MARKS, LUCAS RICHARD. Catalyst Design for Asymmetric Organozinc Addition to Aldehydes and Progress Toward the Total Synthesis of the Marine Alkaloid, (-)-Lepadiformine. (Under the direction of Professor Daniel Lee Comins).

A novel dihydropyridone was synthesized in search for a chiral ligand for the asymmetric addition of an alkyl group to an aldehyde. The target amine was derived from an enamine through a hydrogenation reaction.

A study directed toward the total synthesis of the marine alkaloid (-)-lepadiformine was carried out. Two approaches were investigated toward the core perhydroquinoline system. The first approach utilized a Grignard addition to an N-acylpyridinium salt and a [2+2] photochemical addition as the key synthetic steps. The second approach was based upon quinoline chemistry. The model study was completed with a one-carbon alkene homologation to form a terminal butane. An asymmetric route was examined.
Catalyst Design for Asymmetric Organozinc Addition to Aldehydes and Progress Toward the Total Synthesis of the Marine Alkaloid, (-)-Lepadiformine

by

Lucas Richard Marks

A dissertation submitted to the Graduate Faculty of North Carolina State University In partial fulfillment of the Requirements for the Degree of Doctor of Philosophy

CHEMISTRY

Raleigh

2006

APPROVED BY:

______________________________   _____________________________
Chair of the Advisory Committee
DEDICATION

I would like to dedicate this work to my Grandmother Janice Rothery Marks and my late Grandfather Garson Mink. My Grandmother’s love of science had an innate influence on my life. She was one of the first people to put me on the path of science as a child growing up. I remember her encouragement when I wanted to learn about dinosaurs as a kid. That transferred into my eventual love of chemistry. My Grandfather’s love for his family and drive as an athlete also influenced me. He was the driving force behind my athletic career growing up. His influence taught me to never give up. Without both of those people in my life I would not be where I am today.
BIOGRAPHY

The author, Lucas R. Marks, was born in Newark, New York on February, 15th 1978 to Mr. C. Roger Marks and Mrs. Donna L. Marks. After graduating from high school in Marion, New York he went on to attend Roger Williams University in Bristol, R.I. It was while earning a joint B.S. in Marine Biology and a B.A. in Chemistry that he met his wife Christina E. Krehel. After graduating with honors in May 2000 and getting married, he moved to North Carolina to attend North Carolina State University as a Ph. D. student in organic chemistry. In December 2002, he was invited to join the Phi Lambda Upsilon Chemistry Honors Society at NCSU. He became president of PLU in the summer of 2003 till the summer of 2004. From 2004 to 2005 he served as the co-senior advisor to PLU. After completing his Ph. D., he began an industrial post-doctoral position under the direction of Dr. F. Ivy Carroll at Research Triangle Institute.
ACKNOWLEDGEMENTS

It is said that “we stand on the shoulders of those before us”. While this is very true, I believe as a Ph. D. candidate this quote needs to be amended. After my years here at NC State University, I believe that “we stand on the shoulders of those before and with us”. For while my predecessors paved the way in organic chemistry it is my colleagues who have truly helped me through my years. With that said I would like to acknowledge all the people that have helped me achieve this wonderful goal. First and foremost, I must thank Dr. Daniel Comins for his advice and mentorship through my career. I would also like to thank my committee members Dr. Bruce Eaton, Dr. T. Brent Bunnoe, Dr. Christian Melander, Dr. Suzanne T. Purrington, and Dr. Binghe Wang. A special thanks to Drs. Melander and Purrington for joining my committee after Drs. Eaton and Wang moved on from NC State. I would also like to thank my many professors especially Drs. Carl Bumgardner and Dave Shultz. Dr. Bumgardner’s enthusiasm teaching his classes was very contagious, while Dr. Shultz’s knowledge helped me achieve a new horizon as a student.

While I have many colleagues to thank, there are a few who truly stand out as friends. Without their guidance and assistance I would have been at a lost. I have to thank Ms. Lina A. Gugliotti for her sheer presence. Not only was she a great friend through our undergraduate years at Roger Williams University, she has also been a great friend here at NC State. I must thank Dr. James Dixon. The fours years that we overlapped allowed me a place to go to discuss anything but chemistry. Thanks for the many breaks. I would like to thank Dr. Laurel Goj for her advice and willingness to
answer any question, no matter how inane. I extend my gratitude to both the past and present
members of the Comins group. A few stand out through the years, Mr. Ibrahim Bori, Mr. W.
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Their intellectual input was forefront in my chemistry career. I would like to especially
thank Ms. Florence “Flo” Février and Mr. Jason M. Dinsmore. Not only were they my
friends in the Comins lab, they were my friends in the real world too. These two people
made work fun everyday, even the difficult days.

My family has been the driving force behind my career. I would like to take this time
to acknowledge and thank my parents Mr. C. Roger Marks and Mrs. Donna L. Marks. These
two people taught me that family and education are important first and foremost. They truly
are my inspiration. Both my parents decided to go back to school after almost twenty years.
My father got his certification in Heating Ventilation and Air Conditioning while my mother
received her Bachelors in Education and eventually her Masters. The greatest achievement
of all is that they did this while raising my brother and me. To my brother, Justin, thank you
for showing me that life isn’t always fair and that there is another world besides the sciences.
To Mr. Thomas Krehel and Mrs. Mary Krehel, thank you for your acceptance of me as your
new son and your support through these years. I know I have moved your oldest daughter
many hundreds of miles away but thank you for understanding. And finally to my wife,
Christina Elizabeth Marks, thank you! I doubt I will ever be able to convey how much it
means to me to know that you are always behind me. They say that “behind every great man,
there is a great woman”, this is true with you. Your willingness to follow me to North
Carolina, far away from family
and friends, so I could pursue my dream is the main drive in my career. I know you have put your life on hold for me and for this I am eternally grateful. Everyday I look forward to the life that we will be able to experience together.
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<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>A&lt;sup&gt;(1,3)&lt;/sup&gt;</td>
<td>1,3 allylic</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>[α]&lt;sub&gt;D&lt;/sub&gt;</td>
<td>specific rotation</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
</tr>
<tr>
<td>Aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>Bp</td>
<td>Boiling point</td>
</tr>
<tr>
<td>Br</td>
<td>Broad</td>
</tr>
<tr>
<td>Brine</td>
<td>saturated solution of sodium chloride</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>°C</td>
<td>Degree(s) Celsius</td>
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<tr>
<td>&lt;sup&gt;13&lt;/sup&gt;C NMR</td>
<td>Carbon-13 nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>cm&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>reciprocal centimeters</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>CPC</td>
<td>(-)-(1&lt;sup&gt;R&lt;/sup&gt;,2&lt;sup&gt;S&lt;/sup&gt;,4&lt;sup&gt;R&lt;/sup&gt;)-2-(1-methyl-1-phenylethyl)-4-(2-propyl)cyclohexanol</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
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<tr>
<td>( \delta )</td>
<td>Chemical shift in ppm from tetramethylsilane</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>Dd</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>De</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBALH</td>
<td>Diisobutylaluminium hydride</td>
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<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
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<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
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<td>Dimethylsulfide</td>
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<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>Dt</td>
<td>Doublet of triplets</td>
</tr>
<tr>
<td>Ee</td>
<td>Enantiomeric excess</td>
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<tr>
<td>Et</td>
<td>Ethyl</td>
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<tr>
<td>Et(_2)O</td>
<td>Diethyl ether</td>
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<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
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<td>Ethanol</td>
</tr>
<tr>
<td>G</td>
<td>Gram(s)</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
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H  hour(s)
H⁺  Proton or protic acid
¹H NMR  Proton nuclear magnetic resonance spectroscopy
HPLC  High-performance liquid chromatography
HMDS  Hexamethylphosphoramide
HMQC  Hetero Nuclear Multi Quantum Correlation
HRMS  High resolution mass spectroscopy
Hz  Hertz
i-Pr  Isopropyl
IR  Infrared spectroscopy
J  Coupling constant
L  Liter
L-Selectride ®  Lithium tri-sec-butylborohydride
LDA  Lithium diisopropylamide
LiTMP  Lithium tetramethylpiperidine
μ  Micro
M  Molar
M  Multiplet
M⁺  Parent molecular ion
MeOH  Methanol
Mg  Milligram(s)
<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>Min</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter(s)</td>
</tr>
<tr>
<td>Mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>Mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>Mp</td>
<td>melting point</td>
</tr>
<tr>
<td>N</td>
<td>Normal</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>NOE</td>
<td>Nuclear Overhauser effect</td>
</tr>
<tr>
<td>1D-NOESY</td>
<td>One dimensional nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>R</td>
<td>Alkyl group</td>
</tr>
<tr>
<td>radial PLC</td>
<td>radial preparative-layer chromatography</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
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<td>t</td>
<td>Triplet</td>
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<td>TCC</td>
<td>trans-2-(α-cumyl)cyclohexyl alcohol</td>
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<td>triethylamine</td>
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<td>Trimethylsilyl</td>
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<tr>
<td>TOESY</td>
<td>Total Correlation Spectroscopy</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
</tbody>
</table>
INTRODUCTION

A cornerstone of the Comins group research program has been the synthesis and utilization of \( N \)-acyl-2,3-dihydro-4-pyridones of the type 1. The reactivity of the dihydropyridones has been demonstrated over the past 15 years, and their utility for the total synthesis of various heterocycles continues to be explored (Figure 1).\(^{1-7}\)

![Figure 1. The versatility of the \( N \)-acyl-2,3-dihydro-4-pyridone.](image)

In regard to the reactivity of 1, it is important to note that the carbamate moiety influences the substituent at the 2-position of the dihydropyridone to occupy the axial position by virtue of \( A^{(1,3)} \) strain.\(^8\) By effectively blocking this face, reactions heavily influenced by steric approach control, including enolate alkylations at the 3-position and [2+2] photocycloaddition across the C5-C6 double bond, occur anti to the axial group. Both the enolate alkylation and the [2+2] photocycloaddition lead to the \textit{trans} product in relation to the substituent at the 2-position. Adding to the attractiveness of these compounds as
intermediates is the ease in which dihydropyridones can be synthesized from readily available starting materials (Scheme 1).

**Scheme 1. Preparation of Racemic Dihydropyridones**

The reaction of 4-methoxypyridine with a chloroformate at low temperature affords an \(N\)-acylpyridinium salt intermediate 3. This electrophilic pyridinium salt is activated toward nucleophilic attack at the 2- and 6- positions. Metallo-enolates and Grignard reagents have served as excellent nucleophiles for this reaction.9,10 Attack of the pyridinium salt by these organometallics gives a dihydropyridine 4, which under mild acid hydrolysis yields dihydropyridone 5.11 This process is efficient with overall yields in the upper 90% range.

The Comins group has developed a methodology to obtain dihydropyridones in enantiomerically pure form by using 4-methoxy-3-(triisopropylsilyl)pyridine and a chiral chloroformate (Scheme 2).12
Scheme 2. Preparation of Enantiopure Dihydropyridones

4-Methoxy-3-(triisopropylsilyl)pyridine (6) is acylated by either antipode of the chloroformate of the commercially available trans-2-(α-cumyl)cyclohexyl alcohol (TCC) to form the pyridinium salt which is then treated with a Grignard or metallo-enolate. The bulky C-3 TIPS group effectively blocks the 2-position to cause attack at the 6-position of the salt. In addition, the aryl ring of the chiral auxiliary forms a π-stacking interaction with the electrophilic pyridine ring and blocks one prochiral face (Figure 2).
An acidic work-up affords the dihydropyridone 7 with diastereoselectivities ranging from 85 to 95%. Recrystallization of the crude product provides the major diastereomer. The chiral auxiliary is subsequently cleaved with either sodium methoxide or potassium carbonate in refluxing methanol and recovered. In the same pot, protodesilylation of the TIPS blocking group with aqueous acid provides the enantiomerically pure N-H dihydropyridone 8. Reprotection of the nitrogen with various chloroformates (such as benzyl, t-butyl or phenyl) produces 9, which is available for further synthetic endeavors. Such utilization of enantiopure dihydropyridones has been effective in many asymmetric natural product syntheses and methodology studies.\(^1\)

The utility of 2,3-dihydropyridones as chiral building blocks has been utilized in the synthesis of several natural and unnatural products containing piperidine, indolizidine, quinolizidine and \textit{cis-} and \textit{trans-} decahydroquinoline ring systems.\(^2-6\) Most recently the
ladybug alkaloid, (+)-hyperaspine, was synthesized in 6 steps from 4-methoxypyridine (Figure 3).\(^7\)

\[ \text{(+)-hyperaspine} \]

\[ \text{(+)-luciduline} \]

\[ \text{(-)-1-deoxynojirimycin} \]

\[ \text{(-)-\alpha-conhydrine} \]

\[ \text{(+)-cannabisativine} \]

\[ \text{(-)-\alpha-acetyl-N_\beta-methylphlegmarine} \]

\[ \text{Figure 3. Alkaloid syntheses utilizing enantiopure dihydropyridones as building blocks.} \]

**CHAPTER 1: CATALYTIC ASYMMETRIC ORGANOZINC ADDITIONS**

**I. Introduction.**

The role of a catalyst in a reaction is to lower the energy of activation (\(E_a\)) which thus increases the rate of reaction (Figure 4).
The upper coordinate (dashed line) corresponds to the reaction without a catalyst while the lower coordinate (solid line) corresponds to the same reaction with a catalyst. The TS is the transition state for those reactions. It is important to determine what physical property $E_a$ can be associated with in order to obtain a viable value. $E_a$ can be interpreted as an energy called the Arrhenius activation energy, or activation energy. This activation energy can be inferred as the height of an energy barrier over which reactants must pass on their way to products (Figure 4). The transition state theory is utilized to determine a more precise idea.

In the transition state theory, the transition state is considered a chemical species. Utilizing the Eyring equation the rate constant $k_r$ is defined as

\[ k_r = \left( \kappa kT / h \right) \cdot \exp(-\Delta G^\ddagger/RT) \]  \hspace{1cm} (Eq. 1)

where $h$ is Plank’s constant, $T$ is the absolute temperature, $R$ is the gas constant, $\kappa$ is the transmission coefficient and $k$ is the Boltzmann constant. Through subsequent evaluation and derivations this equation can be rewritten as

\[ k_r = \left( \kappa kT / h \right) \cdot \exp(-\Delta G^\ddagger/RT) \]  \hspace{1cm} (Eq. 1)

Figure 4. Reaction coordinate for a general reaction.
\[ E_a = \Delta H^\ddagger + RT \]  
(Eq. 2)

which shows a direct relationship between the energy of activation and the enthalpy change of the transition state (\(\Delta H^\ddagger\)). Through further evaluation and derivations the entropy change of the transition state (\(\Delta S^\ddagger\)) can be calculated utilizing the \(\Delta H^\ddagger\), \(k_r\), and T for an experiment (equation 3):

\[ \Delta S^\ddagger = R \cdot 2.303 \cdot \log\left(\frac{k_r}{T}\right) + \frac{\Delta H^\ddagger}{T} - R \cdot 2.303 \cdot \log\left(\frac{k}{h}\right) \]  
(Eq. 3)

There is a close relationship between the Arrhenius \(A\) value and \(\Delta S^\ddagger\) as depicted in equation 4:

\[ \Delta S^\ddagger = 4.575 \log A - 60.53 \]  
(Eq. 4)

The value of \(\Delta S^\ddagger\) for a reaction provides an estimate of the change in the order of the system as it goes from reactants to activated complex. Through these various equations and derivations it can be postulated that the \(E_a\) is directly related to the activation enthalpy (\(\Delta H^\ddagger\)) and the Arrhenius \(A\) value is directly related to the activation entropy (\(\Delta S^\ddagger\)). With this information it can be postulated that the catalyst effectively reduces the \(\Delta H^\ddagger\) by decreasing
the energy of activation. Also, the catalyst lowers the $\Delta S^\dagger$ by decreasing the amount of molecular disorder between the starting materials and the transition state.

Enantiomers have the same energy as products; however, a catalyst can also lower the $E_a$ for a specific enantiomer over another (Figure 5)

![Figure 5. Reaction coordinate for a catalytic reaction favoring one enantiomer.](image)

This allows for a product ratio favoring one enantiomer. A small change in the energy of activation for either enantiomer can produce a relative substantial enantiomeric excess (ee). An important field of research involves the use of organozinc catalysis, which can produce ee’s greater than 90% with the addition of diethylzinc to aryl aldehydes.

**II. Organozinc catalysis**

The field of chiral catalysis in organic synthesis has grown significantly since 1984 when Oguni and Omi discovered that the addition of diethylzinc to benzaldehyde in the presence of various optically active 2-amino-1-alcohols produced enantioenriched products. The best
enatioslectivity was observed using (S)-leucinol. The product, 1-phenylpropan-1-ol, was obtained in 96% yield with an ee of 48.8% (Scheme 3).

**Scheme 3. Reaction of Benzaldehyde with Diethylzinc and (S)-Leucinol**

Noyori and coworkers improved the reaction by using chiral catalyst (12) and obtained 11 with an ee of 95%.

Since then, the reaction of diethylzinc with benzaldehyde has become an important benchmark for the design of new ligands in catalytic asymmetric synthesis (Scheme 3). These catalysts allow for the synthesis of chiral alcohols which are ubiquitous among drug candidates and natural products. Many structurally diverse compounds have been synthesized and examined as asymmetric catalysts for synthesizing chiral alcohols including amino alcohols, amino thiols, disulfides, diamines, and diols. These compounds catalyzed the organozinc addition reaction with enantioselectivities over 90% ee with alkyl-, alkenyl-,
aryl-, and alkynylzincs. The mechanistic rationale for asymmetric diethylzinc additions to carbonyl compounds is examined in Scheme 4. The chiral diamine coordinates to the first of two equivalents of diethylzinc forming zinc complex 14. It has been previously established that one equivalent of compound 14 cannot react with benzaldehyde. In other words the Zn-Et group of 14 cannot add to the benzaldehyde and a second equivalent of diethylzinc is needed. The tertiary amine coordinates to a second equivalent of diethylzinc to yield 15. Benzaldehyde then coordinates through the oxygen atom between the zinc atom coordinated to both nitrogens giving the reactive intermediate 16. The second diethylzinc aligns with the benzaldehyde forming a 5/4/4 transition state, 17, placing the alkyl group in position to add directly to the carbon of the carbonyl. It has been shown by molecular orbital and density functional calculations that this ring system is a favorable transition state for the reaction. An alkyl group is selectively added to one face directed by the stereochemistry of the catalyst affording intermediate 18. This intermediate can react with another equivalent of diethylzinc to dissociate either (S)- or (R)-(1-phenyl)propoxy-ZnEt and regenerate 15 (Scheme 4).
In order for a new stereogenic center to form, the compound that the alkyl group is being added to must exhibit prochirality. In certain molecules a non-stereogenic center can be transformed into a stereogenic center by replacement of one or the other “identical” groups by a different one. These ligands are called “heterotopic”. An example is butyric acid.

Replacement of $H_A$ with a new ligand generates a new chiral center, while replacement of $H_B$ with the same ligand produces the enantiotopic molecule (Figure 6).
HA and HB are “heterotopic ligands” while C* is a “prochiral center”.

It is important that the molecule contains heterotopic ligands and not homotopic ligands. If the molecule has homotopic ligands, interchange of either one produces the same molecule through a C₂ symmetry axis (Figure 7).

Substitution of HA on 1,3-dioxolane produces the same molecule as substitution with the same ligand on HD with an 180° rotation around the C₂ axis. Substitution of either H’s also produces the same compound with an 180° rotation. However, HA and HB are heterotopic. Substitution of either atom produces a non-superimposable mirror image.

