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Department of CHEMISTRY

The University of British Columbia
Vancouver, Canada

Date 14 August 2003.

DE-6 (2/88)
Abstract

The photochemically initiated semipinacol rearrangement of a substrate bearing an intramolecular alcohol 1.10 was attempted in order to provide spirocyclic ring systems. The syntheses of carbocyclic ring expansion precursors were achieved. Unfortunately, the use of UV light and a photosensitizer to initiate ring expansion reaction was unsuccessful.

It was found that a majority of siloxy-epoxide ring expansions of cyclobutane rings to form 1-azaspiro[5.4]decanes are unselective. The ring expansion of cyclobutane rings was executed on siloxy-epoxide carbocycles 2.6 and 2.15 and heterocycle 2.34 with the intent of achieving mechanistic elucidation. Three scenarios for the stereochemical outcome of the rearrangements were examined. The rearrangement was deduced to most likely occur via an unselective synchronous mechanism where anti and syn migration of the alkyl (CH₂) group onto the epoxide moiety take place to give 2.4 and 2.5, respectively. Interesting diastereoselectivity was observed by varying the silicon substituent size and the substitution at the 3-position of the heterocycle. Also, chiral Lewis acid initiated ring expansions were attempted as a method of introducing asymmetry.

Finally, synthesis of the A ring of cylindricine B via nitrogen addition (Michael reaction) onto an α,β-unsaturated carbonyl 3.7 was attempted. The synthesis of the B and C ring framework was executed following group precedent. The synthesis of the α,β-unsaturated carbonyl side chain was attempted using Kishi-Nozaki and carbonylative Stille coupling reactions on an azaspirocyclic vinyl triflate 3.1. The Michael acceptor side chain was not successfully appended using these coupling reactions. The synthesis of the A ring is key in performing the first asymmetric total synthesis of cylindricine B. Therefore, further investigations on appending the Michael acceptor side chain are necessary in order to achieve this goal.

![Chemical structures](image)
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   Trimethyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (2.6)
   6-Hydroxyspiro[4.5]decan-1-one (2.7)
   6-Hydroxyspiro[5.5]undecan-1-one (2.10)
   (1-Cyclohex-1-enylcyclobutoxy)-trimethysilane (2.12)
   1-(7-oxa-bicyclo[4.1.0]hept-1-yl) (2.13)
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   Triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (2.15)
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1-(Toluene-4-sulfonyl)-6-(1-trisopropylsilanyloxy)cyclobutyl-
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   undeca-4,7-diene-7-carboxylic acid methyl ester (3.4)

   [3-(tert-Butyl-dimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]
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Ac  acetate
θ  angle
b  broad (spectra)
BINOL  1,1'-bi-2-naphthol
Bu  butyl
Bz  benzoyl
cat.  catalytic
cm⁻¹  wavenumbers
CO  carbon monoxide
CSA  (1R)-(−)-10-camphorsulfonicacid
d  chemical shift
db  doublet
dba  dibena[a, h]anthracene
DBU  1,8-diazabicyclo[5.4.0.]undec-7-ene
dec' n  decomposition
°  degree
DIBAL-H  diisobutylaluminium hydride
DMAP  N,N-dimethylaminopyridine
DMDO  dimethylidioxirane
DMF  N,N-dimethylformamide
dppf  1,1'-bis(diphenylphosphino)ferrocene
dt  doublet of triplets
E  energy
E  entgegen (opposite side in $E$, $Z$ nomenclature)
E1  fist-order elimination reaction
ee  enantiomeric excess
Eq.  equation
eq.  equivalents
Et  ethyl
Er  triplet state energy
Et₃N  triethylamine
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<td>Et₂O</td>
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<tr>
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<td>HCl</td>
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<td>hv</td>
<td>energy of light</td>
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<td>Hz</td>
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<td>infrared</td>
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</tr>
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<td>K₂CO₃</td>
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<tr>
<td>NaHCO₃</td>
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<td>sm</td>
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<td>S_N1'</td>
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<td>zusammen (same side in E, Z nomenclature)</td>
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Acknowledgements

I would like to thank my supervisor, Dr. Gregory Dake, for his guidance, assistance and support. Also, I appreciate being given the opportunity to be educated in such a good learning environment.

I would like to thank the Dake group members; Michael Fenster for his knowledge and advice; Michael Wilson for his support and computer skills; Erik Fenster, Leah Easton, Tyler Harrison and Jacqueline Woo for being such great lab mates. I am especially thankful to Paul Hurley for his constant help, expertise and friendship and Eagranie Yuh for her assistance and proof reading.

I would like to thank all of the Piers group members for their technical support and help.

I would like to thank the Scheffer group members for their help with the UV-lamp, computer modeling, GC-MS and chiral HPLC.

I would also like to thank Dr. Alex Wang for his expertise in computer modeling. Brian Patrick for his efficiency and capability on X-ray crystallography.

I would like to thank all my friends who were always there for me when I needed advice, help or fun.

Finally, I am forever thankful for my family and their love, patience, understanding and advice.
Chapter One

Photochemically Induced Ring Expansions
I. Introduction

A. Photochemistry Background

The regioselective addition of an unsymmetrical reagent such as HCl, to an unsymmetrical olefin proceeds stepwise via the more stable of the two possible carbenium ion intermediates (Markovnikov's rule) (Scheme 1.1). The initial addition of the electrophilic proton forms predominantly, the more stable carbenium ion. This controls the regiochemistry of nucleophilic attack by Cl⁻ and results in the formation of 1-chloro-1-methylcyclohexane as the major product (Markovnikov product).

Scheme 1.1: Mechanism of Electrophilic Addition to Unsymmetrical Alkenes

Usually, the protonation of a simple alkene requires the use of strong acid. However in many cases, the substrate may not be stable to harsh acidic conditions. In 1966, it was discovered by Marshall that the addition of methanol to 1-menthene 1.1 could be carried out under neutral conditions. The reaction was carried out photochemically in the presence of a high-energy sensitizer (such as benzene, toluene, or xylene) to give the Markovnikov addition product 1.2 (Eq. 1.1).
The key intermediate in the addition reaction is believed to be the highly reactive trans isomer of cyclohexene 1.3 (Scheme 1.2). Obviously, a trans double bond is not stable in a six-membered ring and suffers considerable torsional strain. The strained trans double bond 1.3 can formally be written as a zwitterionic species 1.4. In a protic solvent such as methanol, E-cyclohexene can be protonated. Following Markovnikov's rule, the more stable carbenium ion 1.5 is formed. The carbenium ion is then attacked by methoxide (MeO⁻) to give 1.2 as the major product.

Scheme 1.2: Photochemical Addition to 1-Menthene

The double bond isomerization occurs because aromatic compounds such as toluene, xylene, and benzene are high-energy sensitizers (Eₜ sensitizer = 84 kcal/mol) and can photosensitize the Z to E interconversion of simple alkenes.

The isomerization of alkenes takes place via a triplet-excited state in which the two sp² carbons are twisted 90° with respect to one another (Scheme 1.3 and Figure 1.1). The first 90° rotation causes the p orbitals of each carbon to be orthogonal. This perpendicular geometry in the excited state of the system represents an energy minimum where electron repulsion is relieved. This geometry permits the possibility, by another 90° rotation of returning either to the Z- or the E- configuration of the double bond.

Scheme 1.3: Mechanism for Photosensitized Isomerization of Alkenes

Figure 1.1: Triplet-Excited State of Alkenes
B. Proposal for Ring Expansion

Our group is interested in the construction of azaspirocyclic ketones. There are three strategies currently used in our group to build the spiro-connected bicyclic ring system: an acid mediated semipinacol rearrangement, a Lewis acid promoted siloxy-epoxide ring expansion reaction, and a N-bromosuccinimide (NBS) initiated rearrangement (Scheme 1.4).^5

Scheme 1.4: Approaches for the Construction of Azaspirocyclic Ketones

<table>
<thead>
<tr>
<th>BRØNSTED ACID</th>
<th>SILOXY-EPOXIDE / LEWIS ACID</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Reactions" /></td>
<td><img src="image2.png" alt="Reactions" /></td>
</tr>
</tbody>
</table>

The acid initiated semipinacol rearrangement using Brønsted acid was unsuccessful with cyclopentanol substrate 1.6. The ring opened compound 1.7 was the sole isolated product in 45% yield (Eq. 1.2).

![Reactions](image3.png) (1.2)

Because construction of azaspirocyclic ketones are synthetically useful, our group was interested in other methods to promote the ring expansion reaction.

The photosensitized reaction of 1-cyclohexenylcarbinol 1.8, which has an intramolecular alcohol, gave the semipinacol rearranged product 1.9 (Scheme 1.5).^6

Scheme 1.5: Photosensitized Reactions of 1-Cyclohexenylcarbinols

![Reactions](image4.png)
In connection with this reaction, the photosensitized ring expansion of 1-cyclohex-1-enylcyclopentanol 1.10 was examined (Scheme 1.6). The semipinacol rearrangement could provide novel synthetic routes to spirocyclic ring products such as 1.11.

Scheme 1.6: Photosensitized Initiated Ring Expansion

II. Synthesis of Ring Expansion Precursor

The synthesis of 1-chlorocyclohexene 1.13 was achieved by adding cyclohexenone 1.12 to neat phosphorus pentachloride at 0 °C (Eq. 1.3).  

\[ \text{1.12} \xrightarrow{\text{PCl}_5, 0 \degree C \rightarrow \text{rt}} \text{1.13} \]  

(1.3) 

1-Chlorocyclohexene 1.13 reacts with lithium metal in ether, via a lithium-chloride exchange to give the alkenyllithium 1.14 (Eq. 1.4 and Table 1.1).  

Table 1.1: Metalation of 1-Chlorocyclohexene by Lithium

<table>
<thead>
<tr>
<th>entry</th>
<th>1.13 (eq.)</th>
<th>Li (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>comment</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>2.2</td>
<td>25</td>
<td>14</td>
<td>solution is 0.40M</td>
<td>I-40</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>2.0</td>
<td>35</td>
<td>42</td>
<td>LiCl salt observed</td>
<td>II-16</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>1.8</td>
<td>35</td>
<td>48</td>
<td>LiCl salt observed</td>
<td>II-28</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>1.8</td>
<td>35</td>
<td>48</td>
<td>LiCl salt observed</td>
<td>II-29</td>
</tr>
<tr>
<td>5</td>
<td>1.7</td>
<td>4.3</td>
<td>25</td>
<td>18</td>
<td>LiCl salt observed</td>
<td>II-35</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>2.2</td>
<td>35</td>
<td>14</td>
<td>LiCl salt observed</td>
<td>III-16</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>2.2</td>
<td>35</td>
<td>14</td>
<td>LiCl salt observed</td>
<td>III-25</td>
</tr>
</tbody>
</table>

(a) The alkenyllithium 1.14 formed was used in situ in the next step (Eq. 1.5 and Table 1.2), same entry (b) Notebooks
The formation of the alkenyllithium 1.14 was not easily monitored. Under most reaction conditions, lithium metal was recovered. This indicated that the metalation reaction did not proceed to completion. However, the titration of 1.14 showed that the lithium-chloride exchange had occurred to some extent (entry 1). Also, the formation of lithium chloride salt supports the formation of 1.14.

The alkenyllithium 1.14 should, in principle, add to cyclopentanone 1.15 to give the addition product 1.10 (Eq. 1.5 and Table 1.2). \[1.14 + \text{Et}_2\text{O} \rightarrow 1.10\]

Table 1.2: Vinyl Lithium Addition of 1.14 to Cyclopentanone

<table>
<thead>
<tr>
<th>entry</th>
<th>1.14 (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>1.10</th>
<th>comment</th>
<th>Ref. (^8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>0 → 25</td>
<td>1</td>
<td>-</td>
<td>3 products isolated</td>
<td>II-05</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>0 → 35</td>
<td>4</td>
<td>2%</td>
<td>isolated 3 products</td>
<td>II-16</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>-100 → 25</td>
<td>1</td>
<td>-</td>
<td>TLC showed 1.10, dec’n during distillation</td>
<td>II-28</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>-100 → 25</td>
<td>1.5</td>
<td>&lt;1%</td>
<td>TLC showed 1.10</td>
<td>II-29</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>-78 → 25</td>
<td>2</td>
<td>-</td>
<td>TLC showed 3 products but no 1.10</td>
<td>II-35</td>
</tr>
<tr>
<td>6</td>
<td>3.8</td>
<td>-100 → 25</td>
<td>1.5</td>
<td>12%</td>
<td>TLC showed 3 products and 1.10</td>
<td>III-16</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>-100 → 25</td>
<td>2.5</td>
<td>15%</td>
<td>TLC showed 4 products and 1.10</td>
<td>III-25</td>
</tr>
</tbody>
</table>

(a) Notebooks

The formation of cyclopentanol 1.10 was followed by TLC, \(^1\)H NMR and IR spectroscopies. The \(^1\)H NMR of 1.10 should have a signal around 5 to 6 ppm for the olefin proton, and another signal at 4 ppm for the tertiary alcohol (Fig. 1.2). The IR spectrum of 1.10 should have a strong band around 3400 cm\(^{-1}\) for the alcohol stretch.

Figure 1.2: Anticipated Chemical Shift in \(^1\)H NMR of 1.10

\[\delta_{\text{O-H}} = 4 \text{ ppm}\]

\[\delta_{\text{O-H}} = 5-6 \text{ ppm}\]
The addition product 1.10 was first observed by crude $^1$H NMR and IR spectrometries (entry 2). 1-Cyclohex-1-enylcyclopentanol 1.10 seems to decompose under the slightly acidic conditions of SiO$_2$ column chromatography. Pre-washing the silica gel with 1% triethylamine allowed for the isolation of the addition product 1.10, albeit in low yield. Generally, because of the low yield of the product, the reaction was carried out on large scale. For example, 5 g of cyclopentanone gave 200 mg (2%) of addition product 1.10. After several trials, the product $R_f$ was identified, and subsequent experiments could be monitored by TLC instead of by $^1$H NMR and IR spectrometries (entries 3-7).

The reaction conditions were “optimized” and the condensation product 1.10 was obtained in 15% yield (entry 7). The “optimized” reaction was done by adding 2.5 equivalents of cyclopentanone 1.15 to a $-100 \, ^\circ$C solution of alkenyllithium 1.14. The formation of the addition product appears to be temperature dependent. If the alkenyllithium solution was cooled to $-78 \, ^\circ$C instead of $-100 \, ^\circ$C, the addition product was not observed (entry 5).

Three other major products were isolated after the condensation reaction but only two of them could be identified. The aldol product 1.16 was obtained in 43% yield and the dehydration product 1.17 was isolated in 7% yield (Fig. 1.3).

Figure 1.3: Identified Side Products of the Addition Reaction (Eq. 1.5)

![Figure 1.3](image)

The formation of bicyclopentyliden-2-one 1.16 results from the aldol condensation of cyclopentanone 1.15. Alkenyllithium 1.14 deprotonates cyclopentanone at its $\alpha$-position. The resulting enolate condenses with another cyclopentanone molecule, then undergoes $\beta$-elimination to give product 1.16. The dehydration product 1.17 was presumably produced by elimination of the tertiary alcohol of 1.10 to give the observed conjugated diene.

Compound 1.10 was difficult to isolate. On the TLC plate, the addition product 1.10 had a $R_f$ between 1.16 and an unidentified product (Fig. 1.4). Because the three compounds have similar $R_f$ values, purification by flash column chromatography could not separate them properly. Unfortunately, purification by distillation only resulted in decomposition of the addition product 1.10 (entry 3). Ultimately, purification via rotary column chromatography using a chromatotron was successful.
The $^1$H NMR spectrum of 1.10 in deuterodimethylsulfoxide showed the resonances for the olefin proton (δ 5.67 (m, 1H)) and the tertiary alcohol (δ 4.08 (s, 1H)). The IR spectrum of 1-cyclohex-1-enylcyclopentanol exhibited one strong stretch for the alcohol functional group (ν 3368 cm$^{-1}$).

The lithium-chloride exchange of 1.13 was also attempted using tert-butyl lithium (Eq. 1.6). The reaction was sluggish by TLC. Five products, having similar Rf values, were observed. One isolated product had a tertiary alcohol signal (δ 4.03 (s, 1H)) by $^1$H NMR spectrum but the olefinic proton expected for 1.10 (δ5.67 (m, 1H)) was absent. The other isolated products had no $^1$H NMR signals characteristic of 1.10. Therefore, this method was deemed to be unsuitable.

The formation of the alkenyllithium intermediate 1.14 was also attempted using the Shapiro reaction (Eq. 1.7). Quenching the alkenyllithium intermediate with cyclopentanone gave a mixture of products by TLC. 1-Cyclohex-1-enylcyclopentanol was not observed by $^1$H NMR spectrum. Therefore, this method of forming the vinyliclithium species was also deemed unsuitable.

The synthesis of 1-cyclohex-1-enylcyclobutanol 1.19 was also conducted via the same strategy as for 1-cyclohex-1-enylcyclopentanol 1.10. However, use of cyclobutanone as the electrophile gave a much cleaner reaction by TLC (Eq 1.8). The dehydration and aldol
condensation products were not observed. Without formation of these side products, the addition product 1.19 was achieved in higher yield (73%). The overall yield was probably dependent on the extent of formation of alkenyllithium species 1.14 (Table 1.1).

\[
\begin{align*}
\text{1.13} & \xrightarrow{1) \text{Li}^+/\text{Et}_2\text{O}} \xrightarrow{35^\circ \text{C}} \text{1.19} \\
& \xrightarrow{2) \text{OH}^-} \xrightarrow{-100^\circ \text{C} \rightarrow \text{rt}} 73\%
\end{align*}
\]

The observation that the yield of addition product is higher with cyclobutanone than cyclopentanone indicates one of two things: (a) that the hydrogens next to the carbonyl in cyclobutanone are less acidic, or (b) that the rate of nucleophilic addition to cyclobutanone is faster than the rate of deprotonation.\(^{10}\)

In the case of cyclopentanone, the formation of the aldol product 1.16 as the major product shows that the rate of nucleophilic addition is slower than the rate of deprotonation. It is known that cyclopentanone undergoes nucleophilic addition much slower than cyclobutanone and cyclohexanone, due to angle strain in the transition state (Table 1.3).\(^{11}\)

**Table 1.3: Rates of Reduction of Cyclic Ketones by Sodium Borohydride**\(^ {11a}\)

<table>
<thead>
<tr>
<th>cyclic ketones</th>
<th>(k_2 \times 10^4 \text{ (M}^{-1}\text{s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclobutanone</td>
<td>264</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>7</td>
</tr>
<tr>
<td>cyclohexanone</td>
<td>161</td>
</tr>
</tbody>
</table>

It has been found that reactions in which an sp\(^2\) carbon is converted to an sp\(^3\) carbon in a four-membered ring, are more favourable than corresponding reactions in a five-membered ring.\(^{11d}\) The explanation for this difference lies in the relative angle strain in the two systems. In a five-membered ring, converting an sp\(^2\) atom to an sp\(^3\) atom increases the strain because of the increase in the number of eclipsing interactions (Scheme 1.7). In a four-membered ring the reactivity is enhanced because of the strain decrease in going from an sp\(^2\) to an sp\(^3\) hybridization.

