ANIONIC REARRANGEMENT OF 2-BENZYLOXYPYRIDINE DERIVATIVES AND A
SYNTHETIC APPROACH TO ALDINGENIN B

By

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This manuscript is dedicated to my mother, father, brother and all my friends who supported me all the time.
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ABSTRACT

[1,2]-Anionic rearrangements are important tools for altering the complexity of molecules at hand. In Part I of this dissertation, an anionic rearrangement of 2-benzylloxypyridine is described. Pyridine-directed metallation of the benzylic carbon leads to 1,2-migration of pyridine via a postulated associative mechanism (addition / elimination). Several aryl pyridyl carbinols were obtained in high yields. A formal synthesis of carbinoxamine, an antihistamine drug used for the treatment of seasonal allergies and hay fever, emerges from this methodology. As an update, the [1,2]-anionic rearrangement of benzyl 2-pyridyl ethers can also be accessed by a distinct and unusual mechanism: addition of alkyllithium reagents to α-(2-pyridyloxy)-styrene triggers anionic rearrangement to tertiary pyridyl carbinols. This will be presented in Chapter 4 and the process is explained by invoking contraelectronic, pyridine-directed carbolithiation of the enol ether π-system.

Part II of this dissertation is focused on a synthetic approach to aldingenin B. The synthesis of the tricyclic core of aldingenin B from a key internal alkyne was completed. Synthesis of alkynes by fragmentation is an on-going interest of the Dudley lab. One current goal is to apply our methodology in conjunction with an innovative oxidative alkyne ketalization to achieve a short and efficient synthesis of aldingenin B. The specific goal for this dissertation was to prepare a model alkyne by conventional methods and establish the feasibility of the oxidative alkyne ketalization. The preparation and selenium-mediated cyclo-ketalization of an alkyne-diol will be described as a model study for the synthesis of aldingenin B in Chapter 8. The oxidative cyclization is a simplifying transformation for aldingenin B, as it provides a convenient method for generating the tricyclic core of the natural product from a functionalized carbocycle. Some preliminary experiments to guide future efforts for completing the synthesis of aldingenin B will be presented in Chapter 9.
PART 1: ANIONIC REARRANGEMENT OF 2-BENZYL-OXOPYRIDINE DERIVATIVES

CHAPTER ONE

BACKGROUND OF [1,2]–ANIONIC REARRANGEMENTS

[1,2]-Anionic rearrangements, such as those pioneered by Wittig\(^1\) and Brook\(^2\), are important tools for altering the complexity of molecules. Rearrangement reactions interconvert pairs of structural isomers; this interconversion is especially valuable if one of the two isomers is more accessible than the other. Parallels can be drawn between the Wittig and Brook reactions as well as the new anionic rearrangement of pyridyl ethers discovered in our lab (Figure 1). This new [1,2]-anionic rearrangement of 2-benzyloxypyridine derivatives will be discussed in this manuscript after a brief introduction of the [1,2]-Wittig rearrangement and [1,2]-Brook rearrangement.

\[\begin{align*}
\text{(A)} & \quad \text{O}^\ominus & \quad \text{R'} & \quad \text{M} & \quad \text{R} \\
\text{R} & \quad \text{O} & \quad \text{R'} & \quad \text{M} & \quad \text{R} \\
\text{Wittig rearrangement} & \quad \text{1,2-migration of an alkyl radical} \\
\text{(B)} & \quad \text{M} & \quad \text{O} & \quad \text{R} & \quad \text{SiR}_3 & \quad \text{R} \\
\text{R} & \quad \text{SiR}_3 & \quad \text{O} & \quad \text{R} & \quad \text{M} \\
\text{Brook rearrangement} & \quad \text{1,2-migration of a trialkysilyl group} \\
\text{(C)} & \quad \text{N} & \quad \text{M} & \quad \text{O} & \quad \text{R} \\
\text{R} & \quad \text{M} & \quad \text{N} & \quad \text{R} \\
\text{this work} & \quad \text{1,2-migration of a pyridine ring} \\
\end{align*}\]

Figure 1: Representative [1,2]-Anionic Rearrangement
1.1 [1,2]-Wittig Rearrangement

In 1942, Georg Wittig and Lisa Löhman reported the migration of an alkyl group from an oxygen center to the α-carbanion center in the isomerization reaction of a benzylic ether with phenylthium (Figure 2, Equation 2a).\(^1\) This is the first example of the Wittig rearrangement, which involves conversion of an α-alkoxy-carbanion into a more stable oxanion with concomitant migration of the alkyl group. While studying this new rearrangement reaction, it was found that the rearrangement of allylic ethers can follow a different pathway (Figure 2, Equation 2b). This [2,3]-sigmatropic version of the carbanion rearrangement is now called the [2,3]-Wittig rearrangement\(^3\), while the original is often called the [1,2]-Wittig rearrangement\(^4\).

![Figure 2: [1,2]-Wittig Rearrangement and [2,3]-Wittig Rearrangement](image)

Experimental evidence generally points to a stepwise, dissociative mechanism for the [1,2]-Wittig rearrangement. The mechanism involves carbon-oxygen-bond homolysis and recombination of the resulting pair of intermediate radicals (cf. Figure 1, Scheme 1A).\(^5\) In the 1960s, Schöllkopf and co-workers observed that the optically active benzyl 2-butyl ether and benzyl 2-phenyl-2-butyl ether afforded the corresponding alcohol products with retention of configuration in 20% and 80% enantiomeric excess, respectively (Figure 3).\(^6\) This finding further supports a dissociative mechanism.
In order to illustrate the scope and limitation of the [1,2]-Wittig rearrangement, the Nakai group designed a series of reactions using tin/lithium trans-metalation to induce the rearrangement of various ethers. They first employed a propyl group as the carbanion terminus (R=C_2H_5, Figure 4, Equation 4b) and a benzyl group as the migrating group (R'=Bn, Figure 4, Equation 4b) in the Wittig reaction and obtained the rearrangement product in 90% yield (Figure 4, Equation 4b). This is in contrast to the observation that the Still group found, which was that no rearrangement occurred when the carbanion terminus was a methyl group (R'=H, Figure 4, Equation 4c). Instead of the Wittig product, the Still group only obtained the addition product of the initial carbanion without rearrangement by quenching the reaction with cyclohexanone (Figure 4, Equation 4c). It indicates that in [1,2]-Wittig rearrangement, the secondary carbanion terminus is more reactive than the primary carbanion terminus. However, even with a secondary carbanion terminus (R=C_7H_15, Figure 4, Equation 4d), the isopropyl ether did not rearrange (Figure 4, Equation 4d). The comparison between equations 4c and 4d in Figure 4 shows that the benzyl group is a better migrating group than isopropyl group. The last two reactions that the Nakai group used to define the structure requirements were carried out on two tetrahydrofuranyl ethers (Figure 4, equation 4e & 4f). For the two tetrahydrofuranyl ethers with a benzylic carbanion terminus (R=Ph, Figure 4, Equation 4e), the rearrangement product was observed; in contrast, with a propyl group as the counterpart (R=C_2H_5, Figure 4, Equation 4f), no rearrangement product was observed. These two reactions indicate that a benzylic carbanion terminus has higher reactivity in Wittig rearrangement than secondary carbanion terminus.

All of these observations reveal that [1,2]-Wittig rearrangement requires at least one, if not both, of the radical-stabilizing factors in either the carbanion terminus or the migrating group. The migratory aptitude of the R’ group decreases in the following order: benzyl > tertiary alkyl > secondary alkyl > primary alkyl; while the migratory aptitude of the carbanion terminus
decreases in the same order: benzylic carbanion terminus > secondary carbanion terminus > primary carbanion terminus.

\[
\begin{align*}
\text{M} & \quad \text{R'O} \quad \text{R} \\
\text{R'O} \quad \text{R} & \quad \rightarrow \quad \left[ \begin{array}{c}
\text{R'}^+ \\
\text{O} \quad \text{M} \quad \text{R}
\end{array} \right] \\
\text{R'}^+ \quad \text{M} & \quad \rightarrow \quad \text{R'} \quad \text{MO} \quad \text{R}
\end{align*}
\]

- 1,2-migration of an alkyl radical
- Wittig rearrangement

\[\text{SnBu}_3 \quad \text{BnO} \quad \text{C}_2\text{H}_5 \quad \text{THF} \quad n-\text{BuLi} \quad \text{BnO} \quad \text{C}_2\text{H}_5 \quad \text{yield:} \quad 90\% \quad (b)\]

\[\text{SnBu}_3 \quad \text{BnO} \quad \text{C}_2\text{H}_5 \quad \text{THF} \quad n-\text{BuLi} \quad \text{BnO} \quad \text{yield:} \quad 98\% \quad (c)\]

\[\text{SnBu}_3 \quad \text{i-PrO} \quad \text{C}_7\text{H}_{15} \quad \text{THF} \quad n-\text{BuLi} \quad \text{i-PrO} \quad \text{C}_7\text{H}_{15} \quad \text{yield:} \quad 75\% \quad (d)\]

\[\text{SnBu}_3 \quad \text{O} \quad \text{Ph} \quad \text{THF} \quad n-\text{BuLi} \quad \text{O} \quad \text{Ph} \quad \text{yield:} \quad 16\% \quad (e)\]

\[\text{SnBu}_3 \quad \text{O} \quad \text{C}_2\text{H}_5 \quad \text{THF} \quad n-\text{BuLi} \quad \text{O} \quad \text{C}_2\text{H}_5 \quad \text{yield:} \quad 40\% \quad (f)\]

**Figure 4:** Study for the Scope Of the [1,2]-Wittig Rearrangement by Nakai

The [1,2]-Wittig rearrangement provides insight into the reactivity profile of reactive carbanion intermediates, but its value in synthesis is limited due to difficulties associated with guiding complex molecular systems along the high-energy radical reaction pathway. As a result,
there are only a few examples of the purely synthetic application of the [1,2]-Wittig rearrangement. In 1987, Schreiber and co-workers employed the [1,2]-Wittig rearrangement in the synthesis of syn-1,3-diol monoethers from β-alkoxyalkyl allyl ethers. The syn-1,3-diol products were obtained in 14-32% yield with 90-95% diastereoselectivity (Figure 5). 10

![Figure 5: Synthetic Application of the [1,2]-Wittig Rearrangement](image)

1.2 [1,2]-Brook Rearrangement

In the [1,2]-Brook rearrangement, 11 it is a silyl group that migrates between the carbinol center to the adjacent oxygen atom (Figure 6). The R group can be either alkyl or aryl groups and various trialkyl silyl groups rearrange (SiMe₃, SiEt₃, SiMe₂t-Bu, etc.). Silyl migration is reversible (see the retro-Brook 12 reaction) and likely proceeds via a pentavalent silicate intermediate. The first retro-Brook reaction was reported by Speier in 1953 13 with later studies by West et al 12.

![Figure 6: [1,2]-Brook Rearrangement and Retro-Brook Rearrangement](image)

In order to elucidate the mechanism of the retro-Brook rearrangement, Linderman and Ghannam designed several reactions on different stannanes. 14 In these reactions, transmetalations
occurred first and the rearrangement was driven by the formation of the more stable lithium alkoxide. The Linderman group showed that the retro-Brook reaction is an intramolecular process by carrying out a cross-over experiment (Figure 7). A 1 : 1 mixture of two stannanes were treated with 3 equiv. of butyllithium at -78 °C. The reaction was complete for both starting materials after 15 minutes and only the two intramolecular products were obtained in high yields. By GC analysis of the crude reaction product mixture, no trace amount of any cross-over product was observed.

![Figure 7: Evidence for an Intramolecular Process of the Retro-Brook Rearrangement](image)

Linderman and Ghannam also found evidence to support the conclusion that the rearrangement reaction does not involve radical intermediates in the reaction pathway. A cyclopropyl-substituted stannane was synthesized for this purpose (Figure 8). Cyclopropyl-substituted radicals rapidly undergo ring opening reactions. If there are radical intermediates involved in the reaction pathway in the retro-Brook rearrangement, the cyclopropyl ring is easily opened to yield an enol ether as the product. However, only the alcohol product was observed in 45% yield. Both GC and MS analysis showed no trace amount of the enol ether product.
Figure 8: Evidence for No Radical Intermediates Involved in the Retro-Brook Rearrangement

Recently, the retro-Brook rearrangement has received renewed interest, in part due to acylsilane methodologies that produce $\alpha$-silyl alcohol substrates for the [1,2]-Brook reaction.\(^\text{16}\) One of the synthetic applications for the retro-Brook rearrangement is the synthesis of optically active ($\alpha$-hydroxyalkyl)alkylsilanes (Figure 9).\(^\text{14}\) The synthesis started from the enantioselective reduction of a hexanal, followed by TMS protection. The retro-Brook rearrangement reaction finally provided the $\alpha$-silyl alcohol product in 91% yield and 97% ee. The rearrangement occurred with retention of configuration and without racemization.

Figure 9: Synthetic Application of the retro-Brook Rearrangement
2.1 Introduction: Known chemistry of 2-benzyloxy pyridine

2-Benzyloxy pyridine is readily available from coupling 2-chloropyridine with the potassium salt of benzyl alcohol in refluxing toluene. It can be methylated with methyl triflate in toluene to yield 2-benzyloxy-1-methylpyridinium triflate (Bn-OPT), which is a commercially available benzylation reagent patented by the Dudley group (Figure 10). This triflate salt is a white crystalline solid, which is stable to be stored at room temperature. It can be used to protect alcohols as benzyl ethers or carboxylic acids as benzyl esters under mild conditions.

\[ \text{OH} \quad \text{KOH} \quad \text{18-crown-6} \quad \text{toluene, reflux} \quad \text{MeOTf} \quad \text{toluene} \]

**Figure 10:** Synthesis of 2-Benzyloxy-1-methylpyridinium Triflate (Bn-OPT)

2.1.1 Benzylation of alcohols by 2-benzyloxy-1-methylpyridinium triflate (Bn-OPT)

Solutions of 2-benzyloxy-1-methylpyridinium triflate (Bn-OPT) with primary, secondary, or tertiary alcohols under mild heating gave rise to the corresponding benzyl ethers. The best condition developed for the efficient benzylation is to stir the mixture in PhCF₃ at 83 °C for 24 h.
The typical acid scavenger added to the reaction mixture is magnesium oxide. The yields of the benzylisation reactions are generally above 80%.

![Chemical structure](image)

**Figure 11:** Benzylisation of Alcohols by 2-Benzylxyloxy-1-Methylpyridinium Triflate (Bn-OPT)

2.1.2 Benzylisation of Carboxylic acids by 2-benzylxyloxy-1-methylpyridinium triflate (Bn-OPT)

After being recognized as a successful benzyl transfer reagent, 2-benzylxyloxy-1-methylpyridinium triflate (Bn-OPT) was then used to prepare benzyl esters from carboxylic acids. The conditions optimized for benzylating alcohols were first employed for the benzylisation of carboxylic acids, but MgO was proved to be a poor acid scavenger. Actually, the reaction results were better (fewer byproducts) in the absence of MgO added. After a brief screening of different bases, it was found that triethylamine (Et$_3$N) provided complete conversion to benzyl esters from carboxylic acids, and the formation of the byproduct (Bn$_2$O) was completely suppressed (Figure 12). As a result, the optimized condition, which was to heat a PhCF$_3$ solution of carboxylic acid with 2-benzylxyloxy-1-methylpyridinium triflate and triethylamine (Et$_3$N) at 83 °C for 24h, gave the corresponding benzyl esters in 81-99% yield.
As mentioned above, 2-benzyloxypyridine can be converted into 2-benzyloxy-1-methylpyridinium triflate for use as a benzyl transfer reagent. It can also be used directly to protect alcohols. The Dudley group provided a revised benzyl transfer protocol for alcohols, in which N-methylation of 2-benzyloxypyridine produced the active benzyl transfer reagent in situ (Figure 13). The new protocol is as follows: a mixture of the alcohol substrate, 2-benzyloxypyridine and magnesium oxide in toluene was cooled to 0 °C and treated with methyl triflate. The resulting reaction mixture was allowed to warm up to room temperature and then heated at 90 °C for 24 h. The yields for this one-step protocol were comparable to those using 2-benzyloxy-1-methylpyridinium triflate as the benzyl transfer reagent. Trifluorotoluene was the preferred solvent and it was uniquely effective in one case, although toluene was an appropriate solvent for most cases.

![Figure 12: Benzylation of Carboxylic Acids by Benzylloxypyridinium Triflate (Bn-OPT)](image)

**Figure 12:** Benzylation of Carboxylic Acids by Benzylloxypyridinium Triflate (Bn-OPT)

**2.1.3 Benzylation of alcohols by methylation of 2-benzyloxypyridine**

![Figure 13: Benzylation of Alcohols by Methylation of 2-Benzyloxypyridine](image)

**Figure 13:** Benzylation of Alcohols by Methylation of 2-Benzyloxypyridine
After the introduction about the known chemistry of 2-benzyloxypyridine, we will talk about how the new [1,2]-anionic rearrangement was discovered while we studied the synthetic chemistry of 2-benzyloxypyridine.

