A NOVEL APPROACH TOWARD THE SYNTHESIS OF
SUBSTITUTED PIPERIDINES AND IMINOSUGARS

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ABSTRACT

Polyhydroxylated piperidines, also known as iminosugars, have received much attention in the past few decades as potential drug leads and the development of new methods for their synthesis is therefore of considerable interest. The most common drawback to current iminosugar syntheses is their reliance on carbohydrate chemistry which involves multiple protecting group manipulations that render these syntheses laborious and target specific. In this thesis, a new and concise synthetic process for the synthesis of iminosugars is described. This synthesis employs, as the key step, an intramolecular inverse electron demand Diels-Alder reaction between a hydroxymethyl oxazole and enolate joined through a silicon tether. Remarkably, the synthesis of iminosugars can now be accomplished in a two-pot reaction sequence that initiates with 4-hydroxymethyl oxazole and provides an unnatural analogue of a biologically active iminosugar in good overall yield.

Keywords: iminosugars; substituted piperidines; inverse electron demand Diels-Alder reaction

Subject Terms: iminosugars; inverse electron demand Diels-Alder reaction; silyl tethers.
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LIST OF ABBREVIATIONS

Ac – Acetyl
Bn – Benzyl
CDI – N,N’-carbonyl diimidazole
D-A – Diels-Alder
DIBAL – Diisobutylaluminium hydride
LiAlH₄ – Lithium aluminiumhydride
NaBH₄ – Sodium borohydride
Ph – phenyl
TBSCI – tert-butyldimethylsilyl chloride
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1: INTRODUCTION

1.1 Glycosidases

Carbohydrates are generally classified into monosaccharides and oligosaccharides. Monosaccharides are the simplest forms of carbohydrates that cannot be hydrolyzed into smaller sugars, while oligosaccharides are more complex forms of carbohydrates that can be hydrolyzed into smaller sugars. Carbohydrates are ubiquitous in nature and because of their vital role as energy reservoirs and as carriers of biological information they are essential building blocks for all living organisms\(^1\). For example, they play an important role in cell-cell interactions, in blood group determination, and in antigen/antibody recognition\(^1\). Carbohydrates are also key constituents of many important biological macromolecules such as glycoproteins (proteins attached to oligosaccharides), DNA, and RNA, and consequently have attracted attention as therapeutic agents. However, the stereochemical diversity of carbohydrates and their hydrophilic nature make them challenging targets for medicinal chemistry.

In the body, carbohydrates must be hydrolyzed to their component monosaccharides to be utilized in different biological courses, an event known as carbohydrate processing that can involve a wide range of enzymes. Amongst these, glycosidases (e.g. O-GlcNAcase and β-hexosaminidase), which catalyze the cleavage of the glycosidic linkage in oligosaccharides and glycoconjugates, are the most important and are involved in key biological events such as
intestinal digestion and post-translational processing of glycoproteins.\textsuperscript{1} For example, in some proteins, co-translational modification initiates with the attachment of oligosaccharides to the NH\textsubscript{2} group of an asparagine residue to produce a glycoprotein, then glucosidase I and II catalyze the cleavage of three glucose residues from this \textit{N}-linked oligosaccharide. Further modification of these immature glycoproteins by glycosidases and glycosyltransferases results in glycoconjugates that are vital for several biological processes such as immune response, protein folding, and intercellular recognition.\textsuperscript{1} It is not surprising then that inhibitors of these glycosidases can significantly alter the function or response of the cell and, consequently, represent potential leads for the treatment of many diseases such as cancer, tuberculosis, and lipid storage diseases (e.g. Tay-Sachs and Gaucher’s disease).\textsuperscript{2} One class of carbohydrate mimics, the iminosugars, possess potent glycosidase inhibitory activity and have found several therapeutic applications. For example, miglitol (1)(Glyset) and \textit{N}-butyl-1-deoxynojirimycin (2) (Zavesca) are used in the treatment of type II diabetes and Gaucher’s disease respectively (Figure 1).\textsuperscript{1} It has been demonstrated that iminosugars (e.g. 1 and 2) inhibit glycosidases by many different modes of action including alteration of the glycosylation or catabolism of glycoproteins, or by blocking the recognition of their natural substrates.\textsuperscript{3}
1.1.1 Glycosidases Inhibitors - Iminosugars

Iminosugars are alkaloids that mimick sugars in size and shape, and possess similar hydroxyl substitution patterns around the heterocyclic ring. The key difference between iminosugars and sugars is the replacement of the endocyclic oxygen atom with a nitrogen atom (Figure 2). This atom replacement confers many unique biological properties to iminosugars, rendering them desirable targets in the treatment of various carbohydrate mediated diseases such as diabetes, AIDS, and cancer.

A variety of iminosugars have been isolated as natural products from both plants and microorganisms (e.g. fungi and bacteria) and are generally classified into five structural groups: polyhydroxylated pyrrolidines, piperidines, indolizidines, pyrrolizidines and nortropanes, with polyhydroxylated piperidines comprising the main class of glycosidase inhibitors. The discovery of iminosugars dates back to 1966, when nojirimycin (4) was reported as an
antibiotic produced by *Streptomyces roseochromogens*.\(^1\) Nojirimycin (4) is the polyhydroxylated piperidine version of glucose in its pyranose configuration and has been found to be a potent and competitive inhibitor of both \(\alpha\)- and \(\beta\)-glucosidases. However, the instability of the hemiaminal function in nojirimycin has been reported to interfere with many biological assays.\(^3\) Polyhydroxylated piperidine analogues of mannose (e.g. mannonojirimycin 5)\(^5\) and galactose (e.g. \(\beta\)-galactostatin 6),\(^5\) have also been isolated as natural products and are known to inhibit \(\alpha\)-mannosidase and \(\beta\)-galactosidase, respectively. Both 5 and 6 were isolated from the fermentation broths of species of *Streptomyces*, however, due to the inherent instability of the hemiaminal function, these natural products are often converted to the more stable bisulfite adducts.\(^5\)

![Figure 3. Iminosugar analogues of pyranose sugars.](image)

Since the discovery of nojirimycin in 1966, additional iminosugars have been identified from Nature. For example, 1-deoxynojirimycin (7), first obtained by chemical reduction of nojirimycin,\(^1\) was isolated from the roots of mulberry trees, 1,2-dideoxynojirimycin, also known as fagomine (8), was isolated from the seeds of Japanese Buckwheat (*Fagopyrum esculentum*), and 1-deoxy-mannojirimycin (9) has been reported from the seeds of the legume *Lonchocarpus sericeus*.\(^1\)
Following the isolation of 1-deoxynojirimycin, it was found that the absence of the C1-hydroxyl group or hemiaminal function in this molecule does not detract from its glycosidase inhibitory activity, and instead confers an enhanced stability. This finding triggered a considerable amount of interest in iminosugars as potential therapeutic agents and rendered 1-deoxynojirimycin as the model compound in this area of research. The interest in iminosugars stems from the fact that both conformationally and electrostatically they resemble the proposed transition structure present during the enzyme-catalyzed hydrolysis of glycoconjugates. Thus, during glycoside hydrolysis, protonation of the anomeric ether linkage is followed by formation of an oxocarbenium ion intermediate that adopts a half-chair conformation and possesses a positively charged endocyclic oxygen atom. Thus, iminosugars bear a structural resemblance to the enzyme’s natural substrate and mimic the oxocarbenium ion transition structure (Figure 5), as the amino group is protonated under physiological conditions. As a result, iminosugars are referred to as transition state mimics, and are often capable of binding more tightly in the enzyme active site than the natural substrate. For example, 1-deoxynojirimycin (7) has a binding affinity to α-glucosidase 5-fold greater than the natural substrate glucose.
Importantly, the replacement of the endocyclic oxygen atom in normal sugars with a nitrogen atom in iminosugars also renders the latter compounds metabolically inert, yet does not affect their recognition by glycosidases. Not surprisingly then, there is considerable interest in screening iminosugars as drug leads. However, while approximately 25 iminosugar glycosidase inhibitors have been isolated from natural sources, their costly and time-consuming extraction and purification and/or scarcity from the natural source has thus far limited their utility.

1.1.1.1 Previous Iminosugar Syntheses

As a result of their important biological activities and the lack of material available from natural sources, the synthetic organic chemistry community has focused much effort on pioneering synthetic routes to iminosugars, and the chemical literature is rich with publications describing their syntheses. Generally, the syntheses of these substances initiate with the protection of the alcohol functions of a commercially available sugar, as depicted in Scheme 2 and the requisite endocyclic amine is later introduced through reductive amination of an aldehyde or hemiacetal. Illustrated below is a typical retrosynthetic analysis of iminosugars from commercially available carbohydrates (Scheme 1).
Scheme 1. A general retrosynthesis of iminosugars from commercially available carbohydrates.

While a number of synthetic routes to iminosugars have been published, a common drawback to these efforts is the reliance on natural sugars as synthetic precursors, which often steers the focus of the synthesis towards the preparation of a single target iminosugar. As depicted in Scheme 2, typical synthetic approaches to these substrates are linear in nature, which often results in an overall low yielding synthetic process. For example, a typical carbohydrate-based synthesis of 1-deoxynojirimycin (7) initiates with the iodo-protected glucopyranoside 18 (Scheme 2) which is available from glucose in two steps. The iodo-glucopyranoside 18 is then subjected to acetolysis followed by reaction with azidotrimethylsilane and tin (IV) chloride and subsequent base promoted elimination of hydrogen iodide to give the alkene 20. The alkene 20 is then converted to the epoxide 22, which is opened in the presence of camphorsulfonic acid and methanol to afford the ketal 23. Subsequent removal of acetate protecting groups and catalytic hydrogenation yields 1-deoxynojirimycin (7) in nine steps and 4.4% overall yield.
Scheme 2. A typical iminosugar synthesis from glucose.

Following the discovery that 1-deoxynojirimycin (7) is a potent glucosidase inhibitor and has a decreased selectivity toward α- and β- glycosidases, efforts were devoted to the synthesis of derivatives bearing lipophilic substituents at C1 (Scheme 3). An example of an efficient synthesis of C1-substituted deoxynojirimycin analogues is summarized in Scheme 3. In this work, the amino group was introduced by reaction with benzylamine, followed by treatment of the resulting hemiaminal with allylmagnesium bromide (d.r. = 18:1). Subsequent oxidation and reductive amination (d.r. = 9:1) afforded the 2-alkyl substituted nojirimycin analogue 26 in 36% overall yield over six steps.10

Scheme 3. Synthesis of C1-substituted deoxynojirimycin derivative.

While undoubtedly the most common method to access iminosugars, there are several drawbacks to chemical syntheses that initiate with carbohydrates. The foremost of these is the requirement for protecting group and functional
group manipulations, which often adds to the overall length and complexity of the synthesis. In addition, a reliance on naturally occurring sugars limits the diversity of structures accessible; an obvious concern when probing the relationship between structure and biological activity of the iminosugar is of interest. To avoid this reliance on naturally occurring sugars as building blocks, a number of syntheses that utilize non-carbohydrate starting materials have been reported. For example, it was demonstrated that deoxynojirimycin can be prepared from the tetrahydropyridine \(29,8\) which comes from hydroxydihydropyridone \(28\) through acetoxylation of the \(\alpha\)-carbon with \(\text{Pb(OAc)}_4\) followed by acetate hydrolysis and reduction of the ketone function. The hydroxydihydropyridone \(28\) was in turn synthesized in an asymmetric fashion from pyridine \(27\) in three steps using acylpyridinium salt chemistry.\(^{11}\) It has also been shown\(^8\) that the cycloaddition of nitrile oxides with furans provides isoxazolines (e.g. \(32\)) in 75% yield, which are versatile intermediates for iminosugar synthesis (e.g. deoxynojirimycin (7)). Thus, dihydroxylation of the cycloaddition product \(32\) afforded a diol, which, following subsequent protecting group manipulations and separation of enantiomers, was subjected to catalytic hydrogenation followed by deprotection to afford (+) deoxynojirimycin (7) in six steps and 15% overall yield from furan and 2-nitroethanal diethyl acetal.\(^{12}\) More recently, Pandey has reported the synthesis of isofagomines (e.g. \(37\)) through a photoinduced electron transfer cyclization strategy of \(35\) from \(\text{D-(-)-tartaric acid.}^{13}\) Isofagomines are a different variation of carbohydrate mimics called 1-\(N\)-iminosugars, in which the anomeric carbon is replaced by a nitrogen atom, and the ring oxygen is replaced
by a methylene group. The methodology reported by Pandey involves the multistep conversion of tartaric acid to the α-trimethylsilylmethylamine 35, which undergoes cyclization upon irradiation to afford the piperidine 36. Hydroboration followed by deprotection of 36 yields isofagomine 37 in 9 steps and 5.5% overall yield from tartaric acid.

