Towards the Total Synthesis of Gelsemine

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Abstract

Discovered in 1870, in the roots of *Gelsemium sempervirens*, gelsemine has attracted the attention of numerous research groups over the years. Chapter 1 discusses the isolation and structure elucidation of this cage-like alkaloid, along with the synthetic strategies developed to assemble the densely functionalised hexacyclic skeleton.

An overview of the project and optimisation of the synthetic route to the gelsemine core structure are presented in Chapter 2. This sequence involves a [4+3] cycloaddition, a novel access to α,β-unsaturated esters and an elimination - Michael addition step. Finally, a shortened access to the gelsemine core structure from the key step is presented yielding sufficient material for further functionalisation studies.

Chapter 3 discusses two novel strategies towards the construction of the gelsemine spiro-oxindole from a key tricyclic ketone. A series of attempts at α-arylation of ketones using haloacetanilide derivatives are described, culminating an unexpected one-pot indole synthesis. A spiro-oxindole synthesis is presented using a metal catalysed free-radical C–H activation. Progress towards implementing this strategy on the gelsemine core structure is discussed.

In Chapter 4 the functionalisation of the bicyclo[3.2.1]octane core structure is discussed. Selective reduction of the tricyclic ketone gives an axial alcohol that cyclises to afford a lactone as the precursor of the tetrahydropyran ring.

Acknowledgments

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Glossary of Abbreviations

1D	one dimensional
2D	two dimensional
Ac	acetyl
AIBN	2,2'-azobis*iso*butyronitrile
Alloc	allyloxycarbonyl
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	1,1-carbonyldiimidazole
COSY	correlation spectroscopy
CSI	chlorosulfonyl isocyanate
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane

DIB	diacetoxyiodobenzene
DIBAL	di*iso*butylaluminium hydride
DIPEA	*N,N*-di*iso*propylethylamine (Hünig's base)
DMAP	4-dimethylaminopyridine
DMB	2,4-dimethoxybenzyl
DME	dimethoxyethane
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
dppf	1,1'-bis(diphenylphosphino)ferrocene
dtpf	1,1'-bis(di-*o*-tolylphosphino)ferrocene
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
EI	electron ionization
eq.	equivalent
ESI	electrospray ionization
Glu	glucose
HATU	*o*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluroniumhexafluorophosphate
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
$h\nu$	ultraviolet (visible light)
IR	infrared

J	coupling constant
LDA	lithium di*iso*propylamide
lit.	literature
LiTMP	lithium tetramethylpiperidide
m-CPBA	*meta*-chloroperoxybenzoic acid
m.p.	melting point
MAD	methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)
MEM	methoxyethoxymethyl
MOM	methoxymethyl
Ms	mesyl
Mw	microwave
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p-TsOH	*para*-toluenesulfonic acid
PCC	pyridinium chlorochromate
PG	protecting group
Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	parts per million
quant.	quantitative
r.t.	room temperature

R_f	retardation factor
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
TBAB	tetra-*N*-butylammonium bromide
TBAF	tetra-*N*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TDS	thexyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
TFP	2,2,3,3-tetrafluoropropan-1-ol
THP	tetrahydropyranyl
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tol-BINAP	2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphtyl
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl (trityl)
Ts	tosyl

Chapter 1

Introduction

1.1 Alkaloids of the *Gelsemium* Genus

The genus *Gelsemium* is a member of the Loganiaceae family and comprises three different species: *Gelsemium sempervirens*, *Gelsemium Rankinii* and *Gelsemium elegans*. Each of these has been intensively investigated leading to the discovery of more than fifty indole alkaloids classified into six categories based on their complex chemical structures as outlined in Figure 1.1.[1]

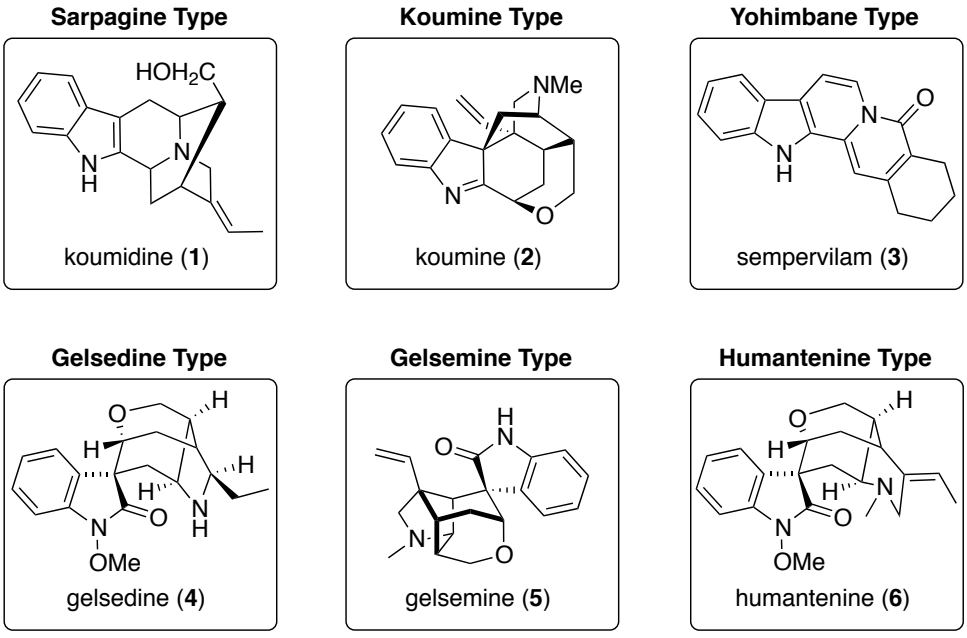
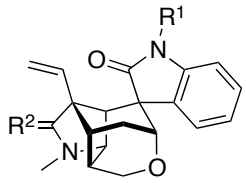


Figure 1.1

The sarpagine and yohimbane type are differentiable by the presence of an indole, the koumine type by an indolenine, while the humantenine, gelsedine and gelsemine type possess

a spiro-oxindole moiety.

The compounds from the gelsemine family are characterised by an assembly of six diverse rings into a compact cage comprising a bicyclo[3.2.1]octane skeleton, a pyrrolidine ring, a tetrahydropyran ring and also a spiro-oxindole, as shown in Table 1.1.



	R^1	R^2
Gelsemine (**5**)	H	H_2
21-Oxogelsemine (**7**)	H	O
Gelsevirine (**8**)	OCH_3	H_2
21-Oxogelseverine (**9**)	OCH_3	O

Table 1.1

Much of the interest around these alkaloids has been driven by their complex and compact structures, but also by their high toxicity. *Gelsemium elegans*, more commonly known as "Gou-Wen" or "Duan-Chang-Cao" in Asia, was traditionally used as a medicinal plant in Chinese folk medicine under the name of "Yakatsu".[2] The remedy was used to treat skin ulcers, spasticity and migraine. More recent investigations attribute potent anxiolytic, antitumour, analgesic and anti-inflammatory effects to some alkaloids from this species.[3] *Gelsemium sempervirens* was also used in medicine as an analgesic and antispasmodic agent and these properties have recently been confirmed.[4,5] As far as *Gelsemium rankinii* is concerned, few investigations have been carried out but extracts from this plant could have promising antitumour activities.[6]

1.2 Isolation and Structure Elucidation

In 1870, Wormley isolated an impure alkaloidal product from the roots of *Gelsemium sempervirens*, a woody vine originating from North Carolina USA, more commonly known as Carolina or yellow jasmine.[7] In 1876, Sonnenschein discovered the principal component of the species as an amorphous base, gelsemine (**5**),[8] followed eleven years later by the isolation of a second alkaloid as an amorphous solid, gelseminine.[9]

In 1910, the isolation of gelsemine (**5**) as a pure crystalline compound led Moore to the correct molecular formula ($C_{20}H_{22}N_2O_2$) but eighty years of degradation studies failed to elucidate the structure.[10] Eventually, in 1959, Lovell and co-workers managed to determine the structure using X-ray crystallography,[11] while Conroy and Chakrabarti derived the same structure from a combination of biosynthetic rationale and proton NMR spectroscopy.[12] Those experiments suggested the structure shown in Figure 1.2.

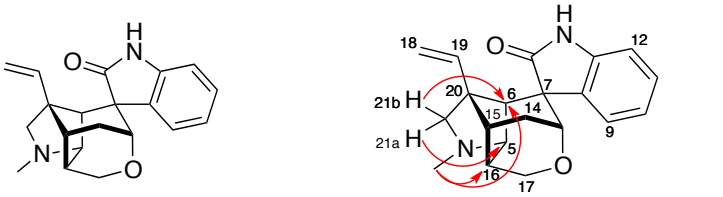


Figure 1.2

Gelsemine (**5**) was also the first alkaloid whose ^{13}C NMR spectrum was assigned, in 1970.[13] Although most of the assignments in the ^{1}H and ^{13}C NMR spectra were correct, the introduction of two dimensional spectra helped to revise the previous attributions.[14] Using homonuclear 2D correlation spectra (COSY) the tetrahydropyran ring assignments, between 2.0 - 2.9 ppm, were modified. More specifically the protons H-14a (2.83 ppm instead of 2.37 ppm), H-15 (2.30 ppm instead of 2.83 ppm) and H-16 (2.43 ppm instead of 2.30 ppm) were

revised. A mixture of HMBC and NOESY experiments were necessary to differentiate the H-21b *endo* from the H-21a *exo*. The NOESY experiment revealed a long range coupling between H-21a (2.78 ppm) and H-5 (3.46 ppm), and also highlighted an interaction between H-21b (2.32 ppm) and H-6 (1.98 ppm). Some significant corrections were brought to the ^{13}C NMR data for position C-6 (50.5 ppm) and N-CH_3 (40.2 ppm), with the assignments reversed based on the nOe correlations (Figure 1.2).

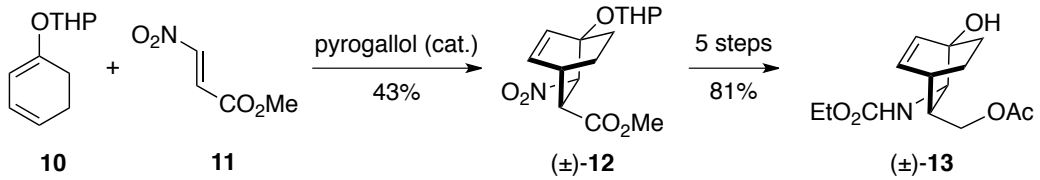
More recently, in the 1980's, gelsemine (**5**) was reported in the roots of *Gelsemium elegans*, a plant originating from Southeast Asia,[15] and trace quantities were found in the stems of *Gelsemium rankinii*, discovered in south-eastern USA.[6]

1.3 Synthesis of the Gelsemine Core Structure

The alkaloids of the genus *Gelsemium* have attracted the attention of several groups worldwide due to their complex chemical structures. In particular, gelsemine has generated intense efforts leading to eight total syntheses. These studies stimulated the development of many innovative synthetic methods towards a densely functionalised ring system assembled into a compact cage.

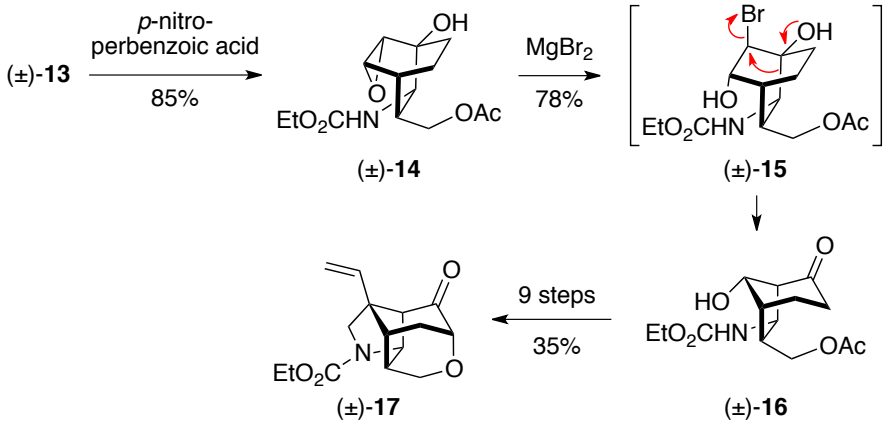
1.3.1 Assembly of the Bicyclo[3.2.1]octane *via* Ring Expansion

In 1988, Ian Fleming and co-workers achieved the formation of the bicyclo[3.2.1]octane core structure from a bicyclo[2.2.2]octene as part of their approach to the synthesis of gelsemine.[16]



Scheme 1.1

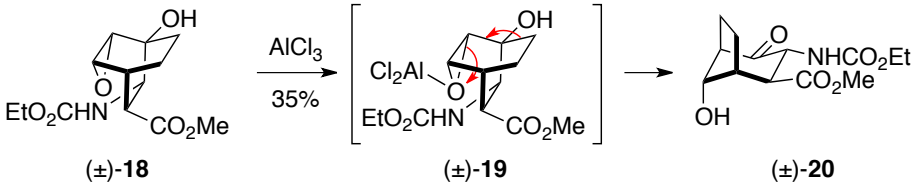
The bicyclo[2.2.2]octene necessary for the rearrangement was set up using a Diels-Alder cycloaddition between *β*-nitroacrylate (**11**) and diene **10** (Scheme 1.1). Unfortunately, two bicyclic adducts were observed during the transformation due to the low *endo* selectivity of the nitro group, giving **12** in only 43% yield. Some modifications of the key intermediate **12** proved to be necessary to remove any chance of retro-Henry reaction once the alcohol was deprotected. To accomplish this the nitro and the ester groups were reduced and protected first, to provide the intermediate **13**. To achieve the desired rearrangement a directed epoxidation introduced an epoxide on the most hindered face affording **14**.



Scheme 1.2

The choice of the Lewis acid appeared to be crucial. Subjecting **14** to $MgBr_2$ led to epoxide opening and formation of the bicyclo[3.2.1]octane **16** (Scheme 1.2). Further modifications

gave a more advanced core structure (**17**), but Fleming and co-workers were unable to transform this to the natural product.

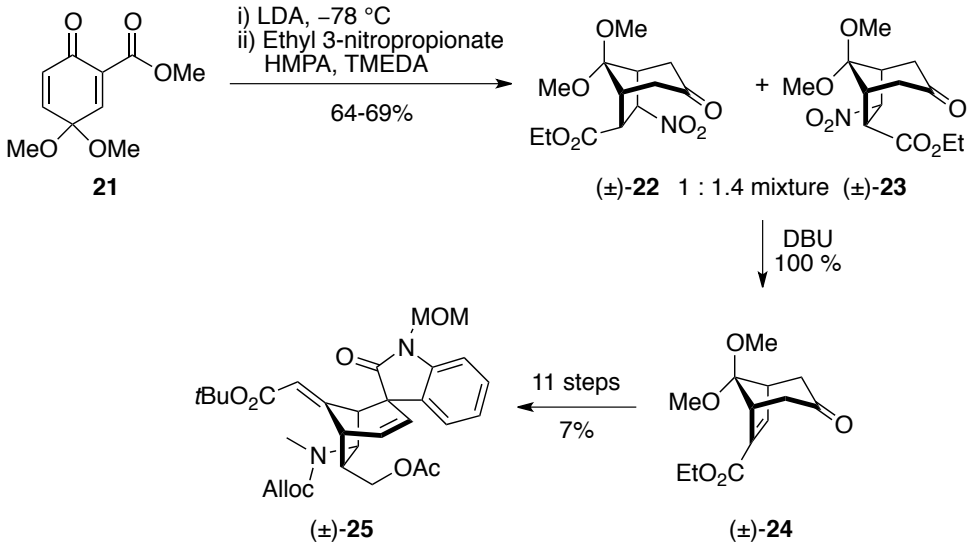


Scheme 1.3

Some preliminary studies on a different intermediate (**18**) helped to model the Lewis acid effect. Treatment with $AlCl_3$ failed to furnish the desired product due to a bond migration affording **20** instead (Scheme 1.3).

1.3.2 Double Conjugate Addition

In 2007 Aubé and co-workers envisaged accessing the bicyclo[3.2.1]octane using a double conjugate addition of a bisfunctional nucleophile onto a quinine ketal in their synthesis of an advanced intermediate of gelsemine, **25**.[17]

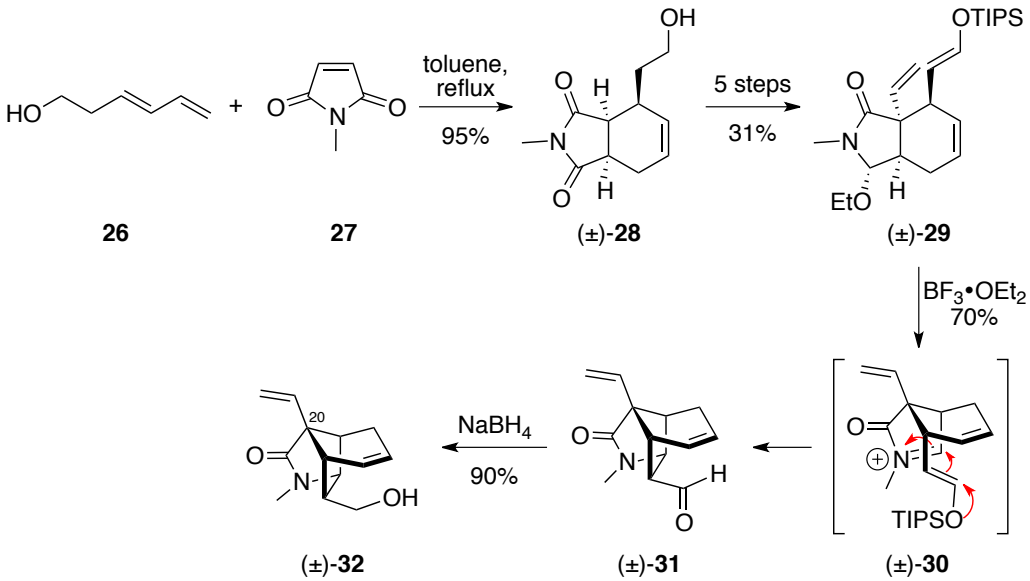


Scheme 1.4

First the lithium dianion of ethyl 3-nitropropionate was generated with 2.1 equivalents of lithium di*iso*propylamide (LDA) and was coupled with *para*-benzoquinone dimethyl ketal (**21**) in the presence of an additive affording a mixture of bicyclooctanones **22** and **23** as a 1:1.4 mixture of inseparable diastereoisomers (Scheme 1.4). The additive appeared to be crucial to increase the yield and a mixture of hexamethylphosphoramide (HMPA) and tetramethylethylenediamine (TMEDA) was proven to be more effective than each of them separately. Fortunately in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) both isomers were converted solely into compound **24**. Further modifications allowed them to reach intermediate **25** (previously prepared by Fukuyama; *vide infra*), completing their formal synthesis of gelsemine.[18]

1.3.3 Mannich Cyclisation

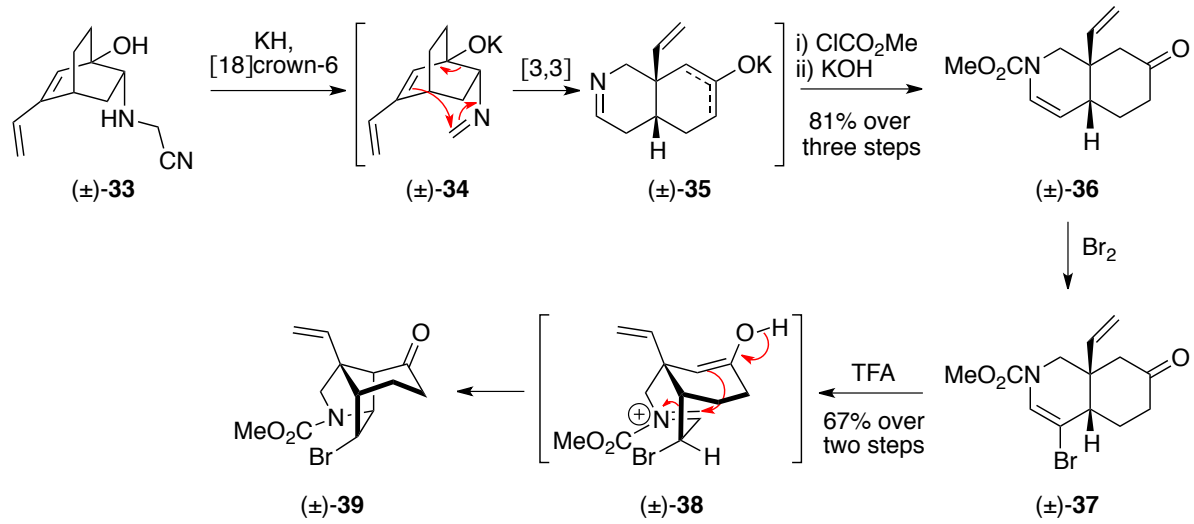
The Mannich cyclisation appeared to be a powerful tool to install the pyrrolidine ring, creating an advanced core structure. This reaction was used in the total synthesis of gelsemine by the Speckamp group.[19]



Scheme 1.5

The precursor for the Mannich cyclisation **29** was prepared from a Diels-Alder reaction between *N*-methylmaleimide (**27**) and (*E*)-hex-3,5-dien-1-ol (**26**) in good yield and was functionalised in five more steps (Scheme 1.5). Several Lewis acids such as $SnCl_4$, $TiCl_4$ and BF_3•OEt_2 were screened to perform the cyclisation with a good stereoselectivity in favour of the desired product. It was found that, in the presence of 1.1 equivalent of BF_3•OEt_2, the cyclisation gave **31** in 70% yield from the (*E*)-silyl enol ether. The remaining aldehyde was reduced into the corresponding alcohol **32** to afford a precursor of the tetrahydropyran ring on a structure already possessing the pyrrolidinone and the vinyl group at the C-20 position.

In their total synthesis, Overman and co-workers developed a similar approach to reach their core structure.[20]

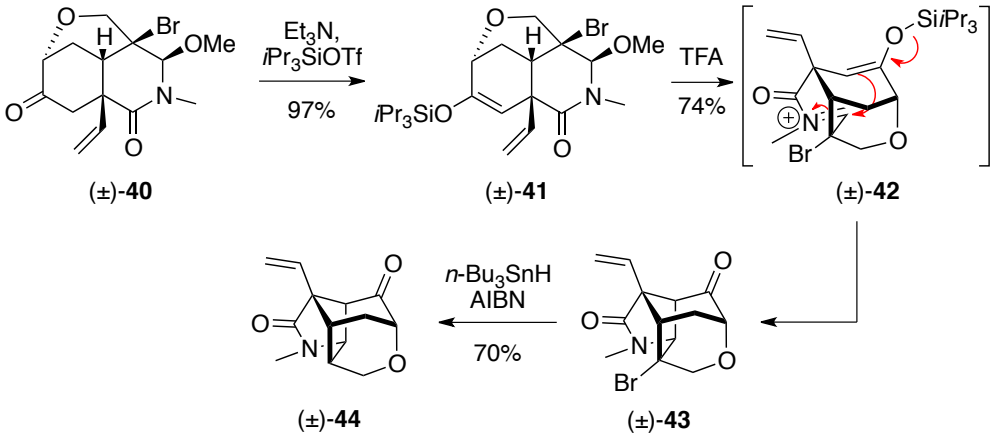


Scheme 1.6

The synthesis commenced with the formation of the bicyclo[2.2.2]octene **33**, as seen in Fleming's approach (Scheme 1.1).[16] The intermediate **33** was obtained by Diels-Alder reaction between 1-tri*iso*propylsiloxy-3-methyl-1,3-cyclohexadiene and methyl acrylate, followed by eight functionalisation steps, in 32% overall yield. Treatment of the amine with

potassium hydride promoted a base-catalysed aza-Cope rearrangement yielding, after addition of methyl chloroformate, the *cis*-hexahydroisoquinolinone (**36**) (Scheme 1.6). Once in hand, **36** was selectively brominated to afford the bicyclic adduct **37**, which was treated with refluxing trifluoroacetic acid (TFA) to form the *N*-acyliminium **38**. During this step, it was supposed that the tetrahydropyridine ring would adopt a boat conformation to allow the Mannich cyclisation to take place, leading to the thermodynamically favoured tricyclic core **39** in 67% yield over two steps.

Likewise, the Mannich cyclisation appeared in the gelsemine synthesis completed by Johnson *et al*. in 1994. A complex precursor was built in twenty steps from readily available starting materials giving an advanced intermediate **40**.[21]



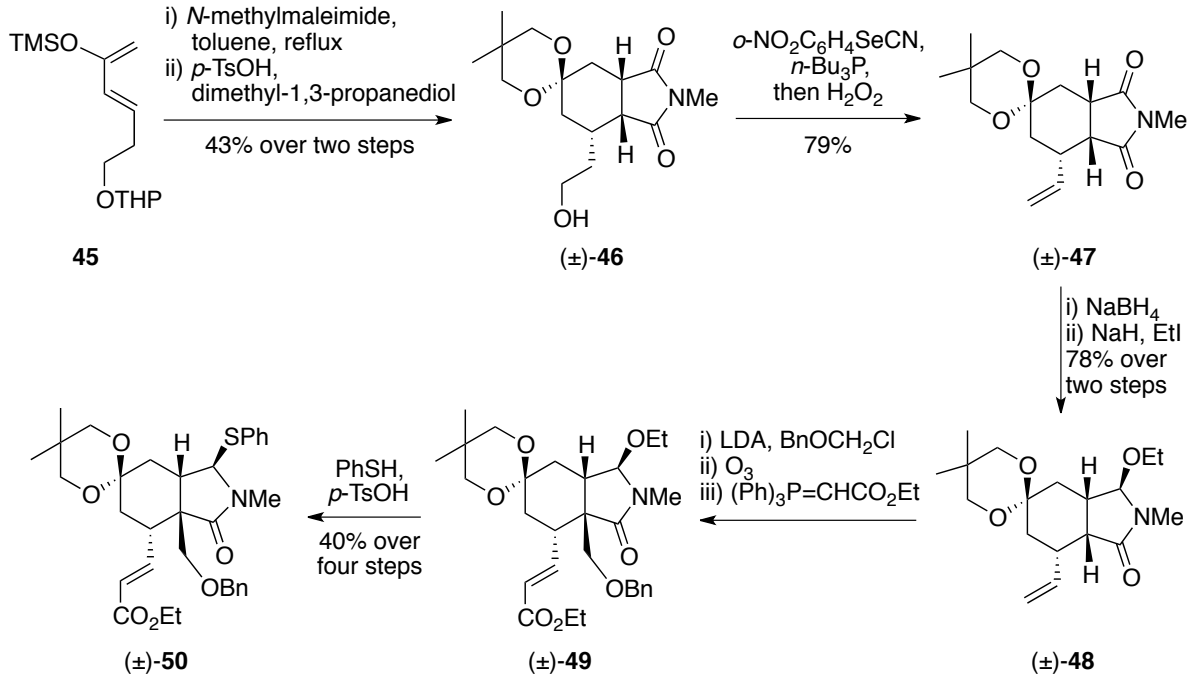
Scheme 1.7

Upon treatment with *i*Pr$_3$SiOTf and Et$_3$N, the keto-lactam **40** was transformed into its corresponding silyl enol ether (**41**). As before in the presence of refluxing trifluoroacetic acid the *N*-acyliminium ion (**42**) was generated *in situ* engendering the intramolecular *5-endo-trig* cyclisation leading to the desired product **43** in 74% yield (Scheme 1.7). Debromination by treatment with *n*-Bu$_3$SnH and 2,2'-azobis*iso*butyronitrile (AIBN) gave the

bicyclo[3.2.1]octane **44**, possessing a tetrahydropyran ring and the pyrrolidinone ring that could easily be reduced into its pyrrolidine derivative.

1.3.4 Radical Cyclisation

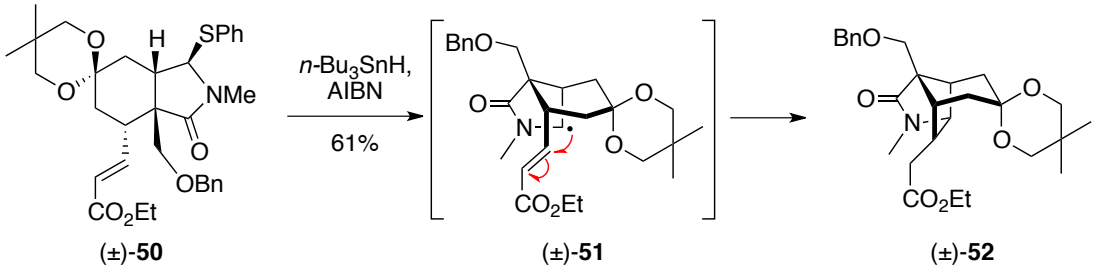
In 1989, Hart *et al*. published an access to the tetracyclic substructure of gelsemine using an α-acylamino radical cyclisation.[22] This methodology was employed to lead to the total synthesis of 21-oxogelsemine in 1994.[23,24]



Scheme 1.8

In a similar way to Speckamp and co-workers (Scheme 1.5, *vide supra*), the synthesis commenced with a Diels-Alder reaction between *N*-methylmaleimide and diene **45**, followed by acidic treatment to give derivative **46** (Scheme 1.8). Dehydration of **46** took place in good yield affording the alkene adduct **47**. After reduction of the imide and protection of the remaining carbinol lactam giving **48**, the most acidic bridgehead position was alkylated with benzyl chloromethyl ether. Preliminary studies had shown that alkene **48** was not suitable for

the radical step as no cyclisation was observed in the presence of AIBN / *n*-Bu_3SnH. Reasoning that this was due to electronic effects an electron deficient olefin was installed followed by an ethoxy - thiophenoxy exchange providing intermediate **50**.[24]

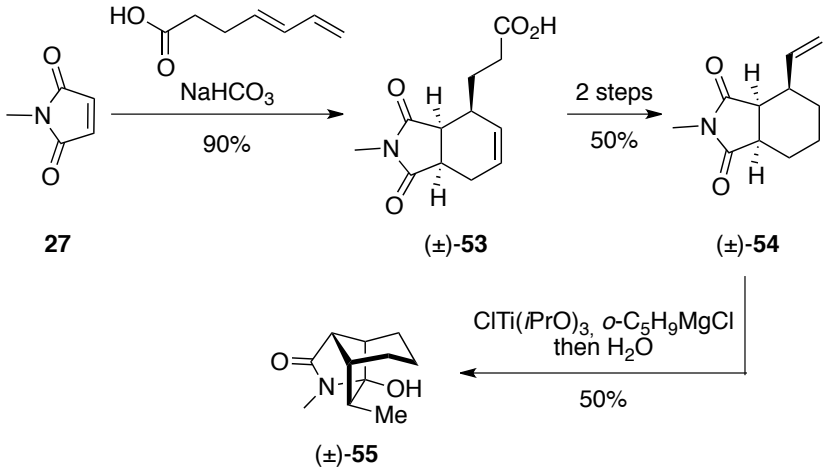


Scheme 1.9

Finally, the desired *5-exo-trig* cyclisation took place upon treatment of **50** with AIBN / *n*-Bu_3SnH leading to the core structure **52** (Scheme 1.9).[24]

1.3.5 Titanium-Mediated Cyclisation

In 1999, Cha *et al*. scoped some conditions to cyclise a similar vinylimide in a tricyclic core structure.[25]

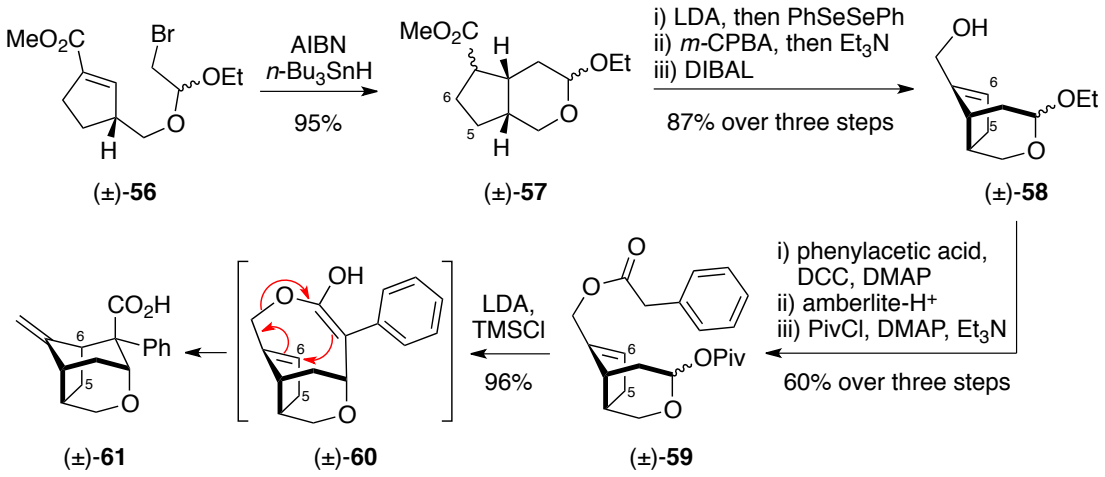


Scheme 1.10

The bicyclic intermediate **53** was easily accessible by Diels-Alder reaction between *N*-methylmaleimide **27** and hepta-4,6-dienoic acid (Scheme 1.10). Hydrogenation of the double bond was followed by oxidative decarboxylation leading to replacement of the carboxylic acid chain with a vinyl group affording **54**. This key intermediate could undergo the titanium-mediated cyclisation furnishing the gelsemine core **55** in one step.

1.3.6 Introduction of the Spiro-Oxindole

The strategy developed by Stork's group to approach gelsemine involved the formation of a tricyclic structure possessing the tetrahydropyran ring and the functionalities for construction of the spiro-oxindole.[26]

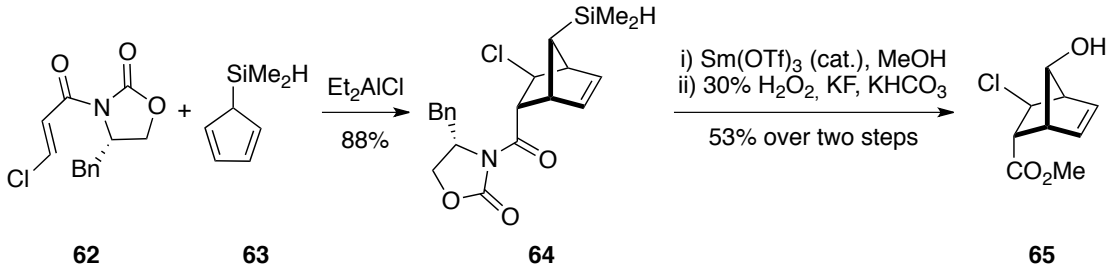


Scheme 1.11

The synthesis started with a radical-initiated cyclisation of **56** using *n*-Bu_3SnH / AIBN, providing the bicyclic adduct **57** in good yield (Scheme 1.11). Structure **57** was converted into **58** by selenation followed by oxidation - elimination with *meta*-chloroperbenzoic acid (*m*-CPBA) and further di*iso*butylaluminium hydride (DIBAL) reduction of the ester into the corresponding alcohol. The primary alcohol was coupled with phenylacetic acid generating a new ester. The intermediate **59** for the Claisen rearrangement was obtained by replacing the

ethoxy group with a better leaving group, in this case a pivaloyl group (Piv), hence allowing the lactone formation. In the presence of LDA the Claisen rearrangement took place, giving the desired tricyclic structure (**61**) possessing the tetrahydropyran and an advanced intermediate of the spiro-oxindole.

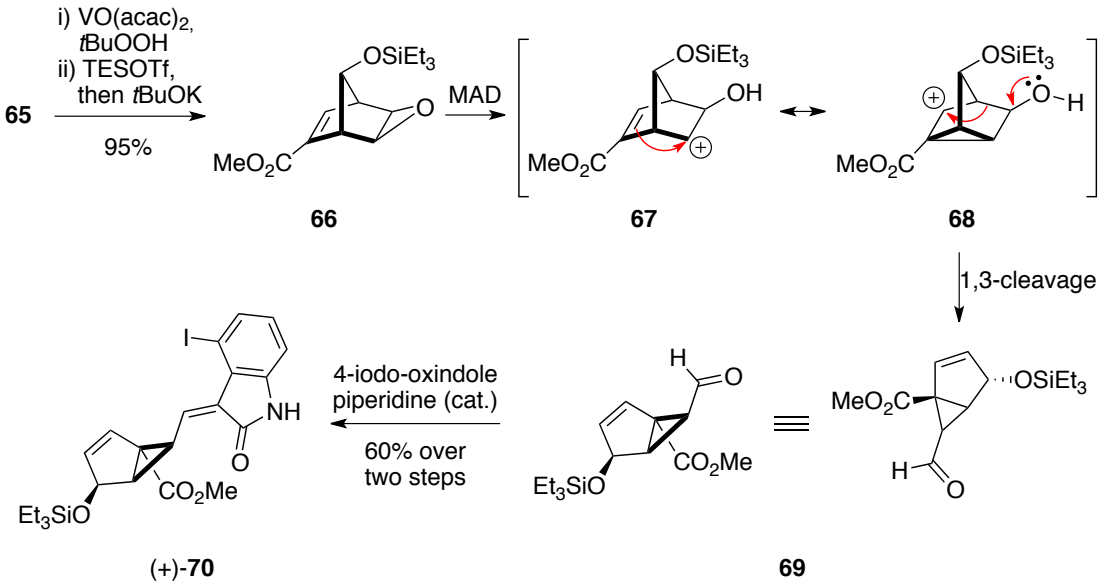
In 1996, Fukuyama *et al*., developed a divinylcyclopropane - cycloheptadiene rearrangement allowing them to access the bicyclo[3.2.1]octane core in one step with the spiro-oxindole already in place.[18] A few years later, in 2000, the same key step was used to perform the first enantioselective approach to (+)-gelsemine.[27]



62 **63** **64** **65**

Scheme 1.12

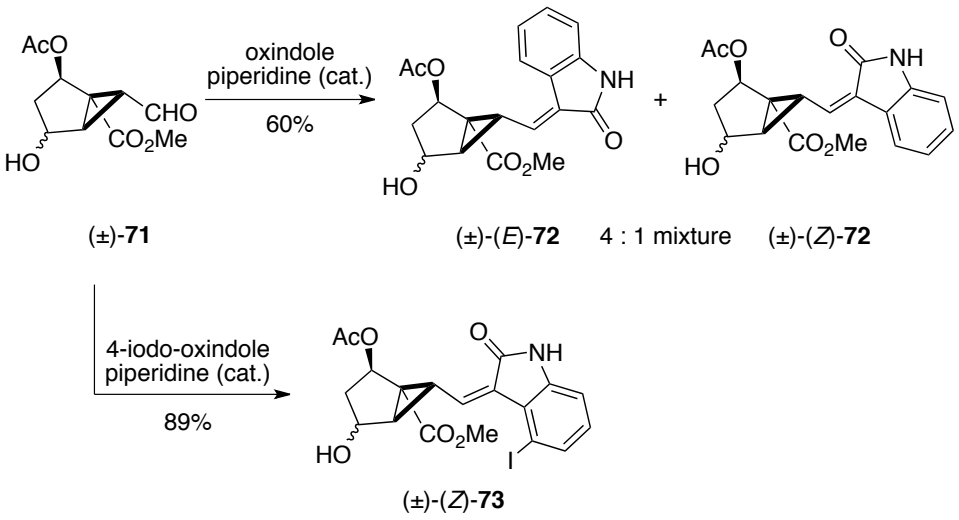
The total synthesis started with an asymmetric Diels-Alder reaction between **62** and 5-methylsilylcyclopentadiene (**63**) giving the product **64** as a single isomer, due to the presence of the Evans chiral auxiliary on the dienophile **62** (Scheme 1.12).[27] Treatment with a catalytic amount of $Sm(OTf)_3$ in methanol replaced the chiral auxiliary with a methyl ester in 99% yield. The alcohol adduct **65** was finally obtained by oxidation of the dimethylsilyl group with hydrogen peroxide in the presence of potassium fluoride.



Scheme 1.13

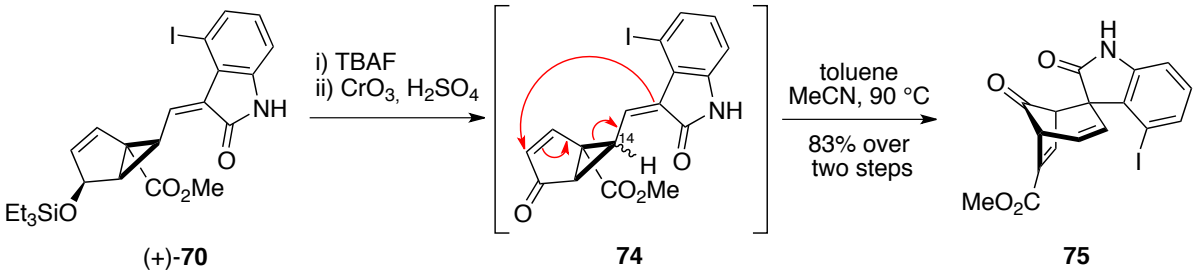
Sharpless epoxidation of the intermediate **65** took place stereoselectively in excellent yield. After protection of the secondary alcohol with a triethylsilyl group, dehydrochlorination became possible in basic media affording a suitable *α,β*-unsaturated intermediate (**66**) for the desired rearrangement (Scheme 1.13). The key acid-catalysed ring opening was first developed by Meinwald in 1963, in their studies on oxidation of bicyclo[2.2.1]heptadiene.[28] Treatment of **66** with methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) caused epoxide opening and migration of the double bond. Subsequent 1,3-cleavage of the resulting tricycle afforded a new intermediate **69** with a cyclopropane ring at the *α*-position of the methyl ester and an aldehyde suitable for a Knoevenagel-like condensation of the oxindole.

In 1996, the group published a synthesis of gelsemine containing the first stereoselective installation of the spiro-oxindole moiety.[18]



Scheme 1.14

The first attempt to apply the Knoevenagel-like condensation using a simple oxindole gave a 4:1 mixture of (*E*)-**72** and (*Z*)-**72** isomers as shown above in Scheme 1.14. To displace the ratio towards the desired isomer, a bulky iodine was introduced at the 4-position of the oxindole, affording exclusively the (*Z*)-**73** isomer in 89% yield. The same procedure was also applied to the enantioselective route furnishing the expected intermediate **70** as a single isomer, in 60% yield over two steps, from **69** (Scheme 1.13, *vide supra*).

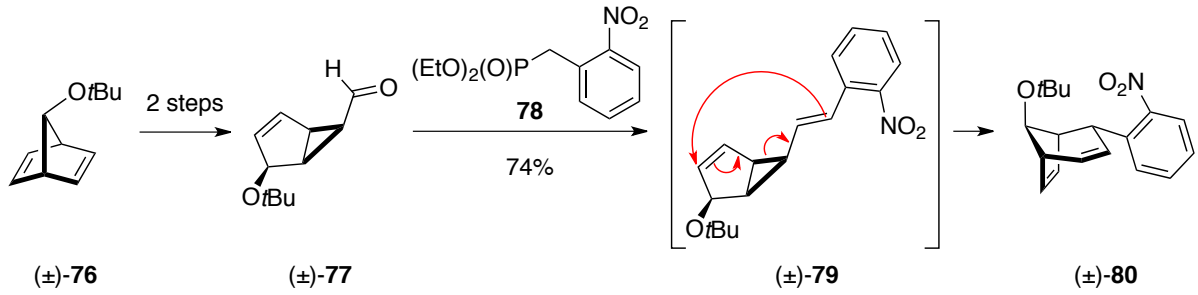


Scheme 1.15

To complete the construction of the core structure, tetra-*N*-butylammonium fluoride (TBAF) mediated removal of the triethylsilyl group was followed by Jones oxidation of the corresponding alcohol providing a mixture of epimers (**74**) at the C-14 position, both of which

were converted at 90 °C into the bicyclic core **75** *via* a divinylcyclopropane - cycloheptadiene rearrangement (Scheme 1.15).[27] In 2011, Fukuyama's group reused the divinylcyclopropane - cycloheptadiene rearrangement as a key step to build the framework of a gelsemium alkaloid named gelsemoxine.[29]

In 1998, Danishefsky's group reported a similar divinylcyclopropane - cycloheptadiene rearrangement to construct the bicyclo[3.2.1]octane.[30] This step was later applied to their total synthesis of gelsemine in 2002.[31]



Scheme 1.16

As seen in Fukuyama's synthesis, the intermediate **77** was prepared in two steps starting from 7-*tert*-butoxynorbornadiene **76** using a Meinwald acid-catalysed rearrangement promoted by exposure to alumina (Scheme 1.16).[28] The aldehyde **77** was treated with nitro-benzyl phosphonate derivative **78** to generate the alkene **79** which underwent a similar divinylcyclopropane - cycloheptadiene rearrangement, furnishing the desired core structure **80** in 74% yield.

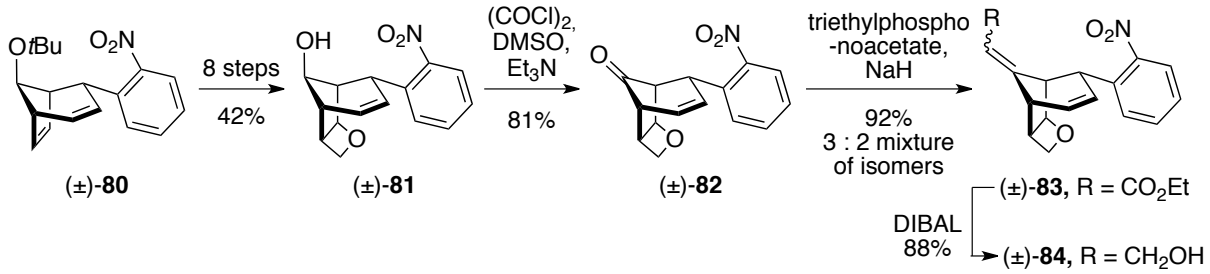
1.4 Synthesis of the Pyrrolidine Ring

1.4.1 Construction of the Core Structure

As described in the previous sections, some groups managed to introduce either the pyrrolidinone or the pyrrolidine ring directly onto their core structure. Speckamp's (Scheme 1.5)[19] and Johnson's (Scheme 1.7)[21] groups assembled the pyrrolidinone ring at the same time as the bicyclo[3.2.1]octane using a Mannich cyclisation. The same reaction led to a more advanced core structure possessing the desired pyrrolidine ring in Overman's synthesis (Scheme 1.6).[20] In their total synthesis of 21-oxogelsemine, Hart *et al*. simultaneously generated the tricylic core and the pyrrolidinone *via* a radical mediated process (Scheme 1.9).[24]

1.4.2 Claisen Rearrangement

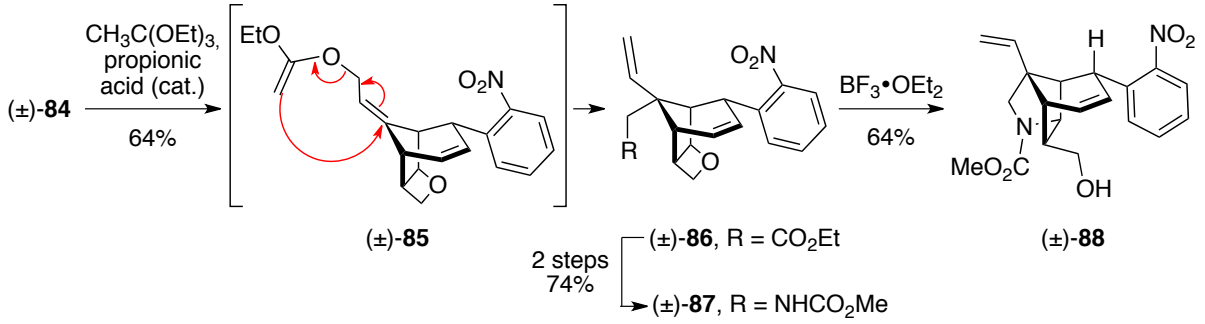
Danishefsky's group reported a construction of the pyrrolidine ring system involving a Claisen rearrangement.[31]



Scheme 1.17

From the intermediate **80**, previously described in Scheme 1.16, eight more steps were necessary to add an oxatane ring and deprotect the secondary alcohol on the core (**81**) (Scheme 1.17). To reach the intermediate for the key step the alcohol was subjected to a Swern oxidation to form ketone **82**, which underwent an Emmons-type condensation

furnishing the required olefin **83** as a 3:2 mixture of isomers. The ester was then reduced to the corresponding alcohols (**84**) with DIBAL.

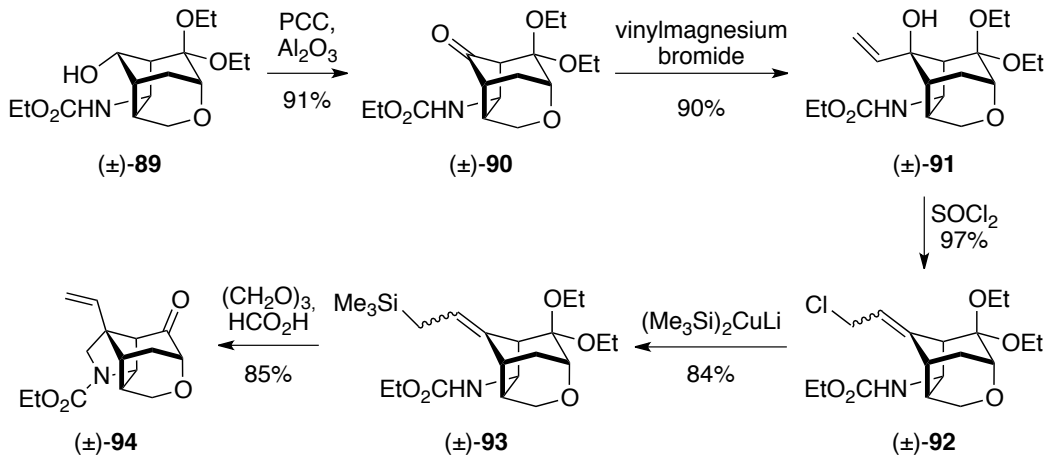


Scheme 1.18

Upon treatment with triethylorthoacetate the allylic alcohol **84** was transformed into the Claisen intermediate **85** (Scheme 1.18). Fortunately, both isomers converged towards the same adduct which underwent a [3,3] rearrangement affording **86** in good yield. To construct the pyrrolidine ring, the ester group was replaced by a carbamate group which, on exposure to a Lewis acid (BF_3•OEt_2) cyclised and opened the oxatane ring, giving the desired product **88**.

1.4.3 *5-endo-trig* Cyclisation

In their approach towards the total synthesis of gelsemine, Fleming and co-workers built the pyrrolidine ring using an intramolecular reaction between an *N*-acyliminium ion and an allylsilane group.[16]

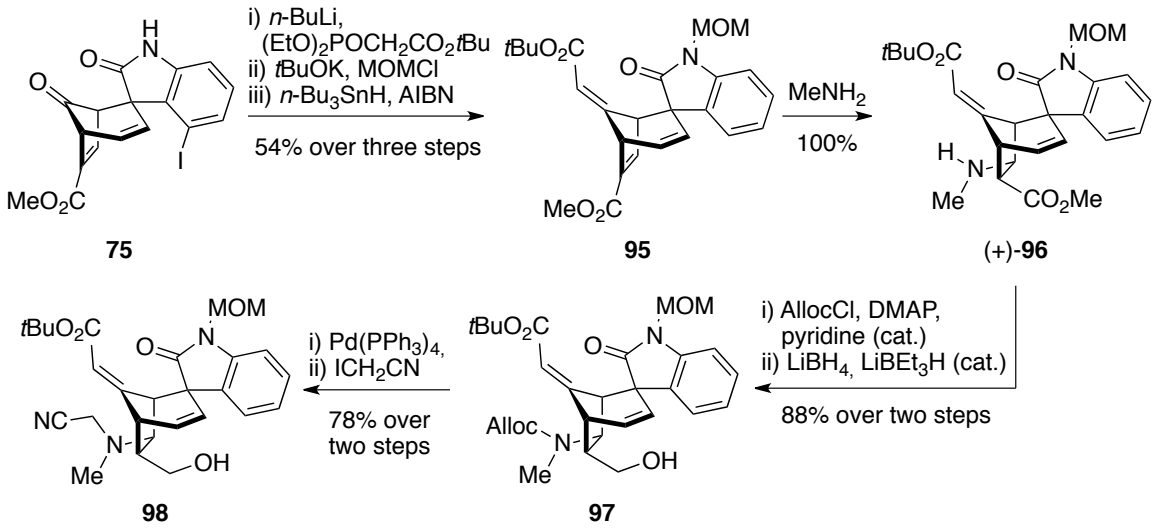


Scheme 1.19

The intermediate **89**, prepared in 15 steps and 11.7% overall yield from phenol, was first subjected to oxidation with pyridinium chlorochromate (PCC) to convert the secondary alcohol into the corresponding ketone **90** in good yield (Scheme 1.19). As direct Wittig reaction of ketone **90** was unsuccessful, a two-step procedure was preferred with addition of vinylmagnesium bromide followed by chlorination and loss of the allylic alcohol to afford **92**. The allylic chlorine was replaced with a silane group by treatment with a trimethylsilyl cuprate reagent to provide **93** in 84% yield. In 1985, Hiemstra and Speckamp had reported an intramolecular cyclisation between an allylsilane group and an *N*-acyliminium ion.[32-34] Following this procedure, addition of formic acid and trioxane converted **93** into an acyliminium ion intermediate, which spontaneously cyclised giving the expected pyrrolidine ring (**94**). Unfortunately for Fleming's group, all of their attempts to install the spiro-oxindole using their methodology to complete the total synthesis were unsuccessful.[35-37]

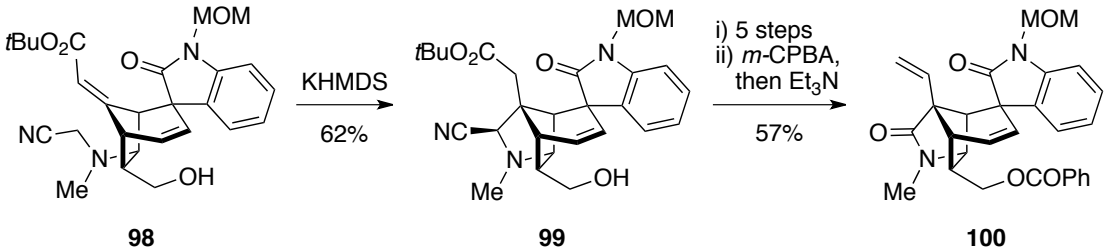
1.4.4 Intramolecular Michael Addition

In 2000, Fukuyama's group reported the first enantioselective total synthesis of (+)-gelsemine, using an intramolecular Michael addition to construct the pyrrolidine ring.[27]



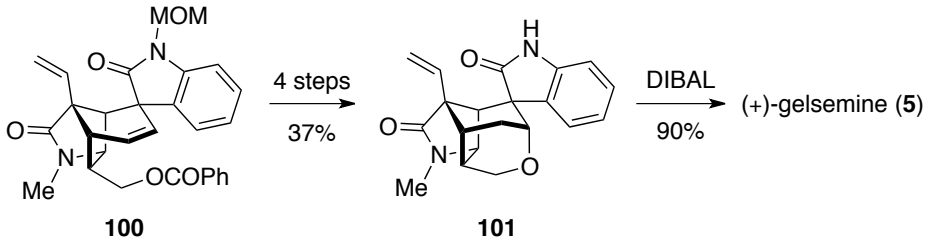
Scheme 1.20

The sequence started with a Horner-Emmons olefination of ketone **75**, followed by methoxymethyl (MOM) protection of the lactam and radical deiodination on the oxindole moiety, yielding **95** in 54% over three steps (Scheme 1.20). The Michael addition of methylamine to the α,β-unsaturated ester took place from the less hindered face giving compound **96**. After protection of the secondary amine with an allyloxycarbonyl group (Alloc), the ester was reduced to the corresponding primary alcohol upon treatment with $LiBH_4$ in the presence of a catalytic amount of $LiBEt_3H$, affording **97** in good yield. Removal of the allyloxycarbonyl protecting group allowed the coupling between the secondary amine and cyanomethyl group to proceed, providing precursor **98** for the Michael addition.



Scheme 1.21

The Michael addition took place upon treatment of **98** with potassium bis(trimethylsilyl)amide (KHMDS) yielding pyrrolidine **99** as a single isomer (Scheme 1.21). Finally, *m*-CPBA oxidation of the nitrile group afforded the *N*-oxide which was then converted to the lactam by triethylamine treatment to furnish pyrrolidinone **100** in good yield over six steps.

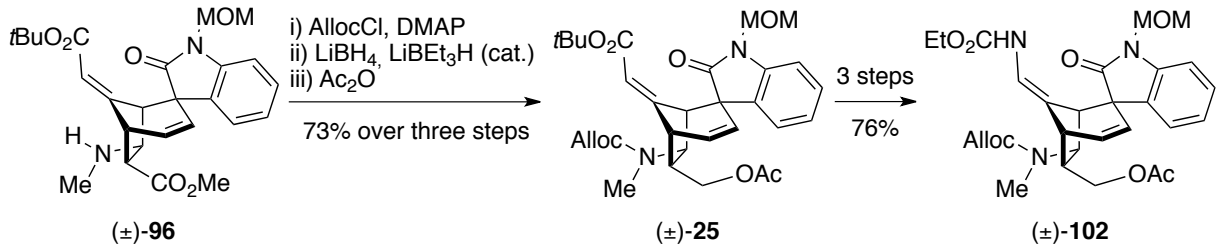


Scheme 1.22

Methanolysis of **100** provided the free primary alcohol, which was used to perform the tetrahydropyran ring formation *via* intramolecular oxymercuration followed by reductive demercuration and N-MOM protecting group removal, affording compound **101** in 37 % over four steps. To complete the synthesis, DIBAL reduction of pyrrolidinone **101** into the corresponding pyrrolidine ring afforded the natural product gelsemine **5** (Scheme 1.22).

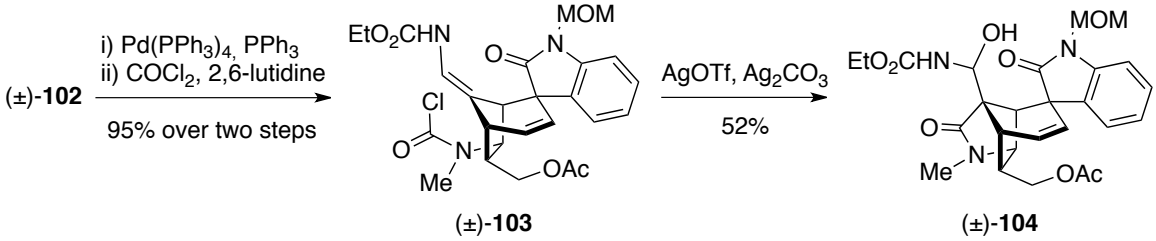
1.4.5 Silver Mediated Cyclisation

In their total synthesis of (±)-gelsemine, published in 1996, Fukuyama *et al.* used a silver mediated cyclisation step to construct the pyrrolidinone ring.[18]



Scheme 1.23

The secondary amine **96** was protected with an allyloxycarbonyl group (Alloc), the ester was reduced with $LiBH_4$ / $LiBEt_3H$ (catalytic amount) and the primary alcohol was protected with an acetyl group, yielding **25** (Scheme 1.23).



Scheme 1.24

After transformation of **25** into **102**, palladium-catalysed removal of the Alloc group was followed by carbamoyl chloride formation using phosgene, to give **103** in good yield. Upon treatment with silver carbamate and silver triflate the system cyclised to furnish a lactam ring along with a secondary alcohol **104** (Scheme 1.24).

Aubé *et al*. adopted a similar strategy and used the intermediate **25** as a relay compound in their formal synthesis of gelsemine published in 2007.[17]

1.5 Strategies Towards the Spiro-Oxindole Moiety

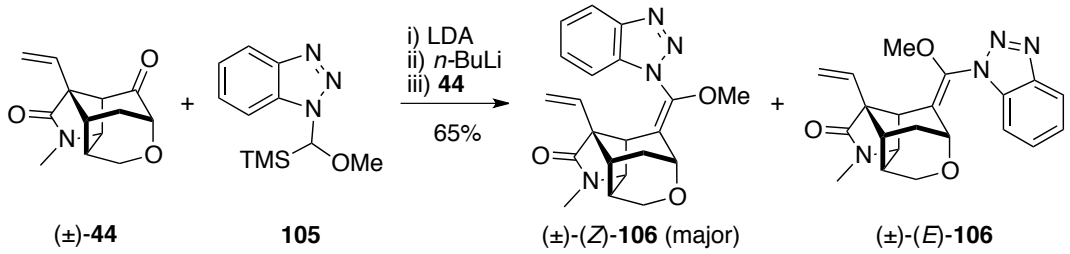
1.5.1 Oxindole Condensation

A strategy involving condensation of an aldehyde with an oxindole was first demonstrated in a gelsemine synthesis by Fukuyama's group in 1996.[18] The reaction was also present in their enantioselective approach of gelsemine in 2000 (Scheme 1.13 and Scheme 1.14),[27] and in their total synthesis of gelsemoxonine in 2011.[29]

This condensation was also used recently in the biomimetic approach towards gelsemine reported by Qin and co-workers, which is discussed in detail later in this chapter.[38]

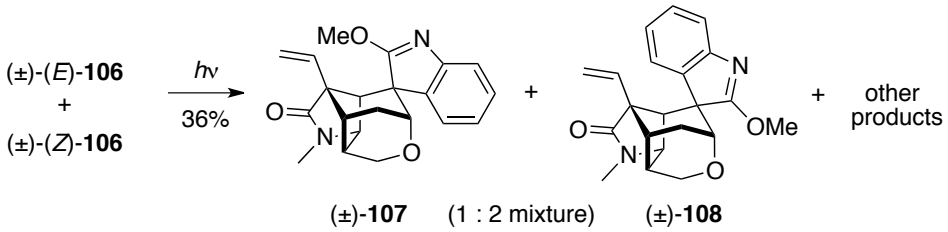
1.5.2 Radical Cyclisation

In 1994, Johnson *et al*. constructed the spiro-oxindole using a photo-induced radical cyclisation of a substituted benzotriazole.[39]



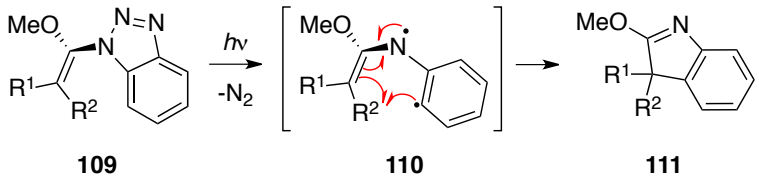
Scheme 1.25

Ketone **44** (Scheme 1.7, *vide supra*) was condensed with a lithiated benzotriazole to afford a mixture of (*E*)-**106** and (*Z*)-**106** isomers in a combined yield of 65% (Scheme 1.25).



Scheme 1.26

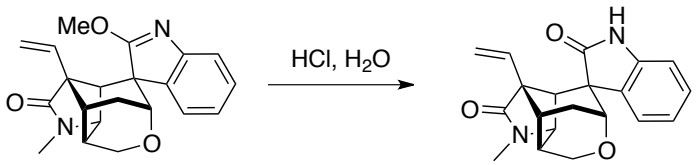
Each isomer when irradiated gave the same products, a mixture of two cyclised compounds **107** and **108** in a 1:2 ratio, along with un-identified side-products (Scheme 1.26). Unfortunately, only the minor isomer **107** possessed the correct stereochemistry at the spiro-oxindole position. Johnson's group proposed a mechanism for this photochemical synthesis of oxindole, based on a Wender methodology paper from 1986.[40]



109 **110** **111**

Scheme 1.27

As outlined in Scheme 1.27, from the photolysis of the benzotriazole compound **109** on which R^1 and R^2 represent the core structure, radical recombination of intermediate **110** formed by elimination of molecular nitrogen, furnished the desired product **111**.

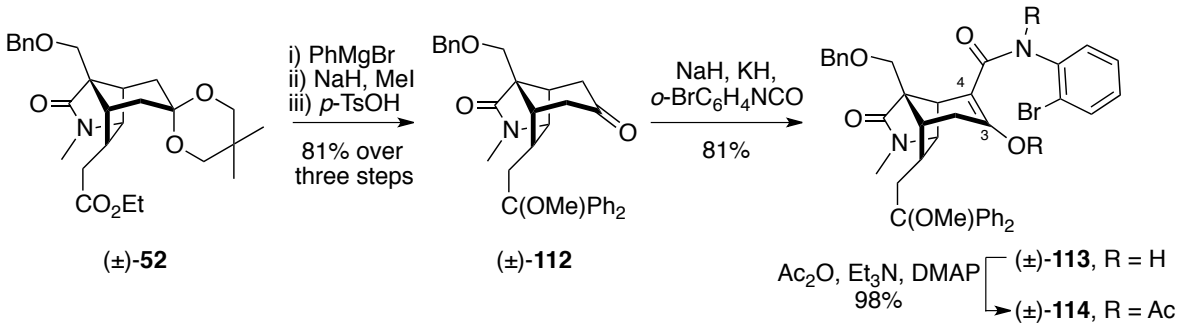


(±)-**107** (±)-21-oxogelsemine (**7**)

Scheme 1.28

Finally, upon treatment with aqueous hydrochloric acid, the methyl-protecting group was removed to release 21-oxogelsemine (**7**) as outlined in Scheme 1.28.

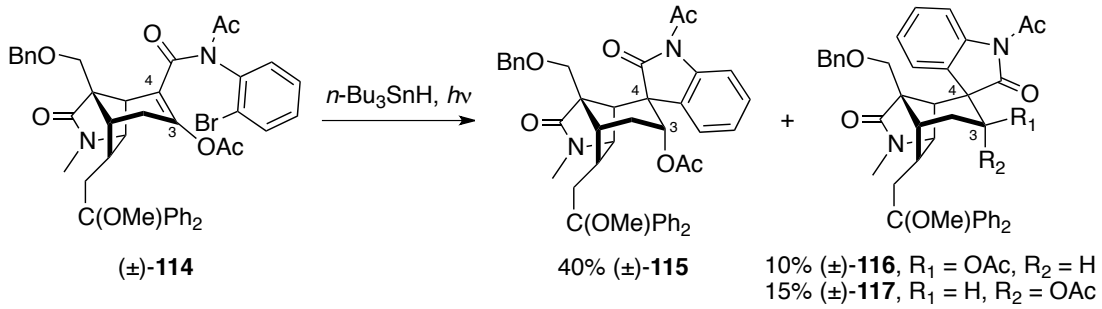
The same year, Hart and co-workers reported a free-radical cyclisation for the generation of the spiro-oxindole moiety.[23]



(±)-**52** (±)-**112**

Scheme 1.29

Prior to the introduction of the oxindole structure, **52** was modified by arylation of the ethyl ester with phenyl magnesium bromide, followed by protection of the tertiary alcohol with methyl iodide (Scheme 1.29). The ketone was then un-masked by treatment with *para*-toluenesulfonic acid to afford **112**. Acylation with *o*-bromophenyl isocyanate gave compound **113** in good yield. Next, double protection with acetic anhydride afforded the desired precursor **114** for the key radical cyclisation.



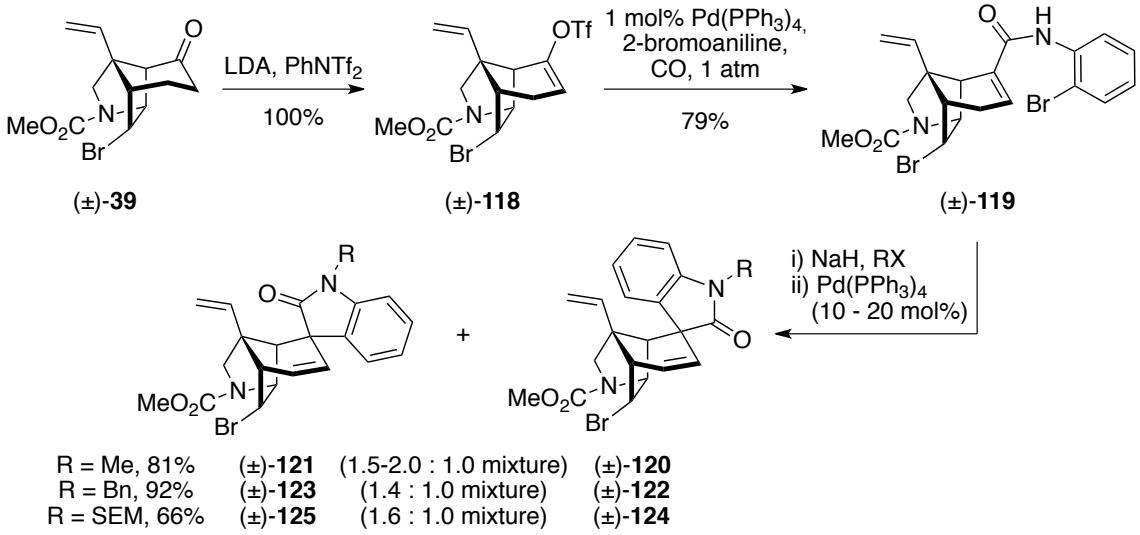
(±)-**114** 40% (±)-**115** 10% (±)-**116**, R_1 = OAc, R_2 = H; 15% (±)-**117**, R_1 = H, R_2 = OAc

Scheme 1.30

Treating **114** with tri-*n*-butyltin hydride under photochemical conditions gave the desired spiro-oxindole **115** in 40% yield along with two other products **116** and **117** in respectively 10% and 15% yield (Scheme 1.30). Interestingly, the choice of protecting group proved crucial for the control of the stereochemistry at the C-3 and C-4 positions. The best results were obtained when adduct **113** was double protected with excess acetic anhydride.