2.2 Discovery of the reaction

The novel [1,2]-anionic rearrangement of 2-alkoxy pyridines (Figure 14) was identified while studying the synthetic chemistry of 2-benzyloxypyridine (1a, Figure 15) as part of our interest in developing electrophilic reagents for the synthesis of arylmethyl ethers and esters.\textsuperscript{19} We had envisioned making derivatives of 1a via directed metalation using the complex-induced proximity effect (CIPE),\textsuperscript{20} followed by trapping with electrophiles (1a $\rightarrow$ 3 $\rightarrow$ 4, Figure 15, not observed). Instead, prior to addition of the electrophile, we observed an unexpected product: phenyl-(2-pyridyl)-methanol (2a, Figure 15).

\[ \text{Figure 14: [1,2]-Anionic Rearrangement of 2-Benzoxypyridine} \]

\[ \text{Figure 15: Discovery of the Anionic Rearrangement of 2-Benzoxypyridine 1a} \]
Rearrangement of benzyllithium 3 accounts for the formation of α-pyridyl alcohol 2a. The mechanism likely involves an associative process, akin to the Brook pathway, in which the migrating carbon atom transiently expands to a tetrahedral (sp$^3$) intermediate (cf. 5, Scheme 15) that is hypervalent relative to the trigonal planar (sp$^2$) ground state structure. Complexation between the pyridine nitrogen and the lithium ion is maintained throughout the nucleophilic aromatic substitution (addition / elimination) of the electron-deficient pyridine ring. Related [1,2]-anionic rearrangements of α-carbamoyloxy-carbanions (from directed metallation of carbamates) are known, as is the [1,4]-migration of pyridine rings onto urea-derived α-amino-carbanions.

2.3 Development of the reaction (Optimization & Scope)

α-Pyridyl alcohols (2) are of general interest in synthesis and medicinal chemistry. For example, the Ducharme group has synthesized different 2-pyridinemethanol derivatives as a novel series of phosphodiesterase-4 (PDE4) inhibitors, which can be used for the treatment of asthma, chronic obstructive pulmonary disease (COPD) and atopic dermatitis. The α-pyridyl alcohol bellow (Figure 16) has been shown to exhibit excellent in vitro activity and good efficacy in guinea pig and sheep models of bronchoconstriction. In order to gain access to different α-pyridyl alcohols, the [1,2]-anionic rearrangement pathway can be employed. To the best of our knowledge, the [1,2]-anionic rearrangement of 2-alkoxypyridines has not been observed previously.

**Figure 16:** Bioactive α-Pyridyl Alcohol
Key experiments related to identifying optimal conditions for the n-butyllithium-promoted rearrangement of 2-benzyloxypyridine are recounted in Table 1. The efficiency of the reaction is highly sensitive to minor changes in the reaction protocol. Full conversion requires a slight molar excess of \( n \)-BuLi (1.2 equiv), but too much base is detrimental (Table 1, Entries 1–3 and 7). In order to understand this result better, MeOD was used to quench the reaction. When using specifically 1.2 equiv of \( n \)-BuLi, a reaction temperature of \(-60^\circ C\) provides results superior to slightly higher or lower reaction temperatures (Table 1, Entries 4–6). Optimally, treatment of 2-benzyloxypridine (1a) in THF \(^i\) with 1.2 equiv of \( n \)-BuLi at \(-60^\circ C\) furnishes phenyl-(2-pyridyl)-methanol (1a \(\rightarrow\) 2a) in 85% yield (Table 1, entry 5). The delicate balance of reaction conditions required for optimal results is indicative of a complicated reaction pathway. It appears that \( n \)-BuLi competitively metallates both the substrate and the product.\(^{ii}\)

\(^i\) A brief screening of other solvents and/or co-solvents — Et\(_2\)O, toluene, hexane, HMPA, DMPU — failed to identify a superior option.

\(^{ii}\) Deuterium is incorporated to a minor extent into the product alcohol (at the carbinol carbon) when the reaction is quenched with MeOD. Thus, in situ-metalation of the product must be occurring, which consumes \( n \)-butyllithium and explains the need for a precise excess of \( n \)-butyllithium for optimal results.
Table 1. Optimization of the n-Butyllithium-promoted [1,2]-Anionic Rearrangement of 2-Benzylxopyridine (1)

<table>
<thead>
<tr>
<th>entry</th>
<th>n-BuLi</th>
<th>Temp</th>
<th>Recovery of 1a(^a)</th>
<th>Yield of 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1 equiv</td>
<td>–78°C to rt</td>
<td>5–10%</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>1.2 equiv</td>
<td>–78°C to rt</td>
<td>—(^b)</td>
<td>77%</td>
</tr>
<tr>
<td>3</td>
<td>2.0 equiv</td>
<td>–78°C to rt</td>
<td>—(^b)</td>
<td>n.d. (^c)</td>
</tr>
<tr>
<td>4</td>
<td>1.2 equiv</td>
<td>–78°C</td>
<td>42%</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>1.2 equiv</td>
<td>–60°C</td>
<td>—(^b)</td>
<td>85%</td>
</tr>
<tr>
<td>6</td>
<td>1.2 equiv</td>
<td>–40°C</td>
<td>17%</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>1.3 equiv</td>
<td>–60°C</td>
<td>—(^b)</td>
<td>77%</td>
</tr>
</tbody>
</table>

\(^a\) Estimated by 1H NMR spectroscopy. \(^b\) Complete consumption of 1a. \(^c\) Significant decomposition was apparent in the TLC analysis of the reaction mixture.

Changing the substrate from 2-benzyloxyopyridine to related derivatives changes the kinetic profile of the reaction; the conditions described in entry 5 of Table 1 are not generalizable (Table 2). For example, the reaction conversion drops significantly for methoxy-substituted ethers 1b and 1c, likely due to competing metallation pathways, although the yields of 2 based on recovered starting material remain high (estimated >95%, Table 2, Entries 1 and 2). \(\alpha\)-Branching in 1d was detrimental in other ways (Table 2, Entry 3): conversion to tertiary alcohol 2d was incomplete, and a new by-product emerged, resulting from addition of \(n\)-butyllithium to the pyridine ring.\(^iii\)

\(^iii\) The byproduct was determined to be 2-butyl-6-(1-phenyl-ethoxy)-pyridine (shown below), from addition of \(n\)-butyllithium to the pyridine ring followed by autoxidation.
Table 2. Substituent Effects and An Alternative Set of Conditions for Promoting the [1,2]-Anionic Rearrangement

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>R</th>
<th>Yield of 1</th>
<th>base</th>
<th>Temp</th>
<th>Yield of 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-MeO-C6H4</td>
<td>H</td>
<td>90% (1b)</td>
<td>(n)-BuLi</td>
<td>–60 °C</td>
<td>48%(^a) (2b)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeO-C6H4</td>
<td>H</td>
<td>92% (1c)</td>
<td>(n)-BuLi</td>
<td>–60 °C</td>
<td>33%(^a) (2c)</td>
</tr>
<tr>
<td>3</td>
<td>C6H5</td>
<td>Me</td>
<td>96% (1d)</td>
<td>(n)-BuLi</td>
<td>–60 °C to rt</td>
<td>24%(^b) (2d)</td>
</tr>
<tr>
<td>4</td>
<td>C6H5</td>
<td>Me</td>
<td>96% (1d)</td>
<td>LDA(^c)</td>
<td>rt</td>
<td>95% (2d)</td>
</tr>
</tbody>
</table>

\(^a\) Mass balance was recovered starting material (52% of 1b and 67% of 1a). \(^b\) Starting material and undesired by-products recovered. \(^c\) 1.3 equiv of LDA employed.

Rather than attempt to re-optimize the reaction protocol for each substrate (1 → 2) individually, a unified set of conditions with applicability across a broader range of substrates was sought. Lithium diisopropylamide (LDA) was the preferred choice from among several\(^iv\) potential bases (Table 2, entry 4).

\(^iv\) The bases included \(s\)-BuLi, \(t\)-BuLi, PhLi, BnLi, \(Ph_3\)CLi, LDA, LiHMDS, LiDMSO, LiN(OMe)Me, LiTMP, LiH, and alkyl Grignard reagents. LDA was sufficiently reactive to promote the rearrangement, and no competing addition to the pyridine ring was observed. After brief optimization (not shown) and screening against multiple substrates, 1.3 equiv of LDA at rt emerged as the optimal set of conditions.
The reaction conditions involving LDA as the base instead of \( n \)-BuLi were then used to explore the scope of the rearrangement reaction (Table 3). The title substrate (2-benzylxopyridine, 1a) rearranged to 2a in 98% yield (Table 3, Entry 1). Electron-donating groups on the benzene ring are well tolerated: rearrangement of substrates with either an ortho-methoxy (1b) or para-methoxy (1c) substituent proceeded each in 99% yield (Table 3, Entries 2 and 3). The yield of 2 decreased to 70% when the electron-withdrawing para-chloro substituent was in place (1f \( \rightarrow \) 2f, Table 3, Entry 5), and para-trifluoromethylated substrate 1e decomposed under the reaction conditions (Table 3, Entry 4).

For making tertiary \( \alpha \)-pyridyl alcohols (Table 3, Entries 6–10), the anionic rearrangement seems to depend on whether or not metallation occurs. Sterics and kinetic acidity play an

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**Table 3. Scope and Limitations of the LDA-promoted [1,2]-Anionic Rearrangement of Arylalkoxypyridines**

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>R</th>
<th>Yield of 1</th>
<th>Yield of 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C(_6)H(_5)</td>
<td>H</td>
<td>95% (1a)</td>
<td>98% (2a)</td>
</tr>
<tr>
<td>2</td>
<td>2-MeO-C(_6)H(_4)</td>
<td>H</td>
<td>90% (1b)</td>
<td>99% (2b)</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C(_6)H(_4)</td>
<td>H</td>
<td>92% (1c)</td>
<td>99% (2c)</td>
</tr>
<tr>
<td>4</td>
<td>4-CF(_3)-C(_6)H(_4)</td>
<td>H</td>
<td>75% (1e)</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>H</td>
<td>93% (1f)</td>
<td>70% (2f)</td>
</tr>
<tr>
<td>6</td>
<td>C(_6)H(_5)</td>
<td>Me</td>
<td>96% (1d)</td>
<td>95% (2d)</td>
</tr>
<tr>
<td>7</td>
<td>C(_6)H(_5)</td>
<td>Et</td>
<td>96% (1g)</td>
<td>86%(^a) (2g)</td>
</tr>
<tr>
<td>8</td>
<td>C(_6)H(_5)</td>
<td>Cy(^b)</td>
<td>63% (1h)</td>
<td>20%(^a) (2h)</td>
</tr>
<tr>
<td>9</td>
<td>C(_6)H(_5)</td>
<td>t-Bu</td>
<td>57% (1i)</td>
<td>0%(^a)</td>
</tr>
<tr>
<td>10</td>
<td>C(_6)H(_5)</td>
<td>Ph</td>
<td>99% (1j)</td>
<td>97% (2j)</td>
</tr>
</tbody>
</table>

\(^a\) Mass balance was recovered starting material (1). \(^b\) Cy = cyclohexyl
important role (Table 3, Entries 6–9); the reaction conversion of alkyl-substituted pyridyl ethers and the isolated yield of the α-pyridyl alcohol relate inversely to the size of the branching substituent at the benzylic ether position. The relevance of thermodynamic acidity can be inferred from entry 10; 2-(diphenylmethoxy)-pyridine (1j), presumably the most acidic of the substrates included in Table 3, furnishes tertiary alcohol 2j in 97% yield.

2.4 Application of the reaction (Synthesis of Carbinoxamine)

α-Pyridyl alcohol (±)-2f (see Table 3, entry 5) has been converted in one step into (±)-carbinoxamine26 (Figure 17), the resolution of which is accomplished using d-tartaric acid.27, 28 Carbinoxamine is an antihistamine drug (histamine H1 antagonist) used for the treatment of seasonal allergies and hay fever.29

Figure 17. Synthesis of Carbinoxamine

In conclusion, a [1,2]-anionic rearrangement of 2-benzyloxypyridine and its derivatives is reported. According to our postulated mechanism, pyridine-directed metallation at the benzylic position triggers an intramolecular nucleophilic aromatic substitution reaction (addition / elimination) via an intermediate spiroepoxide (5, Figure 15). This new discovery provides a link between two disparate reaction pathways: the [1,2]-Wittig rearrangement (in which arene migration is rare) and the tandem directed metallation / nucleophilic acyl substitution methodologies developed by Snieckus, Gawley, Clayden, and others.21,22 Pyridyl ethers 1 are
readily available from the corresponding alcohols and 2-chloropyridine. A variety of secondary and tertiary α-pyridyl alcohols were prepared in good to excellent yield.
CHAPTER THREE

EXPERIMENTAL: [1,2]-ANIONIC REARRANGEMENTS OF 2-BENZYLOXYPYRIDINE DERIVATIVES

General information

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on a 300 MHz spectrometer using CDCl$_3$ as the deuterated solvent. The chemical shifts ($\delta$) are reported in parts per million (ppm) relative to internal TMS (0 ppm for $^1$H NMR) or the residual CDCl$_3$ peak (7.26 ppm for $^1$H NMR, 77.0 ppm for $^{13}$C NMR). The coupling constants ($J$) are reported in Hertz (Hz). IR spectra were recorded on an FT-IR spectrometer from PerkinElmer. Mass spectra were recorded using electrospray ionization (ESI) or electron ionization (EI) techniques. All chemicals were used as received unless otherwise stated. Cyclohexyl-(phenyl)methanol$^{30}$, tert-butylphenylcarbinol$^{31}$, 1-phenyl-1-butene-3-ol$^{32}$ were prepared using reported procedures. The solvents used for the reactions were all freshly distilled. Glassware, NMR tubes, stir bars, needles, and syringes were dried overnight in an oven heated at 120 °C. All reactions were performed under argon atmosphere unless otherwise noted. Neutral organic compounds were purified by flash column chromatography using silica gel F-254 (230-499 mesh particle size). Yields refer to isolated material judged to be >95% pure by $^1$H NMR spectroscopy.

General experimental procedures

**Etherification:** We prepared benzylpyridines 1 by a modified version of a procedure first reported in 1980:$^{33}$ A toluene solution of the appropriate benzyl alcohol derivative (500 mg, 0.5 M, 1.0 equiv), the corresponding 2-chloropyridine derivative (1.1 equiv), KOH (3.3 equiv), and 18-crown-6 (0.05 equiv) were heated at reflux until all of the alcohol was consumed. The resulting mixture was cooled to room temperature and then diluted with H$_2$O (20 mL). The
mixture was extracted with EtOAc (4 x 15 mL). The combined organic extract was washed with H₂O until the aqueous layer becomes neutral, then with brine and dried (Na₂SO₄), filtered, concentrated under vacuum, and purified on silica gel to yield benzyloxypyridines 1.

[1,2] Anionic rearrangement by n-BuLi: To a solution of benzyloxypyridines 1 (100 mg, 1.0 equiv) in THF (1 mL) at –60 °C was added n-BuLi (1.2 equiv) dropwise, and the solution was stirred at that temperature for 2 h before being quenched with MeOH. The resulting mixture was warmed up to room temperature and then diluted with H₂O (5 mL). The mixture was extracted with EtOAc (4 x 5 mL). The combined organic extract was then washed with brine, dried (Na₂SO₄), filtered, concentrated under vacuum, and purified on silica gel to yield pyridine alcohols 2.

[1,2] Anionic rearrangement by LDA: To a solution of LDA (1.3 equiv) in THF at room temperature was added benzyloxypyridines 1 (100 mg, 1.0 equiv) in THF (1 mL) dropwise, and the solution was stirred over night or until all the starting material was consumed. The resulting mixture was diluted with H₂O (5 mL), then extracted with EtOAc (4 x 5 mL). The combined organic extracts were then washed with brine, dried (Na₂SO₄), filtered, concentrated under vacuum, and purified on silica gel to yield pyridine alcohols 2.

Characterization Data

![Structure of 2-Benzylxoypyridine](image)

2-Benzylxoypyridine (1a); yellow oil (95%); ¹H NMR (300 MHz, CDCl₃) δ 8.18 (dd, J=5.06, 1.94 Hz, 1H), 7.61-7.55 (m, 1H), 7.48-7.25 (m, 5H), 6.88 (dd, J=7.07, 5.11 Hz, 1H), 6.81 (d, J=8.37 Hz, 1H), 5.38 (s, 2H).
2-[(2-Methoxyphenyl)methoxy]-pyridine (1b); white crystals (90%); \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.20 (dd, \( J=4.99, 1.44 \) Hz, 1H), 7.61-7.55 (m, 1H), 7.47 (d, \( J=7.35 \) Hz, 1H), 7.33-7.27 (m, 1H), 6.99-6.81 (m, 4H), 5.42 (s, 2H), 3.86 (s, 3H).

