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PROGRESS TOWARDS THE TOTAL SYNTHESIS OF *N*-METHYLWELWITINDOLINONE C ISOTHIOCYANATE

by

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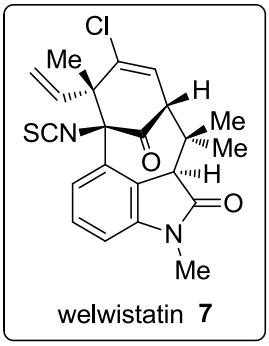
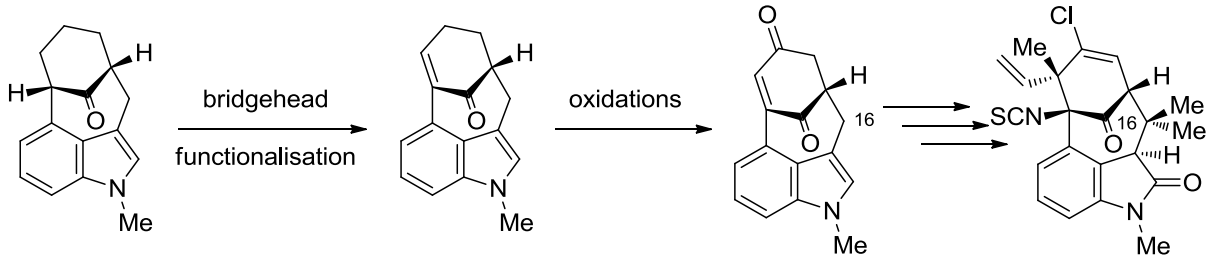
Abstract

This thesis focuses on our progress towards the total synthesis of *N*-methylwelwitindolinone C isothiocyanate **7**, commonly called welwistatin. This major alkaloid of the welwitindolinone family, which was isolated from *Hapalosiphon welwitschii* in 1994, represents a particularly attractive target due to both its interesting biological activities (MDR reversing agent) and its challenging structure. Welwistatin possesses a complex bicyclo[4.3.1]decane ring system consisting of four stereogenic centres, three quaternary carbons and two unusual reactive functionalities: the isothiocyanate bridgehead and a vinyl chloride group.



welwistatin **7**

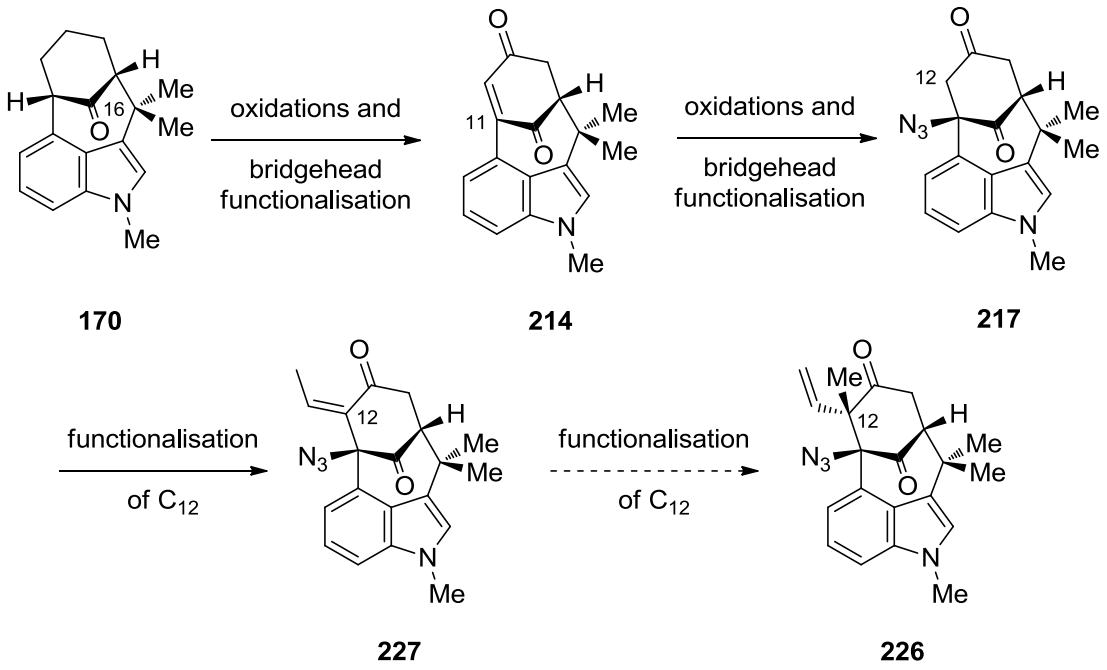
Inspired by the synthetic challenge of this complex architecture, the Simpkins group reported an expedient four-step synthesis of the core structure of welwistatin **7** in 2005. Three years later, our group had also investigated the reactivity at the bridgehead enolate positions. After synthesising skeleton **88**, we successfully functionalised the bridgehead positions using the bridgehead enolate chemistry developed by our group to access bridgehead alkene **126**. With bridgehead alkene **126** in hand, we turned our attention towards the other features present on welwistatin and successive oxidations led to the formation of enone **198**.



88 **126** **200** welwistatin **7**

At this stage, the tetracyclic model system **88** presented certain difficulties. Based on preliminary studies carried out in our group, these issues would be avoided by the preparation of skeleton **170**, which possesses the *gem*-dimethyl moiety already present at position C_{16}. We turned our attention to the synthesis of tetracycle **170** and its subsequent functionalisation. Preliminary studies to enone **227** had also been carried out in our group which demonstrated the lability of the azide functionality at the bridgehead position.

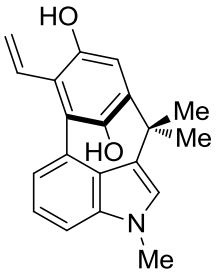
In this present work, which builds on the past efforts of the Simpkins group, we optimised the synthetic route to azide **217** as well as pursuing the previous studies of our group towards the functionalisation of position C_{12}. The vinyl fragment would be introduced *via* a regioselective aldol reaction followed by dehydration, whilst the methyl group could be introduced by quenching a regioselectively introduced enolate with excess methyl iodide. We studied various methods for installing the desired quaternary centre at position C_{12} of the tetracyclic structure. Unfortunately, despite the formation of advanced intermediates, we were unable to introduce the required methyl group at position C_{12}.



170 **214** **217**

227 **226**

An unexpected product was obtained while attempting to reduce and protect azide **227**. The initial analysis of the spectral data suggested the formation of highly strained cyclophane **285**. However, this highly provocative structure was eventually discarded, as subjecting enone **214** to similar conditions did not afford the analogous cyclophane **286**. Under these conditions, the bis-phenol products **291** and **292** were obtained.



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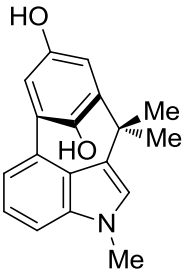

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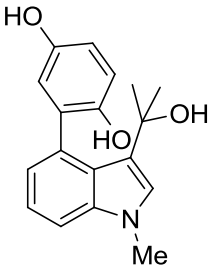

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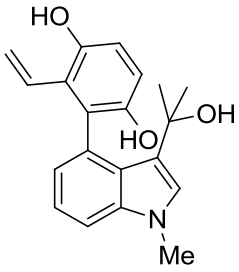

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Acknowledgements

Firstly, I would like to thank Professor Nigel Simpkins for giving me the opportunity to join his group for my PhD and for providing me with this challenging and exciting project. Thank you Nigel for your advice, inspiration and guidance over my PhD, we finally made it to the end of this bumpy road. I am also taking the opportunity to thank the EPSRC for the financial support and the School of Chemistry for the work premises and facilities.

I would like to thank the members of the Simpkins group, past and present, for their help, support and friendship; particularly, Mark, Mike, Jimm, Same, Valerie, Fred, Pete, Ilias, Yang, Jennifer, François, Alex. Thank you all for contributing to the great atmosphere at work and good times outside the lab.

Many thanks go to the analytical services for their support and assistance: Dr Neil Spencer for taking care of the NMR facilities as well as his contribution for the nOe analyses in this thesis, Pete Ashton, Nick May, Dr Chi Tsang and Lianne Hill for the mass spectroscopy and Graham Burns.

I would also like to thank the administrative team as well as Stuart Arkless for their help.

A special thank goes to the person who helped me through this PhD. Katie, thank you for your help in the lab. Bhaven, Pete J., Mike, Jimm, Yang, Anne and Mazou, your help and support have been a blessing particularly through all this proof reading of my work in the final stages of my PhD, I am really grateful to have such friends.

Thank all my friends in Birmingham and France, it will be impossible for me to give an exhaustive list but I would like to thank more particularly Mazou (for her smile and happiness), Alex, Hassan, Mark and Amanda, Bhav (for being such a good friend), Katie (for your support and our funny conversations), Mona and Anne (for the great time together), Hind, Charlie and Stu for their friendship but also Matt, my half-marathon partner, I miss running with you.

Most importantly, I cannot thank enough Arten for being part of my life. This last year with you has been wonderful and I want many (many...) more to come. Thank you Doudou for your patience, support and most importantly your love. Thank you for teaching me how to take break and enjoy life. I love you.

Last but not least, I would like to thank my family from the bottom of my heart for your support and devotion that you showed me over my PhD. Mum, Dad, you always believed in me. I would never have done it without you. Thank you so much. I love you. I would also like to thank my two brothers, Alex and Flo, as well as my grand-parents and uncle for their love and support.

Declaration

I declare that this thesis is the result of my own work except where due references have been made to other authors, and has not, whether in the same or different form, been submitted for any other degree at this or any other university.

Cynthia Paulin

To my family,

To Margotte and Orka, whom I miss greatly.

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Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BRSM	based on recovered starting material
Boc	*tert*-butyloxycarbonyl
br	broad
Bz	benzoyl
°C	Degrees Celsius
cat.	catalysed, catalyst or catalytic
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
conc.	concentrated or concentration
^{1}H-^{1}H COSY NMR	Correlation Spectroscopy-Nuclear Magnetic Resonance
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone

DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMF	*N*,*N*-dimethylformamide dimethyl acetal
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
E^+	electrophile
ee	enantiomeric excess
EI	electron impact
eq.	equivalent
EQ	external quench
ES^+	electrospray, positive ionisation
ESI	electrospray ionisation
FGI	Functional group interconversion
FT	Fourier transform
gem	geminal

g	gramme(s)
h	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
ISQ	*in situ* quenching
J	coupling constant (in Hz)
KHMDS	potassium hexamethyldisilazide
L	litre
L	ligand
LDA	lithium di*iso*propylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	*meta*
m	multiplet
M	molar

*m*CPBA	*meta*-chloroperoxybenzoic acid
MDR	multidrug resistance
min	minute(s)
MMPP	magnesium monoperoxyphthalate
mol	mole(s)
Mont.	Montmorillonite
mp	melting point (°C)
MS	mass spectrometry
M.S.	molecular sieves
MW	microwave
m/z	mass/charge
n	number of atoms (on a ring system)
n	linear
n	normal
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidone

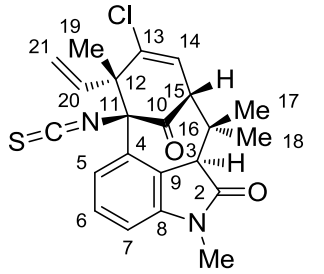
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
o	*ortho*
[O]	oxidation
o/n	overnight
p	*para*
PCC	pyridinium chlorochromate
PEPPSI	1,3-bis(2,6-di*iso*propylphenyl)imidazol-2-ylidene)-(3-chloropyridyl)-palladium(II) dichloride
P-gp	P-glycoprotein
PMB	*para*-methoxybenzyl
ppm	part(s) per million
*p*TSA	*para*-toluenesulfonic acid
q	quartet
quant.	quantitative
rt	room temperature
s	singlet
(S)	sum of the atoms on a bicyclic motif

(S)	chirality of the ligand
t	*tert*
t	triplet
T (°C)	temperature in degrees Celsius
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFEF	2,2,2-trifluoroethyl formate
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol, tolyl	4-methylphenyl
Tosyl, Ts	4-toluenesulfonyl
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin

UV	Ultraviolet-visible spectroscopy
w	weak
Å	Angström
δ	chemical shift
Δ	reflux
ΔE	variation of energy
λ	wavelength of absorbance
μ	micro
ν	frequency

Nomenclature

The numbering of the isolation paper of welwistatin published by Moore and co-workers in 1994 was used for our spectral data assignments (Figure 1).



7 *N*-methylwelwitindolinone C isothiocyanate

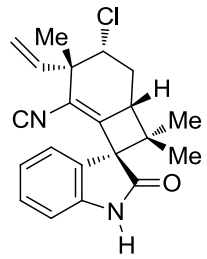
Figure 1

CHAPTER ONE

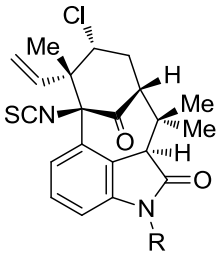
WELWITINDOLINONES: ISOLATION, STRUCTURES, BIOLOGICAL ACTIVITIES AND SYNTHETIC WORK

1.1 ISOLATION AND CHARACTERISATION OF THE WELWITINDOLINONE FAMILY

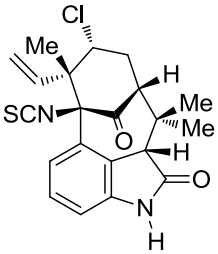
In 1994, Moore and co-workers reported the isolation of fifteen novel alkaloids as part of their research towards new useful natural products.[1] The fifteen structures were isolated from the lipophilic extracts of Australian cyanobacteria, two blue-green algae named *Hapalosiphon welwitschii* W. & G. S. West (UH strain IC-52-3) and *Westiella intricata* Borzi (UH strain HT-29-1). *Hapalosiphon welwitschii* and *Westiella intricata* were found to display potent biological activities such as antifungal, larvacidal and insecticidal activities. The major component of these blue-green algae, *N*-methylwelwitindolinone C isothiocyanate **7**, was also shown to reverse multidrug resistance in chemotherapeutic cancer treatment.[2] Along with *N*-methylwelwitindolinone C isothiocyanate **7**, fourteen alkaloids were isolated as minor constituents: a unique spiro-cyclobutane named welwitindolinone A isonitrile **1**, five compact tetracyclic oxindoles (**2**-**6**) related to **7** and eight biogenetically related structures including four fischerindoles (**8**-**11**) and four hapalindoles (**12**-**15**) (Figure 1.1). The structure and absolute stereochemistry of *N*-methylwelwitindolinone C isothiocyanate **7** was determined by X-ray crystallography.[1]



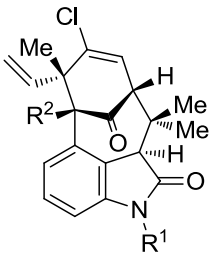
1 welwitindolinone A isonitrile



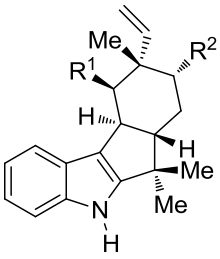
2 R=H welwitindolinone B isothiocyanate
3 R=Me *N*-methyl-welwitindolinone B isothiocyanate



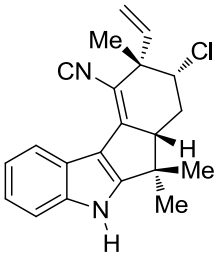
4 *epi*-welwitindolinone B isothiocyanate



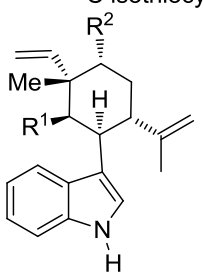
5 R^1=H, R^2=NCS welwitindolinone C isothiocyanate
6 R^1=Me, R^2=NC *N*-methylwelwitindolinone C isonitrile
7 R^1=Me, R^2=NCS *N*-methylwelwitindolinone C isothiocyanate



8 R^1=NC, R^2=Cl 12-*epi*-fischerindole G isonitrile
9 R^1=NC, R^2=H 12-*epi*-fischerindole U isonitrile
10 R^1=NCS, R^2=H 12-*epi*-fischerindole U isothiocyanate



11 12-*epi*-fischerindole I isonitrile

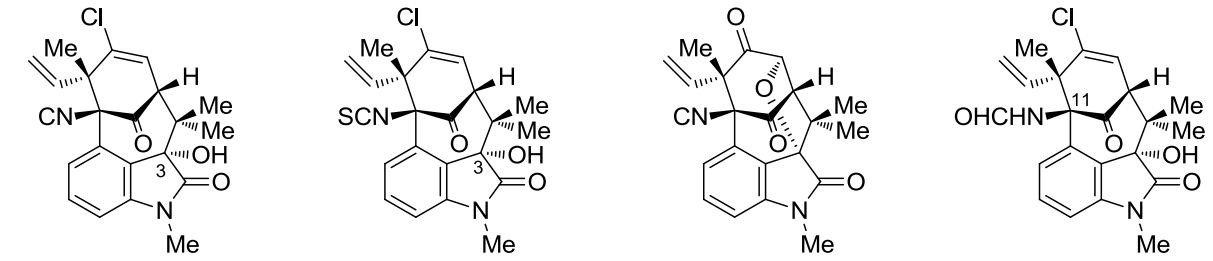


12 R^1=NC, R^2=Cl 12-*epi*-hapalindole E isonitrile
13 R^1=NC, R^2=H 12-*epi*-hapalindole C isonitrile
14 R^1=NCS, R^2=Cl 12-*epi*-hapalindole F isothiocyanate
15 R^1=NCS, R^2=H 12-*epi*-hapalindole D isonitrile

Figure 1.1

In 1999, Moore and co-workers reported the isolation and characterisation of several oxidised welwitindolinones from the strains of terrestrial *Fischerella muscicola* Gomont (HG-39-5) and *Fischerella major* Gomont (HX-7-4).[3] Eight alkaloids were isolated from these strains including four previously identified compounds, welwitindolinone A isonitrile **1**,

N-methylwelwitindolinone C isonitrile **6**, *N*-methylwelwitindolinone C isothiocyanate **7** and 12-*epi*-fischerindole I isonitrile **11**, and four novel oxidised welwitindolinones, 3-hydroxy-*N*-methylwelwitindolinone C isonitrile **16**, 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate **17**, *N*-methylwelwitindolinone D isonitrile **18** and welwitindolinone **19** (Figure 1.2). While welwitindolinones **16** and **17** were simply the result of an oxidation of their respective analogues **6** and **7** at the C_3 position, *N*-methylwelwitindolinone D isonitrile **18** contains a bridging spiro-ether functionality that was believed to arise from a photo-oxidation-cyclisation of *N*-methylwelwitindolinone C isonitrile **6**. Finally, welwitindolinone **19**, possessing a formamide functionality at the benzylic bridgehead position C_{11}, was described as an artifact obtained during the isolation process of 3-hydroxy-*N*-methylwelwitindolinone C isonitrile **16** (Figure 1.2).



16 3-hydroxy-*N*-methyl welwitindolinone C isonitrile

17 3-hydroxy-*N*-methyl welwitindolinone C isothiocyanate

18 *N*-methyl-welwitindolinone D isonitrile

19 3-hydroxy-*N*-methyl welwitindolinone C formamide

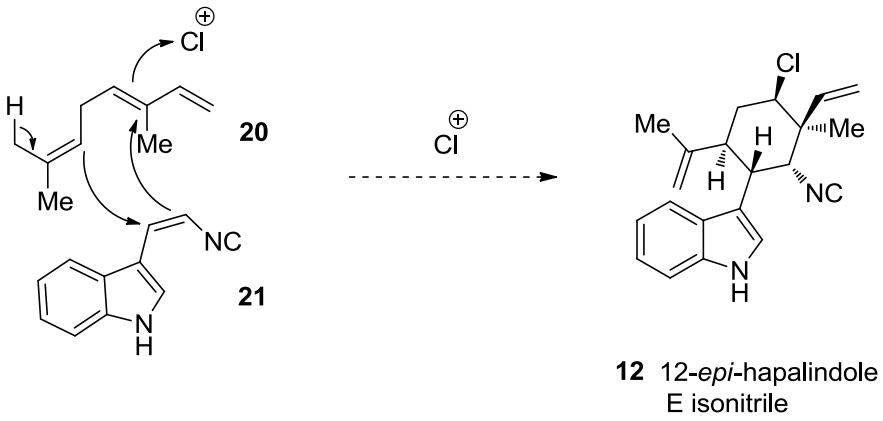
Figure 1.2

1.2 BIOSYNTHETIC ROUTE

1.2.1 A common intermediate for the 15 alkaloids of *Hapalosiphon welwitchii*

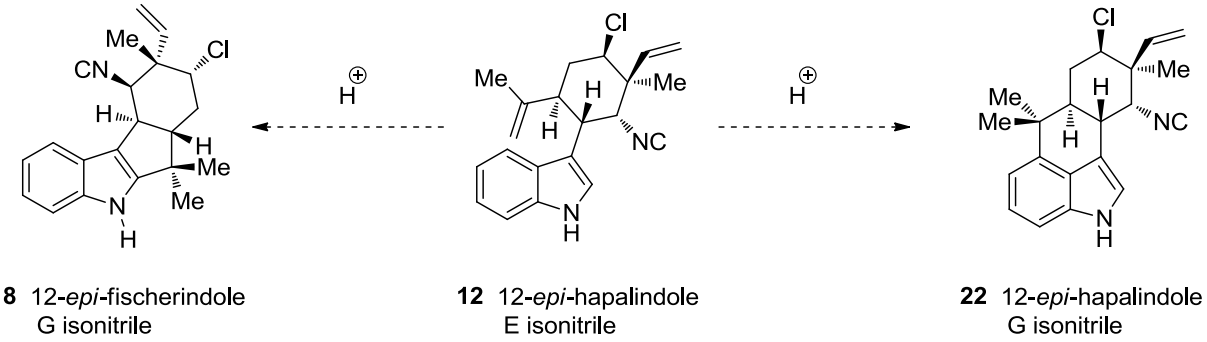
In addition to the isolation and characterisation studies carried out on the fifteen alkaloids isolated from *Hapalosiphon welwitschii*, Moore proposed a biogenesis of the welwitindolinones, fischerindoles and hapalindoles.[1] Moore noticed that the relative stereochemistry of the welwitindolinones, fischerindoles and hapalindoles matched that of 12-*epi*-hapalindole E isonitrile **12** or its isothiocyanate analogue **14**. He therefore proposed these two entities (**12** and **14**) as common precursors of the biogenesis of the diverse chlorine-containing alkaloids isolated from the blue-green algae.

First isolated by Schwartz and co-workers in 1987, 12-*epi*-hapalindole E isonitrile **12** was found to be the second most abundant component in *Hapalosiphon welwitschii*.[4] Hapalindole **12** could be generated from the chloronium ion-induced cyclisation of a geranyl pyrophosphate derivative, *(Z)*-3,7-dimethyl-1,3,6-octatriene **20** and a L-tryptophan derivative, 3-((*Z*)-2'-isocyanoethenyl)indole **21** (Scheme 1.1).



Scheme 1.1

From 12-*epi*-hapalindole **12**, an enzyme-controlled or an acid-catalysed condensation of the isopropenyl group onto the C_2 or C_4 position of the indole motif would respectively lead to the formation of the tetracyclic fischerindole **8** or hapalindole **22**.[1] Further modifications of **8** or **22** would lead to the biogenesis of their whole families (Scheme 1.2).



8 12-*epi*-fischerindole G isonitrile

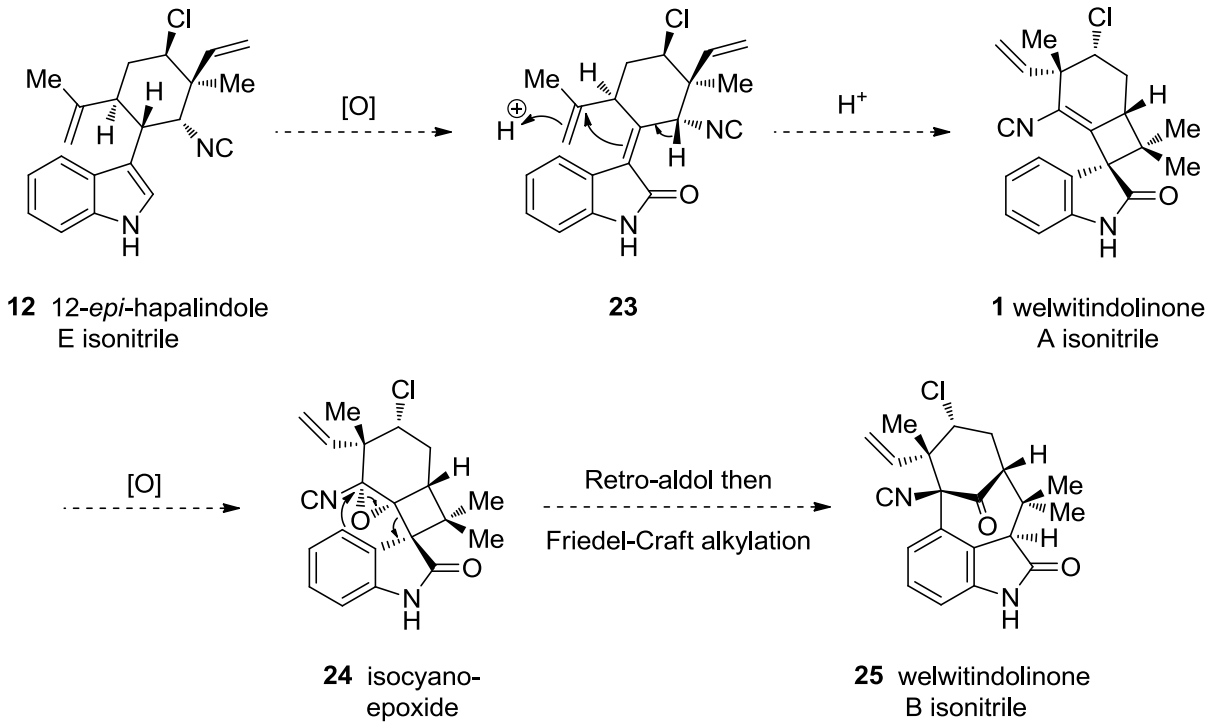
12 12-*epi*-hapalindole E isonitrile

22 12-*epi*-hapalindole G isonitrile

Scheme 1.2

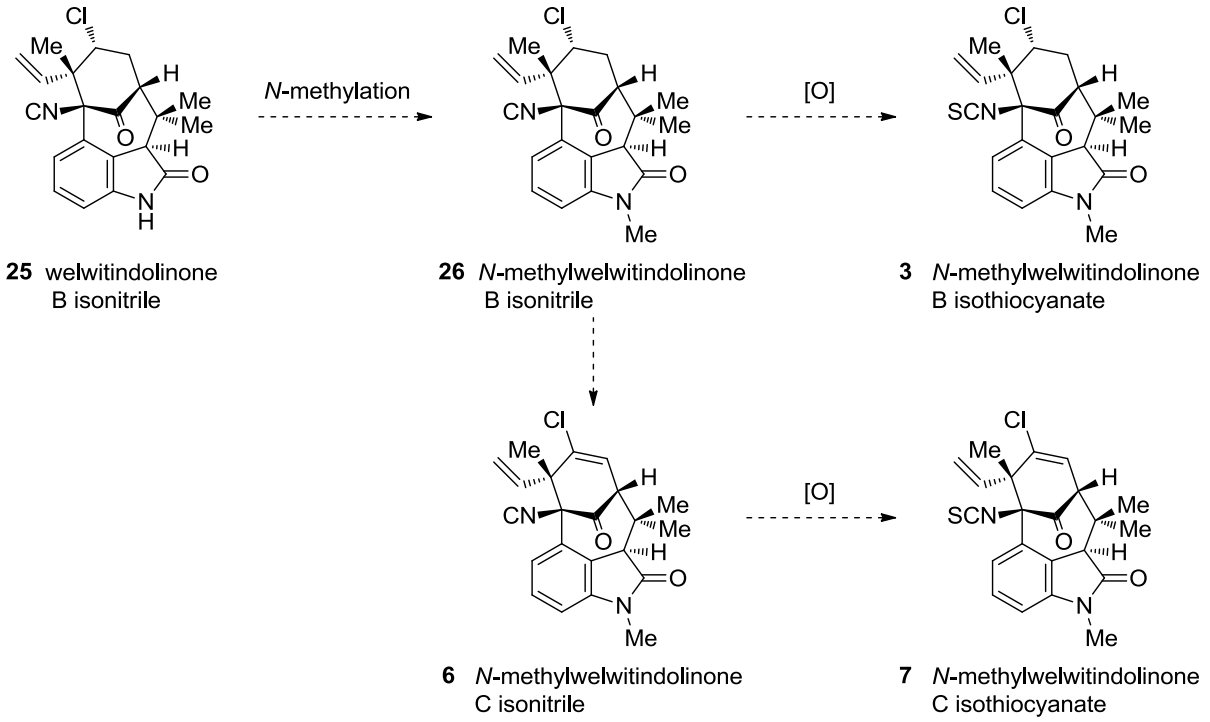
1.2.2 Biogenesis of the welwitindolinones

An oxidation of the indole of 12-*epi*-hapalindole E isonitrile **12** was envisaged in the early stages of the biogenesis of the welwitindolinone family.[1] Indeed, the absence of an indole possessing the characteristic skeleton of the welwitindolinone family shows the crucial role of the oxidation step in the formation of this unusual compact structure. Welwitindolinone A isonitrile **1** could then be obtained *via* an acid-catalysed cyclisation performed on oxindole **23**. Oxidation of spiro-oxindole **1** could generate the isocyano-epoxide intermediate **24** which could undergo skeletal rearrangement *via* a tandem retro-aldol type-fragmentation/Friedel-Crafts alkylation sequence to afford, after tautomerisation, welwitindolinone B isonitrile **25** (Scheme 1.3).



Scheme 1.3

Even though welwitindolinone B isonitrile **25** was not present in the extracts of *Hapalosiphon welwitschii*, Moore considered welwitindolinone **25** as a potential common precursor of the remaining members of the family.[1] *N*-Methylwelwitindolinone B isonitrile **26** would arise from the methylation of welwitindolinone **25**. At this stage, Moore described the origin of the isothiocyanate functionality as unclear; however, along with the hypothesis of the presence of a thiocyanate inorganic fragment in the early stages of the biogenesis, he postulated that sulfur could be introduced at a late stage of the biogenesis on the isonitrile intermediate. Based on this assumption, introduction of a sulfur would lead to isothiocyanate analogue, *N*-methylwelwitindolinone B isothiocyanate **3**. Finally, appropriate oxidations, likely to be facilitated enzymatically, are required to lead to the other members of the family, *N*-methylwelwitindolinone C isonitrile **6** and *N*-methylwelwitindolinone C isothiocyanate **7** (Scheme 1.4).



25 welwitindolinone B isonitrile

26 *N*-methylwelwitindolinone B isonitrile

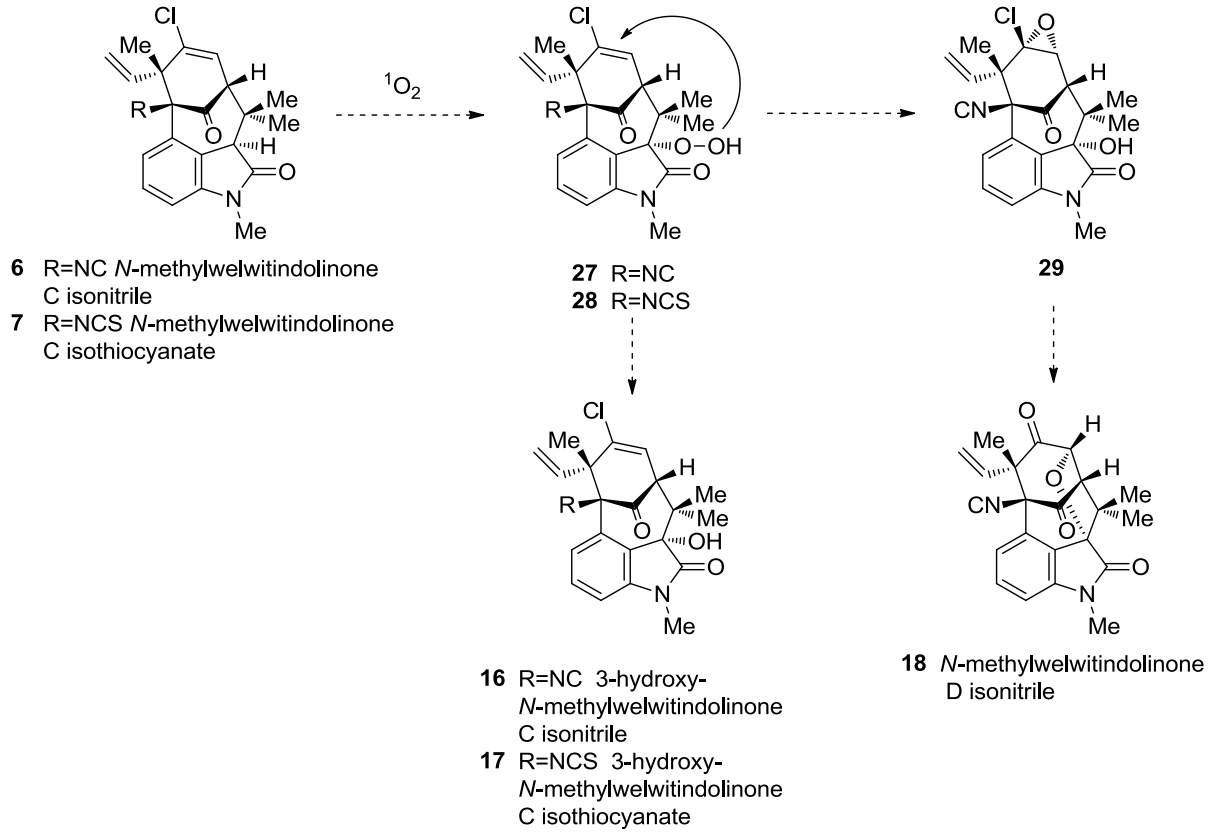
3 *N*-methylwelwitindolinone B isothiocyanate

6 *N*-methylwelwitindolinone C isonitrile

7 *N*-methylwelwitindolinone C isothiocyanate

Scheme 1.4

A photo-catalytic oxidation performed on *N*-methylwelwitindolinone C isonitrile **6**, or its isothiocyanate analogue **7**, could provide the hydroperoxy intermediates **27** or **28** that, under subsequent reduction, would afford 3-hydroxy-*N*-methylwelwitindolinone C isonitrile **16** and isothiocyanate **17**.[3] Alternatively, intramolecular epoxidation of the vinyl chloride present on **27** followed by cyclisation and ring-opening of the epoxide by the hydroxy group in position C_3 would give *N*-methylwelwitindolinone D isonitrile **18**. This oxidative pathway hypothesis was reinforced as exposure of welwitindolinone **6** in methanol to singlet oxygen for four days gave the oxidised welwitindolinones **16** and **18** (respective yields of 4.9% and 3.2%) (Scheme 1.5).



6 R=NC *N*-methylwelwitindolinone C isonitrile
7 R=NCS *N*-methylwelwitindolinone C isothiocyanate

27 R=NC
28 R=NCS

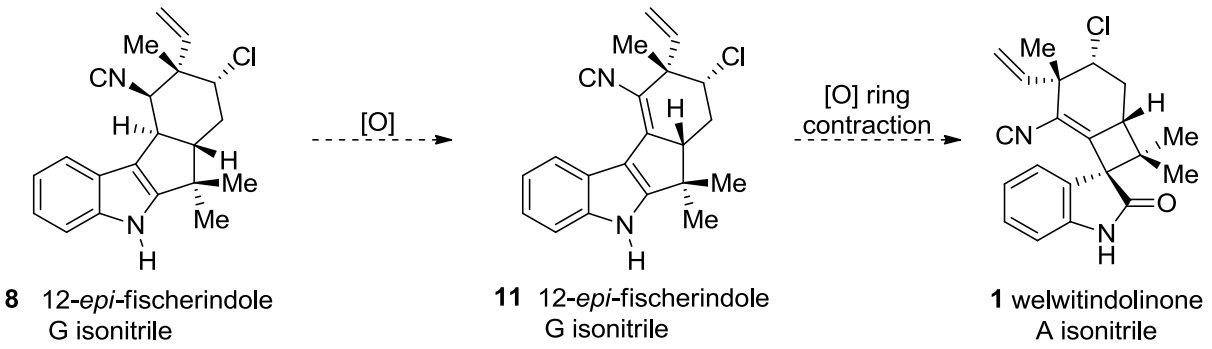
29

16 R=NC 3-hydroxy-*N*-methylwelwitindolinone C isonitrile
17 R=NCS 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate

18 *N*-methylwelwitindolinone D isonitrile

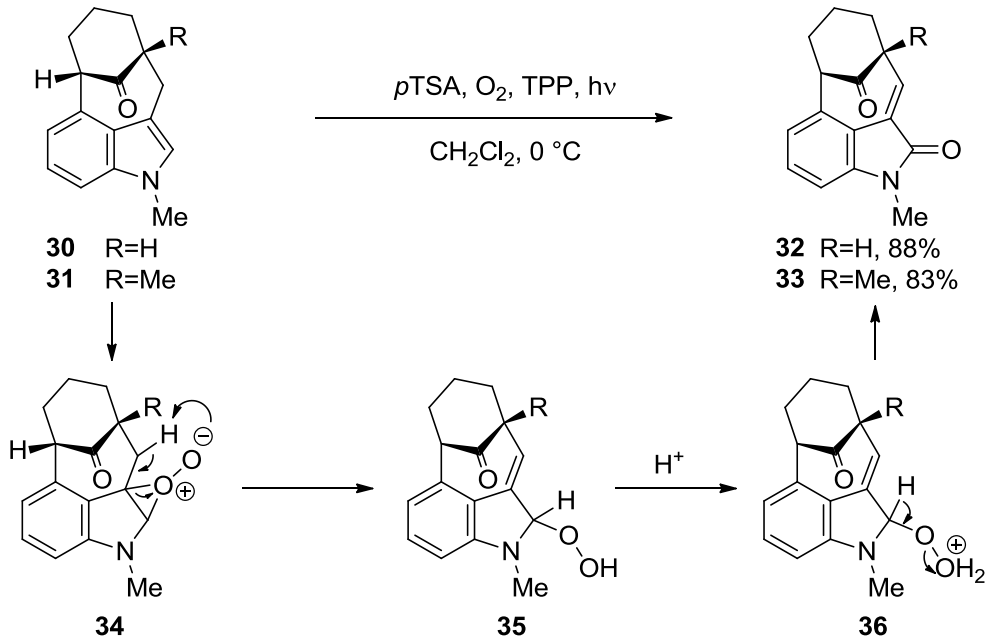
Scheme 1.5

In 2005, Baran underlined the unlikely architecture of intermediate **23**, highlighting the fact that Moore's pathway would require an unusual cationic cyclisation to afford welwitindolinone A isonitrile **1**.[1,5] He proposed an alternative biogenesis of welwitindolinone A isonitrile **1**, involving a benzylic oxidation of 12-*epi*-fischerindole G isonitrile **8** followed by an oxidative ring contraction of 12-*epi*-fischerindole I isonitrile **11** (Scheme 1.6). This hypothetical biogenesis is reinforced by the fact that the two fischerindoles **8** and **11** involved in this process were initially co-isolated from the *Hapalosiphon welwitchii* algae.



Scheme 1.6

In 2009, our group supported the proposal of Baran and Richter regarding the unlikely architecture of intermediate **23**, presented in the initial biogenesis proposed by Moore and co-workers. Experimental procedures involving a singlet oxygen transfer on members of the hapalindole family (such as hapalindole A) did not yield the desired oxindole motif.[6]



Scheme 1.7

Our group presented an acid-mediated oxidation of a large range of tetracyclic indoles into the corresponding α,β-unsaturated oxindoles (such as oxindoles **32** and **33**) as well as a potential mechanism for the transformation (Scheme 1.7). The strained welwitindolinone scaffold was presented as a key feature of this intriguing equilibration, thus reinforcing the improbable character of biosynthetic intermediate **23**.[6]

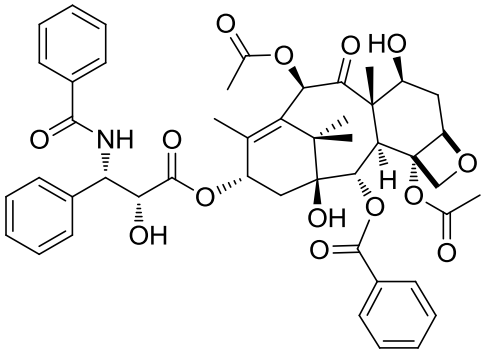
1.3 BIOLOGICAL PROPERTIES OF THE WELWITINDOLINONES

As photosynthetic organisms which produce biologically active metabolites, cyanobacteria represent an attractive source of pharmaceutical leads. In 1984, Moore and co-workers reported the isolation and characterisation of several alkaloids from *Hapalosiphon intricatus* and *Hapalosiphon fontinalis*.[7] Most of these novel natural products displayed antifungal and/or antibacterial activities. Therefore, ten years later, as part of their effort to identify new biologically active natural products, Moore and colleagues re-investigated the blue-green algae. While the isonitrile functionality was known to be responsible for antifungal activities (e.g. expressed in welwitindolinone A isonitrile **1**, welwitindolinone D isonitrile **18**), *N*-methylwelwitindolinone C isothiocyanate **7** demonstrated both multidrug resistance (MDR) reversing activity and larvicidal properties.[1,2]

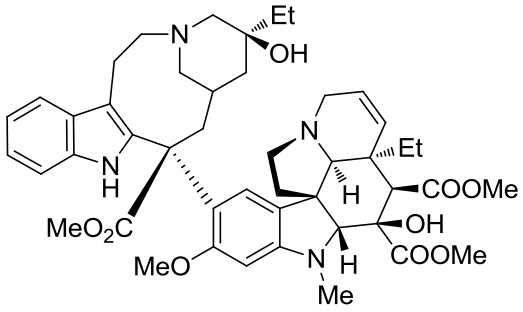
1.3.1 Definition of MDR and how to overcome the MDR process

Cancer consists of a large group of almost 100 diseases that is defined by an uncontrolled growth of malignant cells and their ability to multiply and spread inside the human body. One of the many treatments of cancer is known as chemotherapy and involves the selective

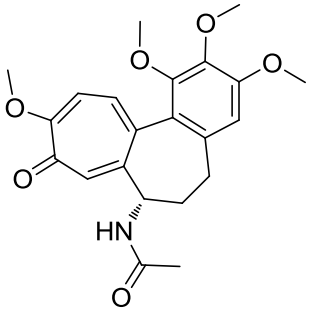
destruction of malignant cells by use of chemical substances (e.g. taxol **37**, vinblastine **38**, colchicine **39**, see Figure 1.3). This technique has shown an impressive success in many cancer therapies (e.g. lung or breast cancers) reducing considerably the number of infected cells over the first weeks of medication. However, over time, the tumour cells seem to develop an ability to resist the cytotoxic agent, which represents a significant obstacle to providing effective and sustainable treatments against cancer. Formally known as multidrug resistance, this phenomenon enables a disease-causing organism, or cancerous cell, that has been exposed to one chemotherapeutic agent to develop cross-resistance towards distinct drugs of a wide variety of structures and functions targeted at eradicating the organism or cancerous cell.



37 taxol



38 vinblastine



39 colchicine

Figure 1.3

Diverse mechanisms have been invoked to explain the MDR process including a decrease in the permeability of the cell (also compromising accessibility of the active substances in the tumour cell), alteration of the binding sites and an increase in the efflux of chemotherapeutic drugs. After extensive research over the past few decades, a correlation has been established between the MDR phenomenon and the over-expression of plasma membrane proteins such as P-glycoprotein (P-gp).[8] P-Gp has been identified on the surface of cancer cells of the liver, kidneys, intestine and ovaries. It is responsible for the efflux migration of diverse cytotoxic agents from the intracellular milieu, which serves to reduce the presence of the active substance in the tumour cells.

As illustrated on the left-hand side of Figure 1.4, the chemotherapeutic drugs were able to penetrate the affected cells but were later pumped out by the MDR efflux pump mechanism of the P-gp.[9] In order to overcome the MDR phenomenon, a chemical substance would need to inhibit the action of the P-gp and thereby allow the accumulation of chemotherapeutic substances in the infected cells.

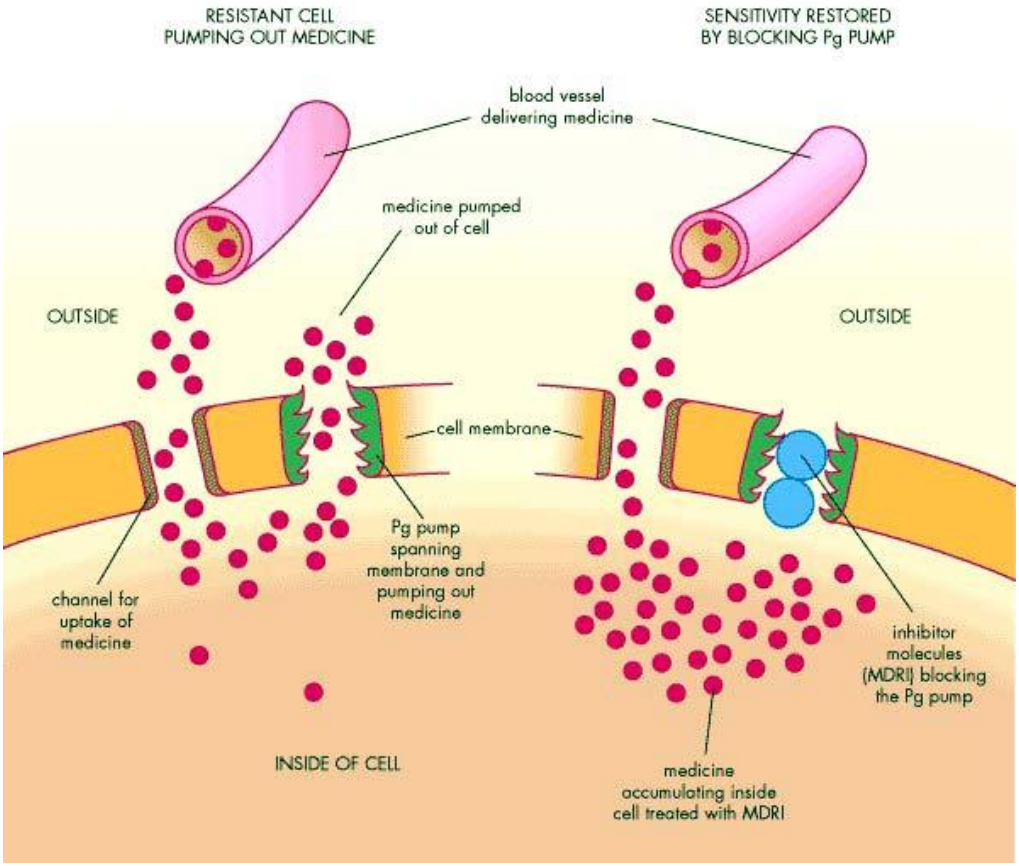
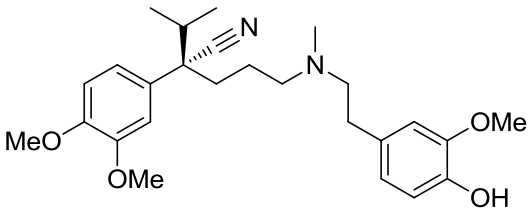


Figure 1.4

Extensive studies have already been carried out to identify chemical substances that are able to antagonise the P-gp pump effect (illustrated on the right side of Figure 1.4).[9] Several blocking agents (e.g. verapamil **40**, see Figure 1.5), commonly called MDR reversing agents, MDR modulators or MDR chemosensitisers, have already proved their efficiency in reducing the resistance of the cancer cells *in vitro*, however, none of these chemosensitisers has been clinically tested due to their high cytotoxicity.



40 verapamil

Figure 1.5

Research to identify non-cytotoxic MDR reversing agents that inhibit the P-gp pump effects is still an important area in cancer chemotherapy.

1.3.2 Welwitindolinones as MDR reversing agents

Measurement of the ability of a chemical substance to reverse MDR activity *in vitro* can be carried out by treating an infected cell with a combination of several doses of anticancer drugs (such as taxol **37** or vinblastine **38**, see Figure 1.3) as well as the agent in question. Analyses of the percentage of cancer cells killed versus a control would then determine the capacity of the agent to antagonise the MDR agent.

In their effort to identify novel MDR inhibitors, Moore and colleagues screened an extensive collection of extracts from *Hapalosiphon welwitschii* to define their ability to antagonise P-gp.[1,2] Tested *in vitro* on MCF-7/ADR (infected cells from breast cancer cell line) and SK-VLB-1 (infected cells from ovarian cancer cell line selected for their resistance to vinblastine **38** due to the presence of over-expressed P-gp), the extracts were identified as possessing MDR reversing agents that were able to promote the accumulation of the

chemotherapeutic drug, [^{3}H]-vinblastine, in the infected cells. Components of these extracts, specifically three members of the family were studied: *N*-methylwelwitindolinone C isothiocyanate **7** and welwitindolinone C isothiocyanate **5** were chosen for their ability to reduce considerably the resistance of the infected cells to the anticancer drugs (Figure 1.3), *N*-methylwelwitindolinone C isonitrile **6** was investigated due to its chromatographic similarity with **7**.

In SK-VLB-7 cells, Moore and colleagues studied the accumulation of actinomycin D and daunomycin. *N*-Methylwelwitindolinone C isothiocyanate **7** was identified as being as potent as verapamil **40** (the best characterised MDR chemosensitiser to date) at lower doses (20 µM of **40** against 5 µM of welwitindolinone **7**). Welwitindolinone C isothiocyanate **5** was able to promote the accumulation of actinomycin D at similar doses and efficiency to welwitindolinone **7** but was not able to accumulate the anti-cancer agent daunomycin. Finally, *N*-methylwelwitindolinone C isonitrile **6** was considered inactive as similar results were obtained in the absence of MDR reversing agent.

In moderately resistant MCF-7/ADR cells, the activity of *N*-methylwelwitindolinone C isothiocyanate **7** was investigated in the presence of diverse chemotherapeutic drugs, including taxol **37**, colchicine **39** and actinomycin. Natural product **7** demonstrated modulation of MDR activity 20 to 100 times greater than verapamil **40** at non-cytotoxic doses (0.1 µM). Welwitindolinone C isothiocyanate **5** was shown to be less active than **7**, whilst *N*-methylwelwitindolinone C isonitrile **6** was totally inactive towards the MCF-7/ADR cells.

It is interesting to observe that the inactivity of *N*-methylwelwitindolinone C isonitrile **7** as a modulator suggests that the isothiocyanate functionality plays an important role in the binding with the P-gp.

A combination of low cytotoxicity and an excellent efficacy in chemosensitisation could promote *N*-methylwelwitindolinone C isothiocyanate **7** as a promising candidate for medical testing as a MDR reversing agent.

1.3.3 Microtubule definition

Tubulin molecules present in the cytoplasm are known as microtubules.[10] These long hollow cylindrical structures are found in almost all eukaryotic cells and play a critical role in the cytoplasmic skeleton, the formation of the mitotic spindle and the transport of organelles such as mitochondria or chromosomes. The assembly and disassembly of tubulins is crucial to promoting the development and dynamic equilibrium of cells. Alteration of microtubules could disturb the cell cycle in the mitotic phase. This principle has been envisaged in the treatment of cancer to perturb the multiplication of infected cells. Drugs able to damage the microtubule process are known as anti-microtubules. Taxol **37**, vinblastine **38** and colchicine **39** are the most common anti-microtubule agents (see: Figure 1.3). They are often used as anticancer drugs due to their ability to block cell growth by interference with microtubules.

1.3.4 Welwitindolinones as anti-microtubule agents

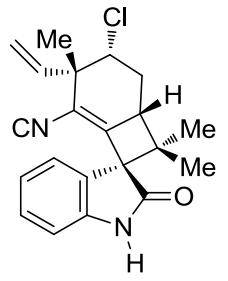
In 1995, Smith and co-workers reported the screening of the welwitindolinones as anti-microtubule agents. Incubations of the mutant cells were carried out with three members of the family, welwitindolinone C isothiocyanate **5**, *N*-methylwelwitindolinone C isothiocyanate **7** and its isonitrile analogue **6**.[11] A dose-dependent disruption of the microtubule activity was observed when the mutant cells were incubated with

welwitindolinone C isothiocyanate **5**. Welwitindolinone **5** could considerably reduce the polymerisation of microtubules without suffering from the P-gp pump effect.

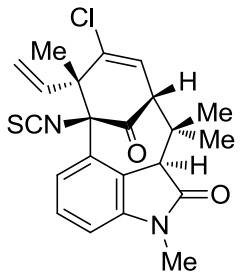
N-Methylwelwitindolinone C isothiocyanate **7** was shown to be a less potent anti-microtubule agent than **5**. Finally, despite a limited amount of its isonitrile analogue **6** tested, the latter appeared to display similar activity to **5**.

1.4 WELWITINDOLINONE, SYNTHETIC INTEREST FROM 1994 TO 2010

Since their isolation in 1994, the members of the welwitindolinone family have represented fascinating synthetic targets due to both their unique architecture and their impressive biological activities.[1] Two welwitindolinones have been particularly targeted by the synthetic community: welwitindolinone A isonitrile **1**, due to its unusual tetracyclic structure which links an oxindole to a cyclohexene *via* a spirocyclic, four-membered ring system, and welwitindolinone C isothiocyanate **7** (Figure 1.6).



1 welwitindolinone A isonitrile



7 *N*-methylwelwitindolinone C isothiocyanate

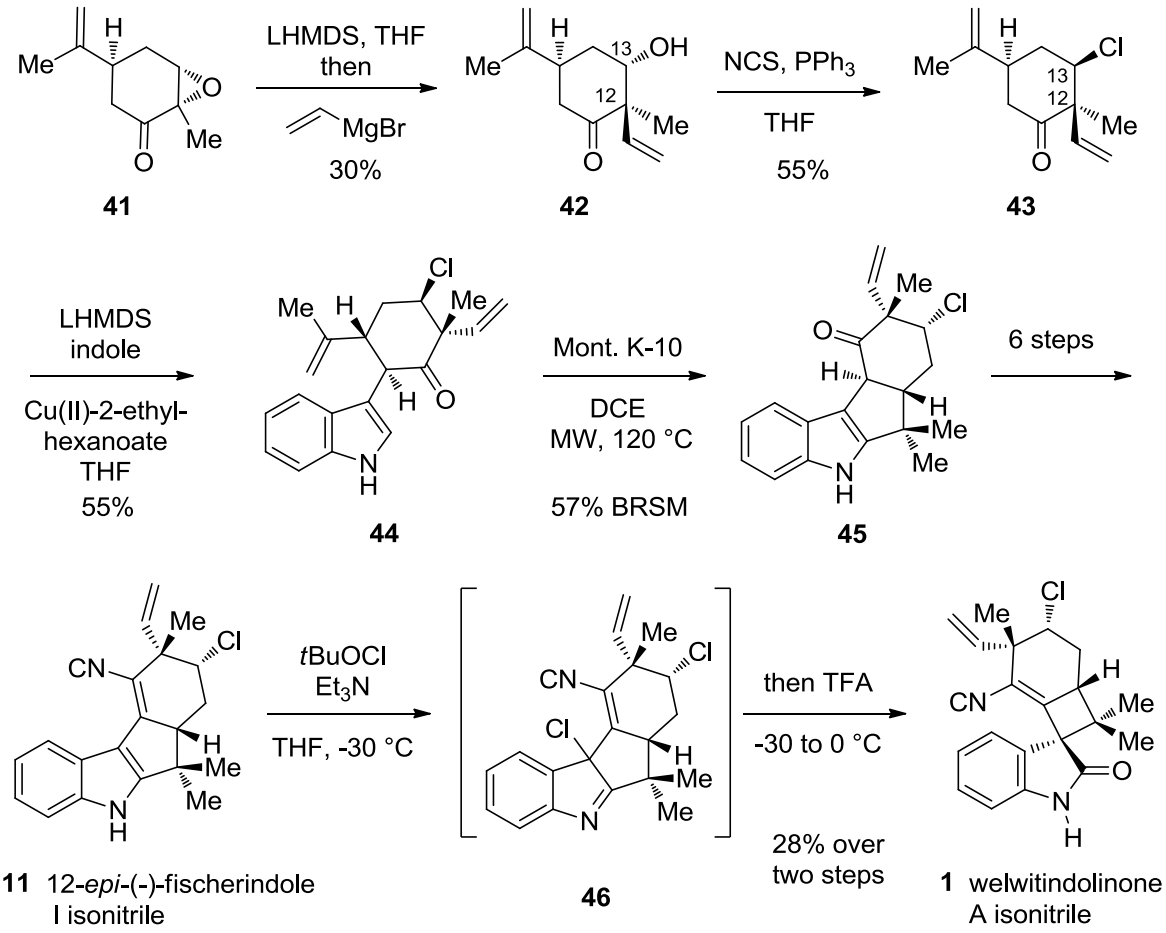
Figure 1.6

1.4.1 Syntheses of welwitindolinone A isonitrile 1

Despite its challenging structure, welwitindolinone A isonitrile **1** was the first welwitindolinone to be synthesised. In 2005, the first total synthesis of enantiomerically pure (+)-welwitindolinone A isonitrile **1** was published by the research group of Baran.[5] A few months later, Wood and co-workers reported an alternative approach to the spiro-oxindole.[12]

In 2004, Baran and Richter developed a direct coupling of indoles with carbonyl compounds, allowing access to the hapalindole and fischerindole alkaloid families.[13] A year later, the same authors reported the first enantioselective syntheses of three natural products isolated from the blue-green algae, welwitindolinone **1**, fischerindole I isonitrile **11** and fischerindole G isonitrile **8**.[5]

Their approach consists of a very efficient protecting-group-free sequence, based on their proposed biogenesis of the alkaloids of the cyanobacteria (see: Scheme 1.6).[5] A novel sequence of enolisation of *(S)*-carvone oxide **41** followed by regioselective Grignard opening of the epoxide afforded alcohol **42**. At this stage, chlorination using *N*-chlorosuccinimide (NCS) in the presence of PPh_3 was performed to introduce the required chlorine atom at position C_{13} with the required relative stereochemistry. Direct coupling of chloroketone **43** with indole was completed using the conditions developed in 2004. Montmorillonite K-10 was used as the acid catalyst for the intramolecular Friedel-Crafts cyclisation that generated tetracyclic **45** as a single diastereoisomer. Transformation of the ketone to the vinyl isonitrile afforded the key intermediate **11** in six steps. After chlorination at low temperature, **46** was subjected to acidic conditions at higher temperatures to provide welwitindolinone A isonitrile **1** in 28% yield (Scheme 1.8).

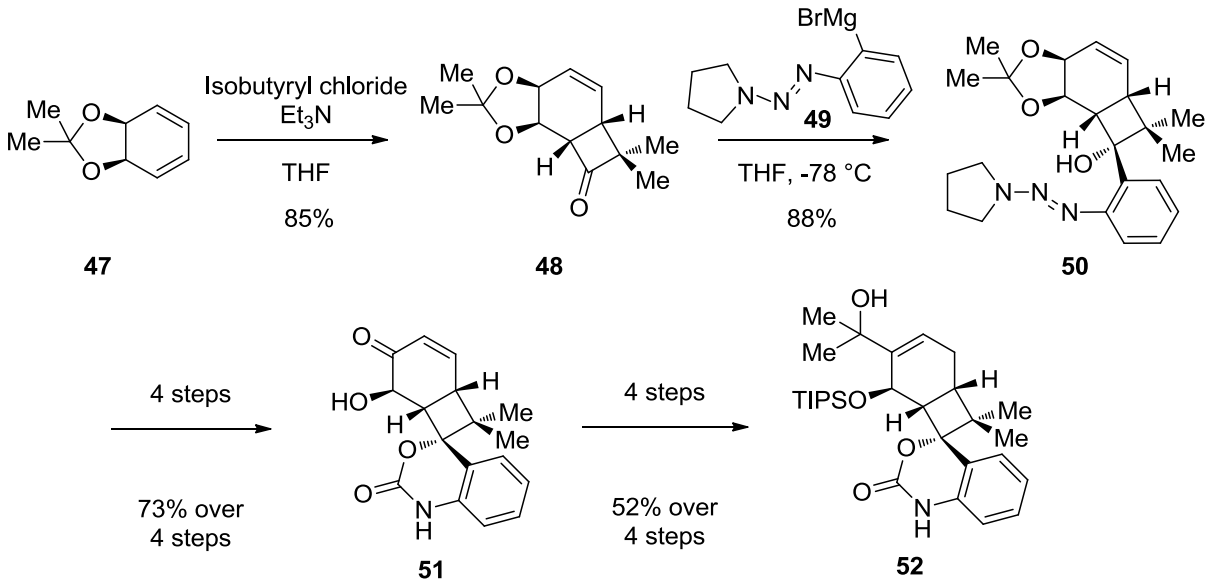


Scheme 1.8

In 2006, Wood and colleagues reported an alternative total synthesis of (±)-welwitindolinone A isonitrile **1** with an overall yield of 2.5%.[12,14] Wood based his strategy on previous work regarding the formation of a spiro-oxindole *via* a mild SmI_2-mediated approach and an unusual synthesis of an α-chloro-quaternary centre.[15]

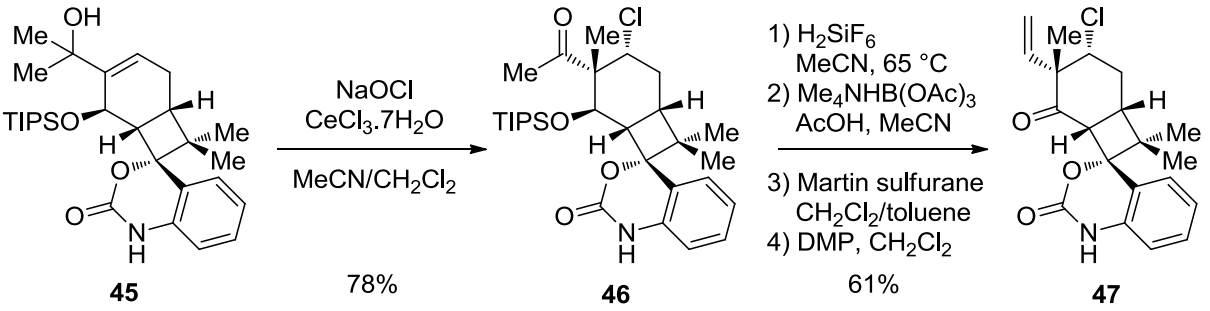
A regio- and stereoselective [2+2] cycloaddition using isobutyryl chloride was performed on acetal **47** to afford tricyclic ketone **48** in 85% yield. Addition of the unusual triazene Grignard reagent **49** gave access to the required alcohol **50** in high yield. A four-step sequence involving chemoselective reduction of the triazene motif, protection of the resultant amino alcohol, acetonide removal and selective oxidation of the allylic alcohol was carried out on **50**

to give tetracycle **51**. Tertiary allylic alcohol **52** was prepared from keto-alcohol **51** in four steps (Scheme 1.9).



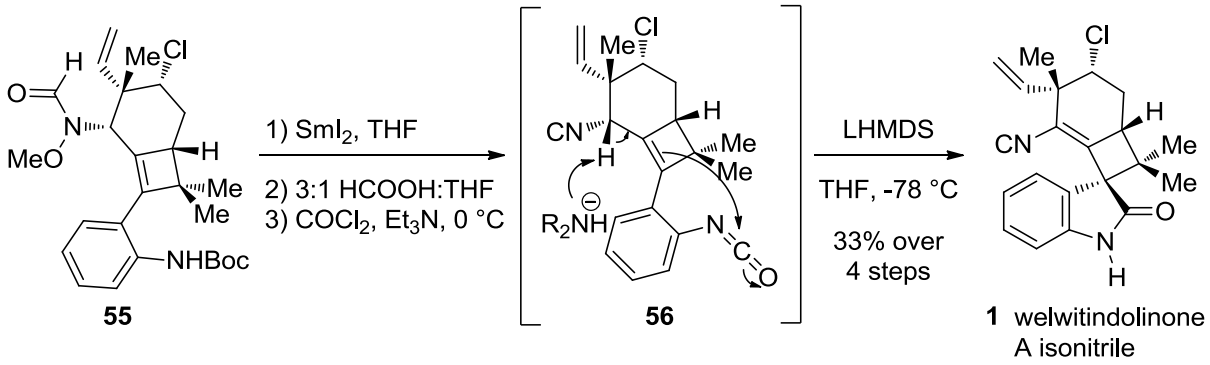
Scheme 1.9

At this stage, the unusual chloronium-ion mediated semi-pinacol rearrangement successfully generated intermediate **53** with a chlorine atom next to the quaternary centre. Rearrangement proceeded smoothly and chloroketone **53** was obtained with an excellent control of the relative stereochemistry as a single diastereoisomer in 78% yield. After desilylation and stereoselective reduction of the ketone, the diol was subjected to a highly regioselective dehydration process before oxidation of the remaining alcohol, urethane **54** was obtained in 61% yield over four steps (Scheme 1.10). Urethane **54** was then converted into the corresponding *N*-formamide **55** in 40% overall yield following six further steps.



Scheme 1.10

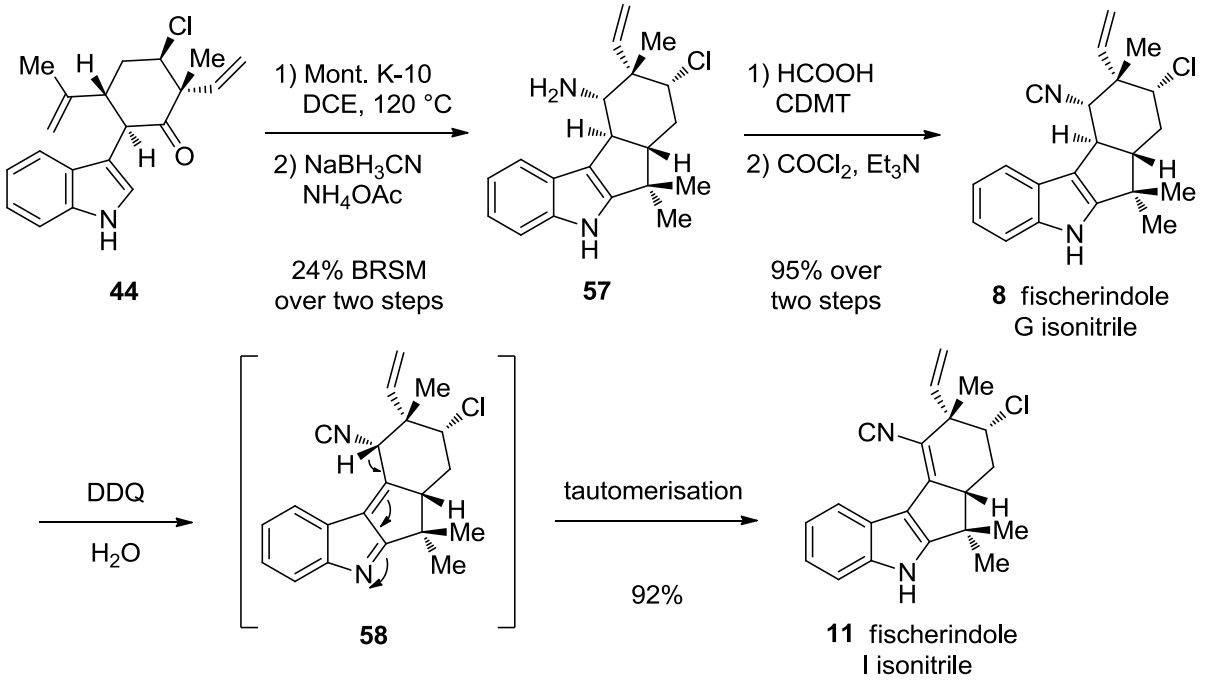
Exposure of deprotected amine **55** to phosgene in the presence of Et_3N furnished the required isocyanate **56** which, after deprotonation using LHMDS at low temperature, provided the desired welwitindolinone A isonitrile **1** as a single diastereoisomer (Scheme 1.11).



Scheme 1.11

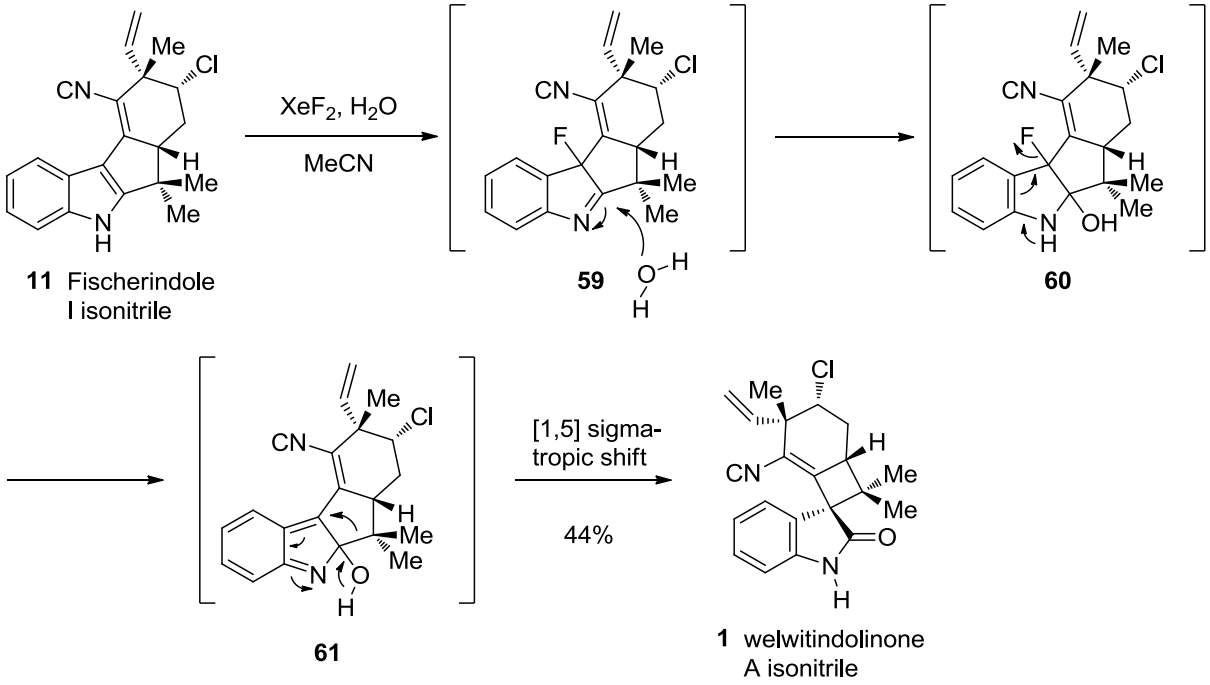
Finally, a few years after reporting the first example of the direct formation of a spirocyclic-four-membered ring system from an annulated five-membered ring, Baran published a new sequence that involves both fischerindoles G **8** and I **11** as intermediates in the synthesis of spiro-oxindole **1**, thus reinforcing his proposed biogenesis.[16] Carried out on a gramme scale, the sequence starts by the preparation of ketone **44** from carvone oxide **41** as previously described.[5] Fischerindole G isonitrile **8** was obtained in 95% yield upon

formylation and dehydration of single diastereoisomer **57**. Oxidation of **8** by DDQ in presence of water afforded fischerindole I isonitrile **11** in excellent yield (Scheme 1.12).



Scheme 1.12

Motivated by the intention to improve their previous sequence, Baran and Richter developed an alternative route to synthesise welwitindolinone A **1** (Scheme 1.13). Xenon difluoride was added to fischerindole I isonitrile **11** in the presence of water to form intermediate **60**, which, after expulsion of fluoride, was converted into welwitindolinone A isonitrile **1** *via* a [1,5] sigmatropic shift.



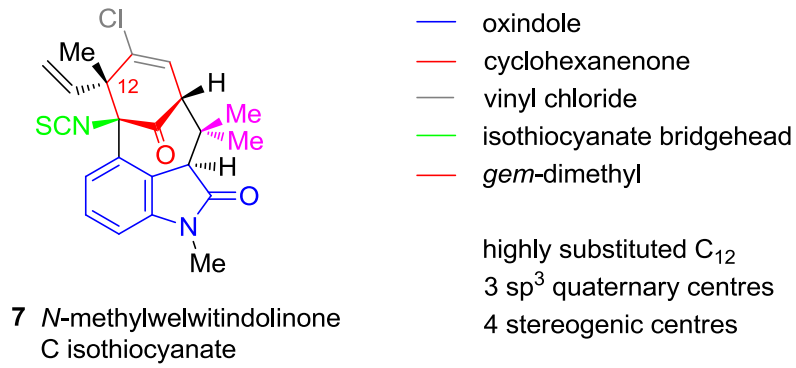
Scheme 1.13

Despite its challenging and unique structure, welwitindolinone A isonitrile **1** was successfully synthesised by Baran and Wood. While Baran described a very rapid access to the enantiomerically pure (+)-welwitindolinone A isonitrile **1** based on the biogenesis, Wood proposed an approach involving a samarium-mediated closure of the spiro-oxindole as well as an intriguing semi-pinacol rearrangement.

1.4 .2 Syntheses towards *N*-methylwelwitindolinone C isothiocyanate 7

Since its isolation in 1994, *N*-methylwelwitindolinone C isothiocyanate **7**, commonly called welwistatin, has attracted the attention of many synthetic chemists. A combination of remarkable biological activities and a fascinating structure has made welwistatin **7** an intriguing target over the past two decades. As previously reported, its ability to reverse MDR

action and its low cytotoxicity make it potentially interesting in cancer therapies.[2] This synthetically challenging natural product consists of a tetracyclic compact structure, which links an oxindole to a cyclohexenone *via* a seven-membered ring system. Moreover, welwistatin **7** displays a number of characteristic features on its highly functionalised core structure, including four stereogenic centres, three sp^3 quaternary centres, a *gem*-dimethyl group, a vinyl chloride and an unusual isothiocyanate functionality in a bridgehead position (Figure 1.7).

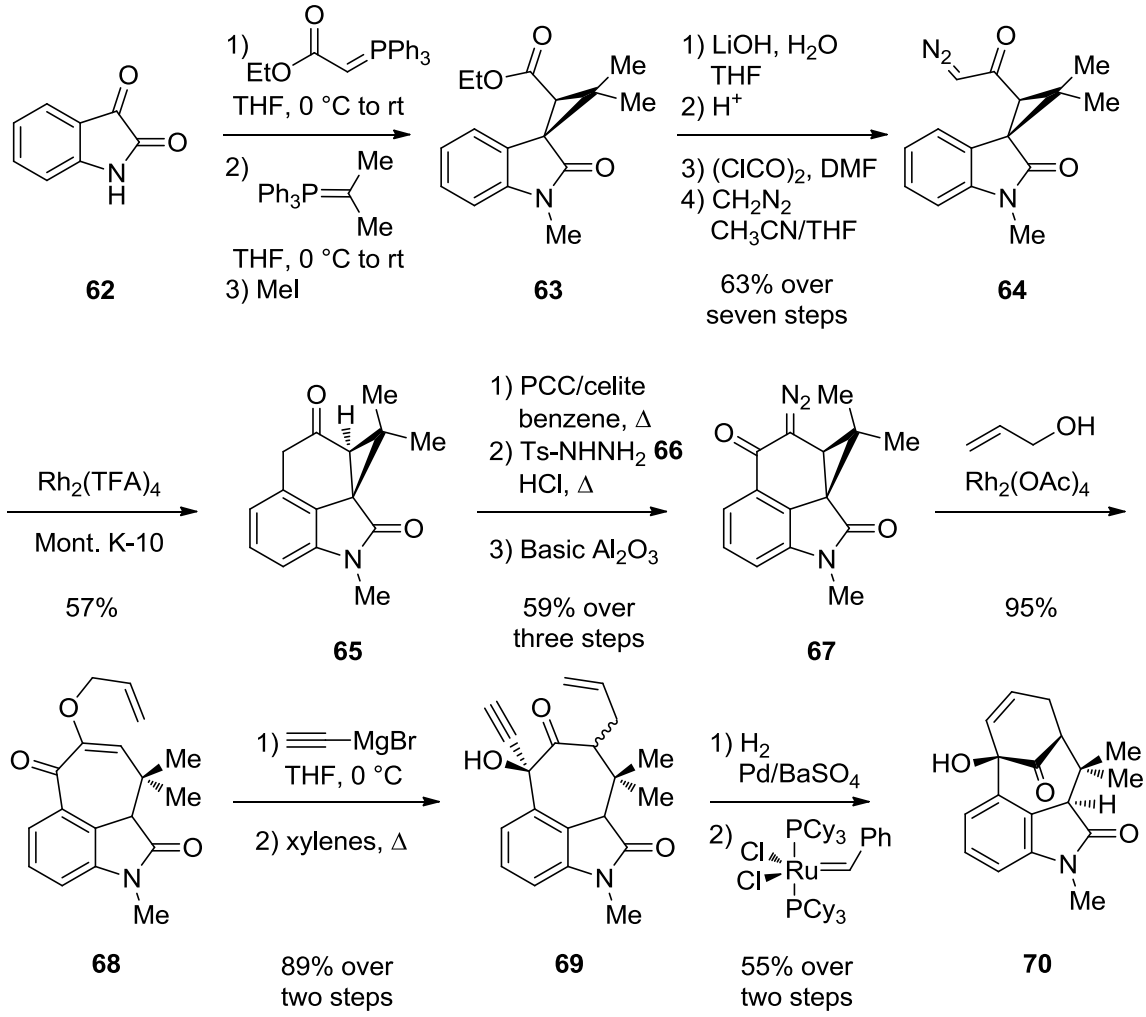


7 *N*-methylwelwitindolinone C isothiocyanate

Figure 1.7

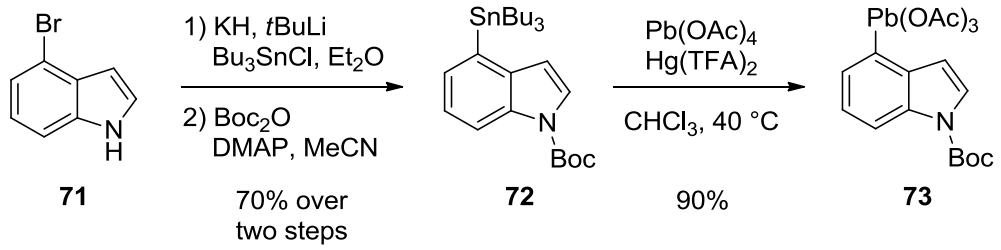
Five years after its isolation, Wood and co-workers presented the first work towards the synthesis of a member of the welwitindolinone family.[17] They reported a fifteen-step stereoselective synthesis based on two key features: a catalytic C-H insertion and a ring-closing metathesis. Reaction of commercially available isatin **62** with two phosphorus ylides was followed by exposure to iodomethane to furnish ester **63**. After saponification of ester **63**, the carboxylic acid was converted into its corresponding acid chloride. Treatment with diazomethane gave the required α-diazoketone **64** that participated in a rhodium-catalysed aryl C-H insertion reaction performed in the presence of montmorillonite K-10. At this stage, ketone **65** was oxidised to the corresponding diketone using PCC.

Regioselective diazotisation of this diketone using hydrazine **66** followed by treatment with basic alumina provided α-diazoketone **67**. Interestingly, coupling of diazo **67** with an allylic alcohol framework under rhodium catalysis was accompanied by the opening of the cyclopropane motif and generation of the desired seven-membered ring system to give **68**. Grignard addition to ketone **68** followed by a [3,3] sigmatropic rearrangement led to tertiary alcohol **69**. Treatment of terminal alkyne **69** with H_2 and Lindlar catalyst, followed by ring-closing metathesis in the presence of Grubbs' first-generation catalyst, yielded tetracyclic compound **70**, possessing the core structure of the welwitindolinone family (Scheme 1.14)



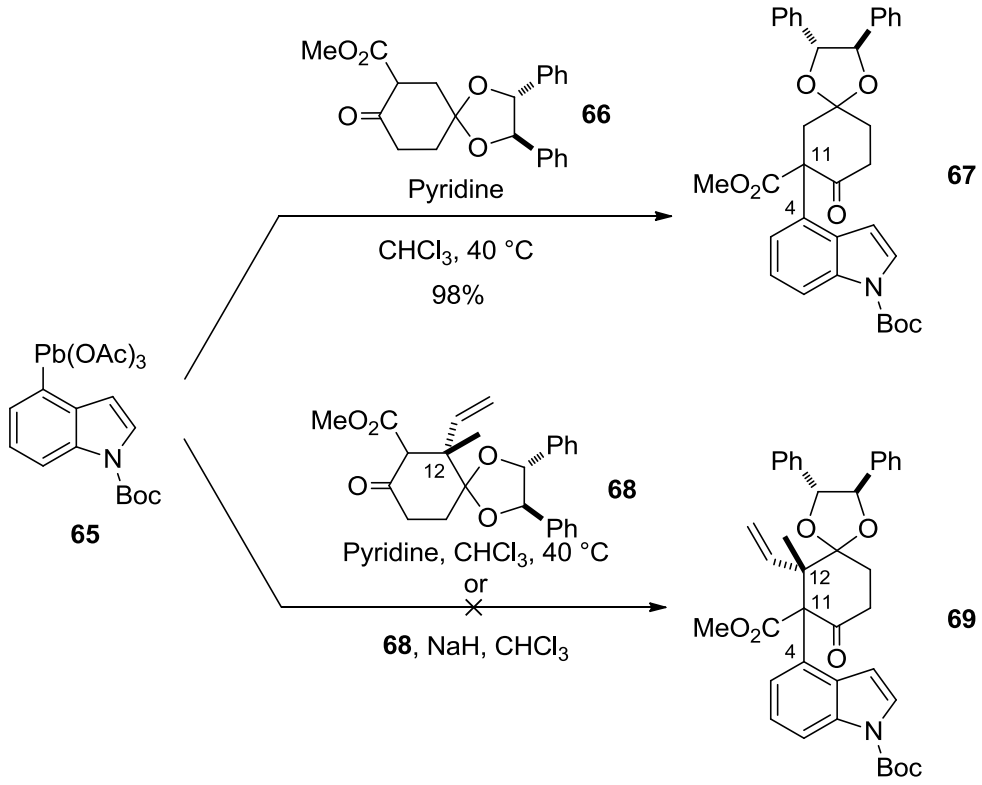
Scheme 1.14

In 2001, Konopelski and Deng envisaged a coupling between an organolead indole and a suitably functionalised cyclohexanone and an aldol-type condensation as the key features of their approach to the core structure of the welwitindolinones.[18] Unable to perform a direct plumbation, lead(IV) 4-indolyl triacetate **73** was built from commercially available 4-bromoindole **71** *via* a stannane-indole intermediate **72**. Treatment with KH to deprotonate the nitrogen of the indole was necessary to avoid side reactions on position C_2 or C_3 during the halogen-lithium exchange. Tri-*n*-butyltin chloride was chosen for the quench of the dianion. After protection of the indole nitrogen, organolead **73** was easily prepared by metal exchange in the presence of a mercury(II) catalyst (Scheme 1.15).



