1-ACYLDIHYDROPYRIDONES AS SYNTHETIC INTERMEDIATES

by

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of the requirements for the degree
of
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in
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DEDICATION

To my parents, Dermot and Eileen Foley, my brother, Timothy, and sisters, Maureen, Margaret and Frances.
ACKNOWLEDGMENTS

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Michael Andrew Foley
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ABSTRACT

1-Acyldihydropyridones as Synthetic Intermediates

by

Michael Andrew Foley, Master of Science

Utah State University, 1988

Major Professor: Dr. Daniel L. Comins

Department: Chemistry and Biochemistry

The most efficient and stereoselective total synthesis of (+/-)-lausbine II to date has been achieved. The key steps in this are the copper-mediated conjugate addition reaction of the Grignard reagent of 1-bromo-4-chlorobutane to a dihydropyridone and a stereoselective reduction of a quinolizidinone.

Methodology has been developed for the convenient synthesis of 1-acyl-2-substituted-1,2,5,6-tetrahydropyridines. This was accomplished by adding novel alkylzinc iodides to the 1-acyliminium ion derived from N-phenoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine.

(74 pages)
INTRODUCTION

The first isolation of a Lythraceae alkaloid was in 1962 by Ferris.¹ Since that time, more than forty alkaloids have been isolated from plants of the Lythraceae family. Included in this family is the naturally occurring Lasubine II. Lasubine II was isolated in 1978 by Fuji et al.² from the Lagerstromia subcostata Koehne (Japanese name: Shimasarusuberi) found in the Amami Islands,³ Taiwan⁴ and the central region of China.⁵ Lasubine II was isolated from the methanol extract of the leaves of L. subcostata collected before flowering on Amami-Oshima Island along with lasubine I and subcosine I and II.

Lasubine II is a very important target molecule as it may be a biogenetic intermediate in the formation of more complex natural products.⁶ Naturally occurring quinolizidine alkaloids have both trans and cis-quinolizidine configuration as shown in the isomeric alkaloids lasubine I (1) and lasubine II (2). Structural elucidation has relied on x-ray studies,¹ spectroscopic methods and chemical degradation.²

Despite the importance of these Lythraceae alkaloids and the large number of groups that have synthesized them, there are very few efficient routes which lead to their formation stereospecifically.⁷-¹⁸ We
have developed a novel, efficient and stereoselective synthesis of (+/-)-lasubine II based on methodology developed by Comins and Brown in the total synthesis of (+/-)-epi-lasubine II. (Scheme 1). Comins and Brown have shown that Grignard reagents will add to the 1-acylpyridinium salt of 4-methoxypyridine (3) regiospecifically at the 2-position as shown in the conversion of 3 to dihydropyridone 4. Dihydropyridone 4 was converted to piperidone 5 by a stereoselective conjugate addition reaction with the Grignard reagent of the OEE protected 1-chlorobutanol (Cul, BF<sub>3</sub>-OEt<sub>2</sub>). This reaction yielded the desired piperidone 5 in a stereoselective manner (cis:trans ratio; 6:1). The alcohol was deprotected with oxalic acid (THF, H<sub>2</sub>O) and converted to the chloride 6 with triphenylphosphine and N-chlorosuccinimide. Compound 6 was reduced with L-Selectride and cyclized to yield (+/-)-epi-lasubine II.

We believed that Brown’s work could be modified in such a way that the desired (+/-)-lasubine II could be obtained stereoselectively. This thesis will discuss how Brown’s work was modified into a highly stereocontrolled, 4-step total synthesis of (+/-)-lasubine II.

Also discussed in this thesis is the synthesis of N-phenoxy carbonyl-2-substituted-1,2,5,6-tetrahydropyridines. Work done by Kozikowski and co-workers<sup>20</sup> described a useful entry to N-carboethoxy-2-substituted-1,2,5,6-tetrahydropyridines. (Scheme 2)

![Scheme 2. Kozikowski’s synthesis of N-carboethoxy-2-substituted-1,2,5,6-tetrahydropyridines.](image)
1) RMgBr, THF
2) PhCH₂OCOCl, -23°C
3) 10% HCl

OMe

1) L-Selectride, -78°C
2) H₂O₂

NCS, DMF, Ph₃P

PhCH₂OCO

1) BF₃·Cu·OEE, THF, -78°C

oxalic acid, THF, H₂O

NCS, DMF, Ph₃P

50°C
Scheme 1. Brown’s synthesis of epi-lasubine II
We initiated a project to broaden the synthetic utility of this methodology by using novel organozinc iodides as our nucleophiles and treating them with the appropriate N-acyliminium ion precursor.

A convenient preparation of alkylzinc iodides from alkyl iodides and Zn(Cu) couple has recently been reported. Alkylzinc iodides are of interest because of their mild reactivity. Organozinc iodides are unreactive toward esters, alkyl chlorides and acid chlorides in the absence of a Pd\(^0\) catalyst. It has been shown that Grignard reagents will add regiospecifically to the 1-acylpyridinium salt of 4-methoxypyridine. It has also been shown that 4-chlorobutylzinc iodide can be added to a 1-(phenoxy carbonyl)pyridinium salt and subsequently converted to a quinolizidinone. As a result of these findings, we studied the addition of alkylzinc iodides to a 1-acyliminium ion derived from 4-methoxypyridine.

The organozinc reagents were prepared by heating the alkyl iodide in benzene with 3 equiv of Zn(Cu) couple and 3.3 equiv of DMA.

\[
\text{Alkyl iodide} \xrightarrow{\text{Zn(Cu) 3 eq., refluxing benzene}} \text{Alkylzinc iodide}
\]

The organozinc reagents were added to the 1-acyliminium ion affording the 2-substituted tetrahydropyridine.
We had hoped that we could apply this chemistry to the total synthesis of elaeokaine A (19) starting from the 1-acyl-5-bromo-2,3-dihydropyridinium salt 18, derived from 5-bromo-4-methoxy-1,2,3,4-tetrahydropyridine 17.

In contrast to the results obtained in our previous study, the alkylzinc iodide added to the 1-acyl-5-bromoiminium ion exclusively at the 4-position. Therefore, this approach could not be used in the synthesis of elaeokanine A.
REVIEW OF THE LITERATURE

A. Preparation of (+/-)-lasubine II

Since the first isolation of a Lythraceae alkaloid in 1962, more than forty alkaloids have been isolated from the plants of the Lythraceae family. Most of these alkaloids possess a trans or cis quinolizidine ring system.

Synthesis of Lythraceae alkaloids have generally been achieved through the condensation of isopellitrine with aromatic aldehydes\textsuperscript{27}, or via a [2 + 3] cycloaddition reaction of tetrahydropyridine N-oxide.\textsuperscript{28-29}

The first total synthesis of (+/-)-lausbine II was reported in 1984 by Kibayshi et al.\textsuperscript{30} (Scheme 3). The crucial reaction in this synthesis involves the intermolecular thermal [3+2] dipolar cycloaddition of 1-(3,4-dimethoxyphenyl)butadiene (20) with 2,3,4,5-tetrahydropyridine-1-oxide 21. The synthesis starts from 3,4-dimethoxybenzaldehyde (22), which is reacted with the phosphorane 23 (derived from allytriphenylphosphonium bromide) to afford the Wittig product 20. Compound 20 consists of a 9:5 mixture of E and Z isomers which were inseparable by column chromatography on silica gel. The 1-(3,4-dimethoxyphenyl)butadiene (20) was reacted with 2,3,4,5-tetrahydropyridine-1-oxide 21 in refluxing toluene yielding cycloadducts 24 and 25 in 49% and 22% yields, respectively. It was then determined that both the E and Z isomers where mixtures of cis and trans isomers, with a preference for the trans isomer in each case. The E isomer was treated with hydrogen chloride, followed by hydrogen and palladium on carbon in ethanol, to give (+/-)-lausbine I (1) and (+/-)-epi-lasubine II (26) in 44% and 14% yields, respectively.
Scheme 3. Kibayshi's attempted synthesis of (+/-)-lausbine II.
(+/-)-Lasubine II was obtained through the Mannich reaction of isopellitirine (27) with 3,4-dimethoxybenzaldehyde (22), using a procedure originally described by Matsunaga et al. in the preparation of other Lythraceae alkaloids. The condensation product afforded the cis and trans-quinolizidinones 28 and 29 in 46% and 22% yields, respectively. Reduction of the cis-quinolizidinone 28 with sodium borohydride gave (+/-)-lasubine I in 83% yield. Reduction of the trans-quinolizidinone 29 gave (+/-)-lasubine II and (+/-)-epi-lasubine II (26) in 19% and 70% yields, respectively (Scheme 4).