2-[(4-Methoxyphenyl)methoxy]-pyridine (1c); yellow oil, (92%); \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.18 (dd, \( J=5.07, 1.30 \) Hz, 1H), 7.57 (ddd, \( J=8.44, 7.09, 2.01 \) Hz, 1H), 7.40 (d, \( J=8.72 \) Hz, 2H), 6.94-6.86 (m, 3H), 6.78 (d, \( J=8.37 \) Hz, 1H), 5.30 (s, 2H), 3.82 (s, 3H).

2-(1-Phenylethoxy)-pyridine (1d); yellow oil, (96%); \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.17 – 8.03 (m, 1H), 7.54 (ddd, \( J=8.3, 7.2, 2.0 \) Hz, 1H), 7.50 – 7.40 (m, 2H), 7.40 – 7.14 (m, 3H), 6.89 – 6.67 (m, 2H), 6.22 (q, \( J=6.5 \) Hz, 1H), 1.64 (d, \( J=6.6 \) Hz, 3H).

2-[(4-Trifluoromethylphenyl)methoxy]-pyridine (1e); white crystals (75%); mp 35-36°C; \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.16 (dd, \( J=5.05, 1.36 \) Hz, 1H), 7.64-7.55 (m, 5H), 6.91 (dd, \( J=6.24, 5.15 \) Hz, 1H), 6.83 (d, \( J=8.36 \) Hz, 1H), 5.45 (s, 2H); \( ^13C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 163.2, 148.8, 141.6, 138.7, 129.8 (q, \( J=32.32 \) Hz), 127.7, 125.3, 124.2 (q, \( J=270.34 \) Hz), 117.2, 111.2, 66.4; IR (cm\(^{-1}\)) 3020, 2943, 2888, 2550, 1931, 1824, 1613, 1596, 1572, 1511, 1467, 1434, 1419, 1363, 1324.
1306, 1286, 1269, 1250, 1190, 1159, 1141, 1125, 1112, 1068, 1040, 1019, 1000; HRMS (EI+)
Calcd for C_{13}H_{10}OF_{3}N: 253.0715, found: 253.0710.

2-[(4-Chlorophenyl)methoxy]-pyridine (1f); yellow oil, (93%); ¹H NMR (300 MHz, CDCl₃) δ 8.24 – 8.06 (m, 1H), 7.59 (ddd, J = 9.0, 7.1, 2.0 Hz, 1H), 7.51 – 7.18 (m, 4H), 6.89 (ddd, J = 6.9, 5.1, 0.8 Hz, 1H), 6.80 (dd, J = 8.4, 0.7 Hz, 1H), 5.35 (s, 2H).

2-(Ethylphenylmethoxy)-pyridine (1g); colorless oil (96%); ¹H NMR (300 MHz, CDCl₃) δ 8.14 – 8.00 (m, 1H), 7.52 (ddd, J = 8.4, 7.2, 2.0 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.35 – 7.16 (m, 3H), 6.77 (ddd, J = 8.4, 5.9, 4.8 Hz, 2H), 5.98 (t, J = 6.6 Hz, 1H), 2.19 – 1.78 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 163.4, 146.9, 142.0, 138.5, 128.1, 127.2, 126.5, 116.5, 111.4, 77.7, 30.1, 10.0; IR (cm⁻¹) 2970, 2250, 1595, 1569, 1471, 1431, 1361, 1309, 1286, 1269, 1250, 1205, 1143, 1083, 1044; HRMS (Cl⁺) Calcd for [C_{14}H_{16}ON]⁺: 214.1232, found: 214.1232.

2-(Cyclohexylphenylmethoxy)-pyridine (1h); colorless oil (63%); ¹H NMR (300 MHz, CDCl₃) δ 8.03 (dd, J = 5.3, 1.4 Hz, 1H), 7.54 – 7.41 (m, 1H), 7.41 – 7.33 (m, 2H), 7.28 (dd, J = 11.2, 4.1 Hz, 2H), 7.24 – 7.14 (m, 1H), 6.79 – 6.64 (m, 2H), 5.81 (d, J = 7.3 Hz, 1H), 2.11 – 1.37 (m, 6H), 1.36 – 0.84 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ ¹³C NMR (75 MHz, CDCl₃) δ 163.6, 146.9, 140.9, 138.4, 127.9, 127.2, 127.1, 116.4, 111.2, 80.7, 43.8, 29.2, 29.0, 26.4, 26.1, 26.0; IR (cm⁻¹)
3032, 2927, 2853, 1596, 1470, 1451, 1430, 1357, 1310, 1285, 1268, 1251, 1141, 1098, 1082, 1042; HRMS (Cl+) Calcd for [C_{18}H_{22}ON]^+: 268.1701, found: 268.1693.

2-((tert-Butylphenylmethoxy)-pyridine (1i); white crystals (51%); mp 61-62°C; 1H NMR (300 MHz, CDCl₃) δ 7.94 (dd, J = 4.9, 1.0 Hz, 1H), 7.54 – 7.36 (m, 1H), 7.36 – 7.26 (m, 2H), 7.16 (tdd, J = 14.1, 6.0, 1.3 Hz, 3H), 6.76 – 6.60 (m, 2H), 5.67 (s, 1H), 0.93 (s, 9H); 13C NMR (75 MHz, CDCl₃) δ 163.6, 147.0, 139.5, 138.4, 128.0, 127.3, 127.0, 116.4, 111.2, 83.5, 35.5, 26.2. IR (cm⁻¹) 3031, 2956, 2870, 1593, 1570, 1470, 1453, 1430, 1393, 1363, 1308, 1283, 1267, 1203, 1184, 1141, 1080, 1043, 1028; HRMS (Cl+) Calcd for [C_{16}H_{20}ON]^+: 242.1545, found: 242.1541.

2-(Diphenylmethoxy)-pyridine (1j); white crystals (99%); mp 53-54°C; 1H NMR (300 MHz, CDCl₃) δ 8.14 – 8.04 (m, 1H), 7.59 – 7.49 (m, 1H), 7.44 (d, δ = 7.2 Hz, 4H), 7.38 – 7.18 (m, 6H), 6.94 – 6.71 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 162.9, 146.9, 141.5, 138.6, 128.3, 127.4, 127.2, 116.9, 111.6, 77.4. IR (cm⁻¹) 3062, 3030, 1951, 1595, 1569, 1495, 1468, 1454, 1429, 1306, 1283, 1265, 1247, 1186, 1141, 1101, 1080, 1041; HRMS (Cl+) Calcd for [C_{18}H_{16}ON]^+: 262.1232, found: 262.1239.

Phenyl(2-pyridyl)methanol (2a); white crystals, (85%); 1H NMR (300 MHz, CDCl₃) δ 8.52 (d, J=4.20 Hz, 1H), 7.58 (dt, J=7.72, 1.68 Hz, 1H), 7.39-7.13 (m, 7H), 5.74 (s, 1H), 5.43 (broad s, 1H).
\( \alpha-(2\text{- Methoxyphenyl})2\text{- pyridinemethanol (2b); } \) colorless crystals, (48\%); mp 61-62°C; \( ^1\text{H} \) NMR (300 MHz, CDCl₃) \( \delta \) 8.53 (d, \( J = 4.76 \text{ Hz}, 1\text{H} \)), 7.58 (dt, \( J = 7.74, 1.69 \text{ Hz}, 1\text{H} \)), 7.32-7.13 (m, 4H), 6.95-6.88 (m, 2H), 6.20 (s, 1H), 3.85 (s, 3H); \( ^{13}\text{C} \) NMR (300 MHz, CDCl₃) \( \delta \) 161.2, 156.6, 147.7, 136.6, 131.6, 128.7, 127.7, 122.1, 121.2, 120.9, 110.7, 69.1, 55.4; IR (cm⁻¹) 3132, 3008, 2840, 1595, 1570, 1488, 1475, 1460, 1440, 1332, 1288, 1271, 1238, 1214, 1188, 1150, 1113, 1092, 1040, 1024, 1005; HRMS (ESI⁺) Calcd for C₁₃H₁₃O₂NNa: 238.0844, found: 238.0856.

\( \alpha-(4\text{- Methoxyphenyl})2\text{- pyridinemethanol (2c); } \) colorless crystals, (33\%); \( ^1\text{H} \) NMR (300 MHz, CDCl₃) \( \delta \) 8.56 (d, \( J = 4.88 \text{ Hz}, 1\text{H} \)), 7.61 (dt, \( J = 7.70, 1.70 \text{ Hz}, 1\text{H} \)), 7.30-7.26 (m, 2H), 7.21-7.12 (m, 2H), 6.89-6.84 (m, 2H), 5.71 (s, 1H), 5.22 (broad s, 1H), 3.78 (s, 3H).

\( \alpha\text{-Methyl-} \alpha\text{- phenyl-2-pyridinemethanol (2d); } \) light yellow oil, (98\%); \( ^1\text{H} \) NMR (300 MHz, CDCl₃) \( \delta \) 8.52 (d, \( J = 4.9 \text{ Hz}, 1\text{H} \)), 7.65 (td, \( J = 7.7, 1.7 \text{ Hz}, 1\text{H} \)), 7.48 (d, \( J = 7.1 \text{ Hz}, 2\text{H} \)), 7.33-7.16 (m, 5H), 5.85 (s, 1H), 1.93 (s, 3H).
α-(4-Chlorophenyl)-2-pyridinemethanol (2f); off-white solid, (70%); 1H NMR (300 MHz, CDCl₃) δ 8.57 (d, J = 4.9 Hz, 1H), 7.64 (td, J = 7.7, 1.7 Hz, 1H), 7.31 (s, 4H), 7.22 (dd, J = 7.3, 5.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 5.72 (d, J = 2.5 Hz, 1H), 5.33 (d, J = 3.5 Hz, 1H).

α-Ethyl-α-phenyl-2-pyridinemethanol (2g); white crystals, (86%); mp 75-76°C; 1H NMR (300 MHz, CDCl₃) δ 8.43 (dd, J = 4.9, 0.6 Hz, 1H), 7.57 (td, J = 8.0, 1.7 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.34 – 6.94 (m, 5H), 5.87 (s, 1H), 2.56 – 1.92 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H); 13C NMR (300 MHz, CDCl₃) δ 163.6, 147.2, 146.4, 136.9, 128.2, 126.8, 126.0, 121.9, 120.5, 77.3, 33.8, 8.0; IR (cm⁻¹) 3360, 3058, 2969, 2936, 2878, 1591, 1570, 1492, 1467, 1447, 1432, 1391, 1323, 1294, 1194, 1153, 1134, 1090, 1062, 1031; HRMS (CI+) Calcd for [C₁₄H₁₆ON]⁺: 214.1232, found: 214.1227.

α-Cyclohexyl-α-phenyl-2-pyridinemethanol (2h); colorless oil, (20%); 1H NMR (300 MHz, CDCl₃) δ 8.45 (d, J = 4.3 Hz, 1H), 7.65 (dd, J = 10.6, 4.4 Hz, 3H), 7.46 (dd, J = 8.1, 0.9 Hz, 1H), 7.40 – 7.23 (m, 2H), 7.23 – 7.03 (m, 2H), 6.12 (s, 1H), 2.40 (dd, J = 15.0, 6.6 Hz, 1H), 1.84 – 1.46 (m, 4H), 1.46 – 0.89 (m, 6H); 13C NMR (300 MHz, CDCl₃) δ 163.3, 146.8, 145.9, 137.0, 128.1, 126.4, 125.9, 121.7, 120.4, 79.4, 77.2, 46.3, 26.9, 26.7, 26.6, 26.4; IR (cm⁻¹) 3341, 3057, 2930, 2851, 1713, 1591, 1571, 1491, 1467, 1446, 1432, 1392, 1195, 1173, 1153, 1124, 1095, 1068, 1033; HRMS (CI+) Calcd for [C₁₈H₂₂ON]⁺: 268.1701, found: 268.1696.
α, α-Diphenyl-2-pyridinemethanol (2j); white solid, (86%); mp 102-103°C; 1H NMR (300 MHz, CDCl₃) δ 8.60 (d, J = 4.3 Hz, 1H), 7.65 (td, J = 7.7, 1.7 Hz, 1H), 7.45 – 7.19 (m, 11H), 7.12 (d, J = 7.9 Hz, 1H), 6.30 (s, 1H); 13C NMR (300 MHz, CDCl₃) δ 163.2, 147.7, 146.1, 136.4, 128.1, 127.9, 127.3, 122.9, 122.3, 80.8; IR (cm⁻¹) 3376, 3058, 1590, 1572, 1490, 1466, 1447, 1432, 1375, 1169, 1039; HRMS (Cl⁺) Calcd for [C₁₈H₁₆ON]⁺: 262.1232, found: 262.1232.
CHAPTER FOUR

AN ALTERNATIVE ENTRY INTO THE ANIONIC REARRANGEMENT OF BEZYLOXYPYRIDINES---PYRIDINE-DIRECTED ORGANOLITHIUM ADDITION TO AN ENOL ETHER

In this part, we will present indirect evidence of a unique and unexpected carbolithiation of an enol ether (pyridyl ether 7, Figure 18, Equation 18a),\(^{34}\) in which organolithium nucleophiles\(^{35}\) add \textit{inter}-molecularly across the electron-rich alkene in a manner opposite the normal polarization preferences of an enol ether (contra-electronically).\(^{36}\) This observation provides insight into the unusual behavior of highly reactive species\(^{37,38}\) and reveals an alternative entry into our reported anionic rearrangement of benzyloxypyridines (Figure 18, Equation 18b).\(^{39}\)

\[\text{O} \quad \text{Li} \quad \text{O} \quad n-\text{Bu} \quad \text{N} \quad + \quad \text{–} \quad \text{–} \quad n-\text{Bu} \quad \text{Li} \quad \text{–} \quad \text{–} \quad \text{THF, rt} \]

\[\text{HO} \quad n-\text{Bu} \quad \text{N} \quad 84\% \text{ yield} \]

(a)

\[\text{HO} \quad \text{CH}_3 \quad \text{N} \quad 86\% \text{ yield} \]

(b)

Figure 18: Formation of Pyridyl Alcohol from Enol Ether 7 and Benzyloxypyridine 1g
4.1 The chemistry of enol ethers

Enol ethers have shown reactivity toward different electrophiles and it is believed to be due to the high electron density on the β-C atom (Figure 19). As a result, the fundamental types of reactions for enol ethers are (1) Cationic polymerization in the presence of Lewis acids (Figure 20, Equation 20a), and (2) Reactions with X — Y type compounds resulting in bond formation between the less electronegative atom (Y) of the compound and the β-C atom of the enol ether (Figure 20, Equation 20b). One typical example for the second type of reaction for enol ethers is the addition of alcohols to enol ethers under acidic condition to form acetals (Figure 20, Equation 20c).

Figure 19: High Electron Density on the β-C in Enol Ethers

Figure 20: Fundamental Reactions of Enol Ethers.
4.2 Overview of the new pyridine directed organolithium addition to enol ether 7

The observation of this new type of reaction for enol ethers is as follows: addition of 1.3 equiv of n-butyllithium to a solution of α-pyridyloxy-styrene 7 in THF provides an 84% yield of tertiary pyridyl carbinol 8a (Figure 21, Equation 21a). To explain this, one must account for (1) C–C bond formation at the β-carbon of the enol ether, and (2) migration of the pyridyl group from oxygen to the α-carbon.

![Figure 21](image)

**Figure 21:** The Formation of Pyridyl Alcohol from Enol Ether 7 and Benzyloxypyridine 1g.

Given that directed mettallation of benzyl pyridyl ethers triggers an anionic rearrangement to give tertiary pyridyl carbinols (e.g., Figure 21, Equation 21b), the simplest explanation involves carbolithiation of enol ether 7 (7 → [Ia], Figure 21, Equation 21a).

The presumed carbolithiation (7 → [Ia]) is the first example to our knowledge of the enol ether π-system reacting with an electron-rich (nucleophilic) reagent. Moreover, *the nucleophilic attack occurs at the more electron-rich terminus of the enol ether.*

---

v Ockham’s razor favors the simplest explanation, but it is not an irrefutable principle of logic.

vi Calculations at the B3LYP 6-31+G(d,p) level suggest that the pyridyloxy group, like the methoxy group, is electron-releasing. Although the pyridyloxy group is a weaker donor than
4.3 Evidence of the contra-electronic organolithium addition to α-(2-pyridyloxy)-styrene 7

The contra-electronic organolithium addition to 7 proceeded with the exclusion of alternative potential reaction pathways (Figure 23). Namely, pyridine-directed carbolithiation could be envisioned to occur in alignment with the polarization of enol 1, but the expected products of such a process (9 and 10, Equation 23a, arising from β-elimination of the lithium alkoxide) could not be detected. Another “reasonable” reaction process would be for the alkyllithium reagent to attack the electron-deficient pyridine ring (addition at C2, followed by elimination of the enolate, Figure 23, Equation 23b). Although nucleophilic aromatic substitutions at the 2-position of pyridine are well known, no such products are observed in this process.

methoxy, the majority (51.46%) of the alkene π-electron density is localized near the β-carbon of 7 (Fig. 22). A similar pattern is calculated for [IV], after complexation of the alkyllithium.