**Scheme 4.** Various synthetic approaches to iminosugars from non-carbohydrate precursors.

Other reported non-carbohydrate based syntheses of iminosugars employ the chemo- and stereoselective palladium-catalyzed amination of silylated butanediol dicarbonates (e.g. 38, Scheme 5) which, following epoxidation and intramolecular aldolization afford the piperidine core. Regioselective epoxide ring opening and Tamao-Flemming oxidation of the C-Si bond, followed by deprotection led to deoxymannojirimycin (9).14
Scheme 5. Palladium-catalyzed amination of silylated butanediols in the synthesis of iminosugars.

Other chiral synthons have proven to be useful tools in the total synthesis of iminosugars. For example, optically pure 2-(1’-amino-2’-hydroxyalkyl)furans obtained from L- or D-serine were used as the starting material for the synthesis of a variety of piperidine derivatives as shown in Scheme 6. Oxidation of furan 43 followed by protection of the hemiaminal function afforded enone 45 that underwent a stereoselective reduction under Luche reduction conditions to give compound 46. The ethoxy group was then removed to provide an allylic alcohol 47. Dihydroxylation followed by deprotection gave the unnatural iminosugar 48.
1.2 Research Goals

In light of the real and significant therapeutic potential of iminosugars, devising a general method for their synthesis as well as the synthesis of unnatural congeners that does not rely on natural sugars as synthetic precursors is an important pursuit. In general, the syntheses of these scaffolds involve numerous synthetic transformations that require multiple protecting group manipulations, lack convergence, and consequently limit efforts in diversity-oriented synthesis and/or render structure-activity relationship (SAR) studies a difficult task. In order to address the shortfalls associated with iminosugar synthesis, we set out to investigate a new approach to substituted piperidines that will allow the rapid synthesis of a library of iminosugars via a common synthetic pathway and be applicable to the synthesis of biologically active iminosugars. Thus, the primary goal of this project was to develop a novel, general, and concise synthetic route to iminosugars that is not reliant on carbohydrate-based starting materials.

Scheme 6. Chiral furans derived from serine in synthesis of iminosugars.
2: PROPOSED IMINOSUGAR SYNTHESIS

2.1 Retrosynthetic Analysis

In pursuit of our research goals to access iminosugars from non-carbohydrate precursors we envisioned that substituted piperidine structures could be derived from a Diels-Alder reaction between a heterodiene (e.g. 51 or 53) and dienophile as depicted in the retrosynthetic analysis in Scheme 7.

\[
\begin{align*}
49 & \rightarrow R_1 R_2 \quad + \quad R_3 \\
12 & \rightarrow \\
50 & \rightarrow R_5 R_6 \quad + \quad R_7 R_8
\end{align*}
\]

Scheme 7. Retrosynthetic analysis of iminosugars.

To control both the regio- and diastereoselectivity of the key Diels-Alder reaction, it was envisaged that the union of the two moieties (azadiene and dienophile) would be facilitated by a silicon tether. The choice of silicon as the tether for this process stems from their purported chromatographic stability and high yielding preparation (see section 2.1.2).\textsuperscript{16}
2.1.1 Diels-Alder Reactions of Heterodienes

One method for the synthesis of six-membered nitrogen containing heterocycles is a [4+2] cycloaddition.\textsuperscript{17} As depicted in Scheme 8, the intramolecular Diels-Alder reaction of a 2-cyano 1-azadiene \textbf{55} affords the cyanoenamine \textbf{56}.\textsuperscript{18}

![Scheme 8. Heterodienes in Diels-Alder reaction.](image)

Oxazoles have also found use as heterodienes in Diels-Alder reactions and afford 7-oxa-2-azabicyclo[2.2.1]hept-2-ene intermediates that when subjected to either basic or acidic conditions, to promote dehydration, afford substituted pyridines. Oftentimes, due to the instability of the 7-oxa-2-azabicyclo[2.2.1]hept-2-ene intermediates, these substances also undergo spontaneous dehydration to afford pyridines directly.\textsuperscript{19} An example illustrating the use of oxazoles as heterodienes in Diels-Alder reaction is shown in Scheme 9,\textsuperscript{20} where the urea-functionalized oxazole \textbf{57} was reacted with acrylonitrile to provide the pyridopyrimidine \textbf{60}, an analogue of the biologically active pteridines.\textsuperscript{20}
2.1.2 Silicon Tethers in Intramolecular Diels-Alder Reaction

In tethering two substrates together, an intermolecular reaction is transformed into an intramolecular one, conferring several advantages to the process that include: 1) decreased entropy of subsequent reaction, which leads to faster reactions and consequently the requirement for milder conditions than those typically required for the corresponding intermolecular reaction; and 2) lower degrees of freedom in the transition state, which often improves both the regio- and stereoselectivity of a reaction. Bearing this in mind, intramolecular Diels-Alder reactions often proceed at or below room temperature with a high degree of regio- and stereochemical control.\textsuperscript{16a} A key aspect of the intramolecular Diels-Alder reaction is the choice of tethering group, which should: 1) be readily accessible or commercially available; 2) be introduced into the synthesis by a robust procedure; 3) be selectively removed after cycloaddition under mild conditions; and 4) not interfere with or hinder the cycloaddition.\textsuperscript{16b}

While many different tethers have been employed in Diels-Alder cycloaddition reactions (e.g. esters, ethers, amides, ureas, carbamates) and shown to have variable effects on the regio- and stereochemical outcome of these processes,\textsuperscript{16a} silaketal tethers have many favourable characteristics that include their lack of
reactivity with Lewis acids and other reagents that are often used to promote the cycloaddition reactions. As a result, silaketals are often the tether of choice for these reactions.\textsuperscript{16a} An example illustrating the regiochemical control imparted by a silaketal tether is highlighted in Scheme 10, where the only products derived from the intermolecular Diels-Alder reaction between the activated diene 61 and dienophile 62 are the expected \textit{endo} and \textit{exo} regioisomers 63. In contrast, in the intramolecular Diels-Alder reaction of 65, the regioselectivity is controlled by the topological constraints imposed by the silicon tether, leading to a reversal in regioselectivity and preferred formation of the single \textit{endo} adduct 66.\textsuperscript{16a}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme10}
\end{center}
\end{scheme}

\textbf{Scheme 10.} An example of intermolecular and Intramolecular Diels-Alder reaction.
2.2 Iminosugars From β-aminoacrolein

In line with the proposed retrosynthetic analysis outlined previously in Section 2.1, the search for a heterodiene was paramount in achieving our stated goals. The main tenet of our proposed synthetic methodology, *to rapidly produce iminosugars via an intramolecular Diels-Alder reaction* also requires the judicious selection of a temporary silicon tether to achieve both regio- and stereochemical control. We initially anticipated that the sequential coupling of malonaldehyde derived imines (e.g. 69, Scheme 11) and acrylic acids (e.g. 70) or allyl alcohols with silicon tetrachloride would provide an appropriate substrate (e.g. 71) for a subsequent intramolecular 1-azadiene Diels-alder reaction. Notably, the product of this process 72 would be suitably functionalized for further modification through oxidation or reduction, affording rapid access to diverse families of natural and unnatural iminosugars.
Scheme 11. Initial efforts toward iminosugar synthesis.

In line with this proposed synthetic strategy, our synthesis of iminosugars started with the preparation of β-aminoacrolein (76) from commercially available 1,1,3,3-tetramethoxypropane (74), methods of preparation for (76) and results are summarized in Table 1.
Table 1. Results of $\beta$-aminoacrolein (76) synthesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Step 1</th>
<th>Purification 1</th>
<th>Step 2</th>
<th>Purification 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH$_4$Cl</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>decomposition$^c$</td>
</tr>
<tr>
<td>2</td>
<td>Dowex H$^+$</td>
<td>-$^a$</td>
<td>NH$_3$(g)</td>
<td>-</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>2M HCl</td>
<td>-</td>
<td>NH$_3$(g)</td>
<td>-</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>2M HCl</td>
<td>-</td>
<td>NH$_4$OH</td>
<td>column chromatography$^d$</td>
<td>10% conversion,$^e$ decomposition on column</td>
</tr>
<tr>
<td>5</td>
<td>2M HCl</td>
<td>-</td>
<td>NH$_4$OH/</td>
<td>-</td>
<td>20% conversion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflux</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2M HCl</td>
<td>extraction with chloroform$^b$</td>
<td>NH$_4$OH + MeOH</td>
<td>recrystallization$^f$</td>
<td>60% conversion, did not recrystallize</td>
</tr>
<tr>
<td>7</td>
<td>2M HCl</td>
<td>extraction with chloroform</td>
<td>NH$_3$ in MeOH</td>
<td>recrystallization</td>
<td>100% conversion, 12% yield$^d$</td>
</tr>
<tr>
<td>8</td>
<td>2M HCl</td>
<td>extraction with chloroform</td>
<td>7N NH$_3$ in MeOH</td>
<td>dissolve in MeOH/ wash with hexanes</td>
<td>100% conversion, 58% yield</td>
</tr>
</tbody>
</table>

$^a$ Formation of intermediate 75 was followed by $^1$H NMR spectroscopy, when all the starting material had been consumed an ammonia source was added to the reaction mixture until the pH reached 12; $^b$ chloroform was removed in vacuo and crude product was used in step 2; $^c$ as determined by $^1$H NMR spectroscopic analysis of crude reaction mixture; $^d$ eluent 15% MeOH:CH$_2$Cl$_2$; $^e$ conversion to 76 as determined by $^1$H NMR spectroscopic analysis of crude reaction mixture; $^f$ recrystallization solvent: 1:1 hexane-chloroform; $^g$ yield calculated from 74.
As indicated in Table 1 (entry 8), the optimal conditions for producing the β-
aminoacrolein involved the isolation of malonaldehyde (75) by extraction with
chloroform followed by imine/enamine formation, carried out in MeOH containing
ammonia. The product from this sequence of reactions was dissolved in MeOH
and the impurities were extracted with hexanes. It is notable that when the
amination step was carried out in aqueous medium (entries 1-5), very little
product was formed. This result was attributed to the decomposition of the
unstable malonadehyde (75) over time in water. The trans configuration of the β-
aminoacrolein 76 was confirmed by 1H NMR spectroscopic analysis in DMSO-d₆,
where the coupling constant between H2 and H3 (J = 12.7 Hz) was indicative of
a trans alkene. As we were cognizant of the potential problems associated with
the subsequent step in the proposed synthesis (i.e. the formation of the
aminoacrolein-silicon tether) we chose to first explore the reaction of
dichlorodimethylsilane with the β-aminoacrolein 76. As a result of its decreased
reactivity relative to SiCl₄ it was anticipated that reactions of 76 with
dichlorodimethylsilane would allow us to gauge the reactivity of 76 and,
consequently, assess the feasibility of this approach. The results of these efforts
are summarized in Table 2.
Table 2. Results of coupling of β-aminoacrolein (76) with dichlorodimethylsilane.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N</td>
<td>rt</td>
<td>CH₂Cl₂</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>-78</td>
<td>THF</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>NaH</td>
<td>rt</td>
<td>THF</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>NaHCO₃</td>
<td>0</td>
<td>THF</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>NaHCO₃</td>
<td>0</td>
<td>CH₂Cl₂</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

As outlined in Table 2, the coupling reaction between the aminoacrolein 76 and dichlorodimethylsilane was unsuccessful under a variety of conditions, an indication of the instability of β-aminoacrolein (76) or the expected product 78 under these reaction conditions. Before abandoning this route, however, we chose to further assess the reactivity of the nitrogen and the oxygen atoms in 76, through the reaction of β-aminoacrolein with the much less reactive TBSCl silylating agent. To the best of our knowledge, literature precedent for the bis-silylation of β-aminoacrolein does not exist and, unfortunately, after considerable effort (e.g. NaH / -78 °C, Et₃N / -78 °C, NaHCO₃ / 0 °C) we were unable to promote silylation of both the nitrogen and the oxygen atoms in 76. While the product of this process proved difficult to isolate and decomposed on silica gel, the observation of a resonance attributed to an aldehyde proton (δ 9.0 ppm) in
the crude $^1$H NMR spectrum, as well as, the presence of one NH resonance ($\delta$ 7.5 ppm) as opposed to two NH resonances observed in the $^1$H NMR spectrum of the starting material indicated that the all of the starting material had been converted to a product in which only the nitrogen atom was silylated.

\[
\begin{align*}
\text{H} & \text{O} \\
\text{NH} & \text{Cl} \\
\end{align*}
\]

\[
\text{H} \quad \text{76} \quad + \quad \text{Si} \\
\text{Cl} \quad \text{1. LiHMDS} \\
\text{H} \quad \text{79} \quad \text{2. TBSCI}
\]