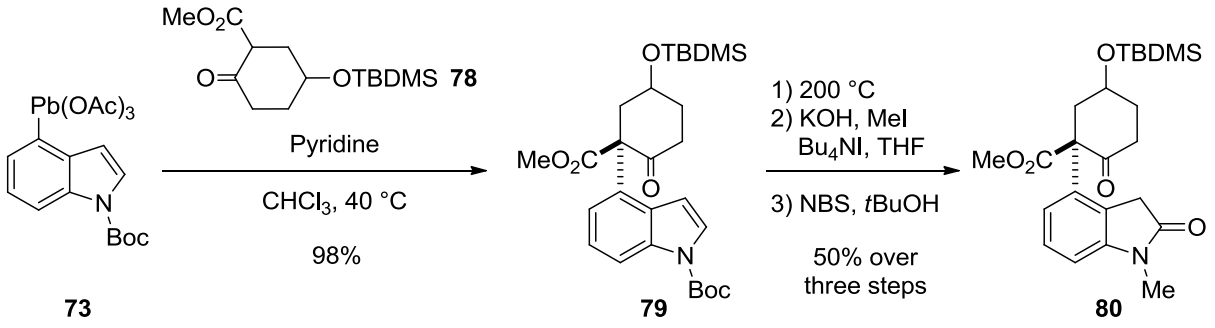
Scheme 1.15

With lead(IV) 4-indolyl triacetate **73** in hand, the coupling with two different β-ketoesters was investigated. Although coupling with cyclohexanone **74** in the presence of pyridine gave the desired adduct **75** in excellent yield, coupling with cyclohexanone **76** did not occur. Substitution of the position C_{12} of the cyclohexanone partner seemed to have a dramatic effect on the formation of the C_4-C_{11} bond (Scheme 1.16).



Scheme 1.16

Moreover, attempts to cyclise intermediate **79** (and its unprotected analogue) *via* an aldol-type reaction remained unsuccessful (Scheme 1.17).

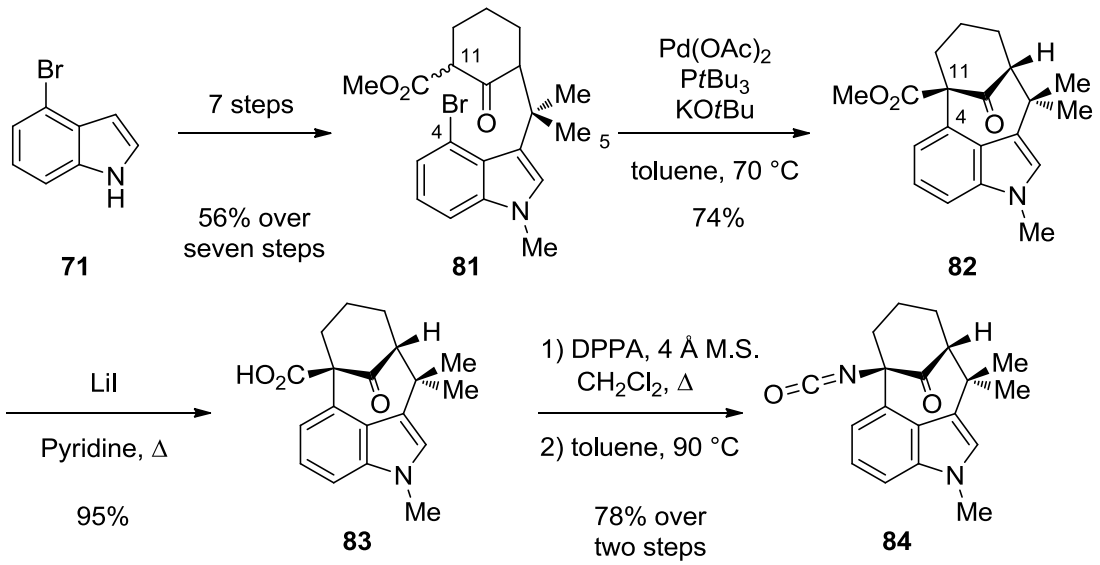


Scheme 1.17

In 2005, Rawal and co-workers reported a ten-step sequence to the skeleton of the welwitindolinone alkaloids based on the late-stage construction of the seven-membered ring by formation of the C_4-C_{11} bond.[19] Their strategy involves an intramolecular Pd-catalysed enolate arylation to build the bicyclo[4.3.1]decane core of the molecule, followed by a Curtius rearrangement to functionalise the bridgehead position.

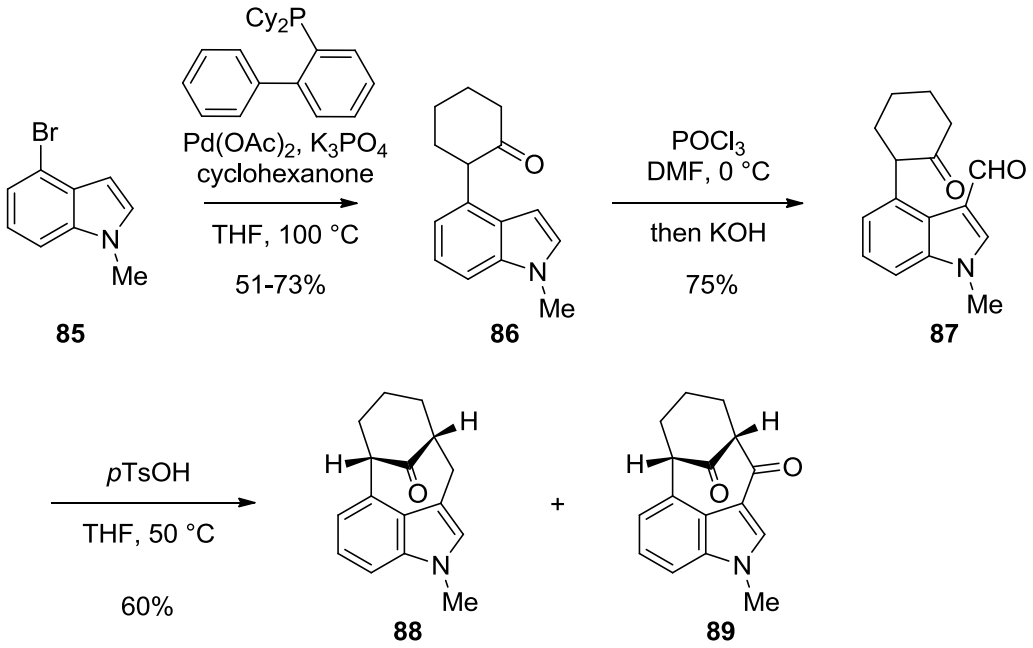
Seven steps were required to prepare advanced intermediate **81** from 4-bromoindole **71** in 56% yield. A vast range of experimental conditions, such as the source of palladium and the influence of the ligands, base and solvent, were tested to define the optimum conditions of the formation of the C_4-C_{11} bond. β-Ketoester **81** was treated accordingly using palladium(II) acetate, tri-*tert*-butylphosphine and potassium *tert*-butoxide in toluene at 70 °C to afford desired skeleton **82** in good yield.

Although the ester motif favoured the arylation, its main purpose was to introduce the isothiocyanate bridgehead functionality. Surprisingly, Rawal's group reported their incapacity to perform a basic hydrolysis (60 eq. of LiOH in a mixture H_2O/MeOH at reflux) on ester **82**, reinforcing the hypothesis of a highly encumbered stereocentre in the position C_{11}. Nonetheless, ester cleavage of **82** was achieved using excess lithium iodide in refluxing pyridine to afford carboxylic acid **83** in excellent yield. The required nitrogen at the bridgehead position was introduced by a Curtius rearrangement. Thus, treatment of acid **83** with diphenylphosphoryl azide in the presence of triethylamine furnished isocyanate **84**. Further manipulations towards the isothiocyanate analogue were unsuccessful (Scheme 1.18).



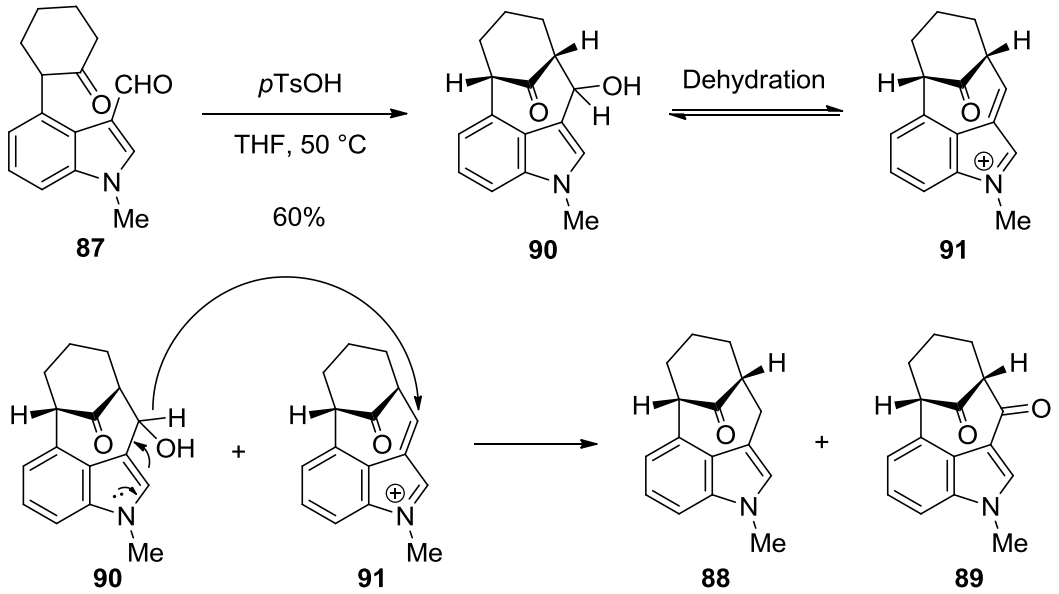
Scheme 1.18

In the same year, our group established a concise access to the tetracyclic skeleton *via* an acid-mediated ring closure of a suitable indole fragment.[20] This expedient three-step synthesis of the bridged structure consists of a Buchwald-type coupling on position C_4 of *N*-methylated indole **85** followed by formylation of position C_3 *via* a Vilsmeier-Haack reaction. Exposure of aldehyde **87** to *p*-toluenesulfonic acid in THF at 50 °C led to a 1:1 mixture of two bridged ketones **88** and **89** (Scheme 1.19).



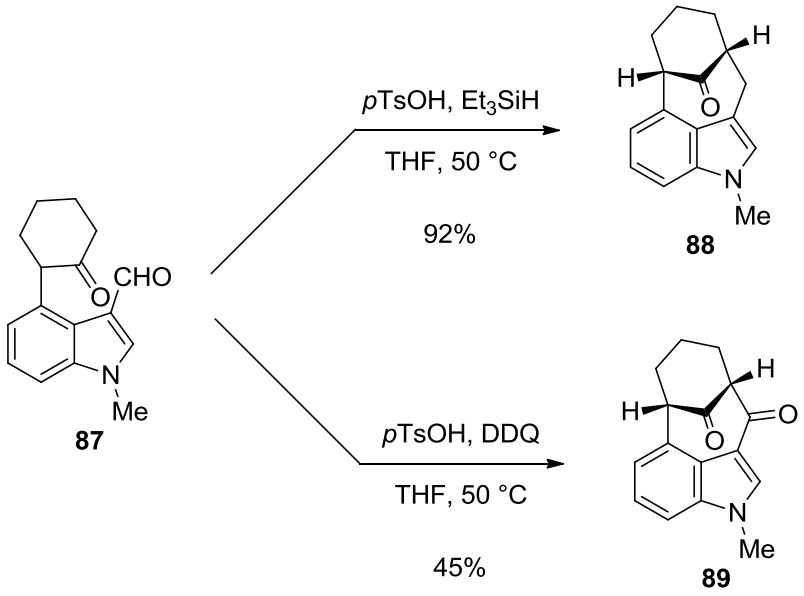
Scheme 1.19

The mixture of ketones **88** and **89** was rationalised with a two-step sequence involving an initial aldol condensation to afford secondary alcohol **90** which could then form iminium **91** by dehydration. An intermolecular hydride transfer could then occur from alcohol **90** to iminium **91** to generate the two ketones **88** and **89** (Scheme 1.20).



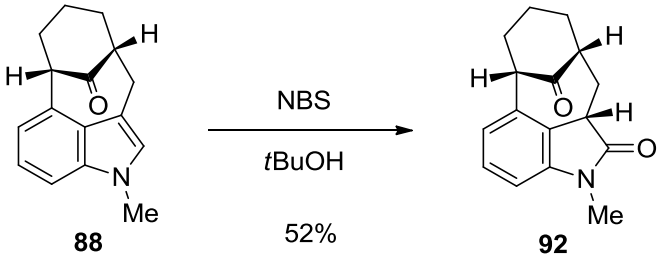
Scheme 1.20

Although it was possible to separate ketones **88** and **89** *via* column chromatography, diverse experimental conditions were screened to access each product separately. Using Et_3SiH a source of hydride in the presence of **87**, it was possible to obtain ketone **88**. Treatment of aldehyde **87** with *p*TSA in the presence of triethylsilane exclusively resulted in ketone **88** in excellent yield. On the other hand, utilisation of a hydride acceptor such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) allowed the formation of only ketone **89** (Scheme 1.21).



Scheme 1.21

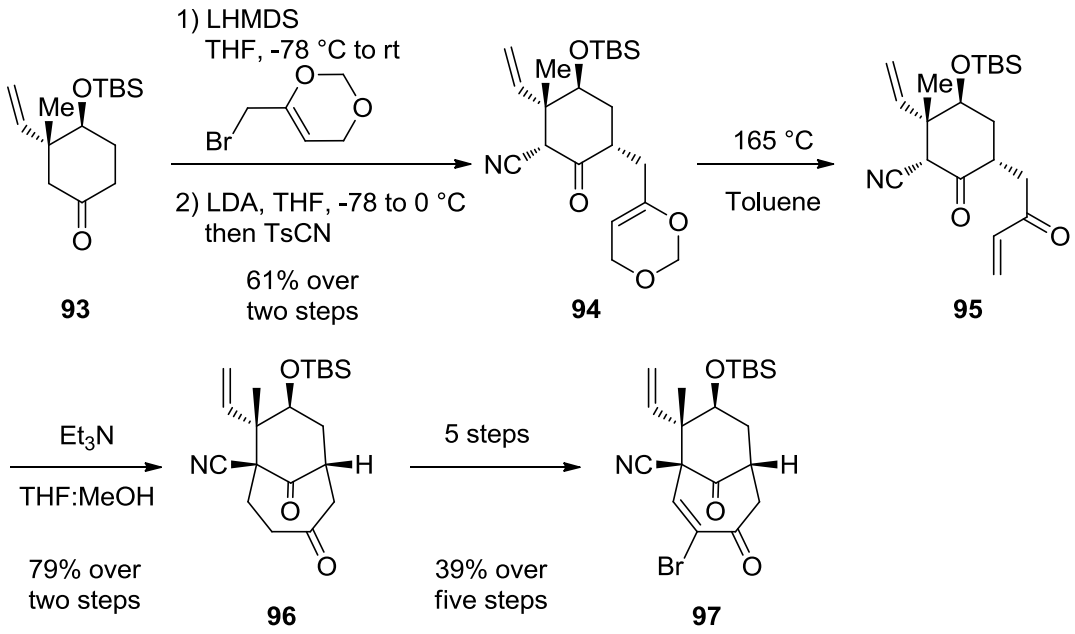
Further manipulations showed that it was possible to convert indole **88** to oxindole **92** using *N*-bromosuccinimide (NBS) in *tert*-butanol. Unfortunately, NMR spectroscopic studies and X-ray analysis confirmed that the stereochemistry of the new stereogenic centre formed in position C_3 corresponds to that of *epi*-welwistatin (Scheme 1.22).



Scheme 1.22

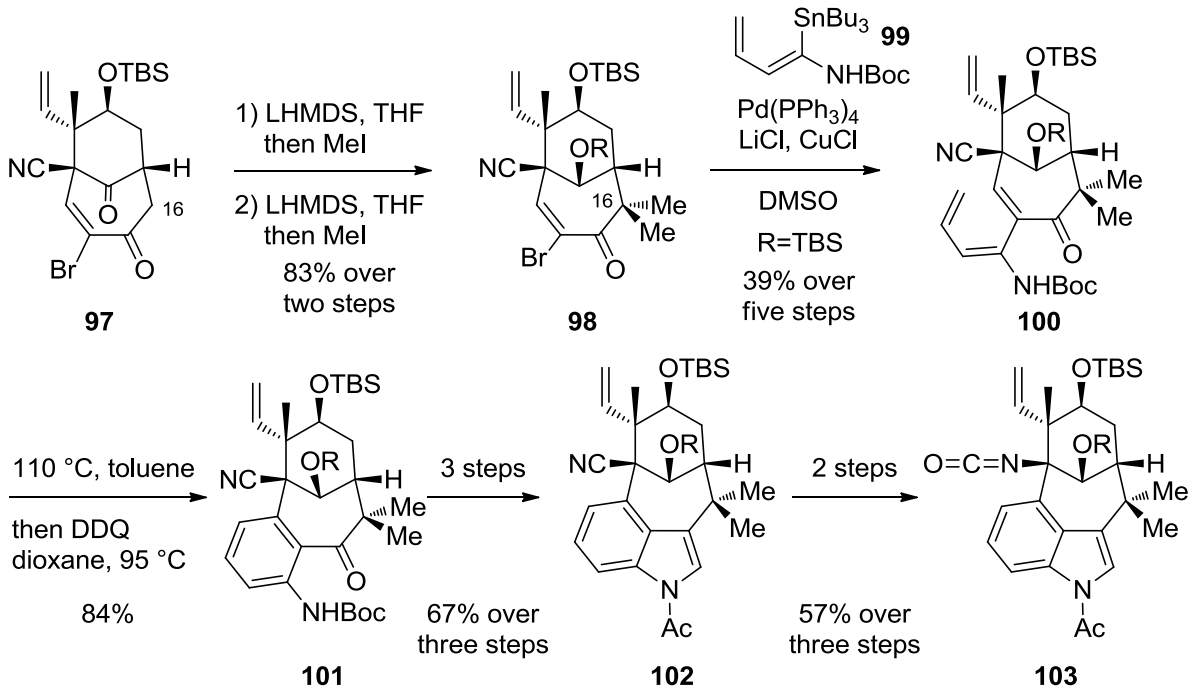
One year later, in 2006, two groups published advanced syntheses of welwitindolinone **7**.

Based on a conceptually different strategy, Funk and Greshock reported the preparation of an advanced intermediate **103** based on the elaboration of a bicyclo[4.3.1]decanone followed by the annulation of the indole/oxindole around the seven-membered ring system.[21] Starting ketone **93** was easily prepared from commercially available 3-methyl-3-cyclohexenone. After alkylation and cyanation using enolate chemistry on ketone **93**, a retrocycloaddition performed under high temperatures gave enone **95**. A key 7-*endo* intramolecular conjugate addition was realised in the presence of triethylamine to give bicyclo[4.3.1]decanone **96**. Further manipulations were carried out on bicyclic compound **96** to obtain α-bromoenone **97** in five steps and 39% yield (Scheme 1.23).



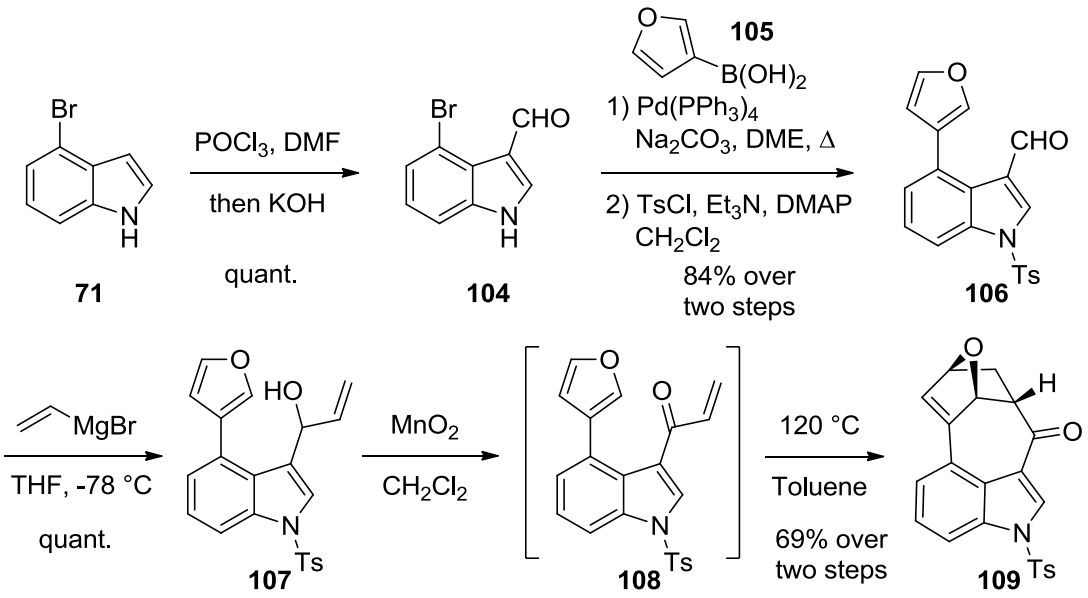
Scheme 1.23

After two successive enolate methylations to generate the *gem*-dimethyl at position C_{16}, a Stille coupling with stannane **99** provided amidotriene **100** in 75% yield. After the 6π electrocyclisation on amidotriene **100**, tetracyclic **102** was formed by closure of the indole. Finally, Funk described the possibility of introducing an isocyanate functionality at the bridgehead position *via* a Hofmann rearrangement (Scheme 1.24).



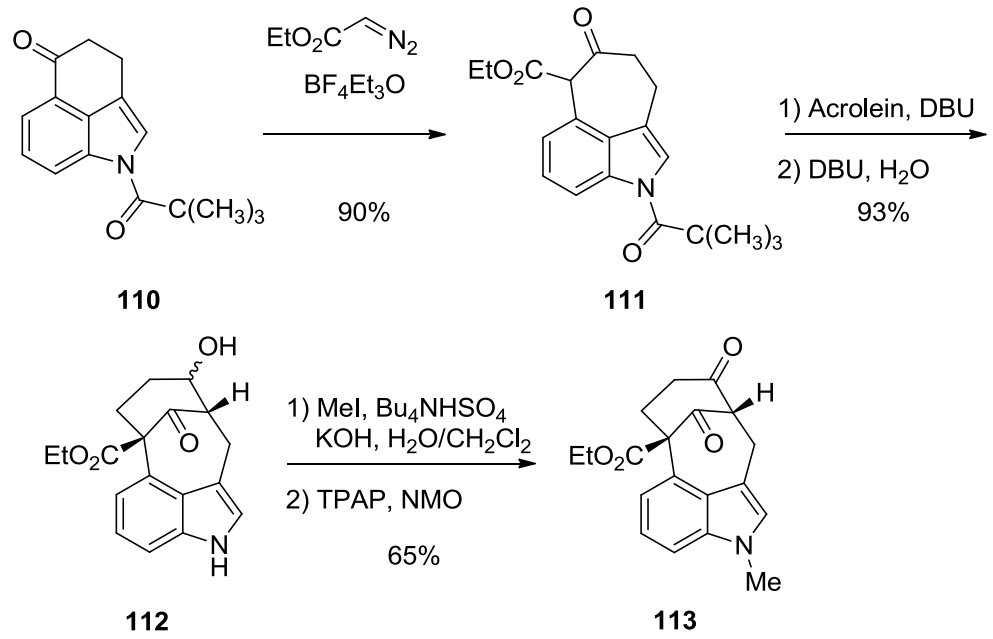
Scheme 1.24

Shortly afterwards, Shea and Lauchli published a synthesis of the core structure of the welwitindolinone alkaloids.[22] Their approach consists of the annulation of bicyclo[4.3.1]decane using a type 2 intramolecular Diels-Alder reaction, where the diene and dienophile are linked by an indole tether. After formylation of 4-bromoindole **71**, a Suzuki coupling was performed in position C_4 of aldehyde **104** using 3-furan boronic acid **106** in the presence of tetrakis(triphenylphosphine)palladium. After *N*-tosylation of the indole, addition of vinyl Grignard converted aldehyde **106** into allylic alcohol **107**. Oxidation of alcohol **107** using manganese dioxide led to the cyclisation precursor **108**, which, upon heating, yielded cycloadduct **109** (Scheme 1.25).



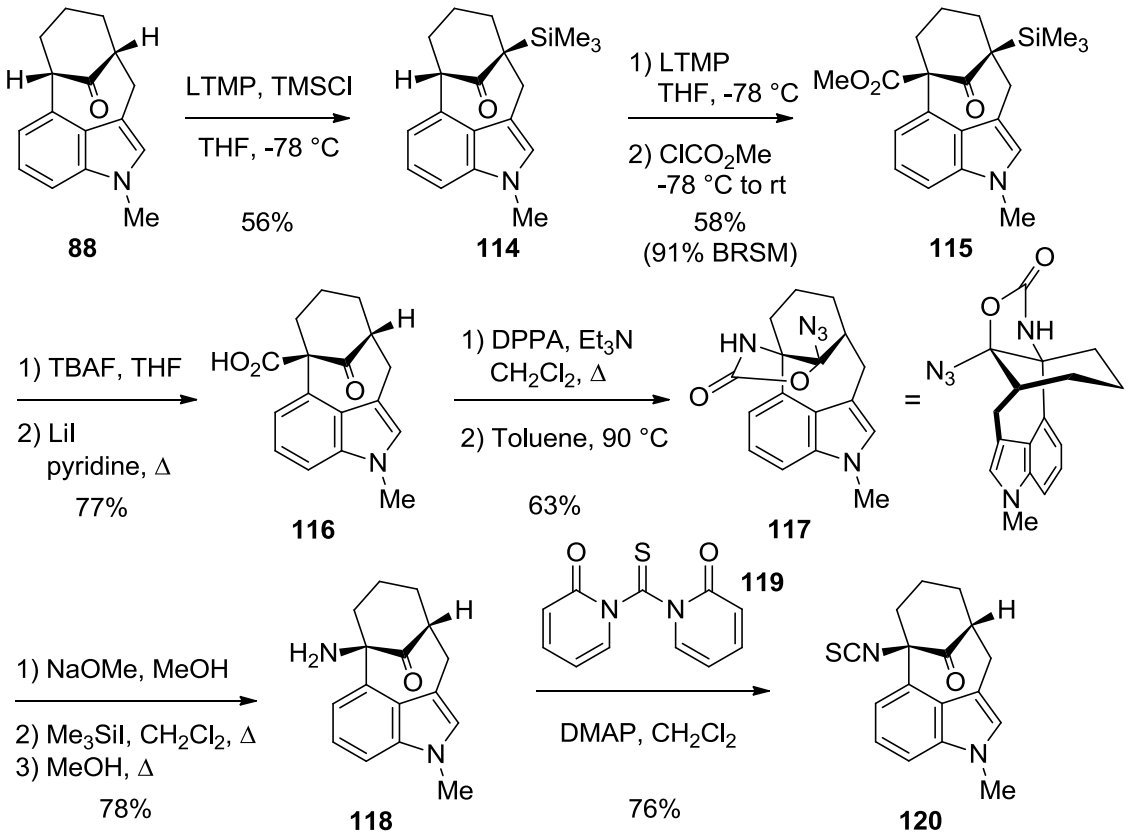
Scheme 1.25

In 2007, Menéndez reviewed the different approaches to the tetracyclic core structure of welwistatin **7**.[23] After methodically organising his report between the failed attempts to the tetracyclic framework and the more successful strategies, Menéndez reported some previously unpublished work from his own group. He presented a four-step sequence starting with the ring expansion of ketone **110** (known as Kornfeld's ketone).[24] The key step consists of a high-yielding anionic domino process, involving a Michael addition followed by an intramolecular aldol reaction, which was accompanied by the hydrolysis of the pivaloyl protection by the use of DBU. A simple methylation of the nitrogen and oxidation of the alcohol gave compact tetracyclic structure **113** (Scheme 1.26).



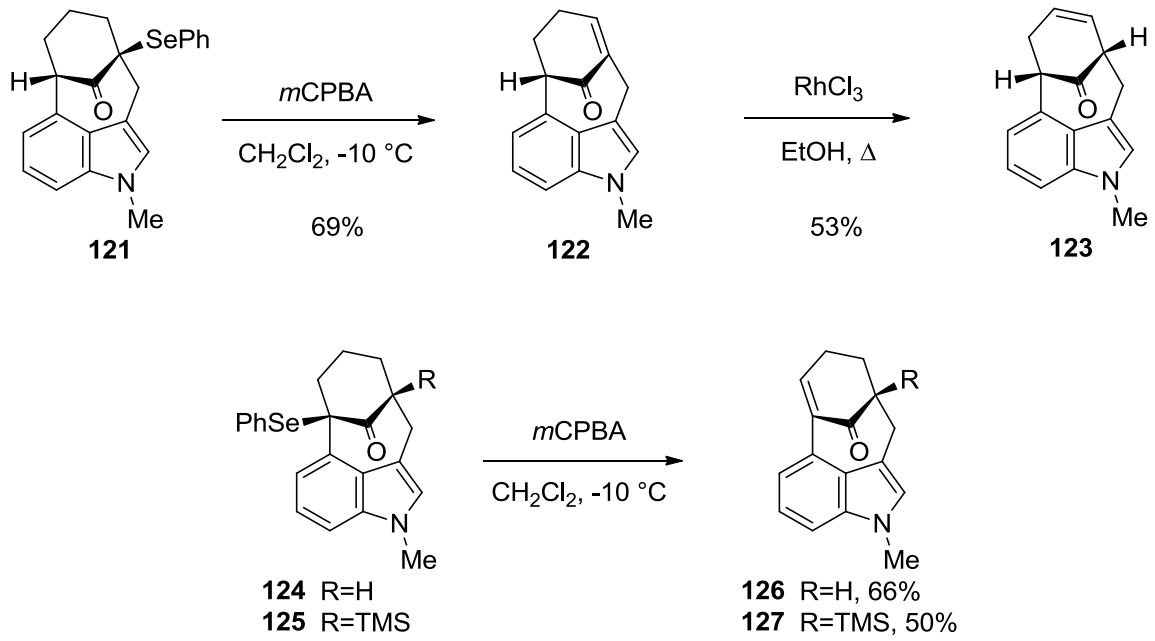
Scheme 1.26

In early 2009, our group published their second paper towards this challenging molecule based on the functionalisation of the bridgehead positions.[25] Simpkins reported the first synthesis towards welwistatin **7** that exhibits the unusual isothiocyanate functionality at the bridgehead position. Starting from tetracyclic ketone **88**, two successive regiocontrolled bridgehead substitutions were carried out in the presence of LTMP to afford ketoester **115**. Removal of the blocking silyl group was achieved by addition of TBAF before hydrolysis of the ester. Surprisingly, treating carboxylic acid **116** with DPPA did not produce the expected isocyanate analogue but the azido oxazolidinone **117** (as determined by X-ray crystallography and NMR spectroscopy studies). Exposure of this oxazolidinone **117** to sodium methoxide led to the corresponding carbamate which was smoothly removed using iodotrimethylsilane under basic conditions. Bridgehead amine **118** was efficiently converted to isothiocyanate analogue **120** using thiocarbonyl reagent **119** (Scheme 1.27).



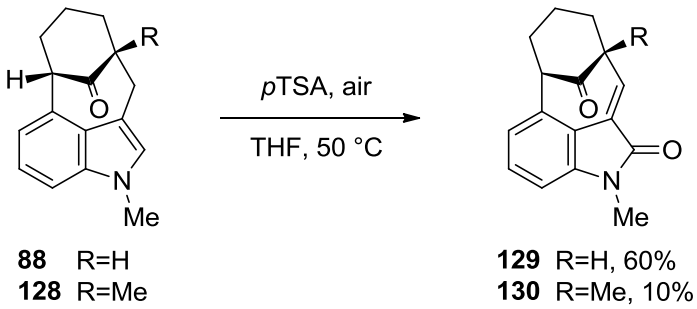
Scheme 1.27

Simpkins also established a strategy to access noteworthy bridgehead alkenes. Selenides **121**, **124** and **125**, obtained using the bridgehead enolate chemistry previously described, were treated with oxidising agent *m*CPBA to give bridgehead enones **122**, **126** and **127**.[19] Further manipulations on alkene **122** showed the feasibility of an isomerisation of the double bond using rhodium(III) chloride in refluxing ethanol. Ketone **123** was presented as a potential precursor for the installation of the vinyl chloride functionality in position C_{13} (Scheme 1.28).



Scheme 1.28

In a separate communication, Simpkins also reported the formation of α,β-unsaturated oxindoles from the corresponding indoles *via* a singlet oxygen transfer.[6] Delighted by the obtention of oxindole **129** *via* an autoxidation process under air conditions, our group decided to investigate the feasibility of the reaction with a large range of bridgehead substituted core structures. However, bridgehead substituents seem to have a dramatic effect on the oxidation process (such as a methyl group in the oxidation of **128**), reducing the yield considerably (Scheme 1.29).

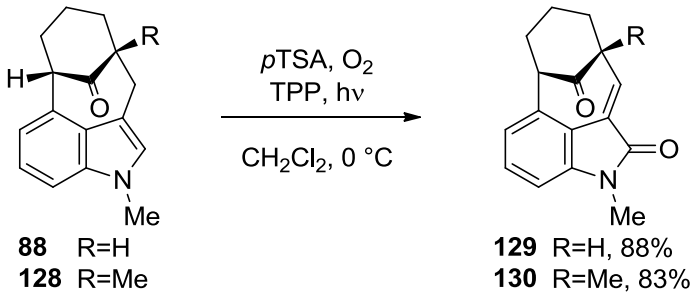


88 R=H
128 R=Me

129 R=H, 60%
130 R=Me, 10%

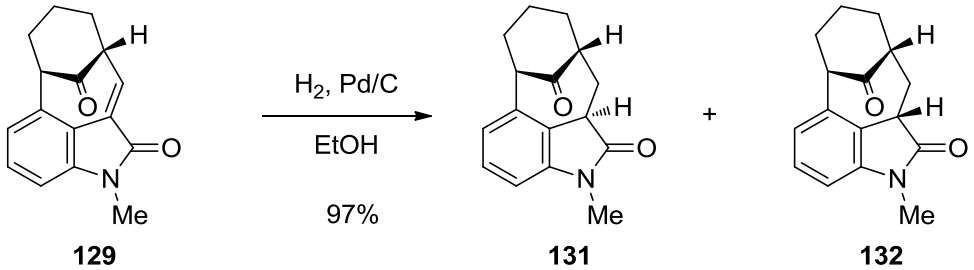
Scheme 1.29

Further investigations led our group to study photo-oxygenation conditions. Tetraphenylporphyrin was used as a sensitiser and the transformation of methylated ketone **128** proceeded smoothly to give oxindole **130** in 83% yield. A high-yielding conversion was observed for the majority of substrates; however the presence of other oxidisable sites on the starting indole compromised the formation of the α,β-unsaturated oxindoles. Finally, hydrogenation of oxindole **129** gave a mixture of oxindoles **131** and **132** (ratios between 1:1 and 1:2) (Scheme 1.30).



88 R=H
128 R=Me

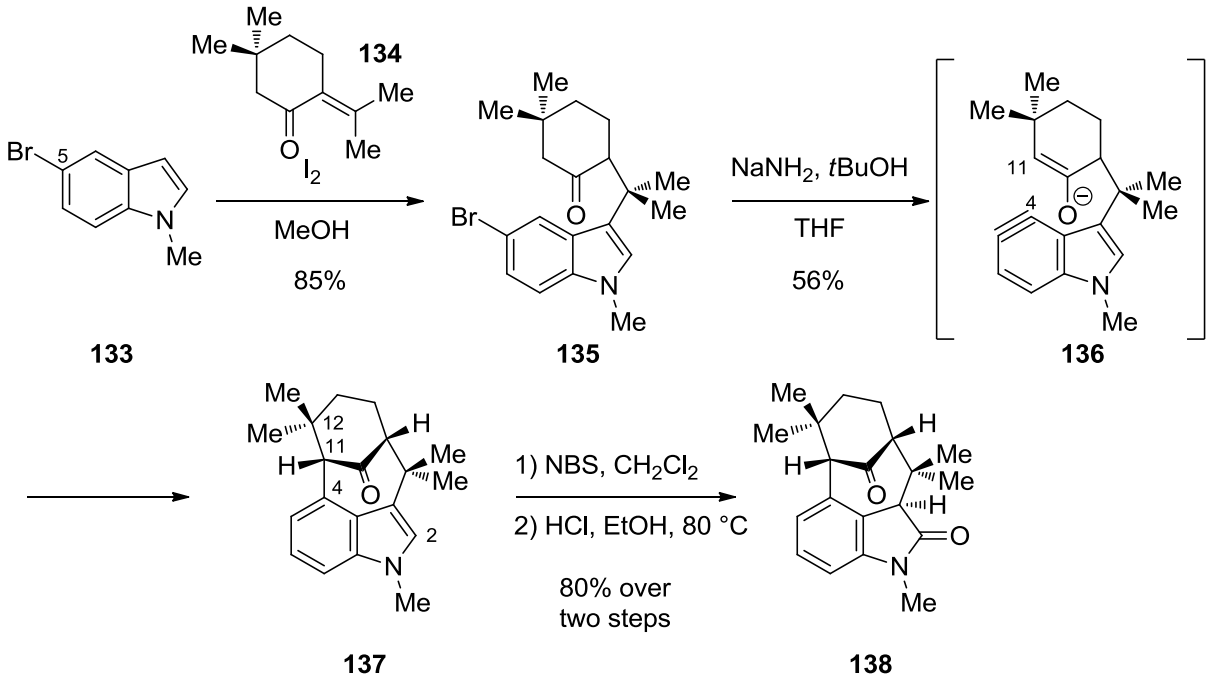
129 R=H, 88%
130 R=Me, 83%



129 **131** **132**

Scheme 1.30

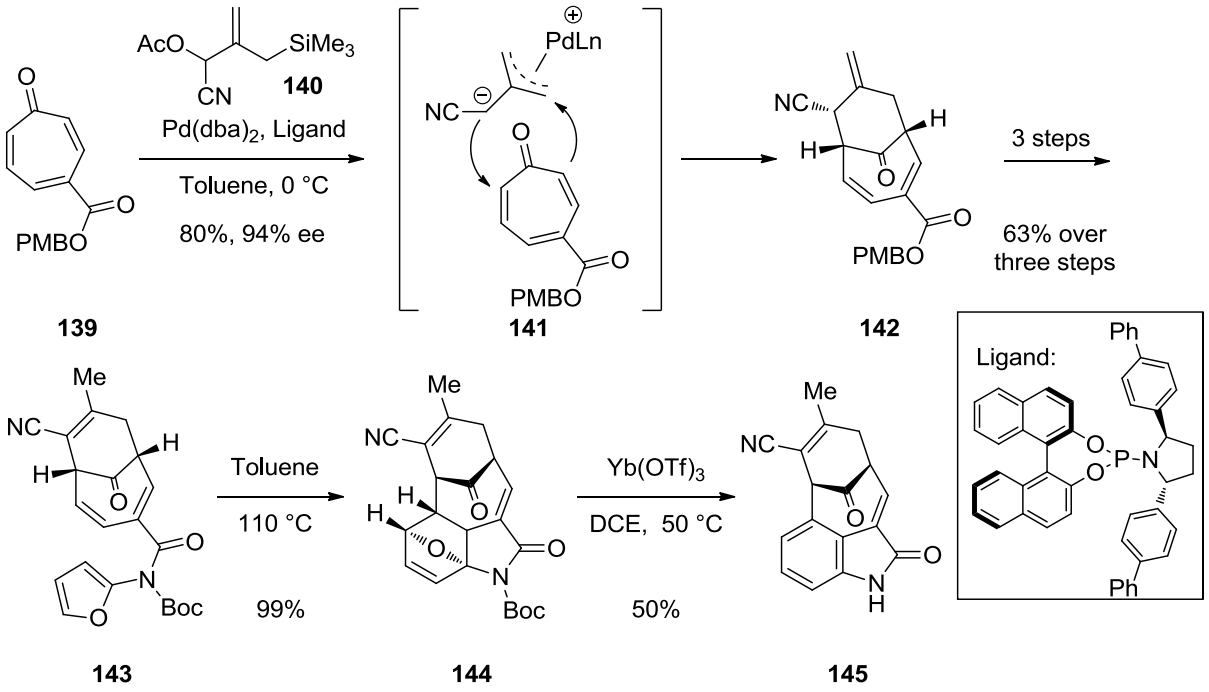
In 2009, Garg and colleagues published a four-step sequence of the welwitindolinone skeleton, involving an indolyne cyclisation.[26] Coupling of commercially available 5-bromoindole **133** with enone **134** occurred in high yield in the presence of a catalytic amount of iodine.[27] Treatment of **135** with $NaNH_2$/*t*BuOH formed the corresponding aryne **136**, which, upon reaction with the enolate, afforded bicyclo[4.3.1]decane **137**. Interestingly, Garg reported tetracycle **137** as being the first molecule obtained by formation of the C_4-C_{11} bond adjacent to a quaternary centre at the C_{12} position. Finally, bromination of the C_2 position of indole **137** followed by HCl hydrolysis gave the desired oxindole **138** as a single diastereoisomer in good yield (Scheme 1.31).



Scheme 1.31

Also in 2009, Trost and McDougall disclosed the synthesis of α,β-unsaturated oxindole **145** in ten steps from commercially available anisole.[28] Their strategy to build the tetracyclic core is based on sequential cycloadditions. Enantioselective formation of bicyclo[4.3.1]decadiene

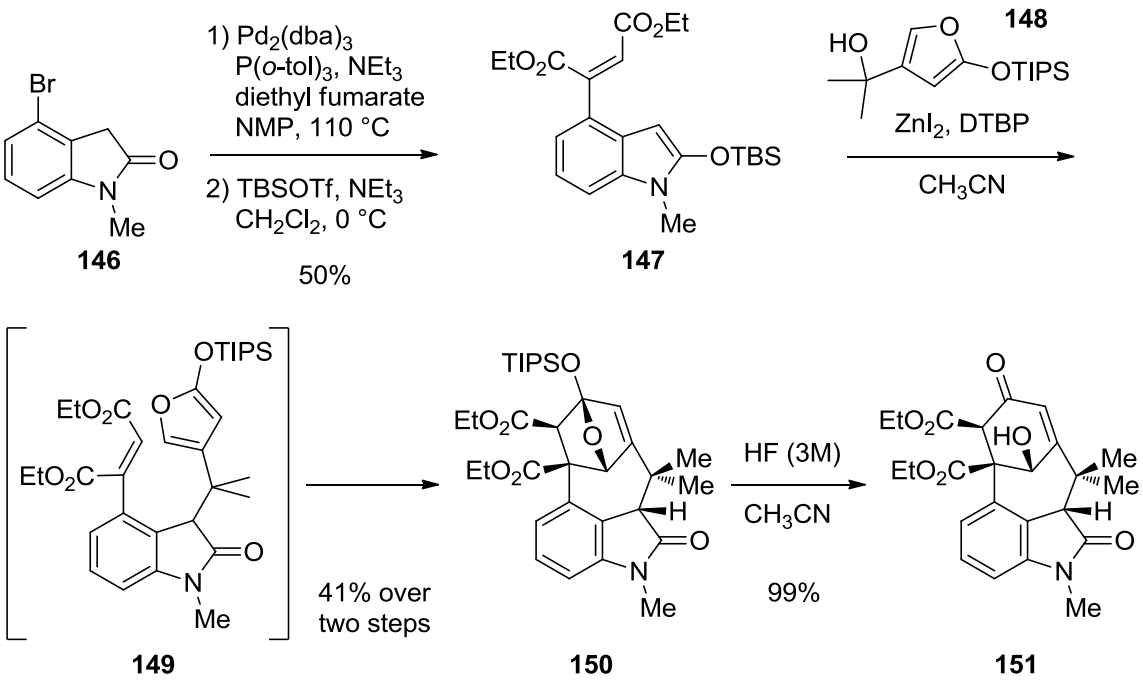
142 was achieved by a powerful Pd-catalysed [6+3] cycloaddition of cyano-trimethylenemethane **140** onto tropone **139**. Obtained as a single regio- and diastereoisomer, **142** was transformed into imidofuran **143** in 63% yield over three steps. An intramolecular Diels-Alder reaction was performed in refluxing toluene to afford oxabicycle **144** as a single diastereoisomer. Due to the electron-withdrawing effect of the Boc protecting group, ring-opening of oxabicycle **144** followed by dehydration did not occur. However, exposure of **144** to a catalytic amount of ytterbium(III) triflate gave unprotected oxindole **145** in 50% yield (Scheme 1.32).



Scheme 1.32

Three years after the preparation of the tetracyclic structure *via* an intramolecular Diels-Alder process, Shea and colleagues revealed their strategy towards advanced intermediate **151**.[29] Prepared from 4-bromoindole **71**, oxindole **146** was coupled with diethyl fumarate *via* a Heck reaction. The resulting mixture of isomers was treated with TBSOTf and silylketene aminal

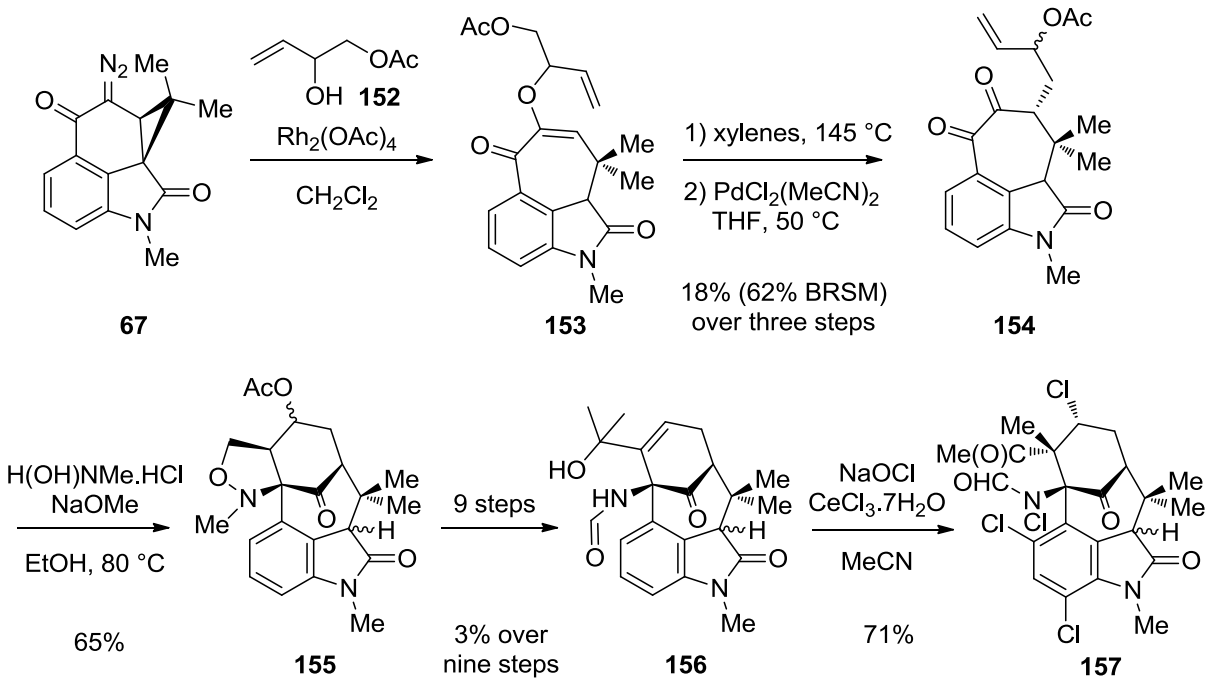
147 was obtained. An alkylation of aminal **147** was carried out with furan **148** in the presence of Lewis acid (ZnI_2) to afford the required Diels-Alder precursor **149**. Spontaneous cyclisation of **149** resulted in pentacyclic **150**, which, upon desilylation, yielded advanced oxindole **151** (Scheme 1.33).



Scheme 1.33

In 2010, Wood and co-workers described their investigations towards this challenging target.[30] Their synthesis features the insertion of an allylic alcohol fragment into an α-diazoketone in the presence of a rhodium catalyst, followed by a Claisen rearrangement and a transannular nitrone cycloaddition. Cyclopropane **67**, synthesised from isatin as reported in 1999, was coupled to allylic alcohol **152** with opening of the cyclopropane moiety in the presence of the rhodium catalyst. Claisen rearrangement and Pd-catalysed allylic migration were required to convert enol ether **153** into diketone **154**. The last ring of the welwitindolinone core was obtained by treatment of terminal alkene **154** with

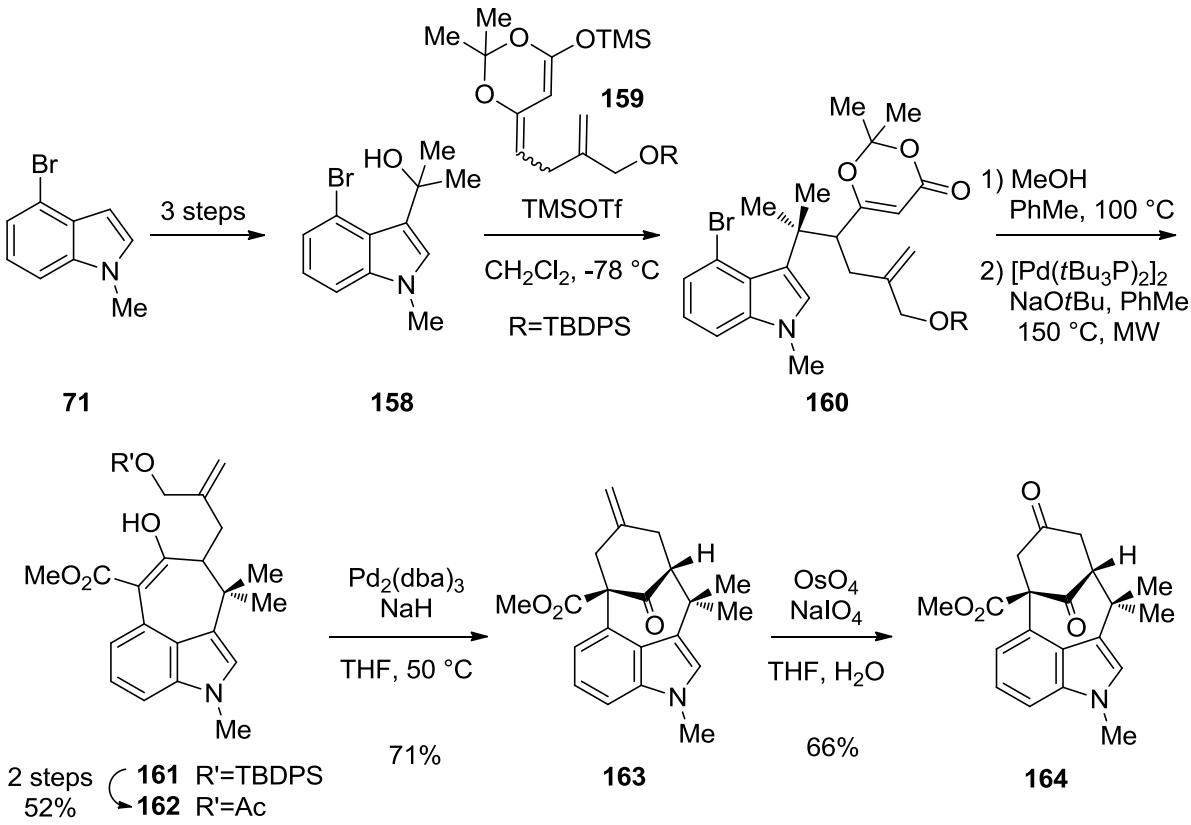
N-methylhydroxylamine in refluxing ethanol. Further manipulations were carried out on intermediate **155** before the chloronium ion-induced semi-pinacol rearrangement afforded over-chlorinated tetracycle **157** (Scheme 1.34).



Scheme 1.34

Also in 2010, Martin and colleagues reported a synthesis of the scaffold of the welwitindolinone family.[31] Their strategy focused on three key steps, involving (i) the coupling of a substituted indole, (ii) a silyl ketene acetal, a palladium-catalysed enolate arylation and (iii) an allylic arylation to generate the tetracyclic structure. Vinylogous silyl enol ether **159** was coupled to tertiary alcohol **158**, obtained in three steps from 4-bromoindole **71**. Acetal removal occurred at high temperature in the presence of methanol to afford the corresponding masked ketoester. The synthesis of tricyclic **161** was achieved by palladium-catalysed intramolecular cyclisation of ketoester in the presence of sodium *tert*-butoxide. Allylic alcohol **162**, accessed *via* a deprotection-protection sequence from **161**,

underwent a second Pd-catalysed cyclisation to form the core structure of welwistatin **7**. An oxidative cleavage performed in the presence of osmium tetroxide and sodium periodate converted the terminal alkene **163** into diketone **164** (Scheme 1.35).

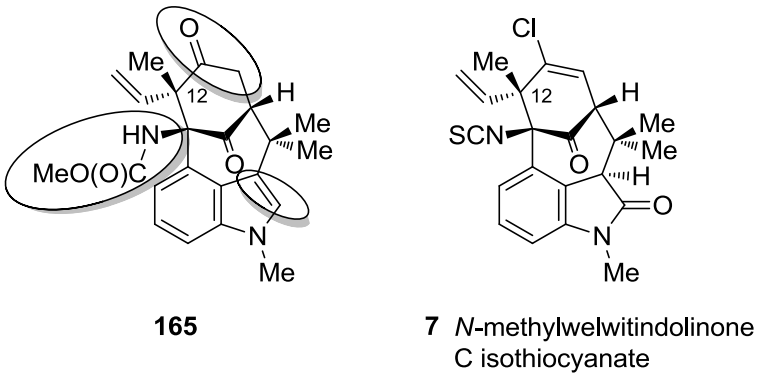


Scheme 1.35

The structural complexity of the welwitindolinone family has made their synthesis exciting as well as ambitious. Up to 2010, sixteen years after their isolation, welwitindolinone A isonitrile **1** was the only welwitindolinone that had been synthesised. Despite an increasing interest and a strong contribution from the synthetic community, by 2010, welwistatin **7** had not been successfully prepared.

1.5 AIMS AND OBJECTIVES

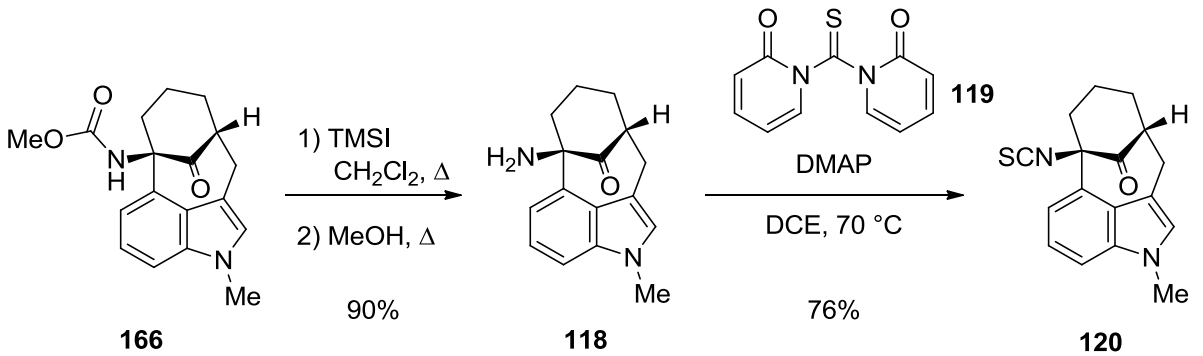
At the start of this project, we speculated that highly functionalised intermediate **165** could be a key target in the synthesis of *N*-methylwelwitindolinone C isothiocyanate **7** (Figure 1.8).



165 **7** *N*-methylwelwitindolinone C isothiocyanate

Figure 1.8

We believed that (i) the vinyl chloride moiety could arise from modification of the ketone adjacent to quaternary centre C_{12}, (ii) amine derivative **165** would be converted into the desired isothiocyanate bridgehead using conditions previously described by our group on similar framework **166** (Scheme 1.36) and (iii) the oxindole would be obtained *via* an oxidation process on the corresponding indole motif following an established procedure from the Simpkins laboratory.[25, 26, 32,]

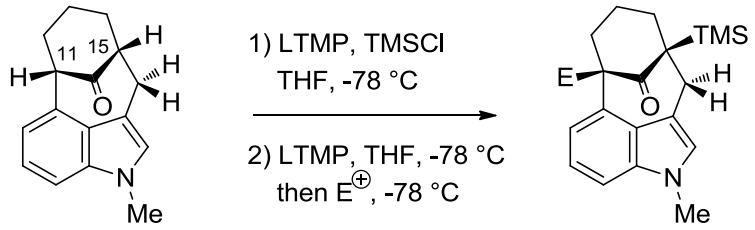


166 **118** **120**

Scheme 1.36

For the purpose of synthesising welwitindolinone **7**, we turned our attention towards key intermediate **165**. Advanced scaffold **165** presents many challenging features of welwistatin **7**; along with this tetracyclic compact structure it also possesses the required *gem*-dimethyl in position C_{16}, a nitrogen group in the bridgehead position C_{11} and the desired stereochemistry for the quaternary centre C_{12} (see Figure 1.8).

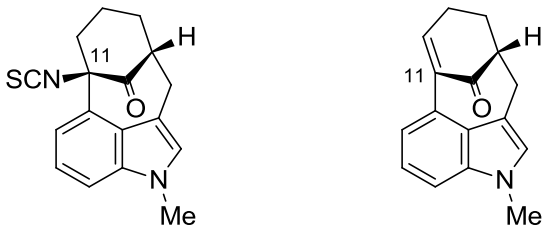
Our aim was to develop some synthetic strategies to functionalise the cyclohexanone motif of the tetracyclic core structure. A few years earlier, the Simpkins group had synthesised compact tetracycle **88** in four steps from commercially available materials. After extensive studies, our group developed an interesting strategy to functionalise the C_{11} position of tetracycle **88**. Successive metallations and substitutions were involved to block the most reactive bridgehead position C_{15} using a trimethylsilyl group (Scheme 1.37).



88 **167**

Scheme 1.37

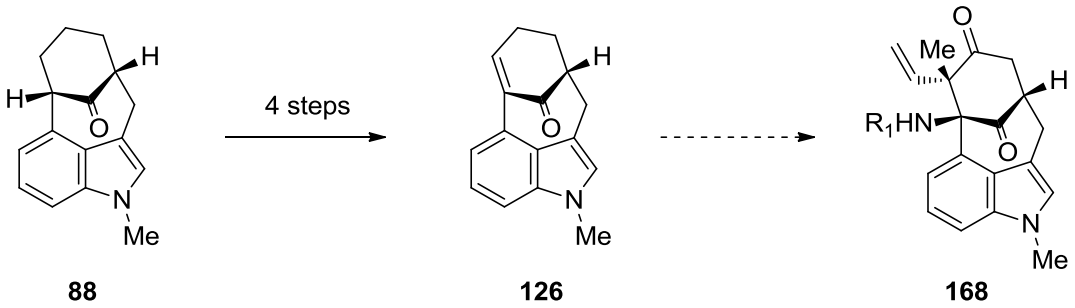
A large range of electrophiles were successfully substituted at the C_{11} position (Scheme 1.37). An appropriate choice of electrophiles gave access to the synthesis of the first isothiocyanate bridgehead analogue **120** as well as a fascinating bridgehead alkene **126** (Figure 1.9).



120 **126**

Figure 1.9

Inspired by this concise and efficient synthetic route, we decided to undertake the synthesis of alkene **126** *via* tetracycle **88**. Alkene **126** was considered as a key intermediate for accessing advanced intermediate **168** (Scheme 1.38).

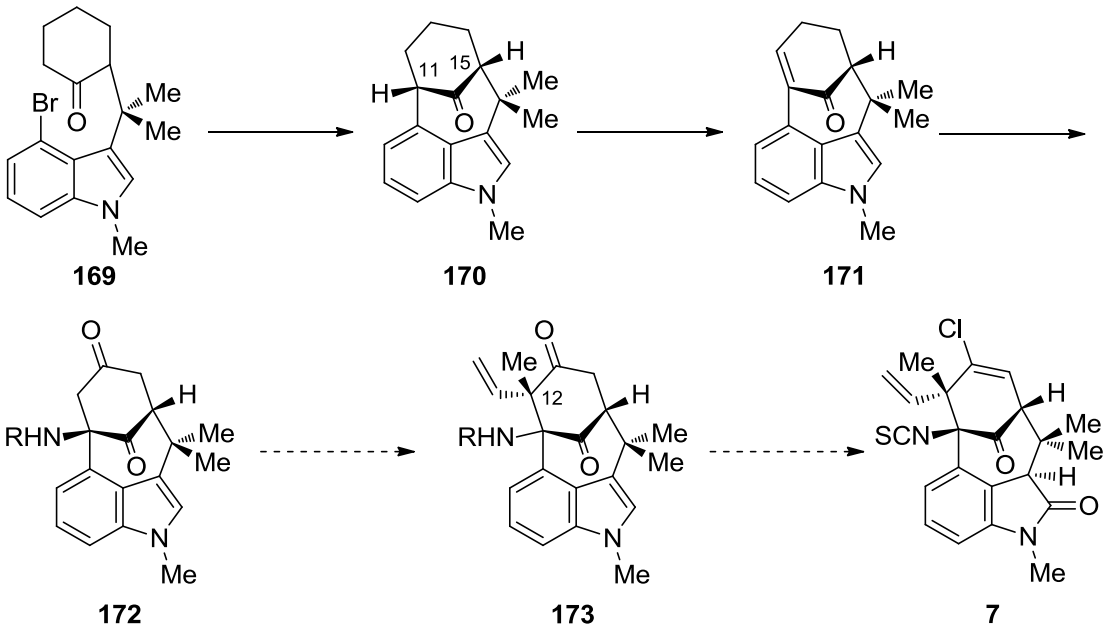


88 **126** **168**

Scheme 1.38

While we were studying the access to more complex tetracyclic structures such as **165**, preliminary studies were carried out within our group on tetracycle **170** possessing the required *gem*-dimethyl in position C_{16}.[33] Facing some difficulties to introduce the *gem*-dimethyl motif on tetracycle **88**, our group decided to include this functionality in the early stage of the synthesis. After deciding to adopt Rawal's strategy to synthesise intermediate **169**, the seven-membered ring system was built *via* a palladium-catalysed arylation.[33]

Direct functionalisation of the C_{11} bridgehead position was achieved on tetracycle **170** with the *gem*-dimethyl and corresponding alkene **171** was successfully synthesised using the oxidative method previously developed. Successive oxidations were performed on alkene **171** to afford diketone **172**. Preliminary studies involving regioselective enolisation of diketone **172** were investigated to build the desired motif on carbon C_{12} (Scheme 1.39).[33]



Scheme 1.39

The difficulties introducing the *gem*-dimethyl portion, combined with the necessity of a blocking group at the C_{15} position for the functionalisation of the C_{11} position, led us to turn our attention to pursue the synthesis on advanced tetracycle **170**. We decided to synthesise tetracycle **170** to develop the route towards welwistatin **7**. After carefully investigating the route to diketone **172** to ensure its reproducibility, we will study the functionalisation of carbon C_{12} (Scheme 1.39).

1.6 REFERENCES

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CHAPTER TWO

FUNCTIONALISATION OF THE TETRACYCLIC INDOLE MODEL SYSTEM USING BRIDGEHEAD ENOLATE CHEMISTRY

2.1 AIMS AND OBJECTIVES

In their isolation paper, Moore and co-workers described the isothiocyanate functionality present in welwistatin **7** as being responsible for the multiple-drug resistance-reversing activity.[1,2] Our group decided to explore how this unusual feature at the C_{11} position influences the biological properties of the molecule. As part of this study, our group synthesised the first isothiocyanate analogues of welwistatin **120** and **174**, built on previous work related to the expedient access to the welwitindolinone scaffold **88** (Figure 2.1).[3,4]

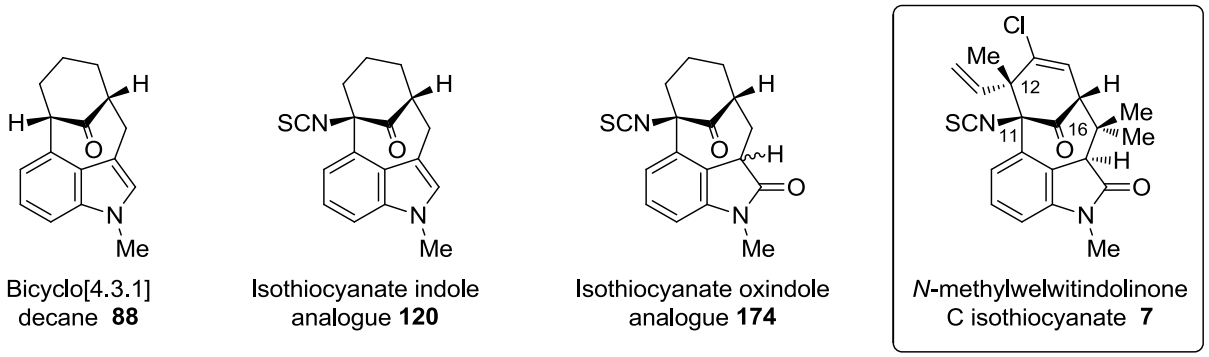


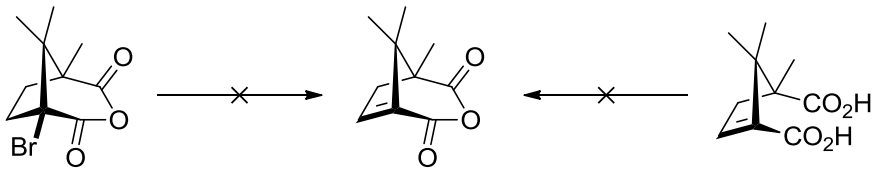
Figure 2.1

Targeting the total synthesis of welwistatin **7**, we judged that it was important to investigate the other functionalities present on its scaffold. The characteristic architecture still remained challenging, particularly due to the presence of a vinyl chloride functionality as well as the two quaternary centres (*gem*-dimethyl at the C_{16} position and the highly substituted C_{12}, adjacent to the vinyl chloride). As a result, we decided to undertake the established route to the bicyclo[4.3.1]decane **88** in order to investigate the functionalisation of the cyclohexanone framework of this model system. Further chemistry would therefore entail reactions being carried out at the bridgehead positions of tetracycle **88** and these are the subject of discussion in this chapter.

2.2 BRIDGEHEAD ALKENES, BRIDGEHEAD ENOLATES, AN ATTRACTIVE METHOD TO FUNCTIONALISE THE WELWISTATIN SCAFFOLD

2.2.1 Bridgehead enolates and bridgehead alkenes, two unusual strained motifs

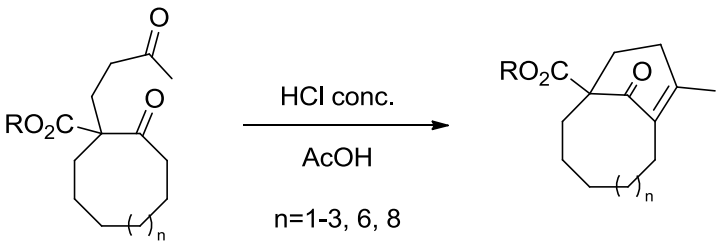
In 1924, despite a number of attempts to form bicyclic bridgehead alkene **176**, including elimination of HBr from **175** or dehydration of the corresponding diacid **177**, Bredt reported difficulties in generating such strained structures (Scheme 2.1).[5] Bredt postulated that the existence of bridgehead alkenes is unlikely, particularly due to the orthogonal orientation of the distorted p orbitals creating an inefficient overlap for the formation of a π-bond. This postulate is nowadays known as Bredt's rule.



175 **176** **177**

Scheme 2.1

However, a number of chemists have tried to investigate the possibility of generating bridgehead alkenes. In 1949, Prelog provided evidence for the limits of Bredt's rule.[6] The preparation of a large range of bridged enones such as **179** achieved by Robinson annulations of the corresponding α-ketoesters **178** under acidic conditions was described (Scheme 2.2). The size of the combined rings was considered to be an important factor as bridgehead enolates were more stable in a larger ring system.



178 R=Me
n=1

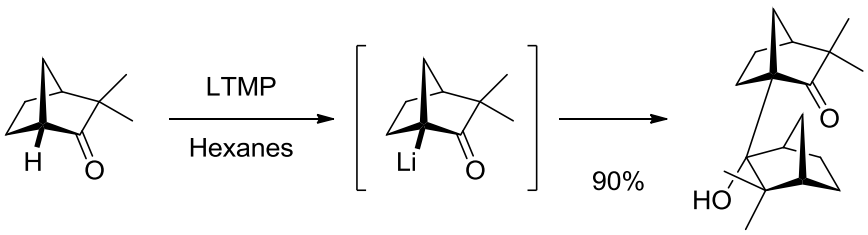
179 R=Me 73%
n=1

Scheme 2.2

In 1950, Fawcett developed the concept of anti-Bredt alkenes and reviewed a large number of these bridgehead entities possessing a double bond at the bridgehead position.[7] Fawcett introduced the sum *(S)* of the atoms on a bicyclic motif. He connected the postulate of Bredt to this number *(S)*, demonstrating that bicyclic systems that possess *(S)* > 8 could display a double bond at the bridgehead position. So for the above example (Scheme 2.2), the sum was *(S)* = 5 + 3 + 1 = 9.

In the same fashion, bridgehead metallation of small carbonyl systems (fewer than eight atoms) was expected to be very difficult as it would require an enolate intermediate that would violate Bredt's rule.

Interestingly, deprotonation of bridgehead ketones can successfully afford the corresponding α-keto carbanions. However, their high reactivity compromises their use for reactions with external trapping reagents and aldol dimers are mainly obtained as illustrated in Scheme 2.3.[8]



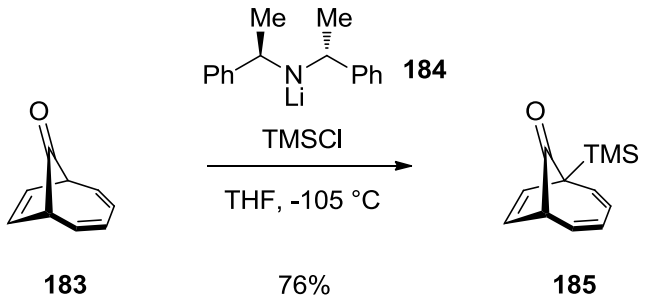
180 **181** **182**

Scheme 2.3

Alternative methods have been developed to circumvent the formation of aldol dimers. In 1984, Corey reported a new strategy, known as *in situ* quenching (ISQ), which enabled the isolation of silylated bridgehead structures.[9] An excess of the silyl trapping agent, present in the reaction mixture prior to the deprotonation, was able to intercept the bridgehead enolate before dimerisation could occur. Two techniques commonly used are: (i) a solution of substrate and TMSCl is added to the solution of base pre-cooled to -78 °C or (ii) a solution of substrate is added dropwise to a mixture of the base and TMSCl at -78 °C.

2.2.2 Previous work on bridgehead enolates in our group

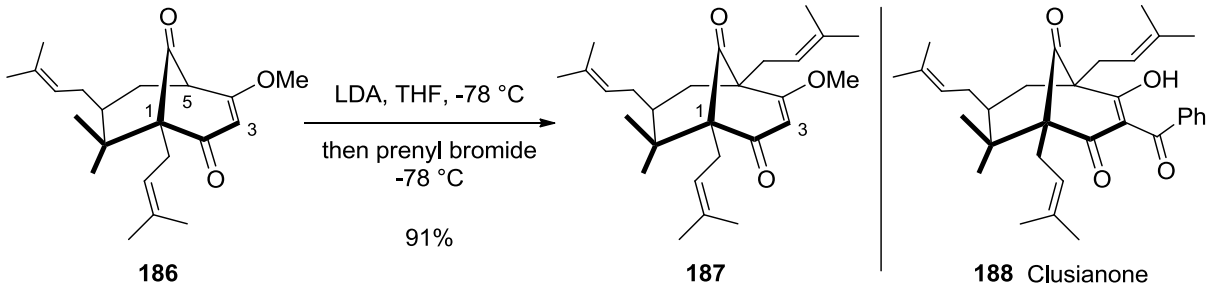
While their high reactivity represents a great challenge for accessing bridgehead-substituted compounds, our group developed unprecedented strategies using chiral lithium amide bases. Silylation of bicycle **183** was achieved in 76% yield at low temperature in the presence of chiral base **184** (Scheme 2.4).[10] A wide range of bridgehead substitutions were successfully undertaken and this methodology was applied in total syntheses.[10]



Scheme 2.4

More recently, the Simpkins group reported the synthesis of clusianone **188**, another complex bridged bicyclic natural product.[11] Clusianone **188** was successfully synthesised using a bridgehead substitution. Deprotonation of the C_5 position of bicyclic compound **186** was

achieved using an excess of LDA at low temperature. Subsequent alkylation using prenyl bromide afforded ketone **187** in 91% yield (Scheme 2.5).[11]



Scheme 2.5

Drawing inspiration from these results, our group decided to apply this strategy to the synthesis of welwistatin **7**. Preliminary computational studies (in collaboration with Prof. Chris Hayes at the University of Nottingham) on the tetracyclic core structure **88** were carried out to determine the required energy of deprotonation of each bridged position.[12] Metallation of bridged positions appeared to be an exothermic process with a slight tendency to occur preferentially in the desired C_{11} position (Figure 2.2).

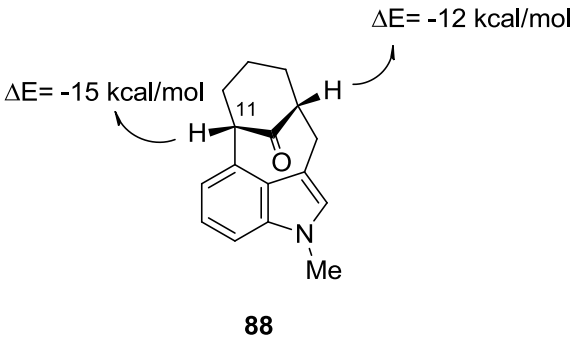


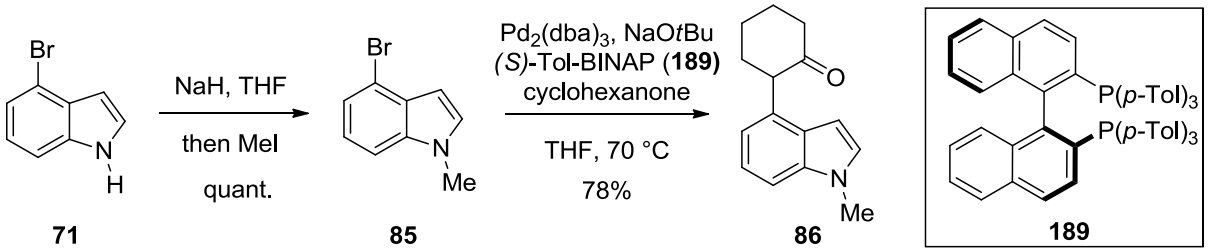
Figure 2.2

Functionalisations at the bridgehead positions of the tetracyclic structure **88** have been extensively investigated in our group and these will be the focus after preparation of the required scaffold **88**.

2.3 PREPARATION OF THE WELWISTATIN SCAFFOLD WITHOUT *GEM*-DIMETHYL *VIA* AN EXPEDIENT FOUR-STEP SYNTHESIS

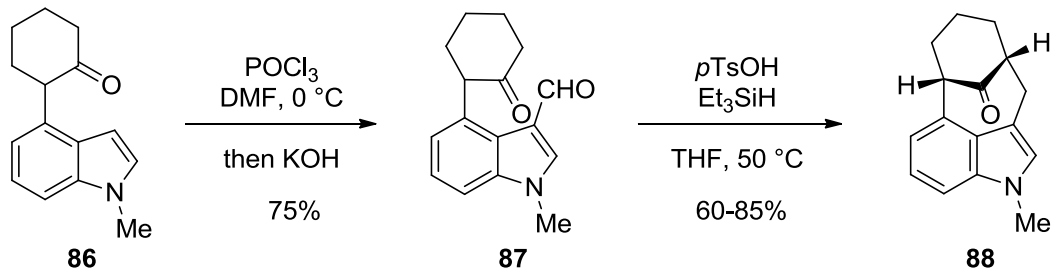
A reproducible four-step sequence to the tetracyclic skeleton **88** had been investigated by previous members of the Simpkins group.[12,3] The high efficiency of this strategy led us to undertake the proposed route to the core structure of welwistatin **88**.[3]

After *N*-methylation of commercially available 4-bromoindole (**71**), keto-indole **86** was isolated in reasonable yield *via* a Buchwald-type reaction using cyclohexanone as a coupling partner (Scheme 2.6). Optimisation of the coupling showed that using a chiral ligand such as *(S)*-Tol-BINAP (**189**) rather than the corresponding racemic ligand dramatically increased the yield of the reaction (from an average of 60% to a reproducible 78% yield). This result was in agreement with previous observations from Buchwald; the higher solubility of *(S)*-Tol-BINAP (**189**) compared to its corresponding racemic analogue seems to be responsible for this increased yield.[3,13]



Scheme 2.6

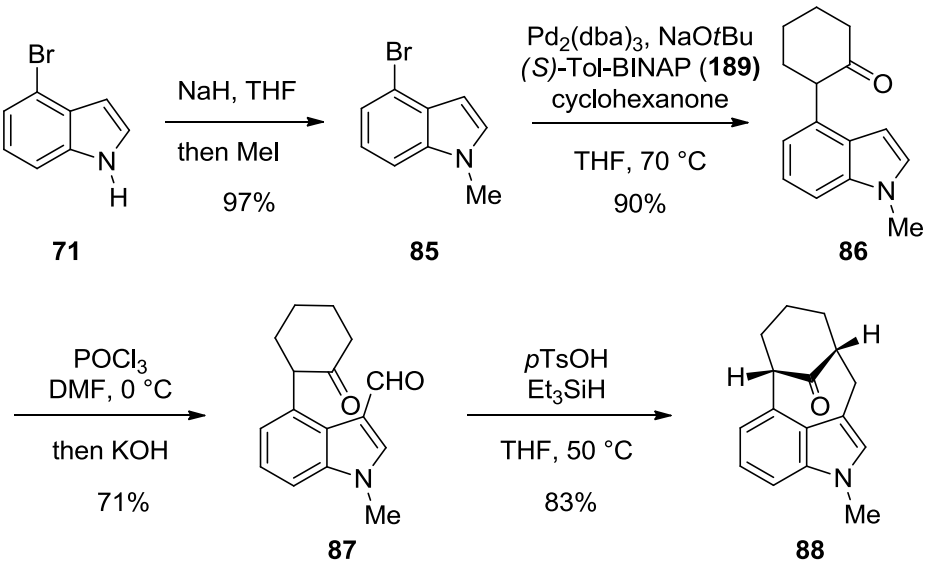
The following steps consist of formylation of the C_3 position of indole **86** under standard Vilsmeier-Haack conditions to afford aldehyde **87** in 75% yield. Cyclisation of aldehyde **87** followed by dehydration resulted in tetracycle **88** (Scheme 2.7).[3]



86 **87** **88**

Scheme 2.7

In our hands, gramme quantities of tetracycle **88** were obtained following this robust and scalable sequence. It was observed that performing the Buchwald-type coupling on larger scale (5 mmol) considerably increased the yield of the reaction from 78% to a reproducible 90% yield (Scheme 2.8).