![Figure 22](image)

**Figure 22:** Calculated π-bond polarization (in italics) and selected net atomic charges (in bold) for 2-pyridyloxy-styrenes 7, complex [IV], and α-methoxystyrene (18).

This unusual reaction would not be classified as an “umpolung” process. The term “umpolung” (meaning, “reversed polarity”) refers to an altered form of a common functional group that displays reactivity opposite to that of the normal pattern (e.g., lithiated 1,3-dithiane vs. aldehyde). In contrast, Equation 1 in Figure 21 represents a rare example in which the unaltered functional group — in this case, an enol ether — displays reactivity opposite to the expected pattern. For discussion on umpolung reactivity strategies, see: D. J. Ager, In *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*, (Eds.: T. A. Hase), John Wiley & Sons, New York, 1987, pp. 19-72.
Figure 23: Evidence Part I for the Contra-electronic Organolithium Addition to α-(2-Pyridyloxy)-styrene 7

The central importance of the 2-pyridyloxy group in directing the alkylolithium addition to 7 is supported by the control experiments shown in Figure 24. Although carbolithiation of styrene derivatives is known, this is not an example of a phenyl substituent overriding the normal reactivity profile of an enol ether. The 2-pyridyloxy group, not the phenyl, controls the regioselectivity of the process: n-butyllithium reacts with stilbene derivative 13 (Figure 24, Equation 24c) to produce tertiary alcohol 14 (i.e., by the addition / rearrangement process, Figure 24, Equation 24a) to the exclusion of 10, the expected product of regioisomeric addition and elimination (Figure 24, Equation 24b). 4-Pyridyloxy analogue 16, in which pyridine complexation does not produce a proximity effect, does not undergo the same addition / rearrangement process (Figure 24, Equation 24d). Instead, starting material is recovered along with small amounts of products derived from addition of n-butyllithium to the 2-position of pyridine. Likewise and as expected, α-methoxystyrene 18 is completely unreactive under these conditions (Figure 24, Equation 24e).
Figure 24: Evidence Part II for the Contra-Electronic Organolithium Addition to α-(2-Pyridyloxy)-styrene
These data, coupled with our earlier report (Figure 25, Equation 25b),\textsuperscript{39} support the reaction pathway outlined in Figure 25, Equation 1: pyridine-directed addition of \textit{n}-butyllithium to enol ether 7 triggers anionic rearrangement of the resulting \(\alpha\)-(2-pyridyloxy)benzyllithium, \([\text{Ia}].\)

![Figure 25: The Formation of Pyridyl Alcohol from Enol Ether 7 and Benzyloxypyridine 1g.](image)

4.4 Proposed mechanisms for the contra-electronic addition

In considering reasonable mechanisms for this unusual addition / rearrangement sequence (7 \(\rightarrow\) 8), we favor a process in which carbolithiation (7 \(\rightarrow\) \[I], Figure 26) leads directly into the previously reported anionic rearrangement ([I] \(\rightarrow\) 8). To explain the apparently contra-electronic carbanion addition, it is helpful to invoke the electron-transfer properties of highly reactive organolithium nucleophiles.\textsuperscript{43} Precomplexation between the lithium reagent and the pyridine nitrogen ([IV], Figure 26) produces the proximity effect\textsuperscript{44} necessary for directed carbolithiation, which is thermodynamically favorable.\textsuperscript{vii} We postulate that carbolithiation of enol ether 7 may

\textsuperscript{viii} The relative energies of alkyllithium [IV], benzyllithium [I], and lithium alkoxide [VII] were calculated at the B3LYP 6-31+G(d,p) level of theory (R = \textit{n}-Bu, Fig. 27). Both the addition
involve rate-determining electron-transfer to produce a transient enol ether radical anion [V], followed almost instantaneously by radical recombination to [I]. The observed regioselectivity would then be consistent with radical recombination ([V] → [I])\textsuperscript{ix} guided by sterics and/or proximity effects. Pyridyloxylithium [I] undergoes anionic rearrangement, as described previously.

and the rearrangement appear to be highly exothermic. We thank a referee for suggesting that we examine the energetics of the conversion of [IV] → [I] → [VII].

\textsuperscript{ix} A more concerted process, in which radical anion [V] undergoes the anionic rearrangement directly without generating α-pyridyloxylithium [I], cannot be ruled out at this time.
Figure 26: Postulated Mechanism: Alkyllithium Addition (7 → [I]) Triggers Anionic Rearrangement ([I] → 8).

4.5 Preparation of α-(2-pyridyloxy)-styrene 7 and scope of the nucleophilic addition

α-Pyridyloxystyrene 7 was prepared as shown in Figure 28. Oxidation of diethylene glycol methyl ether and addition of phenylmagnesium bromide to the resulting aldehyde provided benzyl alcohol derivative 20, which was converted into pyridyl ether 21 using nucleophilic aromatic substitution of 2-chloropyridine.45 LDA-promoted elimination of 2-methoxyethanol from 21x provides α-pyridyloxystyrene 7.

Figure 28: Preparation of α-(2-Pyridyloxy)styrene (7)

A brief screening of organolithium nucleophiles revealed a correlation between organolithium reactivity and reaction efficiency (Table 4). Methyllithium reacted with 7 along

x Incidentally, this reaction was originally designed and performed as a competition experiment between E2 elimination and the anionic rearrangement described previously39. It shows, not surprisingly, that elimination of the lithium alkoxide is faster than the anionic rearrangement (Figure 25, Equation 2). In one compromised run of this competition experiment, we used LDA that was contaminated with a small amount n-butyllithium, which resulted in isolation of 8a and identification of the contra-electronic alkyllithium addition reaction.
the presumed carbolithiation and anionic rearrangement pathway to give 8b in 84% yield (Table 4, Entry 1), which is comparable to the 84% yield observed in the reaction of 7 with n-butyl lithium (Table 4, Entry 3). Methylmagnesium bromide, on the other hand, was unreactive under similar conditions (Table 4, Entry 2). The more reactive secondary and tertiary butyllithium isomers produced higher yields of tertiary alcohol product: xi s-BuLi, 86%, Table 4, Entry 4; t-BuLi, 97%, Table 4, Entry 5. Reaction of 7 with phenyllithium, which is less nucleophilic than most alkyl lithium reagents, gave rise to alcohol 8e in a relatively modest 75% yield (Table 4, Entry 6), and the hydride reagent produced a mixture of products including acetophenone (11), which presumably arises from hydride addition to pyridine at C2 (Figure 29).

Table 4 Scope of the nucleophilic addition to α-pyridyloxystyrene 7.a

<table>
<thead>
<tr>
<th>entry</th>
<th>&lt;R-Li&gt;</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me–Li</td>
<td>8b (R = Me)</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>(MeMgBr)</td>
<td>8b (R = Me)</td>
<td>0%b</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu–Li</td>
<td>8a (R = n-Bu)</td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td>s-Bu–Li</td>
<td>8c (R = s-Bu)</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu–Li</td>
<td>8d (R = t-Bu)</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>Ph–Li</td>
<td>8e (R = Ph)</td>
<td>75%</td>
</tr>
<tr>
<td>7</td>
<td>L-Selectride</td>
<td>8f (R = H)</td>
<td>—%c</td>
</tr>
</tbody>
</table>

a Styrene 7 in THF treated with organometallic reagent at room temperature under nitrogen. b No reaction. c 1H NMR spectroscopic analysis of the crude reaction mixture revealed a complex mixture of products, including starting material and acetophenone (Figure 29).

xi Similar reactivity trends have been documented for other directed carbolithiation reactions; see ref 34a, ref 34d, and ref 37.
In summary, organolithium addition to an enol ether has been observed within the context of a previously reported anionic rearrangement of lithiated benzyl pyridyl ethers. Specifically, pyridine-directed, contraelectronic addition of reactive alkylolithium reagents to α-(2-pyridyloxy)-styrene (7) triggers the anionic rearrangement to provide tertiary pyridyl carbinols. We postulate a mechanism in which the organolithium reagent attacks 7 in a dipole-opposed (contraelectronic) fashion, perhaps via a single electron transfer mechanism, with the carbanionic moiety reacting at the more electron-rich terminus of the enol ether.
CHAPTER FIVE

EXPERIMENTAL: PYRIDINE-DIRECTED ORGANOLITHIUM ADDITION TO AN ENOL ETHER

General information

1H-NMR and 13C-NMR spectra were recorded on a 400 MHz spectrometer using CDCl3 as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to internal TMS (0 ppm for 1H NMR) or the residual CDCl3 peak (7.26 ppm for 1H NMR, 77.0 ppm for 13C NMR). The coupling constants (J) were reported in Hertz (Hz). IR spectra were recorded on an FT-IR spectrometer. Mass spectra were recorded using electrospray ionization (ESI) or electron ionization (EI) techniques. All chemicals were used as received unless otherwise stated. The solvents used for the reactions were all freshly distilled. Glassware, NMR tubes, stir bars, needles, and syringes were dried overnight in an oven heated at 120 °C. All reactions were performed under nitrogen atmosphere unless otherwise noted. Neutral organic compounds were purified by flash column chromatography using silica gel F-254 (230-499 mesh particle size). Yields refer to isolated material judged to be ≥95% pure by 1H NMR spectroscopy.

General experimental procedures & Characterization data

α-[(2-Methoxyethoxy)methyl]-Benzenemethanol (20): To a DMF (6 ml) solution of oxalyl chloride (0.16 ml, 1.83 mmol) was added DMSO (0.28 ml, 3.66 mmol) at -60 °C drop by drop, followed by di(ethylene glycol) methyl ether (0.2 ml, 1.67 mmol) drop by drop. The resulting solution was stirred for 15 min before triethylamine (1.16 ml, 8.32 mmol) was added. The
reaction was then warmed up to room temperature and stirred for another 3 hours. The reaction mixture was then diluted with water (20 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organics were washed with saturated aqueous sodium chloride (20 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product was dissolved in dry THF (4 ml) and phenylmagnesium bromide (2 ml, 1 M, 1.2 equiv) was added drop by drop at room temperature with subsequent stirring for 1 hour. The reaction mixture was quenched with water (10 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organics were washed with saturated aqueous sodium chloride (10 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 50% EtOAc/Hexanes) to provide 111 mg of alcohol 20 as colorless oil (34% yield over two steps); ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.26 (m, 5H), 4.93 (dd, 1H, J=9.30, 2.82 Hz), 3.78-3.67 (m, 3H), 3.62-3.56 (m, 2H), 3.47 (t, 1H, J=9.72 Hz), 3.41 (s, 3H), 3.25 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 140.1, 128.3, 127.7, 126.1, 77.2, 72.7, 71.9, 70.6, 59.1; IR (cm⁻¹) 3415, 3030, 2890, 1605, 1494, 1452, 1356, 1325, 1244, 1199, 1096, 1027; HRMS (ESI+) Calcd for C₁₁H₁₆O₃Na: 219.1023, found: 219.0997.

2-[2-(2-Methoxy-ethoxy)-1-phenyl-ethoxy]-pyridine (21): We prepared benzyloxy-pyridine 21 by a modified version of a procedure first reported in 1980: A toluene solution of benzyl alcohol 20 (0.5 M, 1.0 equiv), 2-chloropyridine (1.1 equiv), KOH (3.3 equiv), and 18-crown-6 (0.05 equiv) was heated at reflux until all of the alcohol was consumed. The resulting mixture was cooled to room temperature and then diluted with H₂O. The mixture was extracted with EtOAc. The combined organic extract was washed with H₂O until the aqueous layer becomes neutral, then with brine and dried (Na₂SO₄), filtered, concentrated under vacuum, and purified on silica gel to yield benzyloxy-pyridine 21 in 81% yield as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ
8.05 (dd, 1H, J = 1.32, 4.88 Hz), 7.54-7.50 (m, 1H), 7.45-7.43 (m, 2H), 7.33-7.23 (m, 3H), 6.83-6.77 (m, 2H), 6.33 (dd, 1H, J = 7.84, 3.72 Hz), 3.97-3.92 (m, 1H), 3.82-3.78 (m, 1H), 3.71-3.70 (m, 2H), 3.52-3.49 (m, 2H), 3.33 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 163.1, 146.9, 139.0, 138.5, 128.3, 127.6, 126.7, 116.8, 111.4, 75.4, 75.0, 71.9, 70.7, 59.0; IR (cm⁻¹) 2876, 1595, 1570, 1469, 1454, 1430, 1357, 1308, 1270, 1250, 1199, 1104, 1050, 1028; HRMS (EI⁺) Calcd for C₁₆H₁₉NO₃: 273.1365, found: 273.1361.

![Chemical Structure](image)

2-[(1-phenylethenyl)oxy]-pyridine (7): A solution of LDA (14.3 ml, 0.5 M in THF, 1.1 equiv) was added to a solution of benzyloxypyridine 21 (1.77g, 6.48mmol) in THF (12 mL) at room temperature dropwise, and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was quenched with water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organics were washed with saturated aqueous sodium chloride (20 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide 856 mg of pyridyl ether 7 in 67% yield as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, 1H, J = 3.32 Hz), 7.64-7.57 (m, 3H), 7.32-7.25 (m, 3H), 6.95-6.90 (m, 2H), 5.41 (d, 1H, J = 1.72 Hz), 4.96 (d, 1H, J = 1.72 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 163.2, 156.2, 148.0, 139.4, 134.9, 128.7, 128.4, 125.6, 118.4, 111.5, 99.2; IR (cm⁻¹) 3057, 1640, 1615, 1592, 1571, 1493, 1467, 1446, 1428, 1263, 1239, 1183, 1142, 1095, 1076, 1043, 1027; HRMS (EI⁺) Calcd for C₁₃H₁₁NO: 197.0841, found: 197.0842.
2-(1,2-Diphenyl-vinylloxy)-pyridine (13): To a solution of benzoin methyl ether (5 g, 22.1 mmol) in THF (20 ml) was added lithium aluminum hydride powder (282.3 mg, 7.1mmol) in portions over 5 min at 0 °C. The reaction mixture was then warmed up to room temperature, stirred for 30 min, and then quenched with H2O (20 ml). The reaction mixture was extracted with ethyl acetate (3 x 20 ml). The combined organics were washed with saturated aqueous sodium chloride (10 ml), dried over Na2SO4, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 20% EtOAc/Hexanes) to provide 4.90g of white crystals tentatively assigned as 2-methoxy-1,2-diphenyl-ethanol (97% yield). A THF solution of this benzyl alcohol (2.08 g, 9.09 mmol), 2-chloropyridine (8.54 ml, 90.9 mmmol), KOH (1.68g, 30.01 mmol), and 18-crown-6 (120.2 mg, 0.045 mmol) was heated at reflux overnight. The resulting mixture was cooled to room temperature and then diluted with H2O (20 ml). The mixture was extracted with EtOAc (3 x 20 ml). The combined organic extract was washed with H2O until the aqueous layer becomes neutral, then with brine (20 ml) and dried (Na2SO4), filtered, concentrated under vacuum, and purified on silica gel (10% EtOAc/Hexanes) to yield 2.55g of a colorless oil tentatively assigned as 2-(2-methoxy-1,2-diphenyl-ethoxy)-pyridine (92% yield). A solution of this benzyloxy pyridine solution (2.55g, 8.34mmol) in THF (10 ml) was treated with a solution of LDA in THF (1.1 equiv) at room temperature dropwise, and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organics were washed with saturated aqueous sodium chloride (20 ml), dried over Na2SO4, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 15% EtOAc/Hexanes) to provide 1.72g of enol ether 13 in 75% yield as a white crystals. ^1H NMR (400 MHz, CDCl3) δ 8.14-8.13 (m, 1H), 7.64-7.61 (m, 5H), 7.40-7.17 (m, 6H), 6.98-6.88 (m, 2H), 6.74 (s, 1H); HRMS (EI+) Calcd for C19H15NO: 273.1154, found: 273.1149.
1,2-Diphenyl-1-pyridin-2-yl-hexan-1-ol (14): Enol ether 13 (50mg, 0.18mmol, 1.0 equiv) was dissolved in THF (1ml) in a 5 ml round bottom flask at room temperature. To this solution was added n-BuLi (80 µl, 1.8M in hexanes, 1.3 equiv) dropwise, and the resulting dark brown solution was stirred over night. The resulting mixture was diluted with H2O (5 mL) and extracted with EtOAc (4 x 5 mL). The combined organic extracts were then washed with saturated aqueous sodium chloride (10ml), dried (Na2SO4), filtered, concentrated under vacuum, and purified on silica gel (15% EtOAc/Hexanes) to yield pyridine alcohol 14 in 25% yield as a 2.4:1 mixture of diastereomers, white solid, mp 116-118°C; 1H NMR (400 MHz, CDCl3) δ 8.52 (d, 1H, J=4.80 Hz), 8.10 (d, 1H, J=4.80 Hz), 7.79-7.68 (m, 4H), 7.50-7.36 (m, 7H), 7.31-7.23 (m, 2H), 7.21-6.87 (m, 13H), 6.36 (s, 1H), 6.09 (s, 1H), 3.68-3.63 (m, 2H), 2.05-1.84 (m, 2H), 1.79-1.70 (m, 1H), 1.27-0.98 (m, 9H), 0.76-0.68 (m, 6H); 13C NMR (100 MHz, CDCl3) δ 163.4, 162.3, 147.2, 146.2, 145.9, 145.8, 141.2, 140.4, 137.1, 136.4, 130.2, 128.4, 127.6, 127.43, 127.36, 126.8, 126.15, 126.12, 126.01, 125.98, 125.92, 122.0, 121.3, 121.1, 120.3, 80.3, 79.9, 77.2, 54.6, 54.3, 30.5, 30.1, 30.0, 29.8, 22.6, 13.97, 13.91; IR (cm⁻¹) 3290, 3061, 2934, 2858, 1593, 1571, 1494, 1446, 1434, 1405, 1127, 1063, 1001; HRMS (ESI⁺) Calcd for C23H26NO: 332.2014, found: 332.2024.