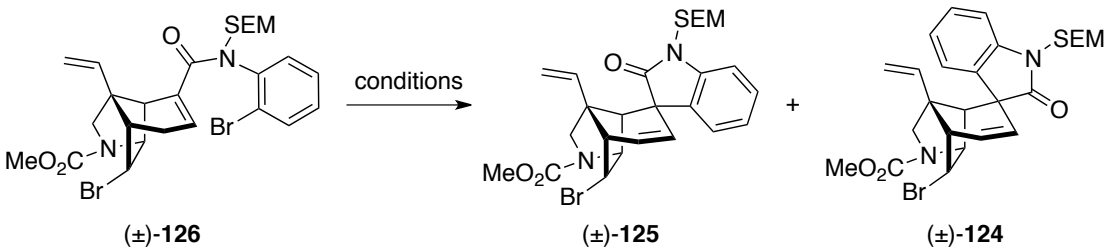
1.5.3 Intramolecular Heck Reaction

The first example of an intramolecular palladium-catalysed arylation of an alkene to form a spiro-oxindole was published by Heck and co-workers in 1979.[41] Early investigations by Overman's group led to the gelsemine spiro-oxindole with the desired stereochemistry at the quaternary position.[42] A year later the group applied their methodology to synthesise an advanced pentacyclic intermediate of gelsemine.[43]



Scheme 1.31

Ketone **39** (Scheme 1.6) was first transformed into the corresponding enol triflate **118**, allowing the palladium-catalysed carbonylation in the presence of 2-bromoaniline to give amide **119** in good yield (Scheme 1.31). After protection of the amide intermediate, the system underwent an intramolecular Heck reaction in the presence of $Pd(PPh_3)_4$ to provide a mixture of spiro-oxindole adducts in good yields. Fortunately, the major isomer (**121**, **123** or **125**) had the desired configuration at the quaternary centre. Further investigations helped to optimise the diastereoisomeric ratios as shown in Table 1.2.[44]

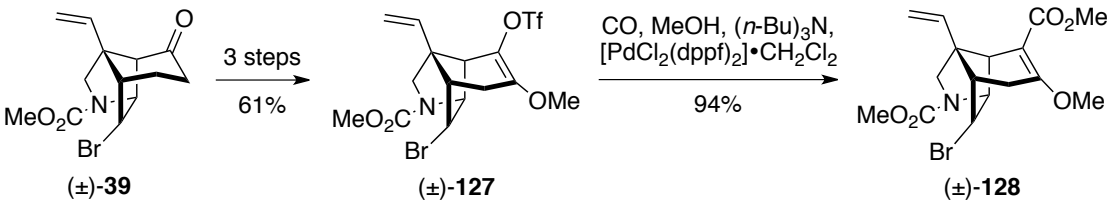


Entry	Conditions	Yield	125 : 124 ratios
1	$Pd(PPh_3)_4$ (10 - 20 mol%), Et_3N, MeCN, 82 °C	66%	60 : 40
2	$Pd_2(dba)_3$ (10 - 20 mol%), Et_3N, toluene, 110 °C	80-95%	89 : 11
3	$Pd_2(dba)_3$ (10 - 20 mol%), Ag_3PO_4, THF, 66 °C	77%	3 : 97

Table 1.2

Overman proposed that a steric interaction between the phosphine ligand and the core structure was responsible for the formation of two oxindole adducts. This interaction was confirmed by treating **126** with tris(dibenzylideneacetone)dipalladium without phosphine ligand when **125** and **124** were obtained as a 9:1 ratio towards the desired oxindole (Entry 2, Table 1.2), in a 80-95% yield. Surprisingly, the opposite diastereoselectivity was observed in the presence of silver salts such as Ag_3PO_4, providing almost exclusively **124** in good yield (Entry 3, Table 1.2). These results were rationalised by the coordination between the palladium species and the vinyl group, enhanced by the dissociation of the bromide leading to a cationic palladium intermediate. This hypothesis was confirmed by reducing the vinyl group prior to the palladium step, leading to a 50:50 mixture of stereoisomers.

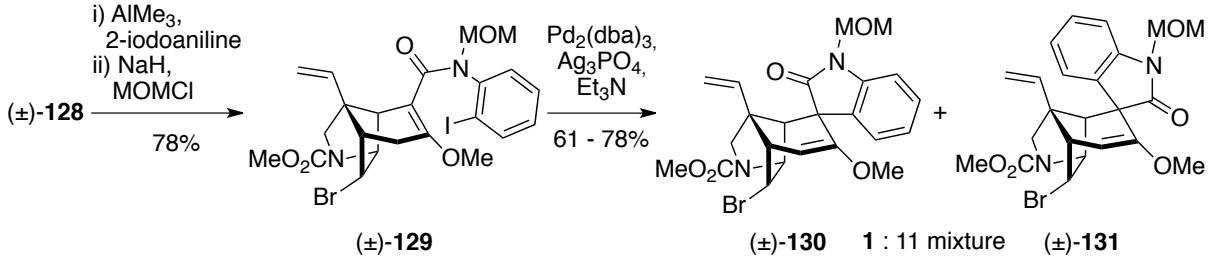
To apply this strategy to the synthesis of the natural product, published in 1999, several modifications were necessary.[20]



Scheme 1.32

First, an oxygen functionality was installed adjacent to the ketone **39** by protecting the ketone with triethylchlorosilane, then oxidizing the enol silane with a mixture of iodosobenzene and BF_3•OEt_2 before subjecting the residual ketone to Comins' reagent (2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine), yielding **127** (Scheme 1.32). Unfortunately, their previous palladium-catalysed amide formation (see Scheme 1.31) was unsuccessful due to the presence of the α-methoxy group and a two-step procedure was

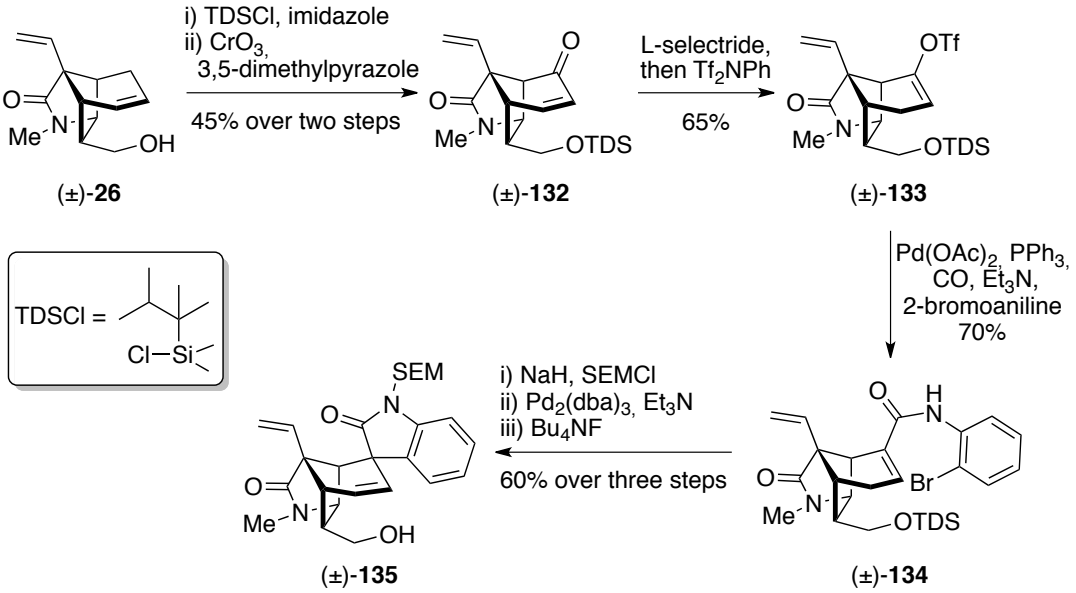
necessary to overcome the problem. In the end, palladium-catalysed carbonylation of the enol triflate **127** gave the methyl ester **128** in excellent yield.



Scheme 1.33

Treatment of methyl ester **128** with trimethyl aluminium and 2-iodoaniline gave the desired secondary amide, which was protected with MOMCl providing the suitable intermediate **129** for the key step (Scheme 1.33). However, all of their tetrahydropyran approaches failed using the adduct with the correct stereochemistry at the spiro-oxindole position so they decided to synthesise the un-natural oxindole, aiming to correct the configuration later on (see section 1.6.1).[45] To accomplish this, the intramolecular cationic Heck conditions were applied to the system affording the spiro-oxindoles **130** and **131** as a 1:11 mixture of isomers with the major product **131** being isolated in 61 - 78% yield.

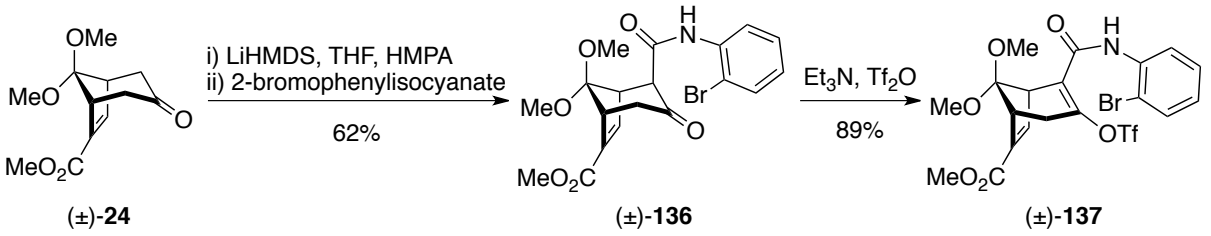
Speckamp, Hiemstra and co-workers also used Overman's palladium-catalysed cyclisation to form the spiro-oxindole moiety.[19]



Scheme 1.34

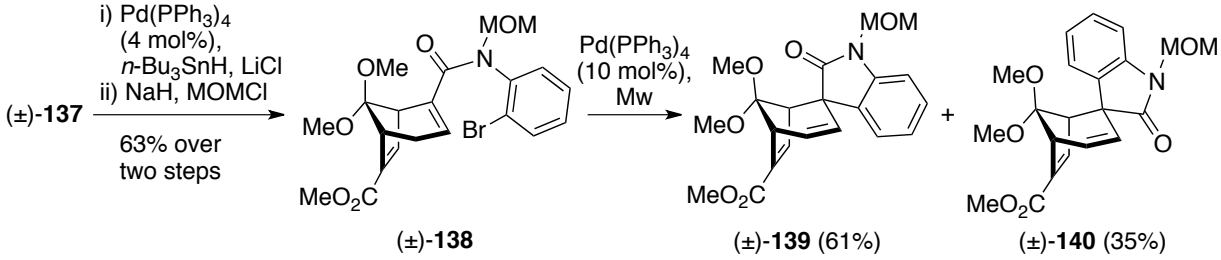
The alcohol group on the intermediate described in Scheme 1.5 (*vide supra*) was protected with a thexyldimethylsilyl (TDS) group then treated with a mixture of chromium oxide and 3,5-dimethylpyrazole to give enone **132** in 45% yield over two steps (Scheme 1.34). Adduct **132** was subjected to an L-selectride reduction, followed by Tf_2NPh to afford enol triflate **133**. Palladium-catalysed carbonylation in the presence of 2-bromoaniline furnished anilide **134** in good yield. Prior to the cyclisation the anilide was protected with SEMCl furnishing the substrate for the intramolecular Heck arylation using the optimised conditions published by Overman's group in 1988.[46] The desired spiro-oxindole **135** with the correct stereochemistry at the quaternary position was obtained in 60% yield after deprotecting the alcohol, along with 30% of the epimeric oxindole.

In 2007, Aubé *et al.* used also the Heck reaction to accomplish the formal synthesis of gelsemine.[17]



Scheme 1.35

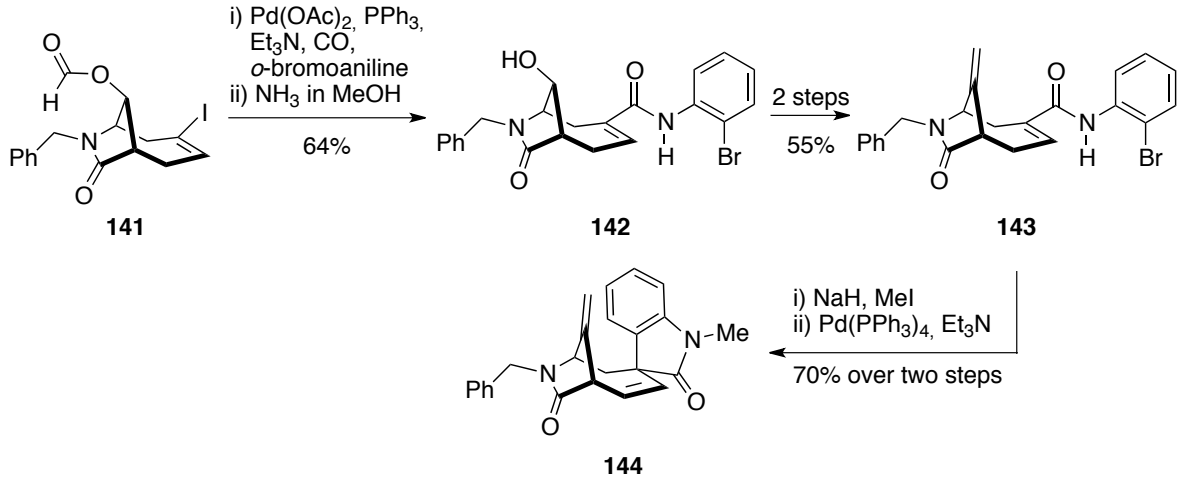
Upon treatment with a lithium base (LiHMDS) followed by 2-bromophenylisocyanate, the desired *β*-keto anilide was introduced to the core (**24**) as described in Scheme 1.4, to yield **136** as a single regioisomer in 62% yield (Scheme 1.35). Unfortunately, the Heck reaction was proved to be difficult in the presence of the ketone. To overcome this problem, the ketone was transformed into the enol triflate **137**.



Scheme 1.36

The enol triflate **137** was then reduced to the corresponding olefin by treatment with palladium-tetrakis(triphenylphosphine) and a *N*-methoxymethyl protection gave the required intermediate **138** for the cyclisation step (Scheme 1.36). However, Overman's palladium-catalysed conditions were unsuccessful on intermediate **138** so the Aubé group screened a number of conditions to yield the desired oxindole in good yield. In the end, the best results were obtained by subjecting **138** to $Pd(PPh_3)_4$ in the microwave leading to a diastereoisomeric mixture of **139** and **140**, with the desired spiro-oxindole **139** being isolated in 61% yield.

A few years later Hiemstra used a similar route to build the spiro-oxindole of the related gelsemium alkaloids, gelsedine (**4**) and *ent*-gelsedine.[47-49]

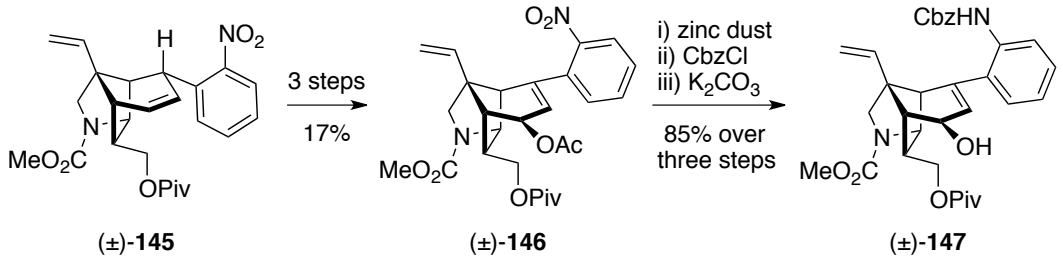


Scheme 1.37

Palladium-catalysed aminocarbonylation and subsequent deformylation afforded anilide **142** in 64% yield (Scheme 1.37). The resulting alcohol was oxidised with pyridinium chloroformate (PCC) followed by a Wittig reaction to give alkene **143**. Protection of the amide with methyl iodide and sodium hydride provided a new adduct which could undergo Heck-cyclisation upon treatment with palladium-tetrakis(triphenylphosphine) in a sealed tube, furnishing the desired spiro-oxindole **144** in 70% yield over two steps.

1.5.4 Eschenmoser-Claisen Rearrangement

Danishefsky and co-workers explored a novel synthetic route to construct the spiro-oxindole present in the gelsemine core structure.[31] Unfortunately, their proposed synthetic pathways were unfortunately shown to be unfeasible leading them to explore a longer alternative route.[50]

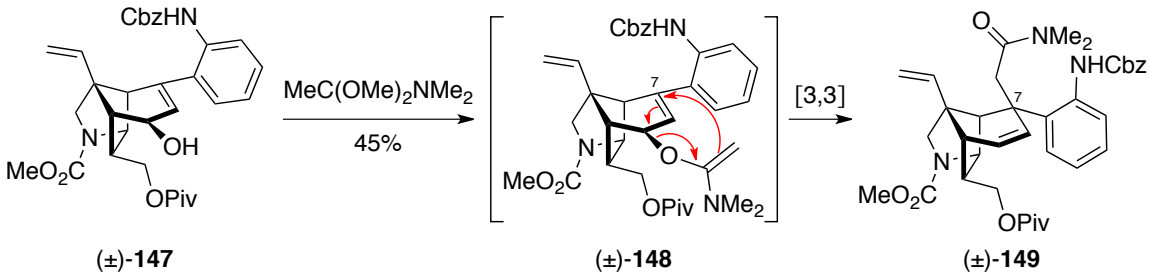


(±)-**145** (±)-**146** (±)-**147**

Scheme 1.38

A protected secondary alcohol was introduced to **145** in three steps, which consisted of bromination with *N*-bromosuccinimide, radical allylic oxidation with double bond transposition and protection of the corresponding alcohol with an acetyl group to furnish compound **146** (Scheme 1.38). The nitro group was then reduced into an amine, which was protected with a benzyloxycarbonyl (Cbz) group, to allow deprotection of the allylic alcohol yielding intermediate **147**.

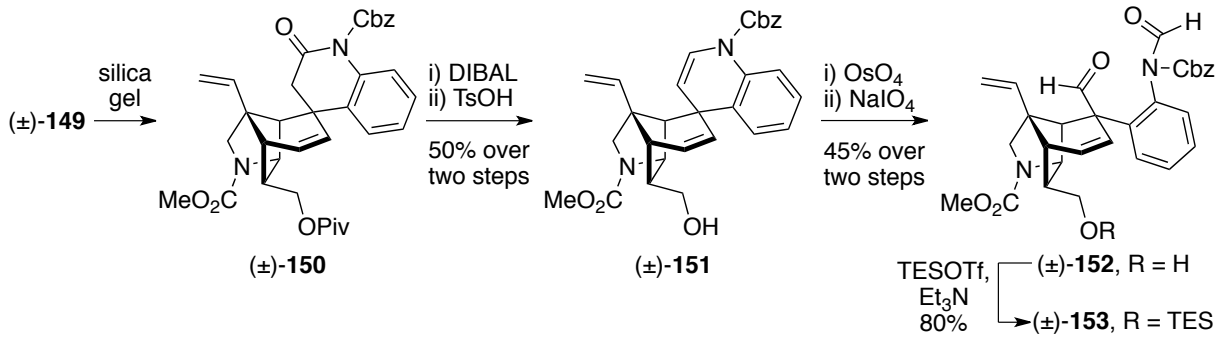
As every trial to introduce an ester group at the C-7 position was unsuccessful, Danishefsky's group decided to use an Eschenmoser amide acetal version of the Claisen rearrangement, as seen below in Scheme 1.39.



(±)-**147** (±)-**148** (±)-**149**

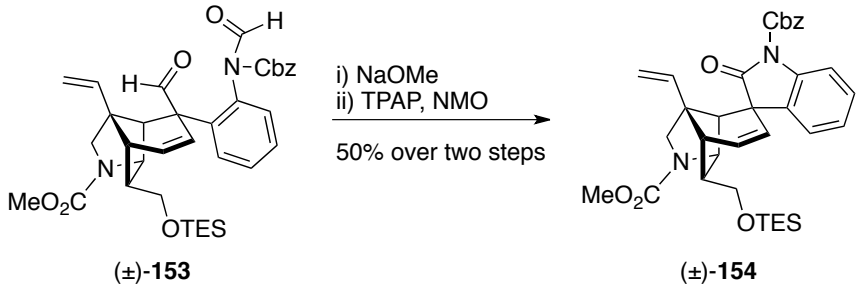
Scheme 1.39

The allylic alcohol was condensed with *N,N*-dimethylacetanamide dimethyl acetal giving **148** as a suitable intermediate for the Claisen-like rearrangement (Scheme 1.39). The [3,3]-sigmatropic shift occurred furnishing **149**.



Scheme 1.40

Compound **149** cyclised spontaneously on silica gel during the purification affording a new spiro-fused 6-membered lactam **150** (Scheme 1.40). This unwanted lactam was reduced with DIBAL and the resulting alcohol eliminated to yield a new enamine adduct **151**, which could be re-opened by dihydroxylation with osmium tetroxide followed by oxidative cleavage in the presence of sodium periodate providing **152** in 45% yield over two steps.



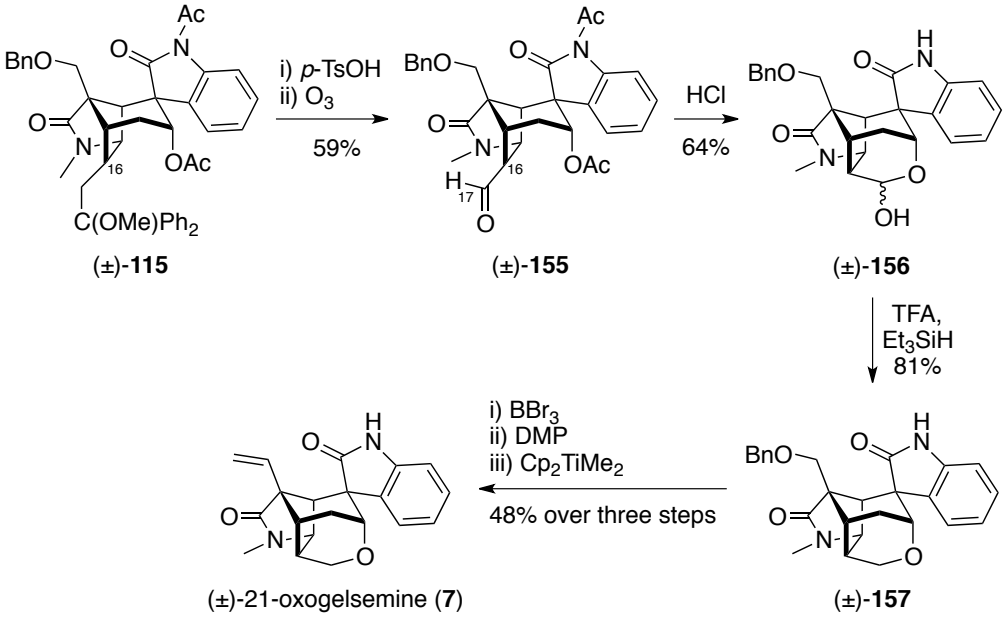
Scheme 1.41

The desired structure was finally obtained by methanolysis of compound **153**, affording a new hemiacetal which was oxidised with a mixture of tetrapropylammonium perruthenate (TPAP) and *N*-methyl morpholine *N*-oxide (NMO), yielding the desired spiro-oxindole **154** in 50% yield over two steps (Scheme 1.41).

1.6 Strategies for the Tetrahydropyran Ring Construction

1.6.1 Lactone or Hemiacetal Formation

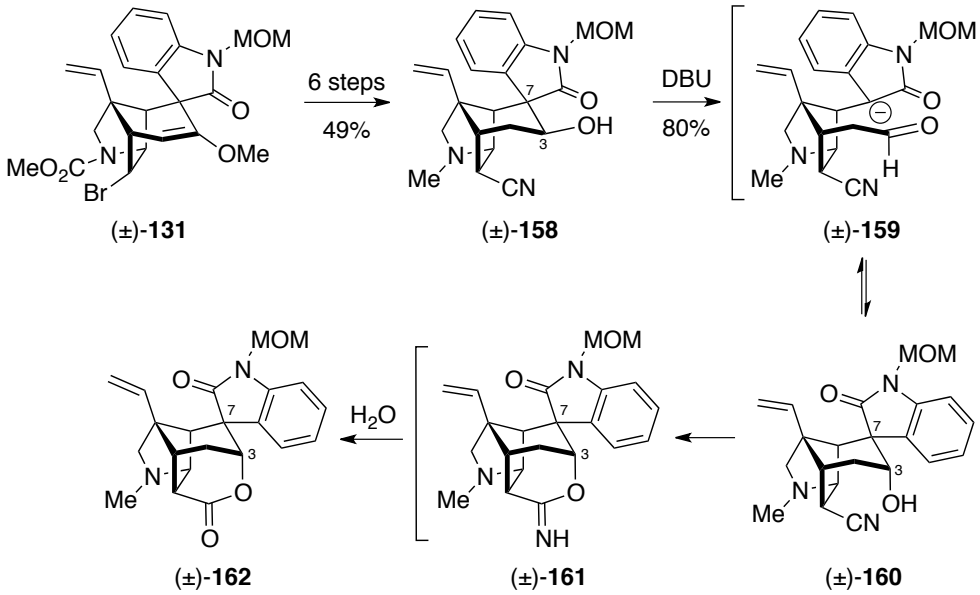
In 1994, Hart and co-workers achieved the total synthesis of 21-oxogelsemine culminating with the construction of the tetrahydropyran ring.



Scheme 1.42

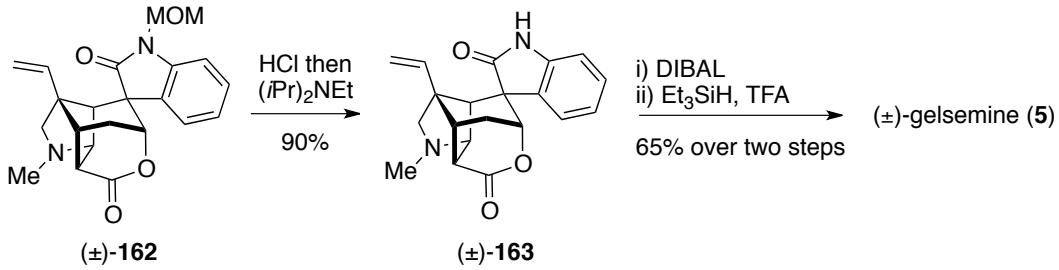
Prior to the formation of the tetrahydropyran ring, the C-17 position was modified first by treatment with *para*-toluenesulfonic acid to form an olefin and then ozonolysis to yield aldehyde **155** in 59% yield over two steps (Scheme 1.42). Acidic wash achieved the acetate hydrolysis both on the spiro-oxindole and the alcohol, leading to epimerisation of the C-16 position and cyclisation providing a mixture of lactols **156**. Fortunately, reduction of the diastereomeric mixture of hemiacetals (**156**) with triethylsilane and trifluoroacetic acid (TFA) afforded the tetrahydropyran adduct **157** in good yield. Finally, 21-oxogelsemine (**7**) was obtained by removal of the benzyl-protecting group followed by Dess-Martin oxidation of the released alcohol providing the desired aldehyde for Tebbe olefination.

In their synthesis of gelsemine, Overman *et al*. needed to correct the stereochemistry at the quaternary position of the spiro-oxindole and form the tetrahydropyran ring structure.[20]



Scheme 1.43

The stereochemistry at the C-7 quaternary position was modified using a retro-aldol rearrangement (Scheme 1.43). Upon treatment of **158** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in refluxing toluene, the C-3 - C-7 bond was cleaved to generate a new adduct, presumably **159**, where the oxindole is free to rotate. The resulting intermediate **160**, on which both C-7 and the alcohol positions were epimerised, was able to form a new hexacyclic imidate (**161**), easily hydrolysed into lactone **162**.

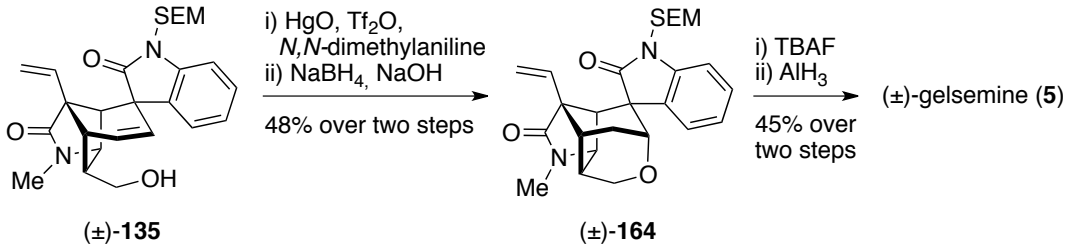


Scheme 1.44

Finally, the spiro-oxindole was deprotected to generate **163** in 90% yield and the lactone was reduced first with di*iso*butylaluminium hydride (DIBAL) to give a mixture of lactols in a similar way to Hart *et al.* (Scheme 1.42). Upon treatment with triethylsilane and TFA, the lactol was reduced to form the tetrahydropyran, affording gelsemine **5** (Scheme 1.44).

1.6.2 Oxymercuration

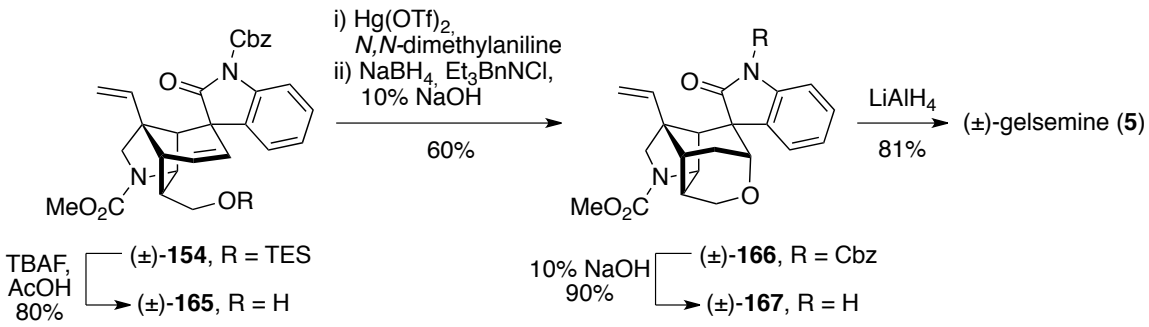
Speckamp and co-workers completed their total synthesis by forming the tetrahydropyran ring using a mercury(II) triflate and *N,N*-dimethylaniline complex.[19]



Scheme 1.45

The previously described intermediate **135** (Scheme 1.34) was treated with a mercury triflate complex in the presence of *N,N*-dimethylaniline, followed by reduction of the organo-mercurial compound with sodium borohydride to afford compound **164** (Scheme 1.45). With the tetrahydropyran ring in hand, the oxindole was deprotected in refluxing TBAF *(tetra-N*-butylammonium fluoride), furnishing 21-oxogelsemine (**7**). Finally, the gelsemine structure (**5**) was achieved by selectively reducing the pyrrolidinone into the pyrrolidine ring using aluminium hydride.

In 2002, Danishefsky's group also used an oxymercuration to form the tetrahydropyran ring.[51]



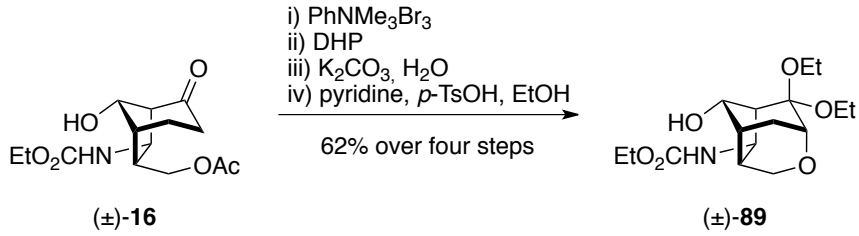
Scheme 1.46

The primary alcohol was deprotected using a 1:1 mixture of acetic acid and TBAF to afford **165** in good yield (Scheme 1.46). The tetrahydropyran ring was formed upon treatment with a mercury triflate complex in the presence of *N,N*-dimethylaniline, followed by a basic demercuration to eliminate all mercury residues, giving the desired tetrahydropyran ring (**166**) in 60% yield. The synthesis was completed by basic removal of the benzyloxycarbonyl group, followed by reduction of the carbamate with lithium aluminium hydride to give gelsemine (**5**).

In the same fashion, Fukuyama and co-workers used the intramolecular oxymercuration step developed by Hiemstra and Speckamp to perform their tetrahydropyran ring closure in both of their total syntheses of gelsemine.[18,27]

1.6.3 Base-Catalysed Ether Formation

In 1988, Fleming and co-workers reported a tetrahydropyran synthesis using a base mediated cyclisation step.[16]



(±)-**16** (±)-**89**

Scheme 1.47

Bromination adjacent to ketone **16** was followed by alcohol protection with a tetrahydropyranyl group (Scheme 1.47). Upon treatment with base the acetyl group was removed, furnishing a primary alcohol that cyclised to form the desired tetrahydropyran ring. To complete the sequence, the secondary alcohol was deprotected and the ketone masked to afford **89** in good yield over the four steps.

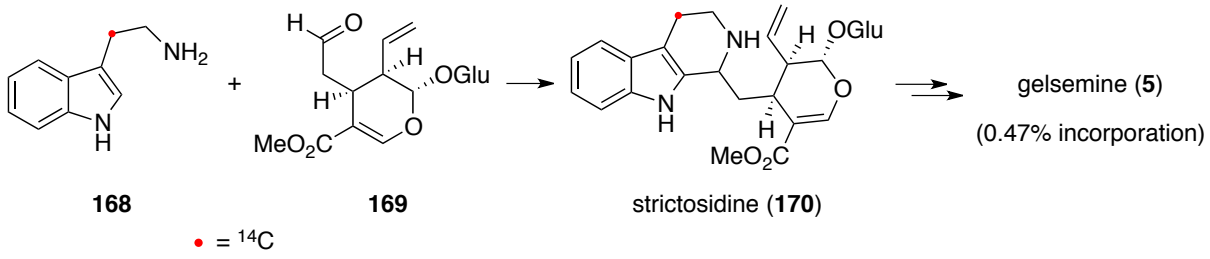
1.6.4 Synthesis of the Tetrahydropyran Ring with the Core Structure

As shown in Section 1.3, two groups constructed the tetrahydropyran ring while building the gelsemine core structure. In 1987, Stork *et al*. developed a novel construction of the core structure using a Claisen rearrangement leading to the formation of the bicyclic core structure possessing a tetrahydropyran ring (Scheme 1.11).[26] A few years later, in 1994, Johnson's group synthesised a tricyclic intermediate, which underwent Mannich cyclisation to afford the tetrahydropyran ring along with the bicyclo[3.2.1]octane and the pyrrolidinone ring (Scheme 1.7).[21]

1.7 Biomimetic Synthesis of Gelsemine

As previously described, Conroy and Chakrabarti used a combination of biosynthetic rationale and ^{1}H NMR spectroscopy to assign the structure of gelsemine (**5**). Their hypothesis,

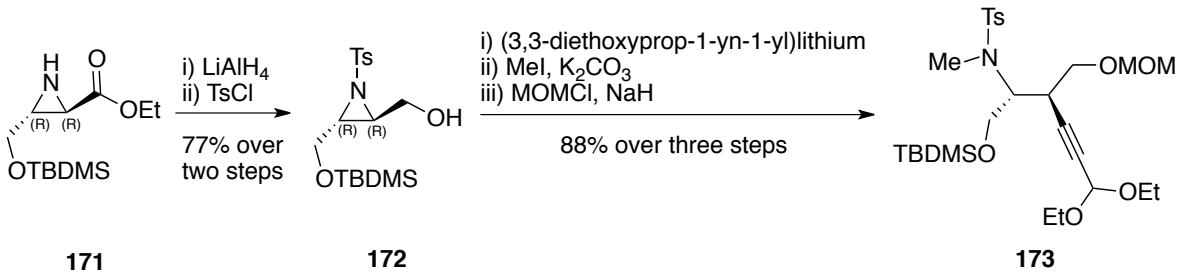
based on Woodward's work, suggested that gelsemine could be obtained from strictosidine.[52] This was confirmed in 1979 when Zenck and co-workers showed that labelled $^{14}C_6$-strictosidine (**170**), obtained by condensation of tryptamine (**168**) and secologanin (**169**), was transformed into gelsemine (0.47% incorporation, Scheme 1.48).[53]



Scheme 1.48

Further hypotheses were advanced in 1988 by Ponglux *et al.* to explain the biosynthetic transformations carried out by *Gelsemium sempervirens*.[15]

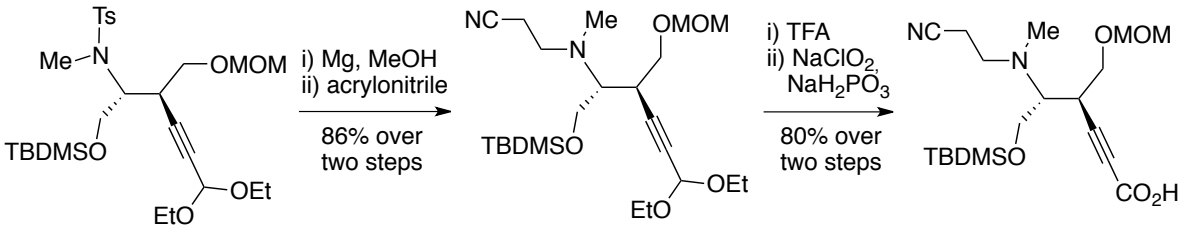
Although the biosynthetic pathway has never been confirmed by labelling studies, Qin's group based their work on this hypothesis and published the first postulated biomimetic total synthesis of (+)-gelsemine in 2012.[38]



Scheme 1.49

The synthesis started with lithium aluminium hydride reduction of ester **171** (prepared as a single enantiomer in four steps from D-diethyl tartrate) followed by tosylation to afford **172**

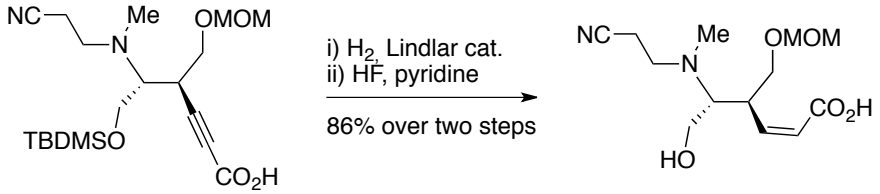
(Scheme 1.49).[54,55] The aziridine ring was opened by attack of (3,3-diethoxyprop-1-yn-1-yl) lithium adjacent to the methanol group, giving the expected product as a single stereoisomer. Two more steps were necessary to protect the secondary amine and the primary alcohol to furnish **173** in good yield.



173 **174** **175**

Scheme 1.50

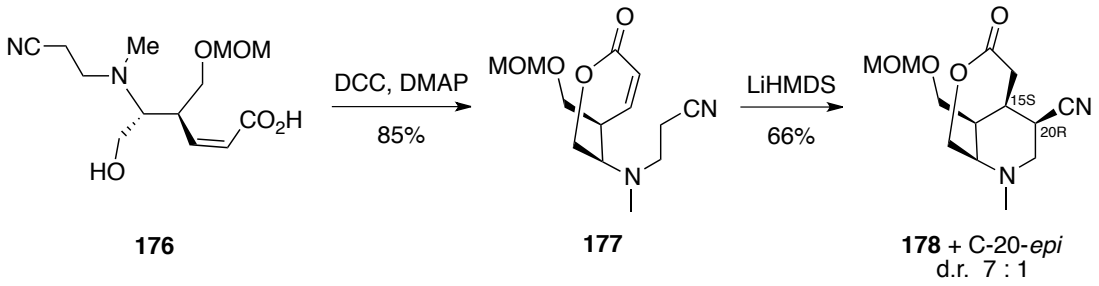
In the presence of magnesium dust the secondary amine was deprotected and immediately coupled with acrylonitrile to yield cyanide **174** (Scheme 1.50). On treatment with trifluoroacetic acid (TFA) the aldehyde was un-masked and finally oxidised with sodium chlorite to obtain a carboxylic acid intermediate **175**.



175 **176**

Scheme 1.51

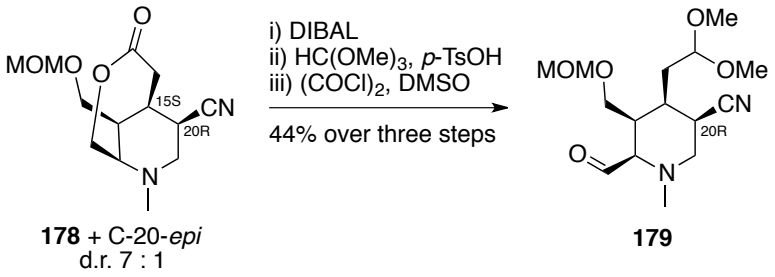
After hydrogenation of the triple bond to the *cis* olefin using Lindlar catalyst, the primary alcohol was deprotected in the presence of hydrogen fluoride to give **176** in 86% yield over two steps (Scheme 1.51).



176 **177** **178** + C-20-*epi* d.r. 7 : 1

Scheme 1. 52

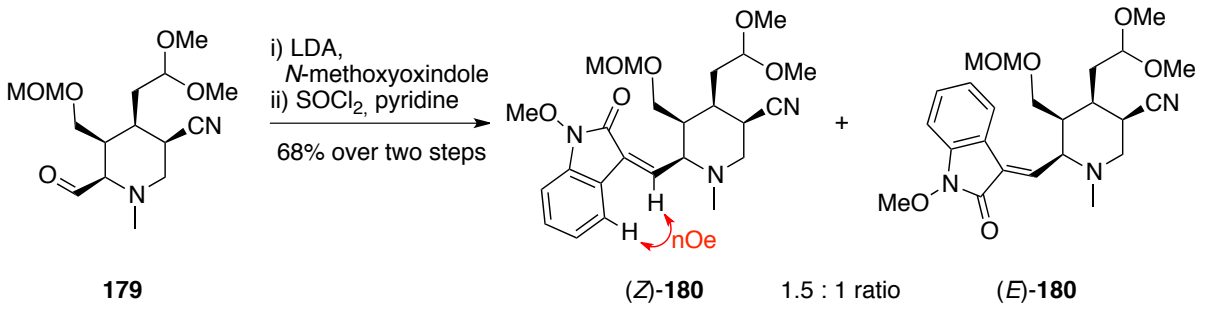
With intermediate **176** in hand, a peptide coupling was performed using *N,N′*-dicyclohexylcarboiimide (DCC) and 4-dimethylaminopyridine (DMAP) to afford lactone **177** which cyclised *via* an intramolecular Michael addition to provide piperidine **178** as an inseparable 7:1 mixture of diastereoisomers (Scheme 1.52).



178 + C-20-*epi* d.r. 7 : 1 **179**

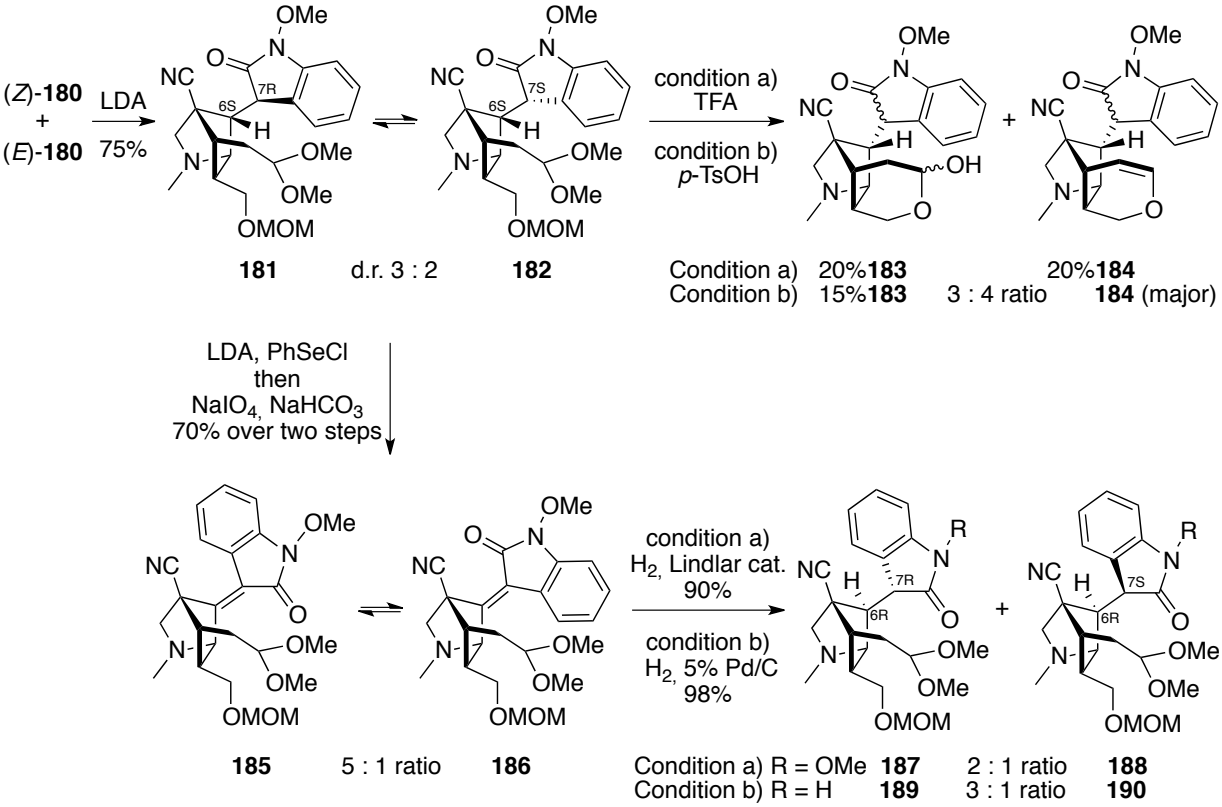
Scheme 1.53

Fortunately, the mixture of diastereoisomers was easily separable once the lactone was reduced with DIBAL to afford an aldehyde and a primary alcohol (Scheme 1.53). The aldehyde was masked as an acetal by addition of a dimethoxy group and the hydroxyl group was oxidised under Swern conditions to afford the *cis* tetra-substituted piperidinoaldehyde **179** as a single isomer.



Scheme 1.54

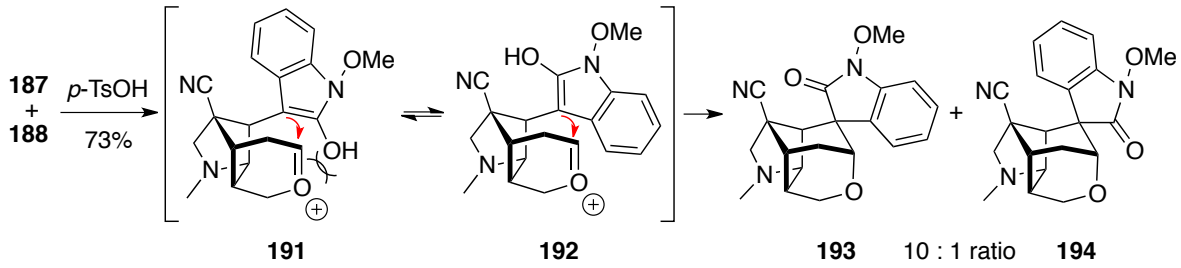
Condensation of aldehyde **179** with a solution of lithiated *N*-methoxyoxindole followed by dehydration gave a mixture of oxindole isomers (*Z*)-**180** (the configuration was established by an nOe experiment) and (*E*)-**180** as a 1.5:1 ratio (Scheme 1.54).



Scheme 1.55

The mixture of oxindole isomers (*Z*)-**180** and (*E*)-**180** was treated with lithium di*iso*propylamide (LDA) to initiate the intramolecular Michael addition to form the

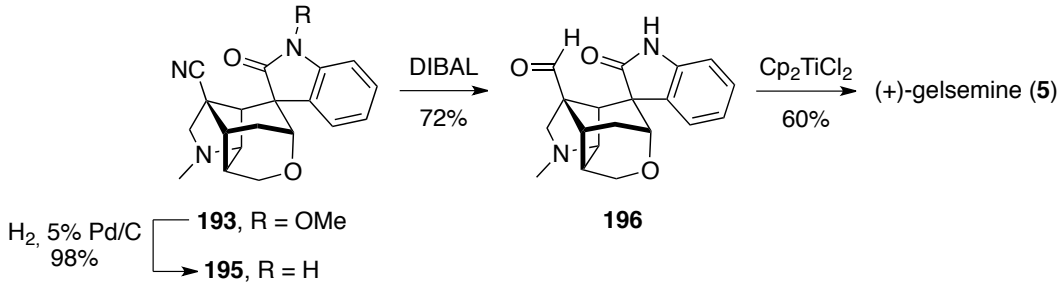
pyrrolidine ring system. This reaction resulted in an inseparable mixture of diastereoisomers **181** and **182** (in a 3:2 ratio) with the undesired stereochemistry at the C-6 position (Scheme 1.55). Attempts to perform the next acid mediated step to lead to the core structure failed as in the presence of either trifluoroacetic acid or *para*-toluenesulfonic acid, a mixture of both dihydropyran **184** and pyranol **183** was observed. To solve the problem, Qin's group decided to invert the C-6*S* configuration by selenation of the **181** and **182** mixture with LDA / PhSeCl followed by oxidative cleavage to install a double bond at the C-6 position. This gave a mixture of separable isomers **185** and **186** in a 5:1 ratio. Reasoning that hydrogenation of the double bond should occur from the less hindered face to furnish the desired C-6*R* configuration some conditions were screened. Using Lindlar catalyst gave **187** and **188** as a 2:1 mixture of inseparable diastereoisomers, both possessing the desired stereochemistry at the C-6 position. Surprisingly, subjecting the system to a more active catalyst such as 5% Pd/C, resulted in deprotection of the oxindole and formation of two new inseparable isomers, **189** and **190**.



Scheme 1.56

Pleasingly, upon treatment of both **187** and **188** with *para*-toluenesulfonic acid the desired enol-oxonium cyclisation took place leading to separable isomers **191** and **192** in a 10:1 ratio. Due to a favoured transition state, as seen Scheme 1.56, the major isomer possessed the desired stereochemistry at the oxindole position. The group also mentioned that in the absence

of a protecting group on the oxindole (such as adducts **187** and **188**), the acidic step did not proceed cleanly towards the expected cyclised products, affording a complex mixture instead.



Scheme 1.57

Once the protecting group on the spiro-oxindole was removed to give **195**, a vinyl group was introduced as outlined in Scheme 1.57. After reduction of the nitrile group into the corresponding aldehyde, **196** was subjected to various olefination conditions. As Wittig reagents failed due to the hindrance of the structure, Tebbe conditions were applied furnishing (+)-gelsemine (**5**) in 60% yield.

1.8 Summary

Natural products have long served to benchmark the existing tools of organic synthesis and also develop new reagents and reaction conditions. Although gelsemine has no medicinal value, this highly functionalised hexacyclic skeleton has attracted the attention of numerous research groups over the years and generated eight total syntheses as outlined in Table 1.3. In 1994, Speckamp, Hiemstra and co-workers published the shortest total synthesis in 19 steps from sorbic acid and 0.82% overall yield. Since then, no other group has managed to reduce the number of steps, although Fukuyama and Qin have both developed enantioselective routes.

Group	Steps	Overall yield
Speckamp 1994, (±)-gelsemine	19	0.82%
Johnson 1994, (±)-gelsemine	29	0.57%
Hart 1994, 21-oxogelsemine	23 (from diene **45**)	0.25%
Fukuyama 1996, (±)-gelsemine	32	0.67%
Overman 1999, (±)-gelsemine	26	1.2%
Fukuyama 2000, (+)-gelsemine	33	0.95%
Danishefsky 2002, (±)-gelsemine	37 (from **77**)	0.015%
Qin 2012, (+)-gelsemine	25	1%

Table 1.3

The problems linked to the installation of the spiro-oxindole with the correct stereochemistry along with the enforced functional-group proximity engendered by the cage-like skeleton of gelsemine are a significant synthetic challenge. Our target was to reach the gelsemine structure in less than 19 steps, using a bridge swapping strategy as a key step.

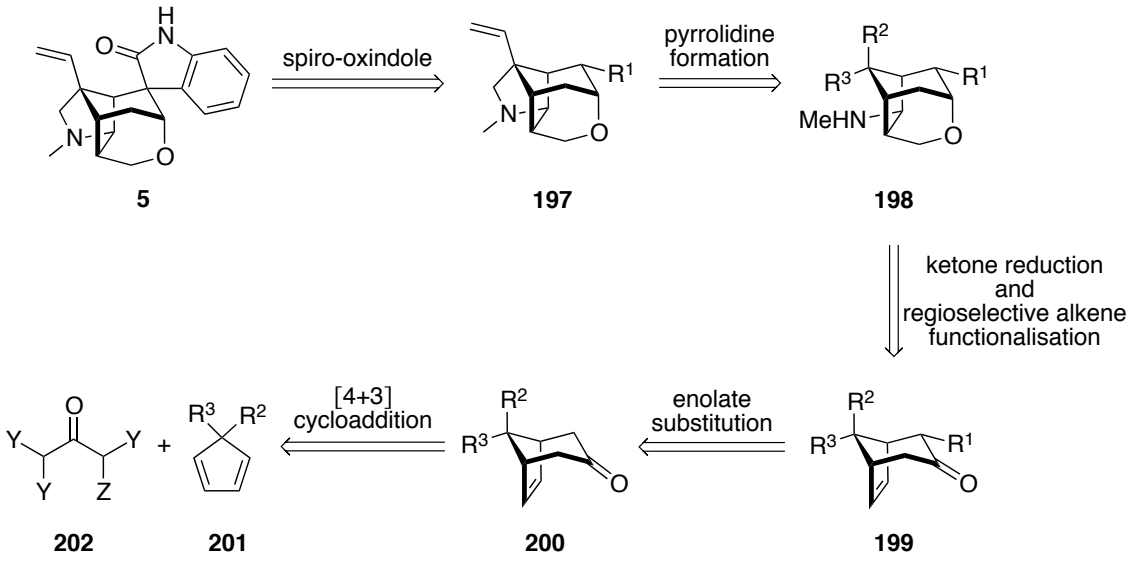
Chapter 2

Synthesis of Gelsemine Core Structures

2.1 Previous Synthetic Work

2.1.1 Retrosynthetic Analysis

Our group's interest in gelsemine (**5**) started a decade ago and a first retrosynthetic analysis was proposed. The analysis focused on a rapid construction of the bicyclo[3.2.1]octane core structure using a [4+3] cycloaddition, as outlined in Scheme 2.1.[56,57]

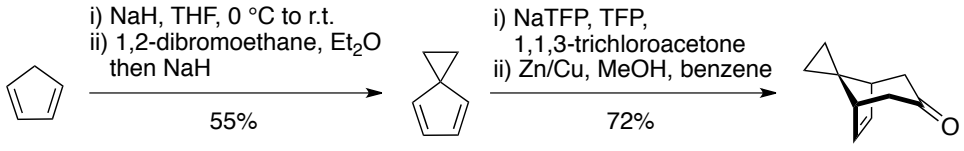


Scheme 2.1

It was envisaged that gelsemine (**5**) would arise from the functionalisation of precursor **197** after formation of the pyrrolidine ring from intermediate **198** by N-R^3 linkage, as seen in Section 1.4. Two different pathways were proposed for construction of the tetrahydropyran ring. In one approach, the ring would be obtained by reducing ketone **199** to the

corresponding axial alcohol and adding a one-carbon fragment to it before cyclisation onto the double bond. The second approach consisted of functionalisation of the double bond with an ester or amide before reduction of the ketone permitting cyclisation onto the axial alcohol to form the ether ring. It was hoped that the precursor for the oxindole moiety could be introduced to **200** *via* enolate chemistry and an appropriate isocyanate perhaps using a chiral base. Finally, the required oxabicyclooctanone adduct **200** would be available using a [4+3] cycloaddition between a 5,5-cyclopentadiene **201** (R^2, R^3 = ester, nitrile, double bond or cyclopropane) and a polyhaloketone **202** (Y = Br or Cl and Z = Br or H).

Wilkinson and Simpkins screened suitable conditions and partners for the [4+3] cycloaddition.[56] The presence of an ester or a nitrile group on the oxabicyclooctane appeared appealing for facile introduction of the pyrrolidine ring but access to this kind of substrate proved difficult and low yielding. The best results were obtained when using the Föhlisch conditions with a cyclopentadiene possessing a cyclopropane ring, affording the spiro-heptadiene adduct **205** in moderate yield. Functionalisation of spiro-heptadiene **205** carried out by Fraser and Simpkins proved successful and led to an advanced gelsemine core structure.[57]

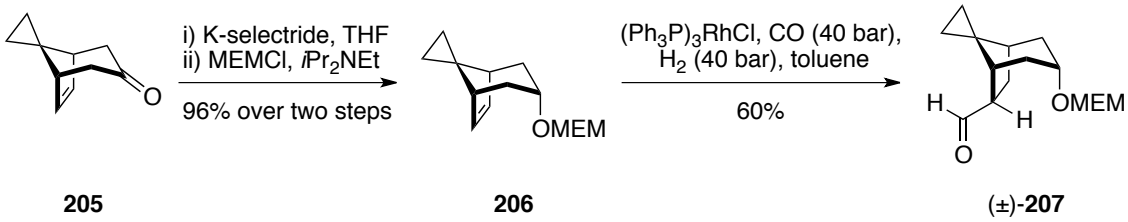


203 **204** **205**

Scheme 2.2

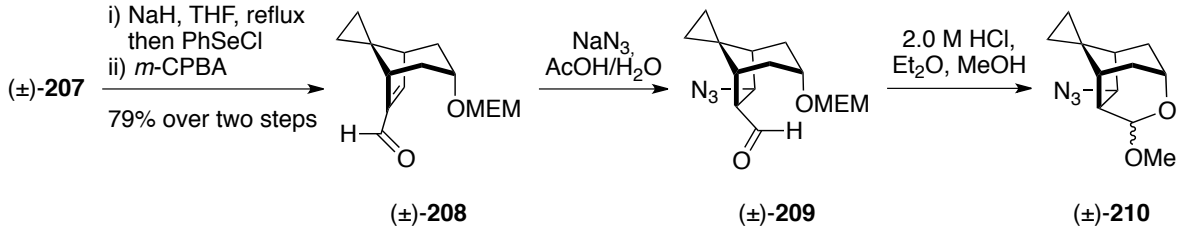
The sequence started with formation of the desired spiro-cyclic cyclopropane **204** from cyclopenta-1,3-diene **203**, obtained by distillation of commercially available

dicyclopentadiene, in 55% yield. Intermediate **204** was then subjected to the Föhlisch conditions in 2,2,3,3-tetrafluoropropan-1-ol (TFP) and bicyclic adduct **205** was obtained in 72% yield (Scheme 2.2).



Scheme 2.3

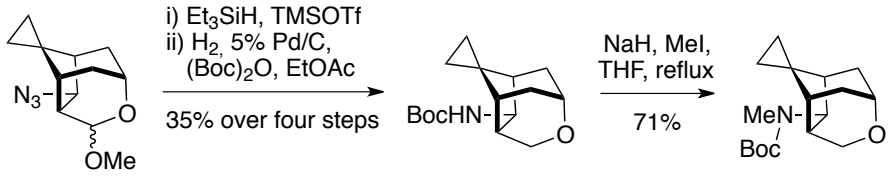
Next, ketone **205** was reduced with K-selectride and the corresponding axial alcohol was protected with a methoxyethoxymethyl (MEM) group to afford a new intermediate **206** in 96% yield (Scheme 2.3). Subjecting the MEM protected adduct **206** to a rhodium catalysed hydroformylation provided the expected aldehyde **207**.



Scheme 2.4

To facilitate the introduction of the amine precursor for the pyrrolidine ring construction, the presence of a double bond appeared necessary. Treatment of **207** with base followed by PhSeCl led to a selenide group alpha to the aldehyde group, which underwent oxidation-elimination in the presence of *m*-CPBA to give the desired α,β-unsaturated aldehyde **208** in 79% yield over two steps (Scheme 2.4). Attempts to perform the 1,4-addition of methylamine onto **208** provided a mixture of expected product along with starting material. To overcome this problem intermediate **208** was treated with sodium azide in 50% acetic acid, which

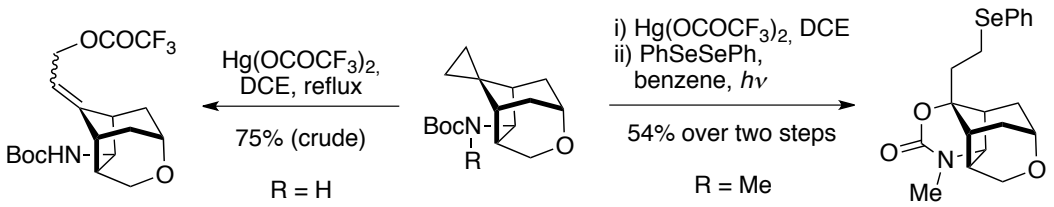
introduced the masked amine exclusively on the *exo* face, yielding **209**. Subsequent acidic treatment furnished acetal **210**.



(±)-**210** (±)-**211** (±)-**212**

Scheme 2.5

Reduction of the mixed acetal **210** with Et_3SiH / TMSOTf and subsequent reduction of the azide group in the presence of di-*tert*-butyl dicarbonate afforded the tetrahydropyran ring (**211**) in 35% yield over four steps (Scheme 2.5). Methylation of the *tert*-butoxycarbonyl (Boc) protected amine provided **212** in 71% yield. Unfortunately, attempts to form the pyrrolidine ring by functionalisation of the cyclopropane proved problematic.



(±)-**213** R = H, (±)-**211**
R = Me, (±)-**212**
(±)-**214**

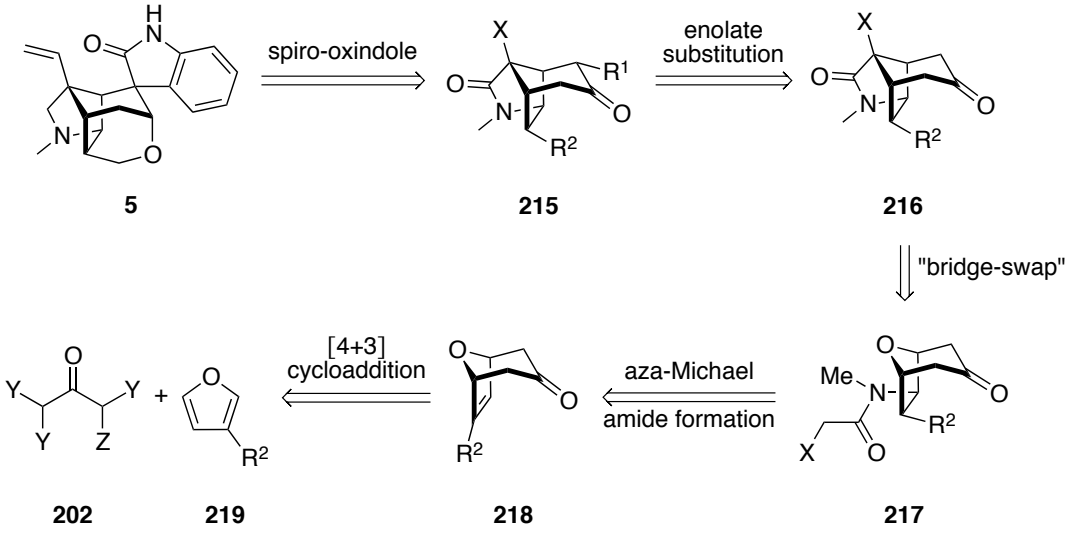
Scheme 2.6

Treatment of compound **211** with a mercury triflate derivative proved to be a good way to open the cyclopropane ring affording **213**, which showed similarities with some pyrrolidine intermediates seen in Fleming's (Section 1.4.3)[16] and Fukuyama's (Section 1.4.4 and Section 1.4.5)[18,27] syntheses. Unfortunately, the presence of a methyl group (R = Me) changed the reactivity of the system and subjecting the N-Boc-N-methyl adduct **212** to the same

conditions led to urethane **214**, after trapping the proposed organo-mercury intermediate with diphenyl diselenide (Scheme 2.6).

2.1.2 Revised Retrosynthetic Analysis

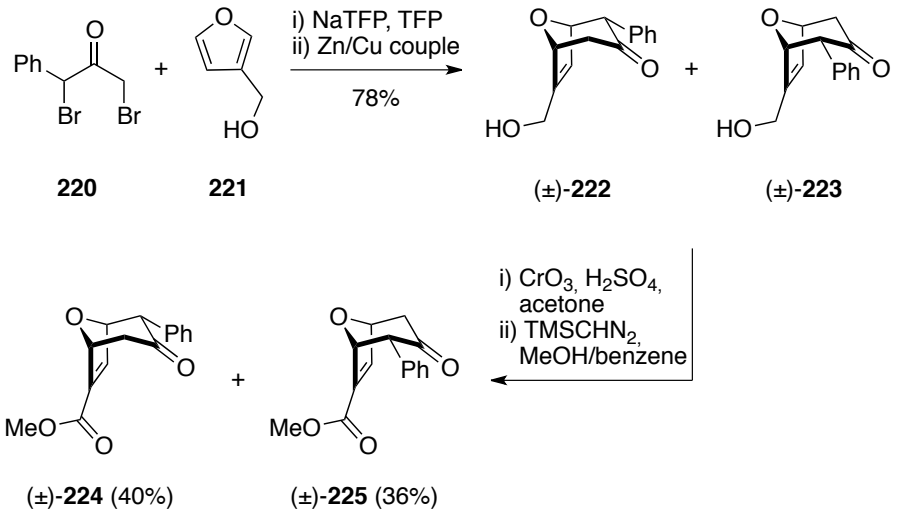
To overcome the previous problems a new route to gelsemine (**5**) was designed involving a double elimination – double Michael addition procedure called "bridge-swapping".



Scheme 2.7

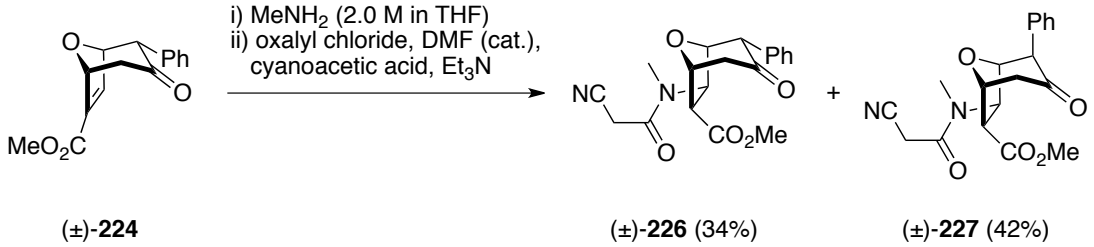
It was envisaged that gelsemine (**5**) would be accessible from intermediate **215** by introduction of the vinyl group (X = ester or nitrile), the spiro-oxindole and the tetrahydropyran ring (Scheme 2.7). The spiro-oxindole precursor **215** could be obtained by treating the tricyclic ketone **216** with base and an appropriate isocyanate derivative. The core structure **216** would arise from a double β-elimination followed by a double Michael addition on oxabicyclooctanone **217**, replacing the bridging oxygen by a one-carbon unit. The required oxabicyclic adduct **217** would be available by functionalisation of the key precursor **218** prepared using a [4+3] cycloaddition reaction between **202** (Y = Br or Cl and Z = Br or H) and a substituted furan **219** (R^2 = nitrile, ester, CH_2OH or CH_2OPG).

Preliminary work carried out by Barry and Simpkins highlighted the challenge in accomplishing the double elimination procedure – the so-called "bridge-swap".



Scheme 2.8

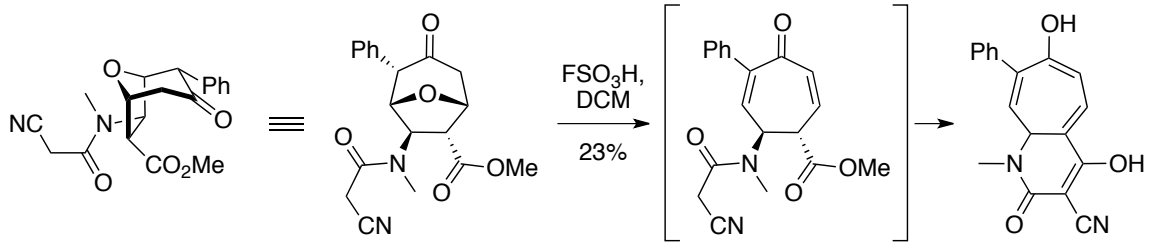
The synthesis commenced with a Föhlisch cycloaddition between furan-3-methanol (**221**) and 1,3-dibromoacetone derivative **220** affording a mixture of inseparable regioisomers **222** and **223** in 78% yield (Scheme 2.8).[58] Jones oxidation of the alcohols **222** and **223** followed by trimethylsilyldiazomethane methylation gave a mixture of separable esters **224** and **225** in 40% and 36% yield respectively. The structures were assigned with the help of X-ray crystal analysis.



Scheme 2.9

The bridge-swap precursor was prepared from ester **224** possessing an equatorial phenyl group, which could be used for late-stage spiro-oxindole formation (Scheme 2.9). Upon treatment of **224** with methylamine followed by acylation with 2-cyanoacetyl chloride a mixture of epimers at the phenyl position, **226** and **227**, was obtained. Regrettably, the major epimer **227** was not as attractive as the minor one **226** for the bridge-swap study due to possible hindrance during the next Michael addition.

The oxabicyclooctane opening methods usually involve the use of a Lewis acid (BF_3 or BF_3•Et_2O and acetic anhydride,[59] Et_2AlCl,[60] BCl_3,[61] BBr_3[61]), strong acid (fluorosulfuric acid,[62] hydrochloric acid[63]) or strong base (lithium di*iso*propylamide[64]). Unfortunately, no product formation was observed when subjecting adduct **226** to BF_3•Et_2O, $TiCl_4$, TfOH or $ZrCl_4$, at different temperatures (−78 °C, 0 °C or room temperature). Treatment of **226** with a mixture of lithium tetramethylpiperidide (LiTMP), titanium chloride and trimethylsilyl chloride gave a mixture of silylated starting material.