There are also examples of prochiral axes and planes. Benzaldehyde is an example of a compound with a prochiral plane. Addition to either plane of the molecule produces non-superimposable mirror images (Figure 8).
The *si* face corresponds to the plane whereby addition produces the *S*-chiral center and the *re* face corresponds to the plane where alkyl addition produces the *R*-chiral center. Upon addition of an alkyl group a new stereocenter is produced creating a chiral compound based upon the *si* or *re* face. This allows benzaldehyde to be used as an excellent test molecule for chiral catalyst reactions.

In 1991, Falorni and co-workers found that \((S)-2-(2'\text{-pyrrolidinyl})\text{pyridine, 13,}\) catalyzed diethylzinc addition to benzaldehyde with products having up to 100% ee.\(^\text{15}\) The yield for the reaction ranged from 50-100% based upon the aldehyde utilized. Seven years later, Asami and co-workers found that diamine ligand \(19\) exhibited high enantioselectivity (91% ee) and yield (89%) for the same reaction (Figure 9).\(^\text{16}\)

![Figure 8. Different prochiral faces of benzaldehyde.](image)

![Figure 9. Falorni’s diamine 13 and Asami’s chiral ligand 19.](image)
Even though these ligands produce good to excellent ee’s for the reaction of benzaldehyde with diethylzinc, they are not applicable in all asymmetric reactions. The use of chiral diamine ligands is of interest to the Comins group due to the possibility of utilizing enantiopure dihydropyridone chemistry as a source of chirality. The use of dihydropyridones, such as 20, as a potential chiral catalyst for asymmetric diethylzinc additions to carbonyl compounds was investigated.

III. Synthetic route to 20

It was envisioned that compound 20 could be prepared from the chiral dihydropyridone 21, which in the forward sense, comes from a metallo enolate addition to an \( N \)-acylpyridinium salt (Scheme 5).
The enolate alkylation to form compound 21 had previously been accomplished in the Comins group by utilizing a zinc enolate (Scheme 6).\textsuperscript{17}

However, employing this reaction proved to be problematic with lower yields (30%) than expected based on the literature precedent. We therefore utilized a magnesium enolate of acetophenone as the nucleophile. Reaction of 4-methoxy-[3-(triisopropylsilyl)]pyridine (6) with the chloroformate of (+/-) TCC and the magnesium enolate provided racemic 21 in a
60% yield. Application of this reaction to the asymmetric synthesis of 21 gave comparable diasteriomerich excess to the literature (85%). The next step was conversion of the keto-functionality on the side chain to a tertiary pyrrolidine. Various conditions for either a reductive amination or enamine formation followed by reduction were examined (Table 1).

**Table 1. Various Conditions for the Attempted Amine Formation Through One or Two Steps**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 equiv pyrrolidine, 4Å sieves, Et₂O, rt, 9 d</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>3.7 equiv pyrrolidine, 5N HCl in MeOH, CH₂Cl₂, 4Å sieves, 1 eq NaBH₃CN, 2.7 eq Aliquat 336, reflux, 3 d</td>
<td>SM/by-product</td>
</tr>
<tr>
<td>3</td>
<td>10 equiv pyrrolidine, 5N HCl in MeOH, MeOH, 4Å sieves, 0.7 equiv NaBH₃CN, Aliquat 336, rt, 8 d</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>7 equiv pyrrolidine, 1.2 equiv TiCl₄, 1.2 equiv Ti(O-iPr)₄, 1.2 equiv BH₃·SMe₂, rt, 15 h</td>
<td>decomp</td>
</tr>
</tbody>
</table>
Revision of the synthetic design was necessitated by failure to convert 21 to either the enamine 22 or amine 23. In previous work from the Comins group, the ketone on the side chain had been converted to an alcohol. We envisioned that mesylation of the newly formed alcohol could be an effective intermediate. The resulting mesylate 25 could then be attacked in an $S_N2$ fashion by pyrrolidine to give desired product 27 (Scheme 7).

Scheme 7. Progress Towards Ligand 27

A selective reduction of the ketone afforded secondary alcohol 24 (63%). Under these conditions the TCC chiral auxiliary was also removed. However, attempts at mesylation were unproductive. Elimination, rather than nucleophilic attack occurred. Compound 26 was formed as vinylic peaks were observed in the crude $^1$H NMR. Compound 26 was not isolated. With the lack of desired product formation and the difficulty in isolation, we decided to end this approach.
At this point, we decided to revisit the reductive amination. Carson and coworkers reported a methodology to form enamines in high yield employing pyrrolidine and TiCl$_4$ (1.0 M in toluene).$^{21}$ Mechanistically, TiCl$_4$ acts both as a Lewis acid and as a water scavenger driving the reaction toward enamine formation.$^{22}$ This procedure gave the desired product 22 (Scheme 8) in 100% crude yield. The enamine obtained is moisture sensitive; therefore the product was carried on crude after filtration of the TiO$_2$ byproduct. Hydrogenation with 5% Pt/C at atmospheric pressure for 4 hours yielded racemic 28 (67% yield) and compound 21 (33% yield). The later product resulted from conversion of the enamine back to the ketone. The TCC chiral auxiliary was removed (65% yield) to give racemic product 27 in 25% yield over 4 steps (Scheme 8).

Scheme 8. Racemic Synthesis of Chiral Ligand 27
This synthetic plan was then implemented for the asymmetric synthesis of the chiral catalyst 32 (Scheme 9). The synthetic scheme was identical to the racemic synthesis except for the utilization of the chiral auxiliary (+)-TCC. We utilized (+)-TCC instead of (-)-TCC as originally proposed due to the greater availability of this chiral auxiliary. It has been shown that typically either enantiomer of a catalyst will work in the reaction producing either enantiomer of the product.\textsuperscript{14} Chiral diamine 32 was obtained in an overall 35% yield in 4 steps. The chiral ligand was obtained as a solid with a diasteriomeric excess greater than 99%. The relative stereochemistry of 32 has yet to be determined.

**Scheme 9. Asymmetric Synthesis of Chiral Ligand 32**
IV. Conclusion

The chiral amine 32 was examined for the reaction of diethylzinc with benzaldehyde under various conditions (Table 2).

Table 2. Conditions for Reaction of Chiral Catalyst 32 with Benzaldehyde and Et₂Zn

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>workup</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>DCM, 1.5 equiv Et₂Zn, 32 cat, 0 °C, 3 d</td>
<td>Base*</td>
<td>NR, cat recovered</td>
</tr>
<tr>
<td>2.</td>
<td>DCM, 1.5 equiv Et₂Zn, 32 cat, 0 °C, 3 d</td>
<td>Acid**</td>
<td>NR, cat decomp</td>
</tr>
<tr>
<td>3.</td>
<td>DCM, 2.0 equiv Et₂Zn, 32 cat, 0 -&gt; RT, 2 d</td>
<td>Acid**</td>
<td>10% 11, 2% ee, cat decomp</td>
</tr>
</tbody>
</table>

* saturated sodium bicarbonate
** 10% HCl

Unfortunately, the reaction only yielded an ee of 2%. While the use of chiral catalysis is an ideal way to obtain a chiral alcohol, we were unable to achieve an acceptable ee for synthesis of 11. It is possible that the free electrons of the nitrogen in the dihydropyridone were less available to chelate effectively to the diethylzinc as needed. It has been shown that without this chelating effect the catalysts are less reactive.14 Also, the slow reaction times support poor coordination because ZnEt₂ is not activated. At this point the project was terminated.
CHAPTER 2: PROGRESS TOWARDS THE SYNTHESIS OF THE MARINE ALKALOID (-)-LEPADIFORMINE

I. Introduction

Ascidians (tunicates) are a rich source of nitrogen containing compounds with wide ranges of biological activities.\(^{23}\) In the early 1990’s, a series of structurally related alkaloids from the marine ascidian *Clavelina cylindrica* were isolated and described by Blackman and co-workers.\(^{24}\) These compounds all contained the core structure of a pyrroloquinoline framework and showed toxicity in a brine shrimp assay. The tricyclic ring system was unprecedented among natural products.\(^{25}\) The main difference between the cylindricines (33) is the functionality at C14 shown below.

\[
\text{R} = \text{Cl cylindricine A} \\
\text{R} = \text{OH cylindricine C} \\
\text{R} = \text{OMe cylindricine D} \\
\text{R} = \text{OAc cylindricine E} \\
\text{R} = \text{SCN cylindricine F}
\]

In 1994, Biard and co-workers discovered a closely related marine alkaloid lepadiformine (34) from the ascidian *Clavelina lepadiformis*. Lepadiformine was found to be moderately cytotoxic toward various tumor cell lines *in vitro*.\(^{23}\) It also has antiarrythmic effects on the cardiovascular system, *in vitro* and *in vivo*. At the time it was believed the alkaloid included
a unique zwitterionic form. Through extensive NMR studies, Biard assigned the structure shown below.23

![Structure 34](image)

However, when the Weinreb group attempted to synthesize lepadiformine in 1998 based on the structure presented, the $^1$H and $^{13}$C NMR spectra of the synthetic compound did not match those of the natural material.26 Eventually in 2000, the Kibayashi group synthesized the trans-fused adduct of 34 which matched with the original NMR spectra provided by Biard.25 At this point the structure was revised and the relative stereochemistry 35 was unambiguously established to be 3$R$, 5$S$, 7$a$R, 11$a$R.

![Structure 35](image)

II. Literature Review.

2.1. Synthetic routes to lepadiformine.

The unique structure of 35 and its reactivity have influenced the pursuit of lepadiformine syntheses by many groups.25-31 To date there are a total of six syntheses of lepadiformine: two enantioselective and four racemic routes. All of the routes utilized different
methodologies to arrive at the tricyclic core system. Discussed below are some of the previous routes.

2.2. Kibayashi’s synthesis of (+)-lepadiformine

The first total synthesis of (+)-lepadiformine was accomplished in 21 steps with a low overall yield by Kibayashi and coworkers in 2000, six years after its discovery. This synthesis was the first to establish the absolute stereochemistry of the natural product. The key step in Kibayashi’s synthesis was a stereocontrolled intramolecular $N$-acylnitroso-Diels-Alder reaction (Scheme 10).

![Scheme 10. Key Step in Kibayashi’s Synthesis](image)

Compounds 37 and 38 were obtained in a 4.8:1 ratio. Since only 37 can lead to the natural product, this left room for improvement on this synthetic route.
2.3. Weinreb’s synthesis of (+)-lepadiformine

In 2001, Weinreb offered a novel approach to the synthesis of (+)-lepadiformine utilizing a stereocontrolled intramolecular spirocyclization of an allylsilane/N-acyliminium ion (Scheme 11).27

Scheme 11. Weinreb’s Key Intermediate in the Synthesis of Lepadiformine

The key intermediate 43 was obtained in 57% overall yield based on recovered starting material. They hypothesized that 43 forms via the N-acyliminium ion conformation 42. The other conformer, 44, would lead to an isomeric spirocycle 45. This is destabilized relative to 42 due to steric interaction between the N-o-nitrobenzoyl group and the cyclohexane ring.
Overall, the synthetic plan was much shorter (15 steps) than Kibayashi’s. The final product was obtained in an overall yield of 11% from 2-methyl-1-pyrroline.27

2.4. Kibayashi’s synthesis of (-)-lepadiformine

To date there are only two enantiopure syntheses of (-)-lepadiformine, with the shortest and highest yielding synthesis obtained by Kibayashi in 2002.30 They utilized an N-acyliminium-ion-initiated intramolecular spirocyclization as the key step for the first synthesis of enantiopure (-)-lepadiformine (Scheme 12).

Scheme 12. Key Step in Kibayashi’s Enantiopure Synthesis of (-)-Lepadiformine

The 6-exo-trig ring closure of compound 46 gave the key intermediate 50 in 88% yield. Kibayashi and coworkers obtained (-)-lepadiformine in nine steps and 31% overall yield; however, the starting materials are not readily available and need to be synthesized.
2.5. Hsung’s synthesis of (-)-lepadiformine

In 2004, the Hsung group synthesized (-)-lepadiformine (11.1% overall yield) and (+)-cylindricines C-E (7.1% overall yield) via a common intermediate derived from an aza-Prins cyclization and Wharton’s rearrangement. Starting from the chiral butyrolactam 51, addition of an alkyl lithium led to the ring-opened Boc-protected amino ketone 52 in 61% yield. The subsequent formic acid-promoted aza-Prins cyclization led to the aza-spirocycle 53. Through various functional group manipulations, the key intermediate 54 for both the cylindricines and (-)-lepadiformine was obtained in 6 steps with a 17.4% overall yield (Scheme 13).
Scheme 13. Hsung’s Synthesis of Cylindricines and (-)-Lepadiformine

Hsung and co-workers were able to obtain (+)-cylindricines C-E in nine steps from 51 for C, and (-)-lepadiformine, in 12 steps from 51, through a common tricyclic intermediate 54.\textsuperscript{31} While this synthesis is not as short nor as high yielding as Kibayashi’s, it is still very elegant. Hsung was able to expand the scope of how these structurally related alkaloids
could be synthesized. This was the first reported concurrent enantiopure synthesis of both (+)-cylindricines and (-)-lepadiformine.

Kibayashi’s and Hsung’s syntheses both involved the use of a non-racemic chiral compound as starting material to establish the chirality throughout the molecule. The use of the chiral auxiliary TCC would allow the synthesis of the natural product from achiral starting material. With the success of dihydropyridone chemistry for various enantiopure syntheses, we feel that lepadiformine is a prime candidate for the expansion of this field. The unique ring system poses a challenge worth confronting. This aspect, along with the biological activity of lepadiformine, influenced our decision to undertake the synthesis of (-)-lepadiformine.

**III. Dihydropyridone-Based Model Studies Toward (-)-Lepadiformine**

**3.1. Retrosynthetic plan**

When one designs a synthetic plan for a molecule, there are several important aspects to consider. The most important criterion is the ability to control the formation of each stereocenter within the molecule. The use of readily available starting materials is also important. Finally, a novel, concise, and high yielding approach is desirable. These aspects, and others, were examined in preparation of our retrosynthetic plan for lepadiformine.

The trans-fused perhydroquinoline ring moiety stands out as a major part of the tricyclic ring system. We envisioned that this ring system could be formed from a [2+2] photocycloaddition reaction followed by a ring-opening/ring-closing sequence. This synthetic route has not previously been utilized for the formation of the trans-fused
perhydroquinoline ring system. The photocycloaddition was chosen due to its potential facial selectivity and steric control. The facial selectivity would come from the A$^{(1,3)}$ strain in the dihydropyridone 58, while steric control would arise from the bulky group in the six position (Scheme 14).

**Scheme 14. Retrosynthetic Plan for (-)-Lepadiformine**

Lepadiformine (35) would arise from a deprotection and cyclization of compound 55. The epoxide of compound 55 would form via a stereoselective epoxidation on the olefin that would result from the reduction of the alcohol after deprotection on compound 56. Compound 56 would come from the ring opening/ring closing of the key intermediate, compound 57. The key intermediate could be obtained in 3 steps, culminating with the photocycloaddition of 58 and 59. Compound 58 can be synthesized from 4-methoxypyridine
via a Grignard alkylation followed by a copper-mediated Grignard addition. With this synthetic plan in mind, we began model studies toward the synthesis of (-)-lepadiformine.

3.2. Photocycloaddition model study

The overall goal of the model study was to obtain a similar product to the key intermediate in a racemic fashion. The reaction of $n$-butyl Grignard with the $N$-acylpyridinium salt of 4-methoxypyridine and phenyl chloroformate gave upon acidic workup dihydropyridone 62 in 52% yield. A copper-mediated Grignard reaction added a propyl group in the C-6 position and trapping with TMSCl gave the silyl enol ether 63. This silyl enol ether was oxidized to the dihydropyridone 64 with Pd(II) under Wacker conditions (Scheme 15).

Scheme 15. First Proposed Model Study
Separation of 64 and 62 via chromatography proved difficult due to similar Rf values. However, compound 64 was obtained, albeit in a low yield (30%). With molecule 64 and the terminal alkene 59 in hand, the photochemical reaction was investigated. Both solvent and light source were varied in an attempt to give the photoadduct 65. Each reaction was attempted with and without a Vycor filter. Unfortunately, the intermolecular [2+2] photocycloaddition did not occur. With the difficulty in the purification of 64 and the failure of the photocycloaddition, we decided to alter the side chain at the C-2 position. We felt changing the polarity of the side chain might alleviate the separation difficulties and positively influence the outcome of the photochemistry (Scheme 16).

Scheme 16. Second Attempt at Obtaining Key Intermediate
The new side chain proved to be beneficial allowing for separation of starting material and 67. However, attempts made at the intermolecular [2+2] photocycloaddition were again unsuccessful. It was rationalized that the intermolecular reactions could have failed due to limitations when utilizing unsymmetrical molecules with a distant electron donating group such as in compound 59. Furthermore, it has been previously determined in the literature that intermolecular photocycloaddition is a more problematic route than an analogous intramolecular one.\textsuperscript{32} Based on this literature precedent, and that tethered [2+2] photocycloadditions have been previously employed successfully in the Comins group, we decided it would be a more advantageous route.\textsuperscript{33,34} Such precedent utilized the C-6 position and the nitrogen as the point for attachment of the side chain. A literature precedent was found for the attachment of a siloxane as a temporary tether for [2+2] photocycloaddition.\textsuperscript{32} It was shown that an intramolecular [2+2] photocycloaddition is generally more regio- and stereoselective. The regioselectivity is due to the geometric constraint while the stereoselectivity is delegated by the chirality of the alcohol to which the siloxane is tethered. Therefore, if the alcohol is \textit{trans} to the C-2 side chain then the tethered chain would add \textit{trans} at the C-6 position. This would afford the key intermediate with the correct stereochemistry. A siloxane was preferred as the temporary tether for the intramolecular [2+2] photocycloaddition (Scheme 17).\textsuperscript{32}
A Luche reduction on 67 gave compound 69 in an 80% yield. The stereochemistry was determined to be trans via $^1$H NMR analysis for the hydroxyl and the C-2 side chain. The silyl chloride 70 was tethered to 69 through an attack by the alkoxide formed from the alcohol and LiHMDS. The compound was isolated via column chromatography (64% yield). However, when the photosubstrate 71 was irradiated under various conditions, no desired product was obtained (Table 3). At this point the synthetic route had to be reexamined.
IV. Quinoline-Based Model Studies Towards the Synthesis of (-)-Lepadiformine

4.1. Introduction and retrosynthetic scheme of a Michael addition approach

The core prehydroquinoline system became our main focus. It is on this ring system that three of the four stereocenters are established (Figure 10). Starting with a readily available quinoline framework, the stereocenters may be set in a similar fashion to our previously reported dihydropyridone chemistry.
Figure 10. (-)-Lepadiformine and the core perhydroquinoline

It has been shown that the chirality at the 2-position of a dihydropyridone can be set when using a chiral auxiliary such as (+) or (-)-TCC (Scheme 2, page 3). Since the core of (-)-lepadiformine is a perhydroquinoline system with a chiral center at the 2-position, this led to the question whether an N-acylpyridinium salt reaction on 4-methoxy-5,6,7,8-tetrahydroquinoline could set the stereochemistry in a similar fashion to 4-methoxypyridine (Scheme 18).

Scheme 18. Proposed Synthesis of Perhydroquinolone

If this reaction does occur, then the fused perhydroquinoline system is already established along with the hexyl group side chain in the 2-position. Following this idea, lepadiformine 35 would come from a ketone reduction of compound 76. Compound 76
would arise from the removal of the nitrogen protecting group of 77, which will lead to a ring closing with the epoxide side chain, followed by a protection of the resulting alcohol. Compound 77 could derive from a 1,4-addition on compound 78 followed by an epoxide formation. The novel N-acylpyridinium salt reaction of 74 would lead to compound 78. Compound 74 could arise from a ring-selective catalytic hydrogenation and subsequent functional group conversion of 4-quinolone 79 (Scheme 19). With the proposed route developed, a model study was performed to examine these two key reactions which might be used to obtain (-)-lepadiformine.

