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Synthesis of Cylindricine C and its Stereoisomers

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Synthesis of Cylindricine C and its Stereoisomers

by

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Abstract

Cylindricine alkaloids are unique in their structural makeup due to the unusual tricyclic pyrrolo[2,1-*j*]quinoline framework having a cis-fused azadecalin skeleton. Novel approaches to synthesising these complex molecules are useful due to the difficulty in isolating these compounds from natural sources.

Acetylenic sulfones have been used by our group in the synthesis of numerous nitrogen-containing heterocycles. We have applied our acetylenic sulfone methodology to the synthesis of 2,13-di-e*pi*-cylindricine C and cylindricine C by employing a tandem conjugate addition and intramolecular cyclisation of a key intermediate β-amino ester. Key steps in our synthesis involve a Curtius rearrangement to install the nitrogen at the quaternary center and an electrophilic cyclisation to construct the tricyclic core. Desulfonylation and reduction of the resulting enaminone double bond moiety yielded 2,13-di-e*pi*-Cylindricine C and Cylindricine C in a diastereomeric ratio of 3:1. A route amenable to an enantioselective approach was also achieved.

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Finally, I would like to acknowledge the University of Calgary, NSERC and the Queen Elizabeth II Scholarship for their financial support.

Dedication

For my Dad.

My wife Shana.

And my princess Kayla.

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List of Symbols, Abbreviations and Nomenclature

Å	Ångstroms
Δ	heat
°C	degrees Celsius
^{13}C NMR	carbon-13 nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azobisisobutyronitrile
Anal.	elemental analysis
aq	aqueous
calc'd	calculated
CM	complex mixture
cm^{-1}	wavenumbers
COSY	^{1}H-^{1}H correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets

ddt	doublet of doublet of triplets
dr	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dt	doublet of triplets
E^+	electrophile
ee	enantiomeric excess
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
h	hours
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	Hertz, sec^{-1}

hν	light
*i*Pr	isopropyl
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
K	Kelvin
KOTMS	Potassium trimthylsilanolate
L	litre
LDA	lithium diisopropylamide
m	multiplet
M	molar
m/z	mass to charge ratio
M+	molecular ion
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
mg	milligrams
MHz	megahertz
mL	millilitres
mol	moles
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry

n	normal chain
NaOTMS	Sodium trimthylsilanolate
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NOESY	Nuclear Overhauser effect spectroscopy
Nu^-	nucleophile
o	ortho
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program
p	para
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
py	pyridine
q	quartet
R	generalized substituent
rt	room temperature
s	singlet
SM	starting material
t	tertiary
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl

TBS	*t*-butyldimethylsilyl
Teoc	2-trimethylsilylethyloxycarbonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl

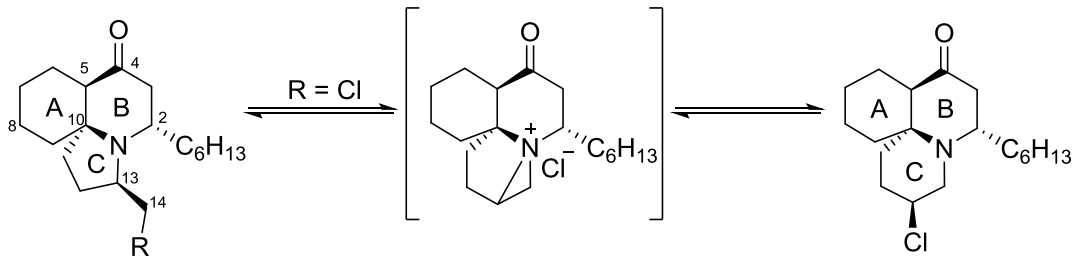
Chapter One: Introduction

1.1 Cylindricine C

1.1.1 ***Background***

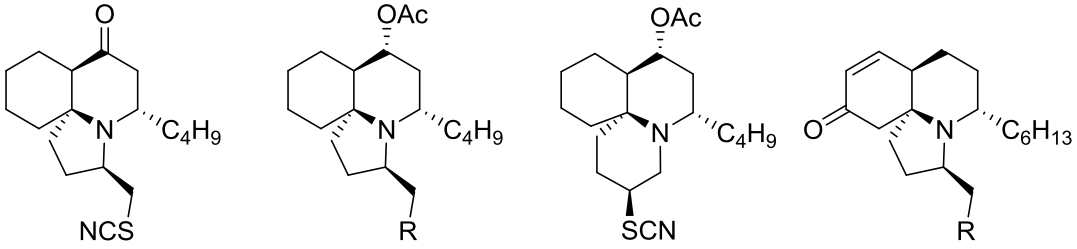
The cylindricine alkaloids are a family of compounds that were isolated from the ascidian (sea squirt) *Clavelina cylindrica* off the coast of Tasmania by Blackman and coworkers in the early 1990s.[(1)] Cylindricine A (**1**) and cylindricine B (**2**) were the major structures isolated, having a unique tricyclic pyrrolo[2,1-*j*]quinoline framework and a C-ring expanded pyrido[2,1-*j*]quinoline respectively. The common numbering, arbitrarily assigned by Blackman,[(1)] is seen in Scheme 1 and will be referred to accordingly.

Scheme 1



R = Cl, Cylindricine A (**1**)
R = OH, Cylindricine C (**3**)
R = OMe, Cylindricine D(**4**)
R = OAc, Cylindricine E(**5**)
R = SCN, Cylindricine F(**6**)

Cylindricine B (**2**)



Cylindricine G (**7**)

R =SCN, Cylindricine H (**8**)
R = NCS, Cylindricine I (**9**)

Cylindricine J (**10**)

Cylindricine K (**11**)

These two compounds were found to be in an equilibrium ratio of 3:2 when pure samples of each were left to equilibrate for 6 days, which led researchers to believe they interconvert via the corresponding aziridinium ion intermediate (Scheme 1).

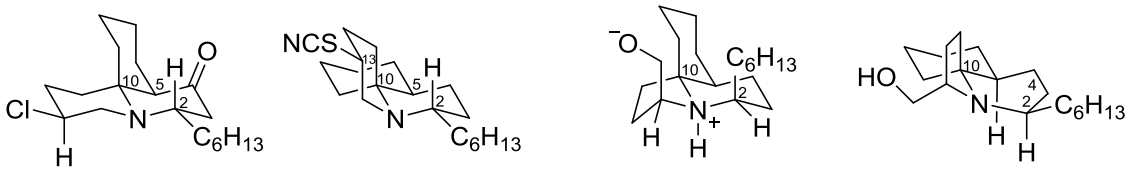
During isolation, a number of minor compounds were found to be structurally related to **1**. These have cis-fused azadecalin skeletons differing only in the substituent on C-14, namely hydroxyl, methoxy and acetoxy groups for cylindricines C, D and E, respectively.[2] Other related compounds include thiocyanates **6** and **7**,[2] and acetoxycylindricines **8**, **9** and **10** having *n*-butyl chains as opposed to *n*-hexyl chains protruding from C-2 of the molecule. The final compound, cylindricine K (**11**), has an α,β unsaturated ketone with the carbonyl group on C-8 as opposed to C-4, concluding a total of eleven characterised structures belonging to the cylindricine family.[3]

Interestingly, Blackman and coworkers undertook a study to see if any variability existed between cylindricine alkaloids and geographic locations around the east coast of Tasmania.[3] They found that cylindricines A and B were often the major alkaloids present except for locations where cylindricine H and K were isolated. In the case where cylindricine H was found to be the major product, trace alkaloids included cylindricine F, G, I and J, whereas cylindricines A and B were not detected. In locations where cylindricine K was present, only trace amounts of cylindricine A and B were isolated, and cylindricine K was obtained as the major alkaloid. To our knowledge, no investigation into why these metabolites vary so significantly across such a small geographical area has been reported, nor is it understood how they are biosynthesised. Unfortunately, the absolute configurations were not determined during the structural studies and, as no

optical rotations could be obtained for the natural enantiomer, comparison with enantiopure synthetic products cannot be made.

Fasicularin (**12**), an alkaloid closely related to cylindricine B bearing the pyridoquinoline structure (Figure 1), was isolated in 1997 from the Micronesian ascidian *Nephteis fasicularis* by Patil and coworkers at SmithKline Beecham Pharmaceuticals.[4]

Figure 1: Structurally related alkaloids



cylindricine B **2** fasicularin **12** lepadiformine A **13a** lepadiformine A **13b**

The only differences between cylindricine B and fasicularin are the *trans*-1-azadecalin A/B-rings (Figure 1), making it epimeric at C-10, a fully reduced carbon at C-4 and a thiocyanate group at C-13. Again, no optical rotation was measured and therefore enantiopure synthetic material cannot be compared for absolute configuration. A third alkaloid related to this family of compounds is lepadiformine **13b**, which was first isolated by Baird and coworkers in 1994 from the HCl extraction of a dichloromethane-soluble extract from the tunicate *Clavelina lepadiformis* (Müller) isolated off the coast of Tunisia, as well as from *Clavelina moluccensis* (Sluiter)[5-6] isolated off the coast of Djibouti. The structure was originally believed to be the tricyclic structure **13a** shown in Figure 1 containing the unusual zwitterionic amino alcohol moiety. However, a synthesis by Weinreb[7] in 1999 brought the assigned structure into question as the synthetic

material did not match the natural product. A synthesis by Kibayashi[8] finally corrected the structure as **13b**, showing the B-ring to be in a boat conformation and proving that the structure was not the orignially proposed zwitterion form. This was followed by a number of total syntheses including the enantioselective synthesis of (-)-lepadiformine by Weinreb,[9] Hsung[10] and Kim,[11] who independently confirmed the correct structure.

With the structure of lepadiformine confirmed, it is now believed that the structure of cylindricines with the pyrrolo[2,1-*j*]quinoline framework are antipodal to that of lepadiformine. Therefore, by comparison and reasonable assumption, researchers believe the natural enantiomer to be (-)-cylindricine; however, re-isolation of the natural product in greater amount is the only way to confirm the absolute configuration.

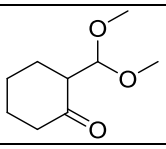
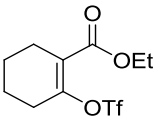
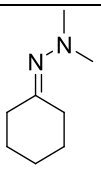
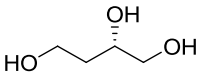
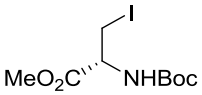
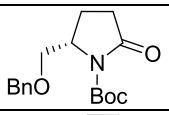
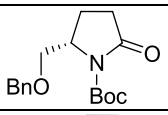
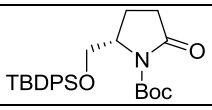
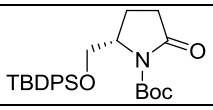
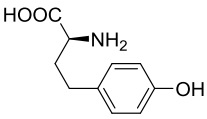
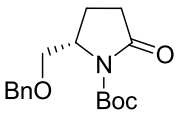
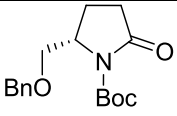
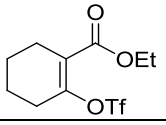
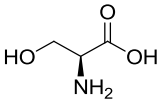
1.1.2 ***Biological activity***

The only biological activity reported for the cylindricine family was toxicity in a brine shrimp assay tested on a mixture of cylindricine A and B.[1] The biological activity of the closely related structure fasicularin **12** showed that this compound displayed protection in a yeast-based DNA damaging assay and that it is cytotoxic against Vero cells with an IC_{50} of 14μg/ml.[4] Additionally, cytotoxicity observed *in vitro* on nasopharynx carcinoma (KB) and non-small-cell lung carcinoma (NSCLC-N6) for lepadiformine[5] led to further biological testing by Petit and coworkers due to possible *in vivo* effects. They found that lepadiformine was active on cardiovascular systems by initiating a blockade of inward rectifying K^+ current (I_{KI}), which determines in part membrane potential and diameter of vascular smooth muscles. This discovery suggests that it may have antiarrhythmic properties.[6]

1.2 Total syntheses of Cylindricine C

Since isolation of the cylindricine alkaloids, a number of racemic and enantioselective syntheses have been accomplished. A review published by Weinreb[12] in 2006 gave a comprehensive summary of the synthetic efforts made by various groups. For comparison, Table 1 gives a summary of the syntheses contained in this review for both racemic and asymmetric syntheses, highlighting the key steps for construction of the rings making up the tricyclic core. Since the Weinreb review, only one asymmetric synthesis and three racemic total synthesis of cylindricine C have been reported which will be reviewed individually.

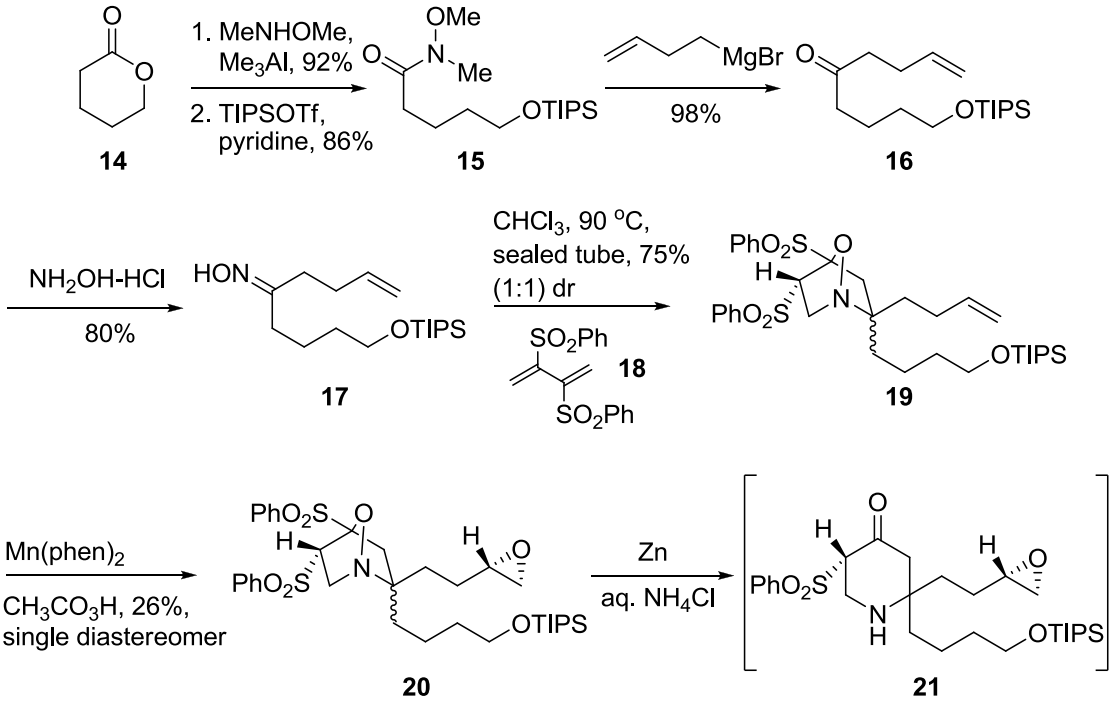
Table 1: Summary of Cylindricine Total Syntheses from Weinreb[12] Review

Authors (Year)	Molecule	A-ring source	B-ring	C-ring source	Source of asymmetry	Number of Steps (Yield)
Snider (1997)[13]	(±)-cylindricine A, D, E		double Michael addition	Copper catalysed radical cyclisation	N/A	7 steps (13% overall)
Heathcock (1999)[14]	(±)-cylindricine A		double Michael addition	Copper catalysed radical cyclisation	N/A	11 steps (19% overall)
Molander (1999)[15]	(-)-cylindricine C		double Michael addition	double Michael addition		11 steps (12% overall)
Trost (2003)[16]	(+)-cylindricine C, D, E	Ruthenium-catalysed hydrative diyne cyclization	double Michael addition	double Michael addition		12 steps (16% linear sequence)
Kibayashi (2004)[17]	(+)-cylindricine C	Enamine cyclisation	Michael addition			19 steps (3% overall)
Hsung (2004)[10]	(+)-cylindricine C	*aza*-Prins cyclisation	Michael addition			9 steps (11% overall)
Ciufolini (2004)[18]	(-)-cylindricine C	Regioselective 1,4 addition, desulfurisation	Reductive amination	Oxidative spirocylisation		14 steps (23% overall)
Kibayashi (2005)[19]	(+)-cylindricine C	*aza*-spiro cyclisation	S_N2 displacement			12 steps (12% overall)
Hsung (2006)[20]	(-)-cylindricine C		*aza*-[3,3] cycloaddition	*aza*-[3,3] cycloaddition		22 steps (4.5% overall)

1.2.1 ***Padwa Synthesis of (±)-Cylindricine C***

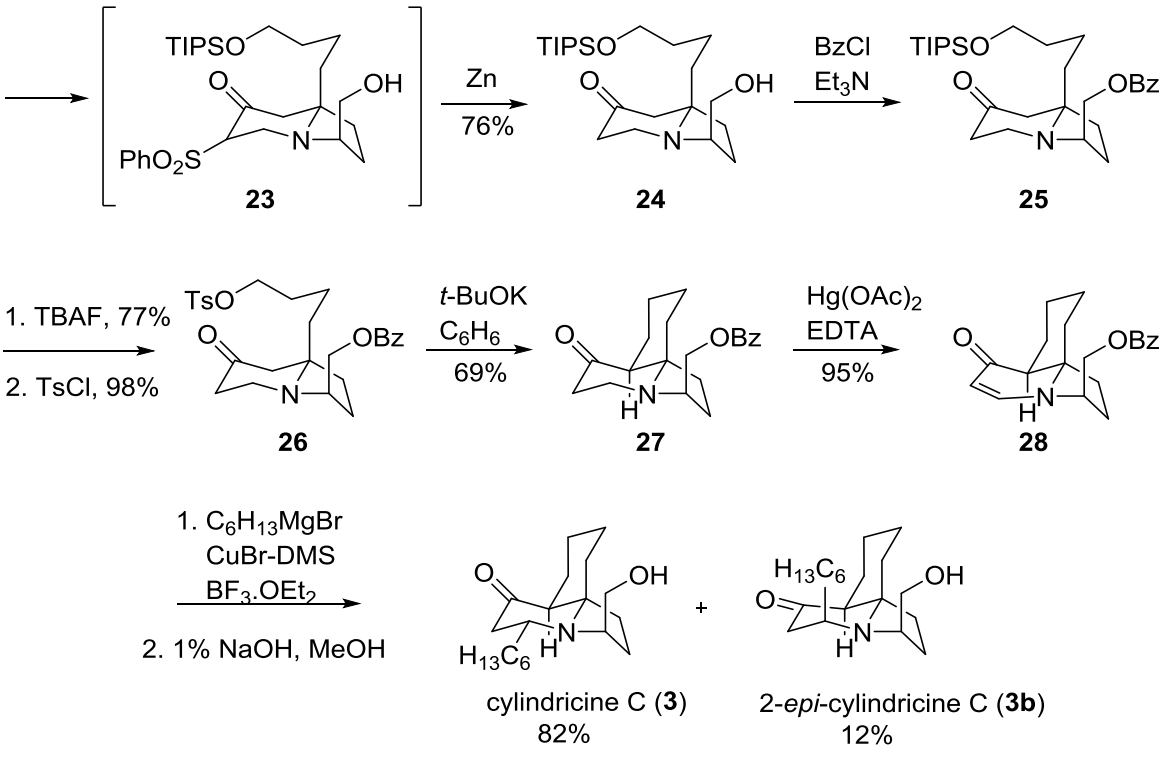
In 2008, Padwa and coworkers first reported a stereocontrolled synthesis based on a conjugate addition and dipolar-cycloaddition cascade developed in their group.[21-23] The synthesis (Scheme 2) commences with the opening of δ-valerolactone as the Weinreb amide followed by TIPS protection of the primary alcohol to give **15**. Alkylation of **15** by Grignard addition yielded keto-olefin **16**, which was then converted to the corresponding oxime **17** by condensation with hydroxylamine hydrochloride. A cascade sequence by conjugate addition of oxime **17** with the diene **18** gave a transient nitrone that underwent a 1,3-dipolar cycloaddition onto the adjacent vinyl sulfone to form the aza-oxanorbornane **19** as an equal mixture of diastereomers in 75% yield.

Scheme 2



Epoxidation of the terminal olefin using Stack conditions[24] yielded **20** as a single diastereomer, albeit in only 26% isolated yield. Reductive cyclisation to form the C-ring was achieved by stirring **20** with excess zinc dust in the presence of aqueous ammonium chloride and THF, resulting in cleavage of the N-O bond and forming the ketone intermediate **21**. Spontaneous desulfonylation and attack of the free amine on the epoxide via a 5-exo-tet cyclisation set up the indolizidine ring system of **24** as a 9:1 mixture of diastereomers, with the major product bearing the hydroxymethyl group in the correct configuration (Scheme 3). Benzoylation of the primary alcohol, desilylation of the TIPS group followed by tosylation of the free hydroxyl group afforded **26**.

Scheme 3



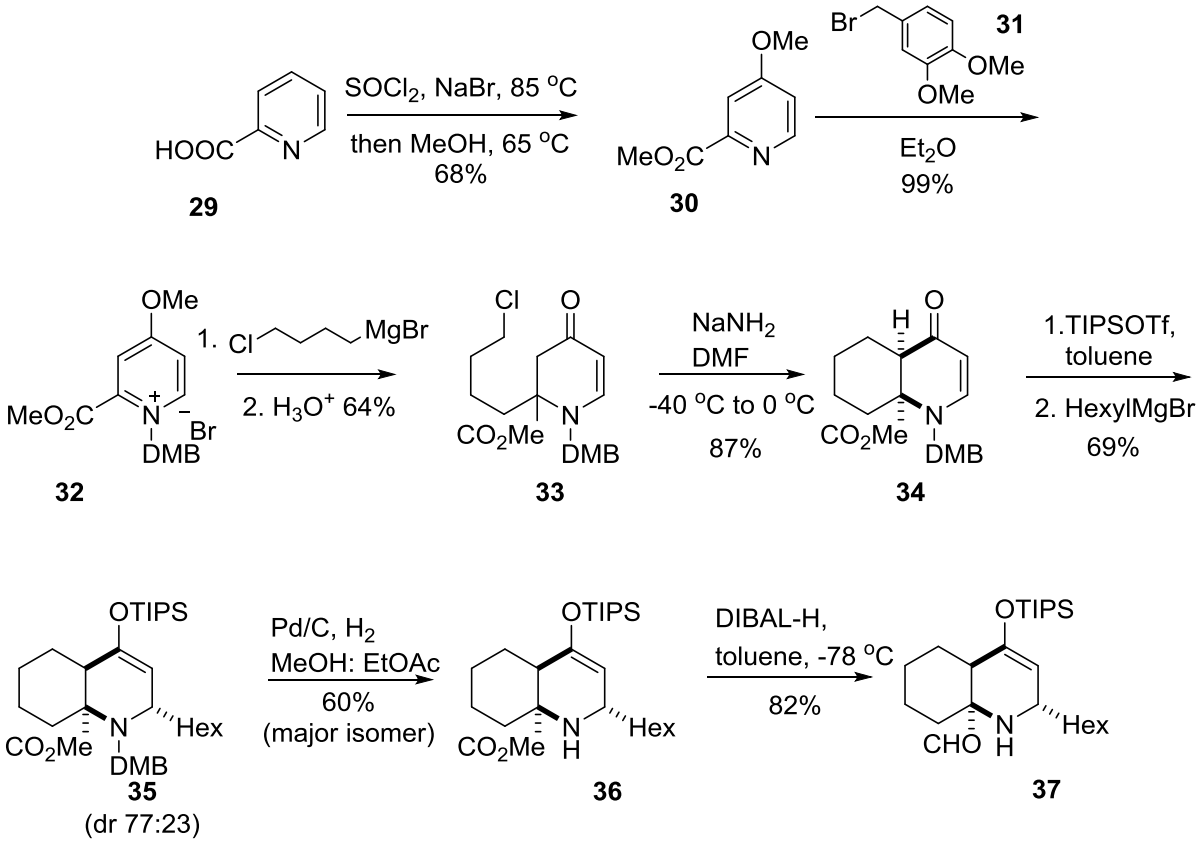
Formation of the A-ring was achieved via intramolecular enolate alkylation to form **27**, which was followed by mercury acetate oxidation to afford enaminone **28**. Finally, copper assisted conjugate addition of the *n*-hexyl group followed by base cleavage of the benzoyl group yielded (±)-cylindricine (**3**) as the major product. The synthesis was completed in 14 linear steps with an overall yield of 3.7%. One notable limitation of Padwa's route was the formation of the epoxide in a disappointing yield of 26%. Two significant successes include the formation of the B-ring via the conjugate addition and dipolar-cycloaddition cascade, as well as the A-ring via the intramolecular enolate cyclisation. The use of sulfone chemistry in the synthesis is well demonstrated and sets high expectations for the sulfone chemistry developed and applied in our own work.

1.2.2 ***Donohoe Synthesis of (±)-Cylindricine C***

The synthesis published in 2010 by Donohoe and coworkers makes use of methodology developed by that group, namely regioselective alkyl Grignard addition to an *ipso* C-2 substituted pyridinium salt to form the dihydropyridone core of the A/B rings.[25] The synthesis shown in Scheme 4 commences with a one pot preparation of **30** from the commercially available picolinic acid **29** followed by formation of the pyridinium salt **32** using 4-(bromomethyl)-1,2-dimethoxybenzene (DMB). Regioselective Grignard addition to the C-2 position generated the fully substituted center on enaminone **33** after acidic workup, which was followed by base induced cyclisation to give **34**, thus setting up the *cis*-fused A/B rings.

Silyl triflate activation of the ketone, followed by an alkylation gave **35** in 69% yield as a 77:23 ratio favouring the desired diastereomer. Cleavage of the DMB group by hydrogenolysis followed by DIBAL-H reduction gave the aldehyde **37**.

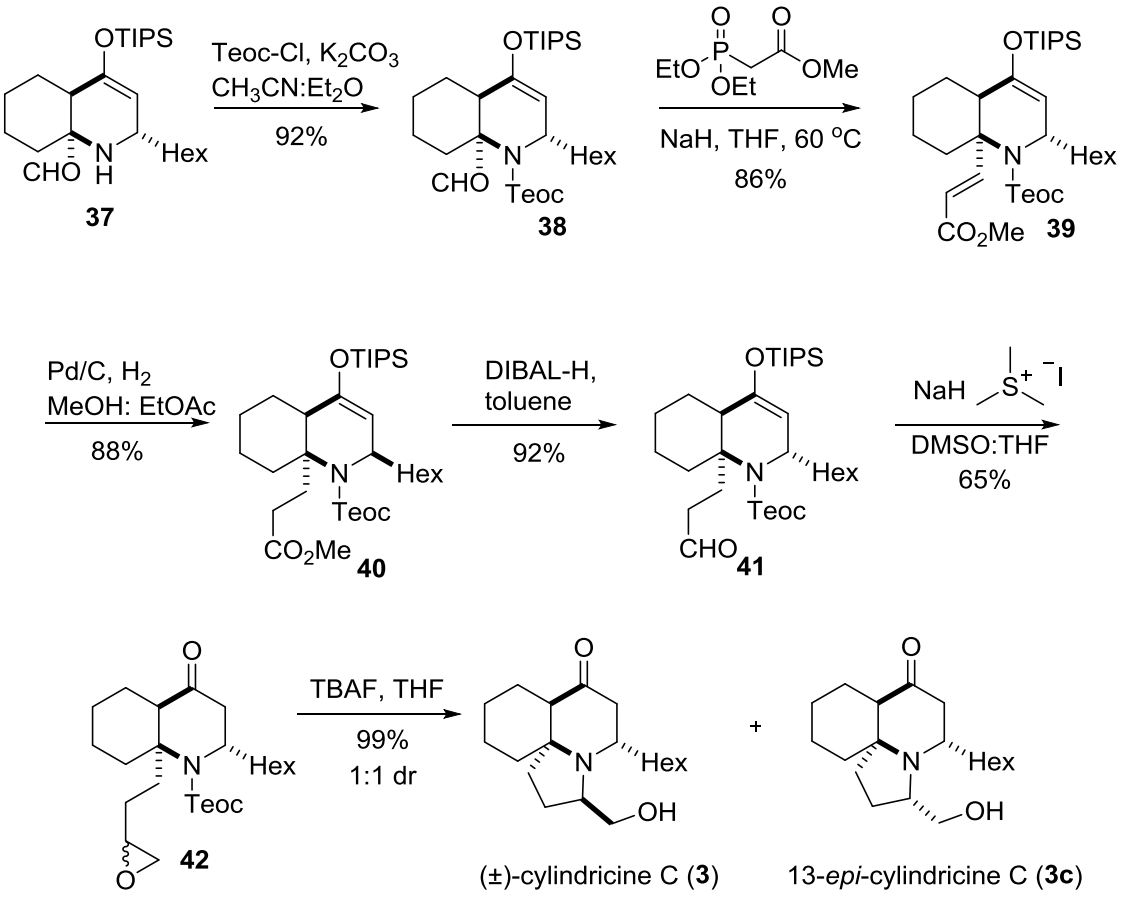
Scheme 4



An important note made by the authors was that protection of the free nitrogen as **38** using 2-trimethylsilylethoxycarbonyl chloride (Teoc-Cl) was essential for completion of the synthesis (Scheme 5). This allowed for homologation of **38** under Horner-Wadsworth-Emmons conditions to give olefin **39**, which could be reduced to aldehyde **41** via intermediary compound **40** in good yield. Epoxide **42** was obtained using the Corey-

Chaykovsky reagent[26] as a 1:1 mixture of diastereomers. Under these conditions, the TIPS group was removed, but surprisingly left the Teoc moiety intact. Removal of Teoc was achieved under TBAF conditions to reveal the nucleophilic nitrogen. This allowed for spontaneous cyclisation of the C-ring by epoxide opening to give a 1:1 mixture of the desired product as well as 13-*epi*-cylindricine C **3c**. The total synthesis was achieved in 13 steps and 3% overall yield. The methodology of regioselective attack of Grignard reagents on substituted pyridinium salts proved to be useful in overcoming the major synthetic challenge of setting up the aza-spirocenter.

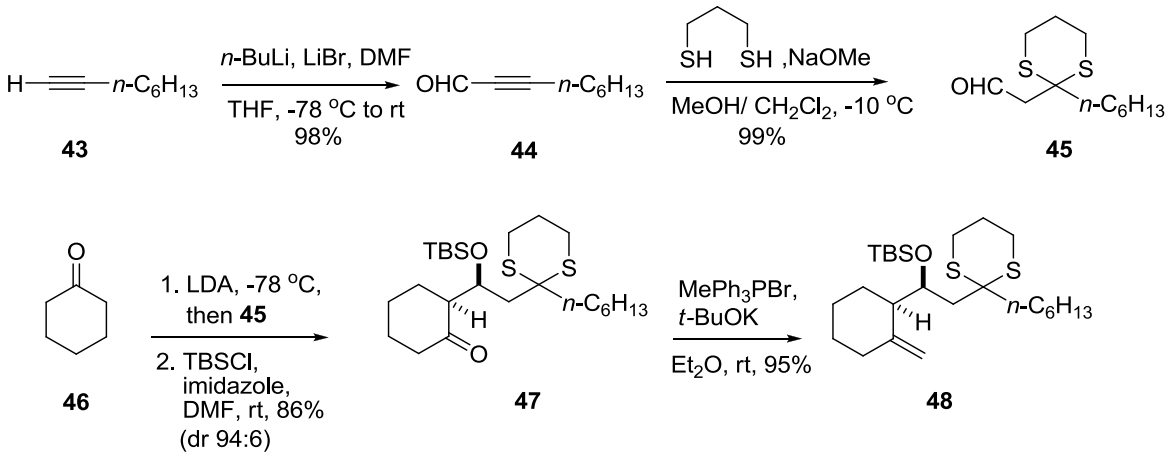
Scheme 5



1.2.3 ***Renaud Synthesis of (±)-Cylindricine***

The strategy used by the Renaud group was to install the aza-spirocenter on the A-ring via radical carboazidation[27] using an α-iodoketone. Preparation of key intermediate **49** commenced with the synthesis of aldehyde **44** by addition of 1-octynyl-lithium to DMF followed by double conjugate addition of 1,3-propanedithiol to give **45** in near quantitative yield. The aldol reaction between the enolate of **46** and aldehyde **45**, followed by silyl protection gave ketone **47** in the ratio of 94:6 in favour of the *anti*-product shown in Scheme 6.

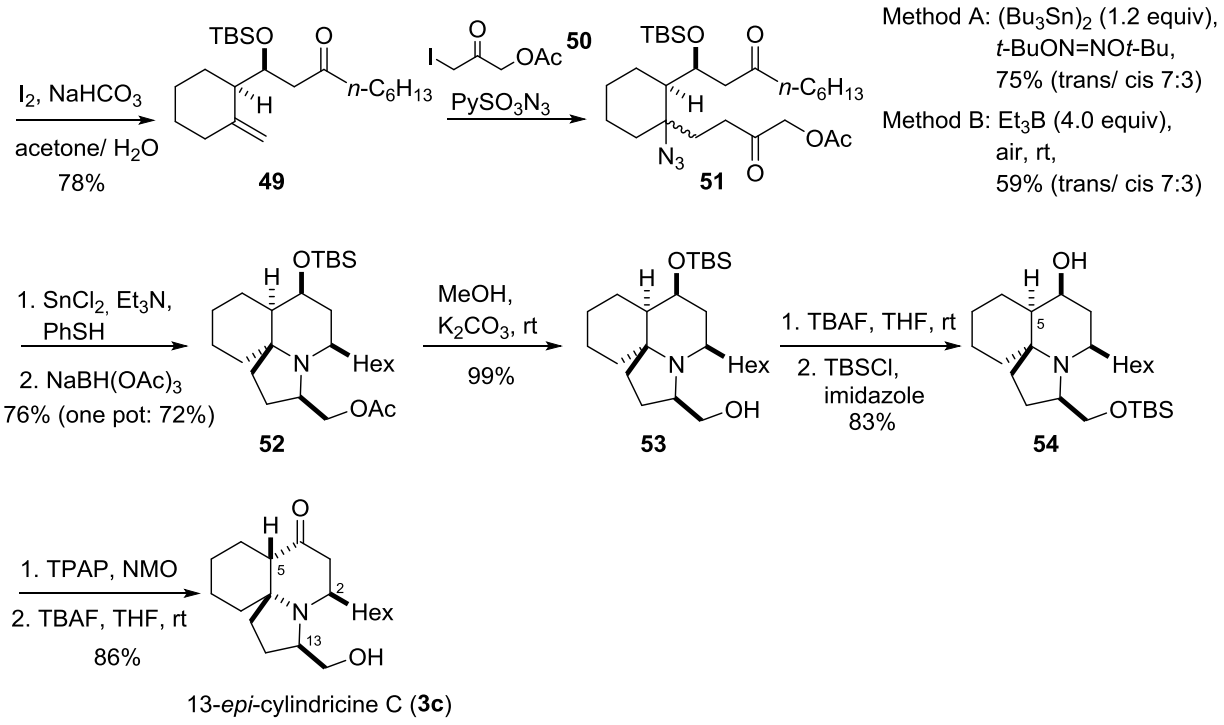
Scheme 6



The ketone was then converted to the exocyclic olefin by Wittig olefination to give **48** and removal of the dithiane by iodine-based oxidation yielded **49** (Scheme 7). With this key intermediate in hand, the carboazidation reaction between **49** and α-iodoketone **50** took place in 75% yield when using hexabutyl-distannane as a radical source. Lower yields were observed when using triethylborane and oxygen. In both cases a ratio of 7:3 was obtained in favour of the desired *trans*-azide **51**. The *trans/cis*

diastereomers were separated and the synthesis was continued with the *trans* isomer of azide **51**. Stannous chloride reduction to the corresponding amine followed by a *bis*-reductive amination using sodium triacetoxyborohydride yielded **52** in a 76% yield from the azide. Unfortunately the X-ray crystal structure of **52** established that the relative configurations of C-5 and C-13 differed to that found in the natural product.

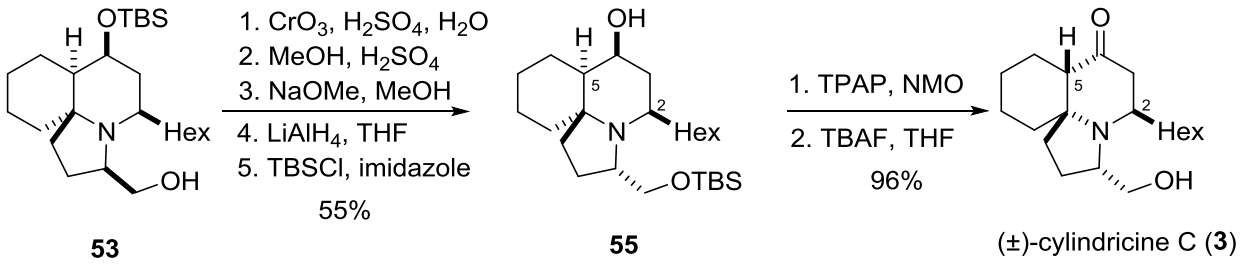
Scheme 7



However, this allowed for the synthesis of 13-*epi*-cylindricine C (**3c**) after a number of steps. These include methanolysis of the acetate, TBAF removal of the silyl group, followed by silylation of the primary alcohol to give **54**. Finally, oxidation of the secondary alcohol using TPAP followed by TBAF deprotection gave the C-13 epimer of

the natural product. The authors noted that during the oxidation, epimerisation of C-5 occurred as expected, as evidenced by the absence of a NOESY correlation in its NMR spectrum, between the C-2 and C-5 hydrogen atoms. The natural product was synthesised from **53** (Scheme 8), via oxidation of the primary alcohol to the carboxylic acid followed by esterification to give the methyl ester. This was then epimerised at C-13[28] using sodium methoxide in methanol followed by reduction to the primary alcohol and silyl protection to give **55** in 55% yield over five steps. As observed before, TPAP-oxidation of the secondary alcohol resulted in epimerisation at C-5 and finally TBAF deprotection gave the desired product.

Scheme 8



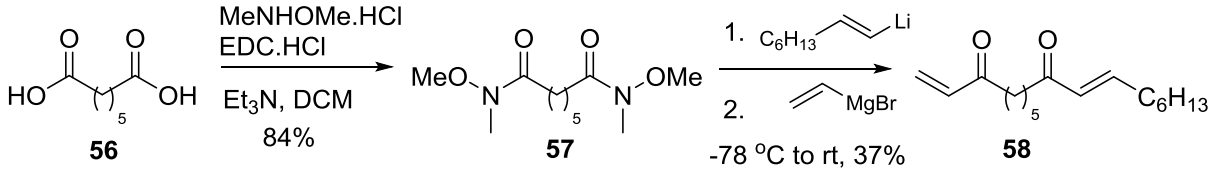
53 **55** (±)-cylindricine C (**3**)

The synthesis was completed in 17 steps with 11% overall yield. Unfortunately two epimerisation steps were required to afford the natural product, which was overcome quite easily by a simple oxidation step and base-induced epimerisation. The major achievements were the setting up of the aza-spirocenter via a carboazidation reaction with 70% diasteroselectivity, followed by two reductive amination cyclisation steps affording both B and C rings in a one pot procedure.

1.2.4 ***Shibasaki Synthesis of (+)-Cylindricine***

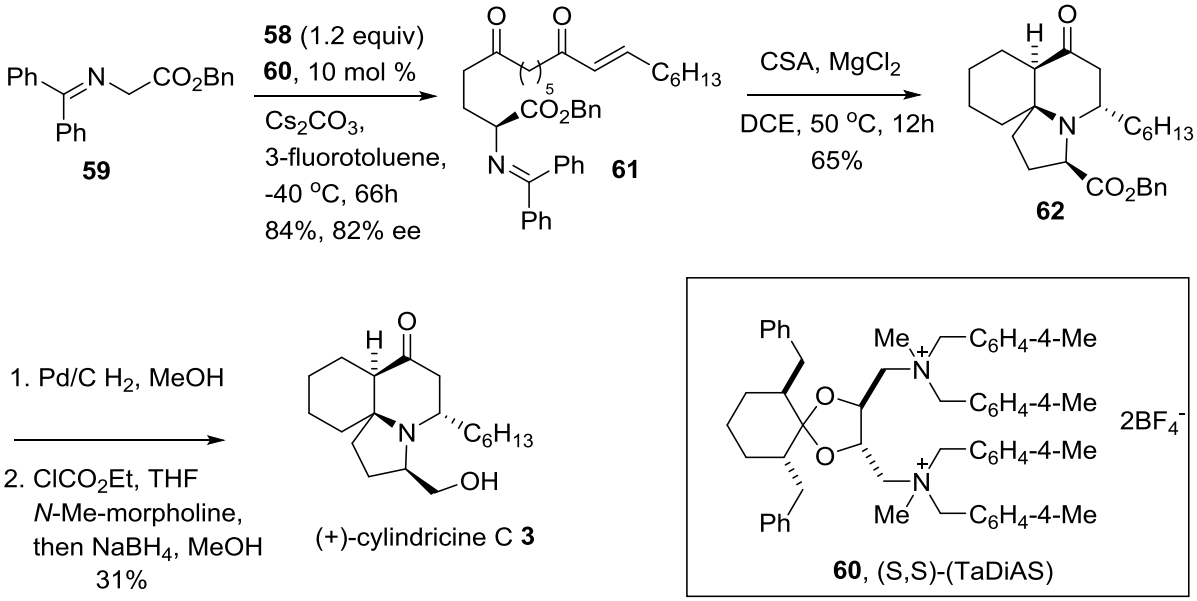
The only enantioselective synthesis since the 2006 review by Weinreb was completed by the Shibasaki group later that same year, in an astonishing 6 steps.[29] The synthesis commenced with the preparation of diketone **58** in two steps from pimelic acid **56** (Scheme 9). A catalytic asymmetric Michael addition between diketone **58** and Schiff base **59**, prepared according to O'Donnell,[30] took place using the organocatalyst (S,S)-TaDiAS **60** (tartrate derived diammonium salt) to give **61** in 84% yield and 82% ee. These results were obtained when **58** and **60** were reacted with stoichiometric amounts of cesium carbonate in 3-fluorotoluene at -40 ^{o}C (Scheme 10).

Scheme 9



The tandem cyclisation was achieved using camphorsulfonic acid (CSA) in 1,2-dichlorethane to give **62** in 65% yield and a diasteriomeric ratio of 84:9:7 favouring the desired product. The reactivity of the tandem cyclisation increased and selectivity of the desired isomer ratio was improved most by addition of $MgCl_2$. The authors suggested the various additives tested were behaving as Lewis acids, resulting in chelation and overall diastereocontrol. Deprotection of the benzyl group and formation of a mixed anhydride, followed by reduction of the resulting ester, formed the desired compound (+)-**3**.

Scheme 10



Although the asymmetric Michael addition to form **61** gave modest selectivity, the acid-induced cyclisation cascade to set up the tricyclic core, including three new stereocenters and the aza-spirocenter, was remarkable.

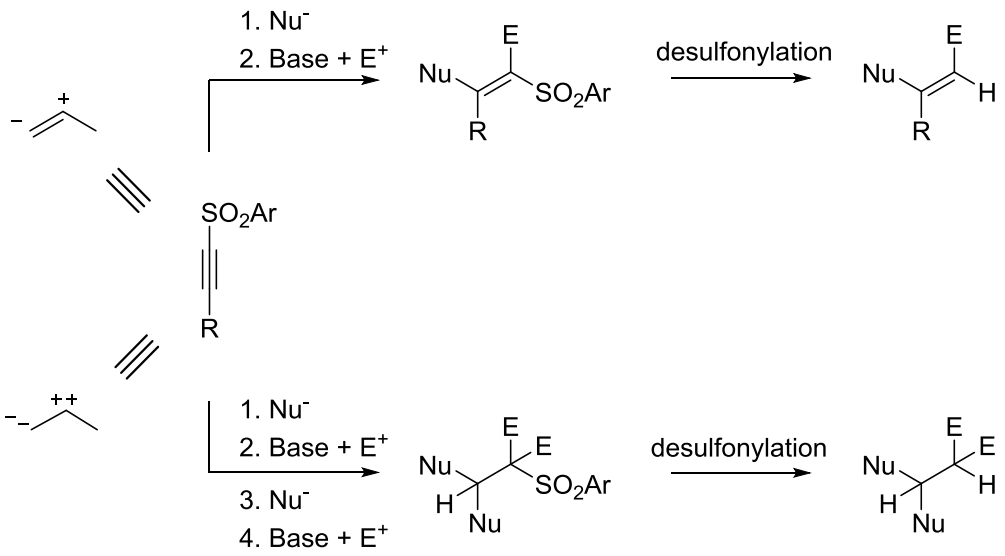
1.3 Acetylenic sulfones

1.3.1 ***Acetylenic Sulfones***

Our interest in cylindricine alkaloids was prompted by the previous synthesis of other alkaloids by our group via exploiting novel applications of sulfone chemistry. Sulfones display some unique properties which allow for a diverse range of applications in organic synthesis. There have been two reviews by our group covering the application of vinylic, allenic, acetylenic and other unsaturated sulfones.[31-32] The sulfone moiety serves as a good activating group of acetylenes due to its strong electron withdrawing

properties. The sulfone thus allows conjugate addition reactions to occur at the β position whilst having a stabilising effect on an α-sulfonyl carbanion, allowing for further reactions with various electrophiles (Scheme 11).

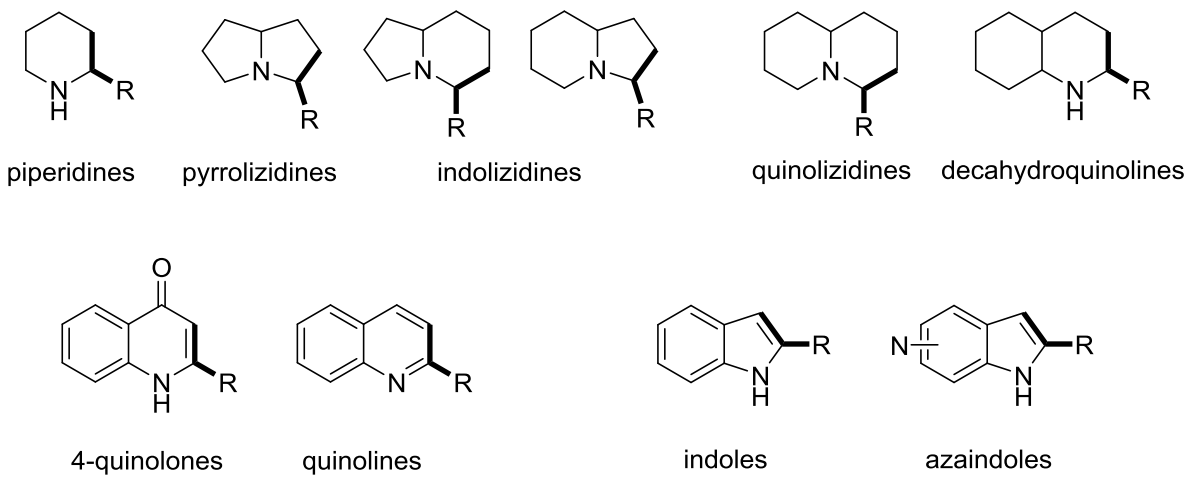
Scheme 11



Nucleophiles react by single addition to give vinyl sulfones or saturated sulfones after double conjugate additions. These in turn can be deprotonated to react with electrophiles via single or double reactions respectively. Removal of the sulfone moiety reductively, oxidatively, alkylatively or via elimination[33-34] allows it to function as a good removable activating group. The use of acetylenic sulfones to form heterocyclic compounds can therefore be achieved by a tandem conjugate addition and intramolecular alkylation or acylation, followed by removal of the sulfone moiety, making this methodology a powerful tool in alkaloid synthesis. This strategy has been employed by

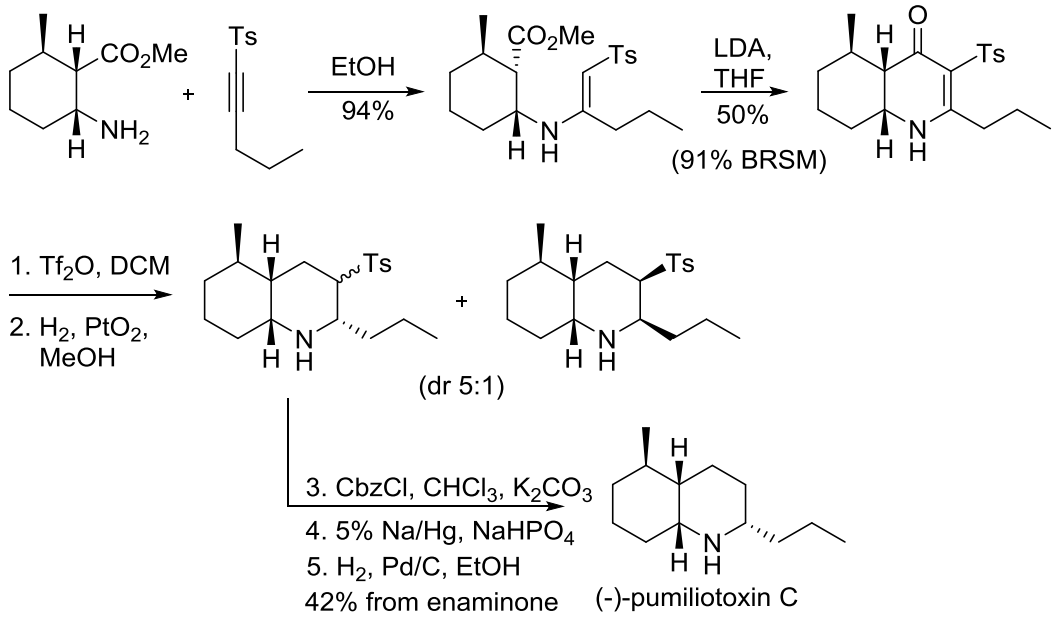
our group for the synthesis of various nitrogen containing heterocycles shown in Scheme 12, including piperidines, pyrrolizidines, indolizidines, quinolizidines[35-36] and decahydroquinolines[37] as well as aromatic heterocycles, namely 4-quinolones, quinolines,[38-39] indoles[40] and azaindoles.[41] The atoms and bonds shown in bold in scheme 12 indicate those originating from the acetylenic sulfone.

Scheme 12

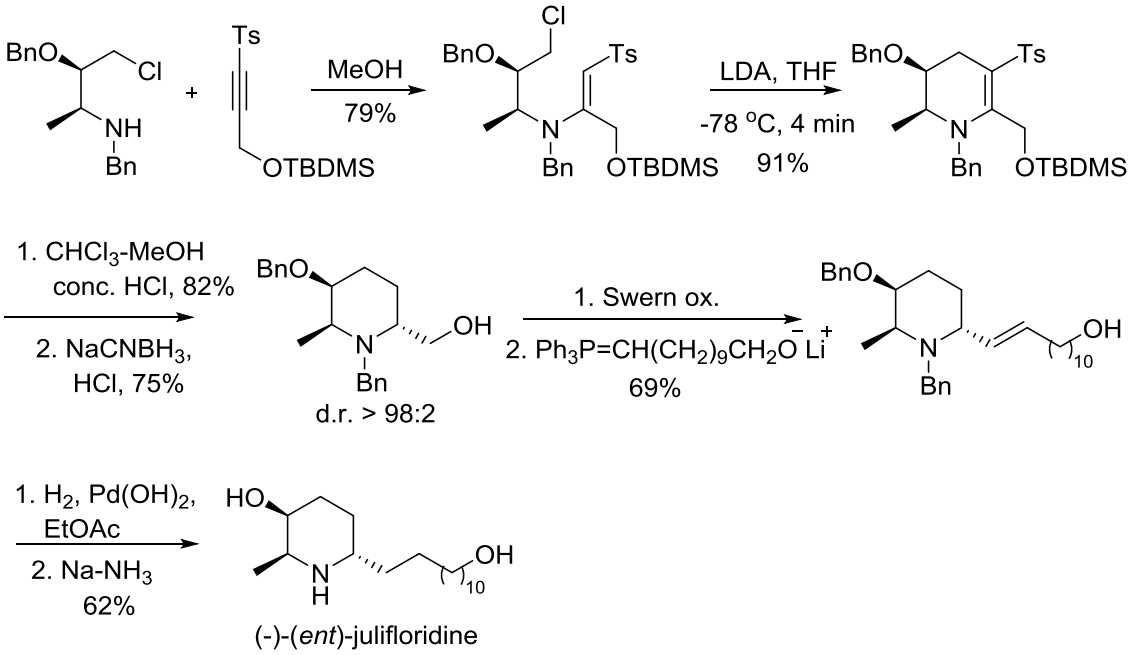


The total synthesis of various alkaloids has been achieved using this chemistry, such as the dendrobatid alkaloids (-)-pumiliotoxin C[37, 42] and (-)-indolizidines 167B, 209B, 209D and 207A.[35-36] Other alkaloids include (-)-lasubine II, (±)-myrtine[43] and (-)-(*ent*)-julifloridine.[44] The enantioselective synthesis of (-)-pumiliotoxin in Scheme 13 and (-)-(*ent*)-julifloridinein Scheme 14, highlight the usefulness of tandem conjugate addition and cyclisations of enantiopure amino esters and enantiopure γ-chloroamines with acetylenic sulfones.

Scheme 13



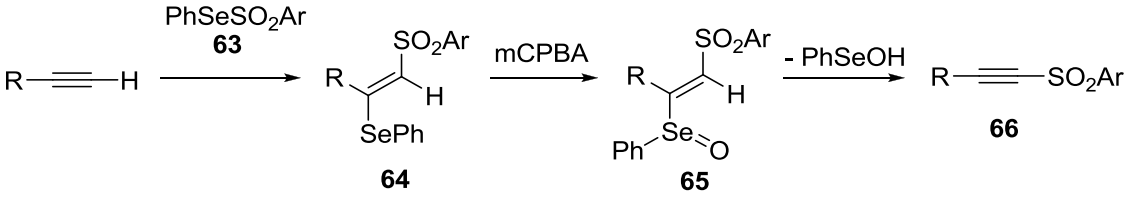
Scheme 14



1.3.2 ***Preparation of acetylenic sulfones***

The chemistry of acetylenic sulfones was reviewed by our group in 2001 and later in 2010 including various preparation methods.[31-32] The contribution to this field by our group[45-47] and independently by the group of Kobayashi,[48] involves a convenient preparation by thermally induced free radical 1,2 addition of **63** to terminal alkynes to produce β-(phenylseleno)vinyl sulfones **64**. This occurs with high regioselectivity favouring *anit*-Markovnikov addition as well as high stereoselectivity giving the *anti*-product. Oxidation of the selenide leads to selenoxide elimination due to the *syn* relationship of the selenoxide and the vinylic proton, yielding acetylenic sulfone **66** (Scheme 15).

