observed.

Although pure AFA can also be prepared by the reaction of formic acid with ketene$^{81}$, a method reported by Vlietstra and coworkers$^{82}$, where trimethylacetic formic
anhydride (111) was employed for N-formylation, looked more attractive. The acetyl group of AFA (110) was substituted with a sterically more hindered trimethylacetyl functionality (111), thus making the α-carbon on the acetyl side less susceptible to nucleophilic attack (Scheme 77).

![Scheme 77: Trimethylacetic formic anhydride as a formylating agent](image)

In our hands this procedure afforded the N-formyltryptamine (109), free of any N-acetyltryptamine (112), in 75% yield. Although the purity of the product (109) was improved, there was a considerable decrease in the yield and simplicity of the procedure employed when compared to AFA (110). The isolation of trimethylacetic formic anhydride (111) proved to be an extremely tedious protocol. In view of the fact that N-acetyltryptamine (112) could not undergo a dehydration reaction, and therefore would not interfere with the dehydration of the N-formyltryptamine (109) to afford the desired isonitrile (68) (Scheme 78) we were satisfied with using AFA for the formylation of tryptamine (13).

![Scheme 78: N-Acetyltryptamine would not interfere with the next step](image)
The presence of small amounts of N-acetyltryptamine (112) was not considered to be an obstacle, and the formylation of tryptamine (13) was therefore conducted with AFA (110) for the remainder of the synthesis.

2.2.1.2 Dehydration of N-formyltryptamine

The dehydration of N-formyltryptamine (109) was investigated using phosphorus oxychloride as the dehydrating agent. Since its first use by Ugi and coworkers\textsuperscript{83}, phosphorus oxychloride has been a popular reagent for the dehydration of formamides\textsuperscript{81} (Scheme 79).

\begin{center}
\begin{tikzpicture}
\draw (0,0) rectangle (2,2);
\draw (0.5,0.5) -- (1.5,0.5);
\draw (0.5,1.5) -- (1.5,1.5);
\node at (0.5,0.5) {113};
\node at (1.5,0.5) {114};
\node at (0.5,1.5) {POCl\textsubscript{3}, Et\textsubscript{3}N};
\node at (1.5,1.5) {R-N=\textbf{C}^-};
\node at (0.5,1) {R-N\text{H}};
\end{tikzpicture}
\end{center}

Scheme 79: Dehydration of formamides

The dehydration of N-formyltryptamine (109) with phosphorus oxychloride, in the presence of Hünig's base DIPEA, was successful in producing the isonitrile 3-(2-isocyanooethyl)indole (68), but in only 10% yield. The dehydration of formamides (113) using phosphorus oxychloride has been reported to produce the isocyanides (114) in good to excellent yields\textsuperscript{83,84}. A closer look at the reaction revealed a very different dehydration product (Scheme 80).
Scheme 80: Cyclization of N-formyltryptamine with POCI₃

The dehydration of N-formyltryptamine (109) using phosphorus oxychloride produced the isonitrile (68) as an intermediate for the Bischler-Napieralski reaction. Kuehne and coworkers have reported the synthesis of 3,4-dihydro-β-carboline (115) through the dehydration of N-formyltryptamine (109) using phosphorus oxychloride, in 85% yield.

The cyclodehydration of N-formyltryptamine (109) to 3,4-dihydro-β-carboline (115) has also been reported using phosphorus pentoxide. The complementary method of formylation/dehydration as a route to 3-(2-isocyanethyl)indole (68) from tryptamine (13) seems therefore to be complicated by the further reaction of the isonitrile (68) under the dehydration conditions, to form the Bischler-Napieralski product (115).
3-(2-Isocyanoeethyl)indole (68) has been synthesized by the Livinghouse group\textsuperscript{17b} by nucleophilic displacement of gramine methiodide (116) with lithiomethyl isocyanide (117), in 64\% yield (Scheme 81).

![Scheme 81: Nucleophilic displacement as a route to the isonitrile]

\textbf{2.2.1.3 Hofmann carbamylamine reaction}

The so-called Hofmann carbamylamine reaction\textsuperscript{86} (Scheme 82) has not enjoyed synthetic popularity because of experimental difficulties and low yields.

![Scheme 82: Hofmann carbamylamine reaction]

The Hofmann carbamylamine reaction generally affords yields around 20\% with chloroform and ethanolic potassium hydroxide. Weber, Gokel\textsuperscript{87a} and Ugi\textsuperscript{87b} have reported a procedural modification to the Hofmann reaction utilizing phase transfer catalysis which significantly improves the yield of the reaction to between 41-61\%.
Nei\(^{88}\) recognized the generation of dichlorocarbene (119) as an intermediate for the reaction (Scheme 83). Makosza and Wawrzyniewicz\(^{89}\) have reported the efficient generation of dichlorocarbene from chloroform and 50% aqueous sodium hydroxide utilizing phase transfer catalysis. Weber, Gokel and Ugi\(^{87}\) applied this method of dichlorocarbene (119) generation to the formation of isonitriles (114).

We have investigated the formation of 3-(2-isocyanooethyl)indole (68) using the Hofmann carbylamine reaction on tryptamine (13), using the reported improvements\(^{87}\) on the original procedure (Scheme 84).

The desired isonitrile (68) was isolated in 52% yield as a white solid. The isonitrile produced in this reaction showed a sharp IR spectrum absorption at 2150 cm\(^{-1}\) characteristic of the isonitrile functionality\(^{17b}\). The yield of the one-step reaction with chloroform and 50% aqueous sodium hydroxide is a significant improvement to the overall yield obtained by the two-step formylation-dehydration technique. This method affords the isonitrile (68) in a slightly lower yield than the method of nucleophilic
displacement of gramine methiodide (116) with lithiomethyl isocyanide (117) (Scheme 81), but the formation of the isonitrile (68) from tryptamine (13) using the Hofmann carbamylamine method offers the advantages of convenience and simplicity.

Synthesis of the isonitrile (68) through the reaction of tryptamine (13) with dichlorocarbene (119) does not involve a further a Bischler-Napieralski cyclodehydration (Scheme 80). It is noteworthy that no evidence was seen for the reaction of the dichlorocarbene (119) with the indole nitrogen (Scheme 85), a complication that would have hindered the production of the desired product (68).

