Synthesis Studies Towards

Daphlongeranine B

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Synthesis Studies Towards Daphlongeranine B

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Abstract

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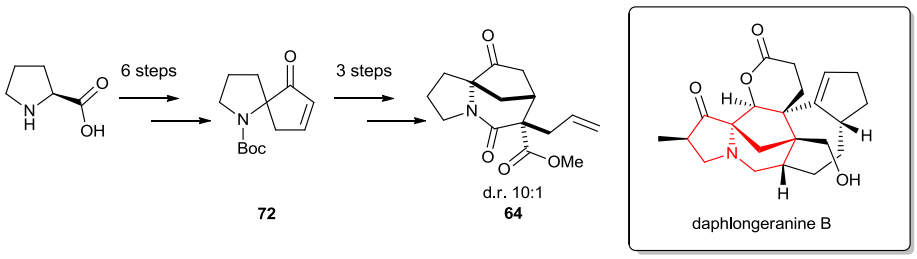
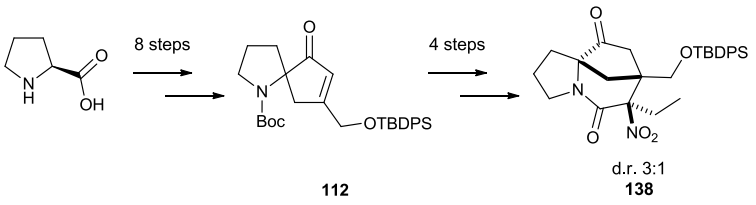
This thesis describes the development of a synthetic route towards daphlongeranine B, an alkaloid isolated from the fruits of *Daphniphyllum longeracemosum*,[6] by utilising an intramolecular Michael addition to form its unique tricyclic core.

Chapter 1 gives a general introduction to the family of *Daphniphyllum* alkaloids together with some recent examples, from the literature, illustrating some synthetic attempts towards structurally similar alkaloids. This chapter also features our retrosynthetic analysis of daphlongeranine B.

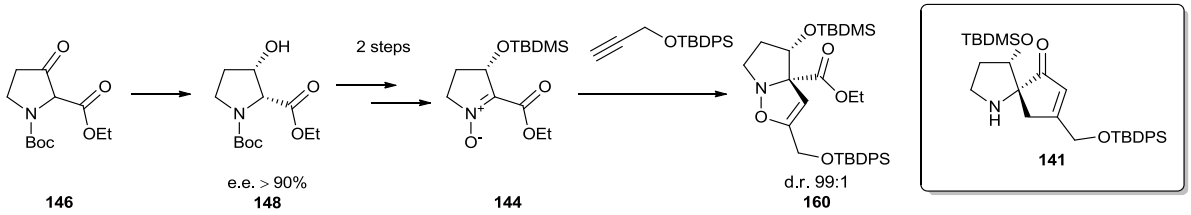
Chapter 2 details the synthesis of the model spirocyclic enone **72** which was the vital building block needed to investigate the key intramolecular Michael addition. This key reaction was then successfully validated and access to the unique tricyclic core **64** of daphlongeranine B was made possible.



Chapter 3 expands the scope of the key intramolecular Michael addition step. This chapter first describes a synthetic route to the β-substituted spirocyclic enone **112** and subsequently validates the key intramolecular Michael addition step to give the tricyclic core **138** of daphlongeranine B.



Chapter 4 details a synthetic route towards the spirocyclic fragment **141** by utilising a Baker's yeast reduction and a tandem addition/cyclisation reaction.



Declaration

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Any work done in collaboration with a research colleague is referenced in the text. All compounds in the experimental section (Chapter 5) were synthesised and characterised by myself unless otherwise stated.

Eddy Källström July 2013

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My gratitude also goes to EPSRC and Pfizer. Without them this work would not have been possible.

I would like to thank all of the staff at the Chemistry Research Laboratory for the high quality analytical services provided. I would like to give a special mention to Dr Barbara Odell and Dr Tim Claridge who conducted the VT NMR and NOE experiments and Miss Tina Jackson for assisting with the provision of the internal NMR submission service. My gratitude also goes to the mass spectrometry research staff for providing the MS service.

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Abbreviations

AA	Arachidonic acid
Ac	Acetyl
ADP	Adenosine diphosphate
AIBN	Azobisisobutyronitrile
app.	apparent
aq.	aqueous
ATP	Adenosine-5'-triphosphate
ATPH	Aluminum tris(2,6-diphenylphenoxide)
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Boc	*tert*-Butyloxycarbonyl
b.p.	boiling point
br.	broad
Bu	Butyl
°C	degrees Celsius
CDI	1,1'-Carbonyldiimidazole
CNS	Central nervous system
conc.	concentrated
COSY	Correlation spectroscopy
$C_{quat.}$	quaternary carbon or fully substituted carbon centre

d	doublet
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DEPT	Distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
d.r.	diastereomeric ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron donating group
EDTA	Ethylenediaminetetraacetic acid
eq.	equivalent molar quantity
ESI(+/-)	Electrospray ionisation, positive ion / negative ion
Et	Ethyl
EWG	electron withdrawing group
FGI	functional group interconversion
FI(+)	field ionization, positive ion
FMO	frontier molecular orbital
g	gram(s)

h	hour(s)
HBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium-hexafluoro-phosphate
HMBC	Heteronuclear multiple-quantum correlation
HMPA	Hexamethylphosphoramide
HOBt	*N*-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
K	Kelvin
KHMDS	Potassium *bis*(trimethylsilyl)amide
LHMDS	Lithium *bis*(trimethylsilyl)amide
LUMO	Lowest unoccupied molecular orbital
LRMS	Low resolution mass spectrometry
lit.	literature
M	Molar (i.e. mol dm^{-3}) / mesomeric effect
m	multiplet
m/z	mass-to-charge ratio
Me	Methyl
min	minute(s)
m.p.	melting point

MS	Mass spectrometry
Ms	Methanesulfonyl
n-	normal
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
PAF	Platelet-activating factor
PE	Petroleum ether
PG	Protecting group
Ph	Phenyl
ppm	parts per million
PPTS	Pyridinium *para*-toluenesulfonate
q	quartet
quant.	quantitative
R	any group
r.t.	room temperature
s	singlet
sat.	saturated

sept	septet
t	triplet
t-	*tert*, prefix for tertiary
TBAH	Tetrabutylammonium hydroxide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
VT	Variable temperature

Abstract

Declaration

Acknowledgement

Abbreviations

Table of Contents

1 CHAPTER 1

1.1 The *Daphniphyllum* alkaloids

The *Daphniphyllum* alkaloids are a family of alkaloids with structurally diverse and complex polycyclic skeletons.[1] More than two hundred *Daphniphyllum* alkaloids have so far been reported since the first member of the group was reported in 1966. These alkaloids are found in the genus *Daphniphyllum* (Daphniphyllaceae), a genus of dioecious evergreen trees and shrubs found in Japan, New Guinea, China and Taiwan. As described in recent reviews, Yamamura and Hirata *et al.*[2a-d] initially classified these alkaloids into six structural types (Figure 1) according to their backbone skeleton (daphniphylline, secodaphniphylline, yuzurimine, daphnilactone A, daphnilactone B and yuzurine), however recent isolations have necessitated the addition of several other structural motifs (bukittinggine, daphnezomine, daphnicyclidin, daphmanidin, daphniglaucin, paxdaphnine, calyciphylline and of particular interest daphlongeranine).[1] These unusual ring systems have attracted much attention regarding their total synthesis and biosynthesis.

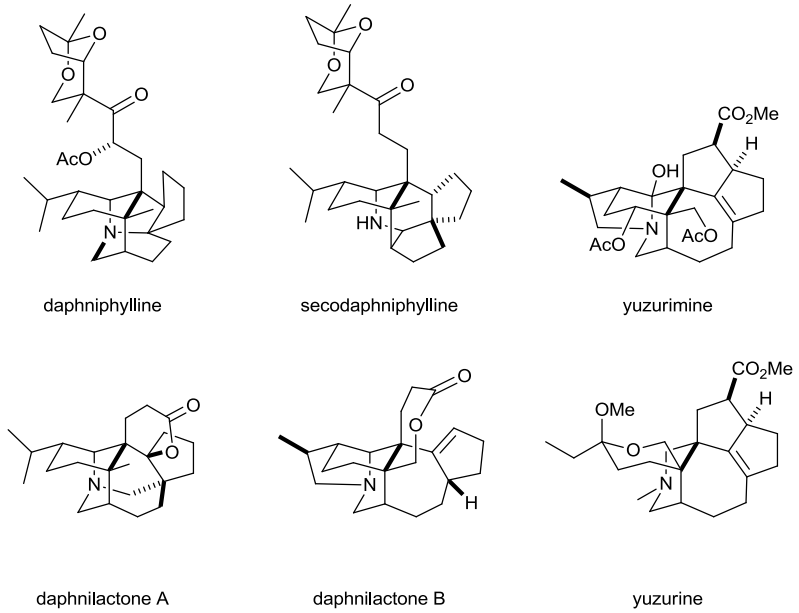
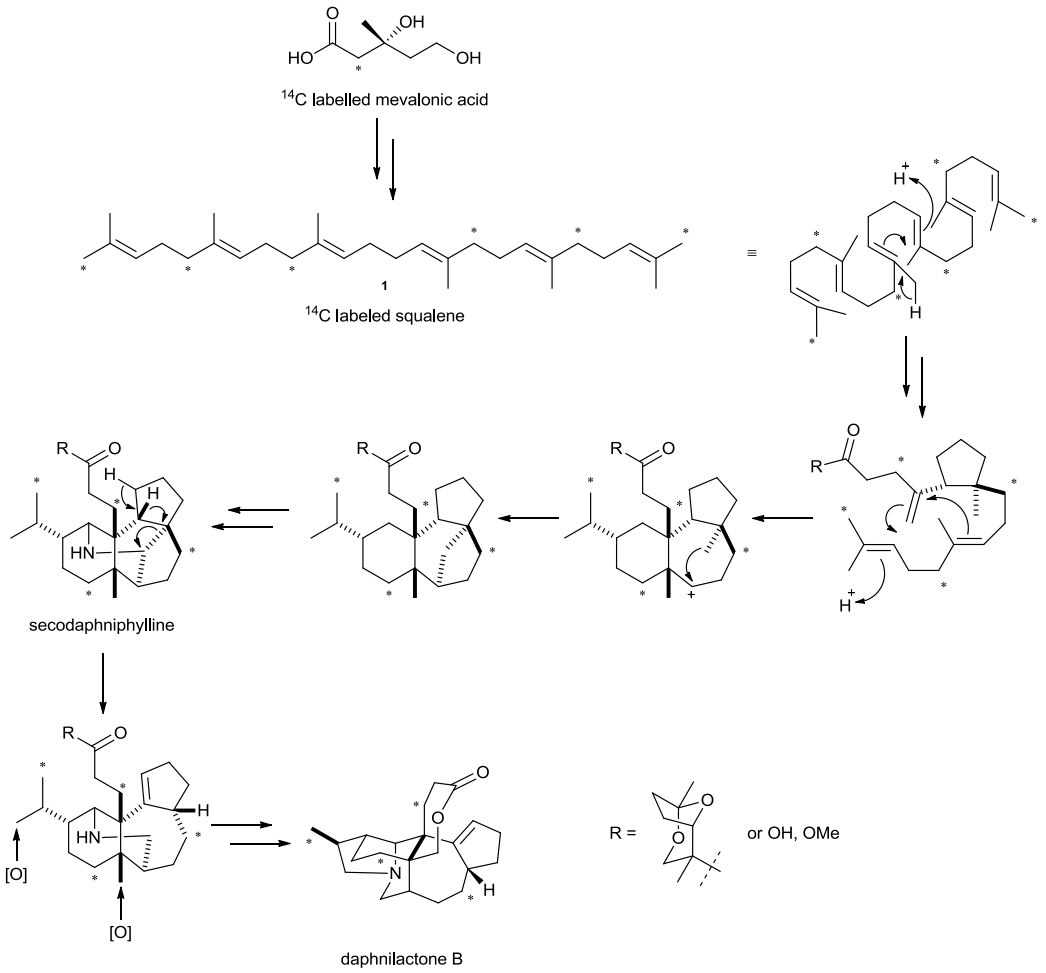


Figure 1. The *Daphniphyllum* alkaloids were initially classified into six structural types according to their backbone skeleton: daphniphylline, secodaphniphylline, yuzurimine, daphnilactone A, daphnilactone B and yuzurine.

1.2 Biosynthesis of *Daphniphyllum* alkaloids

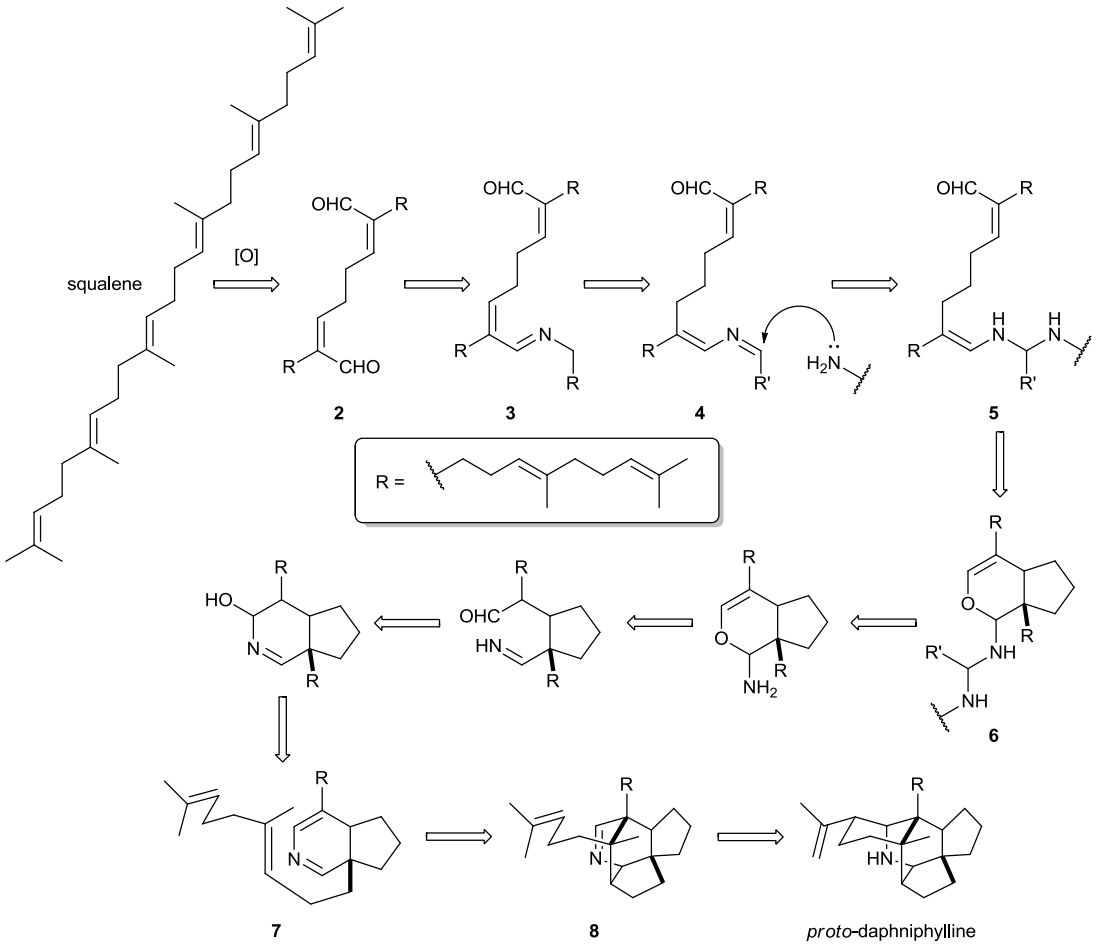
A significant contribution to the understanding of the biosynthesis of *Daphniphyllum* alkaloids was made by Suzuki and Yamamura in 1973.[3] They reported feeding experiments using the fruits of *D. teijsmanni*. By using ^{14}C labelled mevalonic acid, they suggested that daphnilactone B, one of the major C_{22}-type *Daphniphyllum* alkaloids, was formed from four equivalents of mevalonic acid via a squalene intermediate **1** (Scheme 1).[4] The ^{14}C labelled atoms are indicated by asterisks.



Scheme 1. Proposed biosynthesis of daphnilactone B.

While Suzuki and Yamamura outlined a biosynthetic route to the *Daphniyphyllum* alkaloids,[3] a more concerted mechanism was postulated by Heathcock and co-workers.[5a-c.] Their proposed biosynthesis importantly addressed the introduction of nitrogen into these complex alkaloids.

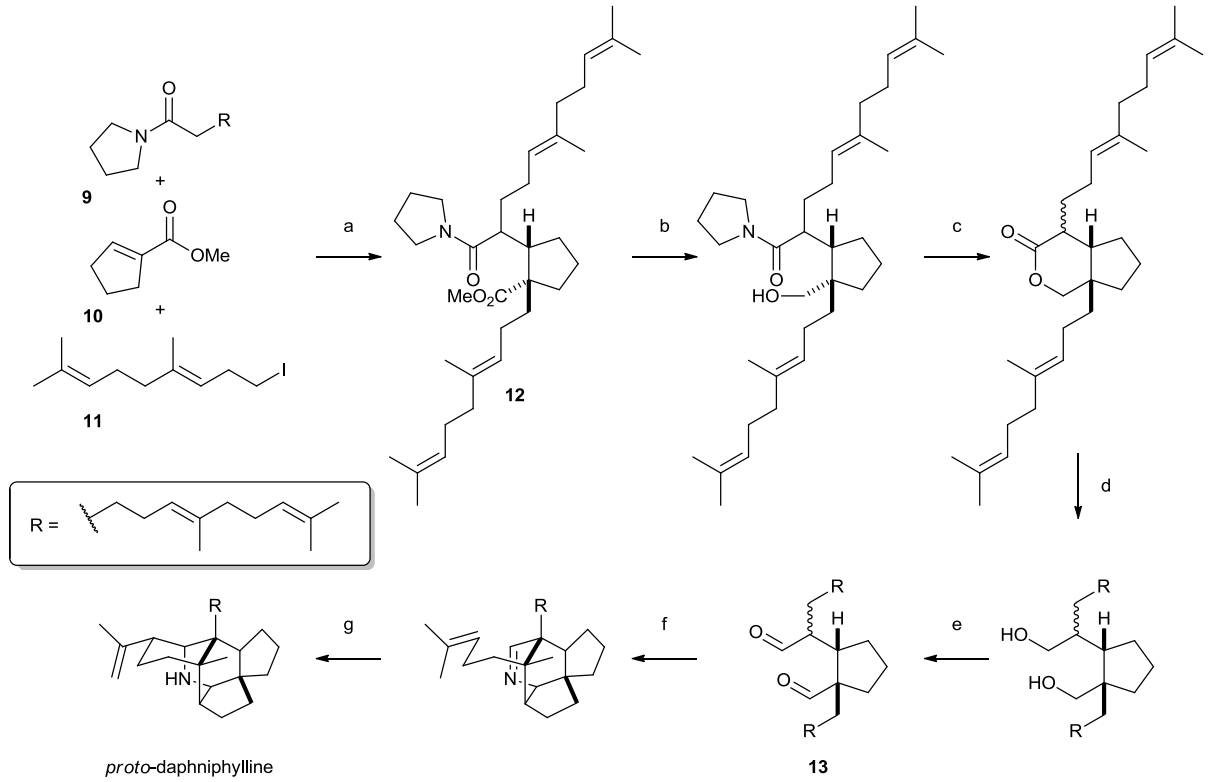
An outline of their suggested biosynthesis is shown in Scheme 2. In the initial step squalene underwent oxidation into dialdehyde **2**. This was followed by condensation of a primary amine (likely an amino acid or pyridoxamine) with one of the aldehydes to afford the imine **3**. Prototropic rearrangement and subsequent nucleophilic addition to the enimine **4** by another amine gave **5**. Cyclisation of the enamine to the α,β-unsaturated aldehyde of **5** gave the bicyclic dihydropyran derivative **6**. This bicycle underwent a series of rearrangements to afford the dihydropyridine **7**. An intramolecular hetero-Diels-Alder reaction gave the tetracyclic imine **8** and finally an ene-like cyclisation gave *proto*-daphniphylline which was given its name from being the first likely pentacyclic alkaloid to occur in the biosynthesis of the *Daphniphyllum* alkaloids.[5b]



Scheme 2. Proposed biosynthesis of *proto*-daphniphylline.

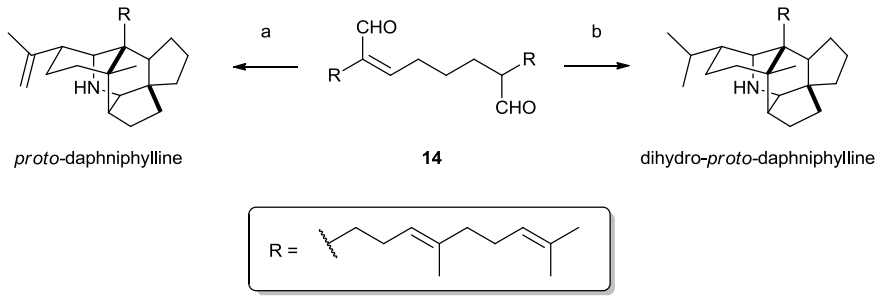
1.3 Biomimetic synthesis

Having outlined a reasonable biomimetic route, Heathcock *et al.*[5c] set out to demonstrate the feasibility of these transformations in a laboratory setting. Their work was initially focused on a polycyclisation cascade (Scheme 3). Three simple building blocks: amide **9**, α,β-unsaturated ester **10** and iodide **11**, were combined in a highly convergent conjugate addition/enolate alkylation process to access ester amide **12** in high yield. The ester amide **12** was further converted into dialdehyde **13**. Not too dissimilar to the proposed biosynthesis, the dialdehyde **13** was treated with ammonia and thereafter heated in acetic acid to afford *proto*-daphniphylline in excellent yield.[5c]



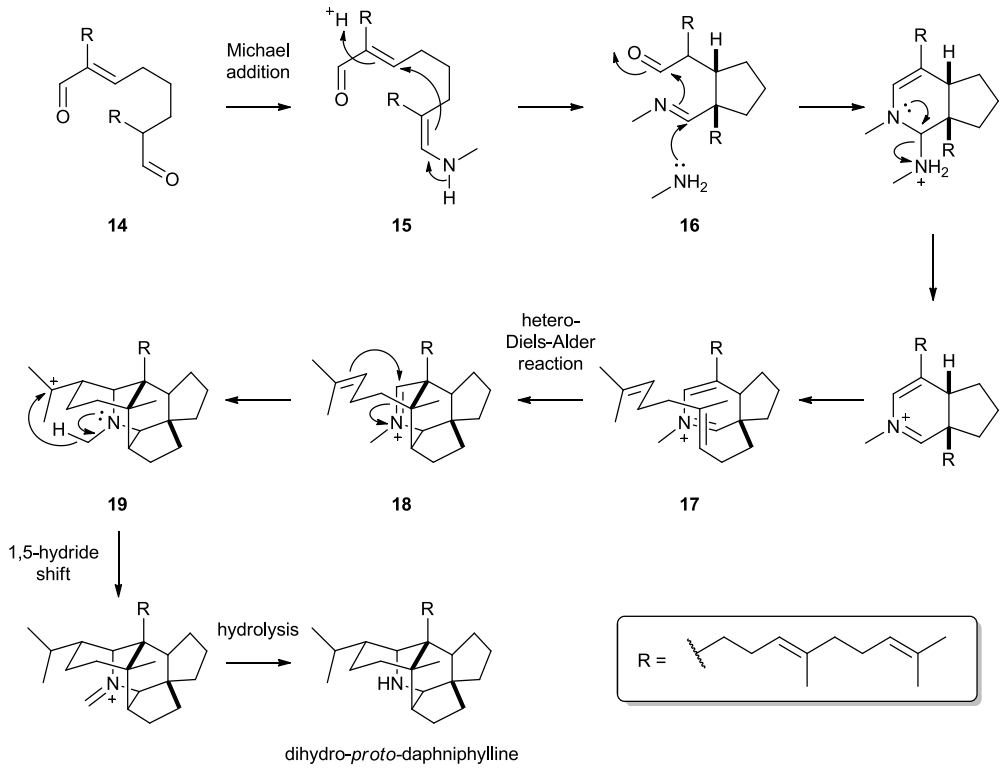
Scheme 3. Synthesis of *proto*-daphniphylline; (a) LDA, THF, amide **9** then α,β-unsaturated ester **10** then iodide **11**, −78 °C to r.t., 12 h, 80%; (b) DIBAL, toluene, −78 °C to r.t., 1 h, 86%; (c) KOH, H_2O, EtOH, 80 °C, 1 h 40 min, 93%; (d) $LiAlH_4$, Et_2O, r.t., 3 h, 96%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 1 h, 95%; (f) NH_3, $Et_3N{\cdot}HCl$, CH_2Cl_2, 0 °C to 25 °C, 1 h; (g) NH_4OAc, AcOH, 75 °C, 2 h, 78% (over 2 steps).

Encouraged by this success, Heathcock *et al.*[5c] sought to intervene at an earlier stage in the hypothetical biosynthetic pathway depicted in Scheme 2. Accordingly, they prepared dialdehyde **14** and following sequential treatment with ammonia and warm acetic acid they isolated the *proto*-daphniphylline in 15% yield (Scheme 4).[5c] Although only in modest yield, it was of great significance as a large number of transformations had been accomplished by the use of very simple reaction conditions. After some further optimisation[5b] it was found that replacement of ammonia with methylamine in this reaction mediated an extraordinary pentacyclisation of dialdehyde **14** to afford dihydro-*proto*-daphniphylline in 65% yield (Scheme 4).[5c]



Scheme 4. Synthesis of *proto*-daphniphylline and dihydro-*proto*-daphniphylline; (a) NH_3, $Et_3N{\cdot}HCl$, CH_2Cl_2, r.t., 16 h, then NH_4OAc, AcOH, 80 °C, 3 h, 15%; (b) $MeNH_2$, Et_3N, CH_2Cl_2, r.t., 2 h, then AcOH, 80 °C, 11 h, 65%.

The suggested mechanism for the biomimetic synthesis of dihydro-*proto*-daphniphylline from dialdehyde **14** (Scheme 5) was shown to be similar to the biosynthesis initially proposed by Heathcock and co-workers (Scheme 2).[5a-c.] Condensation of the more reactive aldehyde with methylamine afforded an enamine **15** which then underwent a cyclisation via an intramolecular Michael addition to give **16**. Nucleophilic addition to the imine **16** followed by elimination by methylamine gave the Diels-Alder precursor **17**. A hetero-Diels-Alder reaction afforded the iminium ion **18**, which via a Prins-like cyclisation formed the pentacyclic core **19**. A 1,5-hydride shift from the methyl group of the tertiary amine to the carbocation, followed by hydrolysis on work-up, completed the synthesis of dihydro-*proto*-daphniphylline.[5c]



Scheme 5. Proposed mechanism for the biomimetic synthesis of dihydro-*proto*-daphniphylline from dialdehyde **14**.

1.4 Daphlongeranine A and B

Two novel alkaloids, daphlongeranine A and daphlongeranine B, belonging to the family of *Daphniphyllum* alkaloids were isolated from the fruits of *Daphniphyllum longeracemosum* by Hao *et al.* in 2007.[6] Daphlongeranines A and B have an unprecedented and unique hepta- and hexacyclic ring system and represent an attractive and as yet unmet synthetic challenge. Daphlongeranine B has seven stereogenic centres of which three are fully substituted carbon centres. It is shown to inhibit *in vitro* platelet aggregation induced by ADP, PAF and AA. At 240 μM concentration, the inhibition of aggregation was found to be 38.7 ± 10.5%, 28.3 ± 9.4% and 24.0 ± 11.2% respectively.[6]

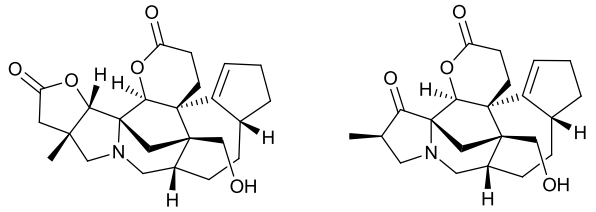
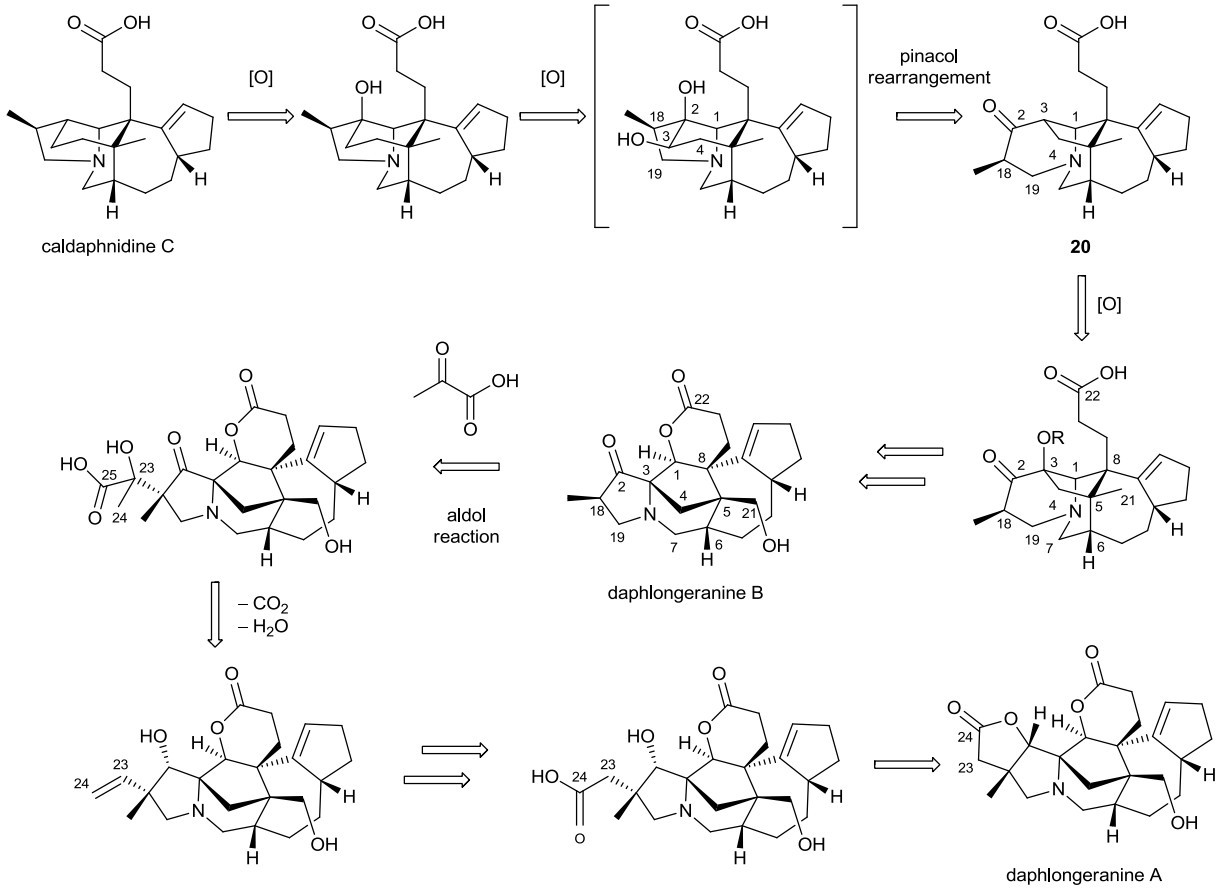


Figure 2. Daphlongeranine A and B with their unique and unprecedented hepta- and hexacyclic ring system.

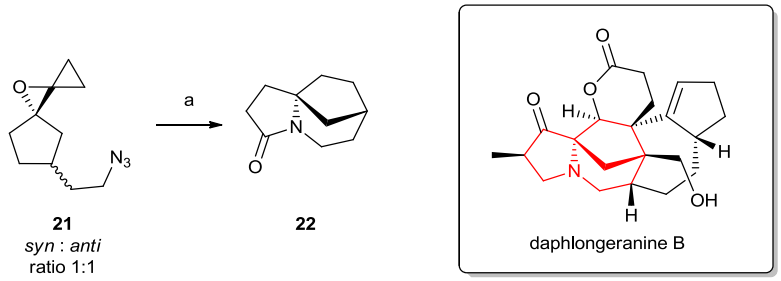
Due to their structural similarity, it is believed that daphlongeranine B is the precursor of daphlongeranine A. Hao *et al.*[6] proposed a biosynthetic pathway shown in Scheme 6 where it was postulated that the biosynthetic precursor of daphlongeranine A and B was caldaphnidine C.[7] Caldaphnidine C would produce a key intermediate **20** through a pinacol rearrangement.[8] Subsequent oxidation of intermediate **20** at *C*-3 followed by further rearrangement through formation of a *C*-3–*N* bond[9] and esterification thereafter would produce daphlongeranine B. Daphlongeranine B could be converted into daphlongeranine A by an aldol reaction with pyruvic acid followed by dehydration and decarboxylation. The vinyl group could be oxidised to give a carboxylic acid and finally a lactonisation would give daphlongeranine A (Scheme 6).



Scheme 6. Proposed biosynthesis of daphlongeranine A and B.

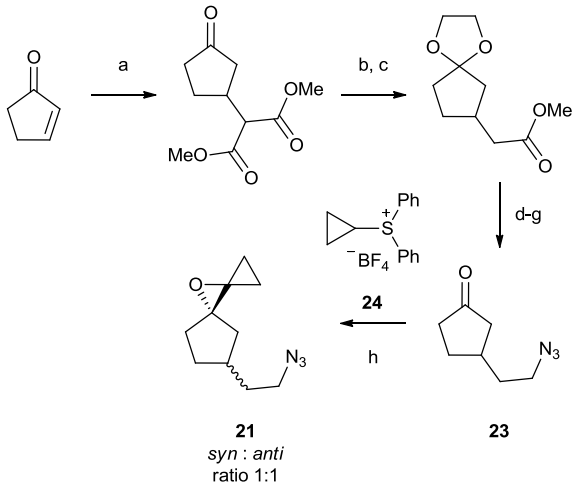
1.5 Synthesis towards daphlongeranine B and related natural products

Very little is known regarding the synthesis of daphlongeranines A and B and no total syntheses have been reported to date. However an enantioselective synthesis of the tricyclic core of daphlongeranine B was recently reported by Baskaran *et al.*[10] They utilised a $TiCl_4$-promoted domino semipinacol–Schmidt cyclisation as a key step to construct the bridged azatricyclic core **22** of daphlongeranine B from oxaspiropentane-azide **21** (Scheme 7).



Scheme 7. Baskaran's synthesis[10] of the tricyclic core of daphlongeranine B using a domino semipinacol-Schmidt cyclisation; (a) $TiCl_4$, CH_2Cl_2, −78 °C to r.t., 4 h, 80% (yield based on the *syn*-isomer).

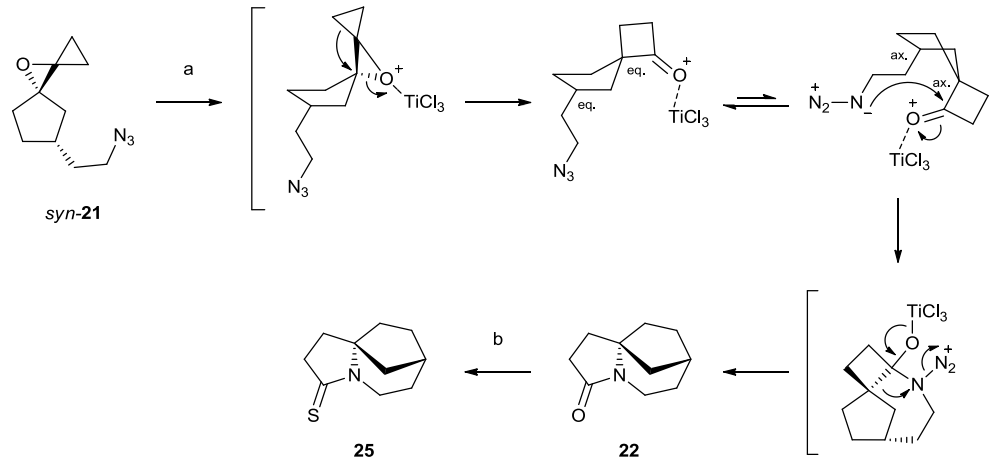
The oxaspiropentane-azide **21** was prepared in a few steps starting from cyclopentenone (Scheme 8) where the azido-ketone **23** underwent a Trost spiro-annulation reaction[11] to give a 1:1 mixture of *syn*- and *anti*-oxaspiropentane-azide **21** in 90% yield. The diastereomeric mixture was then treated with $TiCl_4$ to give the tricyclic core **22** of daphlongeranine B in 80% yield (based on the *syn*-isomer) (Scheme 7).[10]



Scheme 8. Synthesis of oxaspiropentane-azide **21** from cyclopentenone; (a) $CH_2(CO_2Me)_2$, *t*BuOK, THF, r.t., 72 h, 92%; (b) $(CH_2OH)_2$, PTSA, toluene, reflux; 18 h; (c) NaCl, DMSO, 145 °C, 3 h, 62% over two steps; (d) $LiAlH_4$, THF, r.t., 4 h, 94%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (f) NaN_3, DMF, 55 °C; 3.5 h, 82% over two steps; (g) PPTS, acetone, H_2O, reflux, 17 h, 62%; (h) sulfonium ylide **24**, KOH, DMSO, r.t., 3 h, 90%.

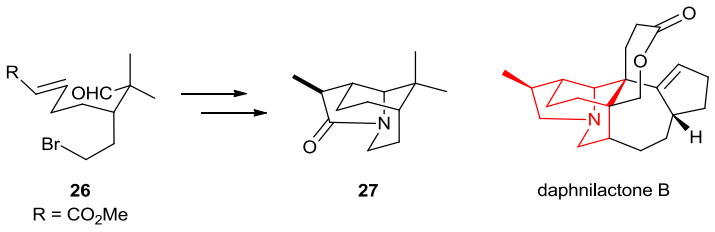
The structure and the relative stereochemistry of the cyclised product **22** was confirmed by single crystal X-ray analysis of the corresponding thiolactam derivative **25**. This is the only report to date of a stereoselective approach for the construction of the tricyclic core of

daphlongeranine B. A plausible mechanism for the formation of the tricyclic core **22** from *syn*-oxaspiropentane-azide **21** via domino semipinacol–Schmidt cyclisation is depicted in Scheme 9.[10]



Scheme 9. Plausible mechanism for the domino semipinacol–Schmidt reaction of *syn*-oxaspiropentane-azide **21** to give the bridged azatricyclic core **22** of daphlongeranine B; (a) $TiCl_3$, CH_2Cl_2, −78 °C to r.t., 4 h, 80%; (b) Lawesson's reagent, toluene, reflux, 30 min, 94%.

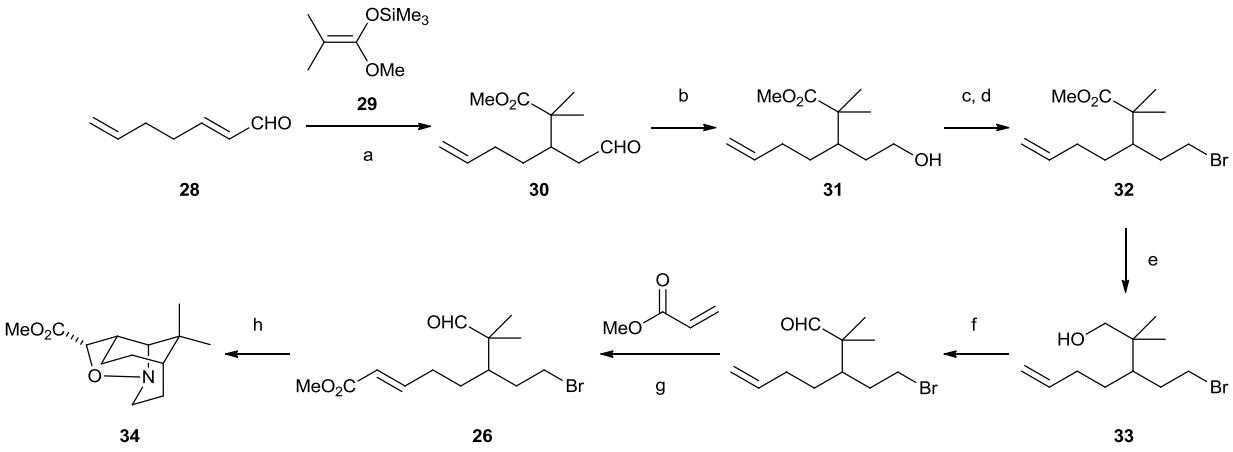
Coldham *et al.*[12] recently reported a one-pot reaction cascade converting the aldehyde **26** to a bridged tricyclic amine **27**. The reaction cascade involved a condensation, cyclisation and an intramolecular dipolar cycloaddition. The resulting tricyclic ring system **27** can be found in the core of daphnilactone B (Scheme 10).



Scheme 10. Coldham's one-pot reaction cascade, starting from the aldehyde **26** affording the bridged tricyclic amine **27**, a ring system found in the core of daphnilactone B.

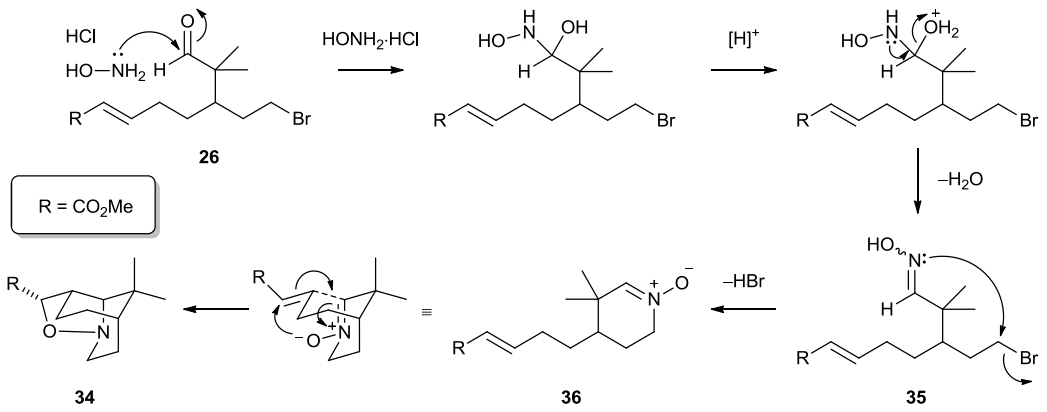
The aldehyde **26** was prepared as shown in Scheme 11. This first involved a conjugate addition to the α,β-unsaturated aldehyde **28** by a method developed by Yamamoto *et al.* using a ketene silyl acetal **29** in the presence of a bulky Lewis acid catalyst.[13] This gave a 1,4-addition rather

than a 1,2-addition to yield the desired aldehyde **30**. The aldehyde **30** was then selectively reduced, in the presence of the ester, to the alcohol **31** using $NaBH_4$. The alcohol **31** was converted to the bromide **32** via the mesylate and the ester functional group of **32** was reduced to the alcohol **33** using DIBAL. Finally a Swern oxidation followed by cross metathesis with methyl acrylate, catalysed by Grubbs' second generation catalyst, gave the desired aldehyde **26**.[12] The aldehyde **26** underwent a one-pot reaction cascade when heated with hydroxylamine hydrochloride and DIPEA in toluene to give the bridged tricyclic product **34** as a single isomer in excellent yield (Scheme 11).[12]



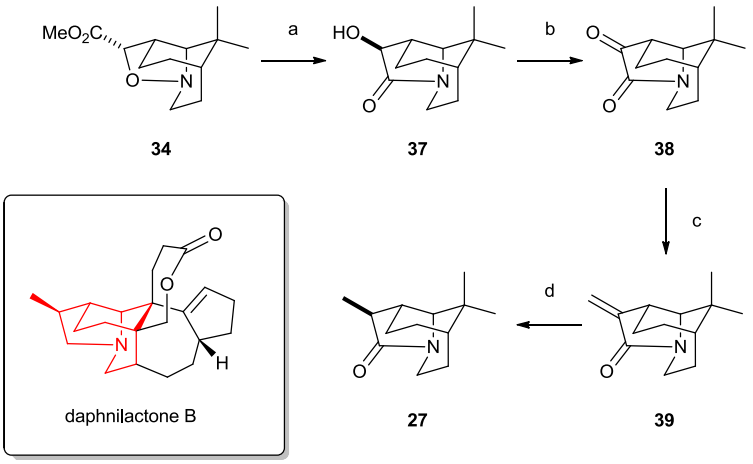
Scheme 11. Synthesis of the bridged tricycle **34**; (a) ATPH, CH_2Cl_2, −78 °C to 0 °C, 4 h, 93%; (b) $NaBH_4$, MeOH, −30 °C to −20 °C, 10 min, quant. yield; (c) MsCl, Et_3N, Et_2O, −30 °C to 0 °C, 2 h, 78%; (d) LiBr, MeCN, reflux, 1 h, 82%; (e) DIBAL, THF, 0 °C to r.t., 1 h, quant. yield; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to r.t., 1 h, 90%; (g) 5 mol% Grubbs' II, CH_2Cl_2, reflux, 12 h, 82%; (h) $HONH_2{\cdot}HCl$, DIPEA, toluene, reflux, 1 h 30 min, 95%.

The mechanistic rationale is shown in Scheme 12. Condensation of the aldehyde **26** with hydroxylamine gave the oxime **35**. This was followed by a 6-*exo*-*tet* cyclisation to form nitrone **36** which then underwent an intramolecular 1,3-dipolar cycloaddition to give the tricyclic product **34**.[12]



Scheme 12. Postulated mechanistic pathway involving a condensation, cyclisation and an intramolecular 1,3-dipolar cycloaddition to convert the aldehyde **26** to the tricyclic product **34**.

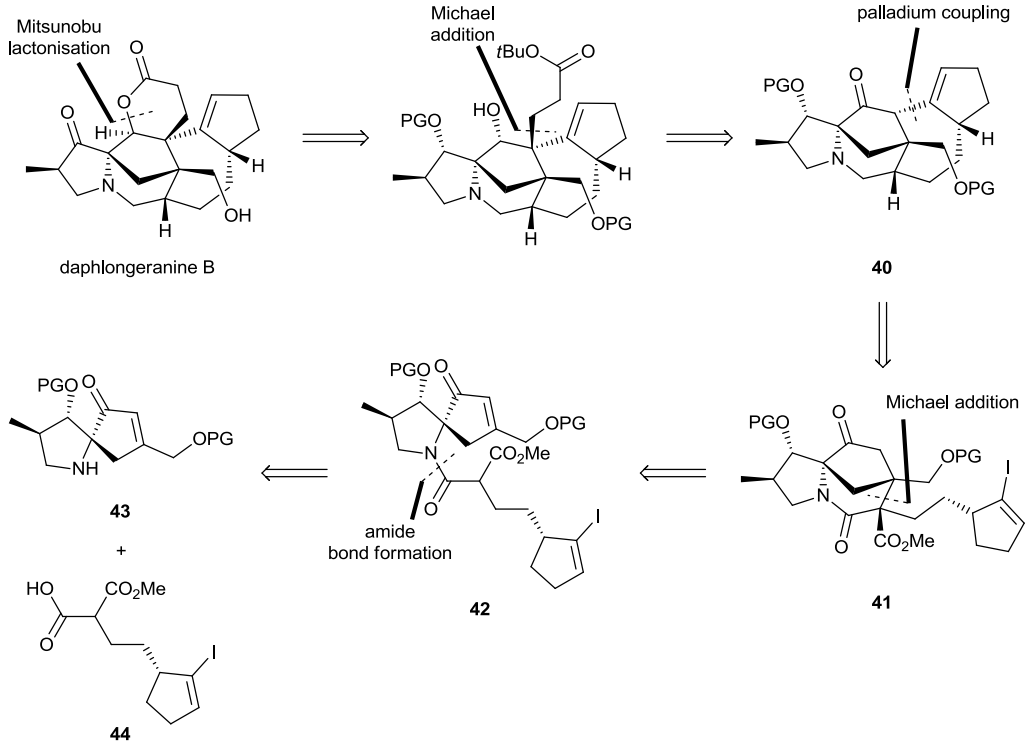
The tricycle **34** was treated with Raney nickel and then sodium methoxide in methanol to give the α-hydroxy lactam **37**. A Parikh-Doering oxidation[14] of **37** resulted in the keto lactam **38** which then underwent a Wittig olefination to give α-methylene lactam **39**. Finally, a nickel boride catalysed hydrogenation[15] of **39** at ambient pressure gave the desired tricyclic ring system **27**, as a single stereoisomer. The stereochemical configuration of the tricyclic ring system **27** was shown to match that of the daphnilactone B by single crystal X-ray analysis (Scheme 13).[12]



Scheme 13. Synthesis of the bridged tricyclic amine **27**, a ring system found in the core of daphnilactone B; (a) Raney-nickel, H_2, MeOH, r.t., 12 h then NaOMe, MeOH, r.t., 1 h, 75%; (b) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, r.t., 2 h 30 min, 97%; (c) Ph_3PMeBr, *n*BuLi, THF, −78 °C to 0 °C, 25 min, then 60 °C, 1 h, 45%; (d) $Ni(OAc)_2·4H_2O$, $NaBH_4$, EtOH, H_2, r.t., 12 h, 90%.

1.6 Retrosynthetic analysis of daphlongeranine B

Our synthetic strategy towards the hexacyclic core of daphlongeranine B was based on a number of key steps (Scheme 14). The δ-lactone would be synthesised by a stereoselective Michael addition reaction on *tert*-butyl acrylate by the enolate of **40** followed by a Mitsunobu lactonisation. Palladium catalysed intramolecular coupling of vinyl iodide and ketone enolate of **41** would furnish the 7-membered ring. A key intramolecular Michael addition step would yield the tricyclic core **41** and the Michael addition precursor **42** would be accessed by an amide bond formation between the advanced spirocyclic intermediate **43** and carboxylic acid **44**.



