Synthesis of Heterocyclic Natural Products
Jaspine B and (-)-Swainsonine

by
Vijay Kumar Dhand
B.Sc. (Hons., Biochemistry), York University, 2010

Thesis Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Science

in the
Department of Chemistry
Faculty of Science

© Vijay Kumar Dhand 2013
SIMON FRASER UNIVERSITY
Summer 2013

All rights reserved.
However, in accordance with the Copyright Act of Canada, this work may
be reproduced, without authorization, under the conditions for
“Fair Dealing.” Therefore, limited reproduction of this work for the
purposes of private study, research, criticism, review and news reporting
is likely to be in accordance with the law, particularly if cited appropriately.
Approval

Name: Vijay Kumar Dhand
Degree: Master of Science
Title of Thesis: Synthesis of Heterocyclic Natural Products Jaspine B and (-)-Swainsonine
Examining Committee: Chair: Dr. Hua-Zhong (Hogan) Yu
                                      Professor
                                      Dr. Robert A. Britton
                                      Senior Supervisor
                                      Associate Professor
                                      Dr. Robert N. Young
                                      Supervisor
                                      Professor
                                      Dr. Krzysztof Starosta
                                      Supervisor
                                      Associate Professor
                                      Dr. Peter D. Wilson
                                      Internal Examiner
                                      Associate Professor
Date Defended/Approved: May 15, 2013
Partial Copyright Licence

The author, whose copyright is declared on the title page of this work, has granted to Simon Fraser University the right to lend this thesis, project or extended essay to users of the Simon Fraser University Library, and to make partial or single copies only for such users or in response to a request from the library of any other university, or other educational institution, on its own behalf or for one of its users.

The author has further granted permission to Simon Fraser University to keep or make a digital copy for use in its circulating collection (currently available to the public at the “Institutional Repository” link of the SFU Library website (www.lib.sfu.ca) at http://summit/sfu.ca and, without changing the content, to translate the thesis/project or extended essays, if technically possible, to any medium or format for the purpose of preservation of the digital work.

The author has further agreed that permission for multiple copying of this work for scholarly purposes may be granted by either the author or the Dean of Graduate Studies.

It is understood that copying or publication of this work for financial gain shall not be allowed without the author’s written permission.

Permission for public performance, or limited permission for private scholarly use, of any multimedia materials forming part of this work, may have been granted by the author. This information may be found on the separately catalogued multimedia material and in the signed Partial Copyright Licence.

While licensing SFU to permit the above uses, the author retains copyright in the thesis, project or extended essays, including the right to change the work for subsequent purposes, including editing and publishing the work in whole or in part, and licensing other parties, as the author may desire.

The original Partial Copyright Licence attesting to these terms, and signed by this author, may be found in the original bound copy of this work, retained in the Simon Fraser University Archive.

Simon Fraser University Library
Burnaby, British Columbia, Canada

revised Fall 2011
Abstract

Tetrahydrofurans and pyrrolidines are important structural motifs that are found in a variety of natural products that exhibit useful biological properties. Owing to their abundance in nature and both varied and potentially useful biological activity, numerous synthetic methods and strategies have been developed for the preparation of substituted tetrahydrofurans and pyrrolidines. The research work presented in this thesis describes the use of α-chloroaldehydes in the synthesis of the tetrahydrofuran-containing natural product pachastrissamine, as well as the development of new methods that provides rapid access to hydroxyalkyldihydropyrroles and iminosugars such as (-)-swainsonine.

Pachastrissamine (also known as jaspine B), is a naturally-occurring anhydrophytosphingosine isolated in 2002 from two different marine sponges Pachatrissa sp. and Jaspis sp., and displays potent activity against numerous cancer cell lines. A total synthesis of this natural product was achieved in 8 steps that included an α-chloroaldehyde aldol reaction and novel thermal cyclization of the aldol adduct as the key steps.

The second part of the thesis details the development of a concise and stereoselective strategy for the synthesis of hydroxyalkyldihydropyrroles. This study involves the nucleophilic addition of protected propargyl amines to α-chloroaldehydes, followed by Lindlar reduction of resultant chlorohydrin and an epoxide formation/cyclization sequence. This methodology was further demonstrated in the synthesis of unnatural iminosugars and in a formal synthesis of natural product (-)-swainsonine, a potent lysosomal α-mannosidase inhibitor.

Keywords: tetrahydrofurans; pyrrolidines; natural products; jaspine B; (-)-swainsonine
“The battle of life is, in most cases, fought uphill, and to win it without a struggle were perhaps to win it without honor. If there were no difficulties there would be no success; if there were nothing to struggle for, there would be nothing to be achieved.”

- Samuel Smiles (Scottish Author 1812-1904)
Acknowledgements

First and foremost, I would like to thank my research supervisor, Dr. Robert Britton, for giving me the opportunity to work in his laboratory here at Simon Fraser University. I am deeply grateful for his high scientific standards, optimism, instructive and timely feedback, patience, and encouragement. I am one of many people who has benefited in multiple ways from his influence and work.

I would like to thank the members of my supervisory committee, Profs. Robert Young and Krzysztof Starosta, for their support and helpful suggestions during my M.Sc. studies. I would also like to thank Prof. Peter Wilson for agreeing to serve as the internal examiner.

I would like to extend my thanks to Dr. Andrew Lewis and Mr. Colin Zhang for the NMR assistance and Mr. Hongwen Chen for mass spectroscopy services. I further want to thank Lynn Wood, Yolanda Broderick and the rest of the Chemistry Department for their support and guidance.

I would also like to thank Dr. Bal Kang, Dr. Jeff Mowat, Stanley Chang, Shira Halperin, Hope Fan, Jason Draper, Jarod Moore, Mike Homes, and Milan Bergeron-Brlek; I was truly fortunate to be able to work alongside these extremely bright and thoughtful people who during this journey have become dear friends. Without them, my experience at SFU would not have been as enjoyable. I have enjoyed many great conversations with my benchmate Stan (C.C.), who was born to teach. You will be a remarkable professor one day. I would like to thank members of both the Wilson and Young research groups past and present for their helpful advice and friendship.

Last, but not least, I would like to thank all my family and friends for providing support, love, guidance and encouragement throughout my studies.
Table of Contents

Approval .......................................................................................................................... ii
Partial Copyright Licence ............................................................................................... iii
Abstract ........................................................................................................................ iv
Quotation ........................................................................................................................ v
Acknowledgements ......................................................................................................... vi
Table of Contents .......................................................................................................... vii
List of Tables ................................................................................................................... ix
List of Figures ................................................................................................................ ix
List of Schemes ............................................................................................................... x
List of Abbreviations ..................................................................................................... xi

1. Introduction .................................................................................................................. 1
   1.1. Introduction to Bioactive Natural Products .......................................................... 1
   1.2. Tetrahydrofuran/Pyrrolidine Containing Natural Products ............................... 3
   1.3. Current Strategies for the Synthesis of 5-Membered Ring Heterocycles .............. 4
   1.4. Application of α-Chloroaaldehydes to the Synthesis of Tetrahydrofuran- and
       Pyrrolidine-Containing Natural Products ............................................................. 9
   1.5. Thesis Overview .................................................................................................. 14
   1.6. References ........................................................................................................... 16

2. Total Synthesis of the Cytotoxic Anhydrophytosphingosine
   Pachastrissamine (Jaspine B) ................................................................................... 19
   2.1. Introduction ......................................................................................................... 19
   2.2. Results and Discussion ....................................................................................... 21
       2.2.1. Exploration of Protecting Group Strategy .................................................. 21
       2.2.2. Cyclization of β-amidochlorohyrdrins: Attempted and Optimization ...... 23
       2.2.3. Total Synthesis of Pachastrissamine (79) .................................................... 25
   2.3. Conclusion ........................................................................................................... 26
   2.4. Experiments ........................................................................................................ 27
       2.4.1. Preparation of (±)-(R)-2-Chloropentanal (95) ........................................... 28
       2.4.2. Preparation of (+)-(R)-2-Chlorohept-6-enal (108) .................................... 29
       2.4.3. Preparation of β-Amidochlorohydrin (100) .............................................. 30
       2.4.4. Preparation of β-Amidochlorohydrin (109) .............................................. 31
       2.4.5. Preparation of γ-Lactone (104) .................................................................. 32
       2.4.6. Preparation of γ-Lactone (110) .................................................................. 33
       2.4.7. Preparation of γ-Lactone (112) .................................................................. 34
       2.4.8. Preparation of Lactol (113) ...................................................................... 36
       2.4.9. Preparation of Carbamate (114) ............................................................... 36
       2.4.10. Preparation of Pachastrissamine (79) ......................................................... 37
   2.5. References ........................................................................................................... 39
3. **A Short, Organocatalytic Formal Synthesis of (-)-Swainsonine and Related Alkaloids**.................................................................................................................. 42

3.1. Introduction ................................................................................................. 42

3.2. Results and Discussion ............................................................................ 43

3.2.1. Synthesis of Hydroxyalkyldihydropyrroles and Unnatural

Iminosugars ........................................................................................................ 43

3.2.2. Formal Synthesis of Natural Product (-)-Swainsonine ....................... 46

3.3. Conclusion .................................................................................................. 48

3.4. Experiments .................................................................................................. 49

3.4.1. Preparation of Chlorohydrin (124) ....................................................... 50

3.4.2. Preparation of Hydroxyalkyldihydropyrrole (127) ......................... 51

3.4.3. Preparation of Chlorohydrin (130a) .................................................... 52

3.4.4. Preparation of N-Boc-1-ethynylcyclohexylamine .......................... 53

3.4.5. Preparation of Chlorohydrin (130b) .................................................... 54

3.4.6. Preparation of Chlorohydrin (130c) .................................................... 55

3.4.7. Preparation of Chlorohydrin (130d) .................................................... 56

3.4.8. Preparation of Hydroxyalkyldihydropyrrole (131a) ...................... 57

3.4.9. Preparation of Hydroxyalkyldihydropyrrole (131b) ...................... 58

3.4.10. Preparation of Hydroxyalkyldihydropyrrole (131c) ...................... 59

3.4.11. Preparation of Hydroxyalkyldihydropyrrole (131d) ...................... 60

3.4.12. Preparation of Protected Aminotriols (132a) and (132b) ............. 61

3.4.13. Preparation of Protected Aminotriol (133) ....................................... 63

3.4.14. Preparation of (-)-(2S)-2,5-Dichloropentanal (136) .................... 65

3.4.15. Preparation of (-)-(4R,5S)-1-(9N-Boc)amino-5,8-dichlorooc-ta-2-yn-4-

ol (138) ........................................................................................................... 66

3.4.16. Preparation of Indolizidine (142) ....................................................... 67

3.4.17. Preparation of Indolizidine (143) ....................................................... 69

3.5. References ................................................................................................ 70

4. **Conclusions** .............................................................................................. 73

Appendices........................................................................................................... 75

Appendix A. NMR spectra (¹H and ¹³C NMR) Concerning Chapter 2 .......... 76

Appendix B. NMR spectra (¹H and ¹³C NMR) Concerning Chapter 3 ........... 84
List of Tables

Table 2.1  Lithium Aldol Reactions between α-Chloroaldehyde (95) and Different α-Amino Amides. ................................................................. 22
Table 2.2  Optimization of γ-Lactone (104) Formation. ................................................. 24
Table 3.1  Asymmetric α-Chlorination of Aldehyde 135............................................... 47

List of Figures

Figure 1.1  Representative Examples of Bioactive Natural Products. ....................... 2
Figure 1.2  Representative Natural Products Containing a Tetrahydrofuran Core. ......................................................................................... 3
Figure 1.3  Representative Natural Products Containing a Pyrrolidine Core......... 4
Figure 1.4  Cornforth Model Rationale for the Stereochemical Outcome of Additions to α-Chloroaldehydes......................................................... 10
Figure 2.1  Anhydrophytosphingosines (79) and (80). .............................................. 20
Figure 3.1  Natural Products Swainsonine (116) and Castanospermine (118). ....... 42
Figure 4.1  Representative Examples of Tetrahydrofuran- and Pyrrolidine-Containing Natural Products............................................................ 74
List of Schemes

Scheme 1.1  Synthesis of the Bicyclic Core 21 of the Miharamycins ........................................ 5

Scheme 1.2  Key Step in the Synthesis of Trisubsituted Tetrahydrofuranols 25 and 26 ........................................ 6

Scheme 1.3  Key Steps in the Total Synthesis of (±)-Kumaussallene (32) ........................................ 7

Scheme 1.4  Key Steps in the Synthesis of Radicamine B (35) and (-)-3-Epi-hyacinthacine A5 (39) ........................................ 8

Scheme 1.5  Key Steps in the Synthesis of (+)-Preussin (43) ........................................ 9

Scheme 1.6  Synthesis of Anti-configured β-Ketochlorohydrin from Lithium Aldol Reaction ........................................ 10

Scheme 1.7  Synthesis of all Configurational Isomers of the 2,5-Disubsituted-3-Hydroxythiophorefuran Scaffold ........................................ 11

Scheme 1.8  Synthesis of Marine Oxylipids 66 and 67 ........................................ 12

Scheme 1.9  Synthesis of (+)-Goniothalesdiol (72) ........................................ 13

Scheme 1.10  Synthesis of Hydroxypyrrolidine (+)-Preussin (77) ........................................ 14

Scheme 2.1  Synthesis of γ-Lactone (82) and a Synthetic Strategy for the Preparation of Pachastrissamine (79) and its Analogues ........................................ 21

Scheme 2.2  Potential Mechanism for the Formation of γ-Lactone (104) ........................................ 23

Scheme 2.3  Total Synthesis of Pachastrissamine (79) ........................................ 26

Scheme 3.1  Synthetic Strategy to Access Dihydropyrroles (e.g., 121) ........................................ 43

Scheme 3.2  Synthesis of Hydroxyalkyldihydropyrrole 127 ........................................ 44

Scheme 3.3  Synthesis of Hydroxyalkyldihydropyrroles 131a-d ........................................ 45

Scheme 3.4  Synthesis of Protected Aminotriols 132a, 132b, and 133 ........................................ 46

Scheme 3.5  Formal Synthesis of (-)-Swainsonine (116) ........................................ 48
List of Abbreviations

\([\alpha]_D\) Specific rotation at the sodium D line (589 nm)
\(\delta\) Chemical Shift in ppm from tetramethylsilane
\(^\circ\text{C}\) Degrees Celsius
Ac Acetyl
aq aqueous
Bn Benzyl
Boc tert-Butyloxycarbonyl
Bu Butyl
Bz Benzoyle
cat Catalytic amount
Cbz Carboxybenzyl
CDI Carboxydiimidazole
COSY Correlation Spectroscopy
DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE Dichloroethane
DET Diethyl tartrate
DIBAL-H Diisobutylaluminium hydride
DMSO Dimethylsulfoxide
Dpe-phos (Oxydi-2,1-phenylene)bis(diphenylphosphine)
dr Diastereomeric ratio
ee Enantiomeric excess
equiv Equivalents
Et Ethyl
HMDS Hexamethyldisilizane
HPLC High-performance liquid chromatography
HRMS High-resolution mass spectrometry
HSQC Heteronuclear Single Quantum Coherence
Hz Hertz
i Iso-
LDA Lithium diisopropylamide
LiHMDS Lithium hexamethyldisilazide
Molar

meta-Chloroperoxybenzoic acid

Methyl

Millimole (s)

Mole (s)