Scheme 85: Mechanism of the dichlorocarbene reaction with tryptamine

The sensitivity of the electron-rich indole nucleus to trace amounts of hydrogen halides\(^{17b}\) prevents the direct reaction of the isonitrile (68) with the imidazolecarbonyl chloride (71). The protection of the indole nitrogen on 3-(2-isocyanooethyl)indole (68) therefore seemed to be a prudent action before the cyclization reaction, one that Livinghouse and his group attained with the use of methyl chloroformate to produce
the N-carbomethoxy derivative (69) (Scheme 86).

![Scheme 86: Protection of the indole nitrogen](image)

In our hands, this reaction afforded the N-carbomethoxy derivative (69) in 99% yield. The methyl group showed a $^1$H-NMR signal at $\delta$ 4.05 in CDCl$_3$ and the carbonyl group showed an IR spectrum absorption at 1726 cm$^{-1}$, consistent with the spectral information provided in the literature$^{17b}$.

### 2.2.2 Synthesis of the imidazole substructure

The synthesis of xestomanzamine B (3) through the Livinghouse cyclization required the reaction of isonitrile (69) with the imidazolecarbonyl chloride (71) (Scheme 87).

![Scheme 87: Retrosynthetic plan to xestomanzamine B](image)
2.2.2.1 Synthesis of 1-methyl-5-imidazolecarbonyl chloride

The synthesis of 1-methyl-5-imidazolecarbonyl chloride (71) was envisaged to be achieved from 1-methyl-5-imidazolecarboxylic acid (123). Katritzky and coworkers\textsuperscript{61} reported a direct synthesis of 1-methyl-5-imidazolecarboxylic acid in a regiospecific manner from 1-methylimidazole (48) (Scheme 88).

\begin{center}
\begin{tabular}{c}
\begin{tikzpicture}
\node[draw] (A) at (0,0) {48};
\node[draw] (B) at (2,0) {123};
\draw[->, thick] (A) edge node[above] {1) BuLi-TMEDA (2 eq)} (B);
\draw[->, thick] (B) edge node[above] {2) Dry CO\textsubscript{2}} (B);
\draw[->, thick] (B) edge node[above] {3) BuLi-TMEDA (1 eq)} (B);
\draw[->, thick] (B) edge node[above] {4) Ethyl formate} (B);
\end{tikzpicture}
\end{tabular}
\end{center}

\textit{Scheme 88: Direct preparation of 1-methyl-5-imidazolecarboxylic acid}

This direct approach did not produce the desired product (123) regiospecifically. Instead a complex mixture of products was obtained.

The preparation of 1-methyl-5-imidazolecarboxylic acid (123) was then conceived to go through a sequence of reactions starting from benzimidazole (120) (Scheme 89).

\begin{center}
\begin{tabular}{c}
\begin{tikzpicture}
\node[draw] (A) at (0,0) {71};
\node[draw] (B) at (1,0) {123};
\node[draw] (C) at (2,0) {122};
\node[draw] (D) at (3,0) {121};
\node[draw] (E) at (4,0) {120};
\draw[->, thick] (A) edge node[above] {} (B);
\draw[->, thick] (B) edge node[above] {} (C);
\draw[->, thick] (C) edge node[above] {} (D);
\draw[->, thick] (D) edge node[above] {} (E);
\end{tikzpicture}
\end{tabular}
\end{center}

\textit{Scheme 89: Retrosynthetic plan towards 1-methyl-5-imidazolecarbonyl chloride}

Efros and coworkers\textsuperscript{90} have reported the preparation of 4,5-imidazoledicarboxylic acid (121) from the oxidation of benzimidazole (120) with potassium dichromate in concentrated sulfuric acid. A reproduction of this work in our laboratory afforded 4,5-imidazoledicarboxylic acid (121) in 58% yield (Scheme 90).
The product (121) was purified by reprecipitation from the alkaline solution with acid. The $^1$H-NMR spectrum of the product (121) showed the H-2 signal at $\delta$ 9.06 in DMSO-$d_6$. The IR spectrum showed a broad, intense absorption in the region 3200-2600 cm$^{-1}$, indicative of a carboxylic acid. The dicarboxylic acid (121) was insoluble in all the common organic solvents and was only solubilized in hot alkaline solutions.

The methylation of 4,5-imidazoledicarboxylic acid (121) to afford 1-methyl-4,5-imidazoledicarboxylic acid (122) in 25% was reported by Efros et al. (Scheme 91)

In our hands, methylation of dicarboxylic acid (121) using this method afforded 1-methyl-4,5-imidazoledicarboxylic acid (122) in only 8% yield. The methylation of the dicarboxylic acid (121) using other methylating agents proved to be equally difficult under the alkaline conditions which would allow the starting material to dissolve.
We were successful in obtaining the N-methylated dicarboxylic acid (122) in 16% yield, using a combination of dimethyl sulfate and iodomethane.

Aleksandrova and coworkers\textsuperscript{91} reported the methylation of methyl imidazoledicarboxylate (124) using iodomethane in methanol in the presence of sodium methoxide, followed by the hydrolysis of the ester with alkaline solution. The ester (124) was obtained through a method reported by Baxter and Spring\textsuperscript{92}. The overall yield of the two-step conversion of 4,5-imidazoledicarboxylic acid (121) to 1-methyl-4,5-imidazoledicarboxylic (122) was reported to be 37% (Scheme 92).

\begin{center}
\includegraphics{Scheme_92.png}
\end{center}

\textit{Scheme 92: Two-step esterification/N-methylation/hydrolysis sequence}

Our attempt to reproduce this work was unsuccessful. The isolation of the imidazole salts from the inorganic salts present in the reaction mixture proved to be an extremely tedious and unrewarding task.

The regiospecific decarboxylation of 1-methyl-4,5-imidazoledicarboxylic acid (122) to produce 1-methyl-5-imidazolecarboxylic acid (123) has been reported by Takahashi and Mitsuhashi\textsuperscript{93} (Scheme 93).
Scheme 93: Selective decarboxylation of 1-methyl-4,5-imidazolodicarboxylic acid

The regiospecific decarboxylation of the dicarboxylic acid (122) was a key step in our retrosynthetic plan towards 1-methyl-5-imidazolecarbonyl chloride (71) (Scheme 89). In an effort to verify the feasibility of obtaining 1-methyl-5-imidazolecarbonyl chloride (71) through this route, the decarboxylation reaction was tested before attempting to improve the preparation of 1-methyl-4,5-imidazolodicarboxylic acid (122).

The decarboxylation reaction (Scheme 93) afforded in our hands 1-methyl-5-imidazolecarboxylic acid (123) in 95% yield with complete regiospecificity. The specificity of the decarboxylation can be rationalized mechanistically on the basis of the “adjacent charge effect”93 (Scheme 94).