Scheme 14. A retrosynthetic analysis of daphlongeranine B from an advanced spirocyclic intermediate **43** based on a few key steps: Mitsunobu lactonisation, Michael addition, intramolecular palladium coupling, intramolecular Michael addition and an amide bond formation.

1.7 Objectives and aims

The primary objective of this work was to develop a concise stereocontrolled total synthesis of daphlongeranine B. There have been no reported total syntheses to date and with so few approaches towards related natural products, the synthesis towards daphlongeranine B would give us an excellent platform for reaction discovery.

The following chapters detail our synthetic efforts towards the total synthesis of daphlongeranine B. Our retrosynthetic strategy pivots on the key intramolecular Michael addition step to yield the tricyclic core **41** of daphlongeranine B (Scheme 14). Therefore our first objective was to validate the key Michael addition step and thereafter devise a synthesis for the advanced spirocyclic intermediate **43**.

2 CHAPTER 2

2.1 Introduction

The work in this chapter deals with the design, synthesis and the subsequent testing of the key intramolecular Michael addition step. A model spirocyclic system needed to be synthesised in order to rapidly validate the key intramolecular Michael addition step.

2.1.1 Synthesis of spirocyclic compounds

Spirocyclic systems are of general interest in synthesis as they are widely present as subunits in many natural products (Figure 3).[16] Commonly, spirocycles contain at least one fully substituted carbon centre linking two rings, which makes these structures attractive but also synthetically challenging. For example (+)-gelsemine found in the plant *Gelsemium sempervirens*[17] has, due to its complex structure, been a target for an extensive number of synthesis projects.[16b, 18a-d.] Among these total syntheses only two were asymmetric and were accomplished by Fukuyama *et al.*[18c] in 2000 and Qin *et al.*[18d] in 2012. The biological activity of gelsemine is somewhat unknown but it is believed to act as a stimulant in the CNS.[19] (−)-Histrionicotoxin is another spirocyclic natural product isolated from the skin of a frog found in Colombia, *Dendrobates histrionicus*.[20] Histrionicotoxin is a neurotoxin and acts as a non-competitive inhibitor of the acetylcholine receptors.[21] It has a complex molecular structure consisting of a spirocyclic skeleton, two enyne side chains, and a secondary hydroxyl group. The first asymmetric synthesis of (−)-histrionicotoxin was completed by Stork *et al.* in 1990.[16d] Spirotryprostatin A is a spirocyclic indole alkaloid isolated in 1996 by Osada *et al.*[22] from the fungus, *Aspergillus fumigatus*. It is found to have anti-mitotic properties so it is of great interest as an anti-cancer drug.[22] The first total synthesis of spirotryprostatin A was reported by Edmondson and Danishefsky in 1998.[16c]

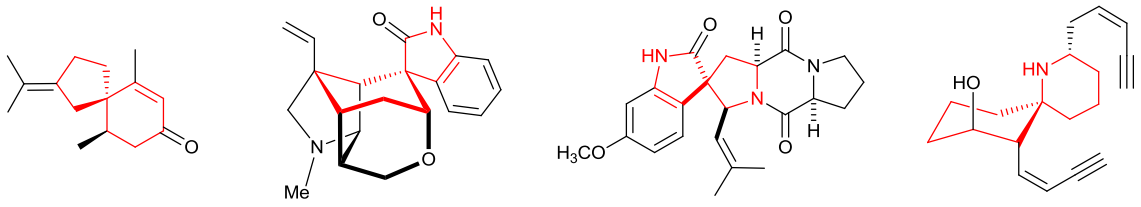
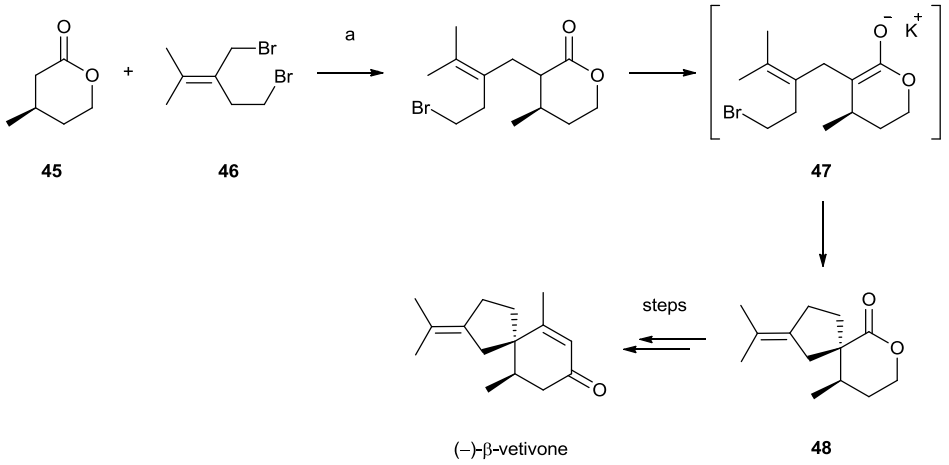


Figure 3. Spirocyclic natural products.[16]

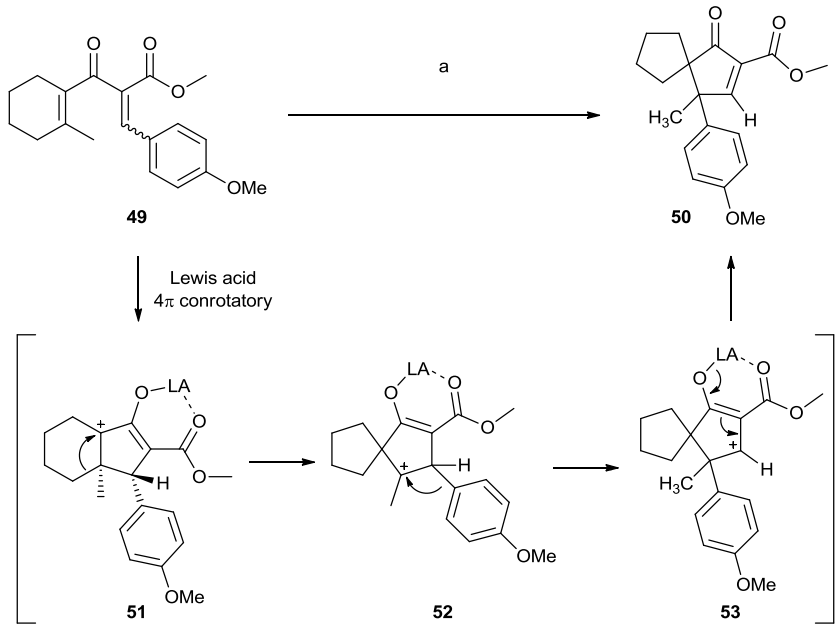
There are a number of synthetic methods directed towards spirocyclic systems reported in the literature[23] which include: alkylations,[27] rearrangement-based approaches,[24] cycloadditions,[25] and transition metal catalysed reactions.[26] Representative examples of these are discussed in sequence below.

Posner and Hamill[27] reported an intramolecular alkylation reaction to synthesize (−)-β-vetivone, a natural product found in vetiver oil which is used as a fragrant in the perfume industry (Scheme 15).[28] Lactone **45** was initially α-alkylated with an allylic-homoallylic dihalide **46** by deprotonation with KHMDS in THF in the presence of HMPA. Subsequent *in situ* enolisation facilitated a stereoselective 5-*exo*-*tet* cyclisation via enolate intermediate **47** to give the spirocyclic ester **48** in 54% yield. The stereocontrol originates from the adjacent methyl group which directs the electrophile to the lower face of the six membered ring. The resulting spirocyclic ester **48** was converted into the natural product (−)-β-vetivone via a series of synthetic transformations (Scheme 15).



Scheme 15. Synthesis of (−)-β-vetivone by a stereocontrolled spiroannulation step; (a) KHMDS, HMPA, THF, −78 °C to r.t., 24 h, 54%.

Huang and Frontier[24] synthesised a variety of spirocycles by a Nazarov cyclisation followed by a Wagner-Meerwein rearrangement. They reported that when compound **49** was treated with a stoichiometric amount of $Cu(SbF_6)_2$, spirocycle **50** was formed in 91% yield (Scheme 16).

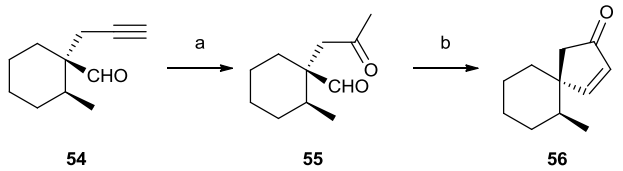


Scheme 16. Synthesis of spirocycle **50** by Nazarov cyclisation and a Wagner-Meerwein rearrangement; (a) $Cu(SbF_6)_2$, CH_2Cl_2, r.t., 30 min, 91%.

The proposed mechanism for the Nazarov cyclisation / Wagner-Meerwein rearrangement is shown in Scheme 16. Initially an oxyallyl cation intermediate **51** is formed after a

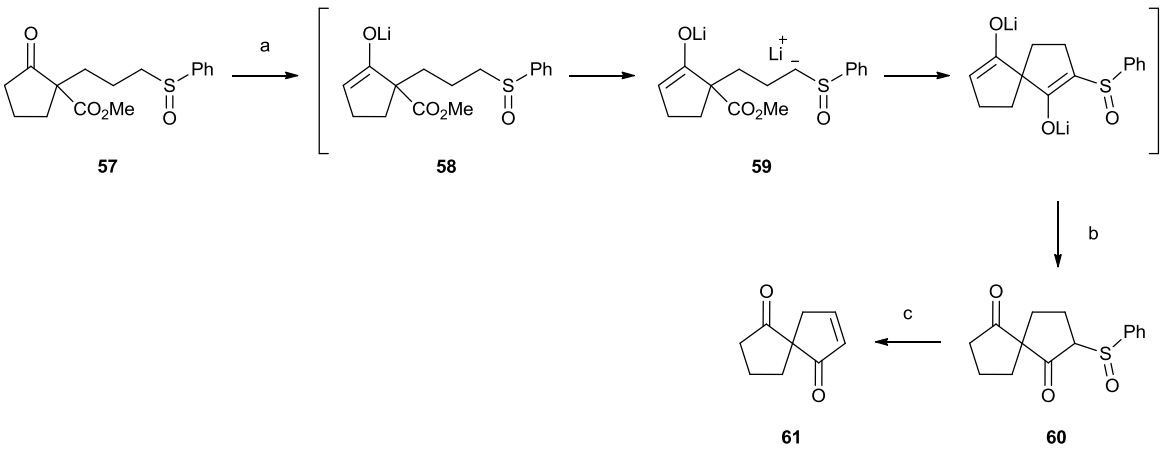
4π-conrotatory electrocyclic cyclisation of **49**. This is then followed by a ring contraction to form spirocyclic cation **52** which then undergoes a 1,2-aryl shift to generate a conjugated carbocation **53**. Finally the loss of the Lewis acid gives the spirocyclic product **50**.

Corey and Boger[29] reported an aldol condensation as the key step to construct spirocyclic enone **56**. Mercury(II) mediated hydration of the terminal alkyne of **54** afforded the crude keto aldehyde **55** which then underwent aldol condensation to give spirocyclic enone **56** in 78% overall yield (Scheme 17).



Scheme 17. Synthesis of spirocycle **56** by an aldol condensation step; (a) $HgSO_4$, THF / H_2O / H_2SO_4 (conc.), r.t., 60 min; (b) 0.5 M NaOH / EtOH, r.t., 60 min, 78% over two steps.

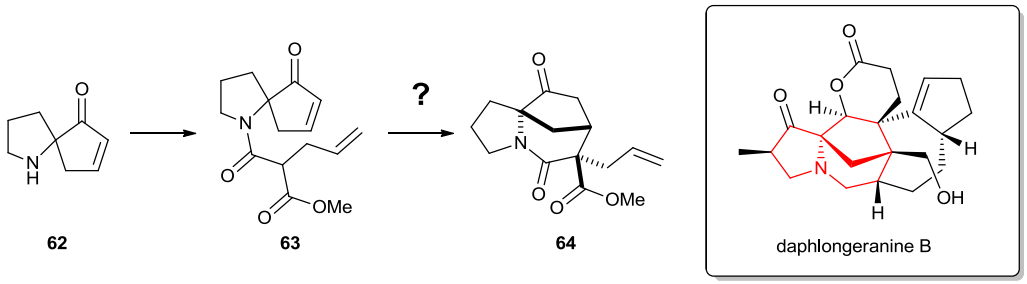
A useful method to synthesise spirocyclic enones by an intramolecular acylation using sulfinyl carbanions was reported by Pohmakotr and co-workers.[34, 35.] Treatment of sulfoxide **57** with excess of LHMDS (4-4.5 eq.) in the presence of HMPA at −78 °C to r.t. overnight and quenching with glacial acetic acid afforded a diastereomeric mixture of spirocyclic dione **60** in 83% yield (Scheme 18). In order to synthesise the desired product **60**, the authors found it necessary to protect the carbonyl as its enolate anion **58** before the sulfinyl carbanion **59** was generated. They argued that this was possible due to the differences in the acidity of the protons alpha to the carbonyl and the sulfinyl group. The spirocyclic dione **60** then underwent a *syn* elimination when heated in dry toluene in the presence of $CaCO_3$ to afford the corresponding spirocyclic enone **61** in 59% yield (Scheme 18).



Scheme 18. Synthesis of spirocyclic enone **61** by intramolecular acylation using sulfinyl carbanions; (a) LHMDS, HMPA, THF, −78 °C to r.t., 12 h, 83%; (b) AcOH; (c) $CaCO_3$, toluene, reflux, 10 h, 59%.

2.2 Aims of the chapter

The aim of this chapter was to investigate and develop a synthetic route to the spirocyclic enone **62** from readily available starting materials. This spirocyclic enone would be the vital building block needed to investigate and validate the key intramolecular Michael addition step to furnish the tricyclic core of daphlongeranine B (Scheme 19). If both of these aims could be met then the framework of a plausible route to daphlongeranine B would be established.

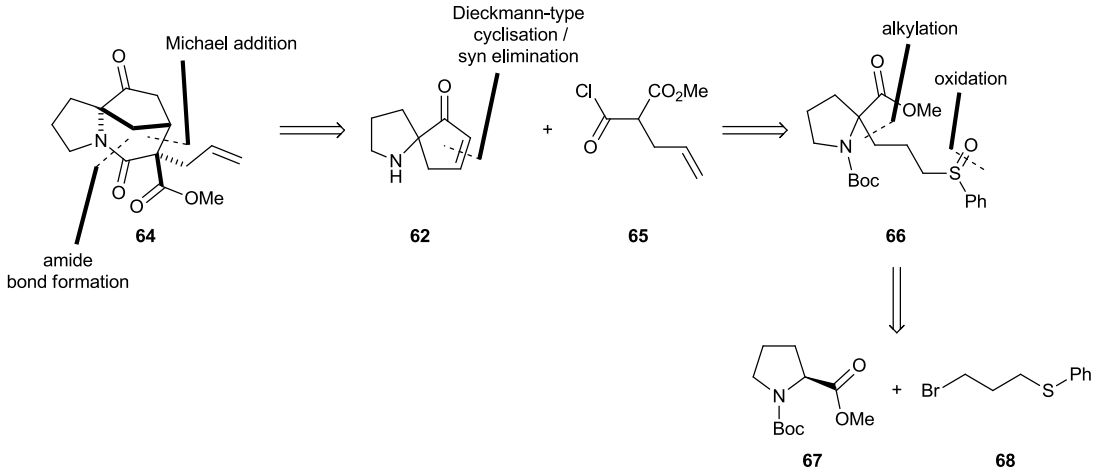


Scheme 19. The spirocyclic enone **62** would be the vital building block needed to validate the key intramolecular Michael addition step to give tricyclic core of daphlongeranine B.

2.3 Retrosynthetic analysis and strategy

A key intramolecular Michael addition step would give the tricyclic core of daphlongeranine B and the Michael addition precursor would be accessed by an amide bond formation between the

spirocyclic enone **62** and carboxylic acid **65** (Scheme 20). Following the work of Pohmakotr and co-workers,[34, 35.] it was proposed that the spirocyclic enone **62** would be synthesised from sulfoxide **66** by a Dieckmann-type cyclisation followed by a *syn* elimination of the sulfoxide. The sulfoxide **66** would be accessed from the corresponding sulfide **68** by oxidation and enolate alkylation of Boc-protected pyrrolidine **67**.



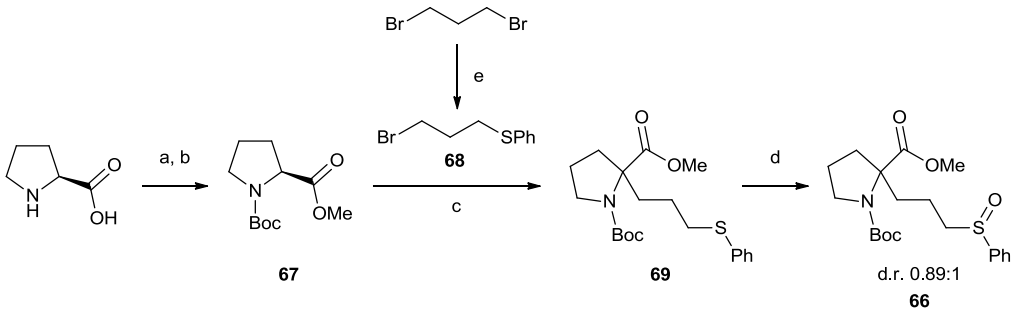
Scheme 20. Retrosynthetic analysis of the tricyclic core **64** of daphlongeranine B.

2.4 Results and discussion

2.4.1 Synthesis of spirocyclic enone 72

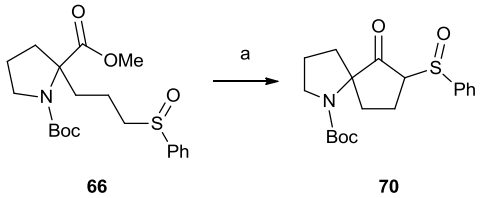
The initial objective was to synthesise the spirocyclic enone **62** which was a vital building block for investigating and validating the key intramolecular Michael addition. Starting the synthesis from the natural and commercial amino acid L-proline, the carboxylic acid was converted to the corresponding methyl ester by refluxing AcCl in MeOH. The crude amine was then treated with $(Boc)_2O$, Et_3N and a substoichiometric amount of DMAP to protect the nitrogen with a Boc-protecting group.[30, 31.] This gave the desired *N*-Boc-proline methyl ester **67** in 79% yield over two steps (Scheme 21). We chose a Boc-protecting group due to its known stability to basic nucleophiles. The Boc-protecting group would also prevent the amine from reacting in subsequent transformations and it would be easily removed under acidic

conditions.[32] *N*-Boc-proline methyl ester **67** was then treated with 1.1 eq. of LHMDS at −78 °C to generate the lithium enolate. The alkylation was performed by dropwise addition of alkyl bromide **68** at −78 °C and then allowing the reaction mixture to slowly warm to r.t. over 6 h. After work-up, extraction of the organic product and purification by silica gel chromatography, afforded the alkylated product **69** in 79% yield. The electrophile **68** was synthesised following a known literature procedure[33] from 1,3-dibromopropane and thiophenol (Scheme 21). The alkylated product **69** was then oxidised using sodium metaperiodate in aqueous methanol at 0 °C to r.t. over 6 h to give the resulting sulfoxide **66** as a mixture of inseparable diastereoisomers (d.r. 0.89:1) in 95% yield. Pleasingly, no over oxidation to the corresponding sulfone was observed following this procedure.[34]



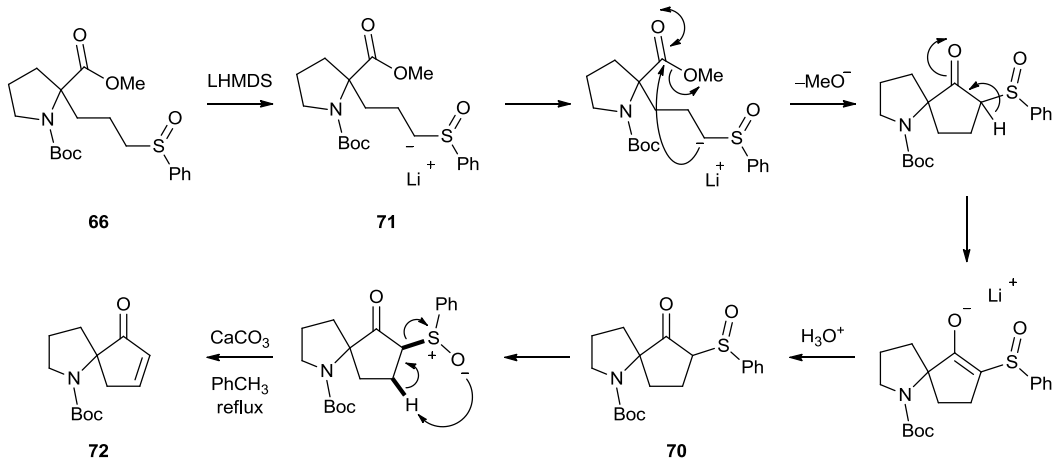
Scheme 21. Synthesis of sulfoxide **66**; (a) AcCl, MeOH, reflux, 12 h; (b) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, r.t., 12 h, 79% over two steps; (c) LHMDS, **68**, THF, −78 °C to r.t., 6 h, 79%; (d) $NaIO_4$, MeOH, r.t., 6 h, 95%; (e) PhSH, NaH, DMF, 0 °C to r.t., 25 h.

The Dieckmann-type cyclisation from the sulfoxide **66** to the expected phenylsulfinyl cyclopentanone **70** was readily accomplished by treatment with 2.2 eq. of LHMDS in THF at −78 °C followed by slowly warming the reaction mixture to r.t. over 7 h (Scheme 22). The product was isolated as a mixture of inseparable diastereoisomers in 66% yield after purification by flash chromatography.



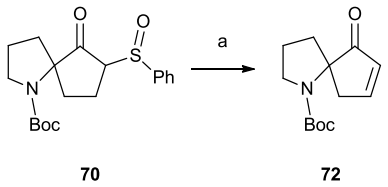
Scheme 22. Synthesis of phenylsulfinyl cyclopentanone **70**; (a) LHMDS, THF, −78 °C to r.t., 7 h, 66%.

The reaction mechanism is shown in Scheme 23. Initially the α-sulfinyl carbanion **71** is formed by removal of the proton alpha to the sulfoxide **66** by LHMDS. The α-sulfinyl carbanion **71** then undergoes an intramolecular addition/elimination cyclisation[35] to yield the desired phenylsulfinyl cyclopentanone **70**.



Scheme 23. Reaction mechanism for the Dieckmann-type cyclisation of the sulfoxide **66** to give the desired phenylsulfinyl cyclopentenone **70** followed by *syn* elimination to give the spirocyclic enone **71**.

Finally by refluxing the phenylsulfinyl cyclopentanone **70** in dry toluene in the presence of anhydrous $CaCO_3$ for 12 h, elimination of the sulfoxide occurred to give the desired spirocyclic enone **71** in 73% yield (Scheme 24). This reaction occurs via a concerted *syn* elimination to yield the desired α,β-unsaturated carbonyl product (Scheme 23).[36] It is worth noting that ^{1}H and ^{13}C NMR spectra of all the *N*-Boc protected compounds **66, 67, 69-72** were complicated by *N*-Boc rotamers at 298 K. The rotamers were confirmed by VT NMR experiments.

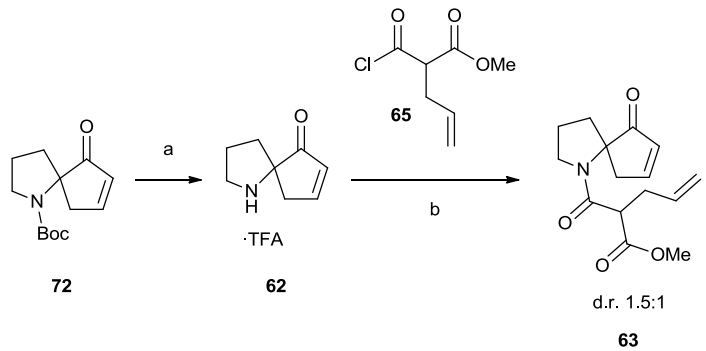


70 72

Scheme 24. Synthesis of spirocyclic enone **72**; (a) $CaCO_3$, toluene, reflux, 12 h, 73%.

2.4.2 Intramolecular Michael addition

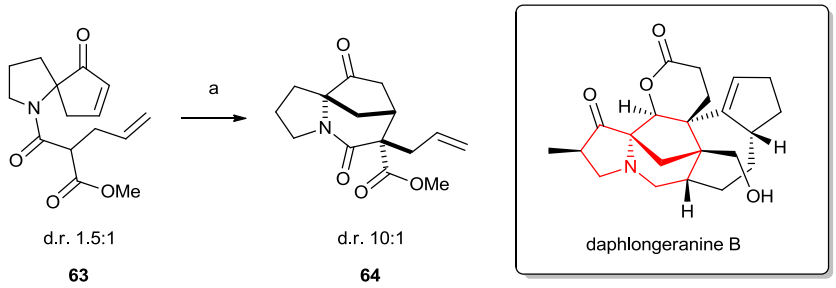
With the spirocyclic enone **72** in hand, attention now turned to the intramolecular Michael addition step. The Boc-protecting group was successfully removed by treating **70** with TFA in CH_2Cl_2 (1:1) at r.t. for 1 hour and amine **62** was afforded as the TFA salt in quantitative yield (Scheme 25). The reactive product was not purified but used crude in the following amide bond forming step. Addition of acyl chloride **65**[37] to a solution of the crude amine salt **62** in Et_3N and dry CH_2Cl_2 at 0 °C gave the amide **63** (Scheme 25). The excess of Et_3N (2.2 eq.) was necessary to trap any formed HCl and to avoid the conversion of the amine to its unreactive HCl or TFA salts.[38] Even with excess of Et_3N only 22% yield of product was obtained, however this gave sufficient material to investigate the next step. We chose to use the acyl chloride **65**, which was readily available in our research group, to synthesise the Michael addition precursor **63**. This Michael addition precursor **63** would serve as a representative model of the real system. The allylic side chain is chemically and structurally comparable with the vinyl iodide and the elongated alkyl chain found on the real system (Scheme 14).



72 62 63

Scheme 25. Synthesis of the Michael addition precursor **63**; (a) TFA, CH_2Cl_2, r.t., 1 h; (b) Et_3N, **65**, CH_2Cl_2, 0 °C, 2 h, 22% over two steps.

Treatment of the Michael addition precursor **63** with 1.1 eq. KHMDS at 0 °C for 1.5 h very pleasingly facilitated the intramolecular Michael addition to give the desired tricyclic core **64** of daphlongeranine B. The product was isolated as a mixture of diastereoisomers (d.r. 10:1) in 12% yield after purification by flash chromatography (Scheme 26).



Scheme 26. Synthesis of tricyclic core **64** of daphlongeranine B; (a) KHMDS, THF, 0 °C, 1.5 h, 12%.

It should be noted that due to the lack of material, this was a single attempt and the reaction conditions were not optimised. However, unequivocally the desired bond formation had occurred. The stereochemistry of the major isomer of the tricycle **64** was assigned by NOE experiments (Figure 4). It was found to have the allylic side chain on the *exo* face of the tricyclic spiro system, i.e. orientated away from the longest bridge. The major isomer was unfortunately undesired as daphlongeranine B has the alkyl chain with the cyclopentene ring, for which the vinyl group is a model of, on the *endo* face of the tricyclic spiro system (Figure 4). From earlier experience in our research group,[39a, b] we believe that the diastereoselectivity could possibly be altered by changing the base or the reaction conditions. The methyl ester group also has to be removed preferably by Krapcho decarboxylation[40] which in the protonation step, could potentially invert the stereochemistry to that possessed by the natural product.[37]

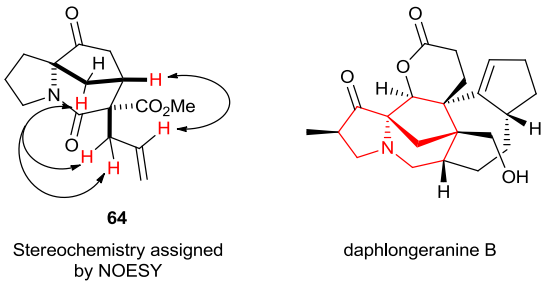
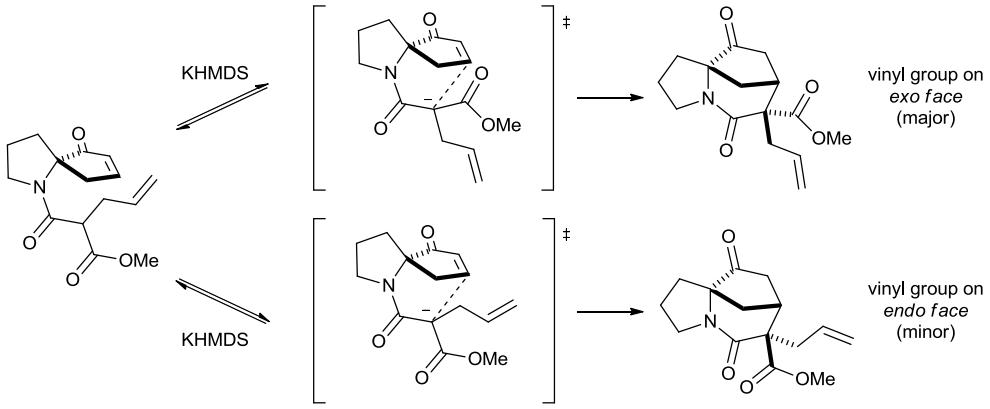


Figure 4. Assignment of the stereochemistry for the major isomer by NOE correlation for the tricyclic core **64** of daphlongeranine B (see Appendix 7.1).

The origin of diastereocontrol is not obvious and is hard to fully understand without further experiments. However it is possible that the stereocontrol could arise by chelation of the enone carbonyl and the ester carbonyl with a potassium ion. It was postulated that the intramolecular Michael addition occurred by nucleophilic attack from the bottom face of the cyclopentanone ring with the proposed transition state as shown in Scheme 27.

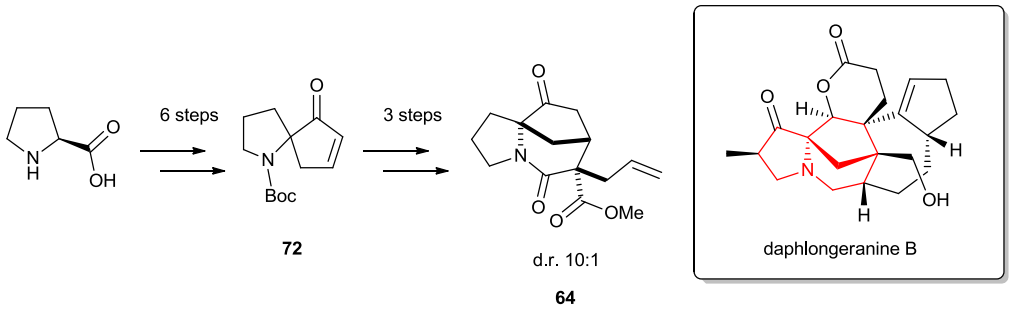


Scheme 27. Proposed transition state models for the intramolecular Michael addition.

2.5 Conclusions

In conclusion, a model route (6 steps) to the spirocyclic enone **72** has been developed starting from the natural and commercial amino acid L-proline. The spirocyclic enone **72** was synthesised in 4 key steps: alkylation, oxidation, a Dieckmann-type cyclisation and finally a *syn* elimination. This spirocyclic enone gave us the vital building block needed to investigate the key intramolecular Michael addition which was successfully validated using KHMDS in

THF and allowed us to access to the tricyclic core **64** of daphlongeranine B in a total of 9 steps (Scheme 28).

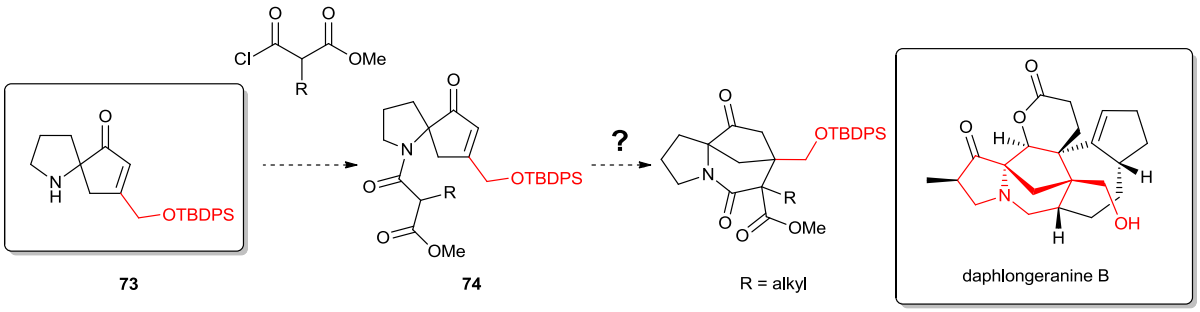


Scheme 28. The tricyclic core **64** of daphlongeranine B was accessed in 9 steps from the natural amino acid L-proline.

3 CHAPTER 3

3.1 Introduction

The key intramolecular Michael addition had now been validated and this chapter will further expand on this key step. We herein aim to synthesise, investigate and if possible validate the Michael addition to the advanced fragment **74** bearing a β-substitutent. If this key step was to be successful it would furnish three fully substituted carbon centres as well as introducing the primary alcohol functional group found in daphlongeranine B (Scheme 29). In order to validate the intramolecular Michael addition step we first needed to synthesise a spirocyclic enone **73** which is substituted at the β-position.

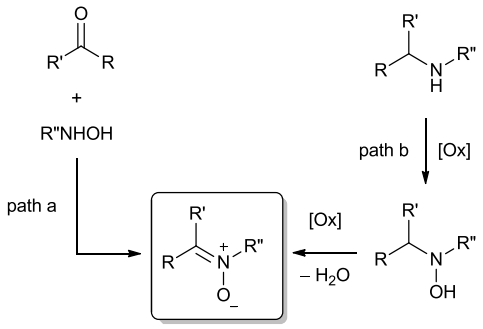


Scheme 29. The key intramolecular Michael addition onto a β-substituted enone **74**.

3.1.1 Synthesis of nitrones

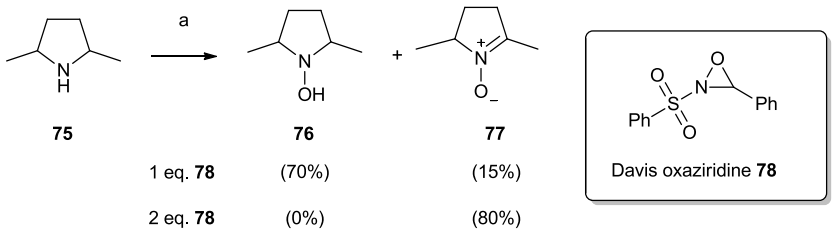
Nitrones are highly versatile synthetic building blocks in organic synthesis and they have been used for the synthesis of a variety of natural products and biologically active compounds.[41] Various procedures[41a, 42.] have been reported for the synthesis of nitrones. Originally they were synthesised via condensation of ketones or aldehydes with *N*-monosubstituted hydroxylamines (scheme 30, path a).[43] Oxidation of amines to hydroxylamine followed by a second oxidation to give a nitrone is a more direct and attractive route due to the high availability of amines. Although it might be less favourable for unsymmetrical secondary amines bearing different groups due to the formation of two possible isomers (Scheme 30, path b). Direct oxidation of

amines to nitrones has been achieved through various procedures for example using oxaziridines,[42a] dioxiranes,[42b] or hydroperoxides (including H_2O_2) paired with diverse metal-catalytic systems.[42c-g.]

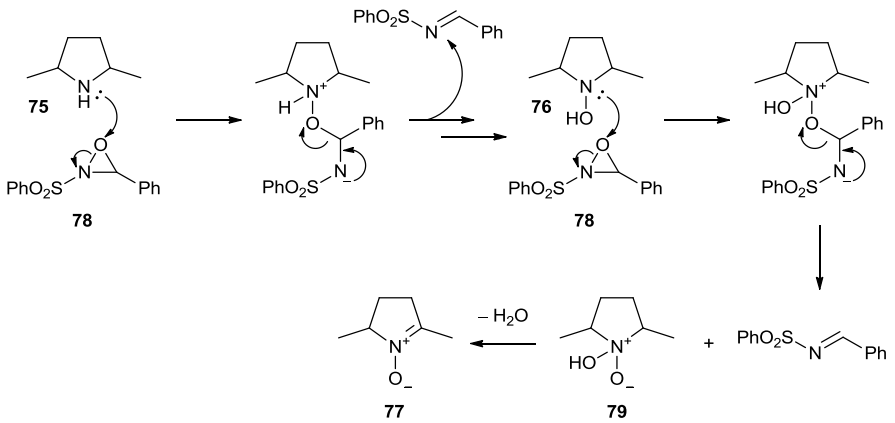


Scheme 30. Synthesis of nitrones via condensation of carbonyl compounds with *N*-monosubstituted hydroxylamine (path a) or the oxidation of secondary amines (path b).

Zajac *et al.*[42a] reported that when secondary amine **75** was reacted with 1 eq. of Davis oxaziridine **78** in $CHCl_3$ two major products were isolated together with some unreacted starting material. These two products were identified as the hydroxylamine **76** and the nitrone **77** (Scheme 31). It was believed that the formation of the nitrone **77** was the result of an initial oxidation to hydroxylamine **76**. The hydroxylamine **76** then reacted with a second molecule of oxidant to form hydroxylamine *N*-oxide **79** which then dehydrates to give the resulting nitrone **77** (Scheme 32). Subsequently when 2 eq. of 2-sulfonyloxaziridine **78** was used to oxidise the secondary amine **75** the nitrone **77** was the major product isolated in 80% yield (Scheme 31).

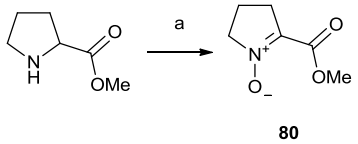


Scheme 31. Oxidation of secondary amine **75** using Davis oxaziridine **78**; (a) Davis' oxaziridine **78**, $CHCl_3$, r.t., 1 h.



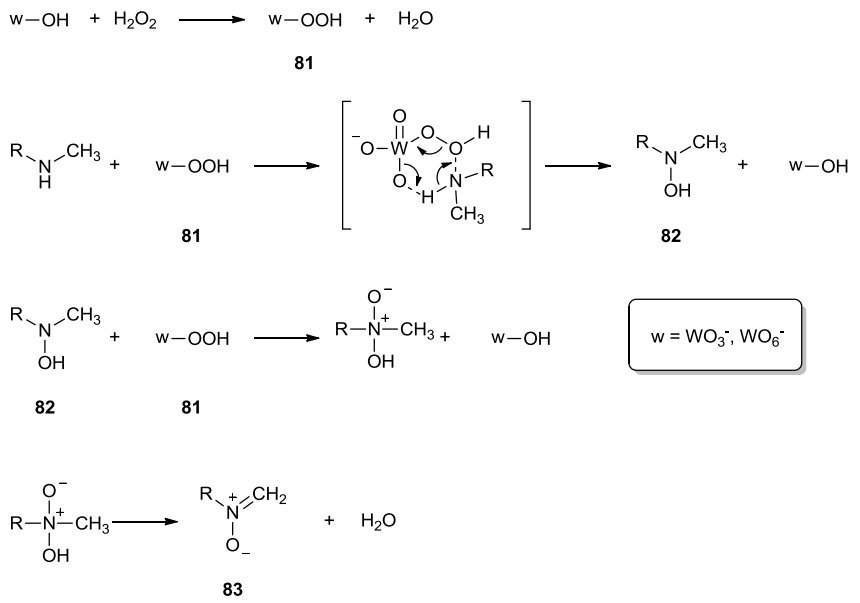
Scheme 32. Proposed reaction mechanism for oxidation of secondary amine **75** to nitrone **77** using Davis oxaziridine **78**.

Murahashi *et al.*[42d] reported that secondary amines such as proline methyl ester could be oxidised to the corresponding nitrone **80** in one single step in 42% yield using hydrogen peroxide and a substoichiometric amount of sodium tungstate (Scheme 33).



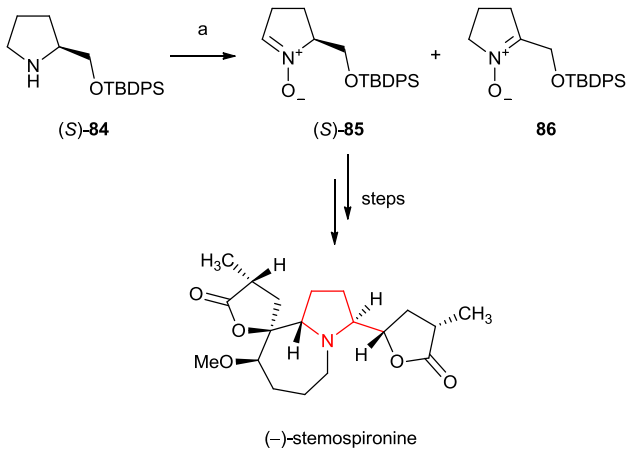
Scheme 33. Oxidation of proline methyl ester using sodium tungstate catalysed oxidation; (a) $Na_2WO_4 \cdot 2H_2O$ (0.04 eq.), 30% H_2O_2 (aq.), water, r.t., 6 h, 42%.

The active catalysts in the reaction are believed to be $HOOWO_3^-$ and $HOOWO_6^-$ that are formed from the reaction of sodium tungstate and hydrogen peroxide. Secondary amines first undergo nucleophilic addition to the active peroxytungstate species **81** to give hydroxylamines **82**. Further oxidation of hydroxylamines **82** with peroxytungstate **81** followed by dehydration yields the desired nitrones **83** (Scheme 34).[42d]



Scheme 34. Proposed reaction mechanism of the sodium tungstate catalysed oxidation of amines to nitrones with hydrogen peroxide.

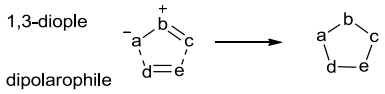
A completely metal free protocol for the direct oxidation of secondary amines to nitrones using Oxone® as the sole oxidant in a biphasic medium was reported by Busqué and co-workers.[44,45] They treated amine (*S*)-**84** in a solution of THF / CH_3CN (1:4) with 2.1 eq. of Oxone®. In the presence of 0.01 M Na_2EDTA (aq.) and $NaHCO_3$ at 0 °C it yielded chromatographically separable mixtures of nitrones (*S*)-**85** and **86** in 1.3:1 ratio in 88% total yield (Scheme 35). The reaction was shown to be readily scaled up to 10 g without detriment to the yield or optical purity of the nitrone product. The resulting nitrone (*S*)-**85** was used as an important building block for the total synthesis of (−)-stemospironine,[45] a natural product with insecticidal properties isolated from the leaves and stems of *Stemona japonica* (Scheme 35).[46]



Scheme 35. Oxidation of TBDPS protected L-prolinol **84** to the corresponding nitrones (*S*)-**85** and **87** using Oxone®. Nitrone (*S*)-**85** was used as a building block for the total synthesis of (−)-stemospironine; (a) Oxone®, $NaHCO_3$, 0.01 M Na_2EDTA (aq.), THF / CH_3CN (1:4), 0 °C, 2 h 20 min, (*S*)-**85** and **86** in 1.3:1 ratio in 88% total yield.

3.1.2 1,3-Dipolar cycloaddition reactions of nitrones to alkynes

The 1,3-dipolar cycloaddition reaction has attracted considerable attention as a convenient tool for constructing various five-membered heterocycles and synthesising a wide variety of natural products.[47a-c.] There is an abundance of literature regarding 1,3-dipolar cycloadditions. Their general application in modern organic chemistry was first systematically established by Huisgen in the 1960's.[48a, b.] At the same time, the new concept of conservation of orbital symmetry was developed by Woodward and Hoffmann.[49] Their work was a landmark for the understanding of the mechanism of concerted cycloaddition reactions. In order to create a five membered heterocycle by 1,3-dipolar cycloaddition, a three atom, four electron 'diene' is required, also called 1,3-dipole (*a*-*b*-*c*), and a multiple bonded two atom section, the dipolarophile (*d*-*e*) (Scheme 36).[50a, b.]



Scheme 36. 1,3-dipolar cycloaddition to form a five membered heterocycle requires a 1,3-dipole (*a*-*b*-*c*) and a dipolarophile (*d*-*e*).

The 1,3-dipole can be presented in a sextet or an octet form. The sextet form has six electrons in the outer shell of atom *a* while the octet form has eight electrons (Figure 5).[50a, b.] There are two main types of 1,3-dipolar compounds; the allyl anion type dipole and the propargyl/allenyl anion type dipole. The allyl anion type dipole is characterised by four electrons in three parallel p_z orbitals perpendicular to the plane of the dipole. It can be drawn as two resonance structures in which the three centers have an electron octet, and two structures in which *a* or *c* has an electron sextet. The dipole is bent and the central atom *b* is sp^2 hybridised (Figure 5).[50 a, b.] The central atom can either be a nitrogen, oxygen or sulfur. Nitrones belong to this class of 1,3-dipoles.

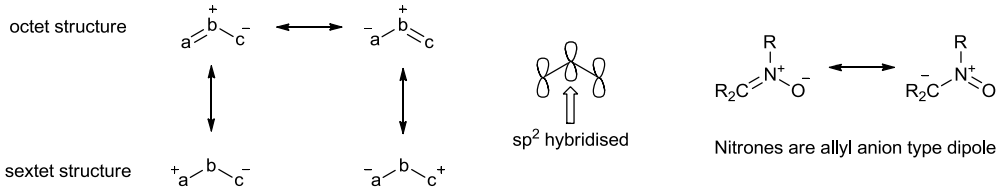


Figure 5. Resonance structures of the allyl anion type dipole where nitrones are a common example.

The propargyl/allenyl anion type has an extra π orbital located orthogonal to the allenyl anion type molecular orbital. This orbital is not directly involved in the resonance structures and reactions of the dipole. The propargyl/allenyl anion type dipole is linear with the central sp hybridised atom *b* (Figure 6).[50 a, b.] The central atom *b* is limited only to a nitrogen atom. Azides are an example of a propargyl/allenyl anion type dipole.

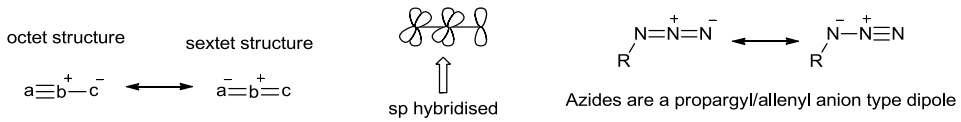


Figure 6. Resonance structures of the propargyl/allenyl anion type dipole where azides are a common example.

The dipolarophile is a two atom 2π-electron unsaturated compound (*d*-*e*) (Scheme 36), which is not limited to an alkene or an alkyne. Several multiple bonded structures containing other elements such as sulphur, nitrogen and oxygen can be dipolarophiles (Figure 7).

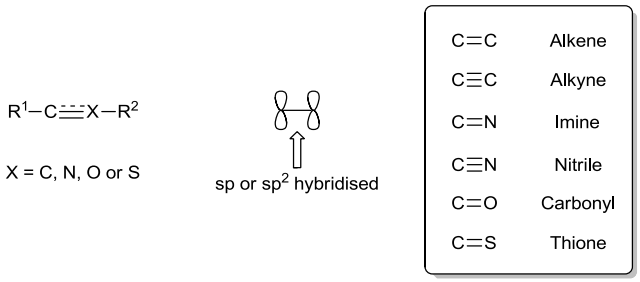
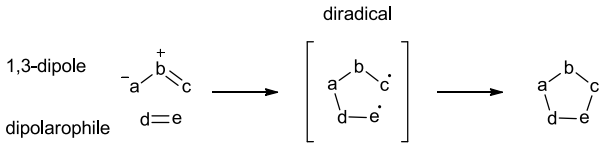


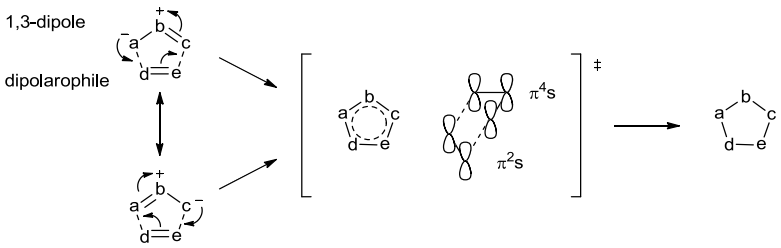
Figure 7. Common dipolarophiles which are two atom 2π-electron unsaturated compounds.

Initially there were two proposals that described the mechanism of the 1,3-dipolar cycloaddition: The first mechanism, proposed by Huisgen, was a concerted pericyclic cycloaddition mechanism.[48a, b.] The second mechanism, proposed by Firestone was a stepwise mechanism involving a diradical intermediate (Scheme 37).[51]



Scheme 37. The 1,3-dipolar cycloaddition was considered by Firestone to proceed via a singlet diradical intermediate.[51]

After some debate the former proposal is now generally accepted. The 1,3-dipolar cycloaddition reaction with an alkene or an alkyne involves 4π electrons from the dipole and 2π electrons from the alkene. The concerted and asynchronous mechanism is thermally allowed [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] according to the Woodward-Hoffmann rules[52] where three p_z orbitals of the 1,3-dipole and two p_z orbitals of the alkyne combine suprafacially (Scheme 38).



Scheme 38. The concerted mechanism of the 1,3-dipolar cycloaddition.

The success of the 1,3-dipolar cycloaddition depends on the favourable interaction between a filled π orbital of one reactant and an empty π* orbital of the other. This interaction must be sterically feasible and the orbitals must be of the same phase for a constructive overlap to form.[53] The smaller the energy gap, the stronger is the interaction and the higher the reactivity. The reactivity is explained by the energy difference between the FMOs. The HOMO and LUMO of the 1,3-dipole interacting with the LUMO and HOMO of the dipolarophile respectively, are the key FMO interactions considered (Figure 8).[54]

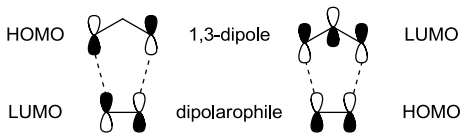


Figure 8. Key interactions between the HOMO and LUMO of the 1,3-dipole with the LUMO and HOMO of the dipolarophile.

