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

by

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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)

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Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

$[\alpha]_D$	Specific rotation at the sodium D line (589 nm)
δ	Chemical Shift in ppm from tetramethylsilane
°C	Degrees Celsius
Ac	Acetyl
aq	aqueous
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
cat	Catalytic amount
Cbz	Carboxybenzyl
CDI	Carbonyldiimidazole
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

M	Molar
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mmol	Millimole (s)
mol	Mole (s)
m.p.	Melting Point
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
MW	Microwave
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
Nu	Nucleophile
PG	Protecting group
Ph	Phenyl
PMB	*para*-Methoxybenzyl
ppm	parts-per-million
Pr	Propyl
r.t.	Room temperature
SCUBA	Self-Contained Underwater Breathing Apparatus
SOMO	Singly Occupied Molecular Orbital
t	Tertiary
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetate
THF	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 19th 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.[15] Some representative examples of drug leads isolated from marine organisms are cortistatin A (**4**), eleutherobin (**5**) and discodermolide (**6**).[16,17,18]

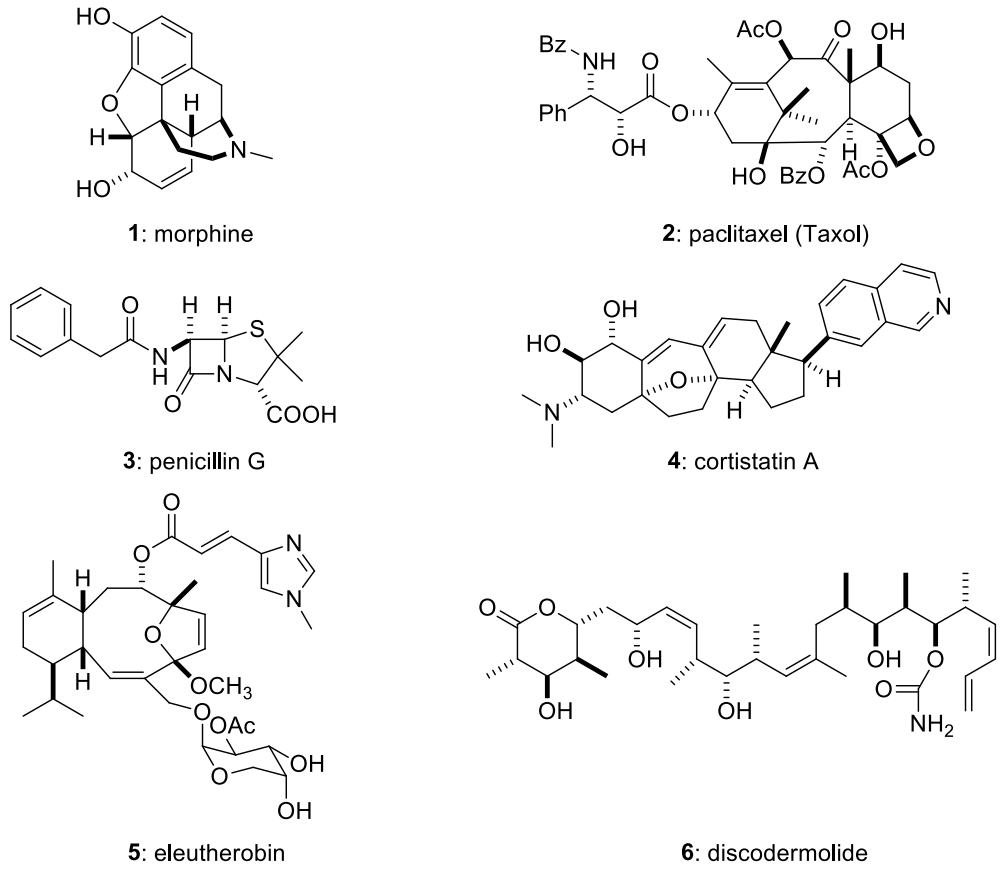
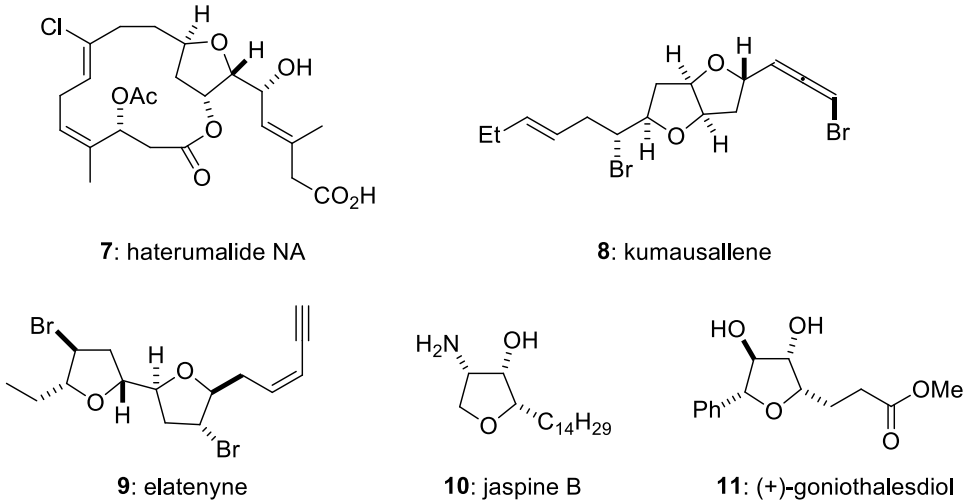


Figure 1.1 Representative Examples of Bioactive Natural Products.

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.[19] These pharmaceuticals are either natural products, semi-synthesized from natural products, or contain pharmacophores originally identified in a natural product.[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.[20]

1.2. Tetrahydrofuran/Pyrrolidine Containing Natural Products

Heterocycles are ubiquitous molecular scaffolds in biologically-active natural products, including polyketides, alkaloids, steroids, and terpenes.[21] Due to their occurrence in many biologically active compounds such as the acetogenins,[22] lignans,[23] macrodiolides[24] and polyether ionophores[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 *Ircinia sp.* in 1999, and displays cytotoxicity against numerous cancer cell lines.[26,27] This molecule consists of a 2,5-disubsituted-3-hydroxytetrahydrofuran, a *Z*-chloroolefin, a *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 *cis*-fused tetrahydrofuran unit halogenated at the C3 position and a bromoallene moiety.[28] Another example of a tetrahydrofuran-containing natural product is elatenyne (**9**), which was isolated in 1983 from *Laurencia elata* and possesses a 2,2'-bifuranyl core and six stereocenters.[29] Jaspine B (**10**) and (+)-goniothalesdiol (**11**) are additional examples of tetrahydrofuran-containing natural products.

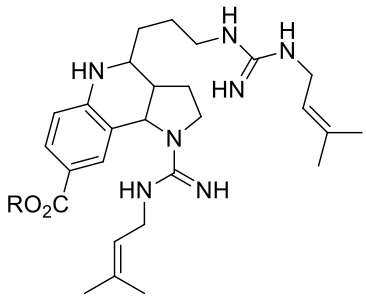


7: haterumalide NA **8**: kumausallene

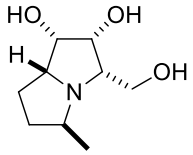
9: elatenyne **10**: jaspine B **11**: (+)-goniothalesdiol

Figure 1.2 Representative Natural Products Containing a Tetrahydrofuran Core.

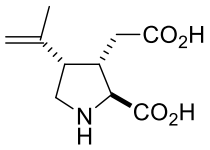
In addition to oxygen-containing heterocycles, heterocycles containing nitrogen atoms are also found in a variety of biologically relevant compounds. Among them, 5-membered ring heterocycles, such as pyrrolidines, are widely prevalent and compounds that incorporate this moiety have demonstrated a range of applications, including use as organocatalysts,[30] chiral ligands[31] or in pharmaceutical agents.[32,33] Pyrrolidines are also found in nature as components of pyrrolizidine and indolizidine alkaloids.[34] Some examples of natural products containing the pyrrolidine moiety include martinellines (**12**), that are potent bradykinin antagonists isolated from the roots of *Martinella iquitosensis*,[35] hyacinthacine A_4 (**13**), an inhibitor of various carbohydrate processing enzymes,[36] (-)-kianic acid (**14**), used in the study of serious neuronal disorders such as Alzheimer's disease and epilepsy,[37,38] (+)-preussin (**15**), an antifungal agent isolated from a liquid fermentation broth of *Aspergillus ochraceus*,[39,40] and (-)-swainsonine (**16**), a potent lysosomal α-mannosidase inhibitor.[41]



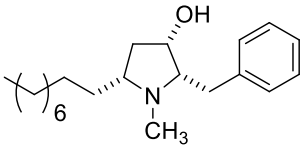
12: martinellines R = H or Me



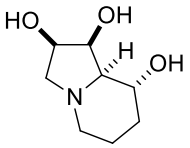
13: hyacinthacine A_4



14: (-)-kainic acid



15: (+)-preussin



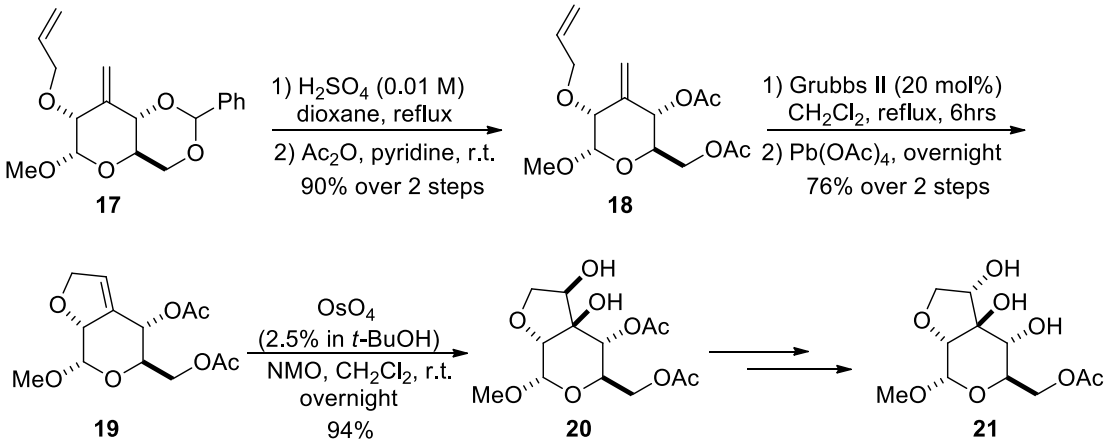
16: (-)-swainsonine

Figure 1.3 Representative Natural Products Containing a Pyrrolidine Core.

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

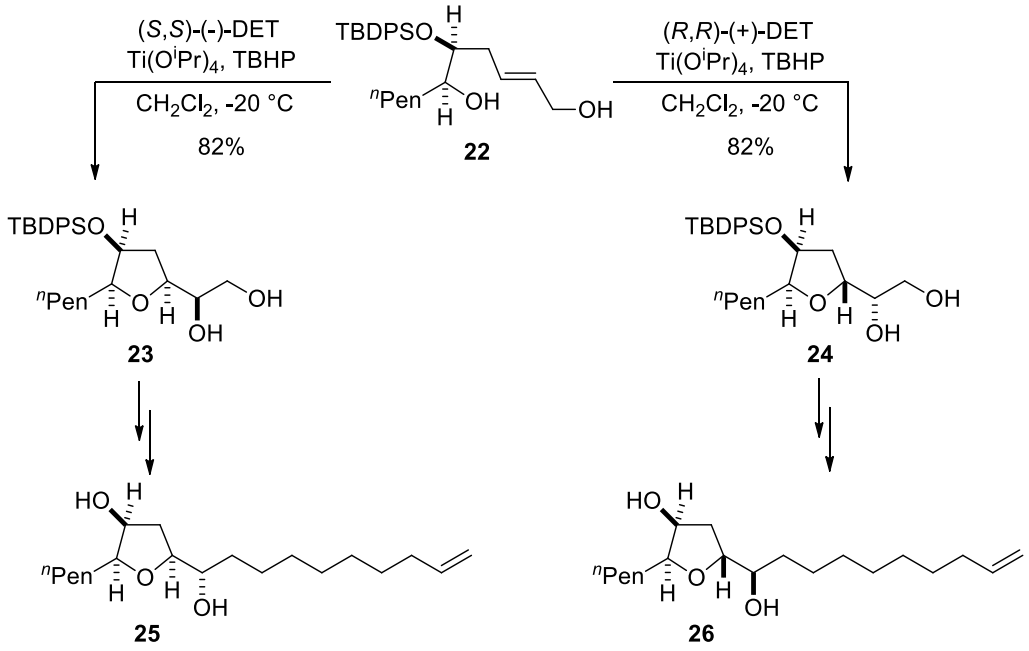
Owing to the therapeutic potential of tetrahydrofuran- and pyrrolidine- containing natural products, there has been longstanding interest in their stereoselective synthesis.

As a result, numerous unique methods have been developed and applied to the synthesis of natural products containing these structural moieties.[42] For example, Etheve-Quelquejeu and co-workers[43] reported the synthesis of the bicyclic core of the miharamycins (e.g., **21**), nucleoside antibiotics, from 3-*C*-methylene sugar **18** 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 **19**. Dihydroxylation of **19** with osmium tetroxide in *tert*-butanol in the presence of NMO gave tetrahydrofuran **20**. Following a further sequence of reactions this latter material was converted into the bicyclic core of the miharamycin **21** in good overall yield.



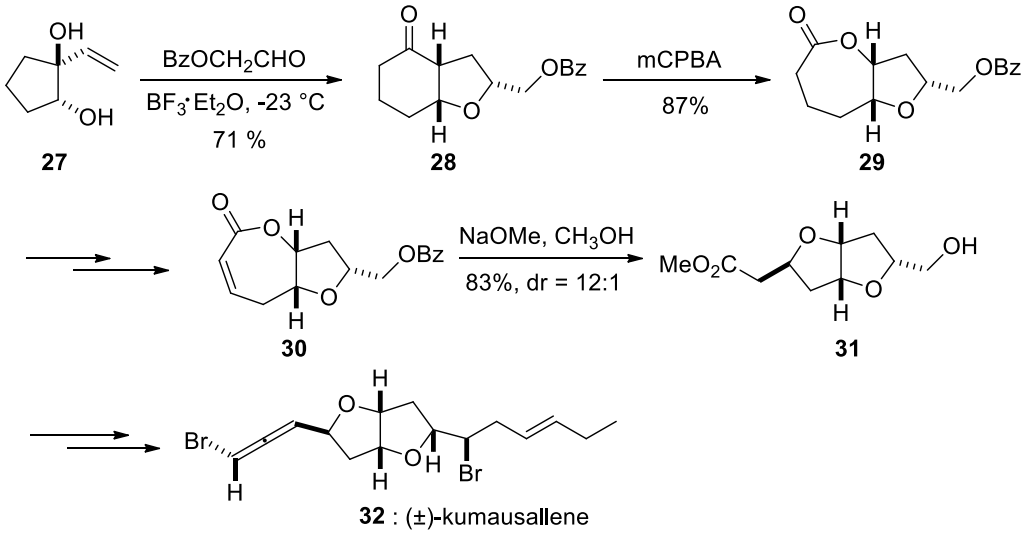
Scheme 1.1 Synthesis of the Bicyclic Core 21 of the Miharamycins.

In 2000, Martin and co-workers[44] reported the asymmetric total synthesis of the tri-substituted tetrahydrofuranols **25** and **26**, isolated from *Notheia anomala*[45]. This synthesis relied on a Sharpless asymmetric dihydroxylation[46] and Katsuki-Sharpless asymmetric epoxidation[47] as tools for the construction of tetrahydrofuran core and controlled introduction of the necessary stereogenic centres (Scheme 1.2). The allylic alcohol **22** 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 **24** as the sole detected stereoisomer. Use of (*S*,*S*)-(-)-DET afforded the corresponding *syn*-tetrahydrofuran **23**. Overall, this synthetic strategy provides access to both *trans*- and *syn*-tetrahydrofurans from a common precursor **22**.



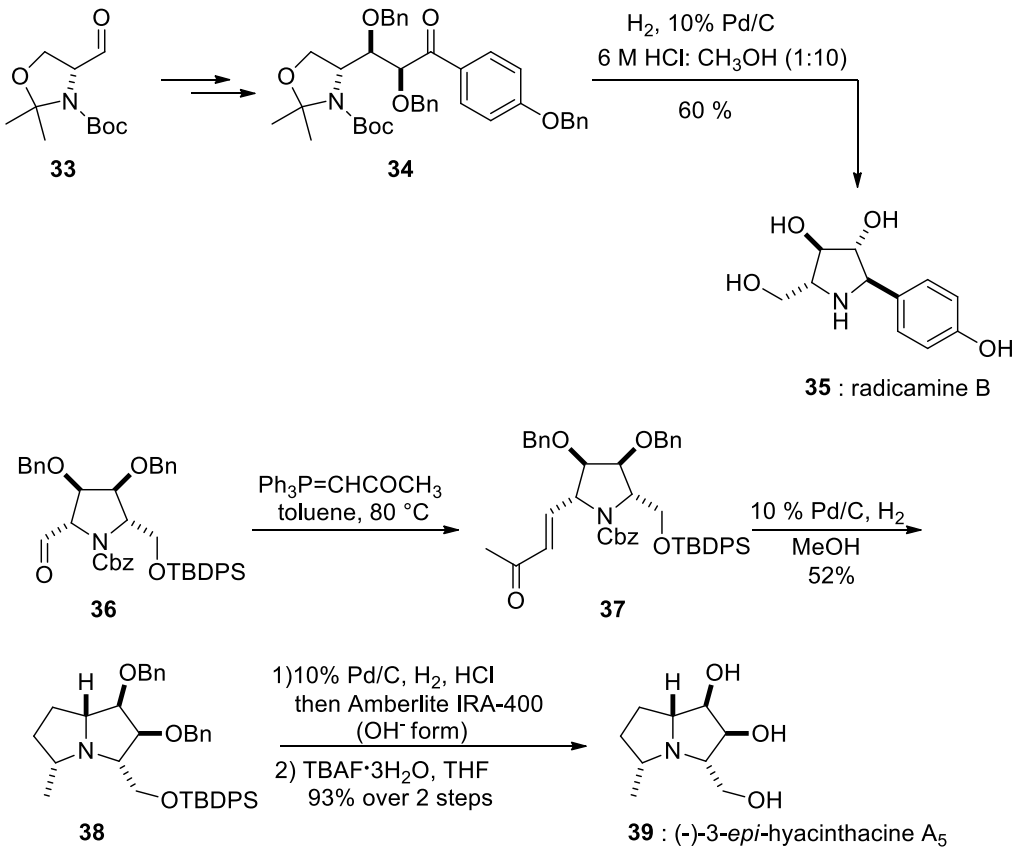
Scheme 1.2 Key Step in the Synthesis of Trisubsituted Tetrahydrofuranols 25 and 26.

(±)-Kumausallene (**32**) is a marine natural product isolated from the Japanese red algae *Laurencia niponica*,[48] 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[49] 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.[42d] Recently, Marco[50] used this strategy as the key transformation in the synthesis of the naturally occurring pyrrolidine radicamine B (**35**), an α-glucosidase inhibitor.[51] 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 A_5 (**39**) (Scheme 1.4).[52] 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 A_5 (**39**).

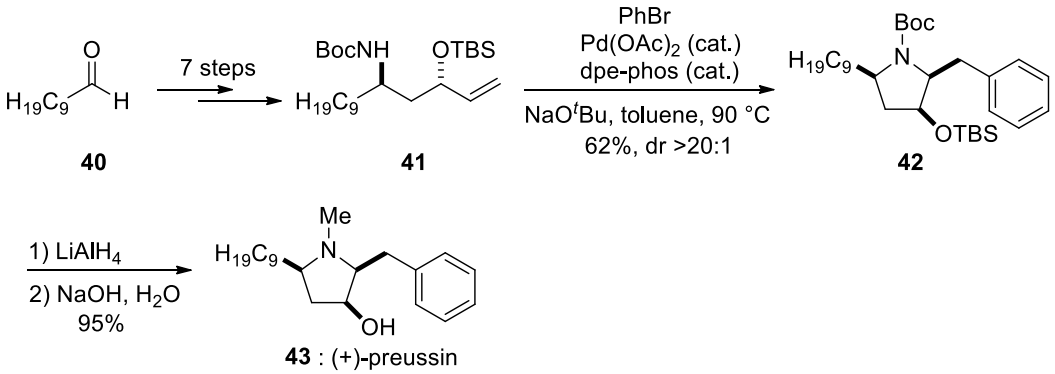


Scheme 1.4 Key Steps in the Synthesis of Radicamine B (35) and (-)-3-Epi-hyacinthacine A_5 (39).

