UNIVERSITY OF BIRMINGHAM

Studies towards the total synthesis of *N*-methylwelwitindolinone C isothiocyanate

by

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Abstract

N-Methylwelwitindolinone C isothiocyanate (**7**), isolated from the blue green algae *Hapalosiphon welwitschii* and *Westiella intricate*, is a structurally novel alkaloid related to the welwitindolinone family. This thesis describes studies towards the total synthesis of this natural product.

Chapter One introduces the biological activities and the proposed biosyntheses of the welwitindolinone alkaloids. The synthetic studies towards the synthesis of this class of natural products will be also discussed.

Chapter Two describes the different strategies towards the synthesis of a bicyclo[4.3.1]decane scaffold possessing a *gem*-dimethyl group present in the natural product **7**. The geminal group was envisioned *via* a methyl addition to a carbonyl, a deprotonation of a sulfone or an intramolecular Michael addition. Generation of the desired skeleton **182** was achieved by using an intramolecular palladium-catalysed α-arylation of a trimethylsilyl enol ether.

Chapter Three describes various attempts to the direct installation of a nitrogen functionality at the bridgehead position. In an indirect mode, a regioselective deprotonation allowed functionalisation of the desired bridgehead position and the access to isocyanate **297** and diketoazide **276**, respectively obtained from a [3,3]-sigmatropic rearrangement and an aza-Michael reaction. A three step sequence involving a regioselective deprotonation of diketoazide **276**, followed by aldol condensation and dehydration led to the advance intermediate **306**.

Chapter Four describes the recent breakthrough in the synthesis of the welwitindolinone alkaloids. The total synthesis of *N*-methylwelwitindolinone D isonitrile (**19**) and *N*-methylwelwitindolinone C isothiocyanate (**7**), along with related studies reported this year.

Chapter Five includes the experimental procedures and analytical data for the preparation of novel compounds described during the course of this study.

Declaration

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

Bick Vivant

To my Mother.

To my sisters Liana and Laura.

Acknowledgements

Firstly, I would like to thank Professor Nigel S. Simpkins for his encouragement, advice and guidance during my PhD, and for the opportunity to work on this challenging and fascinating target.

I would like to acknowledge all the members of the Simpkins group past and present in particular Fred, Pistol, Elias, Damian, Mark and Seb for all these great and memorable times in and out of the lab, and Michael for his hospitality during the last months of my PhD.

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A special thank you to Giorgio and Victoria my fabulous housemates, I am sure now that the *gros sac* restaurant was the best place to eat in Birmingham. I also want to thank Antoine, Manu for the amazing movie sessions, Mich and Perry for all the hours we spend together playing football.

Finally, I would like to address a huge thank to my family, Bene and Jos for their support, “milles mercis” for being there and believing in me. I would not be able to go through this experience without you.

Contents

Abbreviations

ATP	adenosine triphosphate
AIBN	2,2’-azabisisobutyronitrile
Binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
br	broad
cat	catalytic
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
dba	dibenzylideneacetone
DBU	1,5-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DLP	dilauroyl peroxide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*, *N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
DTBHN	di-*tert*-butyl hyponitrite

DTBP	2,6-di-*tert*-butylpyridine
ee	enantiomeric excess
eq	equivalent
Eq.	equation
ESI	electrospray ionization
EWG	electron-withdrawing group
IBX	2-iodoxybenzoic acid
IR	infra-red spectroscopy
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
μ	micro
m	multiplet
MDR	multidrug resistance
Mont K-10	Montmorillonite K-10
mp	melting point
MS	mass spectrometry, molecular sieves
Ms	methanesulfonyl
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methyl morpholine-*N*-oxide

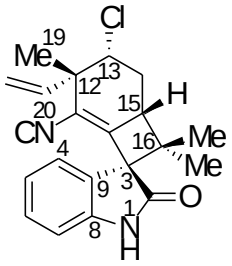
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
P-gp	P-glycoprotein
ppm	parts per million
q	quartet
rt	room temperature
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin
Ts	*para*-toluenesulfonyl (tosyl)
s	singlet

CHAPTER 1

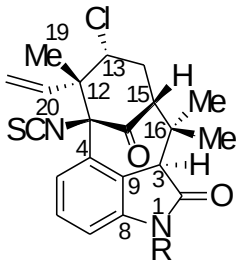
Introduction

1.1 The welwitindolinones: isolation and structural elucidation

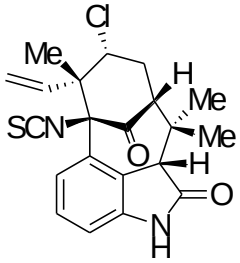
In 1994, Moore and co-workers reported the isolation of structurally unusual oxindole alkaloids from the lipophilic extracts of the blue green algae *Hapalosiphon welwitschii* W. & G.S. West (UH strain IC-52-3) and *Westiella intricate* Borzi (UH strain HT-29-1).[1] The former strain was found to exhibit antifungal and multidrug resistance (MDR)-reversing activities, while the latter displayed insecticidal activity against blowfly larvae. Several alkaloids were isolated from *H. welwitschii*: a unique spirocyclobutane oxindole, welwitindolinone A isonitrile (**1**) and six unprecedented tetracyclic bridged 3,4-oxindoles **2-7** (Figure 1.1).



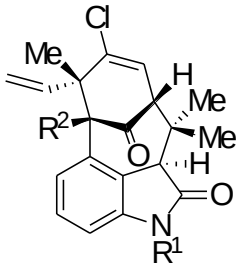
welwitindolinone A isonitrile (**1**)



R = H: welwitindolinone B isothiocyanate (**2**)
R = Me: *N*-methylwelitindolinone B isothiocyanate (**3**)



epi-**2** (**4**)

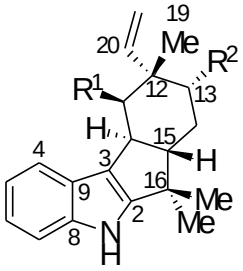


R^1 = H, R^2 = NCS: welwitindolinone C isothiocyanate (welwistatin) (**5**)
R^1 = Me, R^2 = NC: *N*-methylwelwitindolinone C isonitrile (**6**)
R^1 = Me, R^2 = NCS: *N*-methylwelwitindolinone C isothiocyanate (**7**)

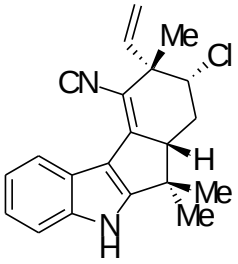
Figure 1.1

The major indole alkaloid isolated from the algal extract, *N*-methylwelwitindolinone C isothiocyanate (**7**), was found to be responsible for the MDR-reversing activity, while welwitindolinone A isonitrile (**1**) showed fungicidal activity.

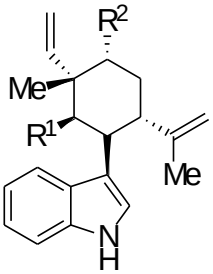
The absolute configuration of *N*-methylwelwistatin **7** was determined by X-ray crystallography and interestingly the relative stereochemistry of C-12, C-13 and C-15 of welwitindolinone A isonitrile (**1**) led to the hypothesis that **1** could be a biogenetic precursor to **2-7**. In its first report, Moore's group also co-isolated eight biogenetically-related alkaloids: these were four novel fischerindoles **8**-**11**, the known tricyclic 12-*epi*-hapalindole E isonitrile (**14**) and three novel hapalindoles **12**, **13** and **15** (Figure 1.2).



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



12-*epi*-fischerindole I isonitrile (**11**)

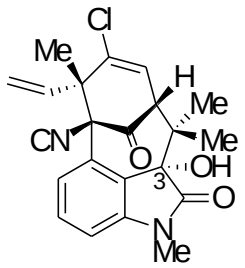


R^1 = NC, R^2 = H: 12-*epi*-hapalindole C isonitrile (**12**)
R^1 = NCS, R^2 = H: 12-*epi*-hapalindole D isothiocyanate (**13**)
R^1 = NC, R^2 = Cl: 12-*epi*-hapalindole E isonitrile (**14**)
R^1 = NCS, R^2 = Cl: 12-*epi*-hapalindole F isothiocyanate (**15**)

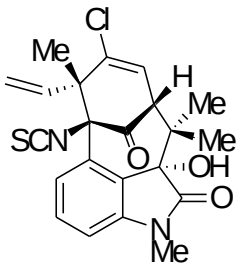
Figure 1.2

Moore and co-workers subsequently reported the isolation of four more highly oxidized welwitindolinones **16**-**19** from strains of cyanobacteria *Fischerella musciola* and *Fischerella major*, along with previously isolated compounds **1**, **2** and **4** (Figure 1.3).[2] Welwitindolinones **16** and **17** are clearly the result of C-3 oxidation of **6** and **7**, respectively, while *N*-methylwelwitindolinone D isonitrile (**19**) possesses an interesting spiro-ether link as a

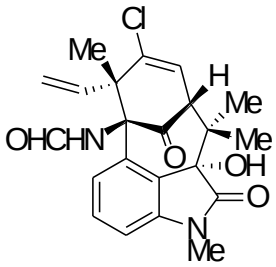
result of a more complex oxidation process. Lastly, formamide derivative **18** seemed to be an artefact formed from **16** during the isolation process.



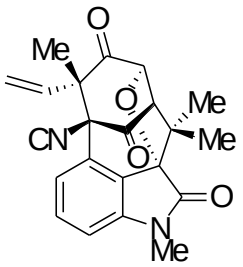
3-hydroxy-*N*-methyl-welwitindolinone C isonitrile (**16**)



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



3-hydroxy-*N*-methyl-welwitindolinone C formamide (**18**)



N-methylwelwitindolinone D isonitrile (**19**)

Figure 1.3

To date, no biological activity has been reported in relation to these oxidised welwitindolinones.

1.2 The welwitindolinones: biological properties

1.2.1 The welwitindolinones as MDR-reversing agents

Chemotherapy is widely utilised as a treatment of many cancers but unfortunately during the last few decades a major drawback of this therapy has been the ability of tumours to develop resistance against anticancer agents.[3] This protective response is usually developed by tumour cells against chemotherapeutic agents. To understand the MDR process, extensive studies were conducted and revealed a correlation with the over-expression of plasma membrane

glycoprotein (P-gp).[4,5] This protein was found to be located in many tissues, e.g. kidney, pancreas, intestine and adrenal gland and is assumed to play a role in drug regulation in the organism. Significant efforts were made to understand the mechanism of action of P-gp.[6] There are currently a variety of proposed mechanisms of action, however all models suggest that P-gp acts as an ATP-dependent efflux pump.[7,8] In this process, ATP (adenosine triphosphate) hydrolysis provides the required energy to P-gp to transport and expel the drug from the cell, thereby reducing its intracellular concentration. Therefore to limit the effects of MDR resistance in cancer cells, research is directed at the screening and creation of agents, which can interact with, and inhibit, this efflux mechanism.

After isolation of the welwitindolinones, Moore and co-workers investigated their MDR-reversing activities by using drug-resistant SK-VLB-1 and MCF-7/ADR cells (derived, respectively, from ovarian and breast tumours).[9] They found that welwitindolinone **7** demonstrated MDR-reversing efficacy towards the two different MDR cell lines. In the case of MCF-7/ADR, they observed the ability of **7** to chemosensitise the cells at doses as low as 0.1 μM, which means it is 20-100 times more potent than verapamil (a standard MDR-reversing agent). Interestingly, at this dose, the concentration of **7** is 30-fold lower than its IC_{50}, which gives it a reasonably large therapeutic index. *N*-Methylwelwitindolinone C isonitrile (**6**) was found to be inactive, which demonstrated the importance of the isothiocyanate group in the interaction with P-gp. Welwitindolinone C isothiocyanate (**5**, welwistatin) showed moderate MDR-reversing activity, but it was 25 times more cytotoxic than *N*-methylwelwistatin **7**, suggesting that the presence of the methyl group might attenuate cytotoxicity.

1.2.2 The welwitindolinones as antimicrotubule agents

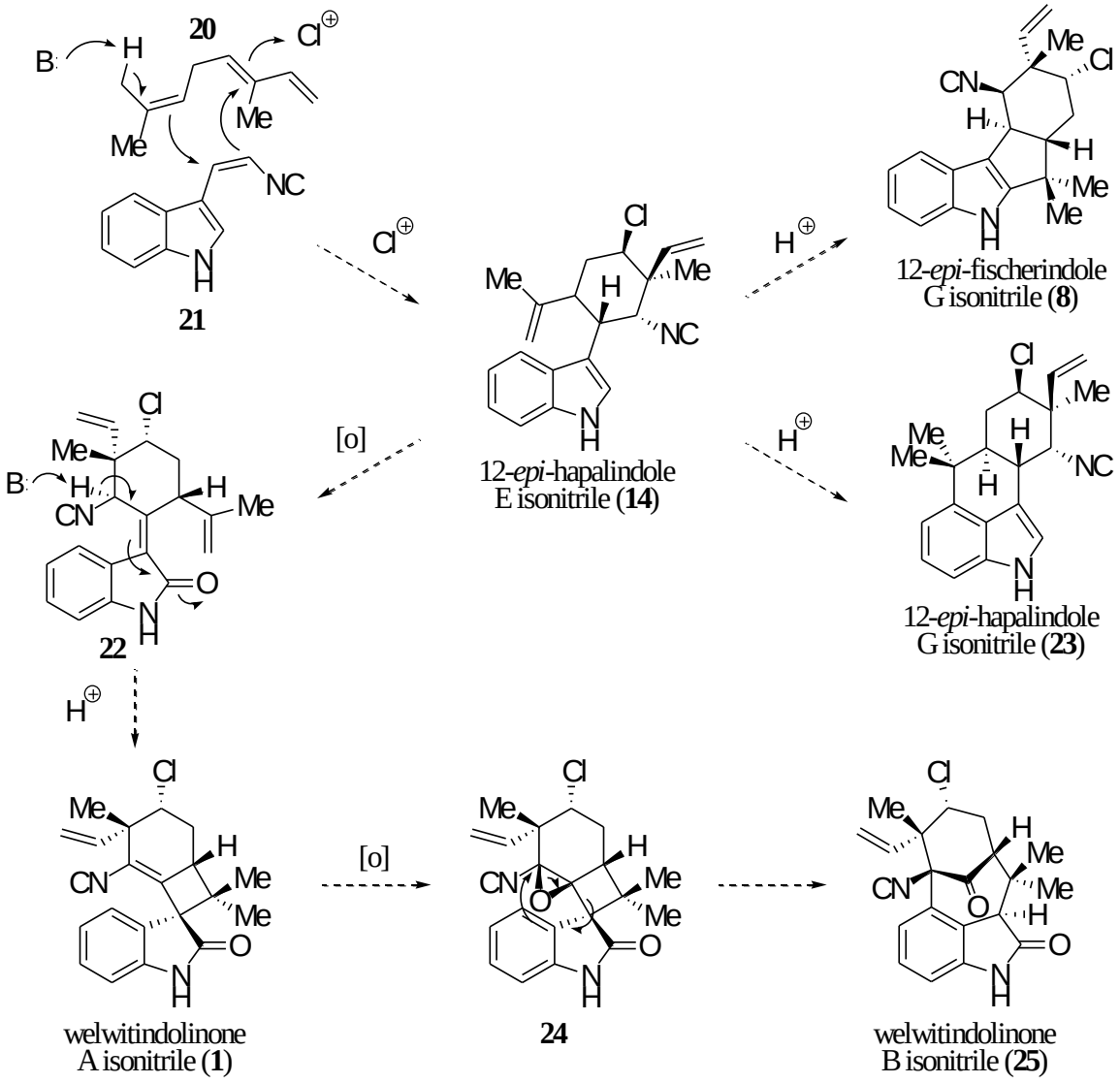
Microtubules are present in cellular cytoplasm and are responsible for a variety of functions including organelle organisation and mitotic spindle formation.[10] Microtubules are made up of straight hollow tubes that undergo constant elongation and contraction. These processes are dependent on the addition and loss of tubulin dimers to microtubules. Several compounds e.g. vinblastine, colchicines and paclitaxel disturb the dynamic equilibrium of microtubule assembly and disassembly, and consequently block the cell division in the mitotic phase.

Antimicrotubule agents have been used as anticancer drugs but tumour cells have acquired resistance to many natural product antimicrotubule agents *via* action of the drug-efflux pump P-gp. To overcome this problem of drug resistance, antimicrotubule agents and P-gp antagonists have to be combined.

Smith and Zhang discovered that welwistatin **5** disrupted microtubule formation in SK-OV-3 human ovarian carcinoma cells and A-10 vascular smooth muscle cells.[11] Interestingly, treatment of A-10 cells with welwistatin disturbs microtubule dynamics but does not cause irreversible loss of tubulin. Moreover, pre-treatment of A-10 cells with paclitaxel prevented microtubule depolymerisation in response to **5**. Finally, overexpression of P-gp did not confer resistance to welwistatin. All of these factors contribute to indicate that welwistatin **5** has potential as a possible chemotherapeutic agent. This study also showed that *N*-methylwelwistatin **7** has lower antimicrotubule activity, while *N*-methylwelwitindolinone C isonitrile (**6**) has similar activity to **5**.

1.3 Biosynthesis of the welwitindolinones

In addition to isolation and characterisation studies, Moore suggested a biogenesis of the welwitindolinones and chlorinated fischerindoles *via* a common intermediate, 12-*epi*-hapalindole E isonitrile (**14**) (Scheme 1.1).[1]

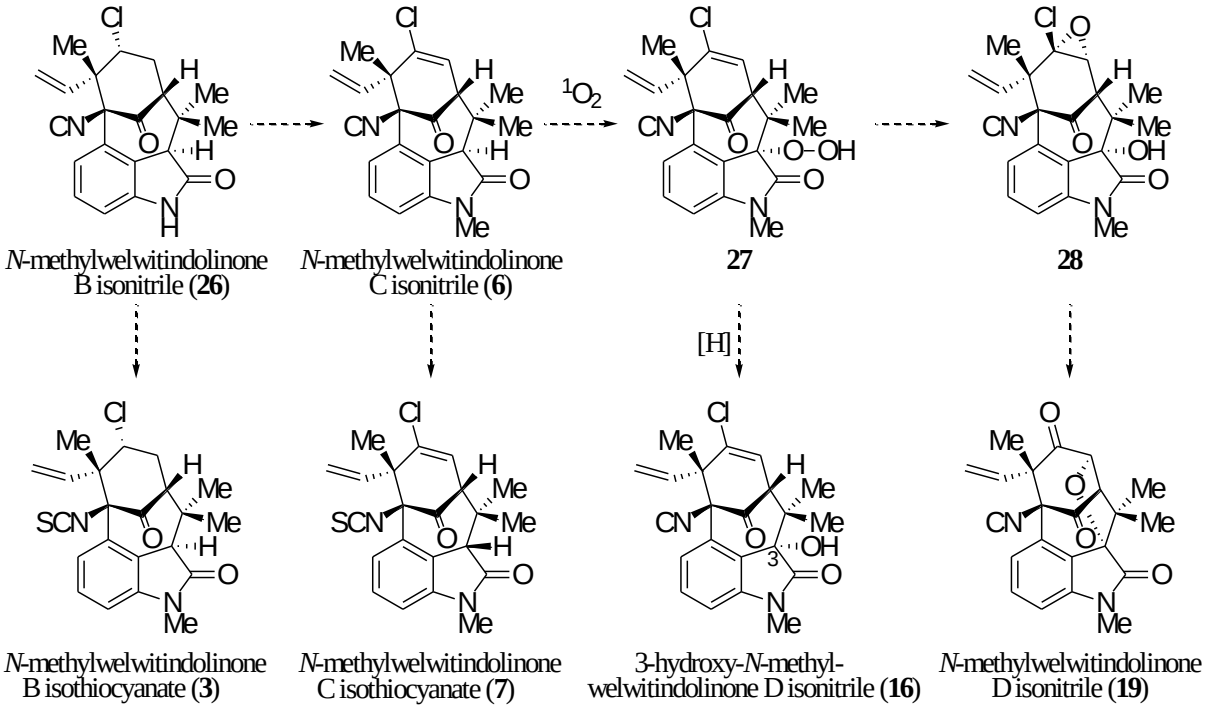


Scheme 1.1

This precursor was isolated by Schwartz and co-workers in 1987 and was found to be the second-most abundant alkaloid in *Hapalosiphon welwitschii*.[12] Key precursor **14** could be obtained from reaction between the triene **20** and the tryptophan derivative **21** *via* a

chloronium-ion promoted polyolefin cyclisation. From this tricyclic precursor, Moore and co-workers suggested that cyclisation of the isopropenyl group to the C-2 or C-4 positions of the indole ring system would lead, respectively, to fischerindole **8** or hapalindole **23**. They further proposed that hapalindole **14** could undergo an oxidation/acid-catalysed cyclisation sequence to provide welwitindolinone A isonitrile (**1**). They also suggested that the bridged 3,4-oxindole present in welwitindolinone B isonitrile (**25**) would arise from a rearrangement of the epoxide **24**.

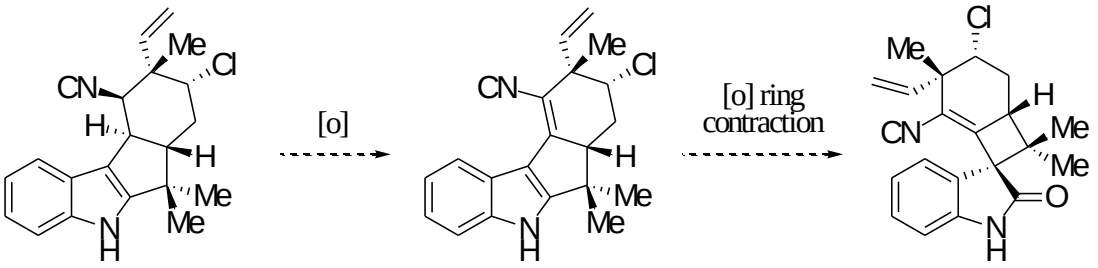
Welwitindolinone **26** could be the common precursor to the remaining members of this alkaloid family. Therefore, *N*-methylation and appropriate oxidation could lead to the formation of welwitindolinones **3**, **6** and **7**. Finally, the highly oxidised welwitindolinones **16** and **19** could arise from the hydroperoxy intermediate **27**, which could be obtained from a photocatalytic oxidation at C-3 of the oxindole **6** (Scheme 1.2).



Scheme 1.2

Reduction of peroxide **27** would give **16** and alternatively, intramolecular epoxidation of vinyl chloride followed by epoxide opening and elimination of chloride would provide *N*-methylwelwitindolinone D isonitrile (**19**). Surprisingly Moore and co-workers did not address the stereochemical conflict arising from this epoxide opening by the 3-OH oxygen. However, they showed that photo-oxidation of welwitindolinone **6** led to **16** and **19**, albeit in low isolated yields, 4.9% and 3.2% respectively.[2]

Baran pointed out that intermediate **22** has not been isolated, its mechanism of conversion into **1** seems unlikely and therefore suggested an alternative biosynthesis to welwitindolinone A isonitrile (**1**) (Scheme 1.3).[13]



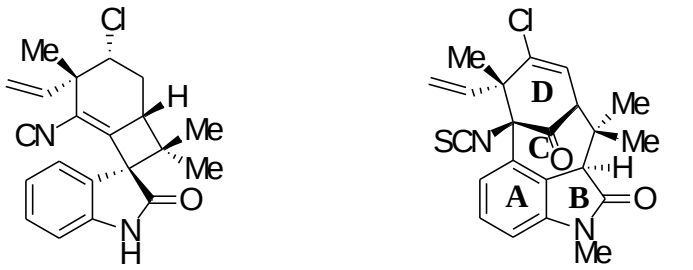
12-*epi*-fischerindole G isonitrile (**8**) → 12-*epi*-fischerindole I isonitrile (**11**) → welwitindolinone A isonitrile (**1**)

Scheme 1.3

Baran suggested that the formation of welwitindolinone **1** could occur *via* a benzylic oxidation of 12-*epi*-fischerindole G **8** followed by an oxidative ring-contraction of 12-*epi*-fischerindole I **11**. Both fischerindoles **8** and **11** were initially co-isolated with the welwitindolinones.

1.4 Studies towards the synthesis of welwitindolinones

The unique and fascinating structures of the welwitindolinones have attracted the attention of many synthetic groups. Welwitindolinone A isonitrile (**1**) and especially *N*-methylwelwitindolinone C isothiocyanate (**7**), which possesses promising MDR-reversing and anticancer properties have received particular attention (Figure 1.4). The compact tetracyclic structure of **7** with four stereogenic centres, three quaternary carbons and two unusual and sensitive functionalities e.g. the isothiocyanate and vinyl chloride groups, represents a real synthetic challenge.



welwitindolinone A isonitrile (**1**)

N-methylwelwitindolinone C isothiocyanate (**7**)

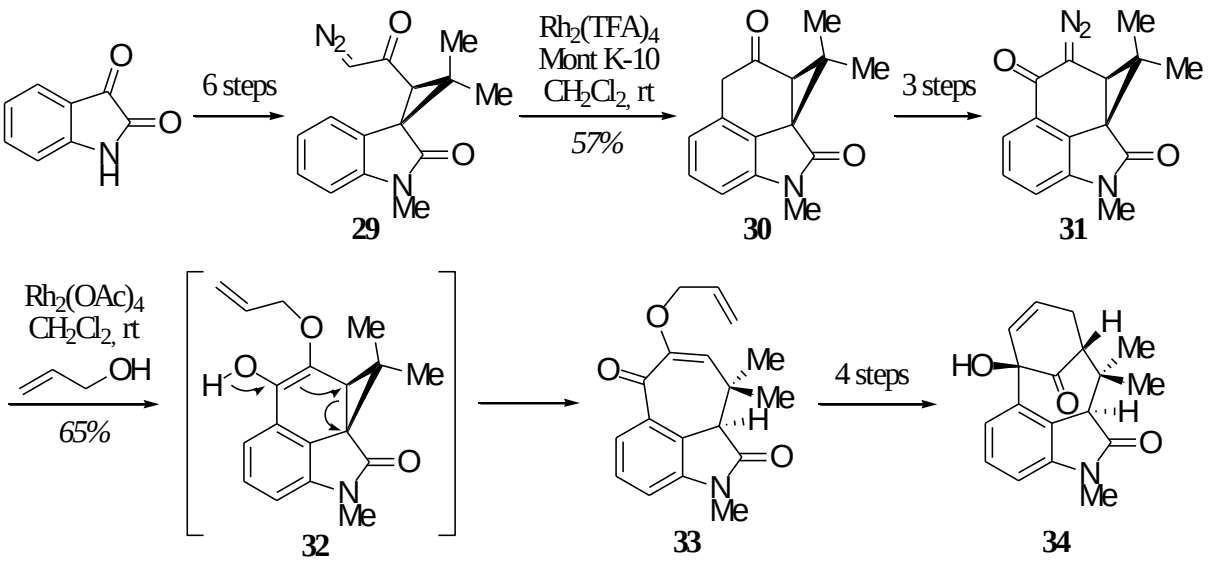
Figure 1.4

This section will review the synthetic work towards the welwitindolinones prior to the commencement of this project and during our studies from 2007 to 2010. The total syntheses of welwitindolinone A isonitrile (**1**) and the synthetic studies towards *N*-methylwelwistatin **7** will be described.

1.4.1 Previous synthetic work towards the welwitindolinones

The first approach towards *N*-methylwelwistatin **7** was published by Wood and co-workers in 1999.[14] In this fifteen-step synthesis starting from isatin, the central seven-membered C ring was generated *via* a rhodium carbenoid-mediated O-H insertion followed by cyclopropane

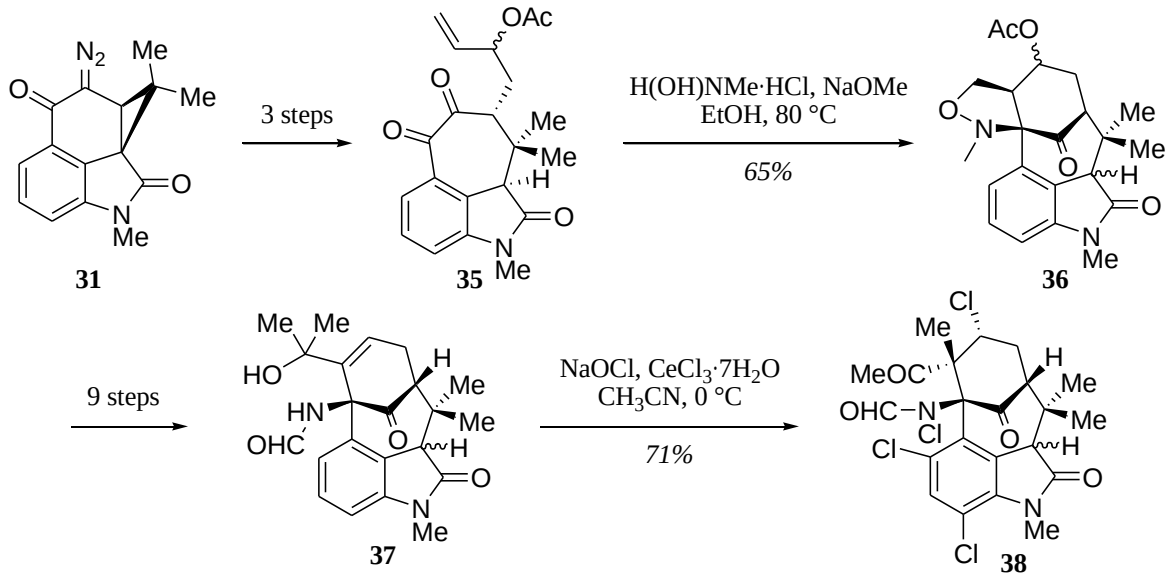
ring-opening. Thus, α-diazoketone **29** was prepared in six steps from isatin and aryl C-H insertion was accomplished upon treatment with $Rh_2(TFA)_4$ in the presence of the mildly Lewis-acidic clay Montmorillonite K-10 to yield derivative **30** in 57% yield. Subsequent benzylic oxidation and regioselective diazotisation furnished α-diazoketone **31** in a three-step sequence. Compound **31** was coupled with allyl alcohol using $Rh_2(OAc)_4$ as a catalyst to provide intermediate **32**, which underwent cyclopropane opening to afford the seven-membered C ring. Further manipulations, including Grignard addition, Claisen rearrangement and ring-closing metathesis to generate the cyclohexanone ring D, led to the first synthesis of the bicyclo[4.3.1]decane core structure **34** (Scheme 1.4).



Scheme 1.4

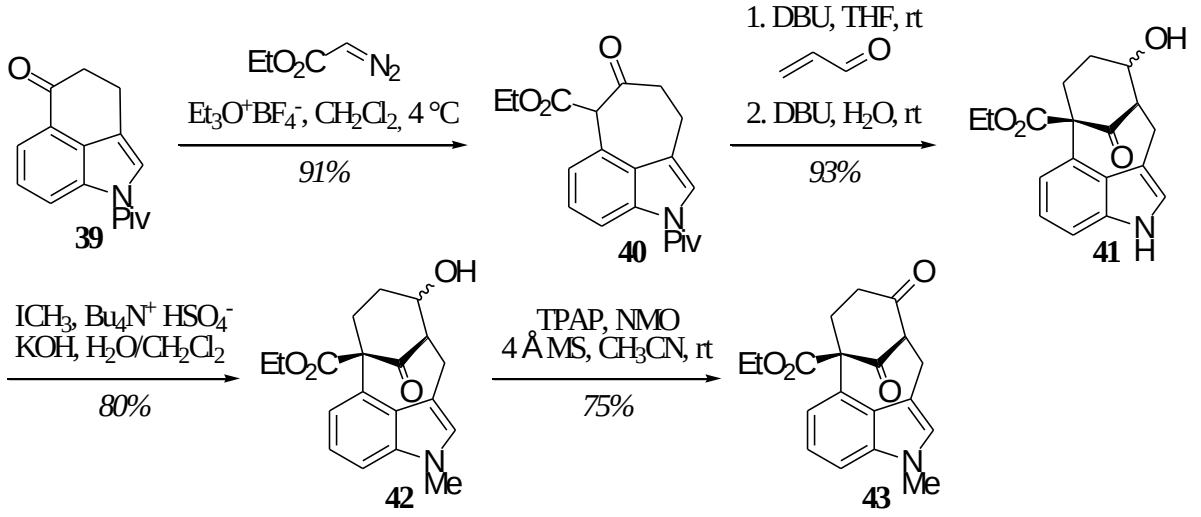
A decade later, Wood and co-workers published a second-generation synthesis.[15] After fruitless attempts to install nitrogen at the bridgehead position from alcohol **34**, they turned their attention to a nitrone-mediated transannular [3+2] dipolar cycloaddition. The key intermediate **35** was prepared in three steps from α-diazoketone **31**. The key [3+2] cycloaddition was achieved by treatment with *N*-methylhydroxylamine to furnish isoxazolidine **36** as a mixture of diastereoisomers. They then envisaged applying their

previous work on the synthesis of welwitindolinone A isonitrile (**1**) using chloronium ion-induced semi-pinacol rearrangement to obtain the desired quaternary centre and neopentyl chlorine.[16] After further manipulation, the target alcohol **37** was obtained in nine steps. Exposure to $CeCl_3 \cdot 7H_2O$ and NaOCl afforded the rearranged compound **38**, but over-chlorination could not be controlled and oxindole **38** was obtained in 71% yield (Scheme 1.5).



Scheme 1.5

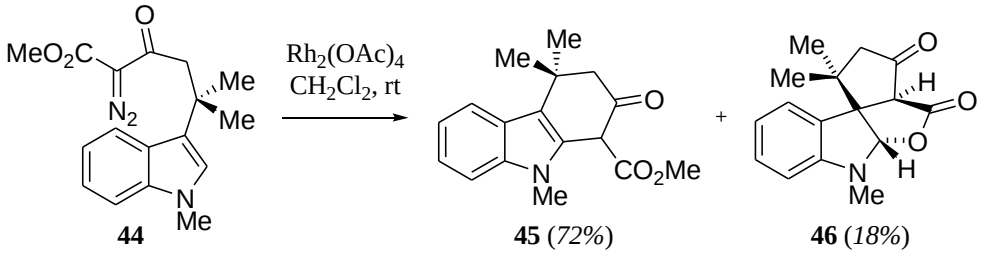
A second synthesis, reported by Menéndez, described the formation of the central C ring by ring expansion from Kornfeld's ketone **39**[17] (obtained in two steps from 3-(indol-3-yl)propionic acid).[18] Thus, ketone **39** underwent ring expansion by treatment with ethyl diazoacetate and triethyloxonium tetrafluoroborate to give **40**. Then a one-pot sequence involving Michael addition, intramolecular aldol condensation and *N*-pivaloyl hydrolysis provided the bicyclo[4.3.1]decane skeleton **41** in 93% yield. *N*-Methylation followed by oxidation of the secondary alcohol led to diketoester **43** (Scheme 1.6).



Scheme 1.6

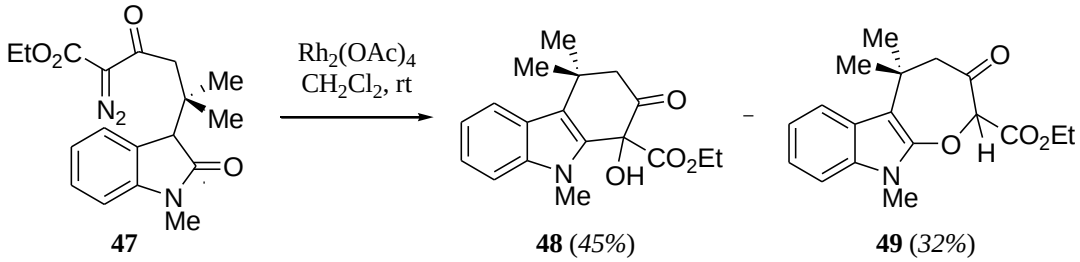
Two groups reported their attempts to generate the cycloheptane ring C directly *via* an aryl C-H insertion at the 4-position of an indole or oxindole ring system.

First, Jung and Slowinski reported their synthetic efforts to construct the seven-membered C ring using rhodium(II) to catalyse the cyclisation reaction.[19] The synthesis of diazo derivative **44** was achieved in three steps from *N*-methyl indole. Unfortunately, upon treatment with $Rh_2(OAc)_4$, insertion of the carbenoid into the 4-position of the indole was not observed; instead reaction occurred at the 2- and 3-position to afford compounds **45** and **46** (Scheme 1.7).



Scheme 1.7

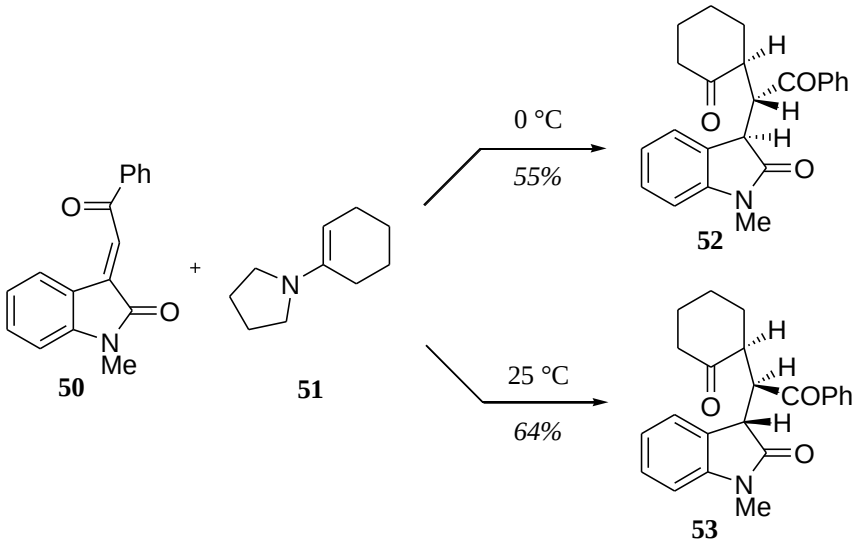
Moreover, the same unwanted reactivity at the 2-position was also observed with the oxindole **47**, which afforded derivatives **48** and **49** (Scheme 1.8).



47 **48** (*45%*) – **49** (*32%*)

Scheme 1.8

Second, Avedaño and co-workers reported the synthesis of oxindoles **52** and **53** by Michael addition of enamine **51** onto oxindole **50** (Scheme 1.9).[20] They demonstrated that the stereoselectivity of this addition could be controlled by the temperature of the reaction. Unfortunately, all attempts to generate the corresponding α-diazoketone cyclisation precursor failed and ultimately led to the abandonment of this route.

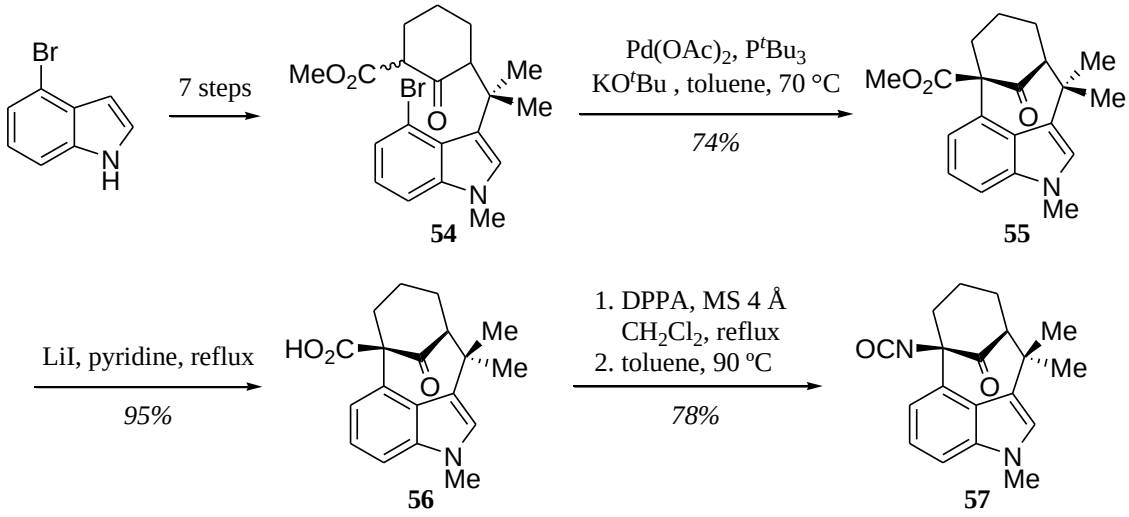


50 **51** **52** **53**

Scheme 1.9

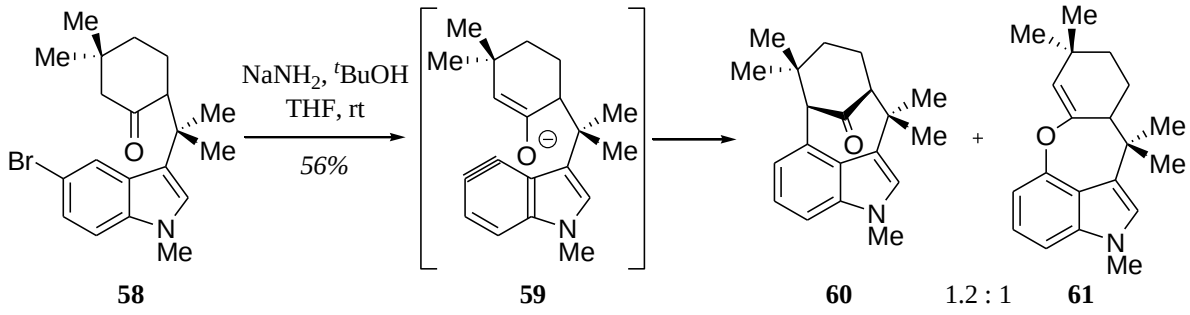
In 2005, Rawal reported the feasibility of generating the bicyclo[4.3.1]decane core from cyclohexanone derivative **54** by formation of the C-4–C-11 bond of the cycloheptane C ring *via* a palladium-catalysed intramolecular enolate arylation reaction.[21] Thus β-ketoester **54**, obtained in seven steps from 4-bromoindole, was treated with palladium acetate, tri-*tert*-butylphosphine and potassium *tert*-butoxide to provide tetracycle **55**. Subsequent nucleophilic

dealkylation using LiI and pyridine afforded carboxylic acid **56**. Curtius rearrangement was achieved by treatment of **56** with diphenylphosphoryl azide (DPPA) to provide isocyanate **57** (Scheme 1.10).



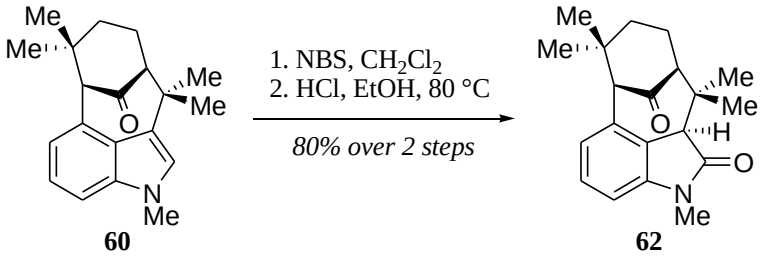
Scheme 1.10

In 2009, Garg and co-workers published a similar strategy in the elaboration of the bicyclo[4.3.1]decane skeleton. Instead of a palladium-catalysed reaction to generate the C ring, they relied on an indolyne cyclisation.[22] Treatment of bromoindole precursor **58**, with $NaNH_2$/^{t}BuOH, led to the formation of 4,5-indolyne intermediate **59** and subsequently to a 1.2:1 mixture of **60** and *O*-arylated product **61** respectively (Scheme 1.11).



Scheme 1.11

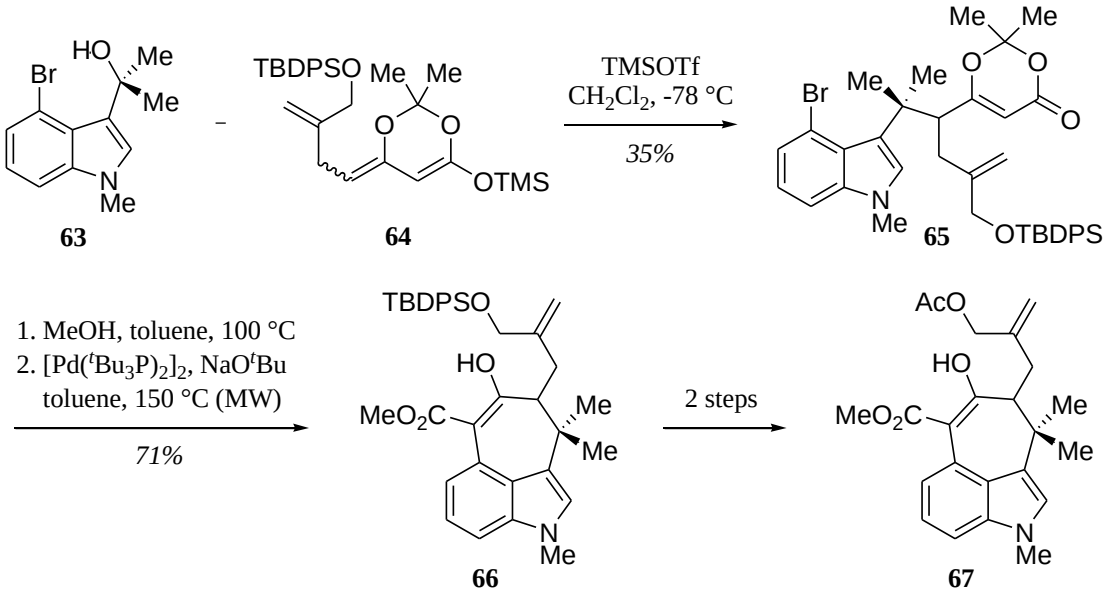
They also showed that oxidation of indole **60** to give oxindole **62** could be achieved in a two-step sequence. Thus, C-2 bromination with NBS followed by hydrolysis furnished oxindole **62** with the correct stereochemistry at C-3 (Scheme 1.12).



60 **62**

Scheme 1.12

In 2010, Martin reported a strategy involving formation of the cycloheptane C ring first and the cyclohexanone D ring second *via* two palladium-catalysed enolate cyclisation reactions (Scheme 1.13).[23]

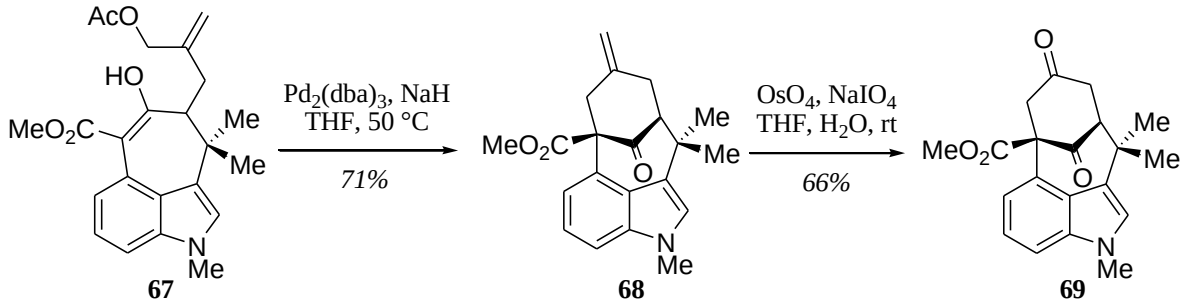


63 **64** **65** **66** **67**

Scheme 1.13

Coupling between vinylogous silyl ketene acetal **64** (obtained in three steps from *tert*-butyl acetoacetate) and tertiary alcohol **63** in the presence of TMSOTf provided bromoindole derivative **65** in 35% yield. The masked ketoester **65** was revealed by heating with methanol and underwent a palladium-catalysed cyclisation to afford **66** in 71% yield over two steps.

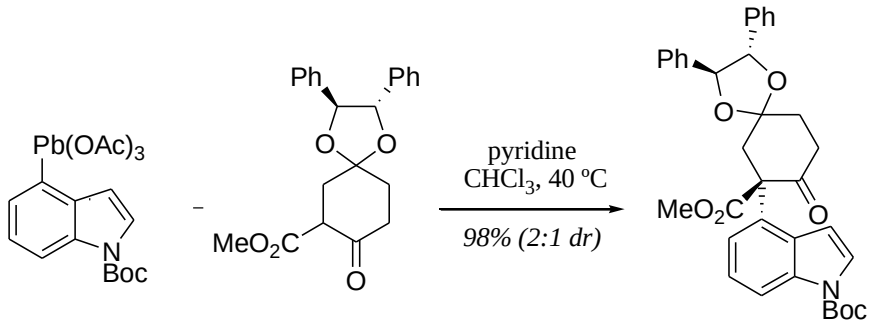
Desilylation, followed by a selective acetylation of the resultant primary alcohol gave precursor **67**. The second enolate cyclisation was achieved using $Pd_2(dba)_3$ and NaH to generate the bicyclo[4.3.1]decane core **68** in 71% yield. Subsequent oxidative cleavage of the exocyclic olefin under Johnson-Lemieux conditions afforded dione **69** (Scheme 1.14).



67 **68** **69**

Scheme 1.14

Konopelski and co-workers developed a strategy to form the C-4–C-11 bond using lead(IV) indole derivatives.[24,25] Thus, an aryllead coupling of cyclohexanone derivative **71** with indolyl lead reagent **70** provided the 4-substituted indole compound **72** in excellent yield with a diastereoselectivity of 2:1 (Scheme 1.15). The workers planned to perform an aldol-type reaction in order to generate the welwistatin framework. Unfortunately, all attempts to generate the bicyclo[4.3.1]decane core in this way failed.

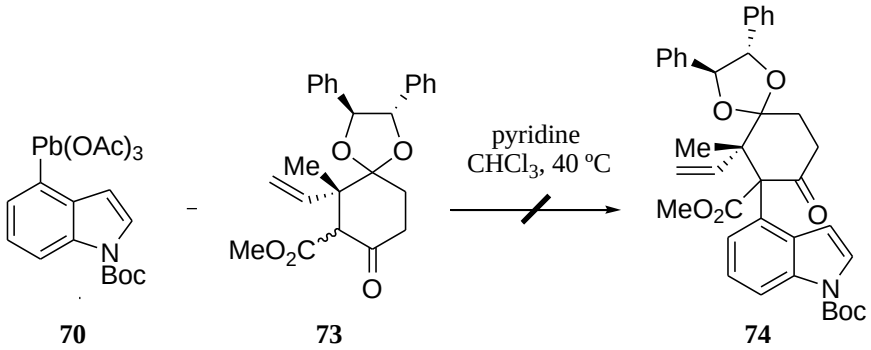


70 **71** **72**

Scheme 1.15

The more elaborate aryllead coupling partner **73**, with additional geminal methyl and vinyl groups, was also submitted to the coupling conditions described above. The expected

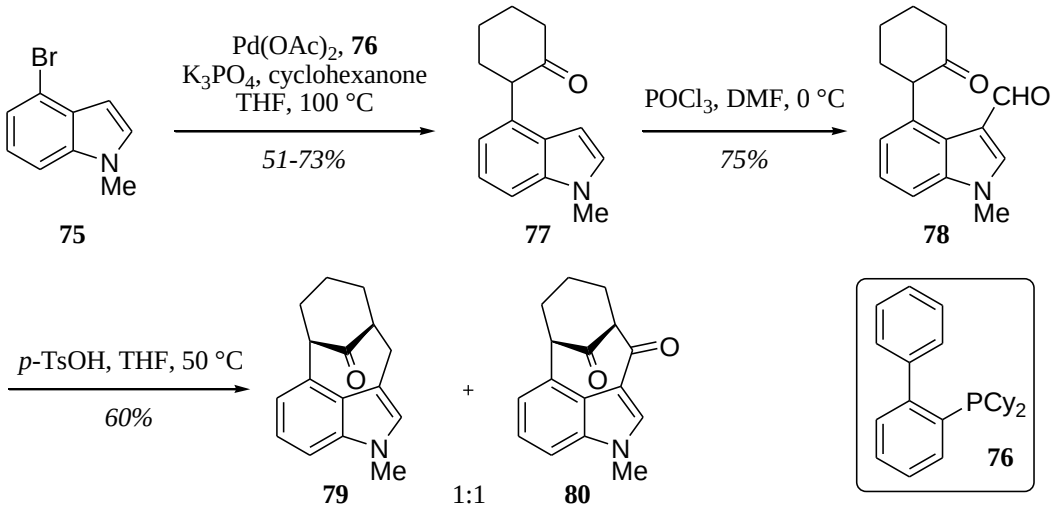
coupling product **74** was not observed presumably due to the increased steric hindrance created by the methyl and vinyl groups (Scheme 1.16).



70 **73** **74**

Scheme 1.16

In 2005, our group published a rapid access to the bicyclo[4.3.1]decane framework in only four steps from commercially available starting materials.[26] The strategy involved palladium coupling between cyclohexanone and *N*-methylbromoindole **75** under Buchwald conditions to afford the indole derivative **77**. Subsequent Vilsmeier-Haack formylation gave indole **78** and following treatment with *p*-TsOH furnished an equimolar mixture of two bridged structures **79** and **80** (Scheme 1.17).