Nitrones are well-known as 1,3-dipoles in cycloaddition reactions with alkenes to afford isoxazolidines and these reactions are widely reported in the literature.[55a, b.] On the other hand, cycloaddition of nitrones with alkynes to afford 4-isoxazolines are less common. This is mainly because the formed 4-isoxazoline products are known to be thermally labile and unstable under the reaction conditions at which they are formed.[56] Cycloadditions between nitrones and monosubstituted alkynes would yield two possible regioisomers (Figure 10, Figure 11).The most common method of rationalising the regioselectivity for this type of 1,3-dipolar cycloaddition is by FMO theory.[57] If considering the FMO of a simple nitrone, the largest

coefficient of the nitrone HOMO is on the oxygen, while the largest coefficient of the nitrone LUMO is at the carbon (Figure 9).[58]

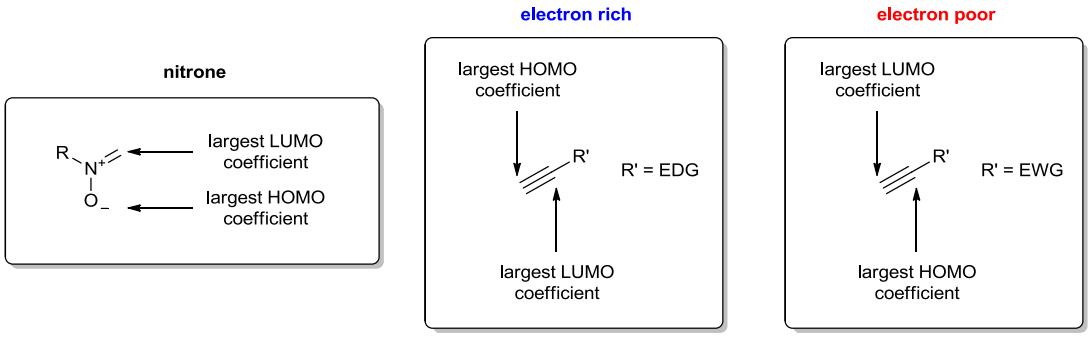


Figure 9. Largest HOMO and LUMO coefficients for simple nitrones and electron rich and electron poor alkynes.

Comparison of these FMO with those of monosubstituted alkynes, where R' is an electron donating group (EDG) (Figure 9), shows that the interaction with the smallest energy gap is the $HOMO_{alkyne}$-$LUMO_{nitrone}$, which leads to 5-substituted 4-isoxazolines **87** (Figure 10).

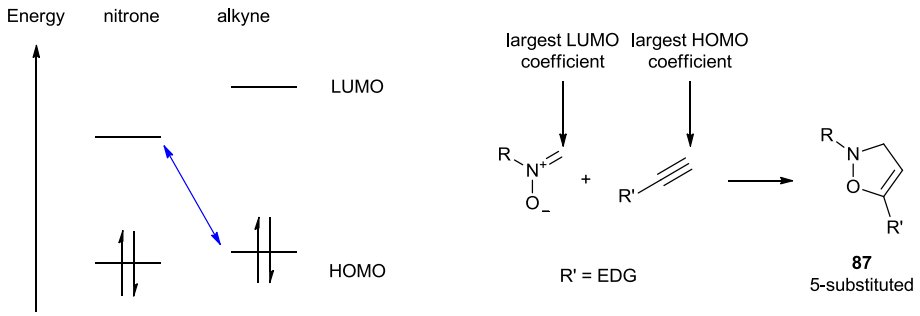


Figure 10. Electron rich alkynes yield 5-substituted 4-isoxazolines **87** as the dominant interaction is between the $HOMO_{alkyne}$-$LUMO_{nitrone}$.

In the case of alkynes having an electron withdrawing group (EWG), the $LUMO_{alkyne}$-$HOMO_{nitrone}$ interaction becomes most significant, and therefore formation of the 4-substituted 4-isoxazolines **88** are favoured (Figure 11).[59, 60.] Consequently the choice of either an electron-donating or an electron-withdrawing substituent on the dipolarophile would assist in determining the regioselectivity of the 1,3-dipolar cycloaddition.

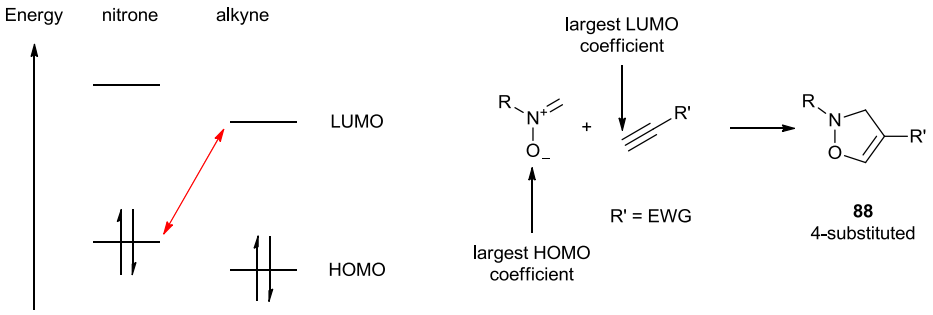
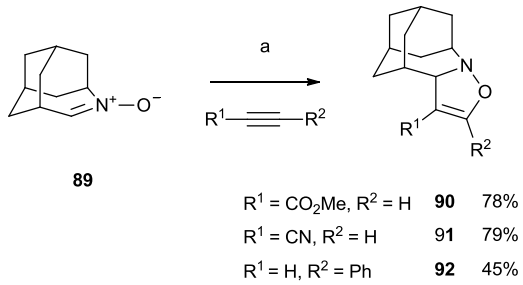


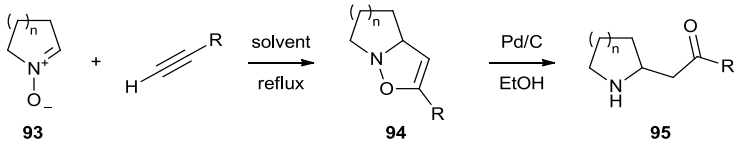
Figure 11. Electron poor alkynes yield 4-substituted 4-isoxazolines **88** as the dominant interaction is between the $LUMO_{alkyne}$-$HOMO_{nitrone}$.

Eguchi *et al.* reported a 1,3-dipolar cycloaddition of a bridged nitrone **89**, incorporated in a homoadamantane ring system, with electron deficient alkynes to give exclusively the 4-substituted 4-isoxazolines **90**, **91**, and **92** in good yields (78-79%). On the other hand when an electron rich alkyne such as phenylacetylene was used the 5-substituted 4-isoxazolines **92** was isolated in 45% yield (Scheme 39).[61]



Scheme 39. 1,3-dipolar cycloaddition of a bridged nitrone **89** with electron deficient and electron rich alkynes.

5-Substituted 4-isoxazolines are very useful compounds as they can be viewed as masked β-aminoketones. Mancuso and Hootelé have reported a 1,3-dipolar cycloaddition between nitrones **93** and a series of alkynes to give the expected 5-substituted 4-isoxazolines **94** in good yields (70-81%).[62] This was achieved by refluxing the nitrone and the alkyne in $CHCl_3$, benzene or trichloroethane. The resulting 5-substituted 4-isoxazolines **94** were subjected to reductive N-O bond cleavage using Pd/C in EtOH to give the anticipated β-aminoketones **95** in good yields (60-86%) (Scheme 40).



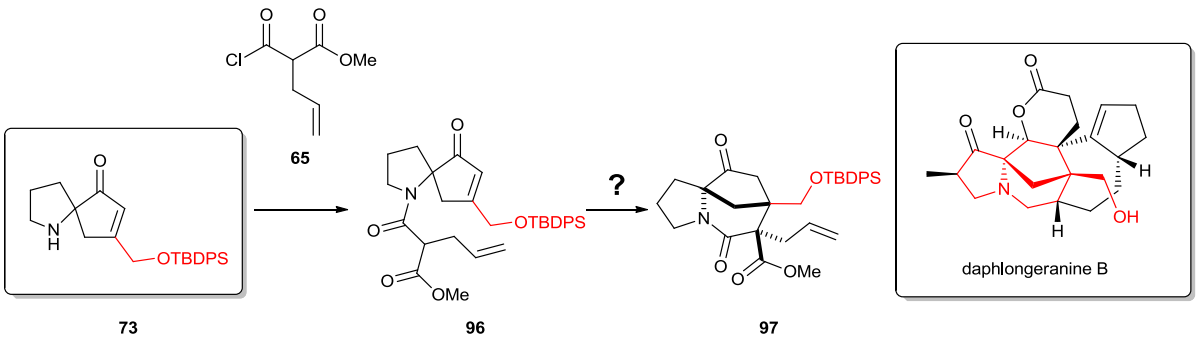
Entry	R	Solvent	n	yield[a]
1	Ph	C_6H_6	1	70% (60%)
2	Ph	$CHCl_3$	2	81% (86%)
3	*n*-pentane	CH_3CCl_3	2	70% (71%)

[a] % yield of isoxazoline, (% yield of β-aminoketone)

Scheme 40. A series of β-aminoketones **95** were synthesised by 1,3-dipolar cycloaddition followed by N-O bond cleavage.

3.2 Aims of the chapter

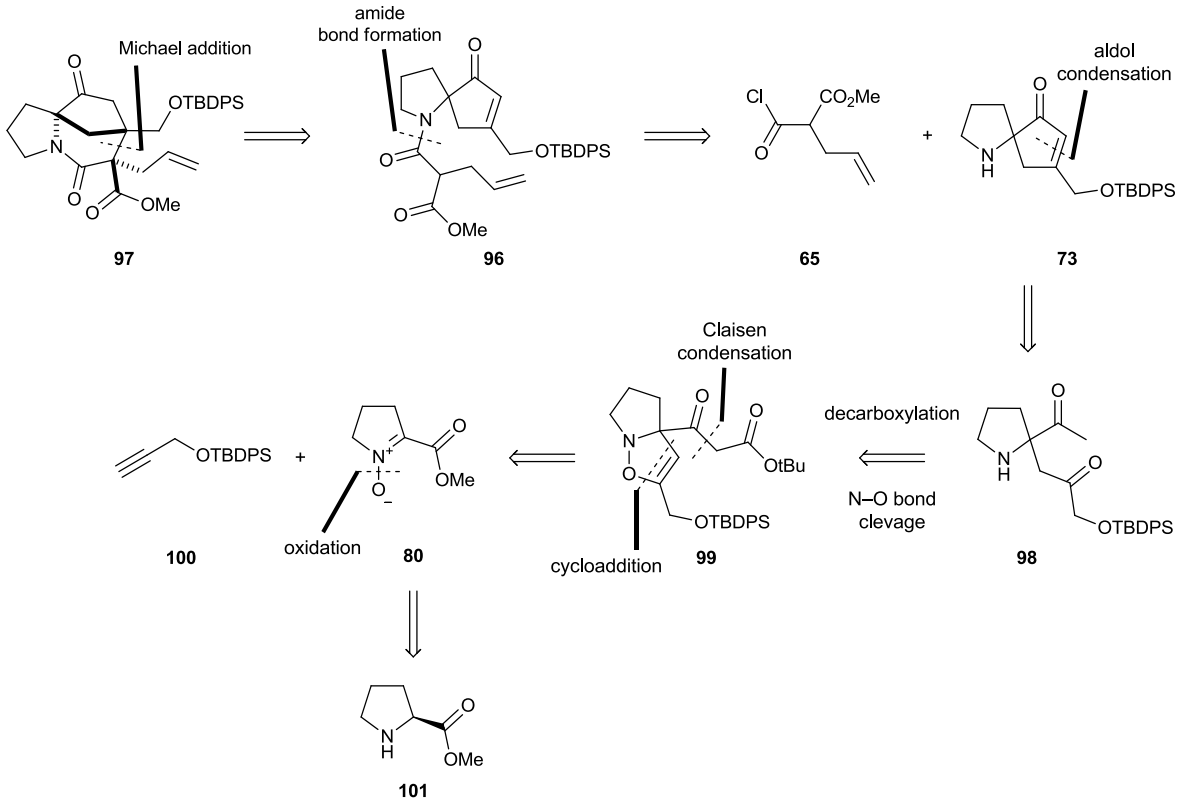
Based on the success detailed in the previous chapter, the key intramolecular Michael addition step was further to be investigated. The first aim was to develop a synthetic route towards the β-substituted spirocyclic enone **73** owing to the hydroxymethyl group present at one of the fully substituted carbon centres in daphlongeranine B. This spirocyclic intermediate would then serve as yet another vital building block as the second aim was investigated: the intramolecular Michael addition using this substrate (Scheme 41). This would in turn furnish a product possessing two contiguous stereocentres as well as introducing the hydroxymethyl functional group. If these two aims were met then our synthetic approach towards the unique tricyclic ring system of daphlongeranine B would be further strengthened.



Scheme 41. The key intramolecular Michael addition using the β-substituted spirocyclic enone **73** as a building block was to be investigated.

3.3 Retrosynthetic analysis and strategy

A new synthetic route had to be developed in order to synthesise the β-substituted spirocyclic enone **73**. Our initial retrosynthetic strategy towards daphlongeranine B to the tricyclic core **97** shown in Scheme 14 would still be applicable. Building on our initial success it was hoped that the tricyclic core **97** would be furnished by an intramolecular Michael addition step. The Michael addition precursor **96** would be accessed as previously demonstrated by an amide bond formation between the β-substituted spirocyclic enone **73** and the methyl malonyl chloride derivative **65** (Scheme 42).



Scheme 42. Retrosynthetic analysis for the tricyclic core **97** of daphlongeranine B.

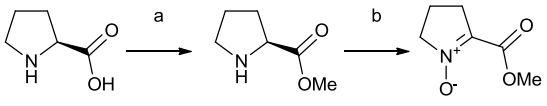
The β-substituted spirocyclic enone **73** would be accessible through a series of key transformations. An intramolecular aldol condensation of diketone **98** would give the β-substituted spirocyclic enone **73** and the diketone **98** would be formed by a decarboxylation followed by N-O bond cleavage of the 4-isoxazoline **99**. A 1,3-dipolar cycloaddition between

nitrone **80** and alkyne **100** followed by Claisen condensation would yield 4-isoxazoline **99**. The nitrone **80** would be derived from the corresponding L-proline methyl ester **101** by oxidation.

3.4 Results and discussion

3.4.1 Synthesis of β-substituted spirocyclic enone 112

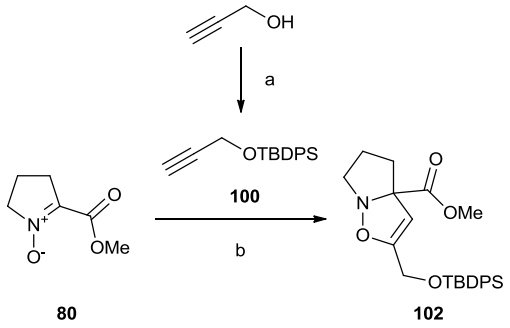
Our synthetic plan required the synthesis of the β-substituted spirocyclic enone **73** as the crucial building block needed for the key intramolecular Michael addition to create the bond linking two quarternary carbon centres (Scheme 41) Starting the synthesis from the natural and commercial amino acid L-proline the carboxylic acid was converted to the corresponding methyl ester using AcCl, MeOH under reflux conditions (Scheme 43).[30] After basic work-up the amine **101** was isolated as its free base in 72% crude yield and taken to the next oxidation step without any further purification. This material was oxidised to the corresponding nitrone **80** under mild conditions using Oxone® as the sole oxidant.[44] Oxone® was added in small portions over 2 h at 5 °C to a biphasic suspension of crude amine **101**, $NaHCO_3$ in MeCN / THF (4:1) and 0.01 M Na_2EDTA (aq.). The nitrone **80** was obtained in 42% yield after work-up and purification by flash chromatography. It is worth noting that this protocol is completely metal free compared to several other procedures reported in the literature.[42c-g] The reaction was easy to perform and could be scaled to multigram quantities without any loss of purity or yield.



101 **80**

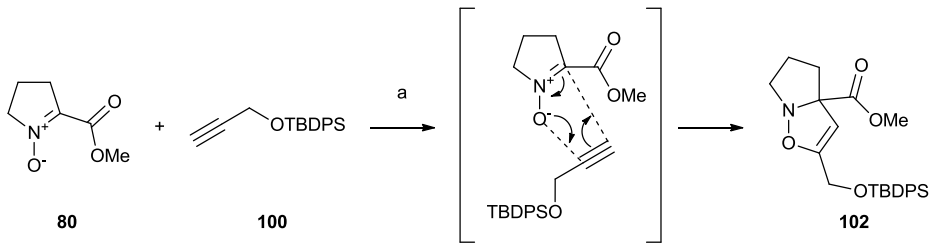
Scheme 43. Synthesis of nitrone **80**; (a) $SOCl_2$, MeOH, reflux, 12 h, 72%; (b) Oxone®, $NaHCO_3$, MeCN / THF (4:1), 0.01 M Na_2EDTA (aq.), 5 °C, 2 h, 42%.

When heated to reflux for 12 h in hexane, the nitrone **80** underwent a 1,3-dipolar cycloaddition with alkyne **100**, to give the desired 4-isoxazoline **102** in 83% yield (Scheme 44). The reaction was screened with different organic solvents such as chloroform and benzene. However hexane proved to be the best reaction solvent, giving clean reactions in excellent yield.



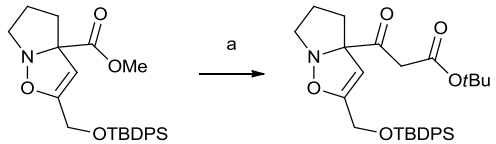
Scheme 44. Synthesis of 4-isoxazoline **102**; (a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C then r.t., 48 h, 99%; (b) **100**, hexane, reflux, 12 h, 83%.

The 1,3-dipolar cycloaddition reaction was proposed to proceed via a concerted mechanism[48a, b] (Scheme 45) and as predicted[63] afforded only one regioisomer, the desired 5-substituted 4-isoxazoline **102**. This was evidenced by ^{1}H and ^{13}C NMR measurements where the vinyl hydrogen at isoxazoline *C*-4 (singlet at δ_H 4.77 ppm) was in agreement with expected values (δ_H 4.50 - 5.50 ppm) previously reported in literature.[62] The dipolarophile **100** was afforded from commercial propargyl alcohol by protecting the alcohol functional group by the very bulky TBDPS protecting group following a known literature procedure (Scheme 44).[64] This protecting group was chosen due to its stability under both acidic and basic reaction conditions. The TBDPS protecting group would be robust to all the subsequent reactions, yet it could be removed selectively at the end of the synthesis with an appropriate fluorine anion source.[32]



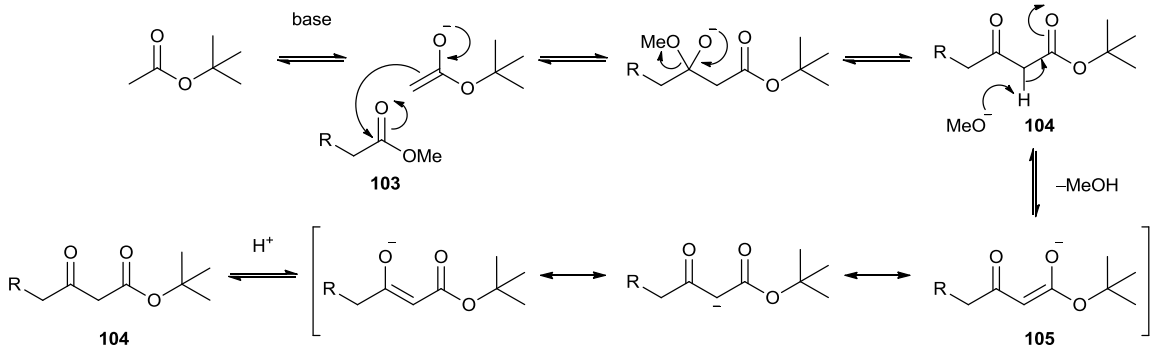
Scheme 45. Proposed concerted mechanism of the 1,3-dipolar cycloaddition reaction with alkyne **99** to give 4-isoxazoline **102**; (a) benzene, reflux, 12 h, 83%.

The 4-isoxazoline **102** underwent a chain elongation via a Claisen condensation which converted the methyl ester functional group to the β-keto ester **99** (Scheme 46).[65] The lithium enolate was first formed by addition of LHMDS to *t*BuOAc in THF at −78 °C. The mixture was stirred for 5 min before addition of the 4-isoxazoline **102**. After stirring for 12 h the reaction mixture was quenched with saturated NH_4Cl (aq.). The β-keto ester **99** was isolated in 72% yield after purification by flash chromatography .



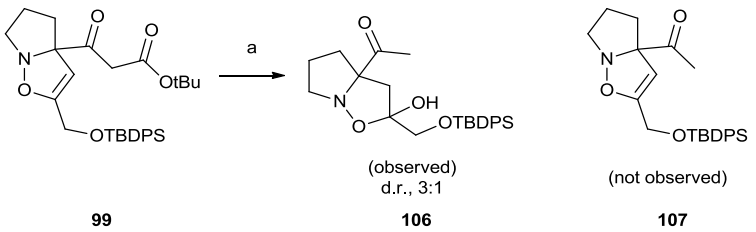
Scheme 46. Synthesis of β-keto ester **99**; (a) LHMDS, *t*BuOAc, THF, −78 °C to r.t., 12 h, 72%.

The mechanism for the Claisen condensation is shown in Scheme 47. Initially the α-proton on *t*BuOAc is removed by a strong base, resulting in the formation of an enolate anion. Addition of methyl ester **103** to the enolate results in nucleophilic attack on the carbonyl of the ester giving a tetrahedral intermediate. The methoxy group is then eliminated and the resulting methoxide deprotonates the α-proton on the newly formed β-keto ester **104** to give the highly resonance-stabilized enolate **105**. Finally, acidic work-up neutralizes the enolate and any base still present to give the desired β-keto ester product **104**.



Scheme 47. Mechanism for the Claisen condensation.

The β-keto ester **99** successfully underwent decarboxylation when treated with TFA:CH_2Cl_2 (1:4) at r.t. for 2 h. Interestingly the 4-isoxazoline product **107** was not isolated but instead, after aqueous work-up and purification by flash chromatography , its hydrated form **106** was isolated as a mixture of diastereoisomers (d.r. 3:1) in 34% yield (Scheme 48). It was evident in the ^{1}H NMR spectrum that no starting material remained as the vinyl hydrogen (singlet at δ_H 4.58 ppm) at the *C*-4 position for 4-isoxazoline **99** was absent. In its place, two doublets (J = 13.0 and 14.0 Hz) for the major and the minor diastereoisomer at δ_H 2.82 ppm and 2.67 ppm were observed for one of the *C*-4 protons. The two other diastereotopic *C*-4 protons were found as a multiplet between δ_H 2.31 - 2.18 ppm. The ^{13}C NMR showed a fully substituted carbon centre at δ_C 108.1 ppm and 104.2 ppm for the minor and major diastereoisomer respectively (Figure 12). This was consistent with the carbon at the *C*-5 position reported for similar compounds in the literature.[66] After careful optimisation the yields were improved to 75% by treating the β-keto ester **99** with a weaker acid such as formic acid over 13 h at 30 °C (Scheme 48).



Scheme 48. Decarboxylation of β-keto ester **99** to form methyl ketone **106**; (a) HCO_2H, 30 °C, 13 h, 75% or TFA:CH_2Cl_2 (1:4), r.t., 2 h, 34%.

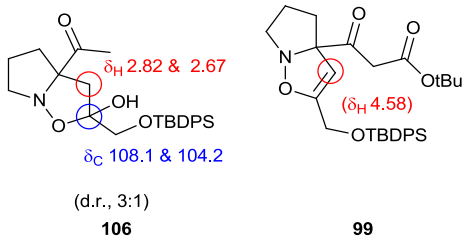
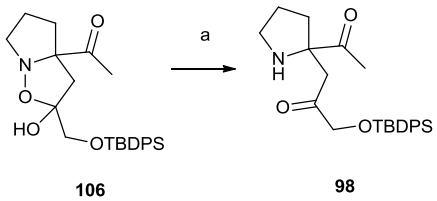


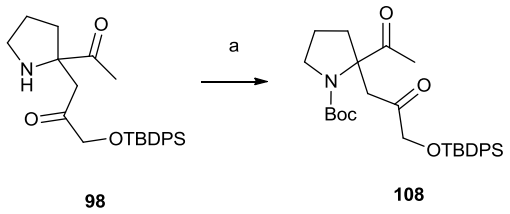
Figure 12. ^{1}H and ^{13}C NMR shifts in ppm for methyl ketone **106** and β-keto ester **99**.

The N-O bond of 5-hydroxyisoxazolidine **106** was cleaved to give the desired diketone **98** (Scheme 49). This was achieved by adding two portions of activated zinc powder (10 eq.) to a solution of the substrate in AcOH / H_2O (3:1).[67] The mixture was stirred at r.t. for 2 h before being quenched. After basic work-up and extraction the desired diketone **98** was isolated in quantitative yield. From the ^{13}C NMR spectrum of the product it was evident that there were two ketones present as two characteristic signals were found at δ_C 207.5 ppm (-CH_2-CO-) and 202.5 ppm (-CO-CH_3) respectively. The crude product was essentially clean from impurities and was taken to the next step without any further purification.



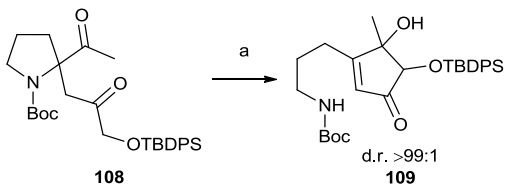
Scheme 49. N-O bond cleavage of 5-hydroxyisoxazolidine **106** to form diketone **98**; (a) Zn powder, AcOH / H_2O (3:1), r.t., 2 h, quant. yield.

The secondary amine was protected with a Boc-protecting group. This protecting group would be stable in basic conditions planned for the aldol condensation step and it would easily be removed thereafter using acidic conditions.[32] Following a procedure by Kibayashi et. al,[68] Boc_2O was added to the amine **98** in a biphasic solution of saturated Na_2CO_3 (aq.) and benzene at r.t. The mixture was stirred at r.t. for 18 h before work-up and purification by flash chromatography. The desired Boc-protected amine **108** was obtained in 62% yield (over 2 steps) (Scheme 50). The ^1H and ^{13}C NMR spectra were complicated by *N*-Boc rotamers at 298 K. This was confirmed by additional VT NMR experiments.



Scheme 50. Synthesis of Boc-protected amine **108**; (a) Boc_2O, benzene, saturated Na_2CO_3 (aq.), r.t., 18 h, 69% over 2 steps.

The diketone **108** was now to be converted to the β-substituted spirocyclic enone **73** by an intramolecular aldol condensation. Treating the diketone **108** with *t*BuOK at −30 °C unfortunately resulted in ring opening of the pyrrolidine ring and resulted in the formation of enone **109** which was isolated in 25% yield as one single diastereoisomer (Scheme 51). It was evident in the ^1H NMR spectrum that product **109** was formed. The ^1H NMR spectrum showed a singlet at δ_H 3.25 ppm for the α-hydrogen and a singlet at δ_H 1.01 ppm was observed for the methyl group (Figure 13).



Scheme 51. Treatment of diketone **108** with *t*BuOK yielded enone **109**; (a) *t*BuOK, THF, −30 °C to r.t., 1.5 h , 25%.

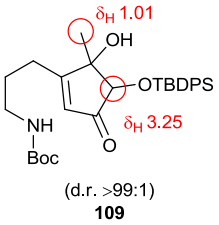
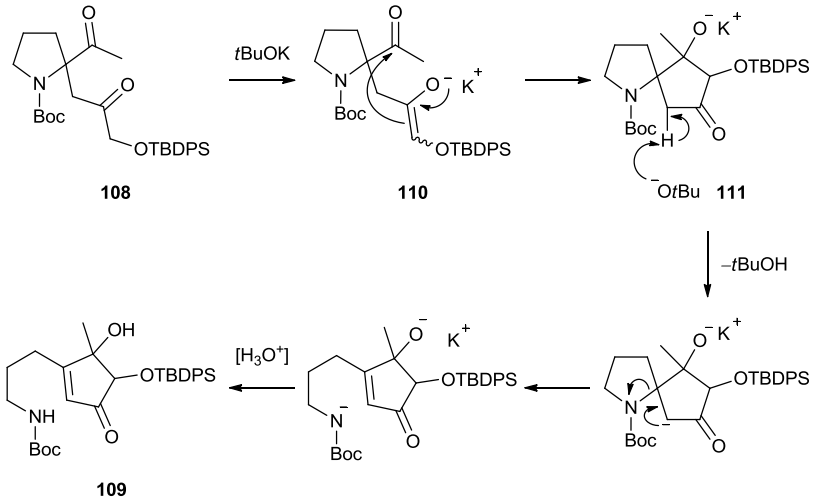


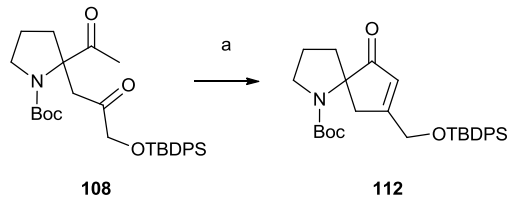
Figure 13. ^{1}H NMR shifts in ppm for enone **109**.

A plausible mechanistic explanation for this transformation is shown in Scheme 52. It was postulated that initial deprotonation of ketone **108** gives rise to ketone enolate **110**. This was followed by a nucleophilic addition to the neighbouring ketone to give the spirocyclic intermediate **111**. Ring opening then occurred by an E1cB-type mechanism via deprotonation of the α-proton of the ketone **111** and finally, aqueous work-up would yield the enone **109**.



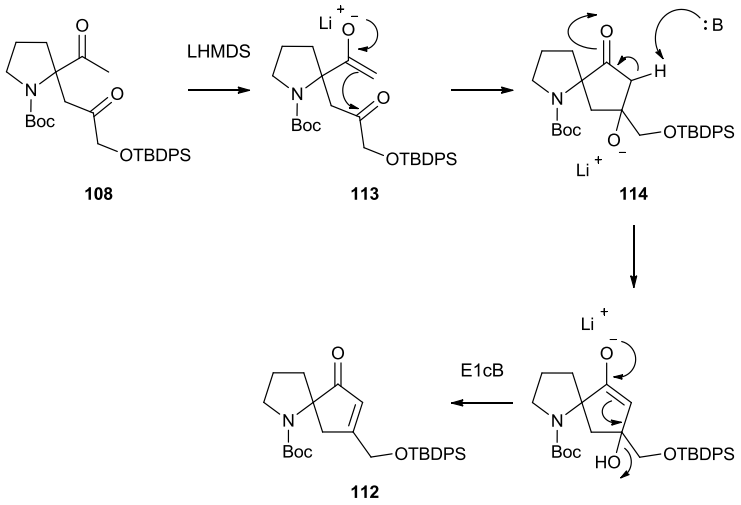
Scheme 52. Postulated mechanism for the formation of enone **109** from diketone **108**.

The formation of the enolate could be controlled by modifying the reaction conditions and by using another base. Slow, dropwise addition of a strong and bulky base such as LHMDS to the diketone **108** in THF at −78 °C followed by slowly warming the reaction mixture to r.t. over 8 h successfully gave the desired β-substituted spirocyclic enone **112** (Scheme 53). The desired product was isolated in modest 45% yield after purification by flash chromatography.



Scheme 53. Synthesis of β-substituted spirocyclic enone **112**; (a) LHMDS (3 eq.), THF, −78 °C to r.t., 8 h, 45%.

The mechanistic rationale is shown in Scheme 54 where the desired ketone enolate **113** formed rapidly and regioselectively, under kinetic control and subsequently underwent a nucleophilic addition to the neighbouring ketone to give a spirocyclic intermediate **114**. Deprotonation of the α-proton and subsequent dehydration, presumably following an E1cB mechanism, gave the desired β-substituted spirocyclic enone **112**.



Scheme 54. Mechanistic rationale for the formation of the desired β-substituted spirocyclic enone **112**.

The ^{1}H and ^{13}C NMR spectra of the β-substituted spirocyclic enone **112** were complicated by *N*-Boc rotamers at 298 K. This was further confirmed by additional VT NMR experiments. It was evident in the NMR spectra that the desired product **112** was formed. The ^{1}H NMR spectra showed two rotameric signals for the α-hydrogen on the enone, a multiplet at δ_H 6.44 - 6.41 ppm and a triplet (J = 2.0 Hz) at 6.36 ppm for the major and minor rotamer

respectively. The ^{13}C NMR spectra showed rotameric signals at δ_C 176.0, 175.7 ppm for the enone β-carbon and δ_C 126.2, 126.0 ppm for the enone α-carbon (Figure 14).

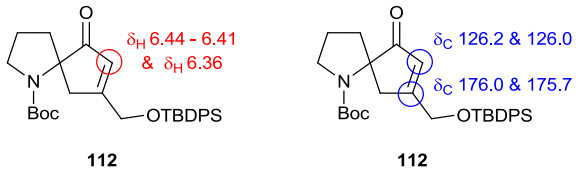
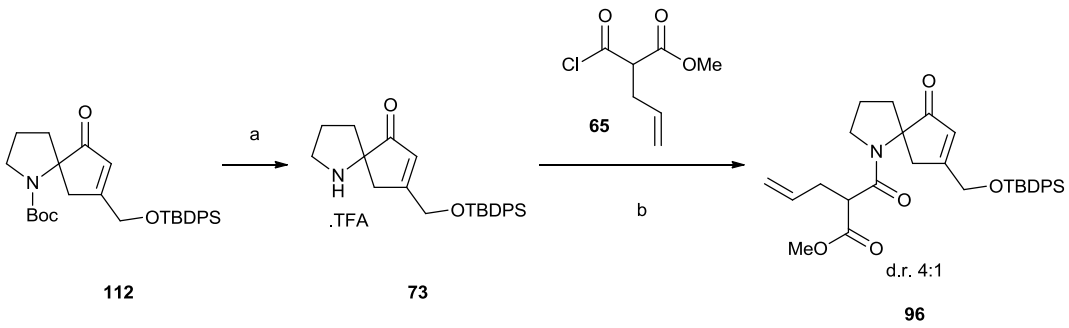


Figure 14. ^{1}H and ^{13}C NMR shifts in ppm for the β-substituted spirocyclic enone **112**.

3.4.2 Intramolecular Michael addition

3.4.2.1 Michael addition with a methyl ester derivative

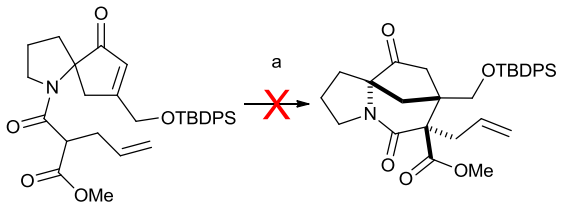
With the β-substituted spirocyclic enone **112** in hand, the intramolecular Michael addition step was now to be investigated. The Boc-protecting group was removed as previously mentioned by treating β-substituted spirocyclic enone **112** with TFA in CH_2Cl_2 (1:1) at r.t. for 1 h to afford the amine **73** as the TFA salt in quantitative yield (Scheme 55).



Scheme 55. Synthesis of the Michael addition precursor **96**; (a) TFA, CH_2Cl_2, r.t., 1 h; (b) Et_3N, **65**, CH_2Cl_2, 0 °C, 2 h, 51% over two steps.

The amine TFA salt **73** was not purified but used crude in the following amide bond forming step. Addition of acyl chloride **65**[37] to a solution of the crude amine salt **73** in dry CH_2Cl_2 containing Et_3N (2.2 eq.) at 0 °C gave the amide **96** as a mixture of separable diastereoisomers (d.r. 4:1) in 51% yield (Scheme 55). The acyl chloride **65**[37] would serve as a direct comparison with the successful Michael addition step validated in the previous chapter (Scheme 26). Based

on the previous result, the intramolecular Michael addition should proceed using this substrate. Unfortunately, when the Michael addition precursor **96** was treated with 1.1 eq. of KHMDS at 0 °C and then left to stir at r.t for 12 h, no reaction was observed (Scheme 56). Only starting material was recovered together with decomposition products. Same results were observed when other bases such as and LHMDS and BEMP were used under the same reaction conditions (Scheme 56).



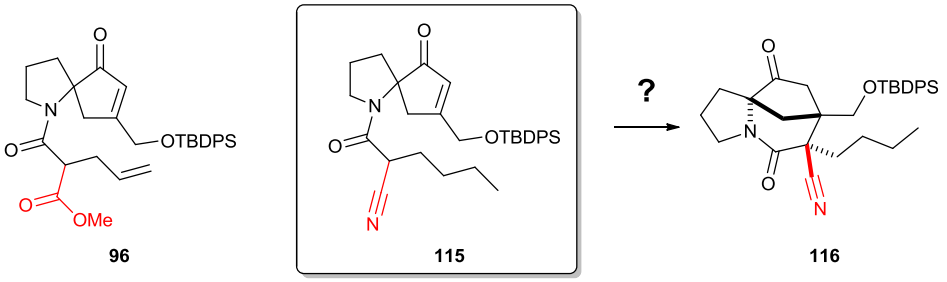
96 **97**

Scheme 56. The intramolecular Michael addition with the Michael addition precursor **96** proved to be unsuccessful; (a) KHMDS, LHMDS or BEMP, THF, 0 °C to r.t., 12 h.

It was assumed that the unreactivity was due to the nucleophilicity of the Michael addition precursor **96** and we believed that decomposition was due to undesired deprotonation of the starting material by the added base. We therefore decided to modify the pro-nucleophile.

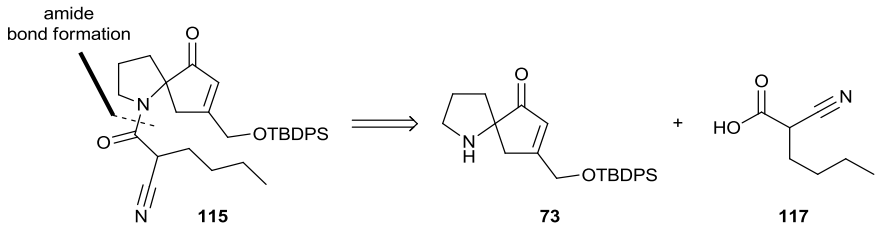
3.4.2.2 Michael addition with a nitrile derivative

As the intramolecular Michael addition reaction with the Michael addition precursor **96** led to decomposition products it was consequently decided that the pro-nucleophile would be changed from a methyl ester functional group to a nitrile functional group (Scheme 57). This would alter the acidity of the α-proton, making the pro-nucleophile more acidic. Deprotonation would therefore occur more readily and this would hopefully lead to an increase in nucleophilicity of the resulting nucleophile.



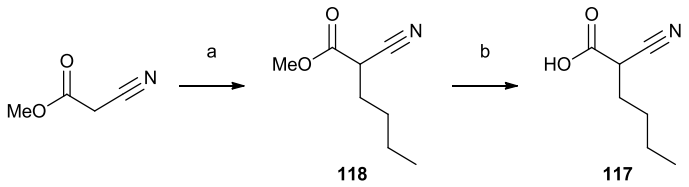
Scheme 57. Changing the pro-nucleophile on the Michael addition precursor from a methyl ester functional group **96** to a nitrile functional group **115**.

The Michael addition precursor **115** was to be synthesised in order to test this hypothesis. This was to be achieved by an amide coupling between the β-substituted spirocyclic enone **73** and the α-nitrile substituted carboxylic acid **117** (Scheme 58). This carboxylic acid was chosen as it would be easily synthesised from cheap and readily available starting materials and it would also serve to provide a good representative model of the real system. The nitrile functional group was to be removed later in the synthesis by hydrolysis to the carboxylic acid followed by decarboxylation.



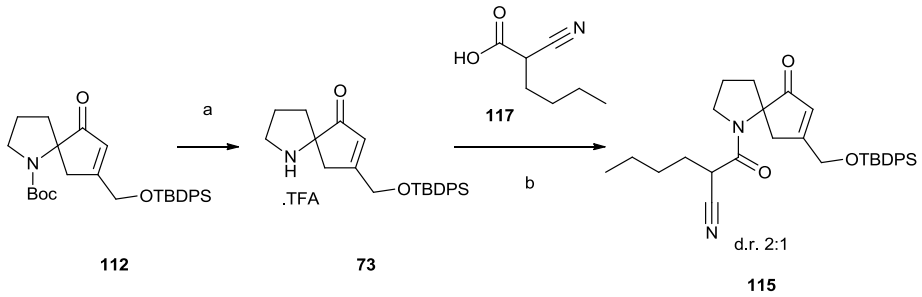
Scheme 58. Retrosynthetic analysis for the Michael addition precursor **115**.

The α-nitrile substituted carboxylic acid **117** was synthesised in two steps as shown in Scheme 59. First methyl cyanoacetate was alkylated with *n*-butyl bromide in benzene using DBU and the alkylated product **118** was isolated in 33% yield after purification by flash chromatography.[69] The ester was then hydrolysed to the acid using KOH in MeOH to give the desired α-nitrile substituted carboxylic acid **117** in 98% yield.



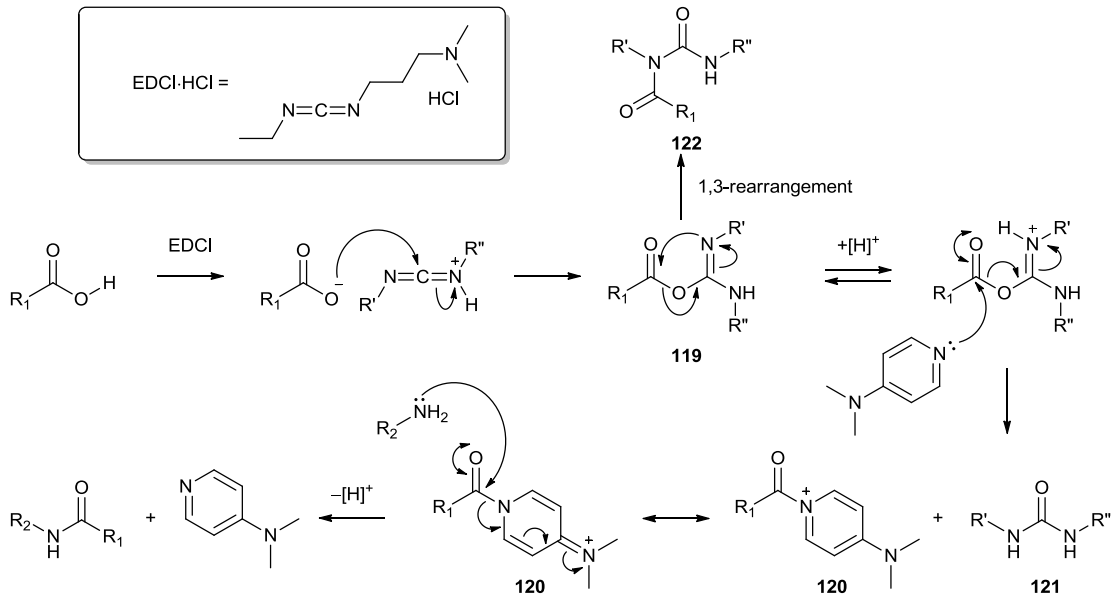
Scheme 59. Synthesis of the α-nitrile substituted carboxylic acid **117**; (a) *n*BuBr, DBU, benzene, r.t., 21 h, 33%; (b) KOH, MeOH, r.t., 3 h, 98%.

The carboxylic acid **117** was then coupled with the β-substituted spirocyclic enone **73** by using EDCI·HCl as coupling reagent together with a substoichiometric of DMAP (0.15 eq.) (Scheme 60).[70] The desired Michael addition precursor **115** was isolated as a mixture of separable diastereoisomers (d.r. 2:1) in 75% yield (2 steps) after purification by flash chromatography.



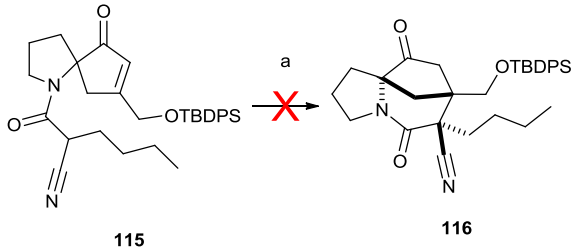
Scheme 60. Synthesis of the Michael addition precursor **115**; (a) TFA, CH_2Cl_2, r.t., 1 h; (b) Et_3N, **117**, EDCI·HCl, DMAP (0.15 eq.), CH_2Cl_2, r.t., 5 h 30 min, 75% over two steps.

The mechanism for the formation of the amide using EDCI·HCl in combination with DMAP is shown in Scheme 61.[70] The carboxylic acid initially reacts with EDCI to form *O*-acylisourea **119**. This intermediate reacts with DMAP to generate a reactive amide **120** and a urea by-product **121**. Finally, nucleophilic addition of an amine to the reactive amide **120** regenerates DMAP and yields the desired amide product. The driving force of the reaction is the formation of the urea by-product **121** which is water soluble and can be easily removed by aqueous work-up. DMAP acts as an acyl transfer reagent and helps to accelerate the reaction. Another role of DMAP is to prevent a common side reaction which is the formation of the unreactive *N*-acyl urea **122** by 1,3-rearrangement of the *O*-acylisourea **119** (Scheme 61).



Scheme 61. Mechanism for amide bond formation using EDCI·HCl as a coupling agent together with a catalytic amount of DMAP.

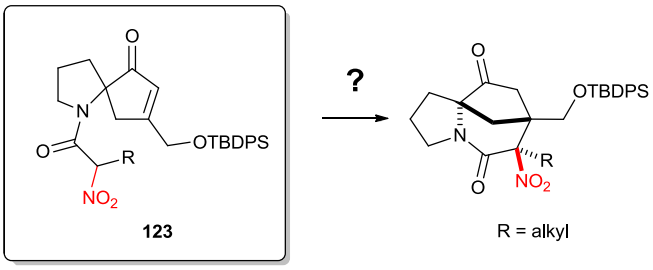
With the Michael addition precursor **115** in hand, its performance in the key intramolecular Michael addition was investigated. Unfortunately no product was observed when the substrate was treated with KHMDS (1.1 eq.) at 0 °C and then left to stir at r.t. for 22 h (Scheme 62). Only starting material was recovered together with decomposition products. Trying other bases such as LHMDS and BEMP using the same reaction conditions also failed to yield the desired product and only starting material was recovered together with decomposition products (Scheme 62). Treatment of a single diastereoisomer of the Michael addition precursor **115** with any of these three bases resulted in epimerization of the starting material, therefore demonstrating that deprotonation had occurred but without resulting in Michael addition.



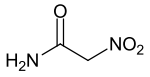
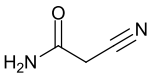
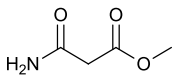
Scheme 62. The intramolecular Michael addition with the precursor **115** proved to be unsuccessful; (a) KHMDS, LHMDS or BEMP, THF, 0 °C to r.t., 22 h.

3.4.2.3 Michael addition with a nitro derivative

As the key intramolecular Michael addition reaction gave slow degradation of the starting material we thought that this could be due to undesired and ultimately destructive deprotonation of the β-substituted enone by the base. This could have led to the observed decomposition of the starting material. Based on this assumption we thought that we would again alter the acidity of the α-proton and adapt the pro-nucleophile to include a nitro functional group **123** (Scheme 63). Consequently this would make the nucleophile less basic than one containing a methyl ester or a nitrile functional group (Table 1). By having a less basic nucleophile we believed that possible deprotonation of the β-substituted enone would not occur and therefore would not give rise to any decomposition of the starting material. The nitro functional group could later be removed by radical denitration using Bu_3SnH and AIBN.[71]



Scheme 63. Changing the pro-nucleophile on the Michael addition precursor to a nitro functional group **123**.

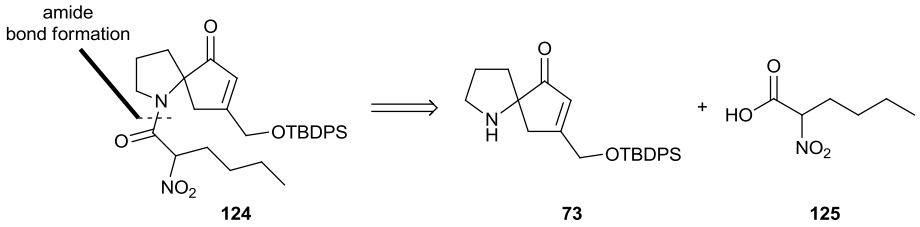
Structure	pK_a[72a, 72b]
	5.18 (in water, 25 °C)
	13.45 (in water, 20 °C)
	13.51±0.46 (25 °C)[a]

a) Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02

Table 1. pK_a values for nitro amide,[72a] nitrile amide[72b] and methyl malonate monoamide.

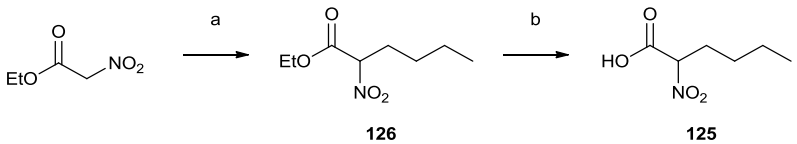
In order to investigate the key intramolecular Michael addition step with a nitro pro-nucleophile we needed to synthesise the Michael addition precursor **124**. We initially

planned to achieve this by an amide bond formation between the β-substituted spirocyclic enone **73** and the α-nitrocarboxylic acid **125** (Scheme 64).



Scheme 64. Synthesis of the Michael addition precursor **124** would be achieved by amide bond formation between the β-substituted spirocyclic enone **73** and the α-nitrocarboxylic acid **125**.