Melting Point

α-Methoxy-α-trifluoromethylphenylacetic acid

Microwave

N-chlorosuccinimide

N-methylmorpholine-N-oxide

Nuclear Magnetic Resonance

Nuclear Overhauser Effect

Nucleophile

Protecting group

Phenyl

para-Methoxybenzyl

parts-per-million

Propyl

Room temperature

Self-Contained Underwater Breathing Apparatus

Singly Occupied Molecular Orbital

Tertiary

Tetra-n-butylammonium fluoride

tert-Butylphenylsilyl

tert-Butyl hydroperoxide

tert-Butyldimethylsilyl

Trifluoromethanesulfonyl

Trifluoroacetate

Tetrahydrofuran
1. **Introduction**

1.1. **Introduction to Bioactive Natural Products**

For much of mankind’s recorded history we have relied on natural products to improve various aspects of our lives.\(^1\) For example, natural products have applications ranging from cosmetics,\(^2\) flavoring agents,\(^3\) pesticides,\(^4\) and dyes\(^5\) to pharmaceuticals.\(^1,6\) Natural products are primary or secondary metabolites produced by living organisms such as plants, animals, and microorganisms, all of which possess the necessary biochemical machinery for the construction of diverse and functionalized carbon frameworks.\(^6\) Notably, the secondary metabolites produced by living organisms are often biosynthesized for the purpose of chemical defense, communication or predation.\(^7\)

Since the beginning of 19\(^{th}\) century, much research has focused on the isolation of single compounds from the complex mixtures contained in bioactive extracts of plants or microorganisms.\(^1\) As an early example, the isolation of morphine (1) from opium poppy *Papaver somniferum* was reported in 1803 by the German pharmacist Sertürner, and morphine has been used as a painkiller for many decades.\(^8,9\) Another well-known example of a plant-derived natural product is paclitaxel (Taxol, 2), which was initially isolated from the bark of the Pacific yew tree, *Taxus brevifolia*.\(^10\) Paclitaxel is used to treat patients with lung, ovarian, and breast cancers.\(^11\) Microorganisms are also rich source of structurally diverse bioactive metabolites. One important discovery in this area was penicillin (3) in 1928 from the fungus *Pencillium notatum*,\(^12\) which ushered in an era of medicine often referred to as “The Golden Age of Antibiotics”.\(^1,13\) While terrestrial organisms (such as plants, microorganisms, insects and fungi) have traditionally been the principal source of bioactive natural products, the marine environment was to a large extent not explored until recently. However, with the advent of SCUBA in the 1960s, natural product chemists and biologists gained ready access to many new sources of natural products.\(^14\) The oceans, covering more than 70% of the surface of our planet, harbour an enormous number of organisms that are now known to produce a diverse
array of novel bioactive compounds. For example, invertebrates (sponges, bryozoans, mollusks and tunicates) as well as cyanobacteria and marine bacteria are now well known sources of drug leads.\textsuperscript{15} Some representative examples of drug leads isolated from marine organisms are cortistatin A (4), eleutherobin (5) and discodermolide (6).\textsuperscript{16,17,18}

Figure 1.1  Representative Examples of Bioactive Natural Products.

With regards to drug discovery, natural products have played an invaluable role in providing lead candidates, and the majority of clinically used drugs originate from nature.\textsuperscript{19} These pharmaceuticals are either natural products, semi-synthesized from natural products, or contain pharmacophores originally identified in a natural product.\textsuperscript{20} Thus, despite the fact that natural products may seem old fashioned when compared to modern drug discovery methods (e.g., high-throughput screening, combinational chemistry, etc.) nature continues to play a dominant role in the discovery of drugs leads.\textsuperscript{20}
1.2. Tetrahydrofuran/Pyrrolidine Containing Natural Products

Heterocycles are ubiquitous molecular scaffolds in biologically-active natural products, including polyketides, alkaloids, steroids, and terpenes.\textsuperscript{21} Due to their occurrence in many biologically active compounds such as the acetogenins,\textsuperscript{22} lignans,\textsuperscript{23} macrodiolides\textsuperscript{24} and polyether ionophores\textsuperscript{25}, oxygen-containing heterocycles (e.g., tetrahydrofurans) represent important synthetic targets. Several examples of natural products containing tetrahydrofuran cores are depicted in Figure 1.2. Haterumalide NA (7) was isolated from the Okinawan sponge \textit{Ircinia} sp. in 1999, and displays cytotoxicity against numerous cancer cell lines.\textsuperscript{26,27} This molecule consists of a 2,5-disubstituted-3-hydroxytetrahydrofuran, a $Z$-chlorooolefin, a \textit{trans}-bridged 14-membered lactone, and contains five stereogenic centres, which make this compound particularly challenging as a target for total synthesis. Kumausallene (8) is a member of a class of halogenated nonisoprenoid sesquiterepenes that contains a \textit{cis}-fused tetrahydrofuran unit halogenated at the C3 position and a bromoallene moiety.\textsuperscript{28} Another example of a tetrahydrofuran-containing natural product is elatervyne (9), which was isolated in 1983 from \textit{Laurencia elata} and possesses a 2,2'-bifuranyl core and six stereocenters.\textsuperscript{29} Jaspine B (10) and (+)-goniothalesdiol (11) are additional examples of tetrahydrofuran-containing natural products.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figures.png}
\caption{Representative Natural Products Containing a Tetrahydrofuran Core.}
\end{figure}
In addition to oxygen-containing heterocycles, heterocycles containing nitrogen atoms are also found in a variety of biologically relevant compounds. Among them, 5-membered ring heterocycles, such as pyrroldinones, are widely prevalent and compounds that incorporate this moiety have demonstrated a range of applications, including use as organocatalysts, chiral ligands or in pharmaceutical agents. Pyrrolidines are also found in nature as components of pyrrolizidine and indolizidine alkaloids. Some examples of natural products containing the pyrrolidine moiety include martellines, that are potent bradykinin antagonists isolated from the roots of *Martinella iquitosensis*, hyacinthacine A₄, an inhibitor of various carbohydrate processing enzymes, (-)-kianic acid, used in the study of serious neuronal disorders such as Alzheimer’s disease and epilepsy, (+)-preussin, an antifungal agent isolated from a liquid fermentation broth of *Aspergillus ochraceus*, and (-)-swainsonine, a potent lysosomal α-mannosidase inhibitor.

![Figure 1.3 Representative Natural Products Containing a Pyrrolidine Core.](image)

1.3. Current Strategies for the Synthesis of 5-Membered Ring Heterocycles

Owing to the therapeutic potential of tetrahydrofuran- and pyrrolidine- containing natural products, there has been longstanding interest in their stereoselective synthesis.
As a result, numerous unique methods have been developed and applied to the synthesis of natural products containing these structural moieties. For example, Etcheve-Quelquejeu and co-workers reported the synthesis of the bicyclic core of the miharamycins (e.g., 21), nucleoside antibiotics, from 3-C-methylene sugar utilizing a ring closing metathesis strategy (Scheme 1.1). Replacement of the 4,6-O-benzylidene protecting group by an acetate followed by ring closing metathesis with Grubbs’ II catalyst afforded the dihydrofuran. Dihydroxylation of with osmium tetroxide in tert-butanol in the presence of NMO gave tetrahydrofuran. Following a further sequence of reactions this latter material was converted into the bicyclic core of the miharamycin 21 in good overall yield.

Scheme 1.1 Synthesis of the Bicyclic Core 21 of the Miharamycins.

In 2000, Martin and co-workers reported the asymmetric total synthesis of the tri-substituted tetrahydrofuranols and isolated from Notheia anomala. This synthesis relied on a Sharpless asymmetric dihydroxylation and Katsuki-Sharpless asymmetric epoxidation as tools for the construction of tetrahydrofuran core and controlled introduction of the necessary stereogenic centres (Scheme 1.2). The allylic alcohol was obtained following a 5 step sequence of reactions from n-heptanal. This intermediate was subjected to asymmetric epoxidation using (R,R)(+)-DET followed by epoxide opening to provide the anti-tetrahydrofuran as the sole detected stereoisomer. Use of (S,S)(-)-DET afforded the corresponding syn-tetrahydrofuran. Overall, this synthetic strategy provides access to both trans- and syn-tetrahydrofurans from a common precursor 22.
Scheme 1.2  Key Step in the Synthesis of Trisubsituted Tetrahydrofuranols 25 and 26.

(±)-Kumausallene (32) is a marine natural product isolated from the Japanese red algae Laurencia niponica, and the synthesis of this compound has attracted great attention due to its unique structure, which features a cis-fused bis-tetrahydrofuran ring and a bromoallene moiety. Overmann and co-workers demonstrated the synthesis of cis-fused bis-tetrahydrofuran core in (±)-kumausallene (32) via a route that involved a sequential Prins cyclization-pinacol rearrangement sequence followed by a ring enlargement of benzofuranone 28 via a Baeyer-Villiger reaction that furnished lactone 29 (Scheme 1.3). This latter material was further elaborated to the unsaturated lactone 30 by a two-step reaction sequence involving selenation and selenoxide elimination. Methanolysis of lactone 30 followed by in situ oxa-Michael addition afforded the cis-fused bis-tetrahydrofuran 31, which was ultimately converted into (±)-kumausallene (32) following several subsequent steps.
Scheme 1.3  Key Steps in the Total Synthesis of (±)-Kumausallene (32).

Reductive amination is one of the most powerful methods available to synthesize nitrogen-containing heterocycles found in pyrrolidine, pyrrolizidine, and indolizidine alkaloids. Recently, Marco used this strategy as the key transformation in the synthesis of the naturally occurring pyrrolidine radicamine B (35), an α-glucosidase inhibitor. This synthesis initiated with Garner’s (R)-aldehyde 33 as the chiral starting material (Scheme 1.4). Hydrogenation of ketone 34 in acidic medium with a palladium catalyst afforded radicamine B (35). Interestingly, 35 was obtained in one pot through a 5 step sequence that included acidic cleavage of the acetonide and the Boc groups, hydrogenolytic cleavage of the three benzyl groups, intramolecular imine formation, and reduction of the imine bond. This process was further demonstrated in the synthesis of pyrrolizidine iminosugar (-)-3-epi-hyacinthacine A5 (39) (Scheme 1.4). Thus, pyrrolidine 36 was subjected to a Wittig olefination to furnish the α,β-unsaturated ketone 37, which was then hydrogenated. This latter reaction effected reduction of the double bond, deprotection of the amine function, and cyclization to afford pyrrolizidine 38. Finally a global deprotection provided (-)-3-epi-hyacinthacine A5 (39).
In contrast to the above described methodologies for natural products synthesis, another versatile strategy that is often used for the construction of nitrogen (or oxygen) containing heterocycles is palladium-catalyzed carboamination (or carboetherification). For instance, Wolfe reported the stereoselective synthesis of antifungal agent (+)-preussin via palladium-catalyzed carboamination of protected amino alcohol, which was synthesized in 7 steps from decanal (Scheme 1.5). Treatment of with NaO\text{Bu} and bromobenzene in the presence of catalytic Pd(OAc)$_2$/dpe-phos furnished pyrrolidine in good yield and high diastereoselectivity. The stereoselectivity of the pyrrolidine forming reaction is controlled by allylic (A$_{1,3}$) strain present in the alkene palladium-amido transition state.

Although many methods have been developed to construct substituted tetrahydrofurans and pyrrolidines, the application of these processes to natural product
synthesis often require multiple protecting and/or functional group manipulations to eventually reach the target compound. These steps necessarily decrease the overall efficiency of the synthesis, which translates to a reduced overall yield. Therefore, it is important to develop strategies that provide access to the tetrahydrofuran and pyrrolidine cores of natural products in more efficient ways.

Scheme 1.5  Key Steps in the Synthesis of (+)-Preussin (43).

1.4. Application of α-Chloroaldehydes to the Synthesis of Tetrahydrofuran- and Pyrrolidine-Containing Natural Products

Over the past few years, the Britton research group has directed considerable effort towards the development of efficient syntheses of substituted tetrahydrofurans and pyrrolidines that also minimize protecting group/functional group manipulations common to current synthetic strategies. Our approach to these substances initiate with the asymmetric chlorination of aliphatic aldehydes (e.g., 44) employing the Jørgensen procedure,⁵⁵ which utilizes L-prolinamide, or MacMillan’s method,⁵⁶ which relies on an imidazolidinone catalyst (Scheme 1.6). Next, an aldol reaction between the enantiomerically enriched α-chloroaldehyde (e.g., 45) and a lithium enolate affords an anti-configured β-ketochlorohydrin (e.g., 47) in good yield and excellent diastereoselectivity.⁵⁷,⁵⁸,⁵⁹ The diastereoselectivity of the aldol reaction can be rationalized by invoking the Cornforth model,⁶⁰ in which the carbonyl oxygen and chlorine atom are aligned anti-periplanar (eg. 48 and 49, Figure 1.4) to minimize the net dipole moment, and the nucleophile (lithium enolate) attacks preferentially from the less hindered face of the aldehyde, leading to 1,2-anti-configured products (e.g., 51).
Scheme 1.6 Synthesis of Anti-configured $\beta$-Ketochlorohydrin from Lithium Aldol Reaction.

Figure 1.4 Cornforth Model Rationale for the Stereochemical Outcome of Additions to $\alpha$-Chloraldehydes.

The resulting $\beta$-ketochlorohydrins (e.g., 47) can then be converted to 2,5-disubstituted-3-hydroxytetrahydrofurans through a 2 or 3 step reaction sequence. As depicted in Scheme 1.7, hydroxyl-directed reduction of the carbonyl function in $\beta$-ketochlorohydrin 47 provides the 1,3-anti- or 1,3-syn-chlorodiols 52 or 53, respectively. Displacement of the chlorine atom by the hydroxyl group at C5 through a silver-promoted cyclization gives tetrahydrofurans 54 and 56. On the other hand, epoxidation of chlorodiols 52 and 53 under basic conditions followed by Lewis-acid induced rearrangement of the resulting epoxylalcohols (not shown) provides tetrahydrofurans 55 and 57. It is noteworthy that this methodology provides access to all configurational isomers of the 2,5-disubsituted-3-hydroxytetrahydrofuran scaffold from a single aldol adduct 47 in 2-3 steps.
Scheme 1.7 Synthesis of all Configurational Isomers of the 2,5-Disubsituted-3-Hydroxytetrahydrofuran Scaffold.

In an effort to further demonstrate the utility of this methodology, a short synthesis of the marine oxylipids 66 and 67 was performed. As illustrated in Scheme 1.8, a lithium aldol reaction between the α,β-unsaturated ketone 58 and the α-chloroaldehyde 59 gave the β-ketochlorohydrin 60 in excellent yield (93%) and diastereoselectivity (dr >20:1). Hydroxyl-directed reduction of the ketone function in 60 afforded the 1,3-anti-diol 61 or the 1,3-syn-diol 62, both of which were accessed in good yield and excellent diastereoecontrol. Then, treatment of either compound 61 or 62 with 1:1 mixture of silver (I) triflate and silver (I) oxide gave the diastereomeric 3-hydroxytetrahydrofurans 63 and 64, respectively. Completion of the synthesis of both natural products involved oxidative cleavage of the alkene function with ozone followed by the reaction of resulting aldehyde (not shown) with an excess of 8-nonenyl magnesium bromide (65), which afforded the marine oxylipids 66 and 67 in excellent overall yield.
Scheme 1.8  Synthesis of Marine Oxylipids 66 and 67.

Although the silver-promoted cyclization of unprotected chlorodiols provides access to highly functionalized tetrahydrofuranols in 3 steps from α-chloroaldehydes, it was later discovered that the same results can be achieved by simply heating the chlorodiols in water or methanol. Kang demonstrated the synthetic utility of this cyclization protocol in the total synthesis of natural product (+)-goniothalesdiol (72). The synthesis of compound 72 began with the treatment of α-chloroaldehyde 69 with the lithium anion derived from (Z)-(2-iodo-vinyl)benzene (68), which provided the alkenyl chlorohydrin 70 in excellent yield and good diastereoselectivity (Scheme 1.9). Hydroxyl-directed dihydroxylation of compound 70 using osmium tetroxide and NMO gave chlorotriol 71 as the major component of 8:1 diastereomeric mixture, which was then subjected to microwave heating in methanol to afford (+)-goniothalesdiol 72 in excellent yield (92%). Notably, the synthesis of (+)-goniothalesdiol (72) was achieved in four steps.
and 49% overall yield, which is a significant improvement over previously reported syntheses that range in length from 10 to 16 linear steps.63

Following the successful stereoselective and concise synthesis of tetrahydrofuran-containing natural products, focus in the Britton group then shifted to the preparation of 2,5-disubstituted 3-hydroxypyrrolidines and the application of this methodology to the synthesis of (+)-preussin (77) and its analogues.64 As depicted in Scheme 1.10, the synthesis of (+)-preussin (77) commenced with a lithium aldol reaction between 2-undecanone (73) and (2R)-2-chloro-hydrocinnamaldehyde (74) affording the β-ketochlorohydrin 75 as the major component of a 4:1 mixture of diastereoisomers. The optically-enriched compound 75 was then converted into the corresponding imine by reaction with methylamine, which cyclized to form a pyrroline intermediate 76 that was reduced with sodium cyanoborohydride to give a 6:1 mixture of (+)-preussin (77) and its C5 epimer 78 in excellent yield (91%). Remarkably, this synthetic approach provides access to (+)-preussin (77) in three steps from commercially-available hydrocinnamaldehyde in excellent overall yield.

