STEPS TOWARD THE SYNTHESIS OF 1,1’-DIDEAZA-QUININE: A PROOF OF CONCEPT

by

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Submitted in partial fulfillment of the requirements for Departmental Honors in the Department of Chemistry and Biochemistry

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May 4, 2020
STEPS TOWARD THE SYNTHESIS OF 1,1’-DIDEAZA-QUININE: A PROOF OF CONCEPT

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Abstract

Quinine is a naturally occurring alkaloid with substantial medicinal relevance due to its historical role as an anti-malarial agent, although it is now used most often for special cases where the organism is resistant to newer drugs.\textsuperscript{1} While quinine is easily extracted from the bark of the Cinchona tree,\textsuperscript{2} the challenge of engineering a set of reactions to synthesize stereochemically pure quinine has captivated chemists for generations. Due to its four stereocenters, the synthesis of this molecule can yield up to sixteen different stereoisomers. The purpose of this study is to validate the conceptual route proposed by Stotter, Friedman, and Minter\textsuperscript{3} for the diastereoselective total synthesis of quinine via the preparation of racemic 1,1’-dideaza-quinine—a quinine analog lacking nitrogen atoms. While the total synthesis of quinine has been completed successfully by several other groups, our proposed route provides a novel process through a tandem, diastereoselective aldol addition and reduction to establish two of the four chiral centers in a single operation. This route avoids overly expensive reagents and provides a more concise synthetic scheme.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Results/Discussion</td>
<td>12</td>
</tr>
<tr>
<td>Conclusion</td>
<td>19</td>
</tr>
<tr>
<td>Experimental Procedures</td>
<td>20</td>
</tr>
<tr>
<td>References</td>
<td>26</td>
</tr>
<tr>
<td>Supporting Information</td>
<td>28</td>
</tr>
</tbody>
</table>
Figures and Schemes

Figure/Scheme: Page:

Figure 1. Chemical structure of quinine with absolute stereochemistry ........................................2
Scheme 1. Rabe’s synthesis of stereoisomeric alcohols from d-quinotoxine ........................................2
Scheme 2. Final step in Woodward’s synthesis of d-quinotoxine .................................................. 4
Scheme 3. Uskoković and Gutzwiller’s synthesis of quinine and quinidine ............................... 5
Scheme 4. Stork’s synthesis by N-1/C-2 bond formation and stereoselective oxidation .......... 6
Scheme 5. Stotter’s model synthetic scheme for the synthesis of quinine .................................... 7
Figure 2. Potential chair-like transition state for the aldol addition ........................................... 8
Figure 3. Likely intermediate for the in situ reduction of the aldol product ............................ 8
Scheme 6. Final steps of Maulide’s synthesis of quinine .......................................................... 9
Figure 4. Structural comparison of quinine and 1,1’-dideaza-quinine ........................................ 11
Scheme 7. Synthetic strategy for 1,1’-dideaza-quinine ............................................................ 11
Scheme 8. Synthetic pathway to 7-methoxy-1-naphthaldehyde (4) ...................................... 12
Scheme 9. Synthetic pathway to 6-vinylbicyclo[2.2.2]octan-2-one (11) ............................... 13
Scheme 10. Current and previous pathways from ester 7 to lactone 8 ................................ 14
Figure 5. Improved selectivity on a published lactonization reaction ...................................... 15
Scheme 11. Incomplete convergent pathway towards 1,1’-dideazaquinine .............................. 16
Introduction

Quinine (Figure 1) has become one of the world’s most well-known medicinal compounds. Present as an alkaloid in the bark of the cinchona tree, quinine has been used to treat malaria for nearly four centuries.\(^1\) The first recorded use of cinchona bark to treat malaria was in the 1630’s by Jesuit missionaries in South America, but it is presumed that natives were using this treatment long before then. The bark itself was dried, ground, and steeped with liquids for administration until the 1820’s, when Pelletier and Caventou successfully extracted pure quinine from yellow cinchona bark.\(^2\) This led to pure quinine replacing cinchona bark as the standard treatment for malaria, making it the first successful treatment of an infectious disease with a chemical compound.\(^1\) The treatment of malaria with just quinine alone remained the most popular option worldwide until the 1920’s with the development of more effective, synthetic anti-malarial drugs. Despite this, quinine has remained viable in the treatment of malaria due to the slow development of drug resistance to quinine in comparison with other pharmaceuticals. As of 2010, the World Health Organization (WHO) recommended the use of quinine in combination with another anti-malarial drug, such as doxycycline or clindamycin, as a second-line treatment for uncomplicated malaria. Despite that recommendation, the majority of African countries have continued to use quinine since 2009 as monotherapy because of its cost efficiency.

Near the beginning of the 20\(^{th}\) century, quinine became of significant interest to synthetic chemists, but not from a need for synthetic mass production.\(^1\) After all, the extraction of quinine from cinchona bark is a highly efficient process. The reason for chemists’ interest in quinine came from its alluring chemical structure shown in Figure 1. Quinine is rightfully considered a complex molecule due to its four stereocenters at carbon atoms C-3, C-4, C-8 and C-9. With these four chiral centers in addition to the presence of a bridgehead nitrogen atom, quinine promised to be a
synthetic challenge. A total synthesis of quinine could open the door to the syntheses of biologically active analogs, but ultimately quinine might serve as a template for developing new methods for stereochemical control that can be incorporated into the synthesis of other complex molecules. While the chemical structure of quinine consists of various heteroatoms as well as both aliphatic and aromatic carbon atoms, the focus of most synthetic chemists lies on the quinuclidine ring consisting of atoms N-1 and C-2 through C-8.