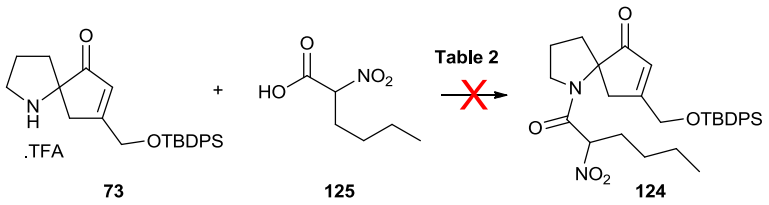
The α-nitrocarboxylic acid **125** was synthesised in two steps from ethyl nitroacetate (Scheme 65). The first alkylation step was carried out under phase transfer conditions using an aqueous solution of TBAH and *n*-butyl iodide in CH_2Cl_2 at r.t.[73] This gave the desired nitro ester **126** in 35% yield after purification by flash chromatography. The ethyl ester **126** was then hydrolysed under basic conditions to give the α-nitrocarboxylic acid **125** in 77% yield using $LiOH.H_2O$ in MeOH / THF at r.t. The desired product was found to be very unstable as it readily underwent decarboxylation to give 1-nitropentane. During work-up, the residual solvent had to be carefully evaporated *in vacuo* under cold conditions to prevent the product from decomposing. Leaving the α-nitrocarboxylic acid **125** in a vial for a few days at r.t. also resulted in decarboxylation into 1-nitropentene. It was therefore necessary to store the product in a freezer to prevent any decomposition.



Scheme 65. Synthesis of the α-nitrocarboxylic acid **125**; (a) *n*BuI, TBAH (40% in H_2O), CH_2Cl_2, r.t., 48 h, 35%; (b) LiOH (aq.), THF, MeOH, r.t., 2 h, 77%.

Having successfully devised a synthesis of the α-nitrocarboxylic acid **125**, the attention now turned to synthesise the Michael addition precursor **124** by an amide coupling with the β-substituted spirocyclic enone **73**. This, unfortunately, proved to be very difficult. Screening

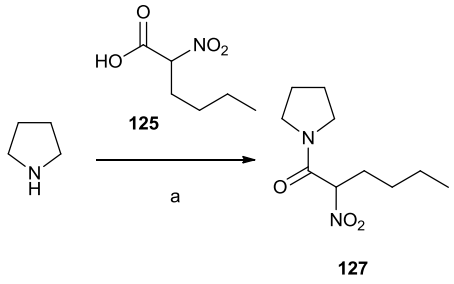
of various coupling conditions failed to give the desired Michael addition precursor **124** (Table 2). Interestingly, when pyrrolidine was used as a representative model nucleophile in the amide bond formation step, the amide product **127** was isolated in 44% yield when DCC was used together with HOBt (Scheme 66). Unfortunately using these conditions with the more hindered spirocyclic amine **73** gave only a trace of the desired Michael addition precursor **124** (Table 2, Entry 4).



73 **125** **124**

Entry	Coupling reagent	Base	Solvent	Result
1	DCC (1.2 eq.), DMAP (0.1 e.q.)	Et_3N (3 eq.)	CH_2Cl_2	No Product
2	HBTU (1.5 eq.)	—	CH_2Cl_2	No Product
3	EDCI·HCl (1.2 eq.), HOBt (1.9 e.q.)	Et_3N (3 eq.)	CH_2Cl_2	No Product
4	DCC (1.2 eq.), HOBt (1.9 e.q.)	Et_3N (3 eq.)	CH_2Cl_2	Trace

Table 2. Screening of various coupling conditions for the amide bond formation between the β-substituted spirocyclic enone **73** and the α-nitrocarboxylic acid **125**.

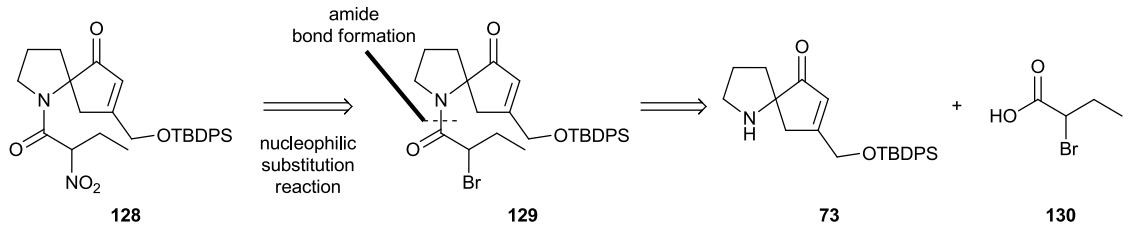


127

Scheme 66. Amide bond formation between pyrrolidine and the α-nitrocarboxylic acid **125**; (a) DCC, HOBt, **125**, CH_2Cl_2, 0 °C, 5 h, 44%.

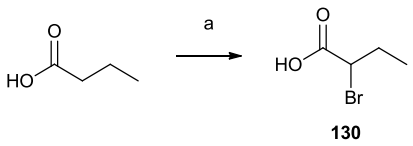
The difficulty with the amide bond formation step was believed to be due to the instability of the α-nitrocarboxylic acid **125** and therefore it was decided to introduce the nitro functional group after the amide coupling step. This would be achieved by amide coupling between β-substituted spirocyclic enone **73** and the α-bromocarboxylic acid **130** followed by a nucleophilic substitution (S_N2) reaction to furnish the desired Michael addition precursor **128**

(Scheme 67). The α-bromocarboxylic acid **130** was chosen as it would be easily synthesised from cheap and readily available starting materials and it would also serve to provide a good representative model of the real system.



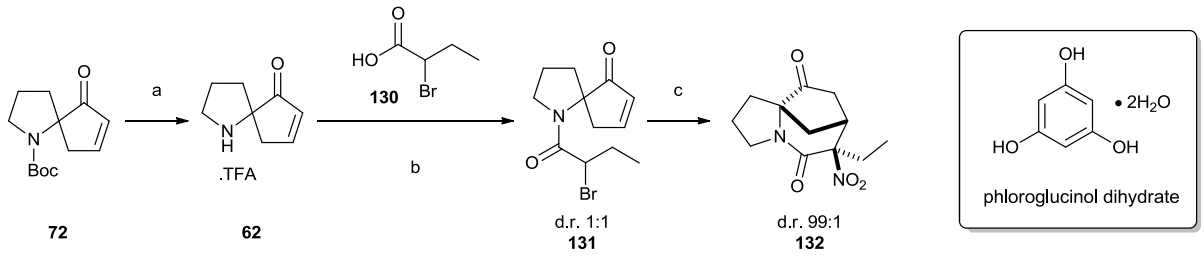
Scheme 67. Retrosynthesis of the Michael addition precursor **128**.

The α-bromocarboxylic acid **130** was synthesised by α-bromination of butyric acid following a procedure developed by Dolbier *et al.* (Scheme 68).[74] The butyric acid was heated together with 1.5 eq. of NBS to 85 °C for 18 h in a solution of TFA and conc. H_2SO_4. The resulting α-bromocarboxylic acid **130** was isolated in 68% yield after purification by distillation.



Scheme 68. α-Bromination of butyric acid to give the α-bromocarboxylic acid **130**. (a) NBS, TFA, conc. H_2SO_4, 85 °C, 18 h, 68%.

The α-bromocarboxylic acid **130** was first coupled with the spirocyclic enone **62** in order to investigate the amide bond formation step without having to use any of our valuable β-substituted spirocyclic enone **73**. When EDCI·HCl was used as a coupling reagent, the desired α-bromoamide **131** was isolated as a mixture of separable diastereoisomers (d.r. 1:1) in 46% yield (2 steps) after purification by flash chromatography (Scheme 69). Interestingly when the α-bromoamide **131** was subjected to treatment of $NaNO_2$ and phloroglucinol dihydrate in DMSO for 26 h at r.t. the tricyclic product **132** was isolated as a single diastereoisomer in 45% yield (Scheme 69).[75b]



Scheme 69. Synthesis of the tricyclic product **132**; (a) TFA, CH_2Cl_2, r.t., 1 h; (b) EDCI·HCl, Et_3N, CH_2Cl_2, 0 °C then r.t., 19 h, 46% over two steps; (c) $NaNO_2$, phloroglucinol dihydrate, DMSO, r.t., 26 h, 45%.

The stereochemical configuration of the tricyclic product **132** was assigned by NOE experiments and it was found to have the nitro group on the *exo* face (Figure 15). We suggested that the substitution/Michael addition cascade was feasible due the basicity of the nitrite in the reaction mixture although further experiments need to be carried out in order to fully identify the reaction mechanism. It was possible that the excess of nitrite present was sufficient for the deprotonation of the α-nitroamide product and as a result Michael addition occurred to yield the tricyclic product **132**.

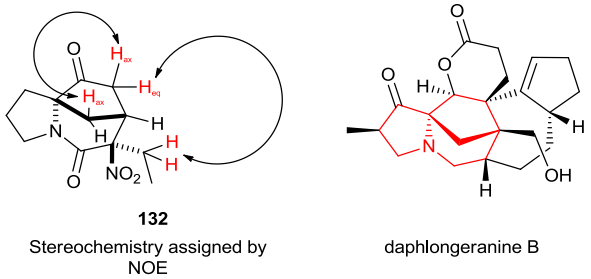
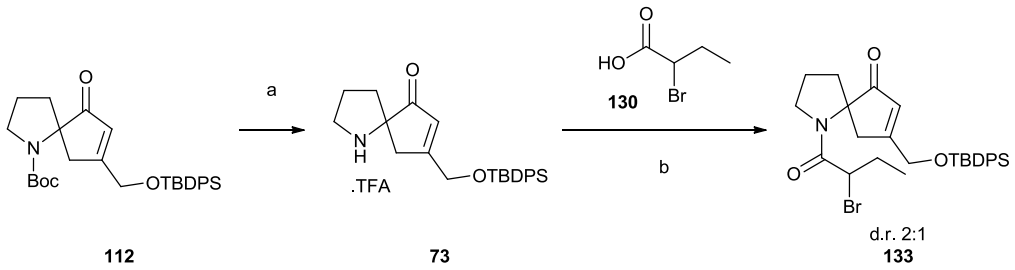


Figure 15. The stereochemical configuration of the tricyclic product **132** was assigned by NOE correlation.

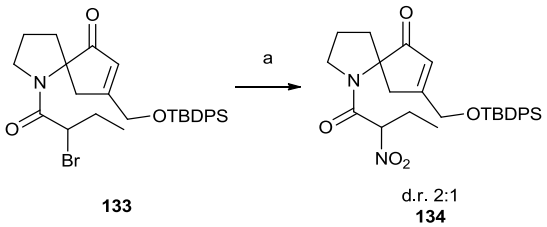
Based on this encouraging result the α-bromocarboxylic acid **130** was coupled with the β-substituted spirocyclic enone **73**. By again using EDCI·HCl as coupling reagent, the desired α-bromoamide **133** product was isolated as a mixture of separable diastereoisomers (d.r. 2:1) in 74% yield (2 steps) after purification by flash chromatography (Scheme 70).



112 73 133

Scheme 70. Synthesis of the α-bromoamide **133** by amide bond formation; (a) TFA, CH_2Cl_2, r.t., 1 h; (b) Et_3N, **130**, EDCI·HCl, CH_2Cl_2, 0 °C then r.t., 20 h, 74% over two steps.

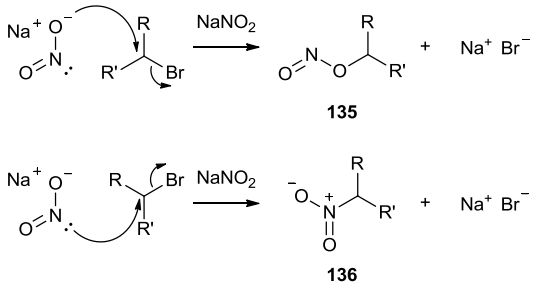
Treating the diastereomeric mixture of α-bromoamide **133** with $NaNO_2$ and phloroglucinol dihydrate in DMSO for 5 h at r.t. gave the desired Michael addition precursor **134** as a mixture of diastereoisomers (d.r. 2:1) in 35% yield after purification by flash chromatography (Scheme 71). It was evident that nucleophilic substitution of bromine by nitrite had occurred to yield the desired Michael addition precursor **134** and not the nitrite ester by observing the IR spectrum of the product. The IR spectrum showed two absorption bands at 1640 cm^{-1} and 1352 cm^{-1} which were characteristic of nitro compounds.[76a, b.]



133 134

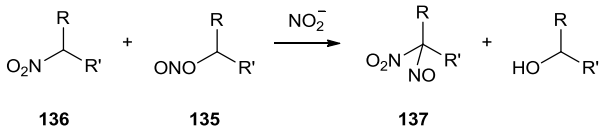
Scheme 71. Nucleophilic substitution of α-bromoamide **133** gave the desired Michael addition precursor **134**; (a) $NaNO_2$, phloroglucinol dihydrate, DMSO, r.t., 5 h, 35%.

The nucleophilic substitution reaction of the α-bromoamide **133** with $NaNO_2$ required a polar solvent such as DMSO in order to fully dissolve both the reactant and $NaNO_2$. Due to the nitrite ion being an ambident nucleophile by having more than one heteroatom carrying a lone pair of electrons, nucleophilic attack could occur either through the oxygen atom to give the undesired nitrite ester **135** or through the nitrogen lone pair to give the desired nitroalkane **136** (Scheme 72).



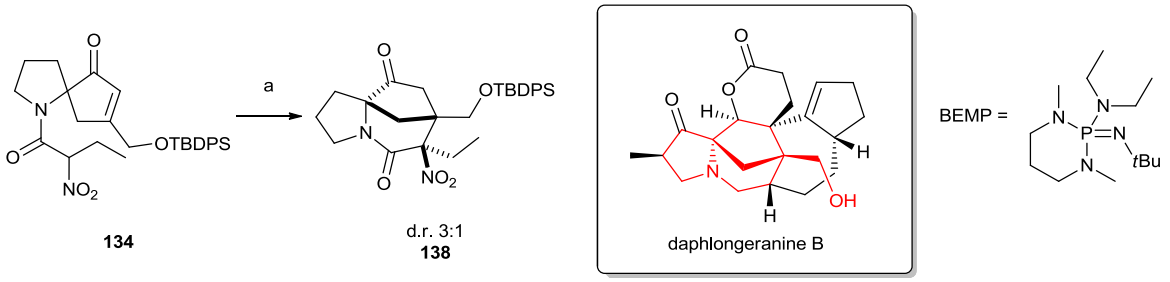
Scheme 72. Nitrite ion is an ambident nucleophile that can react through the oxygen to give nitrites or through the nitrogen to give nitroalkanes.

Kornblum *et al.* found that the reaction time was important in order to prevent any side reactions. It has been found that the nitroalkane product **136** can react with a nitrite anion and the nitrite ester by-product **135** to give pseudonitrole **137** (Scheme 73).[75a] As the reaction of $NaNO_2$ with alkyl halides was found to be faster than the competing side reaction, rapid work-up on the completion of the reaction was essential for obtaining good yields. The importance of the side reaction becomes much more significant if the rate of the reaction is slow, such as when secondary bromides are employed. Therefore a nitrite ester scavenger such as phloroglucinol was added to prevent the side reaction to give pseudonitrole **137**.[75a, b.]



Scheme 73. A common side reaction for the nucleophilic substitution of nitroalkanes by nitrites leading to degradation of the desired nitro alkane product **136** to pseudonitrole **137**.

It was worth noting that no Michael addition occurred when the α-bromoamide **133** was treated with $NaNO_2$. The Michael addition precursor **134** was therefore subjected to a stock solution of BEMP (20 mol%) in CH_2Cl_2 for 12 h at r.t. Pleasingly this facilitated the intramolecular Michael addition to give the desired tricyclic core **138** of daphlongeranine B. The product was isolated as a mixture of separable diastereoisomers (d.r. 3:1) in 80% yield after purification by flash chromatography (Scheme 74).



Scheme 74. Synthesis of tricyclic core **138** of daphlongeranine B; (a) BEMP (20 mol%), CH_2Cl_2, r.t., 12 h, 80%.

It was evident from the ^{1}H and ^{13}C NMR spectra that the key intramolecular Michael addition had occurred to give the desired tricycle **138**. The chemical shifts for the vinyl hydrogen on the spirocyclic enone were absent in the ^{1}H NMR spectrum (δ_H 6.43 & 6.41 ppm, app. t, J = 1.5 Hz) and in its place a doublet was observed for the -CO-C$\underline{H}_{ax}$- at δ_H 2.82 ppm with a geminal coupling constant at J = 19.5 Hz. The ^{13}C NMR spectrum showed two newly formed fully substituted carbon centres at δ_C 98.5 ppm and 47.8 ppm for the -$\underline{C}_{quat.}$-NO_2 and -$\underline{C}_{quat.}$-CH_2-O- respectively (Figure 16).

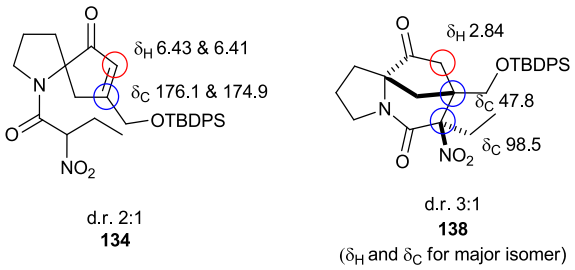


Figure 16. ^{1}H and ^{13}C NMR shifts in ppm for the Michael addition precursor **134** and the tricycle **138**.

The stereochemistry of the tricycle **138** was assigned by NOESY (Figure 17) experiments and the major isomer was found to have the nitro group on the *exo* face of the tricyclic spiro system. This was the desired stereochemical configuration for our synthesis as daphlongeranine B has the alkyl chain with the cyclopentene ring, for which the alkyl chain is a model of, on the *endo* face of the tricyclic spiro system (Figure 17). The opposite diastereoisomer product was

observed as compared to the intramolecular Michael addition with the unsubstituted enone **63** (see Chapter 2, Scheme 26).

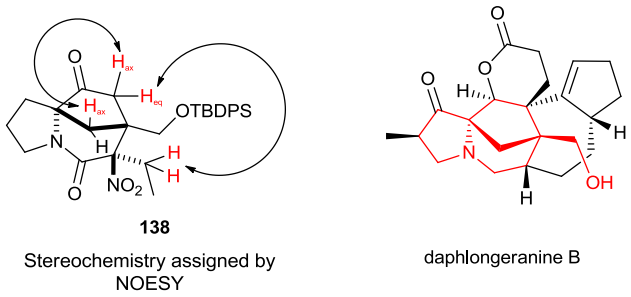
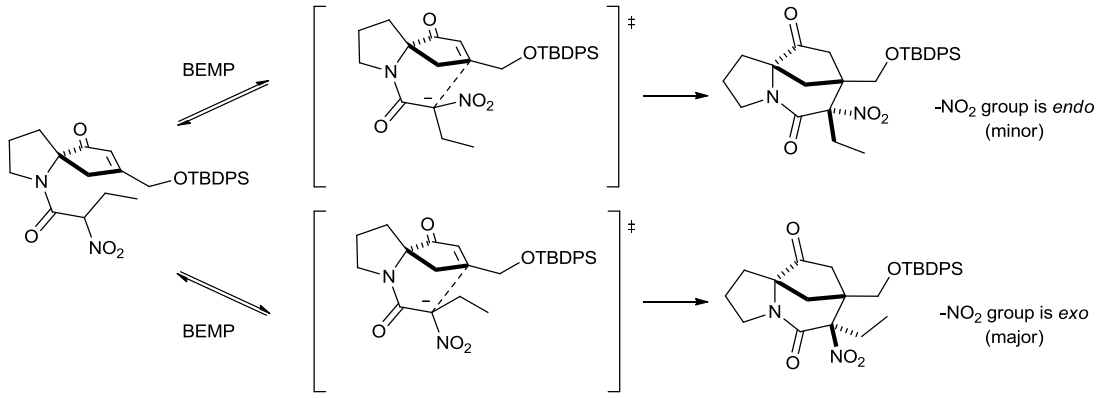


Figure 17. Assignment of the stereochemistry for the major isomer by NOESY correlation for the tricyclic core **138** of daphlongeranine B (see Appendix 7.2).

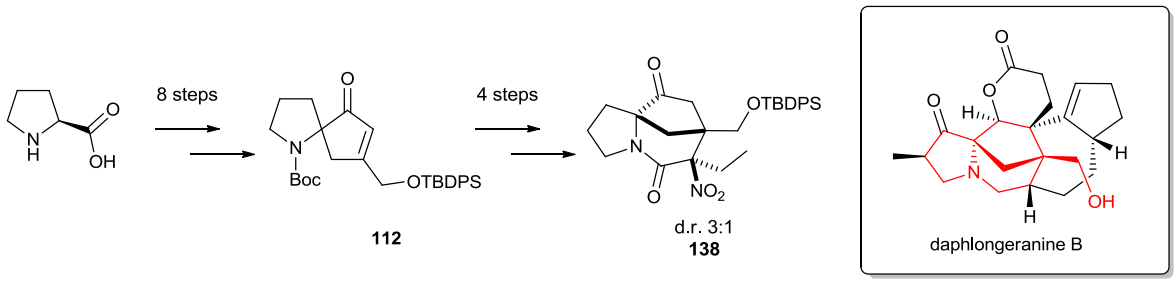
We believe that the variation in diastereoselectivity could be due to the change of pro-nucleophile from an ester functional group to a nitro functional group as well as the change of base from KHMDS to BEMP. BEMP is a strong non-ionic and non-metallic, organic superbase, in contrast to KHMDS which is a strong ionic and metallic base. It is probable that when BEMP is used any stereocontrol through ion chelation is lost in comparison to KHMDS. We postulate that the intramolecular Michael addition occurs by nucleophilic attack from the *Si* face of the cyclopentanone ring. Proposed transition states are shown in Scheme 75. It is difficult to explain the cause of the diastereocontrol when using BEMP as a base without carrying out further experiments. However we were very pleased to find that the key intramolecular Michael addition was successful with the β-substituted spirocyclic enone **73** and this has consequently further validated our synthetic route towards daphlongeranine B. We now have demonstrated that by this key step we can synthesise the unique tricyclic core **138** of daphlongeranine B, containing three fully substituted carbon centres.



Scheme 75. Proposed transition state models for the intramolecular Michael addition.

3.5 Conclusions

To summarise, the scope for the key intramolecular Michael addition step has successfully been expanded. At first a synthetic route over 8 steps was developed for the β-substituted spirocyclic enone **112** starting from the commercial and natural amino acid L-proline. The synthesis involved 3 key steps; cycloaddition, N-O bond cleavage and an intramolecular aldol condensation. This β-substituted spirocyclic enone **112** was a fundamental building block needed for the investigation of the key intramolecular Michael addition. This key step was subsequently confirmed using the β-substituted spirocyclic enone **112** to give the unique tricyclic core **138** of daphlongeranine B in 12 overall steps (Scheme 76).



Scheme 76. The tricyclic core **138** of daphlongeranine B was accessed in 12 steps from the natural amino acid L-proline.

These investigations showed that intramolecular Michael addition onto the β-substituted spirocyclic enone **112** would occur by using an α-nitro amide nucleophile. Employing this key

step would successfully furnish three fully substituted carbon centres as well as introducing the primary alcohol functional group found in daphlongeranine B. Our synthetic approach towards the synthesis of daphlongeranine B was further strengthened by confirming the key intramolecular Michael addition step with the β-substituted spirocyclic enone **112**.

4 CHAPTER 4

4.1 Introduction

We have now validated the basis of utilizing an intramolecular Michael addition reaction as the key step for the synthesis of the tricyclic core of daphongeranine B. To rapidly confirm this synthetic strategy we have synthesised two spirocyclic fragments **62** and **73**. These two spirocyclic fragments served as appropriate models for the advanced spirocyclic intermediate **139** (Figure 18). However to complete our synthesis of daphongeranine B a viable synthetic route to the key spirocyclic intermediate **139** or a close derivative, needed to be developed. In comparison to **73** we need to create the fully substituted carbon centre with stereocontrol as well as introduce the ketone functional group and the 3*R*-methyl group into the pyrrolidine ring of the spirocyclic scaffold (Figure 18).

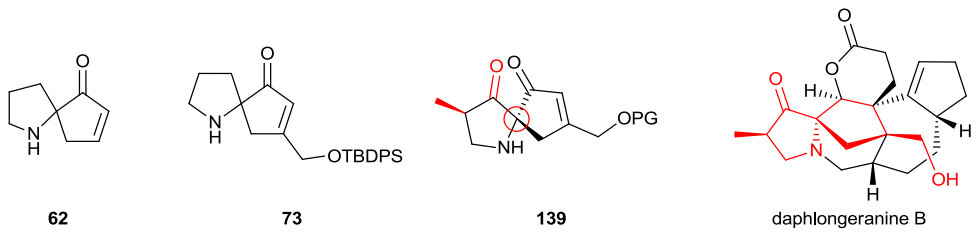


Figure 18. The two spirocyclic fragments **62** and **73** served as appropriate models of the advanced spirocyclic intermediate **139**.

4.2 Aims of the chapter

The aim of this chapter was to investigate and develop a synthetic approach to create the fully substituted carbon centre with stereocontrol as well as introduce a masked ketone functional group into the spirocyclic scaffold. We selected the spirocyclic fragment **140** as an appropriate model target (Figure 19). If this aim could be met then a possible synthetic route towards the advanced spirocyclic intermediate **139** would be established.

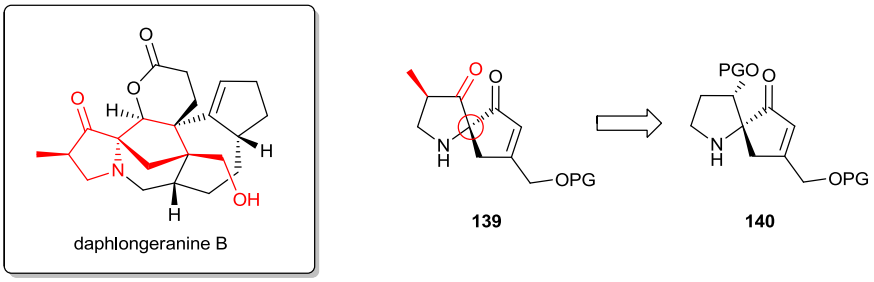
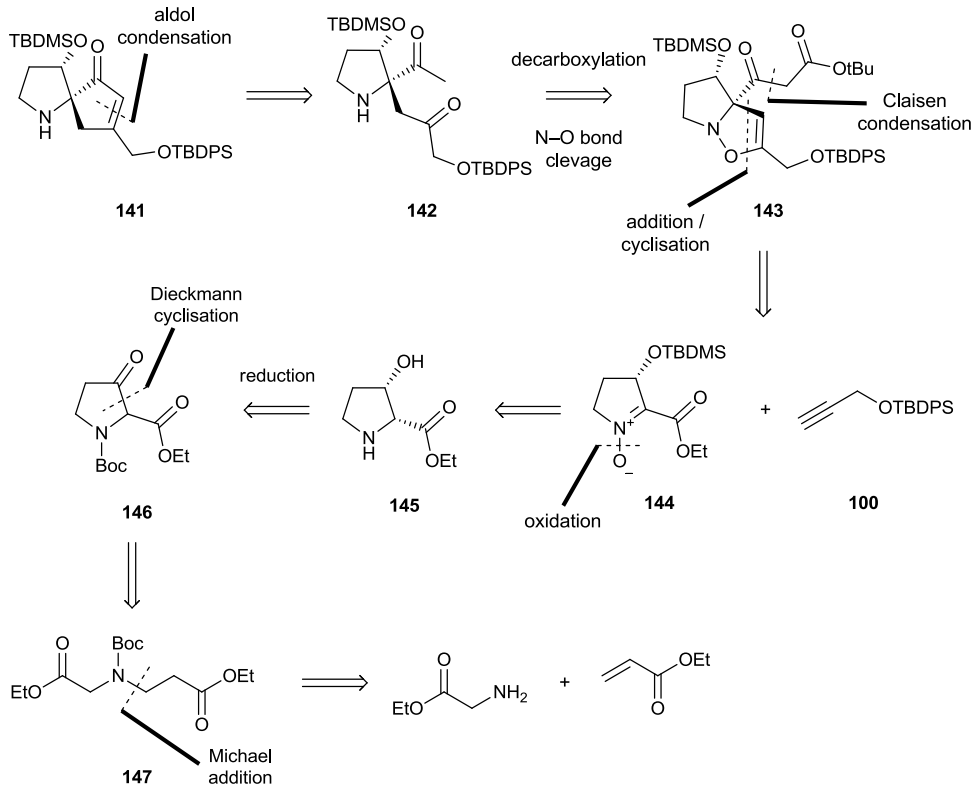


Figure 19. The spirocyclic fragment **140** would serve as a model target for the advanced spirocyclic intermediate **139**.

4.3 Synthetic plan and retrosynthetic analysis

We chose the spirocyclic fragment **140** as our synthetic target as this would allow us to rapidly investigate and validate our synthetic strategy. We decided to have the ketone functional group masked as a protected alcohol. This would serve three purposes: first it would prevent the adjacent stereocentre from epimerisation when using strong bases in the synthesis. Secondly it would avoid any nucleophilic additions to the carbonyl group and lastly the protected chiral alcohol could be used to influence the creation of the fully substituted carbon centre with stereocontrol. At the later stages of the synthesis the alcohol would be deprotected and oxidised to furnish the ketone present in daphlongeranine B. Due to the time constraints we decided to omit the stereogenic methyl group in this model synthesis. We believed that incorporating the methyl group would not give any significant advantage other than adding to the synthetic challenge (Figure 19). We chose to protect the secondary alcohol of **140** with a TBDMS protecting group and the primary alcohol with a TBDPS protecting group. These protecting groups would tolerate both acidic and basic reaction conditions. TBDMS can be removed selectively in the presence of the TBDPS protecting group. This would be important later in the synthesis when the alcohol functional group would be oxidised to the corresponding ketone. The bulkier TBDPS protecting group would be robust to all the subsequent reactions, yet it can be removed selectively at the end of the synthesis with an appropriate fluoride source.[32]

Our retrosynthetic analysis of spirocyclic fragment **141** was similar to that of the β-substituted spirocyclic enone **73** (Scheme 42). An intramolecular aldol condensation of diketone **142** would give the spirocyclic enone **141** and the diketone **142** would be formed by a decarboxylation followed by N-O bond cleavage of the 4-isoxazoline **143**. A Claisen condensation would furnish the β-keto ester and the fully substituted carbon centre would be introduced with stereocontrol by a key addition/cyclisation reaction between alkyne **100** and nitrone **144**. The nitrone **144** would be derived from the corresponding β-hydroxy ester **145** by oxidation which in turn would originate from the β-keto ester **146** by an asymmetric reduction of the ketone. A Dieckmann type condensation of the diester **147** would furnish the β-keto ester **146** and the diester **147** would be accessed by a Michael addition between glycine methyl ester and ethyl acrylate (Scheme 77). To investigate the key addition/cyclisation reaction between alkyne **100** and nitrone **144** we first needed do synthesise the nitrone **144** bearing the TBDMS protected alcohol functional group.



Scheme 77. Retrosynthetic analysis of the model spirocyclic fragment **141**.

4.3.1 Baker's yeast reduction of ketones

$LiAlH_4$ and $NaBH_4$ are very common and effective reducing agents and treatment of various carbonyl compounds with either agent will reduce the carbonyl group to yield an alcohol. In the case of ketones, secondary alcohols are produced. However, with prochiral ketones, these reducing agents do not react to form a single enantiomer because the hydride attacks either side of the planar carbonyl group at equal rates, yielding a 50:50 mixture of the two enantiomers.[54] In order to achieve a single enantiomer, a chiral reducing agent can be used. One of the most efficient chiral reducing agents can be found in nature. For example enzymes resulting from the fermentation of Baker's yeast (*Saccharomyces cerevisiae*) act as an enzymatic reducing agent and can introduce chirality to a molecule.[77] Reactions involving these organisms are advantageous since they occur at ambient temperature and pressure. Baker's yeast is readily available and inexpensive and for these reasons, this type of biocatalyst has been widely used as a chiral reducing agent.[77, 78.] The enzymes provided by the Baker's yeast do not provide the hydride donor for the reduction. These are instead provided by a coenzyme such as NADH or NADPH. The enzyme and coenzyme work together to catalyze the reaction. For example, the reduction with NAD(P)H proceeds as follows:

(1) Coenzyme and substrate bind to an enzyme.

(2) The substrate is reduced, while the coenzyme is oxidized.

(3) The coenzyme and product dissociate from the enzyme.

There are four different stereochemical patterns for transfer of a hydride from coenzyme, NAD(P)H, to the substrate. The hydride attacks either the *Si* face or the *Re* face of the carbonyl group depending on the orientation of the bound substrate to the enzyme which results in the formation of (*R*) and (*S*)-alcohols, respectively. On the other hand, the enzyme transfers either the *pro-R* hydride or the *pro-S* hydride of the coenzyme depending on the kind of enzyme (Figure 20).[77]

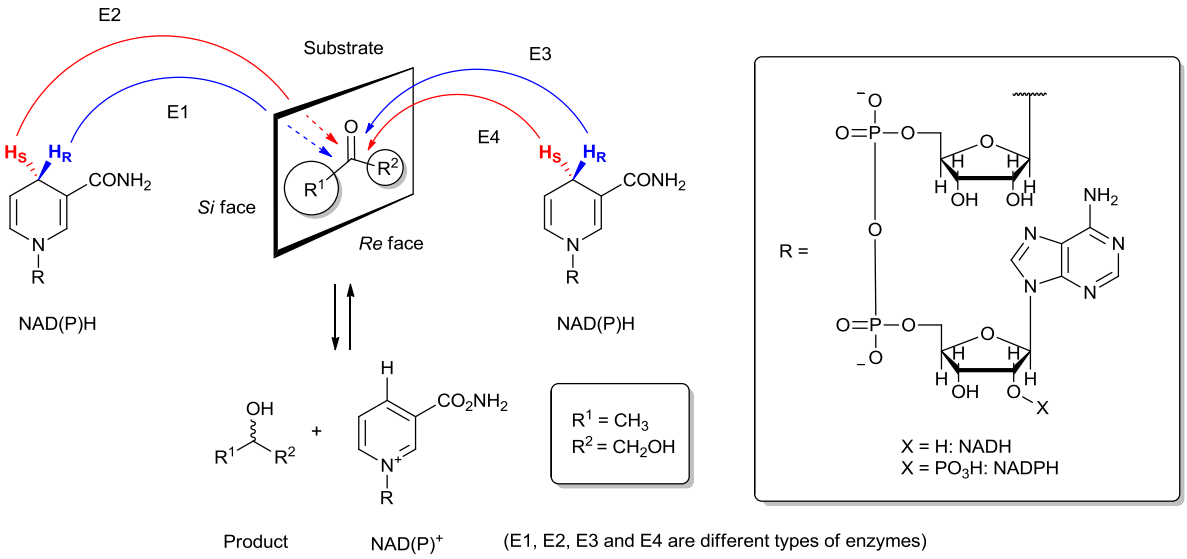
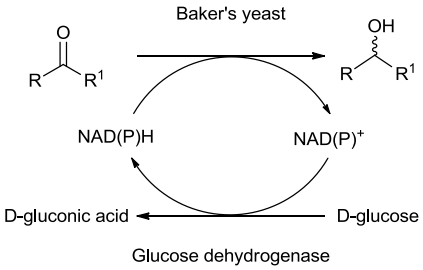


Figure 20. Hydride transfer from coenzyme NAD(P)H to a prochiral carbonyl compound.

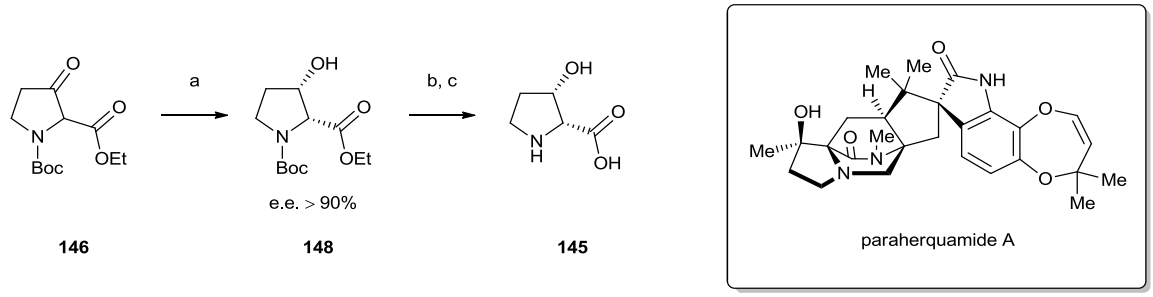
After the hydride has been transferred to the carbonyl carbon, the oxidised form of the coenzyme $NAD(P)^+$, can be transformed back to the reduced form, NAD(P)H. A hydrogen source is therefore necessary to perform this reduction reaction and sugars such as glucose are often added to the reaction mixture for this purpose. In the process, glucose is oxidised to D-gluconic acid by another enzyme present in the Baker's yeast called glucose dehydrogenase (Scheme 78).[77]



Scheme 78. Regeneration of coenzyme NAD(P)H by addition of D-glucose.

Knight *et al.* reported an asymmetric reduction using Baker's yeast as a chiral reducing agent.[79a, b.] They treated β-ketoester **146** with dried Baker's yeast and sucrose in tap water for 24 h at 30 °C to isolate the corresponding β-hydroxyester **148** as a single diastereoisomer in 75% yield (Scheme 79). ^{1}H and ^{19}F NMR spectra of the derived Mosher's ester indicated an

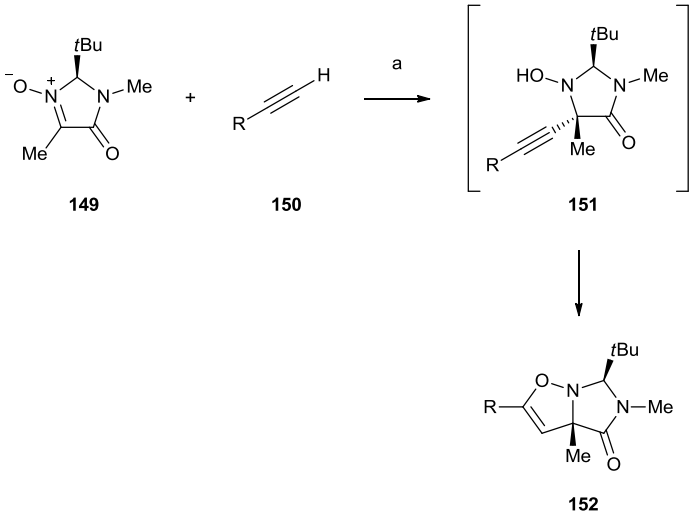
e.e. of ~90% although they reported that these spectra were complicated by rotamers at r.t. They then converted the β-hydroxyester **148** to the corresponding 3-hydroxyproline **145** by first removing the *N*-Boc protecting group then hydrolysing the ester group with KOH (Scheme 79). The ^{1}H NMR spectrum of 3-hydroxyproline **145** showed the $J_{2,3}$ = 4.0 Hz which was consistent with the *cis* stereochemistry shown.[79a, b.] Williams *et al.* showed that this reaction was easily scalable up to 30 g and the resulting β-hydroxyester **148** was then used as an important building block for the first total synthesis of paraherquamide A,[80] a natural product with anthelmintic properties isolated from cultures of *Penicillium paraherquei*.[81, 82.]



Scheme 79. Asymmetric reduction of β-ketoester **146** using Baker's yeast; (a) Dried Baker's yeast, water, commercial table sugar, 30 °C, 24 h, 75%; (b) TFA, CH_2Cl_2, r.t., 2 h; (c) KOH, MeOH, H_2O, r.t., 16 h, 70% over 2 steps.

4.3.2 Addition/cyclisation utilising alkynylzinc

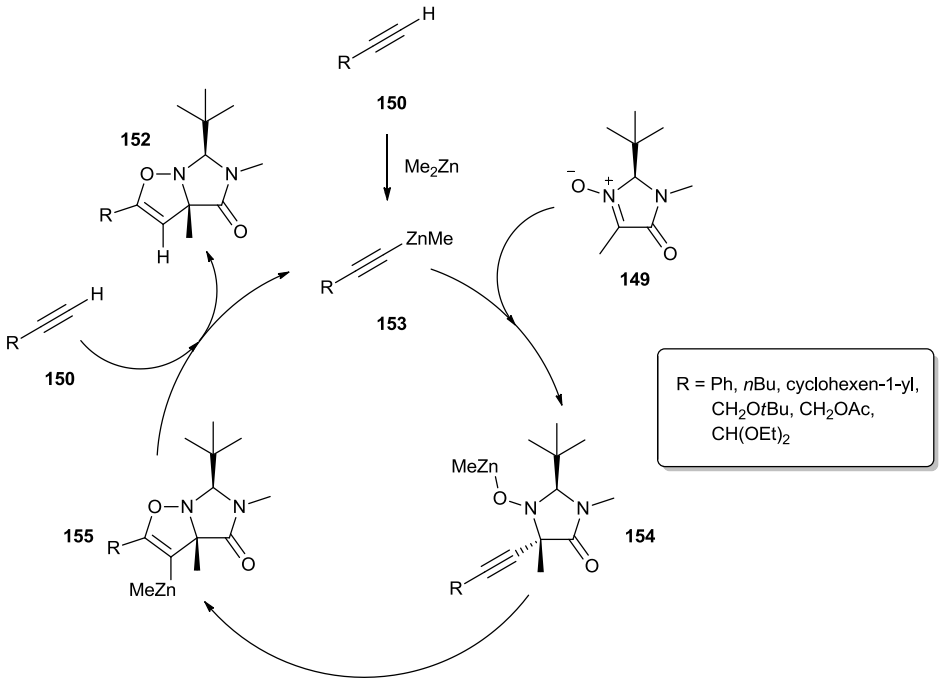
Chavant and co-workers have reported a tandem addition/cyclisation process between the chiral cyclic nitrone **149** and various alkynes **150**.[83] They found that when nitrone **149** and alkyne **150** was treated with Me_2Zn (1.3 eq.) in toluene at 20 °C for 18 h followed by quenching with sat. NH_4Cl (aq.) high yields of the bicyclic 4-isoxazolines **152** were obtained (Scheme 80). The products were isolated as single diastereoisomers and the relative configuration of the newly produced fully substituted stereocenter was assigned by NOE experiments.



Entry	R	Yield
1	Ph	92%
2	*n*Bu	60%
3	cyclohexen-1-yl	94%
4	CH_2O*t*Bu	90%
5	CH_2OAc	76%
6	$CH(OEt)_2$	78%

Scheme 80. Tandem addition/cyclisation reaction between the chiral cyclic nitrone **149** and various alkynes **150** to give bicyclic 4-isoxazolines **152**; (a) Me_2Zn (1.3 eq.), toluene, 20 °C, 18 h, then sat. NH_4Cl (aq), 20 °C, 30 min.

Although the product regioselectivity of the reaction was identical to that of a 1,3-dipolar cycloaddition reaction, it was found that the reaction followed a two-step pathway. This was demonstrated by the authors via TLC analysis of hydrolysed aliquots of the reaction mixture which showed the formation and disappearance of the intermediate **151**.[83] The postulated reaction mechanism for the addition/cyclisation reaction using Me_2Zn is shown in Scheme 81. A nucleophilic addition reaction of alkynyl-methylzinc **153** with the cyclic nitrone **149** gave a MeZn-O- species **154** which could undergo a cyclisation reaction to form the bicyclic vinylzinc intermediate **155**. Protodemetalation of this intermediate by the excess of alkyne **150** then yielded the bicyclic 4-isoxazolines **152** product and regenerated the alkynyl-methylzinc **153** species. This would then react with another cyclic nitrone **149** to continue the reaction cycle.[83] Stereoselectivity in this reaction arose from preferential addition to the nitrone face opposite to the bulky *tert*-butyl group.

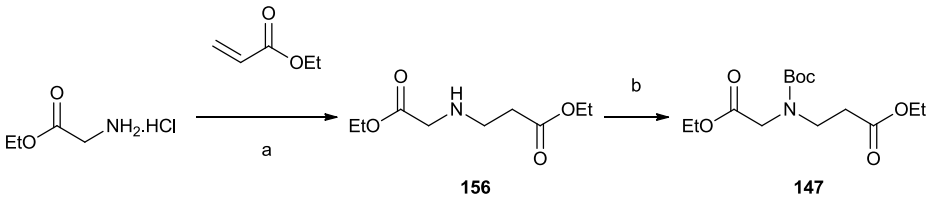


Scheme 81. Postulated mechanism for the tandem addition/cyclisation reaction between the cyclic nitrone **149** and alkyne **150**.

4.4 Results and discussion

4.4.1 Synthesis of nitrone 144

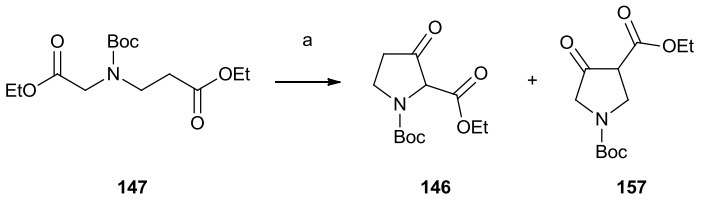
Starting from glycine ethyl ester hydrochloride and ethyl acrylate, the diester **147** was prepared in two steps by an aza-Michael addition followed by *N*-Boc protection of intermediate amine **156**. This gave the desired diester **147** in an overall yield of 69% over 2 steps after purification by flash chromatography (Scheme 82).



Scheme 82. Synthesis of the diester **147**; (a) Et_3N, EtOH, r.t., 96 h, 73%; (b) $(Boc)_2O$, 5% aqueous NaOH, 0 °C for 1 h then r.t. for 12 h, 95%.

Following a procedure developed by Rapoport and co-workers,[84] the diester **147** was subjected to a Dieckmann type condensation to give the desired β-ketoester **146** in 39% yield after

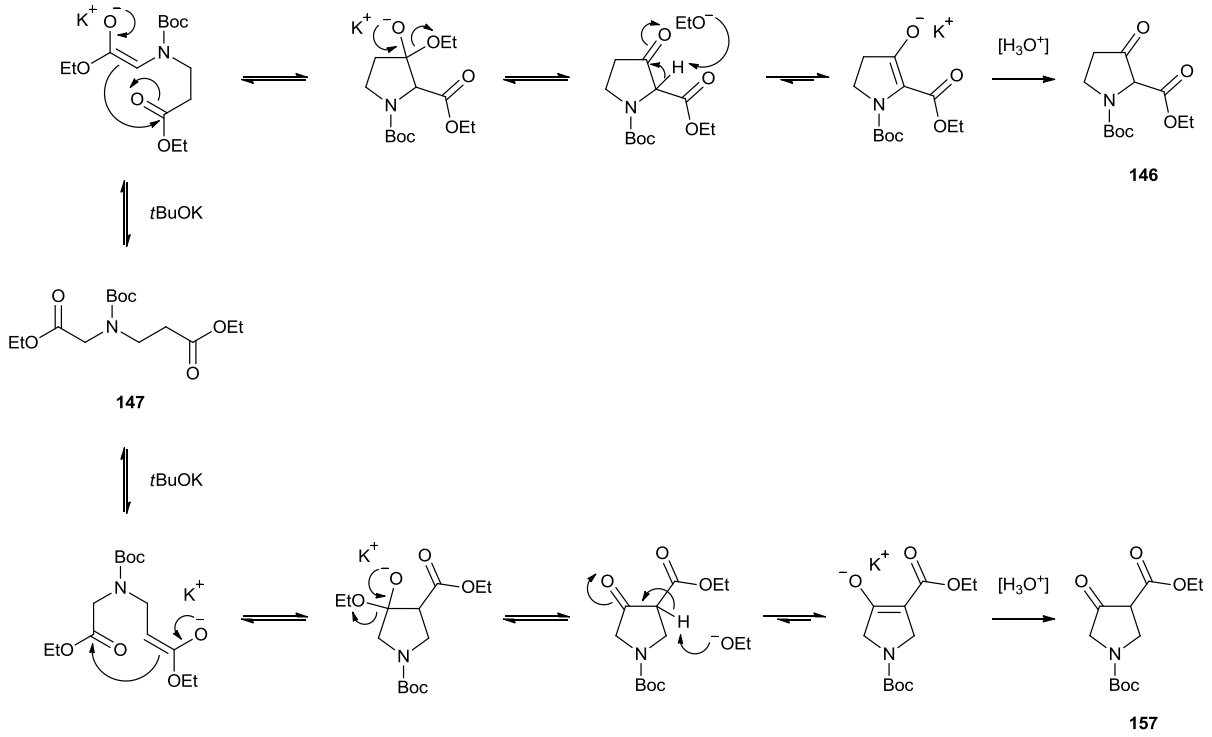
purification by flash chromatography. This gave a mixture of β-ketoesters **146** and **157** by utilising aprotic conditions, *t*BuOK in toluene (Scheme 83). The undesired isomer **157** could easily be separated by extraction into aqueous pH 9.5 phosphate buffer.



147 **146** **157**

Scheme 83. Dieckmann type condensation gave a mixture of the β-ketoesters **146** and **157**; (a) *t*BuOK, toluene, 0 °C, 1 h 25 min, 39% of **146**.

The mechanism for the reaction is shown in Scheme 84. It was found to be important to keep the reaction mixture at 0 °C in order to obtain the required kinetic product **146**. Longer reaction times or warmer temperatures tended to give lower yields and favour the formation of the undesired isomer **157**. The ^{1}H and ^{13}C NMR spectra of the β-ketoester **146** were complicated by *N*-Boc rotamers at 298 K. This was confirmed by additional VT NMR experiments (Figure 21).



Scheme 84. Mechanism for the Dieckmann type condensation of **147** which gave a mixture of β-ketoesters **146** and **157**.