Scheme 1.9 Synthesis of (+)-Goniothalesdiol (72).
1.5. Thesis Overview

The research described in this document is presented in journal article style, with Chapter 1 as general introduction, Chapter 2 and 3 as separate journal articles (manuscript or submitted for publication).

In the second chapter the synthesis of the antitumor agent pachastrissamine (also known as jaspine B), isolated from the marine sponges *Pachatrissa* sp. and *Jaspis* sp. is detailed. The short synthesis of this natural product relied on the development of a lithium aldol reaction between a Boc-protected hydantoin and an enantiomerically enriched α-chloroaldehyde. A microwave-assisted cyclization of aldol adduct afforded the correctly configured core of pachastrissamine, which was further elaborated into the natural product following several subsequent steps. Notably, this synthetic approach to pachastrissamine is flexible and can be readily applied to the synthesis of analogues of the natural product through cross-metathesis or use of different α-chloroaldehydes in the key aldol reaction.

In the third chapter a newly developed method for the preparation of hydroxyalkyldihydropyrroles is described. This work involves the reaction of protected propargyl amines with α-chloroaldehydes, followed by Lindlar reduction of resulting chlorohydrin and a one-pot reaction sequence that includes amine deprotection, epoxide formation and intramolecular 5-exo-tet epoxide opening by the amine. In addition to
identifying a concise route to hydroxyalkyldihydropyrroles, we also extended this methodology to the synthesis of unnatural iminosugars by dihydroxylation, and a formal synthesis of (-)-swainsonine, a natural occurring lysosomal α-mannosidase inhibitor first isolated from the fungal plant pathogen \textit{Rhizoctonia leguminicola}. 
1.6. References


64. Draper, J.A.; Britton, R. *Org. Lett.* 2010, 12, 4034.
2. Total Synthesis of the Cytotoxic Anhydrophytosphingosine Pachastrissamine (Jaspine B)

2.1. Introduction

Pachastrissamine (79), also known as jaspine B, is a natural occurring anhydrophytosphingosine that possesses a tetrahydrofuran core and was first isolated from the Okinawan marine sponge Pachastrissa sp. in 2002 by Higa. More recently, Debitus reported the re-isolation of 79 along with a related anhydrophytosphingosine from the Vanuatuan marine sponge Jaspis sp., and assigned these compounds the common names jaspine A (80) and jaspine B (79). The all-cis trisubstituted tetrahydrofuran ring and absolute configuration (2S,3S,4S) of compound 79 were determined by a combination of detailed NMR spectroscopic studies, mass spectral analysis, and chemical derivatization (e.g., formation of MTPA monoamides). Importantly, pachastrissamine exhibited submicromolar cytotoxicity against P388, A549, HT29, MEL28 and HeLa cell lines, and represents a potential lead for cancer therapy. More recent studies demonstrated that pachastrissamine inhibits the activity of sphingomyelin synthase and consequently increases intracellular ceramide levels, resulting in apoptosis in tumor cells by a caspase-dependent pathway. Owing to its potential importance as a lead for cancer therapy, considerable effort has been devoted to the synthesis of pachastrissamine. However, while more than 25 syntheses of pachastrissamine (79) have been reported, many of the synthetic strategies are lengthy (ranging from 9 to 19 steps) and have limited ability to access analogues or related natural products (e.g. jaspine A (80)) due to their reliance on carbohydrates or amino acids as chiral pool starting materials.
Previously, we have demonstrated that 1,2-anti configured β-ketochlorohydrins can be accessed in a straightforward manner from the reaction of lithium enolates derived from methyl ketones with α-chloroaldehydes. In a single example, it was also shown that heating of the β-amidochlorohydrin 81 in a mixture of methanol-water afforded the β-hydroxy-γ-lactone (82) in excellent yield (Scheme 2.1). While our efforts to date have focused almost exclusively on the reaction of enolates derived from methyl ketones with α-chloroaldehydes, we endeavoured to extend this methodology to the preparation of pachastrissamine (79). As outlined in Scheme 2.1, it was envisaged that the reaction of a conformationally constrained α-aminoenolate (e.g., 83) with an α-chloroaldehyde (e.g., 84) would give rise to an anti-anti-aminochlorohydrin (e.g., 85) based on Evans-Cornforth type stereodirecting effect of the chlorine atom and the progression of the reaction through a chair-like 6-membered ring transition structure. A subsequent thermal cyclization would then provide direct access to α-amino-β-hydroxy-γ-lactones (e.g., 86) and serve as a launching point for the preparation of pachastrissamine and analogues of this potentially important natural product. Notably, and in contrast to chiral pool syntheses of pachastrissamine, this approach would rely on a single chlorine atom introduced via organocatalytic asymmetric α-chlorination to control the relative stereochemistry of the amino alcohol function in 79.
2.2. Results and Discussion

2.2.1. Exploration of Protecting Group Strategy

As summarized in Table 2.1, the total synthesis of pachastrissamine 79 was initiated with an investigation of the lithium aldol reaction between a small collection of α-amino lactams/lactones 87-93\textsuperscript{16,17,18} and α-chloropentanal (95).\textsuperscript{19} As indicated in entry 1, treatment of the TBS protected hydantoin 87 with freshly prepared lithium diisopropylamide, followed by slow addition of the α-chloroaldehyde 95 afforded the desired aldol adduct 97 in 50% yield albeit with low diastereoselectivity (dr = 1:1). Unfortunately, coupling of the lithium enolates derived from compounds 88 or 89 with α-chloroaldehyde (95) under the same conditions failed to provide detectable amounts of the corresponding chlorohydrin (entries 2 and 3). Similarly, reaction of the protected diketopiperazines 90 and 91 with 95 provided only small amounts (<10%) of the corresponding aldol adducts (entries 4 and 5). Based on the modest success obtained with the TBS protected hydantoin 87, we next evaluated the benzyl and Boc protected analogues 92 and 93, respectively. As indicated in entries 6 and 7, these hydantoin derivatives reacted with α-chloropentanal to provide the desired β-amidochlorohydrins 99 and 100 in good yield and diastereoselectivity. In the latter example, formation of 100 also involves a 1,3-migration of a Boc protecting group.\textsuperscript{20} It is noteworthy that this straightforward strategy for the synthesis of 100 could also be potentially exploited for the preparation of a wide variety of β-hydroxy-α-aminoacids\textsuperscript{21} by radical reduction of the
chloromethine function, or more elaborate amino acid derivatives through displacement of the chloride with nitrogen or oxygen nucleophiles.

Table 2.1  Lithium Aldol Reactions between α-Chloroaldehyde (95) and Different α-Amino Amides.

<table>
<thead>
<tr>
<th>entry</th>
<th>enolate precursor</th>
<th>conditions*</th>
<th>product</th>
<th>yield (dr)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87</td>
<td>A</td>
<td>97</td>
<td>50% (1:1)(^c)</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>A</td>
<td>nd(^d)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>89</td>
<td>A</td>
<td>nd(^d)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>A</td>
<td>98</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>5</td>
<td>91</td>
<td>B</td>
<td>nd(^e)</td>
<td>0(^e)</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>C</td>
<td>99</td>
<td>40% (&gt;20:1)</td>
</tr>
<tr>
<td>7</td>
<td>93</td>
<td>C</td>
<td>100</td>
<td>61%(^f) (10:1:1)(^g)</td>
</tr>
</tbody>
</table>

*Conditions: A: LDA, THF, -78 °C, 45 min, then 95; B: LiHMDS, THF, -78 °C to r.t., 45 min, then 95; C: LiHMDS, THF, -78 °C, 45 min, then 95; \(^b\) diastereomeric ratio determined by analysis of \(^1\)H NMR spectra recorded on crude reaction products; \(^c\) the relative stereochemistry of the products was not determined unambiguously; \(^d\) no product detected; \(^e\) major product was the self-condensation of amide 91; \(^f\) Yield based on analysis of \(^1\)H NMR spectrum recorded on crude reaction mixture with internal standard; \(^g\) products partially decompose during purification by column chromatography; \(^h\) major diastereomer is 100 (isolated in 45% yield).
2.2.2. Cyclization of β-amidochlorohydrins: Attempted and Optimization

Following the successful preparation of the β-amidochlorohydrins 97, 99, and 100, we next investigated the thermal cyclization of these compounds. Fortunately, while neither of the β-amidochlorohydrins 97 or 99 cyclized at temperatures ranging from 50 °C to reflux in a variety of solvents (e.g., water, methanol, dimethyl sulfoxide, acetonitrile, pH7 buffered water), heating of the β-amidochlorohydrin 100 in a mixture of methanol-water afforded the γ-lactone (104), which could be isolated in 15% yield along with the fully deprotected β-amidochlorohydrin (105) (Table 2.2, entry 1). Surprisingly, the chloroamide 105 failed to cyclize to the corresponding γ-lactone (104) even after heating at reflux for more than 24 h in water. Together, these results suggest that the formation of the desired γ-lactone 104 most likely proceeds via initial deprotection of the Boc-protected alcohol in 100 to afford the chlorohydrin 101 (Scheme 2.2). A second deprotection event would then afford the chloroamide 105, while a structural rearrangement from the hydantoin 101 to carbamate 102 is a necessary step preceding the formation of γ-lactone (104). The failure of hydantoins 97, 99, and 105 to undergo lactone formation indicates that the amide function in these molecules is not sufficiently nucleophilic for chloride displacement. In an effort to optimize the fortuitous rearrangement of hydantoin 101 to carbamate 102 necessary for the formation of γ-
lactone (104), we screened a variety of solvents and temperatures for this reaction (Table 2.2). As indicated in entries 2 and 3, heating of chlorohydrin 100 in dimethyl carbonate or dimethyl sulfoxide at 60 °C afforded none of the desired γ-lactone (104). Interestingly, formation of the γ-lactone (104) was significantly enhanced when the reaction was heated in a mixture of methanol-water at 100 °C (entry 4). Further increasing the reaction temperature (e.g., 120 °C) in methanol-water (1:1) did not alter the ratio of γ-lactone (104) to β-amidochlorohydrin (105). To further examine this process, a series of aqueous-solvent mixtures were employed. As indicated in entries 5 and 6, heating the β-amidochlorohydrins (100) in water-tert-butyl alcohol or water-2,2,2-trifluoroethanol under the same reaction conditions failed to improve on the results obtained in methanol-water (1:1). After screening the reaction in several different mixtures of methanol-water, we were eventually able to improve the ratio of γ-lactone (104) to β-amidochlorohydrin (105) to an optimal 2.7:1 when the cyclization was carried out with slight excess of methanol (entry 7). Notably, this latter reaction could be carried out in a microwave reactor and was complete in 20 min, affording the desired γ-lactone (104) in 40% yield accompanied with a 18% yield of the deprotected β-amidochlorohydrin (105) (entry 7).

**Table 2.2 Optimization of γ-Lactone (104) Formation.**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent(s)</th>
<th>temp (°C)*</th>
<th>104:105* (%yield)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O:CH₃OH (1:1)</td>
<td>60</td>
<td>1:3 (62%)</td>
</tr>
<tr>
<td>2</td>
<td>dimethylcarbonate</td>
<td>60</td>
<td>nd*</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>60</td>
<td>nd*</td>
</tr>
<tr>
<td>4</td>
<td>H₂O:CH₃OH (1:1)</td>
<td>100</td>
<td>1.7:1</td>
</tr>
<tr>
<td>5</td>
<td>H₂O:tBuOH (1:1)</td>
<td>100</td>
<td>1.1:1</td>
</tr>
<tr>
<td>6</td>
<td>H₂O:CF₃CH₂OH (1:1)</td>
<td>100</td>
<td>1.2:1</td>
</tr>
<tr>
<td>7d</td>
<td>H₂O:CH₃OH (1:1.2)</td>
<td>100</td>
<td>2.7:1 (58%)</td>
</tr>
<tr>
<td>8</td>
<td>H₂O:CH₃OH (1:1.3)</td>
<td>100</td>
<td>2:1</td>
</tr>
</tbody>
</table>

* Reaction carried out in a sealed tube in an oil bath; § determined by analysis of ¹H NMR spectra recorded on crude reaction mixture; combined isolated yield; reaction carried out in microwave reactor; no product detected.
2.2.3. Total Synthesis of Pachastrissamine (79)

Having developed a short synthetic route to the γ-lactone (104), we focused our efforts on applying this strategy to the total synthesis of pachastrissamine (79). As depicted in Scheme 2.3, the synthesis of 79 commenced with the asymmetric α-chlorination of 6-heptenal (106) following the procedure reported by MacMillan. While the chlorination of hexadecanal would eliminate two steps from the total synthesis (see below), the choice of 6-heptenal provides opportunities for the late stage production of pachastrissamine analogues through cross metathesis. A subsequent aldol reaction between the Boc-protected hydantoin 93 and the optically enriched α-chloroaldehyde 108 afforded a mixture of chlorohydrins in good yield (68%) and diastereoselectivity (dr 10:1:1:1:1) from which the desired aldol adduct 109 could be isolated in 52% yield. This latter material was then heated in H₂O-CH₃OH mixture using the optimized (Table 2.2) cyclization conditions to produce a 2.7:1 mixture of the desired the γ-lactone (110) and the chlorohydrin 111 in 60% yield. A cross metathesis of the purified γ-lactone (110) with 1-undecene catalyzed by the 2nd generation Grubbs-Hoveyda catalyst afforded the corresponding C₁₄ alkene, which was directly hydrogenated to afford the lactone 112 in 43% yield over the two steps. Reduction of the lactone function was carried out in two steps and involved treatment of compound 112 with DIBAL-H followed by reaction of the resulting mixture of lactols with Et₃SiH and BF₃·OEt₂. Finally, the carbamate in 114 was cleaved under basic conditions to afford pachastrissamine (79) in 91% yield. The spectroscopic data (¹H NMR, ¹³C NMR, HRMS and IR) of our synthetic pachastrissamine (79) were in complete agreement with that reported in the literature.
2.3. Conclusion

In conclusion, we have developed a short asymmetric synthesis of pachastrissamine (79) that relies on a diastereoselective aldol reaction between a Boc-protected hydantoin and an optically enriched α-chloroaldehyde to secure the correctly configured core of 79. A fortuitous protecting group migration proved key in the thermal cyclization of this material, which proved to be extremely sensitive to both temperature and solvent. Notably, the present synthesis compares well with those that have been reported and should be readily adapted to the production of analogues of
pachastrissamine through cross metathesis or initiation of the process with other readily available α-chloraldehydes. Furthermore, ready access to the optically enriched β-amidochlorohydrins used in this work may also prove useful for the production of β-hydroxy-α-aminoacids and other more elaborate amino acid derivatives.

2.4. Experimental

All reactions described were performed under an atmosphere of dry argon or nitrogen using oven dried glassware unless otherwise specified. Tetrahydrofuran was distilled over Na/benzophenone and dichloromethane was dried by distillation over CaH₂. All other solvents were used directly from EMD drysolv septum sealed bottles unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.²⁷ Thin layer chromatography was carried out on commercial aluminium backed silica gel 60 plates (E. Merck, type 5554, thickness 0.2 mm). Concentration and removal of trace solvents was performed on a Büchi rotary evaporator using dry ice/acetone condenser and vacuum from water or air aspirator.

All reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, and/or TCI America and were used without further purification. All solvents were purchased from Sigma Aldrich, EMD, Anachemia or Caledon and used without further purification.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterochloroform (CDCl₃) or methanol-D₄ as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (CDCl₃: δ 7.26, MeOD: δ 3.34, ¹H NMR; CDCl₃: δ 77.00, MeOD: δ 49.86, ¹³C NMR). Coupling constants (J values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ¹H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants, assignment (where possible). NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz).
Assignments of $^1$H and $^{13}$C NMR spectra are based on analysis of $^1$H-$^1$H COSY, HSQC, HMBC, TOCSY and 1D NOESY spectra.

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS or Bruker microOTOF-II LC mass spectrometer.

Optical rotations were measured on a Perkin Elmer Polarimeter 341 at 589 nm or a Rudolph Research Autopol II Polarimeter at 589 nm.

Diastereomeric ratios were determined by analysis of $^1$H NMR spectra recorded on crude reaction products.

2.4.1. Preparation of (±)-(R)-2-Chloropentanal (95)

To a cold (0 °C), stirred solution of pentanal (5.00 g, 0.058 mmol) in dichloromethane (160 mL), was added L-proline (668 mg, 5.8 mmol) and N-chlorosuccinimide (10.1 g, 0.075 mmol). The reaction mixture was stirred for one hour and then allowed to warm to room temperature slowly over 3 hours at which time the mixture was diluted with pentane (60 mL), cooled to -78 °C, filtered, and concentrated on a rotary evaporator in an ice water bath. The resultant oil was dissolved in pentane (60 mL), cooled (-78 °C), filtered, and concentrated on a rotary evaporator in an ice water bath to give the crude chloropentanal (95), which was purified by vacuum distillation (~50 mmHg, bp = ~45 °C) to afford (±)-(R)-2-chloropentanal (95) (4.90 g, 70%) as a colorless liquid. Spectral data attained for 95 was in agreement with literature reported values.\textsuperscript{10a}

$^1$H NMR (600 MHz, CDCl$_3$) δ: 9.49 (d, 1H, J = 2.5 Hz), 4.16 (m, 1H), 1.94 (m, 1H), 1.81 (m, 1H), 1.56 (m, 1H), 1.47 (m, 1H), 0.96 (t, 3H, J = 7.5 Hz).
$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 195.6, 63.9, 34.1, 19.0, 13.5.

### 2.4.2. Preparation of (+)-(R)-2-Chlorohept-6-enal (108)

![Structure](image)

To a stirred solution of 7-octene-1,2-diol (4.25 mL, 0.028 mol) in water (20 mL), was added an aqueous solution of sodium periodate (6.53 g, 0.031 mol) in water (34 mL) over a period of 20 minutes and the resultant mixture was stirred for 1.5 hours. After this time, mixture was diluted with dichloromethane (60 mL) and brine (60 mL). The phases were separated, and the aqueous phase was washed with dichloromethane (3 x 60 mL). The combined organic phases were dried with MgSO$_4$, filtered, and the solvent was removed in vacuo to give 6-heptenal as a colorless oil (3.38 g), which was used in the next step without further purification. Spectral data obtained for 6-heptenal (106) was in accordance with that reported in the literature.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 9.77 (t, 1H, $J$ = 1.8 Hz), 5.79 (m, 1H), 5.01 (m, 1H), 4.96 (m, 1H), 2.44 (td, 2H, $J$ = 7.3, 1.8 Hz), 2.07 (m, 2H), 1.65 (quint, 2H, $J$ = 7.7 Hz), 1.43 (quint, 2H, $J$ = 7.7 Hz).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 203.0, 138.6, 115.2, 44.1, 33.8, 28.7, 21.8.

IR (neat): 2930, 2859, 2719, 1723, 1640, 994, 910, 633 cm$^{-1}$

To a cold (-10 °C), stirred solution of lithium chloride (1.91 g, 0.045 mol), copper (II) trifluoroacetate hydrate (4.36 g, 0.015 mol), sodium persulfate (7.18 g, 0.030 mol) and water (1.2 mL, 0.066 mol) in acetonitrile (130 mL), was added imidazolidinone catalyst 107 (1.72 g, 6.0 mmol). After the mixture was stirred for 5 minutes, 6-heptenal (106) (3.38 g, 0.030 mol) in acetonitrile (20 mL) was added dropwise and the resultant mixture was stirred at -10 °C for 2 days. The reaction mixture was then allowed to warm to room temperature after which time ethyl acetate (70 mL) and water (70 mL) were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 70 mL). The combined organic phases were washed with brine (70 mL), dried (MgSO$_4$),
filtered, and the solvent was removed in vacuo to give crude chloroaldehyde. Purification of the crude product by flash chromatography (silica gel, 1:1 dichloromethane:pentane) afforded (+)-(R)-2-chlorohept-6-enal (108) (2.60 g, 64% over 2 steps).

\[ \alpha \]_{D}^{25} (c 1.0, CHCl\textsubscript{3}) = +37

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \( \delta \): 9.49 (d, 1H, \( J = 2.4 \) Hz), 5.77 (m, 1H), 5.03 (m, 1H), 5.00 (m, 1H), 4.16 (ddd, 1H, \( J = 8.1, 5.4, 2.4 \) Hz), 2.10 (m, 2H), 2.00 (m, 1H), 1.84 (m, 1H), 1.64 (m, 1H), 1.55 (m, 1H).

\textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) \( \delta \) 195.6, 137.9, 115.9, 64.2, 33.2, 31.7, 25.1.

IR (neat): 2923, 2855, 1736, 1460, 913, 744 cm\(^{-1}\)

Exact mass calcd. for C\textsubscript{7}H\textsubscript{12}ClO: 147.0566 (M+H\(^+\)); found: 147.0571 (M+H\(^+\)).

2.4.3. Preparation of \( \beta \)-Amidochlorohydrin (100)

To a cold (-78 °C), stirred solution of hexamethyldisilazane (1.2 mL, 5.5 mmol) in tetrahydrofuran (4.0 mL), was added \( n \)-butyllithium (2.59 M soln. in hexanes, 2.0 mL, 5.1 mmol) dropwise. The resulting mixture was allowed to warm to room temperature slowly over 15 minutes and then added dropwise via cannula to a cold (-78 °C), stirred solution of Boc-protected hydantoin 93\textsuperscript{16} (1.4 g, 4.6 mmol) in tetrahydrofuran (34 mL). After the mixture was stirred for 45 minutes, (+)-(R)-2-chloropentanal (95) (674 mg, 5.5 mmol) in tetrahydrofuran (4.0 mL) was added dropwise and the resulting mixture was stirred for an additional 1 hour 15 minutes. After this time, the reaction was treated with saturated aqueous solution of sodium dihydrogen phosphate (10 mL) and diluted with ethyl acetate (60 mL) and water (60 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO\textsubscript{4}), filtered, and concentrated to provide the crude
chlorohydrin. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded $\beta$-amidochlorohydrin (100) (876 mg, 45%, dr 10:1:1:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 5.68 (br s, 1H), 5.11 (dd, 1H, $J = 5.2$, 2.1 Hz), 4.39 (dd, 1H, $J = 2.1$, 1.5 Hz), 4.14 (m, 1H), 1.81-1.64 (m, 2H), 1.57 (s, 9H), 1.53-1.41 (m, 2H), 0.94 (t, 3H, $J = 7.8$ Hz).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$: 167.8, 152.2, 152.1, 145.6, 85.7, 84.1, 75.3, 61.2, 56.5, 36.0, 27.7, 27.5, 19.3, 13.3.

IR (neat): 3312, 2980, 2936, 2876, 1813, 1774, 1725, 1274, 1153 cm$^{-1}$

Exact mass calcd. for C$_{18}$H$_{29}$ClN$_2$NaO$_7$: 443.1556 (M+Na$^+$); found: 443.1584 (M+Na$^+$).

2.4.4. **Preparation of $\beta$-Amidochlorohydrin (109)**

![Chemical Structure](structure_image)

To a cold (-78 °C), stirred solution of hexamethyldisilazane (1.4 mL, 6.6 mmol) in tetrahydrofuran (6.0 mL), was added n-butyllithium (2.66 M soln. in hexanes, 2.3 mL, 6.0 mmol) dropwise. The resulting mixture was allowed to warm to room temperature slowly over 15 minutes and then added dropwise via cannula to a cold (-78 °C), stirred solution of Boc-protected hydantoin 93$^{16}$ (1.65 g, 5.5 mmol) in tetrahydrofuran (36 mL). After the mixture was stirred for 45 minutes, (+)-(R)-2-chlorohept-6-enal (108) (886 mg, 6.0 mmol) in tetrahydrofuran (4.0 mL) was added dropwise and the resultant mixture was stirred for an additional 1 hour 15 minutes. After this time, the reaction was treated with saturated aqueous solution of sodium dihydrogen phosphate (10 mL) and diluted with ethyl acetate (60 mL) and water (60 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO$_4$), filtered, and concentrated to provide the crude chlorohydrin. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded $\beta$-amidochlorohydrin (109) (1.28 g, 52%, dr 10:1:1:1).
$\text{[}\alpha\text{]}_D^{25}$ (c 0.65, CHCl$_3$) = -12.3

H NMR (600 MHz, CDCl$_3$) $\delta$: 5.76 (m, 1H), 5.62 (br s, 1H), 5.12 (dd, 1H, $J = 2.1, 5.2$ Hz), 5.01 (m, 2H), 4.39 (br s, 1H), 4.12 (m, 1H), 2.10 (m, 2H), 1.84 (m, 1H), 1.74 (m, 1H), 1.57 (s, 9H), 1.51-1.54 (m, 2H), 1.46 (s, 9H).

C NMR (150 MHz, CDCl$_3$) $\delta$: 167.7, 152.2, 152.1, 145.6, 137.5, 115.6, 85.8, 84.1, 75.2, 61.3, 56.5, 33.4, 32.8, 27.8, 27.5, 25.1.

IR (neat): 3307, 2981, 2936, 1813, 1774, 1725, 1370, 1274, 1153 cm$^{-1}$

Exact mass calcd. for C$_{20}$H$_{31}$ClN$_2$NaO$_7$: 469.1712 (M+Na)$^+$; found: 469.1707 (M+Na)$^+$.

2.4.5. Preparation of $\gamma$-Lactone (104)

To the 80 mL vial containing $\beta$-amidochlorohydrin (100) (876 mg, 2.1 mmol), was added 1:1.2 mixture of deionized water: methanol (25.6 mL) and vial was sealed in a CEM Discover LabMate microwave reactor. The reaction mixture was then heated for 20 minutes at 100 $^\circ$C in a microwave (as monitored by a vertically focused IR temperature sensor). After this time, reaction mixture was diluted with ethyl acetate (30 mL) and water (30 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic phases were washed with brine (30 mL), dried (MgSO$_4$), filtered and concentrated to give the crude lactone. Purification of the crude product by flash chromatography (silica gel, 20:1 dichloromethane:methanol) afforded $\gamma$-lactone (104) (157 mg, 40%) and deprotected $\beta$-amidochlorohydrin (105) (82 mg, 18%).
Data for γ-lactone (104):

$^1$H NMR (500 MHz, CDCl$_3$) δ: 5.68 (br s, 1H), 5.21 (dd, 1H, $J = 4.5, 7.6$ Hz), 4.66 (m, 1H), 4.44 (d, 1H, $J = 7.5$ Hz), 1.96-1.81 (m, 2H), 1.57-1.49 (m, 2H), 1.01 (t, 3H, $J = 7.4$ Hz).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ: 172.5, 156.7, 82.2, 77.0, 54.9, 30.9, 18.5, 13.7.

IR (neat): 3268, 2962, 2877, 1753, 1710, 1222, 968 cm$^{-1}$

Data for deprotected β-amidochlorohydrin (105):

$^1$H NMR (600 MHz, DMSO) δ: 5.87 (d, 1H, $J = 7.5$ Hz), 4.35 (t, 1H, $J = 1.4$ Hz), 4.00 (dt, 1H, $J = 2.7, 9.8$ Hz), 3.69 (ddd, 1H, $J = 1.4, 7.5, 9.4$ Hz), 1.54 (m, 2H), 1.36 (m, 2H), 0.90 (t, 3H, $J = 7.2$ Hz).

$^{13}$C NMR (150 MHz, DMSO) δ: 174.8, 158.1, 72.3, 62.2, 60.3, 35.3, 18.5, 13.3.

2.4.6. Preparation of γ-Lactone (110)

To the 80 mL vial containing β-amidochlorohydrin (109) (1.25 g, 2.7 mmol), was added 1:1.2 mixture of deionized water: methanol (36.6 mL) and vial was sealed in a CEM Discover LabMate microwave reactor. The reaction mixture was then heated for 20 minutes at 100 °C in a microwave (as monitored by a vertically focused IR temperature sensor). After this time, reaction mixture was diluted with ethyl acetate (60 mL) and water (60 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried (MgSO$_4$), filtered and concentrated to give the crude lactone. Purification of the crude product by flash chromatography (silica gel, 20:1 dichloromethane:methanol)
afforded \( \gamma \)-lactone (110) (250 mg, 44%, m.p. 108-111 °C) and deprotected \( \beta \)-amidochlorohydrin (111) (107 mg, 16%).

Data for \( \gamma \)-lactone (110):

\[
[\alpha]_D^{20} (c 1.01, \text{CHCl}_3) = -12.7
\]

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \): 5.79 (m, 1H), 5.63 (s, 1H), 5.21 (dd, 1H, \( J = 4.5, 7.4 \) Hz), 5.02 (m, 1H), 4.65 (m, 1H), 4.44 (dd, 1H, \( J = 0.71, 7.4 \) Hz), 2.15 (m, 2H), 1.95 (m, 1H), 1.88 (m, 1H), 1.60 (m, 2H).

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta \): 172.2, 156.3, 137.5, 115.6, 82.3, 76.9, 54.7, 33.2, 28.4, 24.4.

IR (neat): 3251, 2925, 1774, 1726, 1365, 1218, 1110, 964, 655 cm\(^{-1}\)

Exact mass calcd. for C\(_{10}\)H\(_{13}\)NNaO\(_4\): 234.0737 (M+Na\(^+\)); found: 234.0763 (M+Na\(^+\)).

Data for deprotected \( \beta \)-amidochlorohydrin (111):

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \): 5.89 (d, 1H, \( J = 7.5 \) Hz), 5.80 (m, 1H), 5.04-4.95 (m, 2H), 4.35 (brs, 1H), 3.99 (ddd, 1H, \( J = 9.7, 9.7 \) and 2.4 Hz), 3.70 (ddd, 1H, \( J = 9.3, 7.8 \) and 1.3 Hz), 2.08-1.99 (m, 4H), 1.55 (m, 1H), 1.43 (m, 1H).

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta \): 175.1, 158.3, 138.4, 115.2, 72.4, 62.4, 60.5, 32.8, 32.5, 24.6.

IR (neat): 3183, 3067, 2916, 1772, 1732, 1414, 636 cm\(^{-1}\)

Exact mass calcd. for C\(_{10}\)H\(_{16}\)ClN\(_2\)O\(_3\): 247.0844 (M+H\(^+\)); found: 247.0838 (M+H\(^+\)).

2.4.7. Preparation of \( \gamma \)-Lactone (112)
To a stirred solution of 1-undecene (0.24 mL, 1.2 mmol) in dichloromethane (7.5 mL) was added $\gamma$-lactone (110) (31 mg, 0.15 mmol) in dichloromethane (1.0 mL) followed by second generation Grubbs-Hoveyda catalyst (17 mg, 0.027 mmol). Nitrogen was bubbled through the mixture for 5 minutes, after which time the reaction mixture was stirred at reflux (46 °C) for 3 hours and cooled to room temperature. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) to give cis/trans ambiguous C$_{14}$ alkene (115) (25 mg) as a off-white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 6.28 (br s, 1H), 5.55-5.29 (m, 2H), 5.20 (dd, 1H, $J = 4.2$, 7.0 Hz), 4.65 (m, 1H), 4.47 (d, 1H, $J = 7.3$ Hz), 2.28-1.79 (m, 6H), 1.66-1.46 (m, 2H), 1.46-1.23 (m, 16H), 0.88 (t, 3H, $J = 6.7$ Hz).