**Scheme 1.7: Strain on Nucleophilic Addition to Cyclic Ketones**
III. Photochemistry

A. General Considerations

Irradiations were performed using a 450 W Hanovia medium-pressure mercury lamp in a water-cooled immersion well. A quartz reaction vessel was used and the light from the Hanovia lamp was filtered through Corning glass #9720, which transmits wavelength $\lambda \geq 232$ nm.

The reaction solutions were purged with nitrogen for at least 15 minutes prior to irradiation, and the reactions were performed in sealed reaction vessels. Mixing was accomplished by use of a stirring bar and a magnetic stirrer.

B. Photosensitized Reaction of 1-Cyclohex-1- enylcyclopentanol

The photosensitized reaction of 1-cyclohex-1-enylcyclopentanol $1.10$ could lead, in theory, to the ring expansion product $1.11$ (Eq. 1.9 and Table 1.4).

![Chemical structure](image)

(1.9)

| Table 1.4: Photochemistry Result of 1.10 |
|---|---|---|---|---|---|---|---|
| entry | solvent | sensitizer | t(h) | 1.10 | 1.17 | 1.20 | comment |
| 1 | - | toluene | 5.5 | - | - | - | TLC showed 1.10 and 1.17 | II-38 |
| 2 | - | $o$-xylene | 5.5 | - | - | - | TLC showed 3 products: 1.10, 1.17 and unidentified product | II-40 |
| 3 | - | benzene | 6 | - | - | - | TLC showed 1.10 and 1.17 | II-43 |
| 4 | - | $p$-xylene | 14 | - | - | - | TLC showed 1.10 and 1.17 | II-50 |
| 5 | $t$-BuOH | $p$-xylene | 14 | - | - | - | TLC showed 1.10 and 1.17 | III-04 |
| 6 | MeOH | $p$-xylene | 3 | 55% | 8% | 35% | TLC showed 1.10, 1.17 and 1.20 | III-21 |
| 7 | $t$-BuOH | $p$-xylene | 48 | 100% | - | - | TLC showed only 1.10 | III-27 |
| 8 | $t$-BuOH | $o$-xylene | 48 | 100% | - | - | TLC showed 3 products: 1.10, 1.17 and unidentified product | III-30 |

(a) All the reactions were performed on 20 to 150 mg of 1.10 (b) Notebooks (c) Ratios determined by GC analysis

The photosensitized reactions were followed by TLC, $^1$H NMR and GC–MS spectroscopies. The $^1$H NMR spectrum of 1.11 should have a signal around 2.3 ppm for the
carbonyl alpha protons. Also, the olefin signal present in the spectrum of starting material 1.10 (δ 5.67 (m, 1H)) should not be in the product spectrum. Finally, the GC of 1.11 should have a different retention time than 1.10.

Different reaction conditions were attempted, but none of them gave the spirocyclic ring product 1.11. Under the experimental conditions attempted, the product 1.11 was not synthesized. In some cases, identifiable side products were formed (Figure 1.5 and Table 1.4).

**Figure 1.5: Side Products Formed During the Photosensitized Reaction of 1.10**

![Figure 1.5](image)

The first four trials were performed in aprotic media (entries 1-4). The TLC analysis of each entry showed significant amounts of starting material. One side product of the reaction was 1.17, where the alcohol of the starting material was eliminated. Variation of the sensitizer did not seem to make any difference in the course of the reaction (entries 1-4).

Generally, for $Z$ to $E$ cyclohexene isomerization, a mixture of alcoholic solvent and sensitizer are used (entries 5-8). To be consistent with the literature, $p$-xylene was chosen as the sensitizer, and various protic solvents were tried (entries 5-7). When $t$-butanol or a mixture of $t$-butanol and water were used as solvent, GC analysis indicated the continued presence of starting material (entries 5, 7 and 8).

When methanol was employed as solvent, the products 1.17 and 1.20 were formed (entry 6). Purification and isolation by flash column chromatography afforded the recovery of the starting material in 55%, product 1.20 in 35% and product 1.17 in 8% yield. The formation of 1.17 and 1.20 could be derived from the same intermediate 1.21 (Scheme 1.8).

**Scheme 1.8: Proposed Mechanism of 1.17 and 1.20 Formation**

![Scheme 1.8](image)
Departure of the hydroxyl of 1.10 forms the stable tertiary allylic carbocation 1.21. This intermediate can undergo a $S_N1$ or an $E1$ reaction. Methanol, a good nucleophile, if it is present in the reaction media, can add to the carbocation to give the substitution product 1.20. Also, a base present in solution, can abstract a hydrogen next to the carbocation to produce the conjugated diene 1.17.

In the case where $t$-butanol was used as protic solvent, the substitution product was not observed. This is probably due to the steric hindrance of the bulky nucleophile and the tertiary carbocation. Only the elimination product 1.17 was observed (entry 5).

Some other products were observed by TLC, in minimal yield. Thus, they could not be isolated (entries 2 and 8).

The photochemistry results show us that the double bond in the starting material might not undergo a $Z$ to $E$ isomerization (Table 1.4). This may be due to steric strain where the adjacent sp$^2$-hybridized carbon atoms can not attain the requisite 90° (orthogonal) geometry favoured for the triplet state and essential for $Z$ to $E$ isomerization (Scheme 1.3 and Figure 1.1). Alternatively, the triplet energy of the $Z$ double bond might be too high in energy to be excited by the triplet energy of the sensitizer. This means that the energy transfer from the sensitizer to the reagent is endothermic ($E_T$ sensitizer $< E_T$ reagent).

**IV. Concluding Remarks**

The syntheses of 1-cyclohex-1-enylcyclobutanol 1.19 and 1-cyclohex-1-enylcyclopentanol 1.10 were accomplished via the addition of alkenyllithium species 1.14 to the suitable electrophile (Figure 1.6).

**Figure 1.6: Products Synthesised**

\[
\text{1.14} \quad \text{1.19} \quad \text{1.10}
\]

Photosensitized reaction conditions were applied to 1-cyclohex-1-enylcyclopentanol 1.10 in the hopes of obtaining ring expansion product 1.11 (Eq. 1.10). Unfortunately, none of the attempted reactions afforded the desired product, 1.11.
If the product 1.11 was formed, the ketone may not be stable to the reaction conditions and may undergo different types of reaction such as a Norrish Type I or II fragmentation.\textsuperscript{13}

In conclusion, the photochemically initiated ring expansion project was an interesting approach to the construction of azaspiroyclic ketone, but was not successful.
V. Experimental

General

All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, benzene, toluene were distilled from calcium hydride. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV254 pre-coated TLC plates. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Infrared (IR) spectra were obtained using a Perkin-Elmer 1710 FT-IR spectrometer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in deuterochloroform, deuteromethanol, deuteracetone, deuterobenzene or deuterodimethylsulfoxide using either a Bruker WH-400 or a Bruker AV-300 spectrometer. Carbon nuclear magnetic resonance (^13C NMR) spectra were recorded in the same deuterosolvent as for ^1H NMR using a Bruker AV-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.24 ppm ^1H NMR; 77.0 ppm ^13C NMR), deuteromethanol (δ 5.84 ppm ^1H NMR; 49.0 ppm ^13C NMR), deuteracetone (δ 2.05 ppm ^1H NMR; 30.8 ppm ^13C NMR), deuterobenzene (δ 7.15 ppm ^1H NMR; 128.0 ppm ^13C NMR) or deuterodimethylsulfoxide (δ 2.50 ppm ^1H NMR; 39.4 ppm ^13C NMR). Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on either a Kratos-AEI model MS 50 spectrometer (for EI) or a Kratos MS 80 spectrometer (for CI+ or DCI+). Gas chromatography-mass spectroscopy (GC-MS) data were recorded on an Agilent 6890 plus GC system connected to an Agilent 5973 network mass selective detector with an HP-5MS (30 m x 0.25 mm ID, Hewlett-Packard) column. Analyses were runs with a split injection port (split ratios 100:1) and an electron impact ionization source of 70eV was employed. High pressure liquid chromatography (HPLC) analyses were performed on a Waters 600E system coupled to a tunable UV absorbance detector (Waters 486). The Chiralcel column: AS (250 mm x 4.6 mm ID), and OD (250 mm x 4.6 mm ID) employed were obtained from Chiral Technologies Incorporated. Microanalyses were performed by Mr. Peter Borda or in the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a Fisions CHN-O Elemental Analyzer Model 1108.
1-Cyclohex-1-enylcyclopentanol (1.10)

To a suspension of 135 mg (19.6 mmol) of finely cut lithium, pre-washed with pentane, in 6.0 mL of Et₂O was added 1 mL (8.9 mmol) of cyclohexenyl chloride. The reaction mixture was heated to reflux overnight and then cooled to rt. The solution was cannulated into an empty round bottom flask to remove the unreacted lithium and the lithium chloride salt. The cannulated solution was cooled to −100 °C and a −100 °C solution of 3 mL (33.8 mmol) of cyclopentanone in 3.0 mL of Et₂O was added. The resulting mixture was stirred at −100 °C for 90 min., then 60 min. at rt. The reaction mixture was poured into a saturated aqueous solution of NH₄Cl. The two layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on pre-washed silica gel with 1% Et₃N / hexane (20% ethyl acetate-hexanes) followed by purification by chromatotron (7% ethyl acetate-hexanes) yielded 175 mg (12% after 2 x purification) of a clear liquid.

IR (NaCl): 3367, 2930, 1447, 1220, 1188 cm⁻¹. ¹H NMR (300 MHz, C₆D₆): δ 5.68-5.67 (m, 1H), 2.01-1.85 (m, 6H), 1.58-1.46 (m, 6H), 0.78 (bs, 1H). ¹³C NMR (75 MHz, C₆D₆): δ 142.4, 119.5, 83.9, 38.4, 25.4, 25.2, 23.9, 23.5, 22.9. LRMS (EI+) m/z (relative intensity): 166 (M), 148 (M-H₂O).

Table 1.5: Experimental Details for Table 1.1 and 1.2

<table>
<thead>
<tr>
<th>entry</th>
<th>1.13</th>
<th>Li</th>
<th>1.15</th>
<th>1.10</th>
<th>1.16</th>
<th>1.17</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>7280 (62)</td>
<td>725 (104)</td>
<td>4410 (52)</td>
<td>200 (2%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>1000 (8.9)</td>
<td>135 (19.6)</td>
<td>2850 (34)</td>
<td>175 (12%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>1870 (16.1)</td>
<td>245 (35.5)</td>
<td>3420 (40)</td>
<td>400 (15%)</td>
<td>1050 (43%)</td>
<td>175 (7%)</td>
</tr>
</tbody>
</table>

(a) Entries are: weight in mgs (mmols); for product: weight in mgs (yield)
Bicyclopentyliden-2-one (1.16)\(^{14}\)
IR (NaCl): 2958, 2872, 1709, 1415, 1252, 1170 cm\(^{-1}\). \(^{1}\)H NMR (300 MHz, C\(_6\)D\(_6\)): δ 2.90-2.81 (m, 2H), 2.21-2.13 (m, 2H), 2.05 (t, J=7.7 Hz, 2H), 1.96-1.90 (m, 2H), 1.57-1.36 (m, 6H). \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)): δ 205.1, 156.5, 39.6, 34.0, 32.6, 29.5, 27.2, 25.5, 20.3. LRMS (EI+) m/z (relative intensity): 150 (M).

1-Cyclohex-1-enylcyclohexene (1.17)\(^{15}\)
\(^{1}\)H NMR (400 MHz, C\(_6\)D\(_6\)): δ 5.67 (bs, 1H), 5.61 (bs, 1H), 2.47-2.43 (m, 2H), 2.38-2.35 (m, 2H), 2.23-2.19 (m, 2H), 2.04-1.99 (m, 2H), 1.84-1.77 (m, 2H), 1.60-1.47 (m, 4H).

1-Cyclohex-1-enylcyclobutanol (1.19)
To a suspension of 50 mg (7.25 mmol) of finely cut lithium, pre-washed with pentane, in 3.0 mL of Et\(_2\)O was added 370 μL (3.3 mmol) of cyclohexenyl chloride. The reaction mixture was heated under reflux overnight and then cooled to rt. The solution was cannulated into an empty dry round bottom flask to remove the unreacted lithium and the lithium chloride salt. The cannulated solution was cooled to –100 °C and a –100 °C solution of 247 μL (3.3 mmol) of cyclobutanone in 1.0 mL of Et\(_2\)O was added. The resulting mixture was stirred at –100 °C for 90 min., then 60 min. at rt. The reaction mixture was poured into a saturated aqueous solution of NH\(_4\)Cl. The two layers were separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation \textit{in vacuo}. Purification by column chromatography on pre-washed silica gel with 1% Et\(_3\)N / hexane (20% ethyl acetate-hexanes) yielded 365 mg (73%) of a clear liquid.
IR (NaCl): 3336, 2931, 1440, 1248, 1139 cm\(^{-1}\). \(^{1}\)H NMR (400 MHz, C\(_6\)D\(_6\)): δ 5.59 (m, 1H), 2.25-2.15 (m, 2H), 2.07-1.77 (m, 6H), 1.58-1.41 (m, 6H). \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)): δ 140.0, 119.9, 77.9, 34.5, 25.4, 23.25, 23.20, 23.16, 22.8, 13.6. LRMS (EI+) m/z (relative intensity): 134 (M-H\(_2\)O).
1-(1-Methoxycyclopentyl)cyclohexene (1.20)

IR (NaCl): 2931, 2871, 1447, 1069 cm\(^{-1}\). \(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)SO): \(\delta\) 5.62 (bs, 1H), 2.87 (s, 3H), 2.29-2.11 (m, 2H), 2.06-2.01 (m, 2H), 1.93-1.90 (m, 2H), 1.78-1.74 (m, 2H), 1.62-1.50 (m, 6H).

VI. References

Chapter Two

Mechanistic Studies of Four-Membered Ring Expansion Reactions
I. Introduction

A. Synchronous Five-Membered Ring Expansion / Anti Migration

During the methodology development of the siloxy epoxy semipinacol rearrangement, the cyclopentanol derivative 2.1 rearranged stereoselectively to give one diastereomer 2.2 (Eq. 2.1).\(^1\) The selectivity of the ring expansion reaction indicated that a synchronous reaction is likely occurring. A cis relationship between the carbonyl and the alcohol was obtained in the product. Therefore, compound 2.2 is termed the cis aldol product. Stereoelectronic effects are maximized during a synchronous anti migration of the alkyl CH\(_2\) substituent onto the epoxide moiety (Scheme 2.1).\(^2\)

Scheme 2.1: Stereoelectronic Factors in Anti Migration Reaction

![Scheme 2.1: Stereoelectronic Factors in Anti Migration Reaction](image)

The migrating substituent must be in the same plane as the leaving group. This is because the $\sigma$ orbital of the carbon migrating in the five-membered ring and the $\sigma^*$ orbital of the carbon bonded to the alkoxy leaving group overlap to form a $\sigma$ bond in the ring expanded product. Therefore, the orbitals must overlap in the transition state. There are two ways that the carbon bonded to the five-membered ring and the leaving group can be in the same plane and overlap. They can be parallel to each other either on the same side of the molecule (syn-periplanar) to give the syn migration product, or on the opposite sides of the molecule (anti-periplanar) to give the anti migration product.

The rearrangement reaction most likely involves anti migration due to conformational, steric, orbital overlap and coefficient size arguments.

First, it is apparent that syn migration requires the incoming and the leaving bond of the molecule to be in an eclipsed conformation, while anti migration requires them to be in a
staggered conformation. Because the staggered conformer is more stable, the transition state leading to \textit{anti} migration is lower in energy than the transition state leading to \textit{syn} migration. Consequently, \textit{anti} migration occurs more rapidly.

Secondly, steric interactions are minimized for \textit{anti} migration because the incoming and leaving groups are on opposite sides of the molecule. For \textit{syn} migration, the steric repulsions are maximized for the reason that the incoming and leaving groups are on the same side of the molecule.

Furthermore, \textit{anti} migration undergoes an \textit{S}\textsubscript{N}2-like reaction, in that there is a synchronous direct displacement mechanism without an intermediate, and there is a single rate-determining transition state. The leaving group is displaced by an electron pair from the five-membered ring \(\sigma\) orbital. The maximal orbital overlap occurs with \textit{anti}-periplanar arrangement due to the strongest initial interaction between the filled orbital on the nucleophile and the antibonding \(\sigma^*\) orbital (larger coefficient) on the leaving group. In \textit{syn} migration, the leaving group is also displaced by an electron pair in the five-membered ring \(\sigma\) orbital, but poor orbital overlap occurs with \textit{syn}-periplanar arrangement (smaller coefficient).

Moreover, backside approach by the nucleophile is favoured for steric reasons. The frontside approach, or \textit{syn}-periplanar arrangement, is disfavoured because the coefficient of the \(\sigma^*\) orbital is smaller, resulting in a weaker initial interaction. Also, the frontside approach involves both a bonding and antibonding interaction with the \(\sigma^*\) orbital.

\section*{B. Synchronous-Unsynchronous Four-Membered Ring Expansion / Anti-Syn Migration}

Surprisingly, the siloxy-epoxide ring expansion of the cyclobutane ring in 2.3 gave poor stereoselectivity, having a ratio of 2.6 to 1 for 2.4 versus 2.5, respectively (Eq. 2.2). These results were unexpected and indicated that an unsynchronous reaction pathway might proceed. Compound 2.4 is termed the \textit{cis} aldol product (\textit{anti} migration product) and compound 2.5 the \textit{trans} aldol product.
Because there are only a few examples in the literature where syn migration have been observed during rearrangement reactions, the mechanistic details involving syn migration are not well understood. Our group is interested in studying the mechanism as well as the source of the lack of selectivity in the four-membered ring expansion.

There are three scenarios that could explain this phenomena (Scheme 2.2). The first possibility is that the rearrangement is synchronous (path a). The second option is that the epoxide rearranges before the synchronous ring expansion occurs (path b). Finally, the third scenario involves a rearrangement on a carbocation (path c). More details about those three scenarios are following.