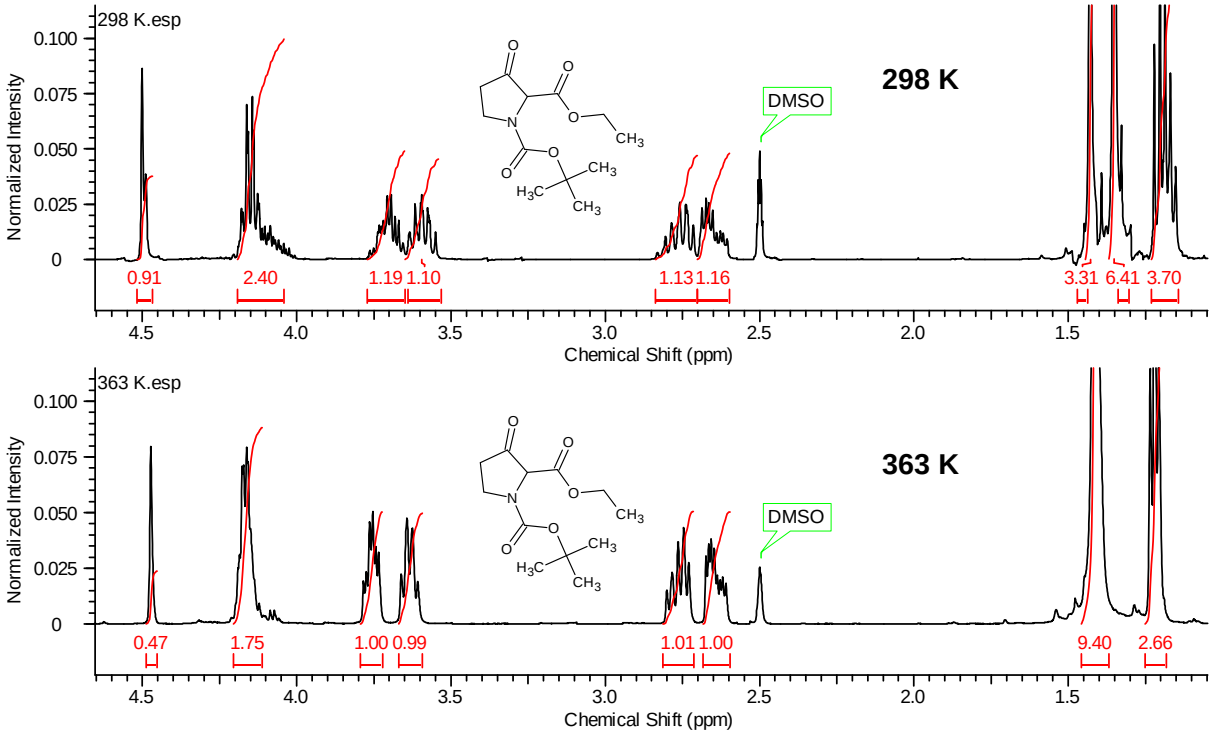
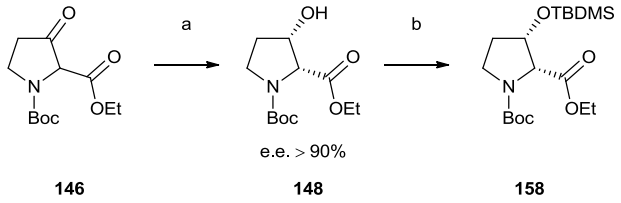


Figure 21. VT NMR experiments showing the ^{1}H NMR spectra of the β-ketoester **146** at 298 K and 363 K confirming the presence of *N*-Boc rotamers at r.t.

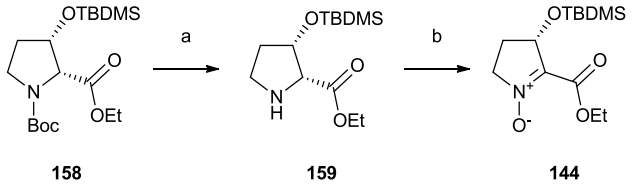
The β-ketoester **146** was subjected to Baker's yeast reduction as described by Knight and Sibley[92] to afford the β-hydroxyester **148**. This reaction was carried out in a heterogeneous medium containing a slurry of the Baker's yeast in tap water, in aerobic and fermenting conditions where the Baker's yeast was added to an aqueous solution of commercial table sugar and β-ketoester **146**. The reaction was kept at 35 °C for 48 h before the Baker's yeast was filtered off through a pad of Celite®. The desired β-hydroxyester **148** was then extracted with EtOAc and isolated as a single diastereoisomer in 66% yield after purification by flash chromatography. The specific rotation $[\alpha]_D^{25}$ = +21.2 (*c* 1.46, CH_2Cl_2) of the β-hydroxyester **148** closely matched the data previously reported in literature[79] $[\alpha]_D^{27}$ = +18.2 (*c* 1.45, CH_2Cl_2) for the 2*R*, 3*S* stereochemistry with an enantiomeric excess of >90% (Scheme 82). The hydroxy group was then protected by treatment with TBDMSCl and imidazole in CH_2Cl_2 at r.t. for 16 h. This gave the desired silyl ether **158** in 79% after purification by flash column chromatography.



Scheme 85. Synthesis of the *N*-Boc protected pyrrolidine **158** (a) Dried Baker's yeast, water, commercial table sugar, 35 °C, 48 h, 66%; (b) TBDMSCl, imidazole, CH_2Cl_2, r.t., 16 h, 79%.

The Boc-protecting group was removed by treating **158** with TFA in CH_2Cl_2 (1:10) at r.t. for 1 h. After basic work-up the amine **159** was isolated as its free base and taken to the next oxidation step without any further purification. The secondary amine **159** was directly oxidised to the corresponding nitrone **144** as previously described by Busqué and co-workers using Oxone®.[44] The nitrone **144** was obtained in 49% yield (over two steps) after work-up and purification by flash chromatography (Scheme 86). It was evident in the ^{1}H NMR spectra that the TBDMS protecting group was attached as a singlet at δ_H 0.87 ppm and two singlets at δ_H

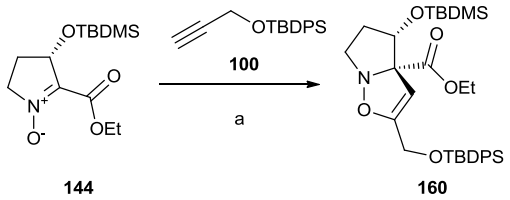
0.14 ppm and 0.10 ppm were observed corresponding to 9 H for -Si(CH_3)$_2$-C(C$\underline{H}_3$)$_3$ and 6 H for the -Si(C$\underline{H}_3$)$_2$-C(CH_3)$_3$ respectively.



Scheme 86. Synthesis of nitrone **144**; (a) TFA, CH_2Cl_2, r.t., 1 h; (b) Oxone®, $NaHCO_3$, 0.01 M Na_2EDTA (aq.), MeCN / THF (4:1), 5 °C, 2 h, 49% over two steps.

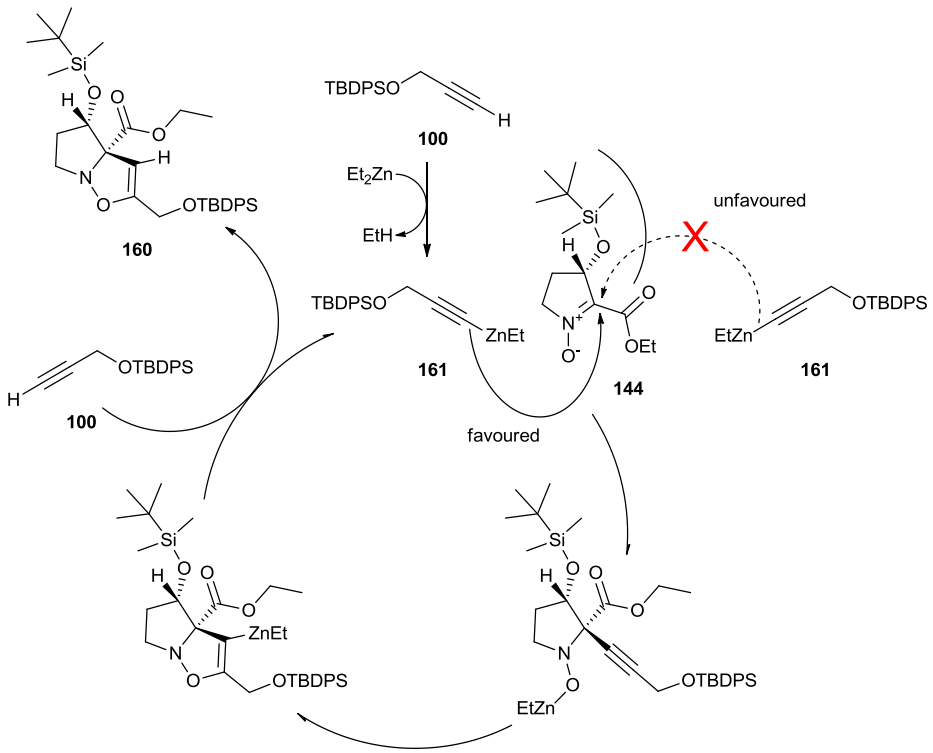
4.4.2 Addition/cyclisation reaction

Having successfully synthesised nitrone **144**, we now turned our attention to the key addition/cyclisation step. Following a protocol developed by Chavant and co-workers[83] treatment of the nitrone **144** with Et_2Zn (1.5 eq.) and excess of alkyne **100** (3 eq.) led pleasingly to a tandem addition/cyclisation reaction giving the bicyclic 4-isoxazoline **160** as one single regio- and diastereoisomer in 52% yield (Scheme 87).



Scheme 87. Synthesis of 4-isoxazoline **160**; (a) **100** (3 eq.), Et_2Zn (1.5 eq.), toluene, r.t, 4 h, 52%.

Based on the extensive mechanistic investigations by Chavant and co-workers[83] we believe that the diastereoselectivity arises by nucleophilic addition by alkynylzinc **161** to the top face of the nitrone **144** as presented by Scheme 88. We postulate that the approach of the nucleophile from the other face of the nitrone **144** is hindered by the bulky TBDMS protecting group and therefore is unfavoured. The nucleophilic addition is followed by a cyclisation to give the desired 4-isoxazoline **160**. The proposed mechanistic pathway is shown in Scheme 88.



Scheme 88. The proposed mechanistic pathway for the tandem addition/cyclisation reaction to give the bicyclic 4-isoxazoline **160**.

As the reaction follows an addition/cyclisation mechanistic pathway, only one regioisomer is formed. The desired regioisomer arises by nucleophilic addition by alkynylzinc **161** to the nitrone **144** as depicted in Scheme 88. It was evident by NMR analysis that the bicyclic 4-isoxazoline **160** had been formed. In the ^{1}H NMR spectrum we observed a singlet at δ_H 5.02 ppm for the vinylic proton and a new fully substituted carbon centre was observed in the ^{13}C NMR spectrum with a chemical shift of δ_C 89.7 ppm. This was in agreement with the expected values previously reported in the literature.[83] The relative stereochemical configuration of the bicyclic 4-isoxazoline **160** was assigned by NOE experiments and it was found that the silyl protected alcohol and the ethyl ester were related *cis* on the ring. The important NOE correlations are shown in Figure 22. This was a very successful result and it proved that this synthetic strategy could be used to construct the correct stereochemistry, for the fully substituted carbon centre present in daphlongeranine B.

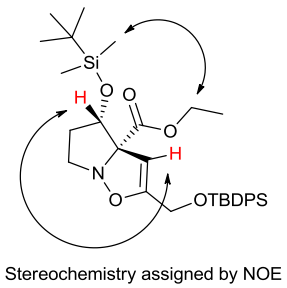
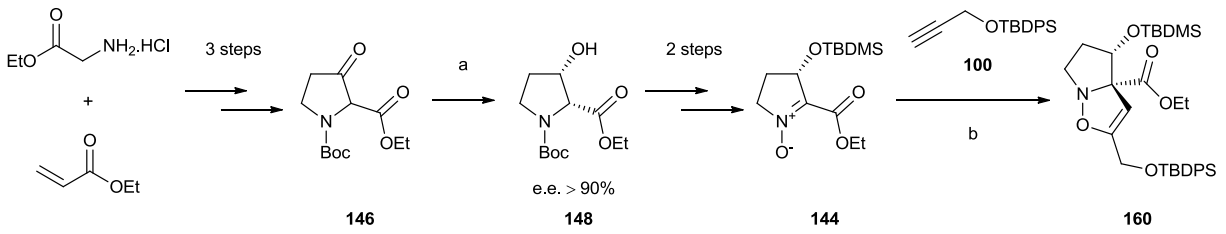


Figure 22. Important NOE correlations for the assignment of the relative stereochemical configuration of the bicyclic 4-isoxazoline **160** (see Appendix 7.3).

4.5 Conclusions

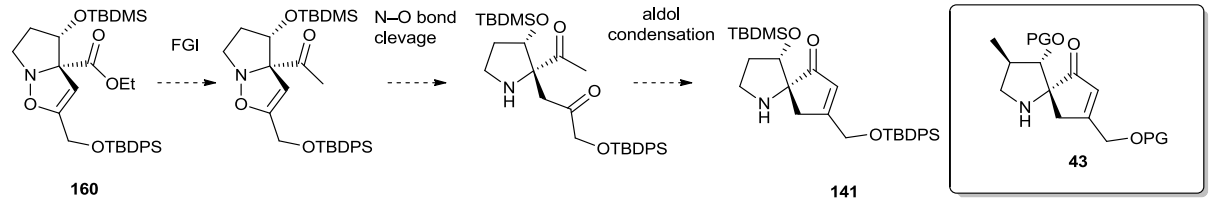
In summary we have successfully developed a synthetic route towards the spirocyclic fragment **141**. We have demonstrated how the protected alcohol functional group can be incorporated into the pyrrolidine ring and how this functional group could control the required configuration of the fully substituted carbon centre by a tandem addition/cyclisation reaction. Our synthesis of the bicyclic 4-isoxazoline **160**, a precursor to the spirocyclic fragment **141**, was completed in 8 steps. The key steps involved a Baker's yeast reduction to afford the β-hydroxyester **148** and an addition/cyclisation reaction between nitrone **144** and alkyne **100** to give the bicyclic 4-isoxazoline **160** (Scheme 89). We believe that this synthetic strategy would form the basis of a viable synthetic route towards the advanced spirocyclic intermediate **141**.



Scheme 89. The bicyclic 4-isoxazoline **160** was accessed in 8 steps involving two key steps, a Baker's yeast reduction and a tandem addition/cyclisation reaction; (a) Dried Baker's yeast, water, commercial table sugar, 35 °C, 48 h, 66%; (b) Et_2Zn (1.5 eq.), toluene, r.t., 4 h, 72%.

4.6 Future work

We believe that we would be able to synthesise the spirocyclic fragment **141** by utilising a Baker's yeast reduction and an addition/cyclisation reaction (Scheme 89) as key steps. Following the synthetic route already developed for the β-substituted spirocyclic enone **73** (Chapter 3), we are confident that a functional group interconversion followed by N-O bond cleavage and an aldol condensation will yield the desired spirocyclic fragment **141** (Scheme 90).



Scheme 90. The remaining synthetic steps to give the spirocyclic fragment **141**, a model of the advanced spirocyclic intermediate **43**.

Based on the results disclosed in this thesis, the synthesis of the advanced spirocyclic intermediate **43** was recently completed by a Yusuke Ogura, a post-doctoral researcher within the research group. He made use of the developed route detailed in this thesis, utilising the 1,3-dipolar cycloaddition step (Scheme 44), to successfully synthesise the advanced spirocyclic intermediate **43**. Based on the investigations and the results described in this thesis, this key intermediate would allow us to synthesise the unique tricyclic core of daphlongeranine B and subsequently enable us to complete the synthesis of daphlongeranine B.

5 CHAPTER 5: Experimental

5.1 General experimental

All reactions involving moisture sensitive reagents were performed under an atmosphere of nitrogen or argon via standard vacuum line techniques and with freshly dried solvents. All glassware was oven dried at 80 °C and allowed to cool under vacuum before use. Room temperature refers to 20 - 25 ˚C. Temperatures of 0 °C and −78 °C were obtained using an ice / water bath and a solid CO_2 / acetone bath respectively. Reflux conditions were obtained using an oil bath equipped with a thermometer or DrySyn® heating block fitted with a contact thermometer. Temperatures are given in degrees Celsius (°C) or in Kelvin (K). Compounds were named according to IUPAC nomenclature using ACD/I-Lab service. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

5.1.1 Solvent and reagents

Anhydrous toluene, tetrahydrofuran (THF), MeOH, CH_2Cl_2, and Et_2O were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. Anhydrous ethanol was obtained by distillation from Mg turnings in I_2. Other solvents were used directly as received from commercial suppliers. Petroleum ether (PE) refers to the fraction of petroleum ether boiling between 30-40 °C. Concentrated *in vacuo* refers to evaporation of organic solvents under reduced pressure using a Büchi rotary evaporator. Triethylamine (Et_3N) was distilled from CaH_2 and stored over KOH under nitrogen. Na_2SO_4 refers to anhydrous sodium sulphate and $MgSO_4$ refers to anhydrous magnesium sulphate. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

5.1.2 Chromatography

Column chromatography was carried out using Merck 60 silica gel (230-400 mesh) in the solvent system stated. Reactions were monitored by thin-layer chromatography (TLC), using Merck Silica gel 60 F254 (230-400 mesh) fluorescent treated silica gel plates, which were visualised under UV light (250 nm) or by staining with 1% aqueous basic $KMnO_4$ solution as appropriate.

5.1.3 Spectroscopy and instruments

All ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on a Bruker spectrometer operating at 200 MHz, 400 MHz or 500 MHz (^{1}H acquisitions) and 50 MHz, 100 MHz, 125 MHz (^{13}C acquisitions). Chemical shifts (δ) are reported in ppm for measurement against a tetramethylsilane (TMS) with the residual solvent peaks as internal standards. All experiments were carried out using the stated deuterated solvent. Coupling constants (*J*) are reported in hertz (Hz). The ^{1}H NMR spectra are reported as follows; δ [multiplicity (s = singlet, d = doublet, dd = doublets of doublets, ddd = doublets of doublets of doublets, t = triplet, q = quartet, quin = quintet, m = multiplet, br. s = broad singlet, app. = apparent), number of protons, coupling constants *J*/Hz (where appropriate) and assignment (where appropriate)]. DEPT 135 and two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy were used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. NOE experiments were used to determine relative stereochemistry.

Low-resolution mass spectra (ESI) were recorded on a Waters LCT Premier XE Micromass mass spectrometer. High-resolution mass spectra (ESI) were recorded on a Bruker Daltonics

MicroTOF mass spectrometer. High-resolution mass spectra (FI) were recorded on a Bruker FT-ICR Apex III mass spectrometer.

Infrared spectra were recorded neat as a thin film on a Bruker Tensor 27 FT-IR spectrometer with a diamond ATR module. Infrared spectra were also recorded on a Perkin-Elmer 1620 FT-IR spectrophotometer using KBr discs (KBr disc) for solids or NaCl plates (thin film) for oils and liquids. Maximum absorbances (ν_{max}) are quoted in wavenumbers (cm^{-1}) and only significant peaks are reported.

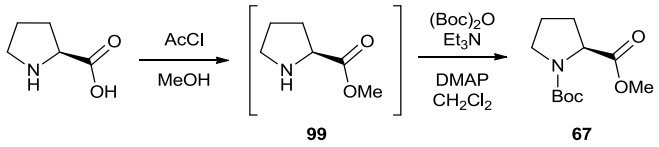
Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

Optical rotations were recorded using a Perkin Elmer 341 polarimeter; $[\alpha]_D^T$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentrations (*c*) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm); Temperatures (T) are given in degrees Celsius (°C).

5.2 Experimental: Chapter 2

Synthesis and Characterisation of 67

1-*tert*-Butyl 2-methyl (2*S*)-pyrrolidine-1,2-dicarboxylate **67**



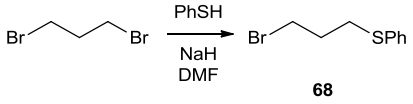
Acetyl chloride (2.8 eq., 14.7 mL, 206 mmol) was added dropwise to MeOH (106 mL) at 0 °C under nitrogen. The resulting mixture was stirred for 5 min before L-proline (1 eq., 8.50 g, 73.7 mmol) was added in one portion. The reaction mixture was heated to reflux for 12 h and thereafter left to cool to r.t. The reaction mixture was concentrated *in vacuo* to give the crude **99** as a pale yellow oil (13.7 g). To a solution of **99** (1 eq., 9.52 g, 73.7 mmol) in CH_2Cl_2 (100 mL), Et_3N (3.0 eq., 30.8 mL, 221 mmol), DMAP (0.1 eq., 900 mg, 7.37 mmol) followed by $(Boc)_2O$ (1.1 eq., 17.7 g, 81.1 mmol) were added at 0 °C. The reaction mixture was warmed to r.t. and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the residue was taken into water (100 mL), and Et_2O (100 mL). The organics were separated and washed with 0.5 M HCl (aq.), saturated $NaHCO_3$ (aq.), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc:PE) to give **67** (13.3 g, 79%) as a pale yellow oil. Characterisation data were corresponding to the literature[31] with the ^1H and ^{13}C NMR spectra complicated by *N*-Boc rotamers at 298 K.

$[\alpha]_D^{25}$ = −57.0 (*c* 1.00, CH_2Cl_2), lit.[31] $[\alpha]_D^{20}$ = −52.5 (*c* 0.99, CH_2Cl_2); **^{1}H NMR** (400 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:0.6) δ 4.31 (dd, *J* = 8.5, 3.0 Hz, 1 H, -C<u>H</u>-CO_2-CH_3, minor rotamer), 4.21 (dd, *J* = 8.5, 4.5 Hz, 1 H, -C<u>H</u>-CO_2-CH_3, major rotamer), 3.72 (s, 3 H, -CO_2-C<u>H</u>$_3$, minor rotamer), 3.73 (s, 3 H, -CO_2-C<u>H</u>$_3$, major rotamer), 3.59 - 3.33 (m, 4 H, -N-C<u>H</u>$_2$-, major and minor rotamers), 2.29 - 2.10 (m, 2 H, major and minor rotamers),

2.02 - 1.78 (m, 6 H, major and minor rotamers), 1.50 (s, 9 H, -C(C<u>H</u>$_3$)$_3$, minor rotamer), 1.36 (s, 9 H, -C(C<u>H</u>$_3$)$_3$, major rotamer); **^{13}C NMR** (100 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:0.6) δ 173.7, 173.4 (-<u>C</u>O$_2$-CH$_3$, rotamers), 154.3, 153.7 (-N-<u>C</u>O$_2$-, rotamers), 79.7 (-<u>C</u>(CH$_3$)$_3$, major and minor rotamer), 59.0 (-<u>C</u>H-CO$_2$-CH$_3$, major rotamer), 58.7 (-<u>C</u>H-CO$_2$-CH$_3$, minor rotamer), 52.0 (-CO$_2$-<u>C</u>H3, minor rotamer), 51.8 (-CO$_2$-<u>C</u>H$_3$, major rotamer), 46.5 (-N-<u>C</u>H$_2$-, minor rotamer), 46.2 (-N-<u>C</u>H$_2$-, major rotamer), 30.8 (-N-CH$_2$-CH$_2$-<u>C</u>H$_2$-, major rotamer), 29.8 (-N-CH$_2$-CH$_2$-<u>C</u>H$_2$-, minor rotamer), 28.3 (-C(<u>C</u>H$_3$)$_3$, minor rotamer), 28.2 (-C(<u>C</u>H$_3$)$_3$, major rotamer), δ 24.2 (-N-CH$_2$-<u>C</u>H$_2$-CH$_2$-, minor rotamer) 23.6 (-N-CH$_2$-<u>C</u>H$_2$-CH$_2$-, major rotamer); **LRMS** (ES+) *m/z* (relative intensity %) 252 (95%, $[M + Na]^+$, 481 (95, $[2M + Na]^+$).

Synthesis and Characterisation of 68

(3-Bromopropyl)(phenyl)sulfane **68**



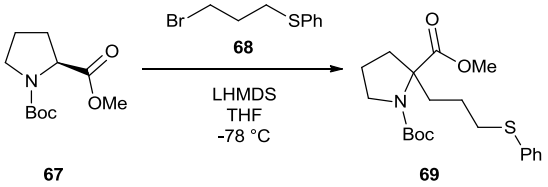
68

To a stirred solution of NaH (0.9 eq., 2.64 g, 66.0 mmol, 60% in mineral oil) in DMF (100 mL) at 0 °C was added thiophenol (1 eq., 8.37 g, 7.80 mL, 76.0 mmol). After 90 min, the suspension containing the thiophenol was transferred by cannula to a solution containing 1,3-dibromopropane (2.6 eq., 39.8 g, 20.0 mL, 197 mmol) in DMF (100 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 25 h before being poured into saturated K_2CO_3 (aq.) solution (300 mL). The reaction mixture was and extracted with CH_2Cl_2 (2 × 100 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by distillation to give **68** (8.22 g, 47%) as a yellow oil. Characterisation data were corresponding to the literature.[33]

B.p. 130-140 °C (5 mBar), lit.[85] 124-126 °C (4 mBar); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 - 7.40 (m, 2 H, ArH), 7.35 - 7.27 (m, 2 H, ArH), 7.25 - 7.19 (m, 1 H, ArH), 3.54 (t, *J* = 6.5 Hz, 2 H, -CH_2-Br), 3.09 (t, *J* = 7.0 Hz, 2 H, -CH_2-SPh), 2.16 (app. quin, *J* = 6.7 Hz, 2 H, -CH_2-CH_2-Br); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.6 (ArC), 129.6 (2 × ArC), 129.0 (2 × ArC), 126.3 (ArC), 32.0 (-CH_2-), 31.9 (-CH_2-), 31.7 (-CH_2-); **LRMS** (ES+) *m/z* (relative intensity %) 252 (54%, $[M + Na]^+$).

Synthesis and Characterisation of 69

1-*tert*-Butyl 2-methyl 2-[3-(phenylthio)propyl]pyrrolidine-1,2-dicarboxylate **69**



67 69

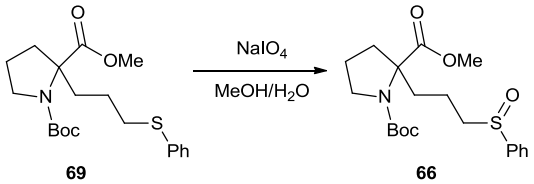
To a solution of Boc-pyrrolidine **67** (1 eq., 2.00 g, 8.73 mmol) in THF (6 mL), LHMDS (1.1 eq., 0.9 M solution in hexanes, 10.7 mL, 9.60 mmol) was added dropwise at −78 °C under nitrogen. The resulting solution was allowed to stir for 15 min before (3-bromopropyl)(phenyl)sulfane **68** (1 eq., 2.02 g, 8.73 mmol) in THF (4 mL) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was warmed to r.t. and stirred for 6 h before being quenched with saturated NH_4Cl (aq.) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc:PE) to give **69** (2.61 g, 79%) as a yellow oil.

IR ν_{max}(thin film)/cm^{-1} 2974 (C-H), 1741 (C=O), 1697 (C=O), 1390, 1163, 739; **^{1}H NMR** (500 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:1.77) δ 7.34 - 7.22 (m, 6 H, ArH,

major and minor rotamers), 7.15 (s, 4 H, Ar<u>H</u>, major and minor rotamers), 3.68 (s, 6 H, -CO_2-C<u>H</u>$_3$, major and minor rotamers), 3.61 - 3.52 (m, 1 H, -N-C<u>H</u>$_2$-, minor rotamer), 3.39 - 3.29 (m, 3 H, -N-C<u>H</u>$_2$-, major and minor rotamers), 2.99 - 2.84 (m, 4 H, PhS-C<u>H</u>$_2$-, major and minor rotamers), 2.39 (app. ddd, *J* = 13.5, 11.5, 5.5 Hz, 1 H, minor rotamer), 2.28 (app. ddd, *J* = 14.0, 12.0, 5.5 Hz, 1 H, major rotamer), 2.13 - 1.80 (m, 8 H, major and minor rotamers), 1.78 - 1.70 (m, 2 H, major and minor rotamers), 1.70 - 1.53 (m, 4 H, major and minor rotamers), 1.41 (s, 9 H, -C(C<u>H</u>$_3$)$_3$, minor rotamer), 1.37 (s, 9 H, -C(C<u>H</u>$_3$)$_3$, major rotamer); **^{13}C NMR** (125 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:1.77) δ 175.1, 174.9 (-<u>C</u>O_2-CH_3, rotamers), 154.0, 153.6, (-N-<u>C</u>O_2-, rotamer), 136.6, 136.5, 128.8, 128.7, 128.6, 125.7, 125.5 (Ar<u>C</u>, rotamers), 79.9, 79.4 (-<u>C</u>(CH_3)$_3$, rotamers), 67.7, 67.2 (-N-<u>C</u>$_{quat.}$, rotamers), 52.0 (-CO_2-<u>C</u>H_3, major and minor rotamers), 48.5 (-N-<u>C</u>H_2-, minor rotamer), 48.4 (-N-<u>C</u>H_2-, major rotamers), 37.5, 36.1, 34.4, 33.8, 33.5, 33.4 (rotamers), 28.3 (-C(<u>C</u>H_3)$_3$, minor rotamer), 28.2 (-C(<u>C</u>H_3)$_3$, major rotamer), 23.7 (PhS-CH_2-<u>C</u>H_2-, minor rotamer), 23.4 (PhS-CH_2-<u>C</u>H_2-, major rotamer), 23.0 (-N-CH_2-<u>C</u>H_2-, minor rotamer), 22.6 (-N-CH_2-<u>C</u>H_2-, major rotamer); **LRMS** (ES+) *m/z* (relative intensity %) 402 (72%, $[M + Na]^+$), 781 (100, $[2M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{20}H_{29}NNaO_4S$) requires *m/z* 402.1710, found *m/z* 402.1708.

Synthesis and Characterisation of 66

1-*tert*-Butyl 2-methyl 2-[3-(phenylsulfinyl)propyl]pyrrolidine-1,2-dicarboxylate **66**



69 **66**

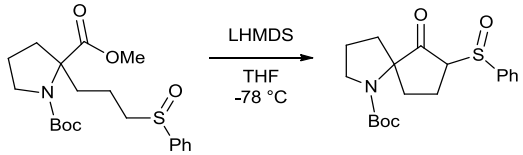
Thioether **69** (1 eq., 1.73 g, 4.56 mmol) in MeOH (19 mL) was added dropwise to a suspension of $NaIO_4$ (1.1 eq., 1.07 g, 5.01 mmol) in water (7 mL) at 0 °C. The reaction mixture was stirred

at r.t. for 6 h and then filtered. The solid precipitate was washed with EtOAc (2 × 10 mL). The organics were separated and the aqueous phase was extracted with EtOAc (10 mL). The organics extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to give **66** (1.71 g, 95%) as a mixture of inseparable diastereoisomers as a colourless oil. The ^{1}H and ^{13}C NMR spectra were complicated by *N*-Boc rotamers at 298 K.

IR ν_{max}(thin film)/cm^{-1} 2974 (C-H), 1740 (C=O), 1695, 1392, 1165, 1047 (S=O), 751; **^{1}H NMR** (500 MHz, 363 K, DMSO-d_6, mixture of diastereoisomers, ratio 1:0.89) 7.68 - 7.62 (m, 4 H, Ar<u>H</u>, major and minor), 7.60 - 7.50 (m, 6 H, Ar<u>H</u>, major and minor), 3.62 (s, 6 H, -CO_2-C<u>H</u>$_3$, major and minor), 3.56 - 3.46 (m, 2 H, -N-C<u>H</u>$_2$-, major and minor), 3.33 - 3.23 (m, 2 H, -N-C<u>H</u>$_2$-, major and minor), 2.96 - 2.70 (m, 4 H, -SO-C<u>H</u>$_2$-, major and minor), 2.27 - 2.11 (m, 2 H, major and minor), 2.06 - 1.70 (m, 2 H, major and minor), 1.66 - 1.55 (m, 10 H, major and minor), 1.49 - 1.39 (m, 2 H, major and minor), 1.35 (s, 9H, -C(C<u>H</u>$_3$)$_3$, major), 1.32 (s, 9 H, -C(C<u>H</u>$_3$)$_3$, minor); **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of diastereoisomers and *N*-Boc rotamers) δ 175.0, 174.8 (-<u>C</u>O_2CH_3), 154.2, 154.1, 153.5 (-N-<u>C</u>O_2-), 144.1, 143.8, 143.7, 131.0, 130.9, 130.8, 129.2, 129.1, 123.9, 123.8 (Ar<u>C</u>), 80.2, 80.1, 79.7, 79.6 (-<u>C</u>$(CH_3)_3$), 67.6, 67.6 (-N-<u>C</u>$_{quat.}$), 58.0, 57.6, 57.4, 57.2 (-SO-<u>C</u>H_2-), 52.1 (-CO_2-<u>C</u>H_3), 48.6, 48.5 (-N-<u>C</u>H_2-), 37.4, 36.1, 36.0, 34.4, 34.1, 33.3, 32.9, 28.3, 28.2 (-C(<u>C</u>$H_3)_3$), 23.1, 22.6 (-N-CH_2-<u>C</u>H_2-), 17.6, 17.4 (-SO-CH_2-<u>C</u>H_2-), 16.7, 16.5 (-SO-CH_2-<u>C</u>H_2-); **LRMS** (ES+) *m/z* (relative intensity %) 418 (90%, $[M + Na]^+$), 813 (100, $[2M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{20}H_{29}NNaO_5S$) requires *m/z* 418.1659, found *m/z* 418.1659.

Synthesis and Characterisation of 70

tert-Butyl 6-oxo-7-(phenylsulfinyl)-1-azaspiro[4.4]nonane-1-carboxylate **70**



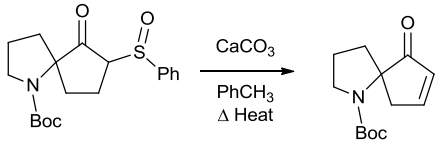
66 **70**

To a solution of sulfoxide **66** (1 eq., 1.80 g, 4.56 mmol) in THF (5 mL), LHMDS (2.2 eq., 0.9 M solution in hexanes, 11.2 mL, 10.0 mmol) was added dropwise at −78 °C under nitrogen. The reaction mixture was warmed to r.t. and stirred for 7 h before being quenched with saturated NH_4Cl (aq.) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc:PE) to give **70** (1.09 g, 66%) as a mixture of inseparable diastereoisomers as a pale yellow oil. ^{1}H and ^{13}C NMR spectra were complicated by a mixture of diastereoisomers and *N*-Boc rotamers at 298 K.

IR ν_{max}(thin film)/cm^{-1} 2975 (C-H), 1750 (C=O), 1690, 1392, 1143 (S=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 - 7.39 (m, 5 H, Ar<u>H</u>), 3.73 - 3.28 (m, 3 H, -N-C<u>H</u>$_2$-, -SO-C<u>H</u>-), 2.52 - 2.21 (m, 3 H), 2.08 - 1.72 (m, 4 H), 1.61- 1.45 (m, 1 H), 1.40 - 1.33 (m, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.3, 209.6 ($C_{quat.}$-<u>C</u>O-), 153.5, 152.4 (-N-<u>C</u>O$_2$-), 141.5, 141.4, 137.5, 131.0, 130.7, 129.2, 128.9, 126.7, 123.6 (Ar<u>C</u>), 80.6, 80.0 (-<u>C</u>(CH$_3$)$_3$), 70.7, 70.5 (-N-<u>C</u>$_{quat.}$), 69.2, 69.0 (-SO-<u>C</u>H-), 48.1, 47.9 (-N-<u>C</u>H$_2$-), 36.3, 35.4, 32.0, 31.2, 28.3, 28.2 (-C(<u>C</u>H$_3$)$_3$), 23.7, 22.5, 13.4, 13.3; **LRMS** (ES+) *m/z* (relative intensity %) 386 (79%, $[M + Na]^+$), 749 (100, $[2M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{19}H_{25}NNaO_4S$) requires *m/z* 386.1397, found *m/z* 386.1396.

Synthesis and Characterisation of 72

tert-Butyl 6-oxo-1-azaspiro[4.4]non-7-ene-1-carboxylate **72**



70 **72**

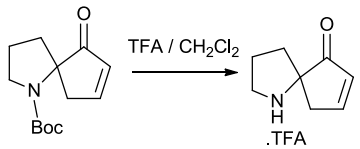
To sulfoxide **70** (1 eq., 590 mg, 1.62 mmol) in toluene (5 mL), $CaCO_3$ (1 eq., 160 mg, 1.62 mmol) was added in one portion. The reaction mixture was heated to reflux under nitrogen for 12 h before being filtered. The white precipitate was washed with EtOAc (5 mL) and the filtrate was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc:PE) to give **72** (281 mg, 73%) as a pale yellow oil. The ^{1}H and ^{13}C NMR spectra were complicated by *N*-Boc rotamers at 298 K.

IR ν_{max}(thin film)/cm^{-1} 2975 (C-H), 1720 (C=O), 1692, 1392, 1142; **^{1}H NMR** (400 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1.4:1.0) δ 7.57 - 7.51 (m, 2 H, -C<u>H</u>=CH-CO-, major and minor rotamers), 6.23 - 6.21 (m, 1 H, -CH=C<u>H</u>-CO-, minor rotamer), 6.18 - 6.16 (m, 1 H, -CH=C<u>H</u>-CO-, major rotamer), 3.58 - 3.47 (m, 4 H, -N-C<u>H_2</u>- major and minor rotamers), 3.11 (dd, *J* = 18.5, 2.0 Hz, 1 H, -C<u>H_2</u>-CH=CH-, minor rotamer), 2.94 (dd, *J* = 18.5, 2.0 Hz, 1 H, -C<u>H_2</u>-CH=CH-, major rotamer), 2.06 - 1.92 (m, 2 H, -C<u>H_2</u>-CH=CH-, major and minor rotamers), 1.90 - 1.67 (m, 4 H, major and minor rotamers), 1.40 - 1.35 (m, 4 H, major and minor rotamers), 1.37 (s, 9 H, -C(C<u>H_3</u>)$_3$, major and minor rotamers), 1.28 (m, 9 H, major and minor rotamers); **^{13}C NMR** (100 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1.4:1.0) δ 208.2 , 208.1 (-CH=CH-<u>C</u>O-, rotamers), 160.3 (-<u>C</u>H=CH-CO-, minor rotamer), 160.0 (-<u>C</u>H=CH-CO-, major rotamer), 153.2, 152.8 (-N-<u>C</u>O_2-, rotamers), 132.3 (-CH=<u>C</u>H-CO-, major rotamer), 132.2 (-CH=<u>C</u>H-CO-, minor rotamer), 80.2, 79.7 (-<u>C</u>(CH_3)$_3$, rotamers), 67.4, 67.2 (-N-<u>C</u>$_{quat.}$, rotamers), 47.9 (-N-<u>C</u>H_2-, minor rotamer), 47.8 (-N-<u>C</u>H_2-, major rotamer), 43.6

(-C<u>H</u>$_2$-CH=CH-, major rotamer), 42.5 (-C<u>H</u>$_2$-CH=CH-, minor rotamer), 39.9 (-N-C$_{quat.}$-<u>C</u>H$_2$-CH$_2$-, major rotamer), 38.8 (-N-C$_{quat.}$-<u>C</u>H$_2$-CH$_2$-, minor rotamer), 28.3 (-C(<u>C</u>H$_3$)$_3$, minor rotamer), 28.1 (-C(<u>C</u>H$_3$)$_3$, major rotamer), 23.8 (-N-CH$_2$-<u>C</u>H$_2$-, minor rotamer), 23.1 (-N-CH$_2$-<u>C</u>H$_2$-, major rotamer); **LRMS** (ES+) *m/z* (relative intensity %) 260 (88%, [M + Na]$^+$), 497 (100, [2M + Na]$^+$); **HRMS (**ES+) exact mass calculated for [M+Na]$^+$ (C$_{13}$H$_{19}$NNaO$_3$) requires *m/z* 260.1257, found *m/z* 260.1257

Synthesis and Characterisation of 62

1-Azaspiro[4.4]non-7-en-6-one trifluoroacetate (1:1) **62**



72 **62**

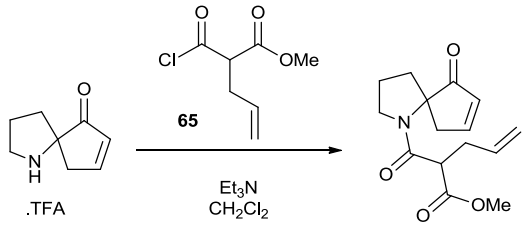
TFA (1 mL) was added dropwise to a solution of **72** (1 eq., 49.0 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred at r.t. for 1 h before being concentrated by blowing a stream of nitrogen over the mixture. The residue was left to dry over high vacuum for 12 h to give the crude product **62** as a yellow oil (63 mg, quant. yield) which was used crude in the next step.

IR ν_{max}(thin film)/cm^{-1} 3427 (N-H), 2976 (C-H), 1720 (C=O), 1676, 1202, 1133; **^{1}H NMR** (500 MHz, D_2O) δ 7.94 (dt, *J* = 5.5, 2.5 Hz, 1 H, -C<u>H</u>=CH-CO-), 6.32 - 6.28 (m, 1 H, -CH=C<u>H</u>-CO-), 3.56 - 3.41 (m, 2 H, -N-C<u>H</u>$_2$-), 3.14 - 2.92 (m, 2 H, -C<u>H</u>$_2$-CH=CH-), 2.26 - 1.98 (m, 6 H, -N-CH$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-, -N<u>H</u>$_2^+$-); **^{13}C NMR** (125 MHz, D_2O) δ 206.2 (-CH=CH-<u>C</u>O-), 166.4 (-<u>C</u>H=CH-CO-), 130.6 (-CH=<u>C</u>H-CO-), 69.0 (<u>C</u$_{quat.}$), 46.5 (-N-<u>C</u>H$_2$-CH$_2$-CH$_2$-), 40.3 (-<u>C</u>H$_2$-CH=CH-), 35.6 (-N-CH$_2$-CH$_2$-<u>C</u>H$_2$-) 22.7 (-N-CH$_2$-<u>C</u>H$_2$-CH$_2$-); **LRMS** (ES+) *m/z*

(relative intensity %) 138 (76%, $[M + H]^+$); **HRMS** (ES+) exact mass calculated for $[M + H]^+$ ($C_8H_{12}NO$) requires *m/z* 138.0913, found *m/z* 138.0913.

Synthesis and Characterisation of 63

Methyl 2-[(6-oxo-1-azaspiro[4.4]non-7-en-1-yl)carbonyl]pent-4-enoate **63**



62 **63**

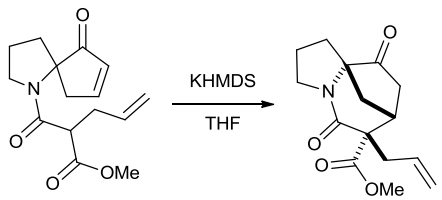
Et_3N (2.2 eq., 0.071 mL, 0.51 mmol) followed by acid chloride **65**[37] (1.1 eq., 0.16 M solution in CH_2Cl_2, 1.59 mL, 0.25 mmol) were added dropwise to a solution of amine **62** (1 eq., 58.0 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred for 2 h before it was diluted with Et_2O (4 mL). The mixture was washed with water (3 × 2 mL), saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (60% EtOAc:PE) to give **63** as a mixture of diastereoisomers (26 mg, 22%, d.r. 1.5:1) as a pale yellow oil.

IR ν_{max}(thin film)/cm^{-1} 2953 (C-H), 1719 (C=O), 1644 (C=O), 1420, 1155; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereoisomers, ratio 1.5:1) δ 7.57 - 7.50 (m, 2 H, -CO-CH=C<u>H</u>-, major and minor), 6.29 - 6.23 (m, 2 H, -CO-C<u>H</u>=CH-, major and minor), 5.86 - 5.69 (m, 2 H, $-CH_2-C\underline{H}=CH_2$, major and minor), 5.16 - 5.00 (m, 4 H, $-CH_2-CH=C\underline{H}_2$, major and minor), 3.80 - 3.60 (m, 10 H, -N-C<u>H</u>$_2$, $-CO_2-C\underline{H}_3$, major and minor), 3.56 - 3.42 (m, 2 H, $-C\underline{H}-CO_2-CH_3$, major and minor), 3.16 - 3.03 (m, 2 H, $C_{quat.}-C\underline{H}_AH_B-CH=CH-$, major and minor), 2.69 - 2.51 (m, 6 H, $C_{quat.}-CH_A\underline{H}_B-CH=CH-$, -C<u>H</u>$_2$-CH=$CH_2$, major and minor), 2.19 -

1.93 (m, 6 H, -N-CH_2-C$\underline{H}_2$-CH_2-, -N-CH_2-CH_2-C$\underline{H}_A$$H_B$, major and minor), 1.83 - 1.71 (m, 2 H, -N-CH_2-CH_2-$CH_A\underline{H}_B$-, major and minor); **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of diastereoisomers, ratio 1.5:1) δ 206.5 (-$\underline{C}$O-CH=CH-, major), 206.2 (-$\underline{C}$O-CH=CH-, minor), 169.6 (-N-$\underline{C}$O-, major), 169.1 (-N-$\underline{C}$O-, minor), 165.9 (-$\underline{C}O_2CH_3$, minor), 165.8 (-$\underline{C}O_2CH_3$, major), 159.4 (-CO-CH=$\underline{C}$H-, major), 159.0 (-CO-CH=$\underline{C}$H-, minor), 134.5 (-CH_2-$\underline{C}$H=CH_2, major and minor), 132.3 (-CO-$\underline{C}$H=CH-, major and minor), 117.2 (-CH_2-CH=$\underline{C}H_2$, major and minor), 68.6 ($C_{quat.}$, major), 68.5 ($C_{quat.}$, minor), 52.5 (-CO_2-$\underline{C}H_3$, minor), 52.4 (-CO_2-$\underline{C}H_3$, major), 50.3 (-$\underline{C}$H-CO_2-CH_3, major and minor), 48.7 (-N-$\underline{C}H_2$-, minor), 48.5 (-N-$\underline{C}H_2$-, major), 42.2 ($C_{quat.}$-$\underline{C}H_2$-CH=CH-, minor), 42.0 ($C_{quat.}$-$\underline{C}H_2$-CH=CH-, major), 37.9 (-N-CH_2-CH_2-$\underline{C}H_2$, minor), 37.9 (-N-CH_2-CH_2-$\underline{C}H_2$ major), 32.9 (-$\underline{C}H_2$-CH=CH_2, major), 32.8 (-$\underline{C}H_2$-CH=CH_2, minor), 24.5 (-N-CH_2-$\underline{C}H_2$-CH_2-, minor), 24.4 (-N-CH_2-$\underline{C}H_2$-CH_2-, major); **LRMS** (ES+) *m/z* (relative intensity %) 278 (36%, $[M + H]^+$), 300 (97, $[M + Na]^+$), 577 (100, $[2M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{15}H_{19}NNaO_4$) requires *m/z* 300.1206, found *m/z* 300.1204.

Synthesis and Characterisation of 64

Methyl 6-allyl-5,9-dioxohexahydro-1*H*,5*H*-7,9a-methanopyrrolo[1,2-*a*]azepine-6-carboxylate **64**



63 **64**

To a solution of diketo ester **63** (1 eq., 26 mg, 0.094 mmol) in THF (1 mL), KHMDS (1.1 eq., 0.5 M solution in toluene, 200 μL, 0.010 mmol) was added at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1.5 h before being quenched with saturated NH_4Cl (aq.). The

reaction mixture was extracted with Et_2O (3 × 3 mL) and the organic extracts were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (60% EtOAc:PE) to give **64** as a mixture of diastereoisomers (3 mg, 12%, d.r. 10:1) as a colourless oil.

Minor diastereoisomer (observable):

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (m, 3 H), 3.47 - 3.41 (m, 1 H), 3.11 (dd, *J* = 14.5, 6.0 Hz, 1 H), 3.03 - 3.00 (m, 1 H), 2.63 - 2.58 (m, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.9 (-$\underline{C}O_2$-CH_3), 166.2 (-N-$\underline{C}O$-), 133.0 (-CH_2-$\underline{C}H$=CH_2), 119.0 (-CH_2-CH=$\underline{C}H_2$), 68.9 (-N-$\underline{C}_{quat.}$), 57.2 (-$\underline{C}_{quat.}$-CO_2-CH_3), 52.8 (-CO_2-$\underline{C}H_3$), 45.2 (-N-$\underline{C}H_2$-), 37.0 (-CO-CH_2-$\underline{C}H$-), 36.2 (-N-$C_{quat.}$-$\underline{C}H_2$-), 28.1 (-N-CH_2-CH_2-$\underline{C}H_2$-), 21.6 (-N-CH_2-$C\underline{H}_2$-).

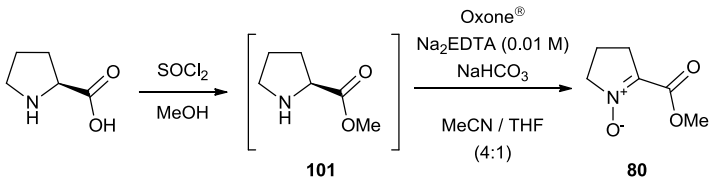
Major diastereoisomer:

IR ν_{max}(thin film)/cm^{-1} 2954 (C-H), 1734 (C=O), 1649 (C=O), 1419, 1231; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.03 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H, -CH_2-$C\underline{H}$=CH_2), 5.21 - 5.12 (m, 2 H, -CH_2-CH=$C\underline{H}_2$), 3.75 (m, 3 H, -CO_2-$C\underline{H}_3$), 3.69 - 3.48 (m, 2 H, -N-$C\underline{H}_2$-), 2.91 (dd, *J* = 14.0, 7.0 Hz, 1 H, -$C\underline{H}_2$-CH=CH_2), 2.83 - 2.78 (m, 1 H, -CO-CH_2-$C\underline{H}$-), 2.78 - 2.70 (m, 1 H, -$C\underline{H}_2$-CH=CH_2) 2.41 - 2.35 (m, 2 H, -CO-$C\underline{H}_2$-), 2.35 - 2.25 (m, 1 H, -N-CH_2-CH_2-$C\underline{H}_2$-), 2.19 - 1.79 (m, 5 H, -N-CH_2-$C\underline{H}_2$-, -N-$C_{quat.}$-$C\underline{H}_2$-, -N-CH_2-CH_2-$C\underline{H}_2$-); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.0 (-$\underline{C}O$-CH_2-), 172.0 (-$\underline{C}O_2$-CH_3), 166.6 (-N-$\underline{C}O$-), 134.0 (-CH_2-$\underline{C}H$=CH_2), 118.6 (-CH_2-CH=$\underline{C}H_2$), 68.4 (-N-$\underline{C}_{quat.}$), 58.1 (-$\underline{C}_{quat.}$-CO_2-CH_3), 52.4 (-CO_2-$\underline{C}H_3$), 45.7 (-N-$\underline{C}H_2$-), 41.6 (-$\underline{C}H_2$-CH=CH_2), 40.4 (-CO-$\underline{C}H_2$-), 36.9 (-CO-CH_2-$\underline{C}H$-), 35.8 (-N-$C_{quat.}$-$\underline{C}H_2$-), 29.0 (-N-CH_2-CH_2-$\underline{C}H_2$-), 22.1 (-N-CH_2-$\underline{C}H_2$-); **LRMS** (ES+) *m/z* (relative intensity %) 278 (28%, $[M + H]^+$), 300 (96, $[M + Na]^+$), 577 (100, $[2M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{15}H_{19}NNaO_4$) requires *m/z* 300.1206, found *m/z* 300.1205. See Appendix 7.1 for NOE spectra.