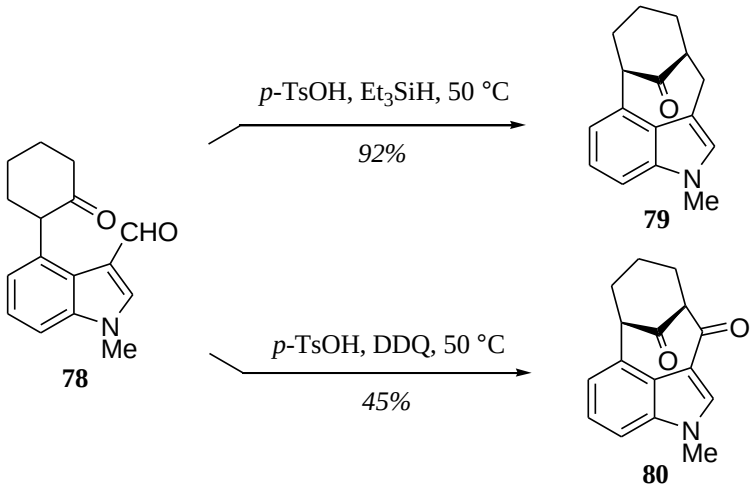
75 **77** **78**

79 1:1 **80**

Scheme 1.17

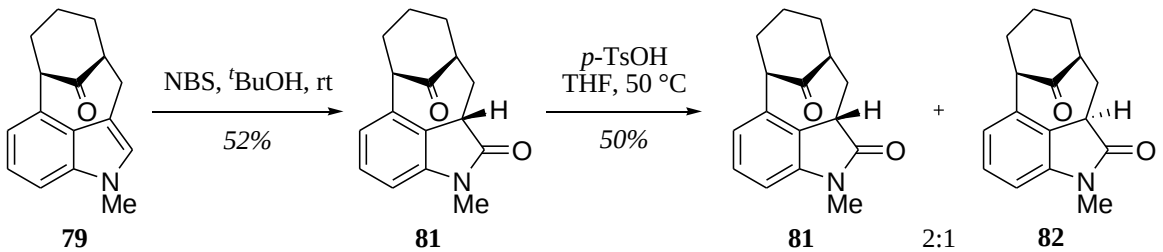
The formation of these two products can be explained by invoking an initial aldol condensation followed by dehydration elimination to give the iminium intermediate. Thus, in

order to obtain only one product, the iminium could be intercepted by an appropriate nucleophile. Satisfyingly, conducting the cyclisation reaction of **78** in the presence of an external source of hydride (Et_3SiH), resulted in the formation of **79** as the sole product in 92% yield. Conversely, in the presence of an oxidant (DDQ), only ketone **80** was obtained in a moderate 45% yield (Scheme 1.18).



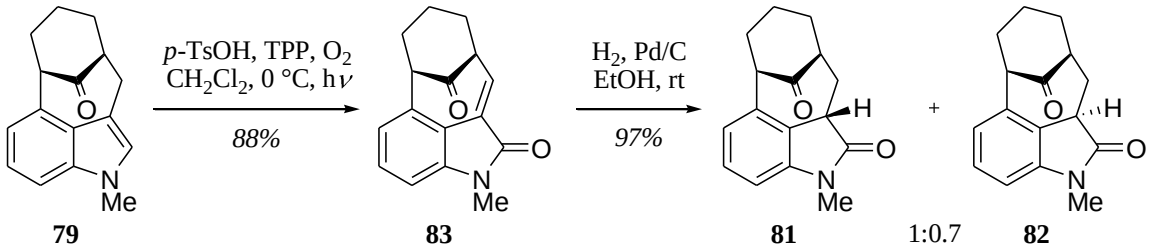
Scheme 1.18

It has been demonstrated in the first instance that formation of the oxindole **81** could be achieved using NBS and ^{t}BuOH, in moderate yield.[26] The structure, confirmed by NMR spectroscopic studies and X-ray analysis, revealed that the C-3 stereochemistry was opposite to that in the natural product (Scheme 1.19). However, epimerisation of oxindole **81** can be achieved upon treatment with *p*-TsOH in THF at 50 °C.



Scheme 1.19

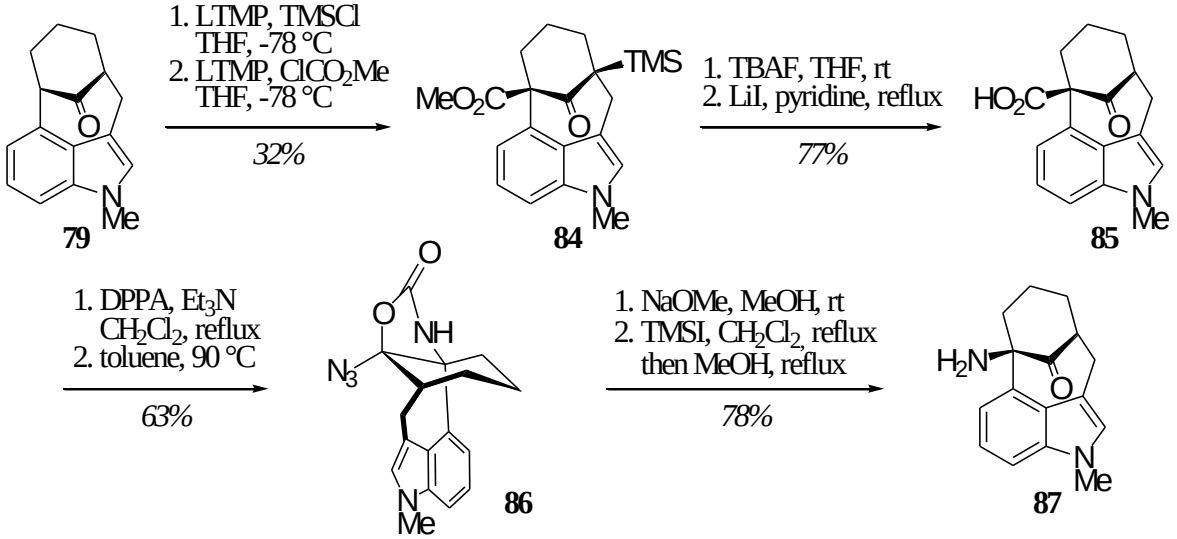
Our group reported another method to obtain oxindole derivatives **81** and **82**.[27] Exposure of indole **79** to singlet oxygen and tetraphenylporphyrin (TPP) as sensitiser afforded unsaturated oxindole **83** in good yield. Subsequent hydrogenation afforded a mixture of epimeric oxindoles **81** and **82** (Scheme 1.20).



79 **83** **81** **82**

Scheme 1.20

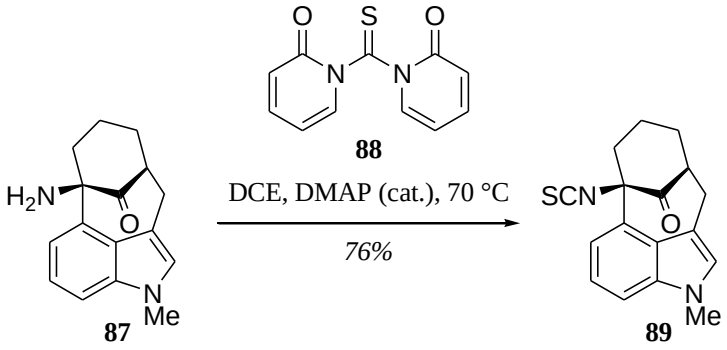
Our group published the first synthesis of the welwistatin core possessing the isothiocyanate functional group present in the natural product.[28] Having the key intermediate **79** in hand, two bridgehead deprotonations were realised sequentially to afford indole **84**. Removal of the silyl group was followed by conversion of the ester to the corresponding carboxylic acid **85**. Surprisingly, β-ketoacid **85** in the presence of an excess of DPPA led to azido oxazolidinone **86** in good yield. Under basic conditions, oxazolidinone **86** undergoes ring-opening and subsequent removal of the resultant carbamate furnished bridgehead amine **87** (Scheme 1.21).



79 **84** **85** **86** **87**

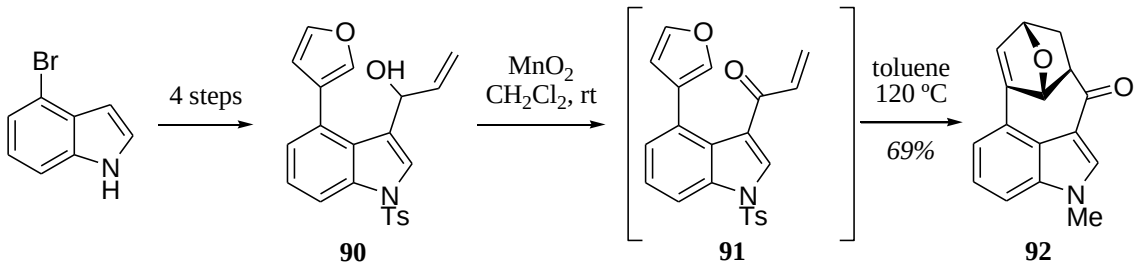
Scheme 1.21

Finally, isothiocyanate **89** was obtained in good yield by exposure of the bridgehead amine **87** to the thiocarbonyl transfer reagent **88** (Scheme 1.22).



Scheme 1.22

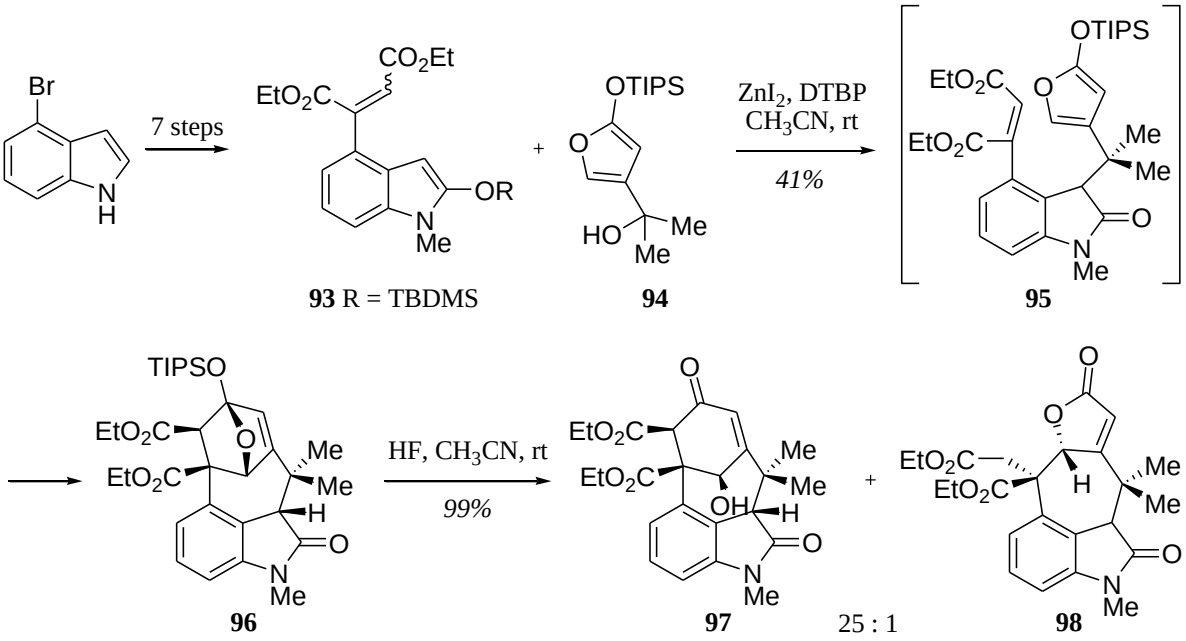
Lauchli and Shea described a synthesis of the welwistatin framework using an intramolecular Diels-Alder cyclisation as a key step.[29] This strategy allowed the creation of the central and cyclohexanone rings in a single step. Indole derivative **90** was obtained in four steps from 4-bromoindole. Oxidation of the allylic alcohol with manganese dioxide provided the indole derivative **91**. Upon heating at 120 °C an intramolecular Diels-Alder reaction took place to generate the central C ring and cyclohexanone D ring in a single step giving the desired bicyclo[4.3.1]decane **92** in 69% yield over two steps (Scheme 1.23).



Scheme 1.23

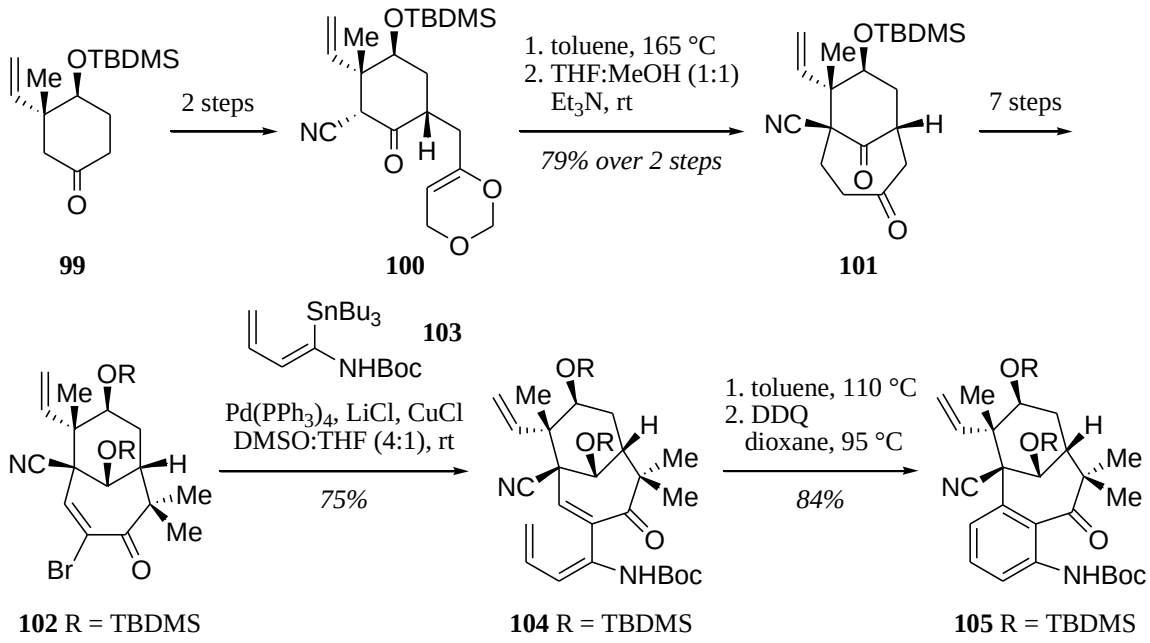
More recently, Shea and co-workers described the synthesis of a more densely functionalised cycloadduct.[30] They utilised the same key step, but with inversion of the position of the diene and dienophile on the indole. In a one-pot sequence, 2-silyloxy indole **93** was alkylated with furan alcohol **94** using ZnI_2 as the Lewis acid and 2,6-di-*tert*-butylpyridine (DTBP) as an acid

scavenger. The intermediate **95** underwent spontaneous intramolecular cyclisation to provide cycloadduct **96**. Removal of the TIPS group led to a mixture of the desired enone **97** alongside lactone **98** in a ratio of 25:1 (Scheme 1.24).



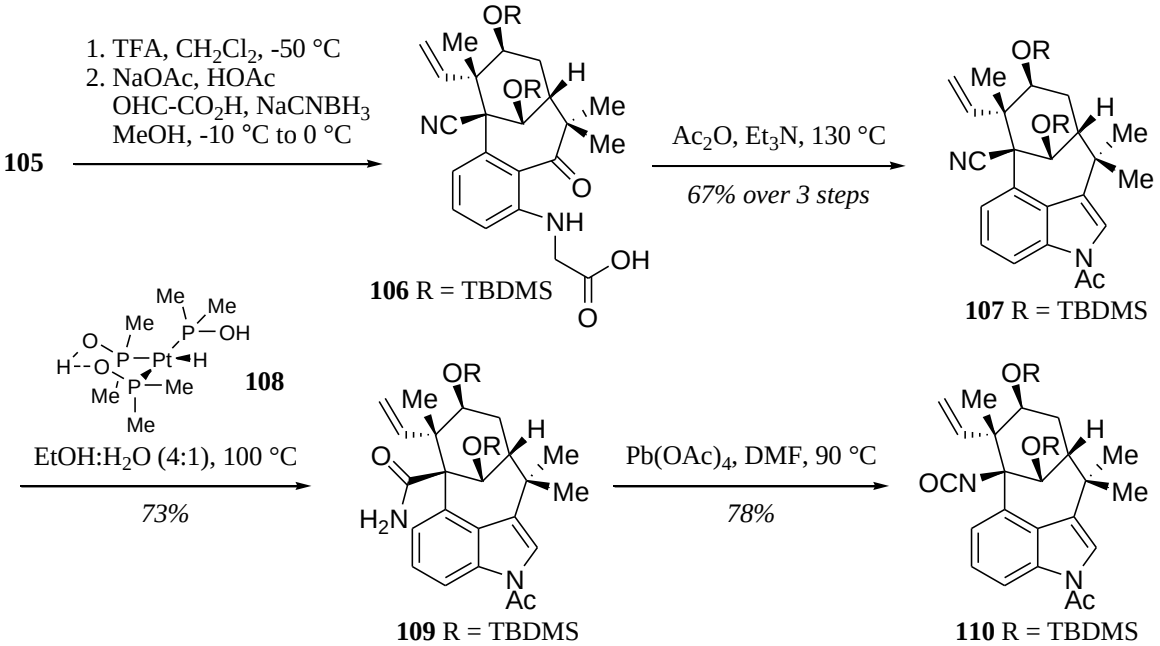
Scheme 1.24

Greshock and Funk were the first to report a strategy towards the welwistatin core not based on indole or oxindole derivatives.[31] They decided to build the indole ring system using an annelation sequence developed in their laboratory.[32] The synthesis started with cyclohexanone derivative **99**, readily available form 3-methyl-3-cyclohexenone, which provided compound **100** through a two-step sequence involving an alkylation and a cyanation. Thermal degradation of **100** followed by intramolecular Michael addition generated the cycloheptanone C ring with no epimerisation at the bridgehead position. Further manipulations furnished α-bromoenone **102**, which underwent Stille coupling with α-stannyl enecarbamate **103** to afford derivative **104**. Subsequent heating of compound **104** in the presence of DDQ led to the expected aryl system **105** (Scheme 1.25).



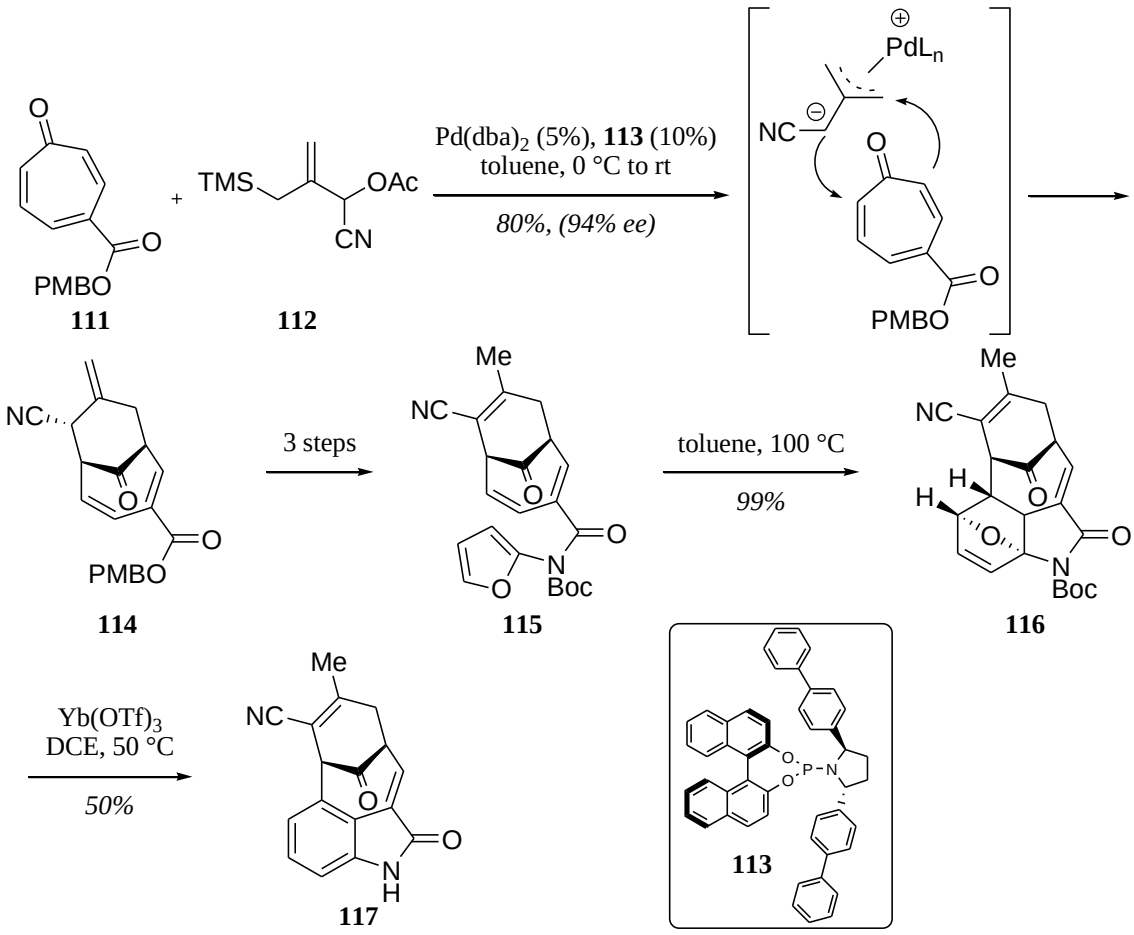
Scheme 1.25

Boc cleavage followed by a reductive amination of the resulting aniline with glyoxylic acid gave intermediate **106**. Indole ring formation using Ac_2O and Et_3N furnished tetracycle **107** and subsequent isonitrile hydrolysis, followed by a Hoffman rearrangement afforded the advance intermediate **110** (Scheme 1.26).



Scheme 1.26

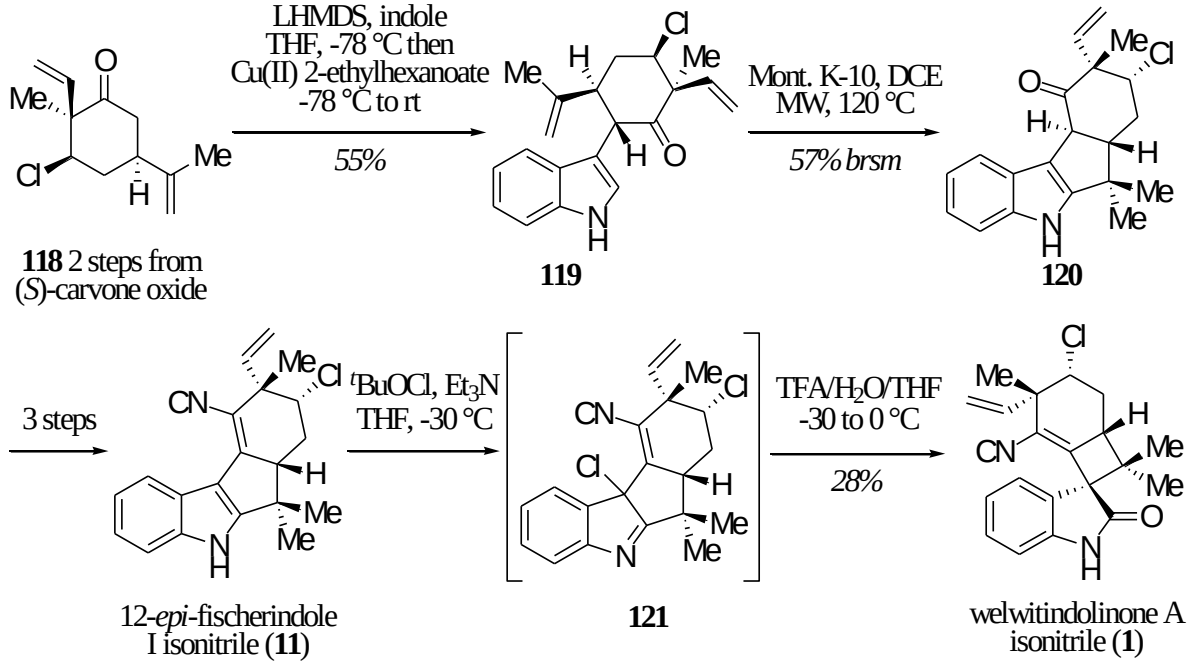
Recently, Trost and McDougall reported another approach to the welwistatin core structure without using an indole or oxindole precursor.[33] The sequence features the use of two cycloaddition reactions to obtain the desired core structure. The first key step is a palladium-catalysed [6+3] cycloaddition between the tropone **111**, obtained in four steps from anisole, and cyano trimethylenemethane precursor **112**. This furnished **114** as a single regio- and diastereoisomer in good yield and high enantioselectivity (94% ee). A three-step sequence from the cycloadduct **114** provided furan-containing intermediate **115**. Thermal [4+2] cycloaddition provided the Diels-Alder adduct **116** in excellent yield as a single stereoisomer. Upon treatment with a catalytic amount of $Yb(OTf)_3$, ring-opening and dehydration of oxabicycle **116** afforded oxindole **117** in moderate yield (Scheme 1.27).



Scheme 1.27

1.4.2 Syntheses of welwitindolinone A isonitrile

In 2005, Baran and Richter reported the enantioselective synthesis of (+)-welwitindolinone A isonitrile as well as fischerindoles I and G.[13] Creation of the key spiro-oxindole was achieved through an efficient oxidative ring contraction. Their synthesis started with the preparation of ketone **118** using (*S*)-carvone oxide. Subsequent enolisation of **118** followed by addition of indole and a source of copper(II) led to **119** as a single diastereoisomer. Upon acidic treament with Montmorillonite K-10, Friedel-Crafts cyclisation provided the fischerindole skeleton **120**. Transformation of the ketone to the vinyl isonitrile function led to 12-*epi*-(–)-fischerindole I isonitrile (**11**) in a further three steps. Treatment with ^{t}BuOCl at -30 °C, followed by warming with aqueous TFA, furnished welwitindolinone A isonitrile (**1**) in 28% yield (Scheme 1.28).

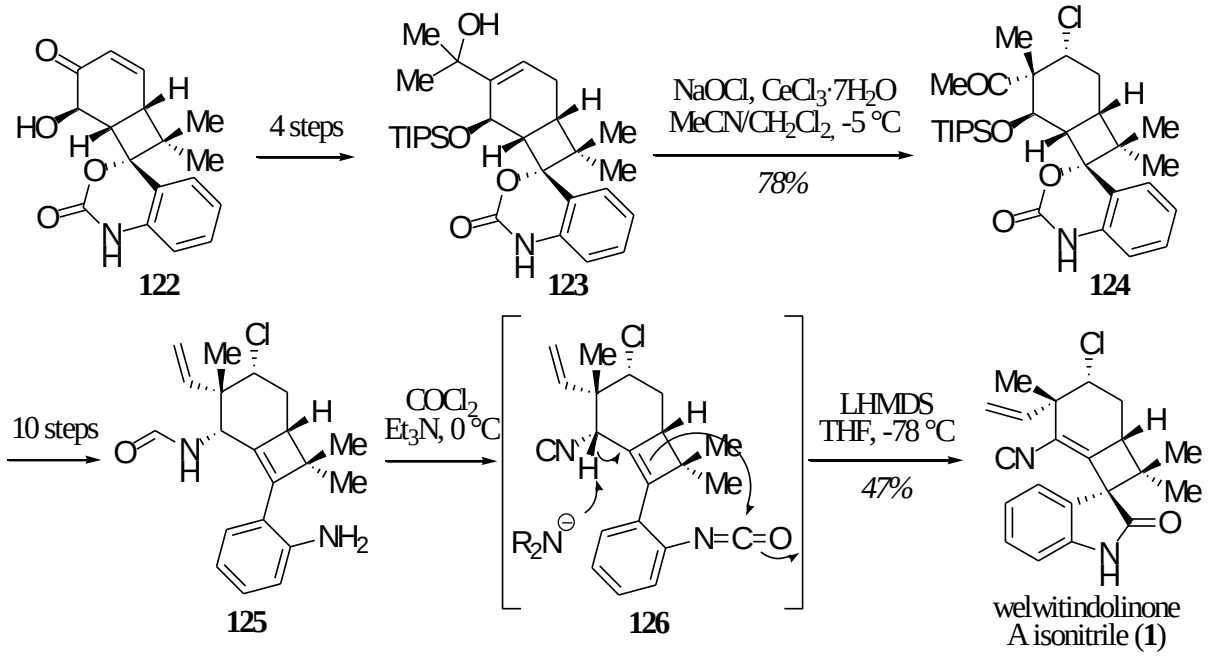


Scheme 1.28

This result indicated a more plausible biosynthesis of **1** than the initial route proposed by Moore. Inspired by the proposed biosynthetic pathway, Baran also described the elegant and

efficient synthesis of members of the hapalindole, fischerindole, welwitindolinone and ambiguine families without using protecting groups.[34,35]

A second synthesis of welwitindolinone A isonitrile was reported shortly after by Wood.[16,36] The synthesis featured a key semi-pinacol rearrangement and highlighted their previous work on the synthesis of spiro-oxindoles (Scheme 1.29).



Scheme 1.29

Key tertiary allylic alcohol **123** was prepared in four steps from enone **122**. Exposure to sodium hypochlorite and cerium trichloride provided the chloro-ketone **124** as a single diastereoisomer in 78% yield. The chloronium-ion mediated semi-pinacol rearrangement occurs with excellent control of the relative stereoselectivity. Based on the relative stereochemistry of **124**, they assume that the TIPS-protected alcohol forced the formation of the chloronium ion on the concave face of the molecule to furnish the desired stereoselectivity. Further manipulations of chloro-ketone **124** gave *N*-formylated amine **125** in ten steps. A one-pot reaction involving dehydration and isocyanate formation using phosgene

provided isonitrile **126** and exposure to LHMDS furnished **1** as a single diastereoisomer. The synthesis was completed in 23 steps and 2.5% overall yield.

In summary, the welwitindolinones have generated interest from many research groups and numerous and remarkable progress in the synthesis of the bicyclo[4.3.1]decane scaffold has been reported. In 2005, welwitindolinone A isonitrile (**1**) was independently synthesised by Baran and Wood as the first synthesis of a member of this family.

1.5 References

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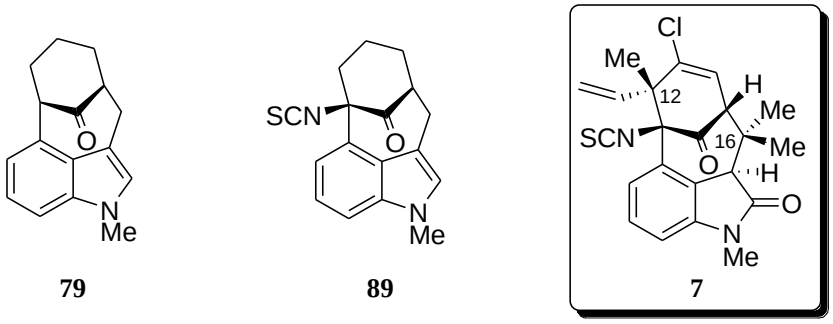
CHAPTER 2

Studies towards the bicyclo[4.3.1]decane scaffold possessing the gem-dimethyl group

2.1 Aims and objectives

A rapid access to the bicyclo[4.3.1]decane framework **79** and the first synthesis of isothiocyanate analogue **89** have been described by our group.[1,2] However, in order to complete the total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**7**), the synthesis of more densely functionalised core structures is required. Access to important functional groups still remains a challenge, such as preparing the vinyl chloride moiety, installing the C-12 quaternary centre possessing methyl and vinyl groups and also the *gem*-dimethyl at C-16 (Figure 2.1).



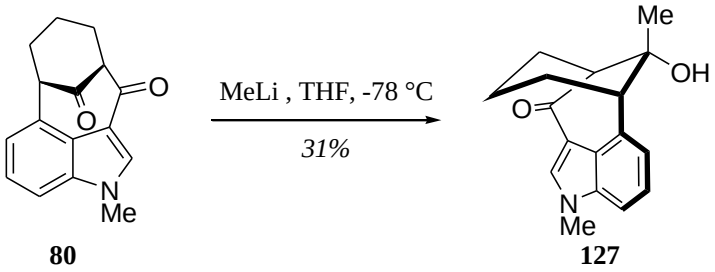
79 **89** **7**

Figure 2.1

The first aim of our project was to investigate the formation of the bicyclo[4.3.1]decane framework possessing the *gem*-dimethyl group.

2.2 Previous studies towards the installation of the *gem*-dimethyl group

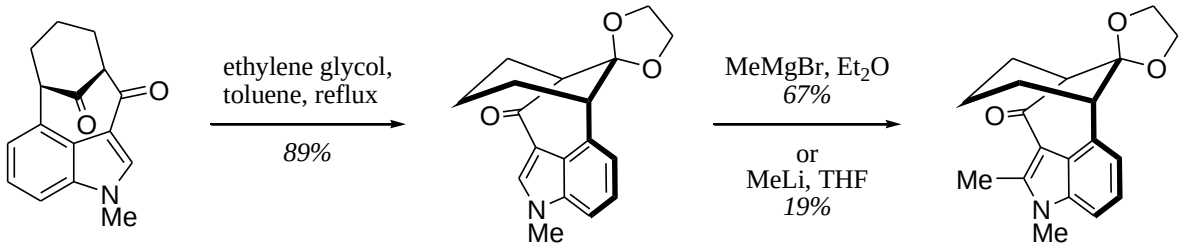
Preliminary studies towards the synthesis of the welwistatin skeleton possessing a *gem*-dimethyl group were carried out by V. Boissel, a former PhD student in our group.[3] Treatment of **80** with MeLi showed that the bridging ketone is more reactive than the carbonyl group at C-16 towards nucleophilic attack (Scheme 2.1).



80 **127**

Scheme 2.1

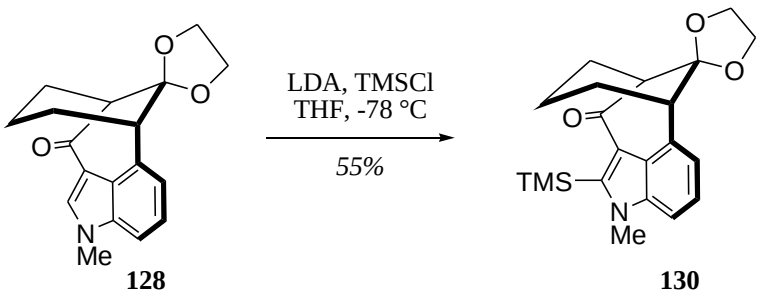
Therefore protection of this ketone was necessary to investigate introduction of a methyl group at C-16 and so ketone **80** was selectively protected as an acetal with ethylene glycol. Treatment of ketone **128** with MeMgBr or MeLi did not lead to addition of a methyl group to the desired position; instead it appeared that the organometallic reagent added at the less hindered C-2 position of the indole *via* a Michael addition reaction (Scheme 2.2).



80 **128** **129**

Scheme 2.2

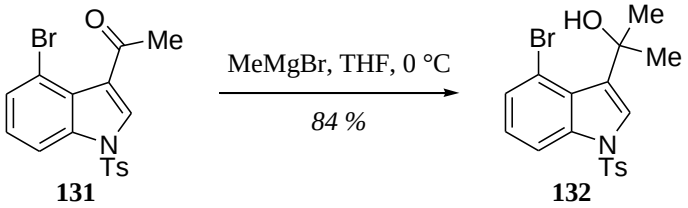
In an attempt to avoid this problem, the 2-position of the indole was blocked with a TMS group but ketone **130** was unreactive upon treatment with MeMgBr, and treatment with MeLi furnished desilylated indole (Scheme 2.3).



128 **130**

Scheme 2.3

Steric hindrance within the cyclic system appeared to prevent addition of the methyl group. In light of these results, an alternative approach to the bicyclo[4.3.1]decane skeleton was considered wherein the indole ring system would possess an electron-withdrawing group (EWG) on the nitrogen to direct addition of Grignard reagents into the carbonyl group and to prevent addition at the C-2 position. For example, tosylated indole **131** was used by Rawal and co-workers in their synthesis of the welwistatin skeleton (Scheme 2.4).[4]



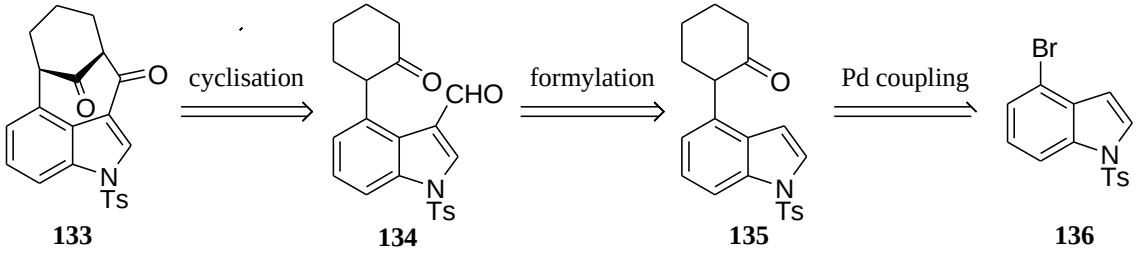
131 **132**

Scheme 2.4

Therefore, the synthesis of a bicyclo[4.3.1]decane scaffold with an EWG on nitrogen, such as a tosyl protecting group, was envisaged and subsequent Grignard addition was anticipated.

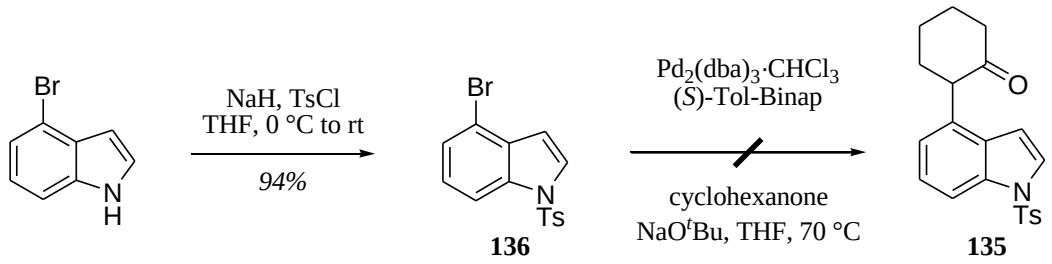
2.3 Synthesis of a bicyclo[4.3.1]decane framework possessing an electron-withdrawing group on the indole

In order to study methylation at C-16, the synthesis of tosylated diketoindole **133** was proposed following the route established for the methylated indolic system (Scheme 2.5).[1] Tosylated diketoindole **133** would be obtained from an acid-mediated cyclisation of formyl indole **134**, which would arise from indole **135**. A palladium-catalysed enolate arylation between tosylated bromoindole **136** and cyclohexanone would provide **135**.



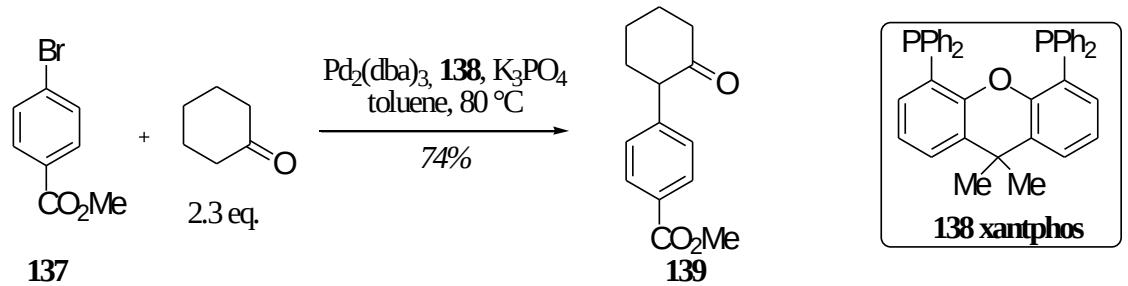
Scheme 2.5

The synthesis began with *N*-tosylation of commercially available 4-bromoindole. Subjection of *N*-tosylated indole **136** to the Buchwald-Hartwig conditions previously optimised for the *N*-methyl series did not afford the coupled product **135**; but instead the removal of the *N*-tosyl protecting group was observed (Scheme 2.6).[3,5] It appeared that the use of NaO^{t}Bu to generate the enolate from the cyclohexanone was not compatible with the tosyl protecting group.



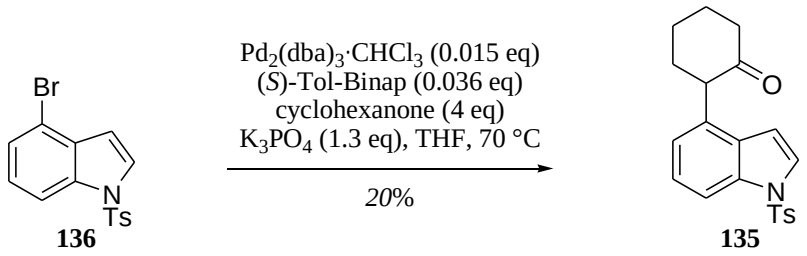
Scheme 2.6

The palladium-mediated α-arylation of ketones has been widely investigated by Buchwald and Hartwig.[6,7] Indeed, Buchwald reported that substrates bearing base-sensitive groups undergo the reaction using a mild base. For example, K_3PO_4 was used in the coupling reaction between aryl bromide **137** and cyclohexanone to provide **139** in good yield (Scheme 2.7).[6]



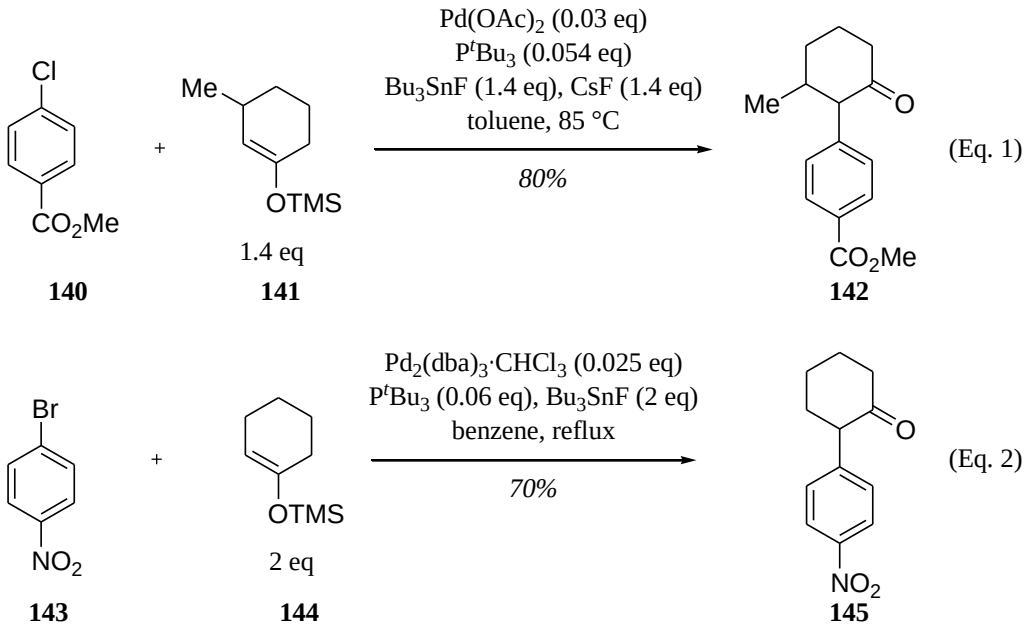
Scheme 2.7

To prevent the removal of the *N*-tosyl protecting group, the milder base K_3PO_4 was used and the desired coupling product **135** was isolated in 20% yield (Scheme 2.8). Even with extensive screening of reaction conditions (bases, palladium sources, ligands, solvents, temperatures) the conversion to indole **135** could not be improved.



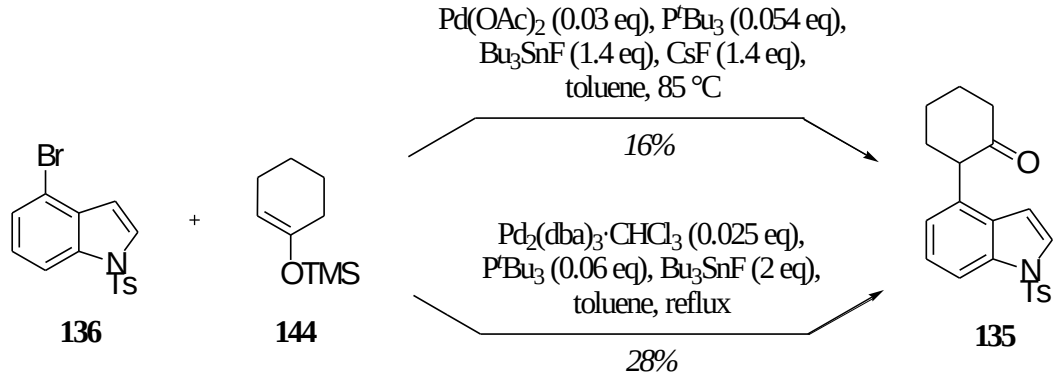
Scheme 2.8

In 2006, inspired by the work of Kuwajima and Urabe,[8] Hartwig[9] and Rawal[10] independently described a palladium-catalysed α-arylation of trimethylsilyl enol ethers with aryl halides. For example, Hartwig (Equation 1) and Rawal (Equation 2) reported coupling reactions with aryl halides **140** and **143** to afford **142** and **145** respectively in good yield (Scheme 2.9).



Scheme 2.9

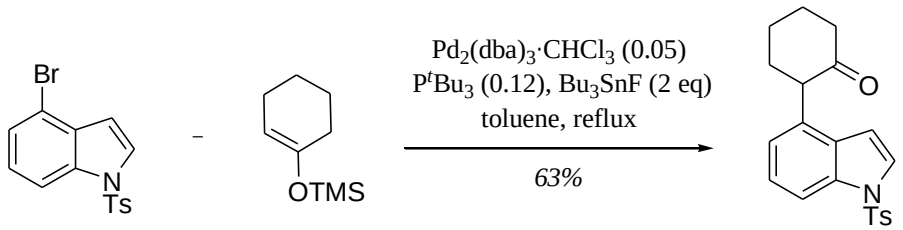
Interestingly, these palladium-catalysed cross-coupling reactions avoid the use of a free base by using a silyl enol ether as coupling partner. It was hoped that these mild reaction conditions might prevent *N*-detosylation of **136** and improve conversion to **135**. Thus, *N*-tosylbromoindole **136** and silyl enol ether **144** were subjected to these two cross-coupling conditions and the desired coupling product **135** was isolated in 16% and 28% yield, respectively (Scheme 2.10).



136 **144** **135**

Scheme 2.10

Initial attempts to obtain **135** gave similar yields to the previous coupling reaction (Scheme 2.8). However after screening different reaction parameters the conversion was improved. Under reflux (130 °C) and by using an increased amount of catalyst and ligand, the desired compound **135** was obtained in 63% yield (Scheme 2.11).

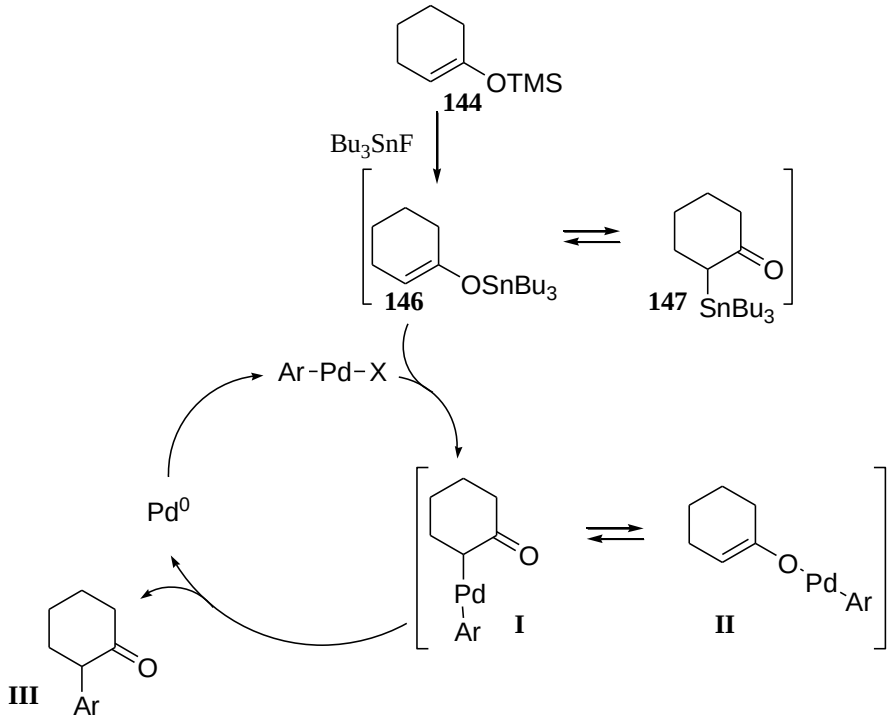


136 **144** (2 eq) **135**

Scheme 2.11

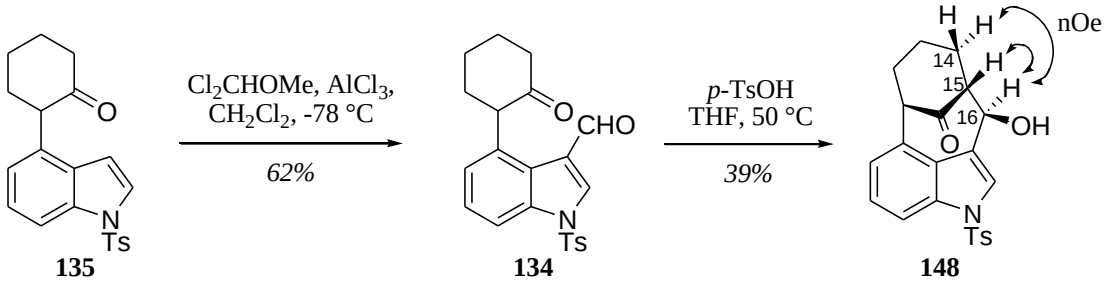
Rawal suggested a plausible mechanism for this coupling reaction wherein the silyl enol ether **144** would react with Bu_3SnF to generate the tin enolate **146**, which would undergo

transmetallation to generate the Pd-enolate species **I**. Reductive elimination would provide the coupling product **III** and regenerate Pd^0 (Scheme 2.12).



Scheme 2.12

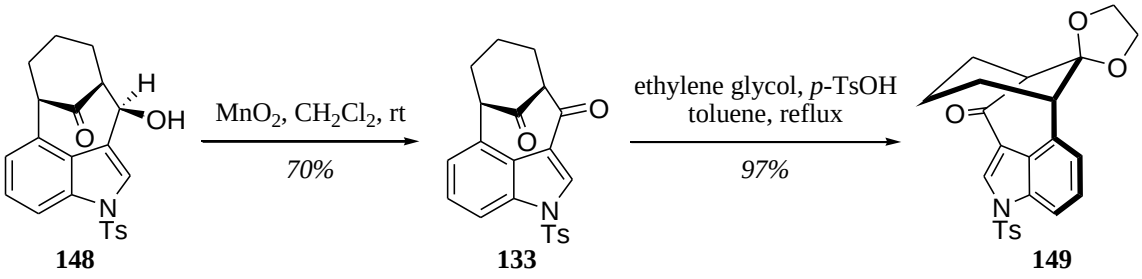
With intermediate **135** in hand, cyclisation precursor **134** was to be obtained *via* a formylation reaction. However, the Vilsmeier conditions used previously in the *N*-methyl series cannot be applied to an electron-deficient ring as the formylating agent is a weak electrophile.[11] Therefore, Friedel-Crafts acylation of indole **135** in the presence of methyl dichloromethylether and $AlCl_3$[12] provided aldehyde **134** in 62% yield. Surprisingly, subsequent treatment with dry *p*-TsOH furnished alcohol **148** as a single diastereoisomer (Scheme 2.13). A mixture of ketone and diketone was expected as observed in the methylated series (See Section 1.4.4, Scheme 1.17) but the electron-withdrawing group prevented disproportionation and allowed isolation of alcohol **148**.



Scheme 2.13

Evidence for the formation of alcohol **148** was provided by IR spectroscopy showing a broad stretching band for the hydroxyl and carbonyl groups at, respectively, 3425 and 1699 cm^{-1} and mass spectrometry showed one peak at $[M+Na]^+$= 418.1074 ($C_{22}H_{21}NO_4SNa$ requires 418.1089). ^1H NMR and ^{13}C NMR spectroscopy confirmed the formation of tetracycle **148** with the presence of three non aromatic CH groups. The stereochemistry at C-16 was determined by nOe which showed a correlation between H-16 and both H-15 and H-14.

Subsequent oxidation of alcohol **148** with MnO_2 gave diketone **133** in 70% yield. Protection of the bridging ketone furnished ketal **149** (Scheme 2.14).

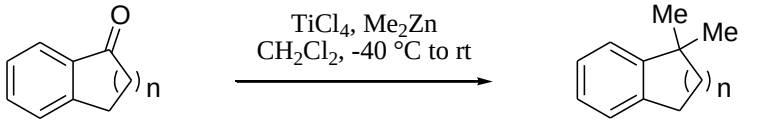


Scheme 2.14

With the desired intermediate **149** in hand, the influence of the tosyl group upon the installation of the *gem*-dimethyl group from the carbonyl functionality at C-16 could be investigated.

2.4 Attempts to install the *gem*-dimethyl group by methyl addition

Reetz and co-workers reported that geminal dimethylation of a carbonyl could be achieved in one step using two equivalents of $(CH_3)_2TiCl_2$, generated *in situ* from an equimolar amount of $TiCl_4$ and $Zn(CH_3)_2$. For example *bis*-methylated compounds **151** were obtained in good yield from the corresponding ketones **150** (Scheme 2.15).[13,14]

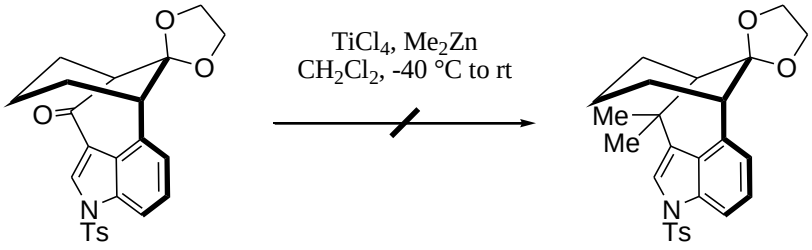


150a n = 1
150b n = 2
150c n = 3

151a n = 1 (86%)
151b n = 2 (88%)
151c n = 3 (85%)

Scheme 2.15

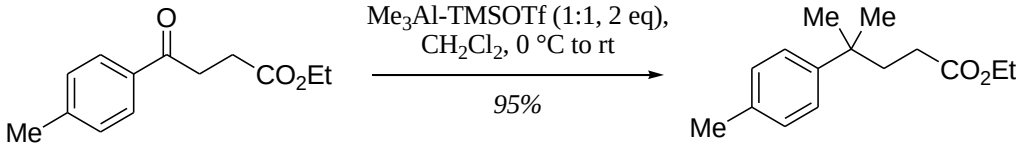
This methodology was applied to ketone **149** but it failed to give the desired methylated derivative **152**; only starting ketone was recovered (Scheme 2.16). The reaction was also attempted at room temperature, but only degradation of starting material was observed.



