Studies on the L-proline catalyzed and the borono Mannich reaction

Qin Yong Mao
University of Wollongong


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Studies on the L-proline Catalyzed and the Borono Mannich Reaction

A thesis submitted in fulfillment of the requirements for
the award of the degree

MASTER OF SCIENCE-RESEARCH

from

UNIVERSITY OF WOLLONGONG

By

Qin Yong Mao

University of Wollongong

Department of Chemistry

Wollongong, Australia

August 2007
Declaration

This is to certify that the work reported in this thesis is my own work, conducted in the Chemistry Department at the University of Wollongong. And no part of the thesis has been submitted to any other University or academic institution.

Qin Yong Mao
31/08/2007
Abstract

This thesis describes the results of two independent research projects. The first project is concerned with the synthesis of chiral 1,2-amino alcohols using an organocatalysed Mannich reaction. Chapter 1 gives an overview of L-proline catalysed Mannich reactions and describes the aims of this project. Chapter 2 reports the results of this study. These reactions were found to be low yielding and poorly diastereoselective with the model compound propanal and did not work with the desired aldehyde O-benzylglycosaldehyde. The stereochemical outcomes of these reactions using NMR analysis were not certain. Future work would require X-ray crystallographic studies to confirm the product relative stereochemistries. This project was thus abandoned and a second project was studied.

Chapter 3 provides an overview of cyclic N-acyliminium ion chemistry.

Chapter 4 describes the results of a study of the borono-Mannich reaction on N-acyliminium ions, generated in situ from hemi-aminals derived from chiral 5-hydroxypyrrolidin-2-ones, to prepare substituted pyrrolidinones. The reactions of these N-acyliminium ions with boronic acids and other nucleophiles can afford the corresponding substituted pyrrolidinones diastereoselectively. The stereochemical assignments of these products were based on NMR coupling constants. X-ray structures of these compounds would be required in the future to confirm these assignments.
The success of these reactions provided a possible strategy for the synthesis of functionalized pyrrolidinones and other potential glycosidases inhibitors.
Acknowledgements

I would like to acknowledge my supervisor Prof Stephen G Pyne for his supervision, guidance and patience. I am very lucky to have such an excellent supervisor. I would also like to thank all members our group for their support and encouragement. I am thankful for the vast support provided by staff of the Chemistry Department, including the NMR staff, Dr Wilford Lie and the mass spectrometry group.

Finally, I dedicate this thesis my grandparents, my parents and my wife......
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List of Abbreviations

Ac    acetyl
$t$-Bu   tert-butyl
Boc   tert-butoxycarbonyl
°C     degrees Celsius
COSY  correlation spectroscopy
$\delta$  chemical shift in parts per million downfield from TMS
d    doublet (spectral)
DMSO  dimethylsulfoxide
DMF   dimethylformamide
d.r.  diastereomeric ratio
ee    enantiomeric excess
EI    electron impact (in mass spectrometry)
Et    ethyl
EtOH  ethanol
Equiv.  Molar equivalents
g    gram(s)
h    hour(s)
HMBC  heteronuclear multiple bond coherence
HRMS  high resolution mass spectrometry
HSQC  heteronuclear single quantum coherence
Hz    hertz
$J$    coupling constant (in NMR)
L    litre(s)
m    multiplet (spectral), milli
M    moles per litre
Me    methyl
MeCN  acetonitrile
MeOH  methanol
MHz            megahertz
min            minute(s)
mmol            millimole(s)
MS            mass spectrometry
m/z            mass to charge ratio (in mass spectrometry)
NMP            N-methylpyrrolidinone
NMR            nuclear magnetic resonance
NOESY            nuclear Overhauser effect spectroscopy
Nu            nucleophile
PMB            p-methoxybenzyl
PMP            4-methoxyphenyl
ppm            parts per million (in NMR)
p-TsOH            para-toluenesulfonic acid
q            quartet (spectral)
Rf            retention factor (in chromatography)
ROESY            Rotating frame Overhauser Effect Spectroscopy
rt            room temperature
s            singlet (spectral)
t            triplet (spectral)
Chapter 1: General Introduction

1.1 Mannich Reaction

The Mannich reaction is a classic C-C bond forming reaction in organic synthesis and it plays a key role in the preparation of N-containing compounds such as β-amino aldehydes and ketones.\(^1\) A typical Mannich reaction catalyzed by acid usually requires a carbonyl compound (1) as a donor, a primary or secondary amine (2) and another aldehyde or ketone as an acceptor (3) (Scheme 1.1).\(^2\)

Scheme 1.1

\[
\begin{align*}
\text{R}_1\text{C}=\text{O} + \text{H-N-R}_3 & \xrightarrow{\text{H}^+} \text{R}_2\text{N}^+\text{R}_3 \\
(1) & \quad (2) \quad (3) \quad \text{R}_4\text{C}=\text{O} \\
\end{align*}
\]

\[\text{R}_2\text{N-C(R}_3\text{)}\text{R}_1\text{C} = \text{R}_4\text{C}=\text{O} \quad (4)\]

A proposed mechanism for the formation of the Mannich base (4) under acid catalysis is shown in Scheme 1.2. The acceptor aldehyde (1) couples with the amine (2) to generate the electrophilic iminium ion (5). Intermediate (5) is subsequently trapped by the enol form (6) of the donor aldehyde or ketone (3) to give the Mannich product (4).
1.2 Asymmetric Mannich Reaction

Although the classic Mannich reaction gives racemic products, the asymmetric version of this reaction has been recently developed.\(^3\),\(^4\),\(^5\) Over the past decade organic catalysts (organocatalysts), such as chiral amino acids, have been used for the asymmetric synthesis of Mannich products.\(^6\) A variety of organocatalysts have been reported in the literature.\(^7\),\(^8\),\(^9\) For example, Ibrahim and coworkers examined a three-component Mannich reaction of the ketone (7), the amine (8) and the aldehyde (9) in the presence of several simple amino acids (Scheme 1.3).\(^9\) The results are summarized in Table 1.1 and show that the use of (11) and (16) afforded
the product (10) with good syn-diastereoselectivity (d.r. = 6/1) (Table 1.1, entries 1 and 6) while others (12, 13, 14 and 15) gave a more moderate syn-diastereoselectivity (d.r. varied from 2/1 to 4/1) (Table 1.1, entries 2-5). Notably, all of the chiral amino acids used resulted in excellent enantiomeric excesses (ee > 82%) of the Mannich syn-product of (10).

Scheme 1.3

![Scheme 1.3 Diagram]
Table 1.1 The Mannich reaction of the ketone (7), the amine (8) and the aldehyde (9) in the presence of the simple amino acids (11-16).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>t (h)</th>
<th>Yield of (10) (%)</th>
<th>d.r. of (10) (syn/anti)</th>
<th>ee&lt;sup&gt;a&lt;/sup&gt; of (10) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>48</td>
<td>60</td>
<td>6/1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>24</td>
<td>32</td>
<td>3/1</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>48</td>
<td>65</td>
<td>2/1</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>48</td>
<td>60</td>
<td>3/1</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>48</td>
<td>61</td>
<td>4/1</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>48</td>
<td>38</td>
<td>6/1</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup> of major syn-product

1.3 L-proline Catalyzed Mannich Reaction

Among numerous organocatalysts developed in the recent years, one of the most successful catalysts has been the natural amino acid, L-proline (Figure 1.1). Many reports have shown that the L-proline mediated Mannich reactions furnish the β-amino carbonyl products with high syn-diastereoselectivity and excellent enantioselectivity.

Figure 1.1

Please see print copy for Figure 1.1
For example, the Mannich reaction of benzaldehyde (17), \( p \)-anisidine (18), and propanal (19) mediated by L-proline was examined by Hayashi in 2003.\(^{11}\) In this study, the reduced Mannich product (20) was obtained in 90% yield with good syn-diastereoselectivity (\( \text{syn/anti} > 95/5 \)) and excellent enantioselectivity (\( \text{ee} = 98\% \)) (Scheme 1.4).

**Scheme 1.4**

\[
\text{PhCHO} + \text{PhCH}_2\text{NH}_2 + \text{MeCHO} \rightarrow \text{PhCH(Me)}\text{NH}_2\text{CH}_2\text{OH} \\
(17) + (18) + (19) \rightarrow (20)
\]

*Reagents* a: 10 mol % L-proline, NMP, -20 °C, 20 h. b: NaBH\(_4\), MeOH, 90%, \( \text{syn/anti}>95/5 \), 98% ee.

### 1.4 Mechanism of the L-proline Catalyzed Mannich Reaction

A reasonable explanation for the resulting high enantioselectivity is due to the formation of a highly organized transition state promoted by L-proline via a hydrogen bonding interaction in the L-proline catalyzed cycle (Scheme 1.5).\(^1\) In this cycle, the nucleophilic enamine (22) generated from the condensation of the donor carbonyl compound (21) with L-proline couples with the \( E \)-iminium ion (23) to give the intermediate (24), which has a highly organized configuration due to the formation of H-bonding bond between the iminium ion N atom and the carboxylic acid group of the enamine. The intermediate (24) is then transformed to the iminium ion (25).
which is subsequently hydrolyzed to give the Mannich product (26) with good enantioselectivity.

Scheme 1.5

**L-proline catalyzed cycle**

L-proline catalyzed cycle
1.5 Methods for the L-proline Catalyzed Mannich Reaction

A number of reports have showed that there are two possible methods for the L-proline catalyzed Mannich reaction to proceed.\(^\text{12}\) The direct Mannich reaction is the one pot, three-component reaction of (26), (27) and (28) in the presence of L-proline. Alternatively, the Mannich product (29) could be derived from the reaction of the preformed imine (30) with an aldehyde or ketone (28), which is the so called indirect Mannich reaction.

**Scheme 1.6**

**Pathway 1: Direct Mannich reaction**

\[
\text{aldo} + \text{amine} + \text{ketone} \xrightarrow{\text{L-proline}} \text{product (29)}
\]

**Pathway 2: Indirect Mannich reaction**

\[
\text{aldo} + \text{amine} \xrightarrow{\text{formation of imine}} \text{imine (30)} \\
\text{imine} \xrightarrow{\text{L-proline}} \text{product (29)}
\]
Hayashi has further examined the direct L-proline catalyzed Mannich reaction of 4-methoxyaniline (18) and propanal (19) with a variety of acceptor aldehydes (31) (Scheme 1.7).\(^{11}\) The resulting Mannich products were reduced with NaBH\(_4\) to give the amino alcohols (32). The corresponding yields, diastereoselectivities and enantioselectivities are shown in Table 1.2. It can be seen that the yield was greatly increased when the reaction was performed at -20 °C (Table 1.2, entry 3). This indicated that the Mannich reaction of this type is preferred at lower temperature. When the temperature was kept at –10 °C or –20 °C, all of the aldehydes attempted in the reaction gave the Mannich products in satisfactory yields (59% to 93%) with excellent diastereoselectivities (syn/anti > 95/5) and good enantioselectivities (ee > 84%) (Table 1.2, entries 3-8).

**Scheme 1.7**

\[
\text{RCHO} + \begin{array}{c}
\text{(31)} \\
\text{(18)} \\
\text{(19)} \\
\end{array} \rightarrow \begin{array}{c}
\text{HN} \\
\text{R} \\
\text{Me} \\
\end{array} + \text{MeOH} \\
\text{MeOH}
\]

*Reagents* a: 10% L-proline, NMP, -10 °C -20 °C, 20 h. b: NaBH\(_4\), MeOH.
Table 1.2 The L-proline catalyzed Mannich reaction of 4-methoxyaniline (18) and propanal (19) with a variety of acceptor aldehydes (31)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (31)</th>
<th>T (°C)</th>
<th>Yield of (32) (%)</th>
<th>syn/anti</th>
<th>ee&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzaldehyde</td>
<td>23</td>
<td>&lt;10</td>
<td>&gt;95/5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>benzaldehyde</td>
<td>0</td>
<td>15</td>
<td>&gt;95/5</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>benzaldehyde</td>
<td>-20</td>
<td>90</td>
<td>&gt;95/5</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>p-nitrobenzaldehyde</td>
<td>-10</td>
<td>93</td>
<td>&gt;95/5</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>p-bromobenzaldehyde</td>
<td>-10</td>
<td>85</td>
<td>&gt;95/5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>p-chlorobenzaldehyde</td>
<td>-20</td>
<td>91</td>
<td>&gt;95/5</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>2-naphthaldehyde</td>
<td>-20</td>
<td>59</td>
<td>&gt;95/5</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>fural</td>
<td>-20</td>
<td>87</td>
<td>&gt;95/5</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup> of the major syn-product

In 2002, List examined the direct L-proline catalyzed Mannich reaction of acetone (33), 3-methylbutanal (34) and aniline derivatives (Scheme 1.8).<sup>8</sup> Table 1.3 shows that the use of p-anisidine and p-chloroaniline afforded the products (35) with good enantioselectivities, 93% and 84%, respectively (Table 1.3, entries 1 and 2). In contrast, low enantioselectivities were obtained when o-anisidine and o-aminophenol were used (Table 1.3, entries 3 and 4).
Scheme 1.8

Reagents 30 mol % L-proline, Ar-NH₂, NMP, rt.

Table 1.3 The direct L-proline catalyzed Mannich reaction of acetone (33), 3-methylbutanal (34) and aniline derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-NH₂</th>
<th>Yield of (35) (%)</th>
<th>ee (%)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-anisidine</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>p-chloroaniline</td>
<td>55</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>o-anisidine</td>
<td>43</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>o-aminophenol</td>
<td>51</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

In 2005, Ibrahim further investigated the indirect L-proline catalyzed Mannich reactions of the preformed imines (36) with protected glycol aldehydes (37) using DMF or NMP as the solvent system (Scheme 1.9). The results summarized in Table 1.4, show that good syn-distereoselectivity (syn/anti = 19:1) for (38) was achieved when the substituents ,R and X, were CO₂Et and Bn, respectively (Table 1.4, entry 1). In contrast, substituents (R = CO₂Et, 4-BrC₆H₄, or furan and X = Bn or TBS) led to a much lower syn-diastereoselectivity (syn/anti = 2/1 to 3/1)
(Table 1.4, entries 2-4). Obviously, the change of substituents did not significantly affect the enantioselectivity as in all cases, good enantioselectivities were obtained (ee = 82—99%).

Scheme 1.9

Reagents 30 mol % L-proline, DMF or NMP, rt, 22-26 h

Table 1.4 The L-proline catalyzed Mannich reactions of the preformed imines (36) with protected glycol aldehydes (37)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>R</th>
<th>X</th>
<th>Yield of (38) (%)</th>
<th>d.r. (syn/anti)</th>
<th>ee (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>CO₂Et</td>
<td>Bn</td>
<td>89</td>
<td>19/1</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>NMP</td>
<td>CO₂Et</td>
<td>TBS</td>
<td>95</td>
<td>2/1</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>NMP</td>
<td>4-BrC₆H₄</td>
<td>TBS</td>
<td>80</td>
<td>3/1</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td></td>
<td>Bn</td>
<td>60</td>
<td>3/1</td>
<td>95</td>
</tr>
</tbody>
</table>

^a of the major syn-product
1.6 The Application of the L-proline catalyzed Mannich Reaction in Synthesis

The application of the L-proline catalyzed Mannich reaction in synthesis has been reported. Some successful highlights include the synthesis of the N-terminal amino aldehyde (39)\textsuperscript{14}, the β-phenyl aspartic acid derivative (40)\textsuperscript{15} and (+)-epi-cytoxazone (41)\textsuperscript{16,17}

Figure 1.2

In 2005, the L-proline catalyzed Mannich reaction was successfully employed in the synthesis of a N-terminal amino acid (39)\textsuperscript{14}, which is an important structural unit of the bioactive nikkomycins natural products (42) and (43)\textsuperscript{18,19}

Figure 1.3

Please see print copy for Figure 1.3

Nikkomycin B (42)  Nikkomycin Bx (43)
In this study, the Mannich product (46), generated from the reaction of propanal (19), 2-furylaldehyde (44) and the aniline (45), was obtained with excellent diastereoselectivity \((\text{syn/anti} = 14/1)\) and enantioselectivity \((\text{ee} = 96\%)\). In this study, pyridine served as a co-catalyst to enhance the diastereoselectivity and enantioselectivity of the desired product (46). Compound (46) was then converted to the \(N\)-terminal amino aldehyde (39) after several synthetic transformations (Scheme 1.10).

**Scheme 1.10**

\[
\begin{align*}
\text{Reagents a: } & \text{10 mol \% L-proline, NMP, } -20 ^\circ \text{C, } \text{syn/anti} = 14/1, \text{ ee} = 96\%. \\
\end{align*}
\]

In 2006, a strategy for the synthesis of the \(\beta\)-phenyl aspartic acid derivatives (50) was developed, in which the Mannich reaction was introduced as a key step. The indirect Mannich reaction of the imine (47)
with phenylacetaldehyde (48) gave the product (49) with excellent diastereoselectivity (syn/anti = 92/8) and good enantioselectivity (ee > 90%). The Mannich adduct (49) then served as an intermediate for the synthesis of (50) through a series of synthetic transformations (Scheme 1.11).

Scheme 1.11

In 2006, the L-proline catalyzed Mannich reaction was used to prepare (+)-epi-cytoxazole (41). The Mannich reaction of (18), (51) and (52) afforded the product (53) in 76% yield as a 2/1 mixture of syn and anti diastereoisomers (Scheme 1.12). The major diastereomer was obtained in 81% ee. The intermediate (53) was then transformed to the target molecule (41) after several synthetic steps.
Scheme 1.12

\[
\begin{align*}
&\text{CHO} \quad \text{OMe} \\
&(51) + \quad \text{OH} \\
&(52) + \quad \text{NH}_2 \\
&(18) \quad \xrightarrow{\text{L-proline} \atop \text{DMSO}} \quad \text{PMP} \\
&\text{MeO} \quad \text{NH} \quad \text{O} \\
&(53) \quad \text{Me} \quad \text{MeO} \quad \text{OH} \\
&\text{MeO} \quad \text{HN} \quad \text{OH} \\
&(41) \quad \text{MeO} \quad \text{HO} \\
\end{align*}
\]
Chapter 2: Preparation of Potential Glycosidase Inhibitors

2.1 Aims of this Project

The literature\textsuperscript{8,13} has demonstrated that the three-component Mannich reaction of benzaldehyde and $p$-anisidine and a variety of aldehydes or ketones is quite successful. This inspired us to develop a strategy for the preparation of potential glycosidase inhibitors\textsuperscript{20} such as analogues of australine (54)\textsuperscript{21} and castanospermine (55)\textsuperscript{22} through an analogous Mannich reaction of cinnamaldehyde (56), $p$-anidine (18) and $O$-benzylglycoaldehyde (57).

Figure 2.1

Please see print copy for Figure 2.1

australine (54)  casuarine (55)

The following scheme shows the proposed synthetic routes to polyhydroxylated pyrrolizidines, indolizidines and quinolizines, where the Mannich product (59), generated from the reaction of cinnamaldehyde (56), $p$-anidine (18) and $O$-benzylglycoaldehyde (57), is modified to the intermediate (61) by reduction, $N$-alkylation, and ring closing metathesis
reactions (RCM) (Scheme 2.13). Intermediate (61) is then transformed to the general bicyclic target molecules (A) and (B) after several synthetic steps.

**Scheme 2.13**

2.2 Results and Discussion

While the aldehydes (57)\(^{13}\) and (56)\(^{23}\) have been used previously as donors and acceptors respectively, in the L-proline catalyzed Mannich reaction they have not been used in the same reaction. Therefore as a model study we first examined the L-proline catalyzed three-component reaction of cinnamaldehyde (56), \(p\)-ansidine (18) and propanal (19), following a procedure similar to that reported by Hayashi.\(^{11}\) After stirring the reaction mixture at rt overnight (14 h), the resulting Mannich product was reduced
by treatment with NaBH₄ in MeOH to give the β-amino alcohol (62) in 10% yield and as a 4/1 mixture of diastereomers (Scheme 2.14). The new olefinic signals for the two isomers in the ¹H NMR spectrum (Figure 2.2) indicated the success of this reaction, for the major isomer these signals were at δ 6.52 (H-5, 1H, d, J 15.9 Hz) and 6.16 (H-4, 1H, dd, J 15.9, 6.9 Hz) and for the minor isomer they were at δ 6.45 (H-5, 1H, d, J 15.6 Hz) and 6.00 (H-4, 1H, dd, J 15.9, 7.5 Hz). The product (62) was further confirmed by an ion at m/z 298 for MH⁺ (100%) in the ESI⁺ mass spectrum.

Scheme 2.14

![Diagram](image)

Reagents a: 10 mol % L-proline, NMP, -20 °C, 14 h. b: NaBH₄, MeOH, 0 °C, 1 h, 10%, syn/anti=4/1.

Figure 2.2 Partial ¹H NMR spectrum (500 MHz, CDCl₃) of (62)
In order to confirm the corresponding syn-diastereoselectivity, the Mannich product (62) was cyclized to form the oxazinan-2-one (63) by treatment with triphosgene$^{24}$ (Scheme 2.15). After an 18 h reaction, the product (63) was obtained as a 3/1 mixture of separable diastereoisomers in 50% combined yield. The success of this reaction was indicated in the $^{13}$C NMR spectrum by the appearance of the carbonyl signal for the major isomer of (63) (δ 159.9) and was further confirmed by an ion at $m/z$ 324 for MH$^+$ (100%) in the ESI$^+$-mass spectrum.

Scheme 2.15

Reagents a: triphosgene, Et$_3$N, DCM, 0 °C to rt, 18 h, 50%. b: chromatography.
In order to determine the corresponding stereochemistry of the two isomers, the structural characteristics of oxazin-2-one ring were studied. It is known that the oxazin-2-one ring of 4,5-diphenyloxazin-2-ones adopts a half-chair conformation due to the partial double bond character of the N-C(O) bond.\textsuperscript{25} The possible half-chair conformations for \textit{cis} and \textit{trans-(63)} are shown in Scheme 2.16. The major isomer of (63) showed $J_{4,5} = 9.5$ Hz. This relatively large coupling constant is consistent with the \textit{trans-A} isomer, in which H-4 and H-5 are \textit{trans-diaxial}.\textsuperscript{25} The smaller $J_{4,5} = 7.5$ Hz for the minor isomer of (63) is more consistent with the \textit{cis}-isomer, however $J_{4,5}$ in \textit{cis-N}-substituted-4,5-diphenyloxazin-2-ones is normally 5.0-5.6 Hz.\textsuperscript{25} If this stereochemical assignment is correct then the Mannich reaction gave the \textit{anti}-adduct as the major product which would be unexpected based upon the literature reports (see Chapter 1, Scheme 1.5). ROESY NMR experiments on these isomeric compounds did not give any useful structural information. Thus the stereochemical assignments of the major and minor isomers of (63) are uncertain and would require X-ray analysis to prove the stereochemistry of these products. Unfortunately, these compounds were not crystalline.
Syn-(63) and anti-(63) were individually hydrolyzed to the Mannich products, syn- and anti-(62) 80% and 75% yields, respectively (Scheme 2.17). The optical rotation of both isomers of (62) were low ([α]^{21}_D = +3.2 and +2.1 (EtOH), respectively) suggesting that their ee was close to zero. The ee of the Mannich products syn-(62) and anti-(62) could not be determined by analysis of their Mosher esters (62a) and (62b) due to the poor resolution of their 1H-NMR spectra.
We next examined the indirect Mannich reaction of the preformed imine (64) with propanal (19) in the presence of L-proline. The imine (64) was
prepared from the condensation of cinnamaldehyde (56) with \( p \)-anisidine (18) in 80\% yield as yellow crystals, according to the literature method.\(^{26}\)

The corresponding proton signals in the \(^1\text{H}-\text{NMR}\) spectrum were consistent with the data reported in the literature. With the preformed imine (64) in hand, the indirect Mannich reaction and the reduction of the resulting Mannich product were then achieved under the same conditions as used in Scheme 1.4. In this case, the \( \beta \)-amino alcohol (62) was obtained in a better yield (25\%) with the same diastereoselectivity (\( \text{syn/anti} = 4/1 \)) compared with that recovered from the initial three-component reaction (Scheme 2.18). We next attempted to optimize the reaction conditions for this indirect type Mannich reaction by adjusting the reaction conditions. The results are summarized in the Table 2.5. In Table 2.5, entry 1, it can be seen that the reaction afforded the product (64) as a 1/1 mixture of diastereoisomers in 10\% yield at 5 \( ^\circ \text{C} \). We suspect that at the higher temperatures the aldehydes (19) undergoes a self-aldol condensation.\(^{11}\) In contrast, a better yield (35\%), and a better diastereoselectivity, were obtained when the reaction proceeded at -20 \( ^\circ \text{C} \) (Table 2.5, entry 2). The yield of (62) was greatly improved when the reaction time was prolonged to 48 h but was not significantly affected by increasing the amount of catalyst (Table 2.5, entries 3 and 4). Notably, the performance of other solvent such as DMSO, DMF or EtOH were not as satisfactory as NMP, as far as the yields and diastereoselectivity were we concerned (Table 2.5,
entries 5-7).