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).[42c] For instance, Wolfe[53] reported the stereoselective synthesis of antifungal agent (+)-preussin **43** *via* palladium-catalyzed carboamination of protected amino alcohol **41**, which was synthesized in 7 steps from decanal **40** (Scheme 1.5). Treatment of **41** with NaO^tBu and bromobenzene in the presence of catalytic $Pd(OAc)_2$/dpe-phos furnished pyrrolidine **42** in good yield and high diastereoselectivity. The stereoselectivity of the pyrrolidine forming reaction is controlled by allylic ($A^{1,3}$) strain[54] present in the alkene palladium-amido transition state.[53]

Although many methods have been developed to construct substituted tetrahydrofurans and pyrrolidines, the application of these processes to natural product

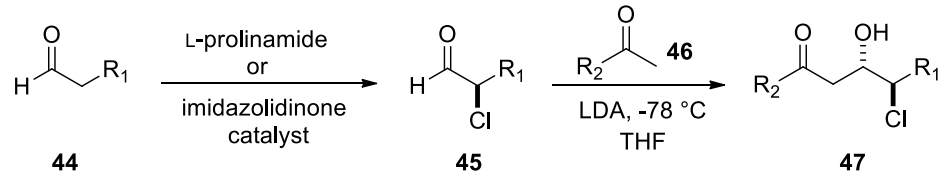
synthesis often require multiple protecting and/or functional group manipulations to eventually reach the target compound. These steps necessarily decrease the overall efficiency of the synthesis, which translates to a reduced overall yield. Therefore, it is important to develop strategies that provide 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 β-Ketochlorohydrin from Lithium Aldol Reaction.

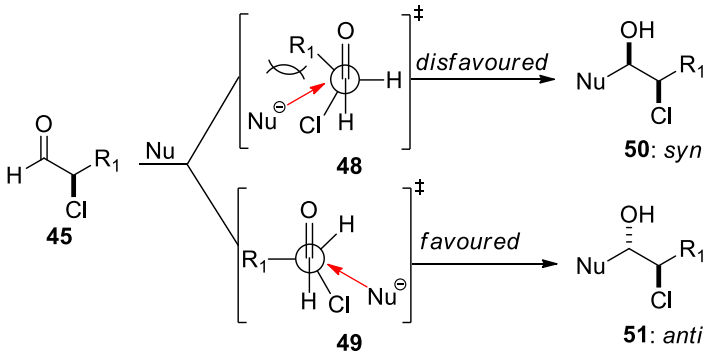
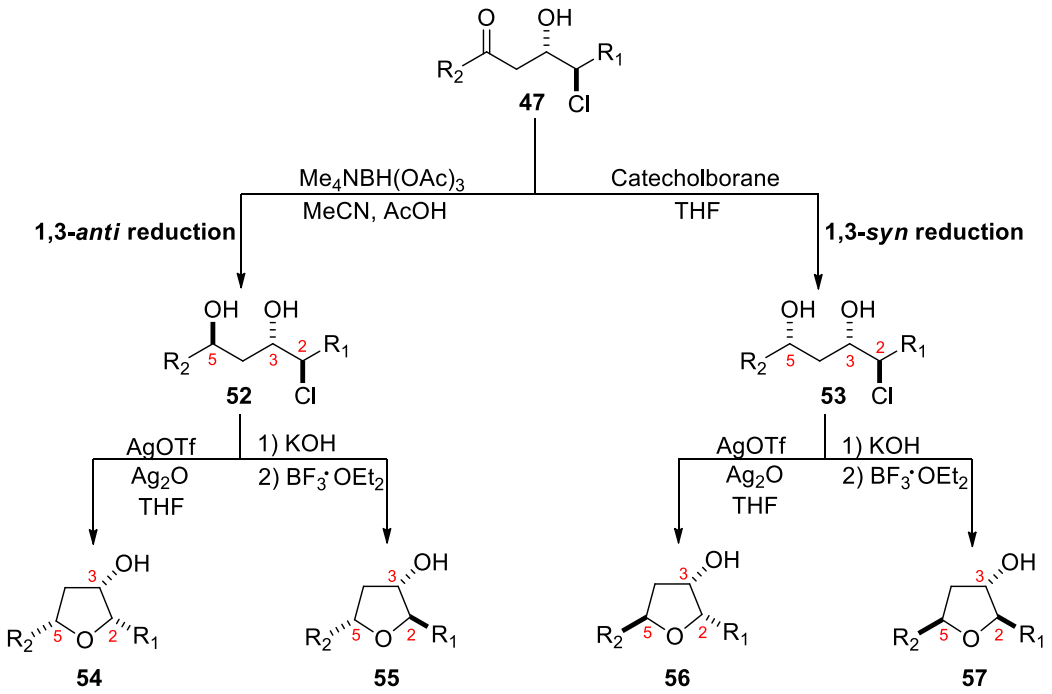


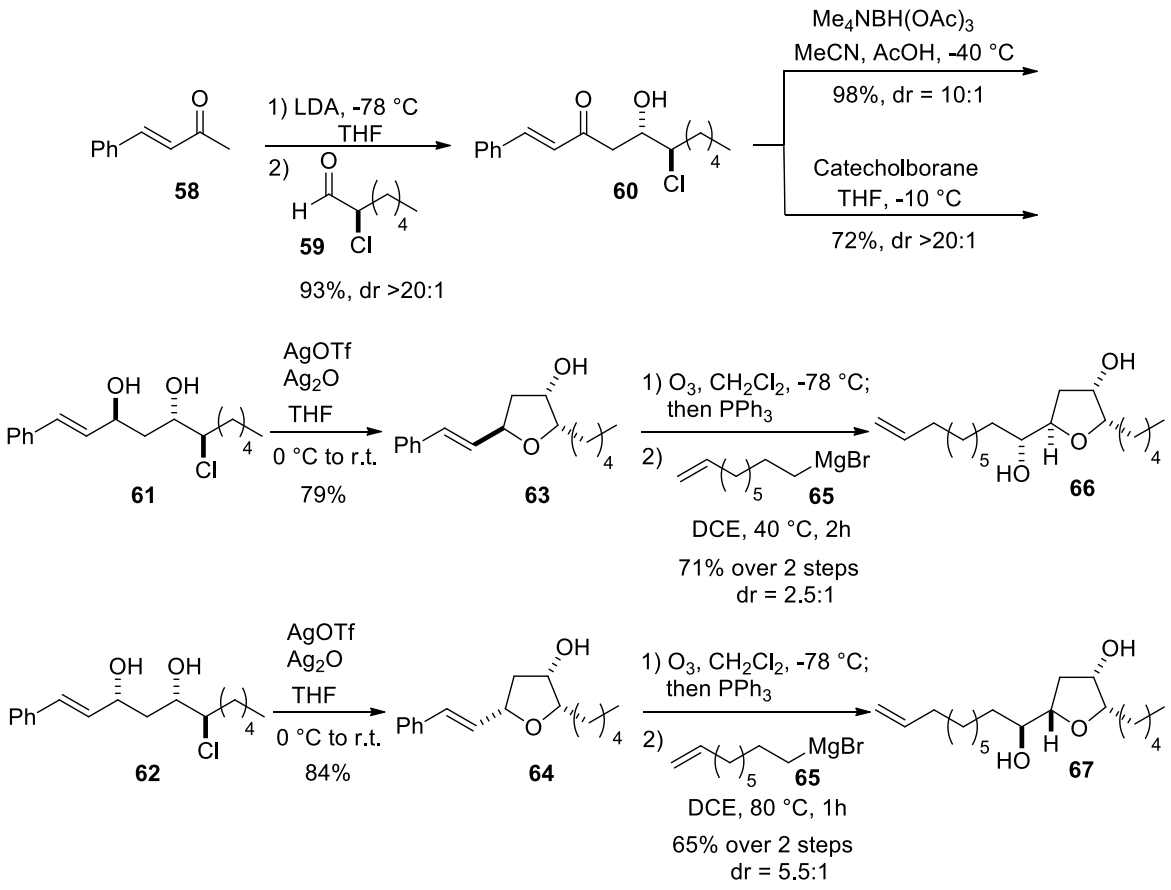
Figure 1.4 Cornforth Model Rationale for the Stereochemical Outcome of Additions to α-Chloroaldehydes.

The resulting β-ketochlorohydrins (e.g., **47**) can then be converted to 2,5-disubsituted-3-hydroxytetrahydrofurans through a 2 or 3 step reaction sequence. As depicted in Scheme 1.7, hydroxyl-directed reduction of the carbonyl function in β-ketochlorohydrin **47** provides the 1,3-*anti*- or 1,3-*syn*-chlorodiols **52** or **53**, respectively.[61] 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 epoxyalcohols (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.

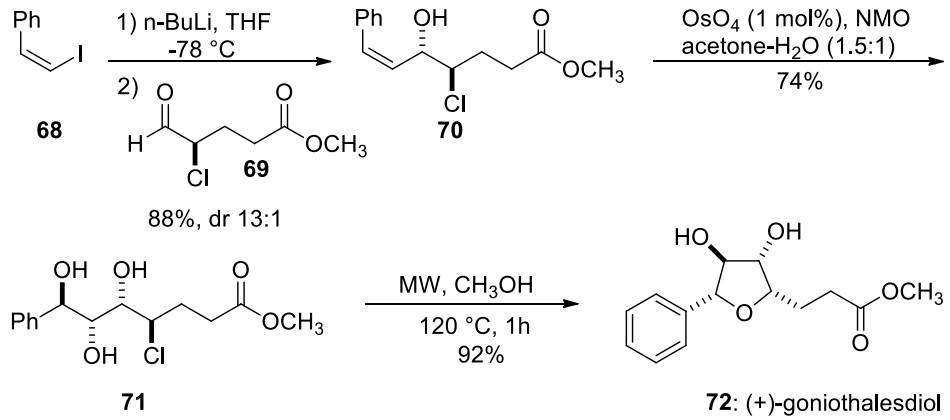
In an effort to further demonstrate the utility of this methodology, a short synthesis of the marine oxylipids **66** and **67** was performed.[57] As illustrated in Scheme 1.8, a lithium aldol reaction between the α,β-unsaturated ketone **58** and the α-chloroaldehyde **59** gave the β-ketochlorohydrin **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 diastereocontrol. 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.

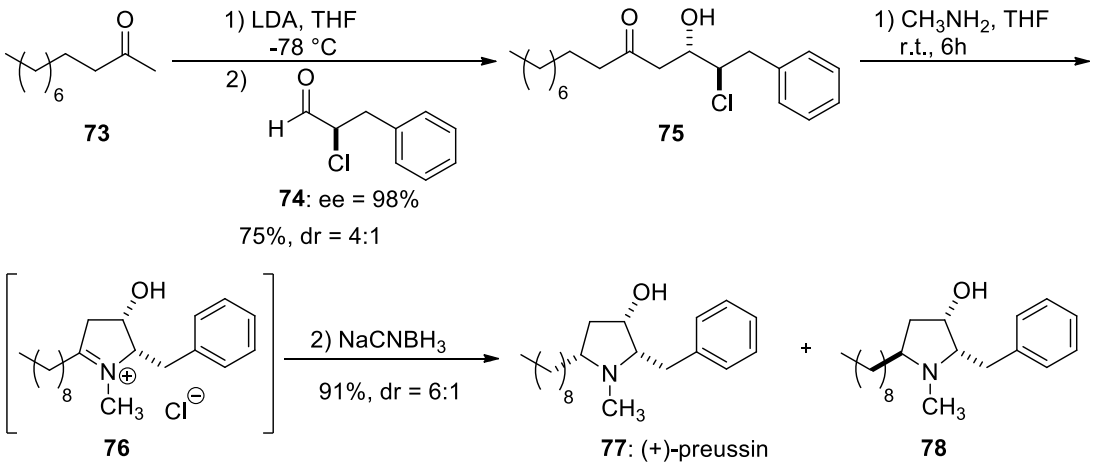
Although the silver-promoted cyclization of unprotected chlorodiols provides access to highly functionalized tetrahydrofuranols in 3 steps from α-chloroaldehydes, it was later discovered that the same results can be achieved by simply heating the chlorodiols in water or methanol.[62] Kang demonstrated 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]



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

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-disubsituted 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 (2*R*)-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 pyrrolinium 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 1.10 Synthesis of Hydroxypyrrolidine (+)-Preussin (77).

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 *Rhizoctonia leguminicola*.

1.6. References

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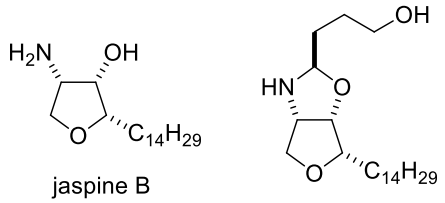
2. Total Synthesis of the Cytotoxic Anhydrophytosphingosine Pachastrissamine (Jaspine B)

2.1. Introduction

Pachastrissamine (**79**), also known as jaspine B, is a natural occurring anhydrophytosphingosine that possesses a tetrahydrofuran core[1] and was first isolated from the Okinawan marine sponge *Pachastrissa* sp. in 2002 by Higa.[2] 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**).[3] The all-*cis* trisubsituted tetrahydrofuran ring and absolute configuration (2*S*,3*S*,4*S*) 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).[2] Importantly, pachastrissamine exhibited submicromolar cytotoxicity against P388, A549, HT29, MEL28 and HeLa cell lines, and represents a potential lead for cancer therapy.[2,3,4] 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.[5] Owing to its potential importance as a lead for cancer therapy, considerable effort has been devoted to the synthesis of pachastrissamine.[6,7,8] 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**))[9] due to their reliance on carbohydrates or amino acids as chiral pool starting materials.

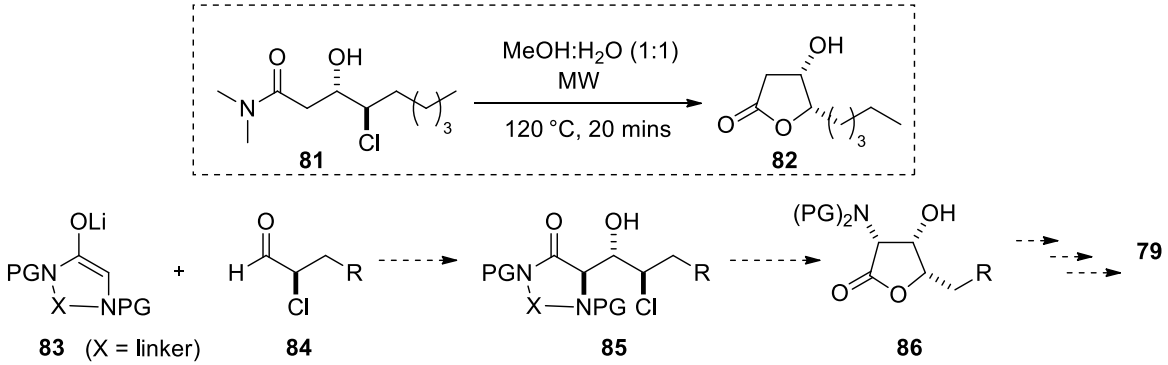


jaspine B (pachastrissamine) **79**

jaspine A **80**

Figure 2.1 Anhydrophytosphingosines (79) and (80).

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.[10] 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).[11] While our efforts to date have focused almost exclusively on the reaction of enolates derived from methyl ketones with α-chloroaldehydes,[12] 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[13] and the progression of the reaction through a chair-like 6-membered ring transition structure.[14] 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[12] to control the relative stereochemistry of the amino alcohol function in **79**.[15]



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

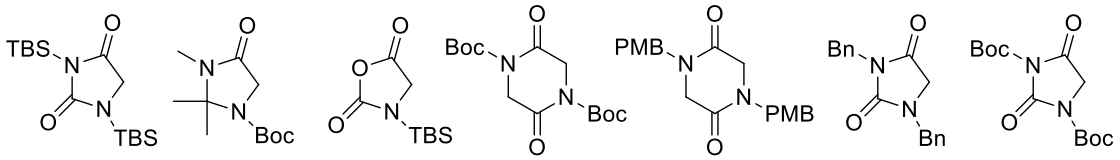
2.2. Results and Discussion

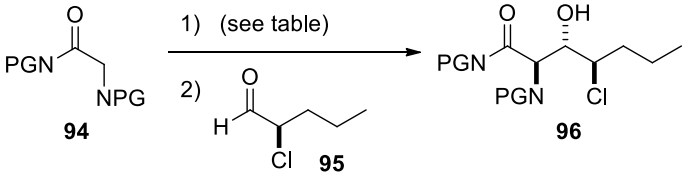
2.2.1. Exploration of Protecting Group Strategy

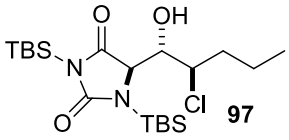
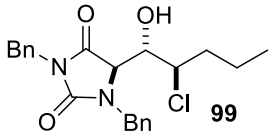
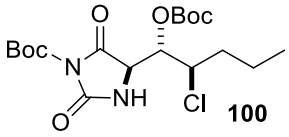
As summarized in Table 2.1, the total synthesis of pachastrissamine **79** was initiated with an investigation of the lithium aldol reaction between a small collection of α-amino lactams/lactones **87**-**93**[16,17,18] and α-chloropentanal (**95**).[19] As indicated in entry 1, treatment of the TBS 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.[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[21] by radical reduction of the

chloromethine function,[22] 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.



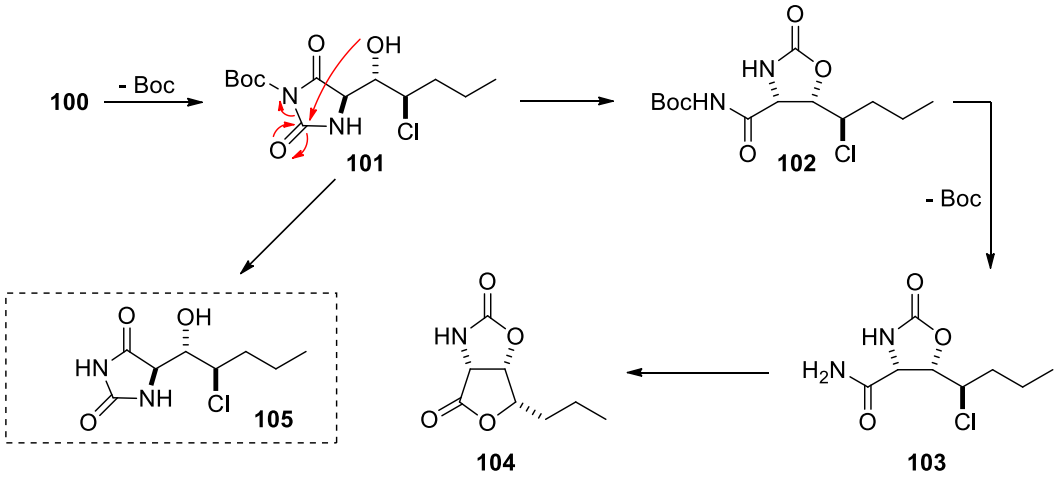


entry	enolate precursor	conditions[a]	product	yield (dr)[b]
1	**87**	A	 **97**	50% (1:1)[c]
2	**88**	A	nd[d]	0
3	**89**	A	nd[d]	0
4	**90**	A	**98**	<10%
5	**91**	B	nd[e]	0[e]
6	**92**	C	 **99**	40% (>20:1)
7	**93**	C	 **100**	61%[f] (10:1:1:1)[g,h]

[a] 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.[11] 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),[11] 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



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

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).