149 **152**

Scheme 2.16

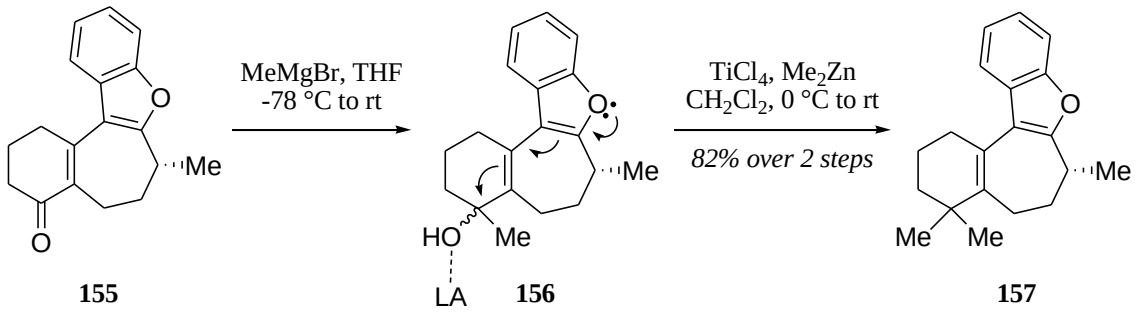
In a similar fashion, Kim and co-workers reported the transformation of ketone **153** into the corresponding *gem*-dimethyl derivative **154** by using a combination of $AlMe_3$ and TMSOTf (Scheme 2.17).[15] Unfortunately, applying the reaction conditions to ketone **149** only resulted in the recovery of starting material even when ten equivalents of Me_3Al-TMSOTf were used.



153 **154**

Scheme 2.17

Unfortunately, installation of the *gem*-dimethyl could not be achieved in a single step. The failure could be due to steric hindrance or a low electrophilicity of the carbonyl group, which is better viewed as a vinylogous amide rather than a ketone. A poorly electrophilic carbonyl group makes the first methyl addition difficult but the second methyl addition should be facilitated as described by Hughes and Trauner in their synthesis (–)-frondonsin B.[16] In this case vinylogous aryl ketone **155** did not undergo direct *gem*-dimethylation using Reetz's procedure and so a two-step process was used. Thus, treatment of ketone **155** with MeMgBr provided tertiary alcohol **156**, which was converted into *gem*-dimethyl derivative **157** in the presence of $(CH_3)_2TiCl_2$ (Scheme 2.18).

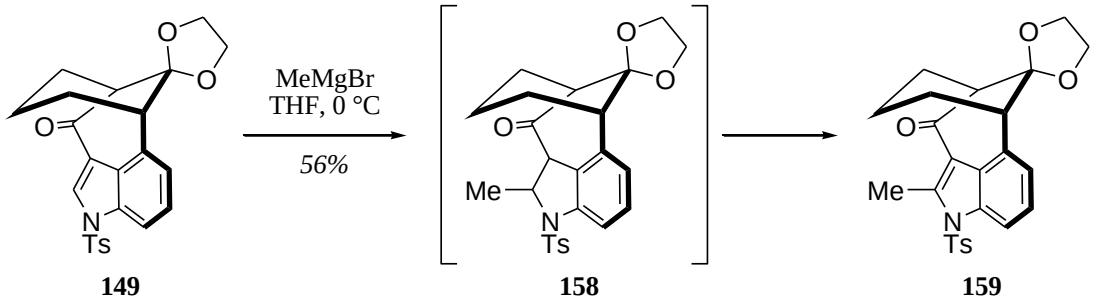


155 **156** **157**

Scheme 2.18

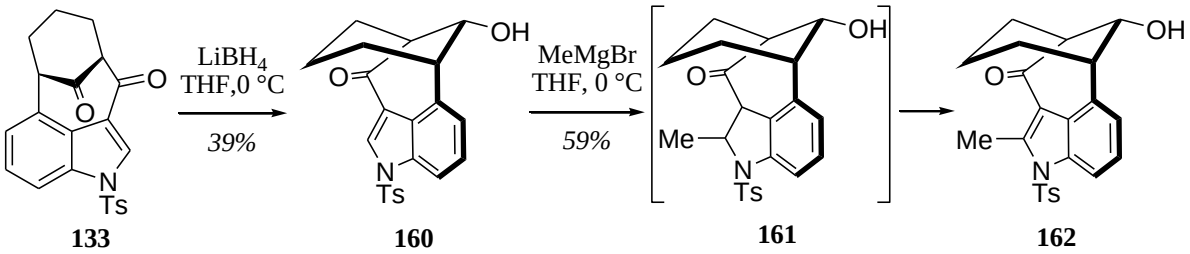
Intermediate **149** was treated with MeMgBr at 0 °C, which led to the formation of a new compound. Work-up, followed by concentration under reduced pressure, gave indoline intermediate **158** as a single diastereoisomer, which rapidly converted to the methylated indole **159** on standing. Prompt mass spectrometry of the residue showed a major peak at $[M+Na]^+ = 476.2$, which corresponded to the indoline intermediate **158** and no traces of indole

159. After purification only 2-methylated indole was isolated, demonstrating that the tosyl protecting group did not change the regioselectivity seen previously in the N-Me series (Scheme 2.19).



Scheme 2.19

An identical study was carried out with alcohol **160**, under the assumption that the O-MgBr functionality would be less sterically demanding than the acetal group but unfortunately, upon treatment with MeMgBr, the same reactivity at C-2 of the indole ring was observed (Scheme 2.20).



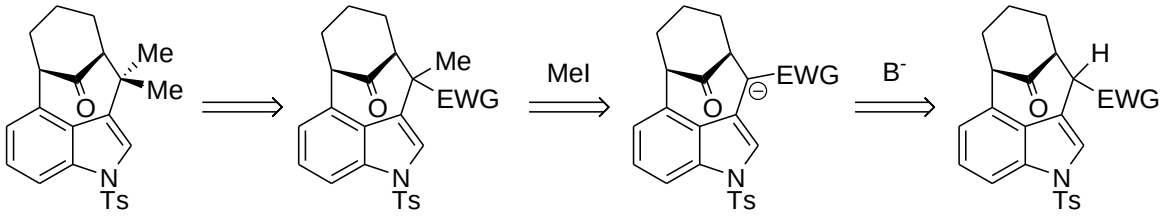
Scheme 2.20

Indoline intermediate **161** was detected by mass spectrometry with a single peak at $[M+Na]^+$= 434.1 and the ^{1}H NMR spectrum showed a doublet at 1.50 ppm corresponding to the methyl group. After three days indoline **161** was oxidised to the corresponding indole **162**, the ^{1}H NMR spectrum showed a characteristic singlet at 3.05 ppm due to the methyl group at C-2.

Considering the cage-like shape of the bicyclo[4.3.1]decane system, it appeared that steric hindrance was preventing Grignard addition to the carbonyl even with the presence of an electron-withdrawing group on the indole.

2.5 Attempts to install the *gem*-dimethyl group using sulfone chemistry

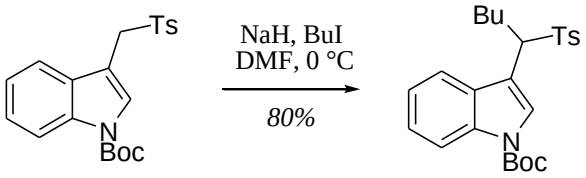
In an alternative approach to the installation of the *gem*-dimethyl group, the presence of an EWG, which also had to be capable of acting as a leaving group, was envisaged in order to change the reactivity at C-16. Thus, *gem*-dimethyl derivative **163** would arise from precursor **166** by deprotonation at C-16 and treatment with MeI to give monomethylated intermediate **164**. Transformation of the electron-withdrawing group would lead to *gem*-dimethyl ketone **163** (Scheme 2.21).



163 **164** **165** **166**

Scheme 2.21

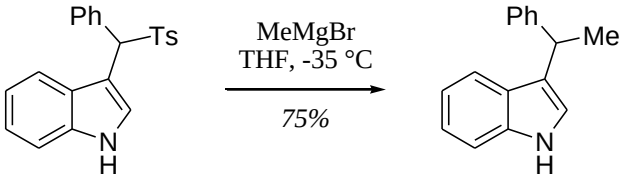
Petrini and co-workers have reported examples of α-deprotonation of sulfone **167**, followed by trapping with a wide range of electrophiles.[17] For example, deprotonation of sulfone **167** was achieved with sodium hydride and trapping with butyl iodide gave **168** in good yield (Scheme 2.22).



167 **168**

Scheme 2.22

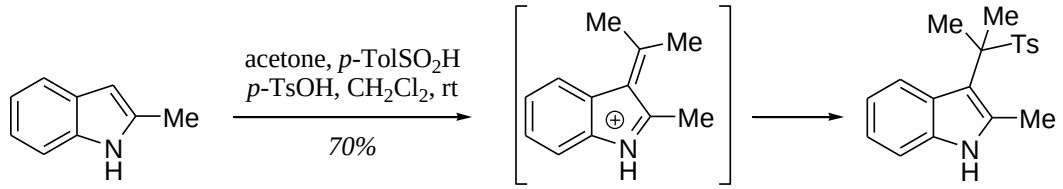
In a different report, they showed that it was possible to remove the sulfone group and replace it with a methyl group by treating indole **169** with three equivalents of MeMgBr. The first equivalent of MeMgBr is used to deprotonate the indole and cleave the sulfone group to generate the corresponding iminium, which can react with a second equivalent of MeMgBr to provide **170** (Scheme 2.23).[18]



169 **170**

Scheme 2.23

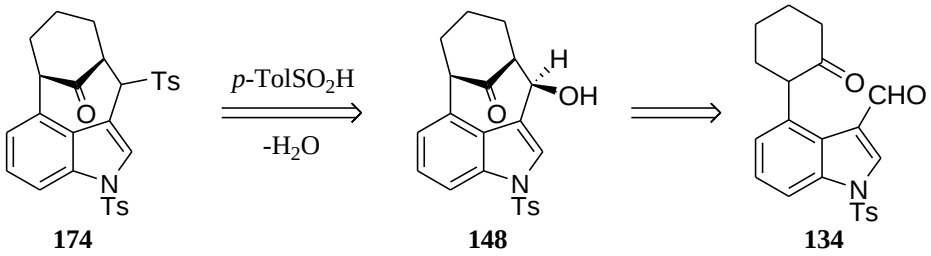
Petrini also described the formation of sulfone **173**, which was obtained from indole **171**. Condensation with acetone followed by dehydration led to iminium intermediate **172**, which could react with *p*-toluenesulfinic acid (*p*-TolSO_2H) to provide sulfone **173** in good yield (Scheme 2.24).[19]



171 **172** **173**

Scheme 2.24

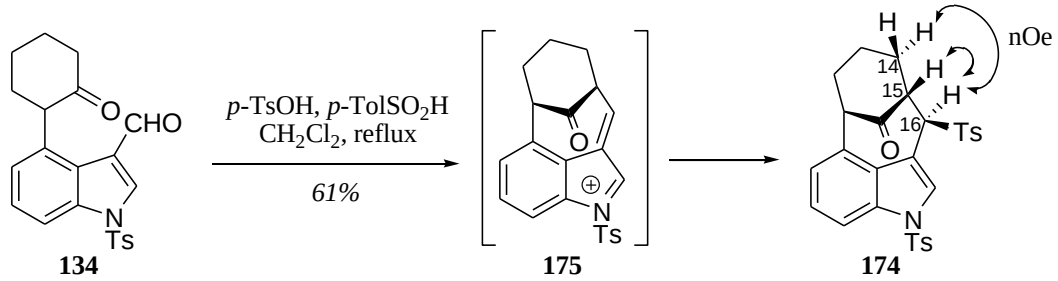
Inspired by Petrini's work, we suggested that a tosyl group at C-16 could be synthetically useful. The sulfone derivative **174** would be generated from dehydration of **148** and treatment of the iminium intermediate with *p*-TolSO_2H (Scheme 2.25).



174 **148** **134**

Scheme 2.25

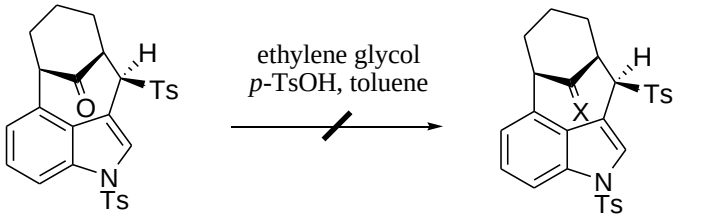
Gratifyingly, a one-pot reaction involving ring-closure/dehydration/tosylation proved possible by heating a solution of aldehyde **134** at reflux in the presence of *p*-TolSO_2H and *p*-TsOH in CH_2Cl_2, to give sulfone **174** in 61% yield as a single diastereoisomer (Scheme 2.26). Evidence for the formation of the bicyclo[4.3.1]decane derivative **174** was provided by ^{1}H NMR and ^{13}C NMR spectroscopy showing the presence of three non-aromatic CH groups as observed in the previous cyclised product **148**. The incorporation of the tosyl group was supported by mass spectrometry ($[M+Na]^+$= 556.1220) and ^{1}H NMR spectroscopy, which showed two singlets at 2.31 and 2.32 ppm, which each integrated for three protons and were attributed to the methyls of the tosyl groups. Identically to **148**, nOe analyses showed a correlation for H-16 with H-15 and H-14.



134 **175** **174**

Scheme 2.26

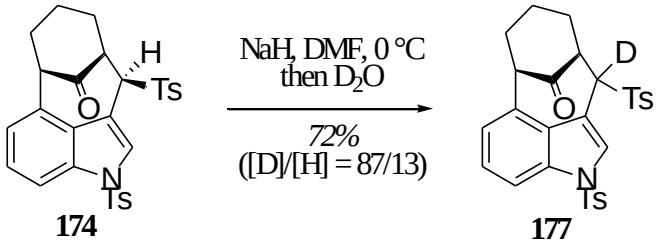
Protection of the bridging ketone as a ketal was attempted without success and this is probably due to the steric hindrance generated by the presence of the tosyl group at C-16 (Scheme 2.27).



174 **176** X = -OCH_2CH_2O-

Scheme 2.27

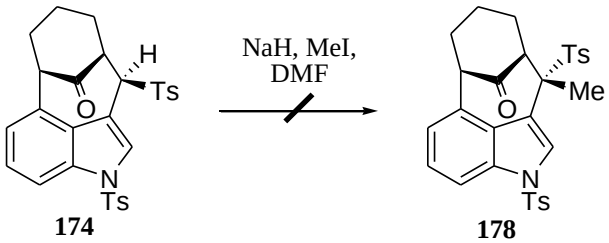
Preliminary investigations to probe the α-deprotonation of the sulfone **174** were encouraging. Treatment of sulfone **174** with sodium hydride followed by trapping with deuterium oxide afforded the deuterated derivative **177** (Scheme 2.28).



174 **177**

Scheme 2.28

Unfortunately, repeating the reaction with methyl iodide as the electrophile failed to provide the desired product **178** and only starting sulfone **174** was detected by ^{1}H NMR spectroscopy (Scheme 2.29).



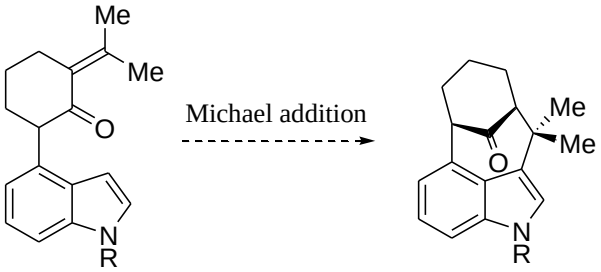
174 **178**

Scheme 2.29

The failed installation of the methyl group to the core structure was probably due to steric hindrance. As we were unable to install the first methyl at C-16, this route was abandoned.

2.6 Synthesis of cyclisation precursors bearing the *gem*-dimethyl group on the cyclohexanone ring

An alternative strategy was considered wherein the cyclisation precursor would bear the *gem*-dimethyl group. This approach was based on an intramolecular Michael addition of enone **179** or **180** possessing the *gem*-dimethyl on the cyclohexanone ring to provide tetracycle **181** or **182**, respectively (Scheme 2.30).

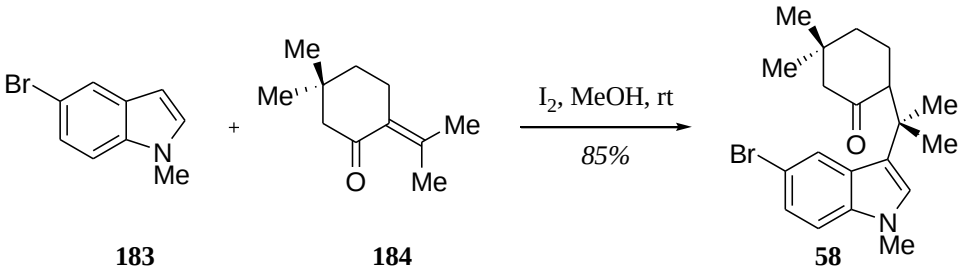


179 R = H
180 R = Me

181 R = H
182 R = Me

Scheme 2.30

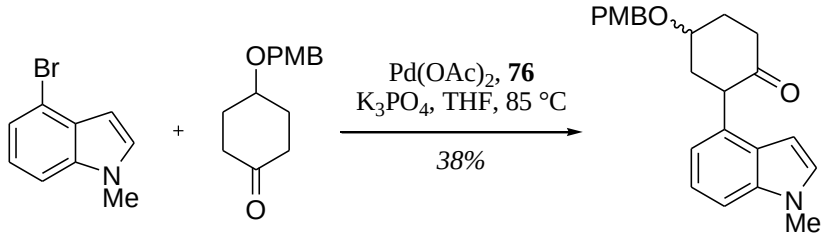
During the course of this study, Garg and co-workers reported, an iodine-promoted Michael addition between 5-bromoindole **183** and tetrasubstituted enone **184** to furnish **58** in good yield (Scheme 2.31).[20]



183 **184** **58**

Scheme 2.31

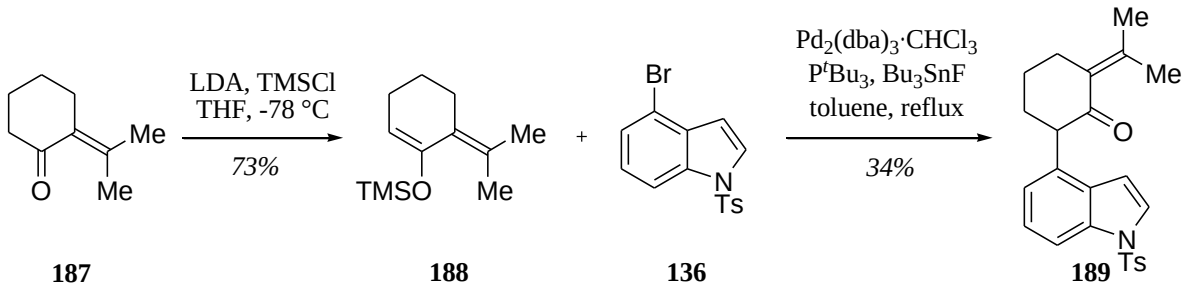
The preparation of cyclisation precursors **179** and **180** was envisaged using a palladium-catalysed cross-coupling reaction. Previous work in our group had showed that in one case, the more complex cyclohexanone **185** underwent a coupling reaction with *N*-methylated bromoindole **75** (Scheme 2.32).[21]



75 **185** **186** (1:1 dr)

Scheme 2.32

During the attemped installation of the *gem*-dimethyl group with an indole possessing an EWG on nitrogen (see Section 2.3), the cross-coupling reaction with functionalised cyclohexanones was studied to enable access to various functional groups present in the natural products. Thus, the coupling reaction between silyl enol ether **188**, obtained from the corresponding enone **187**, and bromoindole **136** afforded the derivative **189** (Scheme 2.33).



187 **188** **136** **189**

Scheme 2.33

Several other coupling products were synthesised to examine the scope of this cross-coupling reaction. Thus, silyl enol ethers **190**, **192** and **194**, obtained from the corresponding ketones, provided the enone **191**, ketal **193** and enol **195** respectively. Silyl enol ether **196**, obtained from an acyloin reaction, furnished the alcohol **197** (Table 2.1). These results demonstrated

that this cross-coupling reaction permitted the introduction of different functionalities on the cyclohexanone ring.

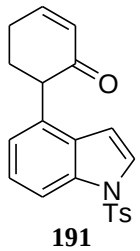
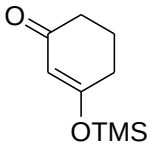
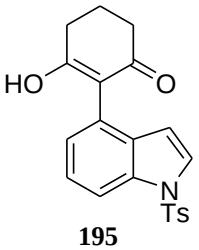
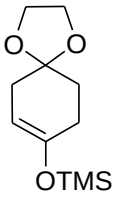
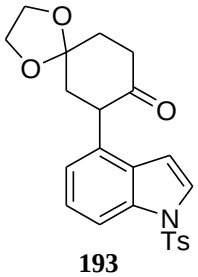
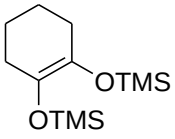
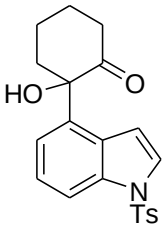
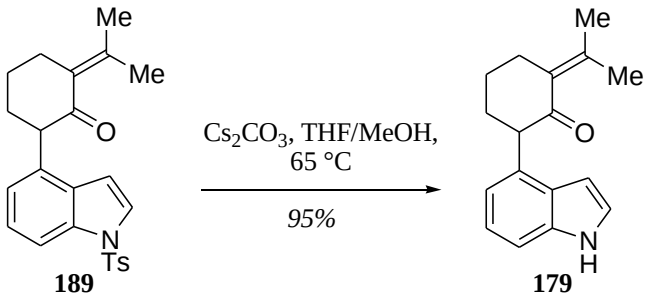
Entry	Silyl enol ether	Product	Yield (%)	Entry	Silyl enol ether	Product	Yield (%)
1	 **190**	 **191**	*52*	3	 **194**	 **195**	*49*
2	 **192**	 **193**	*57*	4	 **196**	 **197**	*18*

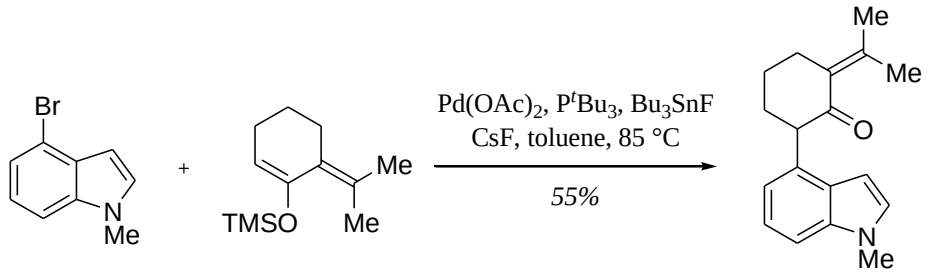
Table 2.1

In order to activate the indole ring, removal of the tosyl group was realised by treatment of tosylindole **189** with cesium carbonate in a mixture THF/MeOH to provide **179** (Scheme 2.34).



Scheme 2.34

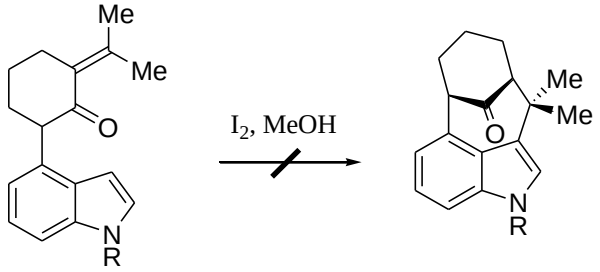
The second cyclisation precursor **180** was obtained from α-arylation of silyl enol ether **188** with indole **75** (Scheme 2.35).



75 **188** **180**

Scheme 2.35

The two cyclisation precursors **179** and **180** were treated with I_2 in methanol[22] but no traces of Michael product **181** or **182** were observed and only the starting enones were detected (Scheme 2.36). Alternative modes of activation were also examined (e.g. $Bi(OTf)_3$,[23,24] $ZrCl_4$,[25] $InCl_3$[26] or phosphoric acid[27]) but unfortunately without success.



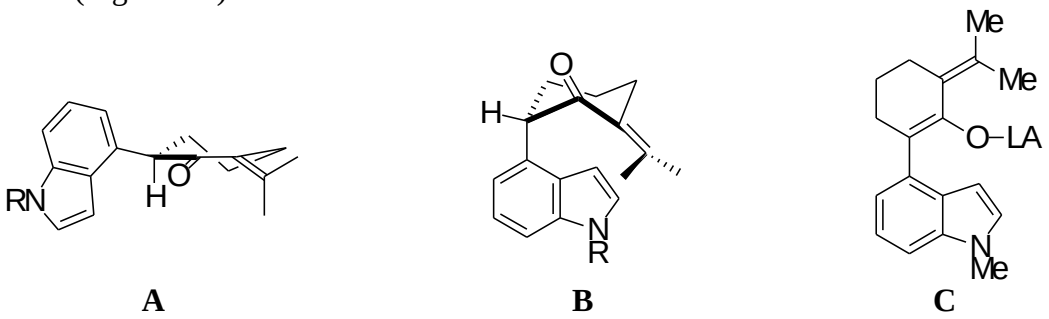
179 R = H
180 R = Me

181 R = H
182 R = Me

Scheme 2.36

The failure of the Michael reaction to generate the bicyclo[4.3.1]decane ring system may be explained by considering the position of the bulky *N*-methylindole in an equatorial orientation on the cyclohexanone (**A**). Therefore C-3 of the indole and the β-position of the enone are kept distant from each other. The conformer **B**, in which the indole ring is placed axially, is disfavoured. Another explanation could be that under Lewis acidic conditions, the formation

of enol **C** might be favoured and this would compromise formation of the seven-membered ring system (Figure 2.2).



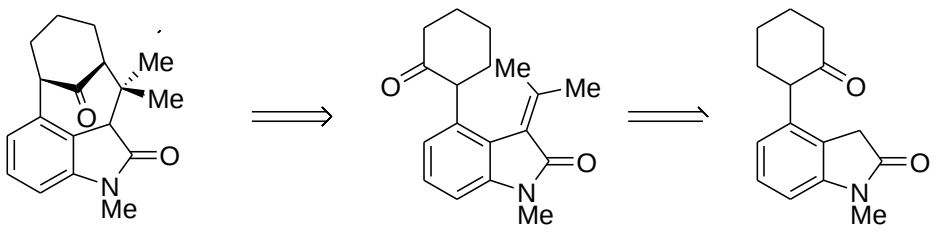
A **B** **C**

Figure 2.2

Although palladium-catalysed cross-coupling with pre-functionalised cyclohexanones was developed, and allowed access to enones **179** and **180** possessing the *gem*-dimethyl group on the cyclohexanone ring, the formation of the bicyclo[4.3.1]decane skeleton *via* an intramolecular Michael addition was unsuccessful.

2.7 Synthesis of cyclisation precursors bearing the *gem*-dimethyl group on the indole

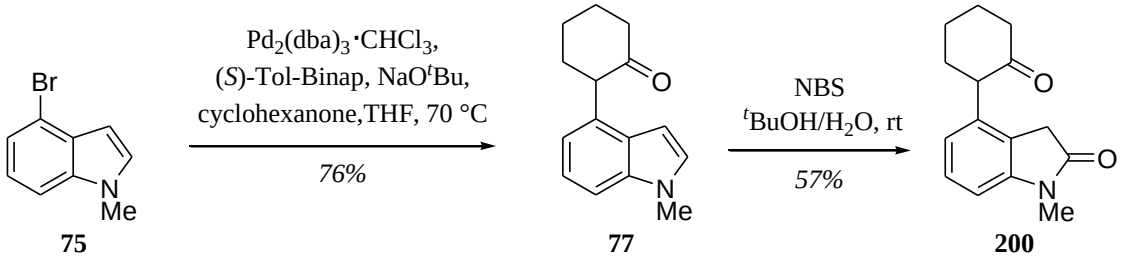
Another route towards the core structure would involve the synthesis of a cyclisation precursor possessing the *gem*-dimethyl group as part of an oxindole. The desired bicyclo[4.3.1]decane core would be obtained by ring closure of isopropylidene **199** *via* intramolecular Michael addition, for example (Scheme 2.37).



198 **199** **200**

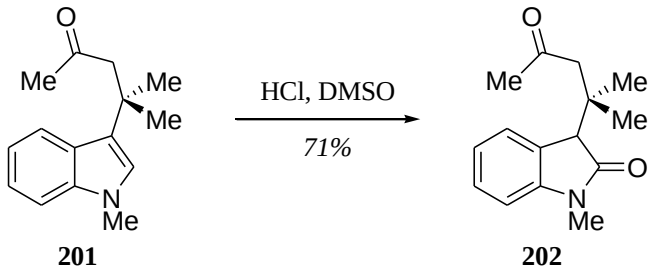
Scheme 2.37

The previously described palladium-catalysed α-arylation reaction between *N*-methylindole **75** and cyclohexanone was realised in 76% yield.[3] Oxidation of indole **77** to give an oxindole was achieved using NBS in a mixture of ^{t}BuOH/H_2O. The product, oxindole **200**, was obtained in 57% yield (Scheme 2.38).



Scheme 2.38

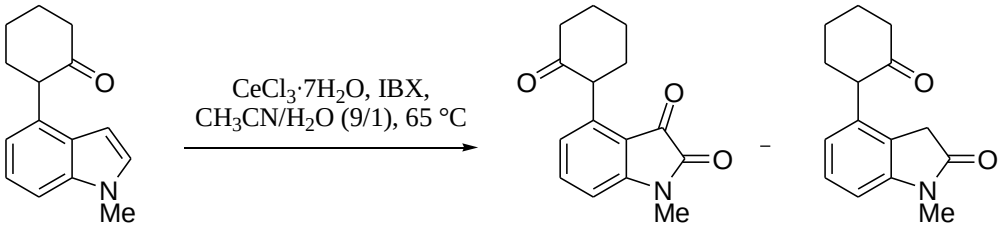
Alternative methods to improve the efficiency of the oxidation step were tested. First, Savige and Fontana reported oxidation of tryptophan-containing peptides and proteins using concentrated HCl and DMSO.[28] This procedure was applied to indole **201** by Jung and co-workers during their study towards the welwistatin core structure (Scheme 2.39).[29] Unfortunately, under these conditions rapid degradation of indole **77** was observed, although traces of oxindole **200** were detected by ^{1}H NMR spectroscopy.



Scheme 2.39

Yadav and co-workers reported the use of IBX in the presence of $CeCl_3 \cdot 7H_2O$ to afford the corresponding isatin derivative.[30] This methodology could be interesting with regard to the installation of the desired *gem*-dimethyl group. Indole **77** was subjected to these oxidation

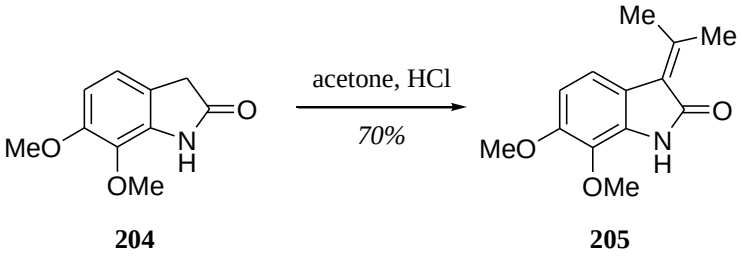
conditions and afforded the desired isatin derivative **203** in only 26% yield, along with oxindole **200** in 11% yield (Scheme 2.40).



Scheme 2.40

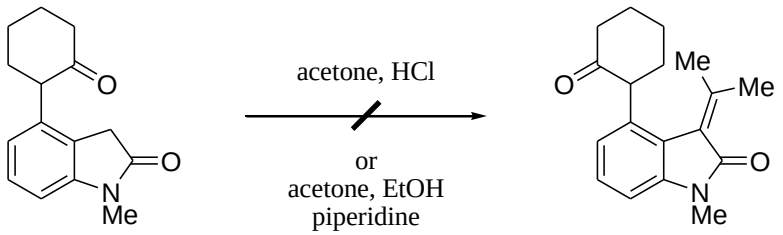
Efforts to improve the conversion of indole **77** into oxindole **200**, or alternatively into isatin derivative **203**, were unsuccessful. The use of NBS in a mixture of ^{t}BuOH/H_2O proved to be the most efficient access to oxindole **200** (Scheme 2.38).

With the desired oxindole **200** in hand, installation of the *gem*-dimethyl group might be realised in one step by condensation with acetone. In the synthesis of marcfortine B, Trost described condensation of acetone with oxindole **204** under acidic conditions (Scheme 2.41).[31] He also reported an alternative procedure using acetone and ethanol in piperidine.[32]



Scheme 2.41

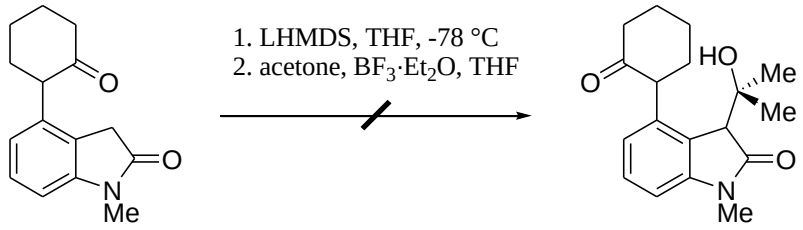
Unfortunately, oxindole **200** was unreactive under both sets of reaction conditions and therefore formation of the desired isopropylidene **199** was not observed (Scheme 2.42). Formation of the isopropylidene might be hampered by the presence of the bulky cyclohexanone at C-4 of the indole ring.



200 **199**

Scheme 2.42

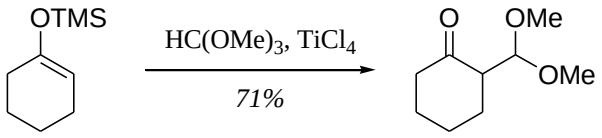
Bordwell and Fried measured equilibrium acidities of several heterocyclic compounds in DMSO and this study revealed a pK_a value of 18.5 for the 3-position of *N*-methyloxindole.[33] Therefore, selective deprotonation of oxindole was anticipated to install the *gem*-dimethyl group onto the oxindole ring *via* an aldol reaction. Treatment of oxindole **200** with LHMDS followed by addition of acetone showed formation of a new compound by TLC and ^{1}H NMR spectroscopic analysis of the crude material. After purification, only the starting oxindole was recovered in 82% yield, probably due to the desired alcohol **206** undergoing a retro-aldol process (Scheme 2.43).



200 **206**

Scheme 2.43

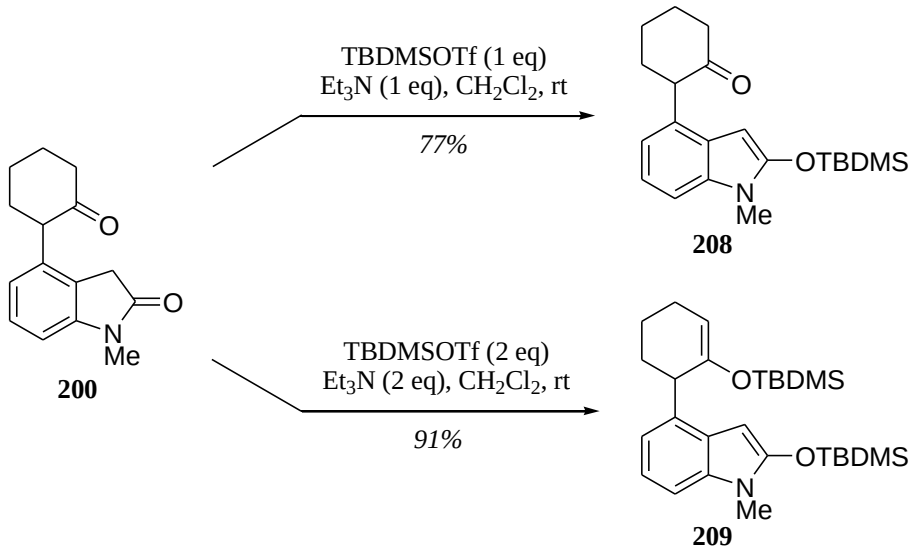
A Mukaiyama condensation with an acetal was envisaged to overcome this retro-aldol problem.[34] Mukaiyama described a method where the use of a silyl enol ether avoids the problem of self-condensation in the aldol reaction.[35] For example, silyl enol ether **144** underwent condensation with trimethyl orthoformate in the presence of $TiCl_4$ to give ketal **207** (Scheme 2.44). The *gem*-dimethyl group could potentially be installed on the oxindole ring using this approach with an appropriate ketal reagent such as 2,2-dimethoxypropane.



144 **207**

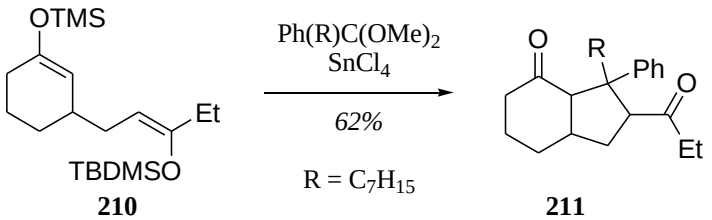
Scheme 2.44

When oxindole **200** was treated with one equivalent of TBDMSOTf and triethylamine, the formation of indole silyl enol ether **208** was achieved. The use of two equivalents of TBDMSOTf and triethylamine generated *bis*-enol silane **209** (Scheme 2.45).



Scheme 2.45

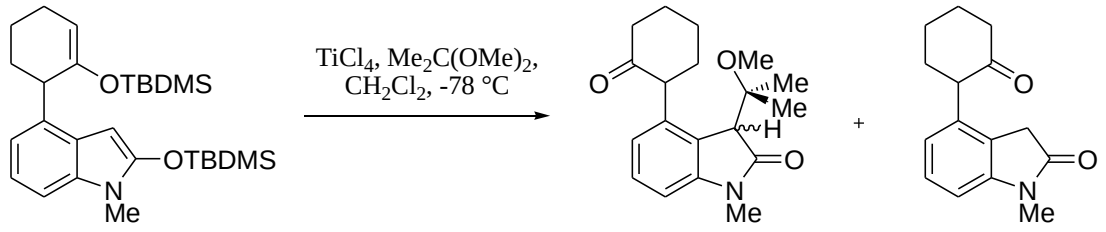
Interestingly, the *bis*-enol silane **209** might be useful to access the bicyclo[4.3.1]decane core structure *via* a cascade Mukaiyama reaction. For example, Kuwajima and co-workers reported direct formation of bicycle **211** *via* a Mukaiyama reaction using $SnCl_4$ and an aromatic acetal. Thus, a five-membered ring was generated from *bis*-silyl enol ether **210** (Scheme 2.46).[36]



210 **211**

Scheme 2.46

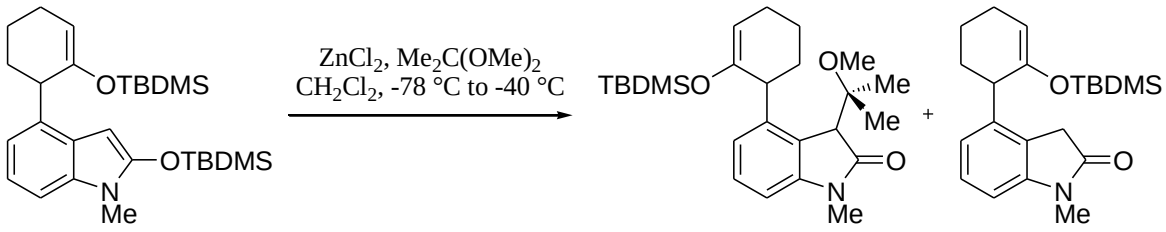
The use of 2,2-dimethoxypropane and $SnCl_4$ with our *bis*-silyl enol ether **209** resulted in cleavage of both silyl enol ethers. However, upon treatment with $TiCl_4$ the condensation product **212** was isolated as a mixture of diastereoisomers in 66% yield, alongside desilylated oxindole **200** in 16% yield (Scheme 2.47). Unfortunately, the desired cyclised product was not detected.



209 **212** (*66%, 2.4:1 dr*) **200** (*16%*)

Scheme 2.47

The use of milder Lewis acids such as $BF_3{\cdot}Et_2O$ and $ZnCl_2$ was also investigated. Treatment of **209** with $BF_3{\cdot}Et_2O$ led to the formation of condensation product **212** in 26% yield alongside desilylated oxindole **200** in 25% yield. The use of $ZnCl_2$ afforded condensation product **213** in 27% yield alongside monosilylated oxindole **214** in 50% yield (Scheme 2.48).



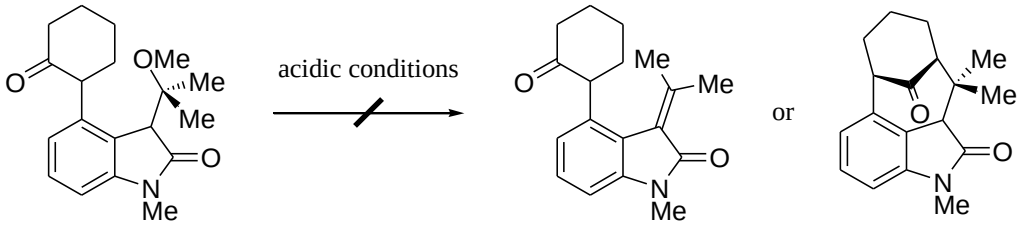
209 **213** (*27%*) **214** (*50%*)

Scheme 2.48

Unfortunately, in both reactions the desired bicyclo[4.3.1]decane product was not observed and formation of the isopropylidene was then investigated.

Elimination of the methoxy group was attempted under acidic conditions. Oxindole **212** was treated with *p*-TsOH or TFA but showed no traces of elimination product **199** or cyclised

derivative **198**, and oxindole **200** was formed instead (Scheme 2.49). Unfortunately, basic treatment with DBU only provided epimerisation at the 3-position of the oxindole.



212 **199** **198**

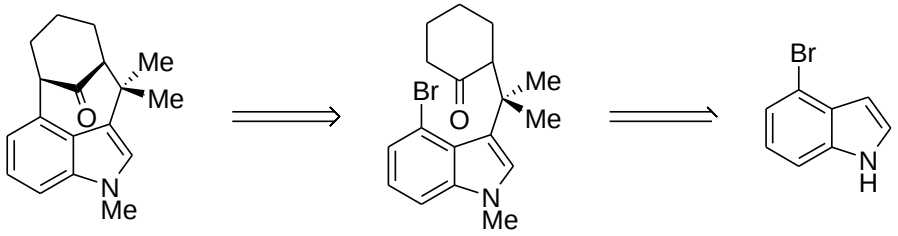
Scheme 2.49

All attempts to synthesise the intermediate **199** from oxindole **200** or **212** were fruitless. These results could be rationalised by the steric hinderance between the methyl group and the cyclohexanone at the 4-position, which prevents the formation of the double bond.

Unfortunately, the installation of the *gem*-dimethyl group at C-16 in a novel way failed to work and a reordering of the steps in the synthesis was envisioned to generate the bicyclo[4.3.1]decane skeleton.

2.8 Synthesis of the bicyclo[4.3.1]decane framework possessing the *gem*-dimethyl group

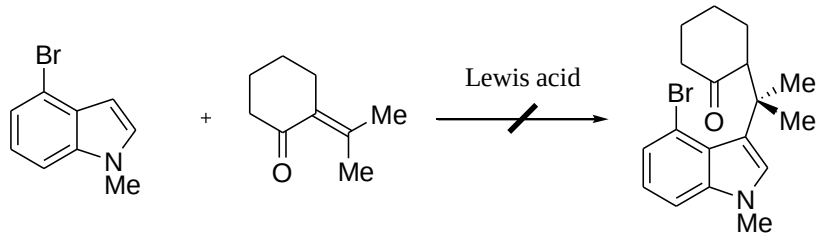
In order to progress towards the synthesis of *N*-methylwelwistatin **7**, the synthesis of the known intermediate **215**, described by Rawal, was envisaged (Scheme 2.50).[4] The core structure **182** would then be obtained by an intramolecular palladium-catalysed enolate arylation.



182 **215**

Scheme 2.50

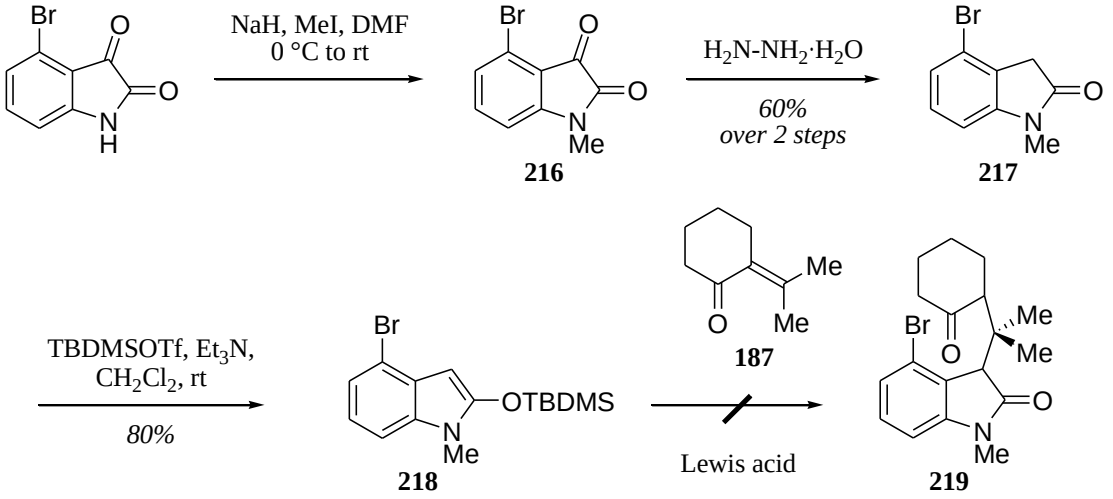
Direct access to the desired intermediate **215** employing a Michael addition reaction was investigated; thus 4-bromoindole **75** and enone **187**[37] were subjected to various Lewis acids e.g. $ZrCl_4$,[25] $RuCl_3$,[38] $Yb(OTf)_3$.[39] Unfortunately, formation of the desired compound **215** was not observed; TLC and ^1H NMR spectroscopic analysis showed only the presence of starting materials (Scheme 2.51). The steric hinderance generated by the bromine atom at the 4-position might be responsible for the failure of the Michael addition to the enone **187**. Moreover during these studies, the same observation was reported by Garg.[20]



75 **187** **215**

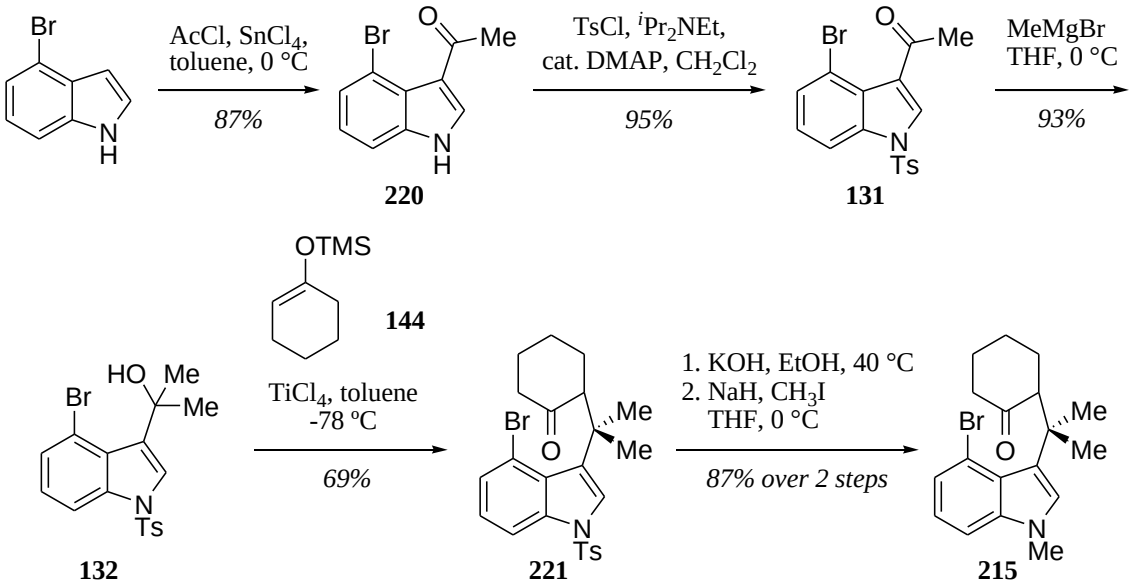
Scheme 2.51

The synthesis of oxindole derivative **219** was also attempted. *N*-Methylation of 4-bromoisatin followed by reduction with hydrazine provided oxindole **217**. Enol silane **218** was obtained by treatment with TBDMSOTf and triethylamine. Subsequent treatment with different Lewis acids e.g. $TiCl_4$, $SnCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, TBDMSOTf and $Cu(OTf)_2$ in the presence of enone **187** resulted only in desilylation of **218** (Scheme 2.52).



Scheme 2.52

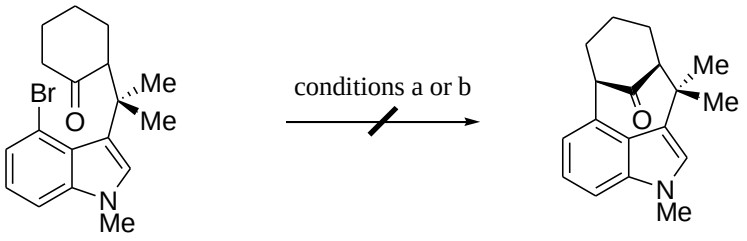
Finally, the synthesis of derivative **215** was obtained following Rawal's synthesis (Scheme 2.53).[4]



Scheme 2.53

Thus, Friedel-Crafts acylation of 4-bromoindole and *N*-tosylation provided indole derivative **131**. Subsequent treatment with MeMgBr followed by alkylative coupling with silyl enol ether derivative **144** promoted by $TiCl_4$ gave the intermediate **221**. After removal of the tosyl protecting group, *N*-methylation was realised to yield derivative **215.**

With precursor **215** in hand, our standard conditions for the palladium-catalysed enolate arylation (previously described) and also Rawal's conditions were tested in order to generate the desired bicyclo[4.3.1]decane. Unfortunately, under these conditions the desired cyclised product was not observed (Scheme 2.54). This could conceivably be due, under thermodynamic conditions, to formation of the thermodynamic enolate, which compromised the formation of cyclised product **182**.

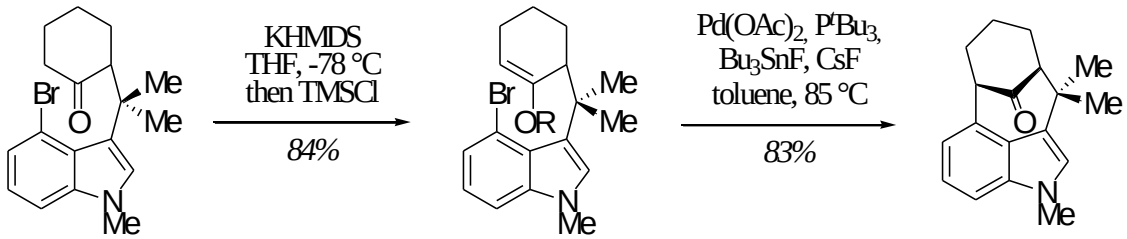


215 **182**

condition a : $Pd_2(dba)_3 \cdot CHCl_3$, (*S*)-Tol-Binap, NaO^tBu, THF, 70 °C
condition b : $Pd(OAc)_2$, P^tBu_3, KO^tBu, toluene, 70 °C

Scheme 2.54

To favour formation of the desired enolate intermediate, kinetic silyl enol ether **222** was generated with KHMDS and trapped with TMSCl. Thus, cyclisation *via* the correct silyl enol ether could be anticipated. Rawal[10] and Hartwig[9] cross-coupling conditions were tried. This time, Hartwig's procedure provided a cleaner reaction and after purification, tetracycle **182** was isolated in 83% yield (Scheme 2.55).



215 **222** R = TMS **182**

Scheme 2.55

The synthesis of the desired bicyclo[4.3.1]decane scaffold possessing the *gem*-dimethyl group was achieved in eight steps from 4-bromoindole by using the first steps of Rawal's approach.[4]

Thus, the formation of the tetracycle **182** was accomplished *via* an intramolecular palladium-catalysed α-arylation of the trimethylsilyl enol ether **222**.

2.9 Summary

We demonstrated that the important *gem*-dimethyl group at C-16 could not be introduced by using our initial disconnection approach with a tosyl group on nitrogen. Moreover any attempts to obtain the bicyclo[4.3.1]decane skeleton *via* an intramolecular Michael addition reaction were fruitless. However, a successful synthesis of the tetracycle **182** possessing the desired *gem*-dimethyl group at C-16 was obtained in eight steps from commercially available 4-bromoindole.