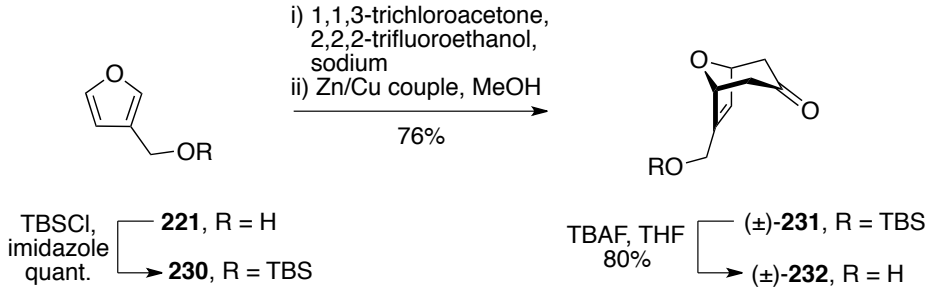


(±)-**226** (±)-**228** (±)-**229**

Scheme 2.10

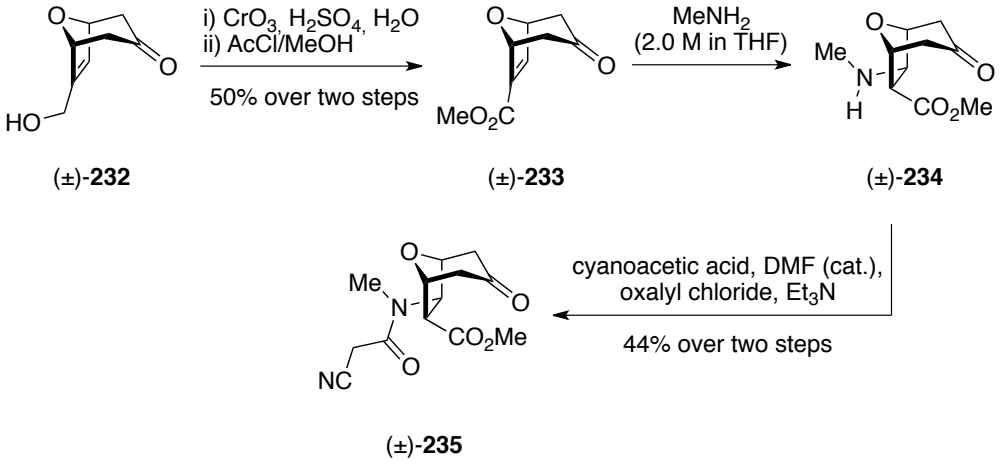
Surprisingly, subjecting the bridge-swap precursor **226** to Noyori's conditions (addition of the superacid fluorosulfonic acid) induced the desired elimination along with a second cyclisation furnishing a novel bicyclic compound **229** (Scheme 2.10).[62]

A new approach to the target was designed including the construction of the spiro-oxindole precursor (phenyl group) at a later stage to avoid the previous regioselectivity and epimerisation problems.



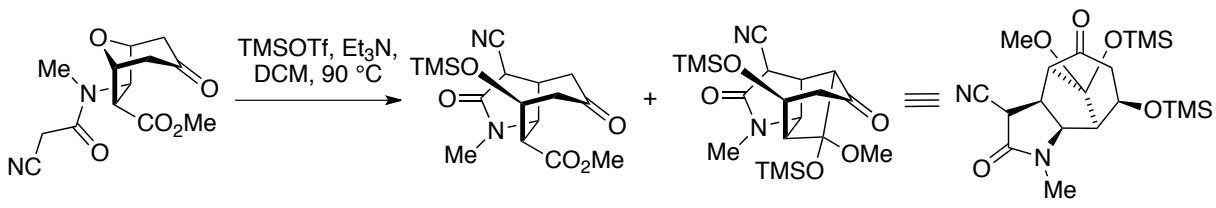
Scheme 2.11

The route towards the bicyclo[3.2.1]octane commenced with a Föhlisch cycloaddition between 1,1,3-trichloroacetone and TBS-protected furan-3-methanol (**230**) providing the oxabicyclic adduct **231** in 76% yield (Scheme 2.11).[65] The *tert*-butyldimethylsilyl (TBS) protecting group was introduced as an attempt to solve the isolation problems encountered while using furan-3-methanol (**221**). Upon treatment of **231** with tetra-*n*-butylammonium fluoride (TBAF) the free alcohol was released furnishing **232** in good yield.



Scheme 2.12

Jones oxidation of the primary alcohol **232** followed by treatment with acetyl chloride in methanol afforded the α,β-unsaturated ester **233** in 50% overall yield (Scheme 2.12). Aza-Michael addition of methylamine to **233** proceeded exclusively on the *exo* face furnishing **234** as a single diastereoisomer, which was converted to the corresponding amide **235**. Unfortunately, as before, full recovery of starting material was observed when **235** was treated with various Lewis acids ($TiCl_4$, $SnCl_4$) and basic conditions (LDA, LiTMP, DBU and Et_3N) in the presence of a TMS derivative (TMSOTf or TMSCl) leading to mixtures of ketone and enol silanes. Interestingly, subjecting compound **235** to Noyori's conditions (FSO_3H) as seen in Scheme 2.10, led to decomposition.[62]

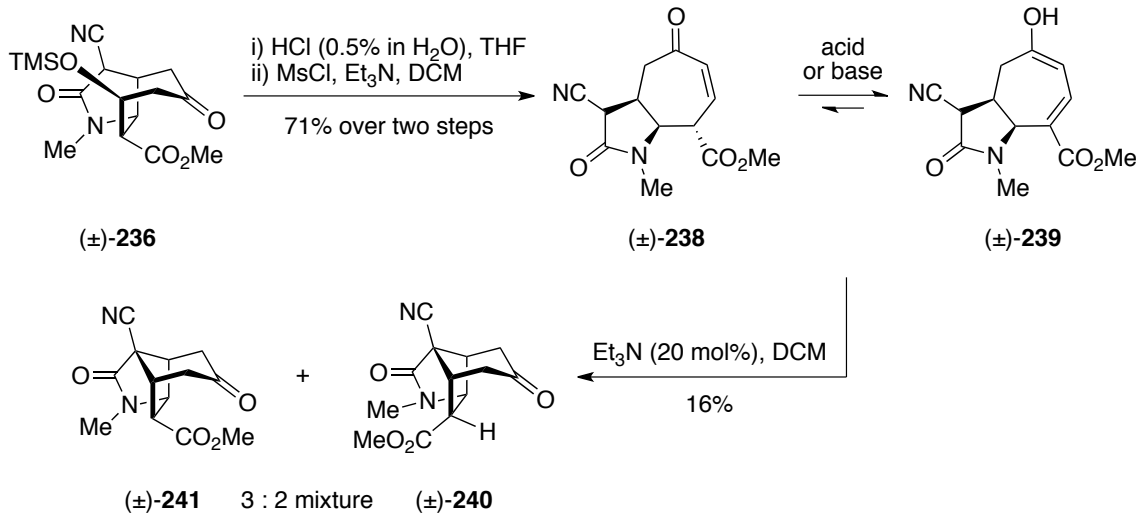


(±)-**235** (±)-**236** (29%) (±)-**237** (32%)

Scheme 2.13

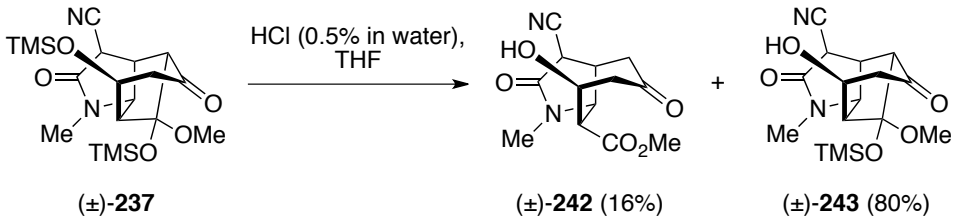
It was finally found that compound **235** underwent double elimination when heated in a sealed tube in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine, similar to conditions first reported in 1989 by Mann and co-workers (Scheme 2.13).[60,66,67] Unfortunately, the base mediated process did not afford the expected core structure, but two new compounds **236** and **237** in 29% and 32% yield respectively. The minor product **236** presumably arises from mono-elimination and Michael addition, while surprisingly the major product **237** arises from an additional intramolecular Claisen condensation. The structure of **237** was confirmed by X-ray crystallographic analysis.

Fortunately, both compounds (**236** and **237**) could be transformed into the desired core structure.



Scheme 2.14

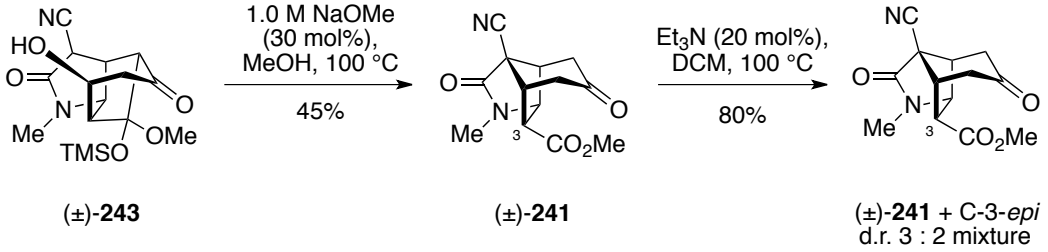
The minor adduct **236** was transformed in three steps and 11% overall yield, as seen in Scheme 2.14. Acid mediated TMS-removal and addition of mesyl chloride led to a mesyl alcohol, which underwent elimination to give **238** before subsequent basic treatment promoted the cyclisation giving the core structure as a 3:2 mixture of epimers **241** and **240** with the stereochemistry assigned by nOe experiments.



Scheme 2.15

The same process was applied to the major adduct **237**, but the acetal appeared to be relatively stable to acidic treatment leading to a small quantity of bicyclic product **242** in 16% yield along with tricyclic adduct **243** in 80% yield (Scheme 2.15). A base mediated retro-

Claisen reaction was tried instead. Subjecting **243** to a solution of sodium methoxide (2 equivalents) in methanol at room temperature gave bicyclic tropone **239**, which could be converted in low yield to an epimeric mixture of core structure as described above in Scheme 2.14.



(±)-**243** (±)-**241** (±)-**241** + C-3-*epi*
d.r. 3 : 2 mixture

Scheme 2.16

Fortunately, heating **243** with 30 mol% of 1.0 M sodium methoxide in methanol induced the retro-Claisen – Michael addition cascade affording the desired core structure **241** in 45% yield (Scheme 2.16). A 3:2 mixture of *endo* (**241**) and *exo* (**240**) ester was obtained while subjecting the core structure to 20 mol% triethylamine at 100 °C in a sealed tube.

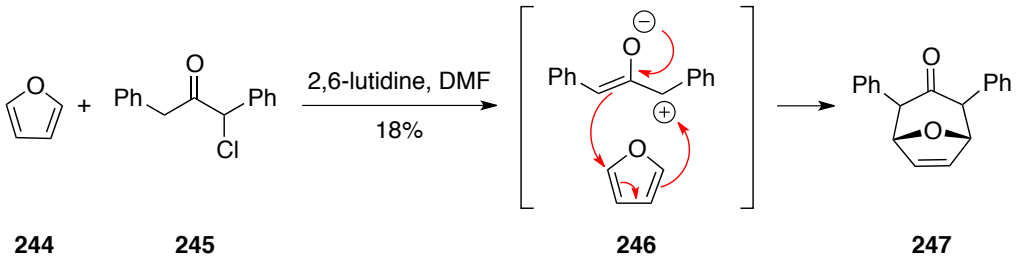
2.1.3 Summary

Gelsemine (**5**) is a challenging target due to its highly functionalised hexacyclic skeleton. It took our group several years and a number of failed attempts before reaching the core structure. Our aim was to build on these previous efforts and optimise the previous synthetic route to the core structure published in 2008 in an attempt to reach our objective: conduct the shortest synthesis of gelsemine to date.

2.2 [4+3] Cycloaddition

The [4+3] cycloaddition has played an important role in synthetic organic chemistry over the years as a rapid way of accessing seven-membered ring systems encountered in numerous natural products. Electronically, the [4+3] cycloaddition is similar to the Diels-Alder reaction and can be classified as a [4π(4C) + 2π(3C)] process. In contrast to the Diels-Alder reaction the numbers in the term [4+3] cycloaddition refer to the number of carbons involved in the reaction and can be simplified as a 4C+3C cycloaddition.

In 1962, Fort reported the first formation of an oxabicyclo[3.2.1]octenone *via* a [4+3] cycloaddition procedure.[68]

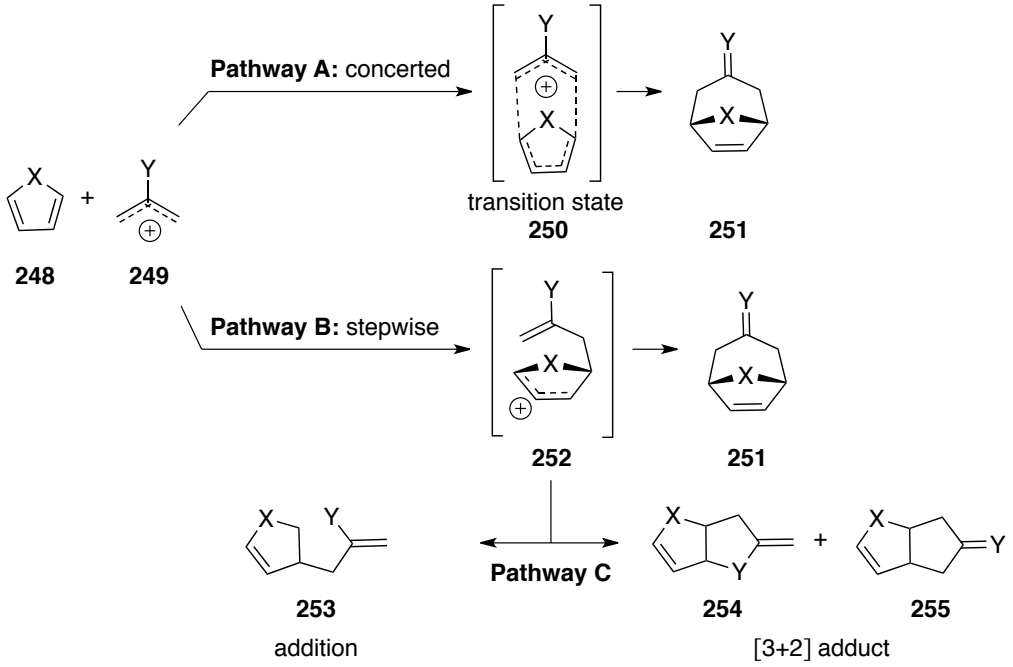


244 **245** **246** **247**

Scheme 2.17

It was observed that addition of furan (**244**) to an α-chlorodibenzylketone (**245**) and 2,6-lutidine solution in dimethylformamide led to a new bicyclic adduct **247** (Scheme 2.17). This reaction presumably starts with the formation of an oxallylic cation from dibenzylketone, which reacts as a dienophile in the presence of a simple furan (**244**). It was later established that the [4+3] cycloaddition occurred between an allyl or oxyallyl cation and a suitable 1,3-diene in the *cis* conformation such as cyclopentadienes, butadienes, pyrroles and furans.

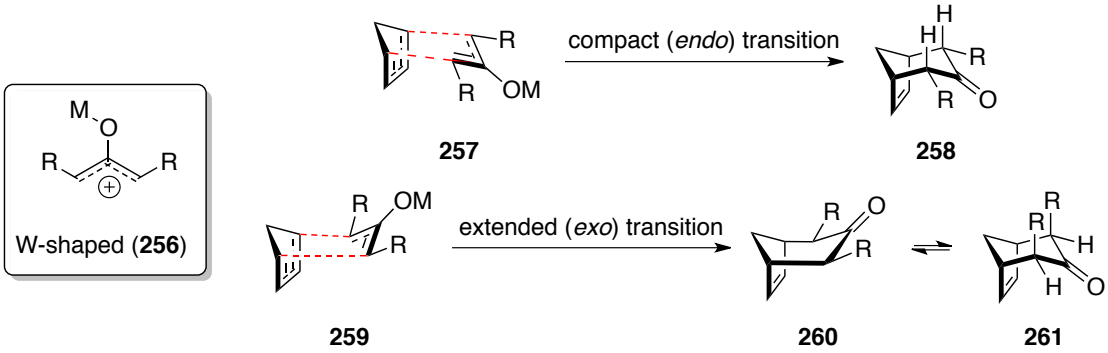
In 1984, Hoffmann proposed a classification of the reactions depending on the mechanistic pathway.[69]



Scheme 2.18

As seen in Scheme 2.18, the reaction mechanism can be either concerted (pathway A) affording a seven-membered ring (**251**) through a concerted transition state, or stepwise (pathway B) giving a seven-membered ring on which the stereochemistry will depend on the conformation of the allylic cation. A third pathway or pathway C is also possible leading to a five-membered ring *via* loss of a proton, giving **253**, or [3+2] addition (products **254** and **255**). The reaction pathway is determined by the nature of the diene and the dienophile. It was observed that a stepwise process is preferred between a highly nucleophilic diene and a strongly electrophilic allylic cation. Likewise, a poorly nucleophilic diene in the presence of a poorly electrophilic dienophile will undergo a concerted pathway.

As mentioned above, the reaction following pathway A can undergo two different transition states the "extended" which can be simplified as *exo* and the "compact" or *endo* type.

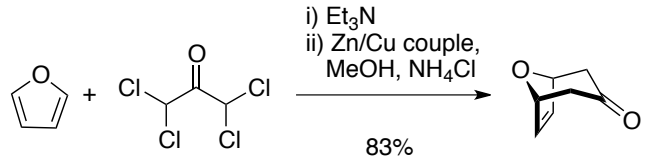


Scheme 2.19

As seen in Scheme 2.19 the *endo* mechanism will proceed *via* a "chair-like" transition state (**257**) between a W-shaped (**256**) oxallyl cation and a diene while the *exo* process will adopt a "boat-like" conformation (**259**). The boat is thermodynamically disfavoured so the newly formed bicyclic adduct will adopt a more stable chair conformation (**261**).

Since the discovery of the reaction in 1962, various groups around the world have participated in the development of methods to form the oxallyl cation and improvement of the reaction conditions. Cycloaddition processes have since been promoted by light,[70] Lewis acids,[69] ring opening of cyclopropanes,[71-73] reducing agents (Cu, Zn, Fe),[73-75] transition metal catalysts (Pd, Pt, Au)[73,76,77] and basic conditions.[58,69,73,78] In the past few years some asymmetric processes have also emerged.[79-82]

The enhancement of Fort's basic conditions was partially due to the contribution of Föhlisch's group.[58,78]



244 **262** **263**

Scheme 2.20

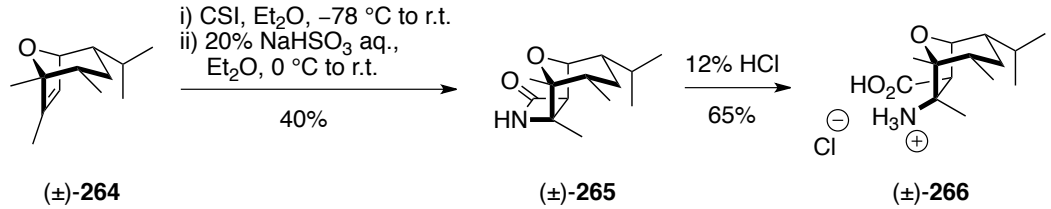
Upon treatment of a tetrachloropropanone (**262**) with triethylamine in the presence of a methanolic solution of furan (**244**), oxabicyclo[3.2.1]octanone (**263**) was isolated in 83% yield (Scheme 2.20).[69,83,84] Föhlisch *et al.* demonstrated that seven-membered rings could also be obtained using mono-haloketones (α-chloro or α-bromo ketones) in good yield, although sluggish reactions were observed with some polyhalogenated ketones. Such reactions were improved by using a less nucleophilic solvent such as 2,2,2-trifluoroethanol (TFE) instead of methanol.[85] The oxallyl intermediate is then formed by treatment of the polyhaloketone with a solution of sodium in 2,2,2-trifluoroethanol (NaTFE). This newly formed dienophile then undergoes, in the presence of a diene, a [4+3] cycloaddition in favour of the *endo* product.

2.3 Results and Discussion: The Bridge-Swap Precursor

In this research project, our objective was to develop a rapid access to the gelsemine core structure **241**. To this end, we explored several new routes to construct the bridge-swap precursor **235** in a minimum of steps.

2.3.1 Towards a Rapid Functionalisation of the Oxabicyclo[3.2.1]octenone

In order to be more step efficient we decided to explore a new route based on the work of Mann and co-workers.[86] This would deliver bridge-swap precursor **235** in just five steps.

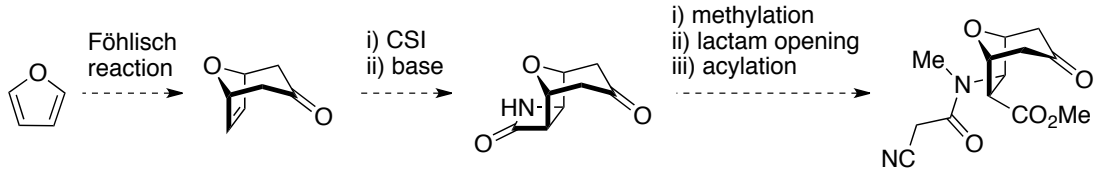


(±)-**264** (±)-**265** (±)-**266**

Scheme 2.21

In 1985, Mann *et al.* reported the formation of a *β*-lactam (**265**) on the *exo* face upon treatment of the bicyclic adduct **264** with chlorosulfonyl isocyanate (CSI) followed by sodium bisulfite (Scheme 2.21). The *β*-lactam (**265**) was then cleaved with acid to afford a new amino acid derivative **266** in 65% yield.

Following the same principle, we designed a new route towards the key step precursor **235**.

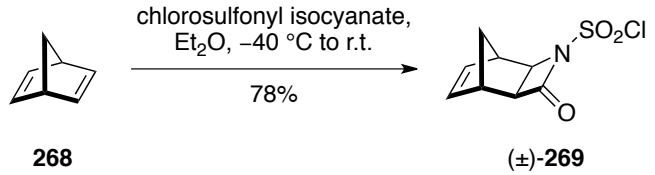


244 **263** **267** **235**

Scheme 2.22

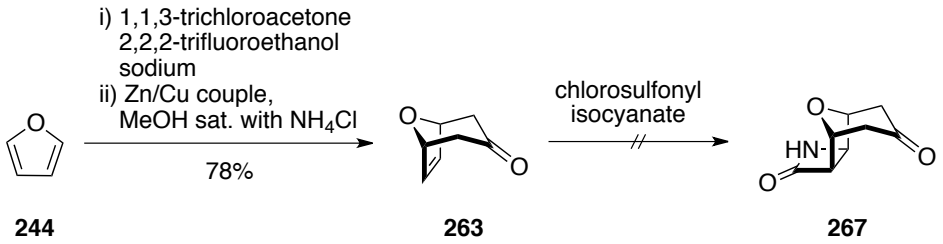
We envisaged that oxabicyclo[3.2.1]octenone (**263**) would easily be available *via* Föhlisch reaction between 1,1,3-trichloroacetone and a simple furan **244** (Scheme 2.22). Next, bicyclic adduct **263** would be treated with chlorosulfonyl isocyanate (CSI) to afford the *β*-lactam **267** on the *exo* face, as reported by Mann and co-workers.[86] After methylation of the lactam with iodomethane,[87] we hoped that subjecting the lactam to sodium methoxide would open it, giving a *trans* amino-ester species after subsequent epimerisation at the ester position as described by Semmelhack and co-workers.[88,89] The amino-ester could then undergo a previously described acylation to yield product **235** (Section 2.1.2).

We started by applying these conditions to norbornadiene, as seen below in Scheme 2.23.[90]



Scheme 2.23

Treating the simple alkene **268** with chlorosulfonyl isocyanate allowed us to isolate lactam **269** in 78% yield (Scheme 2.23). Pleased with this result, we decided to subject our system **263** to the same conditions.

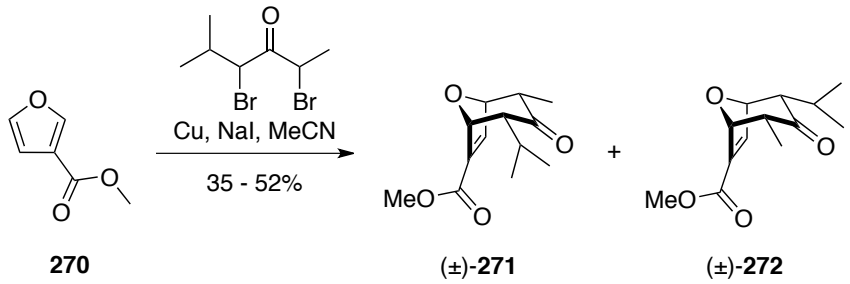


Scheme 2.24

The oxabicyclo[3.2.1]octenone (**263**) was prepared in 78% yield by adding furan into a solution of NaTFE and 1,1,3-trichloroacetone (Scheme 2.24). Unfortunately, no formation of the *β*-lactam **267** was observed on treatment with chlorosulfonyl isocyanate (CSI) in diethyl ether or dichloromethane at −40 °C, −10 °C or after warming to room temperature.[90,91] Degradation of the starting material was observed instead. The drastic conditions reported by Dragovish's group were also tried (neat, −78 °C to room temperature) leading to the same results.[92] As we were unable to perform the desired transformation, we considered an alternative route to access compound **235**.

2.3.2 [4+3] Cycloaddition with Substituted Furans

In 1987, Mann and co-workers reported the construction of substituted seven-membered ring compounds using substituted and deactivated furans.[93]

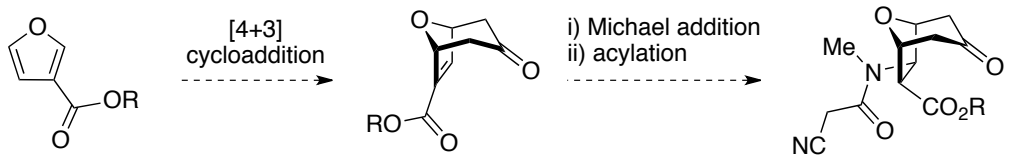


270 (±)-**271** (±)-**272**

Scheme 2.25

The [4+3] cycloaddition between methyl furan-3-carboxylate (**270**) and 1,3-dibromoacetone in the presence of sodium iodide and copper gave the expected oxabicyclic products **271** and **272**, in reasonable yield (Scheme 2.25). The same method was also reported in 2009 by Barbosa *et al*. on a substituted furan possessing an ester group in moderate yields.[94]

Inspired by this approach, we envisaged using this route to access compound **235** in three steps.

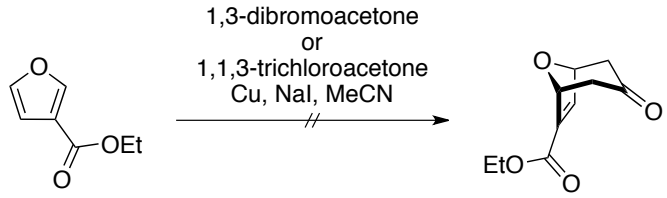


273 **274** **235**

Scheme 2.26

We hoped that cycloaddition with an appropriate furoate **273** (R = Me or Et) derivative would afford compound **274**, which would undergo Michael addition and acylation to provide the desired precursor **235** (Scheme 2.26).

The reaction was applied using commercially available ethyl furoate (**275**).

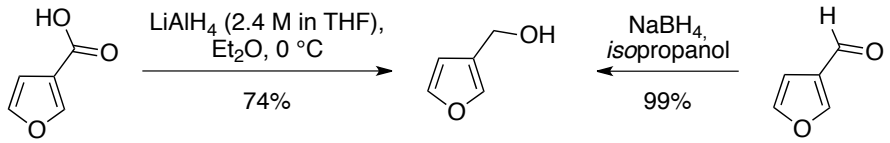


275 **276**

Scheme 2.27

The cycloaddition reaction between ethyl furoate (**275**) and an oxallyl carbocation generated from 1,3-dibromoacetone or 1,1,3-trichloroacetone (both commercially available) was unsuccessful in our hands (Scheme 2.27). As the reaction between an electron-poor furan (such as a furoate) should be favoured in the presence of an electron-rich oxallyl cation, we decided to increase the reactivity of our system by introducing a Lewis acid. In 2010, Krenske and Houk used either zinc chloride or sodium perchlorate to promote their [4+3] cycloaddition with furoates.[81] Unfortunately, adding $ZnCl_2$ (1.0 M in Et_2O) into the reaction led only to full recovery of ethyl furoate (**275**).

To overcome our previous difficulties we decided to optimise the route to the core structure that was published by Simpkins and Tchabanenko in 2008.[65] As the starting material furan-3-methanol (**221**) is expensive some alternatives were explored.

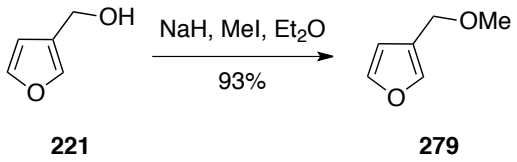


277 **221** **278**

Scheme 2.28

The reduction of 3-furoic acid **277** with lithium aluminium hydride gave the expected alcohol **221** in 74% yield. However, the work-up was complicated by the presence of aluminium salts.[95] Instead, the desired furan-3-methanol **221** was prepared from 3-furancarboxaldehyde **278** in the presence of sodium borohydride in *iso*propanol, in excellent yield (Scheme 2.28).[96]

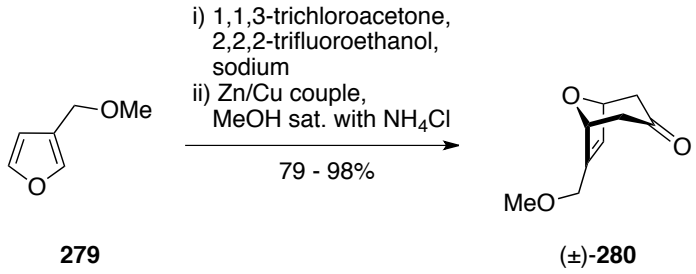
The protection of the furan-3-methanol **221** before the Föhlisch cycloaddition appeared crucial as discussed in Section 2.1.2. In the published route a TBS protecting group was added for the cycloaddition step then removed immediately afterwards (Scheme 2.11). A new step-efficient route was designed and a methyl ether was introduced as a precursor of the methyl ester group of **233**.



221 **279**

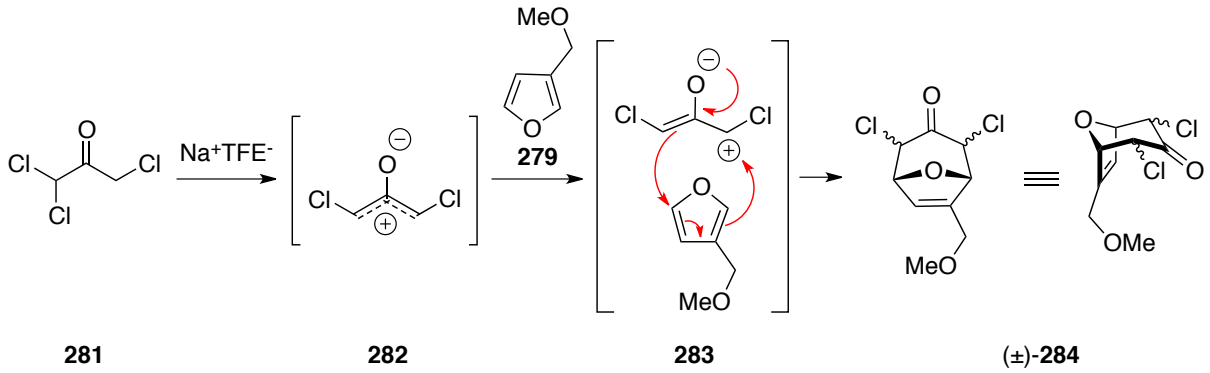
Scheme 2.29

Protection of alcohol **221** with potassium *tert*-butoxide and methyl iodide in tetrahydrofuran gave the desired product in moderate yield (40 to 72% yield). The modest yield and poor reproducibility of the reaction were attributed to the high volatility of **279**.[97] Pleasingly, treatment of furan-3-methanol **221** with sodium hydride and methyl iodide in diethyl ether furnished **279** in 93% yield (Scheme 2.29).[98] With multi-gram quantities of **279** readily available the next step required the formation of the seven-membered ring.



Scheme 2.30

Pleasingly, under the Föhlisch conditions, the reaction between protected furan-2-methanol **279** and 1,1,3-trichloroacetone (**281**) proceeded in good yield (Scheme 2.30). The proposed mechanism of this rearrangement starts with the formation of the oxallylic cation intermediate **282** by treatment of 1,1,3-trichloroacetone (**281**) with TFE / NaTFE (Scheme 2.31).

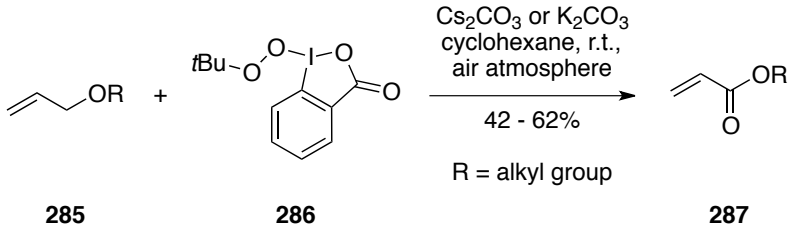


Scheme 2.31

In the presence of the furan derivative **279** the oxallylic cation **282** reacts as a dienophile and undergoes [4+3] cycloaddition, affording a halogenated adduct **284** (Scheme 2.31). The well-known dehalogenation procedure with zinc-copper couple furnished the oxabicyclic adduct **280** (Scheme 2.30).

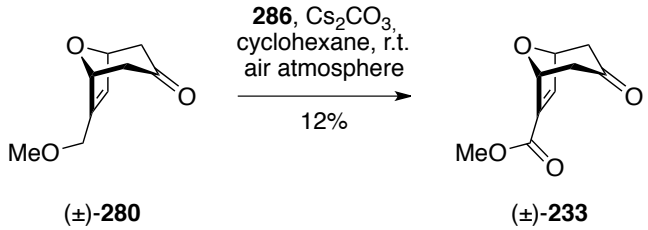
2.3.3 Allylic Oxidation

To avoid the deprotection-oxidation-esterification steps used in the previous synthesis (Scheme 2.12, *vide supra*) a novel and direct allylic oxidation was envisaged to access the desired α,β-unsaturated ester.[65]



Scheme 2.32

In 1996, Ochiai and co-workers reported the first method to oxidise allyl and benzyl ethers into the corresponding esters using a hypervalent iodine reagent.[99] Treatment of the allyl ether **285** with the hypervalent iodine(III) peroxide **286** generated an allylic radical, which reacted with the oxygen in the atmosphere to give a new peroxy acetal adduct. The peroxy acetal readily decomposed in the presence of base (Cs_2CO_3 or K_2CO_3) furnishing the expected α,β-unsaturated ester **287** in moderate yield (Scheme 2.32).



Scheme 2.33

We treated compound **280** with the same conditions after preparing the radical initiator **286** from 2-iodobenzoic acid in 74% yield over two steps.[99,100] Subjecting compound **280** to hypervalent iodine(III) peroxide **286** and cesium carbonate afforded, after 8 days at room

temperature, the desired ester **233** in 12% yield along with starting material **280** (Scheme 2.33). Modifying the number of equivalents of base (2 to 4 equivalents) or the base (K_2CO_3) did not improve the conversion. As the progress of the reaction was easy to follow by ^{1}H NMR spectroscopy (Figure 2.1) we screened a number of conditions in an attempt to improve the conversion.

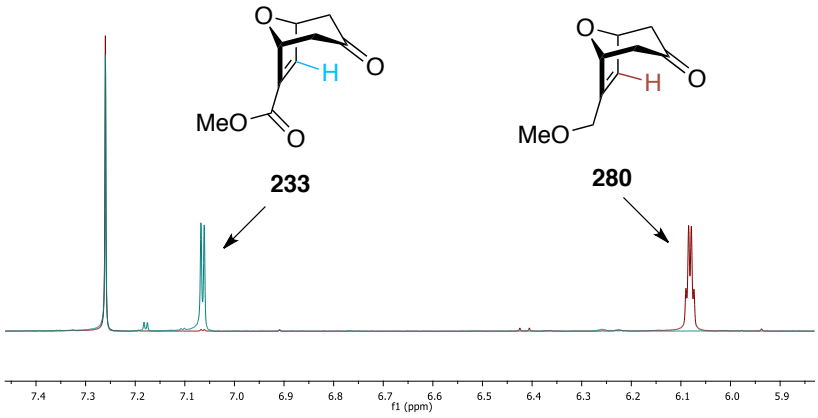


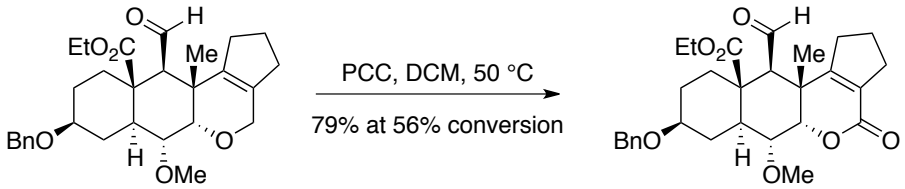
Figure 2.1

A methodological study on the solvent was carried out in attempt to drive the reaction to completion. Unfortunately, despite screening a range of solvents (ethyl acetate, toluene, dichloromethane, acetonitrile, *iso*propanol, 5:1 ethyl acetate/water, 5:1 acetonitrile/water) we were unable to improve the outcome of the reaction.[101]

As cyclohexane appeared to be the best solvent we investigated other parameters. We decided to heat the reaction mixture at 30 °C or 50 °C to improve the reaction speed as reported by Ochiai and co-workers.[99] Unfortunately, in both cases the conversion stopped and the same conclusion was observed while adding more oxygen, changing the concentration or adding slowly the radical initiator **286**. A small effect was nonetheless noticed by increasing the

amount of **286** into the reaction from 2 to 3 equivalents over 10 days of stirring. As our attempts to optimise Ochiai's conditions had no impact on the conversion, different oxidation conditions were reviewed.

To the best of our knowledge, the only other example of direct synthesis of an α,β-unsaturated ester *via* allylic oxidation was reported in 2002 by Nicolaou *et al*. in their approach towards azadirachtin.[102]

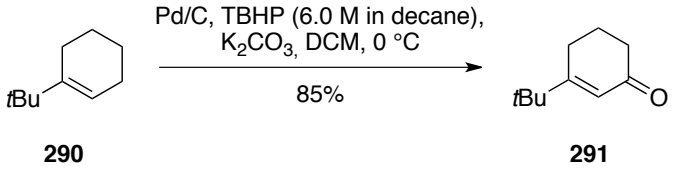


(±)-**288** (±)-**289**

Scheme 2.34

In the presence of pyridinium chlorochromate (PCC) compound **288** was oxidised forming a new α,β-unsaturated lactone **289** in 79% yield based on 56% conversion (Scheme 2.34). Applying these conditions to our substrate proved unsuccessful as no conversion was observed either at reflux or at 90 °C in the microwave. At room temperature, the reaction gave a 0.3:1 mixture of product **233** and starting material **280** (^{1}H NMR ratio).

Disappointed with these results, we decided to screen some allylic oxidations reported to afford α,β-unsaturated ketones using similar reagents as Ochiai's oxidation procedure, such as peroxides and/or hypervalent iodine. In 2002, Corey *et al*. reported a palladium catalysed oxidation in the presence of peroxides.[103]

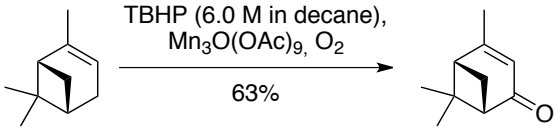


290 **291**

Scheme 2.35

Subjecting 1-(tert-butyl)cyclohex-1-ene **290** to palladium on carbon in the presence of *tert*-butyl peroxide (TBHP) and potassium carbonate at 0 °C gave the oxidised adduct **291** in good yield (Scheme 2.35). Upon treatment of our compound **280** in the same conditions, a 0.4:1 mixture of product **233** and starting material **280** was observed after one day (^{1}H NMR ratios). This ratio improved at room temperature but the reaction never reached completion.

In 2006, Shing's group reported similar conditions using a manganese derivative to oxidise simple or complex alkenes (steroids) with good regioselectivity.[104]

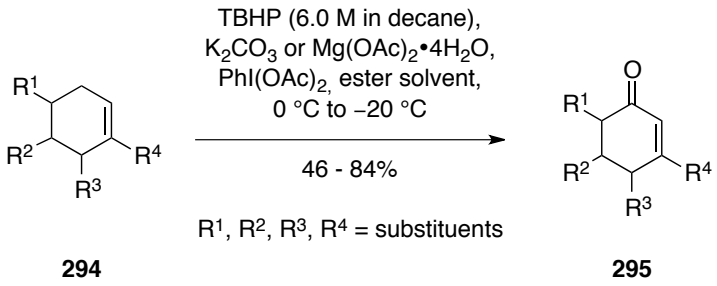


292 **293**

Scheme 2.36

Upon treatment of alpha-pinene **292** with manganese acetate and *tert*-butyl peroxide (TBHP) in the presence of oxygen, the corresponding enone was isolated in 63% yield (Scheme 2.36). Sadly, this result was not transferable to our functionalised substrate **280**.

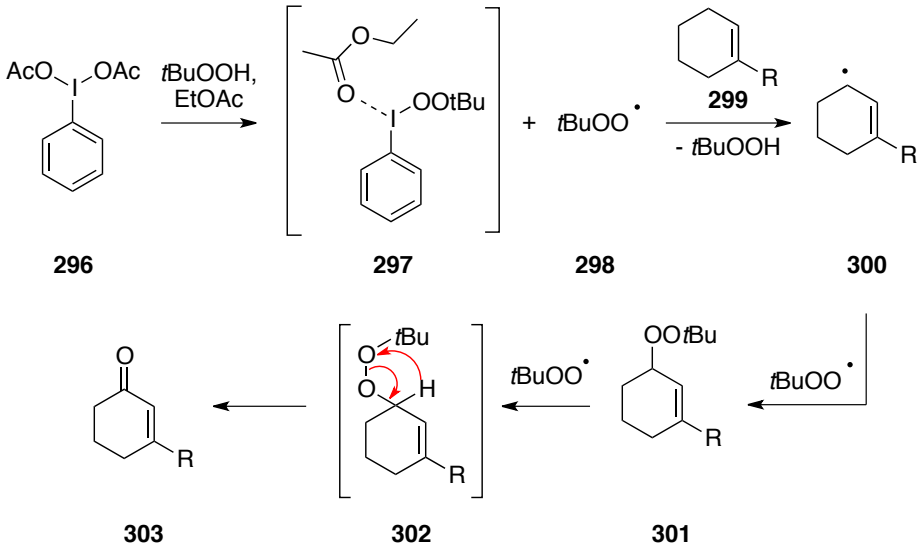
In 2010, Yeung and co-workers reported a new allylic oxidation using a *tert*-butyl peroxide radical generated from a hypervalent iodine, diacetoxyiodobenzene (DIB), and *tert*-butyl peroxide (TBHP).[105]



Scheme 2.37

Subjecting alkene **294** to $PhI(OAc)_2$ (DIB), *tert*-butyl peroxide (TBHP), K_2CO_3 or $Mg(OAc)_2•4H_2O$ in an ester solvent gave them the corresponding enone **295** in moderate to good yield (Scheme 2.37). It was found that an ester solvent stabilised the hypervalent iodine and the best stabilisation effect was observed when using *n*-butyl butanoate.[1]

Yeung *et al*. proposed a mechanism for their allylic oxidation inspired by the work of Milas and co-workers.[106]

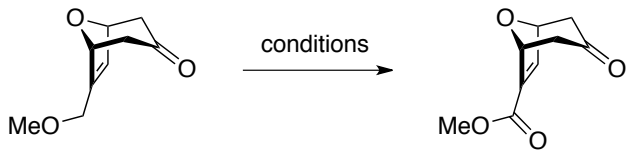


Scheme 2.38

[1] Ruthenium tetroxide could be envisaged as an oxidant for this transformation (Richard J.K. Taylor, personal communication).

They supposed that mixing together diacetoxyiodobenzene **296** and *tert*-butyl hydroperoxide would give a new hypervalent iodine system **297** that could be stabilised by coordination with an ester solvent, in this case ethyl acetate, as outlined in Scheme 2.38. Subjecting the *tert*-butyl peroxide **298** to alkene **299** would generate an allylic radical (**300**), which would react with a second equivalent of *tert*-butyl peroxide **298** to afford a new peroxy species, furnishing the expected enone **303** after rearrangement.

We screened these conditions on our substrate **280** as seen in Table 2.1.



(±)-**280** (±)-**233**

Entry	Conditions	Time (days)	^{1}H NMR ratios 233 : 280
1	DIB, TBHP (6M in decane), K_2CO_3, *n*-butyl butanoate, –20 °C	2	0 : 1
2	DIB, TBHP (6M in decane), $Mg(OAc)_2$•$4H_2O$, *n*-butyl butanoate, 0 °C	2	1.1 : 1
3	DIB, TBHP (6M in decane), K_2CO_3, *n*-butyl butanoate, r.t.	2	6 : 1
4	DIB, TBHP (6M in decane), K_2CO_3, EtOAc, r.t.	2	2.2 : 1
5	**DIB, TBHP (6M in decane), K_2CO_3, EtOAc, –20 °C to r.t.**	**1**	**1 : 0**

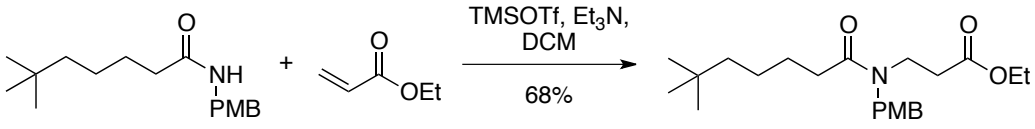
Table 2.1

We started by screening the published conditions (Entries 1-2, Table 2.1) and pleasingly observed a 50:50 ratio of product **233** and starting material **280** when performing the reaction at 0 °C. Higher conversion was observed when carrying out the reaction at room temperature (Entry 3, Table 2.1), but *n*-butyl butanoate proved to be difficult to remove *in vacuo* leading us to investigate ethyl acetate instead. In the presence of ethyl acetate no conversion was observed until we increased the amount of base (1 equivalent instead of 0.5) affording a 2.2:1 ratio of product **233** and starting material **280** (Entry 4, Table 2.1). Surprisingly, scaling up

the reaction we discovered that the reaction was actually exothermic during the addition of *tert*-butyl hydroperoxide (TBHP), possibly causing degradation of our system. Cooling the reaction mixture to –20 °C during the addition of TBHP and leaving it to warm up slowly to room temperature gave us full conversion after a day (Entry 5, Table 2.1). The desired compound **233** was isolated in 55 - 72% yield.

2.3.4 Amide formation

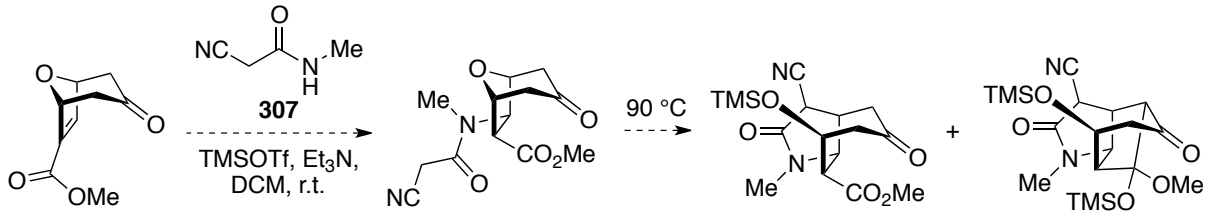
With ester **233** in hand, a direct aza-Michael addition was envisaged to insert the amide group in one step, based on Huang and Queneau's work published in 2009.[107]



304 **305** **306**

Scheme 2.39

Upon treatment with TMSOTf and triethylamine in dichloromethane at room temperature the aza-Michael addition of amide **304** onto α,β-unsaturated ester **305** proceeded smoothly affording the desired compound **306** in 68% yield (Scheme 2.39).

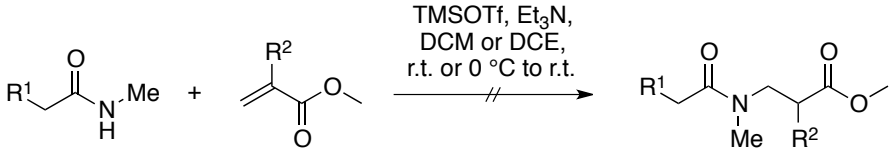


233 **235** **236** **237**

Scheme 2.40

These conditions were appealing to us due to their similarities with our key bridge-swap step. We hoped that increasing the temperature to 90 °C would generate compounds **236** and **237** in

a similar way to that previously described (Scheme 2.40). To explore this concept we used a model system composed of an amide (**307** or **308**) and an α,β-unsaturated ester (**309** or **310**) to study the reaction. Compound **307** was synthesised first in moderate yield (42 – 59% yield) *via* peptide coupling between 2-cyanoacetic acid and methylamine hydrochloride. Better results (72 – 87% yield) were observed while reacting methylcyanoacetate and methylamine (40% solution in water) at –10 °C.[108] Adduct **308** was obtained in one step using methylamine and 2-bromoacetic acid in moderate yield.



307, R^1 = CN
308, R^1 = Br

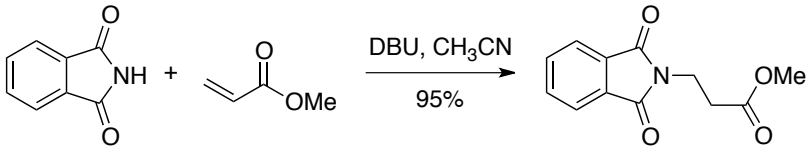
309, R^2 = H
310, R^2 = Me

311

Scheme 2.41

Unfortunately, treatment of the α,β-unsaturated ester **309** or **310** under Queneau and Huang's aza-Michael conditions led to full recovery of starting material at room temperature or from 0 °C to room temperature (Scheme 2.41). Another variant of the reaction reported by Greene and co-workers involving TBDMSOTf at 0 °C was also tried with the same results.[109] The same results were observed when applying both methods to our compound **233**.

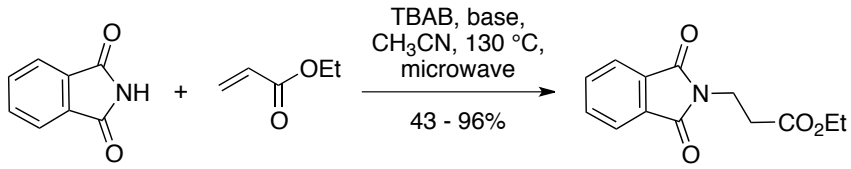
In 2007, Kim and co-workers performed a similar transformation using a base-promoted aza-Michael addition.[110]



312 **309** **313**

Scheme 2.42

Treatment of methyl acrylate **309** and phthalimide **312** with 0.5 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), at room temperature, afforded Michael addition adduct **313** in excellent yield (Scheme 2.42). The reaction was also performed with amines and carbonates in good yields. These conditions were applied to both our model system and compound **233**, at room temperature or reflux, leading to full recovery of starting material. In the same manner, Kim *et al*. reported a similar Michael addition using potassium carbonate or potassium hydroxide in dimethylformamide, which gave the same results when applied to both systems. With these reactions failing, we turned our attention to harsher conditions. In 2006 and 2007 two groups reported an aza-Michael addition on α,β-unsaturated esters using microwave technology.[111,112]

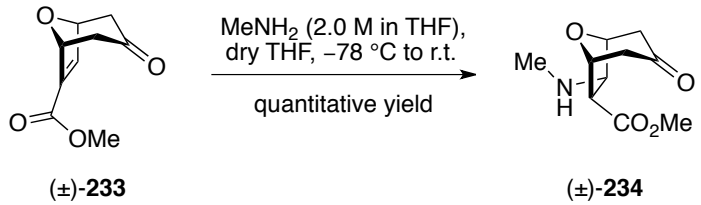


312 **305** **314**

Scheme 2.43

The expected product **314** was obtained by treating ethyl acrylate **305** and phthalimide **312** with base and tetra-*N*-butylammonium bromide (TBAB) in a microwave reactor (Scheme 2.43). Several bases such as Cs_2CO_3, K_2CO_3, *t*BuOK, ZnO, 1,4-diazabicyclo[2.2.2]octane (DABCO) were tried on our model system without success.

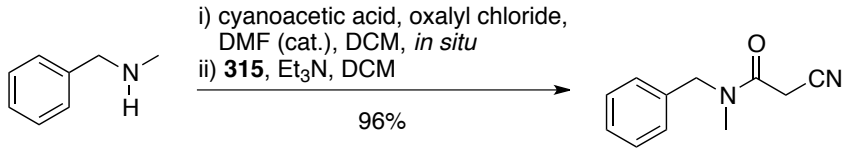
After all these fruitless approaches we decided to go back to the previously reported two step procedure to build our precursor, as described in Scheme 2.12.[65]



(±)-**233** (±)-**234**

Scheme 2.44

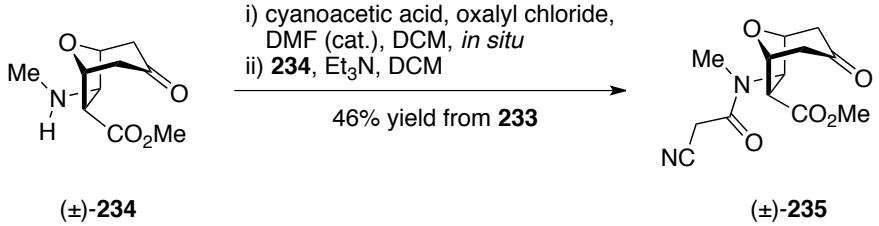
Aza-Michael addition of methylamine onto the α,β-unsaturated ester **233** occurred from the less hindered face, or *exo* face, leading to a single product **234** in quantitative yield (Scheme 2.44). In the previous report, the Simpkins group used a two-step procedure to perform the amide formation. First the cyanoacetyl chloride was prepared and then coupled with the amide in the presence of triethylamine. Unfortunately, this procedure was difficult to reproduce as the cyanoacetyl chloride rapidly degraded on drying *in vacuo*. To overcome the issue a series of conditions were screened such as those by Poli *et al*. using cyanoacetic acid, *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at room temperature, which was unsuccessful in our hands.[113] The conditions of Bonjoch and co-workers consisting of 3-(ethyliminomethyleneamino)-*N,N*-dimethylpropan-1-amine (EDC), cyanoacetic acid and triethylamine afforded the expected product in 6% yield.[114]



315 **316**

Scheme 2.45

In the end, we generated the cyanoacetyl chloride *in situ* and then added it into a solution containing the amine and triethylamine. On our model system these conditions afforded the desired product **316** in 96% yield (Scheme 2.45). Pleased with this result we applied the chemistry to our amine adduct **234**, as outlined below in Scheme 2.47.



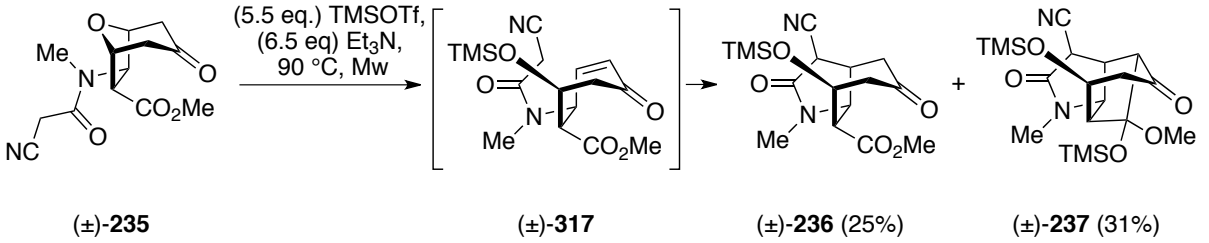
(±)-**234** (±)-**235**

Scheme 2.46

Surprisingly, the reaction did not proceed well in the first instance, furnishing compound **235** in poor yield (Scheme 2.46). Further investigations identified that our starting material was acid sensitive. To overcome the problem fresh nitrogen was bubbled through the cyanoacetyl chloride solution removing excess hydrochloric acid (gas) prior to the reaction and the evolution of acid was monitored using pH paper. When no more acid was observed the cyanoacetyl chloride solution was added to the solution containing **234**, providing amide **235** in moderate yield over two steps.

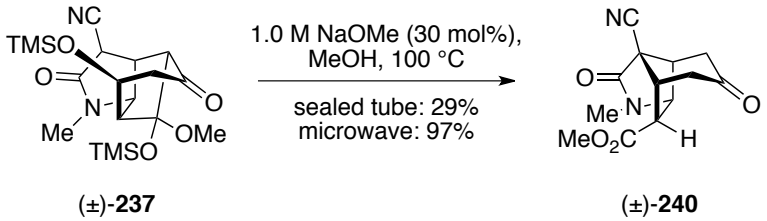
2.4 Construction of the Core Structures

With amide **235** in hand, we were ready to carry out the key "bridge-swap" step. Pleasingly, similar results were observed in our hands as those previously described.



Scheme 2.47

We believe that a mono-elimination occurs during the reaction furnishing intermediate **317**, which undergoes Michael addition yielding compound **236** (Scheme 2.47). The tricyclic compound **237** presumably arises from Michael addition followed by Claisen condensation. We prefer using a microwave reactor to a sealed tube as it assures better temperature control and also a faster reaction time (20 minutes instead of 1 hour) in this case. The reaction was carried out in both dichloromethane and 1,2-dichloroethane (DCE) with similar yields. Both compounds, **236** and **237**, were subjected to various conditions to converge towards the core structure.



Scheme 2.48

Direct treatment of tricycle **237** with 30 mol% of 1.0 M sodium methoxide in methanol, in a sealed tube, resulted in the desired retro-Claisen condensation, hydroxysilyl elimination and Michael addition to afford the core structure **240** in 29% yield after 1 hour (Scheme 2.48). The yield was significantly improved when performed in the microwave, furnishing compound **240** in 97% yield. To our surprise, the reaction proceeded along with epimerisation

at the ester position, affording the *exo* ester (**240**) instead of the expected *endo* adduct **241**. The stereochemistry of the ester was confirmed by an nOe experiment, showing an nOe correlation between H-4 and H-3 (Figure 2.2).

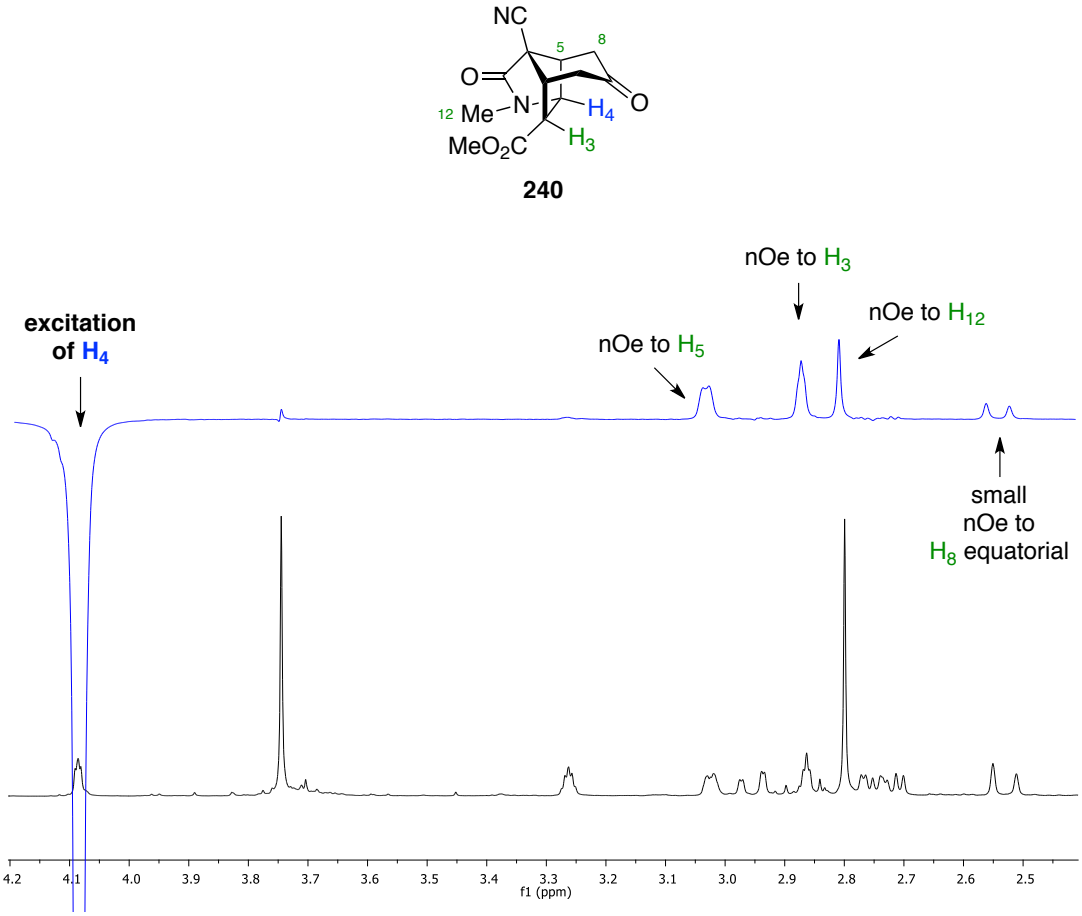
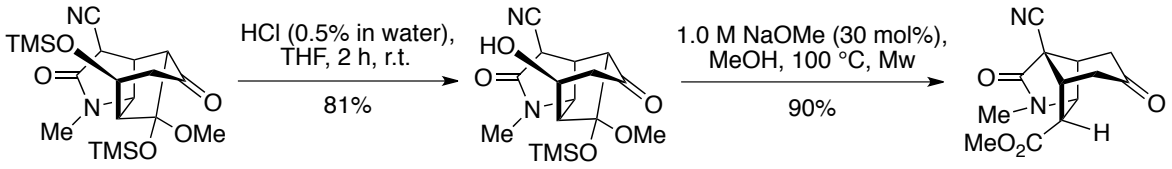


Figure 2.2

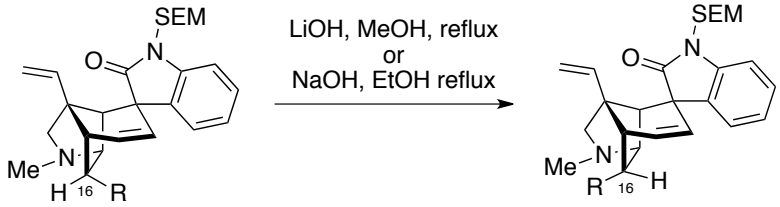
Modification of the reaction conditions (temperature, concentration, reaction time) provided the same epimer **240**. To identify if our one step procedure was responsible for the epimerisation the previously described two-step procedure was repeated.



(±)-**237** (±)-**243** (±)-**240**

Scheme 2.49

Subjecting the tricyclic adduct **237** to 0.5 M aqueous hydrochloric acid in tetrahydrofuran provided the desired mono silylated product **243** in good yield (Scheme 2.49). Compound **243** was heated at 100 °C in the presence of 30 mol% of 1.0 M sodium methoxide in methanol affording core structure **240** in good yield. We again observed solely the *exo* ester. Our attempts to epimerise the position with either mild bases (Et_3N, DBU) or strong bases (LiHMDS, LDA, NaH) proved ineffective. It was not clear whether the deprotonation of the hindered *endo* proton was occurring but a trial to epimerise a small quantity of the *endo* epimer **241** (left over from the previous synthesis) with triethylamine proceeded exactly as reported by Simpkins *et al.*[65] Exploring the literature, we discovered that Overman and co-workers described a similar issue in 2005.[45]



(±)-**318a**, R = CN
(±)-**318b**, R = CO_2H
(±)-**318c**, R = CO_2Me

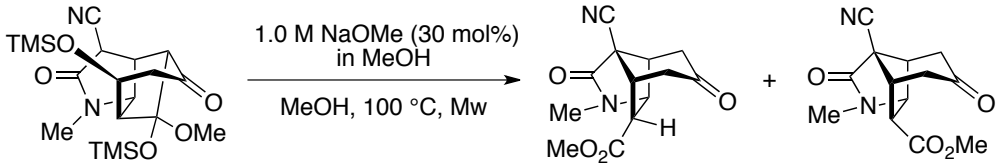
(±)-**319a**, R = CN
(±)-**319b**, R = CO_2H
(±)-**319c**, R = CO_2Me

Scheme 2.50

Overman's group noticed that heating their starting material **318** (R = CN, CO_2H, CO_2Me) in the presence of sodium hydroxide or lithium hydroxide in an alcoholic solvent gave rise to

epimerisation at the C-16 position, as seen in Scheme 2.50, affording **319** as a mixture of epimers (R = CN, CO_2H) or a single *exo* isomer (R = CO_2Me). Exposure of **319c** to strong base (lithium di*iso*propylamide, lithium diethylamide, potassium hydride, potassium di*iso*propylamide, potassium bis(trimethylsilyl)amide, lithium hydride) failed to afford the *endo* epimer.

In their report of 2008, Simpkins and Tchabanenko proposed that the stereochemistry at the ester position was retained by formation of a lactone acetal during the reaction, temporarily locking the configuration of the ester, which then opened during the work-up.[65] Questions about the presence of water in our reaction mixture causing the hydrolysis of the lactone acetal intermediate were raised and different sources of sodium methoxide (NaOMe) were explored.



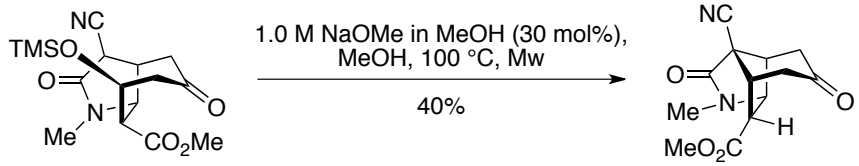
(±)-**237** (±)-**240** (±)-**241**

Entry	1M NaOMe in MeOH Source	^{1}H NMR ratios 240 : 241
1	dissolution of sodium methoxide powder in MeOH	1 : 0
2	dilution of a 5.4 M solution of NaOMe in MeOH	1 : 0
3	freshly cut sodium dissolved in MeOH	4 : 1
4	dissolution of sodium methoxide powder in H_2O	1 : 0

Table 2.2

Using a commercial source of sodium methoxide provided in both cases (Entries 1-2, Table 2.2) the *exo* ester **240** in 97% yield, while making our own sodium methoxide by dissolving some freshly cut oil-free sodium lumps into freshly distilled methanol afforded a mixture of

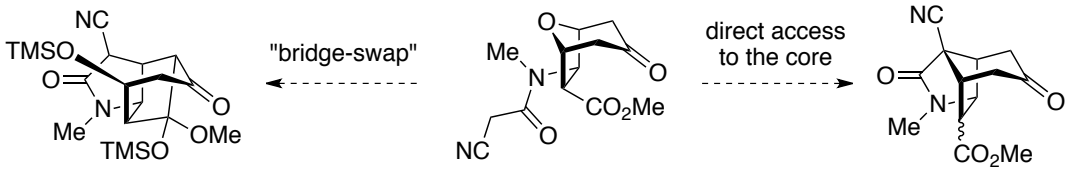
both epimers, **240** and **241**, in a 4:1 ratio (Entry 3, Table 2.2). Repeating the reaction using a solution of sodium methoxide in water furnished compound **240** in 77% yield (Entry 4, Table 2.2). Even if the presence of water, or sodium hydroxide, has been shown to have a slight effect on the reaction, these results mainly highlight that the *exo* ester **240** is the thermodynamic product of the reaction. As it seemed difficult at the time to generate only the *endo* epimer we decided to carry on and concentrate our efforts on converting the second "bridge-swap" adduct **236** into the core structure.



(±)-**236** (±)-**240**

Scheme 2.51

Subjecting compound **236** to the same conditions led to core structure **240** in 40% yield (Scheme 2.51). As the yield was difficult to improve we decided to screen other conditions (30 mol% 1.0 M NaOMe in MeOH at room temperature or reflux; Et_3N at room temperature, reflux or microwave) without success. To improve the conversion the "bridge-swap" conditions were modified.

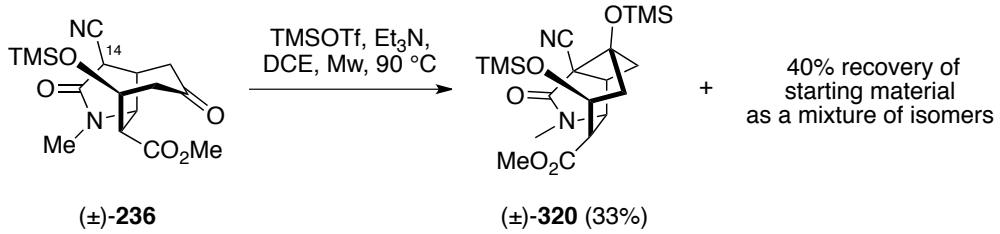


237 **235** **240/241**

Scheme 2.52

We hoped to modify the "bridge-swap" to increase the yield of tricyclic adduct **237** or promote the desired core (**240** / **241**) formation in a single pot (Scheme 2.52). Various

parameters were modified such as increasing the equivalents of triethylamine and/or trimethylsilyltriflate (TMSOTf), the solvent (dichloromethane, 1,2-dichloroethane), reaction time (from 20 minutes to 4 hours) and the temperature (room temperature to 120 °C, in a sealed tube or microwave) with no significant effects.



(±)-**236** (±)-**320** (33%)

Scheme 2.53

To our surprise subjecting the mono-silylated compound **236** to triethylamine and TMSOTf furnished starting material **236** along with a new structure that was assigned as **320** (Scheme 2.53). We propose that compound **320** was obtained *via* a Mukuyama aldol type reaction with formation of a silyl enol ether adjacent to the amine.[115] In the presence of excess Lewis acid (TMSOTf) the ketone was activated, leading to the formation of a new carbon-carbon bond affording a four-membered ring. The stereochemistry of the ester was determined by an nOe experiment (Figure 2.3, below).