**Scheme 12.** Mono-silylation of the nitrogen in $\beta$-aminoacrolein (76) with TBSCI.

Bearing these preliminary results in mind, at this point the original strategy of employing a 1-azadiene derived from $\beta$-aminoacrolein (76) in a hetero Diels Alder reaction was re-evaluated. As a result, a number of variations on this proposed theme (silicon tethered hetero Diels-Alder reaction) were considered and our efforts shifted to investigations involving different heterodiene starting materials.
3: IMINOSUGARS FROM OXAZOLES

3.1 Inverse Electron Demand Diels-Alder Reaction of Oxazolium Salts

Given the setbacks encountered during the synthesis of our targeted aminoacrolein-derived heterodienes, considerable effort was devoted to the identification of a more suitable substrate for this process. As highlighted in Section 2.1.1, oxazoles have demonstrated utility as heterodienes (2-azadienes) in the synthesis of various substituted pyridines. Although the use of oxazoles as a precursor to piperidines has received little attention,\textsuperscript{20} recently, an inverse electron demand Diels-Alder reaction of an oxazolium salt has been reported,\textsuperscript{21} which constitutes the first example of a Diels-Alder reaction of an oxazolium salt.\textsuperscript{20} In this process it was found that methylation of 5-substituted oxazoles containing a pendent olefin (e.g. \textbf{80}, Scheme 13) led to an inverse electron demand intramolecular Diels-Alder reaction that afforded an iminium salt (e.g. \textbf{82}), which was further reduced \textit{in situ} to provide the \textit{trans}-fused decahydroisoquinoline \textbf{83}. It is noteworthy that the bridged cycloadduct \textbf{82} resulting from the initial cycloaddition reaction does not undergo dehydration to form a pyridine ring. Based on the apparent stability of the 7-oxa-2-azoniabicyclo[2.2.1]hept-2-ene moiety and the fact that, to the best of our knowledge, this single report represents the extent of the literature relating to inverse electron demand intramolecular Diels-Alder reactions involving oxazolium
intermediates, we set out to explore this reaction as a potential means to rapidly access hydroxylated piperidine scaffolds.

Scheme 13. Inverse electron demand Diels-Alder reaction of oxazolium salt.

3.1.1 Oxazoles as Building Blocks

The class of heterocycles known as oxazoles represent excellent building blocks for synthesis, as there is an abundance of literature describing their preparation and the reactivity and functionalization of oxazoles at each ring atom other than oxygen is well documented. For example, 2,4-disubstituted oxazoles are readily prepared from the cyclization of commercially available α-haloketones with amides, or from the rearrangement of N-acylaziridines, as shown in Scheme 14.
Scheme 14. Examples of 2,4-disubstituted oxazoles syntheses.

In addition, 2,5-disubstituted oxazoles can be prepared from the reaction of nitriles with methyl ketones. For example, 2-alkyl-5-aryloxazoles can be obtained from the cyclization of aromatic α-methyl ketones (e.g. 92) and nitriles in the presence of thallium triflate generated in situ from thallium acetate and triflic acid (Scheme 15).

Scheme 15. Example of 2,5-disubstituted oxazole synthesis.

Numerous syntheses of 2,4,5-trisubstituted oxazoles have also been reported. For example, propargyl amides (e.g. 95) can be cyclised to trisubstituted oxazoles (e.g. 96) as shown in Scheme 16.

Scheme 16. Example of 2,4,5-trisubstituted oxazole synthesis.

Due to the presence of an aza-diene functionality and little resonance stabilization in oxazoles (as compared to other aromatic heterocycles), oxazoles readily participate in Diels-Alder reactions as either dienophiles or as dienes. As a result, the Diels-Alder reaction of oxazoles has been widely explored and this process has been used for the synthesis of a number of heterocyclic ring systems. For example, pyridines, isoindoles, oxazolines, pyridazines, and thiazolines are just a handful of the heterocyclic ring systems easily accessible from oxazoles. The first Diels-Alder reaction of an oxazole, in which it served as an azadiene, was reported by Kondrat’eva in 1957 (Scheme 17). In this study a variety of substituted oxazoles (e.g. compound 97) underwent cycloaddition reactions with maleic anhydride (98) to provide the cinchomeronic anhydrides 99, instead of the expected bridged furan Diels-Alder adduct.

**Scheme 17.** The first reported Diels-Alder reaction of an oxazole.

While the literature is rich with syntheses describing the cycloaddition chemistry of oxazoles, the vast majority of these examples demonstrate the benefit of oxazoles in the synthesis of highly substituted pyridines and furans, not their utility in the synthesis of substituted piperidines. While these reactions have been extensively reviewed, debate continues as to whether the
cycloaddition reactions of oxazoles proceed via a concerted mechanism\textsuperscript{20} and very few studies have reported the intermediacy of a Diels-Alder adduct in these reactions.\textsuperscript{20} For example, Ishikawa isolated the \textit{endo} (compound \textbf{103}) and \textit{exo} (compound \textbf{104}) adducts in a 2:1 ratio, from the Diels-Alder reaction of 5-ethoxy-4-methyloxazole \textbf{100} with \textit{cis}-2,5-dimethoxy-2,5-dihydrofuran \textbf{101} (Scheme 18).\textsuperscript{23} These two adducts were subjected to methanolic potassium hydroxide solution for several hours to effect the cleavage of oxygen bridge in both adducts to provide dimethoxypyridinol.

![Scheme 18. Isolated \textit{endo} and \textit{exo} adducts of a Diels-Alder reaction.](image)

Despite this and other examples that confirm the intermediacy of a 7-oxa-2-azabicyclo[2.2.1]hept-2-ene Diels-Alder adduct in these reactions, which could be utilized to access substituted piperidines, the application of a Diels-Alder reaction of oxazoles as a piperidine precursor has not been investigated. Instead, the general outcome of these reactions may be summarized as follows: 1) following the formation of the Diels-Alder adduct(s), an elimination reaction that effectively cleaves the ether bridge takes place to provide azadiene intermediate; and 2) these intermediates in turn undergo dehydration or dehydrogenative oxidation to afford more stable pyridine or hydroxypyridine products, depending on the substituents around the six-membered azadiene ring.\textsuperscript{20} For example, upon
formation, the cycloadduct 105 derived from the reaction of 104 and a dienophile undergoes deprotonation and concomitant cleavage of the ether bridge to give the cyclic azadiene intermediate 106. In general, intermediates such as 106 are then involved in one of four possible reaction pathways. The major reaction pathway when neither R³ nor R⁴ is an electron-withdrawing group involves the elimination of water to provide a stable pyridine product. Alternatively, when R³ is an alkoxy, carbonate, cyano, or any other suitable leaving group, elimination of R³H to give the 3-hydroxypyridine 109 is the predominant pathway or where R⁴ is a good leaving group and R³ is H, elimination of R⁴H predominates. As a competing pathway when R³ is H, oxidative loss of H₂ occurs, however, this reaction is rarely seen unless a hydride acceptor (e.g. nitrobenzene, hydrogen peroxide) is present.
Scheme 19. Example of Diels-Alder reactions of oxazoles to make substituted pyridines or hydroxypyridines.

In the case of Diels-Alder reaction of oxazoles with alkynes as dienophiles, the Diels-Alder adduct(s) undergoes a retro-Diels-Alder reaction to provide furans, as illustrated in Scheme 20.

Scheme 20. An example of oxazole-alkyne cycloaddition to make furans.
3.1.3 Proposed General Synthesis of Iminosugars From Oxazoles

The inspiration for our revised strategy to access iminosugars originated from the reaction depicted in Scheme 13, however, the requisite hydroxylation pattern in iminosugars necessitated a more versatile scaffold amenable to oxygen substitution on both the olefin and the oxazole. With this in mind, it was anticipated that an intramolecular Diels-Alder reaction between a suitably functionalized oxazole and a substituted enol ether would deliver the backbone of an iminosugar. We envisaged the union of these two moieties to be facilitated via a silicon tether that would provide the necessary diastereocntrol (vide supra).

To test this hypothesis our initial efforts focused on the synthesis of a silicon tether (115, Figure 6) derived from union of acetaldehyde enolate and 4-hydroxymethyl oxazole.

![Proposed Diels-Alder precursor.](image)

**Figure 6.** Proposed Diels-Alder precursor.

Following the synthesis of the silicon tether depicted in Figure 6, our efforts would focus on activation of the oxazole by N-alkylation to set the stage for an inverse electron demand Diels-Alder reaction (Scheme 21). It was anticipated that the resulting oxazolium salt 116 would undergo the desired intramolecular Diels-Alder reaction to provide the 7-oxa-2-azoniabicyclo[2.2.1]hept-2-ene adduct. Notably, in line with the behaviour of the related bicyclic intermediate in
the example presented earlier (Scheme 13), it was expected that dehydration and formation of pyridines would be avoided in this process. Following the successful formation of the 7-oxa-2-azoniabicyclo[2.2.1]hept-2-ene, *in situ* reduction of this substance followed by treatment with mild acid should then afford the (+/-) iminosugar analogue 120 (Scheme 21).

![Chemical structure](image)

**Scheme 21.** Proposed synthesis of iminosugars.

This remarkable one-pot procedure would provide direct access to unprotected iminosugar scaffolds from readily available starting materials. It is worth mentioning that the key Diels-Alder reaction should proceed with complete diastereoselective control, as the strain in the transition structure that would lead to the diastereomeric Diels-Alder adduct 121 (Figure 7) should prevent the formation of this intermediate, thus ensuring an *anti*-relationship between the C4/C5 stereocenters in 120. The relative stereochemistry at C6 should also be
controlled through a diastereoselective reduction of the intermediate iminium ion 117 from the more accessible $\beta$-face.

![Figure 7](image)

**Figure 7.** The diastereomeric adduct resulting from strained transition state in the Diels-Alder reaction.

It is notable that, if successful, this methodology would pave the path for a more general and succinct synthetic route to substituted piperidines. For example, (+/-)-$N$-methyl deoxynojirimycin 122 may be derived from the Diels-Alder reaction between ($E$)-ethene-1,2-diol (derived from the enolate of 2-hydroxyacetaldehyde) and 4-hydroxymethyl oxazole. Likewise, the (+/-)-1-deoxymannonojiromycin analogue 124 may be accessed from the reaction between a protected ($Z$)-ethene-1,2-diol (from enolate of 2-hydroxyacetaldehyde) and 4-hydroxymethyl oxazole (Scheme 22).
**Scheme 22.** Proposed synthesis of iminosugars from 4-hydroxymethyl oxazol e.

### 3.1.4 Synthesis of 4-Hydroxymethyl Oxazole

Our efforts toward the synthesis of the silicon tether 115 (*vide supra*) began with the synthesis of one of its components, 4-hydroxymethyl oxazole (125) (Figure 8) which would require the introduction of a hydroxymethyl group onto an oxazole scaffold.

**Figure 8.** 4-hydroxymethyl oxazole.

The introduction of functional groups at C2, C4, or C5 is a process that is often carried out through deprotonation of oxazole and subsequent treatment of the oxazole anion with an electrophile. Consequently, the success of these processes depends on discriminating between the oxazole protons based on
their unique acidities, which have been determined theoretically and experimentally. These studies found that the acidity of these protons decreases in the order C2>C5>C4. While this trend in acidity is valid for most substituted oxazoles, exceptions are well documented. Thus metalation reactions of oxazoles have been used to functionalize each position of the heterocyclic ring with lithiation being the most reliable process. Although a number of literature reports describe 2-lithiation of 4-substituted and 4,5-disubstituted oxazoles, reports on lithiation of unsubstituted oxazoles are surprisingly sparse, indicating that substituted oxazoles carrying a hydrogen on C2 are not easily accessible by the usual synthetic methods. Hodges et al. reported that aldehydes are unique in their reaction with unsubstituted lithiooxazole salt in that they afford nearly exclusively 4-substitution products at low temperature. However, their work did not report the preparation of 4-hydroxymethyl oxazole from the reaction of lithiooxazole salt and paraformaldehyde directly so we decided to explore this method as shown in Scheme 23. Unfortunately, after considerable efforts to effect this transformation, the isolated yields of 4-hydroxymethyl oxazole (125) were very low (<10%).

\[
\begin{align*}
\text{1. n-BuLi, } -78 \degree C \\
\text{2. Paraformaldehyde}
\end{align*}
\]

Scheme 23. Synthesis of 4-hydroxymethyl oxazole.
Lithiation of oxazoles is accomplished by their treatment with \( n \)-BuLi in THF/hexanes at -78 °C. According to Hodges\(^\text{24}\), once the 2-lithiooxazole is formed at low temperatures, it undergoes a ring cleavage reaction as shown in Scheme 24.