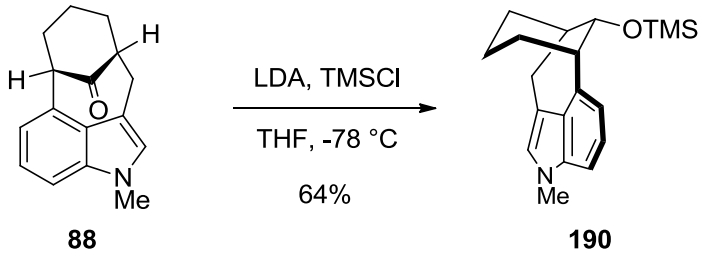
71 **85** **86** **87** **88**

Scheme 2.8

2.4 BRIDGEHEAD ENOLATE CHEMISTRY ON THE MODEL SYSTEM: PREVIOUS WORK IN OUR GROUP

2.4.1 Choice of the base

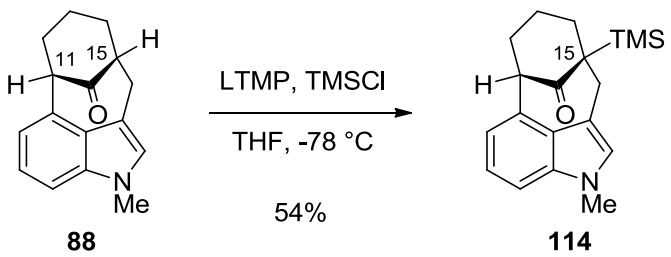
In preliminary studies, the importance of the base had been a key factor. It was demonstrated that treatment of bridged ketone **88** with a solution of lithium di*iso*propylamide (LDA) and TMSCl at low temperature afforded exclusively silyl ether **190** in 64% yield (Scheme 2.9).[12]



88 **190**

Scheme 2.9

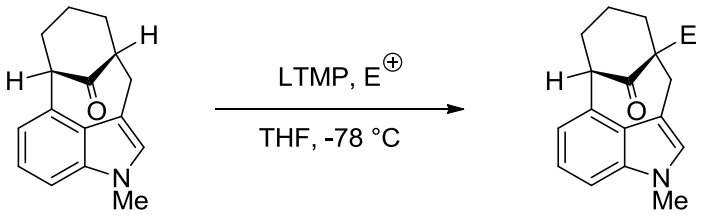
However, metallation of the bridgehead positions was successfully achieved by addition of a solution of lithium 2,2,6,6-tetramethylpiperidide (LTMP) to a solution of substrate **88** with an excess of TMSCl at low temperature (Scheme 2.10). Despite our promising computational calculations, the addition did not occur at the desired position, C_{11}, and silyl ketone **114** was formed as a single regioisomer in 54% yield.[4]



88 **114**

Scheme 2.10

Even though the regioselectivity of the addition did not match our expectations, we were pleased to be able to metallate and substitute the bridgehead C_{15} position using LTMP as the base. Our group decided to examine the addition of a large range of electrophiles (including alkyl, acyl and selenyl groups) to define the scope of this reaction (Scheme 2.11).[4] Many electrophiles were successfully added at the bridgehead position in good to excellent yields.

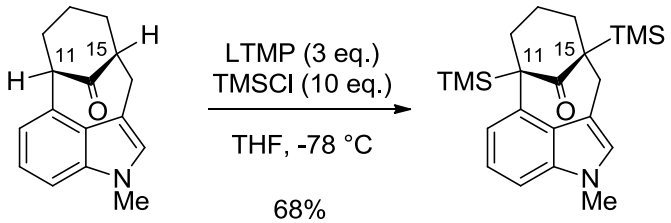


88

191 E = MeI (72%)
193 E = BnBr (73%)
195 E = PrenylBr (57%)
192 E = ClC(O)*t*Bu (85%)
194 E = PhCHO (51%)
121 E = $(SePh)_2$ (88%)

Scheme 2.11

To our delight, our group noticed that the stoichiometry of base used was playing an important role in the reaction. Increasing the number of equivalents of LTMP from one to three would lead solely to the bis-silylated adduct **196** in 68% yield (Scheme 2.12).[4]



88 **196**

Scheme 2.12

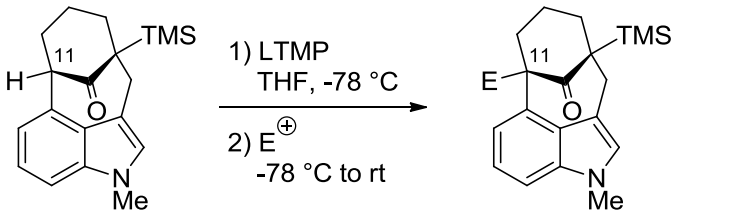
Obtaining this bis-silylated product **196** *via* a bridgehead strategy showed that it was possible to substitute at the C_{11} position.

2.4.2 Synthesis of isothiocyanate analogue and other advanced structures

Even though a direct substitution of the C_{11} position was not possible, the bridgehead metallation was still considered as a powerful technique to functionalise the welwitindolinone skeleton.

An alternative method involving successive substitutions was envisaged. A first substitution was performed on the C_{15} position of tetracycle **88**. Slow addition of a solution of bridged ketone **88** and TMSCl to a solution of lithium tetramethylpiperidide (LTMP) pre-cooled to -78 °C afforded mono-silylated product **114** (see: Scheme 2.10). The TMS group acted as a temporary blocking agent to allow further substitution to occur in position C_{11}.[4]

With the kinetic position blocked with a temporary silyl group, a second metallation of the bridgehead was used to functionalise the C_{11} position.



114

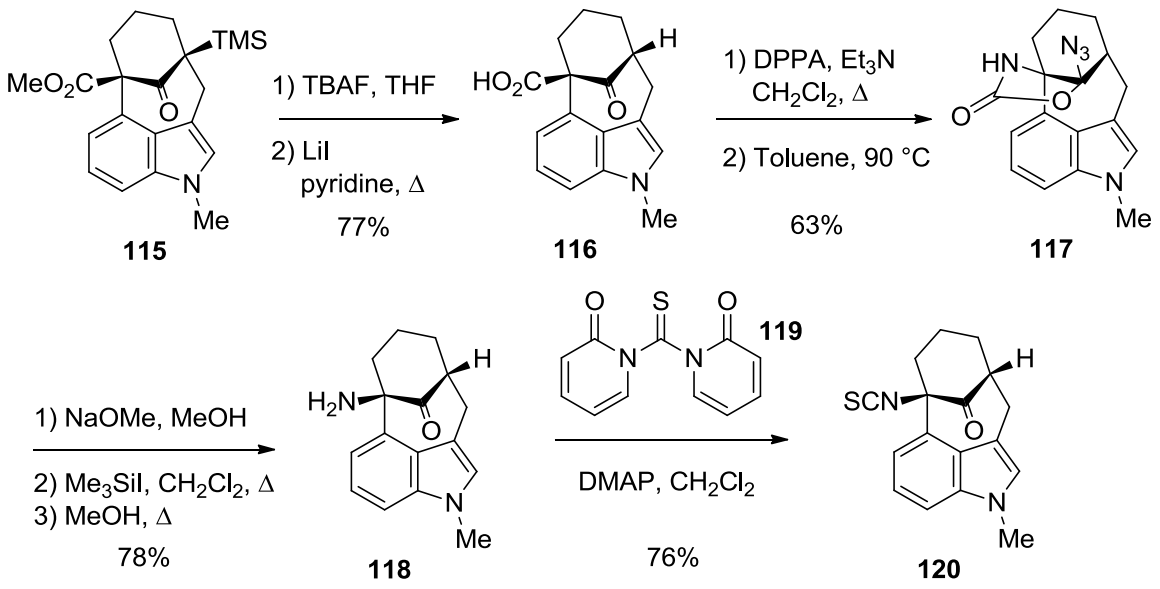
115 E = $ClCO_2Me$ (72%)
125 E = $(SePh)_2$ (88%)

Scheme 2.13

Treatment of mono-silylated bridged ketone **114** with one equivalent of LTMP at low temperature was followed by addition of an electrophile to give the corresponding bridged ketoester **115** or selenide **125** (Scheme 2.13).[4]

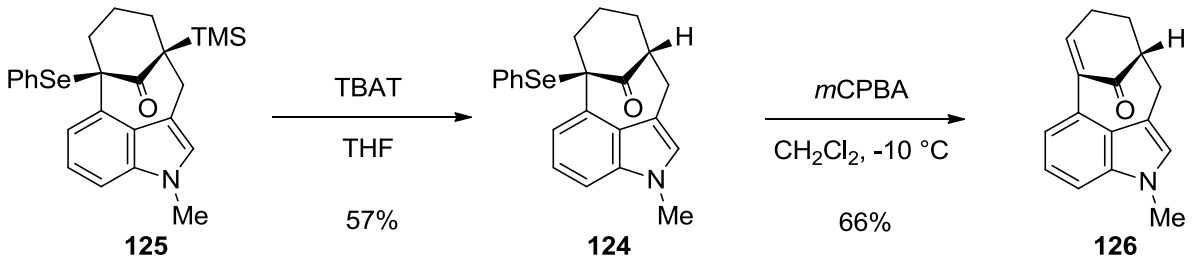
Further manipulations were carried out on ketoester **115** in our group to introduce the isothiocyanate functionality. After desilylation, a Curtius rearrangement was performed to produce isothiocyanate analogue **120** (Scheme 2.14).[4]

However, reaction of diphenylphosphoryl azide (DPPA) with carboxylic acid **116** afforded azido oxazolidinone **117** without any trace of the desired compound possessing the isocyanate functionality at the bridgehead position. Oxazolidinone ring opening was performed upon treatment with sodium methoxide in methanol. After removal of the carbamate protecting group, amine **118** was subjected to thiocarbonyldipyridinone (**119**) to give bridgehead isothiocyanate **120** in good yield (see Scheme 2.14).[4]



Scheme 2.14

Our group has also developed a strategy to access unusual bridgehead alkenes from the selenide compounds (Scheme 2.15).[4,12]

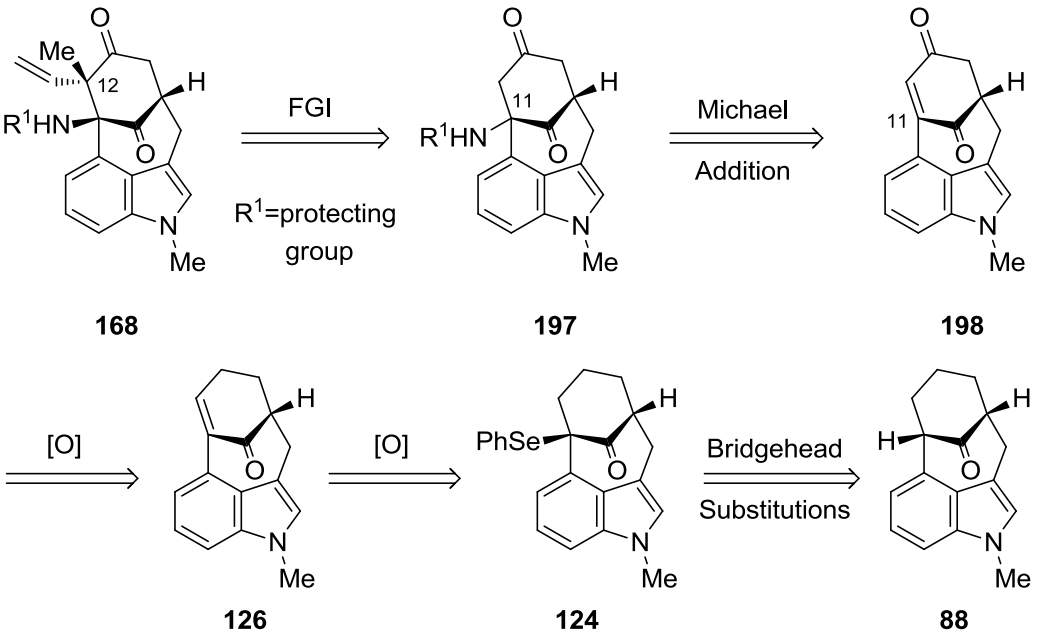


Scheme 2.15

After desilylation of ketone **125**, selenide **124** was converted into a remarkable bridgehead alkene **126** *via* an oxidation and *syn* elimination process (Scheme 2.15).[4,12]

2.5 OUR PROGRESS TOWARDS THE FUNCTIONALISATION OF THE CYCLOHEXANONE MOTIF

Inspired by the work developed within our group, we decided to undertake the same synthetic route to bridgehead alkene **126**. Our objective was to further functionalise the cyclohexanone motif of the welwitindolinone scaffold towards the synthesis of advanced intermediate **168**.

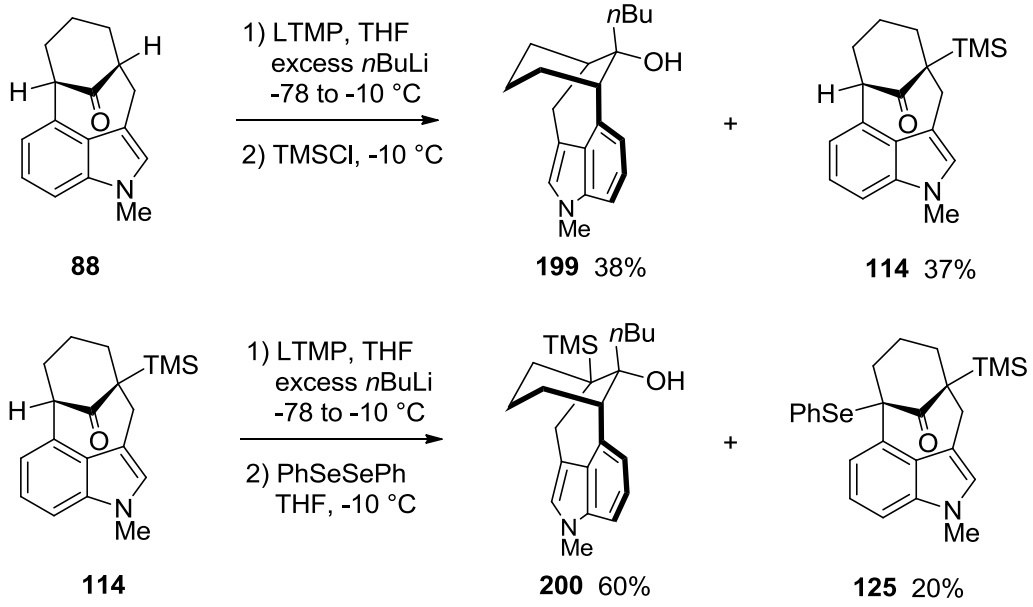


Scheme 2.16

At this stage, tetracycle **88** was considered as a potential intermediate in the synthesis of framework **168** using strategies previously developed in our laboratory. Target **168** would arise from protected amine **197** after successive regioselective additions on carbon C_{12}. A Michael-type addition on enone **198** would introduce the nitrogen at the bridgehead position C_{11}. Diketone **198** could be introduced through successive oxidations on bridgehead alkene **126**, which in turn could be obtained by successive bridgehead substitution on tetracycle **88** following the method developed by our group (Scheme 2.16).

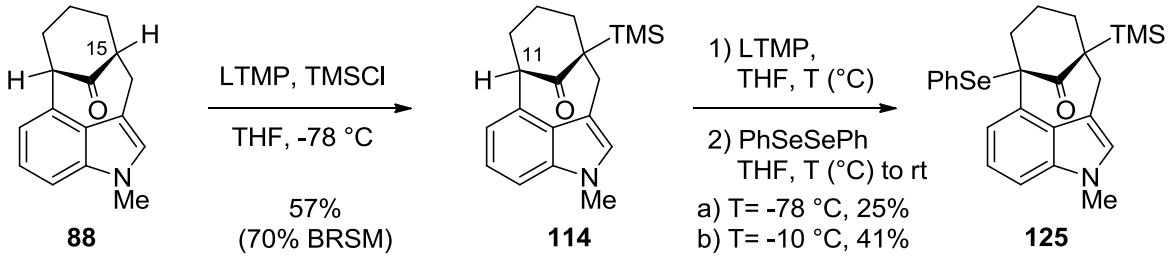
2.5.1 Bridgehead functionalisation

With tetracycle **88** in hand, we confirmed the importance of the choice and preparation of the base for the bridgehead metallation. Utilisation of excess *n*BuLi on tetracycles **88** and **114** resulted in the corresponding alcohols **199** and **200** (due to the presence of a large excess of *n*Bu$^-$) along with the desired adducts **114** and **125** (Scheme 2.17).



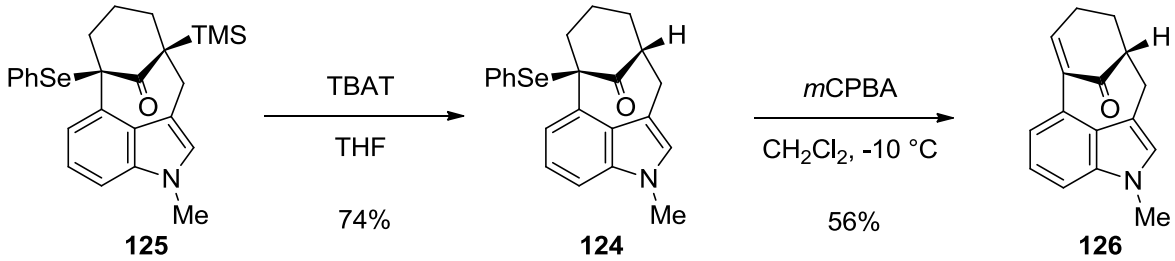
Scheme 2.17

Functionalisation of both bridgehead positions was then achieved using the chemistry developed by our group. Insertion of the silyl temporary blocking agent in position C_{15} was completed in similar yield to the one previously described. However, using the optimum conditions reported by previous members of our group, we were only able to access desired selenide **125** in 25% yield.[12] Facing some difficulties to repeat this reaction, we decided to increase the temperature of the reaction from -78 °C to -10 °C. Using these conditions, selenide **125** was obtained in an improved 41% yield (Scheme 2.18).



Scheme 2.18

The blocking group TMS was then removed using tetrabutylammonium triphenyldifluorosilicate (TBAT) in 74% yield (Scheme 2.19).

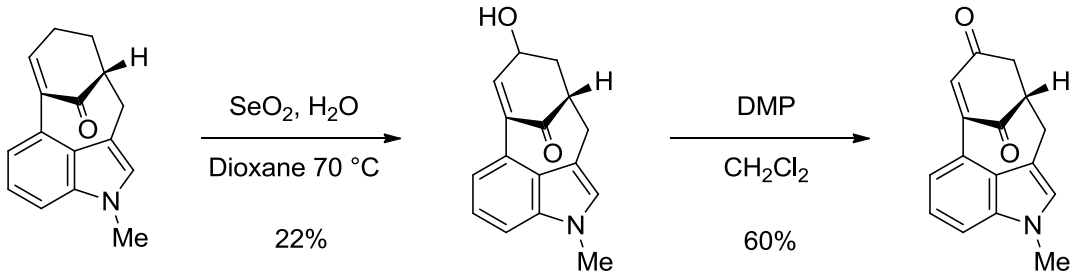


Scheme 2.19

Selenide **124** was oxidised with *meta*-chloroperbenzoic acid (*m*CPBA) to afford the corresponding bridged alkene **126** in 56% yield (Scheme 2.19).

2.5.2 Construction of diketone 198

With bridgehead enone **126** in hand, we turned our preliminary studies towards an oxidative strategy in order to introduce the second ketone functionality. Alkene **126** was converted into allylic alcohol **201** using selenium dioxide as the oxidising agent. Treatment of allylic alcohol **201** with Dess-Martin Periodinane (DMP) afforded the corresponding enone **198**. Unfortunately, the scale of our experiments did not allow us to carry out full data analyses; however from the data collected there was enough evidence for the formation of these two intermediates to justify repeating these steps on the real system (Scheme 2.20).



126 **201** **198**

Scheme 2.20

The ^{1}H NMR spectrum of alcohol **201** showed the presence of a vinylic proton at 6.68 ppm (*d*, 1H, *J* 5.9, H_{12}) as well as a characteristic resonance at 4.70 ppm (*ddd*, 1H, *J* 5.9, 4.5, 1.5, H_{13}) (Figure 2.3).

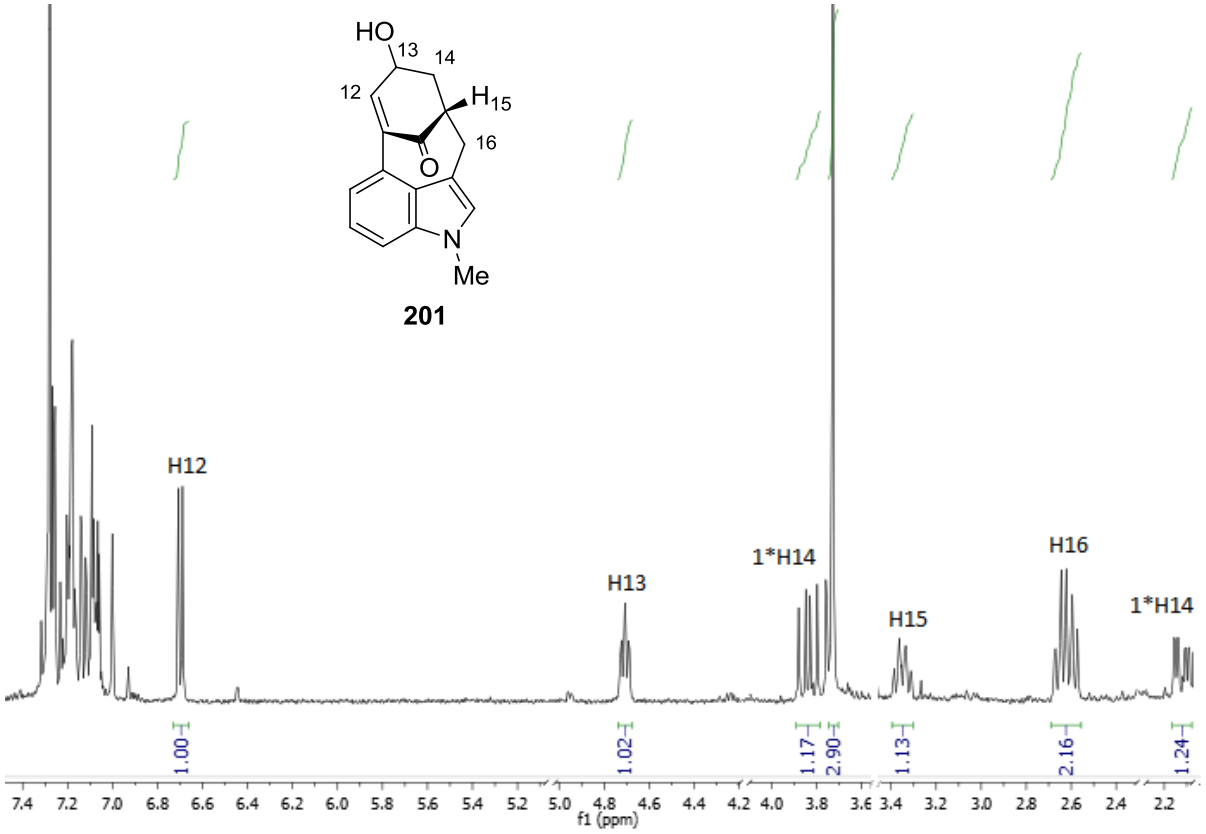
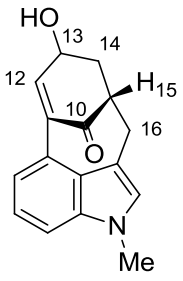


Figure 2.3

The mass spectrum showed a single peak at $[M + Na]^+ = 276.0$. Finally, the IR spectrum displayed a broad band at 3332 cm^{-1} associated with the alcohol, as well as the remaining strong carbonyl band at 1699 cm^{-1}. The combination of these data led us to propose the following structure for intermediate **201** (Figure 2.4).



201

^{1}H NMR
6.68 ppm (*d*, 1H, *J* 5.9, H_{12})
4.70 ppm (*ddd*, 1H, *J* 5.9, 4.5, 1.5, H_{13})

Mass Spectrometry
$[M + Na]^+$=276.0008 ($[C_{16}H_{15}NO_2Na]^+$ requires 276.0000)

IR
3332 cm^{-1} broad band (ν_{OH})
1699 cm^{-1} strong band ($\nu_{C10=O}$)

Figure 2.4

In the same fashion, the ^{1}H NMR spectrum of diketone **198** showed the presence of a vinylic proton at 6.40 ppm (*s*, 1H, H_{12}) (Figure 2.5). The multiplicity of this signal supported the absence of a proton adjacent to H_{12}.

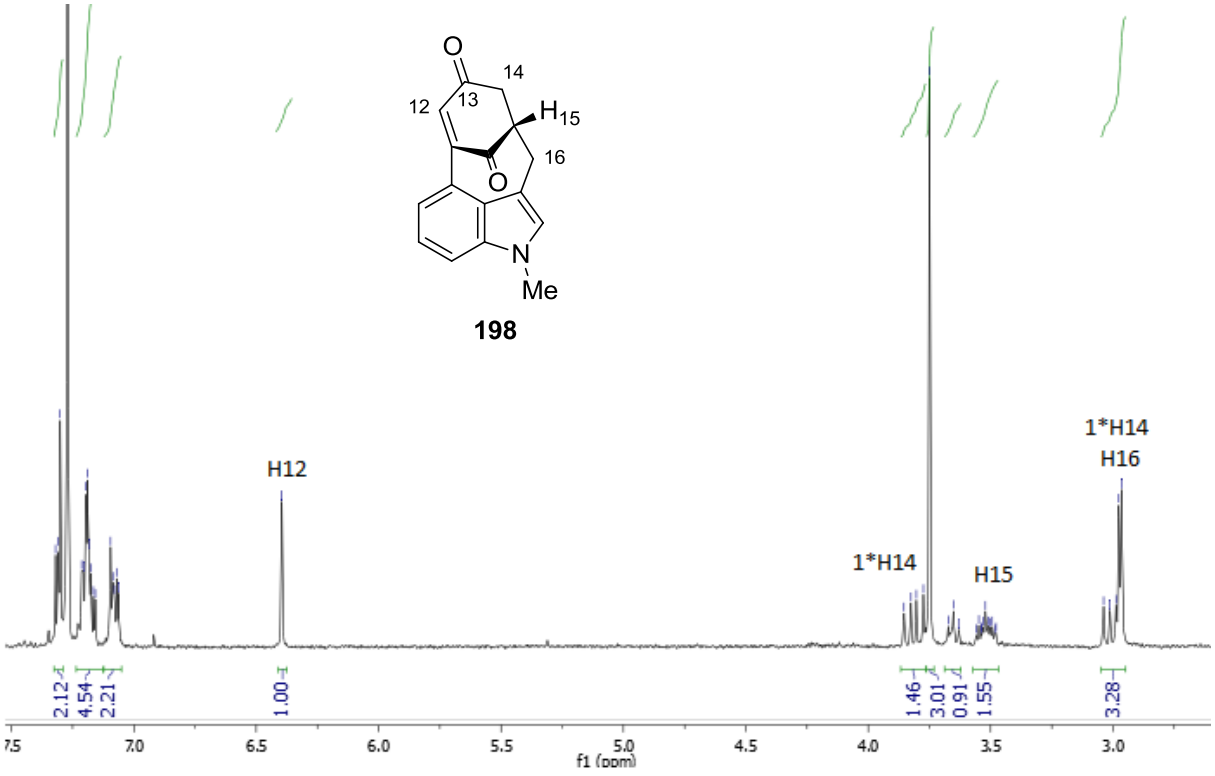
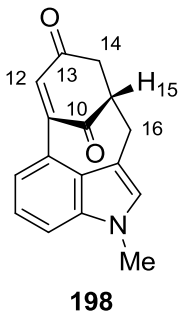


Figure 2.5

Moreover, a combination of mass spectrometry (showing a single peak at $[M + Na]^{+}$ = 274.1) and IR spectroscopy (displaying the presence of two carbonyl bands at 1702 and 1681 cm^{-1}) confirmed the structure of enone **198** (Figure 2.6). Unfortunately, the amount of enone **198** synthesised was not enough to obtain a decent ^{13}C NMR spectrum.



^{1}H NMR
6.40 ppm (*s*, 1H, H_{12})

Mass Spectrometry
$[M + Na]^{+}$=274.0860 ($[C_{16}H_{13}NO_2Na]^{+}$ requires 274.0844)

IR
1702 cm^{-1} strong band ($\nu_{C10=O}$)
1681 cm^{-1} strong band ($\nu_{C13=O}$)

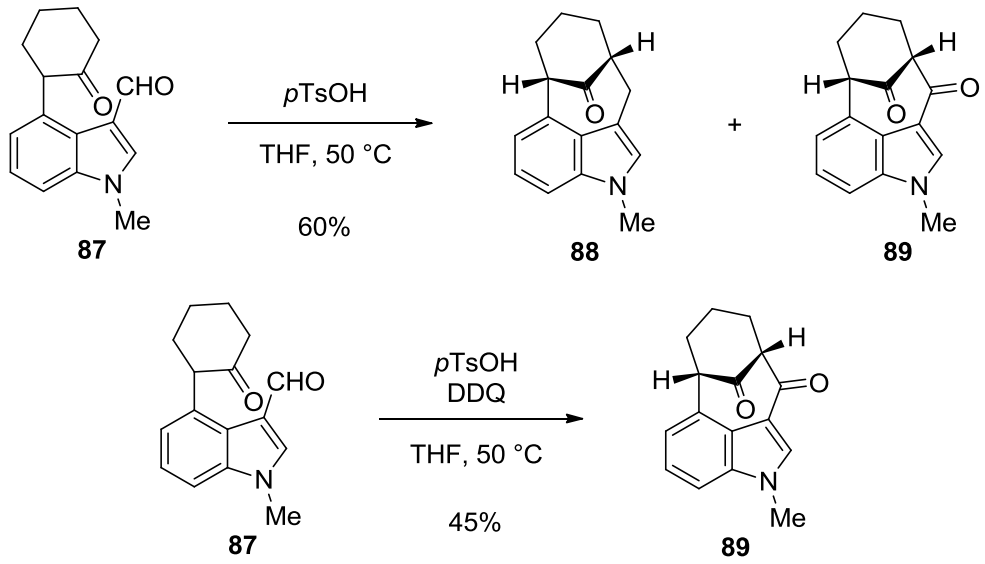
Figure 2.6

2.6 LIMITATIONS OF THIS MODEL SYSTEM

At first, tetracyclic structure **88** was a particularly attractive target due to its extremely short synthesis which made it an easily accessible intermediate. However, this model system showed some limitations (issues to insert the *gem*-dimethyl) as well as difficulties (longer synthetic route, lower yields) that led us to consider working on the real system.

2.6.1 Difficulties encountered introducing the *gem*-dimethyl at the C_{16} position

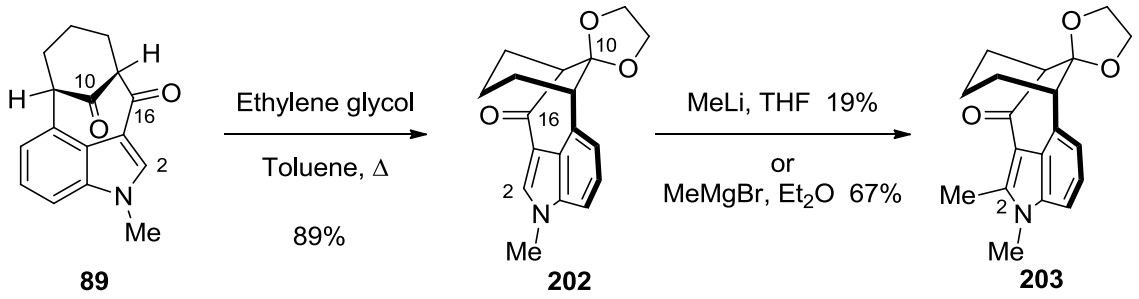
Previous studies carried out by members of our group showed how difficult it was to install the *gem*-dimethyl on tetracyclic cores **88** or **89** (obtained by oxidative treatment of aldehyde **87** in the presence of *p*TSA) (Scheme 2.21).[12,14]



Scheme 2.21

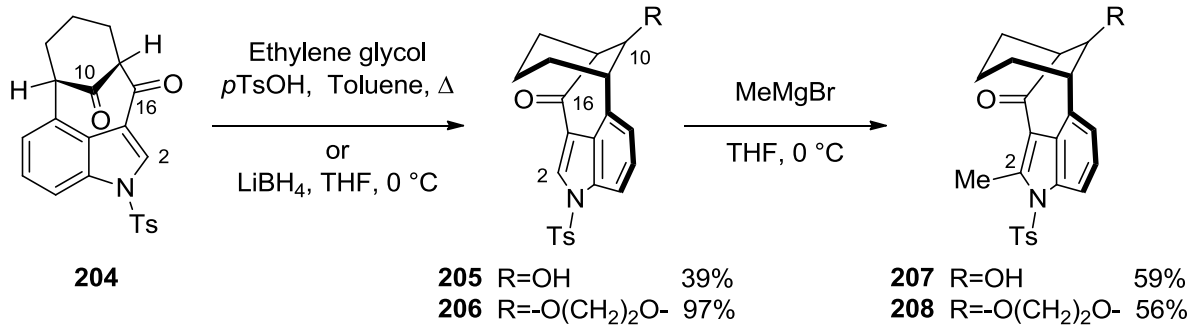
Chosen for its easy access, diketone **89** was then subjected to a range of nucleophiles aiming to react at the C_{16} position. However, due to the high reactivity of the bridged ketone at

position C_{10}, an acetal protection using ethylene glycol was performed as the first step to allow further selective manipulations of the ketone at position C_{16}. Unfortunately, treatment of **202** with a range of nucleophiles (such as MeLi, MeMgBr) did not proceed to the desired alcohol and the product of C_2 addition **203** was obtained (Scheme 2.22). A combination of the hindrance of the carbonyl at the C_{16} position and higher reactivity in the position C_2 of the indole prevented the formation of the *gem*-dimethyl.[12]



Scheme 2.22

The presence of a methyl group on the indole nitrogen was identified as an activating agent for the C_2 addition. Previous work within the group had investigated the influence of the protecting group on the nitrogen for the preparation of the *gem*-dimethyl from carbonyl **204**.[14]

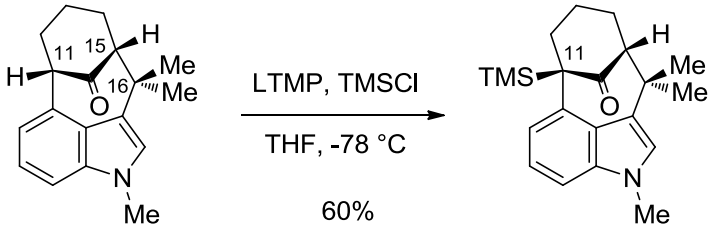


Scheme 2.23

Similar experiments as on the *N*-methyl series were carried out with the *N*-tosyl-substituted indole motif, however the same problem of regioselectivity and the difficulty obtaining the desired *gem*-dimethyl remained (scheme 2.23).

2.6.2 Rapid access to the desired regioselectivity at the bridgehead position C_{11}

Whilst we were working on this model system, the bridgehead chemistry on the scaffold possessing the *gem*-dimethyl in position C_{16} was also being studied within our group.[14]



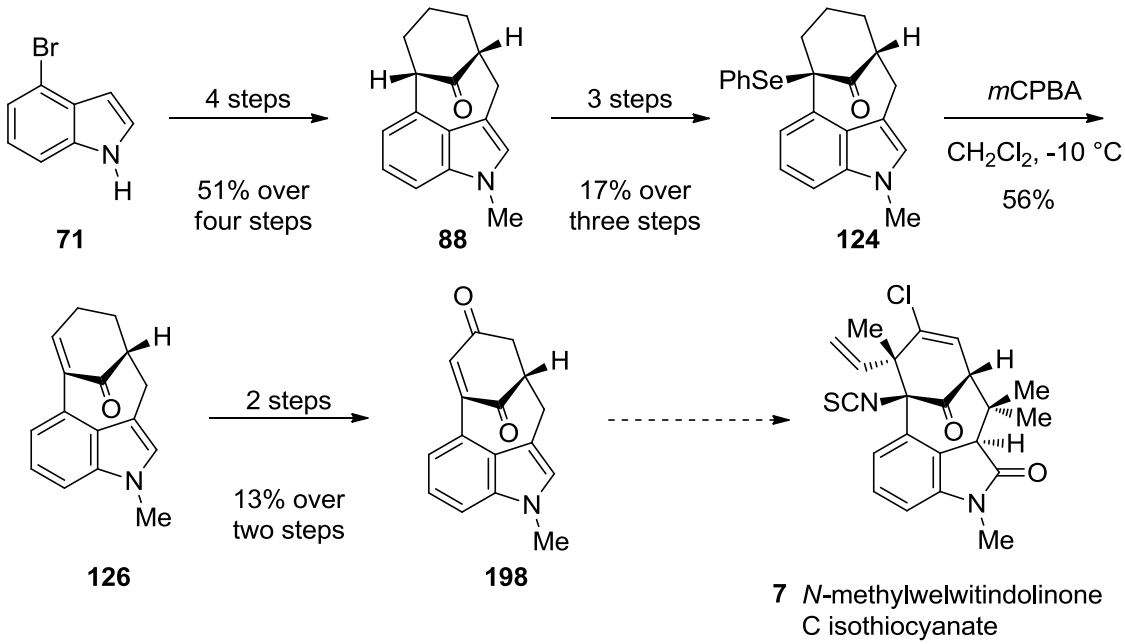
170 **209**

Scheme 2.24

After exposing skeleton **170** to the bridgehead reaction conditions, our group was pleased to discover that the presence of the *gem*-dimethyl in position C_{16} would generate a steric clash at the position C_{15} so favouring the regioselective addition in position C_{11} (Scheme 2.24).[14]

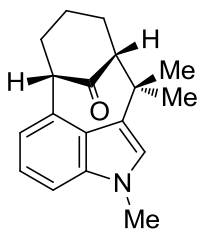
2.7 SUMMARY

The bicyclo[4.3.1]decane **88** has been synthesised in four steps from commercially available 4-bromoindole (**71**). Functionalisation of the bridged positions was successively achieved by metallations and substitutions using strategies developed by previous members of our group. After removal of the TMS blocking agent, selenide intermediate **124** was oxidised into the corresponding bridgehead alkene **126**. Despite the low yields of this synthetic route, preliminary studies on this model system provided encouragement that it was conceivable to functionalise the cyclohexanone motif of the tetracycle towards welwistatin **7** (Scheme 2.25).



Scheme 2.25

Despite the expedient synthesis of tetracycle **88**, we started to encounter diverse issues that we linked to the absence of the *gem*-dimethyl on the tetracyclic scaffold. We realised that functionalisation of the bridgehead position C_{11} could be achieved without the introduction of a temporary blocking agent on position C_{15} when carried out on tetracycle **170**, avoiding some unnecessary protection and deprotection steps (Figure 2.7). In addition, previous studies carried out in our group had highlighted the difficulties when trying to introduce the *gem*-dimethyl framework at a late stage of the synthesis.



170

Figure 2.7

At this stage, we decided to turn our attention towards the synthesis of tetracyclic scaffold **170** (Figure 2.7). We will develop the techniques and strategies that we learned on this model system as well as pursuing the synthesis towards the total synthesis of welwistatin **7**.

2.8 REFERENCES

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CHAPTER THREE

TOWARDS THE TOTAL SYNTHESIS OF

N-METHYLWELWITINDOLINONE C ISOTHIOCYANATE

3.1 AIMS AND OBJECTIVES

As discussed in the previous chapter, we carried out a number of experiments to functionalise our key intermediate **88** with the aim to complete the total synthesis of *N*--methylwelwitindolinone C isothiocyanate **7**. However, converting the C_{16} ketone of **89** into the required *gem*-dimethyl of **170**, proved to be a substantial challenge (Figure 3.1).

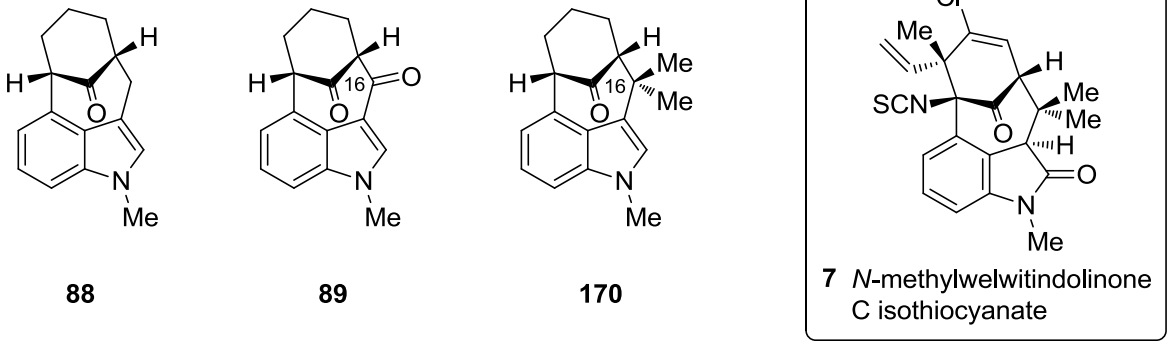


Figure 3.1

With these difficulties in mind, our group decided to synthesise the core structure with the *gem*-dimethyl fragment already in place and, for this purpose, chose to adopt the early stages of Rawal's synthesis to assemble key intermediate **169** (Figure 3.2).[1]

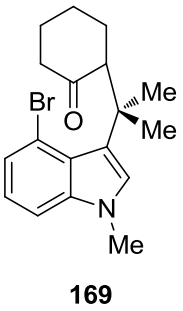
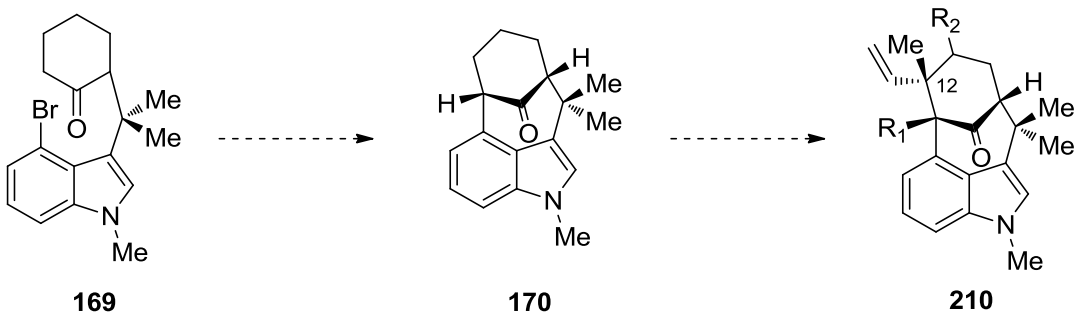


Figure 3.2

This chapter focuses on the formation of the tetracyclic scaffold **170** including the closure of the seven-membered ring system and the functionalisation of the cyclohexanone motif, in the northern part of the molecule, using the bridgehead chemistry previously developed.



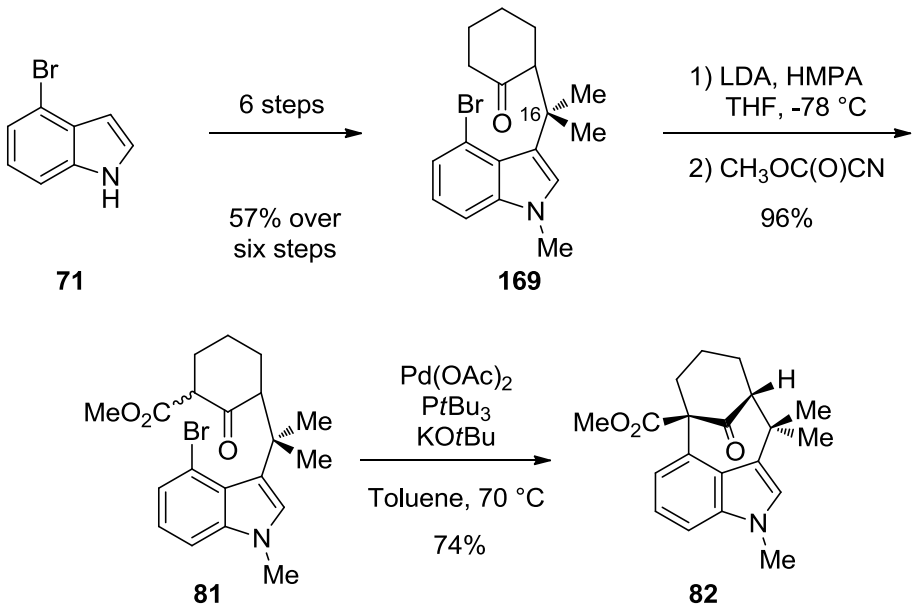
Scheme 3.1

Previous studies on skeleton **170** have been carried out in the Simpkins group.[2] Our work will consist of improving the proposed sequence (optimisation of the yield of the reactions) as well as attempting to install the quaternary centre at the C_{12} position (Scheme 3.1).

3.2 PREVIOUS WORK IN OUR GROUP

3.2.1 Synthesis of enone 214 [1,2]

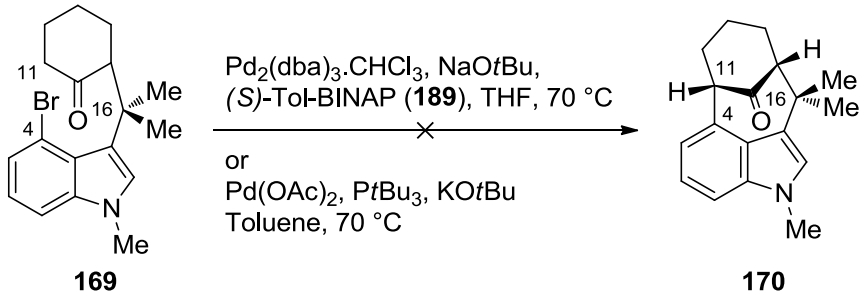
In 2005, Rawal and co-workers reported an efficient and convergent sequence to the welwistatin scaffold based on an intramolecular Pd-catalysed arylation of ketoester **81**, synthesised in seven steps from commercially available 4-bromoindole (**71**) (Scheme 3.2).[1]



Scheme 3.2

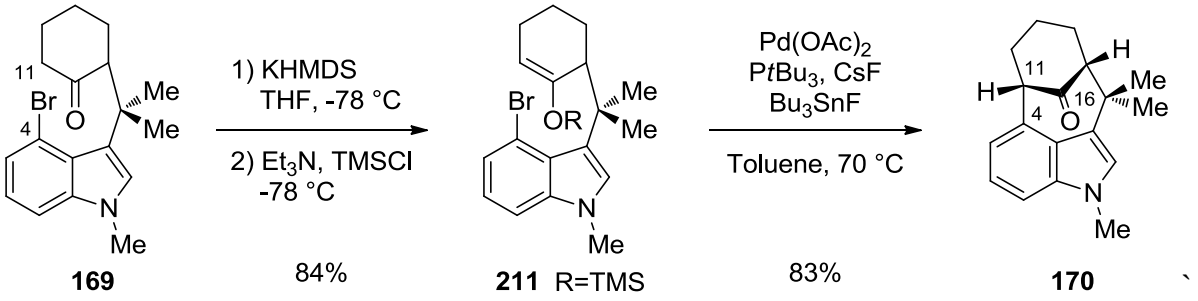
Taking inspiration from Rawal's work, our group decided to adopt their strategy to synthesise functionalised cyclohexanone **169**, possessing the required *gem*-dimethyl moiety on the C_{16} position (Scheme 3.2).

With indole derivative **169** in hand, our group focused on an alternative route towards the desired seven-membered ring system. Attempts to form the C_4-C_{11} bond using the direct standard enolate arylation conditions developed in our laboratory did not afford the desired tetracycle **170**. This was also the case when precursor **169** was subjected to Rawal's cyclisation conditions (Scheme 3.3).[2]



Scheme 3.3

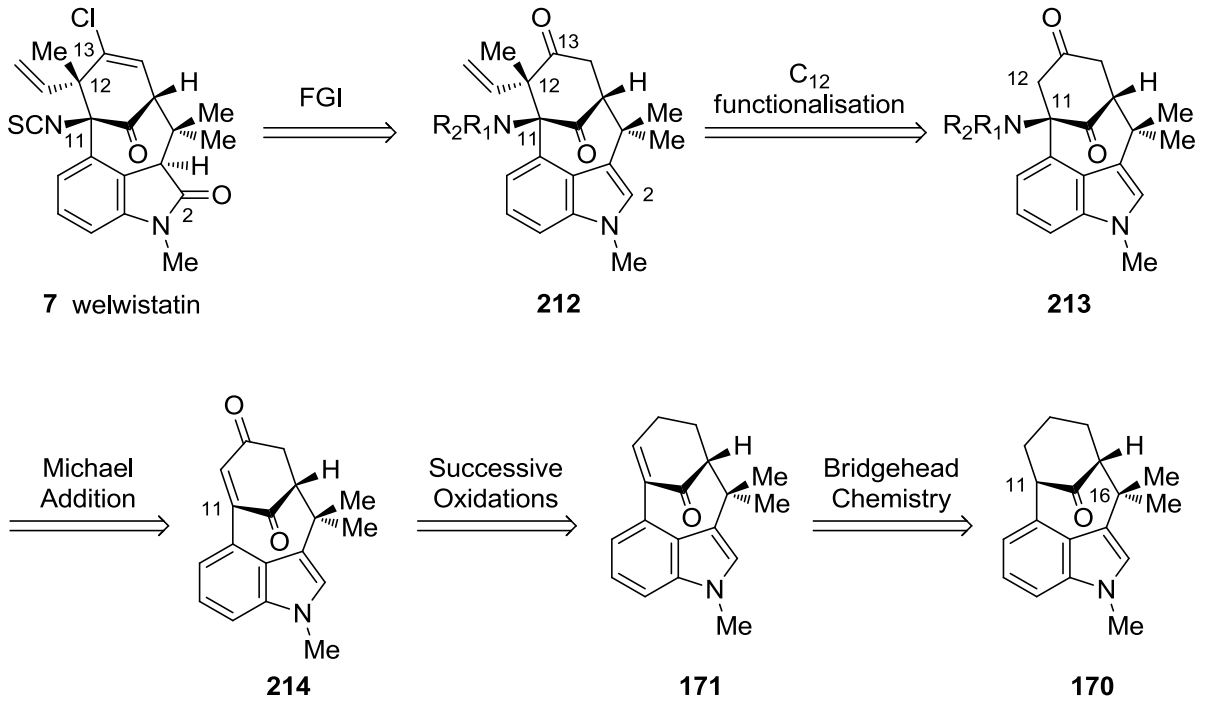
Drawing inspiration from Hartwig's work on cross-coupling reactions, our group established a two-step sequence to construct tetracycle **170**, containing the welwitindolinone skeleton, from the functionalised cyclohexanone **169**.[3] Exposure to KHMDS followed by addition of TMSCl under basic conditions gave enol silane **211**. After optimisation, palladium-catalysed cyclisation of silyl enol ether **211** in the presence of cesium fluoride and tri-*n*-butyltin fluoride using tri-*tert*-butylphosphine as the ligand occurred in high yield, to provide tetracycle **170** (Scheme 3.4).[2]



Scheme 3.4

With tetracycle **170**, possessing the *gem*-dimethyl in the desired C_{16} position, in hand, we turned our attention towards the other features present on welwistatin **7**. We envisaged that welwistatin **7** could be obtained from key intermediate **212** *via* functional group interconversions (FGI) to install the oxindole, the bridgehead isothiocyanate at the C_{11}

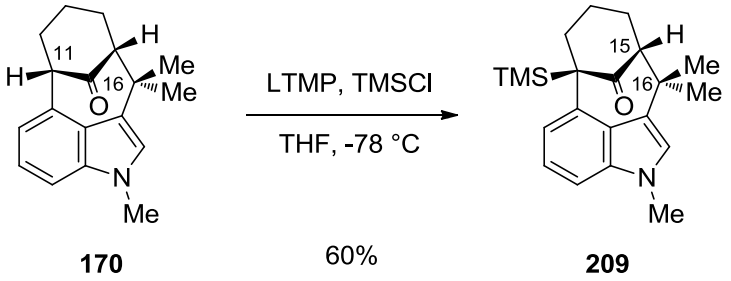
position and to convert the ketone at the C_{13} position into the vinyl chloride. Highly advanced intermediate **212** might be accessible from diketone **213** using regioselective aldol chemistry. An unusual Michael-type addition on enone **214** was envisaged to insert the bridgehead functionality. Bridgehead enone **214** would result from successive oxidations on alkene **171**, which could in turn be accessed from tetracycle **170** *via* a regioselective enolate substitution (Scheme 3.5).



Scheme 3.5

Inspired by the successful bridgehead substitutions carried out on our model system **88** (see: Chapter 2), our group decided to employ the same methodology to functionalise tetracycle **170** possessing the *gem*-dimethyl moiety. They were delighted to discover that subjecting tetracyclic structure **170** to our standard bridgehead deprotonation conditions, using an ISQ, afforded silylated adduct **209** in 60% yield. No trace of either the other regioisomer or the bis-silylated adduct was observed. The steric hindrance imparted by the

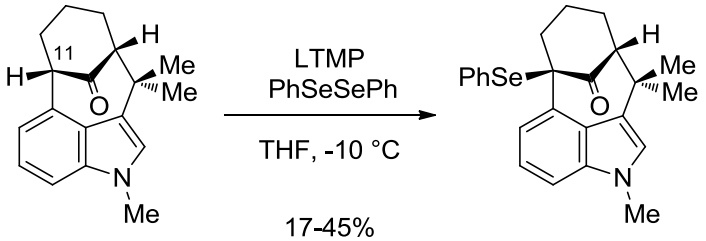
gem-dimethyl in position C_{16} reduced the possibility of the deprotonation of H_{15} in **170** also encouraging the direct formation of the desired regioselective silyl product **209** (Scheme 3.6).[2]



170 **209**

Scheme 3.6

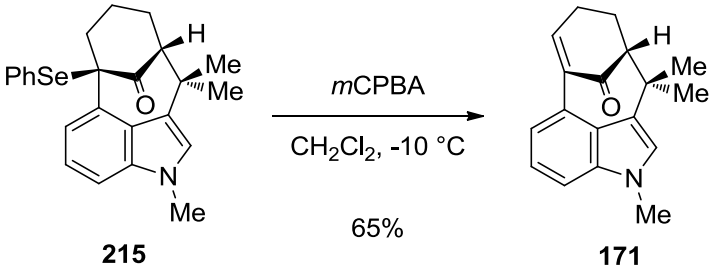
In order to access bridgehead alkene **171**, our group sought the introduction of a selenide group at position C_{11}. Suspecting a lack of reactivity between the enolate formed and the selenium electrophile, the reaction was conducted at an elevated temperature (-10 °C instead of -78 °C) and this allowed bridgehead selenide **215** to be obtained in moderate yield (Scheme 3.7).[2]



170 **215**

Scheme 3.7

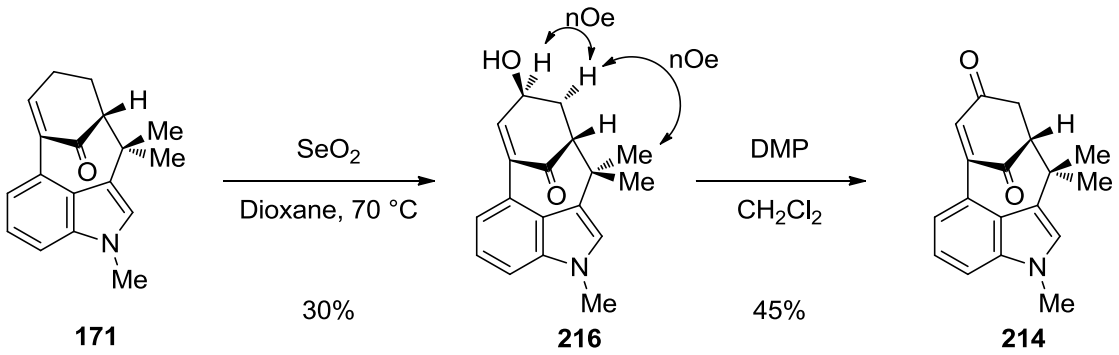
The synthesis of bridgehead alkene **171** was completed in good yield by an oxidative elimination of the selenium species, using *m*CPBA at low temperature (Scheme 3.8).[2]



215 **171**

Scheme 3.8

Precursor **171** was oxidised in the presence of selenium dioxide to provide allylic alcohol **216** in 30% yield, which was then oxidised with Dess-Martin periodinane to give the corresponding enone **214** in 45% yield. The configuration of alcohol **216** was determined by an nOe experiment (Scheme 3.9).[2]



171 **216** **214**

Scheme 3.9

Therefore, the functionalisation of the northern portion of tetracyclic structure **170**, using a regioselective deprotonation of the bridgehead ketone as the key step, successfully afforded advanced enone **214**.

3.2.2 Introduction of a nitrogen-containing group at the bridgehead position C_{11} [2]

The presence of an isothiocyanate functionality at the bridgehead position C_{11} of our target led our group to consider introducing a nitrogen motif at this bridgehead position. At this stage, an azide functionality was chosen as a suitable candidate and our group investigated the addition of azide onto the branching position C_{11} in order to access intermediate **217** (Figure 3.3).[2]

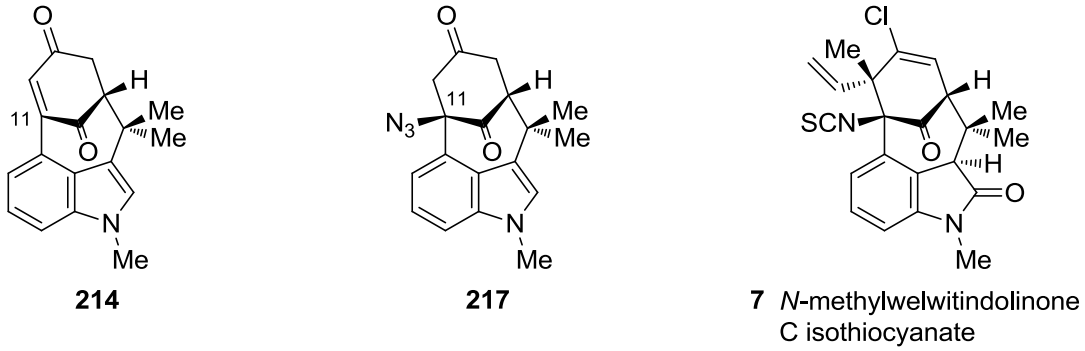


Figure 3.3

The highly strained scaffolds of tetracycles **171** and **214** prevented conjugation between the bridging ketone C_{10} and the alkene C_{11}-C_{12}. However, a molecular model of intermediate **214** suggested a planarity between alkene C_{11}-C_{12} and ketone C_{13}, and therefore suitable conjugation, to allow an eventual Michael addition on C_{11} (Figure 3.4).[2]

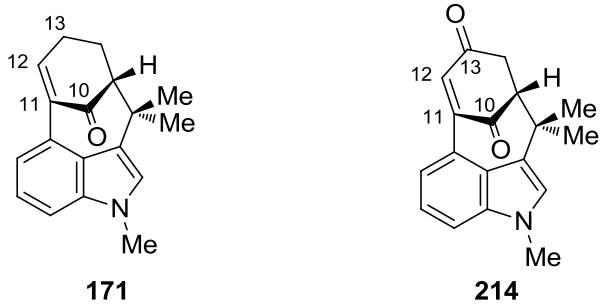
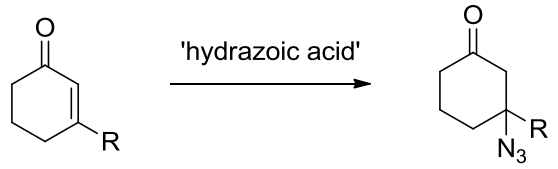


Figure 3.4

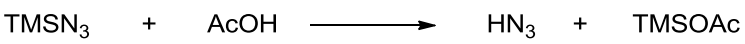
In 1999, Miller and co-workers published an azide ion addition onto a large range of α,β-unsaturated molecules using triethylamine as a catalyst.[4] Miller reported numerous advantages to this strategy, that could be applied to a great variety of structures, including mild reaction conditions, utilisation of commercially available catalyst and substrates and high-yielding reactions (Scheme 3.10).[4]



218 **219**

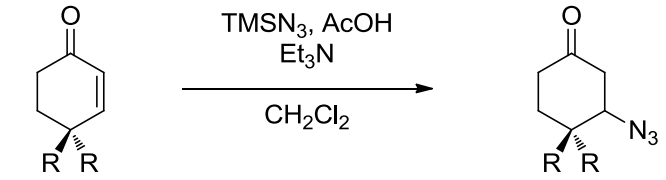
Scheme 3.10

The combination of the high toxicity and the explosive reactivity of a stock solution of hydrazoic acid prompted Miller to pursue its *in situ* preparation.[4] Miller chose commercially available trimethylsilyl azide as an azide derivative owing to its greater stability. Reaction of trimethylsilyl azide with a carboxylic acid, in this case acetic acid (AcOH), would afford trimethylsilyl acetate along with the desired hydrazoic acid, *in situ* (Scheme 3.11).[4]



Scheme 3.11

To this end, Miller found that employing this system, along with a catalytic amount of amine, allowed the conjugate addition of azide ion to occur (Scheme 3.12).[4]

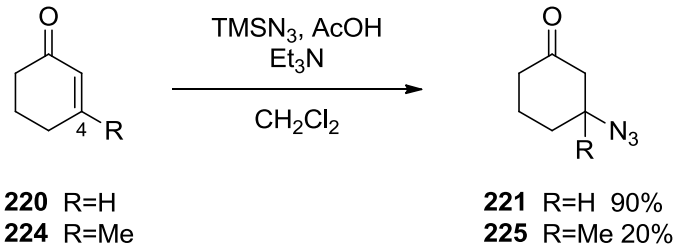


220 R=H
222 R=Me

221 R=H 90%
223 R=Me 87%

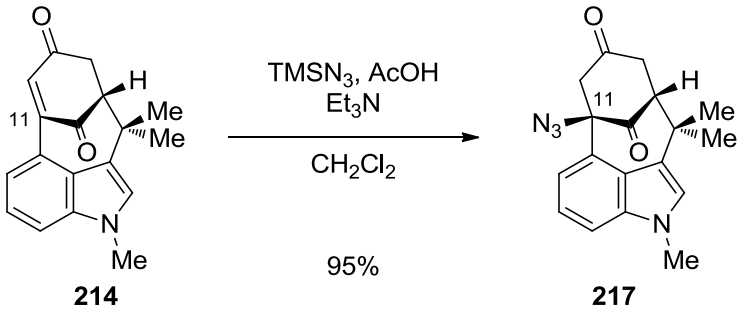
Scheme 3.12

A large range of α,β-unsaturated enones was subjected to these conditions and the corresponding azides were obtained in good yield.[4] However, the presence of an alkyl group at the reaction centre dramatically decreased the yield of the transformation. This was observed for enones **220** and **224**, where the yield of the conjugate addition decreased from 90% to 20% if the hydrogen atom at position C_4 in **220** was replaced with a methyl group (Scheme 3.13).[4]



Scheme 3.13

In order to obtain azide **217**, our group subjected enone **214** to the conditions developed by Miller (Scheme 3.14).[2,14]

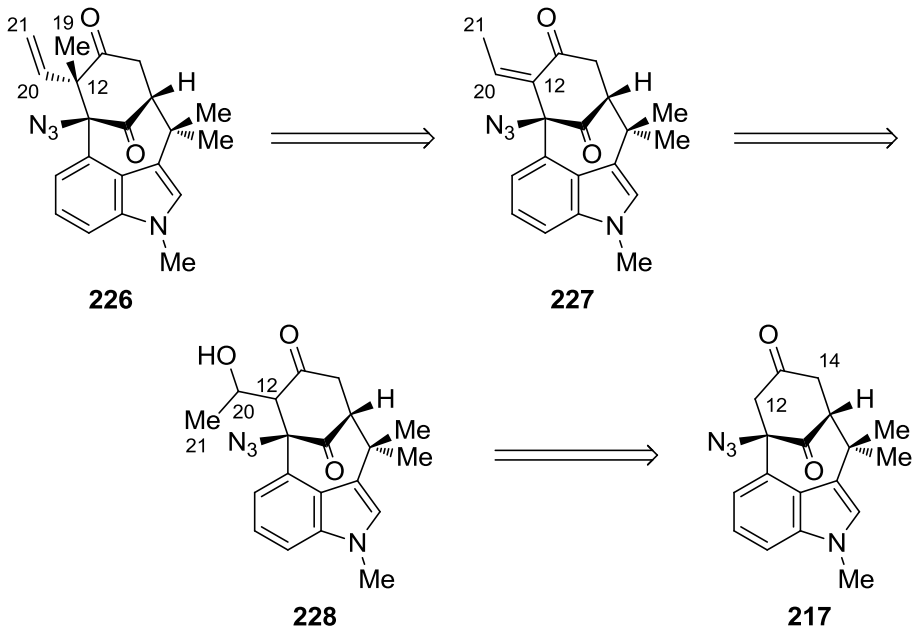


Scheme 3.14

Despite the complex architecture of starting enone **214**, azide **217** was produced in excellent yield.

3.2.3 Studies towards a regioselective functionalisation of carbon C_{12}

With a robust route to synthesise azide **217** in hand, our objective was to functionalise position C_{12} (Scheme 3.15).



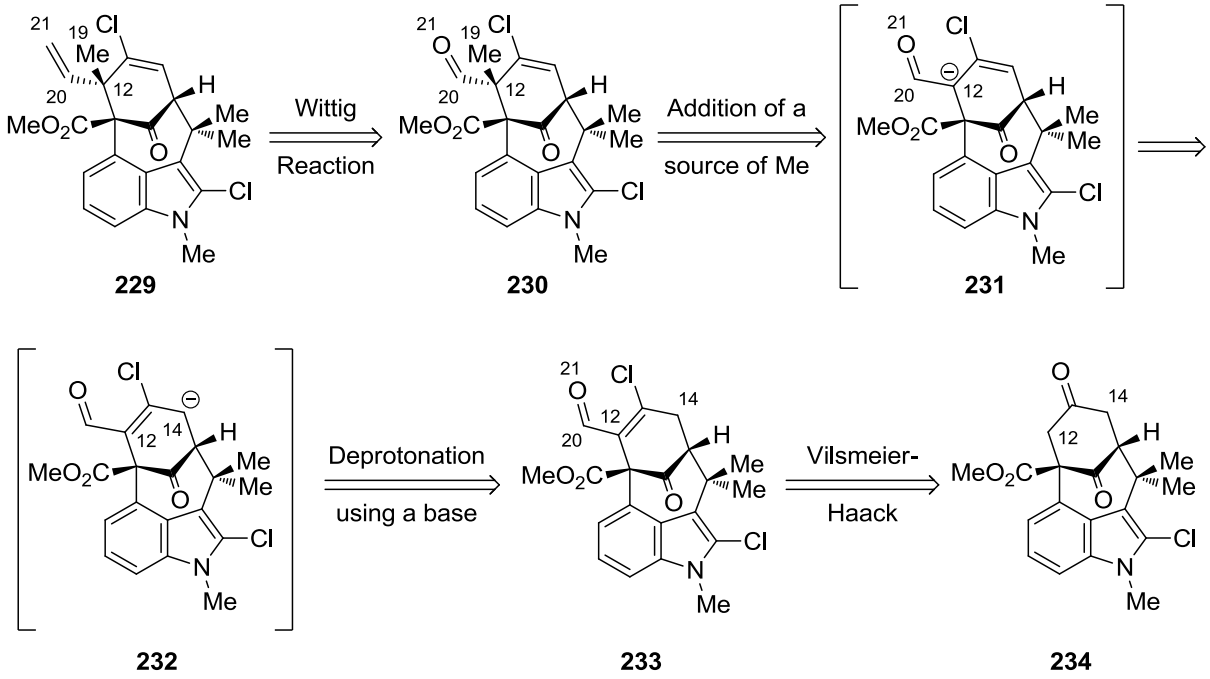
Scheme 3.15

Advanced intermediate **226**, possessing the desired stereochemistry at position C_{12} (imposed by the geometry of the molecule), could be obtained by deprotonation at C_{21} position of enone **227** followed by an external quench with methyl iodide. Enone **227** would be accessed by dehydration of aldol **228**, which in turn can be disconnected to azide **217** by utilising a regioselective aldol reaction with acetaldehyde at the position C_{12} (Scheme 3.15).

3.2.3.1 Rawal's investigations towards a regioselective functionalisation of carbon C_{12}

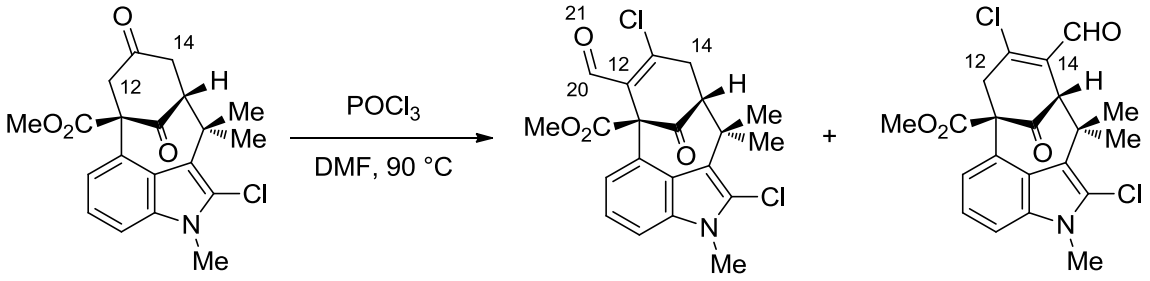
In 2011, Rawal and co-workers published an interesting article regarding the difficulties encountered in their approach towards the welwitindolinone family.[5] This article displayed and rationalised the formation of various unexpected products obtained throughout their synthetic route.

Through this publication, we discovered how Rawal envisaged functionalisation at position C_{12} of the tetracyclic structure. Alkene **229** was to be obtained *via* a Wittig reaction performed on aldehyde **230**. A regioselective deconjugative methylation on vinyl chloride **233** would achieve the desired regiocentre at the C_{12} position of **230**. Aldehyde **233** would be formed from ketone **234** using the Vilsmeier-Haack conditions. The regioselectivity of the chloro-formylation would be enhanced by the presence of the ester group at the bridgehead position that would provide either a favourable electronic inductive effect or chelation for increasing the reactivity at position C_{12} (Scheme 3.16).[5]



Scheme 3.16

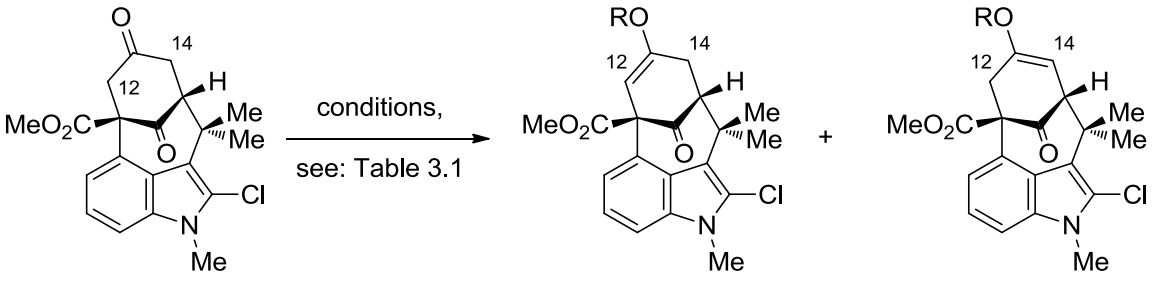
Surprisingly, despite the presence of the ester group, only the undesired regioisomer **235** was formed, in 58% yield, without any traces of addition to the C_{12} position (Scheme 3.17).[5]



234 **233** not observed **235** 58%

Scheme 3.17

Particularly intrigued by this result, Rawal and co-workers investigated the regioselectivity of silyl enol ether formation under various experimental conditions. Whilst treatment of ketone **234** under soft enolisation conditions afforded principally the undesired silyl enol ether **237a**, under kinetic control the reaction seemed to favour deprotonation at the C_{12} position. Indeed, deprotonation of ketone **234** at -100 °C using KHMDS as the base followed by the addition of a silyl chloride reagent gave either silyl enol ether **236a** or **236b** with high regiocontrol (Scheme 3.18, Table 3.1). Rawal justified the choice of bulky silyl groups (TBS or TIPS) by their higher resistance to the acidic conditions involved in the subsequent Vilsmeier-Haack reaction.[5]



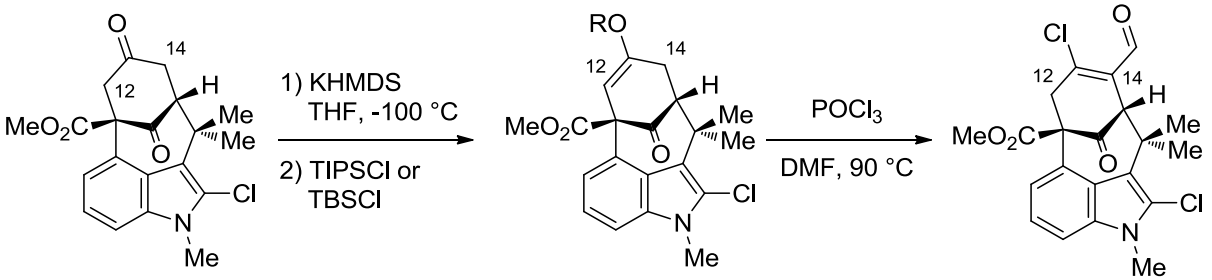
234 **236a** R=TBS **236b** R=TIPS **237a** R=TBS **237b** R=TIPS

Scheme 3.18

Conditions
NEt_3, TBSOTf, -20 °C
KHMDS, TBSCl, -78 °C
KHMDS, TIPSCl/TBSCl, -100 °C

Table 3.1

Pleased by the high regiocontrol of the formation of silyl enol ethers **236a** and **236b**, both enol silanes were formylated following the Vilsmeier-Haack reaction conditions. Unfortunately, undesired aldehyde **235** was the only product of this reaction. The acidic conditions were believed to be responsible for the isomerisation of the double bond to **237a** or **237b**, the precursor of aldehyde **235** (Scheme 3.19).[5]



234 **236a** R=TBS **236b** R=TIPS **235**

Scheme 3.19

This highlighted the regioselectivity issue of this strategy. Despite high regiocontrol for the formation of the desired silyl enol ethers **236a** and **236b**, Rawal demonstrated the limitations of this procedure for introducing the desired fragment at position C_{12}.

3.2.3.2 Studies carried out by our group

Despite the recent work published by Rawal and co-workers, our group chose to pursue their planned synthetic route towards azide **226** (see: Scheme 3.15).[5]

Preliminary studies have been carried out by our group towards the synthesis of aldol **228** from azide **217**. In order to obtain the correct regioisomer, the protons at positions C_{12} and C_{14} would need to be differentiated.

The configuration of the molecule will impose the deprotonation of an *exo*-proton. Preliminary computational studies on azide **217** showed that the *exo*-proton at position C_{12} resides in an axial orientation, whilst the *exo*-proton at position C_{14} is positioned equatorially (Figure 3.5). Thus electronic and steric factors should favour the deprotonation at the position C_{12}.[2]

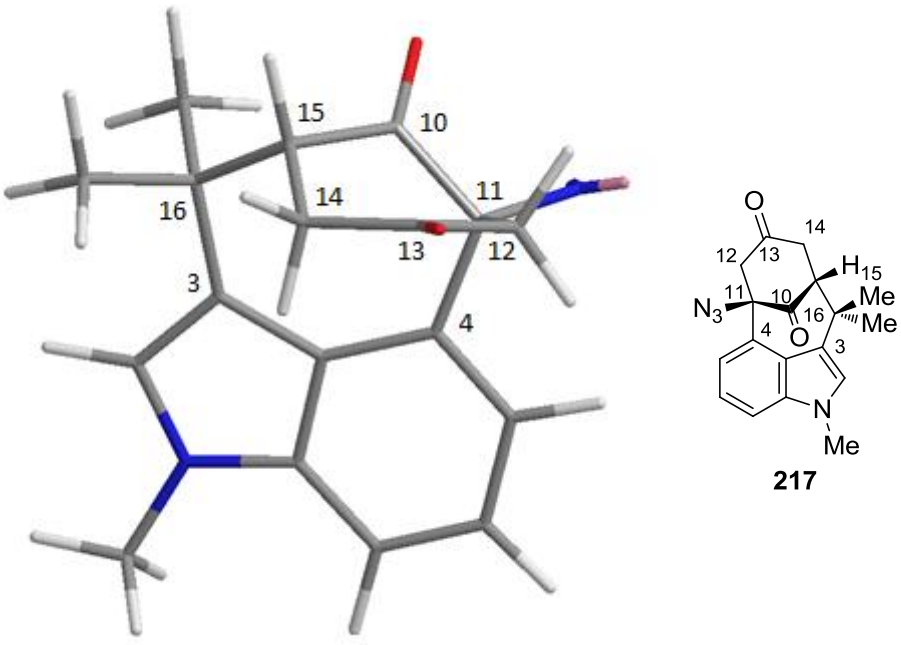
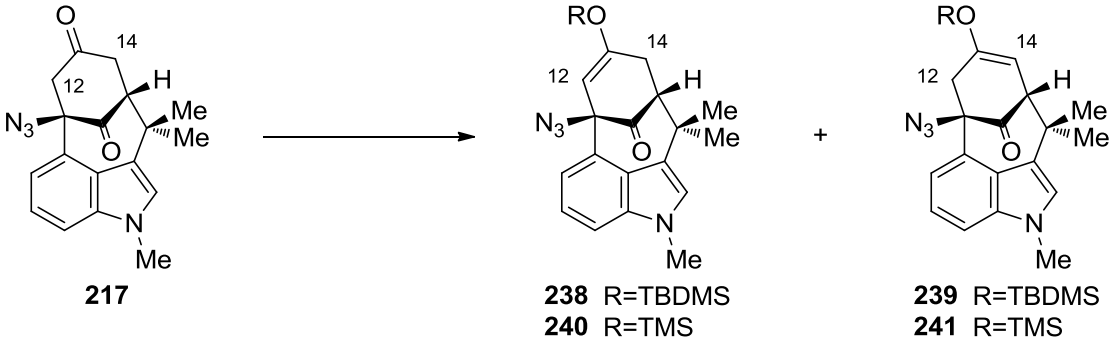


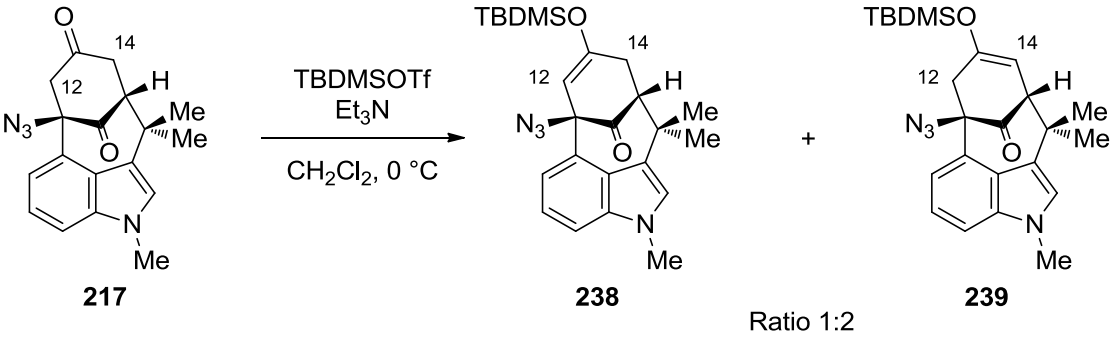
Figure 3.5

Preliminary experiments have been carried out by our group to define the regioselectivity of the deprotonation. Our group studied the ratio of silyl enol ethers **238** or **240** (corresponding to the deprotonation at the C_{12} position) to silyl enol ethers **239** or **241** (corresponding to the deprotonation at the C_{14} position), respectively, formed under thermodynamic and kinetic conditions to define the optimum reaction conditions for affording aldol **228** (Scheme 3.20). Due to the instability of these silyl enol ethers to column chromatography, the ratios of regioisomers were determined by NMR spectroscopic analyses of the crude material.[2]



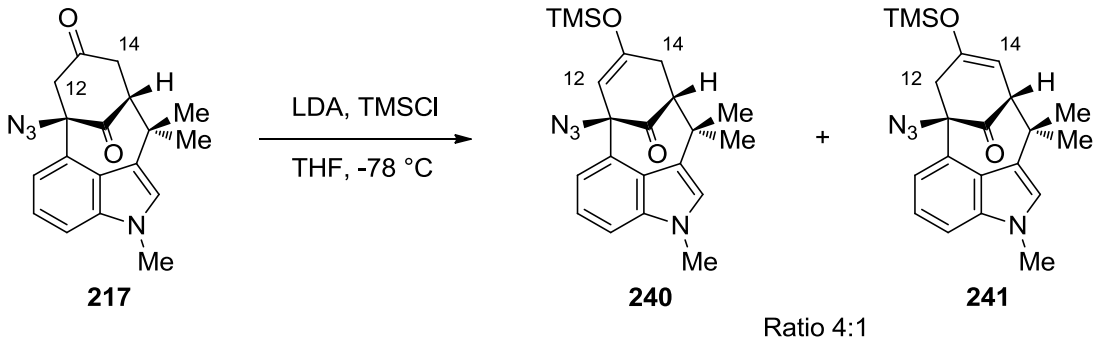
Scheme 3.20

Our group reported that under thermodynamic conditions, azide **217** was mainly deprotonated at the position C_{14}. Thus, the use of TBDMSOTf in the presence of triethylamine at 0 °C afforded a mixture of silyl enol ethers **238** and **239** in a 1:2 ratio (Scheme 3.21).[2]



Scheme 3.21

Under kinetic control, silyl enol ether **240** was formed as the major regioisomer and gratifyingly, subjecting azide **217** to a solution of LDA and TMSCl in THF pre-cooled to -78 °C gave a mixture of enol silanes **240** and **241** in a 4:1 ratio (Scheme 3.22).[2]

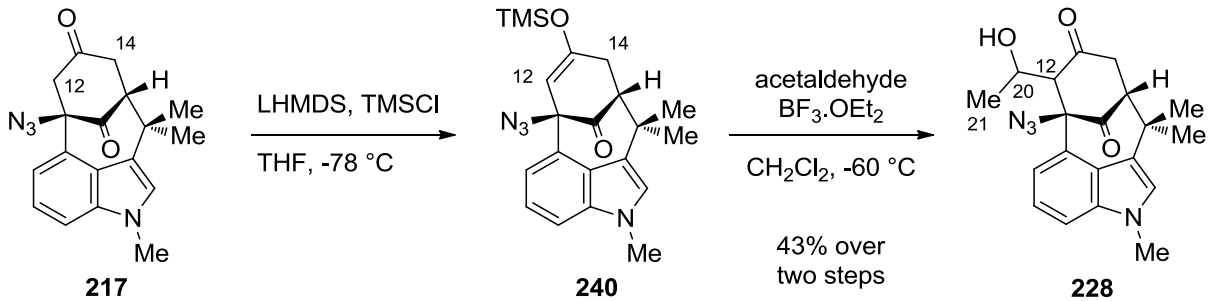


217 **240** **241**

Scheme 3.22

Delighted by these results, our group screened various conditions to define the optimal conditions to access silyl enol ether **240**. Exposure of azide **217** to a solution of LHMDS and TMSCl in THF at -78 °C afforded exclusively enol silane **240** without any trace of the undesired regioisomer **241**.