2.10 References

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CHAPTER 3

Progress towards the total synthesis of

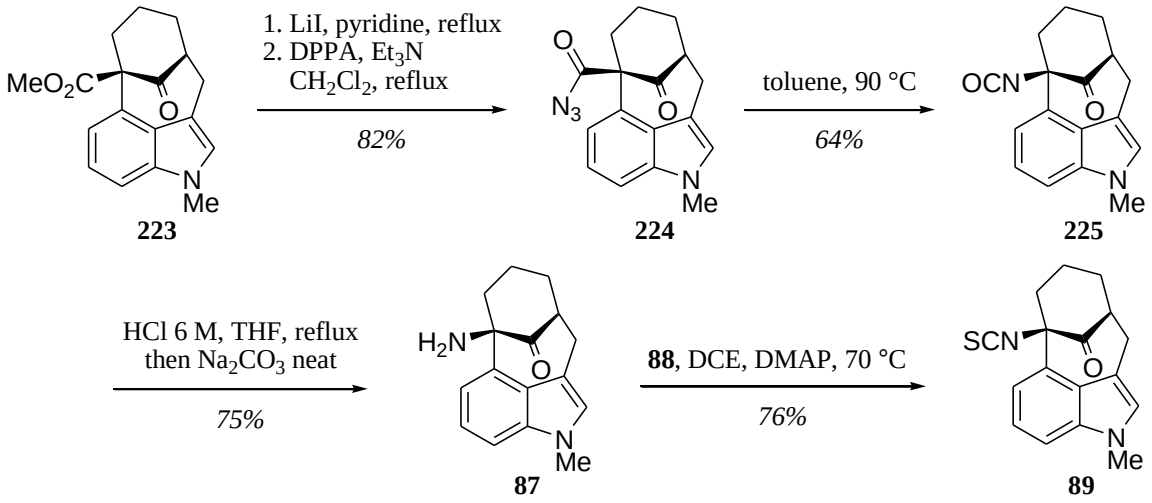
N-methylwelwitindolinone C isothiocyanate

3.1 Aims and objectives

With bicyclo[4.3.1]decane core **182** possessing the *gem*-dimethyl moiety in hand, a new route to the isothiocyanate functionality was investigated to enable installation of the required group in a shorter sequence. This chapter will focus on the installation of nitrogen functionality at the bridgehead position and progress towards installation of the methyl and vinyl groups at C-12.

3.2 New synthetic approach towards the isothiocyanate group

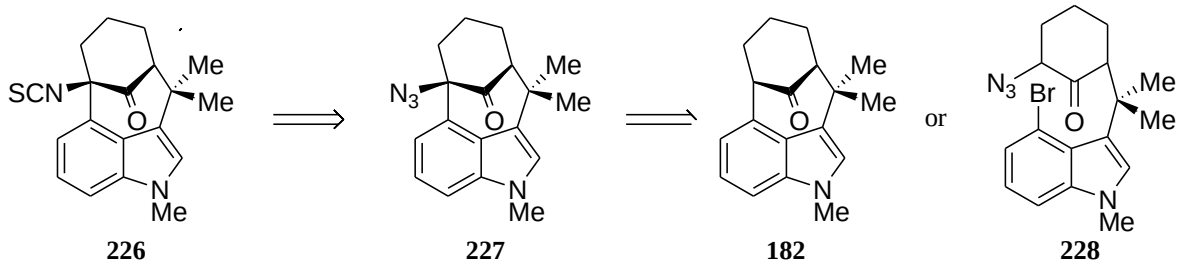
Previous studies in our group demonstrated the synthesis of the bridgehead isothiocyanate derivative **89** in five steps from ester **223** *via* a Curtius rearrangement (Scheme 3.1).[1]



Scheme 3.1

A shorter route to the required isothiocyanate group was proposed *via* direct introduction of a nitrogen at the bridgehead position. Two routes were investigated for installation of the nitrogen, employing either regioselective bridgehead deprotonation of tetracycle **182** or

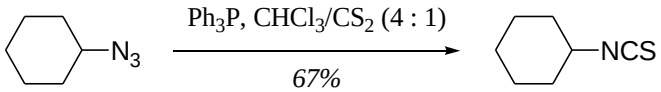
cyclisation of α-ketoazide derivative **228**. Azide derivative **227** could then be converted into isothiocyanate **226** (Scheme 3.2).



226 **227** **182** **228**

Scheme 3.2

The choice of an azide functionality was influenced by the work of Isoda and co-workers, who reported the transformation of azides into isothiocyanates in one step by a tandem Staudinger/aza-Wittig reaction.[2] For example, isothiocyanate derivative **230** was obtained in a single step from the corresponding azide **229** (Scheme 3.3).



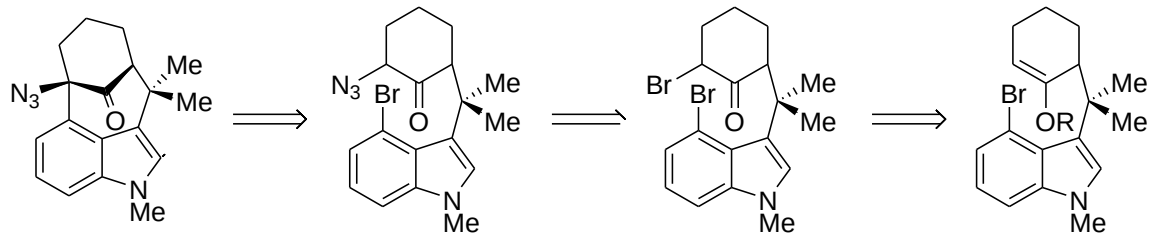
229 **230**

Scheme 3.3

With an azide group at the desired bridgehead position, access to the isothiocyanate functionality should therefore be possible in one step instead of five.

3.2.1 Cyclisation attempts to introduce nitrogen at the bridgehead position

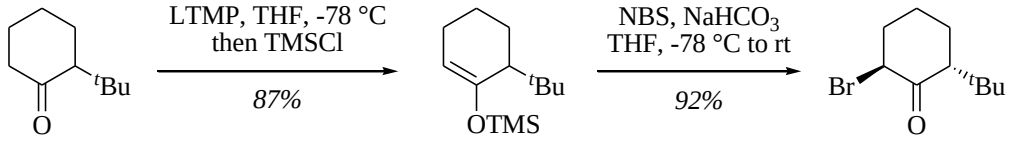
The synthesis of bridgehead azide **227** was first envisaged *via* cyclisation of α-ketoazide **228**, which would be generated through the nucleophilic substitution of α-bromoketone **231** with sodium azide. Ketone **231** could in turn be derived from enol silane **222** described previously (Scheme 3.4).



227 **228** **231** **222** R = TMS

Scheme 3.4

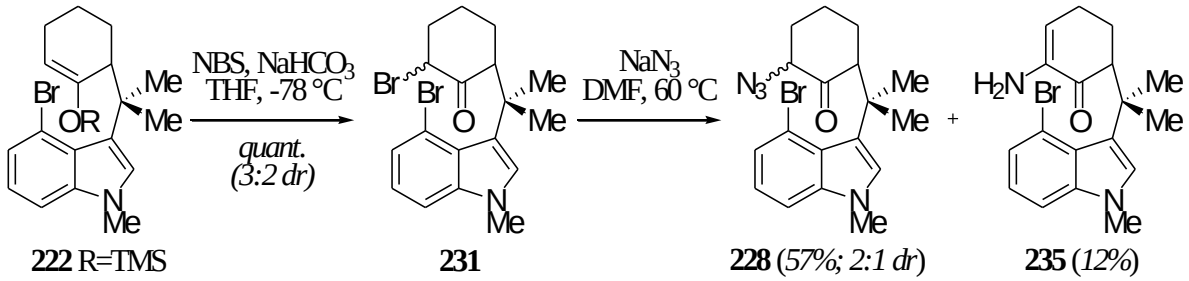
α-Bromoketone **231** could be synthesised following the literature example of Harrowven and co-workers who showed that kinetic silyl enol ether **233** in the presence of NBS provided α-bromoketone **234** in good yield (Scheme 3.5).[3]



232 **233** **234**

Scheme 3.5

Silyl enol ether **222** was treated with NBS to provide α-bromoketone **231** in a quantitative yield as a mixture of diastereoisomers. Azide **228** was obtained in 57% yield as a mixture of diastereoisomers by treatment of **231** with sodium azide (Scheme 3.6).

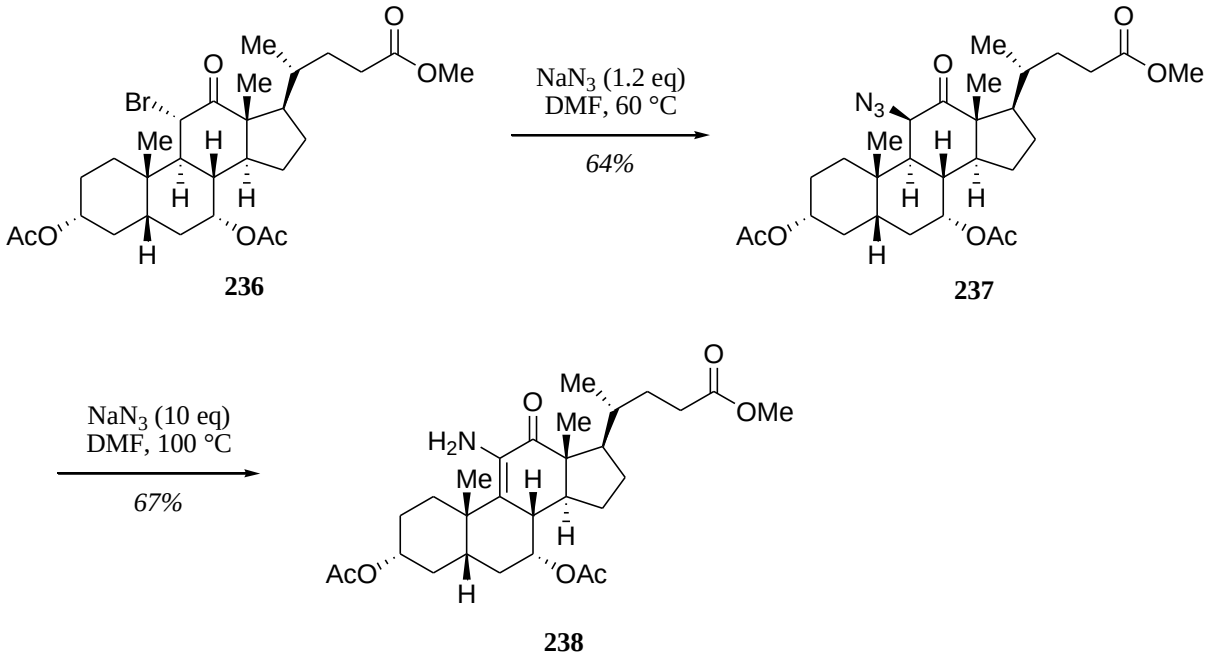


222 R=TMS **231** **228** (*57%; 2:1 dr*) **235** (*12%*)

Scheme 3.6

Surprisingly, the corresponding enamine **235** was also observed and isolated in 12% yield. The formation of an enamine derivative was also observed by Hazra and co-workers, in this case during the transformation of α-bromo ketone **236** into the corresponding azide **237** in

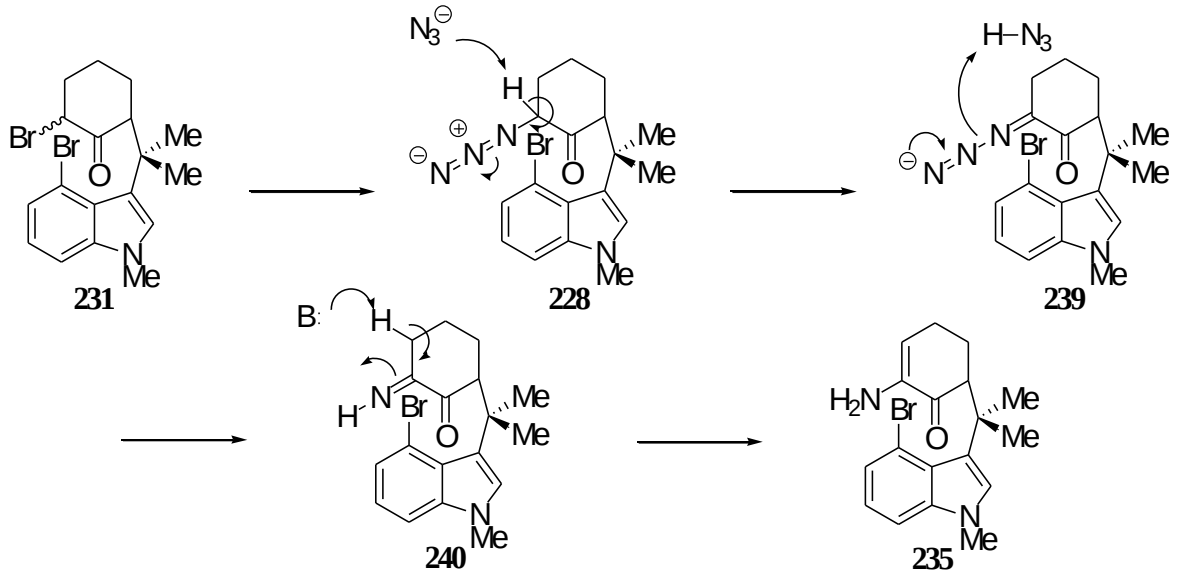
64% yield.[4] Although, α-ketoazides are known to be unstable under basic conditions,[5] a large excess of sodium azide is required to form enamine **238** from **237** (Scheme 3.7).



236 **237** **238**

Scheme 3.7

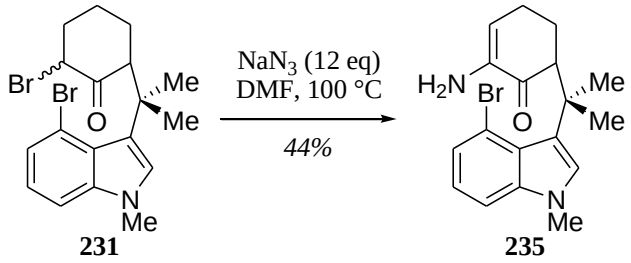
The formation of enamine **235** is proposed to occur by loss of molecular nitrogen to afford α-iminoketone **240**, which undergoes a subsequent tautomerisation (Scheme 3.8).[4]



231 **228** **239** **240** **235**

Scheme 3.8

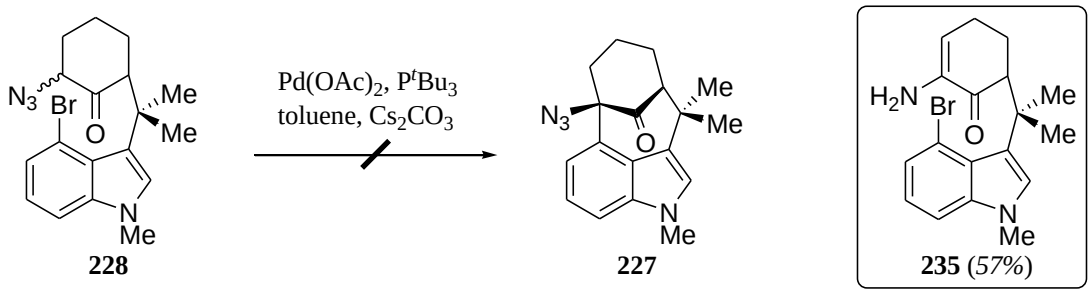
Treatment of α-bromoketone **231** with a large excess of sodium azide in DMF at 100 °C furnished **235** in 44% yield alongside unidentified degradation products (Scheme 3.9).



231 **235**

Scheme 3.9

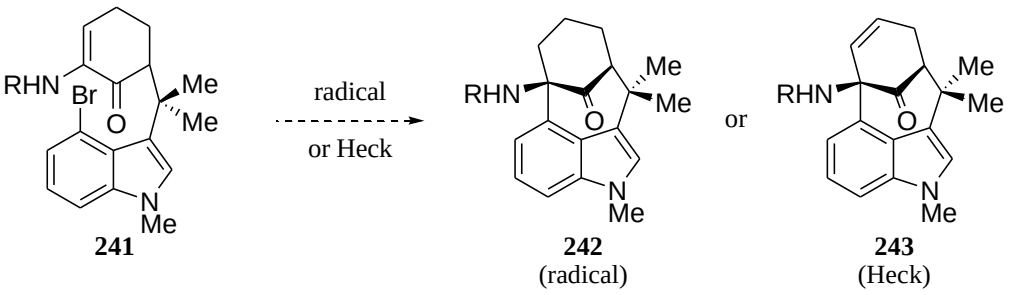
The tendency of the α-ketoazide **228** to generate the corresponding enamine rather than to undergo enolisation and coupling might be an issue for the cyclisation reaction. Indeed, when azide **228** was submitted to Rawal's conditions using the mild base Cs_2CO_3, cyclised product **227** was not observed and instead rapid formation of enamine **235** occurred (Scheme 3.10).



228 **227** **235** (*57%*)

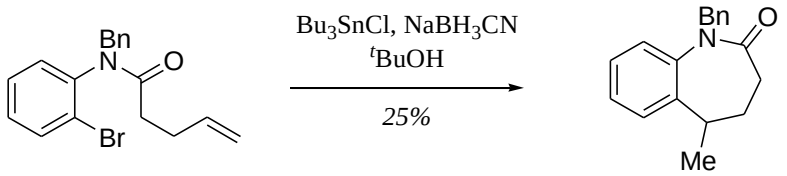
Scheme 3.10

α-Arylation of the corresponding silyl enol ether from azide **228** could be envisaged but there are no reported examples of formation of a silyl enol ether from an α-ketoazide possessing a hydrogen at the β-position. This is probably due to instability of the azide as described above. Although the synthesis of bridgehead azide **227** using α-ketoazide **228** was unsuccessful, the use of enamine **235** could be envisaged. The bicyclo[4.3.1]decane system possessing a nitrogen at the bridgehead position might be accessed *via* an intramolecular cyclisation under Heck or radical conditions to provide respectively derivatives **242** or **243** (Scheme 3.11).



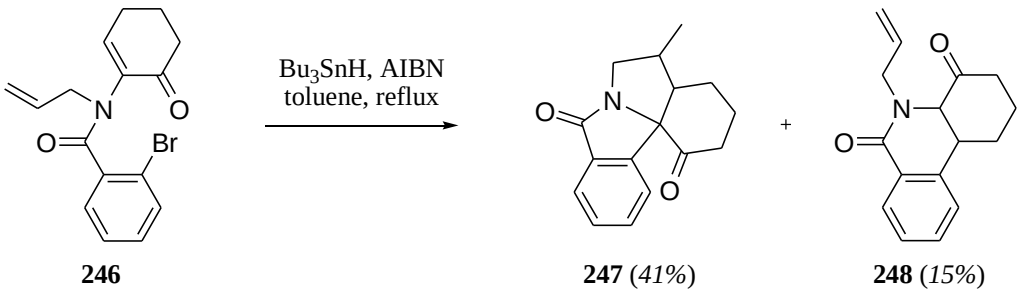
Scheme 3.11

The challenge of these approaches would be the generation of a quaternary centre *via* a 7-*exo*-*trig* cyclisation. Formation of a seven-membered ring fused to an aromatic ring by a radical reaction is relatively rare and of those reported, most proceed in moderate yield.[6] For example, Jones and co-workers reported a 7-*exo*-*trig* cyclisation of bromobenzene derivative **244** providing **245** in 25% yield along with a 60% yield of the reduced compound arising from the 1,5-H transfer (Scheme 3.12).[7]



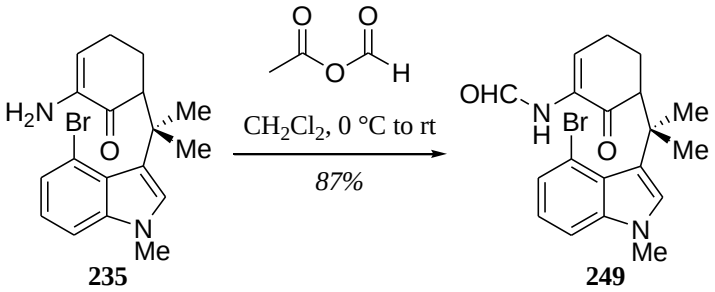
Scheme 3.12

Another point to consider was the regioselectivity of the cyclisation induced by a protected α-ketoenamine function. Interestingly, Parsons and Williams demonstrated the formation of tetracycle **247** as the major compound through a 5-*exo*/5-*exo* tandem reaction of aryl bromide derivative **246** (Scheme 3.13).[8]



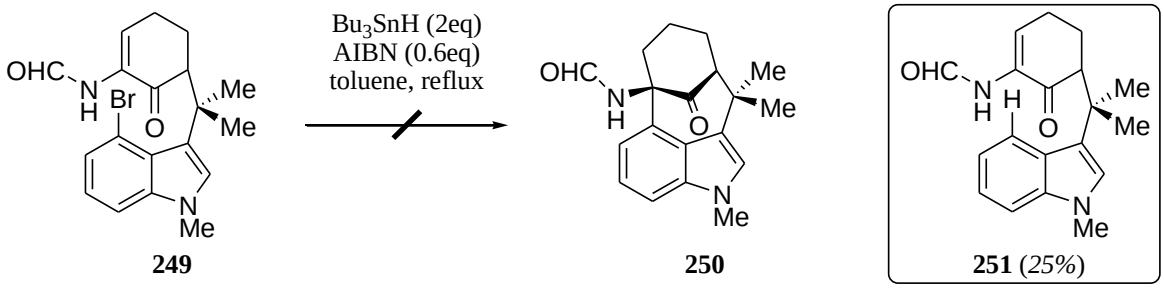
Scheme 3.13

These results encouraged us to examine the feasibility of a radical cyclisation reaction to generate the bicyclo[4.3.1]decane framework and therefore prior to any cyclisation investigations, enamine **235** was protected as the formylated derivative **249** (Scheme 3.14).



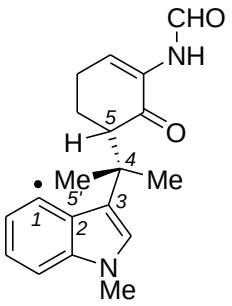
Scheme 3.14

Radical initiation was attempted on protected enamine **249** using tri-*n*-butyltin hydride and AIBN in refluxing toluene. Unfortunately, cyclisation product **250** was not detected from 7-*exo*-*trig* mode and only reduced compound **251** was isolated in 25% yield (Scheme 3.15).



Scheme 3.15

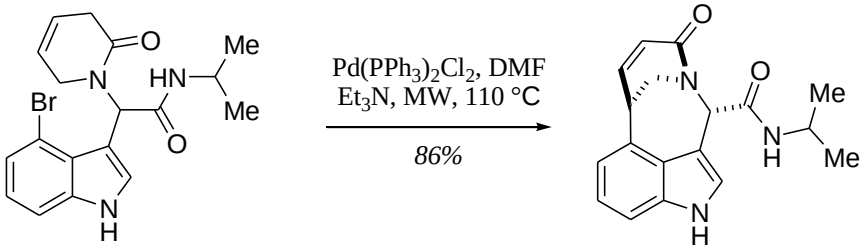
This result provides evidence that the aryl radical species **D** is formed but that it does not add to the enamine double bond. Considering the possibilities of 1,5-H-abstractions, either at the α-position to the ketone or at the geminal methyls, the desired cyclisation reaction might be hampered (Figure 3.1).



D

Figure 3.1

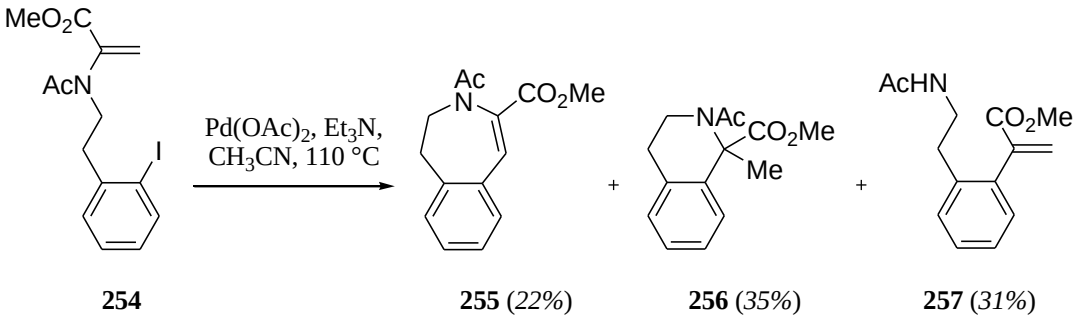
Alternatively, the desired seven-membered ring could be envisioned to be formed by Heck cyclisation of the enamine **249**. Like radical cyclisation, Heck intramolecular cyclisation is well documented for the preparation of five- and six-membered rings by 5-*exo-trig* and 6-*exo-trig* cyclisation processes.[9] Encouragingly, several reports described a palladium-mediated 7-*exo-trig* cyclisation; for example, bromoindole **252** was shown to undergo an intramolecular Heck reaction to give cyclised product **253** in excellent yield (Scheme 3.16).[10]



252 **253**

Scheme 3.16

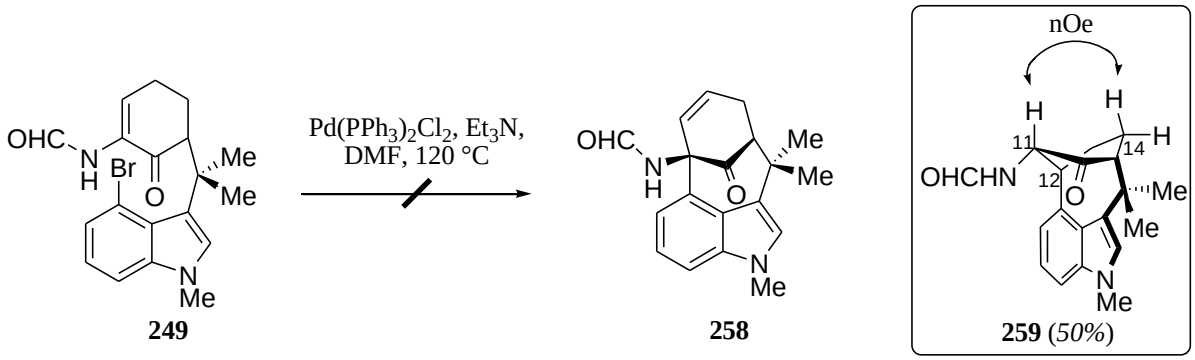
The nature of our olefin could be an issue because it possesses both enamine and enone character. Gibson and Middleton reported the synthesis of 7-, 8- and 9-membered rings *via endo* Heck cyclisations.[11] Cyclisation of iodobenzene derivatives **254** using vigorous Heck reaction conditions generated **255** arising from the 7-*endo* cyclisation, whereas products **256** and **257** are derived from the 6-*exo* cyclisation (Scheme 3.17).



254 **255** (*22%*) **256** (*35%*) **257** (*31%*)

Scheme 3.17

With our substrate, two sources of palladium were tested, namely $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$. Transformation occurred only with $Pd(PPh_3)_2Cl_2$ and the isolated product was the bicyclo[4.2.2]decane **259** arising from 8-*endo* cyclisation (Scheme 3.18).



249 **258** **259** (*50%*)

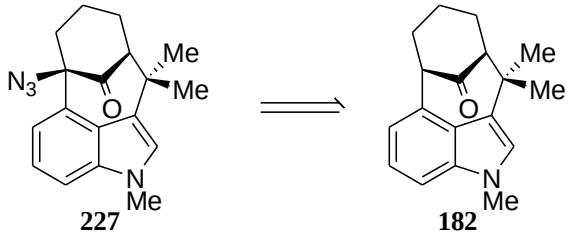
Scheme 3.18

Evidence for the formation of **259** was provided by mass spectrometry, which showed one peak at $[M+Na]^+$= 333.1573 ($[C_{19}H_{22}NO_2Na]^+$ requires 333.1579). Moreover, the ^{13}C NMR spectrum showed the presence of two CH_2 groups at 21.0 and 25.0 ppm and three CH groups at 41.4, 55.9 and 56.9 ppm. ^1H NMR spectroscopy showed the absence of alkene functionality, instead a broad singlet at 5.84 ppm (N*H*CHO), a triplet at 5.14 ppm (J = 6.5 Hz, H-11) and the characteristic multiplet of the benzylic proton at 3.91-3.98 ppm were observed. The stereochemistry of the formamide substituent was determined by nOe showing for H-11 a correlation with H-12 and H-14, which interestingly proved that the cyclohexanone adopts a boat conformation.

In summary, attempts to generate the bicyclo[4.3.1]decane system from either α-ketoazide **228** or enamine **249** failed. Firstly, α-ketoazide **228** was found to be unstable to basic conditions. Secondly, enamine **249** gave the reduced derivative **251** under radical conditions and the undesired 8-*endo* cyclisation product **259** under Heck reaction conditions.

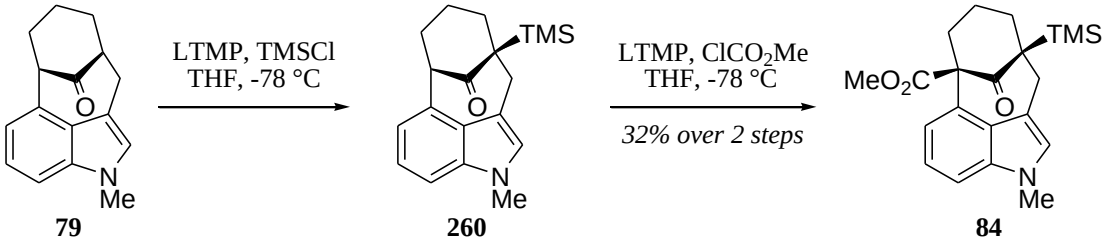
3.2.2 Attempts to install an azide group at the bridgehead position

An alternative approach to bridgehead azide **227** was envisioned *via* bridgehead deprotonation and quench with an electrophilic source of azide such as tosyl azide (Scheme 3.19).



Scheme 3.19

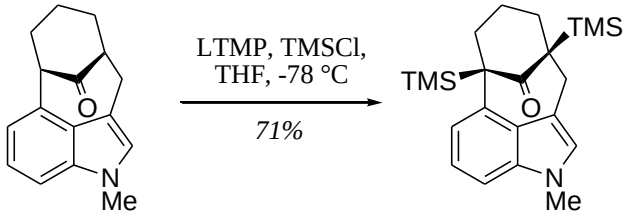
Previous work in our lab demonstrated bridgehead metallation of the model system **79** was possible.[12] The kinetic bridgehead enolate was generated with LTMP and trapped with TMSCl.[13] Subsequent deprotonation of the second bridgehead position followed by reaction with methyl chloroformate provided ester **84** (Scheme 3.20).



Scheme 3.20

The presence of a *gem*-dimethyl group at C-16 in the tetracycle **182** could reverse the preference for bridgehead metallation and allow direct functionalisation at the benzylic position. In order to study the regioselective deprotonation of **182**, previous studies on the

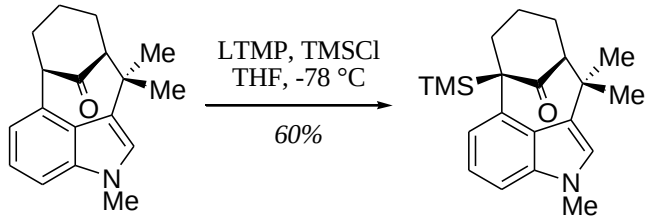
simpler system were reproduced. Indeed, treatment of tetracyle **79** with ten equivalents of LTMP in the presence of ten equivalents of TMSCl (*in situ* quench) provided silylation at both bridgehead positions in 71% yield (Scheme 3.21).[1]



79 **261**

Scheme 3.21

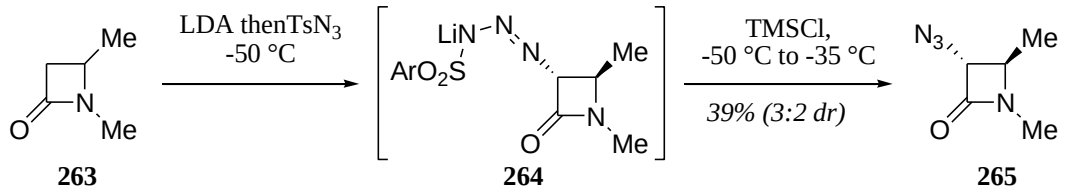
In the same fashion, tetracycle **182** was treated with ten equivalents of the bulky lithium amide, LTMP, in presence of ten equivalents of TMSCl. The formation of doubly silylated product was not observed under these conditions and mono-silylated indole **262** was isolated in 60% yield alongside a 28% yield of unreacted tetracycle **79** (Scheme 3.22).



182 **262**

Scheme 3.22

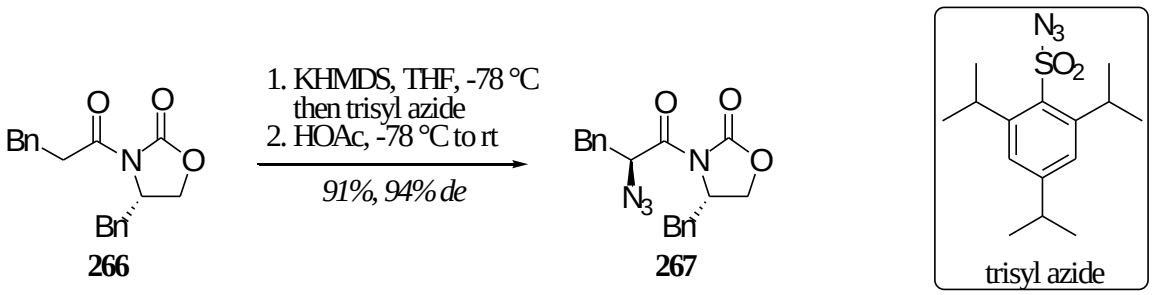
In light of this result, direct installation of nitrogen at the bridgehead position was envisaged in the form of an azide group. Kühlein and Jensen reported the first electrophilic azide transfer onto an enolate using a sulfonyl azide.[14] In this study, β-lactam **263** was sequentially treated with LDA and tosyl azide to form intermediate adduct **264**. Subsequent treatment with TMSCl gave α-azide **265** in moderate yield (Scheme 3.23).



263 **264** **265**

Scheme 3.23

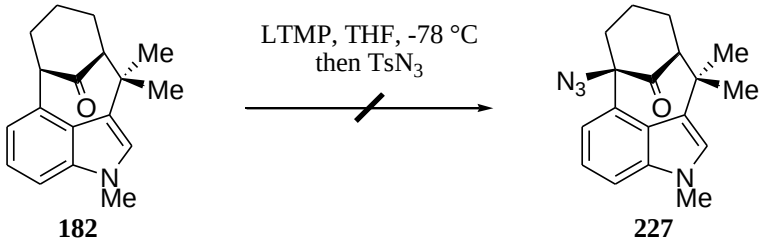
Inspired by Kühlein and Jensen's work, Evans developed an asymmetric version and described optimal conditions to achieve the azide transfer.[15] The screening of several reaction parameters first showed that a potassium enolate minimises side reactions between the enolate and the sulfonyl azide. Second, the use of the sterically bulky trisyl azide prevents the formation of the corresponding diazo-transfer product. Lastly, quenching the reaction with a simple proton source i.e. glacial acetic acid gave the best conversion to azidation products. Applying these optimal conditions to the carboximide **266** furnished the corresponding azido product **267** in excellent yield and diastereoselectivity (Scheme 3.24).



266 **267**

Scheme 3.24

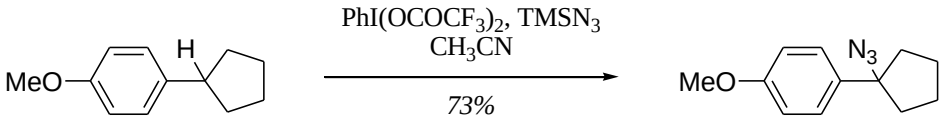
In order to avoid steric congestion of the bulky trisyl azide, tosyl azide was used as the electrophile. Treatment of **182** with LTMP followed by quenching with tosyl azide did not afford the desired azide **227**, and only starting material detected by ^{1}H NMR spectroscopy (Scheme 3.25).



182 **227**

Scheme 3.25

Kita and co-workers have described direct azidation of the benzylic position of several *p*-alkylanisole derivatives under radical conditions[16] by using $PhI(OCOCF_3)_2$ and $TMSN_3$. Benzylic azide **269** was prepared in this fashion in 73% yield (Scheme 3.26). Unfortunately, tetracycle **182** was unreactive to these conditions.



268 **269**

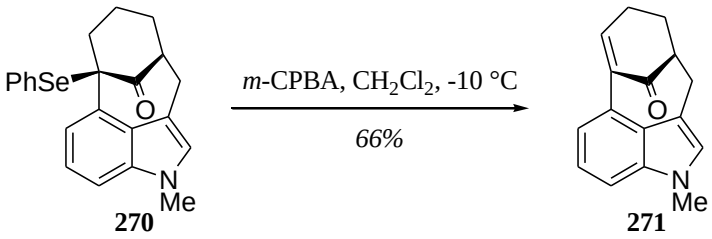
Scheme 3.26

Although the bicyclo[4.3.1]decane derivative **182** was regioselectively metallated and functionalised at the bridgehead position with a TMS group, installation of an azide group using electrophilic azide reagents proved to be fruitless.

3.3 Indirect installation of an azide group at the bridgehead position

3.3.1 New strategies and retrosynthesis

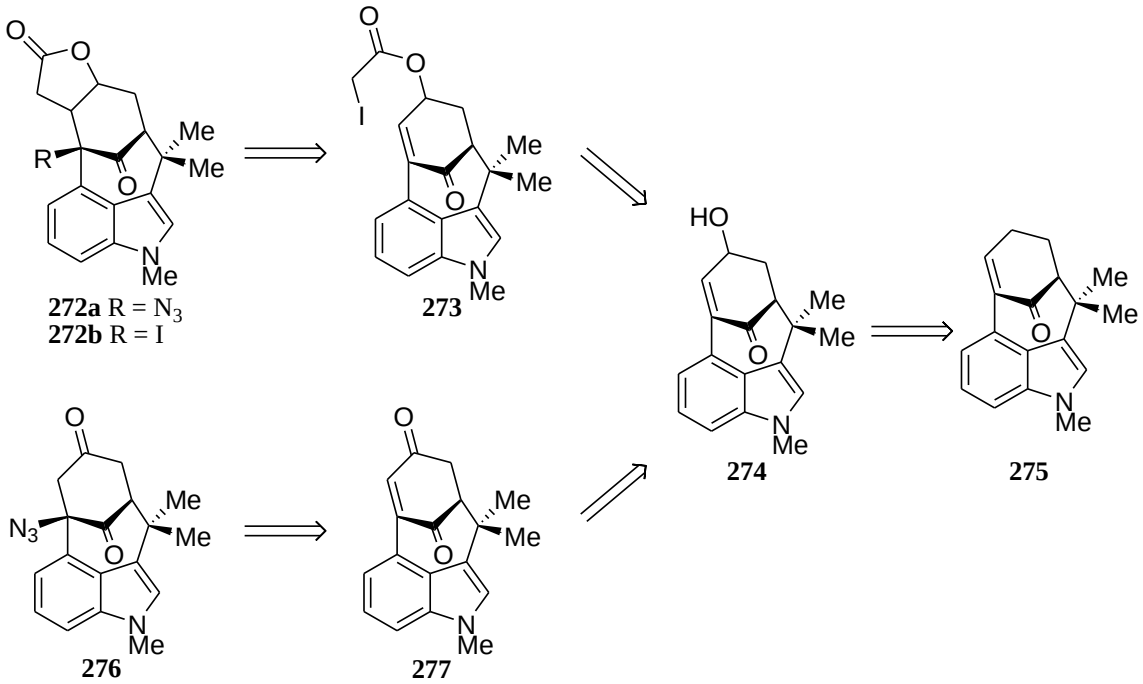
New strategies were explored to install nitrogen at the desired C-11 position of the bicyclo[4.3.1]decane framework. The synthesis of a bridgehead alkene was previously described by our group.[12] Thus, oxidative elimination of selenide **270** using *m*-CPBA afforded bridgehead alkene **271** in 66% yield (Scheme 3.27).[12]



270 **271**

Scheme 3.27

The synthesis of bridgehead alkene **275** possessing the *gem*-dimethyl group was envisaged and synthesis of azide **272a** and **276** could subsequently be investigated. Inspired by Renaud's radical methodology to form carbon-nitrogen bonds,[17] azide **272a** might be obtained from radical cyclisation of iodoester **273** followed by trapping with a sulfonyl azide. Alternatively, it was anticipated that the alkene group of enedione **277** would not be conjugated with the bridging ketone due to strain in the structure. Therefore, bridgehead azide **276** could be generated *via* a regioselective aza-Michael addition of an azide to **277** (Scheme 3.28).



272a R = N_3
272b R = I

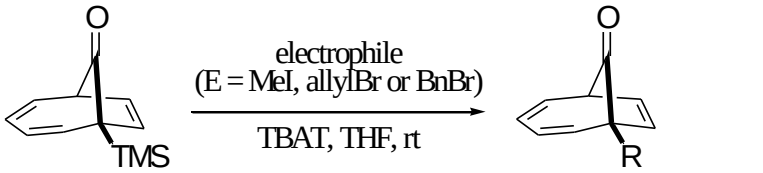
273 **274** **275** **276** **277**

Scheme 3.28

In both cases, a common intermediate, the allylic alcohol **274**, could conceivably be accessed from bridgehead alkene **275**.

3.3.2 Synthesis of oxidised bridgehead alkenes

Studies on enantioselective bridgehead deprotonations, carried out by our group showed the possibility of fluoride-mediated silyl exchange to introduce various substituents.[18] Treatment of **278** with tetrabutylammonium triphenyldifluorosilicate (TBAT),[19] a non-hygroscopic source of fluoride, in the presence of various electrophiles, resulted in the formation of ketones **279**-**281** (Scheme 3.29).

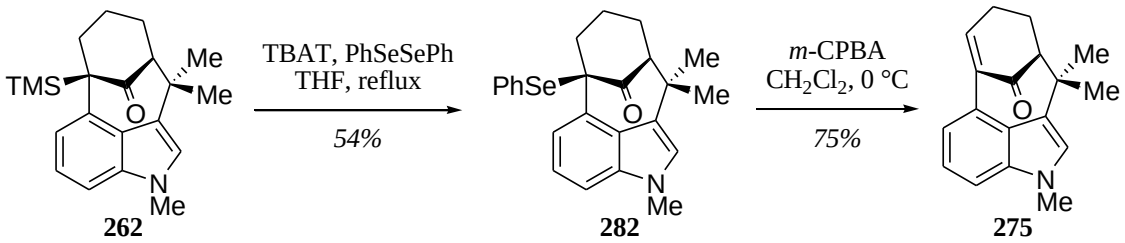


278

279 R = Me (*49%*)
280 R = Allyl (*39%*)
281 R = Bn (*41%*)

Scheme 3.29

Therefore the use of silyl ketone **262**, described previously (see Section 3.2.2), might enable the synthesis of selenide **282**. Indeed, treatment of silyl ketone **262** with TBAT in the presence of diphenyl diselenide afforded bridgehead selenide **282** in a moderate 54% yield. Oxidative elimination using *m*-CPBA provided bridgehead alkene **275** in 75% yield (Scheme 3.30).

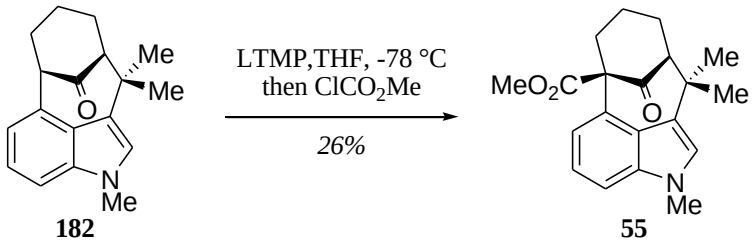


262 **282** **275**

Scheme 3.30

Attempts to install an azide using TsN_3 as the electrophile were unsuccessful and only desilylated compound **182** was observed by ^1H NMR spectroscopy.

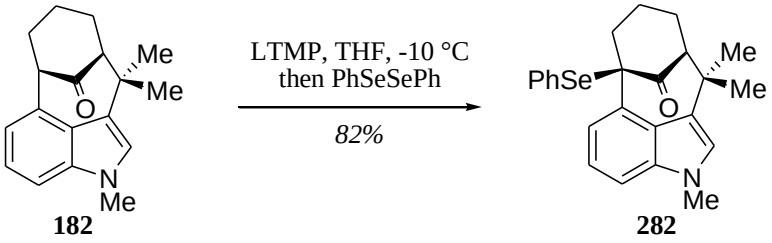
To our surprise, initial studies of regioselective bridgehead deprotonation of **182** followed by an external quench with diphenyl diselenide to obtain **282** proved to be difficult with only traces of the desired compound observed by ^{1}H NMR spectroscopy. Bridgehead deprotonation followed by an external quench with methyl chloroformate proved a little more effective, affording the known ester **55**[20] in 26% yield (Scheme 3.31).



182 **55**

Scheme 3.31

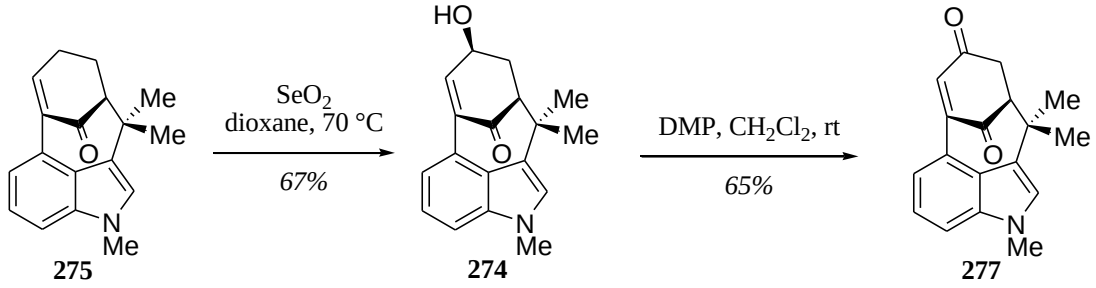
After extensive efforts, it was found that bridgehead selenide **282** was obtained when the reaction was conducted at higher temperatures, to enhance the reactivity between the enolate and the electrophile. Therefore, carrying out the reaction at -10 °C was found to be optimal to obtain **282** in good yield (Scheme 3.32). However these optimised reaction conditions failed to work using tosyl azide in the place of diphenyl diselenide as the electrophile to form azide **227**. At this temperature only degradation was observed.



182 **282**

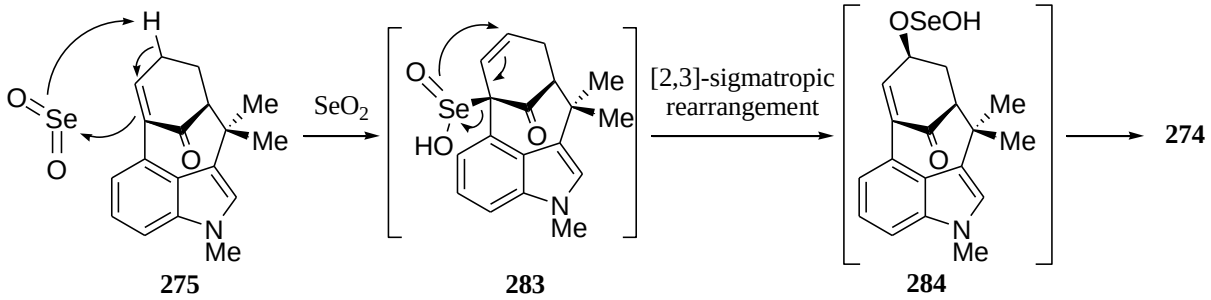
Scheme 3.32

Allylic oxidation of bridgehead alkene **275** using selenium dioxide afforded allylic alcohol **274** as a single diastereoisomer and subsequent treatment with Dess-Martin periodinane (DMP) afforded enedione **277** (Scheme 3.33).



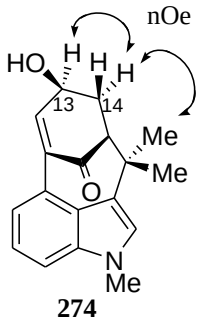
Scheme 3.33

The mechanism of allylic oxidation using selenium dioxide is well established and could explain the stereoselectivity of this reaction.[21,22] The formation of allylic alcohol **274** initiates with an ene reaction between bridgehead alkene **275** and selenium dioxide to give the selenic intermediate **283**. The particular cage-like structure of the tetracycle forces the [2,3]-sigmatropic rearrangement to occur on the exo face of the cyclohexanone to form selenate **284**, which after hydrolysis, provides **274** (Scheme 3.34).



Scheme 3.34

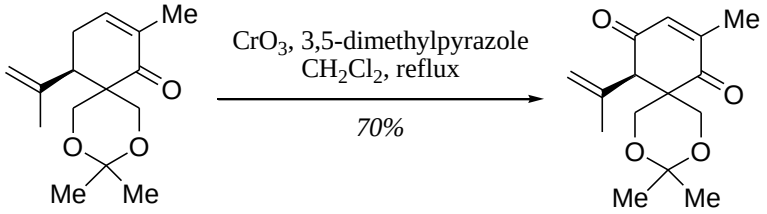
Evidence for the formation of allylic alcohol **274** was provided by mass spectrometry, showing a peak at $[M+Na]^+$ = 304.1317 ($C_{18}H_{19}NO_2Na$ requires 304.1313). Futhermore, the ^1H NMR spectrum showed the presence of a new multiplet integrating for one proton at 4.63-4.66 ppm, and the ^{13}C NMR spectrum showed a CH resonance at 64.8 ppm. Lastly, the stereochemistry at C-13 was determined by its NOESY spectrum, which showed a correlation between the *endo* proton, H-14, and H-13 (Figure 3.2).



274

Figure 3.2

Various methods to convert **275** directly to enedione **277** were also considered. For example, in the synthesis of (–)-samaderine Y, Shing and Yeung described the transformation of enone **285** into enedione **286** upon treatment with CrO_3 and 3,5-dimethylpyrazole (Scheme 3.35).[23]



285 **286**

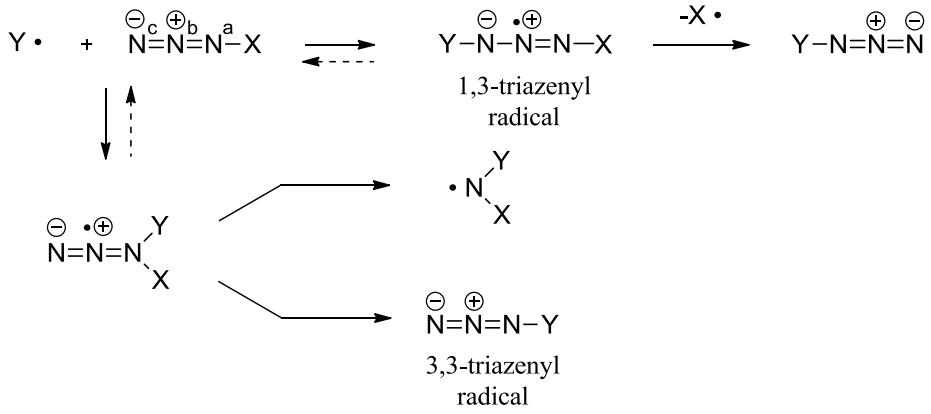
Scheme 3.35

Unfortunately, under these conditions alkene **275** was degraded rapidly. Alternative radical methods using systems such as $Mn_3O(OAc)_9$/^{t}BuOOH,[24] $PhI(OAc)_2$/^{t}BuOOH,[25] or $Pd(OH)_2$-C/^{t}BuOOH,[26] were also attempted. In all cases, degradation was observed without formation of the desired enedione **277** or allylic alcohol **274**.

3.3.3 Allylic alcohol (274) as precursor to a bicyclo[4.3.1]decane core possessing a nitrogen at the bridgehead position

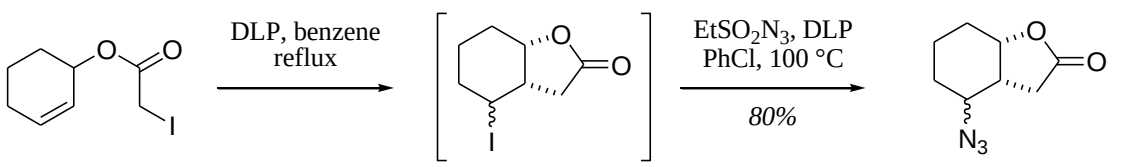
Radical azidation using organic azides has been investigated by Renaud.[17] Organic azides of the type $X\text{-}N_3$ could undergo homolytic addition at N^a or N^c to afford either 3,3- or

1,3-triazenyl radicals. The latter could fragment to liberate radical X• and Y-N_3, which corresponds to an azidation of Y• (Scheme 3.36).