4-(1-Phenyl-vinyloxy)-pyridine (16): A toluene solution of benzyl alcohol 20 (0.5 M, 1.0 equiv), 4-chloropyridine (3 equiv), KOH (6.6 equiv), and 18-crown-6 (0.05 equiv) was heated at reflux for 2 days. The resulting mixture was cooled to room temperature and then diluted with H2O. The mixture was extracted with EtOAc. The combined organic extract was washed with H2O until the aqueous layer becomes neutral, then with brine and dried (Na2SO4), filtered,
concentrated under vacuum, and purified on silica gel to yield a colorless oil tentatively assigned as 4-[2-(2-methoxy-ethoxy)-1-phenyl-ethoxy]-pyridine (53% yield). A solution of this benzyloxy-pyridine (73.6 mg, 0.269mmol) in THF at room temperature was treated with solution of LDA in THF (1.1 equiv) dropwise. The reaction mixture was stirred at room temperature overnight and then quenched with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organics were washed with saturated aqueous sodium chloride (5 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 30% EtOAc/Hexanes) to provide 23.2 mg of pyridyl ether 16 in 44% yield as colorless oil. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 2H), 7.56-7.53 (m, 2H), 7.36-7.34 (m, 3H), 6.96-6.95 (m, 2H), 5.44 (d, 1H, J=1.96 Hz), 4.96 (d, 1H, J=1.96 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 163.8, 156.2, 151.4, 133.7, 129.3, 128.7, 125.5, 112.7, 99.5; IR (cm⁻¹) 3033, 1637, 1584, 1493, 1446, 1417, 1257, 1206, 1097, 1076, 1026; HRMS (EI⁺) Calcd for C₁₃H₁₁NO: 197.0841, found: 197.0846.

General procedure for the addition of organolithium reagents to enol ether 7: Enol ether 7 (20 mg, 1 equiv) was dissolved in 1 mL of THF at room temperature, followed by addition of the organolithium reagent (1.3 equiv) drop by drop. The reaction mixture was stirred overnight or until TLC analysis of the reaction mixture showed complete consumption of the enol ether. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, concentrated under vacuum, and purified on silica gel to yield pyridine alcohols 8a, 8b, 8c, 8d, and 8e.

α-Pentyl-α-phenyl-2-pyridinemethanol (8a): Colorless oil (84%); ¹H NMR (400 MHz, CDCl₃) δ 8.50 (d, 1H, J=4.84 Hz), 7.66-7.61 (m, 1H), 7.54-7.52 (m, 2H), 7.34-7.29 (m, 3H), 7.22-7.14 (m, 2H), 5.96 (s, 1H), 2.31-2.15 (m, 2H), 1.46-1.11 (m, 6H), 0.83 (t, 3H, J=6.90 Hz); ¹³C NMR
(100 MHz, CDCl$_3$) δ 163.8, 147.2, 146.6, 136.9, 128.2, 126.7, 125.9, 121.9, 120.4, 77.1, 41.2, 32.2, 23.2, 22.5, 14.0; IR (cm$^{-1}$) 3362, 3058, 2953, 2929, 2869, 1591, 1571, 1493, 1467, 1446, 1432, 1391, 1293, 1188, 1152, 1134, 1089, 1065, 1033; HRMS (EI+) Calcd for C$_{17}$H$_{21}$NO: 255.1623, found: 255.1629.

3-Methyl-1-phenyl-1-pyridin-2-yl-pentan-1-ol (8c): The reaction was done in 10 min and gave pyridyl alcohol 8c in 86% yield as a 2.4:1 mixture of diastereomers, colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.52 (s, 1H), 8.51 (s, 1H), 7.68-7.62 (m, 2H), 7.59-7.57 (m, 4H), 7.39-7.31 (m, 6H), 7.24-7.16 (m, 4H), 6.08 (s, 1H), 6.03 (s, 1H), 2.44-2.40 (m, 1H), 2.33-2.28 (m, 1H), 2.24-2.19 (m, 1H), 2.12-2.07 (m, 1H), 1.68-1.38 (m, 3H), 1.34-1.05 (m, 3H), 0.92 (d, 3H, J=6.68 Hz), 0.85 (t, 3H, J=7.40 Hz), 0.77 (t, 3H, J=7.40 Hz), 0.71 (d, 3H, J=6.68 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 164.2, 164.1, 147.4, 147.2, 147.1, 147.0, 136.84, 136.79, 128.14, 128.13, 126.7, 125.93, 125.90, 121.9, 120.8, 120.7, 77.6, 47.7, 47.4, 31.3, 30.9, 30.5, 30.2, 21.2, 20.6, 11.22, 11.18; IR (cm$^{-1}$) 3352, 3058, 2958, 2926, 2873, 1591, 1571, 1493, 1465, 1446, 1432, 1392, 1293, 1188, 1153, 1137, 1089, 1065, 1033; HRMS (EI+) Calcd for C$_{17}$H$_{21}$NO: 255.1623, found: 255.1622.

3,3-Dimethyl-1-phenyl-1-pyridin-2-yl-butan-1-ol (8d): The reaction was done in 10 min and gave pyridyl alcohol 8d in 97% yield as colorless crystals; mp 83-84°C; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.46 (d, 1H, J=4.80 Hz), 7.63-7.58 (m, 3H), 7.44-7.42 (m, 1H), 7.30-7.25 (m, 2H), 7.18-7.10 (m, 2H), 6.14 (s, 1H), 2.44-2.32 (m, 2H), 0.85 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 164.5, 148.5, 146.8, 136.7, 128.0, 126.4, 125.6, 121.7, 120.9, 77.4, 52.1, 32.00, 31.6; IR (cm$^{-1}$)
α-Phenyl-α-(phenylmethyl)-2-pyridinemethanol (8e): PhLi (0.11 ml, 1.8 M, 2 equiv) was employed and the reaction gave pyridyl alcohol 8e in 75% yield as a white solid; mp 95-96°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.38 (d, 1H, \(J=4.88\) Hz), 7.65-7.59 (m, 3H), 7.44-7.42 (m, 1H), 7.35-7.31 (m, 2H), 7.25-7.23 (m, 1H), 7.13-7.09 (m, 4H), 6.97-6.95 (m, 2H), 5.48 (s, 1H), 3.71-3.58 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 162.9, 147.1, 146.2, 136.7, 136.5, 130.8, 128.2, 127.6, 127.1, 126.3, 126.2, 121.9, 121.0, 77.4, 47.2; IR (cm\(^{-1}\)) 3342, 3059, 3029, 2924, 1590, 1571, 1495, 1469, 1446, 1433, 1392, 1293, 1188, 1153, 1117, 1090, 1063, 1032; HRMS (ESI+) Calcd for C\(_{19}\)H\(_{18}\)NO: 276.1388, found: 276.1384.
Computational Analysis

All calculations were performed using Gaussian 03 software, and all structures were optimized at the B3LYP 6-13+G(d,p) level. NBO conditions were used to calculate net atomic charges. Total energies in Hartrees and Cartesian coordinates are given for each structure as the following.

![Molecular Structure Image]

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CHAPTER SIX

FUTURE PLANS

The [1,2]-anionic rearrangement of 2-benzyloxy pyridine derivatives affords a variety of α-pyridyl alcohols in good to excellent yield. This reaction may provide a new route to the enantioselective synthesis of tertiary pyridyl alcohols. If this rearrangement process is stereospecific, then chiral tertiary pyridyl carbinols will be available enantiospecifically from chiral secondary alcohols (Figure 30).

Figure 30: [1,2]-Anionic Rearrangement of 2-Benzylloxy pyridine and Related Pyridyl Ethers

In order to test this hypothesis, we should be able to measure the e.e. value of product 2 by HPLC, chiral NMR shift reagents or any other applicable method. We will then look at different methods for controlling absolute stereochemistry of the alcohol product. One approach would be carrying out the rearrangement reaction on a single enantiomer starting molecule using different bases in different solvents and at different temperatures to see if the e.e. value will be retained. The other approach would be treating a racemic starting molecule with chiral base/ligands to see if enantioselectivity could be introduced.

The other goal in the future is to broaden the scope of this novel reaction. We will turn our attention to other aspects of the reaction that we still need to investigate before combining all the findings into a full paper. As shown above in Figure 30, the rearrangement reaction has previously been performed on benzyl pyridyl ethers with varied phenyl ring and R² groups, but not with substituted aromatic heterocycle. Thus the other part of our plan is to study which other aromatic heterocycles can undergo this novel anionic rearrangement.
PART 2: A SYNTHETIC APPROACH TO ALDINGENIN B

CHAPTER SEVEN

INTRODUCTION

The annulation & carbonyl extrusion strategy is a central on-going project in the Dudley lab. Aldingenin B was chosen as the natural product target for the application of this methodology. In this chapter, we will introduce the annulation & carbonyl extrusion strategy and explain how we planned to employ this methodology in the synthesis of aldingenin B.

7.1 Addition/fragmentation of vinylogous acyl triflates (VATs)

The Dudley group reported a fragmentation strategy for generating alkynes under aprotic conditions by exploiting the powerful nucleofugality of triflates. Vinylogous acyl triflates (VATs), typically derived from 1,3-cyclohexanediones (Figure 31), reacted with a wide range of carbanionic nucleophiles in an addition/fragmentation process to provide the desired alkynyl ketone and a metal triflate salt. The two-step sequence achieved the conversion of symmetric, cyclic diones into acyclic alkynyl ketones, which comprised orthogonal and non-contiguous functionalities (ketone and alkyne, Figure 32, Equation 32b). The stability of the triflate anion (an excellent nucleofuge) enables the fragmentation process in much the same way as formation of molecular nitrogen is a driving force in the Eschenmoser-Tanabe reaction (Figure 32, Equation 32a).
Figure 31: Formation of Vinylogous Acyl Triflates (VATs)

\[
\text{The Eschenmoser-Tanabe Fragmentation}
\]

\[
\begin{align*}
\text{R} & \quad \text{R'} \quad \text{NNHTs} \\
\text{R} & \quad \text{R'} \quad \text{NNH}_2\text{Ts} \\
\text{R} & \quad \text{R'} \quad \text{OTf} \\
\end{align*}
\]

- $\text{N}_2$
- $\text{TsH}$

(a)

(b)

Figure 32: Proposed Mechanisms for the Eschenmoser-Tanabe Fragmentation (a) and Tandem Addition/Fragmentation of Vinylogous Acyl Triflates (b)

As shown in Figure 33, this methodology is not limited to the synthesis of alkynyl ketones. Other nucleophiles for promoting fragmentation include enolates, hydride, and lithiated amines, which give rise to alkynes tethered to $\beta$-keto esters, alcohols, and amides.
7.2 Carbonyl extrusion of dihydropyrene (DHP) triflates to yield homopropargyl alcohols

Whereas carbocyclic VATs give rise to alkynyl ketones through a tandem addition / C-C bond cleavage process (Figure 32, Equation 32b, Figure 33), their oxacyclic analogs, 5,6-dihydro-2-pyrone (DHP) triflates, react along a more complicated mechanistic pathway to furnish homopropargyl alcohols (Figure 34). Nucleophilic addition to 5,6-dihydro-2-pyrone triflates provides a tetrahedral intermediate (I) that can either break down along the conventional lines (path a) or undergo immediate fragmentation (path b, not observed). The former path (path a) gives rise to acyclic triflate II, which is then subject to addition / C-C cleavage process. Ultimately, homopropargyl alcohols arise stereospecifically from cyclic dihydropyrene triflates. Addition of methylmagnesium bromide (2.0 equiv) in toluene emerged as the optimal choice from careful optimization efforts.
Carbonyl extrusion is achieved with high efficiency and generality across a range of racemic DHP triflates (Figure 35).\textsuperscript{52} It is important to note that carbonyl extrusion does not impact the stereochemistry of the system. Stereochemical information is retained throughout the process, enabling one to leverage a host of powerful synthetic methods (e.g., Evans aldol, Noyori hydrogenation, etc.) for the synthesis of homopropargyl alcohols.

This methodology will produce the most generally applicable strategy for the synthesis of diverse homopropargyl alcohols. One current goal in the Dudley lab is to apply this annulation & carbonyl extrusion strategy in conjunction with an innovative oxidative alkyne ketalization to achieve a short and efficient synthesis of aldingenin B. We will explain this in detail in the retrosynthetic analysis of aldingenin B (Chapter 7.4).
Figure 36: Annulation & Carbonyl Extrusion Strategy for Homopropargyl Alcohol Fragment 4 in the Total Synthesis of Aldingenin B

7.3 Isolation of aldingenin B

The aldingenin family of bisabolene sesquiterpenes is a collection of brominated marine natural products isolated from a Brazilian strain of the red alga Laurencia aldingensis. Red algae of the Laurencia genus produce a myriad of halogenated secondary metabolites, many of which are useful as taxonomic markers for species identification. It was in this vein that the aldingenins were isolated and characterized: as part of a taxonomic investigation of the Brazilian species of Laurencia. In the aldingenin family, aldingenin A was isolated in 2003, followed by the isolation of aldingenin B, C and D in 2006. Their structures are shown in Figure 37.
Figure 37: Novel Sesquiterpenes Aldingenin A, Aldingenin B, Aldingenin C and Aldingenin D
Isolated from Laurencia aldingeninsis

7.4 Retrosynthetic analysis of aldingenin B

Aldingenin B\textsuperscript{46b} (Figure 38) caught our attention due to its compact and highly oxygenated tetracyclic structure. As a target for stereoselective synthesis, it presents interesting challenges with respect to the controlled oxidation and installation of complex functionality — especially at C5 — into a relatively simple \(\alpha\)-bisabolene carbon framework.

Figure 38: Aldingenin B (1) and \(\alpha\)-Bisabolene

Our retrosynthetic analysis of aldingenin B is presented in Figure 39. A late stage bromoetherification is planned for installation of the C7–C11 oxane ring, leading to the identification of tricyclic keto-ketal 3 as the core target. Figure 39 revolves around the central
alkyne 2: our assembly / carbonyl extrusion strategy coupled with the innovative oxidative alkyne ketalization would greatly simplify the chemical synthesis. The assembly / carbonyl extrusion of DHP triflate 5 would produce anti-homopropargyl alcohol 4 for assembling alkyne-diol 2 (Figure 39). The anti-homopropargyl alcohol 4 would be difficult to assemble by conventional methods such as allenylmetal addition, acetylide opening of a terminal epoxide, or Corey-Fuchs alkynylation.

Figure 39: Retrosynthetic Analysis of Aldingenin B

In the forward direction, our plan is to convert anti-aldol fragment 6 into homopropargyl alcohol 4 using the annulation and carbonyl extrusion sequence. Ring-closing metathesis and asymmetric dihydroxylation under reagent control would convert 4 into the pivotal synthetic intermediate, alkylnyl-cyclohexanediol 2. A novel oxidative cyclo-ketalization of alkyne-diol 2 is envisioned, as is discussed in the following sections (Figure 40).

Figure 40: Carbonyl Extrusion Approach to Alkyne-diol 2 from Anti-aldol Fragment 6
7.5 Oxidative ketalization of alkynes

As shown in the retrosynthetic analysis (Chapter 7.4, Figure 39), there are two key steps for the synthesis of aldingenin B: (1) the assembly / carbonyl extrusion for making homopropargyl alcohol fragment 4; (2) the oxidative keto-ketalization of alkyne-diol 2. The carbonyl extrusion strategy has been reported previously by the Dudley lab, but precedent for the oxidative keto-ketalization has not been established.

