

Tandem Reactions for sp^3 -Rich Scaffold Synthesis

By Wafa Bawazeer, MSc(KAU)

Thesis submitted for the University of Nottingham for
the degree of Doctor of Philosophy
September, 2015

I would like to dedicate this thesis to my loving family ...

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other University.

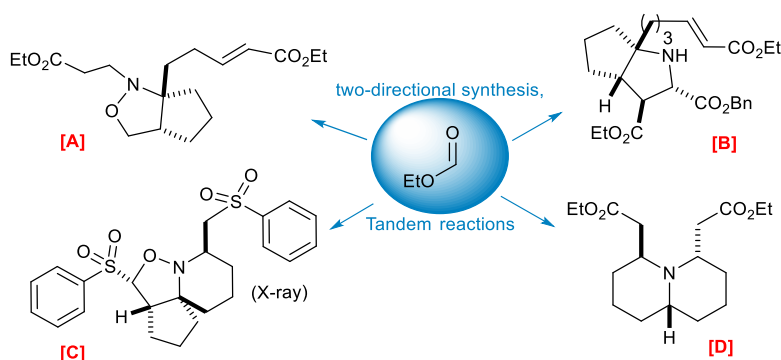
The research described within this thesis is, to the best of my knowledge, original and my own work.

Wafa Bawazeer

Nottingham, Sep 2015

Abstract

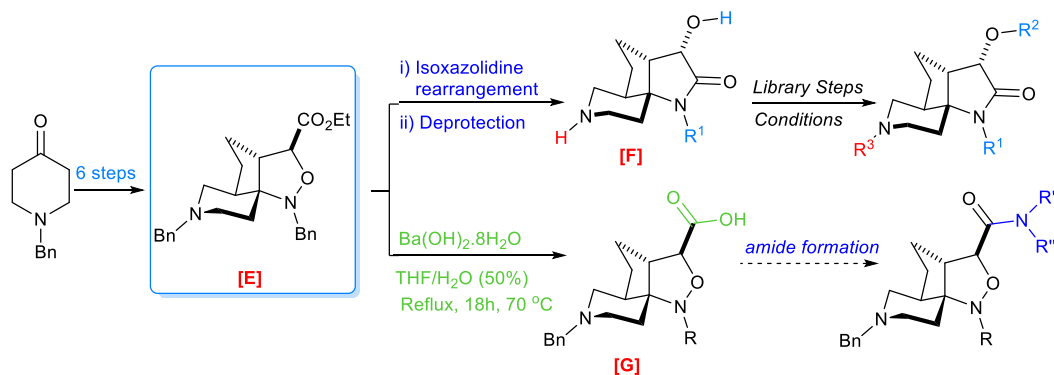
Several novel methodologies were explored with the general purpose of rapid access to molecular complexity and sp^3 -rich scaffolds. A number of novel scaffolds were successfully synthesised, utilising two-directional synthesis and tandem reactions. The chemistries applied have been demonstrated to be capable of readily fabricating many novel and interesting diverse molecular scaffolds. Indeed, the azaspirocyclic cores found in halichlorine and pinnaic acid were synthesised using this approach starting with ethyl formate.



Scheme A. 1. Azaspirocyclic cores obtained using two-directional/tandem cycloaddition

More diverse scaffolds were generated from simple symmetrical linear molecules derived from ethyl formate, utilising the nitron produced *in situ* by the treatment of the central ketone with either hydroxylamine hydrochloride or amino acids. These afforded number novel skeletons [A-C], which are expected to have interesting biological activity. In addition, they are conceivably useful skeletons in the synthesis of natural products, or in drug synthesis due to its high saturation (high F_{sp^3}) characters.

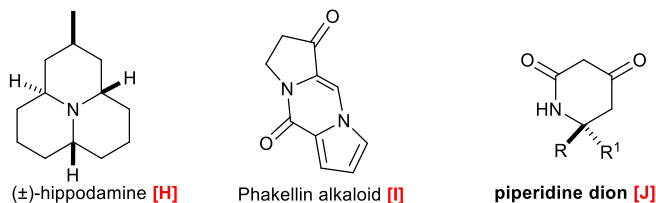
Using the tandem reactions, we have also managed to develop a rapid synthetic route to an sp^3 -rich chemical scaffold **[F]** derived from novel isoxazolidine scaffold **[E]**. This project has been published with a contribution of other group member.¹



Scheme A.2 Tandem Condensation/Intramolecular via Nitrone/[3+2]Cycloaddition

We were interested to synthesise of some natural products. We tried to explore the possibility of developing an enantioselective synthesis approach to the key intermediate in the synthesis of hippodamine **[H]**, few attempts toward the synthesis of the marine alkaloids phakellin **[I]**.

Several novel applications of chiral sulfinimines were explored. Initially some preliminary results toward the synthesis of piperidine dione **[J]** were recorded. Successful attempts of *tert*-butyl sulfinimines with dianion *tert*-butyl-acetoacetate afforded a range of cyclic compound piperidine dione **[J]** in a good yield.



Acknowledgements

It would not have been possible to carry out the work presented forthwith without the efforts of a number of individuals; I would therefore like to thank the following people:

Firstly, Professor Robert Stockman, not only for giving me the opportunity and freedom to work on such interesting and enjoyable projects, but for encouraging, continuous support, guidance and believe in me to do such PhD and in the first place.

Second, Professor. Mohammad Saleh I. Makki, his unlimited support and all time he gave generously. Thanks for supervising me.

Dr. Tom Storr, for taking me under his wing, for giving ideas and advising me to come up with my own, then for being there whenever I need help. And all the members of the Stockman Group, past and present, especially the Dominika Regentova & Elise Rocshette, and all my friends and colleagues from the group.

Justine Dutton, for all her support, suggestions and sharing with me all my PhD hard and lovely times. A friend that made my life in Nottingham much more easy and feeling more safe, and thanks for inviting me to “the Cadbury World” trip.

To all the postdoc team, in particular, Dr. Ross Wilkie, Dr. Mike Rowling, Dr. Irene Geourgiou, Dr. Sarah Cully, who have helped me in one way or another in this work.

My collaborators; Mrs Omaina Olagy. For being always there whenever I need an academic support in King AbdulAziz University, thanks for all her kindness.

I want to thank my Mum and Dad, and all my lovely family, I definitely couldn’t have gotten this far without them.

My husband, for all those days he supports me and being patient to stand beside me to continue doing what I am greatly interesting in, finishing my PhD.

Thanks for King AbdulAziz University in Jeddah, for the fund, and JSP staff especially.

Contents

Abstract	v
Acknowledgment	vii
List of Abbreviations	x
Chapter 1	
1. Introduction	1
1.1. The Mother of Invention in Synthesis	3
1.2. Organic Synthetic Strategies	4
1.2.1. Diversity Oriented and Target Oriented Synthesis	7
1.2.2. Tandem Reactions	10
1.2.2.1. Domino Reactions in Organic Synthesis	11
1.2.2.2. Domino Reactions Classification	13
1.2.2.3. Michael addition in Domino Reactions	15
1.2.3. Nitron in Domino Reactions	15
1.2.3.1. What is nitron?	15
1.2.3.2. Synthesis of nitrons	17
1.2.3.3. Nitron-olefin [3+2] cycloaddition	17
1.2.4. Olefin Cross-Metathesis	19
1.2.4.1. Olefin Cross Metathesis Types	23
1.2.4.2. Enhancement of Olefin Cross- Metathesis	25
1.2.5. Two-directional Organic Synthesis	26
1.3. The Art of Utilising Organic Synthetic Tools	28
1.4. Combining two-directional and tandem reaction toward total synthesis of alkaloid cis-223B	30
1.5. Combining two-directional synthesis and tandem reactions towards the synthesis of the spirocyclic core of halichlorine and the pinnaic acids	34
1.5.1. The First Total Synthesis of (+)-Halichlorine	36
1.5.2. Stockman's concise approach to the spirocyclic core of (±)-halichlorine and pinnaic acid	38
1.5.3. Combining between two-directional and tandem reaction toward synthesis of (±)-hippodamine and (±)-epi-hippodamine	41
1.5.4. Stockman Strategy combining Two-directional and Tandem Reactions	45
1.5.5. Utilising chiral Sulfinimines towards Synthesis of six-membered β -keto lactam	48
1.5.6. Use of Sulfinimines towards Stereoselective Synthesis of (±)hippodamine	49
1.6. Aim of work	51
1.7. Objectives	52
Chapter 2	
2. Results and Discussion	53
2.1. Diversity Oriented Synthesis (DOS)	54
2.1.1. Outline of Our Synthetic Strategy	54
2.1.2. Cross-Metathesis in Two-directional synthesis	56
2.1.3. Combining between Two-directional and Domino Synthesis	59

2.1.3.1.	Future Work	64
2.1.4.1.	Tandem Intra molecular-Cycloaddition Utilising Oxime to Generate Spirocyclic β -amino Acid Derivatives	65
2.1.5.	Tandem Cyclisation with Amino Acids	71
2.1.6.	De-symmetrising and Sequentially homologation for the synthesis of useful azabicyclic systems	76
2.1.7.	Use of Sulfinimines towards Stereoselective Synthesis of ($\pm$)hippodamine	81
2.1.8.	DOS Conclusion.....	83
2.2.	Targeted Oriented Synthesis	86
2.2.1	Synthesis of Highly sp^3 -rich Natural Product-like Chemical Scaffold via A Tandem Condensation/Intramolecular Nitron-Alkene [3+2] Cycloaddition Strategy.....	86
2.2.1.1.	α -C alkylation of pipridinone via hydrazine	87
2.2.1.2	Enhancement of Cross-metathesis	90
2.2.1.3.	Tandem Condensation/Intramolecular [2+3] Cycloaddition via Nitron	92
2.2.1.4.	Toward the Targeted Molecule	94
2.2.1.5.	Hydrolysis of ethylester	97
2.2.1.6.	Conclusion	98
2.2.2.	Targeted Oriented Synthesis TOS	99
2.2.2.1	Synthesis of Natural-Product like “Phakellin substructure”	100
2.2.2.2.	Conclusion	105
2.2.3.	Utilising chiral Sulfinimines towards Synthesis of six-membered β -keto lactam	106
2.2.3.1	Future works	108
2.3.	Conclusion	110
Chapter 3		
3.	Experimental	110
3.1	Experimental procedures	111
References		165
Appendix A		
A.1.	Crystallography Data	175
Appendix B		
B.1.	Published Work	177

Abbreviations

Ac	acetyl
AMY	azo methine ylide
app	apparent
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
br	Broad
calcd	theoretically calculated Mass spec
CAMD	computer aided molecular design
CBz	carboxybenzyl
Cbz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
CM	cross-metathesis
CAAs	cyclic amino acids
CSA	camphorsulfonic acid
d	doublet
d.e.	diastereomeric excess
d.e. <i>ca</i>	diastereomeric excess calibrated
d.r.	diastereomeric ratio
DCE	dichloroethane
DCM	dichloromethane
DMSO	dimethyl sulfoxide
DOS	diversity oriented synthesis
e.e.	enantiomeric excess
equiv.	equivalent
ES	electrospray
Et ₂ O	di ethyl ether
EtOAc	ethyl acetate
gla.AcOH	glacial acetic acid

Hex	hexane
H-G II	Hoveyda-Grubbs catalyst second generation
HOBt	hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
Hünig's base	tri ethyl amine
Hz	hertz
<i>in vacuo</i>	in rota vaporatory
IR	infrared
IUPAC	international union of pure and applied chemistry
<i>J</i>	coupling constant
LDA	lithium diisopropylamide
LG	leaving group
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
m.p.	melting point
m/z	mass to charge ratio
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
n-BuLi	n-butyl lithium
NMR	nuclear magnetic resonance
Nu	nucleophile
<i>o</i>	ortho
<i>p</i>	para
PCC	pyridinium chlorochromate
Pent	pentane
Pet	petroleum ether
PG	protecting group
Ph	phenyl

q	quadruplet
qu	quintet
r.t.	room temperature
s	singlet
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilylchloride
^t Bu	<i>tert</i> -butyl
TEA	tri ethyl amine
THF	tetrahydrofuran
Ti(EtO) ₄	titanium IV ethoxide
TiCl ₄	titanium IV chloride
TLC	thin layer chromatography
TMS	trimethylsilyl
TOS	targeted oriented synthesis
α	alpha
α-AAs	α-amino acids
β	beta
δ	chemical shift in ppm
μw	Microwave
ω	omega

CHAPTER 1

INTRODUCTION

Chapter 1

1. Introduction

The kind of life we enjoy today with all its features could not exist without the science of chemistry. The importance of chemistry is that it acts as a crossing point to most of the sciences. In all its branches scientific information is based on analyses, and interpretation of data. If you have a solid background in chemistry you will have a common ground with other scientific fields. Chemistry can be a “central” science, as its deeply ingrained into so many areas of engineering, business, government, and environmental management.^{2,3}

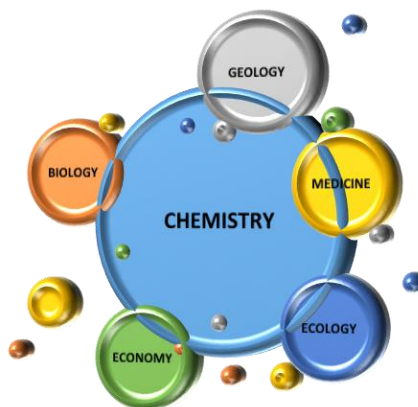


Figure 1. 1. Chemistry is a central science

Synthetic chemistry plays a key role in the multidisciplinary process to find potential drug candidate molecules, and all subsequent operations of creation, exploration, and evaluation

Chapter 1. Introduction

of short, efficient, safe, reproducible, scalable, ecological but still economical syntheses for the selected clinical candidates.⁴

Jöns Jacob Berzelius (1807) coined the term “organic chemistry” for the study of compounds extracted from natural sources. He believed that organic chemicals found in nature have a unique mysterious force of life “*vis vitalis*”/ “vital force” that is acquired by their natural synthesis, therefore, it is impossible they are synthesised in a laboratory from the available pure chemicals.⁵ This theory was believed by the scientists for many years. Providentially, Frederick Wöhler (1828) later in the same century reported a synthesis of urea, a natural component in urine, from inorganic salts, by heating the ammonium cyanate in his laboratory (Figure 1.2). His discovery disproved the “vital force” hypotheses, thus he paved the way for the organic synthetic chemists.⁶

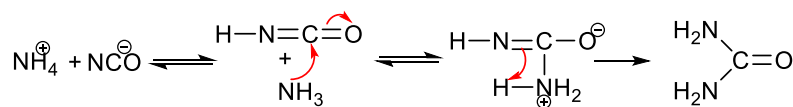


Figure 1. 2. Urea Synthesis

Organic chemistry is one of the oldest and most fertile areas of chemistry. Cyclic molecules of carbon and hydrogen are termed homocyclic but in presence of at least one heteroatom it will be termed as heterocyclic compound.⁷

“Heterocyclic molecules look like jewellery rings studded with precious stones”, said by a Russian scientist, Beketov (1993).⁸ He imagined that several carbon atoms making up the molecular ring, while the role of the jewel is played by an atom of a heteroatom. In general, it is the heteroatom which imparts to a heterocycle its distinctive and sometimes striking properties”, a quotation by Beketov who was the inventor of aluminothermy, and

Chapter 1. Introduction

a founder of physical chemistry.⁹ Heterocyclic chemistry as a big branch of organic chemistry as a mother of a big conflicting and associated family.⁸

1.1 The Mother of Invention in Synthesis

“The true creator is necessity, who is the mother of our invention.” – Plato.¹⁰

Synthetic heterocyclic compounds play a fundamental role in our lives, solving tremendous agrochemical, environmental, industrial, technological, and medicinal problems.

However, some of the most important drugs and chemicals have serendipitous origins. In 1897, an Indian chemist Sapper accidentally broke a thermometer in an organic chemical mixture he was heating; he observed changes which led to the discovery of the catalytic effect of the mercury in the acidic solution (HgSO_4), which oxidized naphthalene to phthalic acid, then known as Indigo, (Figure 1.3).¹¹

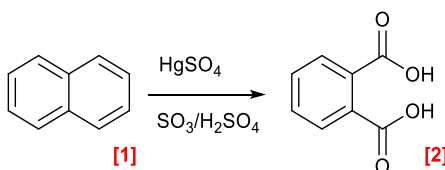


Figure 1.3 . Accidental Indigo discovery

Although most of the early organic synthesis discoveries came about serendipity, impressively synthesis became a planned, designed, and computationally targeted process. Moreover, it developed to be more noteworthy, and the current challenge is to progress towards a more nature friendly and sustainable science to produce widely useful compounds to mimic nature by synthesising natural products and analogues.¹⁰

Now, in drug design for instance, the effective design of targeted-chemical structure with desirable therapeutic properties is a well-established area.

1.2. Organic Synthetic Strategies

The understanding of 3D stereochemistry of molecules in computer aided molecular design (CAMD) are efficient strategies toward synthesising the targeted molecule.¹² Then the chemists mission is to construct the structure by applying convergent synthesis which are often derived by mimicking Nature's synthesis.

Linear synthesis is an approach in which the process is stepwise starting from simple commercially available chemicals without any use of independently prepared intermediate scaffolds, adding molecules sequentially to each side, converting each molecule to the next. This leads to multi-steps analysing sequence synthesis and the overall combined yield undoubtedly drops with each reaction step (Figure 1.4).

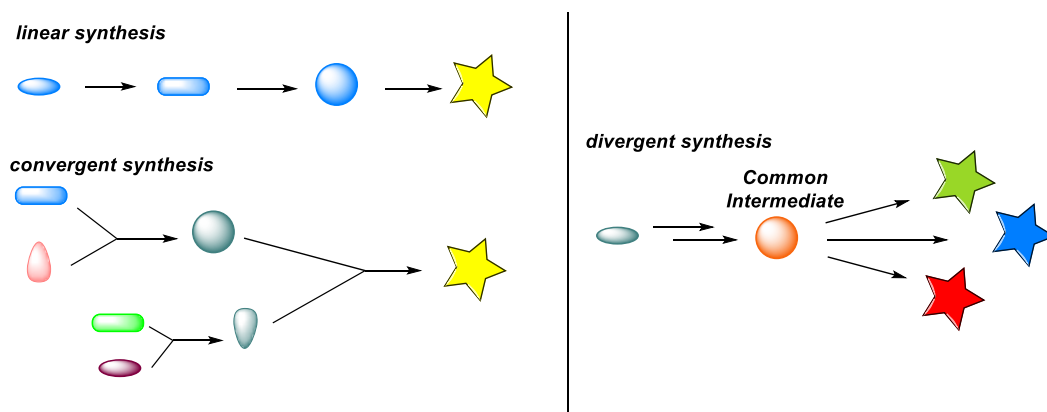


Figure 1. 4. The linear, convergent, and divergent synthesis simplification¹³

Convergent synthesis is a process by which larger molecular fragments are combined together to produce the target molecule. This can strongly improve the overall yield with fewer linear sequences. Divergent synthesis strategy aims to generate a library of chemical compounds by reacting a molecule with a set of diverse reactants and produce different scaffolds. The next generation of compounds is generated by further reactions. This

Chapter 1. Introduction

strategy quickly liberates large numbers of new compounds. The original definition of this ‘Divergent total synthesis’ approach was given by Boger.^{13,14}

The natural product bryostatin first isolated in the 1960s by George Pettit, is a molecule found that could fight cancer, Alzheimer’s disease, and HIV.¹⁵ In 1991 the researchers considered a massive isolation of bryostatin 1 from *B. neritina*, from California coast. 14 tons of the animal were collected, from those 14 tons researchers isolated 18 g of bryostatin 1.¹⁶ The early syntheses of this complex macrocyclic lactone with eleven chiral centres, was reported by Masamune, Evans, and Yamamura provided a starting point for accessing the potent bryostatins (42-45 linear), more than 75 total steps.^{17,18} In 2008 Dong reported the synthesis of bryostatin analogue in only 42 steps.¹⁹ P. Wender found that from the points of convergence of his synthesis which necessitate 14-21 linear steps, followed by the assembly of respective pyran-containing backbones, his synthesis process provided a bryostatin derivative in 25 linear and 42 total steps (Figure 1.5).^{20,18}

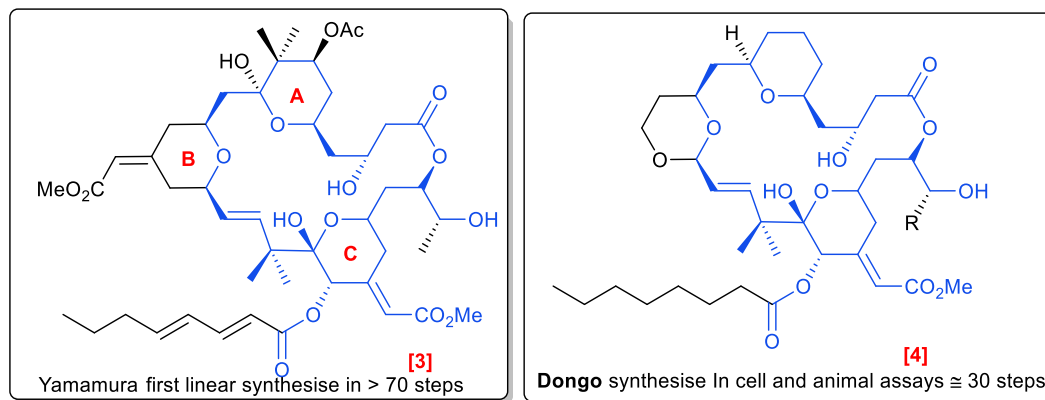


Figure 1.5. Bryostatin 1 Synthesis

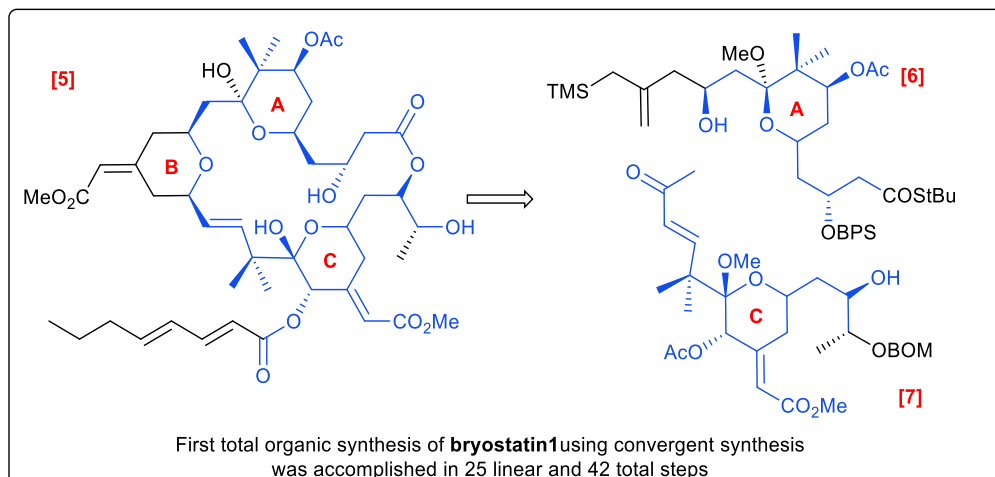


Figure 1. 6. Bryostatin and analogues convergent synthetic strategies

Recently, Michael. Krische and co-workers reported synthesis of bryostatin 7 in 36 steps.²¹

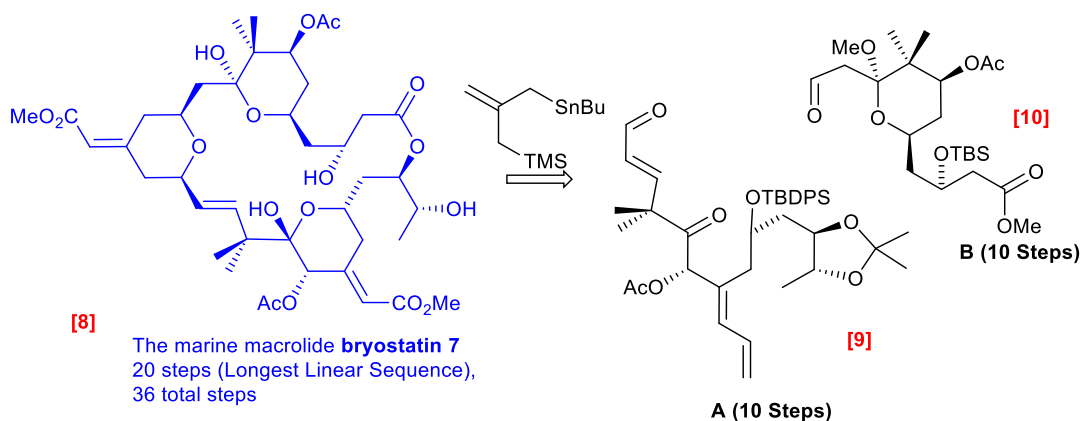
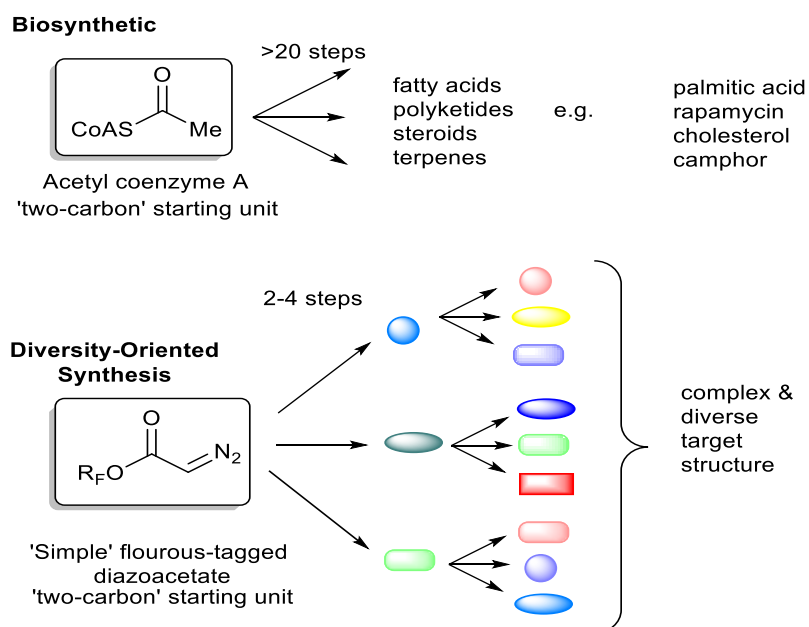


Figure1.7. Krische and co-woorkers synthesis convergent synthesis of bryostatin 7

Noticeably, the ideal synthesis is highly demanded but hard to achieve. Ideal synthesis is the process in which a target molecule is produced in one single operation starting from readily available chemical compounds is prepared in nearly 100% yield of this operation and without any side products. The simple, economic, environmentally friendly, safe and acceptable synthesis is fortunately to achieve through convergent synthesis strategy.²²

1.2.1 Diversity Oriented and Target Oriented Synthesis

Diversity-oriented synthesis (DOS), pioneered by Stuart Schreiber, describes a synthetic strategy by which a single scaffold-forming/generator molecule is built in forward steps, commonly in five synthetic steps at the maximum.²³



Scheme 1. 1. Nature synthesis and Diversity-oriented synthesis

Biochemical synthesis in nature, is capable of forming diverse molecular skeletons by divergent synthesis using the basic 'two-carbon' starting unit acetyl CoA (Scheme 1.1).²³ D. Spring (2006), reported the use of a fluorine-tagged diazoacetate which can be a basic 'two-carbon' pathways to synthesize drug-like and natural product-like compounds in an interesting 2–4 synthetic steps.

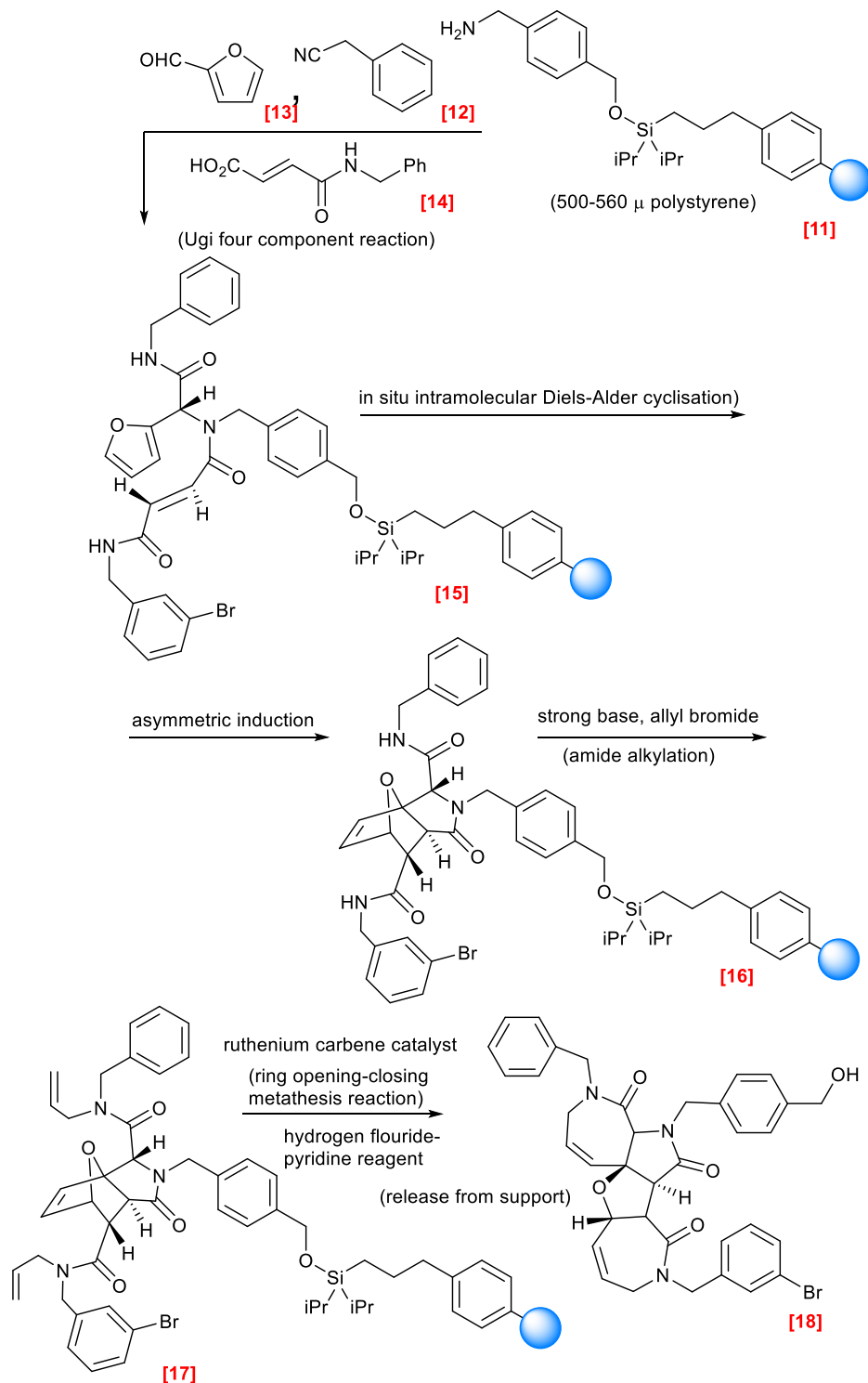
The term 'diversity' is somehow subjective. However, there are four principal components of structural diversity that have been consistently identified in literature; appendage

Chapter 1. Introduction

diversity, modification in structural moieties around a common skeleton; functional group diversity; stereo chemical diversity, and skeletal diversity.²⁴

In contrast to DOS, Target-Oriented synthesis (TOS), historically known as a traditional approach in organic synthesis, first identifies the target molecule, a retrosynthetic analysis is then planned and the synthesis started. It is widely used by chemists since the mid sixties in drug design and discovery.²⁵ Diversity oriented synthesis in first place was designed to mimic what happens in genes naturally, as random mutations procreates diverse conformations. Diversity and complexity should be planned and well-designed forward direction process by applying certain organic reactions. The smart utilisation of tandem reactions is usually powerful in the divergent process. The synthetic process in Scheme 1.2 illustrates where structural diversity has been increased *via* tandem reaction while the tricyclic lactam core un-touched.²⁶

The first reaction in (Scheme 1.2) named as Ugi four-component reaction.²⁷ The reaction then went through condensation/intramolecular Diels-Alder reaction to generate complexity from the diene and dienophile containing substrates. Coupling reactions proceed in a single step converting the four components into a complex tricyclic ring compound **[17]**.



Scheme 1. 2. Strategies to increase the structural complexity of products in diversity-oriented synthesis utilising tandem reactions

Compound **[17]** showed the ring-opening, ring-closing olefin metathesis reactions add more functionality to the substrate making two five-membered rings and two seven-membered rings. Then the consecutive tandem reaction step finalised the reaction to produce the complicated substrate to polycyclic ring skeleton **[18]**.²⁶

1.2.2 Tandem Reactions

Tietze (1996), defined “Tandem” as a word used to express a combination of two or more reactions, but does not describe the time-resolved transformation.

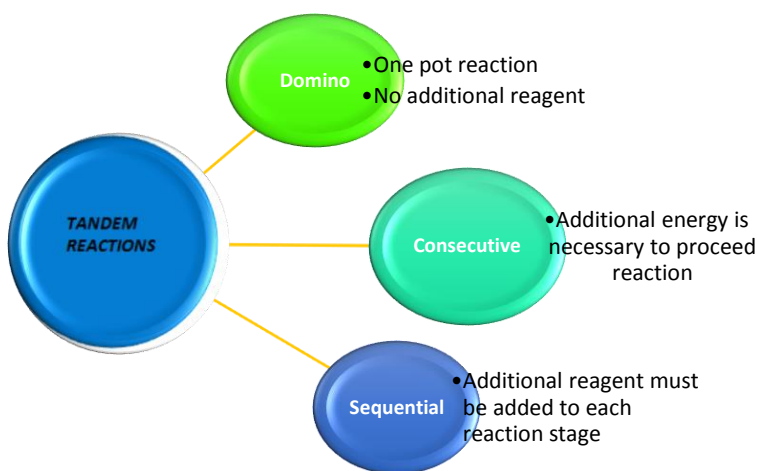


Figure 1. 8. Tandem reaction classification Tietze (1996)

Thus, he suggested not to use this expression anymore, and to employ the word “Domino” as more indicative. Nevertheless, the “Tandem reaction” expression dominates wide area in organic synthesis since then, and up to now but it could be defined according to the time-resolved succession of reactions into three classes; Dominos/cascade, Consecutive and Sequential reaction (Figure 1.6).²⁸

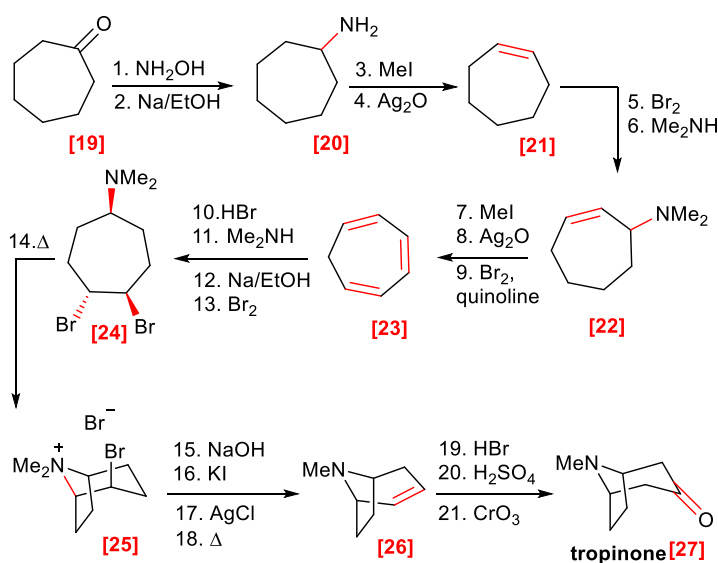
However, Albert Padwa (2007), revealed that the terms “tandem” and “cascade”, could be applied to all these reactions in which several bonds are formed in one operation without

Chapter 1. Introduction

intermediate isolation, changing any of reaction conditions, or these reactions of some changes in its conditions, as long as the transformation of multiple components occurred in a single reaction vessel.²⁹

1.2.2.1 Domino Reactions in Organic Synthesis

Domino reactions are not a new invention; it is an old reaction strategy that has been used in nature to develop its products in biosynthesis. However, it has been defined by Tietze as a synthesis process where two or more bonds are formed under the same conditions without the need of adding any energy or reagents.^{30,31}



Scheme 1. 3. Willstätter first total synthesis of tropinone [50] in 20-step

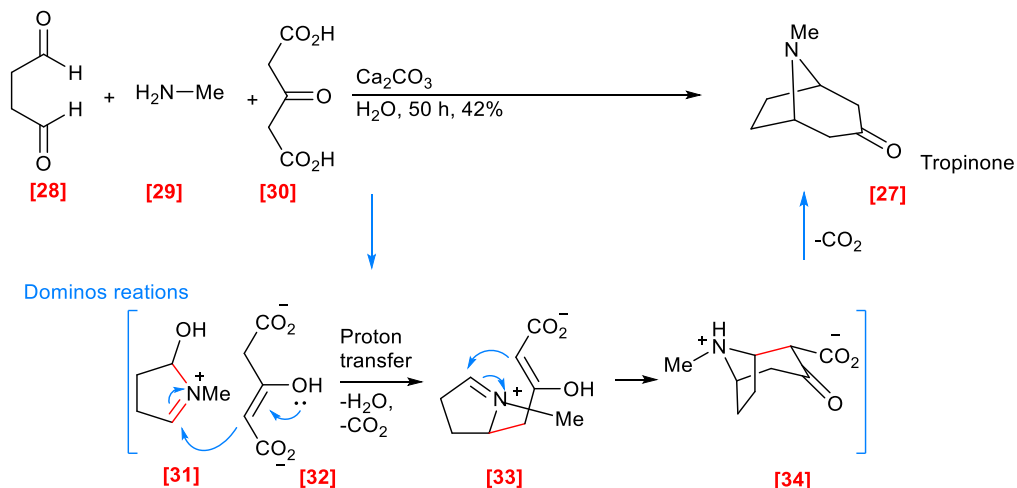
In 1901 Richard Willstätter who was had a special interest in plant natural products, published his total synthesis of tropinone in a 20 steps synthesis with the overall yield being extremely small, of the order of 1% (Scheme 1.3).^{32,33}

Chapter 1. Introduction

Willstätter used cycloheptanone [19] (Scheme 1.3) as starting material, then transformations started by oxime formation *via* condensation with hydroxylamine, reduction to the amine [20] and form after of the quaternary amine, and subsequent elimination to afford cycloheptene [21], repeating the same steps until preparation of cycloheptatriene [23]. Addition of bromine and dimethylamine generated the dimethylaminocycloheptadiene, reduction of double bond using Na in alcohol followed by bromination produced [24].

Then, in a remarkable reaction, heating led to double bond dibromination primed a cyclisation to generate the tropane salt [25], and thereby the first preparation of the tropane nucleus. Alkali treatment of [25] generated [26], subsequent HBr addition allowed isolation of presumably the β -bromide, followed by treatment of bromide with sulfuric acid in a sealed vessel at 200 °C gave β -tropine, but it was the wrong stereoisomer. The relevant α -isomer was obtained by Willstätter after oxidation of tropinone [27].³⁴

Shortly after, Sir Robert Robinson (1917), an organic chemist interested in alkaloids, achieved the biomimic synthesis of tropinone [27] in a landmark synthesis. He utilised one of the very first domino reactions (Scheme 1.4). Moreover, the yield increased from around 1% by Willstätter to 17% yield. The one pot synthesis involved a mixture of three components succinaldehyde [28], methylamine [29] and acetonedicarboxylic acid [30]. The reaction commences with the formation of iminium [31] which undergoes double Mannich reaction to achieve [34] which following decarboxylation, gives the natural product. Several bonds are formed in each step which is only possible when the functionalities in earlier steps are synthesised.³⁵



Scheme 1. 4. Domino process for the synthesis of tropinone [27]

In this thesis we utilised domino reactions, that enabled us to build complex structures in one-pot reactions. Efficiently, few single synthesis step enabled the elaboration of complex molecules.

1.2.2.2. Domino Reactions Classification

Many reactions are available to domino reactions, including Michael reaction, reductive amination, aldol, cycloaddition, lactonization, lactamisation, Mannich reaction, and many others. Thus, it is more convenient to classify domino reactions depending on the mechanism used in bond formation of each step, which can be distinguishable as a cationic, anionic, radical, pericyclic, photochemical, and transition-metal induced transformation. For this classification certain rules must be applied. Domino reactions initiated by nucleophilic substitution mechanisms such as Michael addition are always counted as anionic mechanism, whereas carbocation formation step counted as cationic mechanism. It should be noted that formation of carbocation could be achieved by elimination of water from alcohol or treatment of epoxide or alkene with Lewis acid.

Chapter 1. Introduction

Therefore, the domino reaction which combined between the same reaction mechanism type in the first, second, third, or even in a fourth step is called homo-domino reaction (such as anionic/anionic/anionic), whereas a combination of different reaction mechanisms is called hetero-domino reactions. Tietze has set a possible classification of domino reactions based on different mechanisms (Table 1.1).^{28, 32, 36}

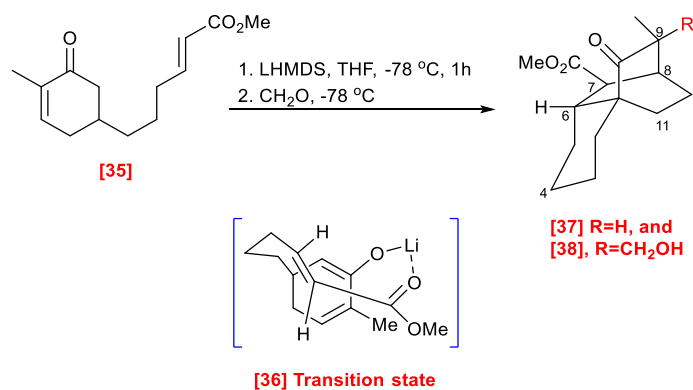
Table 1.1. Classification of Domino Reactions According to the Mechanism

<i>1st step</i>		<i>2nd step</i>		<i>3rd step</i>	
1a	cationic	2a	cationic	3a	cationic
1b	anionic	2b	anionic	3b	anionic
1c	radical	2c	radical	3c	radical
1d	pericyclic	2d	pericyclic	3d	pericyclic
1e	photochemical	2e	photochemical	3e	photochemical
1f	carbinoid	2f	carbinoid	3f	carbinoid
1g	transition metal-catalysed	2g	transition metal-catalysed	3g	transition metal-catalysed
1h	oxidation/reduction	2h	oxidation/reduction	3h	oxidation/reduction

These reactions which this thesis will focus on as; Michael addition, [3+2] cycloaddition, cross-metathesis where tandem classes are, 1a/2b, 1a/2d and 1a/2g respectively.

1.2.2.3 Michael addition in Domino Reactions

The most often used domino reaction found in the literature is anionic homo-domino reaction when double Michael addition is encountered in particular. The natural product seychellene and patchouli alcohol were synthesised using the same strategy (Scheme 1.5).³⁷



Scheme 1. 5. The anionic homo-domino reaction synthesis of tricycle [37]

Three C-C bonds were stereoselectively formed by domino reaction *via* enolate anion formation, supported by coordination with lithium [36] (Scheme 1.5), which was quenched by treatment with gaseous formaldehyde. The intramolecular cascade Michael-Michael-aldol reaction obtained tricyclic compound [37] in 68% yield as a single diastereoisomer.³⁷

1.2.3. Nitrones in Domino Reactions

1.2.3.1. What is a nitrone?

In 1890, the first nitrones (or azomethine oxides) were prepared by Beckmann. Later in 1916, and due to the similarity to ketones, they were named nitrone from a shortening of “nitrogen-ketones” by Pfeiffer. Occasionally, the terms aldo- and keto-nitron may also be used to distinguish between those with or without a proton on the α -carbon. Noticeably, nitrones exist as (*E*)- and (*Z*)- forms which can be interconverted.³⁸ Basically, the nitrone is a functional group in organic chemistry, and the general structure can be described as the *N*-oxide of an imine.

Chapter 1. Introduction

Nitrones play a dominant role in organic synthesis, as a very efficient way to produce heterocyclic compounds in the inter/intra-molecular 1,3-dipolar cycloaddition using alkenes as dipolarophiles, (although other multiply bonded systems may also be used alkynes, allenes, isocyanates, nitriles, thiocarbonyls, etc).

Many cyclic nitrones have been synthesized to avoid the issue of nitrone (*E/Z*) isomerisation, and minimise the number of possible cycloaddition products by controlling reactants thus controlling the geometry about the C=N double bond.³⁸

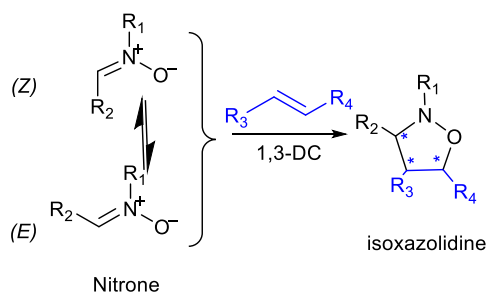


Figure 1. 9. The most common nitrone 1,3-dipolar cycloaddition

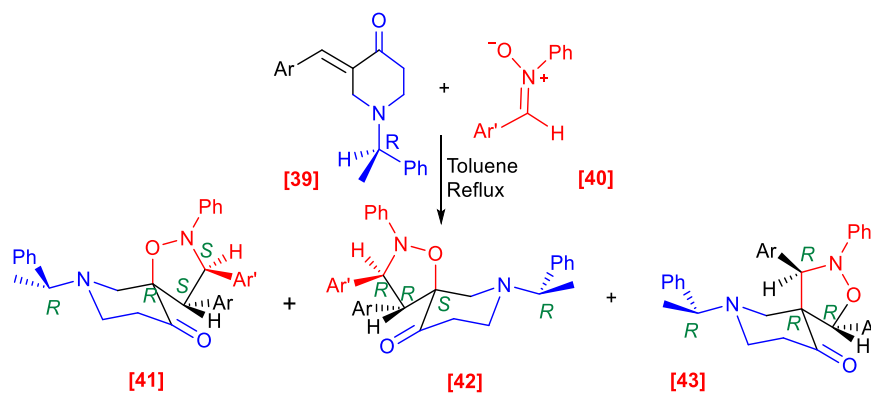
1.2.3.2 Synthesis of nitrones

The methods of synthesising nitrones can be broadly categorised as either oxidative or non-oxidative. Nitrones are most often generated either by the oxidation of hydroxylamines or by condensation of monosubstituted hydroxylamines with carbonyl compounds (ketones or aldehydes). The most common synthesis used in this thesis is highlighted; that of hydroxylamines condensation with ketone.

1.2.3.3 Nitron-olefin [3+2] cycloaddition

When nitrones are combined with either alkenes or alkynes, [3+2] cycloaddition leads to the formation of a new C-C bond and a new C-O bond. The cycloaddition is stereospecific with respect to the configuration of the alkene; however, diastereoselectivity in the reactions of C-substituted nitrones is often low.³⁹ The regioselectivity is controlled by the dominant frontier orbitals interacting during the reaction, and substrates with electronically distinct substituents tend to react with high regioselectivity. Intramolecular versions of the reaction have been used to synthesise complex polycyclic carbon frameworks. The reduction of the N-O linkage leads to 1,3-aminoalcohols.

A series of novel enantiomerically pure spiroisoxazolidines were synthesised regioselectively by Kumar et al, (2010).⁴⁰ The cycloaddition of (R)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene] tetrahydro-4(1H)-pyridinones [39] with nitrones [40], the reaction proceeded regioselectively affording predominantly the diastereomeric spiroisoxazolidines, [41] and [42], both arising from the addition of the oxygen to the α -carbon of the carbonyl group (Scheme 1.6).



Scheme 1. 6. Cycloaddition is stereo-sensitive to the nature of substituents in the dipolarophile

Chapter 1. Introduction

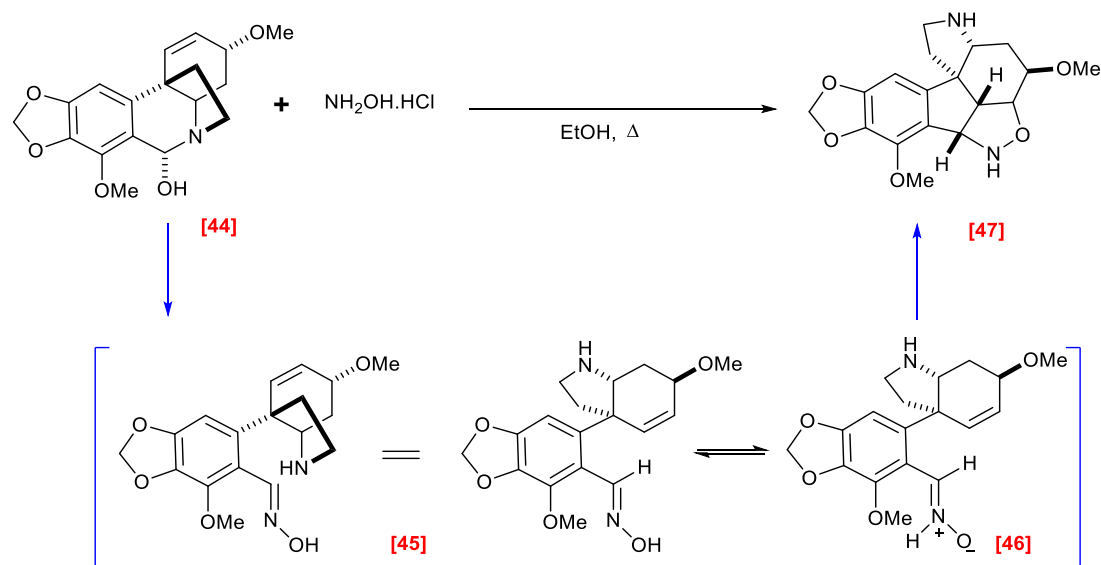
Trying different substituents of Ar and Ar' proved that this cycloaddition was very sensitive to the nature of substituents in the dipolarophile (Table 1. 2).⁴⁰

Table 1. 2. The effect of nature of substituent in the dipolarophile

Comp	Ar	Ar'	Yield ^a (%)		Time H
			[41]	[42]	
a	C ₆ H ₅	C ₆ H ₅	28	22	10
b	C ₆ H ₅	<i>p</i> -MeC ₆ H ₅	30	22	10
c	<i>p</i> -ClC ₆ H ₅	<i>p</i> -MeC ₆ H ₅	33	28	10
d	<i>p</i> -MeC ₆ H ₅	C ₆ H ₅	37	23	10
e	<i>p</i> -MeC ₆ H ₅	<i>p</i> -MeC ₆ H ₅	35	27	10
f	<i>o</i> -ClC ₆ H ₅	C ₆ H ₅	31	25	14
g	<i>o</i> -ClC ₆ H ₅	<i>p</i> -MeC ₆ H ₅	35	23	14
h	2-thienyl	C ₆ H ₅	30	22	16
i	2-thienyl	<i>p</i> -MeC ₆ H ₅	30	20	16
j	1-naphthyl	C ₆ H ₅	45	^b	14
K	1-naphthyl	<i>p</i> -MeC ₆ H ₅	43	^b	14
^a Isolated yield; ^b Formed only in traces					

Chapter 1. Introduction

Wildman reported an interesting one pot domino reaction, while he was studying the synthesis of series of *Amaryllidaceae* alkaloids.⁴¹ A tandem reaction was performed as pericyclic domino class for the formation of isooxazolidines **[45]** (Scheme 1.7).²⁹

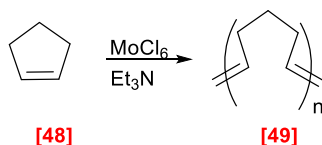


Scheme 1. 7. Formation of nitron promote domino reactions

The cascade reactions initiated 6-hydroxybuphandidrine **[44]** by heating to reflux in ethanol 95% in presence of hydroxylamine started the formation of the intermediate oxime **[45]**. Subsequent 1,2-proton shift obtained the N-H nitron generated *in situ* **[46]**, that acts as dipole promoted the cycloaddition.²⁹

1.2.4. Olefin Cross-Metathesis

“looked like somebody took a pair of scissors, opened up cyclopentene and neatly sewed it up again”, *Eleuterio*, 1956.⁴²



Scheme 1. 8 Eleuterio, 1956

Six decades ago, an industrial chemist first observed olefin metathesis Herbert S. Eleuterio, at DuPont's petrochemicals department. He performed a propylene-ethylene copolymer from a propylene feed passed over a molybdenum-on-aluminum catalyst. Analysis of the output gas found it was a mixture of propylene, ethylene, and 1-butene, then when he tried the experiment with cyclopentene he announced his view and observations Scheme 1.8.⁴³

Few years later a series of patents of novel ethylene polymerisation were reported by industrial chemists but no certain mechanism was postulated. In 1967, Nissim Calderon and others, figured out what was going on, and then the word Cross-Metathesis (CM) was first coined to name this metal-catalyzed redistribution of carbon-carbon double bonds, referring to a Greek word means change of position.⁴⁴ Then, Calderon proposed the first reasonable “Pairwise mechanism”, (Figure 1.10).