**Scheme 19. Second Generation Retrosynthetic Scheme for (-)-Lepadiformine**
4.2. Michael addition approach

4.2.a. Model study for the Michael addition approach

Substituted 4-hydroxyquinolines can be reduced to substituted 4-hydroxy-5,6,7,8-tetrahydroquinolines in moderate to high yields (Scheme 20); however, to date, no synthesis of 74 from ring specific hydrogenation of 4-methoxyquinoline has been reported.

Scheme 20. Synthesis of Substituted 4-Hydroxy-5,6,7,8-tetrahydroquinolines

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
& \quad \text{R}
\end{align*}
\]

\[
\text{80} \quad \text{OH} \quad \text{Ni kieselguhr, H}_2, \quad \text{MeOH, 120 °C, 1570 p.s.i.} \quad \text{81}
\]

60 - 90% yield

Although these reactions utilized substituted hydroxyquinolines, we believed that starting from 4-hydroxyquinoline would yield the desired quinoline based on mechanistic considerations.

Hydrogenation of compound 79 with a catalytic amount of nickel on kieselguhr yielded the 4-hydroxy-5,6,7,8-tetrahydroquinoline 82 in 60% yield. Conversion of the hydroxyl substituent to a methoxy group was accomplished via formation of 4-chloro-tetrahydroquinoline 83 in 90-97% yield. Heating 83 at reflux in freshly made sodium methoxide/ methanol produced 74 in 95-99% yield (Scheme 21).
While we were able to obtain compound 74 by this route, it was not ideal due to the high cost of the starting material 79 and the moderate yield of the first step. We attempted an alternate route starting from the inexpensive 4,7-dichloroquinoline (84). Conversion to 7-chloro-4-methoxyquinoline (85) was accomplished by refluxing a methanol solution of 84 with freshly made sodium methoxide (94% yield). Hydrogenation with a catalytic amount of Pd/C in ethanol produced 4-methoxyquinoline (86) in 84-90% yield (Scheme 22). Different conditions were attempted to form compound 74, such as hydrogenation with a catalytic amount of nickel on kieselguhr in methanol, and either Pd/C or Pt/C in ethanol with lithium carbonate. The best result was attained with Pd/C affording 74 in 60% yield (Table 4).
Scheme 22. Alternate Synthetic Scheme for Compound 74

Table 4. Different Conditions for the Hydrogenation of Compound 86.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield of 74</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ni (kieselguhr), MeOH, balloon pressure, 3 d</td>
<td>NR</td>
</tr>
<tr>
<td>2.</td>
<td>Ni (kieselguhr), MeOH, 120 °C, 1550 p.s.i., 18 h</td>
<td>43%</td>
</tr>
<tr>
<td>3.</td>
<td>5% Pt/C, EtOH, balloon pressure, 3 d</td>
<td>NR</td>
</tr>
<tr>
<td>4.</td>
<td>5% Pd/C, 1.0 equiv Li₂CO₃ EtOH, balloon pressure, 1 d</td>
<td>60%</td>
</tr>
</tbody>
</table>

It was later revealed that compound 74 could be obtained directly from 85 in 60% yield by stirring the hydrogenation reaction for a longer time (3-5 days) (Scheme 23).
With compound 74 in hand, a typical N-acylpyridinium salt reaction was run to afford compound 87 in 87% yield (Scheme 24).

**Scheme 23. Synthesis of 4-Hydroxy-5,6,7,8-tetrahydroquinoline from Compound 85**

![Scheme 23](image)

**Scheme 24. N-Acylpyridinium Salt Reaction on Compound 74**

![Scheme 24](image)

While this was an exciting result, compound 87 is only one of the key intermediates needed. The next step was to attempt a Michael addition to form the quaternary center. Unfortunately, many different conditions failed to produce the desired product (Table 5).
Table 5. Conditions for Michael Addition to Compound 87

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2 equiv (n-Pr)$_2$CuMgCl, 2 equiv BF$_3$·Et$_2$O, diisopropyl sulfide, THF, -78 °C, 24 h</td>
<td>sm and 1,2 addition</td>
</tr>
<tr>
<td>2.</td>
<td>4 equiv (n-Pr)$_2$CuMgCl, 2 equiv BF$_3$·Et$_2$O, diisopropyl sulfide, THF, -78 °C -&gt; -20 °C, 24 h</td>
<td>decomp</td>
</tr>
<tr>
<td>3.</td>
<td>2 equiv (n-Pr)$_2$CuMgCl, 2 equiv HMPA, diisopropyl sulfide, THF, -78 °C, 24 h</td>
<td>sm</td>
</tr>
<tr>
<td>4.</td>
<td>8 equiv CuBr·SMe$_2$, 8.8 equiv BF$_3$·Et$_2$O, THF, 3.5 equiv n-PrMgCl, -78 °C</td>
<td>sm</td>
</tr>
<tr>
<td>5.</td>
<td>2 equiv CuI, 2 equiv n-PrMgCl, 1 equiv BF$_3$·Et$_2$O, THF, -78 °C, 24 h</td>
<td>sm</td>
</tr>
</tbody>
</table>

We believed that the cuprates were not active enough to effect the quaternary center formation. The success of cuprate additions are often dependent on specific reaction conditions, including choice of solvents and presence of additives. It has been shown that the addition of chlorotrimethylsilane (TMSCl) can increase the rate of the reaction and even allow reactions to proceed when they would otherwise fail. To increase reactivity, we therefore attempted the TMS mediated organocuprate addition. The silyl enol ether formed from this reaction (89), would immediately be deprotected to yield the desired compound 88 (Table 6).
Table 6. Attempts at Compound 88 Formation

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2 equiv CuBr·SMe₂, 5 equiv HMPA, 5 equiv TMSCl, 4 equiv n-PrMgCl, THF, -78 °C, 48 h</td>
<td>sm</td>
</tr>
<tr>
<td>2.</td>
<td>2 equiv CuBr·SMe₂, 5 equiv HMPA, 5 equiv TMSCl, 4 equiv n-PrMgCl, THF, -78 -&gt; -20 °C, 18 h</td>
<td>sm/ ?</td>
</tr>
<tr>
<td>3.</td>
<td>6 equiv CuBr·SMe₂, 15 equiv HMPA, 15 equiv TMSCl, 12 equiv n-PrMgCl, THF, -78 °C, 24 h</td>
<td>decomp</td>
</tr>
</tbody>
</table>

Unfortunately, we were never able to obtain the desired compound. However, we did realize that we were able to add a Grignard reagent at the carbonyl carbon (Table 5, entry 1) so we decided to utilize that outcome to our advantage.

4.2.b. Anionic oxy-Cope

At this point we decided to examine a new reaction to form the quaternary center. Addition of an allyl Grignard in a 1,2 fashion to compound 87, would set up an anionic oxy-Cope rearrangement. This would reestablish the carbonyl group and place the allyl side
chain α to the nitrogen similar to the desired compound 88. The first step was accomplished utilizing allylmagnesium chloride. This reaction yielded two diastereomers in a ratio of 7:1 by $^1$H NMR analysis. Both diastereomers were carried forward. When the anionic oxy-Cope was attempted, with potassium hydride with or without 18-crown-6 and Bu$_4$NI, and with or without heat, only starting material was recovered (Scheme 25).

Scheme 25. Attempted Anionic Oxy-Cope Rearrangement of Compound 90

Unfortunately, since neither the Michael addition nor the anionic oxy-Cope rearrangement occurred, we needed to reexamine the proposed route to (-)-lepadiformine. Revision of the synthetic scheme led to an approach utilizing an in situ formation of an iminium ion intermediate.

4.3. Iminium ion mediated approach

4.3.a. Introduction

Ketone 87 was converted to the allyl alcohol 92 by the Luche reduction in 80% yield. While there is a new stereocenter formed in compound 92, it is negligible since the next step removes it. Allyltributyltin was added to compound 92 in the presence of BF$_3$·OEt$_2$ to form
93 in 83% yield (Scheme 26). The stereochemistry of the side chain was assigned cis and confirmed by a series of 1D Noesy experiments (Figure 10). The $^1$H NMR was assigned based on a series of COSY, HMQC and TOECSY experiments. Irradiation of H$_2$ in a NOESY 1D experiment showed no correlation to H$_{11}$, while irradiation of H$_{11}$ showed a correlation to H$_{15}$, thus confirming the assigned stereochemistry.

**Scheme 26. Formation of the Quaternary Center**

With compound 93 in hand, an attempt to reduce the internal double bond in the presence of the terminal double bond using triethylsilane in TFA led to some reduction of the terminal double bond and recovered starting material. The Jacobsen asymmetric epoxidation
or Sharpless epoxidation were considered but rejected since both of these reactions will preferentially attack the more substituted double bond (Scheme 27).

We felt that if the internal double bond could be “blocked” with a bulky group, then the dihydroxylation would occur at the terminal double bond selectively. To this end, ketone 87 was converted to geminal silylalcohol 96 by dimethylphenylsilyllithium addition in 60% yield. This reaction also gave back starting material in 20-30% yield. There was only one diastereomer observed and its assigned stereochemistry was determined by derivatization to the MOM protected ether. The typical allylation reaction produced compound 97 in 95% yield with a 95% de as estimated by $^1$H NMR (Scheme 28). Subsequent dihydroxylation under racemic conditions occurred regioselectively at the terminal double bond (78% yield) (Scheme 29).37
Scheme 28. Iminium Ion Mediated Formation of Quaternary Center

Scheme 29. Dihydroxylation of Compound 97

Since compound 98 is one carbon short of that needed to form the five membered ring, a nucleophile that mimics the allyltributyltin group in reactivity and is one carbon longer was necessary.

4.3.b. Retrosynthetic plan

A new synthetic route was developed utilizing the iminium ion mediated reaction for the formation of the quaternary center. It was envisioned that (-)-lepadiformine could arise from a protodesilylation and reduction of the double bond on compound 99. Removal of the nitrogen protecting group on compound 100 will preferentially cyclize to form the five membered ring by attacking the epoxide. Compound 100 can arise from a protodesilylation
and subsequent dihydroxylation/epoxidation of compound 101. Addition of the side chain 103 to compound 102 is expected to yield the bis-silane 101. Compound 102 would arise from the carbamate exchange and silyl alcohol formation on compound 78. We have already shown that the chemistry to form a similar compound to 102 will work. To set the desired stereochemistry, the chloroformate of (-)-trans-(α-cumyl)cyclohexanol will be used as the chiral auxiliary (Scheme 30).

Scheme 30. Revised Synthetic Scheme

The first challenge of this synthetic approach was the formation of side chain 103. The synthesis started from propargyl alcohol (104) which when treated with n-tributyltin hydride under radical conditions generated compound 105 in 63% yield. The mixture of cis- and trans-isomers was not a problem since the final step in the scheme eliminates the
stereoisomers. Treatment of compound 105 with phenyl isocyanate and a catalytic amount of 4-(dimethylamino)pyridine formed the carbamate 106 in 63% yield. However, when 106 was treated with the copper-mediated S_N2' reaction conditions, only the destannylated compound 107 was recovered (Scheme 31).

Scheme 31. First Attempt at Side Chain Formation

A new route was devised starting from ethyl propiolate, which when treated with trimethylsilylmethyl Grignard and CuBr·SMe_2 formed the α,β-unsaturated ester 109 in 78% yield. These conditions were a modification of a literature preparation that used copper bromide.\textsuperscript{38} We were able to obtain compound 109 as the E-isomer only. Treatment with n-tributyltin lithiate gave the 1,4 addition product 110 in 80 – 90% yield. This compound was taken on crude and reduced with LAH the give the alcohol 111 in 90-95% yield. At this point the compound could be purified by a reduced pressure distillation. Submitting pure alcohol to 2-nitrophenylselenoisocyanate gave compound 112 in 78% yield. A m-CPBA oxidation provided the desired product 103 in 74% yield (Scheme 32).
The side chain 103 was obtained in 5 steps with an overall yield of 31%. We then attempted the side chain addition to a dihydropyridone based model. Conversion of compound 113 to the silyl alcohol was accomplished following the previous protocol for the quinolone system. Only one diastereomer was observed in the $^1$H NMR. However, NOESY 1D experiments were inconclusive as to the exact structure. The tentative structure assigned is based upon the stereochemistry observed in the quinoline system (see pg 48). When side chain 103 was added to 114 the product was obtained in 57% yield. Subsequent examination of the conversion of the allylsilane to the terminal alkene was performed with formic acid and heat in a NMR tube. The terminal alkene was observed in the $^1$H NMR and the dimethyl vinyl silane was still present (Scheme 33).
Scheme 33. Addition of Side Chain 103 to Dihydropyridone Model

However, when compound 103 was added in a similar fashion to compound 96, elimination occurred instead of the desired addition (Scheme 34). It is believed that the bulky TMS group hinders the addition of the side chain.

Scheme 34. Attempts at Side Chain Addition

We attempted to increase the reactivity for the iminium ion formation by converting silyl alcohol, 96, to the methoxy methyl (MOM-) ether. It was found that the best way to form the
MOM ether was by treating compound 96 with Hünnig’s base, MOM chloride and a catalytic amount of potassium iodide. Compound 119 was formed in 62% yield (Scheme 35). Any other reaction to form the MOM ether, such as KHMDS, and MOM chloride in toluene produced a new elimination product 121. The structure was confirmed by COSY and HMBC studies. With the MOM ether 119, either the side chain could be added or possibly an organozinc reagent could be used for the addition. Unfortunately, both routes produced the elimination product 118.

Scheme 35. MOM Protection

\[
\begin{align*}
96 & \xrightarrow{\text{MOMCl, (i-Pr)₂NEt, KI, DMF, -30 °C -> rt, 1 d}} 119 \\
& \quad \xrightarrow{\text{KHMD, MOMCl, Tol.}} 118
\end{align*}
\]

The stereochemistry of the MOM ether 119 was confirmed by a series of NOESY 1D experiments. Irradiation of H₁₀ in a NOESY 1D experiment showed no correlation to H₂,
while irradiation of H₂ showed a correlation to H₁₂, thus confirming the assigned stereochemistry (Figure 12).

![Figure 12. NOESY 1D experiment on 119](image)

Tsuji and coworkers reported the conversion of an allylic carbonate to a terminal alkene utilizing palladium chemistry.³⁹ Unfortunately, there was no chemistry developed that lead directly from an alkene to a carbonate. Grubbs and co-workers had developed chemistry utilizing electron withdrawing groups with Grubbs’ second generation catalyst.⁴⁰ We decided to utilize similar chemistry with a bis-carbonate. We envisioned that if 97 was converted to an allylic carbonate using chemistry already developed, then we could transform that group to a one carbon homologated alkene following literature procedures.³⁹ Compound 97 was treated with bis-methylcarbonate 122 in the presence of Grubbs second generation catalyst to afford carbonate 123 in 39% yield. This compound was subsequently submitted to Tsuji’s conditions to yield the terminal alkene 124 in 54% yield (Scheme 36).
Further examination into whether or not these two reactions could be performed in a one pot reaction is currently being examined on other substrates. These results will not be discussed here. With formation of the terminal butenyl group, the model study was completed. Also, the phenyl carbamate removal uses harsh conditions when it is not attached to a dihydropyridone moiety, therefore it would be virtually impossible for the epoxide to survive if we continued with an $N$-phenylcarbamate intermediate. We decided to utilize this proposed route starting with the chiral auxiliary, TCC.

4.4. Progress toward the asymmetric synthesis of (-)-lepadiformine

To examine the $de$ of the $N$-acylpyridinium salt reaction on compound 74, we utilized the readily available chloroformate of (+)-TCC. Treatment of 4-methoxy-5,6,7,8-tetrahydroquinoline with the chloroformate, and subsequent addition of hexyl Grignard,
yielded compounds 80 in 76% yield with a 24% de (Scheme 37). While this is a low de, we felt that with optimization this ratio would increase. Since we had the material in hand, we decided to examine the synthetic scheme on the major, or “wrong”, enantiomer. Carbamate removal with fresh sodium methoxide, followed by Recrystallization, provided the product in 76% yield. The first synthetic route was to utilize a tert-butylcarbamate as the nitrogen protecting group. Treatment of the free N-H with n-BuLi followed by addition of Boc anhydride afforded the Boc protected hexahydroquinolone 126 in 73% yield (Scheme 38).

Scheme 37. Asymmetric Synthesis

```
OMe

74

1. (+)-TCCOCOCl
2. hexyl Grignard
3. H30+

N

CO2(+)TCC
C6H13

80a

76%
24% de

Scheme 38. Carbamate Removal and Reprotection

```

With compound 126 in hand, the next step was the conversion to the silyl alcohol followed by addition of allyltributyltin. While conversion to the silyl alcohol 127 occurred in
yields similar to previous work, all attempts at the allyl addition to the in situ formed iminium ion resulted in the elimination product 128 by crude $^1$H NMR (Scheme 39).

Scheme 39. Formation and Attempted Allylation of Compound 127

It is believed that the bulk of the Boc group inhibited the addition reaction. We felt this problem could be circumvented by changing the nitrogen protecting group to a benzyl carbamate. We also decided to examine a different chiral auxiliary, $(-)(1R,2S,4R)$-2-(1-methyl-1-phenylethyl)-4-(2-propyl)cyclohexanol ((-)CPC).41 When the chloroformate of (-)-CPC was utilized, compound 129 was obtained in 80% with a de of 50% (Scheme 40).

Scheme 40. Utilization of Chiral Auxiliary (-)-CPC

Subsequent carbamate removal and recrystallization yielded the free N-H compound 130 in 80% yield. Deprotonation with n-BuLi followed by addition of benzyl chloroformate
provided compound 131 in 85% yield from 130. Conversion to the silyl alcohol proceeded in 60% yield with about 30% recovery of starting material. Subsequent allyltributyltin addition occurred in 47% yield with some elimination occurring (Scheme 41).

Scheme 41. Formation and Allylation of Compound 132

Since we were only able to obtain compound 133 in 47% yield, we decided to examine both solvent and reagent effects on the reaction. We first attempted less polar solvents such as toluene and chloroform. However, both of these solvent systems resulted in mainly or complete elimination according to $^1$H NMR analysis. When the polar solvent nitromethane was used, it still resulted in only elimination by crude $^1$H NMR. Our last attempt to improve the yield of compound 133 was to utilize allyltriphenyltin in place of allyltributyltin. This reaction was slow, but unfortunately the only product apparent by $^1$H NMR analysis and TLC was the eliminated compound 134 (Table 7).
Table 7. Examination of Solvent and Reagent Effect on Allylation Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>R:R’</th>
<th>solvent</th>
<th>reagent</th>
<th>Result (133:134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CO₂Ph:Pr</td>
<td>CH₂Cl₂</td>
<td>allyltributyltin</td>
<td>95:5 ratio of 133a:134a</td>
</tr>
<tr>
<td>2.</td>
<td>Boc:Hex</td>
<td>CH₂Cl₂</td>
<td>allyltributyltin</td>
<td>0:100 ratio of 133b:134b</td>
</tr>
<tr>
<td>3.</td>
<td>Cbz:Hex</td>
<td>CH₂Cl₂</td>
<td>allyltributyltin</td>
<td>47:&lt;53 ratio of 133c:134c</td>
</tr>
<tr>
<td>4.</td>
<td>Cbz:Hex</td>
<td>CHCl₃*</td>
<td>allyltributyltin</td>
<td>5:95 (crude NMR) ratio of 133c:134c</td>
</tr>
<tr>
<td>5.</td>
<td>Cbz:Hex</td>
<td>toluene</td>
<td>allyltributyltin</td>
<td>0:100 (crude NMR) ratio of 133c:134c</td>
</tr>
<tr>
<td>6.</td>
<td>Cbz:Hex</td>
<td>nitromethane</td>
<td>allyltributyltin</td>
<td>0:100 (crude NMR) ratio of 133c:134c</td>
</tr>
<tr>
<td>7.</td>
<td>Cbz:Hex</td>
<td>CH₂Cl₂</td>
<td>allyltriphenyltin</td>
<td>0:100 (crude NMR) ratio of 133c:134c</td>
</tr>
</tbody>
</table>

* Temperature = -64 °C

Since none of the variations produced a higher yield for the desired reaction, we were forced to stay with the original conditions (CH₂Cl₂ and allyltributyltin). Next, a one-pot, one-carbon alkene homologation of 133 was utilized yielding 135 in 56% yield (Scheme 43).