![Scheme 24. Lithiooxazole ring opening mechanism.](image)

This ring cleavage was shown to result in \( O \)-substituted side products which could explain why the yield of the reaction with paraformaldehyde (Scheme 23) was very low. In a separate account, it was shown that the outcome of reactions between metalated oxazole and electrophiles is highly dependent on the nature of the electrophile\(^\text{25}\), and given the polymeric nature of paraformaldehyde this electrophile was clearly not compatible with the anion 127. As a consequence, an alternative route was used to prepare 4-hydroxymethyl oxazole starting from ethyl isocyanoacetate as shown in Scheme 25.

![Scheme 25. 4-hydroxymethyl oxazole synthesis from ethyl isocyanoacetate.](image)
The coupling of ethyl isocyanoacetate with formic acid in the presence of base and coupling reagent CDI afforded ethyl oxazole 4-carboxylate 133 in 93% yield. Subsequent reduction of the ester functionality was carried out with several reducing agents. Initially, the reducing conditions (NaBH₄, 9:1 THF-H₂O) utilized by Shioiri et al.²⁶ were employed (Scheme 26). However, it was found that reduction under these conditions required prolonged periods of time (> 2 days) without complete consumption of the starting material. Furthermore, after work-up, 4-hydroxymethyl oxazole was found to partition between the aqueous and the organic layer which resulted in very low yields < 10%. We then resorted to using a stronger reducing agent (LiAlH₄) to convert the ester functionality to the corresponding alcohol as shown in Scheme 27.

![Scheme 26. Reduction of 4-hydroxymethyl oxazole with NaBH₄.](image)

![Scheme 27. Reduction of 4-hydroxymethyl oxazole with LiAlH₄.](image)

However, the yield for hydroxymethyl oxazole using LiAlH₄ was also low (< 10%) is likely as a consequence of over reduction and opening of the oxazole ring, as ¹H NMR spectroscopic analysis of the crude product indicated a number
of compounds had been formed. Alternatively, since aqueous work-up was required to release the product from the aluminum complex, this may also have led to loss of some product in the aqueous layer. To avoid the side reactions (i.e. over reduction and oxazole opening) caused by LiAlH₄, a single hydride donor would likely prove to be a more effective reducing agent and DIBAL was chosen for this purpose. Initially, reactions with DIBAL were carried out in THF at four different temperatures (-78 °C, 0 °C, rt, 40 °C) as shown in Scheme 28. To minimize loss of the product during aqueous work-up, alternative conditions (sodium sulfate dodecahydrate/ MeOH) were used to quench the reactions. As indicated, at each temperature, the reaction failed to reach completion and isolated yields were relatively low (< 20 %). Adding more equivalents of DIBAL and/or extending reaction times (> 24 hours), in an attempt to convert the remaining starting material to product, resulted in decomposition. It was then found that the reduction of esters in coordinating solvents such as THF traditionally requires longer reaction times and more forcing conditions.²⁷ As a result, CH₂Cl₂ was employed as the solvent in which to carry out this reaction and sodium fluoride was used as a de-complexing agent, this reaction afforded 4-hydroxymethyl oxazole in 55% yield as shown in Scheme 29.

![Scheme 28. Reduction of 4-hydroxymethyl oxazole with DIBAL.](image-url)
Scheme 29. Reduction of 4-hydroxymethyl oxazole with DIBAL in CH$_2$Cl$_2$.

3.1.5 Synthesis of the Silane Tether

Despite the well known silicon-based tethering chemistry, general procedures for making unsymmetrical silaketals, especially those containing an ether and an enol ether linkage, are not well established. In addition, the synthesis of unsymmetrical silaketals is complicated by the formation of the undesired symmetrical silaketals. However, we envisioned that the desired silicon tether would be accessible from dichlorodialkylsilanes via first formation of the chloroalkoxydialkylsilane followed by addition of the enolate anion or vice versa as shown in Scheme 30.

Scheme 30. Envisioned sequences to make the silane tether.
Benzyl alcohol was used as a model substrate in place of 4-hydroxymethyl oxazole to find ideal conditions to make the silicon tether. Our initial efforts began with the formation of $\text{139}$ followed by addition of an aldehyde and base to effect enolsilyl ether formation. These reactions were carried out stepwise in the same reaction vessel and the results of this study are summarized in Table 3. Unfortunately, when triethylamine was used as the base for both steps, the major products observed from these reactions were those derived from aldol condensation as determined by $^1\text{H}$ NMR spectroscopic analyses of aliquots taken from the reaction mixtures. As a consequence, it was realized that purification of the intermediate silyl chloride $\text{139}$ would most likely be required to ensure the success of this approach. In addition, conditions for the optimal formation of $\text{139}$ that minimize the production of symmetrical dimmers were also sought.
Table 3. Results of aldehyde addition to dichlorodimethylsilane.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Reagent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N</td>
<td>-15</td>
<td>CH$_2$Cl$_2$</td>
<td>[structure]</td>
<td>Aldol coupling</td>
</tr>
<tr>
<td>2</td>
<td>Et$_3$N</td>
<td>-15</td>
<td>CH$_2$Cl$_2$</td>
<td>[structure]</td>
<td>Aldol coupling</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N</td>
<td>-15</td>
<td>CH$_2$Cl$_2$</td>
<td>[structure]</td>
<td>Aldol coupling</td>
</tr>
<tr>
<td>4</td>
<td>urea</td>
<td>rt</td>
<td>CH$_2$Cl$_2$</td>
<td>TBSO[structure]</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

In order to optimize the formation of the reactive silylchloride 139, our efforts shifted toward monitoring the formation of this intermediate by $^1$H NMR spectroscopy and if possible, identifying a protocol for the purification of this substance. As summarized in Tables 4 and 5, a variety of different dichlorodialkylsilanes were utilized. In addition, a variety of reaction conditions were screened in which the choice of base and reaction temperature were varied.
Table 4. Results of benzyl alcohol addition to dichlorodimethylsilane. \(^a\)

\[
\text{SiMe}_2\text{Cl}_2 + \begin{array}{c} \text{OH} \\
\text{138} \end{array} \xrightarrow{\text{Base 5x Temp Solvent}} \begin{array}{c} \text{Cl} \\
\text{139} \end{array} + \begin{array}{c} \text{O} \\
\text{141} \end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Conversion</th>
<th>Results (139:141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pyridine</td>
<td>rt</td>
<td>CH(_2)Cl(_2)</td>
<td>-</td>
<td>mixture of 5 compounds</td>
</tr>
<tr>
<td>2</td>
<td>pyridine</td>
<td>0</td>
<td>CH(_2)Cl(_2)</td>
<td>-</td>
<td>mixture of 5 compounds</td>
</tr>
<tr>
<td>3</td>
<td>pyridine</td>
<td>rt</td>
<td>pyridine</td>
<td>-</td>
<td>mixture of 5 compounds</td>
</tr>
<tr>
<td>4</td>
<td>imidazole</td>
<td>rt</td>
<td>CH(_2)Cl(_2)</td>
<td>100%</td>
<td>1:1</td>
</tr>
<tr>
<td>5</td>
<td>imidazole</td>
<td>-50</td>
<td>CH(_2)Cl(_2)</td>
<td>100%</td>
<td>1:1</td>
</tr>
<tr>
<td>6</td>
<td>Et(_3)N</td>
<td>rt</td>
<td>CH(_2)Cl(_2)</td>
<td>100%</td>
<td>141 only</td>
</tr>
<tr>
<td>7</td>
<td>Et(_3)N</td>
<td>-50</td>
<td>CH(_2)Cl(_2)</td>
<td>100%</td>
<td>141 only</td>
</tr>
<tr>
<td>8</td>
<td>NaH</td>
<td>rt</td>
<td>THF</td>
<td>100%</td>
<td>141 only</td>
</tr>
</tbody>
</table>

\(^a\) The progress of these reactions was followed by \(^1\)H NMR spectroscopy. Peak assignment for compound 139 vs. compound 141 vs. benzyl alcohol starting material was based on reported chemical shifts for the benzyl protons in related substances.\(^32,33\) It is noteworthy, however, that the chemical shifts of these protons varied between reactions due to the effect of solvent and base.

As indicated in Table 4, the reaction of dichlorodimethylsilane with benzyl alcohol was investigated with various bases and at different temperatures. Reactions with pyridine as the base (entries 1, 2, and 3) resulted in a mixture of more than the three expected compounds (138 starting material, 139, and 141) which led us to believe that hydrolysis and concomitant polymerization of these
compounds was taking place. Although reactions with imidazole as the base (entries 4 and 5) showed the most promising results by $^1$H NMR spectroscopic analysis of crude reaction mixtures, any attempts to purify compound 139 by distillation were unfruitful. Notably, this purification requires a tedious separation from excess dichlorodimethylsilane and dialkoxy silane 141, also, the monochlorosilane 139 was both susceptible to hydrolysis through contact with moisture and had a higher boiling point than dichlorodimethylsilane, which rendered its separation difficult and often led to the decomposition of the desired product. Reactions with triethylamine (entires 6 and 7) and sodium hydride (entry 8) as the base showed one signal for the CH$_2$ group in the $^1$H NMR spectrum of aliquots taken from the reactions. To confirm that this signal belonged to the bis-benzyl product 141, ethoxide was added to the reaction and the reaction mixture was stirred overnight, no signals corresponding to ethanol adduct were evident in the $^1$H NMR spectrum after concentration of the reaction mixture. To overcome the instability problem encountered with dichlorodimethylsilane, dichloro diisopropylsilane and dichlorodiphenylsilane were investigated as alternatives. The results of reactions carried out with the afore mentioned silanes are summarized in Table 5 below.
Table 5. Results of benzyl alcohol addition to dichlorodiphenylsilane and dichlorodiisopropylsilane.

\[ \text{SiR}_2\text{Cl}_2 + \text{OHH} \rightarrow \] base 5x temp CH\textsubscript{2}Cl\textsubscript{2} \[ \rightarrow \text{SiR}_2\text{Cl}_2 \text{OH} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base/Solvent\textsuperscript{a}</th>
<th>Temp (°C)</th>
<th>Conversion</th>
<th>Results (142:143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i\textsubscript{Pr}</td>
<td>Et\textsubscript{3}N</td>
<td>-20</td>
<td>41%</td>
<td>2:3</td>
</tr>
<tr>
<td>2</td>
<td>i\textsubscript{Pr}</td>
<td>imidazole</td>
<td>rt</td>
<td>88%</td>
<td>2:3</td>
</tr>
<tr>
<td>3</td>
<td>i\textsubscript{Pr}</td>
<td>pyridine/pyridine</td>
<td>rt</td>
<td>25%</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>i\textsubscript{Pr}</td>
<td>NaH</td>
<td>rt</td>
<td>-</td>
<td>intractible mixture of compounds</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>imidazole</td>
<td>0</td>
<td>100%</td>
<td>143 only</td>
</tr>
</tbody>
</table>

\textsuperscript{a} solvent is CH\textsubscript{2}Cl\textsubscript{2} unless otherwise specified.

As summarized in Table 5, these efforts revealed that the use of silicon tethers containing larger alkyl groups, that were expected to enhance the stability of the product, introduced new challenges with regards to the formation of dimers. Thus, under our optimized conditions, (Table 5, entry 5) we saw only formation of the dimmer 143. A similar result has been reported by Craig during attempts to selectively functionalize diphenyldichlorosilane\textsuperscript{16b}.

Due to the challenges highlighted above in our efforts to introduce one alcohol function onto a dichlorodialkyl silane, we decided to first investigate the formation of dialkylchlorosilyl enol ethers followed by addition of the alcohol.
Initially we focused on making chloro(vinyloxy) silanes 144-146 (Figure 9) following the procedure described by Komarov,\textsuperscript{28} whereby the reaction of a chloroorganosilane with vinyl acetate 147 in the presence of sodium was reported to form (vinyloxy)silanes as depicted in Scheme 31.

\[
\text{SiR}_2\text{Cl}_2 + \text{Na} + \overset{\equiv}{\text{O}}\text{C} = \overset{\equiv}{\text{O}} \rightarrow \text{SiR}_2\text{Cl}_2 + \text{Na} + \overset{\equiv}{\text{O}}\text{C} = \overset{\equiv}{\text{O}} \rightarrow \\
\text{ether} \quad \text{ether} \\
\]

\[\begin{align*}
& \quad 144 \ R = \text{Me} \\
& 145 \ R = \text{iPr} \\
& 146 \ R = \text{Ph}
\end{align*}\]

**Figure 9.** Chloro(vinyloxy)silane.

As indicated in Scheme 32, using diphenyl-, dimethyl- and diisopropylsilyl chloride a number of attempts were made to couple these reagents with the anion of acetaldehyde, generated \textit{in situ} by the sodium promoted pinacol coupling of two equivalents of vinylacetate. The formation of the compounds 144-146 were monitored by \textsuperscript{1}H NMR spectroscopy as well as the precipitation of NaCl salt. In particular, during the course of the reaction, resonances at $\delta = 6.53$ ppm (dd), $\delta = 4.55$ ppm (d), and $\delta = 4.15$ ppm (d) in \textsuperscript{1}H NMR spectrum replaced those at $\delta = 7.26$ ppm (dd), $\delta = 4.88$ ppm (d), and $\delta = 4.56$ ppm (d) of vinyl...
acetate and were indicative of the formation of chloro (vinylxyloxy) silanes (144-146) or their dimmer counterparts. Benzyl alcohol was then added to promote the formation of the desired compounds (148-150), however, upon the addition of benzyl alcohol these signals were replaced by a resonance at $\delta = 4.86$ ppm that belonged to the benzyl alcohol dimer. Based on this result, those intermediates (144-146) proved to be too unstable to undergo further reaction. Unfortunately, all attempts to isolate or purify those intermediates were unsuccessful.