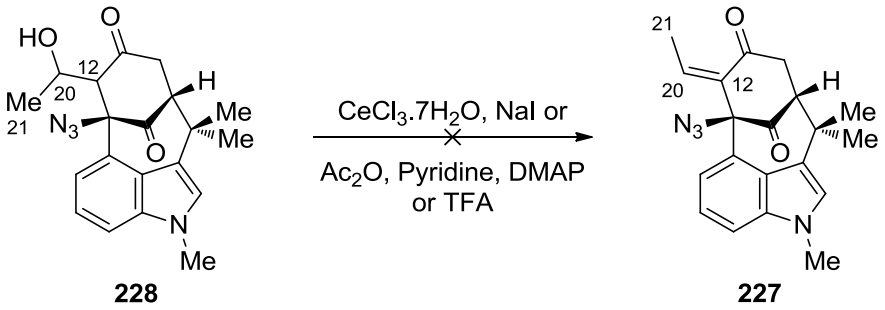
With silyl enol ether **240** in hand, an aldol reaction was performed using acetaldehyde in the presence of $BF_3.OEt_2$ at low temperature. The isolation of aldol product **228** was an issue due to its instability to column chromatography (product was performing a retro-aldol reaction on column chromatography); however, after further investigation, aldol **228** was formed in 43% yield over two steps (Scheme 3.23).



217 **240** **228**

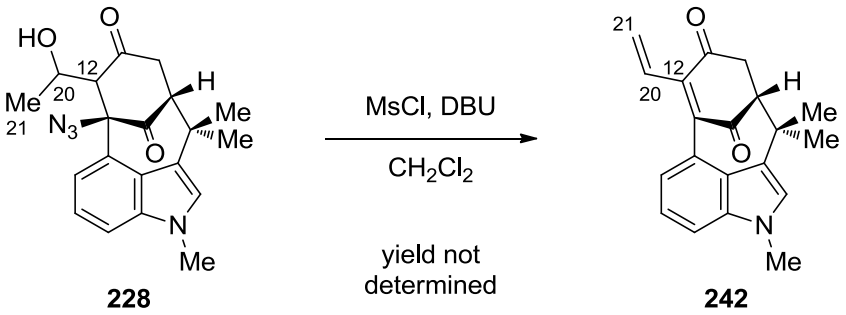
Scheme 3.23

Dehydration of aldol **228** was then required to access enone **227**. Various methods were screened by our group, including treatment with $CeCl_3.7H_2O$ in the presence of sodium iodide,[6] reaction of acetic anhydride using pyridine/DMAP as bases,[7] or addition of TFA[8]. However, no trace of the desired enone **227** was observed (Scheme 3.24).[2]



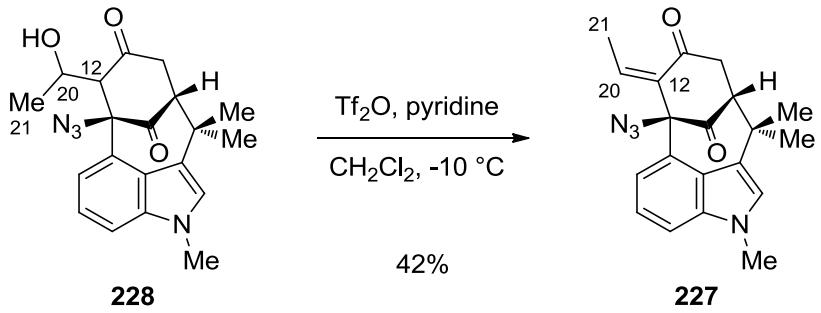
Scheme 3.24

An alternative method using mesyl chloride in the presence of DBU as base afforded an unexpected product that appeared to have lost the azide functionality at the branching position, as well as being dehydrated at the position C_{20}-C_{21}.[2,9] Based on the data collected, our group suggested a structure for this unexpected intermediate **242** (Scheme 3.25).[2]



Scheme 3.25

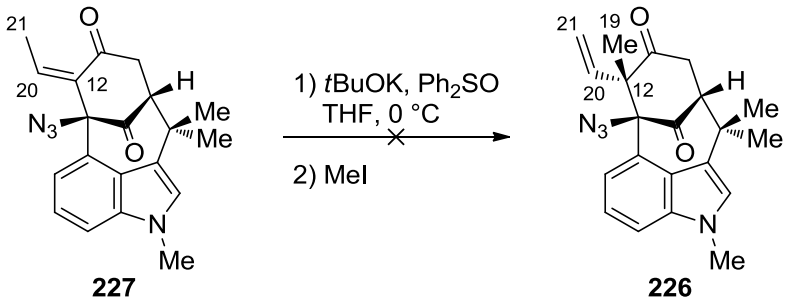
Finally, subsequent treatment of aldol **228** with triflic anhydride in the presence of pyridine yielded enone **227** in 42% yield (Scheme 3.26).[2,10]



Scheme 3.26

Despite a moderate yield for the preparation of enone **227**, our group could now attempt to access advanced intermediate **226**. At this stage, our aim was to deprotonate at position C_{21} of enone **227** and insert a methyl group at position C_{12} *via* an external quench with an excess of methyl iodide.

Our group decided to attempt a two-step strategy following Smith's conditions.[11] Potassium *tert*-butoxide was added to a solution of substrate **227** in the presence of diphenyl sulfoxide, followed by the addition of methyl iodide. Unfortunately, no trace of a product possessing a methyl group at position C_{12} was observed (Scheme 3.27).



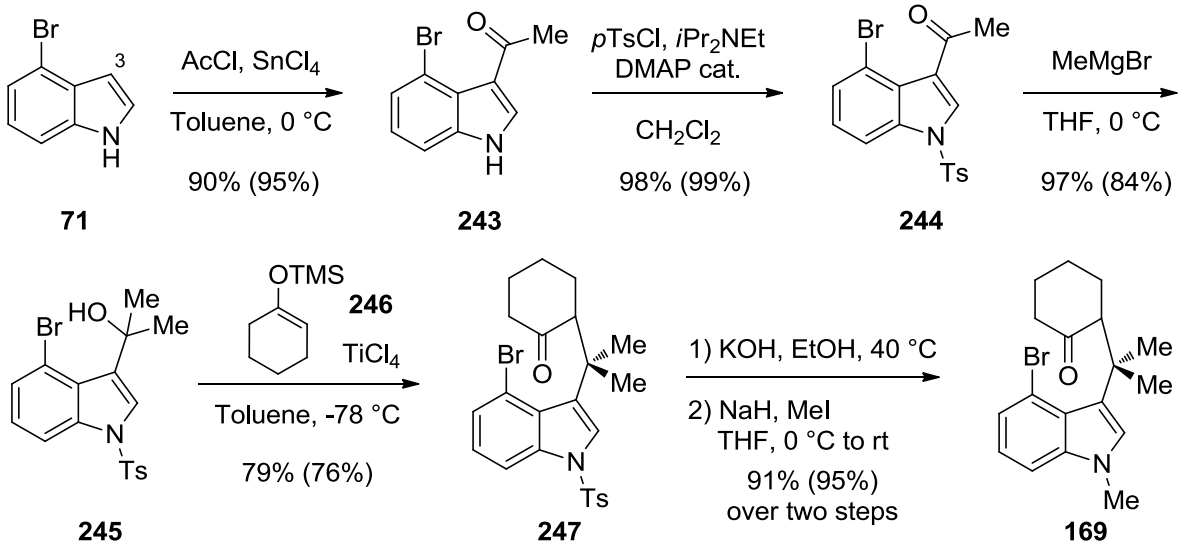
Scheme 3.27

Our group reported the formation of a new product, which possessed similar ^{1}H NMR spectroscopic data in the vinylic region to alkene **242**; however, this product was not fully characterised. The elimination of the azide functionality had once again impeded the synthesis.

Despite the promising results obtained by previous members of our group, the challenging sequence presented a number of drawbacks, including low yields and a lack of reproducibility, which prevented it from becoming a suitable sequence to approach welwistatin **7**. As a result, our first goal became to improve the proposed synthetic route to azide **217** (particularly regarding the preparation of enone **214** from tetracyclic structure **170**). With azide **217** in hand, we would turn our attention towards the functionalisation of the C_{12} position. Diverse approaches were envisaged to insert the required motif at the position C_{12} while preventing the elimination of the bridgehead functionality.

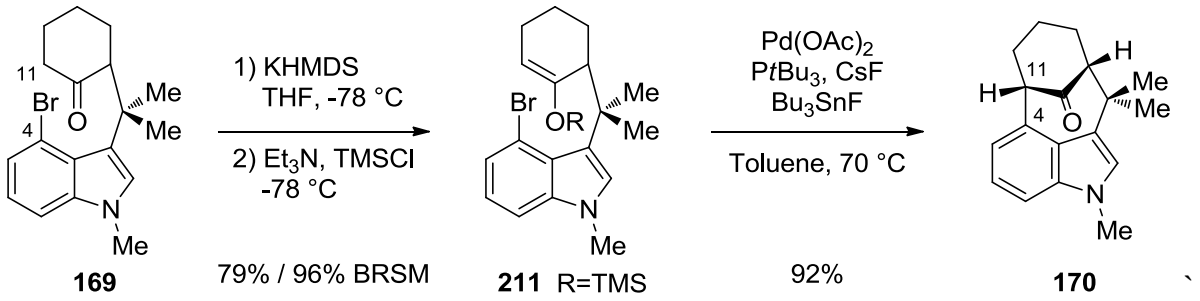
3.3 Our work towards the improvement of the sequence developed by our group

Our work started with the preparation of tetracycle **170** using the route developed by our group. Taking inspiration from Rawal's work, functionalised cyclohexanone **169**, possessing the desired *gem*-dimethyl fragment in the required position, was synthesised from commercially available 4-bromoindole (**71**). Tertiary alcohol **245** was obtained *via* a three-step sequence involving acylation of carbon C_3, tosyl protection and a Grignard addition. Freshly prepared silyl enol ether **246** was then coupled to tertiary alcohol **245**, in the presence of a Lewis acid, presumably through an S_N1 process to form cyclohexanone adduct **247** in 79% yield. Key intermediate **169** was finally accessed from the tosylated derivative **247** in 91% yield after a *N*-deprotection/*N*-methylation sequence (Scheme 3.28). We reproduced this sequence in similar yields compared to the one reported by Rawal and co-workers (displayed in brackets).[1]



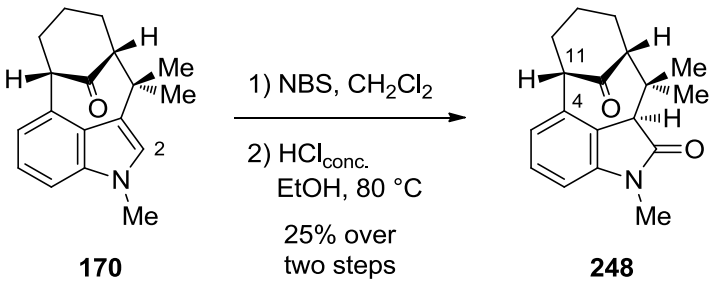
Scheme 3.28

In our hands, silyl enol ether **211** was obtained in 79% yield along with the starting ketone **169** (96% yield BRSM). Following this procedure, we observed that performing the arylation on gramme scale increased the yield of this reaction considerably and tetracycle **170** was obtained in a reproducible 92% yield (Scheme 3.29).



Scheme 3.29

At this stage, the preparation of oxindole **248** from tetracyclic **170** was performed following the two-step procedure developed by Garg and co-workers.[12] Bromination of the C_2 position of bicyclic indole **170** was achieved by addition of NBS, prior to acid-promoted hydrolysis in refluxing ethanol (Scheme 3.30).



170 **248**

Scheme 3.30

The reaction was carried out on a small scale and was not optimised. Despite the low yield obtained (25% over two steps), we were pleased to successfully introduce the oxindole feature present on welwistatin **7** onto tetracyclic skeleton **170**.

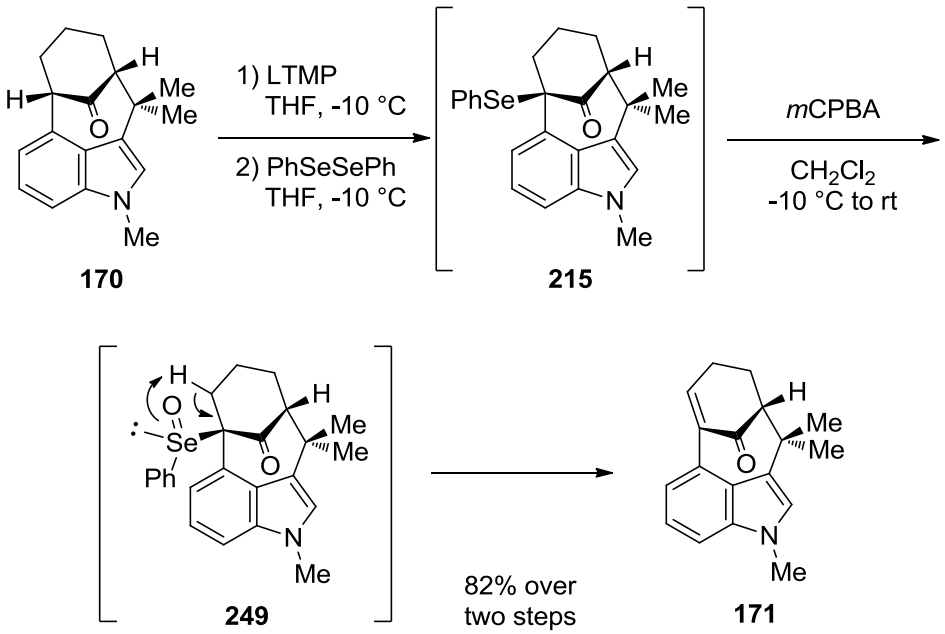
3.3.1 Improvement of the synthesis of enone 214 and preparation of azide 217

Inspired by the work developed by our group and convinced of the high importance of enone **214** in our strategy, we decided to undertake the synthetic route to enone **214** using the conditions previously described.[2] Unfortunately, this synthetic strategy exhibited some reproducibility issues combined with a very low-yielding process and investigations to overcome these difficulties were required.

Our attention turned towards the preparation of bridgehead alkene **171**, obtained by a two-step sequence involving regioselective selenylation of the bridgehead position, C_{11}, followed by oxidation of the selenide adduct. We were particularly concerned that, despite a high conversion observed for each step of this process, alkene **171** was isolated in poor yield (up to 27% yield).

Bridgehead selenide **215** was isolated along with starting ketone **170** (up to 35% yield). The recovery of tetracycle **170** was attributed to the high sensitivity of bridgehead selenide **215** to column chromatography. We assumed that the acidity of the silica could protonate the bridged ketone of selenide **215** and therefore decided to perform the oxidative elimination of the selenide group on unpurified **215**.

Moreover, oxidation of selenide **215** in the presence of *m*CPBA seemed to occur rapidly at low temperature (-10 °C) towards intermediate **249**, as total consumption of starting material **215** was observed by TLC in less than 30 min. However, at this stage only 65% of alkene **171** was isolated. As a result, we believed that the slow elimination process of intermediate **249** to the desired bridgehead alkene **171** was responsible for this moderate yield. A combination of higher temperature (from -10 °C to rt) and longer reaction time (from 30 min to 16 h) was required to complete the conversion of selenide **215** to bridging α,β-unsaturated carbonyl **171** (Scheme 3.31).

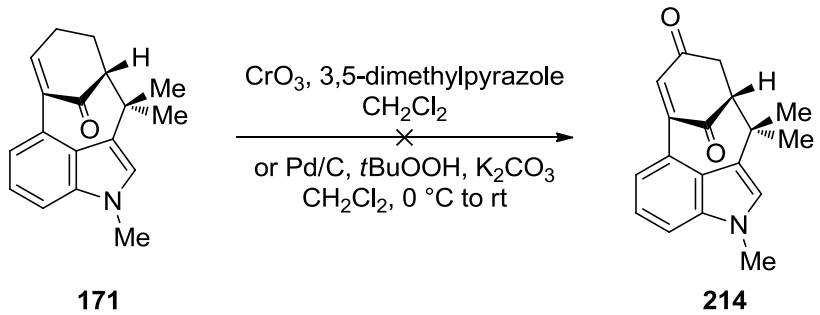


Scheme 3.31

We were particularly delighted that subjecting tetracyclic skeleton **170** to these combined modified procedures gave bridgehead alkene **171** in a reproducible 82% yield over two steps.

With bridged alkene **171** in hand, we turned our attention towards the preparation of enone **214**. Our group proposed that oxidation of alkene **171** by the addition of selenium dioxide in dioxane at 70 °C would give access to allylic alcohol **216**, which could be turned into the corresponding enone **214** using standard Dess-Martin oxidation conditions. Unfortunately, the yields of these two steps were too low to obtain sufficient amount of enone **214** and optimisation of the oxidation was essential to pursue the synthesis towards welwistatin **7**.

Direct oxidations of alkenes into corresponding enones have been extensively studies and many methods have been described. Unfortunately, treatment of alkene **171** with either CrO_3 with 3,5-dimethylpyrazole,[13] or Pd/C in the presence of *tert*-butyl hydroperoxide (*t*BuOOH) under basic conditions,[14] did not afford the desired enone **214** (Scheme 3.32). In both cases, only degradation was observed.

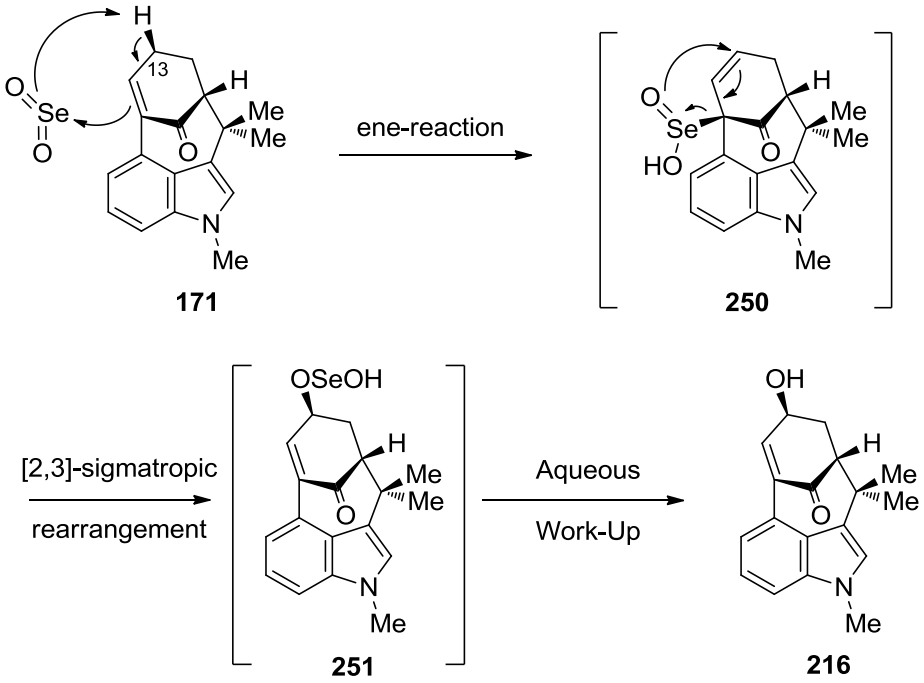


171 **214**

Scheme 3.32

Unable to synthesise enone **214** in one step from alkene **171**, we changed our focus to improving the sequence developed by our group to access enone **214** *via* allylic alcohol **216**.[2]

Despite total consumption of starting allylic methylene **171** during the oxidation process, we were particularly concerned by a low yield of isolated alcohol **216**. The first step of the oxidative mechanism is the formation of the allylic seleninic acid intermediate **250** *via* an ene reaction. The ene reaction proceeds *via* a pericyclic reaction initiated by activation of the C_{13}-H bond. A [2,3]-sigmatropic rearrangement then regenerates the double bond and affords allylic alcohol **216** after hydrolysis of the Se(II) ester **251** (Scheme 3.33).[2]

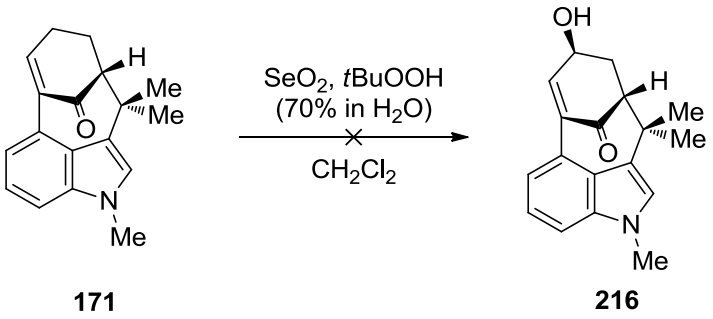


Scheme 3.33

The absence of starting alkene **171** led us to consider that the formation of allylic seleninic acid **250** was proceeding smoothly. At this stage, two hypotheses could be envisaged to explain the low yield of this oxidative procedure: The particular configuration of intermediate **250** forced the rearrangement to occur on the *exo*-face of the molecule that represented a spatially challenging transformation, or alternatively, the selenium could adhere to the

molecule despite the aqueous work-up. A combination of these two hypotheses led us to consider alternative methods for this oxidation.

The formation of allylic alcohols from the corresponding alkenes has been widely reported in the literature and taking inspiration from the work of Sharpless,[15] we subjected alkene **171** to a sub-stoichiometric catalytic amount of SeO_2 in the presence of *t*BuOOH as the co-oxidant. Unfortunately, no trace of the desired allylic alcohol **216** was observed (Scheme 3.34).



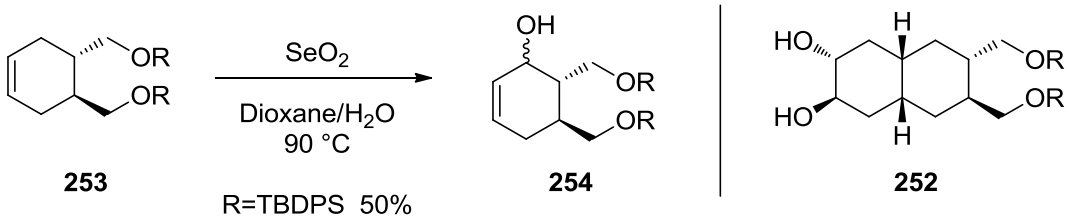
171 **216**

Scheme 3.34

Particularly concerned that alternative methods did not show any trace of the desired enone **214** or allylic alcohol **216**, we decided to optimise the conditions developed by our group by varying the physical parameters such as the temperature, length of reaction and work-up conditions.

Initially, we decided to investigate the work-up conditions. Concerned that removing the selenium adduct could represent an issue in this procedure, we attempted to avoid any aqueous work-up. After removal of the solvent, the residue was purified by column chromatography. However, under these conditions, the yield was reduced to 16% yield (33% yield BRSM).

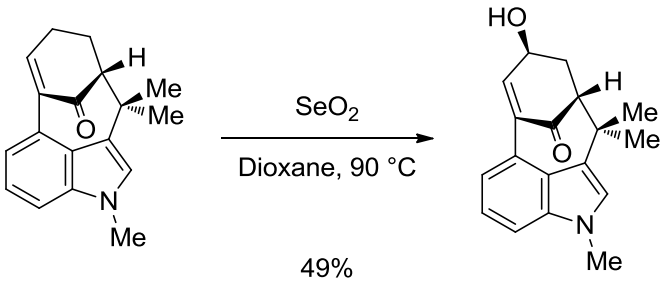
In 2007, Koert's group reported the synthesis of tetrasubstituted decalin **252** *via* an allylic oxidation performed with selenium dioxide in dioxane and water at 90 °C (Scheme 3.35).[16]



253 **254** **252**

Scheme 3.35

Even though the yield for the oxidation of olefin **253** to corresponding allylic alcohol **254** was moderate, the temperature was considered as an important parameter for our reaction.[16] Increasing the temperature of the reaction from 70 °C to 90 °C increased the rate of the reaction. TLC indicated that after 3.5 h, the ratio of starting alkene **171** to allylic alcohol **216** was approximately 1:1. After another 3.5 h, only traces of starting alkene **171** were observed and the reaction was stopped. After neutralising the reaction using the usual aqueous work-up (see page 197), the product was purified to afford allylic alcohol **216** with an average yield of 49% (from 42% to 63%) (Scheme 3.36).



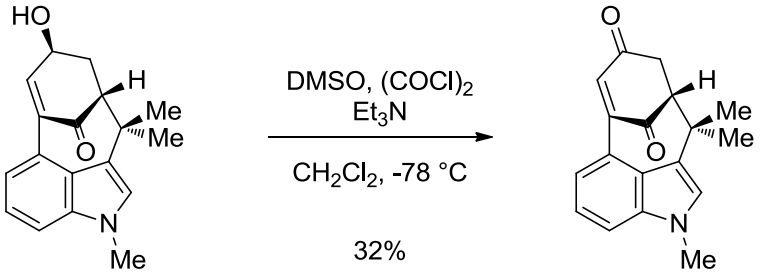
171 49% (42-63%) **216**

Scheme 3.36

Although this yield was not ideal, we decided to turn our attention towards the second oxidation, performed by our group *via* a Dess-Martin oxidation. Even though diverse methods

could be envisaged, the Swern and the Dess-Martin oxidations are the most commonly employed and often the mildest and most efficient strategies.

Allylic alcohol **216** was submitted to Swern oxidation conditions. After one hour, two products were obtained. The desired enone **214** was isolated in 32% yield along with an unidentified compound (Scheme 3.37).



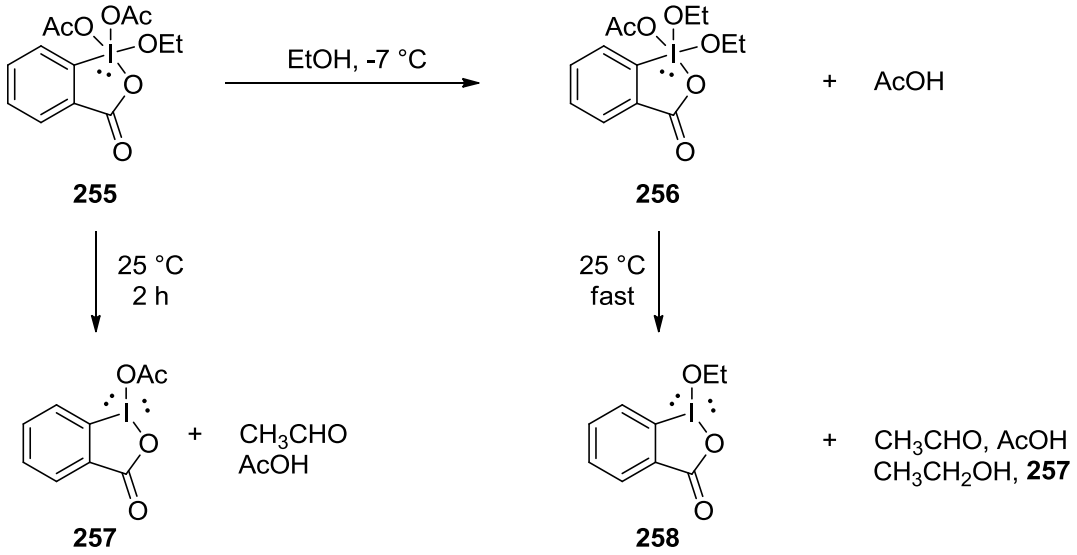
216 **214**

Scheme 3.37

In 1994, Schreiber and Meyer reported an intriguing method to accelerate the Dess-Martin oxidation.[17] Despite the advantages offered by Dess-Martin periodinane (DMP) (including milder reaction conditions and tolerance to sensitive functional groups), Schreiber described the reagent as 'capricious'. Following some observations made by the group of Ireland on the quality of the DMP batch, Schreiber and co-workers studied the influence of the purity of DMP for the oxidation.[17,18]

In 1983, Dess and Martin noticed that the addition of an extra equivalent of ethanol considerably enhanced the rate of the oxidative reaction.[19] This could be explained by the acceleration of the rate of dissociation of the acetate ligand from **256** in the presence of an

alkoxy group due to its higher electron-donating character (compared to the acetate ligand in **255** that required 2 h, see: Scheme 3.38).[19]



Scheme 3.38

Intrigued by this observation, Schreiber investigated the influence of water on the rate of reaction.[17] Water could be introduced in various ways, including addition of an equivalent of water to intermediate **259** or by pre-hydrolysis of DMP prior to the addition of the alcohol (Figure 3.6). However, an alternative strategy based on the dropwise addition of 'wet dichloromethane' was chosen for its excellent reliability. Wet CH_2Cl_2 was prepared by the addition of 1 µL of water per mL of CH_2Cl_2 and this was then added dropwise to the vigorously stirred solution of substrate and DMP in dry dichloromethane.[17]

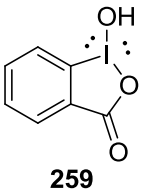
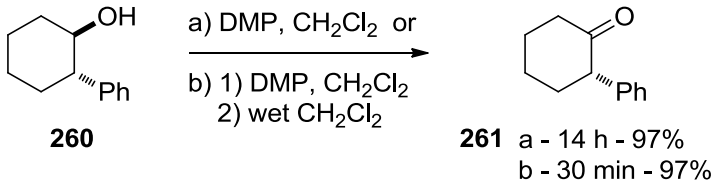


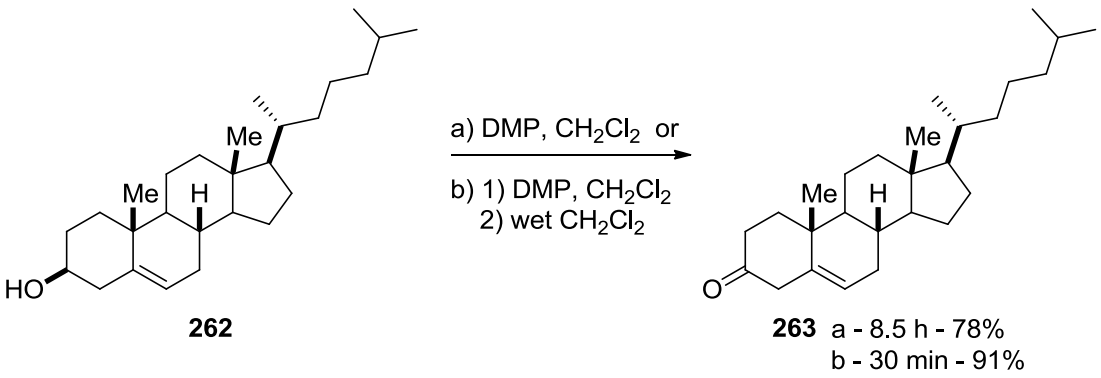
Figure 3.6

The reaction was carried out on a diverse range of substrates and excellent yields were obtained after only 30 min. For example, conversion of alcohol **260** into the corresponding ketone **261** was achieved in 14 h. Performing the same reaction in the presence of wet CH_2Cl_2 decreased the reaction time to 30 minutes (Scheme 3.39).[17]



Scheme 3.39

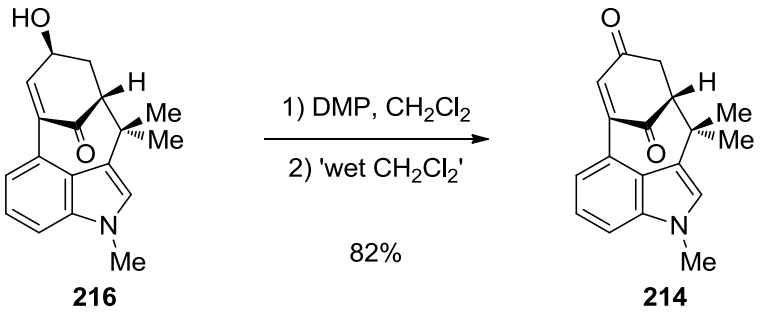
Schreiber also presented the oxidation of cholesterol (**262**). Using the traditional DMP oxidation procedure, 5-cholesten-3-one (**263**) was obtained in 78% yield after 8.5 h. When wet oxidation conditions were employed, 5-cholesten-3-one (**263**) was accessed in 91% after only 30 min (Scheme 3.40).[17]



Scheme 3.40

Concerned that the transformation of alcohol **216** to enone **214** could be facing some issues related to a dissociation process, we chose to undertake the addition of 'wet CH_2Cl_2' during the oxidation. After stirring the substrate and DMP vigorously in CH_2Cl_2 for 20 min, the 'wet

CH_2Cl_2' was added dropwise over 20 min. We were particularly pleased to observe total consumption of starting material by TLC and by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. After purification, enone **214** was isolated in 82% yield (Scheme 3.41).

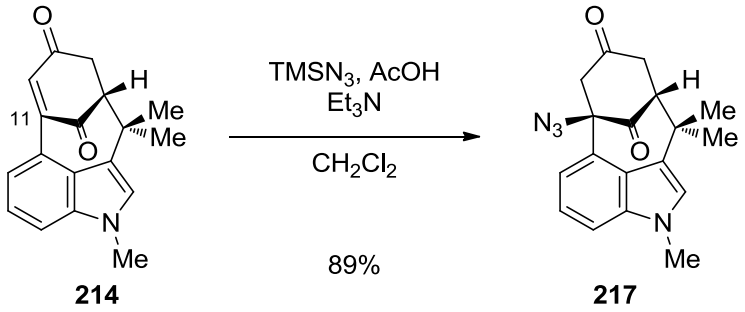


216 **214**

Scheme 3.41

With a robust sequence to access enone **214** in hand, we decided to continue the synthesis towards our target, *N*-methylwelwitindolinone C isothiocyanate **7**. The next objective of this strategy was to introduce a nitrogen atom at the branching position, C_{11}.

In our hands, azide **217** was synthesised using a Michael-type addition on enone **214** as developed by previous members of our group (Scheme 3.42).



214 **217**

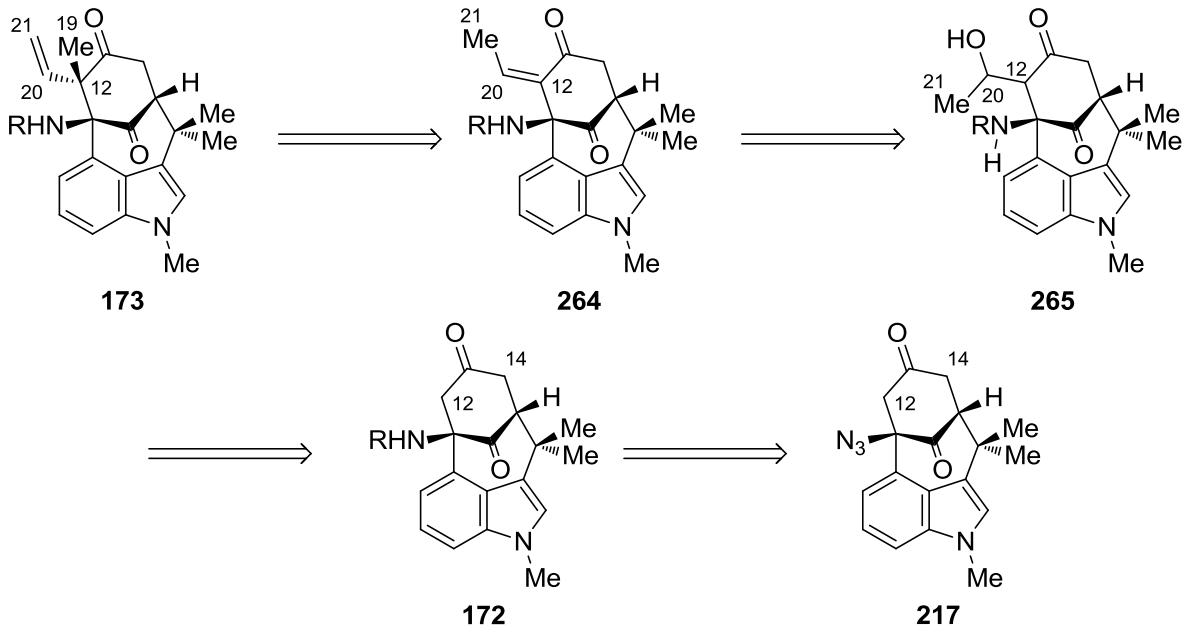
Scheme 3.42

The direct insertion of the nitrogen at the branching position became one of the main characteristics of this sequence. Many groups have shown an interest for this natural target and many tetracyclic structures have been synthesised, however our group was the first to introduce a nitrogen fragment at the bridgehead position without the prior installation of a carbon-containing group.

3.3.2 Introduction of the desired fragment at the C_{12} position

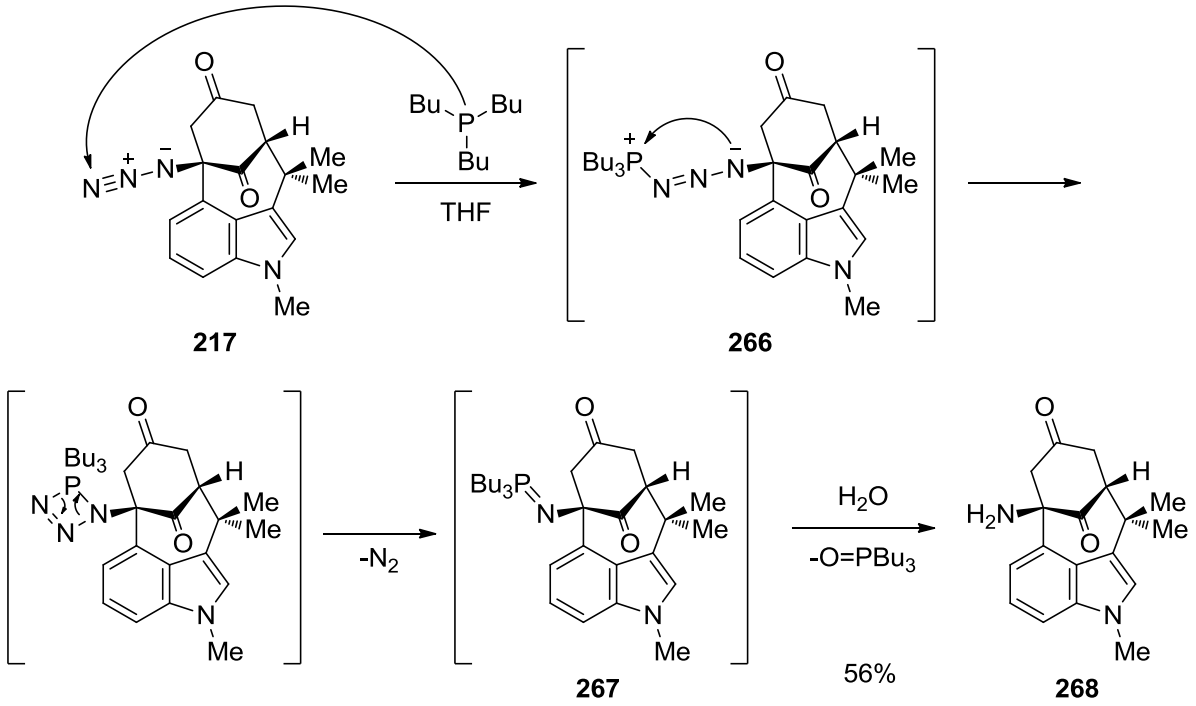
3.3.2.1 Our first investigations: An alternative solution to a labile azide group at the bridgehead position

Aware of the problem of azide elimination previously encountered by our group, we opted to mask the azide functionality as in **172**. An analogous strategy, based on a regioselective aldol reaction, would then build the desired fragment at the C_{12} position present on intermediate **173** (Scheme 3.43).



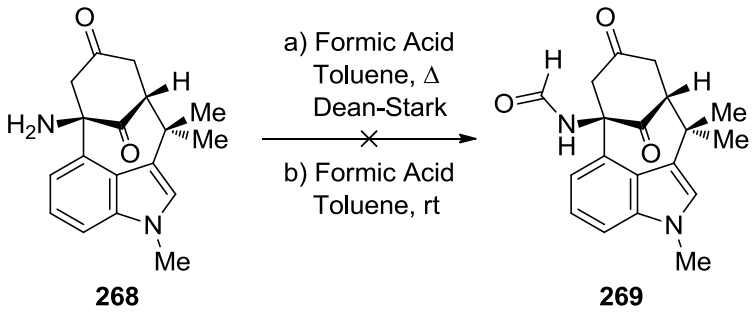
Scheme 3.43

Subsequent reduction of azide **217** into the corresponding amine **268** was achieved *via* a Staudinger reaction using tributylphosphine (PBu_3).[20] Reaction of PBu_3 with the azide generated the phosphazide intermediate **266** which, after elimination of N_2, gave the corresponding iminophosphorane **267**. Due to the higher affinity of the phosphine with oxygen, the presence of water in the reaction allowed the desired amine **268** to be liberated (Scheme 3.44).



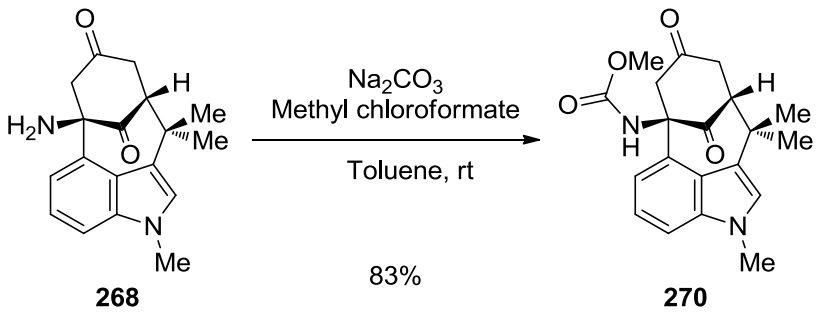
Scheme 3.44

At this stage, we considered protecting amine **268** as the corresponding amide derivative **269**. Unfortunately, the reaction of amine **268** with formic acid in toluene heated at reflux led to degradation, whilst conducting the reaction at room temperature provided the recovery of starting material in 54% yield (Scheme 3.45).[21]



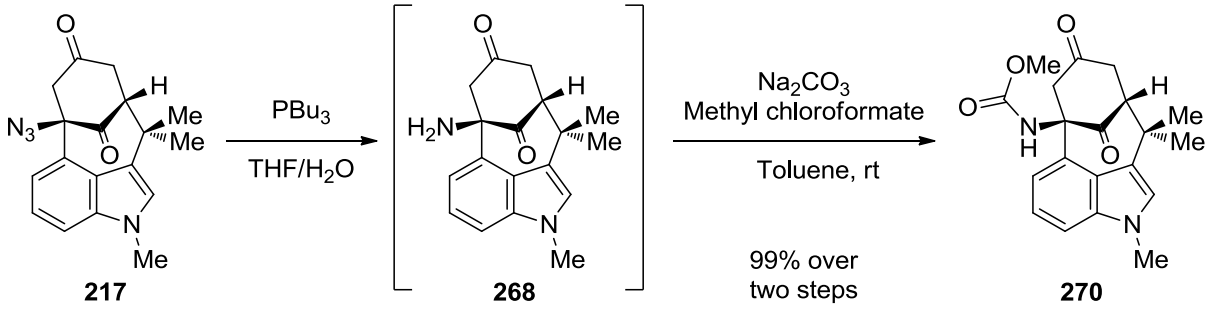
Scheme 3.45

After failing to protect amine **268** as a formamide, we decided to convert amine **268** into the corresponding carbamate derivative **270**. Taking inspiration from the work of Baillie and Leung, we treated amine **268** with methyl chloroformate in the presence of sodium carbonate in toluene at room temperature to access carbamate derivative **270** in 83% yield (Scheme 3.46).[22]



Scheme 3.46

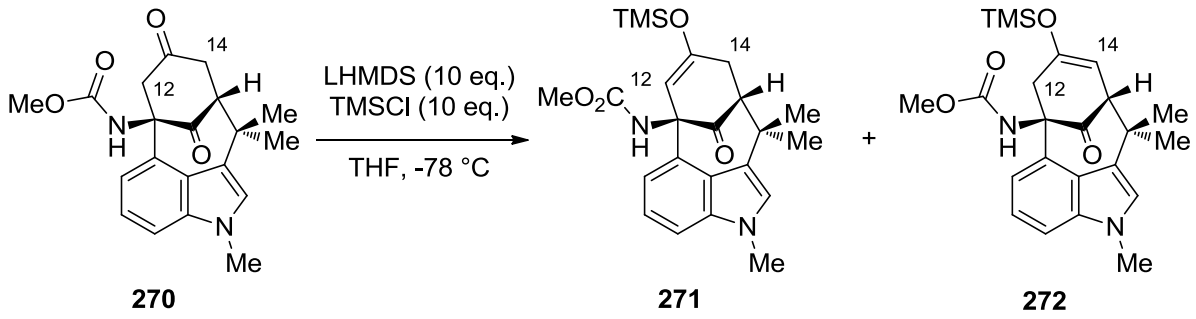
Particularly pleased by the formation of carbamate **270**, we noticed that treatment of crude amine **268** with these conditions afforded carbamate **270** in an excellent 99% yield over the two steps (Scheme 3.47).



Scheme 3.47

At this stage, we aimed to reproduce the regioselective enolate chemistry developed by previous members of our group on carbamate **270** to introduce the desired fragment in the C_{12} position without eliminating the nitrogen bridgehead already in place (see: Scheme 3.43).

The optimised conditions for the preparation of a silyl enol ether developed by our group were applied to our carbamate substrate **270**. A solution of LHMDS was added to a solution of substrate **270** in THF pre-cooled to -78 °C. After 10 min at -78 °C, TMSCl was added dropwise. After 30 min at the same temperature, no trace of starting carbamate was observed. Triethylamine was added prior to the neutralising agent to avoid any formation of acid (Scheme 3.48).

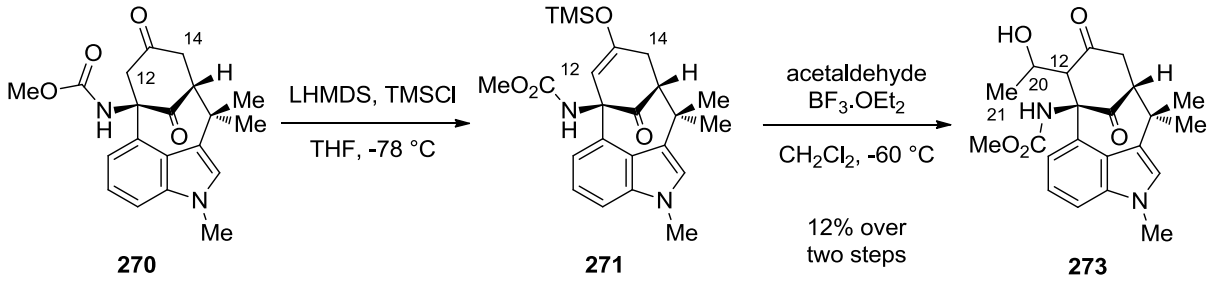


Scheme 3.48

Despite total consumption of starting material prior to the quench, the ^{1}H NMR spectrum of the crude material displayed the presence of two products. The presence of a resonance at 6.90 ppm (*d*, 1H, *J* 4.0) reassured us of the formation of silyl enol ether **271**; however, the ^{1}H NMR spectroscopic data of the crude material also showed the presence of starting material **270**.

A possible interpretation of this phenomenon would be that both silyl enol ethers **271** and **272** were formed but due to the instability of the undesired enol silane **272**, the latter would hydrolyse rapidly into starting ketone **270** (Scheme 3.49).

Despite this issue of regioselectivity, we chose to undertake the aldol reaction on the crude mixture of ketone **270** and enol silane **271** (Scheme 3.49).



270 **271** **273**

Scheme 3.49

After 3.5 h, TLC of the reaction showed total consumption of silyl enol ether **271** and a single new spot appeared along with that of starting ketone **270**. Purification of the crude reaction mixture by column chromatography afforded a new product (2.4 mg).

The ^{1}H NMR spectrum of the new compound showed the presence of rotamers in a ratio 2:1 (due to the introduction of a carbamate group at the bridgehead position). Correlations between the multiplets present at 3.97-4.06 ppm and 3.86-3.94 ppm, corresponding to the

characteristic proton H_{20} for both rotamers, and the protons H_{21} of the methyl group were observed on the ^{1}H-^{1}H COSY spectrum. Unfortunately, the amount of product isolated did not allow us to obtain an useful ^{13}C NMR spectrum (Figure 3.7).

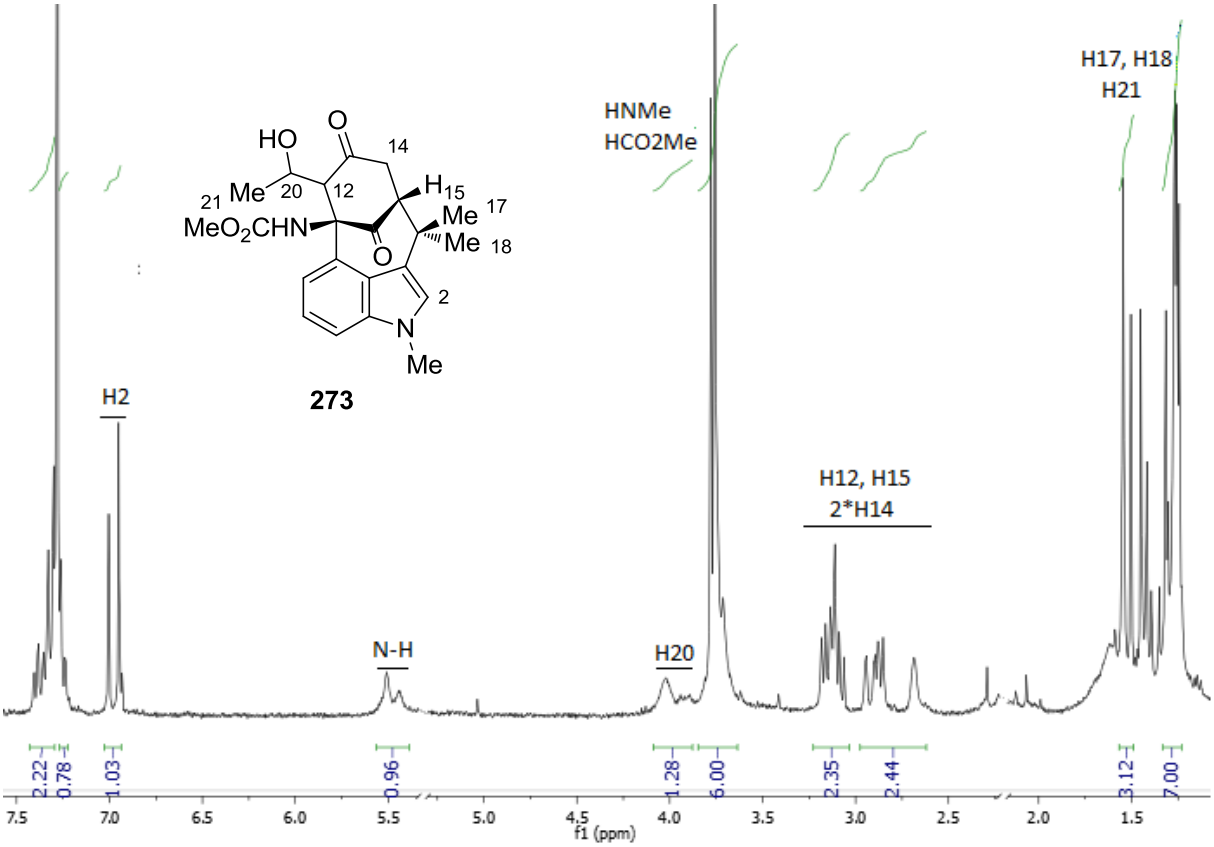
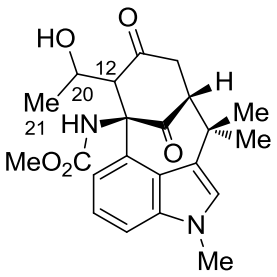


Figure 3.7

The mass spectrum showed a single peak at $[M + Na]^{+} = 421.2$. Finally, the IR spectrum displayed a broad band at 3338 cm^{-1}, associated with an alcohol, as well as three strong carbonyl bands at 1730, 1703 and 1654 cm^{-1}. Combination of these data led us to assume that the reaction afforded the desired aldol **273** (Figure 3.8).

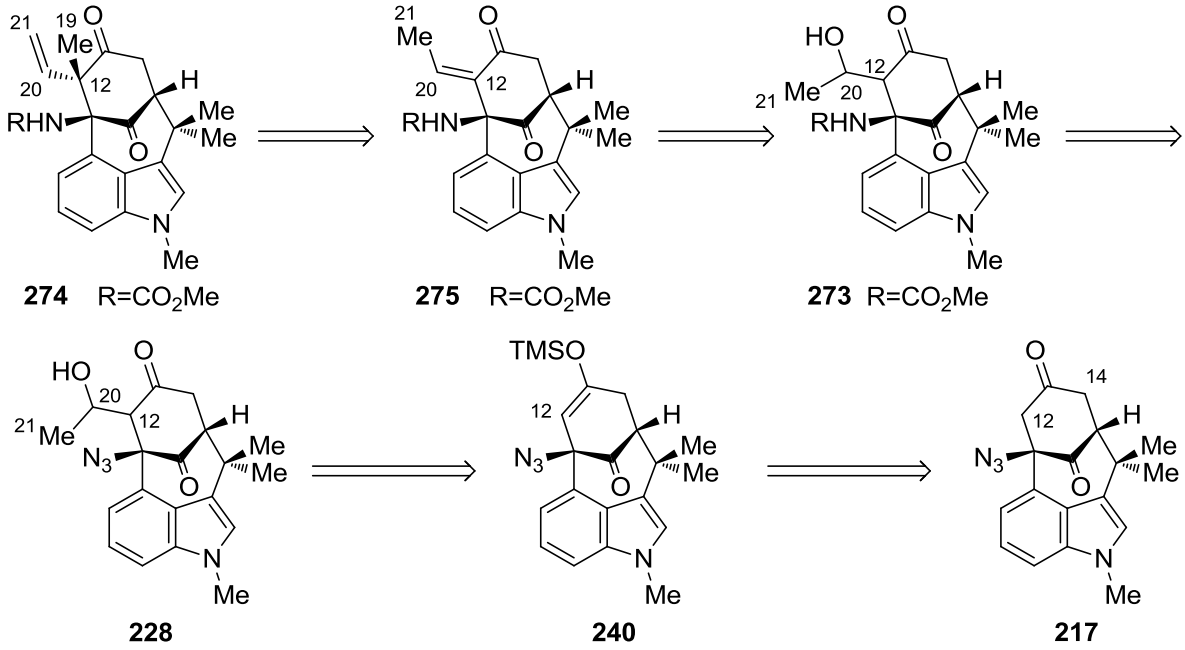


273

Figure 3.8

Despite the successful formation of aldol **273**, the problem of regioselectivity encountered during the formation of the silyl enol ether **271** led us to reconsider this synthetic pathway.

We decided to investigate an alternative synthetic route consisting of the preparation of aldol **228** from azide **217** followed by reduction and protection of the azide bridgehead, before dehydration of the alcohol at position C_{20}. In this way, elimination issues should be avoided (Scheme 3.50).

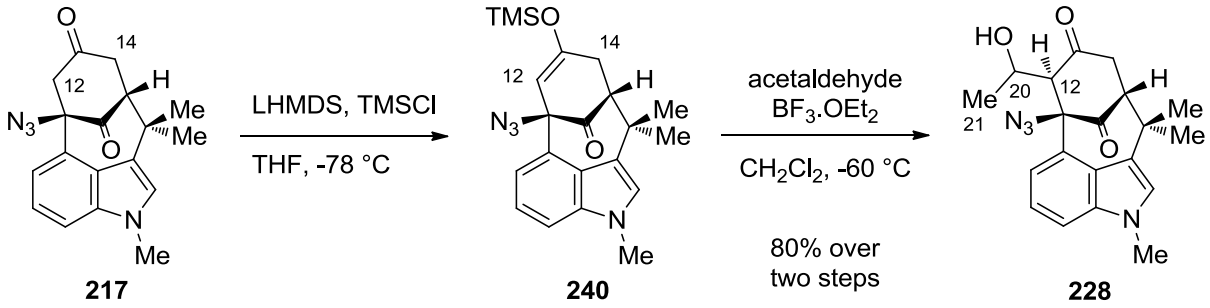


274 R=CO_2Me **275** R=CO_2Me **273** R=CO_2Me

228 **240** **217**

Scheme 3.50

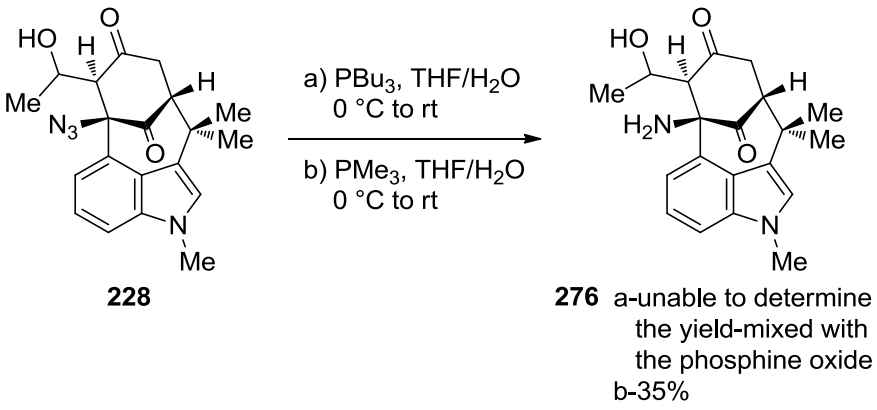
Following the experimental procedure developed by our group, azide **217** was converted into enol silane **240** under kinetic control. Enol silane **240** was achieved by ISQ using LHMDS and TMSCl. Without further purification, the reaction of silyl enol ether **240** with acetaldehyde in the presence of $BF_3.OEt_2$ resulted in aldol **228** in up to 80% yield over two steps (average yield between 50 and 80%) as a single diastereoisomer (Scheme 3.51).



Scheme 3.51

At this stage, azide **228** was subjected to the Staudinger reaction using tributylphosphine (Scheme 3.52). Even though the desired amine **276** was formed, we were unable to separate it from the phosphine oxide formed during the reaction. Various treatments (including column chromatography, aqueous/acid/basic work-up) were attempted to isolate pure amine **276**, unfortunately these efforts proved unsuccessful.

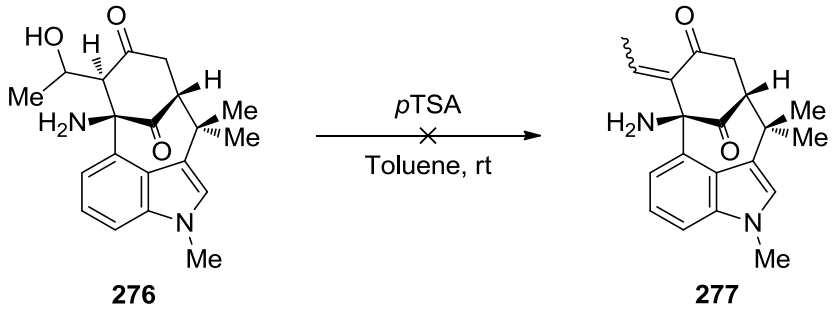
Delighted by the formation of the amine, we considered changing the reducing agent. Despite its high toxicity, trimethylphosphine was chosen, as the trimethylphosphine oxide by-product could be removed by sublimation. Treatment of azide **228** with an excess of PMe_3 in the presence of water afforded bridgehead amine **276** (Scheme 3.52). After removing the remaining traces of phosphine oxide under reduced pressure, the isolated product was obtained in 35% yield (the reaction was not optimised).



228 **276** a-unable to determine the yield-mixed with the phosphine oxide b-35%

Scheme 3.52

Dehydration of amino-alcohol **276** was then attempted using *p*TSA in toluene (Scheme 3.53). After stirring the reaction for 3 h at room temperature and then heating at 65 °C for 2 h, only starting material was recovered from this reaction, in 70% yield. Increasing the temperature to 100 °C led to complete degradation of the starting material.



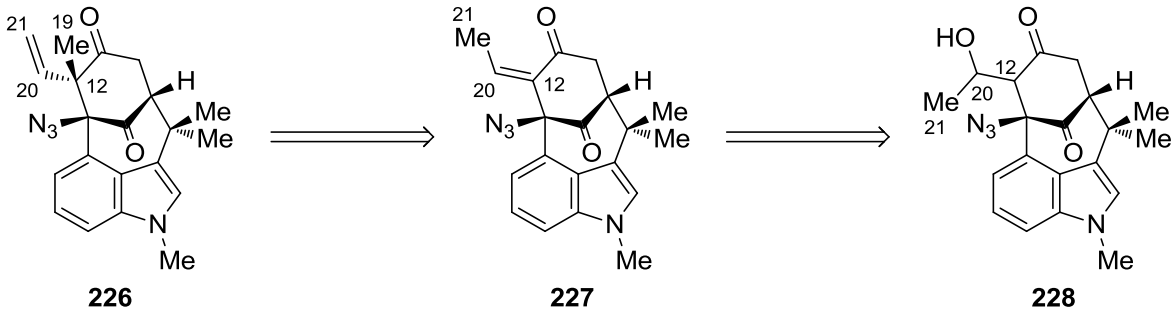
276 **277**

Scheme 3.53

At this point, a combination of lack of material and low-yielding steps led us to investigate the synthetic route developed by previous members of our group with the azide at the bridgehead position C_{11}, this time taking some extra precautions to avoid the elimination.

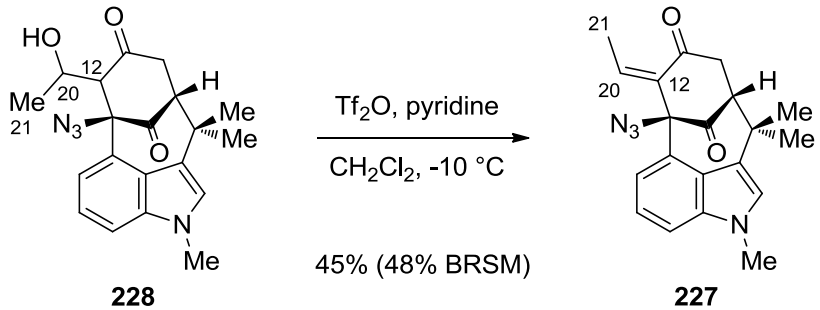
3.3.2.2 Our studies of functionalisation of carbon C_{12} carried out on azide 217

Based on the preliminary studies of our group on aldol **228**, we sought to prepare tetracycle **226** as a key intermediate in our retrosynthetic route (Scheme 3.54).



Scheme 3.54

Despite the low yield reported by previous members of our group, we chose triflic anhydride as a dehydrating agent. Enone **227** was obtained in a 9:1 mixture of double bond isomers in 45% yield (ratio of isomers determined by ^{1}H NMR spectroscopy) (Scheme 3.55).[2]



Scheme 3.55

The configuration of enone **227** was determined by nOe experiments. As shown in Figure 3.9, the proton H_{20} of the *Z* stereoisomer **227a** should show an nOe to aromatic proton H_5, while

no nOe should be observed between protons H_{21} and H_5. For the *E* stereoisomer **227b**, an nOe between the proton H_5 and the protons H_{21} would be expected.

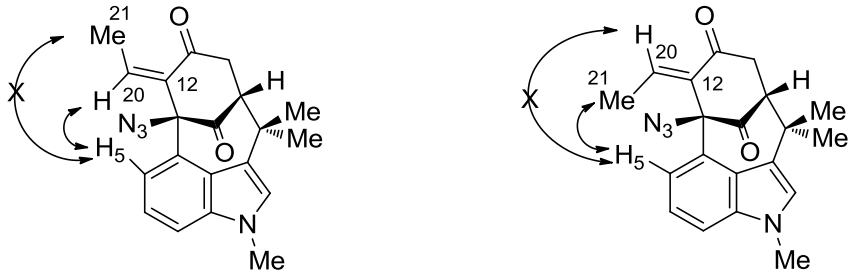


Figure 3.9

In the nOe experiment, irradiation of the doublet present at 2.18 ppm (i.e. major component) revealed an nOe between protons H_5 and H_{20}, indicating the presence of the *Z* stereoisomer **227a** (Figure 3.10).

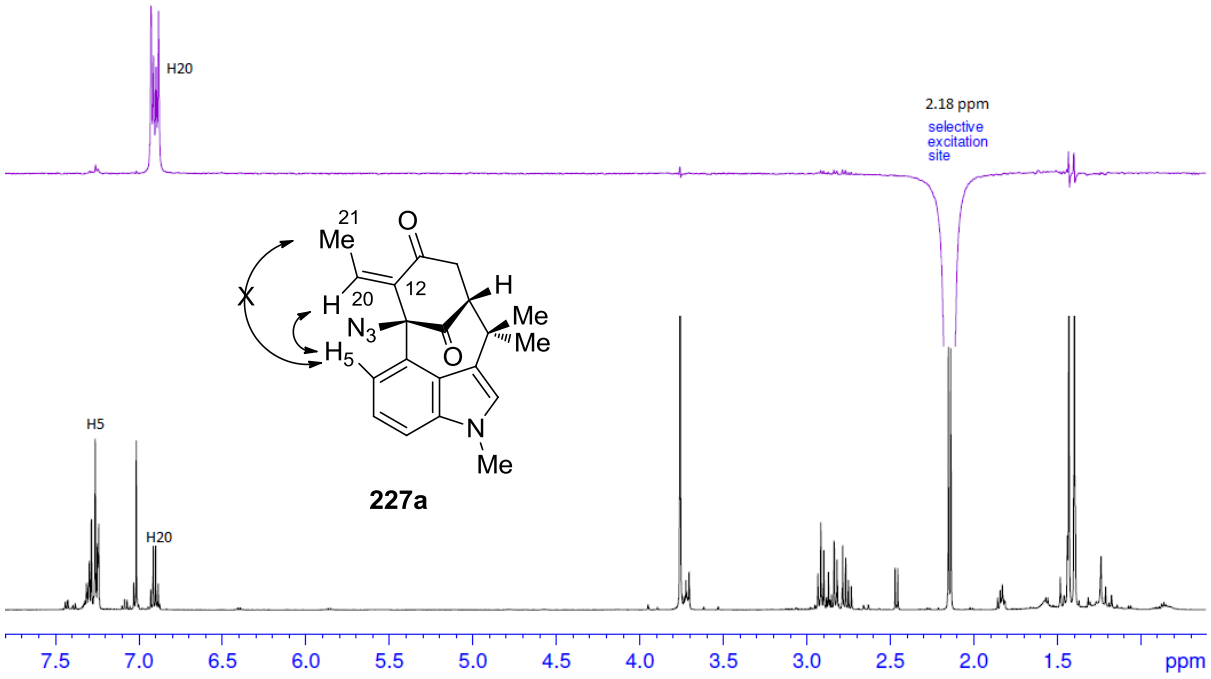


Figure 3.10

Moreover, irradiation of the doublet present at 2.50 ppm (i.e. minor component) confirmed an nOe between protons H_5 and H_{21}, also indicating the presence of the *E* stereoisomer **227b**. This allowed us to conclude that enone **227** was predominantly formed as the *Z* stereoisomer (Figure 3.11).

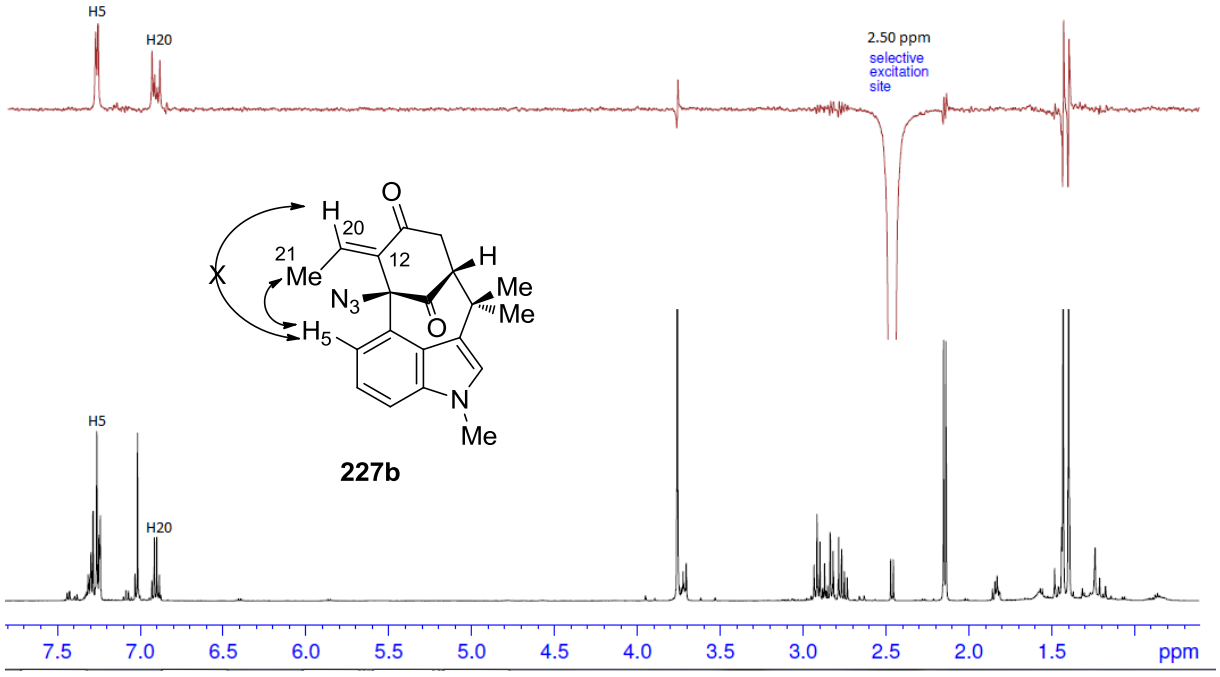
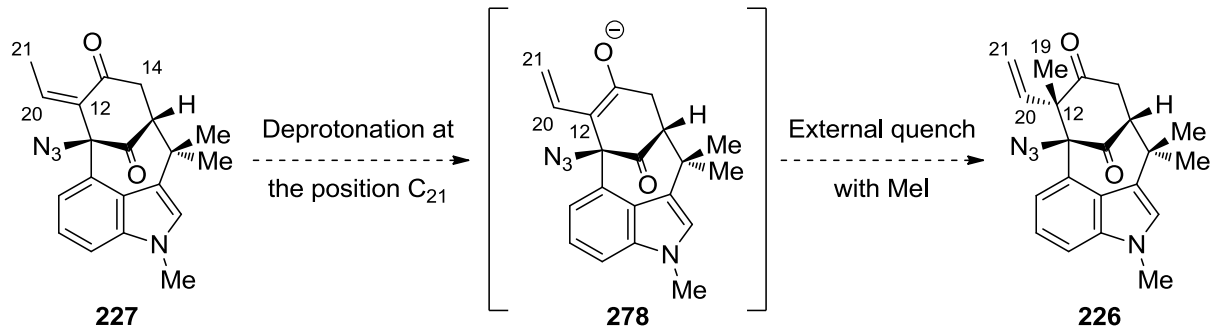


Figure 3.11

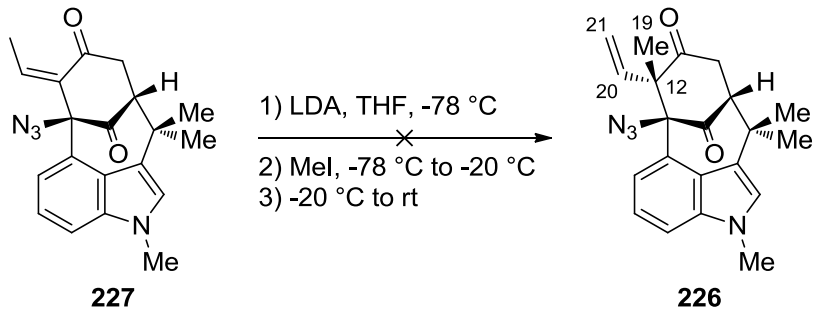
With enone **227** in hand, we aimed to insert a methyl group at position C_{12} in order to access intermediate **226**. Following the work reported by our group, we aimed to deprotonate enone **227** at position C_{21}, resulting in a stabilised extended enolate **278**, that could intercept a methyl group in the α-position C_{12}, provided by the presence of an excess of methyl iodide (Scheme 3.56).



Scheme 3.56

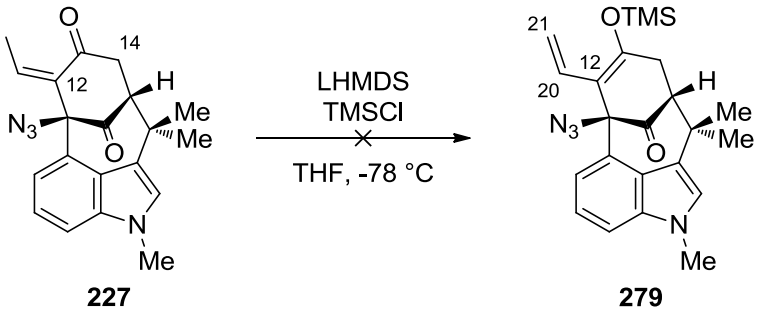
Initially, we were concerned by the regioselectivity of the deprotonation. This could occur at position C_{14} or C_{21}. We postulated that formation of the lithium enolate at position C_{14} would be more challenging due to the spatial orientation of the *exo*-proton H_{14}. Moreover, the stabilisation gained by the formation of an extended enolate should be enhanced by the predominance of the *Z* configuration for enone **227** (transition state stabilised by the obtention of a six-membered ring system),which should favour the formation of enolate **278**.

A solution of enone **227** was added to a solution of LDA at low temperature. After 15 min, a large excess of iodomethane was added at -78 °C. The reaction mixture was slowly warmed up to -20 °C and stirred at this temperature for 20 min. Monitoring the reaction by TLC showed no conversion. Warming the reaction mixture to room temperature only led to degradation and after purification, starting enone **227** was recovered in 56% yield (Scheme 3.57).



Scheme 3.57

Unable to insert the desired fragment by direct methylation, we decided to attempt the formation of the desired silyl enol ether **279** prior to methylation. Substrate **227** was added dropwise to a solution of LHMDS and TMSCl pre-cooled to -78 °C. The reaction mixture was stirred for 1 h at -78 °C whilst being monitored by TLC (Scheme 3.58).



Scheme 3.58

Along with the starting material, a new spot was observed by TLC. As the reaction did not show any further advancement, it was stopped. A new product was isolated along with the starting enone **227** (recovered in 58% yield). The mass spectrum of the new product showed the presence of a peak at $[M + Na]^+ = 443.3$, corresponding to the formation of a silyl enol ether.

The ^{1}H NMR spectrum seemed to show the presence of both *Z*/*E* stereoisomers in a 54:46 ratio. It also displayed the presence of three signals in the vinylic region; H_{14} was present at 5.12 ppm (*d*, 1H, *J* 3.8, H_{14}), while H_{20} was divided into two signals at 6.16 ppm (*q*, 0.55H, *J* 7.4, H_{20}) and 5.96 ppm (*q*, 0.45H, *J* 7.8, H_{20}) that respectively coupled with the signals at 1.89 ppm (*d*, 1.35H, *J* 7.4, H_{21}) and 2.30 ppm (*d*, 1.65H, *J* 7.8, H_{21}) (Figure 3.12).

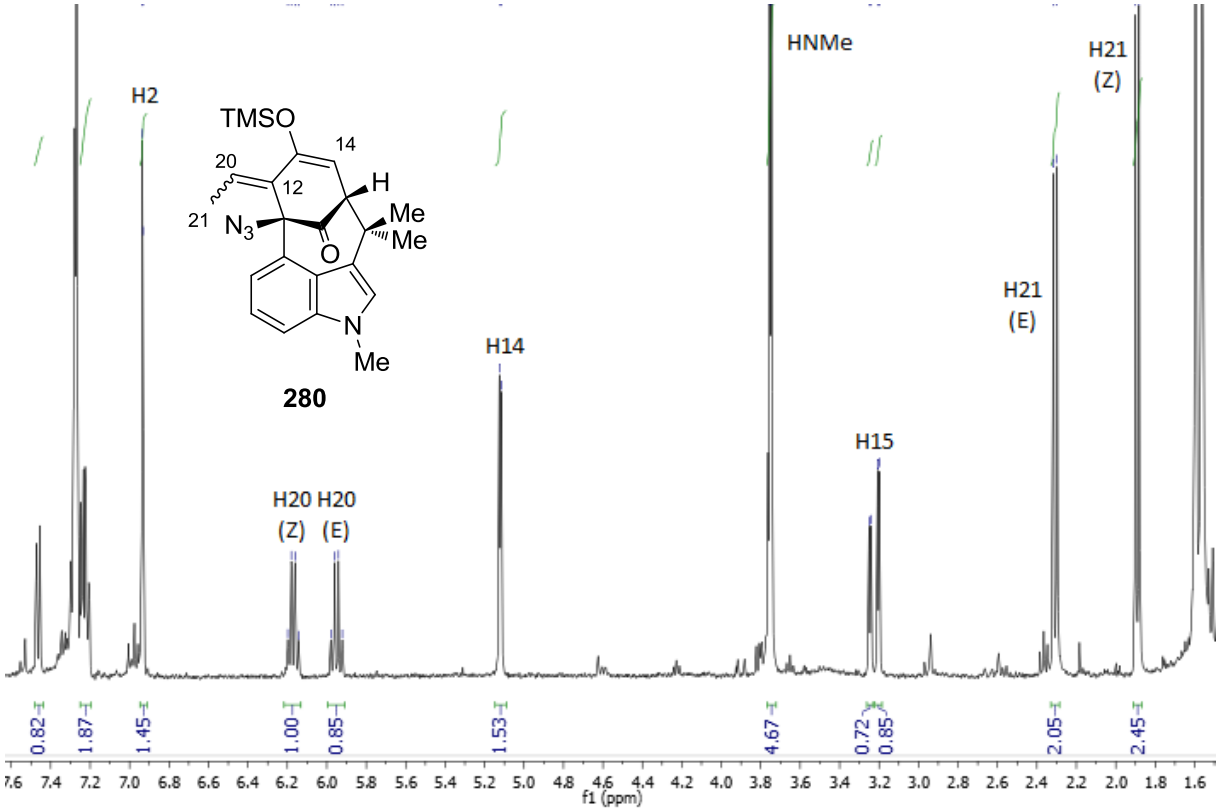


Figure 3.12

These initial observations led us to assume that the undesired silyl enol ether **280** was obtained (Figure 3.13).

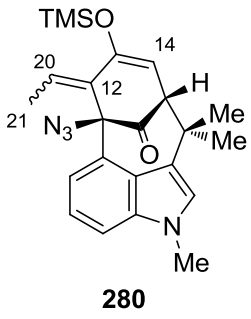
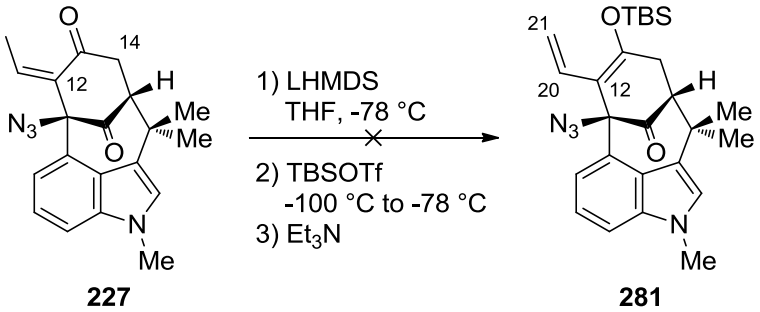


Figure 3.13

Since the use of a labile TMS group was unsuccessful, we decided to investigate the addition of a bulkier group such as a TBS group. Enone substrate **227** was added dropwise to a

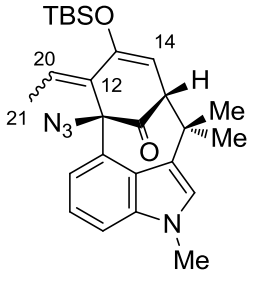
solution of LHMDS pre-cooled to -100 °C. The reaction mixture was stirred for 10 min before TBSOTf was added dropwise at -100 °C (Scheme 3.59). An instantaneous change of colour occurred. The reaction mixture was allowed to warm to -78 °C and at this temperature total consumption of starting material was observed by TLC. The reaction was neutralised by successive addition of triethylamine and a saturated solution of $NaHCO_3$.



227 **281**

Scheme 3.59

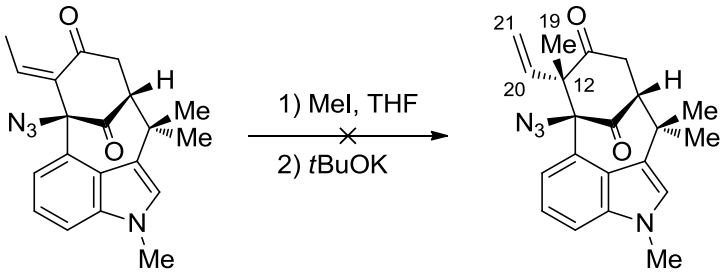
Mass spectrometry of the crude reaction material showed the desired mass for the formation of a silyl enol ether by the presence of a peak at $[M + Na]^+ = 485.2$; however, the presence of similar signals to that of enol silane **280** in the ^1H NMR spectroscopic data led us to conclude the formation of undesired silyl enol ether **282** (Figure 3.14).



282

Figure 3.14

An alternative strategy was envisaged consisting of successive additions of an equivalent of potassium *tert*-butoxide to a mixture of enone **227** and iodomethane in THF at room temperature (Scheme 3.60). After the addition of 3 eq. of *t*BuOK, a new spot appeared by TLC. However, addition of further eq. of *t*BuOK led to degradation, as indicated by TLC, and so the reaction was neutralised. A new product was isolated but unfortunately no trace of desired azide **226** was observed.