To a stirred solution of C$_{14}$ alkene (115) (25 mg, 0.073 mmol) in 1:1 mixture of ethyl acetate: methanol (3.6 mL), was added palladium hydroxide (5.4 mg). Hydrogen was bubbled through the mixture for 30 minutes, and the reaction kept under hydrogen atmosphere for 1.5 hours. After this time, mixture was filtered through a pad of Celite® and filtrate was evaporated in vacuo to afford $\gamma$-lactone (112) (22 mg, 43% over 2 steps) as an off-white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 5.97 (br s, 1H), 5.21 (dd, 1H, $J = 4.4$, 7.4 Hz), 4.65 (m, 1H), 4.45 (d, 1H, $J = 7.4$ Hz), 1.99-1.80 (m, 2H), 1.48 (m, 1H), 1.41-1.20 (m, 23H), 0.88 (t, 3H, $J = 6.5$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 172.4, 156.6, 82.6, 77.0, 54.9, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 29.2, 29.0, 25.2, 22.7, 14.1.

IR (neat): 3260, 2957, 2918, 2850, 1778, 1724, 1217 cm$^{-1}$
2.4.8. Preparation of Lactol (113)

To a stirred solution of γ-lactone (112) (31 mg, 0.090 mmol) in dichloromethane (4.4 mL) at -55 °C, was slowly added diisobutylaluminium hydride in tetrahydrofuran (1.0 M, 0.32 mL, 0.32 mmol) and the resulting mixture was stirred for 12 hours. Another batch of diisobutylaluminium hydride in tetrahydrofuran (1.0 M, 0.32 mL, 0.32 mmol) was added and the resulting mixture stirred for 9 hours at -55 °C. The reaction was then quenched by addition of 1M hydrochloric acid (1.5 mL), diluted with ethyl acetate (10 mL) water (5 mL), and brine (5 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated. Purification of the crude material by flash chromatography (silica gel, 7:3 ethyl acetate:hexanes) afforded lactol 113 (26 mg, 85%) as a white solid (m.p. = 94-96 °C).

¹H NMR (400 MHz, CDCl₃) δ: 6.54 (br s, 1H), 5.30 (br s, 1H), 5.03 (dd, 1H, J = 3.6, 7.2 Hz), 4.27-4.20 (m, 2H), 3.46 (br s, 1H), 1.74 (m, 2H), 1.48-1.41 (m, 24H), 0.88 (t, 3H, J = 6.7 Hz).

¹³C NMR (100 MHz, CDCl₃) δ: 159.4, 100.9, 80.5, 80.1, 62.8, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 28.0, 26.0, 22.7, 14.1.

IR (neat): 3428, 3304, 2918, 2850, 1762, 1733, 1071, 1014 cm⁻¹

2.4.9. Preparation of Carbamate (114)
To a cold (-78 °C), stirred solution of lactol 113 (26 mg, 0.076 mmol) and triethylsilane (0.12 mL, 0.76 mmol) in dichloromethane (3.6 mL), was slowly added boron trifluoride diethyl etherate (0.050 mL, 0.38 mmol) and the reaction mixture was allowed to warm to room temperature. After 19.5 h, the reaction was treated with saturated aqueous solution of sodium bicarbonate (5 mL) and diluted with ethyl acetate (10 mL). The phases were separated, and the aqueous phase was washed with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated. Purification of the crude material by flash chromatography (7:3 ethyl acetate:hexanes) provided carbamate 114 (8.0 mg, 32%) as a white solid (m.p. = 112-115 °C).

\([\alpha]_D^{20} \ (c \ 0.72, \ CHCl_3) = +54\]

$^1$H NMR (400 MHz, CDCl₃) δ: 6.06 (br s, 1H), 4.95 (dd, 1H, $J = 3.6, 7.4$ Hz), 4.37 (dd, 1H, $J = 3.6, 7.4$ Hz), 3.94 (d, 1H, $J = 10.4$ Hz), 3.54-3.48 (m, 2H), 1.83-1.71 (m, 2H), 1.51-1.20 (m, 24H), 0.88 (t, 3H, $J = 6.6$ Hz).

$^{13}$C NMR (150 MHz, CDCl₃) δ: 159.2, 83.2, 80.9, 73.3, 57.1, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 28.1, 26.0, 22.7, 14.1.

IR (neat): 3330, 3242, 2921, 2848, 1756, 1720, 1070 cm$^{-1}$

2.4.10. Preparation of Pachastrissamine (79)

To a stirred solution of carbamate 114 (7.1 mg, 0.022 mmol) in ethanol (1.5 mL), was added aqueous potassium hydroxide (1M in water, 1.2 mL) and the mixture was refluxed (85 °C) overnight for 15 h. After the reaction mixture had cooled to room temperature, the mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (4 x 10 mL). The combined organic layer was washed with brine, dried (MgSO₄), and evaporated in vacuo to give the crude amino alcohol. Purification of the crude product by flash chromatography
(silica gel, 95:8:1 chloroform: methanol: aq. ammonium hydroxide) afforded pachastrissamine (79) (5.9 mg, 91%) as a white solid (mp = 83-85 °C) (lit.\textsuperscript{6b} mp = 70-72 °C).

\([\alpha]_D^{20} (c 0.48, \text{CHCl}_3) = +10\)

$^1$H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta: 3.92 (\text{dd, 1H, } J = 7.7, 7.7 \text{ Hz}), 3.87 (\text{m, 1H}), 3.73 (\text{m, 1H}), 3.65 (\text{m, 1H}), 3.52 (\text{dd, 1H, } J = 7.7, 7.7 \text{ Hz}), 2.25 (\text{br s, 2H}), 1.72-1.59 (\text{m, 2H}), 1.47-1.19 (\text{m, 24H}), 0.88 (\text{t, 3H, } J = 6.8 \text{ Hz}).$

$^{13}$C NMR (150 MHz, CDCl\textsubscript{3}) \(\delta: 83.2, 72.3, 71.7, 54.3, 31.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.4, 29.4, 29.3, 26.3, 22.7, 14.1.$

IR (neat): 3341, 2917, 2849, 1583, 1470, 1034 cm\textsuperscript{-1}
2.5. References


19. The racemic α-chloroaldehyde 95 was prepared using the procedure reported by Jørgenson in ref 12c.


3. A Short, Organocatalytic Formal Synthesis of (-)-Swainsonine and Related Alkaloids

3.1. Introduction

Swainsonine (116) is an indolizidine alkaloid that was originally isolated from the fungal plant pathogen *Rhizoctonia leguminicola* and structurally assigned as the piperidine 117 (Figure 3.1).1 Several years later, the correct structural assignment for 116 was reported following its re-isolation from the Australian flowering plant *Swainsona canescens,*2 and it was shown to be the causative agent of a livestock disease clinically similar to mannosidosis.2 Subsequently, it was found that swainsonine is a potent inhibitor of lysosomal α-mannosidase3a and Golgi α-mannosidase II,3b and 116 has been implicated as a lead candidate for the treatment of a variety of diseases.4 Most notably, in preclinical models, swainsonine suppressed the growth of several carcinoma xenografts,5a and GD0039 (the HCl salt of 116) progressed as far as Phase II clinical trials for the treatment of renal cell carcinoma.5b It is not surprising then that swainsonine has been the subject of numerous synthetic efforts.6,7,8 In fact, swainsonine has become

![Figure 3.1](image)

*Figure 3.1  Natural Products Swainsonine (116) and Castanospermine (118).*

---

1 Work presented in this chapter has been submitted to *Organic Letters* (2013). Initial development of the method, optimization of the asymmetric α-chlorination of 5-chloropentanal, and a formal synthesis of (-)-swainsonine were performed by Mr. Jarod Moore and Mr. Jason Draper. The preparation of all compounds presented in Schemes 3.3→3.4, and the characterization of these materials were performed by the author.
a classic target for the demonstration of new synthetic methods and/or strategies relevant to pyrrolidine, piperidine, or indolizidine synthesis. Presently, more than 40 syntheses of swainsonine have been reported that range in length from 8 to >20 steps (average approximately 14 steps), the most recent of which was a 14-step synthesis that originates with L-glutamic acid. Based on the importance of swainsonine as a biological tool and potential therapeutic, and the ongoing need for selective Golgi $\alpha$-mannosidase II inhibitors, we endeavored to develop a short and flexible synthesis of compound 116 that does not rely on chiral pool starting materials. Specifically, our efforts in the synthesis of trans-epoxides and various heterocycles from chlorohydrins suggested that optically enriched aminoepoxides of general structure 120 should be readily available and may well serve as precursors to the pyrrolidine core (e.g. 121) of the indolizidine alkaloids via a 5-exo-tet epoxide opening reaction, and subsequently iminosugars following alkene oxidation. Elaboration of these later substances into swainsonine (116), analogues of 116, or other inhibitors of carbohydrate processing enzymes (e.g., castanospermine (118)), would then involve a second annulation event.

\[ \text{Scheme 3.1 Synthetic Strategy to Access Dihydropyrroles (e.g., 121).} \]

3.2. Results and Discussion

3.2.1. Synthesis of Hydroxyalkyldihydropyrroles and Unnatural Iminosugars

As depicted in Scheme 3.2, our initial efforts focused on defining a concise synthesis of 1,2-anti-chlorohydrins that incorporate a cis-allylamine functionality. It was anticipated that this would be accomplished through the addition of an alkynyllithium derived from propargyl amine to an $\alpha$-chloroaldehyde, followed by partial hydrogenation. Toward this goal, $\alpha$-chloroundecanal (122) was prepared in good yield from undecanal and treated with the dianion generated from the reaction of propargyl amine with 2 equivalents of $n$-BuLi. Although these conditions provided the desired
chlorohydrin (not shown) as a single stereoisomer, this compound was produced in modest yield (22%) and proved difficult to isolate and purify by flash chromatography. In an effort to improve the yield of this reaction and generate a more tractable product, the addition of lithium anions derived from a variety of protected propargyl amines to the α-chloroaldehyde 122 was explored. While reaction of the dianion derived from commercially available N-Boc-propargyl amine with 122 afforded the chlorohydrin 124 in improved yield (44%), addition of the monoanion 123 to this aldehyde consistently provided the desired chlorohydrin 124 in yields >50%. Notably, this latter material proved stable to flash chromatography and underwent smooth reduction to provide the desired cis-alkenyl chlorohydrin 125 in good yield. After surveying conditions to promote a sequence of reactions involving deprotection, epoxide-formation and epoxide opening, we found that treating the alkenyl chlorohydrin 125 with aqueous acid effected removal of the Boc protecting group, and that direct basification of the reaction mixture then promoted epoxide formation followed immediately by epoxide opening, furnishing the dihydropyrrole 127 in excellent overall yield. The relative stereochemistry of the vicinal amino alcohol function in 127 was confirmed following its conversion to the cyclic carbamate 128 and comparison of spectral data derived from 128 to that reported for the related dihydropyrrole 129.

Scheme 3.2  Synthesis of Hydroxyalkyldihydropyrrole 127.
As depicted in Scheme 3.3, this strategy for dihydropyrrole synthesis was further explored through the preparation of compounds 131a-d. Toward this end, the alkynyl chlorohydrins 130a-d were synthesized following addition of the requisite Boc-protected propargylamine to 2-chloropentanal or 2-chlorohydrocinnamaldehyde. Pleasingly, Lindlar reduction of the corresponding alkynylchlorohydrins followed by direct treatment of the crude reduction products with aqueous acid then base (a one-pot procedure) afforded hydroxyalkyldihydropyrroles 131a-d in good overall yield.

Considering the brevity of the entire reaction sequence (four steps), this strategy should serve as an efficient means to access a wide variety of natural and unnatural iminosugars. For example, the dihydropyrroles 131c and 131d were converted into the protected iminosugar analogues 132a/132b and 133, respectively, via reaction with phosgene followed by dihydroxylation (Scheme 3.4). The relative stereochemistry of these new iminosugars was assigned based on analysis of 1D NOESY spectra. Structurally, this latter spirocyclic compound resembles the pyrrolidine 134, which is a selective inhibitor of \(\alpha\)-L-fucosidase.
3.2.2. Formal Synthesis of Natural Product (−)-Swainsonine

Having established a four-step synthesis of hydroxyalkyl dihydropyrroles, we focused on applying this process to a short synthesis of (−)-swainsonine (116). For this purpose, it was envisaged that a second annulation event involving displacement of a primary alkyl chloride would secure the indolizidine core of 116. Toward this end, L-prolinamide catalyzed chlorination of 5-chloropentanal (135) using the procedure reported by Jørgensen provided the dichloroaldehyde 136 in modest yield and enantioselectivity (Table 3.1, entry 2). For comparison purposes, using identical reaction conditions the chlorination of pentanal is complete in 4 hours (>97% yield) and proceeds with much higher enantioselectivity (85% ee). Unfortunately, when repeated at 0 °C, the extended reaction time corresponded with an erosion in enantioselectivity, presumably through prolinamide-catalyzed racemization of the chloroaldehyde 136. Considering these challenges, we next explored the use of MacMillan’s SOMO-activated aldehyde α-chlorination procedure as the imidazolidinone catalyst 137 does not affect racemization of chloroaldehyde products. Unfortunately, using these conditions (entry 3), the α-chloroaldehyde 136 was prepared in only modest optical purity (30% ee). At lower temperatures, the reaction rate decreased substantially (e.g. entries 4 and 5), however, racemization of the chloroaldehyde product was not observed. Ultimately, chlorination at −35 °C afforded the desired α-chloroaldehyde 136 in good yield and enantioselectivity (82% ee).
Table 3.1  Asymmetric α-Chlorination of Aldehyde 135.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>conditions</th>
<th>temp (°C)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-proline (20)</td>
<td>A</td>
<td>0–r.t.</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>L-prolinamide (20)</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0–r.t.</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>137 (20)</td>
<td>B&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0–r.t.</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>137 (20)</td>
<td>B&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−25</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>137 (20)</td>
<td>B&lt;sup&gt;e&lt;/sup&gt;</td>
<td>−35</td>
<td>75</td>
<td>82</td>
</tr>
</tbody>
</table>

Conditions: A: NCS, CH₂Cl₂, 4 h; B: Cu(TFA)<sub>2</sub>, LiCl, Na₂S₂O₅, H₂O, MeCN. <sup>a</sup>Determined by chiral HPLC analysis; <sup>b</sup> 24 h; <sup>c</sup> 4 h; <sup>d</sup> 3 days; <sup>e</sup> 19 days.

With the α-chloroaldehyde 136 in hand, treatment of this material with the lithium anion derived from the protected propargyl amine 123 afforded the 1,2-<i>anti</i> chlorohydrin 138 in good yield and diastereoselectivity (dr >20:1) (Scheme 3.5). Initial attempts to effect dihydropyrrole formation from 138 through the sequence of reactions described in Scheme 3.3 afforded 144 as the major product. After some experimentation, however, it was found that when both the equivalents and rate of addition of NaOH to the alkenylchlorohydrin 140 were strictly controlled, formation of the undesired tetrahydrofuran 144 could be largely avoided. Thus, slow addition of 3 equivalents of aqueous NaOH to compound 140 in MeOH reproducibly afforded the indolizidine 142 in good yield (54% over 3 steps from 138) accompanied by minor amounts (<10%) of compound 144. As expected, dihydroxylation of the indolizidine 142 provided an inseparable mixture of trihydroxy-indolizidines 116 and 145, in which (-)-swainsonine (116) was the major component (dr = 3:2). To improve the facial selectivity of the dihydroxylation, the unprotected indolizidine 142 was also converted into the corresponding TBS ether 143, which undergoes selective dihydroxylation (dr ~ 8:1) to provide swainsonine (116) following deprotection. The spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, MS, IR, [α]<sub>D</sub>) recorded on the TBS ether 143 were in agreement with that reported
for this material by Pyne.\textsuperscript{29} Notably, preparation of the indolizidine 142 in 5 steps from commercially available 5-chloropentanol constitutes a 6 step formal synthesis of (-)-swainsonine, the shortest of all reported routes.