Scheme 94: The two possible decarboxylated transition states

In the presence of acetic anhydride the second nitrogen on the imidazole ring is acetylated. The decarboxylated transition state [123-II] is postulated to be more stable than transition state [123-I] due to the adjacent charge effect, therefore producing 1-methyl-5-imidazolecarboxylic acid (123) regiospecifically.
The successful regiospecific preparation of 1-methyl-5-imidazolecarboxylic acid (123) prompted us to return to the preparation of the precursor for this reaction, 1-methyl-4,5-imidazoledicarboxylic acid (122). The imidazole ring in \( N \)-methylbenzimidazole (125) unfortunately does not survive the oxidation conditions which produce 4,5-imidazoledicarboxylic acid (121) from benzimidazole (120) \(^{90}\) (Scheme 95).

\[
\begin{array}{c}
\text{125} \quad \text{X} \quad \text{122}
\end{array}
\]

*Scheme 95: Instability of imidazole ring in \( N \)-methylbenzimidazole*

It became apparent that the solubility of 4,5-imidazoledicarboxylic acid (121) was a major obstacle for the \( N \)-methylation. Under aqueous basic conditions, where the solubility of the starting material (122) was improved, the yield of the reaction suffered due to the destruction of the methylating agent. Several attempts were made to modify the di-acid functionality of the dicarboxylic acid (121) to improve the solubility in organic solvents.

Esterification of the dicarboxylic acid (121) did not afford a product (124) soluble in common organic solvents. The preparation of ethyl and butyl esters was also not successful, due to the solubility problems associated with the starting material (121). The formation of the anhydride (126) was thought to increase the solubility of the 4,5-imidazoledicarboxylic acid (121) since the proton donating ability of the compound would be removed. The dicarboxylic acid (121) was allowed to react with
methyl chloroformate, hence activating the carbonyl group for nucleophilic attack (Scheme 96). This strategy was, however, unsuccessful and the anhydride was not isolated. The functionalization, hence increased solubility, of 4,5-imidazoledicarboxylic acid (121) was next sought through the formation of an N-substituted imide, the tetrahydropyrrolo[3,4-d]imidazole-4,6-dione (127). The nucleophilic attack of an amine (128) was imagined, where the ring closure was not an essential step. The failure of the amine to affect a ring closure was not important, as long as the solubility of the imidazole was increased in the form of the amide (129) (Scheme 97).

Scheme 96: Possible mechanism for the formation of the anhydride

Scheme 97: Functionalization of imidazoledicarboxylic acid to improve solubility
This route did not afford the desired imide (127) and the amide (129) was isolated as a salt which was found to be slightly soluble in dimethyl sulfoxide only.

Dichlorodimethylsilane has been a traditional reagent for protecting acidic functionalities. Wieber and Schmidt have reported the use of dichlorodimethylsilane as a protecting group for both the acid and an adjacent alcohol or an amine (Scheme 98).

![Scheme 98: Dichlorodimethylsilane as a protecting group](image)

Eleftheriou and coworkers have used dichlorodimethylsilane as a protecting group for the amino and carboxyl functionality of histidine (Scheme 99).

![Scheme 99: Protection of the terminal end of histidine](image)

An attempt to protect the two carboxylic acid functionalities with dichlorodimethylsilane was not successful in our case and the starting material was recovered (Scheme 100).
Having failed to improve the solubility, hence the effective reactivity, of 4,5-imidazoledicarboxylic acid (121), formylation, regiospecific decarboxylation and subsequent reduction of the formyl group was seen as a plausible route to 1-methyl-5-imidazolcarboxylic acid (123) (Scheme 101).

An investigation of this route, however, again did not afford the desired product (123). The reaction of 4,5-imidazoledicarboxylic acid (121) with acetic formic anhydride and subsequent attempted reduction with sodium borohydride gave a complex mixture of products which were not characterized.

Chen and Janda\textsuperscript{97} have demonstrated the versatility of soluble, non-cross-linked chloromethylated polystyrene\textsuperscript{98} (138) in synthesis. This copolymer (138) is soluble in common organic solvents such as ether, THF, dichloromethane, chloroform, and ethyl acetate, but insoluble in water and methanol. The copolymer (138) was prepared by the copolymerization of styrene (136) and 4-(chloromethyl)styrene (137) (3 mol\%) in the
presence of 2,2'-azobis(isobutyronitrile) (AIBN) (Scheme 102). The functional group content was quantified via NMR.

The copolymer (138) was subjected to nucleophilic substitution in the presence of sodium hydroxide in DMF to afford the hydroxymethylated polystyrene (139). The progress of the reaction was monitored through TLC analysis. The conversion was complete in 48 hr (Scheme 103).

The solubility of 4,5-imidazolecarboxylic acid (121) could be controlled by attaching the acid to the polymer (139) (Scheme 104).
The excess unreacted hydroxy termini of the copolymer (139) can be protected with the acetyl functionality. The imidazole-polymer [139-I] can be methylated with excess of methylating agent. 1-Methyl-4,5-imidazolecarboxylic acid (122) can be removed from the polymer by hydrolysis, which will also remove the acetyl protection from the polymer to reproduce the polymer (139) for recycling. This synthesis of 1-methyl-4,5-imidazolecarboxylic acid (122) offers an immediate solution to the solubility and isolation problems encountered earlier. The non selective nature of this reaction sequence would also prove to be an advantage. In an effort to realize this reaction sequence, many attempts were made to attach the dicarboxylic acid (121) to the polymer (139). This proved to be a more difficult task than first imagined, and all our attempts were met with failure.

The insoluble nature of 4,5-imidazolecarboxylic acid (121) coupled with our previously discussed difficulties in methylation of the imidazole nitrogen convinced us to examine an alternative route to 1-methyl-5-imidazolecarboxylic acid (123).
2.2.2.2 Cobalt insertion on 5-iodo-1-methylimidazole

Carbonylation of halogenated aromatics is a well known reaction. These reactions have traditionally been performed under high carbon monoxide pressures (100-300 atm) and at high temperatures (200-350 °C) in the presence of transition metal catalysts. Brunet and coworkers have shown phase transfer catalysis in combination with photoradiation to be an effective method for the cobalt carbonylation of aryl halides. Kashimura and coworkers have demonstrated the versatility of this method under very mild conditions (Scheme 105).

\[
\text{Cl} + \text{CO (2 atm)} \xrightarrow{\text{Co}_2(\text{CO})_8, \text{NaOH (aq), h} \nu} \text{COONa}
\]

*Scheme 105: Carbonylation of aryl halides under mild conditions*

The carbonylation of 5-iodo-1-methylimidazole (92) was examined using this method. Since the superior reactivity of iodide aromatic compounds compared to chlorides is well established, carbon monoxide was used under normal atmospheric pressure (Scheme 106).

\[
\text{CO (1 atm), Co}_2(\text{CO})_8 \xrightarrow{\text{NaOH (aq), h} \nu} \text{NaOOC-}
\]

*Scheme 106: Carbonylation of 5-iodo-1-methylimidazole*
The amphoteric nature of 1-methyl-5-imidazolecarboxylic acid salt (142) proved to be an obstacle, and the carbonylated product (142) could not be isolated from the reaction mixture.