Scheme 3.36

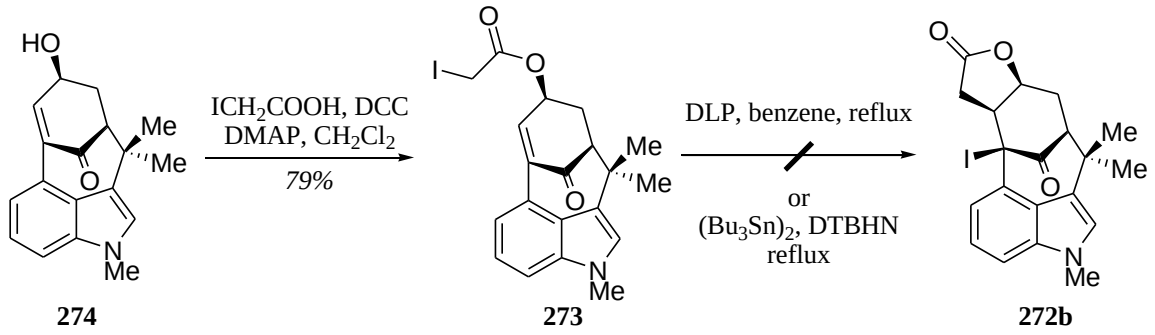
In his work, Renaud used azides as radical traps. Several methods involving the use of sulfonyl azides permitted the formation of new carbon-nitrogen bonds. For example, iodoester **287** underwent radical cyclisation initiated by dilauroyl peroxide (DLP) and iodine transfer provided intermediate **288**. Subsequent treatment with DLP and ethanesulfonyl azide furnished azide **289** in good yield (Scheme 3.37).[27] The reactivity of these sulfonyl azides however suffers from a major drawback in that they do not react with electrophilic radicals. In the case of our study, the first aim was to investigate radical cyclisation followed by the iodine transfer. Curran described iodine transfer cyclisation reaction of **287** using a tin radical initiator and Renaud reported the same transformation using dilauroyl peroxide to obtain lactone **288**.[28,29]



287 **288** **289** (*exo/endo* 74:26)

Scheme 3.37

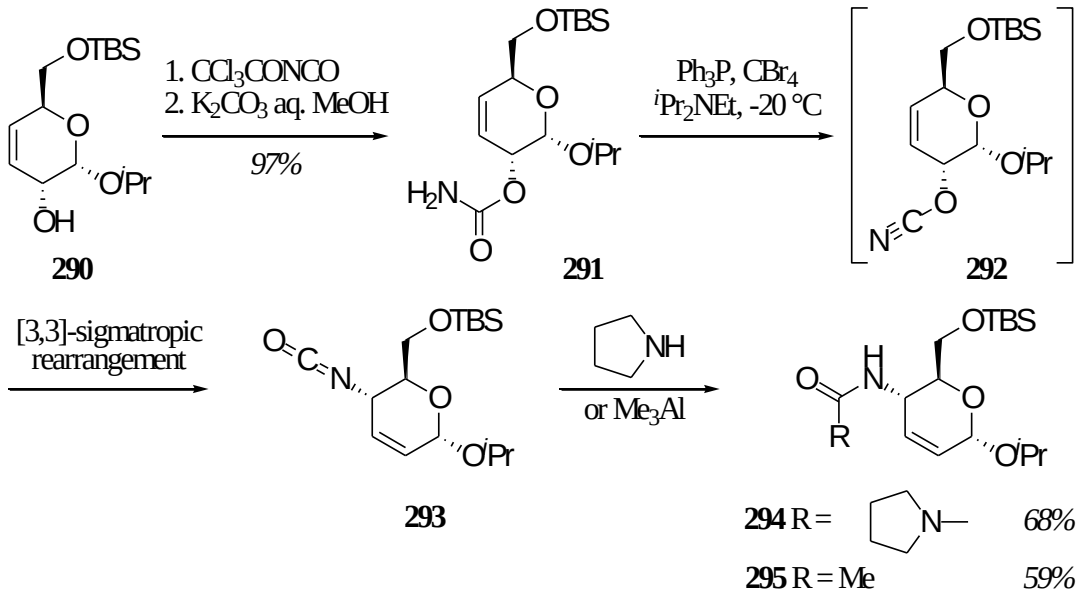
Thus, esterification of allylic alcohol **274** was accomplished by treatment with iodoacetic acid in the presence of DCC and DMAP to afford the radical precursor **273** (Scheme 3.38). With radical precursor **273** in hand, the feasibility of the radical reaction with iodine exchange was first investigated. Radical initiation was attempted using DLP or di-*tert*-butyl-hyponitrite (DTBHN) in the presence hexabutylditin. Unfortunately, the desired lactone **272b** functionalised at the bridgehead position was not observed, instead addition of lauroyl was detected by mass spectrometry, when DLP was used as initiator.



274 **273** **272b**

Scheme 3.38

An alternative route to install nitrogen at the bridgehead position was inspired by studies published by Ichikawa (Scheme 3.39).[30]



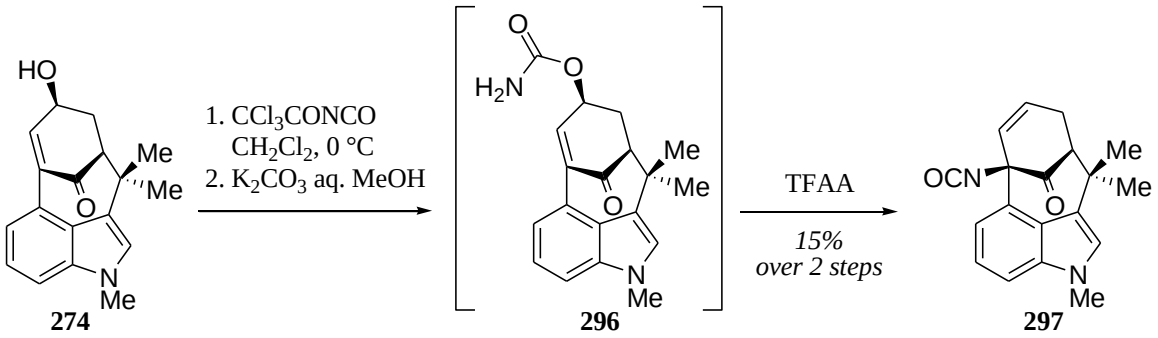
290 **291** **292**

293

Scheme 3.39

His work described the transformation of allyl cyanate to isocyanate *via* a concerted [3,3]-sigmatropic rearrangement. Upon treatment with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate, allylic alcohol **290** afforded carbamate **291** in 97% yield. Subsequent dehydration followed by [3,3]-sigmatropic rearrangement of allyl cyanate **292** furnished allyl isocyanate **293**. Due to the instability of the isocyanate group, **293** was converted into urea **294** or acetamide **295**.[31]

Applying Ichikawa's reaction conditions to allylic alcohol **274** followed by dehydration with triphenyl phosphine and carbon tetrabromide was unsuccessful in our hands. Instead, an alternative dehydration method, also described by Ichikawa, was employed and trifluoroacetic anhydride (TFAA) was used providing allyl isocyanate **297** in 15% yield (Scheme 3.40).

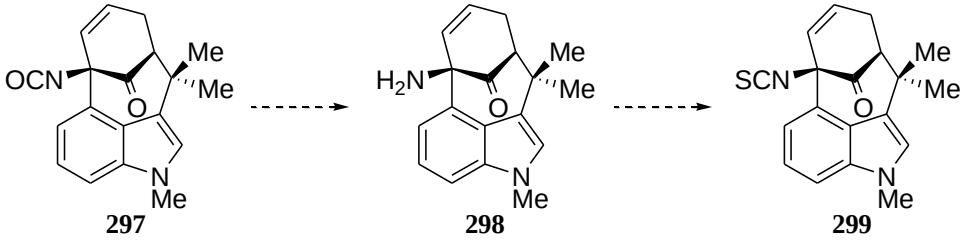


274 **296** **297**

Scheme 3.40

Synthesis of isocyanate **297** was confirmed by IR spectroscopy with an intense stretching band for N=C=O (2223 cm^{-1}), while the ^1H NMR spectrum showed the presence of an alkene group with a multiplet at 5.51-5.57 ppm and a signal at 5.79 ppm (dd, J = 9.4 and 3.0 Hz). Mass spectrometry showed a peak at $[M+Na]^+$= 329.1271 ($C_{19}H_{18}N_2O_2Na$ requires 329.1266).

Although the synthesis of isocyanate **297** was not achieved in good yield, nitrogen functionality was introduced at the desired bridgehead position. Transformation of this isocyanate **297** into the corresponding isothiocyanate **299** should be possible in the same fashion as described (See Scheme 3.1) for the model system (Scheme 3.41).



Scheme 3.41

Although a new route has been established to functionalise the bridgehead position, the low yield of this procedure led back to the primary objective, installation of a bridgehead azide group.

3.3.4 Enedione 277 as precursor to the bicyclo[4.3.1]decane core possessing a nitrogen functionality at the bridgehead position

Molecular models showed that in the bicyclo[4.3.1]decane model system **271** the bridgehead alkene group is not conjugated with the bridging ketone due to strain in the structure (Figure 3.3).[12]

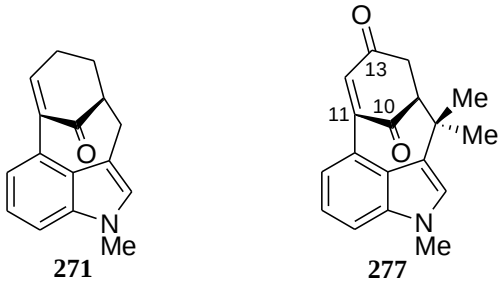
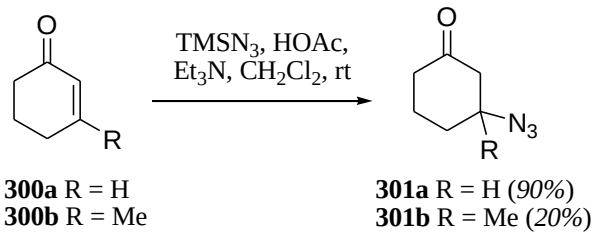


Figure 3.3

In the case of enedione **277**, substantial planarity with the carbonyl at C-13 was expected and so Michael addition of an azide group at C-11 was envisaged.

In 1951, Boyer reported the addition of hydrazoic acid to several conjugated systems.[32] The drawback of this method is the use of this highly toxic and explosive reagent. Therefore, several methods have been developed to avoid to the use of hydrazoic acid, either using safer azide donors[33] or by generating hydrazoic acid *in situ* from trimethylsilyl azide and a carboxylic acid.[34] For example, Miller and co-workers described the addition of azides to α,β-unsaturated compounds, using five equivalents of $TMSN_3$ and acetic acid in the presence of an amine to initiate the formation of hydrazoic acid *in situ* (Scheme 3.42).



300a R = H
300b R = Me

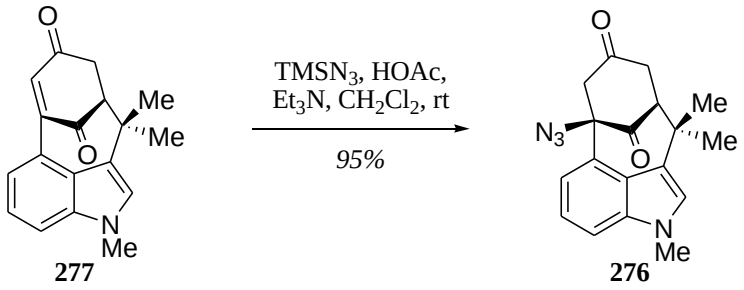
301a R = H (*90%*)
301b R = Me (*20%*)

Scheme 3.42

Under these conditions cyclohexenone **300a** was converted into β-keto azide **301b** in good yield. However, they showed that the efficiency of the azide addition decreased dramatically with enone **301b** disubstituted at the β-position.

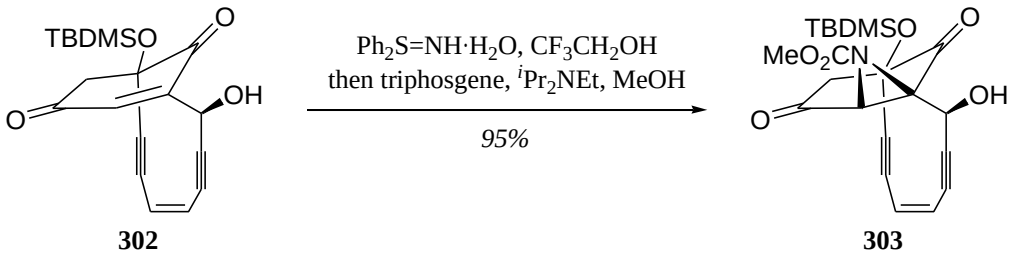
When enedione **277** was subjected to Miller's reaction conditions, we were delighted to observe that the desired azide **276** was isolated in 95% yield (Scheme 3.43). Evidence for the azide group was provided by IR spectroscopy showing an intense stretching band at 2115 cm^{-1}. The regioselectivity of the addition was confirmed by ^{13}C NMR spectroscopy, which showed a quaternary carbon at 74.9 ppm and the presence two CH_2 groups at 42.7 and

55.5 ppm. Mass spectrometry showed one peak at $[M+Na]^+$= 345.1337, which confirmed installation of an azide group ($C_{18}H_{18}N_4O_2Na$ requires 345.1327).



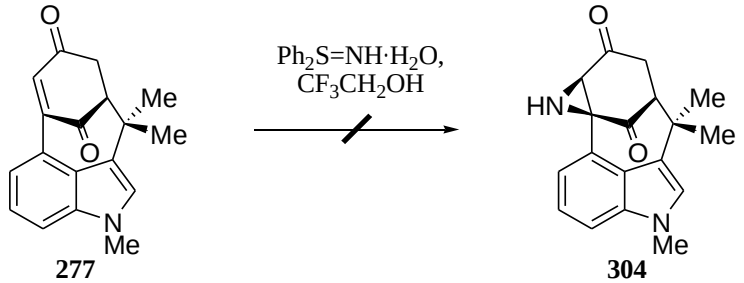
Scheme 3.43

Aziridination of enedione **277** was also envisaged as an alternative route to install nitrogen at the bridgehead position. For example, in studies towards the synthesis of calicheamicinone, Magnus described aziridination of intermediate **302** in 95% (Scheme 3.44).[35]



Scheme 3.44

Unfortunately, upon treatment with diphenylsulfilimine, enedione **277** not even traces of the corresponding aziridine were observed by ^{1}H NMR spectroscopy and mass spectrometry (Scheme 3.45).

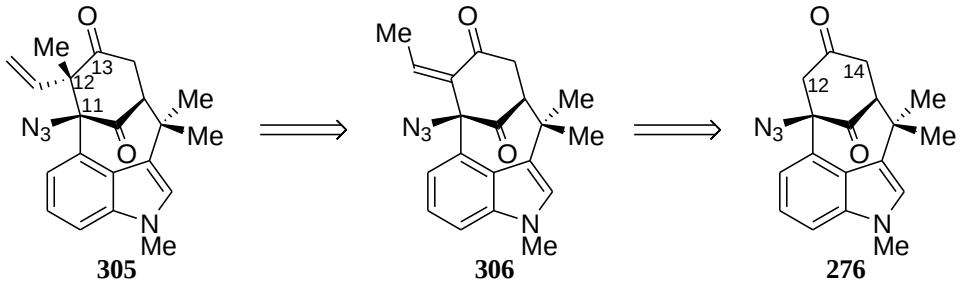


Scheme 3.45

In summary, we have demonstrated the synthesis of isocyanate **297** and azide **276** possessing nitrogen at the bridgehead position, which could lead to the isothiocyanate function present in *N*-methylwelwistatin (**7**).

3.4 Studies towards the installation of the geminal methyl and vinyl groups

It was proposed that the synthesis of the advanced intermediate **305** could arise from azide **276**. Introduction of the methyl group at C-12 might be possible by deprotonation at the γ-position of enone **306** followed by an external quench with methyl iodide. A regioselective aldol reaction at C-12 of **276** with acetaldehyde and subsequent dehydration would give enone **306** (Scheme 3.46).



Scheme 3.46

To functionalise the C-12 position, a regioselective deprotonation of **276** was desired, and so the protons at C-12 and C-14 needed to be differentiated. A computational study of **276** based on MM2 energy minimisation was used to identify its stable conformation. Therefore, the *exo* proton at C-12 seems to be axial while the *exo* proton at C-14 looks equatorial, so a regioselective deprotonation of diketoketone **276** might be possible (Figure 3.4).[36]

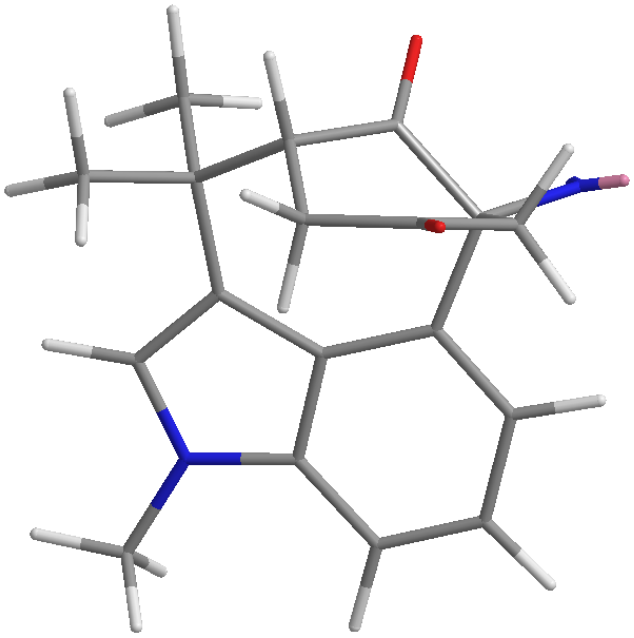
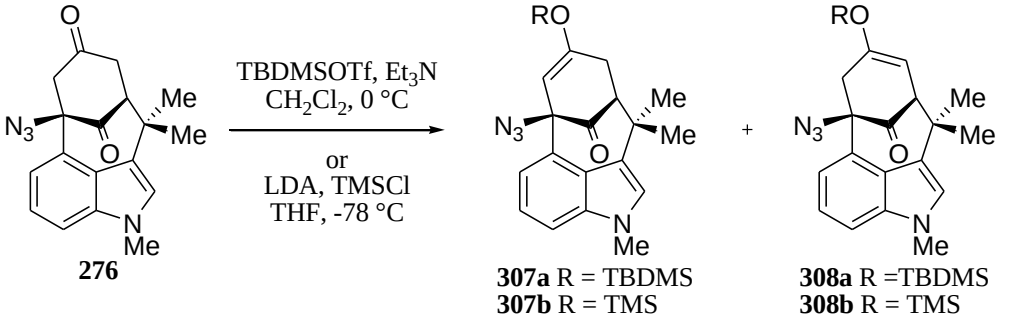


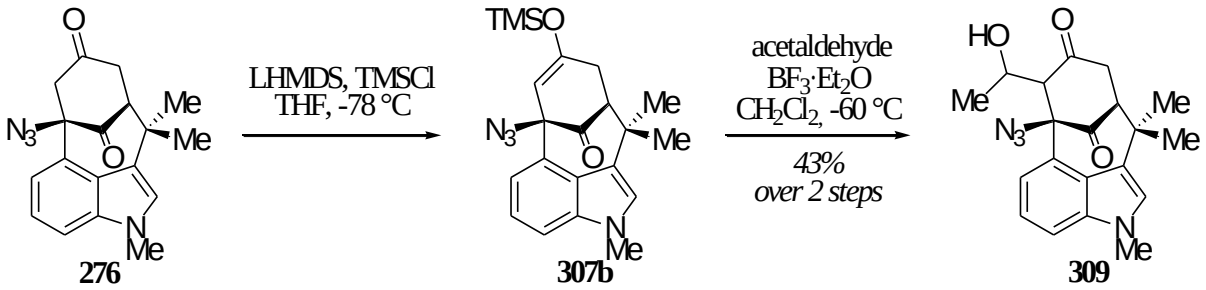
Figure 3.4

To study the regioselectivity of the deprotonation at the α-position, C-12 *versus* C-14, of ketone **276**, formation of the corresponding enol silane was carried out under both thermodynamic and kinetic conditions. Encouraging results were observed, with experimental work confirming the computational study. Under thermodynamic conditions, deprotonation occurred mainly at C-14 and **307a** and **308a** were observed in a 1:2 ratio determined by ^{1}H NMR spectroscopy. Under kinetic conditions, the desired deprotonation at C-12 was favoured in a 4:1 ratio as determined by ^{1}H NMR spectroscopy (Scheme 3.47). Ratios were determined by integration of the signal of the proton of the silyl enol ether at 4.88 ppm (doublet J = 2.3 Hz) and 4.94 ppm (apparent triplet J = 2.9 Hz), respectively attributed to enol silane **307** and **308**. Attempts to purify the product by column chromatography using basified silica resulted in desilylation, so aldolisation was envisaged without any purification.



Scheme 3.47

Satisfyingly, after screening different kinetic conditions in an attempt to favour the formation of the desired enol silane **307b**, an internal quench with TMSCl and the use of LHMDS as the base were found to form exclusively the silyl enol ether **307b**. Subsequent treatment of **307b** with $BF_3{\cdot}Et_2O$ and acetaldehyde at -60 °C provided aldol product **309** as a single diastereoisomer (Scheme 3.48).

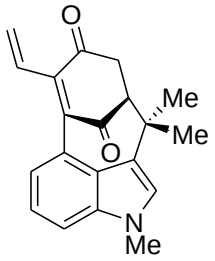


Scheme 3.48

Attempts to purify the alcohol **309** afforded very small quantities of the desired product (27% yield), suggesting a retro-aldol reaction was occurring during the purification process, and demonstrating the instability of this aldol product. However, it was found that column chromatography using a more polar system than normal (toluene/Et_2O, 80/20) minimised retroaldolisation, providing alcohol **309** in 43% yield.

Many methods to perform the dehydration of aldol products to give the corresponding enones have been described. MsCl/DBU,[37] Ac_2O/DMAP/pyridine,[38] TFA,[39] $CeCl_3 \cdot 7H_2O$/NaI[40] were tested on very small scale (5-10 mg) but formation of the desired enone was not observed.

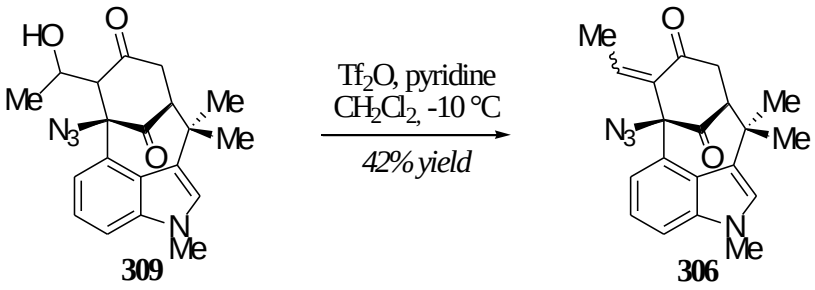
However, when using MsCl and DBU, a new product was isolated (2 mg) and to our surprise, ^{1}H NMR spectroscopy showed the formation of vinyl group with three protons at 5.54 ppm (dd, *J* 11.6 and 1.8 Hz), 6.29 ppm (dd, *J* 17.6 and 1.8 Hz) and 6.67 ppm (dd, *J* 17.6 and 11.6 Hz). Mass spectrometry showed a single peak at $[M+Na]^+$= 328.2, corresponding to loss of HN_3, which was confirmed by IR spectroscopy with disappearance of the intense stretching band of the azide group. Alkene **310** was proposed and was suggested to arise from sequential dehydration and azide elimination (Figure 3.5)



310

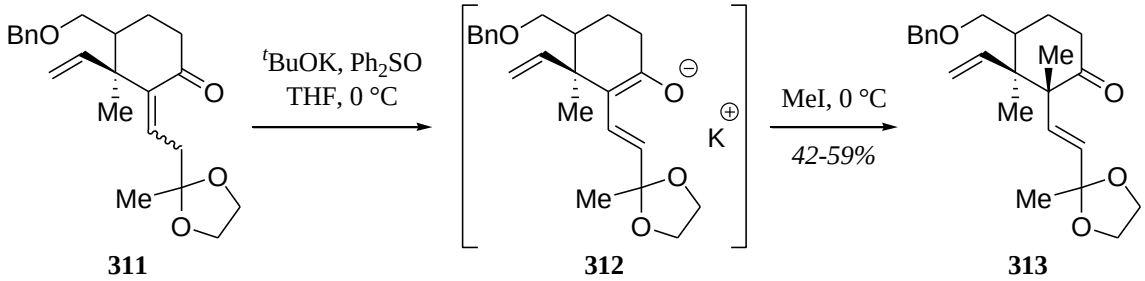
Figure 3.5

Fortunately, the desired enone could be obtained by treatment of **309** with trifluoromethanesulfonic anhydride and pyridine (Scheme 3.49).[41] Evidence for the formation of the desired enone **306** was provided by ^{1}H NMR spectroscopy showing a doublet at 2.14 ppm (*J* = 7.5 Hz), which integrates for three protons and a quadruplet at 6.91 ppm (*J* = 7.5 Hz). IR spectroscopy showed the presence of the azide group (2109 cm^{-1}) and mass spectrometry gave one peak at $[M+Na]^+$= 371.1491 ($C_{20}H_{20}N_4O_2Na$ requires 371.1484).



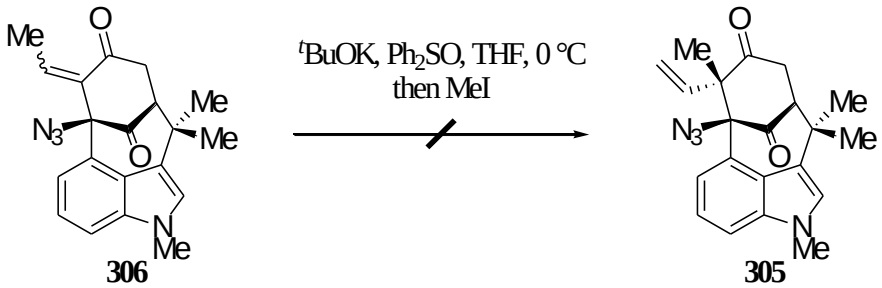
Scheme 3.49

The formation of the vinyl substituent and introduction of the methyl group at C-12 was envisioned in a single step *via* generation of the extended enolate of enone **306** followed by quenching with methyl iodide. Smith and co-workers reported the generation of enolate **312** in their synthesis of a lactone precursor for the synthesis of penitrem D. They used potassium *tert*-butoxide in the presence of diphenyl sulfoxide, followed by addition of methyl iodide, to afford methylated derivative **313** in moderate yield (Scheme 3.50).[42]



Scheme 3.50

Treatment of enone **306** under these reaction conditions did not provide the methylated derivative at C-12 (Scheme 3.51).



Scheme 3.51

The problem encountered seemed to be the azide group at the bridgehead of the enone **306**. The ^{1}H NMR spectrum of the crude material showed the presence of a vinyl group but the vinyl peaks are very similar to those in the byproduct **310**. This could probably be due to the elimination of the azide group as observed previously.

3.5 Summary

We have demonstrated that a nitrogen functionality could be introduced at the bridgehead C-11 position *via* a [3,3]-sigmatropic rearrangement or an aza-Michael addition, which could provide a rapid transformation to the required isothiocyanate functionality present in the natural product **7**. Moreover, a regioselective deprotonation, aldol functionalisation and dehydration afforded enone **306**. This advanced intermediate is potentially very useful for the total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**7**).

3.6 References

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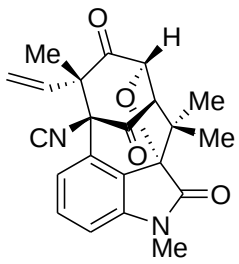
CHAPTER 4

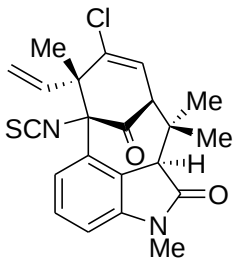
Conclusions

4.1 Epilogue

During the course of this work towards the total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**7**), two research groups recently published the first total syntheses of two members of the welwitindolinone family possessing the bicyclo[4.3.1]decane scaffold. Firstly, Rawal and co-workers reported the synthesis of *N*-methylwelwitindolinone D isonitrile (**19**),[1] and secondly Garg and co-workers described the synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**7**) (Figure 4.1).[2]



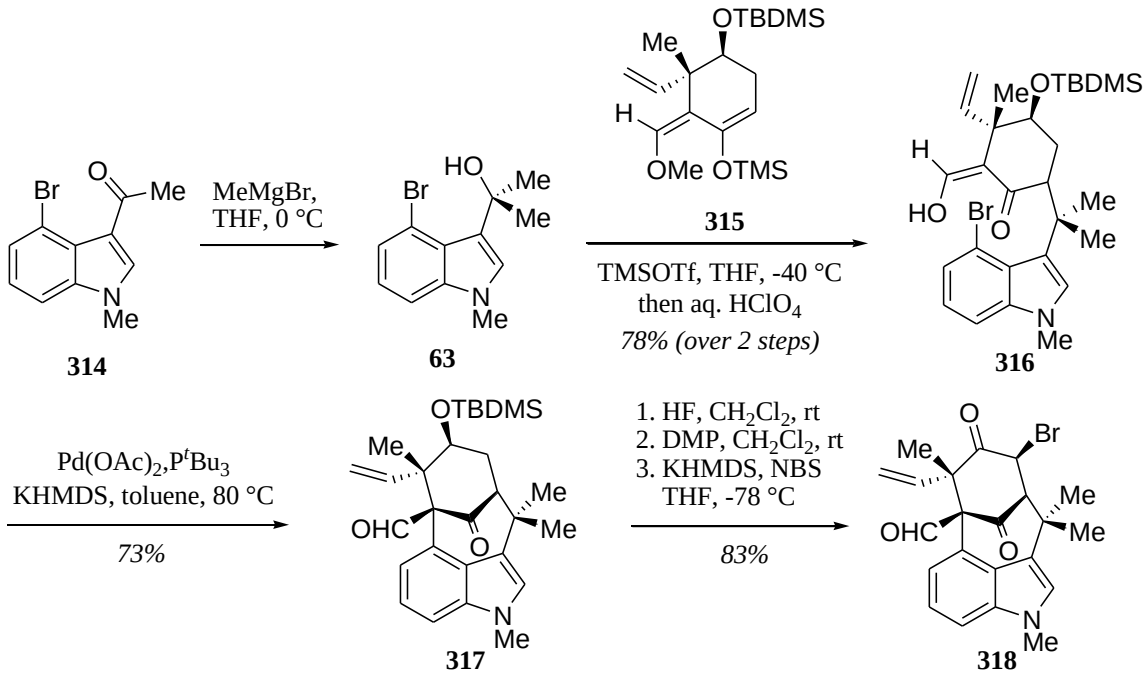
N-Methylwelwitindolinone D isonitrile (**19**)



N-Methylwelwitindolinone C isothiocyanate (**7**)

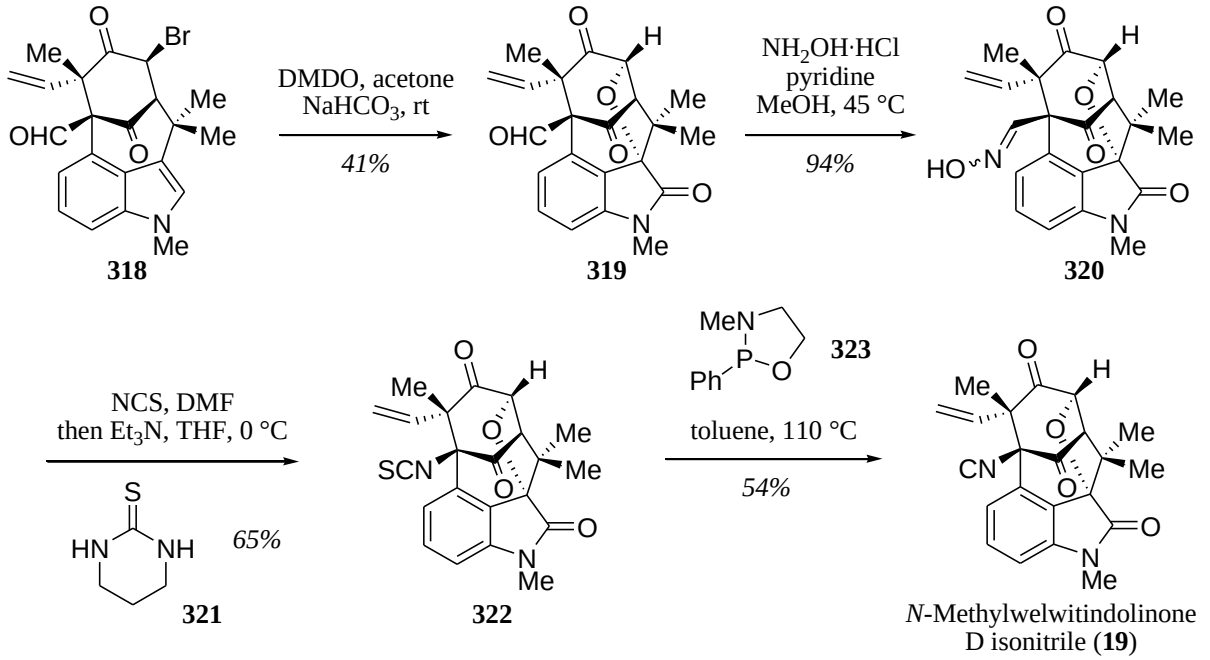
Figure 4.1

The synthesis of **19** began with acetyl indole **314**, which upon addition of methylmagnesium bromide provided the unstable tertiary alcohol **63**. Subsequent alkylative coupling of **63** with cyclohexanone intermediate **315** was achieved using TMSOTf and aqueous acidic work up furnished the vinylogous acid **316** as a single diastereoisomer in 78% yield. The formation of the bicyclo[4.3.1]decane framework was accomplished in 73% yield *via* a palladium-catalysed intramolecular enolate arylation. Removal of the TBDMS protecting group, followed by oxidation of the resultant alcohol and subsequent α-bromination afforded derivative **318** (Scheme 4.1).



Scheme 4.1

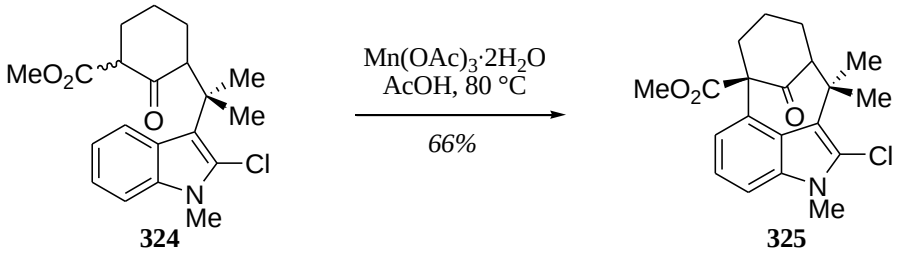
Diastereoselective oxidation of indole **318** with DMDO followed by spontaneous cyclisation provided oxindole **319** in moderate yield (Scheme 4.2).



Scheme 4.2

Conversion of the aldehyde **319** to the corresponding oxime **320** and subsequent treatment with *N*-chlorosuccinimide followed by thiourea **321** and triethylamine furnished isothiocyanate **322**. Desulfurisation of the isothiocyanate functional group using oxazaphospholidine **323** completed the synthesis of *N*-methylwelwitindolinone D isonitrile (**19**) in 14 steps and a 4.8% overall yield.

After reporting the synthesis of *N*-methylwelwitindolinone D isonitrile (**19**), Rawal also described another method to generate the desired tetracycle *via* an oxidative cyclisation using manganese(III) acetate.[3] This type of cyclisation usually occurrs on the pyrrolo part of the indole and therefore protection of C-2 position of the indole was necessary. Chlorine was employed, not only to block the position but to allow a subsequent transformation into the corresponding oxindole. For example, treatment of chloroindole **324** with manganese(III) acetate led to the desired bicyclo[4.3.1]decane framework **325** in 66% yield (Scheme 4.3).

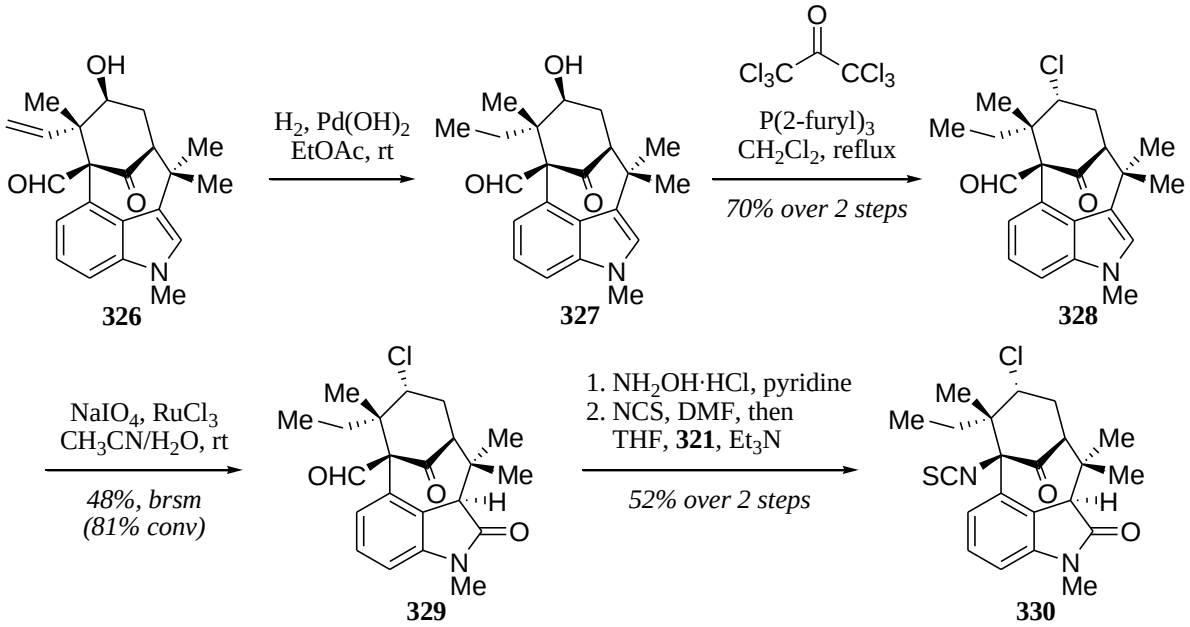


324 **325**

Scheme 4.3

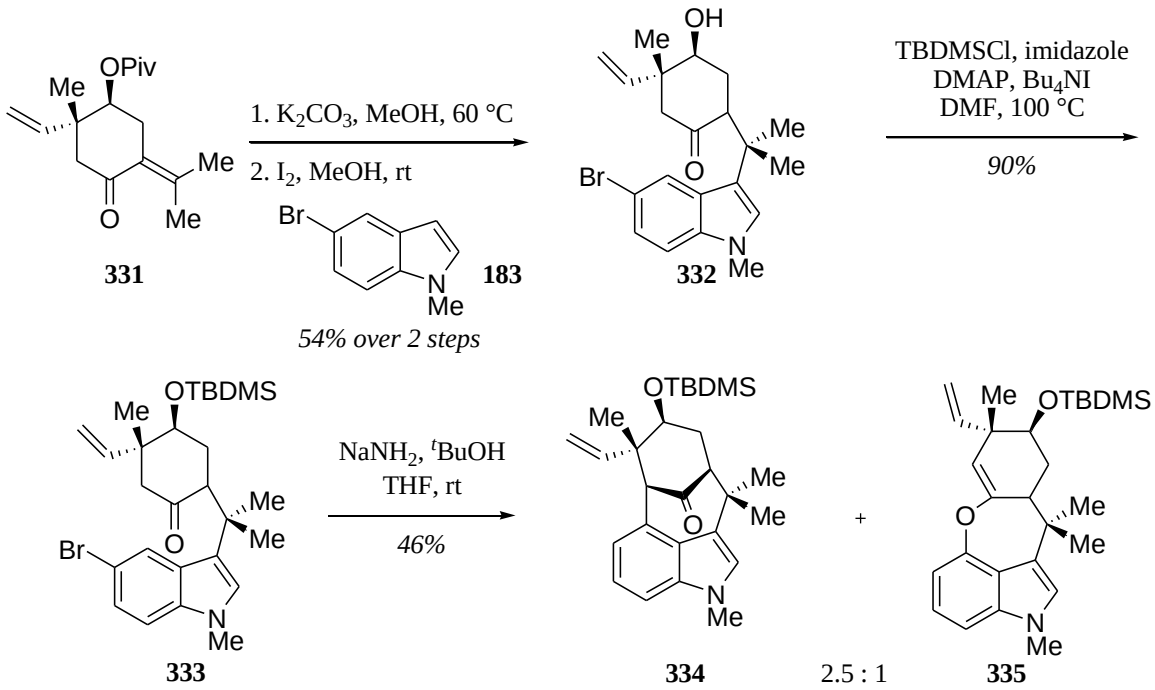
Rawal has also described the synthesis of the 20,21-dihydro *N*-methylwelwitindolinone B isothiocyanate **330**.[4] Aldehyde **326** was available through a seven-step sequence previously employed in the total synthesis of *N*-methylwelwitindolinone D isonitrile (**19**). The vinyl group of **326** was hydrogenated to prevent its participation during the deoxygenative chlorination of the alcohol moiety. Alcohol **327** was treated with the electron-deficient phosphine, tri(2-furyl)phosphine, and hexachloroacetone to afford chloride **328**. Upon

treatment with RuO_4, indole **328** was oxidised to the corresponding oxindole **329** in moderate yield but with the desired stereochemistry at the C-3 position. In the same fashion as in the synthesis of **19**, the isothiocyanate functional group was achieved in two steps to furnish **330** (Scheme 4.4).



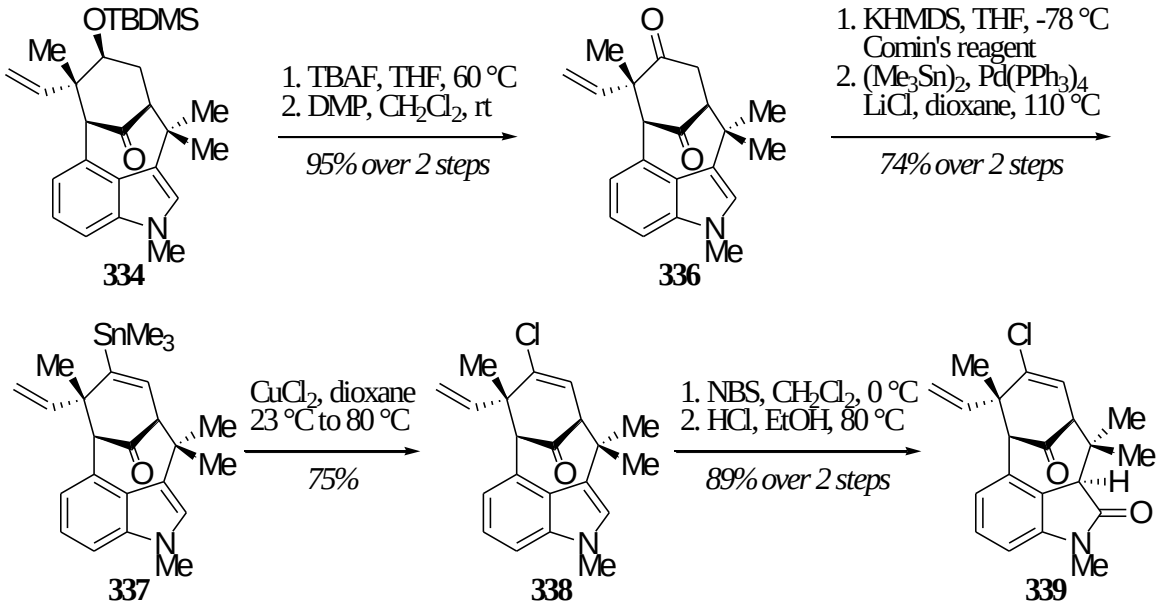
Scheme 4.4

The synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**7**) by Garg and co-workers started with the removal of the pivalate protecting group of enone **331**, obtained in five steps from (*S*)-carvone. Iodine-mediated conjugate addition of indole **183**, followed by protection of the alcohol **332** with TBDMS under relatively forcing conditions, afforded the cyclisation precursor **333**. The bicyclo[4.3.1]decane skeleton was obtained *via* an indolyne cyclisation providing the desired tetracycle **334** alongside **335** in a 2.5:1 ratio, respectively (Scheme 4.5).



Scheme 4.5

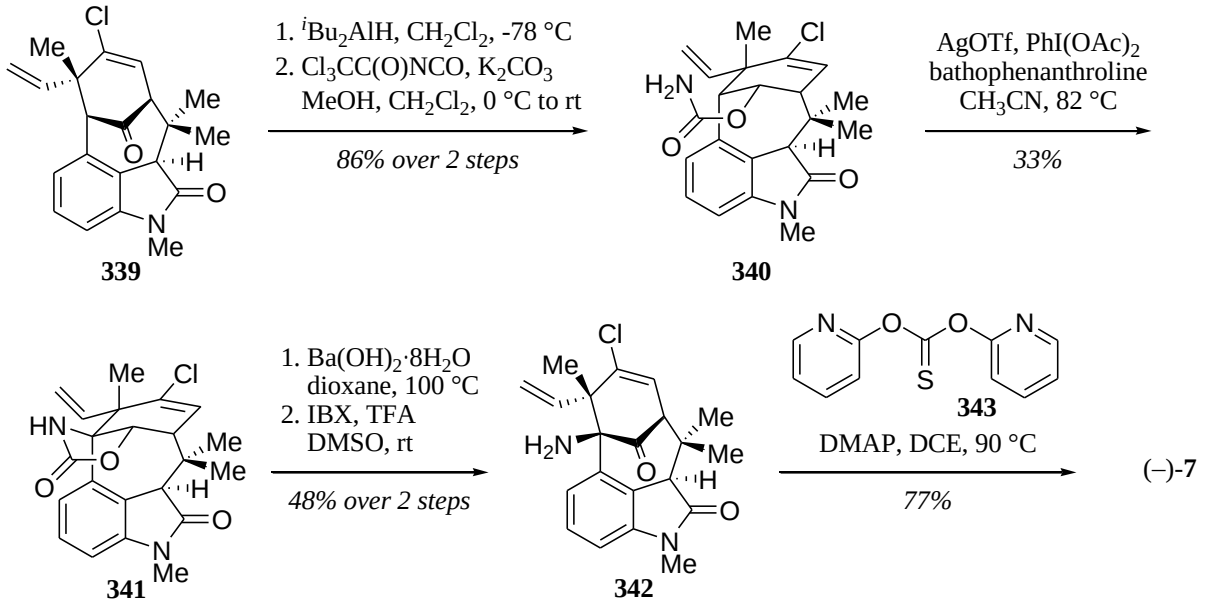
Removal of the TBDMS protecting group with TBAF and oxidation of the resultant alcohol with DMP provided diketone **336**. Vinyl stannane **337** was obtained in a two-step sequence involving the formation of an enol triflate using KHMDS and Comin's reagent, and followed by a palladium-catalysed stannylation (Scheme 4.6).



Scheme 4.6

Chlorodestannylation of **337** with $CuCl_2$ furnished vinyl chloride derivative **338**. Bromination of indole **338** with NBS followed by hydrolysis afforded oxindole **339** with the correct stereochemistry at C-3.

Installation of the isothiocyanate function at the bridgehead position was realised *via* a nitrene insertion (Scheme 4.7). Thus, reduction of the bridging ketone with $^{i}Bu_2AlH$ and subsequent carbamoylation led to carbamate **340**. A nitrene insertion occurred by exposure of **340** to AgOTf, bathophenanthroline and $PhI(OAc)_2$ to yield oxazolidinone **341**. A barium hydroxide-mediated hydrolysis followed by oxidation with IBX provided aminoketone **342**. Finally, transformation of the bridgehead amine into the corresponding isothiocyanate was realised upon treatment with thiocarbonate **343**, which completed the first synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**7**). The synthesis of **7** was accomplished in 17 steps in 0.8% overall yield from carvone derivative **331**.

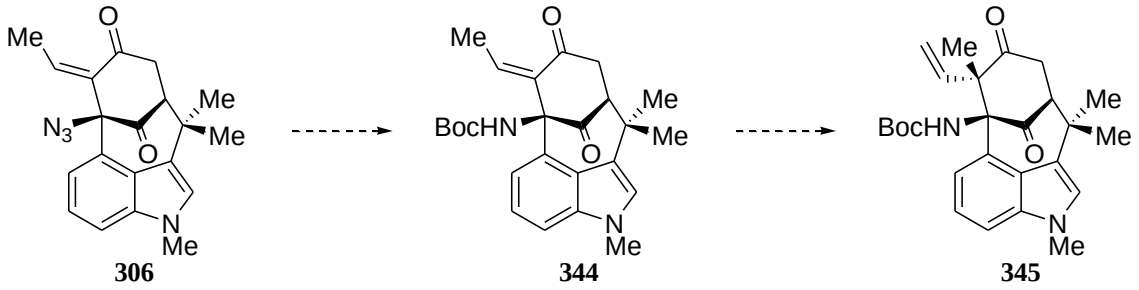


Scheme 4.7

In summary, a breakthrough was achieved in 2011 by Rawal and Garg with respectively the first total syntheses of *N*-methylwelwitindolinone D isonitrile (**19**) and (–)-*N*-methylwelwitindolinone C isothiocyanate (**7**).

4.2 Future studies

The results disclosed in this thesis could provide an alternative route to the synthesis of *N*-methylwelwitindolinone C isothiocyanate (**7**). In order to complete this synthesis, the major challenge is installation of a methyl group on to C-12. A possible approach to prevent the elimination of the azide group at the bridgehead could be envisaged by reduction of this functional group into the corresponding amine, followed by Boc-protection to provide **344**. As originally planned, deprotonation to generate the extended enolate followed by quenching with methyl iodide could furnish diketone **345** (Scheme 4.7).



Scheme 4.7

Further manipulations, involving the formation of the vinyl chloride, oxidation of the indole ring and deprotection of the amine could achieve the formal synthesis of *N*-methylwelwitindolinone C isothiocyanate (**7**).

4.3 References

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CHAPTER 5

Experimentals

General details

All reactions were performed under an atmosphere of argon in dry glassware unless otherwise stated. THF was distilled immediately prior to use from sodium and benzophenone; CH_2Cl_2 was distilled from calcium hydride. All other dry solvents and reagents were used as received from commercial suppliers unless otherwise stated. Solvents and solutions for radical reactions were degassed before use by bubbling a steady stream of dry N_2 gas through them for 30 minutes.

Infra-red spectra were recorded neat on a Perkin-Elmer Spectrum 100 FTIR spectrometer. Wavelengths (ν) are reported in cm^{-1}. Mass spectra were obtained using a VG Micromass 70E or VG Micron Autospec spectrometer, using electrospray ionisation (ESI) with *meta*-nitrobenzyl alcohol as matrix. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected.

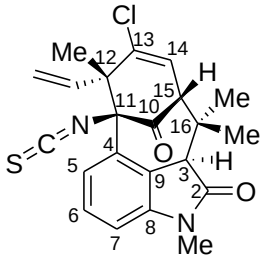
All ^1H NMR and ^{13}C NMR experiments were recorded using Bruker AV300, AV400, AVIII300 and AVIII400, spectrometers at 300 K. ^{13}C NMR spectra were recorded using the PENDANT pulse sequence from the Bruker standard pulse program library. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are quoted in Hz to one decimal place. For spectra recorded in chloroform-*d* the 7.26 ppm resonance of residual $CHCl_3$ for proton spectra and 77.00 ppm resonance of $CDCl_3$ for carbon spectra were used as internal references. For spectra recorded in methanol-d_4 the 3.34 ppm resonance of residual CH_3OH for proton spectra and 49.86 ppm resonance of CD_3OD for carbon spectra were used as internal references. Spectral data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constant, number of protons, assignment); and for ^{13}C NMR spectra: chemical shift (multiplicity, assignment). The following abbreviations were used for multiplicity in ^1H NMR spectra: s (singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublets), td (triplet

of doublets), dm (doublet with unresolved fine coupling), br (broad), app (signal with well defined multiplicity that may not be expected), m (multiplet). In the case of ambiguous assignments, 2-dimensional homonuclear (^{1}H-^{1}H) and heteronuclear (^{1}H-^{13}C) NMR experiments were used. Full assignment has been conducted for several representative structures whereas analogous compounds were only partially assigned.

Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium silica gel plates (Kieselgel 60 F254). Visualisation was achieved by a combination of ultraviolet light (254 nm) and acidic potassium permanganate or anisaldehyde. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and Co.).

Nomenclature

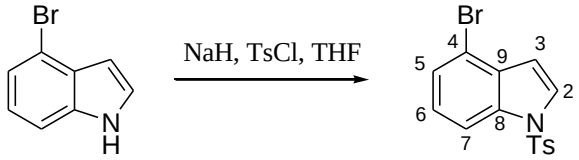
The numbering of compounds (core structure) used for NMR assignments is based on the isolation paper published by Moore and co-workers (*J. Am. Chem. Soc.* **1994**, *116*, 9935) (Figure 5.1).



7

Figure 5.1

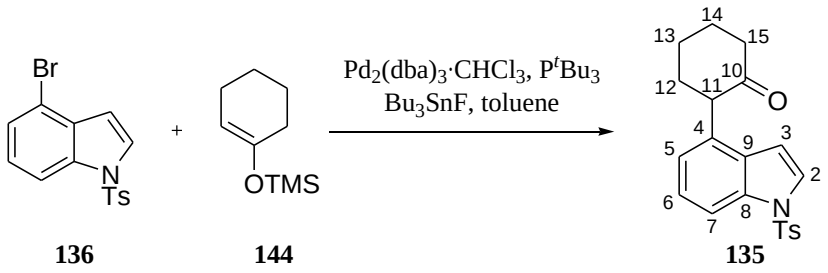
4-Bromo-1-tosyl-1*H*-indole (136)[1]



136

A solution of 4-bromoindole (500 mg, 10.2 mmol) in THF (9 mL) was added slowly, over 5 min, to a suspension of NaH (122 mg, 60% dispersion in mineral oil, 14.9 mmol) in THF (3 mL) at 0 °C. After 30 min, a solution of TsCl (535 mg, 11.2 mmol) in THF (5 mL) was added dropwise, over a period of 5 min, at 0 °C and the mixture was stirred overnight at rt. The excess hydride was destroyed by addition of a solution of MeOH/H_2O (1/1, 20 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 95/5) to provide sulfonamide **136** (864 mg, 97%) as a white solid; mp 120-121 °C [lit.,[1] 120-122 °C]; R_f 0.67 (petroleum ether/EtOAc, 90/10); IR υ_{max} 1369, 1165, 1127, 1003, 751, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, ArC*H*$_3$), 6.73 (d, *J* 3.7, 1H, 3-C*H*), 7.17 (app t, *J* 8.1, 1H, 6-C*H*), 7.24 (d, *J* 8.4, 2H, Ar*H*), 7.39 (d, *J* 7.8, 1H, 5-C*H*), 7.62 (d, *J* 3.7, 1H, 2-C*H*), 7.76 (d, *J* 8.4, 2H, Ar*H*), 7.95 (d, *J* 8.3, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3, $ArCH_3$), 108.8 (CH, 3-CH), 112.6 (CH, 7-CH), 115.0 (C, 4-C), 125.5 (CH, 6-CH), 126.2 (CH, 5-CH), 126.8 (CH, ArCH), 126.9 (CH, 2-CH), 126.9 (C, 9-C), 131.0 (CH, ArCH), 131.4 (C, 8-C), 135.0 (C, ArC), 145.3 (C, ArC); MS (ESI) *m/z* 372.1 ([M+Na]$^+$, 100%), 374.1 (97%); HRMS (ESI) *m/z* 371.9664 [M+Na]$^+$, $C_{15}H_{12}NO_2S^{79}BrNa$ requires 371.9670.