227 **226**

Scheme 3.60

The mass spectrum of the one of the compounds isolated showed a single peak at $[M + Na]^+ = 342.1$ corresponding to the loss of azide and the addition of a methyl group. The ^{1}H NMR spectrum exhibited three signals in the vinylic region at 6.66 ppm (*dd*, 1H, *J* 17.6, 11.6, H_{20}), 6.27 ppm (*dd*, 1H, *J* 17.6, 1.8, H_{21}) and 5.54 ppm (*dd*, 1H, *J* 11.6, 1.8, H_{21}) as well as three intriguing signals at 3.22 ppm (*qd*, 1H, *J* 7.5, 0.8, H_{14}), 2.95 ppm (*d*, 1H, *J* 0.8, H_{15}) and 1.38 ppm (*d*, 3H, *J* 7.5, H_{22}) (Figure 3.15).

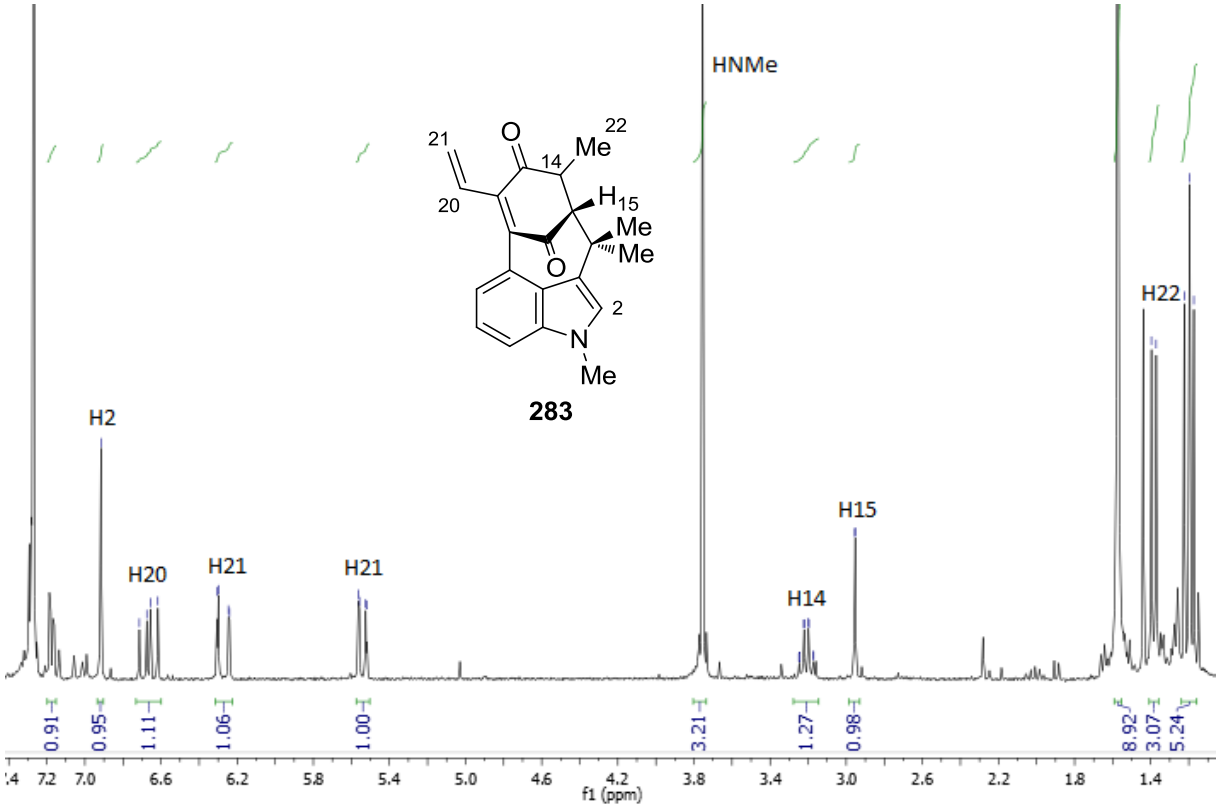


Figure 3.15

A combination of these data led us to propose the following structure for intermediate **283** (Figure 3.16).

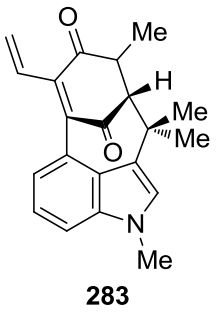
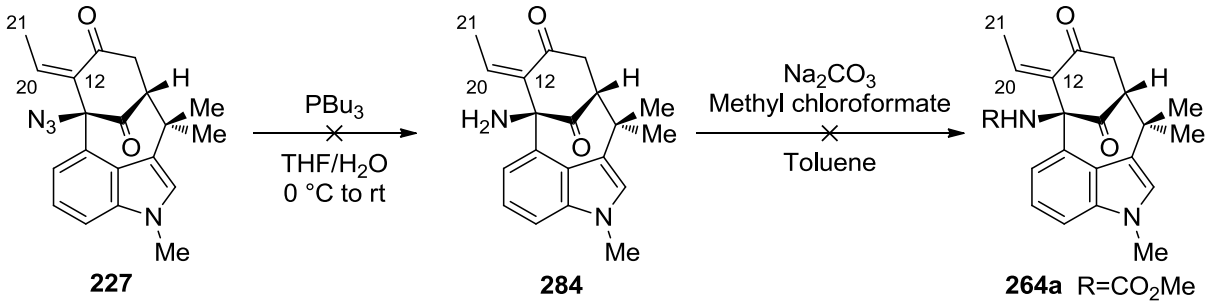


Figure 3.16

Facing some difficulties to install the desired motif at the C_{12} position, we attempted reducing and protecting azide **227** prior to methylation of the intermediate enolate.

A Staudinger reaction was carried out on enone **227** using an excess of tributylphosphine in the presence of water. Reaction of this intermediate with methyl chloroformate in the presence of sodium carbonate was performed in toluene. After 16 h at room temperature, the reaction showed only starting material by TLC. Increasing the temperature to 110 °C led to the completion of the reaction in 3 h (Scheme 3.61).



227 **284** **264a** R=CO_2Me

Scheme 3.61

To our surprise, the ^{1}H NMR spectrum of the isolated product **285** did not show the presence of aliphatic protons between 2.5 ppm and 3.5 ppm and four protons appeared in the vinylic region at the position 6.65 ppm (*dd*, 1H, *J* 17.8, 12.2, H_{20}), 6.07 ppm (*s*, 1H, H_{14}), 5.73 ppm (*dd*, 1H, *J* 12.2, 1.6, H_{21}) and 5.71 ppm (*dd*, 1H, *J* 17.8, 1.6, H_{21}). A variable temperature ^{1}H NMR experiment had been carried out at 0 °C and -20 °C to sharpen the two methyl signals present at 1.80 ppm and 1.30 ppm and characterise of the protons H_{17} and H_{18} (Figure 3.17).

Unconvinced by the presence of two doublets at 6.92 ppm (*d*, 1H, *J* 8.8) and 7.03 ppm (*d*, 1H, *J* 8.8) and a singlet at 1.26 ppm (*s*, 2H), we considered these as an impurity. The ^{1}H-^{1}H COSY NMR spectrum did not show any coupling with any other signals present on the system and this was confirmed by the mass spectrometry. This would require additional purification and analyses to confirm that these signals belonged to an impurity.

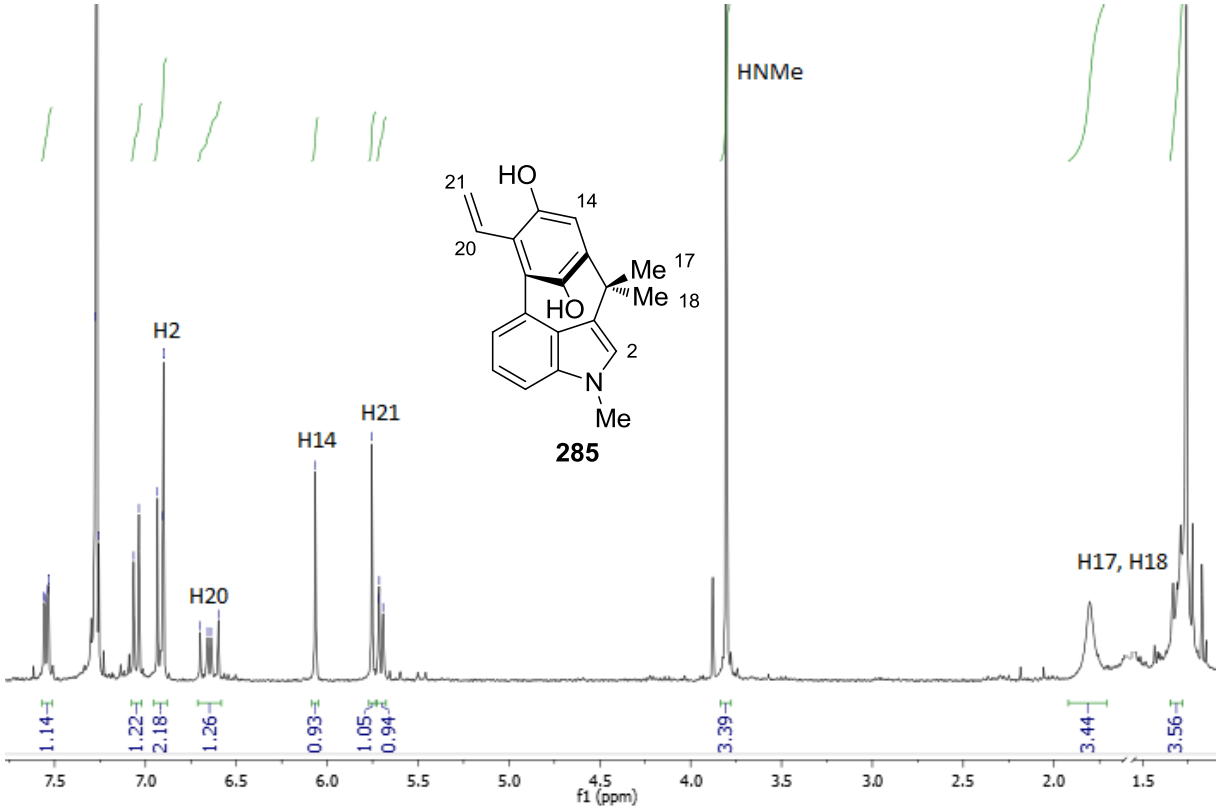


Figure 3.17

Careful studies of our data led us to consider cyclophane **285** as the potential product of the reaction (Figure 3.18). *Meta*-cyclophane **285** would present a remarkable structure as positions C_{11} and C_{15} are connected by only four carbons belonging to an indole.[23]

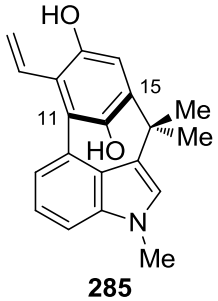
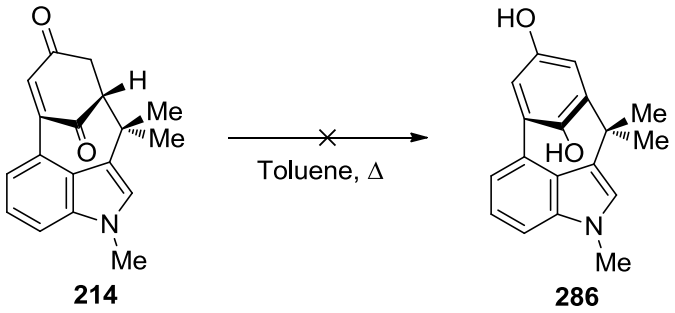


Figure 3.18

At first, the formation of this unusual structure **285** was rationalised by the formation of intermediate **242** by elimination of the azide functionality followed by tautomerisation at high temperature (refluxing toluene was required to overcome the energy barrier).

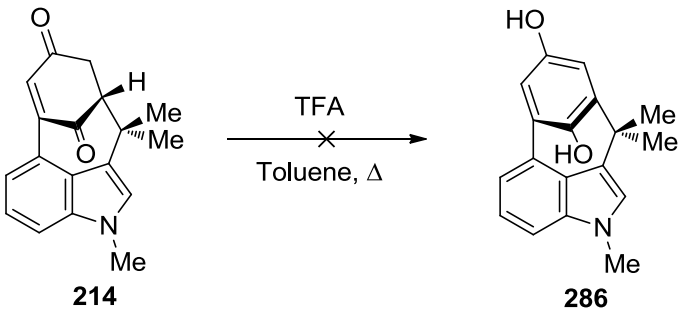
Particularly surprised by the highly provocative structure we attributed to compound **285**, we tried to replicate this phenomenon by heating enone **214** in refluxing toluene. After 30 min at reflux, the reaction did not show any advancement by TLC. At this stage, sodium carbonate was added at room temperature and the reaction was heated again at reflux for another hour, however, only starting material was recovered (Scheme 3.62).



214 **286**

Scheme 3.62

Enone **214** was then heated in refluxing toluene for 1 h prior to the addition of few drops of TFA at room temperature. The reaction was once again heated at reflux and after only 10 min, total consumption of starting material was observed (Scheme 3.63).



214 **286**

Scheme 3.63

After purification, a new product was isolated. The ^{1}H NMR spectrum displayed two new protons at 7.00 ppm (*d*, 1H, *J* 8.5) and 6.68 ppm (*dd*, 1H, *J* 8.5, 3.0). However, the coupling constants obtained for these two protons clearly represented an ortho coupling, thus discrediting the formation of cyclophane **286** (Figure 3.19).

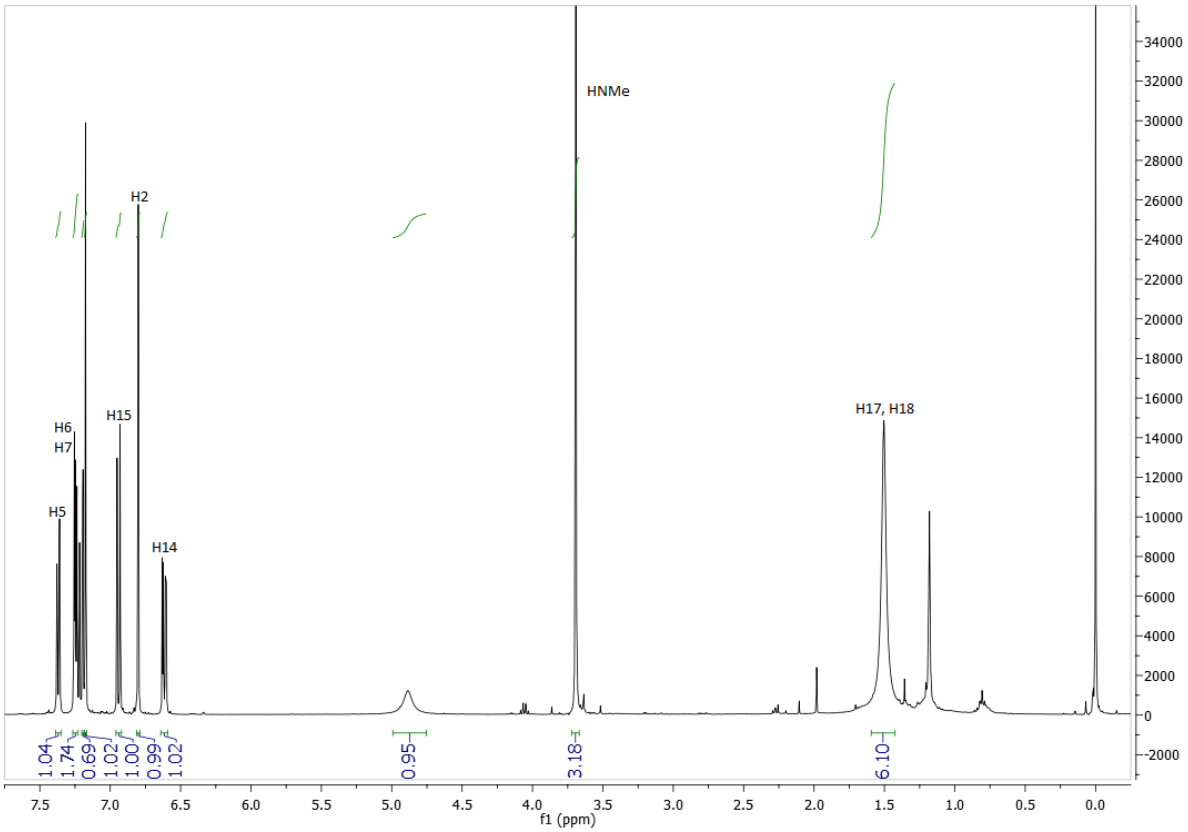
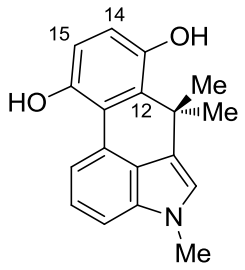


Figure 3.19

The following alternative structure, resulting from a retro-Mannich reaction, was proposed as product of this reaction. However, the data remained inconclusive for this bis-phenol **287** (Figure 3.20)



287

Figure 3.20

Computational studies carried out by Prof. Chris Hayes (at the University of Nottingham) on enone **214** have shown that the formation of cyclophane **287** was particularly unlikely as it would require 36 kcal.mol^{-1} more energy than the starting enone **214** (Figure 3.21).

On the other hand, bis-phenol **287** was found to require 23 kcal.mol^{-1} less energy than the starting enone **214** making this rearrangement more plausible (calculations were made using B3LYP/6-31G* energies on B3LYP/6-31G* optimised structures).

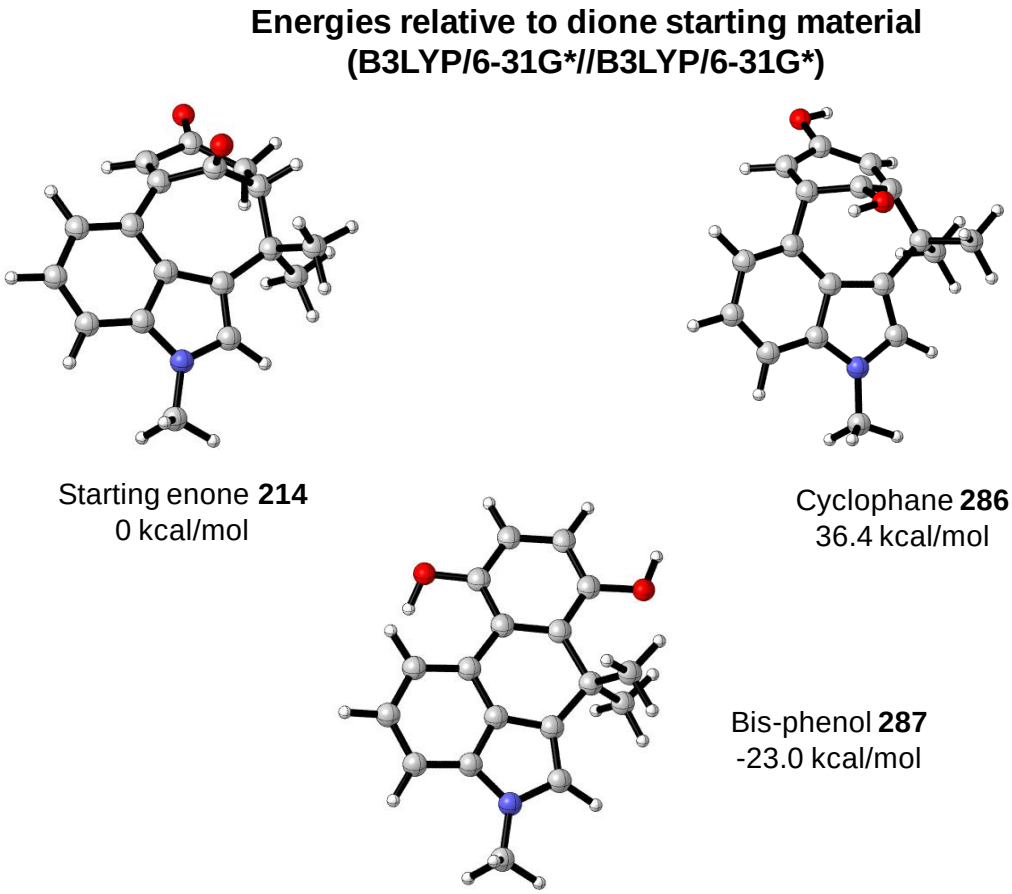
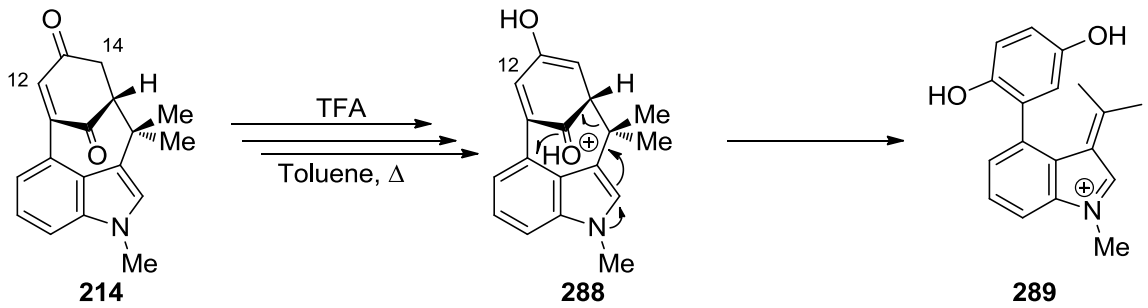


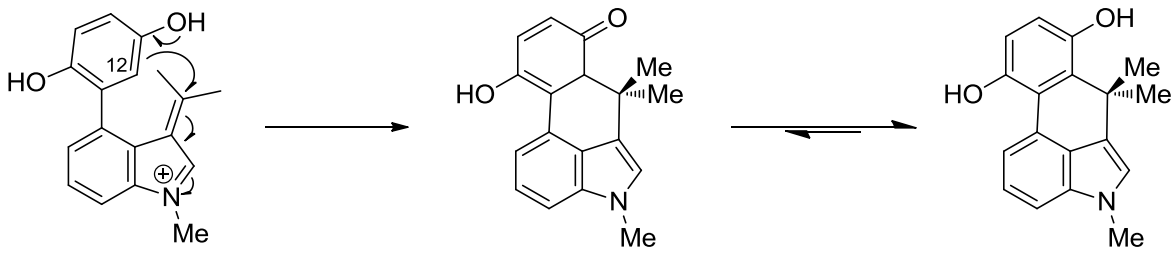
Figure 3.21

The formation of bis-phenol **287** could be rationalised by an acid-promoted retro-Mannich mechanism. An initial protonation of the bridgehead ketone in the presence of a catalytic amount of TFA would afford intermediate **288**. A retro-Mannich reaction would then occur to give indole **289** (Scheme 3.64).



Scheme 3.64

Cyclisation could then be envisaged to afford, after tautomerisation, bis-phenol tetracyclic structure **287** (Scheme 3.65). However, this mechanism could not apply to the reaction of enone **227** due to the presence of the vinyl group at the C_{12} position.



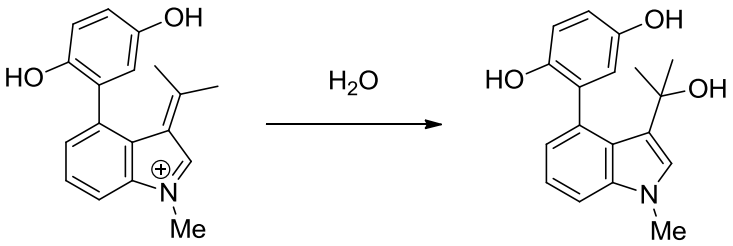
289 **290** **287**

Scheme 3.65

A combination of the data confirmed the bis-phenol **287** as product of the reaction; the mass spectrum showed two peaks at $[M + H]^+$=280.2 and $[M + Na]^+$=302.2 and the IR spectrum displayed a broad stretch at 3355 cm^{-1}.

However, the ^{1}H NMR spectrum showed the presence of a signal at 7.26 ppm (*d*, 1H, *J* 1.5) coupling with the proton at 6.68 ppm (*dd*, 1H, *J* 8.5, 1.5) present on the phenyl ring. This observation led us to reconsider the possible structure of the product, as bis-phenyl **287** did not match the requirements.

An alternative product could be envisaged by an external quench of the iminium salt in the presence of water to afford alcohol **291**. The open-structure **291** was found to be compatible with the ^{1}H NMR spectroscopic data. The mass spectrum of indole **291** confirmed this hypothesis by the presence of a single peak at 302.1, corresponding to the mass of **291** after losing a molecule of water (Scheme 3.66).

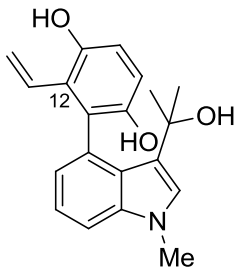


289 **291**

Scheme 3.66

Moreover, additional NMR spectroscopic analyses carried out on the product, obtained by reaction of enone **227** in refluxing toluene, demonstrated that the proton at 6.07 ppm was an alcohol (observed by HSQC, confirmed by D_2O exchange; see: Figure 3.17 with H_{14} being an alcohol). The combination of the NMR spectroscopic data and the energy calculations discarded the cyclophane **285** as a potential product for this reaction.

The bis-phenol **292** could be considered as a possible product for the reaction of enone **227** in refluxing toluene. The ^{1}H NMR spectroscopic data matched the open-structure **292**; moreover, the mass spectrum showed the presence of a single peak, that corresponded to the mass of **292** after losing a molecule of water (formation of the iminium) (Figure 3.22).



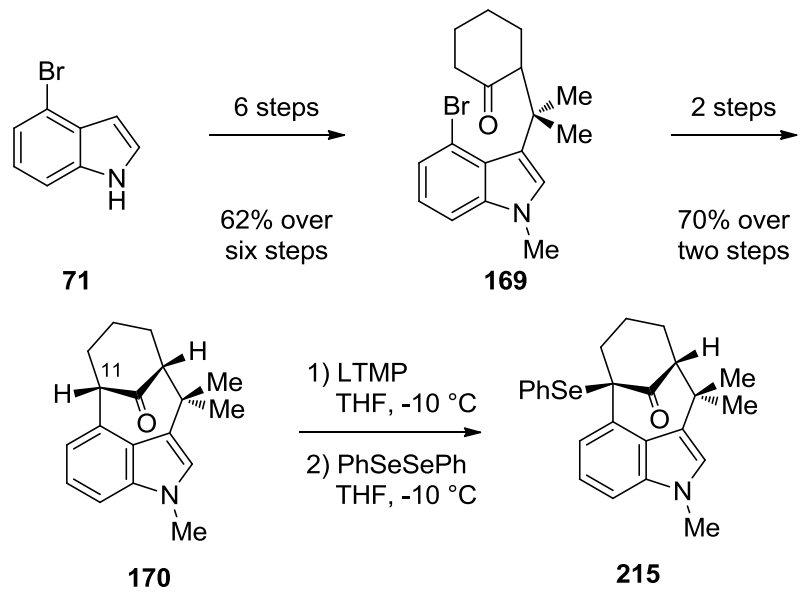
292

Figure 3.22

Unfortunately, at this stage, the combination of the data gathered did not allow us to identify these two new products and therefore additional studies would be required.

3.4 SUMMARY

The bicyclo[4.3.1]decane **170** has been successfully synthesised in eight steps from commercially available 4-bromoindole (**71**).[1,2] Selenation of the bridged position was achieved by direct metallation and substitution of the position C_{11} using strategies developed by previous members of our group (Scheme 3.67).[2]

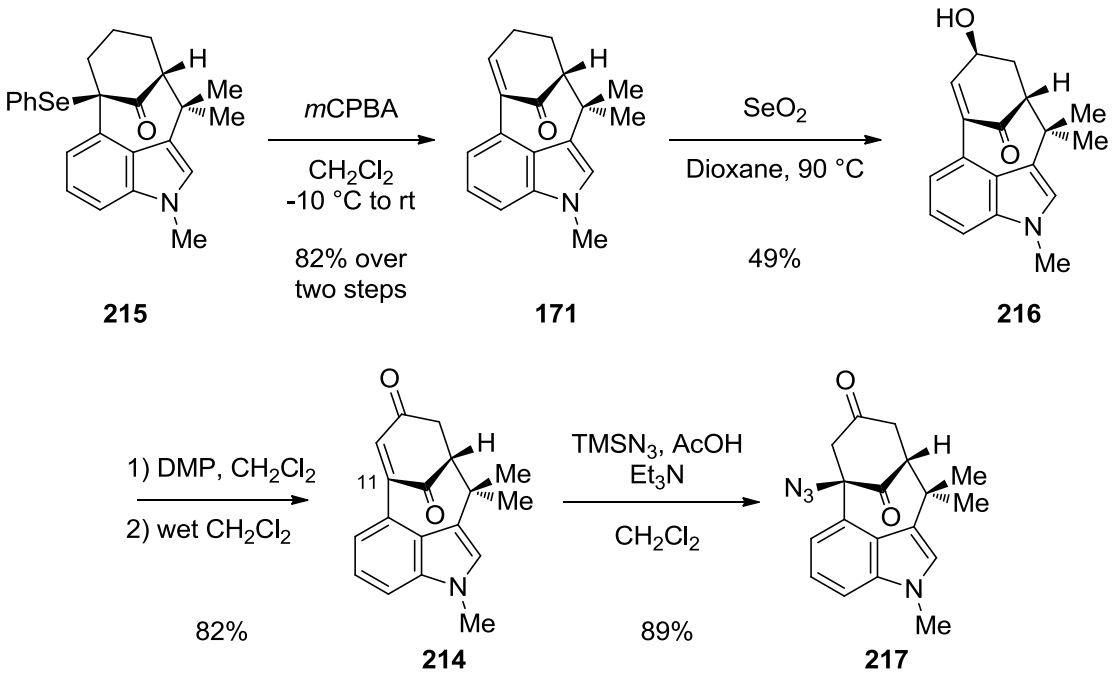


Scheme 3.67

At this stage, we chose to follow the synthetic route to enone **214** previously developed by our group, however the low yields of this oxidative sequence were unsatisfactory and required optimisation.[2] A longer reaction time and a higher temperature were served to increase the yield of the oxidation of selenide **215**. Increasing the temperature of the allylic oxidation

reaction allowed access to alcohol **216** in a reproducible 49% yield. Finally, the Dess-Martin oxidation was enhanced by addition of 'wet dichloromethane' to liberate the key late-stage diketone intermediate.

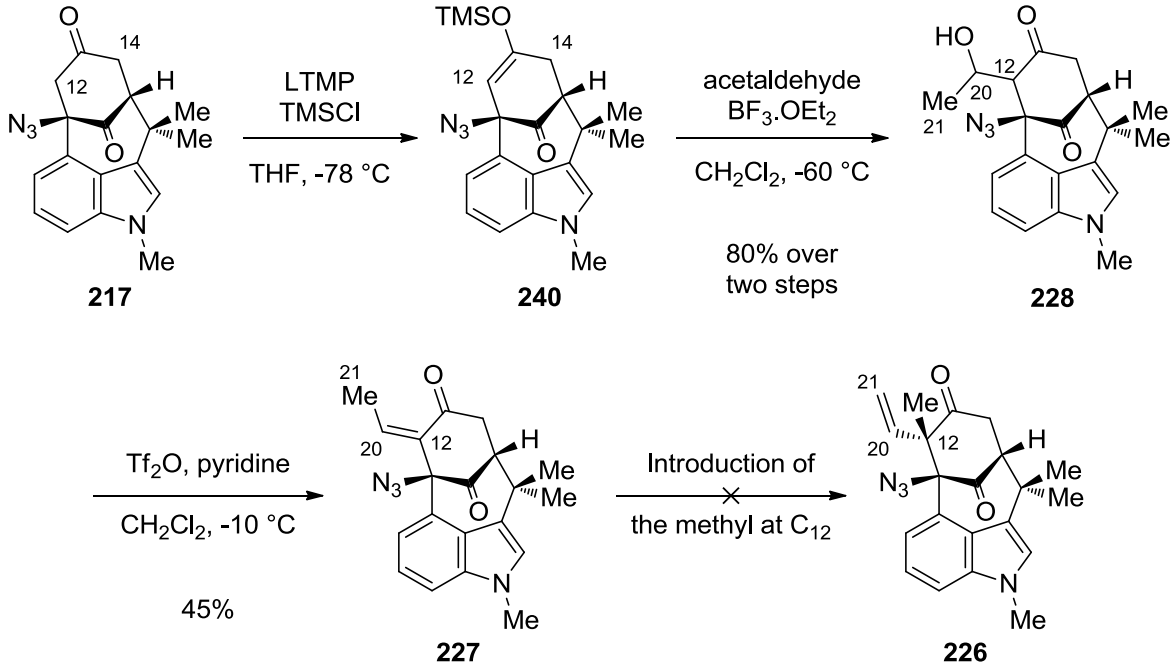
Introduction of the nitrogen fragment at the bridgehead position C_{11} was achieved in high yield following the conditions developed by previous members of our group (Scheme 3.68).[2]



Scheme 3.68

With a robust synthetic route to azide **217**, we attempted to introduce the desired fragment at position C_{12} using enolate chemistry. Some regioselectivity issues as well as the risk of elimination of the bridgehead azide required considerations to avoid side reactions. Formation of enol silane **240** was achieved *via* an ISQ under kinetic control using LHMDS. A regioselective aldol reaction provided alcohol **228** as a single diastereoisomer in 80% yield over two steps. Dehydration was carried out using triflic anhydride in the presence of

pyridine. However, insertion of a methyl group at the C_{12} position remained unsuccessful (Scheme 3.69).



Scheme 3.69

Unable to design the required fragment at the C_{12} position, we envisaged reducing the azide functionality at the bridgehead position C_{11} present on enone **227** and protecting the corresponding amine to avoid elimination issues. The two-step process resulted in an unexpected product that was identified as bis-phenol **292** (Figure 3.23).

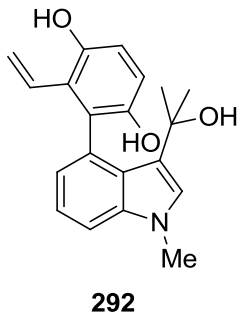


Figure 3.23

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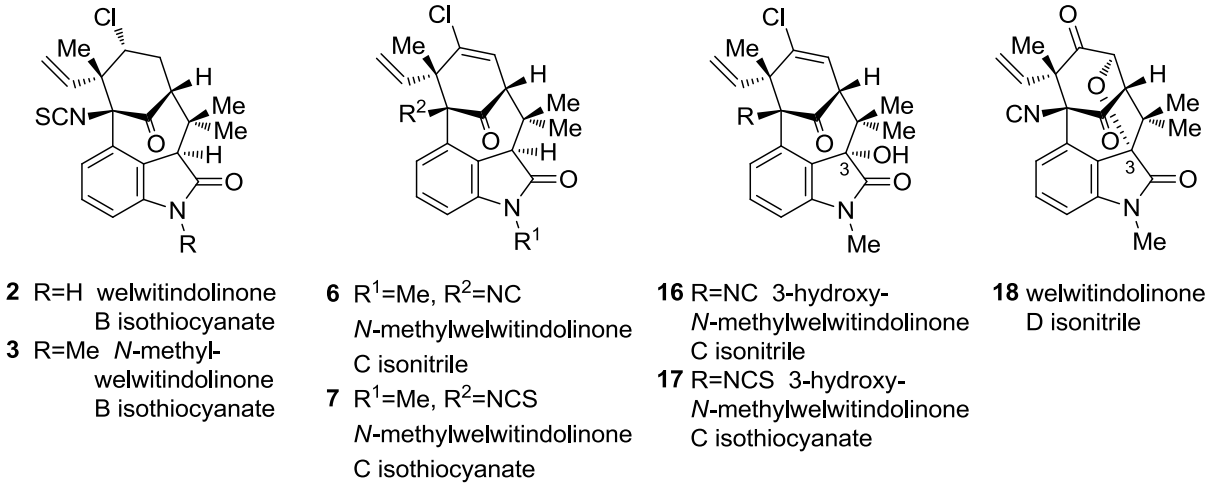
CHAPTER FOUR

EPILOGUE: TOTAL SYNTHESES OF *N*-METHYLWELWITINDOLINONE C ISOTHIOCYANATE

Despite the numerous syntheses of the welwitindolinone scaffold possessing the bicyclo[4.3.1]decane structure, no total synthesis of the compact tetracyclic had been reported when we started this project in 2010. However, the challenging architecture and the particularly attractive biological properties of welwistatin **7** continued to interest many research groups worldwide and since the start of our work, two research groups have reported a total synthesis of welwistatin **7** and other members of the welwitindolinone family (Figure 4.1).[1-4]



2 R=H welwitindolinone B isothiocyanate
3 R=Me *N*-methyl-welwitindolinone B isothiocyanate

6 R^1=Me, R^2=NC *N*-methylwelwitindolinone C isonitrile
7 R^1=Me, R^2=NCS *N*-methylwelwitindolinone C isothiocyanate

16 R=NC 3-hydroxy-*N*-methylwelwitindolinone C isonitrile
17 R=NCS 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate

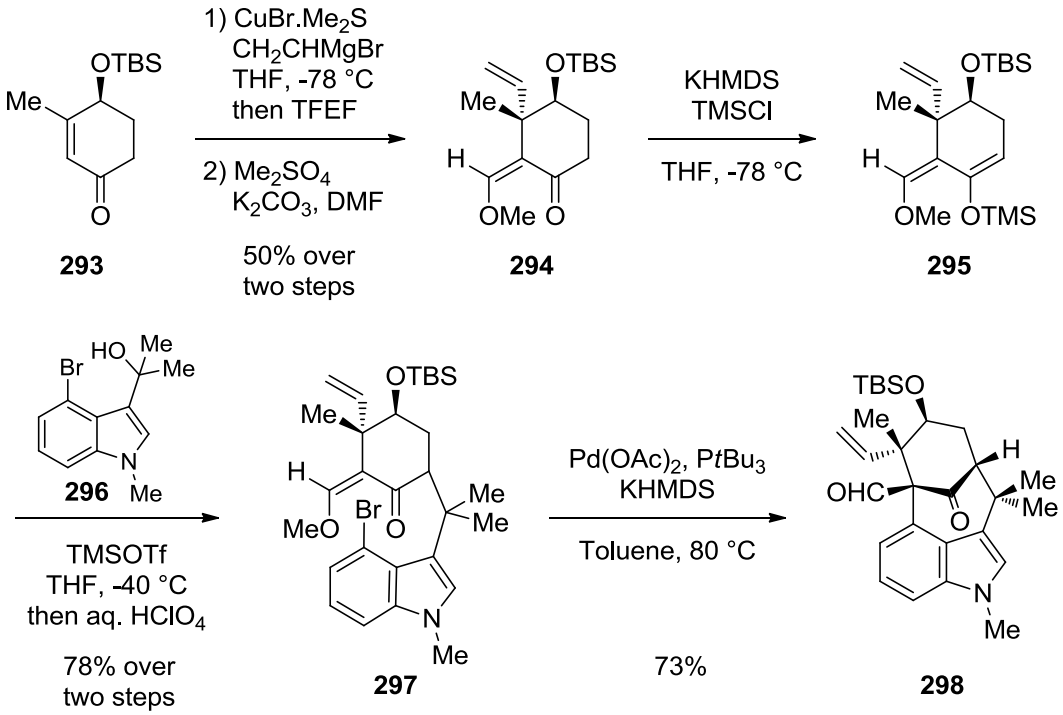
18 welwitindolinone D isonitrile

Figure 4.1

4.1 TOTAL SYNTHESES OF WELWITINDOLINONES

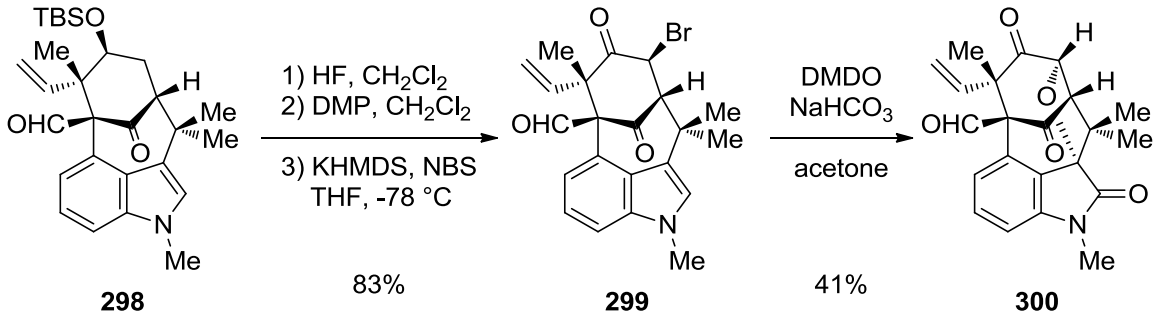
In 2011, Rawal and co-workers were the first to disclose a total synthesis of a compact member of the welwitindolinone family, *N*-methylwelwitindolinone D isonitrile **18**.[1] The tetracyclic skeleton of the oxidised welwitindolinone **18** was rapidly assembled. Taking inspiration from their previous work, precursor **297** was achieved by an alkylative coupling between tertiary alcohol **296** and highly functionalised enone **295** in the presence of TMSOTf, in good yield. Precursor **297**, possessing the required quaternary centre at position C_{12}, was

subjected to a Pd-catalysed enolate arylation to afford aldehyde **298** in 73% yield (Scheme 4.1).



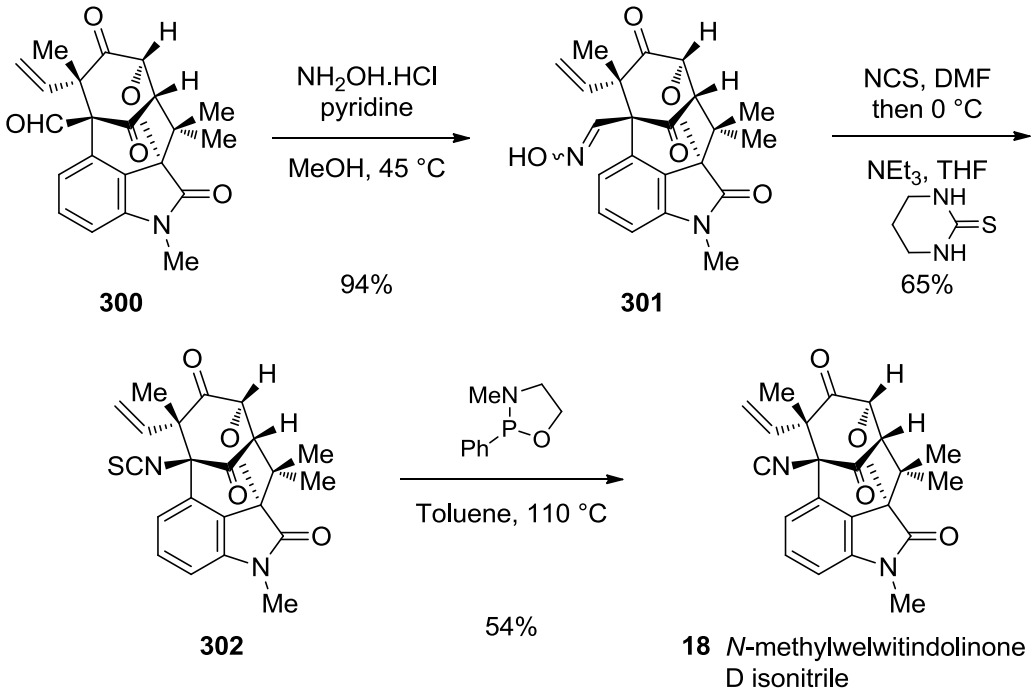
Scheme 4.1

α-Bromoketone **299** was prepared in a three-step sequence involving desilylation and oxidation of protected alcohol **298** followed by bromination of the position C_{14} using enolate chemistry. Surprisingly, oxidation of α-bromoketone **299** using DMDO yielded the spiro-fused pentacycle **300** after spontaneous intramolecular nucleophilic substitution of 3-hydroxyoxindole at the position C_{14} (Scheme 4.2).



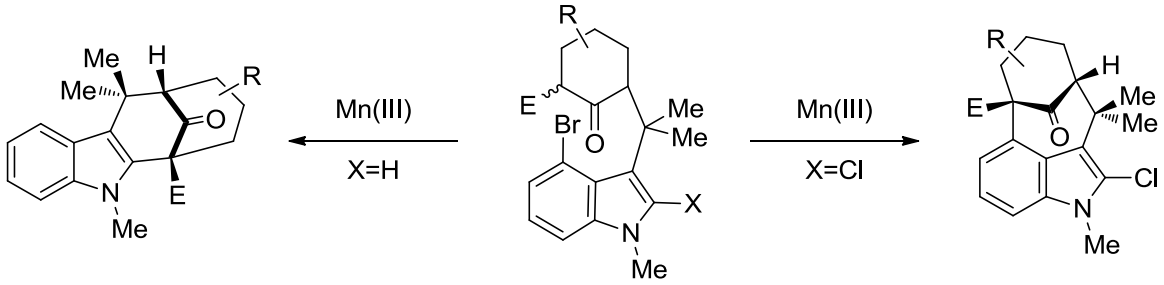
Scheme 4.2

The synthesis of welwitindolinone **18** was completed by the transformation of the aldehyde functionality into an isonitrile. Treatment with hydroxylamine afforded the corresponding oxime **301**, which was then converted into isothiocyanate bridgehead **302**. Desulfurisation afforded the desired *N*-methylwelwitindolinone D isonitrile **18** (Scheme 4.3).



Scheme 4.3

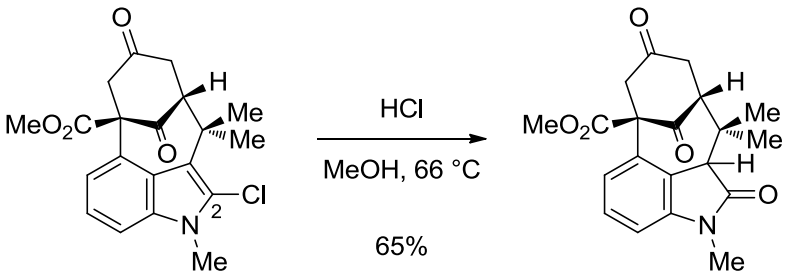
A few months later, Rawal described the influence of a chlorine atom at the C_2 position of the indole on the regioselectivity of the intramolecular oxidative cyclisation, in the presence of manganese(III) acetate (Scheme 4.4).[5]



304 **303a** X=H **303b** X=Cl **305**

Scheme 4.4

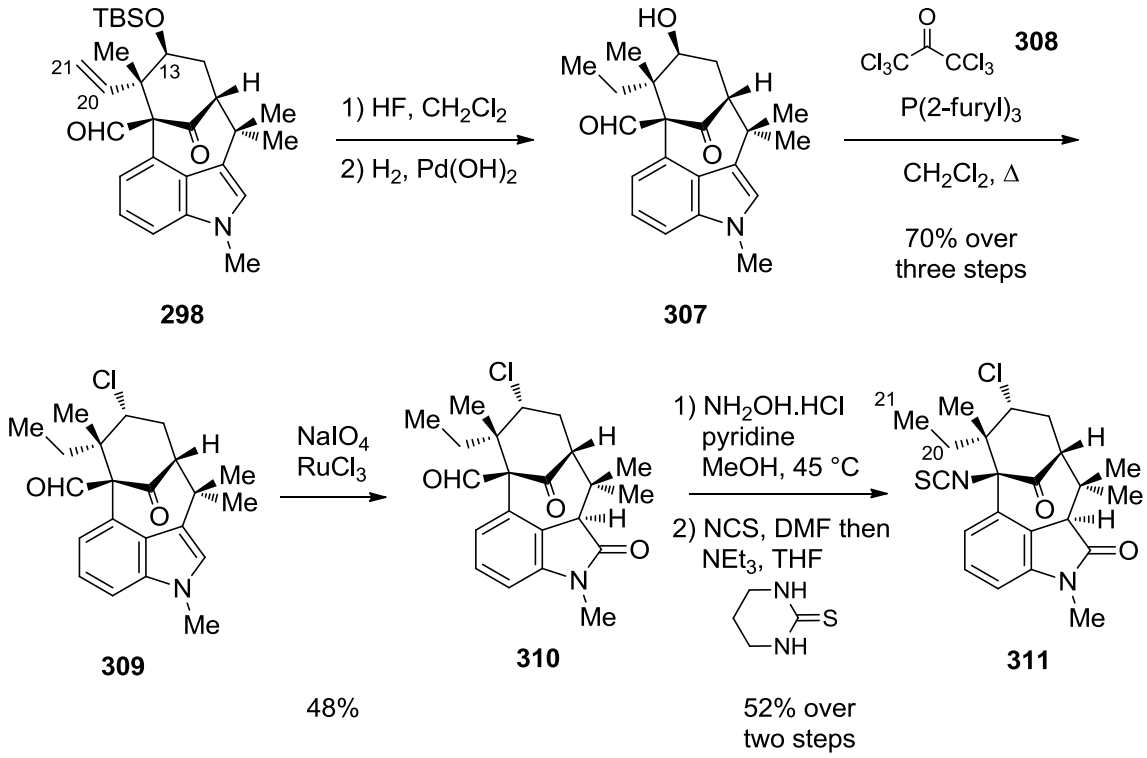
The chlorine at the C_2 position seemed to have a double function: acting as a blocking agent for the cyclisation as well as being a masked oxindole for the purpose of the synthesis.[5] Preparation of advanced intermediate **303a** and its chlorinated analogue **303b** was achieved using a previously reported strategy. Attempts to form the bicyclo[4.3.1]ring system proved unsuccessful in the presence of a proton in the C_2 position of the indolic ring. However, a combination of steric clash and an electronic deactivation induced by the presence of a chlorine atom in the C_2 position of the indole, gave access to the desired scaffold **305**. Finally, acid hydrolysis of chlorinated tetracycle **234** produced oxindole **306**, which could be further manipulated towards total syntheses of the welwitindolinones (Scheme 4.5).



234 **306**

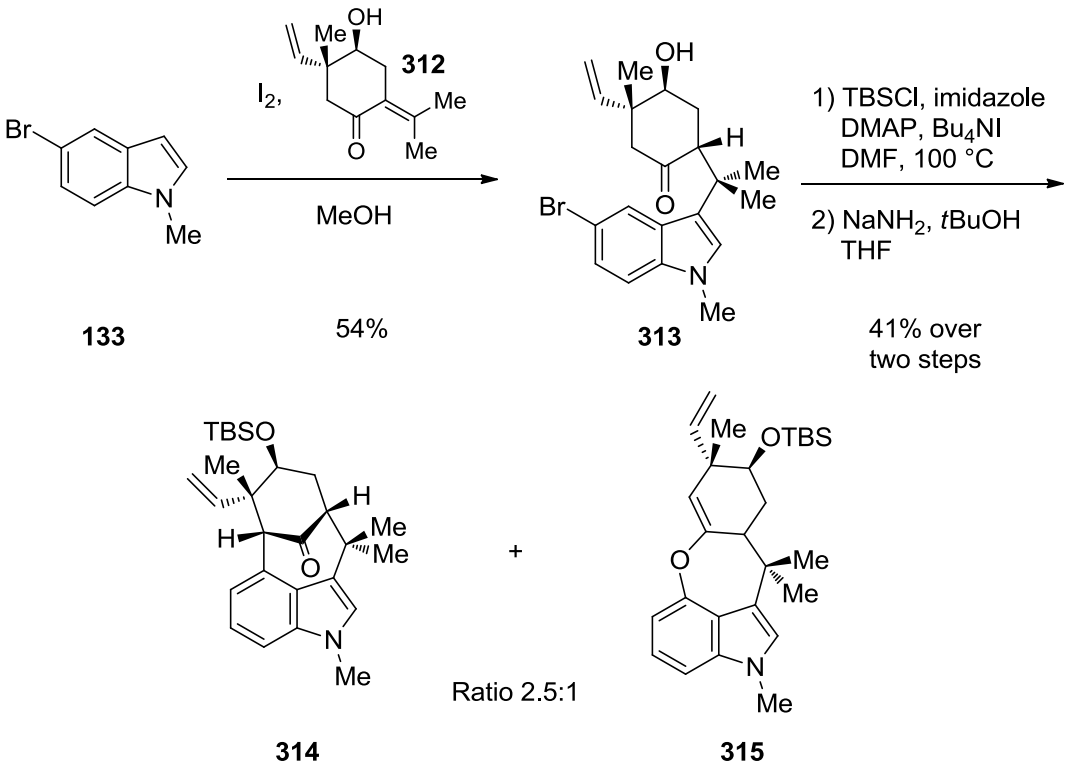
Scheme 4.5

In a separate communication, Rawal described the synthesis of an analogue of *N*-methylwelwitindolinone B isothiocyanate **3**.[6] Key chlorine intermediate **309** was obtained *via* a three-step sequence from silyl ether **298**, built following the route previously described. After desilylation, hydrogenation of alkene C_{20}-C_{21} was required to avoid side reactions during the chlorination of the C_{13} position. Preparation of the oxindole and introduction of the isothiocyanate functionality at the bridgehead position completed the synthesis of 20,21-dihydro-*N*-methylwelwitindolinone B isothiocyanate **311** (Scheme 4.6).



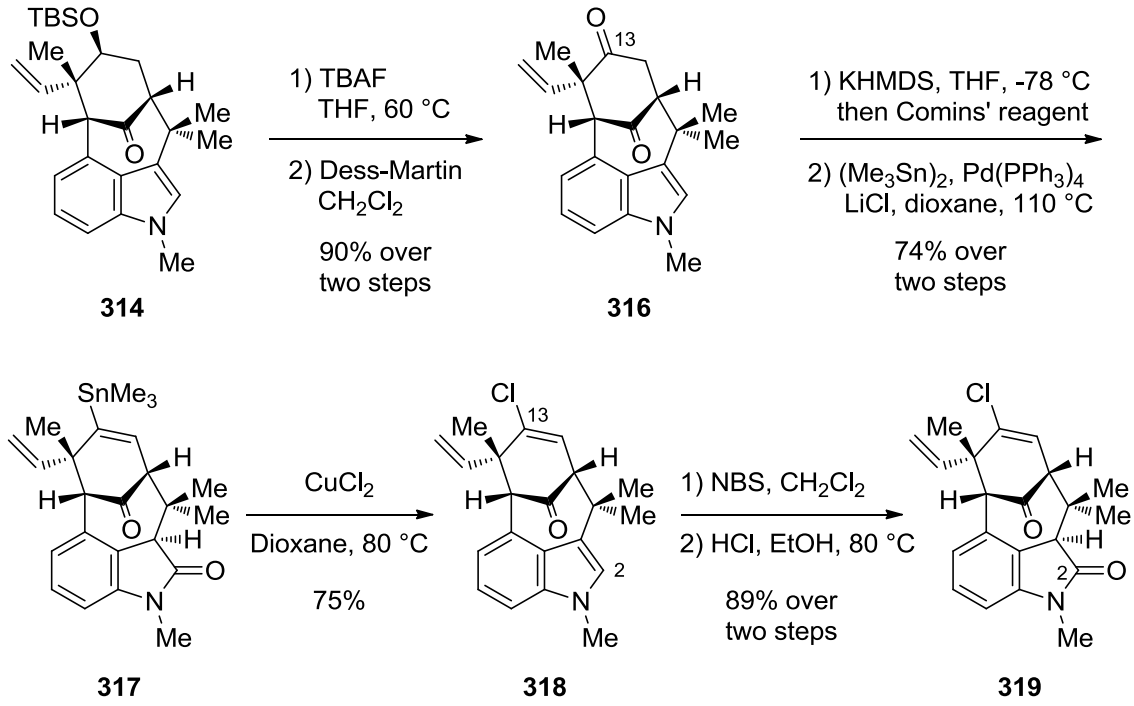
Scheme 4.6

In 2011, Garg and co-workers published the first total synthesis of (-)-*N*-methylwelwitindolinone C isothiocyanate **7**.[2] The sequence began with the iodine-mediated addition of 5-bromo-*N*-methylindole (**133**) to highly substituted enone **312** (obtained in 5 steps from commercially available *(S)*-carvone). After silylation of alcohol **313**, an indolyne cyclisation was carried out in the presence of sodium amide and *tert*-butanol using the procedure previously established by Garg's group.[7] The tetracyclic framework **314** was obtained along with the product of *O*-arylation **315** in a 2.5:1 ratio (Scheme 4.7).



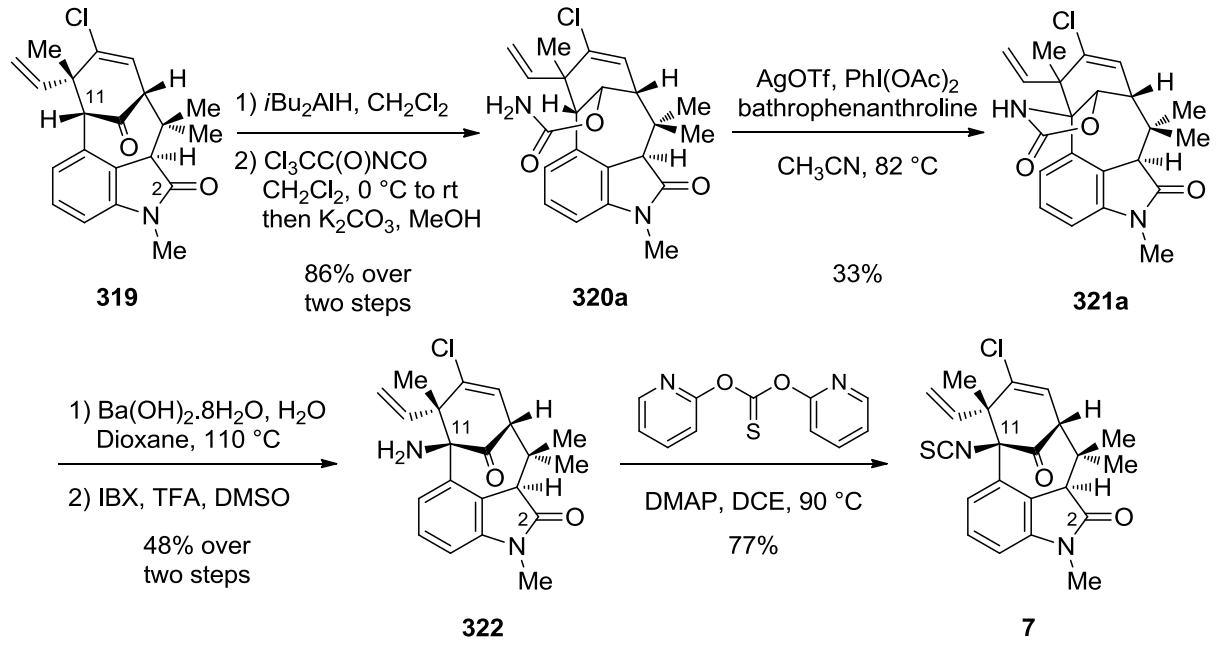
Scheme 4.7

Silyl alcohol **314** was converted into the corresponding ketone **316** in high yield. The vinyl chloride functionality at the C_{13} position was introduced *via* a three-step sequence consisting of the preparation of an enol triflate followed by a Pd-catalysed stannylation to afford stannane **317** which was chlorinated using $CuCl_2$ in refluxing dioxane. Treatment of indole **318** with NBS followed by acid hydrolysis afforded oxindole **319** in high yield (Scheme 4.8).



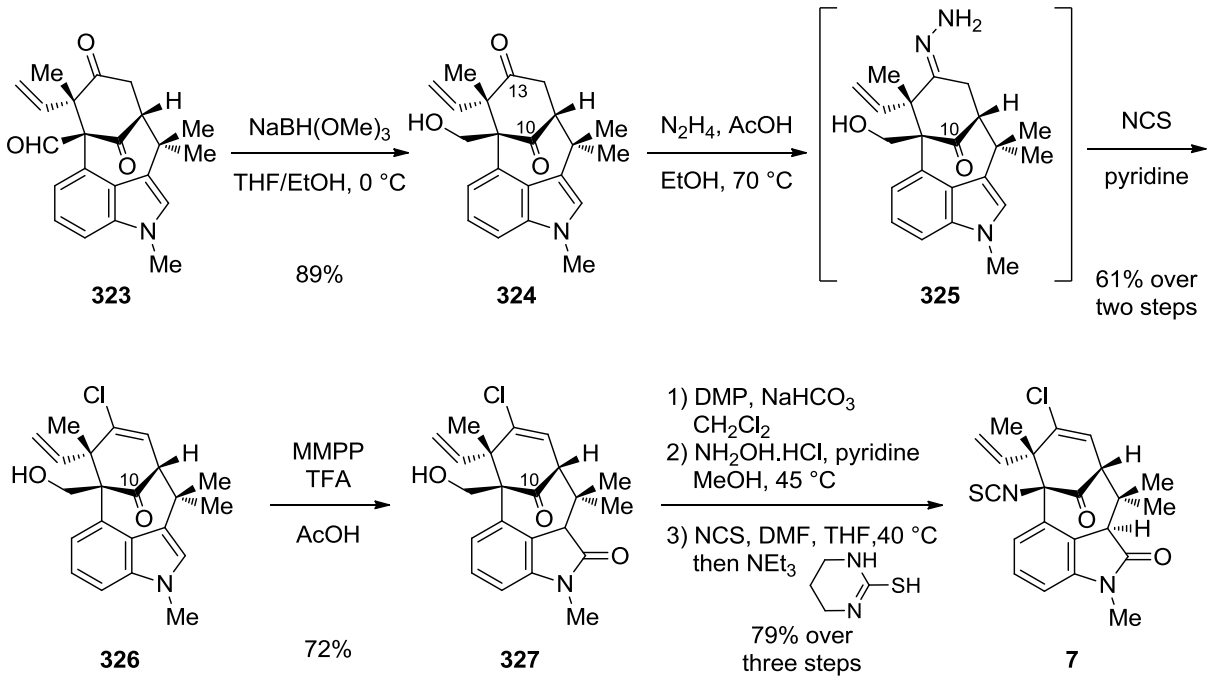
Scheme 4.8

After reduction of the ketone at the C_{10} position, the corresponding bridged alcohol was protected as a carbamate. Formation of oxazolidinone **321a** was achieved by cyclisation of the nitrene intermediate obtained by treatment with bathophenanthroline and diacetoxyiodobenzene in the presence of a silver catalyst. A two-step sequence involving a barium-promoted hydrolysis and an IBX oxidation gave bridgehead amine **322** that was converted into welwistatin **7** by addition of di-(2-pyridyl)thionocarbonate in the presence of DMAP (Scheme 4.9). Garg completed the total synthesis of welwistatin **7** in 17 linear steps from the starting carvone in 0.8% overall yield.



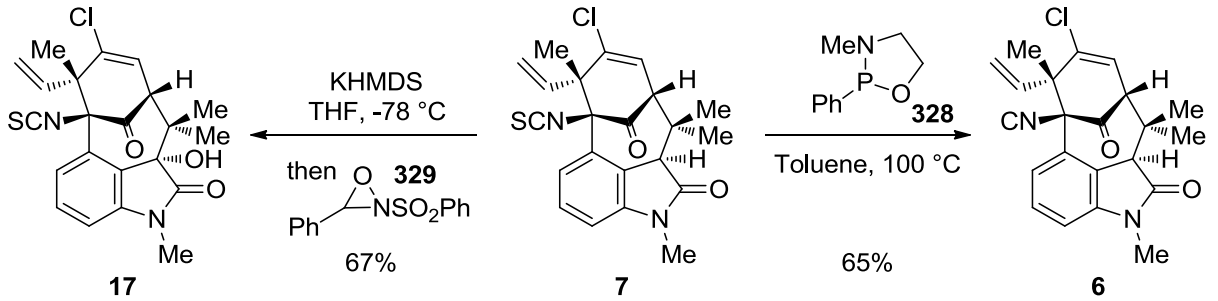
Scheme 4.9

In early 2012, Rawal disclosed the total syntheses of welwistatin **7**, *N*-methylwelwitindolinone C isonitrile **6** and 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate **17**.[3] His strategy took inspiration from his previous work towards *N*-methylwelwitindolinone D isonitrile **18**, as he presented a synthesis starting from advanced aldehyde **323**.[1] After reduction of the bridgehead aldehyde, diketone **324** was regioselectively converted to hydrazone **325**. Subsequent treatment with NCS in the presence of pyridine afforded vinyl chloride **326** in 61% yield over two steps. The oxidation of indole **326** into the corresponding oxindole **327** was achieved using the mild oxidant MMPP in the presence of acid. At this stage, preparation of the isothiocyanate bridgehead functionality was completed *via* a three-step sequence. After oxidation of alcohol **327**, treatment with hydroxylamine afforded the corresponding oxime and this was converted into welwistatin **7** (Scheme 4.10).



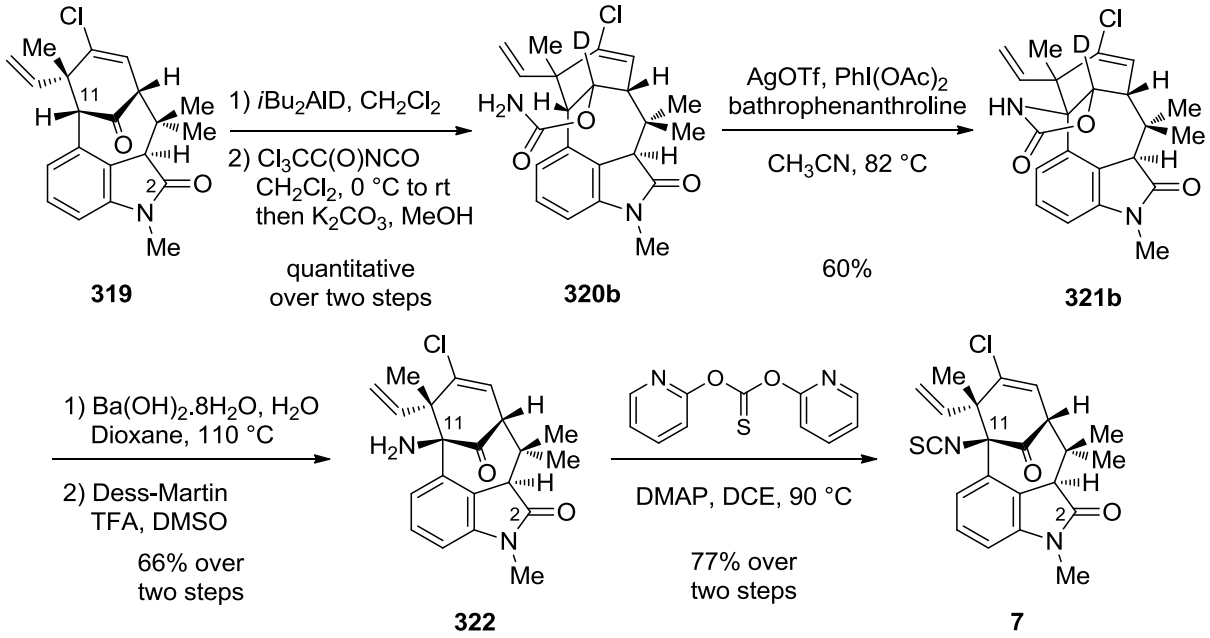
Scheme 4.10

With welwistatin **7** in hand, Rawal turned his attention towards the total synthesis of its isonitrile analogue **6** and its oxidised form **17**. Isonitrile **6** was obtained by desulfurisation of welwistatin **7** under the action of Mukaiyama's oxazaphospholidine **328**. The reaction of welwistatin **7** with LHDMS in the presence of Davis' oxaziridine **329** resulted in welwitindolinone **17** in 67% yield (Scheme 4.11).



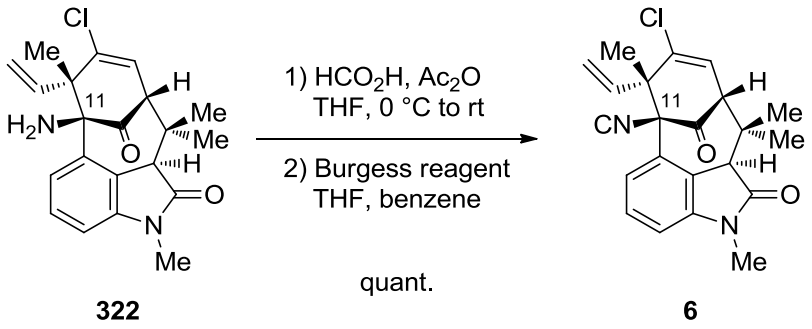
Scheme 4.11

Soon after, Garg and colleagues published an improved synthesis of welwistatin **7** as well as the total syntheses of welwitindolinones **6**, **16** and **17**.[4] Garg showed that the deuterium at the position C_{10} on **320b**, introduced during the reduction of the bridged ketone by a deuterated borane, had a dramatic effect on the sequence. Avoiding some side reactions such as the addition of the nitrene at the position C_{10} instead of C_{11}, **319** was converted in the corresponding bridgehead amine **322** in 40% yield over 5 steps (compared to 13% yield for its analogue **320a**) (Scheme 4.12).[2,4]



Scheme 4.12

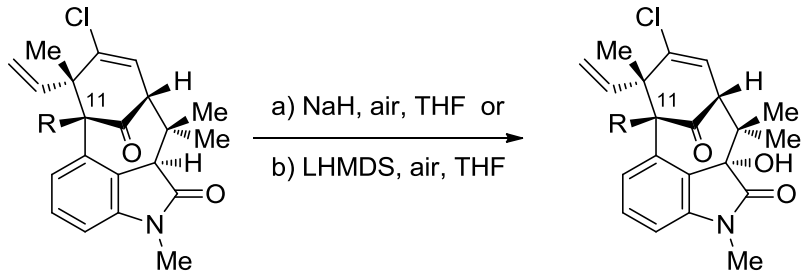
Garg also reported the first total synthesis of *N*-methylwelwitindolinone C isonitrile **6** from amine **322** *via* a two-step sequence consisting of a formylation reaction followed by dehydration (Scheme 4.13).[4]



322 **6**

Scheme 4.13

Finally, Garg reported access to two of the oxidised welwitindolinones. Natural products **6** and **7** were subjected to a direct oxidation to yield oxidised welwitindolinones **16** and **17**, respectively. While **16** was achieved by exposure of **6** to sodium hydride in air, treatment of **7** with LHMDS in THF in air was required to access welwitindolinone **17** (Scheme 4.14).[4]



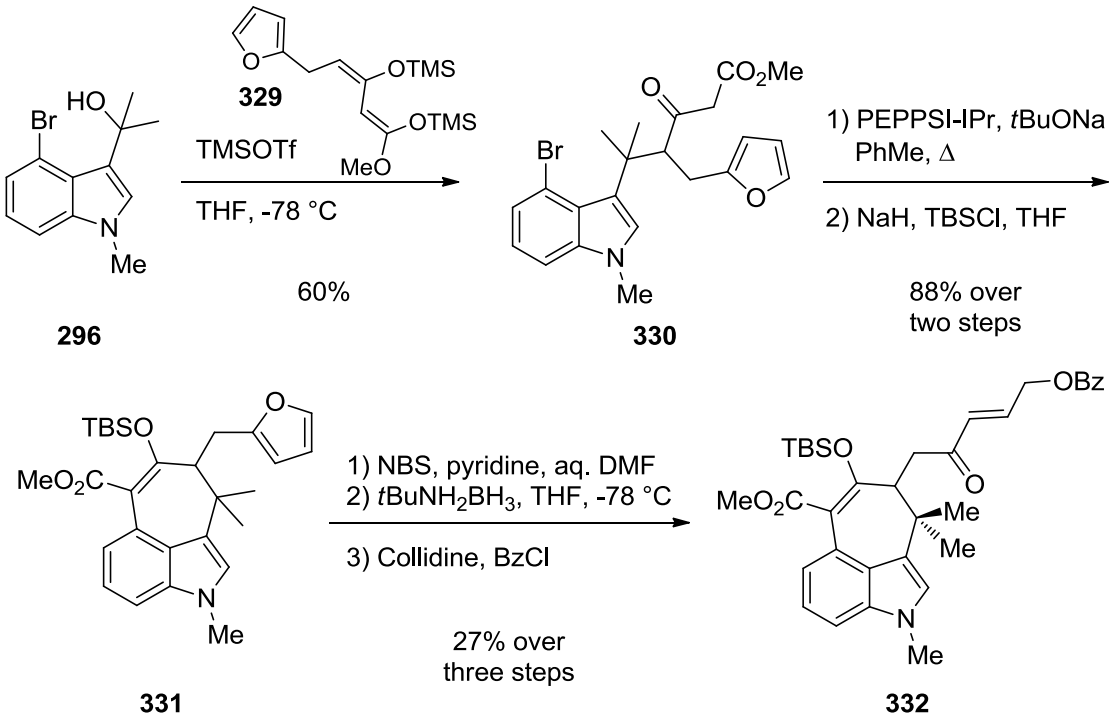
6 R=NC
7 R=NCS

16 R=NC a-47%
17 R=NCS b-48%

Scheme 4.14

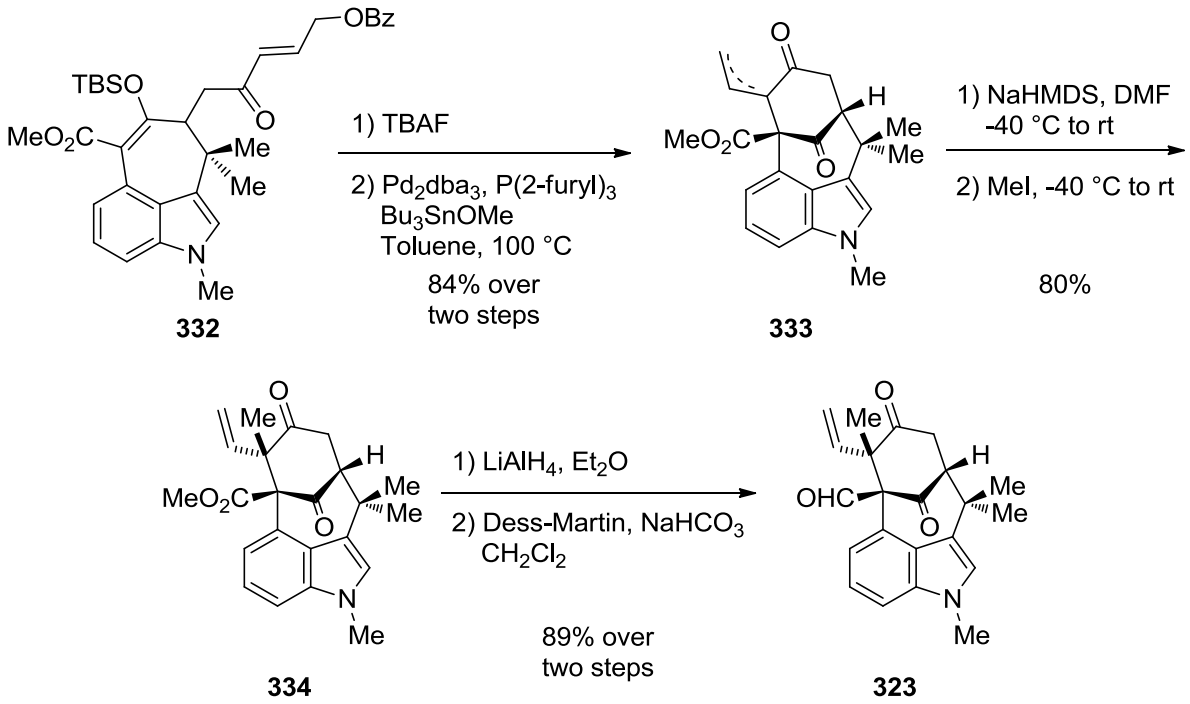
In 2012, Martin and co-workers reported a formal synthesis of the welwitindolinones **6**, **7** and the oxidised members of the family **16**, **17** and **18**, based on a late-stage Pd-catalysed allylic alkylation to access the tetracyclic framework.[8] A Lewis acid-mediated coupling between tertiary alcohol **296** and silyl enol ether **329** was achieved in the presence of TMSOTf. A Pd-catalysed enolate arylation was then performed on ketoester **330** to install the

seven-membered ring system. The furan ring of tricycle **331** was converted to the substituted α,β-unsaturated enone in **332**, which is a precursor for the formation of the last ring (Scheme 4.15).



Scheme 4.15

The last ring of the welwitindolinone skeleton was obtained by treatment of precursor **332** with Pd_2dba_3, P(2-furyl)$_3$ and Bu_3SnOMe in toluene at 100 °C, in 84% yield. A regioselective enolate reaction on ketone **333** was realised by reaction with NaHMDS at -40 °C prior to methylation at the C_{12} position. Ester **334** was then converted into the corresponding aldehyde **323**, a formal intermediate in Rawal's syntheses of three members of the welwitindolinone family (welwitindolinones **6**, **7** and **17**) (Scheme 4.16).



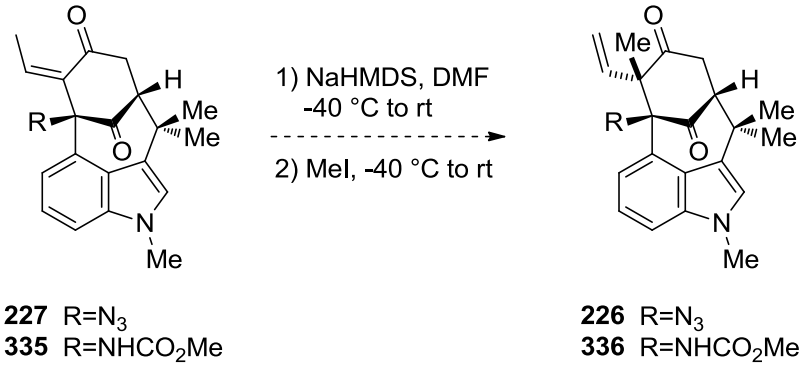
Scheme 4.16

More than 17 years after its isolation, *N*-methylwelwitindolinone C isothiocyanate **7** has been successfully synthesised by the research groups of Garg and Rawal and a formal synthesis was reported by the group of Martin. The total syntheses of other members of the family have also been published.

4.2 FUTURE SYNTHETIC STUDIES

At this stage, the methylation at position C_{12} seemed compromised. However, an alternative approach based on the conditions developed by Martin for the formal syntheses of some welwitindolinone members could be envisaged. In the first instance, we would perform this

reaction on enones **227** or **335** to study the influence of a nitrogen motif at the bridgehead position (Scheme 4.17)

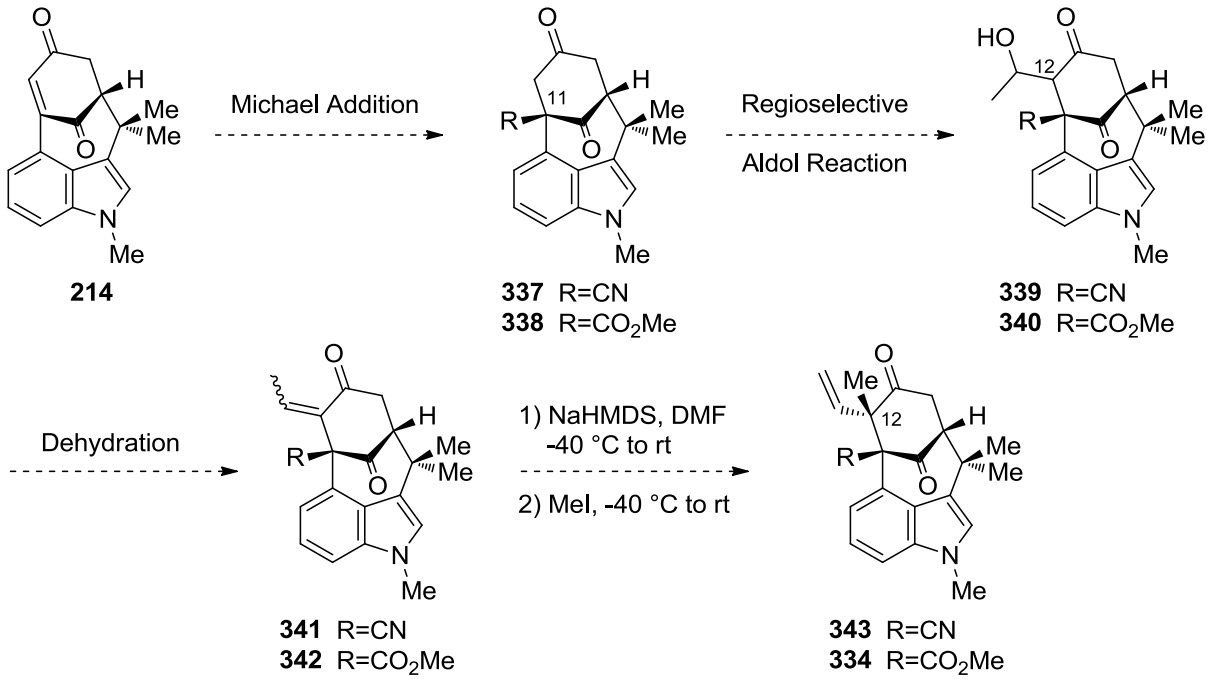


227 R=N_3
335 R=$NHCO_2Me$

226 R=N_3
336 R=$NHCO_2Me$

Scheme 4.17

We could also consider the insertion of a carbon fragment at the bridgehead position, which could be introduced *via* a Michael addition on unusual enone **214**. A cyanide partner could be taken into consideration. The regioselective aldol reaction could afford aldol **339**, which after dehydration would give access to **341**, the precursor of the methylation reaction. Enone **341** could be treated under Martin's conditions to give the desired quaternary carbon at the C_{12} position. A reduction of the nitrile into the corresponding ester could also be envisaged at any stage of this synthetic route to give access to a formal synthesis of welwitindolinone with regards to Martin's work (Scheme 4.18).



Scheme 4.18

Finally, we would examine how the biological properties (particularly the MDR-reversing activity) could be attributed to the features present in welwistatin **7**. Investigations could be carried out on analogues obtained at different stages of our synthetic route. The influence of some functionalities, such as the isothiocyanate, the oxindole, the vinyl chloride, the *gem*-dimethyl at the C_{16} position or the quaternary centre at position C_{12}, could all be evaluated. In this way, a structure-activity relationship of the welwitindolinone family will be developed.

4.3 REFERENCES

(1) Bhat,V.; Allan, K. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *133*, 5798-5801.

(2) Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797-15799.

(3) Allan, K. M.; Kobayashi, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 1392-1395.