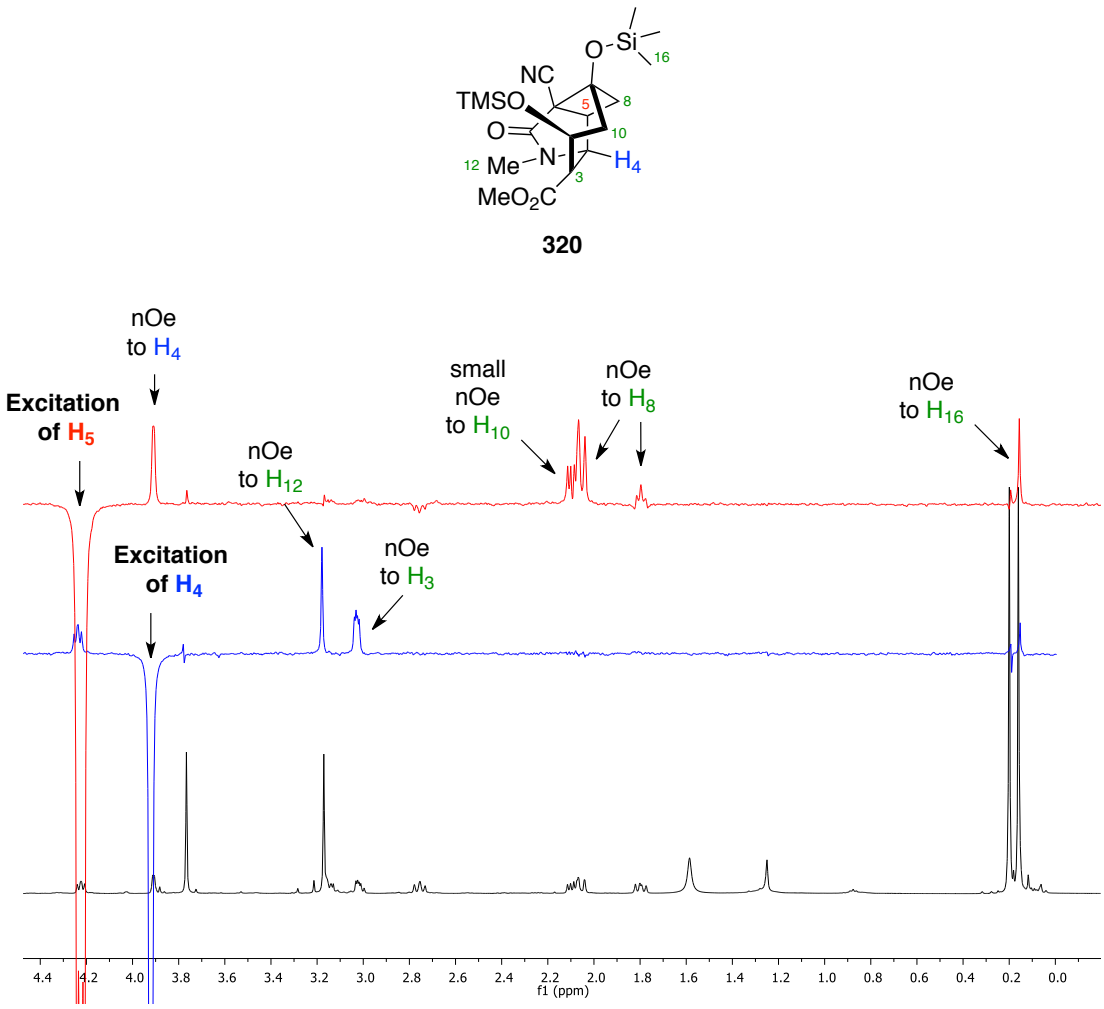


Figure 2.3

Excitation of H-4 showed an nOe to H-3 helping us confirm epimerisation at the C-3 position, leading to an *exo* ester (Figure 2.3). Excitation of H-5 showed an nOe to the H-16 which is consistent with our proposed structure. The four-membered ring in compound **320** was easily re-opened by treatment with 3 mol% 1.0 M NaOMe in MeOH, leading to **236** as mixture of epimers, in quantitative yield.

2.5 Summary

Our group has developed a synthesis of the gelsemine core structure using an oxygen-carbon bridge-swap strategy. However, the published route delivers **241** in only 1.9% yield over ten steps from furan-3-methanol **221**. To continue forward towards gelsemine we needed to develop a higher yielding and more step-efficient route. In this Chapter we presented an optimised sequence involving an improved protecting group strategy, novel direct access to α,β-unsaturated ester **233** and a shortened conversion of the bridge-swap adducts to the core. These improvements enabled access to the gelsemine core **240** in just seven steps and up to 12% overall yield, providing sufficient material to continue our investigation.

Chapter 3

Attempted Installation of the Spiro-Oxindole

3.1 Introduction

Spiro-oxindoles are present in numerous natural and synthetic compounds. The development of enantioselective methods to construct spiro-oxindoles has been an important target due to their presence in several pharmaceutical agents.[116-119] One of the challenges of any gelsemine synthesis is the installation of the spiro-oxindole with the correct regioselectivity and stereochemistry, as seen previously in Section 1.5 and summarised below in Table 3.1.

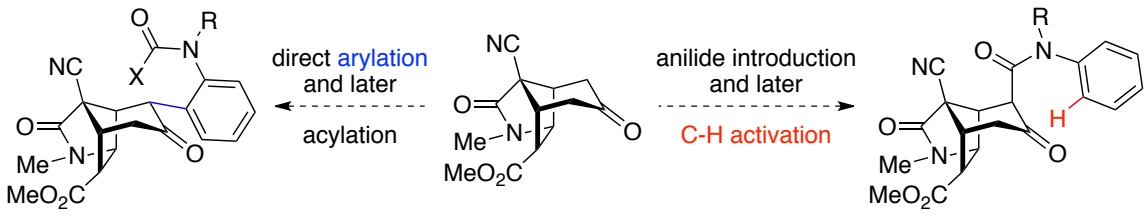
Group	Methods	d.r. Desired/Undesired
Johnson (1994)	photo-induced radical cyclisation	1 : 2
Hart (1994)	radical cyclisation	1.6 : 1
Speckamp (1994)	intramolecular Heck reaction	2 : 1
Fukuyama (1996)	divinylcyclopropane-cycloheptadiene rearrangement	>99 : 1
Overman (1999)	intramolecular Heck reaction	1 : 11
Fukuyama (2000)	divinylcyclopropane-cycloheptadiene rearrangement	>99 : 1
Danishefsky (2002)	Eschenmoser-Claisen rearrangement	>99 : 1
Aubé (2007)	intramolecular Heck reaction	1.7 : 1
Qin (2012)	condensation and acid-mediated cyclisation	10 : 1

Table 3.1

Table 3.1 highlights all of the different methods that have been developed to install the spiro-oxindole on the compact gelsemine structure. Radical cyclisation, the intramolecular Heck reaction and Qin's acid-mediated cyclisation gave a mixture of both isomers. In 1996, Fukuyama reported the first stereoselective installation of the spiro-oxindole towards

(±)-gelsemine *via* Knoevenagel-like condensation followed by a divinylcyclopropane – cycloheptadiene rearrangement to construct the desired quaternary centre.[18] Four years later, Fukuyama's group reiterated their key procedure in the first total synthesis of (+)-gelsemine.[27] The construction of the gelsemine spiro-oxindole is challenging as seen in Danishefsky's synthesis. In 2002, Danishefsky's group reported a rather long and complicated construction of the spiro-oxindole to access the structure as a single isomer.[51]

As some reports in recent years have detailed a number of novel routes to spiro-oxindoles, we turned our attention to several new synthetic methods hoping to be able to install our spiro-oxindole with the correct stereochemistry. There is also the key question of regiocontrol as our core structure possesses two CH_2 groups adjacent to the ketone.



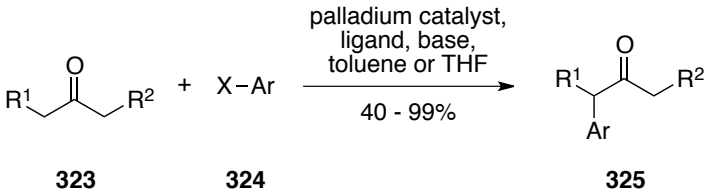
Scheme 3.1

Two approaches were considered for building the spiro-oxindole as highlighted in Scheme 3.1. First, we envisaged using a Buchwald-Hartwig type α-arylation (R = H or PG) of ketone **240** followed by acylation to close the oxindole (X = leaving group such as OMe). Alternatively, introduction of the anilide piece would be followed by cyclisation *via* C–H activation to form the spiro-oxindole.

3.2 Strategies Towards the Arylation of Haloacetanilide

3.2.1 α-Arylation of Ketones

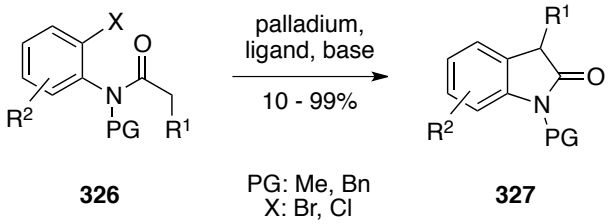
In 1975 Semmelhack and co-workers reported the first example of a nickel catalysed coupling between an aryl iodide and a ketone enolate.[120] Later protocols for nickel or palladium-catalysed arylations required the presence of tin, bismuth, lead and/or enol ethers or enamines.[121,122] In 1997 both the Buchwald and Hartwig groups published direct palladium-catalysed cross couplings using readily available starting materials.[123,124]



323 **324** **325**

Scheme 3.2

The palladium catalysed coupling between a non-substituted or a substituted ketone **323** (R^1, R^2 = alkyl, aryl) and an aryl halide **324** (X = Br, I) afforded an α-arylated ketone **325** in moderate to excellent yield (Scheme 3.2). In the proposed mechanism the aryl halide reacts first with the palladium source ($Pd_2(dba)_3$ or $Pd(OAc)_2$ and a phosphine ligand such as BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene), Tol-BINAP (2,2′-bis (di-*p*-tolylphosphino)-1,1′-binaphthalene), dppf (1,1′-bis(diphenylphosphino)ferrocene) or dtpf (1,1′-bis(di-*o*-tolylphosphino)ferrocene) to create a new palladium species. Addition of the appropriate enolate, formed by treatment of ketone **323** with a base (NaO*t*Bu or KHMDS, afforded the desired product **325**. Since their first reports, both groups have screened ketones and aryl halide partners to increase the scope and selectivity of the reaction.[125-129] Variants of the reaction were also reported in 2002 by Beller *et al*. and in 2006 by Nolan *et al.,* using aryl chlorides.[130,131]



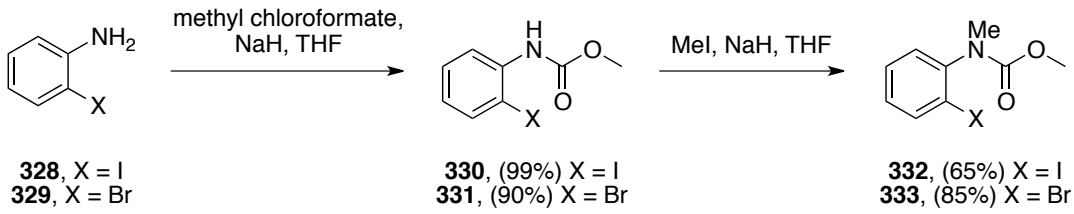
Scheme 3.3

More recently, Hartwig and co-workers reported an intramolecular oxindole formation (Scheme 3.3).[129,132,133] Subjecting a protected acetanilide **326** (X = Br or Cl, PG = Me or Bn) to a mixture of palladium ($Pd(dba)_2$ or $Pd(OAc)_2$, base ($NaO\textit{t}Bu$) and a phosphine ligand, promoted the desired cyclisation leading to substituted oxindoles **327** (R^1 = alkyl, aryl and R^2 = electron donating/withdrawing group) in moderate to good yield.

We hoped to apply a similar strategy to α-arylate ketone **240** with a 2-haloacetanilide derivative and construct the desired spiro-oxindole, as seen in Scheme 3.1. However, no intermolecular coupling between a ketone and a 2-haloacetanilide has been reported in the literature.

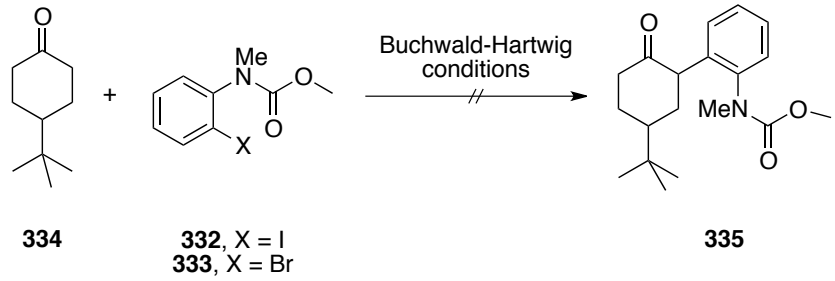
3.2.2 Model System Studies

Different acetanilide derivatives possessing a carbamate group were designed in order to perform our oxindole study.



Scheme 3.4

Two types of halogenated acetanilides were envisaged for the study: the iodo and bromo substituted arenes **332** and **333**. To start with 2-iodoaniline (**328**) and 2-bromoaniline (**329**) were treated with methyl chloroformate to obtain the corresponding carbamates **330** and **331** in 99% and 90% yield respectively (Scheme 3.4). We decided to *N*-methylate the anilides in the same manner as Hartwig's group (Scheme 3.3). Carbamates **330** and **331** were treated with sodium hydride and methyl iodide to afford **332** in 65% yield and **333** in 85% yield. We then screened several conditions to perform the desired α-arylation.

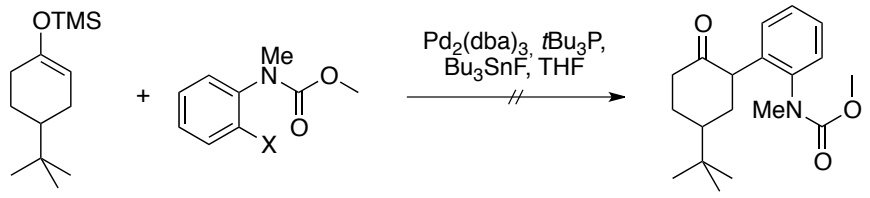


334 **332**, X = I
333, X = Br **335**

Scheme 3.5

The study was carried out on a simple ketone, 4-*tert*-butylcyclohexanone **334** (Scheme 3.5). To perform the desired coupling we used different palladium sources ($Pd(OAc)_2$ or $Pd_2(dba)_3$), phosphine ligands (tBu_3P, (±)-BINAP) and sodium *tert*-butoxide as a base. Several temperatures (room temperature, reflux, 110 °C or 150 °C), reaction times and vessels (Schlenk tube, microwave) were used but we were only able to recover starting material.

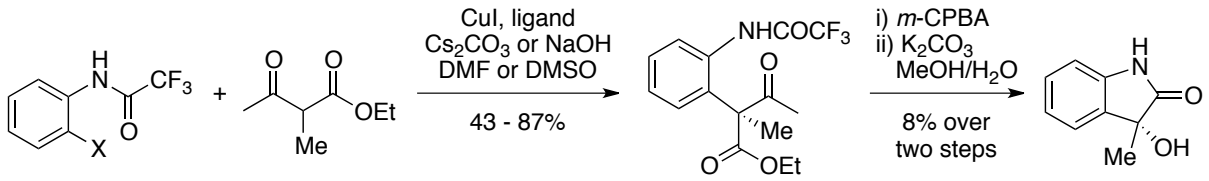
In 2006, Rawal *et al*. reported a palladium-catalysed α-arylation using a silyl enol ether as an enolate equivalent.[134]



(±)-**336** **332**, X = I
333, X = Br **335**

Scheme 3.6

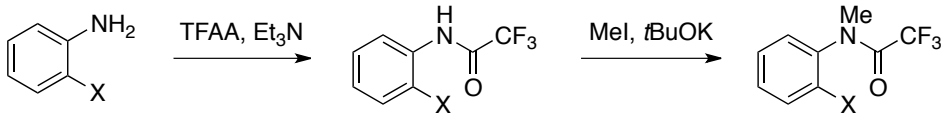
We obtained silyl enol ether **336** by treatment of ketone **334** with lithium di*iso*propylamide (LDA) and trimethylsilyl chloride. Unfortunately, no coupling was observed in the presence of aryl halides **332** or **333** (Scheme 3.6). We hypothesised that the acetanilide derivatives were too electron rich which could be affecting our coupling, so we decided to modify this by introducing an electron-withdrawing substituent.



337, X = I
338, X = Br **339** **340** **341**

Scheme 3.7

In 2006, Ma and co-workers published an enantioselective copper-catalysed arylation of methylacetoacetate (**339**) with a 2-halotrifluoroacetanilide (**337** or **338**) in the presence of a ligand (4-hydroxy-L-proline or L-proline) and base (Cs_2CO_3 or NaOH), in moderate to good yield (Scheme 3.7).[135] The best results were obtained when using iodoacetanilide **337** and the resulting product **340** was then transformed into oxindole **341** in two steps. Based on this, we decided to replace acetanilides **332** and **333** with a 2-halotrifluoroacetanilide.



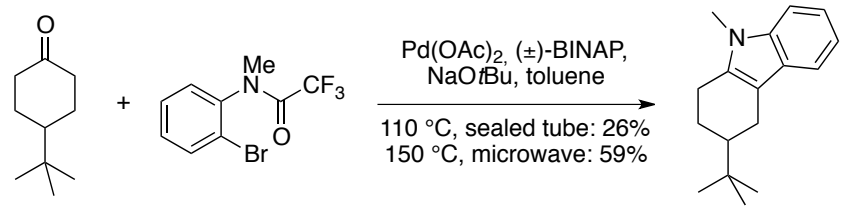
328, X = I
329, X = Br

337, (98%) X = I
338, (75%) X = Br

342, (75%) X = Br

Scheme 3.8

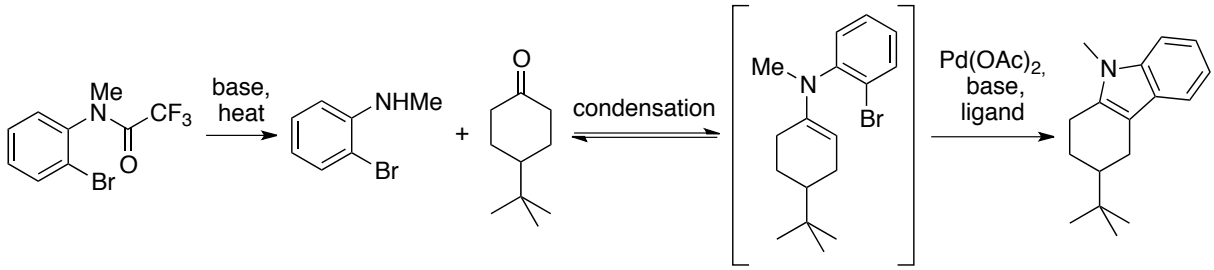
Treatment of 2-iodoaniline (**328**) or 2-bromoaniline (**329**) with trifluoroacetic anhydride (TFAA) furnished the corresponding 2-halotrifluoroacetanilide derivatives, **337** and **338**, in good yields (Scheme 3.8). Unfortunately, all attempts to couple **337** and **338** with 4-*tert*-butylcyclohexanone **334** were unsuccessful. Next, we decided to *N*-methylate bromoacetanilide **338** in the same manner as Hartwig's group, to afford **342** in 75% yield.



334 **342** (±)-**343**

Scheme 3.9

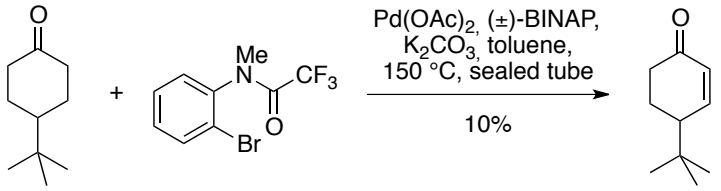
Unexpectedly, subjecting 4-*tert*-butylcyclohexanone **334** and acetanilide **342** to palladium(II) acetate, (±)-BINAP and sodium *tert*-butoxide at 110 °C in a sealed tube gave indole **343** in 26% yield (Scheme 3.9). The same result was observed when performing the reaction in the microwave reactor at 150 °C but in a higher yield. After further investigations we found that the trifluoroacetate group was leaving in warm basic conditions affording 2-bromo-*N*-methylaniline. A mechanism of the reaction was proposed based on Majumdar' s work published in 2011.[136]



342 **344** **334** **345** **343**

Scheme 3.10

The deprotected 2-bromo-*N*-methylaniline (**344**) presumably reacts with ketone **334** affording the enamine intermediate **345**, which undergoes intramolecular palladium-catalysed Heck reaction to furnish indole **343** (Scheme 3.10). In an attempt to stop the 2-bromo-*N*-methylaniline (**344**) formation various conditions were screened. However, no coupling was observed when performing the reaction at room temperature to 50 °C and increasing the temperature to 70 °C led to the formation of tricyclic indole **343**.



334 **342** (±)-**346**

Scheme 3.11

As a final attempt, sodium *tert*-butoxide was replaced by a weaker base (potassium carbonate) but no desired product was formed. A small amount of oxidised product, enone **346**, was recovered instead (Scheme 3.11). No reaction was observed when attempting to perform the coupling in the absence of base.

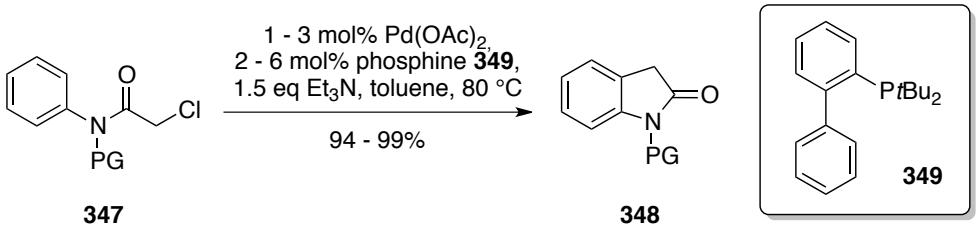
To overcome our previous difficulties we decided to try building the desired spiro-oxindole following the second approach consisting of the introduction of the anilide moiety followed by arylation.

3.3 Oxindole Construction Using C–H Activation

The concept of C–H activation or C–H functionalisation, which consists of replacing a carbon-hydrogen bond by a carbon-carbon bond or a carbon-heteroatom bond, has garnered a significant number of methodology studies in recent years.[137-140] Oxindole synthesis by C–H activation has been reported using catalytic or radical pathways.

3.3.1 Catalytic Pathway

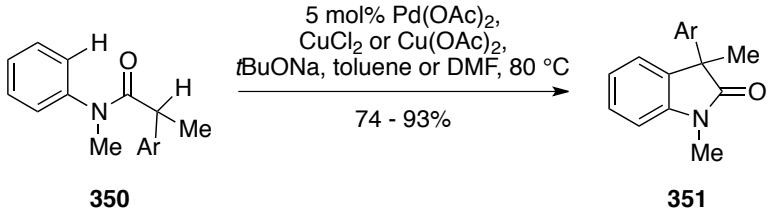
In 2003, Buchwald reported the first oxindole synthesis using palladium catalysed C–H activation.[125]



Scheme 3.12

Upon treatment with palladium acetate and triethylamine in the presence of phosphine **349**, α-chloroacetanilide **347** (PG = Me, Et, Ph, Bn) was smoothly converted in high yield into the corresponding oxindole **348** (Scheme 3.12). Numerous oxindoles were obtained in good yield as this procedure tolerated a variety of *para* or *meta* substituents on the phenyl ring (Me, NO_2,

OTBS, TMS, CF_3, OMe, Cl). The interest in this field expanded in 2009 with the work of Kündig and co-workers.[141]



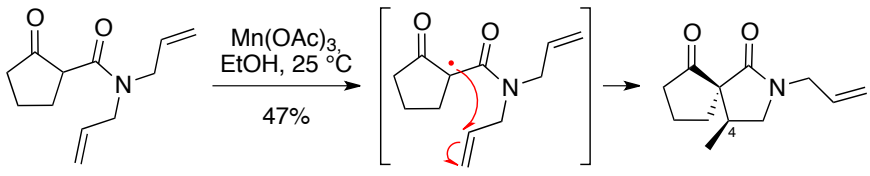
350 **351**

Scheme 3.13

Kündig's group reported the first oxindole formation involving the coupling between a C–H_{sp3} and a C–H_{sp2} under mild conditions. As outlined in Scheme 3.13, the protected acetanilide derivative **350**, possessing an aryl group alpha to the amide, cyclised in the presence of palladium(II) acetate, base and an oxidant ($CuCl_2$ or $Cu(OAc)_2$) affording spiro-oxindole **351** in good yield. Since this report several other groups have developed strategies for oxindole synthesis using palladium and a copper oxidant.[142,143]

3.3.2 Radical Pathway

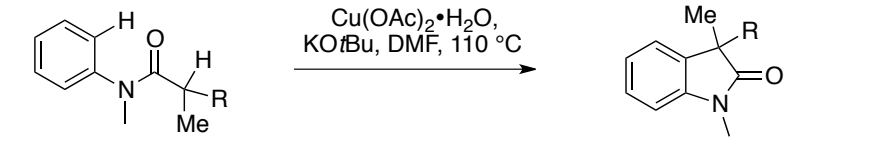
In 1989, Cossy and co-workers reported the first lactam and spiro-lactam syntheses *via* an oxidative free-radical cyclisation induced by manganese(III) acetate.[144]



(±)-**352** (±)-**353** (±)-**354** + C-4-*epi*
d.r. 16 : 1

Scheme 3.14

Upon treatment of *β*-keto amide **352** with manganese(III) acetate in degassed ethanol a single-electron oxidation of the amino-enolate by manganese(III) occurred forming a radical that underwent 5-*exo*-*trig* cyclisation and oxidation affording **354** in 47% yield along with 3% of the epimer at the C-4 position (Scheme 3.14). In 2009, Taylor and co-workers reported an elegant procedure for oxindole synthesis involving a copper mediated transformation.[145]

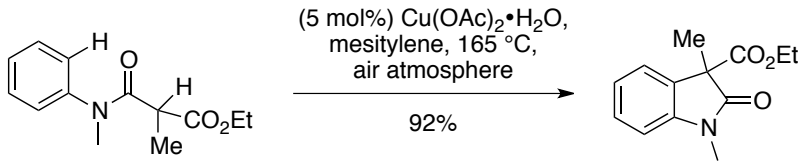


(±)-**355**, R = CN
(±)-**356**, R = CO_2Et
(±)-**357**, R = $P(O)(OEt)_2$

(±)-**358** (95%), R = CN
(±)-**359** (98%), R = CO_2Et
(±)-**360** (89%), R = $P(O)(OEt)_2$

Scheme 3.15

Preliminary studies following Kündig and co-workers conditions (Scheme 3.13, *vide supra*) showed that the presence of palladium(II) acetate was not necessary to access oxindole structures possessing an electron-withdrawing group alpha to the amide (R = CN, CO_2Et, $P(O)(OEt)_2$), and therefore a new mild procedure was developed affording the expected products **358**, **359** or **360** in excellent yield (Scheme 3.15).[145,146] Further investigations were undertaken by Taylor to reduce the amount of copper catalyst.



(±)-**356** (±)-**359**

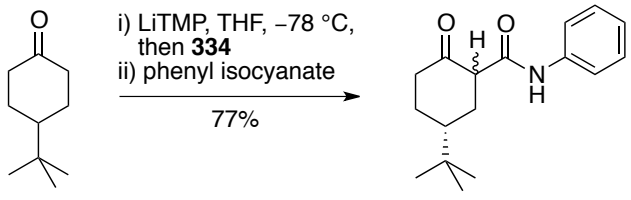
Scheme 3.16

The methodology study led to the identification of new catalytic conditions in which the oxygen in the air played the role of oxidant, regenerating Cu(I) to Cu(II) during the

reaction.[147,148] Heating acetanilide **356** with 5 mol% copper(II) acetate monohydrate, using atmospheric oxygen as an oxidant, furnished the desired oxindole **359** in 92% yield (Scheme 3.16).[147,149,150] These mild conditions appeared optimum for acetanilides possessing an electron-withdrawing group alpha to the amide.

3.3.3 Model System Studies

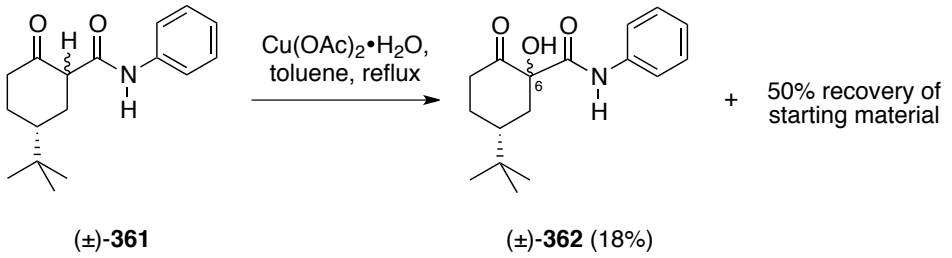
To synthesise a model system for our oxindole cyclisation, we again opted for a simple ketone, 4-*tert*-butylcyclohexanone **334**, and started with the construction of the necessary *β*-keto amide.



334 (±)-**361**

Scheme 3.17

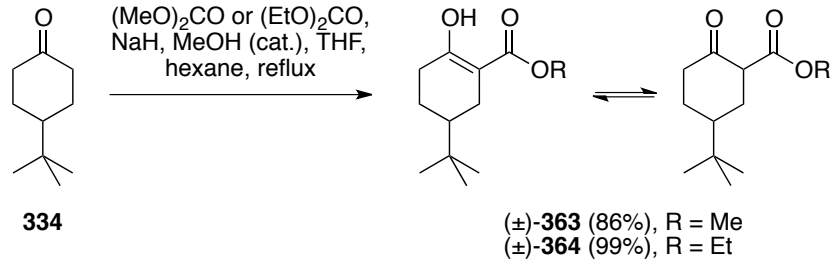
Treatment of 4-*tert*-butylcyclohexanone **334** with LDA at −78 °C followed by addition of phenyl isocyanate surprisingly furnished a urea formed by reaction of phenyl isocyanate with di*iso*propylamide. This side reaction was avoided using a bulkier lithium base, lithium tetramethylpiperidide (LiTMP), affording the desired *β*-keto amide **361** in 77% yield, as a mixture of enol and keto-amide form (Scheme 3.17). We then subjected *β*-keto amide **361** to free-radical cyclisation conditions using either manganese(III) acetate or copper(II) acetate.



Scheme 3.18

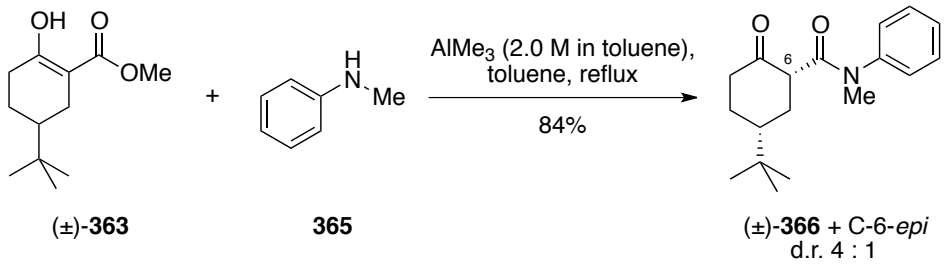
Attempts to cyclise *β*-keto amide **361** using Kündig's protocol ($CuCl_2$, $Pd(OAc)_2$, KO*t*Bu, toluene, reflux) were unsuccessful.[141] We then subjected intermediate **361** to Taylor's conditions ($CuCl_2$, KO*t*Bu, DMF or $Cu(OAc)_2•H_2O$, KO*t*Bu, DMF or toluene) but again no desired product was observed.[145] However, oxidation product **362** was isolated in 18% yield, as a 5:1 mixture of diastereoisomers at the C-6 position, suggesting that the hydrogen of the 1,3-dicarbonyl was abstracted and the resulting radical reacted with oxygen (Scheme 3.18). Unfortunately, we were unable to determine the stereochemistry at the C-6 position using nOe experiments. As a last attempt, a method reported by Snider *et al*. consisting of mixing together copper(II) acetate and manganese(III) acetate was tried with the same result ($Mn(OAc)_3•2H_2O$, $Cu(OAc)_2•H_2O$, AcOH, 25 °C to 80 °C).[144,151] A similar observation was reported by Kündig's group, when using N-H keto-amides only starting material was recovered.[141] Unfortunately, selectively protecting the amide as N-Me, N-Ac or N-Boc appeared challenging as keto-amide **361** exists as a mixture of enol and 1,3-dicarbonyl forms.

As an alternative approach to make the required protected anilide we opted for a two-step procedure: first introducing a *β*-keto ester and then performing an amide coupling.



Scheme 3.19

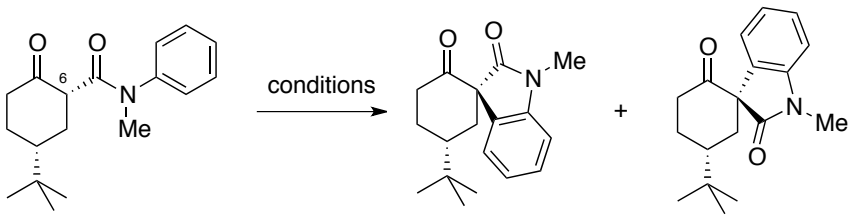
Ketone **334** was heated in the presence of either dimethyl carbonate or diethyl carbonate, sodium hydride and a catalytic amount of sodium methoxide, affording the desired products as enol esters **363** and **364** in 86% and 99% yields respectively (Scheme 3.19).[152] As the literature examples described above possessed methyl groups at the amide position we chose to couple our esters **363** and **364** with commercially available *N*-methylaniline.



Scheme 3.20

Upon treatment of *β*-keto esters (**363** or **364**) and *N*-methylaniline (**365**) with DMAP in refluxing toluene[153,154] or trimethyl aluminium (2.0 M in toluene) in dichloromethane at room temperature, the starting material was recovered.[155] However, heating methyl enol ester **363** and *N*-methylaniline (**365**) with a 2.0 M solution of trimethyl aluminium in toluene afforded the desired *β*-keto amide **366** in 84% yield, as a 4:1 mixture of diastereoisomers (Scheme 3.20). We found that the reaction was somewhat sluggish when ethyl enol ester **364** was used under the same conditions, making this compound less attractive for our model study. With

the desired oxindole precursor **366** in hand we screened several C–H functionalisation methods.



(±)-**366** +C-6-*epi* d.r. 4 : 1 (±)-**367** (±)-**368**

Entry	Conditions	Yield	d.r. 367 : 368
1	(2eq.) $Mn(OAc)_3•2H_2O$, EtOH, 25 °C	no reaction	-
2	(2eq.) $Mn(OAc)_3•2H_2O$, EtOH, reflux	no reaction	-
3	**(2eq.) $Mn(OAc)_3•2H_2O$, AcOH, reflux**	**43%**	**4 : 1**
4	(2eq.) $Cu(OAc)_2•H_2O$, KO*t*Bu, DMF, air atmosphere, 110 °C	degradation	-
5	**(2eq.) $Cu(OAc)_2•H_2O$, toluene, air atmosphere, reflux**	**66%**	**4 : 1**

Table 3.2

In the first instance, Cossy and co-workers conditions were explored without success and the same result was observed at reflux (Entries 1-2, Table 3.2).[156] Snider's group reported some similar conditions using acetic acid as a solvent. We were pleased to find that heating compound **366** with manganese(III) acetate dihydrate in acetic acid afforded the desired cyclised products (**367** and **368**) in 43% yield as a 4:1 mixture of diastereoisomers (Entry 3, Table 3.2).[144] We also decided to explore some milder conditions and hoped that Taylor's protocol could be applied with only a ketone as an electron-withdrawing group.[145] Heating *β*-keto amide **366** with potassium *tert*-butoxide led to degradation of our starting material (Entry 4, Table 3.2). Pleasingly, subjecting compound **366** to the same conditions but in the absence of base furnished the desired spiro-oxindoles (**367** and **368**) in 66% yield as a 4:1 mixture of diastereoisomers (Entry 5, Table 3.2).

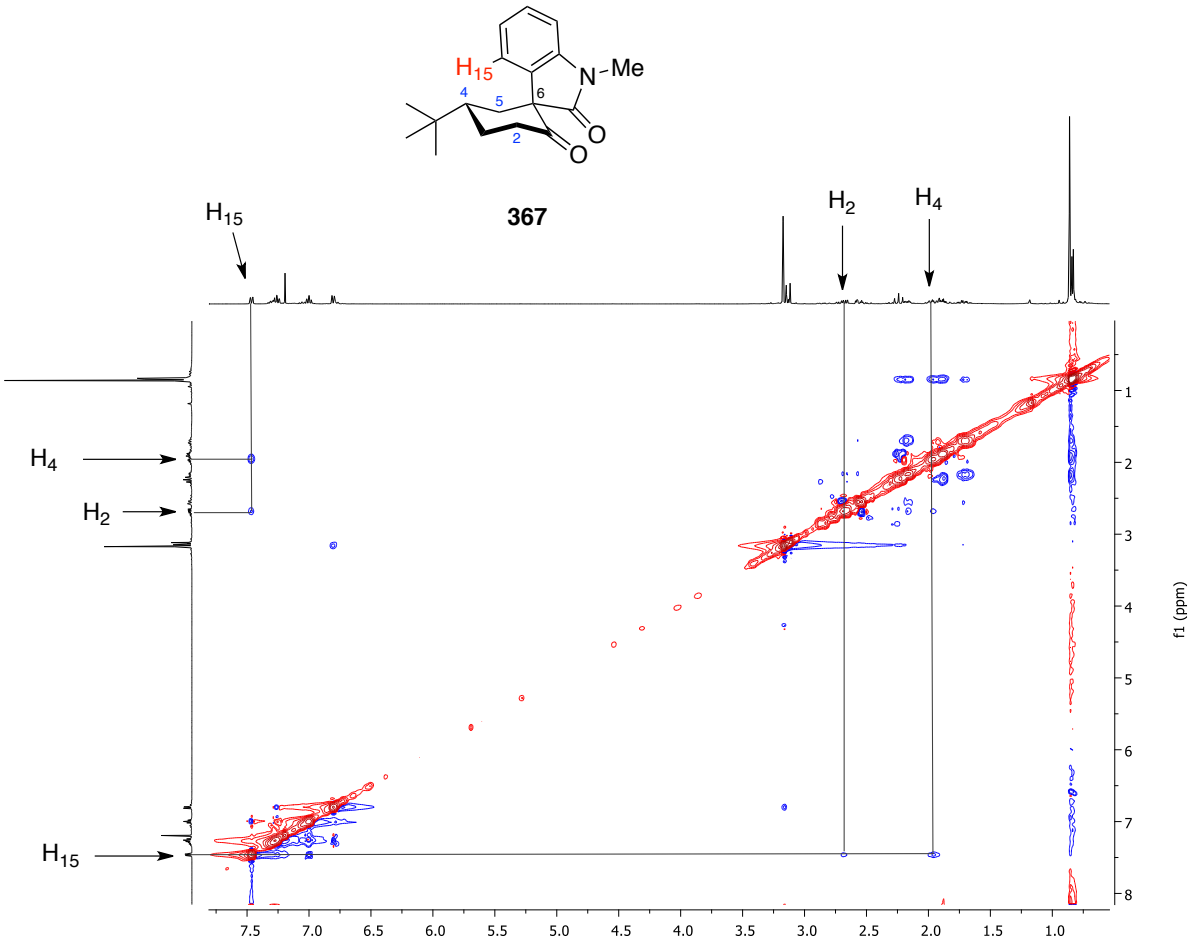
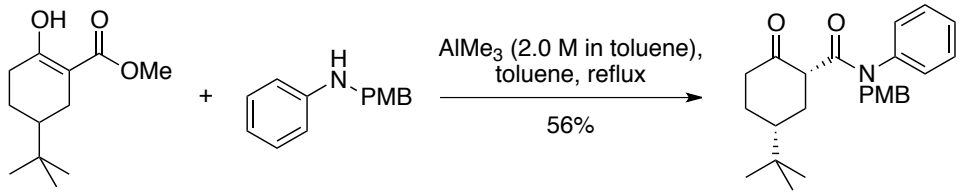


Figure 3.1

We were able to tentatively determine the stereochemistry at the spiro-oxindole position of **367** using an nOe experiment (Figure 3.1 shows the 2D NOESY spectrum of the 4:1 mixture of compound **367** and **368**). Correlations between H-15 of the major isomer **367** and some protons of the *tert*-butylcyclohexanone core (H-2 and H-4) suggested that the spiro-oxindole had the opposite stereochemistry to that required for the gelsemine structure (**5**). Nevertheless, the configuration of the oxindole structure was not our primary concern as Overman's group have shown that the stereochemistry can be corrected at a later stage *via* a retro-aldol rearrangement (See Section 1.6, Scheme 1.43).[45]

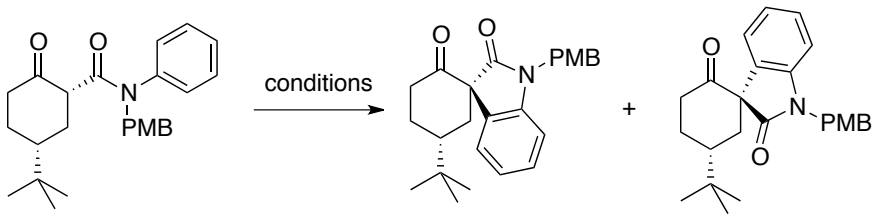
Although these results were promising, we needed to replace the N-Me with a more suitable protecting group. Recently Taylor and co-workers demonstrated that *para*-methoxybenzyl (PMB) and 2,4-dimethoxybenzyl (DMB) were suitable protecting groups for the copper-mediated cyclisation step.[146,150]



(±)-**363** (±)-**369** (±)-**370**

Scheme 3.21

The desired PMB-aniline **369** was prepared in two steps from commercially available aniline and was then treated with a 2.0 M solution of trimethyl aluminium in toluene in the presence of methyl enol ester **363**, as described before, furnishing the desired intermediate **370** in 56% yield as a single isomer (Scheme 3.21).



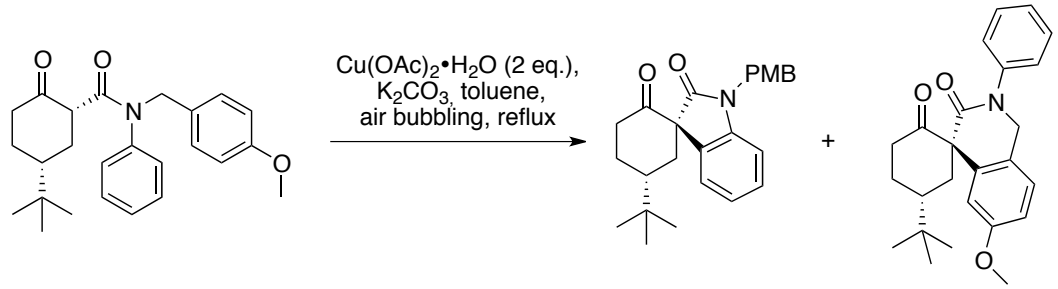
(±)-**370** (±)-**371** (±)-**372**

Entry	Conditions	Yield	d.r. 371 : 372
1	(2eq.) $Mn(OAc)_3 \bullet 2H_2O$, AcOH, reflux	degradation	-
2	(2eq.) $Cu(OAc)_2 \bullet H_2O$, toluene, air atmosphere, reflux	degradation	-
3	(2eq.) $Cu(OAc)_2 \bullet H_2O$, toluene, open to air, reflux	20%	3 : 1
4	(0.1eq.) $Cu(OAc)_2 \bullet H_2O$, toluene, open to air, reflux	40%	3 : 1
5	(2eq.) $Cu(OAc)_2 \bullet H_2O$, toluene, bubbling air, reflux	37%	2 : 1
6	**(0.1eq.) $Cu(OAc)_2 \bullet H_2O$, toluene, bubbling air, reflux**	**51%**	**4 : 1**

Table 3.3

Disappointingly, degradation was observed upon treatment of compound **370** with our previous conditions (Entries 1-2, Table 3.3). Opening the system to air increased the conversion of the reaction and furnished **371** and **372** in 20% yield along with some anisaldehyde, possibly formed by re-oxidation of the PMB group after cleavage (Entry 3, Table 3.3). Reducing the amount of catalyst to 0.1 equivalent in an open system enhanced the yield but the same by-product was observed (Entry 4, Table 3.3). As a final attempt to solve this problem, air was bubbled through the reaction mixture to promote a fast re-oxidation of the copper species and reduce the cleavage of the protecting group (Entries 5-6, Table 3.3). Pleasingly, lowering the amount of copper(II) acetate monohydrate allowed us to isolate the desired product in 51% yield as a 4:1 mixture of diastereoisomers (**371** and **372**). Again, we were able to tentatively assign the stereochemistry of the oxindole using an nOe experiment, allowing us to identify that the spiro-oxindole had the same stereochemistry as the major N-Me oxindole **367** (Figure 3.1).

During this work, we also attempted the reaction under basic conditions. Given that our previous cyclisation did not proceed in the presence of potassium *tert*-butoxide (Table 3.2, *vide supra*), we selected potassium carbonate as a milder base.

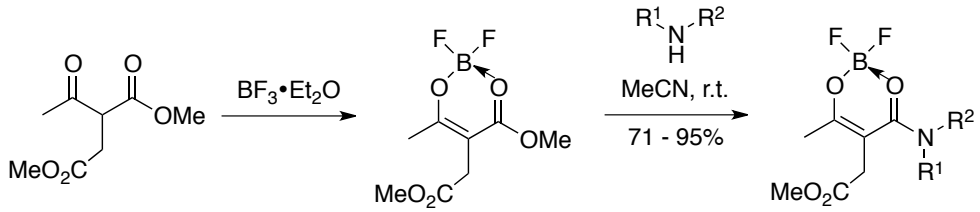


(±)-**370** (±)-**371** (33%) (±)-**373** (14%)

Scheme 3.22

Surprisingly, the expected spiro-oxindole **371** was isolated in 33% yield as a single isomer along with a new spiro-adduct **373** in 14% yield also as a single isomer (Scheme 3.22). We observed that the addition of potassium carbonate could affect the speed of the 5-*exo-trig* reaction allowing the undesired product arising from 6-*exo-trig* cyclisation to be formed. As before, the stereochemistry at the quaternary centre was tentatively assigned by nOe (using a 2D NOESY experiment).

While we were pleased with our cyclisation results, we were concerned that applying this methodology to the gelsemine core structure **240** would be challenging, as synthesis of the precursor would require a new intermediate possessing two ester groups that could affect the regioselectivity of the amide coupling. We hoped that, in the presence of a Lewis acid such as trimethyl aluminium, only one of the esters would be activated enough to react with the necessary protected aniline.

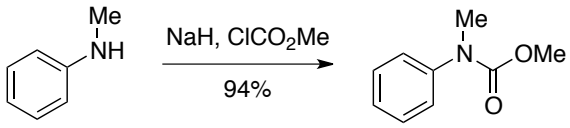


374 **375** **376**

Scheme 3.23

In 2007, Stefane and co-workers reported that in the presence of a Lewis acid it was possible to differentiate two methyl esters (Scheme 3.23).[157] Subjecting keto ester **374** to boron trifluoride diethyl etherate (BF_3•Et_2O) created a new boron difluoride complex (**375**) that activated the ester carbonyl group. The amine (R^1, R^2 = alkyl, aryl, H) reacted solely with the activated carbonyl group affording the desired *β*-keto amide **376**.

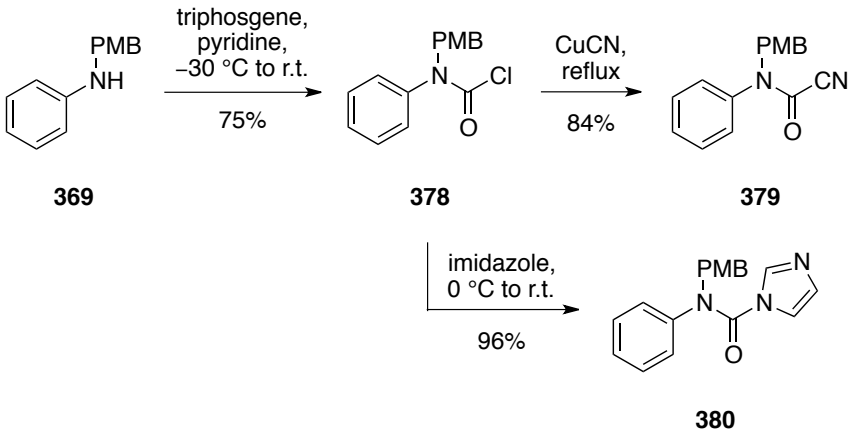
However, as we were not sure of the regioselectivity of the amide coupling, and bearing in mind our step efficient challenge, we hoped to couple the necessary acetanilide moiety in one step. As an attempt to solve the protecting group issue encountered while using phenyl isocyanate (Scheme 3.17 and Scheme 3.18, *vide supra*), we decided to synthesise some new acetanilide derivatives possessing a good leaving group (OMe, Cl, CN, imidazole).



365 **377**

Scheme 3.24

Carbamate **377** was easily prepared from commercially available *N*-methylaniline **365** and methyl chloroformate in high yield (Scheme 3.24).



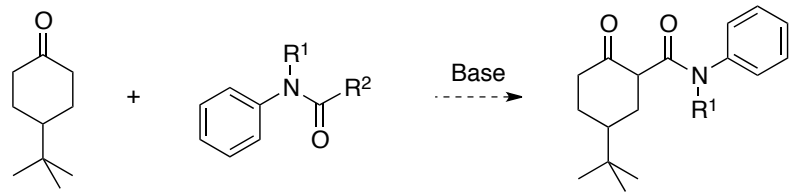
369 **378** **379** **380**

Scheme 3.25

In the same manner a chloride group was chosen as leaving group (Scheme 3.25). The carbamoyl chloride derivative **378** was accessible in 75% yield by reacting triphosgene with *N*-(4-methoxybenzyl)aniline **369** (prepared in two steps and 96% yield). We also designed a cyanoformamide derivative similar to Mander's reagent.[158] Cyanoformamide **379** was easily

obtained upon treatment of carbamoyl chloride **378** with copper cyanide. In 2005, Batey *et al*. reported that carbamoyl imidazole derivatives were as reactive as carbamoyl chloride reagents, but easier to synthesise and store.[159] Carbamoyl imidazole derivative **380** was prepared in 96 % yield by treating carbamoyl chloride derivative **378** with imidazole.

We then tried to perform a *C*-acylation reaction using our acetanilide derivatives and 4-*tert*-butylcyclohexanone **334**.



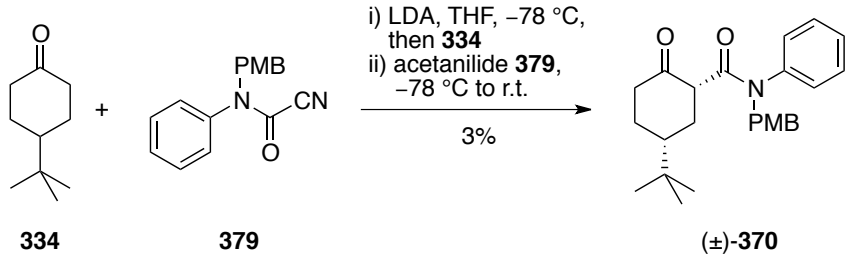
334

377, R^1 = Me, R^2 = OMe
378, R^1 = PMB, R^2 = Cl
380, R^1 = PMB, R^2 = $C_3H_3N_2$
381, R^1 = PMB, R^2 = OMe

367, R^1 = Me
370, R^1 = PMB

Scheme 3.26

Several conditions were attempted to synthesise the desired keto amide (**367** or **370**) (Scheme 3.26). Unfortunately, the desired product (**367** or **370**) was not isolated either using sodium bases (NaH or NaH / NaOMe (cat.), at room temperature or reflux) or lithium bases (LDA, LiTMP, in anhydrous THF, −78 °C to room temperature). Treatment of carbamoyl chloride **378** under the conditions reported by Corey *et al*. (NaH, MeOH (cat.), dry THF, hexane, reflux) led to the substitution of the chlorine with a methoxy group affording a new acetanilide **381**. Unfortunately, the same result was observed when subjecting **381** to the previous screening.

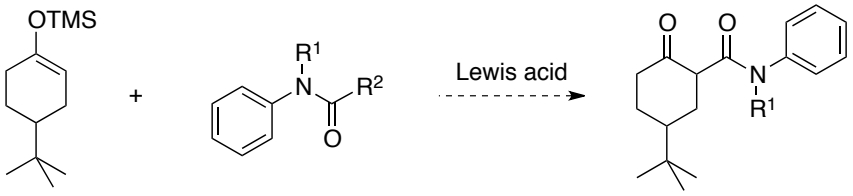


334 **379** (±)-**370**

Scheme 3.27

Our only success came when using cyanoformamide **379** with lithium di*iso*propylamide (LDA). We isolated the desired product **370** in 3% yield (Scheme 3.27). However, all attempts to increase the yield failed (equivalents of electrophile, slowly increasing the temperature or the reaction time).

Given this failure to perform the desired transformation in useful yield, we decided to attempt a Lewis acid mediated acylation of the corresponding silyl enol ether.



(±)-**382**

377, R^1 = Me, R^2 = OMe
378, R^1 = PMB, R^2 = Cl
379, R^1 = PMB, R^2 = CN
380, R^1 = PMB, R^2 = $C_3H_3N_2$
381, R^1 = PMB, R^2 = OMe

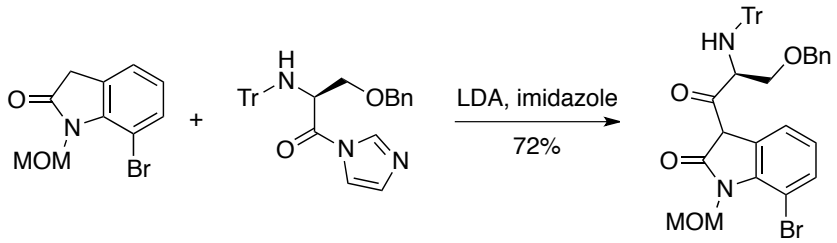
367, R^1 = Me
370, R^1 = PMB

Scheme 3.28

We started by converting our model study ketone **334** into the corresponding silyl enol ether **382** using lithium di*iso*propylamide (LDA) and trimethylsilyl chloride. Various Lewis acids were screened ($AgOTf/Ag_2CO_3$, AgOTf, $AlCl_3$, $BF_3•Et_2O$, $TiCl_4$, $ZnCl_2$) with our acetanilide derivatives. Unfortunately, formation of the desired *β*-keto amide (**367** or **370**) was not

observed and the starting ketone was recovered along with some degraded acetanilide (Scheme 3.28).

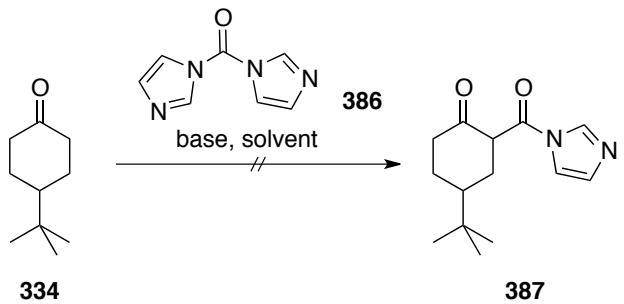
As we were unsuccessful with our one step procedure, we tried to replace the methyl ester with a more reactive group. In 2008, Konopelski's group proposed an acylation using an imidazole derivative.[160]



383 **384** **385**

Scheme 3.29

The *C*-acylation reaction between oxindole **383** and imidazole derivative **384** was performed in 72% yield using lithium imidazolide as a base formed *in situ* (Scheme 3.29). We attempted to perform the same type of conversion on our model study ketone (**334**) using 1,1-carbonyldiimidazole (CDI) as an electrophile.



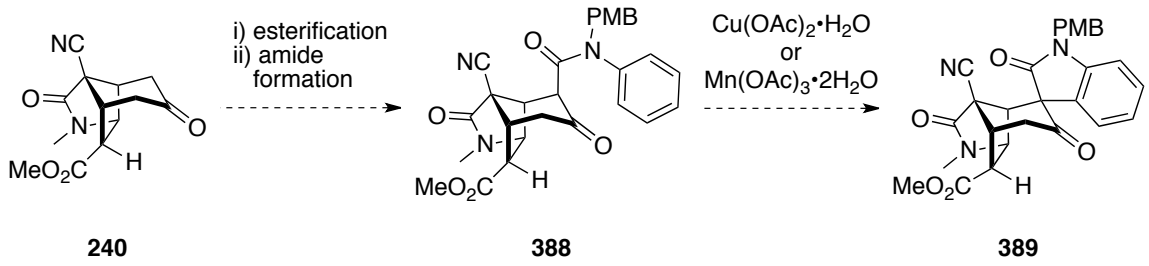
334 **387**

Scheme 3.30

Unfortunately, the desired acylation product **387** was not observed when treating 4-*tert*-butylcyclohexanone (**334**) and 1,1-carbonyldiimidazole (**386**) under Konopelski's conditions (LDA, imidazole). Various conditions using either lithium bases (LDA, LiTMP in anhydrous THF, −78 °C to room temperature) or sodium bases (NaH or NaH / NaOMe (cat.), anhydrous THF, at room temperature or reflux) were tried without success (Scheme 3.30).

3.4 Towards the Spiro-Oxindole Construction

After these fruitless one step *C*-acylation approaches, we decided to install the ester group on our gelsemine core structure **240** and hoped that our amide coupling step would proceed *via* a Lewis acid complex similar as the one reported by Stefane *et al*. as seen in Scheme 3.23.



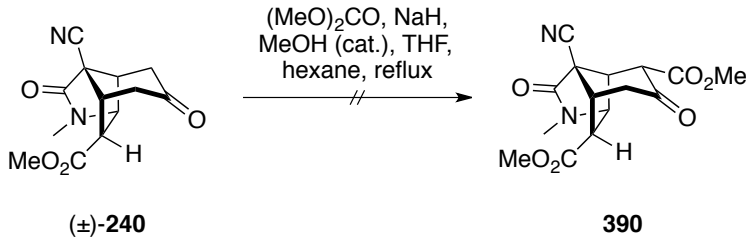
240 **388** **389**

Scheme 3.31

We hoped that esterification of the gelsemine core structure **240** would take place regioselectively affording the desired *β*-keto ester and further treatment with trimethyl aluminium and a protected anilide would furnish the *β*-keto amide **388**, which would undergo free-radical cyclisation with either manganese(III) acetate or copper(II) acetate to provide spiro-oxindole **389** (Scheme 3.31).

3.4.1 Formation of the β-Keto Ester

The gelsemine core **240** was subjected to the same esterification conditions as our model system, as seen in Scheme 3.19.

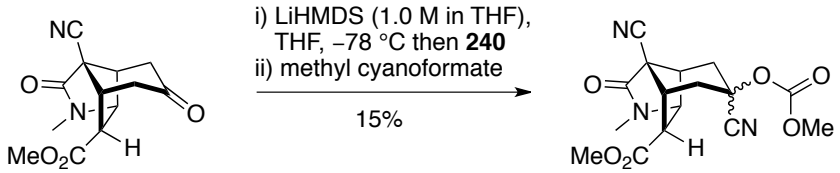


(±)-**240** **390**

Scheme 3.32

Unfortunately, Corey's conditions worked well on the model system but only degradation was observed when applied to our core structure **240** (Scheme 3.32). As an attempt to perform the desired transformation other similar thermodynamic conditions were tried using dimethyl carbonate as the electrophile (NaH, MeOH (cat.), dry THF, hexane, 0 °C to room temperature; NaH, dry THF, room temperature or reflux;[161] NaH, KH, dry THF, room temperature or reflux;[162] NaOMe, dry THF, room temperature or reflux) leading unfortunately to degradation of the starting material. To overcome this problem, modifications of the reaction temperature and procedure were tried. There are various methods and acylating agents that can be used to synthesise 1,3-dicarbonyl compounds but it is important to highlight that the regioselectivity of *O*-acylation / *C*-acylation is dependent on the substrate, the solvent, the temperature and the base.[163]

In 1983, Mander and co-workers reported a regio-controlled procedure involving the use of methyl cyanoformate to perform *C*-acylation of ketones.[158] The desired lithium enolate was formed at −78 °C by treating the ketone with a lithium base (LDA, LiTMP, LiHMDS) and methyl cyanoformate was then added furnishing the desired β-keto ester.

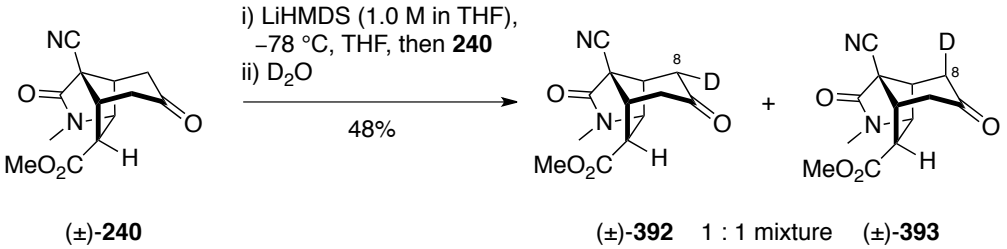


(±)-**240** (±)-**391**

Scheme 3.33

Subjecting our gelsemine core structure **240** to Mander's conditions disappointingly afforded a new cyanohydrin adduct **391** as a 5:1 mixture of diastereoisomers, along with degradation of the starting material (Scheme 3.33). The structure of **391** was assigned by NMR studies. The ^{13}C NMR showed peaks corresponding to a new ester group (CH_3 and CO), a quaternary carbon and two cyanide peaks (117.8 ppm and 114.7 ppm) but no ketone peak around 200 ppm. This assignment was supported by mass spectrometry ($[C_{16}H_{17}N_3O_6+Na]^+$: 370.1015, found: 370.1013). The reaction was repeated using LDA with or without hexamethylphosphoramide (HMPA) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (DMPU), giving the same result. Several papers have reported cyanohydrin formation while using Mander's reagent.[164,165] Fortunately, basic treatment of cyanohydrin **391** (1 drop of 2.0 M sodium hydroxide, water, room temperature overnight) allowed us to recover our starting material (**240**) in quantitative yield.[166-168]

To ensure enolate formation was occurring and finally determine the regioselectivity of the reaction, we tried a deuterium quench procedure.



Scheme 3.34

The gelsemine core structure **240** was treated with lithium bis(trimethylsilyl)amide (LiHMDS) at −78 °C and then quenched after 30 minutes with deuterium oxide, pleasingly affording the desired product in 48 % yield as a 1:1 mixture of isotopomers (**392** and **393**) at the C-8 position, along with degradation of the starting material (Scheme 3.34). The position of the deuterium was determined by NMR studies.

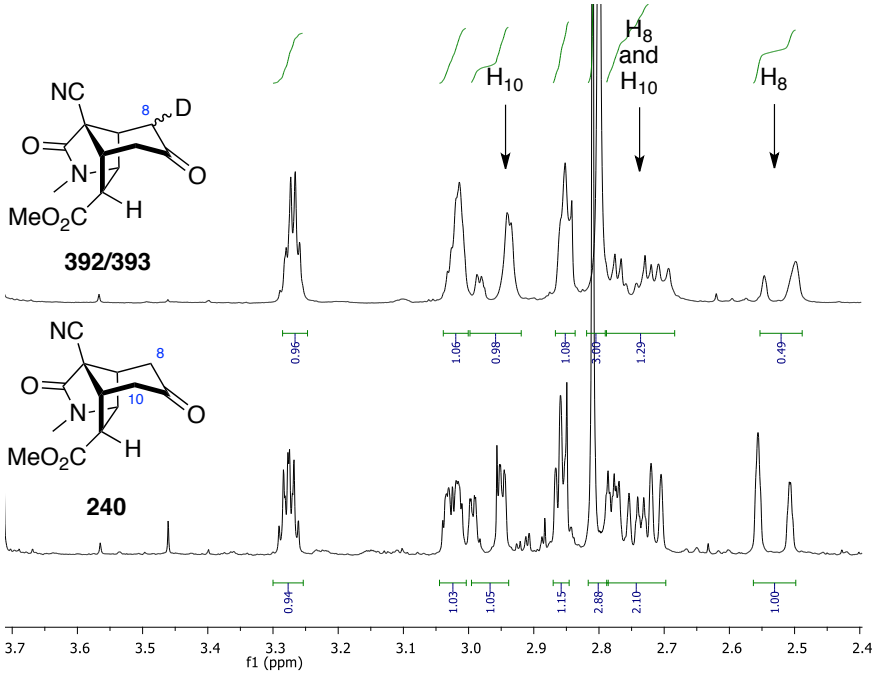


Figure 3.2

The ^{1}H NMR spectroscopy showed a modification of the C-8 position (Figure 3.2). The doublet at 2.54 ppm diminished by half along with the multiplet around 2.71 ppm, suggesting

that the desired product exists as a mixture of **392** and **393**. However, the ^{1}H NMR spectra is not entirely clear about the regioselectivity of the deuteration as the signal corresponding to the remaining C-10 proton at 2.75 ppm seems obscured by the N-methyl peak.

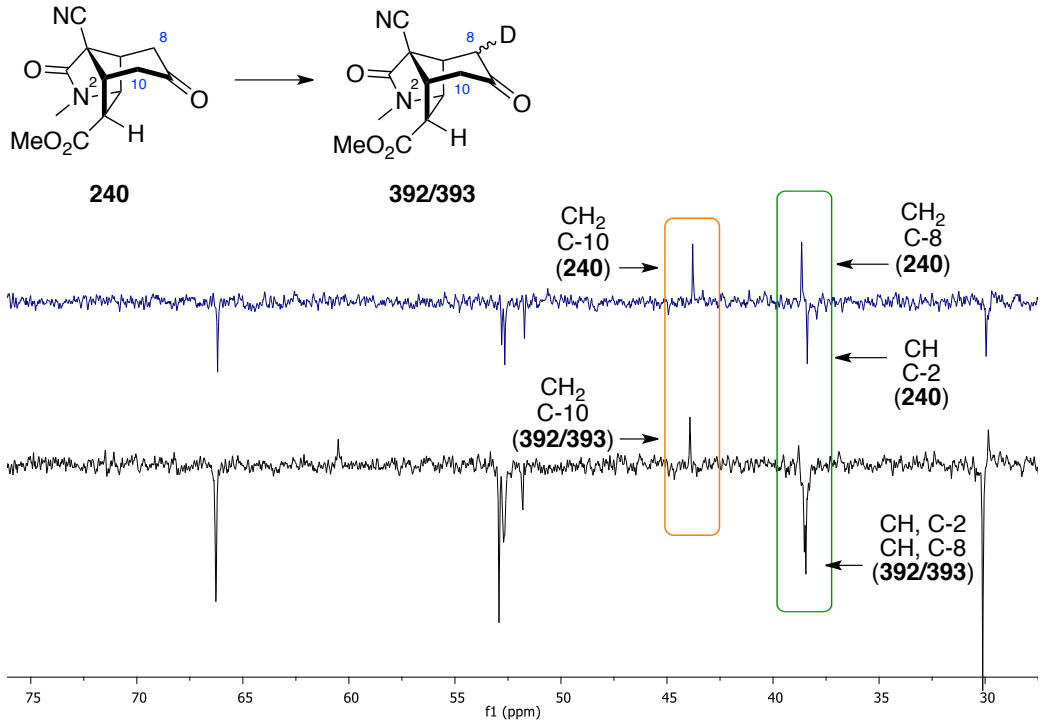
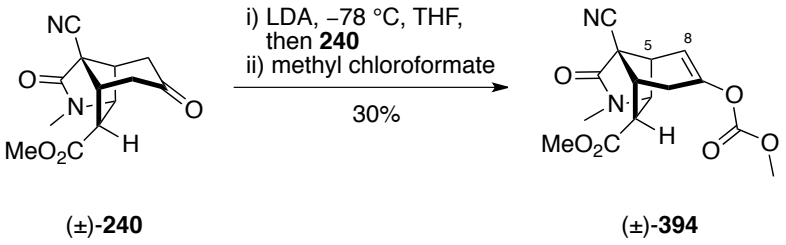


Figure 3.3

Fortunately, the ^{13}C NMR spectra allowed us to attribute the regioselectivity of the reaction without ambiguity by using the PENDANT pulse sequence (Figure 3.3). It is clear by comparing the carbon spectra from the starting material **240** and the product **392** / **393** that the CH_2 at the C-8 position is unequivocally deuterated, while the CH_2 at the C-10 position remains unchanged.

As the deuterium quench procedure proved that the enolate formation was occurring regioselectively at the desired position, we tried other acylating agents.