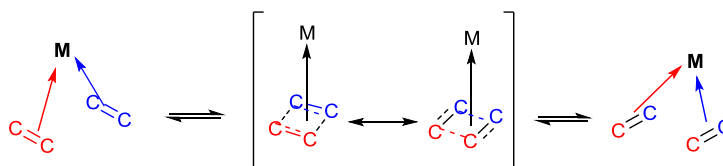
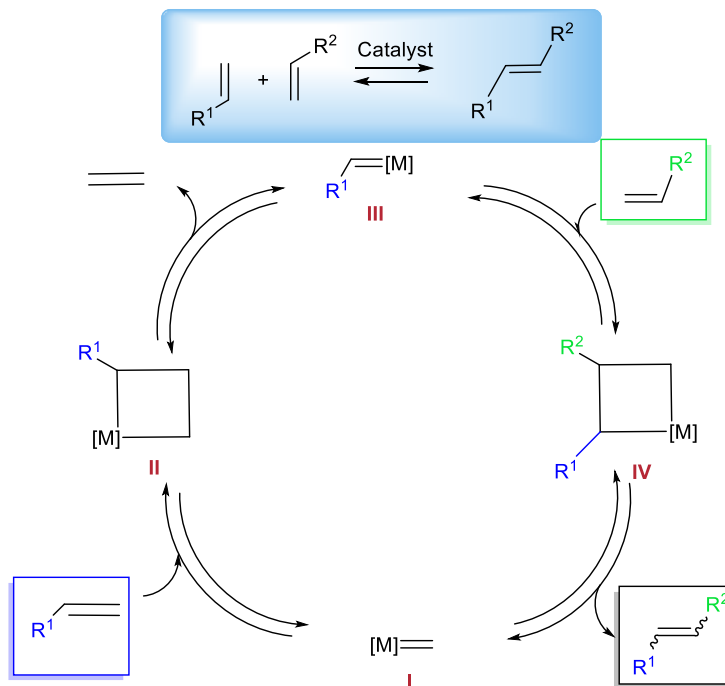


Figure 1. 10. Transalkylenation (pairwise) mechanism

Chauvin and Henrisson in 1970, suggested that the olefin-metathesis process first form the metal-carbene intermediate. Metallacyclobutane generated by the coordination between

Chapter 1. Introduction

the metal and the olefin(s), with series of [2+2] cycloadditions/ cycloreversions, mechanism (Scheme 1.9).⁴⁵



Scheme 1. 9. Chauvin mechanism of catalytic Olefin-Metathesis

The catalysts used in the early metathesis were of multicomponent constitutions that formed *in situ* within the reaction. They were poorly defined as homogeneous and heterogeneous catalysis.

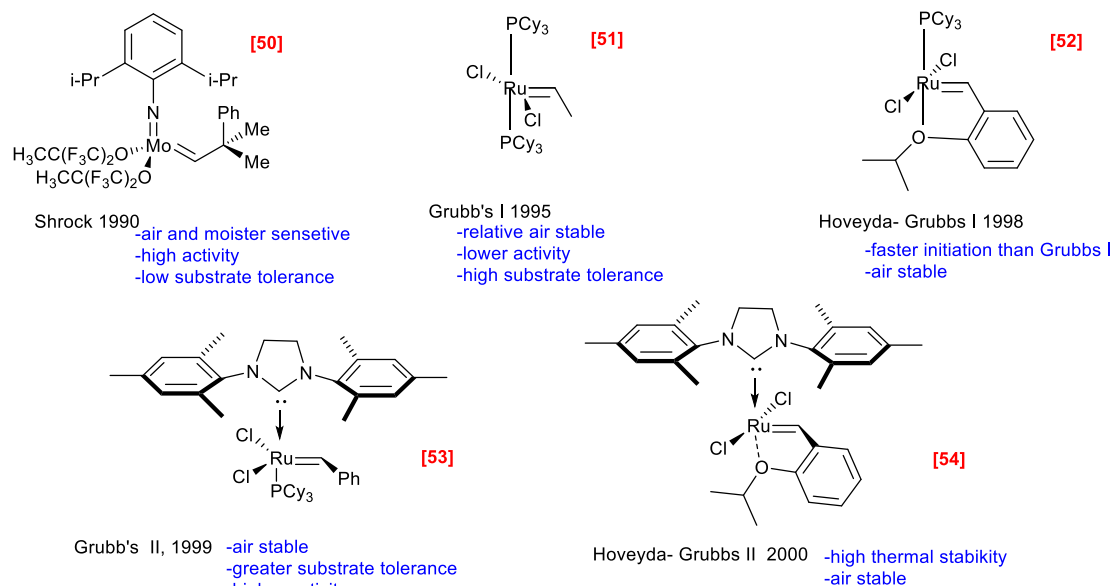
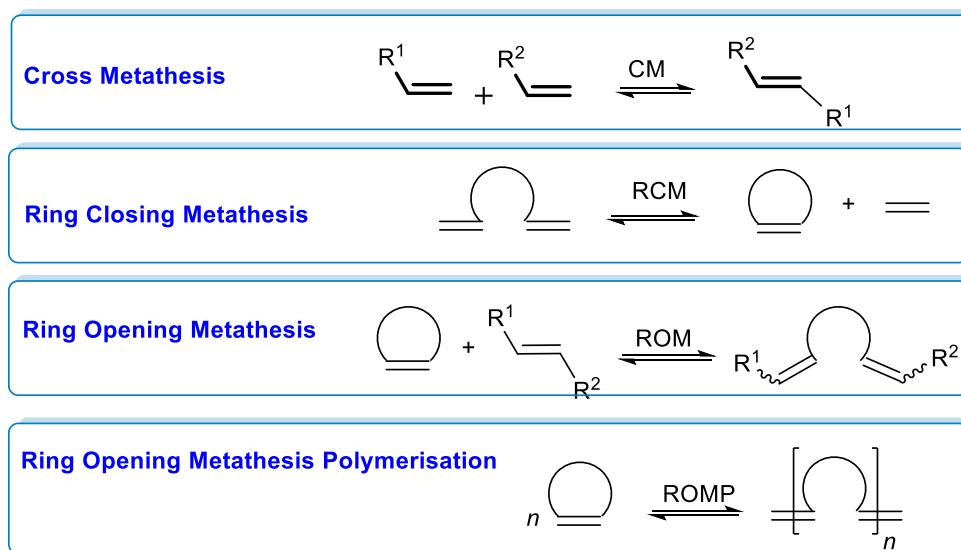


Figure 1. 11. The major Catalyst in CM ^{44,46}

The syntheses were complicated and difficult where the first generation of catalysts were sensitive to air and moisture, and therefore not long-lived.⁴⁷ Basically the catalyst consists of transition-metal halides and main-group metal alkyl co-catalysts and sometime a third component as an activator.^{44,48} The Grubbs catalysts are classified as of two generations and basically it has a ruthenium atom surrounded by five ligands, the type of ligands are what makes each different. When it is $L_2X_2Ru=CHR$ complexes, where L is a phosphine ligand, this is called Grubbs first generation catalysts, and $(L)(L')X_2Ru=CHR$ complexes, where L is a phosphine ligand and L' a saturated N-heterocyclic carbene or NHC ligand, were subsequently developed and are referred to as the second-generation Grubbs catalysts (Figure 1.11).^{46,49}

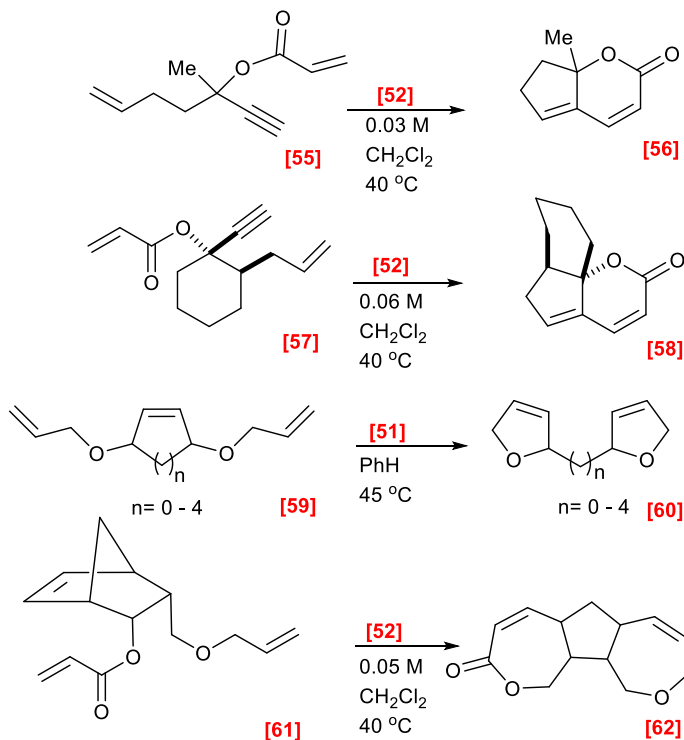
1.2.4.1. Olefin Cross Metathesis Types

There are few well-known types of olefin metathesis reaction. Cross-metathesis (CM), ringclosing metathesis (RCM), ring-opening metathesis (ROM), ring-opening cross metathesis (ROCM), and ring-opening metathesis polymerisation (ROMP) (Scheme 1.10).^{48,50}



Scheme 1. 10. Most Common Types of Olefin Metathesis Reactions

The Grubbs' group utilised the powerful RCM in tandem reactions extensively, using tethered alkynes to generate interesting heterocyclic compounds. For example, in (Scheme 1.11), acyclic ester **[55]** reacted in the presence of 5 mol% of Grubbs catalyst II **[52]** in CH_2Cl_2 at 40 °C, produced the bicyclic lactone **[55]** in 95%. Strained cycloalkenes **[59]** containing tethered olefins showed a tandem ring-opening metathesis/RCM cascade. First generation of Grubbs catalyst **[51]**, was used to transform a series of diallyloxy-cycloalkenes **[59]** into *bis*-furan derivatives **[60]** in acceptable yields (57 - 90%). Bicycloalkene **[61]** was converted into tricyclic **[62]** in 47% yield as well.^{29,51}



Scheme 1. 11. Grubbs Tandem RCM

The stereoselectivity of CM was investigated for ruthenium-based metathesis catalysts bearing *N*-heterocyclic carbene ligands, with the *E*-isomer being found to be favored in general, although, several olefin types showed low selectivity.⁵² Issues with cross-metathesis fall broadly into three factors; firstly, the activity of catalyst is not high enough to promote the reaction with strong enthalpic force as the ring-strain in ROMP or the entropic advantage of intramolecular reactions as in RCM, second, low product selectivity type of olefin, and third, poor selectivity in the newly formed olefin.⁴⁶

1.2.4.2 Enhancement of Olefin Cross- Metathesis

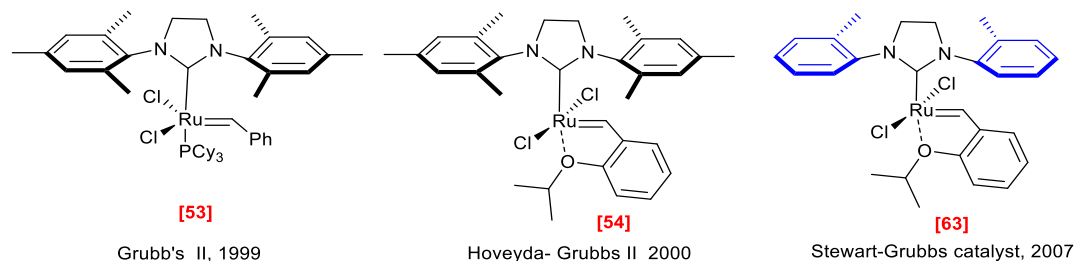
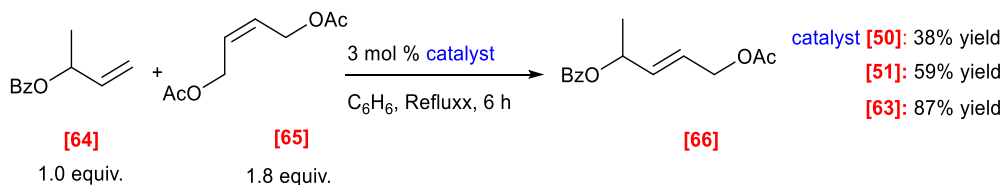


Figure 1. 2. Ruthenium-based olefin metathesis catalysts

The enhancement of cross-metathesis reactions was accomplished by Grubbs and Stewart.

⁵³ Improving the catalyst reactivity by reducing the steric hindrance around the NHC-ligand. *N*-tolyl catalyst **[63]** was a good replacement for *N*-mesityl **[54]** in the NHC-ligand (Figure 1.12).

In order to test the efficiency of the improved catalyst **[63]**, a cross-metathesis reaction was performed with but-3-en-2-yl benzoate **[64]** and *cis*-1,4-diacetoxy-2-butene **[65]** to form allylic benzoate **[66]** (Scheme 1.12). The CM proceeded using phosphine-containing catalyst **[53]** in a moderate to low yield, while both phosphine-free catalysts **[54]** and **[63]** exhibited increased efficiency in CM.



Scheme 1. 12. Catalyst effect on CM

Interestingly, more challenging substrates were investigated in cross metathesis reactions of tri substituted alcohol with olefin (Table 1.2) using the catalysts **[51]** and **[63]**. Again,

[63]catalyst outperformed [50] catalyst in all cases in excellent yields and high stereoselectivity were obtained.⁵³

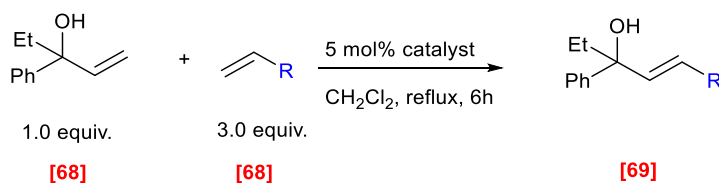
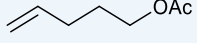
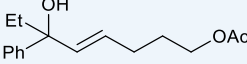
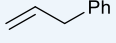
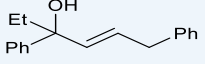
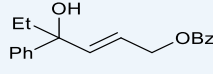
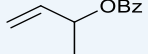
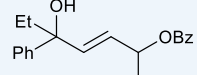


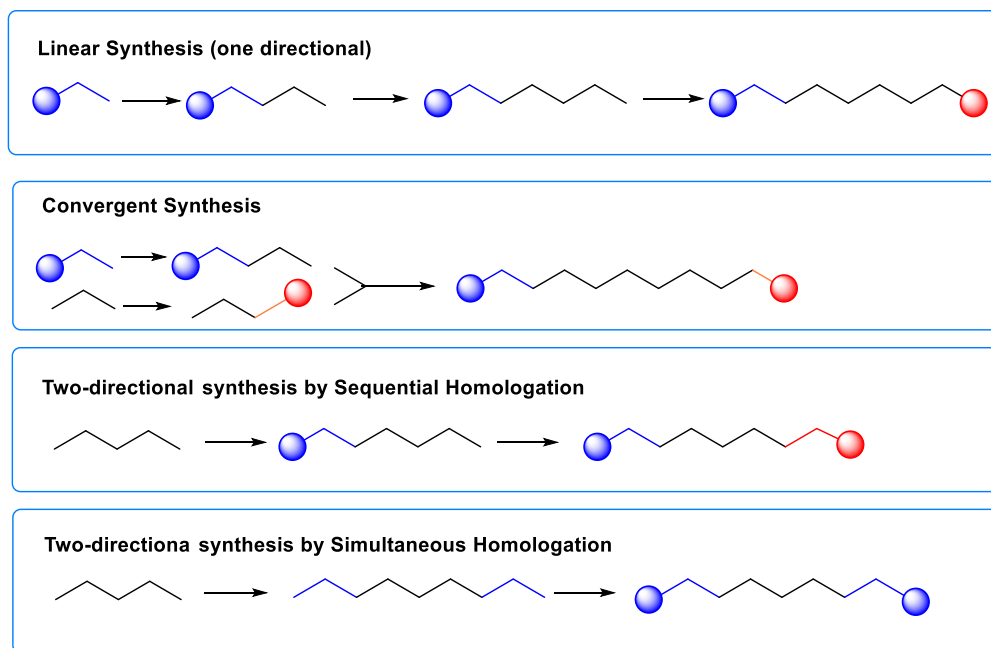
Table 1. 3. Challenging CM reactions of improved catalyst

Entry	Reactant	Product ^a	Yield (%) ^b	
			[50]	[59]
1	 [70]	 [71]	70	89
2	 [72]	 [73]	64	91
3	 [74]	 [75]	81	98
4 ^c	 [76]	 [77]	50	66

^a E/Z > 20:1 in all cases, ^b Isolated yield, ^c Isolated as 3:2 mixture of diastereomers.

1.2.5 Two-directional Organic Synthesis

In recent years, the view of the organic synthesis paradigm has been reformed; multistep synthesis with more than 20 steps should be avoided, modern chemists have to think not only about how to synthesise a compound but they have to consider how to deal carefully with waste chemicals and all the reaction implications as the time factor is greatly considered.³² Therefore, increase the process efficiency and diminish the unreasonable products and reaction steps.



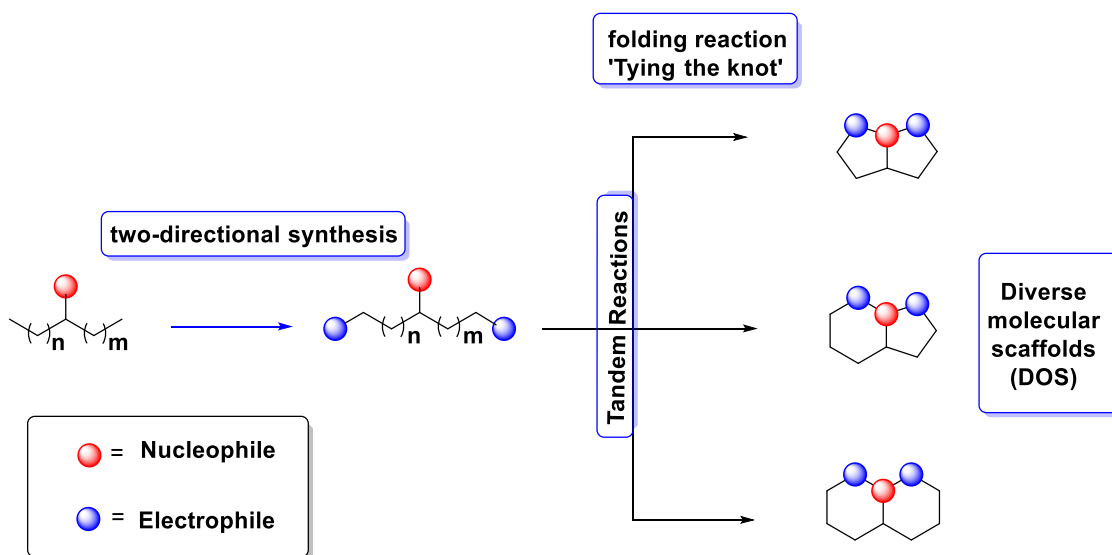
Scheme 1. 13. Four Classic Synthetic routes⁵⁴

One directional linear synthesis is the most common strategy used among the well-known four classified strategies in synthetic routes toward acyclic chain synthesis.

The convergent synthesis as well, are widely used in organic synthesis. The third strategy that comprises homologation of the chain on one side then the other is the two-directional in sequential homologation process, faces the exact challenges as the one-directional synthesis (Scheme 1.12).⁵⁴ Thus, the fourth strategy, two-directional synthesis by simultaneous homologation, received more attention. Moreover, the beauty of this synthesis is when applied to appropriate target molecules, this strategy offers a highly efficient route to stereo-chemically pure products in relatively few steps, compared with the other strategies.

1.3. The Art of Utilising Organic Synthetic Tools

The Stockman research group have pioneered a combination of three synthetic principles; 1) two-directional syntheses, 2) tandem reactions, and 3) DOS strategy.⁵⁵⁻⁵⁶ A part of this inspiring strategy is based on de-symmetrising, functionalising in two-directional synthesis then ‘tying the knot’ of a rope-like substrate *via* tandem reactions. This process affords a number of scaffolds which could be an intermediate for natural product synthesis or from the basis of lead-like compounds library in drug synthesis (Scheme 1.14).^{57,58}



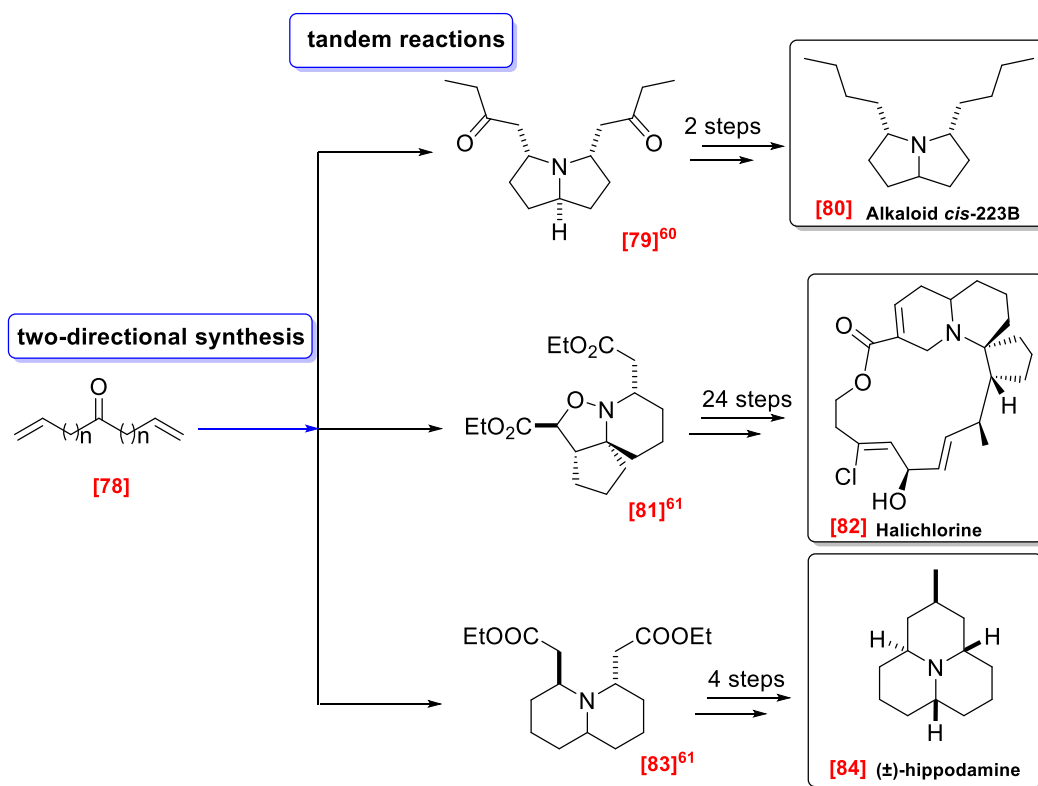
Scheme 1. 14. Stockman ‘tie the knot’ synthetic strategy

Utilising this efficient strategy, a number of natural products total and formal synthesis have been developed with concise routes.

Some representative fused five-membered cyclic compounds such as alkaloid *cis*-223B [80], and other fused six-membered heterocycles such as (±)-hippodamine [84],⁵⁹ and

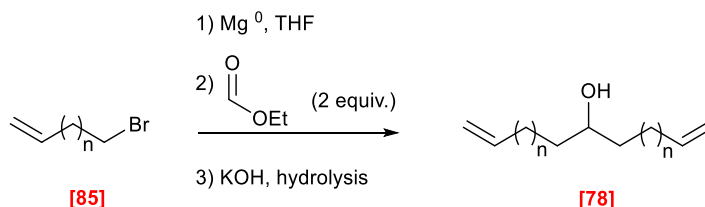
Chapter 1. Introduction

spirocyclic **[81]** was accomplished in forward synthesis of halichlorine **[82]** and pinnaic acid (Scheme 1.15).⁶⁰



Scheme 1. 15. Stockman's laboratory strategies.⁵⁹⁻⁶⁰

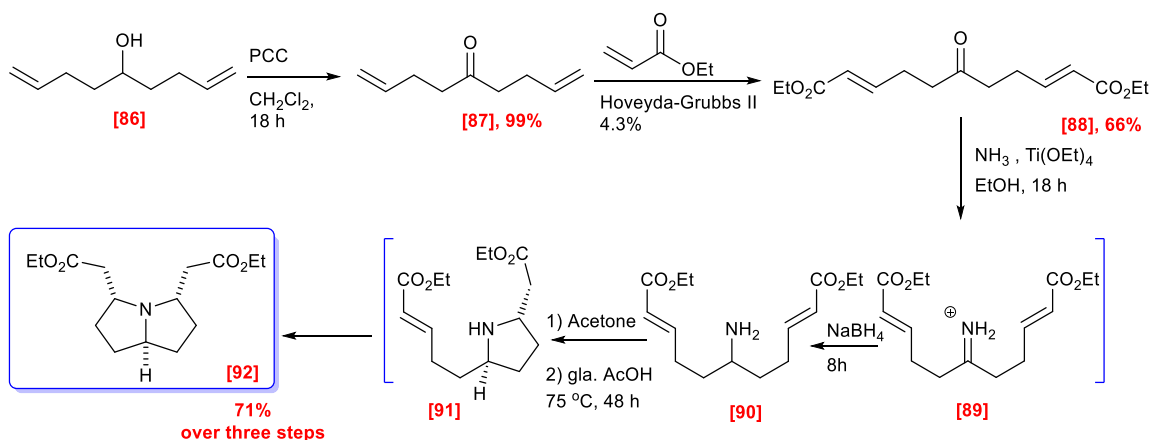
Noticeably, the majority of scaffolds produced by Stockman group start from a symmetrical dienealcohol **[78]**, (Scheme 1.15) which is prepared by using magnesium and alkenylhalide **[85]** to generate Grignard reagent which will react with ethyl formate in two-directional manner to produce the corresponding alcohol.⁶¹



Scheme 1. 16. Preparing the symmetrical substrate **[78]** ⁶¹

1.4. Combining two-directional and tandem reaction toward total synthesis of alkaloid *cis*-223B

Among a variety of approaches for this elegant strategy, the Stockman synthesis of alkaloid *cis*-223B **[80]** is one example of tandem CM/aza-Michael addition.

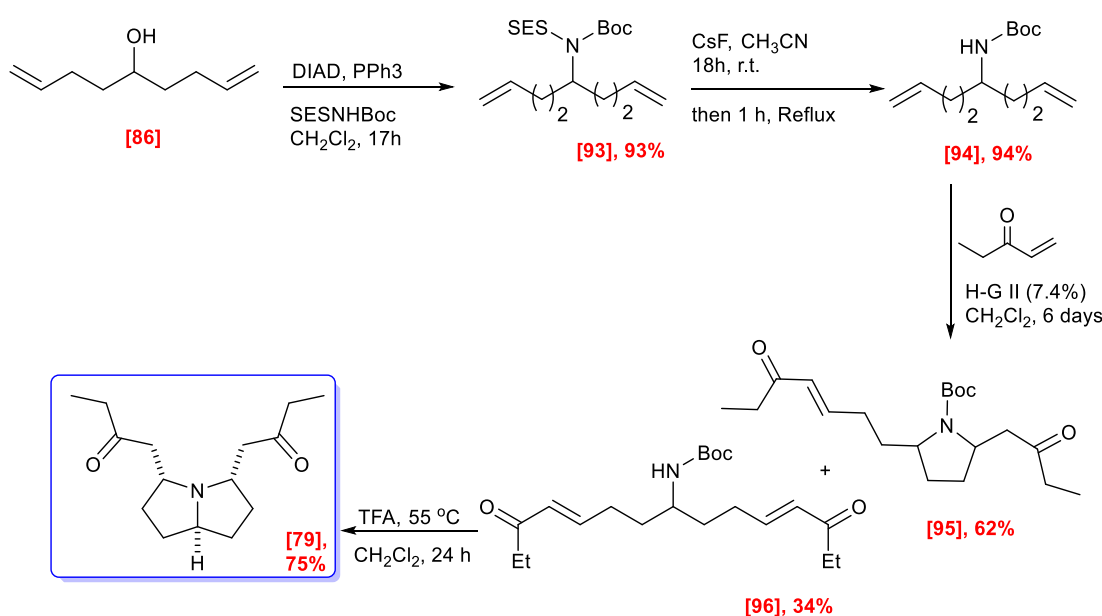


Scheme 1. 17. Two-directional synthesis of *cis*-fused pyrrolizidine **[92]**

Starting by the prepared alcohol **[86]** (having the desired number of carbons, $n=2$), which is then oxidised by appropriate oxidising agent; (PCC) to ketodiene **[87]** (Scheme 1.17). A double CM performed on ketodiene **[87]** using ethyl acrylate, using Hoveyda–Grubbs II generation **[54]** was used, trans–trans diester **[88]** was formed exclusively in 66% yield.

Chapter 1. Introduction

Then, the tandem reactions on the ketodiester **[88]** commencing with the reductive amination on carbonyl ketone with ammonia in EtOH, in presence of $\text{Ti}(\text{OEt})_4$ as a desiccant, followed by the addition of NaBH_4 . The addition of acetone, glacial acetic acid with heating promoted the double intramolecular Michael addition which produced the *cis*-fused pyrrolizidine **[92]** as a single diastereoisomer in an excellent 71% yield over three steps.⁶⁰

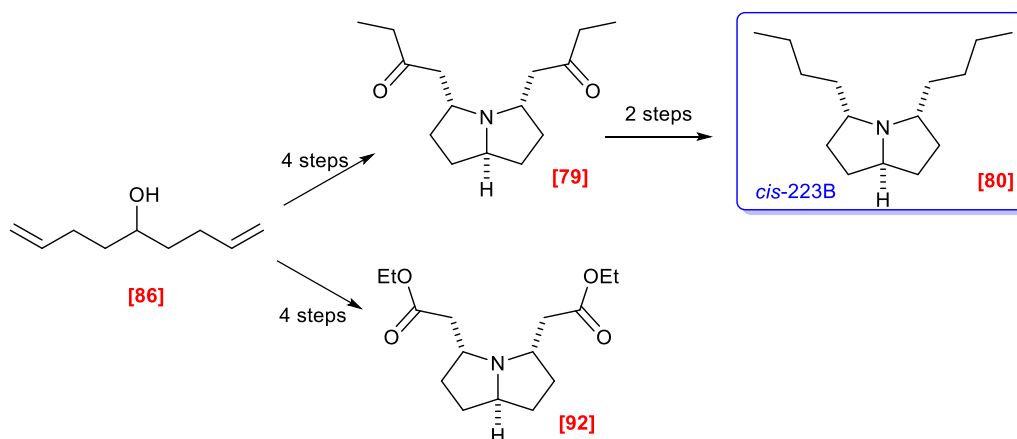


Scheme 1.18. Using diethylketone afforded the efficient intermediate [79]

A slightly different strategy was applied toward the enhanced synthesis of Alkaloid *cis*-223B **[80]** diethyl ketone substrate **[79]** (Scheme 1.15). Starting by protecting the alcohol **[86]**, (Scheme 1.18), using a Mitsunobu reaction on alcohol **[86]**, then deprotection by CsF followed by double CM in two-direction of aminodiene **[90]** produced some of amino protected diketone **[79]** and cyclised pyrrolizidine **[91]** as a mixture, which in a one pot tandem deprotection/cyclisation reaction followed by Michael addition, afforded one diastereomer of pyrrolizidine **[79]**.⁶⁰

Chapter 1. Introduction

Thus, applying a two-directional strategy afforded diverse *cis*-fused pyrrolizidine using diethylketone moiety in a similar successful tandem cyclisation lead to compounds **[79]** and **[92]**, which were considered as a versatile intermediate toward the synthesis of the alkaloid *cis*-223B (Scheme 1.19).⁶⁰



Scheme 1. 19. Synthesis of *cis*-223B, Stockman, 2009

Moreover, in 2013, Alexander Barthleme in the Stockman laboratory developed an interesting concise route toward the synthesis of alkaloid *cis*-223B **[80]**, and (±)-xenovenine **[97]**, (Figure 1.11).⁶²

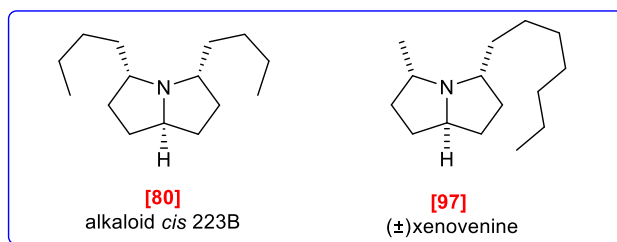
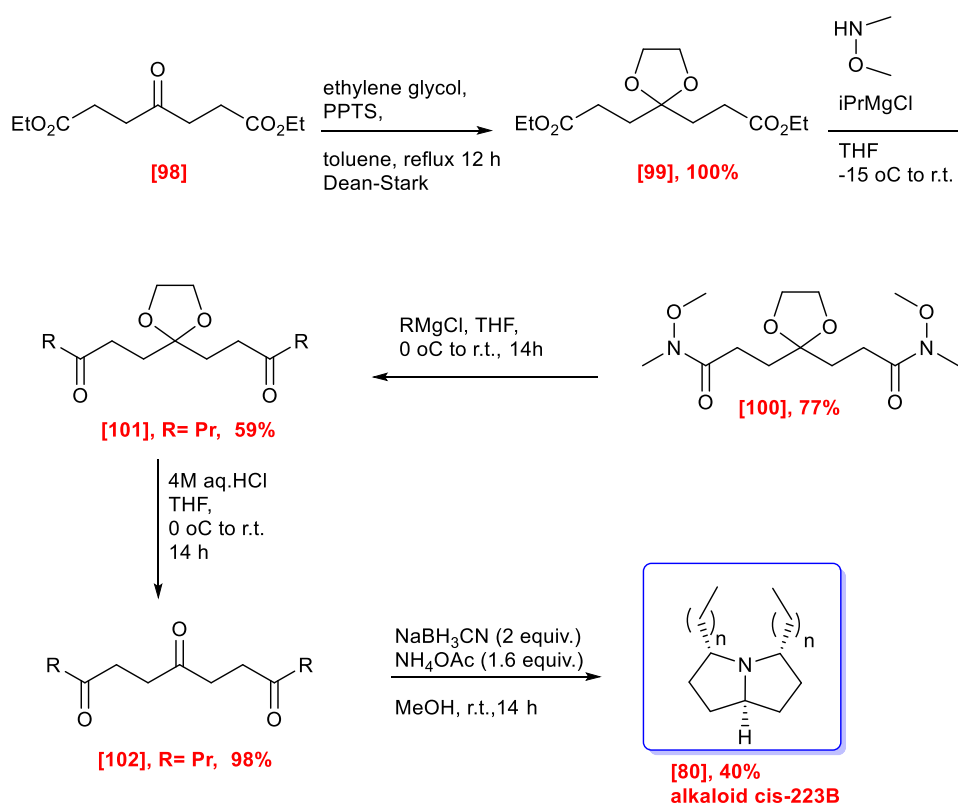


Figure 1. 5 Structures of alkaloid *cis*-223B and xenovenine.⁶²

Chapter 1. Introduction

Total synthesis of alkaloid *cis*-223B with central planar symmetry provides as a meso compound containing two stereogenic centres. The process started by protecting the commercially available diethyl 4-oxopimelate **[98]** as cyclic acetal, the diester **[99]** was then converted to Weinreb diamide in a two-directional reaction **[100]**, (Scheme 1.20).



Scheme 1. 20. Short Chain of total Synthesis of alkaloid *cis*-223B⁶²

A second two-directional reaction was applied using Grignard addition, followed by deprotection and finally the short synthesis was completed by tandem reductive amination using NaBH₃CN in alcoholic solvent to afford the alkaloid *cis*-223B **[80]** in moderately good yield.⁶² The challenge was the synthesis of xenovenine **[97]** (Figure 1.11), whereas a

desymmetrisation was achieved by the sequential addition of different Grignard reagents in the formation of [98] in (Scheme 1.20).

1.5. Combining two-directional synthesis and tandem reactions towards the synthesis of the spirocyclic core of halichlorine/ pinnaic acids

Pinnaic acid, tauopinnaic and halichlorine are closely related structurally (Figure 1.12). In 1986, two Japanese chemists Hirata and Uemura isolated a naturally- occurring compound from the marine sponge *Halichondria okadai* Kadota.⁶³ Attention was immediately drawn when it was found to be extremely potent at killing certain types of cancer cells. In small-scale tests, selective inhibition of vascular cell adhesion molecule-1 (VCAM-1) induction with an (IC₅₀ of 7.0 µg/mL) was discovered. Producing this compound was very hard, rather it was difficult to isolate halichlorine in sufficient amount or due to its complex structure.⁶³ This group of natural products share in common a 6-azaspiro[4.5]decane ring system.

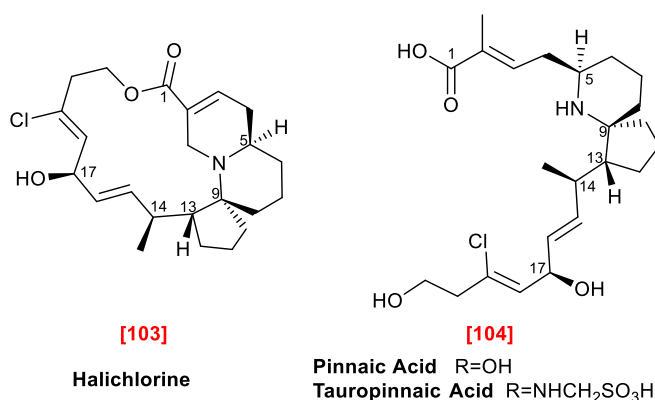
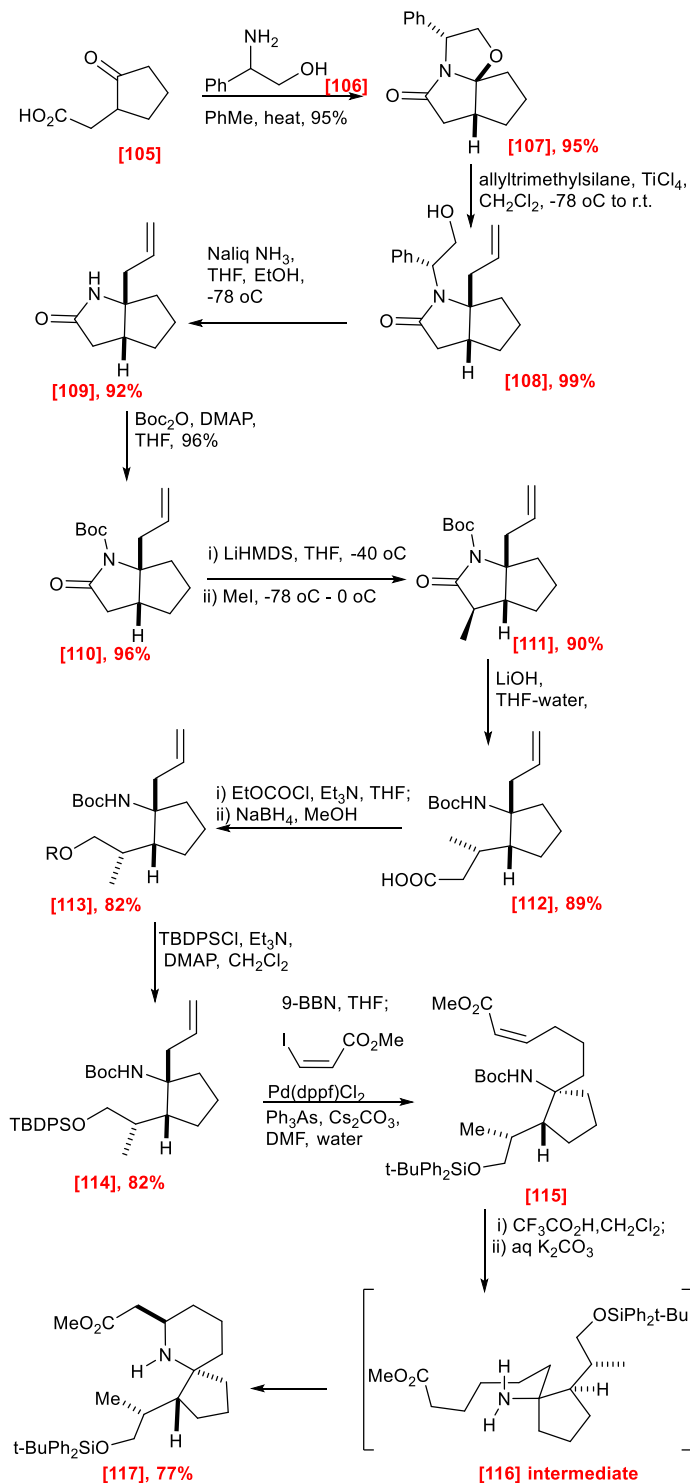


Figure 1. 6. Halichlorine and Pinnaic acids structures

1.5.1. The First Total Synthesis of (+)-Halichlorine

The first asymmetric synthesis of the spiroquinazoline core was reported by Danishefsky's laboratory (2001).⁶⁴ The starting point was a "Meyers lactam" **[106]** which was prepared by addition of a γ -keto acid **[104]** to D-(-)-phenylglycinol **[105]**, (Scheme 1.19).⁶⁴ The prepared lactam was prepared from racemic carboxylic acid and D-(-)-phenylglycinol. The lactam reacted with an excess of allyltrimethylsilane in the presence of Lewis acid to form bicyclolactam **[108]** in 99% yield, the high efficiency probably due to the strain in the bicyclic *N*-acyliminium ion intermediate. This was followed by reductive debenzylation, and amine-protection using the Boc protecting group **[110]**. The bicyclic *N*-Boc lactam was stereoselectively methylated to afford compound **[111]**, which was then hydrolysed to the enantiomerically pure δ -amino acid **[112]**. Reduction of the carboxylic acid *via* a mixed anhydride *in situ* followed by silylation yielded amine **[113]**, the resulting primary alcohol was then protected as tert-butyl-diphenylsilyl derivative. Then after, the allylic side chain was extended by hydroboration and Suzuki cross-coupling of the resulting borane with iodide to afford α,β -unsaturated ester **[114]**. Carbamate cleavage facilitated spontaneous Michael addition affording spirocycle **[115]** with the desired configuration at *C*₅.

Thus, three of the stereogenic centres were created in a fashion conducive to reaching halichlorine's main spirocyclic core in 14 steps (Scheme 1.21).⁶⁴

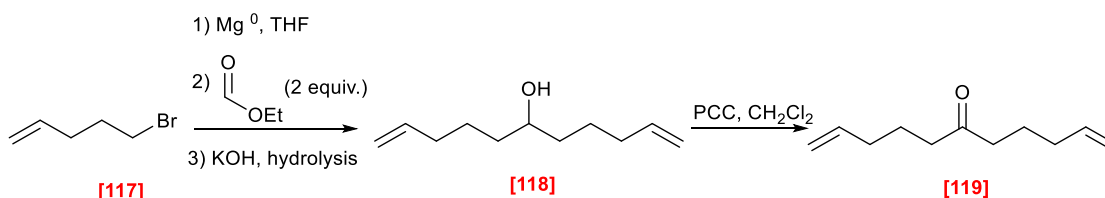


Scheme 1. 21. Total synthesis of the spiro core of halichlorine⁶⁴

1.5.2 Stockman's concise approach to the spirocyclic core of (±)-halichlorine and pinnaic acid

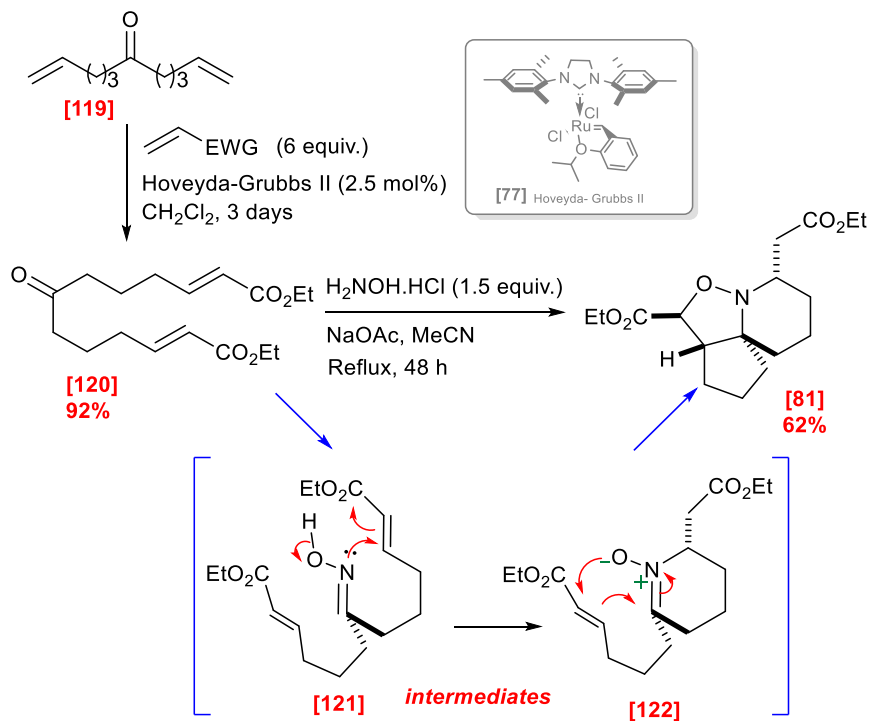
Stockman led a significant approach to complex molecular architectures utilising two-directional synthesis, applying cross-metathesis to the symmetrical linear ketodiene. Treatment of these substrate molecules with a range of nucleophiles through tandem reactions generates diastereoselective processes, to yield polycyclic structures with multiple stereocentres in a single reaction.⁶⁵

In 2004, Stockman and co-workers reported a concise approach to a common intermediate azaspirocyclic core structure of halichlorine and pinnaic acid, applying his strategy of combining two-directional with tandem reactions.⁶⁶



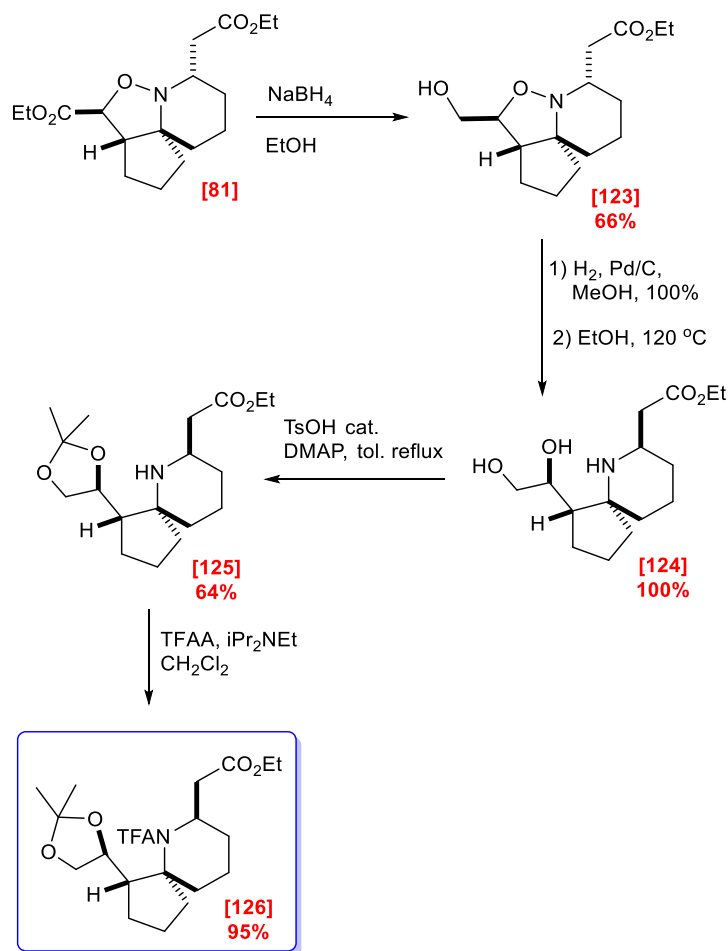
Scheme 1. 22. Preparation of symmetrical ketodiene [119] most of Stockman synthesis use as starting material

The starting material most often used is the symmetrical precursor [119], (Scheme 1.22) prepared initially by Grignard reaction. Then after oxidation to ketodiene, its then ready to be functionalised from both sides in a two-directional type synthesis.



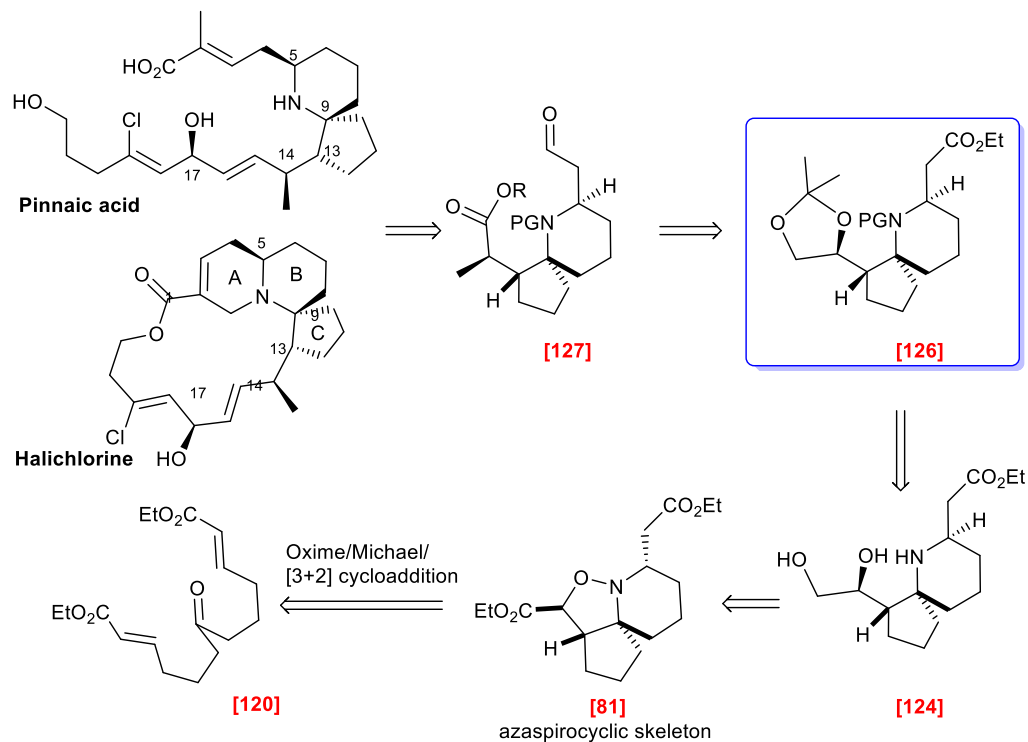
Scheme 1. 23. Tandem cyclisation mechanism

The synthetic route was initially started from ketodiene **[110]** (Scheme 1.23), in two directional homologation afforded symmetrical ketone **[120]**. Then treated with hydroxylamine hydrochloride, so was transformed into the [6,5,5]tricyclic **[81]** in 62% yield, via a tandem oxime formation/Michael addition/1,4-prototopic shift/[3+2]-cycloaddition. Significantly, this tandem one-pot reaction increases the complexity of the molecule, creating three ring systems and four stereogenic centres.⁶⁶



Scheme 1.24. Conversion of diester **[81]** into protected azaspirocycle **[126]**⁶⁶

Retrosynthetic analysis of halichlorine and pinnaic acid in (Scheme 1.24) showed that both marine alkaloids should be approachable through a common intermediate **[126]**, which could be prepared in a very good yield from the precursor **[81]** through a series of functional group manipulations.



Scheme 1. 25. A reasonable retrosynthetic analysis of halichlorine and pinnaic acid⁶⁶

Scheme 1.25, shows the retrosynthesis steps toward the total of halichlorine/ pinnaic acid. An attempt was published by Gignoux a Stockman's group member in 2012, exploiting the functionalised precursor [126] toward generating more advanced stages in the synthesis.⁶⁷

1.5.3 Combining two-directional and tandem reaction toward synthesis of (±)-hippodamine and (±)-epi-hippodamine

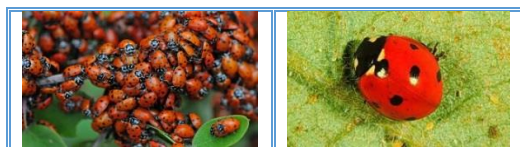


Figure 1. 7. Mass of convergent lady beetles *Hippodamia convergens*⁶⁸

Hippodamine is a naturally occurring alkaloid isolated from a ladybird beetle *Hippodamia convergens* by Tursch and co-workers in 1972.⁶⁹ Adult ladybirds are able to reflex-bleed from the leg joints when needed. The blood has a repulsive smell and contains

Chapter 1. Introduction

various alkaloid toxins such as hippodamine.⁶⁸ Few derivatives of coccinellid alkaloids (Figure 1.14) have shown some potent biological effects as receptor antagonists of the neurotransmitter serotonin, which makes these compounds promising for the treatment of a number of gastrointestinal and brain disorders. One of the most interesting properties is the usage to prevent behavioural consequences of the withdrawal of drugs such as nicotine.⁷⁰

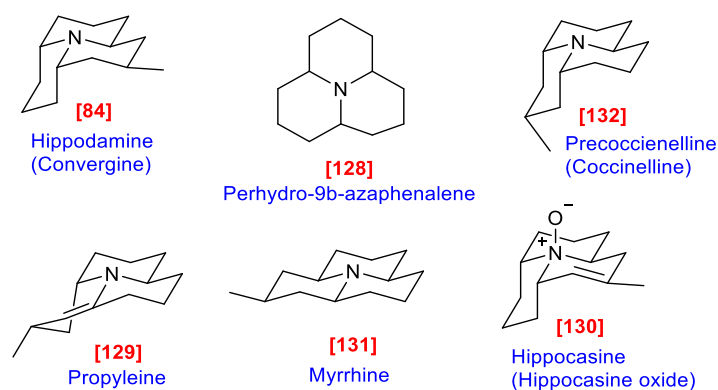


Figure 1. 8. Structures of Coccinellid Alkaloids (*N*-Oxides and their names in brackets).