**Scheme 2.2: Three Possible Scenarios for Siloxy-Epoxide Rearrangement**

1. **Non Selective Synchronous Scenario (path a)**
   
   As suggested above, the ring expansion can take place in a synchronous mechanism having either anti or syn migration of the alkyl CH₂ group onto the epoxide (Scheme 2.3). The stereoselectivity ratio favours the anti migration product over the syn migration product. As seen in section IA for the ring expansion of the five-membered ring 2.1, anti-periplanar migration is favoured for stereoelectronic reasons. But why is some syn migration observed for the ring expansion of cyclobutane ring 2.3?
The only difference between substrate 2.1 and substrate 2.3 is the size of the ring that expands. However, the five-membered ring 2.1 rearranges stereoselectively, whereas the four-membered ring 2.3 does not. It is known in the literature that four-membered rings expand much faster than five-membered rings.\(^4\) This is due to the angle strain in four-membered rings that is released upon ring expansion: 26.3 kcal/mol compared to 7.3 kcal/mol for the five-membered ring.\(^5\) An \(sp^3\)-hybridized carbon has a bond angle of 109.5°, but the bond angle in a square is 90°. The bond angle in cyclobutane is therefore compressed from the desired tetrahedral angle of 109.5° to 90°, resulting in angle strain. The angle strain in a four-membered ring can be appreciated by looking at the orbitals that overlap to form the sigma (σ) bonds (Fig. 2.1).\(^6\) In cyclobutane, the orbitals have to bend in order to overlap. The less effective orbital overlap causes the carbon-carbon bond to be weaker than a normal carbon-carbon bond and therefore more reactive. On the other hand, cyclopentane has good orbital overlap, resulting in lower reactivity towards ring expansion than for cyclobutane. It is also known that more reactive species tend to give less selective reactions.

Figure 2.1: Overlap of \(sp^3\) orbitals in Cyclobutane and Cyclopentane
Because the cyclobutane ring expands much faster than cyclopentane rings, the energy difference in the transition state between anti and syn migration is not well distinguished (Fig. 2.2). This means that cyclobutane ring expansions have an earlier transition state than cyclopentane ring expansions. The earlier transition state is less sensitive to factors such as steric hindrance or orbital steering because the bonds forming are still relatively long and weak. Thus, the lack of discrimination between anti and syn transition states is reflected in the unselective ring expansion of cyclobutanol derivatives.

Figure 2.2: Energy Diagram Proposed for Anti and Syn Migration

2. Rearrangement Scenario (path b)

A second option might be that the ring expansion of 2.3 takes place via a synchronous mechanism but that the initial epoxide undergoes a rearrangement prior to ring expansion (Scheme 2.4). The anti alkyl methylene group migrates onto the initial epoxide to give the cis aldol product 2.4, and onto the rearranged epoxide to give the trans aldol product 2.5. The stereoselectivity ratio slightly favours the ring expansion onto the initial epoxide.
The epoxide reactant, which exists as an equilibrium of two constitutional isomers, can ring expand to produce two products. By the Curtin-Hammett principle, the product ratio, under kinetically controlled conditions, depends on the difference in activation energy of the two isomers, and not on their relative energies. Because the product ratio is similar, the difference in activation energies leading to both cis and trans aldol products in the ring expansion of 2.3 is thought to be small.

If this scenario is correct, it is clear that the rearrangement of the cyclopentanol derivative 2.1 occurs completely on the initial epoxide, giving exclusively the cis aldol product. This means that the difference in activation energy is much smaller for the initial epoxide than for the rearranged epoxide.

3. Carbocation Scenario (path c)

As a third possible explanation for the stereochemical difference in the ring expansion of cyclobutanol substrate 2.3, one can propose an asynchronous epoxide ring opening-ring expansion where the ring expansion occurs on a planar carbocation to give either an anti or syn migration product (Scheme 2.5). The rearrangement slightly favours the anti migration product over the syn migration product. The slight preference for anti migration might be due to 1,2-induction caused by the alkoxy bond Lewis acid.
Scheme 2.5: Asynchronous Epoxide Ring Opening-Ring Expansion

A ring expansion occurring on a carbocation intermediate would result in a non stereoselective reaction. Surprisingly, this lack of stereoselectivity was observed for the ring expansion of cyclobutane 2.3, but not for cyclopentane 2.1 (Eq. 2.1 and 2.2). The stereospecificity of cyclopentane ring expansion suggests a rearrangement mechanism without a carbocation intermediate. So, why does cyclobutane, but not cyclopentane, rearrange through a carbocation intermediate?

It has been suggested that cyclobutane rings, like cyclopropyl rings, stabilize adjacent carbenium ions; however, there has been much debate on this topic (Figure 2.3).\textsuperscript{4b,9,10} However, this hypothesis could explain why the ring expansion of cyclobutane is unselective. Since cyclopentane rings, do not stabilize adjacent carbenium ions, the ring expansion occurs without a carbenium ion intermediate, and stereoselectivity is then observed.

Figure 2.3: Carbenium Ions Stabilized by Adjacent Rings

\[
\begin{align*}
\text{bond } \theta &= 60^\circ \\
\theta \text{ strain } &= 28.1 \text{ kcal/mol}
\end{align*}
\]

\[
\begin{align*}
\text{bond } \theta &= 90^\circ \\
\theta \text{ strain } &= 26.3 \text{ kcal/mol}
\end{align*}
\]

The stabilization of a carbenium ion by cyclopropyl substituents results from the interaction of the electrons in the cyclopropyl C-C bonds with the positive charged carbon. This can occur because of poor \(\sigma\) orbital overlap in the cyclopropane ring. Because cyclobutane has properties similar to cyclopropane such as angle strain value, poor \(\sigma\) orbital overlap and high reactivity, the cyclobutane ring might also stabilize adjacent carbenium ions.
Our group was interested in knowing if the lack of selectivity in the ring expansion of the four-membered ring 2.3 was due to cyclobutane reactivity (scenario 1), epoxide rearrangement (scenario 2) or formation of a carbenium ion intermediate (scenario 3).

To determine whether the trans aldol product is derived from the rearranged epoxide (scenario 2), one can shift the equilibrium between the two epoxides. Increasing the substituent size on silicon should slow the formation of the rearranged epoxide and drive the equilibrium toward the initial epoxide (Eq. 2.3). This process should favour the formation of the cis aldol product 2.4. To test this effect, the synthesis of the ring expansion precursors, where R is bulky, had to be achieved. Depending on the rearrangement stereoselectivity, the hypothesis that the epoxide rearranges prior to the ring expansion of cyclobutane 2.3 could be resolved.

\[
\begin{array}{l}
\text{ratio} \quad ? \quad 2.4 \\
(2.3)
\end{array}
\]

To find out if the cyclobutane ring stabilized and favoured the formation of a carbocation intermediate (scenario 3), ring expansion precursor 2.6 had to be synthesized (Eq. 2.4). Depending on the rearrangement stereoselectivity of 2.6, the hypothesis that cyclobutane rings stabilize adjacent carbenium ions could be tested.

\[
\begin{array}{l}
\text{ratio} \quad ? \quad 2.7 \\
(2.4)
\end{array}
\]

II. Carbocyclic Substrates
A. Early Work

In 1986, Yamamoto and Tsuchihashi discovered that rearrangement of siloxy-epoxide 2.9 gave the spirocyclic cis aldol product 2.10 (Eq. 2.5).\(^{11}\) The ring expansion was highly stereoselective. The observed stereoselectivity can be interpreted as anti migration of the alkyl group to the epoxide moiety because the combination of steric and electronic effects is maximized (Fig. 2.4). The rearrangement reaction is believed to proceed via a synchronous single-step process in which the formation and breaking of bonds occurs simultaneously.
Yamamoto and Tsuchihashi have not reported the rearrangement of siloxy-epoxide 2.6, which contains a cyclobutane moiety (Eq. 2.6). Because the rearrangement of the four- and the five-membered ring in the heterocyclic ring system gave different selectivities, the same relationship might be observed for the carbocyclic ring system.

Thus, the results of the ring expansion of the four-membered ring 2.6 was very important for mechanistic elucidation of the unselective cyclobutane ring 2.3 rearrangement (Eq. 2.7). For this reason, the synthesis of epoxy silyl ether 2.6 was considered.

The diastereoselectivity ratio obtained between 2.7 and 2.8 will allow us to determine whether or not the cyclobutane ring expanded on a carbenium ion intermediate. If the ring expansion of 2.6 is not stereoselective, then the rearrangement most likely occurred on a carbocation intermediate, indicating that cyclobutane rings do stabilize adjacent carbenium ions. If the ring expansion of 2.8 is stereoselective, then the rearrangement proceeds through a probable synchronous mechanism.
B. Substrate Synthesis

One strategy used for the synthesis of the ring expansion precursor 2.6 was to protect the alcohol functionality 2.11 with a trimethylsilyl (TMS) followed by epoxidation of the alkene (Eq. 2.8 and Table 2.1).

![Chemical Structure]

**Table 2.1: Protection of Alcohol 2.11**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>X</th>
<th>Me₃Si-X (eq.)</th>
<th>base</th>
<th>base (eq.)</th>
<th>t (h)</th>
<th>2.12</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>Cl</td>
<td>1.2</td>
<td>Et₃N</td>
<td>2.4</td>
<td>14</td>
<td>-</td>
<td>III-35</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>OTf</td>
<td>1.6</td>
<td>2,6-lutidine</td>
<td>2.5</td>
<td>0.3</td>
<td>81%</td>
<td>III-37</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>OTf</td>
<td>1.6</td>
<td>2,6-lutidine</td>
<td>2.5</td>
<td>1</td>
<td>55%</td>
<td>IV-04</td>
</tr>
</tbody>
</table>

(a) Notebooks

The standard conditions for silyl protection of alcohol 2.11 were tried using trimethylsilyl chloride (TMSCl). No reaction was observed (entry 1). This might be due to the fact that tertiary alcohols are hindered, and are therefore less prone to attack electrophiles, such as silyl chloride. Protection of tertiary alcohols usually requires a more electrophilic silicon species such as silyl triflate. Thus, the protection of the tertiary alcohol compound 2.11 was accomplished using trimethylsilyl triflate (TMSOTf), to give 2.12 in 81% (entry 2). Increasing the reaction time from half an hour to one hour decreased the yield of 2.12 to 55% (entry 3).

The synthesis of the epoxy-silyl ether 2.6 was accomplished by epoxidation of the double bond in 2.12 using an oxidizing reagent (Eq. 2.9 and Table 2.2).

![Chemical Structure]

**Table 2.2: Epoxidation of 2.12**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>ox</th>
<th>ox (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>2.6</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>m-CPBA</td>
<td>1.2</td>
<td>-5 → 0</td>
<td>0.3</td>
<td>-</td>
<td>III-47</td>
</tr>
<tr>
<td>2</td>
<td>(CH₃)₂CO</td>
<td>DMDO</td>
<td>5.0</td>
<td>25</td>
<td>2</td>
<td>-</td>
<td>IV-02</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>m-CPBA</td>
<td>2.2</td>
<td>-5 → 25</td>
<td>4</td>
<td>94%</td>
<td>IV-08</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>m-CPBA</td>
<td>3.2</td>
<td>-5 → 25</td>
<td>4</td>
<td>92%</td>
<td>IV-10</td>
</tr>
</tbody>
</table>

(a) Notebooks
Using *meta*-chloroperbenzoic acid (*m*-CPBA) as the epoxidizing agent in ether gave a messy reaction, with many products (entry 1). Dimethyldioxirane (DMDO) was also tried, but was also messy, giving many products. Finally, the synthesis of ring expansion precursor 2.6 was achieved with dichloromethane and *m*-CPBA. Under these conditions, the product 2.6 was isolated in excellent yield (entry 3). Adding one more equivalent of *m*-CPBA to the reaction mixture did not change the yield of the reaction (entry 4).

The \(^1\)H NMR spectrum of product 2.6 showed the resonance for the proton on the carbon bearing the epoxide (δ 3.11 (bs, 1H)) and did not display a signal for the olefin in 2.12 (δ 5.65-5.63 (m, 1H)).

The synthesis of 2.6 was also attempted by epoxidizing the double bond first, followed by protection of the tertiary alcohol with a silyl reagent. The epoxidation of 2.11 was carried out using *m*-CPBA as epoxidizing agent (Eq. 2.10 and Table 2.3).

![Reaction Scheme](image)

\[ 2.11 \xrightarrow{\text{m-CPBA}} 2.13 \]

**Table 2.3: Epoxidation of 2.11**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th><em>m</em>-CPBA (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>2.13</th>
<th>Ref.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et(_2)O/NaHCO(_3)/H(_2)O</td>
<td>1.2</td>
<td>-5 → 25</td>
<td>3</td>
<td>77%</td>
<td>III-38</td>
</tr>
<tr>
<td>2</td>
<td>Et(_2)O/NaHCO(_3)/H(_2)O</td>
<td>1.4</td>
<td>-5 → 25</td>
<td>3</td>
<td>76%</td>
<td>III-43</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)Cl(_2)/NaHCO(_3)/H(_2)O</td>
<td>3.2</td>
<td>-5 → 0</td>
<td>1</td>
<td>99%</td>
<td>IV-03</td>
</tr>
</tbody>
</table>

(a) Notebooks

Using *m*-CPBA in a solvent mixture of ether, sodium bicarbonate and water gave the product 2.13 in 77% yield (entry 1). Increasing the amount of epoxidizing agent did not increase the yield of the reaction (entry 2). However, using dichloromethane rather than ether in the solvent mixture and 3.2 eq. of *m*-CPBA gave 2.13 in excellent yield (entry 3).
The protection of the tertiary alcohol 2.13 was accomplished with silylating reagent (Eq. 2.11 and Table 2.4).

![Chemical structure and reaction](Image)

Table 2.4: Silyl Protection of Alcohol 2.13

| entry | R  | R₃Si-OTf (eq.) | 2,6-lut. (eq.) | t (h) | 2.6 | 2.14 | 2.15 | Ref.  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>1.6</td>
<td>2.5</td>
<td>0.2</td>
<td>91%</td>
<td>-</td>
<td>-</td>
<td>III-45</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>1.6</td>
<td>2.5</td>
<td>1</td>
<td>28%</td>
<td>28%</td>
<td>-</td>
<td>IV-05</td>
</tr>
<tr>
<td>3</td>
<td>3Pr</td>
<td>1.6</td>
<td>2.5</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>62%</td>
<td>V-03</td>
</tr>
</tbody>
</table>

(a) Notebooks

The protection of tertiary alcohol 2.13 was accomplished using TMSOTf as silylating reagent to give 2.6 in excellent yield (entry 1). A decrease in isolated yield of 2.6 was observed when the reaction mixture was stirred for 1 hour (entry 2). The ring expanded product 2.14 was a side product and was isolated in 28% yield. The protection of the tertiary alcohol 2.13 was also accomplished using triisopropylsilyl triflate (TIPSOTf) as silylating reagent to give 2.15 in good yield (entry 3).

The second method of synthesizing the ring expansion precursor 2.6 proved to be more efficient. By using the tertiary alcohol 2.13, various protecting groups could be appended, giving us the opportunity to synthesize many ring expansion substrates in fewer steps.

Next, the synthesis of one carbon homologue of 2.6 was also attempted. First, substrate 2.16 was epoxidized with m-CPBA (Eq. 2.12 and Table 2.5).

![Chemical structure and reaction](Image)

Table 2.5: Epoxidation of 2.16

| entry | solvent          | m-CPBA (eq.) | T (°C)       | t (h) | 2.17 | Ref.  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O/NaHCO₃/H₂O</td>
<td>1.4</td>
<td>-5 → 25</td>
<td>3</td>
<td>65%</td>
<td>III-39</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂/NaHCO₃/H₂O</td>
<td>1.4</td>
<td>-5 → 25</td>
<td>1</td>
<td>99%</td>
<td>III-50</td>
</tr>
</tbody>
</table>

(a) Notebooks
Using *m*-CPBA as the epoxidizing agent in a solvent mixture of ether, sodium bicarbonate and water gave the product 2.17 in 65% yield (entry 1). Using dichloromethane rather than ether in the solvent mixture gave 2.17 in excellent yield (entry 2).

The protection of the tertiary alcohol 2.17 was tried using two different silylating groups (Eq. 2.13 and Table 2.6).

\[
\text{2.17} \xrightarrow{R_3Si-\text{OTf}, 2.6-lutidine, THF, Table 2.6} \text{2.18} + \text{2.19}
\]

Table 2.6: Protection of Alcohol 2.17

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R₃Si-OTf (eq.)</th>
<th>2,6-lut. (eq.)</th>
<th>t (h)</th>
<th>2.18</th>
<th>2.19</th>
<th>2.20</th>
<th>Ref.²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>1.6</td>
<td>2.5</td>
<td>0.3</td>
<td>-</td>
<td>49%</td>
<td>-</td>
<td>IV-07</td>
</tr>
<tr>
<td>2</td>
<td>'Pr</td>
<td>1.6</td>
<td>2.5</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>60%</td>
<td>V-02</td>
</tr>
</tbody>
</table>

(a) Notebooks

The protection of tertiary alcohol 2.17 was attempted using TMSOTf, but product 2.18 was unstable under the reaction conditions (entry 1). The ring expanded product 2.19 was isolated as the major side product in 49% yield. The protection of the tertiary hydroxyl compound 2.17 was accomplished using triisopropylsilyl triflate (TIPSOTf) to give 2.20 in good yield (entry 2). These results show that substrate 2.18 ring expands more easily under TMSOTf reaction conditions than under TIPSOTf reaction conditions. This might be due to steric interaction between the nucleophile and the silicon substituent. The TMSOTf reagent is less bulky and more reactive than the TIPSOTf reagent, and thus undergoes nucleophilic attack faster.¹²

C. Ring Expansion Reaction

Having synthesized ring expansion precursors, the Lewis acid-initiated siloxy-epoxide rearrangements were executed (Eq. 2.14 and Table 2.7). Titanium tetrachloride was chosen as Lewis acid. The conditions used were the same as described by Yamamoto and Tsuchihashi.¹¹
Initially, the ring expansion was attempted on the trimethylsilyl ether 2.6. The ring expanded product 2.21 was obtained in 62% yield. The lower yield might be explained by the fact that 2.21 is volatile under reduced pressure, and completely evaporated after overnight exposure to reduced pressure.

One relative diastereomer was observed by GC, TLC and $^1$H NMR of the crude product analysis. The fact that the ring expansion of 2.6 is diastereoselective demonstrates that cyclobutane rings do not stabilize adjacent carbenium ions like cyclopropane rings do. The X-ray analysis of 2.21 showed an expected trans relation between the hydroxyl group (O1) and the methylene carbon (C10) (Fig. 2.5). This structure can be derived from synchronous anti alkyl (CH$_2$) migration onto the epoxide moiety (Fig. 2.6).

**Figure 2.5: X-ray Structure of 2.21**

![Figure 2.5: X-ray Structure of 2.21](image)

**Figure 2.6: Anti Migration of the Alkyl Group onto the Epoxide**

![Figure 2.6: Anti Migration of the Alkyl Group onto the Epoxide](image)
The $^1$H NMR analysis of 2.21 showed the resonance for the hydroxy-methine proton (δ 3.51 (dd, $J$=9.2, 4.3 Hz, 1H)) and did not display the trimethylsilyl signal in 2.6 (δ 0.10 (s, 9H)).