Scheme 3.5 Formal Synthesis of (-)-Swainsonine (116).

3.3. Conclusion

In summary, we have developed a concise asymmetric synthesis of hydroxyalkylidihydropyrroles and demonstrated the utility of this process in a formal synthesis of the \(\alpha\)-mannosidase inhibitor (-)-swainsonine (116). While there are more than 40 reported syntheses of swainsonine ranging in length from 8 to over 20 steps (average length of 14 steps), our unique approach provides access to this potentially
important natural product in 6 steps from 5-chloropentanol, does not rely on chiral pool starting materials, and employs an organocatalytic asymmetric α-chlorination as the basis for the controlled introduction of each stereogenic centre. Based on its operational simplicity and reliance on readily available starting materials, this process should be adaptable to the production of a range of indolizidine, pyrrolidine, and pyrrolizidine natural products.

3.4. Experimental

All reactions described were performed under an atmosphere of dry argon or nitrogen using oven dried glassware unless otherwise specified. Tetrahydrofuran was distilled over Na/benzophenone and dichloromethane was dried by distillation over CaH₂. All other solvents were used directly from EMD drysolv septum sealed bottles unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still. Thin layer chromatography was carried out on commercial aluminium backed silica gel 60 plates (E. Merck, type 5554, thickness 0.2 mm). Concentration and removal of trace solvents was performed on a Büchi rotary evaporator using dry ice/acetone condenser and vacuum from water or air aspirator.

All reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, and/or TCI America and were used without further purification. All solvents were purchased from Sigma Aldrich, EMD, Anachemia or Caledon and used without further purification.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterochloroform (CDCl₃) methanol-D₄ as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (CDCl₃: δ 7.26, MeOD: δ 3.34, ¹H NMR; CDCl₃: δ 77.00, MeOD: δ 49.86, ¹³C NMR). Coupling constants (J values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ¹H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants, assignment (where possible). NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or
TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz). Assignments of $^1$H and $^{13}$C NMR spectra are based on analysis of $^1$H-$^1$H COSY, HSQC, HMBC, TOCSY and 1D NOESY spectra.

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS or Bruker micrOTOF-II LC mass spectrometer.

Optical rotations were measured on a Perkin Elmer Polarimeter 341 at 589 nm or a Rudolph Research Autopol II Polarimeter at 589 nm.

Diastereomeric ratios were determined by analysis of $^1$H NMR spectra recorded on crude reaction products.

3.4.1. Preparation of Chlorohydrin (124)

To a cold (0 °C), stirred solution of diisopropylamine (0.36 mL, 2.6 mmol) in tetrahydrofuran (12 mL), was added a solution of $n$-butyllithium (2.59 M in hexanes, 0.85 mL, 2.2 mmol). The mixture was stirred for 20 minutes and then cooled to -78 °C. To this solution was added protected propargylamine$^{26}$ (416 mg, 1.8 mmol) in THF (1.0 mL) dropwise and the resulting mixture was stirred for 40 minutes. A solution of 2-chloroundecanal (122)$^{27}$ (300 mg, 1.4 mmol) in THF (1.5 mL) was added dropwise. After stirring for 20 minutes at -78 °C, a solution of tetrabutylammonium fluoride (1.0 M in THF, 1.5 mL) was added and the reaction mixture was stirred for an additional 15 minutes. After this time, the reaction was treated with a saturated aqueous solution of ammonium chloride (5 mL), and diluted with ethyl acetate (15 mL) and water (15 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3
The combined organic phases were washed with brine (15 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded chlorohydrin 124 (266 mg, 53%, 15:1 diastereomeric mixture) as a colorless oil.

$^1$H NMR (600 MHz, CD$_3$OD) δ: 4.49 (m, 1H), 3.93 (m, 1H), 3.88 (s, 2H), 1.94 (m, 1H), 1.73 (m, 1H), 1.61 (m, 1H), 1.47 (s, 9H), 1.41-1.30 (m, 13H), 0.93 (t, 3H, J = 6.7 Hz).

$^{13}$C NMR (150 MHz, CD$_3$OD) δ: 158.9, 84.6, 81.9, 81.4, 68.1, 67.8, 35.3, 33.9, 31.7, 31.5, 31.5, 31.3, 31.1, 29.6, 28.4, 24.6, 15.3.

IR (neat): 3350, 2922, 2849, 1691 cm$^{-1}$

Exact mass calcd. for C$_{19}$H$_{34}$ClNO$_3$: 359.2227 (M$^+$); found: 359.2223 (M$^+$).

### 3.4.2. Preparation of Hydroxyalkylidihydropyrrole (127)

To a cold (0 °C), stirred solution of chlorohydrin 124 (100 mg, 0.27 mmol) and quinoline (4.4 μL, 0.037 mmol) in ethanol (5.0 mL) was added 5% Pd-BaSO$_4$ (30 mg, 0.014 mmol). The resulting mixture was stirred under an atmosphere of H$_2$ (balloon) at room temperature for 30 minutes and monitored by $^1$H NMR spectroscopy. After reduction of the alkene was complete, the mixture was diluted with dichloromethane (4 mL) and filtered through a pad of Celite$^\circledR$. The solvent was removed in vacuo to give the crude cis-alkene 125 (80 mg, 82%), which required no further purification.

$^1$H NMR (500 MHz, CD$_3$OD) δ: 5.62 (m, 2H), 4.54 (m, 1H), 3.94 (m, 1H), 3.81 (dd, 1H, J = 15.6, 5.6 Hz), 3.73 (dd, 1H, J = 15.6, 4.6 Hz), 1.87 (m, 1H), 1.62 (m, 1H), 1.46 (s, 9H), 1.43-1.28 (m, 14H), 0.93 (t, 3H, J = 6.9 Hz).

To a vial containing the crude cis-alkene 125 (20 mg, 0.055 mmol) was added ethereal HCl (2M, 0.5 mL). The reaction mixture was stirred at room temperature for 20 hours after which time the solvent was removed in vacuo. The resultant residue was dissolved
in methanol (1.0 mL) and treated with aqueous solution of sodium hydroxide (2M, 1.0 mL). The reaction mixture was stirred for 3 hours after which time it was diluted with water (5 mL) and dichloromethane (5 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 70:30:1 dichloromethane:methanol:ammonium hydroxide) afforded hydroxyalkyldihydropyrrole 127 (11 mg, 89%) as a colorless liquid.

$^1$H NMR (500 MHz, CD$_3$OD) δ: 5.99 (m, 1H), 5.92 (m, 1H), 3.95 (m, 1H), 3.79 (m, 1H), 3.71 (m, 1H), 3.51 (m, 1H), 1.59 (m, 2H), 1.46-1.29 (m, 14H), 0.93 (t, 3H, J = 6.7 Hz).

$^{13}$C NMR (125 MHz, CD$_3$OD) δ: 131.3, 130.1, 75.4, 72.4, 55.1, 36.0, 33.9, 31.7, 31.6, 31.6, 31.3, 27.9, 24.6, 15.3.

IR (neat): 3266, 2921, 2851 cm$^{-1}$

Exact mass calcd for C$_{14}$H$_{28}$NO: 226.2293 (M+H$^+$); found: 226.2163 (M+H$^+$).

3.4.3. Preparation of Chlorohydrin (130a)

To a cold (−78 °C), stirred solution of N-Boc-propargylamine (200 mg, 1.3 mmol) in THF (7.0 mL) was added a solution of n-butyllithium (2.66 M in hexanes, 1.0 mL, 2.7 mmol) dropwise. The resulting mixture was stirred at −78 °C for 1 hour. After this time, a solution of 2-chloropentanal$^5$ (155 mg, 1.3 mmol) in THF (0.8 mL) was added dropwise and the resulting mixture was stirred for an additional 20 minutes. The reaction mixture was then treated with a saturated aqueous solution of ammonium chloride (5 mL), and diluted with ethyl acetate (10 mL) and water (10 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo.
Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded chlorohydrin **130a** (158 mg, 44%, 14:1 diastereomeric mixture) as a colorless oil.

$^1$H NMR (600 MHz, CD$_3$OD) δ: 4.49 (m, 1H), 3.95 (dt, 1H, $J = 10.1, 3.8$ Hz), 3.88 (br s, 2H), 1.90 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.47 (s, 9H), 1.45 (m, 1H), 0.98 (t, 3H, $J = 7.4$ Hz).

$^{13}$C NMR (150 MHz, CD$_3$OD) δ: 158.9, 84.6, 81.9, 81.4, 67.8, 67.7, 37.3, 31.7, 29.6, 21.5, 14.7.

IR (neat): 3379, 2999, 2961, 1691, 1367 cm$^{-1}$

Exact mass calcd. for C$_{13}$H$_{22}$ClNO$_3$: 275.1288 (M)+; found: 275.1287 (M)+.

**3.4.4. Preparation of N-Boc-1-ethynylcyclohexylamine**

![N-Boc-1-ethynylcyclohexylamine](image)

To a stirred solution of 1-ethynylcyclohexylamine (0.66 mL, 4.8 mmol) in THF (40 mL) was added di-tert-butyl dicarbonate (1.2 mL, 5.4 mmol) at 40 °C and the mixture was allowed to stir for 22 hours. After this time, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 15:1 hexanes:ethyl acetate) afforded N-Boc-1-ethynylcyclohexyl amine (1.1 g, 99%) as a white solid (m.p. 96-98°C).

$^1$H NMR (600 MHz, CDCl$_3$) δ: 4.59 (br s, 1H), 2.36 (s, 1H), 2.07 (m, 2H), 1.71-1.54 (m, 7H), 1.45 (s, 9H), 1.26 (m, 1H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ: 154.0, 86.0, 79.5, 70.8, 51.1, 37.2, 28.4, 25.2, 22.3.

IR (neat): 3291, 3243, 3127, 2969, 2926, 2852, 1692 cm$^{-1}$

Exact mass calcd. for C$_{13}$H$_{22}$NO$_2$: 224.1672 (M+H)+; found: 224.1644 (M+H)+.
3.4.5. Preparation of Chlorohydrin (130b)

To a cold (−78 °C), stirred solution of N-Boc-1-ethynylcyclohexyl amine (150 mg, 0.67 mmol) in THF (4.0 mL) was added a solution of n-butyllithium (2.66 M in hexanes, 0.53 mL, 1.4 mmol) dropwise and the mixture was stirred for 1.5 hours. After this time, a solution of 2-chloropentanal (81 mg, 0.67 mmol) in THF (0.45 mL) was added dropwise and the resulting mixture was stirred for an additional 20 minutes. The reaction mixture was then treated with a saturated aqueous solution of ammonium chloride (3 mL), and diluted with ethyl acetate (10 mL) and water (10 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na₂SO₄), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded chlorohydrin 130b (200 mg, 87%, 10:1 diastereomeric mixture) as a colorless oil.

$^1$H NMR (600 MHz, CD₃OD) δ: 4.53 (d, 1H, $J = 4.1$ Hz), 3.98 (dt, 1H, $J = 9.9, 3.7$ Hz), 2.11 (br s, 2H), 1.94 (m, 1H), 1.79-1.58 (m, 10H), 1.47 (s, 9H), 1.30 (m, 1H), 0.98 (t, 3H, $J = 7.4$ Hz).

$^{13}$C NMR (150 MHz, CD₃OD) δ: 157.5, 90.1, 82.8, 80.9, 68.1, 67.9, 53.0, 39.2, 37.6, 29.7, 27.4, 24.4, 24.4, 21.6, 14.7.

IR (neat): 3356, 2995, 2926, 1692, 1367, 1275 cm⁻¹

Exact mass calcd. for C₁₈H₃₀ClNO₃K: 382.1614 (M+K)+; found: 382.1555 (M+K)+.
3.4.6. Preparation of Chlorohydrin (130c)

To a cold (−78 °C), stirred solution of N-Boc-propargylamine (700 mg, 4.5 mmol) in THF (20 mL) was added a solution of n-butyllithium (2.66 M in hexanes, 3.6 mL, 9.5 mmol) dropwise. The resulting mixture was stirred at −78 °C for 1 hour. After this time, a solution of 2-chlorohydrocinnamaldehyde (760 mg, 4.5 mmol) in THF (3.2 mL) was added dropwise and the resulting mixture was stirred for an additional 20 minutes. The reaction mixture was then treated with a saturated aqueous solution of ammonium chloride (6 mL), and diluted with ethyl acetate (15 mL) and water (15 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine (15 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded chlorohydrin 130c (669 mg, 46%, 11:1 diastereomeric mixture) as a colorless oil.

$^1$H NMR (600 MHz, CD$_3$OD) δ: 7.33-7.23 (m, 5H), 4.48 (m, 1H), 4.17 (m, 1H), 3.92 (br s, 2H), 3.38 (s, 1H), 3.30 (dd, 1H, $J = 14.3, 5.5$ Hz), 3.00 (dd, 1H, $J = 14.3, 9.0$ Hz), 1.47 (s, 9H).

$^{13}$C NMR (150 MHz, CD$_3$OD) δ: 158.9, 139.9, 131.3, 130.3, 128.6, 85.3, 81.5, 81.5, 68.4, 67.1, 42.0, 31.7, 29.6.

IR (neat): 3368, 2977, 2930, 1691, 1396, 1366 cm$^{-1}$

Exact mass calcd. for C$_{17}$H$_{22}$ClNO$_3$: 323.1388 (M)$^+$; found: 323.1288 (M)$^+$.
3.4.7.  **Preparation of Chlorohydrin (130d)**

![Chemical structure](image)

To a cold (–78 °C), stirred solution of N-Boc-1-ethynylcyclohexyl amine (700 mg, 3.1 mmol) in THF (18 mL) was added a solution of n-butyllithium (2.66 M in hexanes, 2.5 mL, 6.6 mmol) dropwise and the mixture was stirred for 1.5 hours. After this time, a solution of 2-chlorohydrocinnamaldehyde\(^5\) (528 mg, 3.1 mmol) in THF (2.5 mL) was added dropwise and the resulting mixture was stirred for an additional 20 minutes. The reaction mixture was then treated with a saturated aqueous solution of ammonium chloride (7 mL), and diluted with ethyl acetate (15 mL) and water (15 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine (15 mL), dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded chlorohydrin 130d (800 mg, 66%, 9:1 diastereomeric mixture) as a colorless oil.

\(^1\)H NMR (600 MHz, CD\(_3\)OD) δ: 7.33-7.24 (m, 5H), 4.51 (d, 1H, \(J = 3.8\) Hz), 4.19 (m, 1H), 3.37 (s, 1H), 3.36 (m, 1H), 3.03 (dd, 1H, \(J = 14.4, 8.8\) Hz), 2.17 (m, 2H), 1.76 (m, 2H), 1.65 (m, 5H), 1.47 (s, 9H), 1.33 (m, 1H).

\(^13\)C NMR (150 MHz, CD\(_3\)OD) δ: 157.5, 140.0, 131.3, 130.3, 128.6, 90.8, 82.3, 81.0, 68.9, 67.2, 53.1, 42.1, 39.3, 29.7, 29.7, 27.4, 24.4, 24.4.

IR (neat): 3342, 2965, 1692, 1490 cm\(^{-1}\)

Exact mass calcd. for C\(_{22}\)H\(_{30}\)ClNO\(_3\)Na: 414.1914 (M+Na)+; found: 414.1815 (M+Na)+.
3.4.8. Preparation of Hydroxyalkyldihydropyrrole (131a)

\[
\begin{array}{c}
\text{HO} \\
\text{H} \\
\text{H} \\
\text{CH}_3 \\
\end{array}
\]

To a cold (0 °C), stirred solution of chlorohydrin 130a (101 mg, 0.36 mmol) and quinoline (2.2 μL, 0.018 mmol) in ethanol (3.0 mL) was added 5% Pd-BaSO₄ (103 mg, 0.048 mmol). The resulting mixture was stirred under an atmosphere of H₂ (balloon) at room temperature for 30 minutes (reaction monitored by \(^1\)H NMR spectroscopy). After this time the mixture was diluted with dichloromethane (4 mL) and filtered through a pad of Celite©, and the solvent was removed in vacuo to afford the crude cis-alkene (104 mg), which was used in the next step without further purification.