Stockman group (2002) reported a total synthesis of the tricyclic skeleton of Hippodamine.⁷¹ The Azaphenalene alkaloids core was synthesized with controlled stereochemistry in a few steps. The challenge was to establish the axial or equatorial C2 methyl substituents of the title compounds (Figure 1.15).⁵⁸

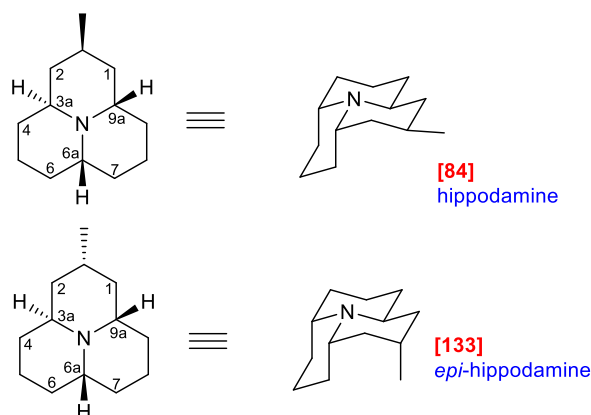
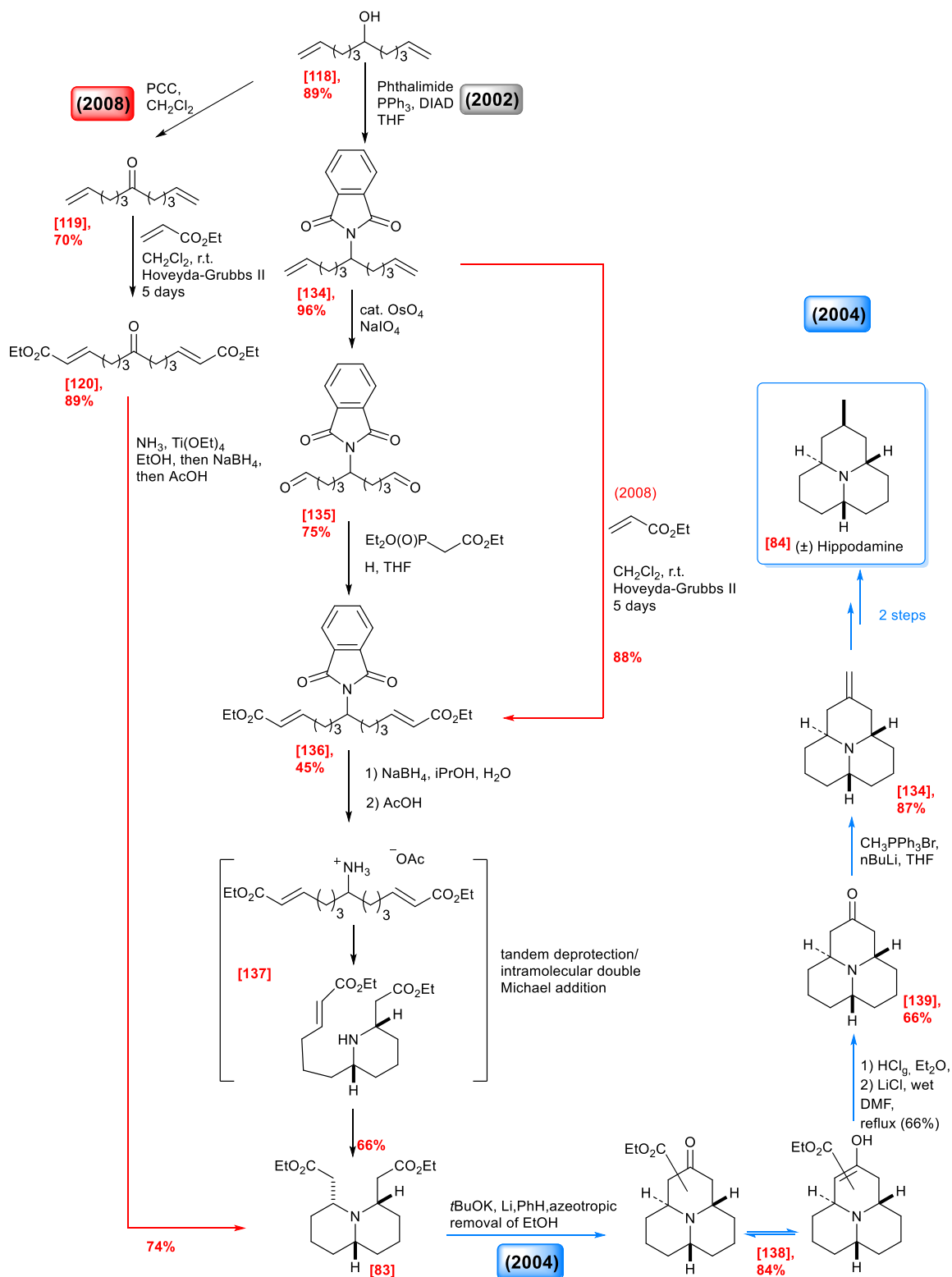


Figure 1. 9. Structures of hippodamine [84] and *epi*-hippodamine [133]

Over a few publications, the Stockman's group revealed an interesting synthesis toward the total synthesis of hippodamine (Scheme 1.26).^{59,71,72} The first route used a Horner-Wadsworth-Emmons reaction for double chain extension, and gave a good yield of the doubly homologated compound **[136]**. Following Ganem's protocol for deprotection, the phthalimide group was removed by selective hydride reduction, then an addition of acetic acid to the reaction solution promotes lactonisation and liberating the amine hydroacetate **[137]** in cascade reactions afforded the quinolizidine skeleton **[83]**.⁷¹ In 2004 Stockman group continued on the same route, and disclosed further steps, completing the synthesis of (±)-hippodamine. The desired cyclisation produced when the quinolizidine **[83]** was treated with *t*-BuOK in refluxing benzene under continuous azeotropic condition to continuous removal of EtOH using a Dean–Stark trap with lithium in the trap to remove EtOH, a mixture of β -ketoester **[137]** and its corresponding enol form was obtained. De-ethoxycarbonylation of all both possible isomers, would lead to the ketone **[138]** when the mixture was directly subjected to LiCl in wet refluxing DMF, after passing HCl_(g) in Et₂O prior to the treatment with LiCl in wet refluxing DMF. Thus, minimise the recovered enol form and method gave the desired ketone **[139]** in 66% yield.



Scheme 1. 26. Stockman routes toward total synthesis of hippodamine 70,71,72

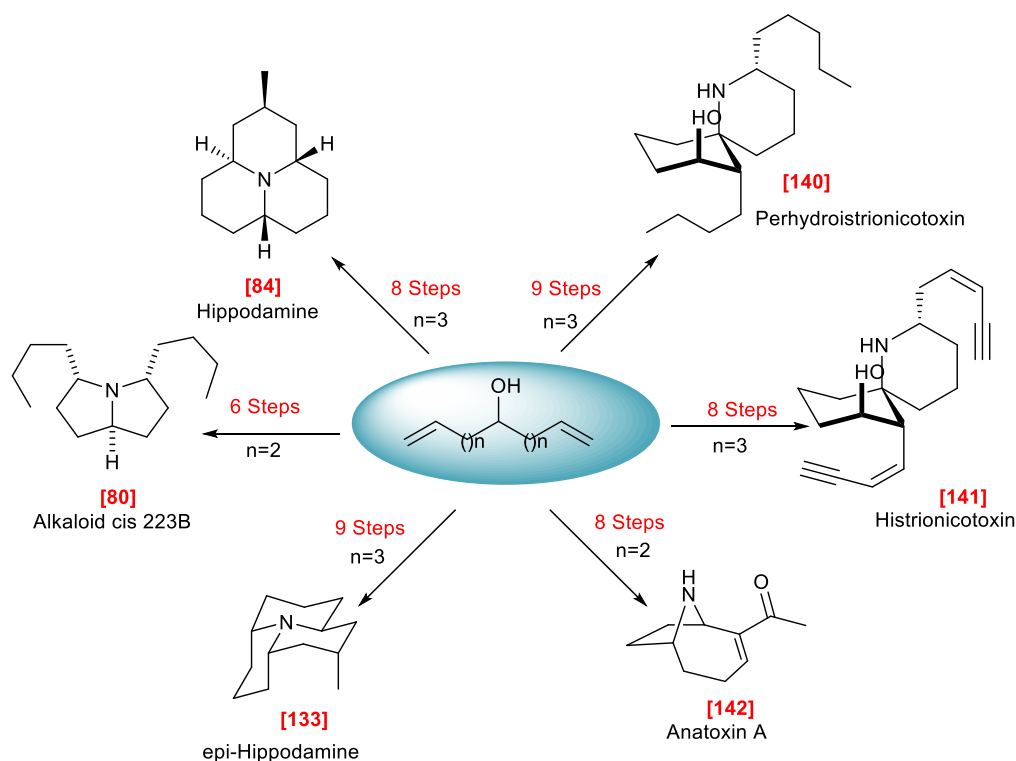
Chapter 1. Introduction

Wittig olefination performed on the ketone **[138]** using methyltriphenylphosphonium bromide in THF and nBuLi, after a short reflux of the reaction mixture, gave the desired product **[139]** in a good yield. Hydrogenation of the camphor sulfonic acid salt then provided afforded the racemic mixture of ($\pm$)-hippodamine **[84]**.⁵⁹

A further refinement of this synthesis utilising the two-directional synthesis employing CM and tandem reactions strategy, was published in 2008. Using ammonia in the presence of Lewis acid Ti(OEt)₄, the quinolizidine **[83]** was formed in dramatically shorter route *via* tandem reductive amination/double intramolecular Michael addition.⁷²

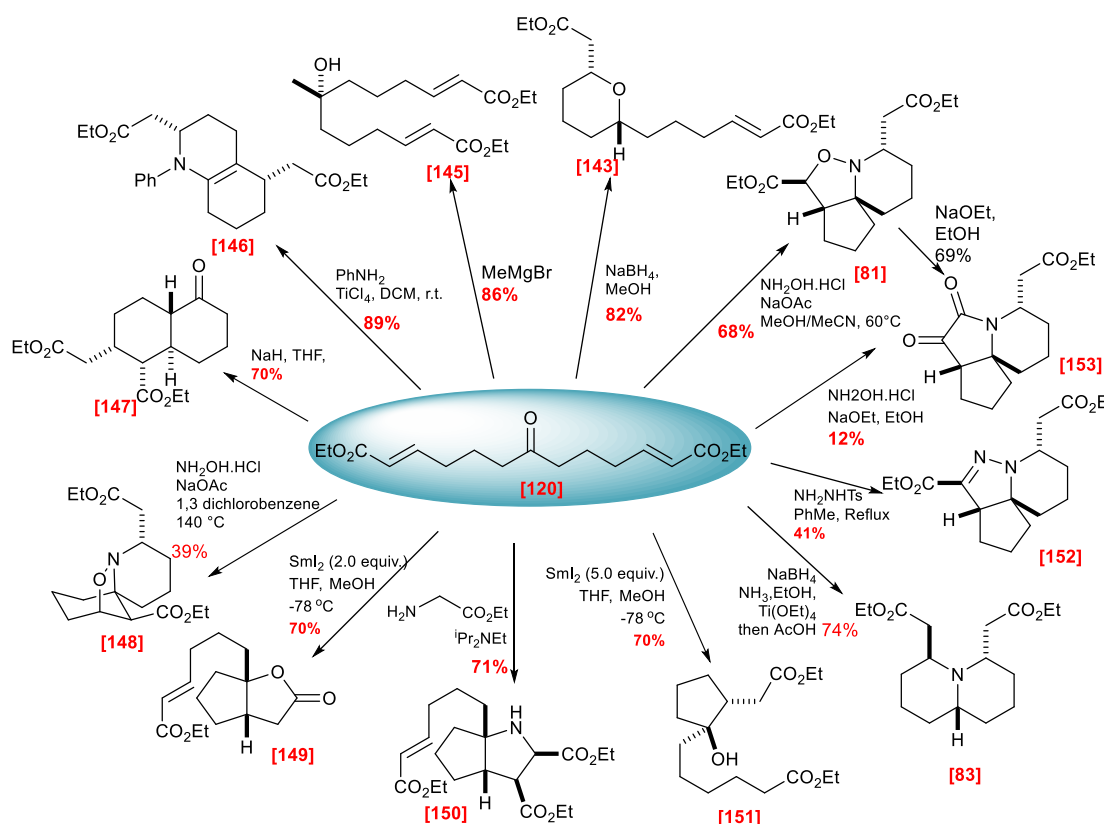
1.5.4 Stockman Strategy combining Two-directional and Tandem Reactions

The Stockman group have exploited the use of two-directional synthetic methodology and tandem cascade reactions as a powerful strategy to facilitate the synthesis of various natural products. All of these published natural product syntheses originate from a common symmetrical starting material usually it is the dieneol with various number of carbon on both sides (Scheme 1.27).



Scheme 1.27. Previously published natural products synthesise in the Stockman group, using two-directional synthesis and tandem cascade reactions ^{55,62,61,72}

Two-directional cross-metathesis established within the group has enabled ketodiester to be synthesised in high yields in just 3 steps. Since then a diverse set of compounds have been generated using this ketone-based trifunctional tandem reaction precursor. Scheme 1.27 outlines a range of one-pot tandem reactions that have already been investigated within the group, which convert the central ketone into a variety of reactive species *via* tandem reductive amination, aza-Michael addition, [3+2] cycloaddition, Mannich reaction. These can then undergo reactions at both electron deficient alkenes giving rise to a diverse range of complex polycyclic skeletons in a single step.

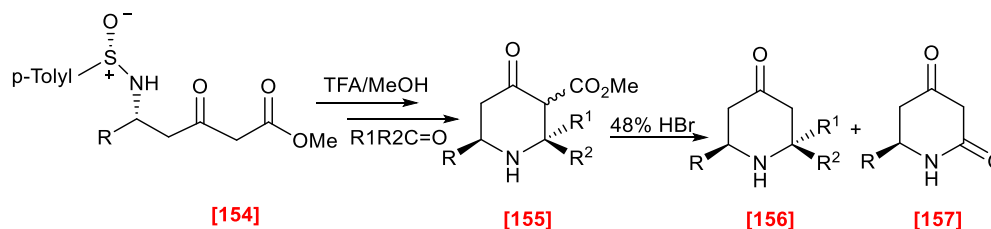


Scheme 1. 28. One-pot tandem reactions from ketodiester [88] in Stockman group

As one can tie a number of different knots in a piece of rope to give a variety of different three-dimensional knots/shapes, a range of tandem or cascade reactions can be used to “tie” the linear “rope-like” molecules into a multitude molecular architectures, laden with stereogenic centres, which are suitable for synthesising various natural products, natural product-like compounds, drug-like compounds, and many other complicated structures.⁵⁵

1.5.5 Utilising chiral Sulfinimines towards Synthesis of six-membered β -keto lactam

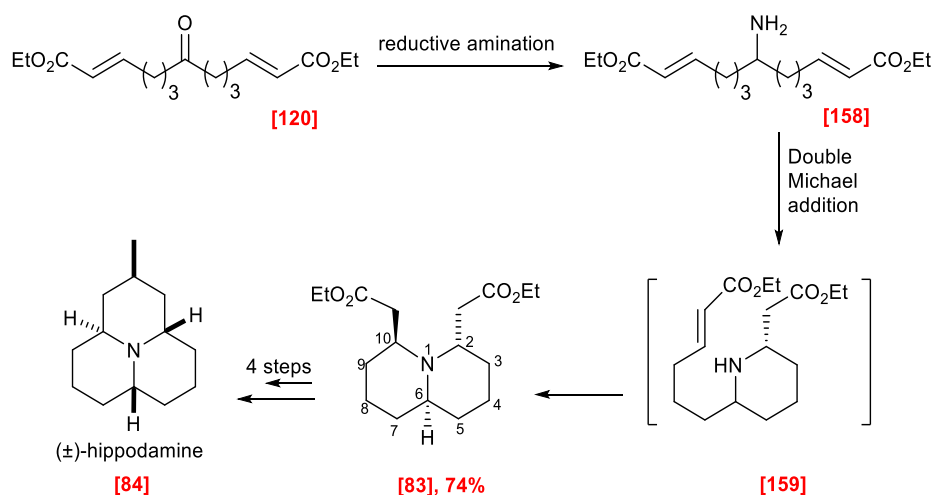
Alkaloids containing substituted piperidines are widely found in nature and exhibit significant biological properties. Accordingly, numerous methods have been explored for their asymmetric synthesis. However, these procedures frequently require lengthy synthetic operations and extensive protection/deprotection chemistry.⁷³ We aimed at developing new protocols that avoid these problems; we introduced *N*-sulfinyl δ -amino β -keto esters, as new polyfunctionalised chiral building block. Franklin Davis and co-workers in 2001, reported a similar intramolecular synthesis protocol using Mannich reaction, but, he used an additional ketone (Scheme 1.29).^{73,74}



Scheme 1. 29. Syntheses of Piperidines⁷³

It was thought that keto piperidinone scaffolds **[157]** could be valuable for library synthesis or in the synthesis of complex natural products or for its biological activity. In this thesis we tried to envisage a simple 3-step route to those versatile intermediates through a key dianion-addition to sulfinimines followed by acidic promoted deprotection/ ring closure.

1.5.6 Use of Sulfinimines towards Stereoselective Synthesis of (±)hippodamine



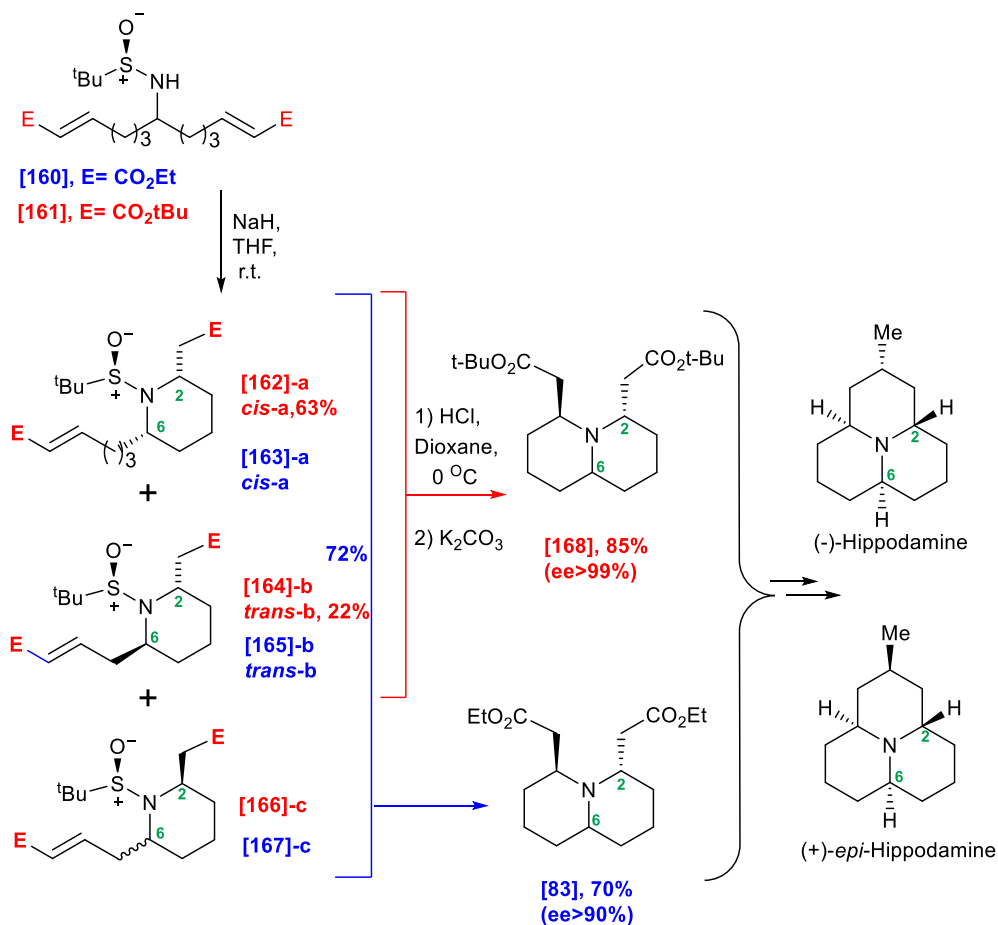
Scheme 1. 30. Stockman Quinolizidine Synthesis⁷¹

The Stockman group have published a synthetic route to (±)-hippodamine that involved the reaction of ketodiester **[88]**⁷¹ in a reductive amination using a solution of ammonia in methanol, to form primary amine intermediate **[158]**. This is followed by a tandem Michael addition to form the non-isolated intermediate piperidine **[159]** which in turn undergoes a second Michael addition to form the quinolizidine **[83]**. This tandem process generates 6 new bonds having 2 stereogenic centres and two ring-system, giving a single diastereomer in a single operational step (Scheme 1.30).⁷²

Recently, a closely related paper reported, wisely took advantage of the formation of a sulfinimine, and in a tandem fashion, intramolecular aza-Michael reactions, and Mannich reactions of very closely related molecules (Scheme 1.31).⁷⁵ In this case, after the isolation

Chapter 1. Introduction

of the sulfinyl amine, treatment under basic conditions allowed further transformations involving intramolecular alkylations.



Scheme 1. 31. Overall Process toward total synthesis of Hippodamine⁷⁵

1.6. Aim of work

The work described in this thesis sought to investigate and explore a range of two-directional synthesis and tandem reactions. Exploiting these reactions using different electron withdrawing groups toward rapid synthesis via tandem reactions.

We expected a novel range of complicated heterocyclic scaffolds having three dimensional properties; potential to be biologically active compounds, and potentially useful for the synthesis of alkaloid natural products and scaffolds for early stages drug chemistry.

Few sulfinimines were investigated as well, toward synthesis of some heterocyclic compounds, utilising their ability to act as intramolecular nucleophile source.

1.7. Objectives

In this thesis, and toward the synthesis of fused-, hetero-, or spiro-cyclic compounds, we utilised the organic synthesis tools such as cross-metathesis, two-directional synthesis, and tandem reaction cyclisation. Tandem reactions, in some cases were one-pot reaction as domino and in some others were consecutive reactions using Michael additions, Mannich, [3+2] cycloaddition. Trying the efficient contribution of these tools/strategies together toward rapid access to unique scaffolds, building more than three bonds at one reaction. Generating collection of novel molecules with diverse stereogenic centres render them to have a biological activity or to build a considerable library of molecules.

Target oriented synthesis was applied as well toward synthesise of some novel biologically active compounds, utilising a tandem nitron formation/intramolecular Michael addition and consecutive [3+2] nitron cycloaddition reaction to generate a tricyclic isoxazolidinone. Further functionalization of this synthetic compound from three points of diversity is detailed.

CHAPTER 2

RESULTS & DISCUSSION

2. Results and Discussion

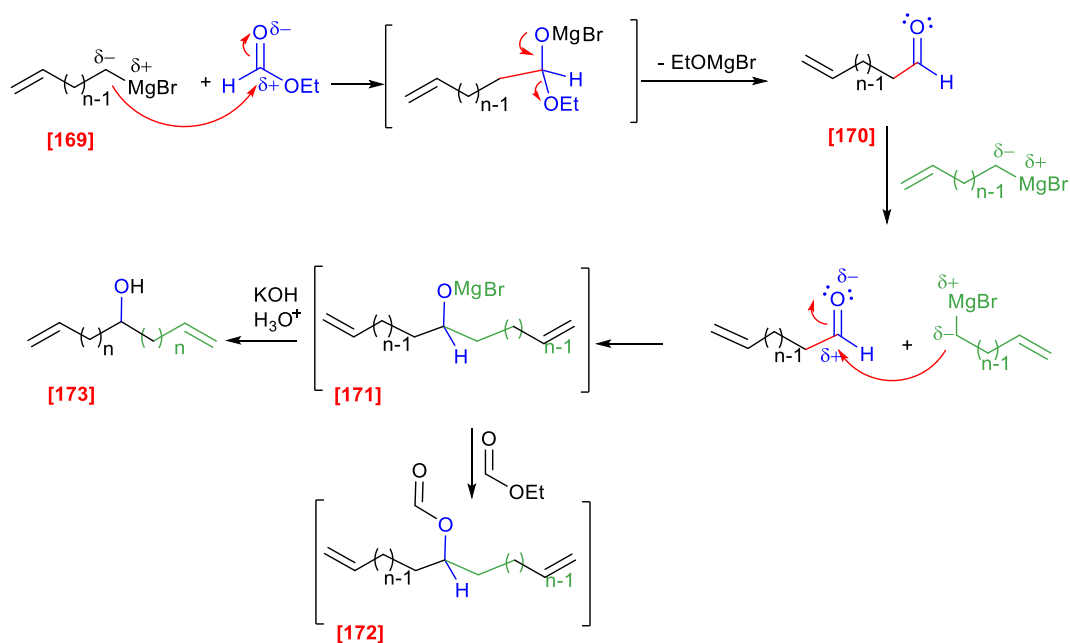
2.1 Diversity Oriented Synthesis (DOS)

2.1.1 Outline of Our Synthetic Strategy

Our aim is to develop some new sp^3 -rich scaffolds having three-dimensional properties and a level of complexity measured by F_{sp^3} (where $F_{sp^3} = (\text{number of } sp^3 \text{ hybridised carbons} / \text{total carbon count})$). The second feature in these compounds are having several chiral centres. These properties render them to success in the drug discovery.⁷⁶ Furthermore, synthesis of some scaffolds inspired by natural products, which have a large structural diversity will be performed.⁵⁵ Some of similar scaffolds (Scheme 1.28) were synthesised in our group earlier found to have an interesting biological activity.⁷⁷

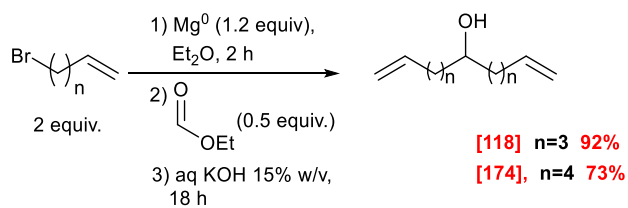
Our initial goal was to synthesise the symmetrical alcohol **[86]** in (Scheme 1.22) using the sequential two-directional synthesis previously developed in the Stockman laboratory.⁷¹ First, the derived Grignard reagent **[169]** was generated when magnesium metal reacted with bromoalkenes in diethyl ether then nucleophilic attack on ethyl ester was performed.⁷⁸

Grignard reagent **[169]** can nucleophilically attack the carbonyl carbon of ethyl formate to generate the intermediate aldehyde **[170]** (Scheme 2.1), which is more reactive than the ethyl ester, thus the sequential reaction happens more rapid than the first alkenyl magnesium bromide. The dieneol **[172]** was isolated *via* simple treatment by KOH solution, which was added to remove a small amount of the formate ester **[171]**, which formed by the slow reaction of **[170]** with excess ethyl formate.⁷⁹



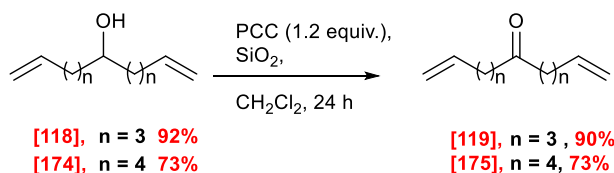
Scheme 2. 1. Two-directional synthesis to prepare our starting material

Two types of alkenylhalides 5-bromopentene and 6-bromohexene were used to produce two different symmetrical alcohols [118] and [174] respectively (Scheme 2.2).



Scheme 2. 2. Synthesis of the symmetric ketone

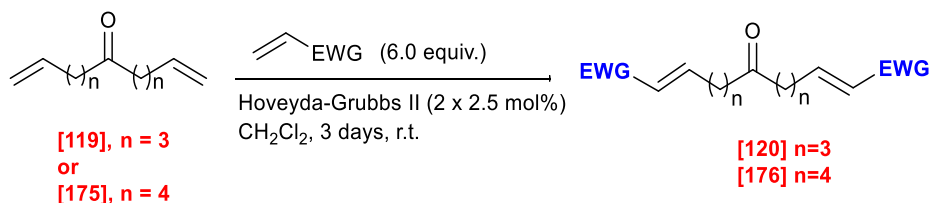
Oxidation of the prepared alcohols [118] and [174], to the respective ketones was carried out using pyridinium chlorochromate (PCC) oxidation. Silica gel was added to facilitate removal of polymeric reduced chromium by-products (Scheme 2.3).⁸⁰



Scheme 2. 3. Synthesis of the symmetric ketone

2.1.2. Cross-Metathesis in Two-directional Synthesis

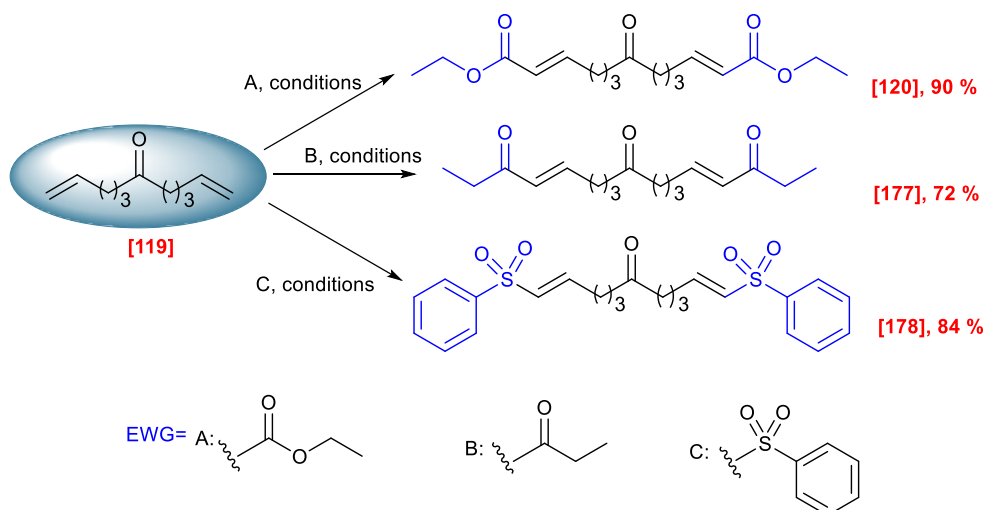
Homologation of the chain in two directions was then carried on the dienone, using cross-metathesis reaction.⁸¹ A symmetrical substrate chain was elongated simultaneously in two directions by this reaction, which has been reported by Stockman group.⁸¹ Grubbs-Hoveyda second generation catalyst⁸² was used in the conversion of dienes to double homologated diene(s).



Scheme 2. 4. Main scheme of Cross-metathesis reactions

The synthesis of a variety of compounds of type **[176]** (Scheme 2.4), with different electron deficient alkenes have been accomplished. The process was found to produce *E,E*-dienes selectively.⁸¹ The reactions were all carried out at room temperature in dichloromethane using 6 equivalents of alkene possessing an electron withdrawing group (EWG) (Scheme 2.4). It was found that the reactions were relatively slow, but clean, giving over 95% purity by ¹H NMR. Addition of the catalyst was carried out in two portions during the long

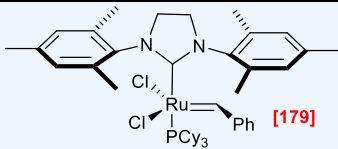
reaction, the second portion being added in all cases after 24 h. Thus, two additions of 2.5 mol% of catalyst were used, with the reaction being run at room temperature.



Scheme 2. 5. Homologation in two-directional using cross-metathesis

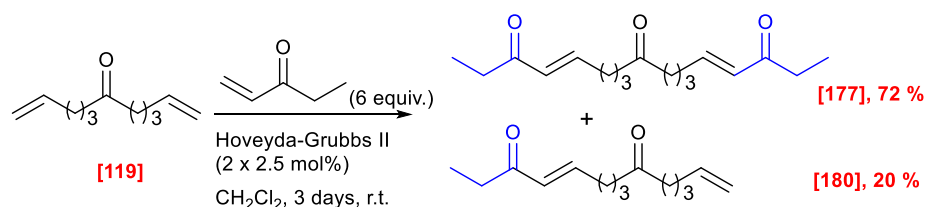
The olefins we used in these reaction are of the three olefin categories has been classified by Grubbs and co-workers in selective cross-metathesis (Table 2.1).⁴⁶

Table 2. 1. Olefin Categories for Selective Cross Metathesis⁴⁶

Olefin type	
Type I (fast homodimerisation)	Terminal olefins, 1° allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes, allyl phosphonates, allyl silanes, allyl phosphine oxides, allyl sulphides, protected allyl amines
Type II (slow homodimerisation)	Styrenes (large ortho substit.), acrylates , acrylamides, acrolein, vinyl ketones , unprotected allylic alcohols, perfluorinated alkane olefins
Type III (no homodimerisation)	1,1-disubstituted olefins, non-bulky trisub. Olefins, vinyl phosphonates, phenyl vinyl sulfone , 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)
Type IV (spectators to CM)	Vinyl nitro olefins, trisubstituted allyl alcohols(protected)

Chapter 2. Results & Discussion

According to Grubbs classification of olefin activities toward the homodimerisation (Table 2.1).⁴⁶ Ethyl acrylates which were classified as the olefin type II in reactivity, we found that in the case of the reaction of ketodiene **[119]** with ethyl acrylate to give **[120]** (Scheme 2.6), the reaction was very slow, so that after 3 days and two additions of catalyst, the doubly homologated product of ketone was isolated as the main product. Whereas ethyl vinyl ketone was found to be the least reactive of the olefin arranged, it produced the mono homologated **[180]** in 20% and the double homologated ketodiene **[177]** in 72% yield (Scheme 2.6).⁸¹



Scheme 2. 6. Mono homologation was observed in the case of ketone [177]

However, although the phenyl vinylsulfone is considered as a less reactive olefin based on the Grubbs categorisation toward homodimerisation, the yield of the isolated phenylsulphone substrate **[178]**, was very good.⁸¹

From symmetrical simple ketodiene **[119]** we functionalised both sides alkene in two-directional process. We used CM synthesis with three different olefins, afforded three different ketodienoates activated by terminal electron withdrawing groups **[120]**, **[177]** and **[178]**. Although Substrates have been recorded before by Anabella from Stockman group 2009⁸¹, but there were no further reactions carried on both substrates **[177]** and **[178]**.

2.1.3. Combining Two-Directional and Domino Reaction in Synthesis

With a set of three keto-diene precursors in hand, we now set about investigating their use as domino reaction precursors. Figure 2.1, shows the domino reaction to one of these precursor **[120]**, that both sides were functionalised simultaneously, then conditions were controlled to ignite the oxime cyclisation *via* aza-Michael addition followed by [3+2] cycloaddition, this reaction was investigated by Stockamn, in 2003.⁵⁸

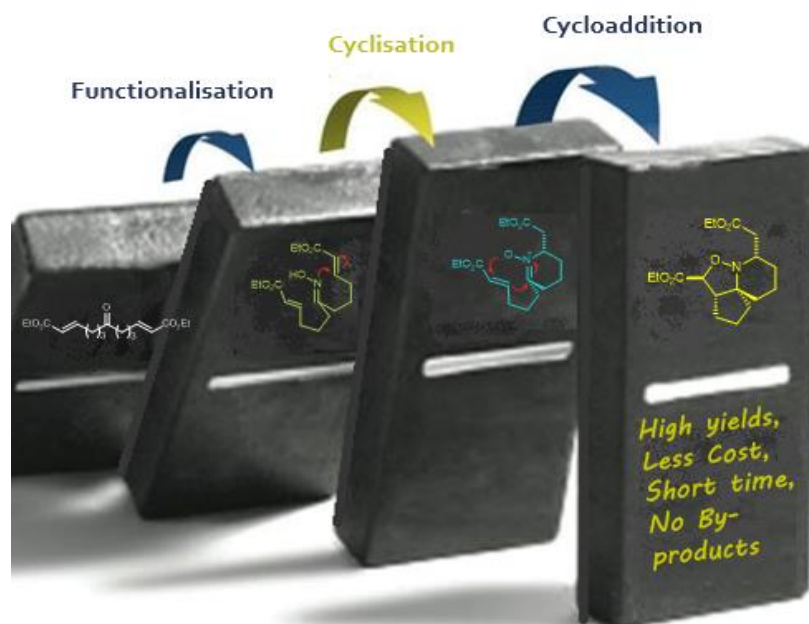
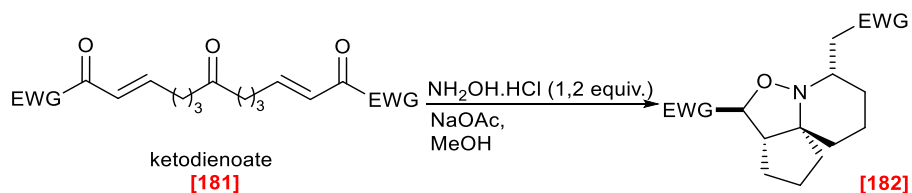


Figure 2. 1. Combining two-directional and Domino reactions (*modified image*)⁸³

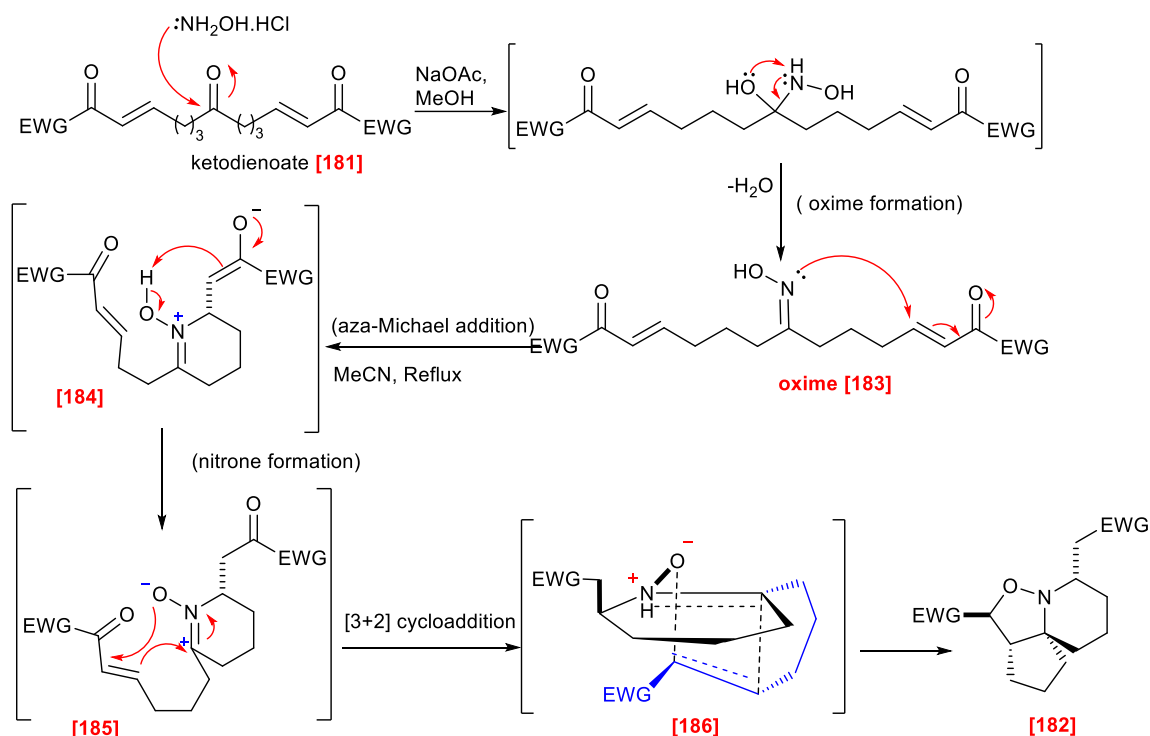
Treating the ketone **[181]** (Scheme 2.7) with hydroxylamine hydrochloride (1.2 equiv.) in presence of sodium acetate for 3 h in dry methanol as a solvent to produce the oxime

reactive intermediate **[182]** which did not need to be purified or isolated, as it went through a domino reaction to generate the tricyclic compound **[182]**.



Scheme 2. 7. One-pot reaction and formation of tricyclic compound [205]

The domino reactions were performed on oxime by heating the mixture to reflux in acetonitrile. First, an aza-Michael addition takes place when an α,β -unsaturated ester (Michael acceptor) is attacked by the nitrogen of the centre oxime forming a six-membered ring moiety **[184]**, proposed reaction mechanism is shown in (Scheme 2.8) . This reaction stage of 2 hours is sufficient to complete cyclisation through a domino aza-Michael reaction followed by 1,4-prototopic shift to form the nitron **[185]** *in situ*. Upon heating Intramolecular [3+2] cycloaddition of the nitron gave isoxazoldine fused to cyclopentane **[183]** as a single diastereoisomer.^{84,85}

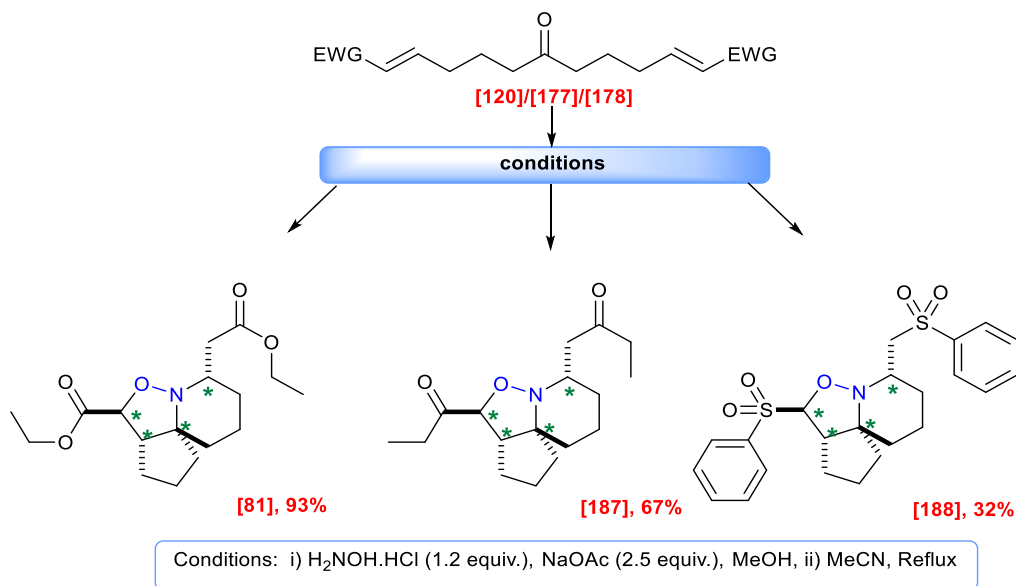


Scheme 2. 8. Postulated mechanism of tandem aza-Michael/1,4-prototropic shift/intramolecular [3+2] cycloaddition

When nitrones such as **[185]**, are combined with alkenes, [3+2] cycloaddition will lead to the formation of two new bonds; C–C bond and C–O bond, performing this process yields the isoxazolidine directly.⁸⁶ The cycloaddition is stereospecific with respect to the configuration of the alkene, herein the alkene is of *trans* configuration with an electron withdrawing group which makes it a more diastereo-controlled [3+2] dipolar cycloaddition (Scheme 2.8).

Chapter 2. Results & Discussion

This reaction strategy has been applied to the three different substrates **[120]**, **[177]** and **[178]** thus, tricyclic scaffolds were afforded in moderate to excellent yields due to different reactivity of the electron withdrawing groups (Scheme 2.9).



Scheme 2. 9. Tandem synthesis of tricyclic scaffolds using 3 different substrates

The relative configuration of these molecules was expected to be of a single diastereomers. As the key step of this synthesis relies on diastereodivergent intramolecular aza-Michael addition step. The structure of ($\pm$) **[188]** has been confirmed by the X-ray crystallography: (S)-4-(phenylsulfonyl)-7-((phenylsulfonyl)methyl)hexahydro-1H,4H-3a,3,4l,3,7l,3-cyclopenta [3,4] isoxazolo[3,2-f]pyridine. The crystal was obtained by a vapour diffusion technique from chloroform/pentane.

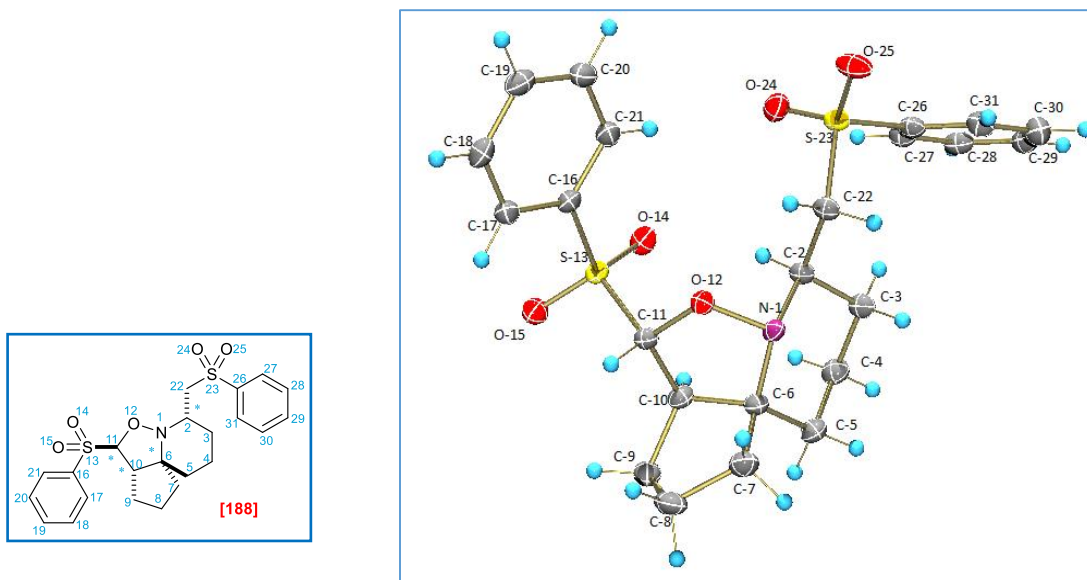
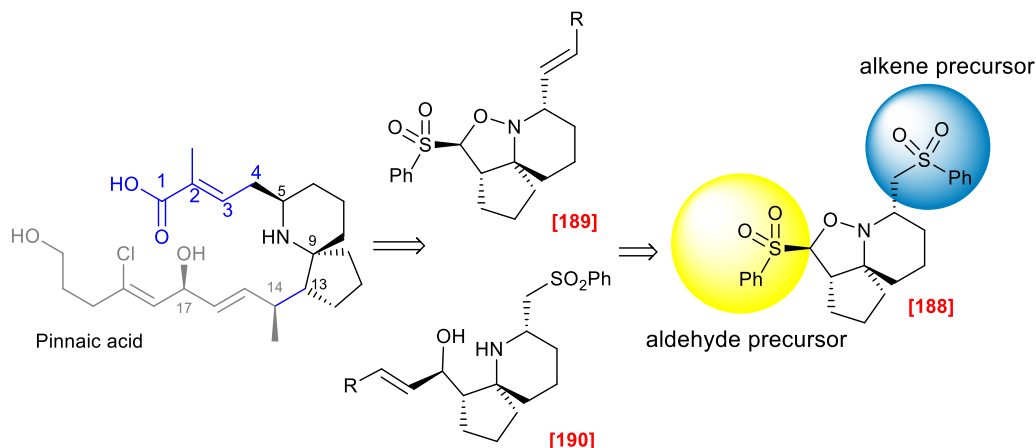


Figure 2. 2. Ortep diagram of [188] (thermal ellipsoid shown at 50%)

With the efficient synthesis of a range of azaspiro[4.5]decane core structures in hand; our aim was to investigate the progression of these towards the target natural products halichlorine/ pinnaic acid. As this core has been developed independently in the group of Shishido, Zhao, Pilli, White, and the Stockman group (Scheme 2.11).⁶⁶⁻⁶⁷ Prior investigations were carried out previously within the Stockman group toward functionalising the scaffold **[81]** toward halichlorin/pinnaic acid synthesis.^{67,88}

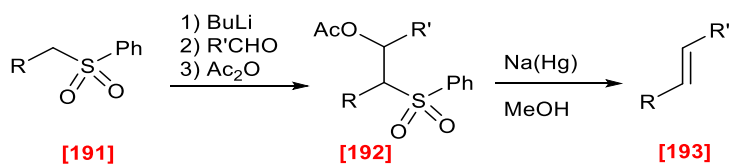
2.1.3.1. Future Work

Our novel diphenyl sulfone scaffold [188] seemed to be, a more promising to approach toward the pinnaic acid structure, we could apply Julia olefination for example.⁸⁹



Scheme 2. 10. Suggested synthetic route toward pinnaic acid

A suggested step by functionalising either of the sulfone groups (Scheme 2.10), could be applied on the scaffold **[188]**. Julia olefination conditions (Scheme 2.11),⁹⁰ could be applied on the phenyl sulfonyl group by treating with an appropriate ketone/aldehyde and possibly the formaldehyde would generate terminal alkene on C-4 or C-14, which will render the cross-metathesis reaction to couple with a well-designed constructed chain.



Scheme 2. 11. Julia Olefination

In summary, we have demonstrated the formation of three tricyclic compounds with a small range of different substrates from a simple linear ketodiene molecule. Transformation of the central ketone in tandem reactions as an interesting and very direct approach for the efficient formation of a range of three-dimensional molecular architectures with natural product-like features. This approach is able to access a range of fused or spiro polycyclic

structures from a single substrate. Thus, these scaffolds main core, will enrich the field of natural product synthesis studies such as halichlorine/ pinnaic acid especially.

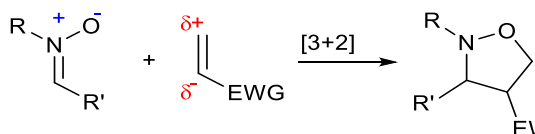
2.1.4. Tandem Intra Molecular-Cycloaddition Utilising Oxime to Generate Spirocyclic β -amino Acid Derivatives

Although β -amino acids are less abundant than their α -analogues, they have interesting pharmacological effects. This structure is also present in some peptides and in some natural products.⁹¹ Over a hundred years ago bicyclic β -amino acids and their derivatives were very challenging to synthesise.^{92,93} Moreover, these compounds have been broadly explored as intermediates in the synthesis of natural products or natural product-like compounds. These scaffolds are good examples of drug-like compounds useful for medicinal chemistry.⁹² Thus, in our seeking to build the main core of halichlorine/pinnaic acid, we tried to construct a tricyclic aza-spiro cyclic system.

In the previous study we used the electrophile-induced transformation of an oxime to a nitron in an intramolecular sequence to initiate a cascade reaction. We decided to investigate an inter-molecular approach, which will lead to a range of different scaffolds *via* cascade process.⁹⁴

Grigg and co-workers⁹⁵ have previously demonstrated a series of both inter- and intramolecular aza[3 + 2] cycloadditions *via in situ* generation of a nitron by the addition of an oxime to an electron-withdrawing alkene and subsequent 1,3-dipolar cycloaddition

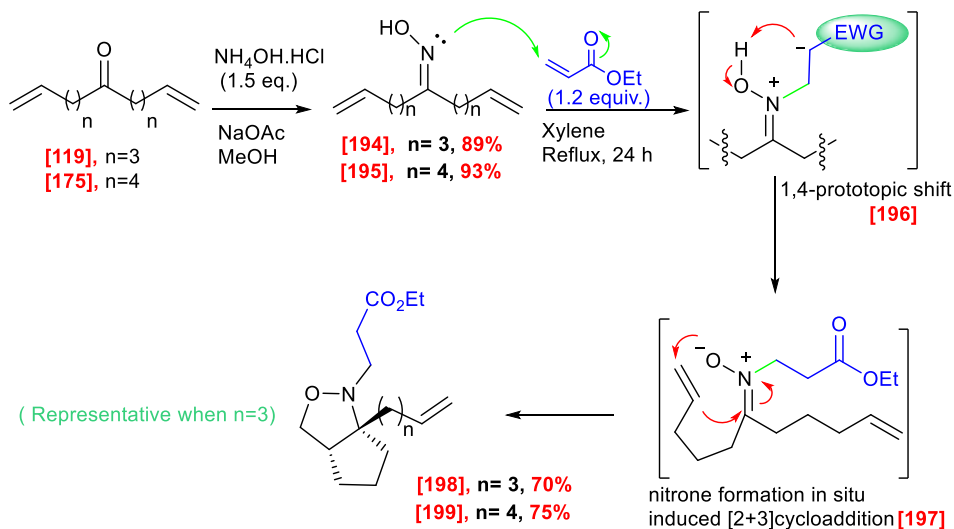
of the resulting nitron to an appropriate olefin (Scheme 2.12). In most cases, the cycloaddition reaction is both regio- and stereospecific.⁹⁶



Scheme 2. 12. Nitron dipolar [3+2] cycloaddition

Thus, we started with the treatment of the symmetrical ketones **[119]/[175]** with hydroxylamine hydrochloride to afford oxime **[194]/[195]** respectively in good yields. Heating oxime with ethyl acrylate in xylene at 140 °C in a similar manner as described by Grigg and co-workers^{94,95} afforded cyclised adduct **[198]/[199]** as one diastereoisomer (Scheme 2.13) a similar tandem cycloaddition and isomerization have accomplished in a short and general synthesis of the azaspirocyclic core structure of halichlorine and pinnaic acid was recorded by Zhao, 1999.⁹⁷

Utilising the oxime function, a conjugate addition will result in aza-Michael addition manner of acrylate to form **[194]** and **[195]**, followed by an intramolecular 1,4-proton shift, generated a 1,3-dipole as a reactive intermediate **[196]** to form the nitron **[179]** in situ. An intramolecular 1,3-dipolar cycloaddition afforded one diastereomer *N*-substituted isoxazolidine fused to five or six membered ring **[198]/[199]** respectively.⁹⁸



Scheme 2. 13. Tandem cycloaddition utilising oxime

The formation of the bicyclic compounds **[198]** and **[199]** (Figure 2.3), was confirmed by ^1H NMR, mainly HMBC showed the significant correlation shifts for H-10,11 and H-12.

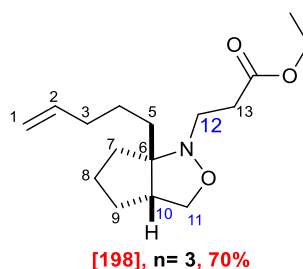
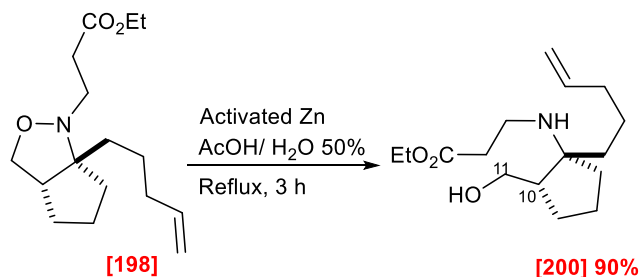


Figure 2. 3. Bicyclic [198]

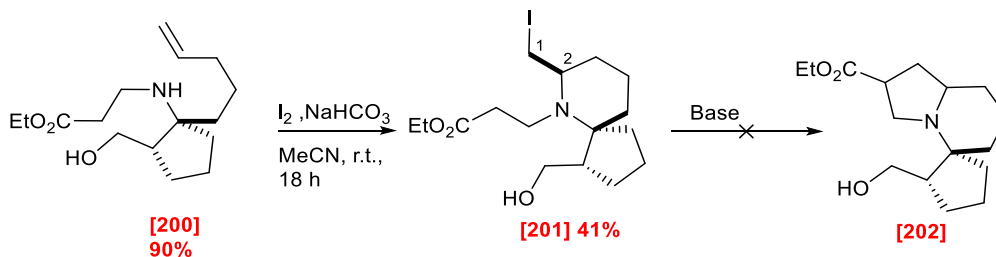
Some attempts were made on the precursors **[198]** toward forming the azaspiro[4.5]decane core structures halichlorine/pinnaic acid stereoselectively. The N-O bond was reductively cleaved using activated zinc dust, affording the 1,3-amino alcohol in a very good yield

[200] (Scheme 2.14), the complete cleavage was confirmed by ^1H NMR a new apparent single shift at low field 4.64 ppm for free OH appeared.