2.2.3 Attempted synthesis of xestomanzamine B

To avoid the isolation of the amphoteric 1-methyl-5-imidazolecarboxylic acid (138), the in situ synthesis of the imidazolicarbonyl substructure was considered.

2.2.3.1 Cobalt mediated cyclization

The cobalt insertion in 5-iodo-1-methylimidazole (92) was examined under a carbon monoxide atmosphere and photosensitization. The N-protected isonitrile (69) was introduced to the reaction mixture in the presence of silver tetrafluoroborate to undergo the anticipated subsequent Livinghouse cyclization (Scheme 107).

![Scheme 107: In situ generation of carbonyl in the synthesis of xestomanzamine B](image)

This strategy was not successful in the synthesis of xestomanzamine B. The carbon monoxide insertion was apparently not accomplished since the 5-iodo-1-methylimidazole (92) was recovered.
The carbonylation of 5-iodo-1-methylimidazole (92) in the presence of the isonitrile (69) using ultraviolet radiation was also attempted. The isonitrile underwent a photo-induced isomerization to the nitrile (143) (Scheme 108). The IR spectrum of the nitrile (143) showed a strong absorption at 2200 cm\(^{-1}\) indicative of the C\(=\)N stretch. The photochemical isomerization of isonitriles to nitriles is certainly not a new observation\(^{102}\).

Scheme 108: Photoinduced isomerization of isocyanide to nitrile

The carbonylation of 5-iodo-1-methylimidazole (92) using different transition metal catalysts remains a possibility. Alper and coworkers\(^ {103}\) have demonstrated the effectiveness of metal catalyzed carboxylation of aryl halides to aryl carboxylic acids. This method was not investigated, but seems to be a promising route to avoid ultraviolet radiation and to effect the Livinghouse cyclization.

2.3 Bischler-Napieralski Approach (xestomanzamine B)

The one-pot synthesis of xestomanzamine B (3) was also envisaged through a Bischler-Napieralski type cyclodehydration (Scheme 109).
The reaction of the Grignard reagents with oxalyl chloride has been shown to be an effective route towards 1,2-diones\(^{104}\) (144) (Scheme 110).

The magnesium exchange on 5-iodo-1-methylimidazole (92) had already proven to be effective. The addition of two equivalents of oxalyl chloride in a dilute solution of the Grignard was expected to afford the 2-oxoethanoyl chloride [67-I] (Scheme 111).
Reaction of oxoethanoyl chloride [67-I] with tryptamine (13) would give the α-oxoamide [67-II], which in turn might undergo a Bischler-Napieralski type cyclodehydration to give xestomanzamine B.

This approach, unfortunately, did not give the desired natural product (3) and produced a complex mixture of compounds which were not characterized.
Conclusion

Practicality and efficiency are of the utmost importance when preparing precursors in a synthetic sequence. The four-step preparation of 5-iodo-1-methylimidazole (92) is an example of such an approach (Scheme 69). We believe that 5-iodo-1-methylimidazole (92) has the potential to undergo various synthetic transformations to accommodate the synthesis of many natural products with the N-substituted C-5 functionalized imidazole substructure.

The total synthesis of xestomanzamine A (2) has been achieved through a modified Grignard reaction of 5-iodo-1-methylimidazole (92) with the β-carboline ester (66), in which xestomanzamine A was prepared in four steps from tryptamine (13) (53 % yield) and five steps from imidazole (5) (59 %).

The amphoteric nature of imidazolecarboxylic acids (121-123), redirected the synthetic pathway employed for the synthesis of xestomanzamine B (3) towards 5-iodo-1-methylimidazole (92) as a key precursor. The Hofmann carbylamine reaction was shown to afford 2-(3-indolyl)ethyl isonitrile (68) in one step, through a simple process which we believe to offer an attractive alternative to the current methods of preparing the isonitrile, without the risk of concomitant cyclization.
IV Experimental

Methanol and dichloromethane were distilled prior to use. Methanol was dried over magnesium. Xylenes and dichloromethane were dried over calcium hydride. Dimethylformamide was dried over phosphorus pentoxide. Anisole and dioxane were distilled before use on to 3Å sieves. Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl. Chloroform was rendered alcohol-free over activated alumina. Benzene was degassed by repeated cycles of freezing, vacuum evacuation and dissolving under an atmosphere of argon. 3Å sieves were activated by heating in a furnace to 500 °C for 3 hours. All glassware for anhydrous reactions was dried overnight prior to use and these reactions were carried out under argon. Reactions were carried out using one-, two- or three-neck round bottom flasks unless specified otherwise. All mixing was carried out by a magnetic stirring bar. TLC was run on Merck silica gel 60 F254 plates. Spots were detected by means of a 254nm UV visualizer.

All melting points were determined using an Electrothermal capillary melting point apparatus and are not corrected. IR spectra reported were recorded on a Nicolet FTIR spectrophotometer in the form of KBr disks, unless specified otherwise. The 1H-NMR spectra were obtained from a Varian XL200 spectrometer (1H 200 MHz) and the 13C-NMR spectra were obtained from a Mercury 500 spectrometer (13C 125 MHz). All 1H-NMR, unless specified otherwise, were obtained in CDCl3 with an internal standard
of tetramethylsilane (TMS). Mass spectra were run under electron impact conditions on a VG11-250s instrument.