(+/-)-Lasubine II was also synthesized by Hoffman and Endesfelder via an intramolecular thermal [3+2] dipolar cycloaddition reaction. Nitrone 30 was generated by stirring 31 with 5-oxapentanoate 32 over molecular sieves. Cyclization in refluxing toluene gave three 7-oxa-1-azanorboranes 33, 34, and 35 in 60% overall yield. Reduction of 33 gave 36, which was ring closed to afford the lactam 37. Inversion of configuration at C-2 gave 38, which on LAH reduction gave racemic lasubine II (Scheme 5).

In a novel and unrelated synthesis, Naraska et al. made (+/-)-lasubine II via an acyclic syn-1,3-amino alcohol. In this synthesis, 2-(3,4-dimethoxyphenyl)-1,3-dithiane (39), derived from veratraldehyde, was alkylated with 2-bromo-1,1-dimethoxyethane (40), which upon acidic work up gave 41. Reaction of 41 with the kinetic enolate of 5-hexene-2-one (42) gave β-hydroxy ketone 43. The aldol product 43 was converted to the O-benzylxoxime 44. Reduction of 44 by LAH in the presence of potassium methoxide gave the syn-1,3-amino alcohol 45. The amino group of 45 was protected and the thioaketal was hydrolized to generate 46.
Scheme 4. Kibayashi's synthesis of (+/-)-lasubine
II through the Mannich reaction of isopellitrine.
Scheme 5. Hoffman's synthesis of (+/-)-lausbine II.
The hydroxy ketone 46 was cyclized to the piperidinol 47 with TFA followed by reduction with LAH. Hydroboration of 47 with disiamylborane followed by treatment with p-toluene sulfonate chloride gave (+/-)-lausbine II. (Scheme 6). This synthesis of (+/-)-lasubine II required 11 steps from veratraldehyde.

B. Nucleophilic addition to 1-acyliminium ions

There have been several methods for generating dihydropyridones reported; however, the addition of nucleophiles to 1-acyliminium ions derived from dihydropyridones has received very little attention. Initially, Haider and co-workers reported that the reduction of 4-methoxypyridine using Fowler's method gave only 10%-15% of the desired dihydropyridone. Raucher and Macdonald reinvestigated this work and were able to obtain an 80% yield of the desired dihydropyridone. Kozikowski and co-workers showed that the 1-acyldihydropyridone could be converted to the 4-hydroxy-1,2,3,4-tetrahydropyridine with CeCl₃·7H₂O and sodium borohydride. Kozikowski also showed that a 1-acyliminium ion could be formed from and trapped by a nucleophile to give the 2-substituted-1,2,5,6-tetrahydropyrididine 50.

\[
\begin{align*}
\text{48} & \quad \stackrel{\text{NaBH₄, CeCl₃}}{\longrightarrow} \quad \text{OH} \quad \stackrel{\text{Nuc}^- \text{Lewis Acid}}{\longrightarrow} \quad \text{Nuc}\text{2-substituted} \\
\end{align*}
\]
Scheme 6. Naraska's synthesis of (+/-)-lausbine II.
We decided to look at this type of reaction using organozinc reagents as the nucleophilic species. This project was based on Kozikowski's work and the work of Comins and O'Connor. Comins and O'Connor showed these nucleophiles, made by the methods of Yoshida et al., could be used in reactions with 1-acylpyridinium salts.
RESULTS AND DISCUSSIONS

A. Preparation of (+/-)-lasubine II

(+/-)-Lasubine II (2) was synthesized stereoselectively using a method described by Comins and Brown for the synthesis of (+/-)-epi-myrtine. Two routes to the desired (+/-)-lasubine II were attempted. The first route involved the attempted conjugate addition of the diaryl cuprate of 4-bromoveratrole to the dihydropyridone 51. This route was abandoned due to low yields and lack of diastereoselectivity.

\[
\begin{align*}
&\text{CO}_2\text{CH}_2\text{Ph} \\
&\begin{array}{c}
\text{Cl} \\
\text{51}
\end{array} \\
\rightarrow &\begin{array}{c}
\text{Cl} \\
\text{6}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{H}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{H}
\end{array} \\
&\begin{array}{c}
\text{CO}_2\text{CH}_2\text{Ph} \\
\text{CH}_3
\end{array}
\end{align*}
\]

The second route involved the addition of the Grignard reagent of 4-bromoveratrole (52) to the 1-acylpyridinium salt of 4-methoxypyridine (3) and benzyl chloroformate. This reaction afforded the dihydropyridone 4 in 73% yield.

\[
\begin{align*}
&\text{Br \quad OCH}_3 \\
&\text{OCH}_3 \\
&\text{OCH}_3 \\
&\text{52} \\
&\begin{array}{c}
\text{Mg, THF} \\
12 \text{ h R.T.}
\end{array} \\
&\begin{array}{c}
\text{BrMg} \\
\text{OCH}_3 \\
\text{OCH}_3 \\
\text{OCH}_3
\end{array} \\
&\begin{array}{c}
\text{-23° C} \\
4 \text{ h}
\end{array} \\
&\begin{array}{c}
\text{PhCH}_2\text{OCOCl} \\
\text{THF}
\end{array} \\
&\begin{array}{c}
\text{OCH}_3 \\
\text{CO}_2\text{CH}_2\text{Ph}
\end{array}
\end{align*}
\]
In compound 4, it appears that the large aryl group could occupy either the axial or equatorial position. However, it is well documented in the literature that if the large aryl group were to occupy the equatorial position there would be significant $A^{(1,3)}$ strain as shown in structure 53.\(^{39}\) As a result of the strong $A^{(1,3)}$ strain, the large aryl group lies exclusively in the axial position as shown in structure 54.

![Structure 53 and 54](image)

The diastereoselective conjugate addition of functionalized Grignard reagents to 54 proved to be the greatest synthetic challenge in the \((+/-)\)-lasubine II project. Piperidone 5 was synthesized by adding the Grignard reagent of the OEE protected 1-chlorobutanol (Cul, BF$_3$·OEt$_2$) to 4 at -78° C. This reaction leads to 5 stereoselectively with a cis:trans ratio of 5.2:1.

![Reaction Scheme](image)

Piperidone 5 was deprotected and converted to the chloro compound 6 in two synthetic steps.
Subsequent studies showed that the diastereoselectivity of the conjugate addition reaction could be dramatically improved and that piperidone 6 could be made directly from 4. The reaction of 4 with the Grignard reagent of 1-bromo-4-chlorobutane (CuBr·S(CH₃)₂, BF₃·OEt₂) at -78°C gave piperidone 6 directly with a very high degree of stereoselectivity (cis:trans ratio of 60:1). The best results of this study are summarized in Table I.

The results of these conjugate addition reactions can be explained in terms of stereoelectronic effects. Conjugate addition reactions generally occur by the addition of a carbon nucleophile to the β-position in an anti-fashion. The preference for anti addition is explained by Felkin’s generalization that the incoming nucleophile and the forming non-bonded pair of electrons prefer to be in an anti-periplanar relationship.
Table I. Synthesis of \( \mathbf{6} \) by Conjugate Addition.