Oxidation of alkynes to \(\alpha\)-diketones can be accomplished with reagents including permanganate ion\(^{52}\) and ozone\(^{53}\), as well as several transition metal-catalyzed processes\(^{54}\), etc. The Lee group reported a general method for the oxidation of alkynes by potassium permanganate to the corresponding 1,2-diones in aqueous acetone solutions (Figure 41).\(^{53}\) In order to obtain good yields, the reaction mixture was maintained as a neutral solution. This is achieved by addition of sodium bicarbonate and magnesium sulfate, which serve as a buffer (pH 7.0-7.5 initially) and neutralize hydroxide ions which are produced during the reduction of permanganate.

\[
\text{R} \equiv \text{R}' \xrightarrow{\text{KMnO}_4} \text{R} = \text{R}'
\]

**Figure 41:** Oxidation of Alkynes by Potassium Permanganate in Aqueous Acetone

Another frequently used method for the oxidation of alkynes is ozonolysis, such as the oxidation used by the Fuganti group in the synthesis of 2-acetyl-1-pyrroline and 2-propionyl-1-pyrroline\(^{54}\) (the key roast-smelling odorants in food). The N-phenylacetyl amides were oxidatively converted by ozone at low temperature to 4,5-diketones after being treated with \(\text{Me}_2\text{S}\). The 4,5-diketones were finally converted to 2-acetyl-1-pyrroline and 2-propionyl-1-pyrrolone (Figure 42).
Besides the stoichiometric oxidation of alkynes, catalytic oxidations can also be achieved by transition-metal-catalyzed oxidations. One example among these conditions is the oxidation with hydrogen peroxide, catalyzed by methylrhenium trioxide (MTO), which was published by the Espenson group in 1995 (Figure 43).55

We were interested in potentially coupling one of these methods with ketal formation, such that cyclization to the ketal is concerted with the alkyne oxidation. However, these methods generally involve harsh oxidants with poor functional group tolerance and are best suited for use on simple alkynes with aryl and/or tert-alkyl substituents. At the same time, it was tempting retrosynthetically to unravel the keto-ketal to α-diketone 7, but strategic analysis of 7 prompted concerns (Figure 44). α-Diketones easily undergo tautomerization to enols, and the enol of C7 (7’) would both compromise C6 stereochemistry and threaten to promote elimination of the protected C5 alcohol. Note that keto-ketal 3 cannot tautomerize (Bredt’s rule). Therefore, we prioritized the goal of installing the C7-C8 keto-ketal of 3 without producing an intermediate.
C7-C8 diketone, and our synthetic efforts focused on alkyne 2. As a result, we needed to avoid the formation of α-diketone 7. Specifically, we required a method suitable for oxidation of dialkylalkynes to α-keto ketals in the presence of alcohols.

A thorough scan of the literature revealed a single example of the type of keto-ketalization envisioned for the synthesis of aldingenin B. As part of a larger study on selenium-mediated oxidations, Tiecco reported the oxidation of 4-octyne to 5,5-dimethoxy-4-octanone using ammonium peroxydisulfate and diphenyl diselenide in methanol\(^\text{56}\) (Scheme 45, \(R =\) methyl; \(R^1, R^2 = n\)-propyl, 51% yield). Two features of this reaction were especially attractive for our purposes: use of methanol as solvent suggests compatibility with alcohols, and the postulated mechanism does not involve an intermediate α-diketone. However, despite significant interest in the oxidation of alkynes, Tiecco’s methodology has received no reported follow-up attention in recent decades.\(^\text{57}\) We planned to employ an intramolecular version of Tiecco’s
oxidative keto-ketalization of alkynes as a simplified transformation in the synthesis of the tricyclic core of aldingenin B (Chapter 8).

In summary, we have chosen aldingenin B as an ideal target system in which to apply and test our assembly / carbonyl extrusion strategy. The synthesis and subsequent oxo-ketalization of alkyne-diol 2 would rapidly build the dense polycyclic core of aldingenin B. While our assembly / carbonyl extrusion strategy has been well studied, we knew nothing about the oxo-ketalization. As a result, the specific goal for this dissertation was to prepare a complex model (alkyne-diol 2) by conventional methods and establish the feasibility of the oxidative alkyne ketalization. This will be shown in the following chapter (Chapter 8).
CHAPTER EIGHT
SYNTHESIS TOWARDS THE TRICYCLIC CORE OF ALDINGENIN B

This chapter describes the completion of an aldingenin B model study that provides the foundation for the key oxidative keto-ketalization. Proving that this unprecedented reaction is possible was one of the central goals of my dissertation research.

8.1 Model study--- test of the oxidative ketalization step

We launched a preliminary investigation to establish the feasibility of the proposed oxidative alkyne-diol oxo-ketalization. Model alkyne-diol 10 was prepared as a mixture of diastereomers by a lengthy but straightforward reaction sequence (Figure 46): Diels-Alder reaction between acrylaldehyde and isoprene afforded cyclic aldehyde 8, which was converted to alkyne 9 via Corey-Fuchs reaction. The alkyne-ene 9 was oxidized by osmium tetroxide to yield alkyne-diol 10 — the key compound for testing the oxidative ketalization. Alkyne-diol 10 was subjected to the Tiecco conditions and the oxo-ketalization provided α-keto dioxolane 11 in 40% estimated yield based on the diastereomeric purity of alkyne-diol 10 (Figure 47). From this result we concluded that the intramolecular Tiecco oxidation viably served as a simplifying transformation in the synthesis of aldingenin B. However, the isolated yield of 11 could not be established, because the diol 10 comprised the mixture of diastereomers.
8.2 Synthesis of the alkyne-diol 2a for the oxidative ketalization

We then started the synthesis towards the tricyclic core (2a) of aldingenin B (Figure 48). As mentioned above, we planned an intramolecular oxo-ketalization on alkyne-diol 2a to yield tricyclic core 12a. The synthesis of alkyne-diol 2a began with the known Diels–Alder reaction between propiolic acid and isoprene, which provides cyclohexadienyl acid 13 (Scheme 49). After conversion to the methyl ester, regioselective dihydroxylation of the more electron-rich alkene gave diol 14. Diol 14 was initially protected as an acetonide (15), but downstream in the synthetic sequence is a hydroboration that proved not to be satisfactory with the acetonide in place (15 → 16). Therefore, the protection strategy was altered to feature TBS ethers (17) in lieu of the acetonide. Reduction of the methyl ester of 17 and hydroboration / oxidation gave diol 18 as a single diastereomer, in contrast to non-selective hydroboration leading to acetal 16.
Figure 48: The Tricyclic Core (12a) of Aldingenin B.

Figure 49: Synthesis of Diol 18 (See Chapter 10 for Details)

The secondary alcohol of diol 18 was converted to a PMB ether using a standard two-step sequence (18 → 19). Primary alcohol 19 was oxidized to the aldehyde with PCC and then converted to terminal alkyne 21 using the Ohira–Bestmann reagent (20). Finally, methylation of alkyne 21 (n-BuLi; Mel) and desilylation with TBAF completed the synthesis of alkyne-diol 2a (Figure 50).
8.3 Oxidative keto-ketalization on alkyne-diol 2a

The mechanism envisioned for the oxidation and diol cyclization process is outlined in Figure 51. The first steps involve coordination of the active selenium oxidant and cyclohexane ring-flipping into a conformation (IV) in which cyclization is possible. Cyclohexane conformations with multiple axial substituents are typically disfavored because of diaxial interactions, but in this case one diaxial interaction is believed to be favorable, leading to bond construction and formation of vinylselenide intermediate V. A second oxy-selenenylation would result in seleno-ketal VI, the hydrolysis of which provides keto-ketal 12a. In the event, treatment of alkyne-diol 2a with one equiv of diphenyl diselenide and two equiv of ammonium persulfate in aqueous acetonitrile at 85 °C provided tricyclic α-keto ketal 12a in 52% yield (Figure 51).

This novel cyclo-ketalization reaction using Tiecco’s conditions simplifies the synthesis of aldingenin B by building two new heterocycles into the monocyclic carbon framework. Optimization of this key step remains a work in progress, but we have concluded that water is a critical co-solvent with acetonitrile and 85 °C seems to be the optimal temperature. As we shift our attention to the natural product, what remains is to construct a more elaborate analog of alkyne 2a, with functionality in place to facilitate bromoetherification and complete the fourth and final ring of aldingenin B.
In summary, this is the first example of an alkyne-diol oxidative cyclo-ketalization as a model study for the synthesis of aldingenin B. The selenium-mediated process delivers the complex tricyclic core of aldingenin B from a modestly functionalized cyclohexane precursor. As it is shown in this chapter, we achieved our goal of establishing the viability of oxidative cyclo-ketalization in the tricyclic core of aldingenin B. It provided the foundation for the others in the lab to combine this novel step together with our carbonyl extrusion chemistry towards the enantioselective synthesis of this natural product in the future.

**Figure 51:** Oxidative Alkyne-diol Keto-ketalization [and Proposed Mechanism] for the Synthesis of Aldingenin B. (See Chapter 10 for details)
CHAPTER NINE

PRELIMINARY EXPERIMENTS TO GUIDE FUTURE EFFORTS

Based on the success of the oxidative cyclo-ketalization on alkyne-diol \(2a\), some preliminary experiments were carried out to guide future efforts for the total synthesis of aldingenin B. In general, three useful observations were collected.

1) The oxidative keto-ketalization did not work on alkynes with an alkenyl chain

We prepared alkyne-diol \(2b\) with a prenyl group on the alkyne for the oxidative cyclo-ketalization (Figure 52), however, the prenyl group was not stable under the oxidative condition.

![Figure 52: Preparation and Oxidative Cyclo-ketalization of Alkyne-diol 2b.](image)

2) The oxidative keto-ketalization did work on alkynes with an alkyl chain

We then tried to make alkyne-diols with different alkyl chains \((2c, 2d, 2e)\) and planned to craft an alkene for the bromoetherication after the oxidative keto-ketalization. However, we were not able to make alkyne-diol \(2c\) due to difficulty in the deprotection of TBS groups. Relatively
mild conditions, such as formic acid, HCl, CsF, etc., were not strong enough to take off the two TBS groups; while harsh conditions, such as TBAF destroyed the bromo-side chain (Figure 53).

![Chemical structure](image)

**Figure 53**: Intended Preparation of Alkyne-diol 2c. (See Chapter 10 for Details)

Alkyne-diol 2d gave rise to the tricyclic α-keto ketal 12d in 37% yield (Figure 54). We envisioned a directed oxidation (Figure 55, Equation 55c) at a later stage to introduce a hydroxyl group at the tertiary carbon of the 2-methylbutyl group (12d → 12d'). The combination of catalytic RuCl₃ and pyridine with KBrO₃ efficiently promoted the hydroxylation of unactivated tertiary C — H bonds and selectively toward tertiary C — H centers (Figure 55, Equation 55a). The hydroxylation showed some selectivity when there were multiple tertiary C — H centers (Figure 55, Equation 55b). As a result, even though there are multiple tertiary C — H centers in α-keto ketal 12d, we anticipated the oxidation at the tertiary carbon of 2-methylbutyl group due to the directing ability of the oxygen atom next to it. However, strategic analysis of α-keto ketal 12d raised concerns. It is possible that α-keto ketal 12d can undergo a retro-aldol process to destroy the tricyclic core for the synthesis of aldingenin B (Figure 56). As a result, we removed the carbonyl group by Grignard addition to α-keto ketal 12d. The addition provided tertiary alcohol 23a in 70% yield. But the directed oxidation of tertiary alcohol 23a did not afford the desired diol 24. Instead, the PMB group was oxidized and fell off the tricyclic core (Figure 57).
Figure 54: Synthesis of α-Keto Ketal 12d. (See Chapter 10 for Details)

Figure 55: Ruthenium-Catalyzed Hydroxylation of Unactivated Tertiary C-H Bonds.

Figure 56: Potential Retro-aldol Process for α-Keto Ketal 12d.
In order to avoid the problem caused by PMB group, we switched it to a pivaloyl group (Piv) and a TBS group separately (Figure 58). However, in both cases, the oxidation reaction did not give the desired product. It appeared that alcohols 23b and 23c were oxidized not on the desired tertiary carbon, but on other carbons within the rings (Figure 58).

Fortunately, we were able to prepare alkyne-diol 2e with a benzyloxypropyl side chain and preliminary result of the oxidative cyclo-ketalization showed formation of tricyclic α-keto ketal 12e (Figure 59).
3) A way to craft the alkenyl chain for final bromoetherification was proposed.

In order to complete the first total synthesis of aldingenin B, we intend to convert the benzyloxylpropanyl side chain of α-keto ketal 12e into a prenyl group after addition of methyl Grignard (25→→28). Bromoetherification and deprotection are expected to provide aldingenin B (Figure 60).
In summary, the preparation and selenium-mediated cyclo-ketalization of an alkyne-diol was described as a model study for the synthesis of aldingenin B in this dissertation. The intramolecular oxidative keto-ketalization was an unprecedented reaction before this dissertation; my goal to prepare a model alkyne-diol by conventional methods and establish the feasibility of the oxidative alkyne ketalization was accomplished. The oxidative cyclization is a simplifying transformation for aldingenin B, as it provides a convenient method for generating the tricyclic core of the natural product from a functionalized carbocycle. The synthesis of the tricyclic core of aldingenin B provides the foundation for others to combine the novel oxidative keto-ketalization together with carbonyl extrusion chemistry towards the enantioselective synthesis of this natural product in the future. Preliminary experiments to guide future efforts towards the total synthesis of aldingenin B were also presented in this dissertation.
CHAPTER TEN

EXPERIMENTAL: A SYNTHETIC APPROACH TO ALDINGENIN B

General information

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on a 400 MHz (or 300 MHz) spectrometer using CDCl$_3$ as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to internal TMS (0 ppm for $^1$H NMR) or the residual CDCl$_3$ peak (7.26 ppm for $^1$H NMR, 77.0 ppm for $^{13}$C NMR). The coupling constants (J) were reported in Hertz (Hz). IR spectra were recorded on an FT-IR spectrometer. Mass spectra were recorded using electrospray ionization (ESI), electron ionization (EI), chemical ionization (CI) or fast atom bombardment (FAB) techniques. All chemicals were used as received unless otherwise stated. Tetrahydrofuran (THF) was purified by passing over a column of dry alumina. Methylene chloride (CH$_2$Cl$_2$) was distilled from calcium hydride (CaH$_2$). Other solvents were used without any purification. Glassware, NMR tubes, stir bars, needles, and syringes were dried overnight in an oven heated at 120 °C. All reactions were performed under nitrogen atmosphere unless otherwise noted. Neutral organic compounds were purified by flash column chromatography using silica gel F-254 (230-499 mesh particle size). Yields refer to isolated material judged to be $\geq95\%$ pure by $^1$H NMR spectroscopy.

General experimental procedures & Characterization data

\[ \text{H} + \text{O} \xrightarrow{\text{AlCl}_3, \text{THF}, 30^\circ\text{C}, \text{65\%}} \text{C} \]

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4-Methylcyclohex-3-enecarbaldehyde (8): A screw-capped vial equipped with a magnetic stirrer was charged with AlCl₃ (0.74 mmol) and THF (1.5 mmol). After 15 minutes acrylaldehyde was added (15 mmol) into the vial and isoprene (15 mmol) was added after additional 15 minutes at room temperature. The resulting mixture was warmed up to 30 ºC for 3 hours before quenched with saturated NaHCO₃ solution (15 mL). The reaction mixture was then extracted with diethyl ether (3 x 15 mL). The combined organics were washed with saturated aqueous sodium chloride (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product. It was purified by chromatography on silica gel (elution with 20% EtOAc/Hexanes) to provide 1.21 g of aldehyde 8 in 65% yield. The ¹H NMR of aldehyde 8 matched with the reported data.

1-Methyl-4-(prop-1-ynyl)cyclohex-1-ene (9): To a solution of CBr₄ (1.7 g, 5.1 mmol) in DCM (30 mL) was added PPh₃ (1.3 g, 5.1 mmol) and Zn dust (0.33g, 5.1 mmol) at room temperature. The resulting solution was stirred for 1 hour before addition of aldehyde 8 (0.30g, 2.4 mmol) in one portion. The reaction mixture was then stirred for another 2 hours and ethyl acetate (50 mL) was added to precipitate triphenyl phosphorus oxide as a white solid. The mixture was then filtrated through Celite and the filter liquor was concentrated under reduced pressure to give the crude product. The crude product was purified by chromatography on silica gel (elution with 20% EtOAc/Hexanes), then dissolved in THF (8 mL) and used in the next step. To this THF solution was added n-BuLi (1.1 mL, 2.5 M, 4.8 mmol) at -78 ºC and stirred for 45 minutes before MeI (2.4 mmol) was added. The resulting solution was then stirred for another 15 minutes and quenched with saturated NH₄Cl solution (10 mL). The reaction mixture was then extracted with diethyl ether (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 20% EtOAc/Hexanes) to provide 232 mg of alkyne 9 in 72% yield over two steps; ¹H NMR
(300 MHz, CDCl₃) δ 5.35 (s, 1H), 2.59-2.46 (m, 1H), 2.18-1.74 (m, 4H), 1.65 (3, 3H), 1.56-1.43 (m, 1H).