Scheme 2.18

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{O} & \\
\text{Me} & \\
\text{NH}_2 & \\
\text{Ph} & \quad \text{N} \\
\text{MeO} & \\
\text{HO} & \quad \text{Ph} \\
(56) & \\
(18) & \quad (64) \\
(19) & \\
\end{align*}
\]

Reagents a: EtOH, 15 h, 80%. b: L-proline, solvent, -20 °C, 14 h. c: NaBH₄, MeOH, 0 °C, 1 h.

Table 2.5 The L-proline catalyzed Mannich reaction of the preformed imine (64) with propanal (19) in the presence of L-proline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>L-proline (equiv)</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Yield of (62) (%)</th>
<th>d.r. (syn/anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMP</td>
<td>0.1</td>
<td>24</td>
<td>5</td>
<td>10</td>
<td>1/1</td>
</tr>
<tr>
<td>2</td>
<td>NMP</td>
<td>0.1</td>
<td>24</td>
<td>-20</td>
<td>35</td>
<td>4/1</td>
</tr>
<tr>
<td>3</td>
<td>NMP</td>
<td>0.1</td>
<td>48</td>
<td>-20</td>
<td>50</td>
<td>4/1</td>
</tr>
<tr>
<td>4</td>
<td>NMP</td>
<td>0.3</td>
<td>24</td>
<td>-20</td>
<td>33</td>
<td>4/1</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>0.1</td>
<td>48</td>
<td>-20</td>
<td>14</td>
<td>1.5/1</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>0.1</td>
<td>48</td>
<td>20</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>0.1</td>
<td>48</td>
<td>-20</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>
In order to extend the scope of this reaction and to achieve the aims of our project (Scheme 2.13), we examined the reaction of the imine (64) with the commercial aldehydes (57, 65a and 65b) in the presence of L-proline (Scheme 2.19). Unfortunately, these reactions resulted in a large amount of the reduced form of the imine (66a) and aldehyde components (66b) and did not afford the corresponding Mannich product at all. In the case of the aldehydes (57) and (65b), this is possibly due to the oxygen substitute which is electron withdrawing, which would reduce the nucleophilicity of the enamine intermediate (A) (R = OH, OCH₂Ph) compared with (A) (R = Me). The Ph derivative of (A) (R = Ph) would be also expected to be less reactive than (A) (R = Me) due to stabilization of (A) (R = Ph) by conjugation.
We next examined the reactions of several related preformed imines (70, 71 and 72) with propanal (19) in the presence of L-proline. According to the methods stated in the literature, the imines (70, 71 and 72) were prepared via the reaction of cinnamaldehyde (56) with the individual amines (67), (68) and (69), respectively. The desired imines (70-72) were obtained in 60%, 80% and 45% yields, respectively and their individual NMR data were consistent with that reported in the literature.
Scheme 2.20

Reagents a: CH₃CH₂OH, 15 h, rt, 60%. b: CH₂Cl₂, 15 h, rt, 80% c: CH₂Cl₂, 15 h, rt, 45%.

The indirect Mannich reactions of propanal (19) with the preformed imines (70-72) were then examined under the same conditions developed above. Unfortunately, only the imine (70) gave the desired adduct (76) as a 9/1 mixture of diastereoisomers in 35% yield while the others, (71) and (72), did not afford any Mannich products except a large amount of reduced imines (77) and (78) (Scheme 2.20). The lack of reactivity of imine (71) may be due to its hydrolysis by the water generated in the production of enamine (22) (Chapter 1, Scheme 1.5). This reaction would produce benzylamine (and cinnamaldehyde), which could remove the L-proline catalyst from the reaction by formation of salt (L-proline⁻BnNH₃⁺). Such a
hydrolysis step would be slower for the more conjugated and thus more stable imine (70). Furthermore, any free 2-methoxyaniline generated in the reaction of propanal with imine (70) would not be basic enough to form a salt with L-proline. The \( N\text{-}\text{tert-} \text{butylamine (72)} \) could also undergo hydrolysis to generate \( \text{tert-} \text{butylamine in situ, which could also form a salt with L-proline. This imine would also be expected to be less reactive based on steric factors. For the product (76), the two isomers were indicated by their individual olefinic signals in the } ^1 \text{H NMR spectrum, including } \delta \text{ 6.53 (H-5, 1H, d, } J \text{ 16.2 Hz) and } \delta \text{ 6.20 (H-4, 1H, dd, } J \text{ 16.2, 6.0 Hz) for the major isomer and } \delta \text{ 6.42 (H-5, 1H, d, } J \text{ 16.2 Hz) and } \delta \text{ 6.08 (H-4, 1H, dd, } J \text{ 16.2, 6.0 Hz) for the minor isomer. The product (76) was further confirmed by an ion at } m/z \text{ 298 for MH}^+ (100\%) \text{ in the ESI}^+ \text{ mass spectrum.}
Scheme 2.21

Reagents a: 10 mol % L-proline, NMP, -20 °C, 48 h. b: NaBH₄, MeOH, 0 °C, 1h, 35%, d.r. = 9/1. c: 20 mol % L-proline, NMP, -20 °C, 72 h. d: NaBH₄, MeOH, 0 °C, 1h. e: 10 mol % L-proline, NMP, -20 °C, 72 h. f: NaBH₄, MeOH, 0 °C, 1h.

These frustrating results let us to investigate the more reactive imine (80) and to revisit the L-proline catalyzed Mannich reaction. The imine (80) was easily prepared from the reaction of the p-nitrocinnamaldehyde (79) with p-aniside (18) in 95% yield as yellow crystals. The ¹H NMR spectrum indicated the corresponding proton signals, including the imine methine (CH= N) at δ 8.33 (1H, d, J 8 Hz) and the OCH₃ group at δ 3.84 (3H, s). The product (80) was further confirmed by an ion at m/z 283 for MH⁺.
(100%) in the ESI$^+$ spectrum. This imine (80) was expected more reactive than the imine (64) as the electron withdrawing group (-NO$_2$) would decrease the electronic density of the imine (80) and hence make the imine carbon (C=\(\text{N}\)) more electrophilic towards nucleophiles.

**Scheme 2.22**

![Scheme 2.22](image)

*Reagents a: CH$_3$CH$_2$OH, 15 h, rt, 95%.*

The reactions of the imine (80) with the previous attempted aldehydes (19), (57), (65a) and (65b) were examined individually, by treatment with L-proline in NMP under the same reaction conditions described before. Unfortunately, the use of the expected more reactive imine (80) achieved the same poor results found for the imine (65), with only propanal (19) affording the corresponding Mannich adduct (81) as a 2/1 mixture of diastereoisomers in 40% yield. For the product (81), the individual olefinic signals in the $^1$H NMR spectrum were at $\delta$ 6.64 (H-5, 1H, d, $J$ 16.2 Hz) and 6.30 (H-4, 1H, dd, $J$ 16.2, 6.0 Hz) for the major isomer and at $\delta$ 6.56 (H-5, 1H, d, $J$ 16.2 Hz) and 6.26 (H-4, 1H, dd, $J$ 16.2, 6.0 Hz) for the minor isomer. The product (81) was further confirmed by an ion at $m/z$ 343 for MH$^+$ (100%) in the ESI$^+$ spectrum. These poor results suggested that the
proposed Mannich reactions between the imines derived from cinnamaldehyde and O-benzylglycoaldehyde (57) would not be a feasible way to achieve the proposed synthetic targets. This study was then abandoned and another approach was examined. The results of this approach are reported in the following Chapters.

**Scheme 2.23**

\[
\text{Reagents } a: 10\% \text{ L-proline, NMP, } -20^\circ\text{C, 14 h. b: NaBH}_4, \text{MeOH, 0 }^\circ\text{C, 1 h, 40\% for (19)} \\
d.r. = 2/1. 0\% \text{ for (57), (65a) and (65b).}
\]
Chapter 3: Introduction to N-acyliminium Ions

3.1 N-acyliminium Ions

N-acyliminium ions are useful intermediates in organic synthesis. The reactions of N-acyliminium ions and nucleophiles (Nu\(^-\)) has allowed the introduction of substituents at the \(\alpha\)-carbon of nitrogen-containing compounds with high stereoselectivity (Scheme 3.24).\(^ {29}\)

**Scheme 3.24**

\[
\begin{align*}
\text{W} \quad \text{N} &= \\
\text{R}_1 \quad \text{R}_2 &+ \text{Nu}^- \\
\Rightarrow &\quad \text{W} \quad \text{N} \\
\text{R}_1 \quad \text{R}_2 &\quad \text{Nu}
\end{align*}
\]

\(W = \text{electron withdrawing group}\)

The addition of nucleophiles to \(N\)-acyliminium ions can involve intermolecular or intramolecular reactions. For example, **Scheme 3.25** shows an intermolecular example, where the cyclic \(N\)-acyliminium ion (83), generated from the pyrrolidone (82) in the presence of InCl\(_3\), reacted with allyltrimethylsilane and subsequently gave the corresponding adduct (84) with good yield (70%) and with modest \(\text{trans}\)-diastereoselectivity \((\text{cis}/\text{trans}=1/3)\).\(^ {30}\)
In 2006, Nilson and Funk reported a novel method for the total syntheses of the bioactive natural product nakadomarin A (88) via intramolecular cyclization of the N-acyliminium ion (86) generated from the acetate (85).31

In this study, the intermediate (86) was generated from (85) by treatment with TsOH and was trapped intramolecularly by the furan group to give the tetracycle (87), a potential precursor of nakadomarin A (88) (Scheme 3.26).
3.2 Methods to Generate $N$-acyliminium Ions

There are a number of methods developed for the preparation of $N$-acyliminium ions. These electrophilic intermediates can be generated from $N$-acylamines substituted with an $\alpha$-halo, $\alpha$-hydroxy, $\alpha$-alkoxy, $\alpha$-acetoxyl or $\alpha$-sulfonyl group by treatment with a Lewis acid. These Lewis acids include, BF$_3$·Et$_2$O, TiCl$_4$, SnCl$_4$, InCl$_3$, NbCl$_5$ and Zn(OTf)$_2$ or silylating agents (such as TMSOTf).
Scheme 3.27

For example, Klitzke and Pilli reported a variety of Lewis acids are available for the preparation of the \( N \)-acyliminium ion (91), derived from the pyrrolidone (90) for the synthesis of hydroxylated indolizidines (93) (Scheme 3.28).\(^{33}\) Table 3.6 shows the Lewis acids used in this reaction and their effect on the yield and diastereoselectivity of the adducts (92) from the addition of allylsilane to the \( N \)-acyliminium ion (91). In this study, the use of the Lewis acid TiCl\(_4\) gave the best diastereoselectivity (Table 3.6, entry 6).

\( X = \) halogen, OH, OR, OAc

\( W = \) electron withdrawing group
Scheme 3.28

![Chemical structures and reactions](image)

Table 3.6 The effect of some Lewis acids on the diastereoselectivity of the adducts (92)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yield of (92) (%)</th>
<th>Cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf</td>
<td>90</td>
<td>1/3.5</td>
</tr>
<tr>
<td>2</td>
<td>BF₃·OEt₂</td>
<td>84</td>
<td>1/2.5</td>
</tr>
<tr>
<td>3</td>
<td>SnCl₄</td>
<td>88</td>
<td>1/3.2</td>
</tr>
<tr>
<td>4</td>
<td>InCl₃</td>
<td>82</td>
<td>1/4</td>
</tr>
<tr>
<td>5</td>
<td>TiF₄</td>
<td>76</td>
<td>1/2</td>
</tr>
<tr>
<td>6</td>
<td>TiCl₄</td>
<td>80</td>
<td>1/7</td>
</tr>
</tbody>
</table>

In addition to the use of Lewis acids, p-nitrobenzenesulfonyl peroxide (NBSP) and some other peroxides have been used to generate N-acyliminium ions. It was reported that the diethylamide (94), upon
treatment the NBSP, gave the corresponding \( N \)-acyliminium ion (96) via \( N \)-nosyloxyamide (95) as an intermediate (Scheme 3.29).^{34}

**Scheme 3.29**

\[
\begin{align*}
\text{(94)} & \xrightarrow[pNBSP (2.0 eq)]{\text{EtOAc/H}_2\text{O}} \text{(95)} \\
\text{(96)} & \xrightarrow{-\text{NsOH}}
\end{align*}
\]

Some \( N \)-acyliminium ions can be prepared under mild conditions in the absence of a Lewis acid or any other inducing agents. For example, \( N \)-sulfonyloxyamines (97), which have a weak N-O bond, readily undergo elimination reactions to generate \( N \)-acyliminium ions (98) upon heating (Scheme 3.30).^{34}

**Scheme 3.30**

\[
\begin{align*}
\text{(97)} & \xrightarrow{\Delta} \text{(98)} + \text{R}_3\text{SO}_3^-
\end{align*}
\]
3.3 Addition of Nucleophiles to $N$-acyliminium Ions

A variety of nucleophilic reagents can react with $N$-acyliminium ions, including organometallic compounds, enol derivatives, aromatics, and even alkenes.

For example, in 1989, Yamada reported the alkylation of the $N$-acyliminium ion (100) prepared from $N$-acylamine (99) in the presence of TiCl$_4$ with organolead and organozinc reagents. The results summarized in Table 3.7 show that the products (101) were isolated in satisfactory yields (Scheme 3.31).

**Scheme 3.31**

![Scheme 3.31](image)

**Table 3.7** Reactions of 99 with Organo-Pb and Zn Compounds catalyzed by TiCl$_4$

<table>
<thead>
<tr>
<th>Entry</th>
<th>RM (equiv)</th>
<th>Temp ($^\circ$C)</th>
<th>Yield of 101 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_4$Pb (1.2)</td>
<td>-78→0</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Et$_4$Pb (2.0)</td>
<td>-78→rt</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>$n$-Bu$_4$Pb (2.0)</td>
<td>-78→rt</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$Zn (1.2)</td>
<td>-78→0</td>
<td>72</td>
</tr>
</tbody>
</table>
Yamada also examined the distereoselectivity of the alkylated adduct (104) obtained from precursor (102) using TiCl₄ or BF₃·Et₂O as the catalysts and the above organo-Pb and Zn reagents as nucleophiles (Scheme 3.32). The stereochemical outcome shown in Table 3.8 indicated that the use of Et₂Zn and Et₄Pb (Table 3.8, entries 1 and 2) in the presence of TiCl₄ and BF₃·Et₂O, respectively, afforded products with moderate distereoselectivity. However, Et₄Pb and n-Bu₄Pb (Table 3.8, entries 3 and 4) in the presence of TiCl₄ gave much better distereoselectivity. In all cases, the cis-isomers of (104) were preferred.

Scheme 3.32

Table 3.8 Alkylation of (102) with Organo-Pb and Zn Compounds in the presence of Lewis acids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RM</th>
<th>Lewis acid</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂Zn</td>
<td>TiCl₄</td>
<td>74/26</td>
</tr>
<tr>
<td>2</td>
<td>Et₄Pb</td>
<td>BF₃·Et₂O</td>
<td>75/25</td>
</tr>
<tr>
<td>3</td>
<td>Et₄Pb</td>
<td>TiCl₄</td>
<td>91/9</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu₄Pb</td>
<td>TiCl₄</td>
<td>94/6</td>
</tr>
</tbody>
</table>
Reactions of enol acetates and alkenes with \(N\)-acyliminium ion have been reported Hoffman in 1994.\(^{34}\) Scheme 3.33 shows the intermolecular nucleophilic addition of the enol acetate (107) and the alkene (108) to the \(N\)-acyliminium ions formed from (105) and (106), catalyzed by BF\(_3\)\cdot\text{Et}_2\text{O} and TiCl\(_4\), respectively.\(^{34}\) Although the diastereoselectivity of (110) was not studied, both of the nucleophilic adducts (109, 110) were obtained in satisfactory yield, 51% and 56%, respectively.

**Scheme 3.33**

\[
\begin{align*}
(105) + (107) &\xrightarrow{a} (109) \\
(106) + (108) &\xrightarrow{b} (110)
\end{align*}
\]

*Reagents* a: BF\(_3\)\cdot\text{Et}_2\text{O}, CH\(_2\text{Cl}_2\), -78 °C, 51%; b: TiCl\(_4\), CH\(_2\text{Cl}_2\), -78 °C, 56%.

### 3.4 Addition of Organoboronic Acids to \(N\)-acyliminium Ions

The use of organoboronic acids and their esters in asymmetric synthesis has been frequently reported.\(^{38,39}\) Compared with other nucleophilic reagents, organoboronic acids have the following advantages: air and water stability, low toxicity, low environmental impact and relatively low cost.\(^{40}\) Recently, the diastereoselective addition of organoboronic acids (or esters) to
*N*-acyliminium ions for C-C formation has proved successful. For example, the reactions of the pyrrolidine (111) with several boronic acids (esters) in the presence of BF$_3$·Et$_2$O was reported by Batey in 1999 (Scheme 3.34).\textsuperscript{41} Table 3.9 shows in all cases the products were obtained in good yields and with excellent 4,5-\textit{cis}-diastereoselectivity.

**Scheme 3.34**

![Scheme 3.34](image)

**Table 3.9** Addition of Boronates to *N*-acyliminium ions derived from the pyrrolidine (111)

<table>
<thead>
<tr>
<th>Entry</th>
<th>OR, OR</th>
<th>Yield of 113 (%)</th>
<th>d.r (cis/trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH, OH</td>
<td>57</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>2</td>
<td>O(CMe$_2$)$_2$O</td>
<td>66</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>3</td>
<td>iPrO, iPrO</td>
<td>75</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>4</td>
<td>O(CH$_2$)$_2$O</td>
<td>93</td>
<td>&gt;98:2</td>
</tr>
</tbody>
</table>
3.5 Addition of Nucleophiles to Pyrrolidone Based $N$-acyliminium Ions

Many natural and unnatural compounds with important biological activities contain chiral pyrrolidines as common subunits.\textsuperscript{42,43} Chiral pyrrolidines and their derivatives have proved useful precursors for elaboration to these essential compounds. In order to synthesize these chiral molecules, creation of new stereocenters is always required and is usually carried out by introducing substitutes to certain positions of the pyrrolidines in an diastereoselective way. Usually, this goal can be achieved by the diastereoselective addition of nucleophiles to pyrrolidines based on $N$-acyliminium ions.

In 1999, Lennartz reported the addition of substituted allyltrimethylsilanes to the $N$-acyliminium ion (115) derived from the pyrrolidone (113) in the presence of TiCl$_4$ (Scheme 3.35).\textsuperscript{44} The summarized results in Table 3.10 show the substituents (H, CH$_2$Cl and Br) favour the 4,5-\textit{cis} adducts in good yield (Table 3.10, entries 1, 2 and 4). In contrast, the substituent, CH$_2$OH, favoured the 4,5-\textit{trans} adduct in low yield (Table 3.10, entry 3).

\textbf{Scheme 3.35}
**Table 3.10** Addition of allyltrimethylsilanes (substituted) to N-acyliminium ions derived from the pyrrolidone (114)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substitutes (R)</th>
<th>Yield of 116 (%)</th>
<th>d.r (cis/trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>89</td>
<td>83/17</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl</td>
<td>85</td>
<td>84/16</td>
</tr>
<tr>
<td>3</td>
<td>CH₂OH</td>
<td>44</td>
<td>22/78</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>72</td>
<td>73/27</td>
</tr>
</tbody>
</table>

In 2000, Pilli reported the reactions between some bulky silylated carbon nucleophiles (ROSiMe₃) and the cyclic N-acyliminium ions (118) derived from 5-acetoxy lactams (117) in the presence of InCl₃ as the Lewis acid (Scheme 3.36). In this study, the stereochemical outcome of the given adducts (119) was examined and the results are summarized in Table 3.11. In Table 3.11, entries 1-5 the major diastereomer of (119) had the 4,5-trans-stereochemistry while the 4-OTBS derivative of (117) favoured for the 4,5-cis adduct with poor diastereoselectivity (Table 3.11, entry 6). The reaction of (117) (R₁ = R₂ = OMe) with Rc (allyltrimethylsilane) proceeded with no diastereoselectivity (Table 3.11, entry 7).
Scheme 3.36

```
\[
\begin{array}{cccc}
\text{O} & \text{N} & \text{OAc} & \text{R}_1 \text{ R}_2 \\
\text{InCl}_3 & \text{CH}_2\text{Cl}_2 & & \\
\text{Nucleophiles} & & & \\
\text{cis/ trans} & & & \\
\text{Yield of} & & & \\
\text{(119)} & & & \\
\end{array}
\]
```

Nucleophiles

\[
\begin{array}{ccc}
\text{A:} & \begin{array}{c}
\text{TMSO} \\
\text{Ph}
\end{array} & \\
\text{B:} & \begin{array}{c}
\text{TMSO} \\
\text{MeO}
\end{array} & \\
\text{C:} & \begin{array}{c}
\text{H}_2\text{C}=\text{CHCH}_2\text{TMS}
\end{array}
\end{array}
\]

Table 3.11 Addition of silylated carbon nucleophiles to N-acyliminium ions derived from 5-acetoxy lactams (117)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophiles</th>
<th>5-acetoxy lactams</th>
<th>cis/trans (%)</th>
<th>Products (119)</th>
<th>Yield of 119 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R&lt;sub&gt;1&lt;/sub&gt;</td>
<td>R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>R&lt;sub&gt;3&lt;/sub&gt;</td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>H</td>
<td>OAc</td>
<td>9:91</td>
<td>H</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>OAc</td>
<td>OAc</td>
<td>25:75</td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>H</td>
<td>OAc</td>
<td>4:94</td>
<td>Me</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>OAc</td>
<td>OAc</td>
<td>2:98</td>
<td>Me</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>H</td>
<td>OAc</td>
<td>25:75</td>
<td>H</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>H</td>
<td>OTBS</td>
<td>66:34</td>
<td>H</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>OAc</td>
<td>OAc</td>
<td>50:50</td>
<td>H</td>
</tr>
</tbody>
</table>

In 2000, Schuch examined the reactions between allyltributyltin and
several $O$-TBS protected pyrrolidones with alkyl substituents (R) attached to the $\alpha$-carbon of the nitrogen. The $\alpha$-hydroxy lactams (121) were prepared via addition of organolithium to the chiral imide (120) in THF at -78°C (Scheme 3.37). The resulting lactams were then transformed to the corresponding $N$-acyliminium ions (122) in the presence of BF$_3$·Et$_2$O followed by nucleophilic attack by allyltributyltin to give the adducts (123). According to the summarized results in Table 3.12, it can be seen that the $n$-butyl substituent led to an excellent diastereoselectivity of the given product (123) (Table 3.12, entry 2). In contrast, the methyl substituted $N$-acyliminium ion (122) gave the product (123) with poorer diastereoselectivity (Table 3.12, entry 1).