<table>
<thead>
<tr>
<th>Entry Yield(^a)</th>
<th>Alkyl Halide</th>
<th>Copper Halide</th>
<th>Cis:Trans Ratio(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>ClCH(_2)(CH(_2))(_3)OEE</td>
<td>Cul</td>
<td>5.2 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73(^b)</td>
</tr>
<tr>
<td>b</td>
<td>ClCH(_2)(CH(_2))(_3)Br</td>
<td>Cul</td>
<td>1 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50(^b)</td>
</tr>
<tr>
<td>c</td>
<td>ClCH(_2)(CH(_2))(_3)Br</td>
<td>CuBr-S(Me)_2</td>
<td>60 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>57(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Yield of isolated products (rplc, SiO\(_2\)). \(^b\)In entries a and b, the Grignard reagent was added to the dihydropyridone \( \mathbf{5} \) and copper halide at \(-78^\circ\) C followed by BF\(_3\) OEt\(_2\). Stirring was continued for 4 h and the mixture was poured into 20% NH\(_4\)Cl/NH\(_4\)OH (50:50) solution. \(^c\)In entry c, the Grignard reagent was added last to a mixture of the dihydropyridone \( \mathbf{5} \) CuBr SMe\(_2\) and BF\(_3\) OEt\(_2\) in THF at \(-78^\circ\) C and worked up as described above. \(^d\)Ratios were determined by NMR and verified by purification by radial preparative layer chromatography.
Corey and Boaz have shown that the organocuprates form a complex with the π-system that is reversible in the absence of a Lewis acid as shown in figure 1.\textsuperscript{42}

![Figure 1. Corey’s reaction of conjugated carbonyls with combined organocuprate-chlorotimethylsilane compounds.](image)

The axial π-complex is rapidly converted to the β-adduct in the presence of a Lewis acid and the organic reagent is delivered to the same face of the π-complex resulting in an axial product. This chemistry was applied to our enone 4 as can be seen in figure 2.

![Figure 2. Possible transition state for the formation of 6.](image)

Piperidone 6 was easily cyclized to the trans-quinolizidinone 7 with 10% Pd/C, H\textsubscript{2} and Li\textsubscript{2}CO\textsubscript{3} in EtOAc in a one-pot procedure developed by Comins and Brown.\textsuperscript{19} The last step in the synthetic sequence was the stereospecific reduction of the C-2 carbonyl of quinolizidinone 7.

![Diagram 1](image)

1) LS-Selectride
-78°C, 1/2 h.
2) 1 N. NaOH, EtOH
Reflux, 1h.

Axial : Equitorial
98 : 2
(+/-)-lasubine II

\[ Ar = 3,4-\text{MeO}_{2}\text{Ph} \]
Several reducing agents were utilized to effect this reduction. LS-Selectride (Aldrich Chemical Company) proved to be the best reagent for this transformation affording (+/-)-lasubine II and (+)-epi-lasubine II in a ratio of 98:2. The results of this study are summarized in Table II.

B. Nucleophilic addition to 1-acyliminium ions

In a project aimed at developing new organic methodology, organozinc reagents were added to a 1-acyliminium ion generated from 1-(phenoxy carbonyl)-4-methoxy-1,2,3,4-tetrahydropyridine (13). Compound 13 was made in three steps from 4-methoxypyridine.

\[
\begin{align*}
\text{OCH}_3 & \quad 1) \text{K (i-PrO)}_3 \text{BH} \\
\text{N} & \quad 2) \text{PhOCCl} \\
\text{CO}_2 \text{Ph} & \quad 3) \text{10\% HCl}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{CeCl}_3 \cdot 7\text{H}_2 \text{O} \\
\text{OH} & \quad \text{NaBH}_4 \\
\text{CO}_2 \text{Ph} & \quad \text{PPTS} \\
\text{MeOH} & \quad \text{11}
\end{align*}
\]

Conversion of 4-methoxypyridine to the dihydropyridone 10 in high yield proved challenging. Potassium triisopropoxyborohydride was the best reducing agent for this conversion, providing the desired dihydropyridone in 53% purified yield (see Table III). The dihydropyridone 10 was readily converted to the 4-hydroxy analog 11 with CeCl$_3$·7H$_2$O and NaBH$_4$\textsuperscript{43}. The 1-methoxycarbonyl-4-hydroxy-1,2,3,4-tetrahydropyridine 11 was then converted to the 1-methoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine 13 with PPTS in MeOH.

The reactive 1-acyliminium ion intermediate was generated by adding the Lewis acid BF$_3$·OEt$_2$ to 1-methoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine (13) in the presence of an organozinc reagent.
Table II. Reduction of Quinolizidone 7.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Reducing Agent</th>
<th>Axial:Equatorial Ratio&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>LS-Selectride</td>
<td>94 : 7</td>
<td>83</td>
</tr>
<tr>
<td>b</td>
<td>L-Selectride</td>
<td>88 : 12</td>
<td>82</td>
</tr>
<tr>
<td>c</td>
<td>Thexyllumonylborohydride</td>
<td>75 : 25</td>
<td>60</td>
</tr>
<tr>
<td>d</td>
<td>LS-Selectride</td>
<td>98 : 2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>81</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield of isolated products (rplc, SiO<sub>2</sub>).  
<sup>b</sup>Thexyllumonylborohydride.  
<sup>c</sup>Reactions were run at -65° C (isopropanol/dry ice) for 20 min, followed by pH 7 buffer solution, isolation of the borate and refluxing with 1 N NaOH (THF/H<sub>2</sub>O) 1 h.  
<sup>d</sup>Axial: Equatorial ratios were determined by <sup>1</sup>H NMR.  
<sup>e</sup>This reaction was run at -78° C.
Table III. Synthesis of Dihydropyridone 10.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reducing Agent/Eq.</th>
<th>Chloroformate</th>
<th>Temp.</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>triisopropoxyborohydride/2</td>
<td>Phenyl</td>
<td>-23° C</td>
<td>53</td>
</tr>
<tr>
<td>b</td>
<td>sodium borohydride / 1.5</td>
<td>Phenyl</td>
<td>-78° C</td>
<td>34</td>
</tr>
<tr>
<td>c&lt;sup&gt;c&lt;/sup&gt;</td>
<td>B.E.R. / 1.5g per mol</td>
<td>Phenyl</td>
<td>0° C</td>
<td>45</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield of isolated products (rplc, SiO<sub>2</sub>).  
<sup>b</sup>The chloroformate was added dropwise to 4-methoxypridine in isopropanol and potassium triisopropoxyborohydride at -23° C. The mixture was stirred for 1 h, then poured into 10% HCl.  
<sup>c</sup>The solvent for this reaction was methanol.
The organozinc reagents were conveniently prepared by the method of Yoshida et al.21-23 The organozinc iodides added to the 1-acyliminium ion of N-phenoxy carbonyl-4-methoxy-1,2,3,4-tetrahydropyridine in excellent yields (64%-98%). The results of this study are summarized in Table IV. A 2-D NMR study was done on the compounds listed in Table IV to prove that the nucleophiles had added to the 2-position. Results are shown in the Appendix A.

We attempted to use this methodology in the total synthesis of elaeokanine A (19). The key step in this synthetic sequence was the addition of the organozinc reagent of the OEE protected 1-iodopropanol to the 1-acyliminium ion of 1-methoxycarbonyl-3-bromo-4-methoxy-1,4,5,6-tetrahydropyridine 17.

The 1-methoxycarbonyl-3-bromo-4-methoxy-1,2,5,6-tetrahydropyridine (17) was made in four steps from 4-methoxypyridine as shown in Scheme 7.

Scheme 7. Synthesis of 1-methoxycarbonyl-3-bromo-4-methoxy-1,2,5,6-tetrahydropyridine.
Table IV. Synthesis of 1-Acyl-2-substituted-1,2,5,6-tetrahydropyridines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkylzinc iodide&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;ZnI</td>
<td>![Pyridine Structure]</td>
<td>93</td>
</tr>
<tr>
<td>b</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;ZnI</td>
<td>![Pyridine Structure]</td>
<td>71</td>
</tr>
<tr>
<td>c</td>
<td>Cl(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;ZnI</td>
<td>![Pyridine Structure]</td>
<td>77</td>
</tr>
<tr>
<td>d</td>
<td>IZn(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>![Pyridine Structure]</td>
<td>97</td>
</tr>
<tr>
<td>e</td>
<td>IZn(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>![Pyridine Structure]</td>
<td>82</td>
</tr>
<tr>
<td>f</td>
<td>IZn(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;OEE</td>
<td>![Pyridine Structure]</td>
<td>64</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield of isolated products (rplc, SiO<sub>2</sub>).<sup>b</sup>Reactions were run by adding the alkylzinc iodide to N-phenoxy carbonyl-4-methoxy-1,2,3,4-tetrahydropyridine followed by BF<sub>3</sub>:OEt<sub>2</sub>. After stirring at RT for 10 min, 10% aqueous hydrochloric acid was added. Extraction with ether provided the crude products.
The success of this synthesis depended upon the addition of the organozinc nucleophile to the 2-position of the 1-acyliminium ion. Based on our earlier results, where the organozinc iodide added to the 2-position of the 1-acyliminium ion exclusively, we expected the same result for this system. Unfortunately, the organozinc iodide added to the 4-position of the 1-acylpyridinium salt and this approach to elaeokanine A had to be abandoned.
SUMMARY AND CONCLUSIONS

This study has resulted in a four-step stereoselective synthesis of (+/-)-lasubine II. The key step in this synthesis was the diastereoselective (60 : 1) conjugate addition reaction that resulted in the cis-2,6-disubstituted piperidone 6. Also important in this study was the diastereoselective reduction of quinolizidinone 7. During the course of this study we developed an understanding of how the molecule’s conformation affects the stereochemistry of the reduction reaction. By using the very large reducing agent LS-Selectride, we were able to obtain the desired axial alcohol in an axial : equatorial ratio of 98:2.