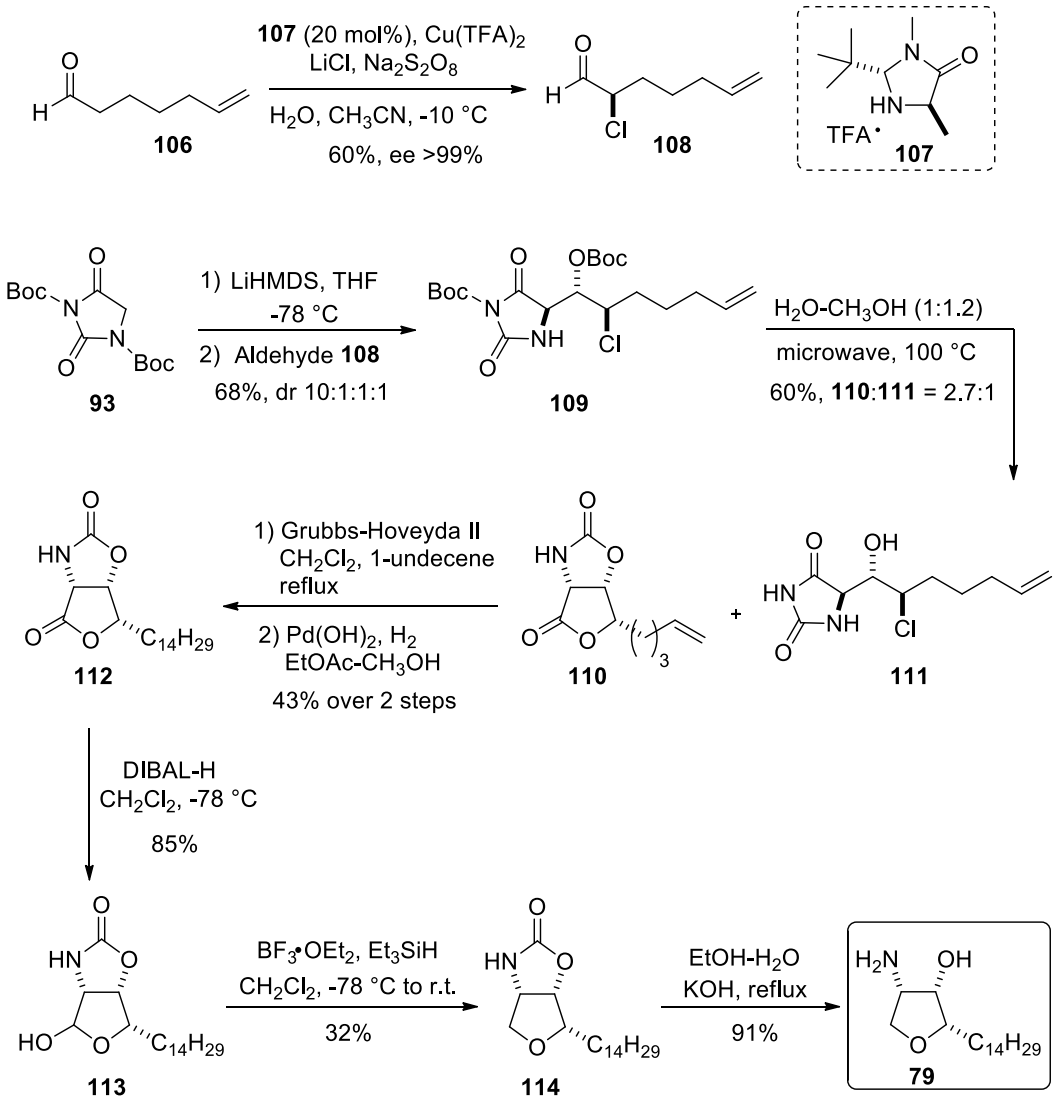
Table 2.2 Optimization of γ-Lactone (104) Formation.

entry	solvent(s)	temp (°C)[a]	104:105[b] (%yield)[c]
1	H_2O:CH_3OH (1:1)	60	1:3 (62%)
2	dimethylcarbonate	60	nd[e]
3	DMSO	60	nd[e]
4	H_2O:CH_3OH (1:1)	100	1.7:1
5	H_2O:*t*BuOH (1:1)	100	1.1:1
6	H_2O:CF_3CH_2OH (1:1)	100	1.2:1
7[d]	H_2O:CH_3OH (1:1.2)	100	2.7:1 (58%)
8	H_2O:CH_3OH (1:1.3)	100	2:1

[a] Reaction carried out in a sealed tube in an oil bath; [b] determined by analysis of ^1H NMR spectra recorded on crude reaction mixture; [c] combined isolated yield; [d] reaction carried out in microwave reactor; [e] 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.[12] 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.[23] 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) from which the desired aldol adduct **109** could be isolated in 52% yield. This latter material was then heated in H_2O-CH_3OH 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[24] of the purified γ-lactone (**110**) with 1-undecene catalyzed by the 2nd generation Grubbs-Hoveyda catalyst[25] afforded the corresponding C_{14} 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 Et_3SiH and $BF_3{\cdot}OEt_2$.[26] Finally, the carbamate in **114** was cleaved under basic conditions to afford pachastrissamine (**79**) in 91% yield. The spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS and IR) of our synthetic pachastrissamine (**79**) were in complete agreement with that reported in the literature.[6g]



Scheme 2.3 Total Synthesis of Pachastrissamine (79).

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-chloroaldehydes. 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. Experimentals

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 CaH_2. 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 ($CDCl_3$) or methanol-D_4 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 ($CDCl_3$: δ 7.26, MeOD: δ 3.34, ^{1}H NMR; $CDCl_3$: δ 77.00, MeOD: δ 49.86, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (*Hz*) and are reported to the nearest 0.1 Hz. ^{1}H 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.

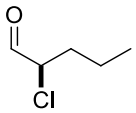
Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

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.

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

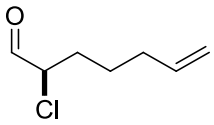


To a cold (0 °C), stirred solution of pentanal (5.00 g, 0.058 mmol) in dichloromethane (160 mL), was added L-proline (668 mg, 5.8 mmol) and *N*-chlorosuccinimide (10.1 g, 0.075 mmol). The reaction mixture was stirred for one hour and then allowed to warm to room temperature slowly over 3 hours at which 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.[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, $CDCl_3$) δ 195.6, 63.9, 34.1, 19.0, 13.5.

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



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.[28]

^{1}H NMR (600 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ 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, $CHCl_3$) = +37

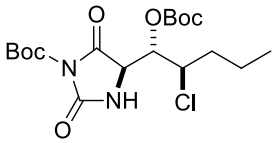
^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.49 (d, 1H, *J* = 2.4 Hz), 5.77 (m, 1H), 5.03 (m, 1H), 5.00 (m, 1H), 4.16 (ddd, 1H, *J* = 8.1, 5.4, 2.4 Hz), 2.10 (m, 2H), 2.00 (m, 1H), 1.84 (m, 1H), 1.64 (m, 1H), 1.55 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 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 $C_7H_{12}ClO$: 147.0566 (M+H)+; found: 147.0571 (M+H)+.

2.4.3. Preparation of β-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**[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 ($MgSO_4$), filtered, and concentrated to provide the crude

chlorohydrin. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded β-amidochlorohydrin (**100**) (876 mg, 45%, dr 10:1:1:1).

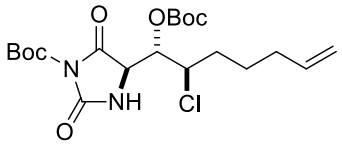
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.68 (br s, 1H), 5.11 (dd, 1H, *J* = 5.2, 2.1 Hz), 4.39 (dd, 1H, *J* = 2.1, 1.5 Hz), 4.14 (m, 1H), 1.81-1.64 (m, 2H), 1.57 (s, 9H), 1.53-1.41 (m, 2H), 0.94 (t, 3H, *J* = 7.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 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 $C_{18}H_{29}ClN_2NaO_7$: 443.1556 (M+Na)+; found: 443.1584 (M+Na)+.

2.4.4. Preparation of β-Amidochlorohydrin (109)



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 β-amidochlorohydrin (**109**) (1.28 g, 52%, dr 10:1:1:1).

$[\alpha]_D^{25}$ (c 0.65, $CHCl_3$) = -12.3

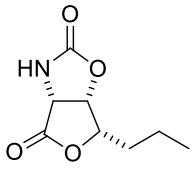
^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.76 (m, 1H), 5.62 (br s, 1H), 5.12 (dd, 1H, *J* = 2.1, 5.2 Hz), 5.01 (m, 2H), 4.39 (br s, 1H), 4.12 (m, 1H), 2.10 (m, 2H), 1.84 (m, 1H), 1.74 (m, 1H), 1.57 (s, 9H), 1.51-1.54 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 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 $C_{20}H_{31}ClN_2NaO_7$: 469.1712 (M+Na)+; found: 469.1707 (M+Na)+.

2.4.5. Preparation of γ-Lactone (104)



To the 80 mL vial containing β-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 °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 γ-lactone (**104**) (157 mg, 40%) and deprotected β-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.

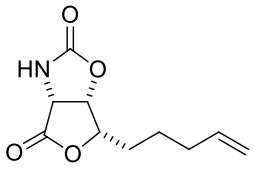
IR (neat): 3268, 2962, 2877, 1753, 1710, 1222, 968 cm^{-}

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 γ-lactone (**110**) (250 mg, 44%, m.p. 108-111 °C) and deprotected β-amidochlorohydrin (**111**) (107 mg, 16%).

Data for γ-lactone (**110**):

$[\alpha]_D^{20}$ (c 1.01, $CHCl_3$) = -12.7

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.79 (m, 1H), 5.63 (s, 1H), 5.21 (dd, 1H, *J* = 4.5, 7.4 Hz), 5.02 (m, 2H), 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, $CDCl_3$) δ: 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 β-amidochlorohydrin (**111**):

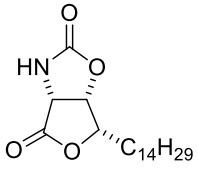
^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.89 (d, 1H, *J* = 7.5 Hz), 5.80 (m, 1H), 5.04-4.95 (m, 2H), 4.35 (brs, 1H), 3.99 (ddd, 1H, *J* = 9.7, 9.7 and 2.4 Hz), 3.70 (ddd, 1H, *J* = 9.3, 7.8 and 1.3 Hz), 2.08-1.99 (m, 4H), 1.55 (m, 1H), 1.43 (m, 1H).

^{13} C NMR (150 MHz, $CDCl_3$) δ: 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 $C_{10}H_{16}ClN_2O_3$: 247.0844 (M+H)+; found: 247.0838 (M+H)+.

2.4.7. Preparation of γ-Lactone (112)



To a stirred solution of 1-undecene (0.24 mL, 1.2 mmol) in dichloromethane (7.5 mL) was added γ-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).

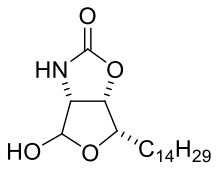
To a stirred solution of C_{14} alkene (**115**) (25 mg, 0.073 mmol) in 1:1 mixture of ethyl acetate: methanol (3.6 mL), was added palladium hydroxide (5.4 mg). Hydrogen was bubbled through the mixture for 30 minutes, and the reaction kept under hydrogen atmosphere for 1.5 hours. After this time, mixture was filtered through a pad of Celite® and filtrate was evaporated in *vacuo* to afford γ-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)



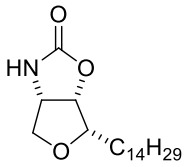
To a stirred solution of γ-lactone (**112**) (31 mg, 0.090 mmol) in dichloromethane (4.4 mL) at -55 °C, was slowly added diisobutylaluminium hydride in tetrahydrofuran (1.0 M, 0.32 mL, 0.32 mmol) and the resulting mixture was stirred for 12 hours. Another batch of diisobutylaluminium hydride in tetrahydrofuran (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 ($MgSO_4$), 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).

^{1}H NMR (400 MHz, $CDCl_3$) 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).

^{13}C NMR (100 MHz, $CDCl_3$) 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 ($MgSO_4$), 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).

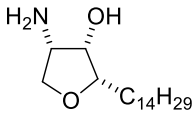
$[\alpha]_D^{20}$ (c 0.72, $CHCl_3$) = +54

^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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, 29.6, 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 ($MgSO_4$), 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.[6b] mp = 70-72 °C).

$[\alpha]_D^{20}$ (c 0.48, $CHCl_3$) = +10

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.92 (dd, 1H, *J* = 7.7, 7.7 Hz), 3.87 (m, 1H), 3.73 (m, 1H), 3.65 (m, 1H), 3.52 (dd, 1H, *J* = 7.7, 7.7 Hz), 2.25 (br s, 2H), 1.72-1.59 (m, 2H), 1.47-1.19 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 83.2, 72.3, 71.7, 54.3, 31.9, 29.8, 29.7, 29.7, 29.6, 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^{-1}

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3. A Short, Organocatalytic Formal Synthesis of (-)-Swainsonine and Related Alkaloids[1]

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-mannosidase[3a] 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

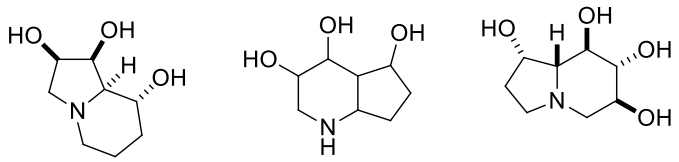
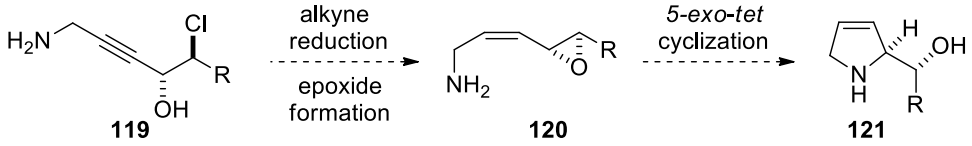


Figure 3.1 Natural Products Swainsonine (116) and Castanospermine (118).

[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.[7] 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.[9s] Based on the importance of swainsonine as a biological tool and potential therapeutic, and the ongoing need for selective Golgi α-mannosidase II inhibitors,[5] 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[10] and various heterocycles[11] 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,[12] 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**)[13]), would then involve a second annulation event.



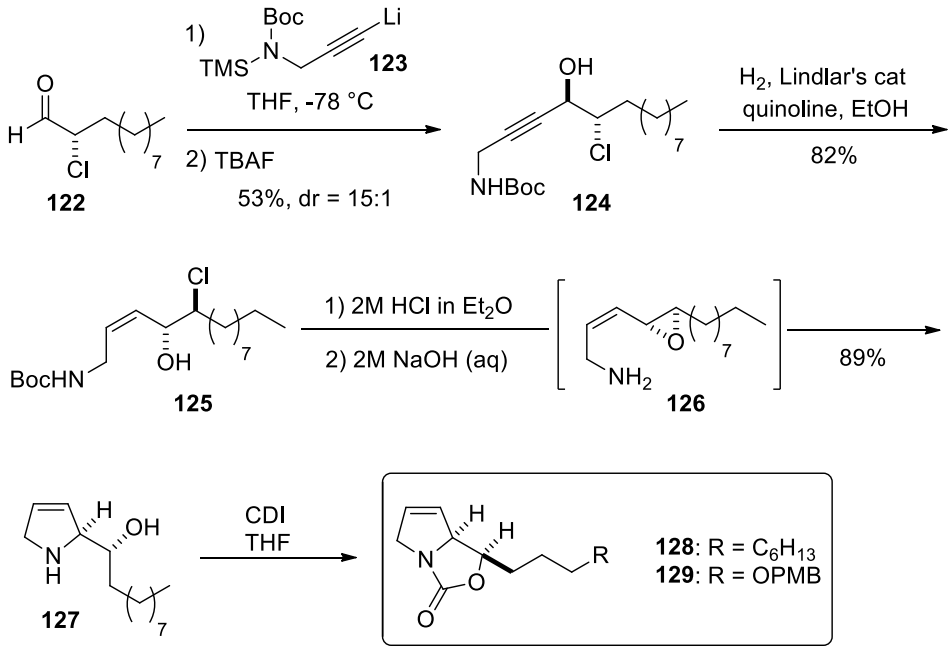
Scheme 3.1 Synthetic Strategy to Access Dihydropyrroles (e.g., 121).

3.2. Results and Discussion

3.2.1. Synthesis of Hydroxyalkyldihydropyrroles and Unnatural Iminosugars

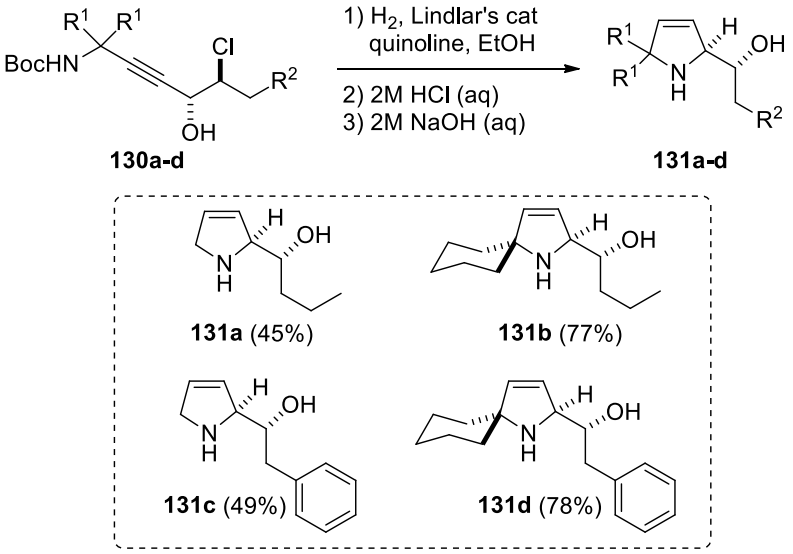
As depicted in Scheme 3.2, our initial efforts focused on defining a concise synthesis of 1,2-*anti*-chlorohydrins that incorporate a *cis*-allylamine functionality. It was anticipated that this would be accomplished through the addition of an alkynyllithium[10] derived from propargyl amine to an α-chloroaldehyde,[11e,14] followed by partial hydrogenation. Toward this goal, α-chloroundecanal (**122**) was prepared in good yield from undecanal[14b] 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**[15] to this aldehyde consistently provided the desired chlorohydrin **124** in yields >50%.[16] 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**.[17]



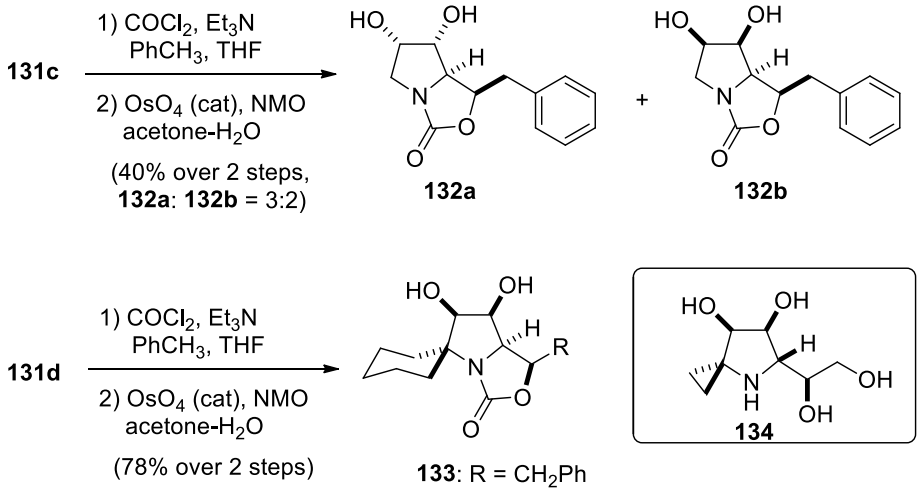
Scheme 3.2 Synthesis of Hydroxyalkyldihydropyrrole 127.

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.[14b,18] 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.[19]



Scheme 3.3 Synthesis of Hydroxyalkyldihydropyrroles 131a-d.

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 α-L-fucosidase.[20]

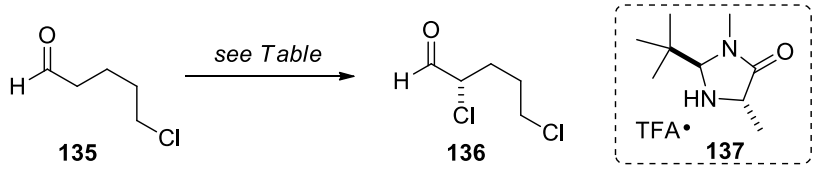


Scheme 3.4 Synthesis of Protected Aminotriols 132a, 132b, and 133.

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**.[21] Toward this end, L-prolinamide catalyzed chlorination of 5-chloropentanal (**135**)[22] using the procedure reported by Jørgensen[14b] 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).[10] 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,[14c] as the imidazolidinone catalyst **137** does not affect racemization of chloroaldehyde products.[14c] 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.



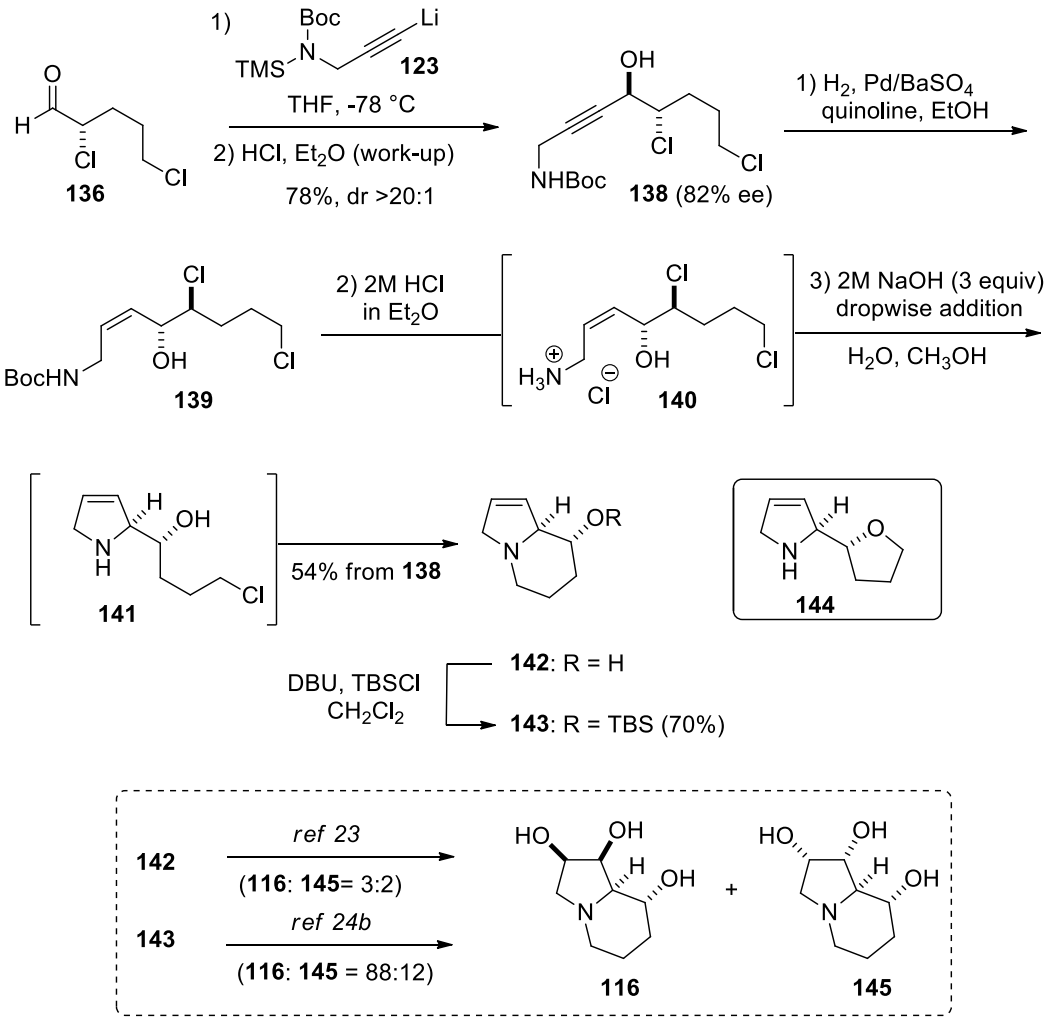
135 **136** **137**

entry	catalyst (mol%)	conditions	temp (°C)	yield (%)	ee (%)[a]
1	L-proline (20)	A	0–r.t.	49	0
2	L-prolinamide (20)	A[b]	0–r.t.	58	62
3	**137** (20)	B[c]	0–r.t.	61	30
4	**137** (20)	B[d]	–25	62	58
5	**137** (20)	B[e]	–35	75	82

Conditions: A: NCS, CH_2Cl_2, 4 h; B: $Cu(TFA)_2$, LiCl, $Na_2S_2O_8$, H_2O, MeCN. [a] Determined by chiral HPLC analysis; [b] 24 h; [c] 4 h; [d] 3 days; [e] 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-*anti* 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,[23] 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.[24] The spectral data (^{1}H NMR, ^{13}C NMR, MS, IR, $[\alpha]_D$) recorded on the TBS ether **143** were in agreement with that reported

for this material by Pyne.[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 hydroxyalkyldihydropyrroles and demonstrated the utility of this process in a formal synthesis of the α-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. Experimentals

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 CaH_2. 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.[25] 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 ($CDCl_3$) methanol-D_4 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 ($CDCl_3$: δ 7.26, MeOD: δ 3.34, ^{1}H NMR; $CDCl_3$: δ 77.00, MeOD: δ 49.86, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (*Hz*) and are reported to the nearest 0.1 Hz. ^{1}H 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.