\(^1\)H NMR (400 MHz, CD₃OD) δ: 5.63-5.60 (m, 2H), 4.54 (m, 1H), 3.95 (m, 1H), 3.82 (dd, 1H, J = 15.7, 6.2 Hz), 3.72 (dd, 1H, J = 15.7, 4.4 Hz), 1.84 (m, 1H), 1.72-1.58 (m, 3H), 1.46 (s, 9H), 0.98 (t, 3H, J = 7.4 Hz).

To a vial containing the crude cis-alkene (104 mg, 0.37 mmol) was added ethereal HCl (2M, 0.8 mL). The reaction mixture was stirred at room temperature for 23 hours after which time the solvent was removed in vacuo. The resulting residue was dissolved in methanol (1.5 mL) and treated with aqueous solution of sodium hydroxide (2M, 1.6 mL). The reaction mixture was stirred for 4 hours after which time it was diluted with water (10 mL) and dichloromethane (10 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na₂SO₄), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 70:30:1 dichloromethane:methanol:ammonium hydroxide) afforded hydroxyalkyldihydropyrrole 131a (23 mg, 45% over 3 steps) as a white solid (m.p. 101-103°C).

\(^1\)H NMR (500 MHz, CDCl₃) δ: 5.95 (m, 1H), 5.75 (m, 1H), 4.13 (m, 1H), 3.84 (m, 1H), 3.75 (m, 1H), 3.49 (m, 1H), 1.56 (m, 1H), 1.47-1.36 (m, 3H), 0.94 (t, 3H, J = 7.4 Hz).

\(^13\)C NMR (125 MHz, CDCl₃) δ: 130.7, 126.9, 72.9, 69.4, 53.9, 35.5, 19.5, 14.2.

IR (neat): 3351, 2956, 2923 cm⁻¹
Exact mass calcd. for C₈H₁₆NO: 142.1254 (M+H)+; found: 142.1232 (M+H)+.

3.4.9. Preparation of Hydroxyalkylidihydropyrrole (131b)

![Diagram]

To a cold (0 °C), stirred solution of chlorohydrin 130b (183 mg, 0.53 mmol) and quinoline (3.1 μL, 0.027 mmol) in ethanol (4.0 mL) was added 5% Pd-BaSO₄ (150 mg, 0.071 mmol). The resulting mixture was stirred under an atmosphere of H₂ (balloon) at room temperature for 2.5 hours (reaction monitored by ¹H NMR spectroscopy). After this time, the mixture was diluted with dichloromethane (5 mL) and filtered through a pad of Celite®, and the solvent was removed in vacuo to afford the crude cis-alkene (172 mg), which was used in the next step without further purification.

¹H NMR (400 MHz, CD₂OD) δ: 5.66 (d, 1H, J = 12.1 Hz), 5.49 (dd, 1H, J = 12.9, 10.6 Hz), 4.85 (m, 1H), 3.92 (m, 1H), 2.02 (m, 1H), 1.94 (m, 1H), 1.83-1.48 (m, 12H), 1.46 (s, 9H), 0.96 (t, 3H, J = 7.1 Hz).

To a vial containing the crude cis-alkene (172 mg, 0.49 mmol) was added ethereal HCl (2M, 1.2 mL). The reaction mixture was stirred at room temperature for 20 hours after which time the solvent was removed in vacuo. The resulting residue was dissolved in methanol (2 mL) and treated with aqueous solution of sodium hydroxide (2M, 2.4 mL). The reaction mixture was stirred for 1 hour after which time it was diluted with water (10 mL) and dichloromethane (10 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na₂SO₄), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 95:5:1 dichloromethane:methanol:ammonium hydroxide) afforded hydroxyalkylidihydropyrrole 131b (85 mg, 77% over 3 steps) as a white solid (m.p. 69-71°C).

¹H NMR (400 MHz, CDCl₃) δ: 5.90 (dd, 1H, J = 6.0, 2.1 Hz), 5.61 (dd, 1H, J = 6.0, 1.6 Hz), 4.16 (m, 1H), 3.40 (m, 1H), 1.62-1.35 (m, 14H), δ: 0.95 (t, 3H, J = 6.9 Hz).
\[ ^{13}\text{C} \text{ NMR (100 MHz, CDCl}_3 \] \delta: 138.6, 124.6, 71.5, 67.6, 67.6, 40.0, 38.4, 35.4, 25.6, 23.7, 23.4, 19.6, 14.2.

IR (neat): 3394, 2926, 2848 cm\(^{-1}\)

Exact mass calcd. for C\(_{13}\)H\(_{24}\)NO: 210.1980 (M+H)+; found: 210.1852 (M+H)+.

3.4.10. Preparation of Hydroxyalkyldihydropyrrole (131c)

To a cold (0 °C), stirred solution of chlorohydrin 130c (43.5 mg, 0.13 mmol) and quinoline (2.1 μL, 0.018 mmol) in ethanol (1.0 mL) was added 5% Pd-BaSO\(_4\) (14.3 mg, 0.0067 mmol) and the resulting suspension was stirred under an atmosphere of H\(_2\) (balloon) at room temperature for 1 hour (reaction monitored by \(^1\text{H} \text{ NMR spectroscopy}). After this time, the mixture was diluted with dichloromethane (2 mL) and filtered through a pad of Celite\textsuperscript{®}, and the solvent was removed in vacuo to afford the crude cis-alkene (45 mg), which was used in the next step without further purification.

\[^1\text{H} \text{ NMR (400 MHz, CD}_3\text{OD) } \delta: 7.33-7.24 \text{ (m, 5H), 5.72-5.64 \text{ (m, 2H), 4.59 \text{ (m, 1H), 4.18}} \text{ (m, 1H), 3.78 (dd, 1H, J = 15.6, 6.1 Hz), 3.71 (dd, 1H, J = 15.7, 5.1 Hz), 3.26 (dd, 1H, J = 14.5, 4.2 Hz), 2.86 (dd, 1H, J = 14.5, 9.3 Hz), 1.46 (s, 9H).\]

To a vial containing the crude cis-alkene (45 mg, 0.14 mmol) was added ethereal HCl (2M, 0.9 mL). The reaction mixture was stirred at room temperature for 30 hours after which time the solvent was removed in vacuo. The resulting residue was dissolved in methanol (2 mL) and treated with aqueous solution of sodium hydroxide (2M, 1.8 mL). The reaction mixture was stirred for 3 hours after which time it was diluted with water (5 mL) and dichloromethane (5 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 70:30:1 dichloromethane:methanol:ammonium hydroxide) afforded hydroxyalkyldihydropyrrole 131c (12 mg, 49% over 3 steps) as a white solid (m.p. 98-100°C).
\[^{1}\text{H NMR (500 MHz, CD}_3\text{OD)}\delta: 7.32-7.29 (m, 4H), 7.22 (m, 1H), 6.02 (m, 2H), 4.03 (m, 1H), 3.86-3.74 (m, 3H), 2.94 (dd, 1H, J = 13.8, 4.5 Hz), 2.73 (dd, 1H, J = 13.8, 8.7 Hz).\]

\[^{13}\text{C NMR (125 MHz, CD}_3\text{OD)}\delta: 141.0, 131.4, 131.3, 130.2, 129.7, 128.1, 76.6, 71.9, 55.1, 42.4.\]

IR (neat): 3341, 3042, 2922, 1494, 1455 cm\(^{-1}\)

Exact mass calcd. for C\(_{12}\)H\(_{16}\)NO: 190.1254 (M+H\(^+\)); found: 190.1244 (M+H\(^+\)).

3.4.11. Preparation of Hydroxyalkylidihydropyrrole (131d)

![Hydroxyalkylidihydropyrrole (131d)](image)

To a cold (0 °C), stirred solution of chlorohydrin 130d (96.6 mg, 0.25 mmol) and quinoline (1.5 μL, 0.012 mmol) in ethanol (2.5 mL) was added 5% Pd-BaSO\(_4\) (69.9 mg, 0.033 mmol) and the resulting suspension was stirred under an atmosphere of H\(_2\) (balloon) at room temperature for 1.5 hours (reaction monitored by \[^{1}\text{H NMR spectroscopy}.\) After this time, the mixture was diluted with dichloromethane (4 mL) and filtered through a pad of Celite\(^{\circledast}\), and the solvent was removed in vacuo to afford the crude cis-alkene (101 mg), which was used in the next step without further purification.

\[^{1}\text{H NMR (400 MHz, CD}_3\text{OD)}\delta: 7.31-7.22 (m, 5H), 5.73 (d, 1H, J = 12.0 Hz), 5.58 (dd, 1H, J = 12.0, 9.6 Hz), 5.00 (dd, 1H, J = 9.6, 3.9 Hz), 4.12 (m, 1H), 3.26 (dd, 1H, J = 14.5, 2.6 Hz), 2.79 (dd, 1H, J = 14.6, 10.9 Hz), 2.06 (m, 1H), 1.94 (m, 1H), 1.75 (m, 2H), 1.62-1.49 (m, 6H), 1.39 (s, 9H).\]

To a vial containing the crude cis-alkene (101 mg, 0.26 mmol) was added ethereal HCl (2M, 3.5 mL). The reaction mixture was stirred at room temperature for 2 days after which time the solvent was removed in vacuo. The resulting residue was dissolved in methanol (3 mL) and treated with aqueous solution of sodium hydroxide (2M, 7.0 mL). The reaction mixture was stirred for 2 hours after which time it was diluted with water (10 mL) and dichloromethane (10 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic phases were
washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 95:5:1 dichloromethane:methanol:ammonium hydroxide) afforded hydroxyalkyldihydropyrrole 131d (50 mg, 78% over 3 steps, 9:1 diastereomeric mixture) as a white solid (m.p. 65-67°C).

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.31-7.20 (m, 5H), 5.96 (dd, 1H, $J = 6.1, 2.0$ Hz), 5.75 (dd, 1H, $J = 6.0, 1.6$ Hz), 4.20 (m, 1H), 3.71 (m, 1H), 2.87 (dd, 1H, $J = 13.8, 8.2$ Hz), 2.76 (dd, 1H, $J = 13.8, 5.6$ Hz), 1.63-1.39 (m, 10H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ: 138.9, 138.7, 129.2, 128.4, 126.2, 124.5, 73.0, 67.6, 67.2, 39.7, 38.2, 25.5, 23.7, 23.4.

IR (neat): 3377, 2921, 2844, 1490, 1448 cm$^{-1}$

Exact mass calcd. for C$_{17}$H$_{24}$NO: 258.1980 (M+H)$^+$; found: 258.1852 (M+H)$^+$.

### 3.4.12. Preparation of Protected Aminotriols (132a) and (132b)

To a cold (0 °C), stirred solution of hydroxyalkyl dihydropyrrole 131c (40 mg, 0.21 mmol) in THF (1.2 mL) was added phosgene (20% in toluene, 123 μL, 0.23 mmol) dropwise. After the mixture was stirred at 0 °C for 15 minutes, triethylamine (71 μL, 0.51 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 15 minutes, then warmed to room temperature and stirred for an additional 45 minutes. After this time, the reaction mixture was diluted with ethyl acetate (4 mL) and filtered through a pad of Celite®, and the solvent was removed in vacuo. The residue was dissolved in hexanes (4 mL) and water (4 mL), and the phases were separated. The aqueous phase was extracted with hexanes (4 x 4 mL). The combined organic phases were washed with brine (4 mL), dried (Na$_2$SO$_4$), and concentrated to give the crude carbamate (43 mg), which was used in the next step without further purification.
\(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta\): 7.34-7.21 (m, 5H), 5.96 (m, 1H), 5.83 (m, 1H), 4.84 (m, 1H), 4.49-4.31 (m, 3H), 2.79 (dd, 1H, \(J = 13.8, 4.1\) Hz), 2.68 (dd, 1H, \(J = 13.8, 9.2\) Hz).

To a cold (0 °C), stirred solution of the crude carbamate (43 mg, 0.19 mmol) in acetone (1.3 mL) and water (0.9 mL) was added a crystal of osmium tetroxide followed by 4-methylmorpholine \(N\)-oxide (35 mg, 0.29 mmol). The reaction mixture was allowed to warm to room temperature slowly over 24 hours. After this time, the mixture was treated with a saturated aqueous solution of sodium hydrosulfite (4 mL), and diluted with ethyl acetate (5 mL) and water (5 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried (\(\text{Na}_2\text{SO}_4\)), and concentrated in \textit{vacuo}. Purification of the crude product by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) afforded protected aminotriols 132\textit{a} and 132\textit{b} (21 mg, 40% over two steps) as an inseparable 3:2 mixture of diastereomers (colorless oil).

**Data for protected aminotriols 132\textit{a}**

\(^1\text{H NMR (600 MHz, CDCl}_3\) \(\delta\): 7.34-7.24 (m, 5H), 4.97 (m, 1H), 4.34 (m, 1H), 4.02 (m, 1H), 3.99 (dd, 1H, \(J = 13.5, 5.6\) Hz), 3.90 (dd, 1H, \(J = 8.9, 7.3\) Hz), 3.27 (dd, 1H, \(J = 13.4\) Hz, 1.2 Hz), 3.19 (dd, 1H, \(J = 15.0, 4.2\) Hz), 3.11 (dd, 1H, \(J = 15.0, 9.2\) Hz), 2.74 (d, 1H, \(J = 2.8\) Hz), 2.71 (d, 1H, \(J = 8.1\) Hz).

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) \(\delta\): 161.1, 136.6, 129.0, 128.8, 127.1, 76.7, 71.1, 70.5, 64.2, 53.1, 36.1.

**Data for protected aminotriols 132\textit{b}**

\(^1\text{H NMR (600 MHz, CDCl}_3\) \(\delta\): 7.34-7.24 (m, 5H), 4.93 (m, 1H), 4.43 (m, 1H), 3.98 (m, 1H), 3.60 (d, 1H, \(J = 7.3\) Hz), 3.53 (dd, 1H, \(J = 14.4, 7.3\) Hz), 3.49 (dd, 1H, \(J = 11.4, 8.2\) Hz), 3.43 (dd, 1H, \(J = 11.6, 7.5\) Hz), 3.31 (dd, 1H, \(J = 14.3, 7.3\) Hz), 3.03 (d, 1H, \(J = 4.1\) Hz), 2.79 (d, 1H, \(J = 5.7\) Hz).

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) \(\delta\): 162.5, 136.6, 129.0, 128.7, 127.0, 76.9, 73.9, 71.0, 65.1, 50.1, 35.7.

\(\text{IR (neat): 3406, 3031, 2958, 2925, 1728, 1402, 1112 cm}^{-1}\)
Exact mass calcd. for C_{13}H_{16}NO_4: 250.1074 (M+H)^+; found: 250.1068 (M+H)^+

Key nOe correlations for compound 132a and 132b (in CDCl_3):

3.4.13. Preparation of Protected Aminotriol (133)

To a cold (0 °C), stirred solution of hydroxyalkyl dihydropyrrole 131d (25 mg, 0.097 mmol) in THF (1.0 mL) was added phosgene (20% in toluene, 57 μL, 0.11 mmol) dropwise. After the mixture was stirred at 0 °C for 15 minutes, triethylamine (33 μL, 0.23 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 15 minutes, then warmed to room temperature and stirred for an additional 45 minutes. After this time, the reaction mixture was diluted with ethyl acetate (4 mL) and filtered through a pad of Celite®, and the solvent was removed in vacuo. The residue was diluted with hexanes (5 mL) and water (5 mL), and the phases were separated. The aqueous phase was extracted with hexanes (4 x 5 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give the crude carbamate (30 mg), which was used in the next step without further purification.