The addition of novel alkylzinc iodide nucleophiles to the 1-acyliminium ion derived from N-phenoxy carbonyl-4-methoxy-1,2,3,4-tetrahydropyridine 13 was also studied. This reaction gave the 1-acyl-2-substituted-1,2,5,6-tetrahydropyridines in high yields. This study has provided methodology and conditions for convenient preparation of 1-acyl-2-substituted-1,2,5,6-tetrahydropyridines.

We attempted to apply this methodology to the synthesis of elaekanine A. The key step in this synthesis was the regioselective addition of an alkylzinc iodide to the 2-position of the 1-acyliminium ion prepared from N-methoxycarbonyl-3-bromo-4-methoxy-1,2,3,4-tetrahydropyridine. Addition was exclusively at the 4-position, so this methodology could not be applied to the synthesis of elaekanine A and this synthetic plan was abandoned.
EXPERIMENTAL SECTION

All glassware was dried at 140° C overnight (12-18 h.), assembled hot and allowed to cool under a purge of nitrogen. All reactions were carried out under a static pressure of nitrogen in flasks fitted with rubber septa and were stirred magnetically using oven dried, Teflon-coated stirring bars. All transfers of organic and organometallic reagents were done with either oven-dried, nitrogen purged hypodermic syringes fitted with stainless steel needles or by double tipped needle technique. BF$_3$OEt$_2$ was purchased from the Aldrich Chemical Company and used directly. Zn(Cu) couple was prepared by a literature procedure. Industrial-grade Mg was used in the preparation of Grignard reagents. The organic halides were freshly distilled and stored over sieves. Anhydrous ether from Mallinckrodt (analytical reagent grade) was stored over sieves and used directly. THF was distilled over sodium and benzophenone and stored under nitrogen prior to use. CuBr·S(Me)$_2$ was purchased from the Aldrich Chemical Company. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Radial preparative layer chromatography was carried out using a Chromatotron (Harrison Associates, Palo Alto, CA.). Microanalyses were performed by M.H.W. Laboratories, Phoenix, AZ. Nuclear magnetic resonance spectra ($^1$H, $^{13}$C) were recorded on a Varian XL-300 (300 MHz) and a JOEL FX-90 (90 MHz) spectrometer. Chemical shifts were expressed in δ units (ppm) with tetramethylsilane (0.1%) as an internal standard. Coupling constants (J) are reported in hertz; splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet, q, quartet; br. broad. Infrared spectra were recorded on Perkin-Elmer 1310 spectrometer and are calibrated with the 1601-cm$^{-1}$ peak of
polystyrene. All absorption frequencies are reported in reciprocal centimeters.

**N-Phenoxy carbonyl-4-oxo-1,2,3,4-tetrahydropyridine (10).**

To a 50 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added 4-methoxypyridine (1.0 mL, 10 mmol) in dry iso-propanol (20 mL). This solution was cooled to -23° C and potassium triisopropoxyborohydride (20 mL), 1 M solution in THF) was added. To this stirred solution, phenyl chloroformate (1.14 mL, 11 mmol) in dry diethyl ether (3 mL) was added dropwise over a 10 min period. The reaction mixture became heterogeneous and turned a pale yellow color. Stirring was continued for 1 h and the reaction mixture was poured into 10% HCl (30 mL). Stirring was continued for 10 min and the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO₄. The solution was filtered and concentrated to give the crude product. Purification by radial preparative layer chromatography (SiO₂, 30% EtOAc/hexanes) and recrystallization (CH₂Cl₂/hexanes) gave 1.15 g (53%) of 10 as white needles: mp 103-104° C; ¹H NMR (CDCl₃) δ 7.9 (d, 1H), 7.5-7.1 (m, 5H), 5.6-5.4 (br s, 1H), 4.3-4.1 (br s, 2H), 2.7 (t, 2H); ¹³C NMR (CDCl₃) 193, 151, 143, 130, 126, 125, 121, 108, 32, 36; IR (CDCl₃) 3083, 2902, 1742, 1669, 1605, 1495, 1464, 1422, 1374, 1354, 1331, 1305, 1251, 1216, 1201, 1183, 1165, 1117, 1083, 1046, 1025, 985, 970, 909, 810, 730 cm⁻¹.

N-Phenoxycarbonyl-4-hydroxy-1,2,3,4-tetrahydropyridine (11).

To a 25 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-phenoxycarbonyl-4-oxo-1,2,3,4-tetrahydropyridine (605 mg, 2.78 mmol) in MeOH (12 mL). The solution was cooled to O°C and CeCl₃·7H₂O (1.04 g, 2.78 mmol) was added. After stirring for 10 min, NaBH₄ (151 mg, 4 mmol) was added slowly in 25-mg portions. Stirring at O°C was continued for 1/2 h. The mixture was allowed to warm up to room temperature and poured into H₂O (25 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over K₂CO₃. The solution was filtered and concentrated to afford 467 mg (76%) of crude product as a clear oil: ¹H NMR (CDCl₃) δ 7.4-7.0 (m, 6H), 5.3-5.1 (m, 1H), 4.2-4.0 (m, 1H), 3.7-3.5 (m, 1H), 2.1-1.9 (br s, 2H); IR (CDCl₃) 3333, 2254, 1722, 1646, 1495, 1417, 1377, 1304, 1237, 1204, 1165, 1051, 996 cm⁻¹.

N-Phenoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine (13).

To a 50 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-phenoxycarbonyl-4-hydroxy-1,2,3,4-tetrahydropyridine (863 mg, 4.2 mmol) in MeOH (20 mL). To this solution was added pyridinium p-toluenesulfonate (530 mg, 2.1 mmol). After stirring for 1 h at room temperature, the reaction mixture was poured into saturated NaHCO₃ (25 mL). Stirring was continued for 10 min, then the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over K₂CO₃. The solution was filtered and concentrated to afford the crude product. Purification by radial
preparative layer chromatography (SiO$_2$, 30-50% EtOAc/hexanes) gave 727 mg (74%) of 13 as a clear oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.4-7.0 (m, 6H), 5.3-5.1 (m, 1H), 4.1-3.9 (m, 1H), 3.8 (q, 1H), 3.7-3.4 (m, 1H), 3.38 (s, 3H), 2.1 (m, 1H), 1.8 (m, 1H); $^{13}$C NMR (CDCl$_3$) 158, 151, 130, 128, 126, 122, 118, 108, 48, 38, 24; IR (CDCl$_3$) 3403, 3044, 2933, 2888, 2821, 1726, 1651, 1594, 1496, 1472, 1415, 1365, 1327, 1304, 1236, 1205, 1165, 1141, 1103, 1074, 1025, 1000, 915, 863; 752 cm$^{-1}$.

Anal. Calcd. for C$_{13}$H$_{15}$NO$_3$: C, 67.23; H, 6.07; N, 6.03; Found: C, 67.13, H, 6.16; N, 5.96

N-Phenoxy carbonyl-2-methyl-1,2,5,6-tetrahydropyridine (61).