**Scheme 32.** Reaction of silanes with vinyl acetate.

Given the multitude of challenges that we had faced in attempts to selectively monofunctionalize dichlorodialkylsilanes, our efforts shifted toward the use of an alternative bifunctional silicon source. In an account by researchers at Merck Frosst, the difficulties associated with selectively functionalizing dichlorodialkylsilanes were addressed through the synthesis of a di-$t$-butylchlorosilane monotriflate. The tenet of their approach was to utilize the different leaving group abilities of the chloro and triflate groups to achieve unsymmetrical functionalization of a silicon tether. The formation of di-$t$-butylchlorosilane monotriflate was achieved by selective protolysis of di-$t$-butylchlorosilane with triflic acid at low temperature as shown in Scheme 33.
Our attempts with this reaction yielded similar results to those reported by the Merck Frosst group and $^1$H NMR spectroscopic analysis of the crude reaction mixture revealed a 9:1 ratio of compounds 152 and 153. These compounds were readily distinguished by the unique chemical shifts of the t-butyl protons which resonate at $\delta = 1.19$ and 1.12 ppm in 152 and 153, respectively. In addition, the reaction could be monitored by the disappearance of the starting material by GC analysis. Unfortunately, purification of the desired product 152 required separation from excess triflic acid and the triflic silane byproduct 153. While the purification of this substance has been reported by distillation at low pressure and relatively high temperature (64 °C at 0.1 mmHg) on medium-scale (25 g), through personal communication with the authors of this report we were warned of a number of complications associated with this procedure. Most likely as a result of our working on a smaller scale, our efforts to repeat the distillation were unsuccessful and all attempts to perform subsequent reactions on the crude mixture of products failed.

At this point, we decided to re-visit what had provided the most promising results: The coupling of enolates with dichlorodialkylsilanes (Scheme 31). However, armed with an improved knowledge of the stability of the intermediate
enolsilylchloride derived from acetaldehyde, we elected to synthesize a more stable silyl enol ether derived from trimethylsilyl enol ether of valeraldehyde 154 as shown in Scheme 34.

Scheme 34. Synthesis of silyl enol ethers 158 and 159 of valeraldehyde.

In the procedure illustrated in Scheme 34, MeLi was added to an E/Z mixture of the trimethylsilyl enol ether (155 and 156) to unveil the enolate 157, which was transferred into excess dichlorodiisopropylsilane (3 equiv.). Excess silane was used in attempt to minimize the formation of the undesired dimmer. In addition, the reaction was scaled up ten-fold (1 g from 100 mg) to allow more facile distillation of E/Z mixture 158 and 159. Upon completion of the reaction, excess dichlorodiisopropylsilane was removed by distillation (47 °C, 8 mmHg) and the crude material was carried through to the next reaction (Scheme 35) due to the purported instability of a structurally related compound (hexanal derivative 160, Figure 10). 

$^1$H NMR spectroscopic analysis of the crude material indicated the presence of two major compounds in approximately 1:1 ratio amongst five other compounds. The structures 161 and 159 (Figure 11) were proposed for these two compounds based on similarities with the reported chemical shifts for H1 $\delta = 6.30$ (dt, $J = 12.0, 1.6$ Hz) and H2 $\delta = 5.13$ (dt, $J = 12.0, 7.6$ Hz) in compound 160 (Figure 10). The crude $^1$H NMR spectrum for the
mixture of 161 and 159 showed two different signals for H1 at δ 6.32 (dt, \( J = 12.0, 1.6 \) Hz) with a coupling constant characteristic of a trans geometry of the double bond and at δ = 6.30 (d, \( J = 7.0 \) Hz) a coupling constant characteristic of a cis alkene. Also, there were two unique resonances for H2 at δ = 5.07 (dt, \( J = 12.0, 1.6 \) Hz) and at δ = 4.55 (q, \( J = 7.0 \) Hz) confirming a mixture of both a trans and cis configured enol silyl ether. The observed discrepancy between the chemical shifts for H1 and H2 (δ = 6.32 and 5.07 ppm, respectively) in the trans enol silyl ether 161 and those reported\(^{29}\) for H1 and H2 (δ = 6.30 and 5.13, respectively) in compound 160 suggested that former compound was not a silyl chloride and was instead the dimmer 161 (Figure 11). While the presence of desired product 158 was evidenced by resonances at δ = 6.30 and 5.13 ppm (Figure 12), unfortunately, this substance was only a minor product of the reaction (17% relative to cis-silyl enol ether 159).

![Figure 10. Product synthesized by Posner et al.\(^{29}\)](image1.png)

![Figure 11. Products of enolate addition to excess dichlorodiosopropylsilane.](image2.png)
Figure 12. Minor compound of addition reaction to diisopropyl dichlorosilane.

Scheme 35. First successful synthesis of tether.

With a mixture of (E) and (Z)-enol silyl chlorides 158 and 159 in hand, treatment of these substances with 4-hydroxymethyl oxazole (125) and Et$_3$N in CH$_2$Cl$_2$ afforded the desired silyl ether as a 1:5 mixture of E:Z isomers in 40% yield over two steps. Given the success of this process, we attempted to apply these conditions to the trimethylsilyl enol ether derived from acetaldehyde as shown in Scheme 36. Unfortunately, after considerable effort, we were not able to produce the monochlorosilyl enol ether 145, a result that was perhaps not too surprising given the increased lability of the resultant enol silyl ether and inherent reactivity of the two-carbon lithium enolate salt.
Scheme 36. Reaction with trimethylsilyl enol ether derivative of acetaldehyde.

Based on the observed preference for the formation of the \textit{cis} enol silyl chloride as depicted in Figure 11, it was anticipated that selection of aldehydes or ketones that can only form \textit{cis} enolates would allow for a cleaner formation of the desired tethered Diels-Alder precursors. This theory was tested with cyclopentanone (167) and isobutyraldehyde (172) as illustrated in Schemes 37 and 38, respectively. In the case of cyclopentanone the yield of the resultant silicon tether 171 was 55\% compared to 40\% for silicon tether derived from valeraldehyde. Likewise, when isobutyraldehyde was employed as the source of enolate and a one-pot procedure was used, the corresponding silicon tether 173 was isolated in 43\% yield.

Scheme 37. Reaction with trimethylsilyl enol ether derivative of cyclopentanone.
Scheme 38. One pot procedure to access silane tether of isobutyaldehyde.

With the silyl tethers 162/163, 171, and 173 in hand, we were ready to proceed with the proposed inverse electron demand Diels-Alder reaction (vide supra). As detailed in Table 6, our initial efforts started with the E/Z mixture of the silicon tether 162/163 and we focused our efforts on activation of the oxazole via methylation of the nitrogen atom to produce an oxazolium ion that should trigger the inverse electron demand intramolecular Diels-Alder reaction. The results of this study are summarized in Table 6. It is noteworthy that our first attempts to realize this process were carried out in an NMR tube and the progress of each reaction was monitored by $^1$H NMR spectroscopy. Methyl triflate is one of the most reactive methylating agents and consequently our initial attempts to promote this process utilized this reagent in CDCl$_3$ at room temperature, where it was observed that methylation of the oxazole nitrogen took place within five minutes as evidenced by the downfield shift of the oxazole protons at $\delta = 7.98$ and 10.22 ppm. However, this reaction was complicated by concomitant hydrolysis of the silyl enol ether to provide valeraldehyde, the presence of which was confirmed by a diagnostic resonance at $\delta = 9.77$ ppm (triplet, $J = 1.8$ Hz). The formation of valeraldehyde may be attributed to the presence of small amounts of triflic acid in
the methyl triflate. As a result, we resorted to using a weaker methylating agent (i.e. iodomethane), which was passed through an alumina plug to ensure complete removal of any hydroiodic acid. The reactions with iodomethane were carried out in a variety of solvents (entries 3-6) at 80 °C, unfortunately, no evidence of Diels-Alder product was observed in the crude \(^1\)H NMR spectra of these reactions, and only hydrolysis of the silyl enol ether occurred. Trimethyloxonium tetrafluoroborate (Meerwein's salt) was also explored as a methylating agent, and again a variety of solvents and reaction temperatures were screened (for example see entries 7-10). When DMSO was used as the solvent (entry 7), methylation of oxazole nitrogen of both the cis- and trans-isomers of silyl tether 162/163 required 72 hours at room temperature and was accompanied with minimal (approximately 15%) hydrolysis. Unfortunately, under these conditions there was no sign of the expected Diels-Alder product. Furthermore, after prolonged reaction times only additional hydrolysis of the enol silyl ether occurred. When CD\(_3\)CN was used as the solvent (entry 8), \(N\)-methylation of both the cis- and trans- isomers occurred faster than in DMSO (30 minutes at room temperature) and was accompanied by 18% hydrolysis. The reaction temperature was then increased by 10 °C increments every 30 minutes in an effort to promote the Diels-Alder reaction but, unfortunately, this only led to further hydrolysis of the enol silyl ether, as indicated by the formation of additional amounts of valeraldehyde. When C\(_6\)D\(_6\) was used as the reaction solvent (entry 9), methylation took place in 30 minutes at 80 °C, however, no sign of the Diels-Alder product was present in the \(^1\)H NMR spectrum. In CDCl\(_3\) (entry
10) at room temperature, negligible amounts of methylated oxazole were observed after 1.5 hours and, after heating at reflux (70 °C) for 24 h only hydrolysis occurred. Fortunately, in CD$_2$Cl$_2$ (entry 11) at room temperature more promising results were obtained. As illustrated in Figure 13, after one hour 25% of the cis isomer 163 was methylated as evidenced by the signal for H1 at $\delta = 4.60$ ppm (td, 1H, $J = 7.2, 7.2$ Hz) with 30% hydrolysis as confirmed by the diagnostic resonance for valeraldehyde at $\delta = 9.77$ ppm (triplet, $J = 1.7$ Hz), in addition, the trans- isomer 162 was also methylated as evidenced by the more complex signal for H1 at $\delta = 5.10$ ppm. However, determining the exact proportion of the methylated trans- isomer was not possible as the resonances for both the starting material and methylated oxazole overlapped in CD$_2$Cl$_2$. After 4 hours, more of the methylated cis- and trans- products 174 and 175 were formed and upon closer inspection of the base line of the $^1$H NMR spectrum, we observed new resonances at $\delta = 4.40$ ppm (d, 1H, $J = 18.6$ Hz), 4.7 ppm (t, 1H, $J = 7.77$ Hz), 5.59 ppm (d, 1H, $J = 7.77$ Hz), and 7.25 ppm (bs, 1H) that were consistent with the formation of the desired Diels-Alder product. In order to gain more structural information about this minor product, a series of 1D TOCSY experiments (Figure 14) were performed. Thus, irradiation of the proton resonance at $\delta = 4.40$ ppm indicated that it belonged to the same spin system as a proton that resonated at $\delta = 4.50$ ppm. The coupling constant between these protons ($J = 18.6$ Hz) was consistent with that expected for two geminal protons and consequently these resonances were assigned as H1 and H2 as shown in Figure 14. Irradiating the proton that resonated at $\delta = 5.59$ ppm, which was
tentatively assigned as H3, indicated that it belonged to the same spin system as a proton that resonated at $\delta = 4.65$ ppm (triplet, $J = 7.77$ Hz) and assigned as H4. Furthermore, a signal at $\delta = 2.35$ ppm, which was assigned as H5, also belonged to the same spin system and the broad singlet that resonated at $\delta = 7.26$ ppm was assigned as H6. Prolonged reaction times (48 hours) at room temperature resulted in the complete disappearance of the methylated oxazole with a trans- configured enol silyl ether and no further formation of the Diels-Alder product, which led us to believe that only the trans isomer was undergoing an inverse electron demand Diels-Alder reaction. In an attempt to promote the Diels-Alder reaction of the cis isomer, the reaction was carried out at reflux (40 °C) as shown in Table 6 (entry 12). At this temperature, $N$-methylation of both the cis- and trans- isomers occurred faster than that at room temperature (20 minutes) and after 1.5 hours all of the methylated trans isomer 174 was converted into the desired Diels-Alder adduct as shown in Figure 15. Unfortunately, heating the reaction at reflux for longer periods of time resulted in only additional hydrolysis. Thus, it would appear that under these reaction conditions the methylated cis isomer 175 does not undergo an inverse electron demand Diels-Alder reaction. This may be the result of the increased steric interactions between the oxazole and the $n$-propyl group in the transition structure 175 b (Figure 16) that would lead to 177 (Table 6). It is noteworthy that the exo transition structure that would avoid these steric interactions suffers from angle strain that realistically precludes the formation of the diastereomeric Diels-Alder product 178 (Scheme 39).
Table 6. Results of inverse electron demand Diels-Alder reaction.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Methylating agent</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Time (h) Step 1</th>
<th>Time (h) Step 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>80</td>
<td>C(_6)D(_6)</td>
<td>5</td>
<td>-</td>
<td>no reaction(^b)</td>
</tr>
<tr>
<td>2</td>
<td>CF(_3)OSO(_3)Me</td>
<td>rt</td>
<td>CDCl(_3)</td>
<td>0.25</td>
<td>-</td>
<td>methylation then hydrolysis (^c)</td>
</tr>
<tr>
<td>3</td>
<td>MeI</td>
<td>80</td>
<td>CD(_3)CN</td>
<td>8</td>
<td>-</td>
<td>hydrolysis</td>
</tr>
<tr>
<td>4</td>
<td>MeI</td>
<td>80</td>
<td>DMSO</td>
<td>3</td>
<td>-</td>
<td>methylation then hydrolysis</td>
</tr>
<tr>
<td>5</td>
<td>MeI</td>
<td>80</td>
<td>C(_6)D(_6)</td>
<td>48</td>
<td>-</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>MeI</td>
<td>40</td>
<td>CD(_2)Cl(_2)</td>
<td>48</td>
<td>-</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>Me(_3)OBF(_4)</td>
<td>rt</td>
<td>DMSO</td>
<td>72</td>
<td>-</td>
<td>methylation then hydrolysis</td>
</tr>
<tr>
<td>8</td>
<td>Me(_3)OBF(_4)</td>
<td>rt-70</td>
<td>CD(_3)CN</td>
<td>0.5</td>
<td>-</td>
<td>methylation then hydrolysis</td>
</tr>
<tr>
<td>9</td>
<td>Me(_3)OBF(_4)</td>
<td>60-80</td>
<td>C(_6)D(_6)</td>
<td>0.5</td>
<td>-</td>
<td>hydrolysis</td>
</tr>
<tr>
<td>10</td>
<td>Me(_3)OBF(_4)</td>
<td>rt-70</td>
<td>CDCl(_3)</td>
<td>24</td>
<td>-</td>
<td>methylation then hydrolysis</td>
</tr>
<tr>
<td>11</td>
<td>Me(_3)OBF(_4)</td>
<td>rt-40</td>
<td>CD(_2)Cl(_2)</td>
<td>4</td>
<td>3</td>
<td>hydrolysis + D-A reaction of (E) isomer only</td>
</tr>
<tr>
<td>12</td>
<td>Me(_3)OBF(_4)</td>
<td>40</td>
<td>CD(_2)Cl(_2)</td>
<td>0.5</td>
<td>1</td>
<td>hydrolysis + D-A reaction of (E) isomer only</td>
</tr>
</tbody>
</table>