Scheme 2. 14. N-O bond Cleavage of isoxazolidine to 1,3-amino alcohol

Iodoamination cyclisation of *N*-alkylaminoalkene was performed in a stereocontrolled process to give trans-2,6-disubstituted piperidine **[201]**. The amino alcohol precursor **[200]** was reacted with iodine (3.0 equiv.), heated to reflux in acetonitrile to successfully cyclise as β -amino acid derivative (Scheme 2.15).⁹⁹

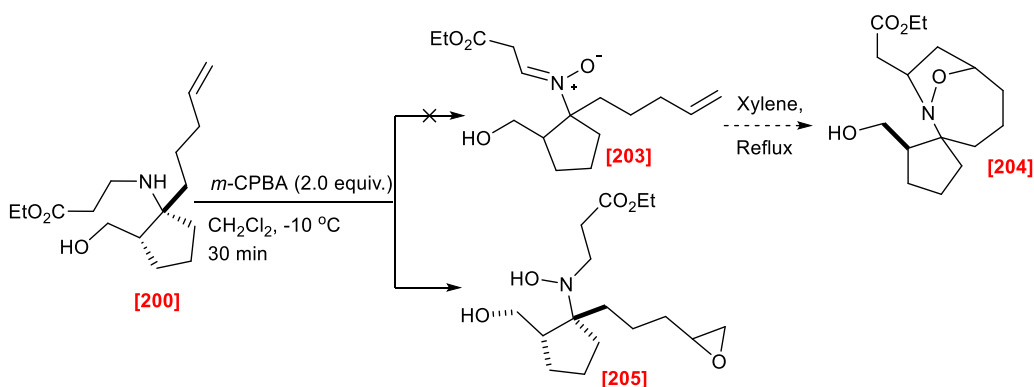


Scheme 2. 15. Iodine-induced cyclisations of *N*-alkylaminoalkene[200]

With the success of forming the [5.6]-spirocycle **[201]** as a single diastereomer, we decided to investigate a further cyclisation to give the tricyclic structure **[202]**, (Scheme 2.16). Unfortunately, however, we were unable to achieve this transformation using KHMDS. We believe this scaffold to be investigated in different approach. So, we sought to investigate a different approach.

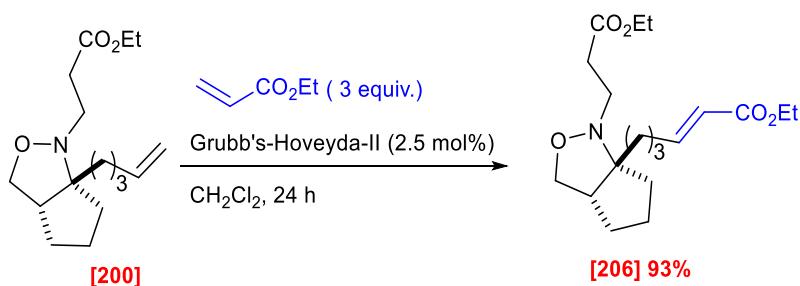
Chapter 2. Results & Discussion

With amino alcohol **[200]** in hand, our aim was to form a [4:2:1] bridged scaffold **[204]**, by treating **[200]** with *m*CPBA (2.0 equiv.) we expected a ring-closure *via* nitron formation *in situ*, but the was unstable and couldn't be **[205]** (Scheme 2.19).



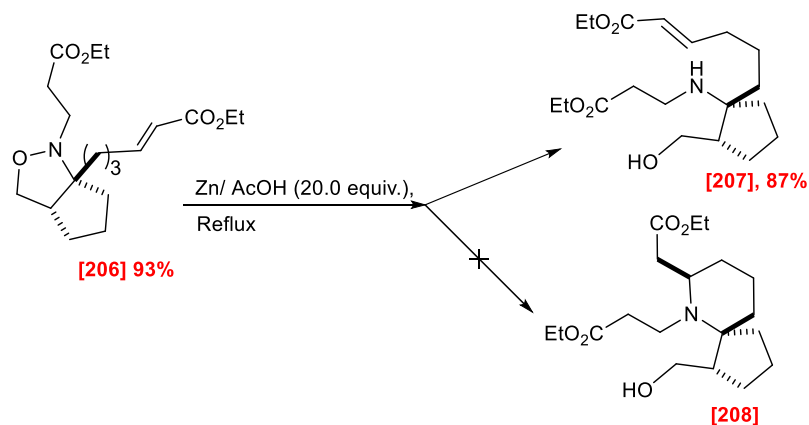
Scheme 2. 16. Nitron formation by oxidation attempts

Generally, we required activated alkenes; electron-withdrawing groups are more reactive toward aza-Michael cycloaddition, thus, we elaborated the terminal alkenes using olefin cross-metathesis. An attempt of treating **[198]** with ethyl acrylate using Grubb's-Hoveyda-II catalyst, successfully gave the alkene yield the ester **[207]** in 93% yield (Scheme 2.17).



Scheme 2. 17. Functionalising terminal alkene

Compound **[206]** was subjected to reducing conditions to perform N-O bond cleavage and with the expectation that an intr-molecular aza-Michael addition would occur in the same vessel, to generate azaspiro[4.5]decan-6-yl propanoate **[208]** (Scheme 2.18).



Scheme 2. 18. Toward intra-molecular aza-Michael addition reaction

Compound **[206]** was treated with zinc in acetic acid to induce the reaction by cleaving the bond N-O and subsequently heated the reaction at reflux to attempt the Michael addition. Unfortunately, cyclisation was not successful but amino alcohol **[207]** was produced in 84%.¹⁰⁰

2.1.5. Tandem Cyclisation with Amino Acids

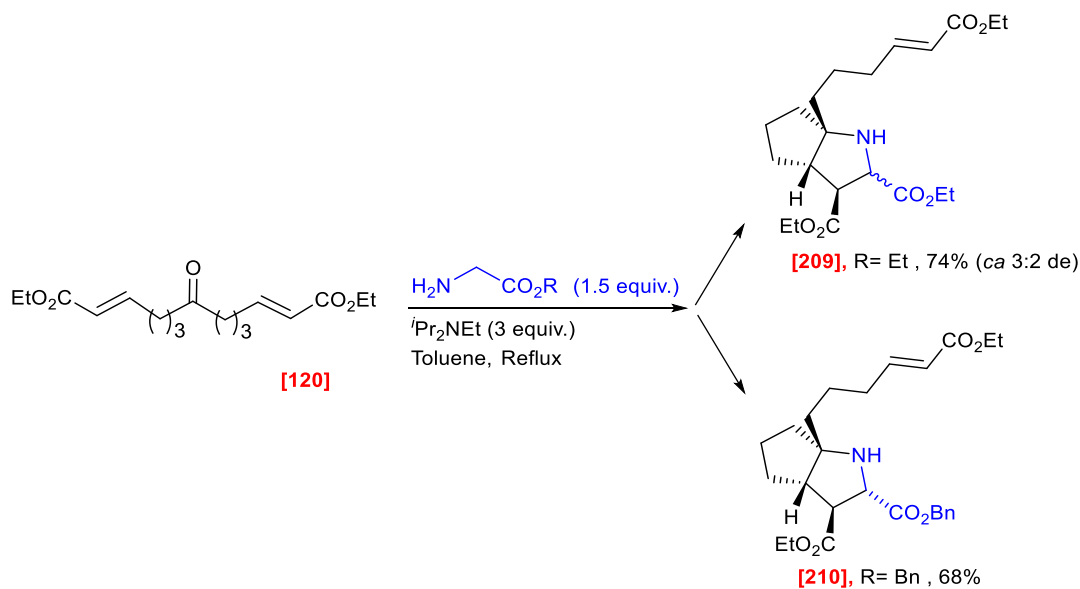
There is much synthetic and pharmaceutical interest in cyclic α -amino acid derivatives. Rigidified (α -CAAs) have been found to have important roles in drug design, because of their ability to exert conformational constraints while maintaining the hydrophobic character of the linear alkyl chains. Cyclic α -amino acids (α -CAAs) in peptide surrogates have been particularly useful for probing the structural requirements of receptor-bound ligand conformations.^{101,102} As a result, some 5- or 6-membered CAAs have been synthesised by condensation of some simple α -amino acids (Figure 2.4) with our symmetrical precursor ketodiester **[120]** (Scheme 2.19). In order to explore this approach,

we tried different α -amino acids in addition to one earlier fruitful amine-induced transformation published by our group.^{55,103}



Figure 2. 4. Amino acids used in our investigations

The ketodiester **[120]** has been subjected to condensation with ethyl glycinate, benzyl glycinate and β -alanine ethyl ester (1.5 equiv.) in the presence of Hünig's base (3.0 equiv.). A [3+2] cycloaddition was created successfully *via* azomethine ylide formation afforded the bicyclic product as a mixture of two diastereomers (ca 3:2 ratio), in the ethyl glycine ester case **[231]** (Scheme 2.19).



Scheme 2. 19. Successful intramolecular [3+2] cycloaddition, formation of CAAs

We anticipated that due to more sterically bulky, benzyl glycinate would undergo a more stereoselective [3+2] cycloaddition. Fortunately, one diastereomer was successfully generated **[210]**, upon the reaction of **[120]** with benzyl glycinate in toluene at reflux

(Scheme 2.19). The ^1H NMR spectrum showed a number of signals from which the coupling constants were used to assign structure (Figure 2.5) includes: $J_{\text{HH}} = 6.4$ Hz, (H-15) & (H-14), and $J_{\text{HH}} = 2.4$ Hz of (H-14) & (H-13), and $J_{\text{HHH}} = 8.5, 6.4, 2.3$ for 1H (H-13).

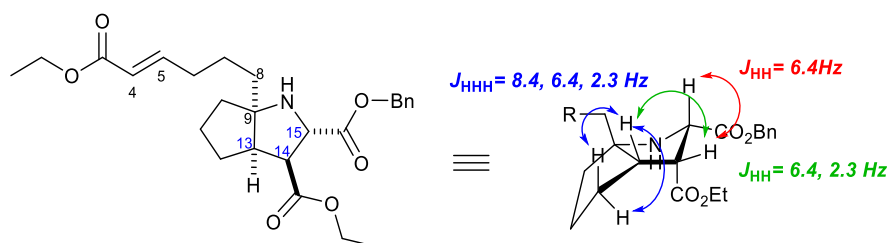
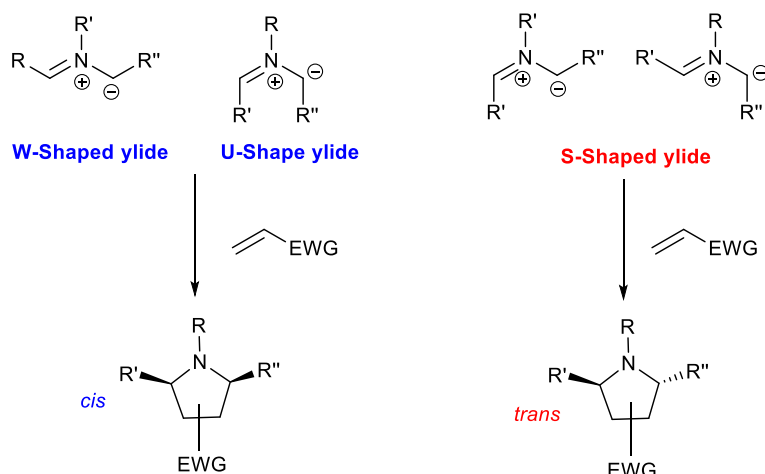


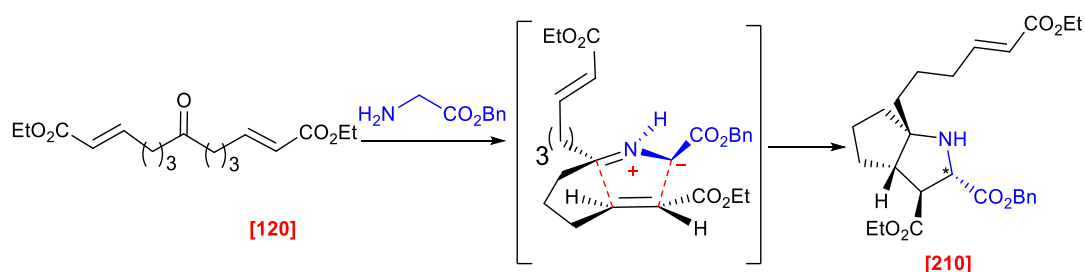
Figure 2. 5. Bicyclic adduct [210] ^1H NMR

In order to explain the achieved diastereoselectivity, we need to consider the transition state of the cycloaddition.¹⁰⁴ Azomethine ylides have four electrons in three parallel atomic π orbitals perpendicular to the plane of the dipole. This unit could be represented in W-shaped, U-shaped or S-shaped dipoles, which direct the stereochemistry of the generated pyrrolidine (Scheme 2.20).



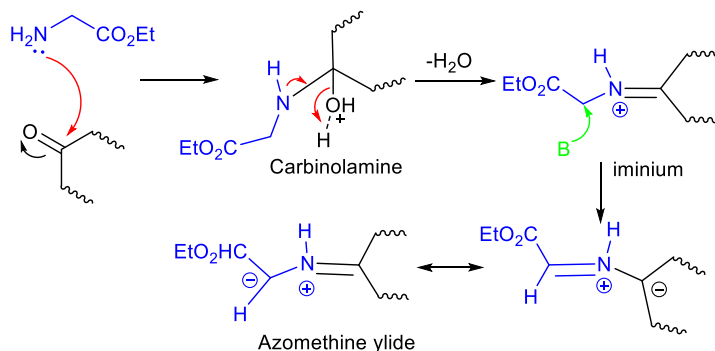
Scheme 2. 20. The stereochemical outcome of the cycloaddition of AMY is dependent on the geometries of the dipole

The *cis*-2,5-disubstituted pyrrolidine product would be formed by the involvement of W- and U-shaped dipole of *cis*- configuration, while *trans*-2,5- disubstituted product emerges from the two possible S-shaped ylides. Therefore, a suggested mechanism for the pyrrolidine cycloadducts [209]/[210] as illustrated in (Scheme 2.21).



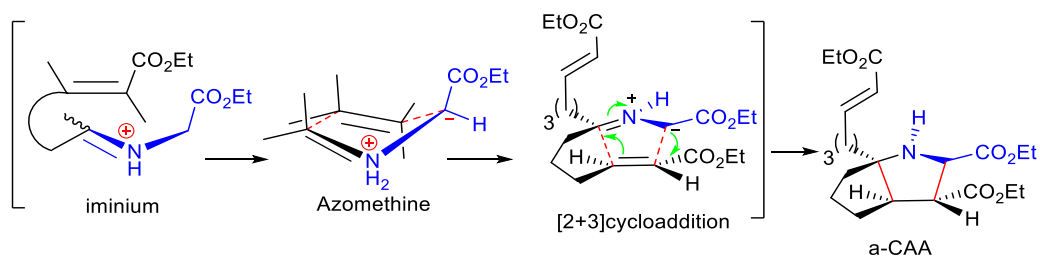
Scheme 2. 21. Suggested mechanism for CAAs generated [210]

The mechanism of the cyclisation of [209] and [210] proceeds with condensation between the amino acid nitrogen and the ketone. The generated carbinolamine loses a water molecule to form an iminium species. In presence of Hunig's base a deprotonation occurs in the α - position to produce azomethine ylide as a reactive intermediate (Scheme 2.22).



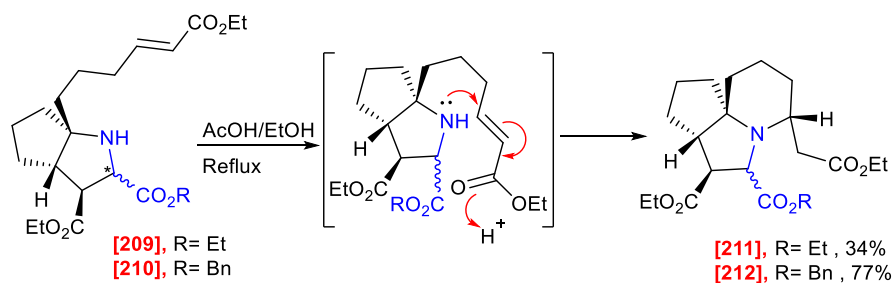
Scheme 2. 22. Azomethine ylide formation mechanism

The azomethine ylide, formed *in situ*, underwent [3+2] cycloaddition through a five-membered transition state. In this case *trans*-substituents dipolarophilic alkene end up *trans* in the resulting five-membered cyclic compound (Scheme 2.23).¹⁰⁵



Scheme 2. 23. Proposed mechanism of cycloaddition

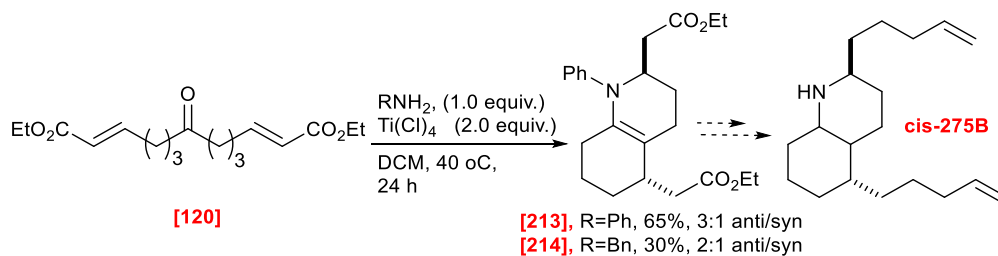
Subsequently, the cyclic adduct **[209]** and **[210]**, were subjected heating to reflux in ethanol and acetic acid (5.0 equiv.), in an attempt to induce aza-Michael reaction. Happily, spiro containing five membered heterocyclic scaffolds **[211]** and **[212]**, were generated again with good stereochemical control a diastereoselectivity (Scheme 2.24).



Scheme 2. 24. Condensation/azomethine/[2+3]cycloaddition of ketodiester with glycines

2.1.6. De-Symmetrisation and Sequential Homologation for the Synthesis of Useful Azabicyclic Systems

The reaction of aniline with the symmetrical precursor ketodienoate **[120]** has been explored by the Stockman laboratory for the formation of set enamine product which is a common intermediate toward the synthesis of the alkaloid *cis*-**275B**.¹⁰⁶ It has been found that the formed enamine can be reacted with an enoate side chain by a Michael addition, which generates an azabicyclic product. Various primary amines have been used under different reaction conditions (Scheme 2. 25). Aniline in dichloromethane was found to be the best reagent and conditions, based upon the produced yield and its diastereoselectivity.^{106,76}



Scheme 2. 25. Reaction of keto diester with aniline toward the synthesis of alkaloid *cis*-275B⁷⁷

In order to increase the substrate scope and to be able to access the core scaffolds present to the lepadin class of natural products, we attempted to de-symmetrise our precursor; keeping one side chain bearing $\alpha\beta$ -unsaturated ethylester while epoxidising the other, before subjecting the central ketone to a condensation reaction with aniline (Figure 2.6).

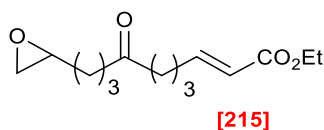
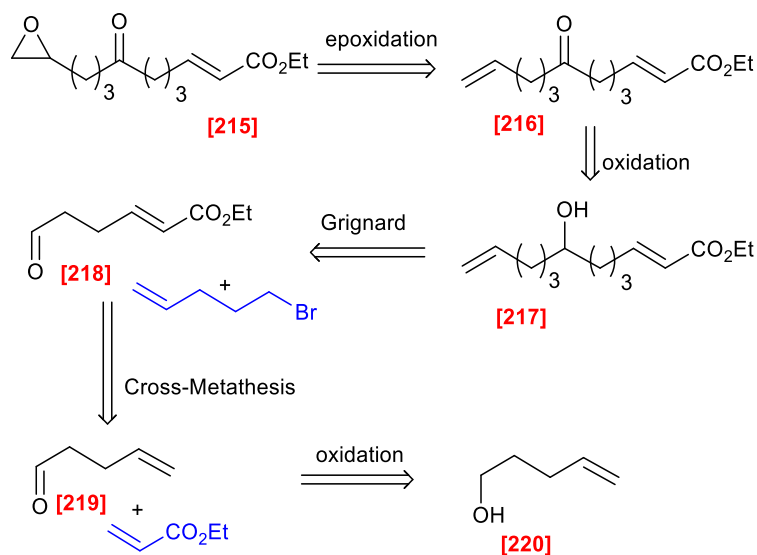


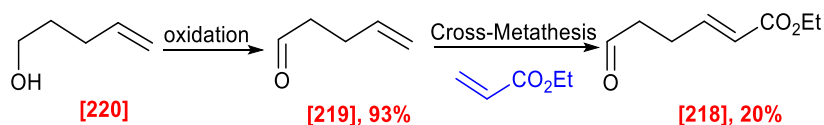
Figure 2. 6. The target de-symmetrised skeleton

Scheme 2.29, shows a retrosynthetic analysis of this new tandem cyclisation precursor **[215]**. We received an unsymmetrical substrate to start the synthesis.



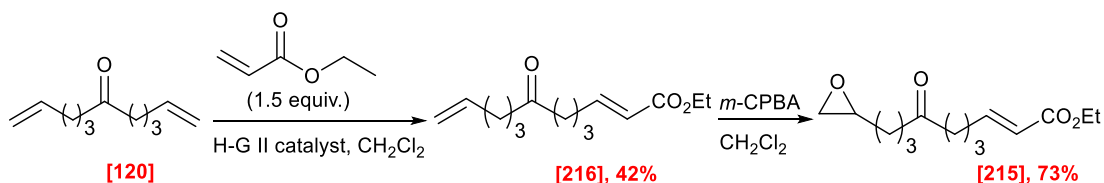
Scheme 2. 26. Proposed synthetic plan to prepare unsymmetrical ketone [215]

Our initial route for the preparation of the epoxide **[215]** (Scheme 2.26), began by oxidation of hexenol *via* standard Swern oxidation conditions,¹⁰⁷ 93% yield. Subsequently the aldehyde product **[219]** was reacted with ethyl acrylate through a CM reaction to generate the aldehydic ester **[218]**. Following our proposed route to prepare the precursor **[217]**, we found Grignard addition to aldehyde **[218]** gave a moderate to low yield.



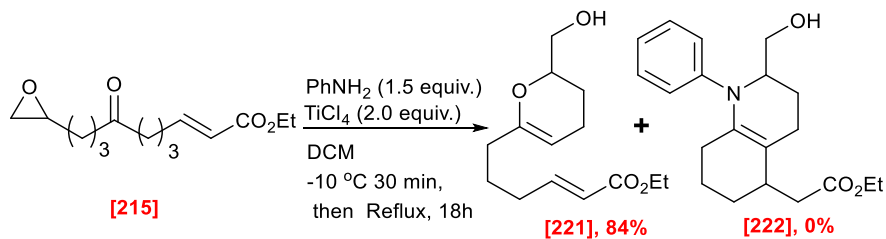
Scheme 2. 2. Following proposed steps

We tried an alternative approach, using a new cross-metathesis reaction of the ketodiene precursor [120] with ethyl acrylate in a CM reaction, which provided a shortened synthesis of [216], 94%. With the ketoester [217] in hand it is possible to form the epoxide [215] using *m*-CPBA (Scheme 2.31).



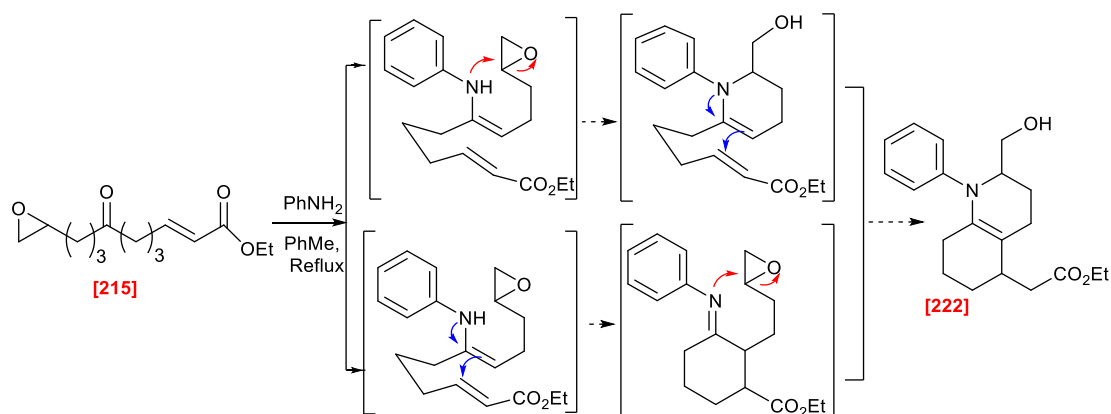
Scheme 2. 3. Direct route to produce ketoester precursor [215]

The reaction of the unsymmetric precursor [215] with aniline in presence of the Lewis acid $\text{Ti}(\text{Cl})_4$ was next attempted. However, upon reaction, we isolated an unexpected product, the disubstituted pyran [221] was formed (Scheme 2.31).



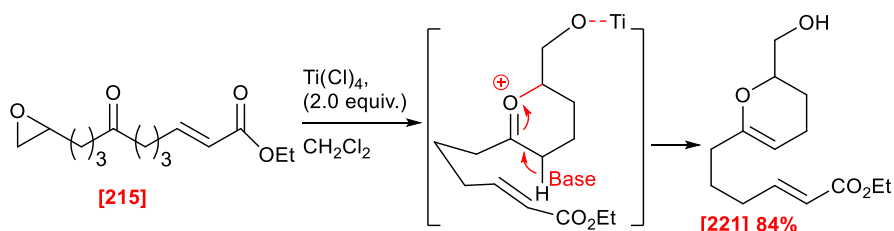
Scheme 2. 4. Reaction in presence of Lewis Acid

Scheme 2.33, describes a hypothesis of the reaction mechanism to produce the desired azabicyclic compound **[222]**.¹⁰⁶



Scheme 2. 5. Hypothesised reaction mechanism toward the synthesis of [222]

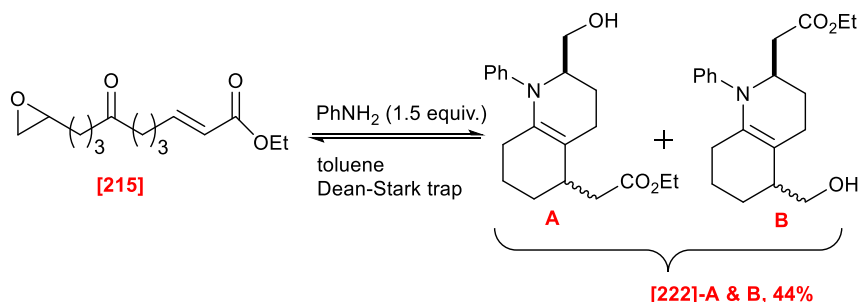
Scheme 2.34, shows the obtained substituted pyran **[221]** instead of **[222]**, being produced. We assumed that epoxide ring in **[215]** was activated in presence of Titanium (IV), and an intramolecular attack of the ketone cycloaddition to the pyran.



Scheme 2. 6. Two Paths applied on De-symmetrised Substrate

We had hoped the ketone **[215]** would react to form an enamine followed by ring-closure of the enamine onto the epoxide enoate. Summarising that we needed to have the enamine first. A further attempt was performed, treating **[215]** with aniline in toluene under Dean-Stark conditions. Unfortunately, the product generated was a mixture of two regio isomers

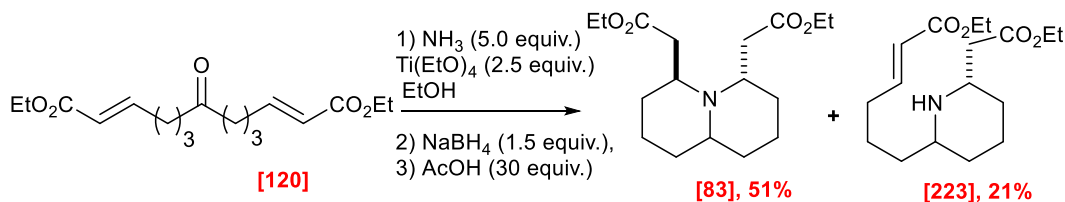
(Scheme 2.35). This does show the strakes is capable of working, but fine tuning of the reaction itself required.



Scheme 2. 7. Condensation of unsymmetric precursor with aniline

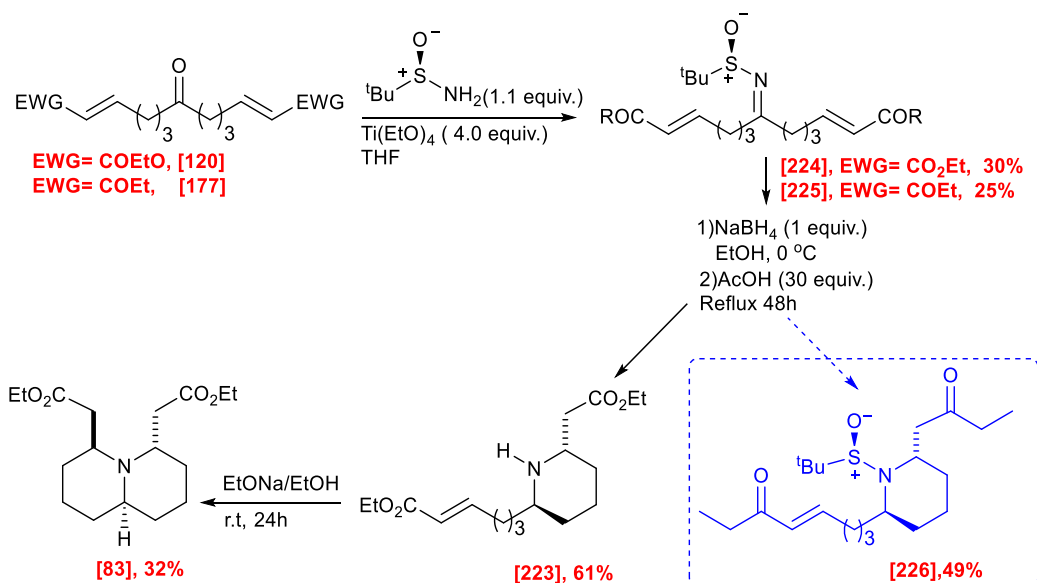
2.1.7. Use of Sulfinimines towards Stereoselective Synthesis of ($\pm$)hippodamine

We next turned our attention to the total synthesis of ($\pm$)-hippodamine and ($\pm$)-epi-hippodamine, initially, we repeated the racemic synthesis in order to have a racemic sample of quinolizidine **[83]**. The reductive amination involved an addition of an ethanolic solution of ammonia in the presence of titanium(IV) ethoxide to the ketodiester **[120]**, followed by addition of sodium borohydride, and finally the addition of acetone to remove any remaining active hydride. Double Michael addition reaction was observed when the amine **[223]** heated to reflux in acetic acid (30.0 equiv.), leading to product **[83]** in 51% yield along with some of the intermediate piperidine **[223]** which was isolated in a 20% yield (Scheme 2.37).



Scheme 2. 8. Applying earlier procedure

We then tried utilising the sulfinimine as the nitrogen source and chiral auxiliary involved in the intramolecular aza-Michael reaction to produce enantiomerically pure piperidine derivatives.



Scheme 2. 9. Improved Synthetic Process

Ketodienoates **[120]** and **[177]** were condensed with (*R*)-(+)-2-methyl-2-propanesulfinamide in the presence of titanium(IV) ethoxide to form sulfinimines **[224]** and **[225]** respectively (Scheme 2.12). We then treated these with NaBH_4 to induce reduction leading to subsequent aza-Michael addition of the resulting amine. We expected

Chapter 2. Results & Discussion

to form the sulfinyl piperidine scaffold **[226]** with stereo-control, but this were obtained only in 49% using the diketone substrate **[223]**, whereas only mono cyclised scaffolds **[223]** of ketodiester scaffold was produced in a 61% yield. For substrate **[224]** the sulfinyl group was liberated in situ due to the highly acidic reaction conditions.

Sulfinamides have played a critical role in the asymmetric synthesis of a variety of structurally diverse nitrogen-containing molecules, where they act as chiral auxiliaries to maintain the stereoselectivity. Usually, after nucleophilic addition, once the sulfinyl group has exerted its directing effect, it is removed under acidic conditions and the free amino group is susceptible to further transformations.

This established a useful route to access enantiomerically pure piperidine derivatives, which was then to be applied toward the total synthesis of the natural products.

As we were carrying on this work, another group published a similar approach. Our initial goal and the overall process in the first stage, was similar to that published work (Scheme 1.31) see introduction.⁷⁵ The synthesis was similar to stage **I** in our process, but it exploited the use of *t*-Bu as a bulky group in **[226]** which enhance the stereoselectivity and yield.

It was worth mentioning that this is the first total synthesis of (+)-*epi*-hippodamine and the second of (–)-hippodamine, the first asymmetric total synthesis of (–)-hippodamine has been accomplished *via* the concise construction of its azaphenalene core was done by Katsumura, 2012.¹⁰⁸

2.1.8. DOS Conclusion

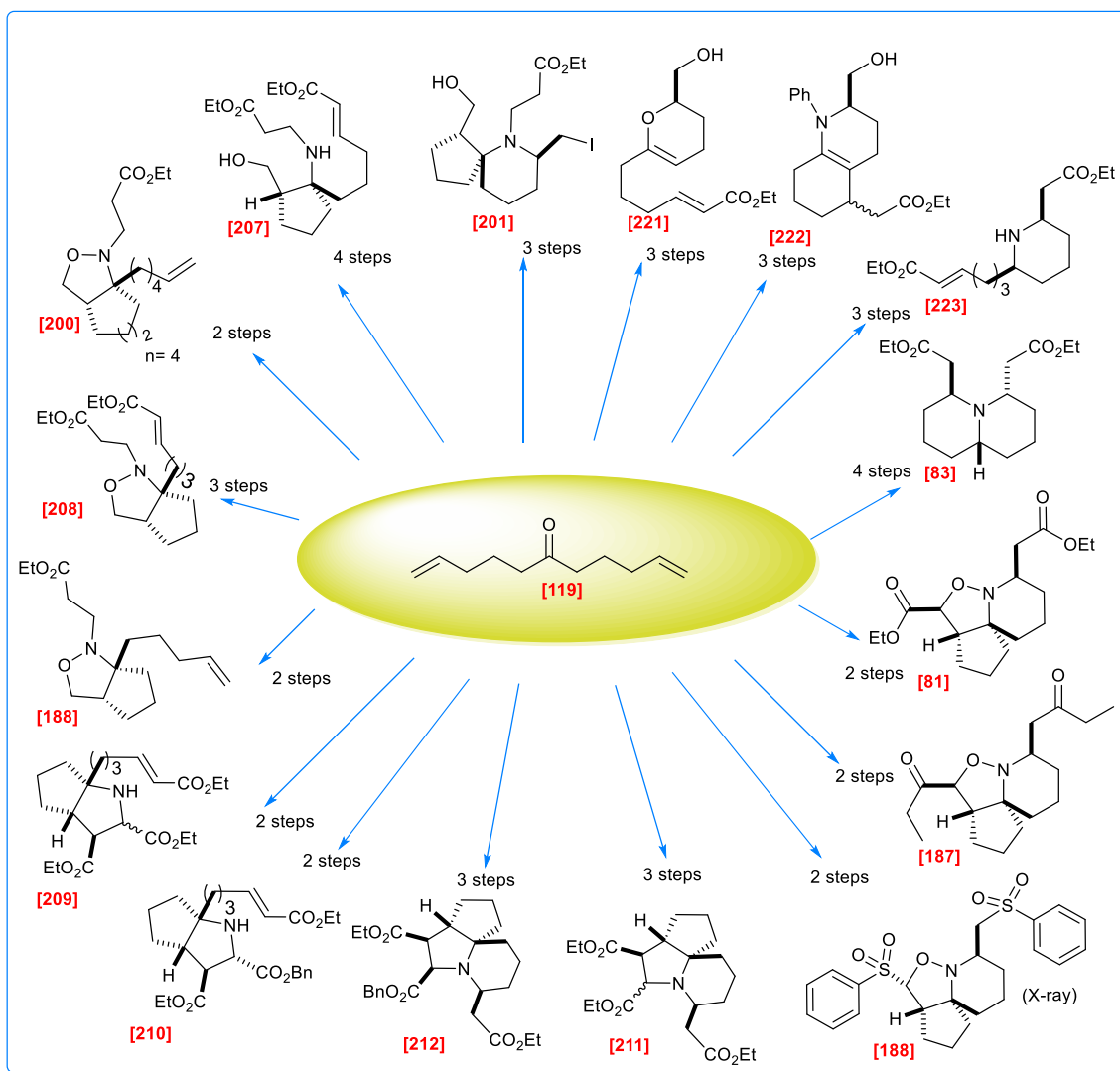
A number of highly branching pathways have been developed utilising a combination between two-directional synthesis and of new tandem reactions sequences of keto-diene-type substrates. This enabled the exceptionally short synthesis of a wide range of diverse skeletons of relevance for the generation of lead-like libraries for screening and for natural product synthesis.

Moreover, we have used some of these new tandem reactions as towards the concise synthesis of the core of natural product, lepadin B which shows potent activity at the nicotinic acetyl choline receptor α_4 , β_2 and α_7 .

Most of the synthesised scaffolds meet the drug industry requirements of not only satisfy the Lipinski “rule of 5”,¹⁰⁵ but also have an increased fraction of sp^3 atoms F_{sp^3} as well as containing more polar functionality. Furthermore, taking a lead from natural products, which have a large structural diversity, the synthesis of “natural product-like” libraries, and “biologically-oriented-synthesis”. We believe our approach provides a useful collection of skeletally diverse compounds that display many natural-product-like properties; fused heterocyclic rings, spirocyclic systems, azacycles, lactams systems, and amino acid derivatives and so on. Furthermore, all of these diverse structures will be available in under an average of 3 synthetic steps per compound from ketodiene **[119]**, due to the highly branching nature of the synthetic routes, and its ability of going through tandem reactions. Most of these scaffolds and will have MW in the range 200-250.

The majority of these compounds are novel or possess new moieties which render them likely to have good biological activities. A part from compounds **[83]**, **[81]**, **[177]**, **[178]**,

and [209] which have been reported by Diane, Anabella, Camille and other colleagues from Stockman group earlier,^{55,72} all compounds in Scheme 2.40, are unique and novel scaffolds. These could play a building block role in a complicated molecule synthesis or further diversification.

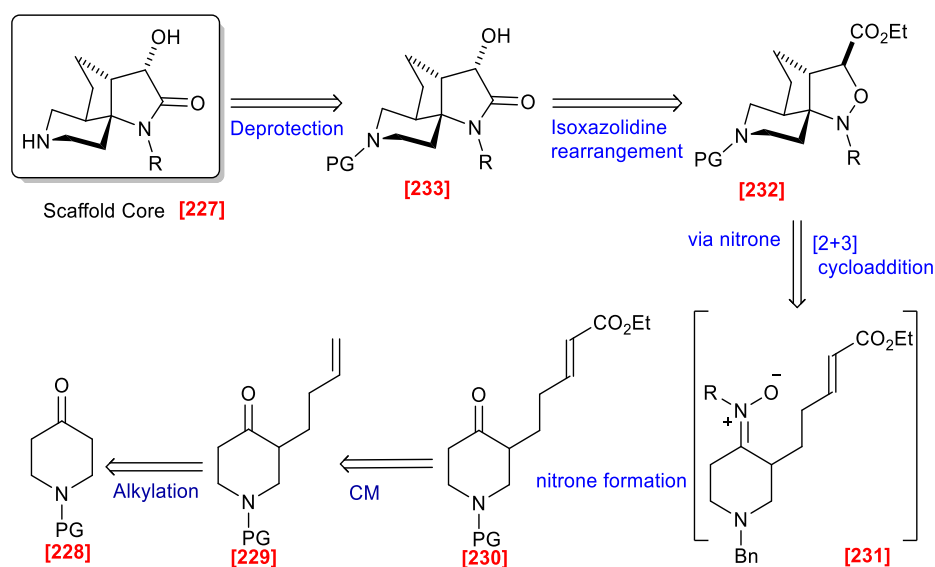


Scheme 2. 10. Summary of 10 novel compounds among 16 branched scaffolds obtained by the Diversity Oriented Synthesis

2.2. Targeted Oriented Synthesis

2.2.1. Synthesis of Highly sp^3 -rich Natural Product-like Chemical Scaffold via a Tandem Condensation/Intramolecular Nitron-Alkene [3+2] Cycloaddition Strategy

In our laboratory we also work on Targeted Oriented Synthesis (TOS) strategies toward some natural products-like molecules. Following the Stockman groups strategy of tandem condensation cyclisation, we considered the following retrosynthetic analysis of a novel, heterocyclic chemical scaffold [227] (Scheme 2.14).¹



Scheme 2. 11. Proposed Retrosynthesis of compound [227]

Nitron cycloaddition would yield a tricyclic isoxazolidine, which we could transform into pyrrolidinone containing scaffold [227], which has three orthogonal vectors (NH, amide, OH) for better diversification.

2.2.1.1. α -C alkylation of piperidinone via hydrazone

Synthesis started by the preparation of the C-3 alkylated *N*-protected piperidinone [229]. Initially, we tried to convert *N*-Boc-piperidinone to a hydrazone as a ketone synthetic equivalent, to avoid well known issues associated with the direct alkylation of ketones. Moreover, although the acidity of H at α -C of hydrazone is much lower than that of ketone by *ca.* 10 orders of magnitude, compared to the C-H acidity of the parent carbonyl compound; the evaluated pKa of the hydrazone is *ca.* 30 compared to the pKa of the corresponding ketone of *ca.* 20. Further advantages have been reported; the selective alkylation of azaenolates regioselectively functionalise α -C to carbonyl, where cyclic ketones show some *O*-alkylation competes with *C*-alkylation. Moreover, in hydrazones the C=N bond is susceptible to be hydrolysis, restoring the carbonyl group easily after alkylation (Figure 2.7).¹⁰⁹

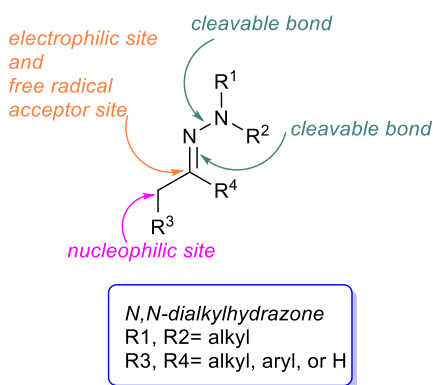
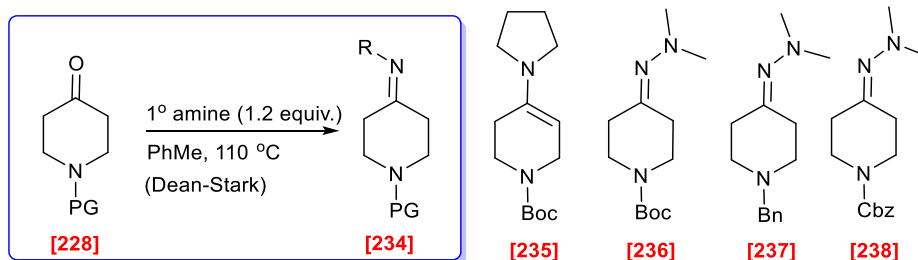


Figure 2. 7. Typical Reactivity sites of *N,N*-dialkylhydrazones

A range of piperidine hydrazones were prepared *via* condensation of the ketone with 2° amine/hydrazine in azeotropic conditions using Dean-Stark apparatus and toluene as

solvent, see (Scheme 2.15), formation of the hydrazones were observed in quantitative yield.



Scheme 2. 12. Carbonyl converted to a ketone synthetic equivalents

The hydrazones [236]-[238], were then subjected to the alkylation process. Various alkylation conditions were tested (Table 2. 4). We explored the α -deprotonation of *N,N*-dimethylhydrazone *N*-Boc-piperidineone [236], and *N*-pyrrolidinyl *N*-Boc-piperidineone [235] but unfortunately, alkylation was not successful for either substrates, perhaps due to a presence of the *N*-Boc group. Thus, we tried the *N*-benzyl protected piperidine hydrazone [237] and it worked successfully in a good yield, while *N*-Cbz-piperidineone [238] has been tested as well but found to be non-productive substrates that starting material recovered only.

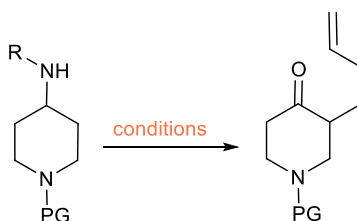


Table 2. 2. Exploring alkylation different conditions

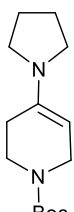
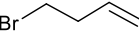
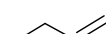
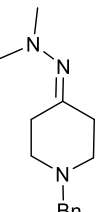
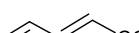
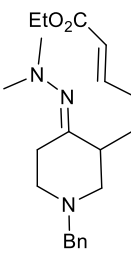
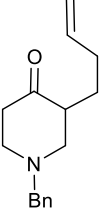
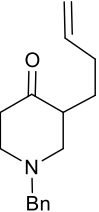
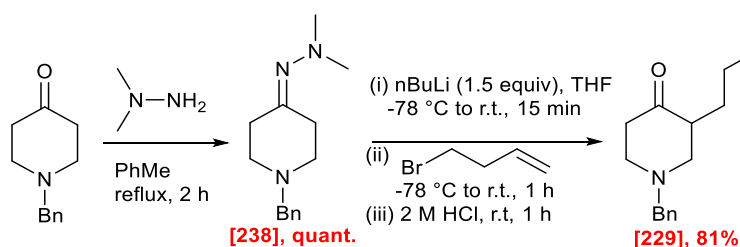
Substrate	Conditions	Product
 [235]	i)  PdII, dppf, THF	SM recovered
	ii)  MeOH, 24 h, r.t.	SM recovered
 [238]	iii)  n-BuLi (1.1 equiv.)	 [240] 11%
	iv)  i) n-BuLi (1.5 equiv.) THF, -78 oC, 2.5 h ii) Hydrolysis	 [229] 60%
	v)  i) n-BuLi (1.5 equiv.) THF, -78 oC, 2.5 h ii) Hydrolysis	 [229] 60%

Table 2.2, summarises a few attempts toward the α -C alkylation of piperidinone. Firstly, we used palladium-catalysed asymmetric allylic alkylation method.¹¹⁰ treatment of pyrrolidinyl *N*-Boc-piperidine **[235]** in entry (i) with allyl palladium(II) chloride dimer (1.2 % mol) in the presence of dppf as a ligand (3% mol) in dry THF, but only the substrate

[235] piperidinone recovered. Thus, we tried another method by stirring the hydrazone [235] with allylbromide in methanol but no alkylated product was obtained.

The hydrazone [238] was then prepared as a good ketone synthetic equivalent. Thus, deprotonation by treatment with *n*-BuLi, was followed by addition of freshly prepared ethyl (*E*)-penta-2,4-dienoate [239], but unfortunately, the reaction proceeds in low yield giving [240] in 11%. We therefore decided to use an alkyl iodide. Thus, we prepared the 4-iodobut-1-ene [241] from 4-bromobut-1-ene [242] using the same conditions in Table 2.2, giving a yield 60%.

We found the most successful conditions were to use the *N*-benzyl piperidinhydrazone [234], using *n*-BuLi (1.1 equiv.) then *C*-alkylation by 4-bromo-1-butene (1.5 equiv.), followed by hydrolysis of the hydrazone moiety (2.0 M HCl). This provided the homoallylated piperidinone [229] in excellent overall yield (81%) (Scheme 2.16).¹¹¹



Scheme 2. 13. *C*-3 Alkylated piperidinone preparation

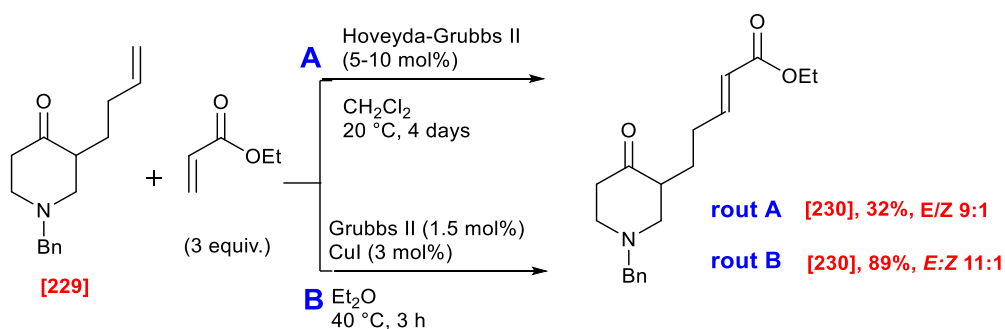
2.2.1.2 Enhancement of Cross-metathesis

With the alkylated piperidinone [229] in hand, the *trans*- α,β -unsaturated ester substrate [230] was prepared by reaction of the terminal olefin of [229] with ethyl acrylate by typical cross-metathesis reaction using Hoveyda-Grubbs II generation catalyst.

Chapter 2. Results & Discussion

Standard conditions involved addition of the catalyst in two portions of (2.5 mol%), ethyl acrylate (3.0 equiv.) in CH_2Cl_2 solution. This reaction produced **[230]** in 32% yield (*E:Z* 9:1) after 4 days.

An enhanced yield for olefin cross-metathesis was accomplished by addition of copper (I) iodide (3.0 mol%) as a co-catalyst.¹¹² Thus, we used Grubbs-II (3.0 mol%), the reaction was carried at 40 °C in Et_2O as a solvent and after 3 h the reaction was complete produced the *trans*- α,β -unsaturated ester substrate **[256]** in 89% yield (*E:Z* 11:1) (Scheme 2.17).

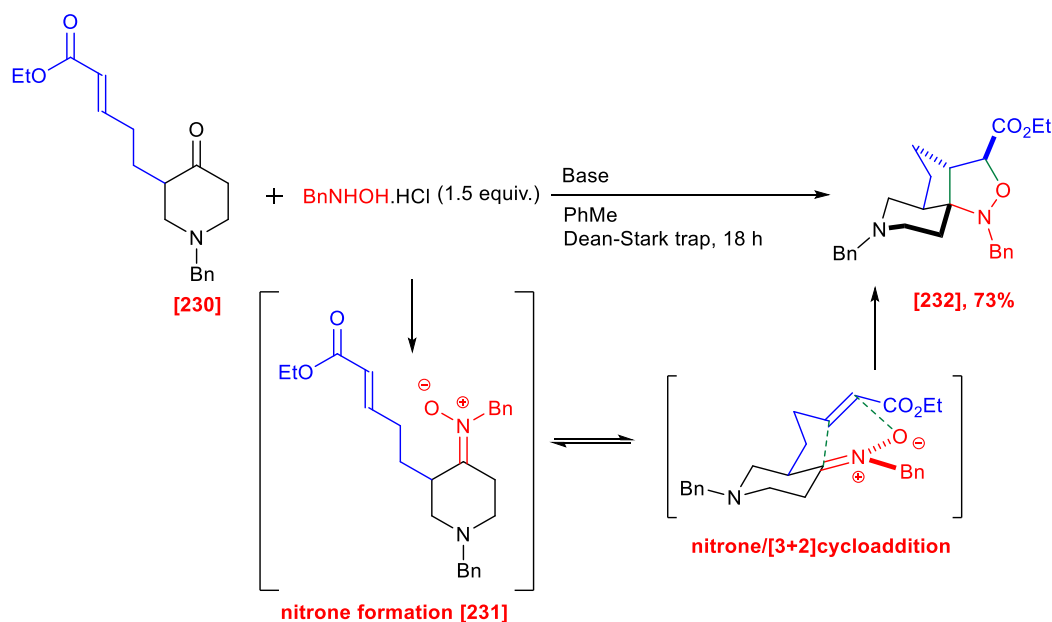


Scheme 2. 14. Enhanced Cross-metathesis conditions applied toward

Overall, these enhancements made to the classical conditions of the cross-metathesis procedure reduced the usage of halogenated solvents and minimised the use of costly ruthenium catalyst.

2.2.1.3. Tandem Condensation/Intramolecular [2+3]Cycloaddition via Nitron

Piperidinone **[230]** was treated with *N*-benzylhydroxylamine hydrochloride (1.5 equiv.) in the presence of NaOAc (3.0 equiv.), and then heated to reflux in toluene, affording key intermediate tricyclic isoxazolidine **[232]** in 73% isolated yield, in a one pot domino reaction, generating three new stereogenic centres and two new rings with high diastereoselectivity.



Scheme 2.15. Tandem Condensation/Intramolecular via Nitron/[3+2]Cycloaddition

The tandem reaction of piperidinone **[230]** to isoxazolidine **[232]** was considered as the key step for the synthesis of this scaffold our mechanistic rational for this transformation is shown in (Scheme 2.45). Initially, the condensation of the ketone with *N*-benzylhydroxylamine, afforded the nitron **[231]** *in situ*, then intramolecular nitron [3+2]

Chapter 2. Results & Discussion

cycloaddition with the electron deficient alkene gave the core scaffold [232], in 73% overall yield. Significantly, only a single regio- and diastereo isomer was observed by ¹H NMR spectroscopy.

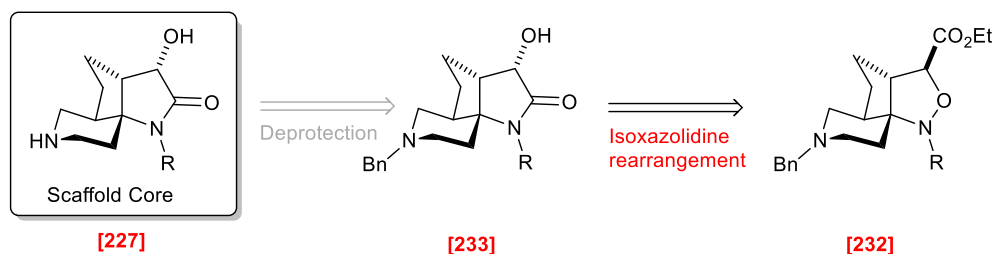
In order to enhance the yield of the nitron formation step, different bases were evaluated and various solution concentrations were tested. The conditions described in entry 4 (Table 2.3) were determined to be the best conditions.