The IR spectrum of the ring expanded product exhibited strong stretches for the carbonyl functional groups (ν 1723 cm$^{-1}$) and for the alcohol (ν 3488 cm$^{-1}$).

The ring expansion of the alcohol protected by the TIPS 2.15 was also tried. The bigger isopropyl substituent on the silicon might change the course of the reaction to give different selectivity. A ring expanded product was obtained in 95% yield. The higher yield might be explained by the fact that 2.21 was only briefly exposed to reduced pressure in this case.

One relative diastereomer was observed by GC, TLC and by $^1$H NMR of the crude product analysis. The diastereomer isolated is identical to 2.21 by GC, TLC and $^1$H NMR comparison. So, changing the size of the substituent on the silicon did not change the sense of the reaction.

The conformational behaviour of 2.21 was observed by changing the $^1$H NMR solvent polarity. In chloroform, the $^1$H NMR spectrum showed a small coupling constant ($J$) between Ha and Hb ($J \approx 3.8$ Hz) (Fig. 2.7). This suggests that Ha is equatorial and that the hydroxyl and the alkyl CH$_2$ subtituent in the five-membered ring are axial, giving 2.23 as the favourable conformation.

![Figure 2.7: Possible Conformations of Ring Expansion Product of 2.21](image)

Groups on the axial positions cause 1,3-diaxial interactions, or gauche-butane interaction. The hydroxyl group in the axial position causes a destabilization of 0.9 kcal/mol and the alkyl group (CH$_2$) of 1.7 kcal/mol. The addition of these two 1,3-diaxial interactions give a net destabilization energy of about 2.6 kcal/mol (Fig. 2.8).

![Figure 2.8: 1,3-Diaxial Interactions between Axial Hydrogens and Axial Substituent](image)

Additive dipole interactions between the carbonyl and the hydroxyl bond also destabilize the product 2.21. Usually, the conformation having the smaller dipole moment is favoured. Thus,
it was surprising to observe that conformation 2.23 was the more stable conformer in chloroform. In an aprotic solvent, conformation 2.23 is lower in energy, as the carbonyl and the hydroxyl position themselves in such a way that intramolecular hydrogen bonding occurs via a chair-like conformation (Fig 2.9). Hydrogen bonding between a hydrogen and an electron donating group such as oxygen stabilizes the molecule by 5 kcal/mol. This stabilization overcomes the energy cost of the gauche interaction and the dipole moment.

**Figure 2.9 : Dipole Moment of the Ring Expanded Product**

In methanol however, the $^1$H NMR spectrum showed a larger coupling constant ($J$) between Ha and Hb ($J = 9.2$ Hz). This indicates that Ha is axial and that 2.24 is the lower energy conformer. In this case, the protic solvent surrounds and forms hydrogen bonds to the electron pairs on the oxygen groups. The oxygen on the carbonyl is thus electropositive, making intramolecular hydrogen bonding unlikely. Without the stabilization effect of intramolecular hydrogen bonding, the carbonyl and the hydroxyl position themselves so as to minimize dipole moments and 1,3-diaxial interactions. Thus, 2.24 is the more stable conformation in protic solvents.

Having synthesized 2.21 with good diastereoselectivity, it was wondered whether this selectivity was temperature dependent. Thus, the addition of Lewis acid to the silyl epoxy ether 2.6 was conducted at different temperatures (Eq. 2.15 and Table 2.8).

<table>
<thead>
<tr>
<th>entry</th>
<th>T(°C)</th>
<th>TiCl$_4$ (eq.)</th>
<th>t(h)</th>
<th>2.21$^a$</th>
<th>2.22</th>
<th>colour of the reaction solution</th>
<th>Ref.$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>1.1</td>
<td>0.3</td>
<td>100%</td>
<td>-</td>
<td>yellow clear</td>
<td>IV-14</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1.1</td>
<td>0.3</td>
<td>100%</td>
<td>-</td>
<td>light purple clear / cloudy</td>
<td>IV-14</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>1.1</td>
<td>12</td>
<td>100%</td>
<td>-</td>
<td>brown</td>
<td>IV-14</td>
</tr>
</tbody>
</table>

(a) Ratios were analyzed by GC  (b) Notebooks
The diastereoselectivity ratio was analysed by TLC, GC and $^1$H NMR spectroscopy of the crude product. As mentioned earlier (Eq. 2.14), when titanium tetrachloride was added at $-78$ °C, only one diastereomer, 2.21 was observed (entry 1). When the reaction is carried out at $-78$ °C, the solution is clear and yellow. However, at 0 °C, the reaction mixture became purple. Still only the cis aldol product 2.21 was detected (entry 2). Further, only a single diastereomer was isolated when titanium tetrachloride was added at room temperature and the reaction mixture was stirred for twelve hours (entry 3).

The siloxy-epoxide rearrangement was shown to be independent of the temperature at which titanium tetrachloride is added, and of the reaction time. These results indicate that either the product formed is the more thermodynamically stable diastereomer, or that the reaction is irreversible and the kinetic product is isolated.

In principle, the reaction could be reversible since the ring expanded product 2.21 is an aldol product (β-hydroxy ketone). Aldol condensation reactions are known to be reversible, going through a retro-aldol mechanism to give the most stable aldol product. The retro-aldol reaction could have occurred onto the β-hydroxy ketone 2.21 to give the most stable aldol product (Scheme 2.6). However, because product 2.21 is already the most stable aldol product, so there is no equilibration between 2.21 and 2.22. Computer calculation using Gaussian 03 showed that product 2.21 is more stable than product 2.22 by 2 kcal/mol.

**Scheme 2.6 : Retro-Aldol Reaction of 2.21**

![Scheme 2.6](image)
The ring expansion of 2.20 was also tried using triisopropylsilyl as protective group (Eq. 2.16). The $^1$H NMR spectrum indicated the presence of only one relative diastereomer which matched the $^1$H NMR spectrum of 2.10.

\[
\text{CFeO}S/Pr_3 \xrightarrow{TiCl_4} \text{CH}_2\text{Cl}_2 \xrightarrow{-78^\circ C} \xrightarrow{90\%} \text{one relative diastereomer}
\]

The rearrangement of 1-cyclohex-1-enylcyclobutanol 2.11 using bromonium ion methodology was also attempted (Eq. 2.17). The rearrangement proceeds through a bromonium ion, which is produced using N-bromosuccinimide as an electrophilic bromine source. The bromonium ion bridge is formed by double bond addition onto the bromine, which then ring expands. This gave product 2.25 as the only observed compound by TLC, GC and $^1$H NMR analysis of the crude product. The relative stereochemistry between the bromide and the alkyl (CH$_2$) is assumed to be trans where anti migration of the methylene onto the brominium ion bridge occurred (Fig. 2.10).

**Figure 2.10: Anti Migration of the Alkyl Group onto the Bromonium Ion**

The $^1$H NMR analysis of 2.25 showed the resonance for the bromine-methine proton ($\delta$ 3.98 (dd, $J$=11.9, 5.0 Hz, 1H)) and did not display the signal for the olefin in 2.11 ($\delta$ 5.61-5.57ppm (m, 1H)). The IR spectrum of the ring expanded product exhibited one strong stretch for the carbonyl functional groups ($\nu$ 1734 cm$^{-1}$).
D. Discussion

The syntheses of ring expansion precursors were accomplished. The ring expansions of these epoxy-silyl ether derivatives were accomplished stereoselectively. An anti migration of the methylene group onto the epoxide moiety was observed in each case, giving a trans relationship between the alcohol and the alkyl (CH$_2$) group as the relative diastereoselectivity (Eq. 2.18).

\[
\text{OSiR}_3 \quad \text{TiCl}_4 \quad \text{CH}_2\text{Cl}_2 \quad -78 \degree C \quad 62-95\%
\]

\[
\begin{align*}
n=1 & \quad R = \text{Me} & 2.6 & \quad 2.21 \\
      & \quad R = \text{'Pr} & 2.15 & \\
n=2 & \quad R = \text{'Pr} & 2.19 & \quad 2.10
\end{align*}
\]

The rearrangement stereoselectivity of 2.6 to give diastereomer 2.21 suggested that the ring expansion of the four-membered ring 2.3 does not involve the formation of a carbenium ion intermediate but instead, proceeds through an unselective synchronous reaction (path a) or an equilibrium between two epoxide isomers (path b) (Scheme 2.7).

Scheme 2.7: Elimination of One of the Three Limiting Scenarios

[Diagram of reaction pathways and structures]
III. Heterocyclic Substrates

A. Early Work

As mentioned earlier, the ring expansion of the four-membered ring 2.3 gave a poor selectivity ratio of 2.6 to 1 for the cis aldol product 2.4 over the trans aldol product 2.5 (Eq. 2.19).

![Chemical structure of 2.3](image)

\[
\text{TiCl}_4, -78 \, ^\circ\text{C} \xrightarrow{\text{CH}_2\text{Cl}_2} 95\% \quad \text{ratio} \quad 2.6 : 1 \quad 2.4 \quad 2.5
\] (2.19)

Previous research in our group showed that the ring expansion of the siloxy-epoxy substrate 2.3 was found to be more selective towards anti migration when milder and softer Lewis acids were employed (Eq. 2.20 and Table 2.9).

![Chemical structure of 2.3](image)

\[
\text{Lewis acid} \xrightarrow{\text{CH}_2\text{Cl}_2, T \, ^\circ\text{C}} \text{Table 2.9} \quad 2.4 \quad 2.5
\] (2.20)

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis acid</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>yield</th>
<th>ratio 2.4 : 2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtAlCl₂</td>
<td>-78</td>
<td>0.5</td>
<td>95%</td>
<td>4.6 : 1</td>
</tr>
<tr>
<td>2</td>
<td>ZrCl₄</td>
<td>-78</td>
<td>1</td>
<td>89%</td>
<td>6.1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Yb(OTf)₃</td>
<td>-45 → 0</td>
<td>7</td>
<td>99%</td>
<td>7.4 : 1</td>
</tr>
</tbody>
</table>

(a) 1.1 eq. of Lewis acid was used (b) Isolated yield (c) Ratios are determined by GC analysis of the mixture

Using ytterbium (III) triflate as the Lewis acid gave the most selective and synthetically useful result. Ytterbium (III) triflate initiated the ring expansion of 2.3 to produce 2.4 and 2.5 in 99% yield, with a 7.4 : 1 ratio of diastereomers. The milder Lewis acid might have attenuated the reactivity of the substrate to give a good diastereoselectivity. Keeping this in mind, our group was interested in knowing if changing the protecting group on the alcohol had an effect on cyclobutane ring reactivity.

For scenario 1 (see section IB1), the non-selectivity of the synchronous rearrangement is believed to be due to the ability of the cyclobutane ring to readily undergo ring expansion. In
order to modulate this reactivity, one can think about changing the alcohol protecting group on the heterocyclic substrate (Eq.2.21). For scenario 2 (see section IB2), changing the substituent size on the silicon should modify the equilibrium between the initial and the rearranged epoxide.

\[
\text{Ts}^+ - 1\text{TiCl}_4, \text{CH}_2\text{Cl}_2 - 78 \degree \text{C} \rightarrow \begin{array}{c}
\text{ratio} \\
2.4 \\
2.5 
\end{array}
\]

In order to further understand the mechanism of the cyclobutanol rearrangement, a study on the modification of the oxygen protecting group was initiated. The observed ratio for the ring expanded product 2.4 versus 2.5 could lead to some useful mechanistic information facilitating the understanding of the cyclobutanol rearrangement.

B. Substrate Synthesis

In order to study the effect of the alcohol protecting group on ring expansion stereoselectivity, the synthesis of substrate 2.29 had to be achieved. This was accomplished according to a literature procedure published by the Dake group. \(^1\) First, \(N\)-\(p\)-toluenesulfonyl-2-piperidone 2.26 was treated with potassium hexamethyldisilazide and phenyl \(N\)-triflamide to form vinyl triflate 2.27 in 63\% yield (Scheme 2.8). Next, the vinyl triflate 2.27 was converted to vinylstannane 2.28 by palladium (0)-catalyzed cross-coupling with hexamethyldistannane with 65\% yield. The vinylstannane 2.28 was submitted to tin-lithium exchange using methyllithium. Quenching the anionic vinyl species with cyclobutanone gave the cyclobutanol product 2.29 in 75\% yield.

**Scheme 2.8: Synthesis of the Cyclobutanol 2.29**

\[
\text{N}^+ \quad \text{PhNTf}_2 \quad \text{KHMDSTHF} \quad -78 \degree \text{C} \rightarrow \text{rt} \quad 63\%
\]

\[
\text{N}^+ \quad \text{OTf} \quad \text{Ph}_3\text{AsPd} \text{dba}_3 \quad \text{THF, rt} \quad 65\%
\]

\[
\text{N}^+ \quad \text{SnMe}_3 \quad \text{MeLi, Et}_2\text{O} \quad -78 \degree \text{C} \rightarrow 0 \degree \text{C} \quad \text{MgBr}_2\cdot\text{OEt}_2
\]

\[
\text{Ts} \quad \text{SnMe}_3 \quad -100 \degree \text{C} \rightarrow \text{rt} \quad 75\%
\]

39
Next, the protection of alcohol 2.29 with a bulkier silicon protecting group was attempted (Eq. 2.22 and Table 2.10).

\[
\text{R}_3\text{Si-OTf} \quad \xrightarrow{2,6\text{-lutidine} \quad \text{THF, rt}} \quad \text{OSiR}_3
\]

**Equation 2.22**

| Table 2.10: Protection of Alcohol 2.29 |
|-------------------------------|--|--|--|--|--|--|
| entry | R \(^a\) | R\(_3\text{Si-OTf}\) (eq.) | 2,6-lutidine (eq.) | t (h) | yield | comments \(^b\) | Ref. \(^c\) |
| 1 | Me | 1.6 | 2.5 | 2 | 96% | - | VII-01 |
| 2 | 'Pr | 1.6 | 2.5 | 14 | 99% | - | IV-33 |
| 3 | TBDPh | 2 | 3 | 14 | - | sm recovered | VI-29 |
| 4 | TBDPh | 3 | 4 | 14 | - | sm recovered | VII-07 |

\(^a\) Me=methyl : \(^b\) Pr = isopropyl : TBDPh = \(t\)-butyldiphenyl \(^c\) sm = starting material (c) Notebooks

The protection of the allylic tertiary alcohol 2.29 using TMSOTf and TIPSOTf to give 2.30 and 2.31, respectively, was successful (entries 1 and 2). A similar protection was also attempted using \(t\)-butyldiphenyl triflate (TBDPhOTf), but was unsuccessful as only starting material was recovered (entries 3 and 4).\(^{15}\)

The conversion of alcohol 2.29 to an ester was also attempted (Eq. 2.23 and Table 2.11).

\[
\text{OH} \quad \xrightarrow{\text{base, solvent} \quad T (°C)} \quad \text{OBz}
\]

**Equation 2.23**

| Table 2.11: Protection of Alcohol 2.29 by Ester Group |
|-------------------------------|--|--|--|--|--|--|
| entry | Bz \(^a\) (eq.) | base (eq.) | T (°C) | solvent | t (h) | 2.33 | comments | Ref. \(^b\) |
| 1 | 1.2 | BuLi (1.05) | -78 → 25 | THF | 14 | - | sm recovered | IV-40 |
| 2 | 1.2 | pyr. (70) | 25 | CH\(_2\)Cl\(_2\) | 14 | - | sm recovered | IV-42 |
| 3 | 3.0 | BuLi (1.10) | -78 → 25 | THF | 5 | - | sm recovered | IV-45 |

\(^a\) Bz = benzoyl \(^b\) Notebooks
However, the protection of 2.29 using benzoyl chloride to give ester 2.33 was unsuccessful (entries 1-3). In each attempt, starting material was recovered. As seen in section IIIB, the protection of the tertiary allylic alcohol on the carbocyclic substrate was difficult and required highly reactive electrophilic species such TMSOTf.

Alcohol protection of 2.29 using acetic anhydride was also unsuccessful, yielding only starting material (Eq. 2.24).

\[
\text{Ac}_2\text{O}, \text{rt} \quad \overset{\text{Pyridine, DMAP}}{\longrightarrow} \quad \text{sm recovered}
\]

2.29

Appending a protecting group on the tertiary allylic alcohol 2.29 seems to be quite difficult. Because alcohol 2.29 is not that reactive towards electrophilic species, no other attempts were made to protect it.

Attempts to epoxidize the allylic double bond using \( \mathbf{m}\)-CPBA in a solvent mixture of dichloromethane, sodium bicarbonate and water instead gave the ring expansion product. The ratio observed was 1.5:1 of the \textit{cis} aldol product 2.4 versus the \textit{trans} aldol product 2.5 (Eq. 2.25).

\[
\text{CH}_2\text{Cl}_2 \quad \overset{\text{m-CPBA, NaHCO}_3 / \text{H}_2\text{O}}{\longrightarrow} \quad \begin{array}{c}
\text{OH} \\
\text{Ts}
\end{array} \quad \begin{array}{c}
\text{OH} \\
\text{Ts}
\end{array} \quad \frac{\text{ratio}}{1.5:1}
\]

2.29

2.4 
2.5

The double bond of 2.30 was epoxidized using DMDO in dichloromethane. The siloxy-epoxide substrate 2.3 was obtained in 92% yield (Eq. 2.26).

\[
\text{2.30} \quad \overset{\text{DMDO = O-O}}{\longrightarrow} \quad \text{2.3}
\]

2.30

2.3

The double bond of 2.31 was epoxidized using \( \mathbf{m}\)-CPBA in dichloromethane. The siloxy-epoxide substrate 2.34 was obtained in 88% yield (Eq. 2.27).
The $^1$H NMR spectrum of product 2.34 showed a resonance for the proton on the carbon epoxide ($\delta$ 3.13 (bs, 1H)) and did not display the olefin signal in 2.31 ($\delta$ 5.82-5.78 (m, 1H)).

C. Ring Expansion Reaction

Having synthesized the ring expansion precursor 2.34, the siloxy-epoxide ring expansion initiated by titanium tetrachloride was executed. The isopropyl substituent on the silicon (TIPS) is much bigger than the methyl substituent (TMS). By being bulkier, the TIPS group will probably change the course of the reaction and the reactivity of the cyclobutane to ring expansion.

Due to steric interaction, a bulkier alkyl substituent on the silicon should reduce the bridging equilibrium. Thus if scenario 2 is relevant, this will favour the ring expansion on the initial epoxide (Scheme 2.9). An increase in the formation of cis rather than trans aldol product should be observed. Or, in an ideal case, the cis aldol product should be the only product isolated.