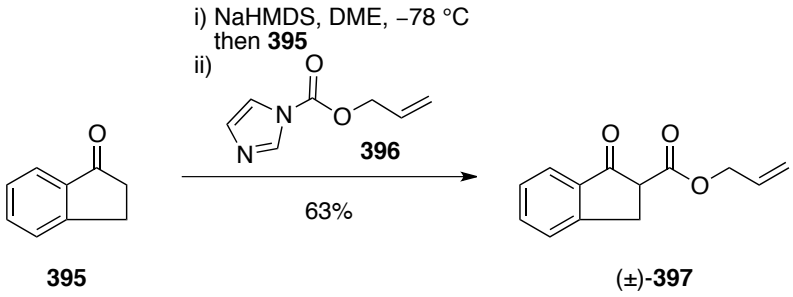


(±)-**240** (±)-**394**

Scheme 3.35

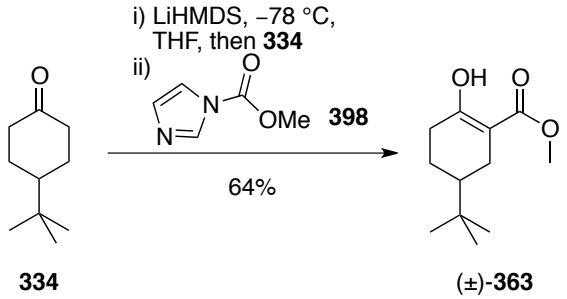
As Mander's reagent failed to provide the desired *β*-keto ester, we chose to perform the reaction with methyl chloroformate,[169,170] even though acid chlorides are usually difficult to handle and can give mixtures of *O*-acylation and *C*-acylation.[171] The core structure **240** was treated with lithium di*iso*propylamide (LDA) and the enolate was quenched with methyl chloroformate furnishing the *O*-acylated product **394** in 30% yield along with degradation of the starting material **240** (Scheme 3.35). The structural assignment of compound **394** was carried out by NMR studies. The ^{1}H NMR spectra showed a doublet at 5.57 ppm indicating the presence of a double bond. The signal was attributed to the presence of a CH group at the C-8 position as the COSY spectra demonstrated a coupling between H-8 and H-5. A new methyl peak was also observed at 3.73 ppm and the ketone peak at 203 ppm (^{13}C NMR spectroscopy) was absent. Unfortunately, the *C*-acylated adduct was not formed during the reaction or not stable enough and decomposed during the work-up.[158] Next, we turned our attention towards a different type of acylating agent, the *N*-acylimidazole.

An early report from Kurozumi *et al*. showed that *N*-acylimidazole derivatives are good electrophiles for *C*-acylation reactions.[172] Recently, Trost and co-workers carried out some methodology studies using *N*-acylimidazole derivatives.[173,174]



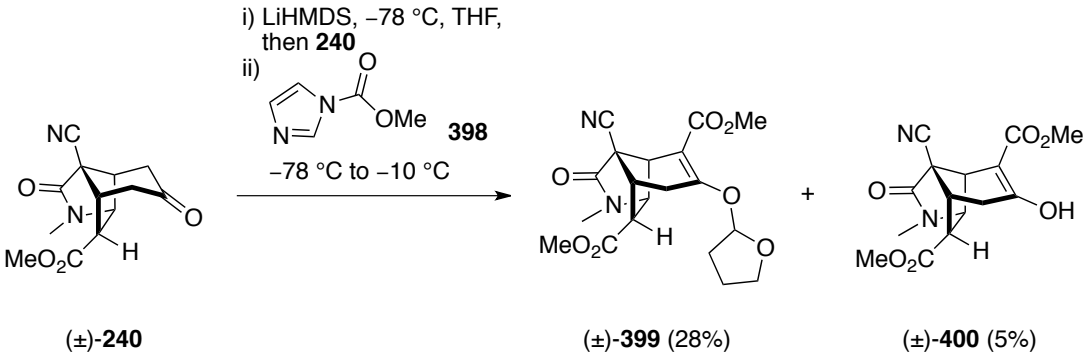
Scheme 3.36

Treatment of the sodium enolate of ketone **395** with the allylimidazole carboxylate **396** furnished the desired *C*-acylation product **397** in 63% yield (Scheme 3.36). Various ketone enolates and electrophiles were screened giving the corresponding 1,3-dicarbonyl compounds in good yields. We decided to apply this methodology to our substrate and started by synthesising the necessary imidazole carboxylate (**398**) by adding methyl chloroformate to a solution of imidazole at 0 °C.



Scheme 3.37

Treatment of the sodium enolate of 4-*tert*-butylcyclohexanone **334** with imidazole methyl ester **398** under Trost's conditions (NaHMDS, anhydrous DME, −78 °C) did not afford the desired keto ester (**363**). Modifications of the reaction conditions such as the solvent (THF instead of DME) and the base (LiHMDS instead of NaHMDS) led to the formation of the desired product **363** as the enol form, in 64% yield (Scheme 3.37).



Scheme 3.38

Subjecting the lithium enolate of the gelsemine core structure **240** to imidazole methyl ester **398** afforded the desired compound **400** as an enol form (characterised by a signal in the ^{1}H NMR spectra at 12.3 ppm) in 5% yield along with starting material (37% yield) and a new compound **399** in 28% yield (Scheme 3.38). Unfortunately, none of our modifications improved the yield towards the desired product **400** (temperature, reaction time, LDA instead of LiHMDS, anhydrous diethyl ether instead of dry tetrahydrofuran). Surprisingly, the mass spectrum from compound **399** suggested the presence of the methyl ester (3.80 ppm) and insertion of tetrahydrofuran.

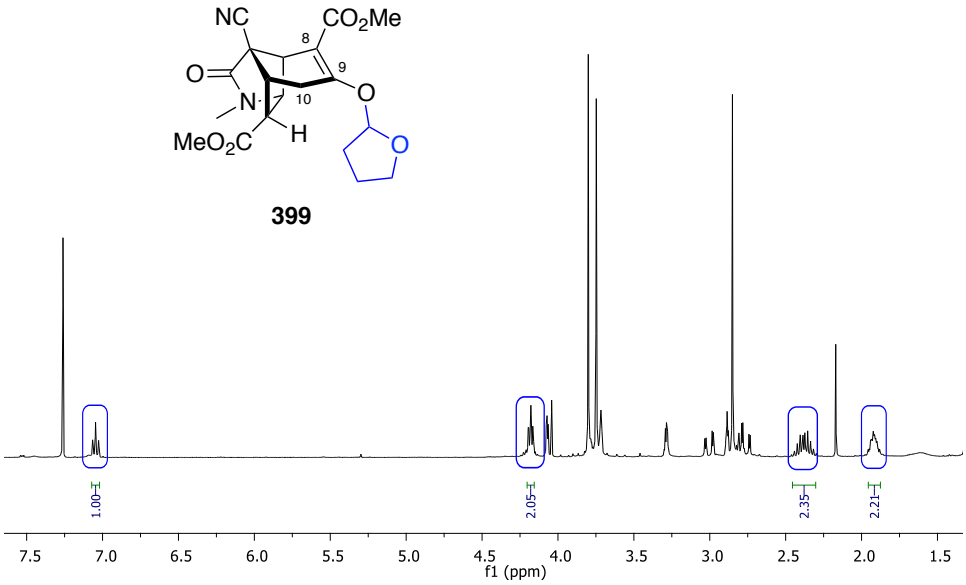


Figure 3.4

The ^{1}H NMR spectroscopy showed characteristic signals of a substituted tetrahydrofuran ring, highlighted in blue in Figure 3.4. As the tetrahydrofuran signals showed no apparent coupling with the protons of the core structure we concluded that the tetrahydrofuran ring had possibly reacted with the ketone. This was supported by the absence of the ketone peak at 203 ppm (^{13}C NMR spectroscopy). We supposed that the methyl ester was introduced by *C*-acylation at the C-8 position. The ^{13}C NMR spectra also demonstrated the presence of a quaternary carbon at 130.8 ppm suggesting the presence of a double bond signal attributed to the C-8 position as no CH peak corresponded to this position.

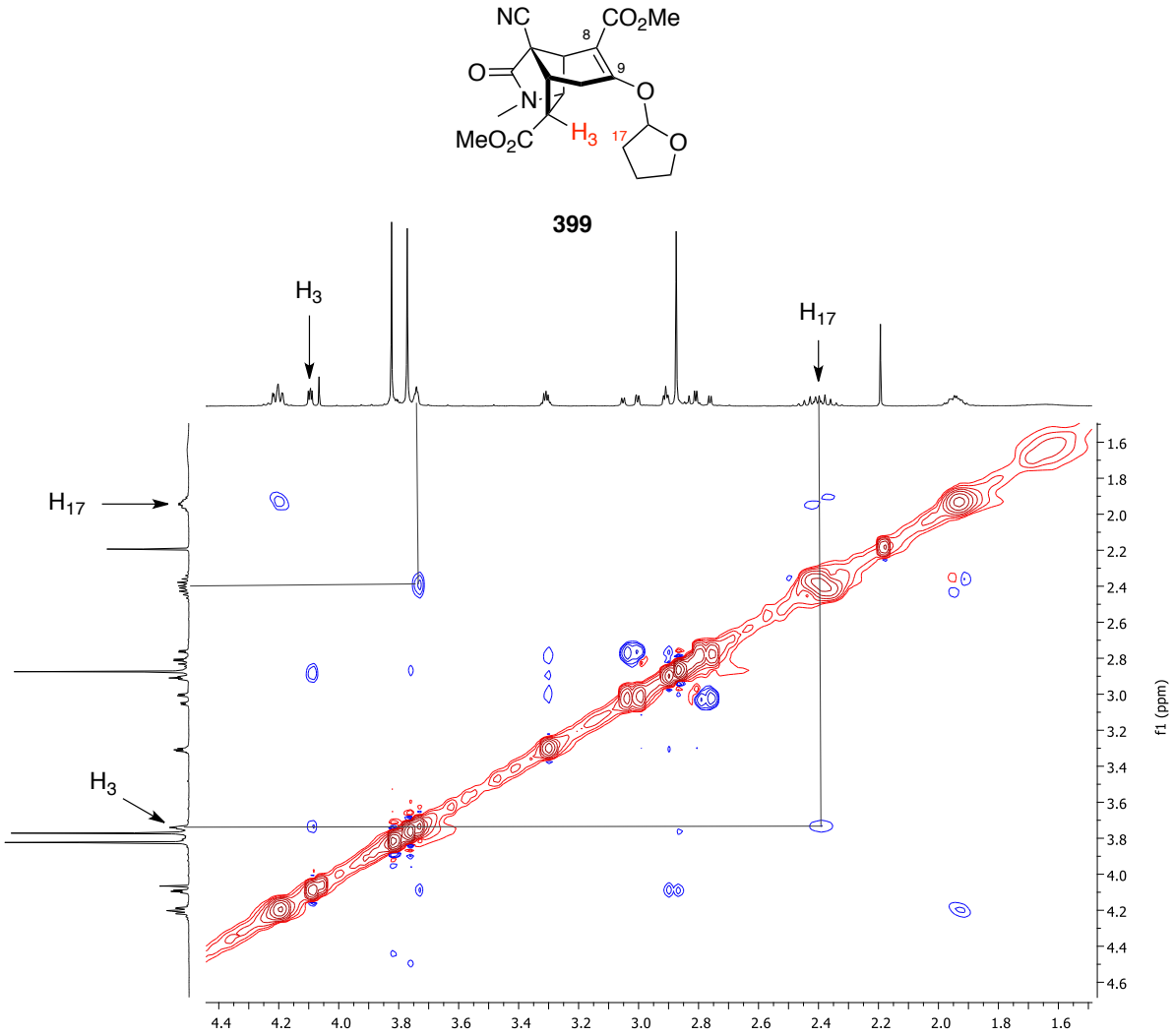
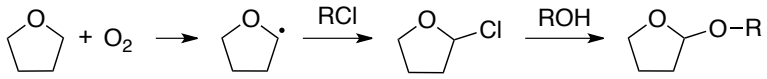


Figure 3.5

The nOe experiment seemed to confirm the assignments, demonstrating a correlation between H-17 on the tetrahydrofuran ring and H-3 of the core structure (Figure 3.5 shows the 2D NOESY spectrum of compound **399**).

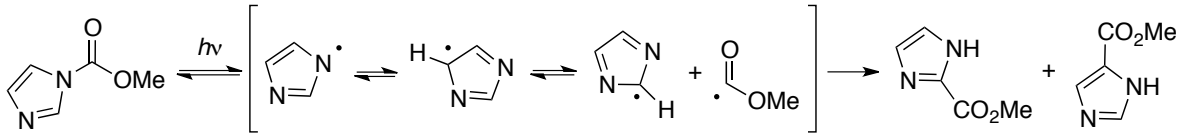
The formation of tetrahydrofuranyl ethers has previously been reported by Troisi's and Mioskowski's groups.[175,176]



401 **402** **403** **404**

Scheme 3.39

Both groups proposed a radical mechanism involving formation of a radical at the two position of the tetrahydrofuran initiated by atmospheric oxygen (Scheme 3.39). The furanyl radical **402** reacts with an organo-chloride to give a new furanyl chloride **403** that furnishes the desired tetrahydrofuranyl ether **404** by addition of an alcohol. In our case, the presence of an imidazole carboxylate might promote this pathway.



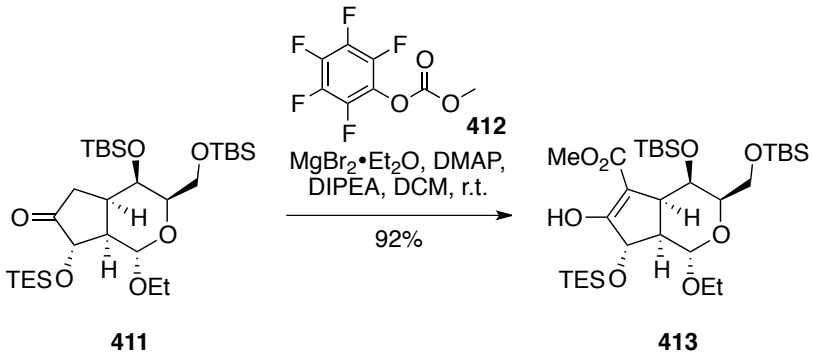
398 **405** **406** **407** **408** **409** **410**

Scheme 3.40

In 1976, Iwasaki reported a photo-rearrangement of imidazole carboxylate leading to the formation of imidazole radicals (Scheme 3.40).[177] Consistent with photo-induced radical formation, we performed the reaction in the dark and observed only degradation of the

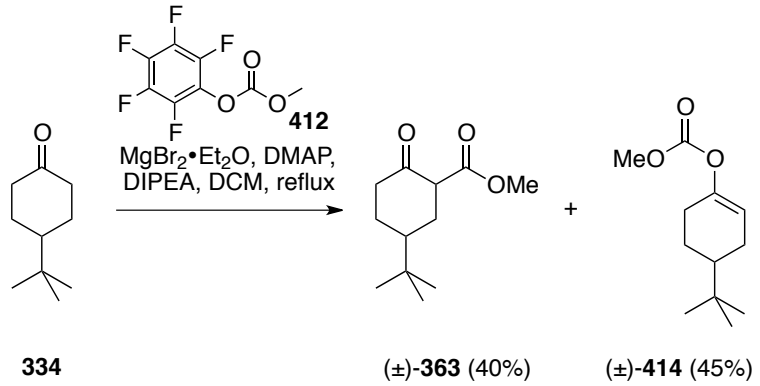
starting material. Attempts to remove the tetrahydrofuran ring (**399)** by acid mediated treatment led, unfortunately, to degradation.

In 2013, Hale and co-workers reported difficulties attempting a key *C*-acylation in the synthesis of (−)-echinosporin.[168,178] Attempts to install an ester group alpha to the ketone using LiHMDS or KMHDS and a suitable electrophile (methyl chloroformate, methyl cyanoformate, imidazole carboxylate) produced either the desired product in low yield or undesired by-products. Their best result was obtained when treating their starting material under Coltart's "soft" enolisation conditions.[179]



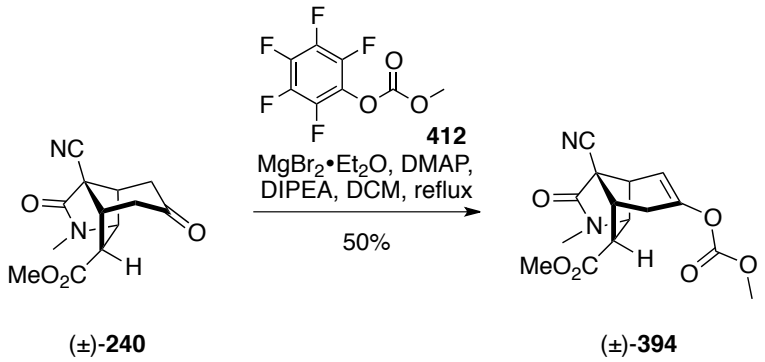
Scheme 3.41

A bromomagnesium enolate was obtained when ketone **411** was treated with magnesium bromide ethyl etherate and DIPEA (Hünig's base). The resulting enolate was then treated with methyl pentafluorophenylcarbonate **412** and DMAP to afford the desired enol ester **413** in 92% yield (Scheme 3.41). Methyl pentafluorophenylcarbonate **412** was easily synthesised in 77% yield by subjecting pentafluorophenol to methyl chloroformate in the presence of *N*-methylmorpholine.



Scheme 3.42

Treatment of 4-*tert*-butylcyclohexanone **334** under Hale's conditions afforded a 1:1 mixture of ester **363** and carbonate **414** by ^{1}H NMR (Scheme 3.42). This result was in accordance with Hale's observations using a simple cyclohexanone as starting material, when a mixture of keto ester (24% yield) and carbonate adduct (63% yield) was obtained. However, given the difference of reactivity of our core structure compared to our model system, we tried to apply the conditions to our gelsemine core structure **240**.



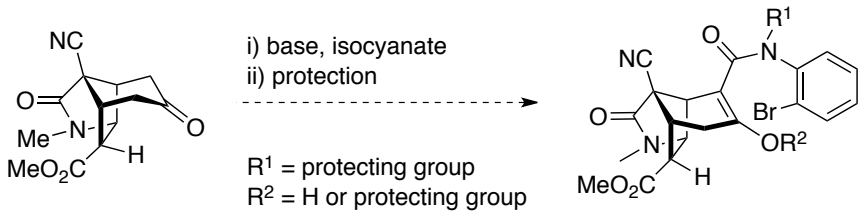
Scheme 3.43

Unfortunately, no conversion was observed when treating the bromomagnesium enolate of the gelsemine core structure **240** with methyl pentafluorophenylcarbonate **412** in the presence of DMAP at room temperature under nitrogen. Frustratingly, increasing the temperature to

reflux furnished solely carbonate **394** along with some recovery of starting material (Scheme 3.43).

3.4.2 Formation of the Keto Amide

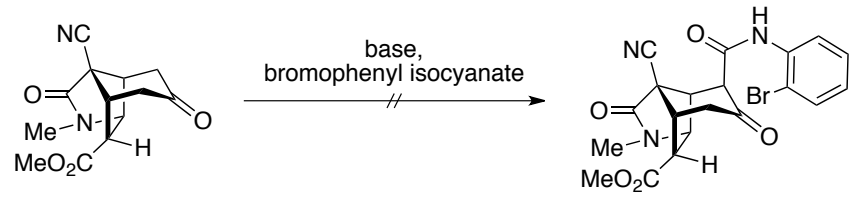
After these fruitless attempts to add a methyl ester group, we decided to install a phenyl amide group on our gelsemine core structure **240** using bromophenyl isocyanate. We hoped we would be able to carry out a series of regioselective protections to afford the desired precursor for the spiro-oxindole.



240 **415**

Scheme 3.44

As seen in Section 1.5, we hoped to add bromophenyl isocyanate and proceed to the spiro-oxindole cyclisation after protecting the anilide and perhaps the ketone, in the same manner as Hart and co-workers and Aubé *et al*. (Scheme 3.44).[17,23]



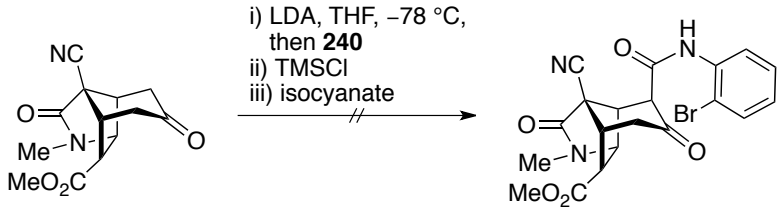
(±)-240 **416**

Scheme 3.45

We first attempted to perform the *C*-acylation with bromophenyl isocyanate on the gelsemine core structure **240** using the conditions seen in Hart's synthesis of 21-oxogelsemine (NaH,

KH, dry THF, room temperature or reflux; NaH, dry THF, room temperature or reflux), leading to full degradation of the starting material (Scheme 3.45).[23] In an attempt to overcome the degradation issue we tried to perform the *C*-acylation of bromophenyl isocyanate under Aubé's conditions (LiHMDS, anhydrous THF, −78 °C) with unfortunately the same results.[17]

As the direct *C*-acylation appeared difficult we moved to a two-step addition of bromophenyl isocyanate (Scheme 3.46).



Scheme 3.46

Reports in the literature showed that it is possible to couple a silyl enol ether and an isocyanate under neat conditions or in the presence of an organozinc (dimethyl zinc).[180,181] Unfortunately, treatment of the gelsemine core **240** with a lithium base (LDA, LiHMDS) in the presence of trimethylsilyl chloride, followed by addition of bromophenyl isocyanate led to degradation of the starting material and formation of a urea adduct by reaction of bromophenyl isocyanate with di*iso*propylamide as seen in Section 3.3.3. Likewise, we found several reports using an enamine intermediate instead of silyl enol ether.[182-188] The desired transformation was unsuccessful in our hands (pyrrolidine, then addition of bromophenyl isocyanate or methyl chloroformate, room temperature) affording full recovery of starting material.

3.5 Summary

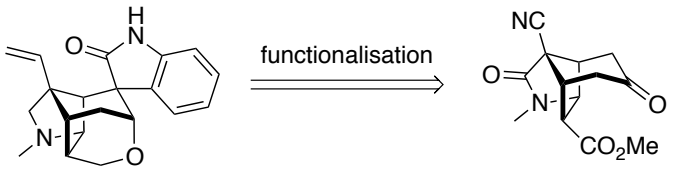
Both approaches, α-arylation and C–H activation, were carried out on our model system giving some interesting results. First the α-arylation of 4-*tert*-butylcyclohexanone **334** using different haloacetanilides was unsuccessful but a one-pot synthesis of indole was found. Instead, a spiro-oxindole construction adjacent to a ketone was developed using a metal catalysed free-radical C–H activation providing oxindoles **367** and **371** in good yield. Application of this methodology to the gelsemine core structure **240** proved challenging due to a lack of stability and unexpected reactivity of the core to a variety of bases and electrophiles.

Chapter 4

Towards Gelsemine

4.1 Introduction

As discussed in Chapter 2, we hoped that gelsemine (**5**) would arise by functionalisation of the core structure **241** as highlighted below in Scheme 4.1.



5 **241**

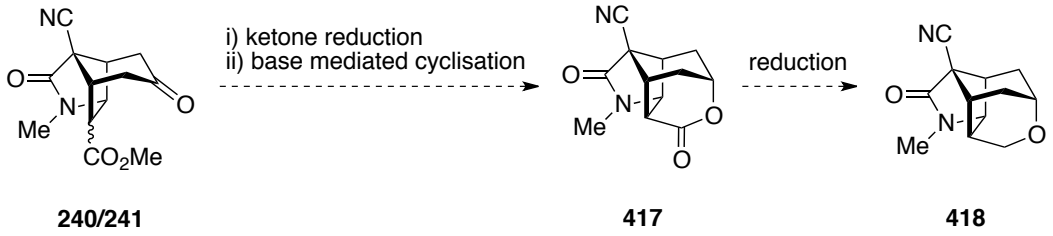
Scheme 4.1

According to our retrosynthetic analysis gelsemine (**5**) would arise from core **241** by installation of the spiro-oxindole, formation of the tetrahydropyran ring, reduction of the pyrrolidinone into the corresponding pyrrolidine ring and finally transformation of the nitrile group into a vinyl group (Scheme 4.1). In this Chapter we describe some modifications of the gelsemine core structure towards gelsemine (**5**).

4.2 Strategy Towards the Tetrahydropyran Ring

As described in Section 1.6 different approaches were implemented in previous gelsemine syntheses to construct the tetrahydropyran ring: a base-catalysed ether transformation (Fleming's transformation),[16] an oxymercuration (Speckamp's, Danishefsky's and

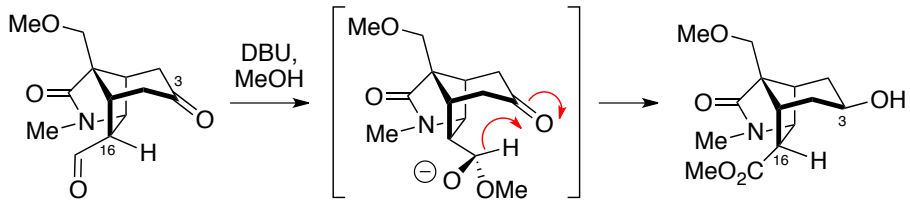
Fukuyama's approaches)[18,19,27,51] or the formation of a lactone or a hemiacetal intermediate (Hart's and Overman's method).[20,23]



240/241 **417** **418**

Scheme 4.2

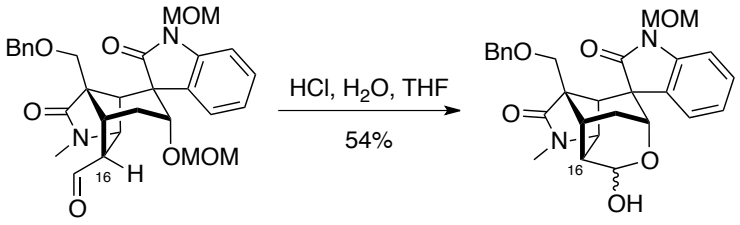
Our initial approach consisted of reducing ketones **240** / **241** to the corresponding axial alcohol followed by treatment with base to initiate the cyclisation with the ester to furnish lactone **417**. This would be readily transformed into the desired tetrahydropyran ring by a further reduction (Scheme 4.2). Although this route seemed straightforward, we were unsure of the effect the ester stereochemistry would have on the lactone formation.



(±)-**419** (±)-**420** (±)-**421**

Scheme 4.3

Interestingly, in 1997, Hart's group attempted to epimerise the C-16 position of compound **419** with DBU in methanol, hoping to generate an intermediate such as **420** under basic conditions and reach the tetrahydropyran ring (Scheme 4.3). Surprisingly, subjecting **419** to an *in situ* source of methoxide gave the hydroxy ester **421**, possessing an *exo* ester, in 58% yield, instead of the desired acetal. This result helped Hart and co-workers to revise their conditions and develop a "trap" procedure.



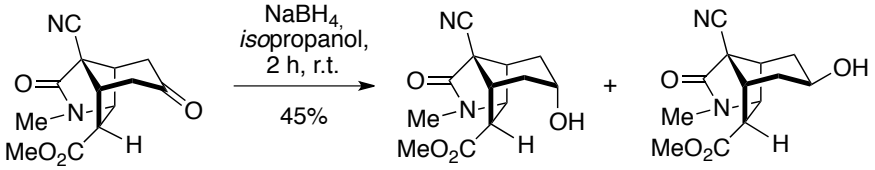
(±)-**422** (±)-**423**

Scheme 4.4

The "trapping" idea consisted of using an axial alcohol to promote the epimerisation at the C-16 position and was successfully employed by Hart's group.[23,24] Acidic treatment of **422** promoted methoxymethyl (MOM) group removal releasing the axial alcohol, which trapped the slowly epimerising aldehyde to give the desired hemiacetal **423** (Scheme 4.4).

4.2.1 Ketone Reduction

The same principle was applied to our core structure **240**.



(±)-**240** (±)-**424** d.r. 4 : 1 (±)-**425**

Scheme 4.5

Ketone **240** was readily reduced upon treatment with sodium borohydride in *iso*propanol, affording a 4:1 mixture of diastereoisomers **424** and **425** (Scheme 4.5). However, the reaction was somewhat sluggish and some starting material remained after 1 hour. Nevertheless, we were pleased to find that the major isomer had the desired stereochemistry as determined by an nOe experiment (Figure 4.1).

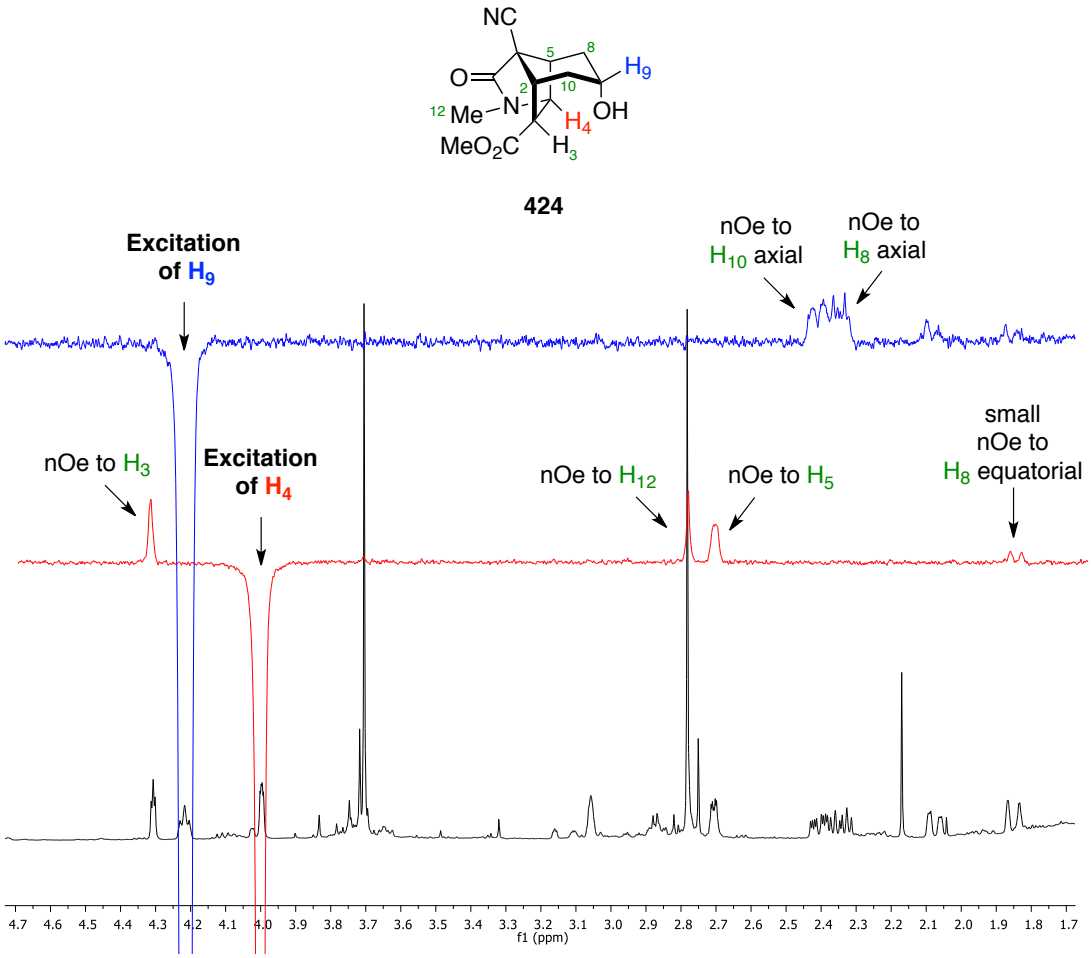
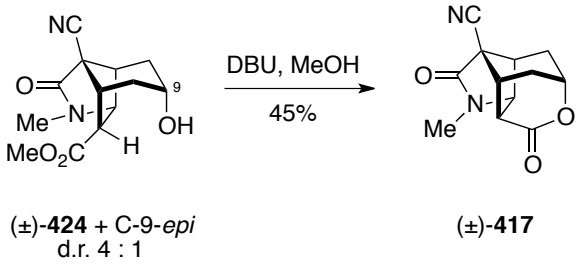


Figure 4.1

Excitation of H-9 of the major isomer **424** showed an nOe to both H-8 axial and H-10 axial, helping us to determine that the alcohol was axial (Figure 4.1). Further nOe experiments were used to confirm the position of the ester group at this stage. Excitation of H-4 showed an nOe correlation to H-3 confirming that the ester group was still *exo*.

4.2.2 Lactone Formation

Once the structure of the major isomer **424** was assigned the "trapping" procedure was attempted. We hoped that in the presence of base the axial alcohol would promote the epimerisation of the ester leading to the formation of the desired lactone.

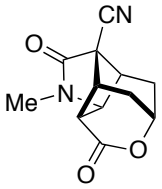


(±)-**424** + C-9-*epi*
d.r. 4 : 1

(±)-**417**

Scheme 4.6

Pleasingly, the slow epimerisation of the *exo* ester was possible in the presence of the axial alcohol. Upon treatment of the 4:1 mixture of alcohols (**424** and **425**) with DBU in methanol, the cyclisation afforded the desired lactone **417** in 45% yield (Scheme 4.6).



417

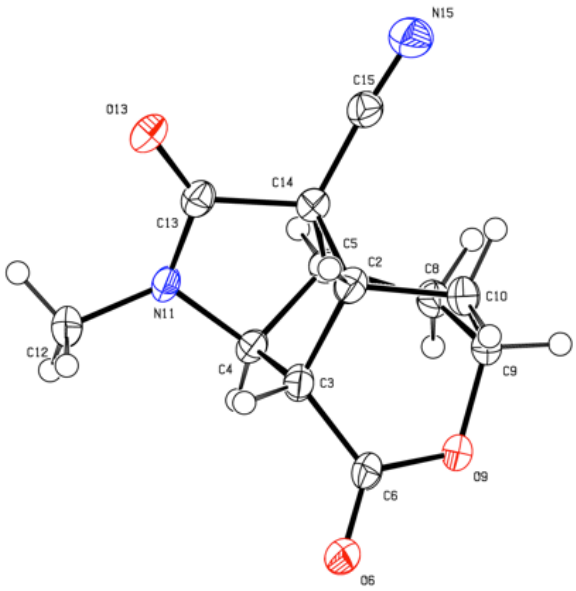
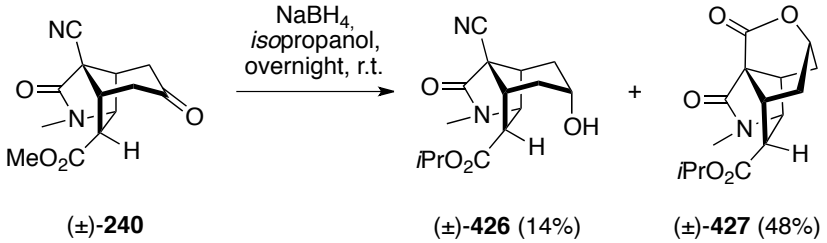


Figure 4.2

Pleasingly, thanks to the crystallographers of the University of Southampton and the calculations of Louise Male at the University of Birmingham, the structure of **417** was confirmed by X-ray crystallography as seen in Figure 4.2.

4.2.3 Optimisation Studies

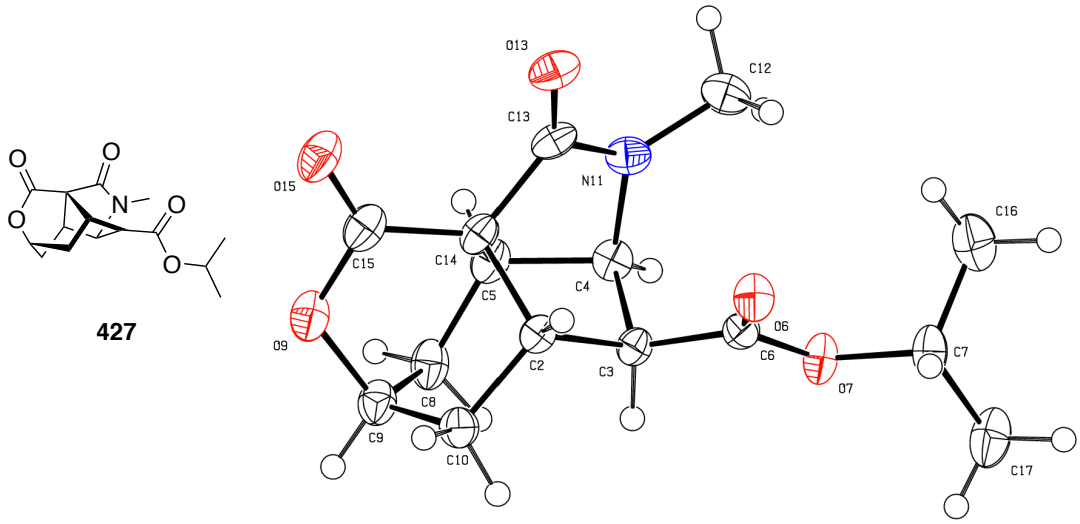
While we were investigating the optimal conditions to reduce ketone **240** in good yield we found that both the reaction time and the solvent were important.



(±)-**240** (±)-**426** (14%) (±)-**427** (48%)

Scheme 4.7

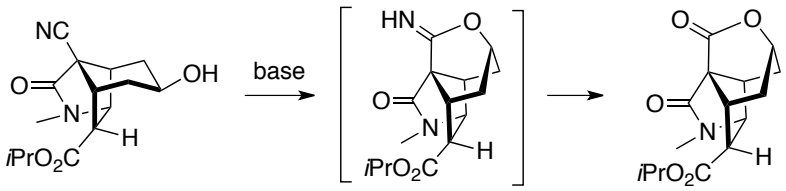
Surprisingly, subjecting ketone **240** to sodium borohydride in *iso*propanol overnight gave two new compounds **426** and **427** in 14% and 48% yields respectively (Scheme 4.7). The minor product **426** was identified as the axial alcohol possessing an *iso*propyl ester due to a transesterification with the reaction solvent (the stereochemistry was tentatively assigned by comparison of the chemical shifts with those of compound **417**). The second product **427** seemed also to have undergone transesterification as the isopropyl signals where evident at 5.04 ppm (CH) and 1.28 ppm (two methyl peaks) on the ^{1}H NMR spectra, but the nitrile peak usually observed at approximately 116 ppm was missing on the ^{13}C NMR spectra. Fortunately, thanks to the crystallographers of the University of Southampton and the calculations of Louise Male at the University of Birmingham, the structure of **427** was assigned by X-ray crystallographic analysis (Figure 4.3).



427

Figure 4.3

The X-ray crystallography confirmed that the methyl ester underwent transesterification (as for compound **426**) without modification of the stereochemistry at the ester position furnishing a new *exo isopropyl* ester as seen Figure 4.3. The structure also showed that the reduction of the ketone presumably gave a mixture of alcohols with the equatorial cyclising onto the nitrile to give a new lactone (Scheme 4.7).



(±)-**428** (±)-**429** (±)-**427**

Scheme 4.8

Based on this result we proposed a possible mechanism for the transformation (Scheme 4.8). We supposed that ketone **240** was reduced furnishing a mixture of axial alcohol **426** (Scheme 4.7) and equatorial alcohol **428**. The equatorial alcohol **428** was then able to cyclise onto the nitrile in the presence of small amounts of sodium hydroxide formed during the reaction, furnishing a hexacyclic imidate (**429**). The imidate (**429**) readily hydrolysed to the lactone

427 during the reaction as seen in Scheme 4.8, in a similar fashion to Overman's lactone protocol (Scheme 1.43).[20]

The formation of lactone **427** is puzzling (Scheme 4.7). The reaction was repeated in methanol to avoid the transesterification and followed by ^{1}H NMR spectroscopy. The reaction was somewhat sluggish in methanol, but after two days a lactone corresponding to **427**, possessing a methyl ester, was observed. It was unclear to us how leaving the reaction overnight could change the outcome and afford a lactone such as **427** as a major product. Unfortunately, we have not found any convincing rationale to explain these results.

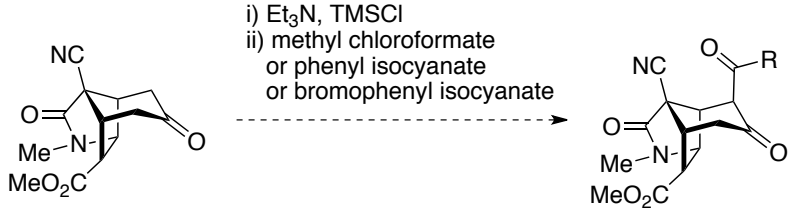
4.2.4 Summary

Reduction of ketone **240** to the corresponding axial alcohol **424** generated a powerful "trap" allowing epimerisation of the *exo* ester and formation of the desired tetrahydropyran precursor **417** in a one-pot procedure. Interestingly, extended reaction times in the reduction step led to a new rearrangement furnishing a rather hindered lactone **427** assigned with the help of X-ray crystallography.

4.3 Conclusion and Future Work

The highly functionalised hexacyclic skeleton of gelsemine **5** has attracted the attention of numerous research groups over the years and generated eight total syntheses. Although we did not reach our goal to complete the total synthesis of gelsemine, we improved our previous route to the gelsemine core structure **240** (12% yield over seven steps from furan-3-methanol **221**). This protecting group-free route involved a novel direct access to α,β-unsaturated ester **233** and a shortened conversion of the bridge-swap adducts to the core.

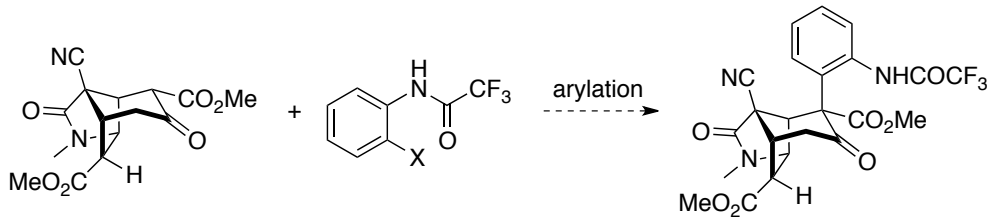
Two novel strategies were envisaged to install the spiro-oxindole on the gelsemine core structure: an α-arylation or a C–H activation. Although the α-arylation in the presence of different haloacetanilides was unsuccessful on our model system, 4-*tert*-butylcyclohexanone **334**, affording an indole instead, we would be intrigued to apply these conditions to a more hindered system such as our gelsemine core structure **240**. The metal catalysed free-radical C–H activation was successful on our model system, affording the desired spiro-oxindoles **367** and **371** in good yield. Applying the methodology to the gelsemine core structure **240** proved challenging due to a lack of stability and unexpected reactivity of the core to a variety of bases and electrophiles. The addition of a methyl ester or an isocyanate derivative on the core structure, or maybe at an earlier stage of the synthesis, is under investigation.



Scheme 4.9

One of the possibilities would be to treat the core structure under mild conditions such as triethylamine and TMSCl to afford a silyl enol ether (Scheme 4.9).[189-192] The silyl enol ether would then be subjected to methyl chloroformate or an isocyanate derivative (phenyl isocyanate or bromophenyl isocyanate) with or without the addition of a Lewis acid, as seen in Section 3.4.2, to afford **430**.[180,181] Another possibility would be to replace Trost's imidazole ester **398** with a benzotriazole ester. In 2000, Katritzky reported the used of acylbenzotriazoles to perform *C*-acylation reaction and prepare β-diketones from ketone

enolates, but the method has never been extended to the synthesis of β-keto esters or amides.[193] If β-keto ester **400** was successfully prepared, we could then apply the methodology developed on our model system as seen in Section 3.3, which consists of amide coupling with a protected aniline and metal catalysed free-radical cyclisation with $Mn(OAc)_3 \bullet 2H_2O$ or $Cu(OAc)_2 \bullet H_2O$.



400 **337**, X = I; **338**, X = Br **431**

Scheme 4.10

We could also envisage a similar procedure to Ma and co-workers as seen in Scheme 3.7.[135] The gelsemine core structure **240** would be treated with a haloacetanilide derivative such as **337** or **338** to perform the desired arylation to obtain **431**, a precursor to the spiro-oxindole (Scheme 4.10).

In our work on the synthesis of other elements of the gelsemine structure (**5**) we found that reduction of ketone **240** to the corresponding axial alcohol **424** generated a powerful "trap" allowing epimerisation of the *exo* ester and formation of the desired tetrahydropyran precursor **417** in a one-pot procedure. Reduction of intermediate **417** would be interesting and would presumably furnish an advanced core structure possessing the tetrahydropyran and the pyrrolidine ring.

Chapter 5

Experimental

5.1 General Methods

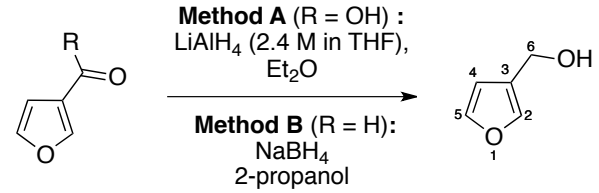
All reactions were performed under an atmosphere of nitrogen or argon in dry glassware unless otherwise stated. Tetrahydrofuran was distilled from sodium and benzophenone; dichloromethane was distilled from calcium hydride; diethyl ether, toluene, acetonitrile and methanol were dried on the Innovative Technology solvent purification system (alumina columns) and transferred under argon. Triethylamine and trimethylsilyl chloride were distilled from calcium hydride. All other solvents and reagents were used as received from commercial suppliers. Infra-red spectra were recorded neat on a Perkin-Elmer Spectrum 100 FTIR spectrometer and the wavelengths (ν) are reported in cm^{-1}. Mass spectra were obtained using a VG Micromass 70E or VG Micron Autospec spectrometer, using electrospray ionization (ESI) with *meta*-nitro benzene alcohol as a matrix or electron impact (EI). All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brüker AVIII300, AVIII400 or DRX500 spectrometers at 300 K. ^{13}C NMR spectra were recorded using the PENDANT pulse sequence from the Brüker standard pulse program library. Chemical shifts (δ) are quoted in ppm, coupling constants (*J*) in Hz to one decimal place and the spectra were calibrated on the solvent signal. For spectra recorded in chloroform-*d*, δ_H = 7.26 ppm resonance of residual $CHCl_3$ and δ_C = 77.16 ppm resonance of $CDCl_3$ were used as internal references. For spectra recorded in methanol-d_4, δ_H = 3.34 ppm resonance of residual CH_3OH and δ_C = 49.86 ppm resonance of CD_3OD were used as internal references. For spectra recorded in DMSO-d_6, δ_H = 2.50 ppm

resonance of residual $(CH_3)_2SO$ and δ_C = 39.52 ppm resonance of $(CD_3)_2SO$ were used as internal references. Spectral data for ^1H NMR spectra is reported as follows: chemical shift (multiplicity, coupling constant, number of protons, assignment); and for ^{13}C NMR spectra: chemical shift (carbon type, assignment). The multiplicities were described as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), q (quadruplet), m (multiplet) and further qualified as a br (broad signal). In the case of ambiguous assignments 2-D homonuclear (^1H-^1H) and heteronuclear (^1H-^{13}C) NMR experiments were used. For simplicity of assignments all atoms are labelled but these numbers do not necessarily follow IUPAC naming conventions. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Reaction progress was monitored by thin layer chromatography (TLC) performed on plastic plates coated with keiselgel F254 with 0.2 mm thickness. Visualisation was achieved by a combination of ultraviolet light (254 nm) and acidic potassium permanganate or anisaldehyde. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and Co.). The microwave reactions were performed in a CEM microwave synthesizer (Discover S, CEM). Suitable crystals for X-Ray Crystallography were selected and datasets were measured on a Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator ($\lambda_{Mo\text{-}K_\alpha}$ = 0.71075 Å) with HF Varimax optics at University of Southampton. The data collections were driven and processed by Louise Male at the University of Birmingham. Absorption corrections were applied using CrystalClear-SM Expert 3.1 b24 (2012, Rigaku). The structures were solved and refined by a full-matrix least-squares procedure on F^2 in ShelXL-97.[194] All hydrogen atoms were added at calculated positions and refined by use of a riding

model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

5.2 Experimental for Chapter 2

Preparation of furan-3-methanol 221.[95,195]



277, R = OH
278, R = H

221

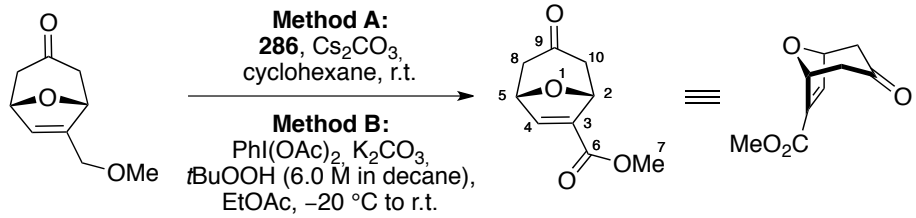
Method A: 3-Furancarboxylic acid (4.00 g, 35.69 mmol) was dissolved in diethyl ether (64 mL), under nitrogen. The solution was cooled to 0 °C and a 2.4 M solution of lithium aluminium hydride in tetrahydrofuran (19 mL, 46.39 mmol) was added slowly. The reaction mixture was stirred for 30 minutes at 0 °C before warming slowly to room temperature and was kept at that temperature for 1 hour. The reaction mixture was then cooled to 0 °C and carefully quenched by addition of water (65 mL) and stirred for 1 hour. The precipitate was filtered and diethyl ether (65 mL) was added. The layers were separated and the organic phase was washed with water (2 x 65 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to give the desired alcohol (yellow oil, 2.60 g, 26.53 mmol, 74% yield).

Method B: Sodium borohydride (0.50 g, 13.20 mmol) was added to a solution of 3-furaldehyde (5.00 g, 52.03 mmol) in 2-propanol (150 mL). The reaction mixture was stirred at room temperature under nitrogen. After 2 hours the reaction was quenched with water (200 mL) and diethyl ether (300 mL) was added. The layers were separated, the aqueous phase was extracted with diethyl ether (2 x 300 mL) and the combined organic phases were washed with

water (300 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the desired alcohol (yellow oil, 5.04 g, 51.38 mmol, 99% yield).

R_f: 0.56 (50:50 ethyl acetate/cyclohexane); FTIR ν_{max} 3310, 3148, 2942 - 2882, 1502, 1157; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 - 7.38 (m, 2H, H-5 and H-2), 6.42 (s, 1H, H-4), 4.53 (s, 2H, H-6), 2.00 (br. s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.8 (CH, C-2), 140.1 (CH, C-5), 125.4 (C, C-3), 110.1 (CH, C-4), 56.7 (CH_2, C-6); HRMS (EI) calculated for $[C_5H_6O_2]^+$: 98.0368, found: 98.0370 (error = 2.0 ppm). Data in agreement with those previously reported.[95,195,196]

Preparation of (±)-(1*S*,5*R*)-methyl 3-oxo-8-oxabicyclo[3.2.1]oct-6-ene-6-carboxylate 233.[65]



280 **233**

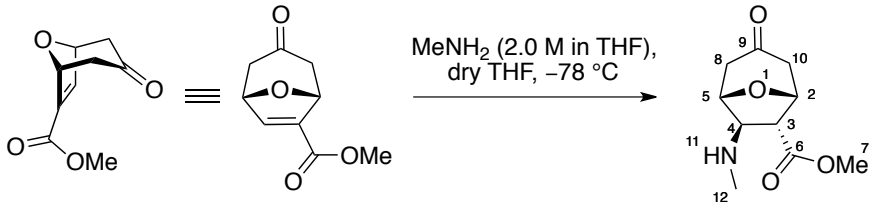
Method A: A mixture of radical initiator **286** (8.00 g, 23.80 mmol), cesium carbonate (7.70 g, 23.80 mmol) and compound **280** (2.00 g, 11.90 mmol) was dissolved in cyclohexane (300 mL). The reaction mixture was stirred at room temperature under nitrogen. After 9 days, the brown precipitate was filtered and washed with dichloromethane (3 x 50 mL). The solvent was then removed *in vacuo* to afford a brown oil which was partitioned between dichloromethane (50 mL) and $NaHCO_3$ (50 mL, saturated aqueous solution). The layers were separated and the organic phase was washed with $NaHCO_3$ (50 mL, saturated aqueous solution) then brine (50 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude oil was purified by column chromatography using a gradient of 0% to 50%

ethyl acetate in petroleum ether to provide the desired product (yellow oil, 256 mg, 1.40 mmol, 12% yield).

Method B: Compound **280** (2.16 g, 12.86 mmol) was dissolved in ethyl acetate (60 mL) at room temperature, under an atmosphere of air. Iodosobenzene diacetate (8.28 g, 25.71 mmol) was added followed by potassium carbonate (3.40 g, 25.71 mmol). The suspension was cooled to –20 °C and a 6.0 M solution of *tert*-butyl hydroperoxide in decane (8.6 mL, 51.44 mmol) was added slowly. The reaction mixture was stirred for 1 hour at –20 °C before slowly warming to room temperature overnight. The remaining solids were filtered and the filtrate was concentrated *in vacuo* to afford a yellow paste. The crude paste was purified by column chromatography using a gradient of 20% to 60% ethyl acetate in petroleum ether to provide the desired product (yellow oil, 1.40 g, 7.69 mmol, 60% yield). (*NB*: some degradation of this compound was observed on silica and on *vacuo*).

R_f: 0.48 (50:50 ethyl acetate/cyclohexane); FTIR ν_{max} 3020 - 3000, 2950, 1718, 1710, 1629, 1437; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 1.9, 1H, H-4), 5.20 (dd, *J* = 5.1, 0.9, 1H, H-2), 5.16 (ddd, *J* = 5.5, 1.9, 1.0, 1H, H-5), 3.76 (s, 3H, H-7), 2.84 (dd, *J* = 16.7, 5.5, 1H, H-8), 2.78 (dd, *J* =16.7, 5.1, 1H, H-10), 2.56 (d, *J* = 16.7, 1H, H-10), 2.36 (d, *J* = 16.7, 1H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.1 (CO, C-9), 162.7 (CO_2, C-6), 143.0 (CH, C-4), 139.7 (C, C-3), 78.2 (CH, C-5), 76.9 (CH, C-2), 52.1 (CH_3, C-7), 46.3 (CH_2, C-8), 45.1 (CH_2, C-10); HRMS (EI) calculated for $[C_9H_{10}O_4]^+$: 182.0579, found: 182.0574 (error = 2.7 ppm). Data in agreement with those previously reported.[65]

Preparation of (±)-(1*S*,5*R*,6*R*,7*R*)-methyl 7-(methylamino)-3-oxo-8-oxabicyclo[3.2.1] octane-6-carboxylate 234.

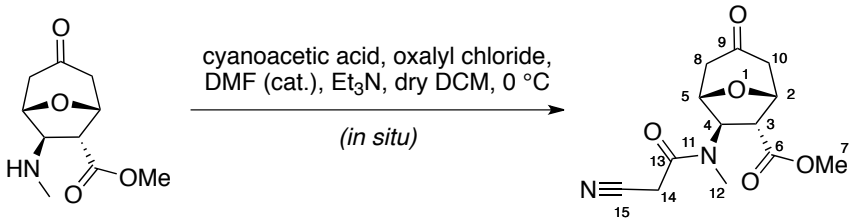


233 **234**

A 2.0 M solution of methylamine in tetrahydrofuran (2.27 mL, 4.53 mmol) was added dropwise to a solution of ester **233** (0.55 g, 3.02 mmol) in dry tetrahydrofuran (33 mL), at −78 °C under nitrogen. The yellow solution was stirred for 3 hours at −78 °C, then 1 hour at 0 °C before warming slowly to room temperature overnight. The reaction mixture was concentrated *in vacuo* to give the desired crude intermediate (yellow oil, 0.63 g), which was used without further purification. An analytical sample of **234** could be obtained by column chromatography using a gradient of 60% to 100% ethyl acetate in petroleum ether affording a yellow oil.

R_f: 0.41 (80:20 dichloromethane/methanol); FTIR ν_{max} 3391 (NH), 2962 - 2850, 1734 (CO_2Me), 1719 (CO), 1234 - 1168, 1113 (COC); ^1H NMR (400 MHz, $CDCl_3$): δ 4.93 (dd, *J* = 7.4, 5.7, 1H, H-5), 4.59 (d, *J* = 5.7, 1H, H-2), 3.71 (s, 3H, H-7), 3.56 (d, *J* = 4.7, 1H, H-3), 3.22 (dd, *J* = 7.4, 4.7, 1H, H-4), 2.74 (dd, *J* = 16.7, 5.7, 1H, H-10), 2.64 (dd, *J* = 16.7, 5.7, 1H, H-8), 2.51 (d, *J* = 16.7, 1H, H-10), 2.43 (s, 3H, H-12), 2.39 (br. s, 1H, H-11), 2.34 (d, *J* = 16.7, 1H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.0 (CO, C-9), 170.5 (CO_2, C-6), 79.8 (CH, C-2), 76.0 (CH, C-5), 67.1 (CH, C-3), 56.3 (CH, C-4), 52.6 (CH_3, C-7), 47.4 (CH_2, C-10), 44.7 (CH_2, C-8), 33.8 (CH_3, C-12); HRMS (ESI) calculated for $[C_{10}H_{15}NO_4+H]^+$: 214.1079, found: 214.1081 (error = 3.5 ppm).

Preparation of (±)-(1*S*,5*R*,6*R*,7*R*)-methyl-7-(2-cyano-*N*-methylacetamido)-3-oxo-8-oxa bicyclo[3.2.1]octane-6-carboxylate 235.[65]



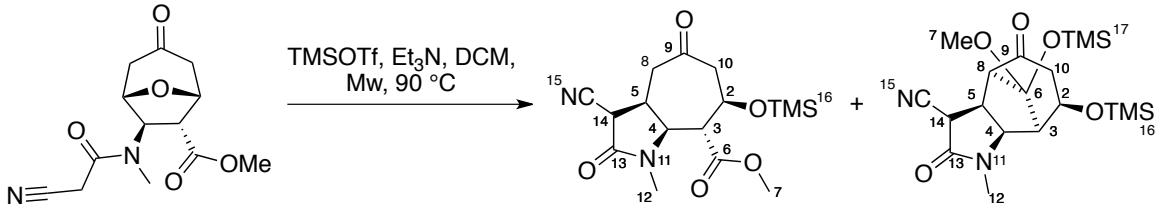
234 **235**

Oxalyl chloride (0.31 mL, 3.63 mmol) was added slowly to a solution of cyanoacetic acid (334 mg, 3.93 mmol) in anhydrous dichloromethane (15 mL) at 0 °C, followed by dimethylformamide (5 drops). The solution was stirred for 30 minutes at 0 °C under nitrogen, then 1 hour at room temperature. The pale yellow solution was degassed to remove the excess HCl gas and was then introduced dropwise to a 0 °C solution of crude **234** (3.02 mmol) and freshly distilled triethylamine (1.1 mL, 7.56 mmol) in dry dichloromethane (15 mL). The reaction was quenched after 30 minutes with water (50 mL) and dichloromethane (50 mL) was added. The layers were separated and the organic phase was washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford a dark yellow oil which was purified by column chromatography using a slow gradient of 80% to 100% ethyl acetate in petroleum ether to provide the desired product (beige foamy solid, 390 mg, 1.39 mmol, 46% yield over two steps).

R_f: 0.28 (50:50 ethyl acetate/petroleum ether); m.p. 129 - 130 °C, lit. m.p.: 129 - 130 °C;[65] FTIR ν_{max} 2960 - 2930, 2266 (CN), 2197 (CN), 1719, 1650, 1221, 1185, 1100 (COC); ^{1}H NMR (400 MHz, $CDCl_3$): δ **major rotamer** 5.02 - 4.97 (m, 1H, H-2), 4.64 - 4.52 (m, 1H, H-5 and H-4), 3.83 - 3.63 (m, 2H, H-14), 3.77 (s, 3H, H-7), 3.40 - 3.43 (m, 1H, H-3), 2.94 (s, 3H, H-12), 2.82 - 2.60 (m, 4H, H-8 and H-10); ^{1}H NMR (400 MHz, $CDCl_3$): δ **minor rotamer** 5.43 (d, *J* = 5.4, 1H, H-4), 5.02 - 4.97 (m, 1H, H-2), 4.64 - 4.52 (m, 2H, H-5), 3.71

(s, 3H, H-7), 3.49 (s, 2H, H-14), 3.31 - 3.27 (m, 1H, H-3), 3.06 (s, 3H, H-12), 2.82 - 2.60 (m, 2H, H-8), 2.39 - 2.31 (m, 2H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$): δ **major rotamer** 202.9 (CO, C-9); 170.0 (CO_2, C-6), 162.0 (CON, C-13), 114.4 (CN, C-15), 78.5 (CH, C-5), 75.8 (CH, C-2), 64.5 (CH, C-4), 54.5 (CH, C-3), 53.2 (CH_3, C-7), 48.0 (CH_2, C-8), 44.4 (CH_2, C-10), 29.0 (CH_3, C-12), 25.2 (CH_2, C-14); ^{13}C NMR (101 MHz, $CDCl_3$): δ **minor rotamer** 202.8 (CO, C-9), 169.9 (CO_2, C-6), 162.4 (CON, C-13), 113.6 (CN, C-15), 78.6 (CH, C-5), 76.0 (CH, C-2), 61.6 (CH, C-4), 53.6 (CH, C-3), 52.8 (CH_3, C-7), 47.2 (CH_2, C-8), 44.4 (CH_2, C-10), 31.2 (CH_3, C-12), 25.7 (CH_2, C-14); HRMS (ESI) calculated for $[C_{13}H_{16}N_2O_5+Na]^+$: 303.0957, found: 303.0959 (error = 0.7 ppm). Data in agreement with those previously reported.[65]

Preparation of (±)-(3*S*,3a*R*,7*R*,8*R*,8*aS*)-methyl-3-cyano-1-methyl-2,5-dioxo-7-((trimethyl silyl)oxy)decahydrocyclohepta[b]pyrrole-8-carboxylate 236 and (±)-(3*S*,3a*R*,4*S*,7*R*,8*R*, 8*aS*)-9-methoxy-1 methyl-2,5-dioxo-7,9-bis((trimethylsilyl)oxy)decahydro-4,8-methano cyclohepta[b]pyrrole-3-carbonitrile 237.[65]



235 **236** **237**

Compound **235** (50 mg, 0.18 mmol) was dissolved in dry dichloromethane (0.5 mL) at room temperature under nitrogen and the solution was cooled to 0 °C. Freshly distilled triethylamine (170 µL, 1.15 mmol) and trimethylsilyl trifluoromethanesulfonate (180 µL, 0.98 mmol) were added slowly. The reaction mixture was allowed to warm slowly to room temperature, then heated for 30 minutes at 90 °C in the microwave and finally quenched with

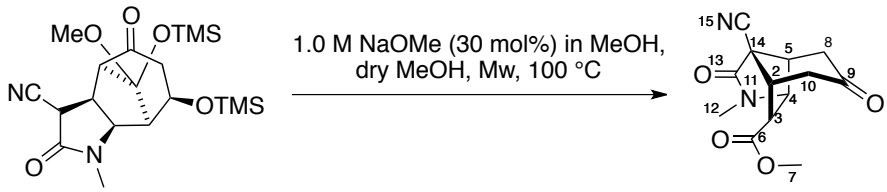
$NaHCO_3$ (1.3 mL, saturated aqueous solution). The reaction mixture was partitioned between dichloromethane (3 mL) and $NaHCO_3$ (3 mL, saturated aqueous solution). The layers were separated and the organic phase was washed with $NaHCO_3$ (2 x 3 mL, saturated aqueous solution), dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography using a gradient of 40% to 60% ethyl acetate in petroleum ether to provide product **237** (white solid, 24 mg, 0.056 mmol, 31% yield) followed by product **236** (yellow oil, 16 mg, 0.045 mmol, 25% yield) as an epimeric mixture at the C-14 position.

Data for **236**: R_f: 0.40 (50:50 ethyl acetate/petroleum ether); FTIR ν_{max} 2960 - 2855, 2234 (CN), 1733, 1703, 1657, 1437, 1231, 1082; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (dd, *J* = 10.4, 5.5, 1H, H-2), 4.18 (d, *J* = 5.4, 1H, H-4), 3.88 (s, 3H, H-7), 3.53 (s, 1H, H-14), 3.48 - 3.45 (m, 1H, H-5), 3.13 (s, 3H, H-12), 3.14 - 3.05 (m, 2H, H-8 and H-3), 2.73 (dd, *J* = 18.4, 5.5, 1H, H-10), 2.55 (dd, *J* = 13.4, 6.8, 1H, H-8), 2.39 (dd, *J* = 18.4, 10.4, 1H, H-10), 0.15 (s, 9H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.5 (CO, C-9), 169.8 (CO_2, C-6), 159.8 (CON, C-13), 117.4 (CN, C-15), 69.2 (CH, C-2), 66.0 (C, C-4), 53.1 (CH_3, C-7), 48.2 (CH_2, C-10), 45.1 (CH_2, C-8), 43.5 (CH, C-5), 37.8 (CH, C-14), 37.2 (CH_3, C-12), 33.9 (CH, C-3), 0.10 (CH_3, C-16); HRMS (ESI) calculated for $[C_{16}H_{24}N_2O_5Si+Na]^+$: 375.1352, found: 375.1356 (error = 1.1 ppm).

Data for **237**: R_f: 0.83 (50:50 ethyl acetate/petroleum ether); m.p. 132 - 133 °C, lit. m.p. 132 – 135 °C;[65] FTIR ν_{max} 2958 - 2859, 2266 (CN), 1702, 1671, 1431 - 1400, 1097; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 - 4.28 (m, 1H, H-8), 4.21 (dd, *J* = 10.2, 6.4, 1H, H-4), 3.28 (s, 3H, H-7), 3.25 - 3.20 (m, 1H, H-3), 3.12 (d, *J* = 7.8, 1H, H-2), 3.10 (d, *J* = 6.4, 1H, H-5), 2.99 (s, 3H, H-12), 2.70 - 2.66 (m, 2H, H-14 and H-10), 1.92 (dd, *J* = 17.9, 9.5, 1H, H-10), 0.18 (s, 9H, H-17 or H-16), 0.11 (s, 9H, H-17 or H-16); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.9 (CO, C-9), 166.1

(CON, C-13), 117.3 (CN, C-15), 106.5 (C, C-6), 66.9 (CH, C-8), 62.7 (CH, C-4), 59.6 (CH, C-2), 49.8 (CH_3, C-7), 49.4 (CH, C-14), 46.4 (CH_2, C-10), 38.2 (CH, C-3), 34.9 (CH, C-5), 32.5 (CH_3, C-12), 0.1 (CH_3, C-16 or CH_3, C-17), 0.0 (CH_3, C-16 or CH_3, C-17); HRMS (ESI) calculated for $[C_{19}H_{32}N_2O_5Si_2+Na]^+$: 447.1747, found: 447.1758 (error = 2.5 ppm). Data in agreement with those previously reported.[65]

Preparation of (±)-(3*aS*,4*R*,7*aR*,8*R*)-methyl 3a-cyano-2-methyl-3,6-dioxooctahydro-1,4-methanoisoindole-8-carboxylate 240.[65]



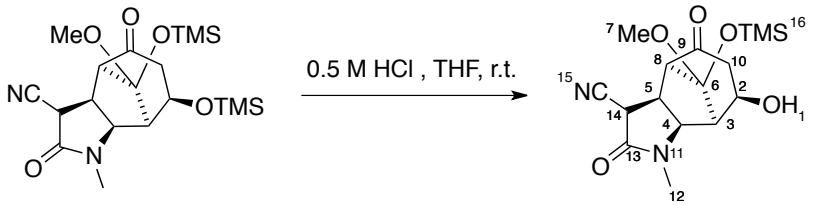
237 **240**

A freshly prepared solution of 1.0 M sodium methoxide in methanol (20 µL, 0.02 mmol) was introduced to a solution of starting material **237** (28 mg, 0.066 mmol) in anhydrous methanol (2.8 mL) at room temperature under nitrogen. The pale orange solution was stirred for 10 minutes at room temperature before heating at 100 °C, for 1 hour, in the microwave. The reaction was then quenched by addition of solid NH_4Cl (10 mg) and the volatiles were removed *in vacuo*. The crude material was purified by column chromatography using 100% ethyl acetate to provide the desired product (yellow oil, 17 mg, 0.064 mmol, 97% yield).

R_f: 0.46 (100% ethyl acetate); FTIR ν_{max} 2922 - 2852, 2250 (CN), 1734, 1698, 1634, 1536, 1435, 1399; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 (dd, *J* = 3.0, 2.0, 1H, H-4), 3.75 (s, 3H, H-7), 3.30 - 3.26 (m, 1H, H-2), 3.04 - 3.01 (m, 1H, H-5), 2.97 (dd, *J* = 16.9, 2.8, 1H, H-$10_{equatorial}$), 2.87 - 2.84 (m, 1H, H-3), 2.81 (s, 3H, H-12), 2.80 - 2.70 (m, 2H, H-8_{axial} and H-10_{axial}), 2.53 (d, *J* = 19.3, 1H, H-$8_{equatorial}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.4 (CO, C-9),

169.5 (CO_2, C-6), 167.8 (CON, C-13), 115.2 (CN, C-15), 66.3 (CH, C-4), 59.9 (C, C-14), 52.9 (CH_3, C-7), 52.8 (CH, C-5), 51.9 (CH, C-3), 43.9 (CH_2, C-10), 38.8 (CH_2, C-8), 38.5 (CH, C-2), 30.1 (CH_3, C-12); HRMS (ESI) calculated for $[C_{13}H_{14}N_2O_4+Na]^+$: 285.0851, found: 285.0853 (error = 0.7 ppm). Data in agreement with those previously reported.[65]

Preparation of (±)-(3*S*,3*aR*,4*S*,7*R*,8*R*,8*aS*)-7-hydroxy-9-methoxy-1-methyl-2,5-dioxo-9-((tri methylsilyl)oxy)decahydro-4,8-methanocyclohepta[b]pyrrole-3-carbonitrile 243.[65]



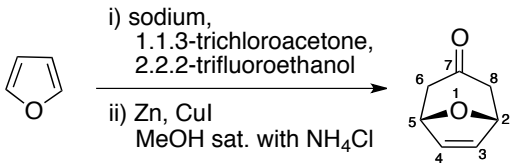
237 **243**

A 0.5 M aqueous solution of hydrochloric acid (2.2 µL, 0.001 mmol) was added to a solution of starting material **237** (15 mg, 0.035 mmol) in dry tetrahydrofuran (0.4 mL), at room temperature under nitrogen,. After 2 hours the reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography using a gradient of 70% to 100% ethyl acetate in petroleum ether to afford the desired product (white solid, 10 mg, 0.028 mmol, 81% yield).