\(^a\) reactions were carried out in an NMR tube and a \(^1\)H NMR experiment was run at \(t_0\) and every 15 minutes thereafter; \(^b\) only starting material observed; \(^c\) methylation refers to the methylated nitrogen atom in the oxazole moiety. The methylated product resulted in new sets of resonances.
in the spectrum. Hydrolysis refers to the decomposition of the enol ether, which was monitored by integration of the resulting valeraldehyde resonance at δ = 9.77 ppm (triplet, J = 1.7 Hz).

Figure 13. $^1$H NMR spectrum of methylation reaction at $t_0$ (top), $t = 1h$ (middle), and $t = 4h$ (bottom).
Figure 14. 1D TOCSY spectra of the inverse electron demand Diels-Alder product.
Figure 15. $^1$H NMR spectrum of methylation reaction at 40 °C for 1.5 hours.

Figure 16. Steric interactions in the methylated cis- isomer that preclude the inverse electron demand Diels-Alder reaction.
At this point, we utilized the optimized conditions presented above in Table 6 (entry 12) in attempts to promote the inverse electron demand Diels-Alder reaction of the silicon tethers 171 and 173 as illustrated in Scheme 40. Unfortunately, while N-methylation was observed in the \(^1\)H NMR spectrum in each reaction, prolonged reaction times resulted only in hydrolysis of the silyl enol ether to give the corresponding aldehyde or ketone, and no Diels-Alder products were detected. Given the challenges discussed above in promoting the Diels Alder reaction of the cis-enol silyl ether derived from valeraldehyde, this result was not too surprising.
In order to proceed with the proposed methodology and confirm the structural identity of the Diels-Alder product discussed above, we set out to make silyl tether 162 as a single geometric isomer. To the best of our knowledge, only one method has been reported\textsuperscript{29} for the preparation of the $E$-monochlorosilyl enol ether containing more than four carbons. This method employs hydrosilylation of $trans$-2-hexenal as depicted in Scheme 41.

\begin{center}
\textbf{Scheme 41.} Synthesis of the $E$- Enol silaketal by Ponser et al.\textsuperscript{29}
\end{center}

In order to make our target compound we used $trans$-2-pentenal (182) instead of $trans$-2-hexenal (181). After 48 hours, the formation of the $E$-enol silaketal was detected by $^1$H NMR spectroscopic analysis of reaction aliquots by the presence of new resonances at $\delta = 6.30$ (dt, 1H, $J = 12.0$, 1.6 Hz) and 5.13 (dt, 1H, $J = 12.0$, 7.6 Hz). Following formation of 158, 4-hydroxymethyl oxazole was added to crude silyl enol ether 158 to yield the silyl tether 162 in 56\% (calculated from oxazole weight) as illustrated to in Scheme 42.

\begin{center}
\textbf{Scheme 42.} Preparation of the desired $E$- silicon tether 162 via hydrosilylation.
\end{center}
With the silicon tether 162 in hand, the optimized Diels-Alder reaction conditions described above in Table 6 (entry 12) were employed on this substance (Scheme 43) and the reaction was monitored by $^1$H NMR spectroscopy. The signals obtained for the product of this reaction (Figure 17) were identical to those obtained in the reaction of E/Z mixture of silyl tether 162/163 (Figure 15), confirming our original hypothesis that only the trans isomer was engaging in the desired Diels-Alder reaction.

\[
\text{Scheme 43. Inverse electron demand Diels-Alder reaction of silyl tether 162.}
\]
Figure 17. Crude $^1$H NMR spectrum of inverse electron demand Diels-Alder reaction of silyl tether 162.

Upon confirming the formation of the Diels-Alder product, *in situ* reduction of the 7-oxa-2-azoniabicyclo[2.2.1]hept-2-ene intermediate 176 was carried out in a series of NMR tube experiments using Pd/C or NaBH$_4$, however, any attempts to purify the resulting iminosugar product were unfruitful. However, the formation of the iminosugar was confirmed by mass spectrometric analysis and the desired product was detected by analytical LCMS and purified for the first time on a preparative LCMS X-bridge C18 2.1 x 30 mm, 5 mm particle size column (mobile phase 5-20% CH$_3$CN:H$_2$O with 10 mM NH$_4$CO$_3$ and 0.375% NH$_4$OH v/v). Based
on this result, which confirmed the success of this route, the reaction was scaled up and the product was purified by flash column chromatography to provide iminosugar 183 in 29% yield. The peaks in the $^1$H NMR spectrum (Figure 18) of the iminosugar product confirmed its structure. Those peaks were assigned based on several other NMR experiments (see experimental Section). For example, the proton resonances at $\delta = 3.92$ ppm and $3.85$ ppm belonged to the two diastereotopic protons at C6 which was confirmed by COSY correlation. Those two protons showed a correlation to another proton at $\delta = 2.04$ ppm which was assigned as H5. H5 showed a COSY correlation with a triplet at $\delta = 3.37$ ppm which was assigned as H4. H4 showed a COSY correlation with H3 at $\delta = 3.15$ ppm, H3 correlated with H2 and H2 with the axial and equatorial protons at $\delta = 2.10$ ppm and $\delta = 2.94$ ppm, respectively.
Figure 18. $^1$H NMR spectrum of (+/-) 2-hydroxymethyl-1-methyl-5-propylpiperidine-3,4-diol (183) (recorded in D$_2$O at 600 MHz).

3.1.6 Summary

Since the discovery of their potent glycosidase inhibitory activity, iminosugars have gained a foothold as potential therapeutic agents for the treatment of glycosidase mediated disease such as diabetes and cancer. Current methodologies for the synthesis of substituted piperidines often commence with naturally occurring sugars and consequently involve considerable functional group manipulation, which adds to the overall length and complexity of these
processes. In order to address the disadvantages associated with these current approaches to iminosugar synthesis, we have developed a novel and concise sequence of reactions that provides access to these substances that exploits the reactivity of an oxazolium species and, most importantly, initiates with commodity chemicals (e.g. oxazole, aliphatic aldehydes) as opposed to carbohydrates. Our approach employs an inverse electron demand Diels-Alder reaction between a 4-hydroxymethyl oxazole and an enolsilyl ether connected together via a silicon tether. The tethering of these reagents imparts regio-control on their subsequent Diels-Alder reaction and precludes the formation of diastereomers (e.g. see Scheme 10). For the purpose of this study, activation of the oxazole was achieved through $N$-methylation with trimethyloxonium tetrafluoroborate, which triggered an inverse electron demand Diels-Alder reaction to provide the 7-oxa-2-azoniabicyclo[2.2.1]hept-2-ene intermediate 176 that was subsequently reduced and deprotected to provide the unnatural iminosugar 183 in 29% yield. The successful application of this methodology represents the most concise route to iminosugars from carbohydrate or non-carbohydrate starting materials.

Scheme 44. Concise route for the synthesis of iminosugars.
4: FUTURE PROJECT DIRECTION

The successful synthesis of the unnatural iminosugar 183 employing the methodology described in Chapter 3 demonstrated the potential utility of this route, however, the generality and scope of this methodology needs to be assessed through the synthesis of a wider range of natural and unnatural iminosugars. For example, the iminosugar analogue 184 could be derived from the inverse electron demand Diels-Alder reaction of silicon tether derived from 2-phenylacetaldehyde and 4-hydroxymethyl oxazole as depicted in Scheme 45. Similarly, N-methyl fagomine should be accessed through a Diels-Alder reaction involving the silicon tether 189, while N-methyl deoxynojirimycin could be derived from the Diels-Alder reaction of a silicon tether derived from protected 2-hydroxyacetaldehyde.