Scheme 3.37

![Scheme 3.37](image)

Reagents a: R-Li, THF, -78 °C, 63%. b: BF$_3$·Et$_2$O, CH$_2$Cl$_2$, -78 °C. c: allyltributyltin BF$_3$·Et$_2$O, CH$_2$Cl$_2$, -78 °C to 0 °C.
3.6 Addition of Nucleophiles to Pyrrolidone Based N-acyliminium Ions in Synthesis

A variety of products has been synthesized by the addition of nucleophiles to N-acyliminium ions as a key reaction. For example, in 1996, Yoda, et al. reported the total synthesis of (-)-codonopsinine (128) from the chiral pyrrolidone (124) (Scheme 3.38).\(^{46}\) This natural product was isolated in 1969 from *Codonopsis clematidea* and had hypotensive pharmacological activity without any impact to the central nervous system.\(^{47}\) The key reactions for creation of the desired 4,5-*trans* stereochemistry of (127) involved diastereoselective reduction of the N-acyliminium ion (126) with Et$_3$SiH catalyzed by BF$_3$·Et$_2$O. The reduction gave the pyrrolidinone (127) in 99% yield. The intermediate (127) was used as a chiral precursor and transformed to codonopsinine (128) after several synthetic steps (Scheme 3.38).

### Table 3.12 Addition of allyltributyltin to cyclic N-acyliminium ions (122)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield of (123) (%)</th>
<th>d.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Bu</td>
<td>65</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>C≡C—Ph</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>C≡C—CH$_2$OTBS</td>
<td>36</td>
<td>67</td>
</tr>
</tbody>
</table>
Scheme 3.38

\[ \begin{align*}
\text{Reagents a: MeMgBr, THF, -78^\circ C, 91\%; b: Et_3SiH, BF_3\cdot Et_2O, CH_2Cl_2, -78^\circ C, 98%.} 
\end{align*} \]

Indolizidine alkaloids such as lentiginosine\(^4^8\) (129), swainsonine\(^4^9\) (130), and castanospermine\(^5^0\) (131) show potential against cancers, viruses, and diabetes and are important for drug design.\(^5^1\) An important strategy for the synthesis of indolizidine alkaloids are diastereoselective addition of \(N\)-acyliminium ions to chiral pyrrolidones. There have been several reported synthesis of these products including lentiginosine (129)\(^3^3\) and polyhydroxy indolizidines (132), (133) and (134).\(^4^0,^5^2\)
The total synthesis of the polyhydroxy indolizidines (132) and (133) was reported by Leeper and Howard in 1995. The key reaction involved in the synthetic routes was the intramolecular cyclization of the $N$-acyliminium ion (137) generated from (136) to the bicyclic precursor (138) in the presence of BF$_3$·Et$_2$O. The precursor (138) was then transformed to the indolizidines (132) and (133) in several synthetic steps (Scheme 3.39).
In 2001, Pilli reported a successful synthesis of the hydroxylated indolizidine alkaloid lentiginosine (129) using allylation of a chiral N-acyliminium ion with allyltrimethylsilane and ring-closing metathesis as key reactions. Scheme 3.40 shows the short synthetic route to (129). N-allyl imide (140) was prepared from inexpensive L-tartaric acid (139) followed by reduction by NaBH₄ and then acetylated to give the intermediate (141). Addition of allyltrimethylsilane to the N-acyliminium ion generated from (141) in the presence of BF₃·Et₂O gave (142) in 95% yield as a 2.5:1 mixture of the cis and trans isomers. The trans-adduct (142) underwent ring-closing metathesis to give the bicyclic product (143) which
was then hydrogenated and reduced by LiAlH$_4$ to give the target alkaloid (129).

Scheme 3.40

Reagents: (a) (i) AcCl, reflux; (ii) allylamine, CH$_2$Cl$_2$, rt; (iii) AcCl, reflux; (b) (i) NaBH$_4$, EtOH, $-23^\circ$C; (ii) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$ (69%); (c) b: allylsilane, BF$_3$·Et$_2$O, CH$_2$Cl$_2$, 0$^\circ$C, 95%, cis/tran=2.5/1 (d) 4 mol% Grubbs’ catalyst, CH$_2$Cl$_2$ (44%); (e) (i) H$_2$, Pd/C, AcOEt; (ii) LiAlH$_4$, THF, reflux (78%).

In 2002, Batey and co-workers successfully synthesized the polyhydroxylated indolizidine (134) involving the reaction of boronic ester (145) with the $N$-acyliminium ion (146) derived from the chiral
dihydroxylated pyrrolidine (144) in the presence of BF$_3$·Et$_2$O.$^{40}$ The adduct (147) was afforded in 80% yield with excellent cis-diastereoselectivity and was then transformed to the indolizidine (134) after a number of synthetic steps (Scheme 3.41).

Scheme 3.41
Chapter 4: Diastereoselective Addition of Organoboronic Acids to N-acyliminium Ions

4.1 Aims of this Project

The aims of this project were to examine the reactions of the pyrrolidone hemi-aminal (A) with aryl and vinylboronic acids as a method to diastereoselectively prepare pyrrolidones (B). These compounds could be useful precursors to glycosidase inhibitors or polyhydroxylated pyrrolidine alkaloids (Scheme 4.42).

Scheme 4.42

4.2 Preparation of O-TBS-protected Pyrrolidones

In this study, the 3,4-di-O-TBS protected pyrrolidone (152) and the 3-O-TBS protected pyrrolidone (153) were prepared via three individual steps, as shown in Scheme 4.43. This route includes: (a) formation of the pyrrolidone (149) from L-tartaric acid (148), (b) and (c) protection of the hydroxyl groups of the derived pyrrolidone (149) as their TBS ethers and (d)
and (e) reduction of the imides (150) and (151) by NaBH₄.

Scheme 4.43

\[ \text{HOOC} \quad \text{COOH} \quad \text{HO} \quad \text{OH} \]
\[ \text{TBSO} \quad \text{OTBS} \quad \text{O} \quad \text{OH} \]
\[ \text{Ph} \quad \text{N} \quad \text{OTBS} \quad \text{O} \quad \text{OH} \]
\[ \text{Ph} \quad \text{N} \quad \text{TBSO} \quad \text{OH} \quad \text{TBSO} \]
\[ \text{Ph} \quad \text{N} \quad \text{TBSO} \quad \text{OTBS} \quad \text{O} \quad \text{OH} \]

**Reagents**
a: PhCH₂NH₂, xylene, reflux, 5 h (80%); b: TBSCl (3 equiv), imidazole (3 equiv), DMF, 55 °C, 48 h (98%); c: TBSCl (1 equiv), imidazole (3 equiv), DMF, 55 °C, 20 h (70%); d: NaBH₄ (5 equiv), MeOH, -20 °C, 1 h (81%); e: NaBH₄ (5 equiv), MeOH, -20 °C, 1 h (87%).

The literature reports two feasible ways to prepare 3,4-dihydroxypyrrolidones. The preparation of (149) from (148) by treatment of AcCl and BnNH₂ has been described.³³ Alternatively, compound (149) can be prepared by heating a solution of L-tartaric acid with BnNH₂ in xylene at reflux under Dean-Stark conditions, in 90% yield.⁵³ This easier method has been applied in our experiments and afforded an 80% yield of (149) after heating at reflux for 5 h. The ¹H NMR data of compound (149) was consistent with that was reported.⁵³,⁵⁴ Silylation of (149) to give the O-TBS ethers (150) and (151) was carried...
out in the following step. Treatment of (149) with imidazole and 3 molar equiv of TBSCI in DMF at 55 °C, transformed (149) to the corresponding bis-O-TBS ether (150) in an excellent yield (98%). The success of the silylation was confirmed in the $^1$H NMR spectrum by the appearance of characteristic signals of the corresponding TBS groups. The two identical TBS groups of (150) were clearly visible in the $^1$H NMR spectrum, at $\delta$ 0.06 and 0.00 ($\text{Si(CH}_3\text{)}$) and $\delta$ 0.77 ($\text{SiCH}_3$). The structure of compound (150) was further confirmed by an ion at $m/z$ 450 for MH$^+$ (100%) in the ESI$^+$-mass spectrum. By reducing the amount of TBSCI to 1 equiv under the same conditions, the mono-O-TBS ether (151) was obtained in 70% yield together with 10% of the undesired bis-O-TBS ether (150). In the $^1$H NMR spectrum, the structure of (151) was indicated by its TBS signals at $\delta$ 0.20 and 0.18 ($\text{Si(CH}_3\text{)}$) and $\delta$ 0.94 ($\text{SiCH}_3$) and was further confirmed by an ion at $m/z$ 336 for MH$^+$ (100%) in the ESI$^+$-mass spectrum. Compounds (150) and (151) were treated with NaBH$_4$ in MeOH for 1 h at –20 °C to give the reduced pyrrolidones (152) and (153), in 81% and 87% yields, respectively. The $^1$H NMR and the $^{13}$C NMR spectrum indicated the two reduced compounds were both single isomers. For compound (152), the $^1$H NMR spectrum was consistent with that reported by Ryu. It showed signals for two different O-TBS groups, with four 3H, singlet peaks at $\delta$ 0.21, 0.19, 0.08, and 0.02 and two 9H, singlet peaks at $\delta$ 0.92 and 0.83. These separate signals indicated that one of the
carbonyl groups had been reduced to a hydroxyl group thus the remaining carbonyl group caused a more downfield shift to the closer TBS group. Hence, both TBS groups could be identified, as the one more downfield, of larger ppm, was on the side of the carbonyl group while the other one more upfield, of smaller ppm, was on the side of the hydroxyl group. For compound (153), the $^1$H NMR spectrum showed signals for the TBS group at $\delta$ 0.18, 0.16 ($(\text{CH}_3)$ Si(CH$_3$)) and 0.92 ($(\text{CH}_3)_3$Si). The relative downfield shift of this TBS group indicated that it was on the side of the carbonyl group and this structure, was also supported by the appearance of a significant cross-peak between H-3 ($\delta$ 3.95, 1H, m, H-3) with one of the methyl protons on the TBS group ($\delta$ 0.18, 3H, s, CH$_3$Si) in the NOESY spectrum. The structure of compound (153) was further confirmed by an ion at $m/z$ 338 for MH$^+$ (100%) in the ESI$^+$-mass spectrum.

4.3 Addition of Organoboronic Acids to the N-acyliminium Ion from the Bis-O-TBS Protected Pyrrolidone (152)

In our initial study, the addition of trans-vinylphenylboronic acid to the bis-O-TBS protected pyrrolidone (152) was attempted. Compound (152) was treated with BF$_3$·Et$_2$O (3 equiv) in dry CH$_2$CH$_2$ at 0 °C for 15 min and then 1.5 equiv of trans-vinylphenylboronic acid was added and the solution was stirred at rt for 5 h. The reaction was quenched with saturated NaHCO$_3$ solution and the resulting products were extracted and separated by column
chromatography. The purified adduct (154) was obtained in 27% yield as an 8/1 mixture of diastereoisomers (Scheme 4.44).

Scheme 4.44

![Scheme 4.44](image)

Reagents BF₃·Et₂O (3 equiv), PhCH=CHB(OH)₂ (1.5 equiv), CH₂Cl₂, 0 °C to rt, 5 h, 27% for (154), 1% for (155).

In the ¹H NMR spectrum of (154) was the appearance of two new olefinic signals for the major diastereomer at δ 6.39 (1H, d, J 16.0 Hz, H-7) and 5.94 (1H, dd, J 15.8, 9.0 Hz, H-6) and for the minor diastereomer at δ 6.47 (1H, d, J 16.0 Hz, H-7) and 6.06 (1H, dd, J 15.8, 9.0 Hz, H-6). The corresponding proton signals for the two TBS groups were at δ 0.99 (9H, s, (CH₃)₃CSi), 0.85 (9H, s, (CH₃)₃CSi), 0.29 (3H, s, CH₃Si), 0.21 (3H, s, CH₃Si), 0.08 (3H, s, CH₃Si) and -0.04 (3H, s, CH₃Si). The structure of (154) was also supported by an ion at m/z 538 for MH⁺ (100%) in the ESI⁺-mass spectrum. The 4,5-trans diastereochemistry of the major isomer was
deduced from NOESY NMR experiments, in which no significant cross peak between H-4 (δ 3.98, 1H, H-4) and H-5 (δ 3.74, 1H, dd, J 9.0 4.5 Hz) was observed. The trans-diastereochimistry of (154) was further confirmed by its coupling constant J_{4,5} (4.5 Hz) in the range of J_{4,5} (4.0-5.0 Hz) for typical trans-isomers of 5-substituted-3,4-di-O-TBS protected pyrrolidones.\textsuperscript{56} In addition to the target product (154), a very small amount of deprotected product (155) (less than 1%) was obtained as an approximate 10:1 mixture of diastereoisomers. This product was due to the cleavage of the TBS group from the pyrrolidone ring of either (152) or (154) by BF\textsubscript{3}·Et\textsubscript{2}O.\textsuperscript{57} The structure of (155) was deduced from its \textsuperscript{1}H NMR signals with olefinic resonances at δ 6.39 (1H, d, J 16 Hz, H-7) and 5.90 (1H, dd, J 15.8, 9.0 Hz, H-6) for the major isomer and the loss of signals for one TBS group. An ion at m/z 424 for MH\textsuperscript{+} (30%) in the ESI\textsuperscript{+}-mass spectrum also supported the structure of (155). The relative more downfield shift of the proton signals for the remaining TBS group (δ 0.29 (3H, s, CH\textsubscript{3}Si) and δ 0.21 (3H, s, CH\textsubscript{3}Si)), suggested its position on the side of the carbonyl group. However, due to peak overlap, we were not able to identify the protons on the pyrrolidone ring, including H-3, H-4 or H-5. Hence, the position of the TBS group could not be further confirmed by NOESY NMR analysis of the cross peak of H-3 and one of the methyl group on the TBS group. In addition, the 4,5-diastereochimistry of (155) could not be deduced by studying the coupling constant (J_{4,5}) as this could not be readily
The formation of the compound (155) might be from deprotection of the product (154) (Pathway A) and/or from addition of trans-vinylphenyl boronic acid to the deprotected starting material (153) (Pathway B), as shown in Scheme 4.45.

**Scheme 4.45**

Reagents a: BF$_3$·Et$_2$O, CH$_2$Cl$_2$; a': BF$_3$·Et$_2$O, CH$_2$Cl$_2$; b': BF$_3$·Et$_2$O, CH$_2$Cl$_2$; c': BF$_3$·Et$_2$O, CH$_2$Cl$_2$; PhCH=CHB(OH)$_2$. 

[detailed chemical structures and reactions shown in the scheme]
In order to solve this problem, addition of *trans*-vinylphenylboronic acid to the mono-\textit{O}-TBS protected pyrrolidone (153) was attempted under similar reaction conditions to those stated above for (152). To our surprise, this reaction gave a large amount of the boronic ester (156) (65%) while no expected compound (155) was recovered (Scheme 4.46). The boronic ester (156) resulted from the condensation of the boronic acid and the compound (153) by elimination of 2 equiv of water. A likely explanation for the occurrence of condensation was that the boronic ester (156) was much more stable than its corresponding boronic acid. The $^1$H NMR spectrum clearly showed the corresponding proton signals of (156), including the aromatic protons at $\delta$ 7.52-7.30 (10H, m, ArH), the olefinic protons at $\delta$ 7.43 (1H, d, $J$ 18.5 Hz, H-6) and $\delta$ 6.14 (1H, d, $J$ 18.5 Hz, H-7), and the TBS protons at $\delta$ 0.98 (9H, s, (CH$_3$)$_3$Si), 0.30 (3H, s, CH$_3$Si) and 0.22 (3H, s, CH$_3$Si). The \textit{cis}-stereochemistry of (156) was indicated by the relatively large coupling constant, $J_{4,5}$ (6.0 Hz) in the $^1$H NMR spectrum and was further confirmed by a significant correlation between H-4 and H-5 in the 2D NOESY NMR spectrum. The fact that the reaction of (153) with *trans*-vinylphenylboronic acid did not afford the product (155) and also no boronic ester was recovered in this reaction indicated that formation of (155) in Scheme 4.44 was via \textbf{pathway A}, rather than \textbf{pathway B}. 
We next attempted to re-silylate the hydroxyl group of (155) to determine its stereochemistry. However, treatment of (155) with imidazole and TBSCl in DMF at 55 °C for 24 h did not afford the desired compound (154) and resulted in recovery of the starting material (155). This may be due to the fact that the hydroxyl group at C-4 was quite hindered thus inhibited the reaction to occur. Hence, this goal could not be achieved by the re-silylation method. The use of TBSOTf could have been a better option, however, this was not tried.

**Scheme 4.47**

*Reagents* TBSCl (3 equiv), imidazole (3 equiv), DMF, 55 °C, 48 h.

Due to the low recovery of the desired product (154) in **Scheme 4.44**, we
decided to optimize the reaction conditions. Several attempts were made including prolonging the reaction time, increasing the amount of trans-vinylphenyl boronic acid and BF$_3$·Et$_2$O, and using the more reactive potassium trans-styryltrifluoroborate instead of trans-vinylphenyl boronic acid. In our investigations, we found an improved yield (38%) was obtained when the reaction time was increased to 15 h (Table 4.13, entry 1). The use of 5 equiv of BF$_3$·Et$_2$O gave essentially the same yield (37%) as the first attempt using 3 equiv of BF$_3$·Et$_2$O after an overnight reaction (16 h) (Table 4.13, entry 2). Treatment of (152) with 3 equiv of trans-vinylphenyl boronic acid resulted in a improved yield (60%) of (154) (Table 4.13, entry 3). This indicated that the yield was greatly improved by increasing the amount of boronic acid but was not significantly affected by the increased concentration of BF$_3$·Et$_2$O. Treatment of (152) with 1.5 equiv of potassium trans-styryltrifluoroborate led to a satisfactory yield (58%), which proved to be a similar yield to that obtained using trans-vinylphenyl boronic acid (Table 4.13, entry 4). Interestingly, these changed reaction conditions had no significant effect to the diastereoselectivity, as the trans/cis ratio remained 8/1, as was obtained in the first reaction. We also observed in all cases, a small amount of the deprotected compound (155) (1%-2%).
### Table 4.13: Addition of trans-vinylphenyl boronic acid to the N-acyliminium ion from (152)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>BF₃·Et₂O (equiv)</th>
<th>Time (h)</th>
<th>Yield of (154) (%)</th>
<th>trans/cis</th>
<th>J₄,₅ for (154)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B(OH)₂ (1.5)</td>
<td>3</td>
<td>15</td>
<td>38</td>
<td>8:1</td>
<td>4.5</td>
</tr>
<tr>
<td>2</td>
<td>B(OH)₂ (1.5)</td>
<td>5</td>
<td>16</td>
<td>37</td>
<td>8:1</td>
<td>4.5</td>
</tr>
<tr>
<td>3</td>
<td>B(OH)₂ (3)</td>
<td>4</td>
<td>16</td>
<td>60</td>
<td>8:1</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>BF₃K (1.5)</td>
<td>4</td>
<td>16</td>
<td>58</td>
<td>8:1</td>
<td>4.5</td>
</tr>
</tbody>
</table>

ᵃ For the major diastereomer

The scope of this reaction was further extended to the reactions of (152) with some other commercially available organoboronic acids in the presence of BF₃·Et₂O (Scheme 4.48). The results were summarized in Table 4.14.
Scheme 4.48

Reagents BF₃·Et₂O (4 equiv), RB(OH)₂, CH₂Cl₂, 0 °C to rt.

Table 4.14: Addition of some other organoboronic acids to the

N-acyliminium ion derived from (152)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R (equiv)</th>
<th>Time (h)</th>
<th>Yield of (157) (%)</th>
<th>Cis/trans (157)</th>
<th>J₄,₅⁺ (Hz)</th>
<th>Yield of (158) (%)</th>
<th>d.r (158)</th>
<th>J₄,₅⁺ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>14</td>
<td>10 (157a)</td>
<td>1:1</td>
<td>7.0</td>
<td>80 (158a)</td>
<td>5/1</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.5</td>
<td>78 (157a)</td>
<td>4:1</td>
<td>7.0</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>24</td>
<td>15 (157b)</td>
<td>1:6</td>
<td>5.0</td>
<td>12 (158b)</td>
<td>1:1</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.5</td>
<td>30 (157c)</td>
<td>2:1</td>
<td>7.0</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

ᵃ For the major diastereomer
The use of 2-furanboronic acid afforded the product (157a) in 10% yield as a 1/1 mixture of diastereomers and the deprotected compound (158a) in 80% yield as a 5/1 mixture of cis- and trans-diastereomers after a 14 h reaction (Table 4.14, entry 1). By decreasing the reaction time to 1.5 h, this reaction gave (157b) as a 4/1 mixture of cis- and trans-diastereomers in 78% yield while no deprotected compound (158b) was recovered (Table 4.14, entry 2). These results suggested that compound (158a) was derived from the deprotection of the compound (157a). This was further supported by the fact that the diastereoselectivity of (157b) was almost identical to the combined diastereoselectivity of (157a+158a) (Table 4.14, entry 1). The use of 4-methoxyphenylboronic acid at rt for 20 h afforded the product (157c) as a 6/1 mixture of trans- and cis-diastereomers in 25% yield and (158c) in 15% yield as a 1:1 mixture of the diastereoisomers (Table 4.14, entry 3). Treatment of (152) with 2-thiopheneboronic acid in the presence of BF$_3$·Et$_2$O yielded 30% of the product (157c) as a 2/1 mixture of cis- and trans-diastereomers (Table 4.14, entry 4). The $J_{4,5}$ values shown in Table 4.14 clearly indicated the 4,5-stereochemistry of the resulting products (157a-157c and 158a). In Table 4.14, entries 1, 2, and 4, the 4,5-cis-stereoselectivity of (157a), (157c) and (158a) was deduced from their large $J_{4,5}$ values, 7.0, 7.0, and 7.5 Hz, respectively. The smaller $J_{4,5}$ value (5.0 Hz) indicated the 4,5-trans-stereoselectivity of the compound (157b) (Table 4.14, entry 3).
4.4 Addition of Organoboronic Acids to the N-acyliminium Ion Derived from Mono-O-TBS Protected Pyrrolidone (153)

The reaction of (153) with 2-furanboronic acid (2 equiv) in the presence of BF₃·Et₂O (4 equiv) was also examined. This reaction yielded the product (159) in 28% yield as a 3.5/1 mixture of diastereomers after 5 h (Scheme 4.49). The large $J_{4,5}$ value (8.0 Hz) for the major diastereomer suggested the cis-diastereochemistry of (159). In order to confirm this, (157a) and (159) were separately hydrolyzed to form (160’) and (160’’) for comparison purposes. Treatment of (157a) and (159) with 10% HCl in the presence of MeOH at RT for 24 h afforded the products (160’) and (160’’), respectively, both in 100% yield as white crystals. The success of their individual hydrolysis was indicated by the disappearance of the signals of their TBS groups in their $^1$H NMR spectra. The $^1$H NMR signals for the major isomers of the two hydrolyzed products (160’) and (160’’) were exactly identical, which confirmed the cis-stereochemistry of (159). Recrystallization of (160’) successfully afforded >95% pure cis-diastereosomer (160), of which the corresponding $^1$H NMR spectrum is shown below.
Figure 4.2 $^1$H NMR (500 MHz, CDCl$_3$) of cis-$(160)$

Please see print copy for Figure 4.2
**Scheme 4.49**

Reagents:
- a: BF₃·Et₂O (4 equiv), 2-furanboronic acid (2 equiv), CH₂Cl₂, 0 °C to rt, 5 hrs, 28%;
- b: MeOH, 10% HCl, RT, 24 h, 100%;
- c: MeOH, 10% HCl, RT, 24 h, 100%;
- d: recrystallization from EtOAc.
4.5 Addition of Some Other Electronic Rich Compounds to the
\( N \)-acyliminiun Ion Derived from the Bis-\( O \)-TBS Protected
Pyrrolidone (152)

The reactions of (152) with styrene, furan and benzofuran catalyzed by
\( BF_3 \cdot Et_2O \) were investigated in this study. The use of styrene did not afford
any desired product (154) even after an overnight reaction, which indicated
that either styrene was not as reactive toward (152) as \( trans \)-vinylphenyl
boronic acid or it was more readily polymerized. Treatment of (152) with
furan gave compound (157a) in 75% yield after a 40 min reaction. Notably,
a much better diastereoselectivity (\( cis / trans = 8:1 \)) of (157a) was obtained
in comparison with the product (157a) recovered from the reaction of (152)
with 2-furanboronic acid. When this reaction was prolonged to 3 h, a large
amount of (158a) (70%), from deprotection of (157a), together with a small
amount of (157a) (10%) were obtained as a 9/1 and 1/1 mixture of
diastereomers, respectively. The use of benzofuran yielded 55% of the
product (161) as a 7/1 mixture of diastereomers. The characteristic signal of
H-7 at \( \delta \) 6.56 (1H, s) in the \(^1\)H NMR spectrum,\(^{58}\) indicated addition had
occurred at C-7 and not at C-6 of the benzofuran ring and supported the
suggested structure of (161). The 4,5-\( cis \)-stereochemistry of (161) was
deduced from the large \( J_{4,5} \) value (7.5 Hz) for the major isomer.
Scheme 4.50

Reagents: a: BF₃·Et₂O (4 equiv), styrene (3 equiv), CH₂Cl₂, 0 °C to rt, 14 h, 0%; b: BF₃·Et₂O (4 equiv), furan (3 equiv), CH₂Cl₂, 0 °C to rt, 40 min, 75%; c: furan (3 equiv), CH₂Cl₂, 0 °C to rt, 3 h, 70% for (157a) and 10% for (158a); d: benzofuran (3 equiv), CH₂Cl₂, 0 °C to rt, 12 h, 55% for (161).
4.6 Preparation of $O$-benzylated Pyrrolidones

Based on the satisfactory results obtained above, we next investigated the analogus reactions of $O$-benzylated pyrrolidones with boronic acids in the presence of BF$_3$·Et$_2$O. In this study, the bis-$O$-benzyl pyrrolidone (164) and mono-$O$-benzylpyrrolidone (165) were prepared as the starting materials.