1-Carboxy-1,2,3,4-tetrahydro-β-carbolin-2-ium chloride (73)

Tryptamine hydrochloride (1.95 g, 9.91 mmol) was dissolved in water (30 mL) while heating with a heat gun. Glyoxylic acid monohydrate (1.10 g, 11.95 mmol) in water (10 mL) was added to this solution, followed by the dropwise addition of potassium hydroxide (0.65 g, 11.58 mmol) in water (10 mL). The pH was adjusted to 4.0 and the mixture allowed to stir at room temperature for 2 h. The solution was then chilled and vacuum filtered, giving an impure yellow solid. The solid was dried under high vacuum and suspended in methanol at 0°C, then quickly filtered by suction to afford the pure white product (1.99 g, 80%) m.p. 210-211°C. IR: v 3343 (NH), 1616 (C=O) cm⁻¹. The ¹H-NMR spectrum was not obtained due to solubility problems.

1-(Methoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolin-2-ium chloride (74)

The carboxylic acid hydrochloride (73) (4.50 g, 20.80 mmol) was stirred in dry methanol (100 mL), while dry HCl gas was bubbled through the mixture for
approximately 2 min. The solid dissolved giving a golden yellow solution. The mixture was then brought to reflux through 3Å sieves in a Soxhlet apparatus for 3 h under argon. Most of the methanol (70 mL) was removed under reduced pressure. The precipitate formed was collected by suction filtration, washed with cold toluene (30 mL) and dried under high vacuum, giving the ester product (74) as yellow crystals (5.23 g, 94%) m.p. 205-208°C; IR: ν 3384 (NH), 1757 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆): δ 3.00 (2H, t, H-4), 3.54 (2H, t, H-3), 3.88 (3H, s, -OCH₃), 5.70 (1H, s, H-1), 7.05-7.20 (2H, m, H-5, H-6), 7.44-7.52 (2H, m, H-7, H-8), 10.30 (2H, s, NH₂⁺), 11.17 (1H, s, NH).

![Methyl β-carboline-1-carboxylate (66)](image)

**Methyl β-carboline-1-carboxylate (66)**

The ester hydrochloride (74) (4.00 g, 15.02 mmol), precipitated sulfur (1.13 g, 35.15 mmol) and 2,2,6,6-tetramethylpiperidine (2.40 g, 17.03 mmol) were refluxed in dry xylenes (200 mL) for 5 h giving a brown solution. Hydrogen sulfide was evolved and could be detected with a paper wet with aqueous lead (II) acetate solution – turning the paper black. The solution was allowed to cool slowly overnight, forming brown needles. The xylenes were removed under reduced pressure with a liquid nitrogen trap and the residual solids were placed in a Soxhlet thimble and extracted with acetone (100 mL) for 3 h. The acetone extracted the ester (66) from the reaction mixture while leaving the insoluble 2,2,6,6-tetramethylpiperidine hydrochloride in the Soxhlet thimble. The acetone was removed under reduced pressure giving a brown solid.
Purification of the solid by column chromatography (ethyl acetate) gave the β-carboline ester (66) as a yellow solid (2.94 g, 87%) m.p. 165-166 °C; IR: ν 3378 (NH), 1678 (C=O) cm⁻¹; ¹H-NMR (CDCl₃): 8.14 (3H, s, -OCH₃), 7.35-7.63 (3H, m, H-6, H-7, H-8), 8.15-8.19 (2H, m, H-4, H-5), 8.60 (1H, d, H-3), 9.90 (1H, s, NH).

![Structure of 2,4,5-Tribromoimidazole (54)](image)

**2,4,5-Tribromoimidazole (54)**

Bromine (28.11 g, 175.9 mmol) in chloroform (60 mL) was added slowly to a stirring solution of imidazole (5.16 g, 75.8 mmol) and sodium acetate (19.121 g, 232.9 mmol) in chloroform (60 mL) at 0 °C until the solution turned red. The excess bromine was destroyed with 10% sodium hydrogensulfite aqueous solution, and the solution turned yellow. The chloroform was removed under reduced pressure and the brown precipitate formed was refluxed in water (150 mL) for 2 h, and the brown crude product was collected with suction filtration. The product was dissolved in 2M sodium hydroxide solution to form a brown solution. The 2,4,5-tribromoimidazole was then fractionally precipitated with 10% hydrochloric acid to afford an off-white product (54), which upon recrystallization from glacial acetic acid gave white crystals (12.84 g, 56%) m.p. 219-222 °C. IR: ν 654 (C-Br) cm⁻¹.
To a refluxing solution of sodium sulfite (12.5 g, 99.6 mmol) in water (80 mL), 2,4,5-tribromoimidazole (54) (1.00 g, 3.30 mmol) was added. After 8-10 h, the aqueous mixture was extracted with diethyl ether, the organic extracts were combined and dried over anhydrous sodium sulfate. The diethyl ether was then removed under reduced pressure to afford the product (85) as a white precipitate. This product was recrystallized from dichloromethane/hexanes as white crystals (0.26 g, 53%) m.p. 130-131 °C; IR: ν 613 (C-Br) cm⁻¹; ¹H-NMR (CDCl₃): δ 7.06 (1H, s, H-4/5), 7.60 (1H, s, H-2).

Method A

1-Methylimidazole (1.52 g, 18.50 mmol) was dissolved in THF (20 mL) in an ice bath with magnetic stirring under argon. DBDMH (2.53 g, 9.89 mmol) in THF (30 mL) also cooled to 0 °C was added to the mixture dropwise using cannulation. A yellow precipitate and solution were formed during the addition. The flask was placed in the freezer (-5 °C) for 24 hr. The yellow precipitate was filtered off, and the yellow filtrate was concentrated under reduced pressure. The concentrated solution was washed with CH₂Cl₂ in a separatory funnel. The organic solution was extracted 3 times with an
acidic aqueous solution, and the acidic extracts were combined and basified. This was then extracted with CH$_2$Cl$_2$ and the combined extracts were dried over anhydrous Na$_2$SO$_4$. The residue obtained was then purified using Kugelrohr distillation to afford the product (77) as a white solid. (0.58 g, 20%) m.p. 45-46 °C.

\[
\begin{align*}
\text{Br} & \quad \text{N} \\
\text{N} & \quad \text{Br}
\end{align*}
\]

4-Bromo-1-methylimidazole (88)  5-Bromo-1-methylimidazole (77)