Scheme 2.9: Silicon Size Effect on the Epoxide Equilibrium in Scenario 2

The ring expansion of the siloxy-epoxide 2.34 was completely selective. Only one relative diastereomer was observed by GC and $^1$H NMR analysis of the crude product (Eq. 2.28). Surprisingly, the $^1$H NMR spectrum of the ring expansion product matched with the trans aldol product 2.5. The X-ray analysis of the ring expanded product from 2.34 clearly showed the cis relation between the hydroxyl (O1) and the methylene carbon (C9) (Fig. 2.11). This experiment
clearly demonstrates that scenario 2 is not applicable. Thus scenario 1 is valid. Product 2.5 probably comes from a syn migration of the alkyl (CH\textsubscript{2}) onto the initial epoxide (Fig 2.12).

\[
\begin{array}{c}
\text{N} \quad \text{Ts} \\
\text{O} \quad \text{OSi'Pr}_3 \\
\text{CH}_2\text{Cl}_2 \\
\text{TiCl}_4 \\
\text{95\%} \\
-78 \degree \text{C}
\end{array} 
\rightarrow 
\begin{array}{c}
\text{N} \quad \text{Ts} \\
\text{O} \\
\text{OH} \\
\text{one relative diastereomer}
\end{array} 
\]

\[2.34 \quad 2.5\]

**Figure 2.11: X-ray Structure of the Siloxy-Epoxide Ring Expansion of 2.34 to 2.5**

The \textsuperscript{1}H NMR analysis of 2.5 showed the resonance for the hydroxy-methine proton (\(\delta 3.82\) (dd, \(J=11.9, 4.0\) Hz, 1H)) and did not display the signal for the epoxide-methine proton in 2.34 (\(\delta 3.13\) (bs, 1H)). The IR spectrum of the ring expanded product exhibited strong stretches for the carbonyl functional groups (v 1730 cm\textsuperscript{-1}) and for the alcohol (v 3436 cm\textsuperscript{-1}). In comparison, the \textsuperscript{1}H NMR analysis of the cis aldol product 2.4 showed the resonance for the hydroxy-methine proton (\(\delta 4.20\) (d, \(J=2.1\) Hz, 1H)).

So, changing the size of the substituent on the silicon did affect the reaction, and lead to unexpected syn migration of the alkyl group to the epoxide.
D. Discussion

The synthesis of O-triisopropylsilyl group ring expansion precursors was accomplished. The ring expansion of the siloxy-epoxide derivative 2.34 was stereoselective. A syn migration of the methylene group onto the epoxide moiety was observed, giving a cis relationship between the alcohol and the alkyl (CH₂) as relative diastereoselectivity of the ring expanded product 2.5 (Eq. 2.29).

$$\text{TiCl}_4 \xrightarrow{\text{CH}_2\text{Cl}_2} 95\%$$

Oddly, as discussed previously, the ring expansion of the four-membered ring 2.15, having the alcohol protected by the O-triisopropylsilyl group, gave the anti migration product and none of the syn migration product (Eq.2.30 and Scheme 2.10).

$$\text{TiCl}_4 \xrightarrow{\text{CH}_2\text{Cl}_2} 95\%$$

Scheme 2.10: Two Possible Rotamers for Anti-Periplanar Migration

These results showed that the combination of the nitrogen functionality with the reactivity of cyclobutane ring is responsible for the complete or partial syn migration during ring expansion reaction of heterocyclic ring derivatives (Scenario 1).

The complete syn migration product can be rationalized as the addition of steric interaction between the nitrogen protecting group and the alcohol protecting group (Scheme 2.11). The two possible rotamers for anti-periplanar alignment are affected by the steric interaction, but in the syn-periplanar arrangement only one configuration is sterically disfavoured. When TMS is used as the alcohol protecting group, syn migration is observed as the minor product. In that case, the electronic effects slightly outweigh the steric effects. But when
TIPS is used as the alcohol protecting group, for which the isopropyl groups are bigger than the methyl groups, steric destabilization overcomes the electronic effects.

**Scheme 2.11: Possible Configuration for Anti-Periplanar or Syn-Periplanar Migration**

Thus, the stereoselectivity of the four-membered ring expansion with a nitrogen substituent in the six-membered ring was found to be affected by the nature of the siloxy protecting group (Eq. 2.31).

\[
\begin{align*}
\text{R} &= \text{Me} & \text{ratio} &= 2.6 & \text{anti} & \text{syn} \\
\text{R} &= \text{Pr} & 0 & 1 & 1
\end{align*}
\]

Future experiments should address the variation of the nitrogen protecting group and its subsequent effect on the ring expansion reaction. It should also be of interest to investigate the effect of having substituents at the 3 position in the heterocyclic ring on the ring expansion reaction.
IV. Heterocyclic Substrates: Effect of Substituent at the 3 Position

A. Early Work

The first attempt to functionalize the 3 position, using chemistry previously carried out in the Dake group, was unsuccessful (Scheme 2.12). The vinyl triflate could not be converted to a vinylstannane using palladium (0)-catalyzed cross-coupling with hexamethyldistannane.

Scheme 2.12: First Attempt on Functionalizing at the 3 Position

![Scheme 2.12]

It was discovered in our group that treating compound 2.35 with 2 eq. of a Lewis acid and 3 eq. of allyl silane gave displacement of the acetal, as well as elimination of the tertiary alcohol (Eq. 2.32). The elimination of the tertiary alcohol probably proceeds through an S_N1' or S_N2' mechanism to give product 2.36 in 90% yield.

![Equation 2.32]

This reaction could be useful in functionalizing compounds such as 2.37 at the 3 position on the heterocyclic ring giving compound 2.38 (scheme 2.13). The tetrasubstituted double bond in 2.38 could be oxidized, followed by ring expansion to give a variety of spirocycles functionalized at the 3 position, such as 2.40.

Scheme 2.13: New Reaction Proposal to Functionalize at the 3 Position

![Scheme 2.13]

B. Substrate Synthesis

Activating the alcohol as a leaving group will allow it to undergo S_N1' or S_N2' substitution more easily. The methanesulfonyl group was chosen, as it is a common alcohol activating group (Eq. 2.33).
The protection of the tertiary alcohol 2.29 by a methanesulfonyl group under standard conditions, such as methanesulfonyl chloride and triethylamine, gave recovery of the starting material in 61% yield. The mass balance was the formation of a side product which could not be identified by $^1$H and $^{13}$C NMR spectroscopy.

The difficulties involved with placing a mesyl group on the hindered alcohol were not surprising given the results of the previous sections in this thesis. Thus, the idea of activating the alcohol as a leaving group was set aside. Instead, attempts were made to activate the alcohol with Lewis acid followed by displacement by a nucleophile. The first nucleophile and Lewis acid attempted were allyltrimethylsilane and boron trifluoride etherate (Eq. 2.34 and Table 2.12).

\[
\begin{align*}
\text{BF}_3\cdot\text{OEt}_2 & \quad \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C} \rightarrow \text{rt} \\
\text{2.29} & \quad \text{2.41} \\
\text{n} = 1 & \quad \text{n} = 2
\end{align*}
\]

Table 2.12: Displacement of Alcohol 2.29 and 2.42 by Allyl Substituent

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>BF$_3$·OEt$_2$ (eq.)</th>
<th>AllylSiMe$_3$ (eq.)</th>
<th>t (h)</th>
<th>yield</th>
<th>Ref. a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>14</td>
<td>46%</td>
<td>VI-47</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>0.45</td>
<td>84%</td>
<td>VII-09</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0.45</td>
<td>89%</td>
<td>VII-09</td>
</tr>
</tbody>
</table>

(a) Notebooks

The allylic tertiary alcohol 2.29 was displaced by the allylsilane presumably via an $S_N 1'$ mechanism to give 2.41 in 46% yield after overnight stirring (entry 1). The same reaction conditions were used, but the reaction mixture was quenched after 45 minutes to give 2.41 in 84% yield (entry 2). Using the same protocol, the tertiary alcohol 2.42 gave 2.43 in excellent yield (entry 3).

The $^1$H NMR spectra characteristics of 2.41 and 2.43 showed signals for the allyl double bond hydrogens ($\delta_{2.41}$ 5.85-5.74 (m, 1H), 5.02-4.96 (m, 2H) and $\delta_{2.43}$ 5.92-5.81 (m, 1H), 5.05-
4.96 (m, 2H). Also, the olefin signal (δ_{2.29} 5.68 (t, J=3.8, 1H) and δ_{2.42} 5.81 (t, J=3.9, 1H)) in the starting material 2.29 or 2.42 is missing.

Having synthesized products 2.41 and 2.43, the epoxidation of the more nucleophilic double bond was executed chemoselectively by using m-CPBA (Eq. 2.35 and Table 2.13).

\[ \text{m-CPBA} \xrightarrow{\text{solvent}} \text{product} \]

\[ \text{(-78 °C → rt)} \]

\( n = 1 \) 2.41
\( n = 2 \) 2.43

\( 2.44 \)
\( 2.45 \)

### Table 2.13: Epoxidation of the Nucleophilic Double Bond in 2.41 and 2.43

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>m-CPBA (eq.)</th>
<th>solvent</th>
<th>t (h)</th>
<th>yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2.4</td>
<td>CH(_2)Cl(_2)/H(_2)O/ NaOH</td>
<td>14</td>
<td>-</td>
<td>VI-48</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2.4</td>
<td>CH(_2)Cl(_2)/H(_2)O/ NaHCO(_3)</td>
<td>14</td>
<td>60%</td>
<td>VII-10</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2.4</td>
<td>CH(_2)Cl(_2)/H(_2)O/ NaHCO(_3)</td>
<td>14</td>
<td>82%</td>
<td>VII-10</td>
</tr>
</tbody>
</table>

(a) Notebooks

The first reaction attempted was unsuccessful, and gave a messy reaction mixture without any recovery of the starting material (entry 1). The same conditions were repeated, but instead of sodium hydroxide, sodium bicarbonate was used as the base. The four-membered ring substrate 2.41 was exposed to the new epoxidizing conditions (entry 2). The TLC of the reaction after stirring overnight showed no remaining starting material, and only one product. This product was the epoxide 2.44, which was isolated in 60% yield. The epoxide 2.44 was unstable during flash column chromatography and decomposed at room temperature to the ring expanded product. The epoxidation of the double bond on the five-membered ring substrate 2.43 gave 2.45 in 82% yield (entry 3). The epoxide product 2.45 seems to be more stable than 2.44, as no ring expansion side product was observed during purification. The epoxidation of both substrates 2.41 and 2.43 was completely diastereoselective by GC and \(^1\)H NMR analysis of the crude product.

The epoxide 2.45 was submitted for X-ray analysis for determination of the relative stereochemistry of the epoxide and the allyl group of substrate 2.45 (Fig. 2.13). By analogy to 2.45, the stereochemistry of the epoxide and the allyl group on 2.44 should be identical.
The X-ray analysis of 2.45 showed the expected *anti* relation of the epoxide moiety (C12-O3-C16) and the allyl group (C13 to C15). This stereochemistry is derived from epoxidation at the less hindered face of the double bond. That is, epoxidation occurs on the opposite face of the allyl group (Scheme 2.14).

Scheme 2.14: Possible Epoxidation Face

The spectral characteristics of 2.44 and 2.45 by $^{13}$C NMR showed signals for the epoxide carbon ($\delta_{2.44}$ 76.2, 72.5 and $\delta_{2.45}$ 77.3, 77.2). Also, the signals of the tetrasubstituted double bond carbon ($\delta_{2.41}$ 138.3, 128.7 and $\delta_{2.43}$ 143.0, 128.3) in the starting material are missing.

C. Ring Expansion Reaction

Having synthesized the ring expansion precursors, the rearrangements of the epoxide initiated by Brønsted acid were executed (Eq. 2.36 and Table 2.14). Hydrochloric acid was chosen as Brønsted acid.
Using hydrochloric acid to initiate the ring expansion of epoxide 2.44 gave the ring expanded product 2.46 with 90% yield after 10 minutes at room temperature (entry 1). At 0 °C, the rearrangement of epoxide 2.44 was slower. The same conditions were used for the epoxide 2.45, which ring expanded at room temperature in 91% yield after 2 hours (entry 2). It is interesting to note that the cyclobutane ring 2.44 ring expanded at least 20 times faster than the five-membered ring 2.45. This result shows again that four-membered rings are more reactive than five-membered ring toward ring expansion reactions. The rearrangement of both substrates 2.44 and 2.45 was found to be completely diastereoselective, providing only one diastereomer by GC and ‘H NMR analysis of the crude reaction sample.

The IR spectrum of the ring expanded product exhibited one stretch due to the carbonyl functional groups (v2.46 1745 cm⁻¹ and v2.47 1715 cm⁻¹).

The ring expanded product 2.46 was submitted for X-ray analysis. The X-ray analysis allowed us to establish the relative stereochemistry between the methylene (CH₂) and the allyl of substrate 2.46 (Fig. 2.14). By analogy to 2.46, the relative stereochemistry between the methylene (CH₂) and the allyl on 2.47 was also determined. Knowing the diastereoselectivity relationship between the methylene (CH₂) and the allyl, the mechanism of the ring expansion may be derived.
The X-ray analysis of 2.46 demonstrates a \textit{trans} relationship between the methylene carbon (C9) and the allyl group (C10 to C12). This stereochemistry can be derived from a ring expansion that takes place in an asynchronous manner, with \textit{anti} migration of the alkyl (CH$_2$) groups onto a carbocation (Scheme 2.15). The migration occurred on the less hindered face which comes from opposite side of the allyl groups to avoid steric interaction between the alkyl and the allyl groups in the transition state (1,2-Induction).

\textbf{Scheme 2.15: Asynchronous Epoxide Ring Opening-Ring Expansion}

\textbf{D. Concluding Remarks}

The synthesis of ring expansion precursors having substituents at the 3 position on the piperidine ring was accomplished. The rearrangement of the epoxide derivatives was conducted stereoselectively, giving an \textit{anti} relationship between the alkyl (CH$_2$) and the allyl (Eq. 2.37). The \textit{anti} relation can be derived from an initial epoxide opening followed by alkyl migration opposite the allyl group to minimize unfavourable steric interactions.
The ring expanded product with substitution at the 3 position can be synthetically useful. The carbonyl and the allyl functional groups may be manipulated to yield a variety of products. Because of the interest and the utility of having a substituent at the 3 position of the spirocycle 2.49, our group is conducting further research on functionalizing at this position (Eq. 2.38).

V. Enantioselective Ring Expansion: Kinetic Resolution

A. Early Work

Our group is interested in the synthesis of optically active spirocyclic rings. The asymmetry in our substrates can be introduced via catalytic asymmetric epoxidation or catalytic kinetic resolution (Eq. 2.39 and 2.40).

One strategy could be the use of Sharpless Ti-catalyzed asymmetric epoxidation. However, the Sharpless method is less efficient in the epoxidation of allylic tertiary alcohols.\(^\text{16}\) The Jacobsen asymmetric epoxidation of alkenes could be another approach.\(^\text{17}\) Unfortunately, this method gives poor enantioselectivity on hindered trisubstituted double bonds. So, kinetic resolution seems to be the method of choice.
In 1999, Yian Shi published an enantioselective enol ester epoxide rearrangement (Eq. 2.41).\(^\text{18}\) The racemic enol ester epoxide \(2.50\) was treated with a chiral Lewis acid catalyst which kinetically resolved the epoxide. The optically active \(\alpha\)-acyloxy ketone \(2.52\) was formed with an enantiomeric excess (ee) of 89\%. The optically active enol ester epoxide \(2.51\) was recovered in 34\% yield with an ee of 99\%.

\[
\begin{align*}
\text{BzO} & \quad 5 \text{ mol\%} \\
\text{[(R)-BINOL]}_2 \text{-Ti(O'Pr)}_4 & \quad \text{Et}_2\text{O}, 0 ^\circ\text{C, 0.5 h} \\
2.50 & \xrightarrow{52\% \text{ conv.}} 99\% \text{ ee} \\
+ & \quad 89\% \text{ ee} \\
2.51 & \quad 2.52
\end{align*}
\] (2.41)

These results led our group to determine whether the siloxy-epoxide on our substrate could rearrange enantioselectively using a chiral Lewis acid (Eq. 2.42).

\[
\begin{align*}
\text{racemic} & \quad \xrightarrow{\text{chiral Lewis acid}} \\
\text{absolute diastereomer} & \quad (2.42)
\end{align*}
\]

C. Enantioselective Ring Expansion Reaction

Having already synthesized the ring expansion precursors from section IIIB, the siloxy-epoxide ring expansions initiated by chiral Lewis acid were executed (Eq. 2.43 and Table 2.15). \(\text{Ti(O'Pr)}_4\) modified with BINOL was chosen as chiral Lewis acid. The conditions used for the rearrangement were the same as described by Yian Shi.\(^\text{18}\)
Table 2.15: Enantioselective Ring Expansion of 2.3 and 2.34

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>BINOL (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>ee %</th>
<th>2.4</th>
<th>2.5</th>
<th>ratio 2.4 : 2.5</th>
<th>Ref.</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>0.03</td>
<td>0 → rt</td>
<td>14</td>
<td>0</td>
<td>75%</td>
<td>-</td>
<td>-</td>
<td>VII-18</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>0.03</td>
<td>0</td>
<td>0.45</td>
<td>0</td>
<td>71%</td>
<td>-</td>
<td>-</td>
<td>VII-22</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>0.03</td>
<td>-78 → -20</td>
<td>3</td>
<td>0</td>
<td>25%</td>
<td>-</td>
<td>-</td>
<td>VII-22</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>'Pr</td>
<td>0.03</td>
<td>0 → rt</td>
<td>14</td>
<td>0</td>
<td>22%</td>
<td>53%</td>
<td>1 : 2.4</td>
<td>VII-20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>'Pr</td>
<td>0.03</td>
<td>0 → 5</td>
<td>48</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>VII-26</td>
<td></td>
</tr>
</tbody>
</table>

(a) Notebooks

No enantiomeric excess was observed by chiral HPLC for product 2.4 during the rearrangement of substrate 2.3 (entries 1-3). Changing the time and the temperature of the reaction did not change the results (entries 2-3). Further, quenching the reaction after 25% conversion did not improve the ee (entry 3). However, an interesting result did occur during the ring expansion of 2.3: only one diastereomer was observed by TLC and $^1$H NMR spectrum of the crude product, which corresponded to 2.4. This was contrary to the results from section IB and section IIIA. So, using a catalytic amount of a bulkier Lewis acid gave a selective rearrangement of 2.3 at 0 °C. The selectivity is probably derived from scenario 1 (section IB1), where treating 2.3 with a catalytic amount of ring expansion initiator allows a more selective rearrangement.