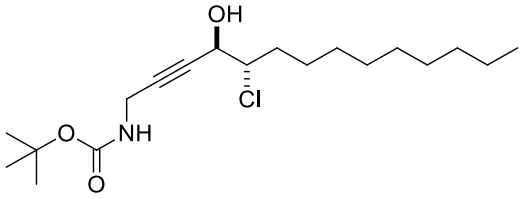
Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

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

x 15 mL). The combined organic phases were washed with brine (15 mL), dried (Na_2SO_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.

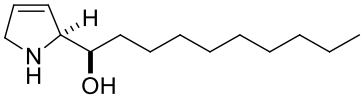
^{1}H NMR (600 MHz, CD_3OD) δ: 4.49 (m, 1H), 3.93 (m, 1H), 3.88 (s, 2H), 1.94 (m, 1H), 1.73 (m, 1H), 1.61 (m, 1H), 1.47 (s, 9H), 1.41-1.30 (m, 13H), 0.93 (t, 3H, *J* = 6.7 Hz).

^{13}C NMR (150 MHz, CD_3OD) 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 $C_{19}H_{34}{}^{35}ClNO_3$: 359.2227 (M)+; found: 359.2223 (M)+.

3.4.2. Preparation of Hydroxyalkyldihydropyrrole (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®. 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_3OD) 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_2SO_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.

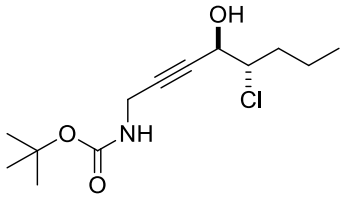
^{1}H NMR (500 MHz, CD_3OD) δ: 5.99 (m, 1H), 5.92 (m, 1H), 3.95 (m, 1H), 3.79 (m, 1H), 3.71 (m, 1H), 3.51 (m, 1H), 1.59 (m, 2H), 1.46-1.29 (m, 14H), 0.93 (t, 3H, *J* = 6.7 Hz).

^{13}C NMR (125 MHz, CD_3OD) 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[3] (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_2SO_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.

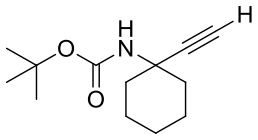
^{1}H NMR (600 MHz, CD_3OD) δ: 4.49 (m, 1H), 3.95 (dt, 1H, *J* = 10.1, 3.8 Hz), 3.88 (br s, 2H), 1.90 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.47 (s, 9H), 1.45 (m, 1H), 0.98 (t, 3H, *J* = 7.4 Hz).

^{13}C NMR (150 MHz, CD_3OD) 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 $C_{13}H_{22}{}^{35}ClNO_3$: 275.1288 (M)+; found: 275.1287 (M)+.

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



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).

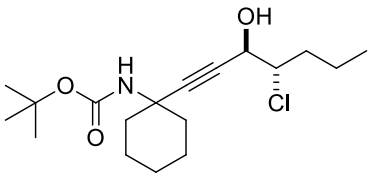
^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.59 (br s, 1H), 2.36 (s, 1H), 2.07 (m, 2H), 1.71-1.54 (m, 7H), 1.45 (s, 9H), 1.26 (m, 1H).

^{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[3] (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 (Na_2SO_4), 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.

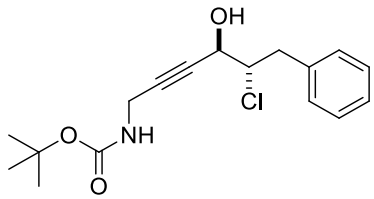
^{1}H NMR (600 MHz, CD_3OD) δ: 4.53 (d, 1H, *J* = 4.1 Hz), 3.98 (dt, 1H, *J* = 9.9, 3.7 Hz), 2.11 (br s, 2H), 1.94 (m, 1H), 1.79-1.58 (m, 10H), 1.47 (s, 9H), 1.30 (m, 1H), 0.98 (t, 3H, *J* = 7.4 Hz).

^{13}C NMR (150 MHz, CD_3OD) 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 $C_{18}H_{30}{}^{35}ClNO_3K$: 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[28] (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_2SO_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.

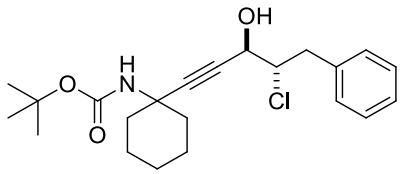
^{1}H NMR (600 MHz, CD_3OD) δ: 7.33-7.23 (m, 5H), 4.48 (m, 1H), 4.17 (m, 1H), 3.92 (br s, 2H), 3.38 (s, 1H), 3.30 (dd, 1H, *J* = 14.3, 5.5 Hz), 3.00 (dd, 1H, *J* = 14.3, 9.0 Hz), 1.47 (s, 9H).

^{13}C NMR (150 MHz, CD_3OD) 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 $C_{17}H_{22}{}^{35}ClNO_3$: 323.1388 (M)+; found: 323.1288 (M)+.

3.4.7. Preparation of Chlorohydrin (130d)



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_2SO_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.

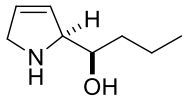
^{1}H NMR (600 MHz, CD_3OD) δ: 7.33-7.24 (m, 5H), 4.51 (d, 1H, *J* = 3.8 Hz), 4.19 (m, 1H), 3.37 (s, 1H), 3.36 (m, 1H), 3.03 (dd, 1H, *J* = 14.4, 8.8 Hz), 2.17 (m, 2H), 1.76 (m, 2H), 1.65 (m, 5H), 1.47 (s, 9H), 1.33 (m, 1H).

^{13}C NMR (150 MHz, CD_3OD) 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 $C_{22}H_{30}{}^{35}ClNO_3Na$: 414.1914 (M+Na)+; found: 414.1815 (M+Na)+.

3.4.8. Preparation of Hydroxyalkyldihydropyrrole (131a)



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-$BaSO_4$ (103 mg, 0.048 mmol). The resulting mixture was stirred under an atmosphere of H_2 (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, CD_3OD) 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 (Na_2SO_4), 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).

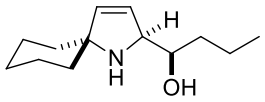
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.95 (m, 1H), 5.75 (m, 1H), 4.13 (m, 1H), 3.84 (m, 1H), 3.75 (m, 1H), 3.49 (m, 1H), 1.56 (m, 1H), 1.47-1.36 (m, 3H), 0.94 (t, 3H, *J* = 7.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_8H_{16}NO$: 142.1254 (M+H)+; found: 142.1232 (M+H)+.

3.4.9. Preparation of Hydroxyalkyldihydropyrrole (131b)



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-$BaSO_4$ (150 mg, 0.071 mmol). The resulting mixture was stirred under an atmosphere of H_2 (balloon) at room temperature for 2.5 hours (reaction monitored by ^{1}H 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.

^{1}H NMR (400 MHz, CD_3OD) 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 (Na_2SO_4), and concentrated in *vacuo*. Purification of the crude product by flash chromatography (silica gel, 95:5:1 dichloromethane:methanol:ammonium hydroxide) afforded hydroxyalkyldihydropyrrole **131b** (85 mg, 77% over 3 steps) as a white solid (m.p. 69-71°C).

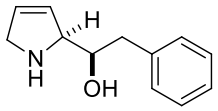
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.90 (dd, 1H, *J* = 6.0, 2.1 Hz), 5.61 (dd, 1H, *J* = 6.0, 1.6 Hz), 4.16 (m, 1H), 3.40 (m, 1H), 1.62-1.35 (m, 14H), δ: 0.95 (t, 3H, *J* = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 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 ^1H NMR spectroscopy). After this time, the mixture was diluted with dichloromethane (2 mL) and filtered through a pad of Celite®, 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.

^1H NMR (400 MHz, CD_3OD) δ: 7.33-7.24 (m, 5H), 5.72-5.64 (m, 2H), 4.59 (m, 1H), 4.18 (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_2SO_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).

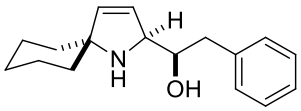
^{1}H NMR (500 MHz, CD_3OD) δ: 7.32-7.29 (m, 4H), 7.22 (m, 1H), 6.02 (m, 2H), 4.03 (m, 1H), 3.86-3.74 (m, 3H), 2.94 (dd, 1H, *J* = 13.8, 4.5 Hz), 2.73 (dd, 1H, *J* = 13.8, 8.7 Hz).

^{13}C NMR (125 MHz, CD_3OD) δ: 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 Hydroxyalkyldihydropyrrole (131d)



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}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 (101 mg), which was used in the next step without further purification.

^{1}H NMR (400 MHz, CD_3OD) δ: 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_2SO_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).

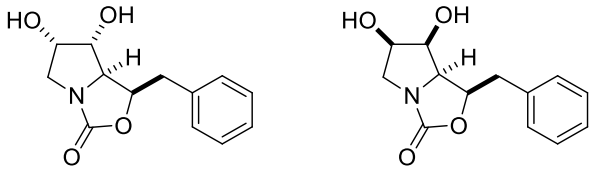
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.20 (m, 5H), 5.96 (dd, 1H, *J* = 6.1, 2.0 Hz), 5.75 (dd, 1H, *J* = 6.0, 1.6 Hz), 4.20 (m, 1H), 3.71 (m, 1H), 2.87 (dd, 1H, *J* = 13.8, 8.2 Hz), 2.76 (dd, 1H, *J* = 13.8, 5.6 Hz), 1.63-1.39 (m, 10H).

^{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, 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_2SO_4), and concentrated to give the crude carbamate (43 mg), which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 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 (Na_2SO_4), and concentrated in *vacuo*. Purification of the crude product by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) afforded protected aminotriols **132a** and **132b** (21 mg, 40% over two steps) as an inseparable 3:2 mixture of diastereomers (colorless oil).

Data for protected aminotriols **132a**

^{1}H NMR (600 MHz, $CDCl_3$) δ: 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}C NMR (150 MHz, $CDCl_3$) δ: 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 **132b**

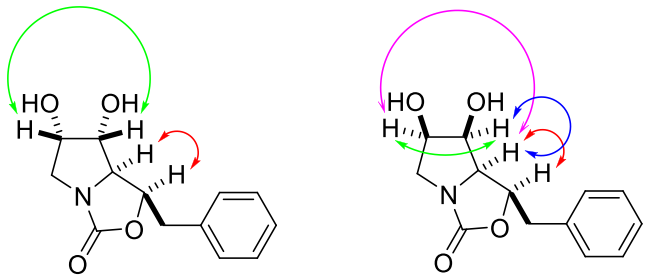
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34-7.24 (m, 5H), 4.93 (m, 1H), 4.43 (m, 1H), 3.98 (m, 1H), 3.60 (d, 1H, *J* = 7.3 Hz), 3.53 (dd, 1H, *J* = 14.4, 7.3 Hz), 3.49 (dd, 1H, *J* = 11.4, 8.2 Hz), 3.43 (dd, 1H, *J* = 11.6, 7.5 Hz), 3.31 (dd, 1H, *J* = 14.3, 7.3 Hz), 3.03 (d, 1H, *J* = 4.1 Hz), 2.79 (d, 1H, *J* = 5.7 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.5, 136.6, 129.0, 128.7, 127.0, 76.9, 73.9, 71.0, 65.1, 50.1, 35.7.

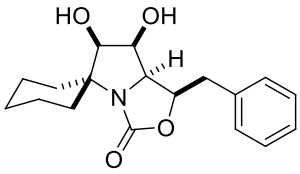
IR (neat): 3406, 3031, 2958, 2925, 1728, 1402, 1112 cm^{-1}

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.

^{1}H 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_2SO_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).

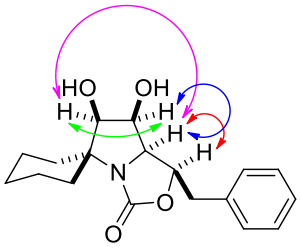
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33-7.24 (m, 5H), 4.86 (m, 1H), 4.09 (m, 1H), 3.93 (dd, 1H, *J* = 7.1, 4.3 Hz), 3.68 (dd, 1H, *J* = 7.8, 2.3 Hz), 3.45 (dd, 1H, *J* = 14.4, 7.3 Hz), 3.32 (dd, 1H, *J* = 14.1, 7.3 Hz), 2.76 (d, 1H, *J* = 1.9 Hz), 2.55 (m, 1H), 2.43 (d, 1H, *J* = 7.2 Hz), 1.98 (m, 1H), 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.

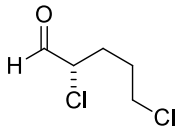
IR (neat): 3371, 2926, 2852, 1716, 1375, 1075 cm^{-1}

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 (-)-(2*S*)-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), $Na_2S_2O_8$ (1.97 g, 8.29 mmol), $Cu(TFA)_2 \cdot 2H_2O$ (1.35 g, 4.15 mmol), in acetonitrile (66 mL) and H_2O (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_2SO_4), and concentrated in *vacuo*. The resulting crude mixture was purified *via* flash chromatography (1:7 EtOAc: Hexanes) to provide (–)-(2*S*)-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.

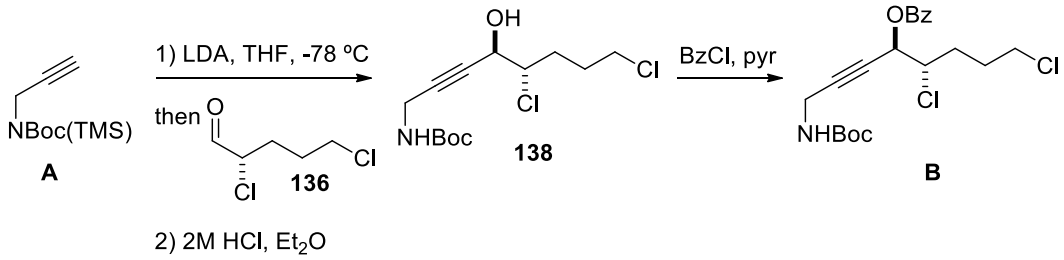
IR (neat): 2964, 1737, 1445, 1285 cm^{-1}

Exact mass calc'd for $C_5H_8{}^{35}Cl_2O$: 153.9952; found: 153.9948 (M)+.

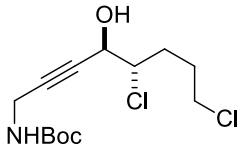
$[\alpha]_D^{23}$: –24.3 (c = 1.11, $CHCl_3$)

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 (Na_2SO_4), 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 (-)-(4*R*,5*S*)-1-(9*N*-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, (–)-(2*S*)-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 (Na_2SO_4), and concentrated in *vacuo*. The resulting crude product was purified *via* flash chromatography (1:4 ethyl acetate:hexanes) to provide (–)-(4*R*,5*S*)-1-(*N*-Boc)amino-5,8-dichloroocta-2-yn-4-ol (**138**) (266 mg, 78%) as a clear oil.

^{1}H NMR (400 MHz, CD_3OD) 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).

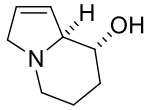
^{13}C NMR (100 MHz, CD_3OD) δ: 172.9, 83.9, 66.9, 66.4, 61.5, 45.2, 31.9, 30.8, 28.7, 20.5, 14.5.

IR (neat): 3331, 2976, 1691, 1367 cm^{-1}

Exact mass calc'd for $C_{13}H_{21}{}^{35}Cl_2NO_3$: 309.0898; found: 309.0901 (M)+.

$[\alpha]_D{}^{23}$: –7.69 (c = 5.9, $CHCl_3$)

3.4.16. Preparation of Indolizidine (142)



To a stirred solution of (4*R*,5*S*)-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 H_2 (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.

^{1}H NMR (400 MHz, CD_3OD) 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 $C_{13}H_{23}Cl_2NO_3$: 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_3OD) δ: 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 $C_8H_{16}Cl_3NO$: 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, $CDCl_3$) δ: 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 (ddd, 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).

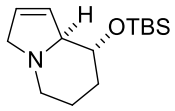
^{13}C NMR (150 MHz, $CDCl_3$) δ: 132.3, 129.7, 74.5, 71.2, 58.3 49.6, 34.2, 24.4.

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

Exact mass calc'd for $C_8H_{13}NO$: 139.0997; found: 139.1003 (M)+.

$[\alpha]_D^{23}$: –40.4 (c = 0.82, $CHCl_3$).

3.4.17. Preparation of Indolizidine (143)



To a solution of indolizidine **142** (21 mg, 0.15 mmol) in dichloromethane (1.5 mL) was added *tert*-butyldimethylsilyl 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_2SO_4), and concentrated in *vacuo*. The resulting crude (yellow oil) was immediately purified by silica get 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[29].

Exact mass calc'd for $C_{14}H_{28}NOSi$: 253.1862; found: 254.1957 $(M)^+$

$[\alpha]_D^{23}$: –50 (c = 0.15, CH_2Cl_2) lit: $[\alpha]_D^{23}$: –59.6 (c = 1.0, CH_2Cl_2)[30]

3.5. References

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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 ^{1}H 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.
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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 A_4 (**13**), and castanospermine (**118**) (Figure 4.1).