Table 2. 3. Optimisation of Nitron formation conditions

<i>Entry</i>	<i>Base</i>	<i>Sol. Conc. (M)</i>	<i>Yield (%)</i>
1	None	0.04	73
2	K ₂ CO ₃	0.10	49
3	K ₂ CO ₃	0.03	61
3	Et ₃ N	0.10	43
4	NaOAc	0.03	70

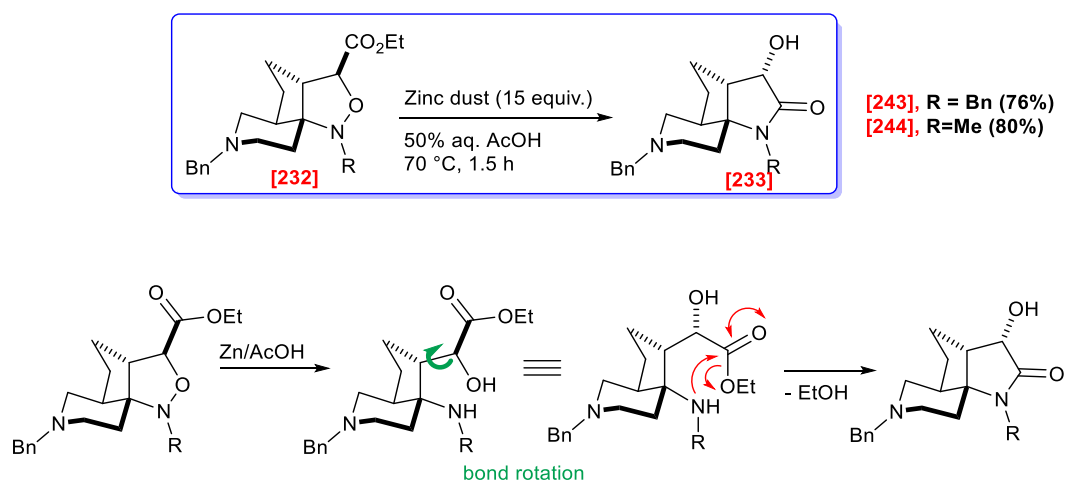
2.2.1.4. Toward the Targeted Molecule

A Stockman group member Dr. M. Rawling added to my work in this project, he carried the isoxazolidine [232] into scaffold core [227] sequence beginning with treatment of [232] with activated zinc in aqueous acetic acid. The corresponding 3-hydroxy lactam [233] was produced in excellent yield (93%) with no need for purification (Scheme 2.19).¹



Scheme 2. 16. Two Steps toward the Target

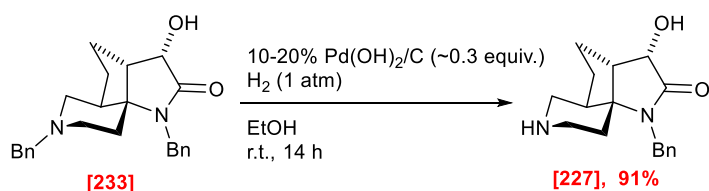
The mechanism of the transformation of [232] to [233] started with the cleavage of N–O bond isoxazolidine [232], followed by C–C bond rotation to allow ring-closure to lactam [233] (Scheme 2.46). On the basis of previous work in literature, we envisioned that the 3-hydroxy lactam unit of scaffold [227] could be derived from key intermediate isoxazolidine [232], by N–O bond reduction followed by cyclisation. It was proposed that spirocyclic isoxazolidine [232] could be obtained diastereoselectively through a tandem nitron formation /intramolecular nitron-alkene [3+2] cycloaddition from piperidinone [230], in a single complexity-generating step.¹



Scheme 2. 17. The mechanism of N–O bond in isoxazolidine [232] reductively cleavage

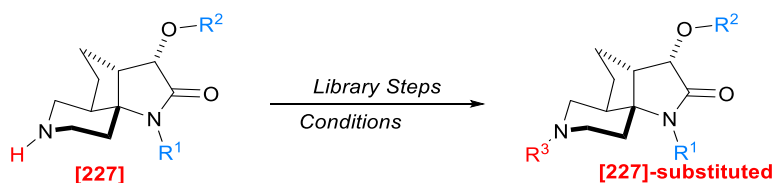
Chapter 2. Results & Discussion

The final step toward the molecule **[227]** was the deprotection of the piperidyl *N*-benzyl moiety of the spirocycle **[233]** which was achieved using hydrogenation using Pearlman's catalyst ($\text{Pd}/(\text{OH})_2$)¹¹³ and hydrogen gas, affording the secondary amines **[227]** in an excellent yield (91%) (Scheme 2.21).¹



Scheme 2. 18. Selective Debenzylation using Pearlman's catalyst

Scaffold **[233]** contains four stereocentres, of which one is a spirocyclic centre, and has a high degree of bond saturation, with an Fsp^3 value of 0.9. Further diversification of this scaffold has been carried out by the Stockman laboratory (Scheme 2.22).



Scheme 2. 19. Diversification of R^3 point

The library steps were based mainly on one point R^3 at the deprotected piperidyl nitrogen atom N1, **[227]** (Scheme 2.22). Functionalising this secondary amine to undergo useful transformation through: (i) amide formation *via* coupling with carboxylic acids, (ii) urea formation through the reaction with isocyanates, (iii) tertiary amine formation *via* reductive amination with corresponding aldehyde or ketone, (iv) sulfonamide formation by treatment with sulfonyl chlorides. A small, exemplary library of compounds was produced in good

yield and published. The relative configuration of 3-hydroxy lactam **[233]** has been confirmed by X-ray crystallography see (Figure 2.8).¹

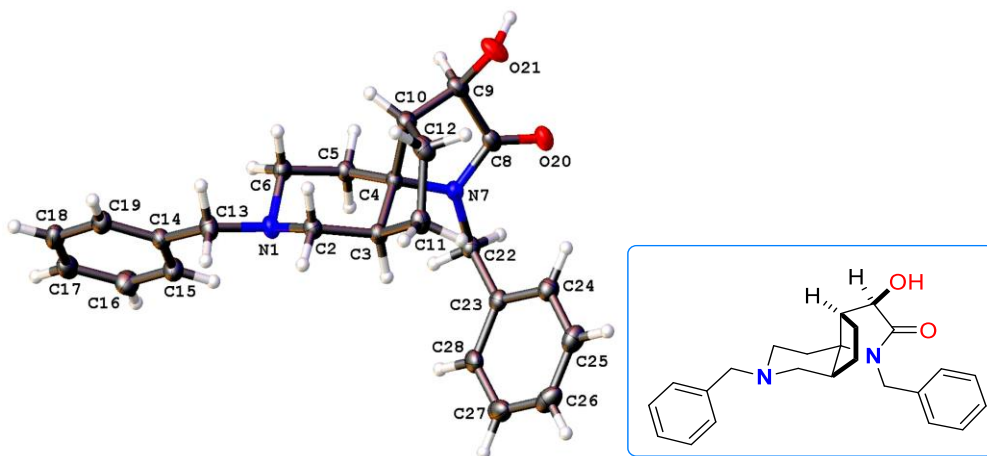
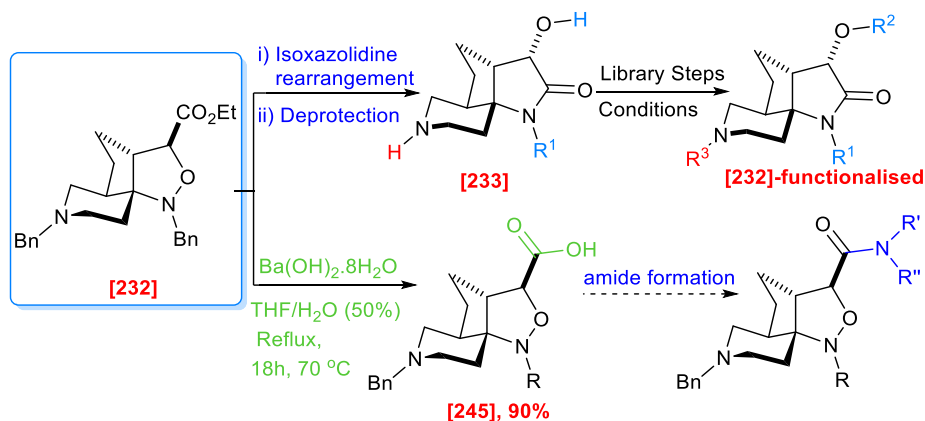


Figure 2. 8. Ortep diagram of **[233]**.¹

2.2.1.5. Hydrolysis of ethyl ester

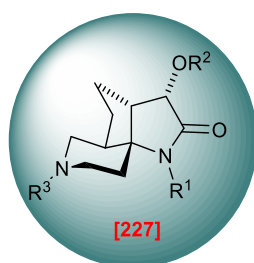


Scheme 2. 20. A second Path of Diversification by ethyl ester hydrolysis

The tricyclic core of isoxazolidine scaffold **[232]**, contains three variable points of diversification (R^1 , R^2 and R^3) therefore to allow exploration of chemical space; scaffold was hydrolysed of the ethyl ester. This was achieved by stirring the substrate with $Ba(OH)_2 \cdot 8H_2O$ in aqueous solution of THF then heating to reflux for 18 h, after which

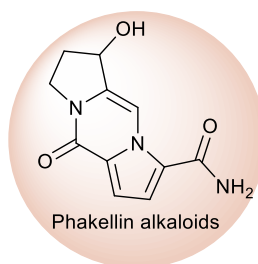
carbon dioxide gas was bubbled through the reaction to form insoluble barium carbonate, filtering to obtain the carboxylic acid as fine white powder **[245]** in an excellent yield (90%). This substrate could undergo library diversification steps through amide bond formation (Scheme 2.23).

2.2.1.6. Conclusion



A rapid synthetic route to scaffold **[227]** was developed starting from commercially available benzylpiperidinone. Alkylation of piperidinone, followed by condensation with mono *N*-substituted hydroxylamine allowed a diastereo selective intramolecular nitron-alkene [3+2] cycloaddition reaction to proceed. The novel key isoxazolidine moiety, was then rearranged to produce the target molecule in high yields. This short synthesis was scaled up to a multi-gram quantities efficiently. Subsequent one-pot reductive cleavage of isoxazolidine N–O bond then induced rearrangement and produced scaffold **[227]**, the relative configuration of which was confirmed by X-ray crystallographic analysis by Dr Rawling in Stockman group. Diversification of the scaffold provided a library of 543 drug-like molecules, which will be screened against various biological targets as part of the European Lead Factory.¹ Moreover, hydrolysis of ethyl ester group in **[232]** produced a new acidic scaffold **[245]** which could lead to more library compounds.

2.2.2. Attempted Synthesis of Natural-Product like “Phakellin substructure”



Phakellin is a family of tetracyclic (and larger) sponge alkaloids presumably based of pyrrole imidazole marine alkaloids.¹¹⁴ The phakellin family is marine-derived alkaloid, isolated from sponge *Acanthella carteri* collected off the Madagascar coast. This compound demonstrated great antimicrobial activity biogenetic insights provided by these new structures.¹¹⁵ Some new phakellin-type bromopyrroles have been characterised. The dibromophakellstatin (Figure 2.8), which is the principal antineoplastic component of the sponge, shows activity against ovarian, brain, kidney, lung, colon, and melanoma human cell lines.¹¹⁶

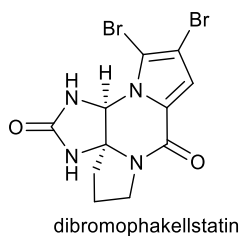
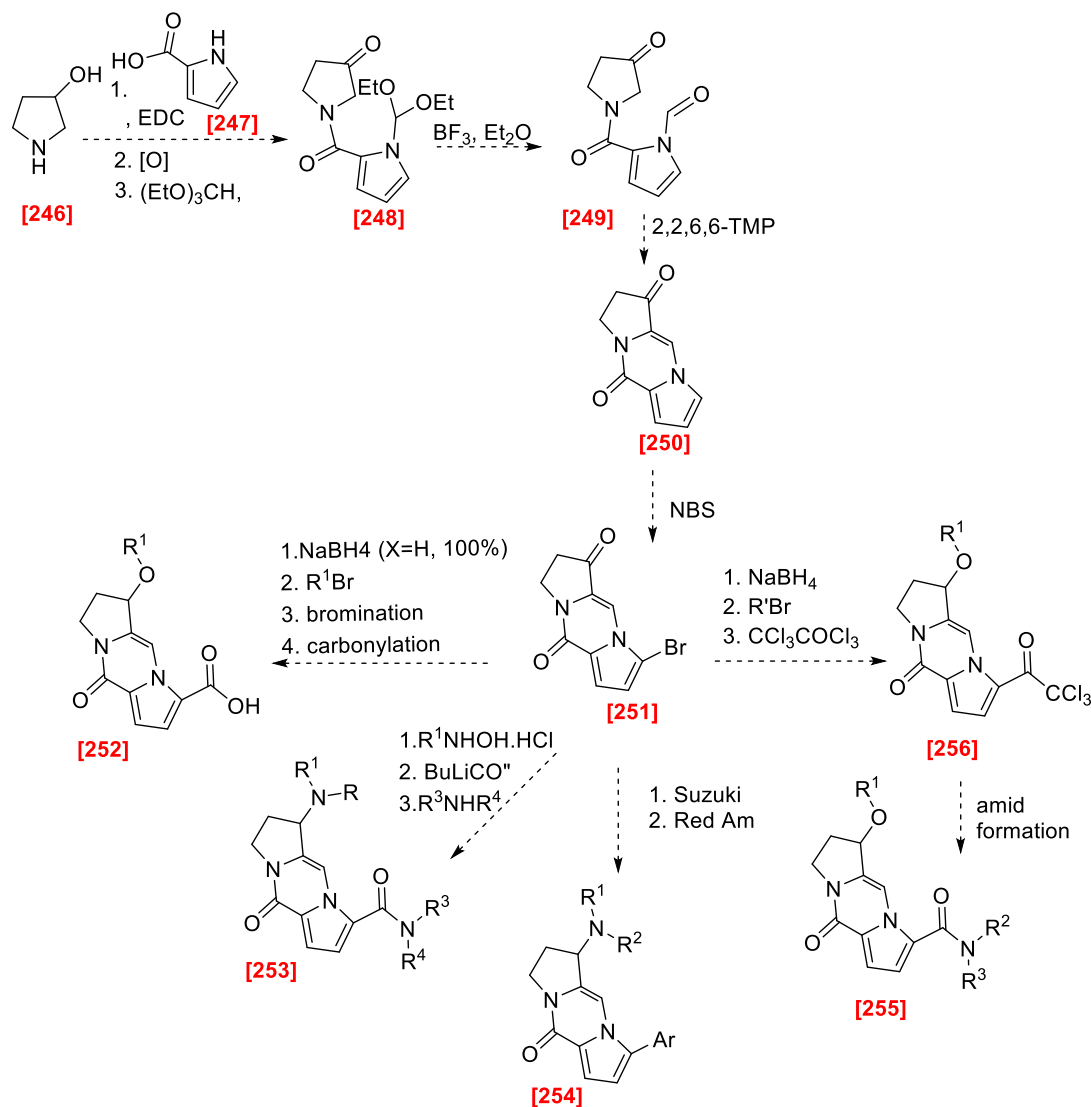


Figure 2. 8. Dibromophakellstatin

Herein we suggested a synthesis of a range of analogues of this alkaloid starting from the commercially available 3-hydroxypyrrolidine [246] (Scheme 2. 24).

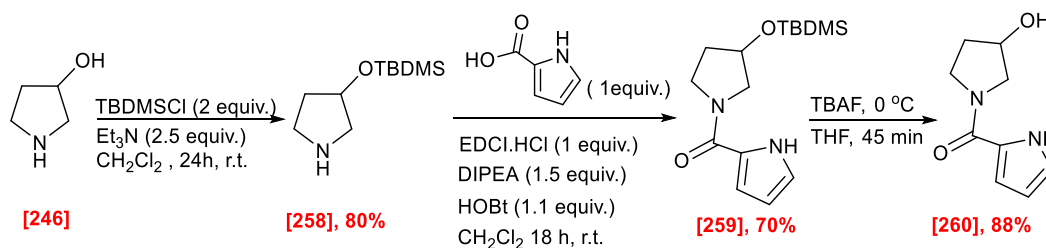
2.2.2.1. Toward total synthesis of phakellin alkaloid



Scheme 2. 21. Suggested Synthetic plan toward Phakellin alkaloid analogues

Our suggested plan toward the synthesis of the fused-ring system **[251]** the main core of phakellin, was to react the commercially available 3-pyrrolidinol **[246]** with pyrrole-2-carboxylic acid **[247]**. We first protected the alcohol group on pyrrolidinol in order to avoid

competing ester formation and self-coupling. TBDMSCl was used to protect the hydroxyl of **[246]** using the standard conditions, yielded 80% of the silyl protected alcohol **[257]** (Scheme 2.51). Coupling of this with pyrrole-2-carboxylic acid **[216]** to form the corresponding amide was carried using EDC.HCl (1.0 equiv.) in the presence of Hunig's base, HOBT (1.1 equiv.) in dichloromethane as solvent (Scheme 2.25), to give the derived O-protected amide **[283]** in 70% yield.



Scheme 2. 22. Amide formation using EDC coupling agent

Deprotection of the TBDMS gave **[259]**, was performed successfully using TBAF in 81% yield. Unfortunately, the next step, the oxidation of the deprotected hydroxyl group, was more difficult than expected. Our results are tabulated in (Table 2.4) below.

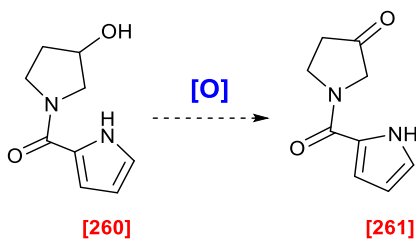
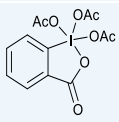


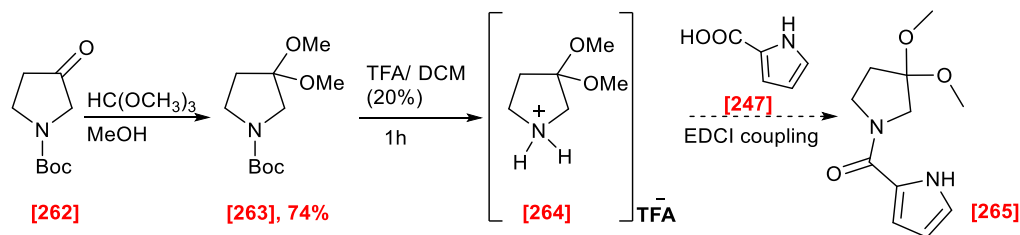
Table 2. 4. Oxidation attempts, different conditions

Entry	Conditions	Results
1-	PCC (1.1 equiv.), SiO ₂ ,	Complex mixture formed by H ¹ NMR
2-	Py.SO ₃ (10 equiv.), Et ₃ N (15 equiv.), DMSO, 1 h, 0 °C - r.t. ¹¹⁷	SM recovered
3-	 Dess-Martin ¹¹⁸	Decomposition during purification by SiO ₂ flash chromatography
4-	TPAP (5%), NMO (5equiv.), 4.0 Å MS, DCM (0.5M), 3h ¹¹⁹	Decomposition during purification by SiO ₂ flash chromatography

The oxidation of alcohol [260] has been explored using a variety of conditions we tried a standard PCC oxidation, but the product could not be identified by nmr or MS. Parikh-Doering oxidation procedure in entry 2 (Table 2.4) afforded the starting material, and under Dess-Martin conditions crude product was gummy and could not be isolated. The last attempt was the oxidation using TPAP and NMO, which also showed complex mixture formed by H¹ NMR with more than two carbonyl signals. We thought that perhaps the pyrrole ring was being oxidised/ polymerised under the oxidative conditions. We found that although the pyrrole ring is stable in dilute acid or / basic solutions, but could easily open the ring in refluxing ethanolic solution. Hydroxylamine hydrochloride has been used to prevent the polymerisation of the produced succinaldehyde. Ring-opening reaction found to be accelerated in alkylated pyrrole.¹²⁰ Moreover, the pyrrole ring can be oxidised by chromium trioxide in acetic acid and with hydrogen peroxide. This could translate the unexpected behaviour of our substrate [260] under the oxidation conditions.

Chapter 2. Results & Discussion

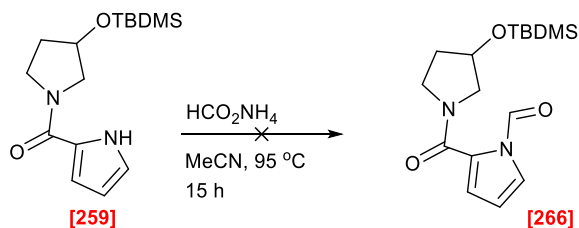
We therefore, tried to find another route to a desired ketone pyrrole **[261]** *N*-Boc-3-pyrrolidinone **[262]**, was first protected as the dimethyl acetal in 74% (Scheme 2.26).



Scheme 2. 23. Revised Route

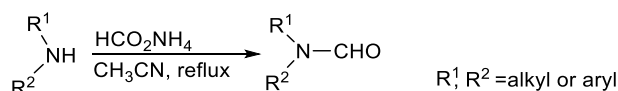
Due to difficulty toward forming the 3-oxo group in oxidising **[261]** to **[262]**, we thought that we may have desired product with ketone protected as its dimethyl ketal **[265]**. Compound **[265]** might be obtained after the coupling of 2-pyrrolecarboxylic acid **[247]** with the 3,3-dimethoxypyrrolidine **[264]**, (Scheme 2.26). Starting from the commercial available **[262]**, the oxo group was protected using trimethyl orthoformate (5.0 equiv.) in presence of *p*-toluene sulfonic acid (4 mole%) in methanol to afford the desired protected pyrrolidinone **[263]**.¹²¹ Then the protected amine group was treated with TFA in DCM.

Unfortunately, after preparing **[263]**, we failed to couple **[264]** with the pyrrole-2-carboxylic acid, due to the polymerisation which occurred upon removal of the Boc- group from the amine of **[263]**, we therefore turned to our earlier prepared substrate **[259]**. We hoped that by *N*-formylation the pyrrole at the protected alcohol stage we might stabilise this group and allow later oxidation of the remaining alcohol. Thus, we subjected **[257]** to the formylation on the nitrogen following atom but it did not work (Scheme 2.27).¹²²



Scheme 2. 24. Attempt to formylation

Numerous methods are available for the *N*-formylation of amines, however, many of these methods involve reagents which are either toxic or expensive. We tried to use ammonium formate as relatively less expensive reagent but, as reported in literature (Scheme 2.28).¹²² This procedure took place readily in acetonitrile at reflux temperature and the yields were very good, representative examples in (Table 2. 5).

Scheme 2. 25. *N*-formylation of secondary amines using ammonium formateTable 2. 5. *N*-Formylation of secondary amines and aniline with ammonium formate

Entry	Substrate	Eq. of HCO_2NH_4	Time (hours)	Product	Yield %
1		1.5	11		96
2		2.0	8		75
3		1.5	7.5		95
4		3.0	8.5		97

Chapter 2. Results & Discussion

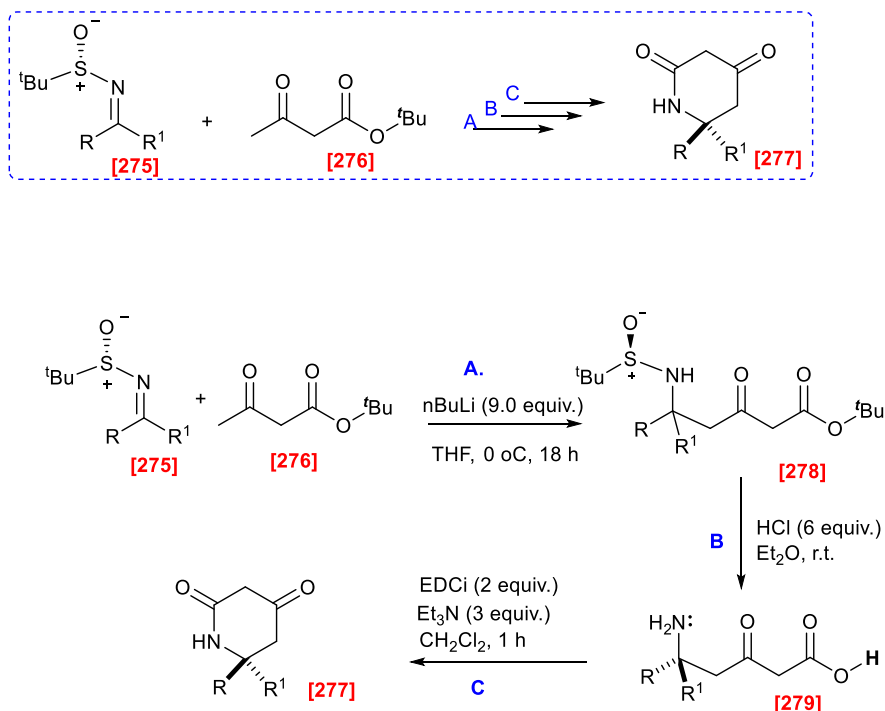
We decided to explore the use of this formylation procedure, for the transformation of [259] to [266]. Thus, [259] was headed in reaction with ammonium formate for 15 hours. Unfortunately, only starting material was observed, and this route was not finished due to time constrain's.

2.2.2.2 Conclusion

In summary, we tried synthesis of phakellin alkaloid starting from the commercialy available *N*-Boc-3-hydroxy pyrrolidine. We succeeded to couple the 2-pyrrole carboxylic acid with 3-hydroxy pyrrolidine. Unfortunately, attempts to oxidise the free alcohol was not successful. An alternative route, starting from protected ketone of pyrrolidine as acetal with the 2-pyrrole carboxylic acid, also did not work due to the free amine appearing to self-coupled and decomposed during purification by SiO₂ flash chromatography. Unfortunately, performing the formylating step on the silyl protected skeleton did not afford a formylated compound. Either more investigation is ongoing in the group.

2.2.3. Utilising chiral Sulfinimines towards Synthesis of six-membered β -keto lactam

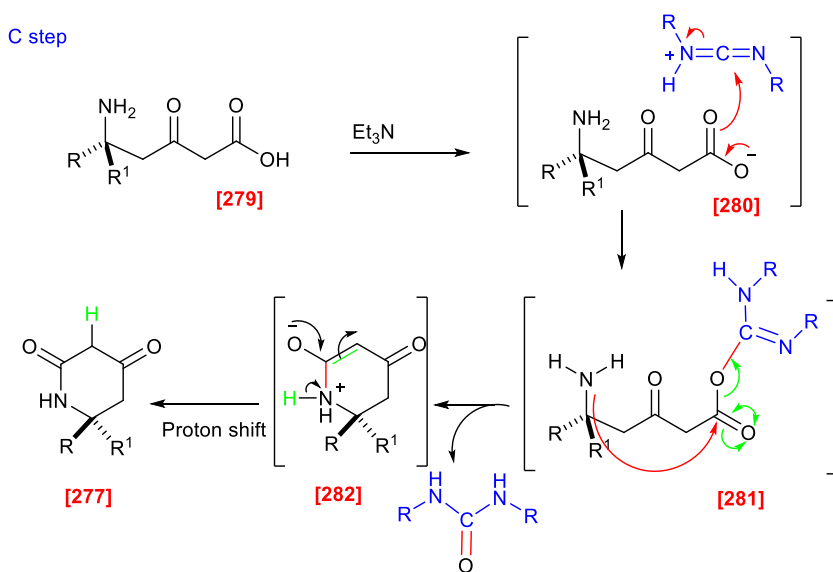
A range of substituted *tert*-butanesulfinimines precursors were prepared using Ellman's standard procedure earlier in our group by Morton, Robinson, and Procopiou.¹²³ Some of these I used, were reacted with *tert*-butylacetacetate in presence of *n*-butyl lithium to induce the double deprotonation of the later forming of a range of substituted *tert*-butyl 5-(((*R*)-*tert*-butylsulfinyl)amino)-3-oxoacetate [278], see (Scheme 2. 29). The amine was then deprotected in acidic media affording the δ -amino β -keto esters substrate [276].



Scheme 2. 26. Rapid Asymmetric Synthesis β -keto lactam

Chapter 2. Results & Discussion

The third step was the intramolecular acylation using EDCI and in presence of TEA, followed by Mannich reaction of δ -amino β -keto esters [278] with the carbonyl within the molecule. Thus, the coupling reagent EDCI (2.0 equiv.) and TEA caused the intramolecular amide formation, see (Scheme 2. 30).



Scheme 2. 27. Intramolecular lactam formation

Table 2.6, describes our transformation of a sulfinimine obtained using Ellman's standard procedure earlier in our group by Morton, Robinson, and Procopiou.¹²³ . Which we investigated, and reacted with the dianion of *tert*-butyl acetoacetate, giving good yields. Some were deprotected using acidic conditions to liberate the sulfone group and the *tert*-butyl group, which was then cyclised using EDCI as a coupling agent (Table 2.6).

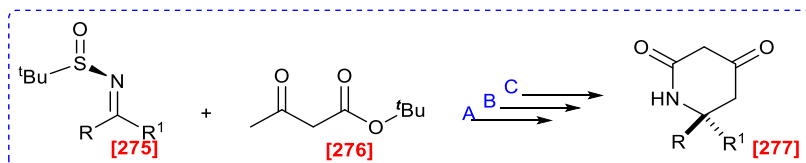
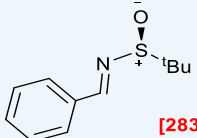
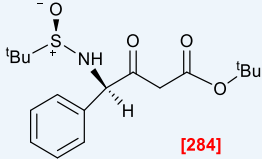
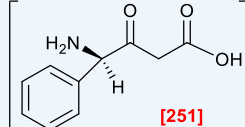
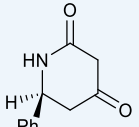
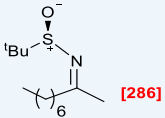
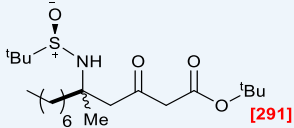
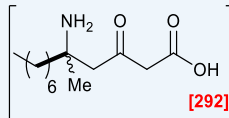
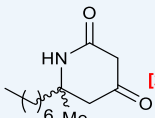
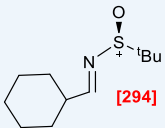
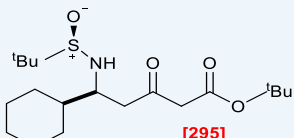
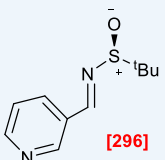
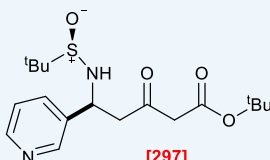
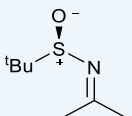
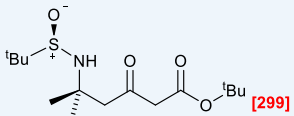


Table 2. 6. Some completed synthesised β -lactam

Entry	Sulfinimine	A	B	C
1-	 *DR, 82%	 *DR	 [251]	 [285] 59%
2-	 DR	 *DR	 [292]	 [293] 65%
3-	 *GP 85%	 79%		
4-	 *GP 99%	 80%		
5-	 *GP 79%	 35%		

*Note: **DR**, **GP**, refer to compounds prepared by Dian Robinson and George Procopiou, respectively.

3.2.3.1 Future work

More sulfinimines are to be investigated by choosing different aldehydes and ketones to explore the reactivity of these sulfinimines toward the cyclisation. Few compounds (not included) showed some difficulties to cyclise due to electron rich properties. Researches

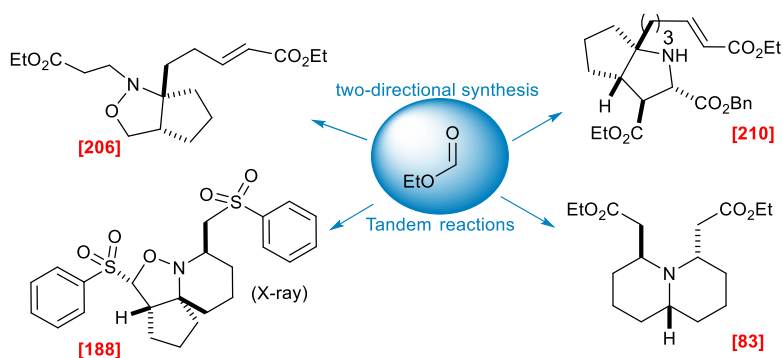
Chapter 2. Results & Discussion

are still going in Stockman group to find out more, and completion of the table and a range of different electron rich and poor substrates. Then performing a mechanistic study to examine the stereochemistry of the final products.

2. 3. Conclusion

Several novel methodologies were explored with the general purpose of rapid access to molecular complexity and sp^3 -rich scaffolds. A number of novel scaffolds were successfully synthesised, utilising two-directional synthesis and tandem reactions. The chemistries applied have been demonstrated to be capable of readily fabricating many novel and interesting diverse molecular scaffolds. For example, the azaspirocyclic cores found in halichlorine and pinnaic acid were produced using this approach, in fewer steps.

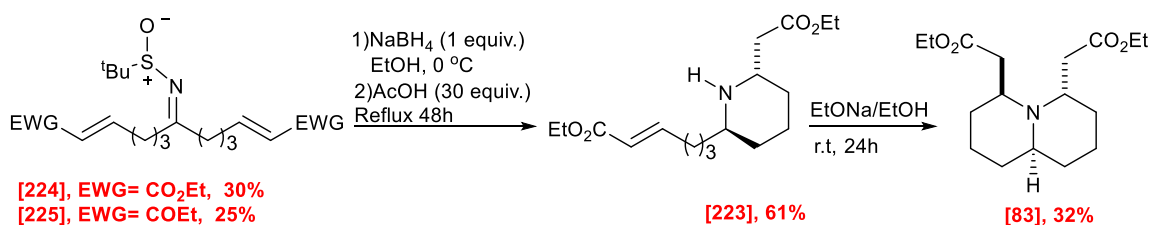
Diverse scaffolds were generated from simple symmetrical linear molecules [119], utilising the nitron produced *in situ* by the treatment of the central ketone with either hydroxylamine hydrochloride or amino acids. These afforded a number novel molecular skeletons which are expected to have interesting biological activity. In addition, they are conceivably useful for the synthesis of natural products, natural product-like, or in drug synthesis due to its high F_{sp^3} .



Scheme 2. 31. Azaspirocyclic cores obtained using two-directional/tandem cycloaddition

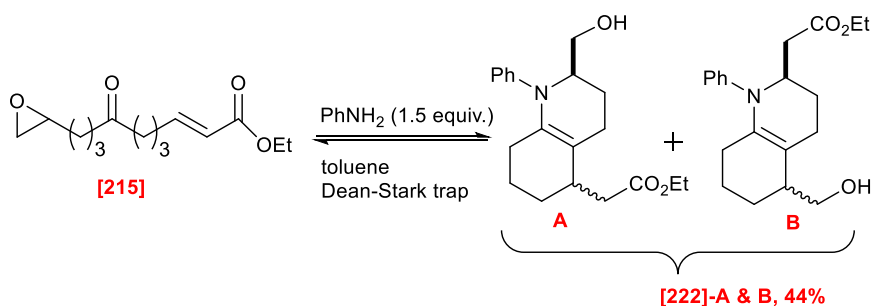
Chapter 2. Results & Discussion

We tried to explore the possibility of developing an enantioselective synthesis approach to the key intermediate in the synthesis of hippodamine. Unfortunately, the sulfinimines **[199]** and **[200]** (Scheme 2.38), by treatment with NaBH₄ reduced to the amine and the chiral auxiliaries liberated *in situ* before the subsequent aza-Michael addition. Thus, the process proceeded without stereo-control to give **[223]** in a good yield.



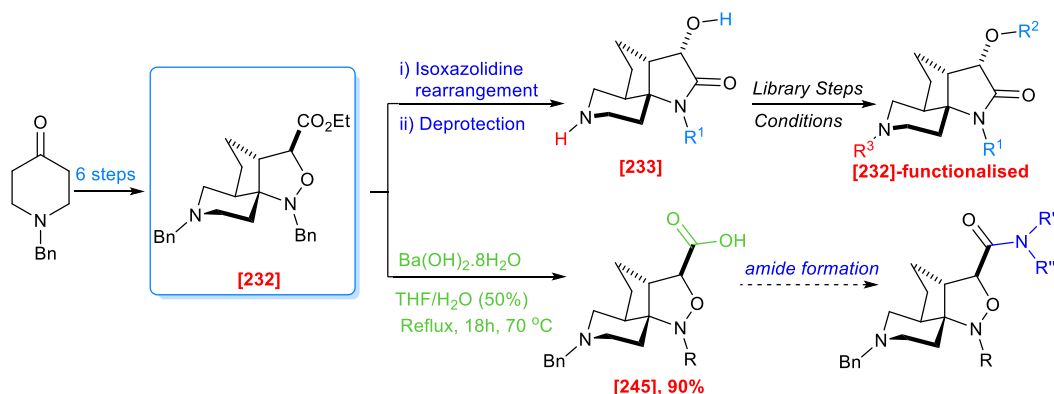
Scheme 2. 32.

Unfortunately, unsuccessful attempts at the synthesis of alkaloid *cis*-**275B** by desymmetrising **[119]** generated only regio-isomeric mixture.



Scheme 2. 33

Using the tandem reactions, we have also managed to develop a rapid synthetic route to an sp³-rich chemical scaffold **[213]** in just 6 steps *via* a highly regio- and diastereo-selective tandem nitron formation/intramolecular nitron-alkene [3+2] cycloaddition reaction from **[178]**. A library of 543 lead-like compounds based on the scaffold core has been produced by industrial company (Sygnature Discovery Ltd.).¹



Scheme 2. 34. Tandem Condensation/Intramolecular *via* Nitrone/[3+2]Cycloaddition

We were interested to synthesise phakellin alkaloids. We started from *N*-Boc-3-pyrrolidinol [246], then we had the hydroxyl group protected by silyl, and then coupled with 2-pyrrole carboxylic acid afforded [259] in a good yield. But unfortunately, the difficulty we faced that the decomposition of the unprotected [260] made it very difficult to continue the synthesis.

Several novel applications of chiral sulfinimines were explored. Initially some preliminary results toward the synthesis of piperidine dione [277] were recorded. Successful attempts of *tert*-butyl sulfinimines with dianion *tert*-butyl-acetoacetate afforded a range of sulfinamines. Treating these chiral sulfinamines in acidic conditions to liberate the sulfonyl group and *tert*-butyl ester group formed the acid which then to go through a tandem intramolecular coupling reaction which yielded the cyclic compound piperidine dione in a good yield [285]-[293]. Ongoing efforts in our group toward synthesising more results in this project.

CHAPTER 3

EXPERIMENTAL

Chapter 3

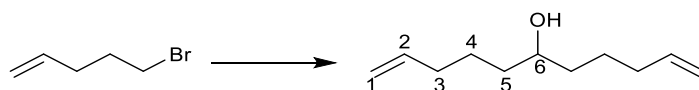
3. Experimental

All reactions were conducted under an inert argon atmosphere, in flame-dried glassware. Nuclear Magnetic Resonance (NMR) spectra were recorded on a 270 MHz (JEOL EX270) or 300 MHz (Bruker[®] DPX300) or 400 MHz (Bruker[®] DPX400, or AV400) or 400 MHz (Bruker[®] AV3400) or 500 MHz (Bruker[®] AV3500) or 600 MHz (Bruker[®] DPX600) NMR spectrometers in CDCl₃ or (CD₃)₂SO or CD₃OD at 300 K (unless stated otherwise). For proton NMR, samples were prepared using ca. 5–10 mg of compound dissolved in 1.0 mL of deuterated solvent and for carbon NMR using ca. 20 mg of compound dissolved in 1.0 mL of deuterated solvent. All spectra were referenced to CDCl₃, (CD₃)₂SO or CD₃OD the residual hydrogen solvent peaks for ¹H NMR (CDCl₃ δ = 7.27 ppm, (CD₃)₂SO δ = 2.50 ppm, CD₂OD δ = 3.31) and the solvent peak for ¹³C and ¹H NMR (CDCl₃ δ = 77.0 ppm, (CD₃)₂SO δ = 39.50, CD₃OD δ = 49.0). NMR Chemical shifts (δ) are reported in ppm; coupling constants (*J*) are reported in Hz; splitting patterns are assigned s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, br = broad signal and app = the apparent multiplicity. High resolution mass spectrometry (HRMS) data was obtained using a Bruker[®] MicroTOF spectrometer measured using electrospray ionization (ESI) in the positive mode. Solvents, unless otherwise stated, were purchased in reagent grade or anhydrous quality and used as received. THF was distilled from Na/benzophenone

immediately prior to use. Reagents were either purchased directly from commercial suppliers or prepared according to literature procedures. All reactions were carried out in round bottomed flasks and sealed with a glass stopper or a rubber septum equipped with an N₂ balloon and heated in oil baths with a thermocouple temperature control. Reactions were monitored using aluminium backed silica thin layer chromatography with a fluorescent dye ($\lambda = 254$ nm) and visualized under UV illumination or staining with basic KMnO₄ or Vanillin dips. Column chromatography was performed manually using Fluka silica gel with 60 Å pore size eluting with different stated solvents. (IR) spectroscopy was performed using a Perkin-Elmer 1600 FTIR spectrometer. X-Ray analysis studies were performed by Dr William Lewis, at the University of Nottingham. Numbering of structures corresponds to ¹H and ¹³C NMR assignment, and is independent of compound nomenclature. References are indicated where applicable refer to the procedures, although some novel compounds.

3.1. Experimental procedures

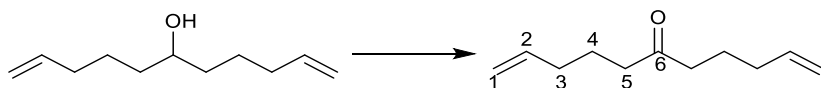
Undeca-1,10-dien-6-ol [118]⁷¹



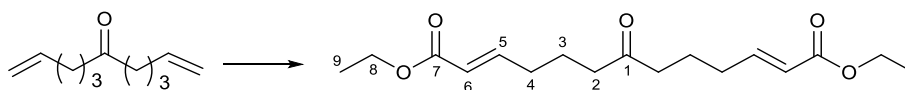
To a suspension of magnesium (4.49 g, 185 mmol, 1.2 equiv.) in anhydrous tetrahydrofuran (30 mL) was added a small amount of iodine crystals, forming a yellow suspension. 5-Bromo-1-pentene (25.0 g, 168 mmol, 1.0 equiv.) was then added slowly, cooling the reaction with further tetrahydrofuran as required (~ 30 mL). The solution was stirred for 3 h. A solution of ethyl formate (6.22 g, 84 mmol, 0.5 equiv.) in tetrahydrofuran (100.0 mL) was then added drop-wise over 3 h and the reaction mixture was stirred for a further 18 h at room temperature and heated to reflux for 1 h. The reaction was cooled and quenched with sat. aqueous ammonium chloride (100.0 mL), and extracted with diethyl ether (3 x 50.0 mL). The solvent was removed *in vacuo*, and the crude product was heated under reflux conditions in aq. potassium hydroxide (15% w/v, 100.0 mL) for 3 h. The solution was extracted with diethyl ether (3 x 50.0 mL), the combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to give a clear oil, which was used without further purification (13.37 g, 79.5 mmol, 95%); ¹H NMR (400 MHz, CDCl₃) δ = 5.82 (ddt, *J* = 17.1, 10.2 and 6.8, 2H, 2-H), 5.00 (dd *J* = 17.1, 1.6, 2H, 1-H_b), 4.94 (dd *J* = 10.2 and 1.2, 2H, 1-H_a), 3.59 (br. s, 1H, 6-H), 2.12-2.03 (m, 4H, 3-H₂), 1.61-1.43 (m, 8H, 4-H₂ and 5-H₂); ¹³C NMR (100 MHz, CDCl₃) δ = 138.7 (C2), 114.6 (C1), 71.7 (C6), 36.9 (C5), 33.7 (C3), 24.9 (C4); IR ν_{max}/cm⁻¹ (thin film, ν/cm⁻¹) 3337, 3077, 2976, 2928, 2858,

1640, 1458, 1440, 1058, 992, 908; MS (ESI): m/z = 191.1 ($[M+Na]^+$, 46), 169.2 ($[M+H]^+$, 21), HRMS = 191.1411 (calcd = 169.1406 $[C_{11}H_{21}ONa]^+$). Data match the literature.⁷¹

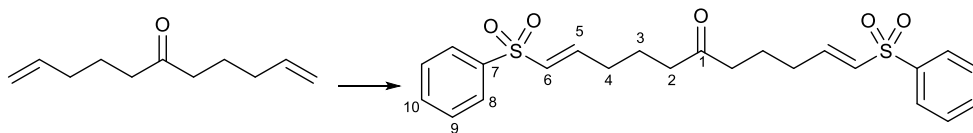
Undeca-1,10-dien-6-one [119]⁷²



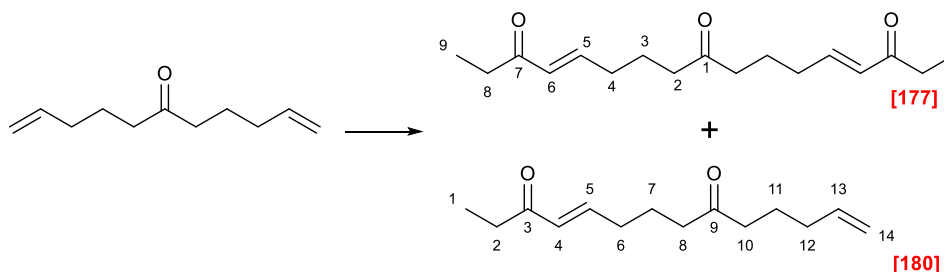
To solution of undeca-1,10-dien-6-ol (2.0 g, 11.9 mmol, 1 equiv.) in dichloromethane (50.0 mL) was added silica gel (6 g) followed by pyridinium chlorochromate (2.8 g, 13.1 mmol, 1.1 equiv.) and the solution was stirred for 18 h. Silica gel was added (3.0 g) and the solution was stirred for a further 30 min, then filtered and concentrated. The resulting dark brown oil was re-dissolved in diethyl ether and filtered through a short pad of silica gel. The filtrate was dried over sodium sulfate and the solvent was removed *in vacuo* to give the product as a clear oil which was used without further purification (1.97 g, 11.8 mmol, 99%); ^1H NMR (400 MHz, $CDCl_3$) δ = 5.69 (ddt, J = 17.0, 10.2, 6.7 Hz, 2H, 2-H), 4.94 (dd, J = 17.0, 1.4 Hz, 2H, 1-H_b), 4.94 (dd, J = 10.2, 1.4 Hz, 2H, 1-H_a), 2.33 (t, J = 7.4 Hz, 4H, 5-H₂), 1.98 (m, 4H, 3-H₂), 1.60 (m, 4H, 4-H₂); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 210.5 (C6), 137.9 (C2), 114.9 (C1), 41.7 (C5), 32.9 (C3), 22.58 (C4); IR (thin film, ν/cm^{-1}) 2931, 1714, 913; MS (ESI) m/z = 184.1696 ($[M+NH_4]^+$, 100), HRMS = 184.1696 (calcd = 184.1696 $[C_{11}H_{22}NO]^+$). Data match the literature.⁷²

(2E,11E)-Diethyl 7-oxotrideca-2,11-dienedioate [120]⁷²

To a solution of undeca-1,10-dien-6-one (1.5 g, 9.0 mmol, 1.0 equiv.) in dichloromethane (50.0 mL) was added ethyl acrylate (5.42 g, 54.0 mmol, 6.0 equiv.), followed by Hoveyda-Grubbs 2nd generation catalyst (135.0 mg, 0.015 mmol, 2.5 mol%) as a solid. The solution was stirred for 24 h, at which time another portion of catalyst (135.0 mg, 0.015 mmol, 2.5 mol%) was added. The solution was stirred for a further 72 h, whereupon the solvent was removed *in vacuo* and purification by column chromatography (over silica gel, eluting with 6:1 Pet/EtOAc) gave the product as a clear oil (2.6 g, 8.3 mmol, 90%): *R*_f 0.34 in 3:1 H/EA; δ ¹H NMR (270 MHz, CDCl₃) δ = 6.91 (dt, *J* = 15.6, 7.2 Hz, 2H, H-5), 5.82 (dt, *J* = 15.6, 1.5 Hz, 2H, H-6), 4.18 (q, *J* = 7.2 Hz, 4H, H-8), 2.35 (t, *J* = 7.2 Hz, 4H, H-2), 2.13-2.08 (m, 4H, H-4), 1.66-1.45 (m, 4H, H-3), 1.28 (t, *J* = 7.2 Hz, 6H, H-9); ¹³C NMR (125 MHz, CDCl₃) δ = 209.3 (C1), 166.4 (C7), 147.9 (C6), 122.0 (C5), 60.2 (C8), 41.7 (C2), 31.3 (C4), 21.8 (C3), 14.2 (C9); MS (ESI) *m/z* = 333.1668 ([M+Na]⁺, 100), 311.853 ([M+H]⁺, 2), HRMS = 333.1668 (calcd = 333.1672 [C₁₇H₂₆NaO₅]⁺), 311.8530 (calcd = 311.853 [M+H]⁺). Data match the literature.⁷²

(1E,10E)-1,11-bis(phenylsulfonyl)undeca-1,10-dien-6-one [178]⁷²

To a solution of undeca-1,10-dien-6-one (1.0 g, 6.0 mmol, 1.0 equiv.) in CH_2Cl_2 (60.0 mL) was added vinyl phenyl sulfone (6.0 g, 36.0 mmol, 6.0 equiv.), followed by Hoveyda-Grubbs 2nd generation catalyst (90.0 mg, 0.015 mmol, 2.5 mol%) as a solid. The solution was stirred at room temperature for 24 h, at which time another portion of catalyst (90.0 mg, 0.15 mmol, 2.5 mol%) was added. The solution was stirred for a further 48 h, whereupon the solvent was removed *in vacuo* and purification by column chromatography over silica gel, eluting with Pet/EtOAc (1:1) v/v ratio, gave the product as a brown dense oil (2.25 g, 5.0 mmol, 84%); ^1H NMR (400 MHz, CDCl_3) δ = 7.73 – 7.68 (m, 4H), 7.47 – 7.42 (m, 2H, Ar), 7.40 – 7.34 (m, 4H, Ar), 6.77 (dt, J = 15.1, 6.8 Hz, 2H, H-5), 6.21 (dt, J = 15.1, 1.4 Hz, 2H, H-6), 2.21 (t, J = 7.2 Hz, 4H, H-2), 2.05-1.75 (m, 4H, H-4), 1.52 (m, 4H, H-3); ^{13}C NMR (600 MHz, CDCl_3) δ = 209.3 (C1), 139.5 (C7), 138.4 (Ar), 133.6 (Ar), 133.3 (Ar), 127.7 (C6), 127.6 (C5), 42.4 (C2), 30.6 (C4), 21.3 (C3); IR (thin film, v/cm^{-1}) 3624, 3550, 3102, 3059, 2935, 2735, 2069, 1969, 1710, 1625, 1608, 1584, 1478, 1447; MS (ESI) m/z = 469.1136 ($[\text{M}+\text{Na}]^+$, 100), 447.1305 ($[\text{M}+\text{H}]^+$, 11), 464.1569 ($[\text{M}+\text{NH}_4]^+$, 4); HRMS = 469.1136 (calcd = 469.1114 $[\text{C}_{23}\text{H}_{26}\text{NaO}_5\text{S}_2]^+$). Data match literature.⁷²

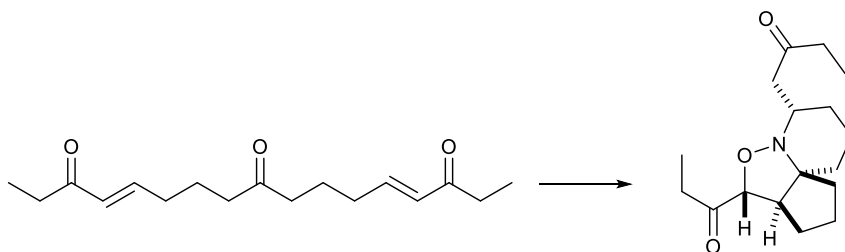
(4*E*,13*E*)-heptadeca-4,13-diene-3,9,15-trione [151], and (*E*)-tetradeca-4,13-diene-3,9-dione [177]

To a solution of undeca-1,10-dien-6-one (1.0 g, 6.0 mmol, 1.0 equiv.) in CH₂Cl₂ (50.0 mL) was added ethyl vinyl ketone (3.0 g, 36.0 mmol, 6.0 equiv.), followed by Hoveyda-Grubbs 2nd generation catalyst (94.0 mg, 0.015 mmol, 2.5 mol%) as a solid. The solution was stirred for 24 h, at which time another portion of catalyst (94.0 mg, 0.015 mmol, 2.5 mol%) was added. The solution was stirred for a further 48 h, whereupon the solvent was removed *in vacuo* and purification by column chromatography (over silica gel, eluting with 10:1 Pet/EtOAc, gave two products first compound came out of the column was the mono substituted product **[180]** as a pale brown liquid (300.0 mg, 1.35 mmol, 22%): *R*_f = 0.8 in Hex/EtOAc (1:1) solvent system; ¹H NMR (270 MHz, CDCl₃) δ = 6.64 (dt, *J* = 15.6, 7.0 Hz, 2H, H-5), 5.94 (dt, *J* = 15.6, 1.5 Hz, 2H, H-4), 5.60 (ddt, *J* = 16.0, 7.2, 6.6 Hz, 1H, H-13), 5.04 (dt, *J* = 16.0, 1.5, 2H, H-14), 4.87 (m, 4H, H-6, H-12), 4.81 (q, *J* = 7.2 Hz, 2H, H-2), 2.35-2.23 (m, 4H, H-8, H-10), 2.17-2.10 (m, 2H, H-11), 1.55-1.15 (m, 2H, H-7), 0.97 (t, *J* = 7.2 Hz, 3H, H-1); ¹³C NMR (68 MHz, CDCl₃) δ = 210.0 (C9), 200.7 (C3), 145.7 (C4), 137.8 (C5), 130.3 (C13), 115.0 (C14), 41.5 (C2), 41.1 (C8), 33.0 (C10), 32.4 (C6), 31.6 (C12), 22.3 (C7), 21.8 (C11), 7.8 (C1); IR (thin film, ν/cm⁻¹) 3609, 3415, 2982, 2939, 2056, 1717, 1654, 1446, 1413, 1369, 1269, 1183, 1043, 980; MS (ESI) *m/z* = 245.1202

($[M+Na]^+$, 57), 241.1202 ($[M+NH_4]^+$, 33), 464.1569 ($[M+NH_4]^+$, 4), HRMS = 245.1202 (calcd = 245.1512 for $[C_{14}H_{22}NaO_2]^+$).