**Method B**

Iodomethane (6.14 g, 43.25 mmol) was added to a solution of 4(5)-bromoimidazole (85) (2.16 g, 14.67 mmol) in acetone (40 mL). This mixture was heated to reflux for 3 h. The solution was then neutralized with an alkaline solution and extracted with ethyl acetate 3 times. The organic extracts were combined and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure afforded a yellow residue, which upon column chromatography (ethyl acetate/methanol : 9/1) afforded product (88) from the earlier fractions as an orange oil (0.47 g, 20%); $^1$H-NMR (CDCl$_3$): δ 3.66 (3H, s, CH$_3$), 6.84 (1H, s, H-5), 7.30 (1H, s, H-2), and product (77) from later fractions as a white solid (0.83 g, 35%) m.p. 45-46 °C; $^1$H-NMR (CDCl$_3$): δ 3.60 (3H, s, CH$_3$), 7.00 (1H, s, H-4), 7.52 (1H, s, H-2).
A solution of iodine (45.0 g, 0.18 mol) in 20% aqueous potassium iodide (300mL) was added dropwise to a stirred solution of imidazole (7.06 g, 0.1 mol) in 2M sodium hydroxide (600 mL) at ambient temperature, and the resulting mixture was stirred overnight. Addition of acetic acid until the mixture was neutral gave a white precipitate, which was filtered off, washed with water, and air dried, to give a crude product (35.4 g, 76%) m.p. 186-190 °C; m.p. 190-192 °C (recryst. from ethanol).

**2,4,5-Triiodoimidazole (93)**

4(5)-Iodoimidazole (94)

Triiodoimidazole (93) (1.0 g, 2.24 mmol) and sodium sulfite (4.2 g, 33.3 mol) were refluxed in 30% ethanol in water solution (50 mL) for 24 h. The ethanol was removed from the solution under reduced pressure. The solution was filtered and the filtrate extracted with diethyl ether (3 x 15 mL). The organic extracts were combined, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to afford the pure product (94) as a white solid (0.43 g, 99%) m.p. 135-137 °C; m.p. 136-137 °C (recryst. from CHCl₃); $^1$H-NMR (CDCl₃): δ 7.18 (1H, s, H-4/5), 7.62 (1H, s, H-2); $^1$H-NMR (D₂O): δ 7.24 (1H, s, H-4/5), 7.66 (1H, s, H-2), $^1$H-NMR (DMSO-$d_6$): δ 7.31 (1H, s, H-4/5), 7.65 (1H, s, H-2).
4-Iodo-1-p-tosylimidazole (99)

To a stirred solution of 4(5)-iodoimidazole (94) (1.52 g, 7.84 mmol) and p-toluenesulfonyl chloride (2.00 g, 10.49 mmol) in dry THF (75 mL) under argon was added triethylamine (1.5 mL, 10.49 mmol) and the solution left to stir for 24 h. The mixture was filtered, and the filtrate was diluted with CH$_2$Cl$_2$ (100 mL), washed with water (35 mL), dried and the solvent removed under reduced pressure to afford a white product, which was recrystallized from ethanol (2.58 g, 98%) m.p. 146-147 °C; $^1$H-NMR (CDCl$_3$): δ 2.46 (3H, s, CH$_3$), 7.37 (1H, s), 7.40 (2H, d, $J = 8.5$ Hz), 7.83 (2H, d, $J = 8.5$ Hz), 7.88 (1H, s).

5-Iodo-1-methylimidazole (92)

To a solution of 4-iodo-1-p-tosylimidazole (99) (0.94 g, 2.81 mmol) in dry CH$_2$Cl$_2$ (30 mL) was added trimethyloxonium tetrafluoroborate (0.46 g, 3.11 mmol). After the mixture was stirred at room temperature for 24 h, methanol (15 mL) was added. The solvent was removed under reduced pressure and the residue was acidified with 1% HCl aqueous solution and extracted with CH$_2$Cl$_2$ (2 x 15 mL). The aqueous solution was then basified with 5% NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The
organic extracts were combined, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to afford the white product (0.58g, 99 %) m.p. 106-107 °C; ¹H-NMR (CDCl₃): δ 3.62 (3H, s, CH₃), 7.13 (1H, s, H-4), 7.62 (1H, s, H-2).

Xestomanzamine A (2)

Ethylmagnesium bromide (1M in hexane) (0.5 mL, 0.50 mmol) was added dropwise to a solution of 5-iodo-1-methylimidazole (0.104 g, 0.50 mmol) in dichloromethane (15 mL) under argon at 0 °C. After completing the addition the solution was heated briefly with a heat gun and allowed to stir for 1 h at room temperature. In another round bottom flask, to a stirring solution of β-carboline ester (3) (0.104 g, 0.46 mmol) and lithium chloride (0.2 g, 4.7 mmol) in dichloromethane (20 mL) under argon at 0 °C, ethylmagnesium bromide (1M in hexane) (0.5 mL, 0.50 mmol) was added dropwise with a syringe. After completion of stirring 1 h, the 5-iodo-1-methylimidazole and ethylmagnesium bromide solution was added by cannula dropwise to the β-carboline ester (3) solution at 0 °C. The temperature of the reaction flask was allowed to reach room temperature and the mixture was stirred for 24 h. After 24 h, the mixture was quenched with 5% NaHCO₃ solution and extracted with dichloromethane (3 x 25 mL). The organic extracts were combined and dried over anhydrous sodium sulfate. The dichloromethane was removed under reduced pressure and the resulting solid was purified by column chromatography (ethyl acetate/methanol: 95/5) to give the final
product (2) as a yellow solid (0.103 g, 81%) m.p. 184-185 °C; IR (nujol): v 3419, 1606, 1214, 1127 cm⁻¹ (lit.⁴ IR (KBr): v 3427, 1612, 1211, 1128 cm⁻¹). ¹H-NMR (CDCl₃): δ 4.11 (3H, s, CH₃), 7.35 (1H, dd, J=7.9, 6.4 Hz, H-6), 7.55 (1H, dd, J=6.4, 7.5 Hz, H-7), 7.60 (1H, d, J=7.5 Hz, H-8), 7.69 (1H, s, H-15), 8.17 (1H, d, J=4.9 Hz, H-4), 8.20 (1H, d, J=7.9, H-5), 8.60 (1H, d, J=4.9 Hz, H-3), 8.94 (1H, s, H-13); (lit.⁴ m.p. 185 °C; lit.⁴ ¹H-NMR (CDCl₃): δ 4.05 (3H, s), 7.30 (1H, dd, J=8.2, 6.2 Hz), 7.55 (1H, dd, J=6.2, 7.3 Hz), 7.57 (1H, d, J=7.3 Hz), 7.66 (1H, s), 8.09 (1H, d, J=5.0 Hz), 8.12 (1H, d, J=8.2 Hz), 8.55 (1H, d, J=5.0 Hz), 8.93 (1H, s); ¹³C-NMR (CDCl₃): δ 184.4 (C-10), 143.8 (C-13), 143.4 (C-15), 141.0 (C-8a), 138.2 (C-3), 136.7 (C-9a), 136.6 (C-1), 131.7 (C-4a), 129.8 (C-11), 129.3 (C-7), 121.8 (C-5), 120.9 (C-4b), 120.7 (C-6), 118.6 (C-4), 111.9 (C-8), 35.3 (N-CH₃); (lit.⁴ ¹³C-NMR (CDCl₃): δ 184.2 (C-10), 143.6 (C-13), 143.3 (C-15), 140.8 (C-8a), 137.9 (C-3), 136.5 (C-9a), 136.4 (C-1), 131.5 (C-4a), 129.7 (C-11), 129.6 (C-7), 121.7 (C-5), 120.6 (C-4b), 120.5 (C-6), 118.4 (C-4), 111.8 (C-8), 35.2 (N-CH₃)).