To a 10 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added Zn(Cu) couple (0.34 g, 5.14 mmol) and benzene (4 mL). To this suspension was added methyl iodide (0.16 mL, 2.57 (mmol) and DMA (0.25 mL). The suspension was refluxed for 3 h. To a separate 25 mL round-bottomed flask equipped with stir bar and purged with nitrogen was added N-phenoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine (0.2 g, 0.86 mmol) in benzene (5 mL). The preformed methylzinc iodide was transferred via cannula to the tetrahydropyridine. Boron trifluoride etherate (0.16 mL, 1.29 mmol) was added via syringe. The suspension was stirred for 10 min and poured into 10% HCl (25 mL). After stirring for 10 min and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO$_4$. The solution was filtered and concentrated to afford the crude product as a light yellow oil. Purification by radial preparative layer chromatography (SiO$_2$, 20% EtOAc/hexanes) gave 174 mg (93%) of 61 as a
clear oil: $^1$H NMR (CDCl$_3$) $\delta$ 7.5-7.1 (m, 5H), 5.9-5.8 (br s, 1H), 5.8-5.7 (br s, 1H), 4.7-4.5 (m, 1H), 4.3 (dd, 1H), 3.2-2.9 (m, 1H), 2.4-2.2 (m, 1H), 2.1-2.0 (m, 1H), 1.4-1.2 (m, 3H); $^{13}$C NMR (CDCl$_3$) 157, 151, 129, 125, 122, 120, 49, 38, 37, 25, 20; IR (CDCl$_3$) 3368, 3038, 2976, 2932, 2360, 2252, 1712, 1657, 1595, 1497, 1456, 1420, 1363, 1331, 1298, 1282, 1264, 1232, 1207, 1164, 1150, 1110, 1087, 1067, 1056, 1025, 1008, 909, 805, 734 cm$^{-1}$.

Anal. Calcd. for C$_{13}$H$_{15}$NO$_2$: C, 71.87; H, 6.96; N, 6.44; Found: C, 71.78; H, 6.87; N, 6.37.

N-Phenoxycarbonyl-2'-n-butyl-1,2,5,6-tetrahydropyridine (62).

To a 10 mL round-bottomed flask equipped with a stir bar and reflux condenser under nitrogen was added Zn(Cu) couple (0.34 g, 5.14 mmol) and benzene (5 mL). To this suspension was added 1-iodobutane (0.3 mL, 0.86 mmol), DMA (0.26 mL) and I$_2$ (2 crystals). This mixture was refluxed for 3 h and cooled to room temperature. To a separate 25 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added $N$-phenoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine (0.2 g, 0.86 mmol) in benzene (5 mL). The preformed alkylzinc iodide was transferred via cannula to the tetrahydropyridine. Boron trifluoride etherate (0.16 mL, 127 mmol) was added to the suspension. Stirring was continued for 10 min, and the reaction mixture was poured into 10% HCl (25 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO$_4$. The solution was filtered and concentrated to afford the crude product as a golden yellow oil. Purification by radial preparative layer chromatography (SiO$_2$, 20% EtOAc/hexanes) gave 159 mg (71%) of 62 as a clear oil: $^1$H NMR (CDCl$_3$
δ 7.4-7.1 (m, 5H), 5.9-5.8 (br s, 1H), 5.8-5.7 (br s, 1H), 4.6-4.5 (br s, 1H), 4.3-4.2 (dd, 1H), 3.2-2.9 (m, 1H), 2.4-2.2 (m, 1H) 2.0 (m, 1H), 1.8 (br s, 2H), 1.4 (m, 4H), 1.0-0.9 (m, 3H); ¹³C NMR (CDCl₃) 154, 152, 129, 128, 125, 121, 53, 38, 37, 34, 28, 26, 23, 14; IR (CDCl₃) 3038, 2959, 2933, 2861, 2360, 2253, 1712, 1654, 1595, 1496, 1458, 1424, 1364, 1338, 1276, 1207, 1164, 1150, 1073, 1050, 1025, 998, 909, 735 cm⁻¹.

Anal. Calcd. for C₁₁H₂₁NO₂: C, 74.10; H, 8.14; N, 5.40; Found: C, 74.19; H, 8.14; N, 5.40.

N-Penoxycarbonyl-6-{4-chlorobutyl}-1,2,5,6-tetrahydro-0pyridine 63.

To a 25 mL round-bottomed flask equipped with a stir bar and reflux condenser under nitrogen was added Zn(Cu) couple (0.82 g, 12.56 mmol) and benzene (12 mL). to this suspension, 1-chloro-4-iodobutane (0.77 mL, 6.28 mmol) was added followed by DMA (0.65 mL). The resulting mixture was refluxed for 2 h, then an aliquot (0.01 mL) was removed. The aliquot was concentrated in vacuo and an ¹H NMR spectrum was obtained which showed that the desired alkylzinc iodide had formed quantitatively. To a separate 25 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-phenoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine (0.49 g, 2.1 mmol) in benzene (5 mL). The alkylzinc iodide was transferred by cannula to the tetrahydropyridine. To the resulting mixture was added boron trifluoride etherate (0.38 mL, 2.09 mmol) and stirring was continued for 10 min. The reaction was quenched by pouring the suspension into 10% HCl (25 mL) and stirring for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over
MgSO$_4$. The solution was filtered and concentrated to give the crude product as a clear oil. Purification by radial preparative layer chromatography (SiO$_2$, 20% EtOAc/hexanes) gave 472 mg (77%) of 63 as a clear oil: $^1$H (CDCl$_3$) NMR $\delta$ 7.4-7.0 (m, 5H), 6.0-5.8 (br s, 1H), 5.8-5.7 (br s, 1H), 4.7-4.5 (d, 1H), 4.3-4.2 (dd, 1H), 3.6 (t, 2H), 3.2-2.9 (m, 1H), 2.4-2.2 (m, 1H), 2.1 (d, 1H), 1.8 (m, 2H), 1.7-1.4 (m, 4H); $^{13}$C NMR (CDCl$_3$) 154, 151, 129, 128, 125, 121, 52, 45, 38, 33, 32, 25, 23; IR (CDCl$_3$) 3037, 2939, 2252, 1711, 1654, 1595, 1496, 1461, 1423, 1364, 1338, 1254, 1207, 1164, 1152, 1070, 999, 909, 732 cm$^{-1}$.

Anal. Calcd. for C$_{16}$H$_{20}$ClNO$_2$: C, 65.41; H, 6.86; N, 4.76; Found: C, 65.40; H, 6.84; N, 4.73.

N-Phenoxy carbonyl-2-(2-ethoxy carbonyl ethyl)-1,2,5,6-tetrahydropyridine (64).

To a 50 mL round-bottomed flask equipped with a stir bar and reflux condenser under nitrogen was added Zn(Cu) couple (1.68 g, 25.8 mmol) and benzene (25 mL). To this suspension was added ethyl 3-iodoproprionate (2.9 g, 4.3 mmol), DMA (1.3 mL) followed by I$_2$ (2 crystals). The mixture was refluxed for 2 h, then an aliquot (0.01 mL) was removed by syringe. The aliquot was concentrated in vacuo and an $^1$H NMR spectrum was obtained. The spectrum revealed that the desired functionalized alkylzinc iodide was formed quantitatively. To a separate 100 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-phenoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine (1 g, 4.3 mmol) in benzene (25 mL). The preformed 1-iodozincethylproprionate was added via cannula. To this mixture was added boron trifluoride etherate (0.77 mL, 6.45 mmol) and stirring was continued for 10 min. The reaction mixture was poured into 10% HCl (50
mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 75 mL). The combined organic extracts were washed with brine (50 mL) and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product as a clear oil. Purification by radial preparative layer chromatography (SiO₂, 30% EtOAc/hexanes) gave 1.27 g (97%) of 64 as a clear oil: ¹H NMR (CDCl₃) δ 7.4-7.0 (m, 5H), 6.0-5.8 (br s, 1H), 5.8-5.6 (br s, 1H), 4.6 (d, 1H), 4.3-4.2 (dd, 1H), 4.2-4.0 (m, 2H), 3.2-2.9 (m, 1H), 2.6-2.2 (m, 3H), 2.1-1.9 (m, 3H), 1.3-1.1 (m, 3H); ¹³C NMR (CDCl₃) 173, 154, 151, 130, 128, 127, 125, 121, 61, 52, 39, 37, 31, 29, 14; IR (CDCl₃) 2935, 2254, 1714, 1595, 1496, 1424, 1374, 1338, 1241, 1207, 1164, 1057, 1026 cm⁻¹.

