ABSTRACT

ENAMORADO GOMEZ, MONICA FELISA. Concise Total Syntheses of (S)-Macrostromine and Cermizine D. (Under the direction of Dr. Daniel Lee Comins).

The Comins research group has dedicated its efforts to the development of methodologies in order to synthesize a large number of alkaloids with a wide array of biological activities. The two main areas of research have been the directed metalation of nitrogen heterocycles, and the development of chiral N-acylpyridinium salts capable of providing addition products with high diastereoselectivity. In this work, we have employed both lines of methodology in order to complete the total syntheses of the natural products (S)-macrostromine and cermizine D. Directed metalation methodologies were utilized in the total synthesis of (S)-macrostromine, accomplished in five steps from natural nicotine in 19% overall yield. Key steps include a Diels-Alder cycloaddition reaction, and a Kumada cross-coupling reaction to furnish the natural product. This work constitutes the shortest synthesis of this natural product published to date, and further demonstrates the value of (S)-nicotine as a chiral building block. The total synthesis of (±)-cermizine D was achieved using a dihydropyridone-based functionalization strategy. The synthesis is concise in six steps from 4-methoxypyridine in 14% overall yield. A key step in the synthesis is an enantioselective copper-mediated 1,4-addition to a bicyclic 2,3-dihydro-4-pyridone. This is the shortest route toward the natural product published to date, and this work restates the utility and versatility of N-acylpyridinium salt chemistry in the concise synthesis of complex molecules.
Concise Total Syntheses of (S)-Macrostomine and Cermizine D

by

Monica Felisa Enamorado Gomez

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, North Carolina

2013

APPROVED BY:

___________________________ _______________________ ___
Dr. Christian Melander  Dr. Reza Ghiladi

___________________________ ___________________________
Dr. Harold Freeman  Dr. Daniel L. Comins
Chair of the Advisory Committee
DEDICATION

This work is dedicated to my beloved husband Julio Romero Agüero for being the continuous source of my inspiration and filling my life with happiness. To my parents Elizabeth Gomez Fuentes and German Enamorado Suazo for all of their unconditional love and support. And, to my sister Ana Enamorado Gomez for igniting in me the duty of setting a good example.
BIOGRAPHY

The author, Monica Felisa Enamorado Gomez, was born in Tegucigalpa, Honduras, to Mrs. Elizabeth Gomez Fuentes and Mr. German Enamorado Suazo. Monica received her B.Sc. in Chemistry and Pharmacy from the National University of Honduras. In 2003, she was one of the four students awarded with a full scholarship by the Organization of American States (OAS), in her case, for pursuing M.Sc. studies in Environmental Technologies at the Institute of Biotechnology at the National University of San Juan, Argentina. Monica conducted her research under the supervision of Dr. Gabriela E. Feresin, and the objective of her M.Sc. thesis was the screening of biological activities of filamentous fungi extracts for their application as natural pesticides. Because of her outstanding performance in the M.Sc. program, she graduated with honors and was the first student in achieving the highest mark in the M.Sc. dissertation. In 2008, she started her Ph.D. dissertation under the supervision of Dr. Daniel L. Comins at North Carolina State University. The main focus of her research was the total synthesis of natural products and other complex molecules of recognized biological activity. Because of the accomplishments in her research, in 2011 she was awarded with a BASF Graduate Fellowship. Her service as a teaching assistant led to the Sara and Chloe Novak Award for Excellence in Teaching (2011), and the NCSU-UGSA Outstanding Graduate Teaching Assistant Award (nominee 2012, awardee 2013). Upon completion of her Ph.D. in synthetic organic chemistry, she joined BASF, through their Professional Development Program, to work as a scientist in the area of polyolefin catalysts.
First, I thank God for all of His blessings, and I consider this work as one of them. To my family: my husband, my parents, my sister, my nephew, my grandparents, uncles, aunts, cousins, and to the ones to come, this is also for you. To all my teachers at Modelo High School for contributing to the first steps of my education, specially Ana Marina Irias and Fredy Ivan Duarte. To all my professors in college during my B.Sc. at National University of Honduras, specially Dr. Edgardo Yescas and Dr. Marta Liliana Rodriguez for their support and advice. To all my professors during my M.Sc. in the National University of San Juan, Argentina, specially to Dr. Gabriela Egly Feresin and M.Sc. Silvia Gouiric for the skills and training that they provided me. To all my professors at North Carolina State University. To my advisor, Dr. Daniel L. Comins for his endless advice and encouragement, and all the knowledge and experience that he has shared with me. To his assistant, Ms. Debbie Sloan for her warmth and kindness, and to all the previous members of the Comins research group, specially Dr. Ibrahim Bori, Dr. Pauline Ondachi, Dr. Sonja Capracotta, Dr. Brandon Cash and Dr. Sergey Tsukanov, all of them have set a model for me to follow. To all other research groups in the Department of Chemistry, for sharing chemicals and other supplies, specially to those under the supervision of Dr. Jonathan Lindsey, Dr. Christian Melander, Dr. Reza Ghiladi, Dr. Alex Deiters, Dr. Joshua Pierce, and Dr. Elon Ison. To all my teaching advisors, specially Dr. Maria Gallardo-Williams, Dr. Phil Brown and Dr. Ana Ison for their guidance. To the staff at NCSU-Chemistry, specially Dr. Sabapathy Sankar, for his help with my NMR experiments, Maria Moreno, Brenda Burgess and Ann Norcross for making the
logistics of the program easy to follow. To Alan Harvell and Leonard Page for their help in the maintenance of the laboratory and the equipment. To all my fellow graduate students, specially to my class for the companionship through this journey. To all my students and mentees, for all the teaching experience that I have gained through them. To the Graduate School at NCSU, specially to Dr. David Shafer for presenting me all the financial opportunities to complete my degree. For the continuous support from BASF, Targacept, Syngenta and Dupont. And finally, to the members of my advisory committee, Dr. Christian Melander, Dr. Reza Ghiladi and Dr. Harold Freeman for their contributions to this work.
TABLE OF CONTENTS

LIST OF TABLES .................................................................................................................. ix

LIST OF FIGURES ................................................................................................................. xi

LIST OF SCHEMES ............................................................................................................. xiii

LIST OF ABBREVIATIONS, SYMBOLS AND TERMS .................................................. xviii

I. Introduction ....................................................................................................................... 1

I.1. Overview of (S)-Nicotine .......................................................................................... 2

I.1.a. Biological relevance .............................................................................................. 2

I.1.b. Synthetic background ........................................................................................... 8

I.2. Overview of N-Acylpyridinium Salt Chemistry ....................................................... 16

I.2.a. Biological relevance of six-membered ring nitrogen heterocycles ....................... 16

I.2.b. Synthetic significance of N-acylpyridinium salt chemistry .................................. 18

I.2.c. Total syntheses based on N-acylpyridinium salt chemistry .................................. 20

II. Total Synthesis of (S)-Macrostomine ......................................................................... 23

II.1. Introduction ............................................................................................................... 24

II.1.a. Abstract ................................................................................................................... 24
II.1.b. Isolation and pharmacological potential of (S)-macrostomine. ......................... 24
II.1.c. Syntheses of (±)-macrostomine. ........................................................................ 25
II.1.d. Wiegrebe’s enantioselective synthesis of (S)-macrostomine. ......................... 31

II.2. Synthesis of (S)-Macrostomine from (S)-Nicotine ............................................ 34

II.2.a. Retrosynthetic plan. ....................................................................................... 34
II.2.b. Diels-Alder reaction. ..................................................................................... 34
II.2.c. Aromatization of the Diels-Alder adducts. .................................................... 45
II.2.d. Metal-catalyzed C-C bond formation. ............................................................ 48
II.2.e. Summary of the total synthesis. ..................................................................... 57
II.2.f. Conclusion. .................................................................................................... 58

II.3. Synthesis of C-4 Derivatives of (S)-6-Chloronicotine ....................................... 59

II.3.a. Synthesis of C-4 amido derivatives of (S)-6-chloronicotine ......................... 59
II.3.b. Pyrrolidine ring of (S)-6-chloronicotine as a chiral transfer group ............... 64

III. Total Synthesis of Cermizine D ........................................................................ 74

III.1. Introduction .................................................................................................... 75

III.1.a. Abstract ....................................................................................................... 75
III.1.b. Isolation and pharmacological potential of cermizine D. .............................. 75
III.1.c. Syntheses of (+)-cermizine D. ..................................................................... 76
III.2. Synthesis of Cermizine D via N-Acylpyridinium Salt Chemistry .......... 83

III.2.a. First generation approach - retrosynthetic plan. ................................. 83
III.2.b. Second generation approach - retrosynthetic plan............................... 91
III.2.c. Summary of the total synthesis. .......................................................... 111
III.2.d. Conclusion. ......................................................................................... 111
III.2.e. Asymmetric plan for the synthesis of (-)-cermizine D ......................... 113

CONCLUSION ......................................................................................................... 114

EXPERIMENTAL ................................................................................................. 115

REFERENCES ..................................................................................................... 143

APPENDICES ...................................................................................................... 161
**LIST OF TABLES**

**Table II-1.** Attempts at the Aromatization of 114 \textit{via} Hydride. .............................................. 46

**Table II-2.** Study of Nickel and Palladium Catalysts for Kumada Cross-Coupling .......... 50

**Table II-3.** Study of Cobalt and Iron Catalysts ................................................................. 51

**Table II-4.** Study of Ni(acac)$_2$ in Combination with PO-Ligands. ........................................ 54

**Table II-5.** Selected Results for the Model Cross-Coupling Reaction. ................................. 55

**Table II-6.** Selected Results for the Ligand-Free Cross-Coupling Reaction ........ 56

**Table II-7.** C-4 Amidation of (S)-6-Chloronicotine (34) \textit{via} 147 ........................................ 63

**Table II-8.** Selected Attempts at the Preparation of $\alpha$-Ketoester 158 .......................... 66

**Table II-9.** Attempts at the Alkylation of 135 using a Grignard Reagent ......................... 67

**Table II-10.** Attempts at the Alkylation of 158 using an Alkylzinc Reagent ..................... 68

**Table II-11.** Attempts at the Alkylation of 158 using a Trialkylzinc Reagent .................. 69

**Table III-1.** Selective Reduction of Nitrile 225 .................................................................. 90

**Table III-2.** Initial Attempts to the Preparation of Triflate 236a ......................................... 94

**Table III-3.** Preparation of Triflate 236a using an Organotin Reagent .............................. 96
Table III-4. Preparation of 239a using a Pre-formed Iminium Salt of 214. .......................... 100

Table III-5. Preparation of Ketone 239a with *in situ* Activation of Enone 214. ................. 102

Table III-6. Optimization of Conditions for the Wittig Olefination of 239a. ...................... 106

Table III-7. Selected Examples at the Reduction of the Acyclic Double Bond in 238 ....... 108

Table III-8. Model Reduction of the Pyridine Ring in 243b. ............................................. 109

Table III-9. Reduction of the Pyridine Ring in 243a.......................................................... 110
LIST OF FIGURES

Figure I-1. Major alkaloids present in tobacco plants. ................................................................. 2

Figure I-2. Conformation of (S)-nicotine in solution. ................................................................. 4

Figure I-3. Functional similarities of (S)-nicotine and acetylcholine. ................................. 4

Figure I-4. Selected examples of neurotransmitters modulated by nAChRs. ...................... 6

Figure I-5. Selected examples of agonists of neuronal nAChRs. ............................................ 7

Figure I-6. Selected examples of nicotinoids........................................................................... 8

Figure I-7. Structure of (S)-macrostomine (44). ................................................................. 15

Figure I-8. Pyridine ring-containing pharmaceuticals. ......................................................... 16

Figure I-9. Piperidine ring-containing pharmaceuticals. ..................................................... 17

Figure I-10. Selected examples of new drugs approved by the FDA in 2012. .................... 18

Figure I-11. Mechanism of asymmetric induction............................................................... 19

Figure I-12. Synthetic versatility of dihydropyridones 61..................................................... 20

Figure I-13. Dihydropyridones 59 as building blocks in total synthesis. ......................... 21

Figure I-14. Structure of cermizine D (68). ........................................................................ 22
Figure II-1. Structure of (S)-macrostomine (44) and related compounds. ......................... 25

Figure II-2. Stabilization of a C-4 lithiated nicotine intermediate (38a). ....................... 36

Figure II-3. Potential pyridyne precursors: Ortho-(trimethylsilyl) triflate derivatives. .... 38

Figure II-4. Structures of the PO-ligands under study.................................................. 53

Figure II-5. Stabilization of protonated 34 by an EDG at C-4. ........................................ 59

Figure II-6. Selected examples of ligands used in copper-mediated amidation reactions. ... 61

Figure II-7. Lactams used in the C-4 amidation of 147................................................. 62

Figure II-8. C-4 amido derivatives of 147....................................................................... 62

Figure III-1. Structure of cermizines A-D..................................................................... 76

Figure III-2. Dihydrodeoxyepiallocernuine (175) and diastereomers of cermizine D.... 76

Figure III-3. Absolute configuration of natural cermizine D (68). ................................. 82

Figure III-4. Undesired silyl enol ethers 240a and 240b. .............................................. 103

Figure III-5. Undesired double bond migration products.......................................... 107
LIST OF SCHEMES

Scheme I-1. First Enantioselective Synthesis of (S)-Nicotine (1) ............................................. 9

Scheme I-2. Six-Step Synthesis of SIB-1508Y (14) .............................................................. 12

Scheme I-3. Five-Step Synthesis of SIB-1508Y (14) ............................................................ 13

Scheme I-4. Six-Step Synthesis of (S)-Brevicolline (43) ...................................................... 14

Scheme I-5. Preparation of N-Acyl-2,3-dihydro-4-pyridones (59) ...................................... 19

Scheme II-1. General Approach for the Synthesis of (S)-Macrostomine (44) ....................... 24

Scheme II-2. Seebach’s Nitrosamine Route towards (±)-Macrostomine. ......................... 27

Scheme II-3. Wiegrebe’s Synthesis of (±)-Macrostomine ................................................... 29

Scheme II-4. Kapil and Sharma’s Synthesis of (±)-Macrostomine, (±)-44. ....................... 31

Scheme II-5. Wiegrebe’s Enantioselective Synthesis of (S)-Macrostomine (44) ............... 33

Scheme II-6. General Retrosynthetic Plan towards (S)-Macrostomine (44) ...................... 34

Scheme II-7. Attempts for the Diels-Alder Reaction using 5,6-Dichloronicotine (38) ....... 36

Scheme II-8. Attempt at the Diels-Alder Reaction using a Fluoride-Induced Elimination .. 37

Scheme II-9. Model Diels-Alder Reaction using Trihalonicotines and Furan .................... 39
Scheme II-10. Attempts at the Diels-Alder Reaction using Trihalonicotines................. 40

Scheme II-11. Preparation of 3,4-Dimethoxyfuran (122)................................................ 41

Scheme II-12. Diels-Alder reaction using 3,4-Dimethoxyfuran and a Trihalonicotine........ 41

Scheme II-13. Study of 4-Bromo-6-chloronicotine (124) as Pyridyne Precursor. ............. 42

Scheme II-14. Deuteration Study of 4,6-Dichloronicotine (128) as Pyridyne Precursor. ..... 43

Scheme II-15. Model Diels-Alder using 4,6-Dichloronicotine (128) and Furan (113). ....... 44

Scheme II-16. Diels-Alder Reaction using 3,4-Dimethoxyfuran (122).............................. 44

Scheme II-17. Model Study for Aromatization of 114 using Zn/TiCl₄. ............................... 47

Scheme II-18. Model Study for Aromatization of 114 using Mg/TiCl₄. ............................. 47

Scheme II-19. Aromatization of the Diels-Alder Adduct 123....................................... 48

Scheme II-20. Preparation of the Grignard Reagent 134........................................... 49

Scheme II-21. Attempts at the Kumada Cross-Coupling using MnCl₂ as Catalyst.......... 52

Scheme II-22. Preparation of PO-Ligand 136............................................................... 53

Scheme II-23. Synthesis of (S)-Normethoxy-Macrostomine (140)................................. 57

Scheme II-24. Five-Step Synthesis of (S)-Macrostomine (44)....................................... 58
Scheme II-25. Preparation of 6-Chloro-4-iodonicotine (147). .............................................. 61

Scheme II-26. Attempts at the C-4 Imidation of 147....................................................... 64

Scheme II-27. Plan for the Synthesis of α-Ketoester 158.................................................. 64

Scheme II-28. Preparation of Thioester 159. ....................................................................... 65

Scheme II-29. Attempts at the Alkylation of 158 via a Cerium Reagent. ......................... 71

Scheme II-30. C-4 Substitution of 34 via a Cerium Reagent........................................... 71

Scheme II-31. Protection of Alcohol 162a. ........................................................................... 72

Scheme II-32. Cyanogen bromide-Induced Ring Opening of 164. ...................................... 72

Scheme II-33. Desylilation of 166. ...................................................................................... 73

Scheme III-1. General Plan for the Synthesis of Cermizine D (68). ................................. 75

Scheme III-2. Takayama’s Synthesis of (+)-Cermizine D. .................................................. 78

Scheme III-3. Carter’s 16-Step Approach toward the Synthesis of (+)-Cermizine D........... 80

Scheme III-4. Carter’s 10-Step Approach toward the Synthesis of (+)-Cermizine D......... 81

Scheme III-5. First Generation Approach - Retrosynthetic Plan........................................ 83

Scheme III-6. N-Acylpyridinium Salt Sequence to Prepare Dihydropyridone 214. ........... 84
Scheme III-7. Attempts at the Zinc-Mediated Alkynylation of 214. ........................................ 85

Scheme III-8. Improved Zinc-Mediated Alkynylation of 214. ............................................. 86

Scheme III-9. Strategy toward Silyl Enol Ether 221. .......................................................... 86

Scheme III-10. Attempts to Prepare Silyl Enol Ether 221. .................................................. 87

Scheme III-11. Attempts at the Addition of Silyl Enol Ether 222. ....................................... 87

Scheme III-12. Installation of C-16 in 218 via Cross-Coupling. ........................................ 88

Scheme III-13. Attempts at the Intramolecular Hydroamination of 226. ............................ 91


Scheme III-15. Plan for the Conjugate Addition toward 231. ............................................ 92

Scheme III-16. Attempts at the Preparation of 2-Methyl-1,2-dehydropiperidine (230). ....... 93

Scheme III-17. Preparation of 2-((Tributylstannyl)methyl)pyridine (235c). ....................... 95

Scheme III-18. Retrosynthesis of Cermizine D via Wittig Olefination. ............................... 98

Scheme III-19. Attempts at the 1,4-Addition to Form Ketone 239a. ............................... 99

Scheme III-20. Preparation of 2-((Trimethylsilyl)methyl)pyridine (241). ......................... 104

Scheme III-21. Conjugate Addition using 2-((Trimethylsilyl)methyl)pyridine (241). ....... 105
Scheme III-22. Six-Step Synthesis of Cermizine D (68) .................................................... 112

Scheme III-23. Asymmetric Plan for the Synthesis of (-)-Cermizine D. ............................ 113
**LIST OF ABBREVIATIONS, SYMBOLS AND TERMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>[α]</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom(s)</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AChR</td>
<td>acetylcholine receptors</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>Al₂O₃</td>
<td>aluminum oxide</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>biph</td>
<td>biphenyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>butyllithium</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>tert-butyllithium</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>potassium tert-butoxide</td>
</tr>
<tr>
<td>BF₃•OEt₂</td>
<td>borontrifluoride diethyl etherate</td>
</tr>
</tbody>
</table>
Bu$_4$NHSO$_4$  tetrabutylammonium sulfate

c  concentration in g per 100 mL

C$_6$D$_6$  hexadeuterobenzene

C-C  carbon-carbon bond

C-O  carbon-oxygen bond

C-N  carbon-nitrogen bond

Ca$^{2+}$  calcium(II)

s-cis  cis in reference to a sigma bond

°C  degree(s) Celsius

calcd  calculated

cat.  catalyst or catalytic amount

Ce  cerium

CHCl$_3$  chloroform

CDCl$_3$  deuterated chloroform

CH$_3$CN  acetonitrile

CF$_3$  trifluoromethyl

cm$^{-1}$  unit of wavenumber

COD  cyclooctadiene
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>conc</td>
<td>concentrated</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>Cp₂TiMe₂</td>
<td>bis(η⁵-cyclopentadienyl)dimethyltitanium</td>
</tr>
<tr>
<td>CsF</td>
<td>cesium fluoride</td>
</tr>
<tr>
<td>Cu</td>
<td>copper</td>
</tr>
<tr>
<td>CuBr•Sme₂</td>
<td>copper(I) bromide methyl sulfide complex</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>day(s)</td>
</tr>
<tr>
<td>D₂O</td>
<td>deuterium oxide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>dl</td>
<td>racemic mixture</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DCM or CH₂Cl₂</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>ddd</td>
<td>doublet of doublet of doublets</td>
</tr>
<tr>
<td>decomp</td>
<td>decomposition</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Diop</td>
<td>(4S,5S)-4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane</td>
</tr>
<tr>
<td>DMAE</td>
<td>2-(dimethylamino)ethanol</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethyaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppf</td>
<td>1,3-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets</td>
</tr>
<tr>
<td>EDG</td>
<td>electron donating group</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric enrichment</td>
</tr>
<tr>
<td>epi</td>
<td>epimer</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>etac</td>
<td>ethylacetoacetate</td>
</tr>
<tr>
<td>et al.</td>
<td>and collaborators</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>FDA</td>
<td>food and drug administration</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GABA</td>
<td>$\gamma$-aminobutyric acid</td>
</tr>
<tr>
<td>Glu</td>
<td>glutamate</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>$H^+$</td>
<td>proton or protic acid</td>
</tr>
<tr>
<td>H</td>
<td>hydrogen</td>
</tr>
<tr>
<td>HBr</td>
<td>hydrobromic acid</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid</td>
</tr>
<tr>
<td>HCOOH</td>
<td>formic acid</td>
</tr>
<tr>
<td>HIV-1</td>
<td>human immunodeficiency virus type I</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyl disilazane</td>
</tr>
<tr>
<td>$^1$H NMR</td>
<td>proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectral analysis</td>
</tr>
<tr>
<td>5-HT</td>
<td>serotonin</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IC$_{50}$</td>
<td>concentration required to obtain 50% effect</td>
</tr>
</tbody>
</table>
in situ  in the reaction mixture

in vacuo  in a vacuum

i-Pr  isopropyl

i-PrO₂  diisopropyl ether

J  coupling constant

K⁺  potassium ion

KCN  potassium cyanide

K₂CO₃  potassium carbonate

K₃PO₄  potassium phosphate

L1210  lymphocytic leukemia cells

LAH or LiAlH₄  lithium aluminum hydride

LDA  lithium diisopropylamine

Li  lithium

LiBH₄  lithium borohydride

lit.  literature

LiTMP  lithium tetramethyl piperidine

LiDMAE  lithium dimethylaminoethoxide

M  number of moles per liter
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>[M+H]^+</td>
<td>sample ionized by protonation</td>
</tr>
<tr>
<td>µg</td>
<td>microgram</td>
</tr>
<tr>
<td>µM</td>
<td>micromolar</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mAChR</td>
<td>muscarinic acetylcholine receptor</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeLi</td>
<td>methyllithium</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>Mg</td>
<td>magnesium</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>mmol</td>
<td>millimolar</td>
</tr>
<tr>
<td>Mn</td>
<td>manganese</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter(s)</td>
</tr>
<tr>
<td>µL</td>
<td>microliter(s)</td>
</tr>
<tr>
<td>MnCl₂•2LiCl</td>
<td>manganese(II) chloride bis(lithium chloride) complex</td>
</tr>
<tr>
<td>mol%</td>
<td>molar percentage</td>
</tr>
<tr>
<td>Symbol</td>
<td>Name</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>Na</td>
<td>sodium</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>sodium borohydride</td>
</tr>
<tr>
<td>nAChR</td>
<td>nicotinic acetylcholine receptor</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>sodium bicarbonate</td>
</tr>
<tr>
<td>NaNO₂</td>
<td>sodium nitrite</td>
</tr>
<tr>
<td>NaOCl</td>
<td>sodium hypochlorite</td>
</tr>
<tr>
<td>NaOME</td>
<td>sodium methoxide</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>NH₄F</td>
<td>ammonium fluoride</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>ammonium chloride</td>
</tr>
<tr>
<td>Ni</td>
<td>nickel</td>
</tr>
<tr>
<td>NMP</td>
<td>1-methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>i-OPr</td>
<td>isopropoxide</td>
</tr>
<tr>
<td>OH⁻</td>
<td>hydroxide</td>
</tr>
<tr>
<td>Otf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>PCy</td>
<td>cyclohexylphosphine</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>Pd/BaSO₄</td>
<td>palladium on barium sulfate</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhOCOCl</td>
<td>phenyl chloroformate</td>
</tr>
<tr>
<td>PhSCH₂I</td>
<td>iodomethyl phenyl sulfide</td>
</tr>
<tr>
<td>Ph₂SiH₂</td>
<td>diphenylsilane</td>
</tr>
<tr>
<td>pH</td>
<td>negative logarithm of the molar concentration of dissolved hydrogen(I) ions</td>
</tr>
<tr>
<td>pKa</td>
<td>negative logarithm of the acid dissociation constant</td>
</tr>
<tr>
<td>PNS</td>
<td>peripheral nervous system</td>
</tr>
<tr>
<td>PO</td>
<td>hydroxyphosphine</td>
</tr>
<tr>
<td>POCl₃</td>
<td>phosphorus oxychloride</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>i-PrMgCl•LiCl</td>
<td>isopropylmagnesium chloride lithium chloride complex</td>
</tr>
<tr>
<td>i-Pr₂S</td>
<td>isopropyl sulfide</td>
</tr>
<tr>
<td>Pt/C</td>
<td>platinum on carbon</td>
</tr>
<tr>
<td>PtO₂</td>
<td>platinum(IV) oxide</td>
</tr>
</tbody>
</table>
q    quartet
qd   quartet of doublets
R    substituent
Radial PLC or RPLC radial preparative layer chromatography
Raney-Ni raney nickel
RCM   ring closing metathesis
rt   room temperature
s    singlet
S₈    elemental sulfur
SIB-1508Y altinicline
SiO₂   silicon dioxide
sm (or SM) starting material
Sn    tin
t    triplet
s-trans trans in reference to a sigma bond
t-amyl alcohol 2-methyl-2-butanol
TBAF    tetrabutyl ammonium fluoride
TBAT   tetrabutyl ammonium triphenylsilyl difluorosilicate
td  triplet of doublets

TEA or NEt₃  triethylamine

TESiH  triethylsilane

Tf₂O  trifluoromethanesulfonic (or triflic) anhydride

TFA  trifluoroacetic acid

TFAA  trifluoroacetic anhydride

THF  tetrahydrofuran

TiCl₄  titanium tetrachloride

TIPS  triisopropylsilyl

TIPSOTf  triisopropyl triflate

TLC  thin layer chromatography

TMPDA  \(N,N,N',N'-\)tetramethyl-1,3-propanediamine

TMS  trimethylsilyl

TMSCl  trimethylsilyl chloride

TMSLi  trimethylsilyllithium

TMSCH₂Li  trimethylsilylmethyllithium

TMSOTf  trimethylsilyl triflate

TESiH  triethylsilane
THF  tetrahydrofuran

via  by means of

X  halide substituent

Zn  zinc
I. Introduction
I.1. Overview of (S)-Nicotine.