*Figure 1. Chemical structure of quinine with absolute stereochemistry.*

Paul Rabe, a German chemist, is credited with determining the correct atom connectivity for quinine near the beginning of the 20th century. As such, Rabe's work provided the foundation for many early attempts to synthesize this famous alkaloid. Several years prior to Rabe, Louis Pasteur had shown that an acid-catalyzed isomerization of quinine produced d-quinotoxine. Rabe set out to develop a synthetic route to reproduce quinine from d-quinotoxine, but ultimately his work resulted in a mixture of the stereoisomers quinine and quinidine (Scheme 1).

*Scheme 1. Rabe's synthesis of stereoisomeric alcohols from d-quinotoxine.*
While Rabe was able to confirm the presence of quinine and quinidine through melting point analysis, the stereochemical relationship between C-8 and C-9 was still unknown in 1918. This rendered a selective synthesis of quinine practically impossible. Once the correct stereochemical structure was determined, however, it became obvious that it was an epimerization at C-8 that caused the production of both quinine and quinidine. Additionally, the isolation of quinine over these three steps was only 2.4%. While this research was inefficient, it laid the foundation for future studies. The formation of the quinuclidine ring by establishing the N-1/C-8 bond became a popular synthetic strategy known as the “Rabe connection”. Rabe’s synthesis drew harsh criticism well into the future and its validity was questioned; but in 2008, researchers at Colorado State University were able to recreate his reactions using only techniques and supplies available in early 20th century labs thus verifying the reproducibility of the chemistry. As well, this research also confirmed the production of epiquinine and epiquinidine, which are C-9 epimers of quinine and quinidine, respectively.

While Rabe was able to convert d-quinotoxine back into quinine, this is not to be considered a synthesis per se since d-quinotoxine was available only from quinine itself. However, Harvard professor Robert Woodward was able to take advantage of this chemistry as described in a well-known article entitled “The Total Synthesis of Quinine” published in 1945. While the title of the article focuses on quinine, the content of the paper is a description of the total synthesis of d-quinotoxine. Woodward then cites the work of Rabe as a means to achieve the full synthesis of quinine. The final steps of the Woodward synthesis of d-quinotoxine are shown in Scheme 2, the first of which is a Claisen condensation that combines two similarly sized molecules using an ester enolate to create a new carbon-carbon bond. The resulting β-keto ester was hydrolyzed and decarboxylated, and the benzoyl protecting group on nitrogen was removed. Pure d-quinotoxine
was obtained by resolving the racemate with the use of diastereomeric ammonium salts. The salts were separated by recrystallization and neutralized to obtain the pure enantiomers.

**Scheme 2. Final step in Woodward’s synthesis of d-quinotoxine.**

Although the Woodward synthesis did provide a synthetic route to quinine, the scientific community was not satisfied. The research was criticized most significantly from its reliance on previous work and its failure to culminate in a complete synthesis. Since Rabe’s chemistry had not been verified at the time, many did not consider this route to be a valid synthesis of quinine. The synthetic design was also very inefficient requiring 16 steps to achieve racemic quinotoxine in 0.56% yield. The process was also not stereoselective and required two stereoisomer separations to reach d-quinotoxine. These factors combined with the low overall yield of the Rabe conversion of d-quinotoxine to quinine resulted in work that could be significantly improved upon.

The next noteworthy contribution to the total synthesis of quinine was published in 1978 from Uskoković and Gutzwiller, research chemists at the Swiss pharmaceutical company Hoffmann-La Roche. This new approach provided a complete synthesis of quinine and benefitted from the evolution of better modes of purification and analysis. The final two steps in this synthetic route are shown in Scheme 3. The strategy is similar to that of Woodward and uses the “Rabe connection” of N-1 and C-8 as the final step in the formation of the quinuclidine ring system. Unfortunately, similar difficulties were encountered regarding stereoselectivity at C-8 during ring
closure, and this resulted in the generation of epimers at that site. This led to a mixture containing mostly quinine and quinidine since the benzylic oxidation reaction was highly stereoselective.

![Scheme 3. Uskoković and Gutzwiller’s synthesis of quinine and quinidine.](image)

It is important to note that the final oxidation using molecular oxygen under basic conditions gave quinine, quinidine, and a mixture of epiquinine and epiquinidine in yields of 32%, 41%, and 15%, respectively. This unexpected stereoselectivity towards quinine and quinidine was a mechanistically intriguing outcome that could be applied to other synthetic targets as well as to future attempts at the synthesis of quinine. This synthetic route also provided quinine and quinidine in 0.64% and 0.84% yields, respectively, over 17 steps. Compared with Woodward’s synthesis, this was a significant improvement. Despite the progress that had been made, there remained the task of designing a completely stereoselective synthesis of quinine.