Scheme 42. One Pot Alkene Homologation
With the terminal butene 135 in hand, the next step was the asymmetric dihydroxylation. Following a literature preparation at room temperature, an ionic liquid (IL), and ADmix_β were utilized, an asymmetric dihydroxylation (AD) was attempted on compound 135. Unfortunately, after 2 days no product was formed (Scheme 43).

Scheme 43. Attempted Dihydroxylation of Compound 135

Since the ionic liquid procedure was not yielding any product, the reaction was then submitted to the typical AD conditions of a 1:1 mixture of t-BuOH and water at 0 °C. After two days only about 15% conversion was observed via ESI mass spectrometry.

4.5. Proposed route for completion of the synthesis

In Sharpless’ early work with the AD reaction, he noted that “if a reaction was sluggish then it should be run at room temperature”. The main difference in the reaction at room temperature is that more of the ADmix_β would need to be added. To continue this synthetic route further examination into increasing the yield of the dihydroxylation and the diasteriomeric excess obtained from this reaction is needed (Scheme 44).
With the diol 136 in hand, there are only four steps remaining to (-)-lepadiformine. The first step would be the formation of the epoxide. Following Kelly’s procedure for the conversion of dihydroxyl groups into epoxides, the epoxidation of compound 136 may be performed by employing bis(neopentyloxy)triphenylphosphorane (BNTP) to yield compound 137. Carbamate cleavage and the subsequent five member ring formation would then be carried out with triethylsilane in the presence of catalytic amounts of Et₃N and PdCl₂. The vinyl silane would be removed with TFA to afford compound 139 (Scheme 45).
Molecular modeling indicates that the most accessible point for a hydrogenation to occur on compound 139 is from the back side of the ring system. This would “push” the cyclohexane ring into the axial position giving (-)-lepadiformine as one enantiomer in 13 steps from commercially available 4-methoxyquinoline (Figure 13).
Figure 13. Molecular model of compound 139

While this would be neither the shortest synthesis nor the highest yielding, it is a novel approach and will be the first to incorporate a chiral auxiliary to establish the stereochemistry.
CONCLUSION

In Chapter 1, a study was performed on the synthesis and subsequent testing of a chiral diamine as a ligand for the asymmetric organozinc addition to aldehydes. The synthesis of the racemic version of the molecule was highlighted by enamine formation and subsequent reduction to the amine. The enantiopure synthesis was then performed with an overall yield of 35% over four steps. Unfortunately, the catalyst only produced an enantiomeric excess of 2%.

In Chapter 2, various model studies were carried out toward the total synthesis of (-)-lepadiformine. The first attempt at a novel [2+2] photocyclization was unfortunately not successful. The next synthetic approach turned to a 4-methoxyquinoline-based system to achieve the substituted perhydroquinoline core system. All attempts at a 1,4 copper-mediated conjugate addition failed. Revision of the synthetic scheme led to a novel route to form the quaternary center utilizing an iminium ion mediated nucleophilic allylation. The racemic route allowed the discovery of a novel reaction which effects a one-pot alkene homologation. The methodology is being examined further in the Comins labs and will be reported in due time. The synthetic scheme was applied toward the enantiopure synthesis of (-)-lepadiformine. Starting with 4-methoxy-5,6,7,8-tetrahydroquinoline and the chloroformate of the chiral auxiliary (-)-CPC, a perhydroquinoline was obtained in 80% yield and 50% de. Functional group
manipulation led to the terminal butenyl group needed for the asymmetric dihydroxylation. Attempts at the dihydroxylation were examined.
EXPERIMENTALS

General Experimental. All reactions were performed in oven or flame dried glassware under a nitrogen or argon atmosphere and stirred magnetically. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Toluene was distilled from sodium. Diisopropylamine, triethylamine, benzene, hexanes and CH$_2$Cl$_2$ were distilled from calcium hydride and stored under argon over 4 Å molecular sieves. $n$-Butyllithium was titrated periodically against diphenylacetic acid according to the method of Kofron and Baclawski. The 4-methoxy-3-(triisopropylsilyl)pyridine was prepared from 4-methoxypyridine according to procedure reported by Comins and coworkers. The chiral auxiliaries, (+)-TCC, (-)-TCC and (-)-CPC, were prepared and resolved according to the method of Comins and Salvador. Other reagents and solvents from commercial sources were stored under argon and used directly. Melting points were obtained from a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial preparative layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2, or 4 mm layers of Kieselgel 60 PF254 containing gypsum. High-resolution mass spectral analysis (HRMS) was performed at either North Carolina State University or Georgia State University. NMR spectra were obtained using Varian Mercury 300 (300 MHz) or Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are in ppm units with TMS (0.0 ppm) used as the internal standard for $^1$H-NMR spectra and the CDCl$_3$ absorption of 77.23 ppm for $^{13}$C NMR. IR spectra were
recorded on a Perkin-Elmer 1430, MIDAC M2000, or JASCO FT/IR-410 spectrometer. HPLC was performed using Waters and Associates (Milifrod, MA) 600 E multi solvent delivery system with a 486 tunable detector equipped with an YMC-pack sil (150 x 4.6 mm I.D.) analytical column or an YMC-pack sil (150 x 100 mm I.D.) preparative column.

\[ \text{OMe} \]
\[ \text{TIPS} \]

\[ \text{6} \quad \rightarrow \quad \text{CO}_2(+)\text{TCC} \]
\[ \text{TIPS} \]
\[ \text{Ph} \]

\( (2R^\circ)-1-[1R^\circ,2S^\circ)-(\alpha\text{-Cumyl})\text{cyclohexyloxy} \text{carbonyl}] \text{-2-}(\text{2-oxo-2-phenylethyl})\text{-5-triisopropylsilanyl-2,3-dihydro-1H-pyridin-4-one (21)} \). To a solution of diisopropylamine (5.0 mL, 35.7 mmol) in 50 mL of THF at -50 °C was added n-butyllithium (14.2 mL, 35.5 mmol). After stirring for 30 min, acetophenone (4.15 mL, 35.6 mmol) was added dropwise via a syringe pump over 30 min. The reaction was stirred for 1 h. In a separate flask, a solution of magnesium bromide diethyl etherate (9.19 g, 35.6 mmol) in 60 mL of THF was cooled to -78 °C. The lithium enolate was added by cannula. The reaction was stirred for 12 h. In a separate flask, a solution of 4-methoxy-3-(triisopropylsilyl)pyridine (1.89 g, 7.12 mmol) in 50 mL of toluene was cooled to -78 °C. The chloroformate of \( \text{trans-(\alpha\text{-cumyl})cyclohexanol} \) (2.01 g, 7.12 mmol) was added. The reaction was stirred for 30 min, and the magnesium enolate was added by cannula. After 4 h, 20 mL of 10% HCl was added and the mixture was warmed to room temperature. The organic layer was separated, and the
aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The product was purified by column chromatography (silica gel, 10% EtOAc/hexanes) to afford 2.63 g (60%) of compound 21 as a white solid. Mp = 121-123 °C, lit mp = 122-123 °C.

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\text{(2R}^+)\text{-(2S}^+\text{-2-Hydroxy-2-phenylethyl)-5-triisopropylsilyl-2,3-dihydro-1H-pyridin-4-one (24).}^{17}
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To a solution of dihydropyridone 21 (0.05 g, 0.08 mmol) in 5 mL of THF at -78 °C was added K-Selectride® (0.03 mL, 0.11 mmol) dropwise over 5 min. The reaction was stirred for 2 h. In sequential order, 30% H₂O₂ (0.2 mL), 3N potassium hydroxide (0.6 mL), 1.0 mL of water, and 2.0 mL of methanol were added. The reaction was warmed to room temperature and stirred for 5 min. The excess H₂O₂ was quenched with 2 mL of a saturated aqueous solution of sodium thiosulfate. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated. The solid residue was dissolved in 50 mL of methanol, and sodium carbonate (0.502 g, 4.73 mmol) was added. The mixture was refluxed for 4 h. The reaction was cooled to room temperature and the methanol was removed in vacuo. The solid residue was stirred with
ether and filtered. The ether was removed by rotary evaporation. Crystallization from hexanes afforded compound 24 as white crystals (19 mg, 63% yield). Mp = 172-174 °C, lit mp 173.5-175 °C.

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\text{(2S')-4-Oxo-2-(2-phenyl-2-pyrrolidin-1-yl-vinyl)-5-triisopropylsilanyl-3,4-dihydro-2H-pyridine-1-carboxylic acid [(1R*, 2S')-(\(\alpha\)-cumyl)cyclohexyloxycarbonyl] ester (22). To a degassed solution of pyrrolidine (0.45 mL, 5.39 mmol) in hexanes (10 mL) at 0 °C was added titanium tetrachloride (0.05 mL, 0.46 mmol) in hexanes (10 mL). Dihydropyridone 21 (0.37 g, 0.6 mmol) in benzene was added to the resulting mixture. The reaction was heated to 70 °C, stirred for 1 h, and filtered through a fine frit funnel under argon atmosphere. The solvent was removed by rotary evaporation to afford 0.402 g (99%) of compound 22 as a yellow oil. The product was carried on immediately without further purification.} \\
\text{\(1^H\) NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.79 (s, 1H), 7.50 (s, 3H), 7.35-7.26 (m, 3H), 7.05 (m, 5H), 4.81-4.76 (m, 1H), 4.34 (d, 1H, \(J = 10\) Hz), 3.99 (br s, 1H), 2.81-2.59 (m, 5H), 2.18 (d, 1H, \(J = 14.8\) Hz), 1.91 (m, 1H), 1.78-1.61 (m, 9H), 1.36-0.97 (m, 36H); \(^{13}C\) NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 197.7, 151.1, 149.0, 148.4, 137.8, 129.4, 128.5, 128.1, 128.0, 125.5, 125.2, 124.8, 110.4, 93.7, 52.7, 50.5, 48.7, 45.5, 40.0, 34.5, 33.4, 31.8, 29.9, 27.3, 26.1, 25.6, 25.5, 25.0, 24.8, 22.8, 19.1, 19.1, 14.3, 11.6, 11.4, 11.1.}
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(2\textsuperscript{R\text{*}})-4-Oxo-2-(2-phenyl-2-pyrrolidin-1-yl-ethyl)-5-triisopropylsilanyl-3,4-dihydro-2\textit{H}-pyridine-1-carboxylic acid [(1\textsuperscript{R\text{*}},2\textsuperscript{S\text{*}})-(\alpha\textsuperscript{-}cumyl)cyclohexyloxycarbonyl] ester (28). In a 100 mL flask were added enamine 22 (0.158 g, 0.236 mmol), 5% platinum on carbon (20 mg) and 10 mL of EtOAc. The flask was charged with H\textsubscript{2}, evacuated, then back filled with H\textsubscript{2}. After 6 h, the reaction was filtered over Celite with warm EtOAc and concentrated \textit{in vacuo}. The product was purified by radial PLC (silica gel, gradient 10% to 30% EtOAc/hexanes) to afford 0.106 g (67%) of compound 28 as an oil. IR (neat) 2936, 2861, 1733, 1715, 1683, 1575, 1506, 1380, 1255 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ 7.70 (br s, 1H), 7.37-7.19 (m, 9H), 7.08 (br s, 1H), 4.92 (br s, 1H), 3.24 (br d, 2H, \textit{J} = 16.8 Hz), 2.38 (br s, 2H), 2.29 (br s, 2H), 2.05-1.87 (m, 4H), 1.78-1.62 (m, 6H), 1.33-1.18 (m, 12H), 0.99 (t, 17H, \textit{J} = 11.2 Hz), 0.89-0.83 (m, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ 197.3, 152.3, 152.1, 147.8, 146.7, 141.0, 128.6, 128.4, 128.2, 127.5, 125.3, 110.5, 66.3, 51.6, 51.2, 50.7, 50.3, 41.8, 40.3, 39.7, 37.3, 35.7, 34.8, 34.0, 31.8, 31.1, 29.9, 27.7, 27.0, 26.0, 25.5, 24.9, 23.4, 23.0, 22.8, 20.0, 22.8, 20.9, 19.1, 19.0, 14.3, 11.5, 11.3, 11.1, 11.0; HRMS ([M+H]\textsuperscript{+}) calcd for C\textsubscript{42}H\textsubscript{62}N\textsubscript{2}O\textsubscript{3}Si 671.4608, found 671.4613.
(2R*)-(2-Phenyl-2-pyrrolidin-1-yl-ethyl)-5-triisopropylsilanyl-2,3-dihydro-1H-pyridin-4-one (27). To a solution of amine 28 (97 mg, 0.15 mmol) in 10 mL of methanol was added K$_2$CO$_3$ (0.20 g, 1.5 mmol). The mixture was heated at reflux for 7 h and then concentrated. Et$_2$O was added and the reaction was filtered through Celite. The filtrate was concentrated and purified by radial PLC (silica gel, 1:20:79 Et$_3$N:EtOAc:hexanes) to yield 0.039 g (63%) of compound 27 as a white solid, mp 183-185 °C; IR (neat) 3208, 3026, 2960, 2943, 2867, 2801, 1698, 1556, 1526, 1457, 1311, 1285, 1192, 1156, 1013, 880.8 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.38-7.31 (m, 3H), 7.20 (d, 2H, $J = 7.2$ Hz), 7.14 (d, 1H, $J = 6$ Hz), 3.89 (m, 1H), 3.70 (m, 1H), 2.64-2.36 (m, 6H), 2.31-2.26 (dd, 1H, $J = 15.6$, 4.8 Hz), 1.81-1.69 (m, 6H), 1.32-1.25 (m, 4H), 1.06-1.02 (m, 18H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 196.5, 156.3, 129.0, 128.4, 128.0, 98.8, 65.5, 53.7, 48.8, 44.2, 36.6, 31.1, 22.9, 19.2, 19.1, 11.4; HRMS ([M+H]$^+$) calcd for C$_{26}$H$_{42}$N$_2$OSi 427.3145, found: 427.3159.
(2S)-[(1S,2R)-(α-Cumyl)cyclohexyloxy-carbonyl]-2-(2-oxo-2-phenylethyl)-5-
trisopropylsilyl-2,3-dihydro-1H-pyridin-4-one (29).\textsuperscript{17} To a solution of
diisopropylamine (1.58 mL, 11.3 mmol) in 15 mL of THF at -23 °C was added \textit{n-}
butyllithium (5.0 mL, 11.2 mmol). After 30 min, acetophenone (1.32 mL, 11.3 mmol) was
added dropwise \textit{via} a syringe pump over 30 min. The reaction was stirred for 30 min and
canulated to another flask containing magnesium bromide diethyl etherate (2.92 g, 11.3
mmol) in 30 mL of THF at -78 °C. The reaction was stirred for 12 h. In a separate flask
containing a solution of 4-methoxy-3-(trisopropylsilyl)pyridine (1.89 g, 7.12 mmol) in 20
mL of toluene at -78 °C was added the chloroformate of (+)-\textit{trans}-(α-cumyl)cyclohexanol
(2.01 g, 7.12 mmol) in 10 mL of toluene. The reaction was stirred for 30 min, and the
magnesium enolate prepared above was added \textit{via} cannula. The reaction was stirred for 4 h
and then 10 mL of 10% HCl was added. After the reaction was warmed to room
temperature, the organic layer was separated, and the aqueous phase was extracted with
EtOAc (3 x 50 mL). The combined organic layers were washed with water (50 mL) and
brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The product was
purified by column chromatography (silica gel, 10% EtOAc/hexanes) to afford 1.46 g (63%)
of the compound 29 as a white solid. \([α]^{30}_D + 40 \ (c \ 0.25, \ CHCl_3).\)
(2R)-Oxo-2-(2-phenyl-2-pyrrolidin-1-yl-vinyl)-5-triisopropysilanyl-3,4-dihydro-2H-pyridine-1-carboxylic acid (1S,2R)-((α-cumyl)cyclohexyloxycarbonyl)cyclohexyl ester (30). To a degassed solution of pyrrolidine 29 (0.59 mL, 7.1 mmol) in 20 mL of hexanes at 0 °C was added titanium tetrachloride (0.75 mL, 0.75 mmol) in hexanes (20 mL) dropwise. A solution of dihydropyridone 29 (0.50 g, 0.81 mmol) in benzene (20 mL) was added. The mixture was heated at reflux for 45 min and filtered through a fine frit funnel under an argon atmosphere. The solvent was removed via rotary evaporation to afford 0.572 g (105%) of crude product which was carried on immediately without further purification. ¹H NMR (CDCl₃, 400 MHz) Major peak in alkene region δ 4.34–4.31 (d, 1H, J = 9.6 Hz)

(2R)-4-Oxo-2-(2-phenyl-2-pyrrolidin-1-yl-ethyl)-5-triisopropysilanyl-3,4-dihydro-2H-pyridine-1-carboxylic acid (1S,2R)-(α-cumyl)cyclohexyloxycarbonyl)cyclohexyl (31). In
a flask was added enamine 30 (0.573 g, 0.86 mmol), 5% platinum on carbon (120 mg), and 20 mL of EtOAc. The flask was charged with H₂, evacuated, and then back filled with H₂. After 6 h, the reaction was filtered over Celite. The solid was rinsed with warm EtOAc, and the filtrate was concentrated by rotary evaporation. The product was purified by radial PLC (silica gel, gradient 10 to 30% EtOAc/ hexanes) to afford 0.322 g (56%) of compound 31 as an oil. [α]_{D}^{29} + 32 (c 0.02, CHCl₃).

\[
\begin{align*}
\text{31} & \quad \text{TIPS} \\
\text{N} & \quad \text{Ph} \\
\text{CO}_{2}(+) & \quad \text{TCC} \\
\text{Ph} & \quad \text{N} \\
\text{32} & \quad \text{TIPS} \\
\text{N} & \quad \text{Ph} \\
\text{H} & \quad \text{N} \\
\end{align*}
\]