R_f: 0.76 (100% ethyl acetate); m.p. 79 - 80 °C; lit. m.p.: 79 - 81 °C;[65] FTIR ν_{max} 3562 - 3312, 2953 - 2852, 1705, 1444, 1293, 1115, 1048, 842; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.42 (br. m, 1H, H-2), 4.20 (dd, *J* = 10.3, 6.2, 1H, H-4), 3.33 - 3.27 (m, 1H, H-5), 3.28 (s, 3H, H-7), 3.15 - 3.10 (m, 2H, H-8 and H-14), 3.06 (s, 3H, H-12), 2.89 - 2.85 (m, 1H, H-3), 2.81 (dd, *J* = 17.8, 7.8, 1H, H-10), 1.95 (dd, *J* = 17.8, 9.7, 1H, H-10), 1.90 (br. s, 1H, H-1), 0.17 (s, 9H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.7 (CO, C-9), 166.3 (CON, C-13), 106.6 (CN, C-15), 66.6 (CH, C-2), 62.6 (CH, C-4), 60.0 (CH, C-14), 49.8 (CH_3, C-7), 47.9 (CH, C-3), 45.8 (CH_2, C-

10), 43.3 (C, C-6), 38.4 (CH, C-5), 34.9 (CH, C-8), 32.4 (CH_3, C-12), 1.44 (CH_3, C-16); HRMS (ESI) calculated for $[C_{16}H_{24}N_2O_5Si+Na]^+$: 375.1352, found: 375.1354 (error = 0.50 ppm). Data in agreement with those previously reported.[65]

Preparation of (1*R*,5*S*)-8-oxabicyclo[3.2.1]oct-6-en-3-one 263.[197]



244 **263**

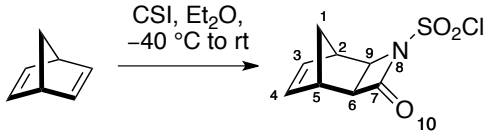
2,2,2-Trifluoroethanol (106 mL, 1.47 mol) was added slowly to oil-free freshly cut sodium pieces (2.70 g, 117.52 mmol) at room temperature under nitrogen. Once the sodium was completely dissolved in 2,2,2-trifluoroethanol, the NaTFE solution and furan (2.2 mL, 29.38 mmol) were added together slowly to 1,1,3-trichloroacetone (12.4 mL, 117.52 mmol) at 0 °C, under nitrogen, to provide an orange precipitate. The ice bath was removed and the reaction mixture was stirred overnight at room temperature, under nitrogen. After 19 hours, dichloromethane (60 mL) was added and the resulting precipitate was filtered through a Celite plug. The filtrate was partitioned between ethyl acetate (300 mL) and water (300 mL). The organic phase was washed with water (2 x 300 mL) then brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide a chlorinated intermediate as a brown oil.

The crude intermediate was added slowly to a suspension of copper iodide (22.40 g, 120 mmol) and zinc dust (28.00 g, 440 mmol) in methanol saturated with ammonium chloride (260 mL). The reaction mixture was stirred overnight at room temperature, under nitrogen. A saturated solution of ethylenediaminetetraacetic acid disodium salt dihydrate (Na_2EDTA, 200 mL) was added dropwise and the reaction mixture was stirred for another 30 minutes at room temperature. The copper and zinc couple was filtered through a celite plug and the filtrate was

concentrated *in vacuo*. The residue was then partitioned between water (200 mL) and ethyl acetate (200 mL). The organic phase was washed with water (2 x 200 mL) then brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography using a gradient of 40% to 80% ethyl acetate in petroleum ether to provide the desired product (brown oil, 2.83 g, 22.80 mmol, 78% yield).

R_f: 0.60 (50:50 ethyl acetate/petroleum ether); FTIR ν_{max} 2974 - 2850, 1709 (CO), 1584, 1339, 1179 (C-O-C), 709; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (s, 2H, H-4 and H-3), 5.01 (d, *J* = 5.1, 2H, H-2 and H-5), 2.73 (dd, *J* =16.5, 5.1, 2H, H-6 and H-8), 2.31 (d, *J* = 16.5, 2H, H-6 and H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.4 (CO, C-7), 133.4 (CH, C-4 and C-3), 77.2 (CH, C-2 and C-5), 46.7 (CH_2, C-6 and C-8); HRMS (EI) calculated for $[C_7H_8O_2]^+$: 124.0524, found: 124.0529 (error = 4.0 ppm). Data in agreement with those previously reported.[197]

Preparation of (±)-(1*R*,2*S*,5*R*,6*S*)-4-oxo-3-azatricyclo[4.2.1]non-7-ene-3-sulfonyl chloride 269.[90]

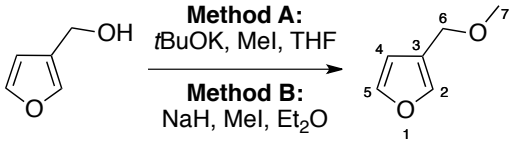


268 **269**

Bicyclo[2,2,1]hepta-2,5-diene (120 μL, 1.08 mmol) was dissolved in dry diethyl ether (0.8 mL), under nitrogen. The solution was cooled to –40 °C and chlorosulfonyl isocyanate (100 μL, 1.08 mmol) was added slowly. The reaction mixture was stirred for 1 hour at –40 °C and at room temperature overnight. Once the starting material was consumed, the reaction mixture was diluted with 2 mL of cyclohexane and then concentrated *in vacuo* to give a crude product purified by column chromatography using a gradient of 50% to 90% ethyl acetate in petroleum ether, affording **269** (yellow-orange oil, 196 mg, 0.84 mmol, 78% yield).

R_f: 0.66 (50:50 ethyl acetate/petroleum ether); FTIR ν_{max} 3078 - 2993, 2889, 1807, 1737, 1705, 1404, 1382, 1180, 1090, 908, 729; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 5.6, 3.2, 1H, H-3 or H-4), 6.21 (dd, *J* = 5.6, 3.2, 1H, H-3 or H-4), 4.22 (dd, *J* = 4.7, 0.7, 1H, H-6), 3.47 (d, *J* = 1.3, 1H, H-2 or H-5), 3.36 - 3.33 (m, 1H, H-9), 3.24 (br. d, *J* = 1.3, 1H, H-2 or H-5), 1.87 (br. d, *J* = 1.3, 2H, H-1); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.6 (CO, C-8), 139.4 (CH, C-3 or C-4), 135.6 (CH, C-3 or C-4), 62.0 (CH, C-6), 58.2 (C, C-9), 43.3 (CH, C-2 or C-5), 41.6 (CH_2, C-1 and CH, C-2 or C-5); HRMS (ESI) calculated for $[C_8H_8NO_3SCl+Na]^+$: 255.9811, found: 255.9801 (error = 3.9 ppm). Data in agreement with those previously reported.[90]

Preparation of 3-(methoxymethyl)furan 279.[97,98]



221 **279**

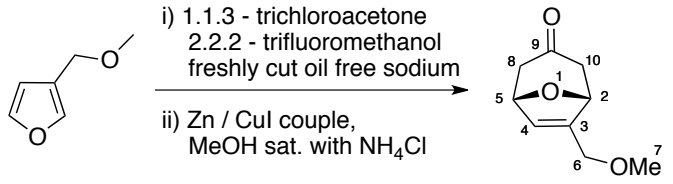
Method A: A solution of potassium *tert*-butoxide in dry tetrahydrofuran (100 mL, 102.00 mmol, 1 mol/L) was slowly added to a solution of furan-3-methanol (2.00 g, 20.40 mmol) in dry tetrahydrofuran (120 mL), under nitrogen, at 0 °C. After 10 minutes, methyl iodide (10 mL, 102.00 mmol) was added dropwise. The reaction mixture was stirred for 2 hours at room temperature until complete consumption of the starting material was observed. The reaction was quenched with water (300 mL) and extracted with diethyl ether (200 mL). The organic phase was washed with water (2 x 200 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide the desired product (yellow oil, 1.60 g, 14.2 mmol, 70% yield).

Method B: A 60% dispersion of sodium hydride in mineral oil (1.50 g, 62.5 mmol) was washed three times with 50 mL of cyclohexane, under nitrogen at room temperature. The

resulting oil-free powder was suspended in dry diethyl ether (93 mL) and cooled to 0 °C. Next furan-3-methanol (4.07 g, 41.52 mmol) was added in one portion and the reaction mixture was stirred for 10 minutes before the dropwise addition of methyl iodide (2.5 mL, 44.01 mmol). The reaction was allowed to warm up slowly overnight. After 5 days, 2 mL of methanol was added and the reaction mixture was stirred for 30 minutes under nitrogen. Then water (100 mL) was added and the solution was extracted with diethyl ether (100 mL). The organic phase was washed with water (3 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide the desired product (yellow oil, 4.31 g, 38.44 mmol, 93% yield).

R_f: 0.80 (50:50 ethyl acetate/cyclohexane); FTIR ν_{max} 2971 - 2927, 1503 - 1464, 1081 - 1020; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 - 7.39 (m, 2H, H-5 and H-2), 6.40 (s, 1H, H-4), 4.32 (s, 2H, H-6), 3.34 (s, 3H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.5 (CH, C-5), 140.8 (CH, C-2), 122.3 (C, C-3), 110.4 (CH, C-4), 66.0 (CH_2, C-6), 57.9 (CH_3, C-7); HRMS (EI) calculated for $[C_6H_8O_2]^+$: 112.0524, found: 112.0522 (error = 1.8 ppm). Data in agreement with those previously reported.[198]

Preparation of (±)-(1*S*,5*R*)-methyl 3-oxo-8-oxabicyclo[3.2.1]oct-6-ene-6-carboxylate 280.



279 **280**

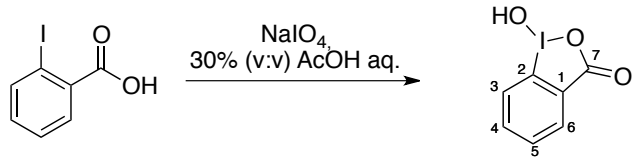
2,2,2-Trifluoroethanol (132 mL, 1.82 mol) was added slowly to oil-free fresh-cut sodium (3.35 g, 140 mmol) at room temperature under nitrogen. Once the sodium was completely dissolved in 2,2,2-trifluoroethanol, the NaTFE solution and 3-(methoxymethyl)furan (4.08 g, 36 mmol) were added slowly, at the same time, to 1,1,3-trichloroacetone (16 mL, 140 mmol) cooled to 0 °C under nitrogen to provide an orange precipitate. The ice bath was removed and

the reaction mixture was stirred overnight at room temperature, under nitrogen. After 24 hours, dichloromethane (75 mL) was added to the reaction and the precipitate was filtered through a Celite plug. The filtrate was partitioned between ethyl acetate (100 mL) and water (100 mL). The layers were separated and the organic phase was washed with water (2 x 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide a first chlorinated intermediate. The crude intermediate was dissolved in methanol saturated with ammonium chloride (200 mL) and a mixture of copper iodide (27.00 g, 0.15 mol) and zinc (36.00 g, 0.55 mol) was added slowly. The reaction mixture was stirred overnight at room temperature. Then a saturated solution of ethylenediaminetetraacetic acid disodium salt dihydrate (Na_2EDTA, 100 mL) was added slowly to the black suspension and the reaction mixture was stirred for another 30 minutes at room temperature under an atmosphere of air. The metal residues were filtered through Celite and the filtrate concentrated *in vacuo*. The crude mixture was partitioned between ethyl acetate (200 mL) and water (200 mL). The layers were separated and the organic phase was washed with water (2 x 200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil which was purified by flash chromatography using a gradient of 50% to 70% ethyl acetate in petroleum ether to provide the desired product (brown oil, 5.98 g, 35.59 mmol, 98% yield).

R_f: 0.33 (70:30 petroleum ether/ethyl acetate); FTIR ν_{max} 3100 - 3080, 2951 - 2828, 1713, 1670, 1104; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (d, *J* = 1.6, 1H, H-4), 5.01 (d, *J* = 5.0, 1H, H-5), 4.93 (d, *J* = 5.0, 1H, H-2), 4.07 (dd, *J* = 13.5, 7.3, 2H, H-6), 3.03 (s, 3H, H-7), 2.76 (dd, *J* = 16.3, 5.0, 1H, H-10), 2.72 (dd, *J* = 16.3, 5.0, 1H, H-8), 2.43 (d, *J* = 16.3, 1H, H-10), 2.30 (d, *J* = 16.3, 1H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.7 (CO, C-9), 145.2 (C, C-3), 22.9 (CH, C-4), 77.7 (CH, C-2), 77.6 (CH, C-5), 67.9 (CH_2, C-6), 58.5 (CH_3, C-7), 46.4 (CH_2, C-

8), 46.0 (CH_2, C-10); HRMS (EI) calculated for $[C_9H_{12}O_3]^+$: 168.0786, found: 168.0779 (error = 4.2 ppm).

Preparation of 2-iodosylbenzoic acid.[100]

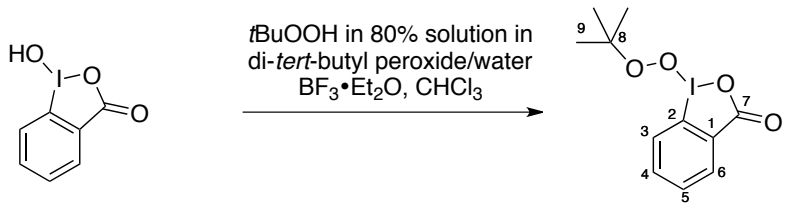


2-iodobenzoic acid **2-iodosylbenzoic acid**

2-Iodobenzoic acid (15.00 g, 60.47 mmol) and sodium periodate (28.50 g, 133.24 mmol) were dissolved in 122 mL of 30% (v/v) aqueous acetic acid. The mixture was heated to reflux. After 24 hours, the reaction mixture was allowed to cool to room temperature and was diluted with cold water (300 mL). The white precipitate was filtered and washed with ice water (3 x 40 mL) and cold acetone (3 x 40 mL) to provide the desired product as a white solid (15.86 g, 60.07 mmol, 99% yield). *NB*: light sensitive compound.

R_f: 0.30 (50:50 ethyl acetate/petroleum ether); m.p.: 253 - 254 °C, lit. m.p.: 254 °C;[100] FTIR ν_{max} 3083 - 3060, 1601 - 1584, 1452 - 1439, 1245, 1160, 1111; ^{1}H NMR (400 MHz, DMSO): δ 8.01 (dd, *J* = 0.5, 0.09, 1H, H-3), 7.96 (ddd, *J* = 0.5, 0.5, 0.09, 1H, H-5), 7.84 (d, *J* = 0.5, 1H, H-6), 7.70 (ddd, *J* = 0.5, 0.5, 0.09, 1H, H-4); ^{13}C NMR (101 MHz, DMSO): δ 167.7 (COO, C-7), 134.5 (CH, C-5), 131.6 (C, C-1), 131.1 (CH, C-3), 124.4 (CH, C-4), 110.3 (CH, C-6), 120.4 (C, C-2); HRMS (ESI) calculated for $[C_7H_5O_3I+Na]^+$: 286.9181, found: 286.9171 (error = 3.5 ppm). Data in agreement with those previously reported.[100]

Preparation of 1-(*tert*-butylperoxy)-1,2-benziodoxol-3-one 286.[100]

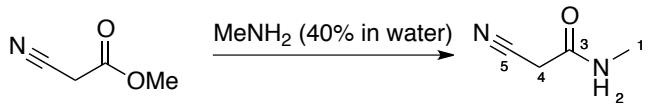


2-iodosylbenzoic acid **286**

A 80% solution of *tert*-butyl hydroperoxide in di-*tert*-butyl-peroxide in water (1.05 mL) was added to a solution of 2-iodosylbenzoic acid (1.40 g, 5.30 mmol) in chloroform (15 mL) at 0 °C under nitrogen, followed by a dropwise addition of boron trifluoride diethyl etherate (0.7 mL, 5.30 mmol). The reaction mixture was stirred for 1 hour at 0 °C under nitrogen before warming gradually to room temperature overnight. The reaction mixture was quenched by addition of water (20 mL) and the white precipitate was filtered. The filtrate was partitioned between dichloromethane (30 mL) and water (30 mL). The layers were separated and the organic phase was washed with water (2 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide the desired product as a white solid (1.25 g, 3.72 mmol, 70% yield).

R_f: 0.48 (50:50 ethyl acetate/cyclohexane); m.p.: 21 - 22 °C (dec.) / lit. m.p.: 22 - 23 °C;[100] FTIR ν_{max} 3100 - 3020, 2973 - 2902, 1666, 1628 -1583, 1444, 1365, 1224; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 0.5, 0.09, 1H, H-3), 8.11 (dd, *J* = 0.5, 0.09, 1H, H-6), 7.92 (ddd, *J* = 0.5, 0.5, 0.09, 1H, H-4), 7.70 (ddd, *J* = 0.5, 0.5, 0.09, 1H, H-5), 1.32 (s, 9H, H-9); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (COO, C-7), 135.6 (CH, C-4), 2.7 (CH, C-3), 131.2 (CH, C-5), 124.0 (C, C-1), 121.7 (CH, C-6), 120.3 (C, C-2), 83.4 (C, C-8), 26.2 (CH_3, C-9); HRMS (ESI) calculated for $[C_{11}H_{13}IO_4+Na]^+$: 358.9756, found: 358.9759 (error = 0.8 ppm). Data in agreement with those previously reported.[100]

Preparation of *N*-methylcyanoacetamide 307.[108]

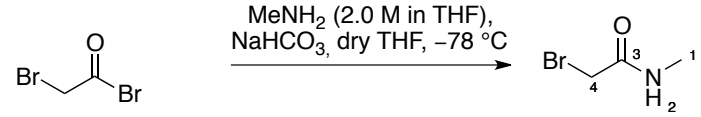


309 **307**

A 40 % solution of methylamine in water (0.63 mL, 7.56 mmol) was added to methyl cyanoacetate (500 mg, 5.04 mmol) at −10 °C, under nitrogen. The resulting white suspension was stirred for 1 hour at 0 °C and then for 3 hours at room temperature. The precipitate was filtered and washed with dichloromethane (10 mL) and ethyl acetate (10 mL) to yield the desired product (white solid, 430 mg, 4.37 mmol, 87% yield).

R_f: 0.26 (80:20 ethyl acetate/petroleum ether); m.p.: 95 - 96 °C, lit. m.p.: 101 °C;[108] FTIR ν_{max} 3283 (NH), 3107, 2969 - 2813, 2261 (CN), 1654 - 1567, 1414, 1385 - 1249; ^{1}H NMR (400 MHz, DMSO): δ 8.15 (br. s, 1H, H-2), 3.59 (s, 2H, H-4), 2.60 (d, J = 4.7, 3H, H-1); ^{13}C NMR (101 MHz, DMSO): δ 162.4 (CON, C-3), 116.2 (CN, C-5), 25.9 (CH_3, C-1), 25.1 (CH_2, C-4); HRMS (EI) calculated for $[C_4H_6N_2O]^+$: 98.0480, found: 98.0478 (error = 2.0 ppm). Data in agreement with those previously reported.[108]

Preparation of *N*-methylbromoacetamide 308.[199]



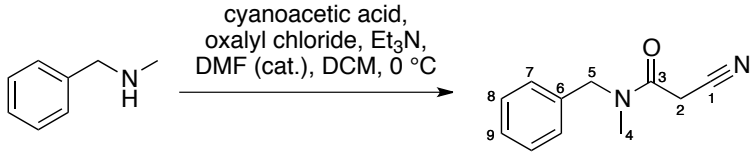
bromoacetyl bromide **308**

Bromoacetyl bromide (1.00 g, 5.00 mmol) was added to a suspension of sodium hydrogencarbonate (840 mg, 10.00 mmol) in dry tetrahydrofuran (30 mL) at −78 °C under nitrogen. A 2.0 M solution of methylamine in tetrahydrofuran (5 mL, 7.50 mmol) was then added slowly. The reaction mixture was stirred for 1 hour at −78 °C, before warming gradually to room temperature overnight. The solution was partitioned between ethyl acetate

(30 mL) and $NaHCO_3$ (30 mL, saturated aqueous solution). The layers were separated and the organic phase was washed with $NaHCO_3$ (2 x 30 mL, saturated aqueous solution), dried over $MgSO_4$ and concentrated *in vacuo* to provide the desired product (white solid, 367 mg, 2.41 mmol, 48% yield).

R_f: 0.20 (50:50 ethyl acetate/petroleum ether); m.p. 41 - 42 °C; lit. m.p.: 44 - 45 °C;[200] FTIR ν_{max} 3282, 3095 - 2902, 2803, 1647, 1564, 1415, 1426, 1209, 1162, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (br. s, 1H, H-2), 3.86 (s, 2H, H-4), 2.85 (d, J = 4.9, 3H, H-1); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1 (CON, C-3), 29.2 (CH_2, C-4), 27.0 (CH_3, C-1); HRMS (EI) calculated for $[C_3H_6NOBr]^+$: 150.9633, found: 150.9632 (error = 0.7 ppm). Data in agreement with those previously reported.[199]

Preparation of *N*-benzyl-2-cyano-*N*-methyl acetamide 316.[201]



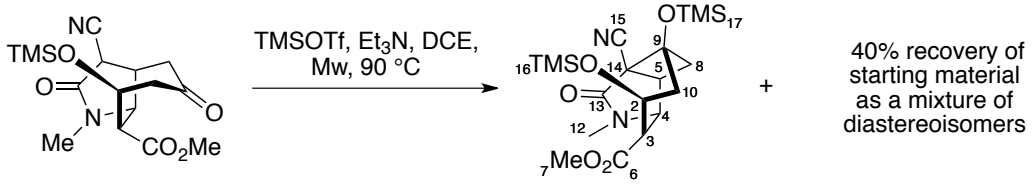
315 **316**

Cyanoacetic acid (516 mg, 6.07 mmol) was dissolved in dry dichloromethane (30 mL), at room temperature under nitrogen. After 30 minutes the suspension was cooled to 0 °C and oxalyl chloride (0.47 mL, 5.60 mmol) was added, followed by dimethylformamide (5 drops). The mixture was then allowed to warm up slowly for 1 hour before cooling again to 0 °C. Benzylamine (0.51 mL, 4.67 mmol) in dry dichloromethane (10 mL) was added dropwise, followed by freshly distilled triethylamine (1.3 mL, 9.34 mmol). The yellow solution was stirred for 1 hour at 0 °C and overnight at room temperature. The brown solution was partitioned between dichloromethane (50 mL) and water (50 mL). The layers were separated and the organic phase was washed with water (2 x 50 mL) and brine (50 mL), dried over

$MgSO_4$ and concentrated *in vacuo* to afford the desired compound as a mixture of rotamers (orange oil, 0.78 g, 4.48 mmol, 96% yield).

R_f: 0.74 (50:50 petroleum ether/ethyl acetate); FTIR ν_{max} 3068 - 3036, 2958 - 2870, 2260 (CN), 1734 (CO), 1653 (C-Ar), 1494 - 1452, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 - 7.42 (m, 3H, H-8 and H-9), 7.25 (d, *J* = 6.6, 2H, H-7$_{(major\ rotamer)}$), 7.16 (d, *J* = 7.2, 2H, H-7$_{(minor\ rotamer)}$), 4.60 (s, 2H, H-5$_{(major\ rotamer)}$), 4.53 (s, 2H, H-5$_{(minor\ rotamer)}$), 3.54 (s, 2H, H-2$_{(major\ rotamer)}$), 3.50 (s, 2H, H-2$_{(minor\ rotamer)}$), 3.03 (s, 3H, H-4$_{(minor\ rotamer)}$), 2.97 (s, 3H, H-4$_{(major\ rotamer)}$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7 (CO, C-3), 129.3 (C, C-6), 128.9 (CH, C-Ar), 128.3 (CH, C-Ar), 128.2 (CH, C-Ar), 127.9 (CH, C-Ar), 126.1 (CH, C-Ar), 113.8 (CN, C-1), 54.1 (CH_2, C-5), 51.7 (CH_2, C-5), 35.4 (CH_2, C-4), 35.1 (CH_2, C-4), 25.4 (CH_2, C-2), 25.1 (CH_2, C-2); HRMS (EI) calculated for $[C_{11}H_{12}N_2O]^+$: 188.0949, found: 188.0948 (error = 0.7 ppm). Data in agreement with those previously reported.[201]

Preparation of (±)-(3*S*,5*S*,6*S*)-methyl 10-cyano-8-methyl-9-oxo-3,5-bis((trimethylsilyl) oxy)-8-azatricyclo[5.3.0.03,10]decane-6-carboxylate 320.



236 **320**

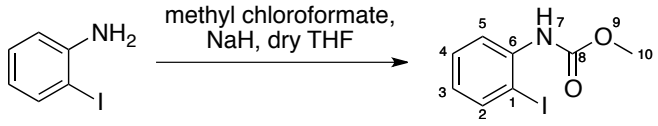
To a solution of starting material **236** (20 mg, 0.06 mmol) in dry 1,2-dichloroethane (0.2 mL) at 0 °C under nitrogen, freshly distilled triethylamine (28 μL, 0.20 mmol) was added slowly followed by trimethylsilyl trifluoromethanesulfonate (25 μL, 0.142 mmol). The reaction mixture was allowed to warm gradually to room temperature and was stirred for 1 hour before being heated to 90 °C for 1 hour in the microwave. The reaction mixture was quenched with

$NaHCO_3$ (1 mL, saturated aqueous solution) and dichloromethane (1 mL) was added. The layers were separated and the organic phase was washed with $NaHCO_3$ (2 x 1 mL, saturated aqueous solution), dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography using a gradient of 80% to 100% ethyl acetate in hexane to provide product **320** (white gum, 8 mg, 0.019 mmol, 33% yield) along with recovery of starting material as a mixture of epimers (yellow oil, 8 mg, 0.023 mmol, 40% yield).

R_f: 0.71 (50:50 ethyl acetate/petroleum ether); FTIR ν_{max} 2956 - 2858, 2248 (CN), 1735, 1664, 1438, 1252, 1180, 1083, 840, 752; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22 (dd, *J* = 9.0, 7.0, 1H, H-5), 3.91 (d, *J* = 2.8, 1H, H-4), 3.77 (s, 3H, H-7), 3.17 (s, 3H, H-12), 3.13 (d, *J* = 5.2, 1H, H-2), 3.04 - 3.00 (m, 1H, H-3), 2.75 (dd, *J* = 12.0, 11.7, 1H, H-10), 2.09 (dd, *J* = 13.4, 4.1, 1H, H-8), 2.05 (dd, *J* = 11.7, 2.7, 1H, H-10), 1.80 (dd, *J* = 13.4, 9.0, 1H, H-8); 0.20 (s, 9H, H-17), 0.16 (s, 9H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9 (CO_2, C-7), 162.9 (CON, C-12), 117.3 (CN, C-15), 76.1 (C, C-9), 68.4 (CH, C-5), 65.2 (CH, C-4), 55.4 (C, C-14), 52.6 (CH_3, C-7), 44.2 (C, C-3), 42.7 (CH_2, C-8), 37.8 (CH_2, C-10), 36.9 (CH_3, C-12), 31.9 (CH, C-2), 2.0 (CH_3, C-17), 0.1 (CH_3, C-16); HRMS (ESI) calculated for $[C_{19}H_{32}N_2O_5Si_2+Na]^+$: 447.1747, found: 447.1748 (error = 0.2 ppm).

5.3 Experimental for Chapter 3

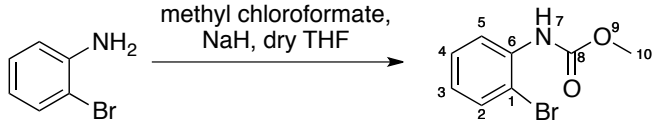
Preparation of methyl-(2-iodophenyl)-carbamate 330.



328 **330**

To a suspension of 2-iodoaniline **328** (500 mg, 2.28 mmol) and sodium hydride (329 mg, 13.70 mmol) in anhydrous tetrahydrofuran (25 mL), methyl chloroformate (0.18 mL, 2.28 mmol) was added slowly at room temperature under nitrogen. The reaction mixture was stirred overnight, in the dark. Then the volatiles were removed *in vacuo* to afford a beige solid which was purified by column chromatography using a gradient of 10% to 20% ethyl acetate in petroleum ether to provide the desired product (yellow oil, 630 mg, 2.27 mmol, 99% yield). R_f: 0.59 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 3376, 2951 - 2844, 1740, 1586, 1521, 1435, 1165, 1067, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br. d, *J* = 8.2, 1H, H-2), 7.76 (dd, *J* = 7.9, 1.4, 1H, H-5), 7.34 (ddd, *J* = 8.2, 7.6, 1.4, 1H, H-3), 6.96 (s, 1H, H-7), 6.80 (ddd, *J* = 7.9, 7.6, 1.5 1H, H-4), 3.81 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9 (CO, C-8), 139.2 (C, C-1), 139.0 (CH, C-3), 129.5 (CH, C-5), 125.2 (CH, C-4), 120.5 (CH, C-6), 120.2 (C, C-2), 52.7 (CH_3, C-10); HRMS (ESI) calculated for $[C_8H_8NO_2I+Na]^+$: 299.9498, found: 299.9484 (error = 4.7 ppm).

Preparation of methyl (2-bromophenyl)-carbamate 331.[202]

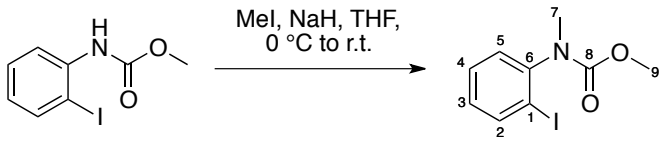


329 **331**

To a suspension of sodium hydride (837 mg, 34.88 mmol) in anhydrous tetrahydrofuran (5 mL) at 0 °C under nitrogen was added a solution of 2-bromoaniline **329** (1.00 g, 5.81 mmol) in anhydrous tetrahydrofuran (5 mL). The suspension was stirred for 30 min at 0 °C and methyl chloroformate (0.50 mL, 6.39 mmol) was slowly added. The reaction mixture was stirred for an additional 30 min at 0 °C before warming gradually to room temperature overnight. The reaction mixture was slowly quenched with water (10 mL) and ethyl acetate (10 mL) was added. The layers were separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to furnish a crude oil that was purified by column chromatography using a gradient of 0% to 20% ethyl acetate in hexane, to provide the desired product (colourless oil, 1.21 g, 5.26 mmol, 90% yield).

R_f: 0.30 (90:10 hexane/ethyl acetate); FTIR ν_{max} 3404, 2953, 1738 (CO_2Me), 1593, 1578, 1520, 1439, 1209, 1072, 1024, 748; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (br. d, *J* = 8.2, 1H, H-2), 7.51 (dd, *J* = 8.0, 1.4, 1H, H-5), 7.31 (ddd, *J* = 8.2, 7.4, 1.4, 1H, H-3), 7.14 (br. s, 1H, H-7), 6.93 (ddd, *J* = 8.0, 7.4, 1.6, 1H, H-4), 3.81 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9 (CO, C-8), 136.0 (C, C-1), 132.5 (CH, C-5), 131.1 (C, C-6), 128.6 (CH, C-3), 124.4 (CH, C-4), 120.4 (CH, C-2), 52.7 (CH_3, C-10); HRMS (EI) calculated for $[C_8H_8NO_2Br(79)]^+$: 228.9738, found: 228.9740 (error = 0.9 ppm). Data in agreement with those previously reported.[202]

Preparation of methyl-(2-iodophenyl)-methylcarbamate 332.

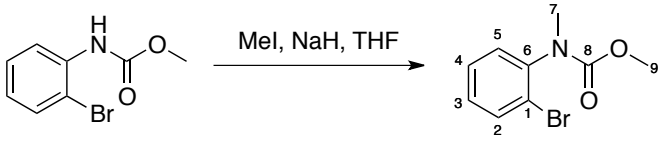


330 **332**

Methyl (2-iodophenyl) carbamate **330** (450 mg, 1.62 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL) and added to a suspension of sodium hydride (43 mg, 1.78 mmol) in dry tetrahydrofuran (3 mL) at 0 °C under nitrogen. After 30 minutes of stirring at 0 °C methyl iodide (0.10 mL, 2.10 mmol) was added slowly and the reaction mixture was warmed slowly to room temperature overnight. The reaction mixture was quenched by addition of 6 mL of water and extracted with ethyl acetate (6 mL). The layers were separated and the organic phase was washed with water (2 x 6 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford an orange solid which was purified by column chromatography using a gradient of 10% to 20% ethyl acetate in petroleum ether to give the desired product (yellow oil, 305 mg, 1.05 mmol, 65% yield).

R_f: 0.64 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 2984 - 2859, 2261, 1759, 1654, 1442, 1364, 1191, 1108; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 7.9, 1.4, 1H, H-2), 7.38 (ddd, *J* = 7.9, 7.7, 1.4, 1H, H-3), 7.24 (dd, *J* = 7.6, 1.4, 1H, H-5), 7.02 (ddd, *J* = 7.7, 7.6, 1.4, 1H, H-4), 3.65 (s, 3H, H-9), 3.20 (s, 3H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.7 (CO, C-8), 139.9 (C, C-6), 139.8 (CH, C-5), 129.7 (CH, C-1), 129.6 (CH, C-4), 129.2 (CH, C-3), 128.7 (CH, C-2), 53.3 (CH_3, C-9), 37.4 (CH_3, C-7); HRMS (EI) calculated for $[C_9H_{10}NO_2I]^+$: 290.9756, found: 290.9766 (error = 3.4 ppm).

Preparation of methyl-(2-bromophenyl)-methylcarbamate 333.



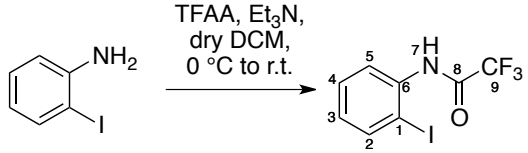
331 **333**

A solution of methyl (2-bromophenyl)carbamate **331** (100 mg, 0.43 mmol) in anhydrous tetrahydrofuran (1 mL) was added to a suspension of sodium hydride (60% in oil, 12 mg, 0.48

mmol) in anhydrous tetrahydrofuran (1 mL) at 0 °C under nitrogen. The reaction mixture was stirred for 15 min at 0 °C and methyl iodide (28 μL, 0.57 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight under nitrogen. Once the starting material consumed, the reaction was quenched slowly with water (5 mL) and extracted with ethyl acetate (5 mL). The layers were separated and the organic phase was washed with water (2 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude oil that was purified by column chromatography using a gradient of 0% to 30% ethyl acetate in hexane, to provide the desired product (colourless oil, 90 mg, 0.37 mmol, 85% yield).

R_f: 0.47 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 2953 - 2852, 1705 (CO_2Me), 1587, 1477, 1444, 1354, 1306, 1192, 1158, 761; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 8.0, 1.3, 1H, H-2), 7.33 (ddd, *J* = 7.7, 7.4, 1.3, 1H, H-4), 7.25 (dd, *J* = 7.7, 1.3, 1H, H-5), 7.17 (ddd, *J* = 8.0, 7.4, 1.3, 1H, H-3), 3.80 (s, 3H, H-$7_{(minor\ rotamer)}$), 3.64 (s, 3H, H-$7_{(major\ rotamer)}$), 3.21 (s, 3H, H-9); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1 (CO, C-8), 142.0 (C, C-1), 133.5 (CH, C-2), 129.5 (CH, C-5), 129.1 (CH, C-3), 128.6 (CH, C-4), 123.4 (C, C-6), 53.3 (CH_3, C-7), 37.3 (CH_3, C-9); HRMS (EI) calculated for $[C_9H_{10}NO_2Br(79)]^+$: 242.9895, found: 242.9893 (error = 0.8 ppm).

Preparation of *o*-iodotrifluoroacetanilide 337.[203]



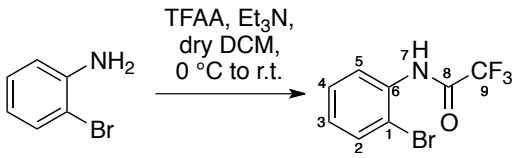
328 **337**

To a solution of 2-iodoaniline **328** (200 mg, 0.91 mmol) in anhydrous dichloromethane (4 mL) at 0 °C under nitrogen was added freshly distilled triethylamine (0.19 mL, 1.37 mmol) followed by trifluoroacetic anhydride (0.25 mL, 1.82 mmol). The reaction mixture was then

allowed to warm up slowly to room temperature and was stirred under nitrogen overnight. Water (10 mL) and dichloromethane (10 mL) were added and the layers were separated. The organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude oil that was purified by column chromatography using a gradient of 0% to 20% ethyl acetate in petroleum ether to afford the desired product (white solid, 282 mg, 0.89 mmol, 98% yield).

R_f: 0.68 (80:20 petroleum ether/ethyl acetate); m.p. 95 - 96 °C; lit. m.p.: 103 - 104 °C;[203] FTIR ν_{max} 3206, 3063, 1708, 1546, 1203, 1166, 1147, 734; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br. s, 1H, H-7), 8.17 (dd, *J* = 8.2, 1.3, 1H, H-2), 7.83 (dd, *J* = 8.0, 1.4, 1H, H-5), 7.44 - 7.34 (m, 1H, H-3), 6.97 (ddd, *J* = 8.0, 7.8, 1.3, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9 (q, *J* = 37.6, C-8), 139.3 (CH, C-5), 135.8 (C, C-6), 129.7 (CH, C-3), 128.0 (CH, C-4), 122.3 (CH, C-2), 115.8 (q, *J* = 288.8, C-9), 90.5 (C, C-1); HRMS (ESI) calculated for $[C_8H_5F_3INO+H]^+$: 315.9447, found: 315.9446 (error = 0.3 ppm). Data in agreement with those previously reported [203]

Preparation of *o*-bromotrifluoroacetanilide 338.[204]



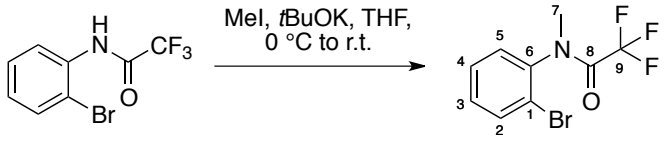
329 **338**

To a solution of 2-bromoaniline **329** (1.00 g, 5.81 mmol) in anhydrous dichloromethane (10 mL) at 0 °C under nitrogen, freshly distilled triethylamine (1.2 mL, 8.72 mmol) was added, followed by slow addition of trifluoroacetic anhydride (1.6 mL, 11.63 mmol). The resulting solution was kept at 0 °C for an additional 30 minutes and then was allowed to warm slowly to room temperature overnight. The reaction mixture was quenched by addition of water (10

mL) and dichloromethane (10 mL) was added. The layers were separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide a pink oil which was purified by flash chromatography using a gradient of 10% to 20% ethyl acetate in hexane, to give the desired product (white solid, 1.17 g, 4.36 mmol, 75% yield).

R_f: 0.48 (90:10 hexane/ethyl acetate); m.p. 58 - 59 °C, lit. m.p.: 57 - 59 °C;[204] FTIR ν_{max} 3290, 2919 - 2852, 1705, 1682, 1585, 1536, 1441, 1156 - 1122, 756; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (br. s, 1H, H-7), 8.28 (br. d, *J* = 8.0, 1H, H-2), 7.59 (br. d, *J* = 8.0, 1H, H-5), 7.37 (br. dd, *J* = 8.0, 7.8, 1H, H-3), 7.11 (br. dd, *J* = 8.0, 7.8, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8 (CO, C-8), 133.3 (C, C-6), 132.8 (CH, C-2), 128.9 (CH, C-3), 127.4 (CH, C-4), 122.2 (CH, C-5), 117.2 (C, C-1), 114.3 (C, C-9); HRMS (ESI) calculated for $[C_8H_5NOBr(79)F_3+H]^+$: 267.9585, found: 267.9568 (error = 6.3 ppm). Data in agreement with those previously reported.[204]

Preparation of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-methylacetamide 342.



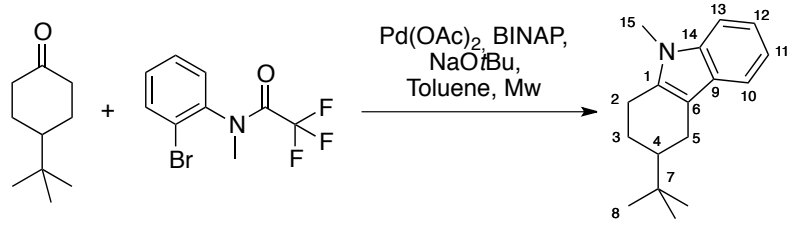
338 **342**

To a stirred solution of *N*-(2-bromophenyl)-2,2,2-trifluroacetamide **338** (300 mg, 1.12 mmol) and potassium *tert*-butoxide (242 mg, 3.36 mmol) in anhydrous tetrahydrofuran (5mL) at 0 °C, under nitrogen, methyl iodide (83 μL, 1.68 mmol) was added slowly. The reaction mixture was then allowed to warm to room temperature overnight. The reaction mixture was quenched slowly with water (5 mL) and dichloromethane (5 mL) was added. The layers were separated and the organic phase was washed with water (2 x 5 mL), dried over $MgSO_4$ and

concentrated *in vacuo* to give a crude oil that was purified by column chromatography using a gradient of 0% to 30% ethyl acetate in petroleum ether, to provide the desired product (colourless oil, 238 mg, 0.84 mmol, 75%).

R_f: 0.45 (80:20 hexane/ethyl acetate); FTIR ν_{max} 3047 - 2989, 2953 - 2896, 1706, 1587, 1477, 1445, 1358, 1192 - 1159, 762, 726; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 7.9, 1.3, 1H, H-2), 7.40 (ddd, *J* = 7.2, 7.0, 1.3, 1H, H-4), 7.34 - 7.28 (m, 2H, H-3 and H-5), 3.32 (s, 3H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.3 (CO, C-8), 139.4 (C, C-6), 133.9 (CH, C-2), 130.9 (CH, C-3 or C-5), 130.0 (CH, C-3 or C-5), 128.7 (CH, C-4), 123.3 (C, C-1), 117.6 (CH, C-9), 38.1 (CH_3, C-7); HRMS (ESI) calculated for $[C_9H_7NOF_3Br(79)+H]^+$: 281.9741, found: 281.9770 (error = 10.3 ppm).

Preparation of (±)-3-(*tert*-butyl)-9-methyl-2,3,4,9-tetrahydro-carbazole 343.



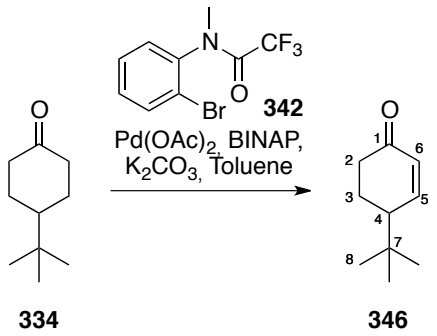
334 **342** **343**

4-*tert*-butylcyclohexanone **334** (50 mg, 0.32 mmol), palladium(II) acetate (2 mg, 0.007 mmol), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (12 mg, 0.02 mmol), sodium *tert*-butoxide (40 mg, 0.42 mmol) and trifluoroacetanilide **342** (100 mg, 0.35 mmol) were added to a microwave vial and dissolved in anhydrous toluene (1 mL) under argon. The reaction mixture was stirred 30 minutes at room temperature and then was heated for 3 hours at 150 °C in the microwave. The reaction mixture was then partitioned between water (3 mL) and dichloromethane (3 mL). The layers were separated and the organic phase washed with water (2 x 3 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to

afford a green oil which was purified by column chromatography using a gradient of 0% to 10% ethyl acetate in hexane to provide product **343** (dark yellow oil, 46 mg, 0.19 mmol, 59% yield).

R_f: 0.80 (80:20 hexane/ethyl acetate); FTIR ν_{max} 3050 - 2950, 2925 - 2845, 1617, 1469, 1376 - 1362, 1012, 733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.8, 1H, H-10), 7.29 (d, *J* = 8.1, 1H, H-13), 7.20 (ddd, *J* = 7.8, 7.1, 1.0, 1H, H-11), 7.12 (ddd, *J* = 8.1, 7.1, 1.2, 1H, H-12), 3.65 (s, 3H, H-15), 2.88 (dd, *J* = 14.9, 14.5, 2H, H-2 and H-5), 2.74 - 2.68 (m, 1H, H-2), 2.53 - 2.43 (m, 1H, H-5), 2.24 - 2.16 (m, 1H, H-3), 1.60 - 1.52 (m, 2H, H-3 and H-4), 1.06 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2 (C, C-14), 135.9 (C, C-1), 127.4 (C, C-9), 120.6 (CH, C-12), 118.7 (CH, C-11), 117.7 (CH, C-10), 109.6 (C, C-6), 108.6 (CH, C-13), 45.5 (CH, C-4), 32.7 (C, C-7), 29.2 (CH_3, C-15), 27.7 (CH_3, C-8), 24.9 (CH_2, C-3), 23.1 (CH_2, C-2), 22.5 (CH_2, C-5); HRMS (ESI) calculated for $[C_{17}H_{24}N+H]^+$: 242.1909, found: 242.1913 (error = 1.7 ppm).

Preparation of (±)-4-(*tert*-butyl)cyclohex-2-enone 346.[205]



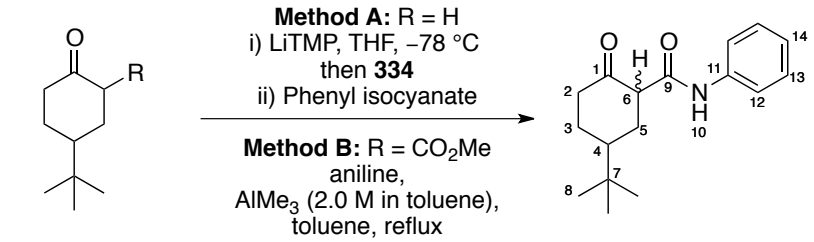
334 **346**

4-*tert*-butylcyclohexanone **334** (50 mg, 0.32 mmol), palladium(II) acetate (7 mg, 0.03 mmol), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (12 mg, 0.02 mmol), potassium carbonate (58 mg, 0.42 mmol) and trifluroacetanilide **342** (100 mg, 0.36 mmol) were added to a sealed tube and dissolved in anhydrous toluene (1 mL) under nitrogen. The septum was removed and

replaced with a Teflon screw cap. The sealed tube was heated at 150 °C for 3 hours. The reaction mixture was partitioned between water (3 mL) and dichloromethane (3 mL). The layers were separated and the organic phase was washed with water (2 x 3 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude brown oil was purified by column chromatography using a gradient of 0% to 20% ethyl acetate in hexane to provide enone **346** (yellow oil, 5 mg, 0.033 mmol, 10% yield).

R_f: 0.59 (80:20 hexane/ethyl acetate); FTIR ν_{max} 3039, 2960 - 2870, 1691, 1602, 1471, 1450, 1199, 1154, 755, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 10.4, 2.0, 1H, H-6), 6.04 (dd, *J* = 10.4, 2.8, 1H, H-5), 2.52 (dt, *J* = 16.6, 4.2 1H, H-2), 2.34 (ddd, *J* = 16.6, 14.3, 4.2, 1H, H-2), 2.23 - 2.17 (m, 1H, H-4), 2.15 - 2.06 (m, 1H, H-3), 1.80 - 1.68 (m, 1H, H-3), 0.98 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2 (CO, C-1), 153.1 (CH, C-6), 130.1 (CH, C-5), 47.0 (CH, C-4), 38.0 (CH_2, C-2), 33.0 (C, C-7), 27.5 (CH_3, C-8), 24.5 (CH_2, C-3); HRMS (ESI) calculated for $[C_{10}H_{16}O+Na]^+$: 175.1099, found: 175.1098 (error = 0.6 ppm). Data in agreement with those previously reported.[205]

Preparation of (±)-(5*R*)-5-(*tert*-butyl)-2-oxo-*N*-phenylcyclohexanecarboxamide 361.



334, R = H
363, R = CO_2Me

361

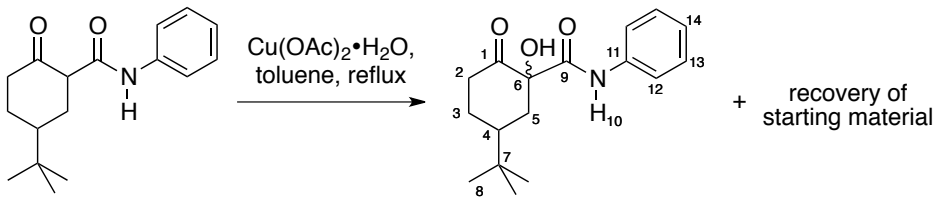
Method A: To a solution of 2,2,6,6-tetramethylpiperidine (0.23 mL, 1.36 mmol) in anhydrous tetrahydrofuran (2 mL) at −78 °C under nitrogen, was added slowly a 1.6 M solution of *n*-butyllithium in hexane (0.81 mL, 1.30 mmol). The resulting solution was stirred for 10

minutes at −78 °C, then 15 minutes at 0 °C followed by another 15 minutes at −78 °C before addition of a solution of 4-*tert*-butylcyclohexanone **334** (200 mg, 1.30 mmol) in anhydrous tetrahydrofuran (2.4 mL). The reaction mixture was stirred for another 40 minutes at −78 °C. Finally phenyl isocyanate (0.14 mL, 1.36 mmol) was added dropwise and the reaction mixture was allowed to warm gradually to room temperature overnight. After 1 hour at −78 °C, the reaction mixture was quenched with 5 mL of NH_4Cl (saturated aqueous solution) and diethyl ether (5 mL) was added. The layers were separated and the organic phase was washed with water (2 x 5 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography using a gradient of 10% to 50% ethyl acetate in petroleum ether to provide the desired product as a mixture of tautomers (yellow oil, 275 mg, 1.00 mmol, 77% yield).

Method B: To a solution of aniline (0.02 mL, 0.22 mmol) in dry toluene (0.5 mL) at 0 °C under nitrogen, was added slowly a 2.0 M solution of trimethyl aluminium in anhydrous toluene (0.06 mL, 0.66 mmol). The reaction mixture was stirred for 15 minutes at 0 °C and then was heated to reflux. Once at reflux, a solution of methyl ester **363** (50 mg, 0.22 mmol) in anhydrous toluene (0.5 mL) was added. The reaction mixture was refluxed for 1 hour until consumption of the starting material, then was cooled to room temperature and quenched by addition of water (1 mL) and 7 drops of 1.0 M HCl. The resulting mixture was partitioned between water (4 mL) and diethyl ether (4 mL). The layers were separated and the organic phase was washed with water (2 x 4 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford a yellow paste. The crude paste was purified by column chromatography using a gradient of 0% to 40% ethyl acetate in petroleum ether to afford the desired product as a mixture of tautomers (yellow oil, 37 mg, 0.13 mmol, 62% yield).

R_f: 0.58 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 3190, 2964 - 2870, 1714, 1624, 1514, 1475, 1439, 1335, 1048, 741; ^{1}H NMR (400 MHz, $CDCl_3$): δ **1,3-dicarbonyl** (major) 9.71 (s, 1H, H-10), 7.58 (d, *J* = 7.7, 2H, H-Ar), 7.37 - 7.30 (m, 2H, H-Ar), 7.16 - 7.08 (m, 1H, H-Ar), 3.30 (dd, *J* = 11.8, 5.4, 1H, H-6), 2.81 - 2.72 (m, 1H, H-5), 2.54 - 2.50 (m, 1H, H-2), 2.45 (dd, *J* = 13.7, 6.0, 1H, H-2), 2.21 - 2.12 (m, 1H, H-3), 1.71 - 1.64 (m, 2H, H-5 and H-4), 1.64 - 1.53 (m, 1H, H-3), 0.95 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.3 (CO, C-1), 172.4 (CON, C-9), 137.9 (C, C-11), 129.0 (CH, C-Ar), 124.4 (CH, C-Ar), 121.3 (CH, C-Ar), 54.7 (CH, C-6), 47.1 (CH, C-4), 42.2 (CH_2, C-2), 34.1 (CH_2, C-5), 32.8 (C, C-7), 28.8 (CH_2, C-3), 27.7 (CH_3, C-8); HRMS (ESI) calculated for $[C_{17}H_{23}NO_2+Na]^+$: 296.1626, found: 296.1629 (error = 1.0 ppm).

Preparation of (±)-(5*R*)-5-(*tert*-butyl)-1-hydroxy-2-oxo-*N*-phenylcyclohexanecarbox amide 362.



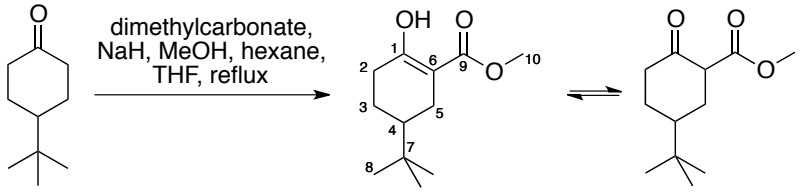
361 **362** + C-6-epi
d.r. 5 : 1

To a solution of starting material **361** (109 mg, 0.40 mmol) in toluene (6.5 mL) was added copper(II) acetate monohydrate (159 mg, 0.76 mmol). The reaction mixture was refluxed under an atmosphere of air for 1 hour and then cooled to room temperature. The reaction mixture was partitioned between diethyl ether (10 mL) and NH_4Cl (10 mL, saturated aqueous solution). The layers were separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 0% to 50% ethyl acetate in

petroleum ether to provide **362** (yellow oil, 21 mg, 0.072 mmol, 18% yield) as a 1:5 mixture of diastereoisomers along with some starting material.

R_f: 0.24 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 3347, 3061, 2962 - 2872, 1685, 1599, 1532, 1498, 1445, 734, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (br. s, 1H, H-10), 7.65 (dd, *J* = 8.5, 1.0, 2H, H-12), 7.37 (dd, *J* = 8.5, 7.9, 2H, H-13), 7.17 (dd, *J* = 7.9, 1.0, 2H, H-14), 3.23 (dd, *J* = 18.9, 4.7, 1H, H-2), 2.73 (dd, *J* = 18.9, 6.3, 1H, H-2), 2.40 - 2.26 (m, 2H, H-5), 2.00 - 1.85 (m, 2H, H-3 and H-4), 1.42 - 1.31 (m, 1H, H-3), 0.90 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5 (CO, C-1), 178.9 (CON, C-9), 157.6 (COH, C-15), 136.3 (C, C-11), 129.3 (CH, C-13), 125.4 (CH, C-14), 119.9 (CH, C-12), 79.4 (C, C-6), 43.1 (CH, C-4), 37.9 (CH_2, C-2), 33.8 (CH_2, C-5), 33.4 (C, C-7), 27.5 (CH_3, C-8), 26.8 (CH_2, C-3); HRMS (ESI) calculated for $[C_{17}H_{22}NO_3]^-$: 288.1600, found: 288.1615 (error = 5.2 ppm).

Preparation of (±)-methyl 5-(*tert*-butyl)-2-oxocyclohexane carboxylate 363.[162]



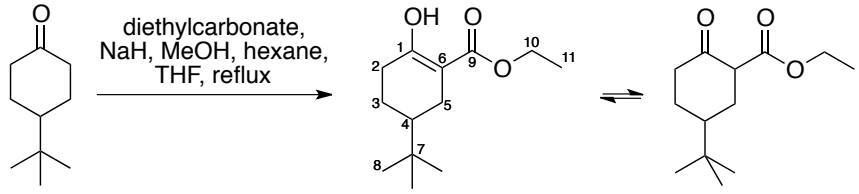
334 **363**

To a suspension of sodium hydride (311 mg, 12.94 mmol) in anhydrous tetrahydrofuran (1.5 mL) and hexane (3.5 mL) at room temperature, dimethylcarbonate (0.55 mL, 6.48 mmol) was added followed by anhydrous methanol (25 μL, 0.26 mmol). The white suspension was heated at reflux for 10 - 15 minutes and a solution of 4-*tert*-butylcyclohexanone **334** (500 mg, 3.24 mmol) in anhydrous tetrahydrofuran (1.8 mL) was added slowly. After 30 minutes a white precipitated formed and the reaction mixture was refluxed for another 40 minutes. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate (5

mL) and water (5 mL) in the presence of acetic acid (1.8 mL, 50% aqueous solution). The layers were separated and the organic phase was washed with water (2 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography using a gradient of 0% to 20% ethyl acetate in petroleum ether to provide the desired product (pale yellow oil, 590 mg, 2.78 mmol, 86% yield).

R_f (enol form): 0.86 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 2953 - 2868, 1656, 1618, 1440, 1218, 1203, 1089, 819; ^{1}H NMR (400 MHz, $CDCl_3$): δ **enol form** 12.11 (s, 1H, OH), 3.76 (s, 3H, H-10), 2.39 - 2.27 (m, 3H, H-5 and H-2), 1.94 - 1.81 (m, 2H, H-3 and H-2), 1.29 - 1.19 (m, 2H, H-4 and H-3), 0.90 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3 (CO, C-1), 172.2 (C, C-9), 97.6 (C, C-6), 51.5 (CH_3, C-10), 44.3 (CH, C-4), 32.4 (C, C-7), 30.3 (CH_2, C-5), 27.5 (CH_3, C-8), 23.9 (CH_2, C-2), 23.2 (CH_2, C-3); HRMS (ESI) calculated for $[C_{12}H_{20}O_3+Na]^+$: 235.1310, found: 235.1317 (error = 3.0 ppm). Data in agreement with those previously reported.[162]

Preparation of (±)-ethyl 5-(*tert*-butyl)-2-oxocyclohexane carboxylate 364.[206]



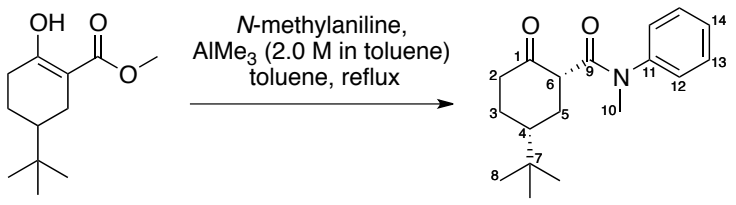
334 **364**

To a suspension of sodium hydride (125 mg, 5.2 mmol) in anhydrous tetrahydrofuran (0.5 mL) and hexane (1.4 mL) at room temperature, diethylcarbonate (0.32 mL, 2.6 mmol) was added followed by anhydrous methanol (10 μL, 0.26 mmol). The white suspension was heated at reflux for 15 minutes and then a solution of 4-*tert*-butylcyclohexanone **334** (200 mg, 1.3 mmol) in anhydrous tetrahydrofuran (0.8 mL) was added slowly. After 30 minutes a white

precipitate formed and the reaction mixture was refluxed for another 60 minutes. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate (3 mL) and water (3 mL) in the presence of acetic acid (0.7 mL, 50% aqueous solution). The layers were separated and the organic layers were washed with water (2 x 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography using a gradient of 0% to 20% ethyl acetate in petroleum ether to give the desired product (yellow oil, 289 mg, 1.28 mmol, 99% yield).

R_f (enol form): 0.88 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 2964 - 2875, 1655, 1617, 1366, 1281, 1232, 1204, 833; ^{1}H NMR (400 MHz, $CDCl_3$): δ **enol form** 12.21 (s, 1H, OH), 4.21 (q, *J* = 8.0, 2H, H-10), 2.38 - 2.27 (m, 2H, H-5 and H-2), 1.88 - 1.81 (m, 2H, H-3 and H-2), 1.30 (t, *J* = 8.0, 3H, H-11), 1.26 - 1.23 (m, 3H, H-4, H-3 and H-5), 0.90 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0 (CO, C-1), 172.0 (CO, C-9), 97.6 (C, C-6), 60.3 (CH_2, C-10), 44.3 (CH, C-4), 32.4 (C, C-7), 30.3 (CH_2, C-5), 27.4 (CH_3, C-8), 23.9 (CH_2, C-2), 23.3 (CH_2, C-3), 14.5 (CH_3, C-11); HRMS (EI) calculated for $[C_{13}H_{22}O_3]^+$: 226.1569, found: 226.1571 (error = 0.9 ppm). Data in agreement with those previously reported.[206]

Preparation of (±)-(1*R*,5*R*)-5-(*tert*-butyl)-*N*-methyl-2-oxo-*N*-phenylcyclohexane carboxamide 366.



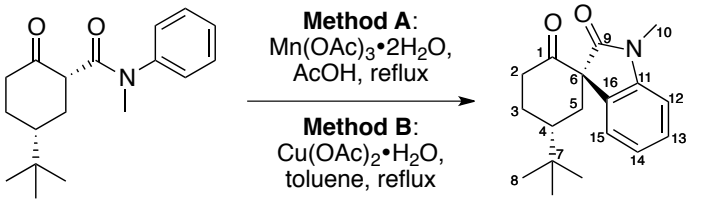
363 **366** + C-6-*epi* d.r. 4:1

To a solution of *N*-methylaniline (0.1 mL, 0.91 mmol) in anhydrous toluene (3 mL) at 0 °C under nitrogen, a 2.0 M solution of trimethyl aluminium in toluene (1.4 mL, 2.74 mmol) was

added. The reaction mixture was stirred for 15 minutes at 0 °C and 1 hour at room temperature. Methyl enol ester **363** (194 mg, 0.91 mmol) was added and the reaction mixture was heated at reflux for 4 hours. The reaction mixture was cooled to room temperature and separated between ethyl acetate (5 mL) and water (5 mL) in the presence of 0.5 M HCl (20 drops). The layers were partitioned and the organic phase was washed with water (2 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography using a gradient of 0% to 60% ethyl acetate in petroleum ether to give the desired product (yellow oil, 220 mg, 0.77 mmol, 84% yield) as a 4:1 mixture of cis/trans.

R_f: 0.26 (90:10 petroleum ether/ethyl acetate); FTIR ν_{max} 2958 - 2869, 1709, 1655, 1596, 1497, 1381, 1118, 821, 776; ^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 7.42 - 7.27 (m, 3H, H-14 and H-13), 7.21 - 7.10 (m, 2H, H-12), 3.26 (s, 3H, H-10), 3.24 - 3.16 (m, 1H, H-6), 2.31 (br. dd, *J* = 9.7, 5.9, 1H, H-2), 2.08 - 1.87 (m, 4H, H-2 and H-3 and H-5), 1.49 - 1.27 (m, 2H, H-4 and H-3), 0.84 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.6 (CO, C-1), 169.7 (CON, C-9), 143.8 (C, C-11), 129.8 (CH, C-13), 128.1 (CH, C-14), 127.1 (CH, C-12), 54.9 (CH_2, C-3), 45.7 (CH, C-4), 41.1(CH_2, C-2), 37.4 (CH_3, C-10), 32.5 (C, C-7), 31.6 (CH_2, C-5), 27.7 (CH, C-6), 27.6 (CH_3, C-8); HRMS (ESI) calculated for $[C_{18}H_{25}NO_2+Na]^+$: 310.1783, found: 310.1787 (error = 1.3 ppm).

Preparation of (±)-(1*S*,5*R*)-5-(*tert*-butyl)-1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione 367 and (±)-(1*R*,5*R*)-5-(*tert*-butyl)-1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione 368.



366 + C-6-*epi*
d.r. 4 : 1

367 + C-6-*epi* (**368**)
d.r. 4 : 1

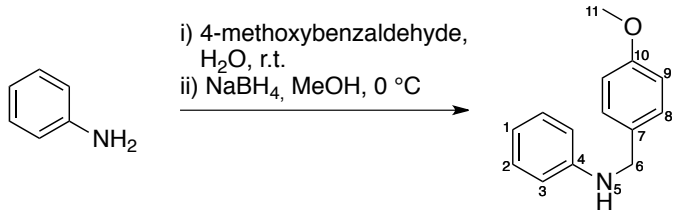
Method A: Starting material **366** (35 mg, 0.12 mmol) was added to a suspension of manganese(III) acetate dihydrate (65 mg, 0.24 mmol) in glacial acetic acid (1 mL), at room temperature under nitrogen. After 40 minutes at reflux the reaction mixture was cooled to room temperature, quenched with Na_2CO_3 (2 mL, saturated aqueous solution) and extracted with ethyl acetate (3 mL). The layers were separated and the organic phase was washed with water (2 x 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 50% to 60% ethyl acetate in petroleum ether to provide the desired product as a 4:1 mixture of diastereoisomers (pale brown oil, 15 mg, 0.053 mmol, 43% yield).

Method B: Starting material **366** (26 mg, 0.09 mmol) was added to a suspension of copper(II) acetate monohydrate (36 mg, 0.18 mmol) in toluene (1 mL), at room temperature under an atmosphere of air. After 60 minutes at reflux the reaction was partitioned between ethyl acetate (3 mL) and NH_4Cl (3 mL, saturated aqueous solution). The layers were separated and the organic phase was washed with NH_4Cl (2 x 3 mL, saturated aqueous solution), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 50% to 60% ethyl acetate in petroleum ether to provide

the desired product as a 4:1 mixture of diastereoisomers (pale brown oil, 17 mg, 0.06 mmol, 66% yield).

R_f: 0.30 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 2960 - 2871, 1724, 1699, 1609, 1470, 1370, 1351, 1249, 1158, 752, 734; ^{1}H NMR (400 MHz, $CDCl_3$): δ **major diastereoisomer** 7.53 (d, *J* = 7.5, 1H, H-12), 7.32 (ddd, *J* = 7.8, 7.7, 1.1, 1H, H-14), 7.06 (ddd, *J* = 7.7, 7.5, 1.5, 1H, H-13), 6.87 (d, *J* = 7.8, 1H, H-15), 3.24 (s, 3H, H-10), 2.74 (dd, *J* = 13.4, 6.0, 1H, H-2), 2.63 (m, 1H, H-2), 2.31 (dd, *J* = 13.0, 13.0, 1H, H-5), 2.24 (ddd, *J* = 13.0, 6.0, 3.1, 1H, H-3), 2.07 - 2.02 (m, 1H, H-4), 2.01 - 1.92 (m, 1H, H-5), 1.84 - 1.75 (m, 1H, H-3), 0.93 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.6 (CO, C-1), 176.0 (CON, C-9), 144.1 (C, C-11), 130.8 (C, C-16), 129.0 (CH, C-14), 123.9 (CH, C-12), 122.4 (CH, C-13), 108.9 (CH, C-15), 63.5 (C, C-6), 42.4 (CH, C-4), 39.6 (CH_2, C-2), 35.9 (CH_2, C-5), 32.8 (C, C-7), 23.6 (CH_3, C-8), 26.7 (CH_2, C-3), 26.6 (CH_3, C-10); HRMS (ESI) calculated for $[C_{18}H_{23}NO_2+Na]^+$: 308.1626, found: 308.1629 (error = 1.0 ppm).

Preparation of *N*-(4-methoxybenzyl)-aniline 369.[207]



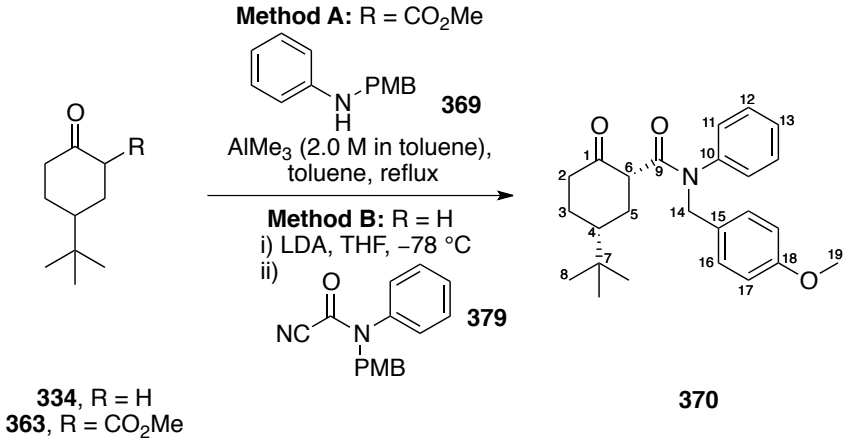
aniline **369**

To a solution of 4-methoxybenzaldehyde (585 mg, 4.30 mmol) in water (6.4 mL), aniline (400 mg, 4.30 mmol) was added slowly. The reaction mixture was stirred at room temperature under an atmosphere of air for 4 hours. The precipitate was filtered, rinsed with cold water and dried to yield an imine (white solid, 901 mg, 4.27 mmol). The crude imine was added to a suspension of sodium borohydride (194 mg, 5.12 mmol) in methanol (13 mL) at 0 °C under

an atmosphere of air. After 2 hours of stirring, the reaction mixture was quenched with NH_4Cl (15 mL, saturated aqueous solution) and poured into ice-cold water. The white precipitate was filtered, washed with cold water and dried to give the desired product (white solid, 865 mg, 4.06 mmol, 95% yield over two steps).

R_f: 0.62 (80:20 hexane/ethyl acetate); m.p. 48 - 49 °C, lit. m.p. 48 - 49°C; FTIR ν_{max} 3397, 3080 - 2836, 1601, 1583, 1512, 1501, 1471, 1415, 1246, 1172, 747, 693; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.7, 2H, H-8), 7.18 (dd, *J* = 8.5, 8.4, 2H, H-2), 6.88 (d, *J* = 8.7, 2H, H-9), 6.72 (dd, *J* = 8.4, 1.0, 1H, H-1), 6.64 (dd, *J* = 8.5, 1.0, 2H, H-3), 4.26 (s, 2H, H-6), 3.99 (br. s, 1H, H-5), 3.81 (s, 3H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0 (C, C-10), 148.3 (C, C-4), 131.6 (C, C-7), 129.2 (CH, C-2), 128.8 (CH, C-8), 117.5 (CH, C-1), 114.0 (CH, C-8), 112.8 (CH, C-2), 55.2 (CH_2, C-6), 47.7 (CH_3, C-11); HRMS (EI) calculated for $[C_{14}H_{15}NO]^+$: 213.1154, found: 213.1150 (error = 1.9 ppm). Data in agreement with those previously reported.[207]

Preparation of (±)-(1*R*,5*R*)-5-(*tert*-butyl)-*N*-(4-methoxybenzyl)-2-oxo-*N*-phenylcyclo hexane carboxamide 370.