Anal. Calcd. for C₁₇H₂₁NO₄: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.30; H, 7.01; N, 4.75.

N-Phenoxycarbonyl-2-(3-ethoxycarbonylpropyl)-1,2,5,6-tetrahydropyridine (65).

To a 50 mL round-bottomed flask equipped with a stir bar and reflux condenser under nitrogen was added Zn(Cu) couple (1.26 g, 19.32 mmol) and benzene (22 mL). To this suspension was added ethyl 4-iodobutyrate (0.98 mL, 1.56 mmol), DMA (1.1 mL) and I₂ (2 crystals). The mixture was refluxed for 2 h, then an aliquot was removed. The aliquot was concentrated and a ¹H NMR spectrum showed that the desired ethyl 4-iodozincbutyrate had been formed quantitatively. To a separate 100 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-phenoxycarbonyl-4-methoxy-1,2,3,4-tetrahydropyridine (0.5 g, 2.15 mmol) in benzene (22 mL). The preformed zinc reagent was transferred via cannula to the tetrahydropyridine in
benzene. To this mixture was added boron trifluoride etherate (0.4 mL, 3.2 mmol), and stirring was continued for 10 min. The reaction mixture was poured into 10% HCl (50 mL) and stirring was continued for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 75 mL). The combined organic extracts were washed with brine (50 mL) and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product as a light yellow oil. Purification by radial preparative layer chromatography (SiO₂, 30% EtOAc/hexanes) gave 562 mg (82%) of 65 as a clear oil: ^1^H NMR (CDCl₃) δ 7.4-7.0 (m, 5H), 6.0-5.8 (br s, 1H), 5.8-5.6 (br s, 1H), 4.7-4.5 (d, 1H), 4.4-4.2 (dd, 1H), 4.2-4.0 (q, 2H), 3.2-2.9 (m, 1H), 2.4-2.2 (m, 3H), 2.1-2.0 (d, 1H), 1.9-1.6 (m, 4H), 1.3 (t, 3H); ^1^C NMR (CDCl₃) 173, 154, 151, 130, 129, 128, 125, 122, 61, 52, 38, 37, 34, 25, 21, 14; IR (CDCl₃) 3083, 2938, 2254, 1713, 1595, 1496, 1483, 1423, 1370, 1339, 1276, 1206, 1163, 1059, 1026, 909 cm⁻¹.

Anal. Calcd. for C₁₈H₂₃NO₄: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.18; H, 7.08; N, 4.44.

**N-Phenoxycarbonyl-2-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridine (66).**

To a 25 mL round-bottomed flask equipped with a stir bar and reflux condenser under nitrogen was added Zn(Cu) couple (1.26 g, 19.3 mmol) and benzene (13 mL). To this suspension was added the OEE protected 1-iodopropanol (1.16 mL, 6.4 mmol), DMA (1.1 mL) and I₂ (2 crystals). The suspension was refluxed for 2 h. After 2 h an aliquot (0.01 mL) was removed and a ^1^H NMR spectrum showed that the desired alkylzinc iodide had formed quantitatively. To a separate 50 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was
added N-phenoxycarbonyl-4-methoxyl-1,2,3,4-tetrahydropyridine (0.5 g, 2.15 mmol) in benzene (13 mL). The preformed alkylzinc iodide was transferred by cannula to the tetrahydropyridine solution. Boron trifluoride etherate (0.4 mL, 3.2 mmol) was added. The suspension was stirred at room temperature for 10 min and poured into 10% HCl (25 mL). Stirring was continued for 10 min and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO₄. The solution was filtered and concentrated. To the residue was added THF (10 mL) and H₂O (4 mL) and oxalic acid (0.27 g, 2.2 mmol) and the solution was stirred at room temperature for 4 h. The reaction mixture was poured into 5% NaHCO₃ (25 mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product. Purification by radial preparative layer chromatography (SiO₂, 2% MeOH/CH₂Cl₂) gave 360 mg (64%) as a cloudy white oil: ¹H NMR (CDCl₃) δ 7.4-7.0 (m, 5H), 5.9-5.8 (br s, 1H), 5.8-5.6 (br s, 1H), 4.6-4.4 (br s, 1H), 4.3-4.1 (dd, 1H), 3.8 (t, 2H), 3.2-2.9 (m, 1H), 2.4-2.2 (m, 1H), 2.2-1.9 (m, 2H), 1.8-1.6 (m, 4H); IR (CDCl₃) 3625, 3448, 3039, 2938, 2253, 1708, 1654, 1595, 1496, 1463, 1424, 1365, 1339, 1259, 1207, 1164, 1149, 1072, 908, 731 cm⁻¹.

N-Methoxycarbonyl-4-oxo-1,2,3,4-tetrahydropyridine (58).

To a 50 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added 4-methoxypyridine (1 mL, 10 mmol) in MeOH (20 mL). The solution was cooled to -78°C and sodium
borohydride (416 mg, 11 mmol) was added. After stirring for 10 min, methyl chloroformate (0.85 mL, 11 mmol) in dry diethyl ether (3 mL) was added dropwise over a 10 min period. Stirring was continued for 1 h then the reaction mixture was poured into 10% HCl (25 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product. Purification by radial preparative layer chromatography (SiO₂, 50% EtOAc/hexanes) gave 680 g (43%) of 58 as a white solid: ¹H NMR (CDCl₃) δ 7.9 (br s, 1H), 5.4 (d, 1H), 4.1 (t, 2H), 3.9 (s, 3H), 2.6 (t, 2H); ¹³C NMR (CDCl₃) 193, 153, 143, 107, 56, 42, 35; IR (CDCl₃) 3089, 2959, 2254, 1735, 1670, 1605, 1464, 1444, 1424, 1410, 1374, 1356, 1343, 1333, 1305, 1254, 1220, 1185, 1115, 1047, 1010, 977, 962, 909, 808, 768, 734 cm⁻¹.

N-Methoxycarbonyl-3-bromo-4-oxo-1,4,5,6-tetrahydropyridine (59).

To a 25 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-methoxycarbonyl-4-oxo-1,2,3,4-tetrahydropyridine (799 mg, 5.2 mmol) in CH₂Cl₂ (15 mL). The solution was cooled to -23° C and bromine (270 mg, 5.3 mmol) was added dropwise. After 5 min cyclohexene (0.7 mL) was added and the solution turned from a bright yellow color to a clear solution. DBU (0.93 mL, 6.3 mmol) was added and the solution was allowed to warm to room temperature. Stirring was continued for 3 h. The reaction mixture was poured into 10% HCl (25 mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and
dried over K$_2$CO$_3$. The solution was filtered and concentrated to afford the crude product as a light yellow oil. Purification by radial preparative layer chromatography (SiO$_2$, 50% EtOAc/hexanes) gave 830 mg (69%) of 59 as a light yellow solid: $^1$H NMR (CDCl$_3$) $\delta$ 8.3 (br s, 1H), 4.1 (t, 2H), 3.9 (br s, 3H), 2.8 (t, 2H); $^{13}$C NMR (CDCl$_3$) 186, 144, 143, 74, 54, 43, 25; IR (CDCl$_3$) 2960, 2254, 1737, 1685, 1595, 1443, 1386, 1346, 1297, 1243, 1206, 1114, 1123, 1048, 1002, 908 cm$^{-1}$.