The aforementioned goal was finally achieved in 2001 by Gilbert Stork at Columbia University. Coincidentally, Stork had been among the loudest critics of the Woodward synthesis of quinine before publishing his own synthesis of the alkaloid. Stork cited Uskoković and Gutzwiller in the publication, as their research proved that a total synthesis of deoxyquinine would lead to a simple synthesis of quinine itself. Stork elected to attempt the synthesis of deoxyquinine via an alternative route—one that did not use the “Rabe connection” as the final step in the formation of the quinuclidine ring. This would avoid generating epimers at C-8 that previous research had encountered. Stork’s route focused on the formation of the quinuclidine ring by
using an S\textsubscript{N}2 reaction to connect N-1 and C-6 as shown in Scheme 4. The final oxidation was performed under similar conditions to prior work\textsuperscript{11,12} but was modified slightly to achieve higher stereoselectivity (~14:1 quinine:epiquinine).\textsuperscript{6}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme4}
\end{center}

\textit{Scheme 4. Stork’s synthesis by N-1/C-2 bond formation and stereoselective oxidation.}\textsuperscript{6}

Stork’s methodology improved upon previous work by creating a stereoselective route to quinine and doing so in 19 steps with an overall yield of 0.96%. Further work on the synthesis of quinine has continued since Stork’s publication. In fact, only three years later, two more total syntheses of quinine were described in which the overall yields increased to 4.3%\textsuperscript{13} and 5%.\textsuperscript{14} Both of these used the “Rabe connection” approach. While these improved yields support an advancement in chemists’ abilities to develop more efficient reactions, none of the synthetic routes represents a departure from the design strategy of forming the quinuclidine ring at a very late stage in the process. The previously shown synthetic routes to quinine are significant in their own right but, in this context of this paper, serve as examples of the same perspective.

The focus of this research is to develop a new approach to the synthesis of quinine by using a convergent route as opposed to a linear pathway. This project was inspired by the 1985 work of Stotter, Friedman, and Minter\textsuperscript{3} and constitutes a model study that will serve as a proof of concept for the total synthesis of quinine. As shown in Scheme 5, the Stotter methodology involves the use of an intact quinuclidinone and an aromatic aldehyde that are coupled in a key step. The coupling reaction itself is an aldol addition using the quinuclidinone enolate to attack the aldehyde carbonyl.
This was followed immediately by an in situ reduction to give a diol as the product. This marquee tandem addition/reduction process served to prevent the loss of the stereochemical control inherent in the addition reaction. In the final stages, the secondary alcohol on the quinuclidine ring was deoxygenated using a classical Barton method.\textsuperscript{15} The model study depicted in Scheme 5 supports the use of an aldol addition reaction to establish the correct stereochemical relationship between the newly formed chiral carbons. Since the vinyl group that would be present on the quinuclidine ring in an actual synthesis of quinine is not present, this model does not answer the questions regarding its steric impact on the aldol addition or subsequent reactions in the sequence.

\begin{center}
\textit{Scheme 5. Stotter’s model synthetic scheme for the synthesis of quinine.}\textsuperscript{3}
\end{center}

The stereoselectivity of the aldol addition that creates the highlighted bond in Scheme 5 is one of most important and unique aspects to the overall synthetic design. The stereoselectivity experienced at the benzylic carbon can be attributed to the expected transition state for the reaction. The lithium enolate of the ketone should coordinate with benzaldehyde to create a six-membered chair-like transition state as shown in Figure 2. The stereoselectivity in this type of reaction comes from the orientation of the aryl group, which is much more sterically favored in a quasi-equatorial position than in a quasi-axial position.\textsuperscript{16,17} There is significant evidence from the literature for the presence of these chair-like transition states for metal-mediated aldol addition reactions.
Figure 2. Potential chair-like transition state for the aldol addition.

Once the aldol addition has taken place, the product exists in solution as the lithium alkoxide shown in Figure 3. If the oxygen is protonated at this point, the resulting hydroxyketone will epimerize and stereochemical integrity will be lost. Because of this, an in situ reduction of the carbonyl was carried out to preserve the stereochemistry established by the aldol addition. With typical reducing agents, such as NaBH₄ or LiAlH₄, this reduction produced a mixture of trans and cis isomers. Interestingly, when the reduction was carried out with the weaker hydride donor Red-Al, only the trans isomer was formed as shown by the highlighted bonds in Figure 3. The selectivity is best explained by a ligand exchange process on aluminum to create intermediate A shown in Figure 3. This forces the hydride to be delivered intramolecularly to only one face of the carbonyl and leads to a single diastereomer of the diol. Since this hydroxyl group was to be removed later, its stereochemistry was actually irrelevant; but having a single isomer facilitated purification of this product.

Figure 3. Likely intermediate for the in situ reduction of the aldol product.
The success of the model study depicted in Scheme 5 suggested that the overall strategy had merit and deserved further development. The two key structural aspects that this model system lacked are the vinyl group located on the quinuclidine ring and the 6-methoxyquinoline group that was replaced by a phenyl ring. Therefore, it is not surprising that this research inspired a 2018 total synthesis of quinine by Nuno Maulide, which was published in *Angewandte Chemie*.\textsuperscript{18} The enolate derived from 5-vinylquinuclidinone was used in an aldol addition with quininaldehyde as shown in Scheme 6 employing the same conditions as the model study by Stotter.\textsuperscript{3}

![Scheme 6. Final steps of Maulide’s synthesis of quinine.\textsuperscript{18}](image)