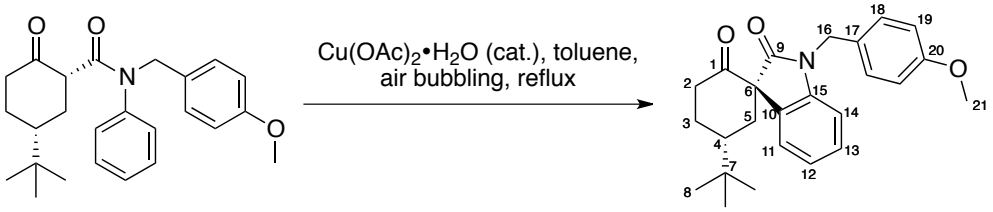
Method A: *N*-(4-methoxybenzyl)aniline **369** (200 mg, 0.94 mmol) was dissolved in anhydrous toluene (3 mL) at room temperature under nitrogen. The solution was cooled to 0 °C before

addition of a 2.0 M solution of trimethyl aluminium in toluene (1.42 mL, 2.83 mmol) and the resulting solution was maintained at 0 °C for an additional 30 minutes. The reaction mixture was stirred for 1 hour at room temperature and then heated at reflux. After 10 minutes, a solution of methyl enol ester (**363**) in dry toluene (3 mL) was added slowly and the solution was refluxed for another 17 hours. Once the starting material was consumed, the reaction was cooled to room temperature and quenched by slow addition of water (2 mL) and glacial acetic acid (0.5 mL). Ethyl acetate (10 mL) was added, the layers were separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide a yellow oil which was purified by column chromatography using a gradient of 0% to 40% ethyl acetate in petroleum ether to afford the desired product (yellow oil, 206 mg, 0.524 mmol, 56% yield).

Method B: To a solution of di*iso*propylamine (28 μL, 0.21 mmol) in anhydrous tetrahydrofuran (1 mL) at −78 °C under argon was added a 1.6 M solution of *n*-butyllithium in hexane (0.12 mL, 0.19 mmol). The solution was maintained at −78 °C for an additional 1 hour before a solution of 4-*tert*-butylcyclohexanone **334** (29 mg, 0.19 mmol) in anhydrous tetrahydrofuran (1 mL) was added. After a further hour at −78 °C and a solution of (4-methoxybenzyl)(phenyl)carbamoyl cyanide **379** (50 mg, 0.19 mmol) in dry tetrahydrofuran (1 mL) was added slowly. The reaction mixture was stirred for 1 hour at −78 °C and then at room temperature overnight. The reaction mixture was quenched by addition of 3 mL NH_4Cl (saturated aqueous solution) and ethyl acetate (3 mL) was added. The layers were separated and the organic phase was washed with water (2 x 4 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 0% to 50% ethyl acetate in petroleum ether to provide the desired product (yellow oil, 2 mg, 0.005 mmol, 3% yield) as a single diastereoisomer.

R_f: 0.32 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 3068 - 2840, 1715, 1654, 1613, 1594, 1512, 1494, 1244, 670; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 - 7.26 (m, 3H, H-12 and H-13), 7.18 (d, *J* = 8.7, 2H, H-16), 6.95 (dd, *J* = 6.9, 2.8, 2H, H-11), 6.80 (d, *J* = 8.7, 2H, H-17), 5.00 (d, *J* = 14.3, 1H, H-14), 4.74 (d, *J* = 14.3, 1H, H-14), 3.77 (s, 3H, H-19), 3.18 (dd, *J* = 12.1, 6.1, 1H, H-6), 2.37 - 2.29 (m, 1H, H-2), 2.12 - 2.05 (m, 2H, H-5), 2.01 - 1.92 (m, 2H, H-2 and H-3), 1.55 - 1.43 (m, 1H, H-3), 1.39 - 1.31 (m, 1H, H-4), 0.88 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.8 (CO, C-1), 169.7 (CON, C-9), 159.0 (C, C-18), 142.0 (C, C-10), 130.2 (CH, C-16), 129.6 (CH, C-13), 128.7 (C, C-15), 128.5 (CH, C-11), 128.3 (CH, C-12), 113.8 (CH, C-17), 55.3 (CH_3, C-19), 55.2 (CH, C-6), 52.6 (CH_2, C-14), 45.9 (CH, C-4), 41.3 (CH_2, C-2), 32.7 (C, C-7), 31.7 (CH_2, C-5), 27.9 (CH_2, C-3), 27.7 (CH_3, C-8); HRMS (ESI) calculated for $[C_{25}H_{31}NO_3+Na]^+$: 416.2202, found: 416.2218 (error = 3.8 ppm).

Preparation of the (±)-(1*S*,5*R*)-5-(*tert*-butyl)-1'-(4-methoxybenzyl)spiro[cyclohexane-1,3'-indoline]-2,2'-dione 371 and (±)-(1*R*,5*R*)-5-(*tert*-butyl)-1'-(4-methoxybenzyl) spiro[cyclo hexane-1,3'-indoline]-2,2'-dione 372.



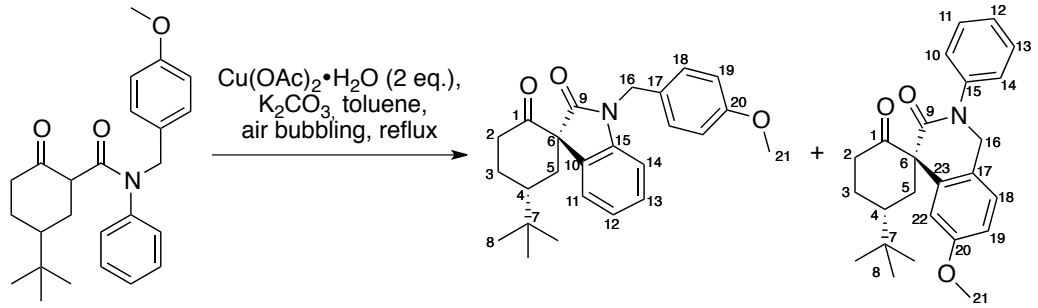
370 **371** + C-6-*epi* (**372**)
d.r. 4 : 1

To a two-neck round-bottom flask charged with copper(II) acetate monohydrate (4 mg, 0.022 mmol) was added a solution of starting material **370** (85 mg, 0.22 mmol) in toluene (8 mL). The suspension was heated at reflux while air was bubbled through. After 5 hours at reflux the reaction was cooled to room temperature. The brown solution was partitioned between NH_4Cl (10 mL, saturated aqueous solution) and ethyl acetate (10 mL). The layers were

separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography using a gradient of 0% to 50% ethyl acetate in petroleum ether to provide the desired product as a 4:1 mixture of diastereoisomers (beige foam, 43 mg, 0.11 mmol, 51% yield).

R_f: 0.30 (80:20 petroleum ether/ethyl acetate); m.p. 60 - 61 °C; FTIR ν_{max} 3070, 2960 - 2836, 1725, 1698, 1608, 1514, 1486, 1465, 1247, 1176, 1033, 737; ^{1}H NMR (400 MHz, $CDCl_3$): δ **major diastereoisomer** 7.53 (d, *J* = 7.4, 1H, H-11), 7.27 (d, *J* = 8.3, 2H, H-18), 7.18 (ddd, *J* = 7.8, 7.6, 1.1, 1H, H-13), 7.01 (ddd, *J* = 7.6, 7.4, 0.9, 1H, H-12), 6.85 (d, *J* = 8.3, 2H, H-19), 6.72 (d, *J* = 7.8, 1H, H-14), 5.04 (d, *J* = 15.6, 1H, H-16), 4.73 (d, *J* = 15.6, 1H, H-16), 3.76 (s, 3H, H-21), 2.78 (ddd, *J* = 15.4, 13.5, 6.0, 1H, H-2), 2.67 - 2.61 (m, 1H, H-2), 2.39 (dd, *J* = 13.0, 13.0, 1H, H-5), 2.30 - 2.22 (m, 1H, H-3), 2.12 - 2.99 (m, 2H, H-4 and H-5), 1.80 (ddd, *J* = 13.0, 13.0, 4.5, 1H, H-3), 0.95 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.5 (CO, C-1), 176.1 (CON, C-9), 159.0 (CO_2, C-20), 143.1 (C, C-15), 129.8 (C, C-10), 128.9 (CH, C-12), 128.6 (CH, C-18), 127.4 (C, C-17), 123.9 (CH, C-11), 122.4 (CH, C-13), 114.3 (CH, C-19), 110.1 (CH, C-14), 63.3 (C, C-6), 55.4 (CH_3, C-21), 43.5 (CH_2, C-16), 42.5 (CH, C-4), 39.5 (CH_2, C-2), 35.7 (CH_2, C-5), 32.9 (C, C-7), 27.7 (CH_3, C-8), 26.7 (CH_2, C-3); HRMS (ESI) calculated for $[C_{25}H_{29}NO_3+Na]^+$: 414.2045, found: 414.2033 (error = 2.9 ppm).

Preparation of (±)-(1*S*,5*R*)-5-(*tert*-butyl)-1'-(4-methoxybenzyl)spiro[cyclohexane-1,3'-indoline]-2,2'-dione 371 and (±)-(1*S*,5*R*)-5-(*tert*-butyl)-6'-methoxy-2'-phenyl-spiro[cyclohexane-1,4'-isoquinoline]-2,3'-dione 373.



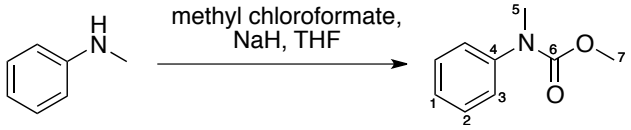
370 **371** **373**

To a round-bottom flask charged with copper(II) acetate monohydrate (86 mg, 0.43 mmol) and potassium carbonate (45 mg, 0.32 mmol) was added a solution of starting material **373** (85 mg, 0.22) in toluene (8 mL). The suspension was heated at reflux under an atmosphere of air. After 4 hours at reflux the reaction mixture was cooled to room temperature. The reaction mixture was partitioned between NH_4Cl (10 mL, saturated aqueous solution) and ethyl acetate (10 mL). The layers were separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 0% to 50% ethyl acetate in petroleum ether to provide **371** as a single diastereoisomer (yellow oil, 28 mg, 0.072 mmol, 33% yield) along with compound **373** as a single diastereoisomer (yellow oil, 12 mg, 0.031 mmol, 14% yield).

Data of **373**: R_f: 0.44 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 3054, 2959 - 2869, 1696, 1612, 1513, 1489, 1466, 1247, 1176, 1103, 733; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 - 7.14 (m, 4H, H-10, H-19, H-14 and H-22), 7.11 - 7.06 (m, 1H, H-12), 6.84 - 6.80 (m, 2H, H-11 and H-13), 6.74 (d, *J* = 7.4, 1H, H-18), 4.82 (dd, *J* = 15.5, 13.6, 2H, H-16), 3.76 (s, 3H, H-21), 3.31 (ddd, *J* = 14.0, 14.0, 5.9, 1H, H-2), 2.68 - 2.54 (m, 2H, H-2 and H-4), 2.32 - 2.24

(m, 1H, H-3), 2.14 (ddd, *J* = 13.6, 13.6, 3.4, 1H, H-5), 1.99 - 1.91 (m, 1H, H-5), 1.72 - 1.62 (m, 1H, H-3), 0.93 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.8 (CO, C-1), 173.9 (CON, C-9), 159.2 (C, C-20), 142.2 (C, C-23), 129.9 (C, C-17), 128.5 (CH, C-10, C-19 and C-14), 127.8 (C, C-15), 124.9 (CH, C-22), 122.9 (CH, C-12), 114.4 (CH, C-11 and C-13), 109.4 (CH, C-18), 63.2 (C, C-6), 55.4 (CH_3, C-21), 43.4 (CH_2, C-16), 40.1 (CH_2, C-5), 40.0 (CH, C-4), 39.8 (CH_2, C-2), 32.4 (C, C-7), 28.2 (CH_2, C-3), 27.5 (CH_3, C-8); HRMS (ESI) calculated for $[C_{25}H_{29}NO_3+Na]^+$: 414.2045, found: 414.2050 (error = 1.2 ppm).

Preparation of *N*-methyl-phenylcarbamate 377.



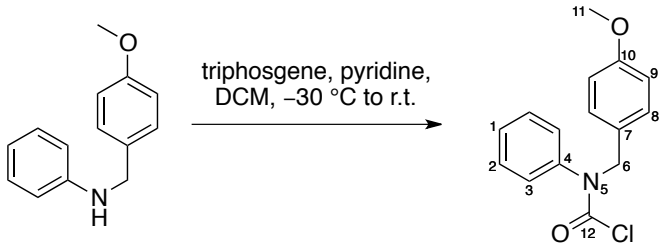
365 **377**

To a suspension of sodium hydride (432 mg, 18.00 mmol) in anhydrous tetrahydrofuran (25 mL) was added slowly *N*-methylaniline **365** (0.51 mL, 4.50 mmol) at 0 °C, followed by methyl chloroformate (0.35 mL, 4.5 mmol). The reaction mixture was stirred for 6 hours at room temperature under nitrogen. The precipitate was then filtered and the filtrate was concentrated *in vacuo* to give a yellow solid. The crude was purified by column chromatography using a gradient of 20% to 30% ethyl acetate in petroleum ether to provide the desired product (pale yellow oil, 700 mg, 4.24 mmol, 94% yield).

R_f: 0.48 (80:20 hexane/ethyl acetate); FTIR ν_{max} 3062 - 2890, 1701, 1598, 1498, 1445, 1358, 1191 - 1153; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 - 7.34 (m, 2H, H-3), 7.21 - 7.27 (m, 3H, H-2 and H-1), 3.72 (s, 3H, H-7), 3.33 (s, 3H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.3 (CO, C-6), 143.4 (C, C-4), 129.0 (CH, C-3), 126.2 (CH, C-2), 125.9 (CH, C-1), 53.0 (CH_3, C-7),

37.9 (CH_3, C-5); HRMS (EI) calculated for $[C_9H_{11}NO_2]^+$: 165.0783, found: 165.0790 (error = 4.2 ppm).

Preparation of (4-methoxybenzyl)(phenyl)carbamic chloride 378.[208]



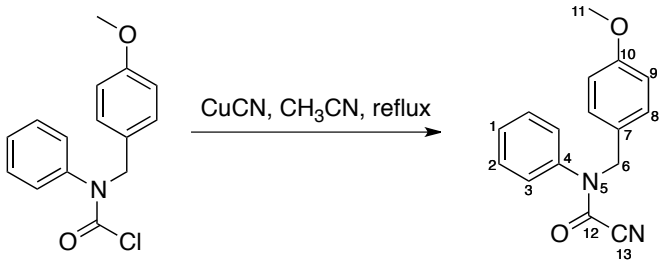
369 **378**

To a solution of triphosgene (700 mg, 2.34 mmol) in anhydrous dichloromethane (20 mL) at –30 °C, under nitrogen, anhydrous pyridine (140 µL, 17.30 mmol) was added slowly. After 30 minutes at –30 °C, a solution of PMB-aniline **369** (1.00 g, 4.68 mmol) in anhydrous dichloromethane (10 mL) was added slowly and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with 1.0 M HCl (30 mL) and extracted with dichloromethane (40 mL). The layers were separated and the organic phase was washed with water (2 x 40 mL), dried over $MgSO_4$ and concentrated *in vacuo* to produce a yellow oil. The crude oil was purified by column chromatography using a gradient of 30% to 50% ethyl acetate in petroleum ether to give the desired product (colourless oil, 970 mg, 3.53 mmol, 75% yield).

R_f: 0.67 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 3064 - 2837, 1724, 1613, 1595, 1512, 1494, 1378, 1223, 1196, 1111, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.33 (m, 3H, H-2 and H-1), 7.12 (d, *J* = 8.6, 2H, H-8), 7.01 (br. s, 2H, H-3), 6.82 (d, *J* = 8.6, 2H, H-9), 4.81 (s, 2H, H-6), 3.79 (s, 3H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6 (C, C-10), 149.7 (C, C-4), 141.6 (C, C-7), 130.6 (CH, C-8), 129.5 (CH, C-2 and C-1), 128.7 (CH, C-3), 127.8 (C,

C-4), 114.0 (CH, C-9), 56.2 (CH_2, C-6), 55.2 (CH_3, C-11); HRMS (ESI) calculated for $[C_{15}H_{14}NO_2Cl+Na]^+$: 298.0597, found: 298.0611 (error = 4.7 ppm). Data in agreement with those previously reported.[208]

Preparation of (4-methoxybenzyl)(phenyl)carbamoyl cyanide 379.



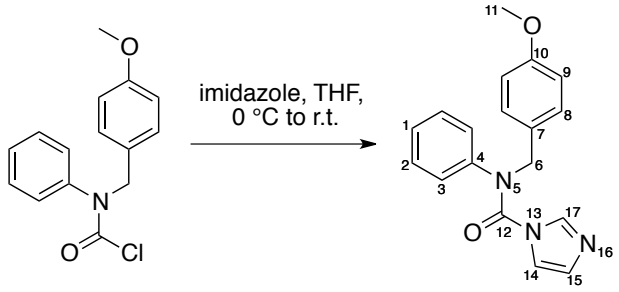
378 **379**

To a copper(I) cyanide (553 mg, 6.18 mmol) suspension in anhydrous acetonitrile (5 mL), a solution of carbamoyl chloride **378** (850 mg, 3.09 mmol) in anhydrous acetonitrile (5 mL) was added at room temperature *via* cannula. The white suspension was refluxed for 4 hours under nitrogen until complete consumption of starting material was observed. The reaction mixture was then cooled to room temperature and partitioned between diethyl ether (30 mL) and water (30 mL). The layers were separated and the organic phase was washed with water (2 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 0% to 50% ethyl acetate in petroleum ether to provide the desired product (yellow oil, 692 mg, 2.60 mmol, 84% yield).

R_f: 0.48 (80:20 hexane/ethyl acetate); FTIR ν_{max} 3070 - 3000, 2961 - 2838, 2230, 1672, 1612, 1595, 1512, 1493, 1393, 1245, 1176, 721, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 - 7.40 (m, 3H, H-1 and H-2), 7.10 - 7.06 (m, 4H, H-3 and H-8), 6.84 - 6.79 (m, 2H, H-9), 4.85 (s, 2H, H-6), 3.79 (s, 3H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7 (CO, C-10), 144.8 (CO, C-12), 138.3 (C, C-14), 130.6 (CH, C-3 or C-8), 130.1 (CH, C-1 or C-2), 130.0 (CH, C-1 or C-2), 128.6 (CH, C-3 or C-8), 126.8 (C, C-7), 114.2 (CH, C-9), 110.7 (CN, C-13), 55.3 (CH_3, C-

11), 52.6 (CH_2, C-6); HRMS (ESI) calculated for $[C_{16}H_{14}N_2O_2+Na]^+$: 289.0953, found: 289.0951 (error = 0.7 ppm).

Preparation of *N*-(4-methoxybenzyl)-*N*-phenylimidazole-1-carboxamide 380.

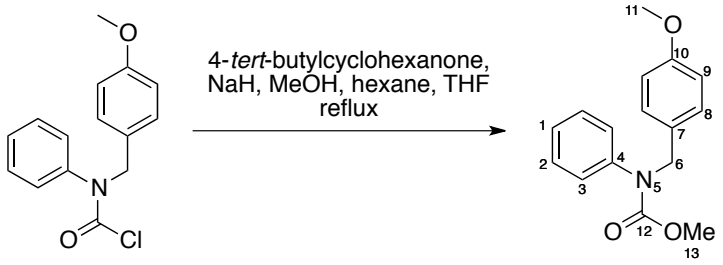


378 **380**

To a solution of carbamoyl chloride **378** (200 mg, 0.72 mmol) in anhydrous tetrahydrofuran (1 mL) at 0 °C under nitrogen, a solution of imidazole (150 mg, 2.17 mmol) in anhydrous tetrahydrofuran (1 mL) was added. After 1 hour at 0 °C, the reaction mixture was allowed to warm slowly to room temperature overnight. The volatiles were then removed *in vacuo* to give a crude oil that was purified by column chromatography using a gradient of 0% to 50% ethyl acetate in petroleum ether, to provide the desired product (colourless oil, 214 mg, 0.70 mmol, 96% yield).

R_f: 0.24 (50:50 petroleum ether/ethyl acetate); FTIR ν_{max} 3125 - 2836, 1698, 1612, 1596, 1514, 1397, 1265, 1246, 1177, 730, 699, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (br. s, 1H, H-14), 7.35 - 7.27 (m, 3H, H-2 and H-1), 7.18 (d, *J* = 8.6, 2H, H-8), 6.99 - 6.94 (m, 2H, H-3), 6.86 - 6.77 (m, 4H, H-9, H-16 and H17), 4.96 (s, 2H, H-6), 3.77 (s, 3H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6 (C, C-10), 150.4 (CO, C-12), 141.5 (C, C-4), 138.1 (CH, C-14), 130.5 (CH, C-8), 130.3 (CH, C-2), 129.1 (CH, C-16), 128.4 (CH, C-1), 128.2 (C, C-7), 127.3 (CH, C-3), 118.8 (CH, C-17), 114.1 (CH, C-9), 55.8 (CH_3, C-11), 55.4 (CH_2, C-6); HRMS (ESI) calculated for $[C_{18}H_{17}N_3O_2+Na]^+$: 330.1218, found: 330.1208 (error = 3.0 ppm).

Preparation of methyl 4-methoxybenzyl(phenyl)carbamate 381.



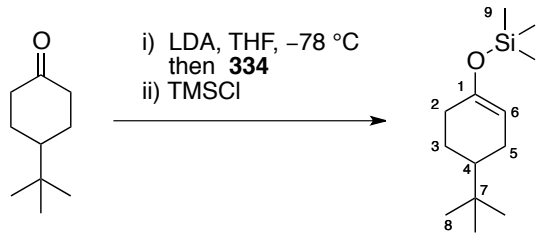
378 **381**

To a suspension of sodium hydride (35 mg, 1.45 mmol) in hexane (0.4 mL), a solution of carbamoyl chloride **378** (100 mg, 0.36 mmol) in anhydrous tetrahydrofuran (0.4 mL) was added followed by a catalytic amount of methanol (3 μL, 0.073 mmol). The reaction mixture was refluxed under argon for 15 minutes before a solution of 4-*tert*-butylcyclohexanone (56 mg, 0.363 mmol) in anhydrous tetrahydrofuran (0.4 mL) was added slowly. After 7 hours at reflux, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate (2 mL) and water (2 mL). The layers were separated and the organic phase was washed with water (2 x 2 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide an orange oil which was purified by column chromatography using a gradient of 0% to 50% ethyl acetate in petroleum ether to furnish compound **381** (yellow oil, 19 mg, 0.070 mmol, 96% yield).

R_f: 0.50 (80:20 petroleum ether/ethyl acetate); FTIR ν_{max} 3070 - 2837, 1703, 1613, 1597, 1512, 1497, 1444, 1381, 1244, 1175, 1033, 730 - 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 - 7.26 (m, 2H, H-2), 7.23 - 7.19 (m, 1H, H-1), 7.16 - 7.11 (m, 2H, H-3), 7.07 (br. d, J = 7.5, 2H, H-8), 6.83 - 6.78 (m, 2H, H-9), 4.78 (s, 2H, H-6), 3.78 (s, 3H, H-11), 3.71 (s, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0 (C, C-10), 156.5 (CO, C-12), 142.0 (C, C-4), 130.1 (C, C-7), 129.6 (CH, C-3), 129.0 (CH, C-2), 127.4 (CH, C-8), 126.8 (CH, C-1), 113.9 (CH, C-9),

55.3 (CH_3, C-11), 54.0 (CH_2, C-6), 53.1 (CH_3, C-13); HRMS (ESI) calculated for $[C_{16}H_{17}NO_3+Na]^+$: 294.1106, found: 294.1116 (error = 3.4 ppm).

Preparation of (±)-((4-(*tert*-butyl)cyclohex-1-en-1-yl)oxy)trimethylsilane 382.[209]

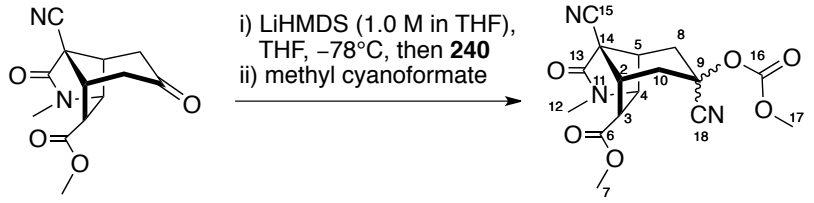


334 **382**

To a stirred solution of di*iso*propylamine (0.11 mL, 0.65 mmol) in anhydrous tetrahydrofuran (7 mL) at −78 °C under nitrogen, was added a 1.6 M solution of *n*-butyllithium in hexane (0.49 mL, 0.78 mmol). A solution of 4-*tert*-butylcyclohexanone **334** (100 mg, 0.78 mmol) in anhydrous tetrahydrofuran (4 mL) was added slowly after 20 minutes, at −78 °C. Finally, 40 minutes later trimethylsilylchloride (0.41 mL, 3.25 mmol) was added at −78 °C. The reaction mixture was quenched after 1 hour with triethylamine (0.5 mL) and $NaHCO_3$ (3 mL, saturated aqueous solution), and was extracted with diethyl ether (10 mL). The layers were separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford the desired product (pale yellow oil, 135 mg, 92% conversion). The conversion of the reaction was determined by gas chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (dt, J = 5.7, 2.1, 1H, H-6), 2.14 - 1.94 (m, 3H), 1.86 - 1.73 (m, 2H), 1.29 - 1.18 (m, 2H), 0.86 (s, 9H, H-8), 0.17 (s, 9H, H-9). Data in agreement with those previously reported.[209]

Preparation of (±)-(3*aS*,4*R*,8*R*)-methyl 3a,6-dicyano-6-((methoxycarbonyl)oxy)-2-methyl -3-oxooctahydro-1,4-methanoisoindole-8-carboxylate 391.



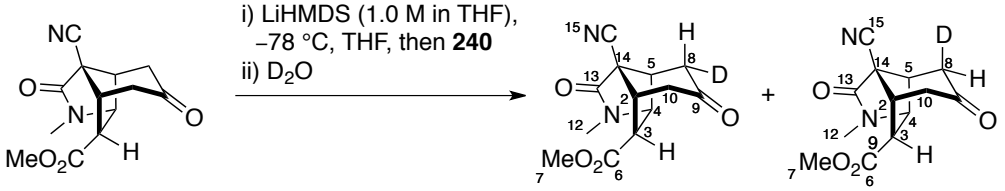
240 **391**

To a solution of starting material **240** (25 mg, 0.095 mmol) in anhydrous tetrahydrofuran (0.5 mL) at −78 °C under argon, a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (115 μL, 0.11 mmol) was added. After 1 hour at −78 °C, methyl cyanoformate (76 μL, 0.95 mmol) was introduced slowly. The reaction mixture was warmed slowly to −10 °C, quenched by addition of water (1.5 mL) and ethyl acetate (3 mL) was added. The layers were separated and the organic phase was washed with water (2 x 2 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude dark oil, which was purified by column chromatography using 100% ethyl acetate to provide cyanohydrin **391** (yellow oil, 5 mg, 0.014 mmol, 15%) as a 5:1 mixture of epimers at the C-9 position.

R_f: 0.78 (100% ethyl acetate); FTIR ν_{max} 2959 - 2851, 2254 (CN), 2246 (CN), 1817, 1760, 1739, 1720, 1440, 1269, 1236, 732; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.06 (dd, *J* = 3.5, 1.2, 1H, H-4), 3.90 (s, 3H, H-17$_{(major)}$), 3.84 (s, 3H, H-17$_{(minor)}$), 3.75 (s, 3H, H-7$_{(minor)}$), 3.74 (s, 3H, H-7$_{(major)}$), 3.69 (dd, *J* = 3.5, 2.2, 1H, H-3), 3.21 (br. dd, *J* = 4.0, 2.2, 1H, H-2), 2.86 (br. dd, *J* = 17.2, 2.2, 2H, H-10), 2.82 - 2.80 (m, 1H, H-5), 2.80 (s, 3H, H-12$_{(minor)}$), 2.79 (s, 3H, H-12$_{(major)}$), 2.77 - 2.73 (m, 2H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6 (CO_2, C-6), 167.6 (CON, C-13), 152.5 (CO_2, C-16), 117.8 (CN, C-18), 114.7 (CN, C-15), 69.0 (C, C-9), 65.1 (CH, C-4), 56.1 (C, C-14), 52.8 (CH_3, C-17$_{(minor\ and\ major)}$), 51.8 (CH_3, C-7$_{(minor\ and\ major)}$), 51.7 (CH, C-5), 48.3 (CH, C-3), 37.5 (CH, C-2), 37.2 (CH_2, C-10), 33.8 (CH_2,

C-8), 30.2 (CH_3, C-12$_{(minor\ and\ major)}$); HRMS (ESI) calculated for $[C_{16}H_{17}N_3O_6+Na]^+$: 370.1015, found: 370.1013 (error = 0.5 ppm).

Preparation of (±)-(3*aS*,4*R*,7*S*,8*R*,8*aR*)-methyl 3a-cyano-7-deutero-2-methyl-3,6-dioxooctahydro-1,4-methanoisoindole-8-carboxylate 392 and (±)-(3*aS*,4*R*,7*R*,8*R*,8*aR*)-methyl 3a-cyano-7-deutero-2-methyl-3,6-dioxooctahydro-1,4-methanoisoindole-8-carboxylate 393.



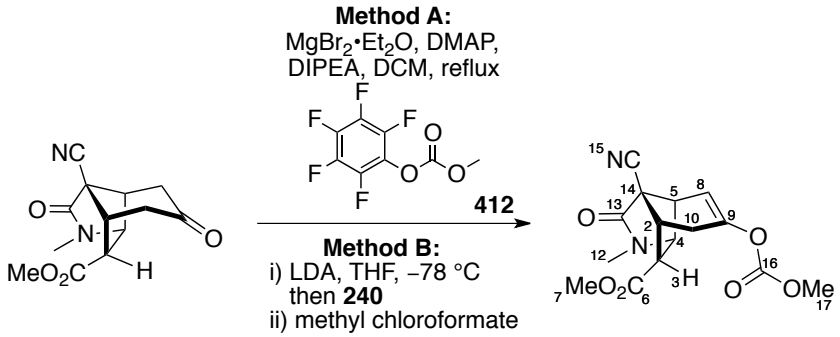
240 **392** 1 : 1 mixture **393**

To a solution of starting material **240** (25 mg, 0.095 mmol) in anhydrous tetrahydrofuran (0.5 mL) at −78 °C under nitrogen, was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (0.12 mL, 0.11 mmol). After 30 minutes of stirring at −78 °C, deuterium oxide (17 μL, 0.95 mmol) was added and the reaction mixture was allowed to warm slowly to room temperature. The yellow solution was partitioned between NH_4Cl (2 mL, saturated aqueous solution) and ethyl acetate (3 mL). The layers were separated and the organic phase was washed with NH_4Cl (2 x 2 mL, saturated aqueous solution), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography using 100% ethyl acetate to provide the desired product as a 1:1 mixture of isotopomers (green oil, 12 mg, 0.045 mmol, 48% yield).

R_f: 0.46 (100% ethyl acetate); FTIR ν_{max} 2961 - 2937, 2860, 2249 (CN), 1713 (CO_2Me), 1438, 1398, 1232, 1056, 731; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (dd, *J* = 3.0, 2.0, 1H, H-4), 3.75 (s, 3H, H-7), 3.27 (dd, *J* = 5.4, 2.4, 1H, H-2), 3.04 - 3.01 (m, 1H, H-5), 2.94 (d, *J* = 18.4,

2.4, 1H, H-$10_{equatorial}$), 2.87 - 2.85 (m, 1H, H-3), 2.81 (s, 3H, H-12), 2.80 - 2.70 (m, 1H, H-10_{axial} and 1H, H-8 (**392**)), 2.53 (d, J = 19.0, 1H, H-8 (**393**)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.6 (CO, C-9), 169.7 (CO_2, C-6), 167.9 (CON, C-13), 115.3 (CN, C-15), 66.4 (CH, C-4), 60.6 (C, C-14), 53.0 (CH_3, C-7), 52.8 (CH, C-5), 51.9 (CH, C-3), 44.0 (CH_2, C-10), 38.9 (br. CH, C-8), 38.6 (CH, C-2), 30.1 (CH_3, C-12); HRMS (ESI) calculated for $[C_{13}H_{13}O_4N_2D+Na]^+$: 286.0914, found: 286.0909 (error = 1.7 ppm).

Preparation of (±)-(3*aS*,4*R*,7*aR*,8*R*)-methyl 3a-cyano-6-((methoxycarbonyl)oxy)-2-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1,4-methanoisoindole-8-carboxylate 394.



Method A: To a solution of methyl pentafluorophenylcarbonate **412** (14 mg, 0.06 mmol) in anhydrous dichloromethane (0.5 mL) at room temperature under nitrogen, magnesium bromide ethyl etherate (32 mg, 0.12 mmol) was added in one portion. The suspension was heated at reflux for 15 minutes and 4-dimethylaminopyridine (22 mg, 0.17 mmol) was added followed by a solution of starting material **240** (13 mg, 0.05 mmol) in anhydrous dichloromethane (1.5 mL). The suspension was refluxed another 30 minutes and *N,N*-di*iso*propylethylamine (30 μL, 0.17 mmol) was added. The reaction was heated at reflux for 17 hours. The reaction mixture was then quenched with water (3 mL) and extracted with ethyl acetate (4 mL). The layers were separated and the organic phase was washed with water

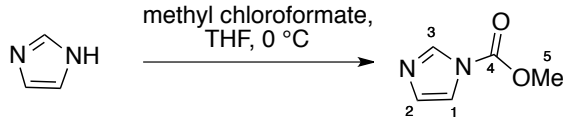
(2 x 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using 100% ethyl acetate to provide carbonate **394** (yellow oil, 8 mg, 0.025 mmol, 50% yield). (*NB*: some degradation of this compound was observed on silica and on *vacuo*).

Method B: To a solution of di*iso*propylamine (26 μL, 0.18 mmol) in anhydrous tetrahydrofuran (0.2 mL) cooled to −78 °C under argon, a 1.6 M solution of *n*-butyllithium in hexane (0.11 mL, 0.18 mmol) was added. After 30 minutes at −78 °C, a solution of starting material **240** (46 mg, 0.18 mmol) in anhydrous tetrahydrofuran (0.4 mL) was added and the orange solution was stirred for an extra 40 minutes at −78 °C before the addition of methyl chloroformate (28 μL, 0.36 mmol). The reaction mixture was quenched by addition of NH_4Cl (1.5 mL, saturated aqueous solution) after an additional 2 hours and 30 minutes at −78 °C and was extracted with ethyl acetate (3 mL). The layers were separated and the organic phase was washed with water (2 x 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 50% to 100% ethyl acetate in petroleum ether to provide carbonate **394** (yellow oil, 17 mg, 0.053 mmol, 30% yield). (*NB*: some degradation of this compound was observed on silica and on *vacuo*).

R_f: 0.54 (100% ethyl acetate); FTIR ν_{max} 3058, 2958 - 2854, 2249 (CN), 1758, 1742, 1719, 1693, 1440, 1264, 1201, 1170, 732; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 (d, *J* = 6.6, 1H, H-8), 4.21 (dd, *J* = 3.0, 2.0, 1H, H-4), 3.84 (s, 3H, H-7), 3.73 (s, 3H, H-17), 3.32 (dd, *J* = 3.0, 2.8, 1H, H-3), 3.26 - 3.22 (m, 1H, H-2), 3.12 (br. dd, *J* = 6.6, 2.0, 1H, H-5), 3.01 - 2.94 (m, 1H, H-10), 2.79 (s, 3H, H-12), 2.50 (dd, *J* = 18.0, 4.0, 1H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6 (CO, C-16), 168.1 (CON, C-13), 153.4 (CO, C-6), 150.6 (CO, C-9), 115.1 (CN, C-15), 110.4 (CH, C-8), 69.8 (CH, C-4), 55.6 (CH_3, C-7), 52.6 (CH_3, C-17), 52.1 (CH, C-5), 51.9

(CH, C-3), 49.6 (C, C-14), 38.7 (CH, C-2), 33.2 (CH, C-10), 29.8 (CH_3, C-12); HRMS (ESI) calculated for $[C_{15}H_{16}N_2O_6+Na]^+$: 343.0906, found: 343.0908 (error = 0.6 ppm).

Preparation of *N*-carbomethoxyimidazole 398.[174]

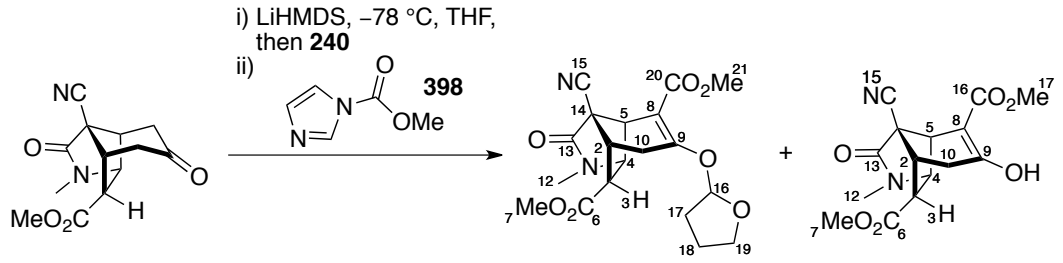


imidazole **398**

To a solution of imidazole (1.44 g, 21.2 mmol) in anhydrous tetrahydrofuran (25 mL) at 0 °C under nitrogen, methyl chloroformate (0.82 mL, 10.6 mmol) was added dropwise. After 2 hours at 0 °C, the resulting precipitate was filtered. The filtrate was concentrated *in vacuo* to give the desired product (white solid, 1.16 g, 9.19 mmol, 87% yield), which was used without further purification. *NB*: The solid degraded at room temperature and was stored under nitrogen in the fridge.

R_f: 0.22 (50:50 ethyl acetate/petroleum ether); m.p. 40 - 41 °C; lit. m.p.: 40 - 42 °C;[210] FTIR ν_{max} 3151, 3135, 3128, 2928, 1756 (CO_2Me), 1440, 1380, 1208, 1255, 1101; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H, H-3), 7.44 (t, *J* = 1.4, 1H, H-2), 7.09 (dd, *J* = 1.4, 0.7, 1H, H-1), 4.05 (s, 3H, H-5); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4 (CO, C-4), 137.2 (CH, C-3), 130.8 (CH, C-2), 117.2 (CH, C-1), 54.8 (CH_3, C-5); HRMS (EI) calculated for $[C_5H_6N_2O_2]^+$: 126.0429, found: 126.0428 (error = 0.8 ppm). Data in agreement with those previously reported.[174]

Preparation of (±)-(3*aS*,4*R*,7*aS*,8*R*)-dimethyl 3a-cyano-2-methyl-3-oxo-6-((tetrahydrofuran-2-yl)oxy)-2,3,3a,4,5,7a-hexahydro-1,4-methanoisoindole-7,8-dicarboxylate 399 and (±)-(3*aS*,4*R*,7*aS*,8*R*)-dimethyl 3a-cyano-6-hydroxy-2-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1,4-methanoisoindole-7,8-dicarboxylate 400.



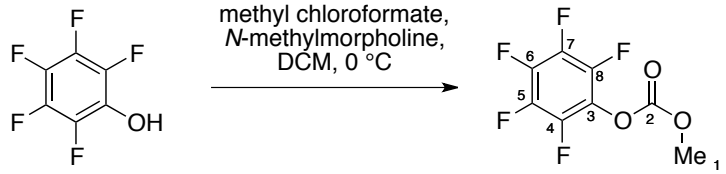
To a solution of starting material **240** (26 mg, 0.099 mmol) in anhydrous tetrahydrofuran (0.2 mL) at −78 °C under nitrogen, a 1.0 M solution of lithium bis(trimethylsilyl)amide (0.12 mL, 0.12 mmol) was added. The reaction mixture was stirred for 1 hour at −78 °C under nitrogen and a solution of imidazole methyl ester **398** (63 mg, 0.50 mmol) in anhydrous tetrahydrofuran (0.2 mL) was added slowly. The reaction mixture was stirred 1 hour at −78 °C and then warmed gradually to −10 °C. The reaction mixture was then quenched with NH_4Cl (1 mL, saturated aqueous solution) and ethyl acetate (1 mL) was added. The layers were separated and the organic phase was washed with water (2 x 1 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 50% to 100% ethyl acetate in petroleum ether to provide the product **399** (yellow oil, 11 mg, 0.028 mmol, 28% yield) as a single diastereoisomer, starting material **240** (37% yield of recovery) along with another product which was purified by preparative thin layer chromatography to afford **400** (2 mg, 0.005 mmol, 5% yield).

Data for **399**: R_f: 0.54 (100% ethyl acetate); FTIR ν_{max} 2958 - 2858, 2249 (CN), 1755 - 1695, 1617, 1439, 1396, 1266, 1208, 1187, 731; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (t, *J* = 7.8, 1H,

H-16), 4.18 (td, *J* = 7.6, 4.2, 1H, H-19), 4.07 (dd, *J* = 2.8, 2.3, 1H, H-4), 3.80 (s, 3H, H-21), 3.75 (s, 3H, H-7), 3.73 - 3.71 (m, 1H, H-3), 3.31 - 3.26 (m, 1H, H-2), 3.00 (dd, *J* = 19.2, 3.3, 1H, H-10), 2.89 (br. d, *J* = 2.8, 1H, H-5), 2.85 (s, 3H, H-7), 2.76 (dd, *J* = 19.2, 3.3, 1H, H-10), 2.46 - 2.30 (m, 2H, H-17), 1.96 - 1.87 (m, 2H, H-18); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.1 (C, C-9), 169.9 (CO_2, C-6), 167.7 (CON, C-13), 155.7 (CO_2, C-20), 147.3 (CH, C-16), 130.8 (C, C-8), 115.0 (CN, C-15), 66.7 (CH_2, C-19), 66.4 (CH, C-4), 55.1 (C, C-14), 54.2 (CH_3, C-12), 52.9 (CH, C-3), 52.4 (CH_3, C-4), 51.8 (CH, C-5), 42.0 (CH_2, C-10), 38.1 (CH, C-2), 30.2 (CH_3, C-12), 27.5 (CH_2, C-18), 24.5 (CH_2, C-17); HRMS (ESI) calculated for $[C_{19}H_{22}N_2O_7+Na]^+$: 413.1325, found: 413.1320 (error = 1.2 ppm).

Data for **400**: R_f: 0.60 (100% ethyl acetate); FTIR ν_{max} 3146, 2962 - 2854, 2257 (CN), 1738 - 1690, 1656, 1613, 1444, 1227 - 1197, 1078, 767; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.3 (br. s, 1H, H-9), 4.14 (dd, *J* = 3.0, 2.0, 1H, H-4), 3.82 (s, 3H, H-17), 3.73 (s, 3H, H-7), 3.54 (dd, *J* = 2.0, 2.0, 1H, H-3), 3.22 - 3.18 (m, 1H, H-2), 3.09 (dd, *J* = 18.9, 2.7, 1H, H-10), 2.99 (dd, *J* = 3.0, 2.0, 1H, H-5), 2.81 (s, 3H, H-12), 2.55 (dd, *J* = 18.9, 2.7, 1H, H-10); HRMS (ESI) calculated for $[C_{15}H_{16}N_2O_6+H]^+$: 321.1087, found: 321.1081 (error = 1.9 ppm).

Preparation of methyl pentafluorophenylcarbonate 412.[168]



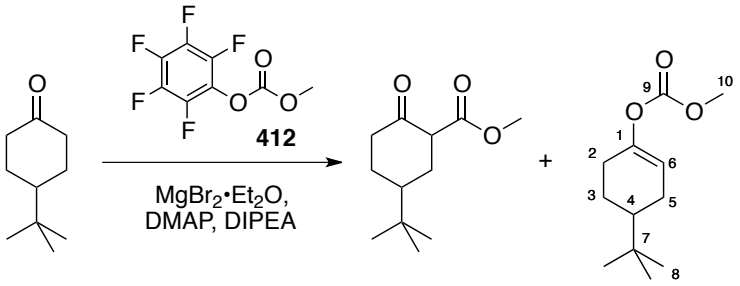
pentafluorophenol **412**

To a solution of pentafluorophenol (2.50 g, 13.58 mmol) in anhydrous dichloromethane (27 mL) at 0 °C under nitrogen, *N*-methylmorpholine (2.2 mL, 20.37 mmol) was added slowly followed by a dropwise addition of methyl chloroformate (1.1 mL, 14.23 mmol). Stirring the reaction mixture 1 hour at 0 °C was sufficient for full conversion of starting material. The

reaction mixture was then filtered through a short pad of silica and the filtrate was partitioned between dichloromethane (30 mL) and water (30 mL). The layers were separated and the organic phase was washed with water (2 x 30 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to afford the desired product (white solid, 2.51 g, 10.37 mmol, 76% yield), which was used without further purification.

R_f: 0.79 (80:20 hexane/ethyl acetate); m.p. 32 - 33 °C; lit. m.p.: 31 - 33 °C;[168] FTIR ν_{max} 2977, 1788 (CO_2Me), 1657, 1519, 1477, 1446, 1321, 1238, 1196, 1153, 974, 925, 773; ^1H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 3H, H-1); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.1 (CO, C-2), 141.6 (dm, *J* = 257.7, C-5 and C-7), 140.0 (dtt, *J* = 254.5, 13.6, 3.6, C-4), 138.1 (dm, *J* = 251.5, C-4 and C-8), 126.4 - 125.5 (m, C-3), 56.9 (CH_3, C-1); HRMS (EI) calculated for $[C_8H_3O_3F_5]^+$: 242.0002, found: 242.0000 (error = 0.8 ppm). Data in agreement with those previously reported.[168]

Preparation of (±)-methyl 5-(*tert*-butyl)-2-oxocyclohexane carboxylate 363 and 4-(*tert*-butyl)cyclohex-1-en-1-yl methylcarbonate 414.



334 **363** **414**

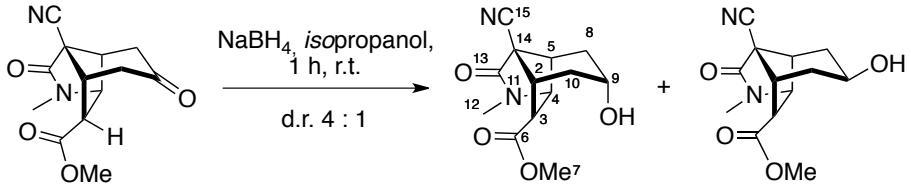
A solution of 4-*tert*-butylcyclohexanone **334** (100 mg, 0.65 mmol) in anhydrous dichloromethane (2 mL) was added to a suspension of methyl pentafluorophenylcarbonate **412** (189 mg, 0.78 mmol), magnesium bromide ethyl etherate (419 mg, 1.62 mmol) and 4-dimethylaminopyridine (16 mg, 0.13 mmol) in anhydrous dichloromethane (7 mL) at room

temperature under nitrogen. *N,N*-di*iso*propylethylamine (0.34 mL, 1.95 mmol) was added and the reaction mixture was heated at reflux for 5 hours. The reaction mixture was quenched with water (10 mL) and 0.5 M HCl aqueous (0.5 mL), and dichloromethane (10 mL) was added. The layers were separated and the organic phase was washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 0% to 50% ethyl acetate in petroleum ether to provide *β*-keto ester **363** (pale yellow oil, 62 mg, 0.29 mmol, 45% yield) along with carbonate **414** (colourless oil, 55 mg, 0.26 mmol, 40% yield).

Data for **414**: R_f: 0.79 (80:20 hexane/ethyl acetate); FTIR ν_{max} 2977 - 2868, 1756, 1699, 1440, 1365, 1249, 1146, 1056, 1038, 940, 784; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 - 5.44 (m, 1H, H-6), 3.80 (s, 3H, H-10), 2.35 - 2.23 (m, 1H, H-2), 2.22 - 2.10 (m, 2H, H-2 and H-5), 1.95 - 1.83 (m, 2H, H-5 and H-3), 1.37 - 1.31 (m, 2H, H-3 and H-4), 0.88 (s, 9H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2 (CO, C-9), 148.7 (C, C-1), 114.2 (CH, C-6), 55.0 (CH_3, C-10), 43.5 (CH, C-4), 32.3 (C, C-7), 27.5 (CH_2, C-2), 27.4 (CH_3, C-8), 25.1 (CH_2, C-5), 24.1 (CH_2, C-3); HRMS (ESI) calculated for $[C_{12}H_{20}O_3+Na]^+$: 235.1310, found: 235.1304 (error = 2.6 ppm).

5.4 Experimental for Chapter 4

Preparation of (±)-(3*aS*,4*R*,6*R*,7*aR*,8*R*)-methyl 3a-cyano-6-hydroxy-2-methyl-3-oxoocta hydro-1,4-methanoisoindole-8-carboxylate 424 and (±)-(3*aS*,4*R*,6*S*,7*aR*,8*R*)-methyl 3a-cyano -6-hydroxy-2-methyl-3-oxooctahydro-1,4-methanoisoindole-8-carboxylate 425.

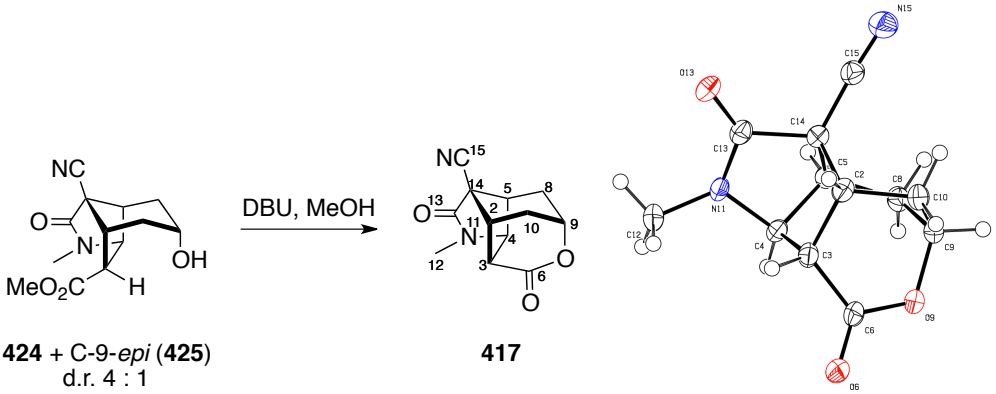


240 **424** (major) **425** (minor)

Starting material **240** (22 mg, 0.08 mmol) was added to a suspension of sodium borohydride (1 mg, 0.02 mmol) in *iso*propanol (2 mL) at room temperature. After 2 hours of stirring at room temperature, the reaction was quenched with 2 mL of water and ethyl acetate (2 mL) was added. The layers were separated and the organic phase was washed with water (2 x 3 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide the desired product as a 4:1 mixture of inseparable diastereoisomers (yellow oil, 10 mg, 0.038 mmol, 45% yield).

Data for **424** (major): R_f: 0.31 (100% ethyl acetate); FTIR ν_{max} 3284, 3100 - 3078, 2976 - 2877, 2250 (CN), 1711, 1664, 1348, 1324, 1237, 1185; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32 - 4.29 (m, 1H, H-3), 4.25 - 4.19 (m, 1H, H-9), 4.00 (dd, *J* = 3.4, 1.9, 1H, H-4), 3.71 (s, 3H, H-7), 3.08 - 3.04 (m, 1H, H-2), 2.78 (s, 3H, H-12), 2.73 - 2.68 (m, 1H, H-5), 2.44 - 2.30 (m, 2H, H-10_{axial} and H-8_{axial}), 2.08 (d, *J* = 15.6, 1H, H-$10_{equatorial}$), 1.85 (d, *J* = 15.6, 1H, H-$8_{equatorial}$), 1.80 (br. s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2 (CO_2, C-6), 169.3 (CON, C-13), 116.3 (CN, C-15), 65.8 (CH, C-4), 62.0 (CH, C-9), 52.7 (CH_3, C-7), 52.3 (CH, C-5), 51.9 (C, C-14), 49.4 (CH, C-3), 38.4 (CH, C-2), 35.5 (CH_2, C-10), 31.9 (CH_2, C-8), 30.1 (CH_3, C-12); HRMS (ESI) calculated for $[C_{13}H_{16}N_2O_4+Na]^+$: 287.1008, found: 287.1009 (error = 0.3 ppm).

Preparation of (±)-(3*S*,3*aR*,5*R*,8*S*,9*R*)-1-methyl-2,7-dioxooctahydro-3,8,5-(epiethane [1,1,2] triyl)oxepino[4,5-b]pyrrole-3-carbonitrile 417.



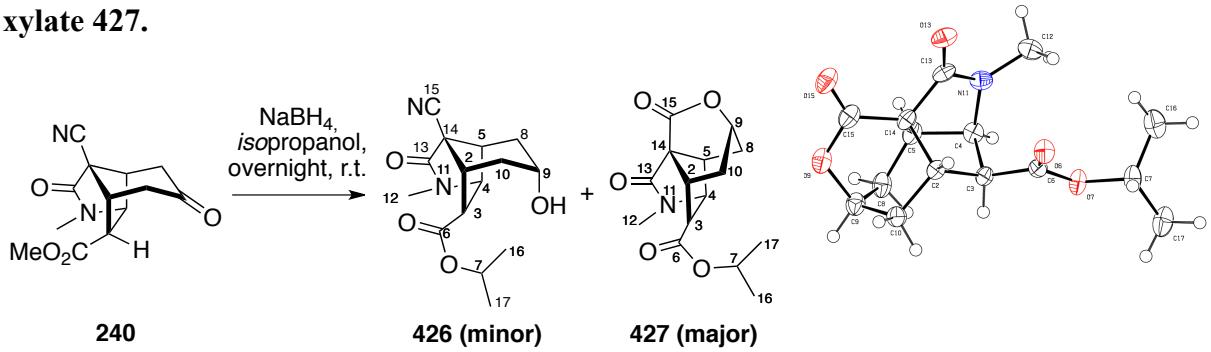
424 + C-9-*epi* (**425**)
d.r. 4 : 1

417

To a solution of **424** and **425** (10 mg, 0.038 mmol) in dry methanol (0.8 mL) at room temperature, a drop of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The reaction was stirred overnight at room temperature under argon. The volatiles were then removed *in vacuo* and the crude product was purified by column chromatography using a gradient of 50% to 100% ethyl acetate in petroleum ether to provide the desired product (yellow oil, 4 mg, 0.017 mmol, 45% yield). Suitable crystals were grown from a 1:1 solution of chloroform/methanol over six months.

R_f: 0.44 (80:20 ethyl acetate/petroleum ether); FTIR ν_{max} 2732 - 2857, 2232 (CN), 1717, 1642, 1434, 1394, 1229, 1194, 1082; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65 (br. s, 1H, H-9), 3.84 (d, J = 1.7, 1H, H-4), 3.00 (dd, J = 7.7, 1.7, 1H, H-3), 2.90 - 2.88 (m, 4H, H-2 and H-12), 2.78 (d, J = 1.7, 1H, H-5), 2.45 (dd, J = 15.4, 2.6, 1H, H-10$_{axial}$), 2.30 - 2.20 (m, 3H, H-8 and H-10$_{equatorial}$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1 (CO_2, C-6), 169.4 (CON, C-13), 110.8 (CN, C-15), 71.2 (CH, C-9), 65.4 (CH, C-4), 60.2 (C, C-14), 49.0 (CH, C-5), 47.7 (CH, C-3), 37.2 (CH, C-2), 29.8 (CH_2, C-10), 29.6 (CH_2, C-8), 28.7 (CH_3, C-12); HRMS (ESI) calculated for $[C_{12}H_{12}N_2O_3+Na]^+$: 255.0746, found: 255.0756 (error = 3.9 ppm).

Preparation of (±)-(3*aS*,4*R*,6*R*,7*aR*,8*R*)-isopropyl 3a-cyano-6-hydroxy-2-methyl-3-oxoocta hydro-1,4-methanoisoindole-8-carboxylate 426 and (±)-(3*S*,5*R*,8*aR*)-isopropyl 7-methyl-1,8-dioxooctahydro-6,8a,3-(epiethane[1,1,2]triyl)pyrano[3,4-c]pyridine-5-carbo xylate 427.

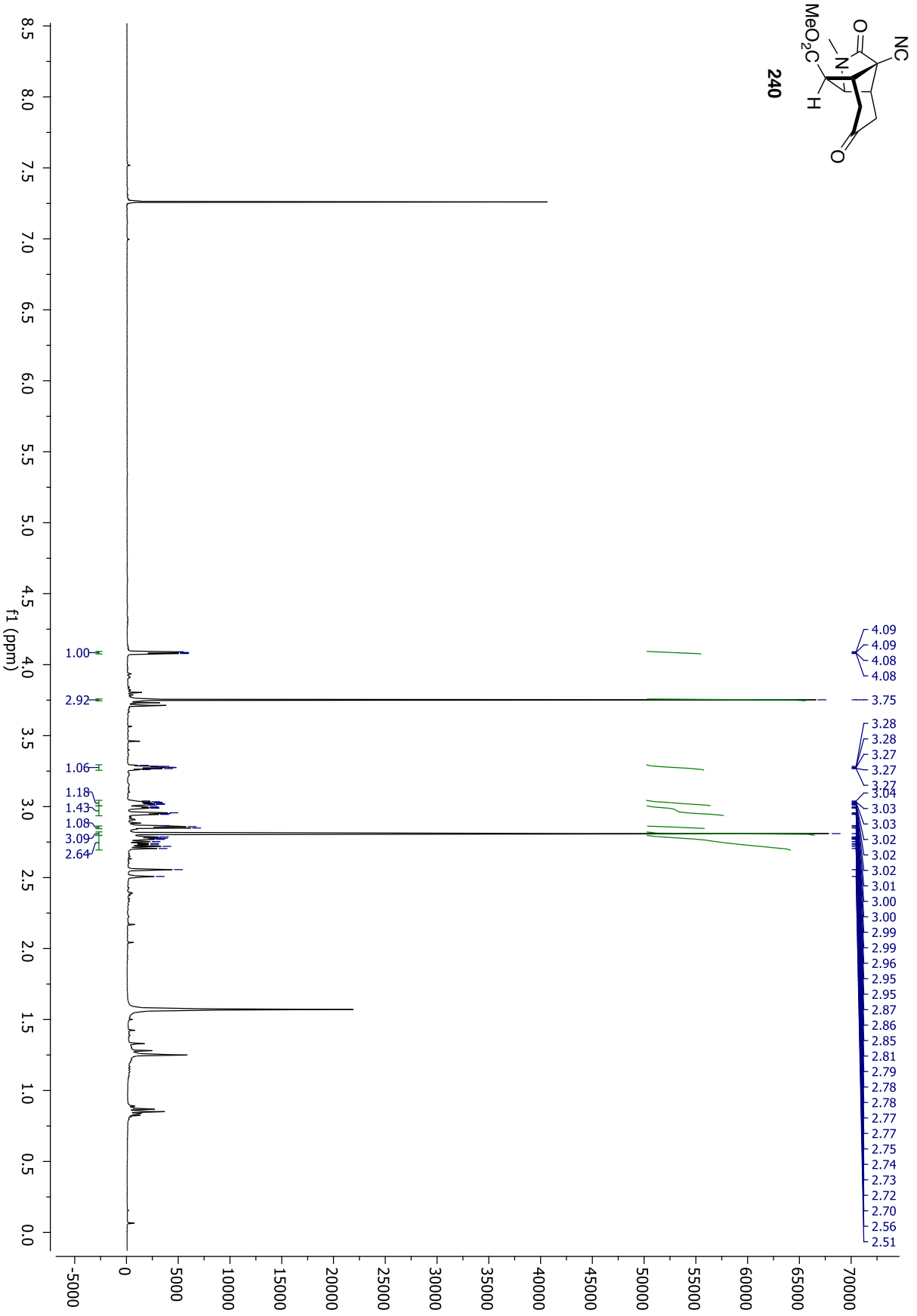


Starting material **240** (13 mg, 0.05 mmol) was added to a suspension of sodium borohydride (1 mg, 0.02 mmol) in *iso*propanol (2 mL) at room temperature. After stirring overnight at room temperature, the reaction was quenched with water (2 mL) and ethyl acetate (2 mL) was added. The layers were separated and the organic phase was washed with water (2 x 2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography using a gradient 90 to 100% ethyl acetate in petroleum ether to provide: **426** (yellow oil, 2 mg, 0.007 mmol, 14% yield) and **427** (yellow oil, 7 mg, 0.024 mmol, 48% yield). Suitable crystals were grown from a 1:1:1 solution of dichloromethane/methanol/ethyl acetate over six months.

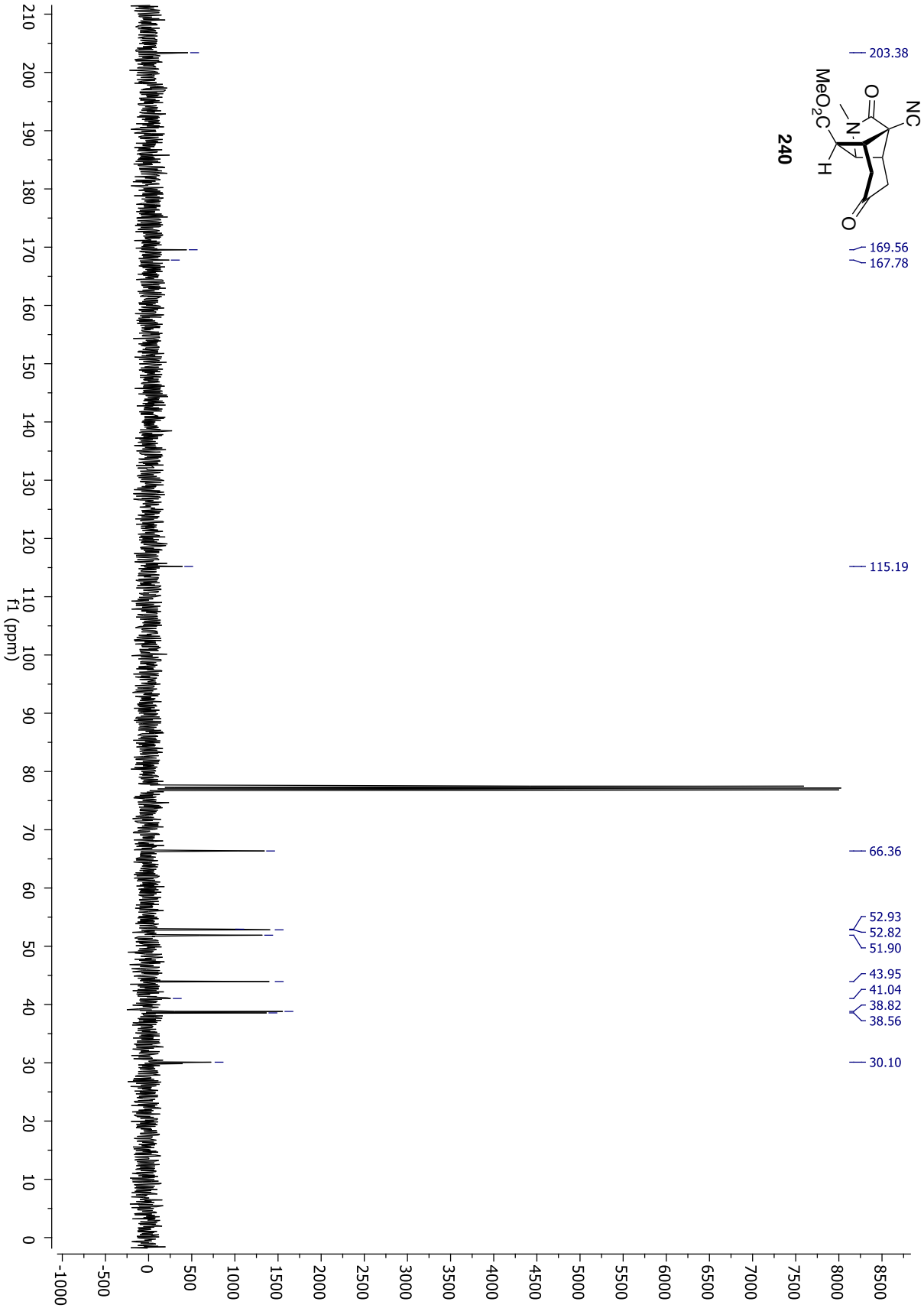
Data for **426**: R_f: 0.51 (100% ethyl acetate); FTIR ν_{max} 3452, 2982 - 2857, 2232 (CN), 1760, 1721, 1438, 1392, 1254, 1200, 1106; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99 (hept, J = 6.3, 1H, H-7), 4.26 - 4.18 (m, 2H, H-9 and H-3), 3.98 (dd, J = 3.3, 1.9, 1H, H-4), 3.07 - 3.03 (m, 1H, H-2), 2.82 (s, 3H, H-12), 2.72 - 2.68 (m, 1H, H-5), 2.46 - 2.38 (m, 1H, H-10_{axial}), 2.38 - 2.31 (m, 1H, H-8_{axial}), 2.03 (d, J = 15.2, 1H, H-$10_{equatorial}$), 1.83 (d, J = 15.2, 1H, H-$8_{equatorial}$), 1.61 (br. s, 1H, OH), 1.25 (d, J = 6.3, 6H, H-16 and H-17); HRMS (ESI) calculated for $[C_{15}H_{20}N_2O_4+Na]^+$: 315.1331, found: 315.1321 (error = 3.2 ppm).

Data for **427**: R_f: 0.20 (100% ethyl acetate); FTIR ν_{max} 2982 - 2857, 1760, 1721, 1696, 1438, 1392, 1372, 1254, 1200, 1185, 1106; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (hept, *J* = 6.3, 1H, H-7), 4.72 (br. s, 1H, H-9), 3.99 (br. s, 1H, H-4), 3.03 (d, *J* = 8.4, 1H, H-2), 2.91 (br. s, 1H, H-3), 2.81 (s, 3H, H-12), 2.69 (d, *J* = 9.1, 1H, H-5), 2.32 - 2.19 (m, 2H, H-8 and H-10), 1.84 (dd, *J* = 14.5, 2.6, 1H, H-10), 1.55 (dd, *J* = 14.5, 1.6, 1H, H-8), 1.28 (m, 6H, H-16 and C-17); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7 (CO_2, C-6), 169.9 (CON, C-13 and CN, C-15), 73.9 (CH, C-9), 69.8 (CH, C-7), 64.0 (CH, C-4), 57.6 (CH, C-3), 52.7 (C, C-14), 48.9 (CH, C-5), 37.3 (CH, C-2), 37.1 (CH_2, C-10), 29.8 (CH_3, C-12), 27.1 (CH_2, C-8), 22.0 (CH_3, C-16 and C-17); HRMS (ESI) calculated for $[C_{15}H_{19}NO_5+Na]^+$: 316.1161, found: 316.1172 (error = 3.5 ppm).