Initially, preparation of the $O$-benzyl pyrrolidones (164) and (165) was attempted by benzylation of the pyrrolidone (149) followed by reduction of the resulting $O$-benzylated products (162) and (163) with NaBH$_4$, using a similar strategy described above for the synthesis of $O$-TBS-protected pyrrolidones. Scheme 4.51 shows the proposed synthetic routes.
Scheme 4.51

Reagents a: NaH (2 equiv), PhCH\textsubscript{2}Br (2 equiv), DMF, rt, 24 h; b: NaH (1 equiv), PhCH\textsubscript{2}Br (1 equiv), DMF, RT 24 h; c: NaBH\textsubscript{4}, MeOH.

The preparation of (162) was investigated first, following the same procedure reported by Inouye.\textsuperscript{59} Treatment of (152) with NaH (2 equiv) at 0 °C in DMF for 15 min followed by the addition of benzylbromide (4 equiv) with stirring for 24 h at rt gave none of the desired product (162) but the undesired compound (166) in 15% yield (Scheme 4.52). Compound (166) was indicated from analysis of its \textsuperscript{1}H NMR spectrum with the following signals, including the aromatic protons at δ 7.50-7.22 (10H, m, ArH), the olefinic proton at δ 5.42 (1H, s, H-3) and the benzyl signals at δ 5.12 (2H, s,
OCH$_3$Ph) and 4.65 (2H, s, NCH$_2$Ph). The structure of (166) was further confirmed by an ion at $m/z$ 294 for MH$^+$ (100%) in the ESI$^+$-mass spectrum.

A possible mechanism for the formation of (166) is shown in **Scheme 4.52**, where the proton H-3, on the initially produced benzylated pyrrolidone (162), was removed by NaH and the newly formed enolate intermediate (162') subsequently gave the product (166) by β-elimination of a benzyoxy group. The proposed mechanism was supported by a recovery of PhCH$_2$OH from the reaction mixture after quenching with H$_2$O.

**Scheme 4.52**

Preparation of (163) was also attempted as shown in **Scheme 4.53**. Treatment of (149) with 1 equiv of NaH and 1 equiv of PhCH$_2$Br in the presence of dry DMF at RT for 12 h, gave 10% of the desired product (163) together with 13% of the elimination compound (166). For compound
(163), the $^1$H NMR spectrum clearly showed the correct structure with signals of the OCH$_2$Ph at $\delta$ 5.00 (1H, d, $J$ 11.7 Hz) and 4.84 (1H, d, $J$ 11.7 Hz) and the broad OH signal at $\delta$ 3.48 (1H, s). Its structure was further confirmed by an ion at $m/z$ 312 for MH$^+$ (100%) in the ESI$^+$-mass spectrum.

**Scheme 4.53**

Reagents NaH (1 equiv), PhCH$_2$Br (1 equiv), DMF, rt, 12 h, 10% for (163) and 13% for (166).

The unsuccessful benzylation of (149) indicated that the preparation of (164) and (165) could not be achieved via the proposed routes described above. Hence, we had to turn our attention to another method to achieve this goal. The newly modified routes are shown in **Scheme 4.54**.

Benzylation of diethyl L-tartrate (167) was achieved to give the benzylated products (168) and (169).$^{59}$ Treatment of (167) with 2 equiv of NaH and 4 equiv of PhCH$_2$Br in the presence of dry DMF at rt for 6 h gave the bis-O-benzylated product (168) in an excellent yield (98%). The appearance of the aromatic signals at $\delta$ 7.29-7.25 (15H, m, ArH) and
signals for two of identical OCH\textsubscript{2}Ph groups at $\delta$ 4.86 (2H, d, $J$ 12 Hz AB system) and 4.45 (2H, d, $J$ 12 Hz AB system) in the $^1$H NMR spectrum clearly indicated compound (168) had been formed. All the $^1$H NMR peaks were consistent with that reported in the literature.\textsuperscript{60} Similarly, by reducing the amount of NaH and PhCH\textsubscript{2}Br to 1 equiv under the same conditions, the mono-O-benzylated product (169) was isolated in 70% yield together with 10% of (168). The product (169)\textsuperscript{61} was confirmed by its characteristic $^1$H NMR signals, including the aromatic protons at $\delta$ 7.41-7.32 (10H, m), the OCH\textsubscript{2}Ph signals at $\delta$ 4.86 (1H, d, $J$ 12 Hz) and 4.42 (1H, d, $J$ 12 Hz) and an ion at $m/z$ 297 for MH\textsuperscript+ (100%) in the ESI\textsuperscript{+}-mass spectrum. By treatment with 10% NaOH in methanol at RT for 24 h, the benzylated compounds (168) and (169) were hydrolyzed to the dicarboxylic acids of (170) and (171) respectively in 100% yield. The structures of these compounds were easily confirmed by the disappearance of the signals for the ethyl groups in the $^1$H NMR spectrum. By heating (170) and (171) at reflux with BnNH\textsubscript{2} in xylene for 20 h under Dean-Stark conditions, the pyrrolidones (162) and (163) were recovered in 60% and 70% yield, respectively. The success of the cyclization of (170) and (171) was clearly indicated by the appearance of the signals for benzyl groups (NCH\textsubscript{2}Ph) at $\delta$ 42.5 for (162) and at $\delta$ 42.6 for (163) in the $^{13}$C NMR spectra. The structure of the two compounds (162) and (163) were further confirmed by an ion at $m/z$ 402 for MH\textsuperscript+ (100%) and an ion at $m/z$ 312 for MH\textsuperscript+ (100%) in their ESI\textsuperscript{+}-mass spectra, respectively.
By treatment with NaBH₄ in MeOH at –20 °C for 30 min, pyrrolidone (162) was reduced to the product (164) in 70% yield. The ¹H NMR spectrum of compound (164) was consistent with that was reported.⁶² An approximate 2/1 mixture of the products (165a) and (165b) resulted from the reduction of (163). The ¹H NMR spectrum of these compounds was quite complicated, especially in the range of between δ 4.0-5.0, which did not provide any clear information about the structures of (165a) and (165b). Evidence for the formation of (165a) and (165b) came from the reaction of this mixture with 2-furanboronic acid. This will be discussed later in this chapter.
Scheme 4.54

Reagents a: NaH (2 equiv), PhCH$_2$Br (4 equiv), DMF, rt, 6 h, 98%. b: NaH (1 equiv), PhCH$_2$Br (1 equiv), DMF, rt, 6 h, 70%. c: NaOH (10%), MeOH, rt, 24 h, 100%. d: NaOH (10%), MeOH, rt, 24 h, 100%. e: PhNH$_2$, xylene, reflux, 20 h, 60%. e: PhNH$_2$, xylene, reflux, 60%, 20 h, 70%. g: NaBH$_4$, MeOH, -20°C, 70%. h: NaBH$_4$, MeOH, -20°C, 75%.
4.7 Addition of Organoboronic Acids to the N-acyliminium Ion Derived from Bis-O-benzylpyrrolidone (164)

With the starting materials (164) and (165a+165b) in hand, addition of trans-vinylphenylboronic acid to these hemi-aminals was investigated. Treatment of (164) with BF$_3$·Et$_2$O (3 equiv) and trans-vinylphenyl boronic acid (3 equiv) in dry CH$_2$Cl$_2$ at 0 °C for 14 h gave the desired adduct (172) in 46% yield and as a 2.3:1 mixture of diastereoisomers. The product (172) was indicated by the appearance of the olefinic signals for the major isomer at δ 6.49 (1H, d, $J$ 15.5 Hz) and δ 5.87 (1H, dd, $J$ 15.5, 9.0 Hz) and for the minor isomer at δ 6.45 (1H, d, $J$ 16.0 Hz) and 6.06 (1H, dd, $J$ 15.5 9.5 Hz) in the $^1$H NMR spectrum. The structure of (172) was further confirmed by an ion at $m/z$ 490 for MH$^+$ (100%) in the ESI$^+$-mass spectrum. The 4,5-trans-stereochemistry for the major isomer was deduced from its relatively small coupling constant ($J_{4,5} = 6.0$ Hz) compared with that of the minor isomer ($J_{4,5} = 8.0$ Hz).

**Scheme 4.55**

![Scheme 4.55]

**Reagents** BF$_3$·Et$_2$O (3 equiv), PhCH=CHB(OH)$_2$ (3 equiv), CH$_2$Cl$_2$, 0 °C to RT, 14 h, 46%.
In order to optimize the yield and diastereoselectivity, the reaction was repeated under different conditions, which were shown in the following Table 4.15.

**Table 4.15: Addition of trans-vinylphenyl boronic acid (3 equiv) to the N-acyliminium ion from (164)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>BF\textsubscript{3}·Et\textsubscript{2}O (equiv)</th>
<th>Time (h)</th>
<th>Yield of (172) (%)</th>
<th>trans/cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>4</td>
<td>24</td>
<td>48</td>
<td>2.3/1</td>
</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>5</td>
<td>15</td>
<td>47</td>
<td>2.3/1</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>4</td>
<td>15</td>
<td>28</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>MeNO\textsubscript{2}</td>
<td>4</td>
<td>15</td>
<td>33</td>
<td>2:1</td>
</tr>
</tbody>
</table>

Table 4.15, entries 1-2 shows that both the yield (47-48%) and the diastereoselectivity (2.3/1) were not significantly affected by either increasing the amount of BF\textsubscript{3}·Et\textsubscript{2}O or prolonging the reaction time when compared to the results in Scheme 4.56. However, the yield and diastereoselectivity were quite affected by the nature of the solvent. The use of MeNO\textsubscript{2} gave (172) in 33% yield as a 2/1 mixture of trans- and cis-diastereomers while the use of MeCN afforded a 1/1 mixture of these diastereomers in 28% yield (Table 4.15, entries 3-4). These results indicated that CH\textsubscript{2}Cl\textsubscript{2} was the best solvent.
We next investigated the reaction of other organoboronic acids with the bis-\(O\)-benzylpyrrolidone (164) catalyzed by \(\text{BF}_3\cdot\text{Et}_2\text{O}\) in \(\text{CH}_2\text{Cl}_2\). The results are summarized in Table 4.16.

**Scheme 4.56**

\[
\begin{align*}
\text{BnO} & \quad \text{O} & \quad \text{BnO} \\
\text{N} & \quad \text{Ph} & \quad \text{O} \\
\text{OH} & \quad \text{R} \quad \text{OH} \\
\text{Ph} & \quad \text{BnO} & \quad \text{OBn} \\
\text{O} & \quad \text{N} & \quad \text{Ph} \\
\end{align*}
\]

**Table 4.16: Addition of boronic acids to the \(N\)-acyliminium ion from bis-\(O\)-benzylpyrrolidone (164)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>RB(OH)(_2)</th>
<th>Amount (equiv) of RB(OH)(_2)</th>
<th>Yield of (173) (%)</th>
<th>cis/trans</th>
<th>(J_{4,5}) for (173) (Hz) (Major isomer)</th>
</tr>
</thead>
</table>
| 1     | 5        | \[
\begin{array}{c}
\text{Ph} \\
\text{BnO} \\
\end{array}
\] | 3                | 95 (173\(_a\))   | 4/1                  | 7.0                      |
| 2     | 20       | \[
\begin{array}{c}
\text{Ph} \\
\text{BnO} \\
\end{array}
\] | 2                | 65 (173\(_b\))   | 6/1                  | 7.0                      |
| 3     | 20       | \[
\begin{array}{c}
\text{MeO} \\
\text{B(OH)}_2 \\
\text{OMe} \\
\end{array}
\] | 3                | 62 (173\(_c\))   | 1/1\(^a\)            | ----                    |

\(^a\) The \(J_{4,5}\) value for the trans- and cis-stereoisomers of (173\(_c\)) are 6.0 and 7.5 Hz, respectively.
The use of 2-furanboronic acid gave the product (173a) as a 4:1 mixture of two diastereoisomers in excellent yield (95%) after a 5 h reaction (Table 4.16, entry 1). A moderate conversion (65%) of (173b) with a good distereoseletivity (d.r. = 6:1) was achieved after an overnight reaction using 2-thiopheneboronic acid (Table 4.16, entry 2). An attempt to the use of 3,4-dimethoxyphenylboronic acid afforded a 1:1 diastereomeric mixture of the product (173c) in 62% yield (Table 4.16, entry 3). The 4,5-\textit{cis}-diastereochemistry of the products (173a) and (173b) was deduced from their coupling constant ($J_{4,5}$) for the major diastereomer. Although the coupling constant for both isomers could not be observed due to peak overlap, the relatively large $J_{4,5}$ value (7.0 Hz) for the major isomers of (173a) and (173b) indicated their 4,5-\textit{cis}-stereochemistries.

4.8 Addition of Organoboronic Acids to the N-acyliminium Ion Derived from Mono-O-benzylpyrrolidone (165)

The reaction of (165a+165b) with \textit{trans}-vinylphenyl boronic acid by treatment of BF$_3$·Et$_2$O in CH$_2$Cl$_2$ was examined initially. This reaction resulted in none of the desired products (174a) or (174b) and a large amount of starting material (165) (Scheme 4.57). Notably, no boronic ester (175) was obtained after column chromatography. A possible reason for this is that the boronic ester (175) was formed in the reaction but was more sensitive to hydrolyze compared with the boronic ester (156) and hence
(175) was hydrolyzed during our chromatography process to give (165a).

**Scheme 4.57**

\[
\begin{align*}
\text{BnOH} & \quad \text{O} & \quad \text{OH} \\
\text{N} & \quad \text{OH} & \quad \text{O} \\
\text{Ph} & \quad \text{B(OH)}_2 & \\
\text{(165a)} & \quad + & \quad \text{B(OH)}_2 \\
\text{HO} & \quad \text{OBn} & \quad \text{O} \\
\text{N} & \quad \text{O} & \quad \text{Ph} \\
\text{HO} & \quad \text{OBn} & \quad \text{O} \\
\text{N} & \quad \text{O} & \quad \text{Ph} \\
\text{Ph} & \quad \text{B(OH)}_2 & \\
\text{(165b)} & \quad \rightarrow & \quad \text{(175)} \\
\text{(174a)} & \quad \rightarrow & \quad \text{(174b)} \\
\end{align*}
\]

*Reagents* BF₃·Et₂O (3 equiv), boronic acids, CH₂Cl₂, 0 °C to RT, 14 h.

Treatment of (165a+165b) with 2-furanboronic acid in the presence of BF₃·Et₂O yielded 28% of (176a) and 10% of (176b), as 10/1 and 9/1 mixtures of diastereomers, respectively (**Scheme 4.58**). The two compounds (176a) and (176b) were indicated by their individual OCH₂Bn resonance in their ¹H NMR spectra, where the one with the more downfield shift at δ 5.19 (1H, d, J 12.0 Hz, OCHHPh) and 4.86 (1H, d, J 12.0 Hz, OCHHPh) was from (176a) and the other more upfield at δ 4.57 (2H, s, OCH₂Ph) was from (176b). The structures of (176a) and (176b) were further confirmed by ions at m/z 346 for MH⁺ (100%) in their individual ESI⁺-mass spectra. For compound (176b), the 4,5-*cis*-stereochemistry was deduced from its large $J_{4,5}$ (8.0 Hz) value. For compound (176a), due to the fact that $J_{4,5}$ value was 6.5 Hz, and in between that for typical *cis* and *trans*...
isomers (Table 4.16), the stereochemistry of the major isomer was uncertain.

**Scheme 4.58**

Reagents BF₃·Et₂O (3 equiv), 2-furan boronic acid (2 equiv), CH₂Cl₂, 0 °C to rt, 12 h, 28% for (176a) and 10% for (176b).

4.9 Addition of some other electronic rich compounds to the N-acyliminium ion derived from (164)

The reactions of styrene, furan and benzofuran with (164) in the presence of BF₃·Et₂O were examined, respectively. Treatment of (164) with styrene and BF₃·Et₂O did not afford the desired product (172) and resulted in a large amount of the starting material (164). The use of furan gave the product (173a) in good yield (86%) as a 8/1 mixture diastereomers after a 15 h reaction. Treatment of (163) with benzofuran in the presence of BF₃·Et₂O affored the product (177) in excellent yield (95%) as a 5/1
mixture of diasteromers after a 15 h reaction. The characteristic signal of H-7 at 6.62 ppm (1H, s) in the \(^1\)H NMR spectrum, suggested the structure of \(177\).\(^{58}\) The major isomers of \(173a\) and \(177\) were expected to have the 4,5-cis-diastereochemistry due to their relatively large coupling constants \(J_{4,5}\) (7.0 and 7.5 Hz, respectively. The stereochemistry of the products \(173a\) and \(177\) would need to be further confirmed by X-ray analysis or other methods.

Scheme 4.59

\[\text{Reagents a: BF}_3\cdot\text{Et}_2\text{O (3 equiv), styrene (3 equiv), CH}_2\text{Cl}_2, 0 \, ^\circ\text{C to rt, 20 h}. \text{ b: BF}_3\cdot\text{Et}_2\text{O (3 equiv), furan (3 equiv), CH}_2\text{Cl}_2, 0 \, ^\circ\text{C to rt, 20 h, 86\% for (173a). c: BF}_3\cdot\text{Et}_2\text{O (3 equiv),} \]
benzofuran (3 equiv), CH₂Cl₂, 0 °C to rt, 20 h, 95% for (177).

4.10 Summary

The reactions of the 3,4-bis-\textit{O}-protected pyrrolidinone hemi-aminals (152) and (164) with vinyl and arylboronic acids and styrene, furan and benzofuran has been examined (Scheme 4.60). These results are presented in Table 4.17, showing the results of the best yielding reactions only. It can be seen that reactions of (152) with (E)-phenylvinylboronic acid (Table 4.17, entry 1) and 4-methoxyphenylboronic acid (Table 4.17, entry 4) favoured formation of the \textit{trans}-products with good diastereoselectivities (dr = 1/6 and 1/8). Whereas the 2-furan- and 2-thiopheneboronic acids both favoured the \textit{cis}-products (Table 4.17, entries 2 and 3), however the diastereoselectivity was lower (d.r. = 4/1 and 2/1). Higher \textit{cis}-diastereoselectivities (d.r. = 8/1 and 7/1) were observed in the reactions of (152) with furan and benzofuran (Table 4.17, entries 6 and 7). Similar results were seen from the reactions of (164) with these nucleophiles (Table 4.17, entries 8-14). However the reaction with (E)-phenylvinylboronic acid (Table 4.17, entry 8) was less \textit{trans}-selective (\textit{cis}/\textit{trans} = 1/2.3) and the reaction with 2-thiopheneboronic acid was more \textit{cis}-diastereoselective (Table 4.17, compare entries 3 and 10).
Scheme 4.60

\[ \text{POOP} \quad \text{N} \quad \text{POOP} \]

\[ \text{O} \quad \text{Bn} \quad \text{O} \quad \text{Bn} \]

\[ \text{CH}_2\text{Cl}_2 \quad \text{BF}_3\cdot\text{Et}_2\text{O} \]

\[ \text{Ph} \quad \text{B(OH)}_2 \quad \text{S} \quad \text{B(OH)}_2 \]

\[ \text{MeO} \quad \text{B(OH)}_2 \quad \text{MeO} \quad \text{B(OH)}_2 \]

\[ \text{R(OH)}_2 \quad \text{Ph} \quad \text{B(OH)}_2 \quad \text{B(OH)}_2 \]

\[ \text{MeO} \quad \text{Ph} \quad \text{B(OH)}_2 \quad \text{MeO} \quad \text{OMe} \]

\[ \text{R} = \text{Ph} \quad \text{B(OH)}_2 \quad \text{Ph} \quad \text{B(OH)}_2 \]

(152) \( P = \text{TBS} \)

(164) \( P = \text{Bn} \)

\[ \begin{align*}
(a) & \quad (b) & \quad (c) \\
(d) & \quad (e) & \quad (f) & \quad (g) & \quad (h)
\end{align*} \]
Table 4.17 Reaction of bis-\(O\)-TBS protected pyrrolidone (152) and bis-\(O\)-benzylpyrrolidone (164) with boronic acids and nucleophilic reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile R(OH)(_2) or RH</th>
<th>Substrate</th>
<th>Product, yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>(152)</td>
<td>(154), 60</td>
<td>1/8</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>(152)</td>
<td>(157a), 78</td>
<td>4/1</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>(152)</td>
<td>(157c), 30</td>
<td>2/1</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>(152)</td>
<td>(157b), 15</td>
<td>1/6</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>(152)</td>
<td>(154), 0</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>g</td>
<td>(152)</td>
<td>(157a), 75</td>
<td>8/1</td>
</tr>
<tr>
<td>7</td>
<td>h</td>
<td>(152)</td>
<td>(161), 55</td>
<td>7/1</td>
</tr>
<tr>
<td>8</td>
<td>a</td>
<td>(164)</td>
<td>(172), 46</td>
<td>1/2.3</td>
</tr>
<tr>
<td>9</td>
<td>b</td>
<td>(164)</td>
<td>(173a), 95</td>
<td>4/1</td>
</tr>
<tr>
<td>10</td>
<td>c</td>
<td>(164)</td>
<td>(173b), 65</td>
<td>6/1</td>
</tr>
<tr>
<td>11</td>
<td>e</td>
<td>(164)</td>
<td>(173c), 62</td>
<td>1/1</td>
</tr>
<tr>
<td>12</td>
<td>f</td>
<td>(164)</td>
<td>(172), 0</td>
<td>--</td>
</tr>
<tr>
<td>13</td>
<td>g</td>
<td>(164)</td>
<td>(173a), 86</td>
<td>8/1</td>
</tr>
<tr>
<td>14</td>
<td>h</td>
<td>(164)</td>
<td>(177), 95</td>
<td>5/1</td>
</tr>
</tbody>
</table>

The trans-diastereomeric products would be expected based on steric grounds with nucleophilic attack occurring anti to the 4-OTBS or OBn substituent (Scheme 4.61). The reasons for the formation of mainly
cis-products from the reactions with electron rich aromatic heterocyclic compounds, however, is more difficult to understand. It should be noted that the stereochemical assignments of these products are only based on NMR coupling constants and X-ray structures of these compounds would be required before further conclusions can be made.