(2S)-2-(2-Phenyl-2-pyrrolidin-1-yl-ethyl)-5-triisopropylsilanyl-2,3-dihydro-1H-pyridin-4-one (32). To a solution of amine 31 (46 mg, 0.07 mmol) in 15 mL of methanol was added K₂CO₃ (95 mg, 0.69 mmol). The mixture was heated to reflux for 18 h, cooled to room temperature, and the methanol was removed \textit{in vacuo}. The solid was dissolved in 20 mL of dichloromethane and filtered through Celite. The solvent was removed by rotary evaporation. The product was purified by radial PLC (silica gel, gradient 10% EtOAc/ hexanes to methanol) to afford 0.027 g (92%) of compound 32 as a light orange solid. [α]_{D}^{30} - 172 (c 0.5, CHCl₃).
rac- 2-Butyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (62). In a 50-mL three-neck flask were added 3 mL of THF and magnesium turnings (0.73 g, 30 mmol) (activated with dibromoethane).\textit{n}-Butyl bromide (1.9 mL, 17.9 mmol) was added dropwise. The reaction was stirred for 6 h. In a separate flask containing a solution of 4-methoxypyridine (1.4 mL, 13.8 mmol) in 5 mL of THF at -50 °C was added phenyl chloroformate (1.9 mL, 15.3 mmol). After 30 min, the Grignard reagent was added dropwise \textit{via} syringe pump over 1 h. The reaction was stirred 18 h, quenched with 5 mL of 10% HCl, and warmed to room temperature. The organic layer was separated and the aqueous phase was extracted with \text{Et}_2\text{O} (3 \times 30 \text{ mL}). The combined organic layers were washed with deionized water (30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 1.98 g (53%) of compound 62 as a yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.89 (d, 1H, $J = 8$ Hz), 7.42 (t, 2H, 7.6 Hz), 7.28 (t, 1H, $J = 8$ Hz), 7.17 (d, 2H, $J = 8$ Hz), 5.43 (br d, 1H, $J = 7.6$ Hz), 4.71 (br s, 1H), 2.93–2.87 (dd, 1H, $J = 16.8$, 6.4), 2.55 (d, 1H, $J = 16.4$ Hz), 1.72 (br s, 2H), 1.36–1.31 (m, 4H), 0.89 (t, 3H, $J = 6.8$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 193.2, 150.6, 141.2, 129.8, 129.7, 126.5, 121.4, 115.6, 108.1, 54.0, 39.9, 30.4, 26.0, 22.6, 14.1.
2-Butyl-4-oxo-6-propyl-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (64). In a 25-mL three-neck round bottom flask were added 2 mL of THF and magnesium turnings (74 mg, 3.04 mmol) (activated with dibromoethane). 1-Bromopropane (0.07 mL, 0.77 mmol) was added dropwise, maintaining a self reflux. The reaction was allowed to stir for 4 h at room temperature. In a separate flask were added dihydropyridone 62 (0.102 g, 0.37 mmol), copper bromide dimethyl sulfide (0.107 g, 0.52 mmol) and 10 mL of THF. The reaction was cooled to -40 °C and the supernate of a mixture of trimethylsilyl chloride (0.09 mL, 0.71 mmol) and triethylamine (0.10 mL, 0.71 mmol), which had been centrifuged, was added. The reaction was stirred for 30 min and then cooled to -78 °C. The Grignard reagent was added dropwise by syringe pump over 1 h. The reaction was stirred 18 h and quenched with 3 mL of a 1:1 mixture of NH₄OH/NH₄Cl. After the reaction was warmed to room temperature, the organic layer was separated. The aqueous phase was extracted with Et₂O (3 x 7 mL), and the combined organic layers were washed with a 1:1 mixture of NH₄OH/NH₄Cl (~3 mL) until the persistent blue color disappeared. The organic layers were dried with K₂CO₃ and filtered through Celite. The solvent was removed by rotary evaporation, yielding 0.14 g (100% crude) of the desired silyl enol ether. To this oil was added palladium acetate (0.9 mg, 0.036 mmol), copper chloride (36 mg, 0.36 mmol), and 3 mL of acetonitrile. The mixture was purged with O₂ and heated to 60 °C under an O₂ atmosphere. After 24 h, the
reaction was cooled to room temperature, filtered through Celite with dichloromethane, and concentrated by rotary evaporation to yield 0.127 g of a mixture of starting material and product. The product was purified by radial PLC (silica gel, 20% EtOAc/ hexanes) to yield a 1:1 mixture of starting material and product (0.093 g) and pure product (0.034 g, 30% yield) as an oil. IR (neat) 2959, 2930, 2869, 1728, 1668, 1595, 1493, 1402, 1325, 1240, 1201, 1167, 1110, 750 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.45-7.40 (t, 3H, J = 7.8 Hz), 7.30-7.28 (d, 1H, J = 7.2 Hz), 7.25-7.13 (m, 2H), 5.33 (s, 1H), 4.96-4.91 (m, 1H), 3.16-3.08 (m, 1H), 2.97-2.89 (dd, 1H, 17.1, 6.0 Hz), 2.46-2.34 (m, 2H), 1.92-1.64 (m, 2H), 1.61-1.42 (m, 3H), 1.37-1.26 (m, 6H), 0.99-0.88 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 193.9, 158.1, 150.7, 129.9, 129.6, 126.4, 125.7, 121.9, 121.6, 113.8, 57.1, 41.7, 38.2, 30.4, 29.2, 21.7, 20.3, 14.2, 14.0.

2-Butyl-4-oxo-6-phenethyl-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (67).

In a 50-mL three-neck flask were added magnesium turnings (0.45, 18.5 mmol) (activated with dibromoethane) and THF (5 mL). To the reaction was added dropwise (2-bromoethyl)benzene (1.0 mL, 7.3 mmol). The Grignard was formed over 18 h at rt. In a separate flask were added copper bromide dimethyl sulfide (1.15 g, 5.6 mmol) and 7 mL of
THF. The reaction was cooled to -78 °C, and dihydropyridone 62 (1.0 g, 3.7 mmol) in 5 mL of THF was added followed by the supernate of the mixture of trimethylsilyl chloride (0.9 mL, 7.1 mmol) and triethylamine (1.0 mL, 7.12 mmol), which had been centrifuged. The Grignard reagent was added dropwise over 15 min. The reaction was stirred for 2 h at -78 °C and then 18 h at -45 °C. The reaction was quenched with 3 mL of a 1:1 mixture of NH₄OH/NH₄Cl and warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 7 mL). The combined organic layers were washed with a 1:1 mixture of NH₄OH/NH₄Cl (~3 mL) until the persistent blue color disappeared, dried over K₂CO₃, and filtered through Celite. The solvent was removed via rotary evaporation yielding 1.65 g (100%) of the desired silyl enol ether. To this oil was added palladium acetate (0.082 g, 0.37 mmol), copper chloride (0.362 g, 3.7 mmol), and 3 mL of acetonitrile. The mixture was purged with O₂ and heated to 60 °C under an O₂ atmosphere. After 24 h, the reaction mixture was cooled to room temperature, filtered through Celite with dichloromethane, and concentrated via rotary evaporation. The product was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.553 g (40%) of compound 67 as an oil. IR (neat) 2929, 2860, 1735, 1670, 1602, 1493, 1403, 1332, 1269, 1189, 749 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.47-7.42 (t, 2H, J = 7.8 Hz), 7.33-7.17 (m, 8H), 5.57 (s, 1H), 5.02-4.97 (m, 1H), 4.02 (s, 1H), 3.47-3.42 (m, 1H), 2.95-2.84 (m, 3H), 1.75-1.70 (m, 2H), 1.51-1.24 (m, 6H), 0.92-0.88 (t, 3H, J = 7.2 Hz) δ; ¹³C NMR (CDCl₃, 75 MHz) δ 193.8, 157.2, 152.2, 150.7, 140.3, 129.9, 128.8, 128.5, 126.6, 126.5, 121.6, 121.5, 114.1, 57.1, 41.5, 40.0, 37.8, 34.6, 30.3, 28.7, 28.0, 22.6, 14.2, 14.1; HRMS ([M+H]+) calcd for C₂₄H₂₇NO 378.2069, found 378.2079.
2-Butyl-4-hydroxy-6-phenethyl-3,4-dihydro-2\textit{H}-pyridine-1-carboxylic acid phenyl ester (69). To a mixture of dihydopyridone 67 (0.60 g, 1.6 mmol) in 10 mL of methanol at -40 °C was added cerium trichloride heptahydrate (0.67 g, 1.8 mmol). After 15 min, sodium borohydride (0.12 g, 3.2 mmol) was added in portions over 20 min. The reaction was warmed to room temperature and 5 mL of deionized water was added. The organic layer was separated, and the aqueous phase was extracted with Et\textsubscript{2}O (4 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered through Celite, and concentrated \textit{via} rotary evaporation. The compound was purified by radial PLC (silica gel, 20% EtOAc/ hexanes) to afford 0.48 g (80%) of compound 69 as an oil. IR (neat): 3336, 2963, 2934, 1742, 1730, 1683, 1600, 1495, 1454, 1337, 1203, 1166 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \(\delta\) 7.42-7.40 (m, 2H), 7.38-7.12 (m, 8H), 5.13 (s, 1H), 4.64-4.63 (m, 1H), 4.38 (m, 2H), 3.30 (m, 1H), 2.89-2.83 (m, 1H), 2.72-2.52 (m, 2H), 0.98-0.88 (m, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz) \(\delta\) 152.9, 151.1, 143.5, 142.6, 138.8, 129.7, 129.6, 129.5, 128.6, 126.2, 125.9, 125.4, 121.8, 115.4, 63.3, 51.0, 37.3, 36.3, 34.9, 30.2, 28.9, 22.7, 14.3 (overlap in aromatic region); HRMS calcd for C\textsubscript{24}H\textsubscript{29}NO\textsubscript{3} ([M+H]+) 379.2147, found 379.2139.
4-(But-3-enyl-dimethyl-silanyloxy)-2-butyl-6-phenethyl-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (71). To a solution of dihydropiperidinol 69 (30 mg, 0.08 mmol) in 2 mL of THF at -78 °C was added a 1.0 M solution of sodium bis(trimethylsilyl) amide (0.05 mL, 0.08 mmol). After 30 min, chlorodimethyl 1-butenesilane (0.033 mL, 0.22 mmol) was added. The reaction was warmed to -30 °C and stirred for 1 h. The mixture was filtered through Celite with Et2O and concentrated by rotary evaporation. The compound was purified via radial PLC (silica gel, 30% EtOAc/ hexanes) to afford 0.025 g (64%) of compound 71 as an oil. IR (neat) 2957, 2929, 2861, 1727, 1651, 1595, 1494, 1454, 1338, 1256, 1205, 1074, 884, 841, 799, 747 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.41-7.38 (t, 2H, J = 5.4 Hz), 7.36-7.11 (m, 8H), 5.94-5.85 (m, 1H), 5.04-4.91 (m, 3H), 4.62-4.60 (m, 1H), 4.45-4.39 (m, 1H), 3.31-3.28 (m, 1H), 2.88-2.83 (m, 1H), 2.69-2.48 (m, 2H), 2.15-1.99 (m, 4H), 1.75-1.70 (m, 2H), 1.40-1.25 (m, 6H), 0.94-0.90 (m, 3H), 0.77-0.70 (m, 2H), 0.17-0.11 (m, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 151.6, 151.2, 143.5, 131.1, 129.6, 129.5, 128.6, 126.2, 126.0, 125.7, 125.3, 122.0, 121.8, 112.9, 63.7, 36.1, 30.5, 29.9, 28.4, 27.6, 22.7, 17.5, 16.0, 14.3, 2.0, 1.4, 0.5, -1.0; HRMS calcd for C₃₀H₄₁NO₃Si ([M+H]+) 491.2586, found 491.2837.
4-Hydroxy-5,6,7,8-tetrahydroquinoline (82). In a 500-mL high pressure reactor was added 4-hydroxyquinoline (0.518 g, 3.6 mmol) and 100 mL of methanol. To this mixture was added 60% nickel on kiselguhr (0.117 g) and the bomb was charged with hydrogen to 880 p.s.i. The apparatus was heated with an oil bath to 120 °C. After 36 h, the reaction was cooled to room temperature and the mixture was filtered through Celite with methanol, and concentrated by rotary evaporation to yield an oil. The crude material was purified by radial PLC (silica gel, 5% MeOH/CH2Cl2) to afford 0.585 g (60%) of compound 82 as a yellow oil. 1H NMR (CDCl3, 400 MHz) δ 7.50-7.48 (d, 1H, J = 7.2 Hz), 6.27-6.25 (d, 1H, J = 6.8 Hz), 2.71-2.692 (m, 2H), 2.55-2.529 (m, 2H), 1.73-1.76 (bm, 4H); 13C NMR (CDCl3, 100 MHz) δ 179.1, 146.9, 136.5, 124.9, 113.6, 27.4, 22.3, 22.3, 21.9.

4-Chloro-5,6,7,8-tetrahydroquinoline (83). In a flask were added 4-hydroxy-5,6,7,8-tetrahydroquinoline (62 mg, 0.41 mmol) and phosphorous oxychloride (0.58 mL, 6.2 mmol). The reaction flask was equipped with a drying tube and the mixture was heated to
100 °C for 18 h. After cooling to room temperature, sodium bicarbonate and wet ice were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with deionized water (20 mL) and brine (20 mL), dried over magnesium sulfate, and filtered through Celite. The solvent was removed via rotary evaporation to afford 0.067 g (97%) of compound 83 as a light yellow oil.

\[ ^1H \text{ NMR (CDCl}_3, 300 MHz) \delta 8.22-8.20 (d, 1H, J = 4.2 Hz), 7.09-7.08 (d, 1H, J = 5.1 Hz), 2.90-2.88 (m, 2H), 2.77-2.75 (m, 2H), 1.83 (bs, 4H); \]
\[ ^13C \text{ NMR (CDCl}_3, 75 MHz) \delta 159.5, 147.0, 144.5, 130.9, 122.0, 33.1, 26.4, 22.7, 22.5. \]

Method A. 4-Methoxy-5,6,7,8-tertahydroquinoline (74). Sodium metal (5.81 g, 25 mmol) was added slowly to 60 mL of methanol at 0 °C. The mixture was stirred overnight. In a separate flask was added 4-chloro-5,6,7,8-tetrahydroquinoline (1.69 g, 10 mmol). The sodium methoxide was added via cannula, and the reaction was heated to reflux until completion (reaction monitored by TLC). The excess methanol was removed in vacuo. To the solid was added EtOAc (50 mL) and water (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated to afford 1.63 g (99%) of 4-methoxy-5,6,7,8-tetrahydroquinoline as a
green-blue oil. IR (neat) 2935, 1578, 1475, 1336, 1289, 1160, 1109, 1089, 1057, 997, 879, 808 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 8.25, (d, 1H, J = 5.6 Hz), 6.57, (d, 1H, J = 5.6 Hz), 3.84 (s, 3H), 2.87 (t, 2H, J = 6.0 Hz), 2.62 (t, 2H, J = 6.4 Hz), 1.80 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.7, 158.0, 121.3, 103.3, 55.3, 32.6, 22.9, 22.4, 22.3; HRMS calcd for C₁₀H₁₃NO ([M+H]+) 164.1075, found 164.1064.

Method B. 4-Methoxy-5,6,7,8-tertahydroquinoline (74). In a high pressure reactor were added 4-methoxyquinoline (0.121 g, 0.76 mmol), 60% Nickel kieselguhr (45.3 mg) and 30 mL of methanol. The bomb was charged to 1250 p.s.i. with hydrogen gas. The reaction vessel was then heated to 120 °C (pressure rose to 1550 p.s.i.) with stirring for 15 h. The reaction vessel was cooled to room temperature, vented, filtered through Celite with hot methanol, and concentrated. The product was purified on radial PLC (silica gel, gradient 10% to 50% ethyl acetate/hexanes) to afford 53 mg (43%) of compound 74.
Method C. 4-Methoxy-5,6,7,8-tertahydroquinoline (74). In a 1-L flask were added 7-chloro-4-methoxyquinoline (19.8 g, 125 mmol), lithium carbonate (9.23 g, 125 mmol), 10% palladium on carbon (13.3 g) and 500 mL of EtOH. The reaction was charged with hydrogen gas at balloon pressure and stirred. After 5 days, the reaction mixture was filtered through Celite with hot methanol. The solvent was removed via rotary evaporation. The oil was purified by column chromatography (silica gel, 5% methanol/ methylene chloride) to afford 10.2 g (60%) of compound 74.

![Chemical structure image]

7-Chloro-4-methoxyquinoline (85). To sodium metal (2.38 g, 103 mmol) at -30 °C was slowly added methanol (50 mL) with stirring. The reaction was warmed to room temperature over 18 h. To 4,7-dichloroquinoline (4.04 g, 20.4 mmol) in 5 mL of methanol was added the sodium methoxide solution, and the mixture was heated to reflux for 24 h. The excess methanol was removed via distillation or rotary evaporation. To the crude material was added EtOAc (50 mL) and deionized water (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), filtered, and concentrated to afford 3.71 g (94%) of 7-chloro-4-methoxyquinoline. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.75-8.73 (d, 1H, $J = 5.6$ Hz), 8.13-8.11 (d, 1H, $J = 8.8$ Hz), 8.02-8.01 (d, 1H, $J = 2.4$ Hz), 7.45-7.42 (dd, 1H, $J = 9.2$, 2.0 Hz).
Hz). 6.73-6.72 (d, 1H, $J = 5.2$ Hz), 4.04 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 162.5, 125.7, 149.9, 135.9, 128.1, 126.7, 123.6, 120.0, 100.5, 56.0.

4-Methoxyquinoline (86). $^{53}$ In a flask was added quinoline 85 (3.71 g, 19.1 mmol), 10% Pd/C (4.07 g), Li$_2$CO$_3$ (16.12 g, 218 mmol) and 200 mL of EtOH. The flask was charged with hydrogen, evacuated, and recharged with hydrogen. After stirring 24 h, the mixture was filtered through Celite followed by a wash with hot methanol. The solvent was removed via rotary evaporation to afford 2.56 g (84%) of compound 86 as an oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.77-8.76 (d, 1H, $J = 5.2$ Hz), 8.21-8.19 (d, 1H, $J = 8.4$ Hz), 8.04-8.02 (d, 1H, $J = 8.4$ Hz), 7.72-7.68 (t, 1H, $J = 8.4$ Hz), 7.52-7.48 (t, 1H, $J = 7.2$ Hz), 6.75-6.73 (d, 1H, $J = 5.6$ Hz), 4.05 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 162.5, 151.6, 149.3, 129.9, 129.1, 125.8, 122.0, 121.6, 100.2, 55.9.
4-Oxo-2-propyl-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid phenyl ester (87).

To a solution of 4-methoxy-5,6,7,8-tetrahydroquinoline (74) (12 mg, 0.7 mmol) in 3 mL of THF at -50 °C was added phenyl chloroformate (0.01 mL, 0.8 mmol). After 30 min, the mixture was cooled to -78 °C, and a 2.0 M solution of n-propylmagnesium bromide (0.07 mL, 0.14 mmol) in THF was added dropwise. After 18 h at -55 °C, 0.5 mL of 10% HCl was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The solution was dried with magnesium sulfate, filtered through Celite, and concentrated via radial evaporation. The crude compound was purified by radial PLC (silica gel, gradient 10% to 30% EtOAc/hexanes) to yield 0.02 g (87%) of compound 87 as an oil. IR (neat) 2934, 2864, 1736, 1667, 1655, 1607, 1495, 1385, 1337, 1287, 1256, 1203, 1137 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.40 (t, 2H, J = 8.4 Hz), 7.24 (t, 1H, J = 7.5 Hz), 7.13 (d, 2H, J = 7.2 Hz), 4.87 (m, 1H), 3.14 (m, 1H), 2.93 (dd, 1H, J = 6.0 Hz, 17.4 Hz), 2.48 (m, 2H), 2.25 (m, 2H), 1.74-1.87 (m, 3H), 1.55-1.35 (m, 5H), 0.96 (t, 3H, J = 7.2 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 193.7, 152.5, 150.9, 150.6, 129.7, 126.1, 121.7, 121.6, 55.9, 42.4, 33.2, 30.8, 22.8, 21.9, 21.7, 19.8, 14.1; HRMS calcd for C₁₉H₂₃NO₃ ([M+H]+) 314.1756, found 314.1767.