The second compound isolated **[177]** as a pale brown oil (1.20 g, 4.3 mmol, 71%); R_f = 0.6 in H/EA (1:1) solvent system; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.77 (dt, J = 15.9, 7.0 Hz, 4H, 2H₂, H-5), 6.09 (dt, J = 15.9, 1.4 Hz, 4H, 2H₂, H-6), 2.55 (q, J = 7.3 Hz, 4H, H-8), 2.42 (t, J = 7.2 Hz, 4H, 2H₂, H-2), 2.81-2.10 (m, 4H, 2H₂, H-4), 1.95-1.62 (m, 4H, 2H₂, H-3), 1.09 (t, J = 7.3 Hz, 6H, 2H₃, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.4 (C1), 200.9 (C7), 145.6 (C6), 130.5 (C5), 41.7 (C8), 33.3 (C2), 31.6 (C4), 21.8 (C3), 8.0 (C9); IR (thin film, ν/cm^{-1}) 3490, 2975, 2938, 2735, 1714, 1672, 1629, 1458, 1413, 1376, 1272, 1200, 1120, 1065, 980; MS (ESI) m/z = 279.1961 ($[M+H]^+$, 100), 301.1782 ($[M+Na]^+$, 60), 296.2223 ($[M+NH_4]^+$, 17); HRMS = 279.1961 (calcd = 279.1955 $[C_{17}H_{27}O_3]^+$), 301.1782 (calcd = 301.1774 $[C_{17}H_{26}NaO_3]^+$).

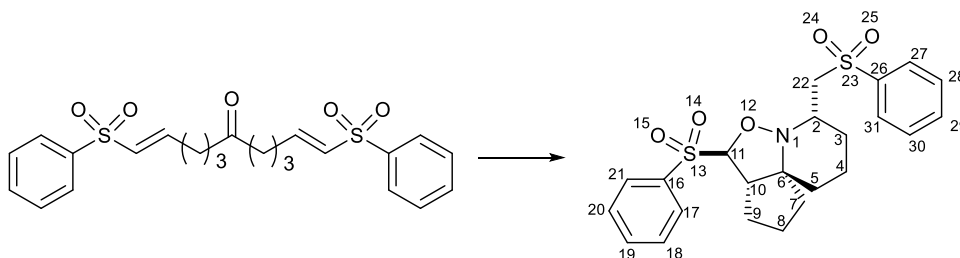
1-((3aS*,4R*,7S*,10aS*)-4-propionyloctahydro-1H-cyclopenta[3,4]isoxazolo[2,3-a]pyridin-7-yl)butan-2-one [197]⁵⁵



To a solution of (4*E*,13*E*)-heptadeca-4,13-diene-3,9,15-trione (50.0 mg, 0.18 mmol, 1.0 equiv.) in anhydrous methanol (5.0 mL) was added hydroxylamine hydrochloride (14.0 mg, 0.19 mmol, 1.1 equiv.) and sodium acetate (37.0 mg, 0.45 mmol, 2.5 equiv.), the

solution stirred at r.t. for 24 h by which reaction quenched with saturated aqueous sodium hydrogen carbonate (2.0 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 5.0 mL), the combined organic layers were dried over MgSO₄ and the solvent was removed *in vacuo*. The residue was re-dissolved in anhydrous MeCN (5.0 mL) and heated to reflux for 2 h, reaction mixture then cooled to r.t. and solvent evaporated and purification by flash column chromatography over silica gel using Hex/ EtOAc (1:2), afforded the titled compound as a single diastereomer a colourless oil $R_f = 0.44$ (35.0 mg, 67%); ¹H NMR (600 MHz, CDCl₃) $\delta = 4.12$ (dd, $J = 14.4, 7.2$ Hz, 2H), 4.03(d, $J = 6.6$ Hz, 1H), 3.1 (dd, $J = 16.2, 2.4$ Hz, 1H), 2.91 (ddt, $J = 11.4, 6.0, 3.0$ Hz, 2H), 2.63-2.56 (m, 3H), 2.53 (t, $J = 7.2$ Hz, 2H), 2.51-2.40 (m, 3H), 2.04 (s, 2H), 2.04-2.01(m, 2H), 1.91 – 1.87 (m, 5H), 1.04 (m, 6H); ¹³C NMR (600 MHz, CDCl₃) $\delta = 210.6, 210.4, 89.5, 84.8, 60.1, 59.4, 49.6, 47.4, 39.2, 37.0, 32.6, 29.8, 29.7, 29.3, 28.4, 20.1, 19.6$; m/z for C₁₇H₂₇NO₃ 293.19 found for [M]⁺ = 293.20.

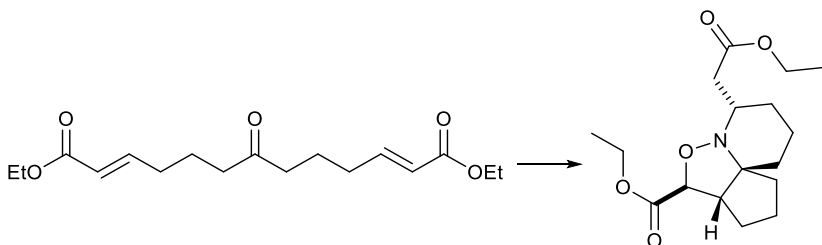
(3a*S*,4*R*,7*R*,10a*S*)-4-(phenylsulfonyl)-7-((phenylsulfonyl)methyl)octahydro-1*H*-cyclopenta[3,4]isoxazolo[2,3-*a*]pyridine [188]⁵⁵



To a solution of (1*E*,10*E*)-1,11-bis(phenylsulfonyl)undeca-1,10-dien-6-one (100.0 mg, 0.22 mmol, 1 equiv.) in MeCN (3.0 mL) hydroxylamine hydrochloride (23.5 mg, 0.33

mmol, 1.5 equiv.) and sodium acetate (72.5 mg, 0.88 mmol, 4.0 equiv.) was added, the solution stirred at r.t. for 3 days by which time reaction quenched with saturated aq. Sodium hydrogen carbonate (2.0 mL) and the aqueous layer was extracted with CH₂Cl₂(3 x 2.0 mL), the combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography over silica gel using Hex/ EtOAc (3:7), to give the titled compound as white solid product, which then crystallised from chloroform (10.0 mg, 0.02 mmol, 10%); R_f = 0.1 in Hex/EtOAc (7:3); ¹H NMR (400 MHz, CDCl₃) δ = 8.12-7.94 (m, 2H, H-31,27/ H-17,21, (Ar Hs)), 7.93-7.90 (m, 2H, H-31,27/ H-17,21, (Ar Hs)), 7.87-7.66 (m, 2H, H-29, H-19, (Ar Hs)), 7.64 -7.54 (m, 4H, H-28,H-30,H-18,H-20), 4.54 (d, *J* = 7.4 Hz, 1H, H-11), 3.98 – 3.88 (m, 1H, H-2), 3.57 (app dd, *J* = 14.0, 2.6 Hz, 1H, H-22_a), 3.40 (m, 1H, H-10), 3.29 (dd, *J* = 14.0, 2.6 Hz, 1H, H-22_b), 2.39 (dt, *J* = 10.3, 2.6 Hz, 2H, H-3), 2.01 (dd, *J* = 7.4, 7.2 Hz, 2H, H-9), 1.97 – 1.82 (m, 2H, H-5), 1.86 –1.77 (m, 2H, H-4), 1.76 – 1.69 (m, 2H, H-8), 1.68-1.65 (m, 2H, H-7); ¹³C NMR (400 MHz, CDCl₃) δ = 141.02 (Ar), 137.69 (Ar), 134.06 (Ar), 133.48 (Ar), 129.23 (Ar), 129.12 (Ar), 128.96 (Ar), 127.78 (Ar), 99.70 (C-11), 76.68 (C-6), 60.36 (C-22), 60.26 (C-2), 48.66 (C-10), 38.29 (C-7), 32.04 (C-9), 29.61 (C-8), 28.05 (C-3), 20.37 (C-5), 19.42 (C-4); IR(neat, v/cm⁻¹) 3083, 2948, 2863, 1733, 1178, 909; MS (ESI) *m/z* = 461.1331 ([M+Na]⁺ , 100); HRMS = 484.1331 (calcd = 484.1228 [C₂₃H₂₇NNaO₅S₂]⁺).

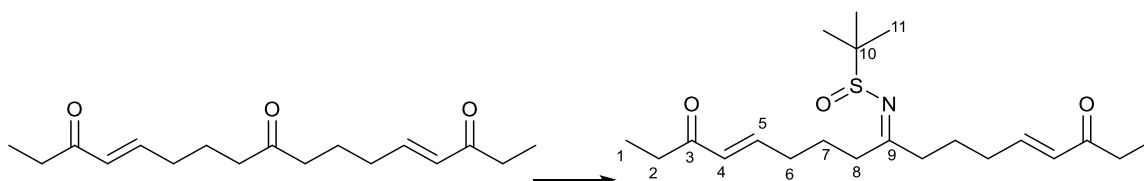
Diethyl 2,2'-((3a*S*,4*S*,7*S*,10a*S*)-octahydro-1*H*-cyclopenta[3,4]isoxazolo [2,3-*a*]pyridine-4,7-diyl)diacetate [81]⁵⁵



To a stirred solution of diethyl (2*E*,11*E*)-7-oxotrideca-2,11-dienedioate (6.00 g, 19.3 mmol, 1 equiv.) in anhydrous methanol (250.0 mL) was added sodium acetate (3.97 g, 48.4 mmol, 2.5 equiv.) and hydroxylamine hydrochloride (1.48 g, 21.3 mmol, 1.1 equiv.). The solution was left to stir at room temperature for 24 h. The solvent was removed *in vacuo* to give a solid that was stirred in CH₂Cl₂ (200.0 mL) for 20 minutes. The solution was filtered, the precipitate disregarded and solution removed *in vacuo*. The resultant orange oil was re-solubilised in acetonitrile (150.0 mL) and heated to reflux for 2 hours at 95 °C. The solvent was removed *in vacuo* and residue re-dissolved in cyclohexane (150 mL). The solution was heated to reflux for 40 minutes at 100 °C and a hot filtration was before followed by concentration *in vacuo* to provide the product (6.01 g, 18.5 mmol, 93%) as an orange oil; ¹H NMR (400 MHz, CDCl₃) δ = 4.26 – 4.15 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.15 (dd, *J* = 15.6, 3.2 Hz, 2H), 3.03 (t, *J* = 5.9 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.29 (dd, *J* = 15.6, 9.8 Hz, 2H), 2.04 (ddd, *J* = 13.4, 10.2 and 6.4 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.93 – 1.77 (m, 3H), 1.70 (td, *J* = 13.9, 13.4 and 4.6 Hz, 1H), 1.56 (ddd, *J* = 13.9, 8.5, 5.6 Hz, 1H), 1.42 – 1.31 (m, 1H), 1.25 (dt, *J* = 14.2, 7.1 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ = 172.8, 172.1, 83.3, 77.4, 61.3, 60.4, 60.0, 50.9, 39.1, 39.1, 32.9, 29.8, 29.1, 21.1, 20.5,

14.2, 13.9; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3012, 2941, 2873, 1265, 1193, 1166; MS (ESI) m/z = 326.1962 ($[\text{M}+\text{H}]^+$, 100), 348.1796 ($[\text{M}+\text{Na}]^+$, 44), 673.3695 ($[\text{2M}+\text{Na}]^+$, 52); HRMS = 326.1962 (calcd = 326.1979 $[\text{C}_{17}\text{H}_{28}\text{NO}_5]^+$), 348.1796 (calcd = 348.1781 $[\text{C}_{17}\text{H}_{27}\text{NNaO}_5]^+$), 673.3695 (calcd = 673.3676 $[\text{C}_{34}\text{H}_{54}\text{N}_2\text{NaO}_{10}]^+$). Data match literature.

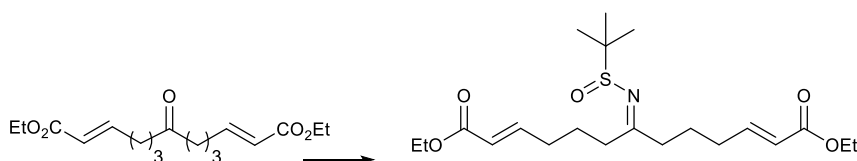
***N*-((4*E*,13*E*)-3,15-dioxoheptadeca-4,13-dien-9-ylidene)-2-methylpropane-2-sulfonamide [225]¹²⁴**



In a 25 mL flame dried round bottom flask, (4*E*,13*E*)-heptadeca-4,13-diene-3,9,15-trione (50.0 mg, 0.18 mmol, 1 equiv.) was stirred under nitrogen gas as a solution in THF (3.0 mL), *R*(+)-2-methyl-2-propansulfonamide (24.0 mg, 0.2 mmol, 1.1 equiv.) was added, followed by $\text{Ti}(\text{EtO})_4$ (164.0 mg, 0.72 mmol, 4.0 equiv.) addition. The mixture was heated at 40 °C for 2 hours before stirring at room temperature for 24 hours, NH_4Cl aqueous solution (2.0 mL) added after which time the mixture was filtered over celite and the resulting cake was washed with warm ethyl acetate. The aqueous layers was partitioned with EtOAc (3 x 3.0 mL), the combined organic phases was dried over anhydrous sodium sulfate, then the solvent was removed *in vacuo*, and purified using a column chromatography on silica gel using Hex/EtOAc (1:1) as a solvent, to give the titled compound (17 mg, 0.4 mmol, 25%) as a colourless oil; R_f = 0.3 in Hex/EtOAc (1:1); ^1H

NMR (400 MHz, CDCl₃) δ = 6.78 (dt, J = 13.8, 7.4 Hz, 2H, H-5), 6.10 (dt, J = 13.8, 1.8 Hz, 2H, H-4), 2.56 (q, J = 7.2 Hz, 4H, H-2), 2.42 (t, J = 7.2 Hz, 4H, H-8), 2.21 (app dq, J = 8.4, 7.4, 1.8 Hz, 4H, H-6), 1.79-1.74 (m, 4H, H-7), 1.22 (s, 9H, H-11), 1.08 (t, J = 7.2 Hz, 6 H, H-1); ¹³C NMR (150 MHz, CDCl₃) δ = 209.4 (C3), 201.0 (C9), 145.6 (C4), 130.5 (C5), 58.9 (C10), 41.7 (C2), 33.2 (C8), 31.6 (C6), 24.1 (C7), 22.0 (C11), 8.0 (C1); IR (thin film, ν/cm^{-1}) 3353, 3266, 2981, 2939, 2359, 1716, 1653, 1447, 1413, 1367, 1269, 1183, 1109, 1044, 980, 862, 709; MS (ESI): m/z = 382.2425 ([M+H]⁺, 100), 404.2221 ([M+Na]⁺, 24), HRMS = 382.2425 (calcd = 382.2410, [C₂₁H₃₆N₁O₃S₁]⁺), (calcd = 404.2230, [C₂₁H₃₅N₁Na₁O₃S₁]⁺).

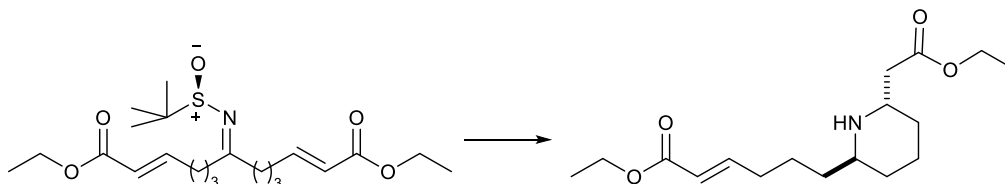
Diethyl (2*E*,11*E*)-7-((*tert*-butylsulfinyl)imino)trideca-2,11-dienedioate [224]¹²⁴



In a 25-mL flame dried round bottom flask, diethyl (2*E*,11*E*)-7-oxotrideca-2,11-dienedioate (400.0 mg, 1.3 mmol, 1.0 equiv.) was stirred under nitrogen gas as a solution in THF (14.0 mL), (+) *R*-2-methyl-2-propansulfonamide (169.0 mg, 1.4 mmol, 1.1 equiv.) was added, followed by Ti(EtO)₄ (1.44.0 g, 5.0 mmol, 4.0 equiv.) addition. Mixture was stir at 40 °C for 2 hours before cooling to r.t. slowly for 24 hours while stirring. NH₄Cl

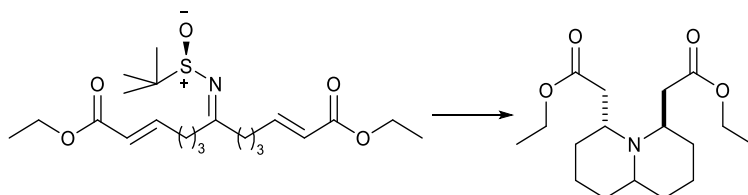
aqueous solution (2.0 mL) added after which time the mixture was filtered over celite and the resulting cake was washed with warm EtOAc, then the aqueous layers was partitioned with EtOAc (3 x 3.0 mL), the combined organic phases was dried over anhydrous sodium sulfate, then the solvent was removed *in vacuo*, and purify using a column of silica gel using Hex/EtOAc, the solvent was removed *in vacuo*, and then purified using a column chromatography on silica gel using Hex/EtOAc (1:1) as a solvent, to provide the titled compound (247.0 mg, 0.59 mmol, 46 %) as a colourless oil; R_f : 0.5 in Hex/EtOAc (1:1); ^1H NMR (270 MHz, CDCl_3) δ = 6.96-6.92 (m, 2H), 5.82 (dt, J = 15.6, 1.6 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.22 (br s, 1H), 2.93 (d, J = 7.1 Hz, 1H), 2.24-2.17 (m, 4H), 1.63-1.41 (m, 8H), 1.32 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (s, 9H). ^{13}C NMR (67.5 MHz, CDCl_3) δ = 186.5, 166.2, 147.9, 147.3, 122.0, 121.8, 59.9, 56.3, 54.7, 41.4, 39.8, 35.9, 31.9, 31.2, 25.8, 23.4, 22.1, 14.1; IR (thin film, v/cm^{-1}) 3608, 3583, 3341, 2975, 2360, 2341, 1694, 1422; MS (ESI) m/z = 414.2319 ($[\text{M}+\text{H}]^+$, 100), 436.2143 ($[\text{M}+\text{Na}]^+$, 33); HRMS = 414.2319 (calcd = 414.2309 $[\text{C}_{21}\text{H}_{36}\text{NO}_5\text{S}]^+$), 436.2143 (calcd = 436.2128 $[\text{C}_{21}\text{H}_{35}\text{NNaO}_5\text{S}]^+$).

Ethyl (*E*)-6-(1-((*R*)-tert-butylsulfinyl)-6-(2-ethoxy-2-oxoethyl) piperidin-2-yl)hex-2-enoate [223]⁷²

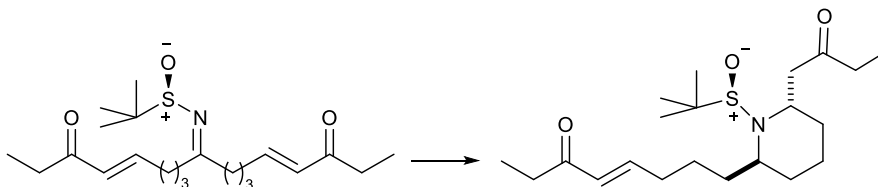


In a flame-dried 10.0 mL one-neck round-bottom flask, a solution of diethyl (2*E*,11*E*)-7-((*tert*-butylsulfinyl)imino)trideca-2,11-dienedioate (50.0 mg, 0.12 mmol, 1.0 equiv.) dissolved in dry ethanol (2.0 mL), cooled to 0 °C and under nitrogen gas atmosphere NaBH₄ (4.5 mg, 0.12 mmol, 1.0 equiv.) was added as one portion before the solution was stirred and the temperature slowly elevated to r.t., reaction was monitored by MS and TLC which revealed the disappearance of the starting material after 24 h, by which time the reaction mixture was cooled to 0 °C and AcOH (2.0 mL) was added dropwise, and then the mixture heated to 80 °C and stirred for 48 h. The reaction mixture was cooled down to r.t. then quenched with saturated aqueous NH₄Cl and extracted with Petroleum ether (3 x 2.0 mL), the combined organic layers were washed with brine (0.5 mL), dried over anhydrous Na₂SO₄, filtered and the solvents were removed under reduced pressure. The crude mixtures were purified by means of column chromatography on silica gel by using mixtures of Pet/ EtOAc were used as eluents in (10:1, 7:3, 3:2, 1:1) v/v ratio, then CHCl₃/ MeOH/ NH₃ solvents system in (90:10:0, 80:20:1) ratio respectively; two compounds were isolated, first was the monocyclic product as yellow oil (12 mg, 0.04 mmol, 32%); *R*_f = 0.8 in Pet/EtOAc (8:1); ¹H NMR (400 MHz, CDCl₃) δ = 6.98 – 6.83 (m, 1H), 5.79 (dq, *J* = 15.6, 1.6 Hz, 1H), 4.20 – 4.09 (m, 4H), 4.08 (d, *J* = 1.7 Hz, 1H), 3.94 (s, 1H), 3.19 (t, *J* = 8.2 Hz, 2H), 2.22 – 2.13 (m, 3H), 1.67 – 1.36 (m, 4H), 1.25 (td, *J* = 7.1, 1.4 Hz, 6H), 1.19 (s, 3H), 1.18 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ = 174.1, 166.5, 148.8, 121.6, 71.0, 60.1, 56.5, 55.9, 36.7, 35.8, 35.1, 31.9, 31.8, 24.1, 23.9, 22.6, 14.1.

(4*S, 6*S**)-(6-Ethoxycarbonylmethyloctahydroquinolizin-4-yl)acetic acid ethyl ester [83]⁷²**



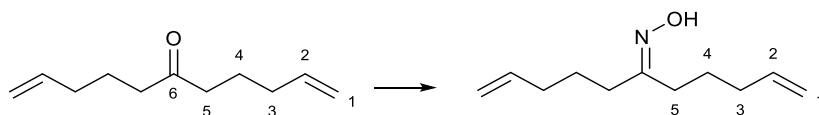
Second product out of the column chromatography using CHCl₃/ MeOH/ NH₃ as solvent system in (90:10:0, 80:20:1) ratio respectively, was the bicyclic compound (22 mg, 0.07 mmol, 61%) as orange oil; *R*_f = 0.79; ¹H NMR (400 MHz, CDCl₃) δ = 4.13 – 4.06 (m, 4H), 3.60 (app dq, *J* = 10.6, 3.6 Hz, 1H), 2.81 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.60 (ddd, *J* = 14.4, 3.5, 1.3 Hz, 1H), 2.48 (dd, *J* = 14.4, 10.6 Hz, 2H), 2.28 – 2.13 (m, 2H), 1.68 (dt, *J* = 12.3, 2.7 Hz, 2H), 1.58 (dt, *J* = 12.3, 3.3 Hz, 4H), 1.53 – 1.45 (m, 2H), 1.22 (td, *J* = 7.1, 2.1 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ = 173.0, 172.3, 60.3, 55.1, 54.4, 50.8, 38.6, 34.3, 34.0, 32.3, 29.0, 27.5, 23.6, 21.7, 18.3, 14.1(2C); IR (neat, ν/cm⁻¹) 2973, 2937, 1712, 1672; MS (ESI) *m/z* = 312.2179 ([*M*+H]⁺, 100); HRMS = 312.2179 (calcd = 312.2169 [C₁₇H₃₀NO₄]⁺)

(E)-8-((2R,6S)-1-((R)-tert-butylsulfinyl)-6-(2-oxobutyl)piperidin-2-yl)oct-4-en-3-one [226]

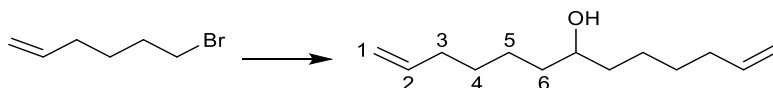
In a flame-dried 10.0 mL one-neck round-bottom flask, a solution of diethyl (2*E*,11*E*)-7-((*tert*-butylsulfinyl)imino)trideca-2,11-dienedioate (50.0 mg, 0.12 mmol, 1.0 equiv.) dissolved in dried over molecular sieves ethanol (2.0 mL), cooled to 0 °C and under nitrogen gas atmosphere NaBH₄ (4.5 mg, 0.12 mmol, 1.0 equiv.) was added as one portion, then the solution was stirred while temperature slowly elevated to r.t., formation of product was monitored by MS and TLC which revealed the disappearance of the starting material (16 h), and then the reaction mixture was cooled to 0 °C and gla. AcOH (2.0 mL) was added dropwise, there after the mixture heated to 80 °C (using a sand bath to control temperature) and stirred for 18 h, the mixture cooled down to r.t. and reaction quenched with saturated aqueous NH₄Cl and extracted with Pet. (3 x 2.0 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and the solvents were removed under reduced pressure. The crude mixtures were purified by means of column chromatography on silica gel by using mixtures of Pet/EtOAc as eluents to give the product as yellow oil (18.0 mg, 0.05 mmol, 49%); R_f: 0.8 in Hex/EtOAc (4:1); ¹H NMR (400 MHz, CDCl₃) δ = 6.76 (ddd, *J* = 15.5, 8.6, 6.6 Hz, 1H), 6.08 (dd, *J* = 15.5, 8.6 Hz, 1H), 2.64 (dt, *J* = 14.4, 7.6 Hz, 2H), 2.58 – 2.49 (m, 4H), 2.43 – 2.35 (m, 4H), 2.28 – 2.15 (m, 4H), 2.02 (d, *J* = 2.3 Hz, 1H), 1.77-1.70 (m, 4H), 1.22 (s, 9H), 1.07 (t, *J* = 7.6 Hz, 6H); ¹³C

NMR (101 MHz, CDCl₃) δ = 200.8, 186.2, 145.5, 130.4, 56.5, 41.7, 41.7, 40.0, 36.0, 33.2, 31.5, 29.7, 25.9, 23.6, 22.2(3 C), 21.8, 20.9, 14.1, 7.9.

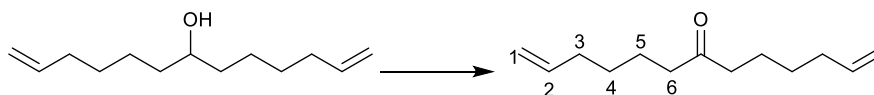
Undeca-1,10-dien-6-one oxime [194]¹²⁵



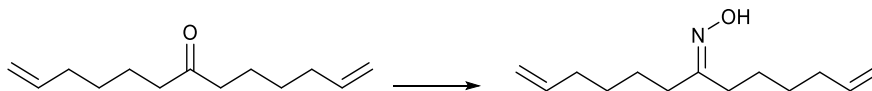
To a solution of undeca-1,10-dien-6-one (2.0 g, 12.0 mmol, 1.0 equiv.) in methanol (15 mL), hydroxyl amine hydrochloride (1.25 g, 18.0 mmol, 1.5 equiv.) was added, followed by sodium acetate (3.96 g, 48.0 mmol, 4.0 equiv.) then added, and then the mixture was stirred for 24 h at r.t., before the reaction was quenched by addition of sat. aqueous sodium hydrogen carbonate(10.0 mL), and extracted with dichloromethane (3 x 50.0 mL), the solvent was removed *in vacuo*, and the crude product was used without any further purifications, as clear yellow oil with pleasant smell (2.17 g, 11.0 mmol, 98%); R_f 0.56 in 4:1 Pet/EtOAc; ¹H NMR (400 MHz; CDCl₃) δ = 9.16 (s, 1H, OH), 5.78 (ddt, J = 16.8, 10.3, 6.7 Hz, 2H, H-2), 5.03 – 4.94 (m, 2H, H-1), 2.35 (t, J = 8.0Hz, 4H, H-5), 2.24-2.16 (m, 4H, H-3), 1.91-1.62 (m, 4H, H-4); ¹³C NMR(100 MHz, CDCl₃) δ = 173.0 (C6), 136(C1), 114(C2), 83.4 (C5), 32.9 (C4), 29.8 (C4), 21.1 (C3); IR (thin film, ν /cm⁻¹) 3244(brd), 3244, 3077, 2927, 2862, 1641(s), 1439, 1039, 991, 908; MS (ESI): m/z = 182.1543 ([M+H]⁺, 100), HRMS = 182.1543 (calcd = 182.1467 [C₁₁H₁₉NO]⁺).

Trideca-1,12-dien-7-ol [174]¹²⁶

To a suspension of magnesium (4.49 g, 185.0 mmol, 4 equiv.) in anhydrous tetrahydrofuran (30.0 mL) was added a small amount of iodine crystals, forming a yellow suspension. 6-Bromo-1-hexene (25.0 g, 168.0 mmol, 2.0 equiv.) was then added slowly, cooling the reaction with further tetrahydrofuran as required (~ 30.0 mL). The solution was stirred for 3 h, until no more of magnesium dissolved, and then a solution of ethyl formate (6.22 g, 84 mmol, 1 equiv.) in tetrahydrofuran (100.0 mL) was then added dropwise over 3 h and the reaction mixture was stirred for a further 18 h at r.t., and then heated to reflux for 1 h. The reaction was cooled and quenched with sat. aqueous ammonium chloride solution (100.0 mL), and extracted with diethyl ether (3 x 50.0 mL). The solvent was removed *in vacuo*, and the crude product was heated under reflux conditions in aq. potassium hydroxide (100.0 mL) 15% (w/v), for 12 h. The solution was extracted with diethyl ether (3 x 50.0 mL), the combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to give a yellow clear oil, which was used without further purification (13.37 g, 68.1 mmol, 95%); ¹H NMR (400 MHz, CDCl₃) δ_H = 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 2H), 5.00 (dd *J* = 17.1, 1.4 Hz, 2H), 4.94 (dd *J* = 10.2, 1.4 Hz, 2H), 3.59 (s, 1H), 2.05 (m, 4H), 1.45 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ_H = 138.7, 114.6, 71.7, 42.8, 36.9, 33.7, 24.9; IR (thin film, ν/cm⁻¹) 3333, 2977, 2855, 1440, 1045, 908; HRMS calculated for C₁₃H₂₄O [M]⁺ 196.1852, found 196.1852.

Trideca-1,12-dien-7-one [175]¹²⁶

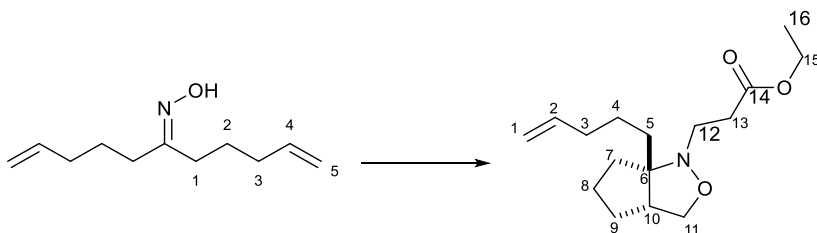
A solution of trideca-1,12-dien-7-ol (2.0 g, 11.9 mmol, 1.0 equiv.) in dichloromethane (50.0 mL) and silica gel (6.0 g) was cooled to 0 °C, before PCC (2.8 g, 13.1 mmol, 1.1 equiv.) addition, solution was stirred for 18 h. then Silica gel was added (3.0 g) and the solution was stirred for a further 0.5 h, then filtered and concentrated. The resulting dark brown oil was re-dissolved in diethyl ether and filtered through a short pad of silica gel. The filtrate was dried over sodium sulfate and the solvent was removed *in vacuo* to give the product as a yellow clear oil which was used without further purification (1.97 g, 10.0 mmol, 85%); ¹H NMR(400 MHz, CDCl₃) δ = 5.69 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 2H), 4.94 (dd, *J* = 17.0, 1.4 Hz, 2H), 4.94 (dd, *J* = 10.2, 1.4 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 4H), 2.01 (dt, *J* = 14.4, 6.6, 4H), 1.57- 1.47 (m, 4H), 1.39- 1.29 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ = 211.4, 138.8, 114.8, 65.0, 42.8, 34.0, 24.8; IR(neat, v/cm⁻¹) 3077, 2926, 2857, 1722, 1461, 1178, 992, 909; MS (ESI): *m/z* = 196.1 ([M+H]⁺, 100), HRMS = 196.1 (calcd = 195.1152 [C₁₃H₂₃O]⁺).

trideca-1,12-dien-7-one oxime [195]

To a solution of trideca-1,12-dien-7-one (1.1 g, 5.66 mmol, 1.0 equiv.) in methanol (12.0 mL), hydroxyl amine hydrochloride (0.59g, 8.49 mmol, 1.5 equiv.) was added, followed

by sodium acetate (1.86g, 22.6 mmol, 4.0 equiv.), then the mixture was stirred at rt for 48 hours by which the reaction was quenched by addition of sat aqueous sodium hydrogen carbonate (6.0 mL), and extracted with CH₂Cl₂ (3 x 25.0 mL), and then the solvent was removed *in vacuo*, and the crude product was used without any further purifications as a clear pale yellow oil (1.0 g, 4.8 mmol, 84%); *R*_f = 0.58 Hex/ EtOAc (4:1); ¹H NMR (400 MHz, CDCl₃) δ = δ 5.73 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 2H), 5.01-4.93 (m, 4H), 4.92 (dd, *J* = 2.2, 1.2 Hz, 2H), 2.37 (t, *J* = 7.4 Hz, 4H), 2.08 – 1.96 (m, 4H), 1.72 – 1.57 (m, 4H), 2.37 (t, *J* = 7.4 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃) δ = 207.0, 161.0, 138.6, 114.5, 114.4, 33.8, 33.5, 29.6, 29.0, 25.6, 24.6; IR(neat, v/cm⁻¹) 3244, 3077, 2927, 1641, 1353, 908.

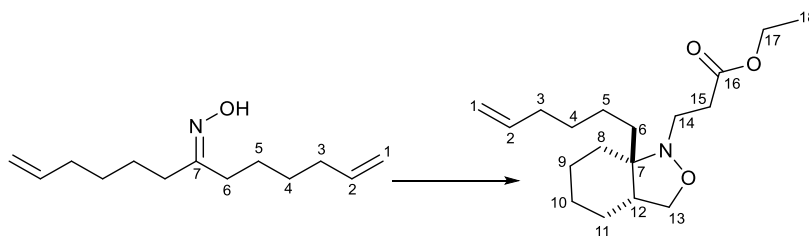
Ethyl 3-((3a*R,6a*S**)-6a-(pent-4-en-1-yl)hexahydro-1H-cyclopenta[*c*]isoxazol-1-yl)propanoate [198]¹²⁷**



To a solution of undeca-1,10-dien-6-one oxime (1.9 g, 10.0 mmol, 1.0 equiv.) and ethyl acrylate (1.2 g, 12.0 mmol, 1.2 equiv.) in xylene (20.0 mL) was maintained for 24 h at 140 °C, the solution was cooled to room temperature and purified by column chromatography on silica gel using Hex/EtOAc (10:1) as an eluent, afforded (1.97 g, 7.0 mmol, 75%) as a clear pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 5.80 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1H, H-2), 5.00 (ddt, *J* = 17.0, 2.1, 1.5 Hz, 1H, H-1a), 4.95 (ddt, *J* = 10.2, 2.1, 1.5, Hz, 1H,

H-1b), 4.13 (app q, $J = 7.1$, Hz, 2H, H-15), 3.82 (app dd, $J = 14.2$, 8.0 Hz, 1H, H-11a), 3.36 (ddd, $J = 14.2$, 8.0, 3.4 Hz, 1H, H-11b), 2.98 – 2.90 (m, 2H, H-12), 2.59 (t, $J = 6.8$ Hz, 2H, H-13), 2.58 – 2.50 (m, 1H, H-10), 2.04 (app q, $J = 6.5$ Hz, 2H, H-3), 1.86 – 1.69 (m, 4H, H-4, H-5), 1.58 – 1.36 (m, 5H, H-7, H-8, H-9a), 1.33 (dd, $J = 11.4$, 5.1 Hz, 1H, H-9b), 1.25 (t, $J = 7.1$ Hz, 3H, H-16); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 169.8$ (C14), 138.0 (C2), 113.9 (C1), 76.4 (C6), 72.0 (C11), 59.1 (C15), 51.5 (C10), 45.6 (C12), 34.0 (C13), 33.5 (C5), 33.4 (C7/8), 32.3 (C3), 25.2 (C4), 23.5 (C7/8), 21.7 (C9), 19.3 (C16); IR (neat, cm^{-1}) 3083, 2948, 2863, 1733, 1178; MS (ESI): $m/z = 282.2063$ ($[\text{M}+\text{H}]^+$, 100), HRMS = 282.2063 (calcd = 282.2064 $[\text{C}_{16}\text{H}_{27}\text{NO}_3]^+$). Data

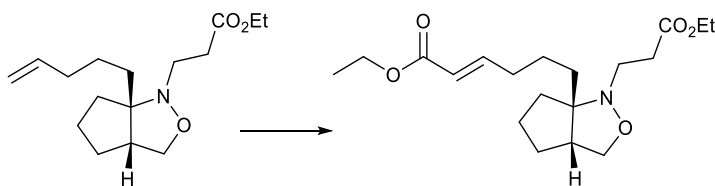
Ethyl3-((3a*S*,6a*R*)-6a-(pent-4-en-1-yl)hexahydro-1*H*-cyclopenta[*c*]isoxazol-1-yl)propanoate [199]



To a solution of trideca-1,12-dien-7-one oxime (500.0 mg, 2.4 mmol, 1.0 equiv.) and ethyl acrylate (288 mg, 2.8 mmol, 1.2 equiv.) in xylene (5.0 mL) was maintained for 24 h at 140 °C, the solution was cooled to room temperature and purified by flash chromatography on silica gel using Hex/EtOAc (10:1) as solvent mixture to afford (506.0 mg, 1.8 mmol, 75%) as a clear pale yellow oil; ^1H NMR (400 MHz, CDCl_3) $\delta = 5.80$ (ddt, $J = 16.8$, 10.2, 6.6

Hz, 1H, H-2), 5.00 (ddt, $J = 16.8, 6.6, 1.8$ Hz, 1H, H-1a), 4.95 (ddt, $J = 10.2, 4.2, 1.2$ Hz, 1H, H-1b), 4.13 (m, 2H, H-17), 3.83 (td, $J = 7.8, 1.3$ Hz, 1H, H-14a), 3.37 (td, $J = 7.8, 3.6$ Hz, 1H, H-14b), 3.41-2.92 (m, 2H, H-15), 2.60 (d, $J = 12.6$ Hz, 2H, H-13), 2.59-2.55 (m, 1H, H-12), 2.05 (td, $J = 12.6, 7.2$ Hz, 2H, H-11), 1.77-1.69 (m, 6H, H-3, H-4, H-5), 1.65-1.50 (m, 2H, H-6), 1.43-1.32 (m, 6H, H-9, H-10, H-8), 1.25 (t, $J = 7.2$ Hz, 3H, H-18); ^{13}C NMR(125 MHz, CDCl_3) $\delta = 172.8$ (C16), 138.7 (C2), 114.6 (C1), 76.2 (C7), 72.4 (C13), 70.2 (C17), 61.0 (C14), 60.1 (C15), 51.5 (C12), 46.3 (C3), 34.4 (C4), 34.0 (C5), 32.2 (C6), 32.0 (C11), 25.2 (C8/9), 24.5 (C8/9), 19.5 (C10), 14.3 (C18); IR(neat, v/cm^{-1}) 3083, 2948, 2863, 1733, 1235, 1178, 1031.

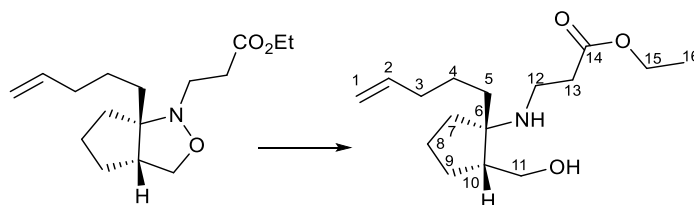
Ethyl (*E*)-6-((3*aS*,6*aR*)-1-(3-ethoxy-3-oxopropyl)tetrahydro-1H-cyclopenta[*c*]isoxazol-6*a*(3H)-yl)hex-2-enoate [206]⁸¹



To a solution of ethyl3-((3*aS*, 6*aR*)-6*a*-(pent-4-en-1-yl)hexahydro-1H-cyclopenta[*c*]isoxazol-1-yl)propanoate (100 mg, 0.36 mmol, 1 equiv.) in dichloromethane (5.0 mL) was added ethyl vinyl ketone (213.0 mg, 2.1 mmol, 6.0 equiv.), followed by Hoveyda-Grubbs 2nd generation catalyst (5.5 mg, 0.8 mmol, 2.5 mol%) as a solid, the solution was stirred for 24 h, at which time another portion of catalyst (5.5 mg, 0.8 mmol, 2.5 mol%) was added,

and then the solution was stirred for a further 24 h, whereupon the solvent was removed *in vacuo* and purification by column chromatography (over silica gel) eluting system was with Pet/EtOAc (6:1) ratio, gave the product as a brown oil (116 mg, 0.32 mmol, 93%); $R_f = 0.4$ in Hex/EtOAc (6:1); ^1H NMR (600 MHz, CDCl_3) $\delta = 6.96$ (dt, $J = 15.6, 7.2$ Hz, 1H), 5.82 (dt, $J = 15.6, 1.2$ Hz, 1H), 4.18 (dq, $J = 7.2, 14.4$ Hz, 2H), 4.15 - 4.1 (m, 2H), 3.82 (t, $J = 7.2$ Hz, 2H), 3.37 (dd, $J = 8.4, 3.0$ Hz, 2H), 2.96 - 2.9 (m, 2H), 2.59 (t, $J = 6.6$ Hz, 2H), 2.58-2.35 (m, 2H), 2.31-2.15 (m, 2H), 1.84 - 1.73 (m, 2H), 1.52 (dd, $J = \text{Hz}$, 2H), 1.50 - 1.44 (m, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) $\delta = 172.8, 166.7, 148.9, 121.5, 72.7, 62.4, 60.3, 60.1, 51.9, 46.3, 34.1, 32.9, 32.7, 28.6, 26.0, 25.9, 23.3, 14.3, 14.2$.

Ethyl 3-(((1R,2S)-2-(hydroxymethyl)-1-(pent-4-en-1-yl)cyclopentyl)amino)propanoate [200]⁹⁸



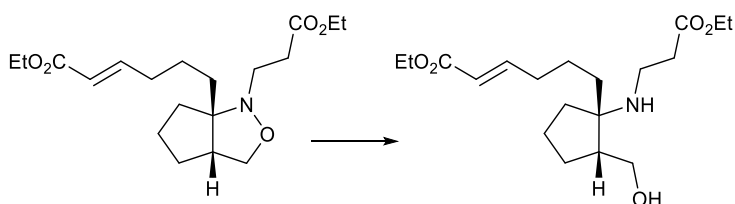
In 25 mL round bottom flask, activated zinc dust* (348.0 mg, 5.32 mmol, 15.0 equiv.) was added to a stirred solution of ethyl 3-(6a-(pent-4-en-1-yl)hexahydro-1H-cyclopenta[c]isoxazol-1-yl)propanoate (100.0 mg, 0.36 mmol, 1.0 equiv.) in 50% aqueous solution of AcOH (6.0 mL), heated to 70 °C until the solution became homogenous and clear after 18 h at which time the solution cooled to r.t. before the solvent removed in *vacuo*

at 50°C, slurry mixture dissolved in DCM and extracted (3 x 2.0 mL), washed with water, aqueous solution of NaHCO₃, dried over MgSO₄, filtered off and concentrated, the product needs no more purification yielded (74.0 mg, 0.26 mmol, 72%) as two diastereomers characterisation of **[200-a]**; ¹H NMR (400 MHz, CDCl₃) δ = 5.80 (ddt, *J* = 16.8, 10.3, 6.6 Hz, 1H, H-2), 5.02 (ddd, *J* = 16.8, 2.7, 1.5 Hz, 1H, H-1a), 4.97 (ddt, *J* = 10.3, 2.7, 1.5 Hz, 1H, C-1b), 4.64 (app s, 1H, -OH), 4.15 (q, *J* = 7.1 Hz, 2H, H-15), 3.92-3.55 (m, 2H, H-12), 3.25-2.75 (m, 2H, H-13), 2.55 (t, *J* = 5.9 Hz, 2H, H-5), 2.11 – 2.04 (m, 2H, H-3), 2.01 – 1.92 (m, 1H, H-10), 1.74-1.69 (m, 4H, H-8/9), 1.68 – 1.55 (m, 2H, H-11), 1.48 – 1.38 (m, 2H, H-4), 1.26 (t, *J* = 7.1 Hz, 3H, H-16); ¹³C NMR (100 MHz, CDCl₃) δ = 172.4 (C-14), 138.3 (C-2), 114.9 (C-1), 67.0, (C-6), 63.4 (C-11), 60.6 (C-15), 46.4 (C-10), 38.4 (C-13), 36.7 (C-7), 36.1 (C-4/5), 34.2 (C-3), 34.0 (C-12), 27.5 (C-8/9), 22.3 (C-4/5), 22.3 (C-8/9), 14.1 (C-16); IR(neat, v/cm⁻¹) 3300 (br), 3120, 2977, 2944, 2604, 2531, 1750, 1610, 1460, 1200; HRMS calculated for C₁₆H₂₉NO₃ 283.2147, found for [M+H]⁺ C₁₆H₃₀NO₃ 284.2220; MS (ESI): *m/z* = 284.2224 ([M+H]⁺, 100), 256.1908 ([M-Et + H]⁺, 14), HRMS = 284.2224 (calcd = 284.2220 [C₁₆H₃₀NO₃]⁺), 256.1908 (calcd = 256.1907 [C₁₄H₂₆NO₃]⁺).

*The zinc activated by the following procedure. Commercial zinc powder (0.5 g.), special grade, was added with stirring to a 25-ml., round-bottomed flask containing 3.0 ml. of 1M hydrochloric acid. Vigorous stirring is continued until the surface of the zinc becomes bright (ca. 4 minutes). The aqueous solution was decanted, and the zinc powder in the flask is washed by decantation with (4 x 3.0 mL) portions of distilled water. The activated zinc powder is transferred to a suction filter with 3.0 ml. of distilled water and washed successively with 5.0 ml. of ethanol, 5.0 ml. of acetone, and 5.0 ml. of dry diethyl ether,

respectively. Filtration and washing should be done as rapidly as possible to minimize exposure of the activated zinc to air. The zinc is finally dried at 85–90 °C for 10 minutes in a vacuum, cooled, and used immediately; the yield is 0.4 g.

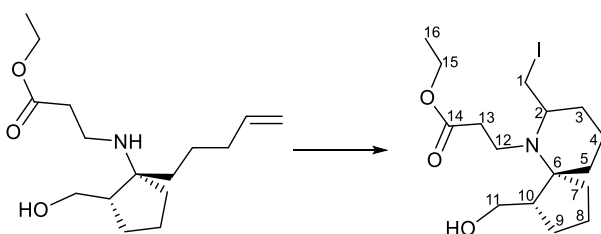
Ethyl (*E*)-6-(1-((3-ethoxy-3-oxopropyl)amino)-2-(hydroxymethyl)cyclopentyl) hex-2-enoate [185]



To a stirred solution of ethyl (*E*)-6-(1-(3-ethoxy-3-oxopropyl)tetrahydro-1H-cyclopenta[*c*]isoxazol-6a(3H)-yl)hex-2-enoate (100.0 mg, 0.28 mmol, 1.0 equiv.) in a 50% aqueous solution of AcOH (14.0 mL) was added zinc dust (261.9 mg, 5.66 mmol, 15 equiv.), the resulting suspension was heated to 70 °C and stirred for 2 h the reaction mixture was diluted with DCM (20.0 mL) and solid NaHCO₃, the mixture then filtered, washed with sat. aqueous Na₂SO₄ solution and then concentrated *in vacuo* to give the title compound (87.0 mg, 0.24 mmol, 87% yield); *R*_f = 0.28 in Pet/EtOAc (6:1); ¹H NMR (270 MHz, CDCl₃) δ = 6.96 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.84 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.94 - 4.15 (m, 4H), 3.63-3.36 (m, 3H), 2.97-2.56 (m, 3H), 2.51 (t, *J* = 6.5 Hz, 2H), 2.23 (app qd, *J* = 6.5, 1.1 Hz, 2H), 1.97 – 1.70 (m, 3H), 1.67 – 1.44 (m, 6H), 1.46 – 1.37 (m, 2H), 1.28 (app td, *J* = 7.1, 5.7 Hz, 6H); ¹³C NMR (68 MHz, CDCl₃) δ = 172.9, 148.7, 131.5, 121.8, 66.3, 64.1, 60.7, 60.3, 46.7, 38.6, 37.5, 36.8, 35.0, 32.6, 27.9, 22.6, 21.9, 14.3, 14.2;

MS (ESI): m/z = 356.2458 ($[M+H]^+$, 100), HRMS = 356.2458 (calcd = 356.2431 $[C_{19}H_{33}NO_5]^+$).

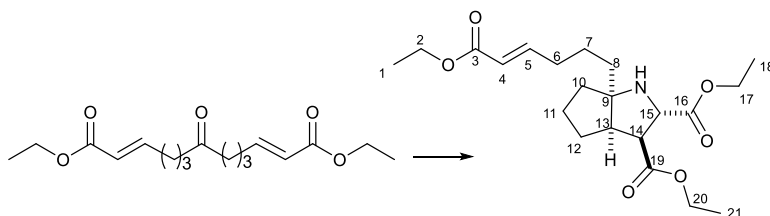
ethyl3-((1*S*,5*S*)-1-(hydroxymethyl)-7-(iodomethyl)-6-azaspiro[4.5]decan-6-yl)propanoate [179]⁹⁹



To a solution of ethyl 3-(((1*R*,2*S*)-2-(hydroxymethyl)-1-(pent-4-en-1-yl)cyclopentyl)amino)propanoate (100mg, 0.35mmol, 1.0 equiv.) in acetonitrile (3.0 mL), $NaHCO_3$ (83.0 mg, 1.06 mmol, 3.0 equiv.) and iodine (269.1 mg, 1.06 mmol, 3.0 equiv.) were added, and reaction stirred for 18 h by which time aqueous Na_2SO_3 solution (5.0 mL). The organic layer was extracted by Et_2O (2 x 5.0 mL), the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*, and then the residue purified by column chromatography on silica gel eluting by Pet/ EtOAc (10:1); R_f = 0.58 in the same solvent system, as colourless oil (302.0 mg, 73.8 mmol, 41%); ^1H NMR (400 MHz, $CDCl_3$) δ = 4.13 (q, J = 7.1 Hz, 2H, H-15), 3.94 (s, 1H, OH), 3.73 (dd, J = 11.7, 6.6 Hz, 1H, H-11), 3.67 (dd, J = 11.7, 5.9 Hz, 1H, H-11), 3.56- 3.34(m, 1H, H-2), 3.31(dd, J = 10.4, 6.9 Hz, 1H, H-1), 3.11 (dd, J = 10.4, 7.6 Hz, 1H, H-1), 2.96-2.77 (m, 1H, H-12/13), 2.76 -2.66(m, 1H, H-12/13), 2.65-2.61 (m, 1H, H-12/13), 2.56-2.40 (m, 1H, H-12/13), 2.37 (q, J = 6.5 Hz, 1H, H-10), 2.01 – 1.55 (m, 2H, H-7), 1.79 – 1.51 (m, 2H, H-8/9), 1.78 – 1.65 (m, 2H, H-8/9), 1.68 -1.39 (m, 4H,

H-4/5), 1.38-1.29 (m, H-3), 1.27 (t, $J = 7.1$ Hz, 3H, H-16); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.4 (C-14), 70.9 (C-6), 65.3 (C-11), 60.6 (C-2), 60.50 (C-15), 41.8 (C-10), 40.5 (C-12/13), 39.1 (C-12/13), 36.8 (C-7), 28.3 (C-3), 26.9 (C-8/9), 24.2 (C-4/5), 21.3 (C-4/5), 20.2 (C-8/9), 14.2 (C-16), 8.5 (C-1); IR (neat, v/cm^{-1}) 2977, 2944, 2604, 2531, 1478, 1397, 1172, 1078; MS (ESI): m/z = 410.1183 ($[\text{M}+\text{H}]^+$, 64), HRMS = 410.1183 (calcd = 410.1187 $[\text{C}_{16}\text{H}_{29}\text{N}_1^{127}\text{I}_1\text{O}_3]^+$).