![Figure 19. Examples for future synthesis of iminosugar analogues.](image-url)
While the benefits of this synthetic route are clear, the adoption of these methods by the broader scientific community will likely hinge on the development of an asymmetric version of this reaction. The development of an asymmetric inverse electron demand Diels-Alder reaction discussed in Chapter 3 is an obvious and important long term goal that was beyond the scope of this thesis. Several strategies that may accomplish this task have been considered and include: (1) the use of a chiral tether linking the oxazole and enol ether (e.g. 193 or 194); (2) activation/acylation of the oxazole with a chiral acid chloride (e.g. 195); (3) protononation/activation of the oxazole with a chiral Bronsted acid (e.g. 196 or 197) or Lewis acid (e.g. 198), (Figure 20).
As outlined in Scheme 46, the use of chiral diols, that are commercially available in one or both enantiomeric forms, as tethers for intramolecular Diels-Alder reactions, have been reported. For example, 1,3-butanediol (193) has been used to tether an enolic silaketal to 2-pyron-3-carboxylate 199 to induce intramolecular Diels-Alder reaction (Scheme 5).\textsuperscript{29} While incorporating this strategy in our methodology will require the use of oxazole-4-carboxylates (e.g. 202, Scheme 47) to relinquish the chiral tether at the end of the synthesis, the carboxypiperidines (e.g. 203) that would be afforded after deprotection represent analogues of glucuronic acid (205), which is often linked to xenobiotic metabolism of substances such as drugs and pollutants.\textsuperscript{30} One example of glucuronic acid mimic 206 (Figure 21), discovered from seeds of the legume \textit{Baphia racemosa}, proved to be a specific inhibitor of human liver D-glucuronidase and \ensuremath{\alpha}-L-iduronidase.\textsuperscript{30} As illustrated by Scheme 47, the successful incorporation of this chiral diol as a tether will afford a single enantiomer of \textit{N}-methylfagomine 204. The second strategy would involve the formation of a chiral oxazolium salt (e.g. 209) via acylation of the oxazole
nitrogen with a chiral acid chloride. A related approach has been used for the activation of pyridine towards nucleophilic attack at C2 by organometallic reagents to provide optically pure hydropyridines (e.g. 208). Applying this strategy to our oxazolium Diels Alder methodology would require the conversion of the resulting N-acyl piperidine (e.g. 211) to the corresponding iminosugar (e.g. fagomine 8), which can be achieved via amide/carbamate hydrolysis (Scheme 49). A third strategy would involve the employment of a chiral Lewis or Bronsted acid in the formation of a chiral oxazolium salt (e.g. 212, Scheme 50), which would consequently activate the oxazole to undergo an inverse electron demand Diels-Alder reaction. While the stability of enolsilanes under these conditions is a concern, examples demonstrating Lewis acid catalyzed cycloaddition of silaketals have been reported (see Scheme 46). Recently, metal-free chiral Bronsted acid catalysts have gained popularity as chiral organic catalysis and Yamamoto has demonstrated the utility of N-triflylphosphoramides (e.g. 197, Figure 20) in promoting the asymmetric Diels-Alder cycloaddition between dienoisilyl ethers and ethyl vinyl ketones. However, chiral Bronsted acids often lack substrate specificity, which limits their use. While this problem is often remedied by increasing the acidity of the chiral Bronsted acid, unfortunately, this may result in an incompatibility with labile enolsilanes. Furthermore, the equilibrium that exists between the oxazole + iminium and oxazolium + imine species 189 + 215 ⇄ 214 + 217 (Scheme 50) may not be favourable for catalyst turnover in our system (i.e. the product is more basic than the starting material, thus leading to difficulty in catalyst turnover). However, this may be
overcome through the addition of stoichiometric amounts of a second acid that is not chiral and is of lower acidity than the chiral bronsted acid, but of sufficient acidity to protonate the formed imine. Thus, activation of oxazole could only occur through protonation by the chiral acid ($pK_A < 2$) while the product ($pK_A \sim 7$) would be protonated by either acid, freeing up the chiral acid to return to the catalytic cycle.$^{33}$

Scheme 46. An example of asymmetry induction in Diels-Alder reaction using diols as chiral tethers.

Scheme 47. Proposed asymmetric synthesis of iminosugars by chiral diol approach.
**Figure 21.** Glucuronic acid (left) and its naturally occurring mimic (right).

**Scheme 48.** An example of asymmetric activation of pyridines.

**Scheme 49.** Proposed asymmetric synthesis of iminosugars by acid chloride approach.
Scheme 50. Proposed asymmetric synthesis of iminosugars by chiral catalysis approach.
5: EXPERIMENTAL PROCEDURES

General Experimental

All reactions described were preformed under an atmosphere of dry argon using oven dried glassware. Et$_2$O, CH$_2$Cl$_2$, THF, and DMF were used from commercial Aldrich dry solvent bottles. Cold temperatures were maintained by the use of following reaction baths: 0 °C, ice-water; -78 °C, acetone-dry ice, -50 °C, acetone-ethylene glycol. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60).

($^1$H NMR) and ($^{13}$C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz).

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with potassium bromide plates. Only characteristic absorption data are provided for each compound.
Preparation of β-aminoacrolein (76).

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

A solution of 1,1,3,3-tetramethoxypropane (10.0 g, 60.9 mmol) in 2N HCl (30 mL) was stirred at rt for 3h. After this time, the mixture was extracted with chloroform and the organic layer was concentrated to provide malonaldehyde (4.4 g) as yellow oil that was used without further purification. A solution of the crude malonaldehyde (4.4 g) in 7N NH\textsubscript{3} in MeOH (9.0 mL) was stirred at rt for 3 days. After this time, the reaction mixture was concentrated, and 20 mL of hexanes was added followed by dropwise addition of MeOH until all materials were dissolved. The mixture was then stirred overnight and the MeOH layer was removed and concentrated to provide a brown residue. The crude product was recrystallized from a hot mixture of hexane-chloroform (1:1) to provide β-aminoacrolein (97) as yellow solid (2.5 g, 58%), mp 104-105 °C (lit.\textsuperscript{34} mp 105-106 °C). The \textsuperscript{1}H NMR spectral data derived from 76 were identical to that reported in the literature.\textsuperscript{35}

\textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}) δ 8.05 (d, 1H, \textit{J} = 8.9 Hz), 6.50 (bs, 1H), 6.4 (dt, 1H, \textit{J} = 12.7, 12.7 Hz), 6.22 (bs, 1H), 4.25 (dd, 1H, \textit{J} = 12.7, 8.9 Hz).
Preparation of ethyl oxazole-4-carboxylate (133).

![Chemical structure](image)

To a stirred solution of formic acid (4.1 g, 88 mmol) in THF (40 mL) at room temperature, was added portionwise N,N’-carbonyldiimidazole (14.3 g, 88 mmol) and the reaction mixture was stirred at rt for 1 h. A mixture of ethyl isocyanoacetate (5.0 g, 44 mmol) and triethylamine (12 mL, 88 mmol) was then added and the mixture was heated at reflux (80 °C) overnight. After this time, the reaction mixture was concentrated to approximately 10 mL, poured into H₂O (250 mL), and extracted with Et₂O (150X3 mL). The combined organic layers were dried over (MgSO₄) and concentrated. The purification of crude product by flash column chromatography (hexanes-EtOAc, 4:1) afforded 133 as yellow oil (5.8 g, 93%). The ¹H and ¹³C NMR spectral data derived from 133 were identical to that reported in the literature.³⁶

¹H NMR (600 MHz, CDCl₃) δ 8.27 (s, 1H), 7.93 (s, 1H), 4.39 (q, 2H, J = 7.1 Hz), 1.39 (t, 3H, J = 7.1 Hz).

¹³C NMR (600 MHz, CDCl₃) δ 161.0, 151.4, 144.0, 133.3, 61.4, 14.3.
Preparation of oxazole-4-yl-methanol (125).

![Chemical structure](image)

To a stirred solution of ethyl oxazole-4-carboxylate (1.1 g, 7.8 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C, was added diisobutylaluminium hydride (1.0 M solution in CH$_2$Cl$_2$, 21 mL, 21 mmol). After the addition was complete, the cold bath was removed and reaction mixture was stirred at rt for 20 minutes. After this time, the reaction mixture was cooled to 0 °C and NaF (1.3 g) was added portionwise, followed by MeOH (60 mL) until gas evolution ceased. After the reaction mixture had been stirred for an additional 1 h at rt, the resultant mixture was filtered and the filtrate was concentrated to provide a brown residue. Purification of the crude product by flash column chromatography (100% EtOAc) provided 125 as yellow oil (0.43 g, 55%). The $^1$H and $^{13}$C NMR spectral data derived from 125 were identical to that reported in the literature.$^{36}$

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.89 (s, 1H), 7.63 (s, 1H), 4.63 (s, 2H), 2.98 (bs, 1H).

$^{13}$C NMR (600 MHz, CDCl$_3$) δ 151.5, 139.9, 135.5, 56.5.
Preparation of (Z/E) mixture of 1-trimethylsiloxypent-1-ene (E 155, Z 156).

\[
\begin{align*}
\text{OTMS} & \quad \text{H} \\
\text{2} & \quad \text{3} \\
\text{E} & \quad \text{Z}
\end{align*}
\]

To a stirred solution of Et\(_3\)N (8.0 mL, 58 mmol) and chlorotrimethyl silane (3.6 mL, 27.8 mmol) in DMF (16 mL) at rt, was added valeraldehyde (2.0 g, 23.2 mmol) and the reaction was heated to 80 °C and maintained at this temperature for 24h. The reaction mixture was then cooled to rt and ether (100 mL) was added to precipitate the triethylamine hydrochloride salt, which was subsequently removed by filtration. The filtrate was washed sequentially with cold (0 °C) 2M HCl (2 x 15 mL), cold (0 °C) saturated aqueous NaHCO\(_3\) (2 x 20 mL), and cold (0 °C) brine (2 x 20 mL). The organic layer was concentrated and the product was purified by distillation at 34-38 °C, 18 mmHg (lit. \(^{37}\) bp. 30-34 °C, 15 mmHg) to provide 155/156 as a 2:3 mixture of E:Z isomers (1.7 g, 46%). The \(^1\)H NMR spectral data derived from 155/156 were identical to that reported in the literature.\(^{37}\)

\(^1\)H NMR (600 MHz, CDCl\(_3\)) E isomer \(\delta\) 6.19 (td, 1H, \(J = 12.1, 1.44\) Hz), 4.99 (td, 1H, \(J = 12.1, 7.8\) Hz), 2.04 (ddt, 2H, \(J = 7.8, 7.8, 1.4\) Hz), 1.32-1.37 (m, 2H), 0.86-0.91 (m, 3H), 0.17-0.18 (m, 9H). Z isomer \(\delta\) 6.14 (td, 1H, \(J = 6.0, 1.4\) Hz), 4.49 (td, 1H, \(J = 6.0, 6.0\) Hz), 1.86 (ddt, 2H, \(J = 6.0, 6.0, 1.4\) Hz), 1.32-1.37 (m, 2H), 0.86-0.91 (m, 3H), 0.17-0.18 (m, 9H).
Preparation of (Z/E) mixture of enol silaketal (E 162, Z 163).

\[
\begin{align*}
\text{Si} & \quad \text{Si} \\
\text{Pr} & \quad \text{Pr}
\end{align*}
\]

To a stirred solution of 1-trimethylsiloxypent-1-ene (155/156) (1.0 g, 6.3 mmol) in THF (2.0 mL) at -78 °C, was added methyllithium (4.5 mL, 1.42 M in Et₂O, 6.4 mmol). After 1h, the cold bath was removed and the reaction mixture was transferred into a solution of dichlorodiisopropylsilane (4.3 mL, 24 mmol) in THF (3 mL) at -78 °C via cannula. The resulting mixture was then allowed to warm to rt over 2.5 hours, concentrated to approximately 10 mL, and excess dichlorodiisopropylsilane was removed by distillation (47 °C, 8 mmHg) to give 1.33 g of a crude mixture of the unstable monochlorosilyl enol ethers (5:1 Z:E), which were immediately used in the subsequent reaction. To a solution of oxazole-4-yl-methanol (125) (0.63 g, 6.3 mmol) in CH₂Cl₂ (10 mL) at -10 °C, was added a solution of the crude monochlorosilyl enol ether (1.33 g) and triethylamine (1.4 mL, 10 mmol) in CH₂Cl₂ (4 mL) and the reaction mixture was allowed to warm to rt overnight. The mixture was then poured into H₂O (10 mL) and extracted with Et₂O (60 mL x 3). The crude product was purified by flash column chromatography (hexanes-EtOAc, 33:1) to afford the enol silane 163/162 (5:1 Z:E) as clear oil (0.75 g, 40%).
$^1$H NMR (600 MHz, CDCl$_3$) $E$ isomer $\delta$ 7.85 (s, 1H), 7.60 (s, 1H), 6.32-6.33 (m, 1H), 5.06 (td, 1H, $J = 12.1$, 7.7 Hz), 4.83 (s, 2H), 1.84 (q, 2H, $J = 7.7$), 1.30-1.39 (m, 2H), 1.04-1.12 (m, 14H), 0.86 (t, 3H, $J = 7.6$ Hz). $Z$ isomer $\delta$ 7.85 (s, 1H), 7.60 (s, 1H), 6.32-6.33 (m, 1H), 4.83 (s, 2H), 4.47 (td, 1H, $J = 7.2$, 7.2 Hz), 2.08 (ddt, 2H, $J = 7.2$, 7.2, 1.4 Hz), 1.30-1.39 (m, 2H), 1.04-1.12 (m, 14H), 0.90 (t, 3H, $J = 7.5$ Hz).

$^{13}$C NMR (600 MHz, CDCl$_3$) $Z$ isomer $\delta$ 151.1, 140.4, 137.6, 135.5, 111.0, 58.3, 25.6, 22.8, 17.1, 13.9, 12.1. $E$ isomer $\delta$ 151.1, 140.4, 139.2, 135.5, 112.1, 58.4, 29.3, 23.4, 17.1, 13.6, 12.0.

Exact mass calcd. for $C_{15}H_{28}NO_3Si$: 298.1838; found: 298.1830

IR (NaCl), neat: 2955, 2869, 1658, 1465, 1087 cm$^{-1}$. 
Preparation of trimethylsilyl vinyl ether (165).