Scheme 4.61
Chapter 5: Conclusions

In this thesis we have examined the potential of the L-proline catalysed Mannich reaction between cinnamaldehyde, \( p \)-anisidine and \( O \)-benzylglycolaldehyde. The Mannich product from this reaction would seem a useful starting material to prepare potential glycosidase inhibitors. Unfortunately these reactions were low yielding and poorly diastereoselective with the model compound propanal and did not work with the desired aldehyde \( O \)-benzylglycosaldehyde. The stereochemical outcomes of these reactions using NMR analysis were not certain. Future work would require X-ray crystallographic studies to confirm the product relative stereochemistries. This project was thus abandoned and a second project was studied.

In this second project the reactions of the 3,4-bis-\( O \)-protected pyrrolidinone hemi-aminals (152) and (164) with vinyl and arylboronic acids and styrene, furan and benzofuran were examined. The reactions of (152) with \((E)\)-phenylvinylboronic acid and 4-methoxyphenylboronic acid favoured formation of the \( trans \)-products with good diastereoselectivities (d.r. = 1/6 and 1/8). Whereas the 2-furan- and 2-thiopheneboronic acids both favoured the \( cis \)-products with a lower diastereoselectivity (d.r. 4/1 and 2/1). Higher \( cis \)-diastereoselectivities (d.r. = 8/1 and 7/1) were observed in the reactions of (152) with furan and benzofuran. Similar results were seen
from the reactions of (164) with these nucleophiles. The stereochemical assignments of these products were only based on NMR coupling constants ($J_{4,5}$). X-ray structures of these compounds would be required in the future to confirm these assignments.

The reaction of (152) with furan was found to be highly cis-diastereoselective and the major diastereomer could be readily obtained as a crystalline solid after removal of the TBS protecting groups. This compound (157a) would be a useful starting material for the synthesis of functionalized pyrrolidinones and other potential glycosidases inhibitors. The furan ring could be readily oxidatively cleaved to a carboxylic acid group which would be a useful handle to prepare bicyclic target molecules (Scheme 4.62).

**Scheme 4.62**
Chapter 6: Experimental

6.1 General Experimental

Nuclear Magnetic Resonance Spectroscopy

$^1\text{H NMR spectra}$

These were obtained at 500 MHz on a Varian spectrometer. Peak frequencies were referenced relative to the 7.26 ppm chemical shift signal of CHCl$_3$, or the residual proton signal of the deuterated solvent used. Resonances were assigned as follows: Chemical shift (number of protons, multiplicity, coupling constant(s), assigned proton(s)). Multiplicities are reported by the convention: s (singlet), d (doublet), t (triplet), q (quartet), p (pentuplet), m (multiplet), br (broad). Uncertainties: Chemical shift ($\pm 0.01$ ppm), coupling constants ($\pm 0.1$ Hz).

$^{13}\text{C NMR spectra}$

These were obtained at 125 MHz on a Varian spectrometer. Peak frequencies were referenced relative to the 77.0 ppm chemical shift signal of CDCl$_3$ or the carbon signal of the deuterated solvent used. Resonances were assigned as follows: Chemical shift (carbon type, assigned carbon(s)). Carbon type is reported by the convention: s (quartenary), d (methine), t (methylene), q (methyl). These assignments were based on DEPT spectra. Uncertainties: Chemical shift ($\pm 0.3$ ppm).
Chromatography

Column Chromatography
This was performed using Merck GF 254 flash silica gel (40-63 µm) packed by the slurry method. Small scale separations (<2.0 g) were performed using a 50 mm diameter column, each with the stated solvent system.

Thin Layer Chromatography
This was performed using aluminium-backed Merck sorbent silica gel. Compounds were detected under a 254 nm ultraviolet lamp if applicable, or by staining with an acidified, aqueous solution of ammonium molybdate and cerium (IV) sulfate, followed by development with a 1400 W heat gun.

Melting Points
These were obtained using a Gallenkamp MF-370 capillary tube melting point apparatus and are uncorrected. Uncertainties in the values quoted is ±2 0.

Polarimetry
Specific rotations were measured using a 10 mm or a 50 mm cell, and a Jasco DIP-370 digital polarimeter. They are reported by the following convention: specific rotation \([10^{-1} \text{ deg.cm}^3 \cdot \text{g}^{-1}]\) (concentration, solvent). Uncertainties in the values quoted is ±5 %.
Mass Spectrometry

These were obtained on a VG Quatro mass spectrometer (low resolution), and on a VG Autospec mass spectrometer (high resolution).

Reagents and Solvents

Anhydrous DMSO, NMP and CH$_2$Cl$_2$ were purchased from Sigma-Aldrich.

6.2 Synthesis Of Imines (64), (70), (71), (72) and (80)

6.2.1

(E)-4-Methoxy-N-((E)-3-phenylallylidene)benzenamine (64)

Cinnamaldehyde (2.64 g, 20.0 mmol) was added to a solution of freshly distilled p-anisidine (2.46 g, 20.0 mmol) in EtOH (40 mL). The mixture was stirred for 2 h at rt. The crude product was collected by filtration, washed with Et$_2$O and recrystallized at -20 °C from EtOH to afford imine (64) (3.79 g, 16 mmol, 80%) as yellow-green crystals. M.p. 113-115 °C (lit.$^{26}$, 122 °C). The NMR spectral data compared favourably with that in the literature.$^{26}$ $\delta$$_H$ (500 , CDCl$_3$) 8.28 (1H, d, $J$ 4.5 Hz, N=CH), 7.53-6.92 (11H, m, ArH and NCH-CH=CH), 3.83 (3H, s, OMe). $\delta$$_C$ (125 MHz, CDCl$_3$) 160.0 (N=CH), 158.3, 144.5, 135.60 (ArC) 142.85 129.2, 128.7, 128.6, 127.2, 122.1, 114.3, (ArCH and NCH-CH=CH), 55.4 (OCH$_3$). MS (ESI$^+$) $m$/z 238 (M+H)$^+$ 100%. HRMS (EI+) calcd.for C$_{16}$H$_{15}$NO (M$^+$) 237.1154; found 237.1136.
6.2.2

*(E)*-2-Methoxy-*N-*((E)-3-phenylallylidene)benzenamine (70)

Na$_2$SO$_4$ (1.5 g) was added to a solution of cinnamaldehyde (2.64 g, 20.0 mmol) and freshly distilled *o*-anisidine (2.46 g, 20.0 mmol) in Et$_2$O (30 mL). The reaction mixture was stirred at rt for 3 h. The residue was filtered and washed with Et$_2$O. The filtrate was evaporated in vacuum to a volume of 5 mL. Crystallization at -20 °C provided the product (70) (2.84 g, 12 mmol, 60%) as yellow crystals. M.p. 60-63 °C (lit.$^{26}$, 67 °C). The NMR spectral data compared favourably with that in the literature.$^{26}$ δ$_H$ (500 MHz, CDCl$_3$) 8.28 (1H, d, *J* 8.7 Hz, N=CH), 7.53-6.95 (11H, m, ArH and NCH-CH=CH), 3.90 (3H, s, OCH$_3$). δ$_C$ (125 MHz, CDCl$_3$) 162.1 (N=CH), 152.7, 141.2, 137.5 (ArC), 143.7 129.5 129.1 128.9 127.5 126.99 120.93 119.41 111.22 (ArCH and NCH-CH=CH), 55.75 (OCH$_3$). MS (ESI$^+$) $m/z$ 238 (M+H)$^+$ 100%. HRMS (EI+) calcd. for C$_{16}$H$_{15}$NO (M$^+$) 237.1154; found 237.1148.
6.2.3

(E/Z)-Phenyl-N-((E)-3-phenylallylidene)methanamine (71)

Na₂SO₄ (1.5 g) was added to a solution of cinnamaldehyde (2.64 g, 20.0 mmol) and benzylamine (2.14 g, 20.0 mmol) in CH₂Cl₂ (30 mL). The reaction mixture was heated at reflux for 20 h and the title compound (71) (4.24 g, 19.2 mmol, 80%). (E)/(Z) = 2/1) was obtained as a brown oil. The NMR spectral data compared favourably with that in the literature.²⁷ δ_H (500 MHz, CDCl₃) (Z)-isomer: 7.91 (1H, d, J 8.0 Hz, N=CH) 7.38-6.82 (12H, m, 10ArH, C₆H₅-CH=CH), 4.71 (2H, s, NCH₂C₆H₅). (E)-isomer: 7.91 (1H, d, J 7.9 Hz, N=CH) 7.38-6.82 (12H, m, 10ArH, C₆H₅-CH=CH), 4.82 (2H, s, NCH₂C₆H₅). MS (ESI⁺) m/z 222 (M+H)⁺ 70%. HRMS (EI⁺) calcd. for C₁₆H₁₅NO (M⁺) 221.1204; found 222.1233.

6.2.4

(E)-2-Methyl-N-((E)-3-phenylallylidene)propan-2-amine (72)

Cinnamaldehyde (2.64 g, 20.0 mmol) was added to tert-butylamine (1.46 g, 20.0 mmol) in CH₂Cl₂ (20 mL). The mixture was heated at reflux for 2 h. The residue was filtered, washed with Et₂O and the filtrate was cooled to recrystallised at -20°C to afford the imine (72) (1.69g, 18 mmol, 45%) as white crystals. M.p. 117-120 °C. The NMR spectral data
compared favourably with that in the literature.$^{28}$ $\delta_H$ (500 MHz, CDCl$_3$) 7.52-6.64 (7H, m, 5ArH, NCH-CH=CH), 1.36 (9H, s, 3CH$_3$). $\delta_C$ (125 MHz, CDCl$_3$) 141.1 (N=CH), 136.1 (ArC), 129.5, 129.2, 128.4, 128.1 126.1 (ArCH and NCH-CH=CH), 60.0 (C(CH$_3$)$_3$), 28.8 (C(CH$_3$)$_3$), MS (ESI$^+$) $m/z$ 188 (M+H)$^+$ 100%. HRMS (EI+) calcd. for C$_{13}$H$_{17}$N (M$^+$) 187.1361; found 187.1359.

6.2.5

(E)-4-Methoxy-N-((E)-3-(4-nitrophenyl)allylidene)benzenamine (80)

\[
\begin{align*}
\text{MeO} & \quad \text{NO}_2 \\
\text{MeO} & \quad \text{NO}_2
\end{align*}
\]

$\text{p}$-Nitrocinnamaldehyde (3.54 g, 20.0 mmol) and $\text{p}$-anisidine (2.46 g, 20.0 mmol) were dissolved in EtOH (40 mL). The mixture was stirred for 2 h at rt. The crude product was filtered, washed with Et$_2$O and then recrystallized at -20°C to afford the imine (80) (5.36 g, 19 mmol, 95%) as yellow crystals. M.p. 120-122 °C. $\delta_H$ (500 MHz, CDCl$_3$) 8.33 (1H, d, $J$ 8.1 Hz, N=CH), 8.24-6.93 (10H, m, ArCH, NCH-CH=CH), 3.84 (3H, s, OCH$_3$). $\delta_C$ (500 MHz, CDCl$_3$) 159.2, 158.1, 148.0, 144.2, 142.3 (ArC and N=CH), 139.7, 133.1, 128.0, 124.5, 122.7, 114.7 (NCH-CH=CH, ArCH), 55.7 (OCH$_3$). MS (ESI$^+$) $m/z$ 283 (M+H)$^+$ 100%. HRMS (EI+) calcd. for C$_{16}$H$_{14}$N$_2$O$_3$ (M$^+$) 282.1004; found 282.0995.
6.3 L-Proline Catalysed Mannich Reactions

6.3.1

(E)-3-(4-Methoxyphenylamino)-2-methyl-5-phenylpent-4-en-1-ol (62)

The prepared imine (64) (0.237 g, 1.0 mmol) and L-proline (0.012, 0.1 mmol) were dissolved in anhydrous NMP (5 mL) and the mixture was cooled to -20 °C. Propanal (0.221 mL, 3.0 mmol) was than added and the reaction was kept at -20 °C for 48 h. The reaction was than quenched with distilled water and the organic materials were extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL) and dried over MgSO₄. After removal of the volatile materials under vacuum, the residue was dissolved in MeOH (3 mL), cooled to 0 °C and then treated with NaBH₄ (0.115 g, 3.0 mmol). The solution was stirred vigorously for 1 h and then quenched with distilled water. The crude product were extracted with EtOAc (3 × 20 mL), dried over MgSO₄ and concentrated under vacuum. Column chromatography (increasing polarity from 15% to 40% EtOAc in pet. sp as eluent) gave the title compound (62) (0.118 g, 0.50 mmol, 50%, d.r. = 4/1, Rf = 0.15, 30% EtOAc/pet. sp) as a brown oil. δH (500 MHz, CDCl₃) major isomer: 7.35-6.64 (9H, m, ArH), 6.52 (1H, d, J 15.9 Hz, H-5), 6.16 (1H, dd, J 15.5 6.9 Hz, H-4), 4.07 (1H, m, H-3), 3.73-3.68 (5H, m, CH₂OH, OCH₃), 3.04 (1H, s, OH), 2.11 (1H, m, H-2), 1.00 (3H, d, J 7.2 Hz,
CH₃). Minor isomer: 7.35-6.64 (9H, m, ArH), 6.45 (1H, d, J 15.6 Hz, H-5), 6.00 (1H, dd, J 15.6 7.5 Hz, H-4), 3.84 (1H, m, H-3), 3.73-3.64 (5H, m, CH₂OH, OCH₃), 3.04 (1H, s, OH), 1.95 (1H, m, H-2), 0.95 (3H, d, J 7.2 Hz, CH₃). δC (125 MHz, CDCl₃) major isomer: 152.7, 141.7, 137.1 (3ArC), 131.7 (C-5), 129.9 (C-4), 128.7, 127.7, 126.6, 116.0, 115.1 (9ArCH), 66.4 (CH₂OH), 60.2 (C-3), 56.0 (OCH₃), 40.0 (C-2), 12.9 (CH₃). Minor isomer (in part): 152.8, 141.2, 137.0 (3ArC), 131.9 (C-5), 129.9 (C-4), 128.7, 127.7, 126.6, 116.0, 115.1 (ArCH), 67.7 (CH₂OH), 62.8 (C-3), 55.9 (OCH₃), 40.2 (C-2), 14.3 (CH₃). MS (ESI⁺) m/z 298 (M+H)+ 100%. HRMS (EI+) calcd.for C₁₉H₂₃NO₂ (M⁺) 297.1728; found 297.1728.

6.3.2

(E)-3-(4-Methoxyphenyl)-5-methyl-4-styryl-1,3-oxazinan-2-one (63)

To a 25-mL round bottom flask containing the Mannich product (62) (128 mg, 0.432 mmol, d.r. = 4/1) purged with N₂ was added dry CH₂Cl₂ (5 mL) and Et₃N (0.065 mL, 0.043 mmol). To this solution was then added triphosgene (64 mg, 0.217 mmol) at 0 °C and the reaction was kept at 0 °C for 18 h. The reaction mixture was concentrated in vacuum and column chromatography (increasing polarity from 10% to 20% EtOAc in
pet. sp as eluent) gave the major isomer (50.3 mg, 0.162 mmol, 37.5%, $R_f = 0.45$, 12% EtOAc/pet. sp) and the minor isomer (17.4 mg, 0.054 mmol, 12.5%, $R_f = 0.48$, 12% EtOAc/pet. sp) as colourless oils.

The major isomer: $[\alpha]^{21}_D +1.2 \ (c \ 1.0, \ \text{CHCl}_3). \ \delta_H \ (500 \text{ MHz, CDCl}_3)$

7.35-6.92 (9H, m, ArH), 6.62 (1H, d, $J 15.5$ Hz, H-8), 6.08 (1H, dd, $J 15.5$ 9.5 Hz, H-7), 4.59 (1H, d, $J 9.5$ 9.5 Hz, H-4), 4.30 (1H, dd, $J 11.0$ 3.5 Hz, H-6a), 4.12 (1H, dd, $J 11.1$ 6.0 Hz, H-6b), 3.85 (3H, s, OCH$_3$), 2.48 (1H, m, H-5), 1.34 (3H, dd, $J 7.0$ Hz, CH$_3$). $\delta_C \ (125$ MHz, CDCl$_3$) 159.9 (CO), 136.0 (C-8), 150.7, 150.2, 135.8 (3ArC), 131.1, 130.1, 128.9, 128.7, 127.0, 114.7 (ArCH), 124.1 (C-7), 73.8 (C-6), 67.6 (C-4), 55.6 (OCH$_3$), 35.1 (C-5), 15.00 (CH$_3$). MS (ESI$^+$) $m/z$ 324 (M+H)$^+$ 90%. HRMS (EI$^+$) calcd.for C$_{20}$H$_{21}$NO$_3$ (M$^+$), 323.1516; found 323.1521.

The minor isomer: $[\alpha]^{22}_D +0.8 \ (c \ 1.0, \ \text{CHCl}_3) \ \delta_H \ (500 \text{ MHz, CDCl}_3)$

7.36-6.92 (9H, m, ArH), 6.62 (1H, d, $J 16.0$ Hz, H-8), 6.00 (1H, dd, $J 16.0$ 9.5 Hz, H-7), 4.60 (1H, dd, $J 11.0$ 4.0 Hz, H-6a), 4.56 (1H, d, $J 9.5$ 7.5 Hz, H-4), 4.43 (1H, dd, $J 11.0$ 6.0 Hz, H-6b), 3.85 (3H, s, OCH$_3$), 2.56 (1H, m, H-5), 0.97 (3H, dd, $J 7.5$ Hz, CH$_3$). MS (ESI$^+$) $m/z$ 324 (M+H)$^+$ 70%. HRMS (EI$+$) calcd.for C$_{20}$H$_{21}$NO$_3$ (M), 323.1516; found 323.1521.
Hydrolysis of syn-(63) and anti-(63)

To a mixture of MeOH (5 mL) and 10% NaOH solution (5 mL) was added syn-(63) (20 mg, 0.062). The mixture was stirred at 60 °C for 24 h and then quenched with a saturated solution of NaHCO₃ (10 mL). The product was extracted with EtOAc (3 × 20 mL) and the combined extracts were dried over MgSO₄ followed by removal of the solvent in vacuum. Syn-(62) (14.6 mg, 0.049 mmol, 80 %) was obtained as a brown oil. \([\alpha]^{21}_D +3.2 \ (c \ 1.3, \ \text{CHCl}_3)\).

By treatment of anti-(63) (10 mg, 0.031) with MeOH (5 mL) and 10% NaOH solution (5 mL) using the method above, anti-(62) (6.9 mg, 0.023 mmol, 75%) was obtained as a brown oil. \([\alpha]^{21}_D +2.1 \ (c \ 0.6, \ \text{CHCl}_3)\). The \(^1\text{H NMR}\) data for these compounds were the same as that reported above.

6.3.3

(\(E\))-3-(2-Methoxyphenylamino)-2-methyl-5-phenylpent-4-en-1-ol (76)

The title compound was prepared from the imine (70) (0.237 g, 1.0 mmol), propanal (0.221 mL, 3.0 mmol), L-proline (0.012, 0.1 mmol), NMP (5 mL), NaBH₄ (0.115 g, 3.0 mmol) and MeOH (3 mL) using the method described above for the synthesis of (62). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) gave the
title compound (0.083 g, 0.35 mmol, 35%, d.r. = 9/1, $R_f$ = 0.20, 30% EtOAc/pet. sp) as a yellow oil. $\delta_H$ (500 MHz, CDCl$_3$) major isomer: 7.47-6.60 (9H, m, ArH), 6.53 (1H, d, $J$ 16.2 Hz, H-5), 6.20 (1H, dd, $J$ 16.2, 6.0 Hz, H-4), 4.18 (1H, m, H-3), 3.87-3.83 (5H, m, CH$_2$OH, OCH$_3$), 2.17 (1H, m, H-2), 1.04 (3H, d, $J$ 7.2 Hz, CH$_3$). Minor isomer (in part): 7.47-6.60 (9H, m, ArH), 6.42 (1H, d, $J$ 16.2 Hz, H-5), 6.08 (1H, dd, $J$ 16.2, 6.0 Hz, H-4). $\delta_C$ (125 MHz, CDCl$_3$) major isomer 152.7, 141.8, 137.2 (3ArC), 131.2 (C-5), 130.1 (C-4), 128.7, 127.6, 126.6, 121.5, 117.0, 111.5, 109.8 (ArCH), 66.1 (CH$_2$OH), 58.1 (C-3), 55.7 (OCH$_3$), 40.5 (C-2), 12.7 (CH$_3$). MS (ESI$^+$) $m/z$ 298 (M+H)$^+$ 100%. HRMS (EI$^+$) calcd. for C$_{19}$H$_{23}$NO$_2$ (M$^+$) 297.1728; found 297.1735.

6.3.4

(E)-3-(4-Methoxyphenylamino)-2-methyl-5-(4-nitrophenyl)pent-4-en-1-ol (81)

The title compound was prepared from the imine (80) (0.282 g, 1.0 mmol), propanal (0.221ml, 3.0 mmol), L-proline (0.012, 0.1 mmol), NMP (5 mL), NaBH$_4$ (0.115g, 3.0 mmol) and MeOH (3 mL) using the method described above for the synthesis of (62). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) gave the
title compound (0.137 g, 0.4 mmol, 40%, d.r. = 2/1, \( R_f = 0.23 \), 30% EtOAc/pet. sp) as a brown oil. \( \delta_H \) (500 MHz, CDCl\(_3\)) major isomer: 8.20-6.65 (8H, m, ArH), 6.64 (1H, d, \( J 16.2 \) Hz, H-5), 6.30 (1H, dd, \( J 16.2, 6.0 \) Hz, H-4), 4.20 (1H, m, H-3), 3.90-3.75 (5H, m, CH\(_2\)OH, OCH\(_3\)), 2.18 (1H, m, H-2), 1.05 (3H, d, \( J 7.2 \) Hz, CH\(_3\)). Minor isomer: 8.20-6.65 (8H, m, ArH), 6.56 (1H, d, \( J 16.2 \) Hz, H-5), 6.26 (1H, dd, \( J 16.2, 6.0 \) Hz, H-4), 3.95 (1H, m, H-3), 3.90-3.75 (5H, m, CH\(_2\)OH, OCH\(_3\)), 2.05 (1H, m, H-2), 1.04 (3H, d, \( J 7.2 \) Hz, CH\(_3\)). \( \delta_C \) (125 MHz, CDCl\(_3\)) major isomer: 152.7, 147.0, 143.5, 141.4 (ArC), 135.5 (C-5), 129.6 (C-4), 127.1, 124.2, 111.5, 115.1 (8ArCH), 66.1 (CH\(_2\)OH), 59.5 (C-3), 55.9 (OCH\(_3\)), 40.0 (C-2), 12.7 (CH\(_3\)). Minor isomer: 153.1, 147.0, 143.4, 141.1 (4ArC), 135.4 (C-5), 129.8 (C-4), 127.1, 124.2, 116.3, 124.2 (8ArCH), 67.2 (CH\(_2\)OH), 62.0 (C-3), 55.9 (OCH\(_3\)), 40.2 (C-2), 14.3 (CH\(_3\)). MS (ESI\(^+\)) \( m/z \) 343 (M+H\(^+\)) 100%. HRMS (EI\(^+\)) calcd. for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_4\) (M\(^+\)) 342.1580; found 342.1576.