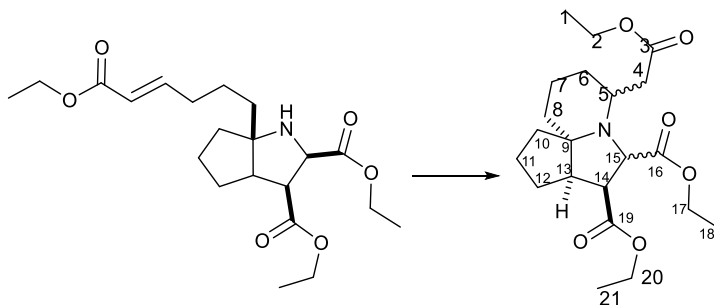
Diethyl 6a-((*E*)-5-(ethoxycarbonyl)pent-4-enyl)octahydrocyclopenta[b]pyrrole- 2,3-dicarboxylate [209]⁵⁵



To a solution of (2*E*, 11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (500.0 mg, 1.6 mmol, 1equiv.) in toluene (16.0 mL) was added glycine ethyl ester hydrochloride (334.0 mg, 2.4 mmol, 1.5 equiv.) and *N,N*-diisopropylethylamine (620.0 mg, 4.8 mmol, 3.0 equiv.) and the mixture heated to reflux overnight, and then the solution was cooled to room temperature and the remaining solvent removed *in vacuo*, the resulting residue was purified using column chromatography on silica gel and the solvent Pet/EtOAc (5:1) ratio, to give the title compound as a clear pale yellow oil (470.0 mg, 1.18 mmol, 74%); R_f = 0.32 in Pet/EtOAc (1:1); ^1H NMR (400 MHz, CDCl_3) δ = 6.94 (dt, $J = 15.6, 6.8$, Hz, 1H, H-5),

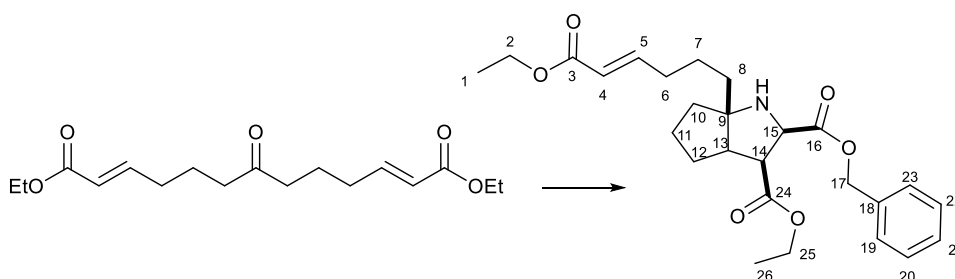
5.80 (dt, $J = 15.6, 1.53$ Hz, 1H, H-4), 4.17 (q, $J = 7.1$ Hz, 2H, H-17/20), 4.08 (q, $J = 7.1$ Hz, 2H, H-17/20), 4.00(d, $J = 6.5$ Hz, 1H, H-15), 3.92- 3.80 (m, 2H, H-2), 3.72 (s, 1H, NH), 2.90 (dd, $J = 6.3, 2.4$ Hz, 1H, H-14), 2.40 (ddd, $J = 8.4, 6.3, 2.40$ Hz, 1H, H-13), 2.20 – 2.15 (m, 2H, H-6), 2.02 (app s, 1H, H-8), 2.01-1.84 (m, 1H, H-12a), 1.69 – 1.64 (m, 2H, H-10/11), 1.57 – 1.52 (m, 4H, H-10/11, H-7), 1.50-1.45 (m, 1H, H-12b), 1.32 (t, $J = 7.1$ Hz, 3H, H-18), 1.30 (t, $J = 7.1$ Hz, 3H, H-21), 1.24 (m, 3H, H-1); ^{13}C NMR (400 MHz, CDCl_3) $\delta = 173.6$ (C-19), 171.5 (C-16), 166.6 (C-3), 148.5 (C-4), 121.8 (C-5), 74.6 (C-9), 62.6 (C-15), 60.7 (C-17/20), 60.1 (C-17/20), 55.5 (C-14), 52.5 (C-13), 52.0 (C-7), 40.1 (C-11), 38.3 (C-12), 33.1 (C-6), 32.5 (C-10), 25.3 (C-8), 23.7 (C-18), 14.2 (C-21), 14.1 (C-1), (20 carbons out of 21 in resonance observed); IR(neat, ν/cm^{-1}) 3468, 3010, 2940, 2869, 1889, 1731, 1652, 1548, 1447, 1370, 1189, 1037, 982, 861, 755; MS (ESI): $m/z = 396.2397$ ($[\text{M}+\text{H}]^+$, 100), 418.2197 ($[\text{M}+\text{Na}]^+$, 3), HRMS = 396.2397 (calcd = 396.2381 $[\text{C}_{21}\text{H}_{33}\text{NO}_6]^+$), 418.2197 (calcd = 396.2200 $[\text{C}_{21}\text{H}_{33}\text{NNaO}_6]^+$),

Diethyl 5a-(2-ethoxycarbonyl)-a-decahydrocyclopenta[i]indolizine-6,7-dicarboxylate [211]



To a solution of diethyl (3aS, 6aS)-6a-((*E*)-6-ethoxy-6-oxohex-4-en-1-yl)octahydrocyclopenta[*b*] pyrrole-2,3-dicarboxylate (50.0 mg, 0.126 mmol, 1.0 equiv.) in ethanol (2.5 mL), gla. AcOH (38.0 mg, 0.63 mmol, 5 equiv.), the mixture heated to reflux at 120 °C for 24h by which solution was cooled to room temperature, diluted with DCM (5.0 mL) and aqueous solution of NaOH (1.0 M) was added dropwise until PH = 9, the resulting mixture extracted of CH₂Cl₂ (3 x 5.0 mL), washed with brine and dried over MgSO₄ filtered off and evaporated *in vacuo*, then the resulting residue was purified using column chromatography on silica gel Pet/EtOAc (5:1) to give the title compound as orange oil (23.0 mg, 0.058 mmol, 46%); ¹H NMR: I believe the product was mix of three inseparable diastereomers and the most significant proton peaks detected were; ¹H NMR(400 MHz, CDCl₃) δ = 4.23 – 4.03 (m, 18H), 3.50 – 3.34 (m, 3H), 2.93 – 2.77 (m, 4H), 2.74 – 2.65 (m, 2H), 2.62-2.57 (m, 2H), 2.56- 2.45 (m, 2H), 2.33 – 2.26 (m, 2H), 2.19- 2.10 (m, 2H), 2.05 – 1.95 (m, 2H), 1.95 – 1.78 (m, 4H), 1.64 – 1.46 (m, 12H), 1.31 – 1.19 (m, 27H); ¹³C NMR (101 MHz, CDCl₃) δ = 175.0, 174.7, 173.6, 173.4, 173.4, 172.5, 172.4, 172.2, 172.2, 172.1, 172.0, 171.7, 74.8, 72.5, 70.7, 70.2, 69.1, 68.4, 63.4, 62.3, 60.8, 60.7, 60.7, 60.5, 60.4, 60.4, 60.3, 60.2, 60.2, 60.1, 60.0, 55.2, 54.0, 53.4, 53.3, 53.1, 53.0, 52.1, 52.0, 51.8, 51.1, 50.9, 50.3, 40.6, 40.1, 40.0, 39.9, 39.6, 38.9, 36.2, 35.1, 34.1, 33.9, 33.5, 32.9, 32.9, 32.8, 31.6, 30.7, 29.6, 28.1, 26.7, 26.4, 25.7, 25.7, 25.2, 24.1, 23.6, 22.8, 22.6, 17.3, 17.1, 14.3, 14.2, 14.1, 14.0, 13.9; IR(neat, v/cm⁻¹) 3479, 2979, 2938, 2870, 2361, 1732, 1652, 1447, 1370, 1270, 1186, 1036, 861; MS (ESI): *m/z* = 396.2399 ([M+H]⁺, 100), 418.2195 ([M+Na]⁺, 2), HRMS = 396.2399 (calcd = 396.2381 [C₂₁H₃₃NO₆]⁺), 418.2195 (calcd = 396.2200 [C₂₁H₃₃NNaO₆]⁺).

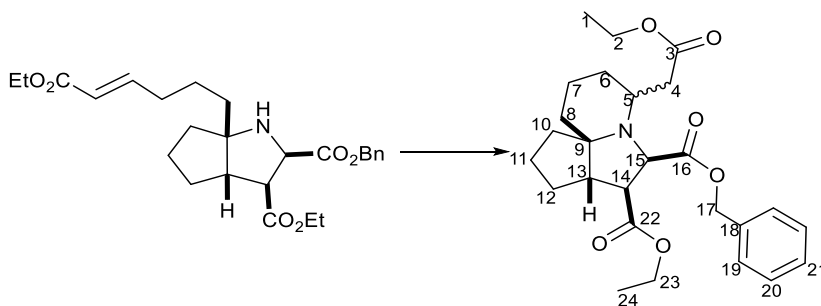
2-benzyl 3-ethyl (3a*S*,6a*S*)-6a-((*E*)-6-(ethoxycarbonyl)hex-4-en-1-yl)octahydrocyclopenta[*b*]pyrrole-2,3-dicarboxylate [210]



To a solution of (2*E*,11*E*)-diethyl 7-oxotrideca-2,11-dienedioate (980.0 mg, 3.16 mmol, 1.0 equiv.) in toluene (32.0 mL) was added glycine benzyl ester hydrochloride (956.0 mg, 4.74 mmol, 1.5 equiv.) and *N,N*-diisopropylethylamine (1.22 mg, 9.48 mmol, 3.0 equiv.) and the mixture heated to reflux overnight, and then the solution was cooled to room temperature and the remaining solvent removed *in vacuo*, the resulting residue was purified using column chromatography on silica gel Pet/EtOAc as (7:1 ratio down to 1:1) to yield the title compound as an orange colored oil (1.0 g, 2.18 mmol, 70%); ¹H NMR (400 MHz, CDCl₃) δ = 7.36 – 7.32 (m, 5H, H-19-23), 6.92 (dt, *J* = 15.6, 7.1 Hz, 1H, H-5), 5.80 (dt, *J* = 15.6, 1.5 Hz, 1H, H-4), 5.13 (d, *J* = 12.1 Hz, 2H, H-17), 4.17 (q, *J* = 7.1 Hz, 2H, H-25), 4.05 (d, *J* = 6.40 Hz, 1H, H-15), 3.97-3.65 (m, 2H, H-2), 3.12-3.00 (m, 2H, H-8), 2.91 (dd, *J* = 6.4, 2.6 Hz, 1H, H-14), 2.67 (s, 1H, N-H), 2.41 (ddd, *J* = 8.5, 5.5, 2.6 Hz, 1H, H-13), 2.23 – 2.14 (m, 2H, H-6/7), 2.0-1.85 (m, 2H, H-12), 1.76 (dt, *J* = 12.0, 5.2 Hz, 2H, H-6/7), 1.69 – 1.61 (m, 2H, H-11/10), 1.58 (t, *J* = 7.4 Hz, 2H, H-11/10), 1.28 (t, *J* = 7.1 Hz, 3H, H-26), 1.15 (t, *J* = 7.1 Hz, 3H, H-1); ¹³C NMR (400 MHz, CDCl₃) δ = 172.9 (C-24), 171.0

(C-3), 166.6 (C-16), 148.6 (C-5), 135.3 (C-18), 129.6 (C-19&23/ C-20&22), 128.5 (C-19&23/ C-20&22), 128.4 (C-21), 121.67(C-4), 74.3 (C-9), 66.8 (C-25), 62.6 (C-15), 60.7 (C-17), 60.1 (C-2), 55.4 (C14), 53.6 (C-13), 41.9 (C-12), 40.1 (C-11), 38.4 (C-10), 32.6 (C-6), 25.3 (C-8), 23.7 (C-7), 14.2 (C-26), 14.1 (C-1); IR(neat, ν/cm^{-1}) 3428, 3352, 3090, 3065, 2950, 2868, 1956, 1882, 1731, 1652, 1545, 1498, 1455, 1188, 1036, 980, 912, 753, 968, 666; MS (ESI): m/z = 458.2560 ($[\text{M}+\text{H}]^+$, 100), HRMS = 458.2560 (calcd = 458.2537 $[\text{C}_{26}\text{H}_{36}\text{NO}_6]^+$).

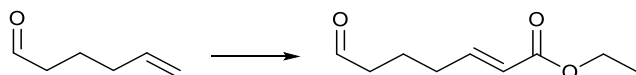
6-benzyl 7-ethyl (7aS,10aR)-4-(2-ethoxy-2-oxoethyl) decahydrocyclopenta[i]indolizine-6,7-dicarboxylate [212]



To a solution of 2-benzyl 3-ethyl (Z)-6a-(6-ethoxy-6-oxohex-4-en-1-yl)octahydrocyclopenta[b]pyrrole-2,3-dicarboxylate (500.0 mg, 1.27 mmol, 1.0 equiv.) in ethanol (25.0 mL), glc. AcOH (380.0 mg, 6.3 mmol, 5.0 equiv.), the mixture heated to reflux at 120 °C for 24h by which time solution was cooled to room temperature, diluted with DCM (20.0 mL) and aqueous solution of NaOH (1.0 M) was added dropwise until nearly PH = 9, the resulting mixture extracted of CH_2Cl_2 (3 x 20.0 mL), washed with brine and dried over MgSO_4 filtered off and evaporated *in vacuo*, and then the resulting residue was purified using

column chromatography on silica gel using Pet/ EtOAc (1:10 gradually down to 1:1) to give the title compound as colorless oil (450.0 mg, 0.99 mmol, 78%); I believe the product was mix of two inseparable isomers (1:1 ratio), and the most significant proton peaks; ^1H NMR(400 MHz, CDCl_3) δ = 7.41 – 7.29 (m, 10H), 5.22 – 5.06 (m, 4H), 4.20 (dd, J = 9.6, 6.9 Hz, 2H), 4.18 – 4.02 (m, 4H), 3.74 – 3.60 (m, 2H), 3.48 – 3.37 (m, 2H), 3.07 (q, J = 7.5 Hz, 2H), 2.89 – 2.78 (m, 4H), 2.73 – 2.62 (m, 2H), 2.58 – 2.43 (m, 4H), 2.36 – 2.21 (m, 4H), 2.10 (dd, J = 14.7, 10.4 Hz, 2H), 1.63 – 1.52 (m, 8H), 1.47 (d, J = 6.8 Hz, 8H), 1.30 – 1.22 (m, 16H), 1.22 – 1.16 (m, 4H), 1.14 – 1.03 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ = 174.8, 173.2, 172.2, 171.6, 128.8, 128.5, 128.4, 128.4, 128.2, 128.0, 127.4, 126.9, 74.7, 70.8, 69.1, 68.4, 66.6, 66.4, 65.1, 63.3, 62.3, 60.8, 60.7, 60.3, 60.2, 60.0, 55.2, 54.0, 53.4, 53.2, 52.1, 51.7, 51.0, 50.9, 50.2, 41.7, 40.5, 39.8, 39.5, 35.1, 34.1, 32.9, 32.7, 31.6, 30.7, 29.6, 27.9, 26.3, 25.6, 25.2, 24.1, 22.7, 22.5, 17.3, 17.1, 14.1, 14.0; IR(neat, v/cm^{-1}) 3448, 3070, 3033, 2936, 2864, 2359, 2340, 1734, 1498, 1453, 1371, 1262, 1185, 1035, 861, 749, 698; MS (ESI): m/z = 458.2562 ($[\text{M}+\text{H}]^+$, 100), 480.2350 ($[\text{M}+\text{Na}]^+$, 1), HRMS = 458.2562 (calcd = 458.2537 $[\text{C}_{26}\text{H}_{36}\text{NO}_6]^+$), 480.2350 (calcd = 458.2357 $[\text{C}_{26}\text{H}_{35}\text{NNaO}_6]^+$),

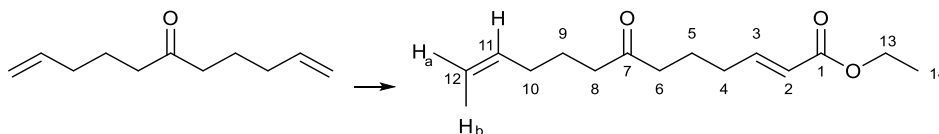
Ethyl (*E*)-7-oxohept-2-enoate [218]⁵¹



To a stirred solution of hex-5-enal¹²⁸ (1.5 g, 15.29 mmol, 1.0 equiv.) and diethyl ether (150.0 mL) was added CuI (88.0 mg, 0.45 mmol, 3% by mole) and ethyl acrylate (10.0

mL, 91.8 mmol, 6 equiv.) then Grubbs-Hoveyda II catalyst (324.0 mg, 0.38 mmol, 2.5 %by mole) in Et₂O (5.0 mL) was added portion wise over an hour. The solution was stirred at 30 °C for more 2 h, and then the solvent was removed *in vacuo* to give a thick black oil which was purified by flash column chromatography on silica gel eluting with Pet/EtOAc (10:1) to give product (400 mg, 3.2 mmol, 20%) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 9.69 (s, 1H), 6.83 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.76 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 3H), 2.41 (td, *J* = 7.4, 1.4 Hz, 2H), 2.25 -2.14 (m, 2H), 1.73 (app qu, *J* = 7.4 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 201.5, 166.3, 147.5, 122.1, 60.2, 42.8, 31.1, 20.2, 14.1; MS (ESI): *m/z* = 193.0843 ([M⁺⁺ Na]⁺, 89), HRMS = 193.0843 (calcd = 193.0841 [C₉H₁₄NaO₃]⁺).

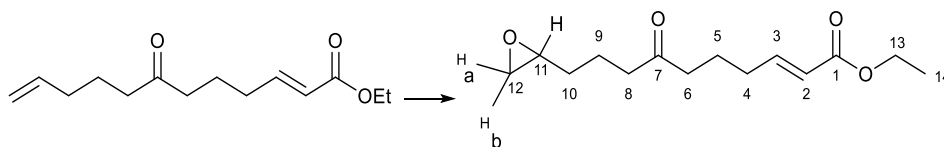
Ethyl (*E*)-7-oxododeca-2,11-dienoate [216]⁵¹



To a solution of undeca-1,10-dien-6-one (2.0 g, 12.0 mmol, 1.0 equiv.) in CH₂Cl₂ (120.0 mL) was added ethyl acrylate (1.4 g, 14.0 mmol, 1.2 equiv.) followed by Hoveyda-Grubbs 2nd generation catalyst (188 mg, 0.3 mmol, 2.5 mol%) as a solid, the solution was stirred for 24 h, whereupon the solvent was removed *in vacuo* and residue purified by column chromatography over silica gel, eluting with PE/EtOAc (6:1) and gave the product as a pale yellow oil (1.18 g, 5.1 mmol, 42%): R_f = 0.34 in PE/EtOAc (7:3) ; ¹H NMR (400

MHz, CDCl₃) δ = 6.92 (dt, J = 15.6, 7.2 Hz, 1H, H-3), 5.82 (dt, J = 15.6, 1.6 Hz, 1H, H-2), 5.75 (ddt, J = 16.9, 10.2, 6.71 Hz, 1H, H-11), 5.04 – 4.69 (m, 2H, H-12), 4.19 (q, J = 7.1 Hz, 2H, H-13), 2.43 (t, J = 7.3 Hz, 2H, H-6), 2.40 (t, J = 7.3 Hz, 2H, H-8), 2.21 (app. qd, J = 7.2, 1.6 Hz, 2H, H-4), 2.08 – 2.02 (m, 2H, H-12), 1.79-1.71 (m, 2H, H-5), 1.71 – 1.64 (m, 2H, H-9), 1.30 (t, J = 7.1 Hz, 3H, H-14); ¹³C NMR (100 MHz, CDCl₃) δ = 209.7, 166.4, 148.1, 121.9, 60.2, 51.9, 46.7, 42.1, 41.6, 31.7, 31.4, 21.8, 20.2, 14.2; MS (ESI): m/z = 261.1464 ([M⁺ + Na]⁺, 100), 239.1649 ([M+H]⁺, 23), HRMS = 261.1464 (calcd = 261.1461 [C₁₄H₂₂NaO₃]⁺), 239.1649 (calcd = 239.1642 [C₁₄H₂₃O₃]⁺).

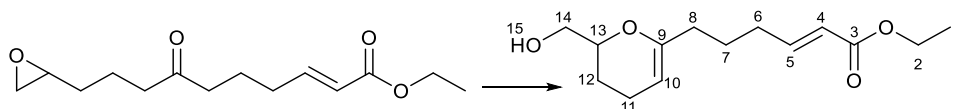
ethyl (*E*)-10-(oxiran-2-yl)-7-oxodec-2-enoate [215]¹²⁸



In a flame dried 250 mL round bottom flask, a solution of ethyl (*E*)-11,12-dimethyl-7-oxotrideca-2,11-dienoate (1.0 gm, 4.2 mmol, 1.0 equiv.) in CH₂Cl₂ (80.0 mL) was cooled to 0 °C, before *m*-CPBA (1.4 g, 8.3 mmol, 2.0 equiv.) was added as a solution in CH₂Cl₂ (20.0 mL), solution stirred overnight at r.t., when the conversion of the starting material was complete monitored by TLC and MS, Na₂SO₃ (20.0 mL) was then added followed by NaHCO₃ addition, then the mixture was extracted with CH₂Cl₂ (3 x 50.0 mL), washed with NaHCO₃ (20.0 mL), Na₂S₂O₃ (20.0 mL) and finally water (10.0 mL). The organic layer was dried over CaCl₂, filtered and evaporated the titled compound did not need any further

purification, as colourless oil (1.0 g, 3.5 mmol, 84%); ^1H NMR (400 MHz, CDCl_3) δ = 6.87 (dt, J = 15.6, 7.0 Hz, 1H, H-3), 5.78 (dt, J = 15.6, 1.5 Hz, 1H, H-2), 4.14 (q, J = 7.1 Hz, 2H, H₂-13), 2.85 (tdd, J = 6.8, 4.2, 2.8 Hz, 1H, H-11), 2.70 (dd, J = 4.7, 4.2 Hz, 1H, H-12_a), 2.53 – 2.25 (m, 4H, H₂-6 and H₂-8), 2.42 (m, 1H, H-12_b), 1.78 – 1.65 (m, 4H, H₂-5 and H₂-9), 1.64 – 1.53 (m, 1H, H-10), 1.43– 1.40 (m, 1H, H-10), 1.24 (t, J = 7.1 Hz, 3H, H₃-14); ^{13}C NMR (100 MHz, CDCl_3) δ = 209.6, 166.3, 147.9, 121.8, 60.1, 51.8, 46.6, 42.0, 41.5, 31.6, 31.2, 21.7, 20.1, 14.1; MS (ESI): m/z = 277.1409 ($[\text{M}^+ + \text{Na}]^+$, 100), HRMS = 277.1409 (calcd = 277.1410 [$\text{C}_{14}\text{H}_{22}\text{NaO}_4$] $^+$).

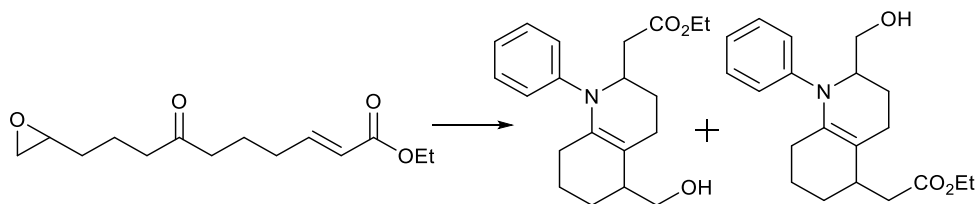
ethyl (*E*)-6-(2-(hydroxymethyl)-3,4-dihydro-2H-pyran-6-yl)hex-2-enoate [221]



To a solution of ethyl 6-(oxiran-2-yl)hex-2-enoate (100.0 mg, 0.39 mmol, 1.0 equiv.) in DCE (13.0 mL) at $-10.0\text{ }^{\circ}\text{C}$ TiCl_4 (1.0 M sol./DCM, 110.0 μL , 0.78 mmol, 2.0 equiv.) was added, the mixture was let to stir for 30 min, before aniline (59.0 μL , 0.59 mmol, 1.5 equiv.) was added, the mixture then was allowed to warm slowly to r.t., then heated to reflux overnight at $80\text{ }^{\circ}\text{C}$, and then the reaction was quenched with saturated aqueous NaHCO_3 (10.0 mL), filtered through a short pad of celite, the filtrate was extracted with EtOAc (3 x 10.0 mL), and the combined organic layers washed with brine (20.0 mL),

dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, the resulting product was purified using column chromatography on silica gel using Pet/EtOAc (6:1) to give the title compound as a yellow oil (75 mg, 0.29 mmol, 76%); $R_f = 0.74$ in Pet/EtOAc (6:1); ^1H NMR (400 MHz, CDCl_3) $\delta = 6.95$ (dt, $J = 15.6, 6.9$ Hz, 1H, H-5), 5.81 (dt, $J = 15.6, 1.5$ Hz, 1H, H-4), 4.57-4.42 (m, 1H, H-13), 4.17 (q, $J = 7.1$ Hz, 2H, H-2), 3.91 (d, $J = 6.8$ Hz, 2H, H-14), 3.80 (t, $J = 6.0$ Hz, 1H, H-10), 2.32-2.15 (m, 2H, H-6), 1.89 – 1.80 (m, 1H, H-12a), 1.82 (s, 1H, O-H), 1.72 – 1.67 (m, 2H, H-8), 1.64 – 1.58 (m, 4H, H-7&8), 1.50 – 1.46 (m, 1H, H-12b), 1.27 (t, $J = 7.1$ Hz, 3H, H-1); ^{13}C NMR (101 MHz, CDCl_3) $\delta = 166.6$ (C-3), 148.9 (C-9), 129.2 (C-10), 121.4 (C-3), 108.5 (C-4), 74.8 (C-13), 69.0 (C-14), 60.0 (C-2), 36.8 (C-11), 32.2 (C-6), 28.3 (C-12), 21.4 (C-7), 16.7 (C-8), 14.2 (C-1); MS (ESI): $m/z = 277.1410$ ($[\text{M}^+ + \text{Na}]^+$, 100), HRMS = 277.1410 (calcd = 277.1416 $[\text{C}_{14}\text{H}_{22}\text{NaO}_4]^+$).

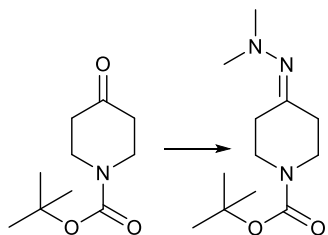
Ethyl 2-(5-(hydroxymethyl)-1-phenyl-1,2,3,4,5,6,7,8-octahydroquinolin-2-yl)acetate [222]-a/b¹⁰⁶



To a solution of ethyl (*E*)-10-(oxiran-2-yl)-7-oxodec-2-enoate (200.0 mg, 0.78 mmol, 1 equiv.) in toluene (8.0 mL) aniline (80.0 mg, 0.86 mmol, 1.1 equiv.) was added, the mixture then was heated to reflux using Dean-Stark apparatus for 18 h, by which time reaction was monitored by TLC and MS showed some of starting material exist then more aniline was added (one more equiv.), and heated to reflux for a further 24 h, solvent evaporated *in*

vacuo and the resulting product was purified using column chromatography on silica gel using the solvents Pet/EtOAc (10:1, 8:2, 7:3, 1:1), CHCl_3 and finally $\text{CHCl}_3/\text{MeOH}$ (5%) respectively, to give the title compound as yellow gummy oil (119.0 mg, 0.361 mmol, 44% yield); $R_f = 0.7$; it appeared to be two inseparable isomers and the most significant proton peaks; ^1H NMR (500 MHz, CDCl_3) $\delta = 7.32 - 7.26$ (m, 4H), $7.24 - 7.08$ (m, 2H), $7.07 - 7.01$ (m, 2H), $4.26 - 4.15$ (m, 4H), $3.98 - 3.92$ (m, 1H), $3.89 - 3.69$ (m, 2H), $3.66 - 3.58$ (m, 2H), $3.47 - 3.39$ (m, 5H), $1.90 - 1.78$ (m, 3H), $1.75 - 1.62$ (m, 4H), $1.60 - 1.52$ (m, 5H), $1.51 - 1.41$ (m, 4H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) $\delta = 173.6$, 173.3 , 149.6 , 147.7 , 133.2 , 129.3 , 128.8 , 128.5 , 125.8 , 124.8 , 123.0 , 117.3 , 99.9 , 66.3 , 65.9 , 63.4 , 61.0 , 60.2 , 60.2 , 49.7 , 39.6 , 38.5 , 36.3 , 35.4 , 32.4 , 32.0 , 29.1 , 28.2 , 27.9 , 22.3 , 22.26 , 20.7 , 20.1 , 19.7 , 14.2 ; IR(neat, v/cm^{-1}) 3588, 3058, 2935, 1731; MS (ESI): $m/z = 330.2047$ ($[\text{M}^+ + \text{H}]^+$, 100), HRMS = 330.2048 (calcd = 330.2064 $[\text{C}_{20}\text{H}_{28}\text{NO}_3]^+$).

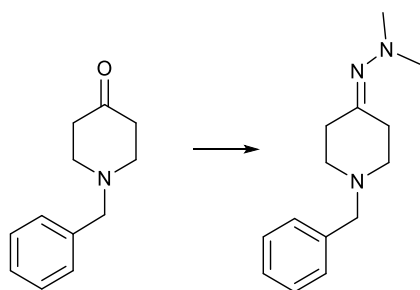
tert-butyl 4-(2,2-dimethylhydrazono)piperidine-1-carboxylate [236]¹²⁹



To a solution of 1-Boc-4-piperidinone (398.0 mg, 2.0 mmol, 1.0 equiv.) in toluene (5.0 mL) was added N,N-dimethyl hydrazine (144.0 mg, 2.4 mmol), the flask was equipped

with a Dean-Stark trap and heated to reflux over 3 h, the remaining solvent was removed *in vacuo* to give the hydrazone as a clear yellow oil (500.0 mg, 2.0 mmol, quant. yield); $R_f = 0.4$ (neat EtOAc); ^1H NMR (270 MHz, CDCl_3) $\delta = 3.57$ (t, $J = 6.1$ Hz, 2H), 3.51 (t, $J = 6.1$ Hz, 2H), 2.63 (t, $J = 6.3$ Hz, 2H), 2.45 (s, 6H), 2.36 (app t, $J = 6.3$ Hz, 2H), 2.29 (t, $J = 5.9$ Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (67.5 MHz, CDCl_3) $\delta = 166.0$, 154.4, 79.7, 47.2, 34.7, 28.4, 21.3; IR (neat, v/cm^{-1}) 3369, 2976, 2931, 1697, 1422, 1274, 1168, 1118,; HRMS calculated for $\text{C}_{12}\text{H}_{23}\text{N}_3\text{O}_2$ 241.1790, found for $[\text{M}+\text{H}]^+$ $\text{C}_{12}\text{H}_{24}\text{N}_3\text{O}_2$ 242.1869; MS (ESI): $m/z = 242.1869$ ($[\text{M}^++\text{H}]^+$, 100), HRMS = 242.1869 (calcd = 242.1869 [$\text{C}_{12}\text{H}_{24}\text{N}_3\text{O}_2$] $^+$).

1-benzyl-4-(2,2-dimethylhydrazono)piperidine [237]



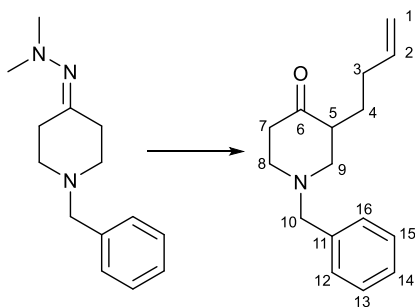
To a stirred solution of 1-benzyl-4-piperidinone (20.0 g, 106 mmol, 1.0 equiv.) in toluene (100.0 mL) was added N,N-dimethyl hydrazine (7.0 g, 117 mmol, 1.2 equiv.), the flask was equipped with a Dean-Stark trap and heated to reflux over 6 h, and then the remaining solvent was removed *in vacuo* to give the hydrazine as a clear yellow oil (23.0 g, 99.0 mmol, 94 %); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.37 - 7.20$ (m, 5H), 3.54 (app s, 2H), 2.66

(app t, $J = 5.9$ Hz, 2H), 2.59 (app t, $J = 6.0$ Hz, 2H), 2.53 (app t, $J = 6.0$ Hz, 2H), 2.44 (s, 6H), 2.39 (app t, $J = 5.9$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 167.0, 138.2, 129.0, 128.1, 127.0, 62.4, 53.8, 52.7, 47.4, 35.0, 28.4$; IR(neat, v/cm^{-1}) 3432, 3085, 3062, 3027, 2981, 1640, 1601, 1258, 1199, 1088, 1022, 984, 739, 698; MS (ESI): $m/z = 232.1818$ ($[\text{M}^+ + \text{H}]^+$, 100), HRMS = 232.1818 (calcd = 232.1814 $[\text{C}_{14}\text{H}_{22}\text{N}_3]^+$).

4-iodobut-1-ene[241]¹³⁰



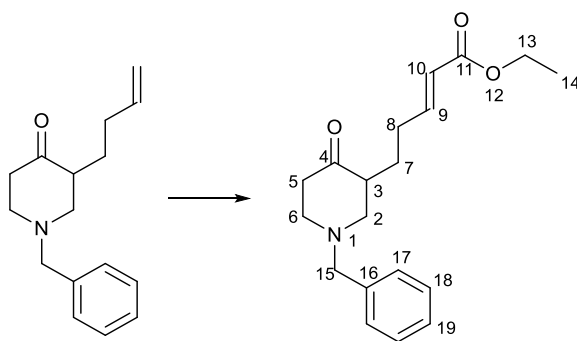
To a stirred solution of NaI (22.2 g, 148.0 mmol, 2.0 equiv.) in reagent grade acetone (150.0 mL) was added 4-bromobutene (10.0g, 74.0 mmol, 1.0 equiv.) and reaction mixture heated to reflux for 24 h, slurry mixture partitioned twice by Et_2O , washed by water and brine then sat. aqueous $\text{Na}_2\text{S}_2\text{O}_3$, and then the colourless solution evaporated *in vacuo*, pressure was adjusted to 400 mbar at 35 °C water bath. Purification done by distillation Kugelrohr apparatus over K_2CO_3 and Copper wire, temperature was elevated gradually from 60, 80, and finally 130 °C afforded the target compound as colourless oil (17.7 g, 97.0 mmol, 80%); ^1H NMR (270 MHz, CDCl_3) $\delta = 5.84 - 5.65$ (m, 1H), 5.12 (dd, $J = 1.7, 1.0$ Hz, 1H), 5.10 – 5.05 (m, 1H), 3.19 (t, $J = 7.2$ Hz, 2H), 2.31 – 2.11 (m, 2H); ^{13}C NMR (67.5 MHz, CDCl_3) $\delta = 136.9, 117.0, 37.6, 4.5$; IR(neat, v/cm^{-1}) 3448 (br), 3079, 3008, 2978, 2928, 1844, 1639, 1425, 1247, 991, 919. *The product must be stored in the dark to avoid rapid decomposition, as evident by a colour change to pink/ orange. The analytical data is consistent with literature values.

1-benzyl-3-(but-3-en-1-yl)piperidin-4-one [229]¹²⁹

A magnetically stirred solution of 1-benzyl-4-(2,2-dimethylhydrazon)piperidine (10.0 g, 43.0 mmol, 1.0 equiv.) in dry THF (86.0 mL) maintained at 0 °C was treated with n-BuLi (4.5 mL of a 1.29 M solution in hexanes, 47.5 mmol, 1.1 equiv.). After 10 min the reaction mixture was cooled to -78 °C and 4-bromobutene (8.7 mL, 86.4 mmol, 2.0 equiv.) was added. After a further 2.5 h (at -78 °C) the reaction mixture was quenched by the slow addition of HCl (120.0 mL of a 1.0 M aqueous solution). The resulting mixture was stirred at 18 °C for 1 h, cooled to 0 °C, basified [with NaOH (ca. 37.0 mL of a 2.0 M aqueous solution)] to pH = 9 then diluted with water (50.0 mL) and Et₂O (50.0 mL). The separated aqueous phase was extracted with DCM (3 x 50.0 mL) and the combined organic phases washed with brine (1 x 20.0 mL) before being dried (Na₂SO₄), filtered and then concentrated under reduced pressure to afford a clear, colourless oil. Subjection of this material to flash chromatography over silica gel and using Hex/EtOAc (4:1) v/v, after concentration of the appropriate fractions; R_f = 0.4 in Hex/EtOAc (7:3), to yield (10.46 g, 43.0 mmol, 81%) as a clear, colourless oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.38 – 7.34 (m, 5H, Ar), 5.75 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, H-2), 4.99-4.93 (m, 2H, H-1), 3.70-3.63 (m, 1H), 3.64-3.60 (m, 2H, H-10), 3.05-2.95 (m, 2H, H-9a, H-8a), 2.58-2.45 (m, 3H, H-7,

H-8b), 2.39-2.35 (m, 1H, H-5), 2.21 (dd, $J = 11.1, 9.8$ Hz, 1H, H-9b), 2.05-1.99 (m, 2H, H-3), 1.96-1.87 (m, 1H, H-4a), 1.33-1.25 (m, 1H, H-4b); ^{13}C NMR (101 MHz, CDCl_3) $\delta = 209.8$ (C6), 138.1 (C2), 138.0 (C11), 128.8 (CH-Ar), 128.4 (CH-Ar), 127.3 (CH-Ar), 115.0 (C1), 61.8 (C10), 58.6 (C9), 53.7 (C8), 49.0 (C5), 41.3 (C7), 31.1 (C3), 26.5 (C4); IR (neat, v/cm^{-1}) 3063, 3028, 2956, 2928, 2869, 2859, 2360, 2341, 1715, 1640, 1602, 1495, 1467, 1354, 1260, 1187, 1027, 911, 799, 739, 699; MS (ESI): $m/z = 244.1691$ ($[\text{M}^+ + \text{H}]^+$, 100), HRMS = 244.1691 (calcd = 244.1696 $[\text{C}_{16}\text{H}_{22}\text{NO}]^+$).

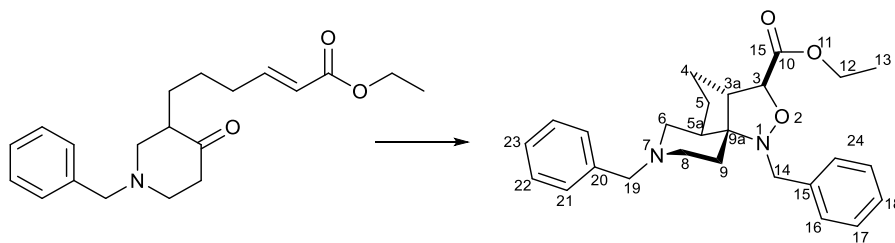
ethyl (*E*)-5-(1-benzyl-4-oxopiperidin-3-yl)pent-2-enoate [230]⁵¹



1-Benzyl-3-(but-3-en-1-yl)piperidin-4-one (2.0 g, 8.24 mmol, 1.0 equiv.) was dissolved in dry DCM (160.0 mL) in a 1-L three-necked flask equipped with a reflux condenser under a nitrogen atmosphere. Ethyl acrylate (24.74 g, 24.72 mmol, 3.0 equiv.) and Hoveyda-Grubbs Catalyst II-Generation (256.0 mg, 0.41 mmol, 5% by mole) were added. The reaction mixture was stirred at r.t. for a further 18 h by which time solvent removed *in vacuo* and the slurry residue was purified by column chromatography over silica gel using

Pet/EtOAc (6:1) and the titled compound was obtained as clear yellow oil (820.0 mg, 2.6 mmol, 32%); ^1H NMR (400 MHz, CDCl_3) δ = 7.35-7.27 (m, 5H), 6.89 (dt, J = 15.7, 6.9 Hz, 1H), 5.77 (dt, J = 15.6, 1.5 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.64 (d, J = 13.1 Hz, 1H), 3.58 (d, J = 13.1 Hz, 1H), 3.04-2.98 (m, 2H), 2.60-2.45 (m, 3H), 2.37 (dt, J = 6.7, 3.7 Hz, 1H), 2.24-2.11 (m, 3H), 1.96 (ddt, J = 13.7, 8.7, 6.9 Hz, 1H), 1.39-1.32 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ = 210.1, 166.4, 148.1, 138.0, 128.8, 128.3, 127.3, 121.8, 61.7, 60.1, 58.5, 53.6, 48.8, 40.9, 29.5, 25.7, 14.2; IR (neat, v/cm^{-1}) 3531, 3412, 3062, 2953, 2915, 2803, 2764, 1954, 1884, 1716, 1653, 1600, 1495, 1454, 1391, 1366, 1268, 1188, 1044, 911, 852, 753, 699; MS (ESI): m/z = 316.1889 ($[\text{M}^+ + \text{H}]^+$, 60), 338.1720 ($[\text{M} + \text{Na}]^+$, 3), HRMS = 316.1889 (calcd = 316.1907 $[\text{C}_{19}\text{H}_{26}\text{NO}_3]^+$), 338.1720 (calcd = 338.1727 $[\text{C}_{19}\text{H}_{25}\text{NNaO}_3]^+$).

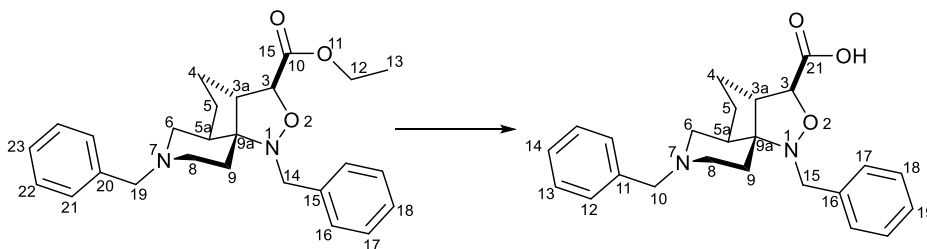
ethyl(3*S*,3*aR*,9*aR*)-1,7-dibenzyl-1,3,3a,4,5,6,7,8,9,9a-octahydro-1*H*,3*H*isoxazolo [3',4':2,3]cyclopenta[1,2-*c*]pyridine-3-carboxylate [232]¹³¹



To a round-bottom flask equipped with a reflux condenser and Dean-Stark trap. The stirring reaction mixture a mixture of ethyl (*E*)-5-(1-benzyl-4-oxopiperidin-3-yl)pent-2-enoate (330 mg, 1.06 mmol, 1.0 equiv.), *N*-benzylhydroxylamine hydrochloride (254 mg,

1.6 mmol, 1.6 equiv.), K_2CO_3 (220 mg, 0.50 mmol, 0.5 equiv.) and toluene (25 mL) was heated at reflux for 18 h, reaction was monitored by TLC and MS. Once complete, the reaction mixture was filtered through celite and the filter cake washed with CH_2Cl_2 three times, solvent removed *in vacuo* and direct purification by column chromatography over silica gel eluting Pet/EtOAc (4:3); $R_f = 0.3$ afforded the corresponding isoxazolidine product as yellow oil (310.0 mg, 0.737 mmol, 73%); ^1H NMR (500 MHz, $CDCl_3$) $\delta = 7.43 - 7.22$ (m, 10H, H-16- H-18, H-21- H-23), 4.25 – 4.14 (m, 3H, H-3 and H-12), 4.04 (d, 1H, $J = 10.3$ Hz, H-14_a), 3.96 (d, 1H, $J = 10.3$ Hz, H-14_b), 3.51 (s, 2H-19), 2.94- 2.87 (m, 1H, H-3a), 2.85 – 2.76 (m, 3H, H-8_a, and H-6_a), 2.10-1.91 (m, 4H, H-4, H-3_a, H-6_b), 2.28 – 2.18 (m, 4H, H-5_a, H-8_b, H-9), 1.79-1.72 (m, 1H, H-5_b), 1.52 – 1.43 (m, 1H, H-4_b), 1.26 (t, $J = 7.1$ Hz, 3H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 171.7$ (C10), 139.1 (C20 or C15), 138.5 (C15 or C20), 129.1 (2C, C16/C17/C16/C17), 128.3 (2C, C21/C22/C16/C17), 128.2 (2C, C16/C17/C21/C22), 127.1 (C23 or C18), 126.9 (C23 or C18), 83.7 (C3), 76.0 (C9a), 63.1 (C19), 61.1 (C12), 55.9 (C6), 54.8 (C3), 54.6 (C14), 51.1 (C8), 40.6 (C5a), 30.4 (C5), 29.0 (C4), 26.6 (C9), 14.3 (C13), 24 carbons out of 26 resonance observed ; IR(neat, ν/cm^{-1}) 3049 (br), 3005, 2928, 2684, 2630, 2558, 2293, 1755, 1416, 1293, 939; MS (ESI): $m/z = 421.2482$ ($[M^+ + H]^+$, 100), HRMS = 421.2482 (calcd = 421.2486 $[C_{26}H_{32}N_2O_3]^+$).

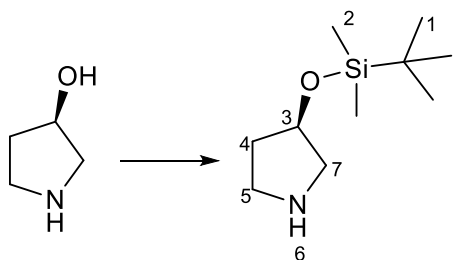
(3*S*,3*aR*,9*aR*)-1,7-dibenzyloctahydro-1*H*,3*H*-isoxazolo[3',4':2,3]cyclopenta[1,2-*c*]pyridine-3-carboxylic acid [245]



In a 25-ml 2-neck round bottom flask equipped with a suitable condenser ethyl (3*S*,3*aR*,9*aR*)-1,7-dibenzyloctahydro-1*H*,3*H*-isoxazolo[3',4':2,3]cyclopenta[1,2-*c*]pyridine-3-carboxylate (100.0 mg, 0.23 mmol, 1.0 equiv.) dissolved in a solution of THF/H₂O 50% v/v (15 mL) to the stirred solution Ba(OH)₂·8H₂O (750.0 mg, 0.315 mmol, 1.3 equiv.) was added. The reaction mixture was refluxed for 18 h at 70 °C, reaction was monitored by TLC and MS. When reaction is complete the solution was allowed to cool before filtration through cotton wool. Then CO₂ (g) was bubbled through into the pale yellow solution for 4 h to reach pH = 6 nearly, before the resultant suspension was filtered through cotton second time and the mixture evaporated *in vacuo* (at 70 mbar) give product as a white powder (84.0 mg, 0.21 mmol, 90%); ¹H NMR (400 MHz, MeOD) δ = 8.60 (s, 1H), 7.58 – 7.01 (m, 10H, H-12 - H-16& H-19 - H-23), 3.99 (dd, *J* = 5.5 Hz, 1H, H-3), 3.69 (s, 2H, H-10), 3.61 (s, 2H, H-17), 3.03 – 2.97 (m, 1H, H-3a), 2.94 – 2.78 (m, 2H, H-4), 2.44 - 2.19 (m, 2H, H-6), 2.11 (t, *J* = 8.3 Hz, 2H, H-8), 2.07 – 1.94 (m, 3H, 2H-5, H-5a), 1.85-1.82 (m, 1H, 9-H_a), 1.41-1.38 (m, 1H, 9-H_b); ¹³C NMR (101 MHz, MeOD) δ = 160.6 (C21), 148.6 (C19 or C14), 139.2 (C19 or C14), 129.5(2C, C12,C13 or C16,C-17), 127.96(2C, C12,C13 or C16,C17), 127.62 (C14 or C18), 127.3 (C14 or C18), 85.7(C3), 68.6(C9a), 62.3(C10),

55.5(C3a), 55.2(C15), 53.6(C6), 50.3(C5a), 50.2 (C8), 42.3(C4), 30.3(C5), 24.1(C9), 20 carbons out of 24 resonance observed; IR(neat, v/cm^{-1}) 3331(brd), 2928, 2281, 2255, 1593, 1427, 1133, 751, 698, 665; MS (ESI): $m/z = 393.2171$ ($[\text{M}^+ + \text{H}]^+$, 100), HRMS = 393.2171 (calcd = 393.21718 $[\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3]^+$).

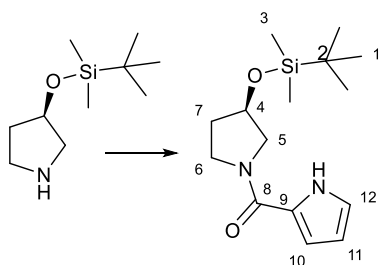
3-((tert-butyldimethylsilyl)oxy)pyrrolidine [258]¹³²



In a flame dried 100 mL round bottom flask, a solution of (R)-3-hydroxy pyrrolidine (600.0 mg, 6.88 mmol, 1.0 equiv.) in CH_2Cl_2 (25.0 mL) was added trimethylamine (1.74 g, 17.2 mmol, 2.0 equiv.), stirred for 15 min before addition of TBDMSCl (2.07 g, 13.7 mmol, 2.0 equiv.) and stirred at r.t. for 24 h. Water (30.0 mL) and 1.0 M HCl (3.0 mL) was added and aqueous phase was extracted with DCM (2 x 30.0 mL), the combined organic layers were washed with brine (50.0 mL) dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography over silica gel eluting with (CHCl_3 / MeOH/ NH_4OH) in 80:25:2.5 (v/v ratio), afforded the titled compound as brown oil (970.0 mg, 4.8 mmol, 80%); ^1H NMR (400 MHz, CDCl_3) δ = 6.83 (s, 1H, H-6), 4.33 (tt, J = 4.4, 2.0 Hz, 1H, H-3), 3.20 -3.10 (m, 2H, H-5), 2.88- 2.40 (m , 1H, H-4), 1.87- 1.70 (m, 2H, H-7), 0.68 (s, 9H, H-1), -0.12 (s, 6H, H-2); ^{13}C NMR (400 MHz, CDCl_3) δ = 70.9 (C3), 53.0 (C7),

43.6 (C5), 34.5 (C4), 25.6 (C1), 17.9 (C), -4.8 (C2); IR(neat, ν/cm^{-1}) 3682, 3280, 3212, 2954, 2856, 2709, 1471, 1408, 1361, 1254, 1068, 1007, 835, 665, 433; MS (ESI): m/z = 202.1627 ($[\text{M}^+ + \text{H}]^+$, 100), HRMS = 202.1627 (calcd = 202.1622 $[\text{C}_{11}\text{H}_{23}\text{NOSi}]^+$).

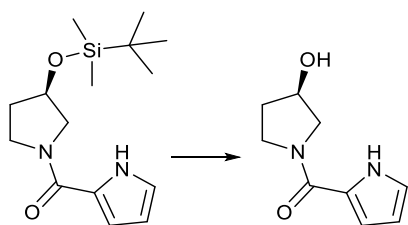
(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)(1H-pyrrol-2-yl) methanone [259]¹³³



EDCI, HCl (3.39 g, 21.8 mmol, 1.1 equiv.) and N, N- diisopropylethylamine (8.7 ml, 49.6 mmol, 2.5 equiv.) were added to a solution 3-((tert-butyldimethylsilyl)oxy)pyrrolidine (4.0 g, 19.8 mmol, 1.0 equiv.), pyrrol-2-carboxylic acid (2.2 g, 19.8 mmol, 1.0 equiv.) and HOBT (2.94 g, 21.8 mmol, 1.1 equiv.) in CH_2Cl_2 (100.0 ml) and stirred for 24 h at r.t., under nitrogen. Then the solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with ($\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$) in 80:25:2.5 (v/v) ratio, to furnish the title compound as creamy white solid (4.4 g, 14.9 mmol, 75%); ^1H NMR (400 MHz, CDCl_3) δ = 6.95-6.80 (m, 1H, H-10), 6.61 (app d, J = 7.8 Hz, 1H, H-12), 6.29 (app dd, J = 4.1, 2.8 Hz, 1H, H-11), 4.60 – 4.39 (m, 1H, H-4), 3.92 – 3.75 (m, 2H, H-5), 3.65 – 3.58 (m, 2H, H-6), 2.03-1.90 (m, 2H, H-7), 0.89 (s, 9H, H-1), 0.10 (s, 6H, H-3); ^{13}C NMR (400 MHz, CDCl_3) δ = 160.7 (C8), 121.3 (C10), 112.5 (C12), 109.8 (C11), 71.9 (C4), 56.3 (C5), 46.1 (C6), 33.0 (C7), 25.82 (C1), 18.0 (C2), -4.7 (C3); IR(neat, ν/cm^{-1})

3608, 3583, 3250, 2958, 2875, 1708, 1580, 1548, 1455, 1331, 1131, 1101, 742; MS (ESI): m/z = 295.1828 ($[M+Na]^+$, 100), 317.1640($[M+H]^+$, 15), 589.3623 ($[2M+H]^+$, 34), HRMS = 295.1828 (calcd = 295.1836 $[C_{15}H_{27}N_2O_2Si]^+$), 317.1640 (calcd = 317.1656 $[C_{15}H_{26}N_2O_2NaSi]^+$), 589.3623 (calcd = 589.3608 $[C_{30}H_{55}N_4O_4Si_2]^+$).

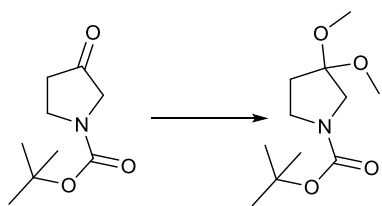
(R)-(3-hydroxypyrrolidin-1-yl)(1H-pyrrol-2-yl)methanone [260]



To a solution of (3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)(1H-pyrrol-2-yl)methanone (1.0 g, 3.6 mmol, 1.0 equiv.) in dry THF (20.0 mL), TBAF (1.13 g, 4.3 mmol, 1.2 equiv.) was added at 0 °C and solution stir for 45 min before warmed up to r.t., and then EtOAc (10.0 mL) was added and water (10.0 mL). Organic layer extracted by EtOAc (3 x 10 mL), combined layers dried over $MgSO_4$, filtered off and solvent evaporated. Residue purified by column chromatography over silica gel using Hex/ EtOAc (70:73) v/v ratio, then using $CHCl_3/MeOH$ (80:20) the target compound obtained as creamy white solid (473 gm, 2.62 mmol, 73%); ^1H NMR (400 MHz, MeOD) δ = 7.92 (s, 1H), 6.80 (dd, J = 2.6, 1.5 Hz, 1H), 6.68 (dd, J = 3.6, 1.5 Hz, 1H), 6.10 (dd, J = 3.5, 2.6 Hz, 1H), 4.42 – 4.38 (m, 1H), 3.37 (s, 1H), 3.33 (dt, J = 3.3, 1.6 Hz, 2H), 3.15- 3.11 (m, 2H), 2.98 (dd, J = 4.4, 2.0 Hz, 2H); ^{13}C NMR (400 MHz, MeOD) δ = 168.7, 119.5, 111.74, 108.1, 71.0, 54.0, 44.1, 34.3, 25.80; IR(neat, ν/cm^{-1}) 3501, 2975, 2892, 2834, 1699, 1407, 1366, 1255, 888,

772; MS (ESI): m/z = 360.3226 ($[2M]^+$, 100), 317.1640 ($[M+H]^+$, 15), 589.3623 ($[2M+H]^+$, 34), HRMS = 360.3226 (calcd = 360.3207 $[C_{17}H_{40}N_6O_2]^+$).