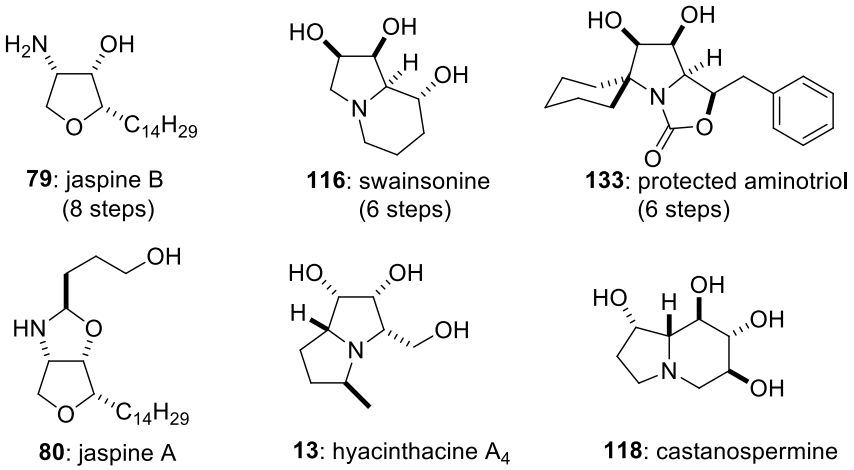
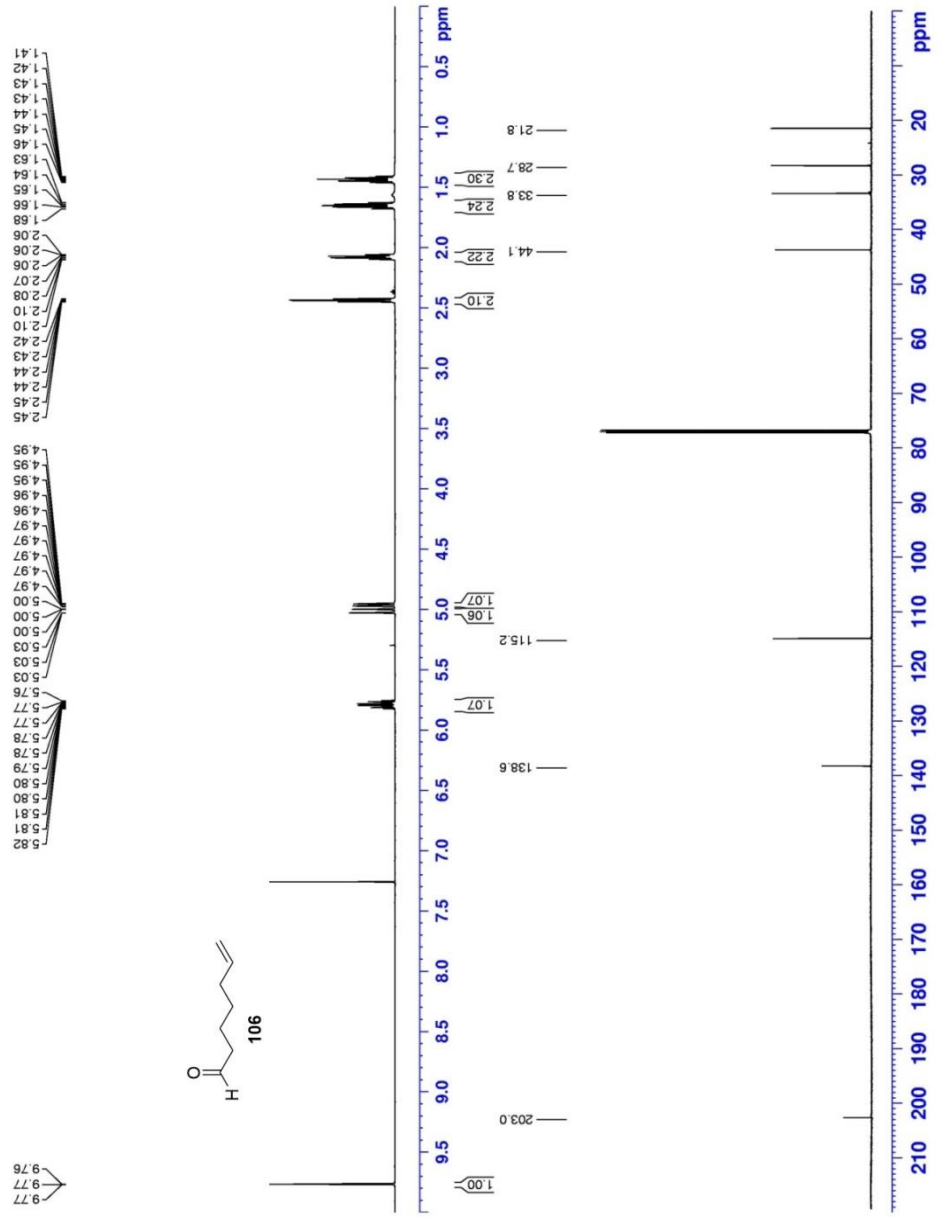


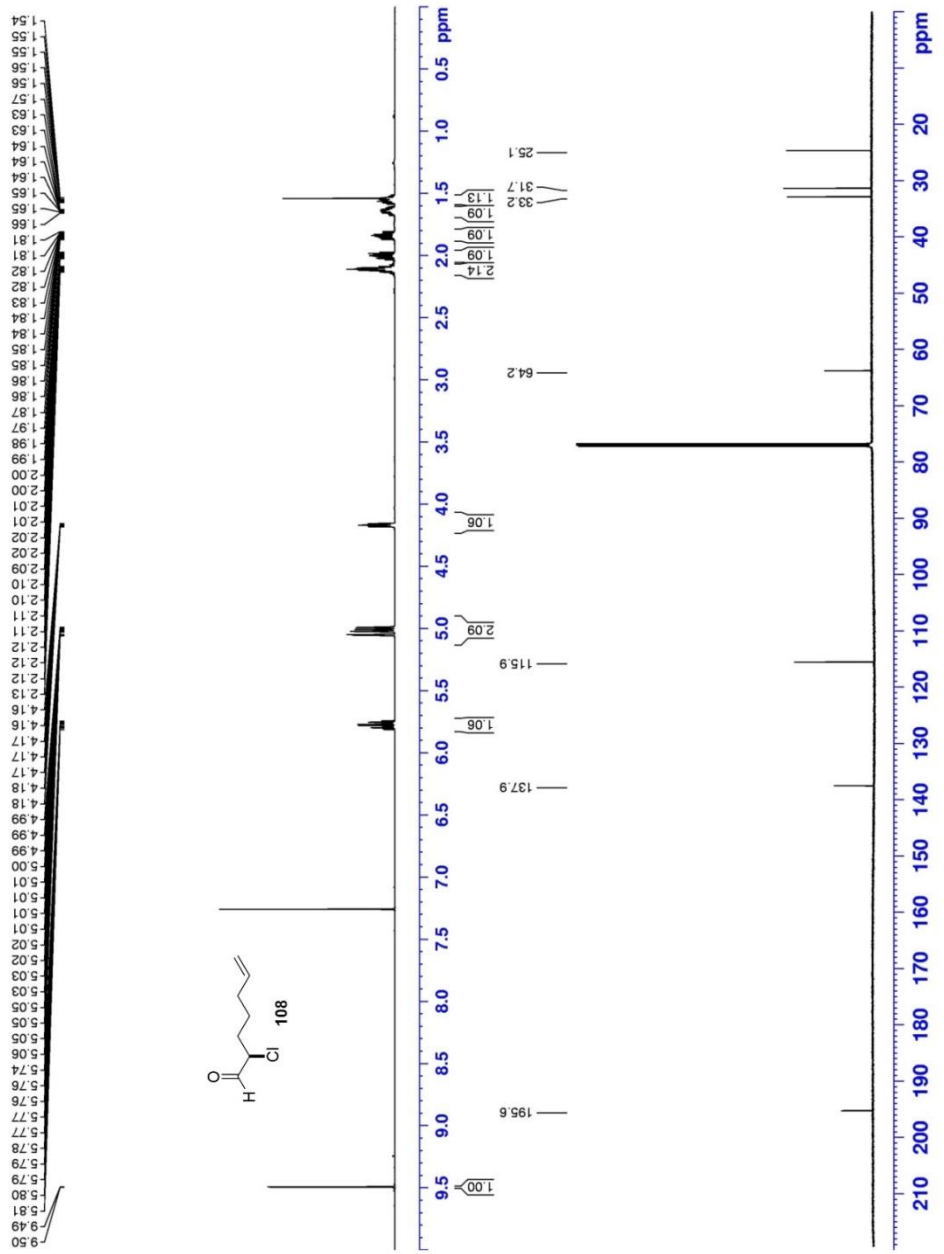
Figure 4.1 Representative Examples of Tetrahydrofuran- and Pyrrolidine-Containing Natural Products

Appendices

Appendix A.

NMR spectra (^{1}H and ^{13}C NMR) Concerning Chapter 2

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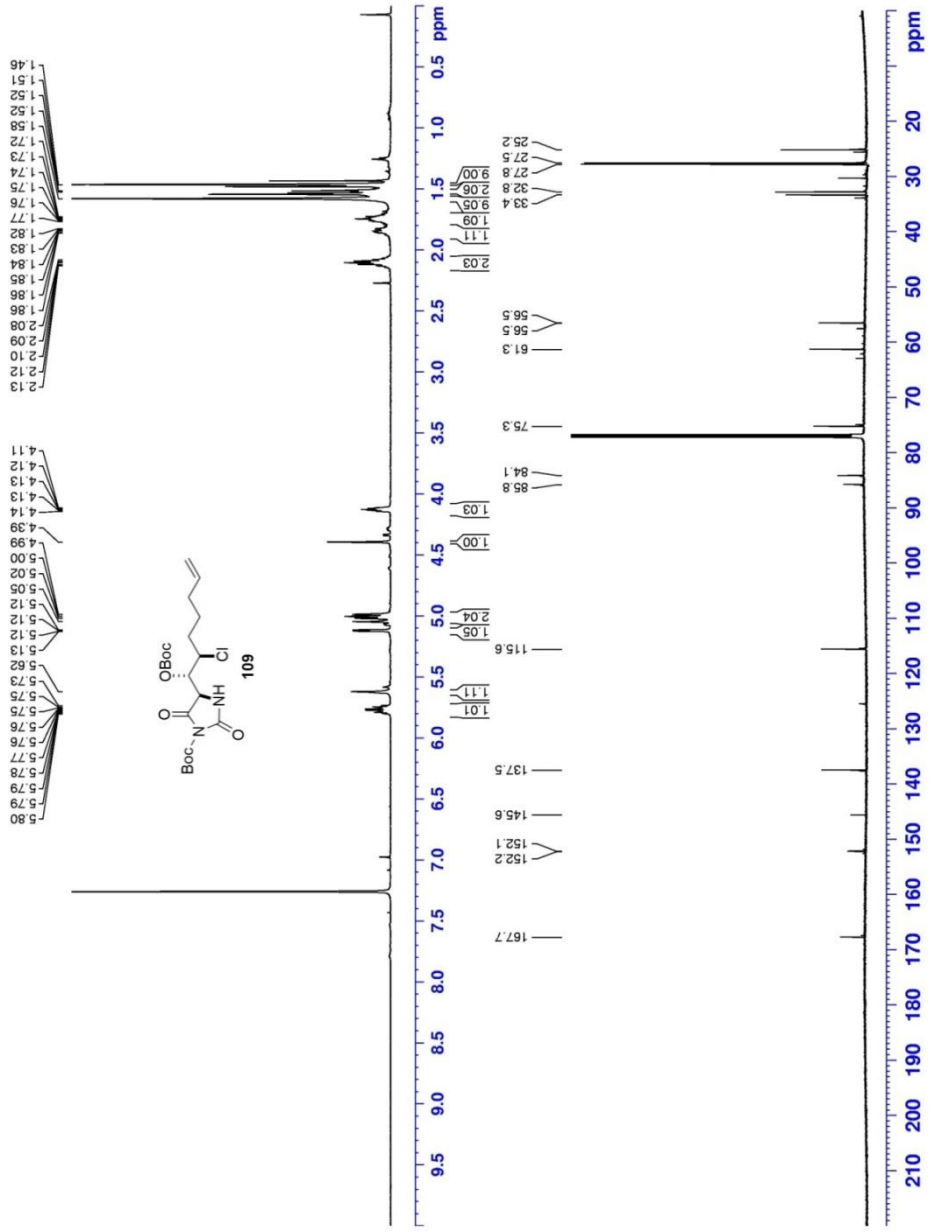
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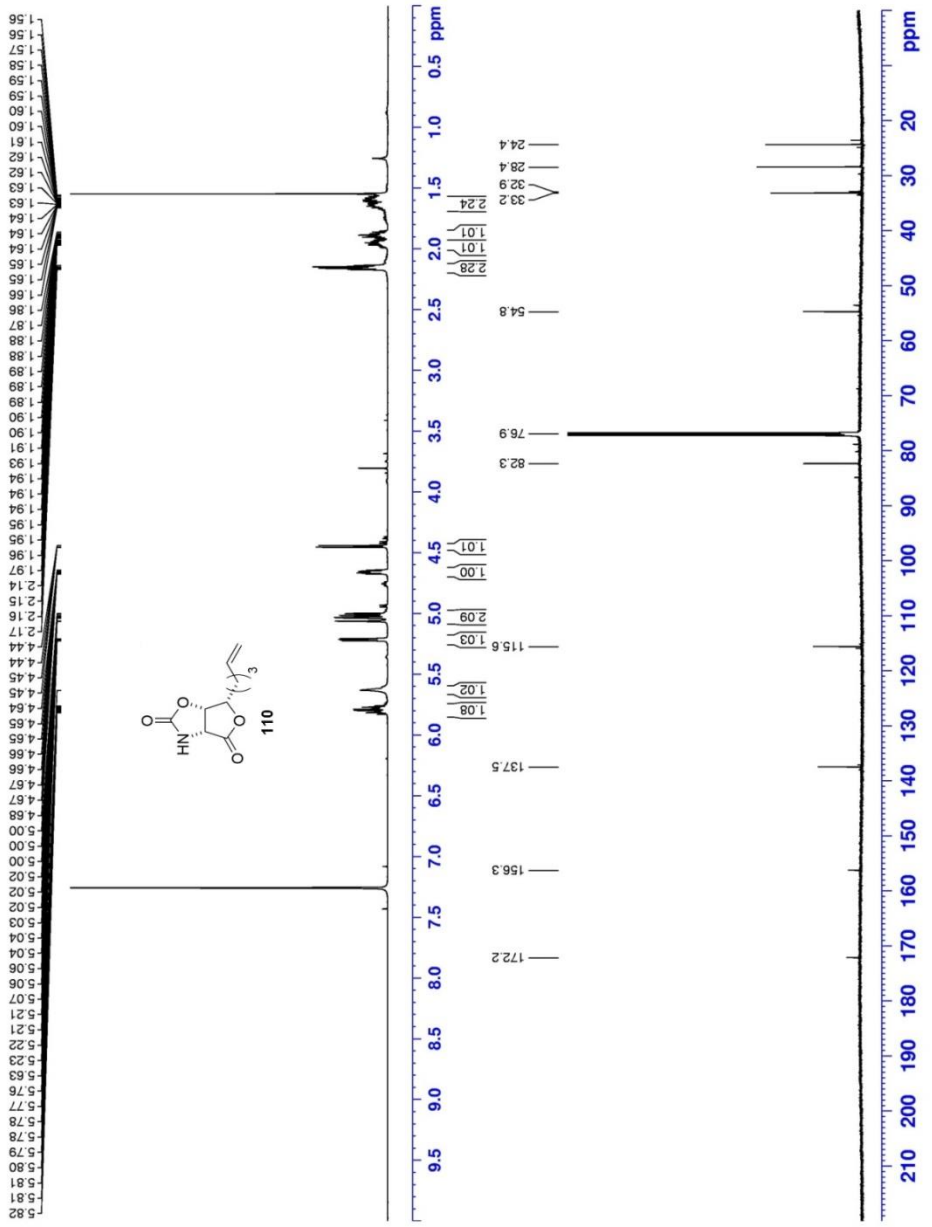
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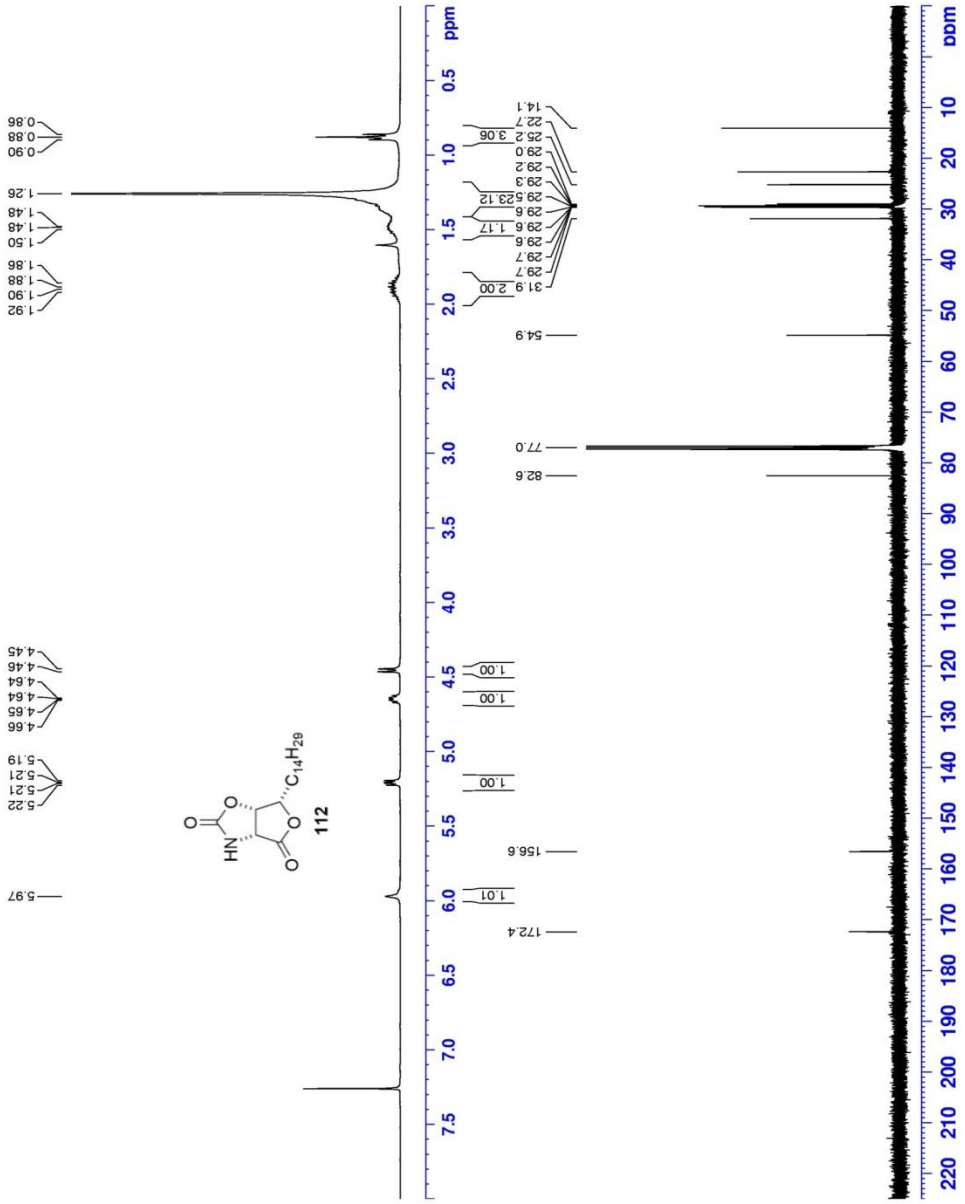
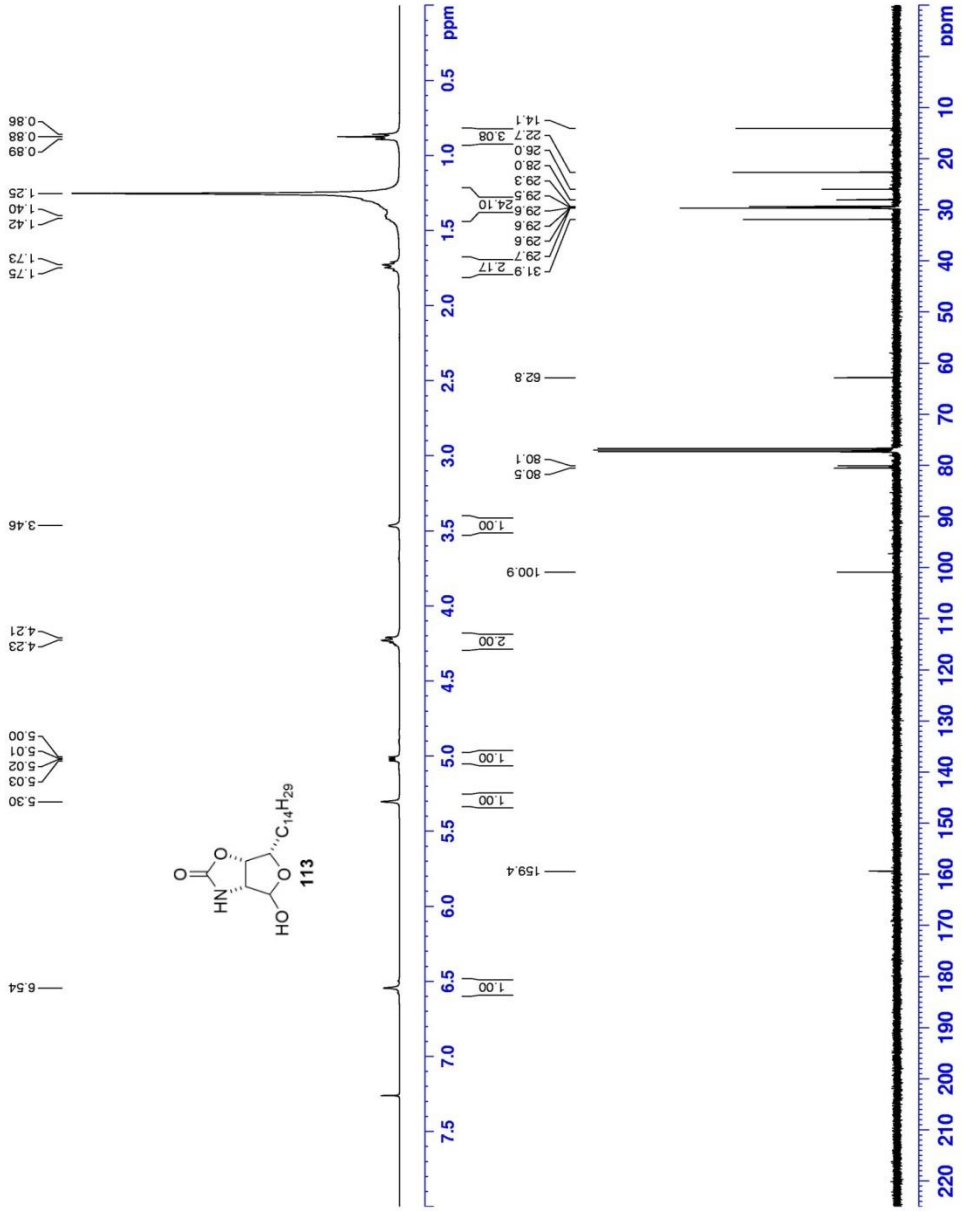
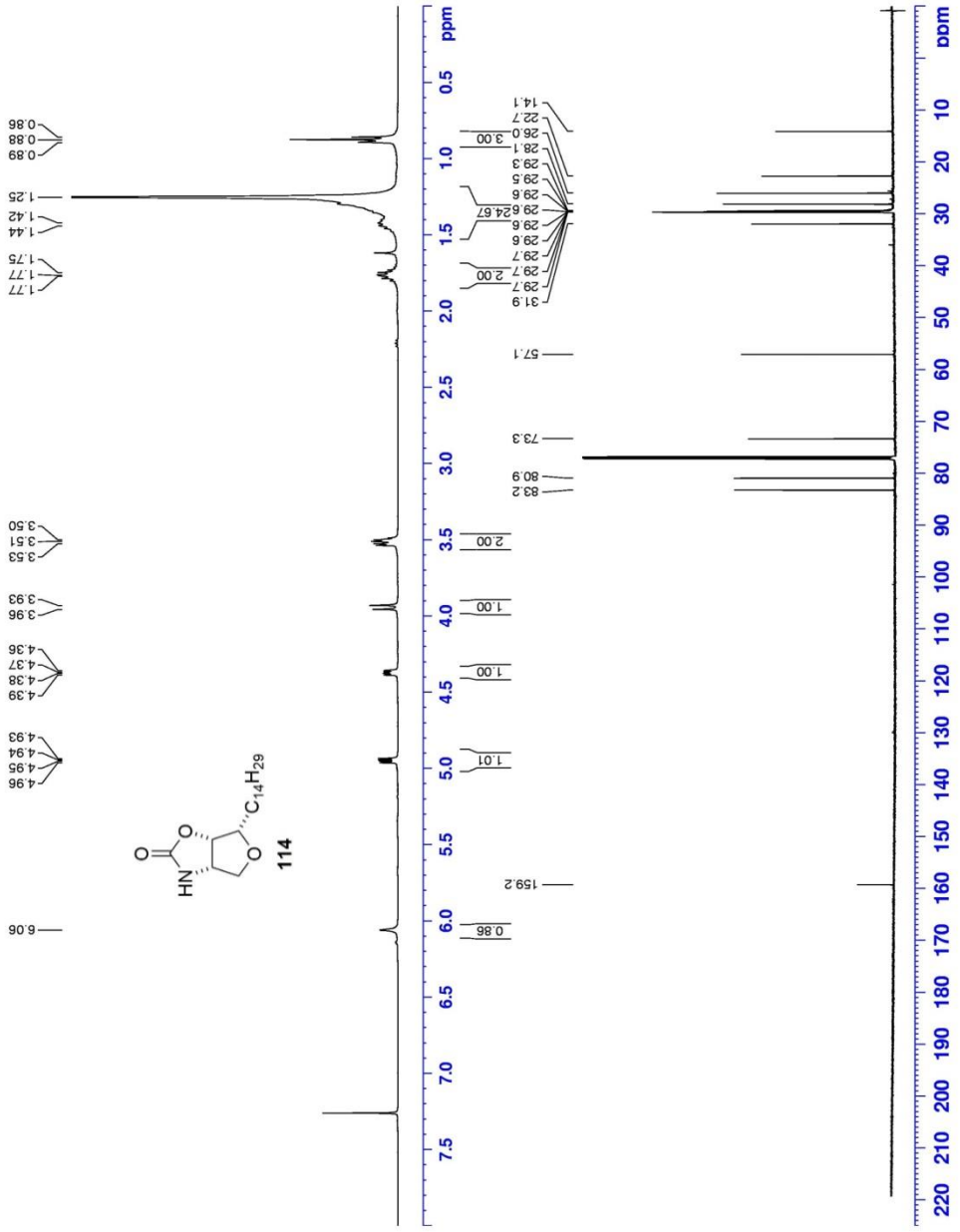
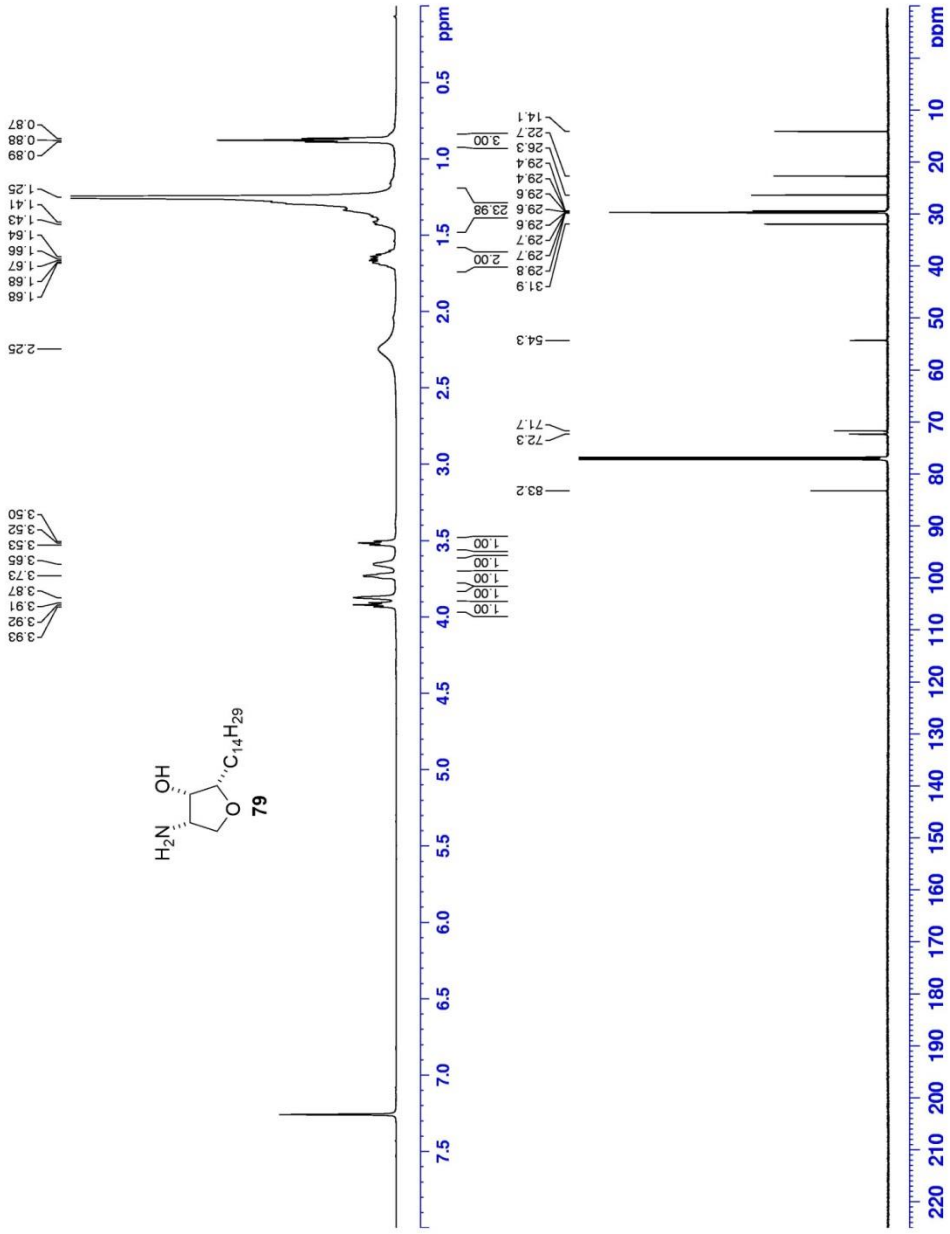