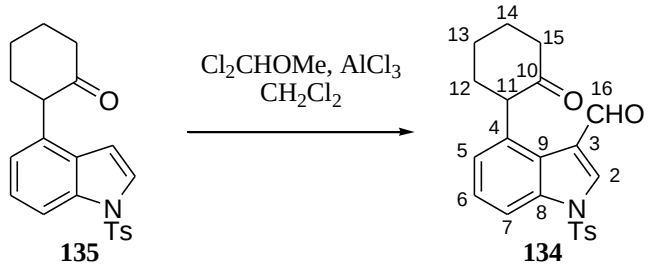
2-(1'-Tosyl-1*H*-indol-4'-yl)cyclohexanone (135)



136 **144** **135**

General procedure A: A solution of P^tBu_3 (1 M solution in toluene, 970 μL, 0.97 mmol) was added to a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (418 mg, 0.40 mmol) and Bu_3SnF (5.00 g, 16.2 mmol) in toluene (20 mL). A solution of indole **136** (2.83 g, 8.08 mmol) and silyl enol ether **144**[2] (2.75 g, 16.2 mmol) in toluene (10 mL) was added and the mixture was heated under reflux (130 °C) for 17 h. After cooling to rt, the mixture was diluted with Et_2O (30 mL), filtered through a plug of silica and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10 then 80/20) to provide cyclohexanone derivative **135** as a yellow foam (1.87 g, 63%); R_f 0.38 (petroleum ether/EtOAc, 70/30); mp 95-97 °C; IR υ_{max} 2937, 1709, 1360, 1164, 1130, 758, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80-1.90 (m, 2H, 13-CH_2 and 14-CH_2), 2.00-2.33 (m, 4H, 12-CH_2, 13-CH_2 and 14-CH_2), 2.35 (s, 3H, CH_3), 2.47-2.61 (m, 2H, 15-CH_2), 3.87 (dd, *J* 12.3, 5.6, 1H, 11-C*H*), 6.50 (d, *J* 3.8, 1H, 3-C*H*), 7.04 (d, *J* 7.4, 1H, 5-C*H*), 7.22 (d, *J* 8.5, 2H, Ar*H*), 7.28 (app t, *J* 7.9, 1H, 6-C*H*), 7.56 (d, *J* 3.8, 1H, 2-C*H*), 7.77 (d, *J* 8.5, 2H, Ar*H*), 7.88 (d, *J* 8.4, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3, $ArCH_3$), 25.5 (CH_2, 13-CH_2), 27.7 (CH_2, 14-CH_2), 34.5 (CH_2, 12-CH_2), 42.3 (CH_2, 15-CH_2), 54.8 (CH, 11-CH), 107.1 (CH, 3-CH), 112.2 (CH, 7-CH), 122.5 (CH, 5-CH), 124.6 (CH, 6-CH), 125.8 (CH, 2-CH), 125.8 (C, 9-C), 126.9 (CH, ArCH), 129.9 (CH, ArCH), 132.0 (C, 4-C), 134.8 (C, ArC), 135.4 (C, 8-C), 144.9 (C, ArC), 209.3 (C, 10-C); MS (ESI) *m/z* 390.1 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 390.1134 $[M+Na]^+$, $C_{21}H_{21}NO_3SNa$ requires 390.1140.

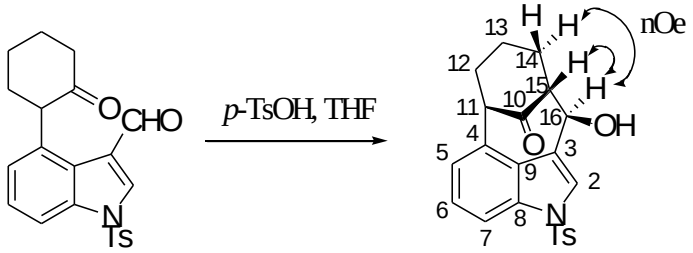
4-(2'-Oxocyclohexyl)-1-tosyl-1*H*-indole-3-carbaldehyde (134)



A solution of indole **135** (1.08 g, 2.94 mmol) in CH_2Cl_2 (12 mL) was added to a solution of dichloromethyl methyl ether (794 μL, 8.82 mmol) and $AlCl_3$ (1.18 g, 8.82 mmoL) in CH_2Cl_2 (12 mL) at -78 °C. The reaction mixture was stirred for 3.5 h at this temperature, and then quenched at -78 °C with $NaHCO_3$ solution (25 mL of a saturated aqueous solution) and warmed to rt. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to give formylated indole **134** as a white solid (720 mg, 62%); R_f 0.46 (petroleum ether/AcOEt, 60/40); mp 190-192 °C; IR υ_{max} 2935, 1704, 1693, 1368, 749, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.54-1.70 (m, 1H, 14-C*H*$_2$), 1.92-2.09 (m, 3H, 13-C*H*$_2$ and 12-C*H*$_2$), 2.14-2.27 (m, 1H, 14-C*H*$_2$), 2.27-2.36 (m, 1H, 12-C*H*$_2$), 2.38 (s, 3H, ArC*H*$_3$), 2.47 (d, *J* 13.0, 1H, 15-C*H*$_2$), 2.75-2.95 (br s, 1H, 15-C*H*$_2$), 5.05-5.23 (br s, 1H, 11-C*H*), 7.18 (d, *J* 7.6, 1H, 5-C*H*) 7.30 (d, *J* 8.4, 2H, Ar*H*), 7.39 (app t, *J* 8.0, 1H, 6-C*H*), 7.86 (dm, *J* 8.4, 3H, Ar*H* and 7-C*H*), 8.27 (s, 1H, 2-C*H*), 9.78 (s, 1H, 16-C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) 21.6 (CH_3, $ArCH_3$), 25.7 (CH_2, 13-CH_2), 28.0 (CH_2, 14-CH_2), 33.9 (CH_2, 12-CH_2), 42.1 (CH_2, 15-CH_2), 54.9 (CH, 11-CH), 111.8 (CH, 7-CH), 123.8 (C, 3-C), 123.8 (CH, 5-CH), 124.0 (C, 9-C), 126.3 (CH, 6-CH), 127.4 (CH, ArCH), 130.4 (CH, ArCH), 134.2 (C, 4-C), 135.1 (C, ArC), 136.1 (C, 8-C), 141.0 (CH, 2-CH), 146.3 (C, ArC), 184.3 (CH, 16-CHO), 210.7 (C, 10-C); MS (ESI) *m/z*

418.1 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 418.1091 [M+Na]$^+$; $C_{22}H_{21}NO_4SNa$ requires 418.1089.

Bicyclo[4.3.1]decane compound (148)

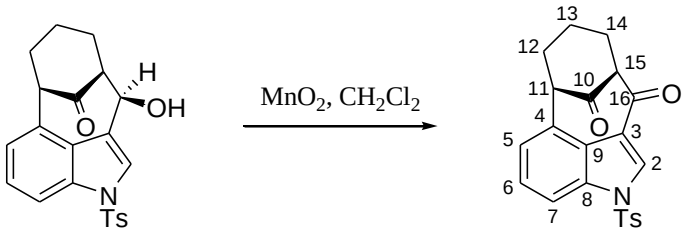


134 **148**

A solution of *p*-TsOH (500 mg, 0.53 M in dry THF) was prepared and dried over 3 Å molecular sieves with stirring for 1 h. The solution of *p*-TsOH (0.36 mL, 0.19 mmol) was added to a solution of aldehyde **134** (74 mg, 0.19 mmol) in THF (3 mL) and the resultant mixture was heated at 50 °C. After 24 h, the solution was cooled to rt and a freshly prepared solution of *p*-TsOH (0.36 mL, 0.19 mmol) was added. The reaction mixture was heated at 50 °C for a further 24 h, then $NaHCO_3$ solution (10 mL of a saturated aqueous solution) was added at rt. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 80/20) to provide cyclised product **148** as a yellow foam (29 mg, 39%); R_f 0.21 (petroleum ether/EtOAc, 70/30); mp 129-130 °C; IR υ_{max} 3425, 2935, 1699, 1368, 1174, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.33 (m, 2H, 13-C*H*$_2$), 1.76-1.91 (m, 2H, 12-C*H*$_2$ and 14-C*H*$_2$), 2.10-2.21 (m, 1H, 12-C*H*$_2$), 2.31-2.42 (m, 1H, 14-C*H*$_2$), 2.35 (s, 3H, ArC*H*$_3$), 3.11-3.14 (m, 1H, 15-C*H*), 3.93 (br s, 1H, 11-C*H*), 4.97 (dd, *J* 5.6, 1.9, 1H, 16-C*H*), 6.97 (d, *J* 7.4, 1H, 5-C*H*), 7.23 (d, *J* 8.4, 2H, Ar*H*), 7.28 (app t, *J* 7.9, 1H, 6-C*H*), 7.75-7.79 (m, 3H, Ar*H* and 2-C*H*), 7.88 (d, *J* 8.4, 1H, 7-C*H*), OH not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (CH_2, 13-

CH_2), 21.6 (CH_3, $ArCH_3$), 24.0 (CH_2, 14-CH_2), 36.8 (CH_2, 12-CH_2), 56.1 (2 × CH, 11-CH and 15-CH), 67.7 (CH, 16-CH), 112.0 (CH, 7-CH), 116.0 (C, 3-C), 123.0 (CH, 5-CH), 123.5 (C, 9-C), 125.4 (CH, 2-CH), 125.4 (CH, 6-CH), 126.9 (CH, ArCH), 127.0 (C, 4-C), 129.9 (CH, ArCH), 133.3 (C, 8-C), 135.1 (C, ArC), 145.2 (C, ArC), 212.3 (C, 10-C); MS (ESI) *m/z* 418.2 $[M+Na]^+$, HRMS (ESI) *m/z* 418.1074 ($[M+Na]^+$, 100%); $C_{22}H_{21}NO_4SNa$ requires 418.1089.

Ketone compound (133)

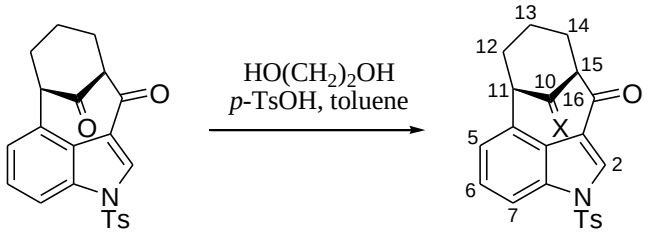


148 **133**

Manganese(IV) oxide (1.18 g, 13.6 mmol) was added to a solution of alcohol **148** (210 mg, 0.53 mmol) in CH_2Cl_2 (17 mL). The resulting suspension was stirred for 3.5 h at rt. The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to provide diketone **133** (146 mg, 70%) as a white solid; R_f 0.37 (petroleum ether/EtOAc, 70/30); mp 104-105 °C; IR υ_{max} 2936, 1705, 1655, 1521, 1377, 1163, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53-1.63 (m, 2H, 13-C*H*$_2$), 2.11-2.31 (m, 3H, 12-C*H*$_2$ and 14-C*H*$_2$), 2.36 (s, 3H, ArC*H*$_3$), 2.43 (dm, *J* 13.9, 1H, 14-C*H*$_2$), 3.75 (dm, *J* 6.3, 1H, 15-C*H*), 4.00-4.04 (m, 1H, 11-C*H*), 7.11 (d, *J* 7.5, 1H, 5-C*H*), 7.28 (d, *J* 8.4, 2H, Ar*H*), 7.36 (app t, *J* 8.0, 1H, 6-C*H*), 7.83 (d, *J* 8.4, 2H, Ar*H*), 7.90 (d, *J* 8.4, 1H, 7-CH), 8.43 (s, 1H, 2-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_2, 13-CH_2), 21.6 (CH_3, $ArCH_3$), 33.5 (CH_2, 14-CH_2), 37.1 (CH_2, 12-CH_2), 55.5 (CH, 11-CH), 66.1 (CH, 15-CH), 112.2 (CH, 7-CH), 120.2 (C, 3-C), 124.7 (CH, 5-CH),

125.5 (C, 9-C), 126.1 (CH, 6-CH), 127.3 (CH, ArCH), 130.3 (CH, ArCH), 131.9 (C, 4-C), 132.6 (CH, 2-CH), 134.1 (C, ArC), 134.8 (C, 8-C), 146.3 (C, ArC), 191.1 (C, 16-C), 207.2 (C, 10-C); MS (ESI) *m/z* 416.2 ($[M+Na]^+$, 100%); HRMS MS (ESI) *m/z* 416.0930 $[M+Na]^+$, $C_{22}H_{19}NO_4S$ requires 416.0932.

Ketal compound (149)

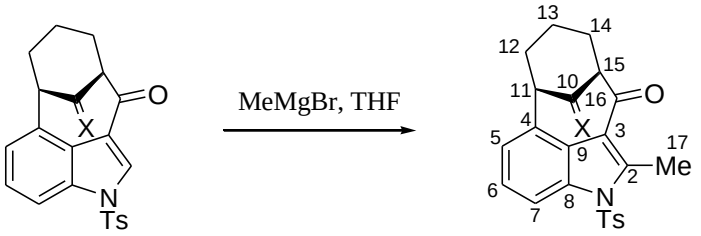


133 **149** X = -$O(CH_2)_2O$-

p-TsOH (8 mg, 0.04 mmol) and ethylene glycol (25 μL, 0.45 mmol) were added to a solution of diketone **133** (160 mg, 0.41 mmol) in toluene (8 mL). After 10 h at reflux, the reaction mixture was cooled to rt, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc; 70/30) to provide ketal **149** (173 mg; 97%) as a white solid; R_f 0.25 (petroleum ether/EtOAc, 70/30); mp 114-116 °C; IR υ_{max} 2935, 1654, 1526, 1374, 1164, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06-1.20 (m, 1H, 13-C*H*$_2$), 1.30-1.40 (m, 1H, 13-C*H*$_2$), 1.83 (dm, *J* 13.2, 1H, 12-C*H*$_2$), 1.99-2.16 (m, 2H, 14-C*H*$_2$), 2.18-2.29 (m, 1H, 12-C*H*$_2$), 2.38 (s, 3H, ArC*H*$_3$), 3.08-3.12 (m, 1H, 15-C*H*), 3.36-3.40 (m,1H, 11-C*H*), 3.85-3.96 (m, 2H, OC*H*$_2$), 3.98-4.03 (m, 2H, OC*H*$_2$), 7.10 (d, *J* 7.4, 1H, 5-C*H*), 7.29 (d, *J* 8.4, 2H, Ar*H*), 7.32 (app t, *J* 7.9, 1H, 6-C*H*), 7.85 (d, *J* 8.4, 1H, 7-C*H*), 7.88 (d, *J* 8.4, 2H, Ar*H*), 8.41 (s, 1H, 2-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (CH_2, 13-CH_2), 21.5 (CH_3, ArCH_3), 29.1 (CH_2, 14-CH_2), 34.2 (CH_2, 12-CH_2), 48.7 (CH, 11-CH), 57.7 (CH, 15-CH), 64.2 (CH_2, OCH_2), 65.2 (CH_2,

OCH_2), 107.3 (C, 10-C), 111.4 (CH, 7-CH), 121.3 (C, 3-C), 125.1 (CH, 5-CH), 125.4 (CH, 6-CH), 126.0 (C, 9-C), 127.4 (CH, ArCH), 130.1 (CH, ArCH), 131.6 (CH, 2-CH), 134.4 (C), 134.6 (C), 134.8 (C), 145.8 (C), 196.1 (C, 16-C); MS (ESI) *m/z* 460.1 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 460.1189 $[M+Na]^+$, $C_{24}H_{23}NO_5SNa$ requires 460.1195.

Methylated indole compound (159)

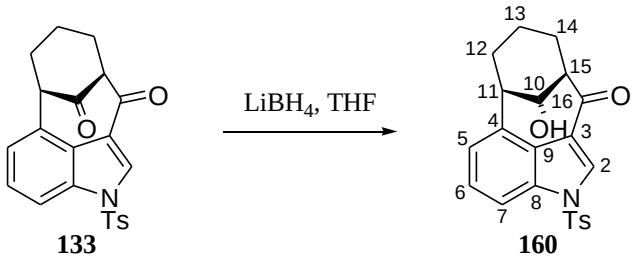


149 X = $-O(CH_2)_2O-$ **159** X = $-O(CH_2)_2O-$

MeMgBr (3 M solution in Et_2O, 150 μL, 0.45 mmol) was added dropwise, over a period of 5 min, to a solution of ketal **149** (66 mg, 0.15 mmol) in THF (1.5 mL) at 0 °C. After 3 h at this temperature the reaction was quenched with NH_4Cl solution (10 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to give methylated compound **159** as a white solid (38 mg, 56%); R_f 0.47 (petroleum ether/EtOAc, 60/40); mp 93-94 °C; IR υ_{max} 2930, 1647, 1526, 1376, 1168, 1111, 1000, 710, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06-1.20 (m, 1H, 13-C*H*$_2$), 1.28-1.37 (m, 1H, 13-C*H*$_2$), 1.83 (dm, *J* 13.2, 1H, 12-C*H*$_2$), 1.97-2.12 (m, 2H, 14-C*H*$_2$), 2.16-2.27 (m, 1H, 12-C*H*$_2$), 2.39 (s, 3H, ArC*H*$_3$), 3.05 (s, 3H, 17-C*H*$_3$), 3.06-3.10 (m, 1H, 15-C*H*), 3.34-3.38 (m, 1H, 11-C*H*), 3.87-3.97 (m, 2H, OC*H*$_2$), 3.98-4.03 (m, 2H, OC*H*$_2$), 7.10 (d, *J* 7.5, 1H, 5-C*H*), 7.26-7.31(m, 3H, Ar*H* and 6-C*H*), 7.78 (d, *J* 8.4, 2H, Ar*H*), 8.20 (d, *J* 8.5, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (CH_3, 17-CH_3), 17.4 (CH_2, 13-CH_2), 21.6 (CH_3, ArCH_3), 29.3 (CH_2, 14-CH_2), 34.5 (CH_2, 12-CH_2), 48.9 (CH,

11-CH), 59.1 (CH, 15-CH), 64.3 (CH_2, OCH_2), 65.3 (CH_2, OCH_2), 107.1 (C, 10-C), 112.4 (C, 7-CH), 117.9 (C, 3-C), 124.6 (CH, 6-CH), 125.6 (CH, 5-CH), 125.7 (C, 9-C), 126.9 (CH, ArCH), 130.1 (CH, ArCH), 133.5 (C, 4-C), 135.6 (C, ArC), 136.0 (C, 8-C), 145.6 (C, ArC), 147.1 (C, 2-C), 197.7 (C, 16-C); MS (ESI) *m/z* 474.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 474.1340 $[M+Na]^+$, $C_{25}H_{25}NO_5SNa$ requires 474.1351.

Alcohol compound (160)

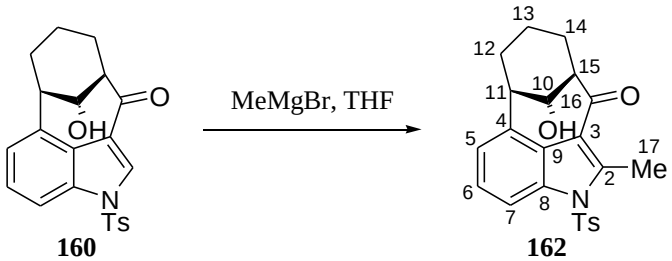


133 **160**

$LiBH_4$ (13 mg, 0.61 mmol) was added portionwise to a solution of diketone **133** (217 mg, 0.55 mmol) in THF (10 mL) at 0 °C. After 2 h at that maintained temperature, the reaction mixture was quenched with NaOH solution (10 mL of a 1 M aqueous solution) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 60/40) to give alcohol **160** as a white solid (84 mg, 39%); R_f 0.30 (petroleum ether/EtOAc, 60/40); mp 115-116 °C; IR υ_{max} 3414, 2929, 1644, 1524, 1374, 1175, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95-1.09 (m, 1H, 13-C*H*$_2$), 1.23-1.32(m, 1H, 13-C*H*$_2$), 1.76-1.87 (m, 1H, 14-C*H*$_2$), 1.88-1.95 (m, 3H, 12-C*H*$_2$ and O*H*), 2.08 (dm, *J* 14.2, 1H, 14-C*H*$_2$), 2.37 (s, 3H, ArC*H*$_3$), 3.29 (app t, *J* 5.5, 1H, 15-C*H*), 3.62-3.68 (m, 1H, 11-C*H*), 4.23 (app t, *J* 5.9, 1H, 10-C*H*), 7.17 (d, *J* 7.4, 1H, 5-C*H*), 7.28 (d, *J* 8.4, 2H, Ar*H*), 7.34 (app t, *J* 7.9, 1H, 6-C*H*), 7.85-7.89 (m, 3H, Ar*H* and 7-C*H*), 8.42 (s, 1H, 2-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (CH_2, 13-CH_2), 21.6 (CH_3, ArCH_3), 29.8 (CH_2, 14-CH_2),

34.9 (CH_2, 12-CH_2), 45.5 (CH, 11-CH), 54.9 (CH, 15-CH), 70.1 (CH, 10-CH), 111.7 (CH, 7-CH), 122.6 (C, 3-C), 126.6 (C, 9-C), 125.6 (CH, 6-CH), 126.2 (CH, 5-CH), 127.4 (CH, ArCH), 130.2 (CH, ArCH), 131.9 (CH, 2-CH), 134.5 (C, 4-C), 134.7 (C, ArC), 135.6 (C, 8-C), 145.9 (C, ArC), 199.1 (C, 16-C); MS (ESI) *m/z* 418.1 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 418.1072 $[M+Na]^+$, $C_{22}H_{21}NO_4SNa$ requires 418.1089.

Methylated indole compound (162)

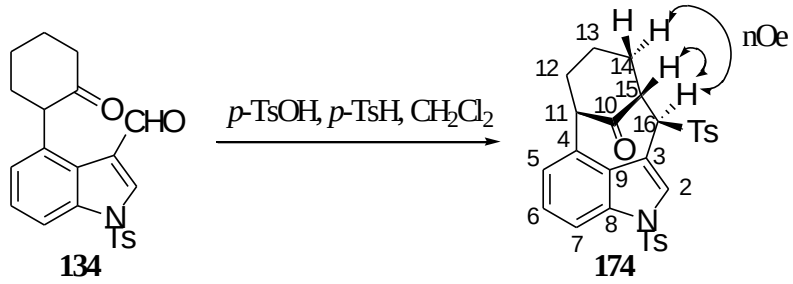


160 **162**

MeMgBr (3 M solution in Et_2O, 106 μL, 0.32 mmol) was added to a solution of **160** (84 mg, 0.21 mmol) in THF (2 mL) at 0 °C and the solution was stirred for 30 min at that maintained temperature. The reaction was quenched with NH_4Cl solution (5 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 60/40) to afford alcohol **162** (51 mg, 59%) as a white solid; R_f 0.16 (petroleum ether/EtOAc, 60/40); mp 103-104 °C; IR υ_{max} 3401, 2935, 1646, 1525, 1376, 1178, 706, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96-1.09 (m, 1H, 13-C*H*$_2$), 1.22-1.33 (m, 1H, 13-C*H*$_2$), 1.71-1.85 (m, 2H, 14-C*H*$_2$ and O*H*) , 1.86-1.99 (m, 2H, 12-C*H*$_2$), 1.06-2.14 (m, 1H, 14-C*H*$_2$), 2.39 (s, 3H, ArC*H*$_3$), 3.05 (s, 3H, 17-C*H*$_3$), 3.27-3.33 (m, 1H, 15-C*H*), 3.61-3.66 (m, 1H, 11-C*H*), 4.17-4.24 (m, 1H, 10-C*H*), 7.18 (d, *J* 7.4, 1H, 5-C*H*), 7.27 (d, *J* 8.4, 2H, Ar*H*), 7.32 (app t, *J* 7.9, 1H, 6-C*H*), 7.77 (d, *J* 8.4, 2H, ArH), 8.23 (d, *J* 8.4, 1H, 7-CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (CH_3, 17-CH_3), 17.4 (CH_2, 13-

CH_2), 21.6 (CH_3, $ArCH_3$), 30.1 (CH_2, 14-CH_2), 35.2 (CH_2, 12-CH_2), 46.0 (CH, 11-CH), 56.4 (CH, 15-CH), 70.0 (CH, 10-CH), 112.7 (CH, 7-CH), 119.2 (C, 3-C), 124.9 (CH, 6-CH), 125.9 (C, 9-C), 126.8 (CH, ArCH), 130.2 (2 × CH, ArCH and 5-CH), 134.1 (C, 4-C), 135.7 (C, ArC), 136.0 (C, 8-C), 145.7 (C, ArC), 147.2 (C, 2-C), 200.4 (C, 16-C); MS (ESI) *m/z* 432.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 432.1244 $[M+Na]^+$, $C_{23}H_{23}NO_4SNa$ requires 432.1245.

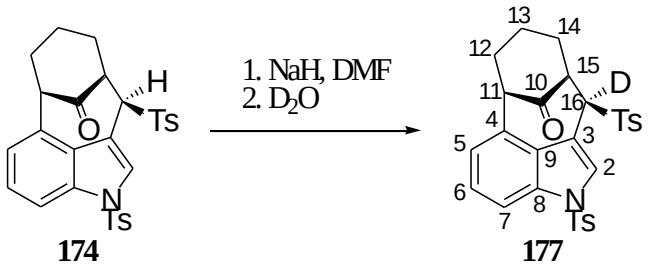
Sulfone compound (174)



A solution of dry *p*-TsOH (500 mg, 0.53 M solution in CH_2Cl_2) was prepared and dried over 3 Å molecular sieves with stirring for 1 h. A dry solution of *p*-TsOH (587 μL, 0.31 mmol) and *p*-$TolSO_2H$ (53 mg, 0.34 mmol) were successively added to a solution of formylindole **134** (123 mg, 0.31 mmol) in CH_2Cl_2 (3 mL). After 24 h at reflux, the reaction mixture was cooled to rt and $NaHCO_3$ solution (5 mL of a saturated aqueous solution) was added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to give cyclised product **174** as a pale yellow solid (100 mg, 61%); R_f 0.44 (petroleum ether/EtOAc, 50/50); mp 209-210 °C; IR υ_{max} 2955, 1710, 1346, 1170, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18-1.35 (m, 2H, 13-CH_2), 1.79 (br d, *J* 12.8, 1H, 12-CH_2), 1.96 (br d, *J* 14.0, 1H, 14-CH_2), 2.01-2.19 (m, 2H, 12-CH_2 and 14-CH_2), 2.31 (s, 3H, ArCH_3), 2.32 (s, 3H, ArCH_3), 3.52 (d, *J* 7.1, 1H, 15-C*H*), 3.96 (br s, 1H, 11-C*H*), 4.44 (br s, 1H, 16-C*H*), 6.90 (d, *J* 7.4, 1H, 5-C*H*), 7.06 (d, *J* 8.3, 2H,

Ar*H*), 7.23-7.29 (m, 3H, Ar*H* and 6-C*H*), 7.41 (d, *J* 8.3, 2H, Ar*H*), 7.83-7.89 (m, 4H, Ar*H*, 7-C*H* and 2-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (CH_2, 13-CH_2), 21.5 (CH_3, ArCH_3), 34.3 (CH_2, 14-CH_2), 39.6 (CH_2, 12-CH_2), 47.2 (CH, 15-CH), 59.0 (CH, 11-CH), 67.7 (CH, 16-CH), 110.4 (C, 3-C), 111.9 (CH, 7-CH), 123.3 (CH, 5-CH), 125.7 (CH, 6-CH), 127.1 (CH, ArCH), 128.8 (C, 9-C), 129.2 (CH, ArCH), 129.5 (CH, 2-CH), 130.2 (2 × CH, 2 × ArCH), 131.6 (C, 4-C), 133.0 (C, 8-C), 134.5 (C, ArC), 134.7 (C, ArC), 144.8 (C, ArC), 145.4 (C, ArC), 208.6 (C, 10-C); MS (ESI) *m/z* 556.1 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 556.1220 [M+Na]$^+$, $C_{29}H_{27}NO_5S_2Na$ requires 556.1228.

Deuterated Sulfone (177)

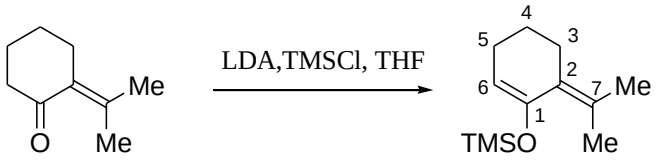


174 **177**

Sulfone **174** (50 mg, 0.09 mmol) was added to a suspension of NaH (5 mg, 60% dispersion in mineral oil, 0.11 mmol) in DMF (0.5 mL) at 0 °C. The reaction mixture was stirred for 20 min and quenched by addition of D_2O (1 mL). The mixture was extracted with Et_2O (3 × 2 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 80/20) to afford a mixture of sulfone **174** and deuterated sulfone **177** as a single diastereoisomer in a 13:87 ratio (36 mg, 72%) as a grey solid; R_f 0.49 (petroleum ether/EtOAc, 50/50); mp 134-135 °C; IR υ_{max} 2928, 1705, 1372, 1176, 661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21-1.31 (m, 2H, 13-CH_2), 1.81 (dm, *J* 13.3, 1H, 12-CH_2), 1.97 (dm, *J* 14.1, 1H, 14-CH_2), 2.04-2.19 (m, 2H, 12-CH_2 and 14-CH_2), 2.34 (s, 6H, ArCH_3), 3.52 (d, *J*

7.0, 1H, 15-C*H*), 3.96 (br s, 1H, 11-C*H*), 6.91 (d, *J* 7.6, 1H, 5-C*H*), 7.06 (d, *J* 8.4, 2H, Ar*H*), 7.24-7.30 (m, 3H, Ar*H* and 6-C*H*), 7.40 (d, *J* 8.4, 2H, Ar*H*), 7.85-7.90 (m, 4H, Ar*H*, 2-C*H* and 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7 (CH_2, 13-CH_2), 21.6 (CH_3, ArCH_3), 34.4 (CH_2, 14-CH_2), 39.7 (CH_2, 12-CH_2), 47.2 (CH, 15-CH), 59.0 (CH, 11-CH), 67.9 (C, t, *J* 33.4, 16-C), 110.4 (C, 3-C), 112.0 (CH, 7-CH), 123.4 (CH, 5-CH), 125.7 (CH, 6-CH), 127.2 (CH, ArCH), 128.9 (C, 9-C), 129.2 (CH, ArCH), 129.6 (CH, 2-CH), 130.1 (2 × CH, 2 × ArCH), 131.6 (C, 4-C), 133.1 (C, 8-C), 134.6 (C, ArC), 134.9 (C, ArC), 144.9 (C, ArC), 145.5 (C, ArC), 208.6 (C, 10-C); MS (ESI) *m/z* 557.2 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 557.1276 [M+Na]$^+$, $C_{29}H_{26}{}^2H_1NO_5S_2Na$ requires 556.1228.

Trimethyl(6-(propan-2'-ylidene)cyclohex-1-enyloxy)silane (188)

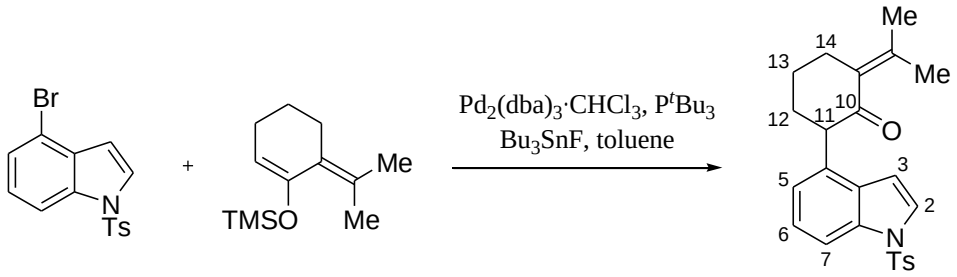


187 **188**

BuLi (1.6 M solution in hexane, 7.1 mL, 10.6 mmol) was added to a solution of $^{i}Pr_2NH$ (1.2 mL, 1.6 mL, 11.5 mmol) in THF (28 mL) at -78 °C. The mixture was stirred for 20 min at this temperature and a solution of enone **187**[3] (1.22 g, 8.83 mmol) in THF (2 mL) was added dropwise over a period of 10 min. After 30 min at -78 °C, TMSCl (2.2 mL, 18 mmol was added and the mixture was stirred for 1 h at -78 °C. The reaction was quenched with brine (6 mL) at -78 °C and extracted with petroleum ether (2 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by reduced pressure distillation (Kugelrohr) providing silyl enol ether **188** (1.36 g, 73%) as a colourless oil; R_f 0.88 (petroleum ether/Et_2O, 90/10); IR υ_{max} 2927, 1611, 1250, 1177, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H, CH_3),

1.59-1.65 (m, 2H, 4-CH_2), 1.71 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.09-2.14 (m, 2H, 5-CH_2), 2.27-2.30 (m, 2H, 3-CH_2), 4.91 (app t, *J* 4.2, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.1 (CH_3), 22.7 (CH_3), 23.1 (CH_3), 23.4 (CH_2, 5-CH_2), 24.8 (CH_2, 3-CH_2), 28.8 (CH_2, 4-CH_2), 108.1 (CH, 6-CH), 126.6 (C, 7-C), 127.8 (C, 2-C), 150.1 (C, 1-C); MS (EI) *m/z* 138.1 (100%), 210.1 ([M]$^+$, 25%); HRMS (EI) *m/z* 210.1446 [M]$^+$, $C_{12}H_{22}OSi$ requires 210.1440.

2-(Propan-2'-ylidene)-6-(1''-tosyl-1*H*-indol-4''-yl)cyclohexanone (189)

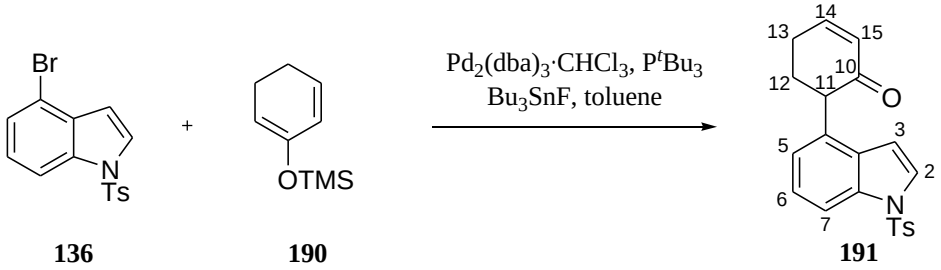


136 **188** **189**

A solution of P^{t}Bu$_3$ (1 M solution in toluene, 197 μL, 0.20 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (85 mg, 0.08 mmol) and Bu_3SnF (508 mg, 1.64 mmol) in toluene (1.5 mL). A solution of indole **136** (144 mg, 0.41 mmol) and silyl enol ether **188** (345 mg, 1.64 mmol) in toluene (1 mL) was added and the mixture was heated under reflux for 15 h. After cooling to rt, the mixture was diluted with Et_2O (5 mL), filtered through a plug of silica and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to provide enone **189** as a yellow foam (56 mg, 33%); R_f 0.25 (petroleum ether/EtOAc, 80/20); mp 78-80 °C; IR υ_{max} 2933, 1676, 1360, 1177, 757, 674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72-1.82 (m, 1H, 13-CH_2), 1.84 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 1.95-2.04 (m, 1H, 13-CH_2), 2.05-2.17 (m, 1H,12-CH_2), 2.17-2.25 (m, 1H, 12-CH_2), 2.32 (s, 3H, ArCH_3), 2.42-2.56 (m, 1H, 14-CH_2), 2.82 (dm, *J* 15.2, 1H, 14-CH_2), 3.87 (dd, *J* 11.4, 6.2, 1H, 11-C*H*), 6.56 (d, *J* 3.7, 1H, 3-C*H*), 7.01 (d, *J* 7.4, 1H, 5-C*H*), 7.20 (d, *J* 8.4, 2H, Ar*H*), 7.27 (app t, *J* 7.9, 1H, 6-C*H*), 7.57 (d, *J* 3.7, 1H, 2-C*H*), 7.78 (d, *J*

8.4, 2H, Ar*H*), 7.89 (d, *J* 8.4, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3, $ArCH_3$), 22.1 (CH_3), 22.9 (CH_3), 23.8 (CH_2, 13-CH_2), 30.0 (CH_2, 14-CH_2), 32.5 (CH_2, 12-CH_2), 55.4 (CH, 11-CH), 107.2 (CH, 3-CH), 111.9 (CH, 7-CH), 122.5 (CH, 5-CH), 124.5 (CH, 6-CH), 125.7 (CH, 2-CH), 126.8 (CH, ArCH), 129.8 (CH, ArCH), 132.6 (C), 133.8 (C), 134.7 (C), 135.2 (C), 142.5 (C), 144.8 (C, ArC), 203.3 (C, 10-C), one C not observed; MS (ESI) *m/z* 430.2 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 430.1446 [M+Na]$^+$, $C_{24}H_{25}NO_3SNa$ requires 430.1453.

6-(1'-Tosyl-1*H*-indol-4'-yl)cyclohex-2-enone (191)

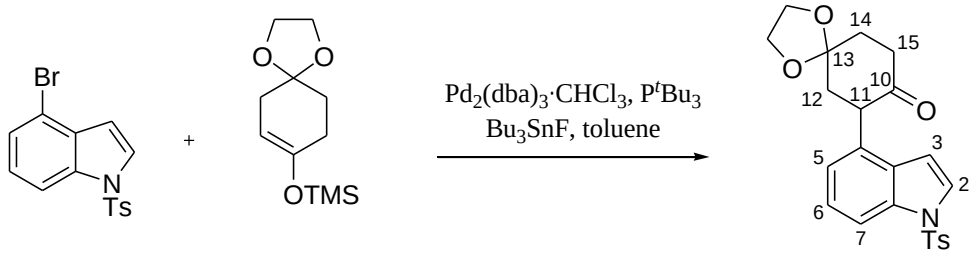


136 **190** **191**

Following the general procedure A (p.112), using indole **136** (545 mg, 1.56 mmol) and silyl enol ether **190**[4] (524 mg, 3.11 mmol) and heated under reflux for 17 h; column chromatography on silica gel (petroleum ether/EtOAc, 70/30) afforded enone **191** (295 mg, 52%) as a yellow foam; R_f 0.40 (petroleum ether/ EtOAc, 70/30); mp 84-85 °C; IR υ_{max} 2971, 1672, 1360, 1130, 1088, 1164, 758, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21-2.40 (m, 2H, 12-CH_2), 2.34 (s, 3H, ArCH_3), 2.45-2.57 (m, 2H, 13-CH_2), 3.89 (dd, *J* 11.7, 5.1, 1H, 11-C*H*), 6.19 (dm, *J* 10.2, 1H, 15-C*H*), 6.54 (d, *J* 3.8, 1H, 3-C*H*), 6.99 (d, *J* 7.4, 1H, 5-C*H*), 7.06-7.12 (m, 1H, 14-C*H*), 7.21 (d, *J* 8.4, 2H, Ar*H*), 7.26 (app t, *J* 8.0, 1H, 6-C*H*), 7.56 (d, *J* 3.8, 1H, 2-C*H*), 7.77 (d, *J* 8.4, 2H, Ar*H*), 7.89 (d, *J* 8.4, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3, $ArCH_3$), 25.7 (CH_2, 13-CH_2), 30.3 (CH_2, 12-CH_2), 51.2 (CH, 11-CH), 107.1 (CH, 3-CH), 112.3 (CH, 7-CH), 122.2 (CH, 5-CH), 124.6 (CH, 6-CH), 126.0 (CH, 2-CH),

126.9 (CH, ArCH), 130.0 (CH, ArCH), 130.4 (CH, 15-CH), 132.8 (C), 134.9 (C), 135.3 (C), 145.0 (C, ArC), 150.5 (CH, 14-CH), 198.7 (C, 10-C), one C not observed; MS (ESI) *m/z* 388.1 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 388.0979 [M+Na]$^+$, $C_{21}H_{19}NO_3SNa$ requires 388.0983.

Ketal compound (193)

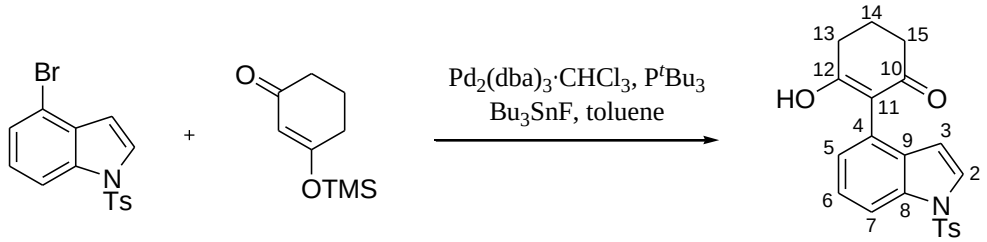


136 **192** **193**

Following the general procedure A (p.112), using indole **136** (239 mg, 0.68 mmol) and silyl enol ether **192**[5] (311 mg, 1.36 mmol) and heated under reflux for 17 h; column chromatography on silica gel (petroleum ether/EtOAc, 70/30) gave ketal **193** (166 mg, 57%) as a pale yellow solid; R_f 0.22 (petroleum ether/EtOAc, 60/40); mp 115-116 °C; IR υ_{max} 2960, 1710, 1366, 1166, 1116, 1018, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13-2.20 (m, 2H, 14-C*H*$_2$), 2.21-2.27 (m, 1H, 12-C*H*$_2$), 2.34 (s, 3H, ArC*H*$_3$), 2.43 (t, *J* 13.5, 1H, 12-C*H*$_2$), 2.50-2.57 (m, 1H, 15-C*H*$_2$), 2.80-2.93 (m, 1H, 15-C*H*$_2$), 3.96-4.13 (m, 4H, OC*H*$_2$), 4.26 (dd, *J* 13.5, 5.7, 1H, 11-C*H*), 6.50 (d, *J* 3.8, 1H, 3-C*H*), 7.01 (d, *J* 7.4, 1H, 5-C*H*), 7.22 (d, *J* 8.4, 2H, Ar*H*), 7.28 (app t, *J* 8.0, 1H, 6-C*H*), 7.56 (d, *J* 3.8, 1H, 2-C*H*), 7.76 (d, *J* 8.4, 2H, Ar*H*), 7.90 (d, *J* 8.4, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3, $ArCH_3$), 34.6 (CH_2, 14-CH_2), 38.5 (CH_2, 15-CH_2), 41.1 (CH_2, 12-CH_2), 50.5 (CH, 11-CH), 64.7 (CH_2, OCH_2), 64.8 (CH_2, OCH_2), 106.9 (CH, 3-CH), 107.3 (C, 13-C), 112.5 (CH, 7-CH), 122.5 (CH, 5-CH), 124.6 (CH, 6-CH), 126.0 (CH, 2-CH), 126.9 (CH, ArCH), 129.9 (CH, ArCH), 130.1 (C), 130.8 (C),

134.8 (C, Ar-C), 135.4 (C), 145.0 (C, Ar-C), 207.8 (C, 10-C); MS (ESI) *m/z* 448.2 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 448.1200 [M+Na]$^+$, $C_{23}H_{23}NO_5SNa$ requires 448.1195.

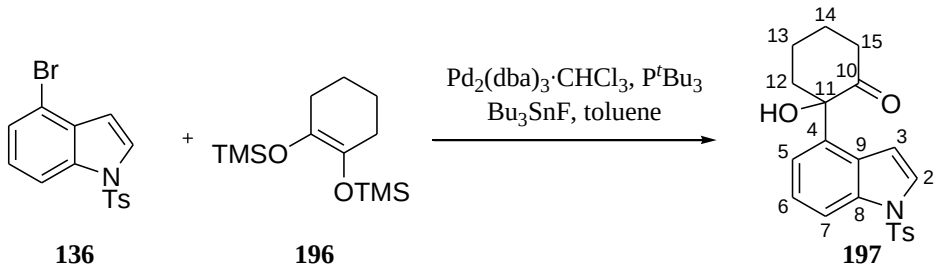
3-Hydroxy-2-(1'-tosyl-1*H*-indol-4'-yl)cyclohex-2-enone (195)



136 **194** **195**

Following the general procedure A (p.112), using indole **136** (300 mg, 0.86 mmol) and silyl enol ether **194**[6] (316 mg, 1.71 mmol) and heated under reflux for 17 h; column chromatography on silica gel (petroleum ether/EtOAc, 70/30) provided **195** (161 mg, 49%) as a yellow solid; R_f 0.12 (petroleum ether/EtOAc, 50/50); mp 94-95 °C; IR υ_{max} 3125, 2925, 1707, 1595, 1356, 1163, 1130, 756, 678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05-2.13 (m, 2H, 14-C*H*$_2$), 2.35 (s, 3H, ArC*H*$_3$), 2.50 (dd, *J* 3.3, 2.1, 2H, 13-C*H*$_2$), 2.62 (t, *J* 6.3, 2H, 15-C*H*$_2$), 6.10 (br s, 1H, O*H*), 6.36 (d, *J* 3.7, 1H, 3-C*H*), 7.04 (d, *J* 7.4, 1H, 5-C*H*), 7.24 (d, *J* 8.4, 2H, Ar*H*), 7.34 (app t, *J* 7.9, 1H, 6-C*H*), 7.57 (d, *J* 3.7, 1H, 2-C*H*), 7.78 (d, *J* 8.4, 2H, Ar*H*), 7.96 (d, *J* 8.4, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH_2, 14-CH_2), 21.5 (CH_3, ArCH_3), 28.1 (CH_2, 15-CH_2), 36.9 (CH_2, 13-CH_2), 107.8 (CH, 3-CH), 113.6 (CH, 7-CH), 115.5 (C, 11-C), 123.8 (C, 9-C), 125.1 (CH, 6-CH), 125.6 (CH, 5-CH), 126.5 (CH, 2-CH), 126.9 (CH, ArCH), 130.0 (CH, ArCH), 130.5 (C, 4-C), 135.1 (C, ArC), 135.2 (C, 8-C), 145.2 (C, ArC), 171.6 (C, 12-C), 196.6 (C, 10-C); MS (ESI) *m/z* 404.2 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 404.0938 [M+Na]$^+$, $C_{21}H_{19}NO_4SNa$ requires 404.0932.

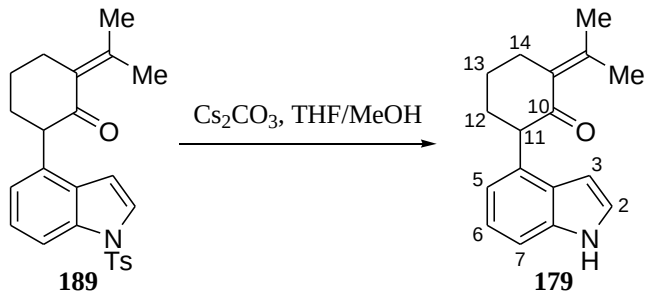
2-Hydroxy-2-(1'-tosyl-1*H*-indol-4'-yl)cyclohexanone (197)



136 **196** **197**

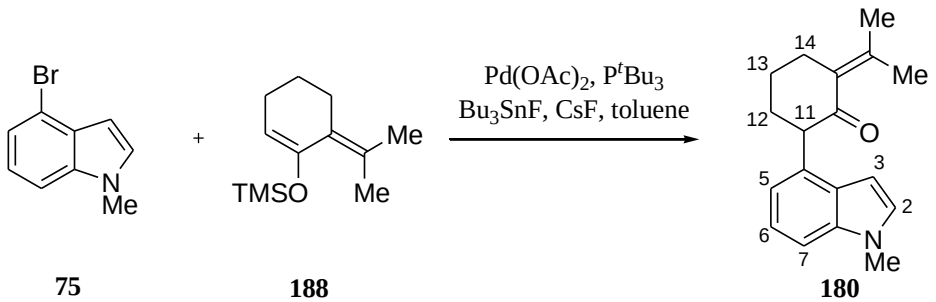
Following the general procedure A (p.112), using indole **136** (691 mg, 1.97 mmol) and silyl enol ether **196**[7] (1.02 g, 3.95 mmol) and heated under reflux for 48 h; column chromatography on silica gel (petroleum ether/EtOAc, 80/20) gave ketal **197** (140 mg, 18%) as a pale yellow solid; R_f 0.34 (petroleum ether/EtOAc, 60/40); mp 68-69 °C; IR υ_{max} 3462, 2941, 1710, 1361, 1166, 1133, 761, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64-1.78 (m, 1H, 14-C*H*), 1.79-1.93 (m, 3H, 13-CH_2 and 15-CH_2), 1.99-2.09 (m, 1H, 14-CH_2), 2.20-2.30 (m, 1H, 12-CH_2), 2.32 (s, 3H, ArCH_3), 2.46 (dm, *J* 12.5, 1H, 12-CH_2), 3.09 (dm, *J* 13.8 1H, 15-CH_2), 4.61 (s, 1H, O*H*), 6.59 (d, *J* 3.8, 1H, 3-C*H*), 7.20 (d, *J* 8.4, 2H, Ar*H*), 7.34 (app t, *J* 8.0, 1H, 6-C*H*), 7.42 (d, *J* 7.6, 1H, 5-C*H*), 7.54 (d, *J* 3.8, 1H, 2-C*H*), 7.74 (d, *J* 8.4, 2H, Ar*H*), 7.99 (d, *J* 8.3, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3, $ArCH_3$), 23.3 (CH_2, 13-CH_2), 29.0 (CH_2, 14-CH_2), 39.0 (CH_2, 12-CH_2), 41.0 (CH_2, 15-CH_2), 80.5 (C, 11-C), 107.6 (CH, 3-CH), 113.8 (CH, 7-CH), 121.1 (CH, 5-CH), 124.2 (CH, 6-CH), 126.4 (CH, 2-CH), 126.8 (CH, ArCH), 129.0 (C, 9-C), 129.9 (CH, ArCH), 131.8 (C, 4-C), 135.1 (C, ArC), 135.6 (C, 8-C), 145.1 (C, Ar-C), 213.8 (C, 10-C); MS (ESI) *m/z* 406.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 406.1082 $[M+Na]^+$, $C_{21}H_{21}NO_4SNa$ 406.1089.

2-(1*H*-Indol-4'-yl)-6-(propan-2''-ylidene)cyclohexanone (179)



Cs_2CO_3 (79 mg, 0.24 mmol) was added to a solution of **189** (33 mg, 0.08 mmol) in a 2:1 mixture of THF/MeOH (8 mL) at rt. After 18 h at 65 °C, the reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 95/10) to afford indole **179** (19 mg, 95%) as a yellow oil; R_f 0.53 (petroleum ether/EtOAc, 80/20); IR υ_{max} 3331, 1670, 1336, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75-1.89 (m, 1H, 13-C*H*$_2$), 1.85 (s, 3H, C*H*$_3$), 1.94 (s, 3H, C*H*$_3$), 1.97-2.09 (m, 1H, 13-C*H*$_2$), 2.09-2.23 (m, 2H, 12-C*H*$_2$), 2.35-2.46 (m, 1H, 14-C*H*$_2$), 2.77-2.89 (m, 1H, 14-C*H*$_2$), 3.94-4.02 (m, 1H, 11-C*H*), 6.41-6.45 (m, 1H, 3-C*H*), 6.91 (d, *J* 7.1, 1H, 5-C*H*), 7.11-7.22 (m, 2H, 2-C*H* and 6-C*H*), 7.29 (d, *J* 8.2, 1H, 7-C*H*), 8.17 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_3), 23.0 (CH_3), 24.0 (CH_2, 13-CH_2), 30.3 (CH_2, 14-CH_2), 32.3 (CH_2, 12-CH_2), 56.1 (CH, 11-CH), 101.1 (CH, 3-CH), 109.8 (CH, 7-CH), 119.0 (CH, 5-CH), 121.9 (CH, 6-CH), 123.8 (CH, 2-CH), 127.0 (C), 133.0 (C), 133.2 (C), 136.0 (C), 141.7 (C), 204.4 (C, 10-C); MS (ESI) *m/z* 276.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 276.1356 $[M+Na]^+$, $C_{17}H_{19}NONa$ requires 276.1364.

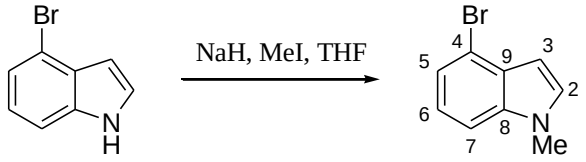
2-(1'-Methyl-1*H*-indol-4'-yl)-6-(propan-2''-ylidene)cyclohexanone (180)



75 **188** **180**

A solution of P^tBu_3 (1 M solution in toluene, 1.3 mL, 0.13 mmol) was added to a solution of $Pd(OAc)_2$ (16 mg, 0.071 mmol), Bu_3SnF (1.03 g, 3.33 mmol) and CsF (506 mg, 3.33 mmol) in toluene (10 mL). A solution of indole **75** (500 mg, 2.38 mmol) and silyl enol ether **188** (700 mg, 3.33 mmol) in toluene (3 mL) was added and the mixture was heated at 85 °C overnight. After cooling to rt, the mixture was diluted with Et_2O (20 mL), filtered through a plug of silica and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 95/5) to provide enone **180** as a yellow oil (347 mg, 55%); R_f 0.29 (petroleum ether/EtOAc, 90/10); IR υ_{max} 2930, 1673, 1443, 1287, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76-1.88 (m, 1H, 13-C*H*$_2$), 1.85 (s, 3H, C*H*$_3$), 1.95 (s, 3H, C*H*$_3$), 1.99-2.07 (m, 1H, 13-C*H*$_2$), 2.26-2.33 (m, 2H, 12-C*H*$_2$), 2.48-2.60 (m, 1H, 14-C*H*$_2$), 2.79-2.87 (m, 1H, 14-C*H*$_2$), 3.78 (s, 3H, NC*H*$_3$), 3.95-4.01 (m, 1H, 11-C*H*), 6.36 (d, *J* 3.1, 1H, 3-C*H*), 6.92 (d, *J* 7.0, 1H, 5-C*H*), 7.03 (d, *J* 3.1, 1H, 2-C*H*), 7.17-7.25 (m, 2H, 6-C*H* and 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_3), 22.9 (CH_3), 24.0 (CH_2, 13-CH_2), 30.3 (CH_2, 14-CH_2), 32.3 (CH_2, 12-CH_2), 32.9 (CH_3, NCH_3), 56.0 (CH, 11-CH), 99.5 (CH, 3-CH), 108.0 (CH, 7-CH), 118.6 (CH, 5-CH), 121.6 (CH, 6-CH), 127.6 (CH, 2-CH), 128.4 (C), 133.2 (C), 133.2 (C), 136.8 (C), 141.5 (C), 204.2 (C); MS (EI) *m/z* 267.2 ($[M]^+$, 100%); HRMS (EI) *m/z* 267.1622 $[M]^+$, $C_{18}H_{21}NO$ requires 267.1623.

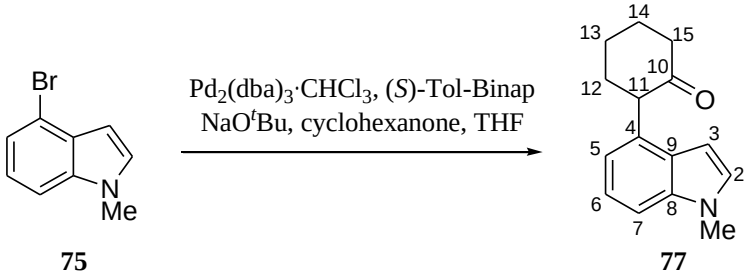
4-Bromo-1-methyl-1*H*-indole (75)[8]



75

A solution of 4-bromoindole (10.0 g, 15 mmol) in THF (30 mL) was added to a suspension of NaH (3.0 g, 60% dispersion in mineral oil, 77 mmol) in THF (40 mL) at 0 °C. After 15 min, a solution of MeI (14.5 g, 102 mmol) was added dropwise, over a period of 10 min, at 0 °C and the mixture was stirred overnight at rt. The excess of NaH was destroyed by addition of MeOH/H_2O solution (1/1, 80 mL). The aqueous layer was subsequently extracted with Et_2O (3 × 80 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 95/5) to provide indole **75** as a yellow oil[8] (10.3 g, 97%); R_f 0.60 (petroleum ether/EtOAc, 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H, NC*H*$_3$), 6.56 (d, *J* 3.2, 1H, 3-C*H*), 7.10 (d, *J* 3.2, 1H, 2-C*H*), 7.12 (app t, 8.0, 1H, Ar*H*), 7.29 (d, *J* 8.0, 1H, 7-C*H*), 7.32 (dd, *J* 7.6, 0.8, 1H, 5-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2 (CH_3, NCH_3), 101.4 (CH, 3-CH), 108.5 (CH, 7-CH), 114.9 (C, 4-C), 122.2 (CH, 6-CH), 122.4 (CH, 5-CH), 129.2 (C, 9-C), 129.4 (CH, 2-CH), 137.0 (C, 8-C); MS (EI) *m/z* 209.1 ([M]$^+$, 100%), 211.1 (97%); HRMS (EI) *m/z* 208.9849 [M]$^+$, $C_9H_8{}^{79}Br$ requires 208.9840.

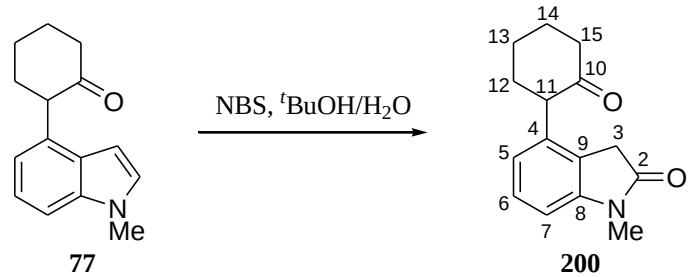
2-(1'-Methyl-1*H*-indol-4'-yl)cyclohexanone (77)[9]



75 **77**

Cyclohexanone (9.8 mL, 0.10 mol) and bromoindole **75** (5 g, 0.02 mol) were sequentially added to a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (370 mg, 0.36 mmol), (*S*)-Tol-Binap (582 mg, 0.86 mmol) and NaO^{t}Bu (3.0 g, 0.03 mol) in THF (125 mL). After 3 h at 70 °C, the mixture was cooled to rt, diluted with with H_2O (125 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 80/20) to give indole **77** as a yellow solid (4.1 g, 76%); R_f 0.30 (petroleum ether/EtOAc, 90/10); mp 121-123 °C [lit.,[9] mp 124-125 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85-1.98 (m, 2H, 13-C*H*$_2$), 1.99-2.11 (m, 1H, 14-C*H*$_2$), 2.22-2.29 (m, 1H, 14-C*H*$_2$), 2.30-2.44 (m, 2H, 12-C*H*$_2$), 2.51-2.68 (m, 2H, 15-C*H*$_2$), 3.79 (s, 3H, NC*H*$_3$), 4.00 (dd, *J* 11.5, 6.5, 1H, 11-C*H*), 6.33 (dd, *J* 3.1, 0.6, 1H, 3-C*H*), 6.85 (dd, *J* 6.9, 0.7, 1H, 5-C*H*), 7.04 (d, *J* 3.2, 1H, 2-C*H*), 7.18-7.28 (m, 2H, 6-C*H* and 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (CH_2, 13-CH_2), 27.8 (CH_2, 14-CH_2), 30.9 (CH_3, NCH_3), 34.2 (CH_2, 12-CH_2), 42.4 (CH_2, 15-CH_2), 55.3 (CH, 11-CH), 99.4 (CH, 3-CH), 108.3 (CH, 7-CH), 118.4 (CH, 5-CH), 121.6 (CH, 6-CH), 128.0 (C, 9-C), 128.5 (CH, 2-CH), 131.4 (C, 4-C), 136.7 (C, 8-C), 209.9 (C, 10-C); MS (EI) *m/z* 250.2 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 250.1202 [M+Na]$^+$, $C_{15}H_{17}NONa$ requires 250.1202.

2-(1'-Methyl-1*H*-oxindol-4'-yl)cyclohexanone (200)

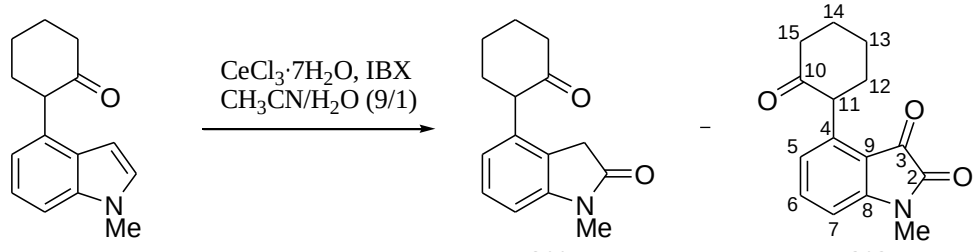


77 **200**

NBS (2.2 g, 12.3 mmol) was added in small portions over a period of 20 min to a solution of indole **77** (2 g, 8.8 mmol) in ^{t}BuOH/H_2O (95/5, 150 mL) and the reaction mixture was stirred

for 3 h at rt. The solution was concentrated under reduced pressure at rt, and H_2O was added to the residue (150 mL). The mixture was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 60/40) to afford **200** as a white solid (1.22 g, 57%); R_f 0.17 (petroleum ether/EtOAc, 60/40); mp 105-106 °C; IR υ_{max} 2948, 1701, 1608, 1470, 1335, 1289, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67-1.91 (m, 2H, 13-C*H*$_2$ and 14-C*H*$_2$), 1.96-2.11 (m, 2H, 12-C*H*$_2$ and 13-C*H*$_2$), 2.14-2.32 (m, 2H, 12-C*H*$_2$ and 14-C*H*$_2$), 2.40-2.61 (m, 2H, 15-C*H*$_2$), 3.19 (s, 3H, NC*H*$_3$), 3.31 (AB system, $J_{A\text{-}B}$ 21.9, 1H, 3-C*H*$_2$), 3.40 (AB system, $J_{A\text{-}B}$ 21.9, 1H, 3-CH_2), 3.56 (dd, *J* 12.8, 5.5, 1H, 11-C*H*), 6.74 (d, *J* 7.8, 1H, 5-C*H*), 6.85 (d, *J* 7.8, 1H, 7-C*H*), 7.28 (app t, *J* 7.8, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4 (CH_2, 13-CH_2), 26.2 (CH_3, NCH_3), 27.4 (CH_2, 14-CH_2), 33.5 (CH_2, 12-CH_2), 34.9 (CH_2, 15-CH_2), 42.1 (CH_2, 3-CH_2), 54.9 (CH, 11-CH), 106.9 (CH, 7-CH), 122.0 (CH, 5-CH), 123.6 (CH, 6-CH), 127.9 (C, 9-C), 135.1 (C, 4-C), 144.9 (C, 8-C), 174.8 (C, 2-C), 208.7 (C, 10-C); MS (ESI) *m/z* 266.1 ($[M+Na]^+$, 100%); HRMS (EI) *m/z* 266.1160 $[M+Na]^+$, $C_{15}H_{17}NO_2Na$ requires 266.1157.

1-Methyl-4-(2'-oxocyclohexyl)indoline-2,3-dione (203)

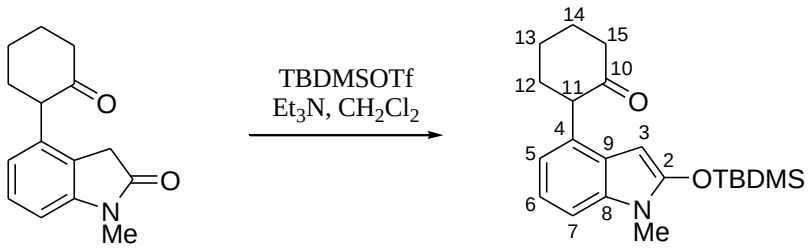


77 **200** **203**

IBX (154 mg, 0.55 mmol) and $CeCl_3{\cdot}7H_2O$ (8 mg, 0.02 mmol) were added to a solution of indole **77** (50 mg, 0.22 mmol) in CH_3CN/H_2O (2.5 mL of a 9/1 solution). The reaction mixture was stirred for 15 h at rt, filtered through Celite® and washed with EtOAc (2 × 3 mL).

The organic layer was washed with $NaHCO_3$ solution (5 mL of a saturated aqueous solution) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to afford oxindole **200** (6 mg, 11%) as a white solid, data as previously described (p.131); along with isatin **203** (15 mg, 26%) as a red solid; R_f 0.14 (petroleum ether/EtOAc, 60/40); mp 65-66 °C; IR υ_{max} 2924,1725, 1707, 1595, 1460, 1068, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.81-1.94 (m, 2H, 13-C*H*$_2$ and 14-C*H*$_2$), 1.95-2.07 (m, 2H, 12-C*H*$_2$ and 13-C*H*$_2$), 2.15-2.27 (m, 2H, 12-C*H*$_2$ and 14-C*H*$_2$), 2.52-2.61 (m, 2H, 15-C*H*$_2$), 3.22 (s, 3H, NC*H*$_3$), 4.30 (dd, *J* 12.6, 5.4, 1H, 11-C*H*), 6.77 (d, *J* 7.8, 1H, 5-C*H*), 6.93 (d, *J* 7.8, 1H, 7-C*H*), 7.53 (t, *J* 7.8, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2 (CH_2, 13-CH_2), 26.1(CH_3, NCH_3), 26.9 (CH_2, 14-CH_2), 32.9 (CH_2, 12-CH_2), 42.0 (CH_2, 15-CH_2), 52.8 (CH, 11-CH), 108.4 (CH, 7-CH), 115.33 (C, 9-C), 124.0 (CH, 5-CH), 137.9 (CH, 6-CH), 141.6 (C, 4-C), 151.8 (C, 8-C), 158.0 (C, 2-C), 183.4 (C, 3-C), 208.0 (C, 10-C), one C not observed; MS (EI) *m/z* 257 ($[M]^+$, 100%); HRMS (EI) *m/z* 257.1043 $[M]^+$, $C_{15}H_{15}NO_3$ requires 257.1051.

2-(2'-(*tert*-Butyldimethylsilyloxy)-1''-methyl-1*H*-indol-4''-yl)cyclohexanone (208)

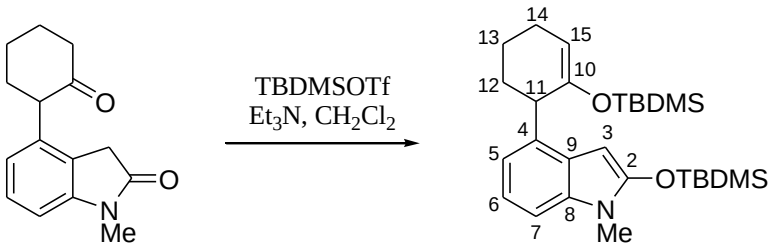


200 **208**

TBDMSOTf (208 μL, 0.94 mmol) was added to a solution of oxindole **200** (200 mg, 0.82 mmol) and Et_3N (137 μL, 0.99 mmol) in CH_2Cl_2 (6 mL) at rt. After 1 h at rt, the reaction was quenched with $NaHCO_3$ solution (6 mL of a saturated aqueous solution) and extracted with Et_2O (10 mL). The combined organic layers were washed with brine (20 mL), dried over

$MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O/Et_3N, 49/49/2) to give silyl enol ether **208** (226 mg, 77%) as a colourless oil; R_f 0.56 (petroleum ether/EtOAc, 90/10); IR υ_{max} 2931, 1709, 1552, 1470, 1254, 840, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.31 (d, *J* 1.7, 6H, C*H*$_3$), 1.04 (s, 9H, C*H*$_3$), 1.81-1.95 (m, 2H, 13-C*H* and14-C*H*), 2.00-2.21 (m, 2H, 13-C*H* and 14-C*H*), 2.22-2.37 (m, 2H, 12-C*H*), 2.46-2.63 (m, 2H, 15-C*H*$_2$), 3.53 (s, 3H, NC*H*$_3$), 3.86 (dd, *J* 11.5, 5.9, 1H, 11-C*H*), 5.37 (s, 1H, 3-C*H*), 6.90 (dd, *J* 5.8, 2.6, 1H, 5-C*H*), 7.05-7.10 (m, 2H, 6-C*H* and 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8 (CH_3), 18.1 (C), 25.5 (CH_2, 13-CH_2), 25.6 (CH_3), 27.4 (CH_3, NCH_3), 27.8 (CH_2, 14-CH_2), 34.0 (CH_2, 12-CH_2), 42.2 (CH_2, 15-CH_2), 54.9 (CH, 11-CH), 79.0 (CH, 3-CH), 107.1 (CH, 7-CH), 118.6 (CH, 5-CH), 119.1 (CH, 6-CH), 126.3 (C, 9-C), 128.9 (C, 4-C), 132.1 (C, 8-C), 148.4 (C, 2-C), 210.1 (C, 10-C); MS (ESI) *m/z* 380.3 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 380.2027 $[M+Na]^+$, $C_{21}H_{31}NO_2SiNa$ requires 380.2022.

2-(*tert*-Butyldimethylsilyloxy)-4-(2'-(tert-butyldimethylsilyloxy)cyclohex-2''-enyl)-1-methyl-1*H*-indole (209)

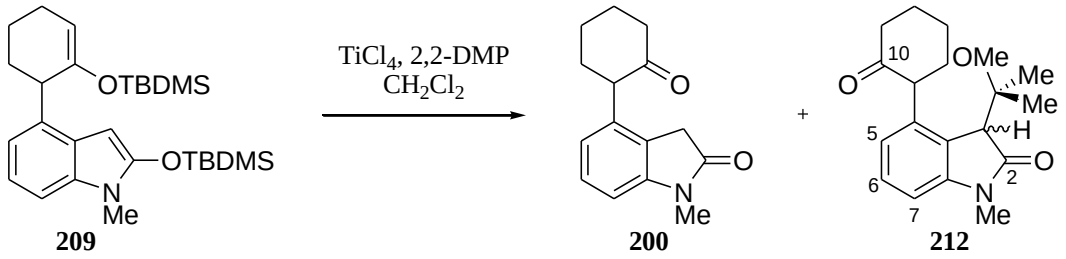


200 **209**

TBDMSOTf (1.22 mL, 5.31 mmol) was added dropwise over a period of 5 min to a solution of oxindole **200** (614 mg, 2.52 mmol) and Et_3N (774 μL, 5.55 mmol) in dry CH_2Cl_2 (15 mL) at rt. After 1 h at rt, the reaction was quenched with $NaHCO_3$ solution (30 mL of a saturated aqueous solution) and extracted with Et_2O (30 mL). The combined organic layers were

washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O/Et_3N, 95/4/1) to provide silyl enol ether **209** (1.08 g, 91%) as a colourless oil; R_f 0.80 (petroleum ether/Et_2O, 99/1); IR υ_{max} 2929, 837, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.04 (s, 3H, C*H*$_3$), 0.07 (s, 3H, C*H*$_3$), 0.34 (s, 3H, C*H*$_3$), 0.34 (s, 3H, CH_3), 0.65 (s, 9H, C*H*$_3$), 1.07 (s, 9H, C*H*$_3$), 1.47-1.58 (m, 1H, 13-C*H*$_2$), 1.60-1.71 (m, 1H, 13-C*H*$_2$), 1.88-1.97 (m, 1H, 12-C*H*$_2$), 1.99-2.09 (m, 1H, 12-C*H*$_2$), 2.11-2.28 (m, 2H, 14-C*H*$_2$), 3.55 (s, 3H, NC*H*$_3$), 3.70 (app t, *J* 5.7, 1H, 11-C*H*), 5.09 (app t, *J* 3.9, 1H, 15-C*H*), 5.63 (s, 1H, 3-C*H*), 6.93 (dd, *J* 6.3, 2.1, 1H, 5-C*H*), 6.99-7.04 (m, 2H, 6-C*H* and 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8 (CH_3), -4.4 (CH_3), 17.8 (C), 18.2 (C), 20.1 (CH_2, 13-CH_2), 24.3 (CH_2, 14-CH_2), 25.4 (CH_3), 25.7 (CH_3), 27.4 (CH_3, NCH_3), 31.0 (CH_2, 12-CH_2), 43.5 (CH, 11-CH), 79.0 (CH, 3-CH), 104.8 (CH, 15-CH), 106.0 (CH, 7-CH), 118.7 (CH, 6-CH), 119.1 (CH, 5-CH), 126.1 (C, 9-C), 132.2 (C, 4-C), 134.0 (C, 8-C), 148.0 (C, 10-C), 151.4 (C, 2-C); MS (ESI) *m/z* 494.3 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 494.2893 $[M+Na]^+$, $C_{27}H_{45}NO_2Si_2Na$ requires 494.2887.

3-(2'-Methoxypropan-2'-yl)-1-methyl-4-(2''-oxocyclohexyl)indolin-2-one (212)

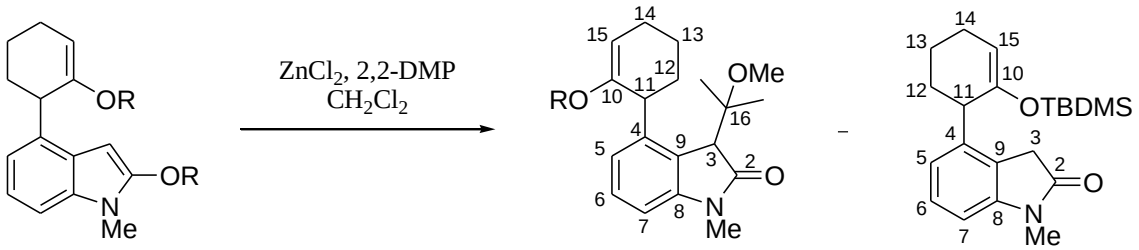


209 **200** **212**

2,2-Dimethoxypropane (26 μL, 0.21 mmol) was added to a solution of $TiCl_4$ (1 M solution in toluene, 212 μL, 0.21 mmol) in CH_2Cl_2 (1 mL) at -78 °C. A solution of **209** (100 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) was added immediately to the reaction mixture, which was stirred for 4.5 h at -78 °C. The reaction was quenched with H_2O (2 mL) at -78 °C. The separated

aqueous phase was extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to give oxindole **200** (8 mg, 16%) as a white solid, data as previously described (p.131) and a mixture of diatereoisomers (ratio 2.4:1) of oxindole **212** (44 mg, 66%) as a white solid; R_f 0.34 (petroleum ether/EtOAc, 60/40); mp 115-117 °C; IR υ_{max} 2936, 1707, 1052, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (s, 3H, C*H*$_3$, major), 0.74 (s, 3H, C*H*$_3$, minor), 1.52 (s, 3H, C*H*$_3$, major), 1.57 (s, C*H*$_3$, minor), 1.70-1.89 (m, 3H), 1.91-2.06 (m, 2H), 2.10-2.24 (m, 1H) 2.38-2.56 (m, 2H), 2.98 (s, 3H, OC*H*$_3$, major), 3.11 (s, 3H, NC*H*$_3$, minor), 3.14 (s, 3H, NC*H*$_3$, major), 3.23 (s, 3H, OC*H*$_3$, minor), 3.43 (s, 1H, 3-C*H*, minor), 3.48 (s, 1H, 3-CH, major), 4.27 (dd, *J* 12.0, 5.0, 1H, 11-C*H*, major), 4.40 (dd, 12.3, 5.3, 1H, 11-CH, minor), 6.60-6.70 (m, 1H, Ar*H*), 6.81 (d, *J* 8.0, 1H, Ar*H*, minor), 6.87 (d, *J* 8.0, Ar*H*, major), 7.20-7.31 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3, major), 18.5 (CH_3, minor), 22.6 (CH_3, minor), 22.7 (CH_3, major), 25.6 (CH_2, minor), 26.0 (CH_2, major), 26.1 (CH_3, NCH_3), 27.7 (CH_2, minor), 28.3 (CH_2, major), 34.9 (CH_2, minor), 36.4 (CH_2, major), 42.3 (CH_2, minor), 42.6 (CH_2, major), 48.7 (CH_3, OCH_3, major), 48.8 (CH_3, OCH_3, minor), 54.4 (CH, minor), 55.0 (CH, major), 55.4 (CH, minor and major), 78.2 (C minor and major), 105.6 (CH, 7-CH, major), 106.1 (CH, 7-CH, minor), 123.1 (CH, 5-CH, minor), 123.3 (CH, 5-CH, major), 126.0 (C, major), 126.2 (C, minor), 127.6 (CH, 6-CH, minor), 127.8 (CH, 6-CH, major), 137.9 (C, minor), 138.4 (C, major), 144.8 (C, major), 145.1 (C, minor), 175.5 (C, 2-C, minor and major), 210.1 (C, 10-C, major), 210.8 (C, 10-C, minor); MS (ESI) *m/z* 338.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 338.1736 $[M+Na]^+$, $C_{19}H_{25}NO_3Na$ requires 338.1732.

4-(2'-(*tert*-Butyldimethylsilyloxy)cyclohex-2'-enyl)-3-(2''-methoxypropan-2'-yl)-1-methylindolin-2-one (213) and 4-(2'-(*tert*-butyldimethylsilyloxy)cyclohex-2''-enyl)-1-methylindolin-2-one (214)



209 R = TBDMS **213** R = TBDMS **214**

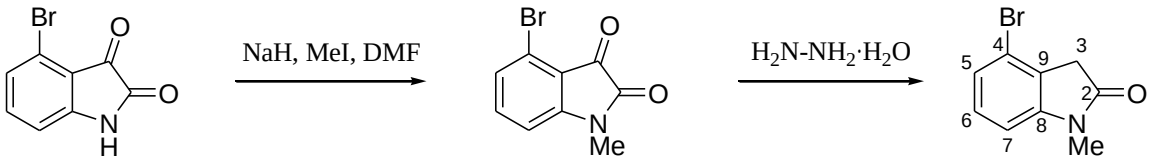
A solution of $ZnCl_2$ (1 M in CH_2Cl_2, 411 μL, 0.41 mmol) was added to a solution of **209** (194 mg, 0.41 mmol) and 2,2-dimethoxypropane (51 μL , 0.41 mmol) in CH_2Cl_2 (2 mL) at -78 °C. The reaction mixture was stirred for 6 h at -78 °C and a further 2 h at -40 °C and quenched with $NaHCO_3$ solution (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O/Et_3N, 95/4/1) to afford enol silane **213** (48 mg, 27%) as a colourless oil and oxindole **214** (73 mg, 50%) as a white solid.

Data for **213**; R_f 0.55 (peteoleum ether/EtOAc, 80/20); IR υ_{max} 2929, 1692, 1252, 832, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H, C*H*$_3$), 0.16 (s, 3H, C*H*$_3$), 0.736 (s, 9H, C*H*$_3$), 0.92 (s, 3H, C*H*$_3$), 1.35-1.48 (m, 3H, 12-C*H*$_2$ and 13-C*H*$_2$), 1.51 (s, 3H, C*H*$_3$), 1.77-1.92 (m, 1H, 12-C*H*$_2$), 2.00-2.17 (m, 2H, 14-C*H*$_2$), 3.13 (s, 3H, NC*H*$_3$), 3.24 (s, 3H, C*H*$_3$), 3.66 (s, 1H, 2-C*H*), 4.47-4.53 (m, 1H, 11-C*H*), 5.00-5.03 (m, 1H, 15-C*H*), 6.61 (d, *J* 7.4, 1H, 5-C*H*), 6.91 (d, *J* 8.0, 1H, 7-C*H*), 7.16 (app t, *J* 7.8, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9 (CH_3), -4.3 (CH_3), 17.9 (C), 19.4 (CH_2, 13-CH_2), 21.1 (CH_3), 23.3 (CH_3), 24.2 (CH_2, 14-CH_2), 25.5 (CH_3), 26.1 (CH_3, NCH_3), 31.9 (CH_2, 12-CH_2), 41.4 (CH, 11-CH), 48.8 (CH_3, OCH_3), 54.1 (CH, 3-CH), 78.5 (C, 16-C), 104.4 (CH, 15-CH), 105.3 (CH, 5-CH), 122.9 (CH,

7-CH), 125.8 (C, 9-C), 127.1 (CH, 6-CH), 143.4 (C, 4-C), 145.4 (C, 8-C), 151.3, (C, 10-C), 176.2 (C, 2-C); MS (ESI) *m/z* 452.2 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 452.2596 [M+Na]$^+$, $C_{25}H_{39}NO_3SiNa$ requires 452.2597.

Data for **214**, R_f 0.23 (petroleum ether/EtOAc, 90/10); mp 96-97 °C; IR υ_{max} 2925, 1701, 1603, 1225, 836, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H, C*H*$_3$), 0.04 (s, 3H, C*H*$_3$), 0.62 (s, 9H, C*H*$_3$), 1.46-1.57 (m, 1H, 13-C*H*$_2$), 1.58-1.70 (m, 2H, 12-C*H*$_2$ and 13-C*H*$_2$), 1.94-2.04 (m, 1H, 12-C*H*$_2$), 2.06-2.22 (m, 2H, 14-C*H*$_2$), 3.19 (s, 3H, NC*H*$_3$), 3.37 (app t, *J* 6.1, 1H, 11-C*H*), 3.49 (d, *J* 3.0, 2H, 3-C*H*$_2$), 5.00-5.05 (m, 1H, 15-C*H*), 6.65 (d, *J* 7.7, 1H, 5-C*H*), 6.89 (d, *J* 7.9, 1H, 7-C*H*), 7.19 (app t, *J* 7.8, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7 (CH_3), 17.7 (CH), 20.7 (CH_2, 13-CH_2), 24.1 (CH_2, 14-CH_2), 25.3 (CH_3), 26.2 (CH_3, NCH_3), 31.2 (CH_2, 12-CH_2), 34.7 (CH_2, 2-CH_2), 44.1 (CH, 11-CH), 105.5 (CH, 5-CH), 105.8 (CH, 15-CH), 122.7 (CH, 7-CH), 122.9 (C, 9-C), 127.5 (CH, 6-CH), 140.5 (C, 4-C), 144.9 (C, 8-C), 149.9 (C, 10-C), 175.3 (C, 2-C); MS (ESI) *m/z* 380.3 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 380.2033 [M+Na]$^+$, $C_{21}H_{31}NO_2SiNa$ requires 380.2022.

4-Bromo-1-methylindolin-2-one (217)[10]

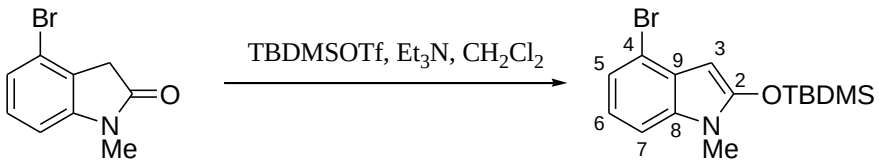


216 **217**

NaH (414 mg, 60% dispersion in mineral oil, 0.01 mmol) was added to a solution of 4-bromoisatin (2.00 g, 0.09 mmol) in DMF (15 mL) at 0 °C. After 30 min at rt, MeI (0.72 mL, 0.06 mmol) was added and the resultant mixture was stirred for 28 h at rt. Addition of ice-cold H_2O and filtration of the solid after evaporation of the solvent under reduced pressure afforded **216**. The crude **216** was dissolved in H_2NNH_2 (12 mL) and heated under reflux for

1.5 h. The mixture was cooled to rt and H_2O (120 mL) and EtOAc (120 mL) were added. The separate aqueous phase was extracted with EtOAc (3 × 60 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 75/25) to give oxindole **217** (1.20 g, 60%) as a pale yellow solid; mp 135-137 °C [lit.,[10] 138-139 °C]; R_f 0.56 (petroleum ether/EtOAc, 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H, NC*H*$_3$), 3.46 (s, 2H, 3-C*H*$_2$), 6.75-6.71 (m, 1H, 6-C*H*), 7.15-7.17 (m, 2H, 5-C*H* and 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (CH_3, NCH_3), 37.1, (CH_2, 3-CH_2), 106.8 (CH, 7-CH), 119.0 (C, 4-C), 125.3 (CH, 6-CH), 125.4 (C, 9-C), 129.5 (CH, 5-CH), 146.1 (C, 8-C), 173.8 (C, 2-C); MS (EI) *m/z* 225.0 ([M]$^+$, 100%), 227.0 (97%); HRMS (EI) *m/z* 224.9783 [M]$^+$, $C_9H_8NO^{79}Br$ requires 224.9789.

4-Bromo-2-(tert-butyldimethylsilyloxy)-1-methyl-1*H*-indole (218)

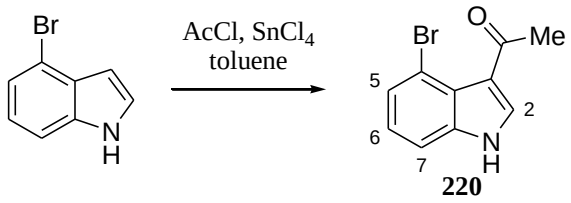


217 **218**

TBDMSOTf (256 μL, 1.11 mmol) was added dropwise over a period of 5 min to a solution of oxindole **217** (229 mg, 1.01 mmol) and Et_3N (184 μL, 1.32 mmol) in dry CH_2Cl_2 (5 mL) at rt. The reaction mixture was stirred for 1 h at rt and then quenched with $NaHCO_3$ solution (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with Et_2O (5 mL). The organic extract was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O/Et_3N, 30/69/1) to provide enol silane **218** (227 mg, 80%) as a yellow oil; R_f 0.79 (petroleum ether/EtOAc, 90/10); IR υ_{max} 2929, 1551, 1470, 1254, 830, 786, 725

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (s, 6H, CH_3), 1.04 (s, 9H, CH_3), 3.54 (s, 3H, NCH_3), 5.57 (s, 1H, 3-C*H*), 6.92 (app t, *J* 7.9, 1H, 6-C*H*), 7.08 (d, *J* 8.0, 1H, 7-C*H*), 7.18 (dd, *J* 7.7, 0.8, 1H, 5-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8 (CH_3), 18.2 (C), 25.6 (CH_3), 27.7 (CH_3, NCH_3), 80.8 (CH, 3-CH), 107.2 (CH, 7-CH), 112.5 (C, 4-C), 120.0 (CH, 5-CH), 122.4 (CH, 6-CH), 127.8 (C, 9-C), 132.5 (C, 8-C); 149.1 (C, 2-C); MS (ESI) m/z 340.1 ($[M+H]^+$, 100%), 342.1 (97%); HRMS (ESI) *m/z* 340.0726 $[M+H]^+$, $C_{15}H_{23}NOSi^{79}Br$ requires 340.0732.

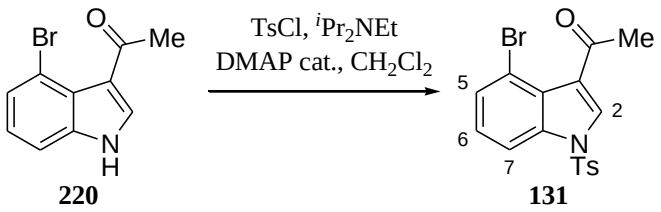
1-(4'-Bromo-1*H*-indol-3'-yl)ethanone (220)[11]



220

AcCl (6.2 mL, 87 mmol) was added to a solution of 4-bromoindole (8.6 g, 44 mmol) in toluene (500 mL) at 0 °C. The mixture was stirred for 15 min at that temperature and a solution of $SnCl_4$ (10.3 mL, 87 mmol) in toluene (200 mL) was added. After 2 h at 0 °C, $NaHCO_3$ solution (750 mL of a 8% aqueous solution) was added and the mixture was extracted with EtOAc (2 × 1 L). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallisation from acetone to provide indole **220** (8.7 g, 88%) as a white solid[11]; mp 166-168 °C [lit.,[11] 167-168 °C]; ^{1}H NMR (400 MHz, CD_3OD) δ 2.56 (s, 3H, CH_3), 7.13 (app t, *J* 7.9, 1H, 6-C*H*), 7.73 (dd, *J* 7.7, 0.8, 1H, 5-C*H*), 7.47 (dd, *J* 8.1, 0.8, 7-C*H*), 8.18 (s, 1H, 2-C*H*);^{13}C NMR (100 MHz, CD_3OD) δ 30.3 (CH_3), 113.2 (CH, 7-CH), 116.2 (C), 120.4 (C), 126.0 (CH, 6-CH), 126.7 (C), 129.2 (CH, 5-CH), 136.8 (CH, 2-CH), 141.2 (C), 196.4 (C); MS (ESI) *m/z* 259.9 ($[M+Na]^+$, 100%), 261.9 (97%); HRMS (ESI) *m/z* 259.9684 $[M+Na]^+$, $C_{10}H_8NO^{79}BrNa$ requires 259.9687.

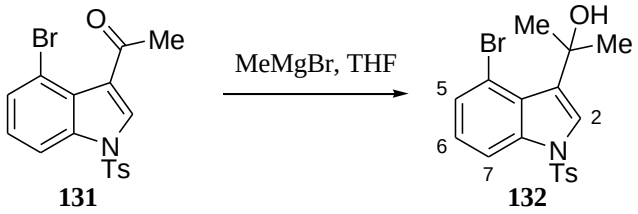
1-(4'-Bromo-1'-tosyl-1*H*-indol-3'-yl)ethanone (131)[11]



220 **131**

DMAP (234 mg, 1.91 mmol), TsCl (8.0 g, 42 mmol) and $^{i}Pr_2NH$ (10 mL, 57 mmol) were added to a solution of **220** (8.7 g, 38 mmol) in CH_2Cl_2 (190 mL). The resultant mixture was stirred overnight at rt and HCl solution (250 mL of a 10% aqueous solution) and CH_2Cl_2 (500 mL) were added and the mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 80/20) to give sulfonamide **131** (14.3 g, 95%) as a white solid; [11] R_f 0.22 (petroleum ether/EtOAc, 80/20); mp 142-144 °C [lit.,[11] 142.5-143 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, ArC*H*$_3$), 2.63 (s, 3H, C*H*$_3$), 7.21 (app t, *J* 8.1, 1H, 6-C*H*), 7.28 (d, *J* 8.3, 2H, Ar*H*), 7.51 (dd, *J* 7.8, 0.6, 1H, 5-C*H*), 7.79 (d, *J* 8.3, 2H, Ar*H*), 7.94 (dd, *J* 8.3, 0.6, 1H, 7-C*H*), 8.04 (s, 1H, 2-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 31.2 (CH_3), 112.4 (CH, 7-CH), 115.0 (C), 124.2 (C), 126.5 (CH, 6-CH), 126.9 (C), 127.1 (CH, ArCH), 129.5 (CH, 5-CH), 130.2 (CH, 7-CH), 130.3 (CH, ArCH), 134.3 (C), 136.1 (C), 146.2 (C), 194.1 (C); MS (ESI) *m/z* 414 ($[M+Na]^+$, 100%), 416 (97%); HRMS (ESI) *m/z* 413.9768 $[M+Na]^+$, $C_{17}H_{14}NO_3S^{79}BrNa$ requires 413.9775.

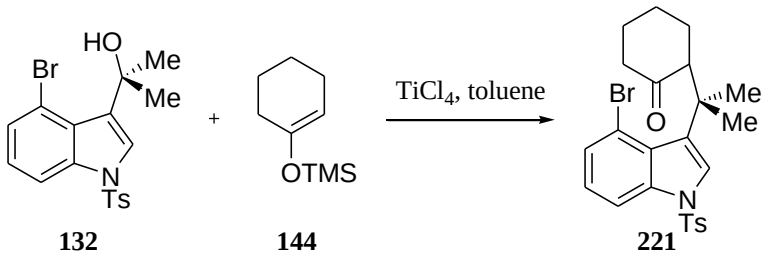
2-(4'-Bromo-1'-tosyl-1*H*-indol-3'-yl)propan-2-ol (132)[11]



131 **132**

MeMgBr (3 M solution in Et_2O, 28 mL, 83 mmol) was added *via* cannula into a solution of **131** (14.3 g, 36 mmol) in THF (325 mL) at 0 °C. After 30 min at 0 °C, a 1:1 mixture (250 mL) of H_2O and NH_4Cl solution (saturated aqueous solution) was added. The resultant mixture was extracted with Et_2O (3 × 400 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 80/20) to afford alcohol **132** (13.8 g, 92%) as a white solid;[11] R_f 0.24 (petroleum ether/EtOAc, 80/20), mp 98-100 °C [lit.,[11] 100-101°C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 6H, C*H*$_3$), 2.36 (s, 3H, ArC*H*$_3$), 3.27 (br s, 1H, O*H*), 7.14 (app t, *J* 8.1, 1H, 6-C*H*), 7.24 (d, *J* 8.4, 2H, Ar*H*), 7.50 (dd, *J* 7.8, 0.9, 1H, 5-C*H*), 7.65 (s, 1H, 2-C*H*), 7.74 (d, *J* 8.4, 2H, Ar*H*), 8.02 (dd, *J* 8.4, 0.9, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.58 (CH_3, $ArCH_3$), 31.7 (CH_3), 68.9 (C), 113.1 (C), 113.1 (CH, 7-CH), 124.2 (CH, 2-CH), 125.3 (CH, 6-CH), 126.9 (CH, ArCH), 128.3 (C), 128.9 (CH, 5-CH), 129.2 (C), 130.1 (CH, ArCH), 134.8 (C), 137.6 (C), 145.4 (C); MS (ESI) *m/z* 430.1 ($[M+Na]^+$, 100%), 431.1 (97%); HRMS (ESI) *m/z* 430.0093 $[M+Na]^+$, $C_{18}H_{18}NO_3S^{79}BrNa$ requires 430.0088.

2-(2'-(4''-Bromo-1''-tosyl-1*H*-indol-3''-yl)propan-2-yl)cyclohexanone (221)[11]



132 **144** **221**

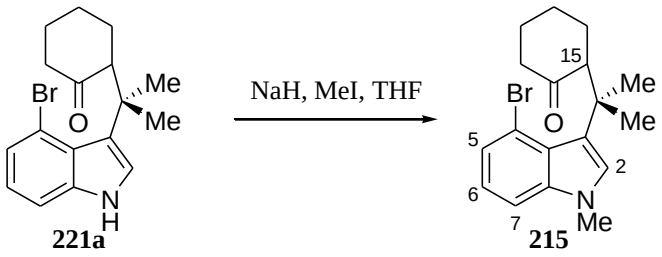
Silyl enol ether **144** (12.2 g, 75 mmol) and $TiCl_4$ (1 M solution in toluene, 71 mL, 71 mmol) were added to a solution of alcohol **132** (13.8 g, 34 mmol) in toluene (560 mL) at -78 °C. After 1 h at -78 °C, $NaHCO_3$ solution (200 mL of a saturated aqueous solution) was added dropwise over a period of 15 min. H_2O (400 mL) and CH_2Cl_2 (600 mL) were added and the mixture was extracted with CH_2Cl_2 (400 mL). The combined organic layers were washed with $NaHCO_3$ solution (400 mL), HCl solution (400 mL of a 10% aqueous solution), and brine, then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene/Et_2O, 98/2) to afford indole **221** (11.3 g, 69%) as a white solid[11]; R_f 0.51 (toluene/Et_2O, 95/5); mp 74-75 °C [lit., 74-75 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43-1.53 (m, 2H), 1.54 (s, 3H), 1.71 (s, 3H, C*H*$_3$), 1.57-1.80 (m, 3H), 1.99-2.03 (m, 1H), 2.27 (br s, 2H), 2.34 (s, 3H, ArC*H*$_3$), 4.04-4.07 (m, 1H), 7.08 (app t, *J* 8.1, 1H), 7.22 (d, *J* 8.4, 2H, Ar*H*), 7.50 (d, *J* 7.8, 1H), 7.55 (br s, 1H), 7.70 (d, *J* 8.4, 2H, Ar*H*), 8.00 (d, *J* 8.3, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3, $ArCH_3$), 26.0 (CH_3), 26.8 (CH_2), 28.3 (CH_2), 30.2 (CH_2), 36.5 (C), 44.3 (CH_2), 55.9 (CH), 113.2 (CH), 113.7 (C), 124.8 (CH), 125.6 (CH), 126.8 (CH, ArCH), 128.9 (CH), 129.8 (C), 129.9 (CH, ArCH), 130.9 (C), 134.6 (C), 138.0 (C), 145.1 (C), 211.8 (C), one CH_3 not observed; MS (ESI) *m/z* 510.3 ($[M+Na]^+$, 100%), 512.2 (97%); HRMS (ESI) *m/z* 510.0720 $[M+Na]^+$, $C_{24}H_{26}NO_3S^{79}BrNa$ requires 510.0714.

2-(2'-(4''-Bromo-1*H*-indol-3''-yl)propan-2'-yl)cyclohexanone (221a)[11]

221 **221a**

Crushed KOH pellets (27.3 g, 0.49 mol) were added to a solution of **221** (11.9 g, 24 mmol) in EtOH (950 mL) and stirred for 3 h at 40 °C. The reaction mixture was cooled to rt and NH_4Cl solution (1 L, of a saturated aqueous solution) was added. The mixture was extracted with EtOAc (4 × 1 L), then the combined organic layers were washed with brine (1 L), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to furnish indole **221a** (7.3 g, 90%) as a white solid;[11] R_f 0.14 (petroleum ether/EtOAc, 90/10), mp 164-166 °C [lit.,[11] 167-168 °C], ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45-1.72 (m, 3H), 1.57 (s, 3H, C*H*$_3$), 1.72-1.87 (m, 2H), 1.77 (s, 3H, C*H*$_3$), 2.00-2.11 (m, 1H), 2.23-2.48 (m, 2H), 4.26 (dd, *J* 11.6, 4.5, 1H), 6.97 (app t, *J* 7.8, 1H, 6-C*H*), 7.10 (d, *J* 2.6, 1H, 2-C*H*), 7.31 (dd, *J* 8.0, 1.0, 1H), 7.41 (dd, *J* 7.6, 1.0, 1H), 8.54 (br s,1 H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_3), 26.1 (CH_2), 27.4 (CH_3), 28.6 (CH_2), 30.5 (CH_2), 36.1 (C), 44.5 (CH_2), 57.3 (CH), 111.1 (CH), 113.6 (C), 122.1 (CH), 123.7 (CH), 124.8 (C), 125.4 (C), 125.8 (CH), 139.5 (C), 213.5 (C); MS(ESI) *m/z* 356.0 ([M+Na]$^+$, 100%), 358.0 (97%); HRMS (ESI) *m/z* 356.0628 [M+Na]$^+$, $C_{17}H_{20}NO^{79}BrNa$ requires 356.0626.

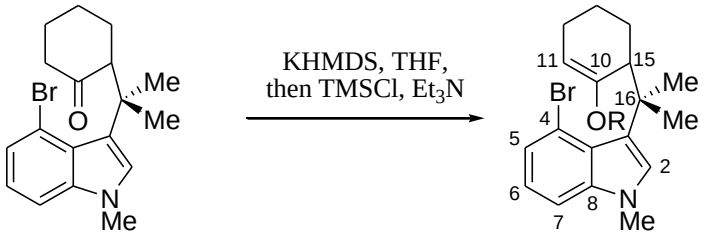
2-(2'-(4''-Bromo-1''-methyl-1*H*-indol-3''-yl)propan-2'-yl)cyclohexanone (215)



221a **215**

NaH (290 mg, 60% dispersion in mineral oil, 7.24 mmol) was added to a solution of indole **221a** (1.86 g, 5.57 mmol) in THF (45 mL) at 0 °C. After 20 min, MeI (416 μL, 6.68 mmol) was added dropwise over a period of 5 min, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched by addition of H_2O (25 mL) and NH_4Cl solution (25 mL of a saturated aqueous solution). The resulting mixture was extracted with EtOAc (3 × 200 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to provide indole **215** (1.88 g, 97%) as a white solid; R_f 0.50 (petroleum ether/EtOAc, 80/20); mp 80-82 °C [lit.,[11] mp 80-81 °C], ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.63 (m, 3H), 1.46 (s, 3H, C*H*$_3$),1.63-1.85 (m, 2H), 1.67 (br s, 3H, C*H*$_3$), 1.90-1.99 (m, 1H), 2.12-2.33 (m, 2H), 3.63 (s, 3H, NC*H*$_3$), 4.12 (dd, *J* 12.2, 4.4, 1H, 15-C*H*), 6.90 (s, 1H, 2-C*H*), 6.92 (app t, *J* 7.9, 1H, 6-C*H*), 7.15 (dd, *J* 8.1, 0.9, 1H, 7-C*H*), 7.30 (dd, *J* 7.6, 0.9, 1H, 5-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_3), 26.1(CH_2), 27.7 (CH_3), 28.7 (CH_2), 30.0 (CH_2), 33.0 (CH_3, NCH_3), 36.1 (C), 44.5 (CH_2), 57.3 (CH, 15-CH), 108.9 (CH, 7-CH), 113.7 (C), 121.7 (CH, 6-CH), 124.0 (C), 125.2 (C), 125.3 (CH, 5-CH), 128.6 (CH, 2-CH), 139.9 (C), 213.0 (C, 10-C); MS (ESI) *m/z* 370.0 ([M+Na]$^+$, 100%), 372.0 (97%); HRMS (ESI) *m/z* 370.0775 [M+Na]$^+$, $C_{18}H_{22}NO^{79}BrNa$ requires 370.0782.

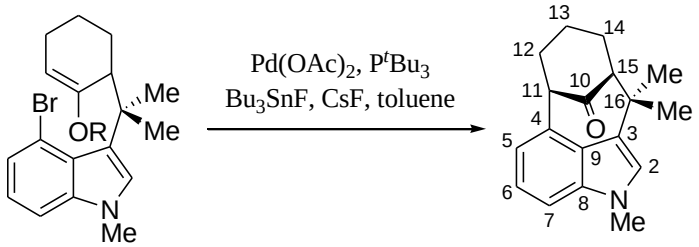
4-Bromo-1-methyl-3-(2'-(2''-(trimethylsilyloxy)cyclohex-2''-enyl)propan-2'-yl)-1*H*-indole (222)



215 **222** R = TMS

A solution of KHMDS (0.5 M solution in toluene, 1.9 mL, 0.95 mmol) was added dropwise, over a period of 5 min, to a solution of **215** (300 mg, 0.86 mmol) in THF (7 mL) at -78 °C. The mixture was stirred 30 min at this temperature. Et_3N (0.24 mL, 1.72 mmol) and TMSCl (0.22 mL, 1.72 mmol) were added and the solution was stirred for 1 h at -78 °C. The reaction was quenched with H_2O (7 mL) and extracted with Et_2O (2 × 7 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 90/10) to give silyl enol ether **222** (296 mg, 82%) as a white solid; R_f 0.72 (petroleum ether/EtOAc, 90/10); mp 95-96 °C; IR υ_{max} 2927, 1163, 839, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (br s, 9H, C*H*$_3$), 1.34 (br s, 3H), 1.48 (s, 3H, C*H*$_3$), 1.61 (br s, 4H), 1.97 (br s, 2H), 3.71-3.78 (m, 1H, 15-C*H*), 3.71 (s, 3H, NC*H*$_3$), 4.90 (br s, 1H, 11-C*H*), 6.91 (s, 1H, 2-C*H*), 7.00 (app t, *J* 7.9, 1H, 6-C*H*), 7.23 (d, *J* 8.1, 1H, 5-C*H*), 7.39 (d, *J* 7.6, 1H, 7-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.1 (CH_3), 22.7 (2 × CH_2), 22.7 (CH_3), 24.5 (CH_2), 27.6 (CH_3), 32.9 (CH_3, NCH_3), 37.0 (C, 16-C), 45.8 (CH, 15-CH), 106.5 (CH, 11-CH), 108.6 (CH, 7-CH), 114.2 (C, 4-C), 121.5 (CH, 6-CH), 125.0 (C), 125.0 (CH, 5-CH), 125.9 (C), 127.5 (CH, 2-CH), 139.6 (C, 8-C), 153.8 (C, 10-C); MS (ESI) *m/z* 442.3 ($[M+Na]^+$, 100%), 444.3 (97%); HRMS (ESI) *m/z* 442.1189 $[M+Na]^+$, $C_{21}H_{30}NO^{79}BrSiNa$ requires 442.1178.

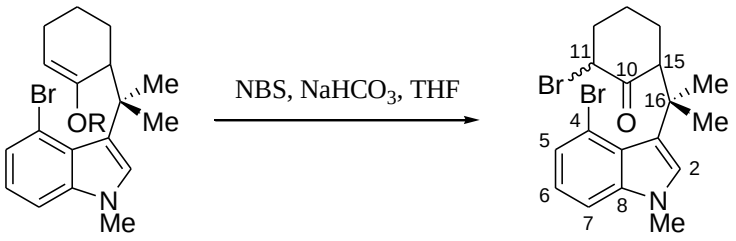
Bicyclo[4.3.1]decane compound (182)



222 R = TMS **182**

A solution of P^tBu_3 (1M solution in toluene, 64 μL, 0.06 mmol) was added to a solution of $Pd(OAc)_2$ (8 mg, 0.04 mmol), Bu_3SnF (442 mg, 1.43 mmol) and CsF (217 mg, 1.43 mmol) in toluene (5 mL). Then, silyl enol ether **222** (500 mg, 1.19 mmol) was added and the reaction mixture was heated for 21 h at 85 °C. After cooling to rt, the reaction mixture was diluted with Et_2O (5 mL) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 90/10) to provide the cyclised product **182** (263 mg, 83%) as a white foam; R_f 0.34 (petroleum ether/EtOAc, 90/10); mp 100-101 °C; IR υ_{max} 2909, 1687, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H, C*H*$_3$), 1.19-1.26 (m, 1H, 13-C*H*$_2$), 1.34-1.47 (m, 1H, 13-C*H*$_2$), 1.55 (s, 3H, C*H*$_3$), 1.83-1.98 (m, 2H, 12-C*H*$_2$ and 14-C*H*$_2$), 2.18-2.32 (m, 2H, 12-C*H*$_2$ and 14-C*H*$_2$), 2.60 (br d, *J* 7.2, 1H, 15-C*H*), 3.75 (s, 3H, NC*H*$_3$), 4.04-4.09 (m, 1H, 11-C*H*), 6.84 (d, *J* 6.8, 1H, 5-C*H*), 6.94 (s, 1H, 2-C*H*), 7.16 (dd, *J* 8.1, 1.2, 1H, 7-C*H*), 7.21 (dd, *J* 8.1, 6.8, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_2, 13-CH_2), 28.1 (CH_3), 28.7 (CH_2, 14-CH_2), 32.8 (CH_3, NCH_3), 34.9 (C, 16-C), 36.3 (CH_3), 39.5 (CH_2, 12-CH_2), 58.3 (CH, 11-CH), 61.3 (CH, 15-CH), 107.2 (CH, 7-CH), 118.3 (CH, 5-CH), 122.3 (CH, 6-CH), 122.7 (C, 9-C), 125.3 (C, 3-C), 126.0 (CH, 2-CH), 132.1 (C, 4-C), 136.9 (C, 8-C), 214.5 (C, 10-C); MS (ESI) *m/z* 290.1 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 290.1506 $[M+Na]^+$, $C_{18}H_{21}NONa$ requires 290.1521.