No enantioselectivity was observed for product 2.5 during the rearrangement of substrate 2.34 (entry 4). Keeping the temperature of the reaction at 5°C did not give any rearranged product after 2 days (entry 5). This clearly demonstrates that substrate 2.3 rearranges much more easily and faster than 2.34 (entries 2 and 5). During the ring expansion of 2.34, a mixture of diastereomers was observed by TLC and in the $^1$H NMR spectrum of the crude product. The ratio observed was 2.4 to 1 of 2.5 versus 2.4. Using a catalytic amount of a bulkier Lewis acid gave some anti-periplanar rearrangement of 2.34 at room temperature. The anti migration product is probably derived from a slower ring expansion reaction where the stereoelectronic favoured the anti-periplanar arrangement.
D. Concluding Remarks

The kinetic resolution of the siloxy-epoxide ring expansion of 2.3 and 2.34 gave no enantioselectivity. Using a catalytic amount of Lewis acid such as Ti(O'Pr)$_4$ modified with BINOL completely changed the diastereoselectivity ratio compared to the equimolar TiCl$_4$ standard condition (Eq. 2.44).

\[
\begin{align*}
\text{R = Me} & \quad \text{TiCl}_4 & \text{ratio} & 2.6 & 1 \\
\text{cat. Ti(O'Pr)$_4$ + BINOL} & 1 & - \\
\text{R = 'Pr} & \quad \text{TiCl}_4 & - & 1 \\
\text{cat. Ti(O'Pr)$_4$ + BINOL} & 1 & 2.4
\end{align*}
\]

One example of kinetic resolution via semipinacol rearrangement of α-hydroxyepoxides was found in the literature (Eq. 2.45).$^{19}$ The best ee obtained for substrate 2.10 was 24% using 40 mol% as catalyst loading and toluene as solvent. This result might discourage further research on this project.

\[
\begin{align*}
\text{2.17} & \quad \text{2.10} \\
\text{ee} & 24\% & 51\%
\end{align*}
\]
VI. General Discussion

The ring expansion of cyclobutane rings was executed on different siloxy-epoxide carbocyclic and heterocyclic substrates (Scheme 2.17). The results of those rearrangements permitted to determine which pathway the ring expansion reactions took place.

**Scheme 2.17: Diastereoselective Ring Expansion Accomplished on Cyclobutane Substrates**

- 
  \[
  \text{R = Me } 2.6 \\
  \text{R = 'Pr } 2.19
  \]

The lack of selectivity of the four-membered ring expansion of 2.3 was found to be derived from a most probable synchronous mechanism where *anti* and *syn* migration of the alkyl \((\text{CH}_2)\) groups onto the epoxide moiety takes place (Scheme 2.18). The non-selective rearrangement of 2.3 is believed to be derived from a combination of the cyclobutane reactivity and the nitrogen substituent.

**Scheme 2.18: Synchronous Epoxide Ring Opening-Ring Expansion**
VII. Experimental

General (see chapter one, section V)

\[
\begin{align*}
\text{10-Hydroxy-6-(toluene-4-sulfonyl)-6-azaspiro[4.5]decan-1-one (2.5)}
\end{align*}
\]

To a \(-78 \, ^{\circ}\text{C}\) solution of 25 mg (0.052 mmol) of \(l\)-(toluene-4-sulfonyl)-\(l\)-(l-triisopropylsilanyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane 2.34 in 2.0 mL of \(\text{CH}_2\text{Cl}_2\) was added 57 \(\mu\text{L}\) of a 1.0 M solution (0.057 mmol) of titanium tetrachloride. The reaction mixture was stirred for 0.5 h at \(-78 \, ^{\circ}\text{C}\) and then warmed to rt and poured into a saturated aqueous NaCl solution. The two layers were separated and the aqueous layer was extracted by \(\text{CH}_2\text{Cl}_2\). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation \(\text{in vacuo}\). Purification by column chromatography on silica gel (30% ethyl acetate-hexanes) yielded 16 mg (62%) of a white solid (m.p.=157-159 \(^{\circ}\text{C}\)).

IR (KBr): 3436, 2951, 1730, 1326, 1155 cm\(^{-1}\). \(^1\text{H NMR (400 MHz, CDCl}_3\)}: \(\delta\) 7.77 (d, \(J=8.2\, \text{Hz, 2H})\), 7.26 (d, \(J=8.2\, \text{Hz, 2H})\), 3.82 (dd, \(J=11.9, 4.0\, \text{Hz, 1H})\), 3.26-3.14 (m, 1H), 2.89 (td, \(J=13.0, 2.8\, \text{Hz, 1H})\), 2.84-2.74 (m, 1H), 2.39 (s, 3H), 2.44-2.13 (m, 4H), 2.04-1.92 (m, 1H), 1.83-1.72 (m, 1H), 1.64-1.51 (m, 1H), 1.44 (ddd, \(J=25.0, 12.5, 3.7\, \text{Hz, 1H})\), 1.38-1.19 (m, 1H). \(^{13}\text{C NMR (75 MHz, CDCl}_3\)}: \(\delta\) 217.6, 143.6, 137.0, 129.5, 127.8, 73.4, 69.7, 43.6, 38.3, 29.3, 27.3, 22.8, 21.5, 18.7.

\[
\begin{align*}
\text{Trimethyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (2.6)}
\end{align*}
\]

To a \(-5 \, ^{\circ}\text{C}\) solution of 20 mg (0.089 mmol) (1-cyclohex-l-enylcyclobutoxy)-trimethylsilane 2.12 in 2.0 mL of \(\text{CH}_2\text{Cl}_2\) was added slowly 18.4 mg (0.107 mmol) \(m\)-CPBA. The reaction mixture was stirred for 4 h at rt. Two other portion of 18.4 mg (0.107 mmol) \(m\)-CPBA chloroperbenzoic acid were added. The reaction mixture was stirred for 14 h at rt and poured into an aqueous 0.5M NaOH solution. The two layers were separated and the aqueous layer was extracted by \(\text{CH}_2\text{Cl}_2\). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation \(\text{in vacuo}\). Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 20 mg (94%) of a clear liquid.
IR (NaCl): 2941, 1447, 1251, 1158 cm\(^{-1}\). \(^1\)H NMR (300 MHz, (CD\(_3\))\(_2\)CO): \(\delta 3.11\) (bs, 1H), 2.15-1.88 (m, 6H), 1.86-1.66 (m, 3H), 1.48-1.16 (m, 5H), 0.10 (s, 9H). \(^13\)C NMR (75 MHz, (CD\(_3\))\(_2\)CO): \(\delta 79.0, 60.8, 54.7, 32.4, 32.0, 24.6, 22.8, 20.6, 19.2, 12.6, 1.2\). LRMS (EI\(^+\)) \(m/z\) (relative intensity): 240 (M, 4), 212 (20), 197 (17), 171 (12), 170 (59), 169 (70), 155 (27), 143 (10), 141 (14), 129 (17), 79 (15), 77 (11), 75 (49), 73 (100), 55 (11).

6-Hydroxyspiro[4.5]decan-1-one (2.7)
To a -78 °C solution of 17.6 mg (0.073 mmol) of trimethyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane 2.6 in 2.0 mL of CH\(_2\)Cl\(_2\) was added 80 uL of a 1.0 M solution (0.08 mmol) of titanium tetrachloride. The reaction mixture was stirred for 0.5 h at -78 °C and then warmed to rt and poured into a saturated aqueous NaCl solution. The two layers were separated and the aqueous layer was extracted by CH\(_2\)Cl\(_2\). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation \textit{in vacuo}. Purification by column chromatography on silica gel (20% ethyl acetate-hexanes) yielded 7.6 mg (62%) of a white solid (m.p.=55-57 °C).

IR (NaCl): 3488, 2932, 2852, 1723, 1447, 1166, 1048 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 3.71\) (bs, 1H), 3.61 (m, 1H), 2.38-2.15 (m, 2H), 2.03-1.67 (m, 7H), 1.60-1.20 (m, 5H). \(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta 4.79\) (s, 1H), 3.51 (dd, \(J=9.2, 4.3\) Hz, 1H), 2.36-2.18 (m, 2H), 2.01-1.71 (m, 6H), 1.66-1.58 (m, 2H), 1.43-1.16 (m, 4H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta 225.9, 70.9, 51.6, 38.4, 32.6, 28.8, 26.9, 20.8, 19.6, 18.7\). LRMS (EI\(^+\)) \(m/z\) (relative intensity): 168 (M, 21), 150 (56), 132 (21), 122 (12), 108 (39), 97 (100), 91 (12), 81 (53), 67 (33), 55 (39). Anal. Cal'd for C\(_{10}\)H\(_{16}\)O\(_2\): C, 71.39; H, 9.59. Found: C, 70.87; H, 9.76.

6-Hydroxyspiro[5.5]undecan-1-one (2.10)²⁰
To a -78 °C solution of 9.0 mg (0.0266 mmol) of triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclopentyloxy]silane 2.20 in 1.0 mL of CH\(_2\)Cl\(_2\) was added 29 uL of a 1.0 M solution (0.029 mmol) of TiCl\(_4\). The reaction mixture was stirred for 0.5 h at -78 °C and then warmed to rt and
poured into a saturated aqueous NaCl solution. The two layers were separated and the aqueous layer was extracted by CH₂Cl₂. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (20% ethyl acetate-hexanes) yielded 8.0 mg (90%) of a clear liquid.

**¹H NMR (400 MHz, CDCl₃): δ 3.41 (bs, 1H), 3.18 (bs, 1H), 2.63-2.52 (m, 1H), 2.31-2.19 (m, 2H), 2.07-1.95 (m, 2H), 1.88-1.58 (m, 7H), 1.43-1.18 (m, 4H). LRMS (EI⁺) m/z (relative intensity): 182 (M).**

(1-Cyclohex-1-enylcyclobutoxy)-trimethylsilane (2.12)

To a solution of 70 mg (0.46 mmol) of 1-cyclohex-1-enylcyclobutanol 2.11 in 5.0 mL of THF was added a pre-mixed solution of 134 µL (1.6 mmol) of trimethylsilyl triflate and 134 µL (2.5 mmol) 2,6-lutidine in 5.0 mL of THF. The reaction mixture was stirred for 0.5 h at rt and poured into a saturated aqueous NaHCO₃ solution. The two layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 80 mg (81%) of a clear liquid.

IR (NaCl): 2935, 1249, 1139 cm⁻¹. ¹H NMR (400 MHz, CD₆D₆): δ 5.65-5.63 (m, 1H), 2.28-2.15 (m, 4H), 2.14-2.09 (m, 2H), 1.98-1.93 (m, 2H), 1.74-1.65 (m, 1H), 1.60-1.54 (m, 2H), 1.52-1.36 (m, 3H), 0.15 (s, 9H). ¹³C NMR (75 MHz, CD₆D₆): δ 140.3, 120.2, 79.4, 35.6, 25.5, 23.20, 23.18, 22.8, 13.8, 1.9. LRMS (EI⁺) m/z (relative intensity): 224 (M).

1-(7-oxa-bicyclo[4.1.0]hept-1-yl) (2.13)

To a −5 °C solution of 150 mg (0.98 mmol) of 1-cyclohex-1-enylcyclobutanol 2.11 in 6.0 mL CH₂Cl₂ and 4 mL of H₂O were added 120 mg (1.11 mmol) of NaHCO₃ and 320 mg (1.85 mmol) m-CPBA. The reaction mixture was stirred for 2 h at rt and poured into a saturated aqueous NaHCO₃ solution. The two layers were separated and the aqueous layer was extracted by CH₂Cl₂. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (20% ethyl acetate-hexanes) yielded 162 mg (99%) of a clear liquid.
IR (NaCl): 3424, 2937, 1151 cm\(^{-1}\). \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)): \(\delta\) 2.95 (d, \(J=2.31\) Hz, 1H), 2.18-2.11 (m, 2H), 2.00-1.67 (m, 6H), 1.58-1.22 (m, 4H), 1.08-1.00 (m, 2H). \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)): \(\delta\) 77.1, 61.7, 54.9, 31.8, 31.5, 25.0, 23.3, 21.0, 19.8, 13.2. LRMS (EI+) \(m/z\) (relative intensity): 168 (M), 150 (M-H\(_2\)O).

![Image of IR spectrum]

**6-Trimethylsilanyloxyspiro[4.5]decan-1-one (2.14)**

IR (NaCl): 2954, 2858, 1734, 1448, 1251, 1091 cm\(^{-1}\). \(^1\)H NMR (300 MHz, (CD\(_3\))\(_2\)CO): \(\delta\) 3.61 (dd, \(J=10.4, 4.2\) Hz, 1H), 2.30-1.58 (m, 11H), 1.35-1.15 (m, 3H), 0.082 (s, 9H). LRMS (EI+) \(m/z\) (relative intensity): 240 (M), 225 (M-CH\(_3\)), 169 (M-Si(CH\(_3\))\(_3\)).

![Image of NMR spectrum]

**Triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (2.15)**

To a solution of 40 mg (0.24 mmoL) 1-(7-oxa-bicyclo[4.1.0]hept-1-yl) 2.13 in 5.0 mL of THF was added a pre-mixed solution of 103 \(\mu\)L (0.384 mmoL) triisopropylsilyl triflate and 70 \(\mu\)L (0.6 mmoL) of 2,6-lutidine in 2.0 mL of THF. The reaction mixture was stirred for 14 h at rt and poured into an aqueous saturated NaHCO\(_3\) solution. The two layers were separated and the aqueous layer was extracted by Et\(_2\)O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation \textit{in vacuo}. Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 48 mg (62% after 3 purifications) of a clear liquid.

IR (NaCl): 2943, 2867, 1463, 1252, 1163, 1038 cm\(^{-1}\). \(^1\)H NMR (300 MHz, (CD\(_3\))\(_2\)CO): \(\delta\) 3.15 (bs, 1H), 2.26-2.19 (m, 1H), 2.17-1.92 (m, 5H), 1.84-1.60 (m, 3H), 1.55-1.42 (m, 2H), 1.35-1.24 (m, 3H), 1.10 (bs, 21H). \(^{13}\)C NMR (75 MHz, (CD\(_3\))\(_2\)CO): \(\delta\) 79.9, 62.5, 55.7, 34.1, 33.8, 24.8, 22.3, 20.5, 19.2, 14.6, 13.3. LRMS (EI+) \(m/z\) (relative intensity): 296 (M), 281 (M-CH\(_3\)).
1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclopentanol (2.17)
To a -5 °C solution of 78 mg (0.45 mmol) 1-cyclohex-1-enylcyclopentanol in 3.0 mL CH₂Cl₂ and 2 mL of H₂O were added 60 mg (0.55 mmol) of NaHCO₃ and 147 mg (0.85 mmol) of m-CPBA. The reaction mixture was stirred for 1 h at rt and poured into a saturated aqueous NaHCO₃ solution. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (20% ethyl acetate-hexanes) yielded 81 mg (99%) of a clear liquid.
IR (NaCl): 3452, 2936, 1435, 1195 cm⁻¹. ¹H NMR (300 MHz, C₆D₆): δ 3.15 (d, J=2.7 Hz, 1H), 1.90-1.31 (m, 14H), 1.06-0.95 (m, 2H). ¹³C NMR (75 MHz, C₆D₆): δ 82.4, 62.7, 55.3, 36.2, 36.0, 25.1, 25.0, 24.71, 24.66, 21.3, 19.6. LRMS (EI+) m/z (relative intensity): 182 (M), 164 (M-H₂O).

7-TrimethylsilyloxySpiro[5.5]undecan-1-one (2.19)
IR (NaCl): 2934, 2862, 1713, 1448, 1251, 1091 cm⁻¹. ¹H NMR (300 MHz, C₆D₆): δ 3.94 (dd, J=5.8, 3.1 Hz, 1H), 2.44-2.30 (m, 2H), 2.26-2.17 (m, 1H), 1.99-1.90 (m, 1H), 1.78-1.00 (m, 12H), 0.064 (s, 9H). ¹³C NMR (75 MHz, C₆D₆): δ 211, 73.4, 53.2, 39.7, 36.6, 30.4, 30.2, 27.7, 21.5, 21.2, 21.1, 0.5. LRMS (EI+) m/z (relative intensity): 254 (M), 239 (M-CH₃), 183 (M-Si(CH₃)₃).

Triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclopentyl]oxy silane (2.20)
To a solution of 37 mg (0.20 mmol) of 1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclopentanol in 5.0 mL of THF was added a pre-mixed solution of 100 μL (0.32 mmol) triisopropylsilyl triflate and 70 μL (0.5 mmol) 2,6-lutidine in 2.0 mL of THF. The reaction mixture was stirred for 14 h at rt and poured into a saturated aqueous NaHCO₃ solution. The two layers were separated and
the aqueous layer was extracted by Et₂O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 40 mg (60% after 3 purifications) of a clear liquid.

IR (NaCl): 2943, 2867, 1462, 1091 cm⁻¹. ¹H NMR (400 MHz, (CD₃)₂CO): δ 3.04 (bs, 1H), 2.25-2.16 (m, 1H), 1.94-1.71 (m, 8H), 1.67-1.43 (m, 4H), 1.42-1.20 (m, 4H), 1.09-1.03 (m, 21H). ¹³C NMR (75 MHz, (CD₃)₂CO): δ 89.2, 63.6, 56.7, 37.9, 37.7, 26.2, 26.15, 26.1, 25.9, 22.2, 20.6, 19.4, 14.9. LRMS (EI⁺) m/z (relative intensity): 310 (M), 295 (M-CH₃).

![Image of 6-Bromospiro[4.5]decan-1-one](image)

6-Bromospiro[4.5]decan-1-one (2.25)

To a -78 °C solution of 56 mg (0.368 mmoL) of 1-cyclohex-1-enylcyclobutanol 2.11 in 1.0 mL isopropanol and 1.0 mL propylene oxide was added 79 mg (0.442 mmoL) of \(N\)-bromosuccinimide. The reaction mixture was stirred for 1 h at -78 °C to rt and then concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 74 mg (87%) of a yellowdish solid (m.p. ≥25 °C).

IR (NaCl): 2938, 1734, 1447, 1200, 1131, 1000 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.98 (dd, \(J=11.9, 5.0\ Hz, 1H\)), 2.69 (qd, \(J=12.7, 4.0\ Hz, 1H\)), 2.52-2.42 (m, 1H), 2.31-2.24 (m, 2H), 2.14-1.24 (m, 10H). ¹³C NMR (75 MHz, CDCl₃): δ 218.1, 58.3, 52.2, 39.5, 37.9, 34.6, 33.4, 27.1, 20.4, 18.6. LRMS (EI⁺) m/z (relative intensity): 151 (M-Br). Anal. Cal'd for C₁₀H₁₅BrO: C, 51.97; H, 6.54. Found: C, 52.28; H, 6.63.

![Image of 1-(Toluene-4-sulfonyl)-6-(1-triisopropylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine](image)

1-(Toluene-4-sulfonyl)-6-(1-triisopropylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine (2.31)

To a solution of 35 mg (0.114 mmoL) of 1-[1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclobutanol 2.29 in 3.0 mL of THF was added a pre-mixed solution of 50 μL (0.16 mmoL) triisopropylsilyl triflate and 50 μL (0.25 mmoL) 2,6-lutidine in 2.0 mL of THF. The reaction mixture was stirred for 14 h at rt and poured into a saturated aqueous NaHCO₃ solution. The two layers were separated and the aqueous layer was extracted by Et₂O. The combined organic layers
were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 62 mg (99%) of a white solid. m.p.=68-69 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.77\) (d, \(J=8.2\) Hz, 2H), 7.23 (d, \(J=8.2\) Hz, 2H), 5.82 (t, \(J=5.8\) Hz, 1H), 3.47-3.43 (m, 2H), 2.73-2.66 (m, 2H), 2.40 (s, 3H), 2.36-2.30 (m, 2H), 1.89-1.83 (m, 2H), 1.77-1.70 (m, 1H), 1.53-1.45 (m, 1H), 1.28-1.21 (m, 2H), 1.11 (s, 21H).