112
$C_{14}H_{29}$
HN
O
ppm

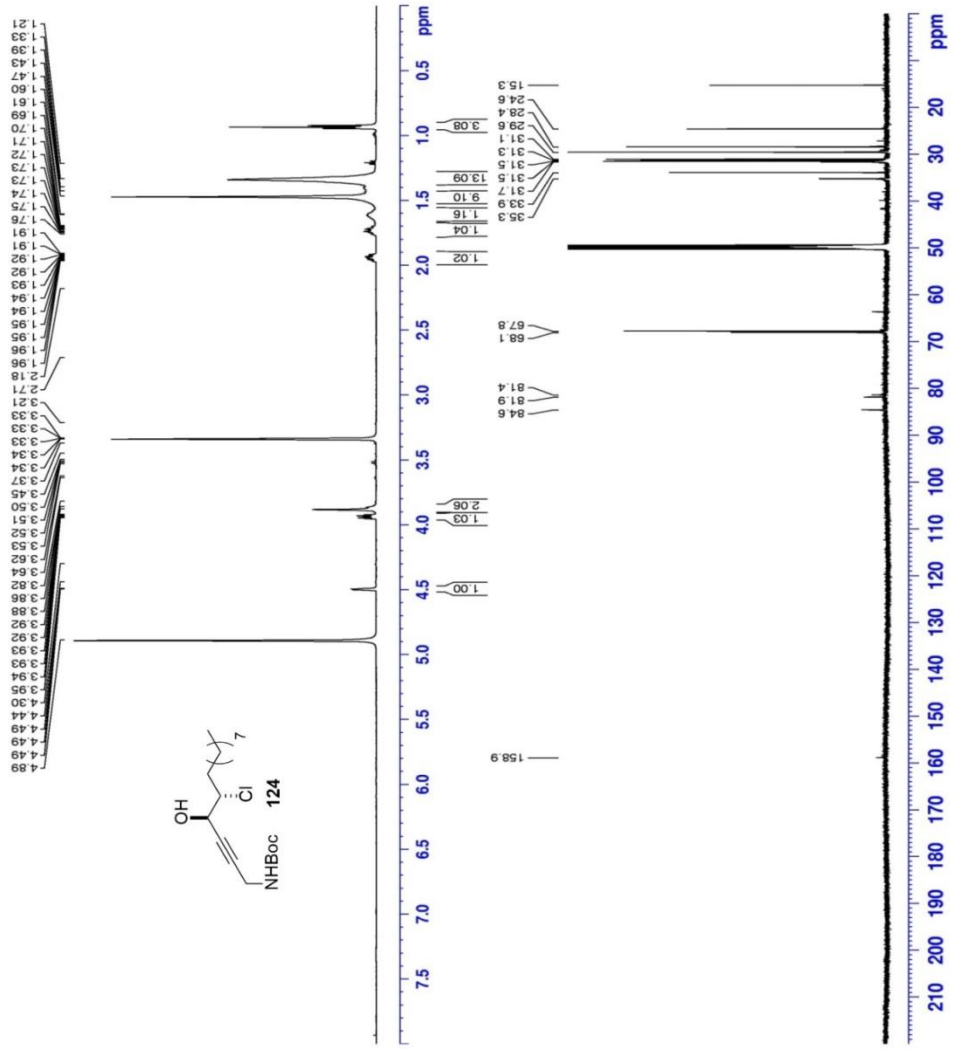

0.86
0.88
0.89
1.25
1.40
1.42
1.73
1.75
3.46
4.21
4.23
5.00
5.01
5.02
5.03
5.30
6.54
1.00
1.00
1.00
2.00
1.00
1.00
14.1
22.7
26.0
28.0
29.3
29.5
29.6
29.6
29.6
29.7
31.9
62.8
80.1
80.5
100.9
159.4
3.08
24.10
2.17
ppm
ppm
O
HN
O
O
HO
$C_{14}H_{29}$
113

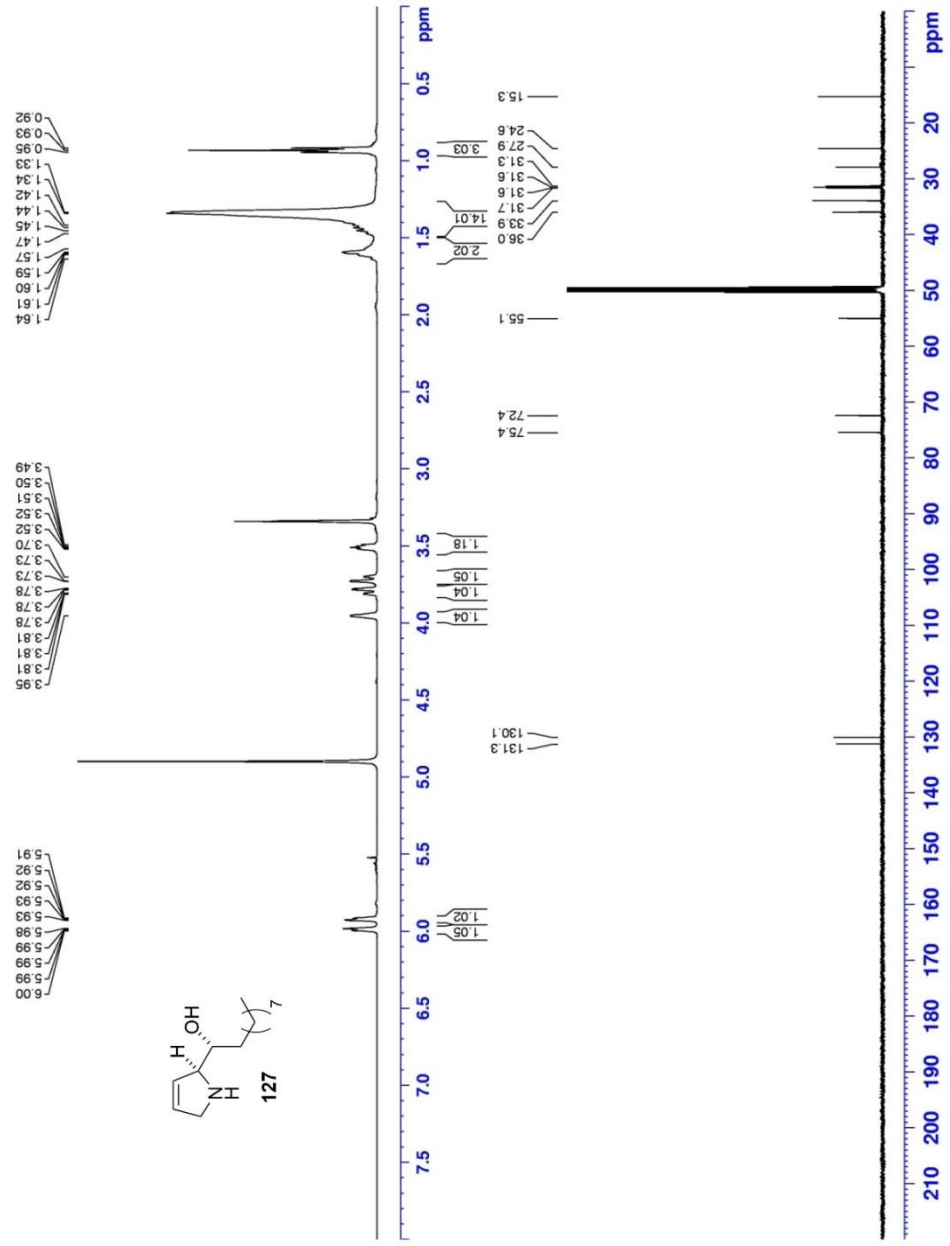

114

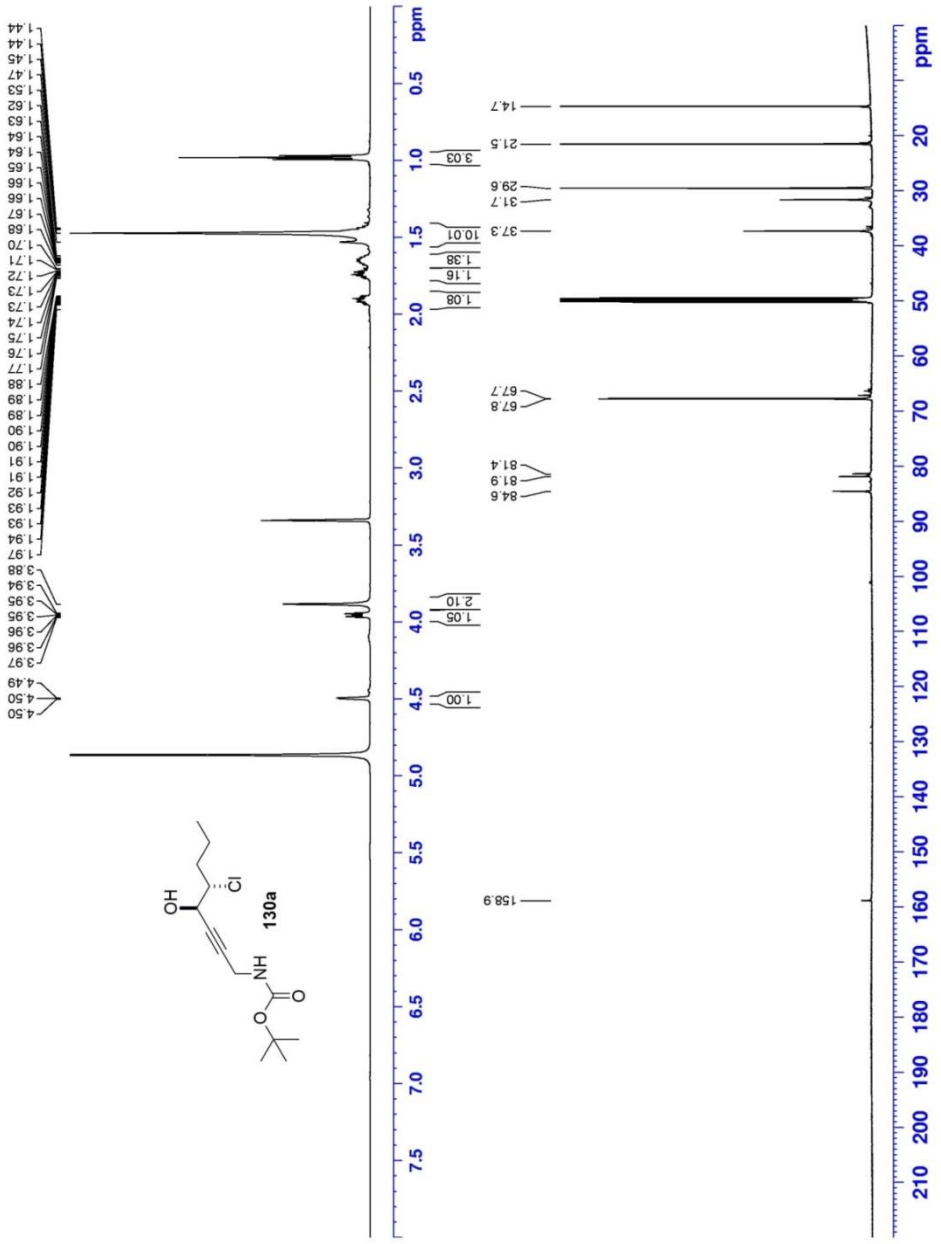

79

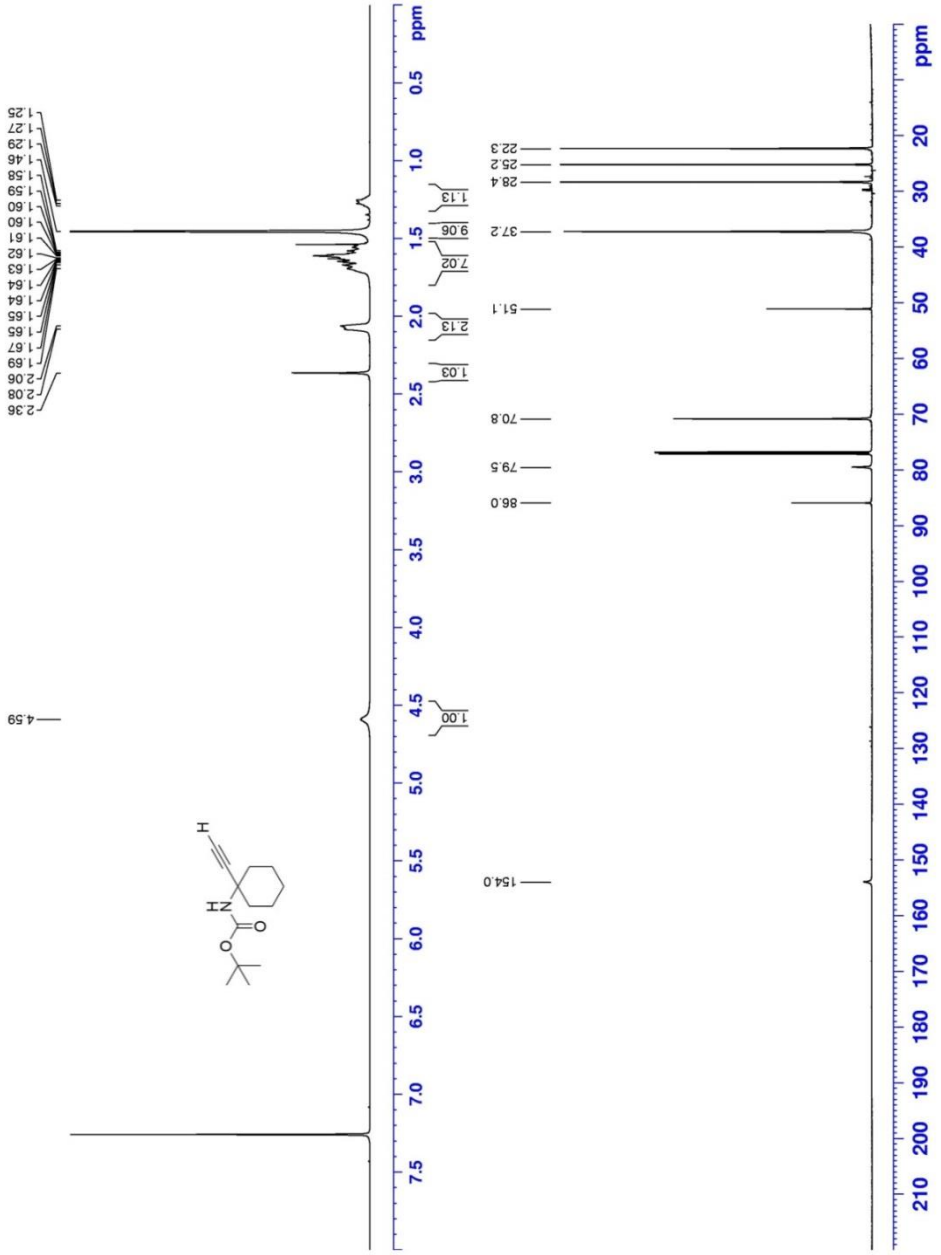
Appendix B.