6.4 Synthesis of Pyrrolidinone Substrates

6.4.1

(3\(R\), 4\(R\))-1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione (149)

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{Ar} & \quad \text{Ar}
\end{align*}
\]

To a suspension of tartaric acid (2.00 g, 13.3 mmol) in xylene (40 mL) was added benzylamine (1.46 mL, 13.3 mmol). The mixture was heated at reflux in a
round bottom flask equipped with a Dean-Stark apparatus for 5 h. After cooling the reaction mixture, the residue was filtered and recrystallized from EtOH (20 mL) to give the title compound (2.35g, 10.6 mmol, 80%) as yellow crystals. M.p. 196-199°C (lit. 53, 200-201°C). \([\alpha]^2_{D} +125 \ (c \ 1.7, \ \text{CHCl}_3) \ (\text{lit.} \ 53, \ [\alpha]^2_{D} +136 \ (c \ 1.87, \ \text{CHCl}_3)). \) The NMR spectral data compared favourably with that in the literature.\(^5\text{3,54}\) \(\delta_{H} \ (500 \text{ MHz, CDCl}_3/\text{DMSO}) \ 7.35-7.2 \ (5\text{H, m, ArH}), \ 6.00 \ (2\text{H, s, br, 2OH}), \ 4.65 \ (2\text{H, s, 2CH}), \ 4.48 \ (2\text{H, s, OCH}_2\text{Ph}). \ \delta_{C} \ (125 \text{ MHz, CDCl}_3/\text{DMSO}) \ 174.3 \ (\text{CO}), \ 135.5 \ (\text{ArC}), \ 128.3, \ 127.9, \ 127.5 \ (\text{ArCH}), \ 74.7 \ (\text{CH}), \ 41.4 \ (\text{NCH}_2\text{Ph}). \ MS \ (\text{ESI}^+ \ m/z \ 222 \ (\text{M+H})^+ \ 40\%. \ HRMS \ (\text{ESI}^+) \ \text{calcd. for } C_{11}H_{12}NO_4 \ (\text{M+H})^+, \ 222.0761; \ \text{found} \ 222.0745.

6.4.2

\((4R,5R)-2\text{-Benzyl-4,5-bis(tert-butyldimethylsilyloxy)pyrrolidin-2,5-dione} \ (150)\)

The diol (149) (0.664 g, 3.00 mmol) and imidazole (1.331 g, 9.00 mmol) were dissolved in dry DMF (10 mL). The mixture was heated at 55°C for 48 h in a sealed tube and then poured into saturated NaHCO\(_3\) solution (20 mL). The product was extracted into CH\(_2\)Cl\(_2\) (3 \times 20 mL) and the combined extracts were dried over MgSO\(_4\), filtered and concentrated in vacuum. Column
chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) gave the title compound (1.316 g, 2.93 mol, 98 %, \( R_f = 0.78 \), 25% EtOAc/pet. sp) as a colorless oil. \([\alpha]^{25}_D +88 \) (c 3.78, CHCl₃) (lit.\(^{55}\), \([\alpha]^{25}_D +98 \) (c 4.25, CHCl₃)). The NMR spectral data compared favourably with that in the literature.\(^{55}\) δ\(_H\) (500 MHz, CDCl₃) 7.21-7.19 (5H, m, ArH), 4.46 (2H, s, NCH₂Ph), 4.30 (2H, d, J 1.2 Hz, 2CH), 0.77 (18H, s, 2(CH₃)₃CSi), 0.06 (6H, s, 2CH₃Si), 0.00 (6H, s, 2CH₃Si). \(^{13}\)C NMR (125 MHz) 178.1 (2CO), 140.4 (ArC), 134.1, 133.7, 133.1 (ArCH), 81.9 (2CH), 47.4 (NCH₂Ph), 30.7 (2(CH₃)₃CSi), 23.2 ((CH₃)₂CSi), 0.57 ((CH₃)₂Si), -0.00 ((CH₃)₂Si). MS (ESI\(^+\)) \( m/z \) 450 (M+H\(^+\)) 100%. HRMS (ESI\(^+\)) calcd for C\(_{23}\)H\(_{40}\)NO\(_4\)Si\(_2\) (M+H\(^+\)), 450.2496; found 450.2517.

6.4.3

\( (3R, 4R)\)-1-Benzyl-3-\((\text{tert-butyldimethylsilyloxy})\)-4-hydroxypyrrolidine-2,5-dione (151)

The title compound was prepared from the diol (149) (0.214 g, 0.967 mmol), imidazole (0.203 g, 2.90 mmol), and DMF (10 mL) using the method described above for the synthesis of (150). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (0.227 g, 0.677 mmol, 70 %, \( R_f = 0.43 \), 25% EtOAc/pet. sp) as white crystals. M.p. 110-113
°C $[\alpha]^2_{D} +98$ (c 2.03, CHCl$_3$). $\delta$ (500 MHz, CDCl$_3$) 7.37-7.28 (5H, m, ArH), 4.63 (2H, s, CH$_2$Ph), 4.51-4.48 (2H, m, H-3, H-4), 3.77 (1H, s, OH), 0.94 (9H, s, (CH$_3$)$_3$Si), 0.20 (3H, s, CH$_3$Si), 0.18 (3H, s, CH$_3$Si). $^{13}$C NMR (125 MHz, CDCl$_3$) 175.0 (CO), 173.2 (CO), 135.2 (ArC), 129.2, 129.0, 128.4 (ArCH), 76.1, 76.0 (C-3, C-4), 42.8 (NCH$_2$Ph), 25.8 ((CH$_3$)$_3$CSi), 18.5 ((CH$_3$)$_3$C=Si), -4.60 ((CH$_3$)$_2$Si), -4.89 ((CH$_3$)$_2$Si). MS (ESI$^+$) $m/z$ 336 (M+H)$^+$ 100%. HRMS (ESI$^+$) calcd. for C$_{17}$H$_{25}$NO$_4$Si (M+H)$^+$, 336.1644; found 336.1648.

6.4.4

(3R, 4R)-1-Benzyl-3,4-bis(tert-butyldimethylsilyloxy)-5-hydroxypyrroldin-2-one (152)

To a solution of (150) (1.23 g, 2.73 mmol) in MeOH (10 ml) was added NaBH$_4$ (0.528 g, 1.36 mmol) at -20 °C. The suspension was stirred vigorously at -20 °C for 30 min. The mixture was poured into a saturated solution of NaHCO$_3$ (20 mL) and the organic material was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuum. Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (0.997 g, 2.21 mmol, 81 %, $R_f = 0.69$, 25% EtOAc/pet. sp) as white crystals. M.p. 113-115 °C (lit.$^{55}$,
116-118 °C). \([\alpha]^{25}_D -1.5 \text{ (c 3.12, CHCl}_3\text{)}\) (lit.\(^{55}\), \([\alpha]^{24}_D -1.7 \text{ (c 3.35, CHCl}_3\text{)}\)). The NMR spectral data compared favourably with that in the literature.\(^{55}\) δ\(_H\) (500 MHz, CDCl\(_3\)) 7.31-7.25 (5H, m, ArH), 4.95 (1H, d, \(J 15.0\) Hz, NCH\(_2\)Ph), 4.57 (1H, dd, \(J 10.6, 1.0\) Hz, C-5), 4.15 (1H, d, \(J 15.0\) Hz, NCH\(_2\)Ph), 3.99 (1H, d, \(J 2.0\) Hz, H-3), 3.88 (1H, dd, \(J 2.0, 2.0\) Hz, H-4), 2.60 (1H, d, \(J 10.6\) Hz, OH), 0.92 (9H, s, (CH\(_3\))\(_3\)CSi), 0.83 (9H, s, (CH\(_3\))\(_3\)CSi), 0.21 (3H, s, 2CH\(_3\)Si), 0.19 (3H, s, 2CH\(_3\)Si) 0.08 (3H, s, 2CH\(_3\)Si), 0.02 (3H, s, 2CH\(_3\)Si). δ\(_C\) (125 MHz, CDCl\(_3\)) 171.9 (CO), 136.4 (ArC), 128.8, 128.2, 127.7 (ArCH), 87.3 (C-5), 78.3 (C-3), 76.9 (C-4), 43.3 (NCH\(_2\)Ph), 25.9 ((CH\(_3\))\(_3\)CSi), 25.8 ((CH\(_3\))\(_3\)CSi), 18.3 ((CH\(_3\))\(_3\)CSi), 18.0 ((CH\(_3\))\(_3\)CSi), -4.33 ((CH\(_3\))\(_2\)Si), -4.61 ((CH\(_3\))\(_2\)Si), -4.64 ((CH\(_3\))\(_2\)Si), -4.85 ((CH\(_3\))\(_2\)Si). MS (ESI\(^+\)) \(m/z\) 452 (M+H)\(^+\) 40%. HRMS (ESI\(^+\)) calcd.for C\(_{23}\)H\(_{42}\)NO\(_4\)Si\(_2\) (M+H)\(^+\), 452.2612; found 452.2662.

6.4.5

(3\(R\), 4\(R\))-1-Benzyl-3-(tert-butyldimethylsilyloxy)-4,5-dihydroxypyrroli din-2-one (153)

The title compound was prepared from the dione (151) (0.103 g, 0.306 mmol), MeOH (10 mL) and NaBH\(_4\) (0.058 g, 1.53 mmol) using the method described above for the synthesis of (152). Column chromatography (increasing polarity from 15%
EtOAc in pet.sp to 60% as eluant) yielded the title product (89.6 mg, 0.266mmol, 87 %, $R_f = 0.45$, 50% EtOAc/pet.sp) as white crystals. M.p. 176-180 °C. $[\alpha]_{D}^{25}+2.3$ (c 2.25, CHCl$_3$). $\delta_H$ (500 MHz, CDCl$_3$) 7.28-7.21 (5H, m, ArH), 4.77 (1H, d, $J$ 15.0 Hz NCH$_2$Ph), 4.63 (1H, dd, $J$ 8.5 3.0 Hz) 4.13-4.10 (2H, m, H-4 and NCH$_2$Ph), 4.00-3.90 (2H, m, H-3 and OH), 3.45 (1H, s, OH), 0.92 (9H, s, (CH$_3$)$_3$CSi), 0.18 (3H, s, CH$_3$Si), 0.16 (3H, s, CH$_3$Si). $\delta_C$ (125 MHz, CDCl$_3$) 172.3 (CO), 136.0 (ArC), 129.0, 128.6, 128.0 (ArCH), 85.1 (C-5), 81.0 (C-4), 76.3 (C-3), 43.1 (NCH$_2$Ph), 26.0 ((CH$_3$)$_3$CSi), 18.5 ((CH$_3$)$_3$CSi), -4.33 ((CH$_3$)$_2$Si), -4.74 ((CH$_3$)$_2$Si). MS (ESI$^+$) $m/z$ 338 (M+H)$^+$ 70%. HRMS (ESI$^+$) calcd.for C$_{17}$H$_{27}$NO$_4$Si(M+H)$^+$, 338.1788; found 338.1803.

6.4.6

(2$R$, 3$R$)-Diethyl 2,3-bis(benzyloxy)succinate (168)

To a solution of diethyl tartrate (0.500 ml, 2.92 mmol) in DMF (25 mL) was added NaH (0.1541 g, 6.43 mmol) at 0 °C. After 15 min, benzylbromide (1.39 ml, 11.7 mmol) was added to the mixture. The reaction was kept for 24 h at rt and then quenched with saturated NaHCO$_3$ solution (20 mL). The product was extracted into EtOAc (3 × 20 mL) and the combined organic layers was washed with brine (3 × 30 mL) and dried over MgSO$_4$. After removal of the solvent, the product was purified by column
chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) to give the title compound (1.10 g, 2.86 mmol, 98 %, $R_f = 0.65$, 25% EtOAc/pet. sp) as a colorless oil. [$\alpha$]$_{D}^{22}$ +12.6 ($c$ 4.77, CHCl$_3$) (lit.$^{60}$, [$\alpha$]$_{D}^{20}$ +13.2 ($c$ 4.91, CHCl$_3$)). The NMR spectral data compared favourably with that in the literature.$^{60}$

$\delta$ (500 MHz, CDCl$_3$) 7.30 (10H, s, ArH), 4.86 (2H, d, $J$ 12.0 Hz, OCH$H$/Ph, OCH$'$H$'$/Ph), 4.45 (2H, d, $J$ 12.0 Hz, OCH$H$/Ph, OCH$'$H$'$/Ph), 4.39 (2H, s, 2CH), 4.20 (2H, m, OCH$H$/CH$_3$, OCH$'$H$'$/CH$_3$), 4.07 (2H, m, OCH$H$/CH$_3$, OCH$'$H$'$/CH$_3$), 1.18 (6H, dd, $J$ 7.0 Hz, 2OCH$_2$H$_3$). $\delta$ (125 MHz, CDCl$_3$) 169.4 (2CO), 137.2 (ArC), 128.6, 128.5, 128.2 (ArCH), 78.7 (2OCH$_2$Ph), 73.5 (2CH), 61.54 (2OCH$_2$CH$_3$), 14.31 (2OCH$_2$CH$_3$). MS (ESI$^+$) $m/z$ 387 (M+H)$^+$ 40%. HRMS (ESI$^+$) calcd.for C$_{22}$H$_{26}$O$_6$ (M+H)$^+$, 387.1808; found 387.1845.

6.4.7

(2$R$, 3$R$)-Diethyl 2-(benzyloxy)-3-hydroxysuccinate (169)

The title compound was prepared from diethyl tartrate (0.500 ml, 2.92 mmol), DMF (25 mL), NaH (0.070 g, 2.92 mmol), and benzylbromide (0.347 ml, 2.92 mmol) using the method described above for the synthesis of (168). Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the title product (0.605 g, 2.04 mmol, 70 %, $R_f = 0.13$, 25% EtOAc/pet. sp) as a colorless oil. [$\alpha$]$_{D}^{22}$ +68 ($c$ 1.02,
CHCl₃) (lit. [α]²⁴ᵣ +73 (c 1.35, CHCl₃)). The NMR spectral data compared favourably with that in the literature. δH (500 MHz, CDCl₃) 7.41-7.22 (5H, m, ArH), 4.86 (1H, d, J 11.5 Hz, OCH/HPh), 4.59 (1H, s, H-2), 4.42 (1H, d, J 11.5 Hz, OCH/HPh), 4.59 (1H, s, H-2), 4.42 (1H, d, J 11.5 Hz, OCH/HPh), 4.32-4.30 (3H, m, H-1 and OCH₂CH₃), 4.21 (1H, m, OCH₂H’CH₃), 4.04 (1H, m, OCH’H’CH₃), 1.76 (3H, dd, J 7.0 7.0 Hz, OCH₂CH₃), 1.33 (3H, dd, J 7.0 7.0 Hz, OCH’₂CH₃). δC (125 MHz, CDCl₃) 171.3, 169.6 (CO), 137.0 (ArC), 128.6, 128.5, 128.3 (ArCH), 78.4 (OCH₂Ph), 73.2, 72.6 (C-1, C-2), 62.3, 61.8 (2OCH₂CH₃), 14.4, 14.3 (2OCH₂CH₃). MS (ESI⁺) m/z 297 (M+H)⁺ 30%. HRMS (ESI⁺) calcd. for C₁₅H₂₁O₆ (M+H)⁺, 297.1338; found 296.1346.

6.4.8

(4R, 5R)-2-Benzyl-4,5-bis(benzyloxy)pyrrol-1,3-dione (162)

To a mixture of MeOH (15 mL) and 10% NaOH solution (15 mL) was added the compound (168) (1.15 g, 2.85 mmol). The mixture was vigorously stirred at rt for 24 h and then acidified with 10% aqueous HCl (15 ml). The organic material was extracted into EtOAc (3 × 20 mL). The combined organic extracts were dried over MgSO₄ followed by removal of the solvent. The product (170) was then dissolved in xylene (25 mL) and
treated with benzylamine (0.305 g, 2.85 mmol). The mixture was heated at reflux for 24 h with stirring in a round bottom flask equipped with a Dean-Stark apparatus. After cooling the reaction mixture, the product was filtered and purified by column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) to give the title compound (0.686 g, 1.71 mmol, 60 %, \( R_f = 0.45 \), 25% EtOAc/pet. sp) as a colorless oil. \([\alpha]^{25}_D +77 \) (\( c \) 1.26, CHCl\(_3\)). \( \delta_H \) (500 MHz, CDCl\(_3\)) 7.37-7.25 (15H, m, ArH), 4.97 (2H, d, \( J \) 12.0 Hz, OCH/Ph, OCH’/H’Ph), 4.74 (2H, d, \( J \) 12.0 Hz, OCH/Ph, OCH’/H’Ph), 4.65 (2H, d, \( J \) 2.0 Hz, 2CH), 4.38 (2H, s, NCH\(_2\)Ph).

\( \delta_C \) (125 MHz, CDCl\(_3\)) 172.6 (CO), 136.7, 135.2 (3ArC), 129.2, 129.0, 128.8, 128.4 (ArCH), 79.1 (2OCH\(_2\)Ph), 73.7 (2CH), 42.5 (NCH\(_2\)Ph). MS (ESI\(^+\)) \( m/z \) 402 (M+H\(^+\)) 100%. HRMS (ESI\(^+\)) calcd.for C\(_{25}\)H\(_{24}\)NO\(_4\) (M+H\(^+\)), 402.1700; found 402.1724.

6.4.9

(3\( R \), 4\( R \))-1-Benzyl-3-(benzyloxy)-4-hydroxypyrrolidine-2,5-dione (163)

To a mixture of MeOH (15 mL) and 10% NaOH solution (15 mL) was added the compound (169) (0.787 g, 2.66 mmol). The mixture was vigorously stirred at rt for 24 h and quenched with saturated solution of NaHCO\(_3\) (15 ml). The organic material was extracted into EtOAc (3 \( \times \) 20 mL). The combined organic extracts were dried over
MgSO₄ followed by removal of the solvent. The product was then treated by benzylamine (0.564 mL, 2.658 mmol) in the presence of xylene (40 mL) using the method described above for the synthesis of (162). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluant) yielded the title product (0.576 g, 1.85 mmol, 70 %, Rᵣ = 0.15, 25% EtOAc/pet. sp) as a colorless oil. [α]ᵣ²+96 (c 1.03, CHCl₃). δₜ (500 MHz, CDCl₃) 7.42-7.25 (10H, m, ArH), 5.00 (1H, d, J 11.7 Hz, OCH₃Ph), 4.84 (1H, d, J 11.7 Hz, OCH₃Ph), 4.64 (2H, s, NCH₂Ph), 4.57 (1H, d, J 5.4 Hz, H-4), 4.36 (1H, d, J 5.4 Hz, H-3), 3.48 (1H, s, OH). δₚ (125 MHz, CDCl₃) 172.6, 172.5 (CO), 137.0, 135.2 (ArC), 129.2, 129.0, 128.8, 128.4 1, 127.6, 127.4 (ArCH), 83.0 (OCH₂Ph), 74.1, 72.2 (2CH), 42.5 (NCH₂Ph). MS (ESI⁺) m/z 312 (M+H)⁺ 60%. HRMS (ESI⁺) calcd.for C₁₈H₁₈NO₄ (M+H)⁺, 312.1230; found 312.1233.

6.4.10

(3R, 4R)-1-Benzyl-3,4-bis(benzyloxy)-5-hydroxypyrrolidin-2-one (164)

The title compound was prepared from the dione (162) (0.800 g, 1.99 mmol), MeOH (15 mL) and NaBH₄ (0.376 g, 9.96 mmol) using the method described above for the synthesis of (152). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (0.540 g, 0.134 mmol, 70 %, Rᵣ = 0.10,
25% EtOAc/pet. sp) as a colorless oil. $[\alpha]^{25}_D +63.0$ (c 1.02, CHCl$_3$) (lit.$^{62}$, $[\alpha]^{25}_D +68.4$ (c 1.22, CHCl$_3$)). The NMR spectral data compared favourably with that in the literature.$^{62}$ $\delta$$_H$ (500 MHz, CDCl$_3$) 7.38-7.21 (15H, m, ArH), 4.98 (1H, d, $J$ 11.7 Hz, OCH$_2$Ph), 4.89 (1H, d, $J$ 15.0 Hz, NCH$_2$Ph), 4.77 (2H, m, H-5, OCH$_2$Ph), 4.56 (1H, d, $J$ 12.0 Hz, OCH'Ph), 4.50 (1H, d, $J$ 12.0 Hz, OCH'Ph), 4.16 (1H, d, $J$ 15.0 Hz, NCH$_2$Ph), 4.10 (1H, d, $J$ 4.5 Hz, H-3), 3.90 (1H, dd, $J$ 4.8 4.8 Hz, H-4). $\delta$$_C$ (125 MHz, CDCl$_3$) 170.30 (CO), 137.4, 137.3, 135.9 (ArC) 129.0, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0 (ArCH) 84.8, 84.3 (2OCH$_2$Ph), 79.7 (C-5), 73.1, 72.4 (C-3, C-4), 43.2 (NCH$_2$Ph). MS (ESI$^+$) $m/z$ 404 (M+H)$^+$ 70%. HRMS (ESI$^+$) calcd.for C$_{25}$H$_{26}$NO$_4$ (M+H)$^+$, 404.1862; found 404.1873.

6.4.11a
(3$R$, 4$R$)-1-Benzyl-3-(benzyloxy)-4,5-dihydroxypyrrolidin-2-one (165a)

6.4.11b
(3$R$, 4$R$)-1-Benzyl-4-(benzyloxy)-3,5-dihydroxypyrrolidin-2-one (165b)

The title compounds were prepared from the dione (163) (0.825 g, 2.65 mmol), MeOH (15 mL) and NaBH$_4$ (0.502 g, 13.2
Column chromatography (increasing polarity from 15% to 100% EtOAc in pet. sp as eluent) yielded a 2/1 mixture of the title products (0.623 g, 1.99 mmol, 75 %, \( R_f = 0.50 \), 100% EtOAc/pet. sp) as white crystals. m.p. 123-126 °C (500 MHz, CDCl\(_3\)) major product (165a): 7.39-7.25 (10H, m, ArCH\(_3\)), 5.01-3.99 (7H, m, OCH\(_2\)Ph, H-3, H-4, H-5, NCH\(_2\)Ph). Minor isomer 7.39-7.25 (10H, m, ArCH\(_3\)), 5.01-3.99 (7H, m, OCH\(_2\)Ph, H-3, H-4, H-5, NCH\(_2\)Ph). δ\(_C\) (125 MHz, CDCl\(_3\)) major product (165b): 170.1 (CO), 137.4, 136.0 (ArC), 129.0, 128.8, 128.6, 128.5, 128.4, 128.1 (6ArCH), 85.0 (OCH\(_2\)Ph), 81.0 (C-5), 79.0 (C-4), 73.2 (C-3), 43.0 (NCH\(_2\)Ph). Minor product (165b) (in part): 87.2 (C-3), 84.0 (OCH\(_2\)Ph), 72.5 (C-4), 43.1 (NCH\(_2\)Ph). MS (ESI\(^+\)) \( m/z \) 314 (M+H)\(^+\) 50%. HRMS (ESI\(^+\)) calcd for C\(_{18}\)H\(_{20}\)NO\(_4\) (M+H)\(^+\), 314.1387; found 314.1389.