***tert*-butyl 3,3-dimethoxypyrrolidine-1-carboxylate [263]¹²¹**

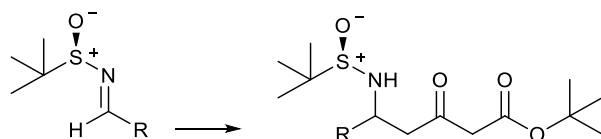


A solution of 1-Boc-3-pyrrolidinone (1.0 g, 5.4 mmol, 1.0 equiv.), trimethylorthoformate (2.86 g, 27.0 mmol, 5.0 equiv.) and *p*-toluene sulfonic acid (37.0 mg, 0.21 mmol, 4% by mole) was prepared in methanol anhydrous (15.0 mL). The solution was heated to reflux for 1 h and then poured into water. The product was extracted into CH_2Cl_2 (3 x 10.0 mL) and the organic layers were washed using aqueous $NaHCO_3$ and brine then dried over Na_2SO_4 . The solvent was evaporated *in vacuo* to a brown oil (985.0 mg as crude) which was purified by distillation using a Kugelrohr apparatus. The ketal was obtained as a pale yellow oil (922.0 mg, 3.9 mmol, 74%); bp 180-190°; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.39 (dt, J = 9.7, 6.7 Hz, 2H), 3.35 (s, 2H), 3.22 (s, 6H), 2.05 (t, J = 6.6 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.4, 107.7, 79.3, 52.1, 49.7, 44.1, 32.9, 28.4; IR(neat, v/cm^{-1}) 3501, 2975, 2892, 2834, 1699, 1407, 1366, 1255, 888, 772; MS (ESI): m/z = 254.1361 ($[M+Na]^+$, 100), 232.1548 ($[M+H]^+$, 100), HRMS = 254.1361 (calcd = 254.1363 $[C_{11}H_{21}N_1Na_1O_4]^+$), 232.1548 (calcd = 232.1543 $[C_{11}H_{22}N_1O_4]^+$).

General Procedure for Sulfinimine Synthesis:

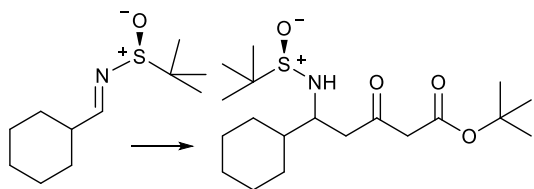
To a ketone/aldehyde (1.0 eq.) solution in dry THF (0.1 M), $\text{Ti}(\text{EtO})_4$ (4.0 eq.) was added, the reaction mixture was stirred for 10 min. sulfunamine (1.1 eq.) was added the solution was reflux at 70 °C for 2 h at r.t., reaction monitored by TLC and MS. Water was added to the mixture when reaction was completed, filtered through a short pad of celit. The aqueous layer was separated and extracted three times from EtOAc. The combined organic phases were dried over MgSO_4 and solvent removed in vacuo and purified by column chromatography on silica gel using the mixture Pet/EtOAc (4:1) v/v ratio as an eluent, to give the desired sulfinimide which to be stored at -20 °C.

Substituted *tert*-butyl 5-(((*R*)-*tert*-butylsulfinyl)amino)



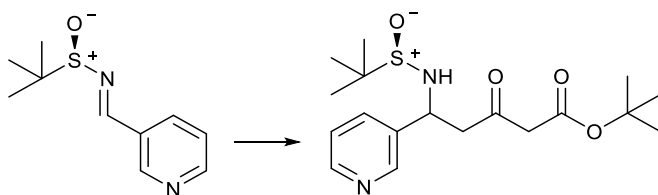
General Procedure: To a solution of *tert*-butylacetoacetate (4.0 equiv.) in THF (0.15 M), *n*-BuLi (9.0 equiv.) was added dropwise the solution was maintained to stir for 1 h at 0 °C before it was added to a solution of sulfinamide (1.0 equiv.) in THF (0.2 M). The reaction was stir overnight and allowed to warm slowly to r.t. The reaction mixture was quenched with sat. aq. NH_4Cl , extracted with EtOAc, dried over MgSO_4 , filtered off and concentrated in *vacuo*, then purified by column chromatography over silica and using mixture solvents Pet/EtOAc (10:1) v/v ratio.

***tert*-butyl 5-(((*R*)-*tert*-butylsulfinyl)amino)-5-cyclohexyl-3-oxopentanoate [295]**



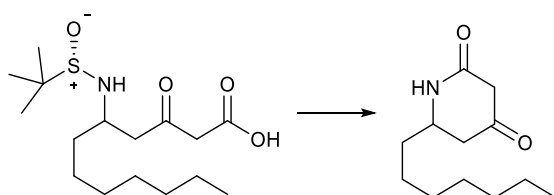
Obtained as bright yellow oil freezes at 20 °C; found R_f: 0.4; ¹H NMR (400 MHz, DMSO) δ = 4.68 (d, *J* = 8.5 Hz, 1H), 3.47 (q, *J* = 7.1 Hz, 2H), 3.36 (dd, *J* = 8.3, 5.7, 1H), 2.82-2.78 (m, 2H), 1.98 (s, 1H), 1.73 – 1.64 (m, 4H), 1.63 – 1.51 (m, 2H), 1.41 (s, 9H), 1.11 (s, 9H), 1.05 – 0.79 (m, 4H); ¹³C NMR (101 MHz, d₆-DMSO) δ = 202.1, 166.3, 80.7, 50.0, 55.3, 50.7, 46.5, 42.2, 29.1, 28.0, 27.6, 26.0, 25.8, 25.7, 22.7; MS (ESI): *m/z* = 396.2181 ([M+Na]⁺, 100), 374.2364 ([M+H]⁺, 34), HRMS = 396.2181 (calcd = 396.2179 [C₁₉H₃₅N₁NaO₄S]⁺), 374.2364 (calcd = 374.2360 [C₁₉H₃₆N₁O₄S]⁺).

***tert*-butyl 5-(((*R*)-*tert*-butylsulfinyl)amino)-3-oxo-5-(pyridin-3-yl)pentanoate [297]**



Different solvent mixture has been used to elute the titled product using the column chromatography; solvent mixture was; Pet/EtOAc (10:1, 8:2, 7:3, 1:1) then $\text{CHCl}_3/\text{MeOH}$ (100:5) v/v ratio, respectively, to obtained colorless oil (87%), found $R_f = 0.3$ in latest solvent; ^1H NMR (400 MHz, DMSO) $\delta = 8.6$ -8.4 (m, 1H (Ar-H)), 8.22- 8.12 (m, 1H, (Ar-H)), 7.47- 7.25 (m, 2H, (Ar-H)), 4.68 (d, $J = 8.5$ Hz, 1H), 3.50- 3.45 (m, 1H), 3.36 (s, 2H), 3.12- 2.80 (m, 2H), 1.41 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 202.16, 166.35, 80.77, 57.03, 55.39, 50.71, 46.54, 42.29, 29.17, 28.01, 27.61, 26.05, 25.86, 25.73, 22.70; MS (ESI): $m/z = 369.1844$ ($[\text{M}+\text{H}]^+$, 100), 385.1785 ($[\text{M}+\text{NH}_4]^+$, 19), 391.1658($[\text{M}+\text{Na}]^+$), HRMS = 369.1844 (calcd = 369.1844 $[\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_4\text{S}]^+$), 385.1785 (calcd = 385.2108 $[\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_4\text{S}]^+$), 391.1658 (calcd = 391.1662 $[\text{C}_{18}\text{H}_{28}\text{N}_2\text{NaO}_4\text{S}]^+$).

6-heptylpiperidine-2,4-dione [293]



A solution of 5-(((S)-*tert*-butylsulfinyl)amino)-3-oxododecanoic acid (25.0 mg, 0.11 mmol, 1.0 equiv.) dissolved in Et_2O (1.0 mL) and HCl (0.34 mL, 0.55 mmol, 5 equiv.) and stir for 1 h, when reaction completed by TLC and MS, solvent evaporated *in vacuo*. The sticky oily brown residue was dissolved in THF (1.0 mL) when EDC (37.0 mg, 0.124 mmol, 1.1 equiv.) as solid, then Et_3N (26.0 μL , 0.186 mmol, 2.0 equiv.) was added to the solution. Brown coloured solution stirred for 1 h before quenched by adding water. Organic

phase was separated by EtOAc (3 x 5.0 mL), dried over Na₂SO₃, then evaporated *in vacuo* to yield the titled compound as brown oil (9.0 mg, 65%); R_f= 0.2; ¹H NMR (400 MHz, CDCl₃) δ = 5.30 (s, 1H, NH), 3.25 – 3.20 (m, 1H), 3.17 (dd, *J* = 13.0, 6.1 Hz, 2H), 2.35 (t, *J* = 6.2 Hz, 2H), 2.23 -2.20 (m, 10H), 1.63 (dt, *J* = 11.8, 5.9 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ = 198.5, 175.7, 68.1, 57.2, 45.7, 45.2, 39.7, 35.3, 27.3, 27.3, 15.4, 15.0; IR(thin film, v/cm⁻¹) 3446, 2977, 2949, 2865, 2824, 2778, 1650, 1533, 1407, 1133.

References

References

- 1 M. J. Rawling, T. E. Storr, W. A. Bawazir, S. J. Cully, W. Lewis, M. S. I. T. Makki, I. R. Strutt, G. Jones, D. Hamza and R. A. Stockman, *Chem. Commun.*, 2015, **51**, 12867–12870.
- 2 C. A. Heaton, *An introduction to industrial chemistry*, Springer Science & Business Media, 1996.
- 3 A. T. Balaban and D. J. Klein, *Scientometrics*, 2006, **69**, 615–637.
- 4 M. Karpf, *From Milligrams to Tons: The Importance of Synthesis and Process Research in the Development of New Drugs*, 2011.
- 5 J. Tao and R. J. Kazlauskas, *Biocatalysis for Green Chemistry and Chemical Process Development*, Wiley, 2011.
- 6 R. L. C. Katherine J. Denniston, Joseph J. Topping, in *General Organic and BioChemistry*, McGraw-Hill Companies, Inc., New York, NY 10020, 3rd edn., 2001.
- 7 A. D. McNaught, *IUPAC Compendium of Chemical Terminology: The Gold Book*, International Union of Pure and Applied Chemistry, 2005.
- 8 A. F. Pozharskii, A. T. Soldatenkov and A. R. Katritzky, *Heterocycles in life and society. An introduction to heterocyclic chemistry and biochemistry and the role of heterocycles in science, technology, medicine and agriculture.*, John Wiley & Sons, 1997.
- 9 Morachevskii, *Russ. J. Appl. Chem.*, 2002, **75**, 856–860.
- 10 B. P. Shenvi RA, O'Malley DP, *Acc. Chem. Res.*, 2009, **42**, 530–541.
- 11 W. B. G. Walter Gratzer, *Eurekas and Euphorias: The Oxford Book of Scientific Anecdotes*, Oxford University Press, 2004.
- 12 O. Deeb, M. D. Aytemir, G. Karakaya, A. Segura-Cabrera, C. A. García-Pérez, M. A. Rodríguez-Pérez, X. Guo, G. Rivera, V. Bocanegra-García, O. Deeb and L. M. M. Gad, in *Medicinal Chemistry and Drug Design*, ed. D. Ekinici, InTech, 2012.
- 13 J. Shimokawa, *Tetrahedron Lett.*, 2014, **55**, 6156–6162.

- 14 A. Okano, R. C. James, J. G. Pierce, J. Xie and D. L. Boger, *J. Am. Chem. Soc.*, 2012, **134**, 8790–8793.
- 15 G. Pettit and C. Herald, *J. Am. Chem. Soc.*, 1982, **104**, 6846–6848.
- 16 D. E. Schaufelberger, M. P. Koleck, J. a Beutler, A. M. Vatakis, A. B. Alvarado, P. Andrews, L. V Marzo, G. M. Muschik, J. Roach, J. T. Ross, W. B. Lebherz, M. P. Reeves, R. M. Eberwein, L. L. Rodgers, R. P. Testerman, K. M. Snader and S. Forenza, *J. Nat. Prod.*, 1991, **54**, 1265–1270.
- 17 P. A. Wender and V. A. Verma, *Org. Lett.*, 2008, **10**, 3331–3334.
- 18 G. E. Keck, Y. B. Poudel, T. J. Cummins, A. Rudra and J. A. Covell, *J. Am. Chem. Soc.*, 2011, **133**, 744–747.
- 19 B. M. Trost and G. Dong, *Nature*, 2008, **456**, 485–488.
- 20 P. A. Wender and B. L. Miller, *Nature*, 2009, **460**, 197–201.
- 21 Y. Lu, S. K. Woo and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 13876–13879.
- 22 T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010–3021.
- 23 E. E. Wyatt, S. Fergus, W. R. J. D. Galloway, A. Bender, D. J. Fox, A. T. Plowright, A. S. Jessiman, M. Welch and D. R. Spring, *Chem. Commun.*, 2006, 3296–3298.
- 24 W. R. J. D. Galloway, A. Isidro-Llobet and D. R. Spring, *Nat. Commun.*, 2010, **1**, 80.
- 25 S. L. Schreiber, *Science*, 2000, **287**, 1964–1969.
- 26 K. Paulvannan, *Tetrahedron Lett.*, 1999, **40**, 1851–1854.
- 27 I. Ugi, A. Dömling and W. Hörl, *Endeavour*, 1994, **18**, 115–122.
- 28 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.
- 29 A. Padwa and S. K. Bur, *Tetrahedron*, 2007, **63**, 5341–5378.
- 30 G. B. Lutz Tietze and Kersten Matthias Gericke, *J. Am. Chem. Soc.*, 2007, **129**, 7476.
- 31 L. F. Tietze and M. E. Lieb, *Curr. Opin. Chem. Biol.*, 1998, **2**, 363–371.

- 32 L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, John Wiley & Sons, 2006.
- 33 R. Willstätter, *Justus Liebigs Ann. Chem.*, 1901, **317**, 204–265.
- 34 A. . J. Humphrey and D. O'Hagan, *Nat. Prod. Rep.*, 2001, **18**, 494–502.
- 35 J. W. Medley and M. Movassaghi, *Chem. Commun.*, 2013, **49**, 10775–10777.
- 36 H. Pellissier, *Asymmetric domino reactions*, Royal Society of Chemistry, RSC Cat Series, 10 edn., 2013.
- 37 M. Ihara, K. Makita, Y. Tokunaga and K. Fukumoto, *J. Org. Chem.*, 1994, **59**, 6008–6013.
- 38 A. Padwa and W. H. Pearson, *Synthetic applications of 1, 3-dipolar cycloaddition chemistry toward heterocycles and natural products*, John Wiley & Sons, 2003, vol. 59.
- 39 J. J. Tufariello, S. A. Ali and H. O. Klingele, *J. Org. Chem.*, 1979, **44**, 4213–4215.
- 40 P. Prasanna, K. Balamurugan, S. Perumal, P. Yogeewari and D. Sriram, *Eur. J. Med. Chem.*, 2010, **45**, 5653–5661.
- 41 M. R. S. and W. C. Wildman, *J. Org. Chem.*, 1971, **36**, 3202–3207.
- 42 A. Maureen Rouhi, *Chem. Eng. News*, 2002, **80**, 29–38.
- 43 H. S. Eleuterio, *J. Mol. Catal.*, 1991, **65**, 55–61.
- 44 G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746–1787.
- 45 Y. Chauvin, *Angew. Chemie - Int. Ed.*, 2006, **45**, 3741–3747.
- 46 A. K. Chatterjee, T. L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370.
- 47 P. Ahlberg, 'Development metathesis method Org. Synth. Adv. Inf. Nobel Prize Chem. 2005, R. Swedish Acad. Sci. Stock. 2005;
http://nobelprize.org/nobel_prizes/chemistry/laureates/2005/chemad, 2005, 1–12.
- 48 J. Tomasek and J. Schatz, *Green Chem.*, 2013, **15**, 2317.
- 49 Y. Schrodi and R. L. Pederson, *Aldrichimica Acta*, 2007, **40**, 45–52.

- 50 R. H. Grubbs and M. Sanford, in *Ring Opening Metathesis Polymerisation and Related Chemistry*, 2002 Kluwer Academic Publishers, 2002, pp. 17–21.
- 51 R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117–7140.
- 52 V. M. Marx, M. B. Herbert, B. K. Keitz and R. H. Grubbs, *J. Am. Chem. Soc.*, 2014, **135**, 94–97.
- 53 I. C. Stewart, C. J. Douglas and R. H. Grubbs, *Org. Lett.*, 2008, **10**, 441–444.
- 54 S. Magnuson, *Tetrahedron*, 1995, **51**, 2167–2213.
- 55 D. Robbins, A. F. Newton, C. Gignoux, J.-C. Legeay, A. Sinclair, M. Rejzek, C. A. Laxon, S. K. Yalamanchili, W. Lewis, M. A. O’Connell and R. A. Stockman, *Chem. Sci.*, 2011, **2**, 2232–2235.
- 56 R. A. Stockman, *Tetrahedron Lett.*, 2000, **41**, 9163–9165.
- 57 K. M. G. O’Connell, M. Díaz-Gavilán, W. R. J. D. Galloway and D. R. Spring, *Beilstein J. Org. Chem.*, 2012, **8**, 850–860.
- 58 R. a Stockman, A. Sinclair, L. G. Arini, P. Szeto and D. L. Hughes, *J. Org. Chem.*, 2004, **69**, 1598–1602.
- 59 M. Rejzek, R. A. Stockman and D. L. Hughes, *Org. Biomol. Chem.*, 2005, **3**, 73–83.
- 60 J.-C. Legeay, W. Lewis and R. A. Stockman, *Chem. Commun.*, 2009, 2207–2209.
- 61 S. J. Roe and R. A. Stockman, *Chem. Commun.*, 2008, **44**, 3432–3434.
- 62 A. Barthelme, D. Richards, I. R. Mellor and R. a Stockman, *Chem. Commun.*, 2013, **49**, 10507–10509.
- 63 D. L. J. Clive, M. Yu, J. Wang, V. S. C. Yeh and S. Kang, *Chem. Rev.*, 2005, **105**, 4483–4514.
- 64 D. Trauner and S. J. Danishefsky, *Tetrahedron Lett.*, 1999, **40**, 6513–6516.
- 65 T. E. Storr, S. J. Cully, M. J. Rawling, W. Lewis, D. Hamza, G. Jones and R. A. Stockman, *Bioorg. Med. Chem.*, 2014, **23**, 2621–2628.
- 66 L. G. Arini, P. Szeto, D. L. Hughes and R. A. Stockman, *Tetrahedron Lett.*, 2004, **45**, 8371–8374.

- 67 C. Gignoux, A. F. Newton, A. Barthelme, W. Lewis, M.-L. Alcaraz and R. A. Stockman, *Org. Biomol. Chem.*, 2012, **10**, 67.
- 68 A. F. C. Aristizabal Luis F, *UF/IFAS Featur. Creat.*, 2014.
- 69 J. M. Pasteels, C. Deroe, B. Tursch, J. C. Braekman, D. Daloze and C. Hootele, *J. Insect Physiol.*, 1973, **19**, 1771–1784.
- 70 M. Rejzek, R. A. Stockman, J. H. van Maarseveen and D. L. Hughes, *Chem. Commun.*, 2005, 4661–4662.
- 71 M. Rejzek and R. A. Stockman, *Tetrahedron Lett.*, 2002, **43**, 6505–6506.
- 72 A. F. Newton, M. Rejzek, M.-L. Alcaraz and R. A. Stockman, *Beilstein J. Org. Chem.*, 2008, **4**, 4.
- 73 F. A. Davis, B. Chao, A. Rao, T. U. V and V. Pennsylv, *Org. Lett.*, 2001, **3**, 3169–3171.
- 74 F. a. Davis, T. Fang, B. Chao and D. M. Burns, *Synthesis (Stuttg.)*, 2000, **2000**, 2106–2112.
- 75 M. Guerola, M. Sánchez-Roselló, C. Mulet, C. del Pozo and S. Fustero, *Org. Lett.*, 2015, 960–963.
- 76 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
- 77 G. Procopiou, P. Aggarwal, A. F. Newton, D. Richards, I. R. Mellor, G. Harbottle and R. A. Stockman, *Chem. Commun.*, 2014, **50**, 15355–15357.
- 78 K. Maruyama and T. Katagiri, *J. Phys. Org. Chem.*, 1989, **2**, 205–213.
- 79 W. Kitching, J. a Lewis, M. V Perkins, R. Drew, C. J. Moore, V. Schurig, W. a Koenig and W. Francke, *J. Org. Chem.*, 1989, **54**, 3893–3902.
- 80 F. A. Luzzio, R. W. Fitch, W. J. Moore and K. J. Mudd, *J. Chem. Educ.*, 1999, **76**, 974–975.
- 81 A. F. Newton, S. J. Roe, J.-C. Legeay, P. Aggarwal, C. Gignoux, N. J. Birch, R. Nixon, M.-L. Alcaraz and R. A. Stockman, *Org. Biomol. Chem.*, 2009, **7**, 2274–2277.
- 82 M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956.

- 83 L. Bui, H. Luo, W. R. Gunther and Y. Román-Leshkov, *Angew. Chemie*, 2013, **125**, 8180–8183.
- 84 A. Padwa, L. Fisera, K. F. Koehler and G. S. K. Wong, *J. Org. Chem.*, 1984, **49**, 276–281.
- 85 M. L. Waters and W. D. Wulff, *The Synthesis of Phenols and Quinones via Fischer Carbene Complexes*, 2004.
- 86 K. N. Houk, J. Gonzalez and Y. Li, *Acc. Chem. Res.*, 1995, **28**, 81–90.
- 87 M. Shindo, Y. Fukuda and K. Shishido, *Tetrahedron Lett.*, 2000, **41**, 929–932.
- 88 A. L. De Sousa and R. A. Pilli, *Org. Lett.*, 2005, **7**, 1617–1619.
- 89 M. Julia and J.-M. Paris, *Tetrahedron Lett.*, 1973, **14**, 4833–4836.
- 90 G. H. Lee, H. K. Lee, E. B. Choi, B. T. Kim and C. S. Pak, *Tetrahedron Lett.*, 1995, **36**, 5607–5608.
- 91 E. Juaristi and V. A. Soloshonok, *Enantioselective Synthesis of Beta-Amino Acids*, Wiley, 2005.
- 92 O. O. Grygorenko, *Tetrahedron*, 2015, **71**, 5169–5216.
- 93 B. Wu, W. Szymański, S. de Wildeman, G. J. Poelarends, B. L. Feringa and D. B. Janssen, *Adv. Synth. Catal.*, 2010, **352**, 1409–1412.
- 94 R. Grigg, J. Markandu, T. Perrior, Z. Qiong and T. Suzuki, *J. Chem. Soc. Chem. Commun.*, 1994, 1267.
- 95 R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1992, **48**, 6929–6952.
- 96 S. Lee and Z. Zhao, *Tetrahedron Lett.*, 1999, **40**, 7921–7924.
- 97 I. S. Young and M. A. Kerr, *Angew. Chemie Int. Ed.*, 2003, **42**, 3023–3026.
- 98 S. Lee and Z. S. Zhao, *Org. Lett.*, 1999, **1**, 2–5.
- 99 D. R. Williams, M. H. Osterhout and G. S. Amato, *Heterocycles*, 2004, **64**, 45–50.
- 100 J. Escalante, M. Carrillo-Morales and I. Linzaga, *Molecules*, 2008, **13**, 340–347.
- 101 K.-H. Park and M. J. Kurth, *Tetrahedron*, 2002, **58**, 8629–8659.

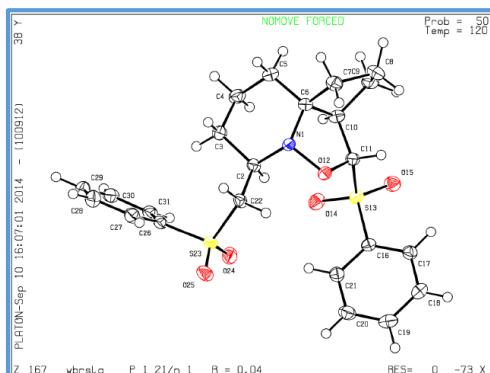
- 102 M. Goodman and H. Shao, *Pure Appl. Chem.*, 1996, **68**, 1303–1308.
- 103 D. Enders and J. Wiedemann, *Liebigs Ann.*, 1997, 699–706.
- 104 G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484–4517.
- 105 R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403–419.
- 106 P. Aggarwal, G. Procopiou, D. Robbins, G. Harbottle, W. Lewis and R. A. Stockman, *Synlett*, 2012, 423–427.
- 107 R. J. Spandl, H. Rudyk and D. R. Spring, *Chem. Commun.*, 2008, 3001–3003.
- 108 S. Fujita, T. Sakaguchi, T. Kobayashi, H. Tsuchikawa and S. Katsumura, *Org. Lett.*, 2013, **15**, 2758–2761.
- 109 R. Lazny and A. Nodzevska, *Chem. Rev.*, 2009, **110**, 1386–1434.
- 110 X. Zhao, D. Liu, F. Xie and W. Zhang, *Tetrahedron*, 2009, **65**, 512–517.
- 111 M. G. Banwell, M. J. Coster, N. L. Hungerford, M. J. Garson, S. Su, A. C. Kotze and M. H. G. Munro, *Org. Biomol. Chem.*, 2012, **10**, 154.
- 112 K. Voigtritter, S. Ghorai and B. H. Lipshutz, *J. Org. Chem.*, 2011, **76**, 4697–4702.
- 113 R. C. Bernotas and R. V. Cube, *Synth. Commun.*, 1990, **20**, 1209–1212.
- 114 T. Imaoka, O. Iwamoto, K. Noguchi and K. Nagasawa, *Angew. Chemie Int. Ed.*, 2009, **121**, 3857–3859.
- 115 S. W. Pelletier, *Alkaloids: Chemical and Biological Perspectives*, Elsevier Science, 1999.
- 116 G. W. Gribble, *Naturally Occurring Organohalogen Compounds - A Comprehensive Update*, Springer Vienna, 2009.
- 117 J. R. Parikh and W. V. E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505–5507.
- 118 D. F. Burdi, R. Hunt, L. Fan, T. Hu, J. Wang, Z. Guo, Z. Huang, C. Wu, L. Hardy, M. Detheux, M. A. Orsini, M. S. Quinton, R. Lew and K. Spear, *J. Med. Chem.*, 2010, **53**, 7107–7118.
- 119 S. V. Ley, J. Norman and A. J. Wilson, *e-EROS Encycl. Reagents Org. Synth.*, 1994.

- 120 S. A. Lawrence, *Amines: synthesis, properties and applications*, Cambridge University Press, 2004.
- 121 R. J. Sundberg, B. C. Pearce and J. P. Laurino, *J. Heterocycl. Chem.*, 1986, **23**, 537–539.
- 122 P. G. Reddy, G. D. K. Kumar and S. Baskaran, *Tetrahedron Lett.*, 2000, **41**, 9149–9151.
- 123 D. Morton and R. A. Stockman, *Tetrahedron*, 2006, **62**, 8869–8905.
- 124 J. a. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.*, 2002, **35**, 984–995.
- 125 S. P. Singh and R. P. Bakale, *Org. Synth*, 2010, **87**, 275–287.
- 126 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **16**, 2647–2650.
- 127 S. Lee and Z. S. Zhao, *Org. Lett.*, 1999, **1**, 681–684.
- 128 M. Mendelovici and E. Glotter, *J. Chem. Soc. Perkin Trans. I*, 1992, 1735–1740.
- 129 M. G. Banwell, M. J. Coster, N. L. Hungerford, M. J. Garson, S. Su, A. C. Kotze and M. H. G. Munro, *Org. Biomol. Chem.*, 2012, **10**, 154–161.
- 130 M. R. Harris, M. O. Konev and E. R. Jarvo, *J. Am. Chem. Soc.*, 2014, **136**, 7825–7828.
- 131 A. Sinclair, L. G. Arini, M. Rejzek, P. Szeto and R. A. Stockman, *Synlett*, 2006, 2321–2324.
- 132 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190–6191.
- 133 P. a. Glossop and C. a L. Lane, *PCT Intl. Pat.*, 2008, WO2010/007561 A1.

APPENDIX-A

X-RAY CRYSTAL DATA

Compound [188] X-Ray Data



Identification code	wbrsla
Empirical formula	C ₂₃ H ₂₇ N O ₅ S ₂
Formula weight	461.57
Temperature/K	120
Crystal system	triclinic
Space group	P1 21/n 1
a/Å	11.4175(4)
b/Å	12.8731(4)
c/Å	15.2933(4)
α/°	90
β/°	101.712(3)
γ/°	90
Volume/Å ³	856.43(9)
Z	4
ρ _{calc} /mm ³	1.393
m/mm-1	2.493
F(000)	976.0
Crystal size/mm ³	0.334 × 0.091 × 0.0297
2θ range for data collection	0.969 to 74.271°
Index ranges	-14 ≤ h ≤ 14, -15 ≤ k ≤ 15, -18 ≤ l ≤ 18
Reflections collected	4345
Independent reflections	3955[R(int) = 0.0384]
Data/restraints/parameters	6425/3/387
Goodness-of-fit on F ²	1.054
Final R indexes [I ≥ 2σ (I)]	R1 = 0.0384, wR2 = 0.1032
Final R indexes [all data]	R1 = 0.0943, wR2 = 0.2417
Largest diff. peak/hole / e Å ⁻³	0.85/-0.53
Flack parameter	-0.02(4)

APPENDIX-B

PUBLISHED WORK



Click for updates

Facile access to a heterocyclic, sp^3 -rich chemical scaffold via a tandem condensation/intramolecular nitron–alkene [3+2] cycloaddition strategy†

M. J. Rawling,^a T. E. Storr,^a W. A. Bawazir,^{a,b} S. J. Cully,^a W. Lewis,^a M. S. I. T. Maki,^b I. R. Stutt,^c G. Jones,^c D. Hamzah^c and R. A. Stoddart^{a*}Received 22nd June 2015,
Accepted 9th July 2015

DOI: 10.1039/C5CC00700g

www.rsc.org/chemcomm

A heterocyclic, sp^3 -rich chemical scaffold was synthesised in just 6 steps via a highly regio- and diastereo-selective tandem nitron–alkene formation/intramolecular nitron–alkene [3+2] cycloaddition reaction. A library of 543 lead-like compounds based on the scaffold core has been produced.

Libraries of small molecules capable of exploring novel, three-dimensional chemical space are highly desired in early stage probe and drug discovery screening programmes.¹ Multiple authors have suggested that molecules containing a high fraction of sp^3 hybridised carbon atoms (F_{sp^3}) and numerous stereocentres have a lower rate of attrition during each stage of the drug discovery and development process once a hit has been established, thus potentially providing higher quality lead compounds.^{2,3} However, the development of facile synthetic routes to libraries of stereochemically rich molecules with a high F_{sp^3} remains a formidable challenge for the chemical community.⁴

Over the past decade our group has been interested in the rapid synthesis of architecturally complex molecules from simple, symmetric starting materials, through de-symmetrising tandem reactions.⁵ This has led to the efficient synthesis of a number of natural products including yervone (4 steps),⁶ alkaloid 223B (3 steps),⁷ hirsutiin (6 steps),⁸ anandamide (10 steps),⁹ hippocampine (8 steps) and epu hippocampine (11 steps).¹⁰ We have recently demonstrated that through tandem reactions involving key complexity generating, ring-forming operations, such as [3+2] dipolar cycloadditions, densely functionalised bicyclic cores containing a spirocyclic centre can be generated in a diastereoselective manner.^{8,11,12}

A current focus within our research group is the exploration of the knowledge gained throughout these investigations, in the

efficient synthesis of sp^3 -rich chemical scaffolds for drug discovery.¹³ Polycyclic scaffolds containing a central spiro ring fusion are desirable in drug discovery due to their structural rigidity resulting in a reduced conformational energy penalty upon ligand–protein binding.¹⁴ In addition, incorporation of a spiro centre often provides greater structural novelty and enhanced physical properties over that of the (hetero)aromatic compounds.¹⁵ To maximise its potential a quality chemical scaffold should: (i) contain multiple points of diversity, (ii) be ‘lead-like’,¹⁶ with a sufficiently low molecular weight (≤ 300 Da) and clog P (≤ 3) to allow derivatisation of the scaffold core into a library of compounds that largely adheres to Lipinski’s Rule of Five,¹⁷ and (iii) not contain any metabolically labile moieties or endophores. From a practical standpoint, the synthetic route to a scaffold should be concise, reliable, safe, and available to provide rapid access to large quantities of material.

Following these guiding principles, we report the facile and diastereoselective synthesis of a novel, heterocyclic chemical scaffold **1** (Fig. 1). The rigid, bicyclic core of scaffold **1** contains four contiguous stereocentres with one spirocyclic centre, and has a high degree of bond saturation,¹⁸ with an F_{sp^3} value of 0.6. The scaffold **1** has three points of diversity (R^1 , R^2 and R^3) to allow exploration of chemical space along three dimensions. The low molecular weight (196 Da) and clog P (−1.2) of the unsubstituted scaffold **1** (R^1 , R^2 , R^3 = H) provides an excellent platform for diversification into a library of drug-like molecules, for screening against various biological targets.

On the basis of previous work, we envisioned that the 3-hydroxy-lactam unit of scaffold **1** could be derived from key intermediate isoxazolidine **2**, by N–O bond reduction followed by cyclisation (Fig. 1).^{19,20} It was proposed that spirocyclic isoxazolidine **2** could be obtained diastereoselectively through a tandem nitron formation/intramolecular nitron–alkene [3+2] cycloaddition from piperidine **3**, in a single complexity generating step. Mono-alkylated piperidine **3** should be readily accessible from a suitable N -protected piperidine **4**.

N -Benzyl piperidine **4a** was selected as the starting point in the synthesis of scaffold **1** due to its commercial availability and low cost. Piperidine **4a** was allylated via hydrazine **5a** to avoid the well-documented issues associated with the direct allylation of

^a School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK

E-mail: robert.stoddart@nottingham.ac.uk; Fax: +44 (0)115 9513466

^b Department of Chemistry, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21581, Saudi Arabia

^c Signature Discovery Unit, 66 City, Parkway Drive, Nottingham, NG7 1DB, UK
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, ¹H and ¹³C NMR spectra, CMC1000 and 10000, X-ray and crystallographic data in CIF or other electronic format as DOI: 10.1039/C5CC00700g

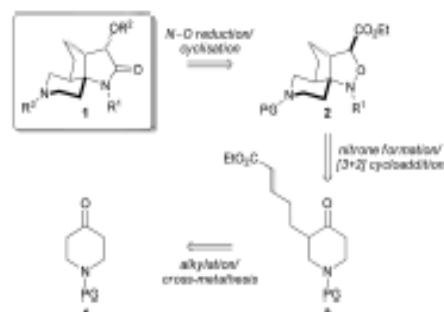
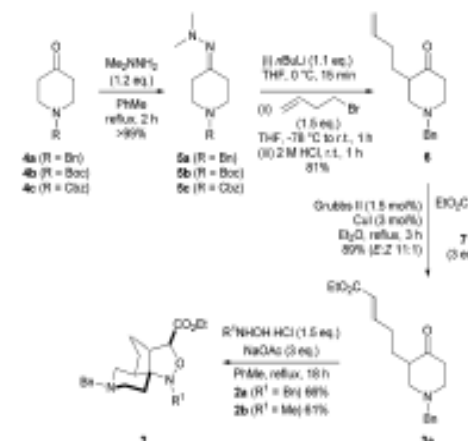


Fig. 1 Retrosynthetic analysis of scaffold 1

ketones (Scheme 1).¹¹ Treatment of piperidineone 4a with a small excess of *N,N*-dimethylhydrazine (1.2 equiv.) under Dean-Stark conditions gave hydrazone 5a in quantitative yield after 2 hours, with no need for purification.¹² Deprotection of hydrazone 5a with *t*-BuLi (1.1 equiv.) then allylation with 4 bromo-1 butene (1.5 equiv.) and in situ hydrolysis of the hydrazone moiety (2 M HCl), gave previously unreported homocyclized piperidineone 6 in excellent overall yield (81%). This one pot procedure was typically performed on large scale, yielding up to 24 g of piperidineone 6 in a single batch. Unexpectedly, attempted allylation of the carbonate protected piperidineone analogues 4b (*N*Boc) and 4c (*N*Chs) resulted in recovered starting material. Further investigation revealed that hydrazones 5b and 5c had formed without incident. However, a deprotection of hydrazones 5b and 5c using either LDA or *t*-BuLi had not occurred, as quenching the reaction with D₂O revealed no deuterium incorporation by mass spectrometry or ¹H NMR spectroscopy. Common additives (LiCl, TMEDA and DMPU) for use with lithium bases were employed,¹³ but failed to have any effect. The reason for the apparent lack of reactivity of *N,N*-dimethylhydrazones 5b and 5c to deprotection is currently unknown, but was not explored further.¹⁴



Scheme 1 Synthesis of key intermediate isocyclidine 2

The α,β -unsaturated ester moiety was incorporated into *N*-benzylpiperidineone 3a by cross metathesis between ethyl acrylate 7 and the terminal olefin of 6. Typical Crubbs cross metathesis conditions (Crubbs II (30 mol%), ethyl acrylate 7 (8 equiv.), CH₂Cl₂, 20 °C)¹⁵ gave α,β -unsaturated ester 3a in a disappointing 32% yield (E:Z 6:1) after 4 days, which could not be improved by varying the catalyst, reagent stoichiometry, solvent or temperature. In an effort to improve both the yield and reaction rate, the 'Copper Iodide Effect' was utilised, as described by Lipshutz and co-workers.¹⁶ Addition of copper iodide (3 mol%) as co-catalyst gave α,β -unsaturated ester 3a (E:Z 11:1) in 84% isolated yield in only 3 hours on large scale (> 30 g), representing a dramatic increase in conversion and reaction rate. Beneficially, the procedure also required considerably less Crubbs II catalyst (1.5 mol%) and ethyl acrylate 7 (3 equiv.) and was performed in ethereal solvent, rather than chlorinated media, deeming it more attractive from a financial, safety and environmental perspective.¹⁷ The two geometric isomers of α,β -unsaturated ester 3a were separated by silica gel column chromatography and the major (E) isomer taken forward in the synthesis.

Treatment of piperidineone 3a with *N*-benzylhydrazonamine hydrochloride (1.5 equiv.) in the presence of NaOMe (3.0 equiv.) in refluxing toluene afforded key intermediate bicyclic isocyclidine 2a in 64% isolated yield (Scheme 1). In a single completely generating operation, three new stereogenic centres and two new rings were formed, to generate a fused, bicyclic, spiroisocyclidine. Subjection of *N*-methyl hydrazonamine hydrochloride to the same reaction conditions resulted in the analogous isocyclidine 2b in 67% isolated yield, showing that one point of diversity can be incorporated into the scaffold at this stage. Significantly, only a single regio- and diastereo isomer was observed by ¹H NMR spectroscopy in both cases.

The tandem reaction of piperidineone 3a to isocyclidine 2b initially proceeds through condensation of 3a with the mono *N*-substituted hydrazonamine to give nitron 8 (Fig. 2). Subsequent intramolecular nitron alkene [3+2] cycloaddition gives two possible regioisomeric isocyclidine products, 2b or 9. Computational analysis of isocyclidines 2b and 9 (Hartree Fock 6-31G*) revealed a small energy difference between the two isomers, with the unsaturated 6/6/5 ring system 9 being 4.62 kJ mol⁻¹ lower in energy

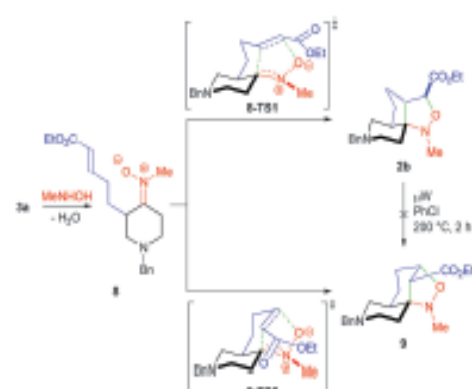


Fig. 2 Formation of regioisomeric isocyclidines 2b and 9

than the observed 6,5,5 ring system 2b. However, the transition state 8TS2 during formation of the lower energy 6,6,5 ring system 2 would experience substantial unfavourable steric interactions arising from the close proximity of the ester function to the developing spirocentre. Conversely, the transition state 8TS1 in the formation of the 6,5,5 ring system 2b has the ester moiety located away from the developing spirocentre, resulting in minimal steric interactions and therefore a more favourable reaction pathway. Attempted isomerisation of 2b to the energetically favoured isomer solidine 9 (μM , PhCl, 200 °C, 2 hours) resulted in a complex mixture of starting material 2b and decomposition products.

Treatment of isoxazolidines 2a and 2b with activated zinc in aqueous acetic acid prompted smooth transformation to the corresponding 3-hydroxy lactams 11a and 11b in excellent yield (83% and 88% respectively) with no need for purification (Scheme 2). Methanolic isonicotinic reduction of the N-O bond in isoxazolidine 2, followed by C-C bond scission to 10, allowed ring closure to lactam 11.

X-ray crystallographic analysis of lactams 11a and 11b confirmed the atom connectivity and relative stereochemistry (Fig. 3). The X-ray images clearly show that the three points of diversification on scaffolds 11a (atoms N1, N7 and O4) and 11b (atoms N1, N7 and O4) will allow library synthesis in three defined and divergent trajectories, providing substantial exploration of three-dimensional chemical space.

With the scaffold core structure 11 in hand, it was important to demonstrate that the remaining two points of diversity on 1 (R^1 and R^2 , Fig. 1) were capable of being functionalised without complication, prior to full library synthesis being undertaken. O-Alkylation of 11 was exemplified by deprotection of the hydroxy function with sodium hydride, then treatment with anisotropic iodomethane to give methyl ethers 12a and 12b in 65% and 61% isolated yield respectively (Scheme 3).

Deprotection of the piperidyl *N*-benzyl moiety of scaffolds 11a, 11b, 12a and 12b occurred cleanly using Pearlman's catalyst under an atmospheric pressure of hydrogen gas to give the secondary amines 13a–13d in excellent yield (88–93%, Scheme 3). Interestingly, the benzyl *N*-benzyl group of 11a and 12a was not cleaved under these conditions, presumably due to steric hindrance around the N-Bn bond imposed by the adjacent spirocentre. Remarkably, increasing the hydrogen pressure (30 atm, 4 days), addition of acid (AcOH or HCl) or employing typical transfer hydrogenation conditions (Pd/C, ammonium formate, MeOH, reflux, 24 h) also proved ineffective at benzyl *N*-debenzylation in 11a (R^1 , Scheme 2).

The deprotected piperidyl nitrogen atom (N1, 11, Fig. 3) represented the main library diversification point on scaffold 1. Secondary amines can undergo an array of useful transformations for library synthesis, including (i) coupling with carboxylic acids to

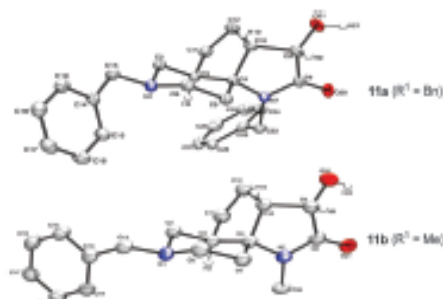
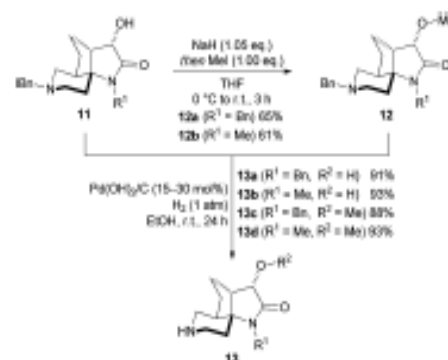


Fig. 3 X-ray crystallographic images of 3-hydroxy lactams 11a and 11b

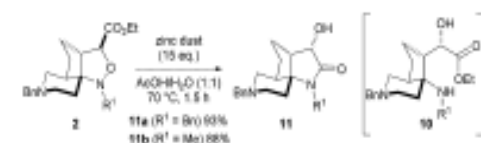


Scheme 3 O-Alkylation and N-debenzylation

make amides,²⁴ (ii) reaction with isocyanates to form ureas,²⁵ (iii) reductive amination with aldehydes or ketones to give tertiary amines,²⁶ and (iv) treatment with sulfonyl chlorides to make sulfonamides. A small, exemplary library of compounds was produced in good yield (30–72%) using typical reductive amination (conditions A), sulfonylation (conditions B) and amidation (conditions C) protocols (11b, 12a, Fig. 4), proving that the final functional handle of scaffold 1 (R^1 , Fig. 1) could be subjected to a variety of standard reactions without issue.

The synthetic route was scaled up to provide a total of 130 mmol of the scaffold core 11. Diversification of R^1 , R^2 and R^3 produced a library of 548 novel compounds (~0.1 mmol each) to be incorporated into the European Lead Factory's screening programme. Computational assessment of the library indicates that it is largely biphasic (rule of five compliant), with an average molecular weight of 426 and logP of 1.6 (Fig. 5). The library also has a high degree of three-dimensionality and bond saturation, with an average Rings^2 of 0.54 (Fig. 5).

The development of efficient synthetic routes to libraries of small, sp^3 -rich molecules for use in drug discovery remains a challenging but important goal. We have reported the facile synthesis and diversification of a novel, heterocyclic chemical scaffold 1. The spirocyclic scaffold core 1b (R^1 = Bn or Me, R^2 = R^3 = H) was accessed in only six operationally simple synthetic steps from



Scheme 2 Reductive cyclisation of isoxazolidine 2 to 3-hydroxy lactam 11

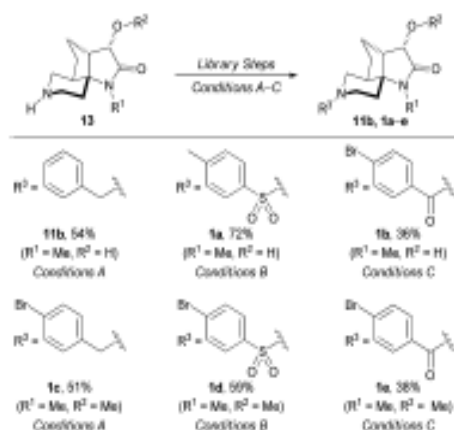


Fig. 4 Conditions A (molecular amine) 13 (1.0 equiv) ArCHO (1.5 equiv), NaHCO₃ (0.2 equiv), AcOH (2.5 equiv), 1,2 DCE or NMP, 18 °C, 18 h; conditions B (molecular amine) 13 (1.0 equiv) ArSO₂Cl (0.3 equiv), pyridine, 18 °C, 18 h; conditions C (amine) 13 (1.5 equiv), ArOC₂H₅ (1.0 equiv), HATU (2.0 equiv), Hunig's base (3.0 equiv), DMF, 18 °C, 18 h

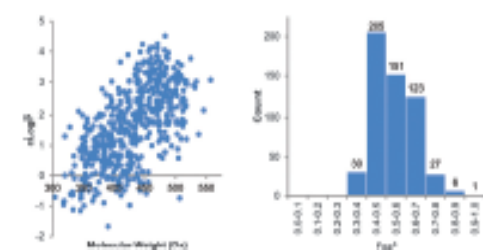


Fig. 5 Plot of clogP versus MW (left) and Fsp³ analysis (mgH) of the 543 compound library based on scaffold 1

commercially available *N*-benzyl piperidinone 4a, in an overall yield of 41% (11a) or 36% (11b) (averaging 87% or 89% yield per step, respectively). The synthetic route to scaffold 1b required just one protecting group manipulation (*N*-debenzylation), and can be completed in less than five working days on a multi gram scale. A highly regio- and diastereoselective tandem condensation/intermolecular nitron alkene [3+2] cycloaddition reaction provided key intermediate isoxazolidine 2 in a single, complexity generating operation, from a functionalised piperidinone 3a. Subsequent one pot isoxazolidine N-O bond reduction and cyclisation gave the scaffold core structure 11, which was confirmed by X-ray crystallographic analysis. Diversification of the scaffold core has provided a library of 543 drug like molecules, which will be screened against various biological targets as part of the European Lead Factory. Work is ongoing within our laboratory to develop efficient routes to novel sp³ rich chemical scaffolds for drug discovery.

This research was done within the European Lead Factory and has received support from the Innovative Medicines Initiative Joint Undertaking (grant no. 115489), with financial contribution from the European Union's Seventh Framework

Programme (FP7/2007-2013) and EFPIA companies in kind contribution. The authors would like to thank Professor Christopher Moody and Tom McInally (University of Nottingham), in addition to Dr John Miller and Dr Clément Jones (Signature Discovery Limited) for useful insight and discussion.

Notes and references

- J. L. Raymond and M. Avale, *ACS Chem. Mater.*, 2012, 2, 648.
- A. W. Young, A. Barakat, Y. Wang, T. J. Day, J. A. Wilson, P. A. Clemens and D. W. Young, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, 108, 6789.
- J. L. Raymond, R. van Daelen, L. C. Blum and L. Rudolph, *MedChemComm*, 2010, 1, 30.
- F. Levesque, J. Bickel and C. Mumbler, *J. Med. Chem.*, 2003, 46, 6752.
- M. Aldeghji, S. Malhotra, D. L. Sedwood and A. W. I. Chan, *Chem. Biol. Drug. Des.*, 2014, 83, 450; F. Levesque, *MedChemComm*, 2013, 4, 513; P. A. Clemens, J. A. Wilson, V. Dancik, S. Muller, K. A. Carreira, B. H. Wagner, A. M. Hoehler and S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, 108, 6817; T. J. Day and S. J. MacDonald, *Drug Discovery Today*, 2003, 14, 1011; Y. K. Kim, M. A. Anai, T. Anai, J. O. Lamas, E. F. Dean, J. M. Bickel, P. A. Clemens and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, 126, 14741.
- J. D. Sundekow and S. F. Martin, *Chem. Rev.*, 2009, 109, 1303; D. S. Tian, *Med. Chem. Biol.*, 2005, 1, 74; S. L. Schreiber, *Science*, 2000, 287, 1264.
- D. Robbins, A. F. Newton, C. Giguere, J. C. Laguerre, A. Sinclair, M. Rajski, C. A. Lewis, S. H. Yalamanchi, W. Lewis, M. A. O'Connell and R. A. Stockman, *Chem. Sci.*, 2011, 2, 2252.
- A. Barthelme, D. Richards, J. R. Miller and R. A. Stockman, *Chem. Commun.*, 2013, 42, 10507.
- J. C. Laguerre, W. Lewis and R. A. Stockman, *Chem. Commun.*, 2009, 2007.
- M. S. Hamedelwala, A. Sinclair, A. F. Newton, M. L. Alvarez, R. A. Stockman and P. L. Puch, *J. Am. Chem. Soc.*, 2005, 127, 12656; R. A. Stockman, *Tetrahedron Lett.*, 2000, 41, 5163.
- S. J. Roe, D. L. Hughes, R. Aggarwal and R. A. Stockman, *Synthetic*, 2009, 3775; S. J. Roe and R. A. Stockman, *Chem. Commun.*, 2008, 3432.
- A. F. Newton, M. Rajski, M. L. Alvarez and R. A. Stockman, *MedChem J. Org. Chem.*, 2003, 4, 4; M. Rajski, R. A. Stockman and D. L. Hughes, *Org. Biomol. Chem.*, 2005, 3, 73.
- C. Giguere, A. F. Newton, A. Barthelme, W. Lewis, M. L. Alvarez and R. A. Stockman, *Org. Biomol. Chem.*, 2012, 10, 67; L. G. Arino, R. Sato, D. L. Hughes and R. A. Stockman, *Tetrahedron Lett.*, 2004, 45, 3371.
- A. Sinclair, L. G. Arino, M. Rajski, R. Sato and R. A. Stockman, *Synlett*, 2006, 2321.
- T. J. Day, S. J. O'Leary, M. J. Rawling, W. Lewis, D. Morris, G. Jones and R. A. Stockman, *Biorg. Med. Chem.*, 2015, 23, 2621-2628; M. C. McLeod, G. Singh, J. M. Hampson, D. Day, J. L. Wang, V. W. Day and J. Aube, *Med. Chem.*, 2014, 6, 133; M. I. Whelan, S. A. Snyder and B. R. Stockwell, *Chem. Opin. Chem. Biol.*, 2010, 14, 347.
- Y. Zhang, C. M. Rice and S. B. Singh, *Biorg. Med. Chem. Lett.*, 2014, 24, 3673; C. M. Rice, *Chem. Soc. Rev.*, 2011, 40, 5514; J. M. Meyer and P. A. Bartlett, *J. Am. Chem. Soc.*, 1994, 116, 4600; J. Ding, M. I. Freese, J. M. Meyer, P. A. Bartlett and M. I. Freese, *J. Am. Chem. Soc.*, 1994, 116, 4610; W. W. Smith and P. A. Bartlett, *J. Am. Chem. Soc.*, 1994, 116, 4622.
- M. Jethi, G. Williams, D. C. Reed and C. W. Murray, *Med. Res. Drug Discovery*, 2013, 12, 644; M. O'Connell, R. Carr, C. Murray and M. Jethi, *Drug Discovery Today*, 2003, 8, 476.
- C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Peasey, *Adv. Drug Delivery Rev.*, 1997, 23, 3.
- R. Jansz and A. Molodtsov, *Chem. Rev.*, 2010, 110, 1306.
- M. G. Sawell, M. J. O'Connell, M. L. Hargreaves, M. J. Gorman, S. Yu, A. C. Hulse and M. G. Moun, *Org. Biomol. Chem.*, 2012, 10, 154.
- D. B. Collins, *Acc. Chem. Res.*, 1992, 25, 448.
- M. Sun, M. M. Miller, J. Ding, H. Abboud and B. A. Mousa, *Tetrahedron Lett.*, 2000, 41, 2001.
- S. J. O'Connell and S. M. Hargreaves, *Angew. Chem., Int. Ed.*, 2003, 42, 1300.
- H. Vögler, S. O'Connell and M. Lipinski, *J. Org. Chem.*, 2011, 76, 4897.
- R. Anand and M. J. Hargreaves, *Chem. Soc. Rev.*, 2010, 39, 301.
- L. A. Carpio, *J. Am. Chem. Soc.*, 1993, 115, 4997.
- A. F. Abdel-Magid, M. G. Coates, B. D. Harris, C. A. Maynard and R. D. Shih, *J. Org. Chem.*, 1996, 61, 3142.