1-Methyl-4-(prop-1-ynyl)cyclohexane-1,2-diol (10): To a solution of NMO (0.18 g, 1.5 mmol) in H₂O (0.5 mL) and acetone (2 mL) was added 1-Methyl-4-(prop-1-ynyl)cyclohex-1-ene 9 (0.13 g, 1.0 mmol) and an aqueous solution of 41 mg/mL OsO₄ (32 μL, 1.3 mg, 0.0050 mmol) were added to NMO (3.71 g, 31.6 mmol) in H₂O (2 mL) and acetone (12 mL) and the reaction mixture stirred vigorously overnight. A slurry of fluorisil (83 mg) and sodium hydrosulfite (28 g) were added to quench the reaction and the mixture were stirred for 30 min at room temperature. After filtered through a pad of celite, the filtrate was concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 50% EtOAc/Hexanes) to provide 98 mg of diol 10 in 58% yield. ¹H NMR showed that diol 10 was a mixture of two diastereomers.

Compound (15): A solution of alkyne-diol 10 (98 mg, 0.58 mmol), diphenyl diselenide (0.18 g, 0.58 mmol) and ammonium peroxydisulfate (0.27 g, 1.2 mmol) in CH₃CN (5 mL) and H₂O (1 mL) was stirred at 85 °C for 2 hours. The reaction mixture was then cooled down to room temperature, diluted with H₂O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 15%-20% EtOAc/Hexanes) to provide 18 mg of keto-ketal 11. ¹H NMR (300 MHz, CDCl₃) δ 4.16 (app d, 1H, J=2.1 Hz), 2.77-2.72 (m, 1H), 2.24-2.18 (m, 1H), 2.00-1.93 (m, 3H), 1.78-1.71 (m, 2H), 1.46 (s, 3H), 1.42 (s, 3H); ¹³C NMR (100 MHz,
CDCl$_3$) $\delta$ 204.1, 106.7, 81.1, 79.7, 41.4, 32.9, 28.7, 27.4, 23.4, 16.8.

4-Methylcyclohexa-1,4-dienecarboxylic acid (13)$^{63}$: A toluene (50 mL) solution of propiolic acid (5.0 g, 68 mmol), isoprene (13.6 mL, 136 mmol) and hydroquinone (60 mg) were heated in a sealed tube to 120 °C for 24 hours. The reaction mixture was then cooled to room temperature, while a white crystal precipitated. The white crystal which is carboxylic acid 13 was then collected by filtration (77% yield) and used in the next step. The $^1$H NMR of carboxylic acid (13) matched with the reported data.

Compound (14): 4-Methylcyclohexa-1,4-dienecarboxylic acid (13) (3.0 g, 22 mmol) was refluxed in 30 mL methanol with 3 drops of sulfuric acid until all the starting material was consumed. The reaction mixture was then diluted with saturated sodium bicarbonate solution (10 mL) and water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organics were washed with saturated aqueous sodium chloride (30 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a colorless oil. This crude product was then added to a 250-mL round-bottomed flask, which was equipped with a magnetic stirrer, charged with AD-mix-$\beta$ (30 g) and methanesulfonylamine (2.1 g, 22 mmol) in a solution of tert-butyl alcohol (100 mL) and water (100 mL) at 0 °C. The heterogeneous slurry was stirred vigorously at 0 °C for 60 h. While the mixture was stirred at 0 °C, solid sodium sulfite (32 g) was added and the mixture was allowed to warm to room temperature and stirred for 60 minutes. The reaction mixture was then extracted with ethyl acetate (4 x 50 mL). The combined organics were washed with 2 N KOH solution (50 mL), saturated aqueous sodium chloride (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a white solid. The crude product mixture was purified by chromatography on silica gel (elution with 50% EtOAc/Hexanes) to provide 3.17 g
of diol 13 as a white solid (79% yield over two steps); mp 85-86 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.88 (m, 1H), 3.74 (s, 3H), 3.11 (s, 1H), 2.60-2.31 (m, 4H), 2.07-1.89 (app br s, 2H), 1.24 (s, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.2, 137.0, 126.5, 72.2, 70.5, 51.7, 37.1, 30.8, 24.8; IR (cm\(^{-1}\)) 3386, 2952, 1701, 1652, 1438, 1321, 1257, 1132, 1049; HRMS (CI+) Calcd for C\(_9\)H\(_{15}\)O\(_4\): 187.0970, found: 187.0961.

**Compound 15:** Methyl 4,5-dihydroxy-4-methylcyclohex-1-enecarboxylate (14) (250 mg, 1.34 mmol) was stirred together with camphorsulfonic acid (31 mg, 0.13 mmol) and 2,2-dimethoxypropane (699 mg, 6.71 mmol) in dichloromethane (5 mL) at room temperature for 1h. The resulting mixture was then diluted with saturated sodium bicarbonate solution (5 mL) and water (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide 258 mg of acetonide 15 in 85% yield as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.98 (m, 1H), 4.13 (m, 1H), 3.74 (s, 3H), 2.90 (app br d, 1H, J=18.0 Hz), 2.49 (app qm, 2H, J=18.0 Hz), 2.16 (app dm, 1H, J=18.0 Hz), 1.37 (s, 6H), 1.32 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.9, 137.6, 127.5, 107.6, 78.6, 78.3, 51.7, 37.1, 27.9, 26.9, 26.7, 25.9; IR (cm\(^{-1}\)) 2986, 1715, 1660, 1436, 1376, 1255, 1212, 1177, 1133, 1098, 1075, 1041; HRMS (CI+) Calcd for C\(_{12}\)H\(_{19}\)O\(_4\): 227.1283, found: 227.1288.

**Compound 12a:** To a solution of acetonide 12 (226 mg, 1.00 mmol) in THF (5 mL) was added
lithium aluminum hydride powder (95%, 88 mg, 2.2 mmol) in portions over 5 min at 0 °C. The reaction mixture was then warmed up to room temperature, stirred for 1 hour and then quenched with H₂O (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 30% EtOAc/Hexanes) to provide 182 mg of alcohol 12a in 92% yield as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.73 (app br s, 1H), 4.12 (dd, 2H, J=4.6, 2.2 Hz), 4.06 (s, 2H), 2.48 (app br d, 1H, J=17.2 Hz), 2.31 (app qm, 2H, J=17.2 Hz), 1.97 (app br d, 1H, J=16.6 Hz), 1.54 (br s, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 135.3, 121.4, 107.4, 79.9, 79.0, 66.5, 36.0, 28.7, 27.8, 26.9, 26.0; IR (cm⁻¹) 3429, 2983, 2932, 1455, 1373, 1241, 1212, 1185, 1156, 1127, 1086, 1049; HRMS (Cl+) Calcd for C₁₁H₁₉O₃: 199.1334, found: 199.1324.

**Compound 17**: To a solution of diol 14 (186 mg, 1.00 mmol) and 2, 6-lutidine (0.46 mL, 4.0 mmol) in DCM (2 mL) was added TBSOTf (0.69 mL, 3.0 mmol) drop by drop at room temperature. The reaction mixture was stirred at room temperature for 30 min, and then quenched with H₂O (10 mL). The reaction mixture was extracted with dichloromethane (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 5% EtOAc/Hexanes) to provide 410 mg of TBS ether 17 in quantitative yield as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 6.75 (m, 1H), 3.73 (s, 3H), 3.52 (t, 1H, J=7.6 Hz), 2.44-2.35 (m, 3H), 2.26-2.19 (m, 1H), 1.26 (s, 3H), 0.91 (s, 9H), 0.81 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 136.5, 128.6, 74.3, 73.1, 51.6, 41.0, 31.0, 26.0, 25.9, 25.8, 18.3, 18.1, -2.0, -2.3, -4.2, -4.8; IR (cm⁻¹) 2954, 2929, 2887, 2857, 1719, 1655, 1472, 1463, 1436, 1388, 1361, 1325, 1291, 1249, 1180, 1137, 1100, 1088, 1063, 1042, 1026, 1005; HRMS (FAB+) Calcd for C₂₁H₄₂O₄Si₂Na: 437.2519, found: 437.2540.
**Compound 17a:** To a solution of TBS ether 17 (415 mg, 1.00 mmol) in THF (5 mL) was added lithium aluminum hydride powder (95%, 88 mg, 2.2 mmol) in portions over 5 min at 0 °C. The reaction mixture was then warmed up to room temperature, stirred for 1 hour and then quenched with H₂O (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 15% EtOAc/Hexanes) to provide 387 mg of alcohol 17a in quantitative as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.44 (s, 1H), 3.98 (s, 2H), 3.56 (dd, 1H, J=9.4, 5.6 Hz), 2.31-2.04 (m, 4H), 1.24 (s, 1H), 0.90 (s, 9H), 0.82 (s, 9H), 0.09-0.02 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 136.1, 119.8, 74.6, 73.7, 66.9, 40.3, 32.8, 26.3, 25.9, 25.8, 18.4, 18.1, -2.0, -2.4, -4.2, -4.8; IR (cm⁻¹) 3322, 2955, 2929, 2886, 2856, 1472, 1463, 1427, 1407, 1388, 1361, 1322, 1294, 1251, 1179, 1146, 1116, 1095, 1053, 1030, 1005; HRMS (EI+) Calcd for C₂₀H₄₂O₃Si₂: 386.2673, found: 386.2658.

**Compound 18:** Alcohol 17a (387 mg, 1.00 mmol) was dissolved in THF (5 mL) in a 25-mL round bottom flask at room temperature. To this solution was added borane tetrahydrofuran complex solution (1.5 mL, 1.0 M in THF) dropwise, and the resulting solution was stirred for 2 hours. Then 3 N NaOH solution (2.8 mL) and H₂O₂ (1.3 mL) were added to the reaction mixture and stirred for another 2 hours. The resulting mixture was extracted with EtOAc (4 x 10 mL). The combined organic extracts were then washed with saturated aqueous sodium chloride (2 x 10mL), dried (Na₂SO₄), filtered, concentrated under vacuum, and purified on silica gel (30% EtOAc/Hexanes) to give diol 18 in 72% yield as a white solid, mp 140-141°C; ¹H NMR (400 MHz, CDCl₃) δ 3.91 (td, 1H, J=10.5, 4.5 Hz), 3.68-3.64 (app br m, 2H, J=11.0, 4.5 Hz), 2.94-2.87 (app br m, 2H), 1.97 (dd, 1H, J=13.0, 4.5 Hz), 1.65-1.60 (m, 1H), 1.50 (q, 1H, J=12.2 Hz), 1.38-1.29 (m, 2H), 1.22 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.10-0.04(m, 12H); ¹³C NMR (100 MHz, CDCl₃) 76.4, 75.6, 72.5, 68.6, 47.8, 44.4, 31.1, 26.8, 26.0, 25.9, 18.5, 18.1, -1.9, -2.1, -4.4, -4.6; IR (cm⁻¹) 3431, 2951, 2927, 2892, 2856, 1472, 1462, 1443, 1407, 1386, 1361, 1330, 1251,
1191, 1141, 1108, 1050, 1014; HRMS (FAB+) Calcd for C_{20}H_{44}O_{4}Si_{2}Na: 427.2676, found: 427.2673.

**Compound 19**: To a solution of diol 18 (405 mg, 1.00 mmol) and pyridinium p-toluenesulfonate (25 mg, 0.1 mmol) in DCM (5 mL) was added anisaldehyde dimethyl acetal (0.34 mL, 2.0 mmol) at room temperature. The reaction mixture was stirred for 2 hours and then diluted with H_{2}O (10 mL). The reaction mixture was extracted with DCM (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (2 x 10 mL), dried over Na_{2}SO_{4}, filtered and concentrated under reduced pressure to give a colorless oil. This crude product was then dissolved in DCM (5 mL) in a 25-mL round bottom flask at room temperature. To this solution was added diisobutylaluminium hydride solution (2.4 mL, 1.0 M in THF) dropwise, and the resulting solution was stirred for 4 hours and then quenched with H_{2}O (10 mL). The reaction mixture was extracted with DCM (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na_{2}SO_{4}, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 15% EtOAc/Hexanes) to provide 367 mg of primary alcohol 19 (70% yield over 2 steps) as colorless oil. ^1H NMR (400 MHz, CDCl$_3$) δ 7.24 (d, 2H, J=8.6 Hz), 6.87 (d, 2H, J=8.6 Hz), 4.57 (d, A part of ABX, 1H, J=11.1 Hz), 4.33 (d, B part of ABX, 1H, J=11.1 Hz), 3.79 (s, 3H), 3.73-3.61 (m, 2H), 3.56-3.49 (m, 1H), 3.36 (dd, 1H, J=11.0, 4.6 Hz), 3.02 (app br d, 1H, J=7.9 Hz), 2.20 (dd, 1H, J=12.9, 4.2 Hz), 1.76-1.68 (app br s, 1H), 1.54 (q, 1H, J=11.4 Hz), 1.47-1.42 (m, 1H), 1.29-1.22 (m, 4H), 0.89 (s, 9H), 0.86 (s, 9H), 0.11-0.04 (m, 12 H); ^13C NMR (100 MHz, CDCl$_3$) δ 159.3, 130.1, 129.4, 114.0, 79.3, 76.5, 75.7, 70.2, 67.9, 55.3, 43.8, 43.5, 31.8, 27.0, 26.0, 25.9, 18.5, 18.1, -1.9, -2.0, -4.4, -4.6; IR (cm$^{-1}$) 3468, 2953, 2929, 2884, 2856, 1613, 1587, 1514, 1471, 1463, 1388, 1361, 1337, 1302, 1248, 1190,
Compound 21: A suspension of primary alcohol 19 (525 mg, 1.00 mmol), Celite (525 mg) and pyridinium chlorochromate (431 mg, 2.00 mmol) in DCM (5 mL) was stirred at room temperature for 12 hours. The reaction mixture was then filtered through a short column and the filtrate was concentrated under reduced pressure to give a white solid. This crude product was added to a 25-mL round-bottomed flask, which was equipped with a magnetic stirrer, charged with Bestmann’s reagent 20 (480 mg, 2.50 mmol) and K₂CO₃ (415 mg, 3.00 mmol) in a solution of methanol (5 mL) at room temperature. The resulting solution was stirred for 5 hours and then diluted with H₂O (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a white solid. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide 327 mg of alkyne 21 (63% yield over 2 steps) as a white crystal, mp 140-141°C; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, 2H, J=8.5 Hz), 6.86 (d, 2H, J=8.6 Hz), 4.64, 4.60 (ABq, 2H, J=11.4 Hz), 3.80 (s, 3H), 3.68 (td, 1H, J=10.8, 4.3 Hz), 3.24 (dd, 1H, J=11.2, 4.3 Hz), 2.39 (tm, 1H, J=10.9 Hz), 2.12 (d, 1H, J=2.2 Hz), 2.04-1.95 (m, 2H), 1.83-1.77 (m, 1H), 1.23-1.17 (m, 4H), 0.89 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 130.9, 129.4, 113.7, 86.2, 76.6, 75.7, 75.5, 71.8, 68.9, 55.3, 44.6, 35.4, 35.1, 26.8, 26.0, 25.9, 18.5, 18.1, -1.9, -2.2, -4.4, -4.7; IR (cm⁻¹) 3313, 2955, 2930, 2886, 2857, 1613, 1587, 1513, 1472, 1463, 1388, 1361, 1302, 1249, 1191, 1172, 1158, 1132, 1109, 1081, 1052; HRMS (FAB+) Calcd for C₂₉H₅₀O₄Si₂Na: 541.3145, found: 541.3147.
**Compound 21a**: To a solution of alkyne 21 (104 mg, 0.200 mmol) in THF (1 mL) was added n-butyllithium (94 μl, 2.25 N, 0.21 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes. Methyl iodide (19 μl, 0.30 mmol) was then added into the reaction mixture and the solution was warmed up to room temperature and stirred overnight. The reaction was quenched with H₂O (5 mL), extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide alkyne 21a in quantitative yield as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, 2H, J=8.5 Hz), 6.86 (d, 2H, J=8.6 Hz), 4.63, 4.60 (ABq, 2H, J=11.8 Hz), 3.80 (s, 3H), 3.58 (td, 1H, J=10.7, 4.3 Hz), 3.23 (dd, 1H, J=11.2, 4.3 Hz), 2.32 (tm, 1H, J=10.8 Hz), 2.00 (dd, 1H, J=13.3, 4.3 Hz), 1.93-1.83 (m, 4H), 1.77-1.71 (m, 1H), 1.21-1.15 (m, 4H), 0.89 (s, 9H), 0.84 (s, 9H), 0.07-0.03 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 131.1, 129.4, 113.7, 80.9, 76.2, 75.9, 75.6, 71.6, 55.3, 44.7, 35.8, 35.4, 26.9, 26.0, 25.9, 18.5, 18.1, 3.7, -1.9, -2.2, -4.4, -4.6; IR (cm⁻¹) 2955, 2929, 2857, 1613, 1587, 1513, 1472, 1463, 1366, 1301, 1248, 1190, 1170, 1153, 1078, 1056, 1039, 1005; HRMS (FAB+) Calcd for C₃₀H₅₂O₄Si₂Na: 555.3302, found: 555.3300.