A three-neck flask was equipped with a condenser, a thermometer, and an adjustable Teflon tube (destined to have one end under the surface of the reaction mixture) was connected as the receiver to a distillation apparatus containing acetaldehyde (34 mL, 0.61 mol) dried over CaSO$_4$. Acetaldehyde was distilled directly into the three-neck flask containing a solution of triethylamine (14 mL, 0.10 mol) and chlorotrimethyl silane (10.1 mL, 0.10 mol) in dry DMF (20 mL). The distillation was continued until 90% of the acetaldehyde had been distilled. The reaction mixture was then allowed to stir at rt for 48 h, after which anhydrous xylenes (10 mL) were added and the product was removed by distillation at atmospheric pressure and fractions were collected between 25-90 °C (vapour temperature) while ensuring the temperature of the crude reaction mixture did not rise above 135 °C. The combined distillate was diluted with xylenes (40 mL) and washed with H$_2$O (30 mL), cold 1.5 N HCl (3 x 15 mL), and saturated aqueous NaHCO$_3$ (10 mL). The organic layer was dried over anhydrous MgSO$_4$ and the product was purified by distillation using a 15-cm Vigreux column at 71 °C (lit bp. 74 °C) to afford (165) as clear liquid (3.3 g, 28%). The $^1$H NMR spectral data derived from 165 were identical to that reported in the literature.$^{38}$

$^1$H NMR (600 MHz, CDCl$_3$) δ 6.40 (dd, 1H, $J = 13.8, 6.05$ Hz), 4.44 (dd, 1H, $J = 13.8, 0.9$ Hz), 4.14 (dd, 1H, $J = 6.1, 0.9$ Hz), 0.20 (s, 9H).
Preparation of cyclopentenyloxytrimethylsilane (168).

To a solution of Et$_3$N (8.5 mL, 60 mmol) and chlorotrimethyl silane (3.7 mL, 29 mmol) in DMF (16 mL), was added cyclopentanone (2.0 g, 24 mmol) and the reaction mixture was heated to 80 °C and maintained at this temperature for 24 h. The reaction mixture was then cooled to rt and ether (100 mL) was added to precipitate triethylamine hydrochloride salt, which was removed by filtration. The filtrate was then washed sequentially with cold (0 °C) 2M HCl (2 x 15 mL), cold (0 °C) saturated aqueous NaHCO$_3$ (2 x 20 mL), and cold (0 °C) brine (2 x 20 mL). The organic layer was concentrated and the product was purified by distillation at 70 °C, 12 mmHg (lit. $^{39}$ bp. 70-71 °C, 12 mmHg) to provide 168 (2.42 g, 65%) as yellow liquid. The $^1$H and $^{13}$C NMR spectral data derived from 168 were identical to that reported in the literature.$^{39}$

$^1$H NMR (600 MHz, CDCl$_3$) δ 4.62 (t, 1H, $J = 2.0$ Hz), 2.23-2.28 (m, 4H), 1.85 (quintet, 2H, $J = 7.4$ Hz), 0.20 (s, 9H).

$^{13}$C NMR (600 MHz, CDCl$_3$) δ 154.9, 102.1, 33.5, 28.7, 21.3, 0.02.
Preparation of enol silaketal (171).

To a stirred solution of cyclopentenyloxytrimethylsilane (168) (102 mg, 0.65 mmol) in THF (1 mL) at -78 °C, was added methyllithium (0.78 mL, 1.0 M in Et₂O, 0.78 mmol). After 1h, the cold bath was removed and the reaction mixture was transferred into a solution of dichlorodiisopropylsilane (0.12 mL, 0.65 mmol) in THF (1 mL) at -78 °C via cannula. The resultant mixture was then allowed to warm to rt over 2.5 hours, concentrated to approximately 2 mL, and excess dichlorodiisopropylsilane was removed by distillation (47 °C, 8 mmHg) to give 0.23 g of crude mixture of the unstable monochlorosilyl enol ether, which was immediately used in the subsequent reaction. To a solution of oxazole-4-yl-methanol (125) (49 mg, 0.49 mmol) in CH₂Cl₂ (1 mL) at -10 °C was added a solution of the crude monochlorosilyl enol ether (0.23 g) and triethylamine (0.10 mL, 0.75 mmol) in CH₂Cl₂ (1 mL) and the reaction mixture was allowed to warm to rt overnight. The mixture was then poured into H₂O (5 mL) and extracted with Et₂O (15 x 3 mL). The organic layer was concentrated and the crude product was purified by flash column chromatography (hexanes-EtOAc, 19:1) to afford the enol silane 171 as clear oil (80 mg, 55%).
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.85 (s, 1H), 7.60 (s, 1H), 4.85 (d, 2H, $J = 1.3$ Hz), 4.62 (t, 1H, $J = 2.0$ Hz), 2.28-2.32 (m, 2H), 2.22-2.26 (m, 2H), 1.85 (quintet, 2H, $J = 7.4$), 1.10-1.15 (m, 2H), 1.05-1.07 (m, 12H).

$^{13}$C NMR (600 MHz, CDCl$_3$) δ 154.3, 151.0, 140.5, 135.6, 103.1, 58.5, 33.2, 28.6, 21.3, 17.1, 12.2.

Exact mass calcd for C$_{15}$H$_{25}$NO$_3$NaSi: 318.1501; found: 318.1495

IR (NaCl) neat: 2946, 2868, 1648, 1464, 1341, 1101, 1060 cm$^{-1}$. 
Preparation of enol silaketal (173).

To a stirred solution of dichlorodiisopropylsilane (100 mg, 0.54 mmol) in DMF (5 mL), was added triethylamine (0.15 mL, 1.08 mmol) and isobutyaldehyde (40 mg, 0.54 mmol) and the mixture was heated to 80 °C and maintained at this temperature for 24h. After this time, hexanes were added to precipitate triethylamine hydrochloride salt, which was removed by filtration, and the filtrate was concentrated to provide the unstable monochlorosilyl enol ether as a brown residue. To a solution of crude monochlorosilyl enol ether in CH₂Cl₂ (5 mL), was added triethylamine (0.11 mL, 0.81 mmol) and oxazole-4-yl-methanol (125) (54 mg, 0.54 mmol) and the reaction mixture was stirred at rt overnight. The mixture was then diluted with H₂O (5 mL) and washed with Et₂O (15 mL x 3). The combined organic layers were washed with brine (5 mL x 1) and concentrated. The crude product was purified by flash column chromatography (hexane-EtOAc, 19:1) to afford 173 as a yellow oil (65 mg, 43%).

¹H NMR (600 MHz, CDCl₃) δ 7.85 (s, 1H), 7.60 (s, 1H), 6.16-6.18 (m, 1H), 4.83 (d, 2H, J = 1.3 Hz), 1.61 (d, 3H, J = 1.3 Hz), 1.52 (d, 3H, J = 1.3 Hz), 1.07-1.09 (m, 14H).
$^{13}$C NMR (600 MHz, CDCl$_3$) $\delta$ 151.0, 140.5, 135.4, 132.6, 113.7, 58.3, 19.2, 17.0, 14.6, 17.1, 12.0.

Exact mass calcd for C$_{14}$H$_{26}$NO$_3$Si: 284.1681; found: 284.1675.

IR (NaCl), neat: 2946, 2868, 1686, 1465, 1341, 1174 cm$^{-1}$. 
Preparation of the \((E)\)-enol silaketel \(162\).

To a 2 mL oven-dried glass vial, was added \textit{trans}-2-pentenal (98 mg, 1.2 mmol) and chlorodiisopropylsilane (181 mg, 1.2 mmol) followed by Wilkinson’s catalyst (56 mg, 0.06 mmol). The vial was tightly capped and the reaction mixture was then stirred at rt for 48 h. After this time, pentane (10 mL) was added and the mixture was filtered through a cotton plug and concentrated to approximately 2 mL to yield the crude monochlorosilyl enol ether, which was immediately used in the subsequent reaction. To a solution of oxazole-4-yl-methanol \(125\) (60 mg, 0.60 mmol) in \(\text{CH}_{2}\text{Cl}_2\) (5 mL) at -10 °C, was added a solution of the crude monochlorosilyl enol ether and triethylamine (0.13 mL, 0.90 mmol) in \(\text{CH}_{2}\text{Cl}_2\) (5 mL) and the reaction was allowed to warm to rt overnight. After this time, the reaction mixture was poured into \(\text{H}_2\text{O}\) (5 mL) and extracted with \(\text{Et}_2\text{O}\) (15 mL x 3). The combined organic layers were concentrated and the crude product was purified by flash column chromatography (hexanes-EtOAc, 33:1) to afford the enol silane \(162\) as clear oil (102 mg, 56%).

\(^1\text{H} \text{NMR} \ (600 \text{ MHz}, \ \text{CDCl}_3) \ \delta \ 7.85 \ (s, \ 1\text{H}), \ 7.60 \ (s, \ 1\text{H}), \ 6.33 \ (d, \ 1\text{H}, J = 12.1 \text{ Hz}), \ 5.06 \ (td, \ 1\text{H}, J = 12.1, \ 7.7 \text{ Hz}), \ 4.83 \ (s, \ 2\text{H}), \ 1.84 \ (q, \ 2\text{H}, J = 7.7 \text{ Hz}), \ 1.32 \ (m, \ 2\text{H}), \ 1.04-1.10 \ (m, \ 14\text{H}), \ 0.86 \ (t, \ 3\text{H}, J = 7.5 \text{ Hz}).
$^{13}$C NMR (600 MHz, CDCl$_3$) $\delta$ 151.1, 140.4, 139.2, 135.5, 112.1, 58.4, 29.3, 23.4, 17.1, 13.6, 12.0.

Exact mass calcd for C$_{15}$H$_{28}$NO$_3$Si: 298.1838; found: 298.1830

IR (NaCl), neat: 2945, 2872, 1661, 1467, 1094 cm$^{-1}$. 
Preparation of (+/-) 2-hydroxymethyl-1-methyl-5-propylpiperidine-3,4-diol (183).

To a stirred solution of the enol silane 162 (100 mg, 0.34 mmol) in CH$_2$Cl$_2$ (5 mL) at 45 °C, was added trimethyloxonium tetrafluoroborate (49 mg, 0.34 mmol) and the reaction mixture was stirred at reflux for 1.5 hours. After this time, the reaction mixture was concentrated to approximately 0.5 mL, MeOH (5 mL) was added and the mixture was cooled to -78 °C. NaBH$_4$ (58 mg, 1.7 mmol) was then added and the reaction mixture was allowed to warm to rt overnight, then it was concentrated to dryness and HCl (4 mL, 2M in Et$_2$O, 8 mmol) was added and the resultant solution was stirred at rt for 15 minutes, resulting in the formation of white solid. The white solid was filtered to provide the hydrochloride salt of 183. Purification of the crude product by flash column chromatography (chloroform-MeOH-NH$_4$OH, 80:19:1) afforded 183 as a clear oil (20 mg, 29%).

$^1$H NMR (600 MHz, D$_2$O) δ 3.92 (dd, 1H, $J = 13.3$, 2.0 Hz), 3.85 (dd, 1H, $J = 13.3$, 2.0 Hz), 3.37 (t, 1H, $J = 9.6$ Hz), 3.15 (t, 1H, $J = 9.6$ Hz), 2.94 (dd, 1H, $J = 12.4$, 3.0 Hz ), 2.37 (s, 3H), 2.10 (t, 1H, $J = 12.4$ Hz), 2.04-2.06 (m, 1H), 1.62-1.66 (m, 1H), 1.57-1.62 (m, 1H), 1.37-1.44 (m, 1H), 1.21-1.29 (m, 1H), 1.12-1.18 (m, 1H), 0.89 (t, 3H, $J = 7.4$ Hz).
$^{13}$C NMR (600 MHz, CDCl₃) δ 76.9, 71.2, 68.3, 58.5, 57.6, 40.9, 39.3, 30.9, 19.0, 13.4.

Exact mass calcd for C₁₀H₂₂NO₃: 204.1599; found: 204.1601.

IR (NaCl), D₂O: 3341, 2529, 1442, 1212 cm⁻¹.
Figure 22. $^{13}$C NMR spectrum of (+/-) 2-hydroxymethyl-1-methyl-5-propylpiperidine-3,4-diol (183) (recorded in D$_2$O at 600 MHz).
Figure 23. COSY spectrum of (+/-) 2-hydroxymethyl-1-methyl-5-propylpiperidine-3,4-diol (183) (recorded in D₂O at 600 MHz).
**Figure 24.** HSQC spectrum of (+/-) 2-hydroxymethyl-1-methyl-5-propylpiperidine-3,4-diol (183) (recorded in D$_2$O at 600 MHz).
Figure 25. HMBC spectrum of (±) 2-hydroxymethyl-1-methyl-5-propylpiperidine-3,4-diol (183) (recorded in D$_2$O at 600 MHz).
Table 7. Selected nOe observed for (+/-) 2-hydroxymethyl-1-methyl-5-propylpiperidine-3,4-diol (183).

![Molecular structure](image)

<table>
<thead>
<tr>
<th>nOe Correlation</th>
<th>% nOe Enhancement</th>
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<td>H1ax-H3</td>
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6: REFERENCE LIST