![Diagram of compounds 87 and 90]
4-Allyl-4-hydroxy-2-propyl-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid phenyl ester (90). To a solution of hexahydroquinolone 87 (79 mg, 0.25 mmol) in 2 mL of Et₂O at -78 °C was added dropwise a solution of 1.35 M 1-propenylmagnesium chloride (0.2 mL, 0.27 mmol) in THF. After 3 h at -78 °C, 2 mL of ammonium chloride was added and the mixture was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over magnesium sulfate. The mixture was filtered through Celite and concentrated via rotary evaporation. The crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 0.061 g (68%) of the major diastereomer as a light yellow oil. IR (neat) 3491, 2932, 2860, 1738, 1732, 1699, 1686, 1681, 1595, 1506, 1495, 1394, 1327, 1204, 1162, 999, 912, 751, 688 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.36 (t, 2H, J = 7.8 Hz), 7.19 (t, 1H, J = 7.2 Hz) 7.09 (d, 2H, J = 7.5 Hz), 5.66-5.80 (m, 1H), 5.18 (s, 1H), 5.14 (d, 1H, J = 5.7 Hz), 4.90-4.35 (m, 1H), 2.98-2.93 (m, 1H), 2.42-2.23 (m, 4H), 2.14 (d, 1H, J = 17.4 Hz), 1.98 (d, 1H, J = 16.5 Hz), 1.83-1.68 (m, 5H), 1.67-1.54 (m, 2H), 1.52-1.33 (m, 3H), 0.95 (t, 3H, J = 6.9 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 153.2, 151.4, 133.5, 130.5, 129.5, 128.3, 125.5, 121.8, 119.5, 70.6, 51.8, 44.8, 42.4, 35.4, 29.5, 23.2, 23.2, 22.8, 20.0, 14.2; HRMS calcd for C₂₂H₂₉NO₃ 355.2147, found 355.2122.
4-Hydroxy-2-propyl-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid phenyl ester (92). To a solution of hexahydroquinolone 87 (52 mg, 0.17 mmol) in 2 mL of methanol at 
-50 °C was added cerium trichloride heptahydrate (68 mg 0.18 mmol). After 10 min, sodium borohydride (15 mg, 0.40 mmol) was added in small portions. The reaction was warmed to room temperature, stirred for 2 hours, and then water (2 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et2O (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. The crude oil was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.045 g (85%) of a mixture of two diastereomers. Further purification by radial PLC (silica gel, 1% EtOAc/ hexanes) afforded 0.022 g (42%) of 92a and 0.023 g (43% ) of 92b as oils. 1st isomer: IR (neat) 3463, 2954, 2937, 2867, 1733, 1718, 1700, 1575, 1456, 1419, 1325, 1207, 1131, 1035 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.36 (t, 2H, J = 7.6 Hz), 7.20 (t, 1H, J = 7.2 Hz), 7.12 (d, 2H, J = 8.4 Hz), 4.54-4.51 (m, 1H), 4.02 (br s, 1H), 2.98 (br s, 1H), 2.54 (m, 1H), 2.29-2.22 (m, 1H), 2.03 (br t, 2H, J = 18 Hz), 1.93 (d, 1H, J = 14.4 Hz), 1.83 (br d, 3H, J = 6.8 Hz), 1.65-1.38 (m, 7H), 0.95 (t, 3H, J = 7.2 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 151.4, 129.5, 125.5, 121.8, 65.5, 51.7, 37.3, 34.1, 29.7, 26.2, 23.6, 22.6, 20.4, 14.2, 0.23; HRMS calcd for C₁₀H₂₅NO₃ ([M+H]⁺) 315.1834, found 315.1834. 2nd
isomer: IR (neat) 3426, 2933, 2859, 1733, 1498, 1496, 1456, 1419, 1394, 1324, 1207, 1163, 1143, 987, 731, 688 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.36 (t, 2H, \(J = 8.4\) Hz), 7.20 (t, 1H, \(J = 7.2\) Hz), 7.12 (dd, 2H, \(J = 8.8, 0.8\) Hz), 4.58-4.55 (m, 1H), 4.13 (q, 1H, \(J = 7.2\) Hz), 2.94-2.87 (m, 1H), 2.51 (d, 1H, \(J = 17.2\) Hz), 2.24-2.17 (m, 1H), 2.06-1.90 (m, 3H), 1.82-1.78 (m, 2H), 1.68-1.55 (m, 3H), 1.50-1.38 (m, 5H), 0.96 (t, 3H, \(J = 6.8\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 153.1, 151.3, 131.7, 129.5, 123.2, 66.9, 55.0, 37.9, 33.2, 29.9, 26.1, 23.4, 22.5, 20.0, 14.2; HRMS calcd for C\(_{19}\)H\(_{25}\)NO\(_3\) ([M+H]\(^+\)) 315.1834, found 315.1842.

\((2R^*,8aS^*)\)-8a-Allyl-2-propyl-3,5,6,7,8,8a-hexahydro-2\(H\)-quinoline-1-carboxylic acid phenyl ester (93). To a solution of alcohol 92 (85 mg, 0.27 mmol) in 3.0 mL of dichloromethane at -78 °C was added allyltributyltin (0.50 mL, 1.6 mmol). After 5 min, boron trifluoride diethyl etherate (0.10 mL, 0.81 mmol) was added dropwise. The reaction was stirred for 3.5 h. Saturated sodium bicarbonate (3 mL) was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over magnesium sulfate. The reaction was
filtered through Celite and the solvent was removed in vacuo. The crude material was purified by radial PLC (silica gel, 5% EtOAc/ hexanes) to afford 0.067 g (83%) of compound 93 as an oil. IR (neat) 2928, 2858, 1738, 1733, 1717, 1652, 1557, 1495, 1455, 1392, 1330, 1206, 1138 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.37-7.33 (t, 2H, J = 7.6 Hz), 7.20-7.16 (t, 1H, J = 7.6 Hz), 7.12-7.06 (d, 1H, J = 16.8 Hz), 5.75-5.68 (m, 1H) 5.08-5.02 (t, 2H, J = 15.2, 8.0 Hz), 4.46-4.43 (m, 1H), 2.90 (m, 1H), 2.35-2.24 (m, 2H), 2.09-2.07 (m, 2H), 1.93-1.49 (m, 10H), 1.43-1.25 (m, 4H), 0.96-0.93 (t, 3H, J = 7.2 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 151.6, 136.3, 129.4, 125.3, 125.2, 122.2, 121.9, 116.8, 53.1, 37.3, 35.2, 34.3, 33.6, 29.8, 28.0, 27.4, 23.4, 23.3, 23.1, 23.0, 19.9, 14.3; HRMS calcd for C₂₂H₂₉NO₂ [(M+H)⁺] 340.2277, found 340.2282.

(2R⁺)-4-(Dimethylphenylsilyl)-4-hydroxy-2-propyl-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid phenyl ester (96). To a mixture of lithium wire (94 mg, 13.5 mmol) in 5.0 mL of THF was added chlorodimethylphenylsilane (0.24 mL, 1.4 mmol) all at once. The reaction was stirred at rt for 4 h. In a separate flask was added hexahydroquinolone 87 (0.206 g, 0.67 mmol) and 5.0 mL of ether. The mixture was cooled to -78 °C, and the dimethylphenylsilyllithium was added dropwise with a syringe pump over
1 h. After 18 h at -78 °C, 5 mL of saturated sodium bicarbonate was added and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and filtered through Celite. The solvent was removed via rotary evaporation, and the crude material was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.177 g (60%) of compound 96 as a clear oil and 0.041 g (20%) of recovered starting material. IR (neat) 3467, 2933, 2857, 2361, 1699, 1685, 1681, 1652, 1495, 1428, 1394, 1325, 1248, 1204, 1162, 1114, 1024, 817, 775, 737, 701 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.60-7.57 (m, 2H), 7.38-7.38 (m, 5H), 7.19 (t, 1H, J = 7.5 Hz), 7.12 (d, 2H, J = 7.5 Hz), 4.32-4.24 (p, 1H), 3.03-2.97 (m, 1H), 2.47-2.40 (dd, 1H, J = 13.8, 7.2 Hz), 2.22-2.16 (m, 1H), 1.96 (d, 1H, J = 16.8 Hz), 1.81-1.60 (m, 5H), 1.57-1.28 (m, 7H), 0.91 (t, 3H, J = 7.2 Hz) 0.40 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 151.4, 136.4, 134.6, 129.8, 129.5, 129.4, 128.1, 125.5, 121.9, 66.9, 50.8, 42.7, 36.2, 29.7, 25.3, 23.4, 22.9, 19.8, 15.9, 14.2, -4.6, -5.1; HRMS calcd for C₂₇H₃₅NO₃Si [(M+H)+] 449.2386, found 449.2378.

(2R,S,8aS)-8a-Allyl-4-(dimethylphenylsilanyl)-2-propyl-3,5,6,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid phenyl ester (97). To a solution of geminal silylalcohol 96 (10
mg, 0.02 mmol) in 2.0 mL of dichloromethane at -78 °C was added allyltributyltin (0.01 mL, 0.03 mmol). After 10 min, boron trifluoride diethyl etherate (0.01 mL, 0.08 mmol) was added dropwise. The reaction was stirred for 4 h, and 1 mL of saturated sodium bicarbonate was added. After the reaction was warmed to room temperature, the organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, and filtered through Celite. The solvent was removed via rotary evaporation, and the crude product was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.01 g (95%) (95% de by ¹H NMR) of compound 97 as an oil. IR (neat) 3069, 2955, 2933, 2863, 1739, 1733, 1720, 1716, 1685, 1614, 1495, 1390, 1209, 1181, 1111, 995, 914, 832, 812, 773, 730, 700 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.53-7.50 (m, 2H), 7.37-7.33 (m, 5H), 7.19-7.15 (t, 1H, J = 7.6 Hz), 7.08-7.06 (d, 2H, J = 7.2 Hz), 5.77-5.67 (m, 1H), 5.09-5.04 (t, 2H, J = 17.2, 3.6 Hz), 4.52-4.50 (d, 1H, J = 6.4 Hz), 3.53 (bs, 1H), 2.89 (bs, 1H), 2.57-2.46 (m, 2H), 2.36-2.32 (bd, 1H, J = 16.4 Hz), 2.17-2.10 (m, 2H), 1.67-1.44 (m, 6H), 1.34-1.18 (m, 4H), 0.95-0.91 (t, 3H, J = 6.8 Hz), 0.39-0.38 (d, 6H, J = 4.8 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 151.7, 149.3, 139.8, 134.6, 133.7, 133.1, 129.4, 129.0, 128.0, 125.2, 122.2, 117.4, 117.1, 63.3, 51.3, 37.4, 36.2, 33.3, 31.9, 31.5, 31.0, 29.9, 27.1, 23.0, 20.3, 14.4, -0.66, -0.80; HRMS calcd for C₃₀H₃₉NO₂Si 474.2828, found 474.2827.
(2\textsuperscript{R},8a\textsuperscript{S})-8a-(2,3-Dihydroxypropyl)-4-(dimethylphenylsilanyl)-2-propyl-3,5,6,7,8,8a-hexahydro-2\textit{H}-quinoline-1-carboxylic acid phenyl ester (98). To a solution of vinylsilane 97 (12 mg, 0.03 mmol) in 1 mL of THF were added 4-methylmorpholine \textit{N}-oxide (7.5 mg, 0.06 mmol), 0.2 mL of water, and a 21\% wt solution of osmium tetraoxide (0.3 mL, 2.5 mmol). After 3 days, the contents were poured into a flask with 2 mL of saturated sodium sulfite and the mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, and filtered through Celite. The solvent was removed via rotary evaporation. The crude product was purified by radial PLC (silica gel, 10\% EtOAc/ hexanes) to afford 0.01 g (78\% yield) of diol 98 as a mixture of diastereomers as an oil. IR (neat) 3416, 2931, 2864, 1711, 1493, 1455, 1392, 1358, 1301, 1251, 1207, 1182, 1110, 813, 731 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \textdollar 7.51 (s, 2H), 7.37-7.33 (m, 5H), 7.21-7.04 (m, 3H, 4.59-4.57 (m, 1H), 3.92 (br s, 1H), 3.70-3.39 (m, 2H), 2.91-2.76 (m, 2H), 2.62-1.98 (m, 7H), 1.70-1.47 (m, 7H), 1.37-1.13 (m, 4H), 0.97-0.92 (t, 3H, \textit{J} = 7.2 Hz), 0.45-0.41 (d, 6H, \textit{J} = 12.0 Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz) \textdollar 152.2, 149.3, 139.0, 133.7, 129.6, 129.4, 129.2, 128.2, 125.5, 122.3, 122.1, 70.2, 67.4, 51.6,
46.2, 37.5, 36.1, 34.0, 33.5, 31.9, 29.2, 28.6, 27.0, 22.8, 20.4, 14.4, -0.95, -1.1; HRMS calcd for C_{30}H_{41}NO_{4}Si [(M+H)^+] 508.2883, found 508.2861.

3-Tributylstannanylprop-2-en-1-ol (105). To a solution of propargyl alcohol (1.0 mL, 17.2 mmol) and AIBN (0.28 g, 1.7 mmol) was added tributyltinhydride (6.2 mL, 23.0 mmol). The solution was heated to reflux for 18 h, and then purified by column chromatography (silica gel, gradient 10% EtOAc/ hexanes to methanol) to afford 3.15 g (63%) of an inseparable mixture of the cis and trans products.

Phenylcarbamic acid 3-tributylstannanylallyl ester (106). To a solution of 3-tributylstannanyl-prop-2-en-1-ol (105) (0.297 g, 0.85 mmol) in 2.0 mL of CH_{2}Cl_{2} and 2.0 mL of pyridine were added phenyl isocyanate (0.13 mL, 1.2 mmol) and N,N-dimethyl-4-aminopyridine (25 mg, 0.21 mmol). After 4 h at rt, 2 mL of 10% HCl was added. The organic layer was separated, and the aqueous phase was extracted with CH_{2}Cl_{2} (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, and filtered through Celite. The solvent was removed via rotary
evaporation. The crude material was purified by radial PLC (silica gel, 30% EtOAc/hexanes) to afford 0.30 g (63%) of compound 106 as an oil. IR (neat) 3323, 2956, 2926, 2848, 1710, 1603, 1541, 1502, 1445, 1313, 1223, 1085, 1027 cm\(^{-1}\), \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.40-7.38 (d, 2H, \(J = 8.0\) Hz), 7.33-7.29 (t, 3H, \(J = 7.6\) Hz), 7.08-7.05 (t, 1H, \(J = 7.2\) Hz), 6.62 (bs, 1H), 6.34-6.30 (d, 1H, \(J = 19.2\) Hz), 6.13-6.05 (dt, 1H, \(J = 18.8, 5.6\) Hz), 6.68-4.67 (dd, 2H, \(J = 5.2, 1.2\) Hz), 1.54-1.46 (m, 6H), 1.34-1.26 (m, 6H), 0.93-0.85 (m, 14H); \(^1\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 141.9, 133.3, 129.3, 123.6, 118.9, 68.5, 29.3, 27.5, 13.9, 9.7, 0.21.

4-Trimethylsilanyl-but-2-enoic acid ethyl ester (109).\(^{38}\) In a three-neck flask were added 8 mL of THF and magnesium turnings (3.61 g, 152 mmol) (activated with dibromoethane). Chlomethyltrimethylsilane (2.2 mL, 15.8 mmol) was added dropwise, maintaining a self-reflux. The reaction was allowed to stir 18 h at room temperature. In a separate flask were added copper bromide dimethyl sulfide (3.25 g, 15.8 mmol) and 30 mL of THF. The reaction was cooled to –10 °C, and the Grignard was added dropwise via syringe pump over 2.5 h. The mixture was cooled to –55 °C, and ethyl propiolate (1.5 mL, 14.8 mmol) was added all at once. After 2.5 h, 60 mL of a 1:1 mixture of NH\(_4\)OH/ NH\(_4\)Cl was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous
phase was extracted with Et$_2$O (3 x 50 mL). The combined organic layers were washed with water (50 mL) and dried over sodium sulfate. The solvent was removed by rotary evaporation to afford an orange liquid. The crude product was purified by filtration through a Celite plug to afford 2.17 g (78%) of compound 109 as a pale yellow oil. IR (neat) 2980, 2956, 2900, 1716, 1640, 1315, 1251, 1195, 1128, 1049 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.03 (m, 1H), 5.62 (d, 1H, $J = 15.3$ Hz), 4.15 (q, 2H, $J = 7.2$ Hz), 1.71 (d, 2H, $J = 9$ Hz), 1.27 (t, 3H, $J = 7.2$ Hz), 0.05 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.8, 147.8, 119.1, 59.8, 24.9, 14.4, -1.5, -1.7, -1.7.

![Chemical Structure](image)

3-Tributylstannanyl-4-(trimethylsilyl)-butyric acid ethyl ester (110). To a solution of diisopropyl amine (3.9 mL, 27.7 mmol) in 50 mL of THF at -23 °C was added a 2.41 M solution of n-butyllithium (11.1 mL, 26.9 mmol) in hexanes. After 30 min, the reaction was warmed to 0 °C, and tributyltin hydride (7.3 mL, 26.9 mmol) was added dropwise. The reaction was stirred for 15 min and then cooled to -78 °C. In a separate flask were added 4-trimethylsilyl-butyric acid ethyl ester (109) (5.01 g, 26.9 mmol) and 10 mL of THF. The flask was degassed with argon for 20 min and added dropwise to the tributyltinlithium. After 15 min, the reaction was quenched with saturated ammonium chloride (20 mL). The organic layer was separated, and the aqueous phase was extracted with Et$_2$O (3 x 20 mL).
The combined organic layers were washed with brine (20 mL) and dried over potassium carbonate. The crude mixture was filtered through Celite and concentrated to afford 12.84 g (100%) of crude compound 110. The material was used crude in the next step. IR (neat) 2955, 2924, 2872, 2854, 1732, 1464, 1346, 1293, 1248, 1183, 1096, 1072, 1029, 855, 839 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 4.13-4.11 (m, 2H), 2.57-2.55 (m, 2H) 1.61-1.58 (m, 8H), 1.49-1.26 (m, 12H), 1.09-0.74 (m, 23H), 0.021 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 174.3, 60.4, 40.7, 30.8, 29.6, 29.5, 29.3, 28.0, 27.8, 27.7, 27.3, 20.6, 15.7, 14.5, 13.9, 10.1, 9.3, -0.59; HRMS calcd for C\(_{21}\)H\(_{46}\)O\(_2\)SiSn [(M-C\(_4\)H\(_9\))+] 421.1585, found 421.1587.