Rather than following the aldol addition with an in situ reduction, Maulide derivatized the ketone as the methanesulfonylhydrazone to minimize the loss of stereochemical control. On a conceptual basis, the hydrazone served the same purpose as reducing the carbonyl group. However, the hydrazone proved extremely difficult to reduce in the last step of the synthesis leading to quinine. Finally, the reaction was accomplished with a LiAlH\textsubscript{4}/methanol reduction system—one that presumably forms trimethoxyaluminum hydride in situ—but the yield was only 53% on a mere 4 mg scale. Maulide even referenced the in situ reduction reported by Stotter\textsuperscript{3} but indicated that the approach “ultimately proved unsuccessful” for the synthesis of quinine. Since no explanation or additional information was given, there is no reason to abandon the approach demonstrated by Stotter. The Maulide synthesis gave (-)-quinine in an overall yield of 5.4% over 10 steps.
The Maulide synthesis serves to confirm many of the aspects of the Stotter proposal, the most important of which is the role of the vinyl group in controlling the approach of the aldehyde in the aldol addition. In the model study, the two faces of the planar enolate were equivalent; and this allowed only the aldol addition stereochemistry to be evaluated. Maulide verified that the vinyl group was sufficiently bulky to force aldol addition from only one face of the enolate. The Maulide synthesis also showed that 6-methoxyquininaldehyde could be used instead of benzaldehyde for the aldol addition reaction with no problems. Where the Maulide synthesis fails is explaining why the tandem aldol addition/reduction sequence was not suitable for quinine synthesis. His use of a hydrazone instead was particularly costly since the low yield occurred in the last step of the synthesis—the worst place a poor step can be. This leaves the door open for an investigation of the Stotter approach with a more appropriate model that incorporates the vinyl group.

The focus of this study is to validate the synthetic route proposed by Stotter and co-workers\(^3\) including the use of a bicyclic ketone with a vinyl substituent to mimic the actual system and an aldehyde that resembles quininaldehyde. To make these required starting materials more readily available, the target for the synthesis will be the quinine analog 1,1’-dideaza-quinine in which the nitrogen atoms are replaced by carbon. The absence of nitrogen in these compounds should have little if any impact on their chemical behavior such that the reactions developed in this model study will be directly applicable to the total synthesis of quinine. A structural comparison of quinine and 1,1’-dideaza-quinine is shown in Figure 4. This non-nitrogenous analog is also a novel compound.
The synthetic strategy for 1,1’-dideaza-quinine is summarized in Scheme 7 and follows the previous model system published by Stotter. Since 7-methoxy-1-naphthaldehyde is a known compound, its synthesis can be found in the literature. However, there are no references to a synthesis of the bicyclic ketone 6-vinylbicyclo[2.2.2]octan-2-one although a previous research student in this laboratory made significant progress toward preparing this molecule. Synthesis of each compound has significant potential for optimization.

In the following pages, the progress that has been made thus far in realizing the synthesis of the target molecule will be presented. This will include not only the completed synthesis of 7-methoxy-1-naphthaldehyde but also the description of a new route to 6-vinylbicyclo[2.2.2]octan-2-one that reduces the number of steps compared with the original synthetic plan. A cursory study of the aldol addition/reduction sequence will also be discussed.
**Results/Discussion**

In order to investigate the aldol addition reaction described previously, the required aldehyde 7-methoxy-1-naphthaldehyde (4) was synthesized according to a published procedure\(^{19}\) as shown in Scheme 8. The bicyclic ketone component in this reaction is a new compound which has not been reported in the literature. Its synthesis will be presented later as outlined in Scheme 9. Once these compounds were available, the key aldol addition/reduction tandem sequence was carried out and evaluated using standard analytical techniques to determine the stereochemical outcome of this reaction.

**A. Preparation of 7-methoxy-1-naphthaldehyde (4)**

\[ \begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{MeO} & \quad \text{CN} & \quad \text{MeO} & \quad \text{CN} & \quad \text{MeO} & \quad \text{H} & \quad \text{O} \\
1 & \quad \xrightarrow{\text{a}} & \quad 2 & \quad \xrightarrow{\text{b}} & \quad 3 & \quad \xrightarrow{\text{c}} & \quad 4
\end{align*} \]

\(28\%\) overall yield

*Scheme 8*. Synthetic pathway to 7-methoxy-1-naphthaldehyde (4).

\(^{a}\text{Conditions: (a) (1) TMSCN, cat. ZnI}_{2}, \text{toluene, (2) pyridine, POCl}_{3}, 130^\circ\text{C.} \)

\(^{b}\text{(b) chloranil, 1,4-dioxane, reflux. (c) DIBAL, CH}_{2}\text{Cl}_{2}, 40^\circ\text{C.} \)

The published synthesis of 7-methoxy-1-naphthaldehyde (4) from the commercially available ketone 1 is fairly straightforward and was accomplished in the four steps shown in Scheme 8. The conversion of 1 to the cyanohydrin using trimethylsilyl cyanide (TMSCN) was followed by dehydration of the alcohol with phosphorus oxychloride (POCl\(_3\)) in pyridine to give 2 in 82% yield over two steps. The dehydrogenation of 2 in the presence of chloranil in refluxing dioxane produced the naphthalene ring in 3; and in the last step, the nitrile was reduced to aldehyde 4 by diisobutylaluminum hydride (DIBAL) leading to an overall yield of 28%.
Previous work on this synthetic scheme achieved a 26% overall yield\(^{19}\) with the use of palladium on charcoal, an expensive reagent, in the aromatization reaction to generate \(3\). By replacing palladium with chloranil, a very efficient reagent for this type of reaction,\(^{21}\) the yield for this step was relatively maintained and the cost was decreased. A previous worker in this laboratory\(^{20}\) had considerable difficulty in reproducing the reduction of \(3\) with DIBAL, but this investigation found the literature procedure to be reproducible as it was reported.\(^{19}\) The problem was almost certainly caused by the use of a DIBAL solution that was no longer pure.

**B. Preparation of 6-vinylbicyclo[2.2.2]octan-2-one (11)**

\[ egin{align*}
\text{Conditions: (a) cat. AlCl}_3, \text{ neat. (b) 5.5 M H}_2\text{SO}_4, \text{ reflux. (c) DIBAL, THF, -78°C. (d) MePh}_3\text{Br (2.2 equivalents), nBuLi, THF, -78°C (e) PCC, CH}_2\text{Cl}_2, 0°C.} 
\end{align*} \]

The required bicyclic ketone 6-vinylbicyclo[2.2.2]octan-2-one (11) was synthesized from 5 and 6 according to Scheme 9. This route was based on research from a previous worker\(^{20}\) in our laboratory and benefits from the discovery that the conversion of 7 to 8 can be done in one step instead of three. The bicyclic ester 7 was generated in acceptable yield using the Lewis acid catalyzed Diels-Alder reaction between the diene 5 and the dienophile 6. Taking advantage of the
syn relationship between the double bond and the ester in 7, an acid catalyzed addition to the alkene produced the tricyclic lactone 8 in 67% yield. A simple DIBAL reduction of 8 yielded the stable lactol 9. The ring opening of the lactol under basic conditions allowed the resulting aldehyde to be trapped using a classic Wittig olefination reaction to give the desired vinyl and hydroxyl groups in 10. In the final step, the hydroxyl group was oxidized by PCC to provide the ketone 11 in 10% overall yield from 5 and 6.

The Diels-Alder reaction between 5 and 6 proved to be difficult to achieve in high yield since the starting materials are inclined to polymerize in the presence of Lewis acids. Other conditions were also examined including the use of a Brønsted acid instead of the Lewis acid, microwave radiation with no catalyst and a combination of the two, but all of these proved unsuccessful. Column chromatography was the best way to remove the polymer and purify 7 on a small scale, but distillation would probably be more efficient for a larger reaction.

The production of 8 directly from the ester 7 was probably the biggest breakthrough in this research study. Scheme 10 shows a comparison between the previous three-step route through 7a and 7b and the direct reaction developed in this investigation. The hydrolysis of 7 to the acid

![Scheme 10. Current and previous pathways from ester 7 to lactone 8.](image-url)
7a followed by an iodolactonization to give 7b is a classical route to making lactones. Finally, the iodine was reduced to provide 8 in 51% yield from 7. The direct conversion of 7 to 8 not only reduces the number of steps and improves the overall yield but also is more cost efficient.

The inspiration to develop a new route came initially from an attempt to reproduce the three-step procedure in Scheme 10 but achieving only a 17% yield overall. However, there was also a report from the literature describing the conversion of 7a to a 5:1 mixture of lactone 8 and the byproduct 8a as shown in Figure 5. Since 8a was likely the result of a rearrangement reaction by Figure 5. Improved selectively on a published lactonization reaction.

which 8 was isomerized under acidic conditions and elevated temperature, a reinvestigation of this process was carried out. Rather than starting with the acid 7a, the ester 7 was used instead under the assumption that it would undergo hydrolysis in aqueous acid first to give 7a in situ. If so, this would cut out another step in the conversion of 7 to 8. The reaction conditions were abated by lowering the temperature to slightly over 100 °C just below the reflux point. Under these conditions, only the lactone 8 was produced in 67% yield. The mechanism of the reaction must involve a protonation of the alkene double bond followed by attack of a carbonyl oxygen on the
resulting carbocation. Since both 7 and 7a can provide the nucleophilic oxygen for this step, we do not know whether or not an acid-catalyzed hydrolysis of the ester actually occurs. Both functional groups can be shown mechanistically to provide the same product.

The final three steps in the synthesis of 11 shown in Scheme 9 are relatively straightforward. The reduction of 8 to the lactol 9 was efficient but required care to assure the use of a quality DIBAL solution and bone-dry THF. The Wittig olefination to produce 10 is actually two steps the first of which opens the lactol to an aldehyde, and the second converts the carbonyl to the vinyl group. Two equivalents of the Wittig reagent are required. Removing triphenylphosphine oxide proved to be quite difficult and led to a significant loss of the product. However, it was discovered that using crude 10 mixed with triphenylphosphine oxide in the subsequent oxidation step with PCC caused no problems. Once the oxidation reaction was done, triphenylphosphine oxide was easily removed during the purification of the ketone 11. The yield of 11 through two steps from the lactol 9 is 42%, but a higher conversion is almost certainly possible with further optimization of this sequence.

C. Steps toward the preparation of 1-1’dideaza-quinine

![Scheme 11c](image)

**Scheme 11c. Incomplete convergent pathway towards 1,1’-dideazaquinine.**

*Conditions: (a) (1) LDA, THF, -78°C, (2) Red-Al, THF, -78°C. (b) Ac₂O, pyridine, cat. DMAP, CH₂Cl₂. (c) TCDI, cat. DMAP, THF, reflux.*
In an attempt to follow the synthetic route demonstrated by Stotter and co-workers\textsuperscript{3}, the next step toward 1,1’-dideaza-quinine would incorporate 4 and 11 as the starting materials according to Scheme 11. As planned, the enolate generated from ketone 11 with LDA and the aldehyde 4 were allowed to react at -78 °C followed by a reduction reaction using Red-Al to complete the tandem aldol addition/reduction sequence. NMR spectral data on the diol product are completely consistent with structure 12, and there is no reason to believe that the stereochemical outcome would differ from that of the diol in Stotter’s model study (Scheme 5). Unfortunately, it was not possible to confirm that the aldol addition stereochemistry had been reproduced. The vicinal coupling constant for the benzylic proton should be approximately 9 Hz; but due to its coupling with the hydroxyl proton, this measurement could not be obtained. The most definitive proof of structure would be an X-ray diffraction analysis, but this has not yet been acquired. Regardless, the next step in the sequence to convert the benzylic hydroxyl group selectively to the acetate was achieved using acetic anhydride, pyridine, and catalytic DMAP to yield 13. The first step of the Barton deoxygenation protocol was also attempted, but 13 could not be forced to react with thiocarbonyldiimidazole to form a thiocarbonyl derivative of the remaining hydroxyl group. The use of harsher reaction conditions led only to decomposition of the starting materials.

The reluctance of 13 to react with thiocarbonyldiimidazole was not completely unexpected. In the model used by Stotter\textsuperscript{3} in the previous study, the vinyl substituent on the quinuclidine unit was missing. Because of the proximity of the vinyl group and the hydroxyl group in 13, one might expect that steric interference could slow or prevent reactions of the alcohol with fairly bulky reagents. Perhaps this is the underlying but unstated reason for Maulide’s declaration that the Stotter approach “ultimately proved unsuccessful.” In any event, a great deal of progress has been made since Barton’s original work\textsuperscript{15} in 1975 on the methodology for the deoxygenation of
secondary alcohols. Two fairly recent reviews on this subject reveal the use of some relatively compact alcohol derivatives as well as new reduction procedures that avoid organotin reagents that can be hazardous to handle.\textsuperscript{23, 24}

\textbf{D. Future Work}

Some work remains in the total synthesis of 1,1’-dideaza-quinine before this investigation is complete. First, an x-ray structure of diol \textbf{12} will confirm the stereochemistry of this product. The most significant challenge is the deoxygenation of the secondary alcohol in \textbf{13}. The use of triethylsilane and boron trifluoride has already been contemplated and other reduction methods have been described in the literature. Once deoxygenation is performed successfully, all that remains is a straightforward deprotection of the benzylic alcohol.

Other improvements that could be made include the optimization of certain reactions along the route. Until recently, our laboratory did not have a reliable source of bone-dry THF. This may have impacted the yields on several reactions most notably the conversion of \textbf{9} to \textbf{10} using the Wittig olefination. As mentioned earlier, the Diels-Alder reaction gave inconsistent yields and should be studied further by varying the reaction temperature and the choice of catalyst. The tandem aldol addition/reduction sequence was tested only once since this provided the diol \textbf{12} in a sufficient amount to continue. There are undoubtedly some modifications that will increase the yield. Several of the molecules synthesized in this project have not ever been reported in the literature and will require a complete characterization before this project is finished.
Conclusion

The purpose of this project was to validate a proposed diastereoselective synthetic route to quinine using a non-nitrogenous analog. Significant strides were made toward this goal during our investigation. First, this study provided a significantly shorter and higher yielding method to prepare one of the key intermediates in the synthesis of ketone 11 using relatively inexpensive reagents. Second, the stereoselectivity of the tandem aldol addition/reduction sequence proposed in a previous study appears to have been confirmed by this research although a more definitive proof of structure remains to be carried out. Finally, the failure of the monoacetate 13 to react in the classic Barton alcohol deoxygenation protocol uncovered a flaw in the original proposal that will require the exploration of an alternate route.
Experimental Procedures

Preparation of the nitrile 2

A suspension containing 5.00 g (28.4 mmol) of 7-methoxy-1-naphthaldehyde (1) and 0.18 g (0.56 mmol) of ZnI$_2$ was prepared in 12.5 mL of toluene and 3.90 mL (3.09 g, 31.1 mmol) of trimethylsilyl cyanide (TMSCN) was added. The reaction mixture was stirred at room temperature and monitored by TLC, which indicated the complete consumption of starting material after 19 hours. The reaction mixture was diluted with 45 mL of pyridine and 4.5 mL (7.4 g, 48.0 mmol) of POCl$_3$ was added. The solution was stirred and heated at 130 °C for two hours when TLC monitoring again showed full conversion. The reaction mixture was cooled to room temperature, poured into a beaker containing 200 mL of 3 M HCl and ice and extracted with ethyl acetate (3 x 60 mL). The combined extracts were washed with brine (50 mL), dried over Na$_2$SO$_4$, and concentrated by rotary evaporation. The resulting dark oil was passed through a silica gel plug using CH$_2$Cl$_2$. The removal of solvent at high vacuum yielded 4.29 g (81.7 %) of 2 as a light orange solid suitable for use in the next step. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.51 (td, 2H), 2.81 (t, 2H), 3.85 (s, 3H), 6.83 (dd, 1H), 6.94 (t, 1H), 7.03 (d, 1H), 7.09 (d, 1H).

Preparation of 7-Methoxynaphthalene-1-nitrile (3)

A solution containing the nitrile 2 (4.29 g, 23.4 mmol) and chloranil (11.50 g, 46.7 mmol) in 40 mL of 1,4-dioxane was stirred at reflux for 24 hours, when TLC monitoring showed the reaction to be complete. Upon cooling, the excess chloranil began to precipitate. The reaction mixture was filtered and concentrated to yield red solid. The product was recrystallized in 2:1 MeOH/H$_2$O to yield 3 (2.89 g, 68.0%) as a pale red crystalline solid: mp 35-37 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.51 (td, 2H), 2.81 (t, 2H), 3.85 (s, 3H), 6.83 (dd, 1H), 6.94 (t, 1H), 7.03 (d, 1H), 7.09 (d, 1H).
**Preparation of 7-Methoxy-1-naphthaldehyde (4)**

A solution of nitrile 3 (1.50 g, 8.19 mmol) in 45 mL of CH$_2$Cl$_2$ was cooled to 0 °C and stirred as 16.4 mL (16.4 mmol) of 1 M DIBAL (diisobutylaluminum hydride) in heptane was added slowly by syringe. The ice bath was removed and the reaction mixture was warmed to 40 °C and stirred for 2 hours. The reaction was quenched with acetone (5 mL) and stirred for another 30 minutes. Then water (40 mL), ethyl acetate (40 mL), and Rochelle’s salt (10 g) were added, and the mixture was stirred vigorously overnight at room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na$_2$SO$_4$, and concentrated by rotary evaporation. Purification by column chromatography (silica gel, 11:1 hexane:ethyl acetate) yielded 0.77 g (51%) of the product 4 as a yellow liquid.

**1H NMR (400 MHz, CDCl$_3$):** δ 4.03 (s, 3H), 7.27 (dd, 1H), 7.52 (dd, 1H), 7.84 (d, 1H), 7.98 (d, 1H), 8.05 (d, 1H), 8.79 (d, 1H), 10.35 (s, 1H).

**Preparation of 7**

A solution containing 5.00 g (62.4 mmol) of 1,3-cyclohexadiene (5) and 10.75 mL (10.21 g, 118.6 mmol) of methyl acrylate (6) was stirred at 0 °C as catalytic AlCl$_3$ powder (0.25 g) was added carefully in portions. The solution was allowed to warm slowly to room temperature, and the reaction was monitored by 1H NMR. The starting diene was fully consumed after 6 hours. The reaction was then quenched with water during which the dark solution changed color to light yellow. At this point the excess methyl acrylate was removed by rotary evaporation. Due to the presence of
polymer, the product was purified via column chromatography rather than distillation to yield 4.52 g (43.6 %) of 7 as a clear liquid: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.28-1.32 (m, 2H), 1.50-1.59 (m, 2H), 1.70-1.77 (m, 2H), 2.61-2.66 (m, 2H), 2.95 (m, 1H), 3.66 (s, 3H), 6.17 (ddd, 1H), 6.34 (ddd, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 24.4, 25.4, 29.4, 29.8, 32.4, 42.7, 51.7, 131.4, 135.2, 176.0.

**Preparation of lactone 8**

The Diels-Alder product 7 (2.34 g, 14.1 mmol) was dissolved in 45 mL of 5.5 M H$_2$SO$_4$ and the solution was stirred at 110°C for three hours using TLC to monitor the progress of the reaction. The reaction mixture was poured onto ice and the product was extracted with chloroform (3 x 25 mL). The combined extracts were dried over Na$_2$SO$_4$ and concentrated by rotary evaporation. The crude product was recrystallized in cyclohexane to yield 1.44 g (67.3%) of pure white crystalline 8: mp 203-205°C (lit.$^{22}$ mp 204-205°C); $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 15.7, 23.5, 26.1, 27.6, 33.2, 34.4, 37.4, 78.6, 181.5.

**Preparation of lactol 9**

The lactone 8 (2.28 g, 15.0 mmol) was dissolved in 45 mL of dry THF and cooled to -78°C. The solution was stirred as 18.0 mL (18.0 mmol) of 1 M DIBAL in heptane was added dropwise for 2 minutes. After stirring at -78°C for 90 minutes, the reaction was quenched with acetone and stirred for an additional 30 minutes. Then water (40 mL) and ethyl ether (40 mL) were added to the solution along with 8 g of Rochelle’s salt, and the mixture was stirred vigorously overnight. The layers were separated, and the aqueous layer was extracted with additional diethyl ether (2 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated by rotary evaporation to yield
an off-white amorphous solid. The product was purified by sublimation under reduced pressure (85 °C, 0.1 mm Hg) to yield 1.92 g (83.1%) of 9 as white crystals: $^{13}$C NMR (400 MHz, CDCl$_3$): δ 15.4, 22.7, 26.8, 30.1, 31.4, 36.5, 40.9, 76.7, 104.2.

**Preparation of 10**

Methyltriphenylphosphonium bromide (3.47 g, 9.72 mmol) was suspended in 23 mL of dry THF and cooled to -78 °C. A solution of 2.5 M n-butyllithium in hexane (3.88 mL, 9.70 mmol) was added dropwise over 4 minutes to the stirring solution, which was maintained at -78 °C for an hour. A solution containing 0.68 g (4.4 mmol) of the lactol 9 in 4 mL of dry THF was added dropwise to the reaction mixture over 10 minutes. The solution was stirred at -78 °C for one hour followed by an additional two hours at 0 °C. The reaction was quenched with 30 mL of sat. NH$_4$Cl, and 10 mL of ethyl acetate was then added. After filtration to remove solids, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were then washed with brine (20 mL), dried over Na$_2$SO$_4$ and concentrated by rotary evaporation to yield a mixture of 10 and triphenylphosphine oxide. Due to the difficulty of separating this mixture, the crude product (1.55 g) was used directly in the next reaction. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.39-1.89 (m, 9H), 2.01 (m, 1H), 2.41 (m, 1H), 3.99 (m, 1H), 5.04 (dd, 2H), 6.24 (m, 1H).

**Preparation of ketone 11**

The crude product mixture containing 10 from the previous step (1.55 g) was dissolved in 10 mL of CH$_2$Cl$_2$ and cooled to 0 °C. Solid pyridinium chlorochromate (1.04 g, 4.85 mmol) was then added to the stirring solution. Several scoops of Celite were also added before allowing the reaction mixture to warm on its own to room temperature overnight. The black solution was filtered through a silica gel plug and
concentrated by rotary evaporation to yield a green liquid. The crude product was purified via column chromatography (silica gel, 10:1 hexane:ethyl acetate) to give 0.274 g (41.5% over two steps) of pure 11 as a colorless liquid: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$, 1.45 (m, 1H), 1.59-1.76 (m, 3H), 1.83-1.92 (m, 2H), 2.02 (m, 1H), 2.18-2.24 (m, 2H), 2.30 (m, 1H), 2.66 (m, 1H), 5.00 (dd, 2H), 5.67 (m, 1H).

**Preparation of 12**

A solution of 0.36 mL (0.27 g, 2.55 mmol) of diisopropylamine in 7 mL of THF was cooled to 0 °C and stirred as 1.56 mL of 1.6 M methyl lithium in ether (2.50 mmol) was added all at once. After 30 minutes, the solution was cooled further to -78°C. A previously prepared solution containing 0.34 g (2.3 mmol) of the ketone 4 in 4.5 mL of THF was added dropwise over 5 minutes and stirred at -78 °C for 30 minutes. The aldehyde 11 (0.43 g, 2.3 mmol) was dissolved in 2.5 mL of THF and the resulting solution was added slowly to the flask. The reaction mixture was maintained at -78°C for 30 minutes. Still at -78°C, sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al) (1.41 mL, 4.35 mmol) was added dropwise to the dark orange solution. The cooling bath was removed to complete the reaction at room temperature; and after 22 hours, the solution was cooled to 0 °C and quenched with water. The resulting precipitate was removed by filtration and 40 mL of ethyl acetate was added to the filtrate. This solution was washed with brine (20 mL), dried over Na$_2$SO$_4$, and rotary evaporated. The product was purified via column chromatography (silica gel, 8:1 hexane:ethyl acetate) to yield 0.33 g (43%) of 12 as an off-white amorphous solid: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.39-1.52 (m, 2H), 1.60-1.67 (m, 2H), 1.72-1.86 (m, 2H), 1.92 (m, 1H), 1.98 (m, 1H), 2.44 (m, 1H), 2.91 (dd, 1H), 3.34 (dd, 1H), 3.67 (m, 1H), 3.96 (s, 3H), 4.95-5.05
(m, 2H), 6.19 (m, 1H), 7.18 (dd, 1H), 7.27-7.32 (m, 2H), 7.48 (d, 1H), 7.68 (dd, 1H), 7.78 (d, 1H).

**Preparation of monoacetate 13**

A solution containing 0.33 g (0.98 mmol) of the diol 12 in 3 mL of CH$_2$Cl$_2$ was stirred at room temperature as 0.08 g (0.98 mmol) of pyridine and 0.05 mL (0.054 g, 0.529 mmol) of acetic anhydride were added. After 6 hours of stirring, the reaction showed little progress by TLC; so a catalytic amount of dimethylaminopyridine (DMAP) was added. Additional acetic anhydride was also added periodically until the reaction was complete according to TLC monitoring. The reaction mixture was diluted with 3 mL of CH$_2$Cl$_2$ and washed with 10 mL of 1 M HCl. The acidic wash was back-extracted once with 5 mL of CH$_2$Cl$_2$. The combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated by rotary evaporation to yield 0.32 g (94%) of 13 as an amorphous solid:

**$^1$H NMR (400 MHz, CDCl$_3$):** δ 1.29 (m, 1H), 1.47 (m, 1H), 1.55 (m, 1H), 1.68 (m, 1H), 1.81-2.00 (m, 3H), 1.95 (s, 3H), 2.10 (1H), 2.39 (m, 1H), 2.92 (dd, 1H), 3.45 (dd, 1H), 3.98 (s, 3H), 4.75 (m, 1H), 4.82-4.92 (m, 2H), 5.99 (m, 1H), 7.18 (dd, 1H), 7.25-7.28 (m, 2H), 7.38 (d, 1H), 7.67 (dd, 1H), 7.77 (d, 1H).

**Attempted Barton Deoxygenation Procedure**

The monoacetate 13 (0.318 g, 0.837 mmol) and thiocarbonyldimidazole (TCDI) (0.323 g, 1.81 mmol) were dissolved in 2.5 mL of THF and heated at reflux overnight. After 20 hours, TLC monitoring showed no reaction; so a catalytic amount of DMAP was added and the reaction was again heated at reflux overnight. THF was removed from the darkened reaction mixture by rotary evaporation and diethyl ether (20 mL) and sat. NaHCO$_3$ (10 mL) were added. The layers were
separated and the organic layer was washed again with 10 mL of NaHCO₃. The organic layer was dried over Na₂SO₄ and rotary evaporated, but only the starting material was recovered.
References


MeO

C

N

3

159.09

144.52

134.26

133.01

130.26

129.57

128.85

128.47

126.13

122.65

120.77

118.27

117.13

114.71

110.20

108.60

103.01

67.11

55.65

25.23

24.15
proposed structure
proposed structure