6.4.12

1-Benzyl-4-(benzyloxy)-1H-pyrrolidin-2, 5-dione (166)

To a solution of compound (149) (204 mg, 0.923 mmol) in DMF (5 mL) was added NaH (55 mg, 2.23 mmol) at 0 °C. After 15 min, benzylbromide (0.26 ml, 2.20 mmol) was added to the mixture. The reaction was kept for 18 h at rt and then quenched with saturated NaHCO\(_3\) solution (10 mL).
The product was extracted into EtOAc (3 × 20 mL) and the combined extracts were washed with brine (3 × 20 mL) and dried over MgSO₄. After removal of the solvent, the product was purified by column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) to give the title compound (29.3 mg, 0.10 mmol, 11 %, \( R_f = 0.33 \), 33% EtOAc/pet. sp) as white crystals. M.p. 113-116 °C \( \delta_H \) (500 MHz, CDCl₃) 7.50-7.22 (10H, s, ArH), 5.42 (1H, s, H-3), 5.12 (2H, s, OCH₂Ph), 4.65 (2H, s, NCH₂Ph). \( \delta_C \) (125 MHz, CDCl₃) 170.1, 169.7 (2CO), 137.2, 133.6 (ArC), 129.4, 129.1, 128.9, 128.7, 128.3, 128.0 (ArCH), 97.7 (C-3), 74.3 (OCH₂Ph), 41.4 (NCH₂Ph). MS (ESI⁺) \( m/z \) 294 (M+H)+ 50%. HRMS (ESI⁺) calcd. for C₁₈H₁₆NO₄ (M+H)+, 294.1125; found 294.1134.

6.5 Reaction of Pyrrolidinones (152) and (153) with Nucleophiles

6.5.1a

\((3R, 4S)-1\)-Benzyl-3,4-bis\((\text{tert}-\text{butyldimethylsilyloxy})\)-5-styrylpyrrolidin-2-one (154)

6.5.1b

\((3R, 4S)-1\)-Benzyl-3-(\(\text{tert}-\text{butyldimethylsilyloxy}\))-4-hydroxy-5-styrylpyrrolidin-2-one (155)
**Method A:** To a solution of (152) (105 mg, 0.233 mmol) and trans-vinylphenylboronic acid (52 mg, 0.350 mmol) in dry CH$_2$Cl$_2$ (5 mL) at 0 °C was added BF$_3$·Et$_2$O (0.118 mL, 0.934 mmol). The reaction was kept for 16.5 h, allowing the temperature to warm up to rt. The mixture was then quenched with saturated NaHCO$_3$ solution (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over MgSO$_4$, filtered and evaporated in vacuum to give yellow oil. Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) gave the title compounds (154) (45 mg, 0.10 mmol, 36%, d.r. = 1/8, $R_f$ = 0.80, 33% EtOAc/pet. sp) and (155) (2 mg, 0.01 mmol, 2%, d.r. = 1/10, $R_f$ = 0.34, 33% EtOAc/pet. sp) as colorless oils.

For compound (154): $\delta_H$ (500 MHz, CDCl$_3$) major diasteromer: 7.36-7.21 (10H, m, ArH), 6.39 (1H, d, $J$ 16 Hz, H-7), 5.94 (1H, dd, $J$ 15.8, 9.0 Hz, H-6), 4.96 (1H, d, $J$ 14.5 Hz, NCH$_2$HPh), 4.21 (1H, d, $J$ 5.0 Hz, H-3), 3.98 (2H, m, H-4 and NCH$_2$HPh), 3.74 (1H, dd, $J$ 9.0 4.5 Hz, H-5), 0.99 (9H, s, (CH$_3$)$_3$Si), 0.85 (9H, s, (CH$_3$)$_3$Si), 0.29 (3H, s, CH$_3$Si), 0.21 (3H, s, CH$_3$Si), 0.08 (3H, s, CH$_3$Si), -0.04 (3H, s, CH$_3$Si). $\delta_C$ (125 MHz, CDCl$_3$) major diasteromer: 171.7 (CO), 136.8, 136.1 (ArC), 136.0 (CH-7), 129.0, 128.8, 128.6, 128.5, 127.6, 126.8 (6ArCH), 126.6
(CH-6), 79.38 (CH-4), 77.98 (CH-3), 66.14 (CH-5), 44.36 (CH-8), 26.1
(\((\text{CH}_3)_3\text{CSi}\)), 25.9 (\((\text{CH}_3)_3\text{CSi}\)), 18.5 (\((\text{CH}_3)_3\text{CSi}\)), 18.1 (\((\text{CH}_3)_3\text{CSi}\)), -3.9
(\((\text{CH}_3)_2\text{Si}\)), -4.0 (\((\text{CH}_3)_2\text{Si}\)), -4.1 (\((\text{CH}_3)_2\text{Si}\)), -4.5 (\((\text{CH}_3)_2\text{Si}\)). MS (ESI\(^+\)) \(m/z\) 538 (M+H)\(^+\) 100%. HRMS (ESI\(^+\)) calcd. for \(\text{C}_{31}\text{H}_{48}\text{NO}_3\text{Si}_2(M+H)^+\), 538.3173; found 538.3189.

For compound (155): \(\delta_H\) (500 MHz, CDCl\(_3\)) major diasteromer (in part):
6.39 (1H, d, \(J\) 16 Hz, H-7), 5.90 (1H, dd, \(J\) 15.8, 9.0 Hz, H-6). Minor
diasteromer (in part): 6.47 (1H, d, \(J\) 16 Hz, H-7), 6.05 (1H, dd, \(J\) 15.8, 9.0
Hz, H-6), 0.29 (3H, s, CH\(_3\)Si), 0.21 (3H, s, CH\(_3\)Si). MS (ESI\(^+\)) \(m/z\) 424
(M+H)\(^+\) 100%. HRMS (ESI\(^+\)) calcd. for \(\text{C}_{25}\text{H}_{34}\text{NO}_3\text{Si}(M+H)^+\), 424.2302;
found 424.2307.

**Method B:** The title compounds (154) and (155) were prepared from (152)
(100.9 mg, 0.224 mmol), potassium trans-styryltrifluoroborate (0.045 g,
0.296 mmol), anhydrous CH\(_2\)Cl\(_2\) (5 mL), and BF\(_3\)-Et\(_2\)O (0.112 mL, 0.895
mmol) using Method A described above (reaction time: 16 h). Column
chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as
eluent) yielded the products (154) (70 mg, 0.130 mmol, d.r. = 1/8, 58%, \(R_f\)
= 0.80, 30% EtOAc/pet. sp) and (155) (2 mg, 0.01 mmol, 2%, d.r. = 1/10,
\(R_f\) = 0.34, 33% EtOAc/pet. sp) as colorless oils. The major diastereomer
was the same as that obtained from Method A.
6.5.2

(3R, 4S)-1-Benzyl-3,4-bis(tert-butyldimethylsilyloxy)-5-(furan-2-yl)pyrrolidin-2-one (157a)

**Method A:** The title compound was prepared from (152) (94.6 mg, 0.210 mmol), 2-furanboronic acid (35.3 mg, 0.315 mmol), anhydrous CH$_2$Cl$_2$ (5 mL), and BF$_3$·Et$_2$O (0.106 mL, 0.840 mmol) using the method described above for the synthesis of (154) (reaction time: 1.5 h). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (82.1 mg, 0.164 mmol, 78%, d.r. = 4/1, $R_f$ = 0.78, 33% EtOAc/pet. sp) as a colorless oil. $\delta$H (500 MHz, CDCl$_3$) major diasteromer: 7.41 (1H, s, H-9), 7.35-7.19 (5H, m, ArH), 6.32 (1H, dd, $J$ 3.0, 2.0 Hz, H-8), 6.20 (1H, dd, $J$ 3.0 Hz, H-7), 5.00 (1H, d, $J$ 14.5 Hz, NCH$_2$Ph), 4.64 (1H, d, $J$ 7.5 Hz, H-3), 4.36 (1H, d, $J$ 7.0 Hz, H-5), 4.29 (1H, dd, $J$ 7.5, 7.0 Hz, H-4), 3.65 (1H, d, $J$ 14.5 Hz, NCH$_2$Ph), 0.99 (9H, s, (CH$_3$)$_3$Si), 0.72 (9H, s, (CH$_3$)$_3$Si), 0.30 (3H, s, CH$_3$Si), 0.22 (3H, s, CH$_3$Si), 0.05 (3H, s, CH$_3$Si), -0.07 (3H, s, CH$_3$Si). Minor diasteromer (in part): 7.44 (1H, s, H-9), 7.35-7.10 (5H, m, ArH), 6.38 (1H, dd, $J$ 3.0, 2.0 Hz, H-8), 6.30 (1H, d, $J$ 3.0 Hz, H-7), 3.50 (1H, d, $J$ 14.5 Hz, NCH$_2$Ph).

$\delta$C (125 MHz, CDCl$_3$) Major diasteromer: 171.7 (CO) 149.4 (C-6), 143.5 (C-9) 135.9 (ArC), 111.1, 110.3 (C-7, C-8), 128.8, 128.6, 127.8, (ArCH),
76.3 (CH-3), 75.8 (CH-4), 56.6 (CH-5), 45.0 (NCH2Ph), 26.0 ((CH3)3Si), 25.7 ((CH3)3CSi), 18.5 ((CH3)3C≡Si), 18.0 ((CH3)3C≡Si), -3.9 ((CH3)2Si), -4.4 ((CH3)2Si), -4.5 ((CH3)2Si), -4.6 ((CH3)2Si). Minor diasteromer (in part): in part 171.1 (CO), 149.3 (C-6), 143.3 (CH-9), 128.7, 128.6, 127.7, (5ArCH), 112.0, 110.7 (C-7, C-8), 78.9 (CH-3), 77.7 (CH-4), 59.1 (CH-5), 44.5 (NCH2Ph), 26.1 ((CH3)3Si), 25.8 ((CH3)3CSi), 18.5 ((CH3)3C≡Si), 18.0 ((CH3)3C≡Si), -3.8 ((CH3)2Si), -4.4 ((CH3)2Si), -5.3 ((CH3)2Si). MS (ESI+) m/z 502 (M+H)+ 100%. HRMS (ESI+) calcd. for C_{27}H_{44}NO_{4}Si_{2} (M+H)+, 502.2822; found 502.2816.

**Method B:** The title compound was prepared from (152) (144.4 mg, 0.32 mmol), furan (0.07 mL, 0.96 mmol), anhydrous CH₂Cl₂ (5mL), and BF₃·Et₂O (0.106 ml, 0.840 mmol) using the method described above for the synthesis of (154) (reaction time: 40 min), except that furan was used instead of the boronic acid. Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (120.2 mg, 0.24 mmol, 75%, d.r. = 8/1, R_f = 0.78, 33% EtOAc/pet.sp) as a colorless oil. The NMR data of the major product was the same as that obtained using Method A.
The title compounds (157b) and (158b) were prepared from (152) (89 mg, 0.197 mmol), 4-methoxylphenylboronic acid (0.045 g, 0.296 mmol), anhydrous CH₂Cl₂ (5 mL), and BF₃·Et₂O (0.099 mL, 0.788 mmol) using the method described above for the synthesis of (154) (reaction time: 24 h). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the products (157b) (16 mg, 0.030 mmol, d.r. = 1/6, 15%, Rᵣ = 0.76, 30% EtOAc/pet.sp) and (158b) (10 mg, 0.023 mmol, d.r. = 1/1, 12%, Rᵣ = 0.39, 30% EtOAc/pet.sp) as colorless oils.

For compound (157b): δₓ (500 MHz, CDCl₃) major diastereomer: 7.28-7.24 (3H, m, ArH), 7.09-7.06 (2H, m, ArH), 6.98 (2H, d, J 9.0 Hz, H-6), 6.86 (2H, d, J 9.0 Hz, H-7), 5.10 (1H, d, J 15.0 Hz, NCH˭Ph), 4.37 (1H, d, J 5.0 Hz, H-5), 4.34 (1H, d, J 5 Hz, H-3), 4.14 (1H, dd, J 8.0 5.5 Hz, H-4),
3.82 (3H, s, OMe), 3.47 (1H, d, J 15 Hz, NCH\textsubscript{HPh}), 0.95 (9H, s, (CH\textsubscript{3})\textsubscript{3}CSi), 0.66 (9H, s, (CH\textsubscript{3})\textsubscript{3}CSi), 0.26 (3H, s, CH\textsubscript{3}Si), 0.18 (3H, s, CH\textsubscript{3}Si), -0.08 (3H, s, CH\textsubscript{3}Si), -0.26 (3H, s, CH\textsubscript{3}Si). Minor diasteromer (in part): 7.28-7.24 (3H, m, ArH\textsuperscript{H}), 7.09-7.06 (2H, m, ArH\textsuperscript{H}), 6.98 (2H, d, J 9.0 Hz, H-6), 6.86 (2H, d, J 9.0 Hz, H-7), 5.25 (1H, d, J 15 Hz, NCH\textsubscript{HPh}) 3.83 (3H, s, OMe), 3.42 (1H, d, J 15 Hz, NCH\textsubscript{HPh}). δ\textsubscript{C} (125 MHz, CDCl\textsubscript{3}) major diasteromer: 172.4 (CO) 159.7, 136.1 (ArC), 130.7 (CH-6), 113.9 (CH-7), 128.7, 128.6, 127.7, (5ArCH), 77.2 (CH-3), 75.7 (CH-4), 63.4(CH-5), 55.6 (OMe), 44.5 (NCH\textsubscript{2}Ph) 26.0 ((CH\textsubscript{3})\textsubscript{3}CSi), 25.7 ((CH\textsubscript{3})\textsubscript{3}CSi), 18.5 ((CH\textsubscript{3})\textsubscript{3}CSi), 18.0 ((CH\textsubscript{3})\textsubscript{3}CSi), -3.9 ((CH\textsubscript{3})\textsubscript{2}Si), -4.5 ((CH\textsubscript{3})\textsubscript{2}Si), -4.6 ((CH\textsubscript{3})\textsubscript{2}Si), -4.7 ((CH\textsubscript{3})\textsubscript{2}Si). MS (ESI\textsuperscript{+}) m/z 542 (M+H)\textsuperscript{+} 100%. HRMS (ESI\textsuperscript{+}) calcd.for, C\textsubscript{30}H\textsubscript{48}NO\textsubscript{4}Si\textsubscript{2} 542.3135; found 542.3139.

For compound (158b): δ\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) peaks for both isomers: 7.31-6.78 (m, ArH\textsuperscript{H}), 5.15-3.46 (m, H-3, H-4, H-5, OMe, NCH\textsubscript{2}Ph), 0.74, 0.65 (2s, (CH\textsubscript{3})\textsubscript{3}CSi), 0.00, -0.09 (2s, CH\textsubscript{3}Si). MS (ESI\textsuperscript{+}) m/z 428 (M+H)\textsuperscript{+} 100%. HRMS (ESI\textsuperscript{+}) calcd.for, C\textsubscript{24}H\textsubscript{34}NO\textsubscript{4}Si 428.2252; found 428.2252.

6.5.4

(3R, 4S)-1-Benzyl-3,4-bis(tert-butyldimethylsilyloxy)-5-(2-thienyl)pyrrolidine-2-one (157c)

The title compound was prepared from (152) (132
mg, 0.327 mmol), 2-thiophenebononic acid (83.7 mg, 0.654 mmol), anhydrous CH₂Cl₂ (5 mL), and BF₃·Et₂O (0.164 mL, 1.31 mmol) using the method described above for the synthesis of (154) (reaction time: 1.5 h). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (50.7 mg, 0.098 mmol, 30%, d.r. = 2/1, Rf = 0.78, 33% EtOAc/pet.sp) as a yellow oil. δ (500 MHz, CDCl₃) major diasteromer: 7.33-6.85 (9H, m, ArH, H-6, H-7, H-8 and H-9), 5.07 (1H, d, J 15.0 Hz, NCH₂Ph), 4.66 (1H, d, J 7.0 Hz, H-5), 4.50 (1H, d, 6.5 Hz, H-3), 4.23 (1H, dd, J 7.0 Hz, H-4), 3.59 (1H, d, J 14.5 Hz, NCH₂Ph), 0.99 (s, 9H, (CH₃)₃CSi), 0.73 (s, 9H, (CH₃)₃CSi), 0.32 (s, 3H, CH₃Si), 0.21 (s, 3H, CH₃Si), 0.03 (s, 3H, CH₃Si), -0.12 (s, 3H, CH₃Si). Minor diasteromer (in part): 7.33-6.85 (9H, m, 5ArH, H-6, H-7, H-8, H-9), 5.07 (1H, d, J 15.0 Hz, NCH₂Ph), 4.30 (1H, d, J 5.0 Hz, H-5), 3.57 (1H, d, J 14.5 Hz, NCH₂Ph). δ (125 MHz, CDCl₃) major diasteromer: 171.4 (CO), 138.6, 135.9 (ArC and C-6), 128.9, 128.7, 128.6, 127.9, 126.7, 126.5, (ArCH), 76.3 (C-3), 75.6 (C-4), 58.9 (C-5), 44.7 (NCH₂Ph) 26.0 ((CH₃)₂CSi), 25.7 ((CH₃)₂CSi), 18.5 ((CH₃)₂CSi), 17.9 ((CH₃)₂CSi), -4.0 ((CH₃)₂Si), -4.4 ((CH₃)₂Si), -4.5 ((CH₃)₂Si), -4.6 ((CH₃)₂Si). MS (ESI⁺) m/z 518 (M+H)⁺ 100%. HRMS (ESI⁻) calcd for C₂₇H₄₄NO₃SSi₂ (M+H)⁺, 518.2545; found 518.2554.
6.5.5

(3R, 4S)-1-Benzyl-4-(tert-butyldimethylsilyloxy)-5-(furan-2-yl)-3-hydroxyprrolidin-2-one (158a)

**Method A:** The title compound was prepared from (152) (70.6 mg, 0.156 mmol), 2-furanboronic acid (26.3 mg, 0.245 mmol), anhydrous CH$_2$Cl$_2$ (5 mL), and BF$_3$·Et$_2$O (0.089 mL, 0.626 mmol) using the method described above for the synthesis of (154) (reaction time: 14 h), except that furan was used instead of the boronic acid. Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (48.3 mg, 0.125 mmol, 80%, d.r. = 5/1, $R_f$ = 0.43, 33% EtOAc/pet. sp) as a colorless oil. $\delta$$_H$ (500 MHz, CDCl$_3$) major diasteromer: 7.38 (1H, s, H-9), 7.34-7.17 (5H, m, ArH), 6.31 (1H, dd, $J$ 3.0, 2.0 Hz, H-8), 6.20 (1H, d, $J$ 3.0 Hz, H-7), 5.00 (1H, d, $J$ 14.5 Hz, NCH$_2$/Ph), 4.60 (1H, d, $J$ 7.5 Hz, H-3), 4.39 (1H, d, $J$ 8.0 Hz, H-5), 4.33 (1H, dd, $J$ 7.5, 7.5 Hz, H-4), 3.68 (1H, d, $J$ 14.5 Hz, NCH$_2$/Ph), 3.16 (1H, s, OH) 0.71 (9H, s, (CH$_3$)$_3$Si), 0.07 (3H, s, CH$_3$Si), -0.04 (3H, s, CH$_3$Si). Minor diasteromer (in part): 7.42 (1H, s, H-9), 7.34-7.05 (5H, m, ArH), 4.93 (1H, d, $J$ 15.0 Hz, NCH$_2$/Ph), 3.51 (1H, d, $J$ 14.5 Hz, NCH$_2$/Ph). $\delta$$_C$ (125 MHz, CDCl$_3$) major diasteromer: 171.4 (CO) 148.6 (C-6), 144.0 (C-9) 135.9 (ArC), 128.8, 128.6, 127.8, (5ArCH), 111.7, 110.8 (C-7, C-8), 76.3
(CH-3), 75.3 (CH-4), 55.8 (CH-5), 45.1 (NCH₂Ph) 26.0 ((CH₃)₃Si), 18.6 
((CH₃)₂Si), 18.0 ((CH₃)₃Si), -4.0 ((CH₃)₂Si), -4.7 ((CH₃)₂Si). MS (ESI⁺) 
m/z 388 (M+H)⁺ 100%. HRMS (ESI⁺) calcd. for C₂₁H₃₀NO₄Si (M+H)⁺, 388.1957; found 388.1955.

**Method B:** The title compound was prepared from (152) (72.2 mg, 0.16 mmol), furan (0.035 mL, 0.48 mmol), anhydrous CH₂Cl₂ (5mL), and 
BF₃·Et₂O (0.053 ml, 0.420 mmol) using the method described above for the 
synthesis of (152) (reaction time: 3 h), except that furan was used instead 
of the boronic acid. Column chromatography (increasing polarity from 
15% to 30% EtOAc in pet. sp as eluent) yielded the title product (43.3 mg, 
0.112 mmol, 70%, d.r. = 9/1, Rf = 0.43, 33% EtOAc/pet. sp) as a colorless 
oil. The NMR data of the major product was the same as that obtained 
using Method A.

6.5.6

(3R, 4S)-1-Benzyl-3-(tert-butyldimethylsilyloxy)-5-(furan-2-yl)-4-hydro 
xyprrolidin-2-one (159)

The title compound was prepared from (153) 
(70.8 mg, 0.210 mmol), 2-furanboronic acid 
(46.0 mg, 0.420 mmol), anhydrous CH₂Cl₂ (5 
ml) and BF₃·Et₂O (0.106 mL, 0.840 mmol) 
using the method described above for the
synthesis of (154) (reaction time: 5 h). Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (22.7 mg, 0.059 mmol, 28 %, d.r. = 3.5/1, \( R_f \) = 0.45, 33% EtOAc/pet. sp) as a colorless oil. \( \delta_H \) (500 MHz, CDCl\(_3\)) major diasteromer: 7.44 (1H, s, H-9), 7.29-7.15 (5H, m, ArH), 6.37 (1H, dd, \( J \) 3.0, 2.0 Hz, H-8), 6.30 (1H, d, \( J \) 3.0 Hz, H-7), 5.00 (1H, d, \( J \) 14.5 Hz, NCH\(_2\)HPh), 4.56 (1H, d, \( J \) 7.5 Hz, H-3), 4.50 (1H, d, \( J \) 8.0 Hz, H-5), 4.33 (1H, dd, \( J \) 7.5, 7.5 Hz, H-4), 3.62 (1H, d, \( J \) 14.5 Hz, NCH\(_2\)HPh), 0.96 (9H, s, (CH\(_3\))\(_3\)CSi), 0.25 (3H, s, CH\(_3\)Si), 0.20 (3H, s, CH\(_3\)Si). Minor diasteromer (in part): 7.42 (1H, s, H-9), 7.30-7.06 (5H, m, ArH), 4.92 (1H, d, \( J \) 15.0 Hz, NCH\(_2\)HPh), 3.51 (1H, d, \( J \) 15 Hz, NCH\(_2\)HPh). \( \delta_C \) (125 MHz, CDCl\(_3\)) major diasteromer: 171.4 (CO) 148.6 (C-6), 144.0 (CH-9) 135.6 (ArC), 128.9, 128.8, 127.9, (5ArCH), 111.7, 110.8 (C-7, C-8) 76.3 (CH-3), 75.3 (CH-4), 56.8 (CH-5), 45.1 (NCH\(_2\)Ph) 26.0 ((CH\(_3\))\(_3\)CSi), 18.3 ((CH\(_3\))\(_3\)CSi), -4.1 ((CH\(_3\))\(_2\)Si), -4.7 ((CH\(_3\))\(_2\)Si). MS (ESI\(^+\)) \( m/z \) 388 (M+H)\(^+\) 100%. HRMS (ESI\(^+\)) calcd.for C\(_{21}\)H\(_{30}\)NO\(_4\)Si (M+H)\(^+\), 388.1957; found 388.1955.