(4) Quasdorf, K. W.; Huters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396-1399.

(5) Bhat,V.; MacKay, J. A.; Rawal, V. H. *Org. Lett.* **2011**, *13*, 3214-3217.

(6) Bhat,V.; Rawal, V. H. *Chem. Commun.* **2011**, 9705-9707.

(7) Tian, X.; Huters, A. D.; Douglas, C. J.; Garg, N. K. *Org. Lett.* **2009**, *11*, 2349-2351.

(8) Fu, T.-H.; McElroy, W. T.; Shamszad, M.; Martin, S. F. *Org. Lett.* **2012**, *14*, 3834-3837.

CHAPTER FIVE

EXPERIMENTAL PROCEDURES

5.1 GENERAL METHODS

All reactions were carried out under an atmosphere of nitrogen in dry glassware unless otherwise stated. All solvents were dried prior to use. Tetrahydrofuran was either distilled from sodium/benzophenone or used from a solvent purification system (alumina columns), Pure Solv-MD Solvent, from Innovative Technology. Dichloromethane, diethyl ether, methanol and toluene were used from a solvent purification system, Pure Solv-MD Solvent (alumina columns), from Innovative Technology, unless otherwise stated. All other reagents were used as received from commercial suppliers unless otherwise indicated. All aqueous solutions of NH_4Cl, $NaHCO_3$ and NaCl were saturated unless otherwise indicated. Reaction temperatures refer to the temperature measured in an external bath unless otherwise indicated.

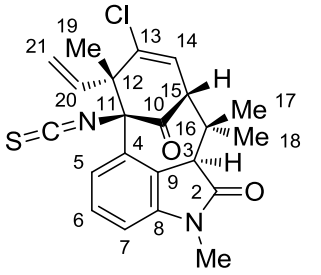
All ^1H NMR and ^{13}C NMR experiments were recorded on a Bruker AC300, AVIII300, AVIII400, AV400 or DRX500 spectrometer at 300 K. ^{13}C NMR spectra were recorded using the PENDANT pulse sequence and using UDEFT pulse sequence from the Bruker standard pulse program library. For NMR experiments recorded in deuterated chloroform, the resonances of the residual solvent peaks at 7.27 ppm for the ^1H spectra and 77.0 ppm for the ^{13}C spectra were used as internal references. For NMR experiments recorded in deuterated methanol, the resonances of the residual solvent peaks at 3.34 ppm for the ^1H spectra and 49.9 ppm for the ^{13}C spectra were used as internal references. Chemical shifts (δ) are measured in ppm and coupling constants (J) are quoted in Hz to one decimal place. Spectral data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, number of protons, coupling constants, assignment); for ^{13}C NMR spectra: chemical shift (assignment). In reporting spectral data, the following abbreviations are used for multiplicity in ^1H NMR spectra: *s* (singlet), *d* (doublet), *dd* (doublet of doublets), *dt* (doublet of triplets), *ddd* (doublet of doublet of doublets), *t* (triplet), *m* (multiplet), *br* (broad), *app* (apparent). In the case of

ambiguous assignments, 2-dimensional homonuclear (^{1}H-^{1}H) and heteronuclear (^{1}H-^{13}C) NMR experiments were recorded.

Reactions were monitored by thin layer chromatography (TLC) using aluminium-backed plates coated with keiselgel F_{254} with 0.2 mm thickness. Visualisation was achieved first by UV light followed by either *p*-anisaldehyde or potassium permanganate unless otherwise stated. Column chromatography was carried out using Davisil 60 Å silica gel in the eluent systems indicated. Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded neat on a PerkinElmer Spectrum 100 FTIR spectrometer. Wavelengths (ν) are reported in cm^{-1}. In reporting spectral data, the following abbreviations are used: s (strong), m (medium), w (weak), br (broad). EI mass spectra were recorded on a VG ZabSpec magnetic sector mass spectrometer. ESI mass spectra were recorded on a Micromass LCT time of flight mass spectrometer. GC mass spectra were recorded on a Micromass GCT Premier using a ZB5MS column from Phenomenix.

5.2 NOMENCLATURE

The numbering of the isolation paper of welwistatin published by Moore and co-workers in 1994 was used for our spectral data assignments (Figure 5.1).

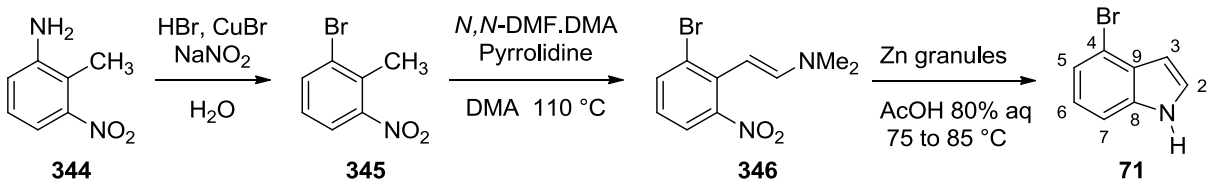


7 *N*-methylwelwitindolinone C isothiocyanate

Figure 5.1

5.3 EXPERIMENTAL PROCEDURES

4-Bromoindole (71)[1]



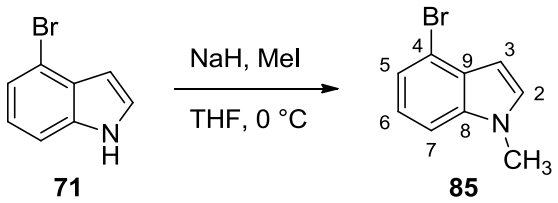
To a solution of 2-methyl-3-amino-nitrobenzene (**344**) (38.87 g, 225 mmol) in H_2O (325 mL) heated at reflux was added dropwise *via* a dropping funnel over 15 min HBr (48% in H_2O, 130 mL, 239 mmol). The solution was heated at reflux for 20 min, then cooled to 0 °C before slow addition over 45 min of a solution of $NaNO_2$ (17.56 g, 225 mmol) in H_2O (90 mL), so as to maintain the temperature below 5 °C. After complete addition, the solution of the diazo-intermediate was stirred for 15 min at 0 °C and quickly transferred to a solution of CuBr (42.03 g, 293 mmol) in H_2O (225 mL) at room temperature. The generated red foamy solution was heated to 100 °C for 20 min. The resulting red suspension was allowed to cool to room temperature before pouring onto water (350 mL). Et_2O (300 mL) was added to the suspension and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 300 mL). The combined green-coloured organic layers were washed with NH_4OH (3 M in H_2O, 500 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude orange solid (52.81 g) was carried on to the next step without further purification.

To a solution of bromo-nitrobenzene **345** (52.81 g, 245 mmol) in DMA (300 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (102.57 mL, 733 mmol) followed by pyrrolidine (20.4 mL, 245 mmol). The resulting black solution was heated at 110 °C for 5 h. The solution was allowed to cool to room temperature, poured onto water (300 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (5 × 300 mL). The combined organic

layers were washed with water (500 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting thick red solution (70.45 g) was used without further purification.

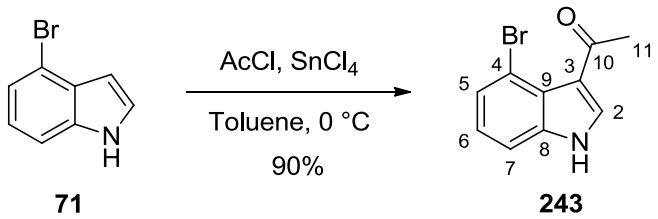
Zn granules (153 g, 2.34 mol) were added to the solution of crude enamine **346** (70.45 g, 260 mmol) in AcOH (80% aq, 1.17 L) preheated to 75 °C. The suspension was then heated at 85 °C for 3 h. After cooling to room temperature, the resulting orange suspension was poured onto water (500 mL). Et_2O (300 mL) was added to the suspension and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 300 mL). The combined organic layers were carefully washed with a solution of $NaHCO_3$ (5 × 200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/CH_2Cl_2 (8/2 to 5/5) as eluent) to afford indole **71** (32.85 g, 75%) as a light blue oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (*br s*, 1H, $H_{N\text{-}H}$), 7.33 (*d*, 1H, *J* 7.8, H_5), 7.29 (*d*, 1H, *J* 7.8, H_7), 7.23-7.25 (*m*, 1H, H_2), 7.05 (*app t*, 1H, *J* 7.8, H_6), 6.61-6.65 (*m*, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (C, C_8), 128.5 (C, C_4), 124.8 (CH_{Ar}, C_2), 122.9 (CH_{Ar}, C_6), 122.7 (CH_{Ar}, C_5), 114.6 (C, C_9), 110.3 (CH_{Ar}, C_7), 102.8 (CH_{Ar}, C_3); IR ν_{max} (film)/cm^{-1}: 3419 (s, br), 1564 (m), 1429 (m), 1413 (m), 1333 (s), 1178 (s), 890 (m), 745 (s); HRMS (EI) *m/z* 194.9682 $[M]^+$, $[C_8H_6N^{79}Br]^+$ requires 194.9684. Data were in agreement with those reported in the literature.

4-Bromo-*N*-methylindole (85)[2]



A solution of 4-bromoindole (**71**) (0.65 mL, 5.15 mmol) in THF (4 mL) was added dropwise over 15 min *via* cannula to a solution of sodium hydride (308 mg of a 60% dispersion in mineral oil, 7.7 mmol) in THF (5 mL) pre-cooled to 0 °C. After 30 min of vigorous agitation, iodomethane (0.64 mL, 10.3 mmol) was added at 0 °C. After removal of the ice-bath, the reaction mixture was allowed to warm to room temperature and stirred for 13 h. After total consumption of the starting material, a 1:1 mixture of MeOH/H_2O (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (30 mL) then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 9/1) to afford methylated indole **85** (1.045 g, 97%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (*dd*, 1H, *J* 7.6, 0.6, H_5), 7.28 (*ddd*, 1H, *J* 8.0, 0.8, 0.6, H_7), 7.12 (*dd*, 1H, *J* 8.0, 7.6, H_6), 7.10 (*d*, 1H, *J* 3.2, H_2), 6.58 (*dd*, 1H, *J* 3.2, 0.8, H_3), 3.89 (*s*, 3H, H_{NCH3}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9 (C, C_8), 129.3 (CH_{Ar}, C_2), 129.1 (C, C_4), 122.3 (CH_{Ar}, C_5), 122.1 (CH_{Ar}, C_6), 114.7 (C, C_9), 108.4 (CH_{Ar}, C_7), 101.2 (CH_{Ar}, C_3), 33.1 (CH_3, C_{NMe}); IR ν_{max} (film)/cm^{-1}: 2941 (w), 1558 (m), 1512 (m), 1480 (m), 1445 (m), 1414 (m), 1333 (s), 1287 (s), 1192 (m), 1109 (s), 889 (s), 824 (w), 740 (s), 710 (m); HRMS (EI) *m/z* 208.9850 $[M+Na]^+$, $[C_9H_8N^{79}BrNa]^+$ requires 208.9840. Data were in agreement with those reported in the literature.

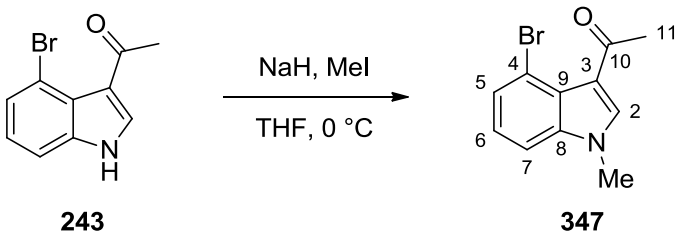
3-Acetyl-4-bromoindole (243)[3]



71 **243**

Acetyl chloride (1.45 mL, 20.5 mmol) was added to a solution of 4-bromoindole (**71**) (2.0 g, 10.3 mmol) in toluene (100 mL) pre-cooled to 0 °C. After stirring the pale yellow solution for 15 min at 0 °C, a solution of tin(IV) chloride (2.4 mL, 20.5 mmol) in toluene (45 mL) was added *via* cannula. A pink precipitate formed and the suspension was stirred for 2 h at 0 °C. The reaction mixture was quenched with a solution of $NaHCO_3$ (150 mL). The resultant slurry was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude residue was recrystallised from acetone to afford ketone **243** (2.21 g, 90%) as a pale pink powder; mp 165-166 °C, [lit.,[3] mp 167-168 °C]; ^{1}H NMR (300 MHz, CD_3OD) δ 8.19 (*s*, 1H, H_2), 7.43-7.47 (*m*, 2H, $H_{5 \text{ and } 7}$), 7.11 (*app t*, 1H, *J* 9.0, H_6), 2.57 (*s*, 3H, H_{11}), H_{NH} was not observed; ^{13}C NMR (75 MHz, CD_3OD) δ 195.6 (C, C_{10}), 140.4 (C, C_8), 136.0 (CH_{Ar}, C_2), 128.4 (CH_{Ar}, C_5), 125.9 (C, C_4), 125.2 (CH_{Ar}, C_6), 119.5 (C, C_3), 115.4 (C, C_9), 112.4 (CH_{Ar}, C_7), 29.5 (CH_3, C_{11}); IR ν_{max} (film)/cm^{-1}: 3236 (m, br), 1642 (s), 1561 (w), 1509 (w), 1400 (s), 1365 (m), 1334 (m), 1303 (m), 1017 (w), 939 (m), 911 (m), 784 (s), 746 (s); HRMS (ESI) *m/z* 259.9692 $[M + Na]^+$, $[C_{10}H_8NO^{79}BrNa]^+$ requires 259.9687. Data were in agreement with those reported in the literature.

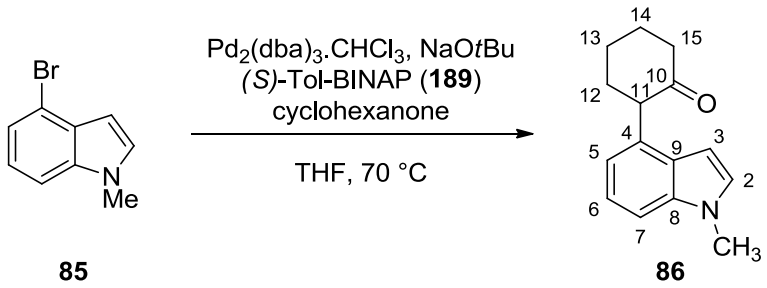
3-Acetyl-4-bromo-*N*-methylindole (347)[4]



243 **347**

A solution of indole **243** (500 mg, 2.1 mmol) in THF (4 mL) was added dropwise over 5 min *via* cannula to a solution of sodium hydride (126 mg of a 60% dispersion in mineral oil, 3.2 mmol) in THF (3 mL) pre-cooled to 0 °C. After 30 min of vigorous agitation, iodomethane (260 µL, 4.2 mmol) was added at 0 °C. After removal of the ice-bath, the reaction mixture was allowed to warm to room temperature. After total consumption of the starting material, a 1:1 mixture of MeOH/H_2O (10 mL) was added dropwise over 10 min and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/EtOAc (85/15 to 50/50) as eluent) to afford methylated indole **347** (280 mg, 53%) as a colourless powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (*s*, 1H, H_2), 7.42 (*dd*, 1H, *J* 7.6, 0.7, H_5), 7.18 (*dd*, 1H, *J* 8.0, 0.7, H_7), 7.06 (*dd*, 1H, *J* 8.0, 7.6, H_6), 3.72 (*s*, 3H, H_{NCH3}), 2.48 (*s*, 3H, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (C, C_{10}), 138.9 (C, C_8), 136.3 (CH_{Ar}, C_2), 127.3 (CH_{Ar}, C_5), 124.9 (C, C_4), 123.8 (CH_{Ar}, C_6), 117.7 (C, C_3), 114.6 (C, C_9), 108.8 (CH_{Ar}, C_7), 33.5 (CH_3, C_{NMe}), 29.7 (CH_3, C_{11}); IR ν_{max} (film)/cm^{-1}: 3108 (w), 2969 (w, br), 2923 (w, br), 1655 (s), 1556 (m), 1525 (m), 1425 (m), 1365 (m), 1325 (m), 1227 (m), 1109 (s), 1001 (m), 923 (m), 774 (m), 733 (s), 639 (m); HRMS (ESI) *m/z* 273.9844 $[M + Na]^+$, $[C_{11}H_{10}{}^{79}BrNNaO]^+$ requires 273.9843. Data were in agreement with those reported in the literature.

2-(1'-Methyl-1*H*-indol-4'-yl)cyclohexanone (86)[5]

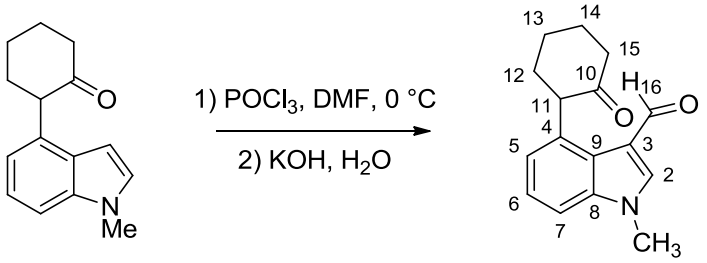


85 **86**

An oven-dried flask was charged with $Pd_2(dba)_3.CHCl_3$ (58.4 mg, 0.06 mmol), (*S*)-Tol-BINAP (**189**) (91.9 mg, 0.14 mmol) and sodium *tert*-butoxide (470 mg, 4.89 mmol), and finally purged with nitrogen to remove any trace of oxygen. Dry THF (11 mL) was added and the reaction mixture turned a reddish brown colour. Cyclohexanone (1.56 mL, 15 mmol) was added and the solution turned dark red. A solution of 4-bromo-*N*-methylindole (**85**) (700 mg, 3.33 mmol) in THF (5 mL) was added. The reaction mixture was heated at 70 °C for 3 h, by which time it turned black in colour and total consumption of the starting material was observed by TLC. The reaction was allowed to cool to room temperature, diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (80/20 to 70/30) as eluent) to afford cyclohexanone **86** as a yellow solid (681 mg, 90%); mp 122-123 °C [lit.,[5] mp 124-125 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.29 (*m*, 2H, $H_{6\text{ and }7}$), 7.05 (*d*, 1H, *J* 3.1, H_2), 6.97 (*dd*, 1H, *J* 6.2, 1.7, H_5), 6.34 (*dd*, 1H, *J* 3.1, 0.4, H_3), 4.00 (*dd*, 1H, *J* 11.6, 6.3, H_{11}), 3.78 (*s*, 3H, H_{NMe}), 2.50-2.66 (*m*, 2H, H_{15}), 2.28-2.40 (*m*, 2H, H_{12}), 2.15-2.25 (*m*, 1H, H_{14}), 2.04-2.11 (*m*, 1H, H_{14}), 1.86-1.99 (*m*, 2H, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (C, C_{10}), 136.6 (C, C_8), 131.3 (C, C_4), 128.4 (CH_{Ar}, C_2), 127.6 (C, C_9), 121.5 (CH_{Ar}, C_6), 118.3 (CH_{Ar}, C_5), 108.2 (CH_{Ar}, C_7), 99.3 (CH_{Ar}, C_3), 55.2 (CH, C_{11}), 42.3 (CH_2, C_{15}), 34.1 (CH_2,

C_{12}), 30.8 (CH_3, C_{NMe}), 27.7 (CH_2, C_{14}), 25.5 (CH_2, C_{13}); IR ν_{max} (film)/cm^{-1}: 3670 (w, br), 2923 (m, br), 2870 (m), 1711 (s), 1497 (m), 1438 (m), 1299 (m), 1129 (m), 1065 (s), 751 (s), 710 (s); HRMS (EI) *m/z* 227.1316 $[M]^+$, $[C_{15}H_{17}NO]^+$ requires 227.1310. Data were in agreement with those reported in the literature.

1-Methyl-4-(2'-oxycyclohexyl)-1*H*-indol-3-carbaldehyde (87)[5]

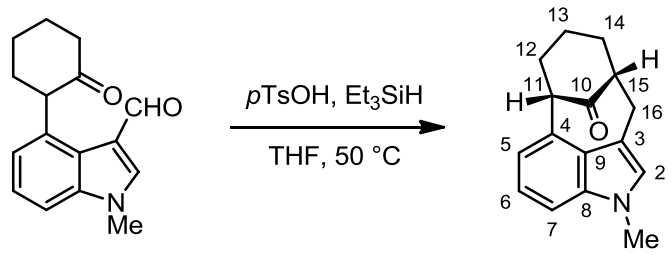


86 **87**

The reaction was carried out in 7 identical reaction tubes using a carousel. To each vessel, phosphorus oxychloride (180 µL, 1.94 mmol) was added dropwise over 1 min to DMF (3.2 mL) pre-cooled to 0 °C. The mixture was stirred at this temperature for 30 min and a solution of cyclohexanone **86** (400 mg, 1.76 mmol) in DMF (3.2 mL) was added at 0 °C. The ice bath was removed and the resulting pale orange solution was stirred for 1 h at room temperature. Ice (2.0 g) was added to the reaction mixture to give a yellowish colour to the mixture. A solution of potassium hydroxide (990 mg, 17.6 mmol) in water (8 mL) was carrefully added. A yellow precipitate was formed. After 3 h, the reaction mixture showed total consumption of starting material by TLC. The 7 carousel fractions were collected together and the solvent was evaporated under reduced pressure. The excess of DMF was removed overnight using a high-vacuum pump and a trap cooled with liquid nitrogen. The residue was diluted with Et_2O (200 mL) and water (200 mL) and the phases were separated.

The aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with a solution of $NaHCO_3$ (200 mL), brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (40/60 to 20/80) as eluent) to afford aldehyde **87** (1.35 g, 43%) as a pale yellow solid; mp 139-141 °C [lit.,[5] mp 139-140 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (*s*, 1H, H_{16}), 7.67 (*s*, 1H, H_2), 7.42 (*app t*, 1H, *J* 7.7, H_6), 7.27-7.30 (*m*, 1H, H_7), 7.20 (*d*, 1H, *J* 7.7, H_5), 5.41 (*br d*, 1H, *J* 7.7, H_{11}), 3.81 (*s*, 3H, H_{NMe}), 2.92-3.08 (*m*, 1H), 2.56 (*m*, 1H), 2.37-2.50 (*m*, 1H), 2.24-2.35 (*m*, 1H), 2.13-2.23 (*m*, 1H), 1.97-2.08 (*m*, 2H), 1.80-1.95 (*m*, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7 (C, C_{10}), 183.1 (CH, C_{16}), 143.9 (CH_{Ar}, C_2), 139.0 (C, C_8), 134.6 (C, C_4), 125.0 (C, C_9), 124.2 (CH_{Ar}, C_5), 121.5 (CH_{Ar}, C_6), 119.2 (C, C_3), 108.6 (CH_{Ar}, C_7), 57.9 (CH, C_{11}), 42.2 (CH_2, C_{15}), 33.8 (CH_2, C_{12}), 33.7 (CH_3, C_{NMe}), 28.1 (CH_2, C_{14}), 25.8 (CH_2, C_{13}); IR ν_{max} (film)/cm^{-1}: 2935 (w, br), 2723 (w), 1703 (s), 1652 (s), 1579 (w), 1534 (m), 1468 (m), 1449 (m), 1406 (m), 1373 (m), 1353 (m), 1198 (m), 1077 (m), 879 (m), 776 (m), 742 (s); HRMS (ESI) *m/z* 278.1154 $[M+Na]^+$, $[C_{16}H_{17}NO_2Na]^+$ requires 278.1157. Data were in agreement with those reported in the literature.

Preparation of bridging ketone 88[5]

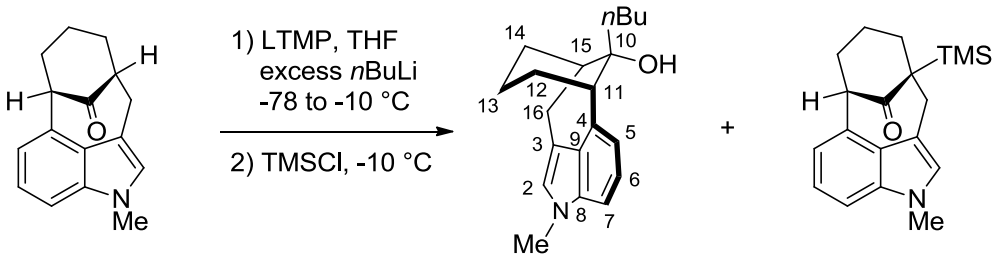


87 **88**

A solution of 0.53 M of *p*TsOH was prepared by adding *p*TsOH (5.01 g, 26.34 mmol) to THF (50 mL). The solution was dried for 2 h over 3 Å molecular sieves. To a solution of aldehyde **87** (1.15 g, 4.50 mmol) in THF (69 mL) was added the freshly prepared solution of *p*TsOH (9.00 mL, 4.73 mmol) and triethylsilane (0.90 mL, 5.40 mmol). The resulting solution was heated at 50 °C for 22 h. The reaction mixture was cooled to room temperature. Further portions of freshly prepared solution of *p*TsOH (9.00 mL, 4.73 mmol) and triethylsilane (0.90 mL, 5.40 mmol) were added at room temperature and the reaction mixture was again heated at 50 °C. This process was repeated every 24 h until the starting material was fully consumed. After 50 h, the reaction was allowed to cool to room temperature. The reaction was quenched using a solution of $NaHCO_3$ (70 mL) and diluted with Et_2O (100 mL). The phases were separated and the aqueous layer was extracted with Et_2O (5 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (80/20 to 70/30) as eluent) to afford tetracyclic **88** (890 mg, 83%) as a colourless solid; mp 113-114 °C, [lit.,[5] mp 114-115 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.27 (*m*, 2H, $H_{6 \text{ and } 7}$), 6.92 (*s*, 1H, H_2), 6.89 (*dd*, 1H, *J* 6.1, 1.5, H_5), 4.11-4.13 (*m*, 1H, H_{11}), 3.73 (*s*, 3H, H_{NMe}), 3.01-3.17 (*m*, 3H, H_{15}, 2 × H_{16}), 2.09-2.26 (*m*, 2H, 1 × H_{12}, 1 × H_{14}), 1.96-2.08 (*m*, 2H, 1 × H_{12}, 1 × H_{14}), 1.42-1.58 (*m*, 1H, H_{13}), 1.27-1.39 (*m*, 1H, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3 (C,

C_{10}), 136.8 (C, C_8), 132.6 (C, C_4), 127.1 (C, C_9), 126.6 (CH_{Ar}, C_2), 121.8 (CH_{Ar}, C_6), 118.1 (CH_{Ar}, C_5), 111.9 (C, C_3), 107.3 (CH_{Ar}, C_7), 58.1 (CH, C_{11}), 47.8 (CH, C_{15}), 37.3 (CH_2, C_{12}), 32.8 (CH_2, C_{14}), 32.6 (CH_3, C_{NMe}), 30.2 (CH_2, C_{16}), 18.3 (CH_2, C_{13}); IR ν_{max} (film)/cm^{-1}: 2917 (m), 2912 (m), 2867 (w), 1694 (s), 1607 (w), 1544 (w), 1446 (m), 1323 (m), 1302 (w), 1246 (w), 1105 (w), 779 (m), 739 (s); HRMS (ESI) *m/z* 262.1210 $[M+Na]^+$, $[C_{16}H_{17}NONa]^+$ requires 262.1208. Data were in agreement with those reported in the literature.

Preparation of bridged alcohol 199



88 **199** **114**

The material was divided in 2 equal parts that were combined for the work-up.

Preparation of the solution of LTMP (0.48 M):

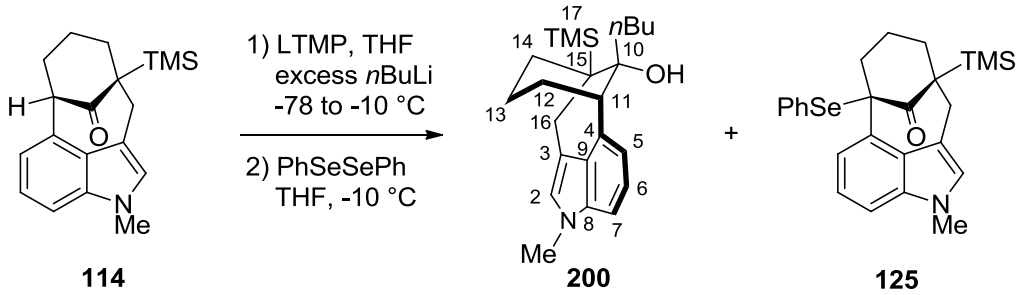
A solution of *n*BuLi (1.6 M in hexanes, 5.8 mL, 3.63 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (782 µL, 655 mg, 2.38 mmol) in THF (5 mL) pre-cooled to -78 °C. The solution was left for 5 min at -78 °C, then warmed up to room temperature for 20 min and cooled to -78 °C prior to its transfer to the solution of the substrate. The LTMP solution was charged with an excess of *n*BuLi.

To each round bottom flask: To a solution of the tetracyclic core **88** (466 mg, 1.95 mmol) in THF (52 mL), pre-cooled to -10 °C, was added the freshly prepared solution of LTMP,

pre-cooled to -78 °C. The resulting orange mixture was stirred for 10 min at -10 °C and a solution of freshly distilled TMSCl (2.48 mL, 19.5 mmol) was added to the mixture. The light orange solution was stirred for an additional 40 min until the TLC showed full consumption of starting material. The mixture was then quenched with a solution of NH_4Cl (30 mL) and the reaction mixtures were allowed to warm to room temperature.

The two flasks were combined and Et_2O (20 mL) was added. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The yellow oil crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford silylated bridged ketone **114** (480 mg, 37%, data page 173) along with alcohol **199** (438.9 mg, 38%) as a white foam; Data for alcohol **199**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (*dd*, 1H, *J* 8.2, 6.4, H_6), 7.20 (*dd*, 1H, *J* 8.2, 1.7, H_7), 6.96 (*dd*, 1H, *J* 6.4, 1.7, H_5), 6.89 (*s*, 1H, H_2), 3.76 (*s*, 3H, H_{NMe}), 3.43-3.49 (*m*, 2H, H_{11}, 1 × H_{16}), 2.95 (*dd*, 1H, *J* 16.8, 2.3, 1 × H_{16}), 2.35 (*app t*, 1H, *J* 5.4, H_{15}), 1.98-2.07 (*m*, 3H, 1 × H_{14}, 1 × H_{17}, 1 × H_{18}), 1.81-1.95 (*m*, 2H, 1 × H_{14}, 1 × H_{18}), 1.55-1.66 (*m*, 3H, H_{12}, 1 × H_{17}), 1.41-1.50 (*m*, 2H, H_{19}), 1.17-1.29 (*m*, 2H, H_{13}), 1.04 (*t*, 3H, *J* 7.2, H_{20}), H_{OH} was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8 (C, C_8), 135.6 (C, C_4), 127.8 (C, C_9), 126.0 (CH_{Ar}, C_2), 121.9 (CH_{Ar}, C_6), 120.5 (CH_{Ar}, C_5), 114.1 (C, C_3), 106.9 (CH_{Ar}, C_7), 75.4 (C, C_{10}), 51.6 (CH, C_{11}), 40.5 (CH, C_{15}), 40.3 (CH_2, C_{14}), 34.4 (CH_2, C_{17}), 32.5 (CH_3, C_{NMe}), 31.6 (CH_2, C_{18}), 28.7 (CH_2, C_{16}), 25.6 (CH_2, C_{12}), 23.4 (CH_2, C_{19}), 18.7 (CH_2, C_{13}), 14.2 (CH_3, C_{20}); IR ν_{max} (film)/cm^{-1}: 3578 (w, br), 2924 (s, br), 2864 (s, br), 1457 (s), 1418 (m), 1311 (s), 1265 (m), 1149 (m), 1079 (m), 1043 (m), 903 (m), 771 (s), 739 (s);-HRMS (ESI) *m/z* 320.1987 $[M+Na]^+$, $[C_{20}H_{27}NONa]^+$ requires 320.1990.

Preparation of bridgehead alcohol 200



114 **200** **125**

The material was divided in 2 equal parts that were combined for the work-up.

Preparation of the solution of LTMP (0.48 M):

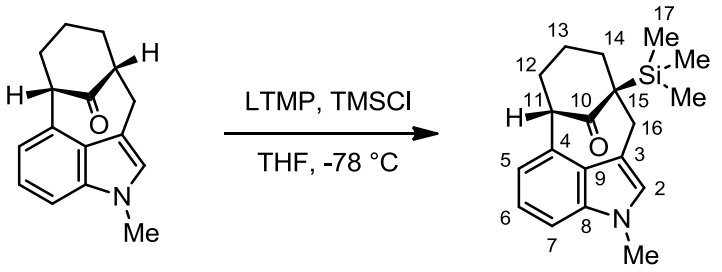
A solution of *n*BuLi (1.6 M in hexanes, 4.34 mL, 6.94 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (586 µL, 490 mg, 3.47 mmol) in THF (3.75 mL) pre-cooled to -78 °C. The solution was left for 5 min at -78 °C, then warmed up to room temperature for 20 min and cooled to -78 °C prior to its transfer to the solution of the substrate. The LTMP solution was charged with an excess of *n*BuLi.

To each round bottom flask: To a solution of the silylated bridged ketone **114** (240 mg, 0.77 mmol) in THF (17 mL), pre-cooled to -10 °C, was added the freshly prepared solution of LTMP, pre-cooled to -78 °C. The resulting orange mixture was stirred for 10 min at -10 °C and a solution of PhSeSePh (1.08 g, 4.5 mmol) in THF (5 mL) was added to the mixture. The dark orange solution was stirred for an additional 40 min until the TLC showed full consumption of starting material. The mixture was then quenched with a solution of NH_4Cl (30 mL) and the reaction mixtures were allowed to warm to room temperature.

The two flasks were combined and Et_2O (20 mL) was added. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The yellow oil crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford

selenide **125** (150 mg, 20%, data page 175) along with bridgehead alcohol **200** (340 mg, 60%) as a white foam; Data for alcohol **200**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (*dd*, 1H, *J* 8.2, 6.6, H_6), 7.17 (*dd*, 1H, *J* 8.2, 1.3, H_7), 6.93 (*dd*, 1H, *J* 6.6, 1.3, H_5), 6.89 (*s*, 1H, H_2), 3.76 (*s*, 3H, H_{NMe}), 3.60 (*dd*, 1H, *J* 4.2, 3.0, H_{11}), 3.43 (*d*, 1H, *J* 16.6, 1 × H_{16}), 2.93 (*d*, 1H, *J* 16.6, 1 × H_{16}), 2.19-2.28 (*m*, 1H, 1 × H_{19}), 1.90-2.01 (*m*, 2H, 1 × H_{12}, 1 × H_{14}), 1.61-1.82 (*m*, 4H, 1 × H_{12}, 1 × H_{14}, 1 × H_{18}, 1 × H_{19}), 1.41-1.57 (*m*, 3H, 1 × H_{18}, H_{20}), 1.31-1.40 (*m*, 1H, 1 × H_{13}), 1.18-1.23 (*m*, 1H, 1 × H_{13}), 1.04 (*t*, 3H, *J* 7.2, H_{21}), -0.23 (*s*, 9H, H_{17}), H_{OH} was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (C, C_8), 135.9 (C, C_4), 127.8 (C, C_9), 126.0 (CH_{Ar}, C_2), 122.0 (CH_{Ar}, C_6), 120.3 (CH_{Ar}, C_5), 115.8 (C, C_3), 106.7 (CH_{Ar}, C_7), 78.6 (C, C_{10}), 49.2 (CH, C_{11}), 40.2 (CH_2, C_{19}), 35.7 (C, C_{15}), 34.7 (CH_2, C_{14}), 32.7 (CH_2, C_{12}), 32.5 (CH_3, C_{NMe}), 30.3 (CH_2, C_{16}), 26.1 (CH_2, C_{18}), 23.6 (CH_2, C_{20}), 19.1 (CH_2, C_{13}), 14.2 (CH_3, C_{21}), -0.05 (CH_3, C_{17}); IR ν_{max} (film)/cm^{-1}: 3522 (w, br), 2924 (m, br), 1459 (m), 1416 (m), 1319 (m), 1249 (s), 838 (s), 759 (m), 735 (s); HRMS (ESI) *m/z* 392.2389 $[M+Na]^+$, $[C_{23}H_{35}NOSiNa]^+$ requires 392.2386.

Preparation of silyl ketone 114[6]



88 **114**

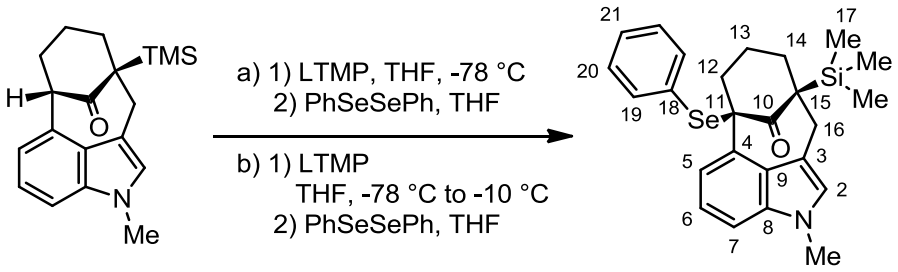
Preparation of the solution of LTMP (0.46 M):

To a solution of freshly distilled TMP (1.51 mL, 8.95 mmol) in THF (10 mL), pre-cooled to -78 °C, was added a solution of *n*BuLi (1.14 M in hexanes, 7.85 mL, 8.95 mmol). The solution was stirred for 5 min at -78 °C, then allowed to warm to room temperature for 15 min, the solution becoming yellow in colour. The lithium amide base solution was then cooled to -78 °C prior to the transfer to the substrate.

A solution of bridged ketone **88** (900 mg, 3.76 mmol) and freshly distilled TMSCl (4.77 mL, 37.6 mmol) in THF (90 mL), pre-cooled to -78 °C, was slowly added *via* cannula into a LTMP solution at -78 °C over 20 min. The resulting solution was stirred at this temperature for 2.5 h. The reaction was quenched using a solution of NH_4Cl (50 mL) at -78 °C. The reaction was allowed to warm to room temperature, the mixture was diluted with Et_2O (75 mL) and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (90/10 to 70/30) as eluent) to afford silyl **114** (668 mg, 57%, 70% BRSM) as a colourless solid; mp 110-111 °C, [lit.,[6] mp 111-114 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.22 (*m*, 2H, $H_{6 \text{ and } 7}$), 6.86 (*dd*, 1H, *J* 7.3, 0.8, H_5), 6.85 (*s*, 1H, H_2), 4.01 (*t*, 1H, *J* 3.3, H_{11}), 3.67 (*s*, 3H, H_{NMe}), 3.13 (*d*, 1H,

J 15.6, H_{16}), 2.91 (*d*, 1H, *J* 15.6, H_{16}), 2.04-2.13 (*m*, 1H, 1 × H_{12}), 1.91-1.99 (*m*, 2H, 1 × H_{12}, 1 × H_{14}), 1.81-1.87 (*m*, 1H, 1 × H_{14}), 1.41-1.53 (*m*, 1H, 1 × H_{13}), 1.28-1.36 (*m*, 1H, 1 × H_{13}), 0.16 (*s*, 9H, H_{17}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.9 (C, C_{10}), 136.9 (C, C_8), 133.3 (C, C_4), 127.3 (C, C_9), 126.4 (CH_{Ar}, C_2), 121.6 (CH_{Ar}, C_6), 118.0 (CH_{Ar}, C_5), 113.2 (C, C_3), 107.2 (CH_{Ar}, C_7), 58.3 (CH, C_{11}), 42.3 (C, C_{15}), 35.7 (CH_2, C_{12}), 33.1 (CH_2, C_{14}), 32.9 (CH_2, C_{16}), 32.5 (CH_3, C_{NMe}), 18.6 (CH_2, C_{13}), -2.8 (CH_3, C_{17}); IR ν_{max} (film)/cm^{-1}: 2917 (w, br), 2852 (w), 1678 (m), 1455 (w), 1418 (w), 1320 (w), 1244 (m), 1224 (w), 968 (w), 915 (w), 832 (s), 739 (s); HRMS (ESI) *m/z* 334.1605 $[M+Na]^+$, $[C_{19}H_{25}NOSiNa]^+$ requires 334.1603. Data were in agreement with those reported in the literature.

Preparation of selenide 125[6]



114 **125**

Method a:

Preparation of the solution of LTMP (0.5 M):

To a solution of freshly distilled TMP (1.27 mL, 7.5 mmol) in THF (8.1 mL), pre-cooled to -78 °C, was added a solution of *n*BuLi (1.14 M in hexanes, 5.98 mL, 6.8 mmol). The solution was stirred for 5 min at -78 °C, and then allowed to warm to room temperature for 15 min, the

solution became yellow in colour. The lithium amide base solution was then cooled to -78 °C prior to the transfer to the substrate.

To a solution of silylated ketone **114** (150 mg, 0.48 mmol) in THF (6 mL), pre-cooled to -78 °C, was added the solution of freshly prepared LTMP (0.5 M in THF, 1.9 mL). The resultant mixture turned brown in colour and was stirred for 1 h at -78 °C before addition of a solution of diphenyldiselenide (451 mg, 1.44 mmol) in THF (3 mL) at -78 °C. The bright yellow mixture was stirred for 1 h at -78 °C and then for 1 h at 0 °C. The yellow solution was allowed to slowly warm to room temperature. After 2 h the reaction was quenched using a solution of NH_4Cl (10 mL) at 0 °C. After returning to room temperature, the mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 9/1) to afford selenide **125** (56.2 mg, 25%, 54% BRSM) as a pale yellow oil.

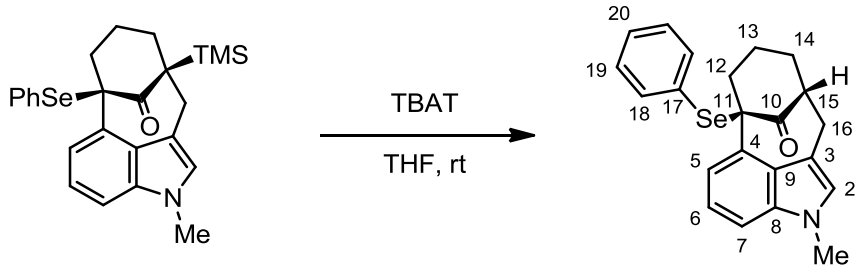
Method b:

Preparation of the solution of LTMP (0.4 M):

To a solution of freshly distilled TMP (461 µL, 2.73 mmol) in THF (4.36 mL), pre-cooled to -78 °C, was added a solution of *n*BuLi (1.37 M in hexanes, 2.00 mL, 2.73 mmol). The solution was stirred for 5 min at -78 °C, then allowed to warm to room temperature for 15 min, the solution became yellow in colour. The lithium amide base solution was then cooled to -78 °C prior to the transfer to the substrate.

To a solution of silylated ketone **114** (189.3 mg, 0.61 mmol) in THF (10 mL), pre-cooled to -10 °C, was added the solution of freshly prepared lithium amide base (0.4 M in THF, 6.81 mL), pre-cooled to -10 °C. A solution of diphenyldiselenide (854 mg, 2.74 mmol) in THF (7 mL) was added to the resultant mixture turned brown in colour. The reaction turned bright yellow in colour, it was stirred for 1 h at -10 °C, and 1 h at 0 °C. The yellow solution was allowed slowly to warm to room temperature. The reaction mixture was quenched using a solution of NH_4Cl (10 mL) at 0 °C. After returning to room temperature, the mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate/toluene (80/5/15 to 80/20/0) as eluent) to afford selenide **125** (118 mg, 41%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (*dd*, 2H, *J* 9.7, 2.0, H_{20}), 7.73 (*dd*, 1H, *J* 7.0, 4.3, H_5), 7.23-7.32 (*m*, 3H, $H_{19 \text{ and } 21}$), 7.16-7.20 (*m*, 2H, $H_{6 \text{ and } 7}$), 6.89 (*s*, 1H, H_2), 3.72 (*s*, 3H, H_{NMe}), 3.26 (*d*, 1H, *J* 20.4, 1 × H_{16}), 2.82 (*d*, 1H, *J* 20.4, 1 × H_{16}), 2.28-2.45 (*m*, 2H, H_{12}), 1.86 (*ddd*, 1H, *J* 13.2, 7.2, 5.9, 1 × H_{14}), 1.65-1.71 (*dm*, 1H, *J* 13.2, 1 × H_{14}), 1.25-1.53 (*m*, 2H, H_{13}), 0.02 (*s*, 9H, H_{17}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.3 (C, C_{10}), 138.0 (CH_{Ar}, C_{21}), 136.9 (C, C_8), 134.3 (C, C_4), 129.7 (C, C_9), 128.4 (CH_{Ar}, C_{20}), 128.1 (CH_{Ar}, C_{22}), 126.9 (CH_{Ar}, C_2), 126.6 (C, C_{19}), 121.7 (CH_{Ar}, C_6), 118.1 (CH_{Ar}, C_5), 113.2 (C, C_3), 108.4 (CH_{Ar}, C_7), 70.9 (C, C_{11}), 43.7 (C, C_{15}), 43.4 (CH_2, C_{12}), 34.7 (CH_2, C_{16}), 32.7 (CH_3, C_{NMe}), 32.4 (CH_2, C_{14}), 21.5 (CH_2, C_{13}), -2.7 (CH_3, C_{17}); IR ν_{max} (film)/cm^{-1}: 3058 (w, br), 2954 (w, br), 2903 (w, br), 2849 (w), 1680 (m), 1446 (m, br), 1414 (m), 1320 (m), 1246 (m), 1087 (m), 1019 (m), 833 (s), 736 (s), 693 (s); HRMS (ESI) *m/z* 490.1085 $[M+Na]^+$, $[C_{25}H_{29}NOSi^{80}SeNa]^+$ requires 490.1081. Data were in agreement with those reported in the literature.

Preparation of selenide 124[6]

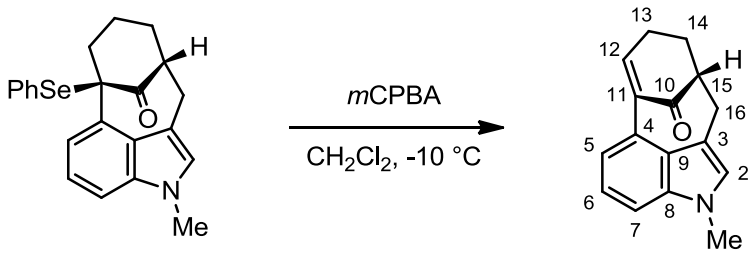


125 **124**

To a solution of substituted bridged ketone **125** (25.1 mg, 0.054 mmol) in THF (1.5 mL) was added dropwise over 1 min a solution of TBAT (32.0 mg, 0.059 mmol) in THF (1.5 mL). The resulting pale yellow solution was stirred at room temperature and the reaction was monitored by TLC. After 2.5 h, the starting material was fully consumed and the reaction was quenched with a solution of NH_4Cl (10 mL) and diluted with Et_2O (10 mL). The phases were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 85/15) to afford selenide **124** (15.7 mg, 74%) as a pale green oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (*dd*, 1H, *J* 5.6, 2.8, H_5), 7.74-7.76 (*m*, 2H, H_{19}), 7.29-7.32 (*m*, 3H, $H_{18\ and\ 20}$), 7.20-7.25 (*m*, 2H, $H_{6\ and\ 7}$), 6.95 (*s*, 1H, H_2), 3.77 (*s*, 3H, H_{NMe}), 3.23-3.32 (*m*, 2H, H_{15}, 1 × H_{16}), 2.99 (*dd*, 1H, *J* 14.9, 2.0, 1 × H_{16}), 2.44-2.50 (*m*, 1H, 1 × H_{12}), 2.40 (*ddd*, 1H, *J* 12.2, 8.4, 3.8, 1 × H_{12}), 1.97-2.07 (*m*, 1H, 1 × H_{14}), 1.88-1.92 (*m*, 1H, 1 × H_{14}), 1.43-1.56 (*m*, 1H, 1 × H_{13}), 1.34-1.40 (*m*, 1H, 1 × H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5 (C, C_{10}), 137.9 (C, C_8), 136.9 (CH_{Ar}, C_{19}), 133.4 (C, C_4), 130.1 (C, C_9), 128.5 (CH_{Ar}, C_{18}), 127.9 (CH_{Ar}, C_{20}), 127.1 (CH_{Ar}, C_2), 126.3 (C, C_{17}), 121.8 (CH_{Ar}, C_6), 118.6 (CH_{Ar}, C_5), 111.6 (C, C_3), 108.5 (CH_{Ar}, C_7), 70.9 (C, C_{11}), 47.7 (CH, C_{15}), 44.5 (CH_2, C_{12}), 32.8 (CH_3, C_{NMe}), 31.6 (CH_2, C_{16}), 31.3 (CH_2, C_{14}), 20.8 (CH_2, C_{13}); IR ν_{max} (film)/cm^{-1}: 2920 (m, br), 2851 (m), 1699 (s), 1475 (m), 1446 (s), 1313 (s), 739 (s), 691 (s); HRMS (ESI) *m/z* 418.0678 $[M+Na]^+$,

$[C_{22}H_{21}NO^{80}SeNa]^+$ requires 418.0686. Data were in agreement with those reported in the literature.

Preparation of bridging enone 126[6]

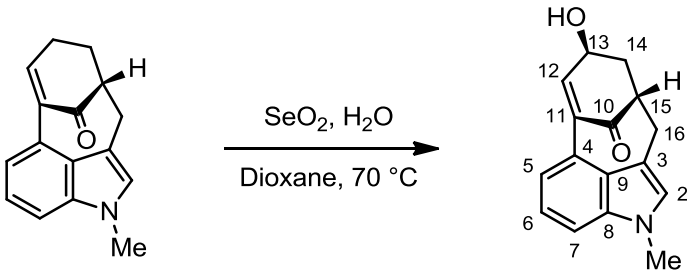


124 **126**

To a solution of bridging ketone **124** (25.8 mg, 0.065 mmol) in CH_2Cl_2 (2.5 mL), pre-cooled to -10 °C, was added *m*CPBA (16.3 mg, 0.065 mmol) in one portion. After 15 min, starting material remained unconsumed. *m*CPBA (16.3 mg, 0.065 mmol) was added to the reaction mixture at -10 °C. The reaction was monitored by TLC and after another 30 min, total consumption of starting material was observed. The reaction was quenched with water (5 mL) and diluted with Et_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with a saturated solution of NaS_2O_3 (10 mL), then brine (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 9/1) to afford bridged enone **126** (8.6 mg, 56%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (*dd*, 1H, *J* 8.4, 6.9, H_5), 7.15-7.21 (*m*, 2H, $H_{6\ and\ 7}$), 7.07-7.10 (*m*, 1H, H_2), 6.38 (*dd*, 1H, *J* 6.8, 3.2, H_{12}), 3.71 (*s*, 3H, H_{NMe}), 3.63 (*dd*, 1H, *J* 15.0, 8.9, 1 × H_{16}), 3.16-3.21 (*m*, 1H, H_{15}), 2.70 (*dd*, 1H, *J* 15.0, 7.2, 1 × H_{16}), 2.43-2.51 (*m*, 1H, H_{13}), 2.28-2.39 (*m*, 2H, 1 × H_{13}, 1 × H_{14}), 1.96-2.06 (*m*, 1H, 1 × H_{14}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3 (C, C_{10}), 142.3 (C, C_{11}), 129.5 ($CH_{C=C}$, C_{12}), 126.3 (CH_{Ar}, C_2), 123.9 (CH_{Ar},

C_6), 114.9 (CH_{Ar}, C_5), 109.1 (CH_{Ar}, C_7), 48.6 (CH, C_{15}), 31.5 (CH_3, C_{NMe}), 29.7 (CH_2, C_{16}), 26.8 (CH_2, C_{14}), 20.2 (CH_{Ar}, C_{13}) ($C_{3,4,8,9}$ were not observed due to the small amount of sample used for this NMR experiment); IR ν_{max} (film)/cm^{-1}: 2923 (m, br), 2851 (m), 1699 (s), 1476 (m), 1448 (s), 1315 (s), 744 (s), 698 (s); HRMS (ESI) *m/z* 260.1059 $[M+Na]^+$, $[C_{16}H_{15}NONa]^+$ requires 260.1051. Data were in agreement with those reported in the literature.

Preparation of allylic alcohol 201

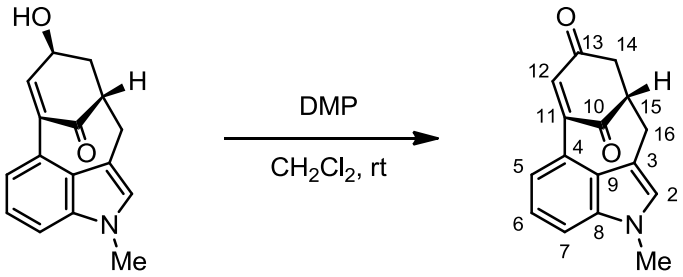


126 **201**

To a solution of bridghead enone **126** (5.5 mg, 0.023 mmol) in dioxane (0.5 mL) was added SeO_2 (2.9 mg, 0.025 mmol) in one portion followed by 2 drops of water. The suspension was stirred at reflux overnight. The precipitated mixture showed total consumption of starting material by TLC and was allowed to cool to room temperature. The reaction was quenched with water (5 mL) and the mixture was diluted with CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (9/1 to 5/5) as eluent) to afford alcohol **201** (1.3 mg, 22%) as a single diastereoisomer as a colourless oil; ^1H NMR (300 MHz, $CDCl_3$)

δ 6.99-7.28 (*m*, 4H, H_{Ar}), 6.68 (*d*, 1H, *J* 5.9, H_{12}), 4.70 (*ddd*, 1H, *J* 5.9, 4.5, 1.5, H_{13}), 3.82 (*dd*, 1H, *J* 14.5, 9.8, 1 × H_{14}), 3.72 (*s*, 3H, H_{NMe}), 3.35 (*dddd*, 1H, *J* 14.9, 9.8, 6.9, 1.2, H_{15}), 2.56-2.66 (*m*, 2H, 2 × H_{16}), 2.10 (*ddd*, 1H, *J* 14.5, 4.5, 1.2, 1 × H_{14}), H_{OH} not observed; No ^{13}C NMR spectroscopic data was recorded considering the limit amount of product obtained; IR ν_{max} (film)/cm^{-1}: 3332 (m, br), 2953 (m), 2927 (w), 2894 (w), 1699 (s), 1377 (m), 1088 (w), 1046 (w), 880 (m), 747 (m), 737 (m); HRMS (ESI) *m/z* 276.0008 $[M+Na]^+$, $[C_{16}H_{15}NO_2Na]^+$ requires 276.0000.

Preparation of enone 198

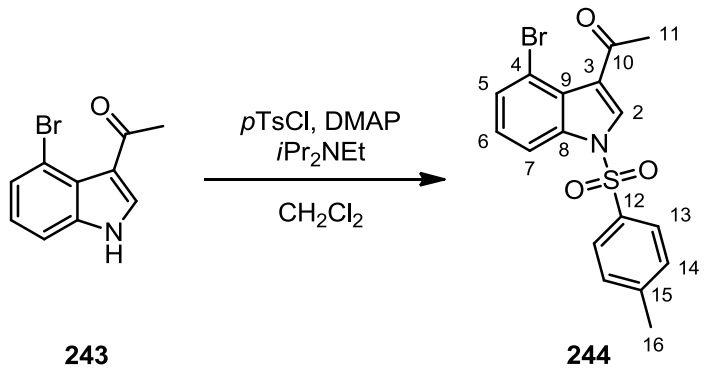


201 **198**

Dess-Martin periodinane (3.3 mg, 7.7 µmol) was added in one portion to a solution of alcohol **201** (1.3 mg, 5.13 µmol) in CH_2Cl_2 (1.0 mL). The resulting yellow solution was stirred at room temperature for 1 h. The reaction mixture was quenched with water (2 mL) and diluted with CH_2Cl_2 (5 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (8/2 to 6/4) as eluent) to afford diketone **198** (0.6 mg, 33%) as pale pink solid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06-7.32 (*m*, 4H, H_{Ar}), 6.40 (*s*, 1H, H_{12}), 3.80 (*dd*, 1H, *J* 15.2, 8.6, 1 × H_{14}), 3.75 (*s*, 3H, H_{NMe}), 3.48-3.56 (*m*, 1H, H_{15}), 3.00 (*dd*, 1H, *J* 15.2, 7.8, 1 × H_{14}), 2.97 (*m*, 2H, H_{16}); IR ν_{max} (film)/cm^{-1}: 2957 (w), 2934 (w),

2921 (w, br), 2866 (w, br), 1702 (s), 1681 (m, br), 1423 (m), 1375 (m), 1368 (m), 1254 (m), 1158 (m), 791 (s), 755 (s), 743 (m); HRMS (ESI) *m/z* 274.0860 $[M+Na]^+$, $[C_{16}H_{13}NO_2Na]^+$ requires 274.0844.

3-Acetyl-4-bromo-*N*-tosylindole (244)[3]

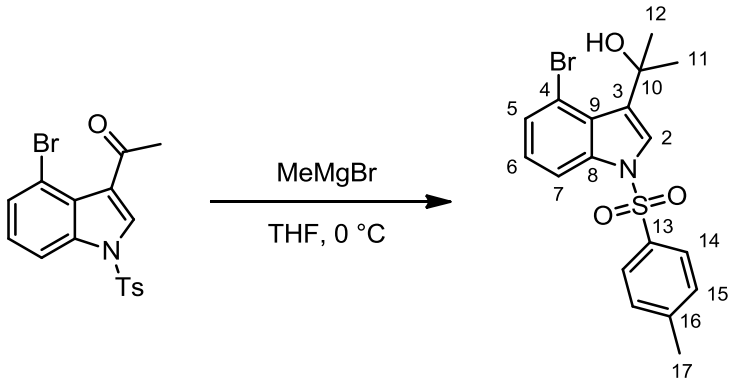


243 **244**

DMAP (122 mg, 1.0 mmol), *p*TsCl (4.20 g, 22.0 mmol) and DIPEA (5.23 mL, 30.0 mmol) were added to a solution of 3-acetyl-4-bromoindole (**243**) (4.76 g, 20.0 mmol) in dry CH_2Cl_2 (105 mL). The resulting solution was stirred at room temperature for 15 h and the reaction was quenched by addition of 10% HCl (100 mL). The reaction mixture was diluted with CH_2Cl_2 (80 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc, 7/3) to afford tosylated indole **244** (7.64 g, 98%) as an off-white foam; mp 141-142 °C, [lit.,[3] mp 142.5-143.0 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (*s*, 1H, H_2), 7.95 (*dd*, 1H, *J* 8.2, 0.9, H_5), 7.78 (*d*, 2H, *J* 8.6, H_{13}), 7.50 (*dd*, 1H, *J* 7.9, 0.9, H_7), 7.28 (*d*, 2H, *J* 8.6, H_{14}), 7.21 (*dd*, 1H, *J* 8.2, 7.9, H_6), 2.63 (*s*, 3H, H_{11}), 2.38 (*s*, 3H, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6 (C, C_{10}), 146.2 (C, C_{12}), 136.1 (C, C_8), 134.2 (C, C_4), 130.3 (CH_{Ar}, C_{14}), 130.2 (CH_{Ar}, C_2), 129.5 (CH_{Ar}, $C_{5\ or\ 7}$), 127.8 (CH_{Ar}, C_{13}), 127.1 (C, C_9), 126.5 (CH_{Ar},

C_6), 124.2 (C, C_{15}), 115.0 (C, C_3), 112.4 (CH_{Ar}, $C_{5\ or\ 7}$), 31.2 (CH_3, C_{11}), 21.6 (CH_3, C_{16}); IR ν_{max} (film)/cm^{-1}: 3116 (w), 1678 (m), 1595 (m), 1529 (m), 1416 (m), 1376 (s), 1305 (w), 1176 (s), 1170 (s), 1157 (s), 1092 (s), 979 (s), 928 (s), 809 (s), 776 (s), 716 (s), 666 (s); HRMS (ESI) *m/z* 413.9778 $[M+Na]^+$, $[C_{17}H_{14}NO_3S^{79}BrNa]^+$ requires 413.9775. Data were in agreement with those reported in the literature.

2-[4'-Bromo-1'-(tosyl)-1*H*-indol-3'-yl]-propan-2-ol (245)[3]

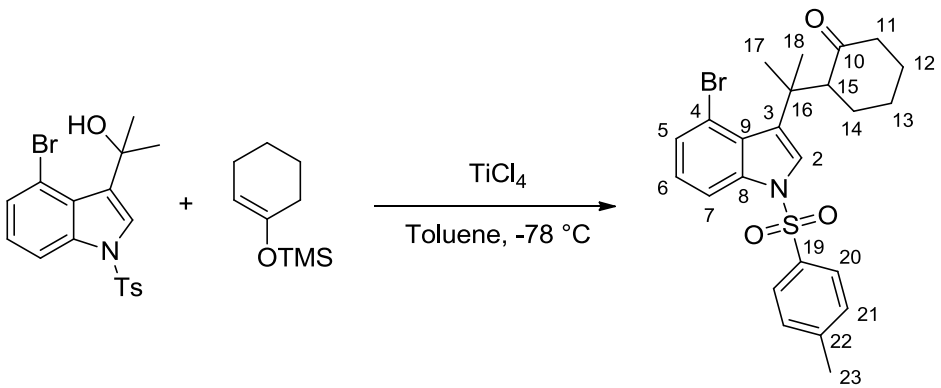


244 **245**

A solution of 3-acetyl-4-bromo-*N*-tosylindole (**244**) (5.99 mg, 15.3 mmol) in dry THF (110 mL) was added dropwise over 15 min *via* cannula to a solution of methylmagnesium bromide (3.00 M in Et_2O, 12.0 mL, 35.2 mmol) in dry THF (20 mL) pre-cooled to 0 °C. After stirring the reaction for 30 min, the starting material was fully consumed and the reaction was quenched with a 1:1 mixture of water and a solution of NH_4Cl (75 mL). The mixture was diluted with Et_2O (75 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 8/2) to afford tertiary alcohol **245** (6.07 g, 97%) as a white foam; mp 99.0-100.7 °C, [lit.,[3] mp 100-101 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02

(*dd*, 1H, *J* 8.2, 1.0, $H_{5\text{ or }7}$), 7.75 (*d*, 2H, *J* 8.6, H_{14}), 7.67 (*s*, 1H, H_2), 7.49 (*dd*, 1H, *J* 7.9, 1.0, $H_{5\text{ or }7}$), 7.25 (*d*, 2H, *J* 8.6, H_{15}), 7.15 (*dd*, 1H, *J* 8.2, 7.9, H_6), 3.06 (*br s*, 1H, H_{OH}), 2.36 (*s*, 3H, H_{17}), 1.81 (*s*, 6H, H_{11}, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (C, C_{13}), 137.5 (C, C_8), 134.7 (C, C_4), 130.0 (CH_{Ar}, C_{15}), 129.2 (C, $C_{9\text{ or }16}$), 128.9 (CH_{Ar}, $C_{5\text{ or }7}$), 128.3 (C, $C_{9\text{ or }16}$), 126.9 (CH_{Ar}, C_{14}), 125.3 (CH_{Ar}, C_6), 124.2 (CH_{Ar}, C_2), 117.8 (C, C_3), 113.1 (CH_{Ar}, $C_{5\text{ or }7}$), 68.9 (C, C_{10}), 31.7 (2 × CH_3, $C_{11\text{ and }12}$), 21.6 (CH_3, C_{17}); IR ν_{max}(film)/cm^{-1}: 3555 (w, br), 3427 (w, br), 2972 (w), 2931 (w), 1596 (m), 1456 (m), 1407 (m), 1366 (s, br), 1294 (m, br), 1169 (s), 1149 (s), 1090 (s), 1042 (m), 968 (m), 941 (m), 745 (m), 713 (s), 663 (s); HRMS (ESI) *m/z* 430.0085 $[M+Na]^+$, $[C_{18}H_{18}NO_3S^{79}BrNa]^+$ requires 430.0088. Data were in agreement with those reported in the literature.

2-[2'-(4''-Bromo-1''-(tosyl)-1*H*-indol-3''-yl]-propan-2'-yl)]cyclohexanone (247)[3]

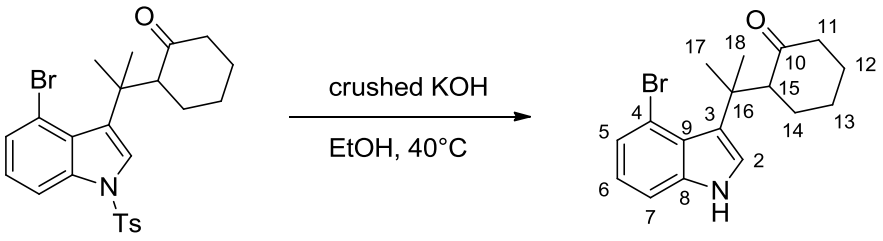


245 **246** **247**

A solution of silyl enol ether **246** (6.84 mL, 35.68 mmol) followed by a solution of $TiCl_4$ (1.00 M in toluene, 34.2 mL, 34.19 mmol) were added to a solution of tertiary alcohol **245** (6.07 mL, 14.87 mmol) in toluene (500 mL), pre-cooled to -78 °C. After stirring the reaction mixture for 1 h at -78 °C, the reaction was quenched by dropwise addition over 15 min of a

solution of $NaHCO_3$ (250 mL) at -78 °C. After warming to room temperature, water (200 mL) and CH_2Cl_2 (300 mL) were added to the reaction mixture and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were washed successively with $NaHCO_3$ (150 mL) then HCl (10% aqueous solution, 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/EtOAc (9/1 to 7/3) as eluent) to afford Mukaiyama product **247** (5.62 g, 79%) as a white solid; mp 73-74 °C [lit.,[3] mp 74-75 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (*d*, 1H, *J* 8.2, $H_{5 \text{ or } 7}$), 7.72 (*d*, 2H, *J* 8.4, H_{20}), 7.56 (*br s*, 1H, H_2), 7.51 (*d*, 1H, *J* 7.8, $H_{5 \text{ or } 7}$), 7.24 (*d*, 2H, *J* 8.4, H_{21}), 7.09 (*dd*, 1H, *J* 8.2, 7.8, H_6), 4.06 (*dd*, 1H, *J* 11.2, 4.6, H_{15}), 2.35 (*s*, 3H, H_{23}), 2.28 (*br s*, 2H, H_{11}), 1.99-2.03 (*m*, 1H), 1.57-1.91 (*m*, 3H), 1.72 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.56 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.42-1.55 (*m*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8 (C, C_{10}), 145.1 (C, C_{19}), 138.1 (C, C_8), 134.7 (C, C_4), 130.6 (C, C_{22}), 130.0 (CH_{Ar}, C_{21}), 129.9 (CH_{Ar}, $C_{5 \text{ or } 7}$), 129.0 (C, C_9), 126.9, (CH_{Ar}, C_{20}), 125.7 (CH_{Ar}, C_2), 124.8 ($CH_{Ar,}$ C_6), 113.8 (C, C_3), 113.3 (CH_{Ar}, $C_{5 \text{ or } 7}$), 56.0 (CH, C_{15}), 44.3 (CH_2, C_{11}), 36.2 (C, C_{16}), 30.2 (CH_2), 28.3 (CH_2), 26.0 (CH_3, $C_{17 \text{ or } 18}$), 25.9 (CH_2), 21.6 (CH_3, C_{23}), one CH_3 signal not observed; IR ν_{max} (film)/cm^{-1}: 2934 (w, br), 2862 (w), 1707 (m), 1596 (w), 1448 (w), 1359 (m, br), 1167 (s), 1090 (m), 966 (m), 721 (m), 668 (s); HRMS (ESI) *m/z* 510.0720 $[M+Na]^+$, $[C_{24}H_{26}NO_3S^{79}BrNa]^+$ requires 510.0714. Data were in agreement with those reported in the literature.

2-[2'-(4''-Bromo-1*H*-indol-3-yl)propan-2-yl]cyclohexanone (348)[3]

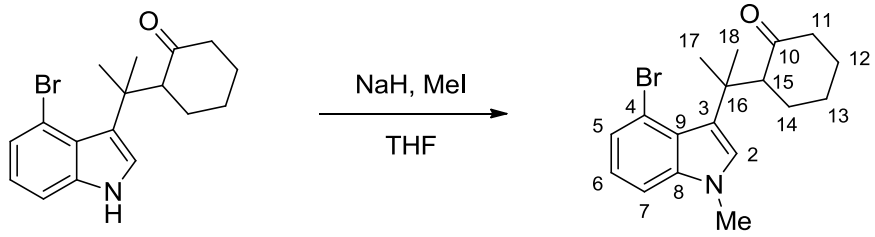


247 **348**

Crushed KOH (19.1 g, 340.3 mmol) was added to a solution of functionalised cyclohexanone **247** (8.3 g, 17.0 mmol) in degassed EtOH (720 mL) and the reaction mixture was stirred for 1 h at 40 °C. The pale yellow solution was cooled to room temperature and quenched with a solution of NH_4Cl (350 mL) to form a white precipitate. The mixture was extracted with Et_2O (2 × 250 mL) and the combined organic layers were washed with brine (350 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 8/2) to afford indole **348** (5.3 g, 93%) as a yellow foam; mp 163-164 °C [lit.,[3] 167-168 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (*br s*, 1H, H_{NH}), 7.41 (*dd*, 1H, *J* 7.8, 1.0, $H_{5 \text{ or } 7}$), 7.32 (*dd*, 1H, *J* 7.8, 1.0, $H_{5 \text{ or } 7}$), 7.13 (*d*, 1H, *J* 2.5, H_2), 6.99 (*app t*, 1H, *J* 7.8, H_6), 4.24 (*dd*, 1H, *J* 11.9, 4.7, H_{15}), 2.26-2.45 (*m*, 2H), 2.01-2.09 (*m*, 1H), 1.76 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.70-1.87 (*m*, 2H), 1.57 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.44-1.70 (*m*, 3H); ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (*dd*, 1H, *J* 8.0, 0.7, $H_{5 \text{ or } 7}$), 7.30 (*dd*, 1H, *J* 7.7, 0.7, $H_{5 \text{ or } 7}$), 7.17 (*s*, 1H, H_2), 6.93 (*app t*, 1H, *J* 8.0, 7.7, H_6), 4.26 (*dd*, 1H, *J* 9.1, 3.4, H_{15}), 2.35-2.43 (*m*, 1H, 1 × H_{11}), 2.20-2.24 (*m*, 1H, 1 × H_{11}), 2.03-2.07 (*m*, 1H, H_{12}), 1.74 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.70-1.87 (*m*, 2H, 1 × H_{13}, 1 × H_{14}), 1.53 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.43-1.70 (*m*, 3H, 1 × H_{12}, 1 × H_{13}, 1 × H_{14}); ^{13}C NMR (100 MHz, CD_3OD) δ 216.5 (C, C_{10}), 142.3 (C, C_8), 130.3 (C, C_4), 127.1 (CH_{Ar}, $C_{5 \text{ or } 7}$), 126.6 (C, C_9), 126.2 (CH_{Ar}, $C_{5 \text{ or } 7}$), 123.6 (CH_{Ar}, C_2), 114.9 (C, C_3), 113.2 (CH_{Ar}, C_6), 59.7 (CH, C_{15}), 46.3 (CH_2, C_{11}), 38.2 (C, C_{16}), 32.9 (CH_2, $C_{13 \text{ or } 14}$), 30.8 (CH_2, C_{12}), 28.0 (CH_2, $C_{13 \text{ or } 14}$), 29.7 (CH_3, $C_{17 \text{ or } 18}$), 26.6 (CH_3, $C_{17 \text{ or } 18}$); IR ν_{max} (film)/cm^{-1}:

3274 (m, br), 2940 (m, br), 1683 (s), 1452 (m), 1326 (m), 1311 (m), 1175 (m), 806 (m), 723 (s); HRMS (ESI) *m/z* 356.0623 $[M+Na]^+$, $[C_{17}H_{20}NO^{79}BrNa]^+$ requires 356.0626. Data were in agreement with those reported in the literature.

2-[2'-(4''-Bromo-1''-methyl-1*H*-indol-3''-yl)propan-2'-yl]cyclohexanone (169)[3]

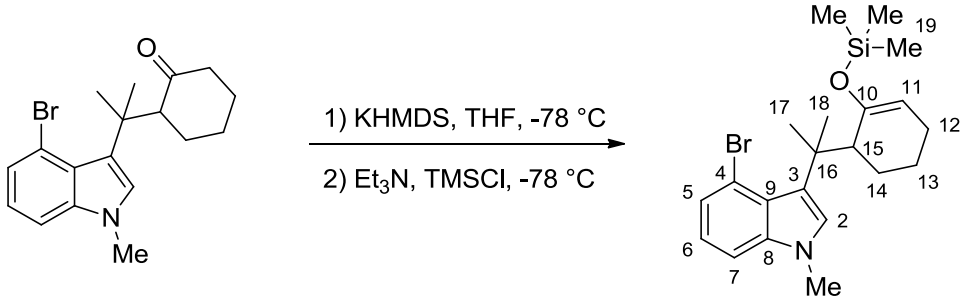


348 **169**

A solution of indole **348** (8.55 g, 25.6 mmol) in THF (50 mL) was added dropwise over 15 min to a suspension of NaH (1.53 g of a 60% dispersion in mineral oil, 38.4 mmol) in THF (20 mL), pre-cooled to 0 °C. After complete addition, the reaction mixture was allowed to warm to room temperature for 45 min. The reaction mixture was cooled to 0 °C before addition of a solution of iodomethane (3.18 mL, 51.2 mmol). The ice-bath was removed and the reaction mixture was stirred overnight at room temperature. After 14 h, the reaction was quenched with a 1:1 mixture of water and methanol (70 mL). The mixture was extracted with Et_2O (2 × 80 mL) and the phases were separated. The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 8/2) to afford methylated indole **169** (8.62 g, 97%) as a white foam; mp 77-78 °C [lit.,[3] 80-81 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (*dd*, 1H, *J* 7.6, 1.0, H_5), 7.26 (*d*, 1H, *J* 8.1, 1.0, H_7), 7.03 (*dd*, 1H, *J* 8.1, 7.6, H_6), 7.01 (*s*, 1H, H_2), 4.23 (*dd*, 1H, *J* 12.6, 4.6, H_{15}), 3.74 (*s*, 3H, H_{NMe}), 2.33-2.42

(*m*, 1H, 1 × H_{11}), 2.24-2.31 (*m*, 1H, 1 × H_{11}), 2.02-2.07 (*m*, 1H, 1 × H_{12}), 1.70-1.95 (*m*, 2H, 1 × H_{13}, 1 × H_{14}), 1.77 (*s*, 3H, $H_{17\ or\ 18}$), 1.55-1.70 (*m*, 2H, 1 × H_{12}, 1 × H_{13}), 1.56 (*s*, 3H, $H_{17\ or\ 18}$), 1.40-1.55 (*m*, 1H, 1 × H_{14}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9 (C, C_{10}), 139.8 (C, C_8), 128.6 (CH_{Ar}, C_2), 125.3 (CH_{Ar}, C_5), 125.2 (C, C_4), 123.9 (C, C_9), 121.7 (CH_{Ar}, C_6), 113.7 (C, C_3), 108.9 (CH_{Ar}, C_7), 57.3 (CH_3, C_{15}), 44.5 (CH_2, C_{11}), 36.1 (C, C_{16}), 33.0 (CH_3, C_{NMe}), 30.8 (CH_2, C_{14}), 28.6 (CH_2, C_{12}), 27.7 (CH_3, $C_{17\ or\ 18}$), 26.1 (CH_2, C_{13}), 26.1 (CH_3, $C_{17\ or\ 18}$); IR ν_{max} (film)/cm^{-1}: 2932 (w, br), 2862 (w), 1703 (s), 1546 (w), 1447 (m), 1416 (m), 1381 (w), 1359 (w), 1317 (w), 1113 (s), 1059 (w), 984 (w), 839 (w), 774 (m), 732 (s); HRMS (ESI) *m/z* 370.0783 $[M+Na]^+$, $[C_{18}H_{22}NO^{79}BrNa]^+$ requires 370.0782. Data were in agreement with those reported in the literature.

4-Bromo-1-(methyl)-3-(2'-(2''-((trimethylsilyloxy)cyclohex-2''-en-1''-yl)propan-2'-yl)-1*H*-indole (211)[7]

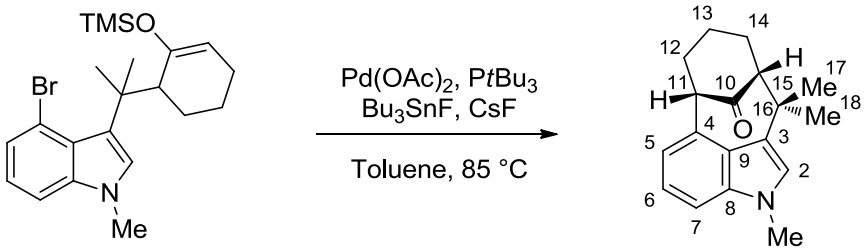


169 **211**

A solution of KHMDS (0.5 M in toluene, 11.02 mL, 5.51 mmol) was added dropwise over 8 min to the solution of cyclohexanone **169** (1.75 g, 5.01 mmol) in THF (43 mL), pre-cooled to -78 °C. The resulting solution turned yellow in colour. The reaction mixture was stirred for 30 min at this temperature before addition of freshly distilled TMSCl (3.18 mL, 25.1 mmol). The reaction mixture was stirred for a further 10 min at -78 °C then freshly distilled Et_3N (7.02 mL, 50.1 mmol) was added to the yellow solution. After 5 min at -78 °C, the reaction

was quenched with a solution of $NaHCO_3$ (20 mL of an aqueous saturated solution). The reaction mixture was allowed to warm to room temperature, then was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 9/1 + 1% Et_3N) to afford silyl enol ether **211** (1.67 g, 79%, 91% BRSM) as a colourless sticky foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (*dd*, 1H, *J* 7.6, 1.0, H_5), 7.25 (*dd*, 1H, *J* 8.1, 1.0, H_7), 7.01 (*app t*, 1H, *J* 8.1, 7.6, H_6), 6.92 (*s*, 1H, H_2), 4.92 (*t*, 1H, *J* 3.6, H_{11}), 3.71-3.78 (*m*, 1H, H_{15}), 3.72 (*s*, 3H, H_{NMe}), 1.97 (*br s*, 2H, H_{12}), 1.62 (*br s*, 4H, 1 × H_{13}, $H_{17\ or\ 18}$), 1.50 (*s*, 3H, $H_{17\ or\ 18}$), 1.36 (*br s*, 3H, 1 × H_{13}, H_{14}), -0.05 (br s, 9H, H_{19}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7 (C, C_{10}), 139.6 (C, C_8), 127.5 (CH_{Ar}, C_2), 125.8 (C, C_4), 125.0 (CH_{Ar}, C_5), 125.0 (C, C_9), 121.5 (CH_{Ar}, C_6), 114.1 (C, C_3), 108.6 (CH_{Ar}, C_7), 106.6 (CH, C_{11}), 45.8 (CH_3, C_{15}), 37.1 (C, C_{16}), 32.9 (CH_3, C_{NMe}), 27.6 (CH_3, $C_{17\ or\ 18}$), 27.5 (CH_2, C_{14}), 24.5 (CH_2, C_{12}), 22.7 (CH_2, C_{13}), 22.7 (CH_3, $C_{17\ or\ 18}$), 0.45 (CH_3, C_{19}); IR ν_{max} (film)/cm^{-1}: 2930 (m, br), 2861 (w), 1596 (w), 1547 (w), 1448 (m), 1405 (m), 1364 (s), 1311 (w), 1172(s), 1152 (s), 1091 (m), 966 (m), 668 (s); HRMS (ESI) *m/z* 442.1175 $[M+Na]^+$, $[C_{21}H_{30}NO^{79}BrSiNa]^+$ requires 442.1178. Data were in agreement with those reported in the literature.

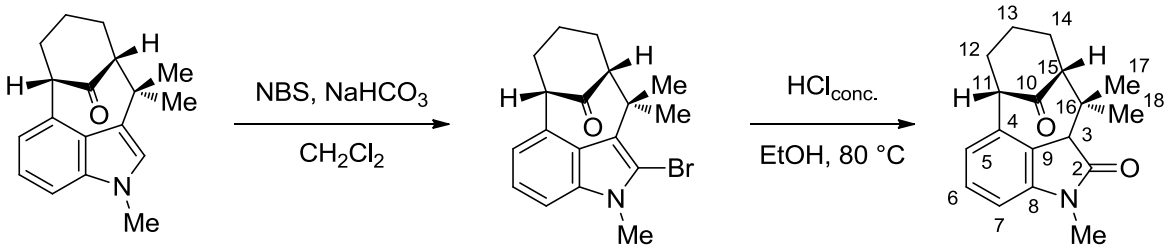
Preparation of bridged ketone 170[7]



211 **170**

A solution of P*t*Bu_3 (1.00 M intoluene, 333 µL, 0.333 mmol) followed by a solution of silyl enol ether **211** (2.80 g, 6.66 mmol) in toluene (12 mL) were added to a solution of palladium acetate (50.8 mg, 0.226 mmol), Bu_3SnF (2.47 g, 7.99 mmol) and CsF (1.21 g, 7.99 mmol) in toluene (50 mL). The reaction mixture was heated at 85 °C for 48 h. The resulting solution was cooled to room temperature and diluted with Et_2O (25 mL). The reaction mixture was filtered through a pad of silica (using Et_2O as eluent) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 85/15) to afford bicyclo[4.3.1]core structure **170** (1.63 g, 92%) as a colourless foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.24 (*m*, 2H, $H_{5\text{ or }7}$, H_6), 6.95 (*s*, 1H, H_2), 6.84 (*dd*, 1H, *J* 6.7, 1.1, $H_{5\text{ or }7}$), 4.05-4.09 (*m*, 1H, H_{11}), 3.76 (*s*, 3H, H_{NMe}), 2.60 (*dt*, 1H, *J* 7.1, 1.9, H_{15}), 2.18-2.32 (*m*, 2H, 1 × H_{12}, 1 × H_{14}), 1.82-1.98 (*m*, 2H, 1 × H_{12}, 1 × H_{14}), 1.55 (*s*, 3H, $H_{17\text{ or }18}$), 1.19-1.26 (*m*, 1H, 1 × H_{13}), 1.33-1.48 (*m*, 1H, 1 × H_{13}), 1.15 (*s*, 3H, $H_{17\text{ or }18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5 (C, C_{10}), 136.9 (C, C_8), 132.0 (C, C_4), 126.0 (CH_{Ar}, C_2), 125.3 (C, C_9), 122.7 (C, C_3), 122.3 (CH_{Ar}, C_6), 118.3 (CH_{Ar}, $C_{5\text{ or }7}$), 107.2 (CH_{Ar}, $C_{5\text{ or }7}$), 61.3 (CH, C_{15}), 58.2 (CH, C_{11}), 39.6 (CH_2, C_{12}), 36.3 (CH_3, $C_{17\text{ or }18}$), 34.9 (C, C_{16}), 32.8 (CH_3, C_{NMe}), 28.7 (CH_2, C_{14}), 28.1 (CH_3, $C_{17\text{ or }18}$), 18.1 (CH_2, C_{13}); IR ν_{max} (film)/cm^{-1}: 2924 (m, br), 1694 (s), 1454 (m), 1419 (m), 1366 (m), 1248 (m), 1227 (m), 1064 (m, br), 789 (m), 743 (s); HRMS (ESI) *m/z* 290.1510 $[M+Na]^+$, $[C_{18}H_{21}NONa]^+$ requires 290.1521. Data were in agreement with those reported in the literature.