1-(Toluene-4-sulfonyl)-1-(triisopropylsilanyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (2.34)

To a -5 °C solution of 58mg (0.125 mmoL) of 1-(toluene-4-sulfonyl)-6-(1-triisopropylsilanyloxycyclobutyl)-1,2,3,4-tetrahydropyridine 2.31 in 5.0 mL of CH\(_2\)Cl\(_2\) was added slowly 43mg (0.250 mmol) \(m\)-CPBA. The reaction mixture was stirred for 4 h at rt. Two other portion of 43 mg (0.250 mmol) \(m\)-CPBA were added. The reaction mixture was stirred for 14 h at rt and poured into a solution of 0.5M NaOH. The two layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 53 mg (88%) of a white solid (m.p.=98-99 °C).

IR (NaCl): 2944, 2866, 1462, 1349, 1163 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.88\) (d, \(J=8.2\) Hz, 2H), 7.26 (d, \(J=8.2\) Hz, 2H), 3.53 (dt, \(J=13.7, 3.3\) Hz, 1H), 3.17-3.07 (m, 2H), 2.87 (td, \(J=12.2, 2.7\) Hz, 1H), 2.41 (s, 3H), 2.30-2.17 (m, 3H), 2.00-1.90 (m, 2H), 1.82-1.66 (m, 4H), 1.10 (d, \(J=3.1\) Hz, 21H). \(^1\)C NMR (75 MHz, (CD\(_3\))\(_2\)CO): \(\delta 144.9, 139.8, 130.7, 129.7, 82.2, 73.8, 55.5, 46.8, 37.0, 34.4, 23.1, 21.9, 19.3, 18.7, 14.8, 14.0, 13.9. LRMS (CI+, ammonia) \(m/z\) (relative intensity): 480 (M\(^+\) + 1, 50), 326 (100), 308 (18), 282 (25), 189 (17), 150 (54), 140 (14), 124 (18), 108 (11). Anal. Cal'd for C\(_{23}\)H\(_{41}\)NO\(_4\)SSi: C, 62.59; H, 8.61; N, 2.92. Found: C, 62.67; H, 8.83; N, 3.08.
3-Allyl-2-cyclobutylidene-1-(toluene-4-sulfonyl)-piperidine (2.41)
To a solution of 100mg (0.325 mmol) of 1-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-cyclobutanol 2.29 in 5.0 mL CH$_2$Cl$_2$ was added slowly 103 µL (0.650 mmol) of allyltrimethylsilane at rt. The reaction mixture was cooled at -78°C and 124 µL (0.975 mmol) boron trifluoride diethyl etherate was slowly added. The reaction mixture was stirred at -78°C for 45 minute. Silica gel and 2.0 mL of Et$_2$O were added and the mixture was concentrated to dryness by evaporation in vacuo. Purification by column chromatography (10% ethyl acetate-hexanes) yielded 90 mg (84%) of a clear oil.
IR (NaCl): 2928, 1336, 1154 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.75 (d, $J$=8.2 Hz, 2H), 7.26 (d, $J$=8.2 Hz, 2H), 5.85-5.74 (m, 1H), 5.02-4.96 (m, 2H),3.59 (dt, $J$=12.8, 3.3 Hz, 1H), 3.14-3.07 (m, 1H), 2.91-2.53 (m, 4H), 2.41 (s, 3H), 2.34-2.25 (m, 2H), 2.00-1.86 (m, 3H), 1.68-1.52 (m, 3H), 1.35-1.29 (m, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 142.8, 138.7, 138.3, 137.4, 129.3, 128.7, 127.3, 115.7, 48.5, 36.1, 36.0, 30.4, 29.4, 29.3, 21.4, 20.6, 16.5. LRMS (EI) $m/z$ (relative intensity): 331 (M). Anal. Cal'd for C$_{19}$H$_{25}$N0$_2$: C, 68.85; H, 7.60; N, 4.23. Found: C, 68.69; H, 7.68; N, 4.35.

3-Allyl-2-cyclopentylidene-1-(toluene-4-sulfonyl)-piperidine (2.43)
To a solution of 100mg (0.311 mmol) of 1-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-cyclopentanol 2.42 in 5.0 mL of CH$_2$Cl$_2$ was added slowly 99 µL (0.622 mmol) of allyltrimethylsilane at rt. The reaction mixture was cooled at -78°C and 118 µL (0.933 mmol) of boron trifluoride diethyl etherate was slowly added. The reaction mixture was stirred at -78°C for 45 minute. Silica gel and 2.0 mL of Et$_2$O were added and the mixture was concentrated to dryness by evaporation in vacuo. Purification by column chromatography (10% ethyl acetate-hexanes) yielded 96 mg (89%) of a clear oil.
IR (NaCl): 2947, 1335, 1155 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.79 (d, $J$=8.2 Hz, 2H), 7.27 (d, $J$=8.2 Hz, 2H), 5.92-5.81 (m, 1H), 5.05-4.96 (m, 2H), 3.73-3.63 (m, 1H), 2.95-2.88 (m, 1H), 2.57-2.21 (m, 6H), 2.41 (s, 3H), 2.13-2.05 (m, 1H), 1.81-1.56 (m, 7H), 1.50-1.40 (m, 1H), 1.30-
1.23 (m, 1H). $^{13}$C NMR (75 MHz, (CDCl$_3$): δ 143.0, 142.6, 138.2, 137.4, 129.1, 128.3, 127.2, 115.4, 76.4, 48.1, 37.3, 35.5, 32.0, 30.1, 28.5, 26.2, 21.2, 19.4. LRMS (EI) $m/z$ (relative intensity): 345 (M), 346 (M$^+$ + 1).

10- Allyl-6-(toluene-4-sulfonyl)-11-oxa-6-aza-dispiro[3. 0. 5. 1]undecane (2.44)

To a solution of 71 mg (0.214 mmol) of 3-allyl-2-cyclobutylidene-1-(toluene-4-sulfonyl)-piperidine 2.41 in 6.0 mL of CH$_2$Cl$_2$ and 4.0 mL of H$_2$O were added 28 mg (0.30 mmol) of NaHCO$_3$ and 117 mg (0.428 mmol) of m-CPBA at rt. The reaction mixture was stirred for 4 h and was uncompleted. An other portion of 28 mg (0.30 mmol) of NaHCO$_3$ and 117 mg (0.428 mmol) of m-CPBA were added. The reaction mixture was stirred for 14h at rt and poured into a saturated aqueous NaHCO$_3$ solution. The two layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel pre-treated with 5% Et$_3$N in hexane (10% ethyl acetate-hexanes) yielded 57 mg (77%) of a white solid (mp=decomposition under heat).

IR (NaCl): 2940, 1330, 1164 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.57 (d, $J$=8.2 Hz, 2H), 7.22 (d, $J$=8.2 Hz, 2H), 5.84-5.73 (m, 1H), 5.13-5.01 (m, 2H), 3.50-3.32 (m, 2H), 2.56-2.41 (m, 4H), 2.37 (s, 3H), 2.35-2.25 (m, 1H), 2.19-2.10 (m, 1H), 2.03-1.94 (m, 2H), 1.86-1.70 (m, 3H), 1.64-1.47 (m, 2H). $^{13}$C NMR (75 MHz, (CDCl$_3$): δ 142.8, 138.9, 136.3, 129.3, 126.3, 116.5, 76.2, 72.5, 47.0, 39.3, 32.7, 30.7, 30.0, 25.4, 21.3, 20.9, 13.2. LRMS (EI) $m/z$ (relative intensity): 347 (M).

11- Allyl-7-(toluene-4-sulfonyl)-12-oxa-7-aza-dispiro[4. 0. 5. 1]dodecane (2.45)

To a solution of 28 mg (0.081 mmol) of 3-allyl-2-cyclopentylidene-1-(toluene-4-sulfonyl)-piperidine 2.43 in 3.0 mL of CH$_2$Cl$_2$ and 2.0 mL of H$_2$O were added 11 mg (0.13 mmol) of NaHCO$_3$ and 44 mg (0.162 mmol) of m-CPBA acid at rt. The reaction mixture was stirred for 4 h and was uncompleted. An other portion of 11 mg (0.13 mmol) of NaHCO$_3$ and 44 mg (0.162 mmol) of m-CPBA acid were added. The reaction mixture was stirred for 14h at rt and poured
into a saturated aqueous NaHCO₃ solution. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate-hexanes) yielded 24 mg (82%) of a white solid (m.p.=89-91 °C).

IR (NaCl): 2951, 1329, 1160 cm⁻¹. **¹H NMR (400 MHz, CDCl₃):** δ 7.64 (d, J=8.2 Hz, 2H), 7.25 (d, J=8.2 Hz, 2H), 5.87-5.74 (m, 1H), 5.18-5.00 (m, 2H), 3.56-3.48 (m, 1H), 3.32-3.22 (m, 1H), 2.70-2.55 (m, 2H), 2.39 (s, 3H), 2.32-2.21 (m, 1H), 2.19-2.05 (m, 2H), 2.03-1.39 (m, 10H). **¹³C NMR (75 MHz, CDCl₃):** δ 143.0, 138.4, 136.5, 129.5, 126.4, 116.5, 79.9, 46.7, 40.1, 33.1, 32.2, 30.7, 25.0, 24.1, 21.4, 19.3. LRMS (EI) m/z (relative intensity): 361 (M). Anal. Cal'd for C₂₀H₂₇NO₃S: C, 66.45; H, 7.53; N, 3.87. Found: C, 66.85; H, 7.65; N, 4.03.

10-Allyl-6-(toluene-4-sulfonyl)-6-aza-spiro[4, 5]decane-1-one (2.46)

To a solution of 10 mg (0.0288 mmol) of 10-allyl-6-(toluene-4-sulfonyl)-11-oxa-6-aza-dispiro[3. 0. 5. 1]undecane 2.44 in 1.0 mL of CH₂Cl₂ was added 29 μL (0.0288 mmol) of 1M HCl at rt. The reaction mixture was stirred for 10 min. and was completed. The reaction mixture was poured into a H₂O. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate-hexanes) yielded 9 mg (90%) of a white solid (mp = 0 °C).

IR (NaCl): 2952, 1744, 1326, 1155 cm⁻¹. **¹H NMR (400 MHz, CDCl₃):** δ 7.88 (d, J=7.9 Hz, 2H), 7.29 (d, J=7.9 Hz, 2H), 5.65-5.54 (m, 1H), 4.98 (bs, 1H), 4.94 (d, J=6.1 Hz, 1H), 3.26 (dt, J=10.4, 3.0 Hz, 1H), 3.11 (td, J=12.2, 3.6 Hz, 1H), 2.68 (qu, J=9.5 Hz, 1H ), 2.56-2.46 (m, 2H), 2.42 (s, 3H), 2.38-2.24 (m, 2H), 2.20-2.11 (m, 1H), 2.05-1.95 (m, 1H), 1.85-1.70 (m, 3H), 1.68-1.48 (m, 2H), 1.38-1.25 (m, 1H). **¹³C NMR (75 MHz, CDCl₃):** δ 214.3, 143.2, 137.7, 136.8, 129.3, 127.8, 116.3, 77.2, 69.0, 43.9, 37.9, 36.6, 34.8, 31.8, 21.5, 19.0, 17.9. LRMS (EI) m/z (relative intensity): 347 (M).
11-Allyl-6-(toluene-4-sulfonyl)-7-aza-spiro[5.5]undecane-1-one (2.47)

To a solution of 13 mg (0.0366 mmol) of 11-allyl-7-(toluene-4-sulfonyl)-12-oxa-7-aza-dispiro[4.0.5.1]dodecane 2.45 in 1.0 mL of CH$_2$Cl$_2$ was added 36 µL (0.0366 mmol) of 1M HCl at rt. The reaction mixture was stirred for 2 h. and was completed. The reaction mixture was poured into a H$_2$O. The two layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (10% ethyl acetate-hexanes) yielded 12 mg (91%) of a white solid (m.p. ≈ 0 °C).

IR (NaCl): 2948, 2870, 1715, 1454, 1322, 1154 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.97 (d, $J$=7.9 Hz, 2H), 7.29 (d, $J$=7.9 Hz, 2H), 5.70-5.58 (m, 1H), 5.00 (d, $J$=6.1 Hz, 1H), 4.97 (bs, 1H), 3.23 (t, $J$=9.5 Hz, 1H), 3.21 (d, $J$=9.5 Hz, 1H), 2.69 (dm, $J$=9.5 Hz, 1H ), 2.53 (t, $J$=9.5 Hz, 2H), 2.42 (s, 3H), 2.28-2.19 (m, 1H), 2.10-1.84 (m, 5H), 1.76-1.70 (m, 2H), 1.69-1.54 (m, 3H), 1.48-1.44 (m, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 142.8, 138.9, 136.3, 129.3, 126.3, 116.5, 76.2, 72.5, 47.0, 39.3, 32.7, 30.7, 30.0, 25.4, 21.3, 20.9, 13.2. LRMS (EI) $m/z$ (relative intensity): 361 (M).

VIII. References


Chapter Three
Progress Toward Cylindricine B
I. Introduction

A. Background

Cylindricine A to K were isolated from the ascidian *Calvelina cylindricia* off the coast of Tasmania (Fig. 3.1). These alkaloids are an interesting target for total synthesis because they exhibit bioactivity against brine shrimp and in a strain of DNA-repair-deficient yeast. They also inhibit growth of murine leukemia and human solid tumour cell lines. Moreover, the spirocyclic amine of the tricyclic system (ABC) of the cylindricine family pose an interesting synthetic challenge. My research efforts concentrated on the synthesis of cylindricine B.

Figure 3.1: Cylindricine Family
Cylindricine A and cylindricine B are constitutional isomers. After 6 days at room temperature, a pure solution of either cylindricine A or B in its free base form will isomerize to give a 3:2 mixture, respectively (Eq. 3.1). The two molecules are believed to interconvert through an aziridinium ion (Scheme 3.1).

Scheme 3.1: Interconversion of Cylindricine A and B via an Aziridinium ion

The ability to interconvert between isomers, made these two natural products an intriguing target for total synthesis. At the outset of this project, no published asymmetric syntheses for any of the cylindricine alkaloids existed, except for one synthesis of (-)-cylindricine C. So, an asymmetric synthesis of cylindricine B provides access to cylindricine A through their interconversion. Subsequent nucleophilic substitution on cylindricine A can lead to cylindricine C, D, E and F (Eq. 3.2).
B. Retrosynthesis

Retrosynthetic analysis of cylindricine B and J reveals a potentially convenient route to these alkaloids (Scheme 3.2). Selective Michael addition onto the appropriate α,β-unsaturated carbonyl could provide cylindricine B and J. The Michael acceptor could be derived from a coupling reaction between the spirocyclic vinyl triflate and an appropriate side chain. A siloxy-epoxide ring expansion would provide the spiro-connected bicyclic ring system, and the ring expansion precursor could come from an anionic vinyl addition onto cyclopentanone. The vinyl substrate could be derived from a lactam, which could arise from L-Glutamic acid. L-Glutamic acid was chosen as the major asymmetric building block for the enantioselective construction of cylindricine.

Scheme 3.2: Retrosynthetic Analysis
II. Synthesis of Azaspirocyclic Ketones

The synthesis of 5-(S)-hydroxylactam was began with L-glutamic acid as a cheap chiral reagent, following a well known literature preparation (Scheme 3.3).\(^5\)

**Scheme 3.3: Synthesis of 5-(S)-Hydroxylactam**

![Scheme 3.3](image)

The synthesis of the ring expansion precursor was executed following a literature procedure published by the Dake group (Scheme 3.4).\(^6\)

**Scheme 3.4: Synthesis of Ring Expansion Precursor**

![Scheme 3.4](image)
Next, the construction of the azaspirocyclic vinyl triflate was performed, also according to a literature preparation from the Dake group (Scheme 3.5).\textsuperscript{6}

**Scheme 3.5: Construction of Azaspirocyclic Vinyl Triflate**

![Scheme 3.5](image)

This preparation was followed because the final azaspirocyclic vinyl triflate is a commonly used intermediate in our group. For example, it is used in the total asymmetric synthesis of fasicularin, another target molecule of the Dake group (Scheme 3.6).

**Scheme 3.6: Common Intermediate Involved in Fasicularin and Cylindricine**

![Scheme 3.6](image)

Thus, having synthesized the B and C rings of cylindricine B and J, the A ring needed to be installed. The strategy chosen to install the A ring was via a Michael addition onto the proper \(\alpha,\beta\)-unsaturated carbonyl (section IB). It was thought that the Michael acceptor could be derived from a coupling reaction between the vinyl triflate and a suitable side chain (Eq. 3.3).
III. Coupling Reactions

A. Kishi-Nozaki Coupling Reaction

One way of appending the side chain responsible for the formation of ring A of cylindricine B was via a Kishi-Nozaki coupling of vinyl triflate 3.1 with aldehyde 3.2 to give the diallylic alcohol 3.3 (Eq. 3.4 and Table 3.1).\(^7\)

\[
\begin{align*}
\text{TBSO} & \quad \text{NiCl}_2 \\
\text{Ts} & \quad \text{CrCl}_2 \\
\text{DMF} & \quad \text{Table 3.1}
\end{align*}
\]

\[
\begin{align*}
3.1 + \text{H}_{\text{C}_9\text{H}_3} & \rightarrow \text{TBSO} & \text{NiCl}_2 & \text{CrCl}_2 & \text{DMF} \\
\text{Ts} & \quad \text{OH} & \text{Table 3.1}
\end{align*}
\]

Table 3.1: Kishi-Nozaki Coupling Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>3.1 (eq.)</th>
<th>3.2 (eq.)</th>
<th>NiCl(_2) (eq.)</th>
<th>CrCl(_2) (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>3.3</th>
<th>comment(^a)</th>
<th>Ref.(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0.02</td>
<td>4</td>
<td>25 (\rightarrow) 60</td>
<td>5</td>
<td>-</td>
<td>70% sm rc</td>
<td>V-49</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>6</td>
<td>0.02</td>
<td>6</td>
<td>25</td>
<td>14</td>
<td>-</td>
<td>sm rc</td>
<td>VI-04</td>
</tr>
</tbody>
</table>

\(^a\) sm=starting material; rc=recovered
\(^b\) Notebooks

Despite using two different literature conditions, the Kishi-Nozaki coupling was unsuccessful (entries 1 and 2). The TLC of the reactions showed no formation of products, and the starting material was recovered in both cases.