![Image of chemical structures](image.png)

**3-Tributylstannanyl-4-trimethylsilanylbutan-1-ol (111).** To a solution of lithium aluminum hydride (0.319 g, 8.4 mmol) in 12 mL of Et\(_2\)O at -10 °C was added dropwise 3-tributylstannanyl-4-trimethylsilanylbutyric acid ethyl ester (4.0 g, 8.4 mmol) in 6 mL of Et\(_2\)O. The reaction was allowed to warm to room temperature and stirred for 18 h. The mixture was cooled to 0 °C and then quenched with 12 mL of saturated ammonium chloride. The organic layer was separated, and the aqueous phase was extracted with Et\(_2\)O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over potassium carbonate, filtered through Celite, and concentrated via rotary evaporation to yield 3.65 g (100%) of crude material 111. The product can be used crude or purified by distillation.
To a solution of 2-nitrophenyl selenocyanate (0.68 g, 3.0 mmol) in 15 mL of THF was added alcohol 111 (1.09 g, 2.5 mmol). After 15 min, tributylphosphine (0.75 mL, 3.0 mmol) was added. The reaction was stirred for 18 h and quenched with 10 mL of NaOH. The organic layer was separated, and the aqueous phase was extracted with Et2O (3 x 50 mL). The combined organic layers were washed with water (10 mL), dried over sodium sulfate, and filtered through Celite. The solvent was removed via rotary evaporation, and the crude material was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 1.12 g (78%) of compound 112 as a orange/yellow oil. IR (neat) 2956, 2924, 2872, 2853, 1592, 1567, 1514, 1461, 1332, 1303, 1248, 839.1, 729 cm^{-1}; ¹H NMR (CDCl₃, 300 MHz) δ 8.30 (d, 1H, J = 8.7 Hz), 7.48 (t, 2H, J = 5.1 Hz), 7.33-7.25 (m, 1H), 2.97-2.88 (m, 1H), 2.83-2.74 (m, 1H), 2.10-1.97 (m, 2H), 1.61-1.39 (m, 6H), 1.36-1.24 (m, 6H), 0.91-0.77 (m, 18H), 0.004 (s, 9H);
$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 147.0, 134.2, 133.6, 129.2, 126.7, 125.5, 34.9, 29.6, 29.5, 27.8, 26.9, 21.8, 20.4, 13.9, 9.2, -0.52; HRMS calcd forC$_{25}$H$_{47}$NO$_2$SeSiSn [(M-C$_4$H$_9$)$^+$] 564.0901, found 564.0859.

Trimethyl-(2-tributylstannanyl-but-3-enyl)silane (103). To a solution of trimethyl-[4-(2-nitrophenylselanyl)-2-(tributylstannanyl)butyl]-silane (112) (0.28 g, 0.46 mmol) in 5 mL of dichloromethane was added saturated sodium bicarbonate (0.21 g in 5 mL of water, 2.47 mmol) and m-chloroperbenzoic acid (0.121 g of 70% by wt, 4.92 mmol). After 2 h, the reaction turned bright orange indicating completion. The organic layer was separated, and the aqueous phase was extracted with hexanes (3 x 20 mL). The combined organic layers were washed with water (2 x 20 mL), dried over sodium sulfate, and filtered through Celite. The solvent was removed via rotary evaporation. The crude material was purified by radial PLC (silica gel, 1% triethylamine, 10% EtOAc/hexanes) to afford 0.140 g (74%) of compound 103 as a pale yellow oil. IR (neat) 2957, 2926, 2872, 2855, 1617, 1464, 1418, 1376, 1247, 1075, 858, 839 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.96-5.84 (m, 1H), 4.71 (d, 1H, $J$ = 17.1 Hz), 4.61 (d, 1H, $J$ = 10.2 Hz), 2.26 (t, 1H, $J$ = 10.5 Hz), 1.58-1.43 (m, 6H), 1.36-1.24 (m, 6H), 1.03-0.73 (m, 17H), -0.021 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 143.6,
4-(Dimethylphenylsilanyl)-4-hydroxy-2-isobutyl-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (114). To a solution of lithium wire (50 mg, 9.8 mmol) in 5.0 mL of THF was added chlorodimethylphenylsilane (0.18 mL, 1.5 mmol) all at once. The reaction was stirred at rt for 4 h. In a separate flask was added dihydropyridone 113 (0.201 g, 0.73 mmol) in 1.5 mL of THF and 9.0 mL of ether. The mixture was cooled to -78 °C, and the dimethylphenylsilyllithium was added dropwise via a syringe pump over 1 h. After 8 h at -78 °C, 2 mL of saturated sodium bicarbonate was added and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over K₂CO₃, and filtered through Celite. The solvent was removed by rotary evaporation and the crude material was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.162 g (54%) of compound 114 as a clear oil and 0.040 g (20%) of recovered starting material. IR (neat) 3436, 2855, 2927, 2856, 1688, 1453, 1427, 1404, 1366, 1329, 1250, 1171, 1135, 1113, 1020, 832, 816, 772 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.62-7.60 (m,
2H), 7.40-7.35 (m, 5H), 7.25-7.22 (d, 1H J = 9.9 Hz), 7.19-7.14 (d, 2H, J = 16.5 Hz), 6.96-6.93 (d, 1H, J = 7.2 Hz), 5.17-5.08 (dd, 1H, J = 17.4, 8.1 Hz), 4.46 (m, 1H), 2.1-1.95 (m, 2H), 1.70-1.55 (m, 4H), 1.27-1.18 (d, 2H, J = 27.6 Hz), 0.91 (br s, 6H), 0.38 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 151.8, 151.2, 135.6, 134.9, 129.8, 129.6, 128.1, 125.8, 125.2, 124.5, 121.8, 121.7, 111.8, 110.5, 61.5, 48.0, 40.4, 34.9, 25.6, 23.2, 22.5, -5.8, -6.1; HRMS calcd for C₂₄H₃₁NO₂Si [(M+H)+] 410.2151, found 410.2142.

4-(Dimethylphenylsilanyl)-2-isobutyl-6-(4-trimethylsilanyl-but-2-enyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (115). To a solution of silyl alcohol 114 (75 mg, 0.18 mmol) in 5 mL of CH₂Cl₂ at -78 °C was added compound 103 (0.135 g, 0.32 mmol). After 10 min, BF₃·OEt₂ (0.05 mL, 0.41 mmol) was added dropwise. After 2.5 h, the reaction was quenched with saturated NaHCO₃ (2 mL) and warmed to room temperature. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with water (10 mL) and dried over K₂CO₃. Filtration and concentration afforded the crude product which was purified by radial PLC (silica gel, 1% TEA, 5% EtOAc/ hexanes) to give 59 mg (36%) of compound 115 as a light
yellow oil. IR (neat) 2954, 2360, 2340, 1715, 1494, 1406, 1389, 1360, 1333, 1300, 1248, 1207, 1162, 958, 835, 773, 733, 687 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.52-7.51 (m, 2H), 7.38-7.33 (m, 5H), 7.21-7.08 (m, 3H), 6.30-6.16 (d, 1H, J = 42.3 Hz), 5.62-5.55 (m, 1H), 5.16-4.98 (m, 2H), 4.19 (br s, 2H), 3.16 (br s, 1H), 2.33-2.07 (m, 2H), 1.43-1.26 (m, 4H), 0.88-0.81 (m, 4H), 0.72-0.54 (m, 5H), 0.39 (s, 6H), -0.03 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 154.6, 151.8, 141.8, 137.7, 136.6, 134.2, 129.5, 128.1, 126.2, 122.0, 116.8, 60.1, 53.5, 50.4, 47.3, 43.1, 31.2, 28.8, 26.4, 25.7, 24.1, 24.0, 23.6, 23.2, 21.4, 20.0, 19.1, -0.48, -1.7, -3.7; HRMS calcd for C₃₁H₄₅NO₂Si₂ [(M+H)⁺] 520.3067, found 520.3066.

6-But-3-enyl-4-(dimethylphenylsilyl)-2-isobutyl-3,6-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (116). In a NMR tube was added compound 115 (2.3 mg), 0.25 mL of CDCl₃ and 0.25 mL of formic acid. The reaction was heated and monitored by ¹H NMR for the shift in the vinyl bond region. ¹H NMR (CDCl₃, 300 MHz) δ 7.52-7.50 (m, 2H), 7.38-7.33 (m, 5H), 7.20-7.11 (m, 3H), 6.10-6.05 (d, 1H, J = 15 Hz), 5.91-5.79 (m, 1H), 5.07-4.94 (m, 3H), 4.59 (br s, 1H), 4.45-4.37 (br d, 1H, J = 24.3 Hz), 2.34-2.17 (m, 3H), 2.07-1.91 (m, 3H), 1.72-1.11 (m, 8H), 0.98-0.83 (m, 8H), 0.39-0.36 (br s, 6H).
4-(Dimethylphenylsilanyl)-2-propyl-5,6,7,8-tetrahydro-2H-quinoline-1-carboxylic acid phenyl ester (118). To a solution of geminal silylalcohol 96 (56 mg, 0.13 mmol) in 2 mL of CH₂Cl₂ at -55 °C was added trimethyl-(2-tributylstannanyl-but-3-enyl)silane (103) (63 mg, 0.15 mmol) in 2 mL of CH₂Cl₂ followed by the dropwise addition of BF₃·OEt₂ (0.04 mL, 0.33 mmol). After 2.5 h, the reaction was quenched with 1 mL of a saturated solution of sodium bicarbonate. The organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered, and concentrated via rotary evaporation. The crude material was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 0.043 g (80%) of compound 118 as a yellow oil. IR (neat) 3051, 2964, 2933, 2861, 1742, 1739, 1733, 1701, 1652, 1506, 1505, 1456, 1436, 1419, 1409, 1334, 1303, 1250, 1205, 1110, 808 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.51-7.49 (m, 2H), 7.36-7.33 (m, 5H), 7.20-7.12 (m, 3H), 6.09 (bs, 1H), 4.60 (bs, 1H), 2.66-2.61 (bd, 1H, J = 16.4 Hz), 2.34-2.21 (m, 4H), 2.13-2.08 (d, 1H, J = 17.6 Hz), 1.69-1.55 (m, 5H), 1.38-1.25 (m, 4H), 0.96-0.93 (t, 3H, J = 7.2 Hz), 0.41-0.38 (d, 6H, J = 14 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 140.5, 139.3, 133.8, 129.4, 129.1, 128.1, 125.3, 121.9, 51.0, 34.1, 33.8, 31.8, 29.9, 25.7, 22.9, 19.4, 14.1, 0.23, -0.86, -1.21; HRMS calcd for C₂₇H₃₃NO₂Si 432.2359, found 432.2367.
4-(Dimethylphenylsilyl)-4-methoxymethoxy-2-propyl-3,4,5,6,7,8-hexahydro-2H quinoline-1-carboxylic acid phenyl ester (119). To a solution of silyl alcohol 96 (44 mg, 0.01 mmol) in 1 mL of DMF was added potassium iodide (~2 mg). The reaction was cooled to -20 °C, and diisopropylethylamine (0.18 mL, 0.70 mmol) was added followed by chloromethyl methyl ether (0.1 mL, 1.3 mmol). The reaction was warmed to room temperature and stirred for 18 h. The excess chloromethyl methyl ether was removed via rotary evaporation. The DMF was removed by kugelrhor distillation (60 °C, 0.25 mmHg). The crude product was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.03 g (62%) of 119 as an oil. IR (neat) 3074, 2955, 2855, 1739, 1733, 1717, 1701, 1697, 1597, 1508, 1496, 1394, 1317, 1206, 1121, 1021, 833, 819 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.62 (dd, 2H, J = 7.2 and 1.6 Hz), 7.38-7.31 (m, 5H), 7.19 (t, 1H, J = 7.6 Hz), 7.11 (d, 2H, J = 7.6 Hz), 4.67 (d, 1H, J = 6.8 Hz), 4.58 (d, 1H, J = 7.2 Hz), 4.35-4.30 (m, 1H), 3.33 (s, 3H), 3.03 (t, 1H, J = 6.8), 2.65 (dd, 1H, J = 15.6 and 8 Hz), 2.31 (dd, 1H, J = 15.6 and 1.6 Hz), 1.93-1.75 (m, 4H), 1.63-1.23 (m, 7H), 0.92 (t, 3H, J = 7.2 Hz), 0.38 (d, 6H, J = 2 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 151.4, 137.0, 135.0, 129.4, 128.5, 127.7, 125.4, 121.9, 94.6, 73.3, 55.6, 49.5, 37.6, 36.0, 29.8, 25.9, 23.4, 23.0, 20.3, 14.2, -4.8, -5.2; HRMS calcd for C₂₉H₃₉NO₄Si [(M+H)⁺] 528.2910, found 528.2900.
4-(Dimethylphenylsilanyl)-2-propyl-3,5,6,7-tetrahydro-2H-quinoline-1-carboxylic acid phenyl ester (121). To a solution of silyl alcohol 96 (62 mg, 0.14 mmol) in 2 mL of toluene at -78 °C was added a 1.0 M solution of KHMDS (0.14 mL, 0.14 mmol). After 5 min, chloromethyl methyl ether (0.06 mL, 0.79 mmol) was added and the reaction was stirred for 18 h at -78 °C. The reaction was quenched with 0.5 mL of a saturated solution of sodium bicarbonate, and the mixture was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered, and concentrated via rotary evaporation. The crude material was purified by radial PLC (silica gel, 10% EtOAc, hexanes) to afford 0.037 g (63%) of the eliminated product 121 as an oil. ¹H NMR (CDCl₃, 400 MHz) δ 7.61-7.51 (m, 2H), 7.41-7.32 (m, 5H), 7.19-7.15 (t, 1H, J = 7.2 Hz), 7.09-7.07 (d, 2H, J = 8.8 Hz), 4.48-4.45 (m, 1H), 4.13-4.09 (t, 1H, J = 8.0 Hz), 2.86-2.84 (m, 1H), 2.45-2.41 (m, 1H), 2.09-1.72 (m, 6H), 1.58-1.51 (m, 3H), 1.42-1.22 (m, 4H), 0.94-0.88 (t, 3H, J = 10 Hz), 0.43-0.42 (d, 6H, J = 4.4 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 151.4, 137.8, 133.8, 131.4, 129.9, 129.4, 128.0, 125.4, 122.7, 121.8, 67.7, 54.7, 37.4, 33.1, 30.2, 26.4, 23.5, 22.5, 19.9, 14.2, -0.77, -1.1; HRMS calcd for C₂₇H₃₃NO₂Si [(M+H)+] 432.2359, found 432.2327.
(2R*, 8aS*)-4-(Dimethylphenylsilanyl)-8a-(4-methoxycarbonyloxy-but-2-enyl)-2-propyl-3,5,6,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid phenyl ester (123). To a solution of vinyl silane 97 (46 mg, 0.1 mmol) in 1.5 mL of CH$_2$Cl$_2$ was added carbonic acid 4-(methoxycarbonyl)oxy-but-2-enyl ester methyl ester 122 (75 mg, 0.37 mmol). The mixture was degassed with argon for twenty minutes and then Grubbs 2nd generation catalyst 40 (8.3 mg, 0.01 mmol) was added. The reaction was stirred for 18 h at rt and the solvent was removed via rotary evaporation. The crude material was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.017 g (39%) of carbonate 123 as a clear oil. IR (neat) 2954, 2933, 2868, 1771, 1717, 1701, 1693, 1698, 1685, 1612, 1596, 1495, 1456, 1356, 1265, 1208, 1111 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.53-7.50 (m, 2H), 7.38-7.34 (m, 5H), 7.18 (t, 1H, $J$ = 7.4 Hz), 7.08 (d, 2H, $J$ = 7.6 Hz), 5.72-5.59 (m, 2H), 4.60 (d, 2H, $J$ = 5.6 Hz), 4.50 (d, 1H, $J$ = 4.4 Hz), 3.76 (s, 3H), 3.53 (br s, 1H), 2.90 (d, 1H, $J$ = 10.4 Hz), 2.56-2.48 (m, 2H), 2.31 (d, 1H, $J$ = 15.2 Hz), 2.18-2.09 (m, 2H), 1.64-1.18 (m, 9H), 0.093 (t, 3H, $J$ = 6.8 Hz), 0.40 (d, 6H, $J$ = 6.8 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 156.0, 151.6, 148.8, 139.7, 134.4, 133.7, 133.0, 132.7, 131.2, 129.4, 129.3, 129.1, 128.7, 128.1, 125.8, 125.2, 122.2,
64.4, 63.1, 54.9, 51.3, 36.3, 35.9, 33.2, 31.9, 27.0, 23.0, 20.2, 23.0, 20.7, 14.2, -0.71, -0.79;
HRMS calcd for C\textsubscript{33}H\textsubscript{44}NO\textsubscript{5}Si [(M+H)+] 562.2989, found 562.2991.

\[
\begin{array}{c}
\text{Ph} \\
\text{Si} \\
\text{N} \\
\text{CO}_2\text{Me} \\
\text{123}
\end{array}
\quad \rightarrow 
\quad
\begin{array}{c}
\text{Ph} \\
\text{Si} \\
\text{N} \\
\text{CO}_2\text{Ph} \\
\text{124}
\end{array}
\]