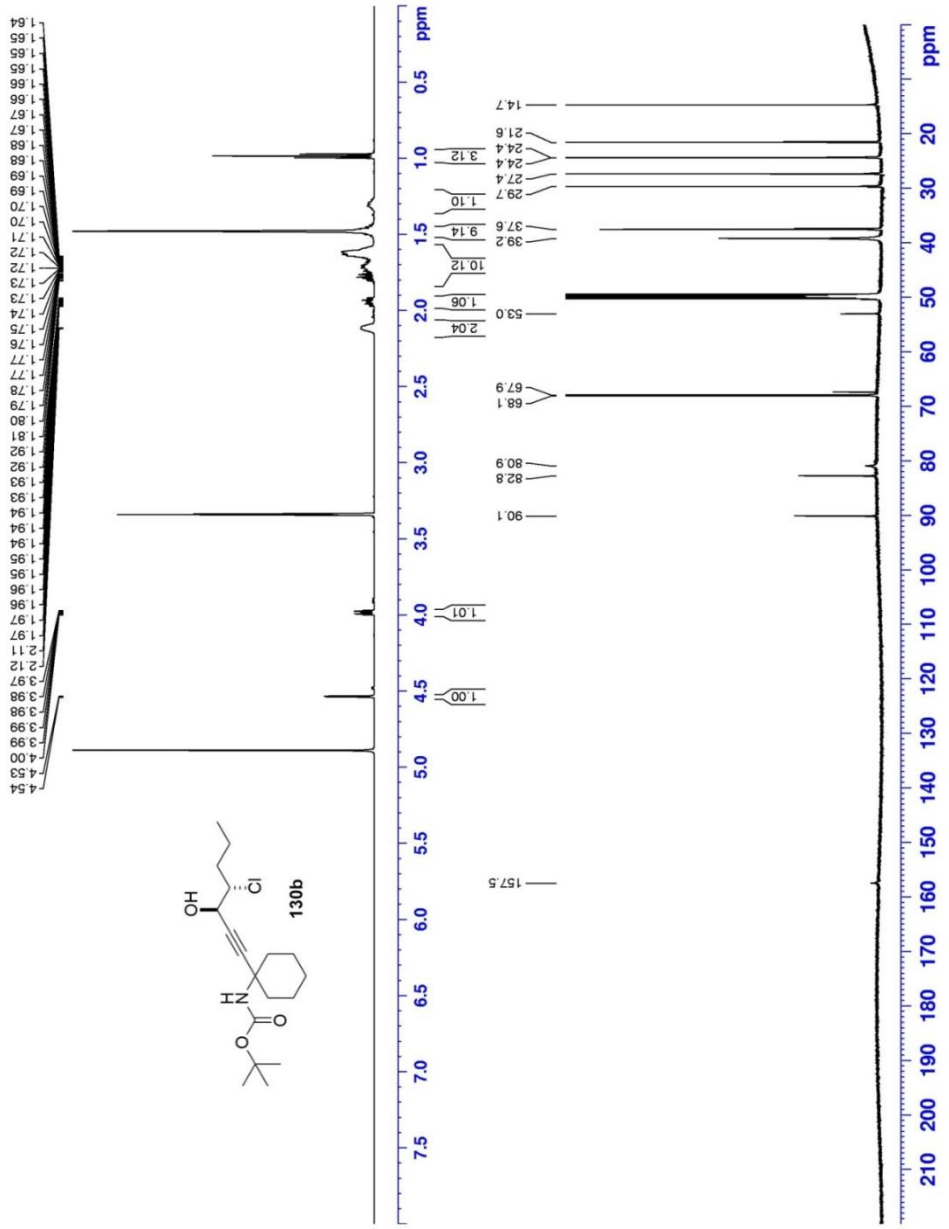
NMR spectra (^{1}H and ^{13}C NMR) Concerning Chapter 3

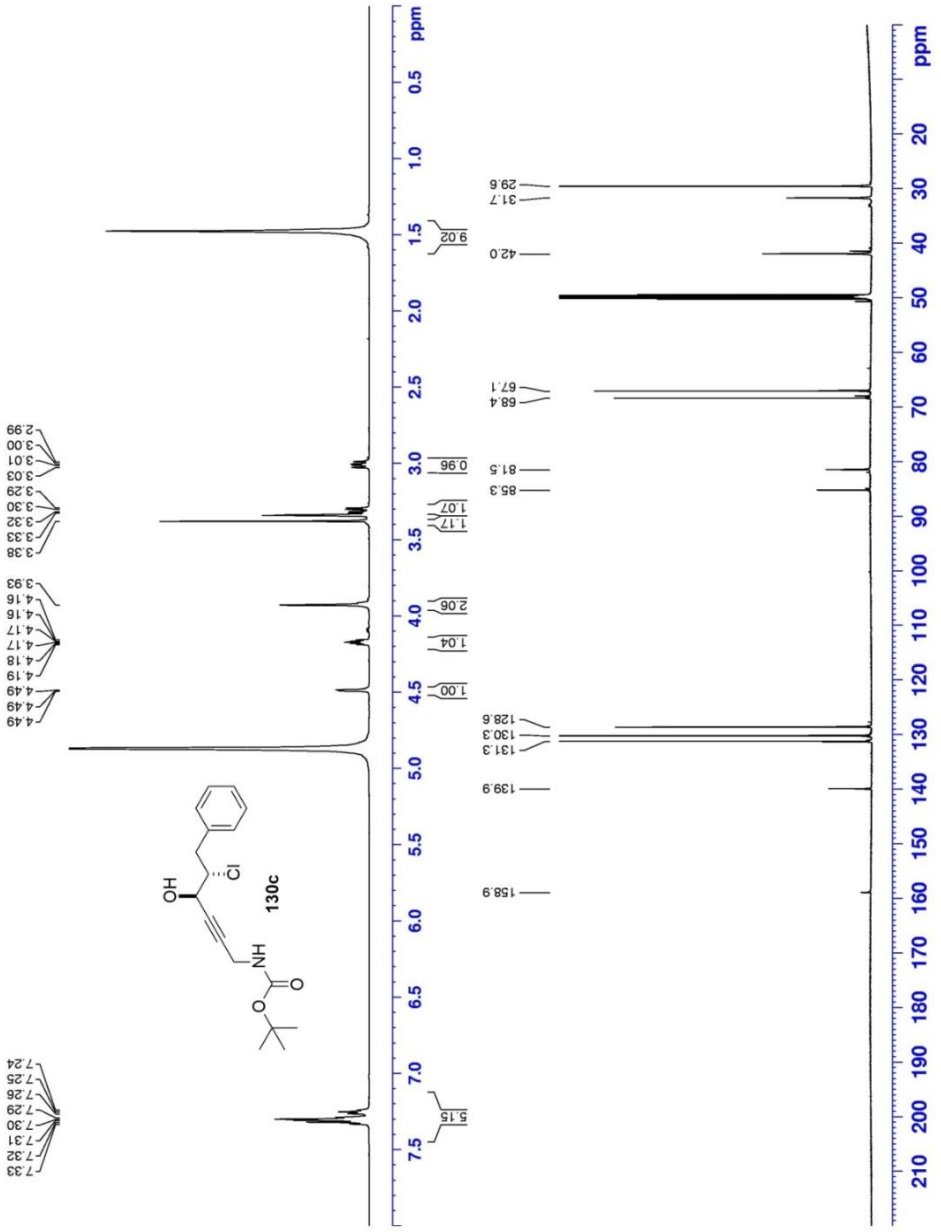


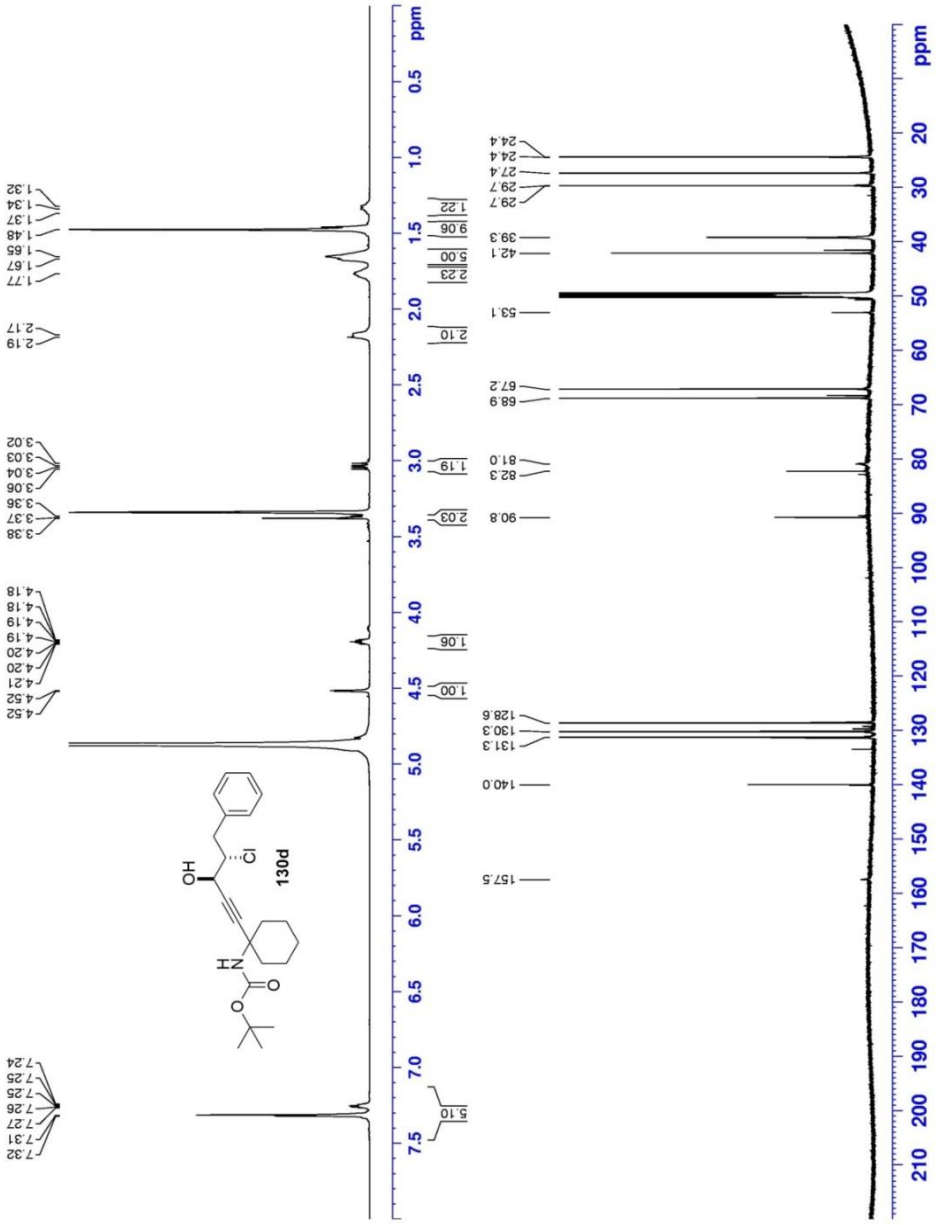

127

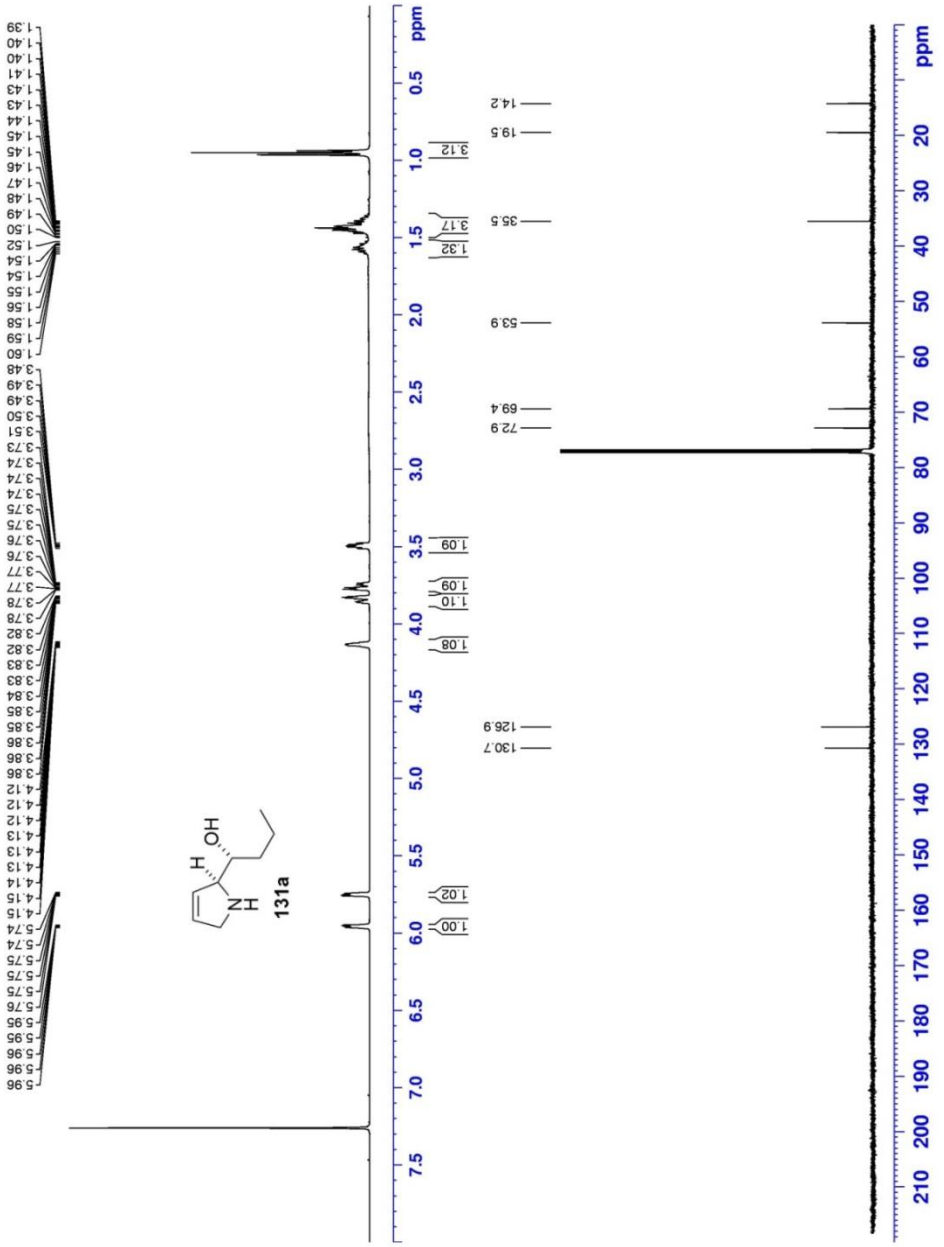

OH
Cl
NH
O
O
130a

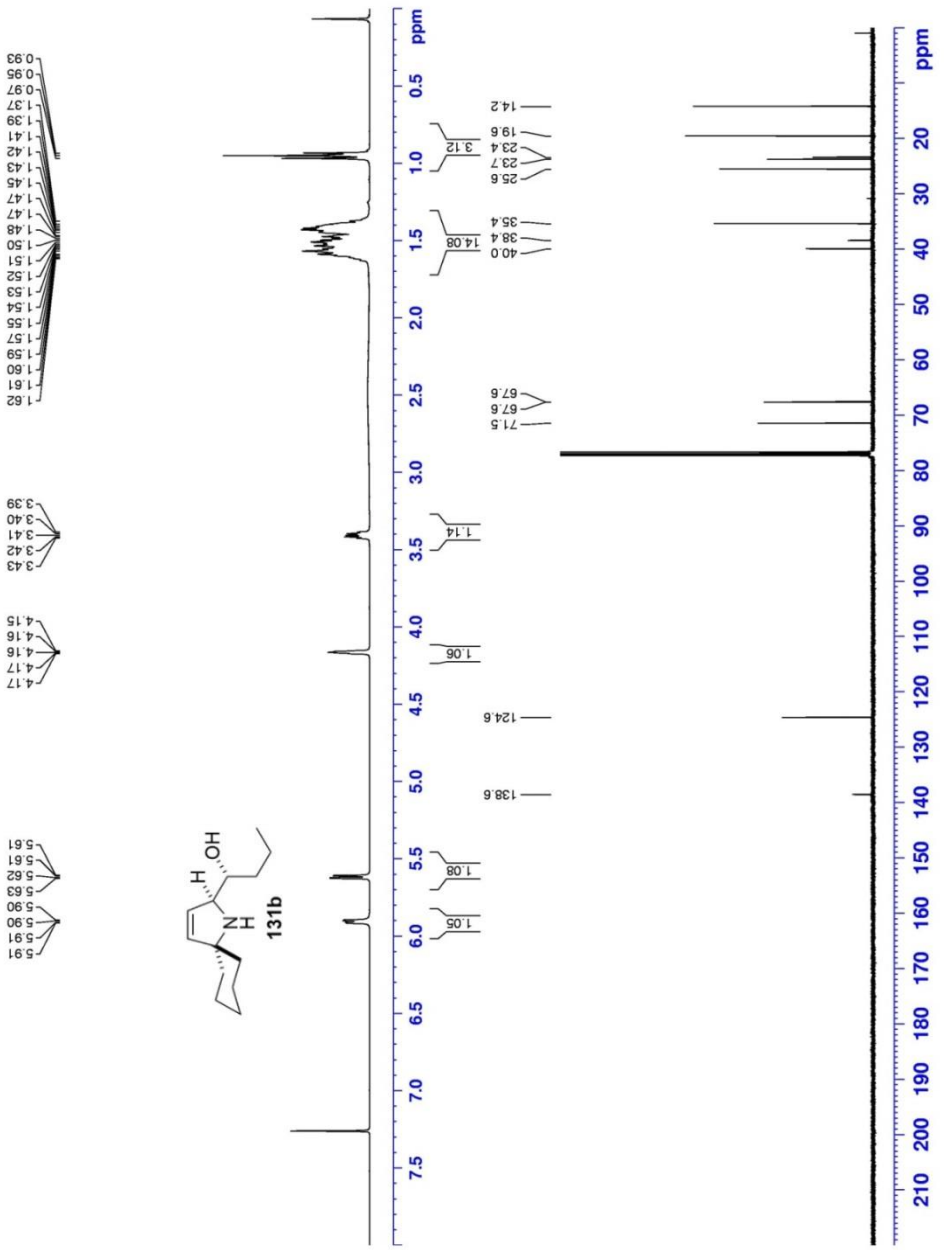

ppm
4.59
1.00
1.03
2.13
7.02
9.06
1.13
2.36
2.08
2.06
1.69
1.67
1.65
1.65
1.64
1.64
1.63
1.62
1.61
1.60
1.60
1.59
1.58
1.46
1.29
1.27
1.25
154.0
86.0
79.5
70.8
51.1
37.2
28.4
25.2
22.3
NH
O
O
H

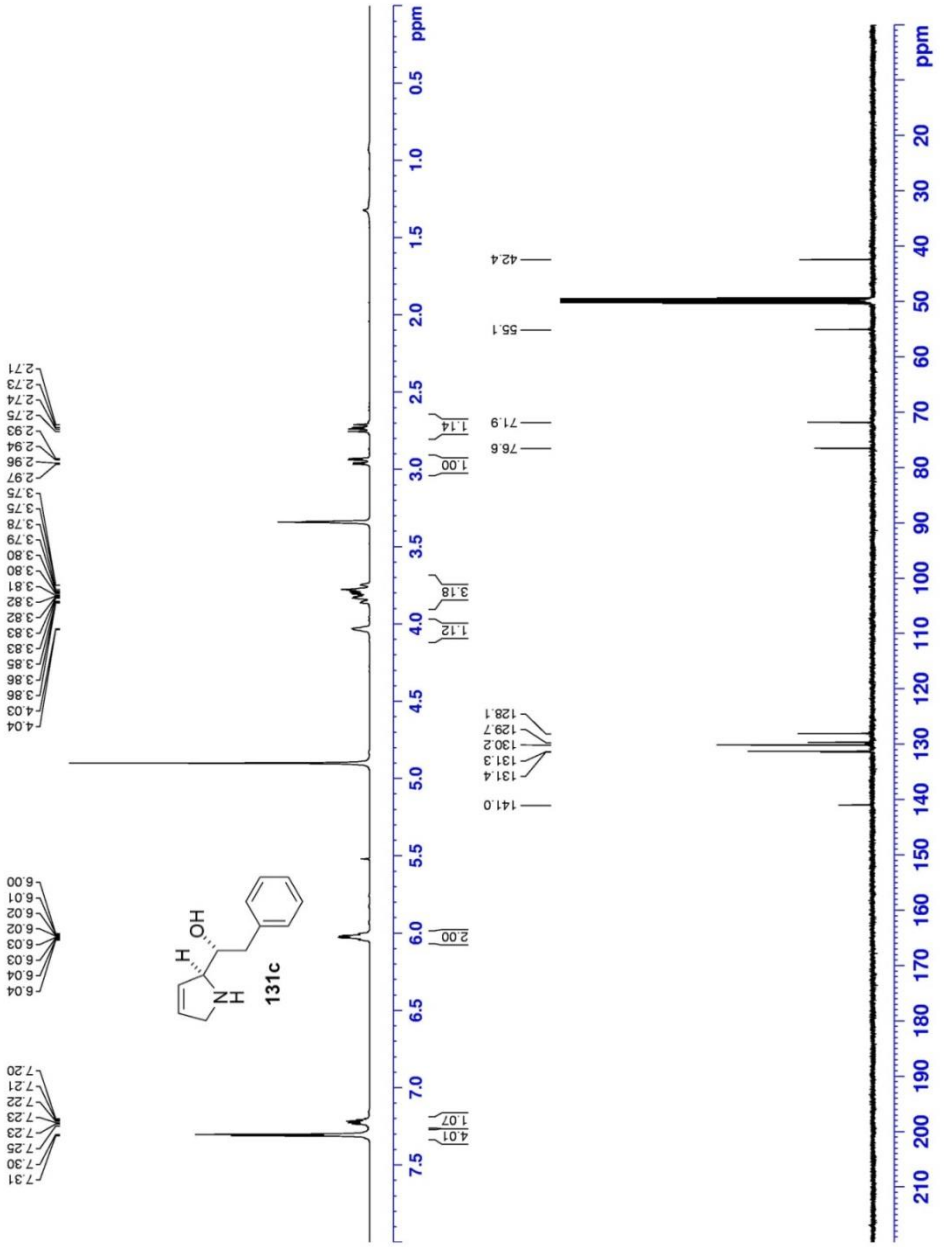

130b
OH
Cl
HN
O
O
ppm

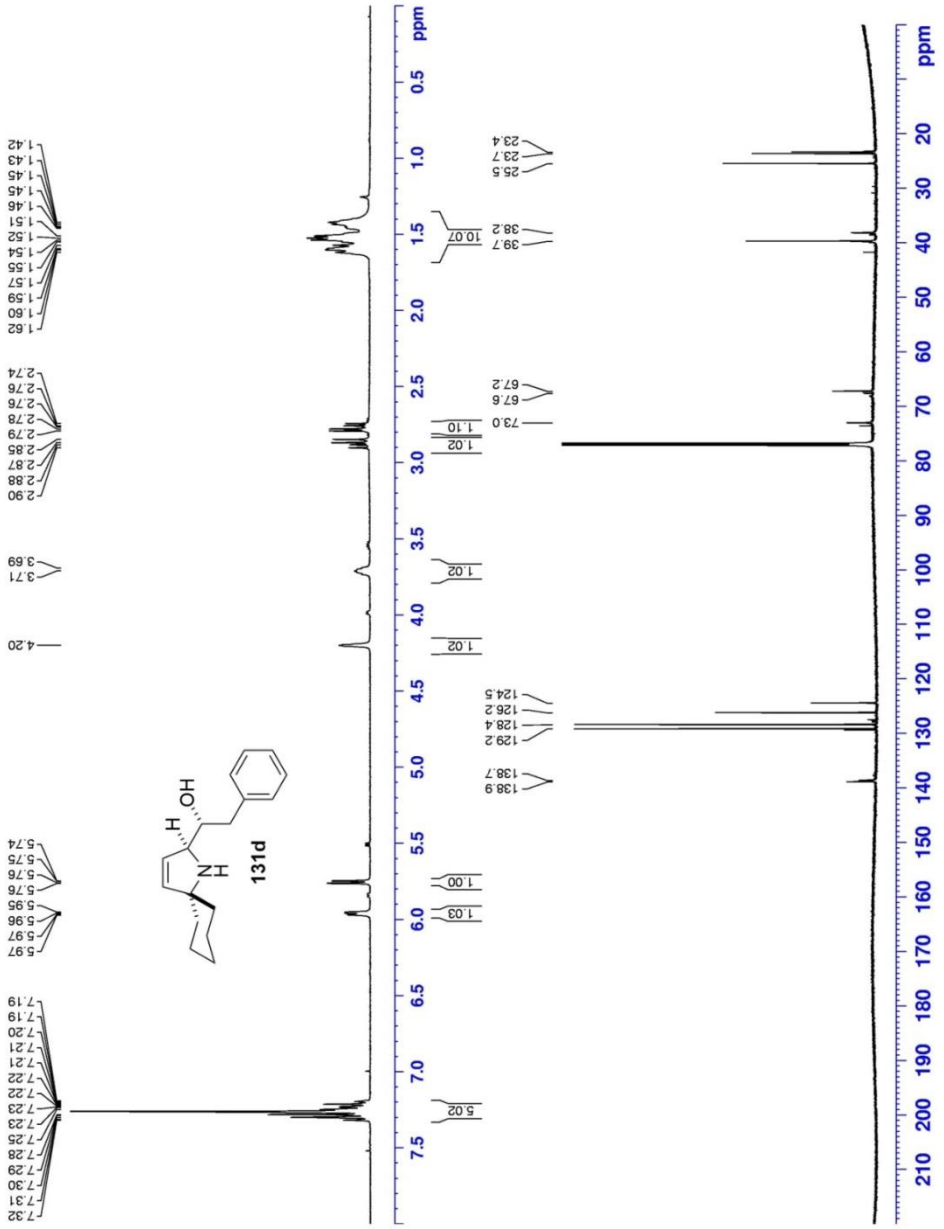

130c
OH
Cl
NH
O
O
ppm

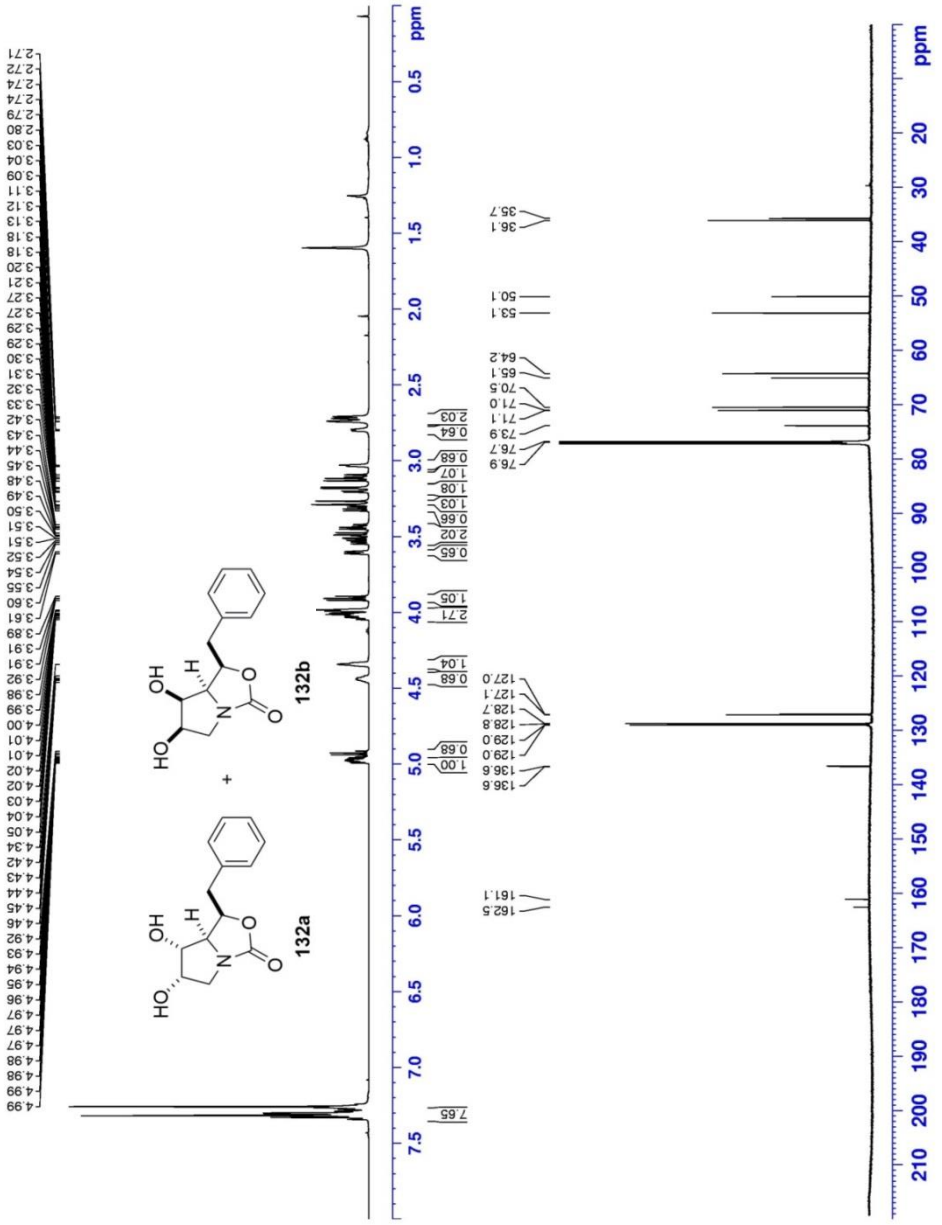

130d
OH
Cl
HN
O
O
ppm

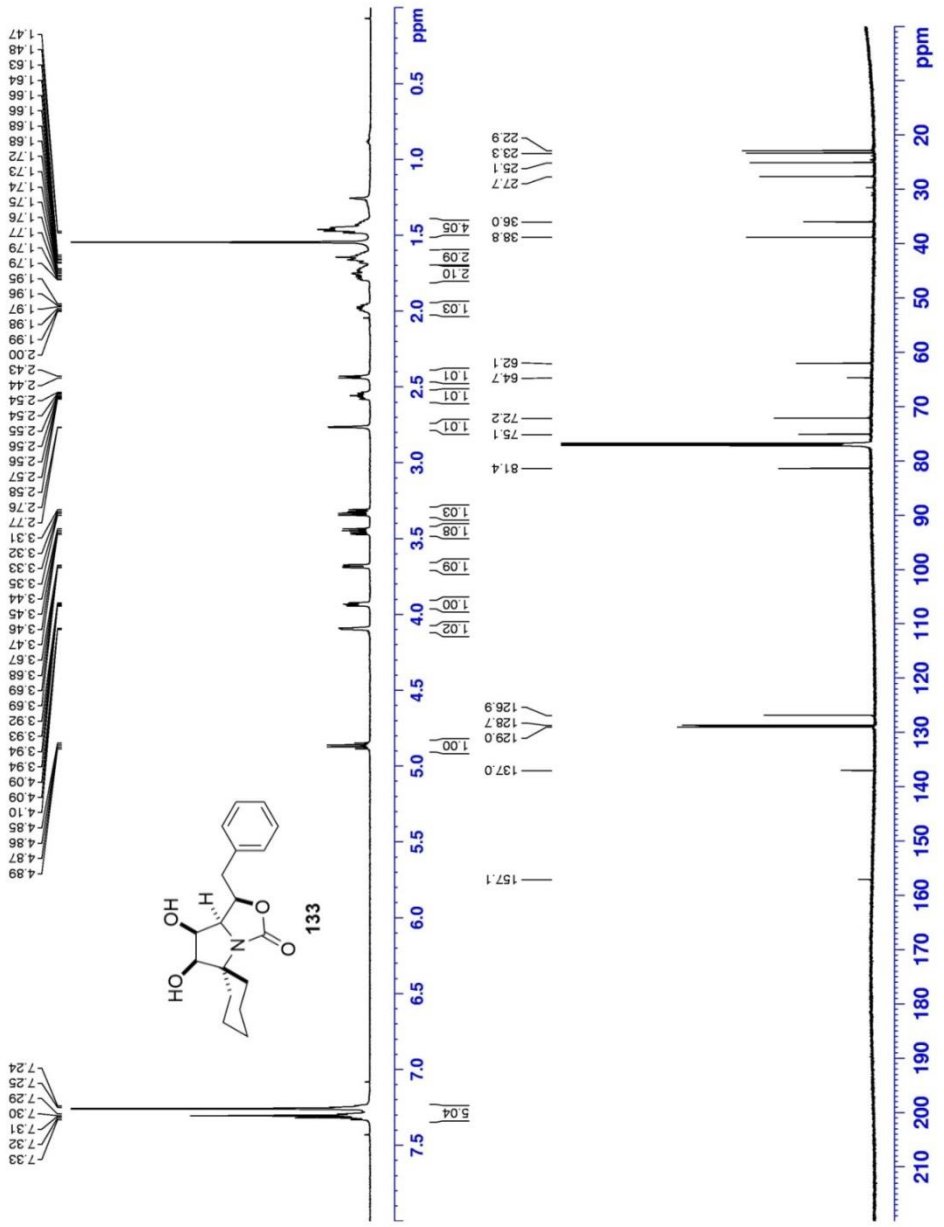

131a
ppm


131b
ppm


131c
ppm


131d
ppm


132b
132a
ppm


133
OH
H
O
N
O
HO
ppm

9.56
9.55
4.27
4.26
4.26
4.25
4.25
4.24
4.24
3.62
2.24
2.08
2.03
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2.00
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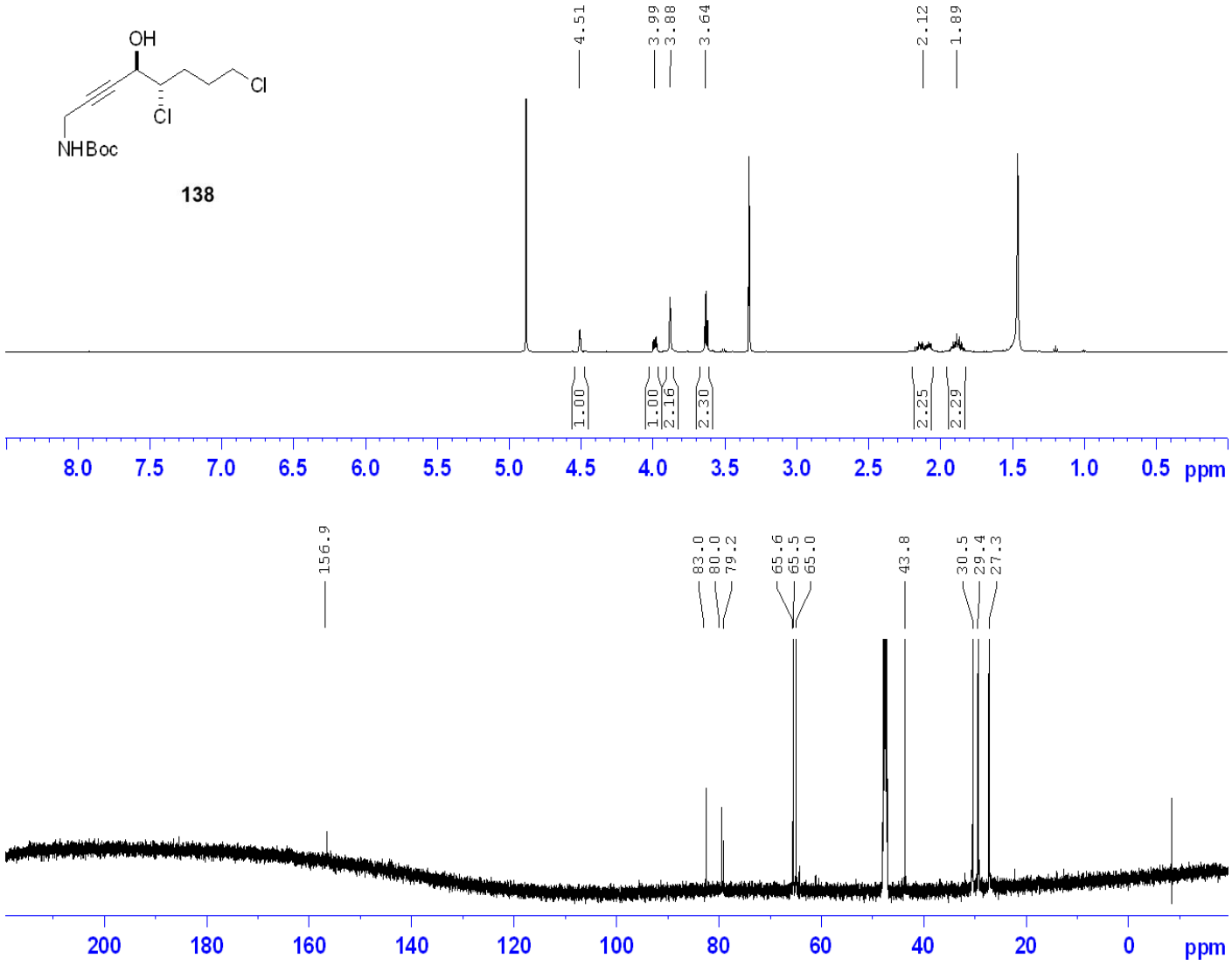
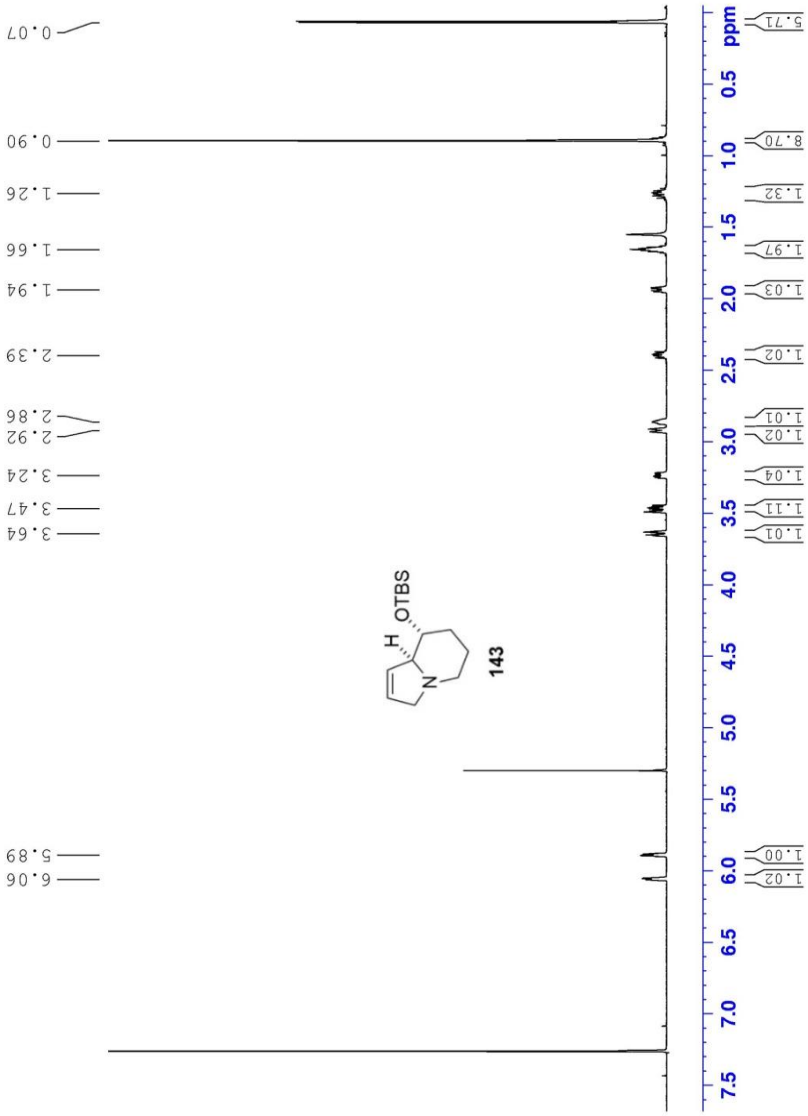
1.97
1.00
2.15
1.02
3.35
1.12
136


OH
Cl
Cl
NHBoc
138
4.51
3.99
3.88
3.64
2.12
1.89
1.00
1.00
2.16
2.30
2.25
2.29
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
156.9
83.0
80.0
79.2
65.6
65.5
65.0
43.8
30.5
29.4
27.3
200
180
160
140
120
100
80
60
40
20
0
ppm

6.14
5.94
3.66
3.64
3.48
3.27
2.95
2.86
2.43
2.06
1.69
1.52
1.24
1.00
1.01
1.06
1.16
1.06
1.06
1.02
1.06
1.04
1.10
2.11
0.95
1.15
p
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
OH
H
N

142


OTBS
H
N
143
ppm