**Compound 2a**: A THF (2 mL) solution of alkyne 21a (107 mg, 0.200 mmol) and tetrabutylammonium fluoride (1 mL, 1 N solution in THF, 1 mmol) was heated at reflux for 3 hours. The resulting mixture was cooled to room temperature, then diluted with H₂O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil. The crude product mixture was purified by chromatography on silica gel (elution with 50% EtOAc/Hexanes) to provide diol 2a in 88% yield as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, 2H, J=8.5 Hz), 6.87 (d, 2H, J=8.6 Hz), 4.66, 4.59 (ABq, 2H, J=11.2 Hz), 3.80 (s, 3H), 3.61 (td, 1H, J=10.4, 4.2 Hz), 3.39 (dd, 1H, J=10.9, 4.5 Hz), 2.38 (tm, 1H, J=10.3 Hz), 2.14 (dd, 1H, J=13.9, 4.2 Hz), 1.99-1.95 (app br m, 3H), 1.84-1.78 (m, 4H),
1.32 (dd, 1H, $J$=13.76, 10.80 Hz), 1.25 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.1, 130.9, 129.4, 113.7, 80.3, 76.92, 76.89, 73.4, 71.90, 71.88, 55.3, 41.8, 35.2, 34.5, 27.1, 3.6; IR (cm$^{-1}$) 3421, 2932, 1613, 1586, 1514, 1455, 1367, 1302, 1247, 1173, 1145, 1060, 1036; HRMS (EI+) Calcd for C$_{18}$H$_{24}$O$_4$: 304.1675, found: 304.1679.

**Compound 2b:** Alkyne-diol 2b was prepared by the same method as for alkyne-diol 2a. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.31 (d, 2H, $J$=8.4 Hz), 6.86 (d, 2H, $J$=8.4 Hz), 5.19 (tm, 1H, $J$=6.9 Hz), 4.68 (d, A part of ABX, 1H, $J$=11.1 Hz), 4.59 (d, B part of ABX, 1H, $J$=11.1 Hz), 3.80 (s, 3H), 3.63 (td, 1H, $J$=9.9, 4.2 Hz), 3.40 (dd, 1H, $J$=10.5, 4.2 Hz), 2.89 (d, 2H, $J$=6.9 Hz), 2.44-2.38 (m, 1H), 2.17-2.11 (m, 1H), 2.02-1.80 (app br m, 2H), 1.70 (s, 3H), 1.62 (s, 3H), 1.38-1.29 (m, 1H), 1.25 (s, 3H).

**3-Bromopropyl trifluoromethanesulfonate:** DCM (10 mL) was added to a mixture of 3-bromopropan-1-ol (1.0g, 7.2 mmol) and 2, 6-lutidine (1.84 mL, 15.8 mmol). The solution was cooled to 0 $^\circ$C and triflic anhydride (2.66 mL, 15.8 mmol) was added drop by drop. The reaction mixture was stirred for 1 hour at room temperature and filtrated through a short silica gel column. The filtrate was concentrated under reduced pressure and 3-bromopropyl trifluoromethanesulfonate was obtained by bulb to bulb distillation of the crude product. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.73 (t, 2H, $J$=5.9 Hz), 3.53 (d, 2H, $J$=6.2 Hz), 2.38 (p, 2H, $J$=6.0 Hz).
**Compound 22:** To a solution of alkyne 21 (13 mg, 0.025 mmol) in THF (0.5 mL) at -78 °C was added *n*-butyllithium (56.0 μL, 2.23 N, 0.125 mmol) dropwise. The reaction mixture was stirred at -78 °C for 30 minutes before the addition of DMPU (15.0 μL, 0.125 mmol). 3-Bromopropyl trifluoromethanesulfonate (27.0 mg, 0.125 mmol) in THF (1 mL) was added into the reaction mixture and the solution was warmed up to room temperature over night. The reaction mixture was then quenched with H2O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide alkyne 22 in 71% yield. 1H NMR (400 MHz, CDCl3) δ 7.30 (d, 2H, J=8.5 Hz), 6.86 (d, 2H, J=8.6 Hz), 4.59 (s, 2H), 3.80 (s, 3H), 3.60 (td, 1H, J=10.7, 4.2 Hz), 3.52 (t, 2H, J=6.5 Hz), 3.23 (dd, 1H, J=11.2, 4.3 Hz), 2.39 (td, 2H, J=6.7, 1.7 Hz), 2.33 (tm, 1H, J=10.6 Hz), 2.06-2.00 (m, 3H), 1.90 (q, 1H, J=11.5 Hz), 1.77-1.71 (m, 1H), 1.22-1.56 (m, 4H), 0.89 (s, 9H), 0.85 (s, 9H), 0.08-0.03 (m, 12H).

**Compound 21d:** To a solution of alkyne 21d (0.12 g, 0.24 mmol) in THF (1 mL) at -78 °C was added *n*-butyllithium (0.16 mL, 2.3 N, 0.36 mmol) dropwise. The reaction mixture was stirred at -78 °C for 30 minutes before the addition of HMPA (0.10 mL, 0.60 mmol). Then 1-iodo-3-methylbutane (94 μl, 0.72 mmol) was added into the reaction mixture and the solution was warmed up to room temperature within two hours. After refluxed at 76 °C for 2 hours, the reaction was cooled down to room temperature, quenched with H2O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide alkyne 21d in quantitative yield.
chloride (5 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide alkyne $21d$ in quantitative yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (d, 2H, $J$=8.6 Hz), 6.85 (d, 2H, $J$=8.6 Hz), 4.64, 4.60 (ABq, 2H, $J$=11.5 Hz), 3.80 (s, 3H), 3.60 (td, 1H, $J$=10.7, 4.3 Hz), 3.22 (dd, 1H, $J$=11.2, 4.3 Hz), 2.33 (tm, 1H, $J$=11.4 Hz), 2.21 (tm, 2H, $J$=7.4, 1.9 Hz), 2.05-1.85 (m, 2H), 1.77-1.70 (m, 2H), 1.42 (q, 2H, $J$=7.2 Hz), 1.22-1.16 (m, 4H), 0.91-0.89 (m, 15H), 0.84 (s, 9H), 0.07-0.02 (m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.1, 131.1, 129.3, 113.7, 81.8, 80.8, 77.2, 75.8, 75.6, 71.8, 55.3, 44.7, 37.9, 36.0, 35.4, 27.2, 26.9, 26.0, 25.9, 22.23, 22.21, 18.5, 18.1, 16.9, -1.9, -2.2, -4.4, -4.7.

**Compound 2d:** A THF (2 mL) solution of alkyne $21d$ (16 mg, 0.027 mmol) and tetrabutylammonium fluoride (0.14 mL, 1 N solution in THF, 0.14 mmol) was heated at reflux for 1 day. The resulting mixture was cooled to room temperature, then diluted with H$_2$O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 50% EtOAc/Hexanes) to provide diol $2d$ in 90% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (d, 2H, $J$=8.6 Hz), 6.87 (d, 2H, $J$=8.6 Hz), 4.67 (d, A part of ABX, 1H, $J$=11.1 Hz), 4.59 (d, B part of ABX, 1H, $J$=11.1 Hz), 3.80 (s, 3H), 3.62 (td, 1H, $J$=10.2, 4.2 Hz), 2.19-2.12 (m, 3H), 2.00-1.96 (m, 1H), 1.86-1.77 (m, 1H), 1.74-1.64 (m, 1H), 1.42-1.31 (m, 3H), 1.26 (s, 3H), 0.89 (d, 3H, $J$=1.4 Hz), 0.88 (d, 3H, $J$=1.4 Hz).
[(3-iodopropoxy)methyl]benzene: To a DCM (9.5 mL) of 3-benzyloxy-1-proanol (1 g, 6 mmol) at 0 °C was added methanesulfonyl chloride (0.94 mL, 12 mmol) and Et₃N (1.68 mL, 12 mmol). The solution was warmed up to room temperature and stirred for 30 minutes before acetone (38 mL) was added. Finally, NaI (9 g, 60 mmol) was added and the solution was stirred overnight. The reaction mixture was then quenched with H₂O (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 5% EtOAc/Hexanes) to provide [(3-iodopropoxy)methyl]benzene in 91% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 4.52 (s, 2H), 3.55 (t, 2H, J=5.8 Hz), 3.31 (t, 2H, J=6.8 Hz), 2.10 (p, 2H, J=6.5 Hz).

Compound 21e: Alkyne 21e was prepared by the same method as for alkyne 21d. ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.26 (m, 7H), 6.84 (d, 2H, J=8.6 Hz), 4.63, 4.59 (ABq, 2H, J=11.5 Hz), 4.48 (s, 2H), 3.77 (s, 3H), 3.63-3.56 (m, 3H), 3.23 (dd, 1H, J=11.2, 4.3 Hz), 2.33 (app t, 3H, J=6.2 Hz), 1.99 (dd, 1H, J=13.3, 4.3 Hz), 1.95-1.80 (m, 3H), 1.77-1.72 (m, 1H), 1.22-1.16 (m, 4H), 0.89 (s, 9H), 0.84 (s, 9H), 0.07-0.03 (m, 12H).
Compound 2e: Alkyne-diol 2e was prepared by the same method as for alkyne-diol 2d. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.26 (m, 7H), 6.85 (d, 2H, $J$=8.6 Hz), 4.65 (d, A part of ABX, 1H, $J$=11.1 Hz), 4.57 (d, B part of ABX, 1H, $J$=11.1 Hz), 4.48 (s, 2H), 3.77 (s, 3H), 3.61 (td, 1H, J=10.3, 4.2 Hz), 3.56 (t, 2H, J=6.3 Hz), 3.39 (dd, 1H, $J$=10.9, 4.6 Hz), 2.39 (tm, 1H, J=10.9 Hz), 2.31 (td, 2H, J=7.0, 2.0 Hz), 2.14 (dd, 1H, $J$=13.9, 4.2 Hz), 1.98-1.93 (m, 1H), 1.83-1.77 (m, 1H), 1.33 (dd, 1H, $J$=13.9, 10.7 Hz), 1.25 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.1, 138.5, 130.9, 129.3, 128.3, 127.6, 127.5, 113.7, 81.5, 80.7, 73.4, 72.9, 72.0, 71.9, 68.9, 55.2, 41.8, 35.3, 34.5, 29.1, 27.1, 15.6.

Compound 12a (Tricyclic core of aldingenin B): A solution of diphenyl diselenide (20.5 mg, 0.066 mmol) and ammonium persulfate (30 mg, 0.13 mmol) in CH$_3$CN (1 mL) and H$_2$O (0.4 mL) was heated to 85 °C for 15 minutes. To this reaction mixture was added an acetonitrile (3 mL) solution of diol 2a (20.0 mg, 0.066 mmol). The resulting mixture was heated at 85 °C for 2 hours and cooled to room temperature. The reaction mixture was then diluted with H$_2$O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 15%-20% EtOAc/Hexanes) to provide keto-ketal 12a in 52% yield as colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25 (d, 2H, $J$=8.4 Hz), 6.89 (d, 2H, $J$=8.5 Hz), 4.53 (d, A part of ABX, 1H, $J$=11.4 Hz), 4.39 (d, B part of ABX, 1H, $J$=11.4 Hz), 4.26 (app s, 1H), 3.82-3.80 (m, 4H), 2.95 (app s, 1H), 2.51 (dd, 1H, $J$=14.4, 7.9 Hz), 2.34-2.20 (m, 2H), 1.73 (dd, 1H, $J$=14.4, 7.4 Hz), 1.44 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.3, 159.3, 129.8, 129.3, 113.9, 113.7, 81.5, 80.7, 73.4, 72.9, 72.0, 71.9, 68.9, 55.2, 41.8, 35.3, 34.5, 29.1, 27.1, 15.6.
107.3, 80.0, 79.8, 73.8, 70.6, 55.3, 47.9, 37.2, 29.3, 27.0, 16.4; IR (cm⁻¹) 2945, 1729, 1613, 1514, 1458, 1388, 1302, 1249, 1177, 1154, 1093, 1050, 1012; HRMS (ESI+) Calcd for C₁₈H₂₂O₅Na: 341.1365, found: 341.1371.

**Compound 12d**: Tricyclic compound 12d was prepared by the same method as for compound 12a. ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, 2H, J=8.6 Hz), 6.87 (d, 2H, J=8.6 Hz), 4.51 (d, A part of ABX, 1H, J=11.4 Hz), 4.37 (d, B part of ABX, 1H, J=11.4 Hz), 4.23 (app br d, 1H, J=2.1 Hz), 3.81-3.77 (m, 4H), 2.91 (s, 1H), 2.49 (dd, 1H, J=14.3, 7.8 Hz), 2.32-2.16 (m, 2H), 1.80-1.69 (m, 2H), 1.58-1.50 (m, 1H), 1.38 (s, 3H), 1.32-1.25 (m, 3H), 0.90 (d, 3H, J=0.72 Hz), 0.88 (d, 3H, J=0.76 Hz).

**Compound 23a**: To a THF (1 mL) solution of 12d (7.6 mg, 0.020 mmol) was added methyl magnesium bromide (33 µL, 1.86 N, 0.061 mmol) at room temperature. The reaction mixture was stirred overnight before quenched with H₂O (5 mL). The reaction mixture was then extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 20% EtOAc/Hexanes) to provide alcohol 23a in 72% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, 2H, J=8.4 Hz), 6.87 (d, 2H, J=8.6 Hz), 4.46 (d, A part of ABX, 1H, J=11.5 Hz), 4.40 (d, B part of ABX, 1H, J=11.5 Hz), 4.15 (t, 1H, J=7.8 Hz), 4.04 (d, 1H, J=1.8 Hz), 3.80 (s, 3H), 2.40
(dd, 1H, J=14.0, 8.1 Hz), 2.01 (s, 1H), 1.93 (t, 2H, J=2.4 Hz), 1.86-1.78 (m, 2H), 1.63-1.60 (m, 1H), 1.50-1.46 (m, 2H), 1.34 (s, 3H), 1.28-1.24 (m, 4H), 0.88 (app dd, 6H, J=6.6, 3.8 Hz).

**Compound 23b:** A mixture of alcohol 23a (8.1 mg, 0.021 mmol) and DDQ (5.7 mg, 0.025 mmol) in DCM (1 mL) and H2O (0.1 mL) was stirred at room temperature for 2 hours. The reaction mixture was then diluted with H2O (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 30% EtOAc/Hexanes) to provide the deprotected diol for the next step. The deprotected diol was then stirred together with excess PivCl and pyridine in DCM at room temperature for 1h. The reaction mixture was diluted with H2O (5 mL) and extracted with DCM (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide alcohol 23b. The structure of 23b was confirmed by 1H NMR. Even though the spectrum was not totally pure, it showed all the necessary peaks for alcohol 23b.

**Compound 23c:** The deprotection procedure for alcohol 23a was the same as for alcohol 23b. The deprotected diol was then dissolved in DCM (1 ml) at -78 ºC, followed by the addition of
access 2, 6-lutidine and TBSOTf. The reaction mixture was stirred at -78 °C for 30 minutes before quenched with H₂O (5 mL). The reaction mixture was then extracted with DCM (3 x 5 mL). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product mixture was purified by chromatography on silica gel (elution with 10% EtOAc/Hexanes) to provide alcohol 23c. The structure of 23c was confirmed by ¹H NMR. Even though the spectrum was not totally pure, it showed all the necessary peaks for alcohol 23c.

![Chemical structure of compounds 2e and 12e](image)

**Compound 12e:** Tricyclic compound 12e was prepared by the same method as for compound 12a. The structure of 12e was confirmed by ¹H NMR. Even though the spectrum was not totally pure, it showed all the necessary peaks for alcohol 12e.
TBSO  OTBS

\[ \text{CH}_3 \]

OPMB

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Publications


**Presentations**


(1) “Synthetic efforts toward the tricyclic core of roseophilin.” Yang, J.; Katukojvala, S.; Dudley, G. B. Presented at the 235th ACS National Meeting, New Orleans, LA, United States, April 6<sup>th</sup>-10<sup>th</sup>, 2008.

**Poster**

“Synthetic efforts toward the tricyclic core of roseophilin.” Yang, J.; Dudley, G. B. Presented at the 58th Southeast Regional Meeting of the American Chemical Society, Augusta, GA, United States, November 1<sup>st</sup>-4<sup>th</sup>, 2006.