8a-But-3-enyl-4-(dimethylphenylsilanyl)-2-propyl-3,5,6,7,8,8a-hexahydro-2\textsubscript{H}-quinoline-1-carboxylic acid phenyl ester (124). To a degassed solution of carbonate 123 (17 mg, 0.03 mmol) in 1 mL of 1,4-dioxane was added Pd\textsubscript{2}(dba)\textsubscript{3} HCCl\textsubscript{3} (1.5 mg, 0.002 mmol), tri-\textit{n}-butylphosphine (1.5 μL, 0.006 mmol), and ammonium formate (3.7 mg, 0.06 mmol) in succession. After stirring at 100 °C for four hours, the solvent was removed \textit{via} rotary evaporation. The crude material was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 7.8 mg (54%) of compound 124 as a pale yellow oil. IR (neat) 2956, 2931, 2866, 1715, 1494, 1390, 1355, 1297, 1251, 1209, 1182, 1160, 1112, 996, 812 cm\textsuperscript{-1}, \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) δ 7.52 (br s, 2H), 7.36 (br s, 5H), 7.20-7.15 (t, 1H, \textit{J} = 7.2 Hz), 7.09-7.07 (d, 2H, \textit{J} = 7.8 Hz), 5.85-5.79 (m, 1H), 5.04-4.92 (m, 2H), 4.54-4.52 (br s, 1H), 2.86 (br s, 2H), 2.48-1.84 (m, 8H), 1.68-1.42 (m, 6H), 0.96-0.86 (m, 3H), 0.40 (s, 6H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz) δ 151.6, 139.8, 139.4, 133.7, 129.5, 129.1, 128.1, 125.2, 122.2, 114.5,
2-Hexyl-4-oxo-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid \[((1S,2R)-(\alpha-\
\hbox{cumyl})\hbox{cyclohexyloxycarbonyl})\hbox{ester}\} (80).  To a solution of 4-methoxy-5,6,7,8-
tetrahydroquinoline (1.06 g, 6.5 mmol) in 3 mL of THF and 9 mL of toluene at -50 °C was
added the chloroformate of (+)-trans-(\alpha-cumyl)-cyclohexane in 3 mL of THF and 9 mL of
toluene. The reaction was stirred for 18 h at -23 °C. The reaction was cooled to -78 °C, and
n-hexylmagnesium bromide (11 mL, 1.2 M) was added dropwise over 1.5 hours. After 12 h,
10 mL of 10% HCl was added dropwise. The organic layer was separated, and the aqueous
phase was extracted with Et\textsubscript{2}O (3 x 50 mL). The combined organic layers were washed with
water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated.
Purification via radial PLC (silica gel, 10% EtOAc/ hexanes) afforded a mixture of both
diasteriomers (2.37 g, 76%). Repurification by radial PLC (5% EtOAc/ hexanes) afforded
1.47 g (62% yield, 47% overall yield) of the major diastereomer and 0.90 g (38% yield, 29%
overall yield) of the minor diastereomer as oils. Major isomer: IR (neat) 2931, 2858, 1733,
1717, 1701, 1693, 1674, 1671, 1668, 1653, 1649, 1616, 1394, 1330, 1263, 1168, 1035, 765,
$700 \text{ cm}^{-1}$; $^1$H NMR (CHCl$_3$, 400 MHz) $\delta$ 7.33-7.26 (m, 4H), 7.11 (t, 1H $J = 7.2$ Hz), 4.83-4.77 (m, 1H), 3.22 (m, 1H), 3.15-3.06 (m, 1H), 2.44-2.33 (m, 2H), 2.26-2.19 (d of t, 1H, $J = 11.6, 3.6$ Hz), 2.17-1.85 (m, 5H), 1.78-1.46 (m, 5H), 1.46-1.07 (m, 22H), 1.01-0.99 (m, 1H), 0.91-0.88 (t, 3H, $J = 6.8$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 194.0, 152.8, 152.5, 152.0, 128.4, 125.3, 125.2, 119.5, 53.6, 50.5, 42.5, 39.8, 33.9, 31.8, 30.6, 30.6, 29.8, 29.2, 27.2, 26.3, 26.1, 24.9, 23.6, 22.9, 22.8, 21.8, 21.6, 14.0; HRMS calcd for C$_{31}$H$_{45}$NO$_3$ 480.3478, found 480.3479; $[\alpha]_{30}^D + 108$ (c 0.34, MeOH). Minor isomer: IR (neat) 2929, 2858, 1717, 1699, 1675, 1653, 1649, 1616, 1388, 1305, 1146, 761, 700 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.26-7.22 (t, 2H, $J = 7.8$ Hz), 7.14-7.10 (t, 2H, $J = 7.6$ Hz), 7.00-6.97 (t, 1H, $J = 7.0$ Hz), 4.86-4.80 (m, 1H), 4.61-4.56 (q, 1H, $J = 13.2, 6.8$ Hz), 2.73-2.67 (dd, 1H, $J = 17.2, 6$ Hz), 2.37-2.28 (m, 3H) 2.15-2.02 (m, 2H), 1.93-1.87 (m, 2H), 1.76-1.42 (m, 7H), 1.38-1.12 (m, 21H), 0.86-0.82 (t, 3H, $J = 6.8$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 194.2, 153.4, 152.2, 150.7, 128.0, 125.2, 125.0, 119.8, 55.2, 51.5, 42.2, 39.7, 33.6, 31.8, 31.3, 30.8, 29.5, 29.1, 27.1, 26.4, 26.1, 24.9, 23.3, 22.8, 22.7, 21.6, 21.4, 14.2; HRMS calcd for C$_{15}$H$_{24}$NO$_2$ [(M+H)$^+$) 480.3478, found 480.3476; $[\alpha]_{30}^D - 145$ (c 0.78, MeOH).
(2S)-2-Hexyl-2,3,5,6,7,8-hexahydro-1H-quinolin-4-one (125). In a flask was added sodium metal (31 mg, 1.4 mmol) and 2 mL of MeOH at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. In a separate flask were added hexahydroquinolone 80a (64 mg, 0.13 mmol) and the sodium methoxide/MeOH solution. The reaction was refluxed for 18 h. Upon cooling to room temperature, the solvent was removed in vacuo. To the solid residue were added 10 mL of EtOAc and 1 mL of H2O. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated via rotary evaporation. The crude product was purified by radial PLC (silica gel, 30 % EtOAc/ hexanes) to afford 23 mg (73%) of compound 125 as yellow powder, mp = 97-99 °C; IR (neat) 3273, 2926, 2855, 1575, 1559, 1538, 1406, 1245, 1157 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 4.09 (s, 1H), 3.55-3.50 (m, 1H), 2.44-2.39 (ddd, 1H, J = 15.6, 4.4, 1.2 Hz), 2.34-2.13 (m, 5H), 1.71-1.68 (m, 2H), 1.61-1.51 (m, 5H), 1.32-1.28 (m, 8H), 0.90-0.87 (t, 3H, J = 6.8 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 192.6, 159.1, 107.1, 53.3, 42.6, 35.0, 31.9, 29.4, 29.3, 25.5, 22.8, 22.7, 22.3, 21.1, 14.2; HRMS calcd for C₁₅H₂₆NO [(M+H)+] 236.2014, found 236.2014; [α]D³¹ - 198 (c 0.35, MeOH).
(2S)-2-Hexyl-4-oxo-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid tert-butyl ester (126). To a solution of hexahydroquinolone 125 (0.127 g, 0.54 mmol) in 2 mL of THF at -78 °C was added n-BuLi (0.23 mL, 2.40M) in hexanes. The reaction was slowly warmed to -23 °C and di-tert-butyl dicarbonate (0.25 mL, 1.1 mmol) was added. The reaction was warmed to room temperature, stirred for 18 h, and quenched with 1 mL of water. The organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.128 g (70%) of compound 126 as an oil. IR (neat) 2927, 2857, 1703, 1699, 1695, 1674, 1662, 1652, 1603, 1453, 1367, 1258, 1164, 1141, 1138, 765 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.30-4.59 (m, 1H), 3.07-3.00 (m, 1H), 2.84-2.79 (dd, 1H, J = 23.2, 6.4 Hz), 2.44-2.33 (m, 2H), 2.20-2.04 (m, 2H), 1.85-1.76 (m, 3H), 1.73-1.66 (m, 1H), 1.64-1.28 (m, 14H), 1.25-0.91 (m, 9H), 0.89-0.85 (t, 3H, J = 7.2 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 194.1, 151.7, 119.8, 82.2, 55.4, 42.2, 31.9, 31.3, 30.9, 29.2, 28.4, 26.3, 22.9, 22.7, 21.8, 21.8, 14.304; HRMS calcd for C₂₀H₃₄NO₃ [(M+H)⁺] 336.2539, found 336.2542; [α]³¹_D +118 (c 0.1 MeOH).

![Chemical Structures](image-url)
(2S)-4-(Dimethylphenylsilanyl)-2-hexyl-4-hydroxy-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid tert-butyl ester (127). To a mixture of lithium metal wire (33 mg, 4.7 mmol) in 1 mL of THF was added chlorodimethylphenylsilane (0.11 mL, 0.66 mmol). The reaction was stirred for 4 h. In a separate flask were added hexahydroquinolone 126 (0.105 g, 0.31 mmol) and 1 mL of Et₂O. The mixture was cooled to -78 °C and the dimethylphenylsilyl lithium was added dropwise over 15 min. After 18 h, 1 mL of a saturated solution of sodium bicarbonate was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered, and concentrated via rotary evaporation. The crude material was filtered through a silica gel plug (10% EtOAc/ hexanes) to yield 99 mg (67%) of compound 127 as a pale yellow oil. The compound was carried on to the next step as a semi-crude mixture.

![NOMe](image)

(2R)-2-Hexyl-4-oxo-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid (1R,2S,4R)-4-isopropyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester (129). To a solution of 4-methoxy-5,6,7,8-tetrahydroquinoline (1.34, 8.2 mmol) in 3.5 mL of THF and 10.5 mL of toluene at –
30 °C was added the chloroformate of \((-\)-(1R,2S,4R)-2-(1-methyl-1-phenylethyl)-4-(2-propyl)cyclohexanol (2.74 g, 8.5 mmol) in 3.5 mL of THF and 10.5 mL of toluene. After 4 h, the reaction was cooled to -78 °C and \(n\)-hexylmagnesium bromide (9 mL, 16 mmol) was added dropwise over 12 h. After stirring the reaction for 4.5 h, 10 mL of 10% aqueous HCl was added and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with \(\text{Et}_2\text{O}\) (3 x 50 mL). The organic layers were combined, washed with water (50 mL) and brine (30 mL), dried over magnesium sulfate, and filtered. The solvent was removed \textit{in vacuo}. The crude oil was purified \textit{via} column chromatography (1% \text{EtOAc/hexnaes}) to yield 2.57 g (60%) of the major diastereomer and 0.86 g (20%) of the minor diastereomer (50% d.e.) as clear oils. Major isomer: IR (neat) 2931, 2860, 1709, 1665, 1605, 1497, 1467, 1399, 1368, 1337, 1258, 1169, 1148, 1106, 1077, 1034, 989, 861, 766 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.33-7.24 (m, 4H), 7.12-7.07 (t, 1H, \(J = 6.9\) Hz), 4.79-4.73 (m, 1H), 3.14-3.06 (m, 2H), 2.43-2.24 (m, 3H), 2.16-1.67 (m, 8H), 1.47-0.85 (m, 34H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 193.9, 152.8, 152.6, 151.9, 119.4, 53.6, 50.0, 43.7, 42.5, 39.8, 33.4, 32.7, 31.7, 30.6, 30.5, 30.2, 29.1, 27.4, 26.2, 23.2, 22.9, 22.8, 21.8, 21.6, 20.3, 19.7, 14.3; HRMS calcd for C\(_{34}\)H\(_{52}\)NO\(_3\) [(M+H)]\(^+\) 522.3947, found 522.3950; \([\alpha]\)\(^{31}\)D - 102 (c 1.79, MeOH). Minor isomer: IR (neat) 2930, 2859, 1696, 1665, 1605, 1386, 1325, 1303, 1168, 1146, 1029, 761, 732 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.26-7.21 (t, 2H, \(J = 7.5, 6\) Hz), 7.14-7.09 (t, 2H, \(J = 7.5\) Hz), 7.00-6.95 (t, 1H, \(J = 6.9\) Hz), 4.84-4.76 (dt, 1H, \(J = 10.8, 4.5\) Hz), 4.60-4.54 (q, 1H, \(J = 6.6\) Hz), 2.73-2.65 (dd, 1H, \(J = 17.4, 6.0\) Hz), 2.38-2.27 (m ,3H), 2.20-1.84 (m, 4H), 1.76-1.60 (m, 4H), 1.50-0.98 (m, 24H), 0.94-0.82 (m, 10H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 194.1, 153.5, 152.2,
150.7, 128.0, 125.2, 125.0, 119.8, 55.2, 52.1, 43.7, 42.1, 39.7, 33.2, 32.7, 31.8, 31.3, 30.8, 30.5, 29.8, 29.1, 27.3, 26.3, 23.0, 22.7, 22.7, 21.6, 21.5, 20.4, 19.7, 14.2; HRMS calcd for C_{34}H_{52}NO_3 [(M+H)^+] 522.3947, found 522.3947; [α]_{D}^{31} + 99 (c 1.25, MeOH)

(2R)-2-Hexyl-2,3,5,6,7,8-hexahydro-1H-quinolin-4-one (130). In a flask were added sodium metal (0.26 g, 11 mmol) and 2 mL of MeOH at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. In a separate flask were added hexahydroquinolone 129 (0.60 g, 1.2 mmol) and the sodium methoxide/MeOH solution. The reaction was refluxed for 18 h. Upon cooling to room temperature, the solvent was removed in vacuo. To the solid residue were added 20 mL of EtOAc and 5 mL of H_2O. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed via rotary evaporation. The crude material was purified by radial PLC (silica gel, 30 % EtOAc/hexanes) to afford 0.226 g (63%) of compound 130 as an orange solid. IR (neat) 2925, 2848, 1651, 1608, 1557, 1524, 1413, 1242, 1147 cm^{-1}; ^1H NMR (CDCl_3, 400 MHz) δ 4.12 (s, 1H), 3.56-3.50 (m, 1H), 2.45-2.13 (m, 6H), 1.70-1.54 (m, 7H), 1.30 (brs, 8H), 0.86 (s, 3H); ^13C
NMR (CDCl₃, 100 MHz) δ 192.5, 159.0, 107.1, 53.3, 42.6, 35.0, 31.9, 29.3, 25.5, 22.8, 22.7, 22.3, 21.1, 14.2; [α]³₁⁰ + 208 (c 0.12, MeOH).

(2R)-2-Hexyl-4-oxo-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid benzyl ester (131). To a solution of hexahydroquinolone 130 (0.16 g, 0.67 mmol) in 2.2 mL of THF at -23 °C was added n-BuLi (0.32 mL, 2.13M) in hexanes. After 1 h, the reaction was cooled to -78 °C and benzyl chloroformate (0.13 mL, 0.91 mmol) was added. The reaction was stirred for 18 h and warmed to room temperature. After cooling to -78 °C, the reaction was quenched with 1 mL of saturated sodium bicarbonate and warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by radial PLC (10% EtOAc/ hexanes) to afford 0.239 g (96%) of compound 131 as a yellow oil. IR (neat) 2930, 2858, 1716, 1667, 1605, 1498, 1455, 1394, 1258, 1169, 1142, 1105, 1035, 976, 762 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.37 (bs, 5H), 5.21 (s, 2H), 4.75-4.68 (m, 1H), 3.10-3.05 (m, 1H), 2.85-2.77 (dd, 1H, J = 16.8, 5.7 Hz), 2.44-2.33 (m, 2H), 2.21-2.12 (m, 2H), 1.82-1.65 (m, 3H), 1.55-1.34 (m, 3H), 1.22 (bs, 8H), 0.88-0.83 (t, 3H, J = 6 Hz); ¹³C NMR
(CDCl₃, 75 MHz) δ 193.8, 153.9, 151.2, 135.8, 128.8, 128.7, 128.6, 128.4, 120.7, 111.7, 68.3, 55.7, 42.2, 31.8, 30.9, 30.8, 29.1, 26.5, 22.8, 22.7, 21.8, 21.7, 14.2; HRMS calcd for C₂₃H₃₁NO₃ [(M+H)⁺] 370.2382, found 370.2388; [α]₃¹D + 150 (c 0.42, MeOH).

(2R)-4-(Dimethylphenylsilanyl)-2-hexyl-4-hydroxy-3,4,5,6,7,8-hexahydro-2H-quinoline-1-carboxylic acid benzyl ester (132). To a solution of lithium metal wire (9.1 mg, 1.3 mmol,) in 1.0 mL of THF was added chlorodimethylphenylsilane (0.05 mL, 0.30 mmol). The reaction was stirred at rt for 3.5 hours. In a separate flask were added hexahydroquinolone 131 (57 mg, 0.34 mmol) and 1.0 mL of Et₂O. The reaction was cooled to -78 °C and the silyllithium reagent was added dropwise over 30 minutes. After the reaction was stirred for 18 h, 1 mL of saturated sodium bicarbonate was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.049 g (63%) of compound 132 as a clear oil. IR (neat) 3462, 3065, 2926, 2855, 1703, 1651, 1427, 1403, 1311, 1249, 1112, 1026, 833, 736 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ
7.53-7.51 (d, 2H, J = 7.2 Hz), 7.35 (bs, 8H), 5.16-5.06 (q, 2H, J = 17.1, 12.6 Hz), 4.18-4.14 (m, 1H), 2.91-2.87 (m, 1H), 2.34-2.26 (dd, 1H, J = 14.1, 6.9 Hz), 2.19-2.13 (m, 1H), 1.80-1.46 (m, 9H), 1.35-1.23 (m, 11H), 0.87-0.83 (t, 3H, J = 6 Hz), 0.27 (d, 6H, J = 1.5 Hz); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 154.5, 136.9, 136.7, 134.6, 129.6, 128.6, 128.3, 128.2, 128.1, 129.0, 111.6, 67.2, 66.7, 50.6, 42.7, 33.7, 31.9, 29.6, 29.3, 26.6, 25.3, 23.4, 23.0, 22.7, 14.2, -4.74, -5.23; \([\alpha]^{31}_D + 41\) (c 0.15 MeOH).

(2R,8aS)-8a-allyl-4-(dimethylphenylsilanyl)-2-hexyl-3,5,6,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid benzyl ester. To a solution of alcohol 132 (47 mg, 0.09 mmol) in 0.75 mL of CH\(_2\)Cl\(_2\) at -78 °C was added allyltributyltin (0.14 mL, 0.47 mmol) followed by BF\(_3\)·OEt\(_2\) (0.017 mL in 0.25 mL of CH\(_2\)Cl\(_2\), 0.14 mmol). After 30 min, 1 mL of saturated sodium bicarbonate was added. The organic layer was separated, and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 23 mg (47%) of compound 133 as a clear oil. IR (neat) 2956, 2928, 2853, 1703, 1699, 1694, 1651, 1615, 1453, 1391, 1260, 1108, 1022, 807 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.50 (m, 2H), 7.34 (bs, 8H), 5.67-5.55 (m,
1H), 5.11 (bs, 2H), 4.96-4.93 (d, 2H, $J = 10.8$ Hz), 4.33 (bs, 1H), 3.55 (bs, 1H), 2.87 (bs, 1H), 2.56-2.41 (m, 2H), 2.23-2.05 (m, 3H), 1.56-1.44 (m, 7H), 1.21 (bs, 10H), 0.88-0.84 (t, 3H, $J = 6$ Hz), 0.35-0.34 (d, 6H, $J = 4.8$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 139.9, 134.6, 133.7, 133.6, 129.0, 128.6, 127.9, 116.9, 66.4, 62.9, 50.9, 37.5, 36.4, 33.9, 33.2, 32.0, 31.3, 29.5, 27.2, 27.1, 23.1, 22.8, 14.3, 0.23, -0.68, -0.80; HRMS calcd for C$_{34}$H$_{47}$NO$_2$Si [(M+H)$^+$] 530.3454, found 530.3458; $[\alpha]_{D}^{31}$ + 77 (c 0.39, MeOH)

![Chemical Structure](image)

(2R,8a$S$)-8a-But-3-enyl-4-(dimethylphenylsilyl)-2-hexyl-3,5,6,7,8,8a-hexahydro-2$H$-quinoline-1-carboxylic acid benzyl ester (135). To a solution of vinylsilane 133 (0.019 g, 0.4 mmol) in 1 mL of CH$_2$Cl$_2$ was added the biscarbonate 122 (0.02 g, 0.98 mmol) and Grubb’s second generation catalyst$^{40}$ (0.9 mg, 0.001 mmol). The mixture was refluxed for 18 h. After cooling to room temperature, triphenylphosphine (1.9 mg, 0.007 mmol) was added and the reaction was stirred for 15 min. Then Pd$_3$(dba)$_2$·HCCl$_3$ (2 mg, 0.002 mmol,) and ammonium formate (6.2 mg, 0.1 mmol) were added. The reaction was refluxed for 18 h. After cooling to room temperature, the reaction was filtered and concentrated in vacuo. The crude material was purified by radial PLC (silica gel, 10% EtOAc/ hexanes) to afford 0.011 g (56%) of compound 135 as an oil. IR (neat) 2929, 2855, 1695, 1612, 1453, 1393, 1344,
1288, 1110, 1024, 811, 770 cm⁻¹; \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.40 (br s, 2H), 7.34 (br s, 8H), 5.80-5.70 (m, 1H), 5.10-5.06 (m, 2H), 4.97-4.88 (m, 2H), 4.34 (br s, 1H), 2.84 (br s, 1H), 2.43-3.39 (m, 1H), 2.21-1.77 (m, 4H), 1.60-1.52 (m, 6H), 1.21 (br s, 9H), 0.89-0.85 (t, 3H, \(J = 5.1\) Hz), 0.36 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 139.9, 139.4, 134.6, 133.8, 129.0, 128.6, 128.0, 114.3, 100.0, 63.2, 62.9, 51.1, 33.8, 33.3, 32.0, 31.4, 29.5, 28.5, 27.3, 27.2, 23.1, 23.0, 22.8, 19.0, 18.4, 14.3, -0.70, -0.82; HRMS calcd for C\(_{35}\)H\(_{50}\)NO\(_2\)Si [(M+H)\(^+\)] 544.3611, found 544.3697; \(\alpha\)\(^{29}\)D + 21 (c 0.35, MeOH).
References


51. Ishi, T. Yakugaku Zasshi 1952, 72, 1317


53. Compound is commercially available from Tyger Scientific Inc. 324 Stokes Avenue, Ewing, NJ 08638 USA.

21
75 MHz
62
100 MHz
82
400 MHz
82
100 MHz
83
300 MHz
83
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87
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90 MHz
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**Spectrum Details**

- **Sample**: 129b
- **Field**: 300 MHz

**Spectrum Image**

The image shows a spectroscopic spectrum with various peaks and labels indicating chemical shifts and signal intensities.
130
400 MHz
130
100 MHz
133
75 MHz