**N-Methoxycarbonyl-3-bromo-4-hydroxy-1,2,3,4-tetrahydropyridine (60).**

To a 25 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-methoxycarbonyl-3-bromo-4-oxo-1,2,3,4-tetrahydropyridine (830 mg, 3.5 mmol) in MeOH (10 mL). The solution was cooled to 0° C and CeCl$_3$·7H$_2$O (1.3 g, 3.5 mmol) was in one portion. To this solution, sodium borohydride (150 mg, 3.9 mmol) was added slowly in 25-mg portions. Stirring was continued at 0° C for 30 min, then the reaction mixture was allowed to warm to room temperature. The solution was poured into H$_2$O (25 mL) and stirring was for 10 min. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic extracts were washed with (25 mL) and dried over K$_2$CO$_3$. The solution was filtered and concentrated to afford 822 mg (99%) of 60. No purification was attempted on this compound and it was used directly in the next step. $^1$H NMR (CDCl$_3$) $\delta$ 7.4 and 7.2 (pair of s due to rotomers, 1H), 4.3 (t, 1H), 4.0 (m, 1H), 3.8 (s, 3H), 3.3 (m, 1H), 2.5 (br s, 1H), 2.0 (m, 2H).
N-Methoxycarbonyl-3-bromo-4-methoxy-1,2,3,4-tetrahydropyridine (17).

To a 50 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-methoxycarbonyl-3-bromo-4-hydroxy-1,2,3,4-tetrahydropyridine (822 mg, 3.5 mmol) in THF (25 mL). The solution was cooled to -23°C and potassium t-butoxide (0.59 g, 5.3 mmol) was added. After 5 min, methyl iodide (10 mmol) was added and stirring was continued at -23°C for 1 h, then the solution was warmed to room temperature for 30 min. The solution was poured into stirred 5% aqueous NaHCO₃ (25 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product. Purification by radial preparative layer chromatography (SiO₂, 30-80% EtOAc/hexanes) gave 722 mg (83%) of 17 as a clear oil: ¹H NMR (CDCl₃) δ 7.4-7.2 (pair of br s due to rotomers, 1H), 4.0 (m, 1H), 3.8 (m, 4H), 3.5 (s, 3H), 3.2 (br s, 1H), 2.2 (br s, 1H), 1.8 (m, 1H); ¹³C NMR (CDCl₃) 152, 128, 100, 75, 57, 53, 37, 27; IR (CDCl₃) 3416, 3105, 2957, 2934, 2886, 2826, 2251, 1713, 1643, 1446, 1391, 1354, 1304, 1276, 1221, 1201, 1127, 1100, 1080, 1044, 1000, 979, 911, 832, 819, 765, 732 cm⁻¹.

N-Methoxycarbonyl-2-(3-hydroxyprpyrrolyl)-3-bromo-1,2,3,4-tetrahydropyridine (19).

To a 25 mL round-bottomed flask equipped with a stir bar and reflux condenser under nitrogen was added Zn(Cu) couple (1.23 g, 18.8 mmol) and benzene (15 mL). To this suspension was added the OEE protected 1-iodopropanol (1.2 mL), 6.26 mmol), DMA (1.1 mL) and I₂ (2 crystals). The reaction mixture was refluxed for 2 h, then an aliquot (0.01 mL) was removed by syringe. The solution was concentrated in vacuo and an ¹H
NMR spectrum showed that the desired alkylzinc iodide had been formed quantitatively. To a separate 50 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-methoxycarbonyl-3-bromo-4-methoxy-1,2,3,4-tetrahydropyridine (0.522 mg, 2.1 mmol) in benzene (10 mL). The preformed alkylzinc iodide was transferred by cannula to the tetrahydropyridine solution at room temperature. To this mixture was added boron trifluoride etherate (0.4 mL, 3.2 mmol), and stirring was continued for 30 min. The suspension was poured into 10% HCl (30 mL) and, after 10 min the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product. The crude product was dissolved in THF (5 mL) and H₂O (5 mL). Oxalic acid (.26 g, 2.1 mmol) was added and the mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and poured into 5% NaHCO₃ (25 mL). After stirring for 10 min the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over K₂CO₃. The solution was filtered and concentrated to afford the crude product. Purification by radial preparative layer chromatography (SiO₂, 2% MeOH/Methylene chloride) gave 0.26 g (45%) of the 4-substituted product.

1-(Benzyloxy carbonyl)-2-(3,4-dimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydropyridine (5).

To a suspension of magnesium metal (0.73 g, 30 mmol) in THF (5 mL) under an atmosphere of nitrogen was added dibromoethane (0.2 mL). The mixture was warmed by hand until a reaction commenced (bubbling
and heating). When all the dibromoethane had reacted, THF (10 mL) was added. The supernatant fluid was removed by syringe and the magnesium was again washed with THF (10 mL). The supernatant fluid was again removed by syringe and THF (10 mL) was added. To this suspension was added 4-bromoveratrole (1.5 mL, 12 mmol). This suspension was stirred for 12 h at room temperature. The resulting Grignard reagent was then added slowly to a solution of 4-methoxypyridine (1.0 mL, 10 mmol) in THF (10 mL) at -23°C. To this solution was added benzyl chloroformate (1.4 mL, 10 mmol) in a dropwise fashion over a 10 min period. The solution was stirred at -23°C for 4 h then poured into stirred 10% HCl (25 mL). After stirring for 10 min the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product as a light yellow solid. Recrystallization (acetone/hexanes) gave 2.8 g (75%) of 5 as white needles: mp. 115°C - 117°C; ¹H NMR (CDCl₃) δ 7.9 (d, 1H), 7.3 (s, 5H), 6.8 (s, 3H), 5.6 (d, 1H), 5.3 (d, 1H), 5.2 (s, 2H), 3.9 (s, 3H), 3.7 (s, 3H), 3.1 (dd, 1H), 2.7 (d, 1H); ¹³C NMR (CDCl₃) δ 192, 153, 148, 149, 142, 135, 131, 128.6, 128.5, 128.3, 128.2, 118, 111, 109, 107, 69, 55.7, 55.5, 5.41; IR (CDCl₃) 3150, 2950, 1720, 1660, 1600, 950 cm⁻¹.

cis-1-(Benzylloxycarbonyl)-2-(3,4-dimethoxyphenyl)-6-(4-hydroxybutyl)-piperidin-4-one (67).

To a 25 mL round-bottomed flask equipped with stir bar and purged with dry nitrogen was added magnesium metal (0.212 g, 8.7 mmol) and THF (5 mL). To this suspension was added the OEE protected 1-chloro-4-hydroxy-butane (0.52 mL, 2.99 mmol) and ethylene dibromide (0.02 mL) as an entrainer. The suspension was warmed by hand until a reaction
commenced (warming and cloudiness), and the suspension was heated to reflux for 4 h. The resulting Grignard was added by cannula to cuprous iodide (0.55 g, 2.9 mmol) in THF (5 mL) at -23° C. The resulting heterogeneous mixture was stirred at -23° C for ten minutes then cooled to -78° C. To this mixture was added boron trifluoride etherate (0.2 g, 1.44 mmol). The mixture stayed heterogeneous, and after ten minutes 1-(benzyloxy carbonyl)-2-(3,4-dimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydropyridine (530 g, 1.44 mmol) in THF (5 mL) was added dropwise over a ten minute period. The mixture briefly became homogeneous. The mixture was stirred at -78° C for 3 h, then poured into 20% NH₄Cl/NH₄OH (50:50) solution (50 mL). The aqueous layer was extracted with ether (2 x 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solution was filtered and concentrated to yield the crude product. No further purification was attempted. The compound was dissolved in THF (5 mL) and water (2 mL). Oxalic acid (0.182 g, 144 mmol) was added and the solution was stirred at room temperature for 4 h. The reaction was quenched by pouring the reaction mixture into 5% NaHCO₃ (25 mL). The aqueous layer was extracted with ether (2 x 50 mL) and the combined organic extracts were washed with brine (25 mL) and dried over MgSO₄. The solution was filtered and concentrated to give the crude product. Purification by radial preparative layer chromatography (SiO₂, 10% methanol-methylene chloride) gave 0.49 g (73%) of 67 as a clear oil. The isolated product consists of two diastereomers which were separated by RPLC (SiO₂, 80% ethyl acetate, 0.5% ethanol/hexanes) to give 396 mg of the cis diastereomer and 84 mg of the trans diastereomer, a product ratio of 5:8:1. ¹H NMR (CDCl₃) δ 7.4 (s, 5H), 6.8 (m, 3H), 5.9 (m, 1H), 5.2 (s,
2H), 4.7 (m, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 3.6 (m, 1H), 3.4 (t, 2H), 3.0 (dd, 2H), 2.9-2.6 (m, 2H), 2.3 (dd, 1H), 1.8-0.9 (m, 6H). IR (CDCl$_3$ 3530, 2975, 1700, 1620 cm$^{-1}$).