I.1.a. Biological relevance.

I.1.a.i. Occurrence in nature.

Nicotine (1, Figure I-1) is an alkaloid found in the tobacco plants *Nicotiana tabaccum* and *Nicotiana rustica*. It was first isolated in 1828 and named after Jean Nicot who imported it to Europe for the first time in the year 1560.\(^1\) (S)-Nicotine is the most abundant of the two enantiomers present in the plant in the range of 2-8%, while (R)-nicotine constitutes only 1.2% of the total nicotine content.\(^2,3\) Other alkaloids present in tobacco include nornicotine (2), anabasine (3), myosmine (4), nicotirine (5) and anatabine (6), representing from 8 to 12% of the total alkaloid content.\(^1\)

![Figure I-1](image.png)

*Figure I-1. Major alkaloids present in tobacco plants.*
I.2.a.i. Chemical properties.

Nicotine was isolated by Posselt and Reimann in 1828, and its empirical formula was described in 1843 by Melsens. The structure of nicotine as we know it today was elucidated by Pinner in 1893. Pictet and Crepieux described the isomerism of the molecule in 1893, and in 1978, Pitner et al. described the spatial conformation of the alkaloid. The structure of nicotine contains two heterocycles, a pyridine and pyrrolidine ring that are perpendicular to each other. The pyrrolidine ring assumes an envelope conformation with the pyridine ring and the $N$-methyl group both in a trans orientation (Figure I-2). The two rings in nicotine cause it to have low polarity and moderate hydrophobicity which results in good solubility in conditions of low polarity.

Nicotine is dibasic, its pyrrolidine nitrogen has a pKa of 7.84, while the pyridine nitrogen has a pKa of 3.04 at 15 °C. At pH 7.4, nicotine exists in two forms, one at which the pyrrolidine nitrogen is positively charged (Figure I-3), and the uncharged form in a 2:1 ratio respectively. Absorption of nicotine as well as other alkaloids across the membranes is pH dependent. Since its neutral form easily penetrates lipophilic environments, an alkaline pH would largely facilitate the absorption of nicotine through the mucous membrane. These properties make nicotine a molecule of endless interest for biological study.
Figure I-2. Conformation of (S)-nicotine in solution.

1.2.a.ii. Nicotine in medicinal chemistry.

Since its isolation, nicotine has attracted attention because of its pharmacological properties, mainly those related to the central nervous system (CNS). Nicotine acts as an agonist on one group of receptors that are targeted by the neurotransmitter acetylcholine (ACh, 7, Figure I-3). At the physiological pH of blood (7.4) and at 37 °C, nicotine exists in 69% as its ionized form 1a, and the rest remains neutral. The ionized nicotine mimics the positively charged quaternary nitrogen in ACh, while the pyridine nitrogen has Lewis-base character such as the carbonyl oxygen of the ester group.¹

Figure I-3. Functional similarities of (S)-nicotine and acetylcholine.
Acetylcholine acts on the CNS and the peripheral nervous system (PNS) through two different types of receptors, the muscarinic (mAChRs) and the nicotinic receptors (nAChRs). The nAChRs are integral membrane proteins involved in ionic responses to ACh and other agonists at the neuro-muscular junction and the central and peripheral nervous system. Based on their sites of expression nAChRs are classified in muscle-type and neuronal-type. These receptors belong to a family of ligand-gated ion channels and are composed of five subunits arranged symmetrically around an axis perpendicular to the membrane. The muscle-type receptors are composed of four homologous subunits, $\alpha_1$, $\beta_1$, $\delta$, $\gamma$ or $\varepsilon$ in a 2:1:1:1 ratio respectively. On the other side, the neuronal-type receptors consist of the homomeric or heteromeric combination of 12 different subunits $\alpha_2$-$\alpha_{10}$ and $\beta_2$-$\beta_4$. Nicotinic AChRs have two binding sites for ACh located on different $\alpha$-subunits. When binding of an agonist occurs, the subunits suffer a change in conformation, opening the channel and therefore allowing positively charged ions to flow across. The nAChRs are permeable to $\text{Na}^+$, $\text{K}^+$ and in some cases to $\text{Ca}^{2+}$. Activation of nAChRs facilitates the release of a number of other neurotransmitters involved in cognitive functions, learning and memory arousal, sensory perception, motor control and analgesia. These neurotransmitters include dopamine (DA), norepinephrine (NE), serotonin (5-HT), glutamate (Glu), and $\gamma$-aminobutyric acid (GABA) (8-12, Figure I-4).
In general, the nAChRs are involved in a wide range of physiological functions. The fact that several important physiological processes appear to be regulated by a single or a few nAChRs subtypes, makes it possible to target specific functions without affecting other aspects of cholinergic neurotransmission. Some pathological conditions such as Alzheimer’s disease (AD), Parkinson’s disease (PD), depression and schizophrenia are largely associated to altered cholinergic pathways.\textsuperscript{12}

Interestingly, nicotine has been observed to show favorable effects on patients suffering from Alzheimer’s disease, Parkinson’s disease and La Tourette’s syndrome along with other CNS related disorders. The alkaloid has also been shown to produce a significant and marked improvement in information processing and short-term memory in patients with dementia of the Alzheimer type.\textsuperscript{14}

\textbf{Figure I-4.} Selected examples of neurotransmitters modulated by nAChRs.
A recent report in the literature indicates that most of the nAChRs agonists (Figure I-5) evaluated in clinical trials to date have been analogs of nicotine and epibatidine (16), whereas other nAChR ligands have attracted limited interest.\(^{10,15}\) Such examples include the 5-ethynyl analog SIB-1508Y (14) which has been in the clinical trials (phase II) for treatment of Parkinson’s disease.\(^{16}\)

**Figure I-5.** Selected examples of agonists of neuronal nAChRs.

\textit{1.2.a.iii. Nicotine in agriculture.}

In addition to nicotine’s potential beneficial use in human health, the alkaloid has been formulated for insecticide purposes since the beginning of the 20\textsuperscript{th} century. Its high efficacy as an insecticide is explained by the fact that, in high doses nicotine blocks the nAChRs.\(^{1,17}\) Synthetic derivatives of nicotine such as imidacloprid (18, Figure I-6) and acetamiprid (19) have been used as insecticides. Recently, \(N\)-acylpyridinium salt chemistry and directed lithiation strategies have been used successfully by Comins to synthesize novel nicotinoids.
(20-22) found to have insecticidal activity, greater than that of nicotine, against aphids, thrips, larval Lepidoptera and house flies.\textsuperscript{18}

![Chemical structures of imidacloprid, acetamiprid, and other nicotinoids](image)

**Figure I-6.** Selected examples of nicotinoids.

1.1.b. \textit{Synthetic background.}

1.1.b.i. \textit{Syntheses of nicotine.}

The first synthesis of nicotine was reported in 1904 by Pictet and Rotschy,\textsuperscript{19} and in 1928 a more explicit route was achieved by Späth and Bretschneider.\textsuperscript{20} In 1982, Chavdarian et al.\textsuperscript{21} accomplished the first enantioselective synthesis of nicotine employing an enantiopure pyrrolidine source onto which the pyridine ring was constructed. Chavdarian’s synthesis (Scheme I-1) of (S)-nicotine started with L-proline which was subjected to a reduction reaction of the carboxylic functional group and methylation of the nitrogen to provide the precursor 23. Conversion of the hydroxyl group to a chloride using thionyl chloride and subsequent nucleophilic substitution with a cyanide group provided compound 25. Condensation of the lithiated 25 with 3-ethoxyacrolein (26) yielded 27 which underwent cyclization upon treatment with a mixture of HBr/AcOH to afford 2-bromonicotine 28.
Hydrogenolysis of 28 to remove the halogen furnished 1 with a 24% enantiomeric enrichment.

Scheme I-1. First Enantioselective Synthesis of (S)-Nicotine (1).

In the past, syntheses of nicotine and its analogues were mainly racemic and involved construction of the pyrrolidine ring around a suitable pyridine ring. However, more recently, a number of asymmetric syntheses of both enantiomers of nicotine and their analogues has been reported as discussed in a recent review article.22

Over the years, synthetic and medicinal chemists have developed special interest in structure-affinity and structure-activity relationships of nicotine and its analogues.\textsuperscript{14,17a} In 1994, Lin and co-workers, after evaluating a series of pyrrolidine-modified nicotine analogs, concluded that there exists a binding pocket of limited size on the nAChRs associated with the pyrrolidine moiety present on the nicotine molecule.\textsuperscript{14} Introduction of different substituents at C-3', C-4' and C-5' positions showed a decrease in the affinity for the receptor; however, the $N$-methyl group has been reported to be optimal for high affinity.\textsuperscript{23}

In contrast, pyridine-substituted nicotine analogs have resulted in compounds that have in several cases displayed higher affinity and enhanced selectivity for nAChRs in the treatment of CNS disorders.\textsuperscript{11,14,24,25} These results have stimulated the interest to develop and optimize methodologies for substitution on the pyridine ring of nicotine. In line with this need, the Comins group has developed a variety of methodologies for the substitution at C-2, C-4, C-5, and C-6 positions of the pyridine ring of commercially available (S)-nicotine, and as a fulfilling result of these efforts, a large library of mono- and poly-substituted nicotine analogs for biological screening have been synthesized in our laboratories.\textsuperscript{22,23,26,27}

In addition, our group has utilized commercially available (S)-nicotine as a chiral building block in enantioselective syntheses of some natural products containing the (S)-nicotine core structure as discussed in the following section.
I.1.b.iii. (S)-Nicotine as a starting material in enantioselective total synthesis.

I.1.b.iii.1. Six-step synthesis of SIB-1508Y from (S)-nicotine.

The remarkable advances in regioselective substitution of nicotine at all positions of the pyridine ring allowed Comins and co-workers to achieve two short syntheses of the nAChR agonist SIB-1508Y\(^{27}\) (14) from natural (S)-nicotine (1). The first synthesis was accomplished in six steps via \(N\)-acylpyridinium chemistry, and the second, in five steps using regioselective lithiations.\(^{27}\) The six-step synthesis (Scheme I-2) started with the treatment of 1 with lithium powder and chlorotrimethylsilane to afford 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (29). Acylation of 29 with methyl carbonate in the presence of TBAF provided the 1-acyl-1,4-dihydronicotine 30 (98% ee). Formylation of 30 under Vilsmeier-Haack conditions\(^ {28}\) gave the desired C-5 aldehyde 31. Removal of the \(N\)-carbomethoxy group under mild conditions (TEA, MeOH, rt, 1 d), followed by rearomatization with elemental sulfur in refluxing toluene, afforded the 5-formynicotine 32. The synthesis was completed using the Seyferth-Gilbert homologation\(^ {29}\) to convert 33 into 14 obtained in a 20% overall yield.

I.1.b.iii.2. Five-step synthesis of SIB-1508Y (14).

In the second synthesis (Scheme I-3), treatment of 1 with n-BuLi-LiDMAE complex followed by addition of hexachloroethane afforded 34. Iodination of 34 after treatment with LiTMP yielded the dihalonicotine 35. A Sonogashira\textsuperscript{30} cross-coupling of 35 with [(triisopropyl)silyl]acetylene afforded intermediate 36 in quantitative yield. Reaction of 36 with Zn/AcOH yielded the dechlorinated product 37. Deprotection of the acetylene with tetrabutylammonium fluoride completed the shortest reported synthesis of enantiopure SIB-1508Y (14) in 32% overall yield.
Scheme I-3. Five-Step Synthesis of SIB-1508Y (14).

1.1.b.iii.3. Synthesis of (S)-brevicolline.

Employing a similar approach, the alkaloid (S)-brevicolline (43, Scheme I-4) was synthesized in six steps from (S)-nicotine with 17% overall yield. The synthesis commenced with the preparation of 5,6-dichloronicotine (38) from (S)-nicotine using ortholithiation methodologies. Treatment of 38 with trimethylboroxine in the presence of a palladium catalyst gave 39. Iodination of 39 at C-4 yielded the tri-substituted nicotine 40. Cross-coupling between the amino boronate ester 41 and 40 afforded compound 42. Intramolecular Buchwald amination was employed to close the indole ring fragment yielding
the natural product 43. This synthesis constitutes the shortest route towards this natural product to date.

Scheme I-4. Six-Step Synthesis of (S)-Brevicolline (43).
In summary, our group has in recent years been studying the synthetic utility of (S)-nicotine (1) and its derivatives. These studies include two syntheses of SIB-1508Y (14) in five and six steps respectively, and a six-step synthesis of (S)-brevicolline (43) using 1 as starting material. Having all this successful experience in hand, and since the natural product (S)-macrostomine (44, Figure I-7) also possesses the core (S)-nicotine structure, it was envisioned that 44 could be synthesized in a few steps from natural nicotine using directed lithiation methodologies developed in our laboratories. This work is presented in Chapter II.

Figure I-7. Structure of (S)-macrostomine (44).
I.2. Overview of N-Acylpyridinium Salt Chemistry.

I.2.a. Biological relevance of six-membered ring nitrogen heterocycles.

The pyridine and piperidine rings are ubiquitous structures in innumerable natural products, pharmaceuticals and drug candidates. One of the main reasons for the continuous interest in these molecules in medicinal chemistry is their demonstrated wide range of biological activities and pharmacological applications including the treatment of cancer, Alzheimer’s disease, Parkinson’s disease, chronic pain, antiulcerant and HIV-1 therapy. (Figure I-8 and Figure I-9).

Figure I-8. Pyridine ring-containing pharmaceuticals.

According to the U.S. Patent and Trademark Office (USPTO), the number of patents in the United States related to pyridines, dihydropyridines and piperidines combined, from 1976 to 2013, is of about 216K.
Figure I-9. Piperidine ring-containing pharmaceuticals.

Furthermore, in 2012 the U.S. Food and Drug Administration (FDA) approved 39 new drugs of which at least 23 (60%) are molecules containing nitrogen heterocycles in their skeleton (Figure I-10). In summary, the wide-ranging biological activity of pyridine and piperidine-based compounds, both naturally occurring and synthetic, makes the incessant development of methodology for the synthesis of these heterocycles of considerable importance, particularly approaches leading to chiral derivatives of these ring systems.
I.2.b.  **Synthetic significance of N-acylpyridinium salt chemistry**

The Comins research group has directed its efforts on the development of methodologies in order to synthesize a large number of alkaloids with a wide array of biological activities. One of the main areas of research has been the development of chiral N-acylpyridinium salts capable of providing addition products with high diastereoselectivity. Particularly, the addition of Grignard reagents to N-acylpyridinium salts of 4-methoxy-3-(triisopropylsilyl)pyridine (57) (Scheme I-5)\(^{37}\) has been of great synthetic utility, since the resulting N-acyl-2,3-dihydro-4-pyridones of type 59 have proven to be exceptional building blocks for the preparation of a variety of alkaloids.\(^{38}\)
Scheme I-5. Preparation of N-Acyl-2,3-dihydro-4-pyridones (59).

Mechanistic studies have served to explain the selectivity of this transformation (Figure I-11). These results have been complemented by our observations, which suggest that there is a π-π stacking interaction between the phenyl group in the chiral auxiliary and the pyridine ring of the pyridinium salt. That stabilization seems to be favored in rotamer A as opposed to rotamer B, where there is a steric interaction between the bulky TIPS substituent and the phenyl ring of the auxiliary. Therefore, while the TIPS group regioselectively blocks one of the α-positions on the pyridine ring, π-π stacking interactions and the chiral auxiliary direct the nucleophilic attack to one face of the pyridinium salt. As a result, a highly enantiopure C-2 substituted dihydropyridone is efficiently delivered.

Figure I-11. Mechanism of asymmetric induction.
This successful approach for the synthesis of substituted dihydropyridones of type 61 has become an essential starting point for a number of transformations (Figure I-12) leading to the synthesis of molecules of diverse synthetic and biological value.

**Figure I-12.** Synthetic versatility of dihydropyridones 61.

**I.2.c.** *Total syntheses based on N-acylpyridinium salt chemistry.*

As it has been described, the reaction of nucleophiles with N-acylpyridinium salts has proven to be a valuable method for the enantioselective synthesis of 2,3-dihydro-4-pyridones types 59 and 61. These dihydropyridones have been utilized as synthetic intermediates for the preparation of numerous types of alkaloids including indolizidine,\textsuperscript{41} piperidine,\textsuperscript{42} quinolizidine,\textsuperscript{43} and others\textsuperscript{44} (Figure I-13).
In summary, over the years our group has developed methodologies to use nitrogen-containing heterocycles for the preparation of $N$-acyl-2,3-dihydro-4-pyridones, powerful building blocks utilized in the concise total syntheses of complex molecules of considerable pharmacological interest.

**Figure I-13.** Dihydropyridones 59 as building blocks in total synthesis.
With this knowledge in hand, we embarked in the study of a concise route for the synthesis of the quinolizidine natural product cermizine D (68, Figure I-14) using N-acylpyridinium salt chemistry methodologies. This work is presented in Chapter III.

Figure I-14. Structure of cermizine D (68).
II. Total Synthesis of (S)-Macrostomine
II.1. **Introduction.**

II.1.a. **Abstract.**

This chapter presents a concise synthesis of (S)-macrostomine (44) accomplished in five steps from natural nicotine (1) in 19% overall yield via a Diels-Alder cycloaddition reaction, as the key step in the synthesis, followed by a Kumada cross-coupling to furnish the natural product (Scheme II-1).

![Scheme II-1. General Approach for the Synthesis of (S)-Macrostomine (44).](image)

**Scheme II-1.** General Approach for the Synthesis of (S)-Macrostomine (44).

II.1.b. **Isolation and pharmacological potential of (S)-macrostomine.**

(S)-Macrostomine (44) is a plant alkaloid containing a benzylisoquinoline ring system. It was first isolated from the plant *Papaver macrostomum* Boiss. et Huet and structurally elucidated in 1974 by Santavy and coworkers. Later, in 1984 the alkaloid was also isolated from the plant *Papaver arenarium* M.B. Santavy’s group reported that (S)-macrostomine has a spasmolytic effect on the smooth muscle of isolated intestines of rats and rabbits, that is greater than that of papaverin (69, Figure II-1), an alkaloid used primarily in the treatment of spasms and approved as a cerebral and coronary vasodilator. (S)-Macrostomine has also
been shown to have some effects on the cardiovascular function of rabbits after intravenous application.\textsuperscript{47} However, there has been no other report in the literature on its biological activity, a shortcoming that may be largely attributed to the lack of concise synthetic routes to the natural product and its analogues.

\textbf{Figure II-1.} Structure of (S)-macrostomine (44) and related compounds.

\textit{II.1.c. Syntheses of (±)-macrostomine.}

The first synthesis of (±)-macrostomine (\textit{dl-44}) was accomplished in 1980 by Wykypiel and Seebach \textit{via} lithiated nitrosamines.\textsuperscript{49} The synthesis of the racemate was also reported by Wiegrebé\textsuperscript{50} and collaborators in 1981 and one year later, in 1982, by Kapil and Sharma\textsuperscript{51}. All three syntheses were being studied simultaneously, which could explain the resemblance of the chemistry employed in all of them.
II.1.c.i. Seebach’s nitrosamine route towards macrostomine.

This synthesis (Scheme II-2) was initiated by preparing the tetrahydroisoquinolinol 73 from 3,4-dimethoxybenzaldehyde (71) and the α-aminoacetaldehyde acetal 72 through a Pomeranz-Fritsch\textsuperscript{52} reaction. Nitrosation of 73 with sodium nitrite, followed by lithiation and alkylation with 3,4-methylenedioxybenzyl bromide (74) and subsequent \textit{in situ} denitrosation with LAH, furnished the aminoalcohol 75 as a mixture of diastereomers. Next, the amine was protected and the alcohol oxidized under phase transfer conditions to obtain ketone 76, which after a 1,2-addition with lithio-nitroso-pyrrolidine (77) furnished 78. Removal of the nitroso group with Raney nickel, followed by reduction of the N-(2)-benzoyl to a benzyl group, and formylation of the pyrrolidine nitrogen provided 79. Finally, 79 was subjected to dehydration and cleavage of the N-benzyl group with Pd/C followed by LAH reduction of the formamide to accomplish the first synthesis of (±)-44.
Scheme II-2. Seebach’s Nitrosamine Route towards (±)-Macrostromine.
II.2.b.i. Wiegrebe’s synthesis of (±)-macrostomine.

Wiegrebe’s synthesis (Scheme II-3) commenced with the condensation of 2-(3,4-dimethoxyphenylacetonitrile (80) with imine 81 to furnish enamine 82. Formylation of 82 provided 83, which was treated with LAH to afford the dihydroderivative 84. Reduction of the nitrile group in 84 led to amine 85 which was converted to the amide 87 by reaction with ester 86. Cyclization of 87 via a Bischler-Napierlaski\textsuperscript{53} reaction followed by dehydrogenation afforded the quinolines 89 and racemic 44. The overall yield for this synthesis was not reported.
Scheme II-3. Wiegrebe’s Synthesis of (±)-Macrostomine.
II.1.c.iii. Kapil and Sharma’s synthesis of (±)-macrostomine.

On the other hand, Kapil and Sharma’s synthesis (Scheme II-4) utilized the nitrostyrene 90 as starting material, which on reaction with N-methylpyrrole (91) afforded compound 92. Catalytic hydrogenation of 92 and subsequent condensation with 94 yielded amide 95. Partial reduction of the pyrrole ring led to the dihydro-intermediate 96. Complete reduction of the pyrrole system to the desired pyrrolidine intermediate was accomplished by hydrogenation of 96 in the presence of palladium. Treatment of the reduced intermediate with phosphoryl chloride furnished isoquinoline 97, which was aromatized with Pd/C in refluxing xylene to afford (±)-44 in 7% overall yield.
Scheme II-4. Kapil and Sharma’s Synthesis of (±)-Macrostomine, (±)-44.

II.1.d. Wiegrebe’s enantioselective synthesis of (S)-macrostomine.

In 1988, Wiegrebes’s group reported the only known enantioselective synthesis of (S)-macrostomine (44) in 13 steps through what they called the preininger alkaloid (70), a crucial
intermediate for their synthesis (Scheme II-5).\textsuperscript{54,55} They accomplished an enantioselective hydrosilylation of 70 in the presence of a rhodium catalyst and a chiral phosphine ligand, (+)-Diop, to afford 44 with 33% ee and 13% overall yield.

The synthesis started with a base-catalyzed condensation of 80 with ethyl acetate to afford a ketone which was protected as a dithioacetal using 1,2-ethanediithiol followed by reduction of the nitrile group to provide 98. Subsequent thermally-induced condensation of the product with compound 86 led to the formation of amide 99. Bischler-Napierlaski conditions effected the intramolecular cyclization of the amide into compound 100, which upon treatment with NaBH\textsubscript{4}, removal of the dithioacetal using mercury (II) perchlorate, and aromatization of the intermediate in the presence of Pd/C afforded the isoquinoline 101. Next, silylation of 101 followed by addition of an Eschenmoser’s salt,\textsuperscript{56} acid-catalyzed desilylation and treatment of the intermediate with the cyanide anion led to the one-pot formation of the β-keto nitrile 102. Reduction of the nitrile followed by an intramolecular cyclization provided the preininger alkaloid, 70. Reductive hydrosilylation of 70 in the presence of a rhodium catalyst and the chiral ligand (+)-Diop, yielded intermediate 103 as an (S)-enriched mixture of enantiomers, which upon treatment with acetic formic anhydride yielded the N-formyl compound 104. Reduction of 104 with LAH afforded the natural product 44 in low ee.
Scheme II-5. Wiegrebe’s Enantioselective Synthesis of (S)-Macrostomine (44).
II.2. **Synthesis of (S)-Macrostomine from (S)-Nicotine.**

II.2.a. **Retrosynthetic plan.**

In our retrosynthetic plan (Scheme II-6), we envisaged that 44 could be obtained from 1 via two key reactions, a Diels-Alder\textsuperscript{57} cycloaddition that would provide the isoquinoline intermediate 105, followed by a metal catalyzed C-C bond formation to introduce the 3,4-methylenedioxy-benzyl portion to complete the synthesis.

![Scheme II-6. General Retrosynthetic Plan towards (S)-Macrostomine (44).]

**II.2.b. Diels-Alder reaction.**

It was anticipated that either a metal-induced halide elimination of a dihalonicotine or a fluoride-induced ortho-(trimethylsilyl) triflate elimination in the presence of a suitable diene would undergo the Diels-Alder cycloaddition to provide the precursor to the isoquinoline isoquinoline intermediate 105.\textsuperscript{58}
II.2.b.i.  *Studies using 2,3-dimethoxybutadiene as a diene.*

II.2.b.i.1.  **5,6-dichloronicotine as a pyridyne precursor.**

Our synthesis commenced with the introduction of a chloride at the C-6 position of (S)-nicotine (1) using Fort’s base as reported in our previous work. A chloride functionality at the C-6 position was essential, first, to direct lithiations at the C-4 and C-5 positions of 1, and second, to serve as a handle in the C-C metal-catalyzed reaction at the last step.

In the initial approach, 2,3-dimethoxybutadiene (106) was employed as the diene system for the Diels-Alder cycloaddition. This diene has been reported in the literature to be effective for the formation of cycloadducts with different dienophiles. Derivatives of (S)-6-chloronicotine (34) substituted at the C-4 and C-5 positions with bromine and iodine or with an ortho-trimethylsilyl group were employed as pyridyne precursors.

The first nicotine derivative studied was 5,6-dichloronicotine (38). It was thought that lithiation of 38 at C-4 would lead to elimination of the ortho-chlorine and subsequent pyridyne formation; however, after treatment of 38 with 1.1 equivalents of n-BuLi at -78 °C and then warming up to rt in the presence of an excess of the diene, only recovery of the starting dichloronicotine 38 occurred (Scheme II-7).
Scheme II-7. Attempts for the Diels-Alder Reaction using 5,6-Dichloronicotine (38).

Two possible reasons could be attributed to this observation, either lithiation was not accomplished or the lithiated intermediate was stabilized in some way. To check the first hypothesis, an experiment was carried out by lithiating under the same conditions and then quenching with D$_2$O. It was observed that the incorporation of the deuterium nucleus at C-4 was confirmed by $^1$H NMR analysis. That result proved that the C-4 lithiated intermediate 38a was stabilized probably by coordination with the lone pair of electrons at the pyrrolidine ring nitrogen (Figure II-2).

Figure II-2. Stabilization of a C-4 lithiated nicotine intermediate (38a).

The introduction of a silyl substituent at C-4 followed by a fluoride-induced elimination was then investigated. Deprotonation of 38 at C-4, and then quenching with trimethylsilyl chloride afforded 108 in 57% yield. Treatment of 108 with tetrabutyl ammonium triphenyl
silyldifluorosilicate (TBAT),\textsuperscript{62} as a fluoride source, and heating in the presence of 106 resulted in the recovery of desilylated product 38 (Scheme II-8).

\begin{equation}
\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{Cl} & \quad \text{N} \\
\text{38} & \quad \text{1)} \ n\text{-BuLi (1.1 equiv), THF, -78°C} \\
& \quad \text{2) TMSCl (1.2 equiv), -78 °C to rt} \\
& \quad \text{57%} \\
\text{Cl} & \quad \text{N} \\
\text{Cl} & \quad \text{N} \\
\text{108} & \quad \text{1) TBAT (2.0 equiv), THF} \\
& \quad \text{2) MeO (5.0 equiv), reflux} \\
\end{align*}
\end{equation}

\textbf{Scheme II-8.} Attempt at the Diels-Alder Reaction using a Fluoride-Induced Elimination.

\textit{II.2.b.i.2. Attempts at the preparation of ortho-(trimethylsilyl) triflate nicotine derivatives.}

Next, attempts were made to utilize ortho-(trimethylsilyl) triflate nicotine derivatives since a successful synthesis of derivative 109 had been accomplished (Figure II-3).\textsuperscript{59} The fluoride induced 1,2-elimination of ortho-(trimethylsilyl) triflates is well known in the literature as a mild method of aryne formation.\textsuperscript{63,58} As such, a study was initiated to synthesize nicotine derivatives 110 and 111 as potential 3,4-pyridyne\textsuperscript{64} precursors toward the natural product 44. In spite of the extensive investigations done, there was no successful route found for the synthesis of the nicotine derivatives 110 and 111 and hence the Diels-Alder reaction could not be explored \textit{via} this route.
II.2.b.i.3. Study of trihalonicotines as pyridyne precursors.

Finally, an alternative route employing the metal-induced method for the 3,4-pyridyne formation, this time using ortho-dihalonicotines at C-4 and C-5 of 6-chloronicotine, was investigated. Due to the setbacks encountered in the previous attempts, it was necessary to confirm the efficiency of not only the pyridyne precursors but also the suitability of 106 as the diene. An exploratory reaction was performed using furan (113) as the diene since it is locked in a s-cis conformation and is known to react with pyridynes. Metal-halogen exchange, either at C-4 of 5-bromo-6-chloro-4-iodonicotine (112) or at C-5 of 4-bromo-6-chloro-5-iodonicotine (115), and then warming to room temperature in the presence of 10.0 equivalents of 113, afforded the cycloadduct 114 as a separable mixture of diastereomers (Scheme II-9).
However, when the same conditions were employed on derivative 112 using 2,3-dimethoxybutadiene (106), and n-BuLi as the base, only recovery of some 6-chloronicotine (34) resulted along with decomposition. Similarly, when derivative 115 was treated with i-PrMgCl•LiCl and the reaction was quenched with an excess of diene 106, recovery of the deiodinated starting material was observed (Scheme II-10).
Scheme II-10. Attempts at the Diels-Alder Reaction using Trihalonicotines.

From the results obtained, it was concluded that diene 106 was the cause for the failure to form the Diels-Alder cycloadduct 107, since 2,3-dimethoxy butadiene (106) exists mostly as its s-trans conformer, instead of the s-cis that is required for a facile cycloaddition to take place. For the synthesis of the natural product (44), it would be necessary to use a furan derivative preferably containing the methoxy substituents at the C-3 and C-4 positions.

II.2.b.ii. Diels-Alder reaction using 3,4-dimethoxyfuran as a diene.

The preparation of 3,4-dimethoxyfuran (122) can be accomplished in one step, from commercially available 3,4-dimethoxyfuran-2,5-dicarboxylic acid (121, Scheme II-11), using a known protocol. In our case, 122 was prepared in five simple steps from diglycolic acid (116) due to its lower cost. The copper (II) complex used as catalyst to decarboxylate 121 was prepared according to a literature procedure.
Scheme II-11. Preparation of 3,4-Dimethoxyfuran (122).

II.2.b.ii.1. A trihalonicotine as pyridyne precursor.

Initial treatment of the trihalonicotine 112 with n-BuLi at -78 °C, then warming to room temperature in the presence of an excess of 122 as the diene, led to the formation of adduct 123 as a mixture of diastereomers; however, the product was obtained in very low yield (Scheme II-12). It is worth mentioning that this reaction was not further optimized.

Scheme II-12. Diels-Alder reaction using 3,4-Dimethoxyfuran and a Trihalonicotine.
A halogen-dance occurring after lithiation of 112 could be a reason for the low yield obtained of the cycloaddition product 123. To prove this theory, and to study the potential of (S)-4-bromo-6-chloronicotine (124) as a pyridyne precursor, a D$_2$O experiment was set up (Scheme II-13). Lithiation of 1-(3,4-dimethoxybenzyl)-4-methylpiperazine with $n$-BuLi at -78 °C to give 125, was followed by treatment of the mixture with 124. Trapping of the anion thus formed with 300 µL of deuterium oxide yielded two products 126 and 127. The fact that the major product obtained was the C-4 deuterated nicotine 127 confirmed that a halogen-dance pathway could be responsible for the low yield found when 112 was used as pyridyne precursor.

Scheme II-13. Study of 4-Bromo-6-chloronicotine (124) as Pyridyne Precursor.
II.2.b.ii.2. A dihalonicotine as pyridyne precursor.

In order to avoid a halogen-dance pathway, the viability of using 4,6-dichloronicotine (128) was explored (Scheme II-14). Treatment of 128 with $n$-BuLi at -78 °C, and quenching with 300 µL of D$_2$O at -78 °C resulted exclusively in the formation of the C-5 deuterated product 129. This result gave the necessary evidence that 128 could be directly lithiated with $n$-BuLi and would not follow a halogen-dance pathway.

![Scheme II-14. Deuteration Study of 4,6-Dichloronicotine (128) as Pyridyne Precursor.](image)

With these results in hand, a furan model study was performed again, this time employing 128 as the dienophile precursor. Lithiation of 128 followed by warming to rt in the presence of 1.0 mL of furan, afforded the desired product 114 in very good yield (Scheme II-15). This outcome revealed that 108 was a more efficient pyridyne precursor than the trihalogenated analog 112.
Scheme II-15. Model Diels-Alder using 4,6-Dichloronicotine (128) and Furan (113).

Finally, after some optimization of the reaction conditions, treatment of 128 with \( n \)-BuLi at -78 °C for 1 h, followed by the addition of 8.0 equivalents of freshly distilled 3,4-dimethoxyfuran (122), and warming to room temperature, provided the adduct 123 in 55% yield as an inseparable 1:1 mixture of diastereomers (Scheme II-16). TLC’s performed at different stages of the cycloaddition reaction showed the presence of adduct 123 even before the mixture reached room temperature. In order to ensure a comparable yield, the estimated time of completion was always kept between 15 and 20 hours in subsequent experiments.

Scheme II-16. Diels-Alder Reaction using 3,4-Dimethoxyfuran (122).

Next, we proceeded to investigate an effective procedure for aromatization of 123 toward the isoquinoline system present in the natural product 44 using 114 as a model. Two different strategies were examined in this study, one based on a hydride-induced ether cleavage, and the other using a low-valent titanium reagent to activate the ether oxygen.

**II.2.c.i. The hydride route.**

Initially and as a model, we attempted the activation of the cyclic ether in 114 (single diastereomer) followed by reduction with a hydride source. It was thought that after activation, a hydride-induced C-O bond cleavage would lead to the aromatized adduct 130 as such, or the neutral form 131 depending on the reaction conditions. Activation was pursued with either trifluoroacetic acid, formic acid or trimethylsilyl triflate. However, after several attempts, the only result obtained was the recovery of starting material (Table II-1).
Table II-1. Attempts at the Aromatization of 114 via Hydride.

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis acid (equiv/amount)</th>
<th>hydride source (equiv)</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA (10.0 equiv)</td>
<td>TESiH (3.0)</td>
<td>rt, 1 h</td>
<td>114</td>
</tr>
<tr>
<td>2</td>
<td>TFA (1.0 mL)</td>
<td>TESiH (3.0)</td>
<td>rt, 20 h</td>
<td>114</td>
</tr>
<tr>
<td>3</td>
<td>HCOOH (3.0 mL)</td>
<td>--</td>
<td>TEA, rt to reflux, 4 h</td>
<td>114</td>
</tr>
<tr>
<td>4</td>
<td>TMSOTf (1.0 equiv)</td>
<td>TESiH (38.0)</td>
<td>0 °C to rt, 1 h</td>
<td>114</td>
</tr>
<tr>
<td>5</td>
<td>TMSOTf (2.0 equiv)</td>
<td>TESiH (48.0)</td>
<td>0 °C to rt, 3 h</td>
<td>114</td>
</tr>
<tr>
<td>6</td>
<td>TMSOTf (2.0 equiv)</td>
<td>TESiH (42.0)</td>
<td>0 °C to reflux, 1 h</td>
<td>114</td>
</tr>
</tbody>
</table>

II.2.c.ii. Via low-valent titanium.

According to literature findings, low-valent titanium reagents can be used for the aromatization of certain Diels-Alder adducts, thus this approach was pursued on the model adduct 114 (Scheme II-17).\(^6\) Addition of 114 (single diastereomer) at 0 °C to a fine suspension of titanium reagent, generated using a Zn/TiCl₄, and then heating to reflux for 2 h, led to either decomposition of the starting material, or to the formation of undesired products.
accompanied by only traces of 131 as verified by $^1$H NMR inspection. Attempts using crude 114 (mixture of diastereomers) also led to decomposition.

![Scheme II-17](attachment:image1.png)

**Scheme II-17.** Model Study for Aromatization of 114 using Zn/TiCl$_4$.

Since the zinc method did not work, milder conditions were then attempted using a more reactive reducing agent. Reports in the literature show Mg/TiCl$_4$ couple is an efficient agent for the cleavage of certain ethers under mild conditions. Fortunately, when 114 (single diastereomer) was added at -78 °C to a fine suspension of the titanium reagent, pre-formed using Mg/TiCl$_4$, and then warmed to rt, the aromatized product 131 was obtained (Scheme II-18). This compound would be later subjected to a model cross-coupling reaction.

![Scheme II-18](attachment:image2.png)

**Scheme II-18.** Model Study for Aromatization of 114 using Mg/TiCl$_4$. 
Next, we turned our attention to the aromatization of the dimethoxy adduct 123. As in the model, the first attempts using Zn/TiCl$_4$ led to decomposition of the starting material, and so, we resorted to the use of Mg/TiCl$_4$ as the low-valent titanium source. Gratifyingly, when adduct 123 was added to a suspension of the pre-formed titanium reagent and then warming to room temperature the expected isoquinoline 105 was successfully obtained in 70% yield (Scheme II-19).

**Scheme II-19.** Aromatization of the Diels-Alder Adduct 123.

**II.2.d.** *Metal-catalyzed C-C bond formation.*

With 131 and 105 synthesized, the C-C bond formation at the C-6 position was addressed. The initial approach was to investigate the Kumada$^{71}$ cross-coupling reaction to effect the transformation. In 1982, Kumada *et al.* described the successful cross-coupling of heteroaryl halides and Grignard reagents in the presence of either palladium or nickel catalysts.$^{72}$ Specifically, their success in the cross-coupling of alkyl and benzylic Grignard reagents with 2- and 6-chloropyridines, as well as with 1-chloroisoquinolines encouraged us to initiate our screening along those lines.$^{71e,72}$
The Grignard counterpart for this reaction was prepared in two steps starting with piperonyl alcohol 132 (Scheme II-20). Treatment of the alcohol with excess thionyl chloride provided the corresponding chloride 133, which is also commercially available, in 96% yield. Addition of 134 to a THF suspension of magnesium powder afforded the Grignard reagent 134. Titration of the reagent was performed, prior to its use, according to Paquette’s procedure.

Scheme II-20. Preparation of the Grignard Reagent 134.

II.2.d.i. Initial study of palladium and nickel catalysts.

Our initial screening for the cross-coupling catalyst included nickel and palladium catalysts (Table II-2). When NiCl₂(dppp) was employed, traces of (S)-macro stomine (44) were observed after ¹H NMR inspection of the crude products. Increasing either the amount of catalyst, time of reaction or temperature did not improve this outcome. Strangely, a one-time result providing 44 in 38% yield was observed when PdCl₂(dppf) was employed as catalyst (entry 6), but the result was not reproducible. Attempts to repeat the reaction only resulted in the recovery of starting material or decomposition in some cases.
Table II-2. Study of Nickel and Palladium Catalysts for Kumada Cross-Coupling.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>Grignard equiv</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl$_2$(dppp)</td>
<td>(3.0)</td>
<td>1.5 0 °C to rt, 21 h</td>
<td>105 + 44 (traces)</td>
</tr>
<tr>
<td>2</td>
<td>NiCl$_2$(dppp)</td>
<td>(22.0)</td>
<td>1.5 0 °C to rt, 21 h</td>
<td>105 + 44 (traces)</td>
</tr>
<tr>
<td>3</td>
<td>NiCl$_2$(dppp)</td>
<td>(26.0)</td>
<td>1.5 0 °C to reflux, 2 h</td>
<td>105 + 44 (traces)</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>(8.0)</td>
<td>1.5 0 °C to rt, 2.5 d</td>
<td>105</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>(10.0)</td>
<td>1.2 0 °C to reflux, 21 h</td>
<td>105</td>
</tr>
<tr>
<td>6</td>
<td>PdCl$_2$(dpf)</td>
<td>(10.0)</td>
<td>1.5 0 °C to reflux, 18 h</td>
<td>44 (38%)</td>
</tr>
<tr>
<td>7</td>
<td>PdCl$_2$(dpf)</td>
<td>(10.0)</td>
<td>1.8 0 °C to reflux, 24 h</td>
<td>105</td>
</tr>
<tr>
<td>8</td>
<td>PdCl$_2$(dpf)</td>
<td>(10.0)</td>
<td>1.8 0 °C to reflux, 36 h</td>
<td>105</td>
</tr>
</tbody>
</table>

Due to the setbacks encountered with the nickel and palladium catalysis, it was considered necessary to expand the screening using other metal catalysts.
II.2.d.ii. Study of cobalt and iron catalysts.

The use of cobalt\(^{75}\) and iron\(^{76}\) as alternative catalysts to achieve Kumada cross-couplings has been reported. The interest in complexes of these metals has grown as a consequence of the high cost and sensitivity of palladium precursors and of the ancillary ligands that usually accompany both palladium and nickel catalysts. The information available for successful cross-coupling between 2-chloropyridines and Grignard reagents when cobalt or iron salts were used, suggested that these catalysts could be effective for the C-C bond formation at C-6 of 105.

**Table II-3.** Study of Cobalt and Iron Catalysts.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>Grignard equiv</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Co(acac)(_2) (10.0)</td>
<td>3.0</td>
<td>THF/1,4-dioxane, 0 °C to rt, 21 h</td>
<td>105</td>
</tr>
<tr>
<td>2</td>
<td>Fe(acac)(_3) (5.0)</td>
<td>2.3</td>
<td>THF, -30 °C, 1 h</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>Fe(acac)(_3) (5.0)</td>
<td>1.2</td>
<td>THF/NMP, 0 °C to rt, 21 h</td>
<td>105</td>
</tr>
<tr>
<td>4</td>
<td>Fe(acac)(_3) (5.0)</td>
<td>1.5</td>
<td>THF/NMP, 0 °C to rt, 2.5 d</td>
<td>105</td>
</tr>
</tbody>
</table>
Exploratory reactions were performed (Table II-3) using two representative cobalt and iron catalysts, but unfortunately, under the reaction conditions investigated the only outcome obtained was the recovery of starting material.

II.2.d.iii. Study of manganese(II) chloride as catalyst.

In our search for other metal complexes of confirmed efficacy in the cross-coupling of Grignard reagents, a report by Rueping and Leawsuwan\textsuperscript{77} was found closely related to our case. They accomplished the manganese-promoted cross-coupling of 1-chloroisoquinolines, 2-chloroquinolines and 2-chloropyridine respectively, with either alkyl or aryl Grignard reagents. The earlier work by Cahiez and co-workers\textsuperscript{78} also supported the suitability of manganese salts to mediate cross-coupling reactions under mild conditions. Following these reports, we employed manganese(II) chloride as the catalyst precursor in our substrate. Sadly, the reaction of 105 with up to 4.0 equivalents of Grignard 134 in the presence of 10-16 mol\% of MnCl\textsubscript{2}\textbullet2LiCl, temperatures ranging from -10 °C to rt, for reaction periods of up to 30 h only led to the recovery of starting material.

\textbf{Scheme II-21.} Attempts at the Kumada Cross-Coupling using MnCl\textsubscript{2} as Catalyst.
II.2.d.iv. **Study of nickel(II) acetylacetonate as catalyst.**

We decided to return to the use of nickel catalysts as a search through the literature revealed the work of Yoshikai and collaborators\(^79\) in which the use of Ni(acac)\(_2\) in combination with hydroxyphosphine (PO) ligands was demonstrated to be effective for the Kumada cross-coupling of many aryl halides, including 2-fluoropyridine, with Grignard reagents. Consequently, our interest to explore this chemistry led us to perform a batch of reactions utilizing Ni(acac)\(_2\) as our precursor, accompanied by two different PO-ligands (Figure II-4).

![Figure II-4. Structures of the PO-ligands under study.](image)

The PO-ligand 136\(^{79b,d}\) was prepared by treating a solution of the commercially available aldehyde 137 in THF with MeLi at 0 °C, stirring for two hours, and quenching with saturated aqueous NaHCO\(_3\) (Scheme II-22).

![Scheme II-22. Preparation of PO-Ligand 136.](image)
Pleasantly, the reaction of 105 with the Grignard reagent 134 in the presence of Ni(acac)$_2$ and ligand 135 finally provided the natural product 44. Eventhough, only modest yields were observed (Table II-4), the reaction was reproducible, unlike previous results. In addition, it is worth noting that PO-ligand 135 was found to be a better aid for the catalyst than the PO-ligand 136.

**Table II-4.** Study of Ni(acac)$_2$ in Combination with PO-Ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>Ni(acac)$_2$ mol%</th>
<th>PO ligand mol%</th>
<th>Grignard equiv</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.0</td>
<td>136 (20.0)</td>
<td>2.0</td>
<td>rt to reflux, 2 h</td>
<td>105</td>
</tr>
<tr>
<td>2</td>
<td>20.0</td>
<td>135 (20.0)</td>
<td>2.0</td>
<td>rt, 16 h</td>
<td>44 (12%)</td>
</tr>
<tr>
<td>3</td>
<td>40.0</td>
<td>135 (45.0)</td>
<td>2.0</td>
<td>-50 °C to rt to reflux</td>
<td>44 (33%)</td>
</tr>
<tr>
<td>4</td>
<td>70.0</td>
<td>135 (80.0)</td>
<td>4.0</td>
<td>-50 °C to rt to reflux</td>
<td>44 (38%)</td>
</tr>
</tbody>
</table>

To further optimize these results, a model study using commercially available 1-chloroisooquinoline (138) was carried out concomitantly, and several catalysts and conditions were used as shown in Table II-5. In contrast to previous results, the use of MnCl$_2$•2LiCl as catalyst provided the cross-coupled product 139 (entry 1). The use of Ni(acac)$_2$ as catalyst in
the presence of PO catalyst 135 resulted in the formation of the cross-coupled product 139 in 40% yield (entry 3). Interestingly, when 138 was subjected to the cross-coupling reaction conditions, using a ligand-free catalyst (entry 6), a surprising 73% yield of 139 was obtained. This result led us to study ligand-free conditions with the precursors of 44.

**Table II-5.** Selected Results for the Model Cross-Coupling Reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>ligand (mol%)</th>
<th>Grignard equiv</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MnCl₂•2LiCl (10.0)</td>
<td>-</td>
<td>2.0</td>
<td>-10 °C to rt, 12 h</td>
<td>139 (51%)</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dppf)Cl₂ (0.8)</td>
<td>-</td>
<td>1.1</td>
<td>rt, 3 d</td>
<td>139 (22%)</td>
</tr>
<tr>
<td>3</td>
<td>Ni(acac)₂ (5.0)</td>
<td>135 (5.0)</td>
<td>2.0</td>
<td>rt to reflux, 17 h</td>
<td>139 (40%)</td>
</tr>
<tr>
<td>4</td>
<td>Ni(acac)₂ (18.0)</td>
<td>135 (18.0)</td>
<td>2.0</td>
<td>rt, 40 h</td>
<td>139 (29%)</td>
</tr>
<tr>
<td>5</td>
<td>Ni(acac)₂ (24.0)</td>
<td>135 (23.0)</td>
<td>1.1</td>
<td>-10 °C to rt °C, 40 h</td>
<td>139 (22%)</td>
</tr>
<tr>
<td>6</td>
<td>Ni(acac)₂ (20.0)</td>
<td>-</td>
<td>1.8</td>
<td>rt, 16 h</td>
<td>139 (73%)</td>
</tr>
</tbody>
</table>
Fortunately, comparable results (Table II-6) were obtained when isoquinoline 105 was treated with Grignard 134, in the presence of Ni(acac)$_2$ under ligand-free conditions. Successive increments in the number of equivalents of 134, time of reaction, and the load of catalyst, led to increasing yields of (S)-macrostomine (44).

**Table II-6.** Selected Results for the Ligand-Free Cross-Coupling Reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>Ni(acac)$_2$ (mol%)</th>
<th>Grignard equiv</th>
<th>time</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.0</td>
<td>1.8</td>
<td>2.5 d</td>
<td>44 (20%)</td>
</tr>
<tr>
<td>2</td>
<td>20.0</td>
<td>3.0</td>
<td>20 h</td>
<td>44 (47%)</td>
</tr>
<tr>
<td>3</td>
<td>50.0</td>
<td>3.1</td>
<td>39 h</td>
<td>44 (55%)</td>
</tr>
<tr>
<td>4</td>
<td>40.0</td>
<td>3.0</td>
<td>4 d</td>
<td>44 (63%)</td>
</tr>
</tbody>
</table>

Finally, after extensive screening for the appropriate catalyst and optimization of the reaction conditions, a ligand-free cross-coupling using Ni(acac)$_2$ as catalyst afforded the natural product 44 in 63% yield (Table II-6, entry 4).
In addition, having established successful Kumada cross-coupling conditions, we decided to employ the product of our model studies, isoquinoline 131, in a cross-coupling reaction using the same protocol (Scheme II-23) to give the cross-coupled product 140 in 78% yield.

Scheme II-23. Synthesis of (S)-Normethoxy-Macrostomine (140).

II.2.e. Summary of the total synthesis.

(S)-Nicotine (1, Scheme II-24), was treated with Fort’s base at -78 °C, followed by the addition of hexachloroethane, to afford 6-chloronicotine (34) in 87% yield. Treatment of 34 with n-BuLi at -78 °C, followed by addition of hexachloroethane, provided (S)-4,6-dichloronicotine (128) in 92% yield. Lithiation of 128 at the C-5 position with n-BuLi at -78 °C, followed by addition of 8.0 equivalents of dimethoxyfuran 122, and warming the reaction to room temperature, afforded 123 in 55% yield as an inseparable 1:1 mixture of diastereomers. Aromatization was accomplished when 123 was added to a solution of Mg/TiCl₄ in THF (-78 °C to rt), to furnish key intermediate isoquinoline 105 in 70% yield. A ligand-free reaction of 105 with 3.0 equivalents of Grignard 134 using Ni(acac)₂ as catalyst afforded the natural product (S)-macrostomine 44 in 63% yield.
In conclusion, after a comprehensive study and optimization, the plant alkaloid (S)-macrostomine (44) was synthesized via a five-step sequence from 1 in a 19% overall yield. This practical synthesis was carried out with retention of configuration on the pyrrolidine ring. Our work constitutes the shortest synthesis of this natural product published to date, and further demonstrates the value of (S)-nicotine (1) as a chiral building block.
II.3. **Synthesis of C-4 Derivatives of (S)-6-Chloronicotine.**

II.3.a. **Synthesis of C-4 amido derivatives of (S)-6-chloronicotine.**

In order to modify the binding properties of protonated (S)-6-chloronicotine (34) derivatives by the presence of an electron-donor group at C-4 capable of hydrogen bonding, a variety of C-4 amido derivatives of 34 were synthesized.

II.3.a.i. **Biological interest.**

As previously reviewed in this report, nicotine is a neurotransmitter that can emulate the binding properties of acetylcholine towards certain neuroreceptors. It was envisioned that intramolecular hydrogen bonding of the protonated pyrrolidine nitrogen of nicotine with an electron-donor group at C-4 could improve the binding efficiency of these derivatives. From this hypothesis, we decided to embark in the preparation of C-4 amido derivatives of (S)-6-chloronicotine (34), since the strategically positioned carbonyl functionality can act as the electron-donor (EDG) in the expected intramolecular stabilization of the protonated nicotine analogs (Figure II-5).

![Figure II-5. Stabilization of protonated 34 by an EDG at C-4.](image)
II.3.a.ii. Synthetic background.


The first example of a regiospecific synthesis of C-4 substituted nicotine derivatives was reported by our group in 2005, consisting in a two-step route from (S)-nicotine via an N-acylpyridinium salt reaction. A year later in 2006, regioselective substitution at the C-4 position was also achieved when (S)-6-chloronicotine was C-4 lithiated employing n-BuLi. A variety of electrophiles were introduced at the C-4 position by applying this methodology. Later, Gros and co-workers reported the use of the mild TMSCH$_2$Li as base to regioselectively lithiate the C-4 position of (S)-nicotine (1).

II.3.a.ii.2. Copper-catalyzed amidation of aryl halides.

It was anticipated that the introduction of amido groups could be accomplished via a transition metal-catalyzed process, since this transformation is well-established for carbon-heteroatom bond formation. Specifically, the copper-catalyzed arylation of amines, amides and carbamates has been a well-documented methodology discovered several decades before palladium and nickel-catalyzed strategies.

The sometimes harsh reaction conditions required for these transformations have limited their scope. However, the economic attractiveness of copper has in recent years led to a resurgence of interest in the Ullman- and Goldberg-type reactions. Particularly, Buchwald and Hartwig have made major contributions in the search for milder conditions in the
copper-catalyzed amidation of aryl halides, often by using bidentate ligands (Figure II-6).\textsuperscript{86,87,88}

![Selected examples of ligands used in copper-mediated amidation reactions.](image)

**Figure II-6.** Selected examples of ligands used in copper-mediated amidation reactions.

**II.3.a.iii. Amidation of (S)-6-chloronicotine (34).**

Based on literature protocols, and our previous knowledge of C-4 substitution of (S)-6-chloronicotine (34), a number of analogs were successfully prepared in two steps. First, iodination at the C-4 position of 34 to provide (S)-6-chloro-4-iodo-nicotine (147) was achieved by employing directed metalation methodologies developed in our group.\textsuperscript{23}

![Preparation of 6-Chloro-4-iodonicotine (147).](image)

**Scheme II-25.** Preparation of 6-Chloro-4-iodonicotine (147).

Next, reaction of 147 with different lactams (148-151, Figure II-7), base, a copper (I) salt and ancillary ligands, afforded the corresponding C-4 coupled derivatives, respectively (152-155, Figure II-8).
Figure II-7. Lactams used in the C-4 amidation of 147.

Under the reaction conditions studied, the use of diamino ligands proved to be effective for the coupling reaction, with the exception of compound 153, which was obtained by employing β-keto ester 146 as ligand. Conversely, when lactam 148 was treated with the same ligand, (S)-6-chloronicotine (34) was recovered. This result suggested that even though insertion of the metal center was accomplished, the cross-coupling did not occur.

Figure II-8. C-4 amido derivatives of 147.
Table II-7. C-4 Amidation of (S)-6-Chloronicotine (34) via 147.

<table>
<thead>
<tr>
<th>entry</th>
<th>RCONHR’</th>
<th>base</th>
<th>X</th>
<th>ligand</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>148</td>
<td>K$_3$PO$_4$</td>
<td>I</td>
<td>143</td>
<td>dioxane, 90 °C, 20 h</td>
<td>152 (36%)</td>
</tr>
<tr>
<td>2</td>
<td>149</td>
<td>Cs$_2$CO$_3$</td>
<td>Br</td>
<td>146</td>
<td>DMSO/THF, 60 °C, 48 h</td>
<td>153 (45%)</td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td>K$_3$PO$_4$</td>
<td>I</td>
<td>143</td>
<td>dioxane/DMSO, 90 °C, 48 h</td>
<td>154 (45%)</td>
</tr>
<tr>
<td>4</td>
<td>151</td>
<td>K$_3$PO$_4$</td>
<td>I</td>
<td>143</td>
<td>dioxane/DMSO, 90 °C, 48 h</td>
<td>155 (67%)</td>
</tr>
</tbody>
</table>

It is worth mentioning, that exploratory experiments employing phthalimide (156) as a model imide under similar reaction conditions were unfruitful (Scheme II-26). Modifications of either with solvent, ligand, temperature, time of reaction or copper pre-catalyst resulted in most cases with the recovery of the deiodinated product 34.
II.3.b. *Pyrrolidine ring of (S)-6-chloronicotine as a chiral transfer group.*

Additionally, we were interested in the C-4 acylation of (S)-6-chloronicotine (34). Our interest in this regard was beyond the stabilization of the protonated form of 34 by an electron donor at C-4. We also intended to explore the intrinsic ability of the chiral pyrrolidine moiety in 34 to stereoselectively direct alkylations to a C-4 carbonyl. Because of the versatility offered by an α-ketoester functionality, our initial target derivative was compound 158 (Scheme II-27). It was anticipated that a mercaptopyridine reagent could easily deliver the required acyl group *via* a substitution reaction of 34.

The study began with the preparation of the electrophile 159 (Scheme II-28). A solution of 2-mercaptopyridine (160) in toluene at 65 °C, was treated with TEA, followed by ethyl oxalyl chloride (161), to furnish the thioester 159 in quantitative yield.

[Scheme II-28. Preparation of Thioester 159.]

With 159 in hand, a number of reactions were attempted in order to obtain the C-4 keto ester derivative 158 (Table II-8). Various metalations using Zn, Mn, Mg, and Cu metal centers were studied; however, substitution at C-4 took place only with copper reagents (entries 8-10), and results were particularly good when diisopropyl sulfide was used as a cosolvent (entries 9 and 10).
Table II-8. Selected Attempts at the Preparation of α-Ketoester 158.

<table>
<thead>
<tr>
<th>entry</th>
<th>MLₙ</th>
<th>conditions A</th>
<th>conditions B</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>--</td>
<td>-78 °C to 0 °C, 3 h</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl₂•TMEDA</td>
<td>-78 °C, 30 min</td>
<td>-78 °C to rt, 17 h</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>MnCl₂•2LiCl</td>
<td>-78 °C to rt, 1 h</td>
<td>-78 °C to rt, 1 h</td>
<td>34</td>
</tr>
<tr>
<td>4*)</td>
<td>MgBr₂•OEt₂</td>
<td>-78 °C to rt, 1 h</td>
<td>-20 °C to rt, 12 h</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>CuSPh</td>
<td>-78 °C to rt, 1 h</td>
<td>-20 °C to rt, 1 h</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>CuCN•LiCl</td>
<td>-78 °C to rt, 1 h</td>
<td>-20 °C to rt, 2.5 d</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>CuCN•LiCl</td>
<td>-78 °C to rt, 1 h</td>
<td>-78 °C to rt, 1 h</td>
<td>34</td>
</tr>
<tr>
<td>8*)</td>
<td>CuCN</td>
<td>-78 °C to rt, 1 h</td>
<td>-20 °C to rt, 12 h</td>
<td>158 (18%)</td>
</tr>
<tr>
<td>9*)</td>
<td>CuBr•S(CH₃)₂</td>
<td>i-Pr₂S, -78 °C to rt, 1 h</td>
<td>-78 °C to rt, 20 h</td>
<td>158 (48%)</td>
</tr>
<tr>
<td>10*)</td>
<td>CuI</td>
<td>i-Pr₂S, -78 °C to rt, 1 h</td>
<td>-78 °C to rt, 1 h</td>
<td>158 (51%)</td>
</tr>
</tbody>
</table>

(*) The electrophile 136 was added neat, in all other cases it was added as a toluene solution.
Next, we proceeded to study organometallic addition to the newly installed ketoester fragment in 158. Initially, we performed experiments using a Grignard reagent (Table II-9).

**Table II-9.** Attempts at the Alkylation of 135 using a Grignard Reagent.

![Diagram showing chemical structures of 158, 162a, and 162b](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>EtMgCl equiv</th>
<th>LA</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>--</td>
<td>THF, -78 °C to rt, 15 h</td>
<td>162a (12%), 162b (9%)</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>CeCl₃</td>
<td>THF, -10 °C, 2 h</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>CeCl₃</td>
<td>THF, -20 °C to rt, 20 h</td>
<td>158</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>Ti(i-OPr)₄</td>
<td>THF, -78 °C to rt, 20 h</td>
<td>158</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>CuBr•SMe₂</td>
<td>THF, -78 °C to -40 °C, 2 h</td>
<td>158</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>ZnCl₂</td>
<td>THF, -20 °C to rt, 24 h</td>
<td>158</td>
</tr>
<tr>
<td>7</td>
<td>3.3</td>
<td>ZnCl₂</td>
<td>THF, -20 °C to rt, 15 h</td>
<td>158</td>
</tr>
</tbody>
</table>

Unfortunately, almost all of these reactions resulted in the recovery of starting material, except for one experiment in which the Grignard reagent was used alone; however, the yield and selectivity of formation of the diastereomeric alcohols 162a and 162b were not encouraging (entry 1). Attempts at the addition of the corresponding zinc(II) ate complex⁸⁹ were unfruitful. Subsequently, and in light of literature reports about successful addition of
dimethylzinc to α-ketoesters, we turned our efforts to the addition of alkylzinc reagents, as shown in Table II-10.

**Table II-10.** Attempts at the Alkylation of 158 using an Alkylzinc Reagent.

<table>
<thead>
<tr>
<th>entry</th>
<th>Et₂Zn equiv</th>
<th>LA</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>--</td>
<td>THF, -78 °C to rt, 20 h</td>
<td>158</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>Ti(i-OPr)₄</td>
<td>toluene, -40 °C to rt, 4 h</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>Ti(i-OPr)₄</td>
<td>THF, -78 °C to rt, 20 h</td>
<td>158</td>
</tr>
<tr>
<td>4(*)</td>
<td>1.4</td>
<td>--</td>
<td>toluene, 0 °C to rt, 20 h</td>
<td>decomp</td>
</tr>
</tbody>
</table>

(*)TMSCH₂Li (1.4 equiv) added.

Despite the amount of organometallic reagent used, Lewis acid, solvent or temperature changes, the results obtained were either decomposition or starting material recovered. Given these and the earlier results, a more reactive nucleophile appeared necessary, thus we decided to explore the use of trialkylzinc reagents (Table II-11).
Table II-11. Attempts at the Alkylation of 158 using a Trialkylzinc Reagent.

<table>
<thead>
<tr>
<th>entry</th>
<th>Et$_2$Zn : EtMgCl equiv</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1 : 1.1</td>
<td>THF, -78 °C to rt, 18 h</td>
<td>158</td>
</tr>
<tr>
<td>2</td>
<td>3.2 : 3.0</td>
<td>THF, -78 °C, 3.5 h</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>3.0 : 3.0</td>
<td>LiCl•THF, 0 °C to rt, 20 h</td>
<td>158</td>
</tr>
<tr>
<td>4</td>
<td>3.0 : 3.0</td>
<td>THF, -78 °C to rt, 24 h</td>
<td>162a (41%), 162b (9%)</td>
</tr>
<tr>
<td>5</td>
<td>4.0 : 3.0</td>
<td>THF, -40 °C to rt, 20 h</td>
<td>162a (36%), 162b (27%)</td>
</tr>
<tr>
<td>6</td>
<td>4.0 : 3.0</td>
<td>THF, -20 °C to rt, 24 h</td>
<td>162a (54%), 162b (36%)</td>
</tr>
<tr>
<td>7</td>
<td>4.0 : 3.0</td>
<td>toluene, 0 °C to rt, 20 h</td>
<td>decomp</td>
</tr>
<tr>
<td>8</td>
<td>5.0 : 5.0</td>
<td>toluene-CF$_3$, -20 °C to rt, 5 h</td>
<td>158</td>
</tr>
</tbody>
</table>

When either a small excess of the trialkylzinc reagent was employed (entry 1), or the reaction was kept at -78 °C along with a short reaction time (entry 2), only starting material was observed and recovered. Use of a LiCl•THF complex as the solvent did not assist the reaction, and again, 158 was recovered (entry 3). These initial attempts indicated that this reaction would require a larger excess of the organometallic reagent, higher temperature after the addition process, and extended reaction periods. Therefore, after these optimizations were
made, promising results were accomplished (entries 4-6). A slight excess of diethylzinc over the Grignard reagent proved to be beneficial in terms of the overall yields (entries 5 and 6). This fact could be attributed to a possible complexation taking place with the neighboring pyrrolidine nitrogen. Also, this reaction furnished the two diastereomeric alcohols 162a and 162b with a selectivity of 1.5:1. Only in one experiment (entry 4), the selectivity observed was 4.5:1; however, those conditions were not attempted again and this preliminary result could be overlooked due to the trends in the ratio observed in later reactions. The use of toluene or trifluorotoluene instead of THF did not promote the transformation, and the starting material was either recovered, or it decomposed during the reaction period (entries 7 and 8).

Additionally, two experiments were performed using 1.3 equiv of a triethyl aluminum/alkoxide complex.\(^91\) In the first experiment, THF was used as the solvent and the reaction proceeded from -50 °C to rt for 16 h (alkoxide: \(t\)-amyl alcohol, \(n\)-BuLi, hexanes/THF, -50 °C, 1 h); unfortunately, these conditions led to decomposition. In the second experiment, toluene was used, and the reaction was carried out from 0 °C to rt over 3 h (alkoxide: \(t\)-amyl alcohol, \(n\)-BuLi, hexanes/toluene, 0 °C, 1 h), but only starting material was recovered. Moreover, an experiment was carried out in which \(\alpha\)-ketoester 158 was treated with EtCeCl\(_2\)\(^92\) (\(t\)-BuLi, iodoethane, ether/pentane, -78 °C to rt, 2 h then CeCl\(_3\), THF, -78 °C to -20 °C, 1 h)\(^93\) at -78 °C for 1.5 h (Scheme II-29). Unfortunately, this reaction did not afford the corresponding alcohols even when the temperature was increased from -40 °C to 0 °C, and starting material (158) was recovered in all cases.
Finally, substitution at C-4 was also attempted by treatment of keto butyric ester 163 with a cerium reagent prepared *in situ* from a C-4 lithiated (S)-6-chloronicotine (34) (Scheme II-30). Despite the low yield found in this reaction, the enhanced selectivity towards diastereomeric alcohol 162a opened an alternative for future optimization.

Scheme II-30. C-4 Substitution of 34 via a Cerium Reagent.

After the alkylation study, the major diastereomeric alcohol 162a was used in a sequence of reactions in order to establish the stereochemistry at the newly formed stereocenter. Direct comparison of polarimetric results with those obtained from other closely-related analogs would allow us to assign the stereochemistry at C-7 in 158. Protection of alcohol 162a as the silyl ether 164, was achieved using TEA and DMAP in the presence of TMSCl (Scheme II-31).
Next, in order to make C-7 the only chiral center in a molecule, **164** was subjected to ring opening by treatment with cyanogen bromide to furnish exclusively the elimination product **166** in 43% yield (Scheme II-32).

De-protection of **166** was accomplished by treatment with 3.0 equiv of cesium fluoride. Curiously, unintended transesterification occurred under the conditions employed to give alcohol **167** in 63% yield. The same conditions using ethanol as the solvent gave compound **168** in 51% yield (Scheme II-33).
Scheme II-33. Desylilation of 166.

Subsequent polarimetric analysis of 168, and comparative study with results obtained for structural analogs in our laboratories, allowed us to conclude that the center at C-7 in 168 had the (R)-configuration. In conclusion, the pyrrolidine moiety in (S)-6-chloronicotine (34), indeed, acted as a chiral auxiliary to set the stereochemistry in the alkylation of C-7 in 158, favoring the (R)- over the (S)-configuration at the newly formed center. This preliminary study provided an opportunity to explore and expand our knowledge regarding the versatility of the pyrrolidine ring in (S)-nicotine derivatives as a chiral transfer group.
III. Total Synthesis of Cermizine D
III.1. **Introduction.**

**III.1.a. Abstract.**

This chapter presents a racemic synthesis of cermizine D (68) accomplished in six steps from 4-methoxypyridine in 14% overall yield. A key step is a stereoselective copper-mediated 1,4-addition to a bicyclic 2,3-dihydro-4-pyridone.

![Scheme III-1. General Plan for the Synthesis of Cermizine D (68).](image)

**III.1.b. Isolation and pharmacological potential of cermizine D.**

Cermizine D (68) is a cernuane-type Lycopodium alkaloid of the quinolizidine family. Along with cermizines A-C (Figure III-1), cermizine D was isolated and structurally elucidated in 2004 by Kobayashi and collaborators from the club mosses *Lycopodium cernuum* and *Lycopodium chinense*. The same group performed bioactivity studies that showed that cermizine D (68) exhibited citotoxicity against murine lymphoma L1210 cells, with an IC₅₀ of 7.5 µg/mL (30 µM). Related cermizine alkaloids have attracted the attention of a number of laboratories.
**Figure III-1.** Structure of cermizines A-D.

**III.1.c. Syntheses of (+)-cermizine D.**

Interestingly, before the isolation of cermizine D in 2003, two diastereomers of the natural product, 173 and 174 were synthesized (Figure III-2) by Ayer\(^\text{96}\) in 1967, and by Ban\(^\text{97}\) in 1975, while both groups were pursuing the synthesis of dihydrodeoxyepiallocernuine (175).

**Figure III-2.** Dihydrodeoxyepiallocernuine (175) and diastereomers of cermizine D.

The first asymmetric total synthesis of (+)-cermizine D ((+)\(-68\)) was reported by Takayama and coworkers in 2008 and consisted of an 18-step route featuring an oxazolidinone intermediate.\(^\text{98}\) Recently, in 2012, a second synthesis including two different approaches, a cuprate addition strategy and a PhSCH\(_2\)I alkylation pathway, 10 and 16 steps respectively, was published by Carter and collaborators.\(^\text{99}\)
III.1.c.i. Takayama’s asymmetric synthesis of (+)-cermizine D.

This approach (Scheme III-2) required 18 steps and commenced with the carbonyl protection of (+)-citronellal (176), followed by Ru-catalyzed oxidative cleavage of the olefin bond. The resulting aldehyde 178 was subjected to α-amination and subsequent reduction to give hydrazinoalcohol 179. After treatment of 179 with K₂CO₃ and reductive N-N bond cleavage of the hydrazine group in 180, oxazolidinone 181 was obtained. Acid-catalyzed cyclization provided aminoacetal 182 which under Hosomi-Sakurai allylation¹⁰⁰ conditions yielded 184 exclusively. After hydrolysis of the oxazolidinone, 185 was subjected to a three-step sequence, acroylation, RCM and hydrogenation to give alcohol 188. This alcohol was oxidized with IBX, and the corresponding aldehyde was subjected to a Wittig reaction,¹⁰¹ and acid hydrolysis to afford aldehyde 190. Kobayashi’s aminoallylation¹⁰² protocol was used to provide homoallylamine 192. Finally, piperidone 194 was obtained using the same three-step sequence used to obtain alcohol 188, starting with acryloylation of 192, followed by RCM and hydrogenation. Reduction of 194 with LiAlH₄ furnished (+)-68.
Scheme III-2. Takayama’s Synthesis of (+)-Cermizine D.
III.1.c.ii. Carter’s enantioselective synthesis of (+)-cermizine D.

In this 16-step approach (Scheme III-3), commercially available amine 195 was used as the starting material. After Boc-protection and cross-metathesis, an intramolecular Michael addition provided heterocycle 200. Homologation via Wittig olefination and enol ether cleavage yielded aldehyde 202. Pinnick oxidation\textsuperscript{103} of 202, followed by coupling with Evans oxazolidinone\textsuperscript{104} and diastereoselective alkylation, gave compound 205. Lithium borohydride reduction of 205 followed by sulfide oxidation and deoxygenation provided sulfone 207. Deprotonation of sulfone 207 and reaction with the previously generated aldehyde 200 gave the hydroxysulfone 208 as a diastereomeric mixture. Oxidation of the undesired diastereomer and subsequent reduction generated a near equal diastereomeric mixture. Desulfurization of the hydroxy sulfone 209 with Raney-Ni followed by deprotection and cyclization furnished (+)-68.
Scheme III-3. Carter’s 16-Step Approach toward the Synthesis of (+)-Cermizine D.

Alternatively, in a 10-step route (Scheme III-4), aldehyde 200 was obtained in 3 steps using the same protocol as in the 16-step approach. Next, sulfone 212 was obtained after treatment of aldehyde 200 using a Horner-Wadsworth-Emmons olefination protocol, and then subjected to a copper-mediated conjugate addition to finally give sulfone 207. The remaining five steps are identical to the 16-step approach.
III.1.c.iii. \textit{Absolute configuration of the natural product cermizine-D.}

Initially, when cermizine D was isolated by Kobayashi in 2004, their published work refers indistinctly to two enantiomers, 68 and \textit{ent-}68, as the natural product (Figure III-3). The specific rotation reported for the TFA salt of cermizine D was $[\alpha]_{D}^{25} = -33$ (c 0.6, MeOH). Later, Takayama in 2008, and Carter in 2012, reported specific rotations of $[\alpha]_{D}^{20} = +24$ (c 0.5, MeOH) and $[\alpha]_{D}^{20} = +16.8$ (c 0.41, MeOH) respectively for the TFA salt of their synthetic cermizine D. By comparison of the synthetic and isolation data, it seems reasonable to conclude that the synthetic results correspond, in fact, to the synthetic enantiomer of cermizine D (\textit{ent-}68); thus, indirectly, the absolute configuration of the natural product has been confirmed to be 68.
Figure III-3. Absolute configuration of natural cermizine D (68).

![Diagram of chemical structures]
III.2. Synthesis of Cermizine D via N-Acylpyridinium Salt Chemistry

III.2.a. First generation approach - retrosynthetic plan.

In our initial approach (Scheme III-14), we envisioned that cermizine D (68) could be synthesized from commercially available 4-methoxypyridine (169) making use of N-acylpyridinium salt chemistry methodologies developed in the Comins group. These protocols would lead to 214, the key intermediate in the synthesis, which after using a zinc-mediated conjugate addition, a cross-coupling reaction, an intramolecular hydroamination, and two consecutive hydrogenations would furnish the natural product.

Scheme III-5. First Generation Approach - Retrosynthetic Plan.

III.2.a.i. N-Acylpyridinium salt reaction.

Accordingly to our ample knowledge of N-acylpyridinium salt chemistry, 4-methoxypyridine (169) was treated with phenyl chloroformate and (4-chlorobutyl)magnesium bromide\(^{106}\) (215) using a known protocol\(^{107}\) to provide the corresponding dihydropyridone 216. As previously described,\(^{108,109}\) treatment of 216 with freshly prepared NaOMe in refluxing methanol afforded the byciclic enone 214, the key intermediate in our route towards cermizine D (Scheme III-6).
Scheme III-6. N-Acylpyridinium Salt Sequence to Prepare Dihydropyridone 214.

III.2.a.ii. 1,4-Addition to the iminium salt of 214.

III.2.a.ii.1. Zinc-mediated alkynylation.

Initially, it was envisioned that addition of an alkynyl nitrile fragment to our enaminone would provide a suitable intermediate for a later cyclization to form the last piperidine ring. Interesting reports\textsuperscript{110} on the zinc-mediated alkynylation of activated imines caught our attention, particularly, Carreira’s approach,\textsuperscript{110} in which zinc-alkynylides were prepared directly from terminal alkynes and zinc salts.

In our case, the alkynyl-zinc reagent was obtained from hex-5-ynenitrile (216) using a zinc triflate, triethylamine and TMPDA system, in toluene at rt (Scheme III-8). The iminium salt 214a was prepared from our enaminone 214 using triflic anhydride. The triflate functionality thus obtained would serve as a handle for the upcoming cross-coupling to install the last carbon in the molecule. Even though only one diastereomer was observed by \textsuperscript{1}H NMR inspection, these reactions were low yielding and optimizations unfruitful.
Scheme III-7. Attempts at the Zinc-Mediated Alkynylation of 214.

From the previous experiments, we learned that our solvent of choice for both, alkynyl-zinc preparation and iminium salt formation, should be DCM; also, the presence of TMPDA proved to be beneficial in terms of the organozinc solubility, and extended reaction times for the preparation of the alkynyl-zinc were required. With these observations in mind, we decided to use a different protocol\textsuperscript{110} to prepare the alkynyl-zinc reagent (Scheme III-8). A solution of hex-5-ynenitrile (217) in DCM was treated with dimethylzinc at rt, in the presence of TMPDA, this mixture was stirred for 20 h before use. After treatment of the iminium salt 214a with the organometallic, triflate 218 was obtained in 44\% yield, a result that was well-received at this point.
III.2.a.ii.2. Silyl enol ether strategy.

Before moving to the next step, we decided to try a different strategy: the use of a silyl enol ether featuring a terminal nitrile, as the nucleophile in the addition reaction to the bicyclic enone 214. Accordingly, silyl enol ether 221 would be easily accessed from ethyl acetoacetate (219, Scheme III-9).


Treatment of 219 with sodium ethoxide followed by addition of acrylonitrile furnished 222 in 38% yield (Scheme III-10). Ester hydrolysis and decarboxylation of 222 gave ketone 220 in 68% yield. In order to prepare the anticipated silyl enol ether 221, ketone 220 was treated with LDA and TMSCl under kinetic conditions; however, several trials proved to
be ineffective, and $^1$H NMR of the different crude products showed formation of initially undesired 223.

Scheme III-10. Attempts to Prepare Silyl Enol Ether 221.

Unable to access silyl ether 221, we resorted to the use of the bis-silyl compound 223 instead for the addition reaction (Scheme III-11). These attempts failed, and only the partially desilylated compound was recovered. Consequently, we decided to proceed to the cross coupling reaction using triflate 218.

Scheme III-11. Attempts at the Addition of Silyl Enol Ether 222.
III.2.a.iii. **Installation of C-16.**

The triflate functionality at C-15 in 218 was anticipated to participate in a Suzuki-Miyaura\textsuperscript{112} cross-coupling in order to install the last carbon in the molecule. Initial attempts were carried out using trimethylboroxine as the methylating agent, but only traces of 225 were isolated as a result.\textsuperscript{113} A similar procedure using methyl boronic acid proved to be efficient for this transformation.\textsuperscript{114} When a mixture of 218, methyl boronic acid, K\textsubscript{2}CO\textsubscript{3} as the base, and PdCl\textsubscript{2}(dppf) as the catalyst was subjected to reflux for 24 h, compound 225 was obtained in 68\% yield.

![Scheme III-12: Installation of C-16 in 218 via Cross-Coupling.](image)

**Scheme III-12.** Installation of C-16 in 218 via Cross-Coupling.

II.1.a.i. **Selective reduction of the nitrile.**

Next, reduction of the nitrile group was investigated. Because of the triple bond present in the molecule, the selection of the reducing conditions was limited. Table III-1 summarizes the different conditions explored.
First, diisopropylaminoborane, with catalytic amounts of LiBH₄, was employed as the reducing agent, since it has been reported that it can reduce nitriles in the presence of other susceptible functional groups including alkynes; however, only starting material 225 was recovered from this reaction. A combination of NaBH₄ and trifluoroacetic acid was also unproductive. Evidence of the reduction of hex-5-yenitrile (217) to the corresponding amine using LiAlH₄ was encouraging, and our results with LiAlH₄ were satisfactory when temperatures were increased (entries 4 and 5). Mass spectra analysis of the crude product confirmed its formation, yet, all attempts to purify this compound failed, and the crude product was used directly in the next step.
**Table III-1.** Selective Reduction of Nitrile 225.

<table>
<thead>
<tr>
<th>entry</th>
<th>reducing agent</th>
<th>solvent</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(i-Pr)₂NBH₃/LiBH₄</td>
<td>THF</td>
<td>rt, 3 h</td>
<td>225</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₃(OCOCF₃)¹¹⁷</td>
<td>THF</td>
<td>rt, 3 h</td>
<td>225</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄</td>
<td>Et₂O</td>
<td>0 °C to rt, 15 h</td>
<td>225</td>
</tr>
<tr>
<td>4(*)</td>
<td>LiAlH₄</td>
<td>i-Pr₂O</td>
<td>reflux, 1 h</td>
<td>226 (69%)</td>
</tr>
<tr>
<td>5(*)</td>
<td>LiAlH₄</td>
<td>THF</td>
<td>reflux, 1 h</td>
<td>226 (85%)</td>
</tr>
</tbody>
</table>

(*)Crude yield.

**II.1.a.ii. Intramolecular hydroamination.**

Inspired by the work of Doye¹¹⁸ which indicates that Petasis reagent¹¹⁹ (Cp₂TiMe₂) is an active catalyst for the intramolecular hydroamination/cyclization of aminoalkynes, we decided to apply these protocols in our molecule. A subsequent hydrosilylation of the imine intermediate would finally provide the piperidine ring in 226 (Scheme III-13). Cp₂TiMe₂ was prepared according to a literature procedure.¹²⁰ Unfortunately, even when the amount of the
titanocene catalyst was increased, the cyclization did not occur, and the starting amine 226 was recovered.

**Scheme III-13.** Attempts at the Intramolecular Hydroamination of 226.

Given these results, we concluded that the demand for amine 226 would be more than expected to continue the screening of cyclization conditions. At the same time, the limited amounts of triflate 218 being produced by the Zn-mediated addition reaction, and the difficult purifications, were restricting our ability to proceed with this route without exploring other alternatives. This initial approach was then paused, so we could dedicate our efforts to modifying the crucial addition step.

**III.2.b. Second generation approach - retrosynthetic plan.**

Our next approach (Scheme III-14) would keep the common intermediate 214, which would be expected to undergo a metal-mediated conjugate addition of a cyclic piperidine precursor. As in our initial strategy, a cross-coupling followed by two consecutive hydrogenations would complete the synthesis of cermizine D (68).

In order to evade a cyclization step, we decided to explore alternative additions in which a cyclic piperidine precursor would be utilized. Later in the synthesis a simple transformation of this moiety should be sufficient to generate the piperidine ring.

III.2.b.i. Addition of 2-methyl-1,2-dehydropiperidine.

It was envisioned that 2-methyl-1,2-dehydropiperidine (230) could be a direct precursor of the piperidine ring in cermizine D (68). Metalation of 230 (Scheme III-15) would make it a suitable partner in the 1,4-addition to the pre-formed iminium salt of 214 to give triflate 231.

We initiated our screening with the attempts to prepare 230 (Scheme III-16). Reports in the literature\textsuperscript{121} indicate that 230 has been prepared from 2-piperidone (232), in two steps: \(N\)-protection of the lactam followed by methylation and deprotection. In our case, while the first step was easily controlled and gave the silylated lactam 233 in 65\% yield, the second step did not work under the conditions studied, and this route was abandoned.

\textbf{Scheme III-16.} Attempts at the Preparation of 2-Methyl-1,2-dehydropiperidine (230).

\textit{III.2.b.\textit{ii.} Addition of 2-methylpyridine – First screening.}

In the meantime, the addition of 2-methylpyridine (235) to enone 214 was also under study. A number of metalation/transmetalation experiments were carried out in our screening for a suitable nucleophile (Table III-2 and Table III-3).
Table III-2. Initial Attempts to the Preparation of Trflate 236a.

Attempts at the addition reaction using the lithiated 2-methylpyridine\(^{122}\) led to decomposition, and transmetalation to the corresponding organozinc nucleophile was equally unsuccessful (Table III-2). Given these initial results, we were interested in the preparation of a pre-formed nucleophile such as the corresponding organotin. Therefore, lithiation of 2-methylpyridine (235) followed by transmetalation using tributyltin chloride provided compound 235c in 47% yield.\(^{123}\)
Next, several experiments were conducted using $235c$ as the nucleophile in the conjugate addition reaction (Table III-3). As a result, it was found that this transformation required low temperature in order to proceed without decomposition. After optimization, it was established that compound $236a$ could be obtained in 47% yield, with a 3:1 diastereomeric ratio.

**Scheme III-17.** Preparation of 2-((Tributylstannyl)methyl)pyridine ($235c$).
Table III-3. Preparation of Triflate 236a using an Organotin Reagent.

![Chemical Structures]

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile equiv</th>
<th>conditions</th>
<th>results (%)</th>
<th>dr&lt;sup&gt;(a)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -20 °C to 0 °C, 1 h</td>
<td>decomp</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -20 °C, 30 min</td>
<td>decomp</td>
<td>--</td>
</tr>
<tr>
<td>3&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>1.05</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78 °C, 4 h</td>
<td><strong>236a</strong> (29%) + <strong>236b</strong></td>
<td>3:1</td>
</tr>
<tr>
<td>4&lt;sup&gt;(b),(c)&lt;/sup&gt;</td>
<td>1.05</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78 °C, 4 h</td>
<td><strong>236a</strong> (39%) + <strong>236b</strong></td>
<td>3:1</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78 °C, 4 h</td>
<td><strong>236a</strong> (37%) + <strong>236b</strong> (10%)</td>
<td>3:1</td>
</tr>
</tbody>
</table>

<sup>(a)</sup>Diastereomeric ratio determined by <sup>1</sup>H NMR inspection of the crude product. <sup>(b)</sup>Minor diastereomer (236b) was not isolated. <sup>(c)</sup>Reverse addition, tin reagent added to enaminone 214, then Tf<sub>2</sub>O.

Finally, eventhough we were not fully satisfied with the selectivity of this transformation, it was a good opportunity to examine the feasibility of the cross-coupling reaction at C-15 on this new substrate.

**III.2.b.iii. Attempts at the cross-coupling reaction to install C-16.**

As in previous experiments, we first aimed for the cross-coupling of the purposely installed triflate functionality in **236a**; however, Pd-catalyzed Suzuki reactions using methyl
boronic acid were fruitless (Table III 4, entries 1 and 2). Secondly, cross-coupling under Kumada conditions was pursued, but all attempts were unsuccessful. Finally, a Gilman cuprate\textsuperscript{124} strategy was employed in order to couple with the vinyl triflate 236a. Unfortunately, once more the transformation did not occur. It was concluded that our new triflate substrate (236a) was either unreactive to the cross-coupling conditions used, or it was simply deactivating the catalysts; therefore, installation of C-16 should be carried out using a different type of transformation.

Table III 4. Attempts at the Methylation of 236a.

<table>
<thead>
<tr>
<th>entry</th>
<th>methylating agent</th>
<th>catalyst (mol%)</th>
<th>base</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeB(OH)\textsubscript{2}</td>
<td>PdCl\textsubscript{2}(dppf) (10.0)</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>THF/H\textsubscript{2}O, 100 °C, 4 h</td>
<td>236a</td>
</tr>
<tr>
<td>2</td>
<td>MeB(OH)\textsubscript{2}</td>
<td>PdCl\textsubscript{2}(dppf) (10.0)</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>THF/H\textsubscript{2}O, 100 °C, 24 h decomp</td>
<td>236a</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>NiCl\textsubscript{2}(dppf) (10.0)</td>
<td>--</td>
<td>Toluene, rt, 3 h</td>
<td>236a</td>
</tr>
<tr>
<td>4</td>
<td>MeMgBr</td>
<td>Ni(acac)\textsubscript{2} (10.0)</td>
<td>--</td>
<td>THF, 0 °C to rt, 4 h</td>
<td>236a</td>
</tr>
<tr>
<td>5</td>
<td>MeMgBr</td>
<td>Fe(acac)\textsubscript{3} (10.0)</td>
<td>--</td>
<td>THF/NMP, -30 °C to rt, 4 h</td>
<td>236a</td>
</tr>
<tr>
<td>6</td>
<td>Me\textsubscript{2}CuLi</td>
<td>--</td>
<td>--</td>
<td>THF, -10 °C, 14 h</td>
<td>236a</td>
</tr>
</tbody>
</table>
Since C-15 methylation through this route proved unsuccessful, the ketone functionality should be recovered after the addition reaction in order to open up alternatives; therefore, activation of the bicyclic dihydropyridone 214, if any, should be provided by a group prone to hydrolysis.

**III.2.b.iv. Initial attempts at a Wittig olefination.**

It was envisioned that after the addition reaction the regenerated keto group at C-15 could be used for a Wittig olefination (Scheme III-18). Subsequent reduction would finally set the C-15 methyl group in place.

![Scheme III-18. Retrosynthesis of Cermizine D via Wittig Olefination.](image)

Consequently, a series of experiments were carried out using TFAA for the iminium salt formation (Scheme III-19). Unfortunately, no evidence of the formation of the salt was collected, and the starting enone 214 was recovered at all instances, in combination with complex mixtures, an indication that the TFAA was presumably being attacked by the nucleophile.
In summary, the stereoselectivity observed at C-7 was unsatisfactory, and our efforts to recover the ketone functionality at C-15 were unsuccessful when the addition reaction was carried out using the organotin reagent 235c. Once again, it was necessary to reassess the addition step.


As a result of the previous experiments, it was decided to continue our screening to generate a suitable nucleophile from 2-methylpyridine (235) that could provide better selectivity in the 1,4-addition reaction, and would not react with any Lewis acid used to promote the addition. First, we continued with the protocol of using a pre-formed iminium salt to undergo the addition reaction, this time either TMSOTf or TIPSOTf was used to form the salt (Table III-4).

**Scheme III-19.** Attempts at the 1,4-Addition to Form Ketone 239a.
Table III-4. Preparation of 239a using a Pre-formed Iminium Salt of 214.

<table>
<thead>
<tr>
<th>entry</th>
<th>R-Li (equiv)</th>
<th>ML&lt;sub&gt;n&lt;/sub&gt; (equiv)</th>
<th>conditions A</th>
<th>conditions B</th>
<th>results (%)&lt;sub&gt;1&lt;/sub&gt;, dr&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>4.0</td>
<td>--</td>
<td>--</td>
<td>-78 °C, 2 h</td>
<td>239a + 239b (1:1)</td>
</tr>
<tr>
<td>2&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>4.9</td>
<td>--</td>
<td>--</td>
<td>-78 °C, 2 h</td>
<td>214</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>ZnCl&lt;sub&gt;2&lt;/sub&gt; (2.0)</td>
<td>-30 °C to rt, 1 h</td>
<td>-60 °C, 1 h</td>
<td>214</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>CuBr•SMe&lt;sub&gt;2&lt;/sub&gt; (1.3)</td>
<td>-30 °C, 2 h</td>
<td>-78 °C, 2 h</td>
<td>214</td>
</tr>
<tr>
<td>5&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>4.0</td>
<td>CeCl&lt;sub&gt;3&lt;/sub&gt; (4.0)</td>
<td>-78 °C, 2 h</td>
<td>-78 °C, 2 h</td>
<td>239a (56%) + 239b (2:1)</td>
</tr>
<tr>
<td>6&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>4.0</td>
<td>MgBr&lt;sub&gt;2&lt;/sub&gt;•OEt&lt;sub&gt;2&lt;/sub&gt; (4.0)</td>
<td>-30 °C to rt, 2 h</td>
<td>-50 °C, 1 h</td>
<td>239a + 239b (1.5:1)</td>
</tr>
<tr>
<td>7</td>
<td>4.0</td>
<td>MnCl&lt;sub&gt;2&lt;/sub&gt;•2LiCl (4.4)</td>
<td>-30 °C, 2 h</td>
<td>-50 °C, 2 h</td>
<td>214</td>
</tr>
<tr>
<td>8</td>
<td>5.3</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;•OEt&lt;sub&gt;2&lt;/sub&gt; (5.3)</td>
<td>-30 °C to 0 °C, 1 h</td>
<td>-78 °C to 0 °C, 2 h</td>
<td>214</td>
</tr>
</tbody>
</table>

<sup>(a)</sup>Crude mixture, diastereomeric ratio determined by <sup>1</sup>H NMR inspection. <sup>(b)</sup>TIPSOTf (1.0 equiv) was used instead of TMSOTf. <sup>(c)</sup>Minor diastereomer (239b) was not isolated.
A variety of organometallic reagents were prepared from the corresponding lithiated 2-methylpyridine 235a. When 235a was used directly, ketones 239a and 239b were obtained; however, there was no selectivity at the newly formed stereocenter (entry 1), and change of the Lewis acid resulted in the recovery of starting material (entry 2). The corresponding organocerium reagent provided 239a and 239b in 56% yield, with a dr = 2:1, respectively (entry 5). An equally disappointing selectivity, dr = 1.5:1, was found when an organomagnesium reagent was employed (entry 6). All other attempts resulted in the recovery of the starting enaminone 214.

Next, continuing our search for better selectivity and to solve some solubility restrictions encountered with the pre-formed salt strategy, a series of experiments using a modified Pirnot’s protocol125 were carried out. Thus, a solution of enone 214 in THF was added to the Gilman cuprate of 235, followed in most cases by addition of a Lewis acid (Table III-5). As expected, when the Lewis acid was not present the addition reaction did not occur, regardless of the amount of organometallic used (entries 1 and 2). When BF₃•OEt₂ was used, the reaction proceeded only when 4.0 equivalents of the Lewis acid were employed; however, no selectivity was observed (entries 3 and 4). Interestingly, when TMSCl126 was used instead, the best selectivity of all instances was found, dr = 3.7:1. Nevertheless, this result seemed to be dependent on the nature of the copper salt employed (entries 5-7).
Table III-5. Preparation of Ketone 239a with \textit{in situ} Activation of Enone 214.

<table>
<thead>
<tr>
<th>entry</th>
<th>LA (equiv)</th>
<th>R-Li (equiv)</th>
<th>CuX (equiv)</th>
<th>results (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>2.2</td>
<td>CuBr\textbullet SMe$_2$ (1.1)</td>
<td>214</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>--</td>
<td>3.0</td>
<td>CuBr\textbullet SMe$_2$ (1.5)</td>
<td>214</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>BF$_3$\textbullet OEt$_2$ (2.0)</td>
<td>2.2</td>
<td>CuBr\textbullet SMe$_2$ (1.1)</td>
<td>214</td>
<td>--</td>
</tr>
<tr>
<td>4$^{(a)}$</td>
<td>BF$_3$\textbullet OEt$_2$ (4.0)</td>
<td>4.0</td>
<td>CuBr\textbullet SMe$_2$ (2.0)</td>
<td>214 + 239a + 239b</td>
<td>--</td>
</tr>
<tr>
<td>5$^{(a)}$</td>
<td>TMSCl (3.0)</td>
<td>3.0</td>
<td>CuBr\textbullet SMe$_2$ (1.5)</td>
<td>239a (31%) + 239b</td>
<td>3.7:1</td>
</tr>
<tr>
<td>6</td>
<td>TMSCl (4.0)</td>
<td>4.0</td>
<td>CuBr\textbullet SMe$_2$ (2.0)</td>
<td>239a (80%) + 239b</td>
<td>3.7:1</td>
</tr>
<tr>
<td>7$^{(b)}$</td>
<td>TMSCl (4.0)</td>
<td>4.0</td>
<td>CuI\textbullet P(O\textit{Pr})$_3$ (2.0)</td>
<td>239a + 239b (100%)</td>
<td>1:1</td>
</tr>
</tbody>
</table>

$^{(a)}$Crude mixture, diastereomeric ratio determined by $^1$H NMR inspection. $^{(b)}$Recovered as a mixture after RPLC (SiO$_2$).

It is worth mentioning that the initial result obtained when using TMSCl was a mixture of the corresponding silyl enol ethers 240a and 240b as evidenced by $^1$H NMR analysis of the crude product mixture (Figure III-4). Attempts to purify this mixture were unproductive,
as these compounds proved to be unstable. However, some adjustments in the work-up, including the use of 20% NH₄F solution for the hydrolysis, were sufficient to completely overcome the early problems.

**Figure III-4.** Undesired silyl enol ethers 240a and 240b.

Eventhough the best results obtained were comparable to the previous screening in terms of selectivity, the improved yields found here were slightly more encouraging. Therefore, in our final tuning of this reaction, the *in situ* activation protocol would be preferred to the pre-formed salt approach, and CuBr•SMe₂ would be kept as the copper salt of choice. Additionally, the poor selectivity shown by the different organometallic reagents under study gave us enough data to believe that in order to improve the selectivity of this reaction we needed to alter the nature of the non-selective 2-methylpyridine nucleophile.
III.2.b.vi. Addition of 2-((trimethylsilyl)methyl)pyridine.

Based on the previous results, it was decided to introduce a substituent on the methyl group of 2-methylpyridine (235) that would cause some steric hindrance in the addition reaction, and that would be easy to remove afterwards. Thus, 2-((trimethylsilyl)methyl)pyridine (241) was prepared according to a literature procedure\textsuperscript{127} from 235 in 80\% yield (Scheme III-20).

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{reaction.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme III-20.} Preparation of 2-((Trimethylsilyl)methyl)pyridine (241).

With 241 in hand, we moved to the addition reaction, employing the previously established best conditions using 235d (Scheme III-21). To our delight, the use of 2-((trimethylsilyl)methyl)pyridine (241) proved to be an excellent choice, since the reaction proceeded in good yield and with full stereoselectivity towards the sought after diastereomer 239a. To the best of our knowledge, this is the first time that 241 has been used to direct the stereochemistry of a conjugate addition reaction. After this outstanding result, the Wittig olefination was revisited.
Finally, as previously described, the next step in our synthesis would be the Wittig olefination to install the last carbon in the molecule at C-15. The Wittig reagent was prepared by treating methyltriphenylphosphonium bromide with \( n\)-BuLi in THF at 0 °C for 1 h. Next, the ylide was treated with a solution of ketone 239a in THF, different temperatures and times of reaction were studied to increase yield (Table III-6, entries 1 and 2). It was observed that this reaction required room temperature and extended reaction periods (entries 3 and 4) to proceed in high yield, but it was also noted that the work-up conditions were equally important. In most cases, the reaction was quenched with saturated NaHCO\(_3\) solution and subsequent extractions performed using DCM to give good yields. However, when the reaction was quenched and the mixture stirred for 4 h with the saturated NaHCO\(_3\) solution, followed by extractions using \( \text{Et}_2\text{O} \), a remarkable increase in the yield of 238 was obtained (entry 4). It was concluded that besides requiring more time for hydrolysis, a crude
containing less amounts of phosphonium by-products would substantially improve the purification process and therefore the yield. No additional optimization was required, and the hydrogenation steps were explored next.

Table III-6. Optimization of Conditions for the Wittig Olefination of 239a.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-20 °C, 1 h</td>
<td>238 (41%)</td>
</tr>
<tr>
<td>2</td>
<td>-20 °C to 0 °C, 2 h</td>
<td>238 (49%)</td>
</tr>
<tr>
<td>3</td>
<td>-20 °C to rt, 20 h</td>
<td>238 (77%)</td>
</tr>
<tr>
<td>4(*)</td>
<td>-20 °C to rt, 24 h</td>
<td>238 (98%)</td>
</tr>
</tbody>
</table>

(*') Reaction mixture was quenched and stirred at rt for 4 h with NaHCO₃ saturated solution.

III.2.c. Hydrogenations.

As it was stated in our retrosynthetic plan, the next steps would involve two consecutive hydrogenations to finally obtain the natural product, cermizine D (68). This new stage of the synthesis was commenced by the reduction of the newly formed double bond in 238.
III.2.c.i. Reduction of the acyclic double bond.

Our first attempts for this reduction were performed using Pd/C as the catalyst (Table III-7, entries 1-6). Unfortunately, in most cases, migration of the double bond was observed (Figure III-5), and changes in the conditions of this reaction were ineffective.

![Figure III-5. Undesired double bond migration products.](image)

The use of the Wilkinson’s catalyst\(^\text{129}\) (entry 7) resulted in the recovery of starting material. Both, Raney-Ni and Pd(OH)\(_2\) on carbon gave diastereomer 243b as the major product, in good yields. Interestingly, when Pt/C was used, the selectivity was reversed, and compound 243a was the major diastereomer obtained, also in good yield. Other solvents gave the same results as with EtOAc (entry 10). These results were captivating, since not only the natural product but the C-15 epimer of cermizine D (68) could be accessed without difficulty using fairly simple hydrogenation reactions.
Table III-7. Selected Examples at the Reduction of the Acyclic Double Bond in 238.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>time (h)</th>
<th>results (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>Pd/C</td>
<td>EtOH</td>
<td>2</td>
<td>238 + 242a + 242b</td>
<td>--</td>
</tr>
<tr>
<td>2&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>Pd/C</td>
<td>EtOH</td>
<td>24</td>
<td>242a + 242b</td>
<td>--</td>
</tr>
<tr>
<td>3&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>Pd/C</td>
<td>EtOH</td>
<td>42</td>
<td>242a + 242b</td>
<td>--</td>
</tr>
<tr>
<td>4&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>Pd/C</td>
<td>EtOAc</td>
<td>30</td>
<td>242a + 242b</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>Pd/C</td>
<td>AcOH</td>
<td>36</td>
<td>complex mixture</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>Pd/C</td>
<td>AcOH</td>
<td>72</td>
<td>complex mixture</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>RhCl(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Benzene</td>
<td>20</td>
<td>238</td>
<td>--</td>
</tr>
<tr>
<td>8&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>Raney-Ni</td>
<td>MeOH</td>
<td>20</td>
<td>243a + 243b, (100)</td>
<td>1:11.5</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OH)&lt;sub&gt;2&lt;/sub&gt;/C</td>
<td>MeOH</td>
<td>20</td>
<td>243a (traces) + 243b (59%)</td>
<td>--</td>
</tr>
<tr>
<td>10&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>Pt/C</td>
<td>EtOAc</td>
<td>20</td>
<td>243a + 243b, (96)</td>
<td>4:1</td>
</tr>
</tbody>
</table>

<sup>(a)</sup>Crude mixture. <sup>(b)</sup>Crude yield, diastereomeric ratio determined by <sup>1</sup>H NMR analysis.
III.2.c.ii. Reduction of the pyridine ring.

In order to complete the synthesis of cermizine D (68), the last step comprised of completing the reduction of the pyridine ring to the corresponding piperidine. The catalyst of choice for this type of transformation is PtO$_2$, and only slight changes in the conditions were studied.

Table III-8. Model Reduction of the Pyridine Ring in 243b.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>time (h)</th>
<th>results (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PtO$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>20</td>
<td>243b</td>
<td>--</td>
</tr>
<tr>
<td>2*)</td>
<td>PtO$_2$</td>
<td>AcOH</td>
<td>20</td>
<td>244a + 244b, (87%)</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>LiBEt$_3$H</td>
<td>THF</td>
<td>1</td>
<td>243b</td>
<td>--</td>
</tr>
</tbody>
</table>

(*) Crude yield, diastereomeric ratio determined by $^1$H NMR analysis.

The results displayed in Table III-8, where compound 243b was used as a model, show that the selection of the solvent was crucial to accomplish the transformation into the reduced products 244a and 244b respectively. In the same way, the substrate pyridine was susceptible
to reduction only when it was protonated (entry 2). In the only case in which superhydride Li\(\text{BEt}_3\text{H}^{131}\) was utilized, starting material was completely recovered (entry 3).

Finally, an experiment using ethanol as the solvent in the presence of oxalic acid proved to be also suitable for the conversion of \(243a\) into \(68\) and \(68a\), respectively (Table III-9, entry 1). Also, as observed with the model \(243b\), the use of AcOH as the solvent also accomplished the reduction of the pyridine ring when \(243a\) was treated with PtO\(_2\) (entry 2).

**Table III-9.** Reduction of the Pyridine Ring in \(243a\).

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>time (h)</th>
<th>results (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{(a),(b)})</td>
<td>PtO(_2)</td>
<td>EtOH</td>
<td>20</td>
<td>68 + 68a, (92%)</td>
<td>1:1</td>
</tr>
<tr>
<td>2(^{(b)})</td>
<td>PtO(_2)</td>
<td>AcOH</td>
<td>20</td>
<td>68 + 68a, (95%)</td>
<td>1:1</td>
</tr>
</tbody>
</table>

\(^{(a)}\) Oxalic acid (1.0 equiv) was added. \(^{(b)}\) Crude yield, diastereomeric ratio determined by \(^1\)H NMR analysis.
III.2.c. **Summary of the total synthesis.**

In summary, cermizine D (68) was synthesized in six steps via N-acylpyridinium salt chemistry. The synthesis commenced with the preparation of dihydropyridone 216, after treatment of 4-methoxypyridine (169) with phenyl chloroformate followed by reaction with (4-chlorobutyl)magnesium bromide (215). Dihydropyridone 216 was then subjected to a base-induced cyclization using sodium methoxide to furnish the bibyclic 1,2-dihydropyridone intermediate 214. Conjugate addition of 214 with the *in situ* generated Gilman cuprate 241b in the presence of TMSCl provided 239a as one diastereomer. A Wittig olefination of ketone 239a gave the corresponding acyclic olefin 238 in 98% yield. Two subsequent hydrogenations finally delivered the racemic natural product cermizine D (68) with an overall yield of 13%, along with C5-epi-cermizine D 68a.

III.2.d. **Conclusion.**

The synthesis of the Lycopodium alkaloid cermizine D was accomplished after extensive optimization, using N-acylpyridinium salt chemistry methodologies, and consisted in a six-step route from 4-methoxypyridine and in 14% overall yield. Central in this synthesis, was an enantioselective copper-mediated 1,4-addition to a bicyclic 2,3-dihydropyridone. A Wittig olefination followed by two consecutive hydrogenations provided the natural product. This is the shortest synthesis toward the natural product published to date, and further reiterates the effectiveness, versatility and robustness of N-acylpyridinium salt chemistry in the concise synthesis of complex molecules.
III.2.e. **Asymmetric plan for the synthesis of (-)-cermizine D**

Having accomplished a successful concise synthesis of the racemic natural product (68), the next step is to proceed with the asymmetric synthesis toward natural (-)-cermizine D. Our retrosynthetic plan is based on the use of N-acyl-2,3-dihydro-4-pyridone 245 as precursor of the key intermediate (R)-214; both chiral intermediates have been successfully prepared in our group utilizing N-acylpyridinium salt methodologies in the synthesis of quinolizidine alkaloids.\(^{43d}\) As previously described, a chiral auxiliary assists in the installation of the stereocenter at C-2 in 245, next, a base-induced cyclization provides the bicyclic enone (R)-214. The final steps, will follow the racemic protocols in their entirety to provide the natural product (-)-cermizine D (68).

**Scheme III-23.** Asymmetric Plan for the Synthesis of (-)-Cermizine D.
CONCLUSION

The total synthesis of the isoquinoline alkaloid (S)-macrostomine was described in Chapter II. After a comprehensive study and optimization, the plant alkaloid (S)-macrostomine was synthesized via a five-step sequence from (S)-nicotine in 19% overall yield. Directed lithiation methodologies were utilized in this total synthesis; which was carried out with retention of configuration at the pyrrolidine ring. Key steps included a Diels-Alder cycloaddition reaction and a Kumada cross-coupling to furnish the natural product. Our work constitutes the shortest synthesis of this natural product published to date, and further demonstrates the value of (S)-nicotine as a chiral building block. The total synthesis of the quinolizidine alkaloid (±)-cermizine D was presented in Chapter III. The synthesis of this club moss alkaloid was accomplished using N-acylpyridinium salt chemistry methodologies in a six-step route from 4-methoxypyridine and in 13% overall yield. A crucial step was an enantioselective copper-mediated 1,4-addition to a bicyclic 2,3-dihydropyridone. A Wittig olefination followed by two consecutive hydrogenations provided the natural product. This is the shortest synthesis of the natural product published to date, and this work reaffirms the utility and versatility of N-acylpyridinium salt methodologies in the concise synthesis of complex molecules.
EXPERIMENTAL

**General Experimental and Procedures.** All reactions were performed in oven and flame-dried glassware under argon atmosphere and stirred magnetically. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl prior to use. *n*-Butyllithium was titrated against diphenylacetic acid according to the procedure of Kofron and Baclawski.\(^{132}\) Commercial alkylzinc reagents were titrated prior to use following Knochel protocol.\(^{133}\) Other reagents and solvents from commercial sources were stored under argon and used directly unless otherwise specified. Molecular sieves were activated at 320 °C over 24 h. 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 Kiesselgel 60 PF-254 or Aluminum oxide GF-254, both containing gypsum. Optical rotations were determined with an autopol II automatic polarimeter (Rudolph Research, Flanders, NJ). Nuclear Magnetic Resonance spectra (NMR) were obtained using a Varian Mercury (400 MHz) spectrometer. Chemical shifts are in δ units (ppm) with either TMS 0.00 or CDCl\(_3\) 7.26 used as an internal standard for \(^1\)H NMR spectra, and the CDCl\(_3\) absorption of 77.23 for \(^{13}\)C NMR. Infrared spectra were recorded on a Perkin-Elmer 1430, MIDAC M2000 or JASCO FT/IR-410 spectrometer. High Resolution Mass Spectral analyses (HRMS) were obtained at the NCSU Department of Chemistry Mass Spectrometry Facility.
(S)-1-Chloro-5,8-dihydro-6,7-dimethoxy-5,8-epoxy-4-(1-methylpyrrolidin-2-yl)isoquinoline (123). Freshly distilled (S)-4,6-dichloronicotine (128) (233 mg, 1.01 mmol) was dissolved in 1.0 mL of dry THF (over 4Å MS) and stirred at rt. After 1 h, the solution was transferred by syringe to a flame-dried flask, cooled to -78 °C, and n-BuLi (520 µL, 2.33 M in hexanes, 1.21 mmol) was added dropwise. After stirring the mixture at -78 °C for 3 h, 3,4-dimethoxyfuran (1.08 g, 8.47 mmol) was added dropwise, and the mixture was allowed to warm to rt. The reaction mixture was stirred at rt for 15 h and then quenched with 2.0 mL of saturated aqueous NaHCO₃. The mixture was extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were dried over K₂CO₃, filtered through a pad of Celite, and concentrated in vacuo. Purification by radial PLC (SiO₂, 1% TEA/20% EtOAc/hexanes) afforded 178 mg (55%) of 123 (1:1 mixture of diastereomers) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H), 8.02 (s, 1H), 5.93 (s, 1H), 5.81 (s, 1H), 5.51 (s, 1H), 5.48 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.11-3.26 (m, 4H), 2.18-2.34 (m, 4H), 2.17 (s, 3H), 2.12 (s, 3H), 1.7-2.02 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 22.7, 23.1, 35.3, 35.4, 40.5, 40.7, 57.0, 57.1, 58.8, 59.1 (2C overlap), 59.3, 67.3, 67.6, 79.9 (2C overlap), 80.1, 80.8, 131.7, 132.0, 140.2, 140.3, 143.7, 143.8, 144.7, 144.9, 145.8, 146.0,
148.6, 148.9, 161.0, 161.1; IR (neat) 3052, 2944, 2846, 2782, 2304, 1685, 1585, 1457, 1423, 1321, 1265 cm\(^{-1}\); HRMS calcd for C\(_{16}\)H\(_{19}\)ClN\(_2\)O\(_3\) (M+H)\(^+\) 323.1157, found 323.1156.

!(Image)

(S)-1-Chloro-6,7-dimethoxy-4-(1-methylpyrrolidin-2-yl)isoquinoline (105). Magnesium powder (89.0 mg, 3.66 mmol) was dried at 120 °C in a sand bath for 2 h while stirring under vacuum. After 2 h, the metal was allowed to cool to rt and 3.0 mL of THF was added under an argon atmosphere. The mixture was cooled to -78 °C and neat TiCl\(_4\) (200 µL, 1.83 mmol) was added dropwise. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After stirring for 20 h, a fine black suspension was obtained. The mixture was cooled to -78 °C and treated with a solution of 123 (118 mg, 0.366 mmol) in dry THF (2.0 mL). After 30 min at -78 °C, the mixture was allowed to warm to rt. The mixture was stirred for 21 h at rt, and then quenched by pouring it into ice-cold saturated aqueous K\(_2\)CO\(_3\) (15 mL). After stirring for 30 min at rt, the mixture was extracted with Et\(_2\)O (2 x 15 mL) and CH\(_2\)Cl\(_2\) (1 x 15 mL). The combined organic layers were dried over anhydrous K\(_2\)CO\(_3\), filtered through a pad of Celite, and concentrated \textit{in vacuo}. Purification by radial PLC (SiO\(_2\), 1% TEA/20% EtOAc/hexanes) afforded 78 mg (70%) of 105 as a pale yellow oil. [\(\alpha\)]\(_D\)^{27} -128 (c 0.67,
CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 (s, 1H), 7.78 (s, 1H), 7.56 (s, 1H), 4.06 (s, 3H), 4.03 (s, 3H), 3.54 (t, $J$ = 8.0 Hz, 1H), 3.30 (t, $J$ = 8.0 Hz, 1H), 2.29-2.42 (m, 2H), 2.24 (s, 3H), 1.85-2.08 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.3, 33.5, 40.9, 56.3 (2C overlap), 57.4, 67.7, 103.1, 105.1, 122.7, 130.9, 133.1, 139.8, 148.8, 150.6, 152.8; IR (neat) 2967, 2834, 2776, 1508, 1263, 1147 cm$^{-1}$; HRMS calcd for C$_{16}$H$_{19}$ClN$_2$O$_2$ (M+H)$^+$ 307.1208, found 307.1208.

(Benzo[d][1,3]dioxol-5-ylmethy)magnesium chloride (134). A suspension of magnesium powder (3.60 g, 146.5 mmol) in THF (5.0 mL) was treated dropwise with 1,2-dibromoethane (381 µL, 4.397 mmol) at rt under an argon atmosphere. After 1 h, the solvent was removed with a syringe, and the residue in the reaction flask was washed with 5 mL of THF (2x), and then fresh THF (5 mL) was added. The mixture was treated with a solution of piperonyl chloride$^{134}$ (133) (5.0 g of the crude material, 29.31 mmol) in THF (5 mL) at rt, added dropwise over a period of 4 h with stirring. The brownish suspension obtained contained the Grignard reagent 134 and was left standing overnight to allow the excess magnesium to settle. The solution of reagent 134 was kept under argon at rt and was titrated prior to use employing a literature procedure.$^{135}$
*(S)-Macrostomine (44).* A solution of 105 (20.0 mg, 0.065 mmol) and Ni(acac)$_2$ (6.8 mg, 0.026 mmol, 40 mol%) in dry THF (2.0 mL) at rt was treated dropwise with piperonylmagnesium chloride (134) (450 µL, 0.44 M in THF, 0.198 mmol). The mixture was stirred at rt for 4 days and then quenched with 2 mL of saturated aqueous NaHCO$_3$. The mixture was extracted with CH$_2$Cl$_2$ (2 x 5 mL). The combined organic layers were dried over K$_2$CO$_3$, filtered through a pad of Celite, and concentrated *in vacuo*. Purification by radial PLC (SiO$_2$, 1% TEA/30% EtOAc/hexanes) afforded 16.7 mg (63%) of amorphous 44. $[\alpha]^{25}_D$ = -54 (c 0.72, CHCl$_3$); lit.$^{136, 137}$ $[\alpha]^{25}_D$ = -51 ± 3 (c 0.892, CHCl$_3$); $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 8.80 (s, 1H), 7.88 (s, 1H), 7.32 (s, 1H), 7.01 (d, $J = 2.0$ Hz, 1H), 6.78 (dd, $J = 8.0$, 1.2 Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 1H), 5.22 (s, 2H), 4.56 (s, 2H), 3.51 (s, 3H), 3.43 (s, 3H), 3.38 (t, $J = 8.0$ Hz, 1H), 3.08 (t, $J = 8.0$ Hz, 1H), 2.13 (s, 3H), 2.01-2.10 (m, 2H), 1.75-1.98 (m, 2H), 1.53-1.63 (m, 1H). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.40 (s, 1H), 7.79 (s, 1H), 7.32 (s, 1H), 6.68-6.80 (m, 3H), 5.86 (s, 2H), 4.48 (s, 2H), 3.99 (s, 3H), 3.89 (s, 3H), 3.54 (t, $J = 8.0$ Hz, 1H), 3.31 (t, $J = 8.0$ Hz, 1H), 2.28-2.42 (m, 2H), 2.25 (s, 3H), 1.86-2.11 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.3, 33.4, 40.9, 42.5, 55.9, 56.0, 57.4, 68.2, 101.0, 103.2, 104.8, 108.3, 109.2, 121.5, 123.1, 129.5, 132.0, 133.8, 140.3, 146.1, 147.9, 149.3, 151.7, 157.0; IR (neat)
(S)-1-Chloro-4-(1-methylpyrrolidin-2-yl)isoquinoline (131). Magnesium powder (39.0 mg, 1.6 mmol) was dried at 120 °C on a sand bath for 2 h while stirring under high vacuum (0.5 mmHg). After 2 h, the metal was allowed to cool to rt and 3.0 mL of THF was added under an argon atmosphere. The mixture was cooled to -78 °C and neat TiCl₄ (88.0 µL, 0.82 mmol) was added dropwise. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After stirring for 20 h, a fine black suspension was obtained. The mixture was cooled to -45 °C and treated with a solution of 114 (31.0 mg, 0.12 mmol) in dry THF (2.0 mL). After 10 min at -45 °C, the mixture was allowed to warm to rt. The mixture was stirred for 24 h at rt, then quenched by pouring it into an ice-cold aqueous solution of saturated K₂CO₃ (5 mL). After stirring for 30 min at rt, the mixture was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over anhydrous K₂CO₃, filtered through a pad of Celite, and concentrated in vacuo. Purification by radial PLC (SiO₂, 1% TEA/1% EtOAc/hexanes) afforded 14.0 mg (48%) of 131 as a pale yellow oil. [α]²⁰ D -38.5 (c 0.13, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.40 (s, 1H), 8.38 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 8.4 Hz, 2H) 7.75 (t, J
= 8.0 Hz, 1H), 7.67 (t, J = 8.4 Hz, 1H), 3.68 (t, J = 8.4, 1H), 3.32 (t, J = 8.0 Hz, 1H), 2.44-2.34 (m, 2H), 2.26 (s, 3H), 1.98-2.08 (m, 1H), 1.78-1.95 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 23.1, 34.2, 41.0, 57.3, 66.9, 123.9, 126.6, 127.2, 128.0, 130.8, 132.4, 136.6, 140.4, 151.0; IR (neat) 3046, 2969, 2778, 1617, 1579, 1558, 1500, 1448, 1322, 1257, 962, 765, 736 cm$^{-1}$; HRMS calcd for C$_{14}$H$_{15}$ClN$_2$ (M+H)$^+$ 247.0997, found 247.0997.

(S)-1-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-(1-methylpyrrolidin-2-yl)isoquinoline (140). A solution of 131 (27.0 mg, 0.11 mmol) and Ni(acac)$_2$ (11.0 mg, 0.044 mmol) in dry THF (2.0 mL) at rt was treated dropwise with piperonylmagnesium chloride (134) (310 µL, 1.42 M in THF, 0.44 mmol). The mixture was stirred at rt for 5 d and then quenched with 2.0 mL of saturated aqueous NaHCO$_3$. The mixture was extracted with CH$_2$Cl$_2$ (2 x 15 mL). The combined organic layers were dried over K$_2$CO$_3$, filtered through a pad of Celite, and concentrated in vacuo. Purification by radial PLC (SiO$_2$, 1% TEA/30% EtOAc/hexanes) afforded 29.7 mg (78%) of 140 as a clear oil. [α]$^D_{25}$ -106 (c 0.81, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.59 (s, 1H), 8.34 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.63 (t, J = 6.8 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 6.69-6.78 (m, 3H), 5.86 (s, 2H), 4.56 (s, 2H), 3.66 (t, J = 8.4 Hz, 1H), 3.32 (t, J = 7.6 Hz, 1H), 2.33-2.41 (m, 2H), 2.26 (s, 3H), 1.98-2.09 (m, 1H),
1.84-1.93 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 23.0, 34.0, 41.1, 41.9, 57.4, 67.4, 100.9, 108.4, 109.3, 121.6, 124.1, 126.4, 126.6, 126.9, 129.4, 130.7, 133.6, 135.3, 140.9, 146.0, 147.8, 159.3; IR (neat) 3434, 2940, 2775, 1503, 1487, 1443, 1242, 1039, 927 cm$^{-1}$; HRMS calcd for C$_{22}$H$_{22}$N$_2$O$_2$ (M+H)$^+$ 347.1754, found 347.1753.

(S)-1-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-yl)pyrrolidin-2-one (152). A mixture of 147 (95.0 mg, 0.29 mmol), K$_3$PO$_4$ (125.0 mg, 0.59 mmol) and CuI (11.0 mg, 0.059 mmol) in freshly distilled 1,4-dioxane (5 mL) was treated at rt with N,N’-dimethylethylendiamine (10.0 µL, 0.094 mmol). The mixture was stirred for 30 min at rt and then 2-pyrrolidinone (148) (30.0 µL, 0.38 mmol) was added. The new mixture was stirred for additional 30 min at rt. After that period, the mixture was warmed up to 90 °C and stirred for 20 h at this temperature. The reaction mixture was allowed to cool to rt and poured into saturated NaHCO$_3$ solution (3 mL). After extracting with CH$_2$Cl$_2$, the combined organic extracts were dried over anhydrous K$_2$CO$_3$, filtered through a pad of Celite, and concentrated in vacuo. Purification was carried out by radial PLC (SiO$_2$, 1% TEA/10% EtOAc/hexanes) to afford 30.0 mg (36%) of 152 as a clear oil. [α]$^2$$_D$ -110 (c 1.30, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.65 (s, 1H), 7.06 (s, 1H), 3.65-3.79 (m, 2H), 3.11-3.21 (m, 2H), 2.55 (t, $J = 8.0$
Hz, 2H), 2.20-2.30 (m, 4H), 2.12 (s, 3H), 1.87-1.96 (m, 1H), 1.74-1.81 (m, 1H), 1.63-1.71 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 19.4, 23.0, 31.2, 34.4, 40.6, 51.1, 57.0, 64.1, 121.2, 136.1, 147.7, 150.2, 151.5, 174.7; IR (neat) 3469, 2850, 2924, 2786, 1700, 1577, 1556, 1464, 1402, 1289, 1119, 1080, 971 cm$^{-1}$; HRMS calcd for C$_{14}$H$_{18}$ClN$_3$O (M+H)$^+$ 280.1211, found 280.1212.

(S)-2'-Chloro-5'-[1-methylpyrrolidin-2-yl]-2H-[1,4'-bipyridin]-2-one (153). A suspension of Cs$_2$CO$_3$ (467.0 mg, 1.43 mmol) and CuBr (9.8 mg, 0.07 mmol) in DMSO (1.0 mL) was treated with a solution of 147 (220.0 mg, 0.68 mmol) in THF/DMSO (1:1, 2.0 mL) followed by ethyl 2-oxocyclohexanecarboxylate (146) (22.0 µL, 0.14 mmol). The mixture was stirred for 30 min at rt and then 2-hydroxypyridine (149) (77.8 mg, 0.82 mmol) was added. This mixture was heated at 60 °C for 14 h. After this period, the mixture was allowed to cool to rt and a mixture of EtOAc/Et$_2$O (1:1, 5.0 mL) was added. The suspension was filtered through a pad of Celite and the filtrate concentrated in vacuo. Purification was carried out by radial PLC (SiO$_2$, 1% TEA/10% EtOAc/hexanes) to afford 50.0 mg (25%) of 153 as a clear oil. [$\alpha$]$^2$D$^2$ -123 (c 0.65, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.55 (s, 1H), 8.23 (dd, $J = 5.2,$
2.4 Hz, 1H), 7.78 (td, J = 7.6, 2.4 Hz, 1H), 7.13 (td, J = 5.2, 1.2 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.95 (s, 1H), 3.45 (t, J = 8.4 Hz, 1H), 3.19 (td, J = 7.6, 1.6 Hz, 1H), 2.16-2.28 (m, 2H), 2.22 (s, 3H), 1.84-1.92 (m, 1H), 1.71-1.78 (m, 1H), 1.62-1.68 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 22.9, 33.9, 40.9, 57.0, 62.6, 112.8, 114.9, 120.4, 130.2, 140.3, 148.1, 150.2, 150.3, 161.2, 161.7; IR (neat) 2942, 2779, 1678, 1586, 1562, 1457, 1428, 1235, 1079, 931, 777 cm−1; HRMS calcd for C15H16ClN3O (M+H)+ 290.1055, found 290.1051.

(S)-1-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-yl)quinolin-2(1H)-one (154). To a mixture of 147 (115.0 mg, 0.36 mmol), K3PO4 (151.0 mg, 0.71 mmol) and CuI (3.0 mg, 0.018 mmol) in freshly distilled 1,4-dioxane (3.0 mL) was added N,N'-dimethylethylenediamine (10.0 µL, 0.036 mmol) at rt. The mixture was stirred for 30 min at rt, 1-hydroxyisoquinoline (150) (62.0 mg, 0.43 mmol) was added, and stirring was continued for 30 min at rt. After that period, the mixture was warmed to 90 °C and stirred for 60 h. The mixture was allowed to cool to rt and poured into saturated NaHCO3 solution (3.0 mL). Extractions were performed with CH2Cl2 (2 x 15 mL), and the combined organic extracts were dried over anhydrous K2CO3, filtered through a pad of Celite, and concentrated in
vacuo. Purification was carried out by radial PLC (SiO<sub>2</sub>, 1% TEA/30% EtOAc/hexanes) to afford 55.0 mg (45%) of 154 as a clear oil. [α]<sup>26</sup><sub>D</sub> -90 (c 1.25, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.64 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 6.8 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 5.6 Hz, 1H), 7.17 (s, 1H), 3.43 (t, J = 8.0 Hz, 1H), 3.15 (t, J = 8.0 Hz, 1H), 2.22 (s, 3H), 2.16-2.20 (m, 2H), 1.83-1.92 (m, 1H), 1.69-1.80 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 22.9, 34.0, 40.9, 56.9, 62.7, 116.6, 118.1, 119.6, 123.7, 126.7, 127.9, 130.9, 131.4, 138.9, 139.5, 150.2, 150.4, 158.7, 160.8; IR (neat) 3058, 2967, 2873, 2840, 2783, 1631, 1586, 1562, 1496, 1455, 1366, 1341, 1233, 1078, 1057, 923, 819 cm<sup>-1</sup>; HRMS calcd for C<sub>19</sub>H<sub>18</sub>ClN<sub>3</sub>O (M+H)<sup>+</sup> 340.1211, found 340.1201.

(S)-2-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-yl)isoquinolin-3(2H)-one (155). To a mixture of 147 (95.7 mg, 0.30 mmol), K<sub>3</sub>PO<sub>4</sub> (126.0 mg, 0.59 mmol) and CuI (6.0 mg, 0.030 mmol) in freshly distilled 1,4-dioxane (5.0 mL) was added N,N’-dimethylethylenediamine (10.0 µL, 0.094 mmol) at rt. After stirring for 30 min at rt, 3-hydroxyisoquinoline (151) (52.0 mg, 0.35 mmol) was added, and the new mixture was stirred for 30 min at rt. The mixture was then warmed to 90 °C and stirred for 48 h. The mixture was
allowed to cool to rt and poured into saturated NaHCO₃ solution (3.0 mL). Extractions were performed with CH₂Cl₂, and the combined organic extracts were dried over anhydrous K₂CO₃, filtered through a pad of Celite, and concentrated in vacuo. Purification was carried out by radial PLC (SiO₂, 1% TEA/30% EtOAc/hexanes) to afford 68.0 mg (67%) of 155 as a clear oil. [α]₂⁶° -112 (c 1.80, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 9.02 (s, 1H), 8.55 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.34 (s, 1H), 6.74 (s, 1H), 3.60 (t, J = 8.4 Hz, 1H), 3.21 (td, J = 8.4, 2.0 Hz, 1H), 2.29-2.37 (m, 2H), 2.27 (s, 3H), 1.85-1.93 (m, 1H), 1.66-1.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 22.9, 33.8, 40.9, 57.0, 62.4, 107.5, 112.8, 126.3, 126.8, 127.2, 127.9, 129.2, 131.4, 139.1, 150.0, 150.2, 152.1, 157.4, 162.5; IR (neat) 2966, 2779, 1630, 1561, 1458, 1436, 1347, 1268, 1235, 1156, 964, 934, 752 cm⁻¹; HRMS calcd for C₁₉H₁₈ClN₃O (M+H)+ 340.1211, found 340.1206.

Ethyl 2-oxo-2-(pyridin-2-ylthio)acetate (159). Solid 2-mercaptopyridine (160) (1.11 g, 10.0 mmol) was transferred to a 100 mL three-neck round-bottom flask equipped with a condenser and a thermometer. The solid was suspended in toluene (50 mL) and heated at 65 °C for 1.5 h. The yellow solution was treated dropwise with dry TEA (1.53 mL, 11.0 mmol) at 65 °C. After stirring for 15 min, the solution was treated with ethyl chlorooxoacetate (1.12
mL, 10.0 mmol). A precipitate forms immediately and the mixture is stirred at 65 °C for 3.5 h. The reaction mixture was cooled to 0 °C and filtered through a pad of Celite, using ice-cold dry Et₂O (30 mL, over 4Å MS) as a wash. The solution was concentrated, and the residue placed in vacuo for about 18 h to give 2.11 g (100%) of crude 159 as an amber oil. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta 8.66 (s, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 6.6 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta 13.9, 64.0, 124.4, 130.2, 137.8, 149.6, 150.6, 158.7, 183.1; \)IR (neat) 3050, 2985, 2939, 1735, 1702, 1582, 1286, 1192, 1023, 983, 769 cm\(^{-1}\); HRMS calcd for C₉H₉NO₃S (M+H)\(^{+}\) 212.0376, found 212.0380.

(S)-Ethyl 2-(2-chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-yl)-2-oxoacetate (158). A solution of n-BuLi (0.45 mL, 1.91 M, 0.85 mmol) in dry THF (2.0 mL) at -78 °C was treated with neat 34 (152.0 mg, 0.77 mmol). After 1 h at -78 °C, a solution of CuI (177.0 mg, 0.93 mmol) in diisopropyl sulfide (1.0 mL) was added at -78 °C. After 1 h, the mixture was treated with ethyl 2-oxo-2-(pyridin-2-yl)acetate (159). The mixture was stirred at -78 °C for 30 min and then allowed to warm up to rt, and stirred for an additional 1 h. After this period,
the reaction was quenched by adding saturated NaHCO$_3$ solution, and then the mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined extracts were dried over K$_2$CO$_3$, filtered through a pad of Celite and concentrated in vacuo. Purification was carried out by radial PLC (SiO$_2$, 1% TEA/30% EtOAc/hexanes) to afford 117.0 mg (51%) of 158 as a clear oil. $[\alpha]_D^{24}$ = -84 (c 1.35, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.23 (s, 1H), 7.18 (s, 1H), 4.30 (q, $J = 7.2$ Hz, 2H), 3.81-3.85 (m, 1H), 2.86 (ddd, $J = 15.6$, 7.2, 4.4 Hz, 1H), 2.47 (td, $J = 10.8$, 7.6 Hz, 1H) 2.22-2.35 (m, 1H), 2.17 (s, 3H), 1.67-1.85 (m, 3H), 1.35 (t, $J = 7.6$, Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.4, 24.8, 34.9, 41.9, 54.8, 62.2, 66.4, 122.1, 139.6, 147.8, 148.0, 150.2, 161.3, 175.6; IR (neat) 2956, 2869, 2211, 1725, 1676, 1583, 1462, 1188, 1095, 1034, 735 cm$^{-1}$; HRMS calcd for C$_{14}$H$_{17}$ClN$_2$O$_3$ (M+H)$^+$ 297.1000, found 297.1010.

(R)-Ethyl 2-(2-chloro-5-((S)-1-methylpyrrolidin-2-yl)pyridin-4-yl)-2-hydroxybutanoate (162a). A solution of ethylmagnesium chloride (0.21 mL, 1.51 M in THF, 0.32 mmol) in THF (1.0 mL) was treated at rt with diethylzinc (0.62 mL, 0.69 M in hexanes, 0.43 mmol). The mixture was stirred at rt for 30 min and then cooled to -20 °C and treated with a solution of 158 (32.0 mg, 0.11 mmol) in THF (1.0 mL). The mixture was stirred for 1 h at -20 °C and
then allowed to warm to rt. After stirring for 24 h, the reaction was quenched by adding saturated NaHCO₃ solution (3.0 mL). The mixture was extracted with CH₂Cl₂ (2 x 15 mL). The extracts were dried over K₂CO₃, filtered through a pad of Celite and concentrated in vacuo. Purification was carried out by radial PLC (SiO₂, 1% TEA/50% EtOAc/hexanes) to afford 19.0 mg (54%) of 162a and 12.6 mg (36%) of 162b as clear oils. (162a): [α]D²⁴ -56 (c 0.89, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 10.37 (br s, 1H), 8.20 (s, 1H), 7.39 (s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.30 (t, J = 8.8 Hz, 2H), 2.33 (q, J = 8.8 Hz, 1H), 2.20 (s, 3H), 2.05-2.19 (m, 5H), 1.80-1.89 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 8.3, 14.2, 21.9, 34.2, 34.3, 40.4, 56.4, 61.8, 71.2, 81.0, 124.0, 133.9, 151.4, 152.6, 154.1, 174.2; IR (neat) 3458, 2965, 2787, 1731, 1576, 1463, 1231, 1025, 883, 735 cm⁻¹; HRMS calcd for C₁₆H₂₃ClN₂O₃ (M+H)⁺ 327.1470, found 327.1475.

(S)-Ethyl 2-(2-chloro-5-((S)-1-methylpyrrolidin-2-yl)pyridin-4-yl)-2-hydroxybutanoate (162b). [α]D²⁴ -50 (c 0.40, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 9.08 (br s, 1H), 8.34 (s, 1H), 7.41 (s, 1H), 4.06-4.24 (m, 2H), 3.28-3.36 (m, 2H), 2.34 (q, J = 9.2 Hz, 1H), 2.03-2.25 (m, 5H), 2.18 (s, 3H), 1.80-1.90 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 8.0, 14.1, 22.4, 33.7, 34.5, 40.3, 56.6, 62.2, 70.0, 79.9, 123.6, 134.6, 151.4, 152.3, 153.7, 174.1; IR (neat) 3458, 2968, 2776, 1732, 1582, 1463, 1240, 1143, 1024 cm⁻¹; HRMS calcd for C₁₆H₂₃ClN₂O₃ (M+H)⁺ 327.1470, found 327.1475.
(R)-Ethyl 2-(2-chloro-5-((S)-1-methylpyrrolidin-2-yl)pyridin-4-yl)-2-((trimethylsilyl)-oxy)butanoate (164). A solution of 162a (30.0 mg, 0.092 mmol), TEA (64.0 µL, 0.46 mmol), and DMAP (11.0 mg, 0.092 mmol) in dry CH₂Cl₂ was treated dropwise at rt with TMSCl (16.0 µL, 0.13 mmol). The reaction mixture was stirred for 20 h at rt, and then quenched with saturated NaHCO₃ solution (3.0 mL). The mixture was extracted with CH₂Cl₂ (2 x 15 mL), the combined organic extracts dried over K₂CO₃, filtered through a pad of Celite. After concentration in vacuo, purification was carried out by radial PLC (SiO₂, 1% TEA/50% EtOAc/hexanes) to afford 25.4 mg (70%) of 164 as a clear oil. [α]²³D -45 (c 0.51, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 7.48, (s, 1H), 4.02-4.20 (m, 2H), 3.26 (t, J = 8.0 Hz, 1H), 3.17 (t, J = 8.0 Hz, 1H), 2.06-2.26 (m, 4H), 2.05 (s, 3H), 1.88-1.98 (m, 1H), 1.70-1.80 (m, 1H), 1.46-1.56 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H), 0.63 (t, J = 7.2 Hz, 3H), 0.19 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 1.6, 7.5, 13.9, 23.0, 31.5, 36.1, 40.0, 56.6, 62.1, 63.8, 81.0, 121.2, 135.8, 150.1, 151.1, 151.9, 172.5; IR (neat) 2967, 2778, 1735, 1580, 1454, 1372, 1251, 1142, 1043, 880, 843 cm⁻¹; HRMS calcd for C₁₉H₃₁ClN₂O₃Si (M+H)+ 399.1865, found 399.1871.
(R,E)-Ethyl 2-(2-chloro-5-(4-(N-methylcyanamido)but-1-en-1-yl)pyridin-4-yl)-2-((trimethylsilyl)oxy)butanoate (166). A solution of 164 (33.0 mg, 0.083 mmol) in dry CHCl$_3$ (2.0 mL) was treated dropwise at rt with cyanogen bromide (86.0 µL, 3.0 M in CH$_2$Cl$_2$, 0.26 mmol). The reaction mixture was stirred for 15 h at rt and then filtered through a pad of Celite. After concentration \textit{in vacuo}, purification was carried out by radial PLC (SiO$_2$, 1%TEA/50% EtOAc/hexanes) to afford 15.1 mg (43%) of 166 as a clear oil. $\left[\alpha\right]_D^{28} = -19$ (c 0.21, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.29 (s, 1H), 7.46 (s, 1H), 6.64 (d, $J = 16.0$ Hz, 1H), 5.95 (dt, $J = 16.0$, 6.4 Hz, 1H), 4.04-4.20 (m, 2H), 3.12 (t, $J = 7.2$ Hz, 2H), 2.90 (s, 3H), 2.54 (q, $J = 6.8$ Hz, 2H), 2.17 (qd, $J = 7.2$, 2.0 Hz, 2H), 1.61 (s, 1H), 1.18 (t, $J = 6.8$ Hz, 3H), 0.74 (t, $J = 7.2$ Hz, 3H), 0.12 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 1.7, 7.6, 14.1, 30.4, 31.2, 39.1, 52.3, 62.0, 80.9, 118.3, 121.5, 127.7, 130.2, 130.5, 148.5, 150.9, 151.0, 172.1; IR (neat) 2960, 2212, 1735, 1575, 1456, 1251, 1147, 889, 844 cm$^{-1}$; HRMS calcd for C$_{20}$H$_{36}$ClN$_3$O$_3$Si (M+H)$^+$ 424.1810, found 424.1804.
(R,E)-Ethyl 2-(2-chloro-5-(4-(N-methylcyanamido)but-1-en-1-yl)pyridin-4-yl)-2-hydroxybutanoate (168). A solution of 166 (16.8 mg, 0.040 mmol) and cesium fluoride (18.2 mg, 0.12 mmol) in dry EtOH (3.0 mL) was stirred at rt for 15 h. After that period, the mixture was filtered through a pad of Celite and the solvents evaporated in vacuo. Purification was carried out by radial PLC (SiO$_2$, 1% TEA/50% EtOAc/hexanes) to afford 7.1 mg (51%) of 168 as a clear oil. [α]$^{	ext{D}}_{25}$ -82 (c 0.355, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (s, 1H), 7.40 (s, 1H), 6.87 (d, $J$ = 15.6 Hz, 1H), 5.88 (dt, $J$ = 15.9, 6.9 Hz, 1H), 4.07-4.30 (m, 2H), 3.12 (td, $J$ = 7.2, 1.8 Hz, 2H), 2.89 (s, 3H), 2.55 (qd, $J$ = 7.2, 1.5 Hz, 2H), 2.10-2.23 (m, 2H), 1.20 (t, $J$ = 7.2 Hz, 3H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 7.65, 14.2, 30.8, 31.1, 39.1, 52.2, 63.1, 78.0, 118.4, 121.5, 128.4, 130.3, 132.3, 149.2, 149.4, 150.8, 173.8; IR (neat) 3365, 2976, 2938, 2212, 1734, 1577, 1460, 1241, 1142, 1023, 799 cm$^{-1}$; HRMS calcd for C$_{17}$H$_{22}$ClN$_3$O$_3$ (M+H)$^+$ 352.1422, found 352.1416.
(4S*,9aR*)-4-(5-Cyanopent-1-yn-1-yl)-4,6,7,8,9,9a-hexahydro-1H-quinolizin-2-yl trifluoromethanesulfonate (218). A solution of TMPDA (0.61 mL, 3.67 mmol) in dry CH₂Cl₂ (4.0 mL) was treated dropwise at rt with hex-5-ynenitrile (0.72 mL, 6.87 mmol), followed by dimethylzinc (2.15 mL, 1.6 M in toluene, 3.44 mmol). The reaction mixture was stirred at rt for 20 h. In a separate flask, a solution of 214 (250.0 mg, 1.65 mmol) in CH₂Cl₂ (2.0 mL) was treated dropwise at -78 °C with triflic anhydride (0.39 mL, 2.29 mmol). The mixture was stirred for 2 h at -78 °C, allowed to warm up to rt, and stirred for additional 1 h. After that period, the reaction mixture was cooled to 0 °C and then treated dropwise with the dialkylzinc reagent. The mixture was allowed to warm up to rt and stirred for 24 h. The reaction was quenched by adding saturated NaHCO₃ solution (5.0 mL). The mixture was extracted with CH₂Cl₂ (3x15 mL). The combined extracts were dried over K₂CO₃, filtered through a pad of Celite, and concentrated in vacuo. Purification was carried out by column chromatography (Al₂O₃, 3-5% EtOAc/hexanes) to afford 276.0 mg (44%) of 218 as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.79 (d, J = 5.2 Hz, 1H), 4.11 (br s, 1H), 2.64-2.74 (m, 2H), 2.38-2.58 (m, 6H), 2.24-2.28 (m, 2H), 1.83 (quintet, J = 6.8 Hz, 2H), 1.66-1.74 (m, 2H), 1.50-1.62 (m, 1H), 1.20-1.32 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 16.3, 18.0, 23.4, 24.7, 25.8, 29.8, 33.4, 35.2, 51.6, 52.1, 76.8, 85.8, 116.9, 119.2 (q), 147.3; IR (neat) 2936, 2857,
2754, 2248, 1704, 1417, 1211, 1142, 1055, 895, 861, 612 cm⁻¹; HRMS calcd for C₁₆H₁₉F₃N₂O₃S (M+H)+ 377.1141, found 377.1158.

6-((4S*,9aR*)-2-Methyl-4,6,7,8,9,9a-hexahydro-1H-quinolizin-4-yl)hex-5-ynenitrile (225). A solution of 218 (160.0 mg, 0.43 mmol), methyl boronic acid (28.0 mg, 0.47 mmol), PdCl₂(dppf) (31.2 mg, 0.038 mmol) and K₂CO₃ (176.3 mg, 1.28 mmol) in THF/H₂O (1:0.1, 8.8 mL) was heated to 100 °C and stirred for 24 h. After that period the mixture was allowed cool to rt and then saturated NaHCO₃ solution (10 mL) was added. The mixture was extracted using CH₂Cl₂ (3 x 15 mL). The combined extracts were dried over K₂CO₃, filtered through a pad of Celite and concentrated in vacuo. Purification was carried out by column chromatography (Al₂O₃, 3-5% acetone/hexanes) to afford 69.6 mg (68%) of 225 as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.42 (br s, 1H), 3.91 (br s, 1H), 2.69 (d, J = 10.0 Hz, 1H), 2.46-2.58 (m, 3H), 2.40 (td, J = 6.8, 2.0 Hz, 2H), 1.76-1.98 (m, 6H), 1.68-1.72 (m, 2H), 1.64 (s, 3H), 1.15-1.28 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 16.3, 18.1, 22.8, 24.2, 25.0, 26.2, 34.1, 38.5, 51.4, 52.2, 52.7, 79.3, 83.7, 119.9, 132.8; IR (neat) 2921, 2851, 2247, 1722, 1450,
1382, 1275, 1226, 1188, 1128, 737 cm\(^{-1}\); HRMS calcd for C\(_{16}\)H\(_{22}\)N\(_2\) (M+H\(^+\)) \(243.1856\), found \(243.1858\).

\((4R^*,9aR^*)\)-4-(Pyridin-2-ylmethyl)-4,6,7,8,9,9a-hexahydro-1\(H\)-quinolizin-2-yl trifluoromethanesulfonate (236a). A solution of 214 (132.0 mg, 0.87 mmol) in CH\(_2\)Cl\(_2\) (2.0 mL) at -78 °C was treated dropwise with triflic anhydride (147 µL, 0.87 mmol). After 1 h at -78 °C, the yellow solution was treated dropwise with 2-((tributylstannyl)methyl)pyridine (400.0 mg, 1.05 mmol). The mixture was stirred at -78 °C for 4 h. After that period, the reaction was quenched by adding NaOH 1.0 M (15 mL), and the mixture was allowed to warm up to rt and then stirred for 1 h. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 x 20 mL). The combined extracts were washed with NaOH 1.0 M (15 mL), saturated aqueous NaHCO\(_3\) (20 mL), and brine (20 mL), and then dried over anhydrous K\(_2\)CO\(_3\). Filtration through a pad of Celite and concentration \textit{in vacuo} gave the crude product. Purification by radial PLC (SiO\(_2\), 1% TEA/10% EtOAc/hexanes) afforded 122.0 mg (37%) of 236a and 34.0 mg (10%) of 236b as clear oils. (236a): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.51 (d, \(J = 5.4\) Hz, 1H), 7.58 (t, \(J = 6.8\) Hz, 1H) 7.10-7.13 (m, 2H), 5.58 (s, 1H), 3.74-3.79 (br s, 1H), 3.15-3.22 (m, 2H), 2.78 (dd, \(J = 12.8, 8.4\) Hz, 1H), 2.70-2.74 (m, 1H), 2.47-2.57 (m, 2H), 2.08 (dd, \(J = 17.2, 4.4\) Hz,
1H), 1.77-1.82 (m, 1H), 1.41-1.61 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.2, 26.0, 29.4, 30.9, 40.9, 49.4 (2C overlap), 60.9, 117.0 (q), 119.7, 121.6, 124.2, 136.4, 146.3, 149.5, 159.0; IR (neat) 2934, 2854, 2809, 1685, 1049, 1590, 1416, 1245, 1209, 1141, 907 cm$^{-1}$; HRMS calcd for C$_{16}$H$_{19}$F$_3$N$_2$O$_3$S (M+H)$^+$ 377.1141, found 377.1136.

(4S*,9aR*)-4-(Pyridin-2-ylmethyl)-4,6,7,8,9,9a-hexahydro-1H-quinolizin-2-yl trifluoromethanesulfonate (236b). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.52 (d, $J$ = 5.2 Hz, 1H), 7.58 (t, $J$ = 7.6 Hz, 1H), 7.16 (d, $J$ = 7.6 Hz, 1H), 7.12 (dd, $J$ = 7.6, 5.2 Hz, 1H), 5.48 (s, 1H), 3.43 (d, $J$ = 11.2 Hz, 1H), 3.33 (m, 2H), 2.75 (dd, $J$ = 14.0, 10.0 Hz, 1H), 2.26-2.44 (m, 2H), 2.12-2.20 (m, 1H), 2.01-2.08 (m, 1H), 1.68-1.78 (m, 3H), 1.52-1.62 (m, 1H), 1.22-1.40 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 24.0, 26.0, 33.5, 35.2, 42.3, 52.6, 58.2, 62.2, 118.2 (q), 118.7, 121.7, 124.4, 136.5, 145.9, 149.6, 158.5; IR (neat) 2934, 2855, 2800, 1708, 1590, 1418, 1245, 1210, 1142, 1052, 918 cm$^{-1}$; HRMS calcd for C$_{16}$H$_{19}$F$_3$N$_2$O$_3$S (M+H)$^+$ 377.1141, found 377.1134.
(4R*,9aR*)-4-(Pyridin-2-ylmethyl)hexahydro-1H-quinolizin-2(6H)-one (239a). A solution of n-BuLi (558 µL, 2.37 M in hexanes, 1.33 mmol) at 0 °C was treated dropwise with a solution of 2-((trimethylsilyl)methyl)pyridine (241) (244 µL, 1.33 mmol) in THF (0.5 mL) and the mixture was stirred at 0 °C for 1 h. In a separate flask, CuBr•SMe₂ complex (136.0 mg, 0.66 mmol) was suspended in THF (2.0 mL) and stirred at rt for 1 h, cooled to -30 °C, and treated dropwise with the organolithium reagent. A dark solution was observed and stirring was continued at -30 °C for 2 h. After that period, the reaction mixture was cooled to -78 °C and treated dropwise with a solution of 214 (50.0 mg, 0.33 mmol) in dry THF (2.0 mL) followed by a one portion addition of TMSCl (168 µL, 1.32 mmol). The mixture was stirred at -78 °C for 2 h, allowed to warm to -40 °C, and stirred for an additional 1 h. After that period, the mixture was cooled to -78 °C and the reaction was quenched by adding 20% NH₄Cl aqueous solution (1.0 mL). The mixture was allowed to warm to rt and stirred for 20 h. The mixture was cooled to 0 °C and saturated aqueous K₂CO₃ (1.0 mL) was added. The mixture was allowed to warm to rt and stirred for 1 h. EtOAc (20.0 mL) and anhydrous K₂CO₃ (5.0 g) were added and the mixture was stirred for 2 h at rt. The mixture was filtered through a pad of Celite and neutral alumina, using EtOAc as wash, and the solvents were evaporated in vacuo. Purification was carried out by radial PLC (Al₂O₃, 1% TEA/1-5% EtOAc/hexanes) to afford 51.0 mg (63%) of 239a as a white solid. M.p. 114-118 °C
(recrystallized from hexanes). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.51 (s, 1H), 7.55 (t, $J = 4.0$ Hz, 1H), 7.05-7.10 (m, 2H), 3.65 (br s, 1H), 3.17 (d, $J = 12.4$ Hz, 1H), 2.97 (d, $J = 10.8$ Hz, 1H), 2.72-2.80 (m, 1H), 2.59-2.69 (m, 2H), 2.46 (dd, $J = 12.8$, 10.8 Hz, 1H), 2.25-2.34 (m, 2H), 2.16 (dt, $J = 13.6$, 2.0 Hz, 1H), 1.58-1.80 (m, 4H), 1.18-1.36 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.4, 26.0, 33.7, 34.7, 45.0, 48.3, 51.5, 54.6, 63.1, 121.3, 124.7, 136.6, 149.8, 159.6, 209.9; IR (neat) 2932, 2360, 1715, 1590, 1568, 1473, 1434, 1044, 730 cm$^{-1}$; HRMS calcd for C$_{15}$H$_{20}$N$_2$O (M+H)$^+$ 245.1648, found 245.1641.

(4$S^*$,9a$R^*$)-2-Methylene-4-(pyridin-2-ylmethyl)octahydro-1H-quinolizine (238). Triphe-nylphosphonium bromide (2.24 g, 3.72 mmol) was dried under reduced pressure at 60 °C for 3 h, then suspended in dry THF (5.0 mL). The suspension was cooled to 0 °C and treated dropwise with $n$-BuLi (1.35 mL, 2.37 M in hexanes, 3.19 mmol), and stirred for 1 h. The reaction mixture was cooled to -20 °C and treated dropwise with a solution of 239a (260 mg, 1.06 mmol) in dry THF (5 mL). When the addition was complete, the reaction mixture was allowed to warm to rt and was stirred for 24 h. Saturated aqueous NaHCO$_3$ (5 mL) was added and the mixture was stirred for additional 4 h. The mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL), and the combined extracts were dried over anhydrous K$_2$CO$_3$. After filtration
through a pad of Celite, the solution was concentrated in vacuo. The residue was suspended in dry Et₂O (20 mL) and the suspension filtered through a pad of Celite using Et₂O (20 mL) as a wash. The filtrate was concentrated in vacuo. Purification was carried out by radial PLC (SiO₂, 1% TEA/5% EtOAc/hexanes) to afford 253.0 mg (98%) of 238 as a clear oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.54 (d, \(J = 4.8\) Hz, 1H), (t, \(J = 7.6\) Hz, 1H), 7.08 (m, 2H), 4.83 (s, 1H), 4.63 (s, 1H), 3.33-3.41 (br s, 1H), 3.04 (d, \(J = 12.4\) Hz, 1H), 2.86 (d, \(J = 11.2\) Hz, 1H), 2.75 (dd, \(J = 12.8, 10.4\) Hz, 1H), 2.62 (t, \(J = 11.6\) Hz, 1H), 2.29-2.47 (m, 2H), 2.22 (d, \(J = 13.2\) Hz, 1H) 1.92-2.08 (m, 2H), 1.57-1.75 (m, 4H), 1.17-1.28 (m, 2H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) δ 24.4, 26.3, 31.7, 34.6, 37.5, 42.4, 52.2, 55.2, 61.9, 110.1, 120.9, 124.5, 136.2, 143.9, 149.7, 161.5; IR (neat) 3068, 2931, 2854, 1652, 1589, 1567, 1471, 1435, 1126, 888, 748 cm\(^{-1}\); HRMS calcd for C\(_{16}\)H\(_{22}\)N\(_2\) (M+H)\(^+\) 243.1856, found 243.1852.

\(2R^*\),\(4S^*\),\(9aR^*)\)-2-Methyl-4-(pyridin-2-ylmethyl)octahydro-\(1H\)-quinolizine (243a). A mixture of 238 (146 mg, 0.60 mmol) and 10% Pt/C (50.0 mg, 0.026 mmol) in EtOAc (4.0 mL) was stirred under \(\text{H}_2\) at atmospheric pressure for 20 h, filtered through a pad of Celite, and concentrated in vacuo. Purification was carried out by radial PLC (SiO₂, 1% TEA/30% EtOAc/hexanes) to afford 99.3 mg (68%) of 243a and 41.0 mg (28%) of 243b as clear oils.
(243a): $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 8.52 (d, $J = 3.6$ Hz, 1H), 7.05 (td, $J = 5.6$, 2.0 Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 6.61 (dd, $J = 7.4$, 4.8 Hz, 1H), 3.59 (ddd, $J = 14.0$, 7.6, 4.4 Hz, 1H), 3.42 (d, $J = 14.8$ Hz, 1H), 3.33 (dd, $J = 13.2$, 4.4 Hz, 1H), 2.94 (ddd, $J = 11.2$, 5.6, 2.8 Hz, 1H), 2.68 (t, $J = 13.2$ Hz, 1H), 2.62 (dd, $J = 13.2$, 8.0 Hz, 1H), 1.30-1.79 (m, 9H), 1.05 (q, $J = 11.6$ Hz, 1H), 0.90-1.01 (m, 1H), 0.77 (d, $J = 6.4$ Hz, 3H); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.56 (br s, 1H), 7.58 (q, $J = 16.2$ Hz, 1H), 7.07-7.17 (m, 2H), 3.40-3.50 (m, 2H), 3.30 (ddd, $J = 13.2$, 8.4, 4.8 Hz, 1H), 3.08 (br s, 1H), 2.70-2.80 (m, 1H), 2.51 (dt, $J = 12.8$, 8.8 Hz, 1H), 1.80-1.97 (m, 2H), 1.57-1.70 (m, 3H), 1.35-1.55 (m, 3H), 1.07-1.16 (m, 2H), 0.89 (q, $J = 10.8$ Hz, 1H), 0.80 (dd, $J = 8.4$, 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, C$_6$D$_6$) $\delta$ 19.5, 22.5, 25.1, 26.0, 26.3, 40.2, 40.5, 42.5, 50.3, 52.3, 57.3, 120.6, 123.9, 135.3, 149.4; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 18.9, 22.6, 24.7, 25.8, 26.0, 40.1, 40.7, 42.9, 50.1, 51.7, 58.0, 121.1, 124.5, 136.3, 149.5, 160.7; IR (neat) 3422, 2926, 2857, 1589, 1568, 1473, 1435, 1104, 749 cm$^{-1}$; HRMS calcd for C$_{16}$H$_{24}$N$_2$ (M+H)$^+$ 245.2012, found 245.2008.

(2S*,4S*,9aR*)-2-Methyl-4-(pyridin-2-ylmethyl)octahydro-1H-quinolizine (243b). $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 8.50 (d, $J = 6.0$ Hz, 1H), 7.06 (td, $J = 7.6$, 2.0 Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.61 (dd, $J = 7.2$, 4.8 Hz, 1H), 3.50-3.53 (m, 1H), 3.16 (ddd, $J = 12.8$, 4.0 Hz, 1H), 2.81 (dd, $J = 12.8$, 10.0 Hz, 1H), 2.73 (d, $J = 8.0$ Hz, 1H), 2.48 (td, $J = 11.6$, 2.8 Hz, 1H), 2.25 (t, $J = 10.4$ Hz, 1H), 1.78-1.86 (m, 1H), 1.41-1.66 (m, 6H), 1.33 (td, $J = 12.8$, 4.4 Hz, 1H), 1.07-1.24 (m, 2H), 0.94 (q, $J = 12.4$ Hz, 1H), 0.82 (d, $J = 6.8$ Hz, 3H); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.51(d, $J = 4.8$ Hz, 1H), 7.56 (td, $J = 7.2$, 2.0 Hz, 1H), 7.06-7.12 (m, 2H), 3.28-3.34 (m, 1H), 3.17 (dd, $J = 12.4$, 3.6 Hz, 1H), 2.84 (dd, $J = 13.2$, 10.4 Hz, 1H),
2.78 (d, \( J = 11.2 \) Hz, 1H), 2.60 (td, \( J = 11.6, 2.8 \) Hz, 1H), 2.38-2.43 (m, 1H), 1.82-1.92 (m, 1H), 1.57-1.73 (m, 5H), 1.37 (d, \( J = 13.6 \) Hz, 1H), 1.18-1.28 (m, 3H), 0.91 (q, \( J = 12.4 \) Hz, 1H), 0.82 (d, \( J = 6.0 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)) \( \delta \) 22.5, 24.8 (overlap 2C), 26.7, 32.4, 34.8, 36.8, 43.1, 52.4, 53.6, 61.5, 120.4, 123.2, 135.5, 149.6; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 22.6, 24.7, 24.8, 26.5, 32.4, 34.7, 36.7, 43.1, 52.4, 53.9, 61.4, 120.9, 123.7, 136.3, 149.6; IR (neat) 3408, 2927, 2854, 1590, 1567, 1473, 1433, 1107, 749 cm\(^{-1}\); HRMS calcd for C\(_{16}\)H\(_{24}\)N\(_2\) (M+H)\(^+\) 245.2012, found 245.2009.

(\(2R^*,4S^*,9aR^*\))-2-Methyl-4-\((R^*)\)-piperidin-2-ylmethyl)octahydro-1\(H\)-quinolizine (68).

A mixture of 243a (173 mg, 0.69 mmol) and PtO\(_2\) (78.0 mg, 0.35 mmol) in glacial acetic acid (3.0 mL) was stirred under H\(_2\) at atmospheric pressure for 20 h and then filtered through a wet (hot EtOAc) pad of Celite using hot EtOAc as wash. The filtrate was concentrated \textit{in vacuo}, the residue was suspended in EtOAc (4 mL), cooled to 0 °C, and saturated aqueous K\(_2\)CO\(_3\) (0.5 mL) was added. The mixture was stirred at rt for 10 min and then anhydrous K\(_2\)CO\(_3\) (5.0 g) was added. After stirring for an additional 5 min, the mixture was filtered through a wet (hot EtOAc) pad of Celite. Concentration \textit{in vacuo} afforded 167.8 mg (95%) of a 1:1 mixture of 68 and 68a. A small portion was purified by radial PLC (Al\(_2\)O\(_3\), 2%
diisopropylamine/5% MeOH/CH₂Cl₂) to afford 68 and 68a as clear oils. (68): ¹H NMR (400 MHz, CD₃OD) δ 3.37 (br d, J = 14.4 Hz, 1H), 3.12-3.19 (m, 1H), 2.98-3.06 (m, 2H), 2.54-2.66 (m, 3H), 2.00 (qd, J = 12.8, 4.4 Hz, 1H), 1.76-1.90 (m, 5H), 1.32-1.70 (m, 9H), 1.14-1.24 (m, 3H), 1.09 (dd, J = 14.0, 9.2, 3.6 Hz, 1H), 0.90 (d, J = 6.0 Hz, 3H), 0.83 (q, J = 11.6 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 18.3, 21.6, 24.1, 24.5, 25.3, 25.5, 33.3, 39.1, 39.9, 40.0, 46.3, 47.4, 48.8, 53.6, 57.9; IR (neat) 3274, 2932, 2849, 1659, 1442, 1373, 1331, 1263, 1116, 1076, 1051, 924, 887, 790, 733 cm⁻¹; HRMS calcd for C₁₆H₃₀N₂ (M+H)⁺ 251.2482, found 251.2484.

(2R*,4S*,9aS*)-2-Methyl-4-((S*)-piperidin-2-ylmethyl)octahydro-1H-quinolizine (68a). ¹H NMR (400 MHz, CD₃OD) δ 3.47 (q, J = 7.2 Hz, 1H), 3.29-3.37 (m, 1H), 3.21 (m, 1H), 3.08 (br d, J = 11.6 Hz, 1H), 2.64-2.80 (m, 2H), 2.00 (qd, J = 14.0, 3.6 Hz, 1H), 1.80-1.96 (m, 5H), 1.55-1.74 (m, 5H), 1.40-1.54 (m, 3H), 1.19-1.38 (m, 6H), 0.92 (d, J = 6.4 Hz, 3H), 0.85-0.96 (m, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 18.5, 21.2, 23.9, 24.2, 24.8, 24.9, 32.6, 38.1, 38.6, 39.0, 45.9, 48.8, 52.3, 53.7; IR (neat) 3396, 2930, 2853, 1730, 1625, 1455, 1374, 1331, 1263, 1116, 1076, 888, 802, 732 cm⁻¹; HRMS calcd for C₁₆H₃₀N₂ (M+H)⁺ 251.2482, found 251.2485.
REFERENCES


(b) Koo, C. H.; Kim, H. S. Daehan Hwahak Hwoejee 1965, 9, 134-141.


Piperonyl chloride was prepared from piperonyl alcohol according to: Porcal, W.; Merlino, A.; Boiani, M.; Gerpe, A.; Gonzalez, M.; Cerecetto, H. *Org. Process Res. Dev.* **2008**, *12*, 156-162.


APPENDICES
Comparison Data for (S)-Macrostomine

<table>
<thead>
<tr>
<th>Literature:</th>
<th>Our synthetic (S)-Macrostomine:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1)H NMR (C(_6)D(_6), 60 MHz)(^1)</td>
<td>(^1)H NMR (C(_6)D(_6), 400 MHz)</td>
</tr>
<tr>
<td>8.72 (1H, s)</td>
<td>8.80 (1H, s)</td>
</tr>
<tr>
<td>7.87 (1H, s)</td>
<td>7.88 (1H, s)</td>
</tr>
<tr>
<td>7.35 (1H, s)</td>
<td>7.32 (1H, s)</td>
</tr>
<tr>
<td>6.97 (1H, d, (J = 1.0) Hz)</td>
<td>7.01 (1H, d, (J = 2.0) Hz)</td>
</tr>
<tr>
<td>6.80 (1H, q, (J = 8.0, 1.0) Hz)</td>
<td>6.78 (1H, dd, (J = 8.0, 1.2) Hz)</td>
</tr>
<tr>
<td>6.55 (1H, d, (J = 8.0) Hz)</td>
<td>6.58 (1H, d, (J = 8.0) Hz)</td>
</tr>
<tr>
<td>5.30 (2H, s)</td>
<td>5.22 (2H, s)</td>
</tr>
<tr>
<td>4.55 (2H, s)</td>
<td>4.56 (2H, s)</td>
</tr>
<tr>
<td>3.55 (3H, s)</td>
<td>3.51 (3H, s)</td>
</tr>
<tr>
<td>3.47 (3H, s)</td>
<td>3.43 (3H, s)</td>
</tr>
<tr>
<td>3.0-3.6 (3H, m)</td>
<td>3.38 (1H, t, (J = 8.0) Hz)</td>
</tr>
<tr>
<td></td>
<td>3.08 (1H, t, (J = 8.0) Hz)</td>
</tr>
<tr>
<td>2.13 (3H, s)</td>
<td>2.13 (3H, s)</td>
</tr>
<tr>
<td>1.5-2.2 (4H, m)</td>
<td>2.01-2.10 (2H, m)</td>
</tr>
<tr>
<td></td>
<td>1.75-1.98 (2H, m)</td>
</tr>
<tr>
<td></td>
<td>1.53-1.63 (1H, m)</td>
</tr>
<tr>
<td>Literature:</td>
<td>Our synthetic (S)-Macrostomine:</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>$^1$H NMR (CDCl$_3$, 250 MHz)$^1$</strong></td>
<td><strong>$^1$H NMR (CDCl$_3$, 400 MHz)</strong></td>
</tr>
<tr>
<td>8.40 (1H, s)</td>
<td>8.40 (1H, s)</td>
</tr>
<tr>
<td>7.80 (1H, s)</td>
<td>7.79 (1H, s)</td>
</tr>
<tr>
<td>7.32 (1H, s)</td>
<td>7.32 (1H, s)</td>
</tr>
<tr>
<td>6.68-6.82 (3H, m)</td>
<td>6.68-6.80 (3H, m)</td>
</tr>
<tr>
<td>5.87 (2H, s)</td>
<td>5.87 (2H, s)</td>
</tr>
<tr>
<td>4.48 (2H, s)</td>
<td>4.48 (2H, s)</td>
</tr>
<tr>
<td>4.02 (3H, s)</td>
<td>3.99 (3H, s)</td>
</tr>
<tr>
<td>3.89 (3H, s)</td>
<td>3.89 (3H, s)</td>
</tr>
<tr>
<td>3.48-3.62 (1H, m)</td>
<td>3.53 (1H, t, $J = 8.0$ Hz)</td>
</tr>
<tr>
<td>3.26-3.38 (1H, m)</td>
<td>3.31 (1H, t, $J = 8.0$ Hz)</td>
</tr>
<tr>
<td>2.18-2.46 (2H, m)</td>
<td>2.28-2.42 (2H, m)</td>
</tr>
<tr>
<td>2.25 (3H, s)</td>
<td>2.25 (3H, s)</td>
</tr>
<tr>
<td>1.81-2.15 (3H, m)</td>
<td>1.86-2.11 (3H, m)</td>
</tr>
</tbody>
</table>

**Specific rotation**

$[\alpha]_{D}^{26} -54$ (c 0.72, CHCl$_3$)

Lit.: $[\alpha]_{D}^{25} -51 \pm 3$ (c 0.892, CHCl$_3$)
Comparison Data for Cermizine D

<table>
<thead>
<tr>
<th></th>
<th>Literature:</th>
<th>Our synthetic cermizine D:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^1$H NMR (CD$_3$OD, 600 MHz)$^3$</td>
<td>$^1$H NMR (CD$_3$OD, 700 MHz)$^4$</td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (CD$_3$OD, 400 MHz)</td>
<td></td>
</tr>
<tr>
<td>3.4 (1H, br d, $J = 14.0$ Hz)</td>
<td>3.39 (1H, br d, $J = 15.4$ Hz)</td>
<td>3.37 (1H, br d, $J = 14.4$ Hz)</td>
</tr>
<tr>
<td>3.25 (1H, m)</td>
<td>3.15-3.19 (1H, m)</td>
<td>3.12-3.19 (1H, m)</td>
</tr>
<tr>
<td>3.13 (1H, m)</td>
<td>3.03-3.07 (2H, m)</td>
<td>2.98-3.06 (2H, m)</td>
</tr>
<tr>
<td>3.06 (1H, bd, $J = 10.7$ Hz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.71 (1H, td, $J = 13.5$, 2.5 Hz)</td>
<td>2.59-2.68 (3H, m)</td>
<td>2.54-2.66 (3H, m)</td>
</tr>
<tr>
<td>2.67 (1H, m)</td>
<td>2.01 (1H, qd, $J = 12.6$, 4.2 Hz)</td>
<td>2.00 (1H, qd, $J = 12.8$, 4.4 Hz)</td>
</tr>
<tr>
<td>2.64 (1H, td, $J = 12.1$, 2.8 Hz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.00 (1H, qd, $J = 12.8$, 4.1 Hz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.76-1.92 (3H, m)</td>
<td>1.78-1.90 (5H, m)</td>
<td>1.76-1.90 (5H, m)</td>
</tr>
<tr>
<td>1.62-1.73 (3H, m)</td>
<td>1.62-1.74 (3H, m)</td>
<td>1.32-1.70 (9H, m)</td>
</tr>
<tr>
<td>1.52-1.62 (2H, m)</td>
<td>1.53-1.60 (2H, m)</td>
<td>1.14-1.24 (3H, m)</td>
</tr>
<tr>
<td>1.43-1.51 (2H, m)</td>
<td>1.43-1.49 (2H, m)</td>
<td>1.09 (1H, ddd, $J = 14.0$, 9.2, 3.6 Hz)</td>
</tr>
<tr>
<td>1.39 (1H, td, $J = 12.6$, 5.0 Hz)</td>
<td>1.40 (1H, td, $J = 12.6$, 5.6 Hz)</td>
<td></td>
</tr>
<tr>
<td>1.24-1.33 (3H, m)</td>
<td>1.19-1.24 (3H, m)</td>
<td></td>
</tr>
<tr>
<td>1.14-1.24 (2H, m)</td>
<td>1.12 (1H, ddd, $J = 14.0$, 9.8, 4.2 Hz)</td>
<td></td>
</tr>
<tr>
<td>0.92 (3H, d, $J = 6.3$ Hz)</td>
<td>0.93 (3H, d, $J = 7.0$ Hz)</td>
<td>0.90 (3H, d, $J = 6.0$ Hz)</td>
</tr>
<tr>
<td>0.87 (1H, q, $J = 12.0$ Hz)</td>
<td>0.83 (1H, q, $J = 11.9$ Hz)</td>
<td>0.83 (1H, q, $J = 11.6$ Hz)</td>
</tr>
</tbody>
</table>

164
## Literature:

<table>
<thead>
<tr>
<th></th>
<th>$^{13}$C NMR (CD$_3$OD, 125 MHz)</th>
<th>$^{13}$C NMR (CD$_3$OD, 175 MHz)</th>
<th>$^{13}$C NMR (CD$_3$OD, 100 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>59.2</td>
<td>57.7</td>
<td>57.9</td>
</tr>
<tr>
<td></td>
<td>54.9</td>
<td>53.5</td>
<td>53.6</td>
</tr>
<tr>
<td></td>
<td>50.2</td>
<td>48.6</td>
<td>48.8</td>
</tr>
<tr>
<td></td>
<td>47.3</td>
<td>46.2</td>
<td>47.4</td>
</tr>
<tr>
<td></td>
<td>40.6</td>
<td>39.9</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>40.4</td>
<td>39.8</td>
<td>39.9</td>
</tr>
<tr>
<td></td>
<td>39.7</td>
<td>39.0</td>
<td>39.1</td>
</tr>
<tr>
<td></td>
<td>34.1</td>
<td>33.2</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>26.4</td>
<td>25.3</td>
<td>25.5</td>
</tr>
<tr>
<td></td>
<td>26.2</td>
<td>25.1</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td>25.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.4</td>
<td>24.3</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>25.3</td>
<td>24.0</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>22.6</td>
<td>21.3</td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td>19.7</td>
<td>18.2</td>
<td>18.3</td>
</tr>
</tbody>
</table>

## Specific rotation

Lit.: $[\alpha]^{25}_D +80$ (c 0.06, MeOH)

$[\alpha]^{20}_D +40.8$ (c 0.90, MeOH)
References:


\[ \text{1H NMR (400 MHz, CDCl}_3) \]
$^{13}$C NMR (100 MHz, CDCl$_3$)
1H NMR (400 MHz, CDCl₃)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
185

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \]
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
189
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

164
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
OTf

218

CN

$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
205b

$^1H$ NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, C$_6$D$_6$)
$^{13}$C NMR (100 MHz, C$_{6}$D$_{6}$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
217

$\text{Me}$

243b

$^1\text{H NMR (400 MHz, C}_6\text{D}_6)$
$^{13}$C NMR (100 MHz, C$_6$D$_6$)
$^1$H NMR (400 MHz, CD$_3$OD)
$^{13}$C NMR (100 MHz, CD$_3$OD)
$^1$H NMR (400 MHz, CD$_3$OD)
$^{13}$C NMR (100 MHz, CD$_3$OD)