5.3 Experimental: Chapter 3

Synthesis and Characterisation of 80

Methyl 3,4-dihydro-2*H*-pyrrole-5-carboxylate 1-oxide **80**



Thionyl chloride (1.0 eq., 9.45 mL, 130 mmol) was added dropwise to MeOH (150 mL) at 0 °C under nitrogen. The resulting mixture was stirred for 5 min before L-Proline (1 eq., 15.0 g, 130 mmol) was added in one portion. The reaction mixture was heated to reflux for 12 h and thereafter left to cool to r.t. The reaction mixture was concentrated *in vacuo*. K_2CO_3 (aq.) was carefully added to the pale yellow residue until pH 11-12. The mixture was extracted with CH_2Cl_2 (3 × 150 mL) and the organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude **101** as a pale yellow oil (12.1 g, 72%). The crude product was taken to next step without any further purification. $NaHCO_3$ (5.0 eq., 39.4 g, 468 mmol) was added to a solution of **101** in MeCN / THF (4:1, 134 mL:34 mL) and 0.01 M Na_2EDTA (aq.) (134 mL) at 5 °C. Oxone® (1.05 eq., 60.5 g, 98.4 mmol) was added in small portions under vigorous stirring to the reaction mixture over 2 h while maintaining the temperature below 5 °C. The reaction mixture was stirred for 30 min before EtOAc (480 mL) was added. The organics were separated and the aqueous phase extracted with EtOAc (2 × 240 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% MeOH:EtOAc) to give **80** (5.63 g, 42%) as a colourless solid. Characterisation data were corresponding to literature[42d, 86.]

M.p. 48 - 50 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.24 - 4.15 (m, 2 H, =NO-C<u>H</u>$_2$-), 3.85 (s, 3 H, -CO_2-C<u>H</u>$_3$), 3.11 - 3.02 (m, 2 H, =N(O)-CH_2-CH_2-C<u>H</u>$_2$-), 2.25 - 2.15 (m, 2 H, =N(O)-CH_2-C<u>H</u>$_2$-); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.0 (-<u>C</u>O_2-CH_3), 133.9 (-N(O)=<u>C</u>(-CO_2-CH_3)-CH_2-), 66.8 (=N(O)-<u>C</u>H_2-) 52.2 (-CO_2-<u>C</u>H_3), 29.7 (=N(O)-CH_2-CH_2-<u>C</u>H_2-), 16.6 (=N(O)-CH_2-<u>C</u>H_2-); **LRMS** (ES+) *m/z* (relative intensity %) 144 (42%, $[M + H]^+$), 166 (44, $[M + Na]^+$), 309 (100, $[2M + Na]^+$).

Synthesis and Characterisation of 100

tert-Butyl(diphenyl)(prop-2-yn-1-yloxy)silane oxide **100**

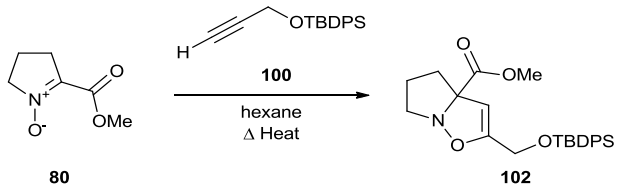
100

TBDPSCl (1.1 eq., 21.6 g, 78.5 mmol) in CH_2Cl_2 (20 mL) was added to a solution of propargyl alcohol (1.0 eq., 4.00 g, 71.4 mmol), imidazole (1.1 eq., 5.34 g, 78.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C under nitrogen. The resulting mixture was stirred for 48 h at r.t. and thereafter quenched with water (50 mL). The organics were separated and the aqueous was extracted with EtOAc (3 × 70 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc:PE) to give **100** (20.9 g, 99%) as a white solid. Characterisation data were corresponding to literature.[64, 87]

M.p. 55 - 57 °C, lit.[64] 61.0 - 61.5 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) 7.78 - δ 7.66 (m, 4 H, Ar<u>H</u>), 7.52 - 7.35 (m, 6 H, Ar<u>H</u>), 4.32 (d, *J* = 2.5 Hz, 2 H, -C<u>H</u>$_2$-O-), 2.40 (t, *J* = 2.5 Hz, 1 H, -C≡C<u>H</u>), 1.08 (s, 9 H, -C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.6 (Ar<u>C</u>), 132.9 (Ar<u>C</u>$_{quat.}$), 129.8 (Ar<u>C</u>), 127.7 (Ar<u>C</u>), 82.0 (-<u>C</u>≡CH), 73.0 (-C≡<u>C</u>H), 52.5 (-<u>C</u>H_2-O-), 26.6 (-C(<u>C</u>H_3)$_3$), 19.1 (-<u>C</u>(CH_3)$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 317 (100%, $[M + Na]^+$).

Synthesis and Characterisation of 102

Methyl 2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-5,6-dihydropyrrolo[1,2-*b*][1,2]oxazole-3a(4*H*)-carboxylate **102**

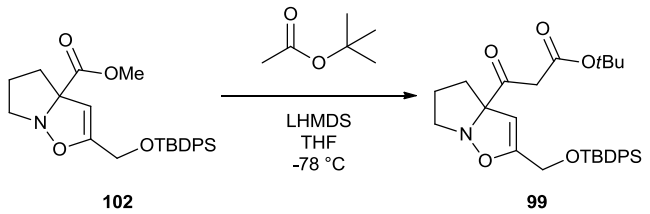


Alkyne **100** (1.3 eq., 2.67 g, 9.08 mmol) was added to a suspension of nitrone **80** (1 eq., 1.00 g, 6.99 mmol) in hexane (40 mL). The reaction mixture was heated to reflux for 12 h and thereafter cooled to r.t. The resulting mixture was concentrated *in vacuo* and the residue was purified by column chromatography (25% EtOAc:PE) to give **102** (2.55 g, 83%) as a pale yellow oil.

IR ν_{max}(thin film)/cm^{-1} 2954 (C-H), 1739 (C=O), 1429, 1113, 823, 704; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 - 7.64 (m, 4 H, Ar<u>H</u>), 7.47 - 7.36 (m, 6 H, Ar<u>H</u>), 4.77 (s, 1 H, -C=C<u>H</u>-), 4.22 (app. dd, *J* = 3.5, 1.0 Hz, 2 H, -O-C<u>H</u>$_2$-), 3.78 (s, 3 H, -CO$_2$-C<u>H</u>$_3$), 3.32 (app. t, *J* = 6.5 Hz, 2 H, -N-C<u>H</u>$_2$-), 2.24 - 2.15 (m, 1 H, -N-CH$_2$-C<u>H</u>$_A$H$_B$-), 2.07 - 1.99 (m, 1 H, -N-CH$_2$-CH$_A$<u>H</u>$_B$-), 1.91 - 1.78 (m, 2 H, -N-CH$_2$-CH$_2$-C<u>H</u>$_2$-), 1.07 (s, 9 H, -C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6 (-<u>C</u>O$_2$-CH$_3$), 155.9 (-O-CH$_2$-<u>C</u>=), 135.5 (Ar<u>C</u>), 132.9 (Ar<u>C</u>), 129.8 (Ar<u>C</u>), 127.71 (Ar<u>C</u>), 96.3 (-O-CH$_2$-C=<u>C</u>H-), 82.0 (-N-<u>C</u>$_{quat.}$-), 60.1 (-N-<u>C</u>H$_2$-), 57.8 (-O-<u>C</u>H$_2$-), 52.6 (-CO$_2$-<u>C</u>H$_3$), 36.6 (-N-CH$_2$-CH$_2$-<u>C</u>H$_2$-), 26.7 (-C(<u>C</u>H$_3$)$_3$), 23.1 (-N-CH$_2$-<u>C</u>H$_2$-), 19.2 (-<u>C</u>(CH$_3$)$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 438 (22%, [M + H]$^+$), 460 (38, [M + Na]$^+$), 897 (100, [2M + Na]$^+$); **HRMS** (ES+) exact mass calculated for [M + Na]$^+$ ($C_{25}H_{31}NNaO_4Si$) requires *m/z* 460.1915, found *m/z* 460.1905.

Synthesis and Characterisation of 99

tert-Butyl 3-[2-({[tert-butyl(diphenyl)silyl]oxy}methyl)-5,6-dihydropyrrolo[1,2b][1,2]oxazol-3a(4H)-yl]-3-oxopropanoate **99**



102 **99**

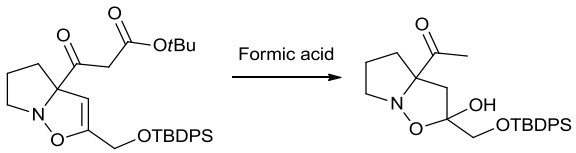
LHMDS (1.5 eq., 1 M in THF, 8.74 mL, 8.74 mmol) was added to a solution of *t*BuOAc (1.5 eq., 1.01 g, 8.74 mmol) in THF (10 mL) at −78 °C under nitrogen. The reaction mixture was warmed to −20 °C, stirred for 5 min and thereafter cooled to −78 °C before a solution of methyl ester **102** (1.0 eq., 2.55 g, 5.83 mmol) in THF (30 mL) was added. The reaction mixture was allowed to slowly warm to r.t. over 12 h before being quenched with saturated NH_4Cl (aq.). The organics were separated and the aqueous phase extracted with EtOAc (2 × 40 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc:PE) to give **99** (2.20 g, 72%) as a yellow oil.

IR ν_{max}(thin film)/cm^{-1} 2933 (C-H), 2859, 1733 (C=O), 1715, 1155, 1113, 703; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 - 7.65 (m, 4 H, Ar$\underline{H}$), 7.48 - 7.36 (m, 6 H, Ar$\underline{H}$), 4.58 (s, 1 H, -C=C$\underline{H}$-), 4.23 (app. d, *J* = 1.0 Hz, 2 H, -O-C$\underline{H_2}$-), 3.79 (d, *J* = 16.0 Hz, 1 H, -C$\underline{H_A}H_B$-CO_2-), 3.45 (d, *J* = 16.0 Hz, 1 H, -C$H_A\underline{H_B}$-CO_2-), 3.30 - 3.16 (m, 2 H, -N-C$\underline{H_2}$-), 2.29 - 2.20 (m, 1 H, -N-CH_2-CH_2-C$\underline{H_A}H_B$-), 1.91 - 1.99 (m, 1 H, -N-CH_2-CH_2-$CH_A\underline{H_B}$-), 1.87 - 1.69 (m, 2 H, -N-CH_2-C$\underline{H_2}$-), 1.47 (s, 9 H, -CO_2-C(C$\underline{H_3}$)$_3$), 1.07 (s, 9 H, (-Si-C(C$\underline{H_3}$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.0 (-$\underline{C}$O-), 167.0 (-$\underline{C}O_2$-$C(CH_3)_3$), 156.8 (-$\underline{C}$=CH-), 135.5 (Ar$\underline{C}$), 132.8 (Ar$\underline{C}$), 129.9 (Ar$\underline{C}$), 127.8 (Ar$\underline{C}$), 96.4 (-C=$\underline{C}$H-), 87.7 (-N-$\underline{C}_{quat.}$-), 81.5 (-CO_2-$\underline{C}(CH_3)_3$), 59.8

(-N-<u>C</u>H_2-), 57.8 (-O-<u>C</u>H_2-), 46.5 (-<u>C</u>H_2-CO_2-), 34.0 (-N-CH_2-CH_2-<u>C</u>H_2-), 28.0 (-CO_2-C(<u>C</u>H_3)$_3$), 26.7 (-Si-C(<u>C</u>H_3)$_3$), 23.1 (-N-CH_2-<u>C</u>H_2-), 19.2 (-Si-<u>C</u>$(CH_3)_3$); **LRMS** (ES+) *m/z* (relative intensity %) 522 (63%, $[M + H]^+$), 544 (100, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{30}H_{39}NNaO_5Si$) requires *m/z* 544.2490, found *m/z* 544.2467.

Synthesis and Characterisation of 106

1-[2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2-hydroxytetrahydropyrrolo[1,2-*b*][1,2]oxazol-3a(4*H*)-yl]ethanone **99**



99 **106**

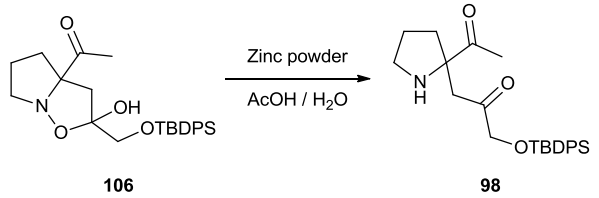
Formic acid (6 mL) was added to β-keto ester **99** (375 mg, 0.72 mmol) at r.t. and the mixture was thereafter heated to 30 °C and stirred for 13 h The reaction mixture was diluted with EtOAc (12 mL) and basified with sat. $NaHCO_3$ (aq.). The organics were separated and the aqueous phase extracted with EtOAc (3 × 12 mL). The organics were combined washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc:PE) to give **106** (237 mg, 75%) as a pale yellow oil as a mixture of diastereoisomers (d.r. 3:1).

IR ν_{max}(thin film)/cm^{-1} 3249 (O-H) 2959 (C-H), 2858, 1713 (C=O), 1446, 1113, 703; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereoisomers, ratio 3:1) δ 7.74 -7.65 (m, 8 H, Ar<u>H</u>, major and minor), 7.48 - 7.36 (m, 12 H, Ar<u>H</u>, major and minor), 3.78 - 3.71 (m, 1 H, -N-C<u>H</u>$_A$H$_B$-, minor), 3.77 - 3.62 (m, 4 H, -O-C<u>H</u>$_2$-, major and minor), 3.53 - 3.45 (m, 1 H, -N-CH$_A$<u>H</u>$_B$-, minor), 3.45 - 3.37 (m, 1 H, -N-C<u>H</u>$_A$H$_B$-, major), 3.13 - 3.03 (m, 1 H, -N-CH$_A$<u>H</u>$_B$-, major), 2.82 (d,

J = 13.0 Hz, 1 H, -$C_{quat.}$-C$\underline{H}_A$$H_B$-, major), 2.67 (d, J = 14.0 Hz, 1 H, -$C_{quat.}$-C$\underline{H}_A$$H_B$-, minor), 2.41 (s, 3 H, -CO-C$\underline{H}_3$, major), 2.24 (s, 3 H, -CO-C$\underline{H}_3$, minor), 2.31 - 2.18 (m, 2 H, -$C_{quat.}$-C$H_A$$\underline{H}_B$-, major and minor), 2.24 - 2.18 (m, 1 H, -N-CH_2-CH_2-C$\underline{H}_A$$H_B$-, minor), 2.16 - 2.08 (m, 1 H,--N-CH_2-CH_2-C$H_A$$\underline{H}_B$-, minor), 2.08 - 1.93 (m, 3 H, -N-CH_2-CH_2-C$\underline{H}_A$$H_B$-, major, -N-$CH_2$-C$\underline{H}_A$$H_B$-, major and minor), 1.92 - 1.83 (m, 1 H, -N-CH_2-CH_2-C$H_A$$\underline{H}_B$-, major), 1.83 - 1.71 (m, 2 H, -N-CH_2-C$H_A$$\underline{H}_B$-, major and minor), 1.08 (s, 18 H, -C(C$\underline{H}_3$)$_3$, major and minor); **^{13}C NMR** (100 MHz, $CDCl_3$, mixture of diastereoisomers, ratio 3:1) δ 210.5 (-$\underline{C}$O-CH_3, major), 210.2 (-$\underline{C}$O-CH_3, minor), 135.7 (Ar$\underline{C}$, major), 135.6 (Ar$\underline{C}$, minor), 135.6 (Ar$\underline{C}$, major), 135.5 (Ar$\underline{C}$, minor), 132.7 (Ar$\underline{C}$, major), 132.6 (Ar$\underline{C}$, minor and major), 132.4 (Ar$\underline{C}$, minor), 129.9 (4 × Ar$\underline{C}$, minor and major), 127.8 (4 × Ar$\underline{C}$, minor and major), 108.1 (-$\underline{C}_{quat.}$-OH, minor), 104.2 (-$\underline{C}_{quat.}$-OH, major), 82.7 (-$\underline{C}_{quat.}$-CO-CH_3, major), 82.1 (-$\underline{C}_{quat.}$-CO-CH_3, minor), 67.4 (-O-$\underline{C}H_2$-, minor), 65.8 (-O-$\underline{C}H_2$-, major), 58.7 (-N-$\underline{C}H_2$-, minor), 57.7 (-N-$\underline{C}H_2$-, major), 47.3 (-$C_{quat.}$(OH)-$\underline{C}H_2$-, major), 46.5 (-$C_{quat.}$(OH)-$\underline{C}H_2$-, minor), 34.6 (-N-CH_2-CH_2-$\underline{C}H_2$-, major), 33.3 (-N-CH_2-CH_2-$\underline{C}H_2$-, minor), 26.8 (-C($\underline{C}H_3$)$_3$, major and minor), 25.8 (-CO-$\underline{C}H_3$, major), 24.9 (-CO-$\underline{C}H_3$, minor), 24.0 (-N-CH_2-$\underline{C}H_2$, major), 23.6 (-N-CH_2-$\underline{C}H_2$-, minor), 19.2 (-$\underline{C}$(CH_3)$_3$, major and minor); **LRMS** (ES+) *m/z* (relative intensity %) 440 (20%, $[M + H]^+$), 462 (20, $[M + Na]^+$), 901 (100, $[2M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + H]^+$ ($C_{25}H_{34}NO_4Si$) requires *m/z* 440.2252, found *m/z* 440.2238.

Synthesis and Characterisation of 98

1-(2-Acetylpyrrolidin-2-yl)-3-{[*tert*-butyl(diphenyl)silyl]oxy}acetone **98**



106 **98**

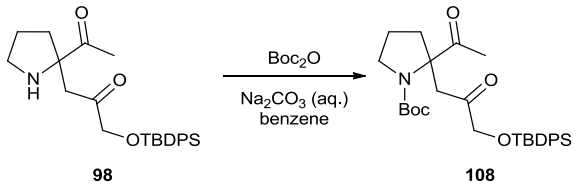
To a vigorously stirred solution of methyl ketone **106** (1 eq., 414 mg, 0.942 mmol) in AcOH:H_2O (3:1, 3 mL:1 mL) was added activated zinc dust (5 eq., 308 mg, 4.71 mmol) in one portion at r.t. The reaction mixture was stirred for 5 min before another portion of activated zinc dust (5 eq., 308 mg, 4.71 mmol) was added and thereafter stirred for 2 h at r.t. The reaction was quenched by carefully adding sat. $NaHCO_3$ (aq.) until pH ~ 7. The mixture was extracted with CH_2Cl_2 (4 × 10 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the desired product **98** as a yellow oil (399 mg, quant.) which was taken directly to next step without further purification.

IR ν_{max}(thin film)/cm^{-1} 3376 (N-H), 2957 (C-H), 2858, 1728 (C=O), 1428, 1112, 704; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 - 7.61 (m, 4 H, Ar<u>H</u>), 7.48 - 7.34 (m, 6 H, Ar<u>H</u>), 4.49 (d, *J* = 18.0 Hz, 1 H, -O-C<u>H</u>$_A$H$_B$-), 4.37 (d, *J* = 18.0 Hz, 1 H, -O-CH$_A$<u>H</u>$_B$-), 4.18 (d, *J* = 20.0 Hz, 1 H, -CO-C<u>H</u>$_A$H$_B$-), 3.67 (dt, *J* = 11.0, 8.0 Hz, 1 H, -NH-C<u>H</u>$_A$H$_B$-), 3.44 (d, *J* = 20.0 Hz, 1 H, -CO-CH$_A$<u>H</u>$_B$-), 3.48 -3.40 (m, 1 H, -NH-CH$_A$<u>H</u>$_B$-), 2.22 - 2.07 (m, 3 H, -NH-CH$_2$-C<u>H</u>$_A$H$_B$-CH$_2$, -NH-CH$_2$-CH$_2$-C<u>H</u>$_2$-), 2.03 (s, 3 H, -CO-C<u>H</u>$_3$), 1.81 - 1.70 (m, 1 H, -NH-CH$_2$-CH$_A$<u>H</u>$_B$-CH$_2$-), 1.10 (s, 9 H, -C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.5 (-CH$_2$-<u>C</u>O-), 202.5 (-<u>C</u>O-CH$_3$), 135.6 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 132.5 (Ar<u>C</u>), 132.1 (Ar<u>C</u>), 130.1 (Ar<u>C</u>), 129.6 (Ar<u>C</u>), 127.9 (Ar<u>C</u>), 127.7 (Ar<u>C</u>), 73.4 (-NH-<u>C</u>$_{quat.}$-), 69.4 (-O-<u>C</u>H$_2$-CO-), 46.7 (-NH-<u>C</u>H$_2$-), 44.4 (-C$_{quat.}$-<u>C</u>H$_2$-CO-),

34.2 (-NH-CH_2-CH_2-$\underline{C}H_2$-), 26.8 (-C($\underline{C}H_3$)$_3$), 23.2 (-CO-$\underline{C}H_3$), 22.7 (-NH-CH_2-$\underline{C}H_2$), 19.2 (-$\underline{C}$(CH_3)$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 424 (93%, $[M + H]^+$), 456 (100, $[M + H + MeOH]^+$); **HRMS** (ES+) exact mass calculated for $[M + H]^+$ ($C_{25}H_{34}NO_3Si$) requires *m/z* 424.2302, found *m/z* 424.2303.

Synthesis and Characterisation of 108

tert-Butyl 2-acetyl-2-(3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-oxopropyl)pyrrolidine-1-carboxylate **108**



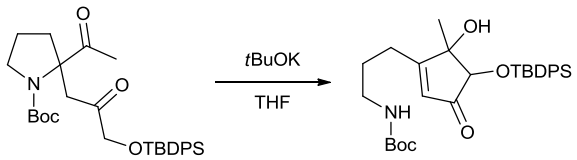
Boc_2O (3 eq., 617 mg, 2.83 mmol) was added to a biphasic solution of amine **98** (1 eq., 399 mg, 0.942 mmol) in saturated Na_2CO_3 (aq.) (1 mL) and benzene (3 mL). The reaction mixture was stirred at r.t. for 18 h The organics were separated and the aqueous phase extracted with EtOAc (3 × 2 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (15% → 20% EtOAc:PE) to give **108** (582 mg, 69% over 2 steps) as a yellow oil. The ^1H and ^{13}C NMR spectra were complicated by *N*-Boc rotamers at 298 K.

IR ν_{max}(thin film)/cm^{-1} 2931 (C-H), 1688 (C=O), 1387, 1111, 702; **^{1}H NMR** (500 MHz, $CDCl_3$, mixture of rotamers, ratio 1:0.85) δ 7.71 - 7.65 (m, 8 H, Ar$\underline{H}$, major and minor rotamers), 7.47 - 7.34 (m, 12 H, Ar$\underline{H}$, major and minor rotamers), 4.48 - 4.22 (m, 4 H, -O-C$\underline{H}_2$-, major and minor rotamers), 3.59 (t, *J* = 7.0 Hz, 2 H, -N-C$\underline{H}_2$-, minor rotamer), 3.50 (t, *J* = 6.5 Hz, 2 H, -N-C$\underline{H}_2$-, major rotamer), 3.26 (d, *J* = 16.0 Hz, 1 H, -CO-C$\underline{H}_A$$H_B$-,

minor rotamer), 3.17 (d, *J* = 15.5 Hz, 1 H, -CO-C$\underline{H}_A$H$_B$-, major rotamer), 2.71 - 2.55 (m, 2 H, -N-CH$_2$-CH$_2$-C$\underline{H}_A$H$_B$-, major and minor rotamers), 2.60 (d, *J* = 15.5 Hz, 1 H, -CO-CH$_A\underline{H}_B$-, major rotamer), 2.42 (d, *J* = 16.0 Hz, 1 H, -CO-CH$_A\underline{H}_B$-, minor rotamer), 2.07 (s, 3 H, -CO-C$\underline{H}_3$, minor rotamer), 2.06 (s, 3 H, -CO-C$\underline{H}_3$, major rotamer), 2.06 - 2.00 (m, 1 H, -N-CH$_2$-CH$_2$-CH$_A\underline{H}_B$-, minor rotamer), 1.99 - 1.87 (m, 5 H, -N-CH$_2$-CH$_2$-CH$_A\underline{H}_B$-, major rotamer, -N-CH$_2$-C$\underline{H}_2$-, major and minor rotamers), 1.41 (s, 9 H, -CO$_2$-C(C$\underline{H}_3$)$_3$, major rotamer), 1.36 (s, 9 H, -CO$_2$-C(C$\underline{H}_3$)$_3$, minor rotamer), 1.11 (s, 9 H, -Si-C(C$\underline{H}_3$)$_3$, minor rotamer), 1.09 (s, 9 H, -Si-C(C$\underline{H}_3$)$_3$, major rotamer); **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers, ratio 1:0.9) δ 207.1 (-$\underline{C}$O-, rotamer), 206.6 (-$\underline{C}$O-, rotamer), 206.5 (-$\underline{C}$O-, rotamer), 206.4 (-$\underline{C}$O-, rotamer), 153.8 (-$\underline{C}$O$_2$-C(CH$_3$)$_3$, rotamer), 152.7 (-$\underline{C}$O$_2$-C(CH$_3$)$_3$, rotamer), 135.6 (Ar$\underline{C}$, rotamer), 135.5 (3 × Ar$\underline{C}$, rotamer), 133.0 (Ar$\underline{C}$, major and minor rotamers), 132.8 (Ar$\underline{C}$, major and minor rotamers), 129.9 (2 × Ar$\underline{C}$, minor rotamers), 129.7 (2 × Ar$\underline{C}$, major rotamer), 127.8 (2 × Ar$\underline{C}$, major rotamer), 127.7 (2 × Ar$\underline{C}$, minor rotamer), 81.2 (-CO$_2$-$\underline{C}$(CH$_3$)$_3$, minor rotamer), 80.2 (-CO$_2$-$\underline{C}$(CH$_3$)$_3$, major rotamer), 72.4 (-N-$\underline{C}_{quat.}$-, rotamer), 72.3 (-N-$\underline{C}_{quat.}$-, rotamer), 70.5 (-Si-O-$\underline{C}$H$_2$-, minor rotamer), 70.4 (-Si-O-$\underline{C}$H$_2$-, major rotamer), 47.7 (-N-$\underline{C}$H$_2$-, major rotamer), 47.6 (-N-$\underline{C}$H$_2$-, minor rotamer), 40.3 (-C$_{quat.}$-$\underline{C}$H$_2$-, minor rotamer), 39.3 (-C$_{quat.}$-$\underline{C}$H$_2$-, major rotamer), 34.7 (-N-CH$_2$-CH$_2$-$\underline{C}$H$_2$-, minor rotamer), 33.6 (-N-CH$_2$-CH$_2$-$\underline{C}$H$_2$-, major rotamer), 28.3 (-CO$_2$-C($\underline{C}$H$_3$)$_3$, major rotamer), 28.2 (-CO$_2$-C($\underline{C}$H$_3$)$_3$, minor rotamer), 26.8 (-Si-C($\underline{C}$H$_3$)$_3$, minor rotamer), 26.7 (-Si-C($\underline{C}$H$_3$)$_3$, major rotamer), 23.4 (-NH-$\underline{C}$H$_2$-, major rotamer), 23.3 (-NH-$\underline{C}$H$_2$-, minor rotamer), 23.0 (-CO-$\underline{C}$H$_3$, minor rotamer), 22.7 (-CO-$\underline{C}$H$_3$, major rotamer), 19.3 (-Si-C($\underline{C}$H$_3$)$_3$, major and minor rotamer); **LRMS** (ES−) *m/z* (relative intensity %) 522 (100%, $[M - H]^-$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{30}H_{41}NNaO_5Si$) requires *m/z* 546.2646, found *m/z* 546.2647.

Synthesis and Characterisation of 109

tert-Butyl [3-(4-{[*tert*-butyl(diphenyl)silyl]oxy}-5-hydroxy-5-methyl-3-oxocyclopent-1-en-1-yl)propyl]carbamate **109**



108 **109**

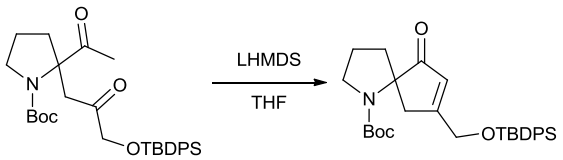
*t*BuOK (2.1 eq., 1 M in THF, 0.080 mL, 0.080 mmol) was added to a solution of ketone **108** (1.0 eq., 20 mg, 0.038 mmol) in THF (0.4 mL) at −30 °C under nitrogen. The reaction mixture was allowed to slowly warm to 0 °C over 1 h 30 min before being quenched with saturated NH_4Cl (aq.). The reaction mixture was extracted with EtOAc (3 × 2 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (15% → 30% EtOAc:PE) to give **109** (5 mg, 25%) as a colourless oil and as one diastereoisomer.

IR ν_{max}(thin film)/cm^{-1} 3361 (O-H), 2931 (C-H), 2859, 1715 (C=O), 1518, 1170, 703; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.0, 1.4 Hz, 2 H, Ar<u>H</u>), 7.74 (dd, *J* = 8.0, 1.4 Hz, 2 H, Ar<u>H</u>), 7.38 - 7.49 (m, 6 H, Ar<u>H</u>), 5.89 (t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-), 4.64 (br. s., 1 H, -N<u>H</u>-CH_2-), 3.84 (s, 1 H, -C(O<u>H</u>)CH_3), 3.25 (s, 1 H, -CO-C<u>H</u>-O-), 3.20 (q, *J* = 6.0 Hz, 2 H, -NH-C<u>H</u>$_2$-), 2.55 - 2.46 (m, 1 H, -NH-CH_2-CH_2-C<u>H</u>$_A$H$_B$-), 2.39 - 2.30 (m, 1 H, -NH-CH_2-CH_2-CH_A<u>H</u>$_B$-), 1.79 (quin, *J* = 7.0 Hz, 2 H, -NH-CH_2-C<u>H</u>$_2$-CH_2-), 1.44 (s, 9 H, -CO_2-C(C<u>H</u>$_3$)$_3$), 1.15 (s, 9 H, -Si-C(C<u>H</u>$_3$)$_3$), 1.01 (s, 3 H, -C(OH)C<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$,) δ 202.4 (-<u>C</u>O-CH=C-), 180.8 (-CO-CH=<u>C</u>-), 155.9 (-N-<u>C</u>O_2-$C(CH_3)_3$), 136.3 (2 × Ar<u>C</u>), 136.0 (2 × Ar<u>C</u>),132.9 (Ar<u>C</u>), 132.1 (Ar<u>C</u>), 130.2 (Ar<u>C</u>), 130.1 (Ar<u>C</u>), 127.8 (2 × Ar<u>C</u>), 127.6 (2 × Ar<u>C</u>), 126.8 (-CO-<u>C</u>H=C), 79.3 (-CO_2-<u>C</u>$(CH_3)_3$), 78.0 (-CO-<u>C</u>H-O-), 75.5 (-<u>C</u>(OH)CH_3), 40.0 (-NH-<u>C</u>H_2-),

28.4 (-CO_2-C($\underline{C}H_3$)$_3$), 27.3 (-NH-CH_2-$\underline{C}H_2$-CH_2-), 27.0 (-Si-C($C\underline{H}_3$)$_3$), 25.3 (-NH-CH_2-CH_2-$\underline{C}H_2$-), 23.5 (-C(OH)$\underline{C}H_3$), 19.6 (-Si-$\underline{C}$(CH_3)$_3$,); **LRMS** (ES+) *m/z* (relative intensity %) 546 (97%, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{30}H_{41}NNaO_5Si$) requires *m/z* 546.2646, found *m/z* 546.2640.

Synthesis and Characterisation of 112

tert-Butyl 8-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-oxo-1-azaspiro[4.4]non-7-ene-1-carboxylate **112**



108 **112**

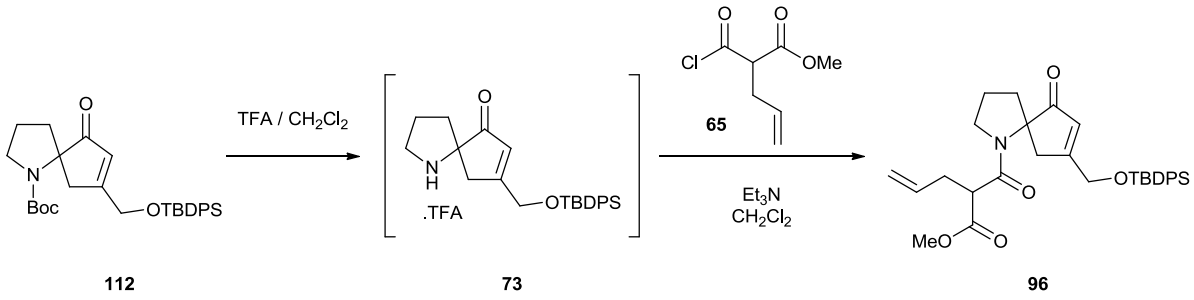
LHMDS (3.0 eq., 0.9 M in methyl cyclohexanes, 0.484 mL, 0.435 mmol) was added dropwise to a solution of ketone **108** (1.0 eq., 76 mg, 0.145 mmol) in THF (1.5 mL) at −78 °C under nitrogen. The reaction mixture was allowed to slowly warm to r.t. over 8 h before being quenched with saturated NH_4Cl (aq.). The reaction mixture was extracted with EtOAc (3 × 3 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% → 30% EtOAc:PE) to give **112** (33 mg, 45%) as a yellow oil. The ^{1}H and ^{13}C NMR spectra were complicated by *N*-Boc rotamers at 298 K.

IR ν_{max}(thin film)/cm^{-1} 2961 (C-H), 2931, 1693 (C=O), 1366, 1141, 702; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers, ratio 1:0.5) δ 7.69 - 7.63 (m, 8 H, Ar$\underline{H}$, major and minor rotamers), 7.49 - 7.36 (m, 12 H, Ar$\underline{H}$, major and minor rotamers), 6.44 - 6.41 (m, 1 H, -CO-C$\underline{H}$=C-), 6.36 (t, *J* = 2.0 Hz, 1 H, -CO-C$\underline{H}$=C-), 4.57 - 4.32 (m, 4 H, -O-C$\underline{H}_2$-, major and

minor rotamers), 3.60 - 3.49 (m, 4 H, -N-C$\underline{H}_2$-, major and minor rotamers), 3.01 (d, J = 17.5 Hz, 1 H, -$C_{quat.}$-C$\underline{H}_A$H$_B$-C=CH-, minor rotamer) 2.85 (d, J = 17.5 Hz, 1 H, -$C_{quat.}$-C$\underline{H}_A$H$_B$-C=CH-, major rotamer), 2.40 (d, J = 17.5 Hz, 1 H, -$C_{quat.}$-CH$_A\underline{H}_B$-C=CH-, major rotamer), 2.34 (d, J = 17.5 Hz, 1 H, -$C_{quat.}$-CH$_A\underline{H}_B$-C=CH-, minor rotamer), 2.13 - 1.94 (m, 4 H, -N-CH$_2$-CH$_2$-C$\underline{H}_A$H$_B$-, -N-CH$_2$-C$\underline{H}_A$H$_B$-, major and minor rotamers), 1.87 - 1.66 (m, 4 H, -N-CH$_2$-CH$_2$-CH$_A\underline{H}_B$-, -N-CH$_2$-CH$_A\underline{H}_B$-, major and minor rotamers), 1.44 (s, 9 H, -CO$_2$-C(C$\underline{H}_3$)$_3$, minor rotamer), 1.34 (s, 9 H, -CO$_2$-C(C$\underline{H}_3$)$_3$, major rotamer), 1.09 (s, 9 H, -Si-C(C$\underline{H}_3$)$_3$, major rotamer), 1.07 (s, 9 H, -Si-C(C$\underline{H}_3$)$_3$, minor rotamer); **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers, ratio 1:0.5) δ 207.4 (-$\underline{C}$O-, rotamer), 207.3 (-$\underline{C}$O-, rotamer), 176.0 (-CO-CH=$\underline{C}$-, rotamer), 175.7 (-CO-CH=$\underline{C}$-, rotamer), 153.3 (-$\underline{C}$O$_2$-C(CH$_3$)$_3$, rotamer), 153.0 (-$\underline{C}$O$_2$-C(CH$_3$)$_3$, rotamer), 135.5 (2 × Ar$\underline{C}$, minor rotamer), 135.4 (2 × Ar$\underline{C}$, major rotamer), 132.9 (Ar$\underline{C}$, rotamer), 132.8 (Ar$\underline{C}$, rotamer), 132.7 (Ar$\underline{C}$, rotamer), 132.6 (Ar$\underline{C}$, rotamer), 130.0 (2 × Ar$\underline{C}$, major rotamer), 129.9 (2 × Ar$\underline{C}$, minor rotamer), 127.9 (2 × Ar$\underline{C}$, major rotamer), 127.8 (2 × Ar$\underline{C}$, minor rotamer), 126.2 (-CO-$\underline{C}$H=C-, minor rotamer), 126.0 (-CO-$\underline{C}$H=C-, major rotamer), 80.3 (-CO$_2$-$\underline{C}$(CH$_3$)$_3$, major rotamer), 79.8 (-CO$_2$-$\underline{C}$(CH$_3$)$_3$, minor rotamer), 68.9 (-N-$\underline{C}_{quat.}$-, minor rotamer), 68.4 (-N-$\underline{C}_{quat.}$-, major rotamer), 64.0 (-Si-O-$\underline{C}$H$_2$-, minor rotamer), 63.9 (-Si-O-$\underline{C}$H$_2$-, major rotamer), 48.1 (-N-$\underline{C}$H$_2$-, minor rotamer), 47.9 (-N-$\underline{C}$H$_2$-, major rotamer), 42.7 (-$C_{quat.}$-$\underline{C}$H$_2$-C=CH-, minor rotamer), 41.4 (-$C_{quat.}$-$\underline{C}$H$_2$-C=CH-, major rotamer), 40.0 (-NH-CH$_2$-CH$_2$-$\underline{C}$H$_2$-, major rotamer) 39.1 (-NH-CH$_2$-CH$_2$-$\underline{C}$H$_2$-, minor rotamer), 28.4 (-CO$_2$-C($\underline{C}$H$_3$)$_3$, minor rotamer), 28.2 (-CO$_2$-C($\underline{C}$H$_3$)$_3$, major rotamer), 26.7 (-Si-C(C$\underline{H}_3$)$_3$, major and minor rotamer), 23.8 (-N-CH$_2$-$\underline{C}$H$_2$-, minor rotamer), 23.2 (-N-CH$_2$-$\underline{C}$H$_2$-, major rotamer), 19.2 (-Si-$\underline{C}$(CH$_3$)$_3$, major and minor rotamer); **LRMS** (ES+) *m/z* (relative intensity %) 528 (72%, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{30}H_{39}NNaO_4Si$) requires *m/z* 528.2541, found *m/z* 528.2542.

Synthesis and Characterisation of 96

Methyl 2-{[8-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-oxo-1-azaspiro[4.4]non-7-en-1-yl]carbonyl}pent-4-enoate **96**



112 **73** **96**

TFA (0.1 mL) was added to a solution of **112** (1.0 eq., 20 mg, 0.040 mmol) in CH_2Cl_2 (0.5 mL) at r.t. The reaction mixture was stirred for 1 h at r.t. before being concentrated *in vacuo* to give **73** as a brown oil (20 mg, quant.) which was taken to next step without any further purification. To a solution of amine / TFA salt **73** (1.0 eq., 20 mg, 0.040 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (2.2 eq. 12 μL, 0.088 mmol) followed by acid chloride **65**[37] (1.1 eq., 8 mg, 0.044 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 5 min and thereafter warmed to r.t. and stirred for a further 2 h. The reaction mixture was concentrated *in vacuo*. The residue was taken into water (2 mL) and extracted with EtOAc (3 × 1 mL). The organics were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% → 30% EtOAc:PE) to give **96** (11 mg, 51%) as a colourless oil and as a mixture of separable diastereoisomers (d.r. 4:1).

Major diastereoisomer:

IR ν_{max}(thin film)/cm^{-1} 2927 (C-H), 2856, 1716 (C=O), 1649, 1427, 1111, 703; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 4 H, Ar<u>H</u>), 7.48 - 7.37 (m, 6 H, Ar<u>H</u>), 6.43 (t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-), 5.88 - 5.71 (m, 1 H, -CH_2-C<u>H</u>=CH_2), 5.16 - 5.05 (m, 2 H, -CH_2-CH=C<u>H_2</u>),

4.52 (d, *J* = 17.5 Hz, 1 H, -O-C$\underline{H}_A$H$_B$-), 4.35 (d, *J* = 17.5 Hz, 1 H, -O-CH$_A$$\underline{H}_B$-), 3.71 (s, 3 H, -CO$_2$-C$\underline{H}_3$), 3.79 - 3.62 (m, 2 H, -N-C$\underline{H}_2$-), 3.51 (t, *J* = 7.5 Hz, 1 H, -N-CO-C$\underline{H}$-), 3.00 (d, *J* = 18.0 Hz, 1 H, -C$_{quat.}$-C$\underline{H}_A$H$_B$-C=CH-), 2.72 - 2.59 (m, 2 H, -C$\underline{H}_2$-CH=CH$_2$), 2.33 (d, *J* = 18.0 Hz, 1 H, -C$_{quat.}$-CH$_A$$\underline{H}_B$-C=CH-), 2.16 - 2.09 (m, 1 H, -N-CH$_2$-C$\underline{H}_A$H$_B$-), 2.09 - 2.02 (m, 1 H, -N-CH$_2$-CH$_2$-C$\underline{H}_A$H$_B$-), 2.01 - 1.91 (m, 1 H, -N-CH$_2$-CH$_A$$\underline{H}_B$-), 1.77 - 1.71 (m, 1 H, -N-CH$_2$-CH$_2$-CH$_A$$\underline{H}_B$-), 1.07 (s, 9 H, -Si-C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 205.6 (-$\underline{C}$O-CH=C-), 175.2 (-CO-CH=$\underline{C}$-), 169.8 (-$\underline{C}$O$_2$-CH$_3$), 165.9 (-N-$\underline{C}$O-), 135.5 (2 × Ar$\underline{C}$), 134.6 (-CH$_2$-$\underline{C}$H=CH$_2$), 132.9 (Ar$\underline{C}$), 132.7 (Ar$\underline{C}$), 129.9 (2 × Ar$\underline{C}$), 127.9 (Ar$\underline{C}$), 127.8 (Ar$\underline{C}$), 126.2 (-CO-$\underline{C}$H=C-), 117.3 (-CH$_2$-CH=$\underline{C}$H$_2$), 69.9 (-N-$\underline{C}_{quat.}$-), 63.8 (-$\underline{C}$H$_2$-O-), 52.4 (-CO$_2$-$\underline{C}$H$_3$), 50.5 (-N-CO-$\underline{C}$H-), 48.6 (-N-$\underline{C}$H$_2$-), 40.9 (-C$_{quat.}$-$\underline{C}$H$_2$-C=CH-), 38.1 (-N-CH$_2$-CH$_2$-$\underline{C}$H$_2$), 33.1 (-$\underline{C}$H$_2$-CH=CH$_2$), 26.7 (-Si-C($\underline{C}$H$_3$)$_3$), 24.4 (-N-CH$_2$-$\underline{C}$H$_2$-), 19.2 (-Si-$\underline{C}$(CH$_3$)$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 546 (10%, [M + H]$^+$), 568 (50, [M + Na]$^+$); **HRMS (**ES+) exact mass calculated for [M + Na]$^+$ (C$_{32}$H$_{39}$NNaO$_5$Si) requires *m/z* 568.2490, found *m/z* 568.2491.

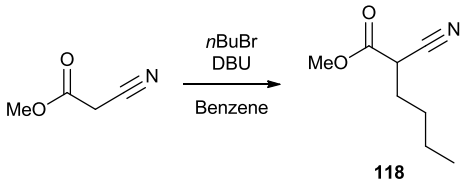
Minor diastereoisomer:

IR ν$_{max}$(thin film)/cm^{-1} 2931 (C-H), 2860, 1722 (C=O), 1651, 1434, 1112, 703; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.68 - 7.65 (m, 4 H, Ar$\underline{H}$), 7.48 - 7.37 (m, 6 H, Ar$\underline{H}$), 6.40 (t, *J* = 1.5 Hz, 1 H, -CO-C$\underline{H}$=C-), 5.77 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 2 H, -CH$_2$-C$\underline{H}$=CH$_2$), 5.10 (dd, *J* = 17.0, 1.5 Hz, 1 H, -CH$_2$-CH=C$\underline{H}_A$H$_B$), 5.03 (dd, *J* = 10.0, 1.5 Hz, 1 H, -CH$_2$-CH=CH$_A$$\underline{H}_B$), 4.51 (d, *J* = 17.5 Hz, 1 H, -O-C$\underline{H}_A$H$_B$-), 4.36 (d, *J* = 17.5 Hz, 1 H, -O-CH$_A$$\underline{H}_B$-), 3.77 (s, 3 H, -CO$_2$-C$\underline{H}_3$), 3.76 - 3.65 (m, 2 H, -N-C$\underline{H}_2$-), 3.53 (t, *J* = 7.5 Hz, 1 H, -N-CO-C$\underline{H}$-), 2.96 (d, *J* = 17.0 Hz, 1 H, -C$_{quat.}$-C$\underline{H}_A$H$_B$-C=CH-), 2.71 - 2.59 (m, 2 H, -C$\underline{H}_2$-CH=CH$_2$), 2.33 (d, *J* = 17.0 Hz, 1 H, -C$_{quat.}$-CH$_A$$\underline{H}_B$-C=CH-), 2.17 - 2.10 (m, 1 H, -N-CH$_2$-C$\underline{H}_A$H$_B$-), 2.09 - 2.04 (m, 1 H, -N-CH$_2$-CH$_2$-C$\underline{H}_A$H$_B$-), 1.99 - 1.90 (m, 1 H, -N-CH$_2$-CH$_A$$\underline{H}_B$-), 1.77 - 1.70 (m, 1 H, -N-CH$_2$-CH$_2$-CH$_A$$\underline{H}_B$-), 1.07 (s, 9 H, -Si-C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 205.3

(-<u>C</u>O-CH=C-), 174.7 (-CO-CH=<u>C</u>-), 169.3 (-<u>C</u>O_2-CH_3), 166.0 (-N-<u>C</u>O-), 135.5 (2 × Ar<u>C</u>), 134.6 (-CH_2-<u>C</u>H=CH_2), 132.9 (Ar<u>C</u>), 132.7 (Ar<u>C</u>), 129.9 (2 × (Ar<u>C</u>), 127.9 (Ar<u>C</u>), 127.8 (Ar<u>C</u>), 126.2 (-CO-<u>C</u>H=C-), 117.3 (-CH_2-CH=<u>C</u>H_2), 69.8 (-N-$\underline{C}_{quat.}$-), 63.8 (-O-<u>C</u>H_2-) 52.6 (-CO_2-<u>C</u>H_3), 50.5 (-N-CO-<u>C</u>H-), 48.8 (-N-<u>C</u>H_2-), 41.1 (-$C_{quat.}$-<u>C</u>H_2-C=CH-), 38.1 (-N-CH_2-CH_2-<u>C</u>H_2), 33.0 (-<u>C</u>H_2-CH=CH_2), 26.7 (-Si-C(<u>C</u>H_3)$_3$), 24.4 (-N-CH_2-<u>C</u>H_2-), 19.2 (-Si-<u>C</u>(CH_3)$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 546 (10%, $[M + H]^+$), 568 (50, $[M + Na]^+$); **HRMS (**ES+) exact mass calculated for $[M + Na]^+$ ($C_{32}H_{39}NNaO_5Si$) requires *m/z* 568.2490, found *m/z* 568.2493.

Synthesis and Characterisation of 118

Methyl 2-cyanohexanoate **118**



118

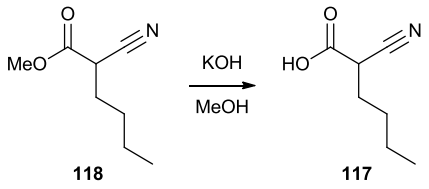
n-Butyl bromide (1.0 eq., 553 mg, 4.04 mmol) was added to a solution of methyl cyanoacetate (1.0 eq., 400 mg, 4.04 mmol) and DBU (1.0 eq., 614 mg, 4.04 mmol) in benzene (8 mL) at r.t. The reaction mixture was stirred for 21 h at r.t. and then filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (10% EtOAc:PE) to give **118** (207 mg, 33%) as a colourless oil.