6.5.7

(3R, 4S)-1-Benzyl-5-(furan-2-yl)-3,4-dihydroxypyrrolidin-2-one (160)

Method A: To a solution of 10% HCl (10 mL) and MeOH (10 mL) was added compound (159) (100 mg, 0.200 mmol). The reaction was kept at rt for 24
h and then saturated NaHCO₃ solution (10 mL) was added. The product was extracted into EtOAc (3 × 15 mL) and the combined extracts were dried over MgSO₄ followed by removal of the solvent. The product was obtained as white crystals (77.4 mg, 0.059 mmol, 100%, d.r. = 4/1) M.p. 184-186 °C δₜ (500 MHz, CDCl₃) major diasteromer: 7.39 (1H, s, H-9), 7.29-7.13 (5H, m, ArH), 6.32 (1H, dd, J 3.0, 2.0 Hz, H-8), 6.29 (1H, d, J 3.0 Hz, H-7), 4.96 (1H, d, J 15.0 Hz, NCH₂Ph), 4.74 (1H, d, J 8 Hz, H-3), 4.50 (1H, d, J 8.0 Hz, H-5), 4.39 (1H, dd, J 8.0, 8.0 Hz, H-4), 3.66 (1H, d, J 15.0 Hz, NCH₂Ph). Minor diasteromer (in part): 7.42 (s, 1H, H-9), 7.30-7.02 (m, 5H, ArH), 4.84 (1H, d, J 14.5 Hz, NCH₂Ph), 3.52 (1H, d, J 14.5 Hz, NCH₂Ph). δ_C (125 MHz, CDCl₃) major diasteromer: 172.7 (CO) 148.4 (C-6), 143.8 (CH-9) 135.2 (ArC), 129.0, 128.5, 128.1, (ArCH), 111.6, 110.6 (C-7, C-8) 74.9 (CH-3), 74.5 (CH-4), 55.9 (CH-5), 45.3 (NCH₂Ph). MS (ESI⁺) m/z 274 (M+H)+ 100%. HRMS (ESI⁺) calcd. for C₁₅H₁₆NO₄ (M+H)+, 274.1688; found 274.1654.

**Method B**: The title compound was prepared from (157a) (100 mg, 0.199 mmol), 10% HCl (10 mL) and MeOH (10 mL) using the method described above. The product was obtained as white crystals (55.4 mg, 0.199 mmol, 100%, d.r. = 3.5/1). The NMR data of the major product was the same as that obtained using Method A.
6.5.8

(3R, 4S)-5-(Benzofuran-2-yl)-1-benzyl-3,4-bis(tert-butyl(dimethyl)silyloxy)pyrrolidin-2-one (161)

The title compound was prepared from (152) (63 mg, 0.140 mmol), benzofuran (0.045 mL, 0.419 mmol) anhydrous CH₂Cl₂ (5 mL) and BF₃·Et₂O (0.110 mL, 0.698 mmol) using the method described above for the synthesis of (154) (reaction time: 12 h), except that benzofuran was used instead of the boronic acid. Column chromatography (increasing polarity from 15% to 30% EtOAc in pet. sp as eluent) yielded the title product (42.4 mg, 0.077 mmol, 55%, d.r. = 7/1, R₇ = 0.76, 33% EtOAc/pet.sp) as a colorless oil. δ_H (500 Mz, CDCl₃) major diasteromer: 7.56-7.18 (9H, m, ArH), 6.56 (1H, s, H-7), 5.07 (1H, d, J 14.5 Hz, NCH₂Ph), 4.69 (1H, d, J 7.5 Hz, H-3), 4.47 (1H, d, J 7.5 Hz, H-5), 4.35 (1H, dd, J 7.5 7.5 Hz, H-4), 3.67 (1H, d, J 1.45 Hz, NCH₂Ph), 0.99 (s, 9H, (CH₃)₃CSi), 0.62 (s, 9H, (CH₃)₃CSi), 0.30 (s, 3H, CH₃Si), 0.21 (s, 3H, CH₃Si), 0.04 (s, 3H, CH₃Si), -0.05 (s, 3H, CH₃Si). Minor diasteromer (in part): 7.56-7.18 (9H, m, ArH), 6.66 (1H, S, H-7), 5.02 (1H, J 14.5 Hz, NCH₂Ph), 3.58 (1H, 14.5 Hz, NCH₂Ph). δ_C (125Mz, CDCl₃) major diasteromer: 173.7 (CO), 156.4, 136.2, 128.8 (3ArC), 152.9 (C-6), 129.9, 129.5, 129.0, 125.5, 123.9, 121.9, 112.3 (9ArCH), 108.4 (C-7), 76.4 (C-3), 76.0 (C-4), 58.1 (C-5), 46.3 (NCH₂Ph) 26.4 ((CH₃)₃CSi),
25.9 ((CH₃)₃CSi), 18.7 ((CH₃)₃C₃Si), 18.2 ((CH₃)₃C₃Si), -3.5 ((CH₃)₂Si), -3.9 ((CH₃)₂Si), -4.0 ((CH₃)₂Si), -4.1 ((CH₃)₂Si). MS (ESI⁺) m/z 552 (M+H)⁺ 100%. HRMS (ESI⁺) calcd. for C₃₁H₄₆NO₄Si₂ (M+H)⁺, 552.2970; found 552.2971.

6.5.9

(3aR, 6R, 6aR)-4-Benzyl-6-(tert-butyldimethylsilyloxy)-2-styryldihydropyrrol-3aH-[1,3,2]dioxaborolo[4,5-b]pyrrol-5(4H)-one (156)

The title compound was prepared from (153) (100 mg, 0.284 mmol), trans-vinylphenylboronic acid (74.9 mg, 0.932 mmol), anhydrous CH₂Cl₂ (5 mL) and BF₃·Et₂O (0.164 mL, 1.31 mmol) using the method described above for the synthesis of (154) (reaction time: 5 h). Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the product (83.0 mg, 0.185 mmol, 65%, Rf = 0.38, 50% EtOAc/pet. sp) as white crystals. M.p. 101-103°C. δH (500 MHz, CDCl₃) 7.52-7.30 (10H, m, ArH), 7.43 (1H, d, J 18.5 Hz, H-2’), 6.14 (1H, d, J 18.5 Hz, H-1’), 5.62 (1H, d, J 6.0 Hz, H-3a), 4.97 (1H, d, J 14.5 Hz, NCH²/Ph), 4.64 (1H, dd, J 5.5 1.5 Hz, H-7), 4.39 (1H, s, H-6), 4.21 (1H, d, J 14.5 Hz, NCH²/Ph), 0.98 (s, 9H, (CH₃)₃CSi), 0.30 (s, 3H, CH₃Si), 0.22 (s, 3H, CH₃Si). δC (125 MHz, CDCl₃) 171.2 (CO), 151.9 (C-2’), 137.2, 135.6 (ArC) 129.7, 129.0, 128.9, 128.8, 128.1, 127.1
(ArCH), 114.1 (C-1’), 88.1 (C-3a), 81.6 (C-7), 76.4 (C-6), 44.7 (NCH₂Ph),
26.0 ((CH₃)₂CSi), 18.5 ((CH₃)₂CSi), -4.0 ((CH₃)₂Si), -4.4 ((CH₃)₂Si). MS (ESI⁺) m/z 450 (M+H)⁺ 100%.
HRMS (ESI⁺) calcd. for C₂₅H₃₂BNO₄Si (M+H)⁺, 450.2216; found 450.2238.

6.6 Reactions of Pyrrolidinones (172) and (165a) and (165b) with Nucleophile

6.6.1 (3R, 4S, E)-1-Benzyl-3,4-bis(benzyloxy)-5-styrylpyrrolidin-2-one (172)

To a solution of (164) (97.3 mg, 0.242 mmol) and trans-vinylphenylboronic acid (71.4 mg, 0.482 mmol) in dry CH₂Cl₂ (5 mL) at 0 °C was added BF₃·Et₂O (0.121 ml, 0.946 mmol). The reaction was kept for 16.5 h, allowing the temperature to warm up to RT. The mixture was then quenched with saturated NaHCO₃ solution (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered and evaporated in vacuum to give yellow oil. Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the title product (54.5 mg, 0.113 mmol, 46%, d.r. = 1/2.3, Rf = 0.35, 33% EtOAc/pet. sp) as a colorless oil.
CDCl₃) major diasteromer: 7.44-7.16 (20H, m, ArH), 6.49 (1H, d, J 15.5 Hz, H-7), 5.87 (1H, dd, J 15.5, 9.0 Hz, H-6), 5.15 (1H, d, J 11.5 Hz, OCH₂Ph), 4.90 (1H, d, J 14.5 Hz, NCH₂Ph), 4.86 (1H, d, J 11.5 Hz, OCH₂Ph), 4.55 (2H, s, OCH₂Ph), 4.25 (1H, d, J 5.5 Hz, H-3), 3.98 (2H, m, H-5, NCH₂Ph), 3.90 (1H, dd, J 9.0 6.0 Hz, H-5). Minor diasteromer (in part): 7.44-7.16 (20H, m, ArH), 6.45 (1H, d, J 16.0 Hz, H-7), 6.06 (1H, dd, J 15.5 9.5 Hz, H-6), 4.52 (1H, d, J 11.5 Hz, OCH₂Ph), 4.46 (1H, d, J 11.5 Hz, OCH₂Ph), 4.39 (1H, d, J 6.0 Hz, H-3), 4.18 (1H, dd, J 7.0 7.0 Hz, H-4), 4.13 (1H, dd, J 8.0 8.0 Hz, H-5). δC (125 MHz, CDCl₃) major diasteromer: 180.0 (CO), 138.0, 137.6, 136.4, 136.1, 135.9 (ArC and C-7), 129.0, 128.9, 128.9, 128.8, 128.7, 128.6, 128.5, 128.1, 128.0 (ArCH), 126.9 (C-6), 83.5 (C-4), 80.9 (C-3), 72.8, 72.6 (2OCH₃Ph), 63.4 (C-5), 44.3 (NCH₂Ph). Minor diasteromer (in part): 170.6 (CO), 126.6 (C-6). MS (ESI⁺) m/z 490 (M+H)⁺ 100%. HRMS (ESI⁺) calcd.for C₃₃H₃₂NO₃ (M+H)⁺, 490.2382; found 490.2387.

6.6.2

(3R, 4S)-1-Benzyl-3,4-bis(benzyloxy)-5-(furan-2-yl)pyrrolidin-2-one (173a)

Method A: The title compound was prepared from (164) (117 mg, 0.290 mmol), 2-furanboronic acid (94.0 mg, 0.870 mmol), anhydrous CH₂Cl₂ (5 mL),
and BF₃·Et₂O (0.228 mL, 1.45 mmol) using the method described above for the synthesis of (154) (reaction time: 5 h). Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the title product (125 mg, 0.276 mmol, 95 %, d.r. = 4/1, Rf = 0.52, 33% EtOAc/pet. sp) as a colorless oil. δₓ (500 MHz, CDCl₃) major diasteromer:

7.42-7.06 (15H, m, ArH), 7.44 (1H, s, H-9), 6.35 (1H, dd, J 3.5 1.5 Hz, H-8), 6.72 (1H, d, J 3.5 Hz, H-7), 5.18 (1H, d, J 12.0 Hz, OCH₂Ph), 5.05 (1H, d, J 14.5 Hz, NCH₂Ph), 4.82 (1H, d, J 11.5 Hz, OCH₂Ph), 4.67 (1H, d, J 8.0 Hz, H-3), 4.58 (1H, d, J 7.0 Hz, H-5), 4.48 (1H, d, J 11.5 Hz, OCH'₂Ph), 4.39 (1H, d, J 11.5 Hz, OCH'₂Ph), 4.27 (1H, dd, J 8.0 7.0 Hz, H-4), 3.60 (1H, d, J 14.5 Hz, NCH₂Ph). Minor diasteromer (in part):

7.42-7.06 (15H, m, ArH), 3.57 (1H, d, J 14.5 Hz, NCH₂Ph). ¹³C NMR (125 MHz, CDCl₃) major diasteromer: 170.9 (CO), 148.9 (C-6), 143.7 (C-9), 138.2, 137.5, 135.7 (ArC), 129.0, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8 (ArCH), 111.0, 110.5 (C-7, C-8), 80.0, 79.9 (2OCH₂Ph), 73.3, 72.1 (C-3, C-4), 54.6 (C-5), 44.9(NCH₂Ph). MS (ESI⁺) m/z 454 (M+H)⁺ 100%. HRMS (ESI⁺) calcd.for C₂₉H₂₈NO₄ (M+H)⁺, 454.2018; found 454.2018.

**Method B:** The title compound was prepared from (164) (68 mg, 0.169 mmol), furan (0.031 mL, 0.431 mmol), anhydrous CH₂Cl₂ (5 mL), and BF₃·Et₂O (0.106 mL, 0.844 mmol) using the method described above for the synthesis of (154) (reaction time: 20 h), except furan was used instead
of the boronic acid. Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the title product (65.8 mg, 0.145 mmol, 86%, d.r. = 7/1, $R_f = 0.52$, 33% EtOAc/pet. sp) as a colorless oil.

6.6.3

(3R, 4S)-1-Benzyl-3,4-bis(benzyloxy)-5-(2-thienyl)pyrrolidin-2-one

(173b)

The title compound was prepared from (164) (132 mg, 0.327 mmol), 2-thiopheneboronic acid (83.7 mg, 0.654 mmol), anhydrous CH$_2$Cl$_2$ (5 mL), and BF$_3$·Et$_2$O (0.165 mL, 1.31 mmol) using the method described above for the synthesis of (154) (reaction time: 20 h). Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the title product (99.7 mg, 0.213 mmol, 65%, d.r. = 6/1, $R_f = 0.45$, 33% EtOAc/pet. sp) as a colorless oil. δ$_H$ (500 MHz, CDCl$_3$) major diastereomer:

7.41-6.91 (18H, m, 15ArH, H-7, H-8, H-9), 5.15 (2H, m, OCH$_2$/Ph, NCH$_2$/Ph), 4.85 (1H, d, $J$ 7.5 Hz, H-3), 4.80 (1H, d, $J$ 12Hz, OCH$_2$/Ph), 4.53 (1H, d, $J$ 7.0 Hz, H-5), 4.45 (1H, d, $J$ 12 Hz, OCH’/$H’$/Ph), 4.37 (1H, d,
$J \ 11.5 \ Hz, \ OCH'\text{H'}Ph$), 4.23 (1H, dd, $J \ 7.0 \ 7.0 \ Hz, \ H-4$), 3.59 (1H, d, $J \ 14.5 \ Hz, \ CH\text{H'}Ph$). Minor isomer (in part): 7.41-6.91 (18H, m, 15ArH, H-7, H-8, H-9), 5.07 (1H, d, $J \ 15.0 \ Hz, \ NCH\text{H'}Ph$). $^{13}$C NMR (125 MHz, CDCl$_3$) major diastereomer: 170.99 (CO), 138.78, 138.42, 137.91, 136.06 (ArC), 129.50, 129.26, 129.10, 129.00, 128.83, 128.68, 128.57, 128.52, 128.44, 128.24, 127.45, 127.44 (ArCH, C-7, C-8, C-9), 80.21, 80.07 (2OCH$_2$Ph), 73.75, 72.66 (C-3, C-4), 57.31(C-5), 45.14 (NCH$_2$Ph). MS (ESI$^+$) $m/z$ 470 (M+H)$^+$ 10%. HRMS (ESI$^+$) calcd. for C$_{29}$H$_{28}$NO$_3$S (M+H)$^+$, 470.1790; found 470.1784.

6.6.4

(3R, 4S)-1-Benzyl-3,4-bis(benzyloxy)-5-(3,4-dimethoxyphenyl)pyrrolidin-2-one (173c)

The title compound was prepared from (164) (100 mg, 0.248 mmol), 4,5-dimethoxyphenylboronic acid (135 mg, 0.744 mmol), anhydrous CH$_2$Cl$_2$ (5 mL), and BF$_3$·Et$_2$O (0.195 mL, 1.24 mmol) using the method described above for the synthesis of (154) (reaction time: 20 h). Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the title product (80.0 mg, 0.153 mmol, 62 %, d.r. = 1/1, $R_f = 0.20$, 33% EtOAc/pet. sp) as a colorless oil. $\delta_H$ (500 MHz,
CDCl₃) cis-diasteromer: 7.45-6.57 (18H, m, ArH), 5.22-3.51 (15H, m, H-3, H-4, H-5, 2OMe, NCH₂Ph, 2OCH₂Ph). Trans-diasteromer: 7.45-6.57 (18H, m, ArH), 5.22-3.51 (15H, m, H-3, H-4, H-5, 2OMe, NCH₂Ph, 2OCH₂Ph). MS (ESI⁺) m/z 524 (M+H)⁺ 100%. HRMS (ESI⁺) calcd. for C₃₃H₃₄NO₅ (M+H)⁺, 524.2437; found 524.2443.

6.6.5a

(3R, 4S)-1-Benzyl-3-(benzyloxy)-5-(furan-2-yl)-4-hydroxypyrrolidin-2-one (176a)

6.6.5b

(3R, 4S)-1-Benzyl-4-(benzyloxy)-5-(furan-2-yl)-3-hydroxypyrrolidin-2-one (176b)

The title compounds were prepared from the mixture of (165a) and (165b) (82.7 mg, 0.278 mmol), 2-furanbronic acid (93.3 mg, 0.834 mmol), anhydrous CH₂Cl₂ (5 mL) and BF₃·Et₂O (0.174 mL, 1.39 mmol) using the method described above for the synthesis of (154) (reaction time: 14 h). Column chromatography (increasing polarity from 15% to 70% EtOAc in pet. sp as eluent) yielded the product (176a) (29.5 mg, 0.078 mmol, 28%,
d.r. = 10/1, \( R_f = 0.22 \), 50% EtOAc/pet. sp) and the product (176b) (10.6 mg, 0.028 mmol, 10%, d.r. = 9/1, \( R_f = 0.30 \), 50% EtOAc/pet.sp) as colorless oils.

For compound (176a): \( \delta_H \) (500 MHz, CDCl\(_3\)) major diasteromer: 7.45-7.15 (11ArH and H-9), 6.34 (1H, s, H-8), 6.28 (1H, s, H-7), 5.19 (1H, d, \( J = 12.0 \) Hz, OCH\(_2\)/Ph), 5.01 (1H, d, \( J = 15.0 \) Hz, NCH\(_2\)/Ph), 4.86 (1H, d, \( J = 12.0 \) Hz, OCH\(_2\)/Ph), 4.47 (2H, m, H-3, H-5), 4.40 (1H, dd, \( J = 6.5 \) Hz, H-4), 3.59 (1H, d, \( J = 15.0 \) Hz, NCH\(_2\)/Ph). Minor diasteromer (in part): 7.45-7.15 (11ArH and H-9), 3.52 (1H, d, \( J = 15.0 \) Hz, NCH\(_2\)/Ph). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) major diasteromer: 170.8 (CO), 148.3 (C-6), 143.9 (C-9), 138.0, 135.5 (ArC), 128.9, 128.6, 128.5, 128.2, 128.0, 127.9 (ArCH), 111.6, 110.7 (C-7 and C-8), 81.0 (OCH\(_2\)/Ph), 73.5, 73.1 (C-3, C-4), 55.8 (C-5), 44.9 (NCH\(_2\)/Ph). MS (ESI\(^+\)) \( m/z \) 364 (M+H\(^+\)) 100%. HRMS (ESI\(^+\)) calcd. for C\(_{22}\)H\(_{22}\)NO\(_4\) (M+H\(^+\)), 364.1549; found 364.1555.

For compound (176b): \( \delta_H \) (500 MHz, CDCl\(_3\)) major diasteromer: 7.43 (1H, s, H-9), 7.36-7.10 (ArH), 6.34 (1H, d, \( J \approx 1.5 \) Hz, H-8), 6.28 (1H, d, \( J = 3 \) Hz, H-7), 5.02 (1H, d, \( J = 15.0 \) Hz, NCH\(_2\)/Ph), 4.84 (1H, d, \( J = 8.5 \) Hz, H-3), 4.58-4.56 (3H, m, H-5 and 2OCH\(_2\)/Ph), 4.20 (1H, dd, \( J = 8.0 \) Hz, H-4), 3.65 (1H, d, \( J = 15.0 \) Hz, NCH\(_2\)/Ph). Minor diasteromer (in part): 7.36-7.10 (ArH), 5.12 (1H, d, \( J = 15.0 \) Hz, NCH\(_2\)/Ph). \(^{13}\)C NMR (125MHz, CDCl\(_3\)) major diasteromer: 172.9 (CO), 149.1 (C-6), 144.1 (C-9), 138.0, 135.8 (2ArC), 129.5, 129.1, 129.0, 128.6, 128.4, 128.2 (10ArCH), 111.5, 110.9
(C-7 and C-8), 81.0 (OCH$_2$Ph), 74.3, 72.4 (C-3, C-4), 55.2 (C-5), 45.7 (NCH$_2$Ph). MS (ESI$^+$) $m/z$ 364 (M+H)$^+$ 100%. HRMS (ESI$^+$) calcd. for C$_{22}$H$_{22}$NO$_4$ (M+H)$^+$, 364.1549; found 364.1555.

6.6.6

(3$R$, 4$S$)-5-(benzofuran-2-yl)-1-benzyl-3,4-bis(benzyloxy)pyrrolidin-2-one (177)

The title compound was prepared from (164) (140 mg, 0.347 mmol), benzofuran (58.0 mg, 0.521 mmol), anhydrous CH$_2$Cl$_2$ (5 mL), and BF$_3$·Et$_2$O (0.174 mL, 1.39 mmol) using the method described above for the synthesis of (154) (reaction time: 20 h). Column chromatography (increasing polarity from 15% to 50% EtOAc in pet. sp as eluent) yielded the title product (148.6 mg, 0.328 mmol, 94.5 %, d.r. = 5/1, $R_f$ = 0.45, 33% EtOAc/pet. sp) as a colorless oil. $\delta_H$ (500 MHz, CDCl$_3$) Major diasteromer: 7.05-7.01 (19H, m, ArH) 6.62 (1H, s, H-7), 5.24 (1H, d, $J$ 11.5 Hz, OCH$_2$/Ph), 5.11 (1H, d, $J$ 15.0 Hz, NCH$_2$/Ph), 4.84 (1H, d, $J$ 11.5 Hz, OCH$_2$/Ph), 4.77 (1H, d, $J$ 8.5 Hz, H-3), 4.68 (1H, d, $J$ 7.5 Hz, H-5), 4.55 (1H, d, $J$ 11.5 Hz, OCH$_2$/Ph'), 4.44 (1H, d, $J$ 11.5 Hz, OCH$_2$/Ph'), 4.34 (1H, dd, $J$ 7.5 7.5 Hz, H-4), 3.64 (1H, d, $J$ 15.0 Hz, NCH$_2$/Ph).

Minor diasteromer (in part): 7.05-7.00 (19H, m, ArH) 6.64 (1H, s, H-7). $^{13}$C
NMR (125 MHz, CDCl$_3$) Major diasteromer: 171.1 (CO), 155.7, 138.1, 135.5, 128.8, (4ArC), 151.8 (C-6), 129.1, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 125.0, 123.3, 121.3, 111.8 (ArC), 107.8 (C-7), 80.1 80.0 (2OCH$_2$Ph), 73.5, 72.3 (C-3, C-4), 55.1 (C-5), 45.1 (NCH$_2$Ph). Minor diasteromer (in part): 172.4 (CO). MS (ESI$^+$) m/z 504 (M+H)$^+$ 100%.

HRMS (ESI$^+$) calcd. for C$_{33}$H$_{30}$NO$_4$ (M+H)$^+$, 504.2175; found 504.2182.
Chapter 7: References


121, 5075-5076.