Preparation of oxindole 248

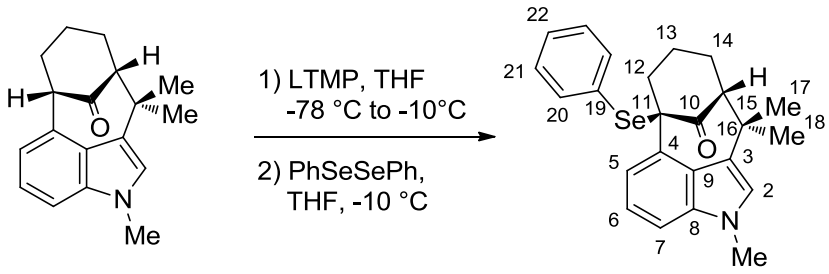


To a colourless solution of indole **170** (29.5 mg, 0.11 mmol) in CH_2Cl_2 (0.6 mL) was added NBS (21.6 mg, 0.121 mmol) in one portion. The reaction turned orange instantaneously. After 15 min of stirring at room temperature, $NaHCO_3$ (12 mg) was added in one portion to the reaction mixture and the suspension was stirred for another 5 min. The resulting suspension was filtered through a pad of silica (petroleum ether/ethyl acetate, 8/2) to afford brominated compound **349** (41.7 mg) as a red solution; HRMS (ESI) *m/z* 368.0630 $[M+Na]^+$, $[C_{18}H_{20}NO^{79}BrNa]^+$ requires 368.0626. Bromide **349** was carried on to the next step without further purification.

Bromide **349** (41.7 mg) was solubilised in absolute EtOH (2.5 mL) and concentrated HCl (2.5 mL) was added dropwise over 1 min. After heating the suspension at 80 °C for 14 h, the reaction mixture was cooled to room temperature. EtOAc (5 mL) and H_2O (5 mL) were added to the black solution followed by addition of solid $NaHCO_3$. The solution was stirred until no more gas evolution was observed. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford oxindole **248** (7.9 mg, 25%) as yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (*app t*, 1H, *J* 7.7, H_6), 6.82 (*d*, 1H, *J* 7.7, H_5), 6.72 (*d*, 1H, *J* 7.7, H_7), 3.92 (*s*, 1H, H_3), 3.62-3.66 (*m*, 1H, H_{11}), 3.20 (*s*, 3H, H_{NMe}), 2.42-2.49 (*m*, 2H, H_{15}, 1 × H_{14}), 2.18-2.26 (*m*, 2H, H_{12}), 1.99-2.13 (*m*, 1H, 1 × H_{14}), 1.80-1.96

(*m*, 1H, 1 × H_{13}), 1.57-1.64 (*m*, 1H, 1 × H_{13}), 1.62 (*s*, 3H, $H_{17\ or\ 18}$), 0.70 (*s*, 3H, $H_{17\ or\ 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (C, C_{10}), 175.3 (C, C_2), 144.5 (C, C_8), 135.0 (C, C_4), 128.8 (CH_{Ar}, C_6), 124.8 (C, C_9), 124.0 (CH_{Ar}, C_5), 106.6 (CH_{Ar}, C_7), 62.3 (CH, C_{15}), 58.3 (CH, C_{11}), 53.0 (CH, C_3), 39.8 (C, C_{16}), 35.9 (CH_2, C_{12}), 27.6 (CH_2, C_{14}), 26.2 (CH_3, C_{NMe}), 26.0 (CH_3, $C_{17\ or\ 18}$), 23.0 (CH_3, $C_{17\ or\ 18}$), 20.1 (CH_2, C_{13}); IR ν_{max} (film)/cm^{-1}: 2967 (w), 2940 (w), 1855 (w), 1698 (s), 1607 (m), 1594 (m), 1463 (m, br), 1343 (w), 1298 (w), 1252 (w), 1038 (w), 985 (w), 775 (m), 727 (m); HRMS (ESI) *m/z* 306.1477 $[M+Na]^+$, $[C_{18}H_{21}NO_2Na]^+$ requires 306.1470.

Preparation of selenide 215[7]



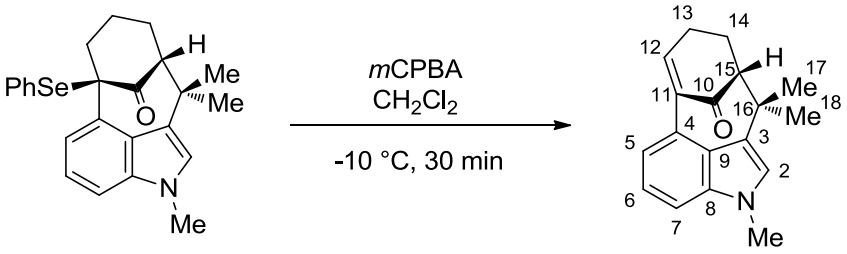
170 **215**

Preparation of the solution of LTMP (0.4 M):

A solution of *n*BuLi (1.6 M in hexanes, 10.2 mL, 17.7 mmol) was added to a solution of freshly distilled 2,2,6,6-tetramethylpiperidine (2.75 mL, 2.50 g, 17.7 mmol) in THF (27.8 mL), pre-cooled to -78 °C, was added. The solution was stirred for 5 min at -78 °C, then was allowed to warm to room temperature for 20 min and cooled to -78 °C prior to its transfer to the solution of the substrate.

The solution of LTMP at -78 °C and immediately afterwards a solution of PhSeSePh (5.08 g, 16.3 mmol) in THF (8 mL) were added to a solution of the tetracyclic core **170** (435.4 mg, 1.63 mmol) in THF (24 mL), pre-cooled to -10 °C. The resulting orange mixture was stirred for 1 h at -10 °C, time by which the starting material was fully consumed. The reaction was quenched with a solution of NH_4Cl (30 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/EtOAc/toluene (9/0.5/0.5 to 8/2/0) as eluent) to afford selenylated product **215** (287.7 mg, 42%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (*dd*, 1H, *J* 7.1, 1.4, H_{22}), 7.65-7.68 (*m*, 2H, $H_{20\ or\ 21}$), 7.15-7.26 (*m*, 5H, $H_{20\ or\ 21}$, H_5, H_6, H_7), 6.96 (*s*, 1H, H_2), 3.74 (*s*, 3H, H_{NMe}), 2.77 (*dd*, 1H, *J* 7.5, 3.4, H_{15}), 2.50 (*dtd*, 1H, *J* 12.8, 2.0, 1.9, 1 × H_{12}), 2.40 (*ddd*, 1H, *J* 12.8, 10.4, 4.8, 1 × H_{12}), 2.10-2.21 (*dm*, 1H, *J* 14.3, 1 × H_{14}), 1.70-1.83 (*m*, 1H, 1 × H_{14}), 1.50 (*s*, 3H, $H_{17\ or\ 18}$), 1.38-1.48 (*m*, 1H, 1 × H_{13}), 1.28 (*s*, 3H, $H_{17\ or\ 18}$), 1.22-1.27 (*m*, 1H, 1 × H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9 (C, C_{10}), 136.7 (C, C_8), 136.3 (CH_{Ar}, $C_{20\ or\ 21}$), 133.0 (C, $C_{4\ or\ 11}$), 130.8 (C, $C_{4\ or\ 11}$), 128.4 (CH_{Ar}, $C_{20\ or\ 21}$), 127.6 (CH_{Ar}, C_5), 126.5 (CH_{Ar}, C_2), 124.4 (C, C_9), 122.3 (C, C_3), 122.1 (CH_{Ar}, C_6), 119.7 (CH_{Ar}, C_{22}), 108.3 (CH_{Ar}, C_7), 60.6 (CH, C_{15}), 46.0 (CH_2, C_{12}), 36.2 (CH_3, $C_{17\ or\ 18}$), 34.9 (C, C_{16}), 32.9 (CH_3, C_{NMe}), 29.3 (CH_3, $C_{17\ or\ 18}$), 27.4 (CH_2, C_{14}), 20.5 (CH_2, C_{13}), C_{11} was not observed; IR ν_{max} (film)/cm^{-1}: 2928 (m, br), 2862 (m), 1697 (m), 1437 (m), 1416 (m), 739 (s), 692 (m); HRMS (ESI) *m/z* 446.1001 $[M+Na]^+$, $[C_{24}H_{25}NOSeNa]^+$ requires 446.0999. Data were in agreement with those reported in the literature.

Preparation of bridehead alkene 171[7]

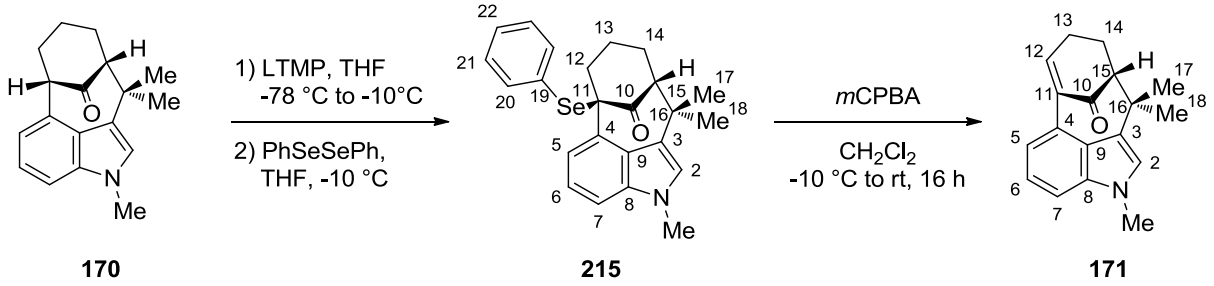


215 **171**

*m*CPBA (70%, 513 mg, 2.08 mmol) was added in one portion to a solution of keto-selenide **215** (877 mg, 2.08 mmol) in CH_2Cl_2 (80 mL), pre-cooled to -10 °C. The reaction was monitored by TLC and after 15-20 min, total consumption of the starting material was observed. The reaction mixture was quenched with water (60 mL) and allowed to warm to room temperature. The phases were separated and the organic phase was washed with a saturated solution of Na_2SO_3 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with a solution of NH_4Cl (30 mL), then brine (2 × 25 mL). The aqueous layers were extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford bridgehead alkene **171** (343.1 mg, 62%) as a yellow solid.

Bridgehead alkene 171

Alternative procedure:



Preparation of the solution of LTMP (0.4 M):

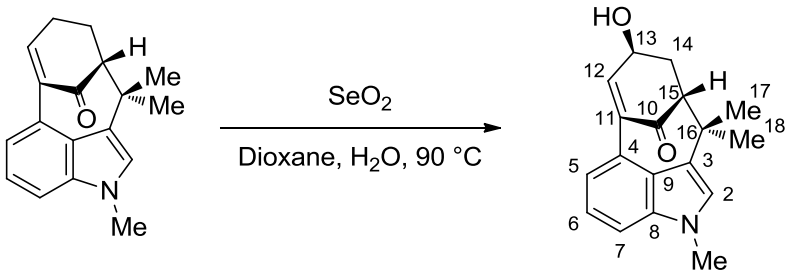
A solution of *n*BuLi (1.6 M in hexanes, 4.8 mL, 7.7 mmol) was added to a solution of freshly distilled 2,2,6,6-tetramethylpiperidine (1.3 mL, 1.09 g, 7.7 mmol) in THF (11.4 mL) pre-cooled to -78 °C. The solution was stirred for 5 min at -78 °C, then allowed to warm to room temperature for 20 min and cooled to -78 °C prior to its transfer to the solution of the substrate.

The solution of LTMP, pre-cooled to -78 °C, was added to a solution of the tetracyclic core **170** (411.7 mg, 1.54 mmol) in THF (15 mL), pre-cooled to -10 °C. The resulting orange mixture was stirred for 10 min at -10 °C and a solution of PhSeSePh (2.4 g, 7.7 mmol) in THF (6 mL) was added. The dark orange solution was stirred for an additional 40 min until the TLC showed full consumption of starting material. The mixture was then quenched with a solution of NH_4Cl (30 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The yellow oil crude product was used into the next step without any further purification.

*m*CPBA (70%, 2.28 g, 9.24 mmol) was added in one portion to a solution of the ketoselenide crude **215** in CH_2Cl_2 (65 mL), pre-cooled to -10 °C. The reaction mixture was allowed to warm to 0 °C and was stirred for 1 h at 0 °C. The ice-bath was then removed and the reaction

was allowed to stir at room temperature for another 18 h. The reaction mixture was quenched with water (30 mL) then $Na_2S_2O_3$ (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with a solution of NH_4Cl (30 mL) then brine (40 mL). A final wash using a solution of Na_2CO_3 (2 × 40 mL) was performed to remove any *m*CPBA adducts. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford bridgehead alkene **171** (336.4 mg, 82%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (*dd*, 1H, *J* 8.3, 6.6, H_6), 7.16 (*dd*, 1H, *J* 8.3, 1.2, H_5), 7.05 (*dd*, 1H, *J* 6.6, 1.2, H_7), 6.92 (*s*, 1H, H_2), 6.33 (*dd*, 1H, *J* 7.2, 4.3, H_{12}), 3.73 (*s*, 3H, H_{NMe}), 2.84 (*dd*, 1H, *J* 7.6, 4.9, H_{15}), 2.28-2.40 (*m*, 1H, 1 × H_{13}), 2.14-2.21 (*m*, 2H, 1 × H_{13}, 1 × H_{14}), 1.97-2.06 (*m*, 1H, 1 × H_{14}), 1.45 (*s*, 3H, $H_{17\text{ or }18}$), 1.36 (*s*, 3H, $H_{17\text{ or }18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6 (C, C_{10}), 142.0 (C, C_{11}), 135.9 (C, C_8), 132.9 (CH, C_{12}), 130.8 (C, C_4), 126.9 (CH, C_2), 124.8 (C, C_9), 123.5 (C, C_3), 122.4 (CH, C_6), 113.7 (CH, C_7), 108.4 (CH, C_5), 59.5 (CH, C_{15}), 36.9 (C, C_{16}), 34.3 (CH_3, $C_{17\text{ or }18}$), 32.8 (CH_3, C_{NMe}), 29.3 (CH_3, $C_{17\text{ or }18}$), 24.6 (CH_2, C_{14}), 22.9 (CH_2, C_{13}); IR ν_{max} (film)/cm^{-1}: 2969 (w), 2940 (w), 2921 (w), 2858 (w), 1704 (s), 1520 (w), 1415 (m), 1254 (m), 1212 (m), 1150 (m), 869 (m), 788 (m), 751 (s); HRMS (ESI) *m/z* 288.1369 $[M+Na]^+$, $[C_{18}H_{19}NONa]^+$ requires 288.1364. Data were in agreement with those reported in the literature.

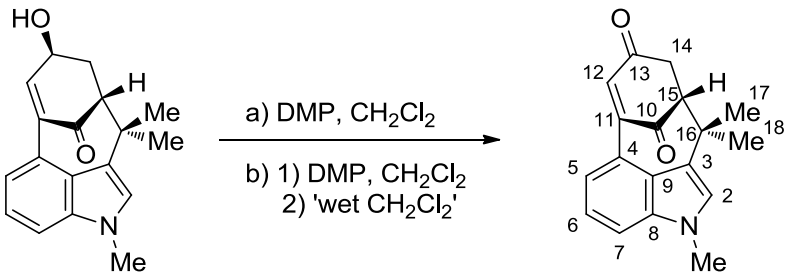
Preparation of allylic alcohol 216[7]



171 **216**

Selenium dioxide (23 mg, 0.207 mol) was added in one portion to a solution of bridged alkene **171** (50 mg, 0.188 mmol) in dioxane (1.2 mL) and H_2O (70 µL). The reaction mixture was stirred at 90 °C overnight. After cooling to room temperature, the mixture was quenched with water (5 mL) and diluted with CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (8/2 to 4/6) as eluent) to afford alcohol **216** (25.7 mg, 49%) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.23 (*m*, 2H, $H_{6 \text{ and } 7}$), 7.05 (*dd*, 1H, *J* 5.9, 2.0, H_5), 6.95 (*s*, 1H, H_2), 6.45 (*d*, 1H, *J* 5.8, H_{12}), 4.66 (*ddd*, 1H, *J* 5.8, 3.0, 2.8, H_{13}), 3.73 (*s*, 3H, H_{NMe}), 2.96 (*dd*, 1H, *J* 7.5, 4.9, H_{15}), 2.43 (*ddd*, 1H, *J* 14.2, 7.5, 2.8, 1 × H_{14}), 2.13 (*ddd*, 1H, *J* 14.2, 4.9, 3.0, 1 × H_{14}), 1.82 (*br s*, 1H, H_{OH}), 1.47 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.40 (*s*, 3H, $H_{17 \text{ or } 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0 (C, C_{10}), 145.9 (C, C_{11}), 135.7 (C, C_8), 134.2 (CH, C_{12}), 130.2 (C, C_4), 127.7 (CH_{Ar}, C_2), 123.9 (C, C_9), 122.9 (C, C_3), 122.3 (CH_{Ar}, C_6), 113.6 (CH_{Ar}, C_5), 108.9 (CH_{Ar}, C_7), 64.8 (CH, C_{13}), 55.6 (CH, C_{15}), 37.2 (C, C_{16}), 35.8 (CH_3, $C_{17 \text{ or } 18}$), 35.2 (CH_2, C_{14}), 32.8 (CH_3, C_{NMe}), 29.2 (CH_3, $C_{17 \text{ or } 18}$); IR ν_{max} (film)/cm^{-1}: 3336 (m, br), 2973 (m), 2927 (w), 2891 (w), 1696 (m), 1377 (m), 1088 (m), 1046 (s), 880 (m), 747 (m), 737 (m); HRMS (ESI) *m/z* 304.1320 $[M+Na]^+$, $[C_{18}H_{19}NONa]^+$ requires 304.1313. Data were in agreement with those reported in the literature.

Preparation of bridgehead enone 214[7]



216 **214**

Method a:

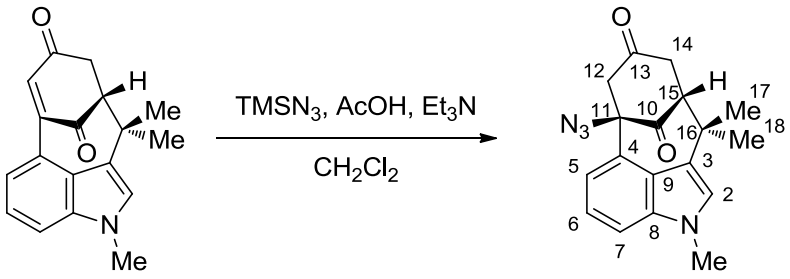
Dess-Martin periodinane (121.1 mg, 0.29 mmol) was added in one portion to a solution of functionalised alcohol **216** (53.5 mg, 0.19 mmol) in CH_2Cl_2 (2.5 mL). The resulting yellow solution was stirred at room temperature for 1 h. The reaction mixture was quenched with water (5 mL) and diluted with CH_2Cl_2 (10 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (8/2 to 6/4) as eluent) to afford enone **214** (17.3 mg, 33%) as dark pink solid.

Method b:

An oven-dried round-bottom flask, purged with nitrogen, was charged with the allylic alcohol **216** (127 mg, 0.45 mmol) in dry CH_2Cl_2 (3 mL). A solution of Dess-Martin periodinane (287 mg, 0.68 mmol) in dry CH_2Cl_2 (3 mL) was added to the yellow solution. The resulting orange solution was stirred vigorously for 20 min. H_2O (9 µL, 0.5 mmol) was solvated in dry CH_2Cl_2 (9 mL) by drawing the solvent mixture into and expelling it from a disposable pipette several times. The "wet CH_2Cl_2" was then added to the orange solution dropwise over 20 min.

The mixture was diluted with Et_2O (10 mL) then concentrated into a few mL of solvent under reduced pressure. The residue was dissolved in Et_2O (25 mL) and washed with a 1:1 mixture of 10% $Na_2S_2O_3$:$NaHCO_3$. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed successively with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 6/4) to afford enone **214** (102.9 mg, 82%) as dark pink solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.27 (*m*, 2H, $H_{6 \text{ and } 7}$), 7.15 (*dd*, 1H, *J* 4.0, 4.0, H_5), 6.94 (*s*, 1H, H_2), 6.41 (*d*, 1H, *J* 1.0, H_{12}), 3.75 (*s*, 3H, H_{NMe}), 3.28 (*dd*, 1H, *J* 5.5, 0.7, H_{15}), 3.18 (*ddd*, 1H, *J* 19.1, 1.8, 0.7, 1 × H_{14}), 2.86 (*ddd*, 1H, *J* 19.1, 5.5, 1.0, 1 × H_{14}), 1.59 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.27 (*s*, 3H, $H_{17 \text{ or } 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5 (C, C_{10}), 195.3 (C, C_{13}), 159.6 (C, C_{11}), 136.6 (C, C_8), 128.7 (C, C_4), 128.0 (CH, C_{12}), 126.5 (CH_{Ar}, C_2), 125.3 (C, C_9), 124.2 (C, C_3), 122.5 (CH_{Ar}, C_6), 113.6 (CH_{Ar}, C_5), 110.5 (CH_{Ar}, C_7), 60.3 (CH, C_{15}), 39.7 (CH_2, C_{14}), 35.5 (C, C_{16}), 32.9 (CH_3, C_{NMe}), 30.7 (CH_3, $C_{17 \text{ or } 18}$), 30.2 (CH_3, $C_{17 \text{ or } 18}$); IR ν_{max} (film)/cm^{-1}: 2969 (w), 2940 (w), 2921 (w, br), 2866 (w, br), 1705 (s), 1677 (m, br), 1520 (w), 1415 (m), 1372 (m), 1363 (m), 1251 (m), 1212 (m), 1150 (m), 868 (w), 788 (s), 751 (s), 741 (s); HRMS (ESI) *m/z* 302.1148 $[M+Na]^+$, $[C_{18}H_{17}NO_2Na]^+$ requires 302.1157. Data were in agreement with those reported in the literature.

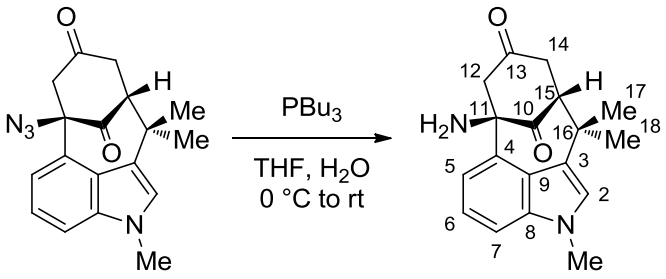
Preparation of azide 217[7]



214 **217**

An oven-dried round-bottom flask, purged with nitrogen, was charged with $TMSN_3$ (318 µL, 2.39 mmol) in dry CH_2Cl_2 (3 mL). AcOH (140 µL, 2.39 mmol) was added to the colourless solution and the resulting solution was stirred vigorously for 20 min. A solution of enone **214** (133.4 mg, 0.478 mmol) in dry CH_2Cl_2 (3 mL) and freshly distilled Et_3N (13 µL, 0.10 mmol) were added to the colourless solution which turned dark orange. The mixture was stirred for 1 h at room temperature and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 6/4) to afford azide **217** (137.5 mg, 89%) as pink needles; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (*dd*, 1H, *J* 7.4, 1.2, H_5), 7.38 (*dd*, 1H, *J* 8.0, 7.4, H_6), 7.32 (*dd*, 1H, *J* 8.0, 1.2, H_7), 7.04 (*s*, 1H, H_2), 3.79 (*s*, 3H, H_{NMe}), 3.10 (*d*, 1H, *J* 17.1, H_{12}), 3.04 (*dd*, 1H, *J* 8.9, 6.9, H_{15}), 2.98 (*d*, 1H, *J* 17.1, H_{12}), 2.86 (*d*, 1H, *J* 6.9, 1 × H_{14}), 2.83 (*d*, 1H, *J* 8.9, 1 × H_{14}), 1.49 (*s*, 3H, $H_{17\ or\ 18}$), 1.33 (*s*, 3H, $H_{17\ or\ 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2 (C, C_{10}), 204.0 (C, C_{13}), 137.3 (C, C_8), 128.1 (CH_{Ar}, C_2), 127.5 (C, C_4), 122.8 (CH_{Ar}, C_6), 122.6 (C, C_9), 119.2 (C, C_3), 118.6 (CH_{Ar}, C_5), 110.2 (CH_{Ar}, C_7), 74.9 (C, C_{11}), 55.4 (CH, C_{15}), 55.4 (CH_2, C_{12}), 42.7 (CH_2, C_{14}), 36.9 (C, C_{16}), 33.0 (CH_3, C_{NMe}), 32.9 (CH_3, $C_{17\ or\ 18}$), 29.0 (CH_3, $C_{17\ or\ 18}$); IR ν_{max} (film)/cm^{-1}: 2970 (w, br), 2921 (w, br), 2117 (s), 1715 (s), 1449 (w), 1418 (w), 1248 (m, br), 995 (w), 733 (s); HRMS (ESI) *m/z* 345.1341 $[M+Na]^+$, $[C_{18}H_{18}N_4O_2Na]^+$ requires 345.1327. Data were in agreement with those reported in the literature.

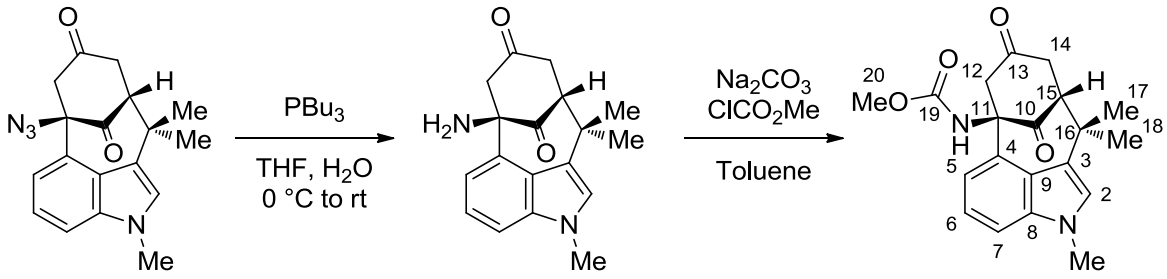
Preparation of amine 268



217 **268**

To a solution of azide **217** (60 mg, 0.19 mmol) in THF (8.5 mL) and H_2O (343 µL) pre-cooled to 0 °C, was added dropwise over 1 min PBu_3 (93 µL, 0.37 mmol). The resulting solution was stirred for 15 min at 0 °C and was then allowed to warm up to room temperature. After 1 h at room temperature, the reaction showed total consumption of starting material. The solvent was evaporated under reduced pressure. The residue was diluted in CH_2Cl_2 (5 mL) and H_2O (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with 1 M NaOH (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The red crude solution was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (5/5 to 3/7) as eluent) to afford amine **268** (30.8 mg, 56%) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (*dd*, 1H, *J* 7.4, 1.1, H_5), 7.32 (*dd*, 1H, *J* 8.1, 7.4, H_6), 7.26 (*dd*, 1H, *J* 8.1, 1.1, H_7), 7.00 (*s*, 1H, H_2), 4.01 (*br s*, 2H, H_{NH2}), 3.77 (*s*, 3H, H_{NMe}), 3.26 (*d*, 1H, *J* 17.0, 1 × H_{12}), 3.01 (*dd*, 1H, *J* 9.4, 6.8, H_{15}), 2.90 (*d*, 1H, *J* 17.0, 1 × H_{12}), 2.75-2.82 (*m*, 1H, 1 × H_{14}), 2.79 (*d*, 1H, *J* 17.0, 1 × H_{12}), 1.47 (*s*, 3H, $H_{17\ or\ 18}$), 1.30 (*s*, 3H, $H_{17\ or\ 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0 (C, C_{10}), 206.0 (C, C_{13}), 137.1 (C, C_8), 132.1 (C, C_4), 127.6 (CH_{Ar}, C_2), 122.7 (CH_{Ar}, C_6), 122.6 (C, C_9), 119.6 (C, C_3), 118.6 (CH_{Ar}, C_5), 109.4 (CH_{Ar}, C_7), 66.6 (C, C_{11}), 58.5 (CH_2, C_{12}), 55.9 (CH, C_{15}), 43.4 (CH_2, C_{14}), 36.7 (C, C_{16}), 33.0 (2 × CH_3, C_{NMe}, $C_{17\ or\ 18}$), 29.7 (CH_3, $C_{17\ or\ 18}$); HRMS (ESI) *m/z* 319.1427 $[M+Na]^+$, $[C_{18}H_{20}N_2O_2Na]^+$ requires 319.1422.

Preparation of carbamate 270



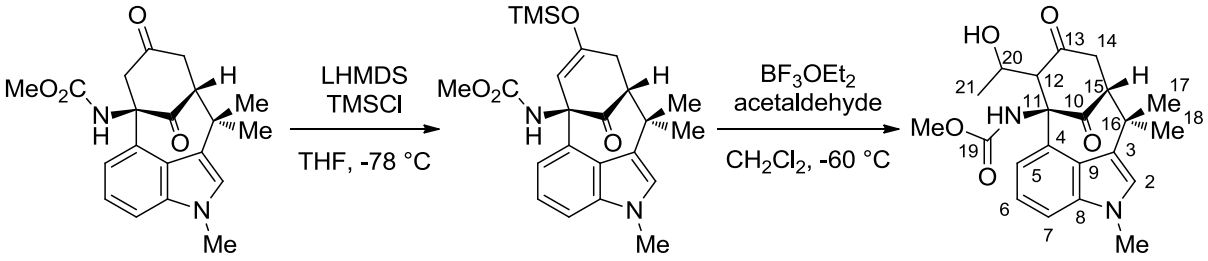
217 **268** **270**

To a solution of azide **217** (47.2 mg, 0.15 mmol) in THF (6.8 mL) and H_2O (271 µL) pre-cooled to 0 °C, was added dropwise over 1 min PBu_3 (74 µL, 0.29 mmol). The resulting solution was stirred for 15 min at 0 °C and was then allowed to warm up to room temperature. After 1 h at room temperature, the reaction showed total consumption of starting material. The solvent was evaporated under reduced pressure. The residue was diluted in CH_2Cl_2 (5 mL) and H_2O (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with 1 M NaOH (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The red crude solution (135.2 mg) was carried on to the next step without further purification.

To a suspension of crude amine **268** and Na_2CO_3 (145 mg, 1.37 mmol) in anhydrous toluene (25 mL) was added methyl chloroformate (106 µL, 1.37 mmol). The resulting orange solution was stirred for 14 h at room temperature. The reaction mixture was quenched with water (20 mL) and the phases were separated. The aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with Na_2CO_3 (10% in H_2O, 30 mL) then water (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (5/5 to 4/6)) to afford carbamate **270** (52.5 mg, 99%) as red liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (*dd*, 1H, *J* 7.0, 1.4, H_5), 7.29 (*dd*, 1H, *J* 8.1, 7.0, H_6), 7.26

(*dd*, 1H, *J* 8.1, 1.4, H_7), 6.99 (*s*, 1H, H_2), 5.45 (*br s*, 1H, H_{NHR}), 3.76 (*s*, 3H, H_{NMe}), 3.72 (*d*, 1H, *J* 16.0, 1 × H_{12}), 3.70 (*br s*, 3H, H_{20}), 3.14 (*d*, 1H, *J* 16.0, 1 × H_{12}), 3.07 (*dd*, 1H, *J* 9.4, 6.8, H_{15}), 2.83-2.87 (*m*, 2H, H_{14}), 1.49 (*s*, 3H, $H_{17\text{ or }18}$), 1.31 (*s*, 3H, $H_{17\text{ or }18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0 (C, C_{10}), 205.2 (C, C_{13}), 176.3 (C, C_{19}), 137.3 (C, C_8), 130.8 (C, C_4), 127.6 (CH_{Ar}, C_2), 122.6 (CH_{Ar}, C_6), 122.3 (C, C_9), 119.7 (C, C_3), 117.0 (CH_{Ar}, C_5), 109.7 (CH_{Ar}, C_7), 68.9 (C, C_{11}), 55.7 (CH, C_{15}), 55.3 (CH_2, C_{12}), 52.2 (CH_3, C_{20}), 42.6 (CH_2, C_{14}), 36.6 (C, C_{16}), 33.0 (2 × CH_3, C_{NMe}, $C_{17\text{ or }18}$), 28.7 (CH_3, $C_{17\text{ or }18}$); IR ν_{max} (film)/cm^{-1}: 3354 (m, br), 2961 (w, br), 2920 (w, br), 2851 (w), 1734 (m), 1707 (s), 1523 (m), 1453 (w), 1421 (w), 1248 (s), 1238 (s), 1038 (s), 791 (w), 745 (s); HRMS (ESI) *m/z* 377.1470 $[M+Na]^+$, $[C_{20}H_{22}N_2O_4Na]^+$ requires 377.1477.

Preparation of aldol 273

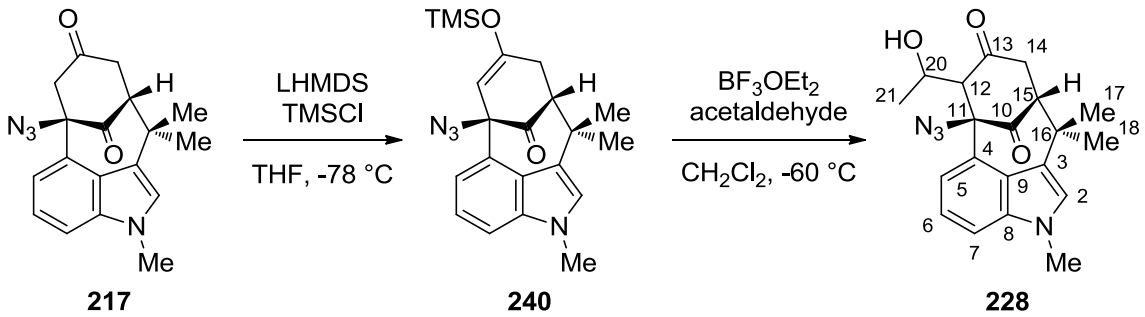


To a solution of carbamate **270** (20 mg, 0.056 mmol) in THF (2 mL), pre-cooled to -78 °C, was added dropwise over 1 min a solution of LHMDS (1.00 M in THF, 565 µL, 0.56 mmol). The resulting yellow solution was stirred for 10 min at -78 °C and a solution of freshly distilled TMSCl (72 µL, 0.56 mmol) was added to the mixture. After 30 min at -78 °C, Et_3N (0.5 mL) was added followed by addition of a solution of $NaHCO_3$ (3 mL). The reaction was allowed to warm up to room temperature. Et_2O (5 mL) was added and the phases were

separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was carried on to the next step without further purification.

To a solution of crude silyl enol ether **271** in CH_2Cl_2 (1 mL) was added acetaldehyde (16 µL, 0.028 mmol). The reaction mixture was cooled to -60 °C and a solution of $BF_3.OEt_2$ (7 µL, 0.056 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise over 1 min to the reaction. After 3 h of stirring at -60 °C, the starting silyl enol ether **271** was fully consumed, however starting ketone **270** appeared along with the desired Mukuyaima product **273** by TLC. The reaction was quenched with a solution of $NaHCO_3$ (20 mL) and the reaction was allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (8/2 to 4/6) as eluent) to afford aldol **273** as a mixture of two rotamers as an orange oil (2.4 mg, 12%); Major rotamer*/Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.40 (*m*, 6H, $H_{5*,\ 6*\ and\ 7*}$, $H_{5,\ 6\ and\ 7}$), 6.99 (*s*, 1H, H_{2*}), 6.94 (*s*, 1H, H_2), 5.50 (*br s*, 1H, H_{NH*}), 5.43 (*br s*, 1H, H_{NH}), 3.98-4.06 (*m*, 1H, H_{20*}), 3.87-3.94 (*m*, 1H, H_{20}), 3.77 (*s*, 3H, H_{NMe}), 3.75 (*s*, 3H, H_{NMe*}), 3.72 (*br s*, 3H, H_{OMe*}), 3.70 (*br s*, 3H, H_{OMe}), 3.12-3.17 (*m*, 2H, H_{12*}, H_{12}), 3.05-3.12 (*m*, 2H, H_{15*}, H_{15}), 2.67-2.93 (*m*, 4H, H_{14*}, H_{14}), 1.44 (*s*, 6H, $H_{17*\ or\ 18*}$, $H_{17\ or\ 18}$), 1.23-1.25 (*m*, 12H, $H_{17*\ or\ 18*,\ and\ 21*}$, $H_{17\ or\ 18,\ and\ 21}$), H_{OH} were not observed; IR ν_{max}(film)/cm^{-1}: 3425 (w, br), 3338 (w, br), 2922 (w, br), 2921 (w, br), 1730 (m), 1703 (s), 1654 (s), 1528 (m), 1450 (m), 1251 (s), 1075 (m), 1047 (s), 916 (m), 735 (s); HRMS (ESI) *m/z* 421.1741 $[M+Na]^+$, $[C_{22}H_{26}N_2O_5Na]^+$ requires 421.1739.

Preparation of aldol 228[7]

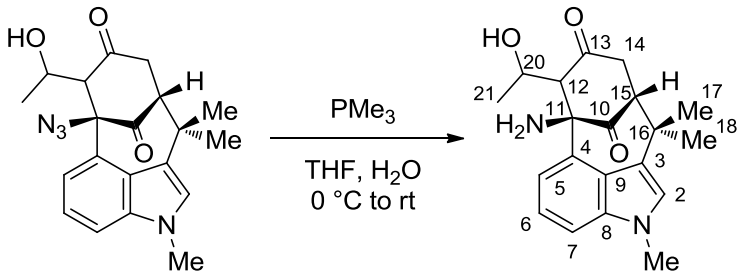


To a solution of LHMDS (1.00 M in THF, 2.13 mL, 2.13 mmol) and a solution of freshly distilled TMSCl (271 µL, 2.13 mmol) in THF (1 mL), pre-cooled to -78 °C, was added dropwise over 3 min a solution of azide **217** (137.5 mg, 0.427 mmol) in THF (3.5 mL), pre-cooled to -78 °C. After 1 h of stirring at -78 °C, the reaction showed total consumption of starting material. The reaction was quenched with a solution of $NaHCO_3$ (3 mL) and was allowed to warm to room temperature. Et_2O (5 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Half of the crude material was carried on to the next step without further purification.

To a solution of crude silyl enol ether **240** in CH_2Cl_2 (4.5 mL) was added a solution of acetaldehyde (60 µL, 1.07 mmol) in CH_2Cl_2 (0.69 mL). The reaction mixture was cooled to -60 °C and a solution of $BF_3.OEt_2$ (30 µL, 0.214 mmol) was added dropwise over 1 min to the reaction at remaining temperature. After 3 h of stirring at -60 °C, another equivalent of $BF_3.OEt_2$ (30 µL, 0.214 mmol) was added dropwise over 1 min to the reaction at remaining temperature. After an additional 2 h of stirring at -60 °C, another equivalent of $BF_3.OEt_2$ (30 µL, 0.214 mmol) was added dropwise over 1 min to the reaction at remaining temperature. After a total of 6 h of stirring at -60 °C, the reaction showed total consumption of starting material and was quenched with a solution of $NaHCO_3$ (5 mL) and was allowed to

warm to room temperature. CH_2Cl_2 (5 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (6/4 to 4/6) as eluent) to afford aldol **228** (62.7 mg, 80%) as a single diastereoisomer as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (*dd*, 1H, *J* 7.4, 1.2, H_5), 7.38 (*dd*, 1H, *J* 8.0, 7.4, H_6), 7.32 (*dd*, 1H, *J* 8.0, 1.2, H_7), 7.01 (*s*, 1H, H_2), 4.07-4.14 (*m*, 1H, H_{20}), 3.85 (*d*, 1H, *J* 3.0, H_{OH}), 3.78 (*s*, 3H, H_{NMe}), 3.08 (*dd*, 1H, *J* 9.4, 4.1, H_{15}), 2.92 (*dd*, 1H, *J* 7.2, 1.3, H_{12}), 2.76 (*d*, 1H, *J* 9.4, 1 × H_{14}), 2.74 (*dd*, 1H, *J* 4.1, 1.3, 1 × H_{14}), 1.52 (*s*, 3H, $H_{17\text{ or }18}$), 1.27 (*s*, 3H, $H_{17\text{ or }18}$), 1.14 (*d*, 3H, *J* 6.3, H_{21}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9 (C, C_{10}), 204.7 (C, C_{13}), 137.4 (C, C_8), 127.5 (CH_{Ar}, C_2), 126.9 (C, C_4), 123.0 (CH_{Ar}, C_6), 122.1 (C, C_9), 119.0 (C, C_3), 118.8 (CH_{Ar}, C_5), 110.5 (CH_{Ar}, C_7), 78.7 (C, C_{11}), 71.8 (CH, C_{12}), 67.2 (C, C_{20}), 55.5 (CH, C_{15}), 41.0 (CH_2, C_{14}), 36.6 (C, C_{16}), 33.1 (2 × CH_3, C_{NMe}, $C_{17\text{ or }18}$), 28.6 (CH_3, $C_{17\text{ or }18}$), 21.0 (CH_3, C_{21}); IR ν_{max} (film)/cm^{-1}: 3506 (w, br), 2921 (w), 2117 (w), 1713 (m), 1705 (s), 1451 (w), 1249 (m), 791 (m), 746 (s); HRMS (ESI) *m/z* 389.1599 $[M+Na]^+$, $[C_{20}H_{22}N_4O_3Na]^+$ requires 389.1590. Data were in agreement with those reported in the literature.

Preparation of amine 276

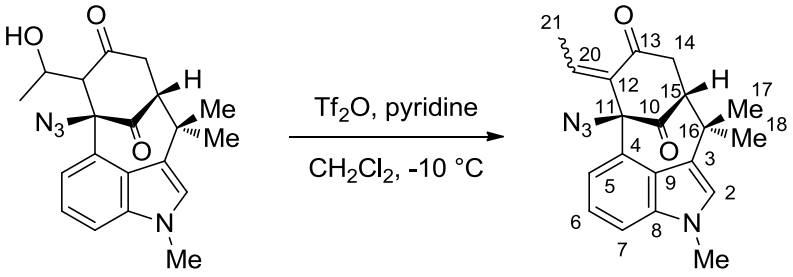


228 **276**

To a solution of azide **228** (28.8 mg, 0.079 mmol) in THF (3.7 mL) and H_2O (147 µL), pre-cooled to 0 °C, was added dropwise over 1 min a solution of PMe_3 (1.00 M in THF, 157 µL, 0.157 mmol). After 25 min of stirring at 0 °C, the reaction was allowed to stir at room temperature for another 45 min. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and H_2O (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 1 M NaOH (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was concentrated under reduced pressure overnight to remove any phosphine oxide generated during the reaction. The crude material was purified by flash column chromatography (using a gradient of petroleum ether/ethyl acetate (6/4 to 4/6) as eluent) to afford amine **276** (9.3 mg, 35%) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (*dd*, 1H, *J* 8.1, 7.6, H_6), 7.26 (*dd*, 1H, *J* 8.1, 0.7, H_7), 7.17 (*dd*, 1H, *J* 7.6, 0.7, H_5), 6.98 (*s*, 1H, H_2), 3.99-4.06 (*m*, 1H, H_{19}), 3.76 (*s*, 3H, H_{NMe}), 3.15 (*dd*, 1H, *J* 8.4, 5.0, H_{15}), 2.93 (*d*, 1H, *J* 9.5, H_{12}), 2.66-2.69 (*m*, 2H, H_{14}), 1.51 (*s*, 3H, $H_{17\text{ or }18}$), 1.25 (*s*, 3H, $H_{17\text{ or }18}$), 1.06 (*d*, 3H, *J* 6.1, H_{20}), none of the exchangeable protons were observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9 (C, C_{10}), 205.3 (C, C_{13}), 137.2 (C, C_8), 133.1 (C, C_4), 127.4 (CH_{Ar}, C_2), 123.0 (CH_{Ar}, C_6), 121.2 (C, C_9), 119.4 (C, C_3), 116.8 (CH_{Ar}, C_5), 109.5 (CH_{Ar}, C_7), 74.1 (CH, C_{12}), 70.1 (C, C_{11}), 67.1 (C, C_{19}), 55.8 (CH, C_{15}), 40.8 (CH_2, C_{14}), 36.5 (C, C_{16}), 33.4 (CH_3, $C_{17\text{ or }18}$), 33.1

(CH_3, C_{NMe}), 28.7 (CH_3, $C_{17\ or\ 18}$), 21.3 (CH_3, C_{20}); HRMS (ESI) *m/z* 341.1869 $[M+H]^+$, $[C_{20}H_{25}N_2O_3]^+$ requires 341.1865.

Preparation of enone 227

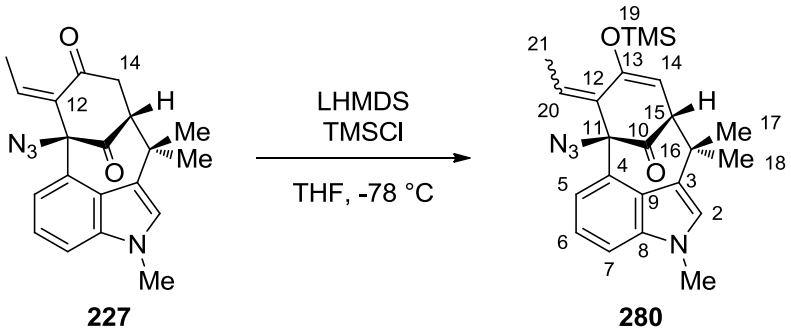


228 **227**

To a solution of azide **228** (79.7 mg, 0.218 mmol) in CH_2Cl_2 (4 mL), pre-cooled to 0 °C, was added dropwise over 1 min Tf_2O (183 µL, 307 mg, 1.09 mmol) followed by pyridine (88 µL, 86 mg, 1.09 mmol). The reaction mixture turned from yellow in colour to brown in colour. After 30 min of stirring at 0 °C, the reaction mixture was allowed to stir at room temperature for another hour. The reaction was quenched with a solution of $NaHCO_3$ (6 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford enone **227** (33.8 mg, 45%, 48% BRSM) as yellow solid; Mixture Z*/E in a 9/1 ratio: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (*d*, 1H, *J* 7.4, $H_{5\ or\ 7}$), 7.42 (*d*, 1H, *J* 7.5, $H_{5\ or\ 7}$), 7.34-7.37 (*m*, 1H, H_6), 7.26-7.36 (*m*, 3H, $H_{5*,\ 6*\ and\ 7*}$), 7.11 (*q*, 1H, *J* 7.9, H_{20}), 7.07 (*s*, 1H, H_2), 7.05 (*s*, 1H, H_{2*}), 6.94 (*q*, 1H, *J* 7.5, H_{20*}), 3.79 (*s*, 6H, H_{NMe*}, H_{NMe}), 2.74-2.78 (*m*, 6H, $H_{14*,\ 15*}$, $H_{14,\ 15}$), 2.50 (*d*, 3H, *J* 7.9, H_{21}),

2.18 (*d*, 3H, *J* 7.5, H_{21*}), 1.52 (*s*, 3H, $H_{17\ or\ 18}$), 1.48 (*s*, 3H, $H_{17\ or\ 18}$), 1.46 (*s*, 3H, $H_{17*\ or\ 18*}$), 1.43 (*s*, 3H, $H_{17*\ or\ 18*}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8 (C, C_{10}), 203.3 (C, C_{10*}), 197.0 (C, C_{13*}, C_{13}), 140.6 (CH, C_{20*}, C_{20}), 137.1 (C, C_{8*}, C_8), 136.3 (C, C_{4*}, C_4), 128.4 (C, C_{2*}), 128.1 (C, C_2), 127.6 (C, C_{9*}, C_9), 123.2 (C, C_{12*}, C_{12}), 122.8 (CH_{Ar}, $C_{5\ or\ 6\ or\ 7}$), 122.4 (CH_{Ar}, $C_{5*\ or\ 6*\ or\ 7*}$), 120.3 (CH_{Ar}, $C_{5\ or\ 6\ or\ 7}$), 120.0 (CH_{Ar}, $C_{5*\ or\ 6*\ or\ 7*}$), 119.4 (C, C_{3*}, C_3), 110.3 (CH_{Ar}, $C_{5\ or\ 6\ or\ 7}$), 109.8 (CH_{Ar}, $C_{5*\ or\ 6*\ or\ 7*}$), 54.2 (CH, C_{15*}, C_{15}), 42.7 (C, C_{11*}, C_{11}), 42.4 (CH_2, C_{14*}, C_{14}), 37.4 (C, C_{16*}, C_{16}), 33.1 (CH_3, C_{NMe*}, C_{NMe}), 32.4 (CH_3, $C_{17*\ or\ 18*}$, $C_{17\ or\ 18}$), 30.0 (CH_3, $C_{17*\ or\ 18*}$, $C_{17\ or\ 18}$), 16.3 (CH_3, C_{21*}, C_{21}); IR ν_{max} (film)/cm^{-1}: 2918 (w, br), 2109 (s), 1719 (m), 1687 (m), 1608 (w), 1421 (w), 1369 (w), 1202 (s, br), 1149 (s, br), 1093 (m), 1056 (m), 1016 (m), 949 (m), 786 (m), 743 (s); HRMS (ESI) *m/z* 371.1483 $[M+Na]^+$, $[C_{20}H_{20}N_4O_2Na]^+$ requires 371.1484.

Preparation of silyl enol ether 280

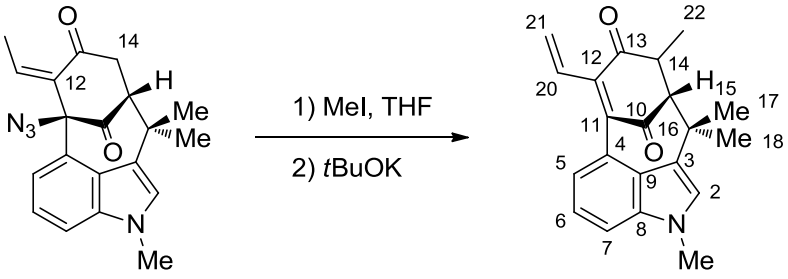


227 **280**

To a solution of LHMDS (1.00 M in THF, 320 µL, 0.32 mmol) and a solution of freshly distilled TMSCl (40 µL, 0.32 mmol) in THF (0.5 mL), pre-cooled to -78 °C, was added dropwise over 1 min a solution of azide **227** (22 mg, 0.063 mmol) in THF (1 mL). The resulting yellow solution was stirred for 1 h at -78 °C while monitored by TLC. Along with

the starting material, a new spot appeared by TLC. As the reaction did not show any further advancement, Et_3N (0.5 mL) was added followed by addition of a solution of $NaHCO_3$ (3 mL). The reaction was allowed to warm up to room temperature. Et_2O (5 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford silyl enol ether **280** (2.2 mg, 8%) as colourless oil as a mixture of *Z*/*E* isomers in a ratio of 54/46 along with starting enone **271** (12.8 mg, 58%); Mixture *Z**/*E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (*dd*, 1H, *J* 7.3, 1.2, $H_{5^* \text{ or } 7^*}$), 7.20-7.30 (*m*, 2H, $H_{6^* \text{ and } (5^* \text{ or } 7^*)}$), 7.20-7.30 (*m*, 3H, $H_{5,\ 6 \text{ and } 7}$), 6.94 (*s*, 1H, H_{2^*}), 6.93 (*s*, 1H, H_2), 6.17 (*q*, 1H, *J* 7.5, H_{20}), 5.95 (*q*, 1H, *J* 7.5, H_{20^*}), 5.13 (*d*, 1H, *J* 4.0, H_{14}), 5.12 (*d*, 1H, *J* 3.4, H_{14^*}), 3.76 (*s*, 3H, H_{NMe^*}), 3.75 (*s*, 3H, H_{NMe}), 3.24 (*d*, 1H, *J* 4.0, H_{15}), 3.20 (*d*, 1H, *J* 3.4, H_{15^*}), 2.30 (*d*, 3H, *J* 7.5, H_{21}), 1.89 (*d*, 3H, *J* 7.5, H_{21^*}), 1.59 (*s*, 6H, $H_{17 \text{ and } 18}$), 1.26 (*s*, 6H, $H_{17^* \text{ and } 18^*}$), -0.25 (*s*, 9H, H_{19}), -0.44 (*s*, 9H, H_{19^*}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7 (C, C_{10}, C_{10^*}), 184.0 (C, C_{13}, C_{13^*}), 126.4 (CH_{Ar}, C_2, C_{2^*}), 123.2 (C=CH, C_{20}, C_{20^*}), 122.1 (CH_{Ar}, $C_{5 \text{ or } 6 \text{ or } 7}$, $C_{5^* \text{ or } 6^* \text{ or } 7^*}$), 118.9 ($CH_{Ar}$, $C_{5 \text{ or } 6 \text{ or } 7}$, $C_{5^* \text{ or } 6^* \text{ or } 7^*}$), 109.2 ($CH_{Ar}$, $C_{5 \text{ or } 6 \text{ or } 7}$, $C_{5^* \text{ or } 6^* \text{ or } 7^*}$), 108.9 ($CH_{Ar}$, C_{14}), 108.0 (CH_{Ar}, C_{14^*}), 89.4 (C, C_{11}, C_{11^*}), 58.5 (C, C_{16}, C_{16^*}), 32.9 (CH_3, C_{NMe^*}), 31.2 (CH_3, C_{NMe}), 29.7 (CH_3, $C_{17^* \text{ or } 18^*}$), 29.2 ($CH_3$, $C_{17 \text{ or } 18}$), 15.1 (CH_3, C_{21}), 14.2 (CH_3, C_{21^*}), -0.95 (CH_3, C_{19}), -0.57 (CH_3, C_{19^*}), quaternary carbons $C_{3,4,8,9,12}$ were missing due to the scale of our reaction; IR ν_{max} (film)/cm^{-1}: 3433 (w, br), 3361 (w, br), 3023 (m), 2968 (s, br), 2920 (s, br), 2851 (m), 2117 (s), 1721 (s), 1453 (m), 1422 (m), 1253 (s), 1218 (s), 326 (m), 857 (m), 746 (s, br), 671(m); HRMS (ESI) *m/z* 443.1877 $[M+Na]^+$, $[C_{23}H_{28}N_4O_2SiNa]^+$ requires 443.1879.

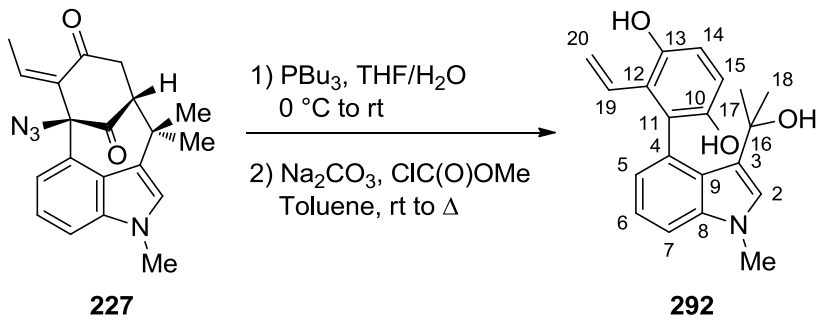
Preparation of methylated cyclohexanone 283



227 **283**

To a solution of enone **227** (10.7 mg, 0.0307 mmol) and MeI (0.5 mL, 0.008 mmol) in THF (0.5 mL) was added *t*BuOK (3.6 mg, 0.0307 mmol) in one portion. The reaction mixture was stirred for 15 min and monitored by TLC. The process was repeated and a new spot was observed along with the starting material. Another eq. of *t*BuOK was added, but the TLC started to show degradation so the reaction was quenched using H_2O (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford methylated cyclohexanone **283** (1.2 mg, 12%) as a single stereoisomer a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.31 (*m*, 2H, $H_{6 \text{ and } 7}$), 7.17 (*dd*, 1H, *J* 6.0, 2.0, H_5), 6.91 (*s*, 1H, H_2), 6.66 (*dd*, 1H, *J* 17.6, 11.6, H_{20}), 6.27 (*dd*, 1H, *J* 17.6, 1.8, H_{21}), 5.54 (*dd*, 1H, *J* 11.6, 1.8, H_{21}), 3.76 (*s*, 3H, H_{NMe}), 3.22 (*qd*, 1H, *J* 7.5, 0.8, H_{14}), 2.95 (*d*, 1H, *J* 0.8, H_{15}), 1.57 (*s*, 3H, $H_{17 \text{ or } 18}$), 1.38 (*d*, 3H, *J* 7.5, H_{22}), 1.20 (*s*, 3H, $H_{17 \text{ or } 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.1 ($CH{=}CH_2$, C_{20}), 126.0 (CH_{Ar}, C_2), 124.2 ($C{=}CH_2$, C_{21}), 122.2 (CH_{Ar}, C_6), 116.7 (CH_{Ar}, C_5), 110.2 (CH_{Ar}, C_7), 77.2 (CH_{Ar}, C_{11}), 68.1 (CH, C_{15}), 45.0 (CH, C_{14}), 32.9 (CH_3, C_{NMe}), 30.5 (CH_3, $C_{17 \text{ or } 18}$), 30.3 (CH_3, $C_{17 \text{ or } 18}$), 19.0 (CH_3, C_{19}), none of the quaternary carbons were observed due to the scale of our reaction; IR ν_{max} ($CHCl_3$)/cm^{-1}: 2966 (m), 2919 (m, br), 2116 (m), 1715 (s), 1682 (s), 1461 (w), 1440 (w), 1419 (w), 1373 (w), 1218 (w), 749 (s); HRMS (ESI) *m/z* 342.1469 $[M+Na]^+$, $[C_{21}H_{21}NO_2Na]^+$ requires 342.1470.

Preparation of bis-phenol 292



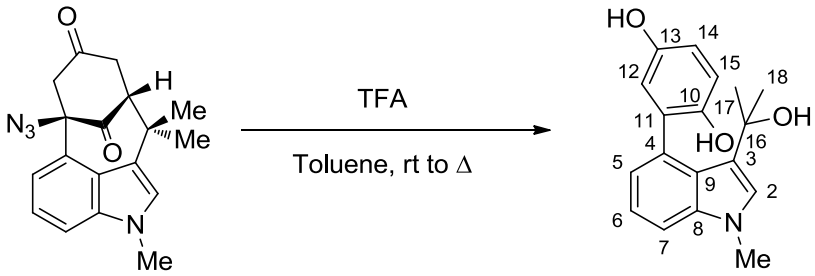
227 **292**

To a solution of azide **227** (20 mg, 0.057 mmol) in THF (2.6 mL) and H_2O (104 µL), pre-cooled to 0 °C, was added dropwise over 2 min a solution of PBu_3 (1.00 M in THF, 115 µL, 0.115 mmol). After 15 min of stirring at 0 °C, the reaction was allowed to stir at room temperature for another 2 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and H_2O (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 1 M NaOH (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

To a suspension of crude amine and Na_2CO_3 (55.5 mg, 0.524 mmol) in anhydrous toluene (10 mL) was added methyl chloroformate (41 µL, 0.524 mmol). The resulting yellow solution was stirred for 14 h at room temperature. The TLC did not show any advancement. The reaction mixture was heated at reflux for 3 h, after which time, the reaction was completed. The reaction mixture was quenched with water (20 mL) and the phases were separated. The aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with Na_2CO_3 solution (10% in H_2O, 30 mL) then water (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 8/2) to afford bis-phenol **292** (5.5 mg, 32%) as a yellow oil; λ_{max} (EtOH)/nm 334 (ε/dm^{3}mol^{-1}cm^{-1} 11 300); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.55 (*dd*, 1H, *J* 6.3, 2.2, H_5), 7.25-7.27 (*m*, 2H, $H_{6 \text{ and } 7}$), 7.03 (*d*, 1H, *J* 8.8, $H_{14 \text{ or } 15}$), 6.92 (*d*, 1H, *J* 8.8, $H_{14 \text{ or } 15}$), 6.90 (*s*, 1H, H_2), 6.65 (*dd*, 1H, *J* 17.9, 12.2, H_{20}), 6.07 (*s*, 1H, H_{OH}), 5.74 (*dd*, 1H, *J* 12.2, 1.6, H_{21}), 5.72 (*dd*, 1H, *J* 17.9, 1.6, H_{21}), 3.80 (*s*, 1H, H_{NMe}), 1.80 (*s*, 1H, $H_{17 \text{ or } 18}$), 1.31 (*s*, 1H, $H_{17 \text{ or } 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4 (C, C_{10}), 149.0 (C, C_{13}), 137.4 (C=CH, C_{20}), 136.7 (C, C_8), 131.5 (C, C_4), 127.9 (C, C_{11}), 125.7 (CH_{Ar}, $C_{14 \text{ or } 15}$), 124.8 (C, C_9), 124.1 (CH_{Ar}, C_5), 122.9 (C, C_3), 122.6 (CH_{Ar}, C_2), 120.9 (CH_{Ar}, C_6), 118.9 (C, C_{12}), 117.7 (C=CH_2, C_{21}), 114.9 (CH_{Ar}, $C_{14 \text{ or } 15}$), 108.8 (CH_{Ar}, C_7), 79.8 (C, C_{16}), 32.9 (CH_3, C_{NMe}), 30.6 (CH_3, $C_{17 \text{ or } 18}$), 29.7 (CH_3, $C_{17 \text{ or } 18}$); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3368 (s, br), 2975 (s), 2927 (s), 2900 (s, br), 1451 (m), 1417 (m), 1381 (m), 1218 (m), 1090 (s), 1050 (s), 881 (m), 758 (s); HRMS (ESI) *m/z* 328.1315 $[M\text{-}H_2O+Na]^+$, $[C_{20}H_{17}NONa]^+$ requires 328.1313.

Preparation of bis-phenol 291



214 **291**

To a solution of bridgehead enone **214** (21.5 mg, 0.077 mmol) in toluene (13 mL) was added a drop of TFA. The reaction turned from yellow in colour to orange in colour. The reaction mixture was heated to reflux for 30 min and was quenched by addition of H_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl

acetate, 8/2) to afford starting enone **214** (4 mg, 19%) along with bis-phenol **291** (11.7 mg, 55%, 68% BRSM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (*d*, 1H, *J* 7.2, H_5), 7.31-7.35 (*m*, 2H, $H_{6 \text{ and } 7}$), 7.29 (*d*, 1H, *J* 1.5, H_{12}), 7.03 (*d*, 1H, *J* 8.5, H_{15}), 6.90 (*s*, 1H, H_2), 6.71 (*dd*, 1H, *J* 8.5, 1.5, H_{14}), 4.98 (*br s*, 1H, H_{OH}), 3.76 (*s*, 3H, H_{NMe}), 1.57 (*s*, 6H, $H_{17 \text{ and } 18}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 (C, C_{10}), 148.8 (C, C_{13}), 137.3 (C, C_8), 132.4 (C, C_4), 129.3 (C, C_{11}), 126.4 (CH_{Ar}, C_{15}), 124.7 (C, C_9), 124.1 (C, C_3), 122.5 (CH_{Ar}, C_2), 122.3 (CH_{Ar}, C_6), 117.4 (CH_{Ar}, C_5), 114.9 (CH_{Ar}, C_{14}), 114.2 (CH_{Ar}, C_{12}), 108.6 (CH_{Ar}, C_7), 78.8 (C, C_{16}), 32.4 (CH_3, C_{NMe}), 29.9 (CH_3, $C_{17 \text{ and } 18}$); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3355 (m, br), 3016 (m), 2980 (m), 2928 (m, br), 1608 (w), 1568 (w), 1485 (m), 1466 (m), 1416 (m), 1215 (s), 1130 (m), 909 (w), 869 (w), 812 (m), 756 (s, br); HRMS (ESI) *m/z* 302.1158 $[M\text{-}H_2O+Na]^+$, $[C_{18}H_{17}NO_2Na]^+$ requires 302.1157.

5.4 REFERENCES

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(4) Bhat,V.; Allan, K. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *133*, 5798-5801.

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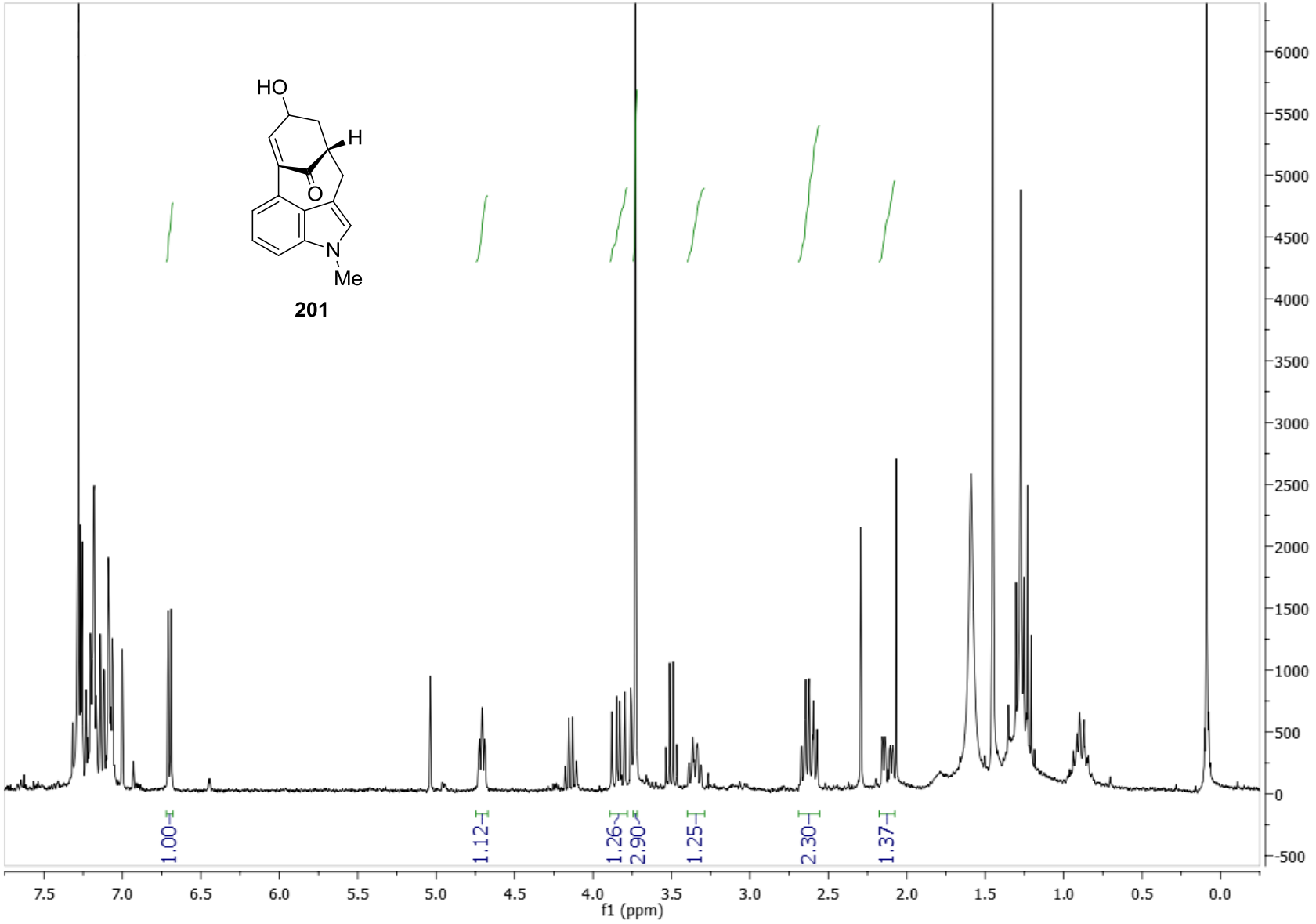
(7) PhD Thesis, Vivant, B., University of Birmingham, **2011**.

APPENDIX

NMR SPECTRA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2.90
1.25
2.30
1.37
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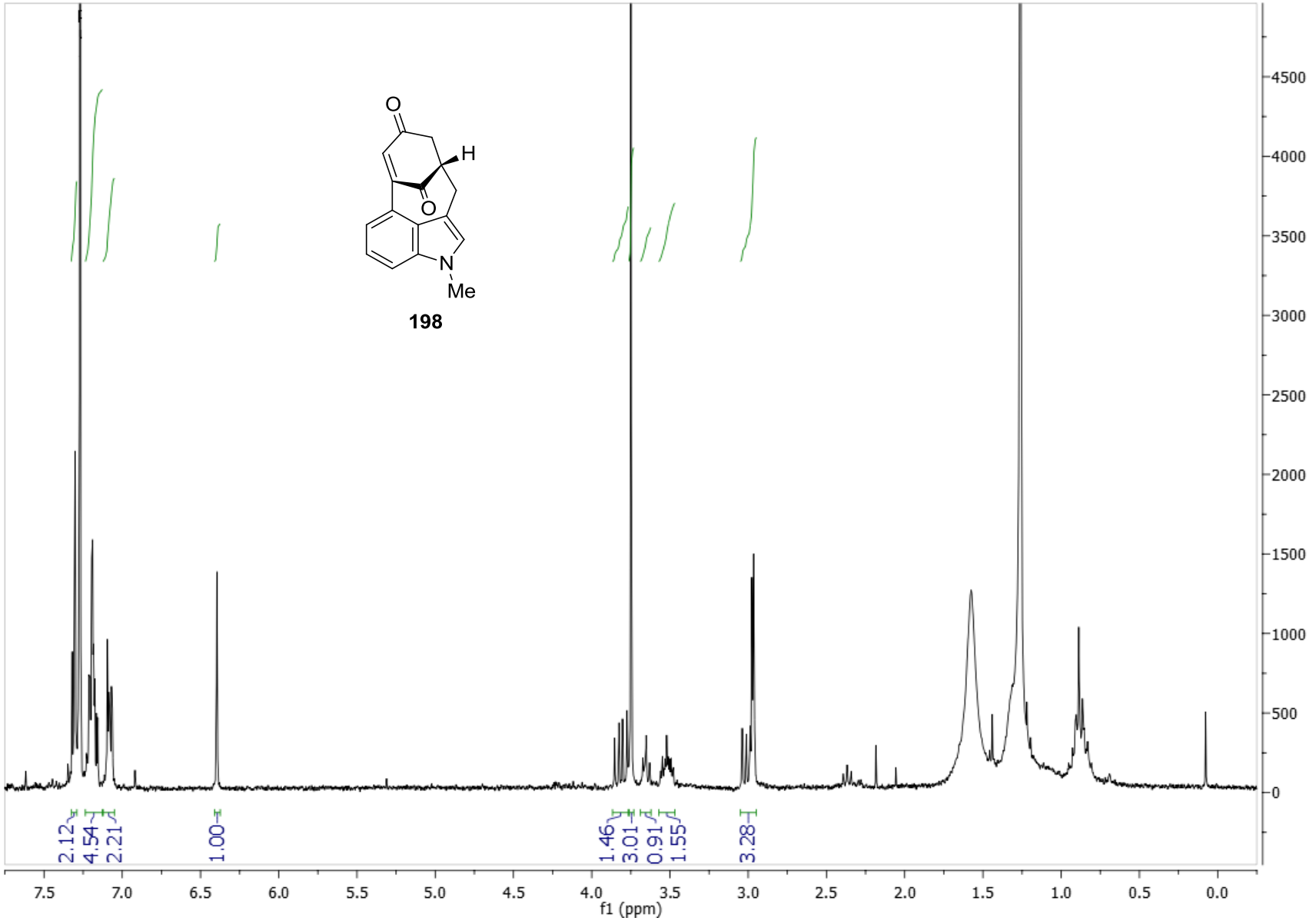
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3.28
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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0.0
f1 (ppm)
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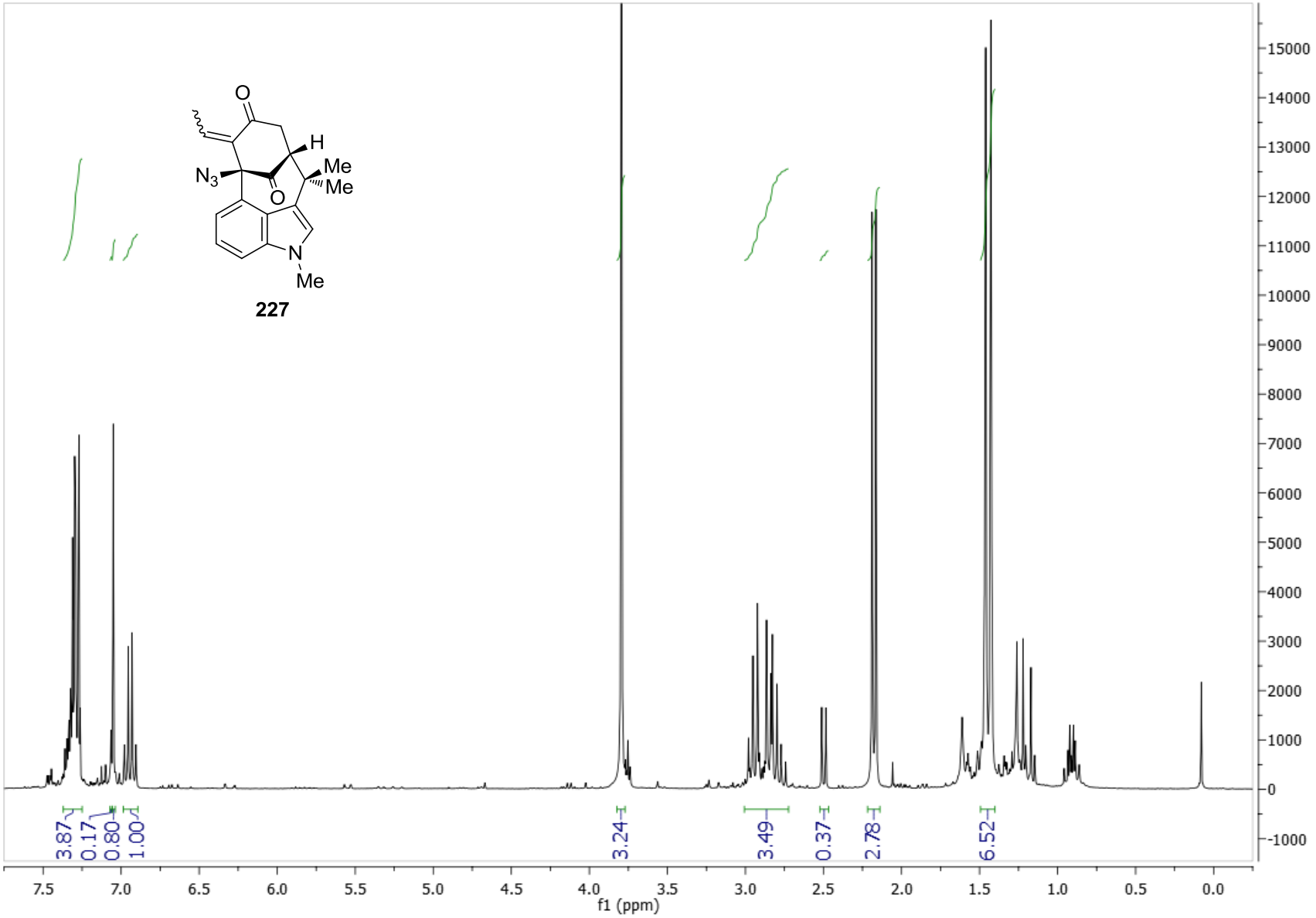
3500
3000
2500
2000
1500
1000
500
0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N3
Me
Me
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N
Me
227
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13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
3.87
0.17
0.80
1.00
3.24
3.49
0.37
2.78
6.52
7.5
7.0
6.5
6.0
5.5
5.0
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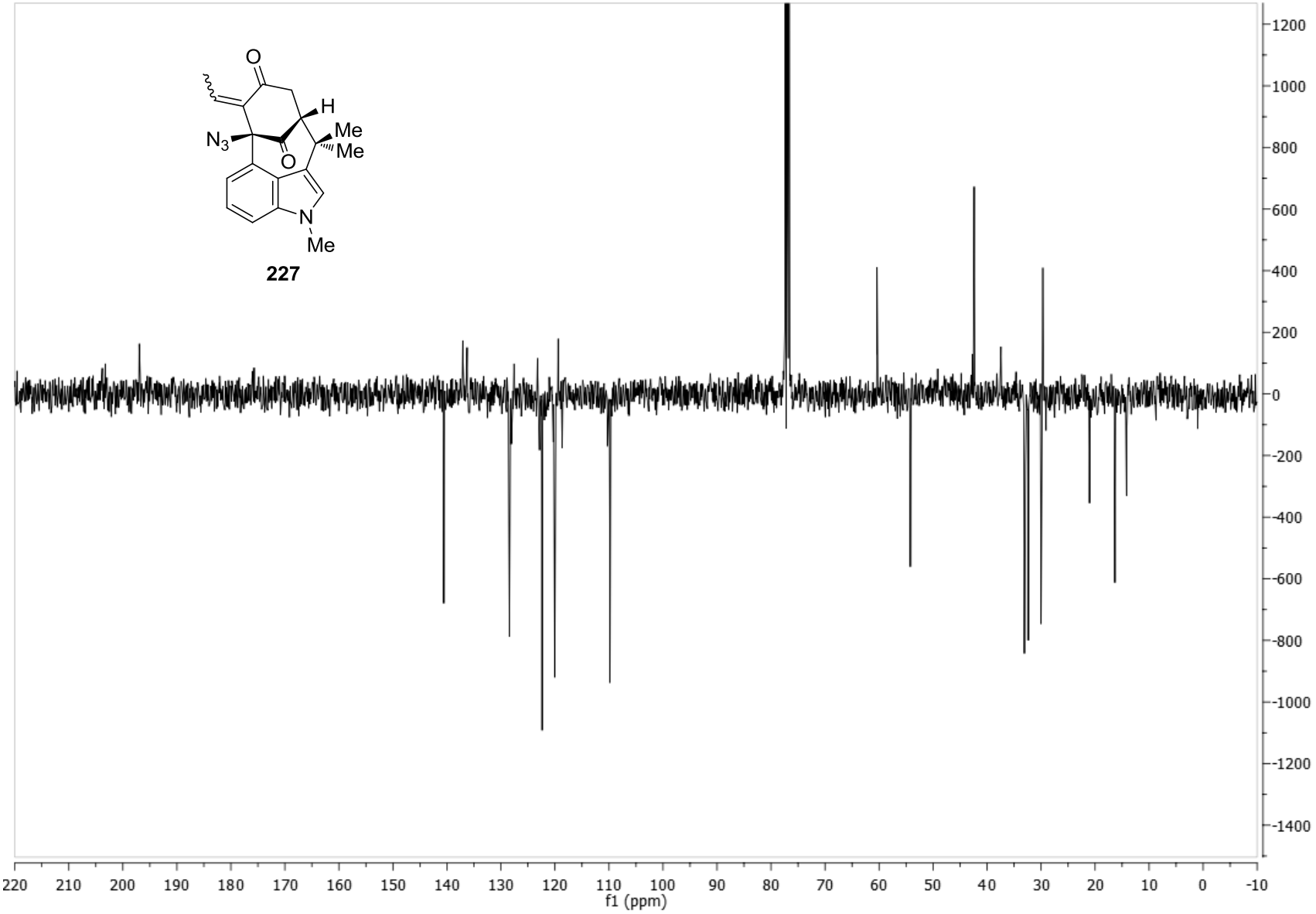
f1 (ppm)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Me
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N
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227
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800
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400
200
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-200
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-800
-1000
-1200
-1400
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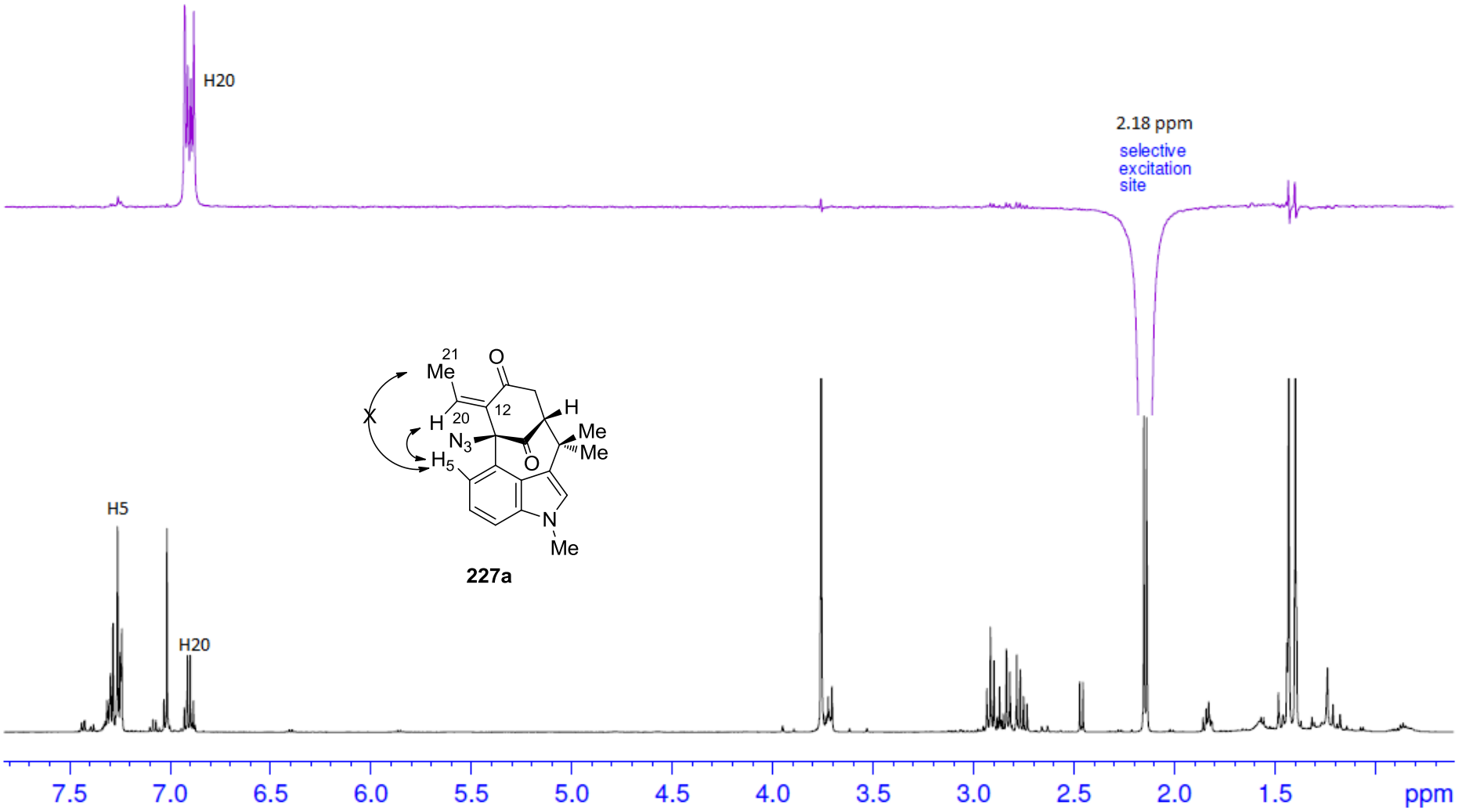
f1 (ppm)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Me
O
H
20
12
H
N3
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Me
H5
O
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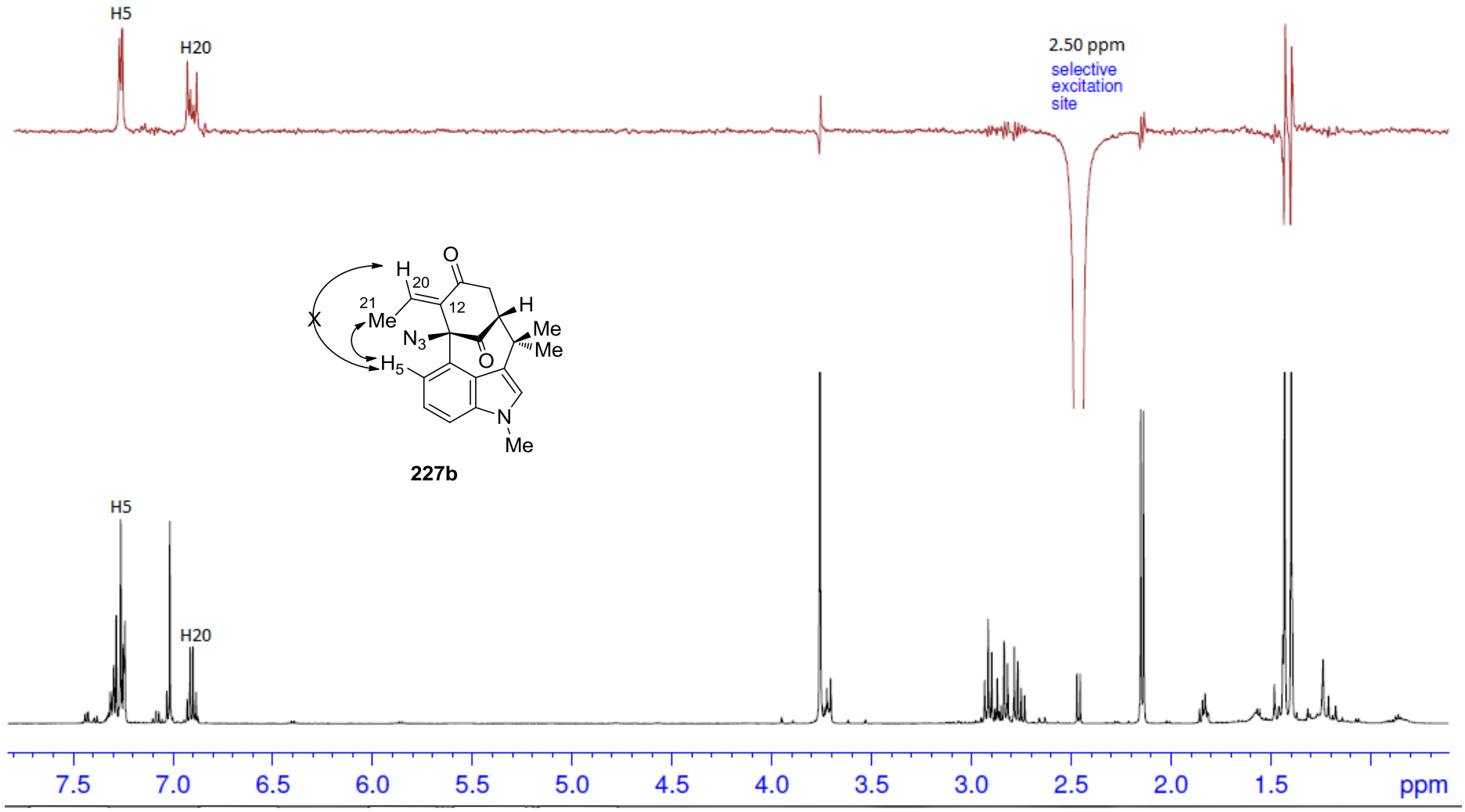
ppm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H20
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excitation
site
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H20
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4.0
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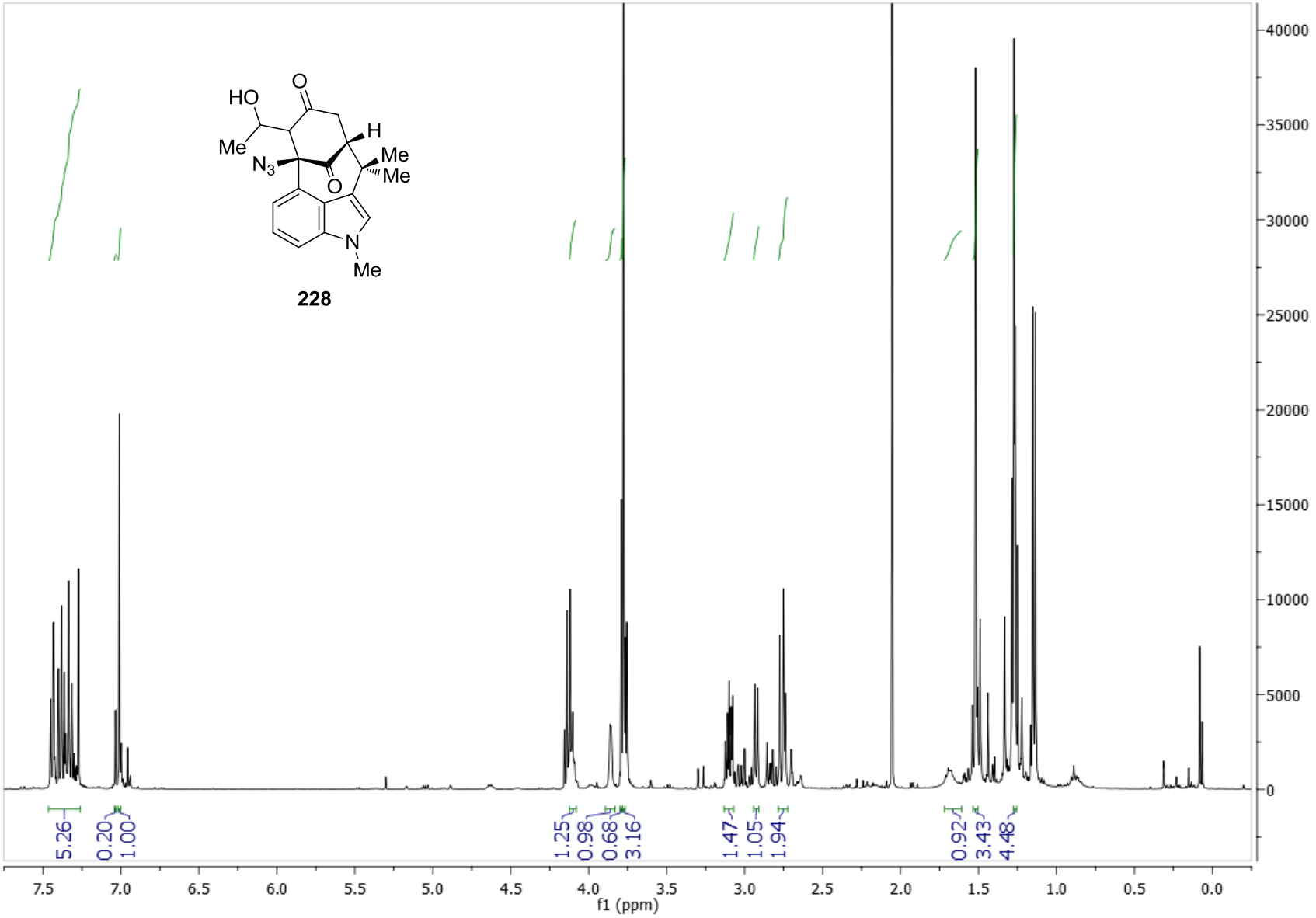
3.0
2.5
2.0
1.5
ppm

227b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Me
O
N
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0
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1.25
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1.05
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0.92
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6.0
5.5
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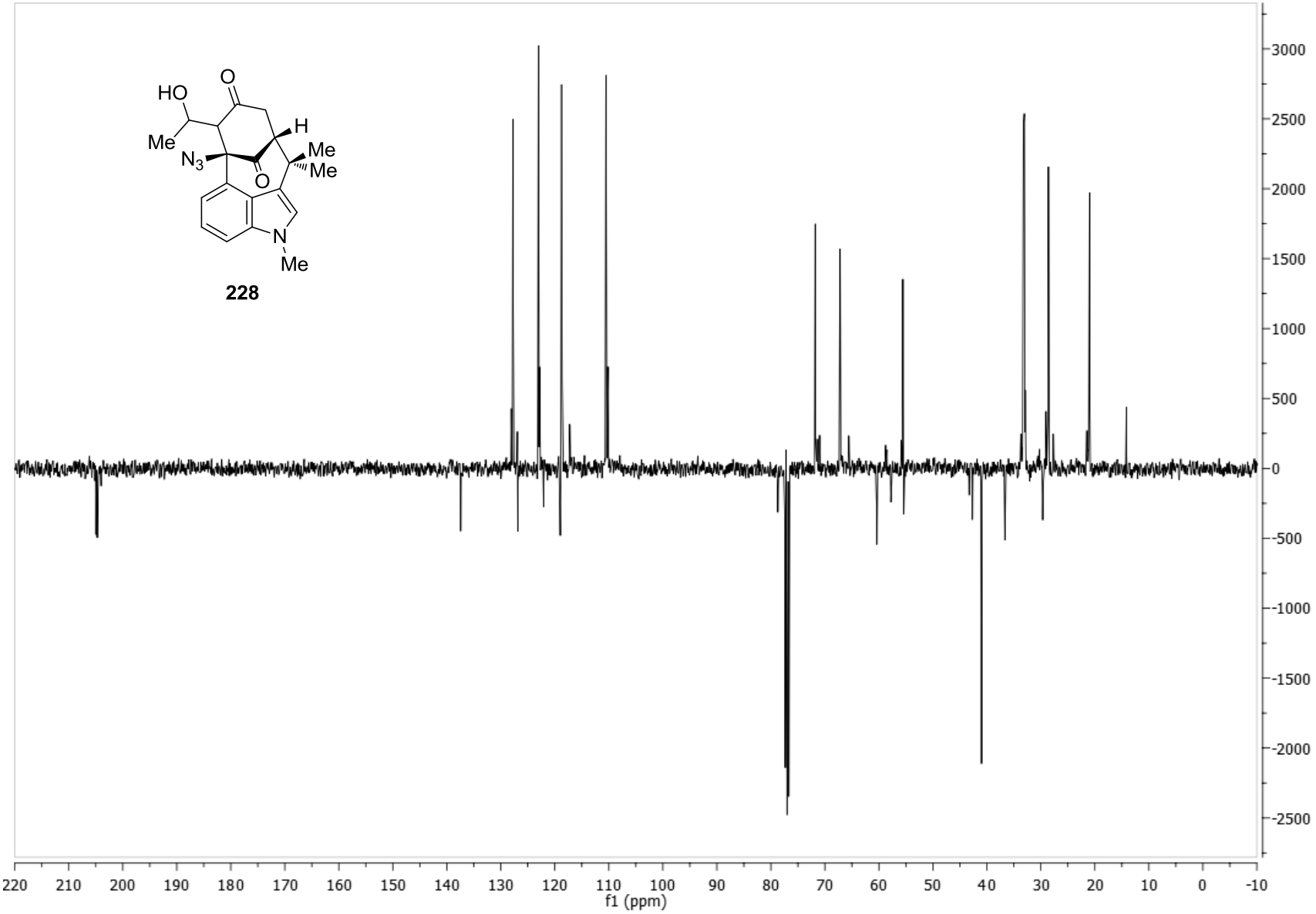
f1 (ppm)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Me
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Me
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1500
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-2500
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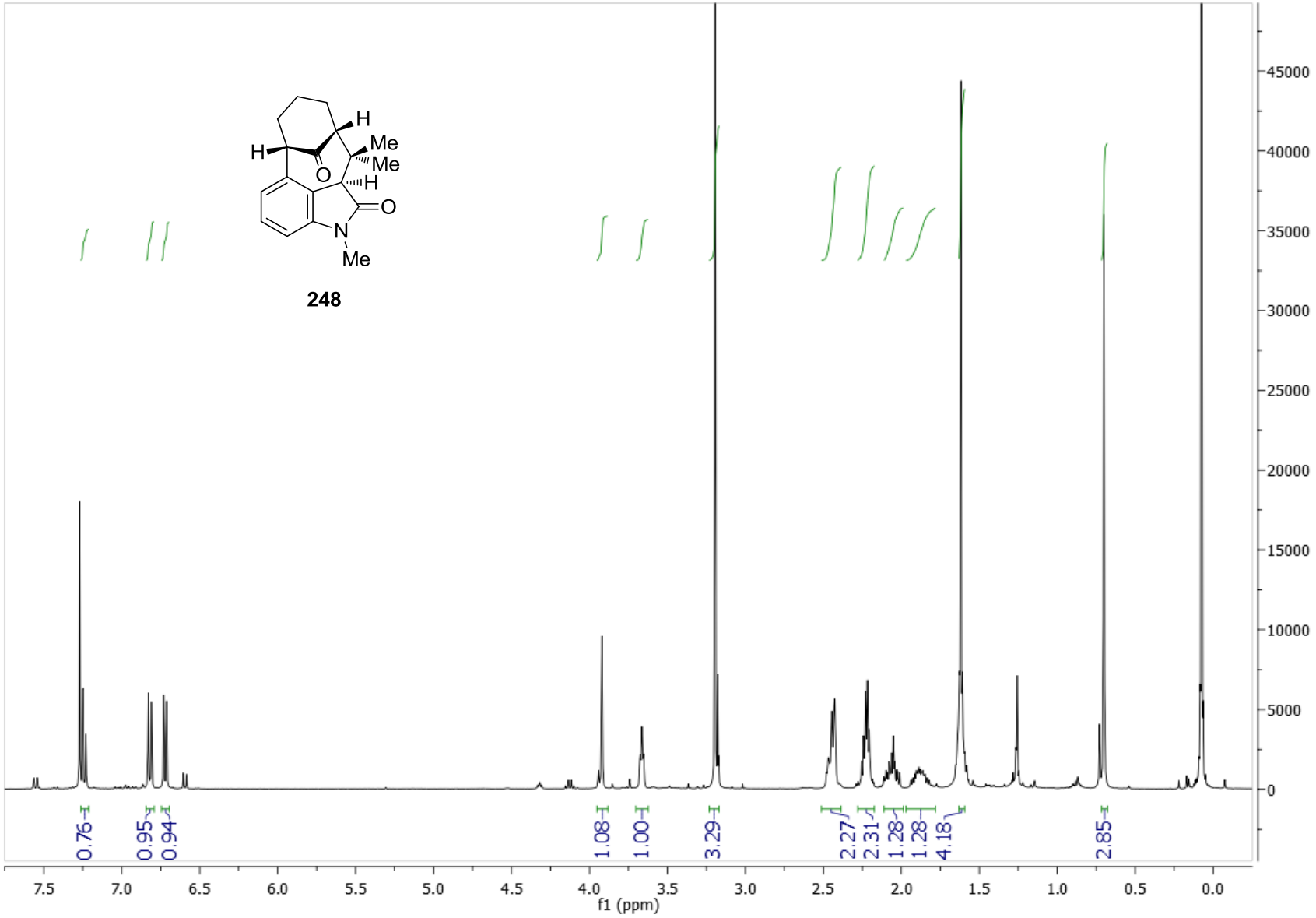
f1 (ppm)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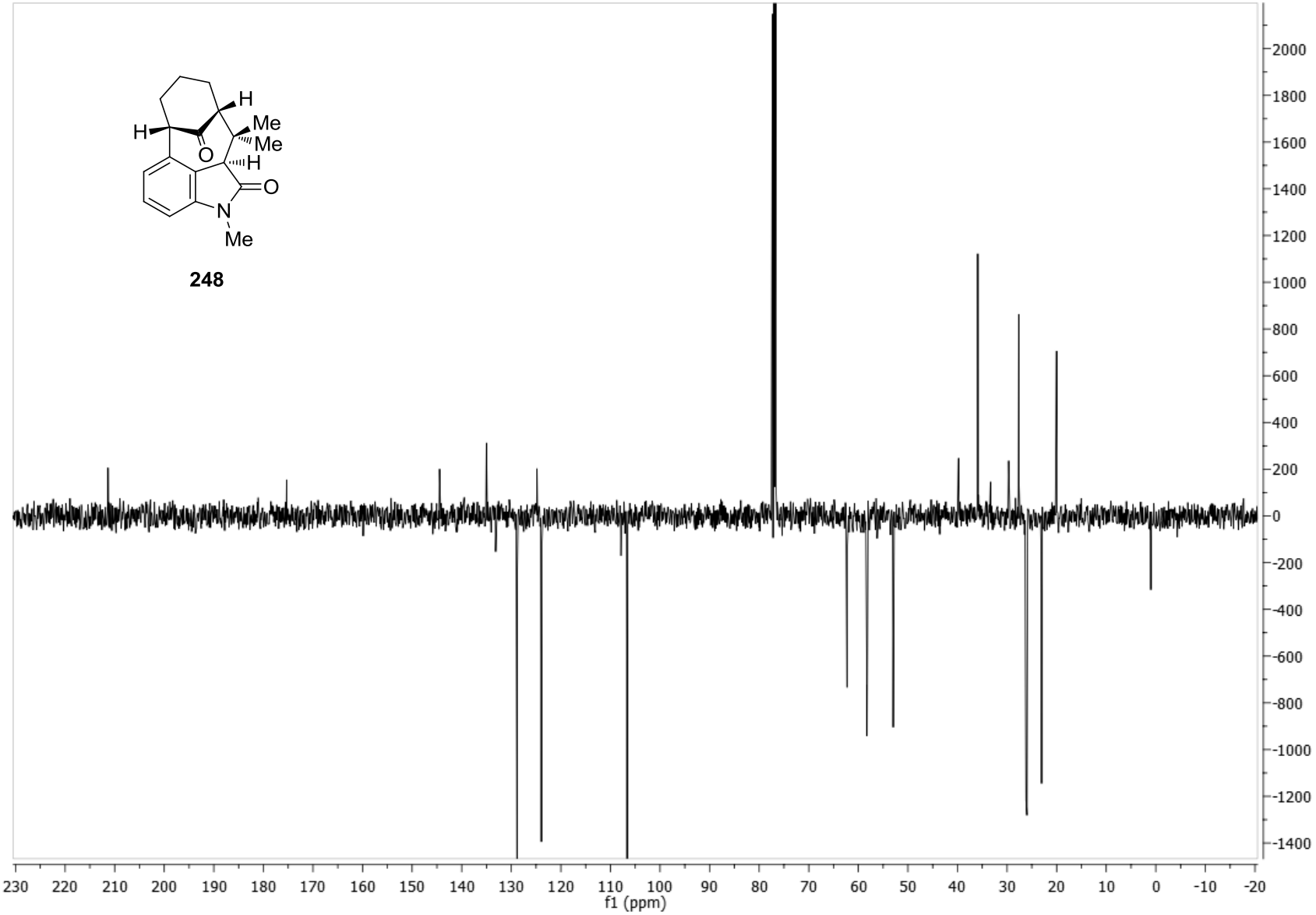
0.0
f1 (ppm)

X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Me
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O
O
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Me
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1600
1400
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800
600
400
200
0
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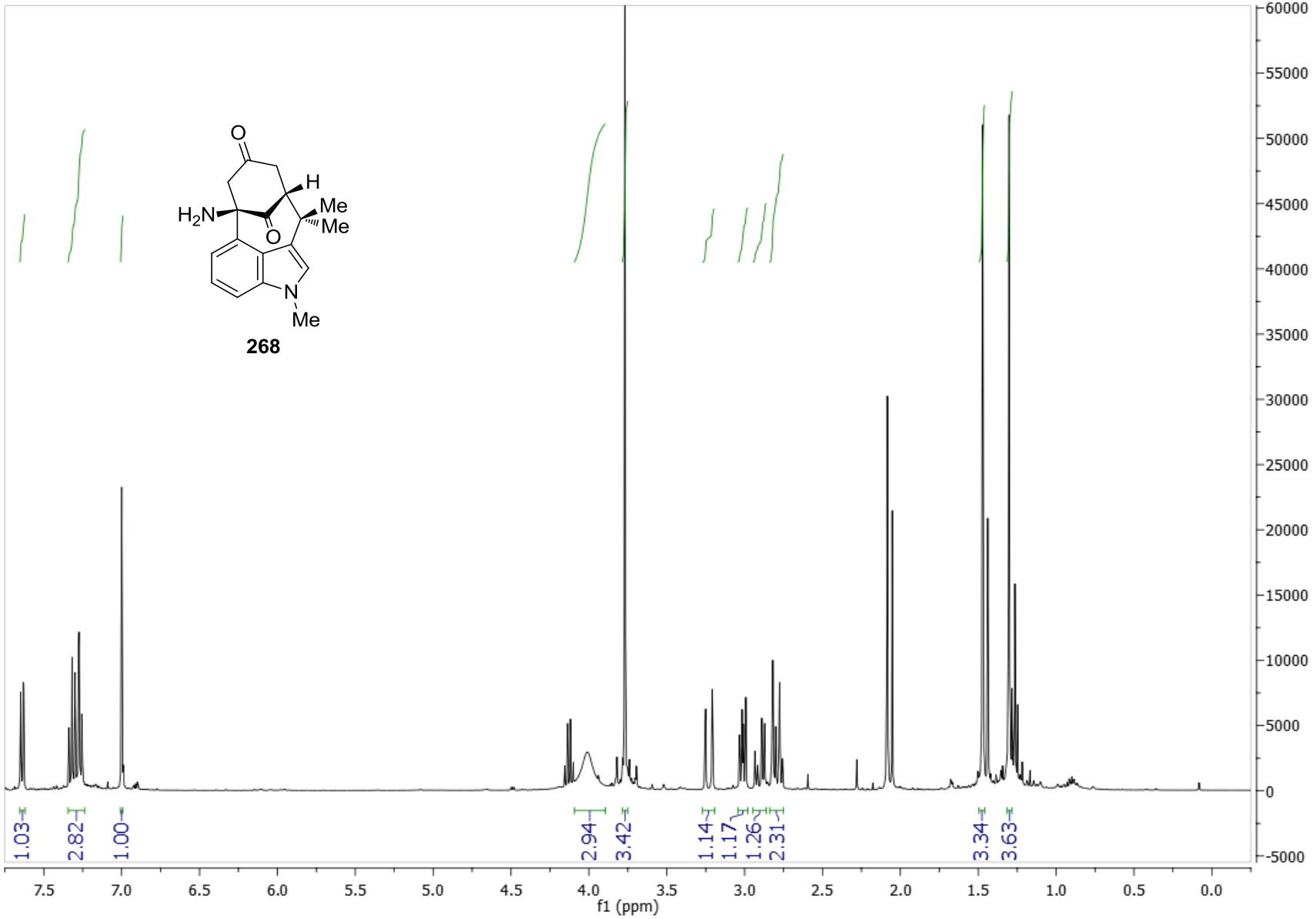
f1 (ppm)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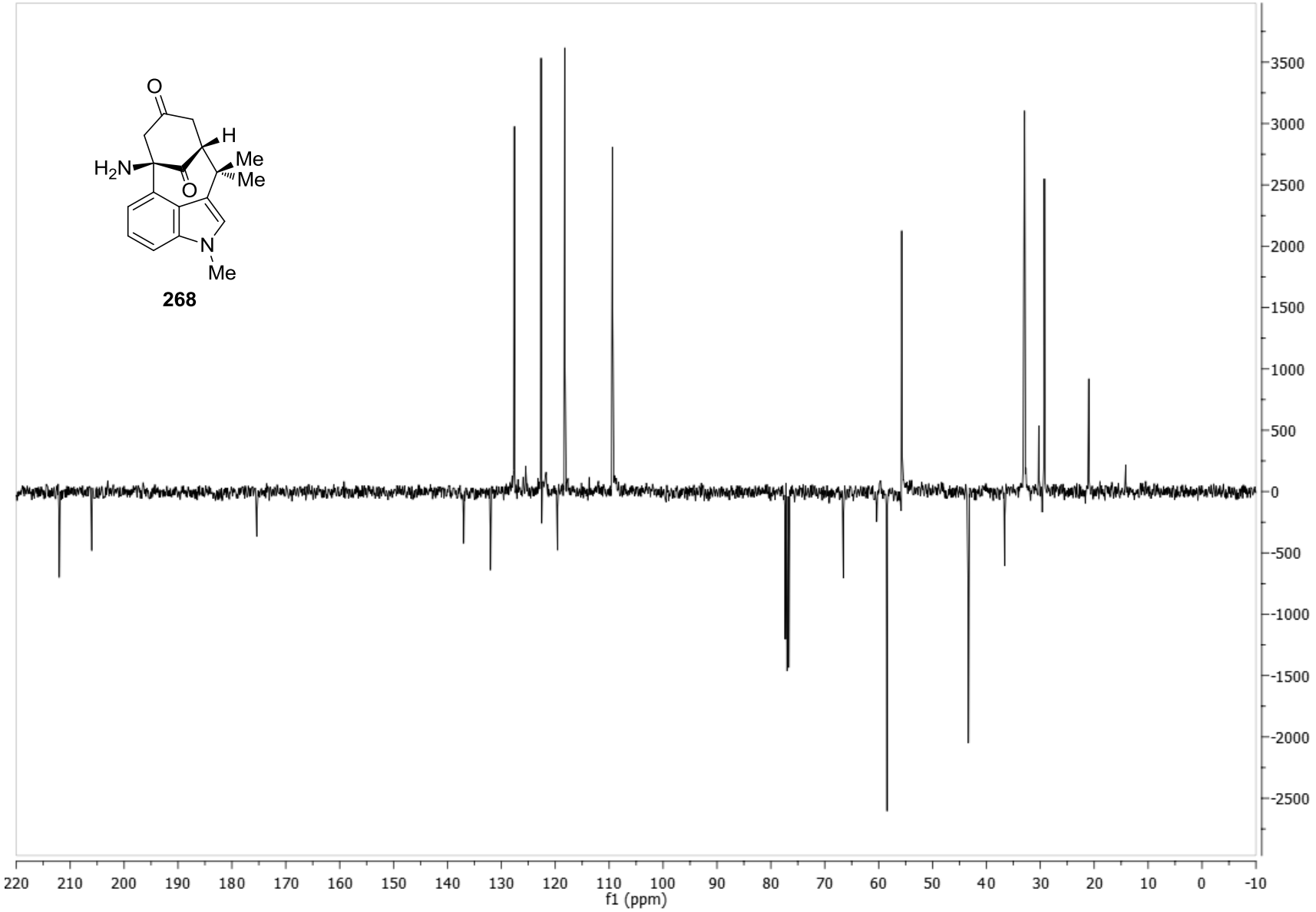
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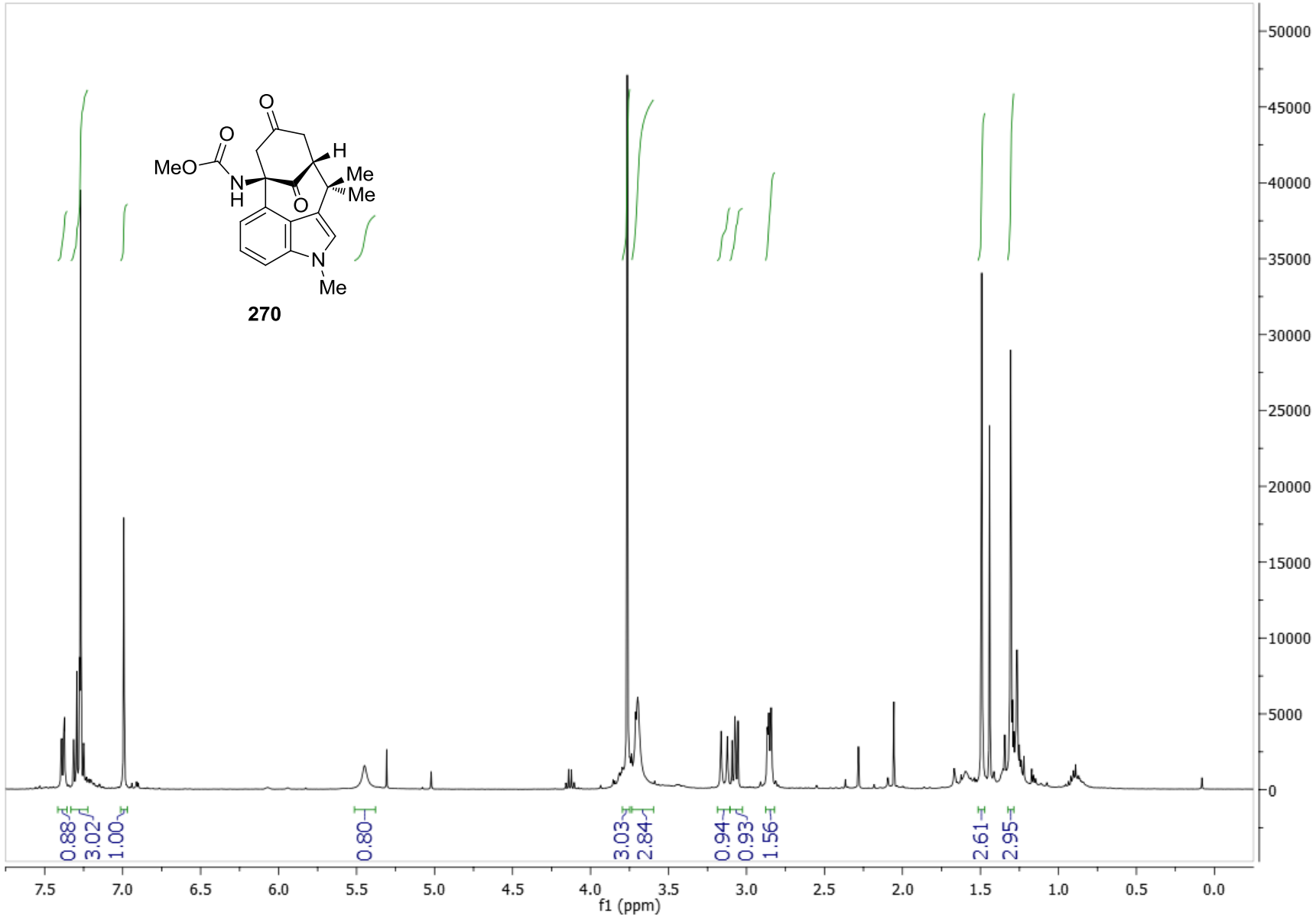
268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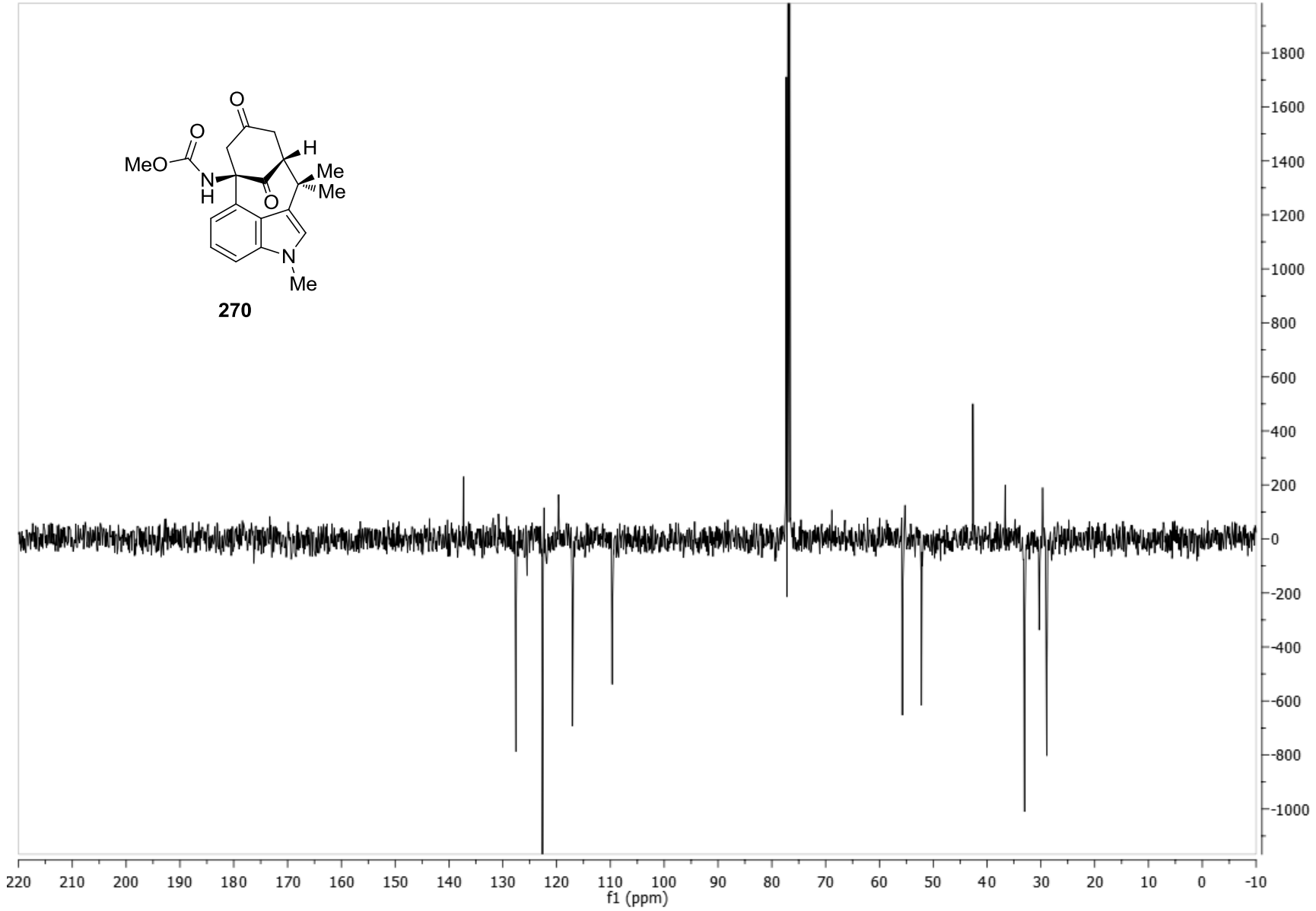
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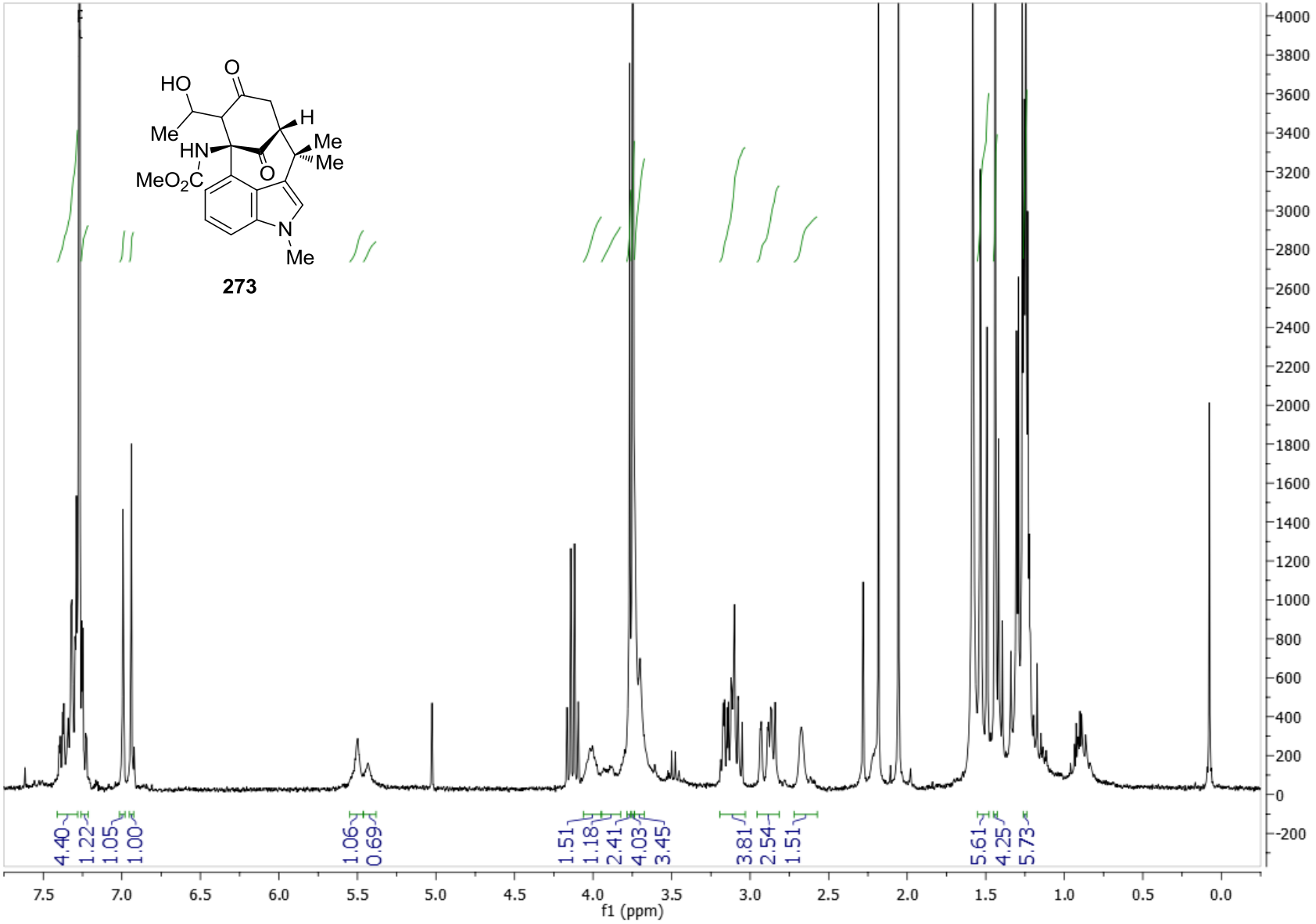
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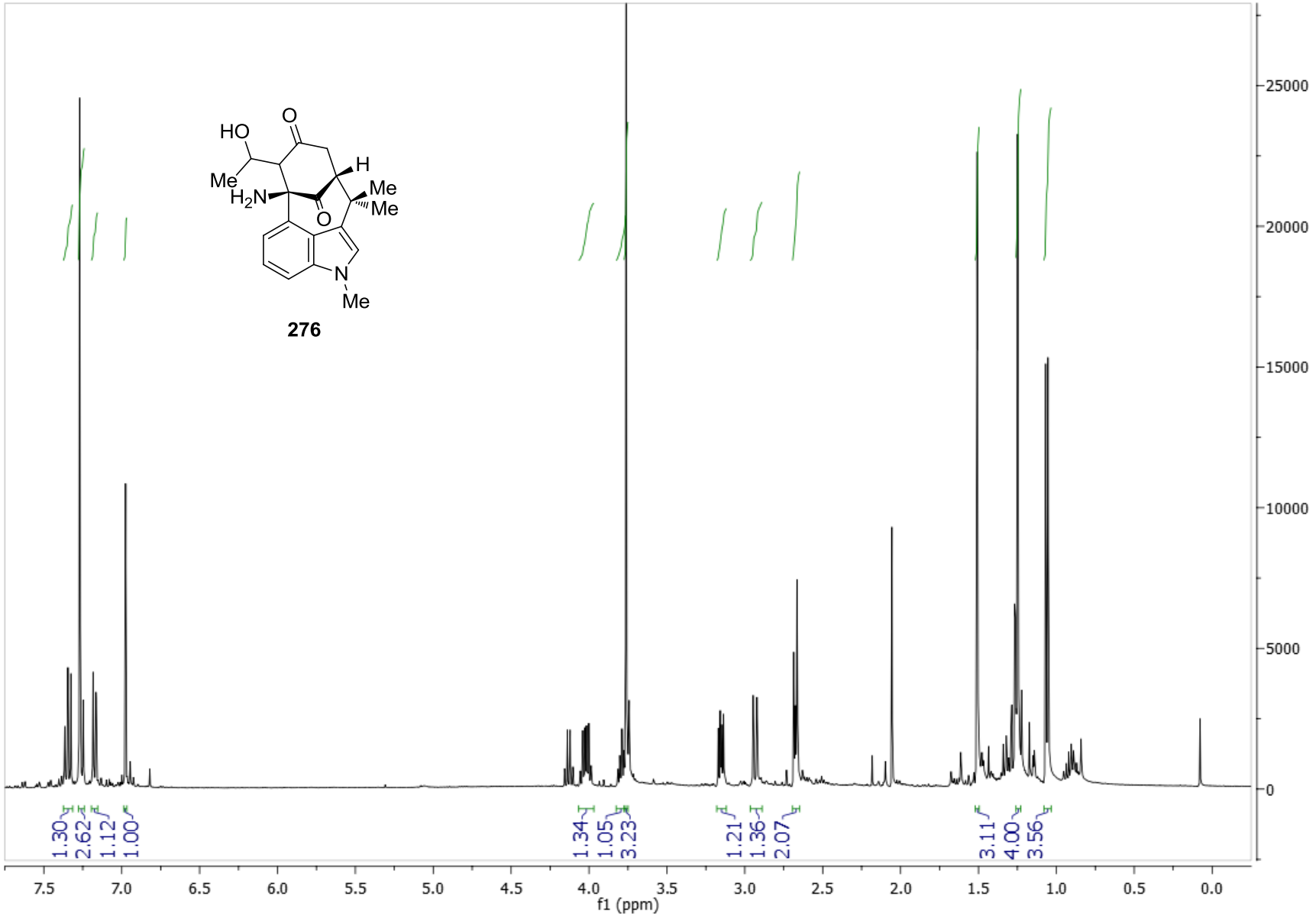
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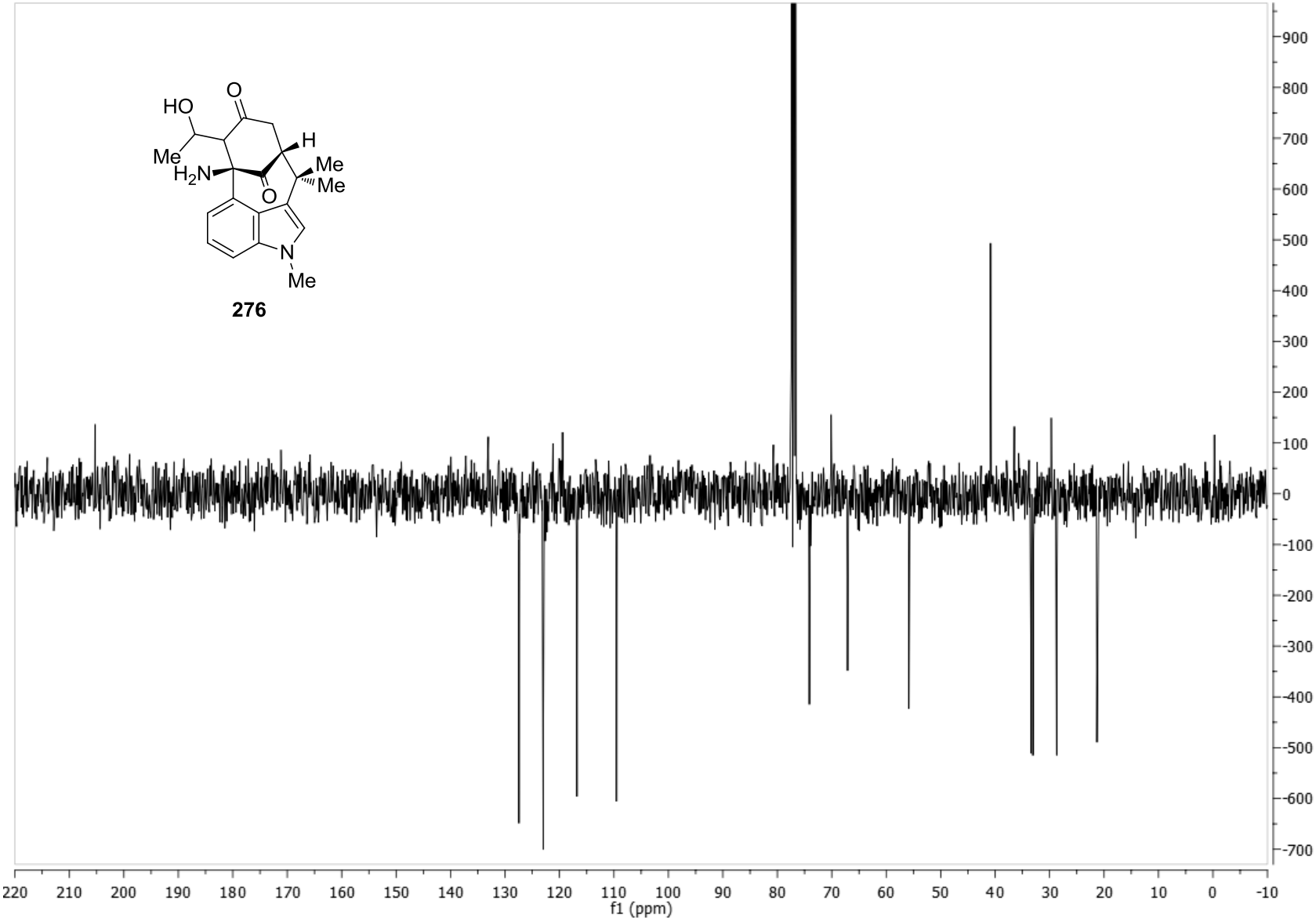
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100
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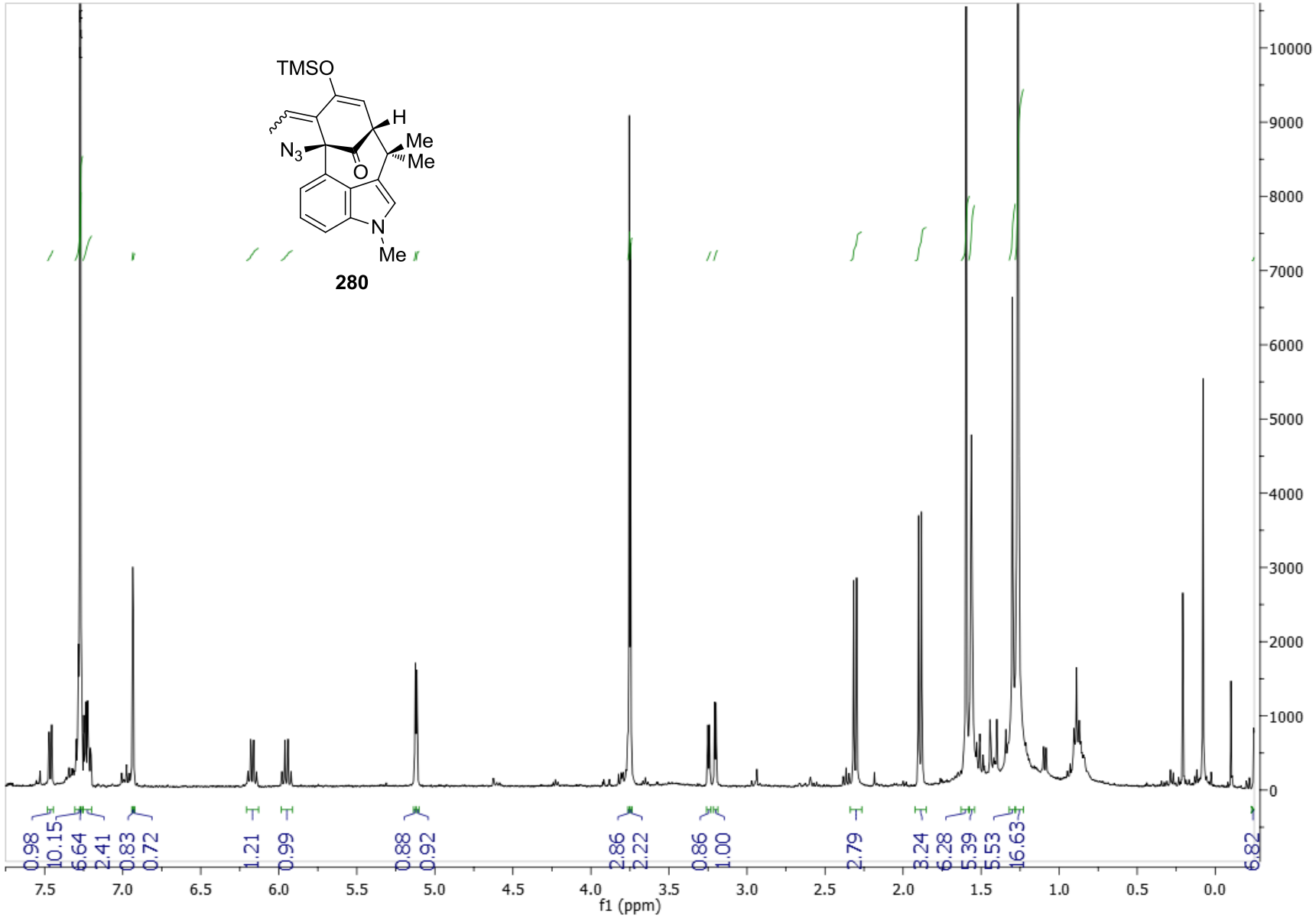
f1 (ppm)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0.99
0.88
0.92
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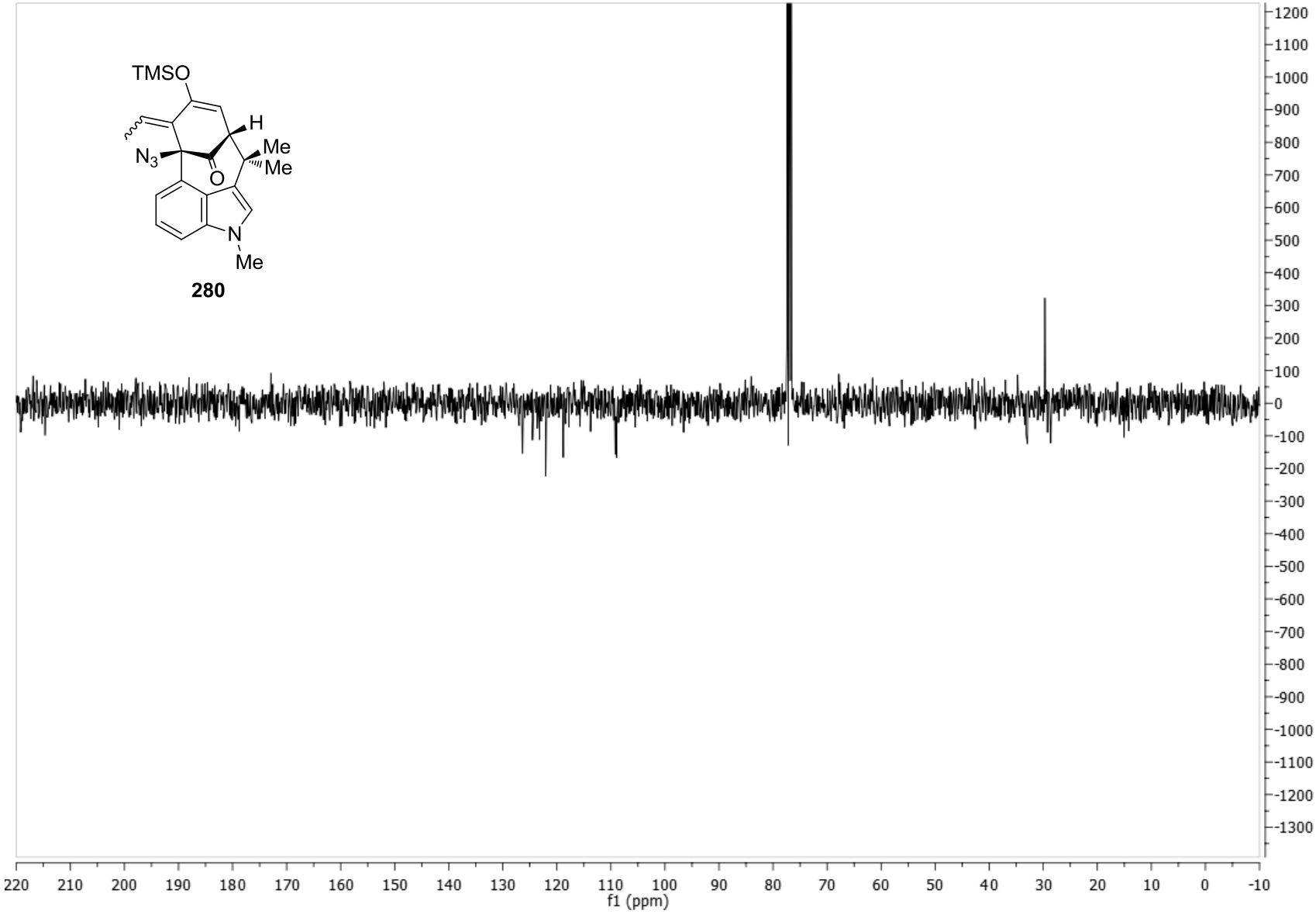
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N_3
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1000
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200
100
0
-100
-200
-300
-400
-500
-600
-700
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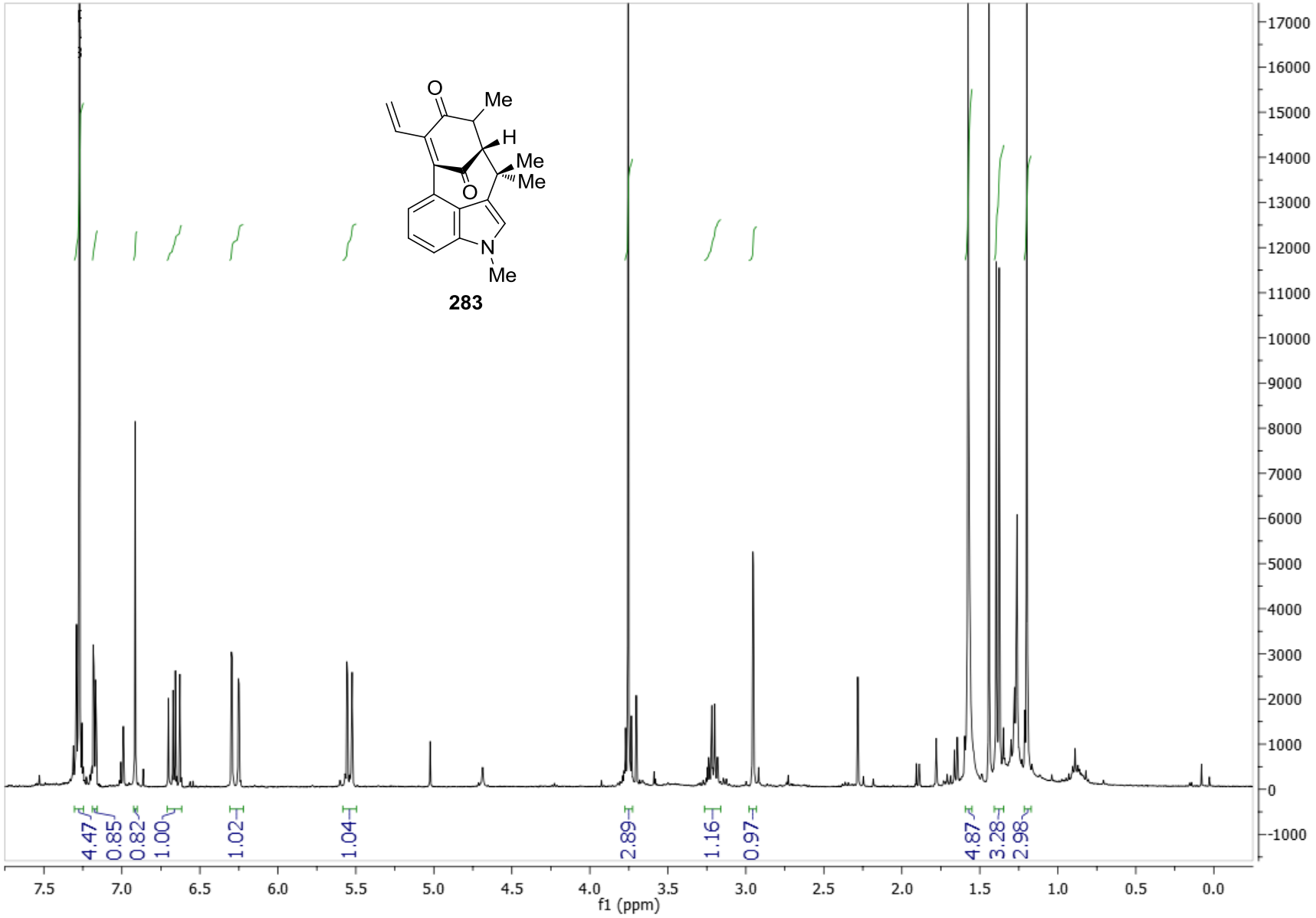
-1100
-1200
-1300
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

XX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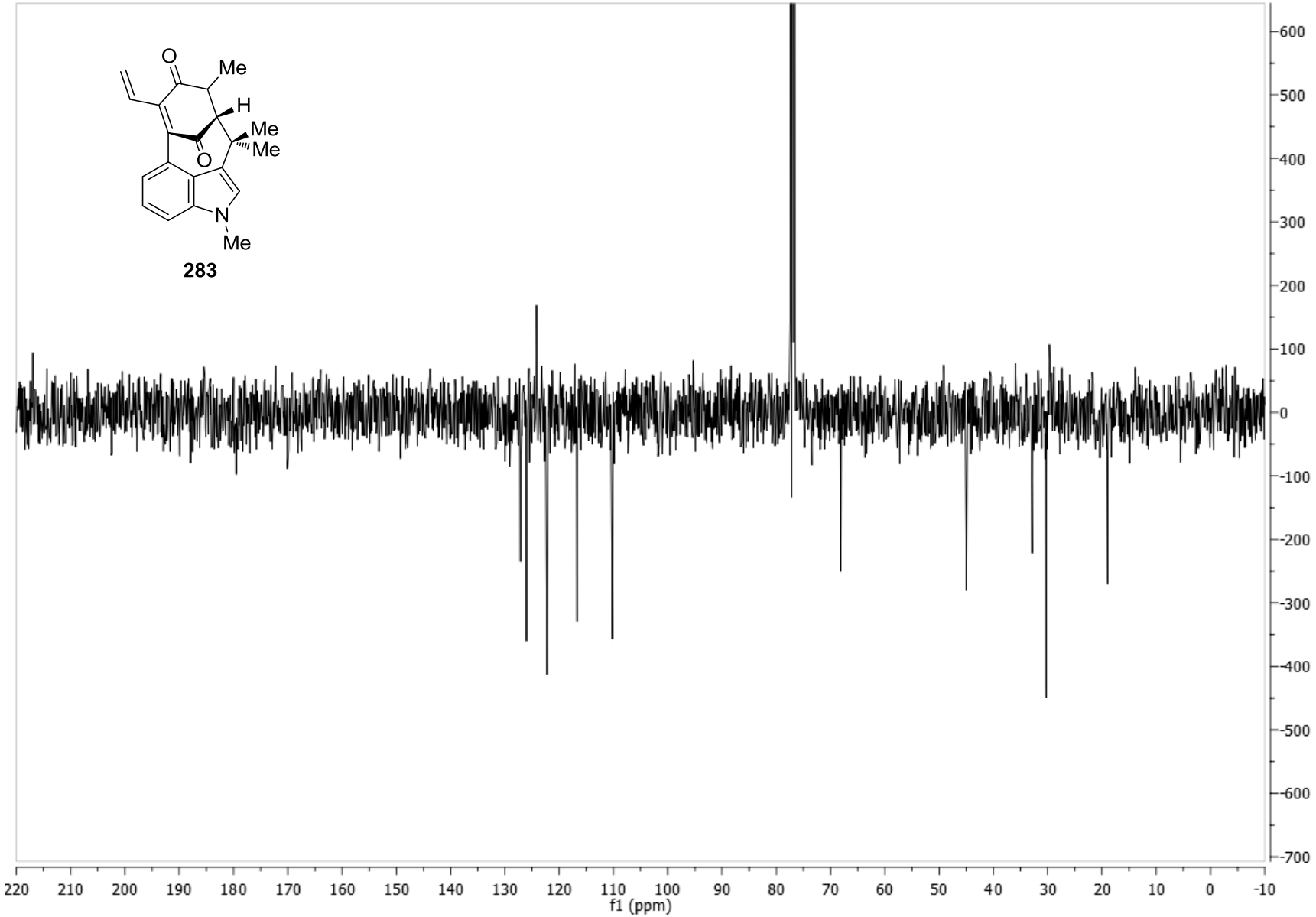
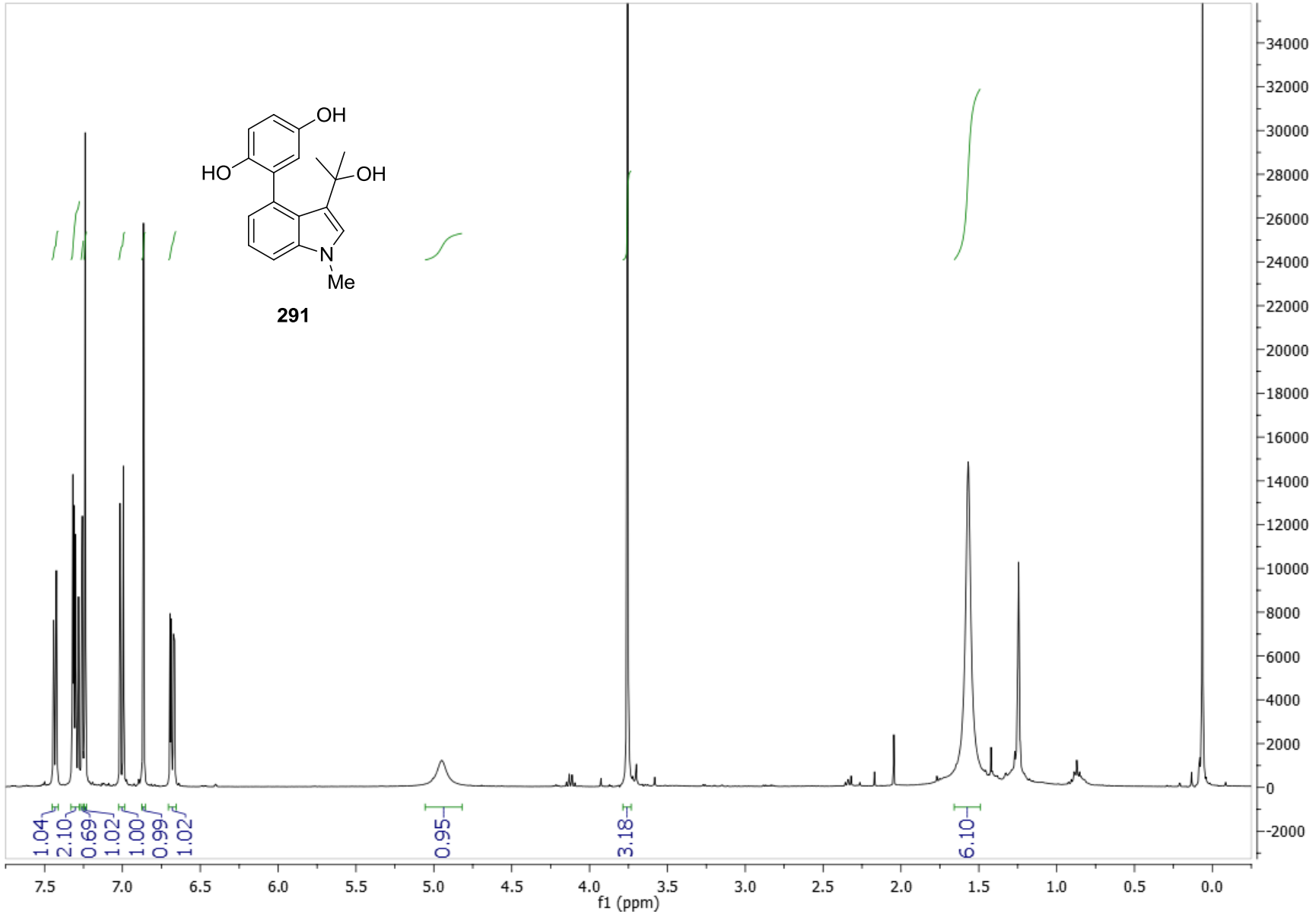
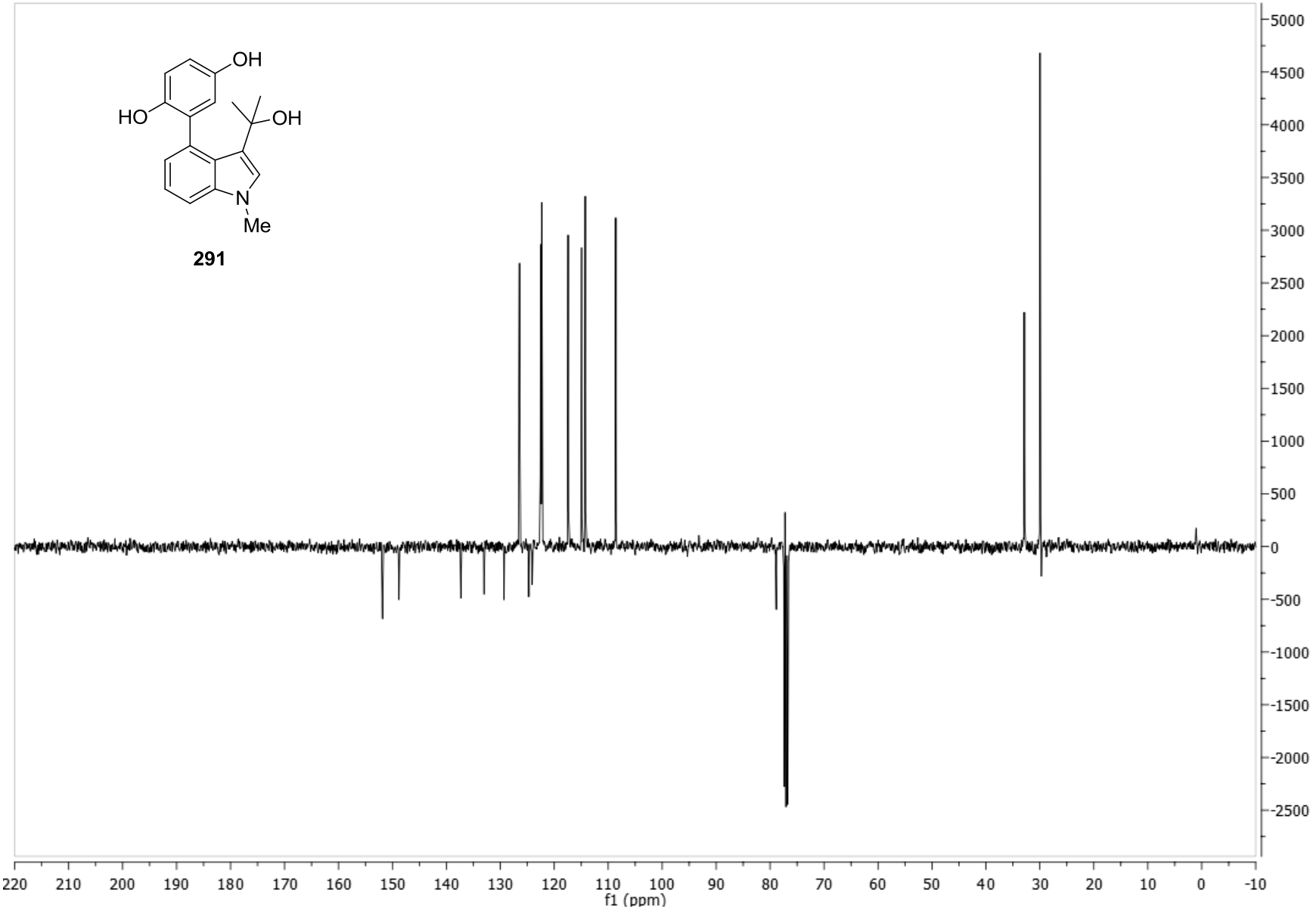
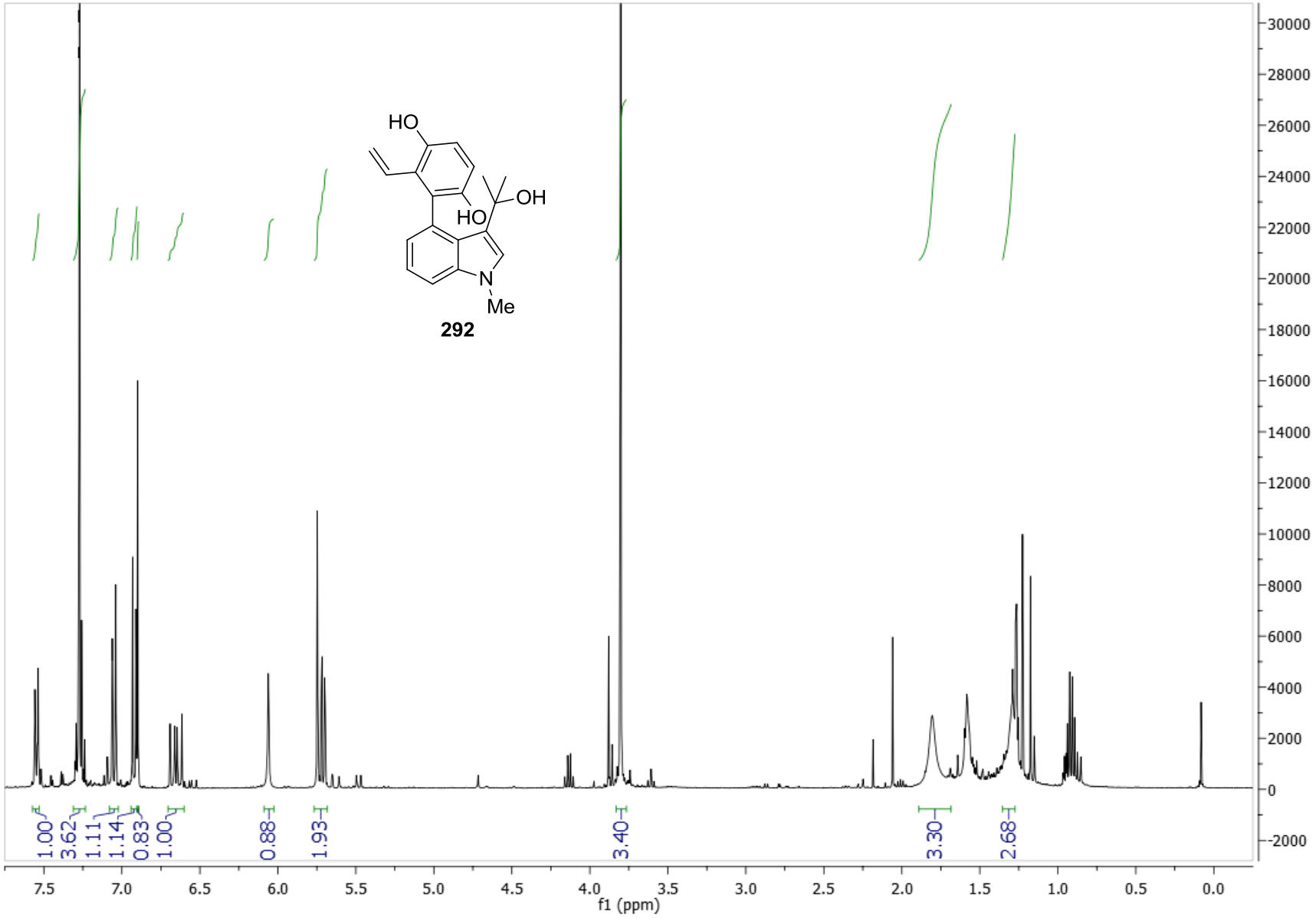
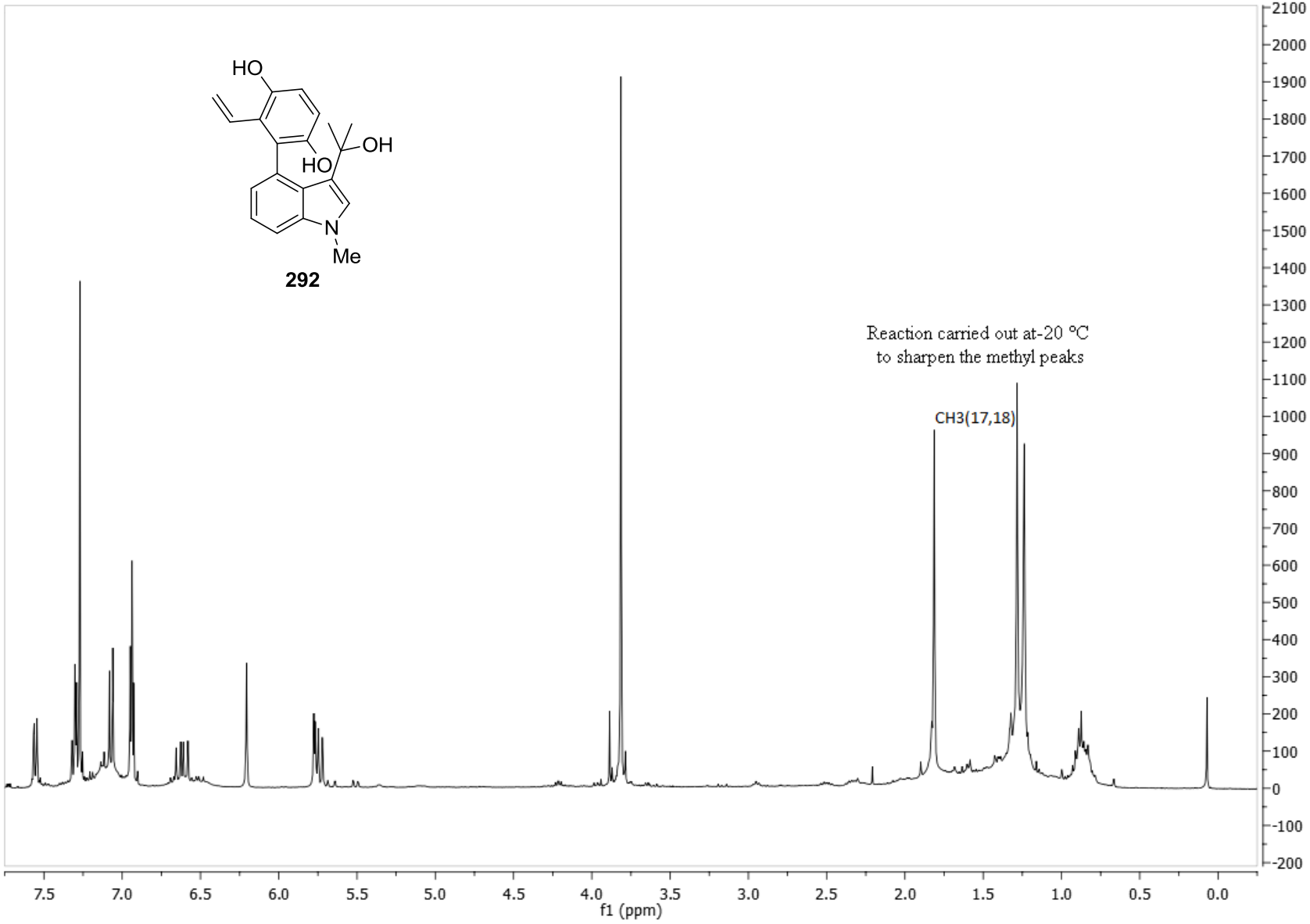
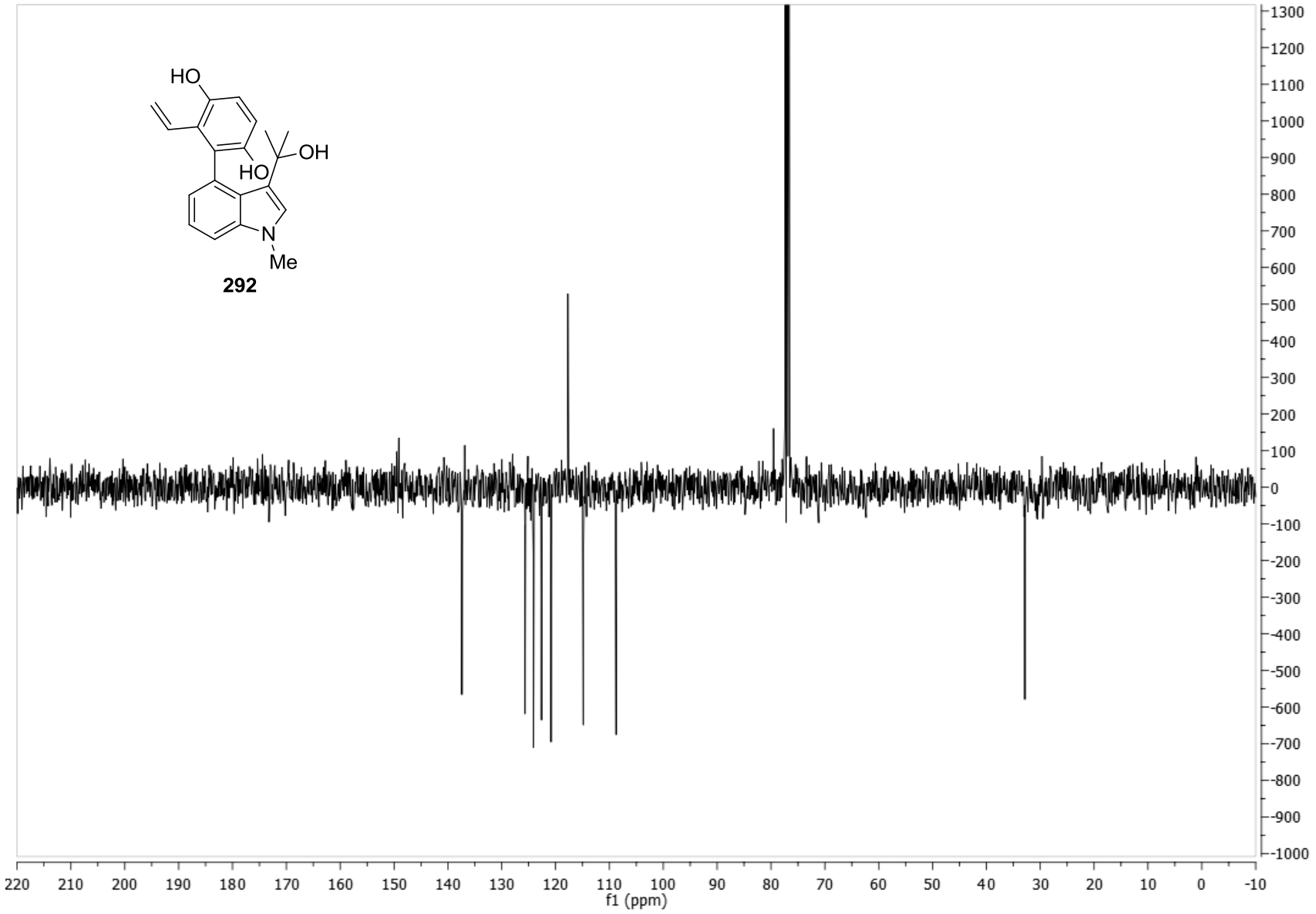

O
Me
H
Me
Me
O
N
Me
283
600
500
400
300
200
100
0
-100
-200
-300
-400
-500
-600
-700
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
HO
OH
N
Me
291
1.04
2.10
0.69
1.02
1.00
0.99
1.02
0.95
3.18
6.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000


OH
HO
OH
N
Me
291
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
-1500
-2000
-2500
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HO
HO
OH
N
Me
292
1.00
3.62
1.11
1.14
0.83
1.00
0.88
1.93
3.40
3.30
2.68
f1 (ppm)


HO
OH
HO
N
Me
292
Reaction carried out at-20 °C
to sharpen the methyl peaks
CH3(17,18)
f1 (ppm)


HO
HO
OH
N
Me
292
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
-300
-400
-500
-600
-700
-800
-900
-1000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)