Scheme 15



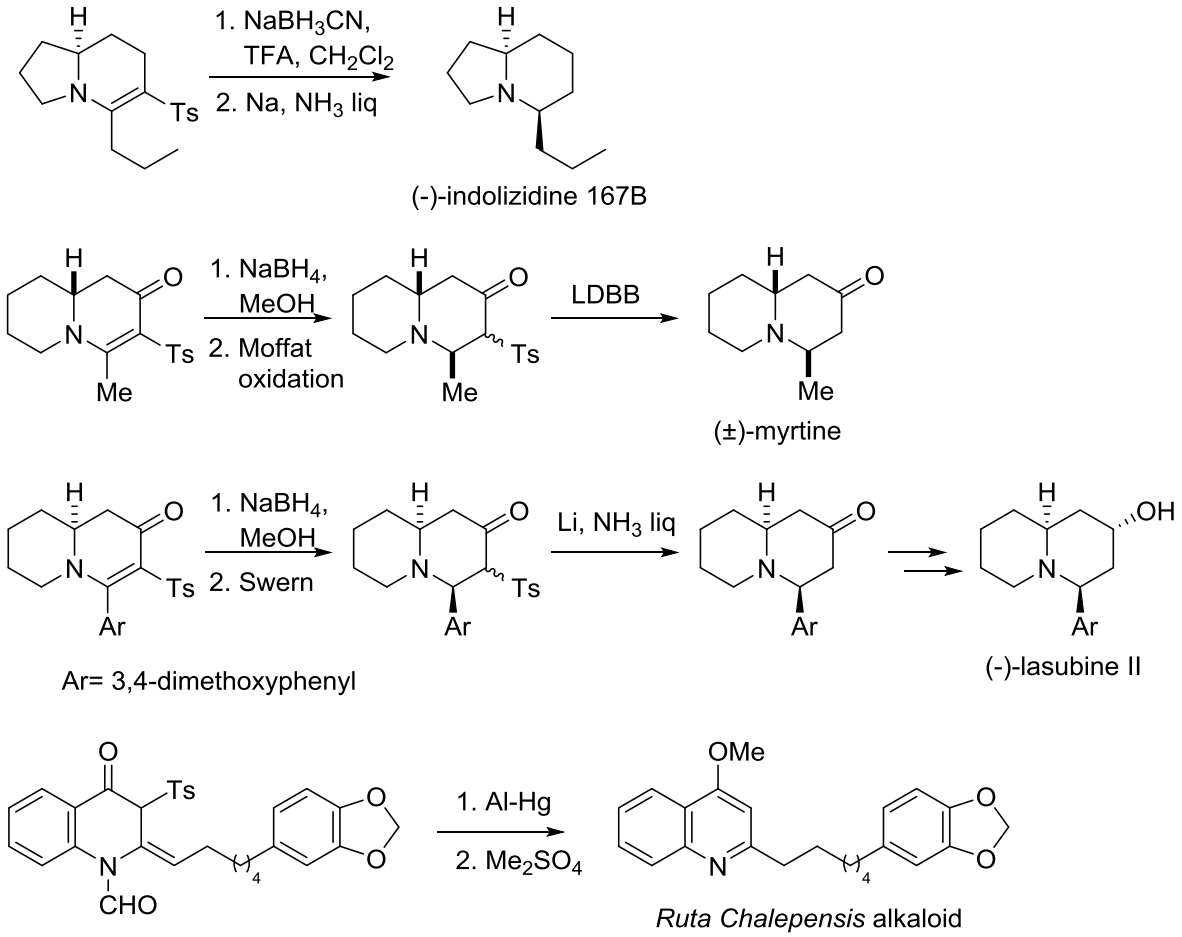
1.3.3 ***Removal of the sulfone moiety***

In order to ensure that the acetylenic sulfone conjugate addition and cyclisation methodology described in section 1.3.1 can be a useful tool for synthesising nitrogen-containing heterocycles such as the alkaloid natural products, selective removal of the sulfone moiety at the desired stage of the synthesis becomes important. Generally the sulfone moiety is removed once the chemical modifications to the remaining molecule have taken place. Desulfonylation reactions have been reviewed[33-34] and include an

oxidative process to produce a carbonyl functional group, alkylative methods resulting in carbon-carbon bond formations or via elimination to form vinyl sulfones if the β-carbon contains a leaving group. However, these methods generally have more specific applications and will not be further discussed. The more common method by reductive desulfonylation, where the sulfone group is substituted by hydrogen, is of interest here as it pertains to our synthesis and will be briefly reviewed.

The most common and general procedure for removal of a variety of sulfones was reported by Trost *et al.* using sodium amalgam (6%) dissolved in methanol, buffered by disodium hydrogen phosphate.[49] Dissolving metal reductions such as Birch reduction conditions[50] using sodium, lithium or potassium in liquid ammonia are also useful for this purpose; however, yields are often irreproducible and over-reduction of other functional groups can occur. Reaction conditions found to be milder than dissolving metal reductions are aluminium amalgam,[51] lithium naphthalenide,[52-53] or lithium 4,4'-di(tert-butyl)biphenylide (LDBB),[43] and work well for β-keto-sulfones. A number of alternative methods include magnesium in methanol, zinc-acetic acid, samarium diiodide, sodium dithionite in DMF or tributylstannane.[54-58] Illustrative desulfonylations which were successfully used by our group in a number of total syntheses are shown in Scheme 16.

Scheme 16

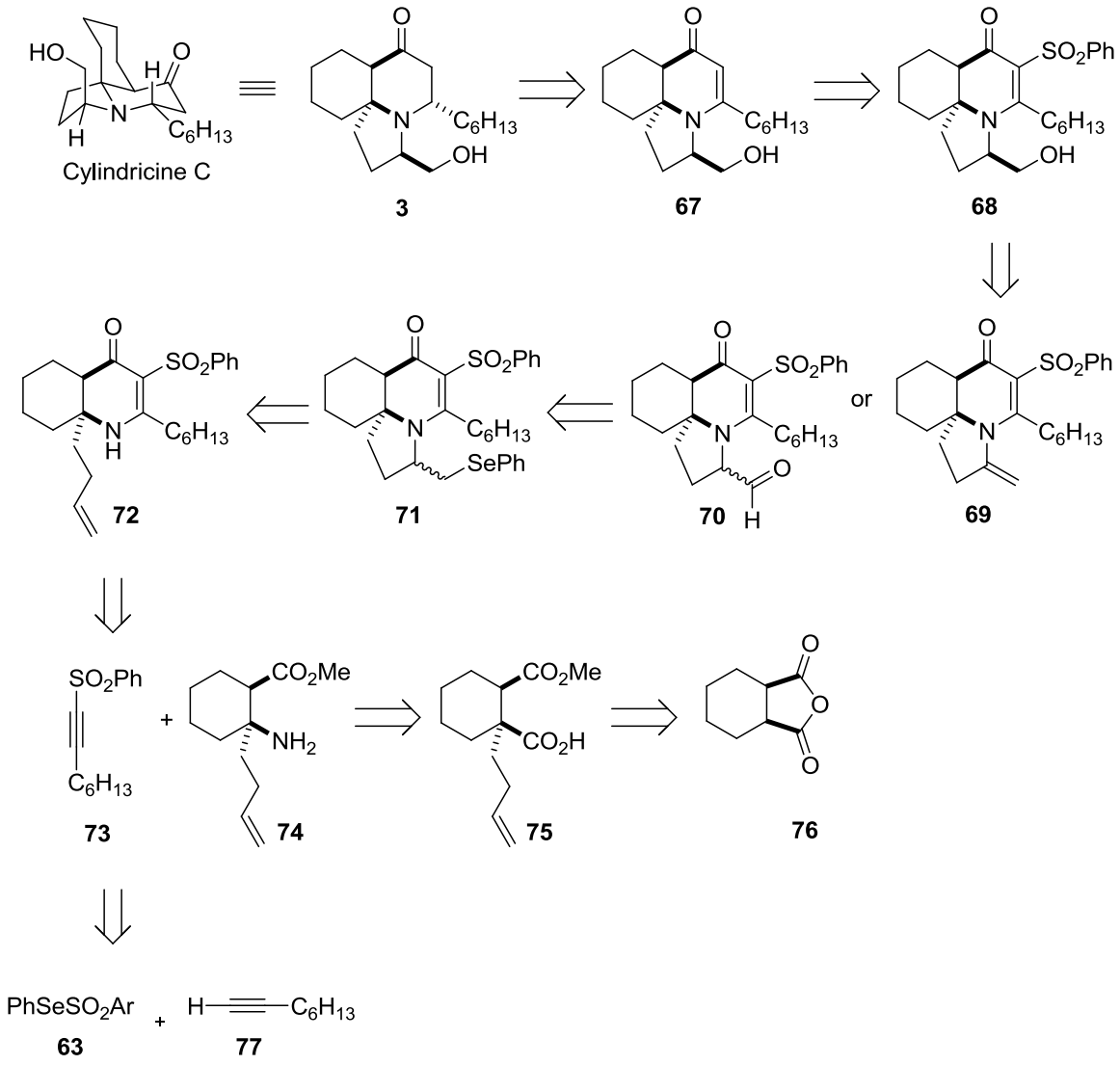

1. NaBH3CN,
TFA, CH2Cl2
2. Na, NH3 liq
(-)-indolizidine 167B
1. NaBH4,
MeOH
2. Moffat
oxidation
LDBB
(±)-myrtine
1. NaBH4,
MeOH
2. Swern
Li, NH3 liq
(-)-lasubine II
Ar= 3,4-dimethoxyphenyl
1. Al-Hg
2. Me2SO4
Ruta Chalepensis alkaloid

1.4 A new approach towards cylindricine alkaloids

1.4.1 ***Retrosynthesis***

Work towards the synthesis of cylindricine alkaloids was initiated by Dr. K. Clary in our group.[59] The retrosynthesis of cylindricine C is shown in Scheme 17 and involves the tandem conjugate addition and intramolecular cyclisation using acetylenic sulfone chemistry in the key step. The target compound **3** would be obtained by reduction of the enaminone moiety of **67** from the less hindered *exo* face of the tricyclic core, following reductive desulfonylation to give the hydroxymethyl compound **68**. The hydroxymethyl group would be prepared by hydroboration of olefin **69** or by reduction of aldehyde **70**. The preparation of **70** was envisaged by a seleno-Pummerer rearrangement and base hydrolysis of selenide **71**, which would be obtained from the electrophilic cyclisation of free base **72**. Enaminone **72** could be prepared by tandem conjugate addition and base promoted intramolecular cyclisation of acetylenic sulfone **73** and β-amino ester **74**. Intermediate **73** can be obtained from the selenoxide elimination after reacting 1-octyne **77** with selenosulfonate **63**. Compound **74** would be obtained from the Curtius rearrangement of half ester **75** which in turn could be obtained from alkylation of a precursor obtained from the readily available starting material 1,2-*cis*-cyclohexanedicarboxylic anhydride **76**.

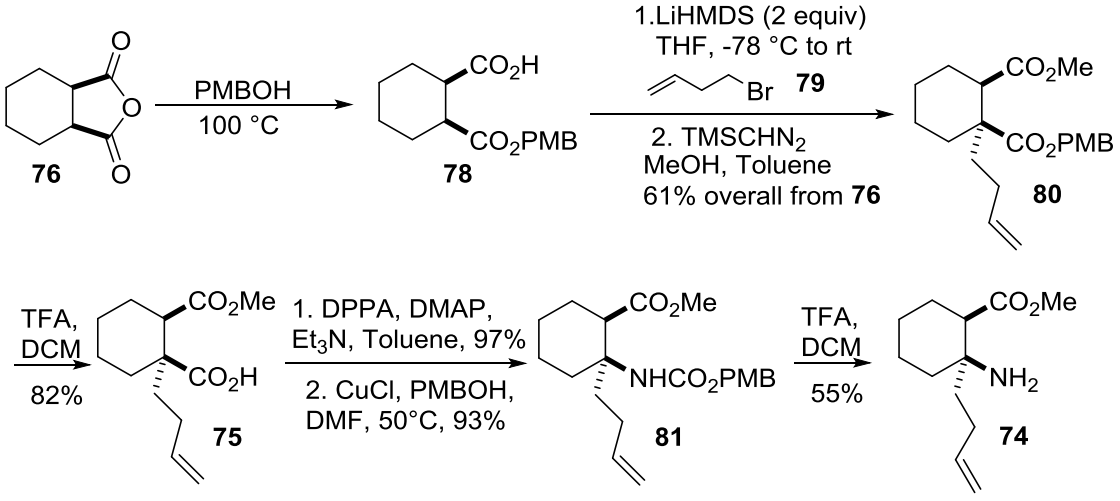
Scheme 17


HO
H
O
N
H
C6H13
Cylindricine C
O
N
C6H13
OH
3
67
68
SO2Ph
SePh
72
71
70
69
or
O
H
SO2Ph
C6H13
CO2Me
NH2
CO2H
73
74
75
76
PhSeSO2Ar
63
H
C6H13
77

1.4.2 ***Preparation of β-amino ester (±)-74***

The synthesis commenced with the ring-opening of the commercially available material *cis*-1,2-cyclohexanedicarboxylic anhydride (**76**) using PMB alcohol to give monoester **78** (Scheme 18). This allowed for the formation of diester **80** in a one pot preparation by forming the enolate of **78**, using two equivalents of base, alkylation by 4-bromobutene **79**, followed by esterification in 61% yield. Acid promoted hydrolysis of the PMB ester afforded the monoester **75**. A Curtius rearrangement of the carboxylic acid using diphenylphosphoryl azide was used successfully to set up a precursor of the challenging aza-spirocenter, with the nitrogen in the form of an isocyanate. Base hydrolysis of the isocyanate proved to be futile as no free amine was observed in any detectable amounts. To obtain the free amine, the isocyanate was protected as carbamate **81** using PMB alcohol and subsequent acid-promoted cleavage gave β-amino ester **74**.

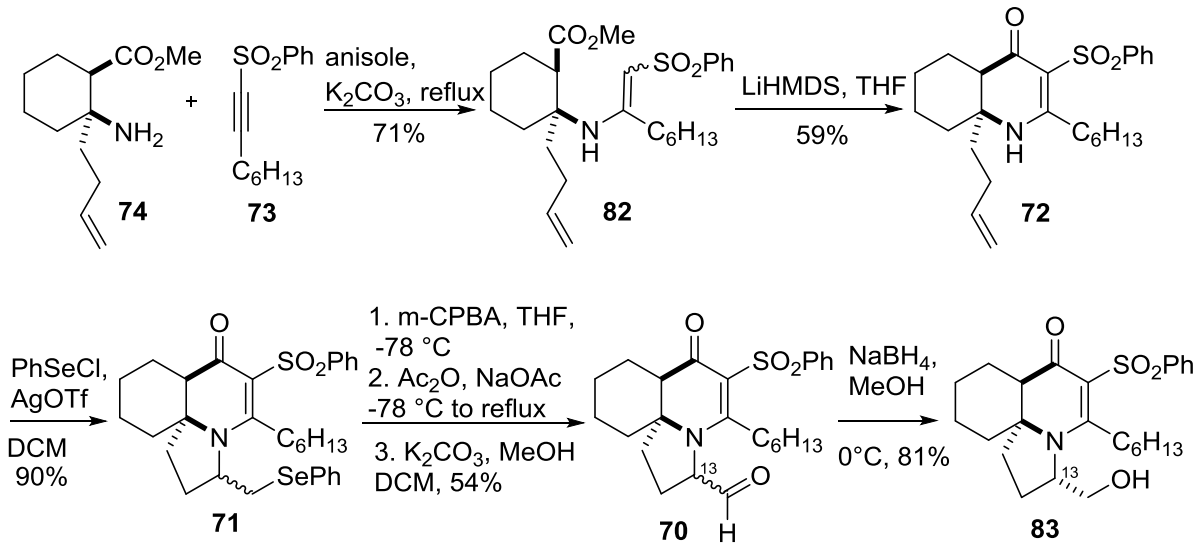
Scheme 18



1.4.3 ***Preparation of the tricyclic core (83)***

With the amino ester **74** in hand, the conjugate addition was carried out in refluxing anisole to acetylenic sulfone **73**, prepared as described in section 1.3.2, to give vinyl sulfone **82** in 71% yield (Scheme 20). The cyclisation of the B-ring was successfully performed by deprotonation of **82** using one equivalent of strong base to give the desired product **72** as the only diastereomer. Attempts at epoxidizing the terminal olefin failed with *m*-CPBA and peracetic acid, or in the presence of Jacobsen's catalyst,[(60)] giving only recovered starting material. Sharpless dihydroxylation conditions also gave recovered starting material. Therefore an electrophilic cyclisation was used to construct the C-ring, using benzeneselenenyl chloride and silver triflate to give selenide **71** in 90% yield as a 3:1 mixture of diastereomers. The use of silver triflate as a halide scavenger was required to ensure complete consumption of starting material and limit the side products observed in the absence thereof. Unfortunately the diastereomers could not be separated by column chromatography at this stage. The selenide was converted to the acetoxyselenide using a seleno version of the Pummerer rearrangement, which was cleaved under basic conditions to give aldehyde **70** as a single diastereomer. Epimerisation of the C-13 stereocenter was therefore possible. Reduction of the aldehyde using $NaBH_4$ in methanol gave alcohol **83** in 81% yield as a white solid. Dr. K. Clary, who first prepared compound **83**, also obtained an X-ray crystal structure of that compound showing epimerisation had in fact occurred at C-13 (Scheme 19), resulting in the undesired diastereomer of alcohol **83** as opposed to the desired alcohol **68** shown in the proposed retrosynthesis (Scheme 17).

Scheme 19



1.5 Objectives

The previous section describes the synthesis of an advanced intermediate **83** by Dr. K. Clary, albeit with the incorrect configuration of the hydroxymethyl group at C-13. Her departure at this point resulted in the tricyclic enaminone **83** as the most advanced intermediate in the envisaged pathway. Most of the yields had not been optimised and completion of the synthesis of cylindricine C (**3**) still required reductive desulfonylation, stereoselective reduction of the enaminone double bond and epimerisation of the hydroxymethyl group to the desired R-configuration.

The new objectives outlined for this thesis were: firstly, to regulate the stereochemistry of the hydroxymethyl group by reviewing the steps required to generate the alcohol from selenide **71**. Ideally we hoped to regulate the stereochemistry without needing to reformulate our retrosynthesis. Secondly, to identify a method for removal of the sulfone group to generate enaminone **67**, as described in section 1.4.1. A third

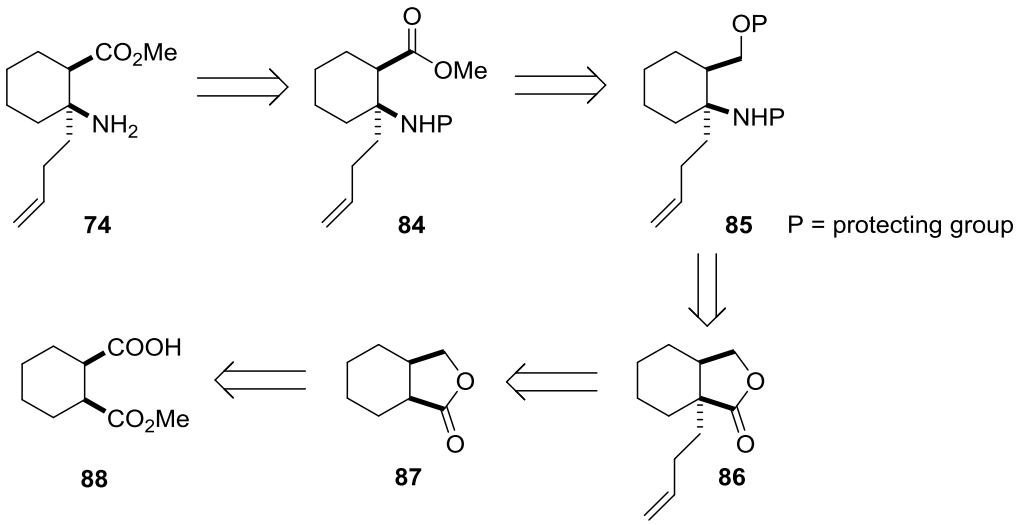
objective was to stereoselectively reduce the enaminone moiety to afford the desired configuration of the *n*-hexyl group, as found in the natural product. The final objective was to develop a route to the racemic alkaloid that could eventually be converted to an enantioselective approach.

Chapter Two: Alternative route to the amino ester intermediate

2.1 Overview

The previous section described a route to the advanced intermediate **83** for the synthesis of cylindricine C (**3**). Even though it was determined by x-ray crystallography that the hydroxymethyl group was in the incorrect configuration at the C-13 position, this work laid the foundation for implementing our tandem conjugate addition and intramolecular cyclisation using acetylenic sulfone chemistry. In light of these results, as well as the objective in section 1.5 to develop a route to the racemic alkaloid that could ultimately be converted into an enantioselective approach, a new synthetic route was established for this intention. This chapter will discuss the synthesis of β-amino ester **74** via an alternative route to the synthesis described in section 1.4.2, via a route that would be amenable towards an enantioselective version for the preparation of cylindricine C (**3**). The retrosynthesis of **74** is shown in Scheme 20 as an alternative to the synthesis described in section 1.4.2.

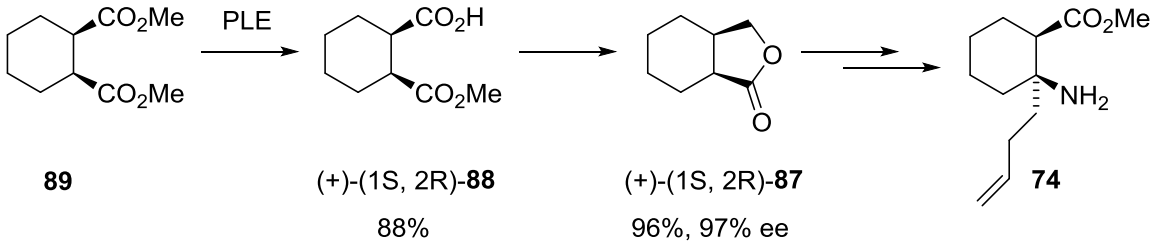
Scheme 20



The alternative route to β-amino ester **74** was envisaged to occur via compound **84** after deprotection of the nitrogen. The methyl ester **84** would result from the oxidation of the primary alcohol after its deprotection in **85**. A key step is installation of the amine at the fully substituted center while maintaining the correct configuration. Hydrolysis of the lactone **86** followed by protection of the primary alcohol would afford the free carboxylic acid. It was envisaged that the free carboxylic acid would undergo a stereospecific Curtius rearrangement with retention of configuration to afford an isocyanate, which would be reacted to form **85**, where the nitrogen is protected as a carbamate. The alkylated lactone **86** would come from installation of the butenyl group on lactone **87** which in turn would be obtained via reduction of the carboxylic acid moeity and lactonisation of known starting ester **88**. The thermodynamically preferred cis-fused rings in **87** would be expected to persist during the alkylation of **87**.

While an asymmetric synthesis was not the focus of this thesis, it is important to showcase how the new synthetic route would eventually enable a straightforward enantiopure approach. Work by Jones *et al.*[61] demonstrated the effective use of the enzyme porcine liver esterase (PLE), to induce asymmetry on cyclic meso diesters. Scheme 21 shows an example of meso diester **89** that would be applicable to our synthesis. When compound **89** was treated with PLE, the hydrolysis of one ester was favoured to yield enantioenriched compound **88** in good yield followed by conversion to γ-lactone **87** with 96% yield and 97% ee.[61] Therefore, this route would be a viable alternative to obtaining compound **74** in an enantiopure form. However, before committing to an enantioselective approach, it was first necessary to establish the synthetic steps in a racemic variation.

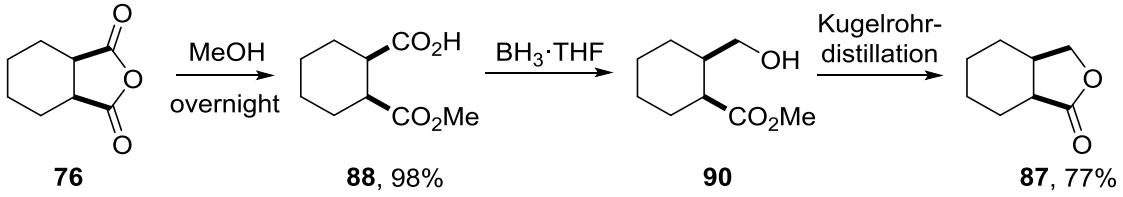
Scheme 21



2.2 Preparation of lactone 87

The synthesis commenced with alcoholysis of the cheap starting material 1,2-cis-cyclohexanedicarboxylic anhydride (**76**) to generate the mono-methyl ester **88** (Scheme 22).[62] A racemic mixture was obtained; however, one enantiomer is shown for clarity of relative stereochemistry. Reduction of the carboxylic acid to primary alcohol **90** was achieved using borane-dimethyl sulfide complex (DMSB).[61] Comparable yields were obtained with a cheaper borane reagent in the form of borane-tetrahydrofuran (BTHF). Isolating compound **90** was challenging due to spontaneous cyclisation to form the desired lactone **87**. Therefore, the reduction step was followed directly with Kugelrohr-distillation to form γ-lactone **87** in 77% yield.

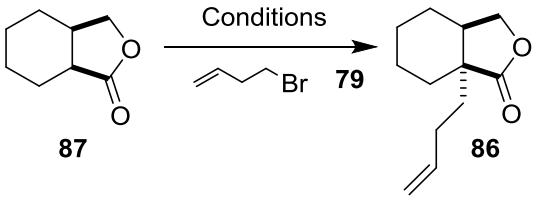
Scheme 22



2.3 Alkylation of lactone 87

Palladium catalysed arylation of compound **87** has been achieved using a variety of aryl halides;[63] however, alkylation of lactone **87** has not been reported. In order to install the butenyl group (Scheme 23), a variety of conditions were investigated and they are tabulated in Table 2.

Scheme 23



Initially, when using LiHMDS as the base, the alkylated product was observed in low yields (entry 1-3). After increasing the equivalents of base or addition of HMPA, which is capable of coordinating to the lithium cation, equivalent or lower yields were observed (entries 2 and 3 respectively). When LDA was used as the base, the yield was increased to 65% when stirred at room temperature overnight.

The counterion in metal-enolate alkylations has been found to be important and increased levels of asymmetric induction have been observed when using chiral bases.[64-68] Lithium salts as additives in enolate alkylations have also been investigated[69-72] and were shown to improve reactivity and selectivity in ketone enolates. When LiCl was used as an additive in addition to LDA, the yield increased to 81% (entry 6). The exact role of lithium additives has been largely speculative, with evidence suggesting the existence of mixed lithium dimers[69] and trimers.[70]

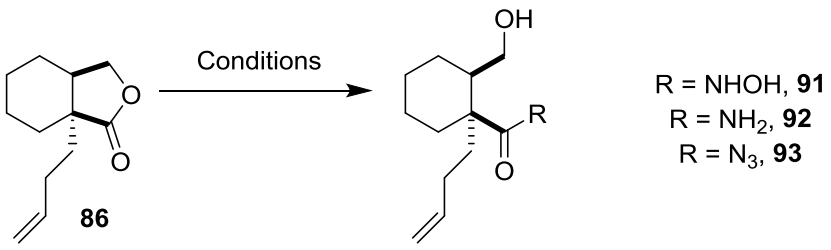
Table 2: Alkylation of lactone 87

Entry	Conditions 1	Result
1	LiHMDS (1 equiv), THF, -78 ^{o}C to rt, **79** (1 equiv), overnight	**86**, 39%
2	LiHMDS (1.5 equiv), THF, -78 ^{o}C to rt, **79** (1 equiv), overnight	**86**, 40%
3	LiHMDS (1 equiv), HMPA, THF, -78 ^{o}C to rt, **79** (1 equiv), overnight	**86**: **87** (1:3) (isolated **86**: 21%)
4	LDA (1 equiv), THF, -78 ^{o}C to rt, **79** (1 equiv), overnight	**86**, 65%
5	LDA (1.5 equiv), THF, -78 ^{o}C to rt, **79** (1 equiv), overnight	**86**, 64%
6	LDA (1 equiv), THF, -78 ^{o}C to rt, **79** (1 equiv), LiCl (0.3 equiv), overnight	**86**, 81%

2.4 Installation of the amine at the quaternary center

With alkylated lactone **86** in hand, various routes for installation of the amine functionality at the quaternary center were investigated. It was envisaged that this could occur via a rearrangement reaction of amides shown in Scheme 24. Hydroxamic acids are known to undergo the Lossen rearrangement to the corresponding isocyanates after activation of the hydroxyl group via acylation, sulfonylation or phosphorylation.[73]

Scheme 24



Attempts to cleave the lactone with hydroxylamine hydrochloride to yield the hydroxamic acid **91** were unsuccessful when reacted in the presence of KOH or Et_3N overnight (Table 3, entries 1 and 2). An alternative method would be the Hoffman rearrangement, which occurs via the reaction of a primary amide with bromine to form the sodium N-bromoamide under basic conditions, followed by α-elimination of HBr and rearrangement to the isocyanate.[74] When reacting lactone **86** with ammonium hydroxide under refluxing conditions overnight only starting material was recovered (entry 3), presumably due to the steric hindrance associated with the adjacent fully substituted center.

Table 3: Cleavage of lactone 86 to afford potential intermediate for rearrangement

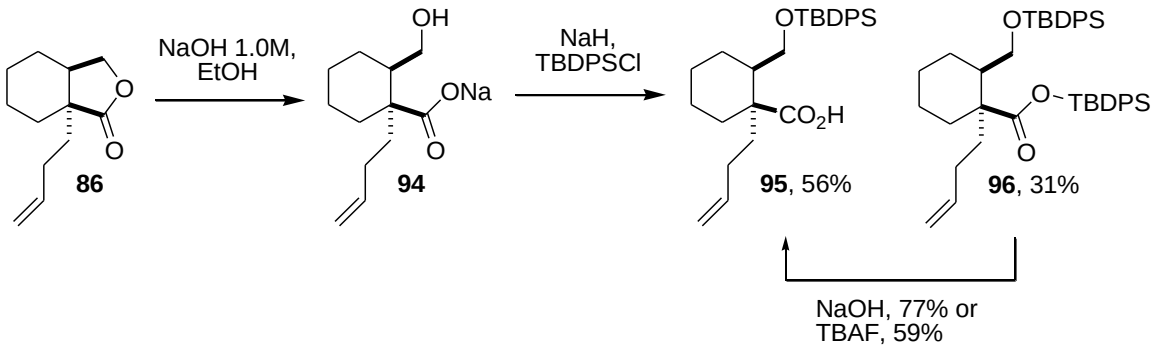
Entry	Conditions 1	Result
1	$NH_2OH.HCl$ (5 equiv), KOH (5 equiv), MeOH, 24 hours	Recovered starting material
2	$NH_2OH.HCl$ (5 equiv), Et_3N (5 equiv), DCM, 24 hours	Recovered starting material
3	NH_4OH, MeOH, reflux, overnight	Recovered starting material
4	NaN_3, H_2O, -10 ^oC, overnight	Recovered starting material

The Curtius rearrangment[75-79] is a useful method for the preparation of isocyanates via acyl azide intermediates. A synthesis of acyl azide intermediate **93** (entry 4) was attempted by cleaving lactone **86** with sodium azide; however, this returned only starting material. This is possibly due to the insolubility of the starting material **86** or the rapid rate of recyclisation of the alkoxide generated from the ring opening reaction, where the azide anion acts as a leaving group. Because of the difficulty in cleaving

lactone **86** to the corresponding nitrogen-containing products **91-93**, routes to yield the carboxylic acid moiety were investigated.

Isolation of the corresponding hydroxy-acid product from the cleavage of 5-membered and 6-membered ring lactones is made difficult due to rapid recyclisation that occurs upon workup and purification.[80] For that reason, careful consideration was given to the reagents for opening and protecting lactone **86**. The base promoted cleavage of lactone **86** occurred quantitatively to give the sodium carboxylate salt **94** (Scheme 25).

Scheme 25



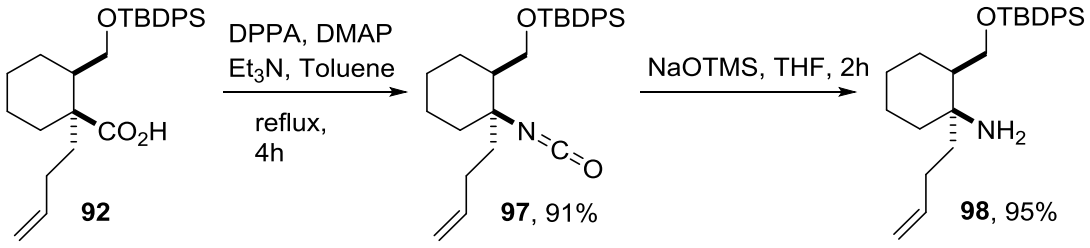
When excess sodium hydroxide was used, shorter reaction times were observed; however, the excess base adversely affected the consequent silyl protection, giving larger amounts of recovered starting material. Therefore, it was essential to use only one equivalent of base in the hydrolysis of lactone **86**. Carboxylate salt **94** was then subjected to silyl protection which afforded the desired silyl ether **95** as well as bis-silylated compound **96**.

Silyl esters are also common protecting groups for carboxylic acids, but they are more labile to mildly basic or acidic conditions than silyl ethers.[81] Thus, the bis-silylated compound **96** was reacted with one equivalent of TBAF, or under milder conditions using

NaOH, to give only the desired compound **95**. With a combined yield of 80%, after recycling the bis-silylated compound to the desired silyl ether **95**, a viable route to the carboxylic acid was thus established.

We then focused our attention on the installation of the amine group via a Curtius rearrangement, shown to be a successful method in the recent synthesis of the anti-inflammatory drug BIRT-377, by our group.[82] The reaction of carboxylic acid **95** with diphenylphosphoryl azide (DPPA)[79] under basic conditions afforded isocyanate **97** in excellent yield (Scheme 26). The isocyanate was stable upon workup and column chromatography, making it easy to handle. This unusual stability could be attributed to the fully substituted stereocenter on the adjacent carbon.

Scheme 26



We next investigated conditions to cleave the isocyanate to the free amine. Isocyanates can be cleaved to primary amines by reacting with water under basic or acidic conditions as a result of decarboxylation of the carbamic acid intermediate.[83-85] When reacting **97** with excess NaOH in dioxanes, only starting material was recovered, while the reaction with KOH in THF gave compound **98** in low yield (entries 1 and 2). The reaction of **97** under acidic conditions using HCl (entry 3) produced only recovered starting material. Mercuration, followed by in situ demercuration has been used as a mild

method for obtaining primary amines from isocyanates.[86] When isocyanate **97** was reacted with mercuric acetate, the solution turned orange after 45 min, suggesting that the mercurial isocyanate intermediate had formed. Attempted cleavage of this intermediate, using $NaBH_4$ dissolved in NaOH (5%), resulted in a colour change from orange to black to colourless. Upon workup, only starting material was recovered (entry 4). Finally, using a mild and simple method reported by Ma and Lee,[87] the reaction of isocyanate **97** with NaOTMS resulted in free amine **98** in 95% yield (entry 5).

Table 4: Cleavage of isocyanate to free amine 98

Entry	Conditions	Result
1	NaOH (4 equiv, 1.0M), dioxane, reflux, overnight	Recovered starting material
2	KOH (1.1 equiv), THF, reflux, overnight	**97**:**98** (2:1) (isolated **98** 35%)
3	HCl (4 equiv, 2.0M), overnight	Recovered starting material
4	$Hg(OAc)_2$ (1 equiv), THF/$H_2$0 45min, then $NaBH_4$ (2 equiv), NaOH 5%, 1 h	Recovered starting material
5	NaOTMS (2 equiv), THF, 2h	**98**, 95%

2.5 Formation of β-amino ester 74

In order to obtain the desired ester functionality of compound **74**, deprotecting the silyl ether and oxidation of the alcohol was investigated. Deprotection of the silyl ether group was explored on compound **97**. Using excess TBAF, both the silyl group and the isocyanate moiety were cleaved to afford amino alcohol **99** in low yields ranging from

35% to 43%. Low yields were not the result of an incomplete deprotection of the silyl group, but rather due to the very polar nature of both the aminol product and tetrabutylammonium salts from TBAF, making purification by column chromatography difficult. We attempted the same transformation using an alternative source of fluoride ion. When reacting compound **97** with excess CsF, amino alcohol **99** was isolated in 63% yield. The fluoride ion likely reacts with the isocyanate moiety to form a carbamoyl fluoride intermediate, which is cleaved upon aqueous workup.

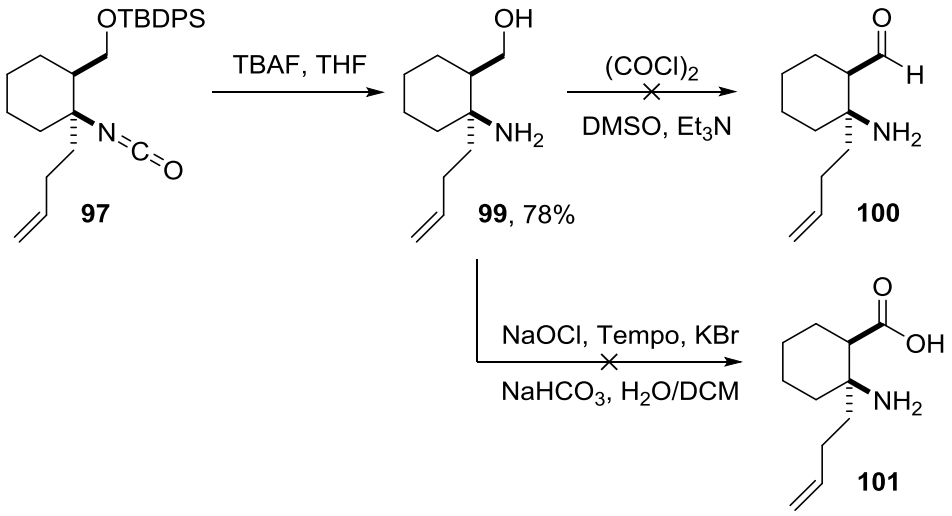
A workup procedure, published by Kaburagi and Kishi,[88] makes use of an acidic resin in the presence of calcium carbonate and methanol for the efficient removal of the byproducts of TBAF deprotections. The basis for this workup is the ability of sulfonic acid resins to bind to the tetrabutylammonium cation, which is then removed by filtration. Addition of calcium carbonate assists in removal of excess fluoride, as it functions as an HF scavenger, producing calcium fluoride as an insoluble salt in THF.

When employing this procedure, but substituting Dowex 50WX8-400 acidic resin for Rexyn 101 acidic resin, the NMR spectra of the reaction mixture indicated the presence of the desired compound and some remaining silyl ether by-product not removed during workup. After flash chromatography, the desired product **99** was isolated in 78% yield (Scheme 27).

Attempts to oxidise the primary alcohol to the corresponding aldehyde using Swern conditions gave a complex mixture of unidentified products, as evident from the NMR spectra of the crude products, with an aldehyde peak representing less than 10% of the product mixture by integration of the ^{1}H-NMR spectrum. Attempted oxidation to the

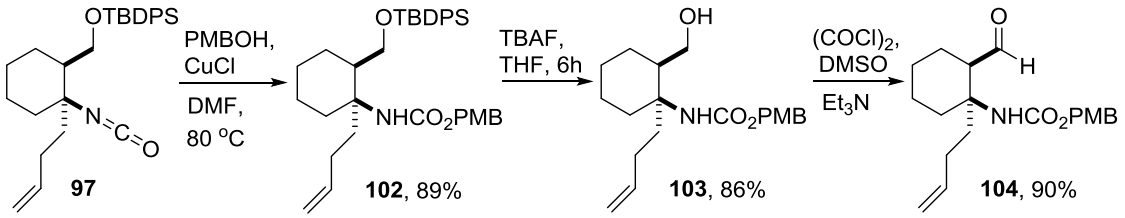
corresponding carboxylic acid using NaOCl catalysed by TEMPO[89] returned only starting material.

Scheme 27



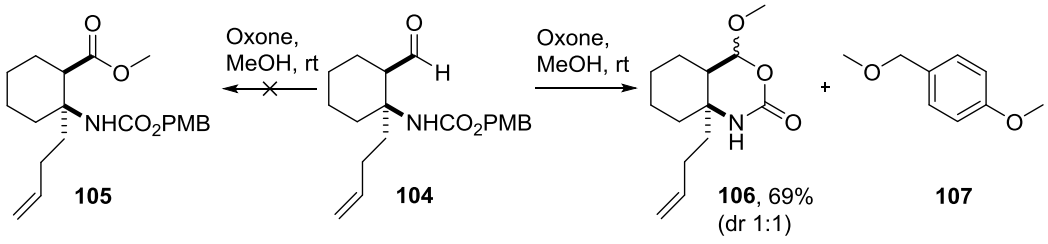
We suspected that protecting the amine would solve the problem encountered in oxidising the primary alcohol. Therefore, instead of cleaving isocyanate **97** to amine **98** and then protecting the free amine, the isocyanate was instead reacted with *p*-methoxybenzyl alcohol and copper(I) chloride in DMF, giving carbamate **102** in good yield (Scheme 28). Deprotection of the silyl group under TBAF conditions, followed by an acidic resin workup as described above and flash chromatography, gave primary alcohol **103** in 86% yield. With compound **103** in hand, we attempted an oxidation under Swern conditions, and not surprisingly, the aldehyde **104** was isolated in 90% yield. The high yield confirmed our speculation that the free amine was hindering the attempts at oxidising compound **99** (Scheme 27).

Scheme 28



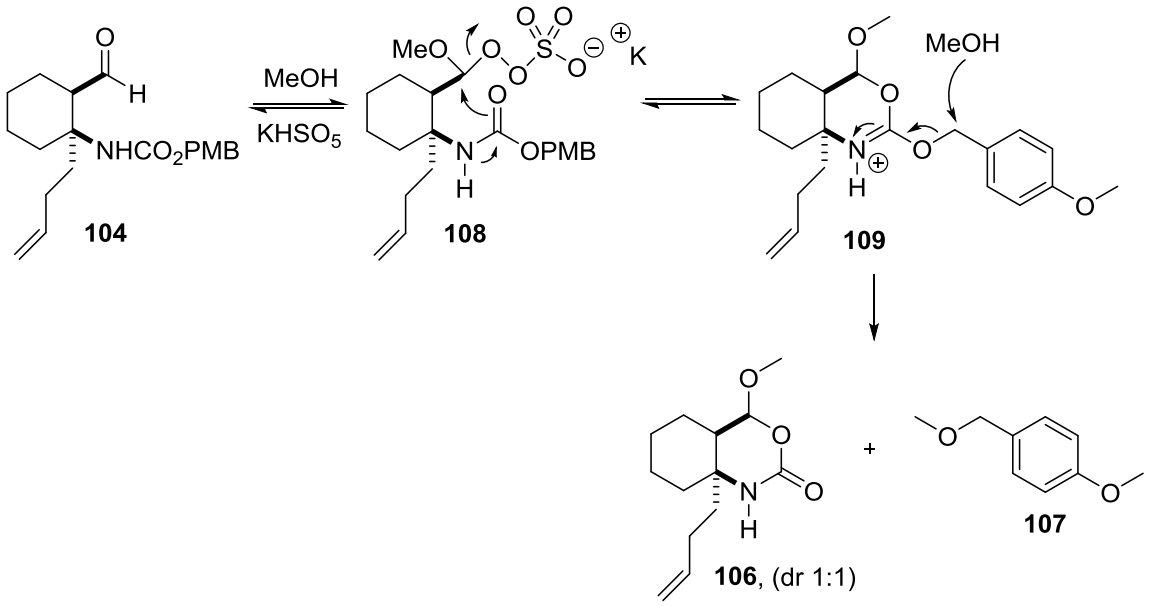
A number of oxidation reactions of aldehydes to carboxylic acids and corresponding esters, under metal free conditions, have recently been reported[(90)] as an alternative to the traditional metal based oxidants such as chromium[(91)] or manganese.[(92)] One pot oxidations of aldehydes to esters have also been of particular interest in recent times, resulting in numerous publications, some of which were highlighted in recent reviews.[(90, 93)] The oxidation of aldehyde **104** was attempted with Oxone® (potassium peroxymonosulfate), in the presence of methanol.[(94)]

Scheme 29



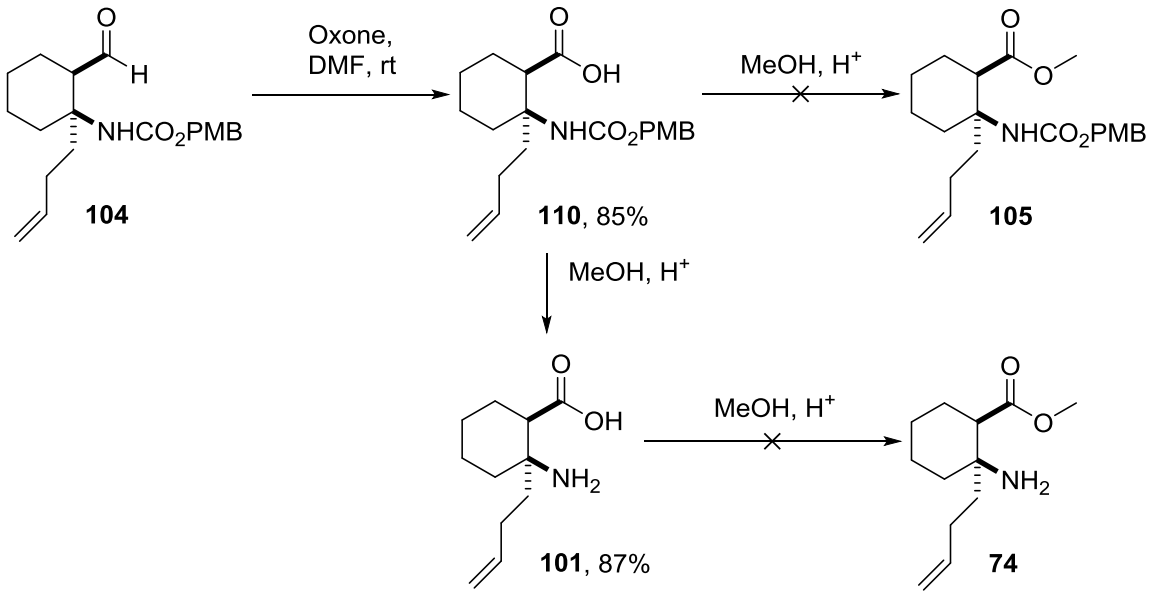
Instead of the one-pot oxidative conditions yielding the desired ester **105**, cyclic carbamate **106** was isolated in good yield as a 1:1 mixture of diastereomers along with methyl ether **107** (Scheme 29). The proposed mechanism for the formation of compound **106** is shown in Scheme 30.

Scheme 30



In the presence of methanol and potassium peroxymonosulfate, aldehyde **104** could form acetal intermediate **108**. The carbonyl oxygen atom of the amide moiety could attack the acetal moiety due to the electron donating ability of the nitrogen atom to form intermediate **109**. In the presence of excess methanol, the PMB protecting group would be cleaved to afford the observed compound **106** as a mixture of diastereomers along with methyl ether **107**.

Scheme 31

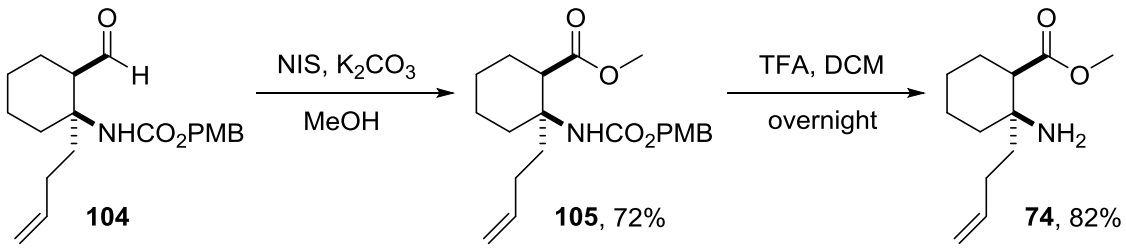


In an attempt to avoid the unwanted cyclic carbamate **106**, we obtained carboxylic acid **110** in 85% yield from the reaction of aldeyhde **104** and Oxone® in DMF as the solvent instead of in methanol (Scheme 31). Rather than forming methyl ester **105**, by reacting the carboxylic acid **110** with methanol under acidic conditions, amino acid derivative **101** was formed due to cleavage of the carbamate. Further attempts at stirring compound **101** in methanol under acidic conditions to form β-amino ester **74** resulted in no reaction.

Due to the PMB ester being labile to acidic conditions, an alternative one pot oxidation method for obtaining methyl ester **105** directly was investigated. This was achieved by reacting aldehyde **104** with *N*-iodosuccinimide and methanol[(95)] under basic conditions to give methyl ester **105** in 72% yield. Finally, removal of the PMB ester

under acidic conditions using TFA in DCM, resulted in β-amino ester **74** in 82% yield (Scheme 32).

Scheme 32



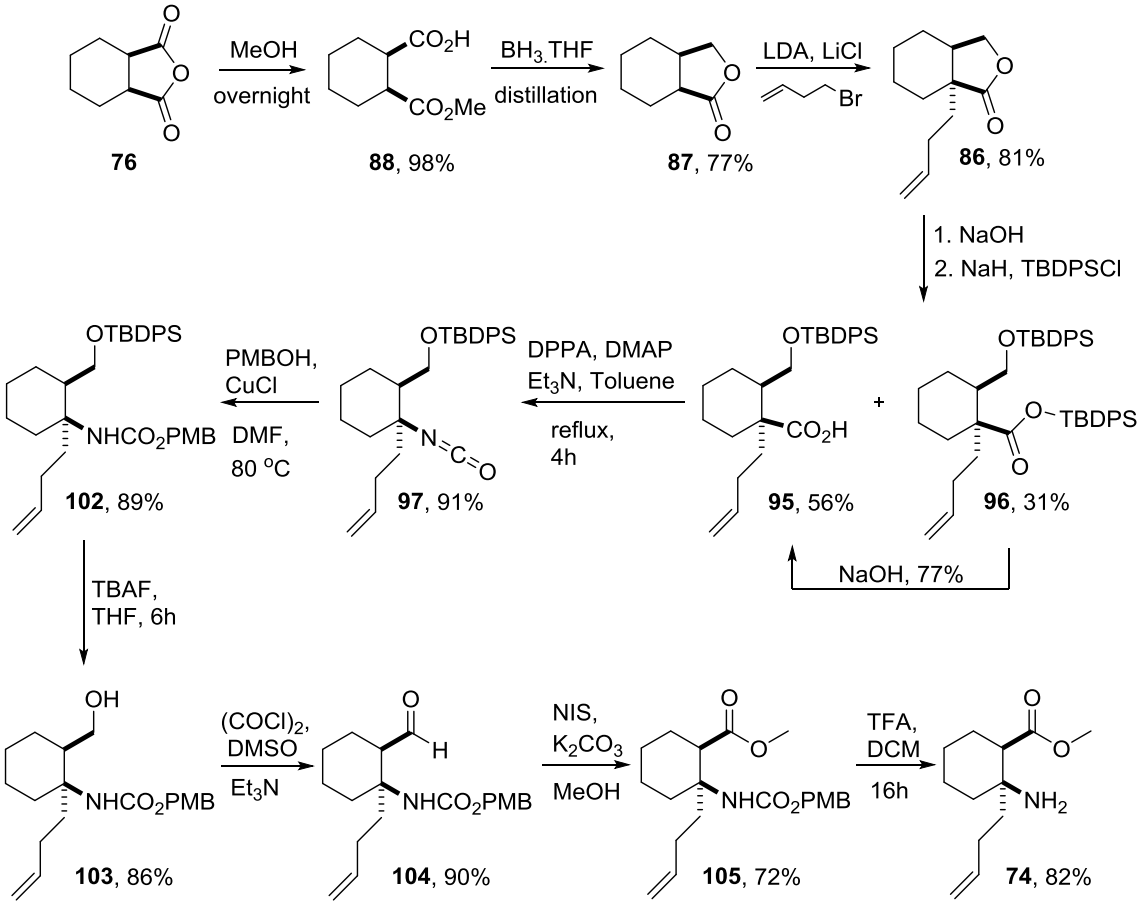
2.6 Summary

Starting from cheap starting material, the lactone **87** was obtained by reduction of the carboxylic acid moiety, followed by cyclisation of the resulting primary alcohol intermediate. After screening a variety of conditions for installing the butenyl group, the alkylation was successfully achieved using LDA as the base with LiCl as an additive. Although attempts at obtaining various amide derivatives by rearrangement reactions yielded no desirable intermediates, an alternative method for freeing the carboxylic acid moiety was achieved by cleaving the alkylated lactone **87** under basic conditions followed by silyl protection of the resulting alcohol.

Stereospecific introduction of the primary nitrogen at the quaternary center was a key step in the synthesis. This was successfully achieved by utilising a Curtius rearrangement to install the nitrogen functionality in the form of isocyanate **97**. The isocyanate was reacted further, leaving the nitrogen protected in the form of carbamate **102**, which allowed for further functional group transformation by desilylation under

TBAF conditions, followed by oxidation to give the desired aldehyde **104**. The aldehyde was further oxidised directly to methyl ester **105** in one step using an iodine-mediated oxidation in methanol, which acted as both a solvent and a nucleophile. Following a deprotection step, β-amino ester **74** was obtained in an overall yield of 15.6% using a linear sequence, or 22.3% yield when including the deprotection of the bis-silylated compound **96**.

Scheme 33

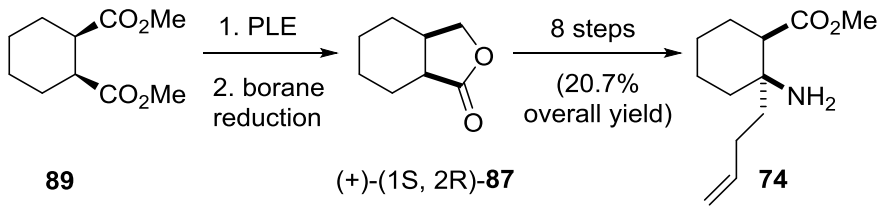


Chapter Three: Early stage desulfonylation and reduction of the enaminone moiety

3.1 Overview

The previous section described an alternative route to β-amino ester **74** via lactone **87** allowing for a potential enantioselective approach towards cylindricine C (**3**). In the future, this could be achieved by using enzymatic desymmetrisation of diester **89**, as established by Jones *et al.*[61] (Scheme 34). With the racemic variation of the synthesis of **74** completed, we focussed our attention on extending the existing synthesis described in section 1.4 towards the total synthesis of cylindricine C.

Scheme 34



This chapter will highlight the synthetic value of a tandem conjugate addition and cyclisation utilising acetylenic sulfones for synthesising nitrogen-containing heterocycles such as the cylindricine alkaloids. In addition, the results of adopting an early stage desulfonylation followed by reduction of the resulting enaminone moiety will be described.

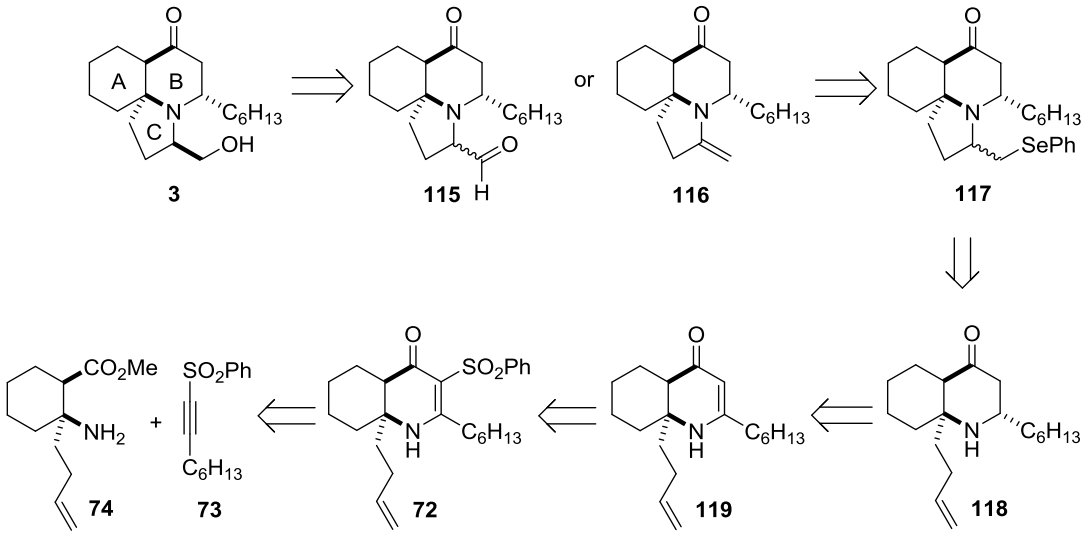
3.2 Retrosynthesis

Reactions such as the desulfonylation and reduction of the double bond moiety remained unexplored after the tricylcic core had been constructed in the synthesis

described in section 1.4. In order to concentrate on these transformation, a retrosynthesis was developed (Scheme 35) to explore these reactions when only two of the three rings were formed, namely the A-ring and the B-ring. Subsequent to cyclisation of the C-ring, attempts to regulate the stereochemistry of the hydroxymethyl group, which had been obtained with the incorrect configuration by Dr. K. Clary, could be explored.

We envisaged the natural product to come from aldehyde **115** or enamine **116**. The aldehyde was envisaged by a seleno-Pummerer rearrangement and base cleavage of selenide **117**. The preparation of enamine **116** was foreseen by a selenoxide elimination after oxidation of selenide **117**. Electrophilic cyclisation would afford enaminone **119**, which in turn would be obtained after an early stage desulfonylation and stereoselective reduction of compound **72**. A conjugate addition and cyclisation of acetylenic sulfone **73** and β-amino ester **74** would yield compound **72**.

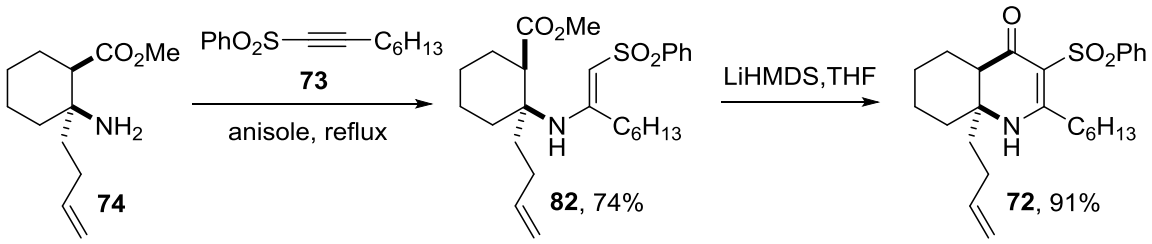
Scheme 35



3.3 Tandem conjugate addition and cyclisation

With an alternative synthetic route to β-amino ester **74** concluded, we turned our attention to the synthesis of the B-ring of cylindricine C by showcasing a tandem conjugate addition and cyclisation of acetylenic sulfones developed in our group.[31-32] Compound **82**, obtained from the conjugate addition of **74** to acetylenic sulfone **73**, was achieved in refluxing anisole in 74% yield (Scheme 36).

Scheme 36

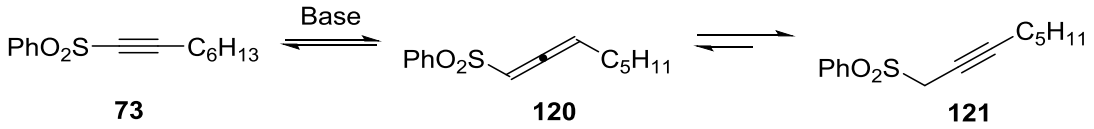


The conjugate addition was initially subjected to basic conditions using one equivalent of K_2CO_3 resulting in a low yield of the desired product. Under these conditions, the propargylic sulfone **121** was observed in the crude mixture, presumably due to the isomerisation of the acetylenic sulfone under basic conditions (Scheme 37). Allene **120** was presumably formed from deprotonation occurring at the γ-carbon atom of acetylenic sulfone **73**, followed by α-protonation. A similar prototropic shift then afforded propargyl sulfone **121**. As a result, the acetylene moiety of compound **121** was unreactive towards conjugate additions.

When 10 mol % of base was used, less than optimum yields were observed and extended reaction times were required. Fortunately, the amine group proved sufficiently basic to achieve a single isomer of **82** in 74% yield, without the need for additional base.

When compound **82** was reacted under strongly basic conditions, cyclisation afforded the desired compound **72** in an excellent yield of 91%. Under basic conditions, the amine group of **82** is deprotonated, resulting in acylation at the α-position to the sulfone, while eliminating methanol from the methyl ester.

Scheme 37

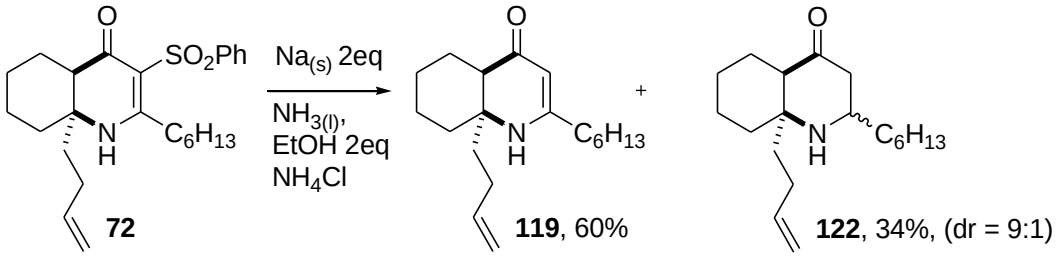


73 **120** **121**

3.4 Early Stage Desulfonylation

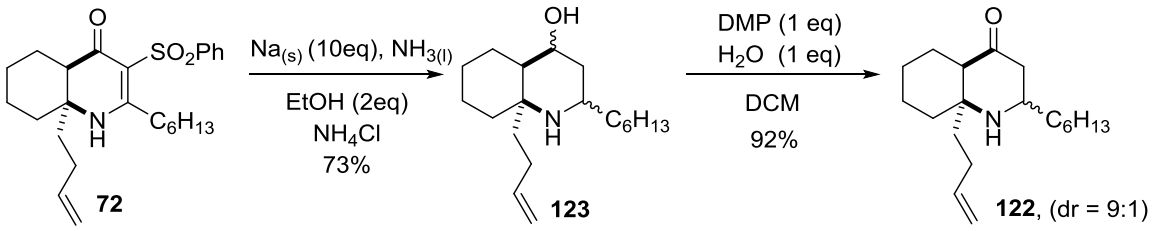
Desulfonylation of **72** occurred using dissolving metal conditions of sodium in liquid ammonia[(50)] to give enaminone **119** as the major product (Scheme 38), along with 34% yield of aminone **122** as an inseparable mixture of diastereomers in a ratio of 9:1 (as determined by integration of the respective peaks in the ^{1}H-NMR spectrum of the crude mixture). At first, the configuration of the *n*-hexyl group of the mixture of aminones was undetermined. We thought that if the major aminone had the relative stereochemistry of the carbon attached to the *n*-hexyl group in the configuration analogous to that of the natural product, we could access the desired aminone **118** (Scheme 35) as the major isomer in a one-pot reduction. This would prevent the need to optimise the desulfonylation conditions to give only compound **119**. At the same time, this would eliminate the need for establishing a stereoselective reduction of the double bond moiety of enaminone **119** to regulate the configuration of the *n*-hexyl group, which up till now, had not been determined.

Scheme 38



Using a stepwise approach, the starting material **72** was added dropwise to a solution of excess sodium in liquid ammonia, which changed from dark blue to milky yellow, followed by addition of ethanol to act as a proton source. Additional sodium was added until the solution was dark blue and finally the reaction was quenched with ammonium chloride to give amino alcohol **123** as an inseparable mixture of diastereomers in 73% yield along with small amounts of aminone **122** (Scheme 39).

Scheme 39

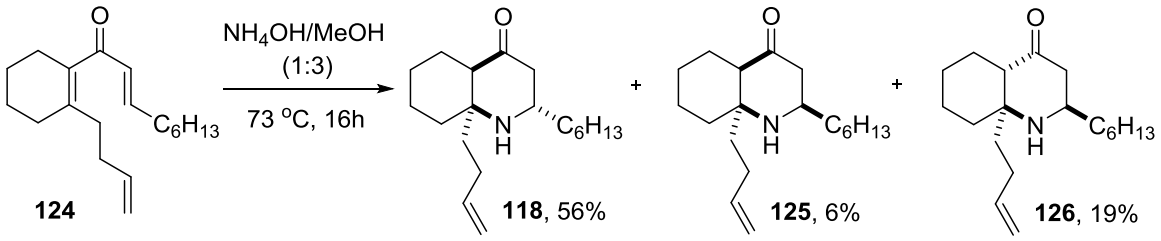


Unfortunately, under these conditions both the double bond and the ketone were reduced in the major product. The relative stereochemistry of the hydroxyl group and the *n*-hexyl group was unknown due to difficulty in separating all possible diastereomers. However, since the ketone was the desired functional group at the C-4 position, alcohol **123** was oxidised using the Dess-Martin periodinane to give aminone **122** in 92% yield as

the same 9:1 mixture of diastereomers obtained previously. We were also able to reduce enaminone **119** obtained in Scheme 38 to aminone **122** in 66% yield in the same diastereoselectivity of 9:1 when using only one equivalent of sodium, with no observed over-reduction of the ketone moiety, and with only a small amount of unreacted starting material remaining (determined by ^{1}H-NMR spectroscopy of the unseparated mixture). After column chromatography of the diastereomeric mixture of aminone **122**, it was possible to isolate some pure material of each stereoisomer for characterisation purposes.

In a previous synthesis by Snider and coworkers of cylindricines A, D and E,[13] the desired aminone **118** was used as an intermediate in the synthesis of all three natural products, as well as in a formal synthesis of cylindricine A by Donohoe *et al.*[25] The synthesis of aminone **118** by Snider *et al.* is shown in Scheme 40 below. Using a double Michael addition, compound **124** was reacted with ammonium hydroxide in methanol to give aminones **118**, **125**, and **126** respectively.

Scheme 40

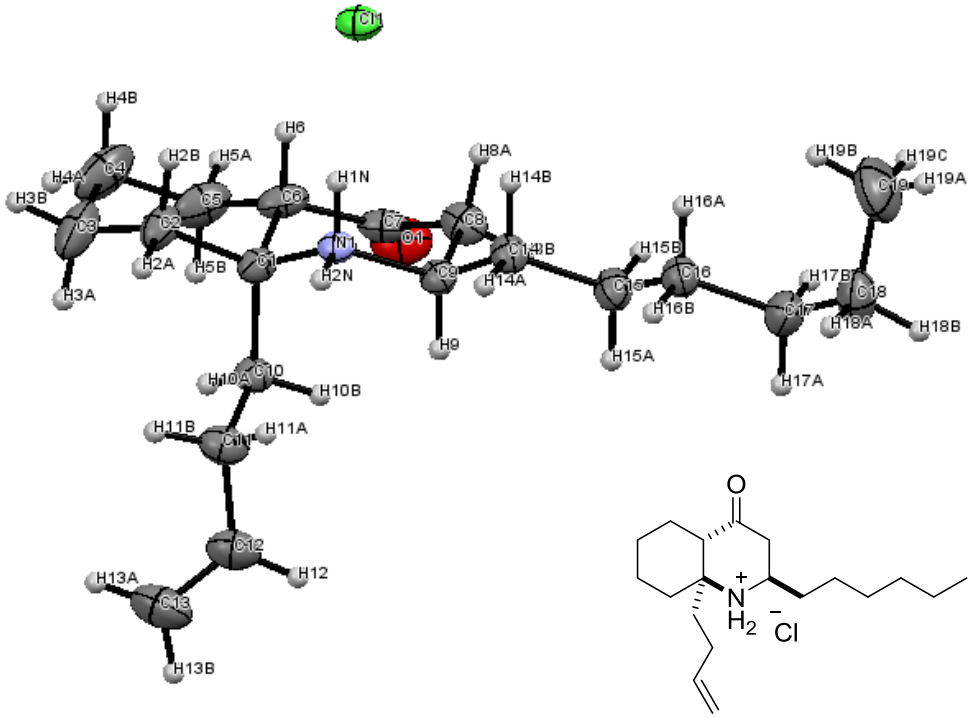


By comparing the ^{1}H-NMR spectra of the pure aminones, to those of Snider *et al.*, it was found that the 9:1 mixture of aminone **122** consisted of stereoisomer **125** as the major product and aminone **118** as the minor product (A detailed comparison of both ^{1}H-

NMR and ^{13}C-NMR spectra can be found in Appendix A). Unfortunately, it was determined that the stereochemistry of the carbon attached to the *n*-hexyl group of the major product possessed the incorrect relative configuration.

In an attempt to prove the stereochemical outcome of the reduction step unequivocally, an x-ray crystal structure of the hydrochloride salt of a sample of aminone **125** was obtained. As shown in Figure 2, the stereochemistry of the carbon attached to the *n*-hexyl group was confirmed to be *trans* to the butenyl group, indicating that the reductive desulfonylation and reduction of the resulting double bond moiety had yielded the undesired stereoisomer as the major product. The x-ray structure also showed that epimerisation had occurred at the C-5 position (see Appendix D for full details).

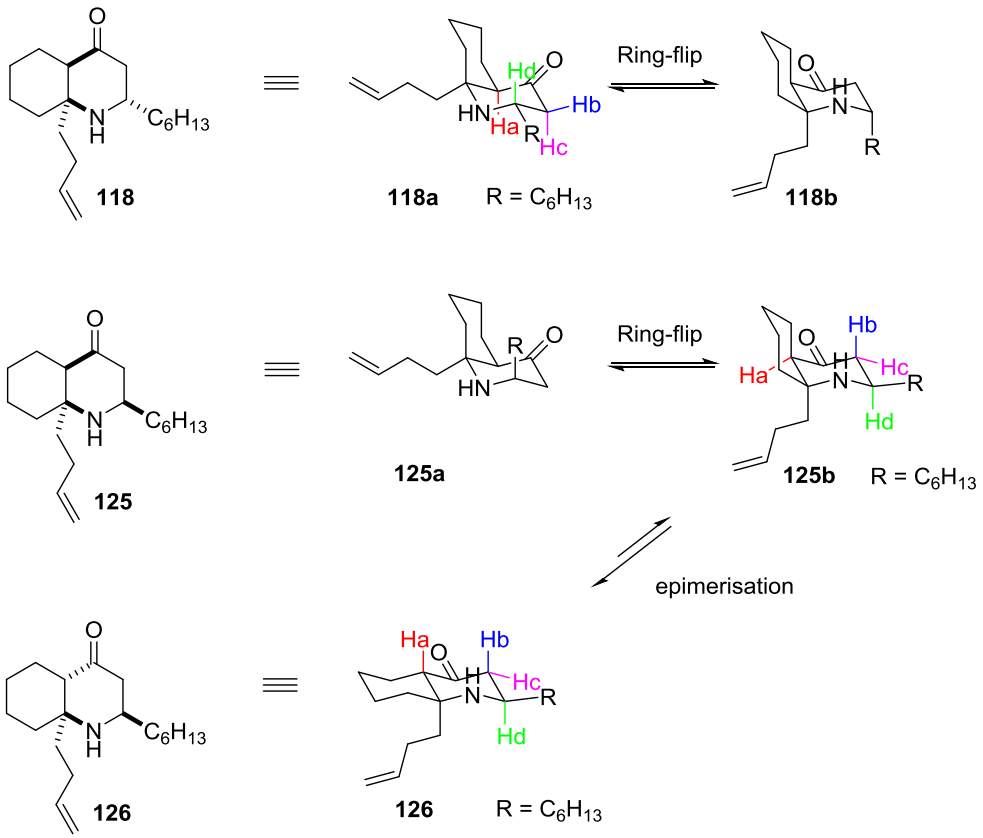
Figure 2: ORTEP diagram of 126.HCl salt (Numbering of atoms in the x-ray structure is arbitrary and does not follow IUPAC rules)



It is important to note here that the sample used to obtain the hydrochloride salt was a small sample of aminone **125** which had been isolated six months previously and was left to sit on the bench-top at room temperature. It is therefore possible that the epimerisation had occurred during this period; however, it is more likely that the epimerisation occurred during the formation of the hydrochloride salt. The structure was therefore the same *trans*-decalin system as the aminone **126** previously reported by alternative methods by the groups of Snyder and Donohoe.

The difference in the NMR data of the isomers can be explained by examining the conformational structures shown in Scheme 41.

Scheme 41



cis-Decalin structures are able to undergo a ring-flip and the possible conformations are shown above. For aminone **118**, proton H_a is a broad singlet with no identifiable coupling constant, while proton H_b is a doublet of doublets with a geminal coupling of J_{bc} = 13.5 and a J_{bd} = 2.9 Hz corresponding to the equatorial/ axial relationship for protons H_b and H_d respectively. The proton H_c should produce a doublet of doublets but shows up as a triplet with a large coupling of J = 12.6 Hz. The large coupling constant corresponds to both the geminal coupling with proton H_b and a trans-diaxial relationship of protons H_c and H_d confirming the axial position of proton H_c. The *n*-hexyl group was determined to be in the equatorial position of the piperidine ring. The butenyl group must therefore also be in the equatorial position of the piperidine ring. Thus, the data shows the conformation of the minor aminone corresponds to **118a** as opposed to the less favourable **118b**, which would have a large 1,3 diaxial strain due to the alkyl chains. Proton H_d shows up as a multiplet at 3.12 ppm shifted slightly downfield relative to H_a, H_b and H_c due to deshielding by the nitrogen atom.

Aminone **125** shows proton H_a as a doublet of doublets with J = 4.1 and J = 12.1 corresponding to coupling with vicinal equatorial and vicinal axial protons respectively. Proton H_b is a doublet of doublets at 2.2 ppm with a geminal coupling of J_{bc} = 14.5 Hz and a large coupling of J_{bd} = 10.8 Hz to the vicinal axial proton H_d. This established that the *n*-hexyl group was in the equatorial position on the piperidine ring and therefore the major aminone isomer corresponds to **125b**.

When comparing the structures shown in Scheme 41, major aminone **125b** might be predicted to be in the conformation shown by **125a**, with the *n*-hexyl group in an axial position and the butenyl group in the equatorial position on the piperidine ring, as this

ring-flip conformation would correspond to the major aminone **118a** described in the ^{1}H-NMR data above. However, analysis of the ^{1}H-NMR data shows the major aminone **125** to be in the conformation shown by **125b** having the *n*-hexyl group in the equatorial position and butenyl group in the axial position on the piperidine ring. This indicates that the *n*-hexyl group adopts the more thermodynamically favorable equatorial position in both aminone isomers. Although an equilibrium is shown between the respective ring-flip conformations, the ring-flips shown as **118b** and **125a** in Scheme 41 would both be higher in energy due to the 1,3 diaxial strain and are therefore not observed on the ^{1}H-NMR spectroscopy time scale.

The ^{1}H-NMR spectrum for aminone **126** shows proton H_a as a doublet of doublets of doublets at 2.29 ppm having a J = 12.2 Hz, J = 3.2 Hz and J = 1.0 Hz. The large coupling constant establishes that it is in an axial position on the piperidine ring while the J = 1.0 Hz corresponds to the long range coupling with proton H_b. The signal of proton H_b is at 2.07 ppm with two large coupling constants of J = 13.3 and J = 11.2 Hz corresponding to the geminal and trans-diaxial coupling with protons H_c and H_d respectively, along with a small coupling of J = 1.2 Hz, corresponding to the long range coupling with proton H_a. A doublet of doublets at 2.35 ppm with a J = 13.4 and J = 3.6 Hz corresponds to proton H_c having coupling with protons H_b and H_d, respectively. Proton H_d appears as a multiplet at 3.00 ppm. The crystal structure of **126.HCl** (Figure 2) confirms the equatorial position of the *n*-hexyl group as well as the configuration at the C-5 position where epimerisation had taken place.

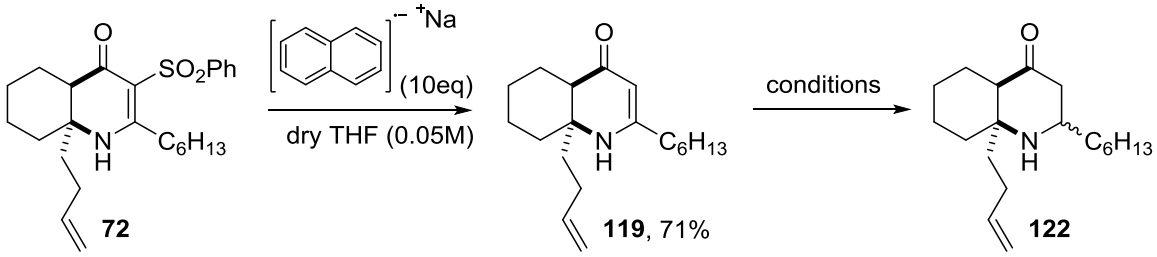
3.5 Reduction of enaminone 119

With the one-pot desulfonylation and reduction step yielding the undesired diastereomer, aminone **125,** as the major product, we explored conditions to selectively reduce the enaminone double bond of **119** to give the desired configuration of the *n*-hexyl group.

The Birch reduction conditions shown in Scheme 39 required condensation of liquid ammonia into a round bottom flask at -78 ^{o}C which was dried over sodium metal, followed by distillation into a separate flask in which the reaction could take place. This allowed for removal of water and any impurities in the ammonia, such as trace iron from the tank, which may have adversely affected the reduction reaction. Nevertheless, the reaction set up was tedious and unnecessarily labour intensive. For that reason, an alternative desulfonylation method was explored for obtaining compound **119**.

A solution of sodium naphthalanide in dry THF was added dropwise to a solution of **72** in dry THF until no starting material was detected by TLC. Enaminone **119** was then isolated in 71% yield. Unlike the Birch reduction conditions in Scheme 39, this procedure resulted in selective desulfonylation without reduction of the enaminone. Ideally we would have liked to improve the yield; however, this method provided easy access to enaminone **119**, and therefore allowed us to explore conditions to reduce the double bond moiety in a separate step (Scheme 42).

Scheme 42



The reaction conditions for attempted reduction of enaminone **119** are found in Table 5. Stirring enaminone **119** with zinc powder in acetic acid[(96)] returned only starting material while an alternative metal reduction, magnesium in refluxing methanol,[(54)] gave a complex mixture of unidentified products by ^{1}H-NMR spectroscopy. Attempts at activating the carbonyl moiety under Lewis acidic conditions using boron trifluoride diethyl etherate, followed by reduction with L-selectride®, also returned only starting material. Reduction using excess sodium borohydride gave no reaction, while lithium aluminium hydride returned only starting material. We expected, at the very least, the carbonyl group would be reduced to the hydroxyl group, resulting in an enamine moiety which could be further reduced by reductive amination; however, no reduced product was observed.

An attempt at reducing only the ketone group using Luche reduction conditions[(97)] also proved to be insufficient for that reduction. Under acidic conditions using TFA and sodium cyanoborohydride, the reduced species was not observed, nor was it observed when sodium triacetoxyborohydride was used with a catalytic amount of acetic acid.

With these somewhat puzzling results, we suspected that the free nitrogen was having an influence on our ability to effect the reduction.

Table 5: Reduction of enaminone 119

Entry	Conditions	Result
1	Zn, AcOH	Recovered starting material
2	Mg, MeOH	CM
3	$BF_3 \cdot OEt_2$, L-selectride, dry THF	Recovered starting material
4	$NaBH_4$, MeOH (1 to 10 equiv)	Recovered starting material
5	$LiAlH_4$, THF (1 to 10 equiv)	Recovered starting material
6	$CeCl_3 \cdot (H_2O)_7$, $NaBH_4$, MeOH	Recovered starting material
7	$NaBH_3CN$, TFA (20 equiv), DCM	Recovered starting material
8	$NaBH(OAc)_3$, AcOH (cat.), chloroform	Recovered starting material

In light of these results, the retrosynthesis outlined in section 3.2 would still be feasible; however, we envisaged that instead of using the fully reduced aminone **118** for the cyclisation of the C-ring, we could accomplish this transformation using enaminone **119**. The reduction of the enaminone double bond moiety would therefore be investigated at a later stage in the synthesis.

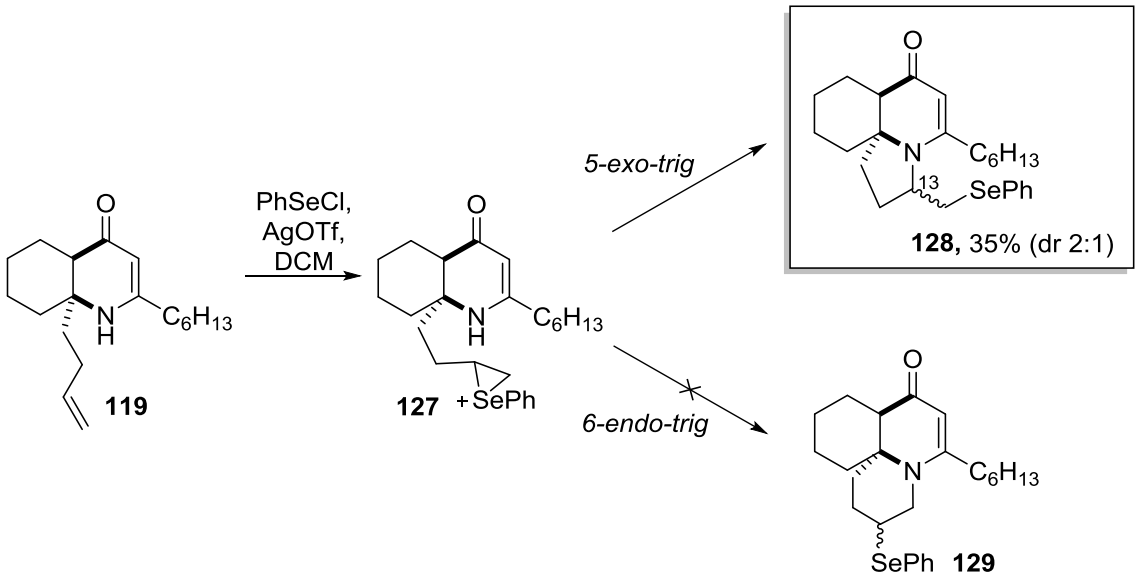
3.6 Electrophilic cyclisation

Reactions of alkenes containing tethered heteroatoms with electrophilic selenium reagents give rise to heterocyclic compounds.[98-100] Nitrogen-containing heterocycles are of particular interest in the context of our target molecule and therefore we explored these conditions to cyclise the five-membered C-ring. These types of reactions typically occur

by anti-addition, proceeding via seleniranium ion intermediate such as **127**, followed by nucleophilic ring-opening by the secondary amine to afford the cyclised product.

When enaminone **119** was subjected to a reaction mixture containing benzeneselenenyl chloride and silver triflate dissolved in DCM and wrapped in foil to avoid exposure to light, the desired selenide product **128** was isolated in 35% yield (Scheme 43). The ring-opening occurred in a regioselective manner on the unsymmetrical seleniranium ion, and resulted in the expected 5-exo-trig product **128** (predicted by Baldwin's rules) as an inseparable 2:1 mixture of diastereomers at the C-13 carbon (determined by integration of the respective peaks in the ^{1}H-NMR spectrum of the crude material). The 6-endo-trig cyclised product **129** was not observed.

Scheme 43

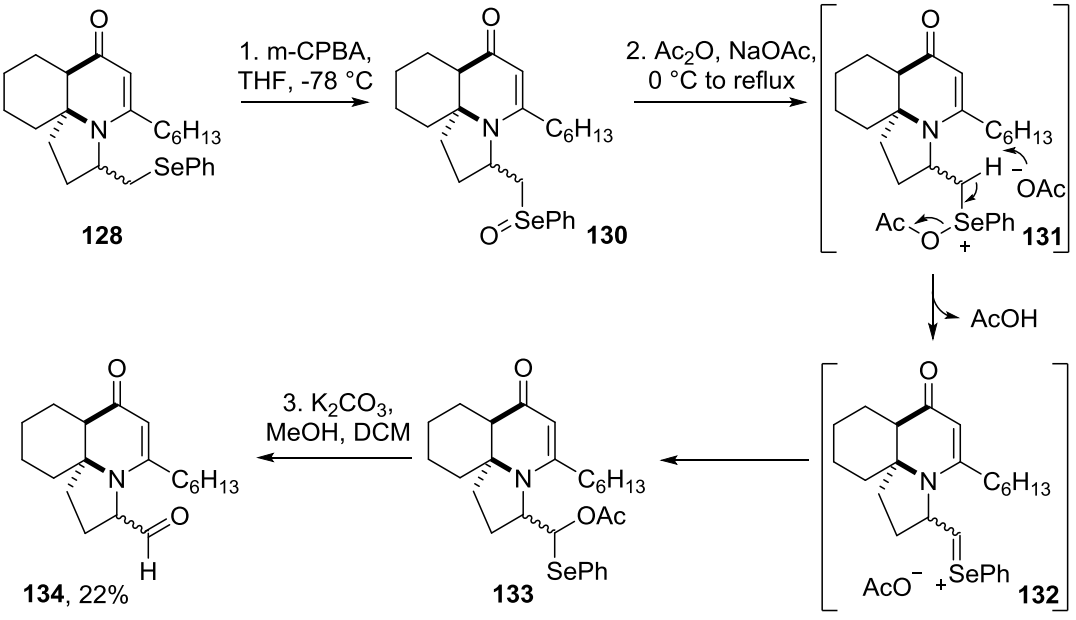


Unfortunately the yield could not be improved by addition of excess benzeneselenenyl chloride; neither did addition of excess silver triflate, acting as a halide scavenger, provide an improvement on the yield.

3.7 Selenide to aldehyde transformation

With the desired compound **128** in hand, albeit in low yield, we investigated conversion of the selenide into an aldehyde. The seleno-Pummerer rearrangement[101-104] allows for the installation of an acyl group geminal to the selenium atom by a sequence involving oxidation of the selenide to the selenoxide, followed by a Pummerer rearrangement to afford the corresponding acetoxy-selenide. Saponification of the acetoxy-selenide then provides the desired aldehyde.

Scheme 44

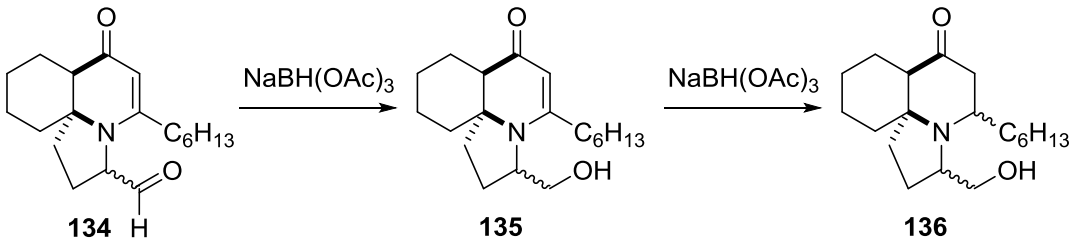


Treatment of selenide **128** with mCPBA at -78 ^{o}C gave the selenoxide **130** which was warmed to 0 ^{o}C and reacted directly with excess sodium acetate and acetic anhydride at reflux (Scheme 44). The reaction mixture, containing a diastereomeric mixture of acetoxy-selenides **133**, was concentrated and subjected to base-catalyzed methanolysis to afford aldehyde **134** in 22% yield over three steps. The ratio of diastereomers remained 2:1 (determined by integration of the ^{1}H-NMR spectrum of the crude reaction mixture), indicating that no epimerisation of the aldehyde had occurred under these conditions. The starting material was recovered in 30%, suggesting that the selenoxide had undergone reduction back to the selenide; however, due to lack of material, conditions to afford the aldehyde were not optimised.

3.8 Reduction of aldehyde 134

With the aldehyde in hand, and the relative stereochemistry of the major and minor stereoisomers being unknown, we explored conditions to reduce the aldehyde moiety to the corresponding hydroxymethyl group. When reacting aldehyde **134** with sodium triacetoxyborohydride, product **136** was isolated as mainly one stereoisomer in which both the aldehyde and the double bond moiety had been reduced (Scheme 45).

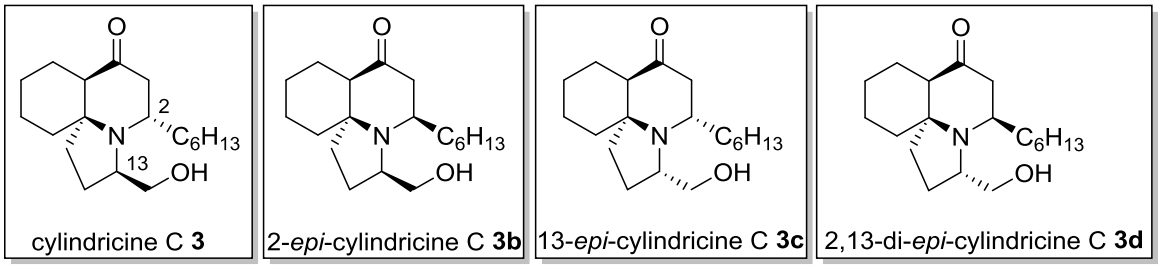
Scheme 45



134 **135** **136**

Upon comparison to the data published for the natural product **3**, as well as that of 2-epi-cylindricine C (**3b**) or 13-*epi*-cylindricine C (**3c**), we speculated that the major product of the reduction was 2,13-di-*epi*-cylindricine C (**3d**) due to it not matching any of the literature data. Unfortunately, the preparation of **3d** has not yet been published and therefore no comparison of data can be made.

Scheme 49



The tentative assignment of the final compound as 2,13-di-*epi*-cylindricine C (**3d**), showed that the major diastereomer had both the *n*-hexyl group and hydroxymethyl group in the opposite configuration to the desired product. Unfortunately, the isomer with the correct configuration at C-13 was not isolated; however, we predict that delivery of the hydride takes place from the same face as the hydroxymethyl group due to coordination of the hydroxy group and the triacetoxyborohydride.

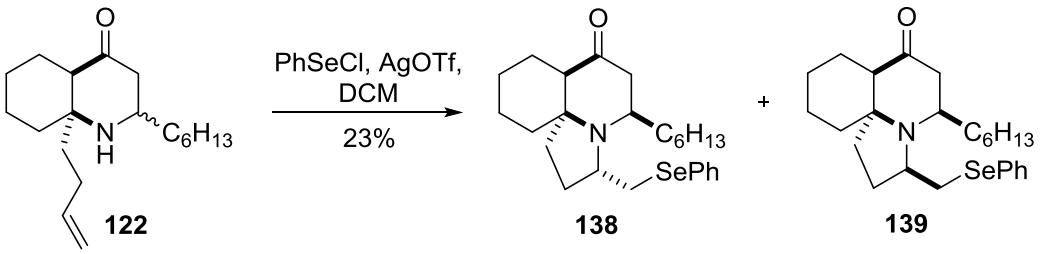
Even though some of the steps remained unoptimised, the outcome of the above synthesis resulted in the major stereoisomer as a novel compound thereby denying the opportunity to compare its spectra with an authentic sample. This leaves some uncertainty about the relative stereochemistry. Therefore, as a side project, we returned to the aminone **122**, with the idea of subjecting the compound to the same steps described

above. If successful, we would achieve the synthesis of the known 2-*epi*-cylindricine (**3b**), and gain confirmation of the stereochemistry of the C-13 center generated during the electrophilic cyclisation.

3.9 Electrophilic cyclisation of 122

Due to the difficulty in separating the 9:1 mixture of diastereomers from aminone **122** (see Scheme 38 and 39), we were forced to subject the product mixture to the electrophilic cyclisation. This approach would result in the formation of four diastereomers, making separation of each compound difficult. That being said, we were only concerned with isolating the major products from the reaction.

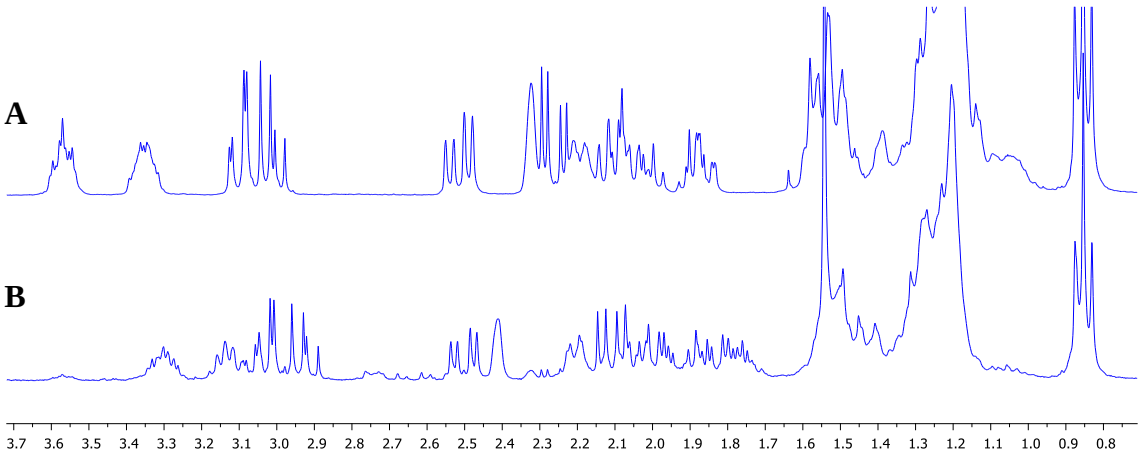
Scheme 46



Stirring a solution of aminone **122**, benzeneselenenyl chloride and silver triflate in DCM in the dark overnight gave a mixture of selenides as a 1:1 mixture of diastereomers in 23% yield. The minor stereoisomers from the 9:1 mixture of aminone **122** were not isolated and therefore the selenides were assigned as structures **138** and **139** respectively. The ^{1}H-NMR spectra of the diastereomers are shown in Figure 3. Spectrum A shows the ^{1}H-NMR spectrum of the diastereomer which was cleanly isolated while spectrum B shows the second diastereomer isolated as an impure mixture. The relative

stereochemistry of the selenide and *n*-hexyl group was difficult to determine from these spectra and therefore the isolated isomer could not definitively be assigned as **138** or **139**.

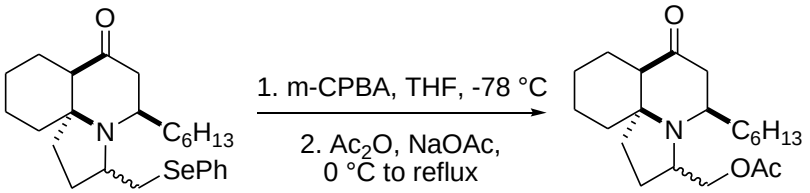
Figure 3: ^{1}H-NMR ($CDCl_3$) spectra of selenides 138 and 139



3.10 Installation of the oxygen functionality to give epimers at the C-13 position

A mixture of selenides **138** and **139** were subjected to the seleno-Pummerer conditions described in section 3.6. This included oxidising the selenide to the selenoxide using m-CPBA, and once all starting material was consumed (monitored by TLC), the reaction mixture was warmed to 0 ^{o}C, at which point, acetic anhydride and sodium acetate were added and the reaction mixture was heating at reflux for 6 h. Surprisingly, compound **140**, with a single acetate and lacking the phenylseleno group, was isolated as a 1:1 mixture of diastereomers in 54% yield (Scheme 47).

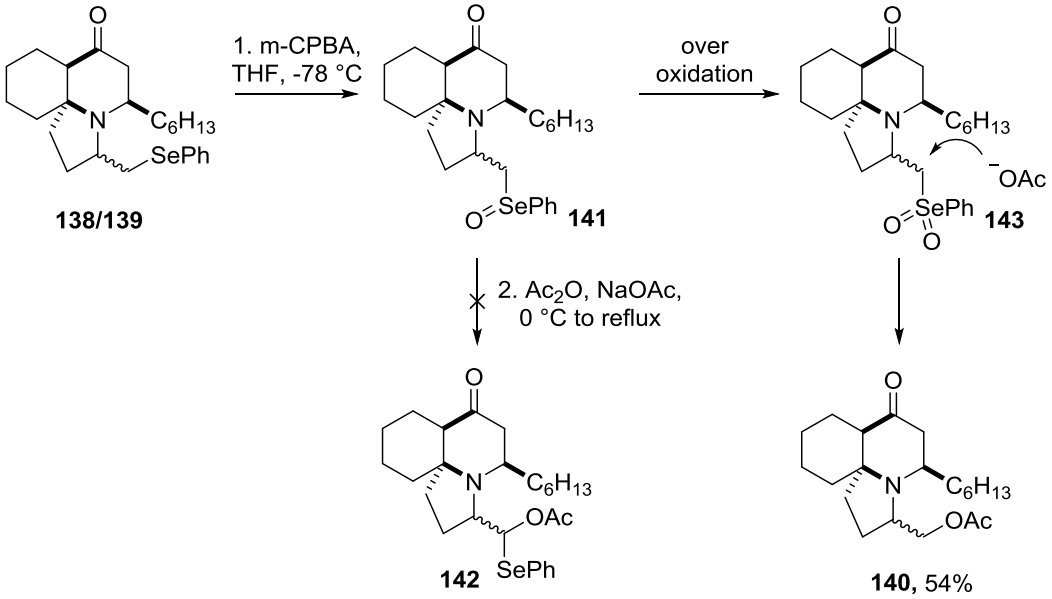
Scheme 47



138/139 **140,** 54%

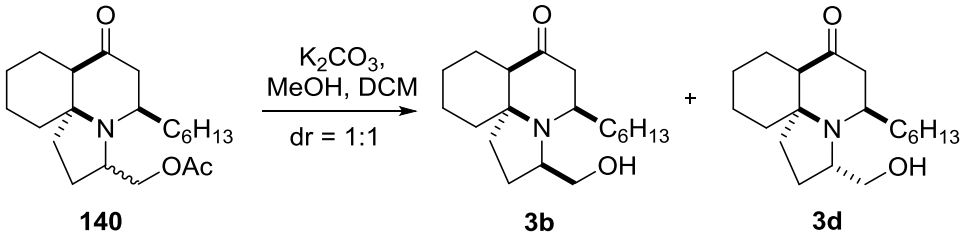
The desired and expected compound was acetoxy-selenide **142** which should have resulted from the rearrangement in the presence of sodium acetate. The formation of acetate **140** led us to believe that instead of the formation of selenoxide **141**, over-oxidation of the selenide had occurred, resulting in selenone **143**, which could undergo substitution in the presence of sodium acetate to give compound **140**. Precedence for selenone formation in the presence of excess oxidising agent and displacement by various nucleophiles is well established.[105-108] It is known that the leaving group ability of the selenonyl moiety ($RSeO_2^-$) is comparable to that of a sulfonate (RSO_3^-)

Scheme 48



When compound **140** was subjected to acetate cleavage by methanolysis, a mixture of epimers, identified as 2-epi-cylindricine C (**3b**) and the putative 2,13-di-epi-cylindricine C (**3d**), was isolated in 57% yield.

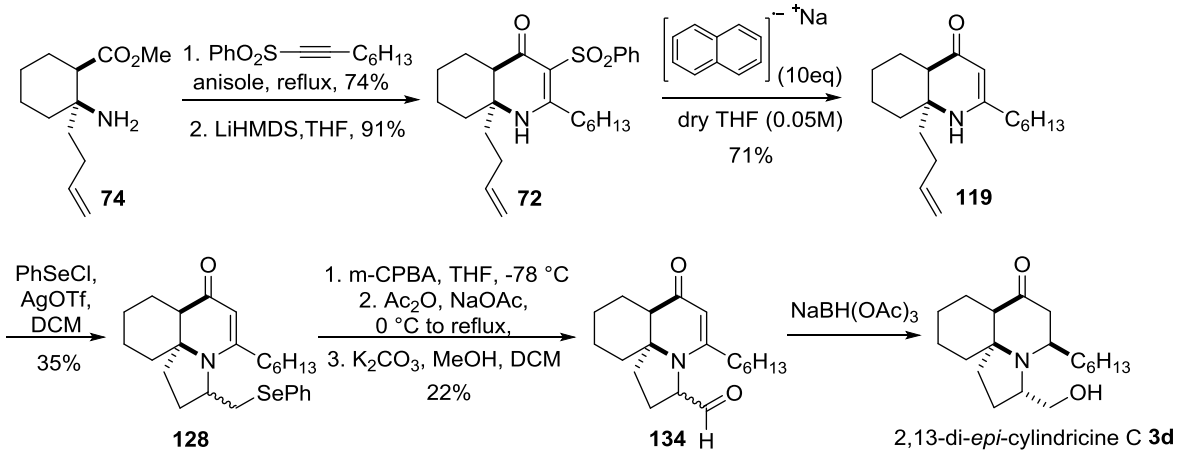
Scheme 49



3.11 Summary

The conjugate addition and cyclisation of β-amino ester **74** with acetylenic sulfone **73** was effectively utilised to establish the six-membered ring in the form of sulfone **72**. The sulfone group was successfully removed by reductive desulfonylation with sodium naphthalenide as the reducing agent to give the desired enaminone in good yield. The five-membered third ring of the heterocyclic core of the alkaloid was achieved by electrophilic cyclisation to give the selenide **128** in modest yield. The seleno-Pummerer rearrangement and base hydrolysis yielded aldehyde **134**. A one pot reduction of both the aldehyde and the double bond moiety led to the tentatively identified 2,13-di-*epi*-cylindricine C (**3d**) as the major diastereomer. Unfortunately, compound **3d** has not yet been reported in the literature, resulting in some uncertainty regarding the relative stereochemistry.

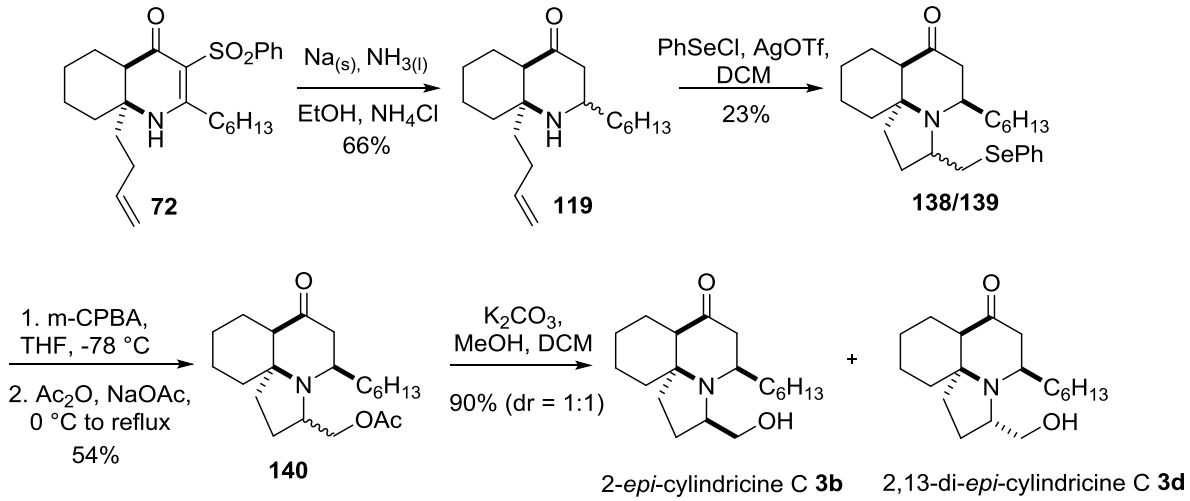
Scheme 50



Consequently, the synthetic route was revised. Compound **72** was subjected to Birch reduction conditions allowing for both desulfonylation and reduction of the double

bond moiety to give aminone **119** as a 9:1 mixture of inseparable diastereomers. The *n*-hexyl group of the major isomer was found to have the incorrect configuration, as evidenced by its subsequent conversion to 13-*epi*-cylindricine C (**3b**). The heterocyclic core was finalised by formation of the C-ring by electrophilic cyclisation using benzeneselenenyl chloride. The resulting selenide was subject to a seleno-Pummerer rearrangement. However, acetate **140** was isolated as the major product, leaving us to speculate that over-oxidation of the selenide to the selenone had occurred, followed by nucleophilic substitution by the acetate anion, thereby resulting in the acetate-protected alcohol. Base hydrolysis of the acetate resulted in an inseparable mixture of 2-*epi*-cylindricine C (**3b**) and 2,13-di-*epi*-cylindricine C (**3d**).

Scheme 51

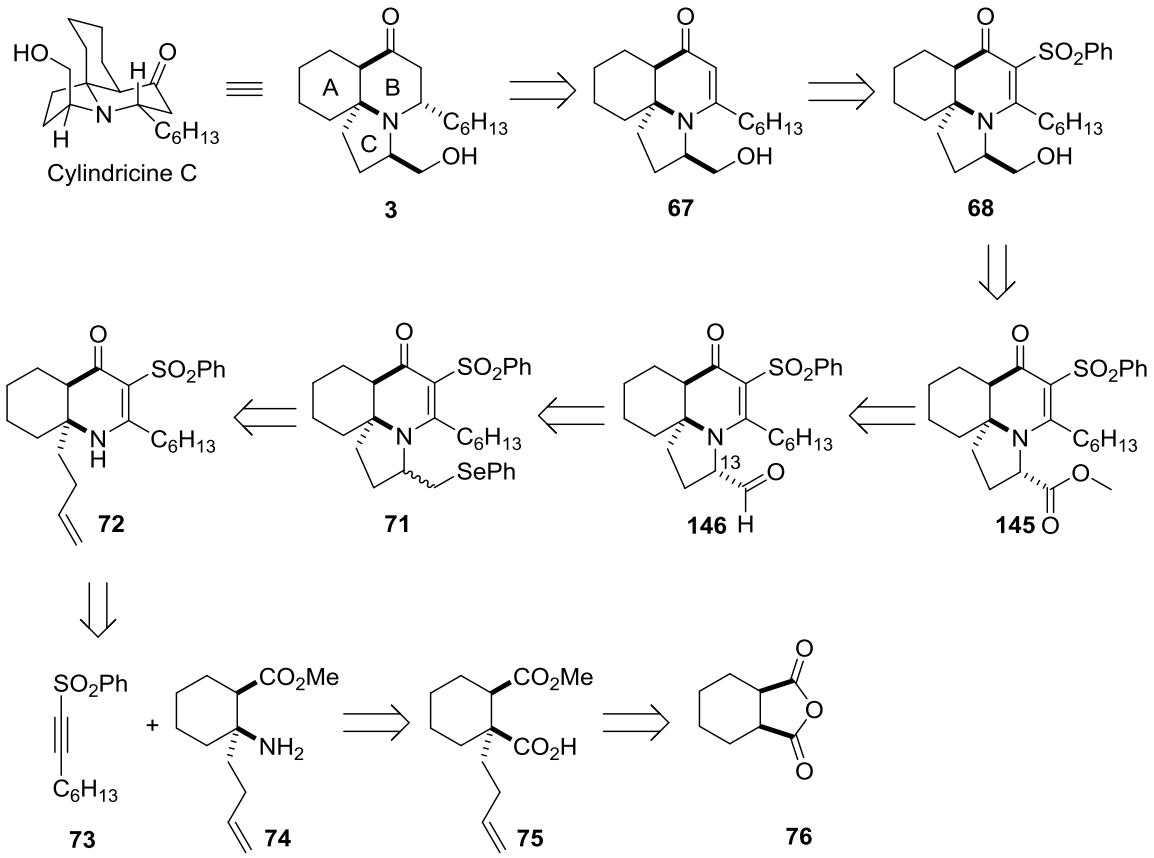


Chapter Four: Alternative route to the amino ester intermediate

4.1 Overview

This chapter will focus on improving and optimising the synthesis reported by Dr. K. Clary described in section 1.4.2 and extending the synthesis beyond advanced intermediate **83** described in section 1.4.3. The retrosynthesis, previously described in section 1.4.1 was revised to incorporate the corrected stereochemistry of the hydroxymethyl group observed by Dr. K. Clary and is shown below for convenience (Scheme 52).

Scheme 52

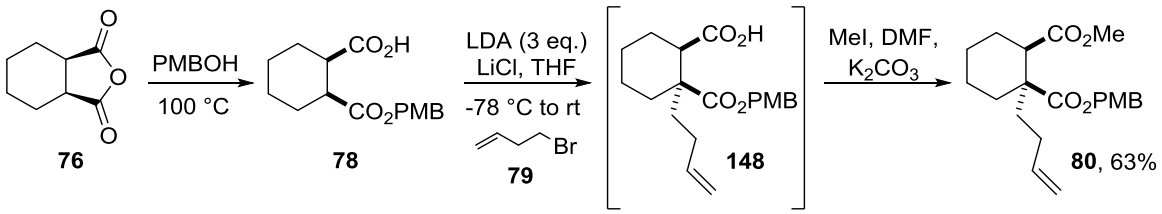


The target compound **3** would result from stereoselective reduction of the enaminone double bond of **67**, following reductive desulfonylation of hydroxymethyl compound **68**. The correct configuration of the hydroxymethyl group would be obtained from base-mediated epimerisation and reduction of methyl ester **145**, which was envisaged by the oxidation of aldehyde **146**. A seleno-Pummerer rearrangement of selenide **71** and base cleavage would afford aldehyde **146** with the incorrect stereochemistry at the C-13 position (based on the stereochemistry of alcohol **83** which had been confirmed by an X-ray crystal structure (see Section 1.4.3). The selenide **71** would be obtained by electrophilic cyclisation of enaminone **72**, which could be prepared by tandem conjugate addition and base promoted intramolecular cyclisation of acetylenic sulfone **73** and β-amino ester **74**.

4.2 Preparation of alkylated diester 151

The synthesis commenced with alcoholysis of cheap starting material 1,2-cyclohexanedicarboxylic anhydride (**76**) using PMB alcohol to generate the mono-PMB ester **78** (Scheme 53). Once again, one enantiomer is shown for clarity of relative stereochemistry; however, a racemic mixture was obtained.

Scheme 53



Alkylation of mono-ester **78** was previously achieved using two equivalents of freshly prepared LiHMDS to generate the dianion of compound **78**, followed by addition of 4-bromobutene and left to stirring for 4 days at room temperature followed by esterification of unseparated reaction mixture to give diester **80** in 61% yield. However, when repeating this reaction under similar conditions, and then attempting to isolate intermediate **148** before esterification, variable yields ranging from 20% to 40% were obtained. The reason for low yields was attributed to the difficulty in isolating compound **148** by column chromatography due to the highly polar carboxylic acid group.

Purification was further complicated by a large amount of unreacted starting material, resulting in co-elution of compounds **78** and **148** during column chromatography. In an attempt to partially purify the reaction mixture before column chromatography, the reaction mixture was extracted using basic conditions to generate the carboxylate salt, followed by acidification and re-extraction with ethyl acetate. However, no material was obtained after concentrating the solvent in vacuo. This is possibly due to the hydrophobicities of the cyclohexane and PMB protecting group making the carboxylate anions of both compound **78** as well as **148** insoluble in aqueous base.

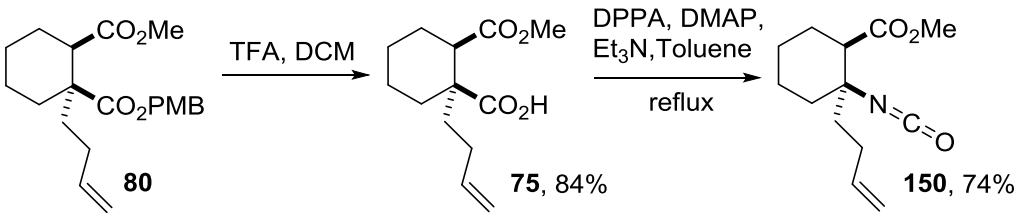
At this time, the one pot synthesis of alkylated diester **80** described in section 1.4.2 was employed; however, due to the inability of purchasing TMS-diazomethane from a chemical supplier, the esterification procedure was altered. The best conditions for a one pot procedure were found to be three equivalents of freshly prepared LDA, LiCl as an additive, and one equivalent of the homoallylic bromide **79**, to give compound **148** as an intermediate. The unseparated reaction mixture, containing carboxylic acid **148** and

some unreacted compound **78**, was reacted with excess methyl iodide under basic conditions to afford alkylated diester **80** in 63% yield which was comparable to that described in section 1.4.2.

4.3 Synthesis of isocyanate 150

The quaternary center of cylindricine C was one of many challenging stereocenters to consider when developing the retrosynthetic pathway. We envisaged that the nitrogen atom, that would later make up the aza-spirocenter, could be installed by a Curtius rearrangement[75-78] via the carboxylic acid group at the quaternary carbon. The main feature of this rearrangement would be the retention of configuration during formation of the isocyanate. Therefore, the PMB ester of compound **80** was selectively cleaved over the methyl ester under acidic conditions using excess TFA in DCM to afford compound **75** in 84% yield (Scheme 54). The carboxylic acid **75** was subjected to the conditions described previously for a Curtius rearrangement using DPPA[79] to afford isocyanate **150** in good yield.

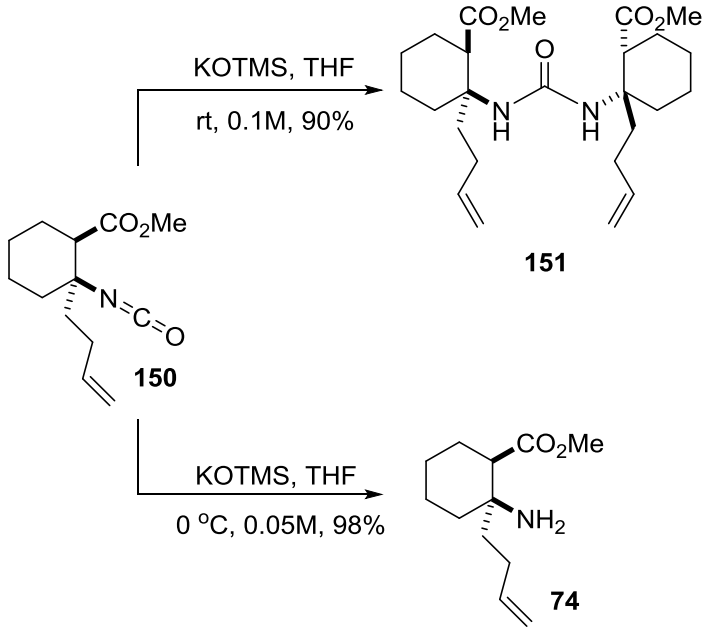
Scheme 54



4.4 Synthesis of β-amino ester 74

The previous route for synthesis of β-amino ester **74** described in section 1.4 was achieved by reacting the isocyanate with PMB alcohol in DMF, with CuCl as an additive affording carbamate **81**. This was followed by cleavage of the PMB moiety under acidic conditions and in situ decarboxylation to give compound **74**. However, in the synthesis of compound **74** via the route described in Section 2.4, KOTMS was found to react with an isocyanate and upon aqueous workup, the free amine was obtained.

Scheme 55



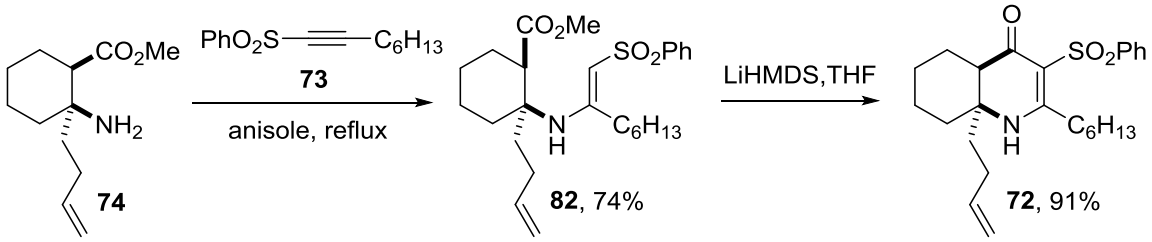
Thus, when isocyanate **150** was subjected to the same conditions described in Section 2.4, ^{13}C-NMR analysis of the reaction mixture revealed double the number of expected carbon peaks, indicating that dimerisation had possibly occurred. Bearing in mind that isocyanates are generally good electrophiles, any free amine formed in situ could react with remaining isocyanate starting material to form a urea. Purification by

column chromatography revealed urea **151** as an unwanted product in excellent yield (Scheme 55). Although compound **151** is shown as a single diastereomer, the product would be a mixture of diastereomers having nearly identical NMR spectra. To avoid formation of urea **151**, a dilute solution of 0.05 M was used while keeping the reaction mixture at zero degrees, affording β-amino ester **74** in nearly quantitative yield with no evidence of urea **151** by ^{13}C-NMR analysis of the reaction mixture.

4.5 Tandem conjugate addition and cyclisation

A conjugate addition of amine **74** to acetylenic sulfone **73** gave vinyl sulfone **82** in 74% yield (described in Section 3.3), followed by cyclisation under basic conditions to give compound **72** in an excellent 91% yield (Scheme 56). Enaminone **72** was thus achievable on a gram scale, with reproducible yields.

Scheme 56



4.6 Cyclisation of the C-ring

The next step was to cyclise the five-membered C-ring using the electrophilic cyclisation described in Section 3.6. Initially, when reacting benzeneselenenyl chloride and silver triflate dissolved in DCM with compound **72**, the desired selenide **71** was

isolated in 92% yield as an inseparable 3:1 mixture of diastereomers (determined by integration of the ^{1}H-NMR spectrum of selenide **71** shown in Figure 4).

The ^{1}H-NMR spectrum of the mixture of stereoisomers, of which a small amount of the major stereoisomer could be separated in sufficient amount for characterisation by NMR spectroscopy, is shown in Figure 4. Proton H_a gave a doublet of doublets with a geminal coupling of J = 12.5 Hz and a large coupling constant of J_{ac} = 11.6 Hz for the trans coupling of protons H_a and H_c. The signal from proton H_b is a doublet with a geminal coupling of J = 12.5 Hz. The multiplet at 4.09 - 4.01 ppm corresponds to proton H_c, while the multiplets at 3.28 ppm and 1.86 ppm correspond to proton H_d in the allylic position.

Scheme 57

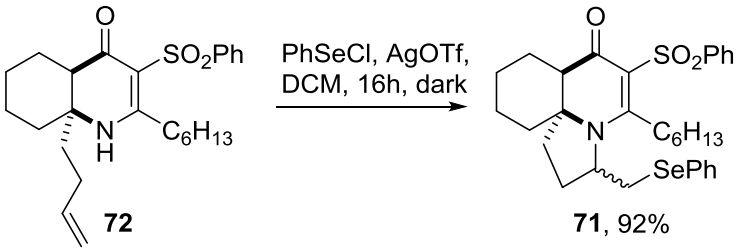
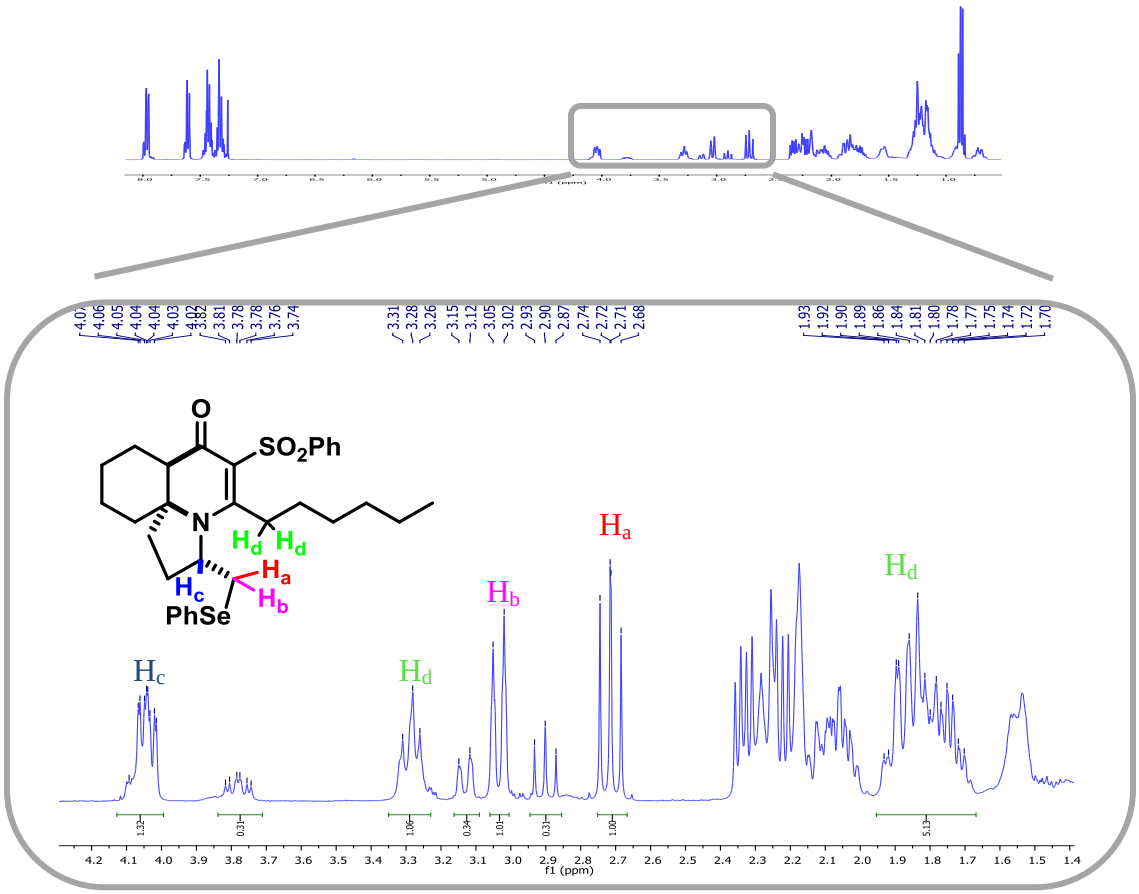


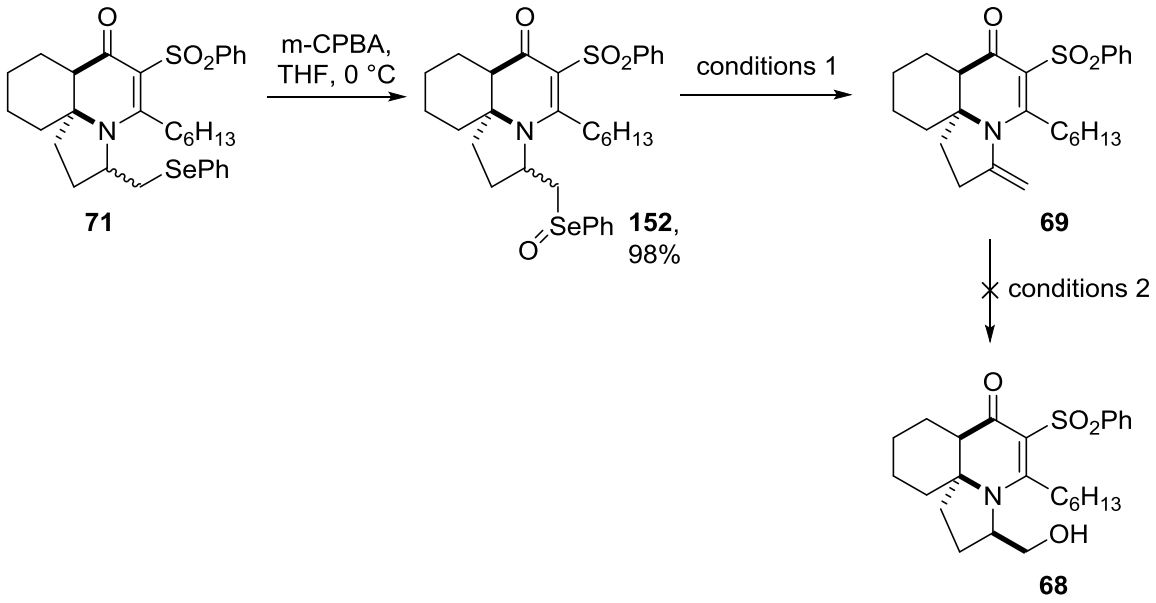
Figure 4: ^{1}H-NMR ($CDCl_3$) spectra of the 3:1 mixture of selenides 71



4.7 Selenoxide elimination and hydroboration

We next investigated a route to regulate the stereochemistry of the hydroxymethyl group to give the desired stereoisomer of alcohol **68**. Conditions to effect a selenoxide elimination to give olefin **69** were explored. Selenide **71** was oxidised in the presence of m-CPBA to give selenoxide **152** in excellent yield. Surprisingly, the selenoxide was stable to basic workup and column chromatography; however, selenoxide **152** existed as a mixture of four stereoisomers which were inseparable by column chromatography, making the mixture difficult to analyse by ^{1}H-NMR spectroscopy.

Scheme 58



Next, conditions for effecting the selenoxide elimination were explored and are tabulated in Table 6. A base-assisted elimination using diisopropylamine in refluxing DCM resulted in enamine **69** in only 15% yield (Scheme 59). When refluxing selenoxide **152** in higher boiling solvents such as chloroform or 1,4-dioxane with K_2CO_3 as the base, no reaction was observed (Entry 2). When adding the starting material to a refluxing solution of diisopropylamine in carbon tetrachloride, a complex mixture of unidentifiable compounds was observed (Entry 3). Changing the base to triethylamine and adding magnesium sulfate to absorb any residual water resulted in only a small amount of olefin **69**, as detected by ^{1}H-NMR analysis of the reaction mixture, while the use of pyridine as the base returned only starting material (Entries 4 and 5). At this stage, we could observe enamine **69** by ^{1}H-NMR spectroscopy; however, due to the inability to isolate sufficient quantities of the product, we speculated that the enamine moiety was too reactive to

aqueous workup conditions. We consequently attempted to react the enamine in situ using hydroboration.

Table 6: Conditions for elimination and hydroboration of compound 152

Entry	Conditions 1	Conditions 2	Result
1	diisopropylamine, DCM, heat		**69** (15% isolated) + SM
2	K_2CO_3, DCM, chloroform/ 1,4-dioxane		No reaction
3	diisopropylamine, CCl_4, heat		CM
4	Et_3N, dry DCM, $MgSO_4$, heat		**69** (by NMR)
5	pyridine, $CDCl_3$		No reaction
6	diisopropylamine, DCM	1.BH_3.THF 2. NaOH 3.0M, H_2O_2 (30%)	CM
7	diisopropylamine, $CDCl_3$	1. 9-BBN, 2. $NaBO_3.4H_2O$ in H_2O, H_2O_2 (30%)	**69** (by NMR) + SM

Returning to conditions used in entry 1, selenoxide **152** was refluxed and concentrated in-vacuo to afford a viscous oil. The resulting oil was reacted with borane-THF complex followed by an oxidative workup; however a complex mixture of unidentified products was observed. A second attempt at a hydroboration was made using 9-BBN on the unseparated reaction mixture, but no desired product was observed by NMR spectroscopy.

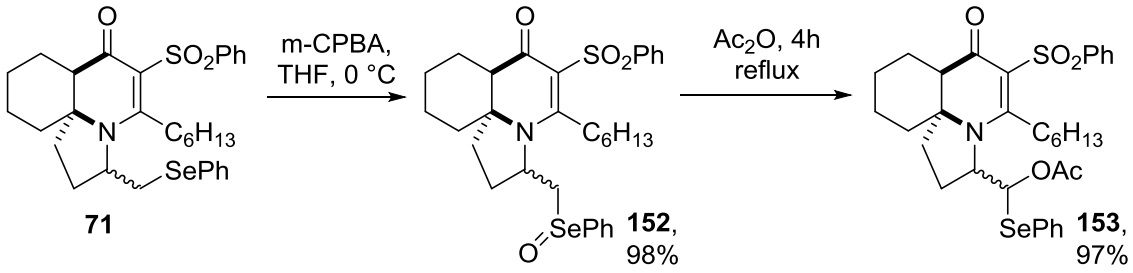
With no conclusive evidence of the selenoxide being eliminated to form sufficient amounts of enamine **69**, nor any success with effecting the hydroboration and oxidative cleavage to afford the desired alcohol, we chose to use the seleno-Pummerer

rearrangement and base cleavage on selenide **71** to install the oxygen functionality and regulate the stereochemistry at the C-13 position at a later stage in the synthesis.

4.8 Seleno-Pummerer rearrangement and saponification to aldehyde 70

In order to improve and optimise the seleno-Pummerer rearrangement and base-mediated cleavage steps, the previously low yielding, three step one-pot synthesis of aldehyde **70** was improved by refining each step and isolating each intermediate.

Scheme 59

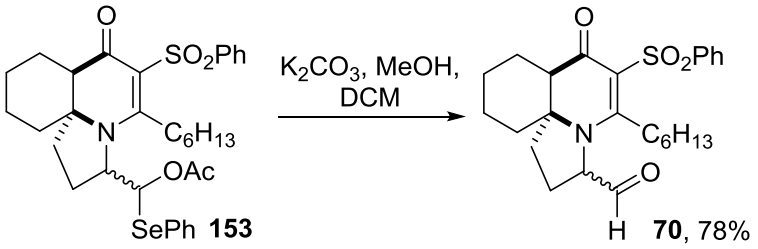


Selenoxide **152** was synthesised in quantitative yield as before by reacting selenide **71** with m-CPBA at 0 ^{o}C. When reacting selenoxide **152** with acetic anhydride at reflux, a diastereomeric mixture of acetoxy-selenides **153** was obtained in 97% yield. Under these conditions, no sodium acetate was needed to drive the rearrangement step to completion, suggesting that only one equivalent of the acetate anion, generated from cleavage of acetic anhydride, was sufficient to afford the desired seleno-Pummerer product **153**.

Acetoxy-selenide **153** was subjected to saponification using K_2CO_3 dissolved in a 2:1 mixture of methanol and DCM, affording aldehyde **70** in 78% yield as an inseparable 3:1 mixture of diastereomers (determined by integration of the respective peaks in the ^{1}H-

NMR spectrum of the unseparated reaction mixture). We found that upon basic workup, the formation of the dimethyl acetal protected aldehyde was detected in the ^{1}H-NMR spectrum of the reaction mixture after workup. Therefore neutral conditions were used during workup to ensure complete cleavage of any acetal product that may have formed.

Scheme 60



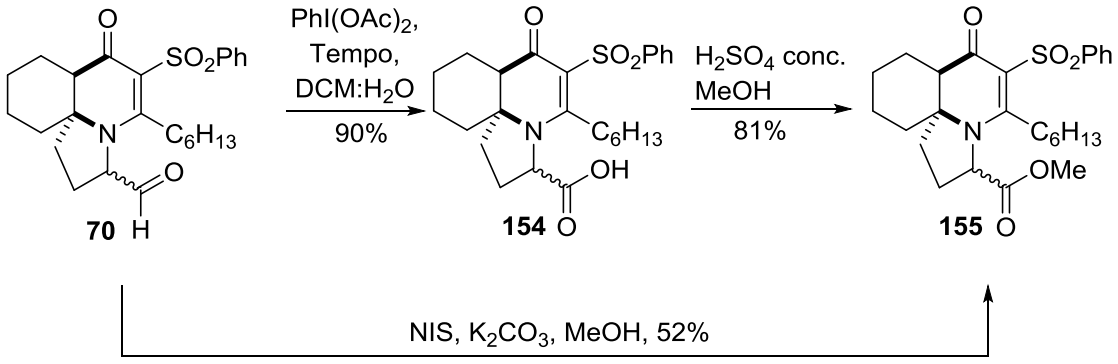
4.9 Oxidation of aldehyde 70

With aldehyde **70** in hand, we explored conditions to epimerise the C-13 carbon to obtain the correct stereochemistry at that position. Attempts to effect an epimerisation under basic conditions using K_2CO_3 were unsuccessful. The aldehyde was always isolated as an inseparable 3:1 mixture of diastereomers. We envisaged the epimerisation potentially being effected on a methyl ester, so we explored conditions to oxidise aldehyde **70** to methyl ester **155**. In section 2.5 a one-pot oxidation of the aldehyde directly to a methyl ester was achieved in good yield using an iodine-mediated oxidation.

Using similar conditions, aldehyde **70** was stirred with *N*-iodosuccinimide in methanol[(95)] under basic conditions to give methyl ester **155** in a modest 52% yield (Scheme 61). We also attempted to oxidise aldehyde **70** to the corresponding carboxylic acid **154**. When aldehyde **70** was subjected to a hypervalent iodide oxidation using

diacetoxyiodobenzene and TEMPO[109] dissolved in a 2:1 mixture of DCM and water, the desired carboxylic acid **154** was obtained in 90% yield.

Scheme 61



Compound **154** was converted to methyl ester **155** by stirring in a solution of methanol and concentrated H_2SO_4 overnight, affording the desired compound in 81% yield. Although the iodine mediated one-pot oxidation yielded the desired methyl ester **155**, no optimisation of the reaction conditions could be performed due to lack of starting material.

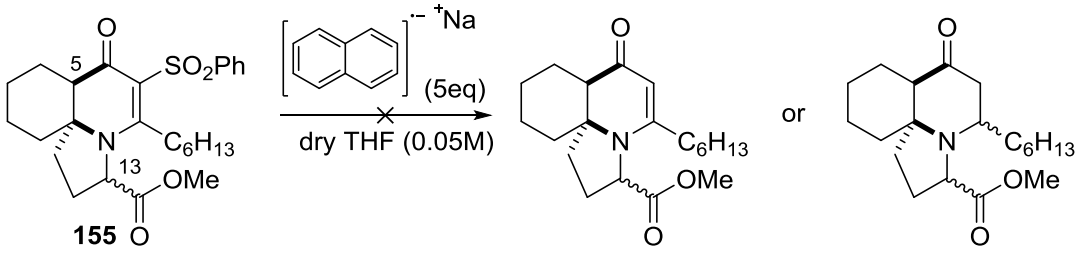
4.10 Epimerisation and desulfonylation of methyl ester 155

With methyl ester **155** in hand, the epimerisation was attempted. The methyl ester was stirred with freshly prepared sodium methoxide in methanol; however, ^{1}H-NMR analysis of the unseparated reaction mixture indicated the presence of a peak corresponding to a methyl ether which may have come from a 1,4-conjugate addition of methoxide. With no conclusive evidence of epimerisation taking place, we decided to investigate the epimerisation at a later stage in the synthesis. We anticipated that we

could revisit the epimerisation after desulfonylation of ester **155** and reduction of the enaminone double bond moiety.

Therefore, the desulfonylation reaction was attempted using conditions shown in Scheme 62. A solution of sodium naphthalenide in dry THF was added dropwise to a solution of methyl ester **155** in dry THF. After addition of five equivalents of sodium naphthalenide, no starting material remained (when monitored by TLC). The ^{1}H-NMR spectrum of the unseparated reaction mixture revealed a complex mixture of unidentified compounds. The lack of the methyl ester moiety in the ^{1}H-NMR spectrum suggested that possible reduction of the ester had occurred. When the reductive desulfonylation of ester **155** was attempted using an alternative reducing agent, LDBB, a complex mixture of unidentified products was obtained.

Scheme 62

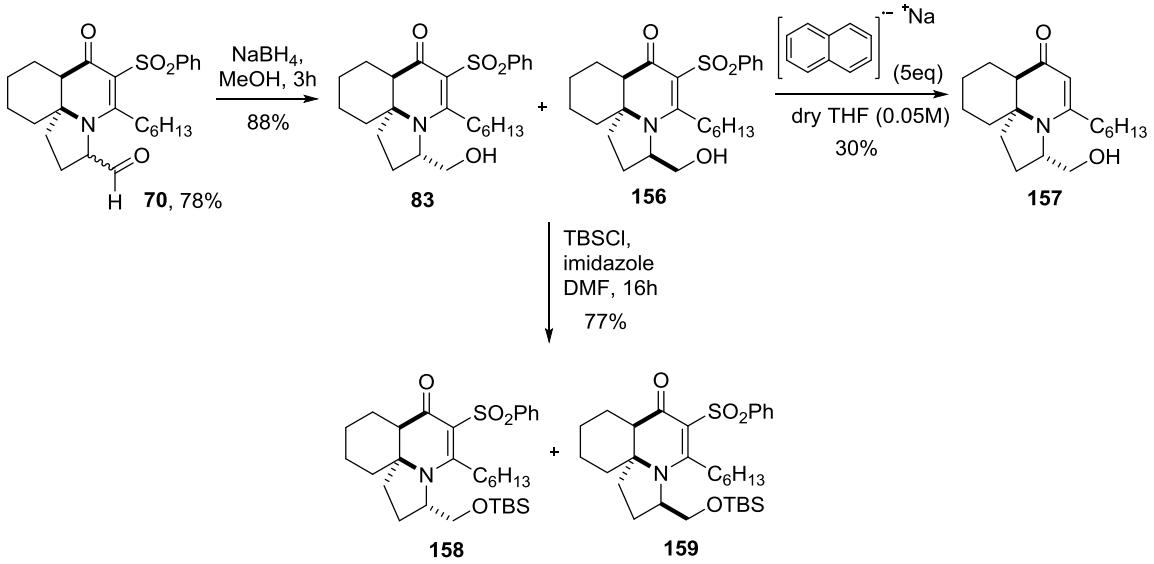


At this stage, neither epimerisation nor desulfonylation could be successfully effected on methyl ester **155**. A number of reasons for this could be the possibility of epimerisation occurring at the C-5 position α to the ketone, resulting in a *trans*-decalin system, thereby complicating the ^{1}H-NMR spectrum of the reaction mixture due to additional diastereomers being formed. Reduction of the enaminone double bond moiety and/ or reduction of the ketone under these conditions might have also occurred.

4.11 Reduction of aldehyde 70

Efforts were refocused on reducing aldehyde **70** prior to reductive desulfonylation. Reduction of aldehyde **70** (Scheme 63), in the presence of $NaBH_4$, gave alcohols **156** in 88% yield as an inseparable mixture of diastereomers in a ratio of 3:1 (determined by integration in the ^{1}H-NMR signals of the isolated alcohols **156**).

Scheme 63

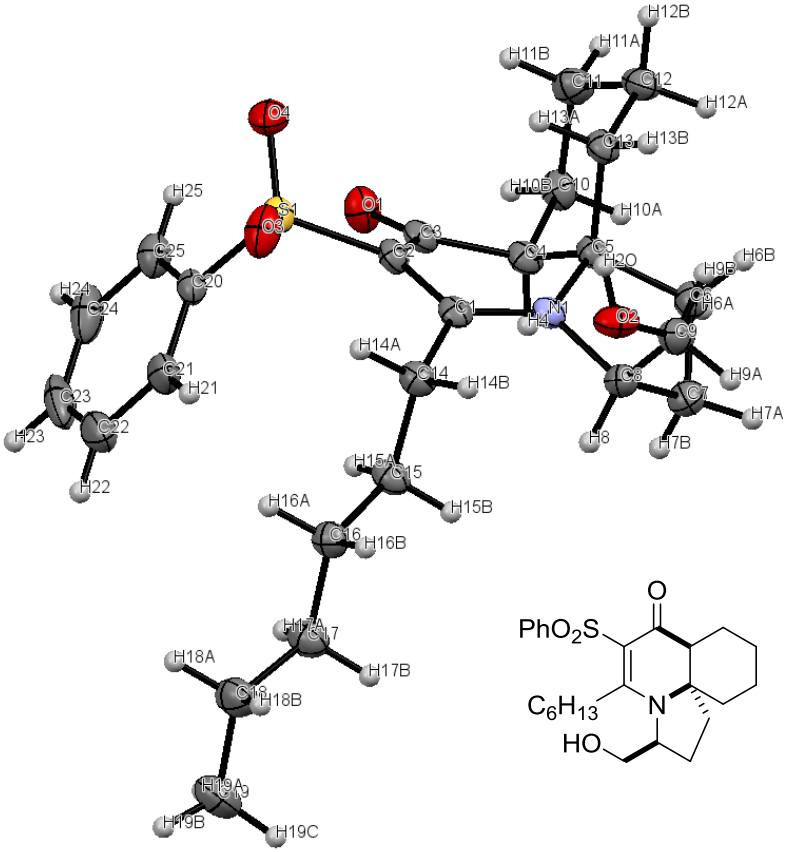


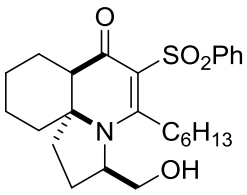
Although stereoisomers **83** and **156** could not be completely separated by column chromatography, collection of clean fractions from both the leading band and tailing band allowed for characterisation of the major and minor isomers respectively.

The x-ray crystal structure obtained by Dr. K. Clary, for major isomer **83**, showed the incorrect stereochemistry of the hydroxymethyl group at the C-13 center. In order to confirm that the minor compound **156** of the mixture of isomers was not due to epimerisation occurring at the C-5 center α to the ketone, but was indeed the minor

isomer having the hydroxymethyl group in the correct configuration, an x-ray crystal structure was obtained (Figure 5), confirming the desired configuration at the C-13 center. The ORTEP diagram shows the enantiomer of compound **156** due to the synthesis being racemic and is shown below for clarity.

Figure 5: ORTEP diagram of compound 156 (Numbering of atoms in the x-ray structure is arbitrary and does not follow IUPAC rules)





156

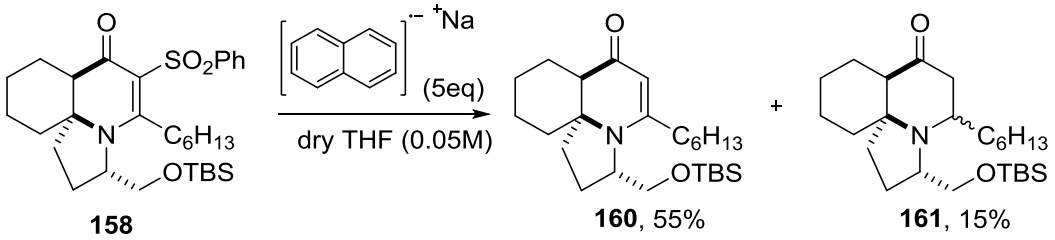
. The alcohol **83** was subjected to desulfonylation conditions using sodium naphthalenide in dry THF to give enaminone **157** in poor yield. Although no optimisation of the reductive desulfonylation reaction was done, a low yield of the desired product

suggested that the free hydroxyl group could be adversely effecting the reduction step. Therefore, alcohols **83** and **156** were subjected to a silyl protection using standard conditions to give TBS protected alcohols **158** and **159** in a combined yield of 77%. With the silyl protecting group in place, the 3:1 mixture of diastereomers could easily be separated by column chromatography. As a result of being able to separate the silyl protected diastereomers, we were able to carry forward pure starting materials, thereby making the identification and characterisation of the resulting products easier.

4.12 Desulfonylation and reduction of major isomer 158

A reductive desulfonylation reaction was explored on compound **158**. Using potassium graphite[110] (commonly referred to as KC_8) in deuterated THF, the desired compound **160** was isolated in 69% yield. Unfortunately, on a larger scale, only minor amounts of the desired compound could be observed by ^{1}H-NMR analysis of the unseparated reaction mixture. Multiple minor products were present but could not be isolated in sufficient quantities for characterisation by NMR spectroscopy. When subjecting compound **158** to a sodium naphthalenide reduction (Scheme 64), the desired enaminone **160** was isolated in 55% yield along with 15% yield of compound **161**.

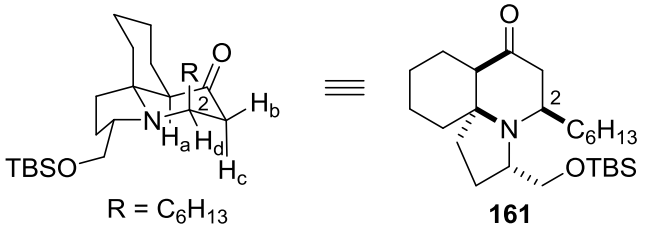
Scheme 64



Over reduction of the enaminone double bond was not unexpected, as this was previously observed in an earlier reduction described in section 3.4. Analysis of the NMR data for compound **161** (Figure 6) shows proton H_a as a broad singlet with no identifiable coupling constant. The proton H_b shows up as doublet of doublets with couplings of 15.7 Hz and 5.6 Hz, while proton H_c shows up as a doublet of doublets with couplings of 15.7 Hz and 7.4 Hz. The larger coupling corresponds to the geminal coupling of protons H_b and H_c, while the smaller coupling correspond to the equatorial/ equatorial and axial/ equatorial relationship for H_b/ H_d and H_c/ H_d respectively. The proton H_d shows up as a multiplet at 3.44 ppm.

Although the NMR data does not prove the stereochemistry with certainty, lack of a larger trans-diaxial coupling between proton H_b and H_d suggested that reduction of the enaminone double bond of compound **160**, using a single electron reduction, did not generate the desired configuration at the C-2 center. Therefore, the sterechemistry of the C-2 center attached to the *n*-hexyl group was tentatively assigned as shown in Figure 6.

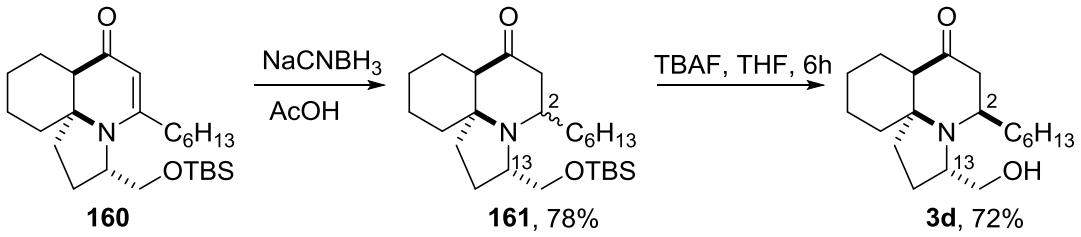
Figure 6: Conformational structure of compound 161



Alternative methods for reduction of the enaminone double bond were therefore explored. Organocuprate reagents are widely used in organic synthesis.[111] One such reagent, highly selective for 1,4-addition reactions, is that of Stryker's reagent[112-115].

This copper hydride reagent, $[(Ph_3P)CuH)]_6$, was added to a solution of degassed toluene along with compound **160** and stirred for 24 hours, at which time, no reaction was observed by TLC. Stoichiometric amounts of the copper hydride reagent were then added and stirred for a further 24 hours, at which time the reaction was quenched due to no sign of any change when monitored by TLC. Upon workup, the ^{1}H-NMR spectrum of the reaction mixture confirmed the presence of only starting material. It is possible that a combination of the bulky ligands, the bulky silyl group and the quaternary carbon center created too much steric hindrance for delivery of the hydride; however, it is also possible that the enaminone double bond moiety is stabilised by extended conjugation and does not react in the same way as an isolated α,β-unsaturated system.

Scheme 65



160 **161**, 78% **3d**, 72%

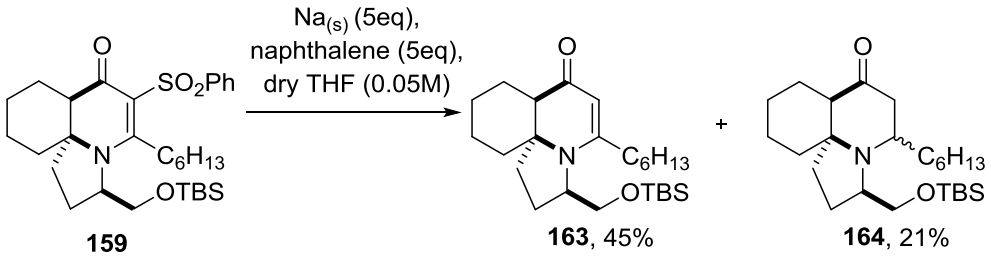
When reacting enaminone **160** with $NaCNBH_3$ in acetic acid, the reduced product **161** was isolated in good yield as a single diastereomer (Scheme 65). The configuration of the C-2 center attached to the *n*-hexyl group was difficult to determine by NMR

analysis; however, deprotection of the TBS group would yield one of two epimers of the natural product. Therefore, we subjected compound **161** to desilylation using TBAF, thus yielding compound **3d** in 72% yield, revealing that the reduction had taken place from the same face as the silyloxymethyl group. Once again, the compound is tentatively assigned as 2,13-di-*epi*-cylindricine C (**3d**), as the preparation of **3d** has not yet been published and therefore no comparison of data can be made.

4.13 Desulfonylation and reduction of minor isomer 159

The minor isomer **159**, was subjected to desulfonylation using excess sodium naphthalenide, yielding the desired enaminone **163** in 45% yield and the over reduced compound **164** in 21% yield (Scheme 66).

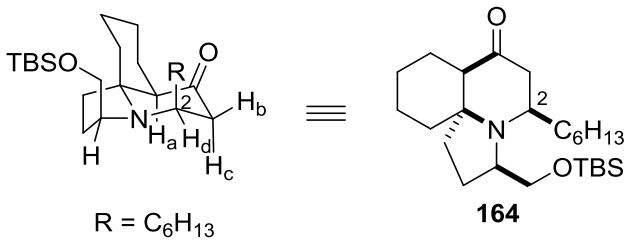
Scheme 66



For compound **164**, the tentative assignment of the stereochemistry of the *n*-hexyl chain at the C-2 center was achieved by analysis of the ^{1}H-NMR spectrum. Proton H_a shows up as a broad singlet at 2.46 ppm with no identifiable coupling constant. The proton H_b shows up as a doublet of doublets with couplings of 15.4 Hz and 5.2 Hz, while proton H_c shows up as a doublet of doublets with couplings of 15.5 Hz and 6.9 Hz. The larger coupling corresponds to the geminal coupling of protons H_b and H_c, while the

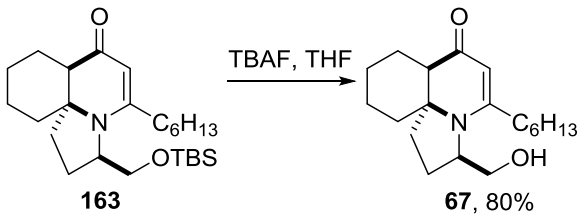
smaller coupling correspond to the equatorial/ equatorial and axial/ equatorial realtionship for H_b/ H_d and H_c/ H_d respectively. The proton H_d shows up as a multiplet at 3.22 ppm.

Figure 7: Conformational structure of compound 164



Once again, the absence of a large coupling corresponding to a trans-diaxial coupling between protons H_c and H_d suggests that proton H_d is orientated in an equatorial position and the *n*-hexyl group is in the axial position on the piperidine ring at the C-2 center. Therefore, the stereochemistry of the C-2 center was assigned as shown in structure **164** (Figure 7).

Scheme 67

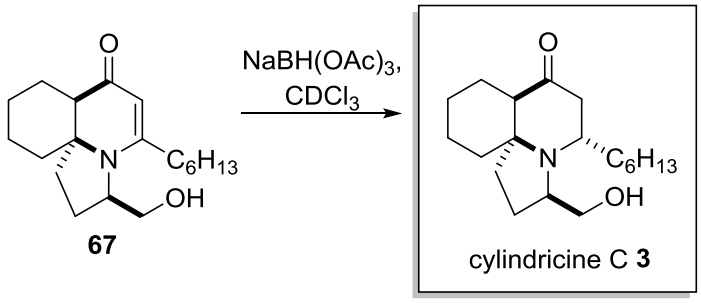


Next, enaminone **163** was subjected to desilylation using TBAF, which yielded 80% of alcohol **67** (Scheme 67). Compound **67** was previously reported by Hsung *et al.*[20] in their synthesis of cylindricine C (**3**), summarised in Table 1 of cylindricine C total

synthesis published in a Weinreb review.[12] Therefore, a detailed comparison of ^{1}H and ^{13}C-NMR spectra for compound **67** was done and can be found in Appendix B.

Finally, reduction of the enamine double bond of compound **67** was achieved by following a slightly modified procedure reported by Hsung *et al.*[20] By reacting compound **67** with 10 equivalents of triacetoxyborohydride, with a catalytic amount of AcOH, dissolved in $CDCl_3$, cylindricine (**3**) was obtained in 50% isolated yield (NMR analysis indicated 75% conversion of starting material to the desired product as determined by integration of the respective peaks in the ^{1}H-NMR spectrum of the crude reaction mixture).

Scheme 68

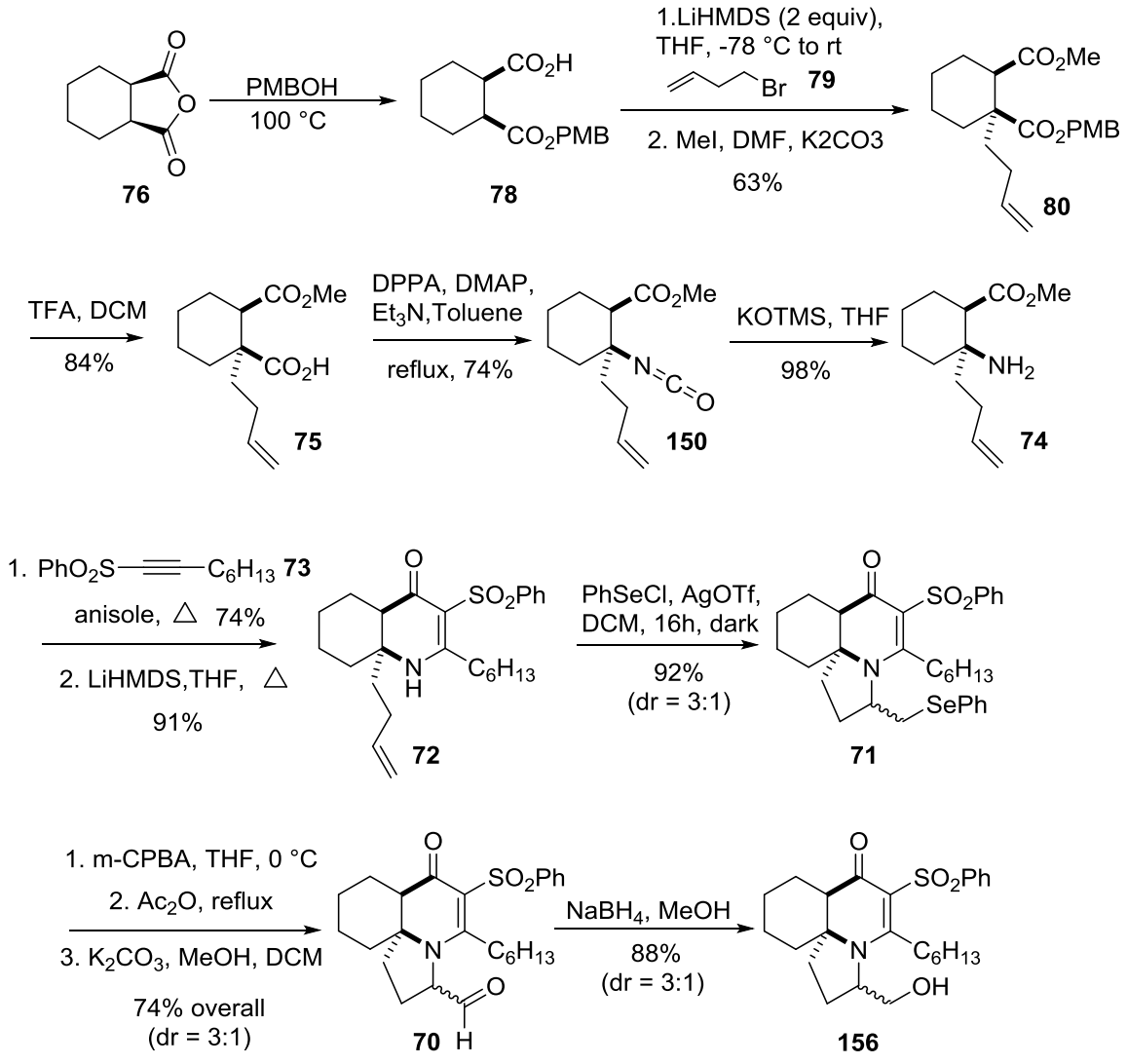


4.14 Summary

Alcoholysis of cheap starting material **76**, followed by a one pot alkylation and esterification, gave diester **80** in comparable yield to that obtained by Dr. K. Clary (Scheme 69). The primary amine was installed at the quaternary center using a Curtius rearrangement and in situ cleavage of the isocyanate. The B-ring was established by a conjugate addition and cyclisation of β-amino ester **74** with acetylenic sulfone **73** to give

sulfone **72**. The C-ring was formed by an electrophilic cyclisation to give selenide **71** in an excellent yield of 92%. The seleno-Pummerer rearrangement and base hydrolysis yielded aldehyde **70** as an inseparable 3:1 mixture of diastereomers followed by reduction of the aldehyde to yield alcohols **156** in 88% yield. The overall yield of alcohols **156** was 15.4% compared with 5% obtained by Dr. K. Clary of the same advanced intermediate.

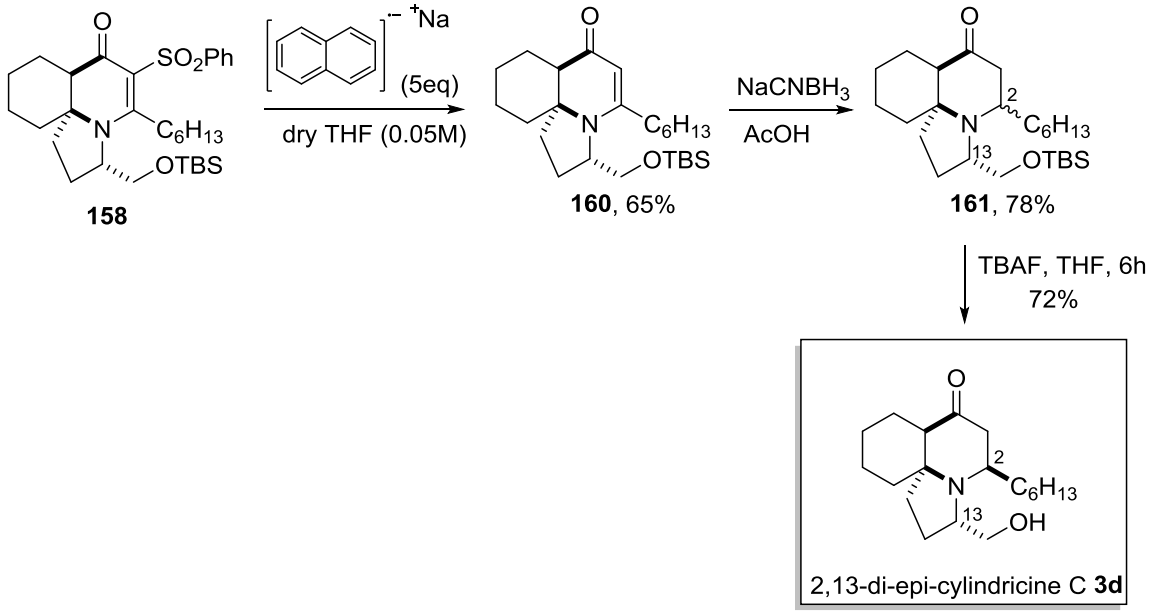
Scheme 69



The mixture of alcohols was separated in sufficient quantities to characterise individually and, although the NMR data of the major isomer compared well with the data reported by Dr. K. Clary, the minor isomer had not yet been characterised. The desired configuration of the hydroxymethyl group attached to the C-13 center was confirmed by an Xray crystal structure that has now been obtained for the minor isomer.

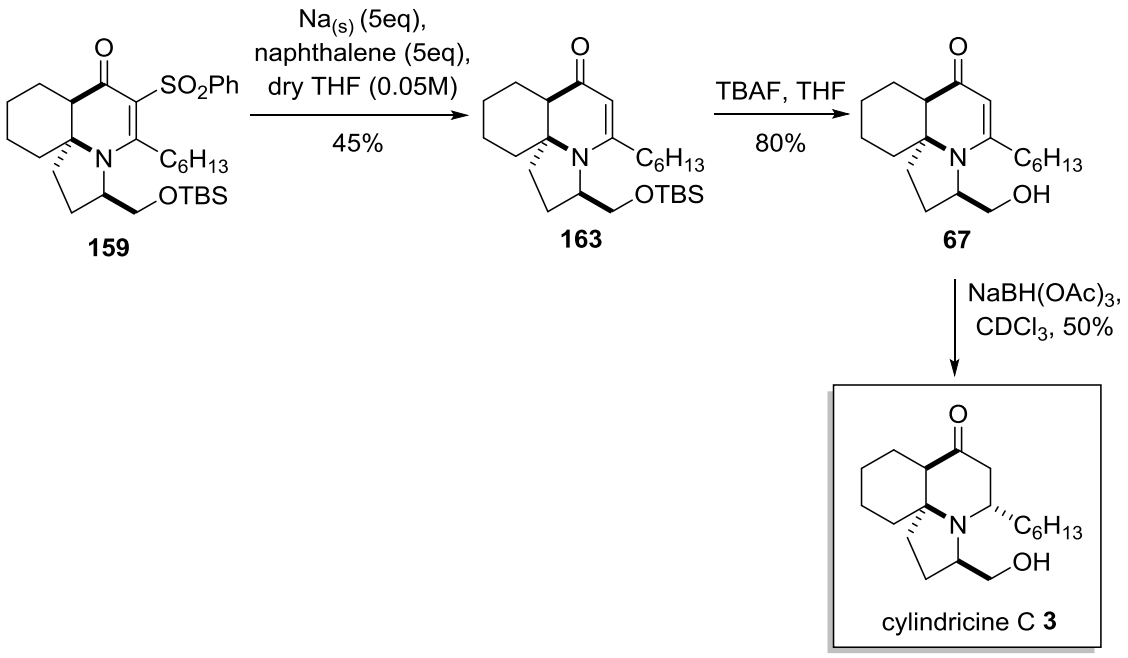
Silyl protection of alcohols **156** enabled the diastereomeric mixture to be cleanly separated to afford compounds **158** and **159** respectively. A sodium naphthalenide desulfonylation of compound **158** afforded enaminone **160** in 65% yield (Scheme 70). Reduction of the enamine double bond followed by desilylation afforded 2,13-di-*epi*-cylindricine C (**3d**) in good yield. Therefore, 2,13-di-*epi*-cylindricine C (**3d**) was synthesised in 14 steps with an overall yield of 5.7%.

Scheme 70



Desulfonylation of compound **159** (Scheme 71), using sodium naphthalenide, afforded enaminone **163** in 45% yield. Desilylation followed by reduction of the enamine double bond, according to the procedure reported by Hsung *et al.*[20] afforded cylindricine C (**3**). Therefore, cylindricine C (**3**) was synthesised in 14 steps, but with an overall yield of only 2%.

Scheme 71



Chapter Five: Summary, conclusions and future work

5.1 Summary and conclusions

In this thesis, an alternative synthetic route to β-amino ester **72**, an important intermediate of our attempts toward cyclindricine C (**3**), was described (see Section 1.4.2 for the previous route). Compound **72** was achieved in ten total steps and a 22.3% overall yield compared to 24% overall yield in six steps obtained by Dr. K. Clary. However, this new route is amenable towards an enantioselective synthesis of 2,13-di-*epi*-cylindricine C (**3d**) and cylindricine C (**3**).

We also describe the total synthesis of the previously unknown 2,13-di-*epi*-cylindricine C (**3d**) and cylindricine C (**3**) in a diastereomeric ratio of 3:1 respectively. The complex tricyclic core of the target compounds was constructed by methodology developed in the Back group using a tandem conjugate addition and intramolecular cyclisation of an acetylenic sulfone. Once this methodology was successfully utilised to form the B-ring, we investigated desulfonylation of the bicyclic intermediate, which yielded the corresponding enaminone in good yield (see section 3.4). Formation of the C-ring by electrophilic cyclisation using the enaminone could only be achieved in low yields (see Scheme 43). After several steps, the aldehyde was installed and, following reduction of both the aldehyde and the enaminone double bond, 2,13-di-*epi*-cylindricine C (**3d**) was afforded as the major product. Alternative conditions for desulfonylation of the bicyclic intermediate afforded aminones **118** and **125** respectively (Scheme 39). Unfortunately, the *n*-hexyl group of the major isomer was found to have the incorrect configuration. We explored desulfonylation and a base-catalysed epimerisation of the C-

13 center of the tricyclic methyl ester intermediate in Scheme 62; however, a complex mixture of unidentified products was obtained and therefore this route was abandoned.

We finally discovered a route for desulfonylation of silyloxy tricyclic intermediate **158** and, following reduction of the enaminone double bond, 2,13-di-*epi*-cylindricine C (**3d**) was afforded as the major product (see Scheme 64 and 65). Desulfonylation of the minor isomer **159** and reduction of the enamine double bond, using the procedure reported by Hsung *et al.*[20] afforded cylindricine C (**3**).

In conclusion, we successfully performed desulfonylation of various intermediates in good yields to give the corresponding enaminone moieties. Unfortunately, reduction of the enaminone double bond using various reduction conditions yielded major products containing the incorrect configuration of the *n*-hexyl moiety. I then set out to attempt a synthesis of the natural product using the minor isomer of the 3:1 mixture of diastereomers, obtained from the electrophilic cyclisation, by reduction of the enaminone double bond moiety of compound **67** (see Scheme 68). Reduction was achieved using sodium triacetoxyborohydride yielding the desired configuration of the *n*-hexyl group and therefore cylindricine C (**3**). This highlights the ability of the hydroxymethyl group to direct the reduction of the enaminone double bond to obtain the correct configuration at the C-2 center. Therefore, it is important to regulate the stereochemistry of the hydroxymethyl group prior to reducing the enaminone double bond.

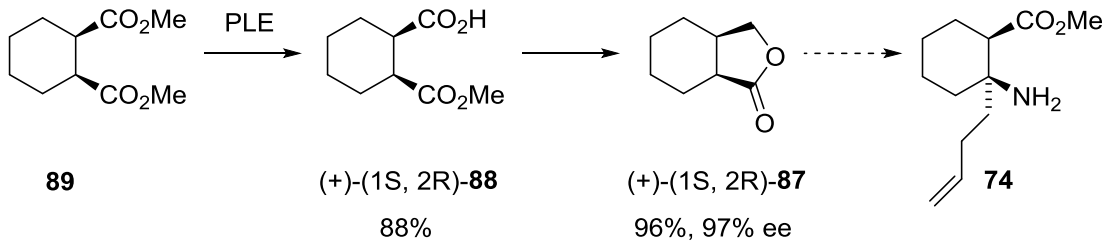
Overall, extensive optimisation of the synthesis described in section 1.4 was performed, thereby achieving the advanced intermediate alcohol **83** in 15.4% yield compared with 5% obtained by Dr. K. Clary. The synthesis was further extended to

afford 2,13-di-*epi*-cylindricine C (**3d**) as the major isomer in 14 steps and an overall yield of 5.7% and cylindricine C (**3**) as the minor isomer in 14 steps and an overall yield of 2%.

5.2 Future work

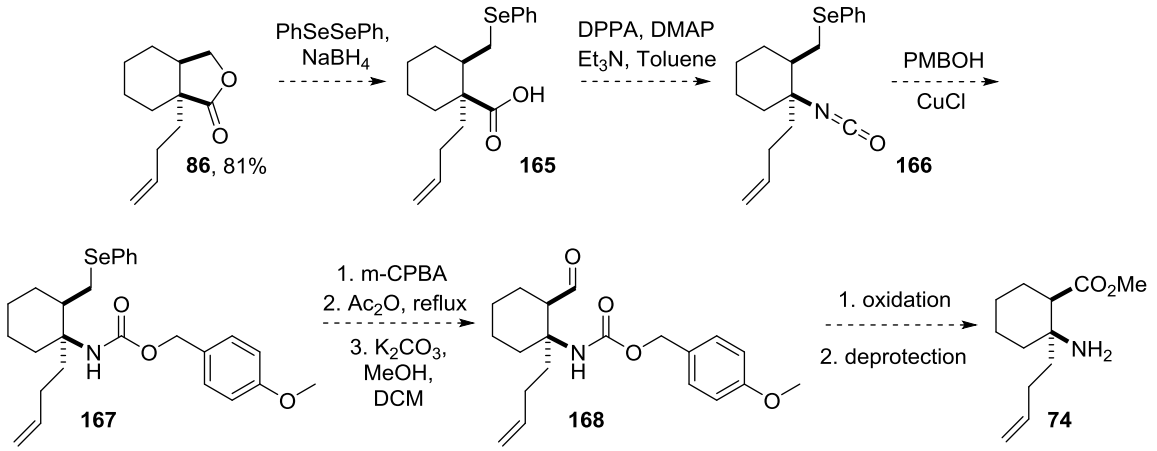
Although an alternative route was achieved for the synthesis of β-amino ester **74**, it is a lengthier variation of the synthesis described in section 4.4. However, this route is amenable to an enantioselective variation for the preparation of cylindricine C (**3**) via the enzyme mediated desymmetrisation described by Jones *et al.*[61] (Scheme 72). A shorter synthesis would therefore make this route even more desirable.

Scheme 72



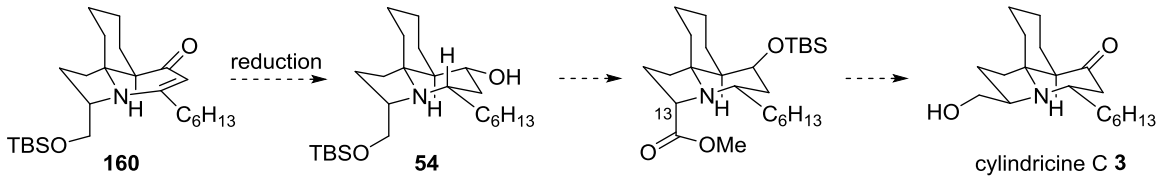
Undergraduate student (Chem 502) Andrew Macdonald performed preliminary experiments towards a shortened pathway to β-amino ester **74**, via alkylated lactone **86** (Scheme 73). Cleavage of lactone **86**, at the methylene carbon, via a phenyl selenolate anion could generate selenide **165**, allowing for installation of the nitrogen at the quaternary center by a Curtius rearrangement. Protection of the amine in the form of the carbamate **167** followed by a seleno-Pummerer rearrangement and base hydrolysis would give aldehyde **168**. Oxidation to the methyl ester and a deprotection step would afford β-amino ester **74**.

Scheme 73



The incorrect configuration of the *n*-hexyl group, obtained from reduction of the enaminone double bond of various tricyclic intermediates, suggests that the bottom face (exo) of the molecule is more accessible. The stereochemistry of the hydroxymethyl group at the C-13 center also appears to have a directing ability on the reduction of the enaminone moiety (Scheme 68). Therefore, regulating the stereochemistry of the C-2 center could be achieved if epimerisation of the C-13 center was accomplished. Section 1.2.3 describes the procedure of Renaud (Scheme 74) whereby compound **54** was utilised in the epimerisation. If compound **160** could be transformed into alcohol **54**, a formal synthesis of cylindricine C (**3**) could be achieved.

Scheme 74



Chapter Six: Experimental Section

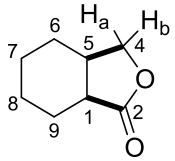
6.1 General remarks

All reagents, unless otherwise noted, were obtained from commercial sources and purified by standard methods as necessary. THF was distilled over $LiAlH_4$ immediately prior to use or obtained from an MBraun MB-SPS solvent purification system. Toluene, dichloromethane and diisopropylamine were dried by distillation over CaH_2. Alkyllithium reagents were titrated with menthol and 2,2'-bipyridyl immediately prior to use.[116] Chromatography refers to flash chromatography on silica gel (230-400 mesh). Analytical TLC was carried out on aluminum backed plates coated with Merck silica gel 60 F-254, with detection by UV light or staining with phosphomolybdic acid solution in ethanol. NMR spectra were recorded in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) and referencing of chemical shifts was relative to the residual solvent (^{1}H NMR δ 7.26; ^{13}C δ 77.16 ppm). Assignments of primary, secondary, tertiary, and quaternary carbons, where indicated, were based upon DEPT-135 or HSQC analyses. Structure elucidations were assigned based on DEPT, COSY, HSQC and HMBC spectra, in addition to standard IR, NMR and mass spectra. Numbering of atoms in structures shown in this thesis was made for convenience in indicating spectral assignments, and does not necessarily reflect IUPAC nomenclature. Melting points were measured using an A. H. Thomas hot-stage apparatus. IR spectra were recorded on a Nicolet *Avatar* spectrometer. ^{1}H NMR, ^{13}C NMR, ^{77}Se NMR, DEPT, COSY, HSQC and HMBC data were collected on a Bruker *DMX-300* (^{1}H, 300 Hz; ^{13}C, 75 MHz), Bruker *AMX-300* (^{1}H, 300 Hz; ^{13}C, 75 MHz), a Bruker DRX 400 MHz (^{1}H,

400 MHz, ^{13}C, 101 MHz), a Bruker Avance III 400 MHz (^{1}H, 400 MHz, ^{13}C, 101 MHz), a Bruker Avance II 400 MHz (^{1}H, 400 MHz, ^{13}C, 101 MHz), and a Bruker Avance 400 MHz (^{1}H, 400 MHz, ^{13}C, 101 MHz). Low and high resolution mass spectra were obtained on a Waters GCT Premier, a Thermo Finnigan *SSQ7000*, a Bruker *Esquire 3000*, a Agilent 6520 Q-Tof, or a Bruker FT-ICR-MS *Apex* mass spectrometer by Ms. Q. Wu, Ms. D. Fox, Mr. J. Li, or Mr. W. White. All mass spectra were obtained by electron impact ionization at 70 eV with direct probe sample introduction unless otherwise indicated. Elemental analyses were determined by Mr. J. Li using a Control Equipment Corporation 440 Elemental Analyzer or a Perkin Elmer Series II 2400 CHNS/O Analyzer. X-ray crystal structural data was collected by Dr. M. Parvez (Appendix D) and Mr. C. Gendy (Appendix E) and the corresponding reports in the Appendices were provided by them.

6.2 Experiments Pertaining to Chapter 2

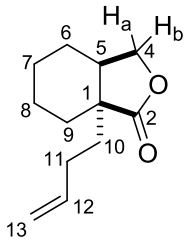
6.2.1 ***Hexahydroisobenzofuran-1(3H)-one (87)***



1,2-Cyclohexanedicarboxylic anhydride **76** (4.20 g, 27.2 mmol) was dissolved in methanol (100 mL) and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated and left under vacuum overnight to afford acid ester **88** (4.97 g, 26.7 mmol, 98%) as a white solid. The acid ester was dissolved in dry THF

(30 mL), kept under nitrogen and cooled to -10 ^{o}C. BH_3.THF (30 mL, 1.0 M) was added and stirred at room temperature for 4 h. Methanol (30 mL) was slowly added and the reaction mixture was stirred for 10 min and concentrated. This methanol addition was repeated twice (60 mL) and the reaction mixture was concentrated to give a colourless oil. Kugelrohr distillation of the oil gave lactone **87** (2.88 g, 20.5 mmol, 77%) as a colourless oil. (bp 90 ^{o}C, 1.5 mmHg); IR (film) 2928, 1771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 8.8, 5.0 Hz, 1H, H-4a), 3.92 (d, *J* = 8.8 Hz, 1H, H-4b), 2.66 – 2.57 (m, 1H), 2.48 – 2.39 (m, 1H), 2.07 (d, *J* = 13.0 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.66 – 1.51 (m, 3H), 1.28 – 1.11 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6 (C, C-2), 71.8 (CH_2, C-4), 39.5 (CH), 35.5 (CH), 27.3 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 22.6 (CH_2); mass spectrum (EI, m/z, %) 140.1 (16, M^+), 81.2 (100), 68.3 (34), 67.3 (56), 55.2 (28); HRMS (EI) calc'd for $C_8H_{12}O_2$: 140.0837 $[M]^+$; found: 140.0833.

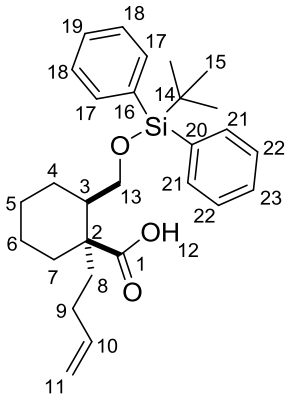
6.2.2 ***7a-(But-3-enyl)hexahydroisobenzofuran-1(3H)-one (86)***



A solution of LDA was prepared by adding *n*-butyllithium (62.0 mL, 2.50 M, 155 mmol) to a solution of diisopropylamine (24.0 mL, 170 mmol) in dry THF (69 mL) at -78 ^{o}C under a nitrogen atmosphere. The solution was warmed to 0 ^{o}C over 1 h and cooled back down to -78 ^{o}C. In a second flask (500 mL) containing the lactone **87** (13.73 g, 97.95 mmol) dissolved in dry THF (277 mL) was added LDA (105 mL, 1.0 M) at -78 ^{o}C

under a nitrogen atmosphere and warmed to room temperature. After 1 h, LiCl (1.37g, 32.4 mmol) and 4-bromobutene (12.0 mL, 106 mmol) were added and the reaction mixture was stirred overnight. Water (150 mL) and ethyl acetate (100 mL) were added and the layers were separated. The aqueous fraction was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (19:1 to 4:1 hexanes: ethyl acetate eluent) to afford alkylated lactone **86** (15.4 g, 79.3 mmol, 86%) as a colourless oil; IR (film) 3075, 2931, 1767, 1641 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H, H-12), 5.04 – 4.97 (m, 1H, H-13), 4.96 – 4.91 (m, 1H, H-13), 4.28 (dd, *J* = 8.9, 6.4 Hz, 1H, H-4a), 3.94 (dd, *J* = 8.9, 5.4 Hz, 1H, H-4b), 2.34 – 2.26 (m, 1H), 2.11 – 2.03 (m, 2H), 1.91 – 1.83 (m, 1H), 1.79 – 1.68 (m, 2H), 1.64 – 1.55 (m, 1H), 1.55 – 1.45 (m, 2H), 1.45 – 1.28 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5 (C, C-2), 137.9 (CH, C-12), 115.1 (CH_2, C-13), 69.5 (CH_2, C-4), 45.1 (C, C-1), 38.7 (CH, C-5), 34.0 (CH_2), 29.6 (CH_2), 28.4 (CH_2), 25.6 (CH_2), 22.3 (CH_2), 22.0 (CH_2); mass spectrum (CI, m/z, %) 195.2 (12, M^++H); HRMS (EI) calc'd for $C_{12}H_{18}O_2$: 194.1307 $[M]^+$; found: 194.1306.

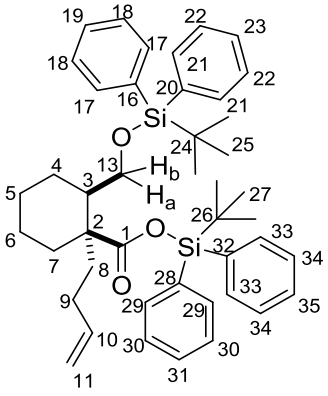
6.2.3 ***1-(But-3-enyl)-2-((tert-butyldiphenylsilyloxy)methyl)cyclohexanecarboxylic acid (95)***



To a solution of alkylated lactone **86** (120 mg, 0.512 mmol) in methanol (0.5 mL) was added NaOH (0.51 mL, 1.0 M) and the reaction mixture was refluxed for 3 h. The mixture was concentrated and the flask kept under vacuum overnight to afford the sodium carboxylate salt **94** quantitatively. To a solution of the sodium carboxylate salt **94** (144 mg, 0.512 mmol) dissolved in dry THF (2 mL) was added NaH (24 mg, 0.55 mmol) at 0 ^{o}C and the reaction mixture was stirred for 30 min. TBDPSCl (0.159 mL, 0.612 mmol) and imidazole (0.042 g, 0.61 mmol) were added and the reaction mixture was stirred for 6 h. The reaction mixture was quenched with brine (3 mL) and ethyl acetate (3 mL) and the layers were separated. The aqueous fraction was extracted with ethyl acetate (3 x 3 mL) and the combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude products were purified by column chromatography on silica gel (19:1 hexanes: ethyl acetate eluent) to afford the desired protected alcohol **95** (130 mg, 0.288 mmol, 56%) as a colourless oil and bis-protected product **96** (109 mg, 0.159 mmol, 31 %) as a yellow oil; For **95**: IR (film) br 3300-2500,

1695, 1470, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H, H-12), 7.70 – 7.62 (m, 4H, H-18 +H-22), 7.45 – 7.31 (m, 6H, H-17 + H-19 + H-21 + H23), 5.71 (ddd, *J* = 17.0, 6.5, 3.7 Hz, 1H, H-10), 5.00 – 4.87 (m, 2H, H-11), 3.86 – 3.72 (m, 2H, H-13), 2.07 – 1.80 (m, 4H), 1.79 – 1.70 (m, 1H), 1.70 – 1.45 (m, 6H), 1.37 – 1.19 (m, 2H), 1.05 (s, 9H, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9 (C, C-1), 138.3 (CH, C-10), 135.8 (CH), 135.7 (CH), 133.4 (C), 133.3 (C), 129.92 (CH), 129.89 (CH), 127.88 (CH), 127.86 (CH), 114.8 (CH_2, C-11), 64.4 (CH_2, C-13), 49.2 (C, C-2), 46.7 (CH, C-3), 36.6 (CH_2), 28.2 (CH_2), 27.0 (CH_3, C-15), 26.0 (CH_2), 24,6 (CH_2), 22.8 (CH_2), 19.3 (C, C-14); HRMS (ESI-TOF) calc'd for $C_{28}H_{39}O_3Si$: 451.2663 $[M+H]^+$; found: 451.2657. Anal. calc'd for $C_{28}H_{39}O_3Si$: C 74.62, H 8.50; found C 74.29, H 8.69

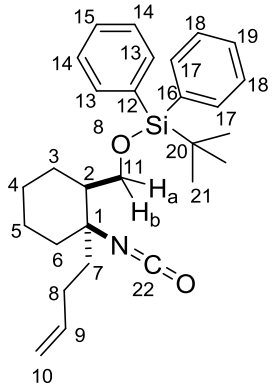
6.2.4 ***tert-Butyldiphenylsilyl-1-(but-3-enyl)-2-((tert-butyldiphenylsilyloxy)methyl) cyclohexanecarboxylate (96)***



IR (film) 2931, 1714, 1471, 1427, 1190, 1113 cm^{-1}; ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 8H, H-18 + H-22 + H-30 + H-34), 7.42 – 7.36 (m, 4H, H-19 + H-23 + H-31 + H-35), 7.31 (m, 8H, H-17 + H-21 + H-29 + H-33), 5.64 (ddt, *J* = 16.7, 10.4, 6.2

Hz, 1H, H-10), 4.92 – 4.80 (m, 2H, H-11), 3.94 (dd, *J* = 10.1, 3.2 Hz, 1H, H-13a), 3.71 (dd, *J* = 9.9 Hz, 1H, H-13b), 2.00 – 1.88 (m, 2H), 1.87 – 1.74 (m, 3H), 1.73 – 1.57 (m, 2H), 1.56 – 1.40 (m, 6H), 1.36 – 1.21 (m, 3H), 1.04 (s, 18H, H-25 + H-27); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5 (C, C-1), 138.5 (CH, C-10), 135.79 (CH), 135.77 (CH), 135.7 (CH), 134.2 (C), 134.1 (C), 132.12 (C), 132.07 (C), 130.1 (CH), 130.0 (CH), 129.7 (CH), 129.6 (CH), 127.8 (CH), 127.7 (CH), 114.5 (CH_2, C-11), 64.1 (CH_2, C-13), 49.8 (C, C-2), 46.7 (CH, C-3), 36.5 (CH_2), 31.2 (CH_2), 28.2 (CH_2), 27.3 (CH_3, C-27), 27.1 (CH_3, C-25), 25.3 (CH_2), 23.9 (CH_2), 22.7 (CH_2), 19.4 (C, C-26), 19.3 (C, C-24). HRMS (ESI-TOF) calc'd for $C_{44}H_{57}O_3Si_2$: 689.3841 $[M+H]^+$; found: 689.3838

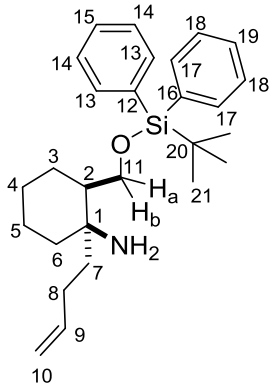
6.2.5 ***2-(But-3-enyl)-2-isocyanatocyclohexyl)methoxy)(tert-butyl)diphenylsilane (97)***



Triethylamine (53.0 µL, 4.15 mmol), DMAP (500 mg, 4.15 mmol) and DPPA (97.0 µL, 4.50 mmol) were added to a solution of toluene (40 mL) containing the starting material **95** (1.70 g, 3.77 mmol) and the mixture was heated at reflux in toluene overnight. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted three times with diethyl ether. The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was

purified by column chromatography on silica gel (19:1 hexanes: ethyl acetate) to afford isocynate **97** (1.54 g, 3.44 mmol, 91%) as a colourless oil; IR (film) 2928, 2259, 1546, 1427, 1261, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 4H, H-13 + H-17), 7.52 – 7.34 (m, 6H, H-14 + H-15 + H-18 + H-19), 5.74 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H, H-9), 5.05 – 4.90 (m, 2H, H-10), 3.89 (dd, *J* = 10.4, 5.2 Hz, 1H, H-11a), 3.46 (dd, *J* = 10.5, 7.1 Hz, 1H, H-11b), 2.12 – 1.96 (m, 2H), 1.95 – 1.73 (m, 4H), 1.70 – 1.46 (m, 4H), 1.46 – 1.35 (m, 1H), 1.33 – 1.17 (m, 2H), 1.08 (s, 9H, H-21); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (C-9), 135.7 (C-14 + C-18), 133.8, 133.7 (total of 2 C's: C-12 + C-16), 129.83, 129.81 (total of 2 C's: C-15 + C-19), 127.9 (C-13 + C-17), 122.0 (C-22), 115.0 (C-10), 64.9 (C-11), 63.1 (C-1), 47.2 (C-2), 40.6, 37.6, 28.1, 27.0 (C-21), 25.8, 25.3, 22.1, 19.3 (C-20); mass spectrum (CI, m/z, %) 448.3 (100, M^{+}+H); HRMS (ESI-TOF) calc'd for $C_{28}H_{37}NNaO_2Si$: 470.2486 $[M+H]^{+}$; found: 470.2478

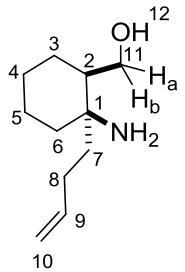
6.2.6 ***1-(but-3-enyl)-2-((tert-butyldiphenylsilyloxy)methyl)cyclohexanamine 98***



NaOTMS (50 mg, 0.44 mmol) was added to a solution of the isocyanate **97** (100 mg, 0.23 mmol) dissolved in THF (1 mL). After 3 h, TLC indicated complete consumption of starting material. The reaction was quenched with HCl (1 mL, 1.0 M) and diethyl ether (2

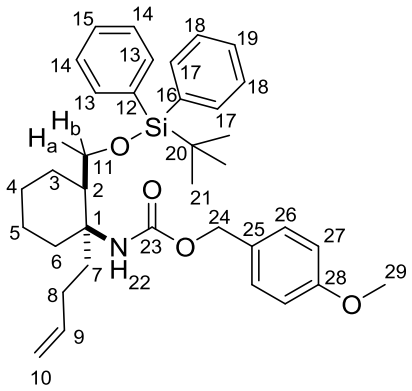
mL). The layers were separated, the aqueous fraction was extracted with diethyl ether (3 x 3 mL) and the combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated to afford the desired amine **98** (90 mg, 0.21 mmol, 95%) as a colourless oil; IR (film) 3070, 2928, 1472, 1425, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H, H-13 + H-17), 7.46 – 7.33 (m, 6H, H-14 + H-15 + H-18 + H-19), 5.75 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H, H-9), 5.02 – 4.85 (m, 2H, H-10), 3.77 (dd, *J* = 10.3, 3.5 Hz, 1H, H-11a), 3.61 (dd, *J* = 10.3, 6.3 Hz, 1H, H-11b), 2.08 – 1.91 (m, 2H), 1.82 – 1.68 (m, 2H), 1.58 – 1.15 (m, 11H), 1.05 (s, 9H, H-21). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4 (CH, C-9), 135.82, 135.78 (CH, total of 2 C's: C-14 + C-18), 133.91, 133.87 (C, total 2 C's: C-12 + C-16), 129.8, 129.7 (CH, total of 2 C's: C-15 + C-19), 127.81, 127.79 (CH, total of 2 C's: C-13 + C-17), 114.2 (CH_2, C-10), 65.0 (CH_2, C-11), 52.7 (C, C-1), 46.1 (CH, C-2), 41.9 (CH_2), 37.8 (CH_2), 27.9 (CH_2), 27.1 (CH_3, C-21), 25.8 (CH_2), 25.5 (CH_2), 21.9 (CH_2), 19.4 (C, C-20); mass spectrum (EI, m/z, %) 421.2 (10, M^+) 364.1 (100) 198.0 (80); HRMS (ESI-TOF) calc'd for $C_{27}H_{40}NOSi$: 422.2874 $[M+H]^+$; found: 422.2880

6.2.7 ***2-Amino-2-((but-3-enyl)cyclohexyl)methanol (99)***



TBAF (2.5 mL, 2.5 mmol) was added dropwise to a solution of isocyanate **97** (0.45 g, 1.00 mmol) in dry THF (9 mL) and stirred at room temperature for 3 h. Rexyn (1g), $CaCO_3$ (300 mg) and methanol (5 mL) were added and the reaction mixture was stirred for 1 hour. The insoluble material was removed by filtration through Celite, and the Celite was rinsed with methanol (15 mL). The filtrate was concentrated to give a yellow oil. The crude product was purified by column chromatography on silica gel (9:1:1 DCM: MeOH: NH_4OH) to afford amine alcohol **99** (143 mg, 0.780 mmol, 78%) as a colourless oil; IR (film) 3339, 2920, 1547, 1261, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H, H-9), 5.01 (m, 2H, H-10), 4.09 (dd, *J* = 11.3, 2.8 Hz, 1H, H-11a), 3.56 (br s, 1H, H-12), 3.53 (dd, *J* = 11.3, 3.1 Hz, 1H, H-11b), 2.12 – 2.03 (m, 2H), 1.86 – 1.70 (m, 3H), 1.70 – 1.40 (m, 7H), 1.39 – 1.19 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4 (C-9), 115.0 (C-10), 64.8 (C-11), 55.5 (C-1), 43.2 (C-2), 39.5, 37.3, 27.7, 25.8, 25.4, 21.8 (total of 6 C's: C-3 to C-8); mass spectrum (EI, m/z, %) 184.2 (30, M^+) 128.1 (78) 110.1 (100); HRMS (CI) calc'd for $C_{11}H_{22}NO$: 184.1701 $[M+H]^+$; found: 184.1705

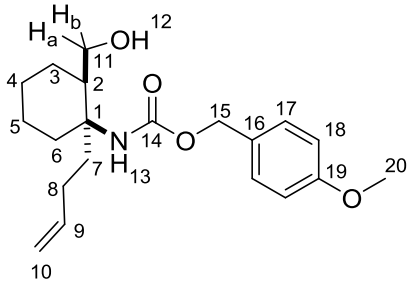
6.2.8 ***4-Methoxybenzyl-1-(but-3-enyl)-2-((tert-butyldiphenylsilyloxy)methyl) cyclohexylcarbamate (102)***



The isocyanate **97** (1.8 g, 4.0 mmol), *p*-methoxybenzyl alcohol (0.7 mL, 5.6 mmol) and copper (I) chloride (395 mg, 3.99 mmol) were dissolved in DMF (20 mL) and stirred at 80 ^{o}C for 4 h. The reaction mixture was poured into water and ethyl acetate was added. $NaHCO_3$ (10 mL) was added to dissolve the solids. The layers were separated and the aqueous fraction was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (19:1 hexanes: ethyl acetate) to afford carbamate **102** (2.10 g, 3.58 mmol, 89%) as a colourless oil; IR (film) 2928, 1721, 1514, 1244, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.61 (m, 4H, H-13 + H-17), 7.48 – 7.32 (m, 6H, H-14 + H-15 + H-18 + H-19), 7.28 – 7.24 (m, 2H, H-27), 6.88 – 6.81 (m, 2H, H-27), 6.62 (s, 1H, NH), 5.74 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H, H-9), 5.05 – 4.86 (m, 4H, H-10 + H-24), 4.00 (d, *J* = 9.3 Hz, 1H, H-11a), 3.80 (s, 3H, H-29), 3.50 (dd, *J* = 10.7, 2.8 Hz, 1H, H-11b), 2.67 (d, *J* = 13.0 Hz, 1H), 2.17 (m, 1H), 2.09 – 1.83 (m, 3H), 1.77 – 1.66 (m, 2H), 1.59 – 1.37 (m, 4H), 1.35 – 1.16 (m, 2H), 1.02 (s, 9H, H-21); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C-23), 155.2 (C-28), 138.8 (C-9),

135.9, 135.8 (total of 2 C's: C-14 + C-18), 132.8, 132.7 (total 2 C's: C-12 + C-16), 130.0, 129.9 (total of 2 C's: C-15 + C-19), 127.91, 127.86 (total of 2 C's: C-13 + C-17), 114.4 (C-10), 113.8 (C-27), 65.65, 65.52 (total of 2 C's: C-11 + C-24), 58.3, 55.4 (total of 2 C's: C-1 + C-29), 43.7 (C-2), 37.3, 32.1, 28.5, 26.9 (C-21), 25.9, 25.8, 21.8, 19.3 (C-20). mass spectrum (CI, m/z, %) 586.4 (42, M^++H) 542.6 (100); HRMS (ESI-TOF) calc'd for $C_{36}H_{48}NO_4Si$: 586.3347 $[M+H]^+$; found: 586.3338

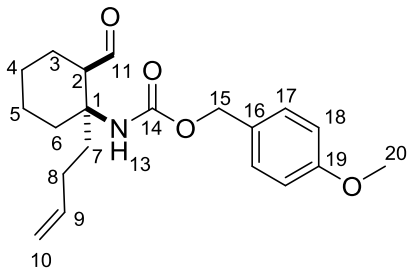
6.2.9 ***4-Methoxybenzyl-1-(but-3-enyl)-2-(hydroxymethyl)cyclohexylcarbamate (103)***



TBAF (2.89 mL, 2.89 mmol) was added dropwise to a solution of carbamate **102** (1.54 g, 2.63mmol) in dry THF (10 mL) and stirred at room temperature for 3 hours. Rexyn (2.48 g), $CaCO_3$ (0.86 g) and methanol (20 mL) were added and the reaction mixture was stirred for 1 hour. The insoluble material was removed by filtration through Celite, and the Celite was rinsed with methanol (20 mL). The filtrate was concentrated to give a yellow oil. The crude product was purified by column chromatography on silica gel (1:1 hexanes: ethyl acetate) to afford alcohol **103** (853 g, 2.46 mmol, 92%) as a white solid: mp 82 - 84 ^oC (from chloroform); IR (film) 3419, 3342, 2933, 1695, 1514, 1242, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2H, H-17), 6.87 (d, J = 8.7 Hz, 2H, H-18), 5.90 (s, 1H, NH), 5.79 (ddt, J = 16.7, 10.1, 6.5 Hz, 1H, H-9), 5.07 – 4.87

(m, 4H, H-10 + H-15), 3.92 (dd, *J* = 11.1, 3.0 Hz, 1H, H-11a), 3.79 (s, 3H, H-20), 3.64 (dd, *J* = 11.2, 3.9 Hz, 1H, H-11b), 2.45 – 2.14 (m, 3H), 2.01 (m, 2H), 1.83 – 1.61 (m, 3H), 1.59 – 1.20 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (C, C-14), 155.4 (C, C-19), 138.8 (CH, C-9), 129.9 (CH, C-17), 129.2 (C, C-16), 114.5 (CH_2, C-10), 114.0 (CH, C-18), 65.9, 63.9 (CH_2, total of 2 C's: C-11 + C-15), 57.9 (C, C-1), 55.4 (CH_3, C-20), 44.2 (CH, C-2), 36.4, 32.9, 28.3, 25.3, 25.1, 21.7 (CH_2, total of 6 C's: C-3 to C-8); HRMS (ESI-TOF) calc'd for $C_{20}H_{29}NNaO_4$: 370.1989 $[M+H]^+$; found: 370.1983

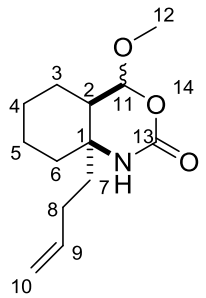
6.2.10 ***4-Methoxybenzyl-1-(but-3-enyl)-2-formylcyclohexylcarbamate (104)***



DMSO (0.84 mL, 12 mmol) was added dropwise to a solution of $(COCl)_2$ (0.504 mL, 5.87 mmol) in DCM (40 mL) at -78 ^{o}C. After 30 min, alcohol **103** (1.7 g, 4.9 mmol) dissolved in DCM (10 mL) was added dropwise and the reaction mixture was stirred for 1 h. Triethylamine (3.15 mL, 24.5 mmol) was added and the reaction mixture was warmed to room temperature and stirred overnight. Water (30 mL) was added to quench the reaction. The layers were separated and the aqueous fraction was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (19:1 to 4:1 hexanes: ethyl acetate) to afford

aldehyde **104** (1.6 g, 4.6 mmol, 90%) as a colourless oil; IR (film) 3352, 2938, 1714, 1509, 1242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (d, *J* = 1.2 Hz, 1H, H-11), 7.30 – 7.25 (m, 2H, H-17), 6.88 (d, *J* = 8.6 Hz, 2H, H-18), 5.85 – 5.71 (m, 1H, H-9), 5.04 – 4.90 (m, 4H, H-10 + H-15), 3.81 (s, 3H, H-20), 2.69 – 2.63 (m, 1H), 2.36 – 2.24 (m, 1H), 2.12 – 1.94 (m, 3H), 1.87 – 1.76 (m, 1H), 1.75 – 1.60 (m, 3H), 1.59 – 1.25 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3 (CHO, C-11), 159.6 (C, 14), 138.2 (CH, C-9), 129.9 (CH), 128.6 (C, C-16), 114.8 (CH_2, C-10), 113.9 (CH, C-19), 66.2 (CH_2, C-15), 56.4 (C, C-1), 55.3 (CH_3, C-20), 55.2 (CH, C-2), 35.5, 33.6, 27.8, 23.7, 22.0, 21.0 (CH_2, total of 6 C's: C-3 to C-8)

6.2.11 ***8a-But-3-enyl-4-methoxy-4,4a,5,6,7,8-hexahydro-1H-benzo[d][1,3]oxazin-2-one (106)***

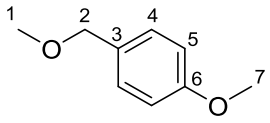


Oxone (166 mg, 0.540 mmol) was added to a solution of aldehyde **104** (170 mg, 0.492 mmol) dissolved in methanol (5 mL) and the reaction mixture was stirred for 24 h. The reaction mixture was quenched with HCl (5 mL, 1.0 M) and ethyl acetate (10 mL) was added. The layers were separated and the aqueous fraction was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was purified by column

chromatography on silica gel (2:1 hexanes: ethyl acetate) to afford cyclic carbamate **106** (81 mg, 0.34 mmol, 69%) as a 1:1 mixture of diastereomers; IR (film) 3233, 3119, 2928, 1700, 1414, 1328, 1138 cm^{-1}; Diastereomer 1: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H, NH), 5.78 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H, H-9), 5.33 (d, *J* = 2.6 Hz, 1H, H-11), 5.10 – 4.94 (m, 2H, H-10), 3.57 (s, 3H, H-12), 2.14 – 2.05 (m, 2H), 1.88 – 1.69 (m, 5H), 1.59 – 1.48 (m, 2H), 1.45 – 1.09 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (C-13), 137.9 (C-9), 115.4 (C-10), 102.1 (C-11), 57.4 (C-12), 53.8 (C-1), 41.9 (C-2), 39.6, 34.6, 27.4, 23.8, 21.0, 19.7 (total of 6 C's: C-3 to C-8); HRMS (ESI-TOF) calc'd for $C_{13}H_{22}NO_3$: 240.1594 $[M+H]^+$; found: 240.1593

Diastereomer 2: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H, NH), 5.75 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H, H-9), 5.02 – 4.86 (m, 3H, H-10 + H-11), 3.51 (s, 3H, H-12), 2.13 – 1.95 (m, 2H), 1.95 – 1.78 (m, 2H), 1.71 – 1.39 (m, 9H), 1.35 – 1.22 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (C-13), 138.2 (C-9), 114.8 (C-10), 104.7 (C-11), 57.0 (C-12), 54.1 (C-1), 39.3 (C-2), 38.4, 35.7, 27.8, 24.3, 22.7, 21.5 (total of 6 C's: C-3 to C-8); HRMS (ESI-TOF) calc'd for $C_{13}H_{22}NO_3$: 240.1594 $[M+H]^+$; found: 240.1592

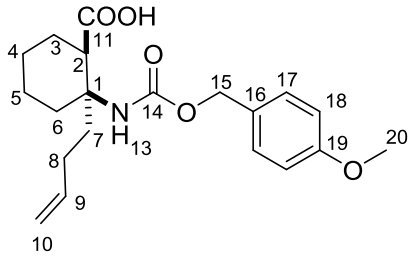
6.2.12 ***1-Methoxy-4-(methoxymethyl)benzene (107)***



Synthesised as a by-product in Scheme 29. NMR spectra matched the literature data.[117] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H, H-4), 6.90 (d, *J* = 8.7 Hz,

2H, H-5), 4.40 (s, 2H, H-2), 3.81 (s, 3H, H-7), 3.37 (s, 3H, H-1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C-6), 130.4, 129.4, 113.8 (C-5), 74.4 (C-2), 57.8 (C-7), 55.3 (C-1); HRMS (EI) calc'd for $C_9H_{12}O_2$: 152.0837 $[M]^+$; found: 152.0839.

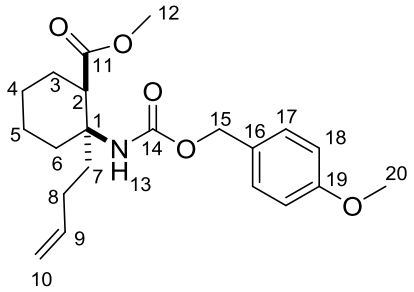
6.2.13 ***2-But-3-enyl-2-[(4-methoxyphenyl)methoxycarbonylamino]-cyclohexanecarboxylic acid (110)***



Oxone (74 mg, 0.24 mmol) was added to a solution of aldehyde **104** (40 mg, 0.11 mmol) dissolved in DMF (1 mL) and the reaction mixture was stirred for 4 h. The reaction mixture was quenched with HCl (1 mL, 1.0 M) and ethyl acetate (2 mL) was added. The layers were separated and the aqueous fraction was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (2:1:0.1 hexanes: ethyl acetate: acetic acid) to afford the desired carboxylic acid **110** (31 mg, 0.34 mmol, 85%) as a colourless oil; IR (film) br 3500 - 2700, 3364, 2935, 1723, 1514, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H, COOH), 7.30 (d, *J* = 8.7 Hz, 2H, H-17), 6.88 (d, *J* = 8.7 Hz, 2H, H-18), 5.99 (s, 1H, H-13), 5.82 – 5.70 (m, 1H, H-9), 5.04 – 4.88 (m, 4H, H-10 + H-15), 3.80 (s, 3H, H-20), 2.82 (d, *J* = 9.8 Hz, 1H), 2.58 – 2.46 (m, 1H), 2.20 – 1.94 (m, 3H), 1.86 – 1.61 (m, 4H),

1.61 – 1.40 (m, 2H), 1.35 – 1.13 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6 (C, C-11), 159.6 (C, C-14), 155.2 (C, C-19), 138.3 (CH, C-9), 130.0 (CH, C-17), 129.0 (C, C-16), 114.7 (CH_2, C-10), 114.0 (CH, C-18), 66.1 (CH_2, H-15), 56.1 (C, C-1), 55.4 (CH_3, C-20), 49.7 (CH, C-2), 38.6, 31.5, 28.3, 25.9, 24.5, 21.0 (total of 6 C's: C-3 to C-8); HRMS (ESI-TOF) calc'd for $C_{20}H_{26}NO_5$: 360.1816 $[M-H]^-$; found: 360.1806

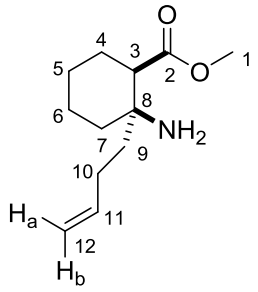
6.2.14 ***Methyl-2-(but-3-enyl)-2-((4-methoxybenzyloxy)carbonylamino)cyclohexane carboxylate (105)***



NIS (517 mg, 2.30 mmol) was added to a solution of aldehyde **104** (280 mg, 0.766 mmol) and K_2CO_3 (295 mg, 2.13 mmol) dissolved in methanol (7.6 mL) and the reaction mixture was stirred overnight. A saturated solution of sodium thiosulfate (10 mL) was added and the reaction mixture was stirred for 30 min. Water (5 mL) and ethyl acetate (10 mL) were added and the layers were separated. The aqueous fraction was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (4:1 hexanes: ethyl acetate) to afford the desired ester **105** (206 mg, 0.548 mmol, 72%) as a colourless oil; IR (film) 3382, 2936, 1723, 1615, 1513, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.7 Hz, 2H, H-

17), 6.88 (d, *J* = 8.7 Hz, 2H, H-18), 6.05 (s, 1H, H-13), 5.74 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H, H-9), 4.98 (s, 2H, H-15), 4.97 – 4.87 (m, 2H, H-10), 3.80 (s, 3H, H-20), 3.67 (s, 3H, H-12), 2.82 (d, *J* = 12.7 Hz, 1H, H-2), 2.48 (dd, *J* = 11.7, 3.7 Hz, 1H), 2.15 – 2.03 (m, 1H), 2.03 – 1.86 (m, 2H), 1.84 – 1.64 (m, 3H), 1.64 – 1.42 (m, 4H), 1.28 – 1.10 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (C, C-11), 159.6 (C, C-13), 155.1 (C, C-19), 138.5 (CH, C-9), 129.9 (C), 129.3 (CH), 114.6 (CH_2, C-10), 114.0 (CH, C-18), 65.9 (CH_2, C-15), 56.2 (C, C-1), 55.4, 51.9 (CH_3, C-12 + C-20), 49.8 (CH, C-2), 38.9, 31.8, 28.4, 25.9, 24.7, 21.1 (CH_2, total of 6 C's: C-3 to C-8); HRMS (ESI-TOF) calc'd for $C_{21}H_{30}NO_5$: 376.2118 $[M+H]^+$; found: 376.2100

6.2.15 ***Methyl 2-amino-2-(but-3-enyl)cyclohexanecarboxylate (74)***

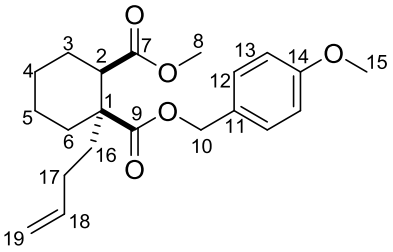


TFA (0.42 mL, 5.5 mmol) was added to a solution of methyl ester **105** (206 mg, 0.548 mmol) in DCM (5 mL) and stirred at room temperature overnight (solution went purple after 1 h). Water (5 mL) was added and the layers were separated. The aqueous fraction was extracted with DCM (3 x 5 mL) and the combined organic layers were dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (2:1 hexanes: ethyl acetate) to afford β-amino ester **74** (95 mg, 0.45 mmol, 82%) as a colourless oil; IR (film) 3390, 2937, 1723, 1637, 1446, 1194

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, H-11), 4.98 (dd, *J* = 17.1, 1.7 Hz, 1H, H-12a), 4.90 (dd, *J* = 10.1, 1.3 Hz, 1H, H-12b), 3.63 (s, 3H, H-1), 2.34 (dd, *J* = 11.8, 3.6 Hz, 1H, H-3), 2.13 – 2.03 (m, 2H, H-10), 1.84 – 1.74 (m, 1H), 1.74 – 1.65 (m, 2H), 1.64 – 1.57 (m, 3H), 1.57 – 1.48 (m, 3H), 1.44 – 1.37 (m, 2H), 1.30 – 1.14 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6 (C, C-2), 139.1 (CH, C-11), 114.4 (CH_2, C-12), 52.1 (C, C-8), 51.3 (CH, C-3), 51.2 (CH_3, C-1), 42.4 (CH_2, C-10), 36.2 (CH_2, C-7), 27.8 (CH_2, C-9), 25.4 (CH_2), 24.9 (CH_2), 21.1 (CH_2); HRMS (ESI-TOF): calc'd for $C_{12}H_{22}NO_2$: 212.1645 $[M + H]^+$; found: 212.1649.

6.3 Experimental pertaining to chapter 3

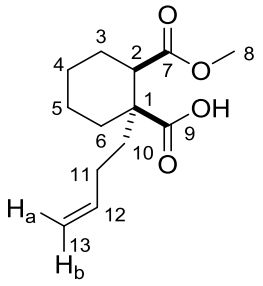
6.3.1 ***1-(4-Methoxybenzyl)-2-methyl 1-(but-3-enyl)cyclohexane-1,2-dicarboxylate (80)***



The anhydride **76** (5.00 g, 32.43 mmol) and *p*-methoxybenzyl alcohol (4.02 mL, 32.39 mmol) were stirred at 100 °C for 2 h. The resulting viscous oil was dried overnight in vacuo. A solution of LDA was prepared by adding *n*-butyllithium (36 mL, 2.5 M, 90 mmol) to a solution of diisopropylamine (13.6 mL, 97.3 mmol) in dry THF (100 mL) at -78 °C under a nitrogen atmosphere. This was warmed to 0 °C, stirred for 30 min and then cooled to -78 °C. At this time LiCl (1.14g, 26.89 mmol) was added to a solution of the acid **78**, dissolved in dry THF (25 mL), and the reaction mixture was warmed to room

temperature. After 1 h, 4-bromobutene (3.62 mL, 35.66 mmol) was added dropwise and the reaction mixture was stirred for 4 days. The reaction was quenched with saturated aqueous ammonium chloride and ethyl acetate was added. The layers were separated and the organic fraction was extracted with saturated aqueous ammonium chloride (3 x 50 mL). The organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated to give a yellow oil. The resulting oil was dissolved in DMF (60 mL) and potassium carbonate (7.18 g, 52.00 mmol) and MeI (3.29 mL, 52.83mmol) were added and the reaction mixture was stirred overnight. The solution was poured into water and ethyl acetate was added. The layers were separated and the organic layer was extracted three times with water. The combined aqueous layers were washed once with ethyl acetate. The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel (19:1 hexanes: ethyl acetate) to yield **80** (7.40 g, 20.53 mmol, 63 %) as a colourless oil; IR (film) 3071, 2952, 1733, 1512, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H, H-12), 6.87 (d, *J* = 8.7 Hz, 2H, H-13), 5.82 – 5.59 (m, 1H, H-18), 5.03 (s, 2H, H-10), 4.97 - 4.86 (m, 2H, H-19), 3.80 (s, 3H, H-15), 3.55 (s, 3H, H-8), 2.80 (t, *J* = 4.7 Hz, 1H, H-2), 2.13 (ddd, *J* = 15.4, 11.3, 4.2 Hz, 1H), 2.03 – 1.50 (m, 8H), 1.49 – 1.20 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (C, C-9), 174.6 (C, C-7), 159.7 (C, C-14), 138.2 (CH, C-18), 130.2 (CH, C-12), 128.5 (C, C-11), 114.9 (CH_2, C-19), 114.0 (CH, C-13), 66.1 (CH_2, C-10), 55.4, 51.6 (CH_3, C-8 + C-15), 46.94 (C, C-1), 46.93 (CH, C-2), 35.0, 28.4, 28.2, 25.0, 22.6, 21.3 (CH_2, total of 6 C's: C-3 to C-8); mass spectrum (CI, *m/z*, %) 361 (100, M+H), 121 (30); HRMS (ESI-TOF): calc'd for $C_{21}H_{28}NaO_5$: 383.1829 $[M + Na]^+$; found: 383.1820.

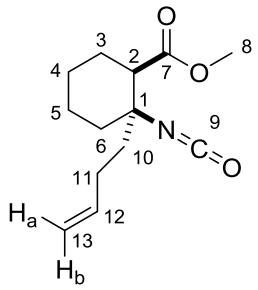
6.3.2 ***1-(But-3-enyl)-2-(methoxycarbonyl)cyclohexanecarboxylic acid (75)***



Trifluoroacetic acid (14.1 mL, 184.5 mmol) was added to a solution of the diester **80** (6.65 g, 18.45 mmol) in dichloromethane (180 mL). The reaction mixture was stirred overnight at room temperature (mixture turned purple after 30 min). The reaction was quenched with aqueous sodium hydroxide (90 mL, 1.0 M) and the solution was allowed to stir for 10 min. The organic fraction was extracted three times with aqueous sodium hydroxide (1.0 M) and the combined aqueous fractions were washed once with dichloromethane. The aqueous phase was acidified with concentrated HCl to pH = 1 and then extracted three times with dichloromethane. The combined organic layers were dried with magnesium sulfate and concentrated to afford **75** (3.77 g 15.69 mmol, 85%) as a white solid; mp 83 - 84 °C (from Hexanes); IR (film) br 3500 - 2500, 3075, 2949, 1737, 1699, 1162, 1006, 908 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H, COOH), 5.76 (ddt, *J* = 14.3, 10.2, 6.5 Hz, 1H, H-12), 5.01 (dd, *J* = 17.1, 1.6 Hz, 1H, H-13a), 4.93 (dd, *J* = 10.2, 1.4 Hz, 1H, H-13b), 3.65 (s, 3H, H-8), 2.77 (t, *J* = 4.7 Hz, 1H, H-2), 2.17 – 2.00 (m, 2H), 2.00 – 1.87 (m, 2H), 1.87 – 1.51 (m, 5H), 1.51 – 1.35 (m, 2H), 1.35 – 1.21 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.4 (C, C-9), 174.9 (C, C-7), 138.0 (CH, C-12), 115.0 (CH_2, C-13), 51.8 (CH_3, C-8), 47.2 (CH, C-2), 46.9 (C, C-1), 34.9 (CH_2, C-11),

28.2 (CH_2, C-10), 28.2 (CH_2), 25.0 (CH_2), 22.7 (CH_2), 21.3 (CH_2); mass spectrum (CI, *m/z*, %) 258 ($M+NH_4^+$) 241 (80, $M+H^+$), 226 (20); HRMS (ESI-TOF): calc'd for $C_{13}H_{19}O_4$: 239.1289 $[M-H]^-$; found: 239.1288.

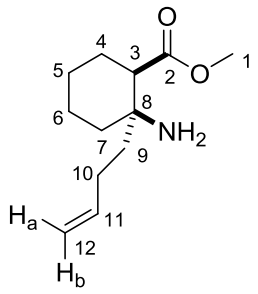
6.3.3 ***Methyl 2-(but-3-enyl)-2-isocyanatocyclohexanecarboxylate (150)***



Triethylamine (2.05 mL, 15.93 mmol), DMAP (1.95 g, 15.93 mmol) and DPPA (3.43 mL, 15.93 mmol) were added to a solution of toluene containing the starting material **75** (3.48 g, 14.48 mmol) and the mixture was heated at reflux for 6 h. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted three times with diethyl ether. The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (19:1 hexanes: ethyl acetate) to afford **150** (3.16 g, 13.32 mmol, 92%) as a colourless oil; IR (film) 2941, 2267, 1736, 1169, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, H-12), 5.04 (dd, *J* = 17.1, 1.6 Hz, 1H, H-13a), 4.98 (dd, *J* = 10.2, 1.5 Hz, 1H, H-13b), 3.72 (s, 3H, H-8), 2.41 (dd, *J* = 11.7, 3.7 Hz, 1H, H-2), 2.23 – 2.08 (m, 2H), 1.92 – 1.72 (m, 5H), 1.62 (m, 3H), 1.34 – 1.15 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C, C-7), 137.8 (CH, C-12), 122.4 (C, C-22) 115.3 (CH_2, C-13), 61.0 (C, C-1), 51.8 (CH, C-2), 51.7 (CH_3, C-8), 41.4

(CH_2, C-10), 36.7 (CH_2, C-6), 28.1 (CH_2, C-11), 25.9 (CH_2), 24.7 (CH_2), 21.8 (CH_2); HRMS (ESI-TOF): calc'd for $C_{13}H_{20}NO_3$: 238.1438 $[M + H]^+$; found: 238.1434.

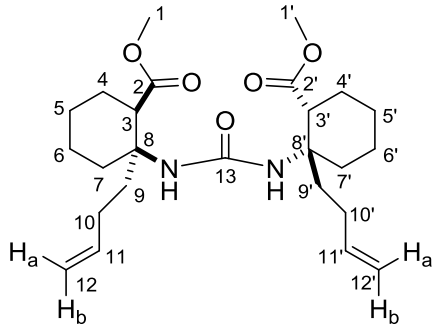
6.3.4 ***Methyl 2-amino-2-(but-3-enyl)cyclohexanecarboxylate (74)***



Potassium trimethylsilanolate (2.0g, 15.5 mmol) was added to a solution of the isocyanate **150** (1.69 g, 7.12 mmol) in THF (300 mL) at 0 °C and the solution was stirred for 2 h. The reaction mixture was warmed to room temperature and quenched with water. Ethyl acetate was added and the layers were separated. The aqueous layer was extracted with ethyl acetate three times and the combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude product was left overnight under high vacuum affording the primary amine **74** (1.45 g, 6.91 mmol, 97%) of as a pale yellow oil (2:1 hexanes: ethyl acetate); 3390, 2937, 1723, 1637, 1446, 1194 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, H-11), 4.98 (dd, *J* = 17.1, 1.7 Hz, 1H, H-12a), 4.90 (dd, *J* = 10.1, 1.3 Hz, 1H, H-12b), 3.63 (s, 3H, H-1), 2.34 (dd, *J* = 11.8, 3.6 Hz, 1H, H-3), 2.13 – 2.03 (m, 2H, H-10), 1.84 – 1.74 (m, 1H), 1.74 – 1.65 (m, 2H), 1.64 – 1.57 (m, 3H), 1.57 – 1.48 (m, 3H), 1.44 – 1.37 (m, 2H), 1.30 – 1.14 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6 (C, C-2), 139.1 (CH, C-11), 114.4 (CH_2, C-12), 52.1 (C, C-8), 51.3 (CH, C-3), 51.2 (CH_3, C-1), 42.4 (CH_2, C-9), 36.2 (CH_2,

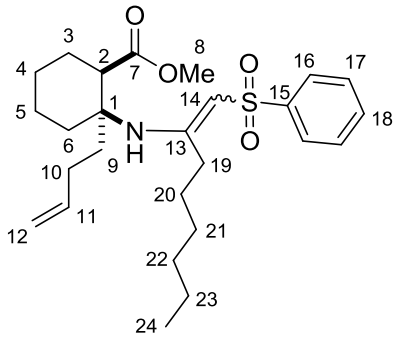
C-7), 27.8 (CH_2, C-10), 25.4 (CH_2), 24.9 (CH_2), 21.1 (CH_2); HRMS (ESI-TOF): calc'd for $C_{12}H_{22}NO_2$: 212.1645 $[M + H]^+$; found: 212.1649.

6.3.5 ***Methyl-2-but-3-enyl-2[(1-but-3-enyl-2-methoxycarbonyl-cyclohexyl)-carbamoylamino]cyclohexanecarboxylate (151)***



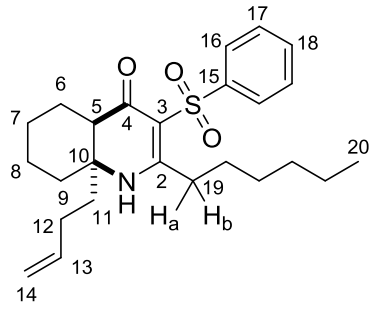
A mixture of meso and D, L-diastereomers;IR (film) 3383, 3073, 2936, 1722, 1690, 1522, 1430, 1248, 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 – 5.69 (m, 2H, H-1 + H-1'), 5.40 (s, 1H, NH), 5.38 (s, 1H, NH'), 5.02 – 4.86 (m, 4H, H-12 + H-12'), 3.69 (s, 6H, H-1 + H-1'), 2.81 (d, *J* = 9.6 Hz, 2H), 2.57 – 2.46 (m, 2H), 2.15 – 1.90 (m, 6H), 1.88 – 1.43 (m, 14H), 1.32 – 1.20 (m, 2H), 1.20 – 1.08 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (C, C-2), 176.3 (C, C-2'), 139.04 (CH, C-11), 138.98 (CH, C-11'), 114.37 (CH_2, C-12), 114.35 (CH_2, C-12'), 56.2 (C, C-8), 56.1 (C, C-8'), 51.83 (CH_3, C-1), 51.79 (CH_3, C-1'), 50.2 (CH), 38.7 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 26.1 (CH_2), 24.7 (CH_2), 21.3 (CH_2), 21.2 (CH_2); HRMS (ESI-TOF): calc'd for $C_{25}H_{40}N_2O_5$: 448.3015 $[M + H]^+$; found: 448.3005.

6.3.6 ***Methyl-2-(but-3-enyl)-2-(-1-(phenylsulfonyl)oct-1-en-2-ylamino)cyclohexane carboxylate (82)***



The amine **74** (2.05 g, 9.70 mmol) and acetylenic sulfone **73** (4.0 g, 16.0 mmol) were stirred in refluxing anisole (90 mL) for 6 h. The reaction mixture was concentrated and chromatographed on silica gel (4:1 hexanes: ethyl acetate) to afford (3.27 g, 7.08 mmol, 74%) of product **82** as an orange oil (4:1 hexanes: ethyl acetate); IR (film) 3366, 2924, 1713, 1590, 1433, 1176, 1134, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 2H), 7.52 – 7.38 (m, 3H), 5.78 – 5.60 (m, 2H, NH + H-11), 5.22 (s, 1H, H-14), 4.99 – 4.87 (m, 2H, H-12), 3.67 (s, 3H, H-8), 2.62 – 2.28 (m, 4H), 2.03 – 1.77 (m, 3H), 1.76 – 1.49 (m, 5H), 1.47 – 1.14 (m, 11H), 0.86 (t, *J* = 7.0 Hz, 3H, H-24); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (C-7), 158.5 (C-13), 146.6 (C-15), 137.7 (C-11), 131.6, 128.8, 126.3, 115.2 (C-12), 93.8 (C-14), 58.2 (C-1), 52.1 (C-8), 50.5 (C-5), 36.8, 33.1, 31.6, 29.2, 28.8, 28.3, 26.2, 24.4, 22.7, 20.8 (total of 10 C's: C-3 - C-6 + C-8 + C-9 + C-19 - C-23), 14.2 (C-24); HRMS (ESI-TOF) calc'd for $C_{26}H_{40}NO_4S$: 462.2673 $[M + H]^+$; found: 462.2676.

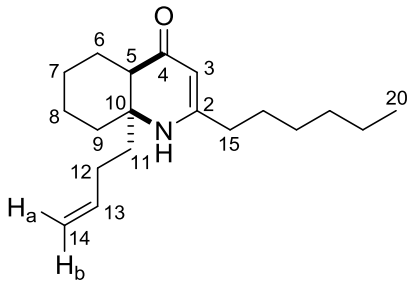
6.3.7 ***8a-(but-3-enyl)-2-hexyl-3-(phenylsulfonyl)-4a,5,6,7,8,8a-hexahydroquinolin-4(1H)-one 72***



LiHMDS (2.15 mL, 2.15 mmol, 1.0M) was added dropwise to a solution of the vinyl sulfone **82** (900 mg, 1.95 mmol) in dry THF (20 mL) at -78 °C. The reaction mixture was warmed to room temperature and stirred for 6 h and then quenched with saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. The product was purified by column chromatography on silica gel (2:1 hexanes: ethyl acetate) to afford the cyclised product **72** (1.073 g, 2.50 mmol, 91%) as a colourless oil; IR (film) 3273, 3075, 2933, 1641, 1624, 1512, 1283, 1147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.87 (m, 2H, H-16), 7.52 – 7.36 (m, 3H, H-17 + H-18), 5.94 (s, 1H, N-H), 5.78 – 5.52 (m, 1H, H-13), 5.03 – 4.82 (m, 2H, H-14), 3.16 (ddd, *J* = 13.0, 9.7, 6.0 Hz, 1H, H-19a), 2.84 (ddd, *J* = 13.0, 9.7, 6.2 Hz, 1H, H-19b), 2.11 – 1.99 (m, 1H), 1.97 – 1.83 (m, 3H), 1.81 – 1.71 (m, 3H), 1.68 – 1.56 (m, 3H), 1.50 – 1.19 (m, 10H), 1.17 – 1.05 (m, 1H), 0.89 (t, *J* = 7.1 Hz, 3H, H-20). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3 (C, C-4), 167.9 (C, C-2), 144.5 (C, C-15), 137.7 (CH, C-13), 132.0 (CH, C-18), 128.3 (CH, C-17), 127.1 (CH, C-16), 115.4 (CH_2, C-14), 106.7 (C, C-3), 56.7 (C, C-10), 51.2 (CH, C-5), 36.5

(CH_2), 34.4 (CH_2, C-19), 32.8 (CH_2), 31.6 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 27.5 (CH_2), 26.1 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 21.6 (CH_2), 14.2 (CH_3, C-20). HRMS (ESI-TOF) calc'd for $C_{25}H_{36}NO_3S$: 430.2410 $[M + H]^+$; found: 430.2407.

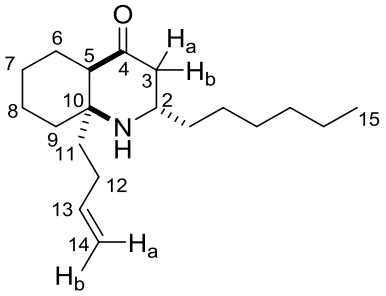
6.3.8 ***8a-(But-3-enyl)-2-hexyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1H)-one (119)***



Liquid ammonia (25 mL) was condensed into a 50 mL round bottom flask at -78 °C in an acetone and dry ice bath, to which sodium metal was added until the solution remained dark blue. The flask was removed from the cold bath and the liquid ammonia was allowed to distill into a second 50 mL round bottom flask at -78 °C under argon. The starting material **72** (500 mg, 1.16 mmol) was dissolved in dry THF (25 mL) added at -78 °C to the flask containing liquid ammonia to which sodium metal (267 mg, 11.6 mmol) was added and stirred for 5 min. EtOH (0.108 mL, 2 equiv) was added and the solution was stirred for 10 min at which time the reaction was quenched with $NH_4Cl_{(S)}$ (0.10 g) and the solution was heated to room temperature over 1 hour. Water (20 mL) and ethyl acetate (20 mL) were added and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. The product was purified by column chromatography on silica gel (4:1 hexanes: ethyl acetate) to afford enaminone **119** (230

mg, 0.791 mmol, 60%) and aminones **125** and **118** (101 mg, 0.344 mmol, 30%) as an inseparable 9:1 mixture of diastereomers; Colourless oil; IR (film) 3274, 2930, 1631, 1514, 1444, 1283, 1148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 16.4, 10.1, 6.4 Hz, 1H, H-13), 5.01 – 4.94 (m, 1H, H-14a), 4.94 - 4.89 (m, 1H, H-14b), 4.83 (s, 1H, H-3), 4.67 (br s, 1H, NH), 2.22 – 2.04 (m, 3H), 2.02 – 1.86 (m, 3H), 1.82 – 1.43 (m, 8H), 1.42 – 1.23 (m, 9H), 1.22 – 1.10 (m, 1H), 0.87 (t, *J* = 6.9 Hz, 3H, H-20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7 (C, C-4), 162.8 (C, C-2), 138.4 (CH, C-13), 114.9 (CH_2, C-14), 95.8 (C, C-3), 57.3 (C, C-10), 51.5 (CH, C-5), 35.8 (CH_2), 35.3 (CH_2), 33.6 (CH_2), 31.6 (CH_2), 28.9 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 27.4 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 14.1 (CH_3, C-20); HRMS (ESI-TOF): calc'd for $C_{19}H_{32}NO$: 290.2478 $[M + H]^+$; found: 290.2482.

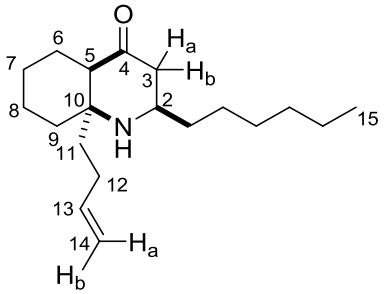
6.3.8.1 8a-(But-3-enyl)-2-hexyloctahydroquinolin-4(1H)-one (118)



Liquid ammonia (25 mL) was condensed into a 50 mL round bottom flask at -78 °C in an acetone and dry ice bath, to which sodium metal was added until the solution remained dark blue. The flask was removed from the cold bath to allow the liquid ammonia to distill into a second 50 mL round bottom flask at -78 °C under argon. The starting material **72** (400 mg, 0.931 mmol) was dissolved in dry THF (20 mL) added at -

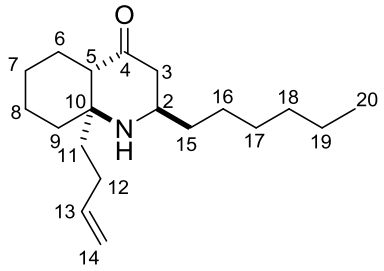
78 °C to the flask containing liquid ammonia to which sodium metal (105 mg, 4.57 mmol) was added and stirred for 5 min. EtOH (0.108 mL, 2 equiv) was added and the solution was stirred for 10 min at which time the reaction was quenched with $NH_4Cl_{(S)}$ (0.100 g) and the solution was heated to room temperature over 1 hour. Water (15 mL) and ethyl acetate (15 mL) were added and the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. The product was purified by column chromatography on silica gel (19:1 hexanes: ethyl acetate) to afford the aminone products **125** and **118** (179 mg, 0.614 mmol, 60%) as an inseparable 9:1 mixture of diastereomers and enaminone **119** (86 mg, 0.30 mmol 30%); Minor isomer **118**; Colourless oil; IR (film) 2928, 1708, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, H-13), 5.07 (ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H, H-14a), 4.98 (ddd, *J* = 10.1, 2.9, 1.1 Hz, 1H, H-14b), 3.18 - 3.07 (m, 1H, H-2), 2.36 (dd, *J* = 13.5, 2.9 Hz, 1H, H-3a), 2.25 (br s, 1H, H-5), 2.22 – 2.05 (m, 2H), 1.96 (t, *J* = 12.6 Hz, 1H, H-3b), 1.84 – 1.21 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0 (C, C-4), 139.0 (CH, C-13), 114.8 (CH_2, C-14), 58.4 (C, C-10), 53.9 (CH, C-5), 50.1 (CH, C-2), 49.0 (CH_2, C-3), 37.9 (CH_2), 37.7 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 27.4 (CH_2), 25.8 (CH_2), 22.73 (CH_2), 22.71 (CH_2), 21.6 (CH_2), 21.3 (CH_2), 14.2 (CH_3, C-15); HRMS (ESI-TOF): calc'd for $C_{19}H_{34}NO$: 292.2635 $[M + H]^+$; found: 292.2638.

6.3.8.2 8a-(But-3-enyl)-2-hexyloctahydroquinolin-4(1H)-one (125)



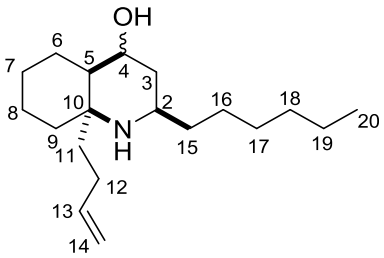
Major isomer **125**; Colourless oil; IR (film) 2927, 1707, 1453, 1242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, H-13), 4.98 (dd, *J* = 17.1, 1.8 Hz, 1H, H-14a), 4.95 – 4.89 (m, 1H, H-14b), 2.99 – 2.90 (m, 1H, H-2), 2.20 (dd, *J* = 14.5, 10.8 Hz, 1H, H-3a), 2.12 (ddd, *J* = 14.5, 4.1, 0.9 Hz, 1H, H-3b), 2.09 – 2.03 (m, 1H, H-5), 2.03 – 1.88 (m, 1H), 1.87 – 1.71 (m, 3H), 1.67 – 1.03 (m, 19H), 0.88 (t, *J* = 6.8 Hz, 3H, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.6 (C, C-4), 138.7 (CH, C-13), 114.6 (CH_2, C-14), 58.3 (CH, C-5), 55.1 (C, C-10), 50.6 (CH, C-2), 44.2 (CH_2, C-3), 38.1 (CH_2), 37.7 (CH_2), 35.8 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 21.0 (CH_2), 14.2 (CH_3, C-15); HRMS (ESI-TOF): calc'd for $C_{19}H_{34}NO$: 292.2635 $[M + H]^+$; found: 292.2632.

6.3.8.3 8a-(But-3-enyl)-2-hexyl-octahydroquinolin-4(1H)-one (126)



Compound isolated after aqueous workup of the hydrochloride salt (see Figure 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, H-13), 5.05 – 4.96 (m, 1H, H-14a), 4.95 - 4.91 (m, 1H, H-14b), 3.07 - 2.95 (m, 1H), 2.35 (dd, *J* = 13.4, 3.6 Hz, 1H), 2.29 (ddd, *J* = 12.2, 3.2, 1.0 Hz, 1H), 2.07 (ddd, *J* = 13.3, 11.2, 1.2 Hz, 1H), 1.96 – 1.56 (m, 7H), 1.53 – 1.13 (m, 17H), 0.88 (t, *J* = 6.9 Hz, 3H, H20). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.9 (C-4), 138.6 (C-13), 114.8 (C-14), 60.6 (C-5), 58.8 (C-10), 51.5 (C-2), 49.1 (C-3), 37.8, 36.1, 31.9, 29.5, 26.27, 26.25, 26.0, 25.2, 22.7, 21.8, 20.4 (total of 11 C's: C-6 to C-9 + C-11 + C-12 + C-15 to C-19) 14.2 (C-20).

6.3.9 ***8a-(But-3-enyl)-2-hexyldecahydroquinolin-4-ol (123)***



Liquid ammonia (50 mL) was condensed into a 100 mL round bottom flask at -78 °C in an acetone dry ice bath, to which sodium metal was added until the solution remained dark blue. The flask was removed from the cold bath to allow the liquid ammonia to distill into a second 100 mL round bottom flask at -78 °C under argon. The starting material **72** (1.04 g, 2.42 mmol) was dissolved in dry THF (50 mL) and added to the flask containing liquid ammonia to which sodium metal (550 mg, 23.9 mmol) was added and stirred for 5 min. EtOH (0.42 mL) was added and the solution was stirred for 10 min at which time the reaction was quenched with $NH_4Cl_{(S)}$ (2.56 g) and the solution

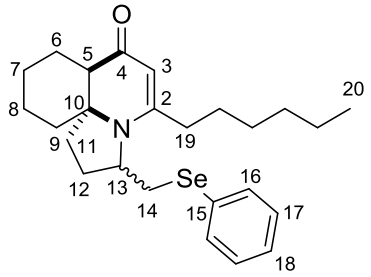
was warmed to room temperature over 1 hour. Water (30 mL) and ethyl acetate (30 mL) were added and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. The product was purified by column chromatography on silica gel (1:2 hexanes: ethyl acetate) to afford the aminol products **123** (514 mg, 1.75 mmol, 73%) as an inseparable mixture of diastereomers; Some clean material could be isolated in sufficient quantities to obtain NMR data.

Mixture of major isomer: Colourless oil; IR (film) 3366, 2928, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 – 5.76 (m, 1H), 5.08 – 4.91 (m, 2H), 3.66 – 3.52 (m, 1H, H-4), 3.33 – 3.23 (m, 1H), 2.77 – 2.66 (m, 1H, H-2), 2.08 - 1.99 (m, 1H), 1.90 (d, *J* = 8.1 Hz, 2H), 1.85 – 0.95 (m, 44H), 0.93 – 0.82 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3 (CH, C-13), 114.5 (CH_2, C-14), 73.7 (C-4), 68.9 (CH, C-4), 55.3 (C), 54.4 (CH), 54.3 (CH), 51.5 (CH), 50.8 (CH), 48.6 (CH), 43.6 (CH_2), 43.4 (CH), 41.8 (CH_2), 40.2 (CH_2), 39.9 (CH_2), 37.5 (CH_2), 36.7 (CH_2), 34.5 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 23.0 (CH_2), 22.8 (CH_2), 22.1 (CH_2), 21.7 (CH_2), 20.9 (CH_2), 14.2 (CH_3); HRMS (ESI-TOF): calc'd for $C_{19}H_{36}NO$: 294.2791 $[M + H]^+$; found: 294.2791.

Minor isomer; Colourless oil; IR (film) 3347, 2928, 1442 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.05 – 4.90 (m, 2H), 4.17 (dt, *J* = 11.8, 4.8 Hz, 1H), 2.80 - 2.71 (m, 1H), 2.05 – 1.91 (m, 2H), 1.84 – 1.72 (m, 2H), 1.68 – 1.54 (m, 4H), 1.51 – 1.07 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H, H-20). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6 (C-13), 114.3 (C-14), 68.2 (C-4), 54.6 (C-10), 49.3 (C-2), 44.3 (C-5),

37.6, 37.2, 36.7, 36.3, 32.0, 29.7, 27.3, 26.1, 25.8, 22.8, 21.4, 19.7 (total of 12 C's: C-6 to C-9 + C-11 + C-12 + C-15 to C-19), 14.3 (C-20).

6.3.10 ***5-Hexyl-3-(phenylselanylmethyl)-2,3,8,9,10,11-hexahydro-1H-pyrrolo[1,2-j]quinolin-7(7aH)-one (128)***



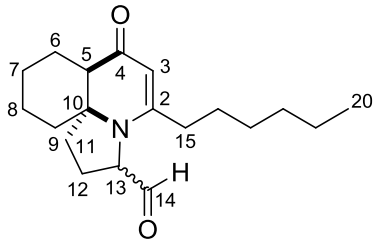
To a round bottom flask, wrapped in foil to avoid exposure to light, was added silver triflate (266 mg, 1.04 mmol) and benzeneselenenyl chloride (109 mg, 0.570 mmol) dissolved in dichloromethane (5 mL) and stirred for 15 min at room temperature. A solution of **119** (150 mg, 0.518 mmol) dissolved in dichloromethane (1.0 mL) was added and stirred overnight. The reaction was quenched with water and extracted three times with dichloromethane. The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (2:1 hexanes: ethyl acetate) afforded the selenide **128** (80 mg, 0.17 mmol, 35%) as a 2:1 mixture of diastereomers; IR (film) 2930, 1718, 1626, 1550, 1435, 1295, 1195 cm^{-1}; HRMS (ESI-TOF): calc'd for $C_{25}H_{36}NO^{80}Se$: 446.1957 $[M + H]^+$; found: 446.1958;

Major Diastereomer: Colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H), 7.34 – 7.25 (m, 3H), 4.98 (s, 1H, H-3), 3.97 – 3.86 (m, 1H, H-13), 2.99 (dd, *J* = 12.5, 1.8 Hz, 1H, H-14a), 2.71 (dd, *J* = 12.5, 11.4 Hz, 1H, H-14b), 2.51 – 2.41 (m, 1H),

2.33 (dd, *J* = 11.6, 6.4 Hz, 1H, H-5), 2.15 – 1.58 (m, 8H), 1.44 – 0.84 (m, 16H), 0.86 (t, *J* = 6.1 Hz, 3H, H-20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.97 (C, C-4), 161.2 (C, C-2), 134.8 (CH, C-17), 129.4 (CH, C-16), 128.5 (C, C-15), 128.2 (CH, C-18), 100.4 (CH, C-3), 67.0 (C, C-10), 58.7 (CH, C-13), 52.0 (CH, C-5), 33.9 (CH_2, C-19), 33.3 (CH_2), 31.6 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 27.2 (CH_2), 25.8 (CH_2), 24.1 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 21.4 (CH_2), 14.1 (CH_3, C-20); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 289.4.

Peaks attributed to the minor Diastereomer: Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H), 7.34 – 7.25 (m, 3H), 4.86 (s, 1H, H-3), 3.98 – 3.85 (m, 1H, H-13), 3.04 (dd, *J* = 12.4, 2.8 Hz, 1H, H-14a), 2.82 (t, *J* = 12.0 Hz, 1H, H-14b), 2.51 – 2.41 (m, 1H), 2.36 – 2.29 (m, 1H), 2.25 (dd, *J* = 12.9, 4.0 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.26 (C, C-4), 161.6 (C, C-2), 134.6 (CH), 129.4 (CH), 128.4 (C), 97.3 (CH, C-3), 67.3 (C, C-10), 60.4 (CH, C-13), 47.8 (CH, C-5), 14.1 (CH_3, C-20); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 293.7.

6.3.11 ***5-Hexyl-2,3,7,7a,8,9,10,11-octahydro-7-oxo-1H-pyrrolo[1,2-j]quinoline-3-carbaldehyde (134)***



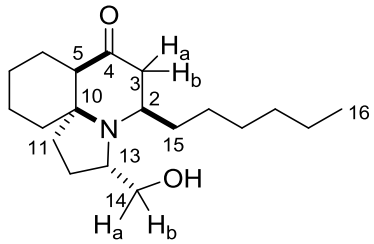
m-CPBA (77%, 34.3 mg, 0.153 mmols) was added to a solution of **128** (80 mg, 0.18 mmol) in THF (3.6 mL) at -78 ^{o}C and warmed to room temperature. Acetic

anhydride (85 µL, 0.90 mmol) and sodium acetate (73 mg, 0.54 mmol) were added and the reaction mixture was heated at reflux. After 4 h, the reaction mixture was cooled, water (3 mL) and ethyl acetate (3 mL) were added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 1 mL) and the combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (4:1 hexanes: ethyl acetate) afforded aldehyde **134** (12 mg, 0.04 mmol, 22%) as a 2:1 mixture of diastereomers; Colourless oil;

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 1.3 Hz, 1H, CHO), 5.07 (s, 1H, H-3), 4.41 (d, *J* = 9.5 Hz, 1H, H-13), 2.50 (s, 1H, H-5), 2.44 – 1.94 (m, 5H), 1.86 (m, 1H), 1.77 – 1.17 (m, 15H), 0.87 (t, *J* = 6.6 Hz, 3H, H-20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0 (CHO), 194.0 (C-4), 161.0 (C-3), 99.8 (C-2), 67.2 (C-10), 66.4 (C-13), 50.7 (C-5), 33.9, 33.8, 31.6, 28.9, 27.5, 26.2, 24.5, 24.3, 22.8, 22.6, 21.5 (total of 11 C's: C-6 to C-9 + C-11 + C-12 + C-15 to C-19), 14.1 (C-20).

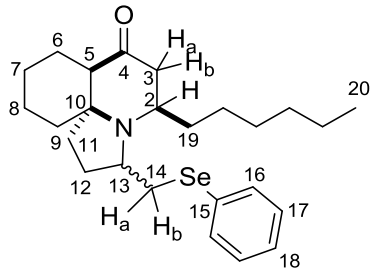
Peaks attributed to the minor Diastereomer: Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 3.0 Hz, 1H, CHO), 4.99 (s, 1H, H-3), 4.38 – 4.31 (m, 1H, H-13), 2.48 – 2.45 (m, 1H, H-5), 0.87 (t, *J* = 6.6 Hz, 3H, H-20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5 (CHO), 192.8 (C-4), 161.2 (C-2), 98.0 (C-3), 68.2 (C-10), 67.1 (C-13), 49.9 (C-5), 35.1, 34.0, 31.6, 29.0, 27.7, 25.3, 23.9, 22.9, 22.7, 22.6, 21.6 (total of 11 C's: C-6 to C-9 + C-11 + C-12 + C-15 to C-19), 14.1 (C-20).

6.3.12 ***5-Hexyl-3-(hydroxymethyl)-1,2,3,5,6,7a,8,9,10,11-decahydropyrrolo[2,1-j]quinolin-7-one (2,13-di-epi-cylindricine C) (3d)***



To a solution of aldehyde **134** (18 mg, 0.059 mmol) dissolved in benzene (1 mL) were added $Na(OAc)_3BH$ (50 mg, 0.24 mmol) in benzene and a catalytic amount of AcOH (1 drop). The reaction mixture was refluxed overnight and quenched with a saturated solution of $NaHCO_3$ (1 mL). The reaction mixture was extracted with $CHCl_3$ (3 x 1 mL), dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (4:1 hexanes: ethyl acetate eluent) afforded 2,13-di-epi-cylindricine C **3d** (13 mg, 0.044 mmol, 75%) as a colourless oil; IR (film) 3369, 2922, 1707, 1602, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (dd, *J* = 10.7, 3.4 Hz, 1H, H-14a), 3.46 (dd, *J* = 10.7, 1.2 Hz, 1H, H-14b), 3.40 – 3.34 (m, 1H, H-13), 3.29 (m, 1H, H-2), 2.60 (dd, *J* = 14.5, 7.6 Hz, 1H, H-3a), 2.40 (s, 1H, H-5), 2.36 (dd, *J* = 14.6, 2.4 Hz, 1H, H-3b), 2.24 – 2.11 (m, 2H), 2.11 – 2.00 (m, 1H), 1.94 – 1.85 (m, 1H), 1.73 - 1.21 (m, 20H), 1.08 (m, 1H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (C, C-4), 67.1 (C, C-10), 61.1 (CH_2, C-14), 57.0, 56.3, 52.7 (CH, total of 3 C's: C-2 + C-5 + C-13), 44.7 (CH_2, C-3), 35.1 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 22.8 (CH_2), 21.8 (CH_2), 14.2 (CH_3, C-16); HRMS (ESI-TOF): calc'd for $C_{19}H_{34}NO_2$: 308.2584 $[M + H]^+$; found: 308.2570.

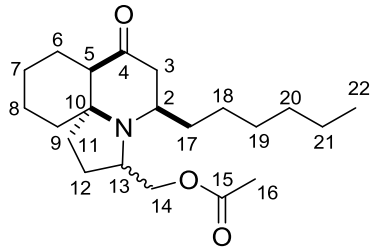
6.3.13 ***5-Hexyl-3-(phenylselanylmethyl)octahydro-1H-pyrrolo[1,2-j]quinolin-7(7aH)-one 138/ 139***



To a round bottom flask, wrapped in foil to avoid exposure to light, was added silver triflate (224 mg, 0.871 mmol) and benzeneselenenyl chloride (122 mg, 0.626 mmol) dissolved in dichloromethane (2.0 mL) and stirred for 15 min at room temperature. A solution of **118** and **125** (170 mg, 0.583 mmol) dissolved in dichloromethane (5.0 mL) was added and stirred overnight. The reaction mixture was quenched with water and extracted three times with dichloromethane. The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (4:1 hexanes: ethyl acetate) afforded the selenide **138/ 139** (60 mg, 0.13 mmol, 23%) as a 1:1 mixture (at the C-13 center) of diastereomers; Colourless oil; IR (film) 2923, 1703, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H, H-17), 7.27 – 7.21 (m, 3H, H16, H-18), 3.63 – 3.56 (m, 1H, H-13), 3.42 – 3.35 (m, 1H, H-2), 3.13 (dd, *J* = 11.5, 2.2 Hz, 1H, H-14a), 3.03 (dd, *J* = 11.5, 8.0 Hz, 1H, H-14b), 2.54 (dd, *J* = 14.9, 6.6 Hz, 1H, H-3a), 2.35 (s, 1H), 2.29 (dd, *J* = 15.0, 4.9 Hz, 1H, H-3b), 2.25 – 2.18 (m, 1H), 2.18 – 2.00 (m, 2H), 1.94 – 1.86 (m, 1H), 1.66 – 1.47 (m, 6H), 1.46 – 1.00 (m, 15H), 0.88 (t, *J* = 7.0 Hz, 3H, H-20). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4 (C,C-4), 132.8 (CH, C-17), 131.0 (C, C-15), 129.2 (CH, C-16), 126.9

(CH, C-18), 66.0 (C, C-10), 56.9 (CH,C-5), 56.8 (CH, C-13), 52.3 (CH,C-2), 44.3 (CH_2, C-3), 34.8 (CH_2), 34.5 (CH_2), 33.7 (CH_2), 32.6 (C-14), 32.0 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 24.5 (CH_2), 23.6 (CH_2), 22.8 (CH_2), 21.6 (CH_2), 14.2 (CH_3, C-20). ^{77}Se NMR (76 MHz, $CDCl_3$) δ 248.6. HRMS (ESI-TOF): calc'd for $C_{25}H_{34}NO^{80}Se$: 448.2113$[M + H]^+$; found: 448.2107.

6.3.14 ***5-Hexyl-7-oxo-1,2,3,5,6,7a,8,9,10,11-decahydropyrrolo[2,1-j]quinolin-3-yl]methyl acetate (140)***

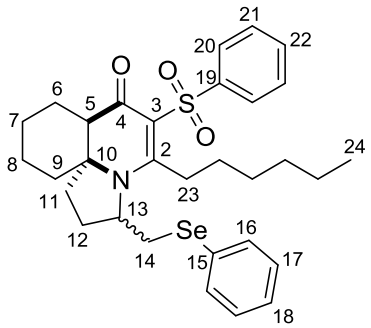


m-CPBA (77%, 34.3 mg, 0.153 mmols) was added to a solution of **138/ 139** (62 mg, 0.14 mmol) in DCM (1 mL) at -78 ^oC and warmed to room temperature. Acetic anhydride (65.0 µL, 0.694 mmol) and sodium acetate (34 mg, 0.42 mmol) were added to the reaction mixture and heated at reflux. After 2 h, the reaction mixture was cooled, water (1 mL) and ethyl acetate (1 mL) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 1 mL) and the combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (19:1 hexanes: ethyl acetate) afforded the acetate **140** (26 mg, 0.074 mmol, 54%) as a 1:1 mixture (at the C-13 center) of diastereomers.

Colourless oil; IR (film) 2926, 1740, 1708, 1457, 1230, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 – 3.95 (m, 2H), 3.78 (dd, *J* = 10.8, 8.5 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.44 – 3.33 (m, 1H), 3.32 – 3.12 (m, 2H), 2.60 – 2.44 (m, 2H), 2.41 (s, 1H, H-5), 2.34 – 2.05 (m, 3H), 2.03 (s, 3H, H-16) 1.89 – 1.03 (m, 14H), 0.84 (t, *J* = 6.7 Hz, 3H, H-22). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4, 212.2 (C-15), 171.2, 171.1 (C-4), 68.3, 68.2 (C-10), 65.4, 65.1 (C-14), 63.2, 58.9 (C-13), 56.9, 56.7 (C-2), 52.4, 51.1 (C-5), 44.5, 43.3 (C-3), 40.7, 37.1, 36.5, 35.8, 34.8, 34.5, 32.0, 32.0, 29.6, 29.5, 27.0, 26.8, 26.2, 26.2, 24.6, 24.5, 23.7, 23.3, 22.8 (2 x CH_2), 21.8, 21.5, 21.21, 21.15 (total of 24 C's: C-6 to C-9 + C-11 + C-12 + C-16 to C-21) 14.2 (C-22); HRMS (ESI-TOF): calc'd for $C_{21}H_{36}NO_3$: 350.2690 $[M + H]^+$; found: 350.2689.

6.4 Experiments Pertaining to Chapter 4

6.4.1 ***6-(Benzenesulfonyl)-5-hexyl-3-(phenylselanylmethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (71)***



In a round bottom flask wrapped in foil to avoid exposure to light was added silver triflate (658 mg, 2.56 mmol) and benzeneselenenyl chloride (490 mg, 2.56 mmol) dissolved in dichloromethane (10.0 mL) and stirred for 15 min at room temperature. A

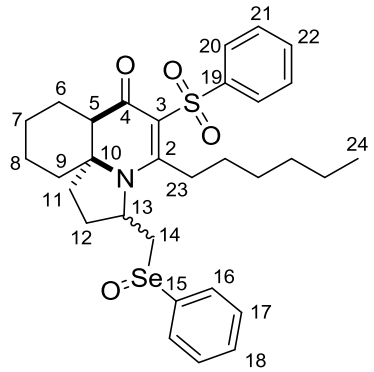
solution of **72** (900 mg, 2.09 mmol) dissolved in dichloromethane (13 mL) was added and the reaction mixture was stirred overnight. The reaction was quenched with water and extracted three times with dichloromethane (60 mL). The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (2:1 hexanes: ethyl acetate) afforded the selenide **71** (1.17 g, 2.00 mmol, 92%) as a 3:1 mixture of diastereomers; IR (film) 2923, 1638, 1490, 1281, 1216, 1137 cm^{-1}; HRMS (ESI-TOF): calc'd for $C_{31}H_{40}NO_3S^{80}Se$: 586.1889 $[M + H]^+$; found: 586.1880.

Major Diastereomer: Colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.62 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.51 – 7.40 (m, 3H), 7.38 – 7.30 (m, 3H), 4.09 – 4.01 (m, 1H, H-13), 3.31 (t, *J* = 9.7 Hz, 1H, H-23), 3.05 (d, *J* = 12.6 Hz, 1H, H-14a), 2.73 (t, *J* = 12.1 Hz, 1H, H-14b), 2.38 – 2.16 (m, 4H), 2.08 (td, *J* = 12.4, 6.3 Hz, 1H), 1.98 – 1.70 (m, 4H), 1.57 (d, *J* = 13.0 Hz, 2H), 1.38 – 1.05 (m, 10H), 1.00 – 0.92 (m, 1H), 0.88 (t, *J* = 7.0 Hz, 3H, H-24), 0.80 – 0.63 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8 (C, C-4), 166.1 (C, C-2), 144.9 (C, C-19), 135.1 (CH), 131.8 (CH), 129.7 (2 x CH), 128.7 (CH), 128.2 (CH), 127.4 (C, C-15), 112.3 (C, C-3), 66.8 (C, C-10), 60.6 (CH, C-13), 52.4 (CH, C-5), 33.14 (CH_2, C-14), 33.06 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 26.32 (CH_2), 26.28 (CH_2), 23.5 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 20.8 (CH_2), 14.2 (CH_3, C-24). ^{77}Se NMR (76 MHz, $CDCl_3$) δ 299.18.

Minor Diastereomer: Colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.11 – 4.06 (m, 1H, H-13), 3.78 (td, *J* = 12.9, 4.7 Hz, 1H), 3.13 (d, *J* = 12.7 Hz, 1H, H-14a), 2.90 (t, *J* = 12.4 Hz, 1H, H-14b), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4 (C, C-4), 166.9 (C, C-2), 144.6 (C, C-19), 134.9 (CH), 131.7 (CH), 128.1 (CH), 127.5

(CH_2), 127.3 (C, C-15), 109.2 (C, C-3), 67.0 (C, C-10), 62.3 (CH, C-13), 47.5 (CH, C-5), 34.1 (CH_2, C-14), 32.6 (CH_2), 31.4 (CH_2), 31.2 (CH_2), 30.5 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 20.9 (CH_2), 14.2 (CH_3, C-24); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 301.02.

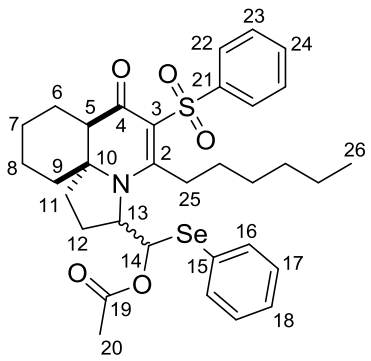
6.4.2 ***6-(Benzenesulfonyl)-5-hexyl-3-(phenylseleninylmethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (152)***



m-CPBA (0.177 mg, 1.02 mmol) was added to a solution of **71** (600 mg, 1.02 mmol) in DCM (10 mL) at 0 ^{o}C and warmed to room temperature. After 1 hour the reaction mixture was quenched with a saturated solution of sodium bicarbonate (10 mL) and the layers were separated. The organic layer was extracted with a saturated solution of sodium bicarbonate (10 mL) and the combined organic fractions were dried with magnesium sulfate and concentrated to afforded the selenoxide **152** (600 mg, 1.00 mmol, 98%) as an inseparable mixture of diastereomers; IR (film) 2924, 1638, 1489, 1440, 1282, 1139 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.90 (m, 2H), 7.79 – 7.68 (m, 2H), 7.64 – 7.53 (m, 3H), 7.51 – 7.37 (m, 3H), 4.63 – 4.57 (m, 1H), 4.56 – 4.50 (m, 1H), 4.49 – 4.46 (m, 1H), 4.42 (dd, *J* = 10.3, 7.4 Hz, 1H), 3.73 (t, *J* = 6.5 Hz, 1H), 3.51 – 3.42

(m, 1H), 3.36 – 3.26 (m, 1H), 3.18 (t, *J* = 11.9 Hz, 1H), 3.12 (d, *J* = 12.1 Hz, 1H), 3.03 (t, *J* = 11.8 Hz, 1H), 2.93 (d, *J* = 12.8 Hz, 1H), 2.82 (dd, *J* = 12.4, 10.4 Hz, 1H), 2.73 (d, *J* = 12.2 Hz, 1H), 2.45 – 2.31 (m, 1H), 2.29 – 2.05 (m, 3H), 2.01 – 1.72 (m, 4H), 1.70 – 1.04 (m, 12H), 0.97 – 0.85 (m, 3H), 0.79 – 0.55 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.63, 188.55 (C-4), 165.84, 165.80 (C-2), 144.50, 144.48, 139.3 (C-19), 132.0, 131.94, 131.92, 130.33, 130.30, 130.25, 128.3, 128.2, 127.5, 127.3, 125.89, 125.85, 125.8, 113.2, 113.1 (C-3), 68.1, 66.7, 66.6, 66.4, 66.1 (C-10), 55.6, 54.2, 54.0, 52.7, 52.4, 52.4, 47.6, 47.5 (C-5), 34.48, 34.46, 33.4, 33.3, 32.5, 32.4, 31.9, 31.73, 31.70, 31.65, 30.0, 29.9, 29.5, 28.2, 27.8, 26.6, 26.3, 26.3, 25.7, 23.51, 23.49, 23.4, 23.0, 22.9, 22.7, 22.6, 20.8, 14.2 (C-24); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 859.1, 857.5, 847.7, 845.7; HRMS (ESI-TOF): calc'd for $C_{31}H_{40}NO_4S^{80}Se$: 602.1825 $[M + H]^+$; found: 602.1838.

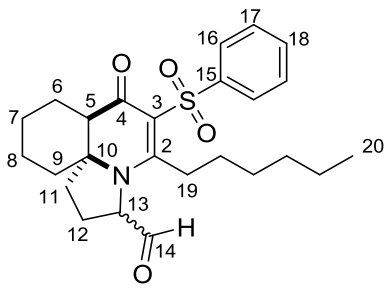
6.4.3 ***6-(Benzenesulfonyl)-5-hexyl-7-oxo-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-3-yl]-phenylselanyl-methyl] acetate (153)***



The selenoxide **152** (600 mg, 1.00 mmol) was dissolved in acetic anhydride (20 mL) and heated at 70 ^{o}C overnight. The reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (1:1 hexanes: ethyl acetate) to

afford the acetatoxy selenide **153** (629 mg, 0.978 mmol, 98%) as an inseparable mixture of diastereomers; IR (film) 2923, 1748, 1642, 1486, 1283, 1214, 1146 cm^{-1}; Data for major isomer which could be cleanly isolated: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.66 – 7.60 (m, 2H), 7.49 – 7.40 (m, 4H), 7.40 – 7.32 (m, 2H), 6.01 (d, *J* = 10.2 Hz, 1H, H-14), 4.15 – 4.08 (m, 1H, H-13), 3.39 (ddd, *J* = 13.2, 11.2, 4.3 Hz, 1H, H-25), 2.37 – 2.23 (m, 3H), 2.17 (br s, 1H, H-5), 2.14 – 1.94 (m, 3H), 1.92 – 1.80 (m, 1H), 1.75 (s, 3H), 1.72 – 1.65 (m, 1H), 1.64 – 1.54 (m, 1H), 1.35 – 1.11 (m, 10H), 1.07 – 0.93 (m, 3H), 0.91 (t, *J* = 7.1 Hz, 3H, H-26), 0.88 – 0.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8 (C, C-4), 169.0 (C, C-19), 167.9 (C, C-2), 144.8 (C, C-21), 137.2 (CH), 132.0 (CH), 129.8 (CH), 129.7 (CH), 128.3 (CH), 127.4 (CH), 124.5 (C, C-15), 113.9 (C, C-3), 73.9 (CH, C-14), 66.8 (C, C-10), 61.7 (CH, C-13), 52.5 (CH, C-5), 33.5 (CH_2), 32.0 (CH_2, C-25), 31.7 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 29.0 (CH_2), 27.0 (CH_2), 26.0 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.8 (CH_2), 20.9 (CH_2), 20.6 (CH_3, C-20), 14.2 (CH_3, C-26); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 452.17; HRMS (ESI-TOF): calc'd for $C_{33}H_{42}NO_5S^{80}Se$: 644.1943 $[M + H]^+$; found: 644.1930.

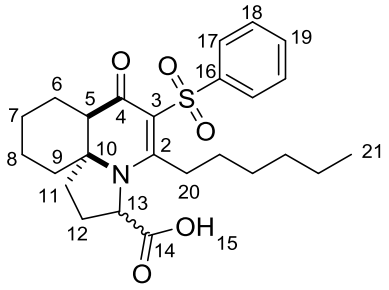
*6.4.4 **6-(Benzenesulfonyl)-5-hexyl-7-oxo-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinoline-3-carbaldehyde (70)***



The acetoxy selenide (550 mg, 0.856 mmol) was dissolved in methanol (20 mL) and stirred with potassium carbonate (1.18g, 8.54 mmol) for 3 hours. The solution was poured into water and extracted with ethyl acetate (3x30ml). The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (1:2 hexanes: ethyl acetate eluent) afforded the aldehyde **70** (391 mg, 0.878 mmol, 78%) as a 3:1 mixture of diastereomers; Colourless oil; IR (film) 2928, 1732, 1637, 1494, 1280, 1142 cm^{-1}; Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) 9.62 (s, 1H, H-14), 8.02 – 7.93 (m, 2H), 7.50 – 7.40 (m, 3H), 4.81 – 4.75 (m, 1H, H-13), 3.45 (t, *J* = 10.0 Hz, 1H, H-19a), 2.41 – 2.23 (m, 3H), 2.22 – 2.10 (m, 2H), 2.06 – 1.86 (m, 4H), 1.69 – 1.54 (m, 3H), 1.52 – 1.08 (m, 10H), 1.00 – 0.91 (m, 1H), 0.88 (t, *J* = 5.3 Hz, 3H, H-20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4 (CHO, C-14), 188.6 (C, C-4), 166.7 (C, C-2), 144.6 (C), 131.9 (CH), 128.3 (CH), 127.2 (CH), 111.7 (C, C-3), 68.1 (CH, C-13), 66.7 (C, C-10), 50.4 (CH, C-5), 33.2 (CH_2), 32.4 (CH_2, C-19), 31.4 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 26.2 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 20.8 (CH_2), 14.1 (CH_3, C-20); HRMS (ESI-TOF): calc'd for $C_{25}H_{34}NO_4S$: 444.2203 $[M + H]^+$; found: 444.2206.

Peaks attributed to the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.1 Hz, 1H, H-14), 8.02 – 7.93 (m, 2H), 7.50 – 7.40 (m, 3H), 4.66 (dd, *J* = 9.3, 3.4 Hz, 1H, H-13), 3.84 – 3.74 (m, 1H, H-19), 0.86 (t, 3H, H-20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6 (CHO, C-14), 186.9 (C, C-4), 167.5 (C, C-2), 144.8 (C, C-15), 131.9 (CH), 128.2 (CH), 127.3 (CH), 110.2 (C, C-3), 68.8 (CH, C-13), 67.8 (C, C-10), 48.8 (CH, C-5), 34.7 (CH_2), 32.3 (CH_2, C-19), 31.4 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 24.7 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 21.0 (CH_2), 14.1 (CH_3, C-20).

6.4.5 ***6-(Benzenesulfonyl)-5-hexyl-7-oxo-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinoline-3-carboxylic acid (154)***

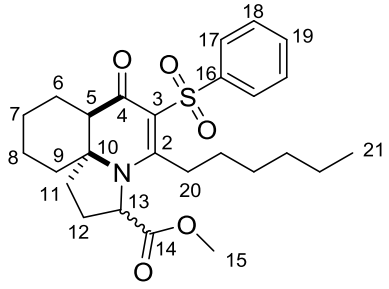


Tempo (7.0 mg, 0.045 mmol) and bis(acetoxy)iodobenzene (181 mg, 0.563 mmol) were added to a solution of aldehyde **70** (100 mg, 0.225 mmol) dissolved in DCM (2 mL) and water (1 mL) and stirred for 2 hours. At this time, TLC indicated complete conversion of starting material and the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ (1 mL), acidified to pH = 2 using HCl (2.0 M) and extracted with DCM (3 x 2 mL). The combined organic fractions were dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (ethyl acetate: AcOH 1%) afforded the carboxylic acid **154** (93 mg, 0.20 mmol, 90%) as a 3:1 mixture of diastereomers.

White solid; IR (film) br 3300 - 2500, 2931, 1732, 1637, 1499, 1285, 1214, 1142 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 7.82 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.58 – 7.48 (m, 3H), 4.80 (d, *J* = 8.4 Hz, 1H, H-13), 3.10 (td, *J* = 12.7, 4.2 Hz, 1H), 2.43 – 2.31 (m, 2H), 2.29 (s, 1H, H-5), 2.15 – 2.08 (m, 1H), 2.02 (d, *J* = 11.6 Hz, 1H), 1.78 – 1.51 (m, 4H), 1.49 – 1.23 (m, 10H), 1.21 – 1.09 (m, 2H), 0.87 (t, *J* = 6.7 Hz, 3H, H-21), 0.58 – 0.45 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 187.6 (C, C-4), 172.9 (C, C-14), 166.6 (C, C-2), 144.7

(C, C-16), 131.8 (CH), 128.3 (CH), 126.7 (CH), 109.9 (C, C-3), 66.2 (C, C-10), 62.0 (CH, C-13), 49.7 (CH, C-5), 33.3 (CH_2), 31.7 (CH_2, C-20), 30.7 (CH_2), 29.1 (CH_2), 27.8 (CH_2), 26.7 (CH_2), 25.7 (CH_2), 22.8 (CH_2), 22.4 (CH_2), 22.1 (CH_2), 20.5 (CH_2), 14.0 (CH_3, C-21). HRMS (ESI-TOF): calc'd for $C_{25}H_{34}NO_5S$: 460.2152 $[M + H]^+$; found: 460.2151.

6.4.6 ***Methyl-6-(benzenesulfonyl)-5-hexyl-7-oxo-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinoline-3-carboxylate (155)***

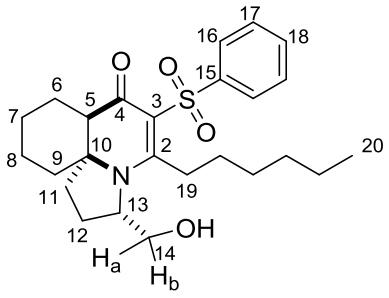


Concentrated H_2SO_4 (1 mL) was added to a solution of carboxylic acid **154** (68 mg, 0.0147 mmol) dissolved in methanol (9 mL) and refluxed for 3 h. The reaction mixture was cooled to room temperature and poured into water and extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated to afford ester **155** (56 mg, 0.012 mmol, 81%) as a 3:1 mixture of diastereomers; Colourless oil; IR (film) 2932, 1742, 1642, 1499, 1445, 1286, 1216, 1144 cm^{-1}; Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.96 (m, 2H), 7.48 – 7.41 (m, 3H), 4.65 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.78 (s, 3H), 3.46 – 3.33 (m, 1H), 2.52 (s, 1H, H-5), 2.41 – 2.27 (m, 3H), 2.24 – 2.11 (m, 2H), 2.06 – 1.88 (m, 2H), 1.82 – 1.73 (m, 1H), 1.68 – 1.55 (m, 2H), 1.51 – 1.38 (m, 3H), 1.36 – 1.25 (m, 7H),

1.23 – 1.12 (m, 1H), 0.93 – 0.84 (t, 3H, H-21). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8 (C, C-4), 171.71 (C, C-14), 166.7 (C, C-2), 144.6 (C, C-16), 131.8 (CH), 128.3 (CH), 127.3 (CH), 112.0 (C, C-3), 66.8 (C, C-10), 61.8 (CH, C-13), 53.3 (CH_3, C-15), 50.5 (CH, C-5), 33.7 (CH_2), 32.2 (CH_2, C-20), 31.4 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 23.7 (CH_2), 23.0 (CH_2), 22.7 (CH_2), 20.8 (CH_2), 14.1 (CH_3, C-21); HRMS (ESI-TOF): calc'd for $C_{26}H_{36}NO_5S$: 474.2309 $[M + H]^+$ found: 474.2308.

Peaks attributed to the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, J = 8.6, 3.8 Hz, 1H, H-13), 3.83 (s, 1H, H-15). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.0 (C, C-4), 171.7 (C, C-14), 167.6 (C, C-2), 144.9 (C, C-16), 131.8 (CH), 128.2 (CH), 127.4 (CH), 110.4 (C, C-3), 68.1 (C, C-10), 62.7 (CH, C-13), 53.2 (CH_3, C-15), 48.6 (CH, C-5), 35.0 (CH_2), 32.3 (CH_2), 31.5 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 23.2 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 21.1 (CH_2), 14.1 (CH_3, C-21).

6.4.7 ***6-(Benzenesulfonyl)-5-hexyl-3-(hydroxymethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (83)***

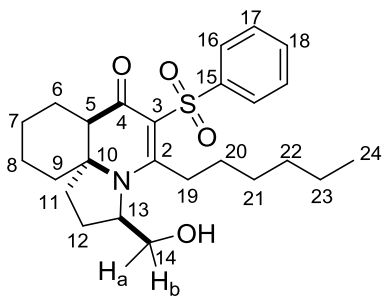


Sodium borohydride (7.8 mg, 0.21 mmol) was added to a solution of aldehyde **70** (90 mg, 0.20 mmol) in methanol (4 mL) at 0 °C. The reaction mixture was stirred for 3 hours and poured into water and extracted with ethyl acetate (3 x 5 mL). The combined

organic fractions were washed once with brine, dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (1:3 hexanes: ethyl acetate eluent) afforded alcohol **83** and **156** (80 mg, 0.018 mmol, 88%) as an inseparable 3:1 mixture of diastereomers;

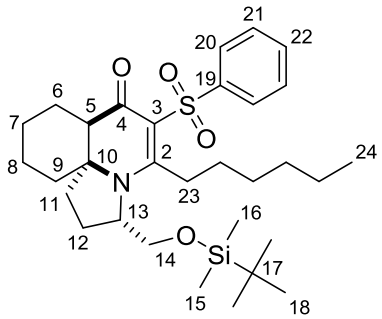
Major isomer: Colourless oil; IR (film) 3471, 2932, 1630, 1506, 1426, 1287, 1217, 1138 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.51 – 7.36 (m, 3H), 4.32 – 4.18 (m, 1H, H-13), 3.78 (dd, *J* = 11.1, 5.3 Hz, 1H, H-14a), 3.71 (dd, *J* = 11.2, 6.2 Hz, 1H, H-14b), 3.47 – 3.35 (m, 1H, H-19), 2.84 – 2.70 (m, 1H, H-19), 2.35 (s, 1H, H-5), 2.26 (dd, *J* = 11.8, 5.4 Hz, 1H), 2.22 – 1.77 (m, 4H), 1.69 – 1.03 (m, 12H), 0.90 (t, *J* = 7.1 Hz, 3H, H-20), 0.50 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9 (C, C-4), 167.9 (C, C-2), 144.8 (C, C-15), 131.8 (CH), 128.2 (CH), 127.5 (CH), 111.9 (C, C-3), 66.9 (C, C-10), 65.4 (CH_2, C-14), 61.6 (CH, C-13), 51.2 (CH, C-5), 33.4 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 26.8 (CH_2), 25.4 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 22.8 (CH_2), 20.9 (CH_2), 14.2 (CH_3, C-20); HRMS (ESI-TOF): calc'd for $C_{25}H_{36}NO_4S$: 446.2360 $[M + H]^+$ found: 446.2344

6.4.7.1 6-(Benzenesulfonyl)-5-hexyl-3-(hydroxymethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (156)



Colourless oil; IR (film) 3468, 2929, 1633, 1498, 1285, 1216, 1142 cm^{-1}; ^{1}H NMR (402 MHz, $CDCl_3$) δ 8.08 – 7.98 (m, 2H), 7.50 – 7.40 (m, 3H), 4.26 – 4.18 (m, 1H, H-13), 4.03 – 3.92 (m, 1H, H-19), 3.79 (dd, *J* = 10.8, 5.8 Hz, 1H, H-14a), 3.70 (dd, *J* = 16.8, 6.3 Hz, 1H, H-14b), 2.56 – 2.46 (m, 1H, H-19), 2.41 – 2.29 (m, 2H), 2.25 (s, 1H, H-5), 2.19 – 1.95 (m, 5H), 1.73 – 1.49 (m, 4H), 1.49 – 1.37 (m, 2H), 1.37 – 1.13 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H, H-24), 0.84 – 0.71 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7 (C-4), 168.1 (C-2), 145.0 (C-15), 131.8, 128.3, 127.4, 109.4 (C-3), 66.9 (C-10), 63.6 (C-14), 63.2 (C-13), 47.7 (C-5), 34.5, 31.9, 31.8, 31.6, 30.4, 29.7, 26.9, 23.6, 23.0, 22.7, 21.1 (total of 11 C's: C-6 to C-9 + C-11 + C-12 + C-19 to C-23), 14.2 (C-24); HRMS (ESI-TOF): calc'd for $C_{25}H_{36}NO_4S$: 446.2360 $[M + H]^+$ found: 446.2362

6.4.8 ***6-(Benzenesulfonyl)-3-[[tert-butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (158)***

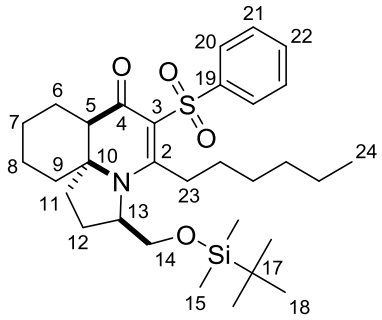


To alcohol **83** and **156** (240 mg, 0.538 mmol) in DMF (6 mL) was added TBSCl (105 mg, 0.697 mmol), DMAP (9 mg, 0.07 mmol) and imidazole (47 mg, 0.69 mmol) and the reaction mixture was stirred overnight. Brine (10 mL) was added to quench the reaction and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The

combined organic fractions were dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (7:3 hexanes: ethyl acetate eluent) afforded **158** and **159** (233 mg, 0.416 mmol, 77%) as a 3:1 mixture of diastereomers;

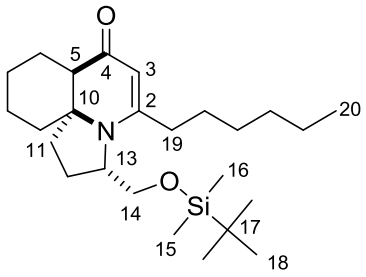
Major diastereomer: Colourless oil; IR (film) 2929, 1640, 1493, 1296, 1215, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.48 – 7.38 (m, 3H), 4.20 – 4.11 (m, 1H, H-13), 3.59 (dd, *J* = 10.2, 4.7 Hz, 1H, H-14a), 3.52 (dd, *J* = 10.2, 7.1 Hz, 1H, H-14b), 3.43 (td, *J* = 12.6, 4.3 Hz, 1H, H-23), 2.63 (td, *J* = 12.6, 3.3 Hz, 1H, H-23), 2.29 (dd, *J* = 12.5, 4.3 Hz, 1H), 2.17 (s, 1H, H-5), 2.10 – 1.93 (m, 4H), 1.82 – 1.68 (m, 1H), 1.62 – 1.11 (m, 14H), 0.89 (t, *J* = 7.0 Hz, 3H, H-24), 0.85 (s, 9H, H-18), 0.02 (s, 3H, H-15), 0.01 (s, 3H, H-16). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0 (C, C-4), 167.2 (C, C-2), 144.9 (C, C-19), 131.7 (CH), 128.1 (CH), 127.4 (CH), 112.1 (C, C-3), 66.7 (C, C-10), 65.7 (CH_2, C-14), 61.6 (CH, C-13), 52.0 (CH, C-5), 33.5 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 26.4 (CH_2), 25.9 (CH_3, C-18), 25.2 (CH_2), 23.6 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 20.9 (CH_2), 18.3 (C, C-17), 14.1 (CH_3, C-24), -5.1 (CH_3, C-15), -5.4 (CH_3, C-16); HRMS (ESI-TOF): calc'd for $C_{31}H_{50}NO_4SSi$: 560.3224 $[M + H]^+$ found: 560.3216

6.4.8.1 6-(Benzenesulfonyl)-3-[[tert-butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (159)



Minor diastereomer: Colourless oil; IR (film) 2930, 1637, 1501, 1295, 1215, 1141 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.52 – 7.35 (m, 3H), 4.19 – 4.12 (m, 1H, H-13), 3.98 (td, *J* = 13.2, 4.9 Hz, 1H, H-23), 3.71 (dd, *J* = 10.3, 6.0 Hz, 1H, H-14a), 3.64 (dd, *J* = 10.3, 7.5 Hz, 1H, H-14b), 2.51 (td, *J* = 13.3, 4.9 Hz, 1H, H-23), 2.35 (d, *J* = 13.3 Hz, 1H), 2.24 (s, 1H, H-5), 2.17 – 1.95 (m, 5H), 1.77 – 1.14 (m, 14H), 0.92 (s, 9H, H-18), 0.88 (t, *J* = 7.0 Hz, 3H, H-24), 0.80 – 0.68 (m, 1H), 0.10 (s, 6H, H-15 + H-16). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.6 (C, C-4), 167.9 (C, C-2), 145.1 (C, C-19), 131.6 (CH), 128.1 (CH), 127.4 (CH), 109.5 (C, C-3), 66.9 (C, C-10), 64.2 (CH_2, C-14), 63.5 (CH, C-13), 47.6 (CH, C-5), 34.6 (CH_2), 31.94 (CH_2), 31.90 (CH_2), 31.5 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 26.8 (CH_2), 25.9 (CH_3, C-18), 23.5 (CH_2), 23.0 (CH_2), 22.7 (CH_2), 21.0 (CH_2), 18.3 (C, C-17), 14.1 (CH_3, C-24), -5.25 (CH_3, C-15), -5.27 (CH_3, C-16); HRMS (ESI-TOF): calc'd for $C_{31}H_{50}NO_4SSi$: 560.3224 $[M + H]^+$; found: 560.3212

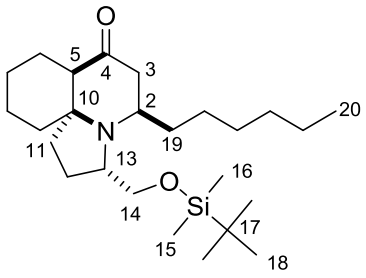
6.4.9 ***3-[[tert-Butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (160)***



A solution of sodium naphthalenide was prepared by adding sodium metal (23 mg, 1.0 mmol) to a solution of naphthalene (128 mg, 0.999 mmol) in dry THF (1 mL) and the reaction mixture was stirred for 2 h at room temperature. In a separate flask, the starting material **158** (56 mg, 0.10 mmol) was dissolved in dry THF (1 mL) and cooled to -78 ^{o}C. The sodium naphthalenide solution (1.0 M) was added in 0.1 mL increments until TLC showed no remaining starting material (~5 equiv). $NH_4Cl_{(S)}$ (50 mg) was added and the reaction mixture was warmed to room temperature, poured into water and the layers were separated. The reaction mixture was extracted with ethyl acetate (3 x 2 mL) and the combined organic fractions were dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (3:1 hexanes: ethyl acetate eluent) afforded the desired compound **160** (23 mg, 0.55 mmol, 55%) and **161** (6 mg, 0.01 mmol, 15%); Colourless oil; IR (film) 2928, 1627, 1547, 1462, 1200, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H, H-3), 3.96 – 3.86 (m, 1H, H-13), 3.55 (dd, *J* = 10.1, 4.3 Hz, 1H, H-14a), 3.42 (dd, *J* = 10.0, 7.8 Hz, 1H, H-14b), 2.48 – 2.41 (m, 1H), 2.41 – 2.33 (m, 1H), 2.33 – 2.25 (m, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 2.05 (m, 1H), 2.03 – 1.95 (m, 1H), 1.79 – 1.70 (m, 1H), 1.68 – 1.61 (m, 1H), 1.57 – 1.10 (m, 15H), 0.90 – 0.88 (m, 12H, H-18 +

H-20), 0.04 (s, 6H, H-15 + H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0 (C, C-4), 162.2 (C, C-2), 100.1 (CH, C-3), 67.0 (C, C-10), 65.9 (CH_2, C-14), 59.8 (CH, C-13), 51.6 (CH, C-5), 33.6 (CH_2), 33.4 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 24.3 (CH_2), 23.1 (CH_2), 22.7 (CH_2), 21.5 (CH_2), 18.4 (C, C-17), 14.2(CH_3, C-20), -5.3 (CH_3, C-15 + C-16); HRMS (ESI-TOF): calc'd for $C_{25}H_{46}NO_2Si$: 420.3292 $[M + H]^+$; found: 420.3288

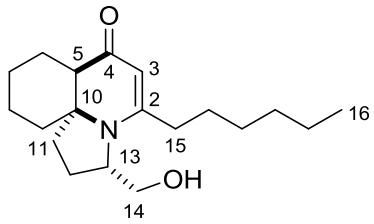
6.4.9.1 3-[[tert-Butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,5,6,7a,8,9,10,11-decahydropyrrolo[2,1-j]quinolin-7-one (161)



Colourless oil; IR (film) 2928, 1710, 1630, 1550, 1462, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (dd, *J* = 10.2, 3.6 Hz, 1H, H-14a), 3.57 (dd, *J* = 10.2, 5.5 Hz, 1H, H-14b), 3.48 – 3.42 (m, 1H, H-2), 3.42 – 3.36 (m, 1H, H-13), 2.53 (dd, *J* = 15.7, 5.6 Hz, 1H, H-3a), 2.40 (s, 1H, H-5), 2.31 (dd, *J* = 15.8, 7.4 Hz, 1H, H-3b), 2.28 – 2.22 (m, 1H), 2.04 (dd, *J* = 10.9, 7.6 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.81 – 1.73 (m, 1H), 1.69 – 1.61 (m, 3H), 1.45 – 1.10 (m, 16H), 0.94 – 0.83 (m, 12H, H-18 + H-20), 0.05 (s, 6H, H-15 + H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.2 (C, C-4), 65.1 (C, C-10), 64.3 (CH_2, C-14), 60.3 (CH, C-13), 56.3 (CH, C-5), 52.2 (CH, C-2), 44.5 (CH_2, C-3), 37.2 (CH_2), 35.2 (2 x CH_2), 32.1 (CH_2), 29.7 (CH_2), 27.1 (CH_2), 26.4 (CH_2), 26.1 (CH_3), 24.8 (CH_2), 23.6

(CH_2), 22.8 (CH_2), 21.5 (CH_2), 18.5 (C, C-17), 14.2 (CH_3, C-20), -5.23 (CH_3,C-15), -5.22 (CH_3,C-16); HRMS (ESI-TOF): calc'd for $C_{25}H_{48}NO_2Si$: 422.3449 $[M + H]^+$; found: 422.3447.

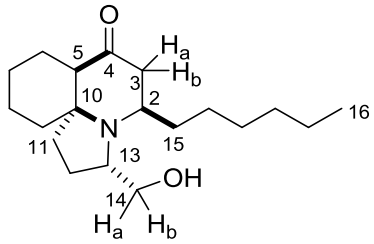
6.4.10 ***5-Hexyl-3-(hydroxymethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (157)***



A solution of sodium naphthalenide was prepared by adding sodium metal (13 mg, 0.55 mmol) to naphthalene (70 mg, 0.55 mmol) in dry THF (2 mL) and the reaction mixture was stirred for 2 h at room temperature. In a separate flask, the starting material **83** (49 mg, 0.11 mmol) was dissolved in dry THF (1 mL) and cooled to -78 ^oC. Sodium naphthalenide solution (1.0 M) was added in 0.1 mL increments until TLC showed no remaining starting material (~5 equiv). $NH_4Cl_{(S)}$ (20 mg) was added and the reaction mixture was warmed to room temperature and poured into water. The layers were separated and the reaction mixture was extracted with ethyl acetate (3 x 2 mL). The combined organic fractions were dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (1:3 hexanes: ethyl acetate eluent) afforded alcohol **157** (10 mg, 0.033 mmol, 30%) as a colourless oil; Colourless oil; IR (film) 3364, 2928, 1603, 1534, 1218, cm^{-1}; ^1H NMR (402 MHz, $CDCl_3$) δ 4.95 (s, 1H, H-3), 4.03 (s, 1H,

OH), 3.97 (dd, *J* = 11.7, 5.9 Hz, 1H, H-13), 3.59 (d, *J* = 5.3 Hz, 2H, H-14), 2.45 – 2.36 (m, 1H), 2.34 (s, 1H, H-5), 2.27 (dd, *J* = 12.1, 5.9 Hz, 1H), 2.22 – 1.97 (m, 2H), 1.90 – 1.77 (m, 1H), 1.63 (d, *J* = 13.6 Hz, 1H), 1.53 – 1.42 (m, 2H), 1.42 – 1.12 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2 (C, C-4), 163.5 (C, C-2) 99.7 (CH, C-3), 67.1 (C, C-10), 65.6 (CH_2, C-14), 60.0 (CH, C-13), 51.0 (CH, C-5), 33.7 (CH_2), 33.6 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 24.2 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 21.5 (CH_2), 14.2 (CH_3, C-16); HRMS (ESI-TOF): calc'd for $C_{19}H_{32}NO_2$: 306.2428 $[M + H]^+$; found: 306.2419.

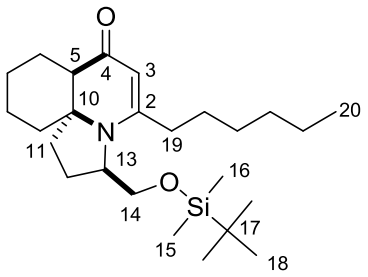
6.4.11 5-Hexyl-3-(hydroxymethyl)-1,2,3,5,6,7a,8,9,10,11-decahydropyrrolo[2,1-j]quinolin-7-one (2,13-di-epi-cylindricine C) (3d)



To a solution of alcohol **135** (16 mg, 0.052 mmol) dissolved in $CDCl_3$ (1 mL) was added $Na(OAc)_3BH$ (55 mg, 0.26 mmol) and a catalytic amount of AcOH (1 drop). The reaction mixture was refluxed overnight and quenched with a saturated solution of $NaHCO_3$ (1 mL). The reaction mixture was extracted with $CDCl_3$ (3 x 1 mL), dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (4:1 hexanes: ethyl acetate eluent) afforded compound **3d** (8 mg, 0.27 mmol, 52%) as a colourless oil; IR (film) 3369, 2922, 1707, 1602, 1530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 3.70 (dd, *J* = 10.7, 3.4 Hz, 1H, H-14a), 3.46 (dd, *J* = 10.7, 1.2 Hz, 1H, H-14b), 3.40 – 3.34 (m, 1H, H-13), 3.29 (m, 1H, H-2), 2.60 (dd, *J* = 14.5, 7.6 Hz, 1H, H-2a), 2.40 (s, 1H, H-5), 2.36 (dd, *J* = 14.6, 2.4 Hz, 1H, H-2b), 2.24 – 2.11 (m, 2H), 2.11 – 2.00 (m, 1H), 1.94 – 1.85 (m, 1H), 1.73 - 1.21 (m, 20H), 1.08 (m, 1H), 0.88 (t, *J* = 6.9 Hz, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (C, C-4), 67.1 (C, C-10), 61.1 (CH_2, C-14), 57.0, 56.3, 52.7 (CH, total of 3 C's: C-2 + C-5 + C-13), 44.7 (CH_2, C-3), 35.1 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 22.8 (CH_2), 21.8 (CH_2), 14.2 (CH_3, C-16); HRMS (ESI-TOF): calc'd for $C_{19}H_{31}NO_2$: 308.2584 $[M + H]^+$; found: 308.2570.

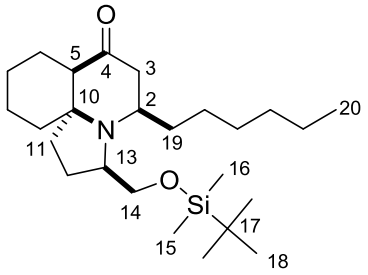
6.4.12 ***3-[[tert-Butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (163)***



A solution of sodium naphthalenide was prepared by adding sodium metal (23 mg, 1.0 mmol) to naphthalene (128 mg, 0.998 mmol) in dry THF (1 mL) and the reaction mixture was stirred at room temperature for 2 h. In a separate flask, the starting material **159** (58 mg, 0.10 mmol) was dissolved in dry THF (1 mL) and cooled to -78 ^{o}C. Sodium naphthalenide solution (1.0 M) was added in 0.1 mL increments until TLC showed no remaining starting material (~5 equiv). $NH_4Cl_{(S)}$ (50 mg) was added and the reaction

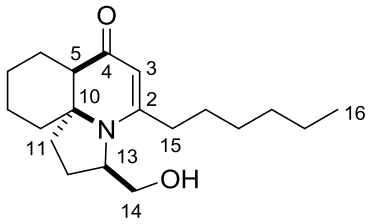
mixture was warmed to room temperature and poured into water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 2 mL). The combined organic fractions were dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (3:1 hexanes: ethyl acetate eluent) afforded the desired compound **163** (19 mg, 0.046 mmol, 45%) and **164** (8 mg, 0.02 mmol, 21%); For **163**: Colourless oil; IR (film) 2928, 1628, 1547, 1461, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H, H-3), 3.96 – 3.88 (m, 1H, H-13), 3.61 (dd, *J* = 10.1, 5.3 Hz, 1H, H-14a), 3.49 (dd, *J* = 10.0, 8.2 Hz, 1H, H-14b), 2.51 (d, *J* = 12.5 Hz, 1H), 2.38 (s, 1H, H-5), 2.33 – 2.16 (m, 3H), 2.11 – 1.95 (m, 4H), 1.71 – 1.63 (m, 1H), 1.55 – 1.16 (m, 14H), 0.90 (s, 9H, H-18), 0.88 (t, *J* = 4.9 Hz, 3H, H-20), 0.07 (s, 6H, H-15 + H-16). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4 (C-4), 162.6 (C-2), 97.4 (C-3), 67.0 (C-10), 64.7 (C-14), 61.9 (C-13), 47.8 (C-5), 34.7, 33.9, 31.7, 31.6, 29.3, 28.5, 27.5, 26.0 (C-18), 23.8, 23.3, 22.7, 21.7, 18.4 (C-17), 14.2 (C-20), -5.2 (C-15 + C-16); HRMS (ESI-TOF): calc'd for $C_{25}H_{46}NO_2Si$: 420.3292 $[M + H]^+$; found: 420.3280.

6.4.12.1 3-[[tert-Butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,5,6,7a,8,9,10,11-decahydropyrrolo[2,1-j]quinolin-7-one (164)



Colourless oil; IR (film) 2930, 1711, 1531, 1461, 1253, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (dd, *J* = 9.8, 4.5 Hz, 1H, H-14a), 3.31 (dd, *J* = 9.7, 9.1 Hz, 1H, H-14b), 3.26 – 3.18 (m, 1H, H-2), 3.16 – 3.08 (m, 1H, H-13), 2.58 (dd, *J* = 15.4, 5.2 Hz, 1H, H-2a), 2.46 (s, 1H, H-5), 2.30 – 2.23 (m, 1H), 2.16 (dd, *J* = 15.5, 6.9 Hz, 1H, H-2b), 2.07 – 1.88 (m, 3H), 1.84 – 1.71 (m, 2H), 1.51 – 1.11 (m, 18H), 0.90 (s, 9H, H-18), 0.88 (t, , *J* = 7.2 Hz, 3H, H-20), 0.06 (s, 6H, H-15 + H-16)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.64 (C, C-4), 68.3 (C, C-10), 67.8 (CH_2, C-14), 66.7 (CH, C-13), 58.9 (CH, C-2), 51.2 (CH, C-5), 43.4 (CH_2, C-3), 40.9 (CH_2), 37.3 (CH_2), 36.4 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 26.2 (CH_2), 26.1 (CH_3, C-18), 25.8 (CH_2), 24.6 (CH_2), 23.4 (CH_2), 22.8 (CH_2), 21.9 (CH_2), 18.5 (C, C-17), 14.2 (CH_3, C-20), -5.07 (CH_3, C-15), -5.11 (CH_3, C-16); HRMS (ESI-TOF): calc'd for $C_{25}H_{48}NO_2Si$: 422.3449 $[M + H]^+$; found: 422.3445.

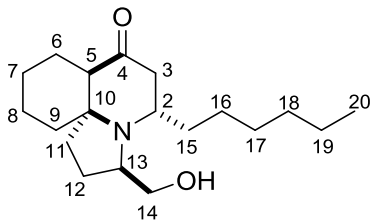
6.4.13 ***5-Hexyl-3-(hydroxymethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (67)***



TBAF (0.13 mL, 1.0 M) was added to a solution of **163** (11 mg, 0.026 mmol) in THF (3 mL) at 0 ^{o}C and the reaction mixture was stirred for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (3 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic fractions were washed once with brine, dried with

magnesium sulfate, and concentrated. Column chromatography on silica gel (1:3 hexanes: ethyl acetate eluent) afforded alcohol **67** (6 mg, 0.02 mmol, 80%) as a colourless oil; IR (film) 3337, 2929, 1602, 1529, 1294, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H, H-3), 4.04 – 3.97 (m, 1H, H-13), 3.68 (dd, *J* = 10.8, 5.4 Hz, 1H, H-14a), 3.57 (dd, *J* = 10.8, 8.1 Hz, 1H, H-14b), 2.55 – 2.47 (m, 1H), 2.40 (s, 1H, H-5), 2.31 – 2.21 (m, 3H), 2.15 – 1.98 (m, 5H), 1.72 – 1.62 (m, 1H), 1.60 – 1.48 (m, 2H), 1.47 – 1.41 (m, 1H), 1.39 – 1.23 (m, 9H), 1.22 – 1.17 (m, 1H), 0.88 (t, *J* = 6.9 Hz, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5 (C, C-4), 162.7 (C, C-2), 97.7 (CH, C-3), 67.0 (C, C-10), 64.3 (CH, C-13), 61.7 (CH_2, C-14), 47.9 (CH, C-5), 34.8 (CH_2), 33.9 (CH_2), 31.7 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 23.8 (CH_2), 23.3 (CH_2), 22.7 (CH_2), 21.7 (CH_2), 14.2 (CH_3, C-16). HRMS (ESI-TOF) calc'd for $C_{19}H_{32}NO_2$: 306.2428 $[M+H]^+$; found: 306.2426

6.4.14 5-Hexyl-3-(hydroxymethyl)-1,2,3,5,6,7a,8,9,10,11-decahydropyrrolo[2,1-j]quinolin-7-one (Cylindricine C) (3)



To a solution of alcohol **67** (6 mg, 0.02 mmol) dissolved in $CDCl_3$ (1 mL) were added $Na(OAc)_3BH$ (39 mg, 0.18 mmol) and a catalytic amount of AcOH (1 drop). The reaction mixture was refluxed overnight and quenched with a saturated solution of $NaHCO_3$ (1 mL). The reaction mixture was extracted with $CDCl_3$ (3 x 1 mL), and the

combined organic fractions were dried with magnesium sulfate, and concentrated. Column chromatography on silica gel (4:1 hexanes: ethyl acetate eluent) afforded the natural product **3** (3 mg, 0.010 mmol, 50%) as a colourless oil; IR (film) 3409, 2923, 1708, 1456 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.56 – 3.50 (m, 2H), 3.43 (d, *J* = 9.3 Hz, 1H), 3.33 – 3.24 (m, 1H), 2.96 (s, 1H), 2.35 – 2.17 (m, 5H), 2.12 (dd, *J* = 12.4, 7.7 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.74 – 1.60 (m, 4H), 1.52 – 1.18 (m, 14H), 0.88 (t, *J* = 7.0 Hz, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ 210.6 (C-4), 70.9 (C-14), 66.5 (C-13), 56.7 (C-10), 55.5 (C-2), 50.5 (C-5), 42.7 (C-3), 36.6, 36.1, 35.4, 31.9, 29.5, 28.9, 27.3, 24.4, 22.9, 22.7, 22.0 (total of 11 C's: C-6 to C-9 + C-11 + C-12 + C-15 to C-19), 14.2 (C-20). HRMS (ESI-TOF) calc'd for $C_{19}H_{34}NO_2$: 308.2584 $[M+H]^+$; found: 308.2570

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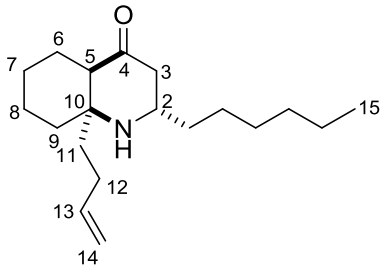
Appendix A: ^{1}H-NMR and ^{13}C-NMR comparison of spectroscopic data for 118a

^{1}H-NMR spectra

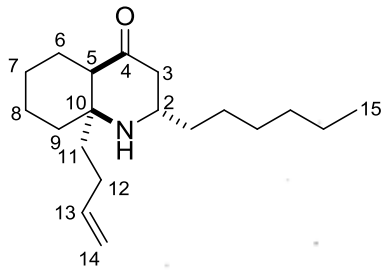
Proton	Snider	Donohoe	Prinsloo	Δ Snider
13	5.87 (ddt, J = 16.9, 10.2, 6.6, 1H)	5.88 (ddt, *J* = 17.0, 10.3 & 6.5, 1H)	5.87 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H)	-
14a	5.07 (br d, J = 16.9, 1H)	5.08 (dd, *J* = 17.0 & 1.6, 1H)	5.07 (ddd, J = 17.1, 3.3, 1.6 Hz, 1H)	-
14b	4.99 (br d, J = 10.2, 1H)	4.99 (dd, *J* = 10.1 & 1.9, 1H)	4.98 (ddd, J = 10.1, 2.9, 1.1 Hz, 1H)	-0.01
2	3.12 (dddd, J = 11.5, 2.7, 6.0, 6.0, 1H)	3.13 (ddd, *J* = 11.8, 6.1 & 2.8, 1H)	3.12 (tdd, J = 9.2, 6.1, 2.9 Hz, 1H)	-
3a	2.37 (dd, J = 13.5, 2.7, 1H)	2.38 (dd, *J* = 13.6 & 2.8, 1H)	2.36 (dd, J = 13.5, 2.9 Hz, 1H)	-0.01
5	2.25 (dd, J = 4.0, 4.0, 1H)	2.26 (m, 1H)	2.25 (br s, 1H)	-
	2.05-2.21 (m, 2H)	2.24-2.08 (m, 2H)	2.22 – 2.05 (m, 2H)	-
3b	1.96 (dd, J = 13.5, 11.5, 1H)	1.97 (t, *J* = 12.5, 1H)	1.96 (t, J = 12.6 Hz, 1H)	-
	1.87-1.20 (m, 20H)	1.82 (ddd, *J* = 14.2, 11.0 & 5.0, 1H)	1.84 – 1.10 (m, 24H)	-
		1.70 (1H, ddd, *J* 14.0, 11.5 & 5.4, 1H)		
		1.59 (td, *J* = 13.0 & 3.6, 2H)		
		1.51-1.36 (m, 6H)		
		1.34-1.26 (m, 10H)		
15	0.88 (3, t, *J* = 6.5)	0.88 (t, *J* = 6.9, 3H)	0.88 (t, *J* = 6.8 Hz, 3H)	-

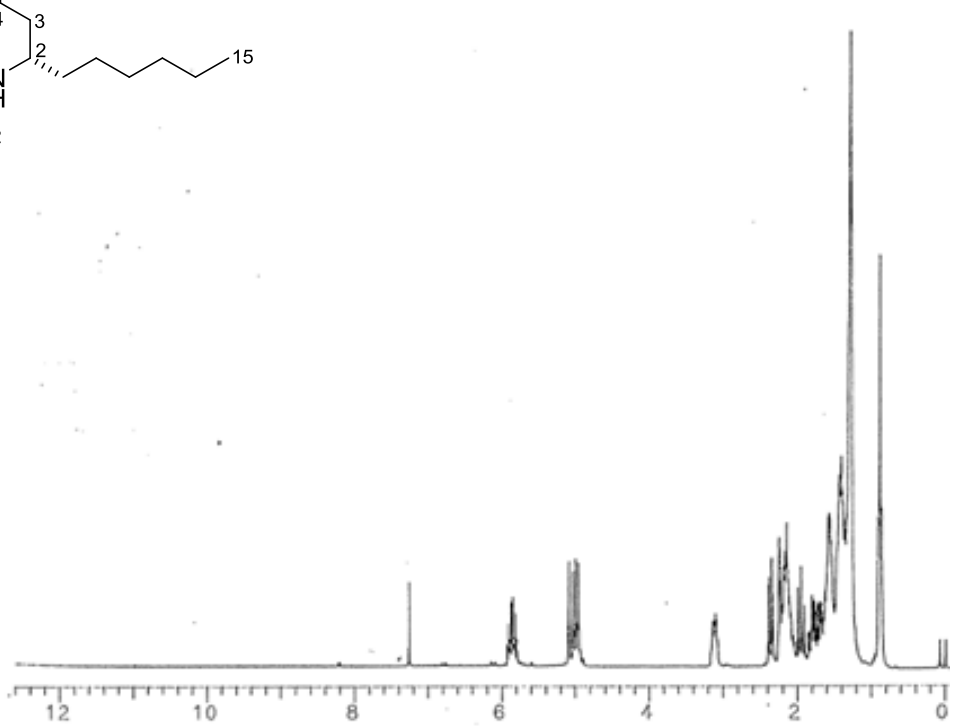
^{13}C-NMR spectra

Carbon	Snider	Donohoe	Prinsloo	Δ Snider
4	210.9	210.9	211.0	+0.1
13	138.8	138.9	139.0	+0.2
14	114.6	114.7	114.8	+0.2
10	58.1	58.2	58.4	+0.3
5	53.8	53.7	53.9	+0.1
2	49.9	49.9	50.1	+0.2
3	48.8	48.6	49.0	+0.2
CH_2	37.8	37.7	37.9	+0.1
CH_2	37.6	37.6	37.7	+0.1
CH_2	31.7	31.7	31.9	+0.2
CH_2	31.6	31.6	31.8	+0.2
CH_2	29.2	29.2	29.4	+0.2
CH_2	27.2	27.2	27.4	+0.2
CH_2	25.6	25.6	25.8	+0.2
CH_2	22.6	22.6	22.73	+0.1
CH_2	22.5	22.5	22.71	+0.2
CH_2	21.4	21.4	21.6	+0.2
CH_2	21.1	21.1	21.3	+0.1
15	14.0	14.0	14.2	+0.2

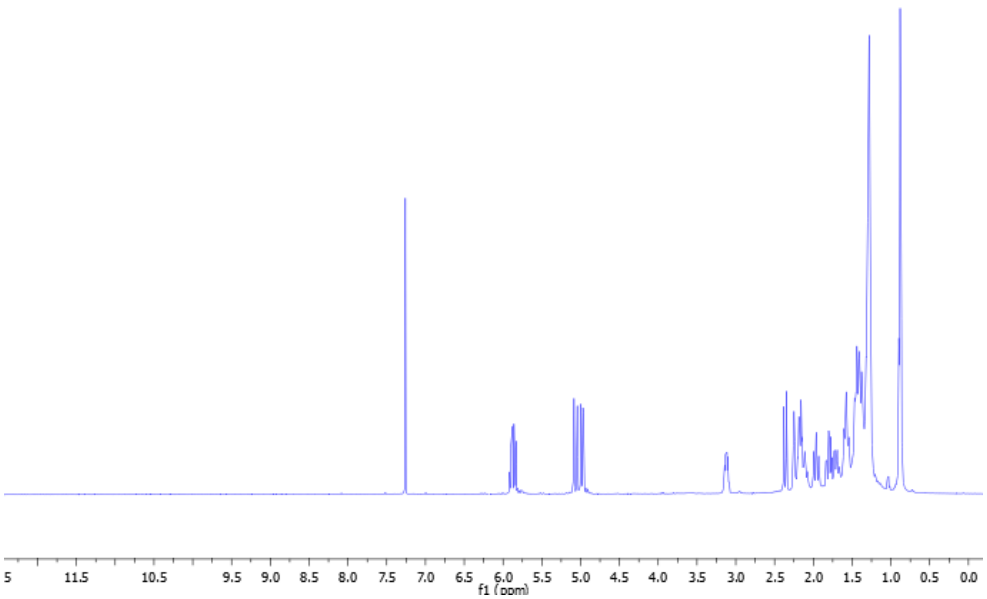


Snider's ^{1}H NMR spectrum for 118a

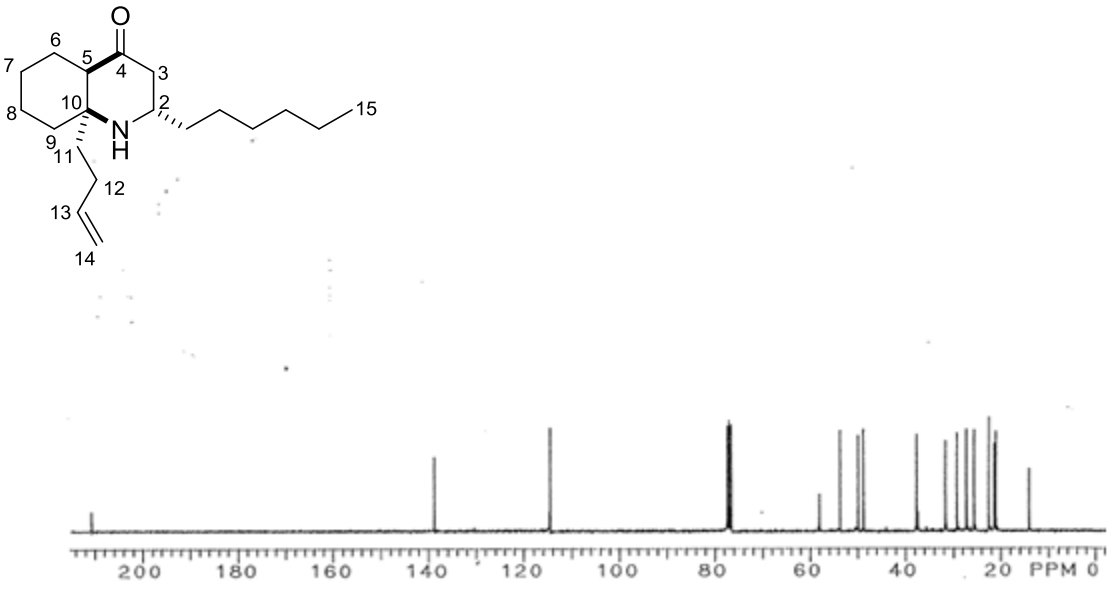




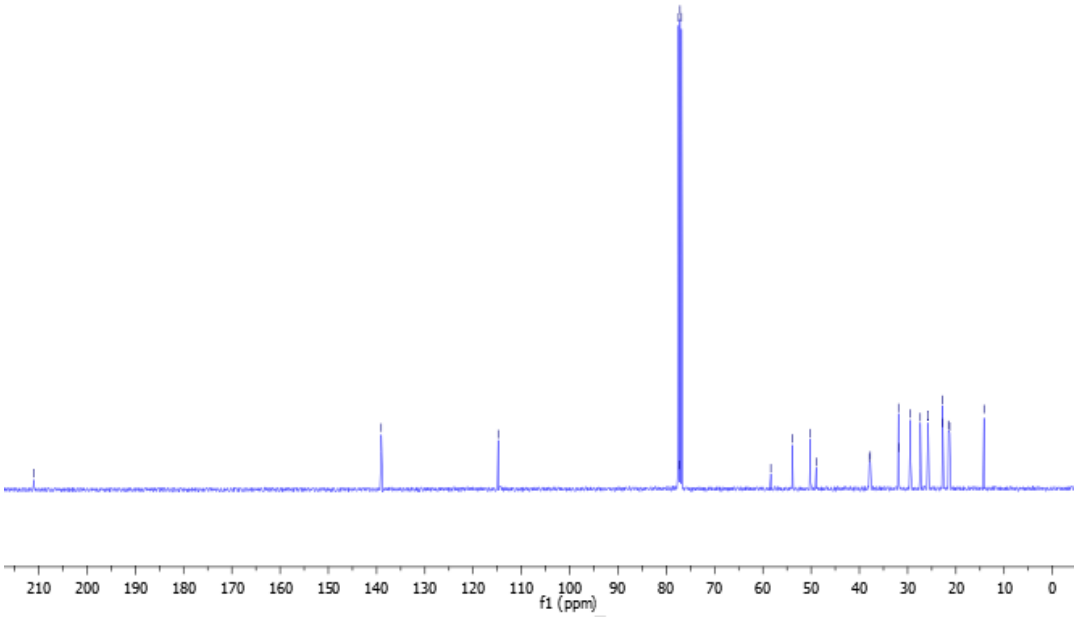
Prinsloo's ^{1}H NMR spectrum for 118a



Snider's ^{13}C NMR spectrum for 118a



Prinsloo's ^{13}C NMR spectrum for 118a

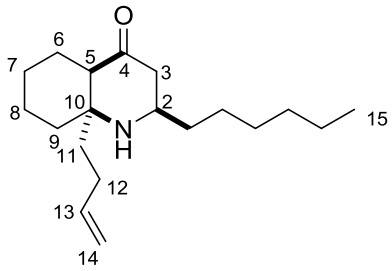


^{1}H-NMR and ^{13}C-NMR comparison of spectroscopic data for 125a

^{1}H-NMR spectra

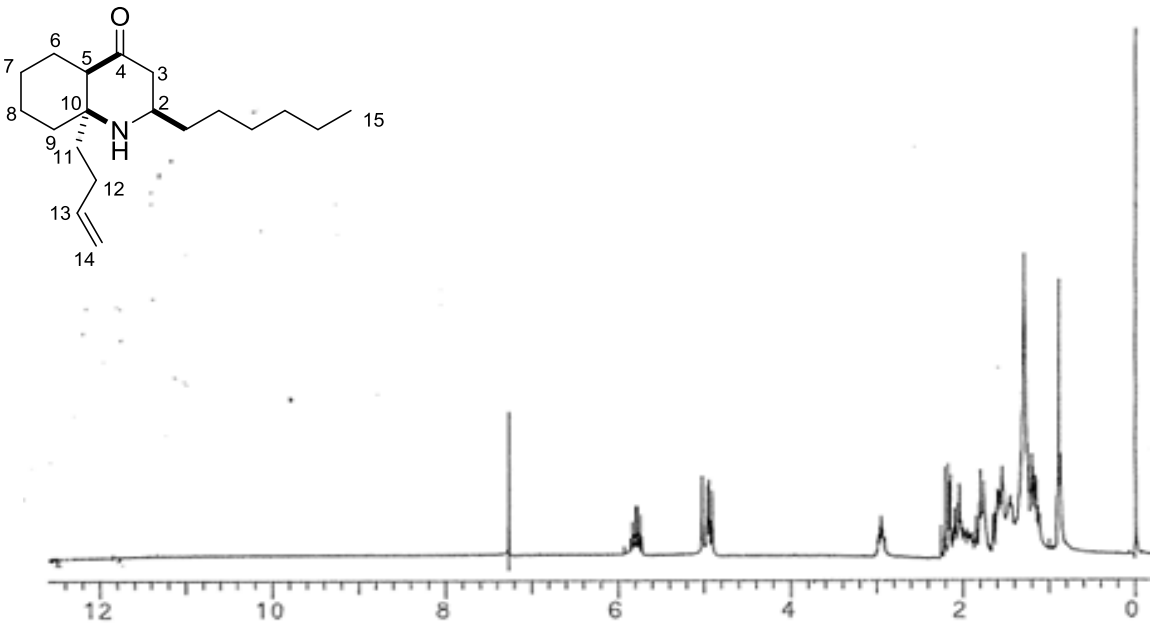
Proton	Snider	Prinsloo	Δ Snider
13	5.79 (ddt, J = 17.1, 10.2, 6.7, 1H),	5.78 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H,)	-0.01
14a	4.99 (ddt, J = 17.1, 1.8, 1.6, 1H)	4.98 (dd, J = 17.1, 1.8 Hz, 1H)	-0.01
14b	4.93 (ddt, J = 10.2, 1.8, 1.2, 1H)	4.95 – 4.89 (m, 1H)	-0.01
2	2.95 (dddd, J = 10.5, 4.2, 7.4, 7.4, 1H)	2.99 – 2.90 (m, 1H)	-
3a	2.21 (dd, J = 10.5, 14.7, 1H)	2.20 (dd, J = 14.5, 10.8 Hz, 1H)	-0.01
3b	2.13 (ddd, J = 4.2, 14.7, 0.8, 1H)	2.12 (ddd, J = 14.5, 4.1, 0.9 Hz, 1H)	-0.01
5	2.07 (ddd, J = 3.9, 12.0, 0.8, 1H)	2.09 – 2.03 (m, 1H)	-
	1.13-2.04 (m, 22H)	2.03 – 1.03 (m, 23H)	-
15	0.89 (t, J = 6.9, 3H)	0.91 – 0.85 (m, 3H)	-

^{13}C-NMR spectra

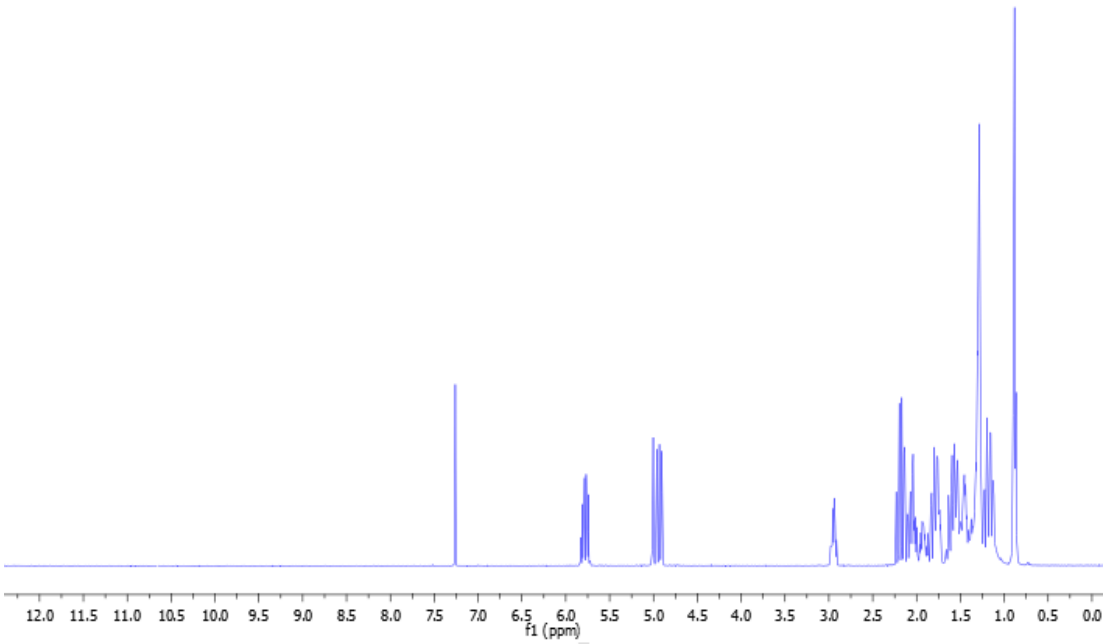


Carbon	Snider	Prinsloo	Δ Snider
4	214.5	214.6	+0.1
13	138.6	138.7	+0.1
14	114.4	114.6	+0.2
5	58.2	58.3	+0.1
10	54.9	55.1	+0.2
2	50.5	50.6	+0.1
3	44.0	44.2	+0.2
CH_2	38.0	38.1	+0.1
CH_2	37.6	37.7	+0.1
CH_2	35.7	35.8	+0.1
CH_2	31.8	31.9	+0.1
CH_2	29.4	29.5	+0.1
CH_2	27.0	27.1	+0.1
CH_2	26.4	26.6	+0.2
CH_2	25.7	25.8	+0.1
CH_2	25.4	25.5	+0.1
CH_2	22.6	22.8	+0.2
CH_2	20.9	21.0	+0.1
15	14.1	14.2	+0.1

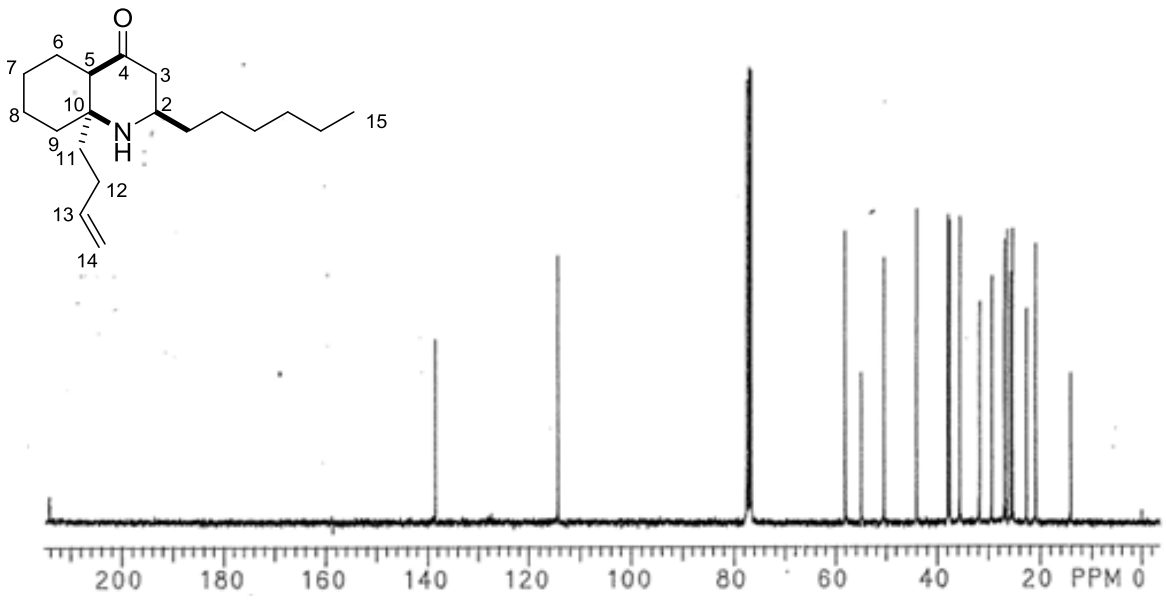
Snider's ^{1}H NMR spectrum for 125a



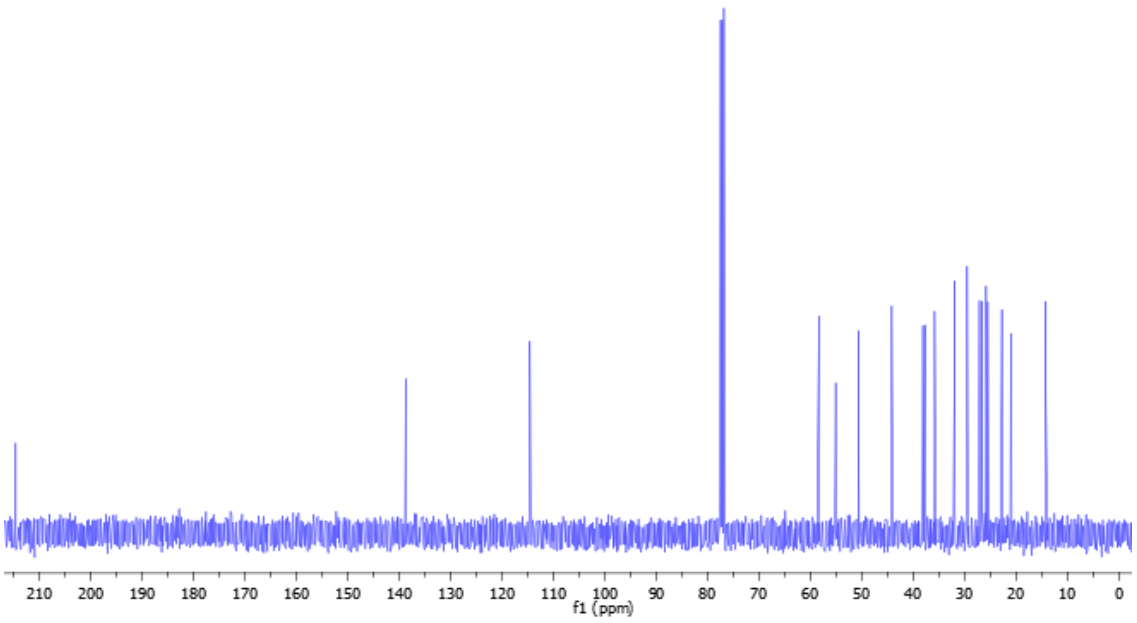
Prinsloo's ^{1}H NMR spectrum for 125a



Snider's ^{13}C NMR spectrum for 125a



Prinsloo's ^{13}C NMR spectrum for 125a



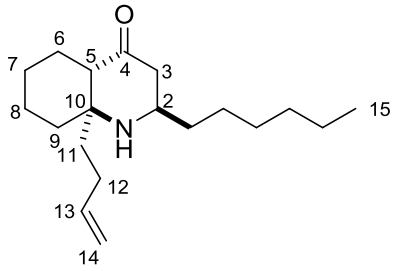
^{1}H-NMR and ^{13}C-NMR comparison of spectroscopic data for 126

^{1}H-NMR spectra

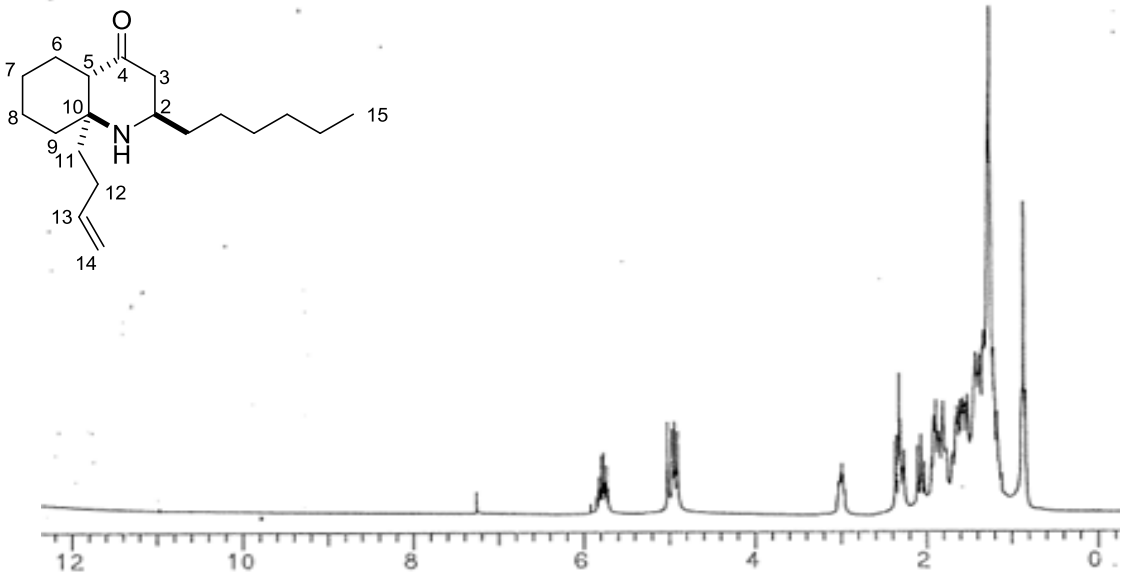
Proton	Snider	Prinsloo	Δ Snider
13	5.79 (ddt, J = 17.1, 10.2, 6.6, 1H)	5.78 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H)	-0.01
14a	5.01 (dd, J = 17.1, 1.2, 1H)	5.00 (ddd, J = 17.1, 3.3, 1.6 Hz, 1H)	-0.01
14b	4.94 (dd, J = 10.2, 1.2, 1H)	4.95 – 4.91 (m, 1H)	-
2	3.02 (dddd, J = 12.0, 3.6, 5.7, 5.7, 1H)	3.00 (ddd, J = 10.8, 6.1, 3.6 Hz, 1H)	-0.02
3a	2.35 (dd, J = 13.4, 3.6, 1H)	2.35 (dd, J = 13.4, 3.6 Hz, 1H)	-
3b	2.08 (ddd, J = 13.4, 12.0, 0.9, 1H)	2.07 (ddd, J = 13.3, 11.2, 1.2 Hz, 1H)	-0.01
5	2.30 (ddd, J = 11.7, 2.9, 0.9, 1H)	2.29 (ddd, J = 12.2, 3.2, 1.0 Hz, 1H)	-0.01
	1.12-1.93 (m, 22H)	1.98 – 1.13 (m, 24H)	-
15	0.89 (3, t, J = 6.5)	0.88 (t, J = 6.9 Hz, 4H)	-0.01

^{13}C-NMR spectra

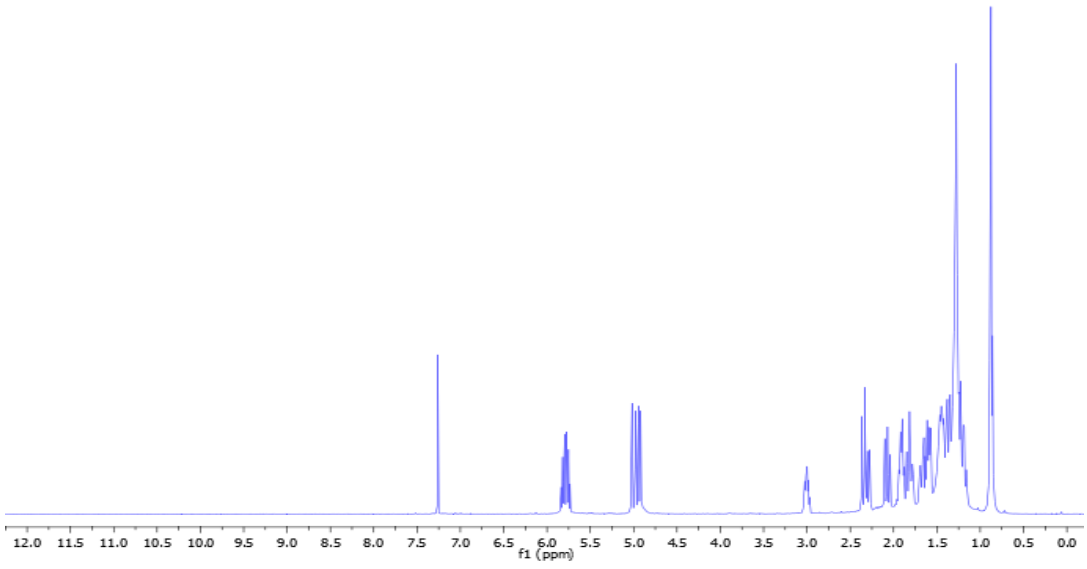
Carbon	Snider	Prinsloo	Δ Snider
4	210.4	210.9	+0.5
13	138.3	138.6	+0.3
14	114.4	114.8	+0.4
5	60.3	60.6	+0.3
10	58.5	58.8	+0.3
2	51.3	51.5	+0.2
3	48.8	49.1	+0.3
CH_2	37.5	37.8	+0.3
CH_2	35.8	36.1	+0.3
CH_2	32.6	31.9	+0.3
CH_2	29.2	29.5	+0.3
CH_2	26.0	26.27	+0.3
CH_2	26.0	26.25	+0.3
CH_2	25.7	26.0	+0.3
CH_2	24.9	25.2	+0.3
CH_2	22.5	22.7	+0.1
CH_2	21.5	21.8	+0.3
CH_2	20.1	20.4	+0.3
15	13.9	14.2	+0.3



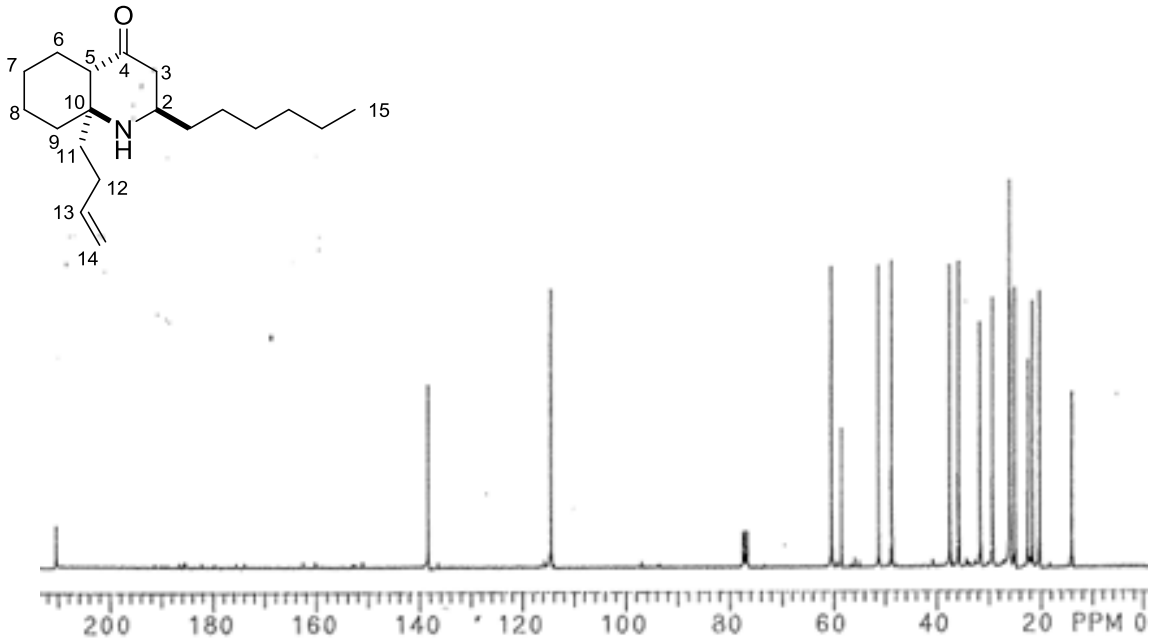
Snider's ^{1}H NMR spectrum for 126



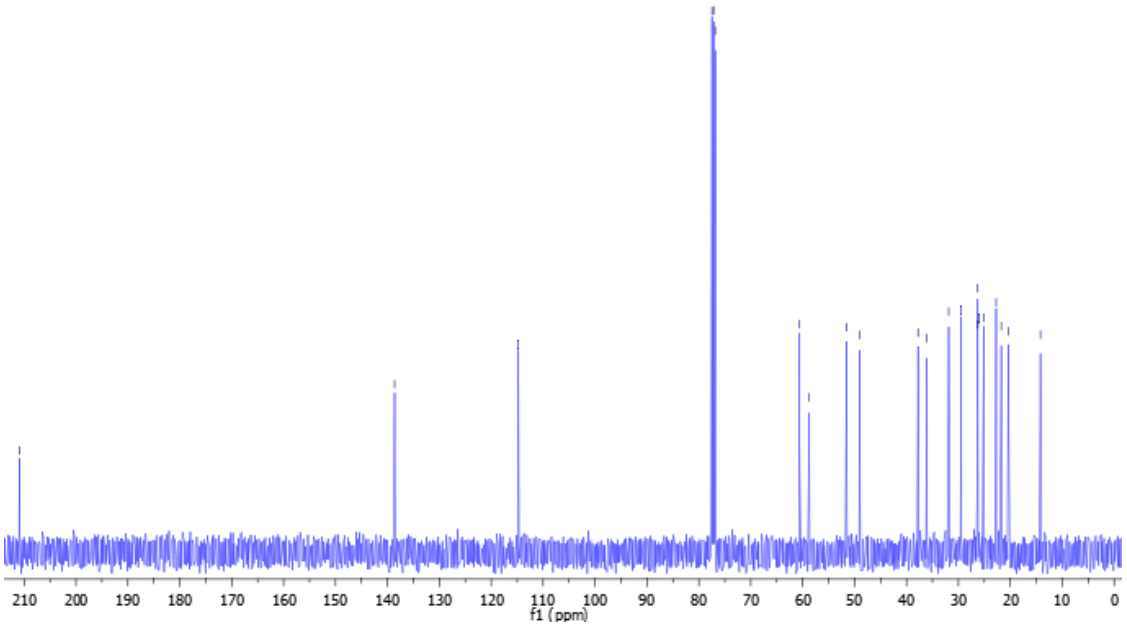
Prinsloo's ^{1}H NMR spectrum for 126



Snider's ^{13}C NMR spectrum for 126



Prinsloo's ^{13}C NMR spectrum for 126

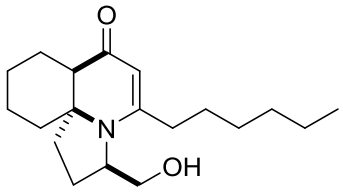


Appendix B: ^{1}H-NMR and ^{13}C-NMR comparison of spectroscopic data for 67

^{1}H-NMR spectra

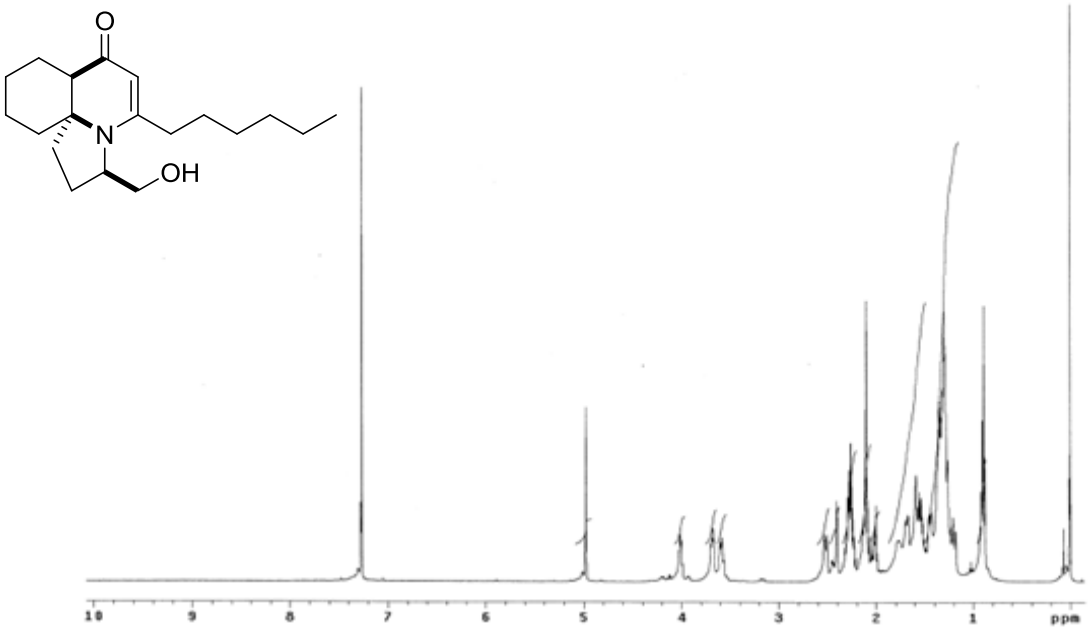
Hsung	Prinsloo	Δ Hsung
4.98 (s, 1H)	4.96 (s, 1H),	-0.02
4.08 - 3.96 (m, 1H)	4.05 – 3.96 (m, 1H),	-
3.68 (dd, J = 10.5, 5.5 Hz, 1H)	3.68 (dd, J = 10.8, 5.4 Hz, 1H)	-
3.58 (t, J = 9.5 Hz, 1H)	3.57 (dd, J = 10.8, 8.1 Hz, 1H),	-0.01
2.51 (dd, J = 2.5, 12.5 Hz, 1H)	2.55 – 2.47 (m, 1H),	-
2.40 (s, 1H)	2.40 (s, 1H),	-0.01
2.35 - 2.20 (m, 3H)	2.32 – 2.19 (m, 3H),	-
2.20 - 1.95 (m, 4H)	2.14 – 1.97 (m, 4H),	-
1.00-1.90 (m, 15 H)	1.72 - 1.15 (m, 15H)	-
0.89 (t, J = 7.5 Hz, 3H)	0.88 (t, J = 6.9 Hz, 3H).	-0.01

^{13}C-NMR spectra

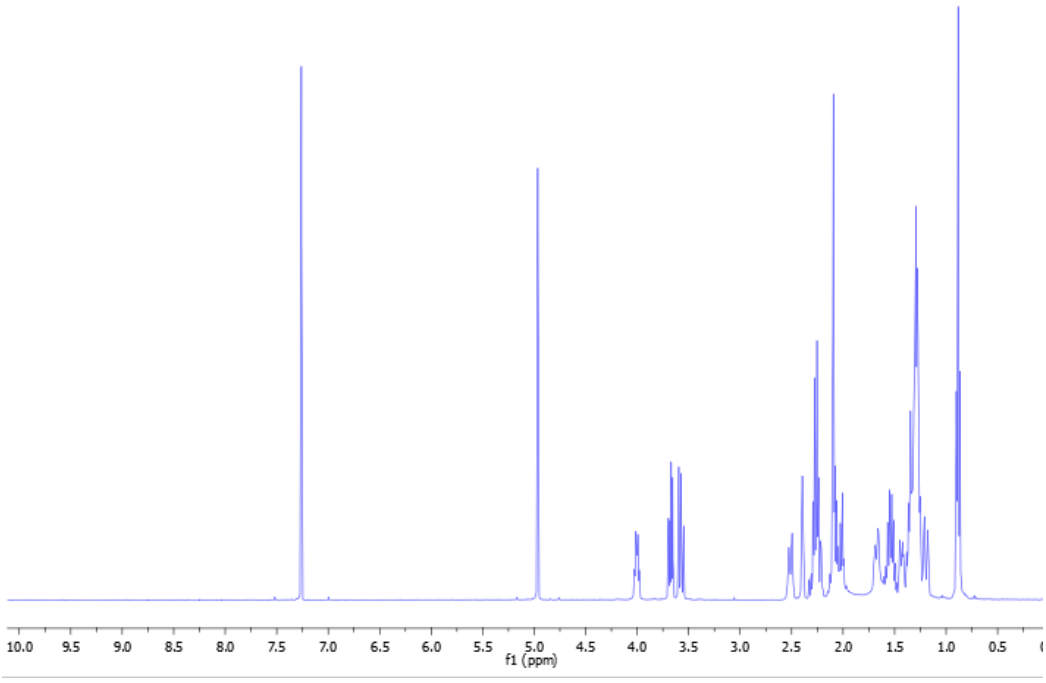


Hsung	Prinsloo	Δ Hsung
not reported	192.5	-
not reported	162.7	-
not reported	97.7	-
66.7	67.0	+0.3
63.9	64.3	+0.4
61.3	61.7	+0.4
47.4	47.9	+0.5
34.4	34.8	+0.4
33.5	33.9	+0.4
31.4	31.7	+0.3
31.3	31.7	+0.4
29.0	29.3	+0.3
28.2	28.5	+0.3
27.3	27.7	+0.4
23.5	23.8	+0.3
22.9	23.3	+0.4
22.3	22.7	+0.4
21.4	21.7	+0.3
13.9	14.2	+0.3

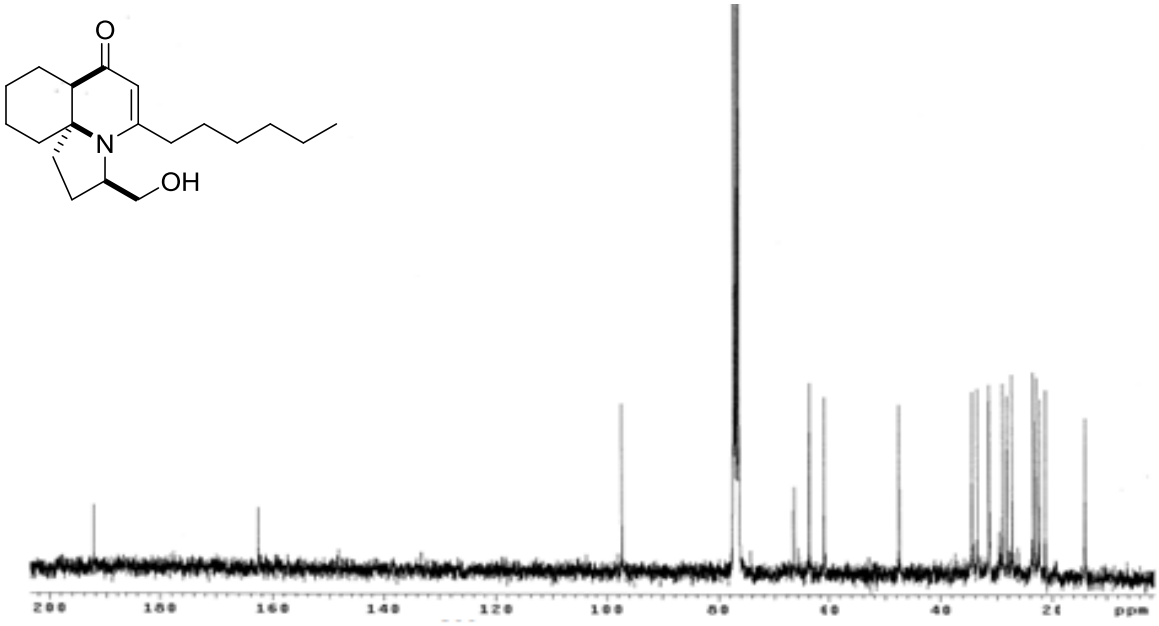
Hsung's ^{1}H NMR spectrum of alcohol 67



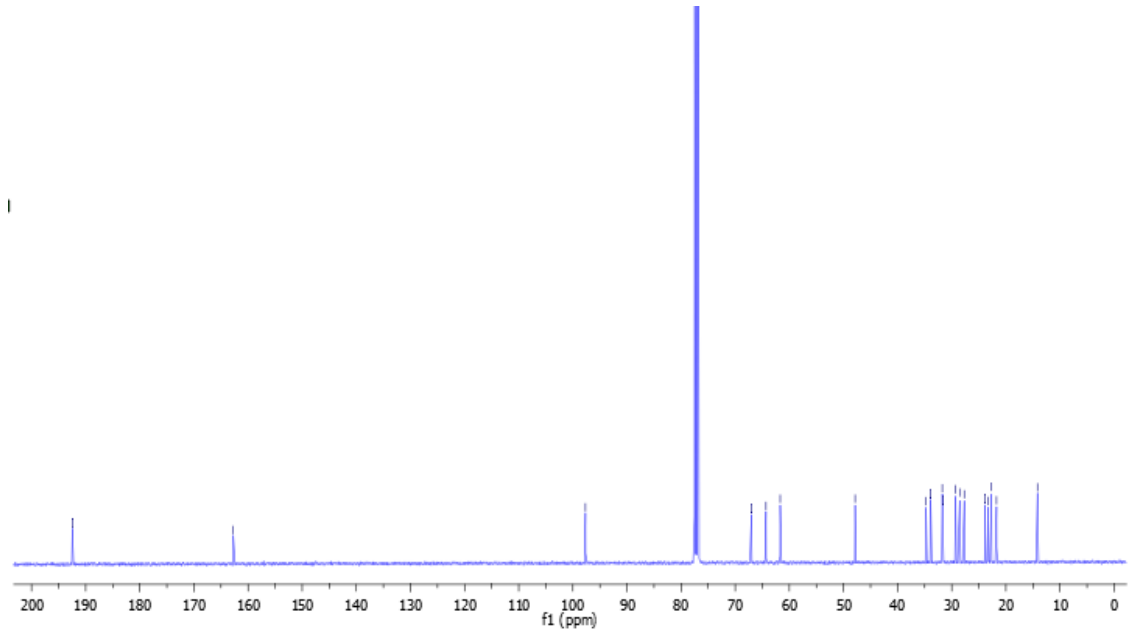
Prinsloo's ^{1}H NMR spectrum of alcohol 67



Hsung's ^{13}C NMR spectrum of alcohol 67



Prinsloo's ^{13}C NMR spectrum of alcohol 67



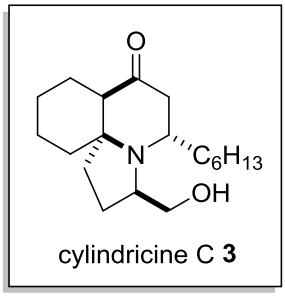
Appendix C: ^{1}H-NMR and ^{13}C-NMR comparison of spectroscopic data for 3

^{1}H-NMR spectra

Hsung	Prinsloo	Δ Hsung
3.54 (m, 2H)	3.56 – 3.50 (m, 2H)	-
3.43 (m, 1H)	3.43 (d, J = 9.3 Hz, 1H)	-
3.29 (m, 1H)	3.33 – 3.24 (m, 1H)	-
2.90 (br s, 1H)	2.96 (br s, 1H)	-
2.31 (t, 2H, J = 12 Hz)	2.35 – 2.17 (m, 5H)	-
2.23 (dd, 2H, J = 3.0, 13.0 Hz)	-	-
-	2.12 (dd, J = 12.4, 7.7 Hz, 1H)	-
1.84 (dd, 1H, J = 8.5, 13.0 Hz)	1.87 – 1.80 (m, 1H)	-
1.74 - 1.18 (m, 19H)	1.74 – 1.18 (m, 18H)	-
0.88 (t, 3H, J = 7.0 Hz)	0.88 (t, J = 7.0 Hz, 3H)	-0.01

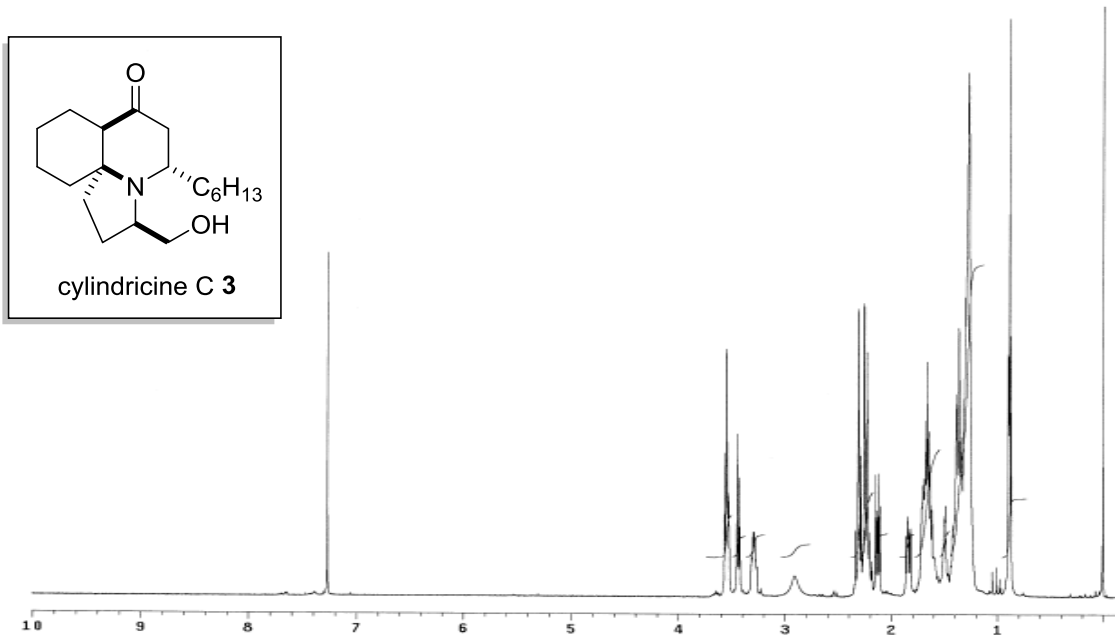
^{13}C-NMR spectra

Hsung	Prinsloo	Δ Hsung
210.5	210.6	+0.1
70.9	70.9	-
66.6	66.5	-0.1
56.8	56.7	-0.1
55.5	55.5	-
50.5	50.5	-
42.8	42.7	-0.1
36.7	36.6	-0.1
36.1	36.1	-
35.4	35.4	-
31.9	31.9	-
29.5	29.5	-
29.0	28.9	-0.1
27.3	27.3	-
24.5	24.4	-0.1
23.0	22.9	-0.1
22.8	22.7	-0.1
22.0	22.0	-
14.3	14.2	-0.1

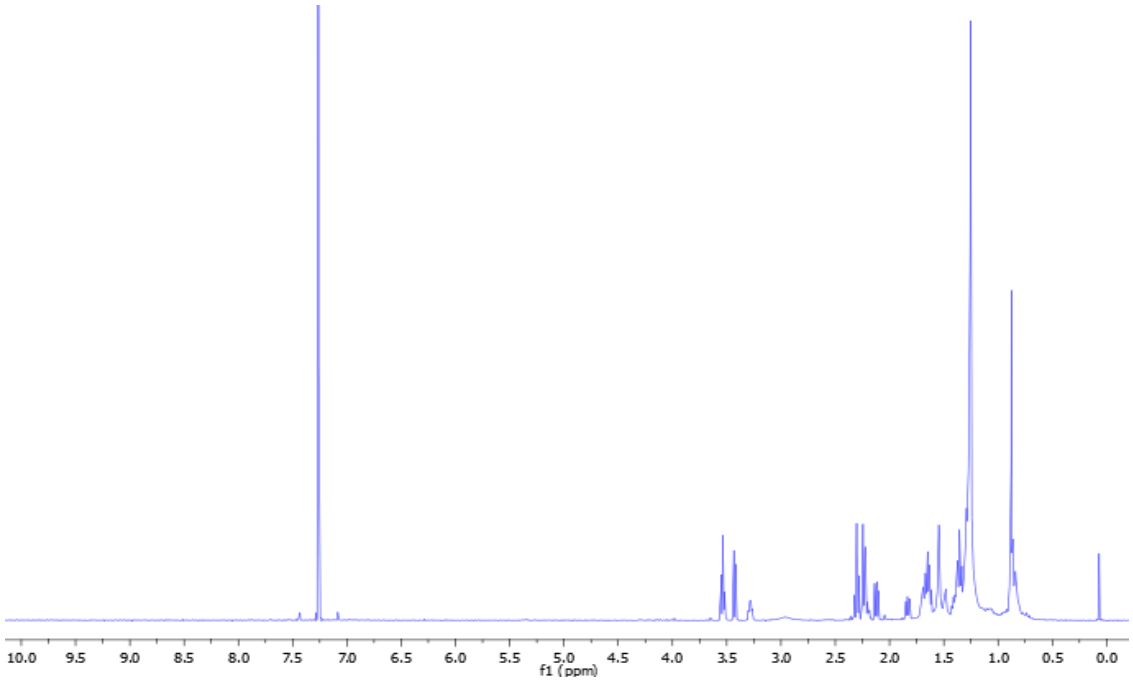


cylindricine C **3**

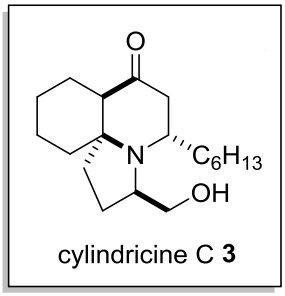
Hsung's ^{1}H NMR spectrum of cylindricine C 3



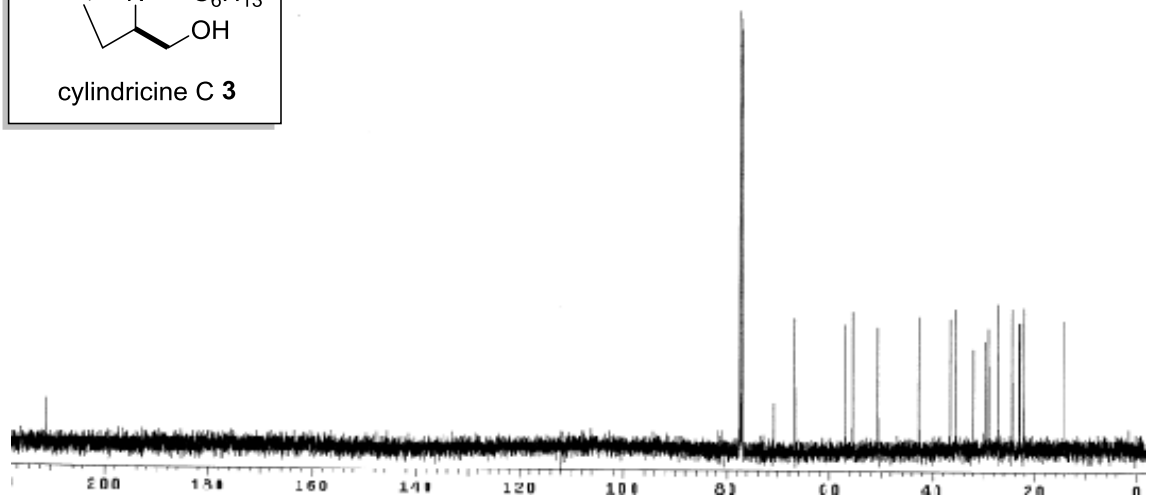
Prinsloo's ^{1}H NMR spectrum of cylindricine C 3



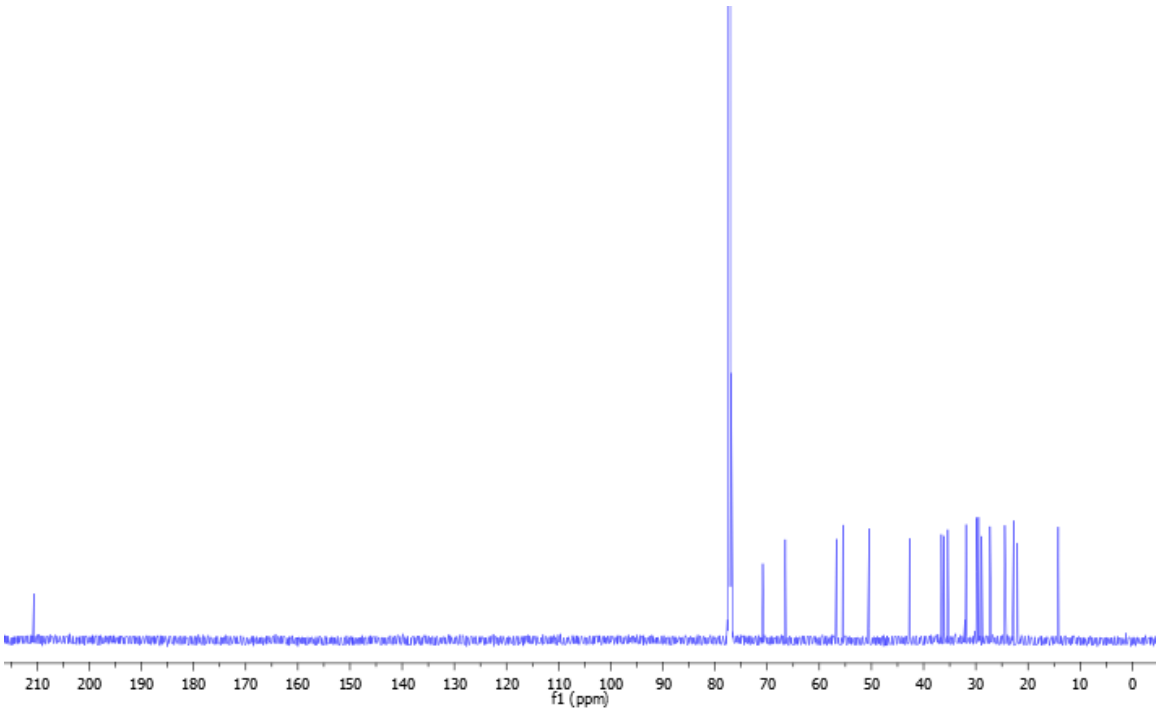
Hsung's ^{13}C NMR spectrum of cylindricine C 3



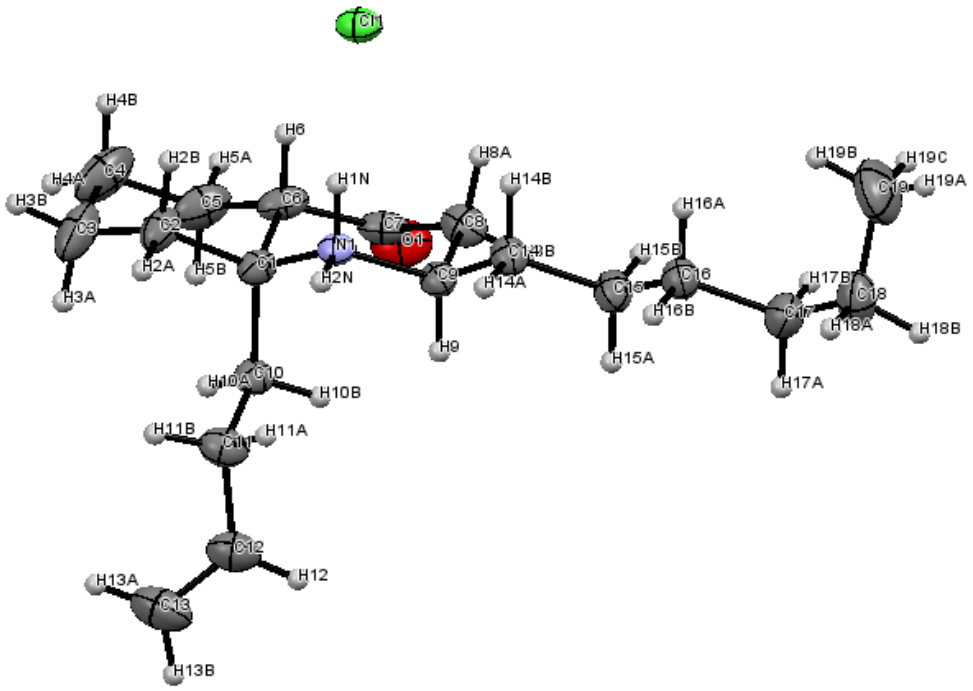
cylindricine C **3**



Prinsloo's ^{13}C NMR spectrum of cylindricine C 3



Appendix D: X-ray Structure Data for 126.HCl salt



Experimental:

A colorless prismatic crystal of C_{19} H_{34} Cl N O was coated with Paratone 8277 oil (Exxon) and mounted on a glass fiber. All measurements were made on a Bruker APEX2 CCD installed on a Nonius Kappa Goniometer diffractometer with graphite monochromated Mo-Kα radiation. Details of crystal data and structure refinement have been provided in Table 1. The data were collected[1] using ω and φ scans. The data were corrected for Lorentz and polarization effects and for absorption using multi-scan method[2].

The structure was solved by the direct methods[3] and expanded using Fourier techniques[4]. The non-hydrogen atoms were refined anisotropically. The H-atoms were included at geometrically idealized positions and were not refined. The final cycle of full-matrix least-squares refinement using SHELXL97[5] converged with unweighted and

weighted agreement factors, R = 0.0420 and wR = 0.1070 (all data), respectively, and goodness of fit, S = 1.057. The weighting scheme was based on counting statistics and the final difference Fourier map was essentially featureless. The figures were plotted with the aid of ORTEP-3 for Windows[6].

References:

1. Otwinowski, Z. & Minor, W. (1997). *Methods Enzymol*. **276**, 307.

2. Hooft, R. (1998). *COLLECT*. Nonius BV, Delft. The Netherlands.

3. Altomare, A., Cascarano, M., Giacovazzo, C.& Guagliardi, A. (1993). *SIR92*. J. Appl. Cryst., **26**, 343

4. Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. & Smits, J.M.M. (1994). The *DIRDIF-94* program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

5. Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112.

6. Farrugia, L. J. (1997). J. Appl. Cryst. **30**, 565.

Table 1. Crystal data and structure refinement for C_{19} H_{34} Cl N O.

Identification code	T.Back - 1501	
Empirical formula	C_{19} H_{34} Cl N O	
Formula weight	327.92	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 10.9277(3) Å	□= 90°.
	b = 8.4938(2) Å	□= 99.1121(15)°.
	c = 21.2500(4) Å	□ = 90°.
Volume	1947.49(8) Å^3	
Z	4	
Density (calculated)	1.118 Mg/m^3	

Absorption coefficient	0.199 mm^{-1}
F(000)	720
Crystal size	0.240 x 0.240 x 0.120 mm^3
Theta range for data collection	1.941 to 27.494°.
Index ranges	-14<=h<=14, -10<=k<=11, -27<=l<=27
Reflections collected	8308
Independent reflections	4424 [R(int) = 0.0234]
Completeness to theta = 25.242°	99.5 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4424 / 0 / 199
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.1008
R indices (all data)	R1 = 0.0502, wR2 = 0.1070
Largest diff. peak and hole	0.220 and -0.198 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C_{19} H_{34} Cl N O. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Cl(1)	3696(1)	1913(1)	327(1)	31(1)
O(1)	6905(1)	2662(2)	2507(1)	48(1)
N(1)	6262(1)	417(1)	814(1)	24(1)
C(1)	7247(1)	1680(2)	929(1)	26(1)
C(2)	7310(2)	2467(2)	286(1)	36(1)
C(3)	8161(2)	3906(2)	365(1)	53(1)
C(4)	7760(2)	5084(2)	835(1)	62(1)
C(5)	7626(2)	4337(2)	1469(1)	47(1)
C(6)	6779(1)	2903(2)	1374(1)	34(1)
C(7)	6523(1)	2134(2)	1979(1)	34(1)
C(8)	5696(1)	709(2)	1885(1)	36(1)
C(9)	6032(1)	-473(2)	1396(1)	27(1)
C(10)	8482(1)	945(2)	1235(1)	27(1)

C(11)	9066(1)	-226(2)	823(1)	37(1)
C(12)	10191(2)	-972(2)	1198(1)	42(1)
C(13)	11333(2)	-600(3)	1157(1)	56(1)
C(14)	5028(1)	-1693(2)	1197(1)	30(1)
C(15)	4799(1)	-2757(2)	1743(1)	34(1)
C(16)	3902(1)	-4087(2)	1524(1)	33(1)
C(17)	3692(2)	-5156(2)	2070(1)	38(1)
C(18)	2741(2)	-6442(2)	1891(1)	48(1)
C(19)	1443(2)	-5824(3)	1693(1)	73(1)

Table 3. Bond lengths [Å] and angles [°] for C_{19} H_{34} Cl N O.

O(1)-C(7)	1.2179(18)
N(1)-C(9)	1.5043(17)
N(1)-C(1)	1.5113(17)
N(1)-H(1N)	0.9100
N(1)-H(2N)	0.9100
C(1)-C(2)	1.5313(19)
C(1)-C(10)	1.5353(18)
C(1)-C(6)	1.546(2)
C(2)-C(3)	1.529(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.526(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.518(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.523(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.507(2)
C(6)-H(6)	1.0000

C(7)-C(8)	1.505(2)
C(8)-C(9)	1.530(2)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(14)	1.5196(19)
C(9)-H(9)	1.0000
C(10)-C(11)	1.530(2)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.496(2)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.304(3)
C(12)-H(12)	0.9500
C(13)-H(13A)	0.9500
C(13)-H(13B)	0.9500
C(14)-C(15)	1.523(2)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.520(2)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.519(2)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.514(2)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.508(3)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800

C(9)-N(1)-C(1)	115.59(10)
C(9)-N(1)-H(1N)	108.4
C(1)-N(1)-H(1N)	108.4
C(9)-N(1)-H(2N)	108.4
C(1)-N(1)-H(2N)	108.4
H(1N)-N(1)-H(2N)	107.4
N(1)-C(1)-C(2)	107.34(11)
N(1)-C(1)-C(10)	109.59(11)
C(2)-C(1)-C(10)	113.29(12)
N(1)-C(1)-C(6)	106.24(11)
C(2)-C(1)-C(6)	108.54(12)
C(10)-C(1)-C(6)	111.52(11)
C(3)-C(2)-C(1)	111.39(12)
C(3)-C(2)-H(2A)	109.4
C(1)-C(2)-H(2A)	109.4
C(3)-C(2)-H(2B)	109.4
C(1)-C(2)-H(2B)	109.4
H(2A)-C(2)-H(2B)	108.0
C(4)-C(3)-C(2)	111.23(17)
C(4)-C(3)-H(3A)	109.4
C(2)-C(3)-H(3A)	109.4
C(4)-C(3)-H(3B)	109.4
C(2)-C(3)-H(3B)	109.4
H(3A)-C(3)-H(3B)	108.0
C(5)-C(4)-C(3)	112.62(15)
C(5)-C(4)-H(4A)	109.1
C(3)-C(4)-H(4A)	109.1
C(5)-C(4)-H(4B)	109.1
C(3)-C(4)-H(4B)	109.1
H(4A)-C(4)-H(4B)	107.8
C(4)-C(5)-C(6)	111.01(14)
C(4)-C(5)-H(5A)	109.4
C(6)-C(5)-H(5A)	109.4
C(4)-C(5)-H(5B)	109.4

C(6)-C(5)-H(5B)	109.4
H(5A)-C(5)-H(5B)	108.0
C(7)-C(6)-C(5)	115.13(13)
C(7)-C(6)-C(1)	110.78(12)
C(5)-C(6)-C(1)	111.44(14)
C(7)-C(6)-H(6)	106.3
C(5)-C(6)-H(6)	106.3
C(1)-C(6)-H(6)	106.3
O(1)-C(7)-C(8)	121.96(15)
O(1)-C(7)-C(6)	122.85(16)
C(8)-C(7)-C(6)	115.10(12)
C(7)-C(8)-C(9)	114.46(12)
C(7)-C(8)-H(8A)	108.6
C(9)-C(8)-H(8A)	108.6
C(7)-C(8)-H(8B)	108.6
C(9)-C(8)-H(8B)	108.6
H(8A)-C(8)-H(8B)	107.6
N(1)-C(9)-C(14)	108.66(10)
N(1)-C(9)-C(8)	108.53(12)
C(14)-C(9)-C(8)	113.41(12)
N(1)-C(9)-H(9)	108.7
C(14)-C(9)-H(9)	108.7
C(8)-C(9)-H(9)	108.7
C(11)-C(10)-C(1)	116.08(11)
C(11)-C(10)-H(10A)	108.3
C(1)-C(10)-H(10A)	108.3
C(11)-C(10)-H(10B)	108.3
C(1)-C(10)-H(10B)	108.3
H(10A)-C(10)-H(10B)	107.4
C(12)-C(11)-C(10)	110.64(12)
C(12)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11A)	109.5
C(12)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11B)	109.5

H(11A)-C(11)-H(11B)	108.1
C(13)-C(12)-C(11)	125.16(19)
C(13)-C(12)-H(12)	117.4
C(11)-C(12)-H(12)	117.4
C(12)-C(13)-H(13A)	120.0
C(12)-C(13)-H(13B)	120.0
H(13A)-C(13)-H(13B)	120.0
C(9)-C(14)-C(15)	112.97(11)
C(9)-C(14)-H(14A)	109.0
C(15)-C(14)-H(14A)	109.0
C(9)-C(14)-H(14B)	109.0
C(15)-C(14)-H(14B)	109.0
H(14A)-C(14)-H(14B)	107.8
C(16)-C(15)-C(14)	112.60(12)
C(16)-C(15)-H(15A)	109.1
C(14)-C(15)-H(15A)	109.1
C(16)-C(15)-H(15B)	109.1
C(14)-C(15)-H(15B)	109.1
H(15A)-C(15)-H(15B)	107.8
C(17)-C(16)-C(15)	112.25(12)
C(17)-C(16)-H(16A)	109.2
C(15)-C(16)-H(16A)	109.2
C(17)-C(16)-H(16B)	109.2
C(15)-C(16)-H(16B)	109.2
H(16A)-C(16)-H(16B)	107.9
C(18)-C(17)-C(16)	114.83(14)
C(18)-C(17)-H(17A)	108.6
C(16)-C(17)-H(17A)	108.6
C(18)-C(17)-H(17B)	108.6
C(16)-C(17)-H(17B)	108.6
H(17A)-C(17)-H(17B)	107.5
C(19)-C(18)-C(17)	113.40(17)
C(19)-C(18)-H(18A)	108.9
C(17)-C(18)-H(18A)	108.9

C(19)-C(18)-H(18B)	108.9
C(17)-C(18)-H(18B)	108.9
H(18A)-C(18)-H(18B)	107.7
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $C_{19}\ H_{34}\ Cl\ N\ O$. The anisotropic displacement factor exponent takes the form:

$$-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	30(1)	36(1)	26(1)	-3(1)	-1(1)	7(1)
O(1)	53(1)	52(1)	33(1)	-16(1)	-9(1)	6(1)
N(1)	23(1)	27(1)	21(1)	-1(1)	-1(1)	2(1)
C(1)	27(1)	24(1)	27(1)	0(1)	-2(1)	-2(1)
C(2)	40(1)	33(1)	31(1)	6(1)	-5(1)	-7(1)
C(3)	64(1)	43(1)	45(1)	16(1)	-8(1)	-20(1)
C(4)	83(2)	29(1)	66(1)	7(1)	-16(1)	-10(1)
C(5)	56(1)	26(1)	52(1)	-7(1)	-11(1)	1(1)
C(6)	35(1)	27(1)	34(1)	-4(1)	-8(1)	8(1)
C(7)	30(1)	39(1)	30(1)	-10(1)	-5(1)	12(1)
C(8)	32(1)	49(1)	25(1)	-6(1)	1(1)	1(1)
C(9)	25(1)	33(1)	21(1)	2(1)	0(1)	1(1)
C(10)	24(1)	28(1)	28(1)	-1(1)	-1(1)	-2(1)
C(11)	31(1)	43(1)	36(1)	-8(1)	-1(1)	3(1)
C(12)	37(1)	45(1)	44(1)	-8(1)	3(1)	9(1)
C(13)	38(1)	78(2)	52(1)	-13(1)	7(1)	14(1)
C(14)	27(1)	37(1)	26(1)	1(1)	2(1)	-4(1)
C(15)	31(1)	42(1)	28(1)	4(1)	3(1)	-4(1)

C(16)	31(1)	36(1)	32(1)	2(1)	6(1)	-2(1)
C(17)	41(1)	38(1)	37(1)	6(1)	9(1)	0(1)
C(18)	58(1)	39(1)	52(1)	1(1)	22(1)	-10(1)
C(19)	47(1)	87(2)	86(2)	11(1)	13(1)	-28(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C_{19} H_{34} Cl N O.

Atom	x	y	z	U(eq)
H(1N)	5538	873	632	29
H(2N)	6483	-285	529	29
H(2A)	7620	1700	-1	43
H(2B)	6467	2794	88	43
H(3A)	9022	3564	519	63
H(3B)	8145	4422	-54	63
H(4A)	8378	5943	908	74
H(4B)	6957	5555	645	74
H(5A)	7281	5118	1739	56
H(5B)	8453	4016	1693	56
H(6)	5962	3287	1147	40
H(8A)	4832	1064	1748	43
H(8B)	5729	167	2300	43
H(9)	6811	-1029	1583	32
H(10A)	9082	1806	1359	33
H(10B)	8349	401	1631	33
H(11A)	8455	-1051	665	44
H(11B)	9300	328	450	44
H(12)	10062	-1782	1489	51
H(13A)	11500	204	872	67
H(13B)	11998	-1132	1413	67
H(14A)	5271	-2349	851	36
H(14B)	4247	-1146	1024	36
H(15A)	5598	-3211	1948	41

H(15B)	4463	-2118	2066	41
H(16A)	3098	-3634	1324	40
H(16B)	4232	-4718	1197	40
H(17A)	4491	-5652	2250	46
H(17B)	3425	-4501	2409	46
H(18A)	2980	-7066	1537	58
H(18B)	2748	-7156	2260	58
H(19A)	874	-6709	1582	87
H(19B)	1423	-5132	1323	87
H(19C)	1189	-5231	2046	87

Table 6. Torsion angles [°] for C_{19} H_{34} Cl N O.

C(9)-N(1)-C(1)-C(2)	-178.37(12)
C(9)-N(1)-C(1)-C(10)	58.21(14)
C(9)-N(1)-C(1)-C(6)	-62.40(14)
N(1)-C(1)-C(2)-C(3)	172.61(14)
C(10)-C(1)-C(2)-C(3)	-66.27(18)
C(6)-C(1)-C(2)-C(3)	58.17(17)
C(1)-C(2)-C(3)-C(4)	-55.87(19)
C(2)-C(3)-C(4)-C(5)	52.9(2)
C(3)-C(4)-C(5)-C(6)	-53.1(2)
C(4)-C(5)-C(6)-C(7)	-176.38(15)
C(4)-C(5)-C(6)-C(1)	56.38(19)
N(1)-C(1)-C(6)-C(7)	56.67(14)
C(2)-C(1)-C(6)-C(7)	171.82(12)
C(10)-C(1)-C(6)-C(7)	-62.69(15)
N(1)-C(1)-C(6)-C(5)	-173.77(11)
C(2)-C(1)-C(6)-C(5)	-58.61(15)
C(10)-C(1)-C(6)-C(5)	66.87(16)
C(5)-C(6)-C(7)-O(1)	3.9(2)
C(1)-C(6)-C(7)-O(1)	131.47(15)
C(5)-C(6)-C(7)-C(8)	-179.46(13)

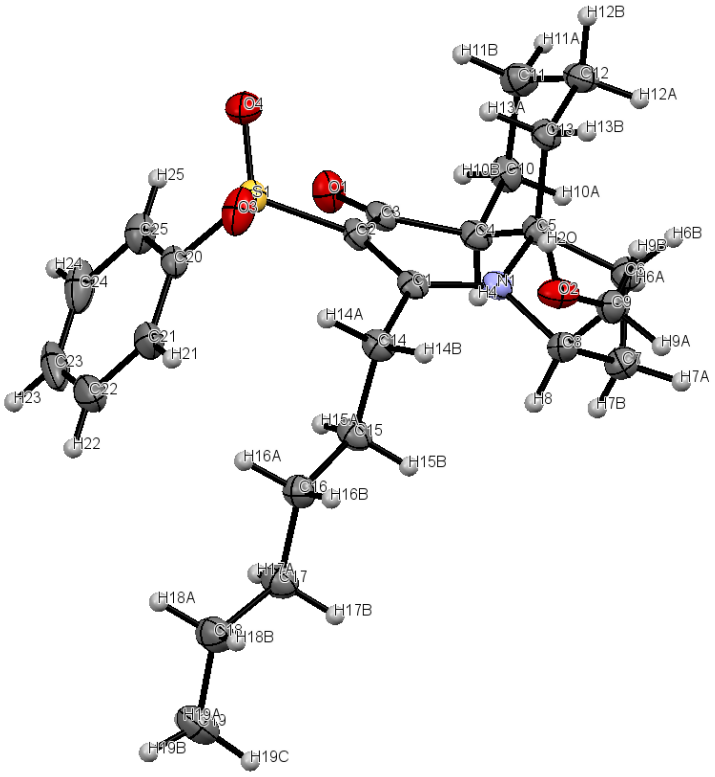
C(1)-C(6)-C(7)-C(8)	-51.89(16)
O(1)-C(7)-C(8)-C(9)	-136.79(15)
C(6)-C(7)-C(8)-C(9)	46.54(17)
C(1)-N(1)-C(9)-C(14)	-179.67(11)
C(1)-N(1)-C(9)-C(8)	56.58(14)
C(7)-C(8)-C(9)-N(1)	-45.79(16)
C(7)-C(8)-C(9)-C(14)	-166.65(12)
N(1)-C(1)-C(10)-C(11)	65.60(16)
C(2)-C(1)-C(10)-C(11)	-54.23(17)
C(6)-C(1)-C(10)-C(11)	-177.04(13)
C(1)-C(10)-C(11)-C(12)	-174.29(13)
C(10)-C(11)-C(12)-C(13)	-102.7(2)
N(1)-C(9)-C(14)-C(15)	175.08(12)
C(8)-C(9)-C(14)-C(15)	-64.13(17)
C(9)-C(14)-C(15)-C(16)	-173.54(13)
C(14)-C(15)-C(16)-C(17)	179.23(13)
C(15)-C(16)-C(17)-C(18)	176.12(14)
C(16)-C(17)-C(18)-C(19)	-66.0(2)

Table 7. Hydrogen bonds for C_{19} H_{34} Cl N O [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...Cl(1)	0.91	2.20	3.1033(11)	171.6
N(1)-H(2N)...Cl(1)#1	0.91	2.27	3.1356(11)	159.3
C(9)-H(9)...O(1)#2	1.00	2.47	3.3708(17)	150.2
C(14)-H(14A)...Cl(1)#1	0.99	2.93	3.7259(14)	138.3

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y,-z #2 -x+3/2,y-1/2,-z+1/2

Appendix E: X-ray Structure Data for compound 156



Experimental:

A colorless prismatic crystal of C_{25} H_{35} N O_4 S was coated with Paratone 8277 oil (Exxon) and mounted on a glass fiber. All measurements were made on a Bruker APEX2 CCD installed on a Nonius Kappa Goniometer diffractometer with graphite monochromated Cu-Kα radiation. Details of crystal data and structure refinement have been provided in Table 1. The data were collected[1] using ω and φ scans. The data were corrected for Lorentz and polarization effects and for absorption using multi-scan method[2].

The structure was solved by the direct methods[3] and expanded using Fourier techniques[4]. The non-hydrogen atoms were refined anisotropically. The H-atoms were

included at geometrically idealized positions with the exception of H8 which was extracted from the fourier difference map. The final cycle of full-matrix least-squares refinement using SHELXL97[5] converged with unweighted and weighted agreement factors, R = 0.0313 and wR = 0.0789 (all data), respectively, and goodness of fit, S = 0.993. The weighting scheme was based on counting statistics and the final difference Fourier map was essentially featureless. The figures were plotted with the aid of ORTEP-3 for Windows[6].

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Table 1. Crystal Data Collection and Refinement Parameters for Complex 1.

formula	$C_{25}H_{35}NO_4S$
fw	445.60
crystal system	orthorhombic
space group	P212121
***a* (Å)**	11.0162(2)
***b* (Å)**	11.2255(2)

***c* (Å)**	18.7921(4)
α (deg)	90
β (deg)	90
γ (deg)	90
***V* (Å^3)**	2323.88(8)
Z	4
***T* (K)**	173(2)
Wavelength (Å)	1.54178
ρ_{calcd} (g·cm^{-3})	1.274
***F*(000)**	960
μ (mm^{-1})	1.485
crystal size, mm^3	0.21×0.19×0.16
transmission factors	0.6802 − 0.7536
***θ* range (deg)**	4.588 − 66.463
data/restraints/param	3962/0/286
GOF	0.993
R_1 [I > 2σ(I)]	0.0313
wR_2 [all data]	0.0789
residual density, e/Å^3	0.272 and -0.251

Table 1: Crystal data and structure refinement.

Identification code	rpvi242b_1_0m_a
Chemical formula	C25 H35 N O4 S
Molecular weight	445.60

Temperature	173(2)
Wavelength	1.54178
Crystal system ; space group	orthorhombic ; P 21 21 21
Unit cell dimentions	a = 11.0162(2) Å ; α = 90 ° b = 11.2255(2) Å ; β = 90 ° c = 18.7921(4) Å ; γ = 90 °
Volume	2323.88(8) Å^3
Z, Calculated density	4, 1.274 g/cm^3
Absorption coefficient	1.485 1/mm
F(000)	960
Theta range for data collection	4.588° to 66.463°
Limiting indices	-13 <= h <= 12 ; -13 <= k <= 13 ; -22 <= l <= 16
Reflexion collected / unique	12393 / 3962 [R(int) = 0.0277]
Completness to theta max	98.2 %
Refinement method	Full-matrix least-square on F^2

Data / restraints / parameters	3962 / 0 / 286
Goodness of fit on F^2	0.993
Final R indices [I>2sigma(I)]	R1 = 0.0313 ; wR2 = 0.0779
Final R indices [all data]	R1 = 0.0327 ; wR2 = 0.0789
Largest diff peak and hole	0.272 and -0.251 e/Å^3

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacements parameters (Å^2 x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Label	x	y	z	U(eq)
C1	6462.9(1.7)	6586(2)	5635.3(1.3)	20.8(4)
C10	7916(2)	9435(2)	4348.7(1.4)	26.8(5)
C11	6724(2)	9856(3)	4020.2(1.4)	31.5(5)
C12	5820(2)	10194(2)	4602.5(1.4)	30.1(5)
C13	5591(2)	9143(2)	5098.4(1.3)	24.1(5)
C14	6312(2)	5550(2)	6134.0(1.3)	24.0(5)
C15	7562(2)	5059(2)	6350.5(1.4)	27.3(5)
C16	7493(2)	3843(2)	6705.9(1.3)	26.5(5)

C17	8723(2)	3388(2)	6954.0(1.5)	31.4(6)
C18	8724(3)	2115(3)	7206.6(1.6)	37.4(6)
C19	9958(3)	1699(3)	7466.1(1.8)	43.9(7)
C2	6639(2)	6439(2)	4889.8(1.3)	21.6(5)
C20	7344(2)	4296(2)	4186.4(1.3)	23.4(5)
C21	7691(3)	3448(2)	4678.7(1.6)	35.1(6)
C22	8678(3)	2735(3)	4537.2(1.9)	49.5(9)
C23	9297(3)	2852(3)	3900(2)	51.3(9)
C24	8935(3)	3692(3)	3406.5(1.8)	43.3(7)
C25	7948(2)	4432(2)	3546.1(1.4)	30.3(6)
C3	7383.8(1.9)	7266(2)	4503.5(1.2)	22.9(5)
C4	7727(2)	8417(2)	4882.9(1.3)	23.6(5)
C5	6784.9(1.9)	8746(2)	5453.8(1.2)	21.6(5)
C6	7261(2)	9676(2)	5985.3(1.3)	27.4(5)
C7	7584(2)	8991(2)	6658.8(1.4)	29.8(5)
C8	6673(2)	7965(2)	6674.8(1.3)	25.0(5)
C9	5455(2)	8339(2)	6991.6(1.3)	28.7(5)

N1	6572.0(1.6)	7668.0(1.8)	5905.9(1.0)	21.5(4)
O1	7799.6(1.7)	7041.5(1.7)	3910.5(1.0)	31.0(4)
O2	4615.7(1.5)	7390.6(1.8)	7018.7(1.0)	31.1(4)
O3	5275.2(1.6)	4534.0(1.7)	4815.6(1.0)	35.6(4)
O4	5616.5(1.6)	5693.8(1.8)	3735.1(1.0)	34.5(4)
S1	6088.4(4)	5232.9(5)	4389.9(3)	22.9(15)

Table 3: Bond lengths (Ångstrom).

Bond	Length (Å)
C1 - C14	1.502(3)
C1 - C2	1.424(3)
C1 - N1	1.323(3)
C10 - C11	1.526(3)
C10 - H10A	0.9900
C10 - H10B	0.9900
C11 - C12	1.528(4)
C11 - H11A	0.9900

C11 - H11B 0.9900

C12 - C13 1.524(4)

C12 - H12A 0.9900

C12 - H12B 0.9900

C13 - H13A 0.9900

C13 - H13B 0.9900

C14 - C15 1.539(3)

C14 - H14A 0.9900

C14 - H14B 0.9900

C15 - C16 1.522(3)

C15 - H15A 0.9900

C15 - H15B 0.9900

C16 - C17 1.522(3)

C16 - H16A 0.9900

C16 - H16B 0.9900

C17 - C18 1.507(4)

C17 - H17A 0.9900

C17 - H17B	0.9900
C18 - C19	1.517(4)
C18 - H18A	0.9900
C18 - H18B	0.9900
C19 - H19A	0.9800
C19 - H19B	0.9800
C19 - H19C	0.9800
C2 - C3	1.436(3)
C2 - S1	1.756(2)
C20 - C21	1.382(4)
C20 - C25	1.383(4)
C20 - S1	1.779(2)
C21 - C22	1.376(4)
C21 - H21	0.9500
C22 - C23	1.385(5)
C22 - H22	0.9500
C23 - C24	1.381(5)

C23 - H23	0.9500
C24 - C25	1.392(4)
C24 - H24	0.9500
C25 - H25	0.9500
C3 - C4	1.524(3)
C3 - O1	1.231(3)
C4 - C10	1.535(3)
C4 - C5	1.538(3)
C4 - H4	1.0000
C5 - C13	1.542(3)
C5 - C6	1.537(3)
C5 - N1	1.497(3)
C6 - C7	1.523(4)
C6 - H6A	0.9900
C6 - H6B	0.9900
C7 - C8	1.527(4)
C7 - H7A	0.9900

C7 - H7B	0.9900
C8 - C9	1.527(3)
C8 - H8	1.0000
C8 - N1	1.487(3)
C9 - H9A	0.9900
C9 - H9B	0.9900
C9 - O2	1.411(3)
O2 - H2O	0.80(4)
O3 - S1	1.4346(18)
O4 - S1	1.433(2)

Table 4: Bond angles (°).

Atoms	Angle (°)
C1 - C14 - C15	110.08(18)
C1 - C14 - H14A	109.6
C1 - C14 - H14B	109.6
C1 - C2 - C3	120.0(2)

C1 - C2 - S1	124.65(18)
C1 - N1 - C5	122.6(2)
C1 - N1 - C8	125.9(2)
C10 - C11 - H11A	109.6
C10 - C11 - H11B	109.6
C10 - C4 - C5	111.67(19)
C10 - C4 - H4	107.6
C11 - C10 - C4	112.21(19)
C11 - C10 - H10A	109.2
C11 - C10 - H10B	109.2
C11 - C12 - H12A	109.5
C11 - C12 - H12B	109.5
C12 - C11 - C10	110.4(2)
C12 - C11 - H11A	109.6
C12 - C11 - H11B	109.6
C12 - C13 - C5	110.35(18)
C12 - C13 - H13A	109.6

C12 - C13 - H13B	109.6
C13 - C12 - C11	110.7(2)
C13 - C12 - H12A	109.5
C13 - C12 - H12B	109.5
C14 - C15 - H15A	109.0
C14 - C15 - H15B	109.0
C15 - C14 - H14A	109.6
C15 - C14 - H14B	109.6
C15 - C16 - C17	113.0(2)
C15 - C16 - H16A	109.0
C15 - C16 - H16B	109.0
C16 - C15 - C14	113.11(19)
C16 - C15 - H15A	109.0
C16 - C15 - H15B	109.0
C16 - C17 - H17A	108.6
C16 - C17 - H17B	108.6
C17 - C16 - H16A	109.0

C17 - C16 - H16B	109.0
C17 - C18 - C19	113.2(2)
C17 - C18 - H18A	108.9
C17 - C18 - H18B	108.9
C18 - C17 - C16	114.5(2)
C18 - C17 - H17A	108.6
C18 - C17 - H17B	108.6
C18 - C19 - H19A	109.5
C18 - C19 - H19B	109.5
C18 - C19 - H19C	109.5
C19 - C18 - H18A	108.9
C19 - C18 - H18B	108.9
C2 - C1 - C14	122.7(2)
C2 - C3 - C4	117.0(2)
C2 - S1 - C20	107.60(10)
C20 - C21 - C22	119.3(3)
C20 - C21 - H21	120.3

C20 - C25 - C24	118.3(3)
C20 - C25 - H25	120.9
C21 - C20 - C25	121.7(2)
C21 - C20 - S1	118.6(2)
C21 - C22 - C23	120.0(3)
C21 - C22 - H22	120.0
C22 - C21 - H21	120.3
C22 - C23 - H23	119.9
C23 - C22 - H22	120.0
C23 - C24 - C25	120.4(3)
C23 - C24 - H24	119.8
C24 - C23 - C22	120.2(3)
C24 - C23 - H23	119.9
C24 - C25 - H25	120.9
C25 - C20 - S1	119.72(19)
C25 - C24 - H24	119.8
C3 - C2 - S1	115.17(17)

C3 - C4 - C10	111.04(19)
C3 - C4 - C5	111.24(18)
C3 - C4 - H4	107.6
C4 - C10 - H10A	109.2
C4 - C10 - H10B	109.2
C4 - C5 - C13	110.08(19)
C4 - C5 - C6	112.69(18)
C5 - C13 - H13A	109.6
C5 - C13 - H13B	109.6
C5 - C4 - H4	107.6
C5 - C6 - H6A	110.5
C5 - C6 - H6B	110.5
C6 - C5 - C13	112.11(19)
C6 - C7 - C8	104.1(2)
C6 - C7 - H7A	110.9
C6 - C7 - H7B	110.9
C7 - C6 - C5	106.1(2)

C7 - C6 - H6A	110.5
C7 - C6 - H6B	110.5
C7 - C8 - C9	112.2(2)
C7 - C8 - H8	110.3
C8 - C7 - H7A	110.9
C8 - C7 - H7B	110.9
C8 - C9 - H9A	109.1
C8 - C9 - H9B	109.1
C8 - N1 - C5	111.00(19)
C9 - C8 - H8	110.3
C9 - O2 - H2O	113(2)
H10A - C10 - H10B	107.9
H11A - C11 - H11B	108.1
H12A - C12 - H12B	108.1
H13A - C13 - H13B	108.1
H14A - C14 - H14B	108.2
H15A - C15 - H15B	107.8

H16A - C16 - H16B	107.8
H17A - C17 - H17B	107.6
H18A - C18 - H18B	107.8
H19A - C19 - H19B	109.5
H19A - C19 - H19C	109.5
H19B - C19 - H19C	109.5
H6A - C6 - H6B	108.7
H7A - C7 - H7B	109.0
H9A - C9 - H9B	107.8
N1 - C1 - C14	118.7(2)
N1 - C1 - C2	118.2(2)
N1 - C5 - C13	110.26(17)
N1 - C5 - C4	107.94(18)
N1 - C5 - C6	103.51(19)
N1 - C8 - C7	101.5(2)
N1 - C8 - C9	111.99(19)
N1 - C8 - H8	110.3

O1 - C3 - C2	122.5(2)
O1 - C3 - C4	120.3(2)
O2 - C9 - C8	112.5(2)
O2 - C9 - H9A	109.1
O2 - C9 - H9B	109.1
O3 - S1 - C2	109.81(11)
O3 - S1 - C20	106.39(12)
O4 - S1 - C2	107.83(12)
O4 - S1 - C20	108.12(11)
O4 - S1 - O3	116.74(12)

Table 5: Hydrogen coordinates (x 10^4) and isotropic displacements parameters (Å^2 x 10^3).

Label	x	y	z	U(eq)
H10A	8311.0	10113.0	4593.0	32.0
H10B	8467.0	9162.0	3965.0	32.0
H11A	6878.0	10554.0	3711.0	38.0
H11B	6378.0	9213.0	3722.0	38.0

H12A	6143.0	10874.0	4880.0	36.0
H12B	5045.0	10446.0	4382.0	36.0
H13A	5243.0	8472.0	4824.0	29.0
H13B	4997.0	9376.0	5469.0	29.0
H14A	5834.0	4916.0	5898.0	29.0
H14B	5864.0	5810.0	6564.0	29.0
H15A	8080.0	4998.0	5921.0	33.0
H15B	7954.0	5627.0	6681.0	33.0
H16A	7142.0	3264.0	6366.0	32.0
H16B	6940.0	3893.0	7120.0	32.0
H17A	9308.0	3465.0	6556.0	38.0
H17B	9013.0	3904.0	7346.0	38.0
H18A	8458.0	1593.0	6811.0	45.0
H18B	8129.0	2030.0	7598.0	45.0
H19A	10573.0	1879.0	7105.0	66.0
H19B	9935.0	838.0	7551.0	66.0
H19C	10161.0	2112.0	7910.0	66.0

H21	7252.0	3357.0	5111.0	42.0
H22	8935.0	2161.0	4877.0	59.0
H23	9973.0	2353.0	3801.0	62.0
H24	9361.0	3766.0	2969.0	52.0
H25	7696.0	5014.0	3210.0	36.0
H2O	4080(30)	7450(30)	6733(17)	36(8)
H4	8518.0	8278.0	5130.0	28.0
H6A	7987.0	10083.0	5792.0	33.0
H6B	6630.0	10280.0	6086.0	33.0
H7A	7497.0	9502.0	7085.0	36.0
H7B	8427.0	8687.0	6636.0	36.0
H8	7015.0	7275.0	6945.0	30.0
H9A	5587.0	8648.0	7479.0	34.0
H9B	5109.0	8993.0	6702.0	34.0