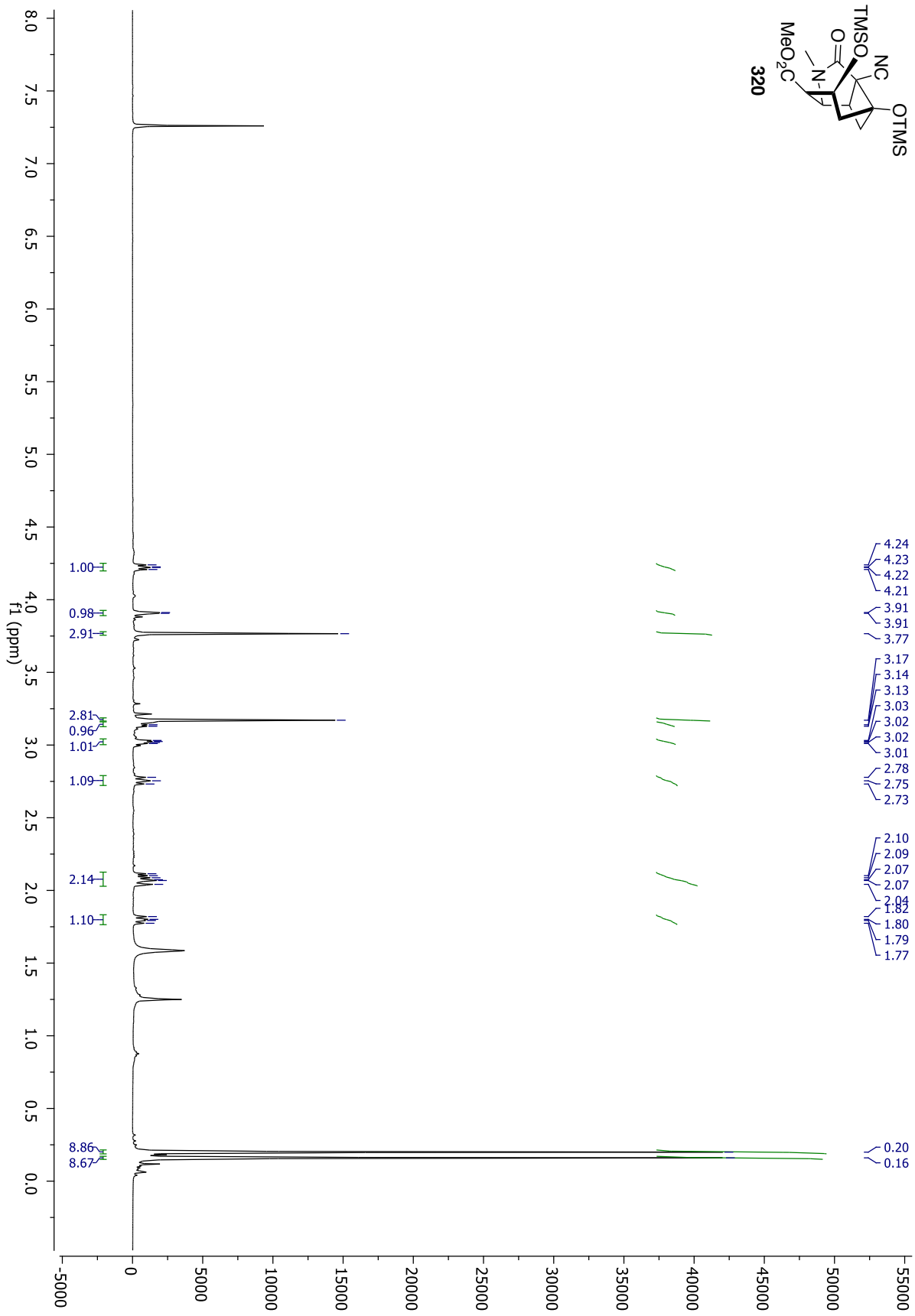
^{1}H NMR spectrum for the core structure **240** (400 MHz, $CDCl_3$)



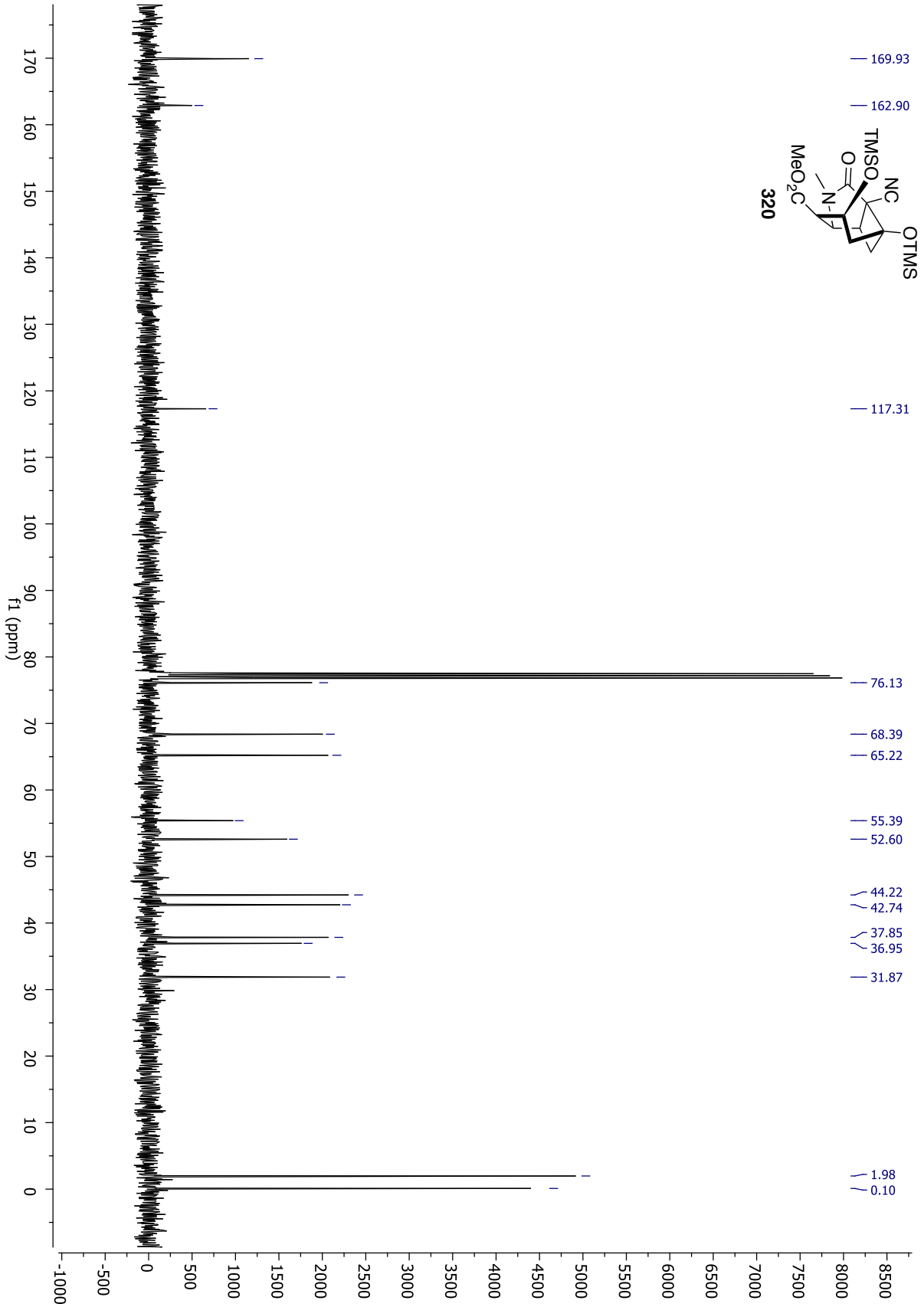
^{13}C NMR spectrum for the core structure **240** (100 MHz, $CDCl_3$)



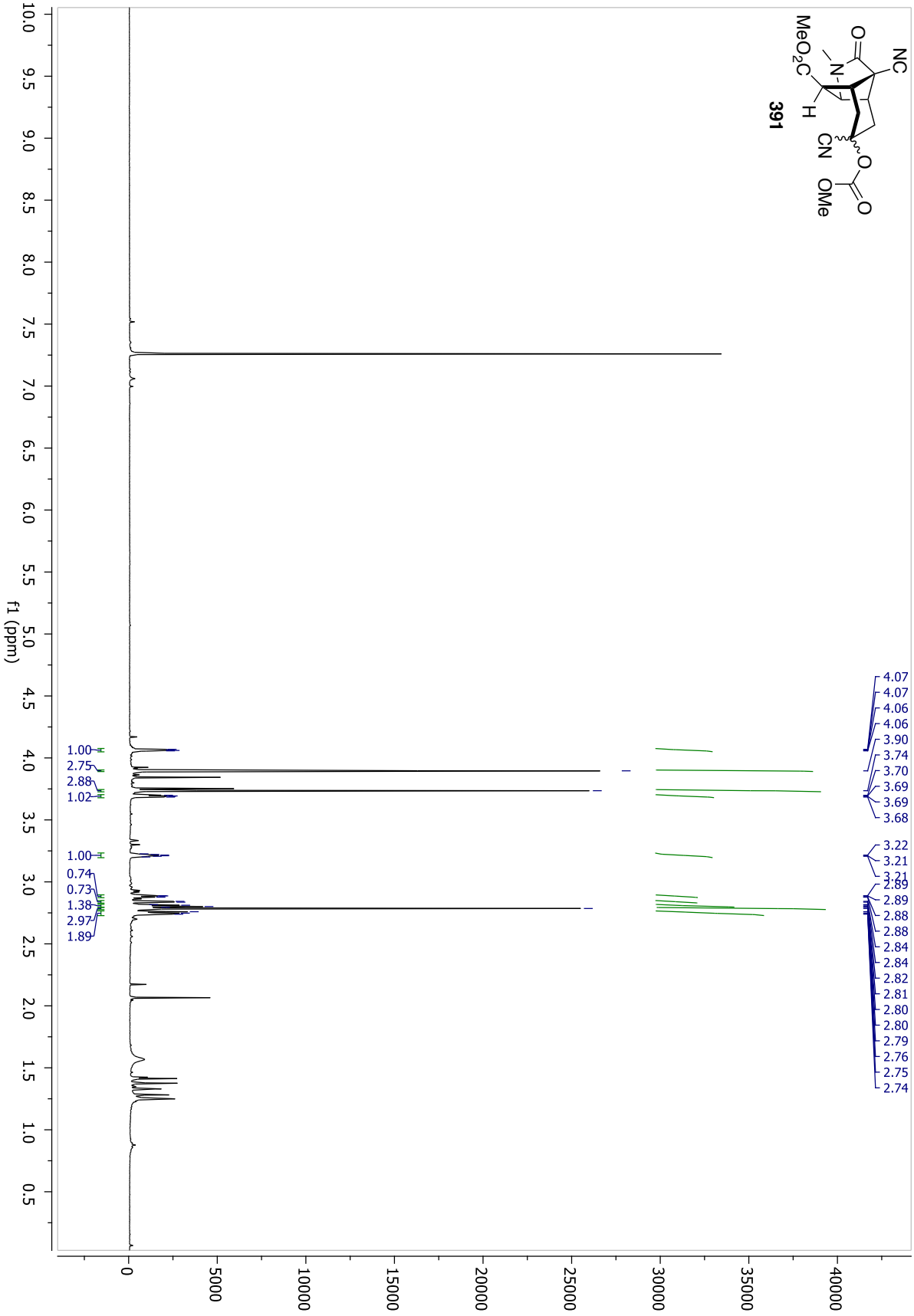
^{1}H NMR spectrum for **320** (500 MHz, $CDCl_3$, +22 °C)



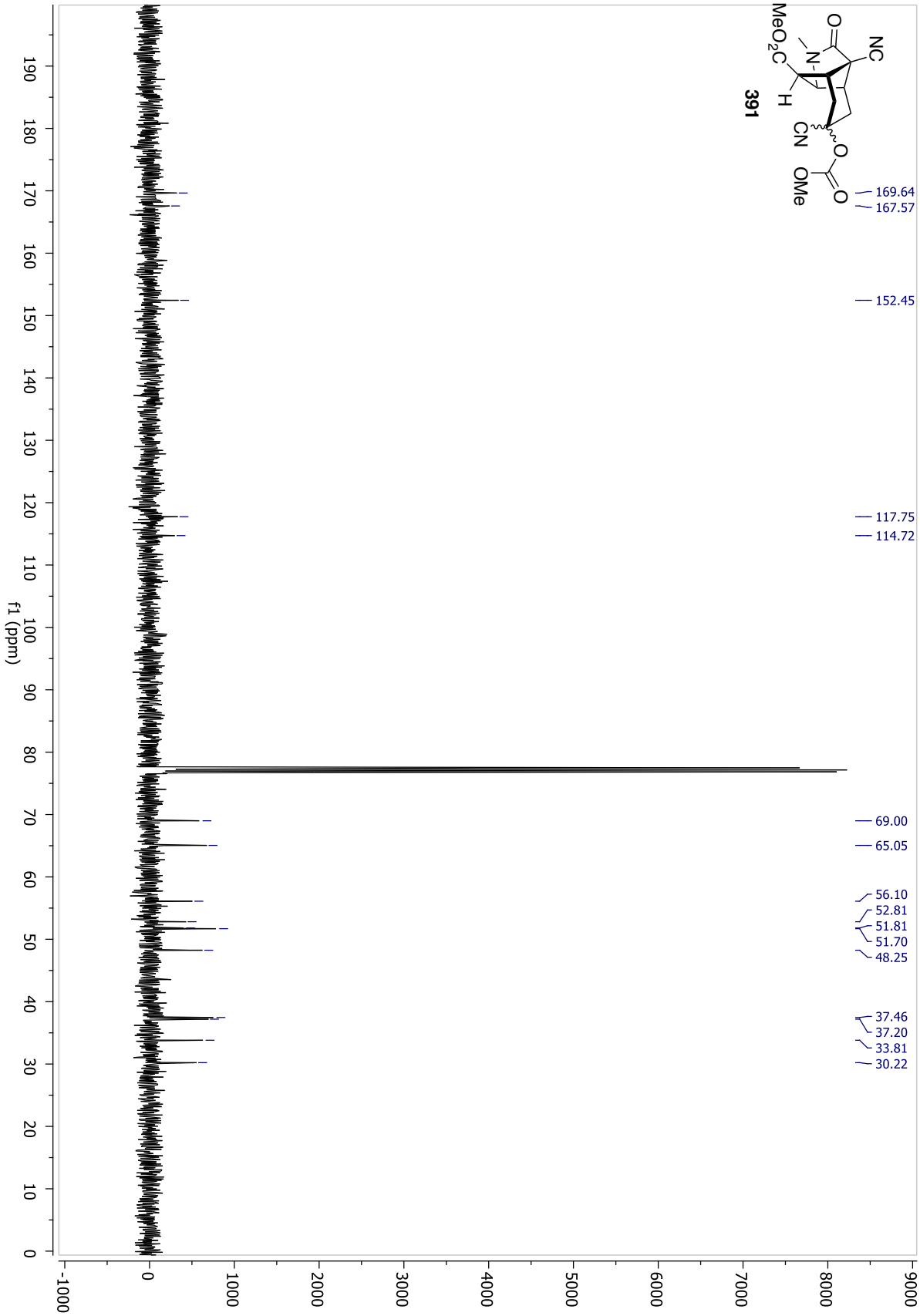
^{13}C NMR spectrum for **320** (100 MHz, $CDCl_3$)



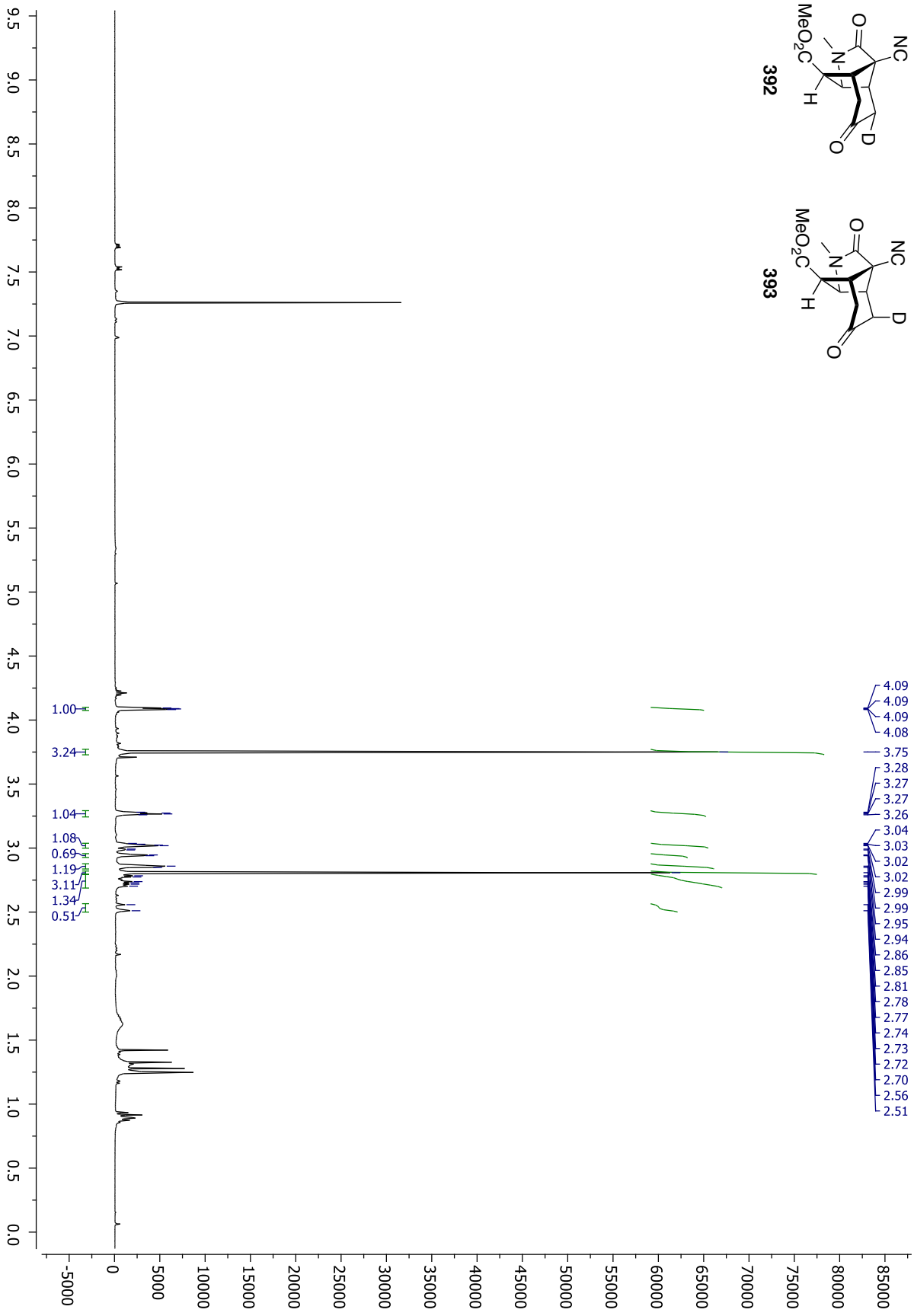
^{1}H NMR spectrum for cyanohydrin **391** (400 MHz, $CDCl_3$)



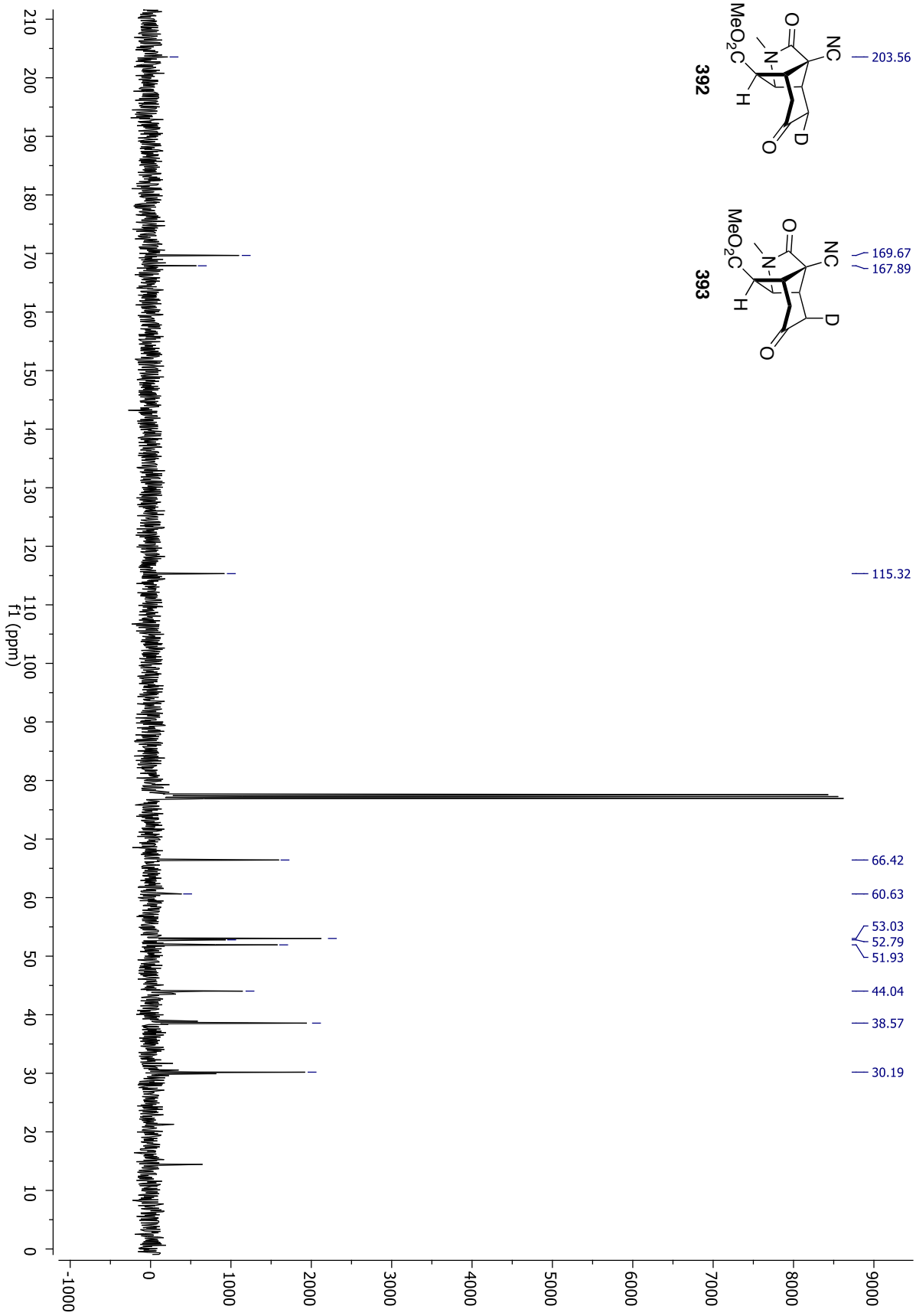
^{13}C NMR spectrum for cyanohydrin **391** (100 MHz, $CDCl_3$)



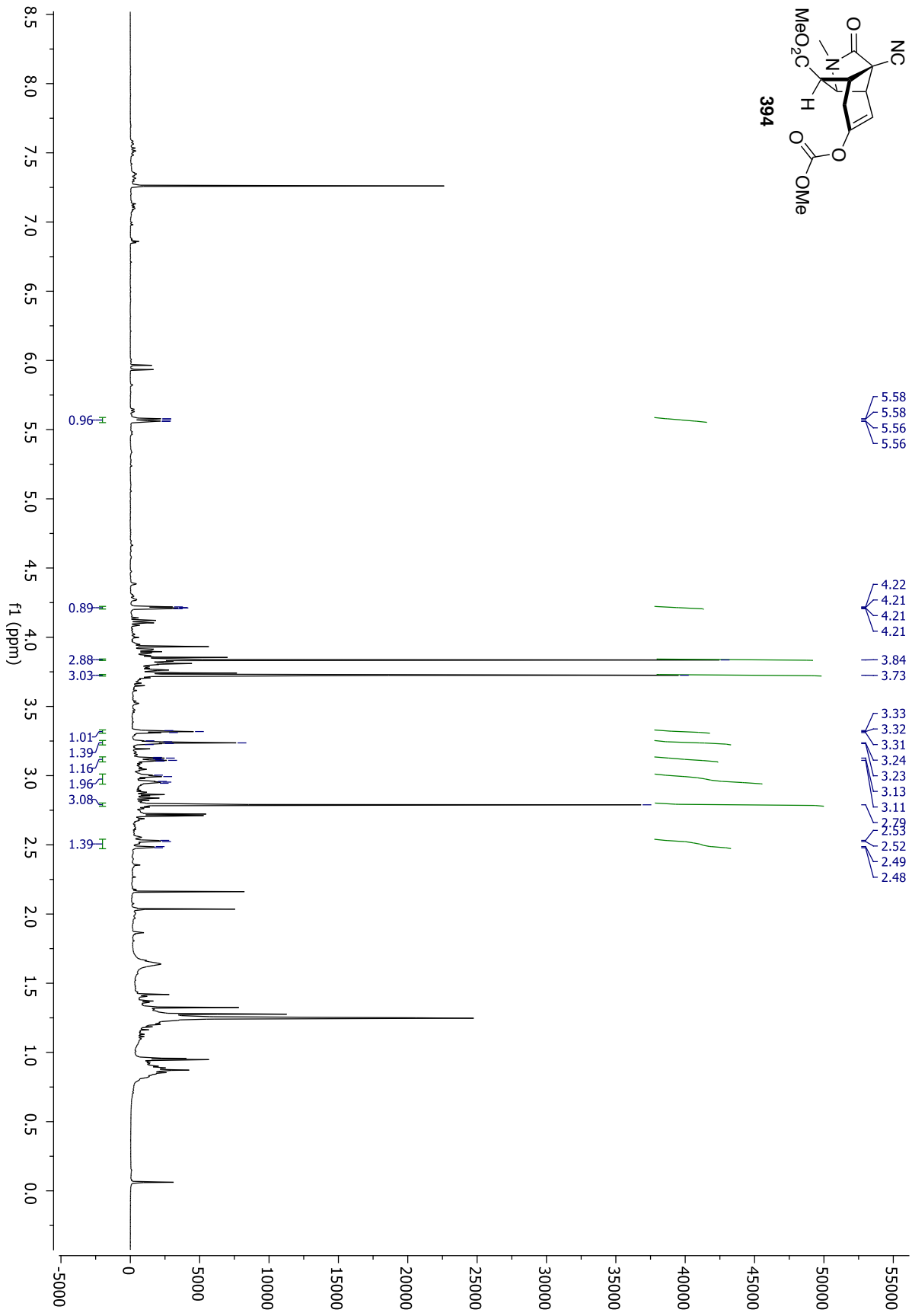
^{1}H NMR spectrum for deuterated core **392** and **393** (400 MHz, $CDCl_3$)



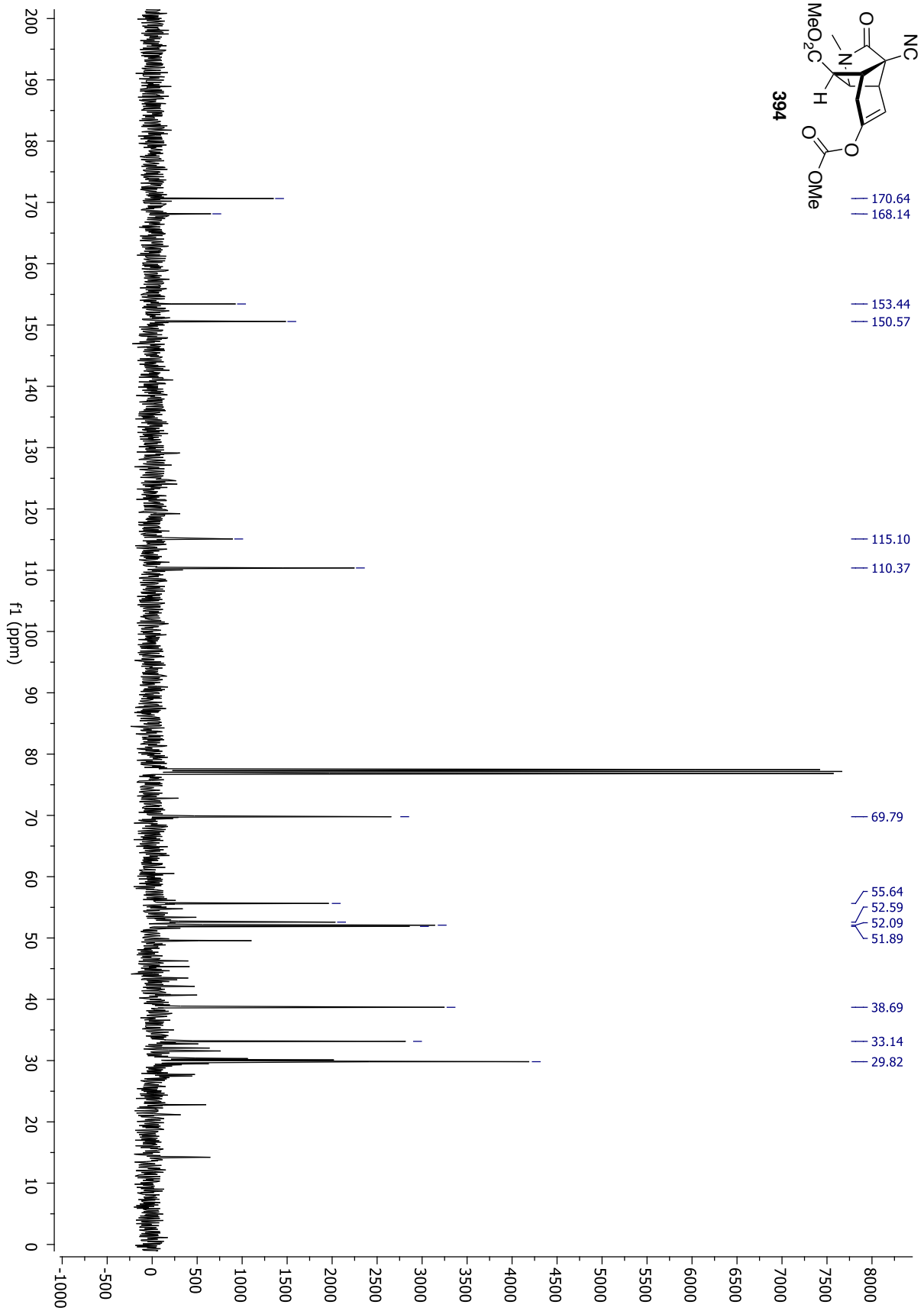
^{13}C NMR spectrum for deuterated core **392** and **393** (100 MHz, $CDCl_3$)



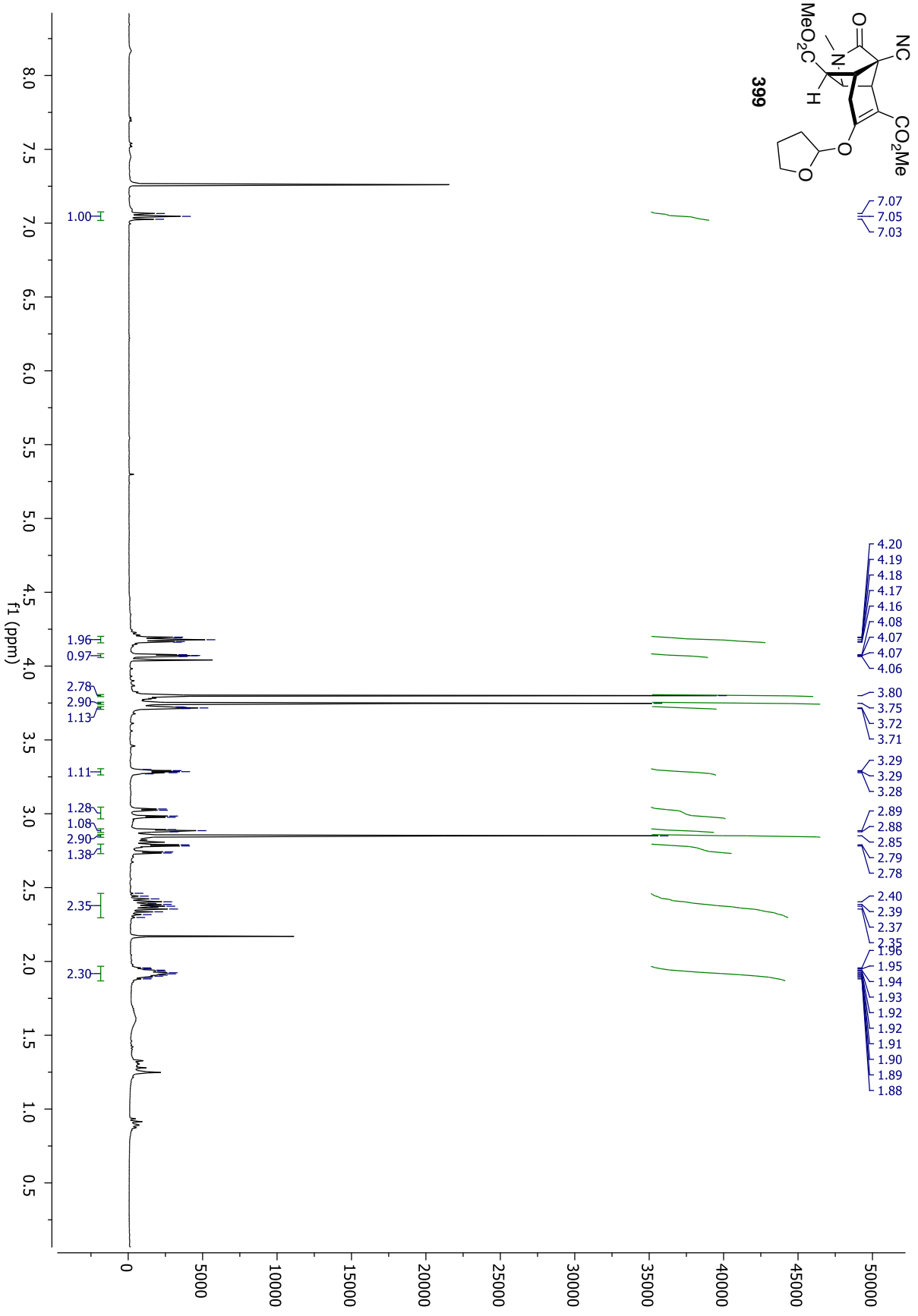
^{1}H NMR spectrum for carbonate **394** (400 MHz, $CDCl_3$)



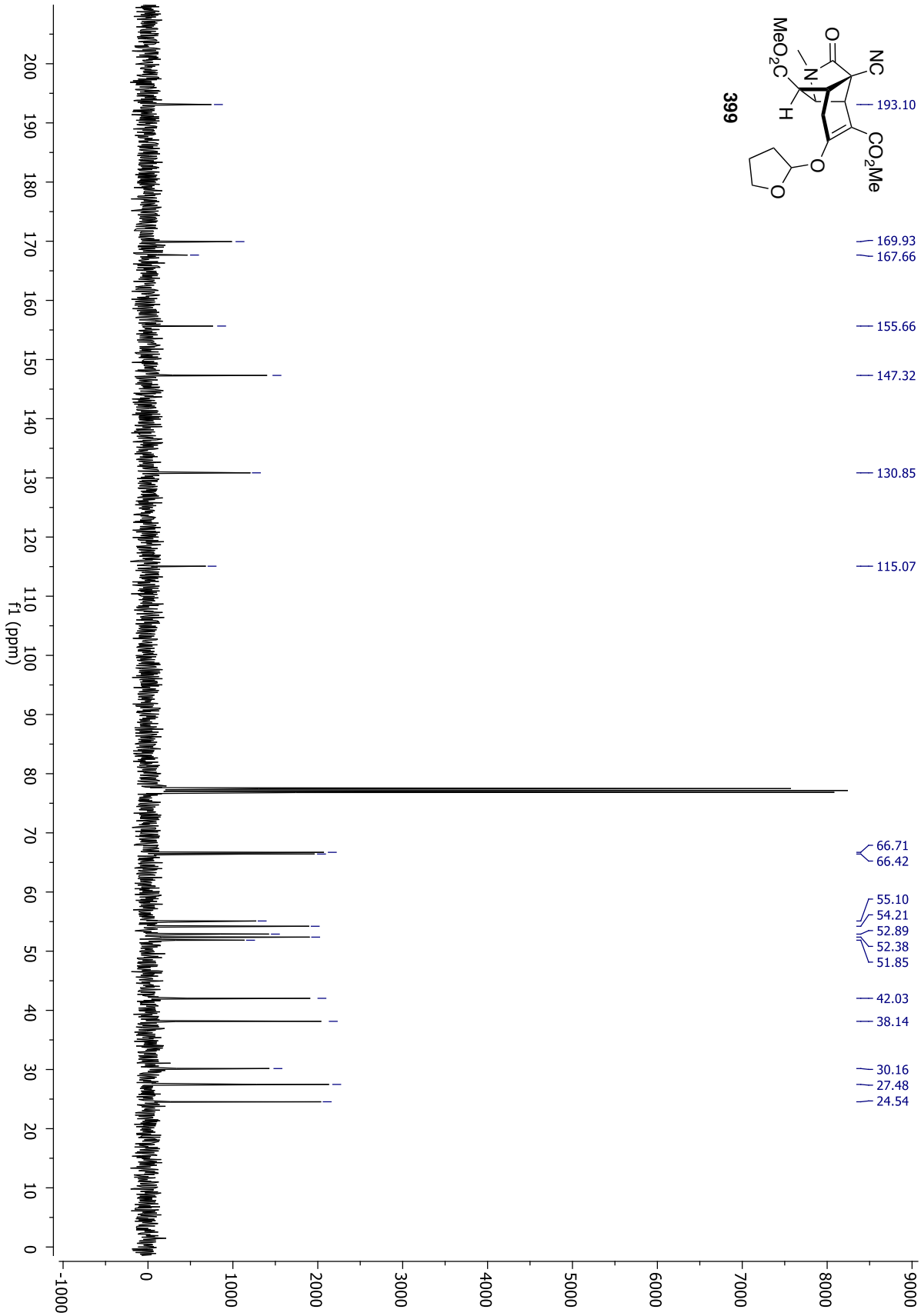
^{13}C NMR spectrum for carbonate **394** (100 MHz, $CDCl_3$)



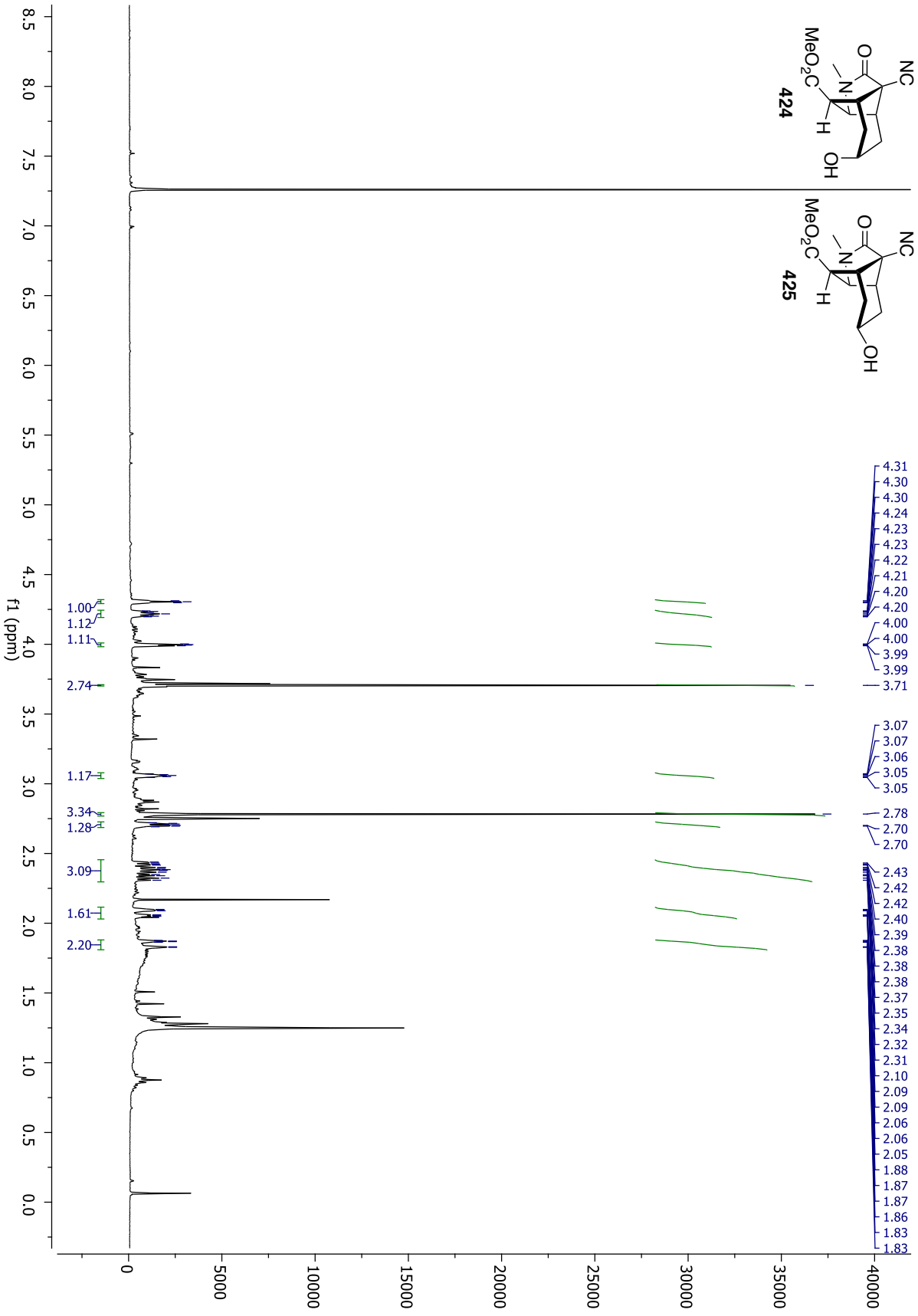
^{1}H NMR spectrum for compound **399** (400 MHz, $CDCl_3$)



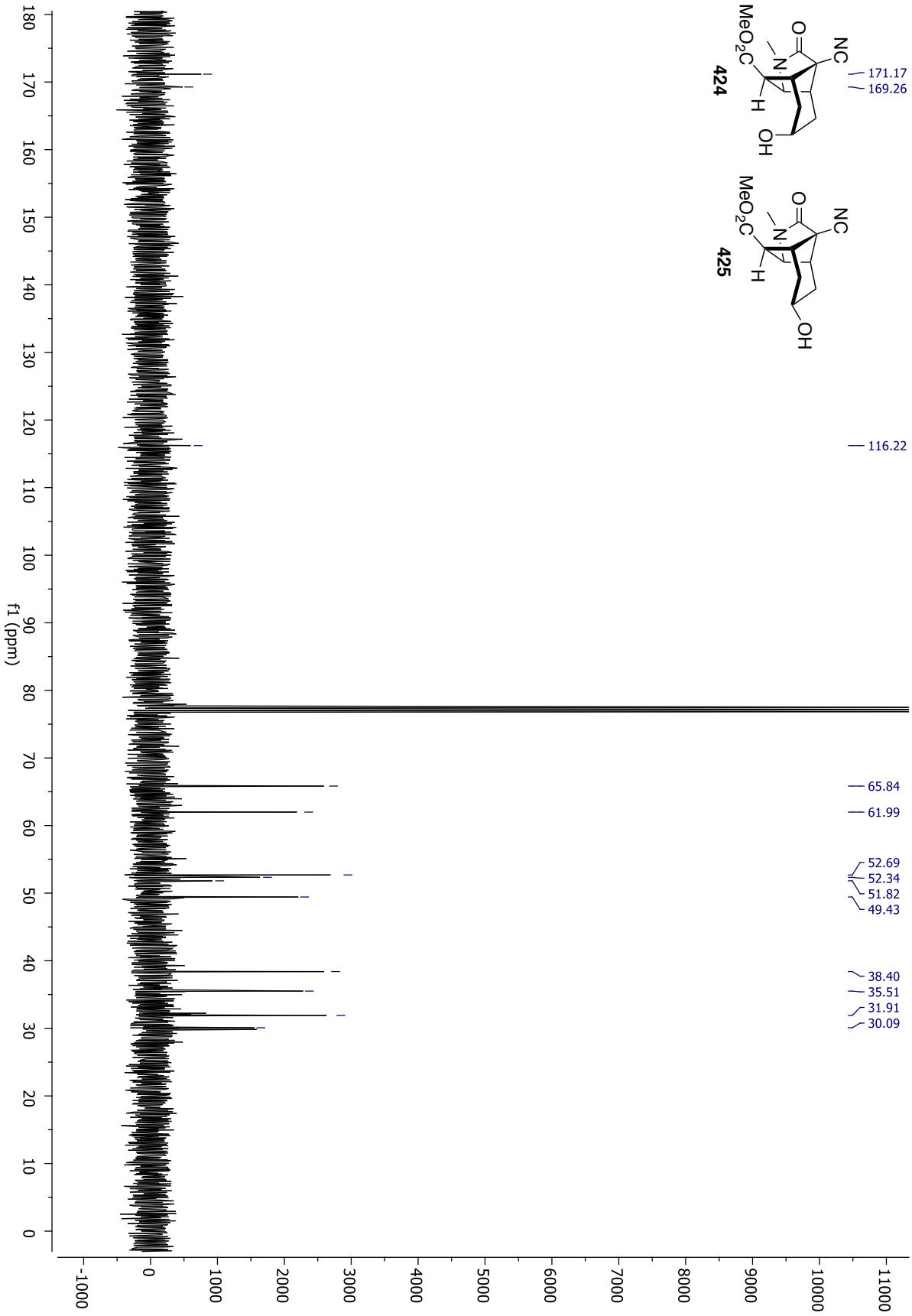
^{13}C NMR spectrum for compound **399** (100 MHz, $CDCl_3$)



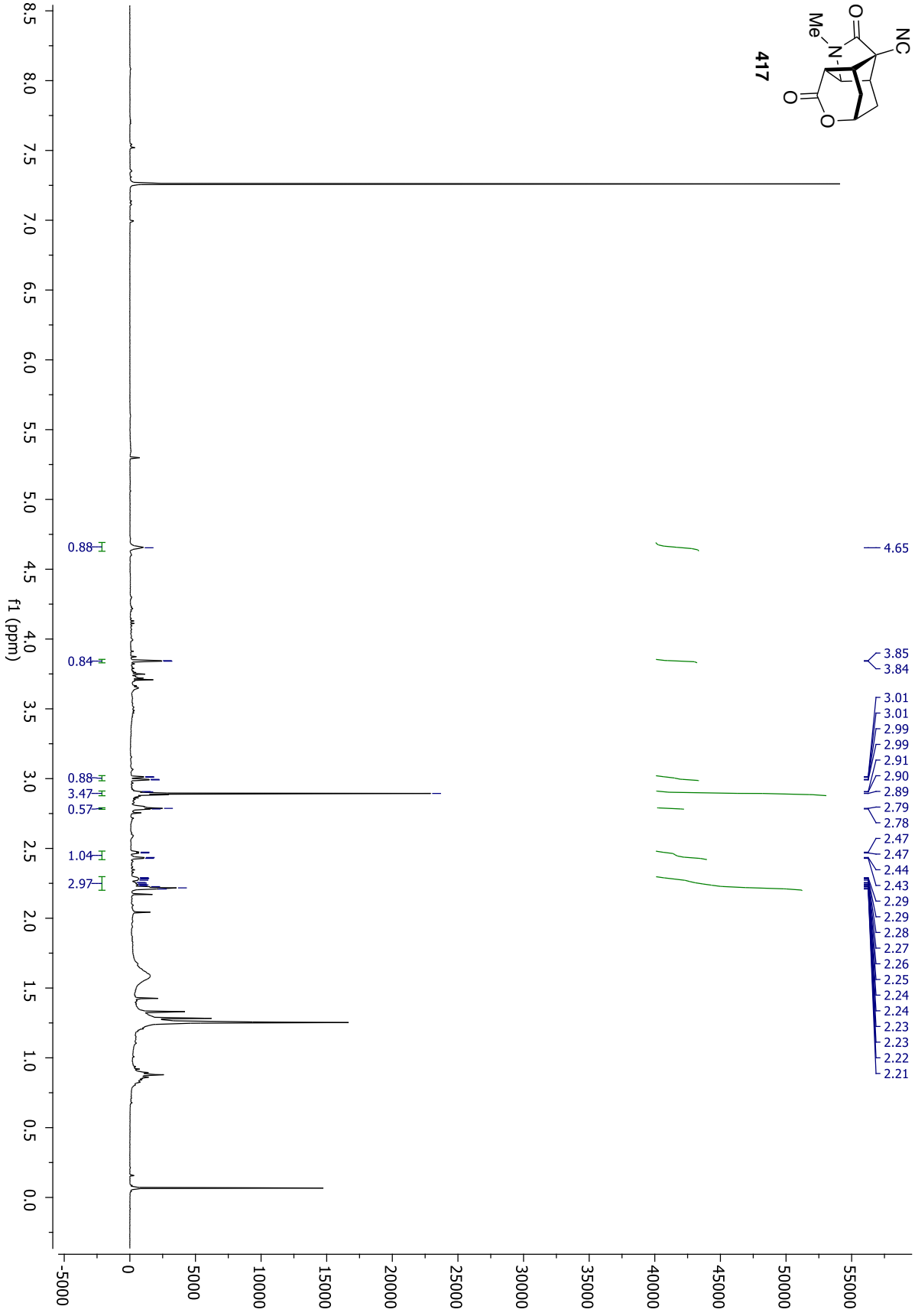
^{1}H NMR spectrum for alcohol **424** and **425** (400 MHz, $CDCl_3$)



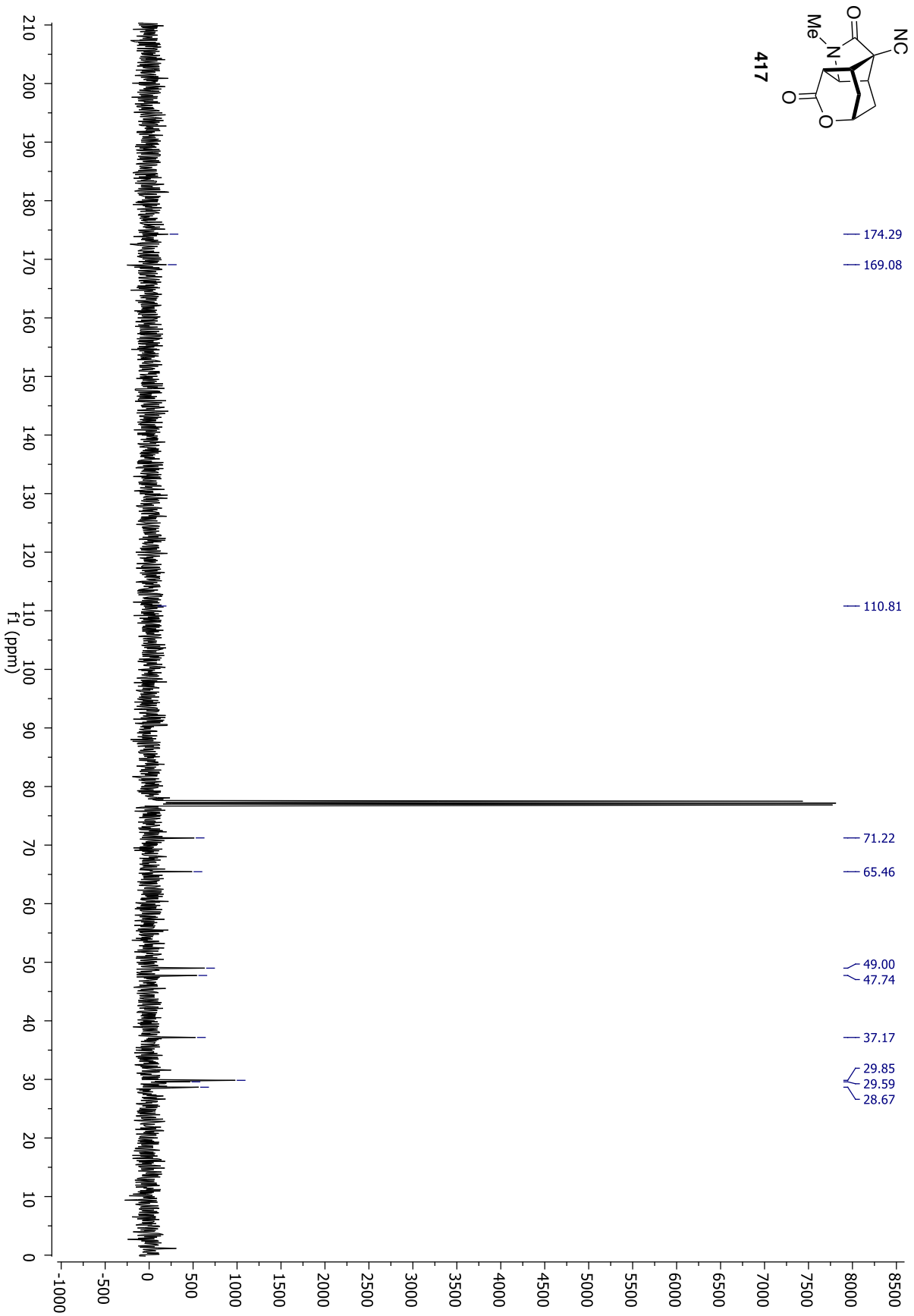
^{13}C NMR spectrum for alcohol **424** and **425** (100 MHz, $CDCl_3$)



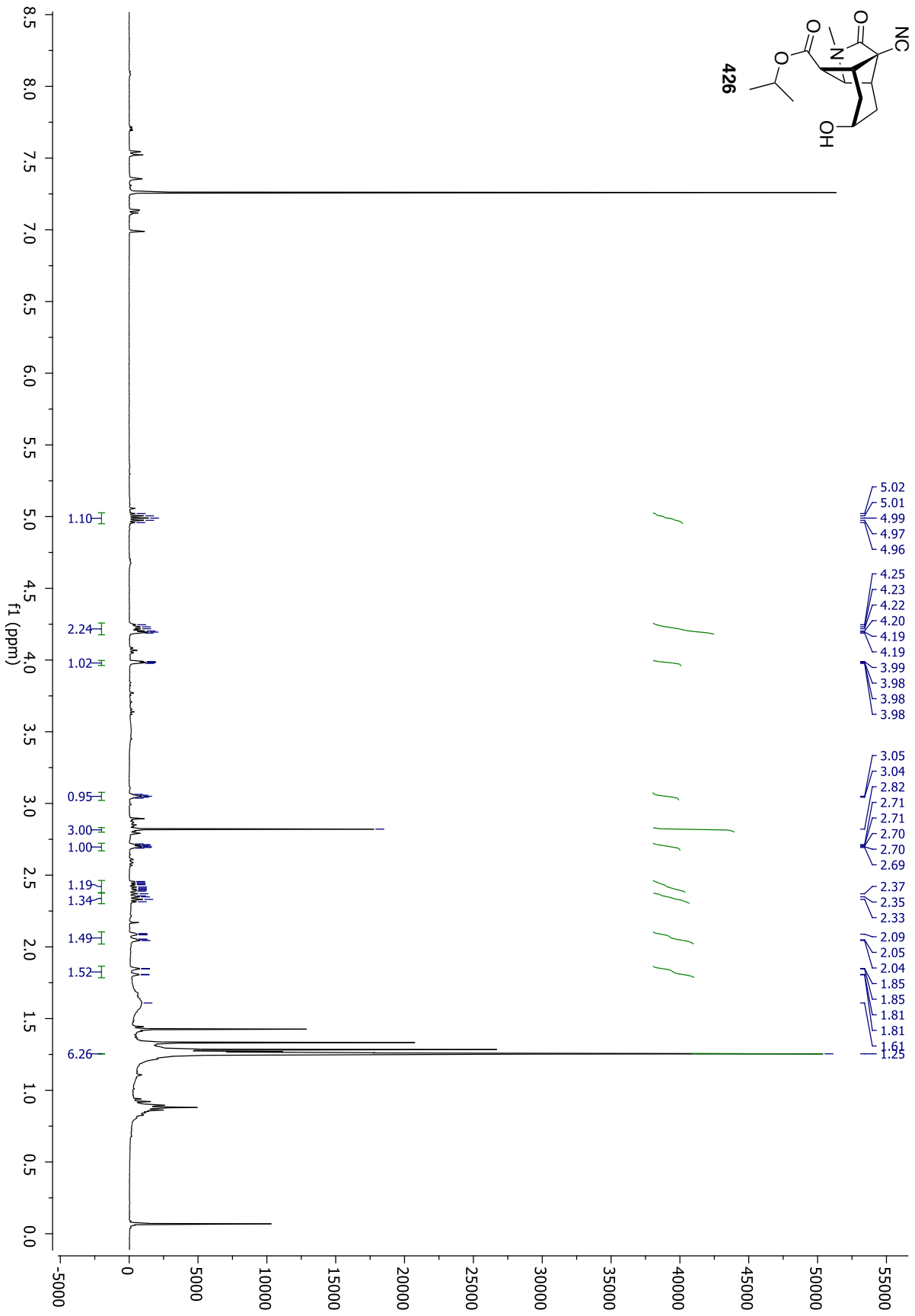
^{1}H NMR spectrum for lactone **417** (400 MHz, $CDCl_3$)



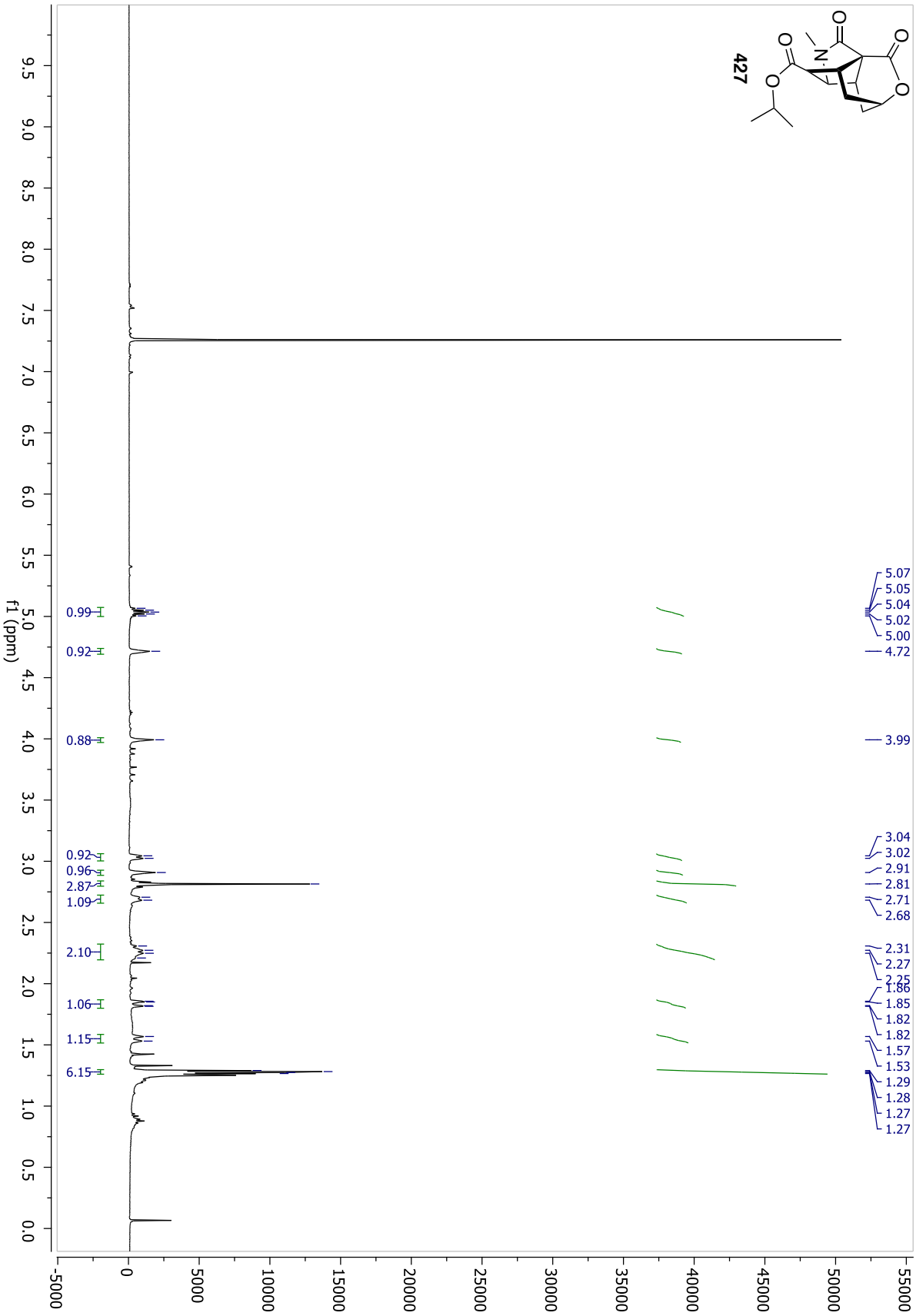
^{13}C NMR spectrum for lactone **417** (100 MHz, $CDCl_3$)



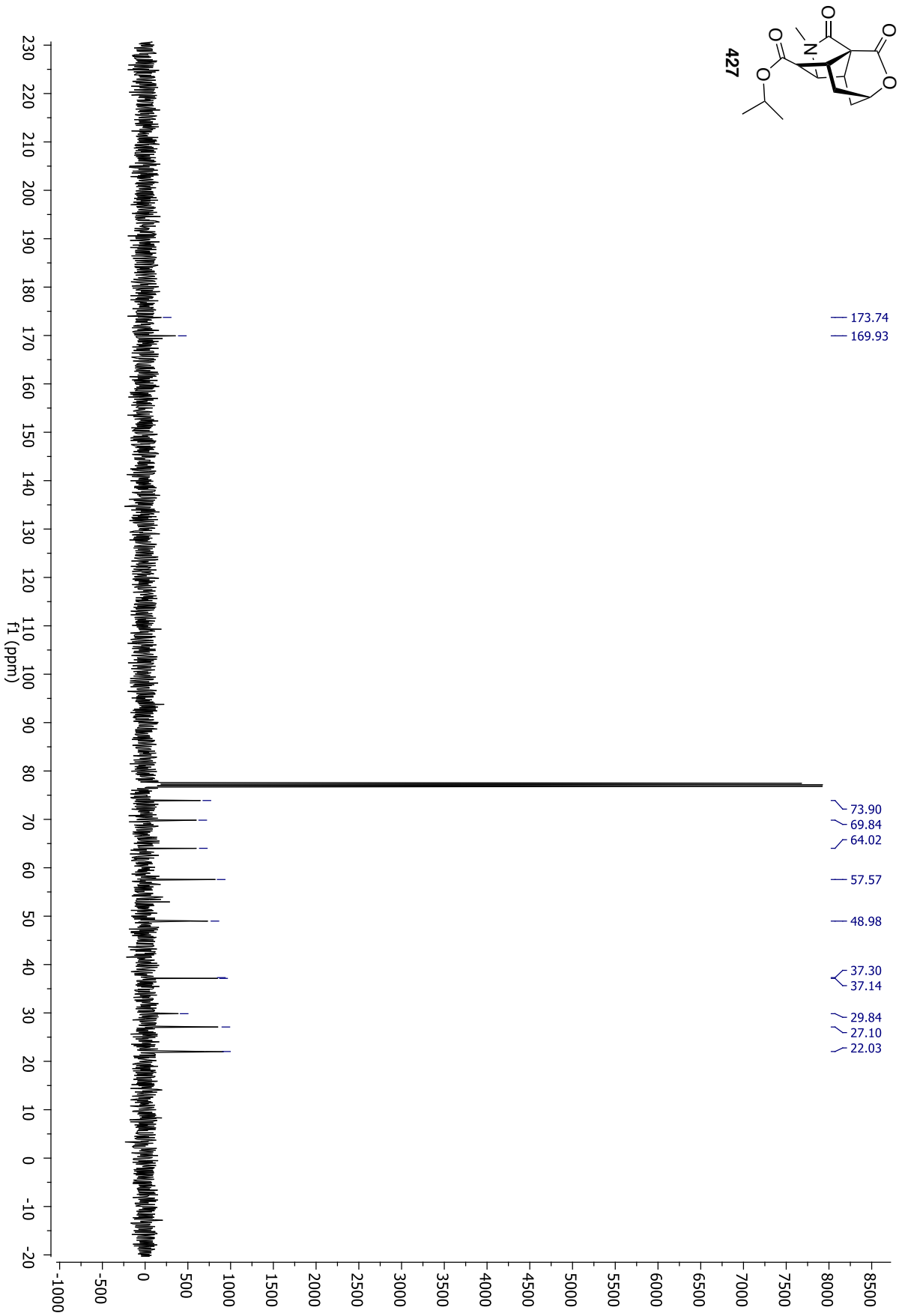
^{1}H NMR spectrum for alcohol **426** (400 MHz, $CDCl_3$)



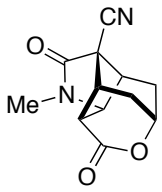
^{1}H NMR spectrum for lactone **427** (400 MHz, $CDCl_3$)



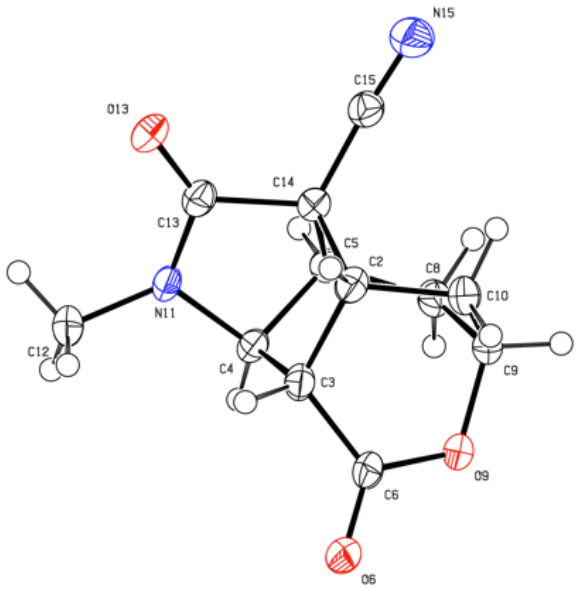
^{13}C NMR spectrum for lactone **427** (100 MHz, $CDCl_3$)



Crystal Structure Data for **417**



417



Crystals were grown from a 1:1 solution of chloroform/methanol.

A single crystal was selected and the data collected at the University of Southampton. The data were processed at the University of Birmingham by Louise Male.

Table 1. Crystal data and structure refinement for Jxa528A1.

Identification code	Jxa528A1	
Empirical formula	$C_{12}H_{12}N_2O_3$	
Formula weight	232.24	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 6.4304(5) Å	a= 90°.
	b = 21.9566(16) Å	b= 97.479(3)°.

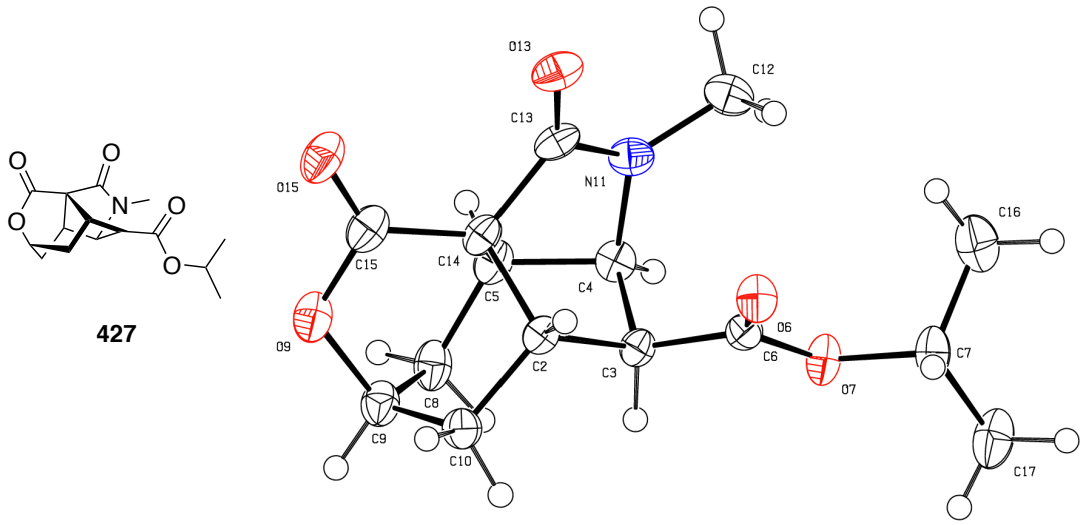
	c = 7.3949(5) Å g = 90°.
Volume	1035.20(13) $Å^3$
Z	4
Density (calculated)	1.490 Mg/m^3
Absorption coefficient	0.109 mm^{-1}
F(000)	488
Crystal size	0.14 x 0.10 x 0.09 mm^3
Theta range for data collection	3.33 to 26.37°.
Index ranges	-8<=h<=8, -24<=k<=27, -9<=l<=9
Reflections collected	6409
Independent reflections	2111 [R(int) = 0.0475]
Completeness to theta = 26.37°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9903 and 0.9849
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2111 / 0 / 155
Goodness-of-fit on F^2	1.081
Final R indices [I>2sigma(I)]	R1 = 0.0466, wR2 = 0.1234
R indices (all data)	R1 = 0.0581, wR2 = 0.1288
Largest diff. peak and hole	0.366 and -0.186 $e.Å^{-3}$

Notes: The hydrogen atoms were fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Jxa528A1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(2)	4088(3)	1301(1)	4128(2)	23(1)
C(3)	4244(3)	1112(1)	2106(2)	23(1)
C(4)	2089(3)	789(1)	1550(2)	22(1)
C(5)	598(3)	1132(1)	2659(2)	22(1)
C(6)	4523(3)	1629(1)	801(2)	24(1)
C(8)	310(3)	1815(1)	2309(2)	25(1)
C(9)	2323(3)	2191(1)	2586(2)	25(1)
C(10)	3821(3)	1989(1)	4240(2)	27(1)
C(12)	3054(3)	-341(1)	1676(3)	29(1)
C(13)	2291(3)	286(1)	4304(2)	24(1)
C(14)	1980(3)	979(1)	4488(2)	23(1)
C(15)	1185(3)	1173(1)	6156(2)	26(1)
N(11)	2230(2)	198(1)	2489(2)	23(1)
N(15)	545(3)	1359(1)	7415(2)	37(1)
O(6)	5598(2)	1586(1)	-416(2)	32(1)
O(9)	3449(2)	2146(1)	985(2)	27(1)
O(13)	2597(2)	-92(1)	5530(2)	28(1)

Crystal Structure Data for **427**



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Crystals were grown from a 1:1:1 solution of dichloromethane/methanol/ethyl acetate.

A single crystal was selected and the data collected at the University of Southampton. The data were processed at the University of Birmingham by Louise Male.

Table 1. Crystal data and structure refinement for Jxa521B1.

Identification code	Jxa521B1	
Empirical formula	C15 H19 N O5	
Formula weight	293.31	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 6.9943(4) Å	a= 90°.
	b = 21.0084(11) Å	b= 100.696(7)°.
	c = 9.6884(6) Å	g = 90°.

Volume	1398.87(14) $Å^3$
Z	4
Density (calculated)	1.393 Mg/m^3
Absorption coefficient	0.105 mm^{-1}
F(000)	624
Crystal size	0.12 x 0.11 x 0.07 mm^3
Theta range for data collection	3.12 to 27.48°.
Index ranges	-8<=h<=9, -24<=k<=27, -11<=l<=12
Reflections collected	9492
Independent reflections	3192 [R(int) = 0.0490]
Completeness to theta = 27.48°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.613
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3192 / 0 / 193
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0524, wR2 = 0.1171
R indices (all data)	R1 = 0.0875, wR2 = 0.1309
Largest diff. peak and hole	0.256 and -0.224 $e.Å^{-3}$

Notes: The hydrogen atoms have been fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Jxa521B1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(2)	3454(3)	3405(1)	2022(2)	22(1)
C(3)	2507(3)	2850(1)	1068(2)	22(1)
C(4)	3466(3)	2920(1)	-242(2)	24(1)
C(5)	3700(3)	3646(1)	-333(2)	26(1)
C(6)	2876(3)	2199(1)	1743(2)	23(1)
C(7)	1916(3)	1097(1)	1498(2)	31(1)
C(8)	1935(3)	4089(1)	-407(2)	30(1)
C(9)	2085(3)	4420(1)	1004(2)	29(1)
C(10)	2018(3)	3947(1)	2164(2)	26(1)
C(12)	6308(3)	2110(1)	-38(2)	35(1)
C(13)	6455(3)	3160(1)	1106(2)	26(1)
C(14)	4967(3)	3678(1)	1153(2)	24(1)
C(15)	5557(3)	4349(1)	1542(2)	30(1)
C(16)	3524(4)	749(1)	973(3)	43(1)
C(17)	-56(3)	812(1)	974(3)	41(1)
N(11)	5523(2)	2739(1)	157(2)	27(1)
O(6)	3992(2)	2087(1)	2819(2)	29(1)
O(7)	1786(2)	1757(1)	968(2)	28(1)
O(9)	3991(2)	4748(1)	1347(2)	33(1)
O(13)	8090(2)	3095(1)	1815(2)	34(1)
O(15)	7166(2)	4555(1)	1952(2)	37(1)

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