![N-[2-(3-Indoly)ethyl]formamide (109)](image)

**Method A**

Ethyl formate (55 mL, 684 mmol) was added to tryptamine (5.17 g, 32.3 mmol) in a round-bottom flask and the mixture was refluxed in an argon atmosphere for 3 h at an oil bath temperature of 105-110 °C. The colour of the solution turned golden brown. The reaction mixture was cooled and the excess ethyl formate was removed under
reduced pressure to give the crude \( N \)-formyltryptamine \( (109) \) as a yellow solid (3.95 g, 65%), m.p. 74-76 °C.

**Method B**

Trimethylacetyl chloride (0.97 g, 8.04 mmol) and 18-crown-6 (2.23 g, 8.44 mmol) were stirred vigorously at 0 °C. Sodium formate (0.61 g, 8.97 mmol) was added in small portions over a period of 15 min. After 3 h the volatile compounds were distilled at 0 °C and 0.02 mm Hg into a cold trap. This distillate was added to tryptamine (1.2 g, 7.49 mmol) dropwise with vigorous stirring. The solvent was removed under reduced pressure and the residue was washed with hexanes (3 x 10 mL). Removal of the last traces of hexanes afforded the product (1.13 g, 75%).

**Method C**

Acetic formic anhydride was generated in a round-bottom flask by dropwise addition of 96% formic acid (25 mL, 0.65 mol), which had been stored over 3Å sieves for 24 h, to acetic anhydride (20 mL, 0.22 mol) at 0 °C, followed by gentle heating (50-60 °C, 2 h). The mixture was cooled to room temperature. Tryptamine (1.03 g, 6.42 mmol) dissolved in THF (15 mL) was added dropwise to the mixture at 0 °C. This mixture was allowed to stir for 4 h. The volatile liquids were removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with NaHCO₃ solution. The organic solvent was evaporated to afford (1.17 g, 97%) of essentially pure \( N \)-formyltryptamine \( (109) \) as an oil. Crystallization of the product was not attempted. \(^1\)H-NMR (DMSO-\( d_6 \)):

\[
\delta 2.98 (4H, \text{apparent s, CH}_2-8,9), 5.80 (1H, \text{br, H-amide}), 6.97-7.13 (2H, \text{m, H}-5,6), 7.22 (1H, \text{s, H}-2), 7.35 (1H, \text{d, J}=7.3 \text{ Hz, H}-7), 7.58 (1H, \text{d, J}=7.3 \text{ Hz, H}-4), 8.50 (1H, \text{s, CHO}), 11.00 (1H, \text{s, H}-1).
\]
Method A

*N*-Formyltryptamine (109) (0.87 g, 4.62 mmol) was dissolved in dry CH$_2$Cl$_2$ (30 mL) under argon and cooled to 0°C. Distilled diisopropylethylamine was added to the stirring solution. Phosphorus oxychloride (1.0 mL, 10.7 mmol) dissolved in CH$_2$Cl$_2$ (5.0 mL) was added dropwise over 15 min from a pressure equalizing addition funnel. The reaction mixture was stirred in an ice bath for 3 h and then slowly brought to room temperature and stirred for an additional 30 min. The solution was next cooled on ice. Cold water (60 mL) was added and the solution allowed to stir for 1 h at room temperature. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a brown oil. This oily residue was subjected to column chromatography (CH$_2$Cl$_2$) to afford the product (68) as a white solid (0.079 g, 10%).

Method B

Tryptamine (13) (3.0 g, 15.25 mmol), benzyltriethylammonium chloride (0.1 g, 0.44 mmol) and alcohol-free chloroform (1.25 mL, 15.62 mmol) in CH$_2$Cl$_2$ (30 mL) were placed in a round-bottom flask equipped with a magnetic stirrer and reflux condenser. 50% Aqueous sodium hydroxide solution (30 mL) was added to the reaction mixture dropwise. The addition of the basic solution was accompanied with spontaneous refluxing of the dichloromethane. After 10 min the refluxing ceased and the solution was allowed to stir for an additional hour. The reaction mixture was diluted with water
(100 mL) and extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to afford an oil which on column chromatography (CH$_2$Cl$_2$) afforded the isonitrile (68) as a white solid (1.35 g, 52%) m.p. 73-74 °C; IR: ν 2150 (N≡C) cm$^{-1}$; $^1$H-NMR (CDCl$_3$): δ 3.15 (2H, apparent t, J=6.9 Hz, CH$_2$), 3.65 (2H, apparent t, J=6.9 Hz, CH$_2$), 7.15 (1H, s, H-2), 7.19 (2H, m, H-5,6), 7.38 (1H, d, J=7.3 Hz, H-7), 7.59 (1H, d, J=7.7 H-4), 8.10 (1H, s, NH).