B. Simple Carbonylation Coupling Reaction

Another way of appending the side chain was via carbonylation of the vinyl triflate 3.1. Using a catalytic amount of palladium, 1 atmosphere of carbon monoxide and methanol, ester 3.4 should be obtained (Eq. 3.5 and Table 3.2).\(^8\)
The carbonylative coupling reaction, following different literature conditions, was unsuccessful using the palladium catalysts \( \text{Pd(OAc)}_2 \), \( \text{Pd(Cl)}_2(\text{PPh}_3)_2 \), \( \text{Pd}_2(\text{dba})_3 \) (entries 1-4). However, using catalytic amount of \( \text{Pd(PPh}_3)_4 \) or \( \text{Pd(dppf)}_2\text{Cl}_2 \) was effective (entries 5 and 7-11). The starting material 3.1 was recovered in most case, except for entries 10 and 11.

Using \( \text{Pd(PPh}_3)_4 \) in THF with triethylamine at room temperature did not give the carbonylative coupling product 3.4 (entry 6). However, in DMF at 60 °C, adding triphenylarsine as co-ligand gave the ester product 3.4 in 18% yield (entry 5). Warming the reaction to 90 and 100 °C increased the yield of product 3.4 to 50 and 63%, respectively (entries 7 and 8). Without adding triphenylarsine as co-ligand at 100 °C, the coupling reaction still proceeded, but with lower yield (entry 9).

Using \( \text{Pd(dppf)}_2\text{Cl}_2 \) in DMF at 60 °C, with triphenylarsine as co-ligand and cesium carbonate as base gave the product 3.4 in excellent yield after 3 hours (entry 10). Increasing the temperature to 110 °C decreased the yield of ester formation to 43% (entry 11).
The $^1$H NMR analysis of 3.4 showed the resonance for the methyl ester proton ($\delta$ 3.68 (s, 3H)) and the change in chemical shift of the double bond ($\delta_{3.1}$ 5.91 (dd, $J= 5.3$, 2.7Hz, 1H) and $\delta_{3.4}$ 7.08 (dd, $J= 4.9$, 3.3Hz, 1H)). The IR spectrum of the ester product 3.4 exhibited one strong stretch for the carbonyl functional groups on the ester ($\nu$ 1720 cm$^{-1}$).

Having determined the conditions for the simple carbonylative coupling, the next step was to try the more complex carbonylative Stille coupling with vinyl triflate 3.1.

C. Carbonylative Stille Coupling Reaction

The vinylstannane compound 3.6 was synthesized according to literature protocol (Eq. 3.6). The appropriate octyne was first treated with diisobutylaluminium hydride (DIBAL-H) followed by trimethyltin chloride. Purification by distillation gave the E vinyl tin 3.6 in 54\% yield.

$$\text{H} = \text{C}_6\text{H}_{13} \xrightarrow{\text{a) DIBAL-H hexane}} \text{Me}_3\text{Sn} = \text{C}_6\text{H}_{13} \quad (\text{Eq. 3.6})$$

Next, attempts were made to append the side chain via carbonylative Stille coupling between vinyl triflate 3.1, carbon monoxide and vinylstannane 3.6 with a catalytic amount of palladium to give the Michael acceptor 3.7 (Eq. 3.7 and Table 3.3).\text{\textsuperscript{10}}

$$\text{TBSO} \text{N}^\text{Ts} + \text{Me}_3\text{Sn} \xrightarrow{\text{Pd}} \text{CO 1atm \text{3 eq. LiCl DMF Table 3.3}} \text{O} \text{TBSO} \text{N}^\text{Ts} \xrightarrow{\text{Er}} \text{C}_6\text{H}_{13} \quad (\text{Eq. 3.7})$$

Table 3.3: Carbonylative Stille Coupling Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd (eq.)</th>
<th>3.6 (eq.)</th>
<th>additive (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>3.7</th>
<th>3.8</th>
<th>Ref.\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh_3)_4 (0.2)</td>
<td>1.3</td>
<td>Ph_3As (0.2)</td>
<td>110</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>VI-37</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh_3)_4 (0.2)</td>
<td>1.3</td>
<td>Ph_3As (0.2) / CuI (0.5)</td>
<td>100</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>VI-42</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh_3)_4 (0.06)</td>
<td>1.3</td>
<td>ZnCl_2 (1.0)</td>
<td>55</td>
<td>14</td>
<td>63%</td>
<td>-</td>
<td>VI-49</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh_3)_4 (1.0)</td>
<td>1.2</td>
<td>-</td>
<td>55</td>
<td>14</td>
<td>78%</td>
<td>-</td>
<td>VI-50</td>
</tr>
<tr>
<td>5</td>
<td>Pd(dppf)_2Cl_2 (0.3)</td>
<td>1.2</td>
<td>Ph_3As (0.3) / CsCO_3 (2.0)</td>
<td>60</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>VII-15</td>
</tr>
<tr>
<td>6</td>
<td>Pd(dppf)_2Cl_2 (1.0)</td>
<td>1.5</td>
<td>Ph_3As (1.0) / CsCO_3 (4.0)</td>
<td>60</td>
<td>2</td>
<td>-</td>
<td>obs\textsuperscript{b}</td>
<td>VII-24</td>
</tr>
</tbody>
</table>

(a) Notebooks (b) obs=observed (not isolated)
Using the two best palladium catalysts found for the simple carbonylative coupling reaction (section IIIB), the carbonylative Stille coupling reaction was attempted. However, none of the reaction conditions were successful. In every case, the vinyl triflate was recovered. In some cases, the coupled product 3.8 between two molecules of vinyl tin and one molecule of CO were observed (entries 3, 4 and 6). A quantitative amount of palladium was tried, but again, no carbonylative Stille coupling product was observed (entries 4 and 6). Also, changing the additive was not effective.

D. Formylation Coupling Reaction

Another method of appending the side chain was via palladium catalyzed formylation of vinyl triflate 3.1 with carbon monoxide and tributyltin hydride, to form aldehyde 3.9 (Eq. 3.8 and Table 3.4).

![Equation 3.8](image)

Table 3.4: Formylation Coupling Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>Pd (eq.)</th>
<th>Bu3SnH (eq.)</th>
<th>additive (eq.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>3.9</th>
<th>Ref. a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>Pd(PPh3)4 (0.2)</td>
<td>1.3</td>
<td>-</td>
<td>50</td>
<td>14</td>
<td>-</td>
<td>VI-12</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>Pd(dppf)2Cl2 (0.1)</td>
<td>1.3</td>
<td>CsCO3 (2.0)</td>
<td>60</td>
<td>14</td>
<td>-</td>
<td>VII-14</td>
</tr>
</tbody>
</table>

(a) Notebooks

Again, as Pd(PPh3)4 and Pd(dppf)2Cl2 were the best catalysts for the simple carbonylative coupling reaction (section IIIB), they were used for the formylation of vinyl triflate 3.1 with carbon monoxide and tributyltin hydride. None of the attempted reaction conditions were successful. In each case, vinyl triflate 3.1 was recovered.

E. Ylide Reaction

Ylide addition on the ketone of 3.10 could be another way of forming aldehyde 3.11, or epoxide 3.12 (Eq. 3.9 and 3.10). Subsequent transformation on these functionalities could lead to a Michael acceptor such as 3.7. Unfortunately, both reactions failed under the reaction conditions attempted.
F. Attempted Transformation of Ester 3.4

Finally, attempts were made to functionalize ester 3.4, by using a vinyl lithium nucleophile. The vinylstannane 3.6 was treated with methylthium to give the corresponding vinyl lithium compound, which was then added to the ester 3.4 (Eq. 3.11). However, no reaction was observed by TLC and the starting material was recovered.

The fact that the vinyl lithium did not add to the ester demonstrates that the $\alpha,\beta$-unsaturated carbonyl of ester 3.4 is not electrophilic enough. It is known that aldehydes are more reactive toward nucleophilic addition than esters. Reduction of the ester 3.4 to the aldehyde should result in increased carbonyl reactivity and allow addition of the vinyl lithium. This was attempted with DIBAL-H in toluene at $-100^\circ C$, to give aldehyde 3.9 (Eq. 3.12). Surprisingly, ester 3.4 was not reduced to the aldehyde. Alcohol 3.13 and starting material 3.4 were the only products observed by $^1$H NMR of the crude mixture.
Ester 3.4 was then completely reduced to alcohol 3.13 using 2.3 eq. of DIBAL-H (Eq. 3.13). The TLC and the $^1$H NMR of the crude mixture showed only the alcohol product 3.13. The allylic alcohol 3.13 was isolated in 93% yield.

\[
\begin{align*}
3.4 & \xrightarrow{\text{DIBAL-H}} 3.13 \\
\text{TLC and } & \text{ the } ^{1} \text{H NMR of the crude mixture showed only the alcohol product 3.13.} \\
\text{The allylic alcohol 3.13 was isolated in 93\% yield.}
\end{align*}
\]

The $^1$H NMR analysis of 3.13 showed the resonance for the allylic methylene alcohol proton ($\delta$ 2.98 (s, 2H)) and the disappearance for the methyl ester proton ($\delta$ 3.68 (s, 3H)). The IR spectrum of 3.13 exhibited one strong stretch for the alcohol functional groups ($\nu$ 3400 cm$^{-1}$).

Having synthesized alcohol 3.13, the next two steps would be to first oxidize alcohol 3.13 to aldehyde 3.9, and then try the addition of the vinyl lithium onto the $\alpha,\beta$-unsaturated aldehyde to form diallylic alcohol 3.3 (Scheme 3.5). However, due to time constraints I was not able to complete this work.

**Scheme 3.5: Future Work**

\[
\begin{align*}
3.13 & \xrightarrow{\text{oxidation}} 3.9 \\
& \xrightarrow{\text{addition of vinyl lithium}} 3.3
\end{align*}
\]

**IV. Discussion**

An direct attempt to append the Michael acceptor side chain 3.7, an important intermediate toward the synthesis of the cylindricines family, was attempted using the palladium-catalyzed carbonylative coupling of vinyl triflate 3.1 with vinylstannane 3.6 (Eq. 3.14). Unfortunately, this method was not successful.

\[
\begin{align*}
3.1 & + \text{Me}_3\text{Sn} & \xrightarrow{\text{Pd, CO, solvent}} & 3.7 \\
& \text{TBSO} & & \text{TBSO}
\end{align*}
\]

(Eq. 3.14)
An indirect way of appending the Michael acceptor side chain to give compound 3.7, was via a simple carbonylation of vinyl triflate 3.1, followed by vinyl lithium addition onto ester 3.4 (Scheme 3.6). Ester 3.4 was synthesized in good yield using a catalytic amount of palladium, 1 atmosphere of carbon monoxide and excess methanol as nucleophile. However, the addition of vinyl lithium onto the α,β-unsaturated ester 3.4 failed.

Scheme 3.6: Indirect way of Appending the Michael Acceptor Side Chain

Further research on the synthesis of the A ring of cylindricine B is continuing in our laboratory (Figure 3.2).

Figure 3.2: Cylindricine B
V. Experimental

General (see chapter one, section V)

\[
\text{TBSO} \quad \text{O} \quad \text{OMe} \\
\text{Ts}
\]

3-(tert-Butyl-dimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-diene-7-carboxylic acid methyl ester (3.4)

To a suspension of 5.6 mg (0.007 mmol) of Pd(dppf)$_2$Cl$_2$CH$_2$Cl$_2$, 3.4 mg (0.081 mmol) of LiCl, 2.1 mg (0.007 mmol) of Ph$_3$As and 17.6 mg (0.054 mmol) of CsCO$_3$ in 0.5 mL of degassed DMF was cannulated a solution of 16 mg (0.027 mmol) of trifluoromethanesulfonic acid 3-(tert-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-dien-7-yl ester 3.1 in 0.5 mL of DMF. 2 mL of degassed MeOH was added and the reaction mixture was warmed to 60 °C and stirred under 1 atm of carbon monoxide for 3 h. The reaction mixture was poured into a saturated aqueous solution of NH$_4$Cl. The two layers were separated and the aqueous layer was extracted with Et$_2$O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (20% ethyl acetate-hexanes) yielded 12 mg (90%) of a yellowish liquid.

IR (NaCl): 2929, 1720, 1324, 1260, 1160 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.79 (d, $J$=8.2 Hz, 2H), 7.27 (d, $J$=8.2 Hz, 2H), 7.10-7.06 (m, 1H), 5.69 (d, $J$=10.1 Hz, 1H), 5.58 (dd, $J$=10.1, 1.6 Hz, 1H), 4.26-4.20 (m, 1H), 3.68 (s, 3H), 3.42 (dd, $J$=12.2, 9.0 Hz, 1H), 2.94 (dd, $J$=12.1, 5.2 Hz, 1H), 2.50-2.31 (m, 2H), 2.40 (s, 3H), 2.30-2.20 (m, 1H), 2.17-2.10 (m, 1H), 1.93-1.84 (m, 1H), 1.76-1.63 (m, 1H), 0.79 (s, 9H), -0.09 (s, 3H), -0.12 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 165.8, 143.3, 141.2, 137.7, 133.5, 132.5, 129.5, 129.4, 127.8, 77.2, 64.7, 60.2, 51.3, 47.8, 34.3, 25.7, 25.62, 25.63, 25.3, 21.4, 19.1, 18.0, -5.0, -5.1. LRMS (EI) m/z (relative intensity): 493 (M).
[3-(tert-Butyl-dimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-dien-7-yl]-methanol (3.13)

To a -78 °C solution of 90 mg (0.183 mmol) of 3-(tert-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-diene-7-carboxylic acid methyl ester 3.4 in 2.0 mL of CH₂Cl₂ was added 0.42 mL (0.420 mmol) of 1M solution of diisobutylaluminium hydride in toluene. The reaction mixture was warmed to rt and stirred for 1.5 h. The reaction mixture was poured into a aqueous 1N solution of HCl. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography on silica gel (30% ethyl acetate-hexanes) yielded 80 mg (93%) of a yellowish foaming solid.

IR (NaCl): 3522, 2952, 2929, 1324, 1255, 1160, 1093 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.81 (d, J=8.0 Hz, 2H), 7.28 (d, J=7.7 Hz, 2H), 6.09-6.01 (m, 1H), 5.60 (d, J=10.0 Hz, 1H), 5.47 (d, J=10.0, 1H), 4.19 (d, J=12.3, 1H), 4.11-3.97 (m, 2H), 3.36 (dd, J=13.1, 7.7 Hz, 1H), 2.77 (dd, J=11.9, 2.7 Hz, 1H), 2.38-2.29 (m, 1H), 2.38 (s, 3H), 2.24-1.91 (m, 3H), 1.83-1.56 (m, 2H), 1.21 (t, J=6.9, 1H), 0.75 (s, 9H), -0.13 (s, 3H), -0.14 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 143.8, 139.8, 137.1, 133.2, 129.8, 129.6, 127.9, 127.7, 65.1, 62.7, 62.0, 60.3, 47.8, 32.8, 25.6, 24.6, 21.4, 21.0, 19.7, 18.0, 14.1, -5.1, -5.2. LRMS (EI) m/z (relative intensity): 465 (M).

VI. References


Appendix A

Selected Spectra for Chapter One
1-Cyclohex-1-enylcyclopentanol (1.10)
Bicyclopentyliden-2-one (1.16)
1-Cyclohex-1-enylcyclohexene (1.17)
1-Cyclohex-1-enylcyclobutanol (1.19)
1-(1-Methoxycyclopentyl)cyclohexene (1.20)
Appendix B

Selected Spectra for Chapter Two
10-Hydroxy-6-(toluene-4-sulfonyl)-6-azaspiro[4.5]decan-1-one (2.4)

Racemic / chiral HPLC spectra

10% EtOH / Hexane
flow 1 mL / min.

<table>
<thead>
<tr>
<th>PK#</th>
<th>Retention Time (minutes)</th>
<th>Peak Area</th>
<th>Type</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
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<td>25.67</td>
<td>9235127</td>
<td>BB</td>
<td>49.90</td>
</tr>
<tr>
<td>2</td>
<td>84.36</td>
<td>9271578</td>
<td>BB</td>
<td>50.10</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>18506706</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10-Hydroxy-6-(toluene-4-sulfonyl)-6-azaspiro[4.5]decan-1-one (2.5)

Racemic / chiral HPLC spectra

10% EtOH / Hexane
flow 1 mL / min.

PK# | Retention Time (minutes) | Peak Area | Type | Area Percent
--- | ------------------------ | ---------- |----- | --------------
1   | 47.23                   | 9724503   | BB  | 41.62
2   | 49.05                   | 13642087  | BB  | 58.38

TOTAL 23366590
Trimethyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (2.6)
6-Hydroxyspiro[4.5]decan-1-one (2.7)

CDCl₃

CH₃OD
6-HydroxySpiro[5.5]Undecan-1-one (2.10)
(1-Cyclohex-1-enylocyclobutoxy)-trimethylsilane (2.12)
1-(7-oxa-bicyclo[4.1.0]hept-1-yl) (2.13)
6-Trimethylsilyloxyspiro[4.5]decan-1-one (2.14)
Triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (2.15)
1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclopentanol (2.17)
7-Trimethylsilyloxyspiro[5.5]undecan-1-one (2.19)
Triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclopentyloxy]silane (2.20)
6-Bromospiro[4.5]decan-1-one (2.25)
1-(Toluene-4-sulfonyl)-6-(1-triisopropylsilyloxy)cyclobutyl-1,2,3,4-tetrahydropyridine (2.31)
1-(Toluene-4-sulfonyl)-1-(1-triisopropylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (2.34)

CDCl$_3$

(CD$_3$)$_2$CO
3-Allyl-2-cyclobutylidene-1-(toluene-4-sulfonyl)-piperidine (2.41)
3-Allyl-2-cyclopentylidene-1-(toluene-4-sulfonyl)-piperidine (2.43)
10-Allyl-6-(toluene-4-sulfonyl)-11-oxa-6-aza-dispiro[3.0.5.1]undecane (2.44)
11-Allyl-7-(toluene-4-sulfonyl)-12-oxa-7-aza-dispiro[4.0.5.1]dodecane (2.45)
10-Allyl-6-(toluene-4-sulfonyl)-6-aza-spiro[4, 5]decane-1-one (2.46)
11-Allyl-6-(toluene-4-sulfonyl)-7-aza-spiro[5, 5]undecane-1-one (2.47)
Appendix C

Selected Spectra for Chapter Three
3-(tert-Butyl-dimethylsilyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-diene-7-carboxylic acid methyl ester (3.4)
[3-\textit{(tert-Butyl-dimethylsilanyloxy)-1-}(toluene-4-sulfonyl)-1-\textit{aza}\textit{spiro}[5.5]\textit{undeca-4,7-dien-7-yl]}-\textit{methanol (3.13)}