^1H NMR (400 MHz, CDCl_3) δ: 7.31-7.20 (m, 5H), 6.34 (dd, 1H, J = 6.3, 2.3 Hz), 5.64 (dd, 1H, J = 6.3, 1.4 Hz), 5.13 (m, 1H), 4.79 (ddd, 1H, J = 8.1, 8.1, 6.0 Hz), 2.84 (dd, 1H, J = 14.3, 8.1 Hz), 2.75 (m, 1H), 2.69 (dd, 1H, J = 14.3, 6.0 Hz), 1.96-1.82 (m, 2H), 1.75-1.25 (m, 7H).
To a cold (0 °C), stirred solution of the crude carbamate (30 mg, 0.10 mmol) in acetone (1.0 mL) and water (0.7 mL) was added a crystal of osmium tetroxide followed by 4-methylmorpholine N-oxide (18.6 mg, 0.16 mmol). The reaction mixture was allowed to warm to room temperature slowly over 24 hours. After this time, the mixture was treated with a saturated aqueous solution of sodium hydrosulfite (4 mL), and diluted with ethyl acetate (5 mL) and water (5 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) afforded protected aminotriol 133 (24 mg, 78% over 2 steps) as a white solid (m.p. 160-162°C).

$^1$H NMR (600 MHz, CDCl$_3$) δ: 7.33-7.24 (m, 5H), 4.86 (m, 1H), 4.09 (m, 1H), 3.93 (dd, 1H, J = 7.1, 4.3 Hz), 3.68 (dd, 1H, J = 7.8, 2.3 Hz), 3.45 (dd, 1H, J = 14.4, 7.3 Hz), 3.32 (dd, 1H, J = 14.1, 7.3 Hz), 2.76 (d, 1H, J = 1.9 Hz), 2.55 (m, 1H), 2.43 (d, 1H, J = 7.2 Hz), 1.98 (m, 1H), 1.75 (m, 2H), 1.65 (m, 2H), 1.48-1.40 (m, 4H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ: 157.1, 137.0, 129.0, 128.7, 126.9, 81.4, 75.1, 72.2, 64.7, 62.1, 38.8, 36.0, 27.7, 25.1, 23.3, 22.9.

IR (neat): 3371, 2926, 2852, 1716, 1375, 1075 cm$^{-1}$

Exact mass calcd. for C$_{18}$H$_{24}$NO$_4$: 318.1700 (M+H)$^+$; found: 318.1692 (M+H)$^+$

Key nOe correlations for compound 133 (in CDCl$_3$)
3.4.14. Preparation of (-)-(2S)-2,5-Dichloropentanal (136)

To a cold (-35 °C) stirred solution of imidazolidinone catalyst 137 (471 mg, 1.66 mmol), LiCl (527 mg, 12.4 mmol), Na$_2$S$_2$O$_8$ (1.97 g, 8.29 mmol), Cu(TFA)$_2$·2H$_2$O (1.35 g, 4.15 mmol), in acetonitrile (66 mL) and H$_2$O (0.329 mL, 18.2 mmol) was added 5-chloropentanal (135) (1.00 g, 8.29 mmol). After this solution was stirred for 19 days at -35 °C, the reaction mixture was quenched with water and diluted with pentane. The two phases were separated and the aqueous phase extracted with pentane (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. The resulting crude mixture was purified via flash chromatography (1:7 EtOAc: Hexanes) to provide (-)-(2S)-2,5-dichloropentanal (136) (797 mg, 62%) as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 9.55 (d, 1H, $J = 1.9$ Hz), 4.25 (ddd, 1H, $J = 7.9$, 4.9, 1.9 Hz), 3.62 (t, 2H, $J = 6.0$ Hz), 2.49 (m, 1H), 2.23 (m, 1H), 1.96-2.10 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 195.0, 63.0, 43.9, 29.2, 28.5.

IR (neat): 2964, 1737, 1445, 1285 cm$^{-1}$

Exact mass calc’d for C$_5$H$_8$$^{35}$Cl$_2$O: 153.9952; found: 153.9948 (M$^+$).

$[\alpha]_D^{23}$ : −24.3 (c = 1.11, CHCl$_3$)

The enantiomeric excess of 82% was determined by chiral HPLC analysis of the benzoyl ester derived from the addition of N-Boc-N-trimethylsilylpropargylamine A to both racemic and optically enriched compound 136. Thus, to a solution of addition adduct compound 138 (22 mg, 0.074 mmol) in dry dichloromethane (0.75 mL) was added pyridine (60 μL, 0.74 mmol), and benzoyl chloride (90 μL, 0.74 mmol). The reaction mixture was allowed to stir overnight. After this time, the reaction was treated with saturated aqueous sodium bicarbonate (2 mL) and diluted with dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (3 x 5 mL) and the combined
organics were washed with brine (5 mL), dried (Na₂SO₄), and concentrated in vacuo. The crude product was purified by flash chromatography (1:4 ethyl acetate:hexanes) to afford racemic or optically active benzoate B. Separation of the enantiomers was accomplished by HPLC (95:5 hexanes:methanol w/ 1% diethylamine, performed on an Agilent 1200 HPLC equipped with a variable wavelength UV-Vis detector and 0.46 cm x 25 cm Chiralcel OD-H chiral column). The retention times of the two enantiomers were 15.5 and 17.9 minutes. When this process was repeated with optically enriched α-chloroaldehyde 136 the ratio of the enantiomers was 9 (15.5 min):91 (17.9 min). The absolute configuration of the major enantiomer was confirmed as depicted for compound (−)-138 (below) by conversion of this material into (−)-swainsonine (116).

3.4.15. Preparation of (−)-(4R,5S)-1-(9N-Boc)amino-5,8-dichloroocta-2-yn-4-ol (138)

To a cold (−78 °C), stirred solution of diisopropylamine (0.20 mL, 1.41 mmol) in dry THF (32 mL) was added was added n-BuLi (2.56 M, 0.47 mL, 1.2 mmol) dropwise over 3 min. After this solution was stirred for 40 minutes, N-Boc-N-trimethylsilylpropargylamine (250 mg, 1.10 mmol) was added at −78 °C. After this solution was stirred for 1 hour, (−)-(2S)-2,5-dichloropentanal 136 (285 mg, 1.84 mmol) was added dropwise over 5 minutes while the reaction temperature was maintained at −78 °C. The reaction mixture was stirred for 20 min then a solution of hydrochloric acid in diethyl ether (2.0 M, 1.21 mL, 2.42 mmol) was added. This mixture was stirred for 5 min then treated with saturated aqueous ammonium chloride (10 mL) and ethyl acetate (10 mL). The resulting phases
were separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na₂SO₄), and concentrated in vacuo. The resulting crude product was purified via flash chromatography (1:4 ethyl acetate:hexanes) to provide (−)-(4R,5S)-1-(N-Boc)amino-5,8-dichloroocta-2-yn-4-ol (138) (266 mg, 78%) as a clear oil.

¹H NMR (400 MHz, CD₃OD) δ: 4.49 (ddd, 1H, J = 6.2, 1.8, 1.8 Hz), 3.96 (m, 1H), 3.86 (s, 2H), 3.61, (t, 2H, J = 6.2 Hz), 2.15-2.03 (m, 2H), 1.78-1.91 (m, 2H), 1.45 (s, 9H).

¹³C NMR (100 MHz, CD₃OD) δ: 172.9, 83.9, 66.9, 66.4, 61.5, 45.2, 31.9, 30.8, 28.7, 20.5, 14.5.

IR (neat): 3331, 2976, 1691, 1367 cm⁻¹

Exact mass calc’d for C₁₃H₂₁Cl₂NO₃: 309.0898; found: 309.0901 (M)+.

[α]D²³ : −7.69 (c = 5.9, CHCl₃)

3.4.16. Preparation of Indolizidine (142)

To a stirred solution of (4R,5S)-1-(N-Boc)amino-5,8-dichloroocta-2-yn-4-ol (138) (134 mg, 0.432 mmol) and quinoline (5 μL, 0.04 mmol) in ethanol (5 mL) was added 5% Pd-barium sulfate (43 mg, 0.020 mmol) at 0 °C. The resulting suspension was allowed to warm to room temperature and stirred under an atmosphere of H₂ (balloon) for 15 min. The reaction mixture was filtered through Celite® and concentrated in vacuo to provide cis-alkene 139 as a clear oil which was used in the next step without further purification.

¹H NMR (400 MHz, CD₃OD) δ: 5.58 (m, 2H), 4.53 (m, 1H), 3.93 (m, 1H), 3.79 (dd, 1H, J = 15.2, 5.1), 3.70 (dd, 1H, J = 15.2, 3.4), 2.06 (m, 2H), 1.88 (m, 2H), 1.74 (m, 2H), 1.43 (s, 9H).

Exact mass calc’d for C₁₃H₂₃Cl₂NO₃: 311.1055; found: 312.1129 (M+H)+.
To the crude cis-alkene 139 was added a solution of hydrochloric acid in diethyl ether (2.0 M, 2.16 mL, 4.3 mmol) at room temperature. The reaction mixture was stirred for 18 h at r.t. then concentrated. The resulting oil was dissolved with cold diethyl ether. The remaining solid was dried in vacuo to afford the crude 140 as a white solid which was used in the next step without further purification.

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 5.88 (ddd, 1H, $J = 11.2, 7.6, 1.6$ Hz), 5.70 (dddd, 1H, $J = 15.1, 8.3, 1.2, 0.7$ Hz), 4.46 (t, 1H, $J = 6.7$ Hz), 3.94 (m, 1H), 3.78 (dd, 1H, $J = 14.6, 7.7$ Hz), 3.71 (dd, 1H, $J = 14.4, 6.1$ Hz), 3.62 (t, 2H $J = 6.1$ Hz) 2.11 (m, 2H), 1.89 (m, 1H), 1.77 (m, 1H).

Exact mass calc’d for C$_8$H$_{16}$Cl$_3$NO: 247.0297; found: 212.0603 (M-Cl)+.

To a solution of crude 140 in methanol (4.3 ml) was added aqueous sodium hydroxide (2.0 M, 0.65 mL, 1.3 mmol) dropwise at room temperature over 3 hours (syringe pump). The reaction mixture was stirred for 15 hours then concentrated in vacuo. The resulting residue was dissolved in a mixture of dichloromethane/methanol/ammonium hydroxide (aq.) (100:1:1), filtered, and concentrated in vacuo. The resulting crude mixture was purified by flash chromatography (99:1 dichloromethane:methanol w/ 1% ammonium hydroxide, then 90:10 dichloromethane:methanol w/ 1% ammonium hydroxide) to provide indolizidine 142 (32 mg, 54% over 3 steps) as a yellow oil.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 6.17 (m, 1H), 5.95 (dddd, 1H, $J = 6.3, 2.1, 2.1, 2.1$ Hz), 3.60 (dddd, 1H, $J = 13.3, 3.8, 2.3, 2.3$ Hz), 3.38 (dd, 1H, $J = 10.8, 9.5, 4.5$ Hz), 3.24 (dddd, 1H, $J = 13.0, 7.4, 2.4, 1.8$ Hz), 2.94 (m, 1H), 2.88 (m, 1H), 2.46 (m, 1H), 2.01 (dddd, 1H, $J = 15.7, 7.3, 3.1, 3.1$ Hz), 1.68 (m, 2H), 1.25 (m, 1H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$: 132.3, 129.7, 74.5, 71.2, 58.3 49.6, 34.2, 24.4.

IR (neat): 3356, 2932 cm$^{-1}$

Exact mass calc’d for C$_8$H$_{13}$NO: 139.0997; found: 139.1003 (M)+.

$[\alpha]_D^{23}$ : $-40.4$ (c = 0.82, CHCl$_3$).
3.4.17. Preparation of Indolizidine (143)

\[
\begin{align*}
\text{\includegraphics[width=0.2\textwidth]{indolizidine.png}}
\end{align*}
\]

To a solution of indolizidine 142 (21 mg, 0.15 mmol) in dichloromethane (1.5 mL) was added tert-butylidemethylsilyl chloride (45 mg, 0.30 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.047 mL, 0.32 mmol) at room temperature. After stirring for 2 hours the reaction mixture was treated with aqueous aq. ammonium chloride solution (1.0 mL) and diluted with dichloromethane (10 mL). The phases were separated, the aqueous phase was extracted with dichloromethane (10 mL x 3), and the combined organics were washed with brine (5 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo. The resulting crude (yellow oil) was immediately purified by silica gel column chromatography using 15:1 dichloromethane/methanol to provide indolizidine 143 (27 mg, 70% yield), as a colorless oil. All data were consistent with those previously reported\textsuperscript{29}.

Exact mass calc'd for C\textsubscript{14}H\textsubscript{28}NOSi: 253.1862; found: 254.1957 (M)\textsuperscript{+}

\[
[\alpha]_D^{23} : -50 \ (c = 0.15, \text{CH}_2\text{Cl}_2) \text{ lit: } [\alpha]_D^{23} : -59.6 \ (c = 1.0, \text{CH}_2\text{Cl}_2)\textsuperscript{30}
\]
3.5. References

16. Reaction of the lithium anion derived from N,N-bis(trimethylsilyl)propargylamine or N,N-bis(Boc)propargylamine with the chloroaldehyde 122 also provided the desired chlorohydrin, albeit in lower (< 45%) yield.
17. Key 1H NMR data for compounds 128 (CDCl3, 600 MHz) and 129 (CDCl3, 300 MHz). H1': δ 4.72 (128), δ 4.70 (129); H2: δ 4.72 (128), δ 4.70 (129); H5α: δ 3.75 (128), δ 3.75 (129); H5β: δ 4.42 (128), δ 4.39 (129). For spectral data for compound 129, see: Lindsay, K. B.; Pyne, S. G. Aust. J. Chem. 2004, 57, 669.
18. See experimentals for details.
19. The lower overall yields for 131a and 131c reflect difficulties associated with the isolation and purification of these substances rather than the efficiency of the reaction sequence.
4. Conclusions

In summary, in this thesis the development of new strategies and methods relevant to the construction of natural products containing tetrahydrofuran or pyrrolidine functionalities is documented. Specifically, the asymmetric chlorination of aldehydes reported by MacMillan provides optically pure α-chloroaldehydes that are then utilized as bifunctional building blocks for these classes of natural products. In Chapter 2 a concise and stereoselective total synthesis of antitumor agent pachastrissamine (jaspine B) was presented. The success of this work relied on diastereoselective lithium aldol reaction between a Boc-protected hydantoin and an α-chloroaldehyde, followed by a thermal cyclization of resultant aldol adduct. The strategy described in this synthesis could be useful for the production of pachastrissamine analogues, β-hydroxy-α-aminoacids, or other more elaborate amino acid derivatives. In Chapter 3 a new method for the preparation of hydroxyalkyldihydropyrroles is described. This work involved the coupling of protected propargylamines with α-chloroaldehydes, followed by Lindlar reduction and a one-pot epoxide formation/opening sequence. The utility of this process was demonstrated in the synthesis of unnatural iminosugars and in a formal synthesis of indolizidine alkaloid (-)-swainsonine. The concise and stereoselective approach to jaspine B (8 steps), hydroxyalkyldihydropyrroles (4 steps) and (-)-swainsonine (6 steps) obviates the need for the multiple protecting groups and/or functional groups interconversions and thus, provides access to these potentially important natural products and their analogues in an efficient manner. Furthermore, the methods developed and demonstrated in this thesis are flexible and could be applied to the synthesis of other natural products such as jaspine A (80), hyacinthacine A₄ (13), and castanospermine (118) (Figure 4.1).
Figure 4.1  **Representative Examples of Tetrahydrofuran- and Pyrrolidine-Containing Natural Products**

- **79**: jaspine B (8 steps)
- **116**: swainsonine (6 steps)
- **133**: protected aminotriol (6 steps)
- **80**: jaspine A
- **13**: hyacinthacine A₄
- **118**: castanospermine
Appendices
Appendix A.

NMR spectra (\(^1\)H and \(^{13}\)C NMR) Concerning Chapter 2
Appendix B.

NMR spectra (\(^1\)H and \(^{13}\)C NMR) Concerning Chapter 3