![Methyl 3-(2-isocyanoethyl)-1-indolecarboxylate (69)](image)

**Methyl 3-(2-isocyanoethyl)-1-indolecarboxylate (69)**

Isocyanide (68) (1.07 g, 6.29 mmol) was dissolved in THF (30 mL) and cooled to −78 °C under argon. Butyllithium (1.6 M in hexane) (4.0 mL, 6.40 mmol) was added and the resulting solution was stirred at −78 °C for 20 min. Methyl chloroformate (0.5 mL, 6.47 mmol) was then added and the reaction mixture was allowed to stir at 0 °C for 2 h. The reaction was then quenched with H$_2$O (40 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over 3 Å molecular sieves. The solvent was removed under reduced pressure to yield the isocyanide (69) as an off-white solid (1.42g, 99%) m.p. 97-99 °C; IR: ν 2150 (N≡C) 1726 (C=O) cm$^{-1}$; $^1$H-NMR (CDCl$_3$): δ 3.12 (2H, apparent t, J=7.1 Hz, CH$_2$), 3.72 (2H, apparent t, J=7.1 Hz, CH$_2$), 4.05 (3H, s, CH$_3$), 7.39-7.56 (4H, m, H-2,5,6,7), 8.20 (1H, d, J=8.4 Hz, H-4).
4,5-Imidazoledicarboxylic acid (121)

Benzimidazole (5 g, 42.32 mmol) was dissolved in concentrated sulfuric acid (70 mL) and water (55 mL). When the temperature of the liquid was 90 °C, potassium dichromate (37 g, 125.77 mmol) was added in small portions at a rate necessary to maintain the temperature of the reaction mixture in the range 90-95 °C. After all the potassium dichromate was added, the reaction mixture was stirred for 15 minutes more and then poured into 400 mL of water. This mixture was then cooled on ice and the off white precipitate was filtered off, washed with water and dried to afford the crude product. The product was purified by two-fold reprecipitation from boiling 2M sodium hydroxide solution with concentrated hydrochloric acid to afford a white solid (3.84 g, 58%), m.p. 278-280 °C; IR: ν 3174-2600 (OH); 1H-NMR (DMSO-d6): δ 9.06 (1H, s, H-2).

1-Methyl-4,5-imidazoledicarboxylic acid (122)

Method A

4,5-Imidazoledicarboxylic acid (121) (874 mg, 5.59 mmol) was dissolved in 0.3M sodium hydroxide aqueous solution (60.0 mL). Dimethyl sulfate (2.0 g, 15.8 mmol) was added to the stirring solution at room temperature. After 10 min the dimethyl sulfate
globules disappeared and concentrated ammonium hydroxide (2.0 mL) was added. The mixture was then brought to a boil, acidified while hot with concentrated hydrochloric acid until red to litmus. The volume of this solution was reduced (to 6 mL) by evaporating the solvent, and the solution was stored at 4 °C overnight. After 18 h the product was collected from this solution as white crystals (71 mg, 7.4%).

*Method B*

4,5-Imidazoledicarboxylic acid (121) (1.26 g, 8.1 mmol) was dissolved in 0.5M sodium hydroxide aqueous solution (40.0 mL). Dimethyl sulfate (2.13 g, 16.8 mmol) was added to the stirring mixture at room temperature. After 1 h more 0.5M sodium hydroxide solution was added (30.0 mL). After another hour iodomethane (2.3 g, 16.2 mmol) was added to the reaction mixture. This mixture was allowed to stir for 2 h at room temperature. The reaction was then acidified with concentrated hydrochloric acid until red to litmus and concentrated to 10% of the original volume. The product was collected as white crystals (0.28 g, 20.5%) and purified by sublimation (0.27 g, 16.1%) m.p. 245-246 °C.

![Chemical Structure](image)

4(5)[1-(tert-Butyl)ammonio]carbonyl-5(4)-imidazolcarboxylate (129)

*Method A*

4,5-Imidazoledicarboxylic acid (0.53 g, 3.39 mmol) and triethylamine (1.5 mL,
10.76 mmol) were stirred in dichloromethane (50 mL) at −5 °C under argon. Methyl chloroformate (0.27 mL, 3.49 mmol) was then added to this mixture. After 30 min tert-butylamine (0.36 mL, 3.43 mmol) was added. The precipitate formed was filtered off and dried to afford the crude product (0.59 g, 84 %) Purification of the salt through sublimation afforded the pure product (0.45 g, 70 %), m.p. 260-261 °C.

Method B

4,5-Imidazolodicarboxylic acid (0.78 g, 5.0 mmol) and 2,6-lutidine (2.0 mL, 17.0 mmol) were stirred in dichloromethane (50 mL). The cloudy mixture was cooled on ice bath and methyl chloroformate (0.4 mL, 5.2 mmol) was added. After stirring at room temperature for 4 h, tert-butylamine (0.6 mL, 5.7 mmol) was added. The reaction mixture was allowed to stir for an additional hour and the precipitate was filtered off to afford the product (0.96 g, 100%) m.p. 259-260 °C; ¹H-NMR (D₂O): δ 1.35 (9H, s, CH₃), 7.88 (1H, s, H-2).

1-Methyl-5-imidazolecarboxylic acid (123)

1-Methyl-4,5-imidazolodicarboxylic acid (122) (68.0 mg, 0.40 mmol) was stirred in acetic anhydride (2.0 mL, 21.2 mmol) and the suspension was heated at 100°C for 4 h. After the reaction mixture became homogeneous, it was concentrated to dryness under reduced pressure. The resulting residue was washed with acetone to give the white product (45.4 mg, 90%) m.p. 277-279 °C; ¹H-NMR (D₂O): δ 4.05 (3H, s, CH₃), 7.75 (1H, s, H-4), 8.68 (1H, s, H-2).
Chloromethylated polystyrene (138)

AIBN (0.32 g, 2.0 mmol) was added to a solution of styrene (45 mL, 392.75 mmol) and 4-(chloromethyl)styrene (1.7 mL, 12.06 mmol) in degassed benzene (140 mL). The vessel was purged of all oxygen using vacuum/argon evacuation flushing cycle and the solution was allowed to stir at 70 °C for 40 h. The mixture was poured dropwise into a vigorously stirred methanol using an addition funnel at 0 °C. The insoluble polymer (138) was collected and dried under reduced pressure (27.4 g). $^1$H-NMR (CDCl$_3$): $\delta$ 7.3-6.2 (5H, m, H-Ar), 4.50 (2H, s, CH$_2$-Cl), 1.3-2.0 (3H, m, -CH-CH$_2$-). The chlorine content (load) of the polymer was determined by NMR; the load was determined from the integration (6%) to be 0.57 mmol of chlorine per 1 g of polymer.

Hydroxymethylated polystyrene (139)

A mixture of chloromethylated polystyrene (138) (10.31 g, 5.88 mmol based on 6% load) and sodium hydroxide (1.5 g, 37.5 mmol) in DMF (250 mL) was refluxed. The progress of the reaction was followed by TLC (toluene/CH$_2$Cl$_2$ : 1/1 - polymer (139) $R_f = 0.0$, polymer (138) $R_f = 1.0$). The conversion was complete after 48 h.
References


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![Chemical structure diagram]

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User: 1-14-87
UNITY-500 *ultra500*

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Width 30165.9 Hz
37987 repetitions

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Power 44 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 2.1 Hz
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