Anal. calcd. for C$_{25}$H$_{31}$NO$_6$: C, 68.01; H, 7.08; N, 3.16. Found: C, 67.90; H, 6.94; N, 3.14

N-(Benzyloxycarbonyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-(4-chlorobutyl)piperidine (6).

To a 25 mL round bottomed flask equipped with a stir bar and purged with nitrogen was added Mg (0.12 g, 4.9 mmol) and diethyl ether (8 mL). To this suspension was added 1-bromo-4-chlorobutane (0.01 mL) at room temperature. The suspension was stirred at room temperature until a reaction commenced (warming, cloudiness) and was cooled to 0°C. Additional 1-bromo-4-chlorobutane (0.5 mL, 4.3 mmol) was added and stirring was continued for 1 h at 0°C. After 1 h, solution was warmed to room temperature and transferred via cannula to an addition funnel. To a separate 100 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added N-benzyloxycarbonyl-2-(3,4-dimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydropyridine (0.5 g, 1.44 mmol) in THF (50 mL). To this solution was added CuBr·S(CH$_3$)$_2$ (0.9 g, 4.3 mmol), which formed a heterogeneous reaction mixture (no attempt was made to solubilize the Cu reagent). The suspension was cooled to -78°C and boron trifluoride etherate (0.26 mL, 22 mmol) was added. The preformed Grignard reagent was added in a dropwise fashion over a 10 min period. The suspension became a golden yellow color and appeared to become homogeneous during the addition of the Grignard reagent. After the addition of the Grignard was complete the reaction mixture returned to a heterogeneous state. The suspension was stirred for 4 h at -78°C and
poured into 20% NH₄C/ NH₄OH 50:50 (100 mL). After stirring 10 min the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 100 mL). The combined organic extracts were washed with brine (50 mL) and dried over MgSO₄. The solution was filtered and concentrated to afford the crude product as a bright yellow oil. Purification by radial preparative layer chromatography (SiO₂, 30% EtOAC/hexanes) gave 380 g (57%) of 6 as a light yellow oil. The isolated product consisted of 2 diastereomers which were separated by radial preparative layer chromatography (SiO₂, 20% acetone/hexanes) to give 370 g of the cis isomer and 5.2 mg of the trans isomer. A cis:trans ratio of 60:1 was determined by ¹H NMR analysis of the crude material. ¹H NMR (CDCl₃) δ 7.5-7.3 (m, 5H), 7.0-6.8 (m, 3H), 6.1-5.8 (m, 1H), 5.2 (s, 2H), 4.8-4.6 (m, 1H), 3.9 (m, 1H), 3.7 (m, 3H), 3.3 (br s, 1H) 3.0 (m, 1H), 2.8-2.6 (m, 2H), 2.4 (m, 1H), 1.6-1.0 (m, 6H); ¹³C NMR (CDCl₃) 206, 156, 150, 148, 136, 134, 128.8, 128.7, 128.5, 128.3, 119, 118, 112, 109, 68, 56, 54, 52, 45, 36, 32, 24; IR (CDCl₃) 2938, 2835, 1717, 1691, 1602, 1589, 1518, 1455, 1410, 1327, 1257, 1147, 1026 cm⁻¹.

Anal. Calcd. for C₂₅H₃₀NO₅: C, 65.28; H, 6.57; N, 3.05; Found: C, 65.11; H, 6.28; N, 304.

4-(3,4-Dimethoxyphenyl)-quino­lizidin-2-one (7).

To a 500 mL Parr bottle was added N-(benzyloxycarbonyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-(4-chlorobutyl)piperidine (0.78 g, 1.7 mmol) in ethyl acetate (15 mL). To this solution was added lithium carbonate (0.12 g, 1.7 mmol) and 5% Pd/C (0.14 g). This mixture was shaken under 40 p.s.i of hydrogen for 12 h. After 12 h the reaction mixture was filtered through celite and concentrated to afford the crude product. Purification
by radial preparative layer chromatography (SiO₂, 5% MeOH/CH₂Cl₂) gave 0.37 g (75%) of \( \mathbf{I} \) as a clear oil. Crystallization from methanol gave colorless crystals: mp 82°-84° C (lit. 83°-84° C); \(^1\)H NMR (CDCl₃) δ 6.9 (s, 1H), 6.8 (s, 2H), 3.9 (s, 3H), 3.8 (s, 3H), 3.2 (dd, 1H), 2.9-2.1 (m, 7H), 1.9-1.1 (m, 6H); \(^{13}\)NMR (CDCl₃) 207, 135, 119, 111, 109, 69, 62, 56, 53, 51, 48, 34, 26, 24; IR (CDCl₃) 2900, 2770, 2725, 1710 cm⁻¹.

**Preparation of (+/-)-lasubine II (2).**

To a 5 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added 4-(3,4-dimethoxyphenyl)quinolizidin-2-one (73 mg, 0.25 mmol) in THF (1 mL). This solution was cooled -78° C in preparation for its delivery to the reducing agent. To a separate 10 mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added LS-Selectride™ (Aldrich Chemical Company) (0.31 mL, 0.31 mmol) in THF (2 mL) cooled to -78° C. The quinolizidone was transferred via cannula to the reducing agent and stirring was continued for 30 min. After 30 min pH 7.0 phosphate buffer (1 mL) was added and the solution was warmed up to room temperature. The reaction mixture was extracted with diethyl ether (2 x 25 mL), and the combined organics were washed with brine (25 mL). The solution was concentrated under reduced pressure to afford the crude boronate. The crude boronate was dissolved in ethanol and 1 N NaOH (1 mL) was added. The mixture was refluxed for 1 h then cooled to room temperature. The mixture was then purged into 5% NaHCO₃ (25 mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (25 mL) and dried over K₂CO₃. The solution was filtered and concentrated to
afford the crude product. Purification by radial preparative layer chromatography (SiO₂, 5% CHCl₃/MeOH) gave 58 mg (81%) of (+/-)-lasubine II as a viscous oil. The product was isolated as a mixture of diastereomers with a hydroxyl group axial:equatorial ratio of 98.2 as indicated by NMR. ¹H NMR (CDCl₃) δ 6.91 (s, 1H), 6.86 (d, j = 7.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 4.15 (t, J = 2.6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.31 (dd, J = 11.5 and 3.2 Hz, 1H), 2.69 (d, J = 11 Hz, 1H), 2.35-2.41 (m, 1H), 1.25-1.91 (m, 12H); ¹³C NMR δ 148, 147, 137, 119, 111, 110, 64, 63, 56, 55.75, 55.7, 53.42, 40, 33, 25, 24. IR (CDCl₃) 3613, 3402, 3155, 3008, 2937, 2859, 2839, 2799, 2254, 1794, 1594, 1516, 1465, 1443, 1421, 1386, 1342, 1314, 1261, 1233, 1197, 1179, 1151, 1135, 1094, 1047, 1029, 908, 736. This is in agreement with reported spectra.³⁰
REFERENCES


APPENDICES
Determination of ratio of cis and trans diastereomers
$\text{Ar} = 3,4-\text{(MeO)}_2\text{Ph}$
VARIAN XL-300
STANDARD IH OBSERVE
EXP 3 PULSE SEQUENCE: COSY
DATE 10-12-87
SOLVENT CDCl3
FILE COSY

COSY PULSE SEQUENCE
OBSERVE PROTON
FREQUENCY 299.93 MHz
SPECTRAL WIDTH 1928 Hz
2D SPECTRAL WIDTH 1927.5 Hz
ACQ TIME 0.266 sec
RELAXATION DELAY 1.0 sec
PULSE WIDTH 90 degrees
FIRST PULSE 90 degrees
AMBIENT TEMPERATURE
NO. REPETITIONS 16
NO. INCREMENTS 128
SPIN RATE 20 Hz
DATA PROCESSING
PSEUDO-ECHO SHAPED
FT SIZE 512 x 512
TOTAL TIME 49.9 minutes
Michael A. Foley
Candidate for the Degree of
Master of Science

Thesis: Dihydropyridones as Synthetic Intermediates

Major Field: Organic Chemistry

Biographical Information:
