Synthesis of Iboga Alkaloids Using Cascade Cyclisation, Nitrone Cycloaddition

Submitted by

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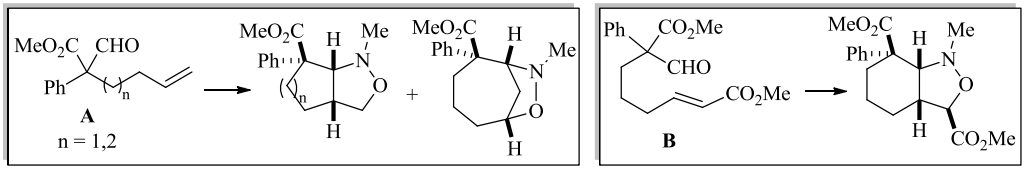
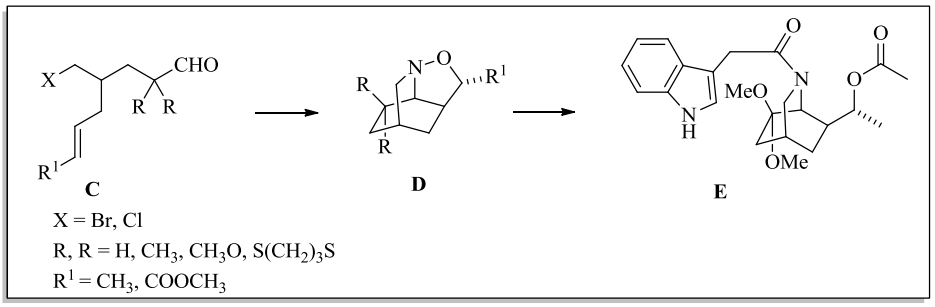
Abstract

This thesis details the study of nitrone cycloadditions to synthesize some novel isoxazolidines. Condensation of aldehydes **A** and **B**, with *N*-methylhydroxylamine led to the formation of nitrones. Cycloaddition of these nitrones gave a range of bicyclic isoxazolidine products.



The cascade chemistry, involving condensation, cyclisation, and nitrone cycloaddition was utilised in the synthesis of the core structure found in iboga alkaloid natural products. Aldehydes **C** were synthesised and condensed with hydroxylamine to obtain a variety of isoquinuclidine cycloadducts.



This cascade chemistry was used for the formal synthesis of 19-hydroxy-ibogamine. Starting with aldehyde **C**, X = Cl, R,R = $S(CH_2)_3S$, $R^1 = CH_3$ gave the cycloadduct **D**. This was converted to the amide **E** that represents the completion of the formal synthesis of this alkaloid.

In addition, some studies were carried out towards an aldehyde needed for the cascade chemistry to investigate a proposed biosynthesis of the alkaloids daphlongeranines A and B.

DEDICATED

My Father

For being my first teacher
For earning an honest living for us and for supporting and encouraging me to believe in myself

My Mother

A strong and gentle soul who taught me to trust in Allah, believe in hard work and that so much could be done with little

I would never get this without you!

Acknowledgements

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One of the most important acknowledgements belong to three men who were a very nice and kind friends and being my family through the long journey of the PhD; Firas, Haider and Haval and of course their families thank you for all the good and nice times. I enjoyed the time spent with you, the fun that we made. I am very lucky to having such friend in my life.

My greatest gratitude is to my father and mother for their love, brothers, and sisters. Thank you very very much for your support and your motivation, encouragement and

support over the years, without your support I would have never finished my PhD. I am so happy to having you in my life!

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Contents

Abbreviations

Ac	acyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat.	catalyst
Cb	*N*,*N*-diisopropylcarbamoyl
Cbz	carboxybenzyl
CI	chemical ionisation
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
CSA	camphor sulfonic acid
Cy	cyclohexyl
DCC	dicyclohexylcarbodiimide
DFT	Density Functional Theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	2,2-dimethoxypropane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereoisomer ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomer excess
EI	electron ionisation (or electron impact)
equiv.	equivalent
ES	electrospray ionisation
EWG	electron withdrawing group
FMO	Frontier Molecular Orbital

GC	gas chromatography
HMPA	hexamethyl phosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
IR	infra red
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
m/z	mass number
m.p.	melting point
m-CPBA	*meta*-chloroperoxybenzoic acid
Ms	methanesulfonyl or mesyl
MW	microwave
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PIFA	(*bis*(trifluoroacetoxy)iodo)benzene
PMB	*para*-methoxybenzyl
Py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
R_f	retention factor
rt	room temperature
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TES	triethylsilyl

Tf	trifluoromethanesulfonyl or triflate
THF	tetrahydrofuran
TIB	2,4,6-triisopropylbenzoyl
TIPB	1,3,5-triisopropylbenzene
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediaimne
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl or tosyl

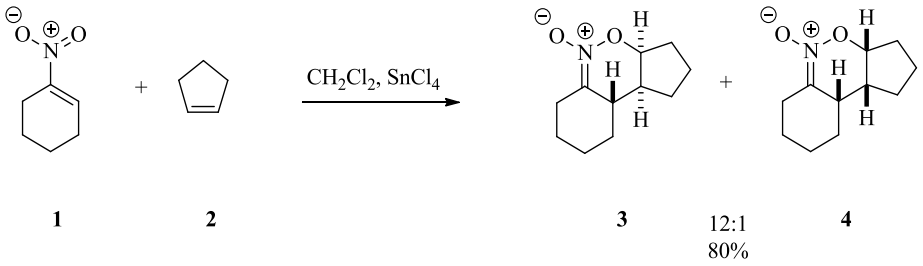
Chapter 1

1.1 Introduction to cascade reactions

A big challenge for the synthetic organic chemist is the synthesis of complex molecules which contain polycyclic structures. Their synthesis typically requires multiple steps, and so the generation of three or more bonds in one step is very useful methodology and is generally known as "cascade" or "tandem" reactions. Cascade reactions have been widely studied, and have seen huge progress in recent years.[1] The benefits of cascade chemistry are apparent and include the generation of polycyclic ring systems in one step, reduction in time and waste, and the high levels of stereocontrol.[2] Therefore, cascade chemistry accords with the principle of "green chemistry".[3] In the Coldham group, extensive research has been carried out on the cascade processes of condensation, cyclisation, and dipolar cycloaddition reactions towards the synthesis of core structures involving fused ring and bridged ring systems. This report will discuss this type of chemistry, and how the methodology which has been developed in the group will be used towards the synthesis of iboga alkaloids, and the formation of a two-carbon bridged system in a single step from an acyclic aldehyde.

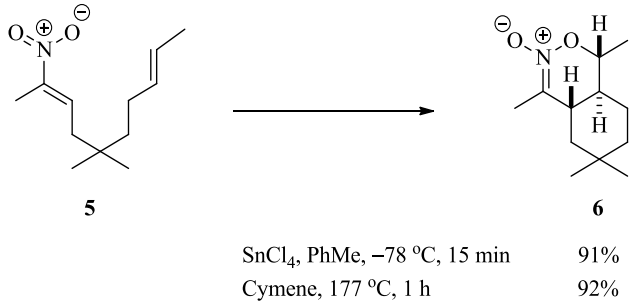
1.2 Cascade cycloadditions with nitroalkenes

Aliphatic compounds having nitro groups are important intermediates in organic synthesis as they are easy to convert into other functional groups, such as amides, hydroxylamines, nitronates, nitrile oxides, amines, nitrones and the remarkable transformation into carbonyl compounds using the Nef reaction.[4] In 1986, Denmark and co-workers[5,6] reported that nitroalkenes undergo Diels–Alder [4 + 2] cycloaddition when treated with a dienophile to yield nitronates. For unactivated dienophiles, such as simple alkenes, a Lewis acid is required to effect the reaction, by lowering the energy of the diene LUMO and reduce the gap between the HOMO of the alkene and the LUMO of the diene (nitroalkene). For example, reacting nitroalkene **1** and cyclopentene **2**, with $SnCl_4$, gave two diastereoisomeric cycloadducts **3** and **4** in a 12:1 ratio (Scheme 1.1).



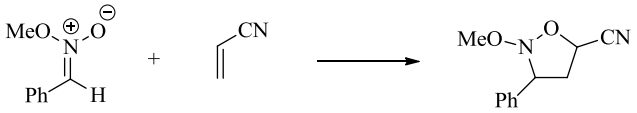
Scheme 1.1

The major cycloadduct **3** comes from the *exo* approach of the alkene towards the nitroalkene, while cycloadduct **4** arises from an *endo* approach.[6] Moreover, the cycloaddition of nitroalkenes can take place in an intramolecular reaction. For example, when treating nitro compound **5** with $SnCl_4$ at −78 °C in toluene, after a short period of time the nitronate **6** was formed as a single diastereoisomer. Similarly, to demonstrate the effect of the Lewis acid, the same reaction was heated at reflux in cymene for 1 h in the absence of a Lewis acid to give the same nitronate **6** (Scheme 1.2).[7]



Scheme 1.2

A 1964 study by Tartakovskii and co-workers showed that nitronates can serve as dipoles and can easily undergo a [3 + 2] dipolar cycloaddition to produce 5-membered cycloadducts.[8] For example, the reaction between nitronate **7** and acrylonitrile yielded nitrile **8** in 46% yield (the stereoselctivity was not reported) (Scheme 1.3).



7 **8** 46%

Scheme 1.3

Denmark and co-workers reported that the use of an inverse electron demand [4 + 2] cycloaddition of a nitroalkene bearing an electron-donating dienophile, followed by a normal electron demand [3 + 2] dipolar cycloaddition of an electron-withdrawing dipolarophile, is very useful as a cascade process. This could allow the generation of four rings and six stereogenic centres in one pot, as shown in Figure 1.1.[4]

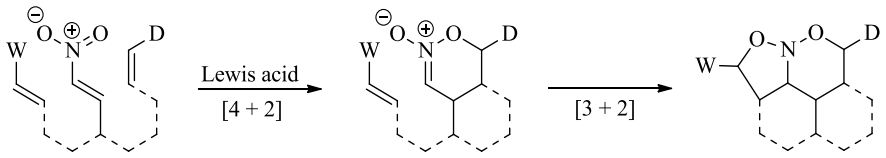


Figure 1.1

The cascade reaction can be classified into four classes, these are inter– and intramolecular versions of both cycloaddition reactions (Figure 1.2). Some of these will be discussed in detail in this section.

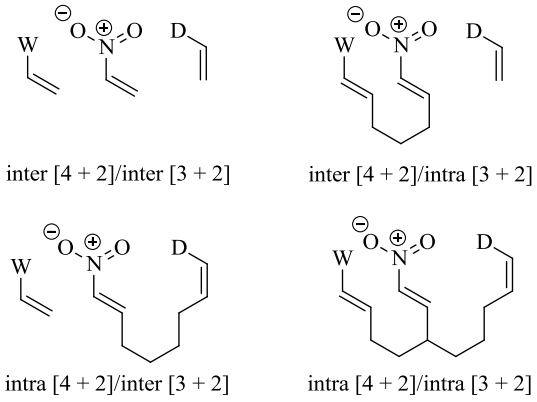


Figure 1.2

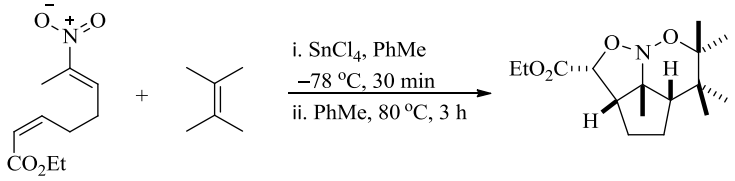
1.2.1 Intermolecular [4 + 2]/intramolecular [3 + 2] cycloadditions

The intermolecular [4 + 2] cycloaddition of a nitroalkene followed by intramolecular [3 + 2] cycloaddition has been widely studied, due to the fact that it can lead to different types of cycloadducts. These are fused and two different types of bridged compounds.

1.2.1.1 Fused ring systems

For formation of a fused ring system, the dipolarophile needs to be connected to the α-carbon of the nitrone, which undergoes the cycloaddition. In 1990, Denmark and co-workers studied the effect of the length of the tether between the dipole and the dipolarophile, nitronate substitution as well as the dipolarophile configuration. The [3 + 2] cycloaddition of the substrates with two or three methylene units between the dipole and dipolarophile formed five or six membered nitroso acetal cycloadducts rapidly in good yield. Following the [4 + 2] cycloaddition, substrates with two methylene units mostly underwent [3 + 2] cycloaddition, while heating is required for the substrates bearing three methylene units to form the desired cycloadduct. On the other hand, substrates with four methylene units failed to form seven membered cycloadducts, and only intermediate nitronates were obtained, even on heating.[9]

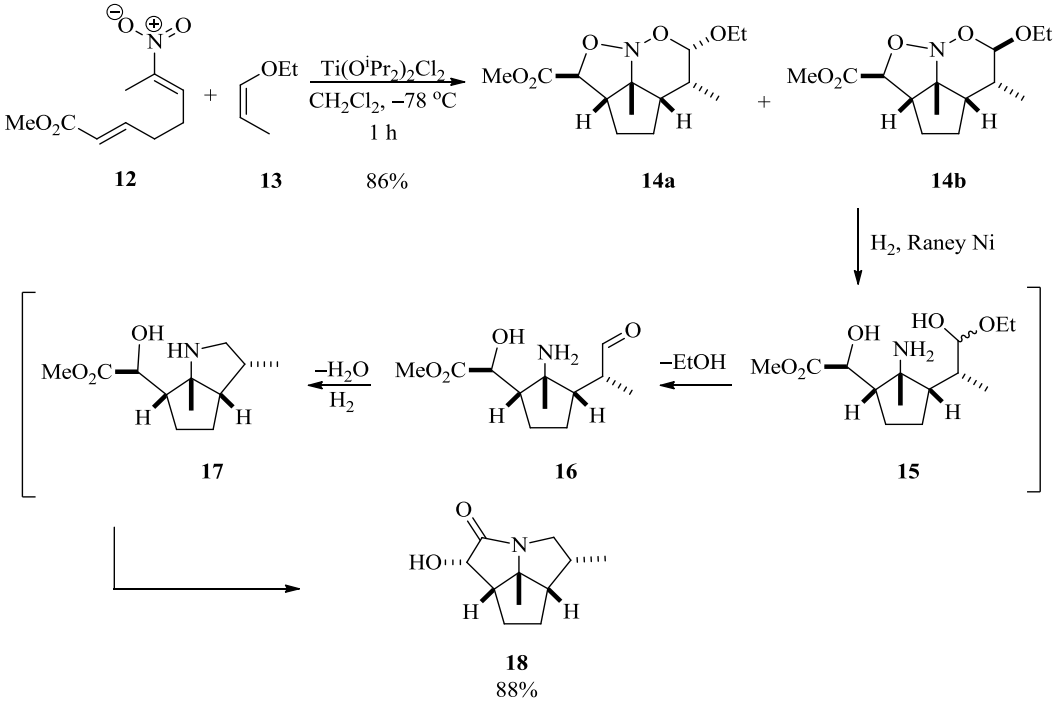
An example of a [4 + 2] then [3 + 2] cycloaddition is shown in Scheme 1.4. Treating the nitroalkene **9** with tetramethylethylene **10** in the presence of $SnCl_4$ in PhMe at –78 °C gave the [4 + 2] cycloaddition product. This was followed by heating at 80 °C in PhMe, which afforded the [3 + 2] cycloadduct **11** in 78% yield and with high diastereocontrol (20:1).[4]



9 **10** **11**
78%

Scheme 1.4

To enhance the complexity of the cascade, 2-substituted vinyl ethers, which are oxygen-containing dienophiles were used in the [4 + 2] cycloaddition, allowing generation of up to six stereocentres in one step. Compound **12** was treated with ether **13**, in the presence of Lewis acid $Ti(O^iPr)_2Cl_2$, to give anomers **14a** and **14b**, in 5.7:4.3 ratio (Scheme 1.5). In the [4 + 2] cycloaddition,[10] the time of reaction affects the anomer ratio; in short time **14a** was the major isomer, which is derived from the *endo* orientation of the ethoxy group, whereas using longer times the proportion of isomer **14b** was increased. The effect of electron deficient dipolarophiles on the [3 + 2] cycloaddition was studied and in many cases the reaction was found to take place in good yield and moderate diastereoselectivity, but occurred more slowly.[11]



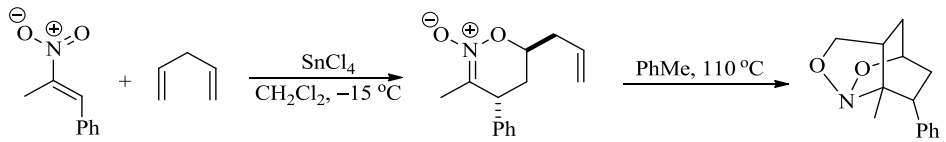
Scheme 1.5

The nitrosoacetals **14a** and **14b** underwent hydrogenolysis leading to the formation of tricyclic lactam **18**. Initially, breaking of the N–O bonds occurs, followed by hemiacetal removal to form the aldehyde **16** which then cyclises and is reduced to give the amine **17**. This then cyclises to form the lactam.[9,10]

This type of chemistry has been used in the synthesis of many natural products, including (–)-rosmarinecine,[12] (–)-mesembrine,[13] (–)-detoxinine,[14] and castanospermine.[15]

1.2.1.2 Bridged ring systems

Bridged systems are different from fused systems, as the dipolarophile connects to the dienophile (either α- or β-) carbon instead of the nitroalkene, to give bridged cyclic compounds. The products after the reduction reaction are either cyclohexanols or cyclopentanols.[16] For example, treating nitroalkene **19** with 1,4-pentadiene in the presence of $SnCl_4$ at −15 °C in CH_2Cl_2 gave the nitronate **20** in 91% yield as a single diastereoisomer, in *exo* oriented conformation. The product was heated at reflux in PhMe to facilitate the [3 + 2] cycloaddition leading to the formation of the bridged cycloadduct **21** (Scheme 1.6).[17,18]



19 **20** 91% **21** 84%

Scheme 1.6

1.2.2 Intramolecular [4 + 2]/intramolecular [3 + 2] cycloadditions

The intramolecular [4 + 2] cycloaddition of a nitroalkene followed by intramolecular [3 + 2] cycloaddition requires the dienophile and the dipolarophile to be attached to the nitroalkene. In terms of tethering there are many ways in which they can be attached together. Denmark has done extensive research on the fused/bridged systems where the dipolarophile is attached at C(6) or C(5) of the nitronate (Figure 1.3).[18,19]

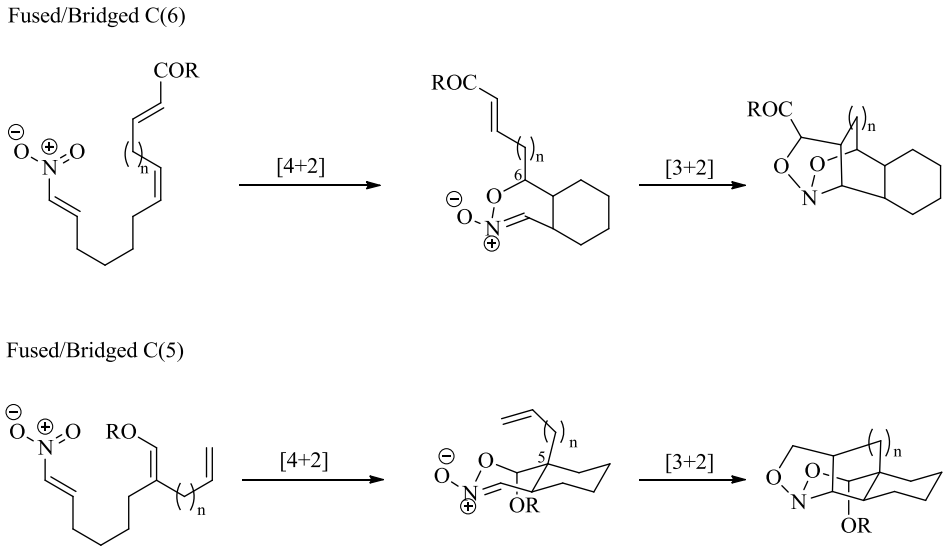
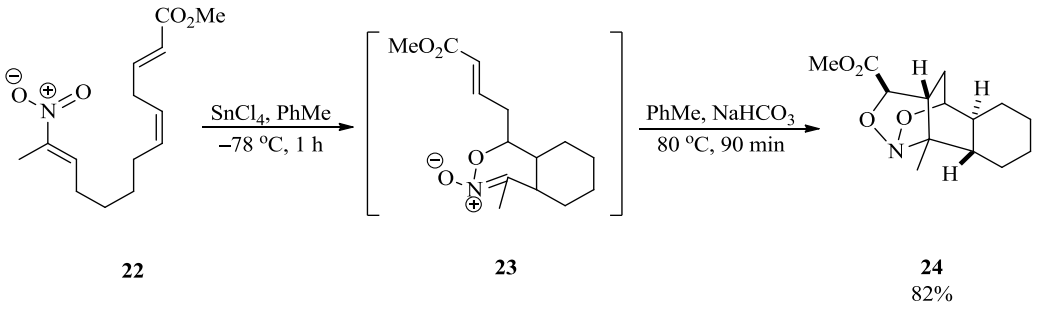


Figure 1.3

An example related to the C(6) position stated that heating the nitroalkene **22** with $SnCl_4$ at −78 °C in PhMe afforded a mixture of nitronates **23** and the nitrosoacetal **24**. Warming the crude mixture yielded a single diastereoisomer of nitrosoacetal **24** in good yield (Scheme 1.7).[18]



22 **23** **24**
82%

Scheme 1.7

In order to rationalize the stereochemistry of the [4 + 2] cycloaddition step there are two possible transition states, *exo* and *endo* (Figure 1.4).[20] The *endo*-shape is the less preferred, due to the steric interaction between the Lewis acid and the R group. In addition, in the *endo* transition state there is an interaction of the methyl group with the allylic proton and a methylene proton within the chain. However, in the favorable *exo*-shape, the steric interaction is less, where the methyl group and Lewis acid interact with alkene protons.

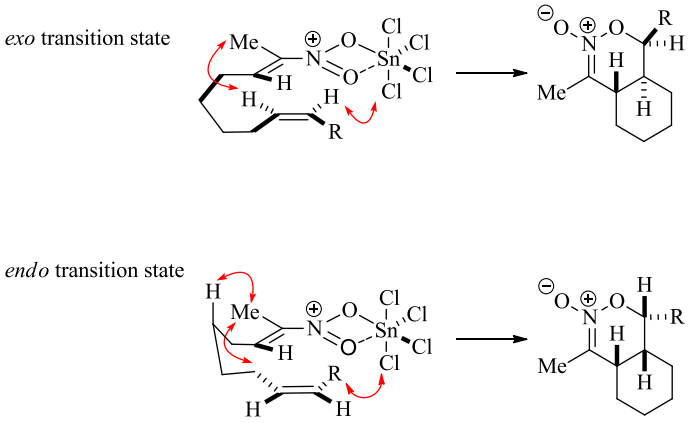
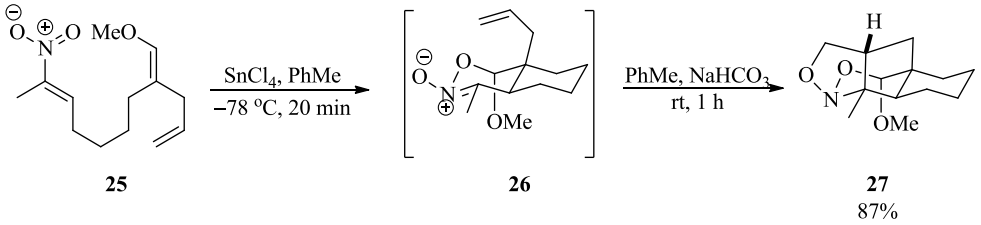


Figure 1.4

To examine the reactivity of the C(5) position, compound **25** was chosen, in which a vinyl ether has been introduced. This allows investigating the effect of tether length. Thus, compound **25** and $SnCl_4$ in toluene were stirred for 20 min at −78 °C, and a mixture of nitronates **26** and the desired product **27** was formed in 3:2 ratio. To effect the intermolecular cycloaddition, the reaction mixture was stirred for 1 h at room temperature to afford cycloadduct **27** as a single diastereoisomer in 87% yield (Scheme 1.8).[18]



25 **26** **27** 87%

Scheme 1.8

1.3 Cascade cycloadditions with nitrones

Nitrones, azomethine ylides, azomethine imines, and nitronates are all classified as dipoles and are valuable intermediates in organic chemistry. A 1,3-dipole is basically a three atom π-electron system, with four π-electrons distributed over the three atoms. The allyl type is bent, involving four electrons in three parallel p_z orbitals perpendicular to the plane of the dipole (Figure 1.5).[21]

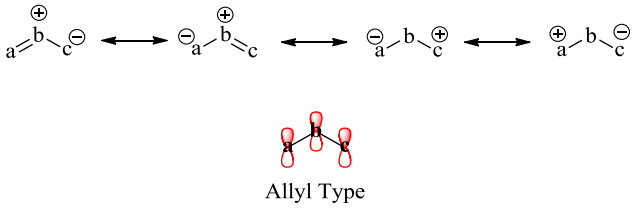
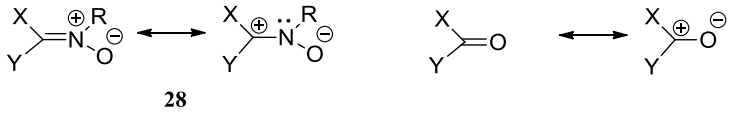


Figure 1.5

This study will be focused on nitrones as 1,3-dipoles, which have been shown to be crucial intermediates in organic chemistry.[22] These were named by Pfeiffer from an abbreviation of "nitrogen-ketone", for compounds have the structure **28**, compared to the similarity with ketones (Figure 1.6).[23]



28

Figure 1.6

1.3.1 Nitrones

A nitrone is a system of three atoms C−N−O over which are delocalised four π electrons. The combination of a nitrone and an unsaturated dipolarophile is a cycloaddition reaction, which is thermally allowed, and involves a total of six electrons [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] in a suprafacial process according to the Woodward–Hoffmann rules (Figure 1.7).[24,25]

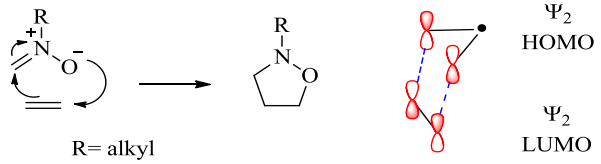


Figure 1.7

The product from the 1,3-dipolar cycloaddition reaction of a nitrone with an alkene is called an isoxazolidine. This concerted reaction leads to the formation of O−C and C−C σ bonds and up to three new stereocentres in the product (Figure 1.8).[21]

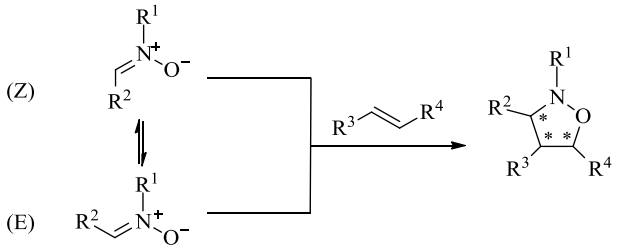


Figure 1.8

In support of frontier molecular orbital (FMO) theory, it is possible to examine the 1,3-dipolar cycloaddition between the nitrone and alkene. The dominant orbital interaction is thought to involve the HOMO (highest occupied molecular orbital) of the electron rich nitrone and the LUMO (lowest unoccupied molecular orbital) of the dipolarophile (Figure 1.9).[26]

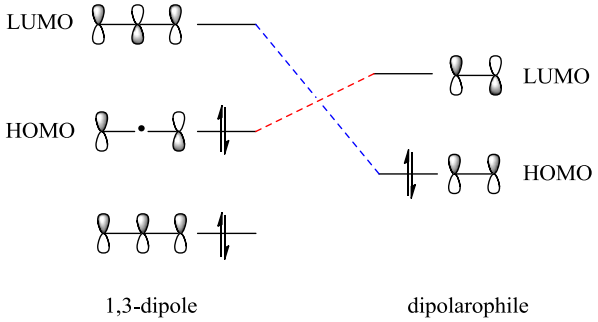


Figure 1.9

Theoretical calculations could help to estimate the relative energies of the HOMO and LUMO of the nitrone and dipolarophiles (Figure 1.10).[27]

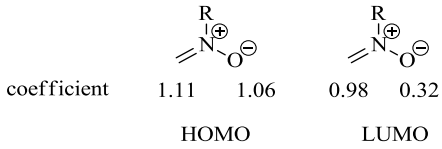


Figure 1.10

The main interaction will be between the orbitals having closer energy and coefficient size. Thus, prediction of regioselectivity of the cycloaddition reaction can be made, based on the known energy and size (Figure 1.11). In addition, the effects of steric factors must be considered.[28] In an intramolecular cycloaddition the

conformational restraints can play a role to enhance the selectivity and might lead to form only one regioisomer.[27]

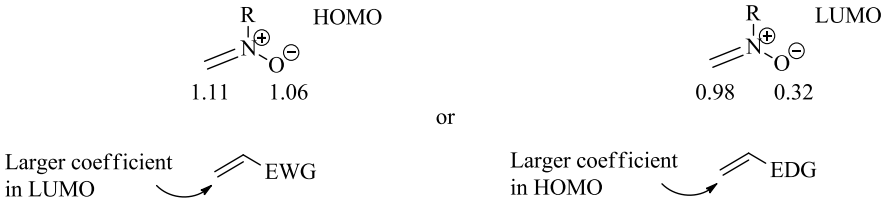
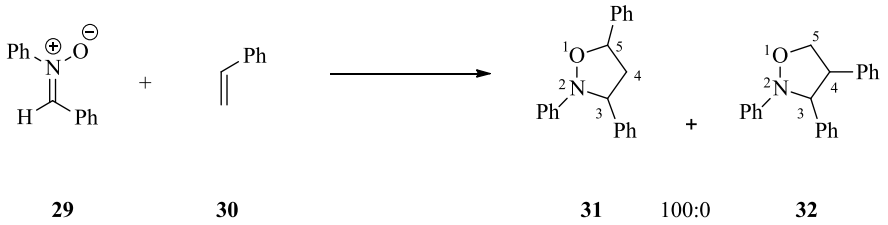


Figure 1.11

The [3 + 2] cycloaddition reaction is a concerted step and the regioselectivity is often controlled by the substituent group that is attached to the dipolarophile. However, easy reactions can occur with dipole LUMO control for electron rich nitrone **29**, and dipole HOMO control with electron deficient alkenes **30**. Introducing a substituent group on the dipole can generate a steric effect, leading to the preferential formation of isoxazolidines **31** in which the substituent from the dipolarophile is located at C-5 (Scheme 1.9).[27]



Scheme 1.9

1.3.2 The formation of nitrones

Nitrones can be generated either by oxidation methods such as oxidation of amines, imines, or hydroxylamines, or non-oxidation methods: from oximes, or *via* the condensation of carbonyl compounds with hydroxylamines (Figure 1.12**)**. Examples of non-oxidation methods are discussed in brief below.

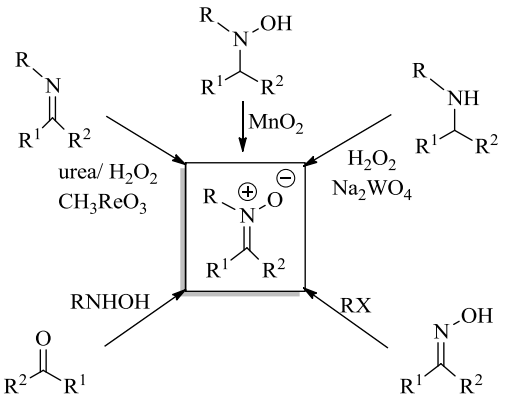


Figure 1.12

1.3.2.1 From oximes

A 1991 study by Grigg and co-workers explored the formation of nitrones from oximes and made a significant development.[29] The preparation of nitrones from oximes can involve a 1,2-prototropy reaction. Heating the oxime results in a small equilibrium concentration of its nitrone (Figure 1.13). He showed that unstable nitrones could be incorporated into the subsequent 1,3−dipolar cycloaddition reaction (for an example of this see Scheme 1.22). The nitrone can undergo either intra- or intermolecular 1,3-dipolar cycloaddition reaction.[30]

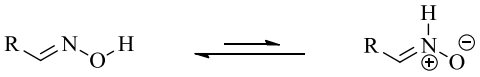


Figure 1.13

Grigg and co-workers reported that the *N*-alkylation of oximes with electron-poor substituted alkenes generated nitrones; this was presumed to proceed through a Michael addition reaction. The group suggested a 1,3-azaprotic cyclotransfer mechanism (Figure 1.14).[31]

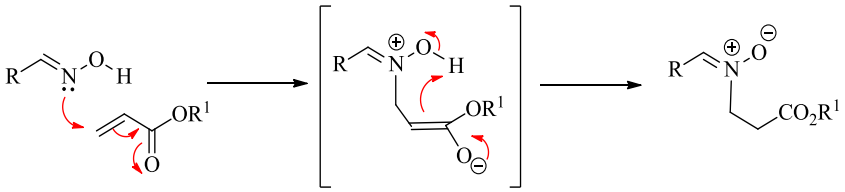
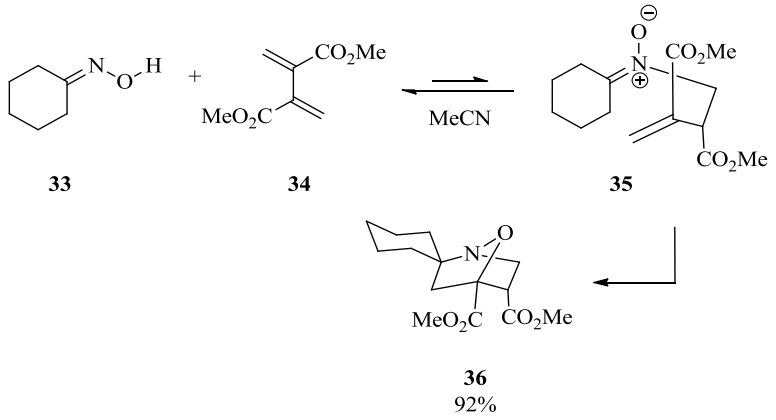


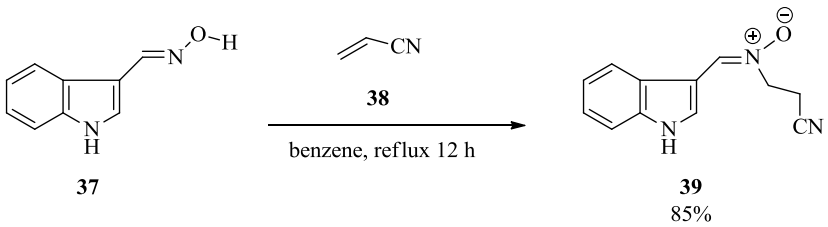
Figure 1.14

For example, the reaction of oxime **33** with diene **34** in acetonitrile at 80 ^{o}C formed the nitrone **35**. Subsequently, the nitrone underwent cycloaddition reaction to give cycloadduct **36** in excellent yield (Scheme 1.10).[31]



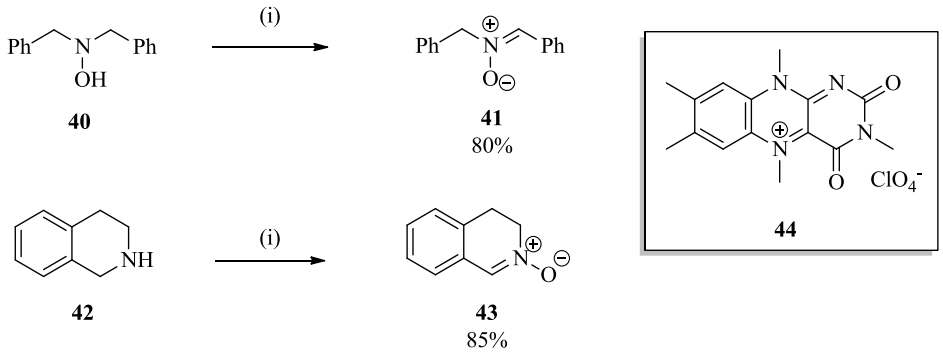
Scheme 1.10

Chakrabarty and co-workers have extended the 1,3-azaprotic cyclotransfer methodology into the synthesis of indol-nitrones from the corresponding oximes. Oxime **37** and acrylonitrile (**38**) were heated at reflux in benzene to afford the nitrone **39** in 85% yield (Scheme 1.11).[32]



Scheme 1.11

In 2007, Imada and Naota reported a catalytic process to form nitrones **41** and **43** from hydroxylamine **40** and secondary amine **42** respectively.[33] The flavin **44** was used as a catalyst and molecular O_2 effected the oxidation reaction. This reaction allows high selectivities and good yield to be obtained (Scheme 1.12).

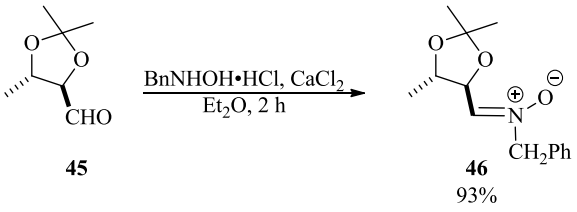


(i) **44** 5 mol %, O_2, NH_2NH_2/H_2O, 60 ^oC, 1 to 6 h

Scheme 1.12

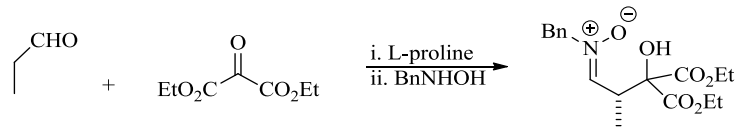
1.3.2.2 Hydroxylamine and carbonyl condensation

A useful and common method for forming nitrones is by treating carbonyl compounds with hydroxylamines. Condensation of aldehydes with hydroxylamine hydrochloride gives nitrones and this method can also be successful with ketones.[23] Philip and co-workers reported that treatment of aldehyde **45** with *N*-benzylhydroxylamine hydrochloride at room temperature gave nitrone **46** in excellent yield (Scheme 1.13).[34]



Scheme 1.13

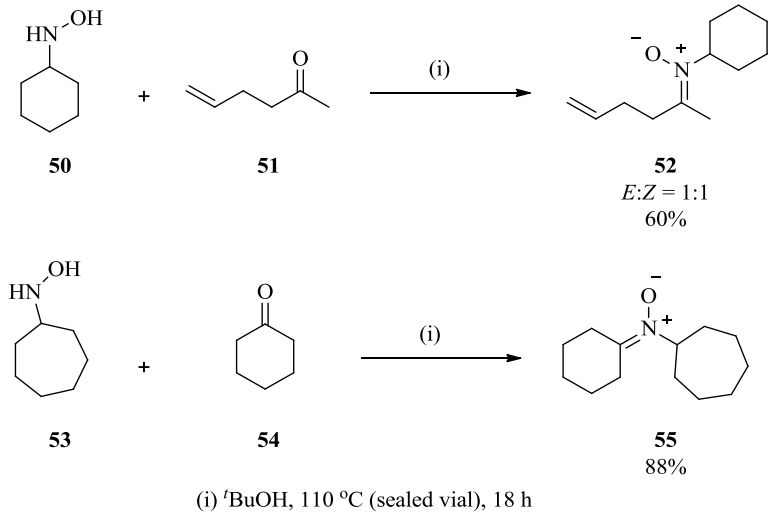
In 2003, formation of a nitrone possessing an α stereocentre was reported by Bøgevig and co-workers.[35] Proline was employed as the catalyst to activate the aldehyde **47** and reaction with ketone **48** gave the aldol product. Finally, the addition of *N*-benzylhydroxylamine *in-situ* formed nitrone **49** (96% ee) in 83% yield (Scheme 1.14).[35]



47 **48** **49**
83%

Scheme 1.14

A 2009 study by Pfeiffer and Beauchemin reported a simple method for the synthesis of nitrones from ketones.[36] The *N*-substituted hydroxylamine **50** and acyclic ketone **51** in ^{t}BuOH were heated in a sealed tube to give ketonitrone **52**. Treating the *N*-substituted hydroxylamine **53** and cyclic ketone **54** gave oxime **55**. This method allowed the formation of acyclic and exocyclic ketonitrones (Scheme 1.15).[36]



Scheme 1.15

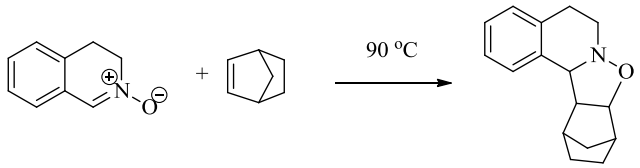
1.4 1,3-Dipolar cycloadditions of nitrones

Out of a wide range of nitrone reactions,[37] the 1,3-dipolar cycloaddition with a dipolarophile is the most useful reaction in which the nitrone behaves as a 1,3-dipole. Nitrones are among the most synthetically useful 1,3-dipolar species, as their cycloaddition reactions with alkenes or alkynes yield isoxazolidines or isoxazolines, respectively, which are suitable intermediates for the synthesis of bioactive compounds, mainly alkaloids. The reductive cleavage of the N–O bond leads to the

formation of 1,3-amino-alcohols that are present in many natural products and biologically active compounds.

1.4.1 [3+2] Intermolecular cycloadditions involving nitrones

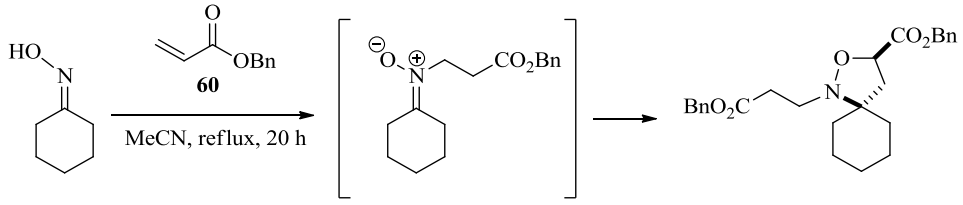
Huisgen and co-workers were the first to report that nitrones could be involved in intermolecular [3 + 2] cycloadditions with alkene dipolarophiles.[38] Nitrone **56** and alkene **57** were heated at 90 ^{o}C to afford cycloadduct **58** in quantitative yield (Scheme 1.16, stereochemistry of **58** was not indicated).



56 **57** **58** 100%

Scheme 1.16

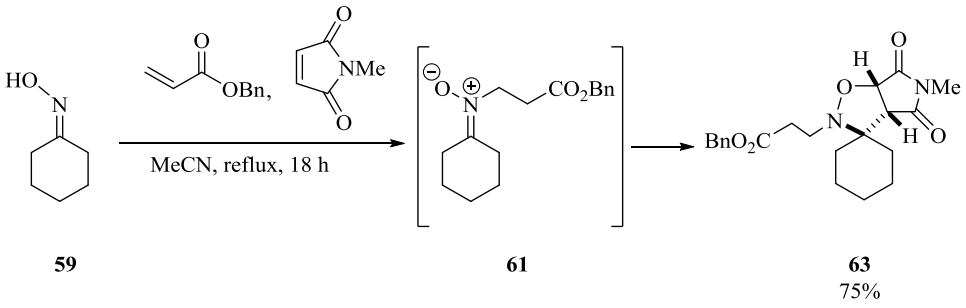
An example of an intermolecular cycloaddition reaction involving Michael addition is shown in Scheme 1.17. Grigg and co-workers showed that reaction between the oxime **59** and benzyl acrylate **60** (which acts as an alkylating agent and a dipolarophile) in acetonitrile for 20 h gave nitrone **61** (Scheme 1.17).[39] The nitrone **61** then underwent intermolecular 1,3-dipolar cycloaddition to afford isoxazolidine **62** in 73% yield.



59 **61** **62** 73%

Scheme 1.17

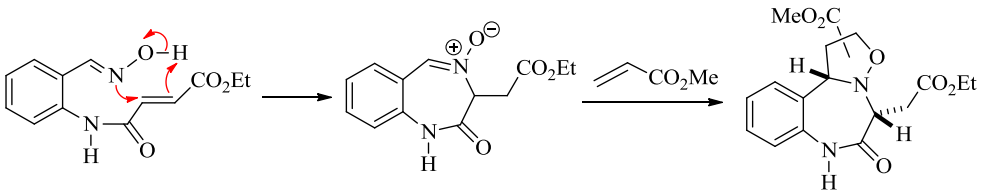
A similar reaction can be set up in which the alkylating reagent and the dipolarophile are different. An example is shown in Scheme 1.18 to give the isoxazolidine product **63**.[39]



59 **61** **63**
75%

Scheme 1.18

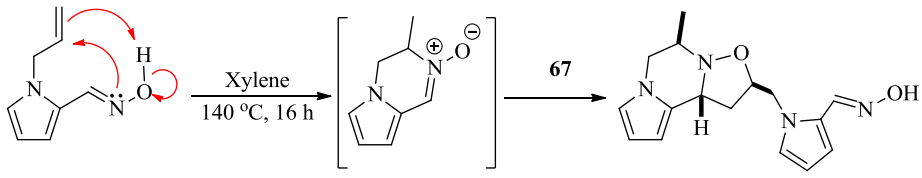
A study[40] by Heaney and co-workers investigated the intermolecular 1,3-dipolar cycloaddition reaction of the nitrone derived from oxime **64**. The oxime **64** underwent cyclization to generate the nitrone **65**. This was heated with methyl acrylate in toluene for 18 h to afford regioisomeric adducts **66** in quantitative yield in a 2:1 ratio (Scheme 1.19).



64 **65** **66**
quantitative

Scheme 1.19

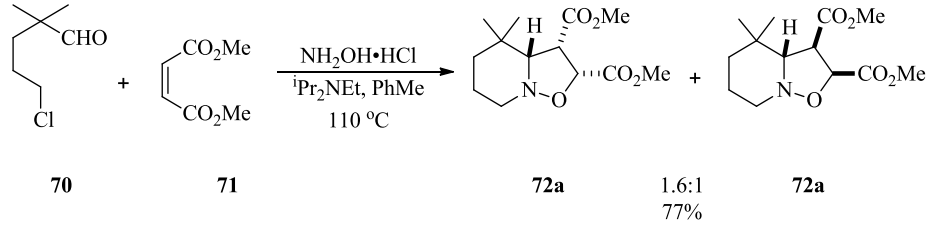
A cyclisation of oxime **67** with an alkene gave the nitrone **68**. Subsequently, the alkene moiety of another molecule of oxime **67** participates in intermolecular 1,3-dipolar cycloaddition reaction to give the cycloadduct **69** (Scheme 1.20).[30] Based on this, the proposed mechanism is that the reaction proceeds *via* an oxime ene-like reaction.



67 **68** **69**
52%

Scheme 1.20

In 2009, Coldham and co-workers reported an intermolecular reaction between the aldehyde **70** and dipolarophile **71** in toluene to form cycloadducts **72a** and **72b** in 77% yield (Scheme 1.21).[41] The condensation reaction took place then the oxime underwent cyclisation to give a nitrone followed by intermolecular 1,3-dipolar cycloaddition to afford the cycloadducts in 1.6:1 ratio.

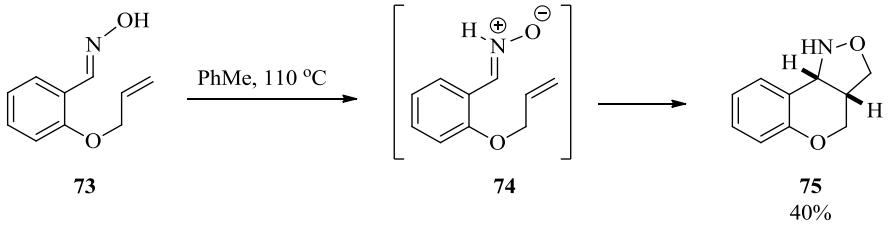


Scheme 1.21

Recent work demonstrated successful reaction even with enolisable aldehydes lacking the *gem*-dimethyl group.[42]

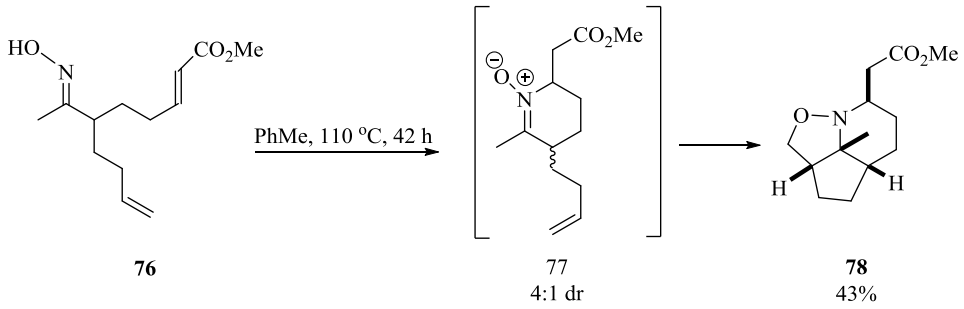
1.4.2 [3+2] Intramolecular cycloadditions involving nitrones

The intramolecular cycloaddition of 1,3-dipoles provides a versatile method to form the heterocyclic rings in bicyclic *O*-polycyclic systems. Oppolzer reported the first example of the 1,2-prototropy and subsequent cycloaddition reaction. Oxime **73** was heated under reflux in toluene to give isoxazolidine product **75** in moderate yield (Scheme 1.22).[43] It is believed that the reaction proceeded *via* nitrone **74**.



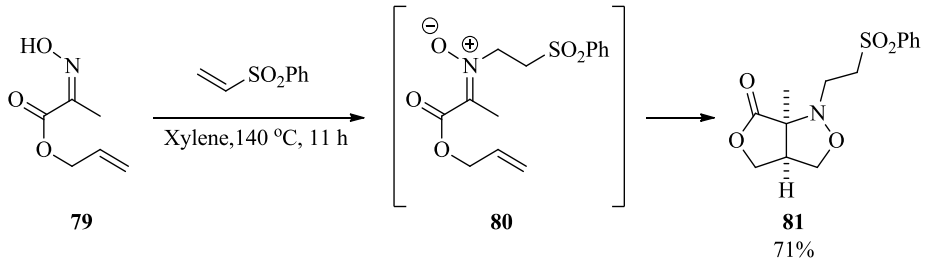
Scheme 1.22

An intramolecular reaction is demonstrated in Scheme 1.23, where the substrate oxime bears both the alkylating agent and the dipolarophile. On heating oxime **76** at reflux in toluene, cyclisation then 1,3-dipolar cycloaddition reaction took place to result in tricyclic product **78** *via* the intermediate nitrone **77**.[44]



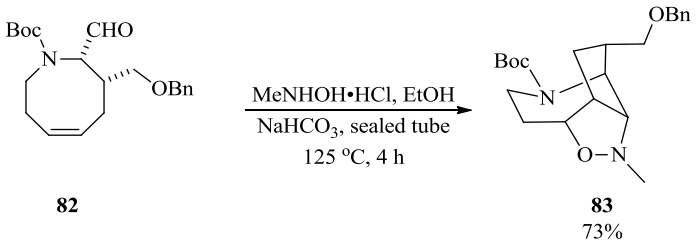
Scheme 1.23

Scheme 1.24 provides an example where the dipole is derived from oxime **79**, which undergoes conjugate addition with phenyl vinyl sulfone followed by a 1,3-dipolar cycloaddition reaction *via* the nitrone **80**, to give isoxazolidine **81** in good yield.[45]



Scheme 1.24

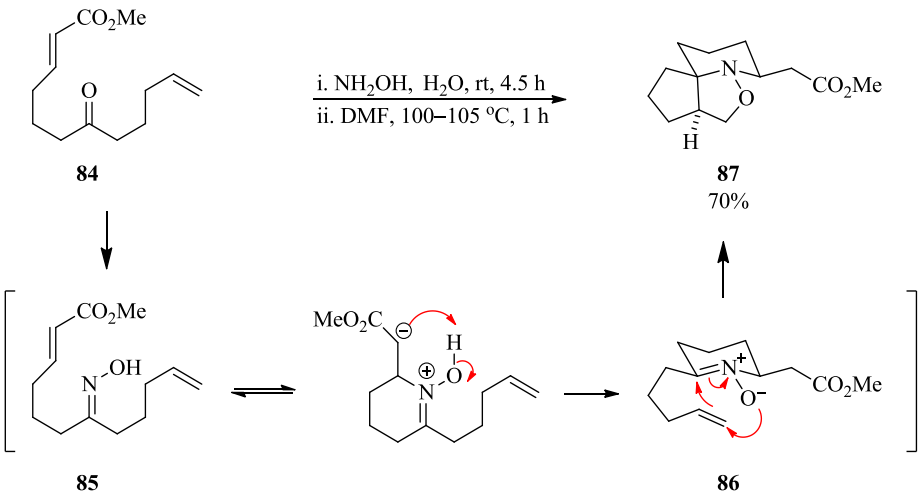
A 2011 study by Coldham and co-workers demonstrated an intramolecular dipolar cycloaddition of aldehyde **82**. A mixture of aldehyde **82** with *N*-methylhydroxylamine and sodium bicarbonate in ethanol was heated in a sealed tube to give cycloadduct **83** in 73% yield (Scheme 1.25).[46]



Scheme 1.25

1.5 Cascade processes including cycloaddition of a nitrone

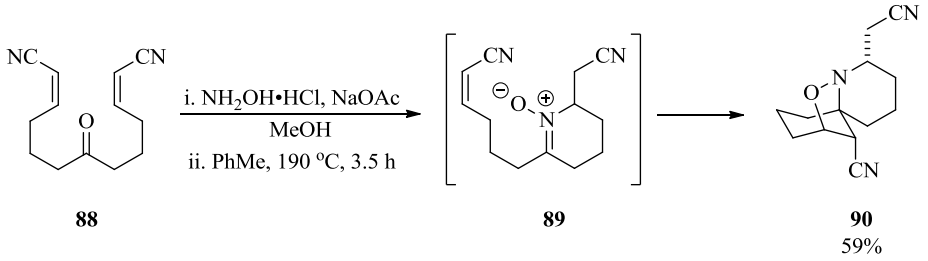
Cascade chemistry using cycloaddition reactions can lead to a variety of ring systems such as bridged and fused modes. Tietze defined cascade reactions as "reactions where two or more bond-forming transformations occur under the same reaction conditions, without the addition of further reagents or catalysts".[47] Grigg and co-workers have shown that a cascade process involving the intramolecular conjugate addition of an oxime, followed by intramolecular cycloaddition, leads to compounds containing three new rings. Thus, treating ketone **84** with hydroxylamine yielded oxime **85**, which underwent conjugate addition to give nitrone **86**, then, 6-5-5 spiro cycloadduct **87** was obtained by cycloaddition with the terminal olefin in 70% yield (Scheme 1.26).[44]



Scheme 1.26

Based on this, a range of ketones of varying of chain length and position of the dipolarophile were synthesized. For example, increasing the chain length between the oxime and dipolarophile would produce a 6-5-6 spiro system. Additionally, increasing the length of the tether between the nitrone and the dipolarophile resulted in less regioselective cycloaddition reactions, as other transition states can now be accessed. The strategy of oxime formation followed by Michael addition and [3 + 2] cycloaddition has been used by several researchers to synthesise the azaspirocyclic core of (±)–histrionicotoxin.[48-50] A 2004 study by Stockman and co-workers showed that condensing ketone **88** and hydroxylamine leads to nitrone **89**. This was then

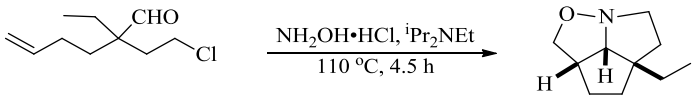
heated at reflux in toluene in a sealed tube to yield the thermodynamically favoured cycloadduct **90** (Scheme 1.27).[49]



88 **89** **90** 59%

Scheme 1.27

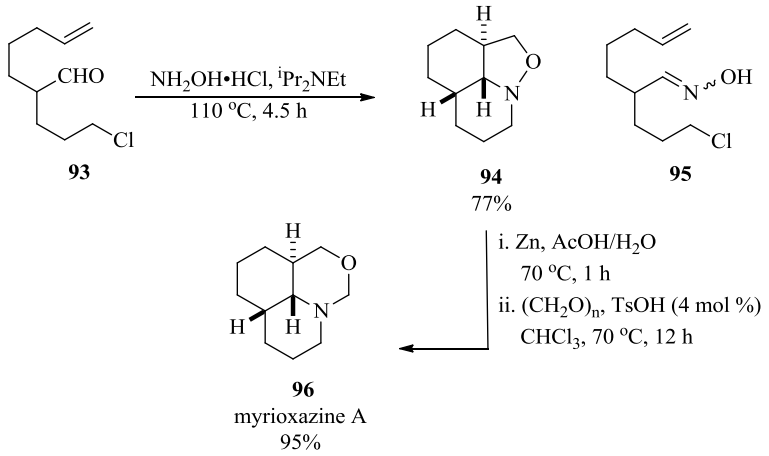
Coldham and co-workers investigated the condensation, cyclisation, cycloaddition cascade reaction for the synthesis of tricyclic compounds. Aldehyde **91** was treated with hydroxylamine hydrochloride and diisopropylethylamine in toluene, to give cycloadduct **92** in 64% yield as a single isomer (Scheme 1.28).[51]



91 **92** 64%

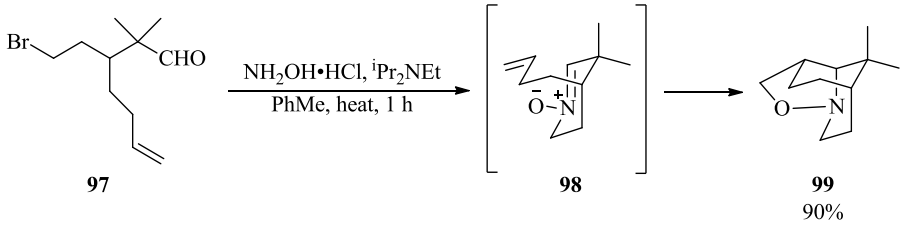
Scheme 1.28

In 2009, Coldham and co-workers reported the synthesis of myrioxazine A by treating aldehyde **93** with hydroxylamine in PhMe at 110 °C. This gave the cycloadduct **94** as a single isomer in 77% yield (with some oxime **95**, which could be converted to **94** on further heating) (Scheme 1.29).[52] This fused cycloadduct was converted to the natural product myrioxazine A **96** in two steps. The oxime **95** presumably cyclised to displace chloride to give the intermediate nitrone which undergoes dipolar cycloaddition.



Scheme 1.29

Later, Coldham and co-workers used cascade chemistry for the formation of one-carbon bridged systems.[53] Tethering the dipolarophile to the *β*- rather than *α*-carbon of the aldehyde can lead to a bridged ring system. For example, the aldehyde **97** was treated with hydroxylamine in PhMe to yield the cycloadduct **99** as a single stereoisomer in 90% yield, and likely occurred *via* the intermediate nitrone **98** (Scheme 1.30).



Scheme 1.30

This introduction has presented examples of cycloaddition and cascade reactions and relevant methods of the synthesis of nitrones and their uses in cascade reactions. We were interested in utilizing this chemistry for the synthesis of some novel isoxazolidines and towards the synthesis of compounds within the iboga alkaloid family. The next chapters will describe this application.

Chapter 2 Cycloaddition of Nitrones Derived from Quaternary Aldehydes

2.1 Introduction

As discussed in the previous chapter, the intramolecular dipolar cycloaddition reactions of nitrones were discovered over 50 years ago.[54] The intramolecular nitrone-alkene cycloaddition reaction can give bridged or fused isoxazolidines (Figure 2.1).[40] Extensive research has been done into the use of nitrones in the intramolecular 1,3-dipolar cycloaddition with a dipolarophile. When the nitrone and dipolarophile are located on the same molecule, a cycloaddition can take place to form a bicyclic molecule. These bicyclic intermediates are very important in the synthesis of natural products. Generally, this type of reaction is synthetically useful, due to its high regio- and stereo- selectivity.[55]

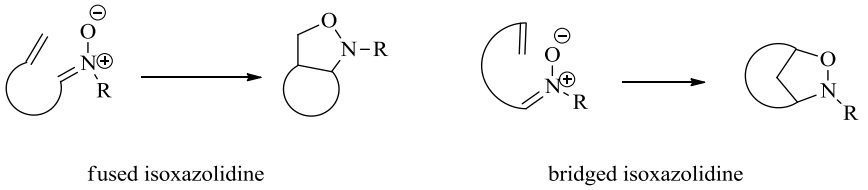
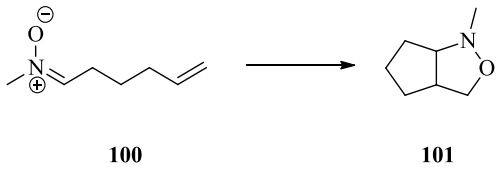


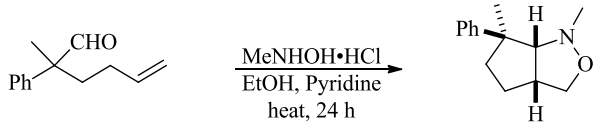
Figure 2.1

Considerable research into intramolecular nitrone cycloaddition has been reported.[56-60] LeBel[61] was the first person who reported the intramolecular cycloaddition reaction of a simple alkene **100** with a nitrone to form a fused bicyclic ring, isoxazolidine **101** (Scheme 2.1). Our research group is interested in this chemistry and extensive work has been done towards natural product synthesis using nitrones.[46,51,61,62]



Scheme 2.1

A lot of initial work has been reported which is related to the intramolecular cycloadditions of nitrones bearing an aromatic substituent attached β to the nitrogen atoms.[37,63-65] To our knowledge, there has been only one use of a quaternary α-aromatic aldehyde **102** in an intramolecular cycloaddition, which was reported by Vinick and co-workers, where a nitrone bearing a neighbouring aromatic substituent and a methyl group was used to give one isomer (Scheme 2.2). The stereochemistry arises from the fact that the less bulky methyl group prefers to locate in the *endo* position, forming the cycloadduct **103**.[66]



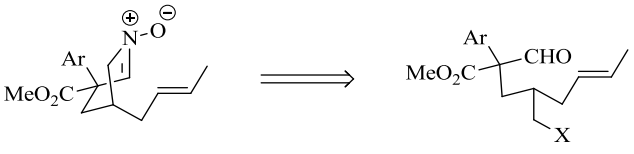
102 **103** 57%

Scheme 2.2

2.2 Synthesis of isoxazolidine 5-5 ring system

2.2.1 Synthesis of requisite aldehyde

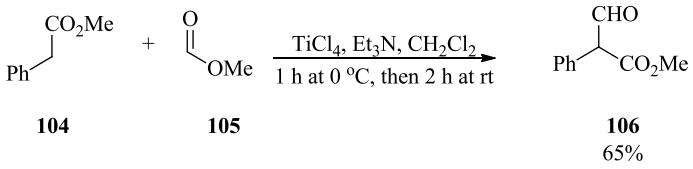
Polycyclic amines are found in many alkaloids, especially those that not only contain an amino group but an aromatic ring as well, often derived from β-arylethylamine precursors. The plan was to investigate the cycloaddition of nitrones that would lead to β-arylethylamines. The ultimate aim was to make compounds of the iboga family, which has this β-arylethylamine core (see chapter 3), and could derive from a quaternary aldehyde (Figure 2.2). However, the initial plan was to study this approch without the CH_2X branch.



X = Br, Cl, I

Figure 2.2

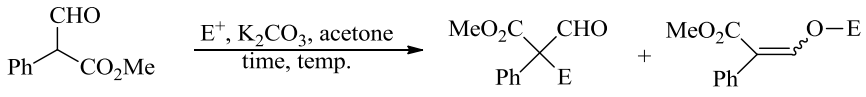
To synthesize the key aldehyde **110**, ester **104** was treated with methyl formate **105** in the presence of titanium tetrachloride and triethylamine. This gave the aldehyde **106** in 65% yield (Scheme 2.3).[67]



104 **105** **106** 65%

Scheme 2.3

The alkylation step involved the reaction of aldehyde **106** with an electrophile and potassium carbonate in dry acetone (Scheme 2.4).[68] Unfortunately all the efforts to optimise the conditions failed to afford the desired product **107** (Table 2.1). ^{1}H NMR spectroscopy for the crude products showed no aldehyde peak and we proposed that *O*-alkylation took place instead of *C*-alkylation. Treatment of aldehyde **106** with allyl bromide in the presence of potassium carbonate in acetone gave two compounds in 60% yield and 30% yield (entry 1). Mass spectrometry showed that both compounds had the same mass. ^{1}H NMR spectra for both compounds showed no aldehyde peak, and instead a singlet peak at 7.64 ppm was observed for the major product. A singlet peak at 6.75 ppm was also noticed for the minor compound. As a result, we suggest that *O*-alkylation took place and these peaks belong to CH protons for *E* and *Z* isomers **108**. For the other reactions (entries 2–6) the ^{1}H NMR of crude products showed no aldehyde peak.



106 **107** **108**

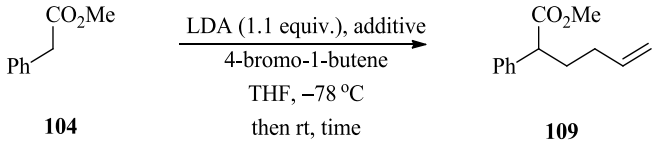
Scheme 2.4

Entry	E^+	Time	Temp. ^oC	Yield% 107	Yield% 108
1	Allyl bromide	45 min	50	0	60/30[a]
2	Allyl bromide	2h	rt	0	-
3	Benzylbromide	45 min	50	0	-
4	Benzylbromide	2 h	rt	0	-
5	Methyl iodide	2 h	rt	0	-
6	4-bromo-1-butene	2 h	rt	0	-

[a] these are separated by column chromatography

Table 2.1

In a slightly different approach, we started with ester **104**, which on treatment with LDA and 4-bromo-1-butene gave alkylated compound **109** (Scheme 2.5). Due to the low yield some optimisation was made to increase the yield. DMPU was used for this purpose, and gave the product **109** in 67% yield (Table 2.2, entry 4).



104 **109**

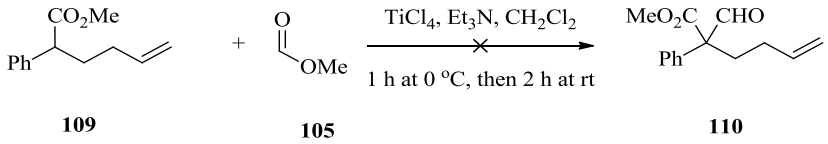
Scheme 2.5

Entry	Time	Additive	Yield%
1	18 h	–	27
2	2 h	DMPU	50
3	6 h	DMPU	60
4	18 h	DMPU	67

Table 2.2

Treating compound **109** with methyl formate **105** in the presence of titanium tetrachloride and triethylamine produced an inseparable mixture (Scheme 2.6). No

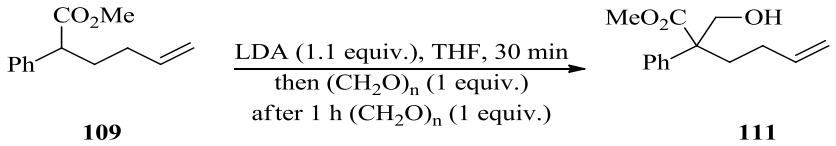
identifiable desired product was observed, either by mass spectrometry or by ^{1}H NMR spectroscopy.



109 **105** **110**

Scheme 2.6

As an alternative, the alkylation of compound **109** using LDA and paraformaldehyde afforded alcohol **111** (Scheme 2.7). Firstly, to a suspension of compound **109** and LDA at –78 °C, paraformaldehyde (1.1 equiv.) was added to give a low yield of alcohol **111** (Table 2.3). Slightly higher yields were obtained at –20 °C, particularly on increasing to two equivalents of paraformaldehyde. A yield of 70% was obtained when 1.0 equivalent of electrophile was added followed by a further 1.0 equivalent after 1 h (Table 2.3, entry 4).



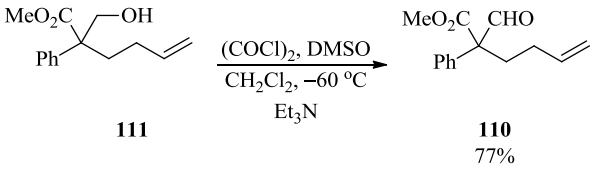
109 **111**

Scheme 2.7

Entry	$(CH_2O)_n$ equiv.	Temp °C	Yield %
1	1.1	–78	30
2	1.1	–20	40
3	2.0	–20	50
4	2.0	–20 to rt	70

Table 2.3

Subsequently, alcohol **111** was oxidised with Swern oxidation[69] to give the aldehyde **110** in 77% yield (Scheme 2.8).

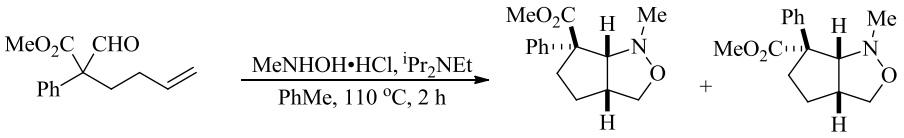


111 **110** 77%

Scheme 2.8

2.2.2 Cyclisation-cycloaddition reaction

From the outcome of the previous results in the group the best result was obtained from the reaction of *N*-alkylhydroxylamines, therefore we decided to start with the same conditions. Aldehyde **110** was heated under reflux with *N*-methylhydroxylamine hydrochloride (1.5 equiv.) and diisopropylethylamine (2.5 equiv.) in toluene. After 2 h TLC analysis showed that all the starting material was consumed, so the mixture was allowed to cool to room temperature. After purification two cycloadducts were isolated, **112a** in 54% yield and **112b** in 32% yield (Scheme 2.9). The *cis* ring junction of both cycloadducts was revealed by single crystal X-ray structure analyses (Figure 2.3).



110 **112a** **112b**

1.6:1
86%

Scheme 2.9

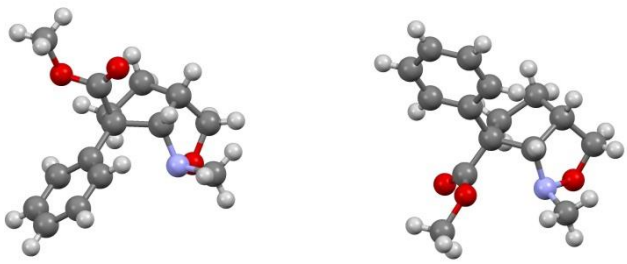


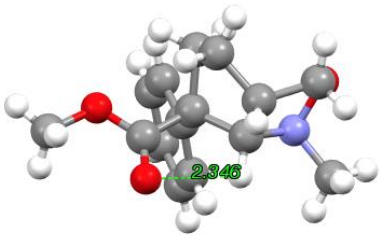
Figure 2.3 X-ray structure of compounds **112a** and **112b**

2.2.3 Stereochemistry of 112a and 112b

The stereochemistry of the major cycloaddition product **112a** must arise from a preference for one transition state (Figure 2.4c) of the nitrone in the cycloaddition. A study by LeBel[54,55] suggested that both *syn*- and *anti*- configurations of the intermediates lead to a *cis* ring junction.

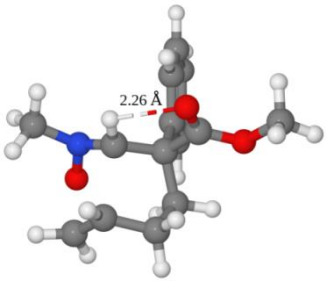
This reaction is a direct comparison with the formation of the cycloadduct **103** (Scheme 2.2, page 24), where a single stereoisomer was reported.[66] In the study by Vinick and co-workers, the phenyl group has a stronger preference for the *exo* position than the methyl group. However, in our work there is a preference for the methyl ester, rather than the phenyl group, to be in the *exo* position. A possible reason to explain why the major cycloadduct came with the *exo* position of the methyl ester is evident in the X-ray crystal structure of **112a** (Figure 2.4a). The ester carbonyl oxygen atom and the proton at the ring junction α to the nitrogen atom are only 2.346 Å apart and the carbonyl is almost directly in line with the C−H bond. A 2015 report by Sartillo-Piscil and co-workers discusses the stabilisation of molecular conformation *via* intramolecular (N)C–H_{α}·····O(C) hydrogen interaction in a cyclic amide.[70] In collaboration with Dr. Anthony Meijer in the Department of Chemistry, University of Sheffield, DFT calculations show that this interaction (calculated C=O·····H−CN distance = 2.26 Å) could be present in the transition state for the cycloaddition (Figure 2.4b) and in the nitrone. This would lead to the preferred transition state **113**, which gives the isomer **112a**.

a)



112a

b)



113

c)

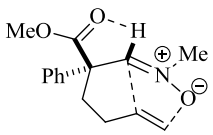
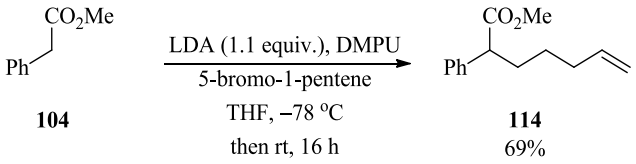


Figure 2.4 a) X-ray of **112a**, b) DFT structure of transition state, c) transition state of **112a**

2.3 Synthesis of isoxazolidine 6-5 and 5-7 ring systems

2.3.1 Synthesis of aldehyde 116

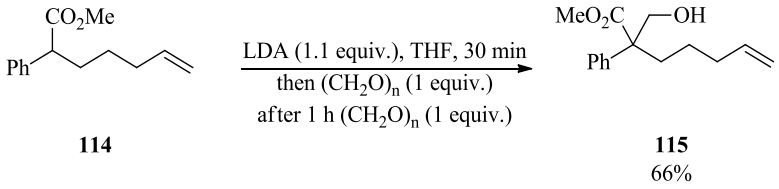
To investigate the effect of the distance between the aldehyde and the alkene on the ring formation, we predicted that alkylation of ester **104** with 5-bromo-1-pentene would provide a longer tether to attempt cycloaddition to give a cyclohexane ring system. In order to prepare the key aldehyde precursor, following the same chemistry as before, the ester **104** was alkylated using 5-bromo-1-pentene to give the ester **114** in 69% yield (Scheme 2.10).



104 **114** 69%

Scheme 2.10

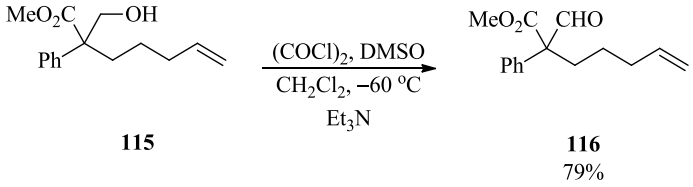
The ester **114** underwent a second alkylation with paraformaldehyde, using the previous conditions to give alcohol **115** in good yield (Scheme 2.11).



114 **115** 66%

Scheme 2.11

The alcohol **115** was oxidised by Swern oxidation[69] to afford the desired aldehyde **116** in 79% yield (Scheme 2.12).

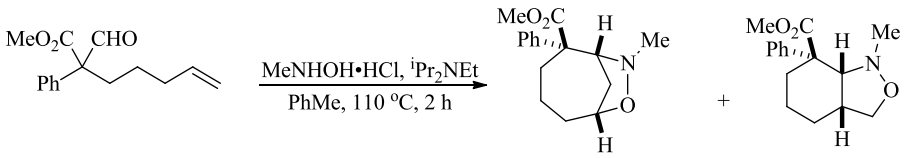


115 **116** 79%

Scheme 2.12

2.3.2 Cycloaddition of the nitrone derived from aldehyde 116

The aldehyde **116** was heated at reflux with *N*-methylhydroxylamine hydrochloride and diisopropylethylamine in toluene to give cycloadducts **117a** and **117b** as a mixture of regioisomers (ratio 2:1) in good yield (assigned based on ^{1}H NMR and ^{13}C NMR spectroscopy) (Scheme 2.13). The two isomers were difficult to separate by flash column chromatography. Successful efforts were carried out to separate the major regioisomer **117a** by recrystallisation. The cycloadduct **117a** was revealed by single crystal X-ray structure analysis (Figure 2.5).



116 **117a** 2:1 75% **117b**

Scheme 2.13

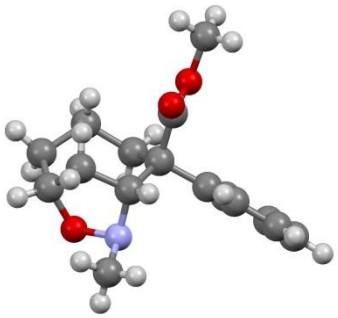


Figure 2.5 X-ray structure of compounds 117a

2.3.3 Stereochemistry

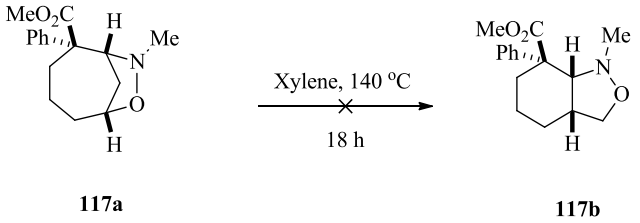
The stereochemistry of the major cycloadduct **117a** was established by single crystal X-ray analysis. Increasing the tether length allows easier access to the transition state to form the bridged cycloadduct.[44] This will be discussed later in this chapter (see section 2.4.2).

The ^{1}H NMR spectra showed that the ring junction proton at 4.66 ppm appeared as a doublet of doublets with *J* values of 9.0 and 4.0 Hz, and the proton at 3.88 ppm as a doublet of doublets with *J* values of 8.0 and 1.5 Hz. The COSY spectrum shows no interaction between these protons. The HSQC spectrum showed that protons at 4.66 ppm and 3.88 ppm are attached to carbons 77.3 ppm and 72.7 ppm respectively. The bridge carbon CH_2 at 32.1 ppm is correlated to proton at 2.74 ppm that appeared as a doublet of triplets *J* values of 13.5 and 9.0 Hz, and proton at 2.30–2.27 ppm appeared as a multiplet (see Appendix 7). The stereochemistry of the ester group was confirmed by the single crystal X-ray analysis (Figure 2.5, and Appendix 3).

The elucidation of the structure of the second isomer **117b** was based on ^{1}H NMR and HSQC spectroscopy. The two CH signals of the OCH_2 appear as a doublet of doublets at δ 4.06 ppm and a doublet at δ 3.52 ppm. The interaction between the two H of the ring junction was confirmed by ^{1}H COSY spectra, and the coupling of these protons is 6.0 Hz, corresponding to *cis* orientation.[71] The HSQC spectrum shows that the ring junction protons at 3.43 ppm and 2.93–2.87 ppm are attached to carbons at 73.2 ppm and 43.4 ppm respectively (see Appendix 8). The stereochemistry of the ester group was proposed based on the previous result with major isomer **112a** and

117a in which the ester group preferred the *exo* position. The mixture of regioisomers was thought to arise from a kinetically controlled reaction with a lower transition state energy for forming isomer **117a**, rather than by a reversible thermodynamically controlled process.

A 2006 study by Weinreb and co-workers reported the retrocycloaddition reaction on a bridged cycloadduct to form fused cycloadduct.[72] So, to test the possibility of the retro 1,3-dipolar cycloaddition reaction, the bridged cycloadduct **117a** was heated in xylene. After 18 h, only the starting material was recovered (Scheme 2.14). If the cycloaddition were under thermodynamic control then a 2:1 mixture of adducts would be expected.

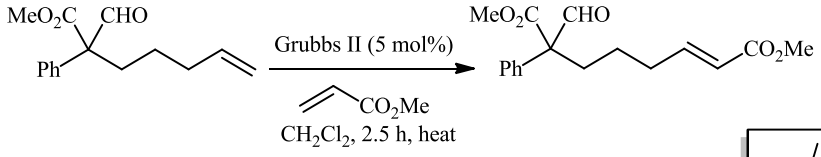


117a **117b**

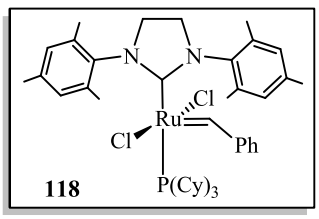
Scheme 2.14

2.4 Cross-metathesis of the aldehyde

We wanted to investigate the effect of an activated alkene on the regioselectivity of the cycloaddition reaction. Therefore, an electron-withdrawing group such as a methyl ester was introduced to the terminal alkene *via* a cross metathesis reaction of alkene **116** using Grubbs' 2nd generation catalyst[73] **118** and methyl acrylate to give the new aldehyde **119** in a good yield (Scheme 2.15).



116 **119** 80%

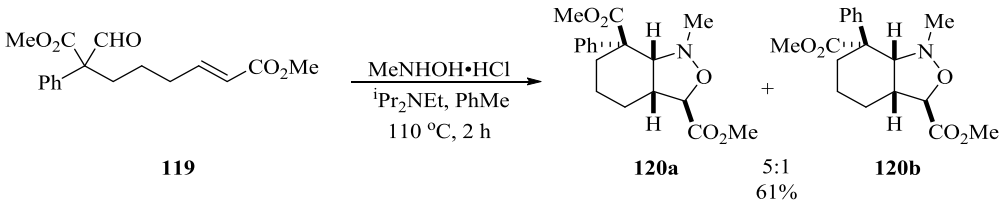


118

Scheme 2.15

2.4.1 Cycloaddition reaction of aldehyde 119

We were pleased to find that heating aldehyde **119** at reflux with *N*-methylhydroxylamine hydrochloride and diisopropylethylamine in toluene yielded a single regioisomer and was highly stereoselective in favour of the isomer **120a** (Scheme 2.16). Clearly, there is a preference to form a fused ring and not a bridged ring, compared to the corresponding reaction with unsubstituted alkene **116**. Figure 2.6 shows the single crystal X-ray structure of the cycloadduct.



Scheme 2.16

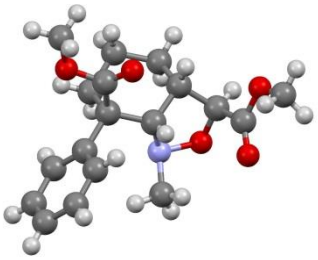


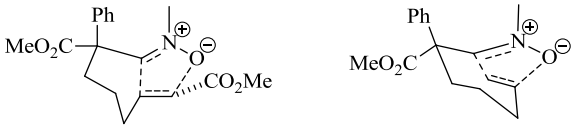
Figure 2.6 X-ray structure of compound 120a

The single crystal X-ray analysis confirmed the stereochemistry of the major isomer **120a**, and shows similarity to all previous cycloadducts, in which the methyl ester group favours the *exo* position. Moreover, the regioselectivity of the cycloaddition reaction was significantly affected by the terminal ester group of the alkene as only a fused ring was observed.

2.4.2 The regioselectivity of the cycloaddition reaction

It is instructive to discuss the regioselectivity of this reaction in comparison to aldehyde **116** in which the bridged cycloadduct is the major product. A 2011 study by Shing and So reported that the *α,β*-unsaturated ester has no effect on the

regioselectivity of the intramolecular 1,3-dipolar cycloaddition reaction with their nitrone to form the bridged cycloadduct rather than the fused cycloadduct.[74] They proposed that the steric effect of the substituted adjacent carbon to the nitrone controls the orientation to give the *endo*–mode.[74] However, Grigg and co-workers showed that the rate and regioselectivity could be affected in the presence of a withdrawing group.[44] In their example the nitrone intramolecular cycloaddition reaction favoured the fused 6/6 rather than the bridged 5/7 ring adduct.[44] Clearly our result shows that the substituent ester group led to a significant change in the selectivity from bridged to fused cycloadducts. The reason behind the stereochemical outcome must be due to the enhancing of the transition state **121** by the terminal ester substituent on the dipolarophile. Molecular models show that the formation of compound **117a** required arranging the pendent alkenes to be oriented to inside the molecule (structure **122**, Figure 2.7). Therefore, introducing a substituent group such as methyl ester could restrict such arrangement sterically and work against this disposition. In intermolecular reactions, generally the nitrone oxygen prefers to add to the more hindered site.[75] Based on this, the fused cycloadduct is formed as a major product and no bridged one is observed.[44,76]



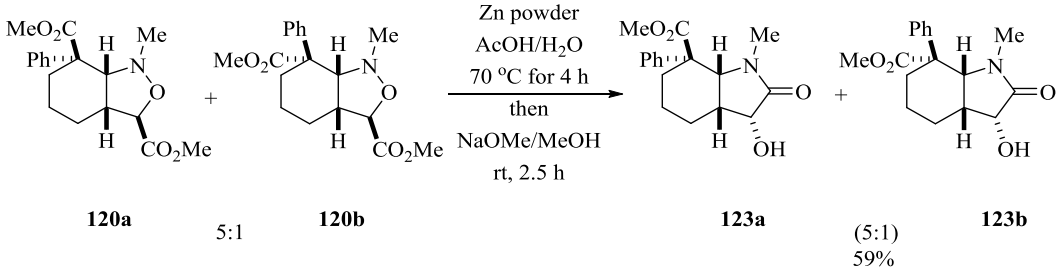
121 **122**

Figure 2.7

2.4.3 Cleavage the N–O bond

The mixture of cycloadducts **120** was treated with zinc in acetic acid to break the N–O bond. Subsequent cyclisation of the amine onto the ester yielded the lactam **123** (Scheme 2.17). Unfortunately, the cyclisation proceeded incompletely, and stirring with sodium methoxide in methanol was required to complete the process. The lactam was isolated together with a small amount of the other stereoisomer in good yield (Scheme 2.17). The major isomer **123a** was recrystallized and the relative stereochemistry was verified by single-crystal X-ray diffraction (Figure 2.8). The

major isomer was confirmed by the ^{1}H NMR spectroscopy of the mixture and of the recrystallized isomer.



120a 5:1 **120b** **123a** (5:1) 59% **123b**

Scheme 2.17

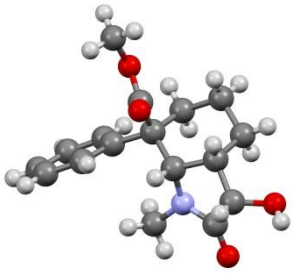


Figure 2.8 X-ray structure of compound **123a**

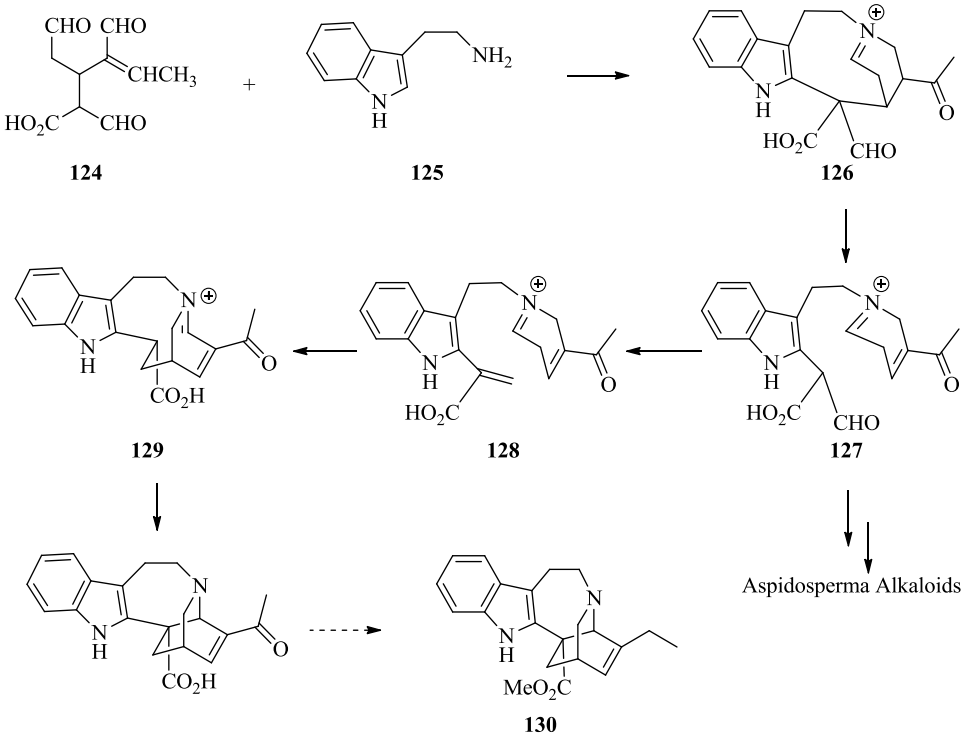
4.5 Conclusion

We have synthesized some aldehydes with quaternary α carbon stereocentres bearing a phenyl, an alkenyl, and a methyl ester group. We subsequently demonstrated the amenability of these aldehydes to intramolecular nitrone cycloadditions to produce a range of isoxazolidine 5-5, 6-5 and 5-7 ring systems. In all cases the methyl ester group preferred the *exo* position over the phenyl group. The regio- and stereochemical outcomes are affected by the length of the tether to the alkene dipolarophile and by the nature of the dipolarophile (terminal alkene or with attached electron-withdrawing group). For example, introducing a methyl ester on the alkene moiety then cycloaddition resulted in a preference to form the fused ring over the bridged ring systems. We investigated the cleavage of the N–O bond then cyclisation to afford the lactam. The chemistry allows the synthesis of bicyclic isoxazolidines containing an α-phenylethylamine moiety. This results from this chapter have published.[77]

Chapter 3

3.1 Biosynthesis of iboga alkaloids

Several publications surrounding the biosynthesis of the iboga alkaloids have been published, mostly concentrating on the existence of the tryptamine fragment present in these compounds. Initial work into this area by Wenkert[78] suggested that the synthesis started from the *seco*-prephenate-formaldehyde (SPF) unit **124** which is present in some plants. It was postulated that the SPF unit could be trapped by tryptamine (**125**) in the cell giving iminium ion **126**. At this point, it was thought that a synthesis pathway could diverge with access to both the iboga and aspidosperma alkaloids possible. Proceeding *via* cyclic iminium species **126**, **127** and **128** access to structures similar to the iboga alkaloid catharanthine **130** was thought to be possible (Scheme 3.1).

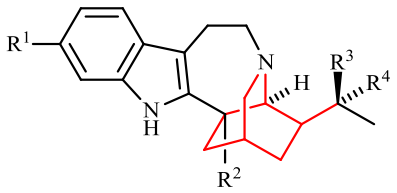


124 125 126 127 128 129 130

Scheme 3.1

3.2 Iboga alkaloids

Iboga alkaloids are found in African shrubs of the Tabernanthe genus.[79] They are indole containing alkaloids which are pharmacologically active. They all contain a seven membered, fused ring system with a rigid isoquinuclidine ring (Figure 3.1).



R^1 = H or OMe, R^2 = H or CO_2Me
R^3 = H or OH, R^4 = H or OH

Figure 3.1 The General Structure of iboga alkaloids, isoquinuclidine shown in red

To date several iboga alkaloids have been characterised as having pharmacological properties.[80,81-83] The indoloazepine ring is a key structural component of the iboga alkaloids. Several routes have been published towards the synthesis of the indoloazepine ring system. Examples of members of the iboga alkaloids include ibogamine **131**,[84] ibogaine **132**,[85,56] heyneanine **133**,[86] 18-methoxycoronaridine **134**,[84,87] isovoacristine **135**,[87] 19(*R*)-hydroxyibogamine **136**,[88] cononuridine **137**,[82] and catharanthine **130**[80] (Figure 3.2).

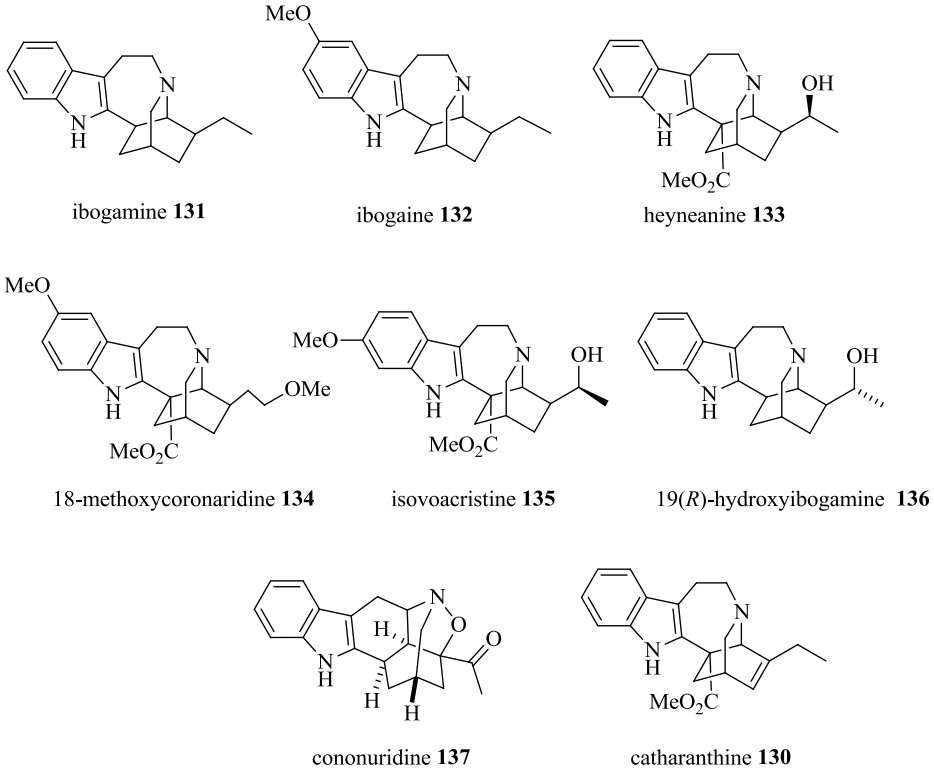


Figure 3.2

3.3 Pharmacological properties of iboga alkaloids

The pharmacological properties of iboga alkaloids have been widely studied.[89-93] Iboga alkaloids have attracted attention of many researchers due to their reported ability to treat the human addition to several drugs, alcohol and cocaine.[93] Ibogaine **132** showed a psychoactive effect based on the anecdotal observations.[94] It was reported that using ibogaine reduced the self-administration of morphine and cocaine.[95] Due to their hallucination side effect at high doses, this has not been used as a medication.[96] Additionally, it shows some degeneration of cerebellar Purkinje cells.[97] Glick and Kuehne reported that 18-methoxycoronaridine **134** is a selective inhibitor of the *α3β4* nicotinic receptor.[98] This possess anti-addiction, anti-fungal, anti-lipase, anti-HIV, anti-leishmanicide and anti-cholinesterasic properties.[99,100] Another example, 19(*R*)-hydroxyibogamine **136** shows marked antibiotic activity.[88]

3.4 Retrosynthetic strategies of iboga alkaloids

Some retrosynthetic strategies of iboga alkaloids are summarized in Figure 3.3. The major routes of the syntheses that have been reported are through the strategy of forming *β*-(indolylacetyl or indolylethyl) isoquinuclidines or indolyl isoquinuclidines. Some of these will be discussed in this chapter.

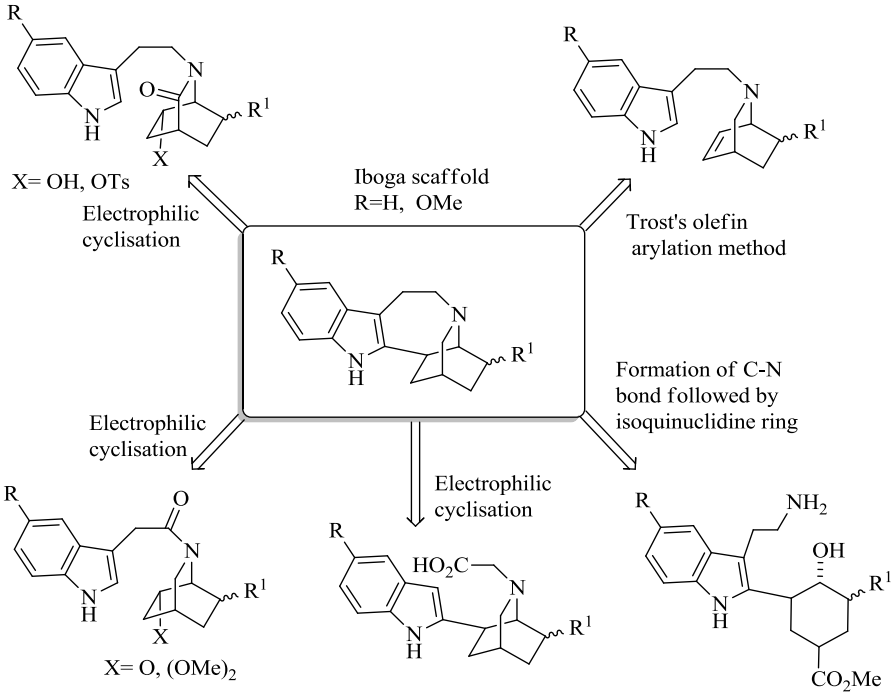


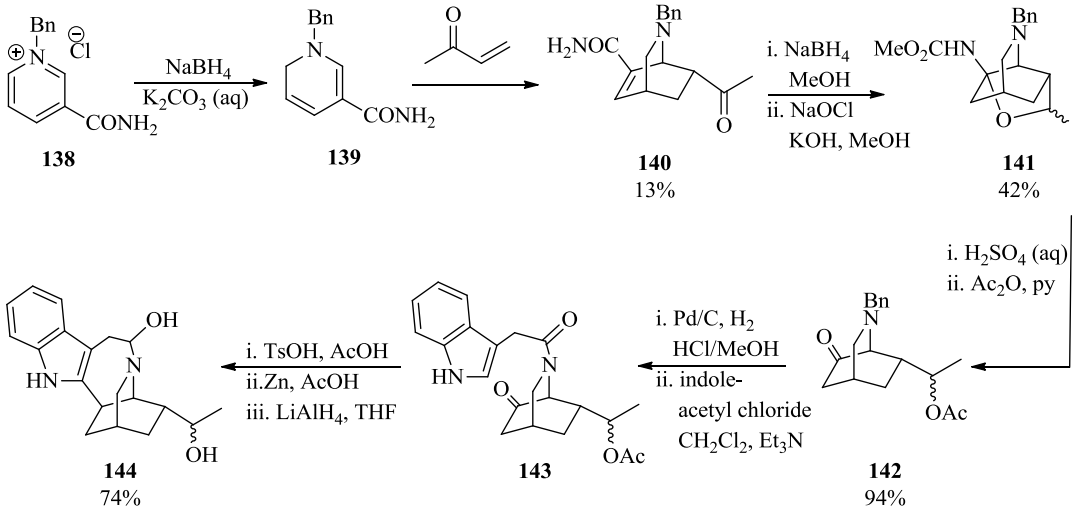
Figure 3.3

3.5 Synthesis of some iboga alkaloids

3.5.1 Büchi's synthesis of ibogamine

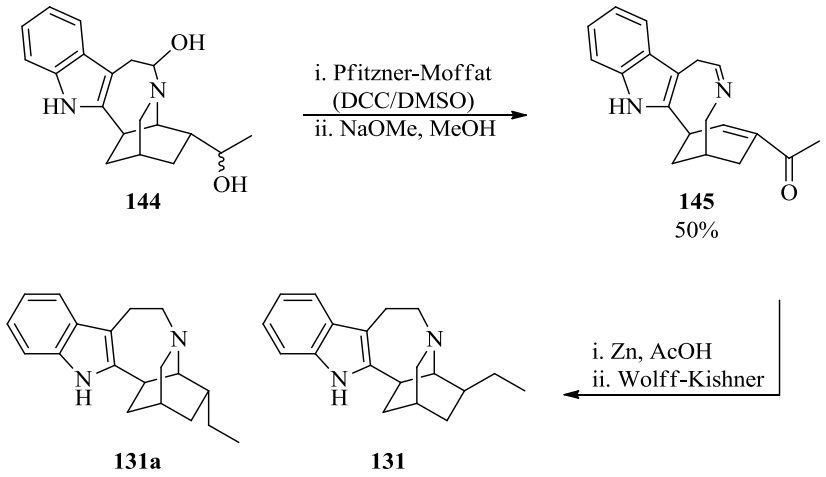
Büchi and co-workers were the first to report a synthesis of an iboga alkaloid in 1965 (Scheme 3.1).[101] They started with a simple pyridine derivative **138** which was reduced using aqueous potassium carbonate and sodium borohydride to give a complex mixture of three dihydropyridine derivatives. From this mixture, only one dihydropyridine **139** could undergo a Diels-Alder reaction with methyl vinyl ketone, to give isoquinuclidine **140** in 13% yield over two steps. Further reduction using

sodium borohydride in methanol afforded a mixture of alcohols. Sodium hypochlorite was used to promote the rearrangement of the amide to give the tricyclic urethane **141** in 42% yield over two steps. Hydrolysis using aqueous sulfuric acid and acetylation using acetic anhydride in pyridine gave acetoxyketone **142** in 94% yield. To introduce the indole ring, **142** was hydrogenated and treated with *β*-indolyl acetyl chloride, followed by *p*-toluenesulfonic acid to form the 7-membered ring product. Treating with zinc in acetic acid partially reduced the lactam and then reduction with lithium aluminium hydride gave carbinolamine **144** in 74% yield (Scheme 3.2).



Scheme 3.2

The imine **145** was obtained in 50% yield by the successful oxidation of alcohol **144** using dicyclohexylcarbodiimide and dimethyl sulfoxide, followed by treatment with sodium methoxide. Reduction using zinc in acetic acid followed by Wolff-Kishner reduction gave both epimers ibogamine **131** and epiibogamine **131a** in 0.01% yield overall (Scheme 3.3).

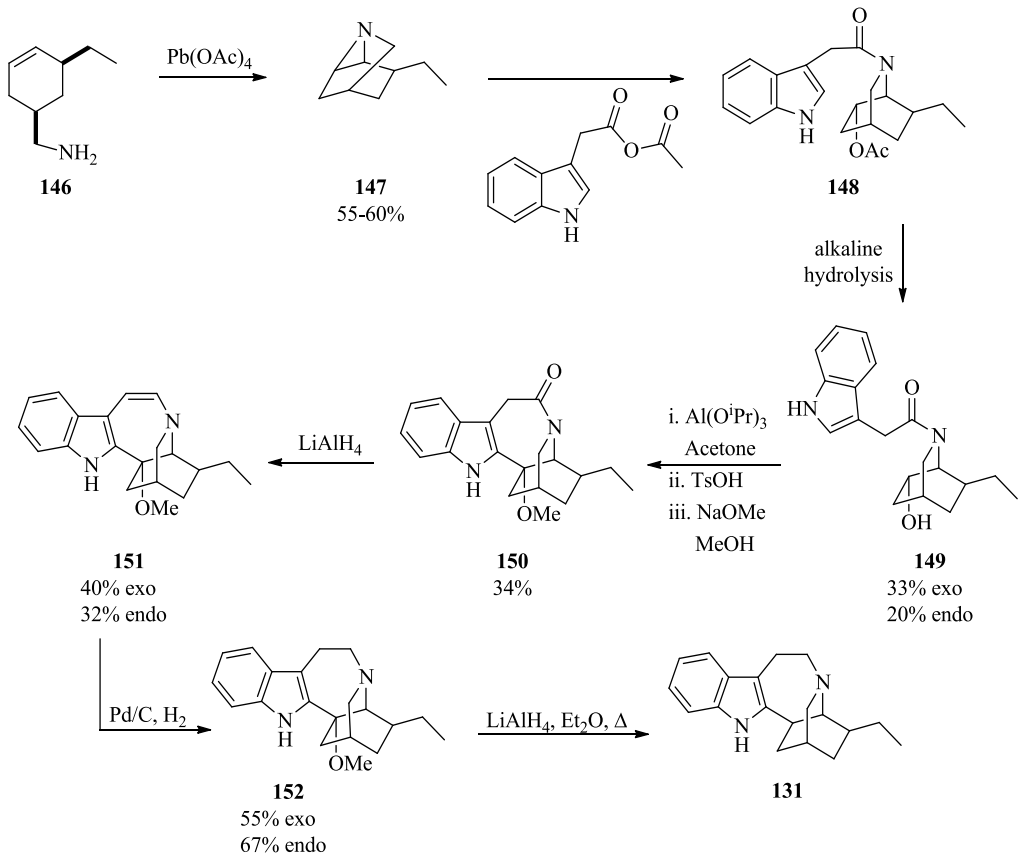


Scheme 3.3

The limitation of Buchi's synthesis is shown by the low yield of the Diels–Alder cycloaddition (due to the mixture of hydropyridines), and that the final reduction step afforded both epimers of the natural product **131** and **131a**.

3.5.2 Nagata's synthesis of ibogamine

Nagata and co-workers[102] reported that treatment of the amine **146** with $Pb(OAc)_4$, gave the aziridine **147** in 55–60% yield. The reaction of aziridine **147** with *β*-indolylacetic anhydride gave isoquinuclidine **148**, which then underwent alkaline hydrolysis to form alcohol **149** in 33% and 20% yield for *exo* and *endo* ethyl epimers respectively, related to a hydroxyl group. Oxidation using the Oppenauer method was followed by cyclisation with tosic acid and treatment with sodium methoxide to afford methoxylactam **150** in 34% yield (over three steps). The product was then reduced with lithium aluminium hydride to give enamine **151**.[103] Catalytic hydrogenation of enamine on palladium afforded compound **152** in 55% for *exo* and 67% for *endo*. Nagata completed the synthesis by removing the methoxy group on the *exo* isomer with $LiAlH_4$ to yield ibogamine **131** (Scheme 3.4).



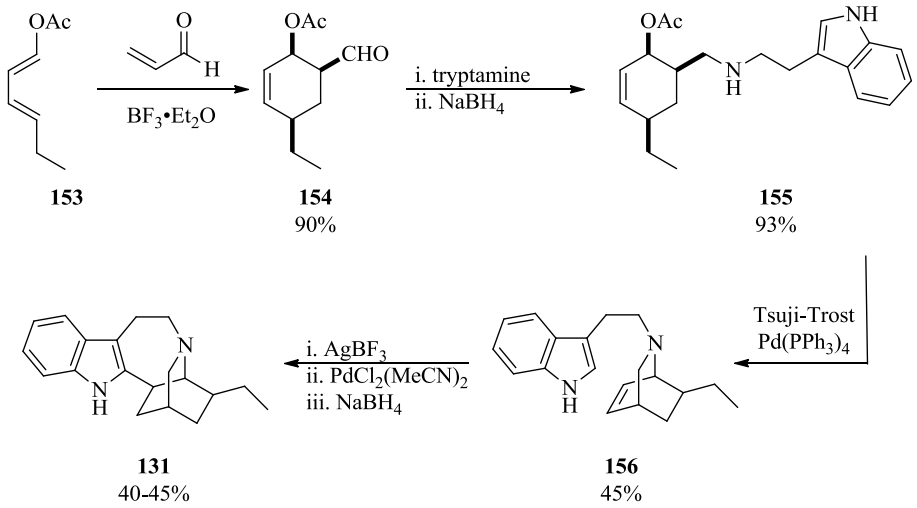
Scheme 3.4

The limitation of this route is that the separation of diastereoisomers for both the *end*o and *exo* ethyl group proved difficult, and that low yields were obtained in several steps of the synthesis.

3.5.3 Trost's synthesis of ibogamine

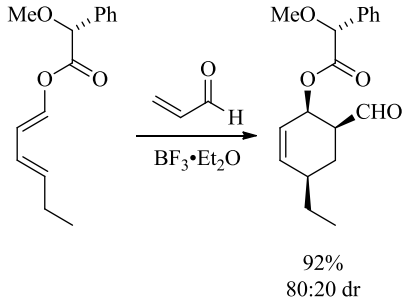
In 1978 Trost and co-workers reported a racemic and asymmetric route towards ibogamine.[104] The reaction of diene **153** with acrolein by a Diels–Alder reaction gave cyclohexene **154** in 90% yield as a single diastereoisomer and regioisomer. This underwent a reductive amination with tryptamine and sodium borohydride resulting in **155** in 93% yield. Using palladium (tetrakis)triphenylphosphine Trost showed the possibility of forming the palladium π-allyl species which in turn gave the cyclised product **156** in 45% yield. This was treated with silver tetrafluoroborate and

bis(acetonitrile)palladium(II) chloride and then $NaBH_4$ to give ibogamine **131** in 40-45% yield over both steps (Scheme 3.5).



Scheme 3.5

An asymmetric version of this route has been reported by Trost using a chiral auxiliary for the Diels-Alder reaction step in 80:20 dr (Scheme 3.6).[104]

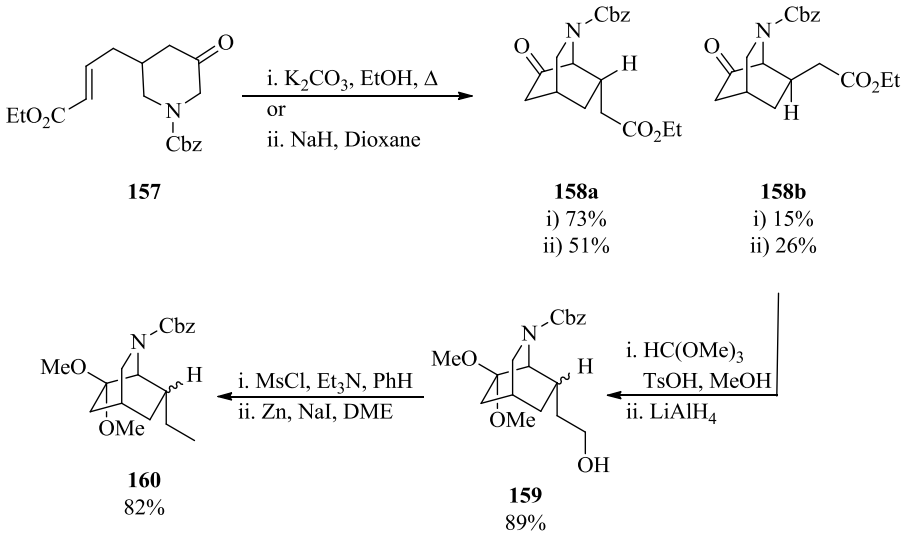


Scheme 3.6

3.5.4 Hanaoka's synthesis of ibogamine

Hanaoka and co-workers began their synthesis towards ibogamine **131** by using 5-(2-oxoethyl)-3-piperidinone to reach the ketone **157** in 70% yield in three steps (Scheme 3.7).[105] Cyclisation occurred *via* a Michael addition done using ethanolic

potassium carbonate under reflux to afford a good yield of the *endo* ester **158a**, while use of sodium hydride favoured formation of *exo* ester **158b**.



157

158a
i) 73%
ii) 51%

158b
i) 15%
ii) 26%

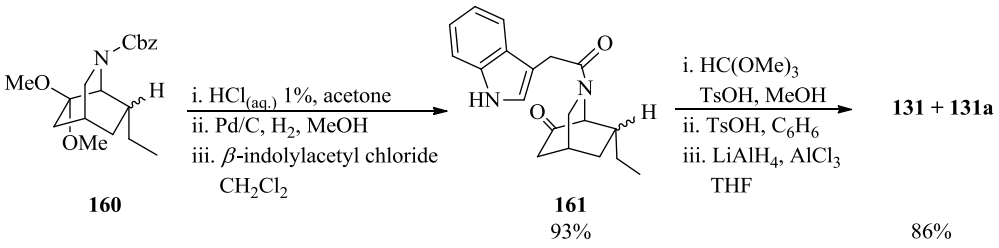
159
89%

160
82%

Scheme 3.7

The mixture of diastereoisomers was treated with trimethylorthoformate to protect the ketone group, followed by ester reduction using lithium aluminium hydride to give the alcohol **159** in 89% yield over both steps. Mesylation of the alcohol and treatment with zinc and sodium iodide gave **160** in 82% yield.

Then compound **160** was refluxed with aqueous HCl (1%) in acetone, followed by hydrogenation on palladium in methanol, and then condensation with *β*-indolylacetyl chloride to give ketone **161** in 93% yield. Compound **161** was treated with trimethylorthoformate in methanol, and then cyclisation was carried out in the presence of TsOH in benzene. The synthesis was completed by the reduction with a complex of $LiAlH_4$ and $AlCl_3$ and a 1:1 ratio of (±)-ibogamine **131** and (±)-*epi*–ibogamine **131a** was obtained in 86% yield (Scheme 3.8).[105]

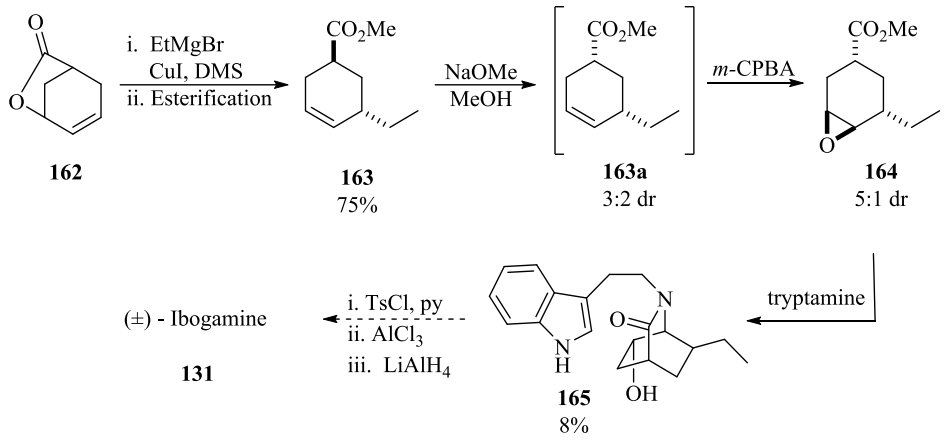


Scheme 3.8

The 6-*exo*-trig conjugate addition of the enolate of **157** onto the unsaturated ester was the novel approach of this synthesis. This key step could be controlled by the nature of the base, with the *endo* product being more favored, but under more strongly basic conditions, the *exo* product was slightly increased. The synthesis used a high number of protection group manipulations in order to obtain a good yield of the natural product.

3.5.5 Huffman's formal synthesis of ibogamine

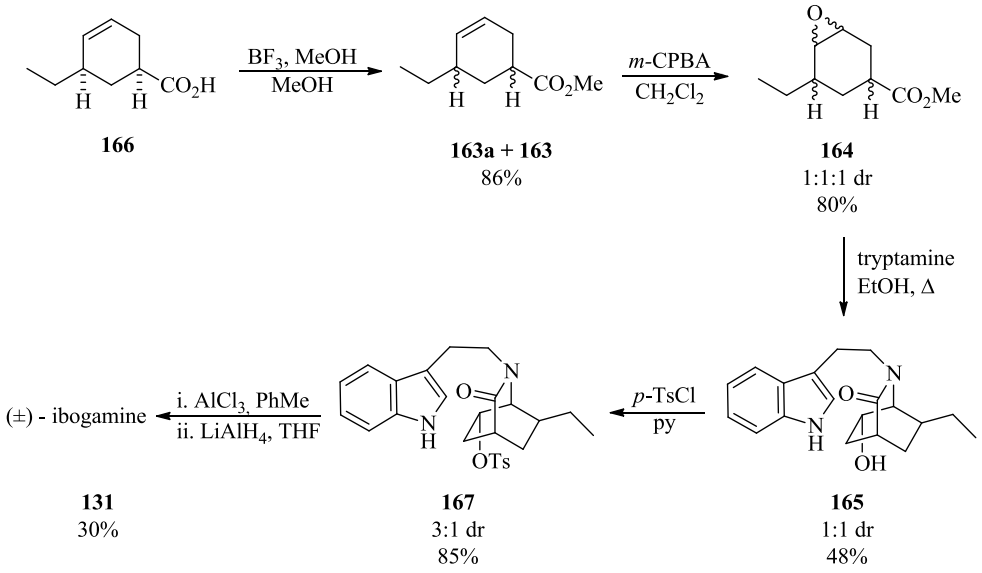
The lactone **162** was the starting material by which Huffman and co-workers began their synthesis towards ibogamine (Scheme 3.9).[106] Treatment with ethyl magnesium bromide in the presence of copper iodide and dimethyl sulfide afforded *trans*-diastereoisomer **163**. For the final product the *cis* isomer was required, and so ester **163** was epimerised using sodium methoxide to obtain ester **163a**. Epoxidation with *m*-CPBA gave epoxide **164** in 5:1 dr, and this was followed by ring opening and amidation using tryptamine, which afforded lactam **165** in poor yield. At this stage the work was stopped because, at the same time, Kuehne and co-workers published the total synthesis of ibogamine, using very similar chemistry from the alkene **163a**.[106,107]



Scheme 3.9

3.5.6 Kuehne's synthesis of ibogamine

The acid **166** underwent esterification using boron trifluoride in methanol to afford ester **163a** in 86% yield as a 1:1 ratio of inseparable diastereoisomers by ^{1}H NMR spectroscopy (Scheme 3.10).[108] Then ester **163a** was treated with *m*-CPBA to give the epoxide product **164** as a mixture of diastereoisomers (1:1:1 dr). This was then treated with tryptamine to give the alcohol **165** (1:1 dr) in 48% yield. After recrystallization, tosylated product **167** 3:1 dr was obtained in 85% yield. The final step was the cyclisation, which was done using aluminium chloride to give an intermediate lactam followed by reduction using lithium aluminium hydride to give (±)-ibogamine **131** in 30% yield. Kuehne's method showed the route of the synthesis of isoquinuclidine ring system by epoxide opening followed by cyclisation using aluminium chloride but with low yield of the desired product. The reason for the low yield can be explained by the formation of the inseparable mixture of **164**. The tosylation of alcohol **165** gave an inseparable mixture even after recrystallization (ratio 3:1), with 25% of the minor isomer (*endo*-ethyl), which was confirmed by ^{1}H NMR spectroscopy.

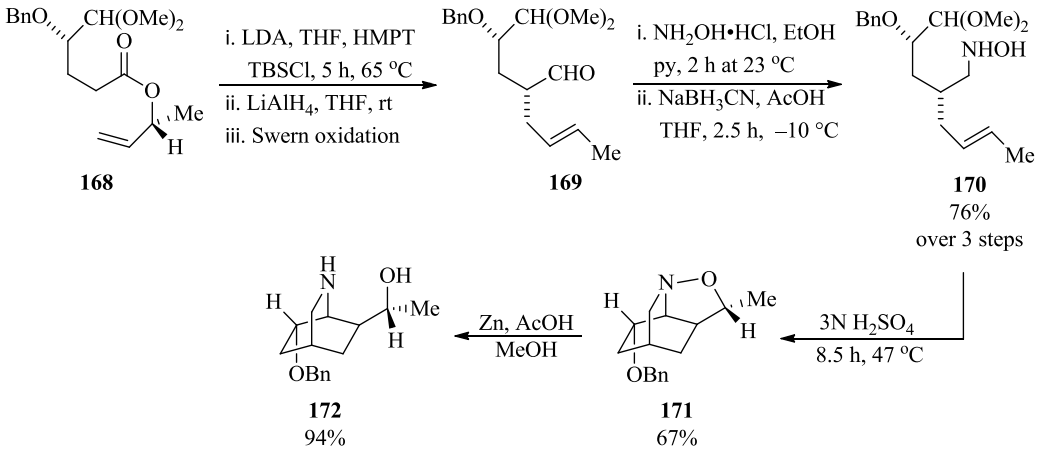


Scheme 3.10

In the last few years, much research has been done towards the synthesis of iboga alkaloids.[109-113] Some of them were a new synthesis of iboga alkaloids and modification of some methods.

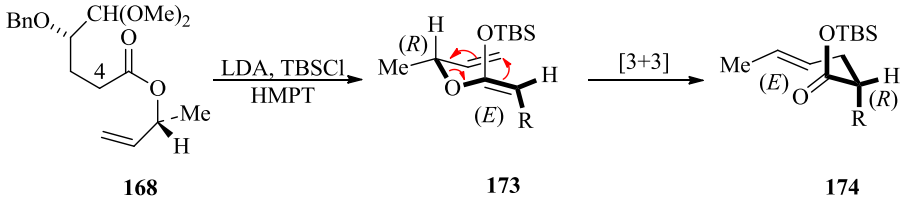
3.5.7 Borschberg's synthesis of (–)-(19*R*)-ibogamin-19-ol

In 2004 Borschberg and co-workers reported a synthesis of the core isoquinuclidine structure of the iboga alkaloids.[114] The ester **168** (single diastereoisomer and enantiomer) was made over 3 steps and underwent an Ireland-Claisen rearrangement followed by reduction with lithium aluminium hydride to give an alcohol. Conversion to the aldehyde **169** by Swern oxidation, followed by formation of the oxime, and reduction using $NaBH_3CN$ gave hydroxylamine **170** in 76% yield over three steps. The key step was a cascade process involving hydrolysis of the acetal, cyclisation, and dipolar cycloaddition resulting in the cycloadduct **171** in 67% yield as a single diastereoisomer. Finally, reduction using zinc and acetic acid gave alcohol **172** in good yield (Scheme 3.11).



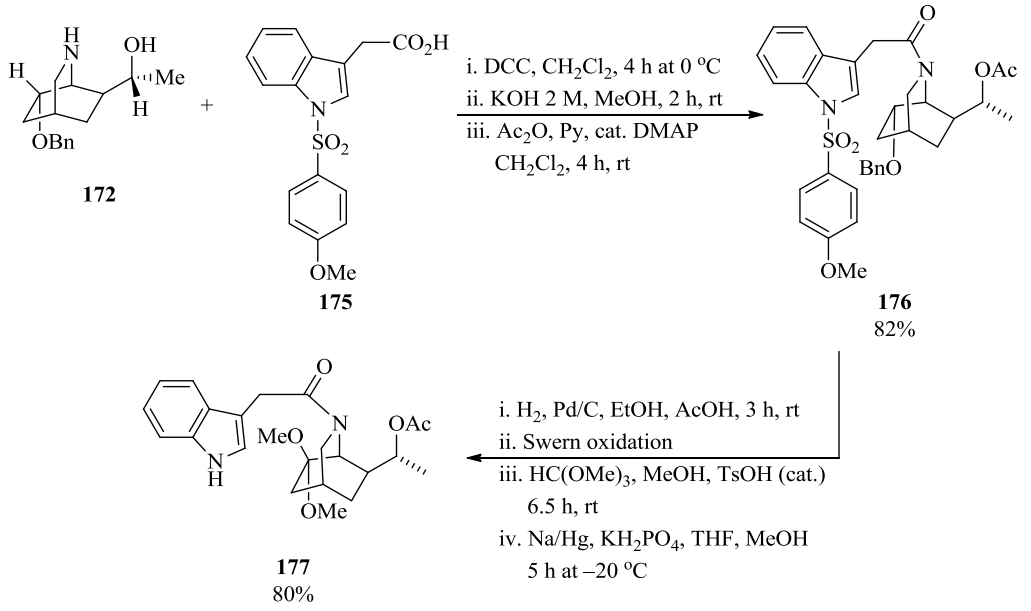
Scheme 3.11

An important step in this synthesis by Borschberg was controlling the stereochemistry at C-4 in the compound **169**. The chirality transfer from the asymmetric centre was done *via* Ireland-Claisen rearrangement.[115] The preference for the *E* silyl ketene acetal and the chair shaped transition state **173** lead to a high stereoselectivity (Scheme 3.12).[114,115]



Scheme 3.12

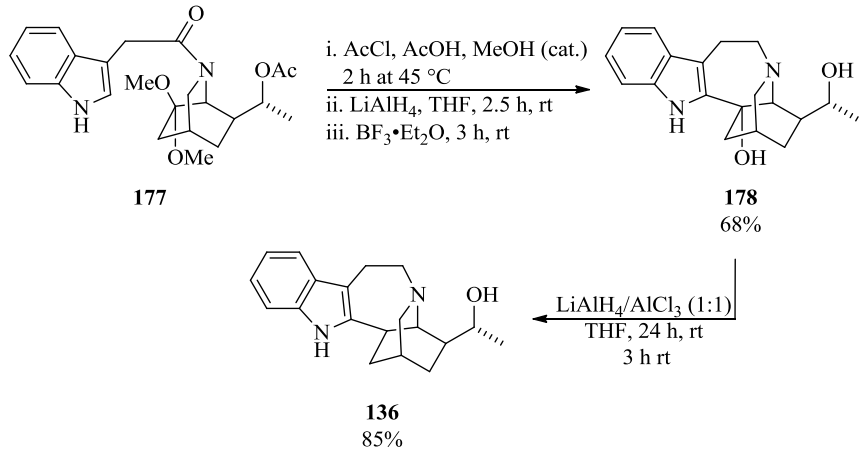
Later in 2006 Borschberg used compound **172** towards the first total synthesis of (19*R*)-ibogamin-19-ol **136**.[116] Amino-alcohol **172** was treated with protected indole acetic acid **175** using DCC as coupling reagent. This was followed by *O*-acetylation to give compound **176**. Hydrogenolysis to remove the benzyl group and oxidation *via* Swern oxidation, followed by ketone protection using trimethyl orthoformate in methanol, and indole deprotection gave amide **177** in good yield (Scheme 3.13).



172 **175** **176** 82% **177** 80%

Scheme 3.13

The synthesis was completed in three further steps. Cyclisation was carried out using acetyl chloride and acetic acid with methanol (cat.) in dry conditions. The amide and the acetyl groups were reduced with $LiAlH_4$ and BF_3 to give compound **178**. Finally, another reduction using $LiAlH_4$ and $AlCl_3$ was carried out to obtain the desired product **136** in good yield (Scheme 3.14).

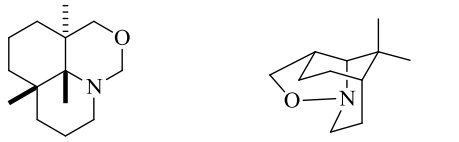


177 **178** 68% **136** 85%

Scheme 3.14

Chapter 4 Synthesis of bridged ring compounds by cascade chemistry

Cascade chemistry within the group has allowed access to fused and one-carbon bridged compounds, including the synthesis of the natural product myrioxazine A and the core of daphnilactone B (Figure 4.1). This was achieved by using a cascade of condensation, cyclisation and cycloaddition reactions. We then decided to explore the possibility of using the cascade chemistry to access the two-carbon bridged ring system, as found in the iboga alkaloids. It was believed that utilising the condensation, cyclisation, cycloaddition sequence would provide an efficient route to access the isoquinuclidine ring system of the iboga alkaloids.



myrioxazine A daphnilactone B core

Figure 4.1

The key aldehyde **180** contains a branch point from which the alkyl halide and alkenyl tethers originate *γ*- to the aldehyde functional group (Figure 4.2). It has been shown in the Coldham group that for access to the fused tricyclic products, the best equivalent precursor for an aldehyde is a nitrile, which can easily undergo an alkylation[117] reaction in the presence of a base. The product generated can then be reduced to give the corresponding aldehyde. The ease by which the nitrile can be alkylated is due to their high-polar inductive effect and their small size.[118] Coldham and co-workers have used the nitrile often as a source of the corresponding aldehyde.[62,119-122] It has been reported that nitrones can undergo intramolecular cycloaddition with terminal alkene dipolarophiles. Herein, we wanted to test the use of nitrones in the cascade reaction and so aldehyde **179** was predicted to give a positive result in the cascade chemistry.

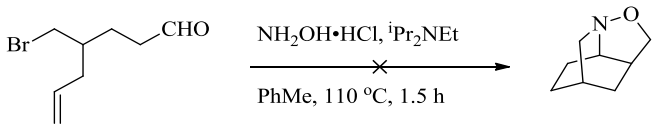
179, X = Cl
180, X = Br

Figure 4.2

4.1 Allyl type compounds

4.1.1 Enolisable aldehyde

Preliminary work that had been tested in the Coldham group showed that aldehyde **180** was unable to undergo the cascade reaction (Scheme 4.1).[123] Therefore we chose to lower the LUMO of the dipolarophile by introducing an electron withdrawing group, and test the effect on the cascade process for aldehyde **188**. To achieve this, a cross-metathesis reaction was used to install a methyl ester group to the alkene moiety.



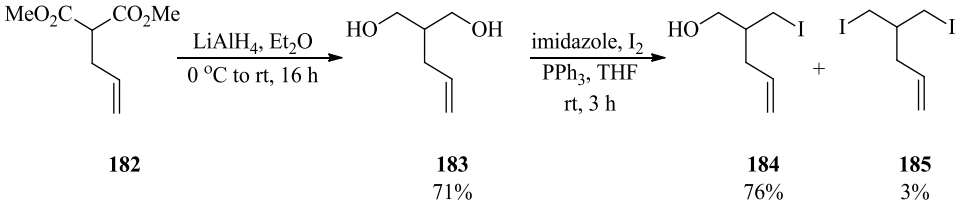
180 **181**

Scheme 4.1

4.1.1.1 Substrate synthesis

The key aldehyde **180**, was originally synthesized in the Coldham group by Guerrand.[123] This chemistry was repeated as described below. Beginning with commercially available diethylallyl malonate **182**, it was possible to reduce both esters using lithium aluminium hydride to give the diol **183** in 71% yield. To provide a good leaving group for alkylation in the next step, the iodination reaction was carried out by adding iodine (1.1 equiv.) portionwise over 30 minutes to a mixture of triphenylphosphine (1.0 equiv.) and diol **183** (1.0 equiv.) in THF. This afforded mono-iodo compound **184** in 76% yield, with 3% yield of the di-iodide **185** (Scheme

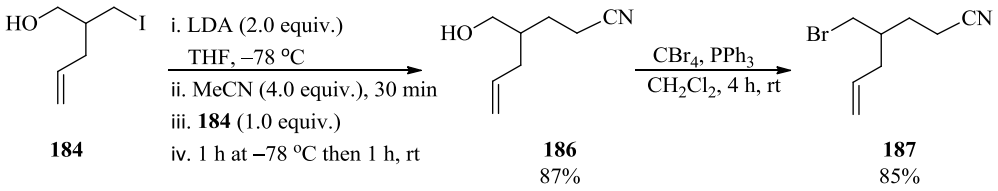
4.2). In order to obtain a good yield of mono-iodide **184**, the reaction was diluted and the iodine was added portionwise.



182 | **183** 71% | **184** 76% | **185** 3%

Scheme 4.2

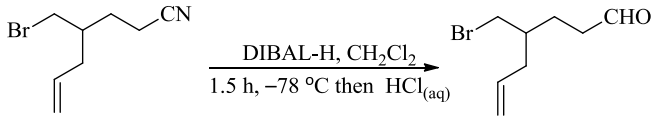
Acetonitrile (4.0 equiv.) was deprotonated using LDA (2.0 equiv.) in THF at –78 °C. The iodo-alcohol **184** was then added to give nitrile **186** in 87% yield. Based on the efforts that have been made in the group in terms of minimizing the by-product, the dialkylated nitrile, 4.0 equivalents of the nitrile were used. To provide a good leaving group for later cyclisation, bromination was carried out using carbon tetrabromide (1.1 equiv.) and triphenylphosphine in dichloromethane, which gave bromo-nitrile compound **187** in 85% yield (Scheme 4.3).



184 | **186** 87% | **187** 85%

Scheme 4.3

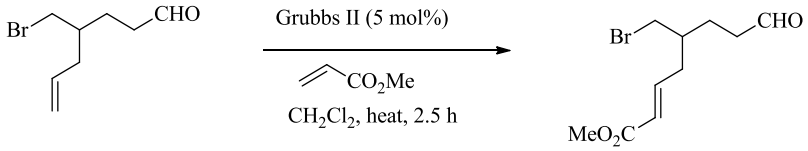
Reduction using DIBAL-H followed by work up with aqueous hydrochloric acid gave the precursor aldehyde **180** in 75% yield (Scheme 4.4). Initially the yield was about 55% due to instability of the aldehyde on purification using dry loading on silica gel. Therefore, purification was performed quickly using column chromatography on silica gel without dry loading, which afforded a better yield of the aldehyde **180**.



187 **180**
75%

Scheme 4.4

Then, a cross–metathesis reaction was used to convert the alkene to the unsaturated ester. For this, aldehyde **180** and Grubbs' 2nd generation catalyst[73] were heated at reflux in dichloromethane with methyl acrylate as the metathesis partner, to give aldehyde **188** in 45% yield (*E* isomer was determined by ^{1}H NMR spectroscopy) (Scheme 4.5). For better yield (67%), the catalyst was added portionwise during the reaction.

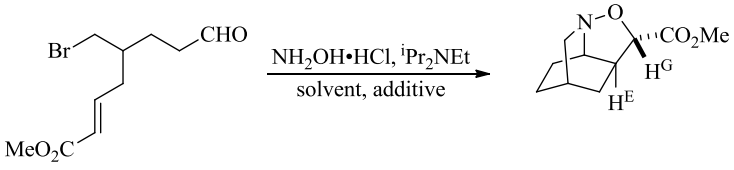


180 **188**
67%

Scheme 4.5

4.1.1.2 Cyclisation–cycloaddition cascade

With the key aldehyde **188** in hand, the cascade reaction was attempted to investigate the activated dipolarophile. The aldehyde **188** was heated at reflux in toluene with hydroxylamine hydrochloride and *N*,*N*-diisopropylethylamine (Scheme 4.6).



188 **189**

Scheme 4.6

Entry	Solvent	Time	Additive	Yield%
1	PhMe	4 h	None	0
2	PhMe	30 min at 60 ^{o}C then 4 h reflux	None	0
3	PhMe	30 min at 60 ^{o}C then 3 h reflux	$MgSO_4$	15
4	PhMe	2.5 h	$MgSO_4$	17
5	PhMe	1.5 h	$MgSO_4$	10
6	PhMe	2.5 h	$MgSO_4$/TBAI	0
7	Xylene	1 h at 60 ^{o}C then 1.5 h reflux	$MgSO_4$	0

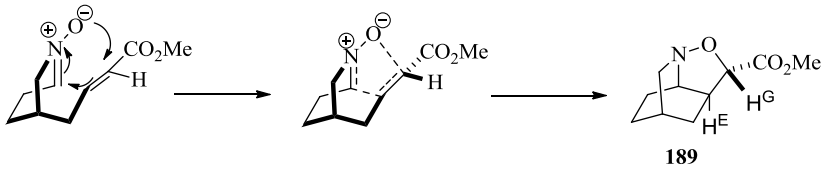
Table 4.1

Initially, aldehyde **188** was heated with hydroxylamine (1.0 equiv.) and base in toluene. No desired cycloadduct **189** was observed. This could be due to the susceptibility for enolisation of the aldehyde **188** when condensed with hydroxylamine. Table 4.1 shows the optimisation of conditions to obtain better yields. Heating the mixture of aldehyde **188** with hydroxylamine hydrochloride and *N*,*N*-diisopropylethylamine in toluene at 60 ^{o}C for 30 min, followed by TLC analysis indicated that most of the starting material was consumed and was probably converted to the oxime. The reaction mixture was then heated at 110 ^{o}C, but subsequent TLC analysis showed many spots on the TLC plate (entry 2). As a result, the reaction was repeated using $MgSO_4$, after 3 h the reaction was cooled to room temperature and a low yield of the cycloadduct was obtained (entry 3). Direct heating gave a similar yield (entry 4), and adding $MgSO_4$ as a dehydrating agent helped to obtain the desired product. We thought that heating for a long time caused decomposition of the product resulting in a low yield, and so the reaction was heated for 1.5 h, but only 10% yield was isolated with 20% yield of recovered starting material (entry 5). We thought that the bromide might not be a suitable leaving group for this type of reaction, and so to initiate the cyclisation, the more reactive iodide could facilitate the step. Indeed, further optimisation would be required in order to increase the yield. Cyclisation promoter TBAI was used, but no desired cycloadduct was observed and the starting material decomposed very quickly (entry 6). It was

suggested that the cyclisation might be slow and xylene was used instead of toluene (entry 7). This proceeded unsuccessfully as the reaction mixture started to quickly decompose after 1.5 h.

4.1.1.3 The stereochemistry of cycloadduct 189

The stereochemistry of the product **189** was proposed initially on the basis of the ^{1}H NMR spectrum in $CDCl_3$ (Figure 4.3). The H^G peak at 4.24 ppm appeared as a singlet rather than a doublet and H^E peak at 2.43 ppm showed as a doublet of doublets with *J* values of 9.5 and 3.0 Hz. This indicated that there is no coupling between the vicinal protons. Based on the Karplus equation,[124] the *J* value is zero when the dihedral angle is 90º. Models of the two diastereomers indicate that the dihedral angles should be a 90º for **189** and 0º for its diastereomer. This suggested that the product is indeed compound **189** as expected based on a concerted cycloaddition of *E* isomer of unsaturated ester.



189

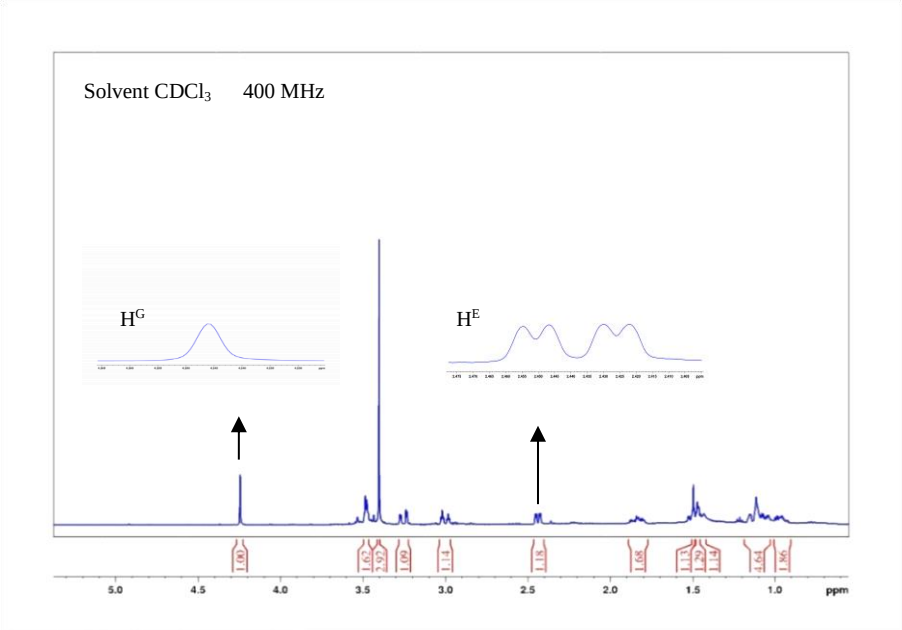


Figure 4.3

Additionally, COSY spectra showed that there is no interaction between the protons H^G and H^E. This is similar to the analogue compound **212** (Appendix 6), which was confirmed by X-ray crystallography as described later in this chapter. The correlation of protons and carbons was assigned *via* 2D HSQC experiments. H^G is connected to the carbon at 86.8 ppm and protons H^D, H^E and H^F are connected to the carbons located at 55.6 ppm, 42.3 ppm and 16.3 ppm respectively (Figure 4.4). The 2D NOESY spectrum indicates that there is no nuclear Overhauser effect between H^G and H^E, but irradiation of proton H^E enhanced H^D and one proton of H^F.

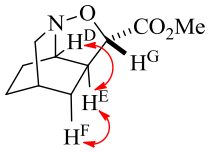
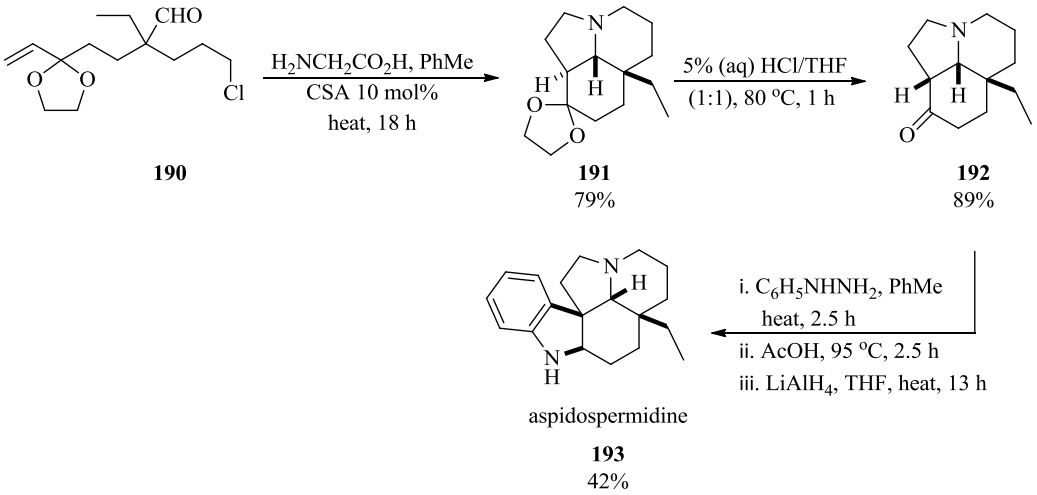


Figure 4.4

4.1.2 Non-enolisable aldehyde

The Coldham group has shown the value of generating cycloadducts from non–enolisable aldehydes. In 2007,[125] Coldham and co-workers reported rapid access to a complex tricyclic amine from an acyclic precursor, which was used for the synthesis of aspidospermidine. Treatment of aldehyde **190** with glycine in toluene gave cycloadduct **191** in 79% yield. Acetal hydrolysis using aqueous HCl (5%) in THF, gave ketone **192** in 89% yield. Aspidospermidine **193** was obtained in 42% yield over three steps (Scheme 4.7).



190

191
79%

192
89%

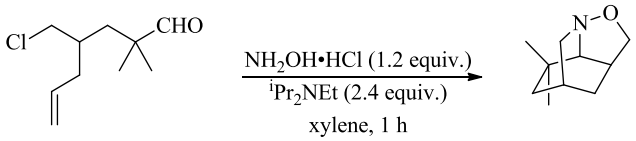
aspidospermidine

193
42%

Scheme 4.7

The chemistry shown in Scheme 4.7 involves an azomethine ylide as the dipole. Coldham and co-workers have extended this to nitrones to give fused and one-carbon bridged compounds (Scheme 1.29 and 1.30).

Further investigation into whether promotion of the cycloaddition reaction would allow any cycloadduct to be obtained in better yield compared to cycloadduct **189** would be of interest in this series. We believed that introducing a *gem*-dimethyl group at the α-carbon to the carbonyl group would prevent enolisation and this could help the cascade reaction. The cascade process on the aldehyde **194** with a terminal alkene was tested in the group previously and gave the cycloadduct **195** in 56% yield (Scheme 4.8).[123]

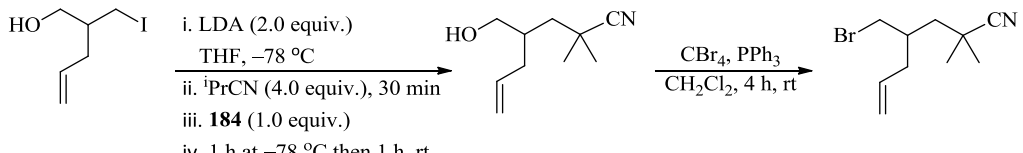


194 **195** 56%

Scheme 4.8

4.1.2.1 Synthesis of aldehyde 199

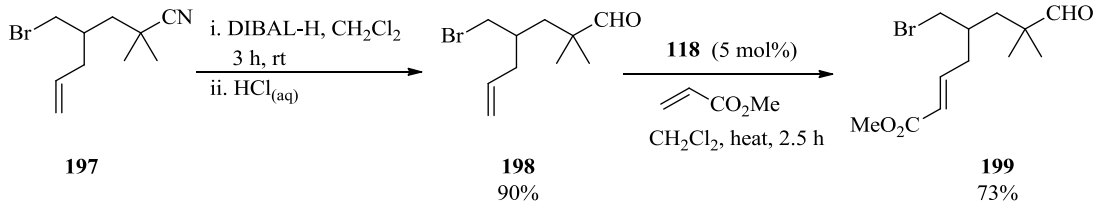
We decided to investigate the cascade reaction for the α,β-unsaturated ester **199**. Therefore, we began with iodo-alcohol **184**, which on alkylation with isobutyronitrile using the same conditions as before, led to compound **196** in 92% yield. Compound **197** was formed by replacing the hydroxyl group with bromide by treating compound **196** with carbon tetrabromide and triphenylphosphine in dichloromethane which gave **198** in excellent yield (Scheme 4.9).



184 **196** 92% **197** 93%

Scheme 4.9

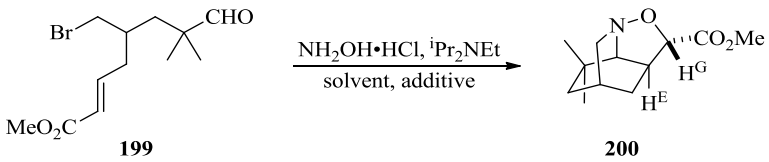
The nitrile **197** was then converted to aldehyde **198** in 90% yield through DIBAL-H reduction (Scheme 4.10). We thought that lowering the LUMO of the alkene could give a good yield of cycloadduct. To do so, cross-metathesis was carried out using Grubbs' 2nd generation catalyst in degassed dichloromethane with methyl acrylate under reflux conditions which gave the key aldehyde **199** (*E* isomer was determined by ^{1}H NMR spectroscopy) in good yield.



Scheme 4.10

4.1.2.2 Cyclisation–cycloaddition cascade

The aldehyde **199** was heated with hydroxylamine hydrochloride and *N,N*-diisopropylethylamine in toluene (Scheme 4.11). After some optimisation was carried out, the desired cycloadduct **200** was obtained in moderate yield (Table 4.2). Heating for 3 h in toluene or xylene using (1.5 equiv.) hydroxylamine hydrochloride did not afford the desired product (entries 1 and 2) and inseparable mixture was obtained. A low yield of the desired product was obtained by first aiming to form the oxime at 60 ºC followed by heating at reflux (entry 3). Decreasing the equivalents of hydroxylamine hydrochloride, which possibly led to a reduction in the conjugation addition reaction, and adding $MgSO_4$, gave better yields (entries 4 and 5).



Scheme 4.11

Entry	Solvent	NH_2OH (equiv.)	Time	Additive	Yield %
1	PhMe	1.5	3 h, 110 ^oC	None	0
2	Xylene	1.5	3 h, 140 ^oC	None	0
3	PhMe	1.5	1 h at 60 ^oC then 3 h reflux	None	26
4	PhMe	1.0	1 h at 60 ^oC then 3 h reflux	$MgSO_4$	47
5	PhMe	1.0	30 min at 60 ^oC then 2 h reflux	$MgSO_4$	60

Table 4.2

4.1.1.3 The stereochemistry of cycloadduct 200

The stereochemistry was tentatively assigned, as based on comparison to cycloadduct **212** that was confirmed by X-ray crystallography (Appendix 6). The ^1H NMR spectrum (Figure 4.5) showed the H^G singlet at 4.19 ppm and H^E doublet of doublets with *J* values of 9.5 and 3.0 Hz at 2.56 ppm, which almost match the outcome from cycloadduct **212**. The higher yield as compared to cycloadduct **189** could be explained by the inability to form an enolate or enamine and the Thorpe–Ingold effect.[126] The moderate yields of the cycloadduct compound could be because of competing conjugate addition to the ester group. The COSY spectrum showed that there is no coupling between protons H^G and H^E, but H^E coupled to one proton of H^F and proton H^D. Importantly, the 2D HSQC spectrum showed that protons H^G is connected to a carbon at 86.7 ppm, and proton H^E is connected to carbon located at 40.3 ppm.

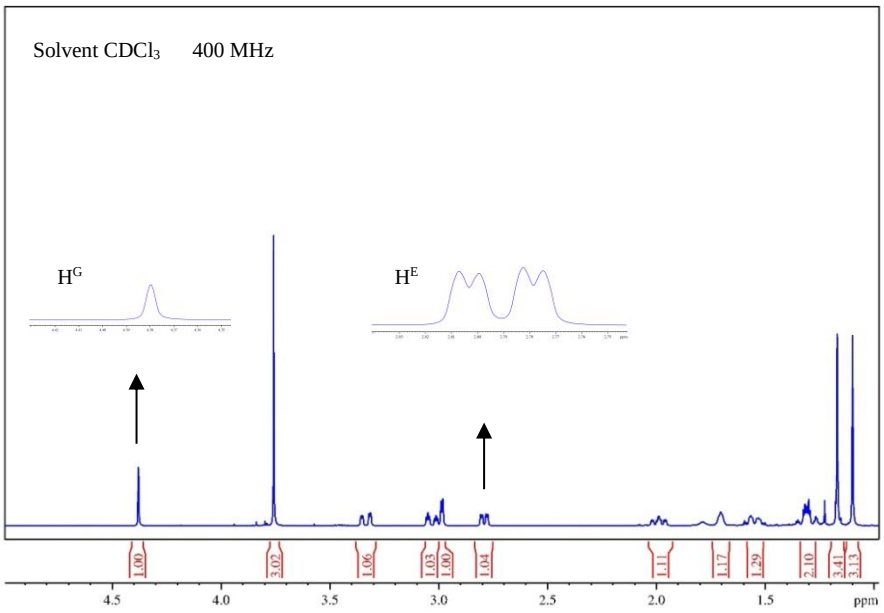


Figure 4.5

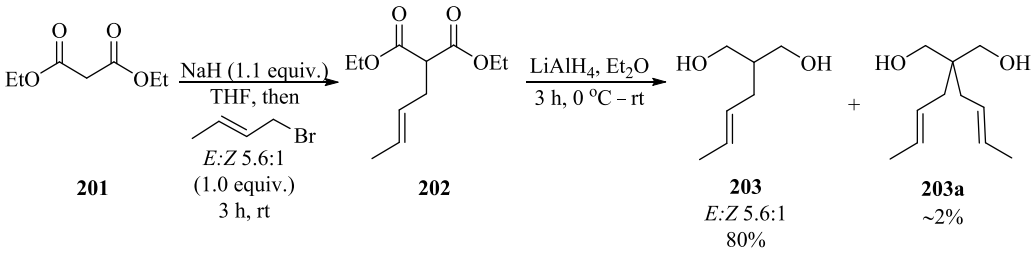
4.2 Crotyl type compounds

Based on the target molecule **136** which contains a methyl group at C(19) and postulating that conjugate addition was preventing the cyclisation step with activated dipolarophile **199** to give the cycloadduct in good yield, we believed that it would be beneficial to use a methyl-substituted alkene as the dipolarophile.

4.2.1 Synthesis of the aldehyde precursor

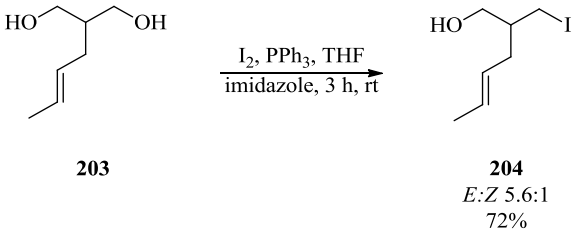
We started our work with the aim to prepare the aldehyde **208**. Crotylation of commercially available diethyl malonate **201** gave the diester **202**. The commercial crotyl bromide is a 5.6:1 *E*:*Z* mixture. The crude mixture **202** was reduced using $LiAlH_4$ in Et_2O to give diol **203** in 80% yield as an inseparable mixture of *E*:*Z* isomers (5.6:1) that was confirmed by NMR spectroscopy and GC/mass spectrometry. A small amount of di-crotylated product (~2%) was formed and could be partially separated by careful column chromatography (Scheme 4.12). The addition sequence of the reactants plays an important role in obtaining a high yield of product and reducing the yield of by-product. The best yield was obtained by adding

the diethyl malonate **201** to a stirred solution of sodium hydride in THF, and then this was added dropwise to crotyl bromide in THF. It was not necessary to purify the crotylated diester and the crude mixture was subjected to $LiAlH_4$ reduction, however purification of **202** by column chromatography resulted in a similar yield of the diol **203**.



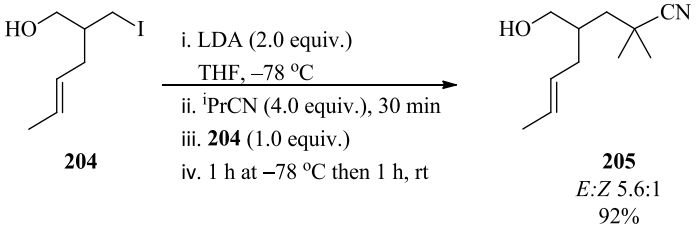
Scheme 4.12

It was necessary to prepare the electrophile **204** that would be used to alkylate isobutyronitrile. Therefore, diol **203** was iodinated using the same conditions as in the allyl series, and the product **204** was obtained in 72% yield (Scheme 4.13)**.**



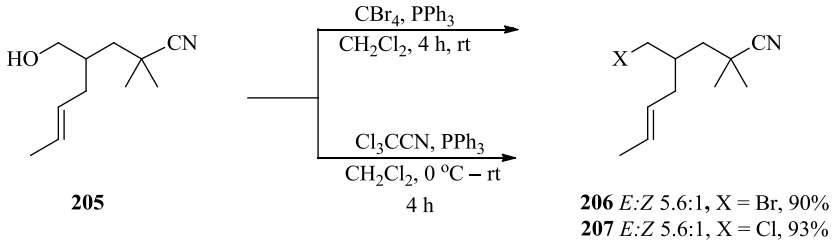
Scheme 4.13

The iodo-alcohol compound **204** was then subjected to the same alkylation conditions as in the allyl series in the previous section, using LDA (2.0 equiv.) and isobutyronitrile (4.0 equiv.). This gave the nitrile **205** in 92% yield (Scheme 4.14).



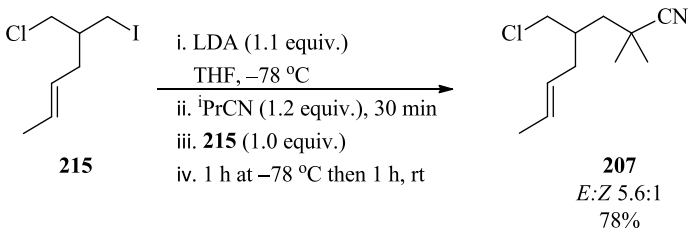
Scheme 4.14

A number of optimisations have been done in the Coldham group to find suitable conditions for halogenation of a similar nitrile.[127] The Appel reaction[128] using trichloroacetonitrile or using carbon tetrabromide provided the best results. Bromination of alcohol **205** with carbon tetrabromide and triphenylphosphine gave bromo-nitrile **206** in 90% yield, while chlorination using trichloroacetonitrile and triphenylphosphine in dichloromethane gave chloro-nitrile **207** in 93% yield (Scheme 4.15).



Scheme 4.15

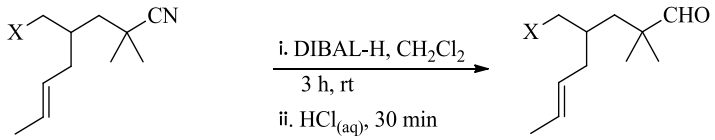
An alternative route to prepare chloro-nitrile **207** was carried out by treating isobutyronitrile (1.2 equiv.) with LDA (1.1 equiv.) in THF, then the chloro-iodo compound **215** (1.0 equiv.) was added to afford the chloro-nitrile **207** in 78% yield (Scheme 4.16). Pleasingly, the reaction was found to be highly selective towards the α–carbon of the iodide over the α–position of the chloride.



Scheme 4.16

The reduction of nitriles **206** and **207** using DIBAL−H and acidic work up to hydrolyse the imine intermediate gave aldehyde **208** in 85% yield and **209** in 91%

yield (Scheme 4.17) respectively. The *E*/*Z* ratio for all compounds maintained the same 5.6:1 ratio, and this was confirmed by using GC/mass spectrometry.



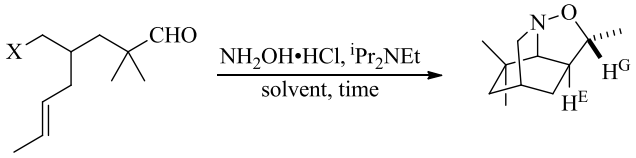
206 *E:Z* 5.6:1, X = Br, 90%
207 *E:Z* 5.6:1, X = Cl, 93%

208 *E:Z* 5.6:1, X = Br, 85%
209 *E:Z* 5.6:1, X = Cl, 91%

Scheme 4.17

4.2.2 1,3-Dipolar cycloaddition of aldehydes 208 and 209

After the successful synthesis of the key aldehydes **208** and **209**, the final step involved attempting the tandem cyclisation–cycloaddition. Using the same conditions from the previous work on the bridged ring system in the Coldham group, the aldehyde **208** was treated with hydroxylamine hydrochloride (1.5 equiv.) and *N*,*N*-diisopropylethylamine (2.5 equiv.) in toluene at 110 ^{o}C overnight which gave the desired cycloadduct **210**. This reaction gave a single stereoisomer of **210** in 60% yield. Carrying out the same reaction in xylene for 3 h provided the same stereoisomer in 70% yield (Scheme 4.18). Heating chloro-aldehyde **209** using the same conditions afforded almost the same yield (Table 4.3). Interestingly, the cycloaddition reaction of the aldehyde **199** with the electron deficient ester group required less time than aldehydes **208** and **209** with a moderate electron donating methyl group. Presumably, this is due to activation of the alkene by the ester group which is not present in the case of compound **208**.



208 *E:Z* 5.6:1, X = Br
209 *E:Z* 5.6:1, X = Cl

210

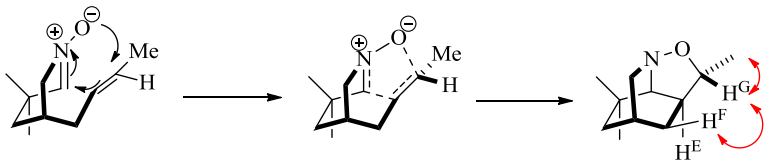
Scheme 4.18

Entry	Solvent	X	Time h	Yield%
1	PhMe	Br	16	60
2	Xylene	Br	3	70
3	Xylene	Cl	3	67

Table 4.3

4.2.3 Assignment of stereochemistry of 210

The prediction of the stereochemistry of the methyl group was based on the starting material *E*/*Z* 5.6:1. Therefore, the concerted cycloaddition across an *E* alkene would give predominantly stereoisomer **210** (Figure 4.5). Only one isomer was isolated after column chromatography. The ^{1}H NMR spectrum showed that the proton H^{G} appeared as a quartet with a *J* value of 6.0 Hz at 4.09 ppm probably because it is interacting with the methyl group but not H^{E} which was observed at 2.17 ppm as a doublet of doublets with *J* values of 9.5 and 3.0 Hz. This exactly matches the observation from cycloadduct **212** that was confirmed by X-ray crystallography (Appendix 6). A molecular model showed that the dihedral angle (ϕ) between these vicinal protons is nearly 90° and based on the Karplus correlation was found, the *J* value is 0 Hz.[124,129] Furthermore, a 2D NOESY correlation was found between H^{G} and the methyl group and H^{F} but not H^{E}. The correlation of protons and carbons was assigned using the 2D HSQC spectrum, this showed that H^{G} is connected to the carbon located at 86.0 ppm, and protons H^{E} and H^{F} are attached to carbons 41.0 ppm and 33.5 ppm respectively.



210

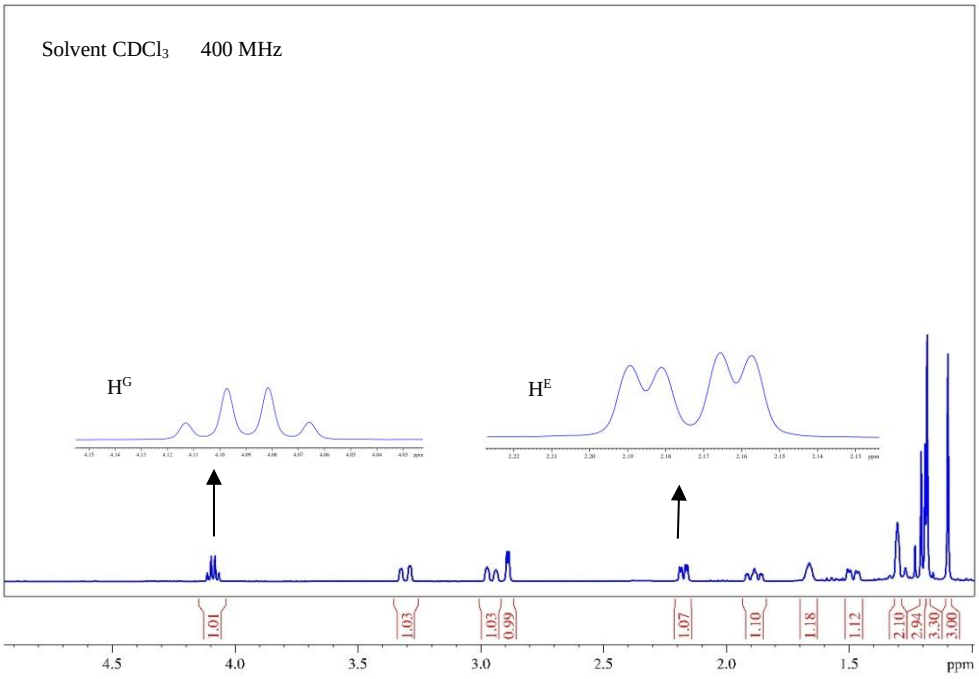
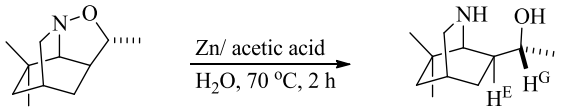


Figure 4.6

The cleavage of the N–O bond was carried out using zinc and acetic acid in H_2O with heating at 70 ^oC to give amino-alcohol **211** in quantitative yield (Scheme 4.19). The structure of the product was confirmed by ^1H NMR spectroscopy, as proton H^G showed at 3.89 ppm as a quartet of doublets with *J* values of 6.5 and 3.0 Hz, which is in contrast to cycloadduct **210**.



210

211
quantitative

Scheme 4.19

4.3 Towards iboga alkaloids

19-Hydroxy-ibogamine is an alkaloid compound which can be isolated from the iboga tree. The compound shows biological activity as an antibiotic agent.[88] With the successful result we had obtained towards the isoquinuclidine core structures, it was initially proposed that a cascade reaction of aldehyde **213** would yield, after acetal hydrolysis, cycloadduct **212** that would require only a few more steps in order to be able to access 19-hydroxy-ibogamine **136** (Figure 4.7).

4.3.1 Retrosynthesis analysis

The retrosynthesis of 19-hydroxy-ibogamine **136** has been proposed by Coldham (Figure 4.7). The disconnection of the indole can give the cycloadduct **212**, which can be prepared from commercially available diethyl malonate. It was thought that crotylation followed by reduction using $LiAlH_4$, halogenation and nucleophilic substitution could generate the key precursor aldehyde **213**. Cascade reaction of **213** with hydroxylamine should give the tricyclic product **212**. This could potentially be transformed into the final product.

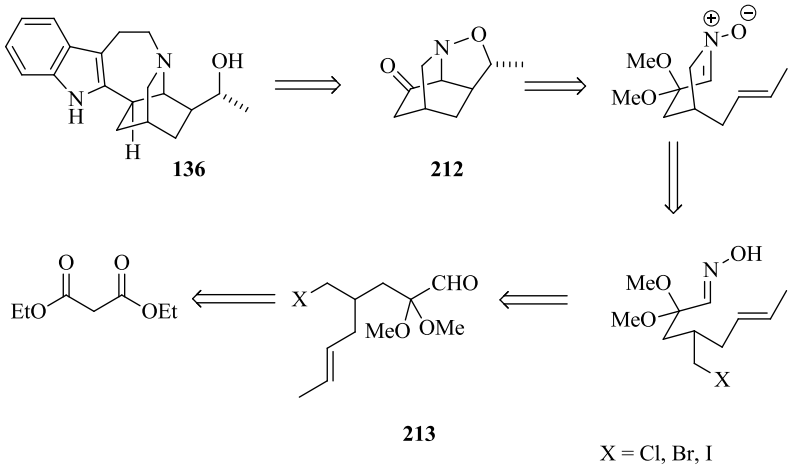


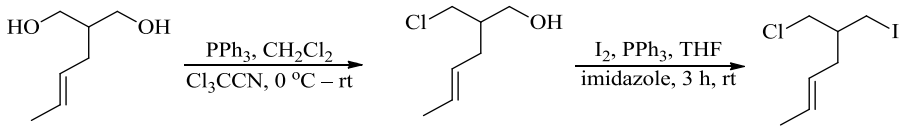
Figure 4.7 Coldham's suggested total synthesis of 19-hydroxy-ibogamine

4.3.2 Synthesis of the key aldehyde

Towards the synthesis of an iboga alkaloid, we decided to investigate this chemistry using a dialkoxyacetal in place of the *gem*-dimethyl group compound **209**. This

would allow installation of a carbonyl group for further functionalisation. We hoped that treating diethoxyacetonitrile **216** with the iodo-compound **215** could allow access to the desired aldehyde and the corresponding cycloadduct should then be able to be converted to the desired natural product using routine chemistry.

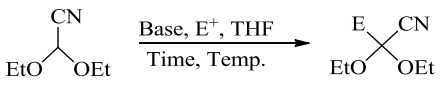
To a mixture of diol **203** and triphenylphosphine (1.2 equiv.) in dichloromethane, trichloroacetonitrile (1.0 equiv.) was added dropwise at 0 ^{o}C, to give mono chloride **214** in 85% yield. In contrast, carbon tetrachloride gave a low yield. This was followed by iodination using triphenylphosphine (1.2 equiv.), imidazole (1.2 equiv.) and iodine (1.1 equiv.) in THF, which afforded iodo-chloro compound **215** in 83% yield (Scheme 4.20).



203 **214** 85% **215** 83%

Scheme 4.20

We thought that using diethoxyacetonitrile **216** would be a good source of a masked carbonyl, which on acetal removal, should give the required functional group for the following steps. A very small number of publications report the use of this nitrile as a nucleophile and in all cases, the reported yield was low.[130] Attempts were made for a reaction of iodide **215** with diethoxyacetonitrile **216**. Unfortunately, all attempts failed to form alkylated compound **217** (Scheme 4.21, Table 4.4). For entries 1 and 2, LC/mass analysis of the crude mixture showed that there were trace amounts of the alkylated product in the mixture. Thus, to understand the reason for the failure of the reaction, two possibilities were considered: either the nitrile anion has a very short life time (insufficient nucleophile), or the iodo-chloro compound **215** was not electrophilic enough to be attacked by the anion.



216 **217**

Scheme 4.21

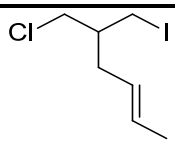
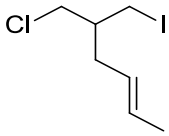
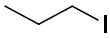
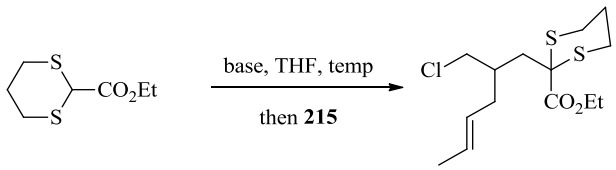
Entry	E^+	Base	Time	Temp (°C)	Yield%
1		LDA	16 h	–78 to rt	trace
2		NaH	16 h	rt	trace
3		NaH	16 h	rt	0
4	MeO_2CCN	^{n}BuLi	10 min	–78	0
5	MeO_2CCN	^{n}BuLi	30 min	–78	0
6	MeO_2CCN	^{n}BuLi	1 h	–78	0

Table 4.4

Table **4.4** shows that changing either the base, electrophile or the time did not affect the yield. Using methyl cyanoformate (1.1 equiv.) as the electrophile and a variety of different conditions for the above reaction, no product was detected either by TLC analysis or by crude ^{1}H NMR spectroscopy. Therefore, we decided to proceed with a different anion and an alternative method was employed for the alkylation.

We envisaged that alkylation of ethyl 1,3-dithiane-2-carboxylate would allow access to the desired aldehyde. Reaction of ethyl 1,3-dithiane-2-carboxylate **218** with NaH and iodo compound **215** in THF at room temperature gave a mixture of the desired product **219** in 32% yield (after purification), together with recovered starting material dithiane (similar polarity), and iodide **215** as well (Scheme 4.22). As expected, this reaction shows selective alkylation at the carbon α to the iodide over the chloride. Efforts to optimise the alkylation were carried out (Table 4.5). To ethyl 1,3-dithiane-2-carboxylate **218**, ^{n}BuLi was added followed by iodo-compound **215** in THF. Using 1.1 equivalent of ^{n}BuLi gave low–moderate yield of the desired ester **219** (entries 3–5).



218 **219**

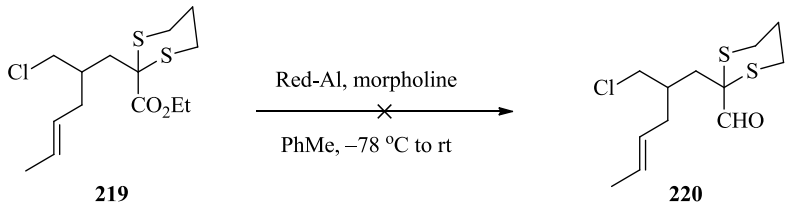
Scheme 4.22

Entry	E^+ (equiv.)	Nu^- (equiv.)	Base	Base (equiv.)	Temp (°C)	Time	Yield %
1	1	1.1	NaH	1.1	rt	16 h	32
2	1	1.2	^{n}BuLi	1.3	–78 – rt	16 h	40
3	1	1.1	^{n}BuLi	1.1	–78 – rt	16 h	35
4	1	1.1	^{n}BuLi	1.1	–78 – rt	2 d	20
5	1.1	1	^{n}BuLi	1.1	–78 − rt	16 h	50
6	1.2	1	^{n}BuLi	1.2	–78 to –40 to rt	16 h	65
7	1.2	1	^{n}BuLi	1.2	–78 to –40 to rt	16 h	75[a]

[a] The molarity of Entry 6 is (0.16 M) and (0.33 M) for Entry 7

Table 4.5

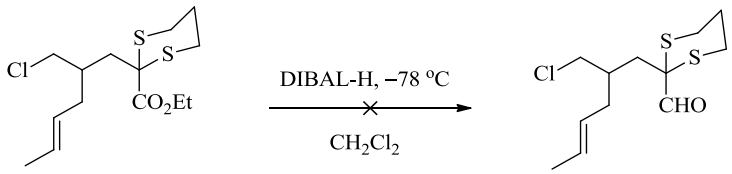
After further optimisation, ^{n}BuLi (1.2 equiv.) was added to ethyl 1,3-dithiane-2-carboxylate **218** (1.0 equiv.) at –78 °C in THF. After 10 min, chloro-iodo compound **215** (1.2 equiv.) was added at –40 °C. The mixture was then warmed and stirred for 16 h at room temperature, after which the ester **219** was obtained in 65% yield (entry 6). Pleasingly, increasing the reaction concentration led to the ester **219** in 75% yield (entry 7). With the ester in hand, the next step was to prepare the aldehyde. However, efforts to obtain the aldehyde **220** in one step, using Red–Al with morpholine in toluene, were not successful and only starting material was recovered (Scheme 4.23).[131]



219 **220**

Scheme 4.23

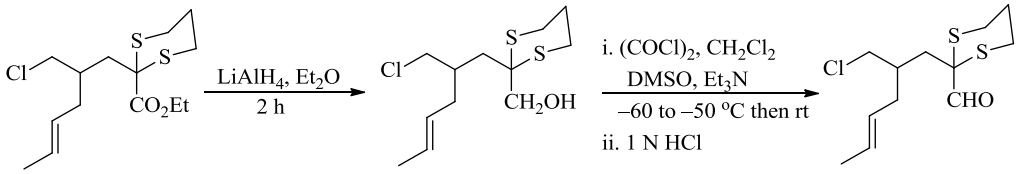
Likewise, using DIBAL-H (1.1 equiv.) was unsatisfactory and a mixture of compounds was formed with many spots observed by TLC analysis. Only a trace of aldehyde was observed by ^{1}H NMR spectroscopy. Adding more equivalents of DIBAL-H and warming the mixture to room temperature for full reduction gave none of the desired alcohol (Scheme 4.24).



219 **220**

Scheme 4.24

As an alternative, ester **219** was reduced using $LiAlH_4$ in Et_2O to give alcohol **221** in 80% yield, which was followed by a Swern oxidation[69] to afford the desired aldehyde **220** in 85% yield with a 1,3-dithiane group α to the aldehyde (Scheme 4.25).

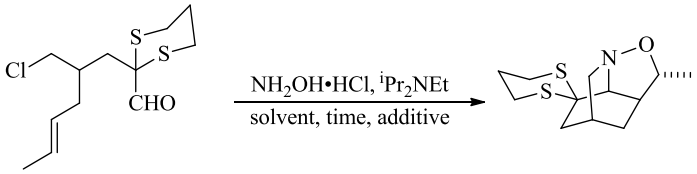


219 **221** 80% **220** 85%

Scheme 4.25

4.3.3 Tandem cyclisation–cycloaddition reaction

With aldehyde **220** in hand, it was now possible to attempt the tandem cyclisation–cycloaddition reaction. Using the same conditions from previous work on the bridged ring system, the aldehyde **220** was treated with hydroxylamine hydrochloride and *N*,*N*-diisopropylethylamine in toluene (Scheme 4.26). Different conditions were tried, but in all cases the cycloadduct **222** was formed in low yield (Table 4.6). We suspected that the reaction required higher temperatures than heating in toluene, though with xylene no enhancement was seen. In all cases a mixture was obtained as judged by many spots on TLC analysis.



220 **222**

Scheme 4.26

Entry	Solvent	Time (h)	Temp (°C)	Additive	222 (%)
1	PhMe	3.5	110		0
2	PhMe	18	110		18
3	PhMe	2 h at 60 °C then 18 h	110	TBAI 0.1 eq.	22
4	PhMe	2 h at 60 °C then 18 h	110	$MgSO_4$	36
5	PhMe	2 h at 60 °C then 18 h	110	Molecular sieves	20
6	PhMe	48	110	$MgSO_4$	decomposed
7	PhMe	18	60	$MgSO_4$	Oxime trace & starting material
8	Xylene	3.5	110		0
9	Xylene	18	110		13
10	Xylene	18	110	TBAI	22

Table 4.6

4.3.4 Reaction optimisation

Table 4.6 shows that the best yield of the cycloadduct was obtained by using $MgSO_4$ as an additive (entry 4). The condensation step is probably reversible, which can explain why using a dehydrating agent is helpful. To explain the low yields in forming the cycloadduct, there are many possibilities, some of which are that:

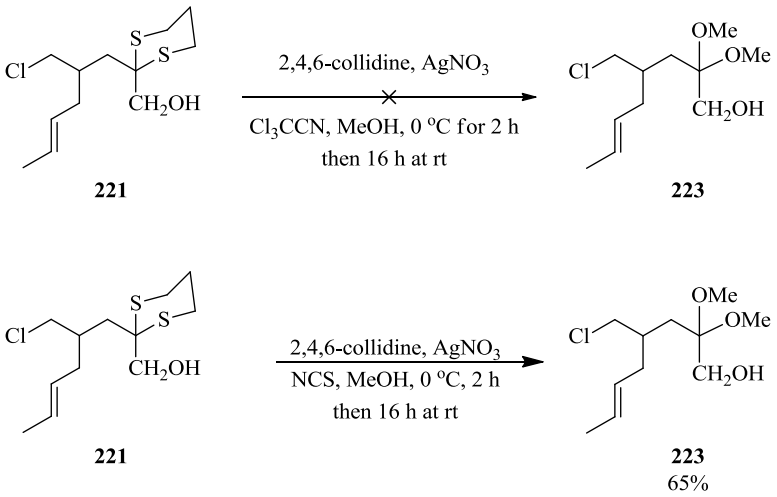
1. The condensation step is difficult to carry out in this case, probably because it is a reversible reaction.

2. The propensity of the dithiane moiety to act as a nucleophile (cyclization with chloride displacement).

3. The chloride is not a sufficiently good leaving group to enable the cyclisation step.

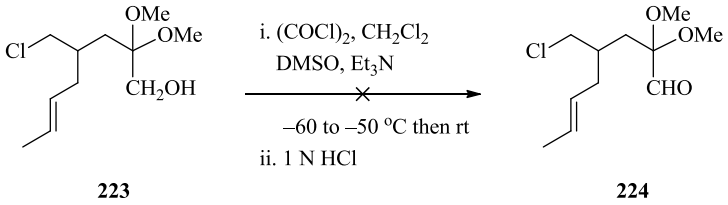
To circumvent this problem, a strategy was devised that would increase the yield. Firstly, the hydroxylamine hydrochloride and *N*,*N*-diisopropylethylamine in toluene were heated at 60 ^{o}C over a variety of times in order to form the oxime; unfortunately the yield was too low and mostly the starting aldehyde **220** was recovered (entry 7). Using molecular sieves did not enhance the cycloadduct yield (entry 5). Heating the reaction mixture for a long time (such as 48 h) led to decomposition. As a result, this indicated that the formation of the oxime is a difficult step under these conditions.

Coldham and co-workers reported that having a dimethyl acetal α to the aldehyde is better than a dithiane for the cycloaddition to give the ABC ring system of the manzamine alkaloids.[132,133] Postulating that steric hindrance or nucleophilicity of the dithiane was causing problems, we decided that it would be better to explore the dimethyl acetal for our synthesis. To do so, the dithiane alcohol **221** was treated with silver nitrate, 2,4,6-collidine and trichloroacetonitrile in methanol but this gave no product and only starting material was recovered. However, using *N*–chlorosuccinimide under the same conditions afforded the diacetal **223** in 65% yield (Scheme 4.28).[133] Attempts were made to purify the desired compound which was difficult because of the 2,4,6-collidine.



Scheme 4.28

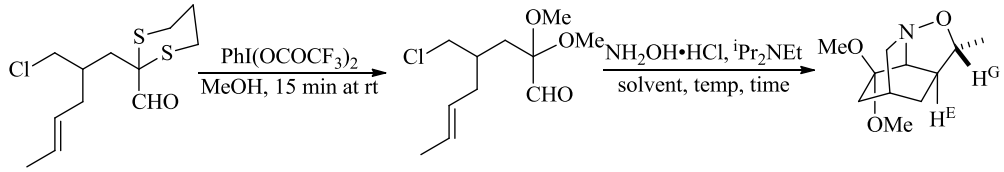
The next step in our synthesis was the oxidation of the alcohol **223** using a Swern oxidation[69] to generate aldehyde **224**. Surprisingly, no desired aldehyde was isolated and the dimethyl acetal had decomposed. We thought that this might be due to the acidic work up of the Swern oxidation, but doing the work up without HCl did not help to obtain the desired product (Scheme 4.29).



Scheme 4.29

To circumvent this, the scope of the search was expanded to find suitable conditions, and we found that the dithiane aldehyde **220** was converted to the diacetal **224** in 65% yield, using [bis(trifluoroacetoxy)iodo]benzene (PIFA) in methanol (Scheme 4.30).[134] We were now at the step to attempt the cascade reaction with our new precursor aldehyde. As such, heating aldehyde **224** at 60 °C in toluene showed the formation of the oxime, then the solution was heated under reflux overnight to give a low yield of **225** (Table 4.7, entry 4). Decomposition products were also obtained.

Although $MgSO_4$ seemed to help the reaction to some extent (entry 4), using a promoter like TBAI gave no effect and the starting material decomposed quickly.



220 **224** 65% **225**

Scheme 4.30

Entry	Solvent	Time	Additive	225 (%)
1	PhMe	16 h	–	0
2	PhMe	16 h	$MgSO_4$	0
3	PhMe	2 h at 60 °C then reflux 16 h	–	0
4	PhMe	30 min at 60 °C then reflux 16	$MgSO_4$	15
5	PhMe	30 min at 60 °C then reflux 16	TBAI 0.1 equiv.	0
6	PhMe	30 min at 60 °C then reflux 16	$MgSO_4$/TBAI 0.1 equiv.	0
7	Xylene	16 h	–	0
8	Xylene	16 h	$MgSO_4$	0

Table 4.7

The stereochemistry was assigned tentatively based on the ^1H NMR spectrum (Figure 4.8). This showed the H^G peak at 4.10 ppm as a quartet with a *J* value of 6.0 Hz, and H^E as a doublet of doublets with *J* values of 9.0 and 3.5 Hz at 2.97 ppm. This is similar to the previous result in the formation of cycloadducts **210** and **222**.

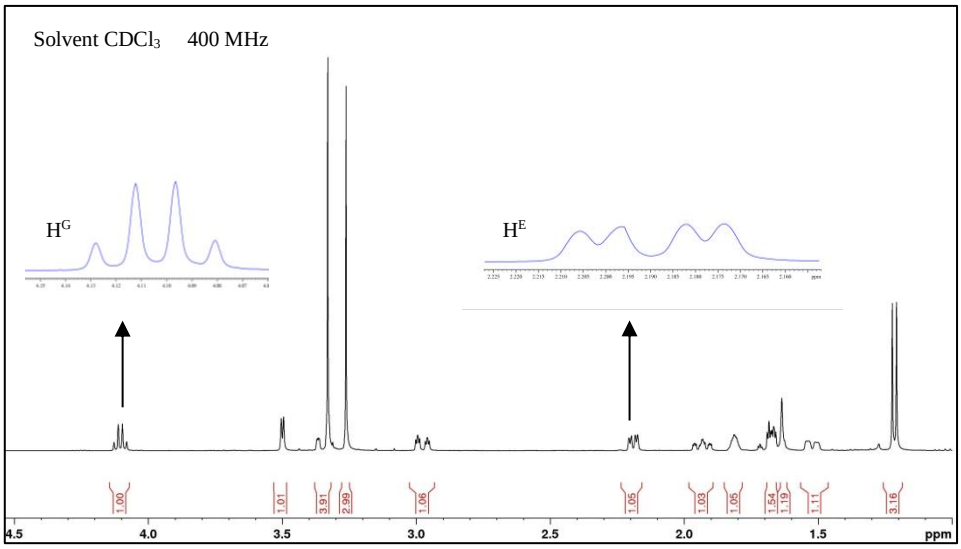
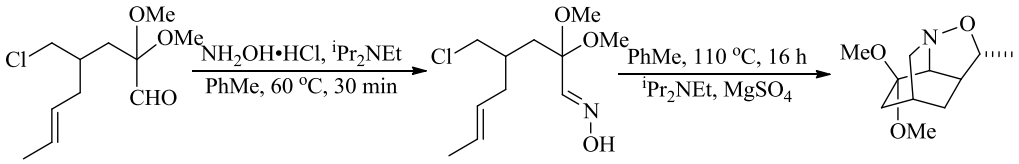


Figure 4.8

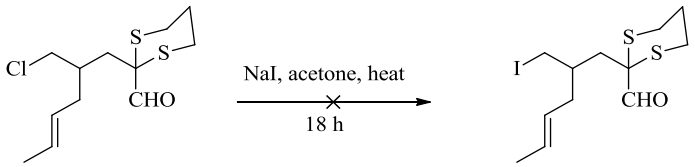
We thought that HCl might be generated *in situ* to hydrolyse the diacetal, and so the oxime **226** was isolated and purified by column chromatography on silica gel, in excellent yield. The oxime **226** was then heated under reflux in toluene with diisopropylethylamine to afford the cycloadduct in low yield (Scheme 4.31).



224 | **226** 90% | **225** 15%

Scheme 4.31

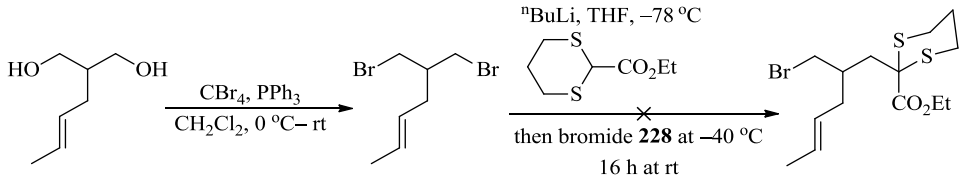
One possibility for the poor formation of the cycloadduct **225** is that the chloride may not be a sufficiently good leaving group for this reaction. Previous work in the Coldham group by Burrell, showed that conversion of a chloride to an iodide *via* a Finkelstein reaction, could improve a related cycloaddition.[62] Aldehyde **220** was treated with sodium iodide in acetone under reflux for 18 h (Scheme 4.32), but unfortunately only aldehyde **220** was recovered.



220 **227**

Scheme 4.32

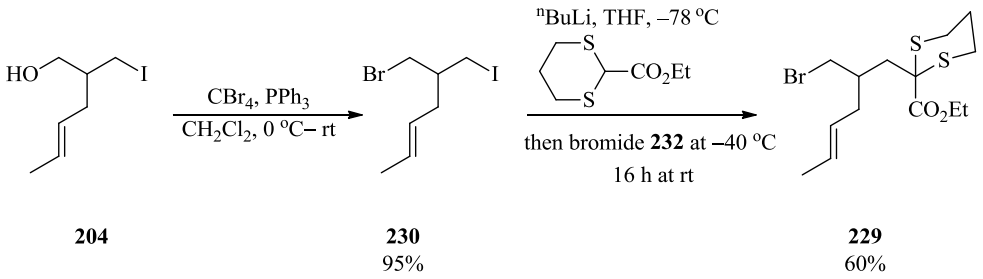
Due to these issues, an alternative route was explored in which we began with crotylated dibromide **228** instead of the iodo-chloro **215** compound. Treatment of the diol **203** with carbon tetrabromide (2.2 equiv.) and triphenylphosphine (2.2 equiv.) in dichloromethane gave dibromide **228** in 95% yield (Scheme 4.33). Using the previously optimised reaction conditions, the dibromide was treated with the ethyldithiane carboxylate using ^{n}BuLi as a base. This gave a complex mixture of products with many spots observable by TLC analyses.



203 **228** 95% **229**

Scheme 4.33

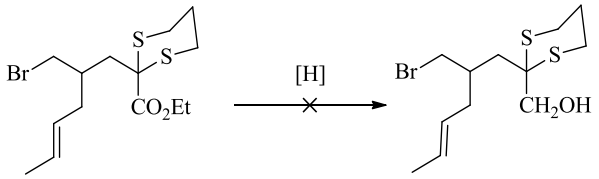
Based on this result, we thought that the iodo-bromo compound **230** would be better to use instead. Therefore, treatment of iodo-alcohol **204** with carbon tetrabromide (1.1 equiv.) and triphenylphosphine (1.1 equiv.) in dichloromethane gave iodo-bromide **230** in 88% yield. Alkylation with the ethyldithiane carboxylate using ^{n}BuLi as the base, gave ester **229** in 60% yield (Scheme 4.34).



204 **230** 95% **229** 60%

Scheme 4.34

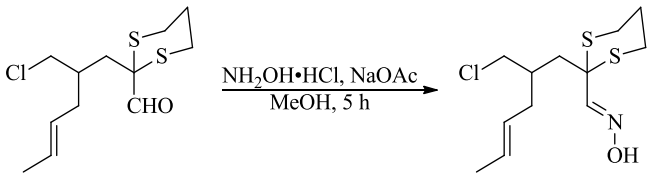
Unfortunately, attempts to reduce the ester **229** using 1.0 equivalent $LiAlH_4$ in THF or DIBAL–H in dichloromethane failed to yield the desired aldehyde and an inseparable mixture was formed (Scheme 4.35). The outcome of this reaction was clearly disappointing. It was thought that the bromide was probably not stable enough to tolerate the reduction.



229 **231**

Scheme 4.35

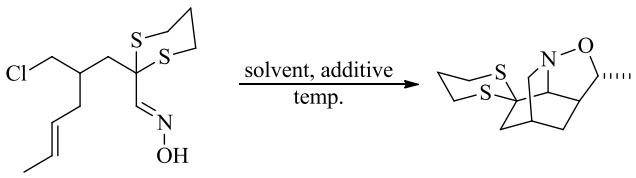
With substrate **220** in hand, it was necessary to optimise the conditions that allowed for successful condensation, cyclisation, then cycloaddition. Therefore, we envisaged that making the oxime (which was partially successful using hydroxylamine hydrochloride and Hünig's base) would be the key to access the cycloadduct. So, aldehyde **220** was treated with hydroxylamine hydrochloride and sodium acetate in anhydrous methanol at room temperature to give the oxime **232** in a quantitative yield using the method reported by Stockman and co-workers (Scheme 4.36).[135]



220 **232** 100%

Scheme 4.36

The oxime **232** was then heated under reflux in toluene for 18 h but surprisingly, no cycloadduct was detected either by TLC or ^{1}H NMR spectroscopy and only aldehyde and oxime were observed. Switching the solvent to xylene did not give the desired cycloadduct either. When $MgSO_4$ was added to the mixture, only 20% yield of the cycloadduct **222** together with degradation products were obtained (Table 4.8, Scheme 4.37). Furthermore, when the reaction was conducted with or without TBAI in acetonitrile for 18 h, only mixtures that were difficult to purify were obtained (Table 4.8, entries 4 and 5). As hydrochloric acid is formed the addition of *N*,*N*-diisopropylethylamine (Hünig's base) could affect the nitrone formation from oxime **232** but heating the oxime with Hünig's base in toluene gave a low yield of the desired cycloadduct.



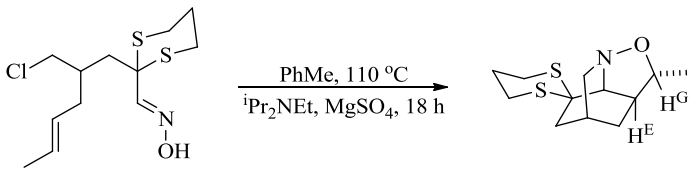
232 **222**

Scheme 4.37

Entry	Solvent	Temp. (ºC)	Time (h)	Additive	Yield%
1	PhMe	110	18		0
2	PhMe	110	18	$MgSO_4$	20
3	PhMe	110	18	TBAI	0
4	MeCN	83	18		0
5	MeCN	83	18	TBAI	0
6	PhMe	110	18	$^{i}Pr_2NEt$	15

Table 4.8

We attempted to form the desired product using both Hünig's base and a dehydrating agent. Interestingly, upon refluxing the oxime with magnesium sulphate and Hünig's base in toluene for 18 h afforded the desired cycloadduct in up to 57% yield (Scheme 4.38). Addition of magnesium sulphate is due to the need to avoid water to hydrolyse the oxime, and Hünig's base was added to remove the generated hydrochloric acid that might promote hydrolysis of the oxime. The reason for the poor cycloadduct formation straight from the aldehyde **220** might be due to the difficulty of the condensation to give the oxime.



232 **222** 57%

Scheme 4.38

4.3.5 Stereochemistry assignment of cycloadduct 222

The stereochemistry of the product **222** was predicted tentatively as compared to other cycloadducts that were mentioned in this chapter. The proton H^G was observed at 4.19 ppm as a quartet with a *J* value of 6.0 Hz, and proton H^E at 2.42 ppm as a doublet of doublets with *J* values of 9.5 and 3.5 Hz (see ^{1}H NMR spectrum, Figure

4.9). The lack of any coupling between protons H^G and H^E indicates the stereochemistry as shown (Scheme 4.38) as this is also observed in the cycloadducts **210** and **212** (page 65 and 84).

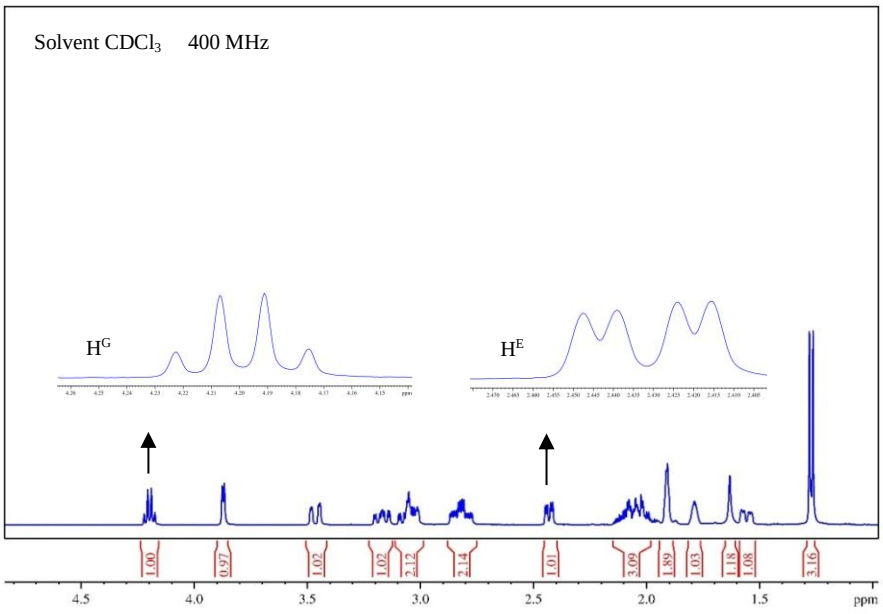
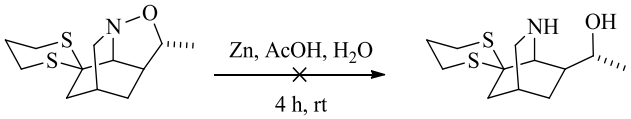


Figure 4.9

Having demonstrated the suitability of the cyclisation−cycloaddition cascade in the synthesis of the bridged system of the iboga alkaloid core structure, we believed that it would be possible now, with the cycloadduct in hand, to complete the synthesis of 19-hydroxy-ibogamine **136**.

4.4 Formal synthesis of the 19-hydroxy-ibogamine

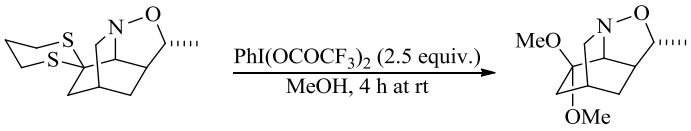
According to the synthetic plan, the next step was to break the N–O bond, using the same method as before. The cycloadduct **222** was heated with zinc and acetic acid in water. After 4 h this method only returned starting material. Leaving the reaction for a longer time led to decomposition (Scheme 4.39). This failure was attributed to the coordination of sulphur to zinc which might have prevented the reaction at the N–O bond.



222 **233**

Scheme 4.39

It was therefore thought that removing the dithiane, and then cleaving the N–O bond could provide the amino-alcohol compound. A decision was made to transform the dithiane to the dimethylacetal. The transketalisation reaction was performed using the same conditions as used for compound **224**. Cycloadduct **222** was treated with PIFA in methanol (Scheme 4.40) but only 35% yield of the diacetal cycloadduct **225** was obtained and mostly the starting material was recovered. All efforts to optimise the yield, such as adding more equivalents of catalyst and leaving the reaction for a longer time, failed to improve the conversion.

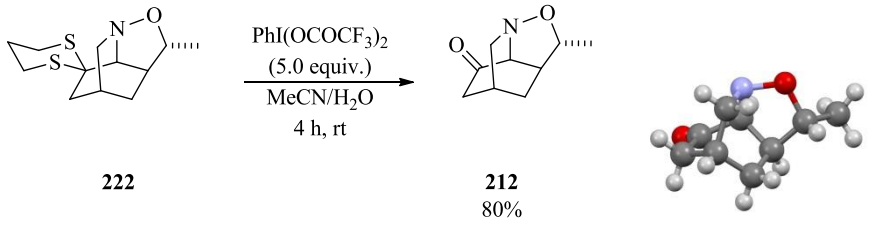


222 **225**
35%

Scheme 4.40

An alternative method involved deprotecting the dithiane to generate the ketone, using the same method as before, but with MeCN/H_2O (9:1) instead of methanol. As the R_f of starting material and the product were almost the same, the reaction was stopped after 4 h, dichloromethane was added and the mixture was neutralised with sodium bicarbonate. Unfortunately, the ^{1}H NMR spectrum showed that the starting material remained with some product. Therefore, further attempts were tried to optimise the conditions. Using MeCN/H_2O (1:1) and increasing the reaction time did enhance the yield slightly. In response to this observation, the reaction was repeated with increasing the amount of PIFA up to 5.0 equivalents. The equivalents were

added in three portions; initially 1.0 equivalent was added, followed by 1.5 equivalents after 30 minutes and then an additional 2.5 equiv. were added to afford the desired ketone **212** in good yield (Scheme 4.41).



222 **212** 80%

Scheme 4.41

The stereochemistry of the product **212** was confirmed by single crystal X-ray crystallography, which showed the orientation of the methyl group. Based on the ^{1}H NMR spectroscopy (Figure 4.10), proton H^{G} was a quartet at 4.26 ppm and the *J* value was 6.0 Hz, while proton H^{E} was observed as a doublet of doublets at 2.45 ppm with *J* values of 9.5 and 3.5 Hz. As before, no coupling between these vicinal protons was observed and this supports the predictions that were made for all of the other cycloadducts that have been discussed previously in this chapter.

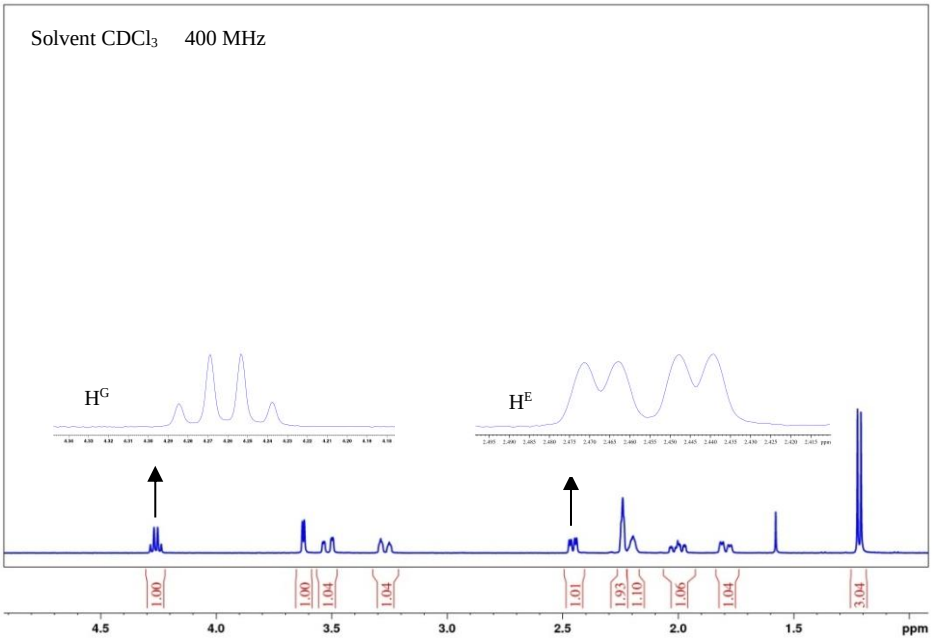
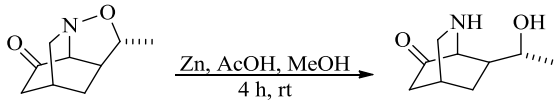


Figure 4.10

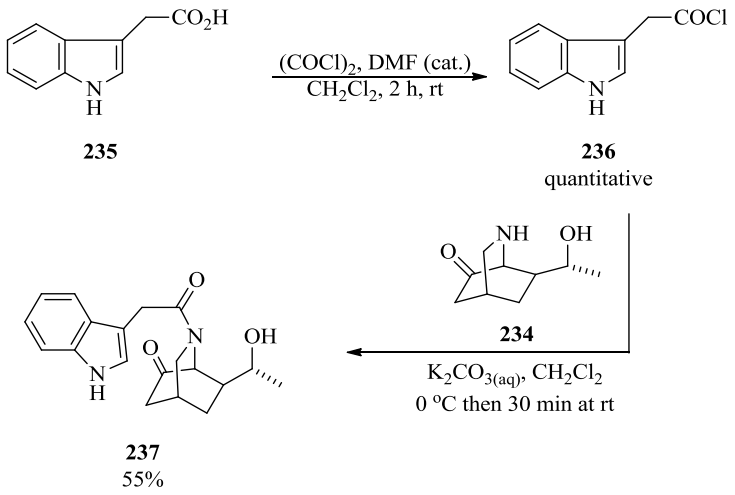
The following step was to cleave the N−O bond, using zinc in acetic acid and water. No reaction occurred while heating the reaction at 70 ºC for 6 h and only starting material was recovered. Repeating the reaction with heating overnight led to decomposition of the starting material. Alternatively, zinc in acetic acid and methanol was used. After 4 h at room temperature, the ^{1}H NMR spectrum of the crude product showed a mixture of product and starting material. Similarly, the reaction was repeated using activated zinc (stirring in 1.0 M HCl freshly prepared, washed with ethanol, ether and dried under vacuum) in acetic acid and methanol for 4 h at room temperature and this gave the desired amino alcohol **234** in quantitative yield (Scheme 4.42).[136]



212 **234** quantitative

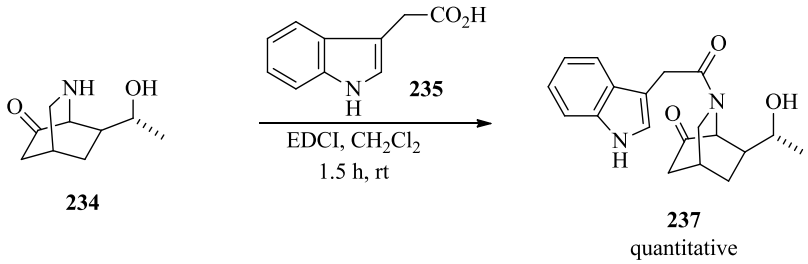
Scheme 4.42

With the amino-alcohol in hand, we were in a position to target the desired molecule **136**. Treating indole-3-acetic acid **235** with oxalyl chloride in DMF and dichloromethane afforded compound **236** in a quantitative yield. The crude product was used with no further purification in a reaction with amine **234**. Using a solution of potassium carbonate in dichloromethane compound **237** was obtained in a moderate yield (Scheme 4.43).



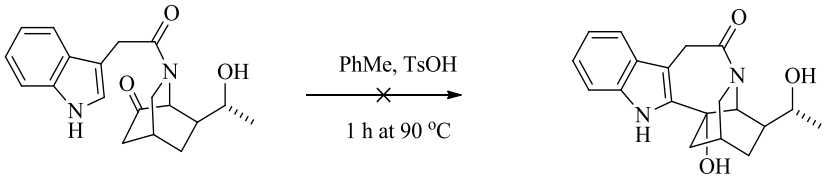
Scheme 4.43

To optimise the yield, the reaction was carried out using pyridine in dichloromethane, but the product was obtained in almost similar yield. Alternatively, a direct condensation by treating secondary amine **234** and indole-3-acetic acid **235** (1.1 equiv.), using EDCI as coupling reagent in dichloromethane, gave amide **237** in quantitative yield (Scheme 4.44).



Scheme 4.44

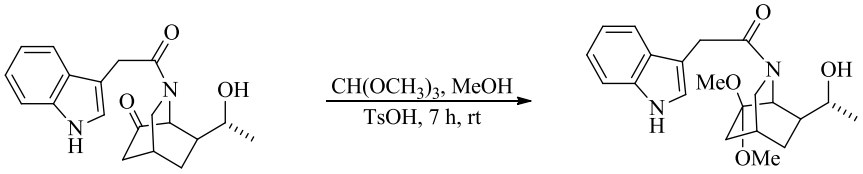
In order to form the 7-membered ring product **238**, Hanaoka[105,137] and co-workers reported that treating the dimethyl acetal formed from ketone **161** (Scheme 3.8) in boiling benzene with *p*-toluenesulfonic acid gave the cyclised product. We wondered whether the same type of chemistry would be successful with the ketone **237**. However, attempts to form the 7-membered ring compound **238** using toluene and *p*-toluenesulfonic acid gave a mixture that was difficult to purify (Scheme 4.45).



237 **238**

Scheme 4.45

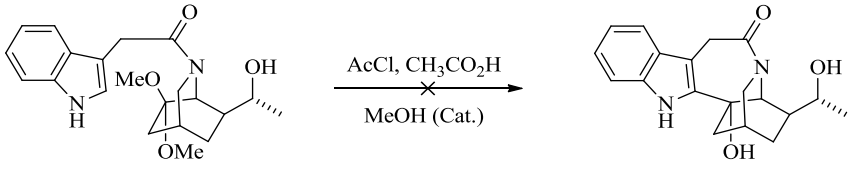
Related chemistry by Höck and Borschberg reported that a similar ketone was inactive towards the cyclisation reaction.[116] However, the acetal **177** (Scheme 3.14) was reported to undergo successful cyclisation. Therefore, we treated ketone **237** with trimethylorthoformate and *p*-toluenesulfonic acid in methanol to give compound **239** in good yield (Scheme 4.46).



237 **239**
85%

Scheme 4.46

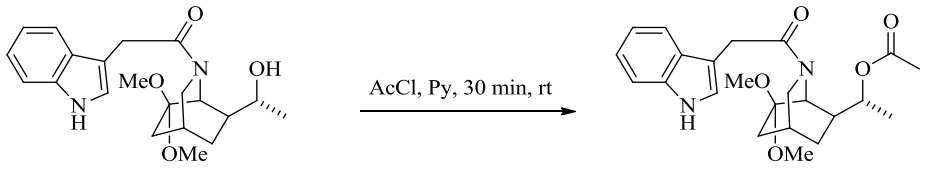
Towards the cyclisation, acetal **239** was treated with acetyl chloride and acetic acid in methanol (cat.) using the same conditions described by Höck and Borschberg,[116] but no cyclised product was observed and a mixture of inseparable products was formed (Scheme 4.47).



239 **238**

Scheme 4.47

It has been reported that reversibility of the cyclisation reaction due to traces of water produces the corresponding ketone which can resist the cyclisation.[116] So we carried out the reaction with dry glacial acetic acid and distilled acetyl chloride in dry methanol but inseparable mixture was formed. Finally, we decided to go through the formal synthesis. Pleasingly, treatment of alcohol **239** with acetyl chloride and pyridine in dichloromethane gave the ester **177** in 87% yield (Scheme 4.48). Ester **177** has been reported by Höck and Borschberg in their synthesis of 19-hydroxy-ibogamine.[116]



239 **177**
87%

Scheme 4.48

4.4.1 The NMR data analysis of ester 177

We compared the NMR data of ester **177** in $CDCl_3$ with that reported by Höck and Borschberg (they report their ^1H NMR spectrum in $CDCl_3$). Our NMR spectra and the one reported by Borschberg are clearly the same. It is possible to see that in the data reported by Borschberg, there are only a few differences in the ^1H NMR data in comparison with our data (Table 4.9, main differences highlighted in red). One aromatic proton appeared as a doublet at 7.57 ppm with *J* value of 7.5 Hz; Borschberg, instead, reported this as ddd at 7.55 ppm with *J* values of 7.8, 1.2 and 0.6 Hz. Protons at 3.77−3.76 ppm and 3.75−3.74 ppm appeared as a multiplet, while they were reported as dd at 3.72 ppm and 3.68 ppm respectively. The proton at 2.22 ppm was reported as a ddd, whilst, in our sample this appeared as a multiplet at 2.29−2.20 ppm. The multiplet protons in the Borschberg data were not reported as a range. Unfortunately, the Borschberg NMR spectra were not available in the supplementary information to be compared to our spectra (see appendix 9).

Borschberg data	Our sample data*
8.26 (1H, br. *s*, NH)	8.30 (1H, br. s, NH)
7.55 (1H, ddd, *J* 7.8, 1.2, 0.6 Hz, ArH)	7.57 (1H, d, *J* 7.5, ArH)
7.34 (1H, dt, *J* 8.0, 0.9 Hz, ArH)	7.36 (1H, dt, *J* 8.0, 1.0 Hz, ArH)
7.21 (1H, m, ArH)	7.23−7.22 (1H, m, ArH)
7.17 (1H, ddd, *J* 8.2, 7.1, 1.2 Hz, ArH)	7.19 (1H, ddd, *J* 8.0, 7.0, 1.0 Hz, ArH)
7.12 (1H, ddd, *J* 7.9, 7.1, 1.1 Hz, ArH)	7.13 (1H, ddd, *J* 8.0, 7.5, 1.0 Hz, ArH)
4.89 (1H, d, *J* 1.5 Hz, CH)	4.91 (1H, d, *J* 1.5 Hz, CH)
4.50 (1H, dq, *J* 10.5, 6.1 Hz, CH)	4.52 (1H, dq, *J* 10.5, 6.0 Hz, CH)
3.72 (1H, dd, *J* 15.2, 1.0 Hz, CH)	3.77−3.76 (1H, m, CH)
3.68 (1H, dd, *J* 15.2, 1.2 Hz, CH)	3.75−3.74 (1H, m, CH)
3.38 (1H, dt, *J* 10.0, 2.3 Hz, CH)	3.39 (1H, dt, *J* 10.5, 2.5 Hz, CH)
3.27 (1H, dt, *J* 10.0, *ca.* 2.5 Hz, CH)	3.29 (1H, dt, *J* 10.0, 2.5 Hz, CH)
3.24 (3H, s, CH_3)	3.26 (3H, s, CH_3)
3.18 (3H, s, CH_3)	3.20 (3H, s, CH_3)
2.22 (1H, ddd, *J* 10.6, 6.1, 1.6 Hz, CH)	2.29−2.20 (1H, m, CH)
2.11 (3H, s, CH_3)	2.13 (3H, s, CH_3)
2.02 (1H, m, CH)	2.05−2.02 (1H, m, CH)
1.76 (1H, dt, *J* 13.7, 2.2 Hz, CH)	1.78 (1H, dt, *J* 14.0, 2.0 Hz, CH)
1.70 (1H, m, CH)	1.70−1.96 (1H, m, C*H*H)
1.64 (1H, dt, *J* 13.7, *ca.* 3.0 Hz, CH)	1.66 (1H, dt, *J* 13.5, 3.0 Hz, CH)
1.20 (1H, d, *J* 6.1 Hz, CH_3)	1.22 (3H, d, *J* 6.0 Hz, CH_3)
0.93 (1H, ddt, *J* 10.9, *ca.* 5.5, 2.5, CH)	0.92(1H, ddt, 13.0, 5.5, 2.5 Hz, CH)

*all our *J* values reported to nearest 0.5 Hz

Table 4.9

For the ^{13}C NMR spectra, the molecule contains 23 carbons. The ^{13}C NMR data are a good match between Borschberg's and ours (Table 4.10). Our conclusion is that our ester had the same NMR spectra as that reported. Finally, this chemistry therefore completes a formal synthesis of 19-hydroxy-ibogamine.

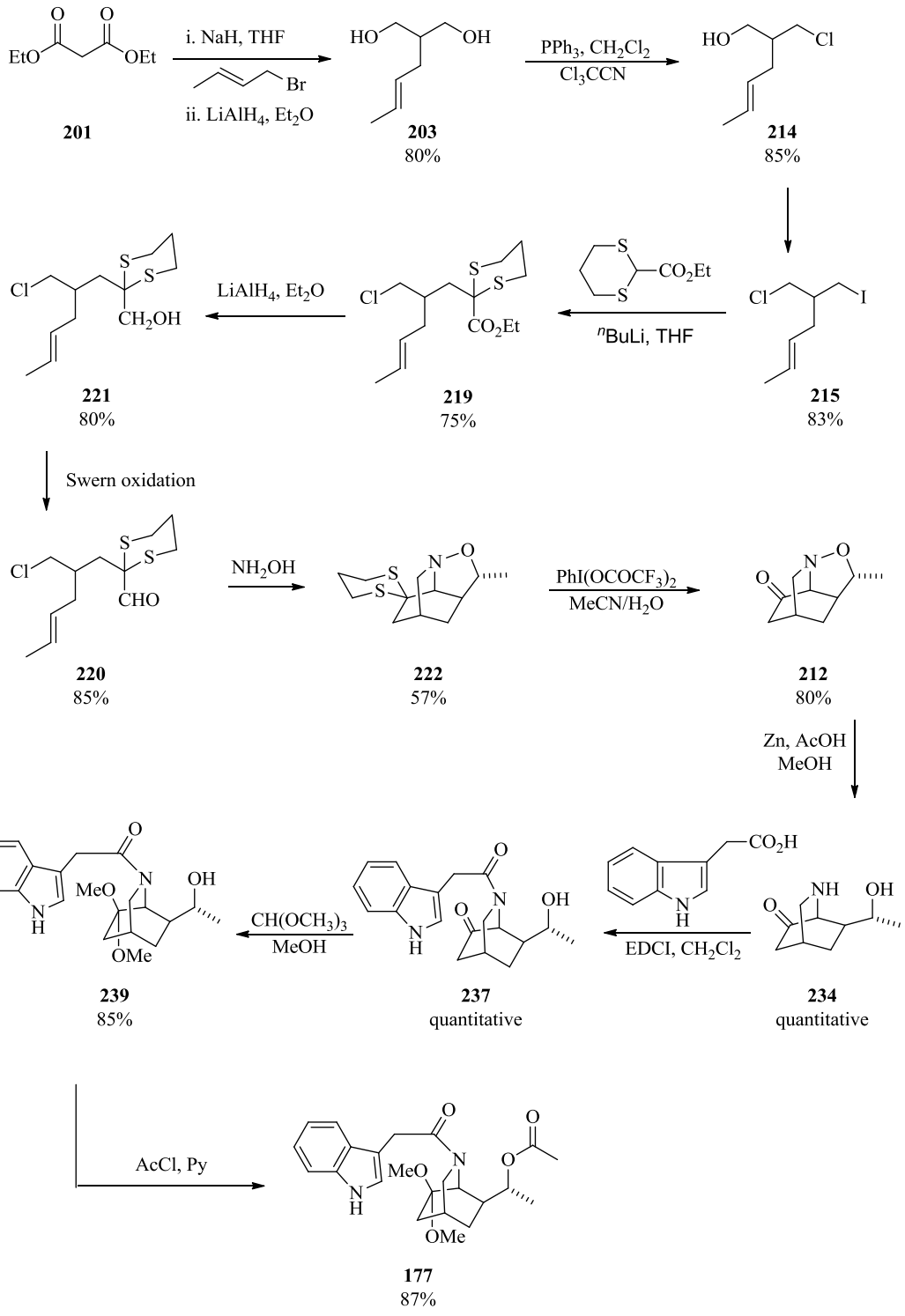
Borschberg	Our sample
171.3 (*s*)	171.3 (C=O)
171.1 (*s*)	171.1 (C=O)
136.1 (*s*)	136.1 (C)
127.4 (*s*)	127.4 (C)
122.9 (*d*)	122.9 (CH)
121.9 (*d*)	121.9 (CH)
119.3 (*d*)	119.3 (CH)
118.4 (*d*)	118.4 (CH)
111.2 (*d*)	111.2 (CH)
109.0 (*s*)	108.8 (C)
101.8 (*s*)	101.7 (C)
71.4 (*d*)	71.4 (CH)
49.0 (*q*)	49.0 (CH_3)
48.9 (*t*)	48.9 (CH_2)
48.1 (*q*)	48.1 (CH_3)
45.8 (*d*)	45.7 (CH)
38.1 (*d*)	38.1 (CH)
36.9 (*t*)	36.9 (CH_2)
30.6 (*t*)	30.6 (CH_2)
28.2 (*t*)	28.2 (CH_2)
27.5 (*d*)	27.5 (CH)
21.5 (*q*)	21.5 (CH_3)
17.8 (*q*)	17.8 (CH_3)

Table 4.10

4.5 Conclusion

In this chapter, we have demonstrated that the cyclisation–cycloaddition methodology developed in the group can be used for the synthesis of two-carbon bridged tricyclic cycloadducts, and this was applied towards the synthesis of the core of the iboga alkaloids. We have synthesized a range of precursor aldehydes and identified optimum conditions for carrying out novel cyclisation, nitrone cycloaddition, cascade chemistry between aldehydes and hydroxylamine to produce a range of two-carbon bridged systems.

An aldehyde bearing enolisable hydrogens was tested in the cascade chemistry, but in this case, the cyclisation-cycloaddition cascade gave a low yield of the desired cycloadduct. Non-enolisable aldehyde substrates were found to give better yield and worked well in the cascade chemistry. We successfully achieved the formal synthesis of one iboga alkaloid called 19-hydroxy-ibogamine. A summary of the complete formal synthesis is shown in Scheme 4.49.


i. NaH, THF
ii. LiAlH4, Et2O
PPh3, CH2Cl2
Cl3CCN
nBuLi, THF
LiAlH4, Et2O
Swern oxidation
NH2OH
PhI(OCOCF3)2
MeCN/H2O
Zn, AcOH
MeOH
EDCI, CH2Cl2
CH(OCH3)3
MeOH
AcCl, Py
201
203
80%
214
85%
215
83%
219
75%
221
80%
220
85%
222
57%
212
80%
234
quantitative
237
quantitative
239
85%
177
87%

Scheme 4.49

Chapter 5 Towards the test of a proposed biosynthetic route of daphlongeranines

5.1 The Daphniphyllum alkaloids

Daphniphyllum alkaloids are a structurally diverse type of natural products isolated from the Yuzuriha tree, found in central and southern Japan.[138] *Daphnimacrine* was first isolated in 1909 by Yagi.[139] It is one of the C30 type of *Daphniphyllum* alkaloids, but the structure was difficult to elucidate using the technology at the time. Extensive research has been done by Hirata into the *Daphniphyllum* alkaloids and to date more than 200 *Daphniphyllum* alkaloids have been discovered and characterised.[140] They are all complex and polycyclic molecules, and have been classified into 6 groups based on their structures: daphnilactone A **240**, daphnilactone B **241**, yuzurimine **242**, yuzurine **243**, daphniphylline **244** and secodaphniphylline **245** (Figure 5.1).[138]

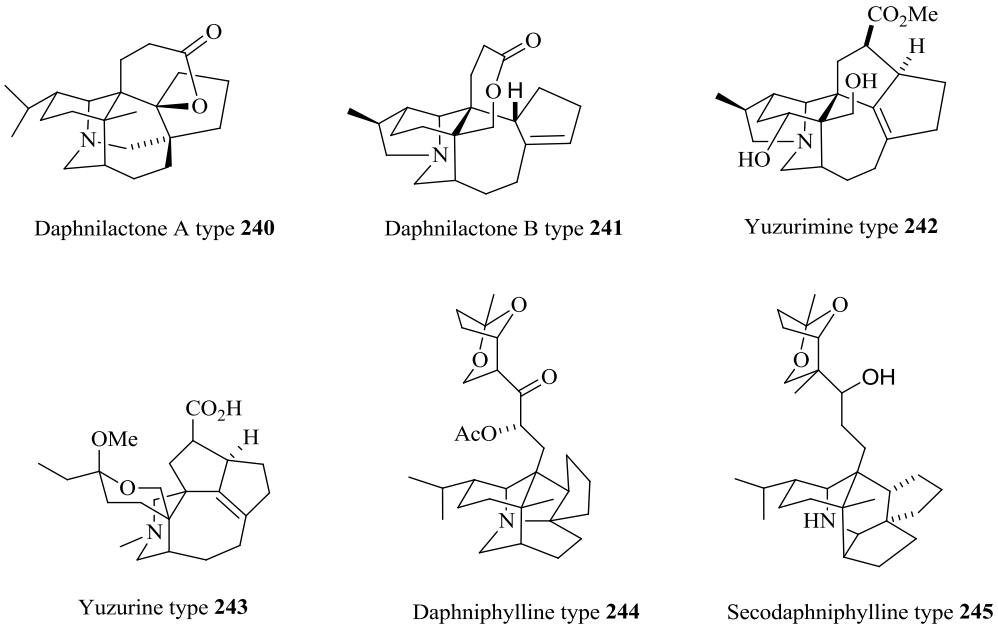


Figure 5.1

As one can imagine, from such a structurally diverse family of natural products, there is a great deal of research interest in the *Daphniphyllum* alkaloids, and as such, several reviews and books have been written on the subject.[141] This large subject area

is too vast to be fully described in this introduction. The *Daphniphyllum* alkaloids possess complex ring systems, which are a real challenge to synthetic chemists looking to synthesize them in the lab. Yamamura and Suzuki and co-workers reported that these alkaloids were derived from squalene,[142] a triterpene that is also important in humans as a biochemical precursor for the synthesis of all steroids. In 1996,[143] Heathcock suggested a laboratory synthesis route and postulated that squalene could be a suitable starting material to give the core ring structure of secodaphniphylline skeleton **246**. The daphniphylline skeleton **248** could potentially be obtained through compound **247** (Figure 5.2).

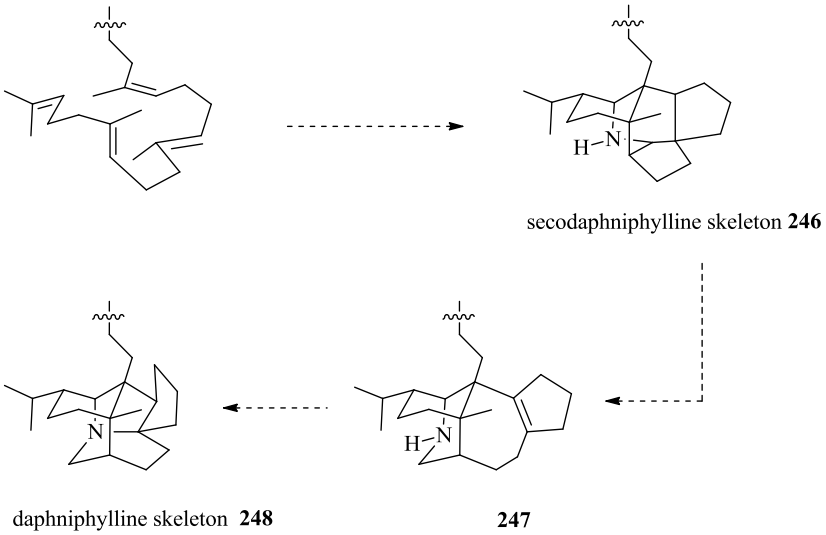
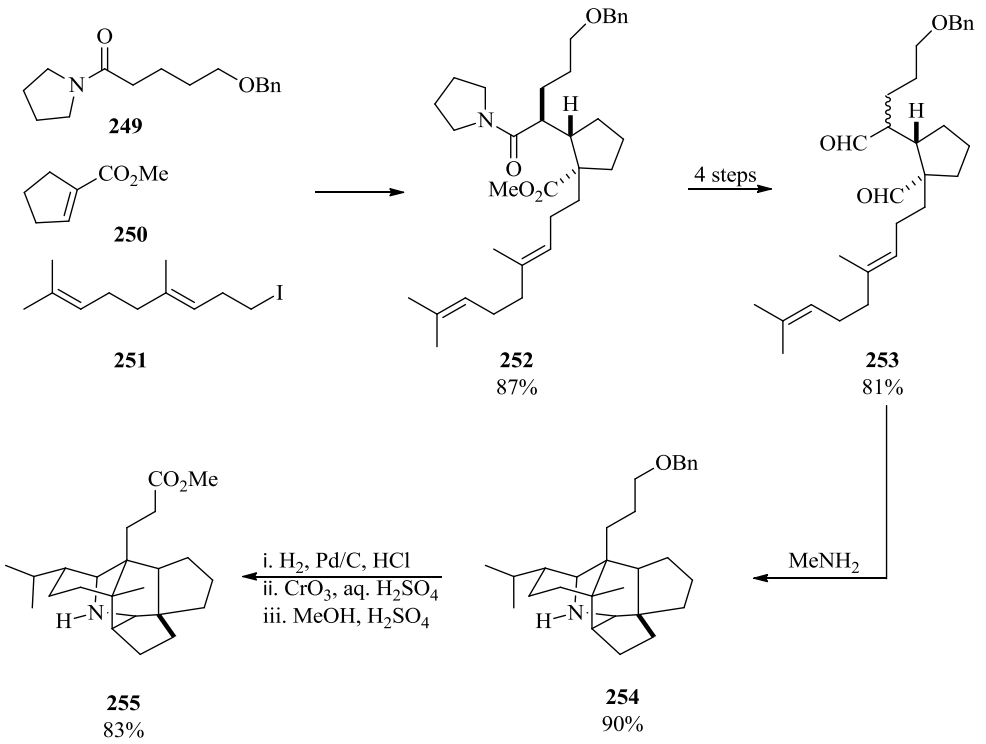


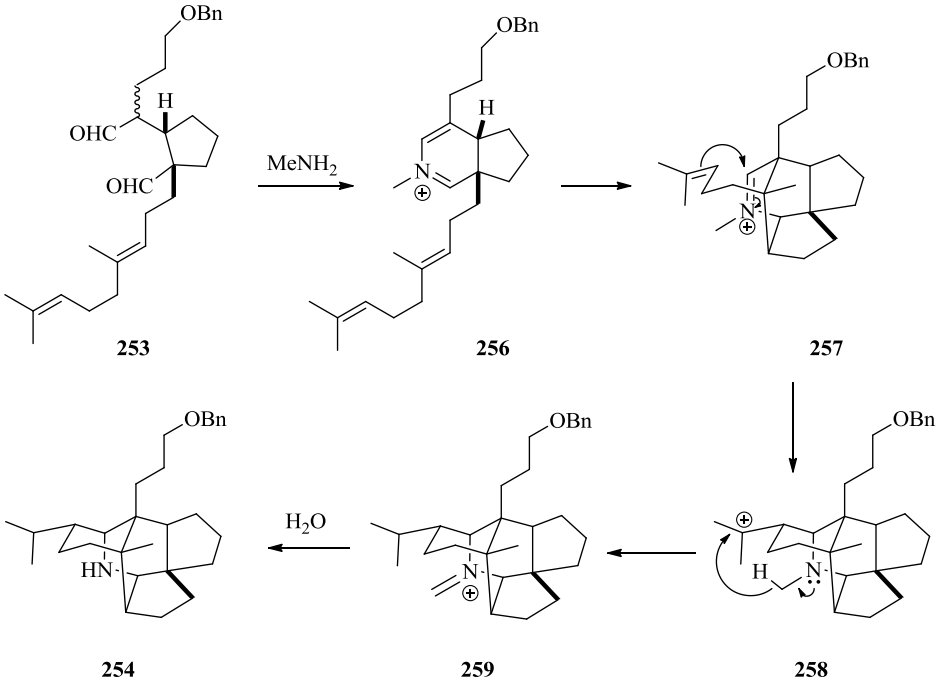
Figure 5.2

To test this, Heathcock and co-workers designed a plan to achieve the total synthesis of methyl homosecodaphniphylline **255**.[144] The amide **249**, ester **250** and iodide **252** were subjected to a cascade 1,4-addition-alkylation to afford compound **252**. This was transformed to aldehyde **253** in several steps, followed by a condensation reaction with methylamine to give cycloadduct **254**. Reduction and oxidation reactions, followed by an esterification reaction afforded methyl homosecodaphniphylline **255** (Scheme 5.1).



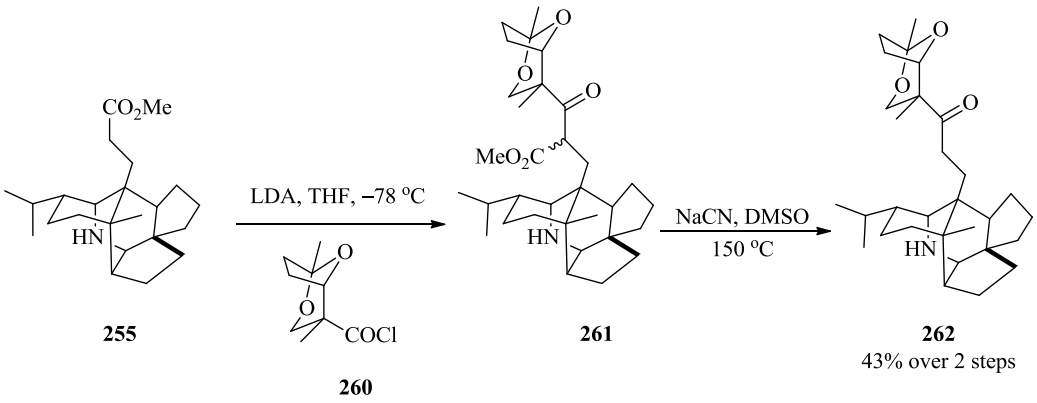
Scheme 5.1

The dialdehyde **253** was converted to **254** through condensation with methylamine to form iminium ion **256** which underwent an intramolecular Diels-Alder reaction to generate **257**. A cyclisation reaction took place followed by hydrolysis to give **254** (Scheme 5.2). Heathcock and co-workers suggested that the tetracyclisation step is a possible biomimetic step and pyridoxamine or the amine group of the amino acid could be used to help the cyclisation process.[145]



Scheme 5.2

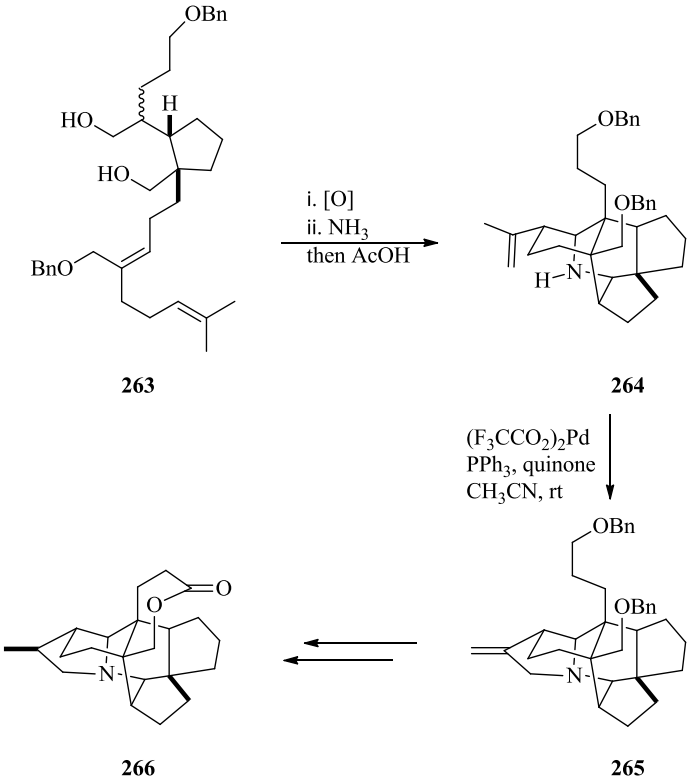
Later, Heathcock[146] and Stafford successfully synthesized the secodaphniphylline **262** from methyl homosecodaphniphylline **255** in two steps. Thus, treatment of ester **255** with LDA, then adding acid chloride **260** formed ketone **261**, which underwent a Krapcho decarboxylation to afford secodaphniphylline **262** (Scheme 5.3).



Scheme 5.3

Bukittinggine alkaloid **266** was extracted from the leaves of *Sapium baccatum*.[147] Due to its unique structure, which shows similarity to secodaphniphylline and the

yuzurimine alkaloids, this compound became a focus of research. Heathcock and co-workers were the first to report the total synthesis of (±)-Bukittinggine **266**.[147] They synthesized the diol **265** using the same Michael addition-alkylation step as before, followed by oxidation and tetracyclisation in the presence of ammonia to give tetracycle **264**. This then underwent cyclisation using palladium di(trifluoroacetate) as a catalyst to afford the *exo* alkene **265**. The cyclisation step using $Pd^{(II)}$ proceeded through reaction where the nucleophilic nitrogen atom attacks the Pd π-allyl complex.[147,148] The final product **266** was obtained in four steps from compound **265** (Scheme 5.4). The total yield was 3% over the whole 18 step synthesis.

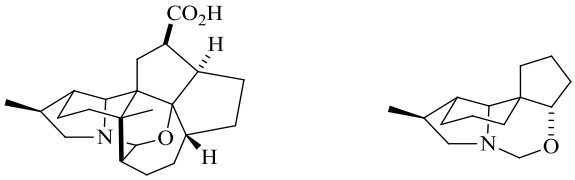


Scheme 5.4

Other research groups have reported the synthesis of part structures of the *daphniphyllum* alkaloids.[149-152]

5.2 Preliminary work in the group

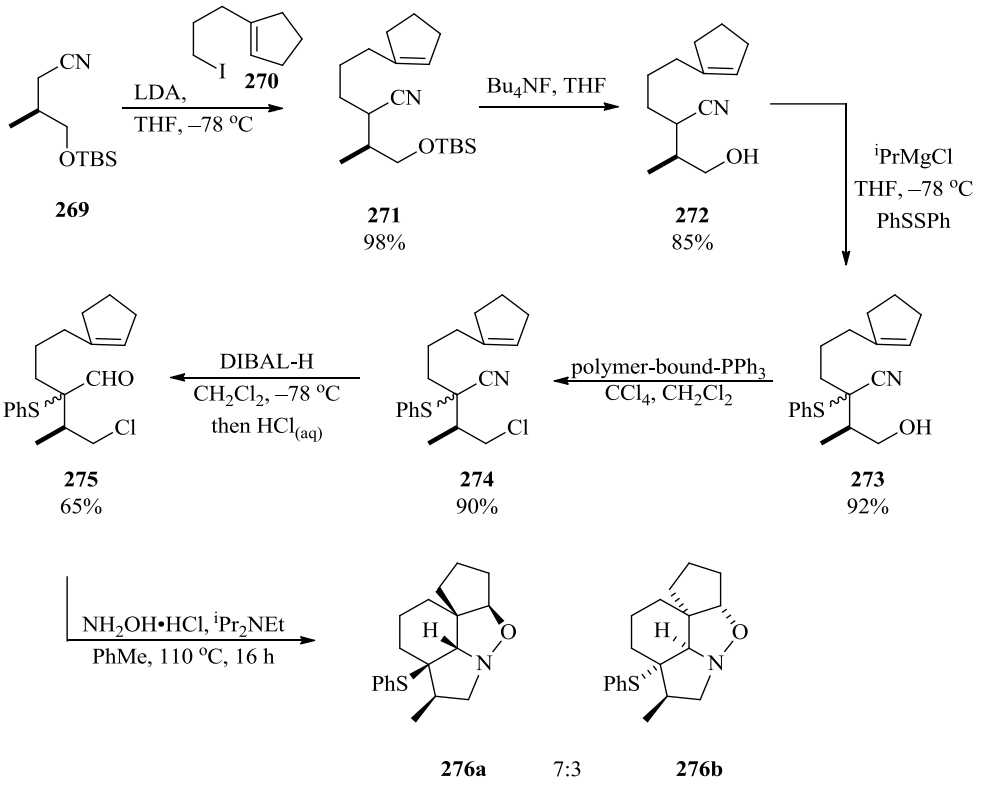
Due to the complex structure of the *Daphniphyllum* alkaloids, they have become an interest to many synthetic organic chemists. A paper in 2004[153] reported the isolation of daphcalycic acid **267** from the seeds of *Daphniphyllum calycinum*.



267 **268**

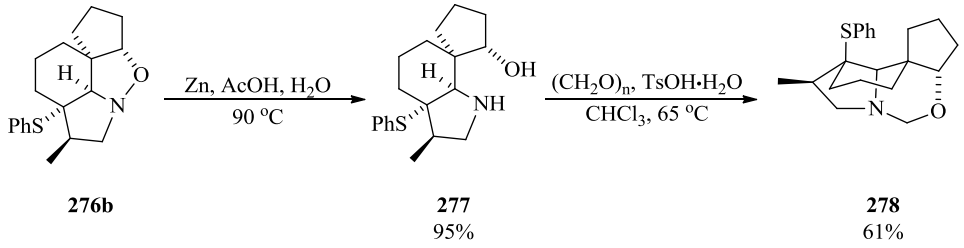
Figure 5.3

Coldham and co-workers had explored the use of cascade cyclisation-cycloaddition chemistry of a nitrone towards the synthesis of core structure **268** (Figure 5.3).[154] To do this, the nitrile **269** (prepared from Roche ester) was alkylated using LDA and iodide **270** to afford nitrile **271** in 98% yield in a 2:1 ratio of diastereoisomers. The hydroxyl group was deprotected to give alcohol **272** in good yield; this was treated with ^{i}PrMgCl, then sulfenylation with PhSSPh formed nitrile **273** as a 2:1 mixture of diastereoisomers in 92% yield. Chlorination was carried out using carbon tetrachloride in dichloromethane, then nitrile **274** was converted to key aldehyde **275** using a DIBAL-H reduction [ratio of diastereoisomers (dr 7:3)]. Aldehyde **275**, hydroxylamine hydrochloride and diisopropylethylamine were then refluxed in toluene to give the cycloadducts **276a** and **276b**. These were separable isomers obtained in 80% yield in the ratio of 7:3 (Scheme 5.5).



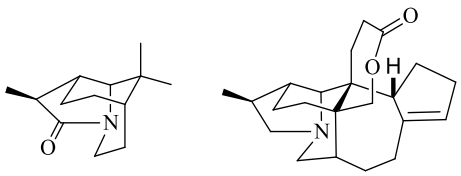
Scheme 5.5

The minor cycloadduct **276b** was treated with zinc in acetic acid to give amino alcohol **277**. The synthesis of the core structure was completed by treating compound **277** with paraformaldehyde in the presence of *p*-toluenesulfonic acid to afford compound **278** in 61% yield (Scheme 5.6).



Scheme 5.6

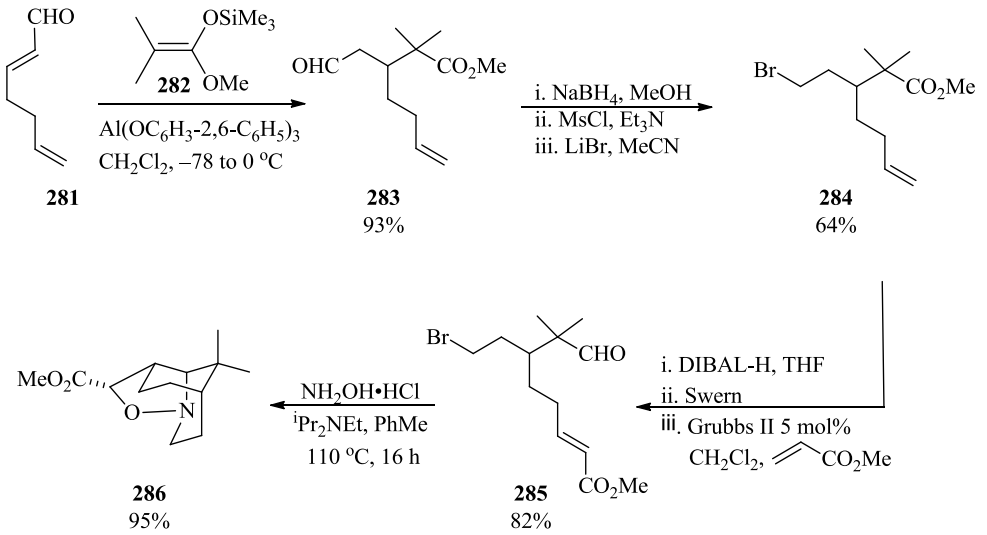
Additionally, Coldham and co-workers reported an efficient route to synthesize the core structure **279** found in daphnilactone B **280** (Figure 5.4).[121]



279 280

Figure 5.4

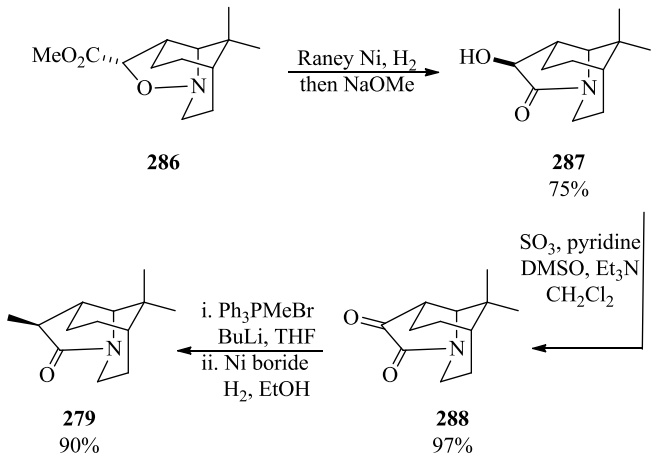
The unsaturated aldehyde **281** was treated with silyl ketene acetal **282** and a bulky Lewis acid to give aldehyde **283** in 93% yield. The aldehyde group was reduced using $NaBH_4$ and the alcohol was converted to bromo-compound **284**. The ester was reduced using DIBAL-H, followed by Swern oxidation, and then cross metathesis using Grubbs 2nd generation catalyst and ethyl acrylate to give aldehyde **285** in 82% yield. Condensation, cyclization cycloaddition cascade reaction was then attempted. The aldehyde **285** with hydroxylamine hydrochloride and diisopropylethylamine was heated under reflux in toluene to give the tricyclic product **286** as a single isomer in excellent yield (Scheme 5.7).



Scheme 5.7

Compound **286** was subjected to Raney nickel and sodium methoxide to give lactam **287** in 75% yield. On oxidation compound **288** was formed in very good yield. This

underwent Wittig reaction to generate an alkene, then reduction was carried out to give the desired core structure **279** in 90% yield as a single isomer (Scheme 5.8).[121]



Scheme 5.8

5.3 Biosynthetic route to daphlongeranines

In a 2007 study[155] Hao and co-workers reported two new compounds called daphlongeranines A and B (Figure 5.5). Isolated from *Daphniphyllum longeracemosum,* their structures were elucidated with an unprecedented ring system.

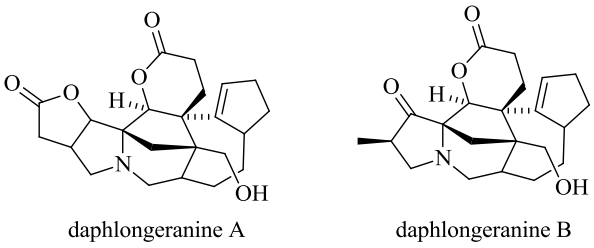
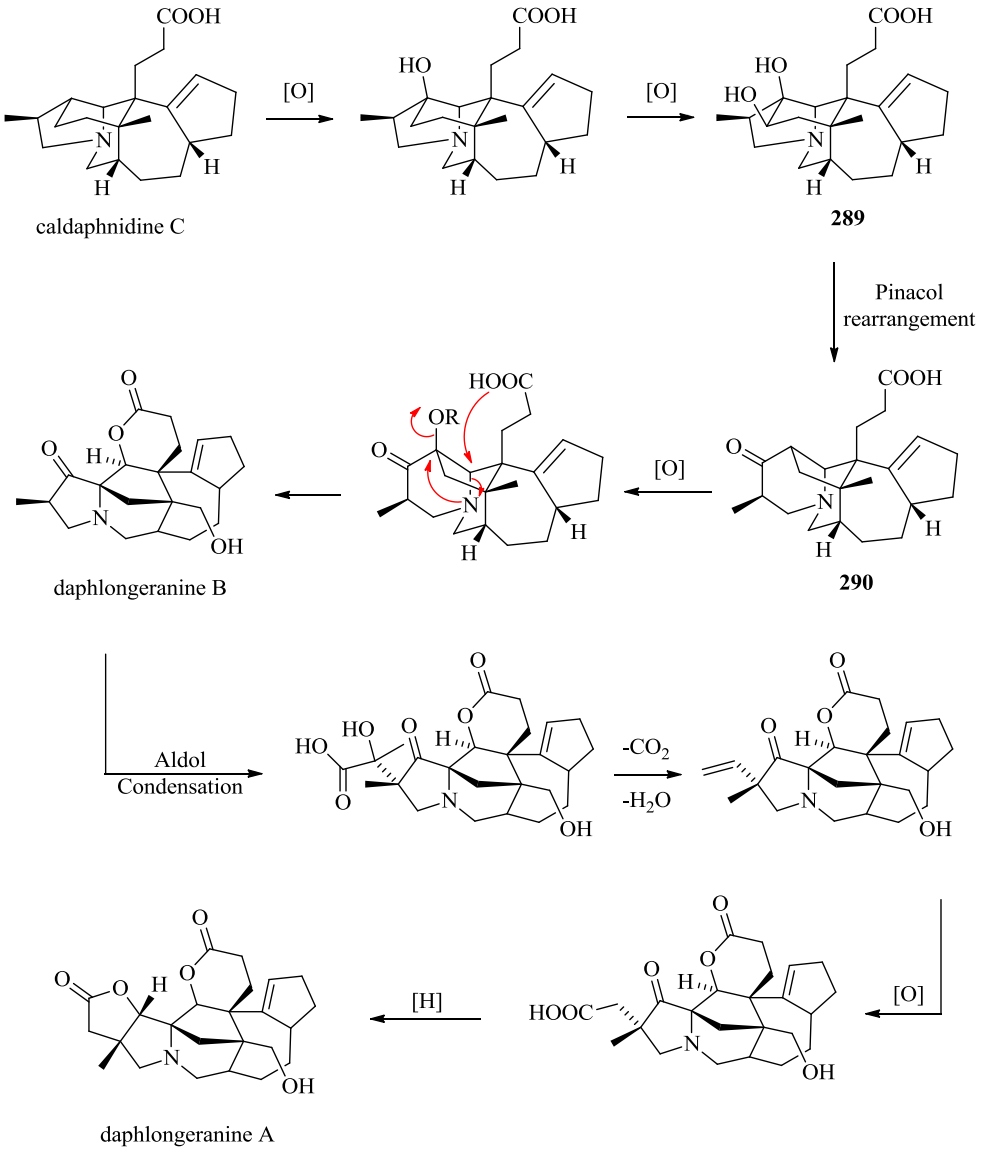


Figure 5.5

Furthermore, to understand the formation of these two compounds they proposed a biosynthetic route (Scheme 5.9), which involved a pinacol rearrangement step (from **289** to **290**).

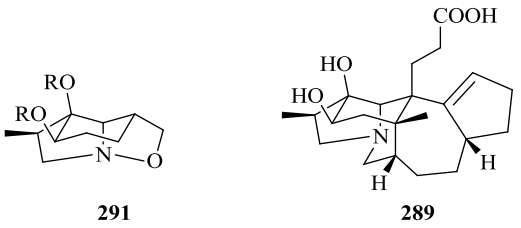


Scheme 5.9

5.4 Aim

The proposed biosynthesis was of interest to the Coldham group as we thought that we could access the core ring system **291** by utilising the condensation, cyclisation, cycloaddition chemistry of a nitrone that had been developed in the group. Therefore, we believed that this would allow us to probe the pinacol rearrangement step, and would provide evidence whether it was possible for it to take place or not. This could then support the proposed biosynthesis. To test this hypothesis, Coldham proposed a strategy to study the key pinacol rearrangement step. The aim was to synthesise the

cyclic structure **291**, which is similar in structure to the daphlongeranine precursor **289** (Figure 5.6).



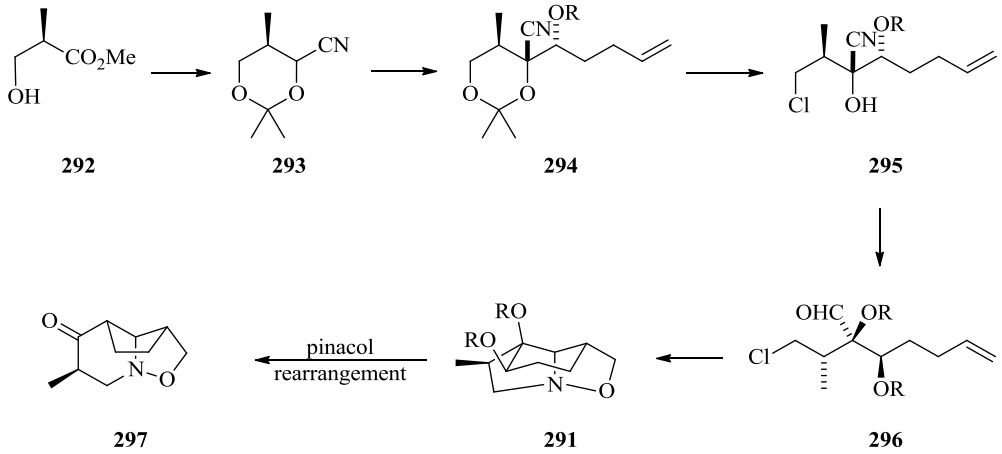
291 **289**

Figure 5.6

5.5 Towards the synthesis of the core structure 291

5.5.1 First strategy

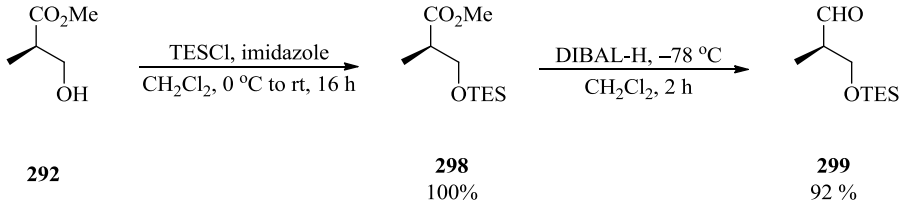
Rychnovsky and co-workers[156,157] reported the synthesis of a cyclic nitrile and scoped the alkylation with a variety of electrophiles. Using similar chemistry, we planned a strategy to access the core structure **297**. Scheme 5.10 outlines the general route that could lead to the cycloadduct **291**. We proposed that the Roche ester **292** would be a suitable starting material. Protection and reduction followed by a cyanation reaction and acetonide protection should give **293**. Alkylation with an electrophile followed by removal of the acetonide and subsequent chlorination, and reduction would form **296**. We believed that this could then undergo a nitrone 1,3-dipolar cycloaddition reaction to create cycloadduct **291** (Scheme 5.10). The final step would be to test the pinacol rearrangement in the lab.



292 **293** **294** **295** **296** **291** **297**

Scheme 5.10

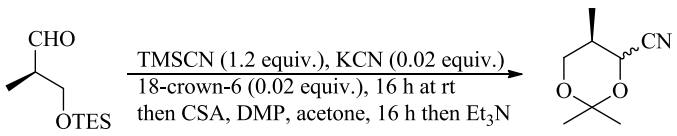
To prepare the nitrile **293**, the Roche ester **292** was treated with TESCl (1.3 equiv.) and imidazole (1.3 equiv.) in CH_2Cl_2 to give compound **298** in 80% yield (Scheme 5.11). Using 1.5 equivalents of both TESCl and imidazole gave 93% yield. A quantitative yield was obtained when the purification used alumina instead of silica gel. This was followed by reduction of the ester group to an aldehyde using DIBAL-H (1.05 equiv.) in CH_2Cl_2 at –78 °C, and after 2 h, the aldehyde **299** was obtained in 92% yield (Scheme 5.11).[158]



292 **298** 100% **299** 92 %

Scheme 5.11

The next step was the synthesis of the cyclic nitrile compound **293** following a method similar to that reported.[156] The cyanation reaction was achieved by treating aldehyde **299** with TMSCN and KCN/[18-crown-6] complex at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The acetonide protection step was carried out *in situ* by adding dry acetone, 2,2-dimethoxypropane and CSA. The reaction mixture was then left for 16 h before adding triethylamine, and the desired product was obtained in 52% yield. A better yield of 64% was obtained when both the cyanation step and the protection step were left for 16 h (Scheme 5.12).



299 **293** 1.1:1 64 %

Scheme 5.12

Two diastereoisomers showed up on the ^{1}H and ^{13}C NMR spectra in (1.1:1) ratio. The ^{13}C NMR spectra in $CDCl_3$ showed four peaks at 28.7 ppm, 25.0 ppm, 24.3 ppm and 19.0 ppm, this correspond to the geminal methyl groups of *syn*-isomer and *anti*-isomer (Figure 5.7, 293a and 293b). Based on the studies that have been reported on substituted 2,2-dimethyl 1,3-dioxanes,[159-161] The studies on compounds A and B showed that the geminal methyl groups of the of *syn*-isomer is about 30.0 ppm and 19.0 ppm and for *anti*-isomer is about 25.0 ppm (Figure 5.7, A and B).

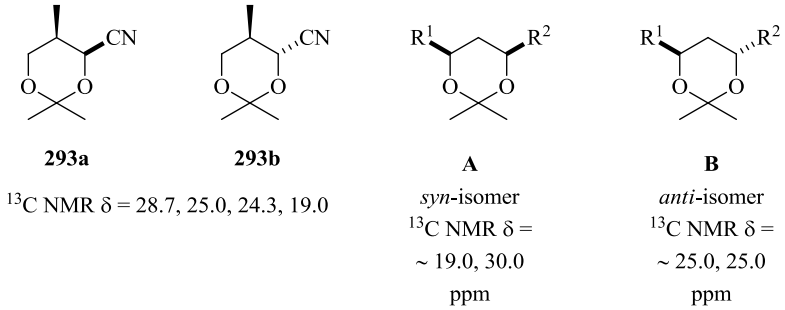
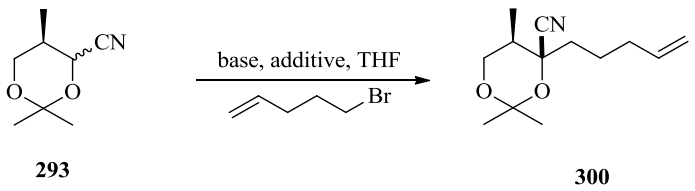


Figure 5.7

5.5.1.1 Alkylation with 5-bromo-1-pentene

Using LDA (1.1 equiv.) in THF at –78 ºC for the deprotonation of nitrile **293**, followed by addition of 5-bromo-1-pentene gave a single isomer **300** in 55% yield (Table 5.1, entry 1). Therefore, to obtain a better yield, some optimisation took place. Increasing the equivalents of LDA did not give a better yield, but reducing the deprotonation time with 1.2 equivalents afforded a slightly better yield (entries 4-6). The best yield was obtained when 1.2 equivalents of LDA was used, with a deprotonation time of 30 minutes, followed by electrophile addition, stirring for 2 h at –78 ºC and then for 1 h at –20 ºC (entry 7). Adding DMPU under the same conditions, to initiate the lithiation step, reduced the yield (entries 8 and 9).



293 **300**

Scheme 5.13

Entry	Base equiv.	Time	Yield (%)	Ratio
1	LDA 1.1	1 h at –78 °C then E^+, 2 h	55	one isomer
2	LDA 1.1	1 h at –78 °C then E^+, 2 h and 2 h at rt	56	one isomer
3	LDA 1.2	1 h at –78 °C then E^+, 2 h and 2 h at –20 °C	50	one isomer
4	LDA 1.2	45 min at –78 °C then E^+, 2 h and 2 h at –20 °C	60	one isomer
5	LDA 1.2	45 min at –78 °C then E^+, 2 h and 2 h at rt	60	one isomer
6	LDA 1.2	45 min at –78 °C then E^+, 2 h	63	one isomer
7	LDA 1.2	30 min at –78 °C then E^+, 2 h and 1h at –20 °C	65	one isomer
8	LDA 1.2	30 min at –78 °C then DMPU and E^+, 2 h and 1 h at –20 °C	35	one isomer
9	LDA 1.2	30 min at –78 °C then DMPU and E^+, 2 h and rt 18 h	40	one isomer

Table 5.1

The stereochemistry of 1,3-dioxanes has been widely investigated by many research groups.[118,162] Alkylations of sterically hindered cyano-1,3-dioxanes are extremely stereoselective. Cyano-1,3-dioxanes selectively alkylate a broad range of electrophiles from the equatorial direction which could arise from steric interactions between the incoming electrophile and the axial methyl group in the acetal or by stereoelectronic control (Figure 5.8).[118] Based on that the stereochemistry of the product **300** was proposed. Additionlly, the methyl group controls the orientation of

the electrophile. As a result, the product resulting from an equatorial approach of the electrophile would be preferentially observed.

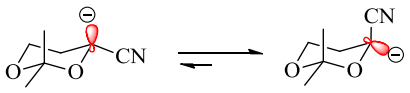
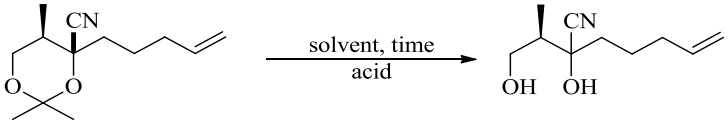


Figure 5.8

The next step was to remove the acetonide and generate the diol–nitrile **301** (Scheme 5.14). The cyclisation reaction can then be tested after chlorination followed by nitrile reduction.



300 **301**

Scheme 5.14

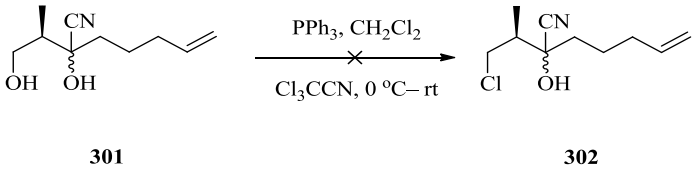
Treatment of compound **300** (50 mg) with aqueous HCl (37%) in hexane for 4 h afforded diol **301** in 50% yield (Table 5.2, entry 1). Unfortunately, all attempts for acetonide deprotection on a bigger scale failed to give one isomer, and for all reactions epimerisation took place to end up with inseparable isomers (Table 5.2). Using acetic acid and water, after 9 days, only 3% yield was obtained in 20:1 ratio, observed by ^{1}H NMR spectroscopy.

Entry	Solvent	Acid	Time	Yield%	Ratio
1	Hexane	HCl 37%	4 h	50	one isomer
2	MeCN	TFA/H_2O 1.2:0.2	4 h	20	two isomers[a] (1:1)
3	THF	AcOH/H_2O 1:3	9 days	3%	20:1[a]
4	THF	HCl in Et_2O 1 M	4 h	20	two isomers[a] (1:1)

[a] Based on the ^{1}H NMR spectrum

Table 5.2

Attempts were made at the chlorination reaction of the mixture of diastereoisomers, but these did not work and many spots were seen by TLC analysis (Scheme 5.15).

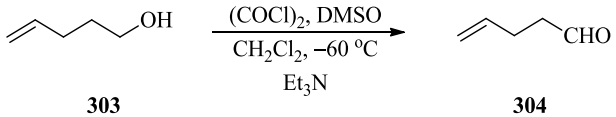


301 **302**

Scheme 5.15

5.5.1.2 Alkylation with 4-pentenal

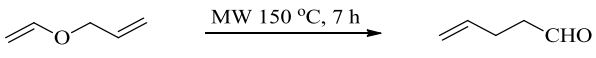
With the positive result of the nitrile alkylation reaction of compound **293**, we believed that using 4-pentenal **304** could provide the key nitrile **294**. Therefore, 5-penten-1-ol **303** was oxidised to the aldehyde **304** using a Swern oxidation. The resulting aldehyde was highly volatile, and was difficult to purify (Scheme 5.16).



303 **304**

Scheme 5.16

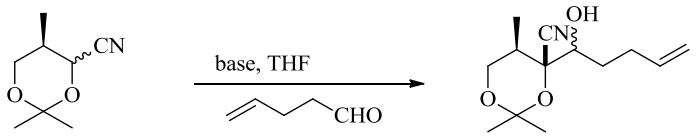
Alternatively, we started with commercially available allyl vinyl ether **305**, which was heated at 150 °C in the microwave to give the aldehyde **304** in quantitative yield *via* a Claisen rearrangement (Scheme 5.17).[123] Compared with the previous method, this provides a clean product **304**, observed by ^{1}H NMR spectroscopy of the crude product, and so it was used without further purification. Following the reaction by ^{1}H NMR spectroscopy showed us that the reaction required 7 h to proceed to full conversion on 2 g scale.



305 **304**
100%

Scheme 5.17

A 1997 study by Rychnovsky and Swenson investigated the alkylation of a cyclic 1,3-dioxane nitrile.[156] Many parameters were scoped such as base, time, temperature and electrophile. The only aldehyde they tested was benzaldehyde, and the yield was only 28%. In our chemistry aldehyde **304** gave varying yields of the desired product **306** (Scheme 5.18). Treatment of cyclic nitrile **293** with *n*-BuLi (1.2 equiv.) in THF at –78 °C, followed by addition of aldehyde **304** gave four diastereoisomers (Table 5.3, entry 1), observed by ^{1}H NMR spectroscopy of the crude product. Furthermore, using NaHMDS (1.5 equiv.) for deprotonation of the nitrile followed by addition of aldehyde **304** afforded 14% yield of the product as a single isomer (entry 2). Deprotonation with KHMDS gave no product and most of the starting material was recovered (Table 5.3).



293 **306**

Scheme 5.18

Entry	Base equiv.	Time	Yield%	Ratio
1	*n*-BuLi 1.2	1 h at –78 °C then E^+, 1 h and 1 h at –20 °C then 30 min rt	–	4 isomers
2	NaHMDS 1.5	2 h at –78 °C then E^+, 2 h and 1 h at 0 °C	14	one isomer
3	KHMDS 1.5	2 h at –78 °C then E^+, 2 h and 1 h at 0 °C	0	

Table 5.3

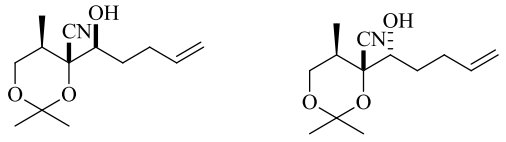
However, the use of LDA showed better results than the other bases (Table 5.4, entry 1). Efforts to optimise the conditions were made to obtain better yields. It was very difficult to find suitable conditions for better yields, which is why each reaction was

repeated many times. Adding a catalyst such as $MgBr_2 \cdot Et_2O$ failed to give a better yield (entry 4–6). Increasing the equivalents of the LDA dropped the yield to 41% only (entry 8). Finally, the nitrile **293** was deprotonated over 30 minutes, the aldehyde **304** was added and the reaction was left for 1 h at –78 ^oC. The reaction mixture was warmed to –20 ^oC, and then room temperature to afford the desired product in good yield (Table 5.4, entry 9).

Entry	LDA equiv.	Time	Yield%	Ratio
1	1.2	30 min at –78 ^oC then E^+, 2 h and 1h at –20 ^oC	65	1.1:1
2	1.2	2 h at –78 ^oC then E^+, 2 h and 2 h at –20 ^oC	50	1.1:1
3	1.2	2 h at –78 ^oC then E^+, 2 h and 1 h at 0 ^oC	50	1.1:1
4	1.2	2 h at –78 ^oC then 0.2 eq $MgBr_2.Et_2O$ and E^+, 2 h and 2 h at –20 ^oC	50	1.1:1
5	1.2	2 h at –78 ^oC then 0.2 eq $MgBr_2.Et_2O$ and E^+, 2 h and 1 h at 0 ^oC	30	1.1:1
6	1.2	2 h at –78 ^oC then 0.1 eq $MgBr_2.Et_2O$ and E^+, 2 h and 1 h at 0 ^oC	0	
7	1.2	2 h at –78 ^oC then E^+, 2 h	55	1.1:1
8	1.3	2 h at –78 ^oC then E^+, 2 h and 2 h at –20 ^oC	41	1.1:1
9	1.2	30 min h at –78 ^oC then E^+ stir 1 h and 1h at –20 ^oC then 30 min rt	75	1.1:1

Table 5.4

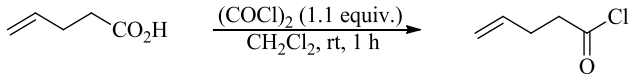
In most cases, the ratio of the cyanohydrin compound was 1.1:1 by ^{1}H NMR spectroscopy, and it was difficult to know which isomer was the major and which was the minor. The possible stereochemistry of the two diastereoisomers is shown in Figure 5.9.



306a **306b**

Figure 5.9

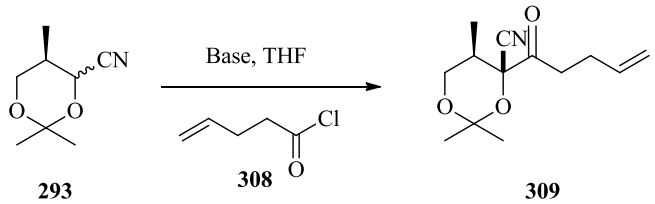
Alternatively, we thought that treating nitrile **293** with acid chloride **308** instead of aldehyde **304**, could generate ketone **309**, which could then be reduced to give either one isomer or give a better ratio. To do this, oxalyl chloride was added to 4-pentenoic acid **307** at room temperature, to give 4-pentenoyl chloride **308** in quantitative yield (Scheme 5.19).



307 **308**
quantitative

Scheme 5.19

With compound **308** in hand, it was possible to test the alkylation reaction. Acetonide **293** was treated with base and 4-pentenoyl chloride **308** in THF was added (Scheme 5.20). Unfortunately, using different bases and different conditions afforded no product and many spots were observed by TLC analysis (Table 5.5). ^{1}H NMR spectroscopy and LC/mass detected no identifiable product.



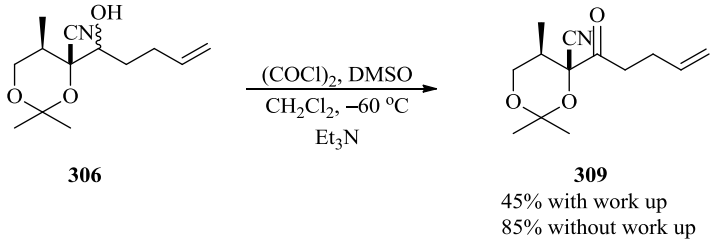
293 **308** **309**

Scheme 5.20

Entry	Base equiv.	Time	Yield%
1	*n*-BuLi 1.2	2 h at –78 ^{o}C then E^{+}, 2 h and 2 h at –20 ^{o}C	0
2	*n*-BuLi 1.2	30 min at –78 ^{o}C then E^{+}, 2 h and 2 h at –20 ^{o}C	0
3	*n*-BuLi 1.05	30 min at –78 ^{o}C then E^{+}, 2 h and 2 h at –20 ^{o}C	0
4	LDA 1.2	2 h at –78 ^{o}C then E^{+}, 2 h and 30 min at –20 ^{o}C	0
5	LDA 1.2	30 min h at –78 ^{o}C then E^{+}, 1 h and 1h at –20 ^{o}C then 30 min rt	0
6	NaHMDS 1.5	2 h at –78 ^{o}C then E^{+}, 2 h and 30 min at –20 ^{o}C	0

Table 5.5

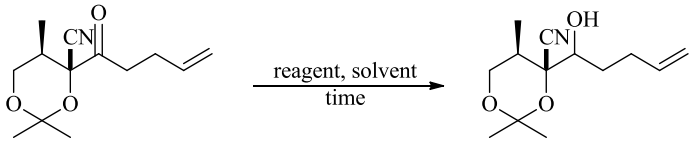
Using another alternative method, oxidation of alcohol **306** *via* a Swern oxidation gave ketone **309** in good yield. Work up with HCl gave a low yield, while a better yield was obtained without the work up (Scheme 5.21).



306 **309**
45% with work up
85% without work up

Scheme 5.21

This compound **309** was then subjected to reduction to give compound **306** in good yield and good selectivity (Scheme 5.22).



309 **306**

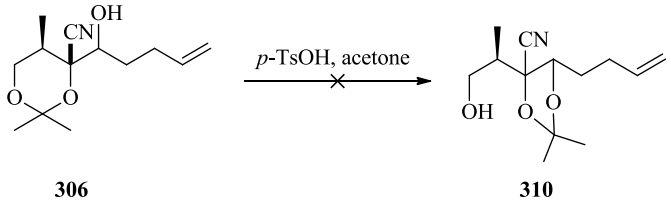
Scheme 5.22

Using K-Selectride in THF as a reducing agent gave only a 3:1 ratio, which was the same ratio that was obtained with sodium borohydride in methanol at room temperature (Table 5.6). Fortunately, the reaction with sodium borohydride[163] in methanol at –78 °C was successful and gave compound **306** in a 11:1 ratio in good yield (entry 3), and this was easily purified by silica gel chromatography.

Entry	Reagent equiv.	Solvent	Time	Yield%	Ratio
1	K-selectride 1.5	THF	1 h at –78 °C then 4 h	65	3:1
2	$NaBH_4$ 1.2	MeOH	2 h at rt	65	3:1
3	$NaBH_4$ 1.2	MeOH	2 h at –78 °C	75[a]	11:1

Table 5.6 [a] the percentage is for pure isomer

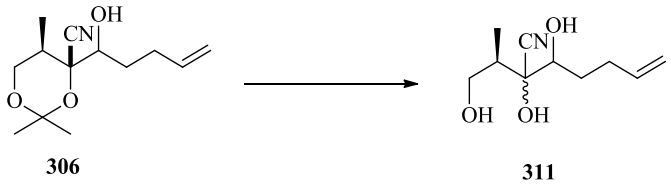
We do not know which is the major isomer at this stage. To investigate the acetonide removal of compound **306**, we carried out a screen of literature procedures that related to five and six membered acetonides.[164-166] Ideally we wanted to convert acetonide **306** to the new acetonide **310** (Scheme 5.23). Unfortunately, by using *p*-toluenesulfonic acid many spots were observed by TLC analysis.



306 **310**

Scheme 5.23

Alternatively, deprotection of one diastereoisomer of the acetonide was attempted (Scheme 5.24). Acetonide **306** (50 mg) was treated with aqueous HCl (37%) in hexane. After 4 h, triol **311** was afforded in 40% yield (Table 5.7, entry 1). Unfortunately, all the attempts to remove the acetonide on a bigger scale failed to give one isomer, using different conditions (Table 5.7, entries 2 and 3).[167] The one isomer of acetonide **306** gave two inseparable isomers of the triol **311** in varied yield (entries 2 and 3). This epimerisation could be due to the reversibility of the formation of the cyanohydrin compound in an acidic medium. The reaction was repeated using THF with aqueous HCl (1 M) but gave two diastereoisomers (entry 4),[168] based on the ^{1}H NMR spectra of the crude product. Other attempts were made using TFA/water in acetonitrile (entries 5-7).[164] Disappointingly, two diastereoisomers were obtained as observed by ^{1}H NMR spectroscopy of the crude product.



306 **311**

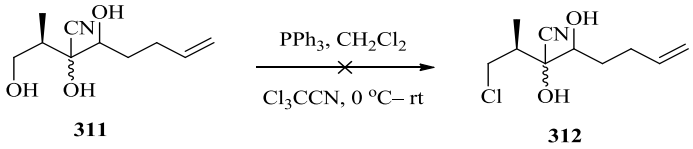
Scheme 5.24

Entry	Solvent	Acid	Time	Yield%
1	Hexane	HCl 37%	4 h	40[a]
2	Hexane	HCl 37%	2 h	30[b]
3	Hexane	HCl/H_2O 1:1	6 h	55[b]
4	THF	HCl 1 M	4 h	-[c]
5	MeCN	TFA/H_2O 5:1	1.5 h at 0 °C	-[c]
6	MeCN	TFA/H_2O 5:1	3 h at rt	-[c]
7	MeCN	TFA/H_2O 1:2	4 h at rt	-[c]

[a] one isomer after purification, [b] two isomers dr 1:1 after purification, [c] dr 1:1 crude product

Table 5.7

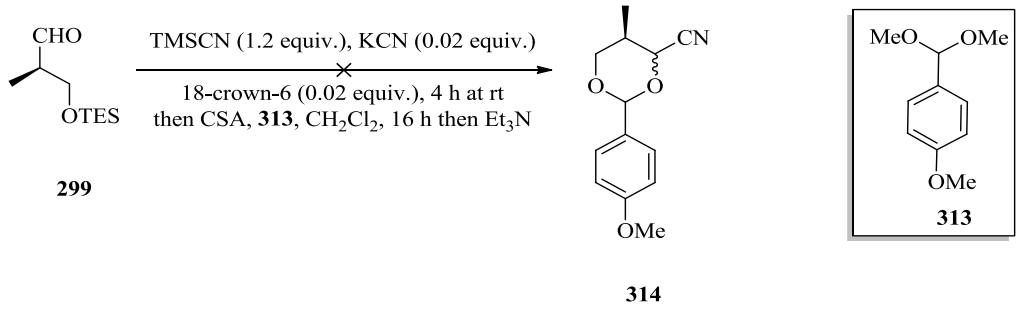
Next, the inseparable mixture of the triol-nitrile was to be subjected to a chlorination reaction to give chloro-compound **312**. Using the earlier conditions trichloroacetonitrile (1.0 equivalent) was added to a mixture of triol **311** and triphenylphosphine (1.0 equivalent) in CH_2Cl_2 (Scheme 5.25). The TLC analysis showed that the starting material was consumed but many new spots appeared. No identifiable product was detected by ^1H NMR spectroscopy or LC/mass spectrometry.



Scheme 5.25

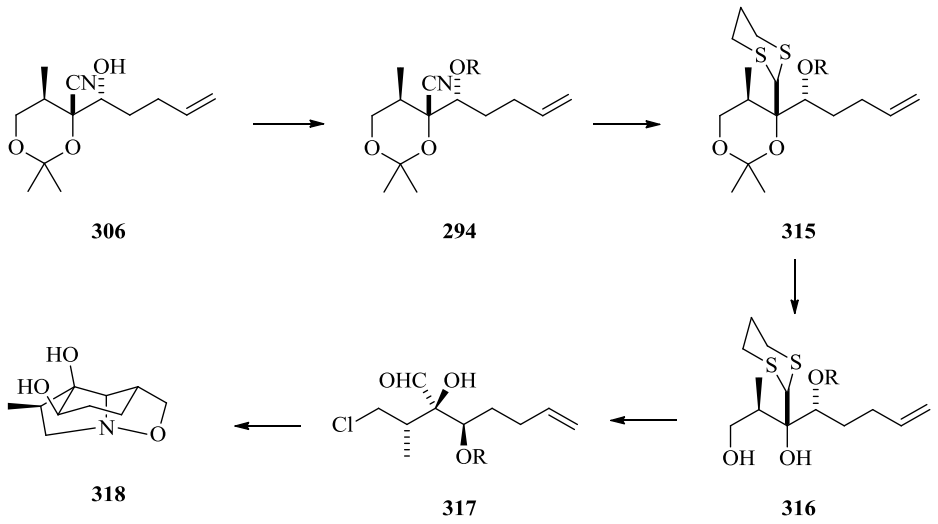
We hypothesised that changing to a different protecting group, which would require non-acidic conditions to be removed later, would be a good idea to control the epimerisation. Therefore, using the same conditions as used for compound **293**, aldehyde **299** was treated with TMSCN and catalytic KCN/[18-crown-6] complex at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. Dichloromethane was then added followed by anisaldehyde dimethyl acetal **313** with CSA. The mixture reaction was then left for 16 h before adding

triethylamine (Scheme 5.26). Unfortunately, no products were detected and the reaction generated an inseparable mixture of products which was difficult to purify.



Scheme 5.26

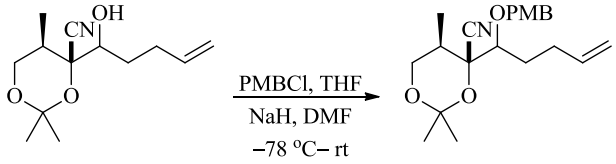
Alternatively, to avoid the epimerisation issue, we planned to reduce the nitrile group to an aldehyde group and then protect with a dithiane to give **315** (Scheme 5.27). Removal of the acetonide would then give diol **316**, which could undergo a chlorination reaction. Subsequent dithiane removal would then form the aldehyde **317**. The free hydroxyl group in alcohol **306** could be protected with a benzyl ether, which was assumed to be stable during the acetonide removal in acidic conditions.



Scheme 5.27

To begin with, a mixture of PMBCl and alcohol **306** in THF was added to a solution of sodium hydride in DMF at –78 ºC. The reaction mixture was allowed to warm to

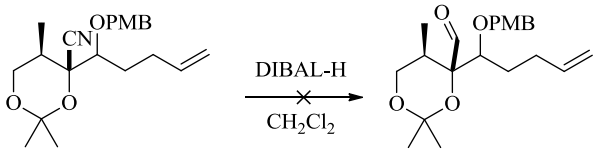
room temperature overnight. The desired compound was obtained in good yield (Scheme 5.28).



306 **319** 80%

Scheme 5.28

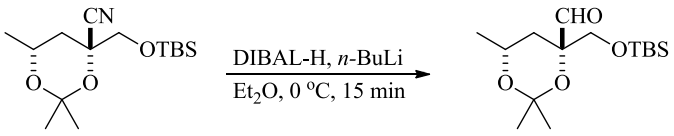
The next step was the conversion of the nitrile **319** to the corresponding aldehyde **320**. As mentioned previously in chapter 4, this type of reaction proceeded smoothly *via* DIBAL-H reduction. Therefore, DIBAL-H (1.5 equiv.) was added to nitrile **319** in CH_2Cl_2 at –78 °C, but unfortunately only starting material was recovered (Scheme 5.29). The reaction was repeated many times using different equivalents of DIBAL-H and temperatures, but only starting material was detected.



319 **320**

Scheme 5.29

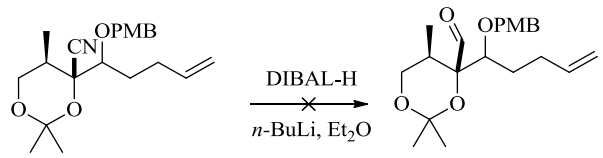
The result of this was clearly disappointing. A study by Kim[169] reported that a cyclic nitrile showed resistance towards reduction and gave a low yield of the corresponding aldehyde. Carreira and co-workers suggested modified conditions through the use of an ate complex formed from DIBAL-H and *n*-BuLi to reduce the acetonide **321** (Scheme 5.30).[170]



321 **322** 94%

Scheme 5.30

Therefore, this complex was reacted with nitrile **319** at 0 °C and room temperature (Scheme 5.31). We were disappointed that only the starting material was recovered.



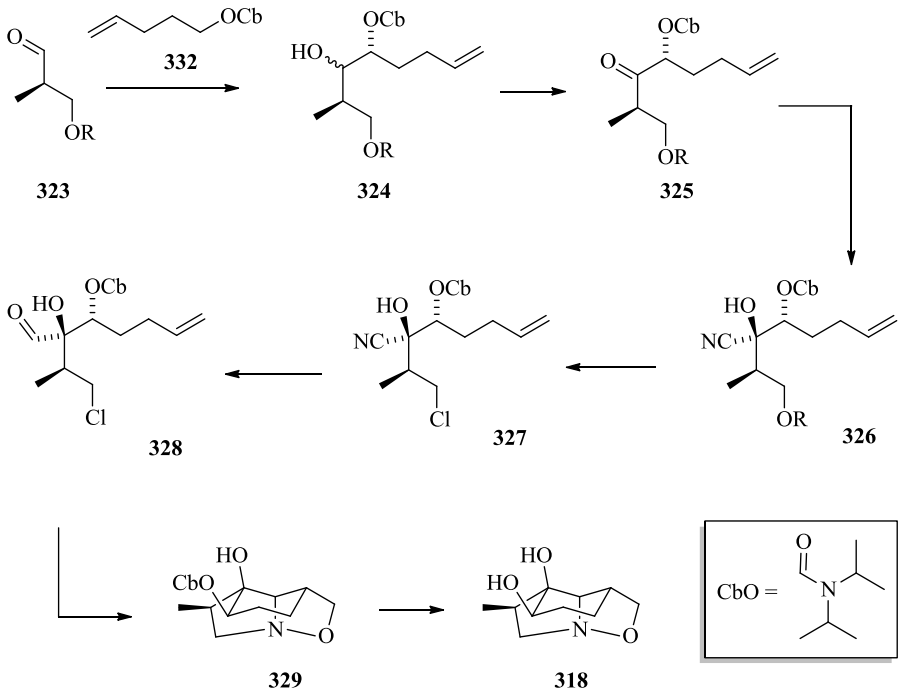
319 **320**

Scheme 5.31

The nitrile is probably too sterically hindered to react. Though we had difficulty in the synthesis of aldehyde **320**, we still thought that it was worth trying to prepare the key aldehyde to accomplish the aim. So an alternative strategy was devised.

5.5.2 Second strategy

In conjunction with a Masters student (Mr James Lyons), we investigated the steps given in Scheme 5.32.[171] In a slightly different strategy, we designed a new route towards the synthesis of the key aldehyde **328**. The chemistry starts with Roche ester and its conversion to the aldehyde **323**. Hoppe[162,172,173] reported the formation of lithiated carbamates that can be subsequently alkylated. So, we considered using similar chemistry in which the aldehyde **323** can react with lithiated carbamate **332** to create alcohol **324**. Oxidation followed by a cyanation reaction would form nitrile **326**.



Scheme 5.32

The next step is to remove the *O*-protecting silyl (R) group, then chlorination to form **327**. Reduction of nitrile **327** would produce the key aldehyde **328**. At this point, we would be able to test the cycloaddition reaction.

To predict the stereoselectivity after the cyanation reaction of the carbonyl group with an adjacent sterogenic centre, the Felkin-Ahn model was used. Thus, the Newman projection of **323** shows that the model deduces the orientation of attack from either side of the alkene group gives the same stereoisomer (Figure 5.10).

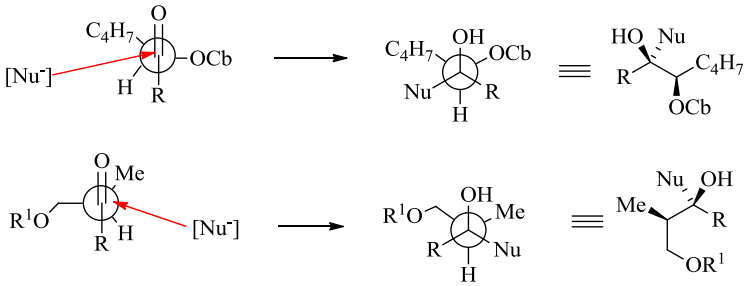
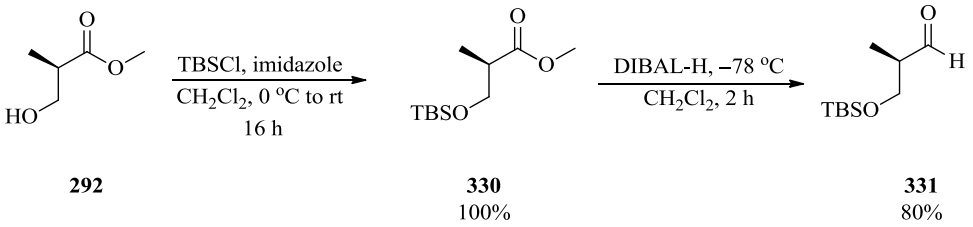


Figure 5.10

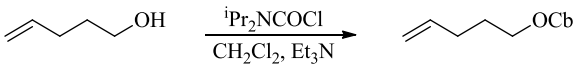
To start this sequence, Roche ester was treated with TBSCl to give the protected ester **330** in quantitative yield, following the earlier method. This underwent a DIBAL-H (1.05 equiv.) reduction to afford aldehyde **331** in good yield (Scheme 5.33).



292 **330** 100% **331** 80%

Scheme 5.33[171]

The next step was to treat the aldehyde **331** with the carbamate **332**. In order to do this, compound **332** was prepared *via* reaction of 4-penten-1-ol **303** with CbCl and Et_3N in dichloromethane. The mixture was heated at reflux for 24 h to afford compound **332** in 95% yield (Scheme 5.34). Alternatively, this was prepared by000. microwave irradiation over 1 h at 150 °C to give the desired product in 63% yield. The second method was quicker but only allowed reaction on a small scale and so the first method was used.

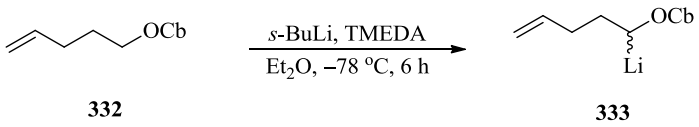


303 **332** 95%

Scheme 5.34[171]

Hoppe and co-workers were the first to report high enantioselectivities using *s*-BuLi and (–)-sparteine in a lithiation of alkyl carbamates.[173] Aggarwal and co-workers have done extensive research on the lithiation of carbamates.[174-176] Therefore, lithiation of the alkyl carbamate **332** was carried out *in-situ* using *s*-BuLi and a diamine in diethyl ether, to afford intermediate **333**. Organolithium chemistry can be affected very much by chiral ligands due to the ligand's ability to transfer chirality to the substrate. Using a chiral diamine, such as sparteine, the lithiation could proceed with high stereoselectivity,[162] leading to a stereoselective reaction of aldehyde **332** to

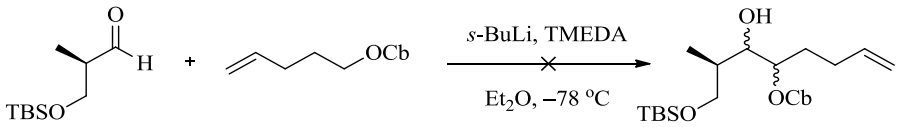
form intermediate **335**. However, to prove the concept, we decided to use achiral, inexpensive TMEDA instead, to find suitable conditions (Scheme 5.35).



332 **333**

Scheme 5.35

Thus, carbamate **332** was lithiated with *s*-BuLi (1.5 equiv.) and TMEDA (1.5 equiv.) at –78 °C over 6 h (Scheme 5.36). Subsequently compound **331** (1.2 equiv.) was added and the mixture was allowed to warm to room temperature. Unfortunately, this reaction was unsuccessful producing a mixture of unidentifiable products while no desired product was detected.



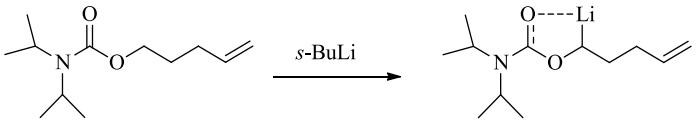
331 **332** **334**

Scheme 5.36

The reaction was repeated again, and the lithiation time was reduced to 1 h instead of 6 h. We were disappointed that after purification, the ^{1}H NMR spectra showed the product was present but in very low yield and there was not enough for any meaningful analysis.

To understand the failure of the reaction two things were explored; the lithiation step and the coupling step choosing a different electrophile. Firstly, monitoring the lithiation by *in-situ* ReactIR spectroscopy would provide information about the time that the reaction takes to occur, depending on the carbonyl stretch in the carbamate group. The lithiation will change the frequency of the C=O bond, due to the coordination between the oxygen and lithium (Scheme 5.37). Thus, *s*-BuLi (1.2 equiv.) was added to the carbamate compound **332** at −78 °C, while monitoring by ReactIR spectroscopy (Figure 5.11). The ReactIR trace shows that the deprotonation

was completed within a few minutes, and only 60% of the carbamate was being deprotonated. After that the lithiated carbamate **335** was not stable enough and started slowly decomposing.



332 **335**

Scheme 5.37

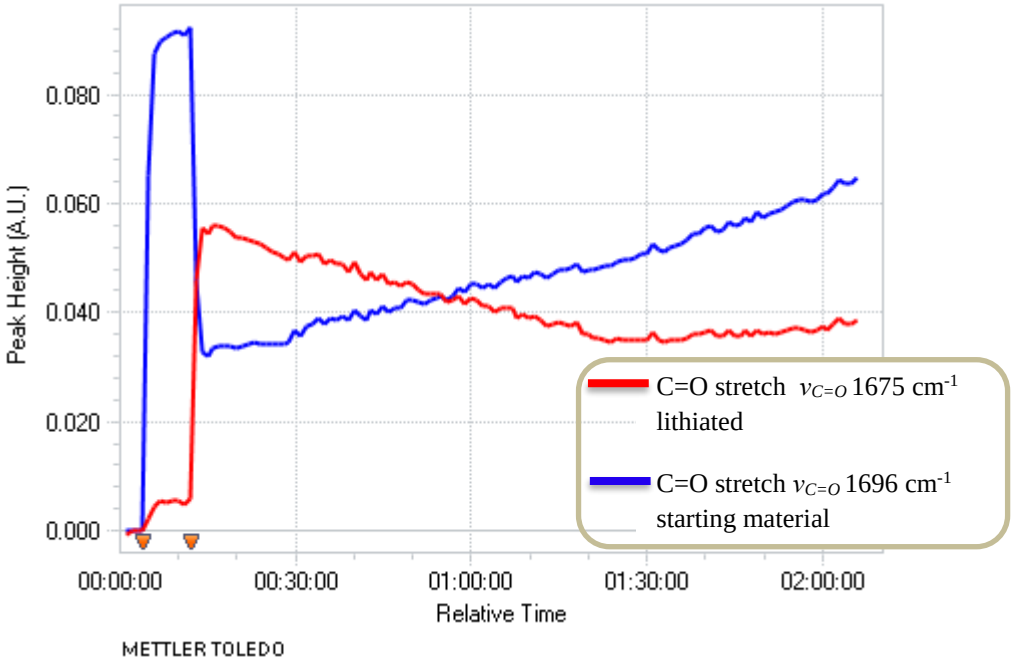
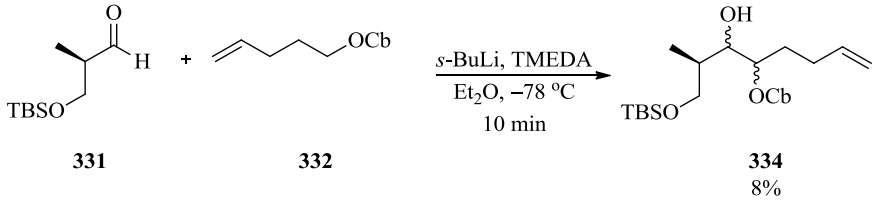


Figure 5.11[171]

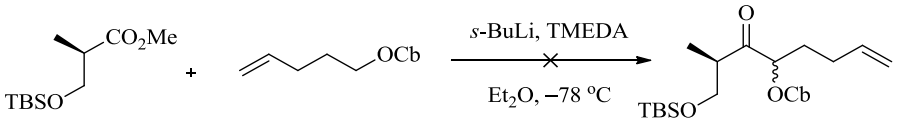
Based on the ReactIR study, we thought that increasing the number of equivalents of *s*-BuLi and shortening the lithiation time would form the product. So, we started by premixing the *s*-BuLi (1.5 equiv.) and the TMEDA (1.5 equiv.), then after 10 min the aldehyde **331** was added. This gave the product **334** in 8% yield as a mixture of isomers (Scheme 5.38). The reaction was repeated using *s*-BuLi (2.0 equiv.) with a 5 min deprotonation time. This resulted in a 7% yield of product. In both cases the ^{1}H NMR spectrum showed two diastereoisomers. As a result, increasing the number of equivalents showed no affect on the yield.



331 **332** **334**
8%

Scheme 5.38[171]

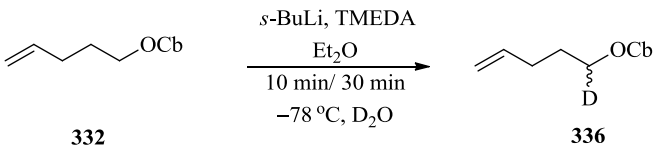
We wondered whether a different electrophile such as ester **330** would give the ketone **335**, as this could save two steps, the reduction of ester **330** and oxidation of alcohol **334**. Despite the lack of literature precedent, the reaction was attempted. The ester **330** was added to a premixed solution of *s*-BuLi (1.5 equiv.) and TMEDA (1.5 equiv.), however, no product was observed (Scheme 5.39).



330 **332** **335**

Scheme 5.39

This outcome was disappointing and we postulate that after lithiation, the lithiated carbamate **333**, may not be sufficiently reactive. To explore this, a study using deuterium oxide as the quench was set up in order to test the lithiation. Two reactions were tested with different lithiation times, using 1.5 equivalents of *s*-BuLi and TMEDA. After 10 minutes, the first reaction was quenched with D_2O, and the second one was quenched after 30 minutes (Scheme 5.40).

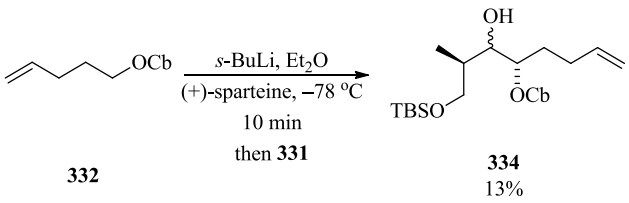


332 **336**

Scheme 5.40[171]

The products were then analysed by comparing the integration of the ^{1}H NMR spectra to the integration of the starting material. Thus, in the complete deuteration, the integration of the CHD in compound **336** should be half compared to the CH_2 in compound **332**. The ^{1}H NMR spectra showed that after 10 minutes lithiation time the carbamate integration is about 60%, whilst after 30 minutes lithiation time, it was less than 10%.

O'Brien and co-workers have investigated the use of a variety of diamines and solvents, and they have explored the effect of these on the yield of the reaction.[177] The study showed that the diamine can affect both yield and enantioselectivity for the chiral amine and proposed that careful consideration be placed into reaction conditions. Based on this, the reaction of carbamate **332** and aldehyde **331** was tried again, and (+)-sparteine was used instead of TMEDA. The chiral amine (–)-sparteine is the ligand that is expected to afford the correct isomer for our product,[178] but for availability reasons (+)-sparteine was used instead. Therefore, to a mixture of carbamate **332** and (+)-sparteine (1.5 equiv.) was added *s*-BuLi (1.5 equiv.). After 10 min, aldehyde **331** was added, and upon purification the alcohol **334** was obtained in 13% yield as a single isomer (Scheme 5.41). The stereochemistry was predicted based on the Felkin-Ahn model (Figure 2.5).

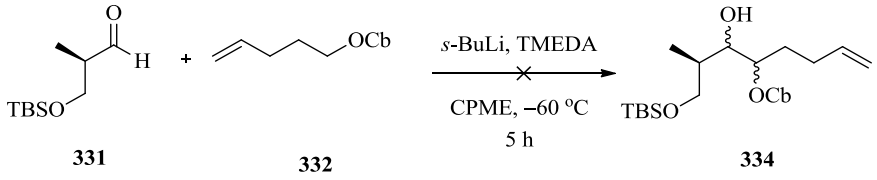


332 **334** 13%

Scheme 5.41[171]

Aggarwal and co-workers investigated the lithiation of secondary alkyl carbamates, using a different protecting/activating group and the solvent cyclopentenyl methyl ether (CPME).[179] It was envisioned that the reported conditions could be used with our carbamate **332**. Therefore, to a mixture of carbamate **332** and TMEDA (6.0 equiv.) in CPME, *s*-BuLi (1.6 equiv.) was added at –60 °C. After 1 h, aldehyde **331** was added dropwise (Scheme 5.42). Unfortunately, only a complex mixture of

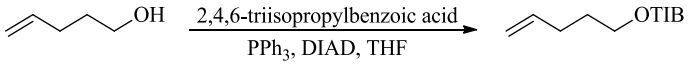
products was obtained based on TLC analysis and ^{1}H NMR spectroscopy of the crude product.



331 **332** **334**

Scheme 5.42

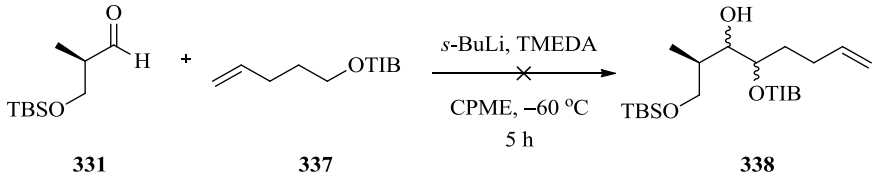
In the same paper it was reported that using 2,4,6-triisopropylbenzoic acid (TIB) as a protecting/activating group could lead to a positive result. Alcohol **303** was treated with triphenylphosphine, triisopropylbenzoic acid and DIAD in THF to give the protected alcohol **337** in 95% yield (Scheme 5.43).



303 **337**
95%

Scheme 5.43

Compound **337** and TMEDA (6.0 equiv.) were treated with *s*-BuLi (1.6 equiv.) at –60 °C in CPME. After 1 h, aldehyde **331** was added dropwise and the mixture was left for 5 h (Scheme 5.44). Disappointingly no desired product was obtained.

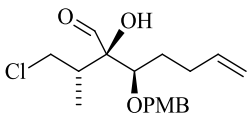


331 **337** **338**

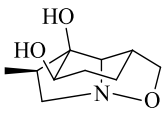
Scheme 5.44

5.6 Conclusion

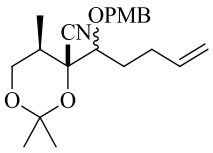
This project has concluded with the successful synthesis of nitrile **319** in good yield. The aims of this project were not fully met, but some problems have been solved, such as acetonide alkylation. Although solutions to some problems have not been solved, most notably verifying the stereochemistry of alcohol **319**, and acetonide removal without epimerisation.



317



318



319

The reduction of nitrile **319** to the correspond aldehyde failed to proceed using DIBAL-H with and without the addition of *n*-BuLi.

An alternative strategy using Hoppe-like lithiation and electrophilic addition gave a low yield with both TMEDA and (+)-sparteine.

This project has a very wide scope for future work; it is obvious that the synthesis of **318** should be completed, ideally by using the cascade precursor **317**. Once the cascade reaction has been completed, full crystal analysis needs to be undertaken to verify that **317** or **318** has been synthesised with the correct stereochemistry upon which the proposed biosynthetic pinacol rearrangement can be tested.

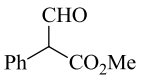
Chapter 6 Experimental

6.1 General

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. CH_2Cl_2, DMF, Et_2O and THF were obtained from Grubbs dry solvent system (model: SPS-200-6). Petrol refers to the fractions that boil between 40 to 60 ^oC and oxalyl chloride was freshly distilled before use. Acetone was dried over CaH_2 and degassed. Thin layer chromatography was performed on Macherey-nagel-Alugram Sil G/UV 254 silica plates and visualized by U.V. irradiation at 254 nm, by staining with alkaline $KMnO_4$ or Brady's Reagent. ^1H NMR spectra were recorded on either a Bruker AC400 (400 MHz), Bruker AV3HD400 (400 MHz) or Bruker AC500 (500 MHz) instrument. Chemical Shifts (δ) are reported in ppm and coupling constants (*J* values) are quoted to one decimal place with values in Hertz (Hz) and were corrected. NMR peak multiplicities are given the abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded on the above Bruker instrument at 101 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Micromass Autospec for Electron Impact (EI) and on a Walters LCT instrument for Electro-Spray (ES/ESI). Infra-red spectra were recorded on a Perkin Elmer Spectrum RX Fourier Transform-IR system. Only selected peaks are reported and absorption maxima are given in cm^{-1}. Crystals were obtained by recrystallising the compound in hexane/CH_2Cl_2 and X-ray data was measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Melting points were recorded on a Gallenkamp hot stage and were uncorrected.

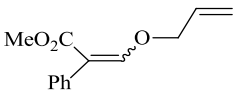
6.2 Experimental procedures

Methyl 2-phenyl-3-hydroxyprop-2-enoate 106



To a mixture of ester **104** (2.0 g, 13.3 mmol) and methylformate **105** (2.4 g, 40 mmol) in CH_2Cl_2 (27 mL) was added $TiCl_4$ (5.0 g, 26.6 mmol) dropwise, followed by addition of Et_3N (4.4 mL, 32 mmol) dropwise at 0 °C. After 1 h, the mixture allowed to warm to room temperature. After 2 h, water (15 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL), the organic layers were combined and washed with brine (20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the ester **106** (1.5 g, 8.6 mmol, 65%) as an oil; R_f 0.45 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.05 (1H, d, *J* 1.5 Hz, CH), 7.38–7.26 (6H, m, ArH and CH), 3.83 (3H, s, CH_3O). Data consistent with the literature.[67]

Methyl 3-(allyloxy)-2-phenylacrylate 108



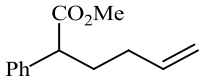
To a stirred solution of aldehyde **106** (500 mg, 2.8 mmol) in dry acetone (9 mL) was added potassium carbonate (0.77 g, 5.6 mmol) followed by allyl bromide (1.7 g, 14 mmol) at room temperature. After 45 min at 50 °C, the mixture was cooled to room temperature, was diluted with CH_2Cl_2 (20 mL) and was filtered. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave two separable isomers **108**;

Data for isomer **108a** (367 mg, 1.8 mmol, 60%) as an oil; R_f 0.48 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (1H, s, CH), 7.38–7.37 (4H, m, ArH), 7.30–7.28 (1H, m, ArH), 5.98–5.90 (1H, m, C*H*=CH_2), 5.38–5.31 (2H, m, CH_2=CH), 4.55–4.52 (2H, m, CH_2), 3.76 (3H, s, CH_3O); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.2

(C=O), 157.9 (CH), 132.6 (C), 132.4 (CH), 130.2 (CH), 127.8 (CH), 127.1 (CH), 118.9 (CH_2), 111.8 (C), 75.0 (CH_2), 51.6 (CH_3); HRMS *m*/*z* (ES) Found: MH^+, 219.1017, $C_{13}H_{15}O_3$ requires MH^+, 219.1021; LRMS *m*/*z* (ES) 219 (MH^+, 100%).

Data for isomer **108b** (184 mg, 0.85 mmol, 30%) as an oil; R_f 0.34 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.33 (2H, m, ArH), 7.30–7.27 (3H, m, ArH), 6.75 (1H, s, CH), 6.06–5.97 (1H, m, C*H*=CH_2), 5.47–5.33 (2H, m, C*H*$_2$=CH), 4.58–4.54 (2H, m, CH_2), 3.79 (3H, s, CH_3O); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.4 (C=O), 156.1 (CH), 135.6 (C), 132.6 (CH), 129.0 (CH), 128.2 (CH), 127.0 (CH), 119.2 (CH_2), 112.5 (C), 75.3 (CH_2), 51.6 (CH_3); HRMS *m*/*z* (ES) Found: MH^+, 219.1005, $C_{13}H_{15}O_3$ requires MH^+, 219.1021; LRMS *m*/*z* (ES) 219 (MH^+, 100%).

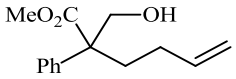
Methyl 2-phenylhex-5-enoate 109



^{n}Butyllithium (9.15 mL, 22 mmol, 2.4 M solution in hexanes) was added to freshly distilled diisopropylamine (3.0 mL, 22 mmol) in THF (40 mL) at −78 °C. After 30 min, methyl phenylacetate **104** (3.0 g, 20 mmol) was added dropwise over 10 min. After 1 h, DMPU (5 mL) was added. After 10 min, 3-bromo-1-butene (2.98 g, 24 mmol) was added. The mixture was allowed to warm to room temperature over 16 h, then saturated aqueous NH_4Cl (15 mL) and brine (15 mL) were added. The mixture was extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.8:0.2), gave the ester **109** (2.75 g, 13.5 mmol, 67%) as an oil; R_f 0.3 [petrol–EtOAc (9.8:0.2)]; IR ν_{max}(film)/cm^{-1} 2950 (C–H), 1730 (C=O), 1430 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.26 (5H, m, ArH), 5.80 (1H, ddt, *J* 17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.05–4.99 (2H, m, C*H*$_2$=CH), 3.67 (3H, s, CH_3O), 3.56 (1H, t, *J* 7.5 Hz, CH), 2.24−2.10 (1H, m, CH), 2.07−2.00 (2H, m, 2 × CH), 1.93−1.85 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.4 (C=O), 138.9 (C), 137.5 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 115.4 (CH_2), 51.9 (CH), 50.7 (CH_3), 32.5 (CH_2), 31.5

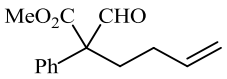
(CH_2); HRMS *m*/*z* (ES) Found: MH^+, 205.1217, $C_{13}H_{17}O_2$ requires MH^+, 205.1223; LRMS *m*/*z* (ES) 205 (MH^+, 100%).

Methyl 2-(hydroxymethyl)-2-phenylhex-5-enoate 111



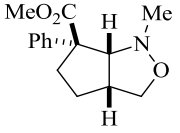
To freshly distilled diisopropylamine (1.13 mL, 8.04 mmol) in THF (20 mL) was added ^{n}butyllithium (3.22 mL, 8.04 mmol, 2.5 M solution in hexanes) at −78 °C. After 30 min, ester **109** (1.5 g, 7.3 mmol) was added dropwise over 10 min. After 30 min, the mixture was warmed to –20 °C and paraformaldehyde (220 mg, 7.3 mmol) in THF (2 mL) was added and the mixture was stirred for 1 h. Additional paraformaldehyde (220 mg, 7.3 mmol) was added and the mixture was allowed to warm to room temperature over 1 h, then saturated aqueous NH_4Cl (15 mL) and brine (15 mL) were added. The mixture was extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), gave the alcohol **111** (1.1 g, 4.70 mmol, 65%) as an oil; R_f 0.27 [petrol–EtOAc (4:1)]; IR ν_{max}(film)/cm^{-1} 3460 (br. OH), 2950 (C–H), 1720 (C=O), 1430 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.34 (2H, m, ArH), 7.32–7.30 (1H, m, ArH), 7.29–7.26 (2H, m, ArH), 5.84 (1H, ddt, *J* 17.0, 10.5, 6.5 Hz, C*H*=CH_2), 5.08–4.98 (2H, m, CH_2=CH), 4.10 (1H, dd, *J* 11.5, 7.5 Hz, CH), 3.99 (1H, dd, *J* 11.5, 6.0 Hz, CH), 3.76 (3H, s, CH_3O), 2.28−2.07 (3H, m, 3 × CH and OH), 2.05–1.95 (1H, m, CH); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 175.7 (C=O), 139.7 (C), 138.0 (CH), 128.6 (CH), 127.3 (CH), 126.4 (CH), 114.8 (CH_2), 66.7 (CH_2), 55.9 (C), 52.2 (CH_3), 32.9 (CH_2), 28.9 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 235.1331, $C_{14}H_{18}O_3$ requires MH^+, 235.1329; LRMS *m*/*z* (ES) 235 (MH^+, 100%).

Methyl 2-formyl-2-phenylhex-5-enoate 110

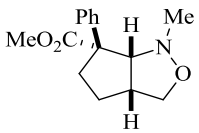


DMSO (0.65 mL, 9.2 mmol) was added to a solution of freshly distilled oxalyl chloride (0.40 mL, 4.6 mmol) in CH_2Cl_2 (15 mL) at −60 °C. After 5 min, the alcohol **111** (980 mg, 4.19 mmol) was added dropwise over 10 min. After 30 min, Et_3N (2.93 mL, 20.9 mmol) was added. After 10 min, the mixture was allowed to warm to room temperature. Water (10 mL), aqueous HCl (10 mL, 1 M), and aqueous saturated Na_2CO_3 (10 mL) were added, the mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the aldehyde **110** (750 mg, 3.25 mmol, 77%) as an oil; R_f 0.43 [petrol–EtOAc (9.2:0.8)]; IR ν_{max}(film)/cm^{-1} 2955 (C–H), 1720 (C=O), 1430 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.95 (1H, s, CHO), 7.44–7.33 (3H, m, ArH), 7.24–7.21 (2H, m, ArH), 5.82 (1H, ddt, *J* 17.0, 10.5, 6.5 Hz, C*H*=CH_2), 5.08–4.97 (2H, m, C*H*$_2$=CH), 3.85 (3H, s, CH_3O), 2.47–2.39 (1H, m, CH), 2.26−2.18 (1H, m, CH), 2.17−2.07 (1H, m, CH), 1.97−1.87 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.5 (C=O), 171.6 (C=O), 137.6 (CH), 135.3 (C), 129.2 (CH), 128.2 (CH), 127.3 (CH), 115.2 (CH_2), 65.7 (C), 52.6 (CH_3), 31.6 (CH_2), 29.3 (CH_2); HRMS *m*/*z* (ES) Found: MH$^+$, 233.1164, $C_{14}H_{17}O_3$ requires MH$^+$, 233.1172; LRMS *m*/*z* (ES) 233 (MH$^+$, 100%).

(±)-(3a*RS*,6*RS*,6a*RS*)-Methyl1-methyl-6-phenylhexahydro-1H-yclopenta[c] isoxazole -6-carboxylate 112a and (±)-(3a*SR*,6*RS*,6a*SR*)-Methyl 1-methyl-6-phenylhexahydro-1H-cyclopenta[c]isoxazole-6-carboxylate 112b



112a



112b

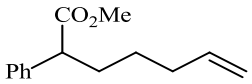
The aldehyde **110** (100 mg, 0.43 mmol), *N*-methylhydroxylamine hydrochloride (45 mg, 0.52 mmol) and diisopropylethylamine (0.18 mL, 1.03 mmol) in toluene (4 mL)

was heated at 110 °C. After 2 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (7:3), gave the cycloadduct **112a** (35.5 mg, 0.14 mmol, 32%) as a solid and the cycloadduct **112b** (60 mg, 0.23 mmol, 54%) as a solid. These were each recrystallized from CH_2Cl_2/hexane (1:1) to give needles.

Data for cycloadduct **112a**: m.p. 90−92.5 °C; R_f 0.43 [petrol–EtOAc (7:3)]; IR ν_{max}(film)/cm^{-1} 2955 (C–H), 1720 (C=O), 1445 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.27 (5H, m, ArH), 4.17 (1H, dd, *J* 8.5, 7.5 Hz, CH), 3.91 (1H, dd, *J* 7.0, 1.0 Hz, CH), 3.66 (3H, s, CH_3O), 3.51 (1H, dd, *J* 8.5, 4.5 Hz, CH), 3.31−3.23 (1H, m, CH), 2.57−2.48 (1H, m, CH), 2.42−2.36 (1H, m, CH), 2.23 (3H, s, CH_3), 1.71−1.65 (2H, m, 2 × CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.5 (C=O), 138.2 (C), 128.4 (CH), 127.4 (CH), 127.2 (CH), 78.1 (CH), 72.4 (CH_2), 62.7 (C), 52.5 (CH_3), 48.0 (CH_3), 45.5 (CH), 31.1 (CH_2), 29.0 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 262.1434, $C_{15}H_{20}NO_3$ requires MH^+, 262.1438; LRMS *m*/*z* (ES) 262 (MH^+, 100%).

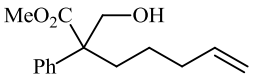
Data for cycloadduct **112b**: m.p. 96−98.5 °C; R_f 0.39 [petrol–EtOAc (7:3)]; IR ν_{max}(film)/cm^{-1} 2955 (C–H), 1735 (C=O), 1445 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.26 (5H, m, ArH), 4.20 (1H, dd, *J* 9.0, 6.0 Hz, CH), 3.91 (1H, d, *J* 8.0 Hz, CH), 3.73 (1H, dd, *J* 9.0, 2.0 Hz, CH), 3.68 (3H, s, CH_3O), 3.21−3.15 (1H, m, CH), 2.76 (3H, s, CH_3), 2.59 (1H, dt, *J* 13.0, 10.0 Hz, CH), 2.07 (1H, dd, *J* 13.0, 6.0 Hz, CH), 1.67−1.32 (2H, m, 2 × CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.8 (C=O), 140.8 (C), 128.6 (CH), 127.1 (CH), 126.2 (CH), 78.4 (CH), 72.4 (CH_2), 63.6 (C), 51.9 (CH_3), 47.8 (CH), 45.6 (CH_3), 34.5 (CH_2), 29.3 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 262.1432, $C_{15}H_{20}NO_3$ requires MH^+, 262.1438; LRMS *m*/*z* (ES) 262 (MH^+, 100%).

Methyl 2-phenylhept-6-enoate 114



In the same way as the ester **109**, ^{n}butyllithium (9.15 mL, 22 mmol, 2.4 M solution in hexanes), diisopropylamine (3.0 mL, 22 mmol), methyl phenylacetate **104** (3.0 g, 20 mmol), DMPU (5 mL), and 4-bromo-1-pentene (3.57 g, 24 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the ester **114** (3.0 g, 13.8 mmol, 69%) as an oil; R_f 0.25 [petrol–EtOAc (9.8:0.2)]; IR ν_{max}(film)/cm^{-1} 2945 (C–H), 1735 (C=O), 1430 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.26 (5H, m, ArH), 5.78 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.03–4.94 (2H, m, CH_2=CH), 3.67 (3H, s, CH_3O), 3.56 (1H, t, *J* 8.0 Hz, CH), 2.15−2.05 (3H, m, 3 × CH), 1.86−1.76 (1H, m, CH), 1.46−1.28 (2H, m, 2 × CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.5 (C=O), 139.2 (C), 138.3 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 114.8 (CH_2), 51.9 (CH), 51.5 (CH_3), 33.5 (CH_2), 33.0 (CH_2), 26.8 (CH_2); HRMS *m*/*z* (ES) Found: M$^+$, 219.1367, $C_{14}H_{18}O_2$ requires M$^+$, 219.1380; LRMS *m*/*z* (ES) 159 (45%), 219 (M$^+$, 100%).[180]

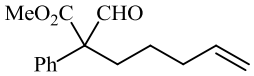
Methyl 2-(hydroxymethyl)-2-phenylhept-6-enoate 115



In the same way as the ester **111**, ^{n}butyllithium (12.6 mL, 5.04 mmol, 2.5 M solution in hexanes), diisopropylamine (0.70 mL, 5.04 mmol), ester **114** (1.0 g, 4.6 mmol), and paraformaldehyde (270 mg, 9.2 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), the ester **115** (750 mg, 3.02 mmol, 66%) as an oil; R_f 0.27 [petrol–EtOAc (4:1)]; IR ν_{max}(film)/cm^{-1} 3455 (br. OH), 2955 (C–H), 1720 (C=O), 1435 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.35 (2H, m, ArH), 7.31–7.25 (3H, m, ArH), 5.80 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.06–4.96 (2H, m, CH_2=CH), 4.07 (1H, dd, *J* 11.5, 8.0 Hz, CH), 3.98 (1H, dd, *J* 11.5, 6.0 Hz, CH), 3.75 (3H, s, CH_3O), 2.19–2.00 (4H, m, 4 × CH and OH), 1.53−1.41 (1H, m, CH), 1.37−1.26 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$)

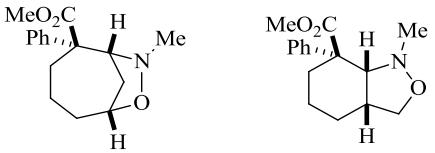
δ = 175.0 (C=O), 140.0 (C), 138.2 (CH), 128.6 (CH), 127.2 (CH), 126.7 (CH), 115.0 (CH_2), 66.7 (CH_2), 56.1 (C), 52.2 (CH_3), 34.1 (CH_2), 33.2 (CH_2), 23.9 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 249.1487, $C_{15}H_{20}O_3$ requires MH^+, 249.1485; LRMS *m*/*z* (ES) 249 (MH^+, 80%), 231 (100%).

Methyl 2-formyl-2-phenylhept-6-enoate 116



In the same way as the aldehyde **110**, oxalyl chloride (0.28 mL, 3.23 mmol), DMSO (0.46 mL, 6.46 mmol), alcohol **115** (730 mg, 2.94 mmol) and Et_3N (2.05 mL, 14.7 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the aldehyde **116** (570 mg, 2.31 mmol, 79%) as an oil; R_f 0.5 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2950 (C–H), 1715 (C=O), 1435 (C–H); ^1H NMR (400 MHz, $CDCl_3$) δ = 9.93 (1H, s, CHO), 7.43–7.32 (3H, m, ArH), 7.23–7.20 (2H, m, ArH), 5.79 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.06–4.96 (2H, m, C*H*$_2$=CH), 3.84 (3H, s, CH_3O), 2.37−2.29 (1H, m, CH), 2.16−2.07 (3H, m, 3 × CH), 1.52−1.40 (1H, m, CH), 1.30−1.19 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.6 (C=O), 171.8 (C=O), 138.0 (CH), 135.5 (C), 129.1 (CH), 128.1 (CH), 127.3 (CH), 115.0 (CH_2), 65.9 (C), 52.5 (CH_3), 34.0 (CH_2), 31.8 (CH_2), 24.9 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 247.1344, $C_{15}H_{19}O_3$ requires MH^+, 247.1334; LRMS *m*/*z* (ES) 247 (MH^+, 100%).

(±)-**(1*RS*,2*RS*,6*RS*)-Methyl 8-methyl-2-phenyl-7-oxa-8-azabicyclo[4.2.1]nonane-2-carboxylate 117a and** (±)-**(3a*RS*,7*RS*,7a*RS*)-Methyl 1-methyl-7-phenyloctahydrobenzo[c]isoxazole-7-carboxylate 117b**



117a **117b**

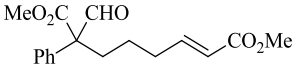
In the same way as the cycloadducts **112**, the aldehyde **116** (100 mg, 0.40 mmol), *N*-methylhydroxylamine hydrochloride (40 mg, 0.48 mmol) and diisopropylethylamine (0.17 mL, 0.96 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), the cycloadducts **117a** and **117b** (84 mg, 0.3 mmol, 75%) as a mixture (ratio 1:2 determined by ^{1}H NMR spectroscopy) as an oil. Cycloadduct **117a** could be partially separated by crystallization using CH_2Cl_2/hexane (1:1). The remaining mixture of **117a** and **117b** was analysed by NMR spectroscopy and the peaks for isomer **117b** could be identified as follows:

Data for cycloadduct **117a**: m.p. 105−108 °C; R_f 0.15 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2950 (C–H), 1715 (C=O), 1445 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.38 (2H, m, ArH), 7.35–7.30 (2H, m, ArH), 7.26–7.21 (1H, m, ArH), 4.66 (1H, dd, *J* 9.0, 4.0 Hz, CH), 3.88 (1H, dd, *J* 8.0, 1.5 Hz, CH), 3.68 (3H, s, CH_3O), 2.74 (1H, dt, *J* 13.5, 9.0 Hz, CH), 2.54−2.47 (1H, m, CH), 2.40 (3H, s, CH_3N), 2.30–2.27 (1H, m, CH), 1.95−1.85 (1H, m, CH), 1.82−1.73 (1H, m, CH), 1.63−1.56 (2H, m, 2 × CH), 1.53−1.41 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$, assignments by DEPT NMR) δ = 175.7 (C=O), 142.4 (C), 128.3 (CH), 126.7 (CH), 126.5 (CH), 77.3 (CH), 72.7 (CH), 58.0 (C), 52.1 (CH_3), 47.6 (CH_3), 33.3 (CH_2), 32.1 (CH_2), 29.0 (CH_2), 20.5 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 276.1598, $C_{16}H_{22}NO_3$ requires MH^+, 276.1600; LRMS *m*/*z* (ES) 276 (MH^+, 100%).

Data for cycloadduct **117b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.24 (5H, m, ArH), 4.06 (1H, dd, *J* 8.0, 3.5 Hz, CH), 3.69 (3H, s, CH_3O), 3.52 (1H, d, *J* 8.0 Hz, CH), 3.43 (1H, d, *J* 5.0 Hz, CH), 2.93−2.87 (1H, m, CH), 2.37–2.33 (1H, m, CH), 2.27−2.22 (1H, m, CH), 1.93−1.86 (1H, m, CH), 1.83 (3H, s, CH_3N), 1.77−1.72 (2H,

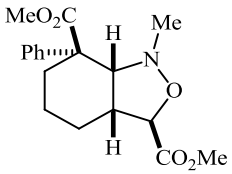
m, 2 × CH), 1.33−1.20 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$, assignments by DEPT NMR) δ = 175.7 (C=O), 141.3 (C), 128.6 (CH), 127.4 (CH), 126.4 (CH), 73.2 (CH), 70.2 (CH_2), 53.9 (C), 52.3 (CH_3), 47.4 (CH_3), 43.4 (CH), 26.7 (CH_2), 25.6 (CH_2), 22.0 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 276.1598, $C_{16}H_{22}NO_3$ requires MH^+, 276.1600; LRMS *m*/*z* (ES) 276 (MH^+, 100%).

(*E*)-Dimethyl 7-formyl-7-phenyloct-2-enedioate 119



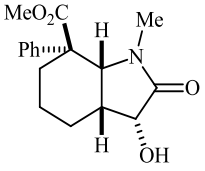
The alkene **116** (136 mg, 0.55 mmol) and methyl acrylate (0.10 mL, 1.2 mmol) in degassed CH_2Cl_2 (5 mL) was heated at 40 °C before adding Grubbs' 2nd generation catalyst (23 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) dropwise over 1 h. After 2.5 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the diester **119** (133 mg, 0.44 mmol, 80%) as an oil; R_f 0.26 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2950 (C–H), 1725 (C=O), 1715 (C=O), 1655 (C–H), 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.91 (1H, s, CHO), 7.41–7.33 (3H, m, ArH), 7.20–7.18 (2H, m, ArH), 6.94 (1H, dt, *J* 15.5, 7.0 Hz, C*H*=CH), 5.84 (1H, dt, *J* 15.5, 1.5 Hz, CH=C*H*), 3.85 (3H, s, CH_3O), 3.74 (3H, s, CH_3O), 2.37−2.22 (3H, m, 3 × CH), 2.15−2.08 (1H, m, CH), 1.59−1.48 (1H, m, CH), 1.36−1.25 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.3 (CHO), 171.5 (C=O), 167.0 (C=O), 148.4 (CH), 135.3 (C), 129.3 (CH), 128.2 (CH), 127.2 (CH), 121.4 (CH), 65.9 (C), 52.6 (CH_3), 51.4 (CH_3), 32.4 (CH_2), 31.8 (CH_2), 23.5 (CH_2); HRMS *m*/*z* (ES) Found: MH^+, 305.1380, $C_{17}H_{21}O_5$ requires MH^+, 305.1384; LRMS *m*/*z* (ES) 305 (MH^+, 100%).

(3*RS*,3a*RS*,7*SR*,7a*RS*)-Dimethyl 1-methyl-7-phenyloctahydrobenzo[c]isoxazole-3,7-dicarboxylate 120a



In the same way as the cycloadducts **112**, the aldehyde **119** (100 mg, 0.33 mmol), *N*-methylhydroxylamine hydrochloride (30 mg, 0.36 mmol) and diisopropylethylamine (0.12 mL, 0.66 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (7:2), the cycloadducts **120a** and **120b** (67 mg, 0.2 mmol, 61%) as a mixture (ratio 5:1 by ^{1}H NMR spectroscopy) from which isomer **120a** was isolated by crystallization from CH_2Cl_2/hexane (1:1) as amorphous solid; m.p. 98−100 ºC; R_f 0.28 [petrol–EtOAc (7:2)]; IR ν_{max}(film)/cm^{-1} 2950 (C–H), 1750 (C=O), 1725 (C=O), 1435 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.34 (2H, m, ArH), 7.31–7.26 (3H, m, ArH), 4.13 (1H, s, CH), 3.79 (3H, s, CH_3O), 3.67 (3H, s, CH_3O), 3.57 (1H, d, *J* 4.0 Hz, CH), 3.23–3.19 (1H, m, CH), 2.46−2.38 (1H, m, CH), 2.35−2.26 (1H, m, CH), 1.97−1.87 (5H, m, 2 × CH and CH_3N), 1.74−1.59 (1H, m, CH), 1.37−1.26 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.1 (C=O), 172.9 (C=O), 140.7 (C), 128.8 (CH), 127.7 (CH), 126.3 (CH), 80.4 (CH), 70.5 (CH), 53.2 (C), 52.4 (CH_3), 52.2 (CH), 48.1 (CH_3), 47.8 (CH_3), 26.9 (CH_2), 26.5 (CH_2), 22.2 (CH_2); HRMS *m*/*z* (ES) Found: MH$^+$, 334.1646, $C_{18}H_{24}NO_5$ requires MH$^+$, 334.1649; LRMS *m*/*z* (ES) 334 (MH$^+$, 100%).

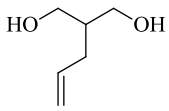
(3*RS*,3a*RS*,7*SR*,7a*RS*)-Methyl 3-Hydroxy-1-methyl-2-oxo-7-phenyloctahydro-1H-indole-7-carboxylate 123



To the cycloadducts **120a** and **120b** (64 mg, 0.19 mmol) (ratio 5:1) in AcOH/H_2O (0.6:0.8 mL) was added Zn powder (50 mg, 0.77 mmol) and the mixture was heated

at 70 °C. After 4 h, the mixture was allowed to cool to room temperature. The zinc salts were filtered, washed with CH_2Cl_2 and the solvent was evaporated. Aqueous ammonia solution (2 mL) and CH_2Cl_2 (2 mL) were added to the residue. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the organic layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in methanol (5.0 mL) and sodium methoxide (31 mg, 0.58 mmol, 25 wt% MeOH) was added at room temperature. After 2.5 h, NH_4Cl (30 mg) was added, and the mixture was stirred for 5 min until complete dissolution was achieved. The solvent was evaporated and the mixture was purified by column chromatography on silica gel, eluting with CH_2Cl_2−MeOH−NH_3 (98:2:0.1), to give the lactam **123** (34 mg, 0.11 mmol, 59%) as needles after recrystallization from CH_2Cl_2/hexane (1:1); m.p. 177−180 °C; R_f 0.18 [CH_2Cl_2−MeOH−NH_3 (98:2:0.1)]; IR ν_{max}(film)/cm^{-1} 3295 (OH), 2955 (C–H), 1725 (C=O), 1680 (C=O), 1430 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.31 (5H, m, ArH), 4.48 (1H, dd, *J* 3.5, 1.5 Hz, CH), 4.34 (1H, d, *J* 6.5 Hz, CH), 3.63 (3H, s, CH_3O), 2.99−2.92 (1H, m, CH), 2.89 (1H, d, *J* 1.5 Hz, OH), 2.72−2.66 (1H, m, CH), 2.02 (3H, s, CH_3N), 1.96−1.90 (1H, m, CH), 1.79−1.67 (2H, m, 2 × CH), 1.32−1.27 (1H, m, CH), 1.19−1.14 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.0 (C=O), 173.6 (C=O), 140.6 (C), 128.9 (CH), 127.9 (CH), 126.2 (CH), 73.0 (CH), 60.1 (CH), 52.6 (CH_3), 52.2 (C), 38.9 (CH), 29.9 (CH_3), 26.5 (CH_2), 21.2 (CH_2), 20.4 (CH_2); HRMS *m*/*z* (ES) Found: MH$^+$, 304.1542, $C_{17}H_{22}NO_4$ requires MH$^+$, 304.1543; LRMS *m*/*z* (ES) 304 (MH$^+$, 100%).

2-Allylpropane-1,3-diol 183



To a solution of $LiAlH_4$ (7.5 g, 200 mmol) in Et_2O (150 mL) was added a solution of diethyl allylmalonate **182** (19.7 mL, 100 mmol) in Et_2O (50 mL) at 0 ºC. The mixture was allowed to warm to room temperature. After 16 h, aqueous sodium hydroxide (30 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through Celite, washed with CH_2Cl_2−MeOH (9:1) (200 mL) and

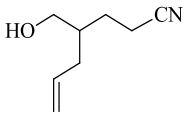
the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (4:6), gave the diol **183** (8.2 g, 70.6 mmol, 71%) as an oil; R_f 0.16 [petrol–EtOAc (4:6)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.81 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.12–5.05 (2H, m, C*H*$_2$=CH), 3.83 (2H, dd, *J* 10.5, 4.5 Hz, 2 × C*H*HO), 3.69 (2H, dd, *J* 10.5, 7.5 Hz, 2 × CH*H*O), 2.42 (2H, s, 2 × OH), 2.10–2.07 (2H, m, CH_2), 1.94–1.85 (1H, m, CH). Data consistent with the literature.[123]

2-(Iodomethyl)pent-4-en-1-ol 184 and 185

To alcohol **183** (4.0 g, 34.5 mmol) in THF (125 mL) were added imidazole (2.35 g, 34.5 mmol) and PPh_3 (9.0 g, 34.5 mmol). After 15 min, ground iodine (9.62 g, 37.9 mmol) was added portionwise at room temperature. After 3 h, CH_2Cl_2 (75 mL) was added and the suspension was filtered through Celite, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (8:2) gave the iodide **184** (5.9 g, 26.11 mmol, 76%) as an oil; R_f 0.33 [petrol−EtOAc (8:2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.74 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.20−5.07 (2H, m, C*H*$_2$=CH), 3.74−3.53 (1H, m, C*H*HO), 3.56−3.51 (1H, m, CH*H*O), 3.39 (1H, dd, *J* 10.0, 5.0 Hz, C*H*HI), 3.29 (1H, dd, *J* 10.0, 6.0 Hz, CH*H*I), 2.19−2.04 (3H, m, 2 × CH and OH), 1.59–1.50 (1H, m, CH). Data consistent with the literature.[123]

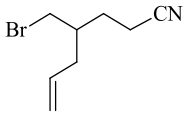
Data for diiodide **185**: R_f 0.75 [petrol–Et_2O (8:2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.70 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.24–5.11 (2H, m, C*H*$_2$=CH), 3.40 (2H, dd, *J* 9.5, 4.5 Hz, 2 × C*H*HI), 3.25 (2H, dd, *J* 9.5, 6.0 Hz, 2 × CH*H*I), 2.23–2.17 (2H, m, CH_2), 1.55–1.40 (1H, m, CH). Data consistent with the literature.[123]

4-(Hydroxymethyl)hept-6-enenitrile 186



To diisopropylamine (3.75 mL, 26.5 mmol) in THF (25 mL) at –78 °C was added ^{n}BuLi (10.60 mL, 26.5 mmol, 2.5 M solution in hexanes). The mixture was stirred for 30 min, and then acetonitrile (2.77 mL, 53.1 mmol) was added dropwise. After 30 min, **184** (3.00 g, 13.3 mmol) was added. After 1 h, the mixture was allowed to warm to room temperature over 1 h, and saturated aqueous ammonium chloride (20 mL) was added. The mixture was extracted with Et_2O (3 × 25 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (6:4), gave the nitrile **186** (1.6 g, 11.5 mmol, 87%) as an oil; R_f 0.3 [petrol–EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.76 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.11−5.04 (2H, m, C*H*$_2$=CH), 3.64−3.59 (1H, m, C*H*HO), 3.55−3.50 (1H, m, CH*H*O), 2.46−2.42 (2H, m, 2 × CH), 2.14−2.06 (3H, m, 2 × CH and OH), 1.78−1.69 (3H, m, 3 × CH). Data consistent with the literature.[123]

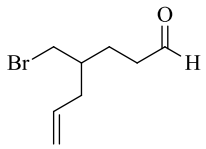
4-(Bromomethyl)hept-6-enenitrile 187



To triphenylphosphine (1.58 g, 8.70 mmol) in CH_2Cl_2 (30 mL) was added carbon tetrabromide (2.0 g, 8.7 mmol) at room temperature. After 5 min, **186** (1.1 g, 7.9 mmol) was added. After 3 h, the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (6:4), gave the bromide **187** (1.35 g, 6.72 mmol, 85%) as an oil; R_f 0.4 [petrol−EtOAc (8:2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.74 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.20−5.13 (2H, m, C*H*$_2$=CH), 3.48−3.47 (2H, m, CH_2Br), 2.47−2.42 (2H, m, C*H*$_2$CH=CH_2), 2.22−2.18 (2H, m, 2 ×

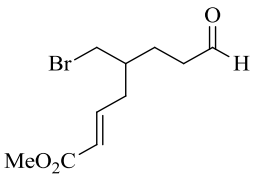
CH), 1.98−1.89 (1H, m, CH), 1.87−1.75 (2H, m, 2 × CH). Data consistent with the literature.[123]

4-(Bromomethyl)hept-6-enal 180



To the nitrile **187** (1.0 g, 5.0 mmol) in CH_2Cl_2 (16 mL) at –78 °C was added DIBAL-H (7.5 mL, 7.5 mmol, 1.0 M solution in hexanes) dropwise. After 1.5 h, aqueous HCl (2.5 mL, 2 M) was added. After 30 min, the mixture was allowed to warm to room temperature. After 30 min, the mixture was extracted with Et_2O (20 mL). The organic layer was washed with aqueous HCl (2.5 mL, 2 M) and the aqueous portions were extracted with Et_2O (3 × 20 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the aldehyde **180** (700 mg, 3.43 mmol, 69%) as an oil; R_f 0.28 [petrol−EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.80 (1H, t, *J* 1.5 Hz, CHO), 5.73 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.17–5.09 (2H, m, CH_2=CH), 3.45 (2H, d, *J* 4.5 Hz, CH_2), 2.54–2.48 (2H, m, 2 × CH), 2.20–2.17 (2H, m, 2 × CH), 1.80–1.74 (3H, m, 3 × CH). Data consistent with the literature.[123]

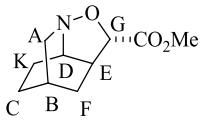
(*E*)-Methyl 5-(bromomethyl)-8-oxooct-2-enoate 188



To alkene **180** (500 mg, 2.45 mmol) in degassed CH_2Cl_2 (16 mL), was added methyl acrylate (0.5 mL, 5.4 mmol). This was heated to reflux before Grubbs' 2nd generation catalyst (100 mg, 0.12 mmol) in CH_2Cl_2 (7mL) was added dropwise. After 2.5 h, the mixture was opened up to air and was allowed to cool to room

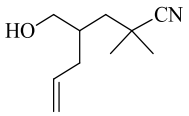
temperature and the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (8:2), gave the aldehyde **188** (430 mg, 1.64 mmol, 67%) as an oil; R_f 0.18 [petrol–EtOAc (8:2)]; IR ν_{max}(film)/cm^{-1} 2952 (C–H), 2862 (C–H), 1717 (C=O), 1660 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.80 (1H, t, *J* 1.4 Hz, CHO), 6.92−6.83 (1H, m, C*H*=CH), 5.95 (1H, dt, *J* 15.5, 1.4 Hz, CH=C*H*), 3.75 (3H, s, CH_3O), 3.42−3.41 (2H, m, CH_2Br), 2.60–2.45 (2H, m, 2 × CH), 2.41–2.30 (2H, m, 2 × CH), 1.93–1.86 (1H, m, CH), 1.77 (2H, q, *J* 7.5 Hz, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.2 (C=O), 166.6 (C=O), 145.3 (CH), 123.7 (CH), 51.6 (CH_3), 40.9 (CH_2), 38.0 (CH), 37.2 (CH_2), 35.2 (CH_2), 24.6 (CH_2); HRMS *m*/*z* (ES) Found: MH$^+$, 263.0279, $C_{10}H_{16}O_3{}^{79}Br$ requires MH$^+$, 263.0283; LRMS *m*/*z* (ES) 263 (MH$^+$ for ^{79}Br, 100%), 265 (MH$^+$ for ^{81}Br, 100%).

(±)-Methyl (1*RS*,5*SR*,6*SR*,7*RS*)-4-oxa-3-azatricyclo[4.3.1.0^{3,7}]decane-5-carboxylate 189



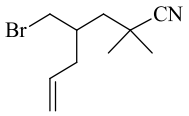
To aldehyde **188** (200 mg, 0.76 mmol) in toluene (4 mL), was added hydroxylamine hydrochloride (80 mg, 1.14 mmol) and *N*,*N*–diisopropylethylamine (0.34 mL, 1.9 mmol) and $MgSO_4$ (200 mg). The mixture was heated at 60 ^{o}C for 30 min, then heated under reflux. After 1.5 h, the mixture was cooled to room temperature, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the cycloadduct **189** (26 mg, 0.12 mmol, 17%) as an oil; R_f 0.14 [CH_2Cl_2–MeOH (97:3)]; IR ν_{max}(film)/cm^{-1} 2945 (C–H), 1735 (C=O); ^{1}H NMR (400 MHz, C_6D_6) δ = 4.25 (1H, s, CH^G), 3.49−3.46 (1H, m, CH^D), 3.40 (3H, s, CH_3O), 3.25 (1H, dd, *J* 15.0, 3.0 Hz, C*H*^{A}H), 3.00 (1H, dt, *J* 15.0, 3.0 Hz, CH^A*H*), 2.43 (1H, dd, *J* 10.0, 3.0 Hz, CH^E), 1.89–1.79 (1H, m, CH^F), 1.49–1.42 (2H, m, 2 × CH^{F+K}), 1.15–1.03 (3H, m, 3 × CH^{B+C+K}), 0.99−0.92 (1H, m, CH^C); ^{13}C NMR (101 MHz, C_6D_6) δ = 171.0 (C), 86.5 (CH), 61.7 (CH_2), 55.6 (CH), 51.3 (CH_3), 42.3 (CH), 34.0 (CH_2), 25.5 (CH_2), 21.4 (CH), 16.3 (CH_2); HRMS *m*/*z* (ES) Found: MH$^+$, 198.1122, $C_{10}H_{16}NO_3$ requires MH$^+$, 198.1130; LRMS *m*/*z* (ES) 198 (100%).

4-(Hydroxymethyl)-2,2-dimethylhept-6-enenitrile 205



Using the same method as the nitrile **186**, diisopropylamine (6.20 mL, 44.25 mmol), *n*-butyllithium (17.70 mL, 44.25 mmol, 2.5 M solution in hexanes), isobutyronitrile (7.94 g, 88.5 mmol), and alcohol **184** (5.0 g, 22.1 mmol) gave, after purification by column chromatography, eluting with petrol–Et_2O (6:4), the nitrile **196** (3.4 g, 20.35 mmol, 92%) as an oil; R_f 0.15 [petrol–Et_2O (6:4)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.81 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.14–5.08 (2H, m, CH_2=CH), 3.71 (1H, dd, *J* 11.0, 5.5 Hz, C*H*HO), 3.65 (1H, dd, *J* 11.0, 5.5 Hz, CH*H*O), 2.32–2.18 (2H, m, 2 × CH), 1.87–1.78 (1H, m, CH), 1.69 (1H, dd, *J* 14.0, 6.0 Hz, C*H*H), 1.58 (1H, t, *J* 5.5 Hz, OH), 1.47 (1H, dd, *J* 14.0, 5.0 Hz, CH*H*), 1.39 (3H, s, CH_3), 1.38 (3H, s, CH_3). Data consistent with the literature.[123]

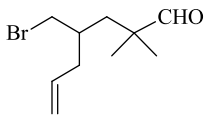
4-(Bromomethyl)-2,2-dimethylhept-6-enenitrile 197



To triphenylphosphine (5.64 g, 21.5 mmol) in CH_2Cl_2 (75 mL) was added carbon tetrabromide (7.10 g, 21.5 mmol) at room temperature. After 5 min, **196** (3.40 g, 19.6 mmol) was added. After 4 h, the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (8:2), gave the bromide **197** (4.15 g, 18.12 mmol, 93%) as an oil; R_f 0.3 [petrol−EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2970 (C−H), 2940 (C−H), 2230 (C≡N), 1725 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.75 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.20−5.13 (2H, m, CH_2=CH), 3.59 (1H, dd, *J* 10.5, 5.0 Hz, C*H*HBr), 3.54 (1H, dd, *J* 10.5, 5.0 Hz, CH*H*Br), 2.37−2.25 (2H, m, 2 × CH), 2.04−1.95 (1H, m, CH), 1.75 (1H, dd, *J* 14.5, 6.0 Hz, C*H*H), 1.55 (1H, dd, *J* 14.5, 5.0 Hz, CH*H*), 1.41 (3H, s, CH_3), 1.40 (3H, s, CH_3); ^{13}C NMR (101

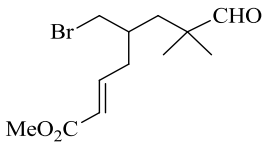
MHz, $CDCl_3$) δ = 134.7 (CH), 125.0 (C), 118.0 (CH_2), 42.8 (CH_2), 39.0 (CH_2), 38.1 (CH_2), 36.6 (CH), 31.3 (C), 27.6 (CH_3), 27.4 (CH_3); HRMS *m/z* (ES) Found: MH^+, 230.0539, $C_{10}H_{17}O^{79}BrN$ requires MH^+, 230.0539; LRMS *m*/*z* (ES), 230 (MH^+ for ^{79}Br, 100%), 232 (MH^+ for ^{81}Br, 98%).

4-(Bromomethyl)-2,2-dimethylhept-6-enal 198



Using the same method as the aldehyde **180**, the nitrile **197** (2.00 g, 8.69 mmol) and DIBAL-H (13.04 mL, 13.04 mmol, 1 M solution in hexanes) gave, after purification by column chromatography, eluting with petrol–EtOAc (9.4:0.6), the aldehyde **198** (1.81 g, 7.82 mmol, 90%) as an oil; R_f 0.4 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2965 (C−H), 2925 (C−H), 1727 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ = 9.52 (1H, s, CHO), 5.69 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.16–5.09 (2H, m, CH_2=CH), 3.43 (1H, dd, *J* 10.5, 4.0 Hz, C*H*HBr), 3.35 (1H, dd, *J* 10.5, 4.5 Hz, CH*H*Br), 2.17–2.12 (2H, m, 2 × CH), 1.81–1.74 (1H, m, CH), 1.74–1.70 (1H, m, CH), 1.57−1.51 (1H, m, CH), 1.11 (3H, s, CH_3), 1.10 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 206.0 (C=O), 135.0 (CH), 118.0 (CH_2), 39.7 (CH_2), 39.4 (CH_2), 38.2 (CH_2), 35.7 (CH), 22.2 (CH_3), 21.7 (CH_3); HRMS *m/z* (ES) Found: M^+, 232.0454, $C_{10}H_{17}O^{79}Br$ requires M^+, 232.0547; LRMS *m*/*z* (ES), 232 (M^+ for ^{79}Br, 100%), 234 (M^+ for ^{81}Br, 95%).

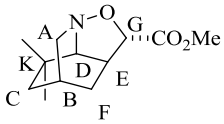
(*E*)-Methyl 5-(bromomethyl)-7,7-dimethyl-8-oxooct-2-enoate 199



Using the same method as ester **188**, to the aldehyde **198** (300 mg, 1.29 mmol) in degassed CH_2Cl_2 (15 mL), was added methyl acrylate (0.26 mL, 2.85 mmol). This was heated to reflux before Grubbs' 2nd generation catalyst **118** (55 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) was added dropwise. Purification by column chromatography,

eluting with petrol–Et_2O (8:2), gave the aldehyde **199** (273 mg, 0.94 mmol, 73%) as an oil; R_f 0.18 [petrol–Et_2O (8:2)]; IR ν_{max}(film)/cm^{-1} 2960 (C−H), 2850 (C−H), 1720 (C=O), 1660 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.51 (1H, s, CHO), 6.88−6.80 (1H, m, C*H*=CH), 5.94 (1H, dt, *J* 15.5, 1.5 Hz, CH=C*H*), 3.76 (3H, s, CH_3O), 3.39 (1H, dd, *J* 10.5, 4.0 Hz, C*H*HBr), 3.32 (1H, dd, *J* 10.5, 5.0 Hz, CH*H*Br), 2.39–2.24 (2H, m, 2 × CH), 1.93–1.85 (1H, m, CH), 1.77 (1H, dd, *J* 15.0, 6.5 Hz, C*H*H), 1.53 (1H, dd, *J* 15.0, 5.5 Hz, CH*H*), 1.12 (3H, s, CH_3), 1.11 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 205.0 (C=O), 166.0 (C=O), 145.3 (CH), 123.9 (CH), 51.6 (CH_3), 45.9 (C), 39.7 (CH_2), 38.8 (CH_2), 36.5 (CH_2), 35.4 (CH), 22.4 (CH_3), 21.5 (CH_3); HRMS *m*/*z* (ES) Found: MH$^+$, 291.0591, $C_{12}H_{20}O_3{}^{79}Br$ requires MH$^+$, 291.0596; LRMS *m*/*z* (ES) 291 (MH$^+$ for ^{79}Br, 100%), 293 (MH$^+$ for ^{81}Br, 100%).

(±)-Methyl (1*SR*,5*SR*,6*SR*,7*SR*)-8,8-dimethyl-4-oxa-3-azatricyclo[4.3.1.0^{3,7}] decane-5-carboxylate 200

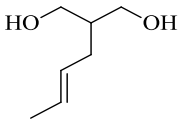


Using the same method as cycloadduct **189**, to aldehyde **199** (100 mg, 0.35 mmol) in toluene (4.0 mL), was added hydroxylamine hydrochloride (23.0 mg, 0.35 mmol) and *N*,*N*–diisopropylethylamine (0.12 mL, 0.69 mmol) and $MgSO_4$ (200 mg), the mixture was heated at 60 °C for 1 h, then the mixture was heated at reflux. After 3 h, the mixture was cooled to room temperature, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the cycloadduct **200** (41.9 mg, 0.18 mmol, 53%) as an oil; R_f 0.20 [CH_2Cl_2–MeOH (97:3)]; IR ν_{max}(film)/cm^{-1} 2955 (C–H), 1450 (C–H); ^{1}H NMR (400 MHz, C_6D_6) δ = 4.19 (1H, s, CH^G), 3.42 (3H, s, CH_3O), 3.16 (1H, d, *J* 3.0 Hz, CH^D), 3.10 (1H, ddd, *J* 15.0, 3.0, 1.5 Hz, C*H*^{A}H), 2.81 (1H, dt, *J* 15.0, 3.0 Hz, CH^A*H*), 2.56 (1H, dd, *J* 9.5, 3.0 Hz, CH^E), 1.47–1.39 (1H, m, CH^F), 1.11–1.07 (1H, m, CH^B), 1.03 (3H, s, CH_3), 1.00–0.94 (1H, m, CH^F), 0.93–0.91 (1H, m, CH^C), 0.88−0.86 (1H, m, CH^C), 0.75 (3H, s, CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ = 171.0 (C=O), 86.7 (CH), 66.6 (CH), 59.7 (CH_2), 51.2 (CH_3), 40.8 (CH_2), 40.3 (CH), 32.4 (CH_2), 31.1 (CH_3),

30.7 (CH_3), 28.5 (C), 23.1 (CH); HRMS *m/z* (ES) Found: MH^+, 226.1444, $C_{12}H_{20}NO_3$ requires MH^+, 226.1443; LRMS *m/z* (ES) 226 (100%).

'The NMR spectra for **200** were also recorded in $CDCl_3$:' ^1H NMR (400 MHz, $CDCl_3$) δ = 4.37 (1H, s, CH^G), 3.75 (3H, s, CH_3O), 3.33 (1H, dd, *J* 15.0, 2.0 Hz, CH^AH), 3.03 (1H, dt, *J* 15.0, 3.0 Hz, CH^AH), 2.98 (1H, d, *J* 3.0 Hz, CH^D), 2.79 (1H, dd, *J* 10.0, 3.0 Hz, CH^E), 2.02–1.95 (1H, m, CH), 1.72–1.68 (1H, m, CH^F), 1.57–1.51 (1H, m, CH^B), 1.32–1.29 (2H, m, 2 × CH), 1.16 (3H, s, CH_3), 1.09 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.2 (C=O), 86.7 (CH), 66.5 (CH), 59.9 (CH_2), 52.2 (CH_3), 41.0 (CH_2), 40.6 (CH), 32.7 (CH_2), 31.3 (CH_3), 31.2 (CH_3), 28.8 (C), 23.2 (CH).

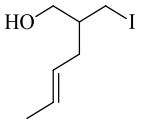
2-[But-2-en-1-yl]propane-1,3-diol 203



To sodium hydride (1.44 g, 60 mmol) in THF (40 mL) was added diethyl malonate **201** (24.0 g, 100 mmol) at room temperature. After 15 min, the suspension was added dropwise to crotyl bromide (6.69 g, 50 mmol, *E*:*Z* 5.6:1) in THF (100 mL). After 3 h, saturated aqueous ammonium chloride (100 mL) and H_2O (100 mL) were added. The aqueous layer was extracted with Et_2O (3 × 75 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. The crude product was added dropwise to a suspension of Et_2O (50 mL) and $LiAlH_4$ (3.7 g, 100 mmol) at 0 °C. After 10 min, the mixture was warmed to room temperature. After 3 h, aqueous sodium hydroxide (ca. 25 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through Celite®, washed with CH_2Cl_2−MeOH (9:1) (200 mL) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (6:4), gave the diol **203** (5.2 g, 40 mmol, 80%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.2 [petrol−EtOAc (1:1)]; IR ν_{max}(film)/cm^{-1} 3315 (O−H), 2915 (C−H), 2885 (C−H); ^1H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.57−5.37 (2H, m, 2 × CH=CH), 3.80 (2H, dd, *J* 10.5, 4.0 Hz, 2 × C*H*HOH), 3.66 (2H, dd, *J* 10.5, 7.5 Hz, 2 × CH*H*OH), 2.55 (2H, s, OH), 1.98 (2H, t, *J* 7.0 Hz, CH_2), 1.87−1.79 (1H, m, CH),

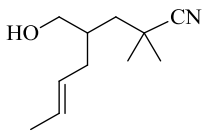
1.67 (3H, dd, *J* 6.0, 1.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.5 (CH), 127.2 (CH), 65.8 (CH_2), 42.2 (CH), 31.3 (CH_2), 18.0 (CH_3); HRMS *m/z* (ES) Found: MH^+, 131.1072, $C_7H_{15}O_2$ requires MH^+, 131.1070; LRMS *m/z* (ES) 131 (MH^+, 60%).

2-(Iodomethyl)hex-4-en-1-ol 204



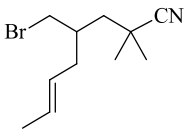
To diol **203** (2.00 g, 15.4 mmol) in THF (75 mL) was added imidazole (1.04 g, 15.4 mmol) and PPh_3 (4.00 g, 15.4 mmol) at room temperature. After 15 min, ground iodine (4.29 g, 16.9 mmol) was added portionwise. After 3 h, CH_2Cl_2 (50 mL) was added and the suspension was filtered through Celite®, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−Et_2O (4:1), gave iodide **204** (2.76 g, 11.50 mmol, 72%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.4 [petrol−Et_2O (3:2)]; IR ν_{max}(film)/cm^{-1} 3328 (OH), 2961 (C−H), 1434 (C–H); ^1H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.57−5.50 (1H, m, C*H*=CH), 5.38−5.30 (1H, m, CH=C*H*), 3.62 (1H, dd, *J* 11.0, 5.0 Hz, C*H*H), 3.50 (1H, dd, *J* 11.0, 7.0 Hz, CH*H*), 3.36 (1H, dd, *J* 10.0, 5.0 Hz, C*H*H), 3.27 (1H, dd, *J* 10.0, 5.5 Hz, CH*H*), 2.36 (1H, br. s, OH), 2.11−1.97 (2H, m, 2 × CH), 1.66 (3H, dd, *J* 6.5, 1.5 Hz, CH_3), 1.53–1.48 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.0 (CH), 127.5 (CH), 65.1 (CH_2), 41.7 (CH), 34.2 (CH_2), 18.0 (CH_3), 11.7 (CH_2); HRMS *m*/*z* (ES) Found: M^+, 240.0003, $C_7H_{13}IO$ requires M^+, 240.0011; LRMS *m*/*z* (ES) 240 (M^+, 17%), 95 (100%) .

3-(Hydroxymethyl)-2,2-dimethylhept-5-enenitrile 205



To diisopropylamine (1.4 mL, 7.5 mmol) in THF (6.5 mL) at –78 °C was added ^{n}BuLi (3.0 mL, 7.5 mmol, 2.5 M solution in hexanes). The mixture was stirred for 30 min, and then isobutyronitrile (1.10 g, 15.0 mmol) was added dropwise. After 30 min, iodide **204** (0.9 g, 3.8 mmol) was added. After 1 h, the mixture was allowed to warm to room temperature over 1 h, and saturated aqueous ammonium chloride (2.7 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et_2O (3:2), gave the nitrile **205** (0.63 g, 3.5 mmol, 92%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.2 [petrol–Et_2O (3:2)]; IR ν_{max}(film)/cm^{-1} 3435 (OH), 2975 (C−H), 2935 (C−H), 2880 (C−H), 2235 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.56−5.49 (1H, m, C*H*=CH), 5.46−5.38 (1H, m, CH=C*H*), 3.69 (1H, dd, *J* 11.0, 5.5 Hz, C*H*HOH), 3.63 (1H, dd, *J* 11.0, 5.0 Hz, CH*H*OH), 2.19−2.15 (2H, m, 2 × CH), 1.81−1.73 (1H, m, CH), 1.69 (3H, dd, *J* 6.0, 1.0 Hz, C*H*$_3$CH=CH), 1.66–1.63 (1H, m, CH), 1.59−1.54 (1H, br. s, OH), 1.46 (1H, dd, *J* 14.0, 5.0 Hz, CH), 1.39 (3H, s, CH_3), 1.37 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.4 (CH), 127.7 (CH), 125.6 (CN), 65.0 (CH_2), 41.0 (CH_2), 37.9 (CH), 35.6 (C), 31.6 (CH_2), 27.6 (CH_3), 27.0 (CH_3), 18.0 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 182.1551, $C_{11}H_{20}NO$ requires MH$^+$, 182.1545; LRMS *m*/*z* (ES) 182 (MH$^+$, 100%).

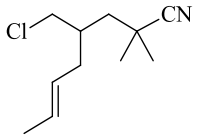
3-(Bromomethyl)-2,2-dimethylhept-5-enenitrile 206



To triphenylphosphine (0.96 g, 3.6 mmol) in CH_2Cl_2 (17 mL) was added carbon tetrabromide (1.21 g, 3.64 mmol) at room temperature. After 5 min, alcohol **205** (0.6

g, 3.30 mmol) was added. After 4 h, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−Et_2O (7:3), gave the bromide **206** (0.71 g, 2.95 mmol, 90%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.4 [petrol−Et_2O (9:1)]; IR ν_{max}(film)/cm^{-1} 2977 (C−H), 2935 (C−H), 2880 (C−H), 2235 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.66−5.54 (1H, m, C*H*=CH), 5.40−5.33 (1H, m, CH=C*H*), 3.58 (1H, dd, *J* 10.0, 4.5 Hz, C*H*HBr), 3.52 (1H, dd, *J* 10.0, 4.5 Hz, CH*H*Br), 2.26−2.16 (2H, m, C*H*$_2$CH=CH), 1.99−1.89 (1H, m, CH), 1.77−1.67 (4H, m, CH and C*H*$_3$CH=CH), 1.52 (1H, dd, *J* 14.5, 5.0 Hz, CH) 1.40 (3H, s, CH_3), 1.39 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.0 (CH), 127.1 (CH), 125.0 (CN), 42.9 (CH_2), 39.3 (CH_2), 37.0 (CH), 36.8 (CH_2), 31.3 (C), 27.6 (CH_3), 27.3 (CH_3), 18.0 (CH_3); HRMS *m*/*z* (ES) Found: MH$^+$, 244.0713, $C_{11}H_{19}N^{79}Br$ requires MH$^+$, 244.0701; LRMS *m*/*z* (ES) 244 (MH$^+$ for ^{79}Br, 100%), 246 (MH$^+$ for ^{81}Br, 87%).

3-(Chloromethyl)-2,2-dimethylhept-5-enenitrile 207



Method 1

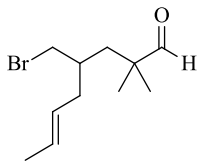
Using the same method as the nitrile **205**, diisopropylamine (1.8 mL, 12.8 mmol) in THF (25 mL) at –78 °C was added ^{n}BuLi (5.32 mL, 12.8 mmol, 2.4 M solution in hexanes). The mixture was stirred for 30 min, and then isobutyronitrile (0.96 g, 13.95 mmol) was added dropwise. After 30 min, iodide **215** (3.0 g, 11.62 mmol) was added. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile **207** (1.80 g, 9.0 mmol, 78%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.37 [petrol−EtOAc (9:1)].

Method 2

To a solution of alcohol **205** (700 mg, 3.86 mmol) in CH_2Cl_2 (50 mL) was added triphenylphosphine (1.33 g, 5.10 mmol) at 0 ºC. After 10 min, trichloroacetonitrile (0.43 mL, 4.25 mmol) was added dropwise. The mixture was allowed to warm to room temperature. After 4 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile **207** (720 mg, 3.60 mmol, 93%) as an oil as a 5.6:1 *E*:*Z* mixture.

IR ν_{max}(film)/cm^{-1} 2977 (C−H), 2935 (C−H), 2880 (C−H), 2235 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.67−5.52 (1H, m, C*H*=CH), 5.42−5.34 (1H, m, CH=C*H*), 3.67 (1H, dd, *J* 11.0, 5.0 Hz, C*H*HCl), 3.61 (1H, dd, *J* 11.0, 5.0 Hz, CH*H*Cl), 2.26−2.20 (2H, m, CH_2CH=CH), 2.00−1.94 (1H, m, CH), 1.75 (1H, dd, *J* 14.5, 5.5 Hz, CH), 1.70 (3H, dd, *J* 6.5, 1.0 Hz, CH_3CH=CH), 1.52 (1H, dd, *J* 14.5, 5.0 Hz, CH), 1.40 (3H, s, CH_3), 1.39 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.8 (CH), 127.2 (CH), 125.0 (CN), 48.6 (CH_2), 41.8 (CH_2), 37.5 (CH), 35.9 (CH_2), 30.2 (C), 27.6 (CH_3), 27.3 (CH_3), 18.0 (CH_3); HRMS *m*/*z* (ES) Found: MH$^+$, 200.1198, $C_{11}H_{19}N^{35}Cl$ requires MH$^+$, 200.1206; LRMS *m*/*z* (ES) 200 (MH$^+$ for ^{35}Cl, 100%), 202 (MH$^+$ for ^{37}Cl, 35%).

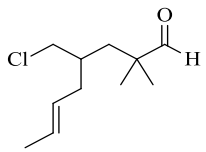
3-(Bromomethyl)-2,2-dimethylhept-5-enal 208



To nitrile **206** (0.6 g, 2.5 mmol) in CH_2Cl_2 (8 mL) at −78 °C was added DIBAL−H (3.5 mL, 3.5 mmol, 1.0 M solution in cyclohexane) dropwise. After 3 h, aqueous hydrochloric acid (3.5 mL, 1 M) was added and the solution was allowed to warm slowly to room temperature over 30 min. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−Et_2O (9:1), gave the aldehyde **208** (0.50 g, 2.05 mmol, 82%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.4 [petrol−Et_2O (9:1)];

IR ν_{max}(film)/cm^{-1} 2960 (C−H), 2930 (C−H), 1725 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 9.51 (1H, s, CHO), 5.57−5.48 (1H, m, C*H*=CH), 5.34−5.25 (1H, m, CH=C*H*), 3.41 (1H, dd, *J* 10.0, 4.0 Hz, C*H*HBr), 3.30 (1H, dd, *J* 10.0, 4.0 Hz, CH*H*Br), 2.07–2.02 (2H, m, CH_2CH=CH), 1.79−1.62 (5H, m, CH_3CH=CH and 2 × CH), 1.57–1.47 (1H, m, CH), 1.10 (3H, s, CH_3), 1.09 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.0 (C=O), 128.5 (CH), 127.4 (CH), 46.0 (C), 39.8 (CH_2), 39.6 (CH_2), 36.9 (CH_2), 36.1 (CH), 22.1 (CH_3), 21.7 (CH_3), 18.0 (CH_3); HRMS *m/z* (ES) Found: M^+, 246.0614, $C_{11}H_{19}O^{79}Br$ requires M^+, 246.0619; LRMS *m/z* (ES), 246 (M^+ for ^{79}Br, 20%), 248 (M^+ for ^{81}Br, 18%), 228 (99%), 230 (100%).

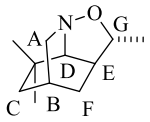
3-(Chloromethyl)-2,2-dimethylhept-5-enal 209



To nitirle **207** (1.7 g, 8.5 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added DIBAL−H (12.75 mL, 12.75 mmol, 1.0 M solution in cyclohexane) dropwise. After 3 h, aqueous hydrochloric acid (10 mL, 1 M) was added and the solution was allowed to warm slowly to room temperature over 30 min. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (9:1), gave the aldehyde **209** (1.57 g, 7.73 mmol, 91%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.5 [petrol−Et_2O (9:1)]; IR ν_{max}(film)/cm^{-1} 2960 (C−H), 2930 (C−H), 1725 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 9.50 (1H, s, CHO), 5.55−5.47 (1H, m, C*H*=CH), 5.35−5.27 (1H, m, CH=C*H*), 3.50 (1H, dd, *J* 11.0, 4.0 Hz, C*H*HCl), 3.45 (1H, dd, *J* 11.0, 4.5 Hz, CH*H*Cl), 2.12–2.00 (2H, m, 2 × CH), 1.80−1.70 (2H, m, 2 × CH), 1.68 (3H, dd, *J* 6.5, 1.0 Hz, CH_3), 1.54–1.47 (1H, m, CH), 1.10 (3H, s, CH_3), 1.09 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.1 (C=O), 128.5 (CH), 127.5 (CH), 48.8 (CH_2), 46.0 (C), 38.7 (CH_2), 36.6 (CH_2), 36.3 (CH), 22.1 (CH_3), 21.7 (CH_3), 18.0 (CH_3); HRMS *m/z* (ES) Found: MH^+, 203.1211,

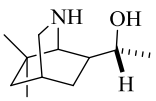
$C_{11}H_{20}O^{35}Cl$ requires MH^+, 203.1203; LRMS *m*/*z* (ES), 203 (MH^+ for ^{35}Cl, 100%), 205 (MH^+ for ^{37}Cl, 25%).

(±)-(1*SR*,5*RS*,6*SR*,7*SR*)-5,8,8-Trimethyl-4-oxa-3-azatricyclo[4.3.1.0^{3,7}]decane 210



To aldehyde **208** (E:Z 5.6:1) (100 mg, 0.40 mmol) in xylene (4 mL), was added hydroxylamine hydrochloride (40 mg, 0.60 mmol) and *N*,*N*–diisopropylethylamine (0.18 mL, 1.0 mmol) and the mixture was heated under reflux. After 3 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the cycloadduct **210** (50 mg, 0.28 mmol, 70%) as an oil as a single stereoisomer; R_f 0.3 [CH_2Cl_2–MeOH (97:3)]; IR ν_{max}(film)/cm^{-1} 2955 (C–H), 1450 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.08 (1H, q, *J* 6.5 Hz, CH^G), 3.30 (1H, dd, *J* 14.5, 1.5 Hz, C*H*^{A}H), 2.95 (1H, dd, *J* 14.5, 3.0 Hz, CH^A*H*), 2.88 (1H, d, *J* 3.0 Hz, CH^D), 2.17 (1H, dd, *J* 9.5, 3.0 Hz, CH^E), 1.92–1.85 (1H, m, CH^F), 1.68–1.64 (1H, m, CH^B), 1.48 (1H, dd, *J* 13.5, 4.5 Hz, CH^F), 1.31–1.28 (2H, m, $CH_2{}^C$), 1.19 (3H, d, *J* 6.5 Hz, CH_3), 1.18 (3H, s, CH_3), 1.09 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 86.0 (CH), 66.6 (CH), 59.9 (CH_2), 41.4 (CH_2), 41.0 (CH), 33.5 (CH_2), 31.5 (CH_3), 31.2 (CH_3), 28.8 (C), 23.4 (CH), 21.0 (CH_3); HRMS *m*/*z* (ES) Found: MH^+, 182.1552, $C_{11}H_{20}NO$ requires MH^+, 182.1545; LRMS *m*/*z* (ES) 182 (100%).

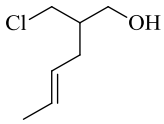
(±)-(1*RS*)-1-[(1*SR*,4*SR*,6*SR*)-7,7-Dimethyl-2-azabicyclo[2.2.2]octan-6-yl]ethanol 211



To the cycloadducts **210** (130 mg, 0.71 mmol) in AcOH/H_2O (2.2:2.8 mL) was added zinc powder and the mixture was stirred at 70 °C. After 2 h the zinc salts were

filtered through celite®, and the solvent was evaporated. The residue was dissolved in MeOH (3.0 mL) and poured onto aqueous sodium hydroxide (2.5 mL, 2.0 M). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–NH_3 (98:2:0.2), gave the cycloadduct **211** (125 mg, 0.69 mmol, 98%) as an oil; R_f 0.3 [CH_2Cl_2–MeOH–NH_3 (98:2:0.2)]; IR ν_{max}(film)/cm^{-1} 3311 (OH), 2960 (N–H), 2860 (C–H), 1450 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.89 (1H, qd, *J* 6.5, 3.0 Hz, CH), 2.97–2.93 (1H, dt, *J* 10.0, 3.0 Hz, CH), 2.90–2.86 (1H, dt, *J* 10.0, 2.5 Hz, CH), 2.59–2.53 (1H, d, *J* 2.0 Hz, CH), 1.90–1.85 (1H, m, CH), 1.79–1.69 (3H, m, 3 × CH), 1.48–1.42 (1H, m, CH), 1.34 (1H, dt, *J* 13.0, 2.5 Hz, CH), 1.25 (3H, d, *J* 6.5 Hz, CH_3), 1.00 (3H, s, CH_3), 0.97 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 71.5 (CH), 53.9 (CH), 45.3 (CH_2), 40.7 (CH_2), 36.7 (CH), 33.0 (C), 29.3 (CH_3), 29.1 (CH_2), 29.0 (CH_3), 27.1 (CH_3), 22.6 (CH); HRMS *m/z* (ES) Found: MH$^+$, 184.1702, $C_{11}H_{22}NO$ requires MH$^+$, 184.1701; LRMS *m/z* (ES) 184 (100%).

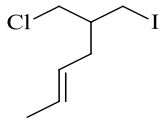
2-(Chloromethyl)hex-4-en-1-ol 214



To a solution of diol **203** (3.0 g, 23 mmol) in CH_2Cl_2 (230 mL) was added triphenylphosphine (7.25 g, 27.6 mmol) at 0 °C. After 10 min, trichloroacetonitrile (2.31 mL, 23.05 mmol) was added dropwise. The mixture was allowed to warm to room temperature. After 4 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), gave the chloride **214** (2.89 g, 19.6 mmol, 85%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.27 [petrol–EtOAc (4:1)]; IR ν_{max}(film)/cm^{-1} 3330 (OH), 2935 (C–H), 2915 (CH), 1435 (C–H), 725 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.57−5.50 (1H, m, C*H*=CH), 5.43−5.35 (1H, m, CH=C*H*), 3.72−3.68 (2H, m, CH_2O), 3.67−3.60 (2H, m, CH_2Cl), 2.13–2.08 (2H, m, C*H*$_2$CH=CH), 1.97−1.90 (1H, m, CH), 1.68 (3H, dd, *J* 6.0, 1.0 Hz, CH_3), 1.64 (1H, br. s, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.0 (CH), 127.7 (CH), 62.8 (CH_2), 45.6 (CH_2), 42.8 (CH), 31.8 (CH_2), 18.0 (CH_3);

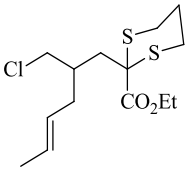
HRMS *m*/*z* (ES) Found: MH^+, 148.0655, $C_7H_{14}{}^{35}ClO$ requires MH^+, 148.0655; LRMS *m*/*z* (ES) 148 (MH^+ for ^{35}Cl, 100%), 150 (MH^+ for ^{37}Cl, 60%).

6-Chloro-5-(iodomethyl)hex-2-ene 215



To alcohol **214** (3.20 g, 21.6 mmol) in THF (75 mL) were added imidazole (1.64 g, 25.9 mmol) and PPh_3 (6.80 g, 25.9 mmol). After 15 min, ground iodine (6.00 g, 23.8 mmol) was added portionwise at room temperature. After 3 h, CH_2Cl_2 (50 mL) was added and the suspension was filtered through Celite® and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol (neat), gave the iodide **215** (4.62 g, 17.9 mmol, 83%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.5 (petrol); IR ν_{max}(film)/cm^{-1} 2960 (C−H), 1435 (C−H); ^1H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.62−5.54 (1H, m, C*H*=CH), 5.38−5.29 (1H, m, CH=C*H*), 3.66 (1H, dd, *J* 11.0, 4.5 Hz, C*H*H), 3.52 (1H, dd, *J* 11.0, 6.5 Hz, CH*H*), 3.40 (1H, dd, *J* 10.0, 4.5 Hz, C*H*H), 3.30 (1H, dd, *J* 10.0, 6.0 Hz, CH*H*), 2.16−2.06 (2H, m, 2 × CH), 1.80–1.72 (1H, m, CH), 1.69 (3H, dd, *J* 6.5, 1.5 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.9 (CH), 126.7 (CH), 47.9 (CH_2), 41.8 (CH), 35.1 (CH_2), 18.0 (CH_3), 10.5 (CH_2); HRMS *m*/*z* (ES) Found: M^+, 257.9669, $C_7H_{12}{}^{35}ClI$ requires M^+, 257.9672; LRMS *m*/*z* (EI) 258 (M^+ for ^{35}Cl, 6%), 260 (M^+ for ^{37}Cl, 2%), 55 (100%).

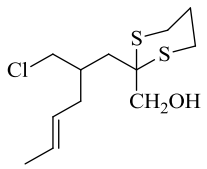
Ethyl 2-[2-(chloromethyl)hex-4-en-1-yl]-1,3-dithiane-2-carboxylate 219



To ethyl 1,3-dithiane-2-carboxylate **218** (2.0 mL, 13.0 mmol) in THF (35 mL) was added ^{n}BuLi (6.2 mL, 15.6 mmol, 2.5 M in hexanes) at –78 °C. After 15 min, the

iodide **215** (4.0 g, 15.6 mmol) in THF (5 mL) was added at –40 °C and the mixture was allowed to warm to room temperature. After 16 h, H_2O (40 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the ester **219** (3.2 g, 9.9 mmol, 75%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.3 [petrol–EtOAc (98:2)]; IR ν_{max}(film)/cm^{-1} 2980 (C−H), 2920 (C−H), 1720 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.60−5.51 (1H, m, C*H*=CH), 5.40−5.32 (1H, m, CH=C*H*), 4.31–4.24 (2H, m, CH_2O), 3.68–3.61 (2H, m, CH_2Cl), 3.33–3.25 (2H, m, CH_2), 2.72 (1H, dd, *J* 4.5, 3.0 Hz, C*H*H), 2.68 (1H, dd, *J* 4.5, 3.0 Hz, CH*H*), 2.27–2.23 (1H, m, C*H*H), 2.20−2.15 (3H, m, 3 × CH), 2.14–2.11 (1H, m, C*H*H), 2.05 (1H, dd, *J* 14.0, 4.0 Hz, CH*H*), 1.93−1.82 (1H, m, CH*H*), 1.68 (3H, dd, *J* 6.0, 1.0 Hz, C*H*$_3$CH=CH), 1.36 (3H, t, *J* 7.0 Hz, C*H*$_3$CH$_2$O); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.0 (C=O), 128.4 (CH), 127.5 (CH), 62.1 (CH_2), 52.9 (C), 49.1 (CH_2), 39.8 (CH_2), 36.8 (CH), 35.9 (CH_2), 27.95 (CH_2), 27.9 (CH_2), 24.4 (CH_2), 18.0 (CH_3), 14.2 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 323.0909, $C_{14}H_{24}O_2S_2{}^{35}Cl$ requires MH$^+$, 323.0906; LRMS *m/z* (ES) 323 (MH$^+$ for ^{35}Cl, 100%), 325 (MH$^+$ for ^{37}Cl, 45%).

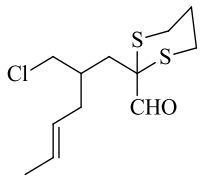
2-[2-(Chloromethyl)hex-4-en-1-yl]-1,3-dithian-2-ylmethanol 221



To a suspension of $LiAlH_4$ (0.56 g, 14.7 mmol) in Et_2O (25 mL) was added ester **219** (3.17 g, 9.8 mmol) in Et_2O (5 mL) at room temperature. After 2.5 h, aqueous NaOH (30 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through celite and washed with CH_2Cl_2−MeOH (9:1) (100 mL) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (8:2), gave the alcohol **221** (2.2 g, 7.84 mmol, 80%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.5 [petrol–EtOAc (4:1)]; IR ν_{max}(film)/cm^{-1} 3275 (OH), 2935 (C–H), 2910 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ =

5.59−5.50 (1H, m, C*H*=CH), 5.42−5.34 (1H, m, CH=C*H*), 3.77−3.74 (2H, m, CH_2O), 3.72–3.66 (2H, m, CH_2Cl), 2.99–2.90 (2H, m, 2 × CH), 2.63 (1H, dd, *J* 4.5, 3.0 Hz, CH), 2.60 (1H, dd, *J* 4.5, 3.0 Hz, CH), 2.28–2.19 (3H, m, 2 × CH and OH), 2.15–2.06 (2H, m, 2 × CH), 1.93–1.78 (2H, m, 2 × CH), 1.73 (1H, dd, *J* 15.0, 3.0 Hz, CH), 1.68 (3H, dd, *J* 6.0, 1.0 Hz, C*H*$_3$CH=CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.3 (CH), 127.7 (CH), 64.0 (CH_2), 54.8 (C), 49.6 (CH_2), 39.0 (CH_2), 36.4 (CH_2), 35.9 (CH), 25.9 (CH_2), 25.8 (CH_2), 24.6 (CH_2), 18.0 (CH_3); HRMS *m*/*z* (ES) Found: MH^+, 281.0796, $C_{12}H_{22}OS_2{}^{35}Cl$ requires MH^+, 281.0801; LRMS *m*/*z* (ES) 281 (MH^+ for ^{35}Cl, 8%), 283 (MH^+ for ^{37}Cl, 3%), 263 (100%), 265 (45%).

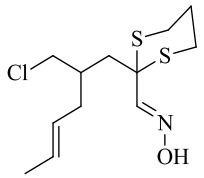
2-[2-(Chloromethyl)hex-4-en-1-yl]-1,3-dithiane-2-carbaldehyde 220



DMSO (0.80 mL, 11.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise to oxalyl chloride (0.50 mL, 5.5 mmol) in CH_2Cl_2 (15 mL) at –60 °C. After 5 min, alcohol **221** (1.4 g, 5.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After 10 min, *N*,*N*-diisopropylethylamine (4.5 mL, 25.0 mmol) was added. After 15 min at –60 °C the mixture was allowed to warm to room temperature, then water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed successively with aqueous HCl (2 × 15 mL, 1 M), H_2O (15 mL), Na_2CO_3 (15 mL, 5%), and H_2O (20 mL), then dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (9:1) gave the aldehyde **220** (1.15 g, 4.13 mmol, 83%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.5 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2930 (C−H), 2855 (C−H), 1705 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 9.03 (1H, s, CHO), 5.57−5.50 (1H, m, C*H*=CH), 5.36−5.28 (1H, m, CH=C*H*), 3.61 (1H, dd, *J* 11.5, 4.0 Hz, C*H*HCl), 3.56 (1H, dd, *J* 11.5, 4.0 Hz, CH*H*Cl), 3.10–2.98 (1H, m, C*H*H), 3.01–2.93 (1H, m, CH*H*), 2.65–2.58 (2H, m, C*H*$_2$CH=CH), 2.24–2.17 (1H, m, C*H*H), 2.13–2.08 (3H, m, 3 × CH), 2.04 (1H, dd, *J* 15.0, 7.0 Hz, CH*H*),

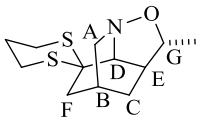
1.87–1.75 (2H, m, 2 × CH), 1.68 (3H, dd, *J* 6.0, 1.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 188.7 (C=O), 128.9 (CH), 127.1 (CH), 57.7 (C), 48.2 (CH_2), 37.0 (CH_2), 35.9 (CH), 30.1 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 24.0 (CH_2), 18.0 (CH_3); HRMS *m/z* (ES) Found: MH^+, 279.0646, $C_{12}H_{20}OS_2{}^{35}Cl$ requires MH^+, 279.0644; LRMS *m/z* (ES) 279 (MH^+ for ^{35}Cl, 100%), 281 (MH^+ for ^{37}Cl, 45%).

2-(2-(Chloromethyl)hex-4-en-1-yl)-1,3-dithiane-2-carbaldehyde oxime 232



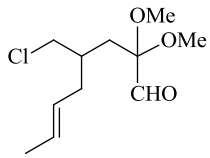
To aldehyde **220** (500 mg, 1.80 mmol) in dry methanol (25 mL) was added hydroxylamine hydrochloride (135 mg, 2.0 mmol) and sodium acetate (365 mg, 4.5 mmol) at room temperature. After 5 h, the solvent was evaporated. The white residue was washed with CH_2Cl_2, and then concentrated to give the oxime **232** in quantitative yield which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$ peaks for major isomer) δ = 7.44 (1H, s, CH=N), 5.62−5.50 (1H, m, C*H*=CH), 5.38−5.30 (1H, m, CH=C*H*), 3.67–3.60 (2H, m, CH_2Cl), 3.16–3.11 (1H, m, C*H*H), 3.10–3.04 (1H, m, CH*H*), 2.73–2.70 (1H, m, C*H*H), 2.69–2.66 (1H, m, CH*H*), 2.27–2.07 (5H, m, 5 × CH), 1.94–1.83 (2H, m, 2 × CH), 1.69 (3H, dd, *J* 6.0, 1.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.0 (CH), 128.6 (CH), 127.4 (CH), 51.5 (C), 48.8 (CH_2), 41.0 (CH_2), 36.2 (CH_2), 35.8 (CH), 27.3 (CH_2), 27.2 (CH_2), 24.8 (CH_2), 18.0 (CH_3); HRMS *m/z* (ES) Found: MH^+, 294.0746, $C_{12}H_{21}NOS_2{}^{35}Cl$ requires MH^+, 294.0753; LRMS *m/z* (ES) 294 (MH^+ for ^{35}Cl, 100%), 296 (MH^+ for ^{37}Cl, 48%).

(±)-(1'*SR*,5'*RS*,6'*SR*,7'*SR*)-5'-Methyl-4'-oxa-3'-azaspiro[1,3-dithiane-2,8'-tricyclo[4.3.1.0^{3},^{7}]decane] 222



Oxime **232**, *N*,*N*-diisopropylethylamine (0.32 mL, 1.8 mmol) and $MgSO_4$ (100 mg) in toluene (15 mL) were heated under reflux. After 16 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the cycloadduct **222** (263 mg, 1.0 mmol, 57%) as an oil as a single stereoisomer; R_f 0.3 [CH_2Cl_2–MeOH (97:3)]; IR ν_{max}(film)/cm^{-1} 2925 (C–H), 2900 (C–H), 1440 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.19 (1H, q, *J* 6.0 Hz, CH^G), 3.87 (1H, d, *J* 3.5 Hz, C*H*^{D}), 3.46 (1H, dd, *J* 14.5, 2.0 Hz, C*H*^{A}H), 3.20–3.13 (1H, m, CH^A*H*), 3.09–3.00 (2H, m, 2 × CH), 2.86–2.76 (2H, m, 2 × CH), 2.42 (1H, dd, *J* 9.5, 3.5 Hz, CH^E), 2.13–2.00 (3H, m, CH^F and 2 × CH), 1.91–1.88 (2H, m, $CH_2{}^C$), 1.79–1.77 (1H, m, CH^B), 1.55 (1H, dd, *J* 13.5, 4.5 Hz C*H*^{F}H), 1.26 (3H, d, *J* 6.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 86.6 (CH), 61.8 (CH), 59.4 (CH_2), 44.7 (C), 44.5 (CH_2), 41.9 (CH), 33.2 (CH_2), 27.5 (CH_2), 27.2 (CH_2), 24.7 (CH_2), 23.0 (CH), 21.1 (CH_3); HRMS *m*/*z* (ES) Found: MH$^+$, 258.0994, $C_{12}H_{20}NOS_2$ requires MH$^+$, 258.0986; LRMS *m*/*z* (ES) 258 (100%).

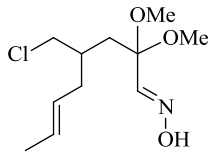
4-(Chloromethyl)-2,2-dimethoxyoct-6-enal 224



To aldehyde **220** (1.12 g, 4.04 mmol) in anhydrous methanol (5 mL) was added bis(trifluoroacetoxy)iodo benzene (3.00 g, 6.85 mmol) at room temperature. After 15 min, saturated aqueous sodium bicarbonate (5 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et_2O (9:1),

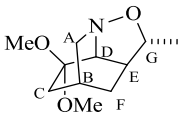
gave the aldehyde **224** (580 mg, 2.5 mmol, 62%) as an oil a 5.6:1 *E*:*Z* mixture; R_f 0.3 [petrol–Et_2O (9:1)]; IR ν_{max}(film)/cm^{-1} 2945 (C−H), 2840 (C−H), 1750 (C=O), 1440 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 9.46 (1H, s, CHO), 5.56−5.47 (1H, m, C*H*=CH), 5.34−5.25 (1H, m, CH=C*H*), 3.60–3.55 (2H, m, CH_2Cl), 3.31 (3H, s, CH_3O), 3.30 (3H, s, CH_3O), 2.17–2.05 (3H, m, 3 × CH), 1.87–1.80 (1H, m, CH), 1.75 (1H, dd, *J* 15.0, 5.0 Hz, CH), 1.67 (3H, dd, *J* 6.0, 1.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.5 (C=O), 128.7 (CH), 127.3 (CH), 102.1 (C), 49.1 (CH_3), 49.7 (CH_3), 48.4 (CH_2), 35.6 (CH_2), 34.3 (CH), 32.6 (CH_2), 18.0 (CH_3); HRMS *m/z* (ES) Found: MH^+, 235.1097, $C_{11}H_{20}O_3{}^{35}Cl$ requires MH^+, 235.1101; LRMS *m/z* (ES) 235 (MH^+ for ^{35}Cl, 100%), 237 (MH^+ for ^{37}Cl, 35%).

4-(Chloromethyl)-2,2-dimethoxyoct-6-enal oxime 226



Aldehyde **224** (100 mg, 0.43 mmol), hydroxylamine hydrochloride (0.04 g, 0.64 mmol), *N*,*N*-diisopropylethylamine (0.18 mL, 1.06 mmol) and ($MgSO_4$) in toluene (4 mL) were heated at 60 °C. After 30 min, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (96:4), gave the oxime **226** (96 mg, 0.38 mmol, 90%) as an oil as a mixture of *E* and *Z* alkene and oxime isomers; R_f 0.3 [CH_2Cl_2–MeOH (96:4)]; IR ν_{max}(film)/cm^{-1} 3340 (OH), 2935 (C−H), 1440 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$ peaks for major isomer) δ = 7.45 (1H, s, OH), 7.31 (1H, s, CH=N), 5.62−5.49 (1H, m, C*H*=CH), 5.37−5.29 (1H, m, CH=C*H*), 3.63–3.60 (2H, m, CH_2Cl), 3.28 (3H, s, CH_3O), 3.26 (3H, s, CH_3O), 2.19–2.10 (2H, m, 2 × CH), 2.08 (1H, dd, *J* 15.0, 7.5 Hz CH*H*), 1.95–1.88 (1H, m, CH), 1.75 (1H, dd, *J* 15.0, 5.0 Hz, C*H*H), 1.68 (3H, dd, *J* 6.0, 1.5 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.0 (CH), 128.4 (CH), 127.6 (CH), 100.7 (C), 49.3 (CH_3), 49.1 (CH_3), 48.6 (CH_2), 35.6 (CH_2), 35.5 (CH_2), 35.4 (CH), 18.0 (CH_3). HRMS and LRMS could not be obtained despite attempts with ES.

(±)-(1*SR*,5*RS*,6*SR*,7*SR*)-8,8-Dimethoxy-5-methyl-4-oxa-3-azatricyclo [4.3.1.0^{3},^{7}] decane 225



Method 1

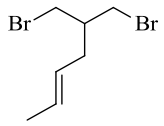
Using the same method as the cycloadduct, the aldehyde **224** (*E*:*Z* 5.6:1) (100 mg, 0.43 mmol), *N*,*N*-diisopropylethylamine (0.18 mL, 1.07 mmol), hydroxylamine hydrochloride (40 mg, 0.64 mmol) and $MgSO_4$ (50 mg) in toluene (4 mL). After 16 h, purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the cycloadduct **225** (13.8 mg, 0.06 mmol, 15%) as an oil as a single stereoisomer; R_f 0.36 [CH_2Cl_2–MeOH (9.7:0.3)];

Method 2

To dithiane cycloadduct **222** (70 mg, 0.27 mmol) in methanol (7.0 mL) was added bis(trifluoroacetoxy)iodo benzene (0.11 g, 0.27 mmol) at room temperature. Additional bis(trifluoroacetoxy)iodo benzene (0.45 g, 1.1 mmol) was added during 1 h period, and the mixture was stirred for 2.5 h. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9.7:0.3), gave acetal **225** (8.7 mg, 0.04 mmol, 15%);

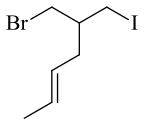
IR ν_{max}(film)/cm^{-1} 2950 (C–H), 2900 (C–H), 1460 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 (1H, q, *J* 6.0 Hz, CH^{G}), 3.49 (1H, d, *J* 3.5 Hz, C*H*^{D}), 3.37–3.01 (4H, m, CH and CH_3), 3.26 (3H, s, CH_3), 2.97 (1H, dt, *J* 14.5, 3.0 Hz, CH), 2.18 (1H, dd, *J* 9.5, 3.5 Hz, CH), 1.96–1.89 (1H, m, CH), 1.82–1.80 (1H, m, CH), 1.67 (1H, t, *J* 3.0 Hz, CH), 1.66 (1H, t, *J* 3.0 Hz, CH), 1.52 (1H, dd, *J* 13.0, 4.0 Hz, CH), 1.21 (3H, d, *J* 6.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 100.0 (C), 85.6 (CH), 60.6 (CH), 60.3 (CH_2), 48.7 (CH_3), 47.8 (CH_3), 40.6 (CH), 39.03 (CH_2), 34.1 (CH_2), 23.0 (CH), 21.0 (CH_3); HRMS *m/z* (ES) Found: MH^{+}, 214.1433, $C_{11}H_{20}NO_3$ requires MH^{+}, 214.1438; LRMS *m/z* (ES) 182 (50%), 214 (MH^{+}, 100%).

6-Bromo-5-(bromomethyl)hex-2-ene 228



Triphenylphosphine (4.45 g, 16.9 mmol) was added over 30 min to diol **203** (1.00 g, 7.68 mmol) and carbon tetrabromide (5.60 g, 16.9 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After 4 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol (neat), gave the bromide **228** (1.8 g, 7.0 mmol, 92%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.6 (petrol); IR ν_{max}(film)/cm^{-1} 2965 (C−H), 2910 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.67−5.55 (1H, m, C*H*=CH), 5.39−5.32 (1H, m, CH=C*H*), 3.59 (2H, dd, *J* 10.0, 4.5 Hz, 2 × CHBr), 3.49 (2H, dd, *J* 10.0, 6.0 Hz, 2 × CHBr), 2.18 (2H, t, *J* 7.0 Hz, CH_2–CH=CH), 2.06–2.01 (1H, m, CH), 1.70 (3H, dd, *J* 6.5, 1.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.9 (CH), 126.7 (CH), 41.9 (CH), 36.0 (CH_2), 34.6 (CH_2) 18.0 (CH_3); HRMS *m*/*z* (ES) Found: MH$^+$, 255.9281, $C_7H_{13}{}^{79}Br_2$ requires MH$^+$, 255.9280; LRMS *m*/*z* (EI) 254 (MH$^+$ for ^{79}Br, 50%), 256 (MH$^+$ for ^{79}Br + ^{81}Br, 100%), 258 (MH$^+$ for ^{81}Br, 47%).

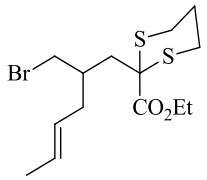
6-Bromo-5-(iodomethyl)hex-2-ene 230



To iodo–alcohol **204** (2.0 g, 8.4 mmol) in CH_2Cl_2 (50 mL) and CBr_4 (3.0 g, 9.2 mmol) was added PPh_3 (2.4 g, 9.2 mmol) over 30 min at 0 °C. The mixture was stirred for 2 h at room temperature then the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol (neat), gave the iodide **230** (2.2 g, 7.28 mmol, 88%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.6 (petrol); IR ν_{max}(film)/cm^{-1} 2960 (C−H), 2915 (C−H); ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.66−5.55 (1H, m, C*H*=CH), 5.37−5.29 (1H, m, CH=C*H*), 3.56 (1H, dd, *J* 10.0, 4.5 Hz, C*H*H), 3.45−3.40 (2H, m, 2 × CH), 3.30 (1H, dd, *J* 10.0, 6.0

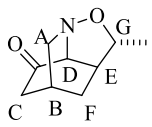
Hz, CH*H*), 2.17−2.11 (2H, m, 2 × CH), 1.73–1.67 (4H, m, CH and CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 128.9 (CH), 126.7 (CH), 41.4 (CH), 37.9 (CH_2), 35.9 (CH_2), 18.0 (CH_3), 11.6 (CH_2); HRMS *m*/*z* (ES) Found: M^+, 301.9176, $C_7H_{12}{}^{79}BrI$ requires M^+, 301.9162; LRMS *m*/*z* (EI) 302 (M^+ for ^{79}Br, 6%), 304 (M^+ for ^{81}Br, 6%), 95 (100%).

Ethyl 2-[2-(bromomethyl)hex-4-en-1-yl]-1,3-dithiane-2-carboxylate 229



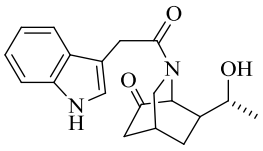
To ethyl 1,3-dithiane-2-carboxylate (1.75 mL, 11.0 mmol) in THF (30 mL) was added ^{n}BuLi (5.2 mL, 13.25 mmol, 2.5 M in hexanes) at –78 °C. After 15 min, the iodide **230** (4.00 g, 13.2 mmol) in THF (5 mL) was added at –40 °C and the mixture was allowed to warm to room temperature. After 16 h, H_2O (35 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.6:0.4), gave the ester **229** (2.4 g, 6.6 mmol, 60%) as an oil as a 5.6:1 *E*:*Z* mixture; R_f 0.3 [petrol–EtOAc (96:4)]; IR ν_{max}(film)/cm^{-1} 2960 (C−H), 2925 (C−H), 1720 (C=O); ^1H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.63−5.53 (1H, m, C*H*=CH), 5.40−5.32 (1H, m, CH=C*H*), 4.30–4.25 (2H, m, CH_2O), 3.58–3.55 (2H, m, CH_2Br), 3.31–3.25 (2H, m, 2 × CH), 2.73–2.70 (1H, m, C*H*H), 2.69–2.66 (1H, m, CH*H*), 2.23–2.10 (5H, m, 5 × CH), 2.07–2.00 (1H, m, C*H*H), 1.94–1.82 (1H, m, CH*H*), 1.68 (3H, d, *J* 6.5, 1.5 Hz, CH_3CH=CH), 1.36 (3H, t, *J* 7.0 Hz, CH_3CH_2O); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.0 (C=O), 128.5 (CH), 127.4 (CH), 62.1 (CH_2), 52.8 (C), 40.8 (CH_2), 40.2 (CH_2), 36.9 (CH_2), 36.3 (CH), 28.0 (CH_2), 27.9 (CH_2), 24.4 (CH_2), 18.0 (CH_3), 14.2 (CH_3); HRMS *m*/*z* (ES) Found: MH^+, 367.0416, $C_{14}H_{24}O_2S_2{}^{79}Br$ requires MH^+, 367.0401; LRMS *m*/*z* (ES) 367 (MH^+ for ^{79}Br, 97%), 369 (MH^+ for ^{81}Br, 100%).

(±)-**(1*SR*,5*RS*,6*SR*,7*SR*)-5-Methyl-4-oxa-3-azatricyclo[4.3.1.0^{3},^{7}]decan-8-one 212**



To dithiane **222** (300 mg, 1.16 mmol) in acetonitrile/water (1:1) (44 mL) was added bis(trifluoroacetoxy)iodo benzene (0.5 g, 1.16 mmol), and trifluoroacetic acid (10.0 equiv.) at room temperature. Additional bis(trifluoroacetoxy)iodobenzene (1.9 g, 4.4 mmol) was added over a 1 h period, and the mixture was stirred for 2.5 h, before being neutralised with saturated aqueous sodium bicarbonate (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9.7:0.3), gave ketone **212** (155 mg, 0.93 mmol, 80%) as a needles, m.p. 62−63.5 ^{o}C; R_f 0.32 [CH_2Cl_2–MeOH (9.7:0.3)]; IR ν_{max}(film)/cm^{-1} 2965 (C–H), 1730 (C=O), 1450 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.26 (1H, q, *J* 6.0 Hz, CH^{G}), 3.62 (1H, d, *J* 3.5 Hz, CH^{D}), 3.51 (1H, dd, *J* 14.5, 2.5 Hz, C*H*^{A}H), 3.30–3.20 (1H, m, CH^{A}*H*), 2.45 (1H, dd, *J* 9.0, 3.5 Hz, CH^{E}), 2.25–2.23 (2H, m, 2 × CH^{C,F}), 2.20–2.18 (1H, m, C*H*^{C}H), 2.03–1.96 (1H, m, CH^{B}), 1.79 (1H, dd, *J* 13.5, 4.5 Hz, C*H*^{F}H), 1.21 (3H, d, *J* 6.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209 (C=O), 85.6 (CH), 68.9 (CH), 61.5 (CH_2), 44.8 (CH), 44.5 (CH_2), 34.1 (CH_2), 23.3 (CH), 20.5 (CH_3); HRMS *m*/*z* (ES) Found: MH^{+}, 168.1020, $C_9H_{14}NO_2$ requires MH^{+}, 168.1019; LRMS *m/z* (ES) 168 (100%).

(±)-**(1*SR*,4*SR*,7*SR*)-7-[(1*RS*)-1-Hydroxyethyl]-2-[2-(1H-indol-3-yl)acetyl]-2-azabicyclo[2.2.2]octan-6-one 237**

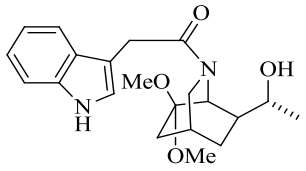


To the cycloadducts **212** (100 mg, 0.60 mmol) in AcOH/MeOH (0.6:0.8 mL) was added activated Zn powder [washed with freshly prepared aqueous HCl (1.0 M), EtOH, then Et_2O] and the mixture was stirred at room temperature. After 4 h the zinc

salts were filtered through Celite®, and the solvent was evaporated. The residue was dissolved in MeOH (3.0 mL) and poured onto aqueous sodium hydroxide (3.0 mL, 2.0 M). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the organic layers were dried ($MgSO_4$) and evaporated.

Indole acetic acid (89 mg, 0.51 mmol) and EDCI (97 mg, 0.51 mmol) was added to a solution of crude product of amino alcohol (100 mg, 0.51 mmol) in CH_2Cl_2 (6 mL) at room temperature. The mixture was stirred for 1.5 h, then was extracted with CH_2Cl_2 (3 × 15 mL), washed with aqueous HCl (1.5 mL, 0.01 M), saturated aqueous solution of K_2CO_3 (1.5 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9:1), gave the amide **237** (195 mg, 0.60 mmol, 100%) as a foam; R_f 0.39 [CH_2Cl_2–MeOH (9:1)]; IR ν_{max}(film)/cm^{-1} 3320 (OH), 2970 (C–H), 1730 (C=O), 1625 (C=O), 1460 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (1H, br. s, NH), 7.59 (1H, d, *J* 7.5 Hz, ArH), 7.38 (1H, d, *J* 7.5 Hz, ArH), 7.24−7.21 (1H, m, ArH), 7.13−7.11 (2H, m, 2 × ArH), 5.01 (1H, d, *J* 1.6 Hz, CH), 3.96–3.93 (2H, m, 2 × CH), 3.83–3.81 (2H, m, 2 × CH), 3.59–3.52 (2H, m, 2 × CH), 2.39−2.37 (2H, m, 2 × CH), 1.85–1.83 (1H, m, CH), 1.82–1.81 (1H, m, CH), 1.16 (3H, d, *J* 6.0 Hz, CH_3), 1.07−1.03 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.6 (C=O), 173.3 (C=O), 136.1 (C), 127.0 (C), 122.8 (CH), 122.3 (CH), 119.7 (CH), 118.3 (CH), 111.5 (CH), 107.7 (C), 68.6 (CH), 45.7 (CH), 50.3 (CH_2), 43.7 (CH), 42.5 (CH_2), 30.7 (CH_2), 28.4 (CH), 27.6 (CH_2), 19.5 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 327.1703, $C_{19}H_{22}N_2O_3$ requires MH$^+$, 327.1703; LRMS *m/z* (ES) 327 (100%).

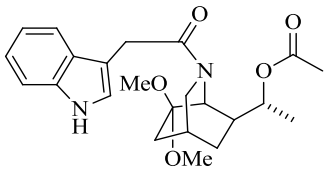
(±)-1-[(1*SR*,4*SR*,7*SR*)-7-[(1*RS*)-1-Hydroxyethyl]-6,6-dimethoxy-2-azabicyclo [2.2.2]octan-2-yl]-2-(1H-indol-3-yl)ethanone 239



p-Toluenesulfonic acid (7.5 mg, 0.04 mmol) was added to a mixture of crude **237** (100 mg, 0.31 mmol), trimethylorthoformate (1.21 mL, 11.0 mmol) and MeOH (1.2 mL) at room temperature. After 7 h, saturated aqueous solution of $NaHCO_3$ (1.5 mL)

was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9.7:0.3), gave amide **239** (98 mg, 0.26 mmol, 85%) as a foam; R_f 0.35 [CH_2Cl_2–MeOH (9.5:0.5)]; IR ν_{max}(film)/cm^{-1} 3319 (OH), 2970 (C–H), 1623 (C=O), 1460 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (1H, br. s, NH), 7.61 (1H, d, *J* 8.0 Hz, ArH), 7.38 (1H, d, *J* 8.0 Hz, ArH), 7.23−7.21 (1H, m, ArH), 7.20−7.18 (1H, m, ArH), 7.16−7.15 (1H, m, ArH), 4.78 (1H, d, *J* 1.0 Hz, CH), 3.81−3.80 (2H, m, 2 × CH), 3.50 (1H, dt, *J* 10.0, 2.0 Hz, CH), 3.36 (1H, dd, *J* 10.0, 3.0 Hz, CH), 3.23 (3H, s, CH_3), 3.14 (3H, s, CH_3), 2.09−2.05 (1H, m, CH), 1.96–1.88 (1H, m, C*H*H), 1.76–1.73 (2H, m, 2 × CH), 1.72−1.96 (2H, m, 2 × CH), 1.15 (3H, d, *J* 6.0 Hz, CH_3), 0.84−0.79 (1H, m, C*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.7 (C=O), 136.1 (C), 127.2 (C), 122.7 (CH), 122.2 (CH), 119.6 (CH), 118.5 (CH), 111.3 (CH), 108.6 (C), 101.4 (C), 69.6 (CH), 49.2 (CH_2), 48.6 (CH_3), 48.1 (CH_3), 47.1 (CH), 40.9 (CH), 37.2 (CH_2), 30.4 (CH_2), 28.7 (CH_2), 27.6 (CH), 19.6 (CH_3); HRMS *m/z* (ES) Found: MH^+, 373.2122, $C_{21}H_{28}N_2O_4$ requires MH^+, 373.2122; LRMS *m/z* (ES) 373 (100%).

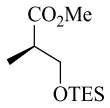
(±)-(1*RS*)-1-[(1*SR*,4*SR*,6*SR*)-2-[2-(1H-Indol-3-yl)acetyl]-7,7-dimethoxy-2-azabicyclo[2.2.2]octan-6-yl]ethyl acetate 177[116]



To a solution of alcohol **239** (100 mg, 0.28 mmol) in dichloromethane (6 mL) and acetyl chloride (20 µL, 0.3 mmol) was added pyridine (24 µL, 0.3 mmol) at room temperature. After 30 min, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9.75:0.25), gave ester **177** (98 mg, 0.24 mmol, 87%) as a foam; R_f 0.26 CH_2Cl_2–MeOH (9.75:0.25)]; IR ν_{max}(film)/cm^{-1} 3280 (OH), 2940 (C–H), 1730 (C=O), 1640 (C=O), 1450 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (1H, br. s, NH), 7.57 (1H, d, *J* 7.5 Hz, ArH), 7.36 (1H, dt, *J* 8.0, 1.0 Hz, ArH), 7.23−7.22 (1H, m, ArH), 7.19 (1H, ddd, *J* 8.0, 7.0, 1.0 Hz, ArH), 7.13 (1H, ddd, *J* 8.0, 7.5, 1.0 Hz, ArH), 4.91 (1H, d, *J* 1.5 Hz, CH), 4.52

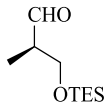
(1H, dq, *J* 10.5, 6.0 Hz, CH), 3.77−3.76 (1H, m, CH), 3.75−3.74 (1H, m, CH), 3.39 (1H, dt, *J* 10.5, 2.5 Hz, C*H*H), 3.29 (1H, dt, *J* 10.0, 2.5 Hz, CH*H*), 3.26 (3H, s, CH_3), 3.20 (3H, s, CH_3), 2.29−2.20 (1H, m, C*H*H), 2.13 (3H, s, CH_3), 2.05−2.02 (1H, m, CH), 1.78 (1H, dt, *J* 14.0, 2.0 Hz, CH), 1.72−1.96 (1H, m, C*H*H), 1.66 (1H, dt, *J* 13.5, 3.0 Hz, CH*H*), 1.22 (3H, d, *J* 6.0 Hz, CH_3), 0.92 (1H, ddt, 13.0, 5.5, 2.5 Hz, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3 (C=O), 171.1 (C=O), 136.1 (C), 127.4 (C), 122.9 (CH), 121.9 (CH), 119.3 (CH), 118.4 (CH), 111.2 (CH), 108.8 (C), 101.7 (C), 71.4 (CH), 49.0 (CH_3), 48.9 (CH_2), 48.1 (CH_3), 45.7 (CH), 38.1 (CH), 36.9 (CH_2), 30.6 (CH_2), 28.2 (CH_2), 27.5 (CH), 21.5 (CH_3), 17.8 (CH_3); HRMS *m/z* (ES) Found: MH^+, 415.2227, $C_{23}H_{31}N_2O_5$ requires MH^+, 415.2227; LRMS *m/z* (ES) 415 (100%). Data corresponds with literature.[116]

(*R*)-Methyl 2-methyl-3-((triethylsilyl)oxy)propanoate 298



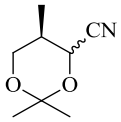
To the alcohol **294** (2.50 g, 21.2 mmol) and imidazole (1.72 g, 31.7 mmol) in CH_2Cl_2 (45 mL), was added TESCl (4.14 g, 31.7 mmol) dropwise at 0 ºC. The mixture was allowed to warm to room temperature. After 16 h, the mixture was diluted with CH_2Cl_2 and was washed with water (3 × 15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.5:0.5), gave the ester **298** (4.74 g, 20.4 mmol, 97%) as an oil; R_f 0.34 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2960 (C−H), 2880 (C−H), 1741 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.81 (1H, dd, *J* 10.0, 7.0 Hz, CH), 3.70 (3H, s, CH_3O), 3.65 (1H, dd, *J* 10.0, 6.0 Hz, CH), 2.72–2.63 (1H, m, CH), 1.16 (3H, d, *J* 7.0 Hz, CH_3), 0.96 (9H, t, *J* 8.0 Hz, 3 × CH_3), 0.60 (6H, q, *J* 8.0 Hz, 3 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.1 (C=O), 65.0 (CH_2), 51.6 (CH_3), 42.6 (CH), 13.6 (CH_3), 6.7 (CH_3), 4.3 (CH_2); HRMS *m/z* (ES) Found: MNa^+, 255.1397, $C_{11}H_{24}O_3SiNa$ requires MNa^+, 255.1392; LRMS *m/z* (ES) 255 (MNa^+, 100%); $[\alpha]_D^{23}$ –41.3 (0.80, $CHCl_3$). No data reported in the literature.[158]

(*R*)-2-Methyl-3-((triethylsilyl)oxy)propanal 299



To ester **298** (4.00 g, 17.3 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added DIBAL−H (19.0 mL, 19.0 mmol, 1 M solution in hexane) dropwise. After 2 h, methanol (20 mL) was added and the solution was allowed to warm to room temperature over 30 min. The mixture was filtered through celite® and the solvent was evaporated. Purification by flash column chromatography on silica gel, eluting with petrol−EtOAc (9.5:0.5), gave the aldehyde **299** (3.18 g, 15.8 mmol, 92%) as an oil; R_f 0.5 [petrol− EtOAc (9.5:0.5)]; IR ν_{max}(film)/cm^{-1} 2952 (C−H), 2935 (C−H), 1734 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.77 (1H, d, *J* 1.6 Hz, CHO), 3.86–3.84 (2H, m, CH_2), 2.61–2.51 (1H, m, CH), 1.11 (3H, d, *J* 7.0 Hz, CH_3), 0.97 (9H, t, *J* 8.0 Hz, 3 × CH_3), 0.61 (6H, q, *J* 8.0 Hz, 3 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.0 (C=O), 63.0 (CH_2), 48.9 (CH), 10.3 (CH_3), 6.7 (CH_3), 4.3 (CH_2); HRMS *m/z* (ES) Found: MNa^+, 225.1298, $C_{10}H_{22}ONaSi$ requires MNa^+, 225.1287; LRMS *m/z* (ES) 225 (MNa^+, 100%); $[\alpha]_D^{23}$ –5.0 (0.80, $CHCl_3$). No data reported in the literature.[158]

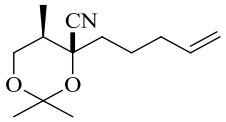
(5*R*)-2,2,5-Trimethyl-1,3-dioxane-4-carbonitrile 293



To the aldehyde **299** (3.98 g, 19.7 mmol) and TMSCN (2.51 g, 25.7 mmol), was added potassium cyanide (25 mg, 0.39 mmol) and 18-crown-6 (100 mg, 0.39 mmol) at 0 °C. The mixture was allowed to warm to room temperature. After 16 h, camphorsulfonic acid (640 mg, 2.76 mmol), acetone (50 mL) and 2,2-dimethoxypropane (29.8 g, 286 mmol) was added. After 16 h, the reaction was quenched with triethylamine (20 mL). The mixture was washed with aqueous Na_2CO_3 (1 M), then was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Purification by column

chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile **293** (1.98 g, 12.7 mmol, 64%) as an oil as a mixture of diastereoisomers (dr 1.1:1); R_f 0.29 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2970 (C−H), 2879 (C−H); ^{1}H NMR (400 MHz, $CDCl_3$) for major isomer δ = 4.36 (1H, d, *J* 10.5 Hz, CH), 3.86 (1H, dd, *J* 12.0, 5.0 Hz, CH), 3.56 (1H, dd, *J* 12.0, 10.0 Hz, CH), 2.26–2.15 (1H, m, CH), 1.59 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.00 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 117.6 (CN), 99.5 (C), 65.8 (CH), 64.8 (CH_2), 33.3 (CH), 25.0 (CH_3), 24.3 (CH_3), 12.4 (CH_3); minor isomer δ = 4.85 (1H, d, *J* 4.5 Hz, CH), 3.94 (1H, dd, *J* 12.0, 4.0 Hz, CH), 3.74 (1H, dd, *J* 12.0, 7.0 Hz, CH), 2.14–2.06 (1H, m, CH), 1.47 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.21 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 117.0 (CN), 100.0 (C), 64.3 (CH), 63.4 (CH_2), 30.8 (CH), 28.7 (CH_3), 19.0 (CH_3), 12.5 (CH_3); HRMS *m/z* (ES) Found: MH^+, 156.1016 $C_8H_{14}NO_2$ requires MH^+, 156.1019; LRMS *m/z* (ES) 156 (MH^+, 100%).

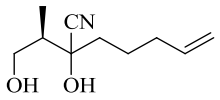
(4*S*,5*R*)-2,2,5-Trimethyl-4-(pent-4-en-1-yl)-1,3-dioxane-4-carbonitrile 300



To diisopropylamine (0.5 mL, 3.5 mmol) in THF (3 mL) at –78 °C was added ^{n}BuLi (1.4 mL, 3.5 mmol, 2.5 M solution in hexane). The mixture was stirred for 20 min, and then nitrile **293** (500 mg, 3.20 mmol) in THF (2 mL) was added dropwise. After 30 min, 4-bromo-1-butene (0.76 mL, 6.4 mmol) was added. The mixture was stirred at –78 °C for 2 h. The mixture was stirred for 2 h at –20 °C, then saturated aqueous ammonium chloride was added and the mixture was allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile **300** (466 mg, 2.10 mmol, 65%) as an oil; R_f 0.45 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2999 (C−H), 2972 (C−H), 2875 (C−H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.09–4.99 (2H, m, C*H*$_2$=CH), 3.83 (1H, t, *J* 12.0 Hz, CH), 3.69 (1H, dd, *J* 12.0, 5.0 Hz, CH), 2.15–2.09 (2H, m, 2 × CH), 2.00–1.87 (2H, m, 2 × CH), 1.78–1.75 (1H, m, CH), 1.69 (3H, s, CH_3), 1.68–

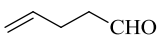
1.62 (2H, m, 2 × CH), 1.40 (3H, s, CH_3), 1.00 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.0 (CH), 120.0 (CN), 115.0 (CH_2), 100.5 (C), 75.0 (C), 63.1 (CH_2), 38.9 (CH_2), 35.9 (CH), 33.3 (CH_2), 30.5 (CH_3), 22.3 (CH_2), 21.0 (CH_3), 12.0 (CH_3); HRMS *m/z* (ES) Found: MH^+, 224.1643, $C_{13}H_{22}NO_2$ requires MH^+, 224.1651; LRMS *m/z* (ES) 224 (MH^+ for 100%).

2-Hydroxy-2-((2*R*)-1-hydroxypropan-2-yl)hept-6-enenitrile 301



To a solution of acetal **300** (50 mg, 0.22 mmol) in hexane (1 mL) was added aqueous HCl (0.7 µL, 37%) at room temperature. After 4 h, water (3 mL) was added and the mixture was extracted with Et_2O (3 × 3 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (7:3), gave the diol **301** (20 mg, 0.11 mmol, 50%) as an oil as a single diastereoisomer; R_f 0.37 [petrol–EtOAc (7:3)]; IR ν_{max}(film)/cm^{-1} 3300 (OH), 2875 (C−H); ^1H NMR (400 MHz, $CDCl_3$) δ = 5.82 (1H, ddt, *J* 17.0, 10.5, 6.5 Hz, C*H*=CH_2), 5.68–5.59 (1H, br. s, OH), 5.09–4.99 (2H, m, CH_2=CH), 4.01 (1H, t, *J* 10.5 Hz, CH), 3.90 (1H, dd, *J* 10.5, 4.0 Hz, CH), 2.17–2.10 (3H, m, 2 × CH and OH), 1.89–1.80 (1H, m, CH), 1.76–1.69 (3H, m, 3 × CH), 1.23–1.09 (1H, m, CH), 0.95 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.0 (CH), 120.4 (CN), 115.3 (CH_2), 77.2 (C), 67.1 (CH_2), 41.2 (CH), 38.2 (CH_2), 33.4 (CH_2), 22.2 (CH_2), 12.2 (CH_3). HRMS and LRMS could not be obtained with ES.

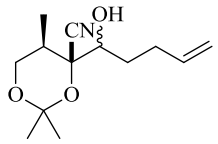
4-Pentenal 304



Allyl vinyl ether (2.0 g, 23.8 mmol) was heated to 150 °C at 200 W in a sealed tube for 7 h. The mixture was allowed to cool to room temperature to afford the desired aldehyde **304** (2.0 g, 100%) as an oil, which was used without further purification; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.79 (1H, t, *J* 1.5 Hz, CHO), 5.85 (1H, ddt, *J* 16.5,

10.5, 6.5 Hz, C*H*=CH_2), 5.09–5.02 (2H, m, CH_2=CH), 2.58–2.54 (2H, m, CH_2CHO), 2.43–2.37 (2H, m, CH_2CH=CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.9 (C=O), 136.4 (CH), 115.7 (CH_2), 42.7 (CH_2), 26.1 (CH_2). Data consistent with that of the literature.[123]

(4*S*,5*R*)-4-(1-Hydroxypent-4-en-1-yl)-2,2,5-trimethyl-1,3-dioxane-4-carbonitrile 306a and 306b



To a solution of diisopropylamine (1.0 mL, 7.68 mmol) in THF (8 mL) at −78 °C was added ^{n}BuLi (3.0 mL, 7.68 mmol, 2.5 M solution in hexane), and the mixture was allowed to stir for 20 min. Nitrile **293** (1.00 g, 6.45 mmol) was added and after 30 min, 4-pentenal **304** (1.00 g, 12.8 mmol) in THF (4 mL) was added. After 1 h, the mixture was warmed to −20 °C. After 1 h, the mixture was allowed to warm to room temperature. After 30 min, the reaction was quenched with H_2O (4 mL) and was extracted with Et_2O (3 × 20 mL). The organic layers were combined and were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the alcohol **306** (1.26 g, 4.83 mmol, 75%) as a partially separable mixture of two diastereoisomers (ratio 1:1.1) as an oil;

Data for **306a** R_f 0.22 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 3050 (OH), 2926 (C–H), 1643 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (1H, ddt, *J* 17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.13–5.03 (2H, m, CH_2=CH), 3.84–3.73 (2H, m, 2 × CH), 3.70 (1H, dd, *J* 12.0, 5.0 Hz, C*H*OH), 2.50–2.33 (2H, m, 2 × CH), 2.22–2.17 (2H, m, CH and OH), 1.87–1.77 (1H, m, CH), 1.71 (3H, s, CH_3), 1.63–1.57 (1H, m, CH), 1.42 (3H, s, CH_3), 1.07 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.6 (CH), 119.1 (C), 115.5 (CH_2), 100.8 (C), 78.3 (C), 75.6 (CH), 63.1 (CH_2), 31.8 (CH_3), 30.2 (CH), 30.1 (CH_2), 30.0 (CH_2), 21.1 (CH_3), 12.7 (CH_3); HRMS *m/z* (ES) Found:

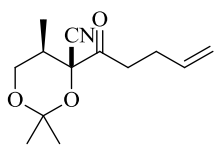
MNa^+, 262.1412, $C_{13}H_{21}NO_3Na^+$ requires MNa^+, 262.1414; LRMS *m/z* (ES) 262 (MNa^+ for 100%).

Data for **306b** R_f 0.18 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 3050 (OH), 2926 (C–H), 1643 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.87 (1H, ddt, *J* 17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.14–5.03 (2H, m, C*H*$_2$=CH), 3.84 (1H, t, *J* 12.0 Hz, CH), 3.75 (1H, dd, *J* 12.0, 5.0 Hz, CH), 3.65 (1H, td, *J* 11.0, 2.0 Hz, C*H*OH), 2.55–2.48 (1H, m, CH), 2.43–2.34 (1H, m, CH), 2.26–2.16 (1H, m, CH), 1.98–1.89 (1H, m, CH), 1.76–1.73 (2H, m, CH and OH), 1.71 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.02 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.6 (CH), 119.0 (C), 115.5 (CH_2), 100.8 (C), 77.9 (C), 72.3 (CH), 62.8 (CH_2), 31.2 (CH_2), 30.8 (CH_3), 30.2 (CH), 30.1 (CH_2), 21.3 (CH_3), 11.7 (CH_3); HRMS *m/z* (ES) Found: MNa^+, 262.1412, $C_{13}H_{21}NO_3Na^+$ requires MNa^+, 262.1414; LRMS *m/z* (ES) X (MNa^+ for 100%).

Formation of nitrile 306b by reduction of ketone 309

To a solution of ketone **309** (500 mg, 2.10 mmol) in MeOH (9 mL) at −78 ºC was added $NaBH_4$ (95.7 mg, 2.53 mmol) in MeOH (2 mL) dropwise. After 2 h, the reaction quenched with water (5 mL). The mixture was extracted with Et_2O (3 × 5 mL), the organic layers were combined and were washed with brine (5 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the alcohol as a mixture of two diastereoisomers (ratio 11:1 by ^{1}H NMR spectroscopy) as an oil. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave alcohol **306b** (0.35 g, 1.47 mmol, 70%) as an oil 'Data as above'.

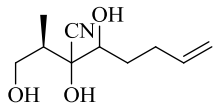
(2*R*)-Methyl-5,5-dimethyl-4-(pentenyl-1-one)-1,3-dioxane-4-carbonitrile 309



To a solution of freshly distilled oxalyl chloride (0.4 mL, 4.6 mmol) in CH_2Cl_2 (20 mL) at −60 ºC was added DMSO (0.65 mL, 9.2 mmol). After 5 min, the alcohol **306**

(1.0 g, 4.2 mmol) was added dropwise over 10 min, followed, after 30 min, by addition of Et_3N (2.9 mL, 21 mmol). The reaction mixture was stirred for 10 min then was allowed to warm to room temperature. Water (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ketone **309** (0.84 g, 3.55 mmol, 85%) as an oil; R_f 0.28 [petrol–EtOAc (9.5:0.5)]; IR ν_{max}(film)/cm^{-1} 2926 (C−H), 2859 (C−H), 1674 (C=O), 1643 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.81 (1H, ddt, *J* 17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.12–5.01 (2H, m, C*H*$_2$=CH), 5.08 (1H, t, *J* 12.0 Hz, CH), 5.05 (1H, dd, *J* 12.0, 5.0 Hz, CH), 2.83 (2H, t, *J* 7.0 Hz, CH_2), 2.40–2.34 (2H, m, CH_2), 2.21–2.11 (1H, m, CH), 1.73 (3H, s, CH_3), 1.48 (3H, s, CH_3), 0.98 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.0 (C), 136.3 (CH), 116.9 (C), 115.9 (CH_2), 101.1 (C), 80.2 (C), 62.5 (CH_2), 35.4 (CH_2), 32.2 (CH_3), 30.2 (CH), 27.2 (CH_2), 21.1 (CH_3), 11.5 (CH_3); HRMS *m/z* (ES) Found: MH^+, 260.1260, $C_{13}H_{19}NO_3Na^+$ requires MNa^+, 260.1263; LRMS *m/z* (ES) 260 (MNa^+ for 100%).

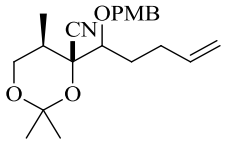
2,3-Dihydroxy-2-((2*R*)-1-hydroxypropan-2-yl)hept-6-enenitrile 311



To a solution of acetal **306** (50 mg, 0.20 mmol) in hexane (1 mL) was added aqueous HCl (0.7 µL, 37%) at room temperature. After 4 h, water (3 mL) was added and the mixture was extracted with Et_2O (3 × 3 mL). The organic layers were combined, dried (MgSO4) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:6), gave the triol **311** (16 mg, 0.08 mmol, 40%) as an oil as a single diastereoisomer; R_f 0.25 [petrol–EtOAc (4:6)]; IR ν_{max}(film)/cm^{-1} 3300 (OH), 2875 (C−H);); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.83 (1H, ddt, *J* 17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.14–5.04 (2H, m, C*H*$_2$=CH), 4.47 (1H, t, *J* 9.0 Hz, C*H*OH), 3.86 (1H, dd, *J* 10.0, 9 .0 Hz, CH), 3.77–3.71 (1H, m, CH), 3.65 (1H, s, OH), 2.90–2.81 (1H, m, CH), 2.46–2.36 (1H, m, CH), 2.29–2.21 (1H, m, CH), 2.06–1.99 (1H, m, CH), 1.61 (1H, s, OH), 1.53–1.44 (1H, m, CH), 1.17 (3H, d,

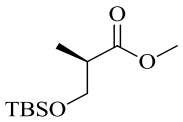
J 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, two quaternary carbons could not be observed) δ = 137.1 (CH), 116.2 (CH_2), 71.9 (CH), 71.3 (CH_2), 39.4 (CH), 31.4 (CH_2), 30.0 (CH_2), 10.4 (CH_3); HRMS *m/z* (ES) Found: MH^+, 200.1279, $C_{10}H_{17}NO_3$ requires MH^+, 200.1281; LRMS *m/z* (ES) 200 (MH^+ for 100%).

(5*R*)-4-(1-(4-Methoxyphenoxy)pent-4-en-1-yl)-2,2,5-trimethyl-1,3-dioxane-4-carbonitrile 319



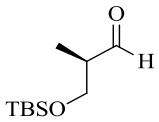
To a solution of NaH (300 mg, 12.6 mmol) in DMF (8 mL) at 0 °C was added, dropwise, a premixed solution of PMBCl (654 mg, 4.18 mmol) and alcohol **306** (500 mg, 2.10 mmol) in THF (2 mL). The solution was left to warm to room temperature overnight. The mixture was then cooled to 0 °C and was quenched with saturated aqueous NH_4Cl (3 mL). The products were extracted with Et_2O (3 × 15 mL), the organic layers were combined and washed with H_2O (3 × 10 mL) and brine (20 mL). The organic solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by using column chromatography on silica gel, eluting with petrol–EtOAc (9:1), afforded nitrile **319** (600 mg, 1.68 mmol, 80%) as an oil; R_f 0.28 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2928 (C–H), 2855 (C–H); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.31 (2H, m, ArH), 6.91–6.89 (2H, m, ArH), 5.85 (1H, ddt, *J* 17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.12–5.00 (2H, m, C*H*$_2$=CH), 4.76 (1H, d, *J* 10.5 Hz, CH), 4.60 (1H, d, *J* 10.5 Hz, CH), 3.82–3.80 (4H, m, CH and CH_3), 3.71 (1H, dd, *J* 12.0, 5.0 Hz, CH), 3.68 (1H, dd, *J* 12.0, 5.0 Hz, CH), 2.38–2.29 (2H, m, 2 × CH), 2.21–2.12 (1H, m, CH), 1.87–1.82 (2H, m, 2 × CH), 1.71 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.02 (3H, d, *J* 7.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.3 (C), 137.9 (CH), 130.0 (C), 129.7 (CH), 120.2 (CN), 115.4 (CH_2), 113.8 (CH), 100.6 (C), 81.4 (CH), 77.5 (C), 73.6 (CH_2), 71.5 (CH_2), 63.1 (CH_2), 55.3 (CH_3), 31.1 (CH_3), 30.3 (CH), 29.0 (CH_2), 21.3 (CH_3), 12.3 (CH_3); HRMS *m/z* (ES) Found: MNa^+, 382.1979, $C_{21}H_{29}NO_4Na^+$ requires MNa^+, 382.1989; LRMS *m/z* (ES) 382 (MNa^+, 100%).

(2*R*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate 330[181]



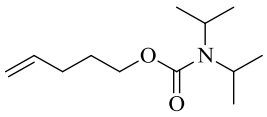
To a solution of imidazole (860 mg, 12.6 mmol) in CH_2Cl_2 (15 mL) was added alcohol **294** (1.0 g, 8.4 mmol). After 10 min, TBSCl (1.69 g, 11 mmol) was added dropwise and the mixture was left to warm for 18 h. The reaction was quenched with H_2O (10 mL), extracted with CH_2Cl_2 (3 × 5 mL), organic layers combined and washed with brine (5 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9.5: 0.5), to give the ester **330** (1.97 g, 8.40 mmol, 100%) as an oil; R_f 0.35 [petrol–EtOAc (9.5:0.5)]; IR ν_{max}(film)/cm^{-1} 2955 (C–H), 2934 (C–H), 1745 (C=O), 1463 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.79 (1H, dd, *J* 10.0, 7.0 Hz, CH), 3.69 (3H, s, CH_3), 3.66 (1H, dd, *J* 10.0, 6.0 Hz, CH), 2.66–2.57 (1H, m, CH), 1.15 (3H, d, *J* 7.0 Hz, CH_3), 0.89 (9H, s, 3 × CH_3), 0.06 (3H, s, CH_3), 0.05 (3H, s, CH_3). Data corresponds with the literature.[181]

(2*R*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylpropanal 331[181]



To a solution of ester **330** (500 mg, 2.15 mmol) in CH_2Cl_2 (10 mL) at –78 ºC was added DIBAL-H (2.26 mL, 2.26 mmol, 1.0 M solution in hexane) dropwise. After 2 h, the reaction was quenched with MeOH (5 mL) and was filtered through Celite®. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.7:0.3), gave the aldehyde **331** (340 mg, 1.72 mmol, 80%) as an oil; R_f 0.42 [petrol–EtOAc (9.7:0.3)]; IR ν_{max}(film)/cm^{-1} 2955 (C–H), 2907(C–H), 2876 (C–H), 1735 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (1H, d, *J* 1.5 Hz, CHO), 3.88 (1H, dd, *J* 10.0, 5.0 Hz, CH) 3.82 (1H, dd, *J* 10.0, 6.0 Hz, CH), 2.59–2.53 (1H, m, CH), 1.11 (3H, d, *J* 7.0 Hz, CH_3), 0.89 (9H, s, 3 × CH_3), 0.07 (6H, s, 2 × CH_3). Data corresponds with the literature.[181]

***N,N*-Diisopropylcarbamoyl 4-pentene 332**[174]



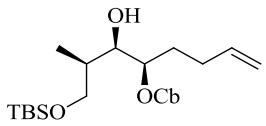
1st method

To a solution of *N*,*N*-diisopropylcarbamoyl chloride (1.90 g, 11.6 mmol) and Et_3N (1.29 g, 12.8 mmol) in CH_2Cl_2 (15 mL) was added 4-pentenol **303** (1.00 g, 11.6 mmol). The reaction mixture was heated under reflux for 24 h, then with H_2O (5 mL) was added. The product was extracted with Et_2O (3 × 5 mL), the organic layers were combined and were washed with brine (5 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.5:0.5), gave the carbamate **332** (2.34 g, 11.0 mmol, 95%) as an oil.

2nd method

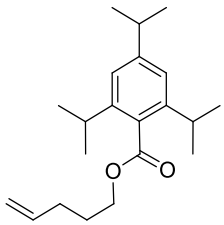
To a solution of *N*,*N*-diisopropylcarbamoyl chloride (230 mg, 1.40 mmol) in PhMe (2 mL) was added 4-pentenol **332** (100 mg, 1.16 mmol) and Et_3N (0.15 g, 1.50 mmol). The reaction mixture was placed in a microwave at 200 W for 1 h at 150 °C. The mixture was cooled to room temperature and was filtered through a silica plug. The solvent was removed under reduced pressure to afford the carbamate **332** (156 mg, 0.73 mmol, 63%) as an oil; R_f 0.68 [petrol–EtOAc (9:1)]; IR ν_{max}(film) /cm^{-1} 2970 (C–H), 2940 (C–H), 1687 (C=O), 1434 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.09–4.98 (2H, m, CH_2=CH), 4.11 (2H, t, *J* 6.5 Hz, CH_2O), 3.83–3.62 (2H, m, 2 × CHN), 2.20–2.14 (2H, m, 2 × CH), 1.80–1.73 (2H, m, 2 × CH), 1.22 (12H, d, *J* 7.0 Hz, 4 × CH_3). Data corresponds with the literature.[174]

(2*R*,3*R*,4*R*)-1-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-2-methyloct-7-en-4-yl diisopropylcarbamate 334



To a solution of (+)-sparteine (160 mg, 0.70 mmol) and *sec*-BuLi (0.60 mL, 0.84 mmol, 1.4 M solution in hexanes) in Et_2O (5 mL) at –78 °C was added the carbamate **332** (100 mg, 0.47 mmol). After 6 h, the aldehyde **331** (110 mg, 0.56 mmol) was added and the mixture allowed to warm to room temperature over 18 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL), and was extracted with Et_2O (3 × 5 mL). The organic layers were combined and were washed with brine (5 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the alcohol **334** (30 mg, 0.07 mmol, 13%) as an oil; R_f 0.16 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2970 (C–H), 2930 (C–H), 1685 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.90–5.78 (1H, m, C*H*=CH_2), 5.09–4.98 (2H, m, C*H*$_2$=CH), 4.18–4.08 (1H, m, CH), 3.77 (1H, dd, *J* 10.0, 4.0 Hz, CH), 3.69–3.62 (1H, m, CH), 3.60–3.54 (1H, dd, *J* 10.0, 8.0 Hz, CH), 2.21–2.11 (1H, m, CH), 2.00–1.93 (1H, m, CH), 1.80–1.74 (1H, m, CH), 1.63–1.60 (1H, m, CH), 1.45–1.37 (1H, m, CH), 1.29–0.92 (3H, m, 2 × CH and OH), 1.22 (3H, d, *J* 7.0 Hz, CH_3), 0.92 (12H, d, *J* 6.5 Hz, 4 × CH_3), 0.85 (9H, s, 3 × CH_3), 0.12 (3H, s, CH_3), 0.09 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, one quaternary carbon (C=O) could not be observed) δ = 138.4 (CH), 114.7 (CH_2), 77.7 (CH), 75.2 (CH), 74.2 (CH), 67.3 (CH_2), 64.0 (CH_2), 37.0 (CH), 35.9 (CH_3), 29.9 (CH_2), 25.8 (CH_3), 18.1 (C), 14.3 (CH_3), –5.7 (CH_3); HRMS *m/z* (ES) Found: MH^+, 416.3191, $C_{22}H_{46}NO_4Si$ requires MH^+, 416.3191; LRMS *m/z* (ES) 416 (MH^+, 100%).

Pent-4-en-1-yl 2,4,6-triisopropylbenzoate 337

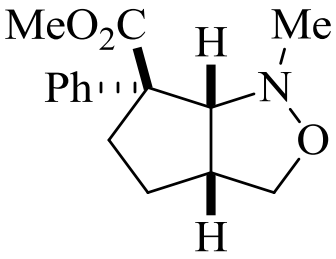


To a mixture of 4-pentenol **303** (2.0 g, 23 mmol), triphenylphosphine (6.7 g, 25 mmol) and 2,4,6-triisopropylbenzoic acid (6.6 g, 27 mmol) in THF (35 mL), was added DIAD (5.2 g, 25 mmol) dropwise at 0 ^{o}C. After 18 h at room temperature, the solvent was removed and the residue was dissolved in pentane. After 5 min, the suspension was filtered. Purification by using column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the alkene **337** (6.9 g, 22 mmol, 95%) as an oil; R_f 0.33 [petrol–EtOAc (9.5:0.5)]; IR ν_{max}(film)/cm^{-1} 2960 (C–H), 2930 (C–H), 1720 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (2H, s, ArH), 5.84 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz, C*H*=CH_2), 5.10–5.01 (2H, m, CH_2=CH), 4.33 (2H, t, *J* 6.5 Hz, CH_2O), 2.94–2.83 (3H, m, 3 × CH), 2.23–2.18 (2H, m, 2 × CH), 1.89–1.82 (2H, m, 2 × CH), 1.27 (12H, d, *J* 7.0 Hz, 4 × CH_3), 1.26 (6H, d, *J* 7.0 Hz, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, two quaternary carbon could not be observed) δ = 150.0 (C=O), 144.7 (C), 137.4 (CH), 120.9 (CH), 115.5 (CH_2), 64.3 (CH_2), 34.4 (CH), 31.5 (CH), 30.2 (CH_2), 27.8 (CH_2), 24.2 (CH_3), 24.0 (CH_3); HRMS *m/z* (ES) Found: M^+, 316.2404, $C_{21}H_{32}O_2$ requires M^+, 316.2397; LRMS *m/z* (ES) 316 (M^+, 100%).

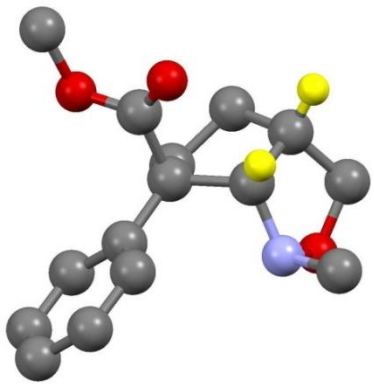
Chapter 7 Appendices

Appendix 1

X-ray crystal structure determination data of **112a**



Xa



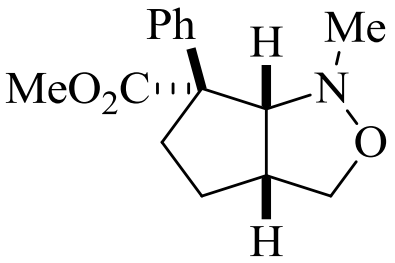
Crystal data and structure refinement for **112a**

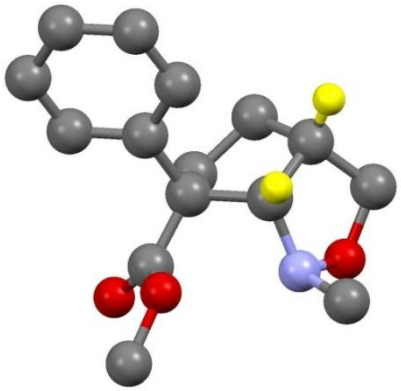
Empirical formula	$C_{15}H_{19}NO_3$	
Formula weight	261.31	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pna21	
Unit cell dimensions	a = 14.3226(3) Å	a= 90°.
	b = 14.6136(3) Å	b= 90°.
	c = 6.2026(2) Å	g = 90°.
Volume	1298.23(6) Å3	
Z	4	
Density (calculated)	1.337 Mg/m3	
Absorption coefficient	0.754 mm-1	
F(000)	560	
Crystal size	0.340 x 0.340 x 0.280 mm3	
Theta range for data collection	4.322 to 65.991°.	
Index ranges	-16<=h<=15, -17<=k<=17, -6<=l<=7	
Reflections collected	17202	
Independent reflections	2091 [R(int) = 0.0273]	

Completeness to theta = 66.000°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.87 and 0.65
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2091 / 1 / 174
Goodness-of-fit on F2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0268, wR2 = 0.0671
R indices (all data)	R1 = 0.0279, wR2 = 0.0680
Absolute structure parameter	0.07(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.134 and -0.174 e.Å-3

Appendix 2

X-ray crystal structure determination data of **112b**





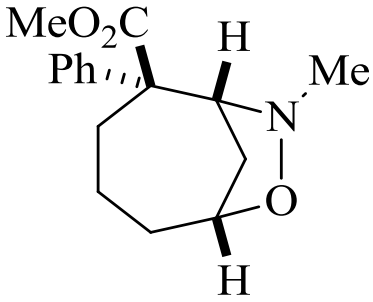
Crystal data and structure refinement for **112b**

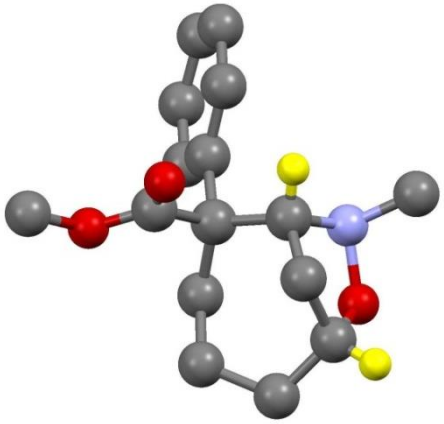
Empirical formula	$C_{15}H_{19}NO_3$
Formula weight	261.31
Temperature	97(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pna21

Unit cell dimensions	a = 13.3032(15) Å	a= 90°.
	b = 15.4042(17) Å	b= 90°.
	c = 6.8015(7) Å	g = 90°.
Volume	1393.8(3) Å3	
Z	4	
Density (calculated)	1.245 Mg/m3	
Absorption coefficient	0.087 mm-1	
F(000)	560	
Crystal size	0.430 x 0.380 x 0.340 mm3	
Theta range for data collection	2.023 to 27.563°.	
Index ranges	-17<=h<=16, -18<=k<=20, -8<=l<=8	
Reflections collected	15491	
Independent reflections	3063 [R(int) = 0.0547]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.87 and 0.77	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	3063 / 1 / 174	
Goodness-of-fit on F2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0419, wR2 = 0.0892	
R indices (all data)	R1 = 0.0551, wR2 = 0.0972	
Absolute structure parameter	?	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.162 and -0.220 e.Å-3	

Appendix 3

X-ray crystal structure determination data of **117a**





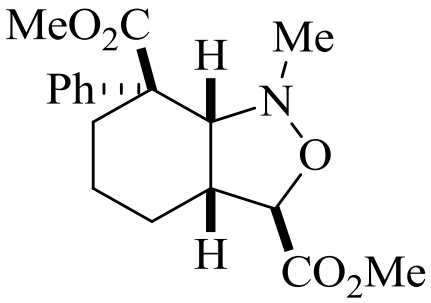
Crystal data and structure refinement for **117a**

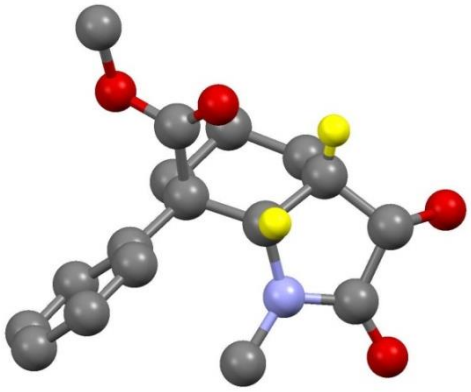
Empirical formula	$C_{16}H_{21}NO_3$	
Formula weight	275.34	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 23.9178(6) Å	a= 90°.
	b = 7.9721(2) Å	b= 112.4190(10)°.
	c = 16.2844(4) Å	g = 90°.
Volume	2870.35(13) Å3	
Z	8	
Density (calculated)	1.274 Mg/m3	
Absorption coefficient	0.707 mm-1	
F(000)	1184	
Crystal size	0.390 x 0.260 x 0.120 mm3	
Theta range for data collection	3.999 to 66.657°.	
Index ranges	-27<=h<=28, -8<=k<=9, -18<=l<=19	
Reflections collected	22494	
Independent reflections	2537 [R(int) = 0.0266]	

Completeness to theta = 66.657°	99.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2537 / 0 / 183
Goodness-of-fit on F2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0353, wR2 = 0.0857
R indices (all data)	R1 = 0.0378, wR2 = 0.0875
Extinction coefficient	n/a
Largest diff. peak and hole	0.252 and -0.233 e.Å-3

Appendix 4

X-ray crystal structure determination data of **120a**





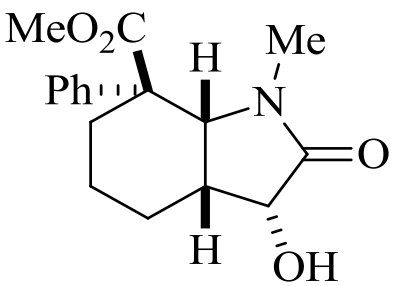
Crystal data and structure refinement for **120a**

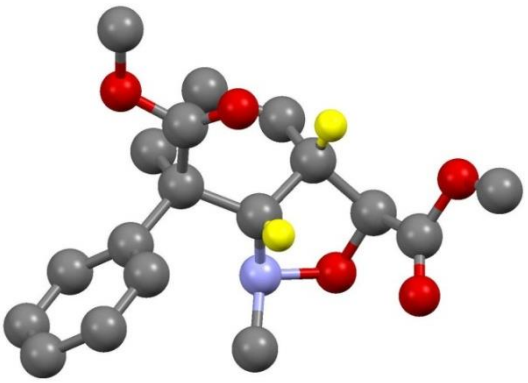
Empirical formula	$C_{18}H_{23}NO_5$	
Formula weight	333.37	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.0628(3) Å	a= 65.4560(10)°.
	b = 10.3241(4) Å	b= 71.9819(10)°.
	c = 11.8540(4) Å	g = 75.4771(11)°.

Volume	844.99(5) Å3
Z	2
Density (calculated)	1.310 Mg/m3
Absorption coefficient	0.787 mm-1
F(000)	356
Crystal size	0.500 x 0.400 x 0.400 mm3
Theta range for data collection	4.216 to 66.492°.
Index ranges	-8<=h<=9, -12<=k<=12, -14<=l<=14
Reflections collected	16743
Independent reflections	2923 [R(int) = 0.0291]
Completeness to theta = 66.500°	98.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.87 and 0.65
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2923 / 0 / 220
Goodness-of-fit on F2	1.964
Final R indices [I>2sigma(I)]	R1 = 0.0359, wR2 = 0.1179
R indices (all data)	R1 = 0.0376, wR2 = 0.1190
Extinction coefficient	n/a
Largest diff. peak and hole	0.289 and -0.246 e.Å-3

Appendix 5

X-ray crystal structure determination data of **123a**



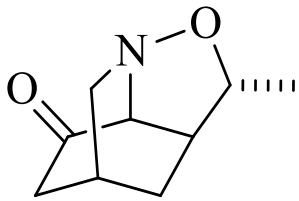


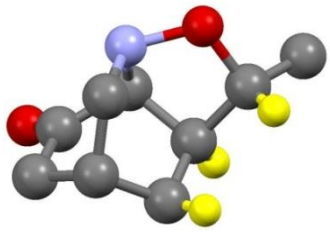
Crystal data and structure refinement **123a**

Empirical formula	$C_{17}H_{21}NO_4$	
Formula weight	303.35	
Temperature	97(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.1998(7) Å	a= 106.900(5)°.
	b = 9.9463(8) Å	b= 98.639(4)°.
	c = 11.1065(10) Å	g = 113.655(4)°.
Volume	756.19(12) Å3	
Z	2	
Density (calculated)	1.332 Mg/m3	
Absorption coefficient	0.095 mm-1	
F(000)	324	
Crystal size	0.320 x 0.210 x 0.180 mm3	
Theta range for data collection	2.012 to 27.642°.	
Index ranges	-10<=h<=9, -12<=k<=12, -14<=l<=14	
Reflections collected	14880	
Independent reflections	3472 [R(int) = 0.0331]	
Completeness to theta = 25.000°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.96	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	3472 / 0 / 202	
Goodness-of-fit on F2	1.104	
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.1040	
R indices (all data)	R1 = 0.0578, wR2 = 0.1258	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.309 and -0.288 e.Å-3	

Appendix 6

X-ray crystal structure determination data of **212**





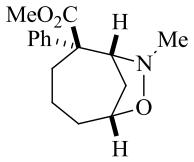
Crystal data and structure refinement for **212**

Empirical formula	$C_7 H_{13} NO2$	
Formula weight	501.61	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 10.8594(4) Å	a= 90°.
	b = 7.3763(3) Å	b= 92.469(3)°.
	c = 15.5152(7) Å	g = 90°.
Volume	1241.65(9) Å3	
Z	2	
Density (calculated)	1.342 Mg/m3	
Absorption coefficient	0.772 mm-1	
F(000)	540	
Crystal size	0.180 x 0.060 x 0.040 mm3	
Theta range for data collection	2.851 to 65.991°.	
Index ranges	-12<=h<=12, -8<=k<=8, -17<=l<=18	
Reflections collected	6309	
Independent reflections	3609 [R(int) = 0.0537]	
Completeness to theta = 65.991°	97.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.93 and 0.84	

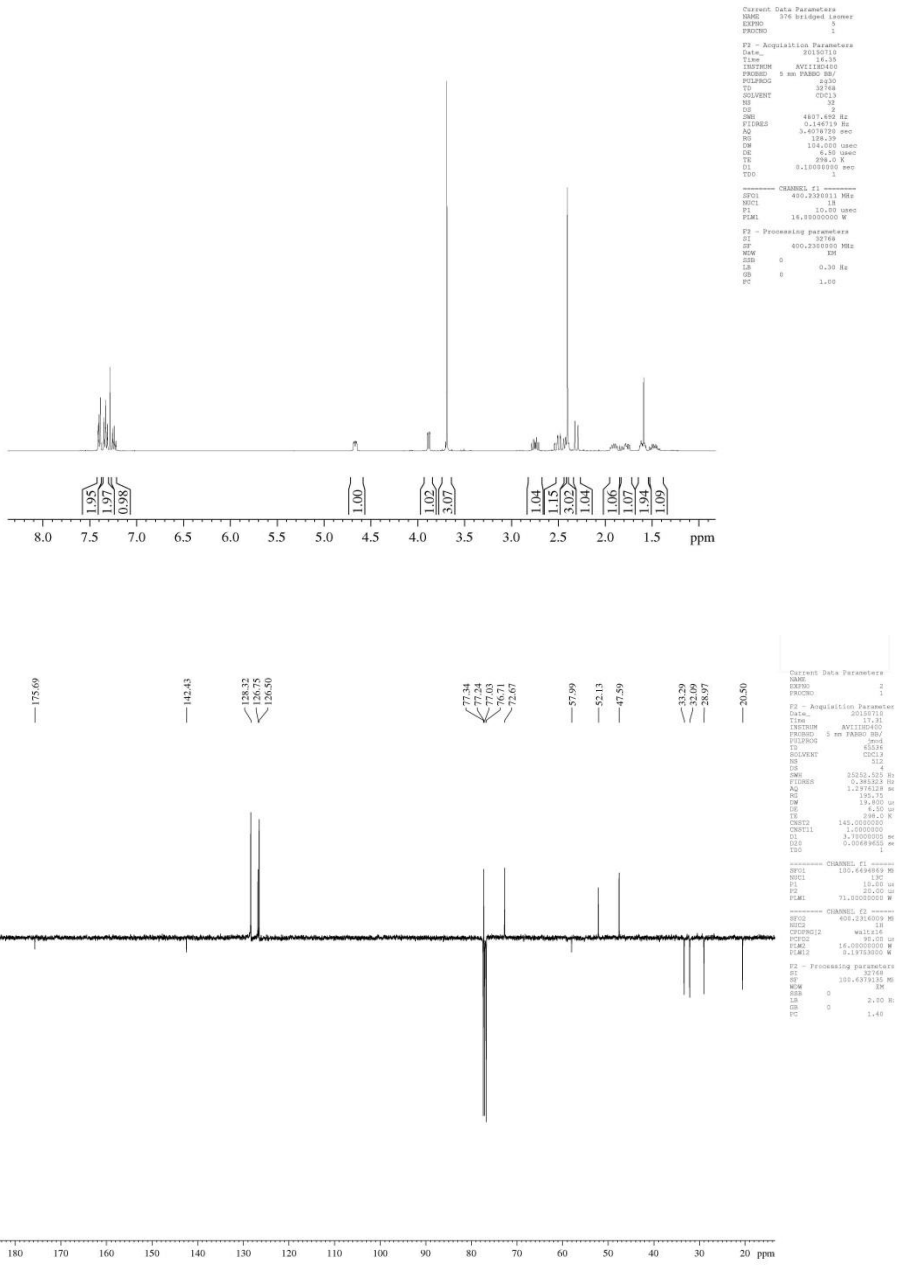
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	3609 / 1 / 329
Goodness-of-fit on F2	1.011
Final R indices [I>2sigma(I)]	R1 = 0.0451, wR2 = 0.0994
R indices (all data)	R1 = 0.0679, wR2 = 0.1112
Absolute structure parameter	?
Extinction coefficient	n/a
Largest diff. peak and hole	0.185 and -0.182 e.Å-3

Appendix 7

^{1}H and ^{13}C NMR spectra bridged cycloadduct **117a** in $CDCl_3$ at 400 MHz and 101 MHz respectively.

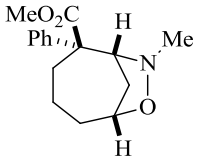


117a

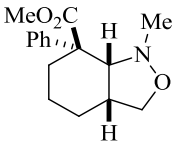


Appendix 8

Cosy and HSQC spectra for the mixture of cycloadducts **117a** and **117b** in $CDCl_3$

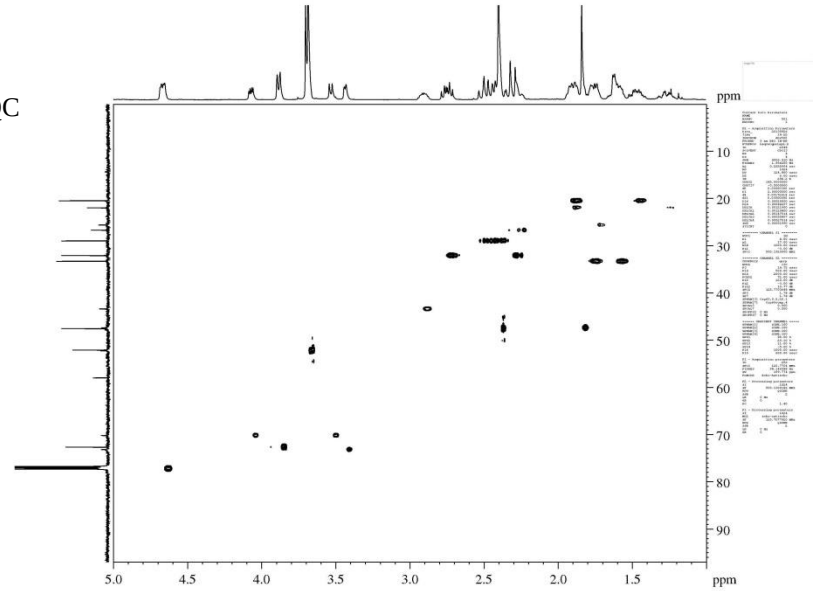


117a

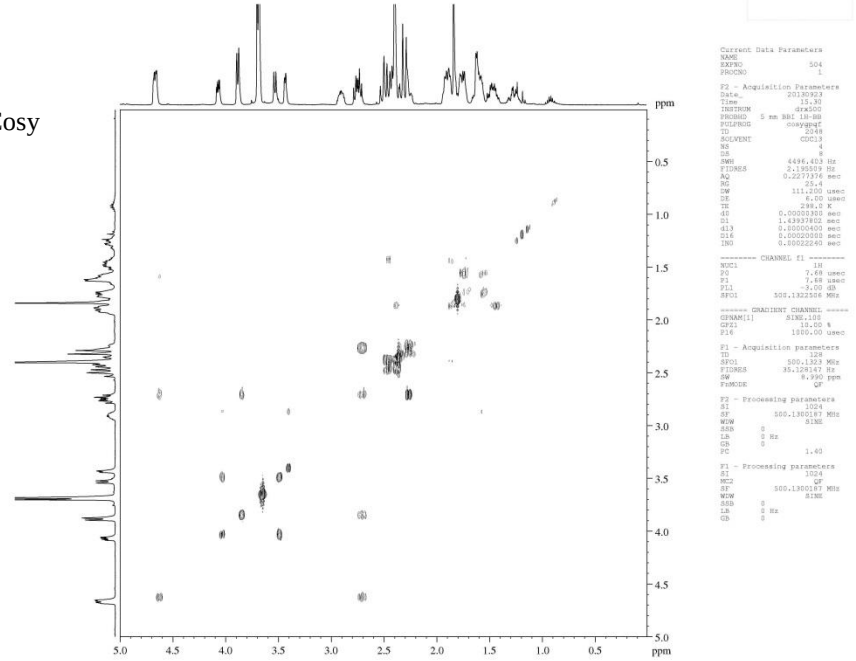


117b

HSQC

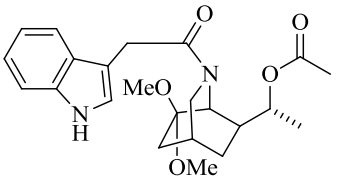


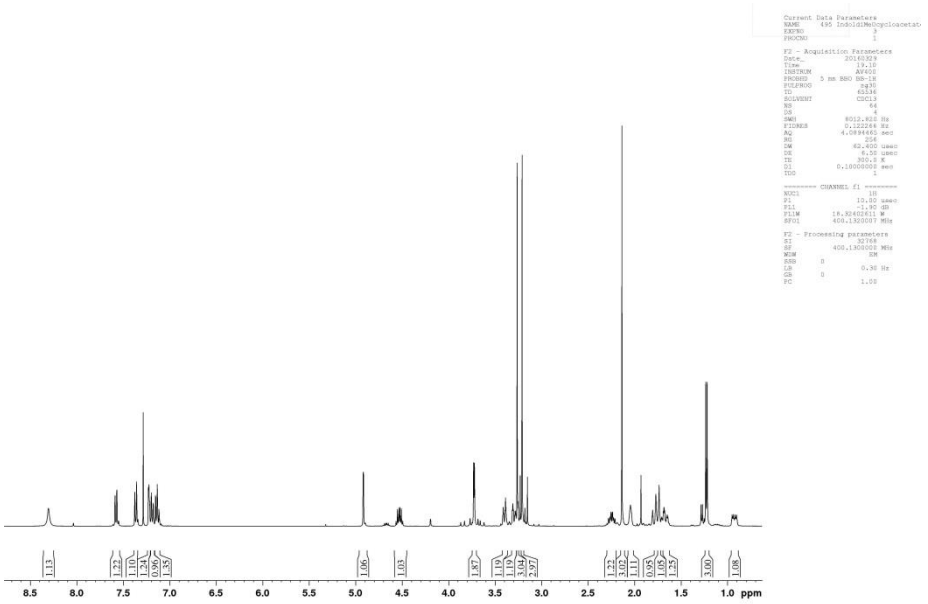
Cosy

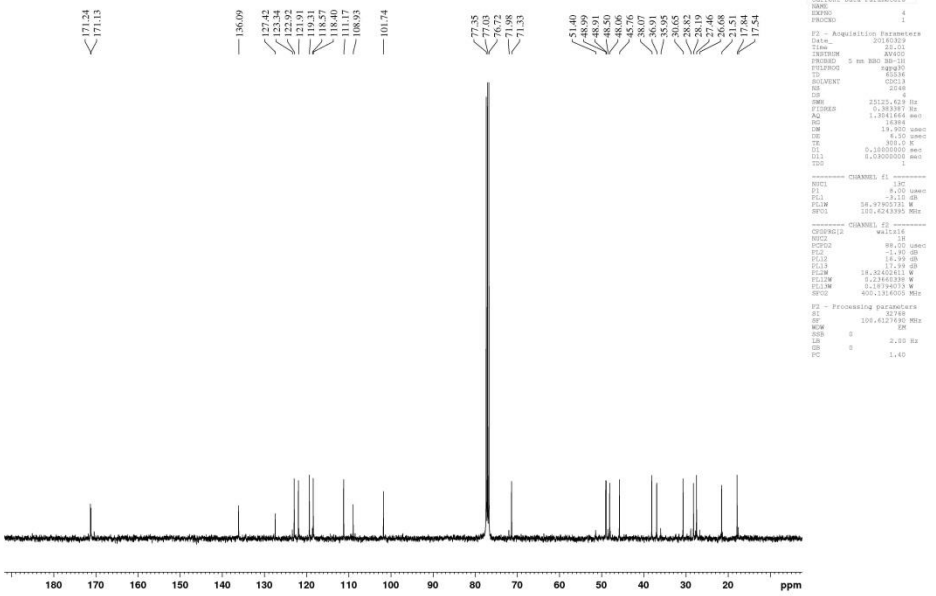


Appendix 9

^{1}H and ^{13}C NMR spectra for compound **177** in $CDCl_3$ at 400 MHz and 101 MHz respectively.







Chapter 6 References

(1) Chauhan, P.; Enders, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 1485.
(2) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
(3) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.
(4) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
(5) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Tetrahedron Lett.* **1986**, *27*, 3693.
(6) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971.
(7) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. W. *Tetrahedron* **1990**, *46*, 7373.
(8) Tartakovskii, V. A. C., I. E.; Smagin, S. S.; Novikov, S. S. *izv. akad. nauk. sssr. chim* **1964**, 549.
(9) Denmark, S. E.; Moon, Y. C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311.
(10) Denmark, S. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1853.
(11) Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579.
(12) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266.
(13) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675.
(14) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668.
(15) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046.
(16) Denmark, S. E. S., M. E.; Thorarensen, A.; Middleton, D. S.; Stolle, A. *Pure Appl. Chem.* **1994**, *66*, 2041.
(17) Denmark, S. E.; Juhl, M. *Helv. Chim. Acta* **2002**, *85*, 3712.
(18) Denmark, S. E.; Gomez, L. *Org. Lett.* **2001**, *3*, 2907.
(19) Denmark, S. E.; Baiazitov, R. Y.; Nguyen, S. T. *Tetrahedron* **2009**, *65*, 6535.
(20) Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68*, 8015.
(21) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
(22) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309.
(23) Delpierre, G. R.; Lamchen, M. *Quarterly Rev., Chem. Soc.* **1965**, *19*, 329.
(24) Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565.
(25) Houk, K. N. *J. Am. Chem. Soc.* **1972**, *94*, 8953.
(26) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717.
(27) Fleming, I. In *Molecular Orbitals and Organic Chemical Reactions*; Wiley Cambridged: 2010, p 253.
(28) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.
(29) Armstrong, P.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4495.
(30) Grigg, R.; Heaney, F.; Markandu, J.; Surendrakumar, S.; Mark, T.-P.; William, W. J. *Tetrahedron* **1991**, *47*, 4007.

(31) Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J. F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1991**, *47*, 8297.
(32) Chakrabarty, M.; Sarkar, S.; Khasnobis, S.; Harigaya, Y.; Sato, N.; Arima, S. *Synth. Comm.* **2002**, *32*, 2295.
(33) Imada, Y.; Naota, T. *Chem. Reco.* **2007**, *7*, 354.
(34) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598.
(35) Bøgevig, A.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *Synlett* **2003**, *2003*, 1915.
(36) Pfeiffer, J. Y.; Beauchemin, A. M. *J. Org. Chem.* **2009**, *74*, 8381.
(37) Chan, T.H.; Chang, Y.F.; Hsu, J.J.; Cheng, W.C. *Eur. J. Org. Chem.* **2010**, *2010*, 5555.
(38) Grashey, R.; Huisgen, R.; Leitermann, H. *Tetrahedron Lett.* **1960**, *1*, 9.
(39) Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4477.
(40) Heaney, F.; Bourke, S. *J. Chem. Sco., Perkin Trans. 1* **1998**, 955.
(41) Coldham, I.; Jana, S.; Watson, L.; Martin, N. G. *Org. Biomol. Chem.* **2009**, *7*, 1674.
(42) Furnival, R. C.; Saruengkhanphasit, R.; Holberry, H. E.; Shewring, J. R.; Guerrand, H. D. S.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2016**, *14*, 10953.
(43) Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, *11*, 1117.
(44) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399.
(45) Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Org. Chem., Chem. Commun.* **1987**, 1325.
(46) Franklin, A. I.; Bensa, D.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 1901.
(47) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, *2007*, 1.
(48) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900.
(49) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598.
(50) Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M.-L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656.
(51) Burrell, A. J.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2008**, *74*, 2290.
(52) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515.
(53) Coldham, I.; Burrell, A. J. M.; Guerrand, H. l. n. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267.
(54) LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759.
(55) Padwa, A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 123.
(56) Alper, K. R. In *The Alkaloids: Chem. Biol.*; Academic Press: 2001; Vol. Volume 56, p 1.
(57) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485.
(58) JM Burrell, A.; Coldham, I. *Curr. Org. Synth.* **2010**, *7*, 312.
(59) Parsons, P. J. *Org. Proc. Res. Dev.* **2004**, *8*, 293.

(60) Berthet, M.; Cheviet, T.; Dujardin, G.; Parrot, I.; Martinez, J. *Chem. Rev.* **2016**, *116*, 15235.
(61) LeBel, N. A.; Whang, J. J. *J. Am. Chem. Soc.* **1959**, *81*, 6334.
(62) Burrell, A. J. M.; Watson, L.; Martin, N. G.; Oram, N.; Coldham, I. *Org. Biomol. Chem.* **2010**, *8*, 4530.
(63) Xie, J.; Xue, Q.; Jin, H.; Li, H.; Cheng, Y.; Zhu, C. *Chem. Sci.* **2013**, *4*, 1281.
(64) Endoma-Arias, M. A. A.; Hudlicky, J. R.; Simionescu, R.; Hudlicky, T. *Adv. Synth. Cata.* **2014**, *356*, 333.
(65) Borsini, E.; Broggini, G.; Contini, A.; Zecchi, G. *Eur. J. Org. Chem.* **2008**, *2008*, 2808.
(66) Vinick, F. J.; Fengler, I. E.; Gschwend, H. W.; Rodebaugh, R. K. *J. Org. Chem.* **1977**, *42*, 2936.
(67) Nakatsuji, H.; Nishikado, H.; Ueno, K.; Tanabe, Y. *Org. Lett.* **2009**, *11*, 4258.
(68) Sprules, T. J.; Lavallee, J.F. *J. Org. Chem.* **1995**, *60*, 5041.
(69) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, *1981*, 165.
(70) Sandoval-Lira, J.; Fuentes, L.; Quintero, L.; Höpfl, H.; Hernández-Pérez, J. M.; Terán, J. L.; Sartillo-Piscil, F. *J. Org. Chem.* **2015**, *80*, 4481.
(71) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Chem. A Eur. J.* **2009**, *15*, 2693.
(72) Jeong, J. H.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 2309.
(73) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(74) Shing, T. K. M.; So, K. H. *Org. Lett.* **2011**, *13*, 2916.
(75) Black, D. S. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, *1975*, 205.
(76) Broggini, G.; La Rosa, C.; Pilati, T.; Terraneo, A.; Zecchi, G. *Tetrahedron* **2001**, *57*, 8323.
(77) Alkayar, Z. T. I.; Adams, H.; Coldham, I. *Synlett* **2016**, *27*, 447.
(78) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98.
(79) Paul, S.; Pattanayak, S.; Sinha, S. *Tetrahedron Lett.* **2011**, *52*, 6166.
(80) Jana, G. K.; Sinha, S. *Tetrahedron Lett.* **2012**, *53*, 1671.
(81) Tang, B.Q.; Wang, W.J.; Huang, X.J.; Li, G.Q.; Wang, L.; Jiang, R.W.; Yang, T.T.; Shi, L.; Zhang, X.-Q.; Ye, W.-C. *J. Nat. Prod.* **2014**, *77*, 1839.
(82) Nge, C.E.; Sim, K.S.; Lim, S.H.; Thomas, N. F.; Low, Y.Y.; Kam, T.S. *J. Nat. Prod.* **2016**, *79*, 2709.
(83) Lim, K.-H.; Kam, T.-S. *Tetrahedron Lett.* **2009**, *50*, 3756.
(84) Kam, T.S.; Sim, K.M. *J. Nat. Prod.* **2002**, *65*, 669.
(85) Lotsof, H. S.; Google Patents: 1991.
(86) Sharma, P.; Cordell, G. A. *J. Nat. Prod.* **1988**, *51*, 528.
(87) Arambewela, L. S. R.; Ranatunge, T. *Phytochem.* **1991**, *30*, 1740.
(88) Achenbach, H.; Raffelsberger, B.; Brillinger, G.U. *Phytochem.* **1980**, *19*, 2185.
(89) Delorenzi, J. C.; Freire-de-Lima, L.; Gattass, C. R.; de Andrade Costa, D.; He, L.; Kuehne, M. E.; Saraiva, E. M. B. *Antimicrobial Agents and Chemotherapy* **2002**, *46*, 2111.
(90) Koenig, X.; Hilber, K. *Molecules* **2015**, *20*, 2208.
(91) Antonio, T.; Childers, S. R.; Rothman, R. B.; Dersch, C. M.; King, C.; Kuehne, M.; Bornmann, W. G.; Eshleman, A. J.; Janowsky, A.; Simon, E. R.; Reith, M. E. A.; Alper, K. *PLOS ONE* **2013**, *8*, e77262.

(92) Staley, J. K.; Ouyang, Q.; Pablo, J.; Hearn, W. L.; Flynn, D. D.; Rothman, R. B.; Rice, K. C.; Mash, D. C. *Psychopharmacology* **1996**, *127*, 10.
(93) Schep, L. J.; Slaughter, R. J.; Galea, S.; Newcombe, D. *Drug and Alcohol Dependence* **2016**, *166*, 1.
(94) Popik, P.; Layer, R. T.; Skolnick, P. *Pharma. Rev.* **1995**, *47*, 235.
(95) Glick, S. D.; Kuehne, M. E.; Raucci, J.; Wilson, T. E.; Larson, D.; Keller Jr, R. W.; Carlson, J. N. *Brain Research* **1994**, *657*, 14.
(96) Carnicella, S.; He, D.Y.; Yowell, Q. V.; Glick, S. D.; Ron, D. *Addict. Biol.* **2010**, *15*, 424.
(97) O'Hearn, E.; Molliver, M. E. *J. Neurosci.* **1997**, *17*, 8828.
(98) Glick, S. D.; Kuehne, M. E.; Maisonneuve, I. M.; Bandarage, U. K.; Molinari, H. H. *Brain Res.* **1996**, *719*, 29.
(99) Terada, Y.; Kitajima, M.; Taguchi, F.; Takayama, H.; Horie, S.; Watanabe, T. *J. Nat. Prod.* **2014**, *77*, 1831.
(100) Popik, P.; Skolnick, P. In *The Alkaloids: Chem. Biol.*; Geoffrey, A. C., Ed.; Academic Press: 1999; Vol. Volume 52, p 197.
(101) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1965**, *87*, 2073.
(102) Nagata, W.; Hirai, S.; Kawata, K.; Okumura, T. *J. Am. Chem. Soc.* **1967**, *89*, 5046.
(103) Nagata, W.; Hirai, S.; Okumura, T.; Kawata, K. *J. Am. Chem. Soc.* **1968**, *90*, 1650.
(104) Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930.
(105) Imanishi, T.; Yagi, N.; Shin, H.; Hanaoka, M. *Tetrahedron Lett.* **1981**, *22*, 4001.
(106) Huffman, J. W.; Shanmugasundaram, G.; Sawdaye, R.; Raveendranath, P. C.; Desai, R. C. *J. Org. Chem.* **1985**, *50*, 1460.
(107) Huffman, J. W.; Rao, C. B. S.; Kamiya, T. *J. Org. Chem.* **1967**, *32*, 697.
(108) Kuehne, M. E.; Reider, P. J. *J. Org. Chem.* **1985**, *50*, 1464.
(109) Kruegel, A. C.; Rakshit, S.; Li, X.; Sames, D. *J. Org. Chem.* **2015**, *80*, 2062.
(110) Zhao, G.; Xie, X.; Sun, H.; Yuan, Z.; Zhong, Z.; Tang, S.; She, X. *Org. Lett.* **2016**, *18*, 2447.
(111) Hodgson, D. M.; Galano, J. M. *Org. Lett.* **2005**, *7*, 2221.
(112) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373.
(113) Jana, G. K.; Sinha, S. *Tetrahedron Lett.* **2010**, *51*, 1994.
(114) Höck, S.; Koch, F.; Borschberg, H. J. *Tetrahedron: Asymm.* **2004**, *15*, 1801.
(115) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.
(116) Höck, S.; Borschberg, H. J. *Helv. Chim. Acta* **2006**, *89*, 542.
(117) Watt, D. S. *Tetrahedron Lett.* **1974**, *15*, 707.
(118) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747.
(119) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Watson, L.; Martin, N. G.; Oram, N. *Beils. J. Org. Chem.* **2012**, *8*, 107.
(120) Guerrand, H. D. S.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 7921.
(121) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267.

(122) Coldham, I.; Jana, S.; Watson, L.; Martin, N. G. *Org. Biomol. Chem.* **2009**, *7*, 1674.
(123) Guerrand, H. D. S., PhD thesis, University of Sheffield, 2012.
(124) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.
(125) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 6159.
(126) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.
(127) Burrell, A. J. M., PhD thesis, University Of Sheffield, 2008.
(128) Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801.
(129) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11.
(130) Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4279.
(131) Shin, W. K.; Kang, D.; An, D. K. *Notes* **2014**, *35*, 2169.
(132) Coldham, I.; Crapnell, K. M.; Fernàndez, J. C.; Moseley, J. D.; Rabot, R. *J. Org. Chem.* **2002**, *67*, 6181.
(133) Pathak, R. B.; Dobson, B. C.; Ghosh, N.; Ageel, K. A.; Alshawish, M. R.; Saruengkhanphasit, R.; Coldham, I. *Org. Biomol. Chem.* **2015**, *13*, 3331.
(134) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
(135) Gignoux, C.; Newton, A. F.; Barthelme, A.; Lewis, W.; Alcaraz, M.-L.; Stockman, R. A. *Org. Biomol. Chem.* **2012**, *10*, 67.
(136) Höck, S.; Borschberg, H. J. *Helv. Chim. Acta* **2003**, *86*, 1397.
(137) Imanishi, T.; Yagi, N.; Hanaoka, M. *Chem. Pharma. Bull.* **1985**, *33*, 4202.
(138) Kobayashi, J. i.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936.
(139) Yagi, S. *Kyoto Igaku Zasshi* **1909**, *6*, 208.
(140) Wu, H.; Zhang, X.; Ding, L.; Chen, S.; Yang, J.; Xu, X. *Planta Med.* **2013**, *79*, 1589.
(141) Yamamura, S.; Hirata, Y.; Academic Press: New York: 1975.
(142) Suzuki, K. T.; Okuda, S.; Niwa, H.; Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 799.
(143) Heathcock, C. H. *PNAS* **1996**, *93*, 14323.
(144) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544.
(145) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2554.
(146) Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566.
(147) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575.
(148) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572.
(149) Shvartsbart, A.; Smith, A. B. *J. Am. Chem. Soc.* **2015**, *137*, 3510.
(150) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461.
(151) Yamada, R.; Adachi, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 6067.
(152) Diaba, F.; Martínez-Laporta, A.; Coussanes, G.; Fernández, I.; Bonjoch, J. *Tetrahedron* **2015**, *71*, 3642.
(153) El Bitar, H.; Hung Nguyen, V.; Gramain, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2004**, *45*, 515.
(154) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360.

(155) Li, C.S.; Di, Y.T.; He, H.P.; Gao, S.; Wang, Y.H.; Lu, Y.; Zhong, J.L.; Hao, X. J. *Org. Lett.* **2007**, *9*, 2509.
(156) Rychnovsky, S. D.; Swenson, S. S. *J. Org. Chem.* **1997**, *62*, 1333.
(157) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550.
(158) Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685.
(159) Tormena, C. F.; Dias, L. C.; Rittner, R. *J. Phys. Chem. A* **2005**, *109*, 6077.
(160) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251.
(161) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
(162) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282.
(163) Bali, A. K.; Sunnam, S. K.; Prasad, K. R. *Org. Lett.* **2014**, *16*, 4001.
(164) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497.
(165) Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035.
(166) Solladié, G.; Colobert, F.; Denni, D. *Tetrahedron: Asymm.* **1998**, *9*, 3081.
(167) Aquino, F.; Pauling, H.; Walther, W.; Plattner, D. A.; Bonrath, W. *Synthesis* **2000**, *2000*, 731.
(168) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.
(169) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.
(170) Ritter, T.; Zarotti, P.; Carreira, E. M. *Organic Lett.* **2004**, *6*, 4371.
(171) Lyons, J., MChem Project report, University of Sheffield, 2016.
(172) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* 1994; Vol. 66, p 1479.
(173) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422.
(174) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem.* **2007**, *119*, 7635.
(175) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491.
(176) Aggarwal, V. K.; Binanzer, M.; de Ceglie, M. C.; Gallanti, M.; Glasspoole, B. W.; Kendrick, S. J. F.; Sonawane, R. P.; Vázquez-Romero, A.; Webster, M. P. *Org. Lett.* **2011**, *13*, 1490.
(177) Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
(178) Firth, J. D.; O'Brien, P.; Ferris, L. *Org. Biomol. Chem.* **2014**, *12*, 9357.
(179) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054.
(180) Paquette, L. A.; Gilday, J. P.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5044.
(181) Cooksey, J. P.; Ford, R.; Kocieński, P. J.; Pelotier, B.; Pons, J.-M. *Tetrahedron* **2010**, *66*, 6462.