IR ν_{max}(thin film)/cm^{-1} 2960 (C-H), 2251 (C≡N), 1749 (C=O), 1458, 1256, 732; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.83 (s, 3 H, -CO_2-C<u>H</u>$_3$), 3.51 (m, 1 H, t, *J* = 7.0 Hz, -C<u>H</u>-C≡N), 2.00 - 1.93 (m, 2 H, -C<u>H</u>$_2$-CH_2-CH_2-CH_3), 1.55 - 1.45 (m, 2 H, -CH_2-C<u>H</u>$_2$-CH_2-CH_3), 1.44 - 1.35 (m, 2 H, -CH_2-CH_2-C<u>H</u>$_2$-CH_3), 0.94 (t, *J* = 7.0 Hz, 3 H, -CH_2-CH_2-CH_2-C<u>H</u>$_3$);

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7 (-$\underline{C}O_2$-CH_3), 116.5 (-CH-$\underline{C}$≡N), 53.4 (-CO_2-$\underline{C}H_3$), 37.4 (-$\underline{C}$H-C≡N), 29.6 (-$\underline{C}H_2$-CH_2-CH_2-CH_3), 28.8 (-CH_2-$\underline{C}H_2$-CH_2-CH_3), 21.9 (-CH_2-CH_2-$\underline{C}H_2$-CH_3), 13.7 (-CH_2-CH_2-CH_2-$\underline{C}H_3$); **LRMS** (ES+) *m/z* (relative intensity %) 178 (98%, $[M + Na]^+$); **HRMS (**ES+) exact mass calculated for $[M + Na]^+$ ($C_8H_{13}NNaO_2$) requires *m/z* 178.0844, found *m/z* 178.0841.

Synthesis and Characterisation of 117

2-Cyanohexanoic acid **117**



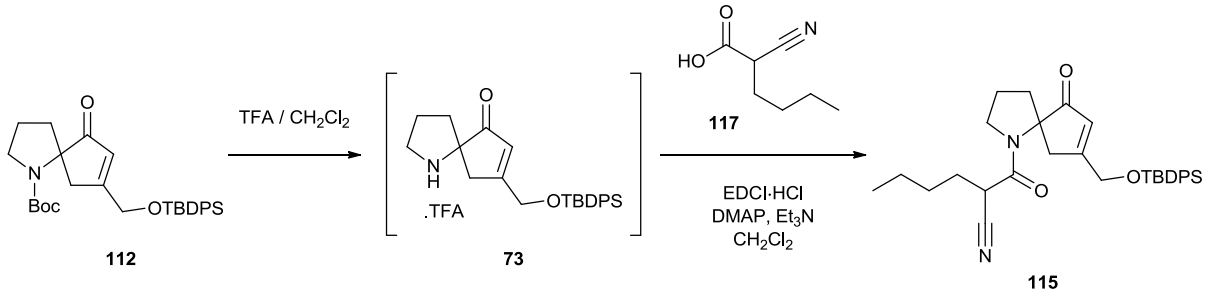
KOH (1.2 eq., 84.0 mg, 1.50 mmol) was added to a solution of methyl ester (1.0 eq., 194 mg, 1.25 mmol) in MeOH (1.1 mL). The reaction mixture was stirred at r.t. for 3 h then acidified to pH 3 with 5% citric acid (aq.). The mixture was extracted with EtOAc (6 × 4 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **117** (173 mg, 98%) as a pale yellow oil which was taken to next step without any further purification.

IR ν_{max}(thin film)/cm^{-1} 3486 (O-H), 2962 (C-H), 2258 (C≡N), 1728 (C=O), 1210, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.97 (br. s., 1 H, -$CO_2$$\underline{H}$), 3.61 (t, *J* = 7.0 Hz, 1 H, -C$\underline{H}$-C≡N), 2.04 - 1.93 (m, 2 H, -C$\underline{H}_2$-CH_2-CH_2-CH_3), 1.57 - 1.46 (m, 2 H, -CH_2-C$\underline{H}_2$-CH_2-CH_3), 1.44 - 1.33 (m, 2 H, -CH_2-CH_2-C$\underline{H}_2$-CH_3), 0.94 (t, *J* = 7.0 Hz, 3 H, -CH_2-CH_2-CH_2-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8 (-$\underline{C}O_2$H), 115.8 (-CH-$\underline{C}$≡N), 37.5 (-$\underline{C}$H-C≡N), 29.4 (-$\underline{C}H_2$-CH_2-CH_2-CH_3), 28.7 (-CH_2-$\underline{C}H_2$-CH_2-CH_3), 21.8 (-CH_2-CH_2-$\underline{C}H_2$-CH_3),

13.5 (-CH_2-CH_2-CH_2-$\underline{C}H_3$); **LRMS** (ES+) *m/z* (relative intensity %) 164 (100%, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_7H_{11}NNaO_2$) requires *m/z* 164.0687, found *m/z* 164.0684.

Synthesis and Characterisation of 115

2-{[8-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-6-oxo-1-azaspiro[4.4]non-7-en-1-yl]carbonyl}hexanenitrile **115**



TFA (0.1 mL) was added to a solution of **112** (1.0 eq., 32 mg, 0.063 mmol) in CH_2Cl_2 (0.5 mL) at r.t. The reaction mixture was stirred for 1 h at r.t. before being concentrated *in vacuo* to give **73** as a brown oil (33 mg, quant.) which was taken to next step without any further purification. To a solution of **73** (1.0 eq., 33 mg, 0.063 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (3 eq. 14 μL, 0.190 mmol). The reaction mixture was stirred for 10 min at r.t. before addition of **117** (1.1 eq., 10 mg, 0.070 mmol) in CH_2Cl_2 (0.2 mL) followed by EDCI·HCl (1.2 eq., 15 mg, 0.076 mmol) and DMAP (0.15 eq., 1 mg, 0.009 mmol). The resulting mixture was stirred at r.t. for 5 h 30 min. The reaction mixture was thereafter diluted with water (2 mL) and extracted with EtOAc (4 × 2 mL). The organics were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc:PE) to give **115** (25 mg, 75%) as a colourless oil and as a mixture of separable diastereoisomers (d.r. 2:1).

Major diastereoisomer:

IR ν_{max}(thin film)/cm^{-1} 2930 (C-H), 2858, 1716 (C=O), 1657, 1427, 1142, 704; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 - 7.64 (m, 4 H, Ar<u>H</u>), 7.48 - 7.37 (m, 6 H, Ar<u>H</u>), 6.41 (t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-), 4.53 (d, *J* = 18.0 Hz, 1 H, -O-C<u>H$_A$</u>H$_B$-), 4.38 (d, *J* = 18.0 Hz, 1 H, -O-CH$_A$<u>H$_B$</u>-), 3.89 - 3.82 (m, 1 H, -N-C<u>H$_A$</u>H$_B$-), 3.67 - 3.60 (m, 1 H, -N-CH$_A$<u>H$_B$</u>-), 3.44 (dd, *J* = 8.0, 7.0 Hz, 1 H, -N-CO-C<u>H</u>-), 3.02 (d, *J* = 18.0 Hz, 1 H, -C$_{quat.}$-C<u>H$_A$</u>H$_B$-C=CH-), 2.37 (d, *J* = 18.0 Hz, 1 H, -C$_{quat.}$-CH$_A$<u>H$_B$</u>-C=CH-), 2.21 - 2.13 (m, 1 H, -N-CH$_2$-C<u>H$_A$</u>H$_B$-), 2.11 - 1.98 (m, 2 H, -N-CH$_2$-CH$_A$<u>H$_B$</u>-, -N-CH$_2$-CH$_2$-C<u>H$_A$</u>H$_B$-), 1.96 - 1.89 (m, 2 H, -C<u>H$_2$</u>-CH$_2$-CH$_2$-CH$_3$), 1.81 - 1.75 (m, 1 H, -N-CH$_2$-CH$_2$-CH$_A$<u>H$_B$</u>-), 1.56 - 1.47 (m, 1 H, -CH$_2$-C<u>H$_A$</u>H$_B$-CH$_2$-CH$_3$), 1.47 - 1.31 (m, 3 H, -CH$_2$-CH$_A$<u>H$_B$</u>-CH$_2$-CH$_3$, -CH$_2$-CH$_2$-C<u>H$_2$</u>-CH$_3$), 1.08 (s, 9 H, -Si-C(C<u>H$_3$</u>)$_3$), 0.94 (t, *J* = 7.5 Hz, 3 H, -CH$_2$-CH$_2$-CH$_2$-C<u>H$_3$</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.2 (-<u>C</u>O-CH=C-), 176.0 (-CO-CH=<u>C</u>-), 162.3 (-N-<u>C</u>O-), 135.5 (2 × Ar<u>C</u>), 132.8 (Ar<u>C</u>), 132.6 (Ar<u>C</u>), 130.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>), 127.9 (2 × Ar<u>C</u>), 126.0 (-CO-<u>C</u>H=C-), 117.2 (-CH-<u>C</u>≡N), 70.4 (-N-<u>C$_{quat.}$</u>-), 63.8 (-O-<u>C</u>H$_2$-), 48.7 (-N-<u>C</u>H$_2$-), 40.7 (-C$_{quat.}$-<u>C</u>H$_2$-C=CH-), 37.9 (-N-CH$_2$-CH$_2$-<u>C</u>H$_2$-), 36.1 (-<u>C</u>H-C≡N), 29.0 (-CH$_2$-<u>C</u>H$_2$-CH$_2$-CH$_3$), 28.9 (-<u>C</u>H$_2$-CH$_2$-CH$_2$-CH$_3$), 26.7 (-Si-C(<u>C</u>H$_3$)$_3$), 24.4 (-N-CH$_2$-<u>C</u>H$_2$-), 22.2 (-CH$_2$-CH$_2$-<u>C</u>H$_2$-CH$_3$), 19.2 (-Si-<u>C</u>(CH$_3$)$_3$), 13.7 (-CH$_2$-CH$_2$-CH$_2$-<u>C</u>H$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 551 (75%, [M + Na]$^+$); **HRMS (**ES+) exact mass calculated for [M + Na]$^+$ ($C_{32}H_{40}N_2NaO_3Si$) requires *m/z* 551.2700, found *m/z* 551.2703.

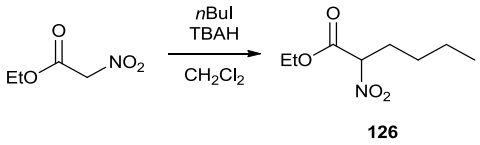
Minor diastereoisomer:

IR ν_{max}(thin film)/cm^{-1} 2927 (C-H), 2857, 1721 (C=O), 1653, 1430, 1140, 703; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 4 H, Ar<u>H</u>), 7.48 - 7.38 (m, 6 H, Ar<u>H</u>), 6.42 (t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-), 4.51 (d, *J* = 18.0 Hz, 1 H, -O-C<u>H$_A$</u>H$_B$-), 4.38 (d, *J* = 18.0 Hz, 1 H, -O-CH$_A$<u>H$_B$</u>-), 3.82 (td, *J* = 9.0, 6.5 Hz, 1 H, -N-C<u>H$_A$</u>H$_B$-), 3.73 - 3.67 (m, 1 H, -N-CH$_A$<u>H$_B$</u>-), 3.47 (dd, *J* = 8.5, 6.5 Hz, 1 H, -N-CO-C<u>H</u>-), 2.95 (d, *J* = 17.5 Hz, 1 H, -C$_{quat.}$-C<u>H$_A$</u>H$_B$-C=CH-), 2.36 (d, *J* = 17.5 Hz, 1 H, -C$_{quat.}$-CH$_A$<u>H$_B$</u>-C=CH-), 2.24 - 2.15 (m, 1 H, -N-CH$_2$-C<u>H$_A$</u>H$_B$-),

2.13 - 2.03 (m, 1 H, -N-CH_2-CH_2-C$\underline{H}_A$$H_B$-), 2.03 - 1.85 (m, 3 H, -N-CH_2-$CH_A\underline{H}_B$-, -C$\underline{H}_2$-CH_2-CH_2-CH_3), 1.79 - 1.73 (m, 1 H, -N-CH_2-CH_2-$CH_A\underline{H}_B$-), 1.57 - 1.49 (m, 1 H, (-CH_2-C$\underline{H}_A$$H_B$-$CH_2$-$CH_3$), 1.49 - 1.31 (m, 3 H, -CH_2-$CH_A\underline{H}_B$-CH_2-CH_3, -CH_2-CH_2-C$\underline{H}_2$-CH_3), 1.10 - 1.05 (m, 9 H, -Si-C(C$\underline{H}_3$)$_3$), 0.93 (t, *J* = 7.5 Hz, 3 H, -CH_2-CH_2-CH_2-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.7 (-$\underline{C}$O-CH=C-), 175.0 (-CO-CH=$\underline{C}$-), 162.5 (-N-$\underline{C}$O-), 135.5 (2 × Ar$\underline{C}$), 132.8 (Ar$\underline{C}$), 132.6 (Ar$\underline{C}$), 130.0 (Ar$\underline{C}$), 129.9 (Ar$\underline{C}$), 127.9 (Ar$\underline{C}$), 127.8 (Ar$\underline{C}$), 126.1 (-CO-$\underline{C}$H=C-), 116.6 (-CH-$\underline{C}$≡N), 70.4 (-N-$\underline{C}_{quat.}$-), 63.8 (-O-$\underline{C}$$H_2$-), 48.8 (-N-$\underline{C}$$H_2$-), 40.9 (-$C_{quat.}$-$\underline{C}$$H_2$-C=CH-), 37.8 (-N-$CH_2$-$CH_2$-$\underline{C}$$H_2$-), 37.2 (-$\underline{C}$H-C≡N), 29.1 (-$CH_2$-$\underline{C}$$H_2$-$CH_2$-$CH_3$, -$\underline{C}$$H_2$-$CH_2$-$CH_2$-$CH_3$), 26.7 (-Si-C($\underline{C}$$H_3$)$_3$), 24.5 (-N-$CH_2$-$\underline{C}$$H_2$-), 22.1 (-$CH_2$-$CH_2$-$\underline{C}$$H_2$-$CH_3$), 19.2 (-Si-$\underline{C}$($CH_3$)$_3$), 13.7 (-$CH_2$-$CH_2$-$CH_2$-$\underline{C}$$H_3$); **LRMS** (ES+) *m/z* (relative intensity %) 551 (70%, $[M + Na]^+$); **HRMS (**ES+) exact mass calculated for $[M + Na]^+$ ($C_{32}H_{40}N_2NaO_3Si$) requires *m/z* 551.2700, found *m/z* 551.2702.

Synthesis and Characterisation of 126

Ethyl 2-nitrohexanoate **126**



126

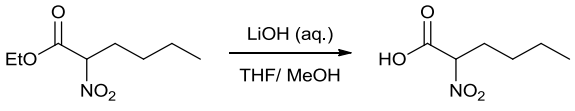
A solution of ethyl nitroacetate (1.0 eq., 2.00 g, 15.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 30 min to a stirred solution of TBAH (1.0 eq., 40 wt.% in water, 9.80 mL, 15.0 mmol). The resulting mixture was stirred for 10 min before *n*BuI (5.0 eq., 13.8 g, 75.0 mmol) was added in one portion at r.t. The mixture was thereafter stirred vigorously for 48 h before the organic layer was separated. The organic layer was washed with water (50 mL) and the aqueous extract was extracted with CH_2Cl_2 (3 × 50 mL). The organics were combined dried ($MgSO_4$), filtered and concentrated *in vacuo*. Dry Et_2O was added to precipitate the

tetrabutylammonium iodide and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc:PE) to give **126** (1.00 g, 35%) as a pale yellow oil.

IR ν_{max}(thin film)/cm^{-1} 2963 (C-H), 1749 (C=O), 1559 (NO_2), 1370 (NO_2), 1192, 860; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.09 (dd, *J* = 9.5, 5.5 Hz, 1 H, -C<u>H</u>-NO_2), 4.28 (q, *J* = 7.0 Hz, 2 H, -CO_2-C<u>H_2</u>-CH_3), 2.34 - 2.21 (m, 1 H, -C<u>H_A</u>H_B-CH_2-CH_2-CH_3), 2.19 - 2.07 (m, 1 H, -CH_A<u>H_B</u>-CH_2-CH_2-CH_3), 1.43 - 1.33 (m, 4 H, -CH_2-C<u>H_2</u>-C<u>H_2</u>-CH_3), 1.30 (t, *J* = 7.0 Hz, 3 H, -CO_2-CH_2-C<u>H_3</u>), 0.92 (t, *J* = 7.0 Hz, 3 H, -CH_2-CH_2-CH_2-C<u>H_3</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.6 (-<u>C</u>O_2-CH_2-CH_3), 88.1 (-<u>C</u>H-NO_2), 62.9 (-CO_2-<u>C</u>H_2-CH_3), 29.9 (-<u>C</u>H_2-CH_2-CH_2-CH_3), 27.6 (-CH_2-<u>C</u>H_2-CH_2-CH_3), 21.9 (-CH_2-CH_2-<u>C</u>H_2-CH_3), 13.8 (-CO_2-CH_2-<u>C</u>H_3), 13.6 (-CH_2-CH_2-CH_2-<u>C</u>H_3); **LRMS** (ES+) *m/z* (relative intensity %) 212 (100%, $[M + Na]^+$); **HRMS (**ES+) exact mass calculated for $[M + Na]^+$ ($C_8H_{15}NNaO_4$) requires *m/z* 212.0899, found *m/z* 212.0896.

Synthesis and Characterisation of 125

2-Nitrohexanoic acid **125**



126 **125**

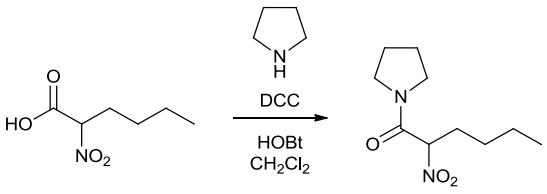
LiOH (aq) (6.8 eq., 2 M solution in water, 3.60 mL, 7.20 mmol) was added to a stirred solution of ethyl ester **126** (1.0 eq., 2.00 g, 1.06 mmol) in THF (3.6 mL) and MeOH (0.9 mL) The resulting mixture was stirred for 2 h at r.t. The reaction mixture was diluted with water (4 mL) and washed with Et_2O (4 mL). The aqueous was carefully acidified with 1 M HCl (aq) to pH 2 then extracted with CH_2Cl_2 (4 × 5 mL). The organics were combined, dried ($MgSO_4$), filtered and

concentrated *in vacuo* using a cold ice bath to give the desired product **125** as a yellow oil (131 mg, 77%).

IR ν_{max}(thin film)/cm^{-1} 3476 (O-H), 2963 (C-H), 1735 (C=O), 1561 (NO_2), 1365 (NO_2), 1249, 770; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.25 (br. s., 1 H, -CO_2<u>H</u>), 5.17 (dd, *J* = 9.5, 5.5 Hz, 1 H, -C<u>H</u>-NO_2), 2.42 - 2.27 (m, 1 H, -C<u>H</u>$_A$H$_B$-CH_2-CH_2-CH_3), 2.23 - 2.11 (m, 1 H, -CH_A<u>H</u>$_B$-CH_2-CH_2-CH_3), 1.47 - 1.34 (m, 4 H, -CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_3), 0.94 (t, *J* = 7.0 Hz, 3 H, -CH_2-CH_2-CH_2-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9 (-<u>C</u>O_2H), 87.7 (-<u>C</u>H-NO_2), 29.8 (-<u>C</u>H_2-CH_2-CH_2-CH_3), 27.6 (-CH_2-<u>C</u>H_2-CH_2-CH_3), 21.8 (-CH_2-CH_2-<u>C</u>H_2-CH_3), 13.5 (-CH_2-CH_2-CH_2-<u>C</u>H_3); **LRMS** (ES−) *m/z* (relative intensity %) 116 (100%, $[M - CO_2H]^-$), 160 (10, $[M - H]^-$); **HRMS** (ES–) exact mass calculated for $[M - H]^-$ ($C_6H_{10}NO_4$) requires *m/z* 160.0615, found *m/z* 160.0618.

Synthesis and Characterisation of 127

2-Nitro-1-(pyrrolidin-1-yl)hexan-1-one **127**



125 **127**

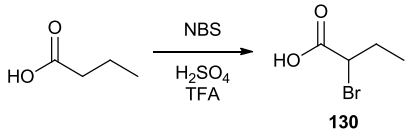
DCC (1.1 eq., 44 mg, 0.21 mmol) was added in one portion to a stirred solution of α-nitrocarboxylic acid **125** (1.0 eq., 31 mg, 0.19 mmol) and HOBt (1.9 eq., 49 mg, 0.37 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C before pyrrolidine (1.1 eq., 15 mg, 0.21 mmol) was added. The reaction mixture was stirred for 5 h at 0 °C then filtered. The filtrate was concentrated *in vacuo* and the residue was taken into EtOAc (5 mL). The organics were washed with saturated $NaHCO_3$ (aq.), dried (Na_2SO_4), filtered and

concentrated *in vacuo*. The residue was purified by column chromatography (30% → 40% EtOAc:PE) to give **127** (18 mg, 44%) as a colourless oil with characterisation data corresponding to literature.[88]

IR ν_{max}(thin film)/cm^{-1} 2959 (C-H), 1655 (C=O), 1552 (NO_2), 1438, 1361 (NO_2), 1257; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.21 (app. dd, *J* = 8.0, 6.5 Hz, 1 H, -C<u>H</u>-NO_2), 3.69 - 3.44 (m, 4 H, 2 × -N-C<u>H_2</u>-), 2.39 - 2.27 (m, 1 H, -C<u>H_A</u>H_B-CH_2-CH_2-CH_3), 2.18 - 2.07 (m, 1 H, -CH_A<u>H_B</u>-CH_2-CH_2-CH_3), 2.07 - 1.87 (m, 4 H, 2 × -N-CH_2-C<u>H_2</u>-), 1.45 - 1.27 (m, 4 H, -CH_2-C<u>H_2</u>-C<u>H_2</u>-CH_3), 0.93 (t, *J* = 7.2 Hz, 3 H, -CH_2-CH_2-CH_2-C<u>H_3</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6 (-N-<u>C</u>O-), 87.0 (-<u>C</u>H-NO_2), 46.9 (-N-<u>C</u>H_2-), 46.7 (-N-<u>C</u>H_2-), 29.9 (-<u>C</u>H_2-CH_2-CH_2-CH_3), 27.6 (-CH_2-<u>C</u>H_2-CH_2-CH_3), 26.0 (-N-CH_2-<u>C</u>H_2-), 24.1 (-N-CH_2-<u>C</u>H_2-), 22.2 (-CH_2-CH_2-C<u>H_2</u>-CH_3), 13.7 (-CH_2-CH_2-CH_2-C<u>H_3</u>); **LRMS** (ES+) *m/z* (relative intensity %) 215 (13%, $[M + H]^+$), 237 (43, $[M + Na]^+$), 451 (100, $[2M + Na]^+$).

Synthesis and Characterisation of 130

2-Bromobutanoic acid **130**



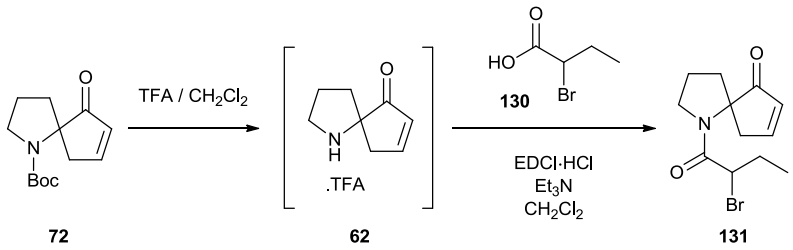
130

To butyric acid (1.0 eq., 4.4 g, 50 mmol) in TFA (25 mL) was added conc. H_2SO_4 (1.75 mL) followed by NBS (1.5 eq., 13.4 g, 75 mmol). The reaction mixture was heated to 85 °C for 18 h and thereafter cooled to r.t. The reaction mixture was taken into water (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by distillation to give **130** (5.67 g, 68%) as a pale yellow oil. Characterisation data were corresponding to literature.[74, 89, 90.]

B.p. 114-116 °C, 16 mBar, lit.[90] 122-126 °C, 33 mBar; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.10 (br. s., 1 H, -CO_2<u>H</u>), 4.20 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1 H, -C<u>H</u>Br-CH_2-CH_3), 1.96 - 2.19 (m, 2 H, -CHBr-C<u>H</u>$_2$-CH_3), 1.06 (td, *J* = 7.3, 1.5 Hz, 3 H, -CHBr-CH_2-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.7 (-<u>C</u>O_2H), 47.0 (-<u>C</u>HBr-CH_2-CH_3), 28.1 (-CHBr-<u>C</u>H_2-CH_3), 11.8 (-CHBr-CH_2-<u>C</u>H_3).

Synthesis and Characterisation of 131

1-(2-Bromobutanoyl)-1-azaspiro[4.4]non-7-en-6-one **131**



TFA (0.2 mL) was added to a solution of **72** (1.0 eq., 34 mg, 0.14 mmol) in CH_2Cl_2 (0.8 mL) at r.t. The reaction mixture was stirred for 1 h at r.t. before being concentrated *in vacuo* to give **62** as a dark yellow oil (36 mg, quant.) which was taken to next step without any further purification. EDCI·HCl (1.3 eq., 29 mg, 0.19 mmol) was added to a solution of **130** (1.2 eq., 29 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) at r.t. The reaction mixture was stirred for 30 min at r.t. and then cooled to 0 °C. A solution of **62** (1.0 eq., 36 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) followed by Et_3N (2 eq. 40 µL, 0.29 mmol) was added dropwise to the reaction mixture at 0 °C. The resulting mixture was warmed to r.t and stirred for 19 h. The reaction mixture was thereafter diluted with water (3 mL) and the organics was separated. The aqueous phase was extracted with EtOAc (3 × 2 mL). The organics were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (50% EtOAc:PE) to give **131** (19 mg, 46%) as a colourless oil and as a mixture of separable diastereoisomers (d.r. 1:1).

Diastereoisomer A:

IR ν_{max}(thin film)/cm^{-1} 2971 (C-H), 2877, 1716 (C=O), 1647 (C=C), 1426, 1128, 799; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 - 7.56 (m, 1 H, -CO-CH=C<u>H</u>-), 6.30 (dt, *J* = 6.0, 2.0 Hz, 1 H, -CO-C<u>H</u>=CH-), 4.15 (t, *J* = 7.5 Hz, 1 H, -C<u>H</u>Br-CH_2-CH_3), 3.91 - 3.85 (m, 1 H, -N-C<u>H$_A$H$_B$</u>-), 3.65 - 3.58 (m, 1 H, -N-CH_A<u>H$_B$</u>-), 3.13 (app. dt, *J* = 18.5, 2.0 Hz, 1 H, -$C_{quat.}$-C<u>H$_A$</u>H_B-CH=CH-), 2.58 (ddd, *J* = 18.5, 3.0, 2.0 Hz, 1 H, -$C_{quat.}$-CH_A<u>H$_B$</u>-CH=CH-), 2.21 - 2.14 (m, 1 H, -N-CH_2-C<u>H$_A$</u>H_B-), 2.14 - 2.07 (m, 1 H, -CHBr-C<u>H$_A$</u>H_B-CH_3), 2.07 - 2.01 (m, 2 H, -N-CH_2-CH_A<u>H$_B$</u>-, -N-CH_2-CH_2-C<u>H$_A$</u>H_B-), 2.01 - 1.86 (m, 1 H, -CHBr-CH_A<u>H$_B$</u>-CH_3), 1.84 - 1.76 (m, 1 H, -N-CH_2-CH_2-CH_A<u>H$_B$</u>-), 1.00 (t, *J* = 7.5 Hz, 3 H, -CHBr-CH_2-C<u>H$_3$</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.6 (-<u>C</u>O-CH=CH-), 166.6 (-N-<u>C</u>O-), 159.7 (-CO-CH=<u>C</u>H-), 132.4 (-CO-<u>C</u>H=CH-), 68.9 (-<u>C$_{quat.}$</u>-CH_2-CH=CH-), 48.1 (-N-<u>C</u>H_2-), 47.3 (-<u>C</u>HBr-CH_2-CH_3), 41.4 (-$C_{quat.}$-<u>C</u>H_2-CH=CH-), 37.9 (-N-CH_2-CH_2-<u>C</u>H_2-), 27.7 (-CHBr-<u>C</u>H_2-CH_3), 24.6 (-N-CH_2-<u>C</u>H_2-), 12.1 (-CHBr-CH_2-<u>C</u>H_3); **LRMS** (ES+) *m/z* (relative intensity %) 308 (95%, ^{79}Br, $[M + Na]^+$), 310 (100, ^{81}Br, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{12}H_{16}{}^{79}BrNNaO_2$) requires *m/z* 308.0257, found *m/z* 308.0253.

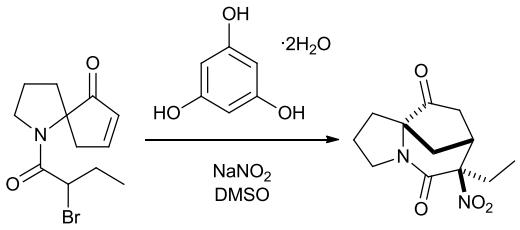
Diastereoisomer B:

IR ν_{max}(thin film)/cm^{-1} 2983 (C-H), 2897, 1723 (C=O), 1643 (C=C), 1420, 1120, 780; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 - 7.53 (m, 1 H, -CO-CH=C<u>H</u>-), 6.30 (dt, *J* = 6.0, 2.0 Hz, 1 H, -CO-C<u>H</u>=CH-), 4.19 (t, *J* = 7.5 Hz, 1 H, -C<u>H</u>Br-CH_2-CH_3), 3.88 - 3.82 (m, 1 H, -N-C<u>H$_A$H$_B$</u>-), 3.70 - 3.65 (m, 1 H, -N-CH_A<u>H$_B$</u>-), 3.13 (app. dt, *J* = 18.0, 2.0 Hz, 1 H, -$C_{quat.}$-C<u>H$_A$</u>H_B-CH=CH-), 2.61 (ddd, *J* = 18.0, 3.0, 2.0 Hz, 1 H, , -$C_{quat.}$-CH_A<u>H$_B$</u>-CH=CH-), 2.24 - 2.17 (m, 1 H, -N-CH_2-C<u>H$_A$</u>H_B-), 2.17 - 2.08 (m, 1 H, -CHBr-C<u>H$_A$</u>H_B-CH_3), 2.11 - 2.01 (m, 2 H, -N-CH_2-CH_A<u>H$_B$</u>-, -N-CH_2-CH_2-C<u>H$_A$</u>H_B-), 2.05 - 1.96 (m, 1 H, -CHBr-CH_A<u>H$_B$</u>-CH_3), 1.83 - 1.77 (m, 1 H, -N-CH_2-CH_2-CH_A<u>H$_B$</u>-), 1.00 (t, *J* = 7.3 Hz, 3 H, -CHBr-CH_2-C<u>H$_3$</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.0 (-<u>C</u>O-CH=CH-), 166.6 (-N-<u>C</u>O-), 158.9 (-CO-CH=<u>C</u>H-),

132.5 (-CO-<u>C</u>H=CH-), 68.7 (-<u>C</u>$_{quat.}$-CH_2-CH=CH-), 48.5 (-N-<u>C</u>H_2-), 46.9 (-<u>C</u>HBr-CH_2-CH_3), 42.4 (-$C_{quat.}$-<u>C</u>H_2-CH=CH-), 37.8 (-N-CH_2-CH_2-<u>C</u>H_2-), 27.7 (-CHBr-<u>C</u>H_2-CH_3), 24.5 (-N-CH_2-<u>C</u>H_2-), 12.3 (-CHBr-CH_2-<u>C</u>H_3); **LRMS** (ES+) *m/z* (relative intensity %) 308 (95%, ^{79}Br, $[M + Na]^+$), 310 (100, ^{81}Br, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{12}H_{16}{}^{79}BrNNaO_2$) requires *m/z* 308.0257, found *m/z* 308.0251.

Synthesis and Characterisation of 132

6-Ethyl-6-nitrotetrahydro-1*H*,5*H*-7,9a-methanopyrrolo[1,2-*a*]azepine-5,9(6*H*)-dione **132**



131 **132**

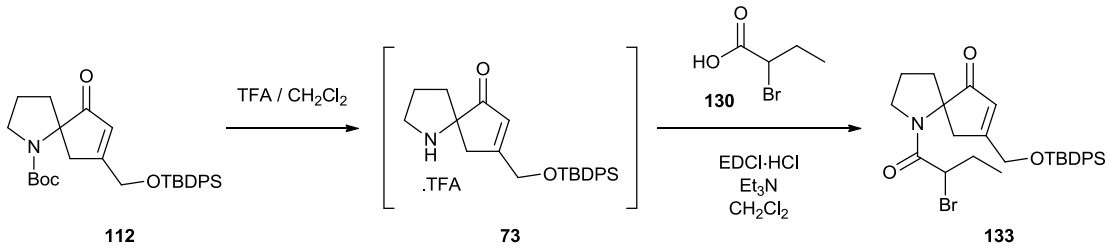
$NaNO_2$ (3 eq., 5 mg, 0.052 mmol) was added to a stirred solution of **131** (1.0 eq., 5 mg, 0.017 mmol) and phloroglucinol dihydrate (1.1 eq., 3 mg, 0.019 mmol) in DMSO (0.6 mL) at r.t. The reaction mixture was stirred for 26 h at r.t. before addition of water (2 mL) and EtOAc (1 mL). The organics was separated and the aqueous was extracted with EtOAc (2 × 1 mL). The organics were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated under a stream of nitrogen. The residue was purified by column chromatography (50% EtOAc:PE) to give **132** (2 mg, 45%) as a single diastereoisomer and as a colourless oil.

IR ν_{max}(thin film)/cm^{-1} 2965 (C-H), 2886, 1756 (C=O), 1658, 1541 (NO_2), 1420, 1358 (NO_2), 872; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.68 - 3.55 (m, 2 H, -N-C<u>H</u>$_2$-), 3.09 - 3.05 (m, 1 H, -CO-CH_2-C<u>H</u>-), 2.49 - 2.30 (m, 4 H, -CO-C<u>H</u>$_2$, -C<u>H</u>$_2$-CH_3), 2.37 - 2.30 (m, 1 H,

-N-CH_2-CH_2-C$\underline{H}_A H_B$-), 2.25 - 2.21 (m, 1 H, -N-$C_{quat.}$-C$\underline{H}_A H_B$-CH-), 2.21 - 2.16 (m, 1 H, -N-CH_2-C$\underline{H}_A H_B$-), 2.16 - 2.11 (m, 1 H, -N-$C_{quat.}$-$CH_A\underline{H}_B$-CH-), 2.02 - 1.94 (m, 1 H, -N-CH_2-$CH_A\underline{H}_B$-), 1.91 - 1.83 (m, 1 H, -N-CH_2-CH_2-$CH_A\underline{H}_B$-), 1.23 (t, *J* = 7.5 Hz, 3 H, -CH_2-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.6 (-$\underline{C}$O-CH_2-), 161.5 (-N-$\underline{C}$O-), 95.3 (-$\underline{C}_{quat.}$-NO_2), 68.6 (-N-$\underline{C}_{quat.}$-), 45.8 (-N-$\underline{C}H_2$-), 39.7 (-CO-CH_2-$\underline{C}$H-), 38.9 (-CO-$\underline{C}H_2$-CH-), 36.9 (-N-$C_{quat.}$-$\underline{C}H_2$-CH-), 31.6 (-$\underline{C}H_2$-CH_3), 28.7 (-N-CH_2-CH_2-$\underline{C}H_2$-), 22.2 (-N-CH_2-$\underline{C}H_2$-), 9.3 (-CH_2-$\underline{C}H_3$); **LRMS** (ES+) *m/z* (relative intensity %) 275 (83%, $[M + Na]^+$), 527 (93, $[2M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{12}H_{16}N_2NaO_4$) requires *m/z* 275.1002, found *m/z* 275.1005. The stereochemical configuration was assigned by NOE experiments and it was found to have the nitro group on the *exo* face.

Synthesis and Characterisation of 133

1-(2-Bromobutanoyl)-8-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-1-azaspiro[4.4]non-7-en-6-one **133**



TFA (0.1 mL) was added to a solution of **112** (1.0 eq., 30 mg, 0.059 mmol) in CH_2Cl_2 (0.5 mL) at r.t. The reaction mixture was stirred for 1 h at r.t. before being concentrated *in vacuo* to give **73** as a dark yellow oil (31 mg, quant.) which was taken to next step without any further purification. EDCI·HCl (1.3 eq., 12 mg, 0.077 mmol) was added to a solution of **130** (1.2 eq., 12 mg, 0.071 mmol) in CH_2Cl_2 (0.8 mL) at r.t. The reaction mixture was stirred for 30 min at r.t. and then cooled to 0 °C. A solution of **73** (1.0 eq., 31 mg, 0.059 mmol) in CH_2Cl_2 (2 mL) followed by Et_3N (2 eq. 17 μL, 0.119 mmol) was added dropwise to the reaction mixture at

0 °C. The resulting mixture was warmed to r.t and stirred for 20 h. The reaction mixture was thereafter diluted with water (3 mL) and the organics was separated. The aqueous phase was extracted with EtOAc (3 × 2 mL). The organics were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc:PE) to give **133** (23 mg, 74%) as a colourless oil and as a mixture of separable diastereoisomers (d.r. 2:1).

Major diastereoisomer:

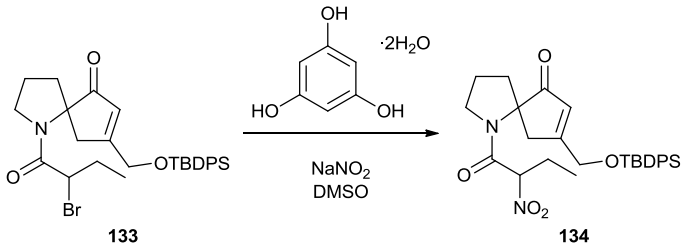
IR ν_{max}(thin film)/cm^{-1} 2931 (C-H), 2857, 1716 (C=O), 1650, 1427, 1111, 702; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 4 H, Ar<u>H</u>), 7.48 - 7.37 (m, 6 H, Ar<u>H</u>), 6.42 (app. t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-), 4.52 (d, *J* = 17.5 Hz, 1 H, -O-C<u>H</u>$_A$H$_B$-), 4.37 (d, *J* = 17.5 Hz, 1 H, -O-CH$_A$<u>H</u>$_B$-), 4.23 - 4.10 (m, 1 H, -C<u>H</u>Br-CH$_2$-CH$_3$), 3.90 - 3.80 (m, 1 H, -N-C<u>H</u>$_A$H$_B$-), 3.68 - 3.57 (m, 1 H, -N-CH$_A$<u>H</u>$_B$-), 2.98 (d, *J* = 17.5 Hz, 1 H, -C$_{quat.}$-C<u>H</u>$_A$H$_B$-C=CH-), 2.34 (d, *J* = 17.5 Hz, 1 H, -C$_{quat.}$-CH$_A$<u>H</u>$_B$-C=CH-), 2.21 - 1.89 (m, 5 H, -N-CH$_2$-C<u>H</u>$_2$-, -CHBr-C<u>H</u>$_2$-CH$_3$, -N-CH$_2$-CH$_2$-C<u>H</u>$_A$H$_B$-), 1.78 - 1.72 (m, 1 H, -N-CH$_2$-CH$_2$-CH$_A$<u>H</u>$_B$-), 1.07 (s, 9 H, -Si-C(C<u>H</u>$_3$)$_3$), 1.00 (t, *J* = 7.5 Hz, 3 H, -CHBr-CH$_2$-C<u>H</u>$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.1 (-<u>C</u>O-CH=C-), 174.7 (-CO-CH=<u>C</u>-), 166.6 (-N-<u>C</u>O-), 135.5 (2 × Ar<u>C</u>), 132.9 (Ar<u>C</u>), 132.7 (Ar<u>C</u>), 129.9 (2 × Ar<u>C</u>), 127.9 (Ar<u>C</u>), 127.8 (Ar<u>C</u>), 126.2 (-CO-<u>C</u>H=C-), 69.9 (-N-<u>C</u>$_{quat.}$-), 63.8 (-O-<u>C</u>H$_2$-), 48.6 (-N-<u>C</u>H$_2$-), 47.0 (-<u>C</u>HBr-CH$_2$-CH$_3$), 41.2 (-C$_{quat.}$-<u>C</u>H$_2$-C=CH-), 37.9 (-N-CH$_2$-CH$_2$-<u>C</u>H$_2$-), 27.7 (-CHBr-<u>C</u>H$_2$-CH$_3$), 26.7 (-Si-C(<u>C</u>H$_3$)$_3$), 24.4 (-N-CH$_2$-<u>C</u>H$_2$-), 19.2 (-Si-<u>C</u>(CH$_3$)$_3$), 12.2 (-CHBr-CH$_2$-<u>C</u>H$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 576 (98%, ^{79}Br, $[M + Na]^+$), 578 (100, ^{81}Br, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{29}H_{36}{}^{79}BrNNaO_3Si$) requires *m/z* 576.1540, found *m/z* 576.1531.

Minor diastereoisomer:

IR ν_{max}(thin film)/cm^{-1} 2929 (C-H), 2856, 1720 (C=O), 1643, 1425, 1114, 703; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 4 H, Ar<u>H</u>), 7.48 - 7.37 (m, 6 H, Ar<u>H</u>), 6.45 (app. t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-), 4.53 (d, *J* = 18.0 Hz, 1 H, -O-C<u>H</u>$_A$H$_B$-), 4.36 (d, *J* = 18.6 Hz, 1 H, -O-CH$_A$<u>H</u>$_B$-), 4.24 - 4.12 (m, 1 H, -C<u>H</u>Br-CH$_2$-CH$_3$), 3.90 - 3.81 (m, 1 H, -N-C<u>H</u>$_A$H$_B$-), 3.68 - 3.57 (m, 1 H, -N-CH$_A$<u>H</u>$_B$-), 2.98 (d, *J* = 18.0 Hz, 1 H, -C$_{quat.}$-C<u>H</u>$_A$H$_B$-C=CH-), 2.33 (d, *J* = 18.0 Hz, 1 H, -C$_{quat.}$-CH$_A$<u>H</u>$_B$-C=CH-), 2.21 - 1.89 (m, 5 H, -N-CH$_2$-C<u>H</u>$_2$-, -CHBr-C<u>H</u>$_2$-CH$_3$, -N-CH$_2$-CH$_2$-C<u>H</u>$_A$H$_B$-), 1.78 - 1.72 (m, 1 H, -N-CH$_2$-CH$_2$-CH$_A$<u>H</u>$_B$-), 1.08 (s, 9 H, -Si-C(C<u>H</u>$_3$)$_3$), 1.01 (t, *J* = 7.0 Hz, 3 H, -CHBr-CH$_2$-C<u>H</u>$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.7 (-<u>C</u>O-CH=C-), 175.7 (-CO-CH=<u>C</u>-), 166.7 (-N-<u>C</u>O-), 135.5 (2 × Ar<u>C</u>), 132.9 (Ar<u>C</u>), 132.6 (Ar<u>C</u>), 130.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>), 127.9 (Ar<u>C</u>), 127.8 (Ar<u>C</u>), 126.2 (-CO-<u>C</u>H=C-), 70.1 (-N-<u>C</u>$_{quat.}$-), 63.8 (-O-<u>C</u>H$_2$-), 48.2 (-N-<u>C</u>H$_2$-), 47.4 (-<u>C</u>HBr-CH$_2$-CH$_3$), 40.2 (-C$_{quat.}$-<u>C</u>H$_2$-C=CH-), 38.0 (-N-CH$_2$-CH$_2$-<u>C</u>H$_2$-), 27.8 (-CHBr-<u>C</u>H$_2$-CH$_3$), 26.7 (-Si-C(<u>C</u>H$_3$)$_3$), 24.5 (-N-CH$_2$-<u>C</u>H$_2$-), 19.2 (-Si-<u>C</u>(CH$_3$)$_3$), 12.1 (-CHBr-CH$_2$-<u>C</u>H$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 576 (98%, ^{79}Br, $[M + Na]^+$), 578 (100%, ^{81}Br, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{29}H_{36}{}^{79}BrNNaO_3Si$) requires *m/z* 576.1540, found *m/z* 576.1533.

Synthesis and Characterisation of 134

8-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-1-(2-nitrobutanoyl)-1-azaspiro[4.4]non-7-en-6-one **134**



133 134

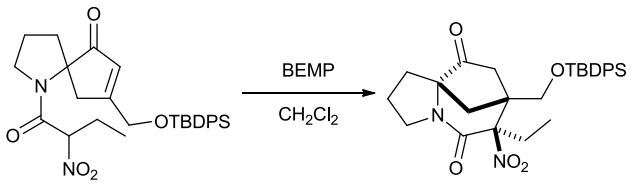
$NaNO_2$ (3 eq., 7 mg, 0.081 mmol) was added to a stirred solution of **133** (1.0 eq., 15 mg, 0.027 mmol) and phloroglucinol dihydrate (1.1 eq., 5 mg, 0.030 mmol) in DMSO (0.6 mL) at r.t. The reaction mixture was stirred for 5 h at r.t. before addition of water (2 mL) and EtOAc (1 mL). The organics were separated and the aqueous phase extracted with EtOAc (2 × 1 mL). The organics were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated under a stream of nitrogen. The residue was purified by column chromatography (30% EtOAc:PE) to give **134** (5 mg, 35%) as a colourless oil and as a mixture of diastereoisomers (d.r. 2:1).

IR ν_{max}(thin film)/cm^{-1} 2952 (C-H), 2875, 1715 (C=O), 1640, (NO_2), 1352 (NO_2), 1088, 702; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereoisomers, ratio 2:1) δ 7.69 - 7.58 (m, 8 H, Ar<u>H</u>, major and minor), 7.50 - 7.37 (m, 12 H, Ar<u>H</u>, major and minor), 6.43 (app. t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-, major), 6.41 (app. t, *J* = 1.5 Hz, 1 H, -CO-C<u>H</u>=C-, minor), 5.16 - 5.10 (m, 2 H, -C<u>H</u>(NO_2)-CH_2-CH_3, major and minor), 4.52 (d, *J* = 18.0 Hz, 1 H, -O-C<u>H_A</u>H_B-, major), 4.51 (d, *J* = 18.0 Hz, 1 H, -O-C<u>H_A</u>H_B-, minor), 4.37 (d, *J* = 18.0 Hz, 2 H, -O-CH_A<u>H_B</u>-, major and minor), 3.91 - 3.82 (m, 2 H, -N-C<u>H_A</u>H_B-, major and minor), 3.73 - 3.66 (m, 2 H, -N-CH_A<u>H_B</u>-, major and minor), 3.01 (d, *J* = 18.5 Hz, 1 H, -$C_{quat.}$-C<u>H_A</u>H_B-C=CH-, major), 2.95 (d, *J* = 18.0 Hz, 1 H, -$C_{quat.}$-C<u>H_A</u>H_B-C=CH-, minor), 2.40 - 2.33 (m, 2 H, -$C_{quat.}$-CH_A<u>H_B</u>-C=CH-,

major and minor), 2.33 - 1.94 (m, 10 H, -N-CH_2-C$\underline{H}_2$-, -CH(NO_2)-C$\underline{H}_2$-CH_3, -N-CH_2-CH_2-C$\underline{H}_A$$H_B$-, major and minor), 1.81 - 1.75 (m, 2 H, -N-CH_2-CH_2-$CH_A\underline{H}_B$-, major and minor), 1.08 (s, 9 H, -C(C$\underline{H}_3$)$_3$, major), 1.07 (s, 9 H, -C(C$\underline{H}_3$)$_3$, minor), 1.06 - 1.00 (m, 6 H, -CH(NO_2)-CH_2-C$\underline{H}_3$, major and minor); **^{13}C NMR** (125 MHz, $CDCl_3$, mixture of diastereoisomers, ratio 2:1) δ 205.0 (-$\underline{C}$O-CH=C, major), 204.3 (-$\underline{C}$O-CH=C-, minor), 176.1 (-CO-CH=$\underline{C}$-, major), 174.9 (-CO-CH=$\underline{C}$-, minor), 161.2 (-N-$\underline{C}$O-, minor) 161.0 (-N-$\underline{C}$O-, major) 135.5 (4 × Ar$\underline{C}$, major and minor), 132.8 (2 × Ar$\underline{C}$, major), 132.6 (2 × Ar$\underline{C}$, minor), 130.0 (2 × Ar$\underline{C}$, major and minor), 129.9 (2 × Ar$\underline{C}$, major and minor), 127.9 (4 × Ar$\underline{C}$, major and minor), 126.2 (-CO-$\underline{C}$H=C-, minor), 126.0 (-CO-$\underline{C}$H=C-, major), 88.3 (-$\underline{C}$H(NO_2)-CH_2-CH_3, minor), 87.6 (-$\underline{C}$H(NO_2)-CH_2-CH_3, major), 70.4 (-N-$\underline{C}_{quat.}$-, major), 70.2 (-N-$\underline{C}_{quat.}$-, minor), 63.8 (-O-$\underline{C}H_2$-, major and minor), 48.8 (-N-$\underline{C}H_2$-, major and minor), 40.6 (-$C_{quat.}$-$\underline{C}H_2$-C=CH-, major and minor), 37.9 (-N-CH_2-CH_2-$\underline{C}H_2$-, major), 37.8 (-N-CH_2-CH_2-$\underline{C}H_2$-, minor), 26.7 (-Si-C($\underline{C}H_3$)$_3$, major and minor), 24.4 (-N-CH_2-$\underline{C}H_2$-, major and minor), 23.8 (-CH(NO_2)-$\underline{C}H_2$-CH_3, major and minor), 19.2 (-Si-$\underline{C}$(CH_3)$_3$), major and minor), 9.7 (-CH(NO_2)-CH_2-$\underline{C}H_3$, major and minor); **LRMS** (ES+) *m/z* (relative intensity %) 543 (100%, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{29}H_{36}N_2NaO_5Si$) requires *m/z* 543.2286, found *m/z* 543.2271.

Synthesis and Characterisation of 138

7-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-6-ethyl-6-nitrotetrahydro-1*H*,5*H*-7,9a-methanopyrrolo[1,2-*a*]azepine-5,9(6*H*)-dione **138**



134 **138**

A stock solution of BEMP (10 μL BEMP : 1500 μL CH_2Cl_2) in CH_2Cl_2 was added (0.2 eq., 84 μL, 0.0019 mmol) to a stirred solution of **134** (1.0 eq., 5 mg, 0.0096 mmol) in CH_2Cl_2 (0.4 mL) at r.t. The reaction mixture was stirred for 12 h at r.t. before being concentrated under a stream of nitrogen. The residue was purified by column chromatography (30% EtOAc:PE) to give **138** (4 mg, 80%) as a colourless oil and as a mixture of separable diastereoisomers (d.r. 3:1).

Major diastereoisomer:

IR ν_{max}(thin film)/cm^{-1} 2926 (C-H), 2855, 1759 (C=O), 1669, 1545 (NO_2), 1428, 1383 (NO_2), 704; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 - 7.65 (m, 4 H, Ar$\underline{H}$), 7.38 - 7.51 (m, 6 H, Ar$\underline{H}$), 3.89 (d, *J* = 10.5 Hz, 1 H, -O-C$\underline{H}_A$H$_B$-), 3.82 (d, *J* = 10.5 Hz, 1 H, -O-CH$_A\underline{H}_B$-), 3.59 - 3.70 (m, 2 H, -N-C$\underline{H}_2$-), 2.84 (d, *J* = 19.5 Hz, 1 H, , -CO-C$\underline{H}_A$H$_B$-), 2.54 (dq, *J* = 14.5, 7.5 Hz, 1 H, -C$\underline{H}_A$H$_B$-CH$_3$), 2.35 - 2.43 (m, 1 H, -N-CH$_2$-CH$_2$-C$\underline{H}_A$H$_B$-), 2.28 - 2.35 (m, 2 H, -CO-CH$_A\underline{H}_B$-, -N-C$_{quat.}$-C$\underline{H}_A$H$_B$-C$_{quat.}$-), 2.16 - 2.26 (m, 1 H, -N-CH$_2$-C$\underline{H}_A$H$_B$-), 2.09 - 2.16 (m, 1 H, -CH$_A\underline{H}_B$-CH$_3$), 1.95 - 2.02 (m, 1 H, -N-CH$_2$-CH$_A\underline{H}_B$-), 1.83 - 1.90 (m, 2 H, -N-CH$_2$-CH$_2$-CH$_A\underline{H}_B$-, -N-C$_{quat.}$-CH$_A\underline{H}_B$-C$_{quat.}$-), 1.07 (s, 9 H, -C(C$\underline{H}_3$)$_3$), 0.93 (t, *J* = 7.5 Hz, 3 H, -CH$_2$-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.8 (-$\underline{C}$O-CH$_2$-), 161.1 (-N-$\underline{C}$O-), 135.6 (Ar$\underline{C}$), 135.5 (Ar$\underline{C}$), 132.4 (Ar$\underline{C}$), 132.0 (Ar$\underline{C}$), 130.2 (2 × Ar$\underline{C}$), 128.0 (2 × Ar$\underline{C}$), 98.5

(-$\underline{C}_{quat.}$-NO_2), 69.4 (-N-$\underline{C}_{quat.}$-), 62.0 (-O-$\underline{C}H_2$-), 47.8 (-$\underline{C}_{quat.}$-CH_2-O-), 45.9 (-N-$\underline{C}H_2$-), 42.0 (-CO-$\underline{C}H_2$-), 38.4 (-N-$C_{quat.}$-$\underline{C}H_2$-$C_{quat.}$-), 29.1 (-N-CH_2-CH_2-$\underline{C}H_2$-), 26.9 (-Si-C($\underline{C}H_3$)$_3$, -$\underline{C}H_2$-CH_3), 22.1 (-N-CH_2-$\underline{C}H_2$-), 19.3 (-Si-$\underline{C}(CH_3)_3$), 10.7 (-CH_2-$\underline{C}H_3$); **LRMS** (ES+) *m/z* (relative intensity %) 543 (100%, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{29}H_{36}N_2NaO_5Si$) requires *m/z* 543.2286, found *m/z* 543.2268.

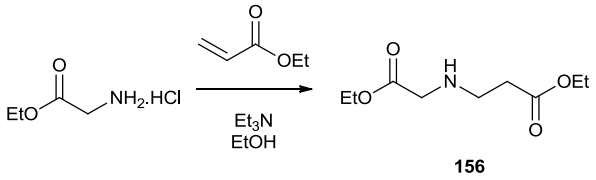
Minor diastereoisomer:

IR ν_{max}(thin film)/cm^{-1} 2930 (C-H), 2851, 1750 (C=O), 1672, 1540 (NO_2), 1431, 1385 (NO_2), 702; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 - 7.62 (m, 4 H, Ar$\underline{H}$), 7.38 - 7.49 (m, 6 H, Ar$\underline{H}$), 3.76 (d, *J* = 10.5 Hz, 1 H, -O-C$\underline{H}_A$$H_B$-), 3.70 - 3.76 (m, 1 H, -N-C$\underline{H}_A$$H_B$-), 3.49 (ddd, *J* = 12.0, 8.5, 3.5 Hz, 1 H, -N-$CH_A\underline{H}_B$-), 3.42 (d, *J* = 10.5 Hz, 1 H, -O-$CH_A\underline{H}_B$-), 2.76 (d, *J* = 19.5 Hz, 1 H, -CO-C$\underline{H}_A$$H_B$-), 2.54 (dd, *J* = 19.5, 4.0 Hz, 1 H, -CO-$CH_A\underline{H}_B$-), 2.40 (dd, *J* = 13.0, 4.0 Hz, 1 H, -N-$C_{quat.}$-C$\underline{H}_A$$H_B$-$C_{quat.}$-), 2.35 (ddd, *J* = 12.5, 7.5, 3.0 Hz, 1 H, -N-CH_2-CH_2-C$\underline{H}_A$$H_B$-), 2.18 - 2.32 (m, 2 H, -C$\underline{H}_2$-CH_3), 2.12 - 2.18 (m, 1 H, -N-CH_2-C$\underline{H}_A$$H_B$-), 2.09 (d, *J* = 13.0 Hz, 1 H, -N-$C_{quat.}$-$CH_A\underline{H}_B$-$C_{quat.}$-), 1.98 - 2.05 (m, 1 H, -N-CH_2-$CH_A\underline{H}_B$-), 1.94 (ddd, *J* = 12.5, 10.5, 8.0 Hz, 1 H, -N-CH_2-CH_2-$CH_A\underline{H}_B$-), 1.10 (t, *J* = 7.5 Hz, 3 H, -CH_2-C$\underline{H}_3$), 1.07 (s, 9 H, -C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.5 (-$\underline{C}$O-CH_2-), 162.4 (-N-$\underline{C}$O-), 135.6 (Ar$\underline{C}$), 135.5 (Ar$\underline{C}$), 132.2 (Ar$\underline{C}$), 130.2 (Ar$\underline{C}$), 128.0 (Ar$\underline{C}$), 96.2 (-$\underline{C}_{quat.}$-NO_2), 69.2 (-N-$\underline{C}_{quat.}$-), 64.0 (-O-$\underline{C}H_2$-), 48.8 (-$\underline{C}_{quat.}$-CH_2-O-), 46.0 (-N-$\underline{C}H_2$-), 40.5 (-CO-$\underline{C}H_2$-), 36.6 (-N-$C_{quat.}$-$\underline{C}H_2$-$C_{quat.}$-), 29.0 (-N-CH_2-CH_2-$\underline{C}H_2$-), 26.9 (-Si-C($\underline{C}H_3$)$_3$, 26.3 (-$\underline{C}H_2$-CH_3), 22.1 (-N-CH_2-$\underline{C}H_2$-), 19.3 (-Si-$\underline{C}(CH_3)_3$), 10.0 (-CH_2-$\underline{C}H_3$);); **LRMS** (ES+) *m/z* (relative intensity %) 543 (100%, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{29}H_{36}N_2NaO_5Si$) requires *m/z* 543.2286, found *m/z* 543.2271.

5.4 Experimental: Chapter 4

Synthesis and Characterisation of 156

Ethyl *N*-(2-ethoxy-2-oxoethyl)-β-alaninate **156**



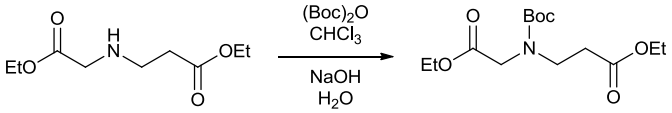
156

To a stirred solution of glycine ethyl ester hydrochloride (1.0 eq., 25.0 g, 179 mmol) in EtOH (300 mL) was added ethyl acrylate (1.1 eq., 19.7 g, 197 mmol) followed by Et_3N (1.0 eq., 25.0 mL, 179 mmol) at r.t. The reaction mixture was stirred for 96 h at r.t. before being concentrated *in vacuo*. The residue was taken into water (300 mL) and extracted with EtOAc (3 × 200 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by distillation to give **156** (26.4 g, 73%) as a colourless oil. Characterisation data were corresponding to literature.[80, 91.]

B.p. 129-131 °C (10 mBar), lit.[80] 104-108 °C (0.8-1.3 mBar); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.0 Hz, 2 H, -CO_2-C$\underline{H}_2$-CH_3), 4.12 (q, *J* = 7.5 Hz, 2 H, -CO_2-C$\underline{H}_2$-CH_3), 3.38 (s, 2 H, -NH-C$\underline{H}_2$-CO_2-), 2.88 (t, *J* = 6.5 Hz, 2 H, -NH-C$\underline{H}_2$-CH_2-CO_2-), 2.48 (t, *J* = 6.5 Hz, 2 H, -NH-CH_2-C$\underline{H}_2$-CO_2-), 1.80 (br. s., 1 H, -N$\underline{H}$-), 1.25 (t, *J* = 7.5 Hz, 3 H, -CO_2-CH_2-C$\underline{H}_3$), 1.24 (t, *J* = 7.0 Hz, 3 H, -CO_2-CH_2-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3 (-$\underline{C}O_2$-CH_2-CH_3), 172.2 (-$\underline{C}O_2$-CH_2-CH_3), 60.7 (-CO_2-$\underline{C}H_2$-CH_3), 60.4 (-CO_2-$\underline{C}H_2$-CH_3), 50.8 (-NH-$\underline{C}H_2$-CO_2-), 44.7 (-NH-$\underline{C}H_2$-CH_2-CO_2-), 34.8 (-NH-CH_2-$\underline{C}H_2$-CO_2-), 14.1 (2 × -CO_2-CH_2-C$\underline{H}_3$); **LRMS** (ES+) *m/z* (relative intensity %) 204 (100%, $[M + H]^+$).

Synthesis and Characterisation of 147

Ethyl *N*-(*tert*-butoxycarbonyl)-*N*-(2-ethoxy-2-oxoethyl)-β-alaninate **147**



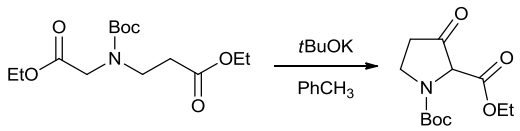
To a stirred solution of **156** (1 eq., 19.4 g, 95.4 mmol) in $CHCl_3$ (210 mL) at 0 °C was added $(Boc)_2O$ (1.4 eq., 29.2 g, 134 mmol,) followed by 5% aqueous NaOH (210 mL). The reaction mixture was stirred at 0 °C for 1 h and then at r.t. for 12 h. The organics were separated and the aqueous phase extracted with $CHCl_3$ (2 × 200 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc:PE) to give **147** (27.6 g, 95%) as a colourless oil. Characterisation data were corresponding to literature[79b] with the ^1H and ^{13}C NMR spectra complicated by *N*-Boc rotamers at 298 K.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:1) δ 4.08 - 4.21 (m, 8 H, -CO_2-C$\underline{H}_2$-CH_3, rotamers), 4.02 (s, 2 H, -NH-C$\underline{H}_2$-CO_2-, rotamer), 3.95 (s, 2 H, -NH-C$\underline{H}_2$-CO_2-, rotamer), 3.56 (t, *J* = 6.5 Hz, 2 H, -NH-C$\underline{H}_2$-CH_2-CO_2-, rotamer), 3.53 (t, *J* = 6.5 Hz, 2 H, -NH-C$\underline{H}_2$-CH_2-CO_2-, rotamer), 2.58 - 2.66 (m, 4 H, -NH-CH_2-C$\underline{H}_2$-CO_2-, rotamers), 1.48 (s, 9 H, -C(C$\underline{H}_3$)$_3$, rotamers), 1.41 (s, 9 H, -C(C$\underline{H}_3$)$_3$, rotamers), 1.22 - 1.30 (m, 12 H, -CO_2-CH_2-C$\underline{H}_3$, rotamers); **^{13}C NMR** (126 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:1) δ 172.4 (-$\underline{C}O_2$-CH_2-CH_3, rotamer), 172.0 (-$\underline{C}O_2$-CH_2-CH_3, rotamer), 170.2 (-$\underline{C}O_2$-CH_2-CH_3, rotamer), 170.1 (-$\underline{C}O_2$-CH_2-CH_3, rotamer), 155.4 (-N-$\underline{C}O_2$-, rotamers), 155.0 (-N-$\underline{C}O_2$-, rotamers), 80.4 (-C(C$\underline{H}_3$)$_3$, rotamers), 80.3 (-C(C$\underline{H}_3$)$_3$, rotamers), 60.9 (2 × -CO_2-C$\underline{H}_2$-CH_3, rotamer), 60.5 (-CO_2-C$\underline{H}_2$-CH_3, rotamer), 60.4 (-CO_2-C$\underline{H}_2$-CH_3, rotamer), 50.8 (-NH-C$\underline{H}_2$-CO_2-, rotamer), 50.0 (-NH-C$\underline{H}_2$-CO_2-, rotamer), 44.8 (-NH-C$\underline{H}_2$-CH_2-CO_2-,

rotamer), 44.7 (-NH-$\underline{C}H_2$-CH_2-CO_2-, rotamer), 34.1 (-NH-CH_2-$\underline{C}H_2$-CO_2-, rotamer), 33.7 (-NH-CH_2-$\underline{C}H_2$-CO_2-, rotamer), 28.3 (-C($\underline{C}H_3$)$_3$, rotamer), 28.1 (-C($\underline{C}H_3$)$_3$, rotamer), 14.2 (-CO_2-CH_2-$C\underline{H}_3$, rotamer), 14.1 (-CO_2-CH_2-$C\underline{H}_3$, rotamer); **LRMS** (ES+) *m/z* (relative intensity %) 326 (100%, $[M + Na]^+$).

Synthesis and Characterisation of 146

1-*tert*-Butyl 2-ethyl 3-oxopyrrolidine-1,2-dicarboxylate **146**



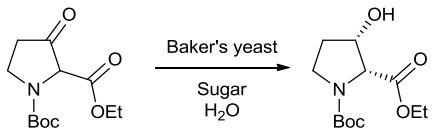
147 **146**

A suspension of potassium *tert*-butoxide (1.5 eq., 8.32 g, 74.2 mmol) in toluene (170 mL) was cooled to 0 °C using an ice-NaCl bath. A solution of **147** (1.0 eq., 15.0 g, 49.4 mmol,) in toluene (27 mL) was added over 12 minutes. The reaction mixture was stirred at 0 °C for 85 min then quenched with acetic acid (5.50 mL, in one portion) followed by a cold solution of $NaH_2PO_4 \cdot H_2O$ (27.0 g) in H_2O (270 mL). The organics were separated and the aqueous phase extracted with $CHCl_3$ (170 mL + 100 mL). The organic extracts were combined, washed with pH 7 phosphate buffer (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken into toluene (250 mL), washed with pH 10 sodium carbonate buffer (5 × 150 mL), followed by water (70 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc:PE) to give **146** (4.96 g, 39%) as a colourless oil. Characterisation data were corresponding to literature[92] with the ^1H and ^{13}C NMR spectra complicated by *N*-Boc rotamers at 298 K which was confirmed by additional VT NMR experiments.

^{1}H NMR (500 MHz, 363 K, DMSO-d_6) δ 4.47 (s, 1 H, -N-C<u>H</u>-CO_2-CH_2-CH_3), 4.13 - 4.22 (m, 2 H, -CO_2-C<u>H_2</u>-CH_3), 3.76 (td, *J* = 9.5, 5.0 Hz, 1 H, -N-C<u>H_A</u>H_B-), 3.63 (app. q, *J* = 9.5 Hz, 1 H, -N-CH_A<u>H_B</u>-), 2.71 - 2.82 (m, 1 H, -N-CH_2-C<u>H_A</u>H_B-), 2.60 - 2.69 (m, 1 H, -N-CH_2-CH_A<u>H_B</u>-), 1.42 (s, 9 H, -C(<u>C</u>H_3)$_3$,), 1.22 (t, *J* = 7.0 Hz, 3 H, -CO_2-CH_2-C<u>H_3</u>); **^{13}C NMR** (126 MHz, 363 K, DMSO-d_6) δ 204.2 (-<u>C</u>O-), 165.8 (-<u>C</u>O_2-CH_2-CH_3), 152.9 (-N-<u>C</u>O_2-C(<u>C</u>H_3)$_3$), 79.5 (-<u>C</u>(CH_3)$_3$), 65.1 (-N-<u>C</u>H-CO_2-CH_2-CH_3), 60.8 (-CO_2-<u>C</u>H_2-CH_3), 41.4 (-N-<u>C</u>H_2-), 35.8 (-N-CH_2-<u>C</u>H_2-), 27.5 (-C(<u>C</u>H_3)$_3$), 13.4 (-CO_2-CH_2-<u>C</u>H_3); **LRMS** (ES+) *m/z* (relative intensity %) 280 (15%, $[M + Na]^+$), 312 (72, $[M + Na + MeOH]^+$).

Synthesis and Characterisation of 148

1-*tert*-Butyl 2-ethyl (2*R*,3*S*)-3-hydroxypyrrolidine-1,2-dicarboxylate **148**



e.e. > 90%

146 **148**

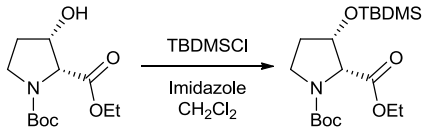
To a gently stirred solution of **146** (1.0 eq., 0.93 g, 3.61 mmol) in tap water (80 mL) was added commercial table sugar (15 g), followed by dried Baker's yeast (10 g, Sainsbury's own brand). The resulting suspension was stirred at 35 °C for 48 h. The reaction mixture was filtered through celite® (water pump suction; filtration can be rather slow) and the semi-solid residue was washed repeatedly with small aliquots of water. The filtrates were combined, saturated with NaCl and extracted with EtOAc (5 × 100 mL). Any emulsions were broken up with a glass rod or by adding a little of MeOH, followed by gentle swirling. The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (50% EtOAc:PE) to give **148** (617 mg, 66%) as a pale yellow oil. Characterisation data were corresponding to literature[92] with the ^{1}H and ^{13}C NMR spectra complicated by *N*-Boc rotamers at 298 K.

$[\alpha]_D^{25}$ = +21.2 (*c* 1.46, CH_2Cl_2), lit.[79] $[\alpha]_D^{27}$ = +18.2 (*c* 1.45, CH_2Cl_2); **^{1}H NMR** (400 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:0.6) δ 4.51 - 4.62 (m, 2 H, -C<u>H</u>(OH)- major and minor rotamers), 4.34 (d, *J* = 7.0 Hz, 1 H, -N-C<u>H</u>-CO_2-CH_2-CH_3, minor rotamer), 4.28 (d, *J* = 7.0 Hz, 1 H, -N-C<u>H</u>-CO_2-CH_2-CH_3, major rotamer), 4.10 - 4.26 (m, 4 H, -CO_2-C<u>H_2</u>-CH_3, major and minor rotamers), 3.52 - 3.67 (m, 2 H, -N-C<u>H_A</u><u>H_B</u>-, major and minor rotamers), 3.34 - 3.48 (m, 2 H, -N-CH_A<u>H_B</u>-, major and minor rotamers), 3.18 (br. s., 2 H, -CH(O<u>H</u>)-, major and minor rotamers), 1.91 - 2.12 (m, 4 H, -N-CH_2-C<u>H_2</u>-, major and minor rotamers), 1.42 (s, 9 H, -C(C<u>H_3</u>)$_3$, minor rotamer), 1.37 (s, 9 H, -C(C<u>H_3</u>)$_3$, major rotamer), 1.21 - 1.28 (m, 6 H, -CO_2-CH_2-C<u>H_3</u>, major and minor rotamers); **^{13}C NMR** (100 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:0.6) δ 170.5 (-<u>C</u>O_2-CH_2-CH_3, rotamer), 170.3 (-<u>C</u>O_2-CH_2-CH_3, rotamer), 154.3 (-N-<u>C</u>O_2-C$(CH_3)_3$, rotamer), 153.8 (-N-<u>C</u>O_2-C(<u>C</u>H_3)$_3$, rotamer), 80.1 (-<u>C</u>$(CH_3)_3$, rotamer), 80.0 (-<u>C</u>$(CH_3)_3$, rotamer), 72.1 (-<u>C</u>H(OH)-, major rotamer), 71.3 (-<u>C</u>H(OH)-, minor rotamer), 63.9 (-N-<u>C</u>H-CO_2-CH_2-CH_3, major rotamer), 63.3 (-N-<u>C</u>H-CO_2-CH_2-CH_3, minor rotamer), 61.0 (-CO_2-<u>C</u>H_2-CH_3, minor rotamer), 60.9 (-CO_2-<u>C</u>H_2-CH_3, major rotamer), 44.1 (-N-<u>C</u>H_2-, minor rotamer), 43.7 (-N-<u>C</u>H_2-, major rotamer), 32.6 (-N-CH_2-<u>C</u>H_2-, minor rotamer), 32.0 (-N-CH_2-<u>C</u>H_2-, major rotamer), 28.3 (-C(<u>C</u>H_3)$_3$, minor rotamer), 28.1 (-C(<u>C</u>H_3)$_3$, major rotamer), 14.2 (-CO_2-CH_2-<u>C</u>H_3, major rotamer), 14.1 (-CO_2-CH_2-<u>C</u>H_3, minor rotamer); **LRMS** (ES+) *m/z* (relative intensity %) 260 (15%, $[M + H]^+$), 282 (80, $[M + Na]^+$), 541 (100, $[2M + Na]^+$).

Synthesis and Characterisation of 158

1-*tert*-Butyl 2-ethyl (2*R*,3*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}pyrrolidine-1,2-dicarboxylate

158



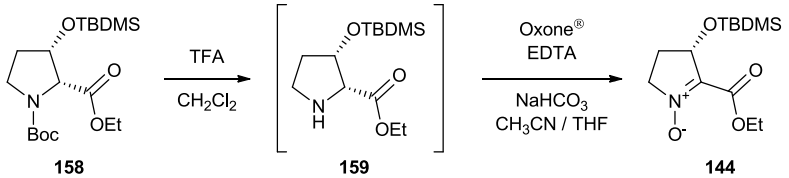
TBDMSCl (1.1 eq., 220 mg, 1.46 mmol) was added to a stirred solution of **148** (1.0 eq., 344 mg, 1.33 mmol) and imidazole (1.5 eq., 135 mg, 2.00 mmol) in CH_2Cl_2 (3 mL) at r.t. The reaction mixture was allowed to stir at r.t. for 16 h before being quenched with water. The reaction mixture was extracted with EtOAc (4 × 5 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc:PE) to give **158** (390 mg, 79%) as a colourless oil. Characterisation data were corresponding to literature[91, 93.] with the ^{1}H and ^{13}C NMR spectra complicated by *N*-Boc rotamers at 298 K.

$[\alpha]_D^{20}$ = −1.11 (*c* 2.70, CH_2Cl_2), lit.[79, 93.] $[\alpha]_D^{26}$ = −1.74 (*c* 2.21, CH_2Cl_2); **^{1}H NMR** (400 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:0.7) δ 4.49 - 4.58 (m, 2 H, -C<u>H</u>(OTBDMS)- major and minor rotamers), 4.35 (d, *J* = 7.0 Hz, 1 H, -N-C<u>H</u>-CO_2-CH_2-CH_3, minor rotamer), 4.18 - 4.30 (m, 3 H, -N-C<u>H</u>-CO_2-CH_2-CH_3, major rotamer, -CO_2-C<u>H_A</u>H_B-CH_3, major and minor rotamers), 4.02 - 4.15 (m, 2 H, -CO_2-CH_A<u>H_B</u>-CH_3, major and minor rotamers), 3.58 - 3.72 (m, 2 H, -N-C<u>H_A</u>H_B-, major and minor rotamers), 3.33 - 3.44 (m, 2 H, -N-CH_A<u>H_B</u>-, major and minor rotamers), 1.95 - 2.08 (m, 4 H, -N-CH_2-C<u>H_2</u>-, major and minor rotamers), 1.46 (s, 9 H, -CO-C(C<u>H_3</u>)$_3$, minor rotamer), 1.42 (s, 9 H, -CO-C(C<u>H_3</u>)$_3$, major rotamer), 1.25 - 1.32 (m, 6 H, -CO_2-CH_2-C<u>H_3</u>, major and minor rotamers), 0.87 (s, 18 H, -Si(CH_3)$_2$-C(C<u>H_3</u>)$_3$, major and minor rotamers), 0.09 (s, 6 H, -Si(C<u>H_3</u>)$_2$-C(CH_3)$_3$, minor rotamer), 0.07 (s, 6 H, -Si(C<u>H_3</u>)$_2$-C(CH_3)$_3$,

major rotamer); **^{13}C NMR** (100 MHz, 298 K, $CDCl_3$, mixture of rotamers, ratio 1:0.7) δ 170.1 (-$\underline{C}O_2$-CH_2-CH_3, rotamer), 170.0 (-$\underline{C}O_2$-CH_2-CH_3, rotamer), 154.2 (-N-$\underline{C}O_2$-$C(CH_3)_3$, rotamer), 153.9 (-N-$\underline{C}O_2$-$C(CH_3)_3$, rotamer), 79.9 (-CO-$\underline{C}(CH_3)_3$, rotamer), 79.7 (-CO-$\underline{C}(CH_3)_3$, rotamer), 72.9 (-$\underline{C}$H(OTBDMS)-, major rotamer), 72.1 (-$\underline{C}$H(OTBDMS)-, minor rotamer), 63.8 (-N-$\underline{C}$H-CO_2-CH_2-CH_3, major rotamer), 63.2 (-N-$\underline{C}$H-CO_2-CH_2-CH_3, minor rotamer), 60.7 (-CO_2-$\underline{C}H_2$-CH_3, minor rotamer), 60.6 (-CO_2-$\underline{C}H_2$-CH_3, major rotamer), 44.1 (-N-$\underline{C}H_2$-, minor rotamer), 43.6 (-N-$\underline{C}H_2$-, major rotamer), 33.1 (-N-CH_2-$\underline{C}H_2$-, minor rotamer), 32.4 (-N-CH_2-$\underline{C}H_2$-, major rotamer), 28.3 (-CO-C($\underline{C}H_3$)$_3$, minor rotamer), 28.2 (-CO-C($\underline{C}H_3$)$_3$, major rotamer), 25.6 (-Si$(CH_3)_2$-C($\underline{C}H_3$)$_3$, minor rotamer), 25.5 (-Si$(CH_3)_2$-C($\underline{C}H_3$)$_3$, major rotamer), 18.0 (-Si$(CH_3)_2$-$\underline{C}(CH_3)_3$, minor rotamer), 17.9 (-Si$(CH_3)_2$-$\underline{C}(CH_3)_3$, major rotamer), 14.3 (-CO_2-CH_2-$\underline{C}H_3$, major rotamer), 14.0 (-CO_2-CH_2-$\underline{C}H_3$, major rotamer), -5.0 (-Si($\underline{C}H_3$)$_2$-$C(CH_3)_3$, major rotamer), -5.1 (-Si($\underline{C}H_3$)$_2$-$C(CH_3)_3$, minor rotamer), -5.2 (-Si($\underline{C}H_3$)$_2$-$C(CH_3)_3$, major and minor rotamers); **LRMS** (ES+) *m/z* (relative intensity %) 374 (22%, $[M + H]^+$), 396 (90, $[M + Na]^+$), 769 (100, $[2M + Na]^+$).

Synthesis and Characterisation of 144

Ethyl (4*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3,4-dihydro-2*H*-pyrrole-5-carboxylate 1-oxide **144**



158 159 144

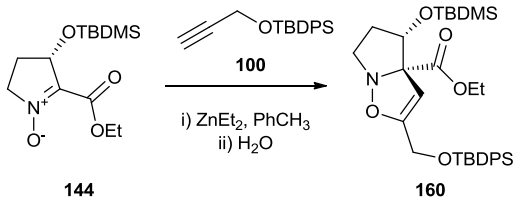
TFA (0.3 mL) was added to a solution of **158** (1.0 eq., 281 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) at r.t. The reaction mixture was stirred for 1 h at r.t. before being quenched carefully with saturated $NaHCO_3$ (aq.) and extracted with CH_2Cl_2 (3 × 7 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **159** as a yellow oil

(200 mg, 97%) which was taken to next step without any further purification. $NaHCO_3$ (5.0 eq., 307 mg, 3.66 mmol) was added to a solution of **159** in MeCN / THF (4:1, 1 mL: 0.25 mL) and 0.01 M Na_2EDTA (aq.) (1 mL) at 5 °C. Oxone® (1.05 eq., 472 mg, 0.77 mmol) was added in small portions under vigorous stirring to the reaction mixture over 2 h while maintaining the temperature below 5 °C. The reaction mixture was stirred for 30 min before EtOAc (4 mL) was added. The organics were separated and the aqueous phase extracted with EtOAc (2 × 2 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (50% MeOH:EtAc) to give **144** (105 mg, 49% over 2 steps) as a pale yellow solid.

M.p. 56 - 58 °C; **IR** ν_{max}(thin film)/cm^{-1} 2930 (C-H), 1725 (C=O), 1549, 1227, 1084, 835, 777; **$[\alpha]_D^{25}$** = +60.7 (*c* 1.27, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$,) δ 5.27 (d, *J* = 7.0 Hz, 1 H, -C<u>H</u>(OTBDMS)-), 4.16 - 4.48 (m, 3 H, -N-C<u>H</u>$_A$H$_B$-, -CO_2-C<u>H</u>$_2$-CH_3), 4.00 (ddd, *J* = 14.5, 9.5, 3.0 Hz, 1 H, -N-CH$_A$<u>H</u>$_B$-), 2.37 - 2.50 (m, 1 H, -N-CH_2-C<u>H</u>$_A$H$_B$-), 1.97 - 2.04 (m, 1 H, -N-CH_2-CH$_A$<u>H</u>$_B$-), 1.34 (t, *J* = 7.5 Hz, 3 H, -CO_2-CH_2-C<u>H</u>$_3$), 0.87 (s, 9 H, -Si(CH_3)$_2$-C(C<u>H</u>$_3$)$_3$), 0.14 (s, 3 H, -Si(C<u>H</u>$_3$)$_2$-C(CH_3)$_3$), 0.10 (s, 3 H, -Si(C<u>H</u>$_3$)$_2$-C(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.1 (-<u>C</u>O_2-CH_2-CH_3), 135.9 (-N=<u>C</u>-), 73.0 (-<u>C</u>H(OTBDMS)-), 65.0 (-N-<u>C</u>H_2-), 61.2 (-CO_2-<u>C</u>H_2-CH_3), 29.0 (-N-CH_2-<u>C</u>H_2-), 25.5 (-Si(CH_3)$_2$-C(<u>C</u>H_3)$_3$), 17.9 (-Si(CH_3)$_2$-<u>C</u>(CH_3)$_3$), 14.2 (-CO_2-CH_2-<u>C</u>H_3), -5.0 (-Si(<u>C</u>H_3)$_2$-C(CH_3)$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 310 (60%, $[M + Na]^+$), 597 (75, $[2M + Na]^+$), 598 (100, $[2M + Na + H]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{13}H_{25}NNaO_4Si$) requires *m/z* 310.1445, found *m/z* 310.1434.

Synthesis and Characterisation of 160

Ethyl (3a*R*,4*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-5,6-dihydropyrrolo[1,2-*b*][1,2]oxazole-3a(4*H*)-carboxylate **160**



Alkyne **100** (3 eq., 289 mg, 0.98 mmol) was added to a solution of **144** (1 eq., 94 mg, 0.33 mmol), in toluene (1 mL) under nitrogen. Et_2Zn (1.5 eq., 1M in hexanes, 0.49 mL, 0.49 mmol) was added at r.t. and the resulting mixture was stirred for 4 h at r.t. Saturated NH_4Cl (aq.). (3 mL) was added and the mixture was stirred for 15 min. The organics were separated and the aqueous phase extracted with EtOAc (3 × 4 mL). The organic extracts were combined, washed with saturated NaCl (aq.) solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc:PE) to give **160** (99 mg, 52%) as a single diastereoisomer and as a pale yellow oil.

IR ν_{max}(thin film)/cm^{-1} 2930 (C-H), 2857, 1730 (C=O), 1472, 1254, 1112, 835; $\mathbf{[\alpha]_D^{20}}$ = -16.7 (*c* 1.05, $CHCl_3$); **^{1}H NMR** (400 MHz, C_6D_6) δ 7.75 - 7.67 (m, 4 H, Ar<u>H</u>), 7.18 - 7.23 (m, 6 H, Ar<u>H</u>), 5.02 (s, 1 H, -C=C<u>H</u>-), 4.24 - 4.20 (m, 1 H, -C<u>H</u>(OTBDMS)-), 4.14 (s, 2 H, -O-C<u>H_2</u>-), 4.16 - 4.08 (m, 1 H, -CO_2-C<u>H_A</u>H_B-CH_3), 4.00 (dq, *J* = 11.0, 7.0 Hz, 1 H, -CO_2-CH_A<u>H_B</u>-CH_3), 3.63 (ddd, *J* = 13.0, 11.5, 5.0 Hz, 1 H, -N-C<u>H_A</u>H_B-), 3.43 - 3.35 (m, 1 H, -N-CH_A<u>H_B</u>-), 1.85 - 1.74 (m, 1 H, -N-CH_2-C<u>H_A</u>H_B-), 1.52 (ddt, *J* = 12.5, 5.0, 2.5 Hz, 1 H, -N-CH_2-CH_A<u>H_B</u>-), 1.13 (s, 9 H, -Si(Ph)$_2$-C(C<u>H_3</u>)$_3$), 1.02 (t, *J* = 7.0 Hz, 3 H, -CO_2-CH_2-C<u>H_3</u>), 0.92 (s, 9 H, -Si(CH_3)$_2$-C(C<u>H_3</u>)$_3$), 0.08 (s, 3 H, -Si(C<u>H_3</u>)$_2$-C(CH_3)$_3$), 0.01 (s, 3 H, -Si(C<u>H_3</u>)$_2$-C(CH_3)$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ 170.6 (-<u>C</u>O_2-CH_2-CH_3), 157.3 (-O-CH_2-<u>C</u>=), 136.3 (Ar<u>C</u>), 133.8

(Ar<u>C</u>), 130.5 (Ar<u>C</u>), 128.5 (Ar<u>C</u>), 95.9 (-O-CH_2-C=<u>C</u>H-), 89.7 (-N-$\underline{C}_{quat.}$-), 80.8 (-<u>C</u>H(OTBDMS)-), 61.1 (-CO_2-C<u>H_2</u>-CH_3), 58.5 (-O-<u>CH_2</u>-), 58.4 (-N-<u>CH_2</u>-), 33.2 (-N-CH_2-<u>CH_2</u>-), 27.3 (-Si(Ph)$_2$-C(<u>CH_3</u>)$_3$), 26.2 (-Si(CH_3)$_2$-C(<u>CH_3</u>)$_3$), 19.8 (-Si(Ph)$_2$-<u>C</u>(CH_3)$_3$), 18.5 (-Si(CH_3)$_2$-<u>C</u>(CH_3)$_3$), 14.6 (-CO_2-CH_2-<u>CH_3</u>), −4.5 (-Si(<u>CH_3</u>)$_2$-C(CH_3)$_3$), −4.6 (-Si(<u>CH_3</u>)$_2$-C(CH_3)$_3$); **LRMS** (ES+) *m/z* (relative intensity %) 604 (100%, $[M + Na]^+$); **HRMS** (ES+) exact mass calculated for $[M + Na]^+$ ($C_{32}H_{47}NNaO_5Si_2$) requires *m/z* 604.2885, found *m/z* 604.2884.

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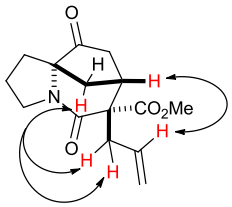
7 Appendices

7.1 NOE data for 64



64

Data obtained at The University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK.

Data includes:

1) Irradiation at 2.30 to 2.50 ppm

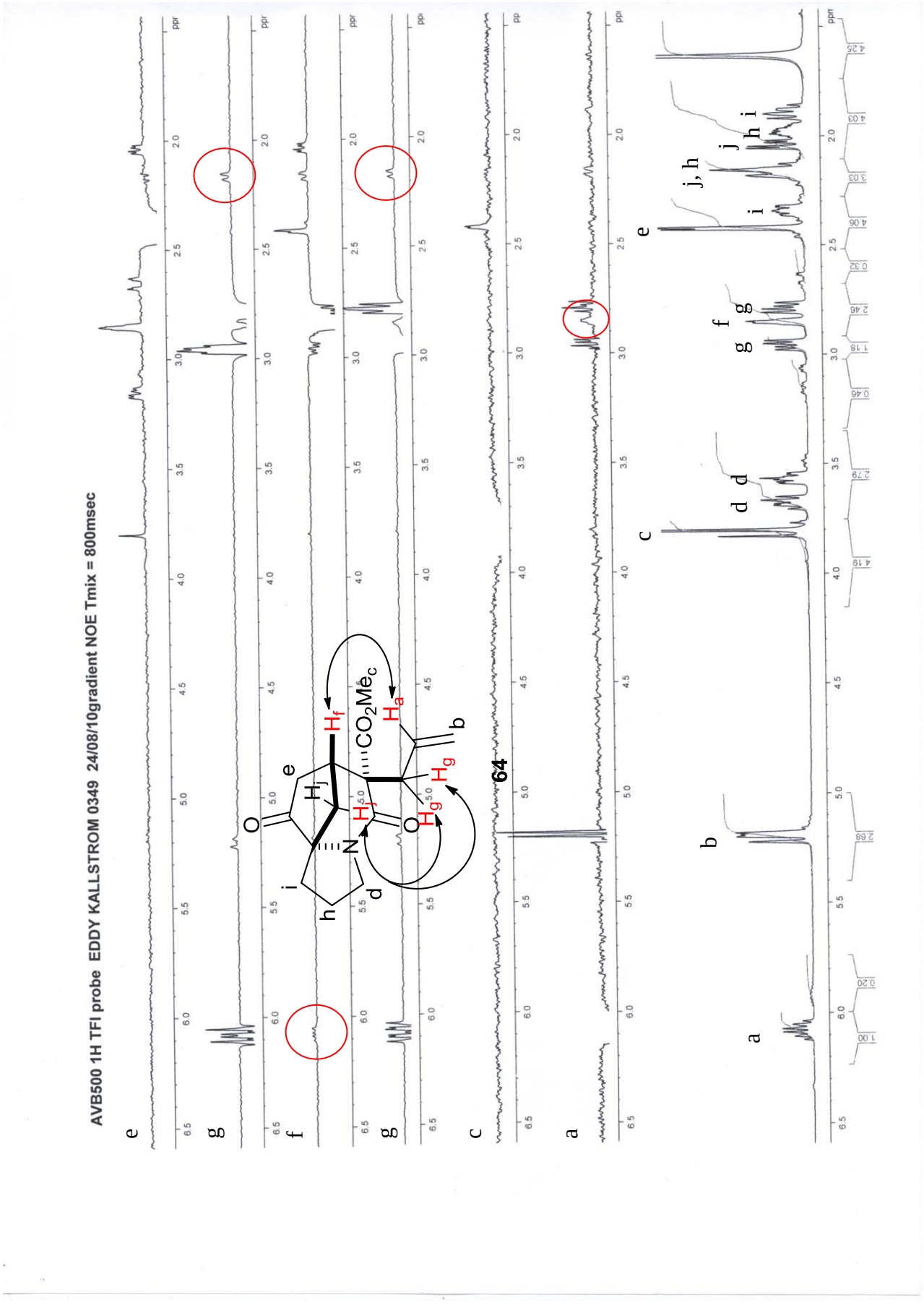
2) Irradiation at 2.80 ppm

3) Irradiation at 2.85 ppm

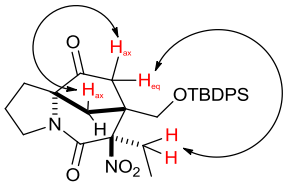
4) Irradiation at 2.95 ppm

5) Irradiation at 2.70 to 2.90 ppm

6) Irradiation at 6.10 ppm


AVB500 1H TFI probe EDDY KALLSTROM 0349 24/08/10gradient NOE Tmix = 800msec
64
H_f
H_j
H_a
H_g
CO_2Me_c
a
b
c
d
e
f
g
h
i
j

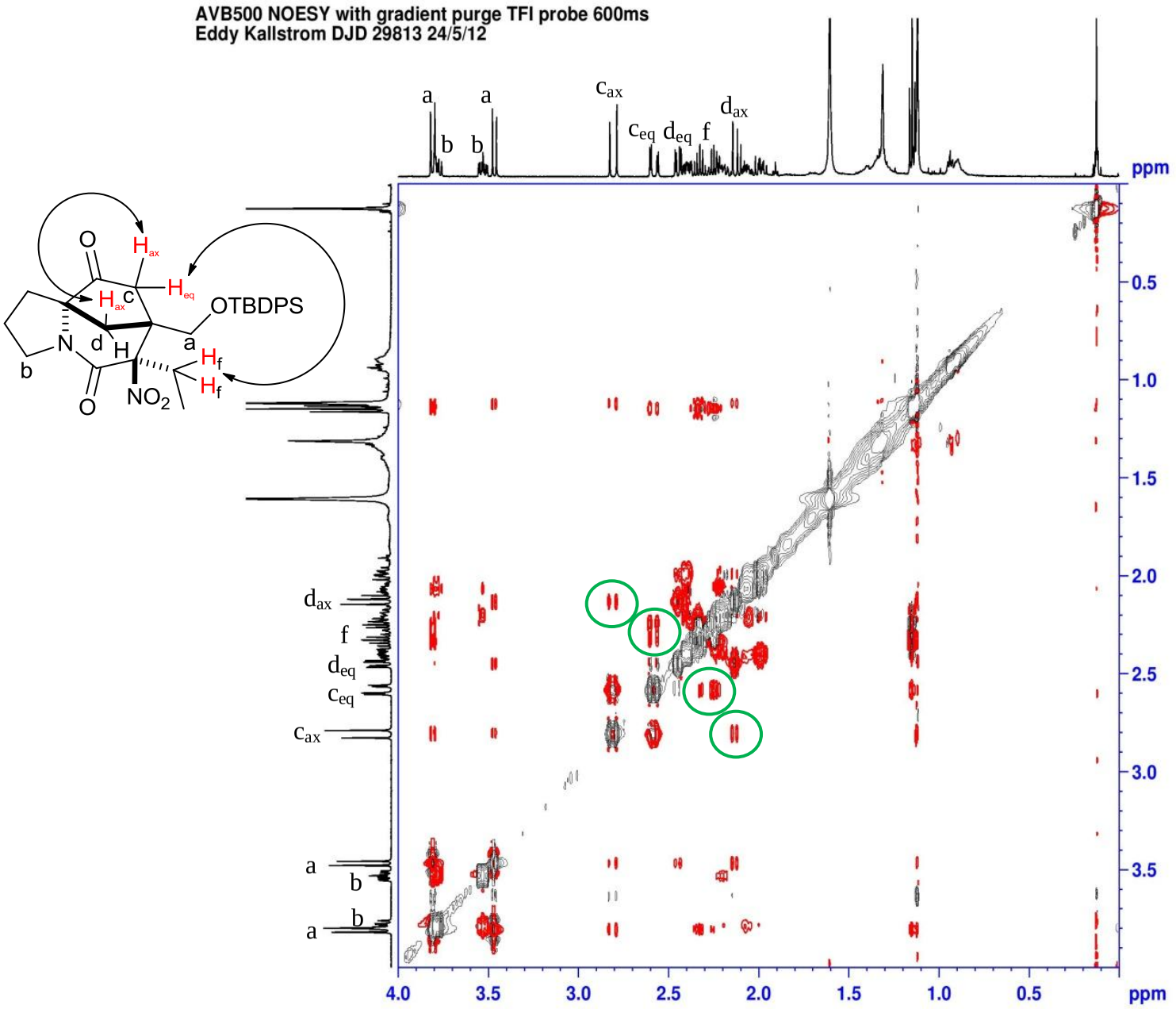
7.2 NOESY data for 138



138

Data obtained at The University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK.

AVB500 NOESY with gradient purge TFI probe 600ms
Eddy Kallstrom DJD 29813 24/5/12



NMR@CHEM.OX

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EXPNO	2
PROCNO	1
Date_	20120524
Time	12.31
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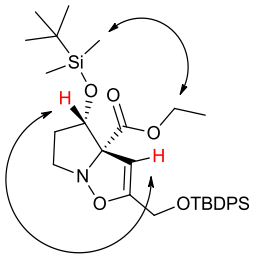
PROBHD	5 mm PATXI 1H/
PULPROG	noesygpph
TD	1024
SOLVENT	CDCl3
NS	16
DS	16
SWH	2000.000 Hz
FIDRES	1.953125 Hz
AQ	0.2560500 sec
RG	912
DW	250.000 usec
DE	6.00 usec
TE	298.0 K
D0	0.00023855 sec
D1	1.50000000 sec
D8	0.60000002 sec
D16	0.00020000 sec
IN0	0.00050000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	9.00 usec
P2	18.00 usec
PL1	1.00 dB
PL1W	13.20863628 W
SFO1	499.9810000 MHz
====== GRADIENT CHANNEL =====	
GPNAM1	SINE.100
GPZ1	40.00 %
P16	1000.00 usec
ND0	1
TD	160
SFO1	499.981 MHz
FIDRES	12.499525 Hz
SW	4.000 ppm
FnMODE	States-TPPI
SI	1024
SF	499.9800000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00
SI	1024
MC2	States-TPPI
SF	499.9800000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

7.3 NOE data for 160

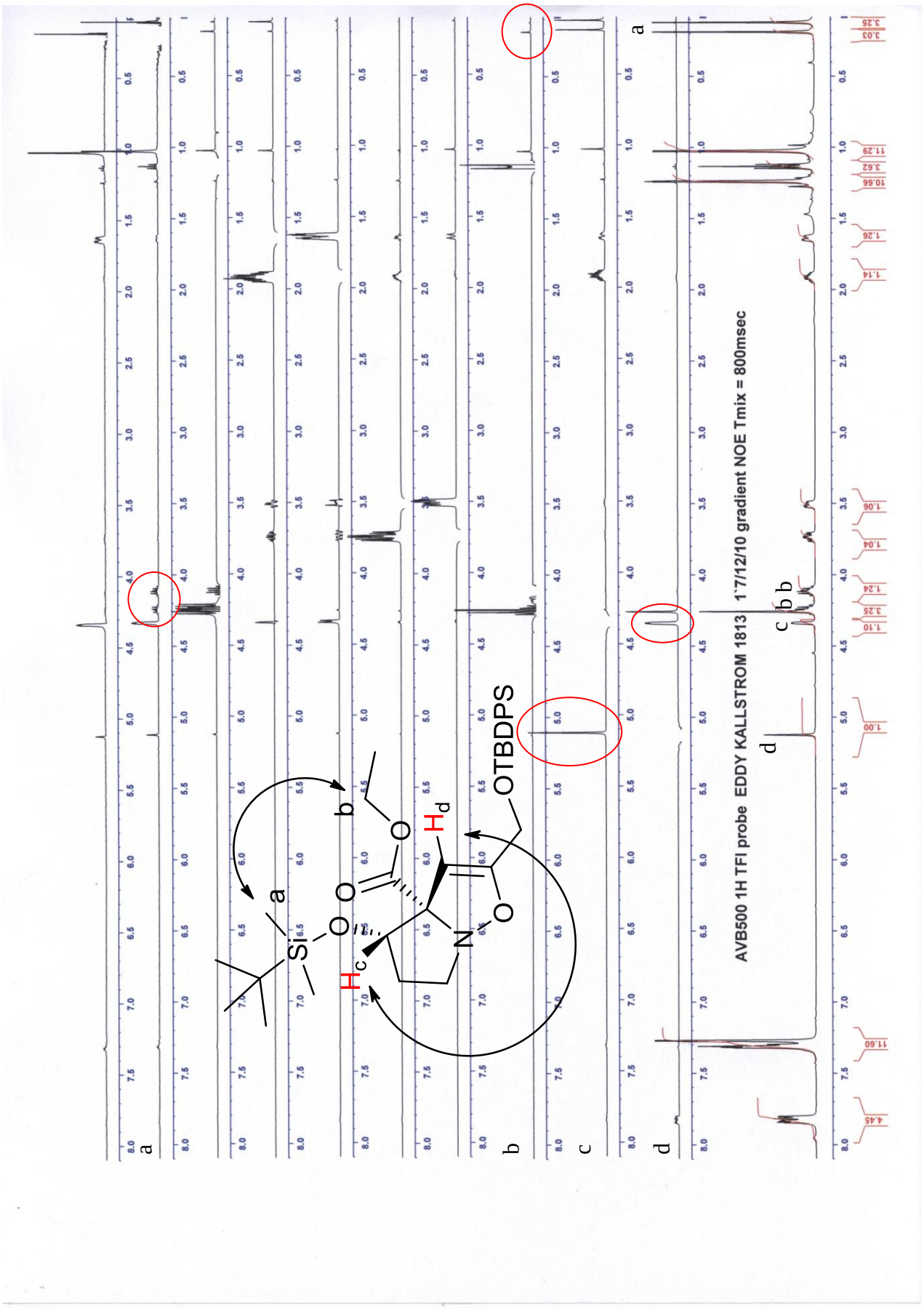


160

Data obtained at the University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK.

Data includes:

1) Irradiation at 0.10 ppm
2) Irradiation at 0.20 ppm
3) Irradiation at 1.25 ppm
4) Irradiation at 1.65 ppm
5) Irradiation at 1.90 ppm
6) Irradiation at 3.75 ppm
7) Irradiation at 3.75 ppm
8) Irradiation at 4.10 ppm
9) Irradiation at 4.35 ppm
10) Irradiation at 5.10 ppm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OTBDPS
Si
O
N
a
b
c
d
H_c
H_d