2-Bromo-6-(2'-(4''-bromo-1''-methyl-1*H*-indol-3''-yl)propan-2'-yl)cyclohexanone (231)

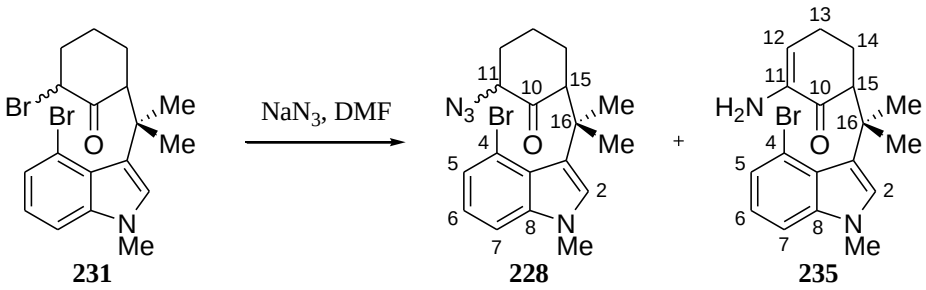


222 R = TMS **231**

Powdered $NaHCO_3$ (21 mg, 0.25 mmol) and NBS were successively added to a solution of silyl enol ether **222** (100 mg, 0.21 mmol) in THF (1.3 mL) at -78 °C. After 2 h at this temperature the mixture was warmed to rt and partitioned between $NaHCO_3$ solution (2 mL of a saturated aqueous solution) and Et_2O (5 mL). The mixture was extracted with Et_2O (5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to afford a mixture of diastereoisomers (1:0.7) of indole **231** (91 mg, quantitative) as a white solid; R_f 0.33 (petroleum ether/EtOAc, 90/10); mp 76-77 °C; IR υ_{max} 2945, 1708, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40-1.66 (m, 2H, C*H*$_2$, minor and major), 1.56 (s, 3H, C*H*$_3$, major), 1.58 (s, 3H, C*H*$_3$, minor), 1.77 (br s, 4H, minor and major), 1.99-2.29 (m, 3H, minor and major), 2.59-2.69 (m, 1H, minor), 3.73 (s, 3H, NC*H*$_3$), 4.24-4.34 (m, 1H, 11-C*H*, major and 15-C*H*, minor), 4.66 (br s, 1H, 11-C*H*, minor), 4.94 (dd, *J* 13.1, 4.9, 1H, 15-C*H*, major), 6.96-7.06 (m, 2H, 2-C*H* and 6-C*H*, minor and major), 7.23-7.28 (m, 1H, 7-C*H*, minor and major), 7.36-7.43 (m, 1H, 5-C*H*, minor and major); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (CH_2, minor and major), 25.1 (CH_3, minor and major), 26.8 (CH_2, major), 27.9 (CH_3, minor and major), 29.8 (CH_2, minor), 33.1 (CH_3, NCH_3, minor and major), 36.2 (CH_2, major), 36.9 (C, 16-C), 41.2 (CH_2, minor), 51.5 (CH, 15-CH, major), 54.2 (CH, 15-CH, minor), 57.2 (CH, 11-CH, major), 58.8 (CH, 11-CH, minor), 108.7 (CH, 7-CH, major), 109.0 (CH, 7-CH, minor), 113.8 (C, 4-C, minor), 114.0 (C,

4-C, major), 121.8 (CH, 6-CH, minor), 121.9 (CH, 6-CH, major), 123.4 (C, major), 124.1 (C, minor), 125.0 (C, major), 125.3 (C, minor), 125.4 (CH, 5-CH, major), 125.5 (CH, 5-CH, minor), 128.8 (CH, 2-CH, minor and major), 139.9 (C, 8-C, major), 140.0 (C, 8-C, minor), 205.3 (C, 10-C, major), 209.8 (C, 10-C, minor); MS (ESI) *m/z* 448.0 (50%), 450.0 ($[M+Na]^+$, 100%), 452.0 (50%); HRMS (ESI) *m/z* 449.9863 $[M+Na]^+$, $C_{18}H_{21}NO^{79}Br^{81}BrNa$ requires 449.9867.

2-Azido-6-(2'-(4''-bromo-1''-methyl-1*H*-indol-3''-yl)propan-2'-yl)cyclohexanone (228) and 2-amino-6-(2'-(4''-bromo-1''-methyl-1*H*-indol-3''-yl)propan-2'-yl)cyclohex-2-enone (235)



NaN_3 (9 mg, 0.14 mmol) was added to a solution of **231** (50 mg, 0.12 mmol) in DMF (4 mL). After 2 h at 70 °C, the reaction mixture was cooled to rt, poured into H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with cold H_2O (2 × 20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to furnish a mixture of diastereoisomers (2:1) of azide **228** (26 mg, 57%) as a brown oil and enamine **235** (5 mg, 12%) as a yellow oil.

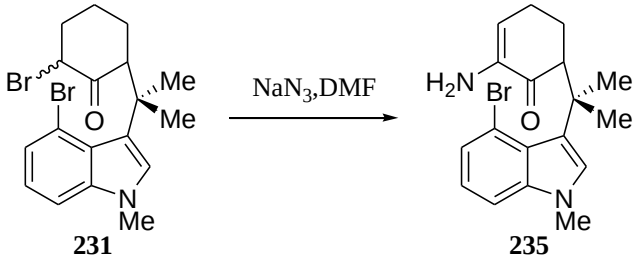
Data for azide **228**; R_f 0.40 (petroleum ether/EtOAc, 80/20); IR υ_{max} 2936, 2097, 1708, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42-1.58 (m, 2H, minor and major), 1.59 (s, 3H, CH_3, minor and major), 1.63-1.73 (m, 2H, minor and major), 1.76 (br s, 3H), 1.81-2.08 (m, 1H,

minor and major), 2.21-2.30 (m, 1H, minor), 2.31-2.40 (m, 1H, major), 3.74 (s, 3H, NC*H*$_3$), 3.77-3.82 (br m, 1H, 11-C*H*, major), 3.92 (app t, *J* 4.9, 1H, 11-C*H*, minor), 4.17-4.29 (m, 1H, 15-C*H*, major), 4.57 (dd, *J* 12.3, 4.9, 1H, 15-C*H* minor), 6.94-7.06 (m, 2H, 2-C*H* and 6-*H*, minor and major), 7.22-7.29 (m, 1H, minor and major), 7.37-7.44 (m, 1H, minor and major); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1 (CH_3, minor and major), 24.1 (CH_2, minor and major), 28.5 (CH_3, minor and major), 30.6 (CH_2, minor and major), 33.1 (CH_3, NCH_3), 32.3 (CH_2, minor), 35.0 (CH_2, major), 35.9 (C, 16-C, minor), 36.2 (C, 16-C, major), 56.8 (CH, 15-CH, major), 57.3 (CH, 15-CH, minor), 68.0 (CH, 11-CH, major), 68.2 (CH, 11-CH, minor), 108.9 (CH, 7-CH, minor), 109.1 (CH, 7-CH, major), 113.6 (C, 4-C, minor), 113.8 (C, 4-C, major), 121.7 (CH, 6-CH, minor), 121.9 (CH, 6-CH, major), 123.1 (C, major), 123.2 (C, minor), 125.0 (C, minor), 125.3 (C, major), 125.4 (CH, 5-CH, minor), 125.5 (CH, 5-CH, major), 128.6 (CH, 2-CH, major), 128.7 (CH, 2-CH, minor) 139.9 (C, 8-C, major), 140.0 (C, 8-C, minor), 208.8 (C, 10-C, major), 213.0 (C, 10-C, minor); MS (ESI) *m/z* 411.1 ($[M+Na]^+$, 100%), 413.1 (97%); HRMS (ESI) *m/z* 411.0785 $[M+Na]^+$, $C_{18}H_{21}N_4O^{79}BrNa$ requires 411.0796.

Data for enamine **235**; R_f 0.18 (petroleum ether/EtOAc, 80/20); IR υ_{max} 3353, 2925, 1726, 1666, 1110, 734 cm$^{-1;}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 3H, C*H*$_3$), 1.64-1.91 (broad m, 5H, C*H*$_3$ and 14-C*H*$_2$), 2.10-2.32 (broad m, 2H, 13-C*H*$_2$), 3.44 (broad s, 2H, N*H*$_2$), 3.74 (s, 3H, NC*H*$_3$), 4.17 (dd, *J* 12.0, 4.6, 1H, 15-C*H*), 5.79 (dd, *J* 5.7, 3.4, 1H, 12-C*H*), 7.00 (s, 1H, 2-C*H*), 7.01 (t, *J* 7.6, 1H, 6-C*H*), 7.25 (dd, *J* 7.6, 1.0, 1H, 7-C*H*), 7.38 (dd, *J* 7.6, 1.0, 1H, 5-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2 (CH_2, 13-CH_2), 26.6 (CH_3), 26.6 (CH_2, 14-CH_2), 28.7 (CH_3), 33.1 (CH_3, NCH_3), 37.2 (16-C), 53.0 (CH, 15-CH), 108.8 (CH, 7-CH), 113.8 (C, 4-C), 116.3 (CH, 12-CH), 121.9 (CH, 6-CH), 123.3 (C), 124.5 (C), 125.4 (CH, 5-CH), 128.2

(CH, 2-CH), 139.8 (C, 8-C), 140.2 (C, 11-C), 197.8 (C); MS (ESI) *m/z* 361.2 ([M+Na]$^+$, 100%), 363.2 (97%); HRMS (ESI) *m/z* 361.0913 [M+H]$^+$, $C_{18}H_{22}N_2O^{79}Br$ requires 361.0915.

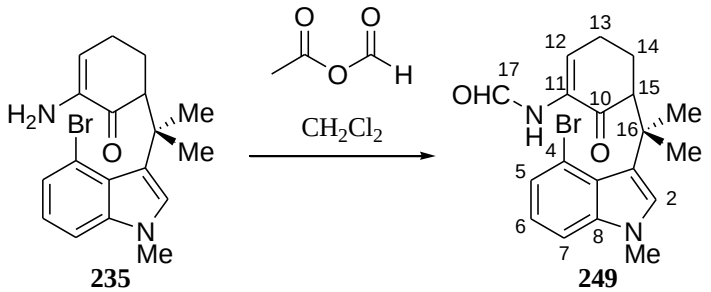
Alternative procedure for the preparation of enamine compound (235)



231 **235**

NaN_3 (2.59 g, 39.9 mmol) was added to a solution of **231** (1.42 g, 3.32 mmol) in DMF (20 mL). After 6 h at 100 °C, the mixture was cooled to rt, poured into H_2O (200 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with cold H_2O (2 × 400 mL) followed by brine (400 mL). The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 80/20) to furnish enamine **235** (526 mg, 44%) as an yellow oil; data as previously described (p.148).

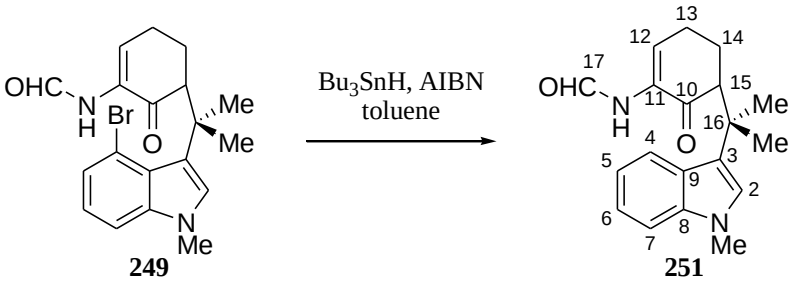
***N*-(5-(2'-(4''-Bromo-1''-methyl-1*H*-indol-3''-yl)propan-2'-yl)-6-oxocyclohex-1-enyl)formamide (249)**



235 **249**

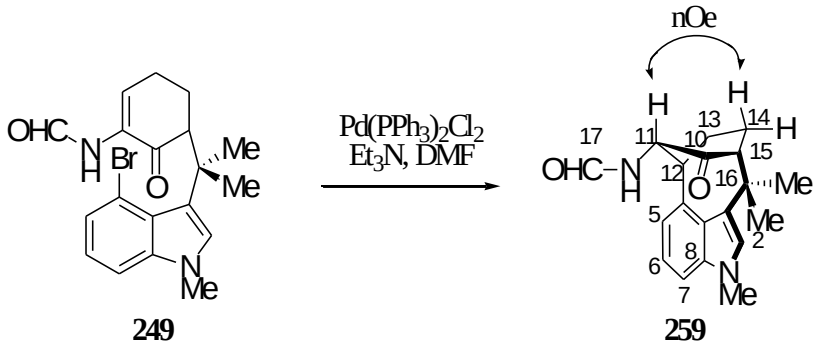
Acetic formic anhydride (prepared by stirring 1 equivalent of acetic anhydride and 1.1 equivalent of formic acid for 2 h at 55 °C; 76 μL, 0.29 mmol) was added to a solution of **235** (100 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to give formamide **249** (94 mg, 97%) as a grey solid; R_f 0.41 (petroleum ether/EtOAc, 60/40); mp 199-200 °C; IR υ_{max} 3344, 2926, 1699, 1662, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 3H, C*H*$_3$), 1.66-1.90 (br s, 5H, C*H*$_3$ and 14-C*H*$_2$), 2.33-2.46 (br s, 2H, 13-C*H*$_2$), 3.75 (s, 3H, NC*H*$_3$), 4.27 (dd, *J* 12.2, 4.8, 1H, 15-C*H*), 7.00 (s, 1H, 2-C*H*), 7.03 (app t, *J* 7.9, 1H, 6-C*H*), 7.27 (dd, *J* 8.1, 0.8, 1H, 7-C*H*), 7.38 (dd, *J* 7.6, 0.8, 1H, 5-C*H*), 7.72 (t, *J* 4.5, 1H, 12-C*H*), 7.97-8.04 (broad s, 1H, N*H*), 8.34 (s, 1H, 17-C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (CH_2, 13-CH_2), 25.2 (CH_2, 14-CH_2), 26.0 (CH_3), 28.7 (CH_3), 33.1 (CH_3, NCH_3), 37.1 (C, 16-C), 52.6 (CH, 15-CH), 109.0 (CH, 7-CH), 113.6 (C, 4-C), 122.0 (CH, 6-CH), 123.8 (C), 125.3 (C), 125.4 (CH, 5-CH), 128.2 (CH, 2-CH), 130.6 (CH, 12-CH), 132.3 (C, 11-C), 139.8 (C, 8-C), 159.2 (C, 17-C), 195.9 (C, 10-C); MS (ESI) *m/z* 411.1 ($[M+Na]^+$, 100%), 413.1 (97%); HRMS (ESI) *m/z* 411.0695 $[M+Na]^+$, $C_{19}H_{21}N_2O_2{}^{79}BrNa$ requires 411.0684.

_N_-(5-(2'-(1''-Methyl-1_H_-indol-3''-yl)propan-2''-yl)-6'-oxocyclohex-1'-enyl)formamide (251)



A solution of Bu_3SnH (69 μL, 0.26 mmol) and AIBN (13 mg, 0.08 mmol) in degassed toluene (18 mL) was added dropwise over 2 h *via* a syringe pump to a solution of **249** in boiling degassed toluene (6 mL). After a further 3 h, the mixture was cooled to rt and Et_2O (5 mL) and KF solution (5 mL of a 10% aqueous solution) were added. The organic layer was separated, washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by colum chromatography on silica gel (petroleum ether/EtOAc, 80/20) to provide **251** (10 mg, 25%) as a white solid; R_f 0.27 (petroleum ether/EtOAc, 70/30); mp 158-160 °C; IR υ_{max} 3246, 2925, 1696, 1662, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 3H, C*H*$_3$), 1.66-1.77 (m, 2H, 14-C*H*$_2$), 1.74 (s, 3H, C*H*$_3$), 2.21-2.40 (m, 2H, 13-C*H*$_2$), 3.14 (dd, *J* 10.6, 5.7, 1H, 15-C*H*), 3.76 (s, 3H, NC*H*$_3$), 6.82 (s, 1H, 2-C*H*), 7.07 (app t, *J* 7.6, 1H, 6-C*H*), 7.22 (app t, *J* 7.6, 1H, 5-C*H*), 7.31 (d, *J* 8.3, 1H, 4-C*H*), 7.68-7.73 (m, 2H, 7-C*H* and 12-C*H*), 7.97 (broad s, 1H, N*H*), 8.36 (d, *J* 1.7, 1H, 17-C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4 (CH_3), 24.8 (CH_2, 13-CH_2), 25.3 (CH_2, 14-CH_2), 28.6 (CH_3), 32.7 (CH_3, NCH_3), 37.9 (C, 16-C), 53.0 (CH, 15-CH), 109.6 (CH, 4-CH), 118.5 (CH, 6-CH), 120.9 (CH, 7-CH), 121.3 (CH, 5-CH), 123.2 (C), 125.8 (CH, 2-CH), 130.8 (CH, 12-CH), 132.4 (C, 11-C), 137.8 (C, 8-C), 159.2 (C, 17-C), 195.7 (C, 10-C), one C not observed; MS (ESI) *m/z* 333.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 333.1566 $[M+Na]^+$, $C_{19}H_{22}N_2O_2Na$ requires 333.1579.

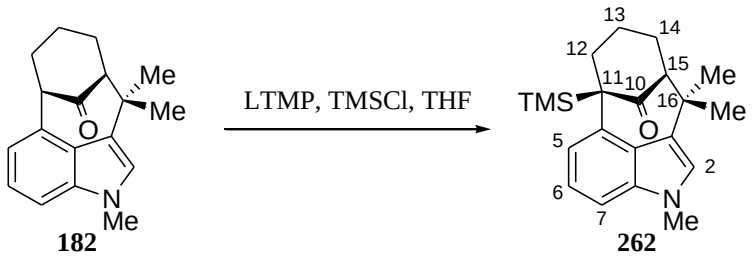
Bicylo[4.2.2]decane compound (259)



249 **259**

A solution of **249** (20 mg, 0.05 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01mmol) and Et_3N (18 μL, 0.13 mmol) in DMF (1 mL) was heated at 150 °C. After 3 h, the reaction was cooled to rt and diluted with EtOAc (1 mL). The organic layer was washed with H_2O (4 × 2 mL) and brine (3 × 2 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70/30) to afford cyclised product **259** (8 mg, 50%) as a grey solid; R_f 0.26 (petroleum ether/EtOAc, 60/40); mp 144-142 °C; IR υ_{max} 3308, 2930, 1714, 1651, 796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H, C*H*$_3$), 1.80 (s, 3H, C*H*$_3$), 2.11-2.24 (m, 1H, 13-C*H*$_2$), 2.24-2.32 (m, 2H, 14-C*H*$_2$), 2.59-2.66 (m, 1H, 13-C*H*$_2$), 2.66-2.70 (m, 1H, 15-C*H*), 3.71 (s, 3H, C*H*$_3$), 3.91-3.98 (m, 1H, 12-C*H*), 5.14 (t, *J* 6.5, 1H, 11-C*H*), 5.84 (broad s, 1H, N*H*), 6.72 (d, *J* 7.1, 1H, 5-C*H*), 7.01 (dd, *J* 8.2, 7.1, 1H, 6-C*H*), 7.04 (s, 1H, 2-C*H*), 7.15 (d, *J* 8.2, 1H, 7-C*H*), 8.13 (s, 1H, HNC*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_2, 14-CH_2), 25.0 (CH_2, 13-CH_2), 32.9 (CH_3, NCH_3), 34.1 (CH_3), 36.9 (CH_3), 38.1 (C, 16-C), 41.4 (CH, 12-CH), 55.9 (CH, 15-CH), 56.9 (CH, 11-CH), 109.0 (CH, 7-CH), 113.4 (C), 120.5 (CH, 6-CH), 121.9 (CH, 5-CH), 122.4 (C), 128.6 (CH, 2-CH), 134.5 (C), 137.3 (C, 8-C), 160.8 (C, 17-C), 210.9 (C, 10-C); MS (ESI) *m/z* 333.1 $[M+Na]^+$; HRMS (ESI) *m/z* 333.1573 ($[M+Na]^+$, 100%), $C_{19}H_{22}N_2O_2Na$ requires 333.1579.

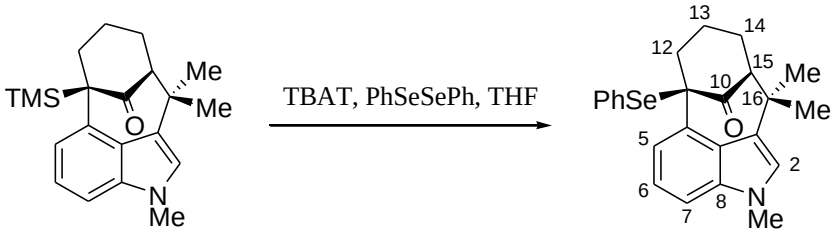
Bridgehead silylated compound (262)



A solution of LTMP was prepared as followed: to a solution of TMP (5.0 mL, 30 mmol) in THF (35 mL) at -78 °C was added ^{n}BuLi (1.6 M solution in hexanes; 18.8 mL, 30 mmol). The solution was allowed to warm to 0 °C and after 10 min, it was cooled to -78 °C. The freshly prepared LTMP solution was added *via* cannula into a solution of indole **182** (1.11 g, 4.15 mmol) and TMSCl (5.2 mL, 41.5 mmol) in THF (60 mL) at -78 °C. After 1 h the reaction was quenched with NH_4Cl solution (40 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 90/10) to provide the silylated compound **262** (853 mg, 60%) as a white solid, alongside unreacted indole **182** (311 mg, 28%); R_f 0.31 (petroleum ether/Et_2O, 90/10); mp 148-149 °C; IR υ_{max} 2955, 1672, 1245, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.31 (s, 9H, C*H*$_3$), 1.24-1.31 (m, 1H, 13-C*H*$_2$), 1.33 (s, 3H, C*H*$_3$), 1.54 (s, 3H, 16- C*H*$_3$), 1.55-1.70 (m, 1H, 13-C*H*$_2$), 1.78-1.88 (m, 1H, 14-C*H*$_2$), 2.00-2.08 (m, 1H, 12-C*H*$_2$), 2.18-2.35 (m, 2H, 12-C*H*$_2$ and 14-C*H*$_2$), 2.51 (dd, *J* 6.6, 3.2, 1H, 15-C*H*), 3.73 (s, 3H, NC*H*$_3$), 6.95 (s, 1H, 2-C*H*), 7.11-7.16 (m, 2H, 5-C*H* and 7-C*H*), 7.20 (dd, *J* 8.0, 7.0, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.26 (CH_3), 18.5 (CH_2, 13-CH_2), 27.7 (CH_2, 14-CH_2), 29.5 (CH_3), 32.7 (CH_3), 35.1 (C, 16-C), 36.9 (CH_3), 39.8 (CH_2, 12-CH_2), 52.4 (C, 11-C), 60.0 (CH, 15-CH), 106.8 (CH, 7-CH), 117.9 (CH, 5-CH), 121.7 (CH, 6-CH), 123.6 (C), 126.1

(CH, 2-CH), 126.2 (C), 136.7 (C), 136.9 (C), 216.5 (C, 10-C); MS (ESI) *m/z* 362.3 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 362.1916 $[M+Na]^+$, $C_{21}H_{29}NOSiNa$ requires 362.1916.

Bridgehead selenide compound (282)

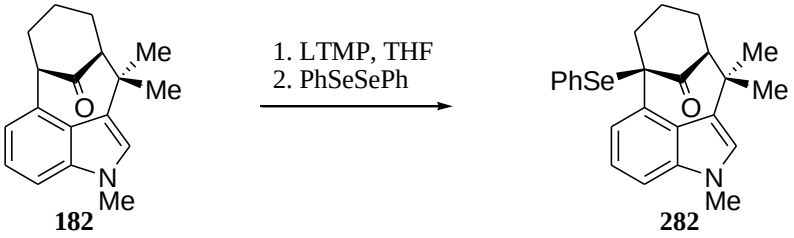


262 **282**

TBAT (95 mg, 0.18 mmol) and PhSeSePh (276 mg, 0.88 mmol) were successively added to a solution of **262** (30 mg, 0.08 mmol) in THF (3 mL). After 1 h at reflux, the solution was cooled down to rt and NH_4Cl solution (3 mL of a saturated aqueous solution) was added and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 95/5) to give indole **282** (19 mg, 51%) as a pale yellow solid; R_f 0.27 (petroleum ether/EtOAc, 90/10); mp 54-55 °C; IR υ_{max} 2949, 1697, 1415, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21-1.27 (m, 1H, 13-C*H*$_2$), 1.28 (s, 3H, C*H*$_3$), 1.38-1.48 (m, 1H, 13-C*H*$_2$), 1.50 (s, 3H, C*H*$_3$), 1.70-1.82 (m, 1H, 14-C*H*$_2$), 2.15 (dm, *J* 14.2, 1H, 14-C*H*$_2$), 2.40 (ddd, *J* 12.9, 10.5, 4.8, 1H, 12-C*H*$_2$), 2.50 (dtd, *J* 12.9, 2.4, 2.0, 1H, 12-C*H*$_2$), 2.77 (dd, *J* 7.6, 3.4, 1H, 15-C*H*), 3.73 (s, 3H, NC*H*$_3$), 6.96 (s, 1H, 2-C*H*), 7-15-7.25 (m, 5H, Ar*H*), 7.65-7.68 (m, 2H, Ar*H*), 7.94 (dd, *J* 7.4, 1.1, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (CH_2, 13-CH_2), 27.4 (CH_2, 14-CH_2), 29.3 (CH_3), 32.9 (CH_3, NCH_3), 34.9 (C, 16-C), 36.1 (CH_3), 46.0 (CH_2, 12-CH_2), 60.6 (CH, 15-CH), 72.3 (C, 11-C), 108.3 (CH, 7-CH), 119.7 (CH, 5-CH), 122.1 (CH, 2-CH), 122.3 (C), 124.4 (C), 126.4 (CH, 6-CH), 127.5 (CH, ArCH), 128.4 (CH, ArCH), 130.8 (C), 133.0 (C), 136.3 (CH, ArCH), 136.7 (C, 8-C), 207.9 (C, 10-C); MS

(ESI) *m/z* 446.0 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 446.0997 [M+Na]$^+$, $C_{24}H_{25}NOSeNa$ requires 446.0999.

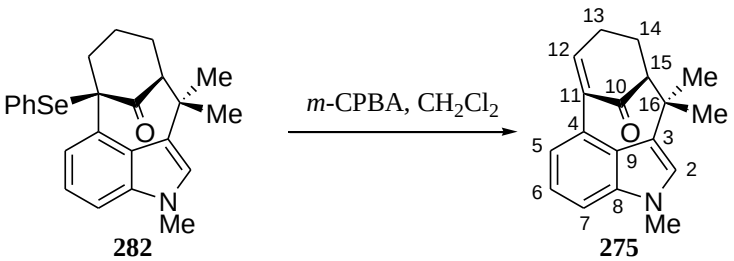
Alternative procedure for the preparation of bridgehead selenide compound (282)



182 **282**

A solution of LTMP was prepared as previously described (p.154): TMP (18.9 mL, 0.11 mol) in dry THF (200 mL) at -78 °C with ^{n}BuLi (1.6 M solution in hexanes; 71 mL, 0.11 mol). The freshly prepared LTMP solution was added *via* cannula into a solution of ketone **182** (6.6 g, 0.03 mol) in THF (400 mL) at -10 °C, immediately followed by a solution of PhSeSePh (35 g, 0.11 mol) in THF (50 mL). The reaction mixture was stirred for 1 h at -10 °C, quenched with NH_4Cl solution (1 L of a saturated aqueous solution) and extracted with Et_2O (3 × 1 L). The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2, 70/30) to give indole **282** (8.6 g, 82%) as a pale yellow solid; data as previously reported (p.155).

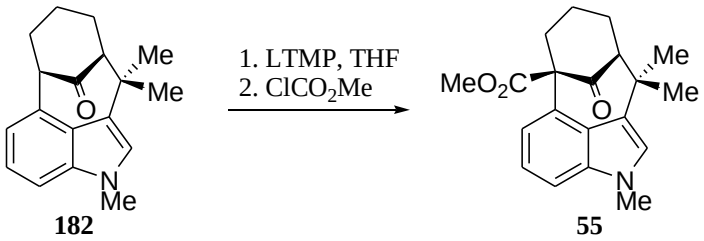
Bridgehead alkene compound (275)



282 **275**

m-CPBA (196 mg, 0.77 mmol) was added to a solution of **282** (326 mg, 0.77 mmol) in CH_2Cl_2 (30 mL) at -10 °C. After 15 min at that maintained temperature, the reaction was quenched with H_2O (75 mL), washed with Na_2SO_3 solution (75 mL of saturated aqueous solution) then brine (75 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with NH_4Cl solution (75 mL of a saturated aqueous solution), brine (75 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to provide bridgehead alkene **275** (159 mg, 76%) as a white solid; R_f 0.19 (petroleum ether/EtOAc, 90/10); mp 103-104 °C; IR υ_{max} 2921, 1691, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H, C*H*$_3$), 1.44 (s, 3H, C*H*$_3$), 1.95-2.06 (m, 1H, 14-C*H*$_2$), 2.12-2.23 (m, 2H, 13-C*H*$_2$ and 14-C*H*$_2$), 2.29-2.39 (m, 1H, 13-C*H*$_2$), 2.84 (dd, *J* 7.6, 4.9, 1H, 15-C*H*$_3$), 3.72 (s, 3H, NC*H*$_3$), 6.33 (dd, *J* 7.3, 4.3, 1H, 12-C*H*), 6.91 (s, 1H, 2-C*H*), 7.04 (dd, *J* 6.8, 1.3, 1H, 5-C*H*), 7.15 (dd, *J* 8.3, 1.3, 1H, 7-C*H*), 7.20 (dd, *J* 8.3, 6.8, 1H, 6-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (CH_2, 13-CH_2), 24.6 (CH_2, 14-CH_2), 29.3 (CH_3), 32.7 (CH_3, NCH_3), 34.3 (CH_3), 36.9 (C, 16-C), 59.5 (CH, 15-CH), 108.4 (CH, 7-CH), 113.7 (CH, 5-CH), 122.4 (CH, 6-CH), 123.5 (C, 9-C), 124.8 (C, 3-C), 126.9 (CH, 2-CH), 130.8 (C, 4-C), 132.9 (CH, 12-CH), 135.9 (C, 8-C), 142.1 (C, 11-C), 208.6 (C, 10-C); MS (ESI) *m/z* 288.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 288.1363 $[M+Na]^+$, $C_{18}H_{19}NONa$ requires 288.1364.

Bridgehead ester compound (55)[11]

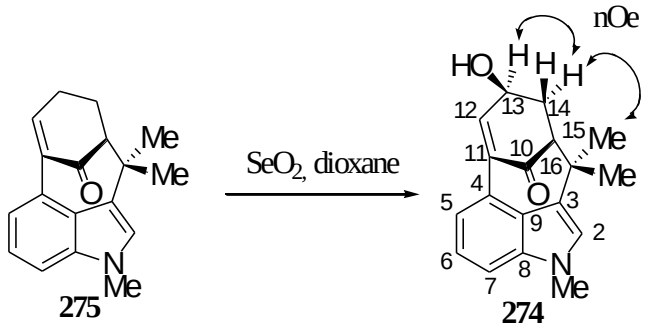


182 **55**

A solution of LTMP was prepared as previously described (p.154): to a solution of TMP (120 μL, 0.71 mmol) in THF (2 mL) at -78 °C was added ^{n}BuLi (1.6 M solution in hexanes; 444 μL, 0.71 mmol). The solution was allowed to warm to 0 °C and after 10 min, it was cooled to -78 °C. The freshly prepared LTMP solution was added *via* cannula into a solution of indole **182** (38 mg, 0.14 mmol) in THF (1 mL) at -78 °C and stirred at that maintained temperature for 1 h. Then methylchloroformate (80 μL, 1.42 mmol) was added and the reaction mixture was stirred for 1 h at -78 °C then for 4 h at rt. The reaction was subsequently quenched with NH_4Cl solution (2 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O, 90/10) to provide bridgehead ester **55** (12 mg, 26%) as a red solid; R_f 0.42 (petroleum ether/ EtOAc, 70/30); mp 150-152 °C [lit.,[11] 153-154 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H, C*H*$_3$), 1.23-1.38 (m, 2H), 1.51 (s, 3H, C*H*$_3$), 1.88-2.00 (m, 1H), 2.08-2.17 (m, 1H), 2.17-2.24 (m, 1H), 2.67 (ddd, *J* 13.5, 13.5, 4.7), 2.74 (dd, *J* 8.2, 2.4, 1H), 3.77 (s, 3H, C*H*$_3$), 3.81 (s, 3H, C*H*$_3$), 6.63-6.69 (m, 1H), 6.98 (m, 1H), 7.19-7.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8 (CH_2), 28.0 (CH_2), 28.4 (CH_3), 32.9 (CH_3), 34.7 (C), 35.4 (CH_3), 42.5 (CH_2), 52.4 (CH), 62.0 (CH_3), 69.8 (C), 107.9 (CH), 118.0 (CH), 121.5 (C), 122.1 (CH), 125.2 (C), 126.5 (CH), 131.2 (C), 136.8 (C), 173.9 (C), 210.8 (C); MS (ESI)

m/z 348.3 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 348.1585 [M+Na]$^+$, $C_{20}H_{23}NO_3Na$ requires 348.1576.

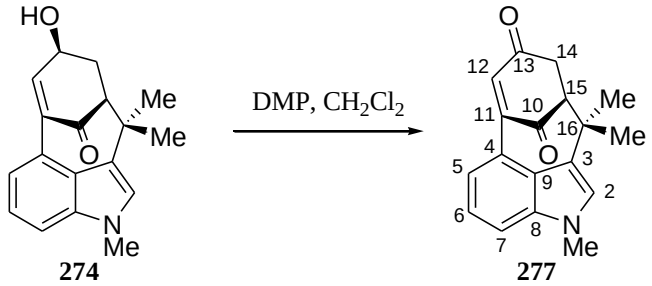
Allylic alcohol compound (274)



SeO_2 (1.81 g, 16.3 mmol) was added in one portion to a solution of bridgehead alkene **275** (3.94 g, 14.8 mmol) in dioxane (80 mL) and H_2O (4.9 mL). After 18 h at 70 °C, the reaction mixture was cooled to rt, diluted with H_2O (400 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 60/40) to give alcohol **274** (2.80 g, 67%) as a pale yellow solid; R_f 0.23 (petroleum ether/EtOAc, 60/40); mp 175-176 °C; IR υ_{max} 3464, 2921, 1696, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H, C*H*$_3$), 1.46 (s, 3H, C*H*$_3$), 2.01 (br s, 1H, O*H*); 2.11 (ddd, *J* 14.2, 4.9, 3.3, 1H, 14-C*H*$_2$), 2.42 (ddd, *J* 14.2, 7.5, 2.6, 1H, 14-C*H*$_2$), 2.95 (dd, *J* 7.5, 4.9, 1H, 15-C*H*), 3.72 (s, 3H, NC*H*$_3$), 4.61-4.68 (m, 1H, 13-C*H*), 6.44 (d, *J* 5.7, 1H, 12-C*H*), 6.95 (s, 1H, 2-C*H*), 7.04 (dd, *J* 5.7, 2.3, 1H, 5-C*H*), 7.17-7.21 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2 (CH_3), 32.8 (CH_3, NCH_3), 35.2 (CH_2, 14-CH_2), 35.7 (CH_3), 37.2 (C, 16-C), 55.6 (CH, 15-CH), 64.8 (CH, 13-CH), 108.8 (CH, 7-CH), 113.6 (CH, 5-CH), 122.3 (CH, 6-CH), 123.0 (C, 9-C), 124.0 (C, 3-C), 127.7 (CH, 2-CH), 130.3 (C, 4-C), 134.3 (CH, 12-

CH), 135.7 (C, 8-C), 145.9 (C, 11-C), 207.0 (C, 10-C); MS (ESI) *m/z* 304.1 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 304.1317 [M+Na]$^+$, $C_{18}H_{19}NO_2Na$ requires 304.1313.

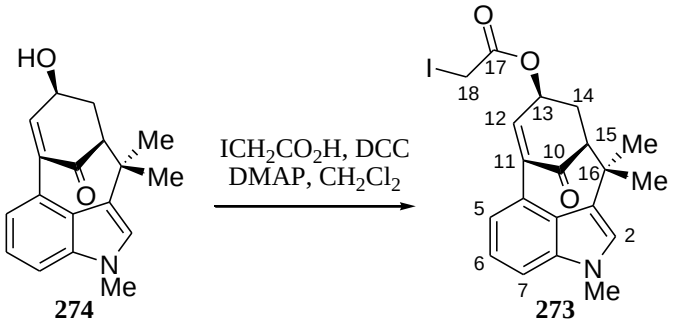
Enedione compound (277)



274 **277**

DMP (52 mg, 0.12 mmol) was added to a solution of **274** (23 mg, 0.08 mmol) in CH_2Cl_2 (1 mL). After 1 h at rt, the reaction mixture was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to provide enedione **277** (15 mg, 65%) as a white solid; R_f 0.35 (petroleum ether/EtOAc, 70/30); mp 193-195 °C; IR υ_{max} 2957, 1719, 1674, 1230, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 2.85 (dd, *J* 19.0, 5.7, 1H, 14-C*H*$_2$), 3.17 (dm, *J* 19.0, 1H, 14-C*H*$_2$), 3.27 (d, *J* 4.8, 1H, 15-C*H*$_2$), 3.74 (s, 3H, NC*H*$_3$), 6.40 (d, *J* 1.7, 1H, 12-C*H*), 6.93 (s, 1H, 2-C*H*), 7.13 (t, *J* 3.9, 1H, 6-C*H*), 7.25-7.27 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1 (CH_3), 30.7 (CH_3), 32.8 (CH_3, NCH_3), 35.5 (C, 16-C), 39.8 (CH_2, 14-CH_2), 60.3 (CH, 15-CH), 110.5 (CH, 7-CH), 113.7 (CH, 6-CH), 122.5 (CH, 5-CH), 124.2 (C, 9-C), 125.4 (C, 3-C), 126.4 (CH, 2-CH), 127.0 (CH, 12-CH), 128.7 (C, 4-C), 136.6 (C, 8-C), 159.6 (C, 11-C), 195.2 (C, 13-C), 204.4 (C, 10-C); MS (ESI) *m/z* 302.1 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* 302.1140 [M+Na]$^+$, $C_{18}H_{17}NO_2Na$ requires 302.1157.

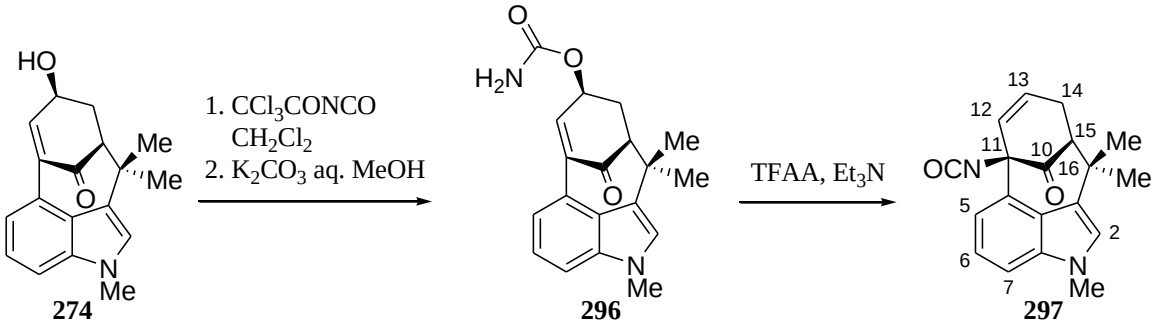
Iodo ester compound (273)



274 **273**

Iodoacetic acid (24 mg, 0.13 mmol), DCC (26 mg, 0.13 mmol) and DMAP (1 mg, 0.08 mmol) were added to a solution of allylic alcohol **274** (30 mg, 0.11 mmol) in CH_2Cl_2 (8 mL). After 30 min at rt, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to provide iodoester **273** (38 mg, 79%) as a white solid; R_f 0.31 (petroleum ether/EtOAc, 70/30); mp 140-142 °C; IR 2962, 1740, 1710, 1110, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 2.28 (dt, *J* 14.8, 4.3, 1H, 14-C*H*$_2$), 2.48 (ddd, *J* 14.8, 7.6, 2.5, 1H, 14-C*H*$_2$), 2.96 (dd, *J* 7.6, 4.3, 1H, 15-C*H*), 3.67 (AB q, *J* 9.9, 2H, 18-C*H*$_2$), 3.73 (s, 3H, NC*H*$_3$), 5.35-5.40 (m, 1H, 13-C*H*), 6.47 (d, *J* 6.0, 1H, 12-C*H*), 6.95 (s, 1H, 2-C*H*), 7.06 (dd, *J* 5.5, 2.5, 1H), 7.18-7.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6 (CH_2, 18-CH_2), 29.3 (CH_3), 31.5 (CH_2, 14-CH_2), 32.8 (CH_3, NCH_3), 35.3 (CH_3), 37.3 (C, 16-C), 55.8 (CH, 15-CH), 68.7 (CH, 13-CH), 109.1 (CH, 7-CH), 113.7 (CH, 5-CH), 122.3 (CH, 6-CH), 122.6 (C), 124.0 (C), 127.7 (CH, 2-CH), 129.2 (C), 129.7 (CH), 135.7 (C, 8-C), 147.2 (C, 11-C), 168.2 (C, 17-C), 205.5 (C, 10-C); MS (ESI) *m/z* 472.1 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 472.0382 $[M+Na]^+$, $C_{20}H_{20}NO_3NaI$ requires 472.0386.

Bridgehead isocyanate compound (297)

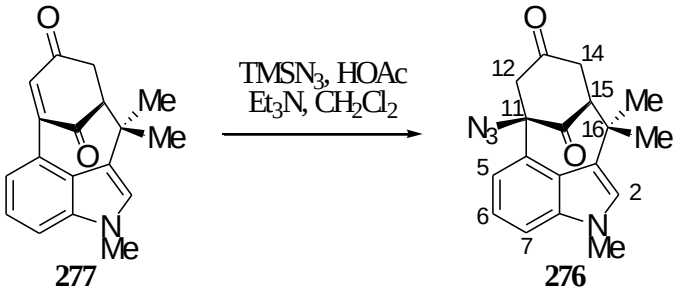


274 **296** **297**

Trichloroacetylisocyanate (19 μL, 0.16 mmol) was added to a solution of allylic alcohol **274** (30 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 1 h at 0 °C, the solvent was evaporated under reduced pressure and the residue was dissolved in a mixture MeOH (711 μL) and H_2O (352 μL). The solution was cooled to 0 °C and K_2CO_3 (44 mg, 0.32 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 3 h. MeOH was evaporated under reduced pressure and the mixture was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude allyl carbamate **296** was dissolved in CH_2Cl_2 (0.8 mL) and cooled down to 0 °C. Et_3N (45 μL, 0.32 mmol) and trifluoroacetic anhydride (15 μL, 0.11 mmol) were added sequentially to the solution. After 15 min at 0 °C, the reaction was quenched with NH_4Cl solution (1 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure to furnish isocyanate **297** (5 mg, 15%) as a white solid; R_f 0.58 (petroleum ether/EtOAc, 70/30); mp 135-136 °C; IR 2920, 2223, 1713, 1143, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H, C*H*$_3$), 1.50 (s, 3H, C*H*$_3$), 2.54-2.64 (m, 1H, 14-C*H*$_2$), 2.66-2.76 (m, 1H, 14-C*H*$_2$), 3.01 (dd, *J* 9.2, 4.8, 1H, 15-C*H*), 3.75 (s, 3H, NC*H*$_3$), 5.51-5.57 (m, 1H, 13-C*H*), 5.79 (dd, *J* 9.4, 3.0, 1H, 12-C*H*), 6.93 (s, 1H, 2-C*H*), 7.23-7.26 (m, 2H, 6-C*H* and 7-C*H*), 7.36-7.38 (dd, *J* 5.8, 2.7, 1H, 5-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (CH_3), 30.0 (CH_2, 14-CH_2), 33.0 (CH_3, NCH_3), 33.7 (CH_3),

37.0 (C, 16-C), 53.8 (CH, 15-CH), 65.9 (C, 11-C), 109.1 (CH, 7-CH), 117.1 (CH, 5-CH), 120.4 (C), 122.2 (CH, 6-CH), 125.3 (CH, 13-CH), 127.1 (CH, 2-CH), 127.3 (C), 129.9 (C), 132.3 (C), 134.5 (CH, 12-CH), 137.8 (C, 8-C), 205.6 (C, 10-C); MS (ESI) *m/z* 329.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 329.1271 $[M+Na]^+$, $C_{19}H_{18}N_2O_2Na$ requires 329.1266.

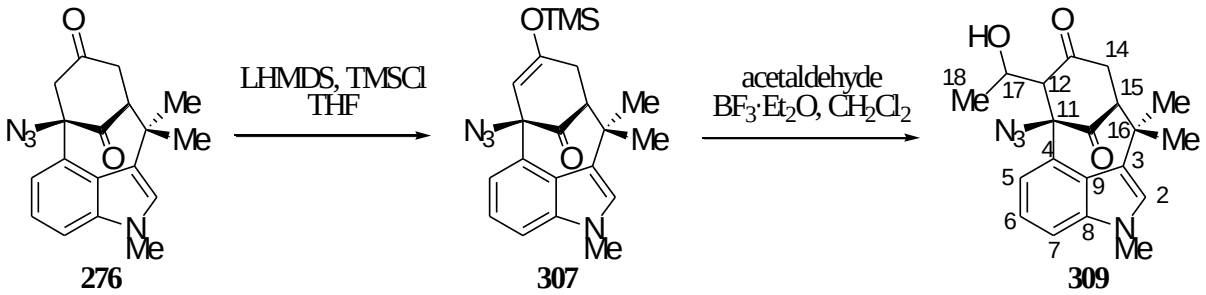
Diketoazide compound (276)



AcOH (119 μL, 2.08 mmol) was added to a solution of $TMSN_3$ (276 μL, 2.08 mmol) in CH_2Cl_2 (2.3 mL) at rt. The mixture was stirred for 20 min and Et_3N (12 μL, 0.08 mmol) was added, followed by a solution of enedione **277** (116 mg, 0.42 mmol) in CH_2Cl_2 (1.3 mL). The resultant solution was stirred for 1 h at rt and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 90/10) to afford azide **276** (127 mg, 95%) as a white solid; R_f 0.40 (petroleum ether/EtOAc, 70/30); mp 153-154 °C; IR υ_{max} 2923, 2115, 1715, 1241, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H, C*H*$_3$), 1.48 (s, 3H, C*H*$_3$), 2.82-2.85 (m, 2H, 14-C*H*$_2$), 2.97 (AB system, $J_{A\text{-}B}$ 17.0, 1H, 12-C*H*$_2$), 3.03 (dd, *J* 9.0, 6.8, 1H, 15-C*H*), 3.09 (AB system, $J_{A\text{-}B}$ 17.0, 1H, 12-C*H*$_2$), 3.78 (s, 3H, NC*H*$_3$), 7.02 (s, 1H, 2-C*H*), 7.32 (dd, *J* 8.1, 1.2, 1H, 7-C*H*), 7.37 (app t, *J* 7.7, 1H, 6-C*H*), 7.43 (dd, *J* 7.4, 1.2, 1H, 5-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1 (CH_3), 32.9 (CH_3), 33.1 (CH_3), 36.9 (C, 16-C), 42.7 (CH_2, 14-CH_2), 55.46 (CH_2, 12-CH_2), 55.48 (CH, 15-CH), 74.9 (C, 11-C), 110.3 (CH, 7-CH), 118.7 (CH, 5-CH), 119.3 (C), 122.7 (C), 122.9 (CH, 6-

CH), 127.7 (C), 128.1 (CH, 2-CH), 137.4 (C, 8-C), 204.0 (C), 205.2 (C); MS (ESI) *m/z* 345.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 345.1337 $[M+Na]^+$, $C_{18}H_{18}N_4O_2Na$ requires 345.1327.

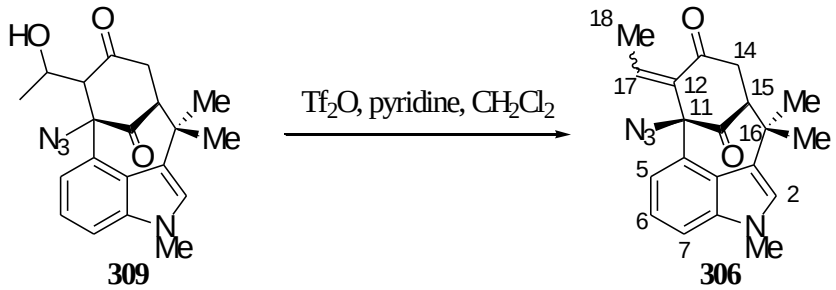
Aldol compound (309)



A solution of azide **277** (206 mg, 0.64 mmol) in THF (4.5 mL) was added *via* cannula into a solution of LHMDS (1 M solution in THF, 3.2 ml, 3.2 mmol) and TMSCl (0.4 mL, 3.2 mmol) in THF (2.3 mL) at -78 °C. After 1 h at -78 °C, the reaction was quenched with $NaHCO_3$ solution (5 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude **307** was dissolved in CH_2Cl_2 (1 mL) and CH_3CHO (179 μL, 3.20 mmol) was added. The mixture was cooled to -60 °C and a solution of $BF_3{\cdot}Et_2O$ (79 μL, 0.64 mmol) in CH_2Cl_2 (0.2 mL) was added *via* cannula. The reaction mixture was stirred at that maintained temperature for 3 h, quenched with $NaHCO_3$ solution (5 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene/Et_2O, 80/20) to afford alcohol **309** (101 mg, 43%) as a white solid; R_f 0.15 (petroleum ether/EtOAc, 70/30); mp 174-176 °C; IR υ_{max} 3506, 2922, 2118, 1712, 1247, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* 6.1, 3H, 18-C*H*$_3$), 1.26 (s, 3H, C*H*$_3$), 1.51 (s, 3H, C*H*$_3$), 2.72-2.74 (m, 2H, 14-C*H*$_2$), 2.91 (dd, *J* 7.3, 1.1, 1H, 12-C*H*), 3.08 (dd, *J* 8.8, 4.8, 1H, 15-C*H*), 3.77 (s, 3H, NC*H*$_3$), 3.84 (d, *J* 3.5, 1H, O*H*), 4.04-4.16

(m, 1H, 17-C*H*), 7.00 (s, 1H, 2-C*H*), 7.31 (dd, *J* 7.9, 1.5, 1H, 7-C*H*), 7.37 (app t, *J* 7.6, 1H, 6-C*H*), 7.43 (dd, *J* 7.3, 1.5, 1H, 5-C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3, 18-CH_3), 28.6 (CH_3), 33.1 (CH_3), 33.2 (CH_3), 36.7 (C, 16-C), 41.0 (CH_2, 14-CH_2), 55.6 (CH, 15-CH), 67.2 (CH, 12-CH), 71.8 (CH, 17-CH), 78.7 (C, 11-C), 110.6 (CH, 7-CH), 118.8 (CH, 5-CH), 119.0 (C, 3-C), 122.1 (C, 9-C), 123.0 (CH, 6-CH), 126.9 (C, 4-C), 127.8 (CH, 2-CH), 137.5 (C, 8-C), 204.7 (C), 205.0 (C); MS (ESI) *m/z* 389.2 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 389.1591 $[M+Na]^+$, $C_{20}H_{22}N_4O_3Na$ requires 389.1590.

Enone compound (306)



Tf_2O (92 μL, 0.55 mmol) and pyridine (44 μL, 0.55 mmol) were successively added to a solution of alcohol **309** (40 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred 30 min at this temperature, quenched with $NaHCO_3$ solution (3 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 × 2mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 95/5) to provide enone **306** (16 mg, 42%) as a white solid; R_f 0.45 (petroleum ether/EtOAc, 90/10); mp 180-182 °C; IR υ_{max} 2919, 2109, 1717, 1689, 1258, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.14 (d, *J* 7.5, 3H, 18-CH_3), 2.76-2.83 (m, 2H, 14-CH_2), 2.92 (app t, *J* 8.5, 1H, 15-C*H*), 3.75 (s, 3H, NCH_3), 6.91 (q, *J* 7.5, 1H, 17-C*H*), 7.02 (s, 1H, 2-C*H*), 7.22-7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (CH_3, 18-CH_3), 30.0

(CH_3), 32.3 (CH_3, NCH_3), 33.1 (CH_3), 37.4 (C, 16-C), 42.4 (CH_2, 14-CH_2), 54.2 (CH, 15-CH), 80.0 (C, 11-C), 109.8 (CH, 7-CH), 119.3 (C), 120.0 (CH, 5-CH), 122.3 (CH, 6-CH), 123.2 (C), 127.5 (C), 128.4 (CH, 2-CH), 136.2 (C), 137.0 (C), 140.5 (CH, 17-CH), 196.9 (C), 203.3 (C); MS (ESI) *m/z* 371.1 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* 371.1491 $[M+Na]^+$, $C_{20}H_{20}N_4O_2Na$ requires 371.1484.

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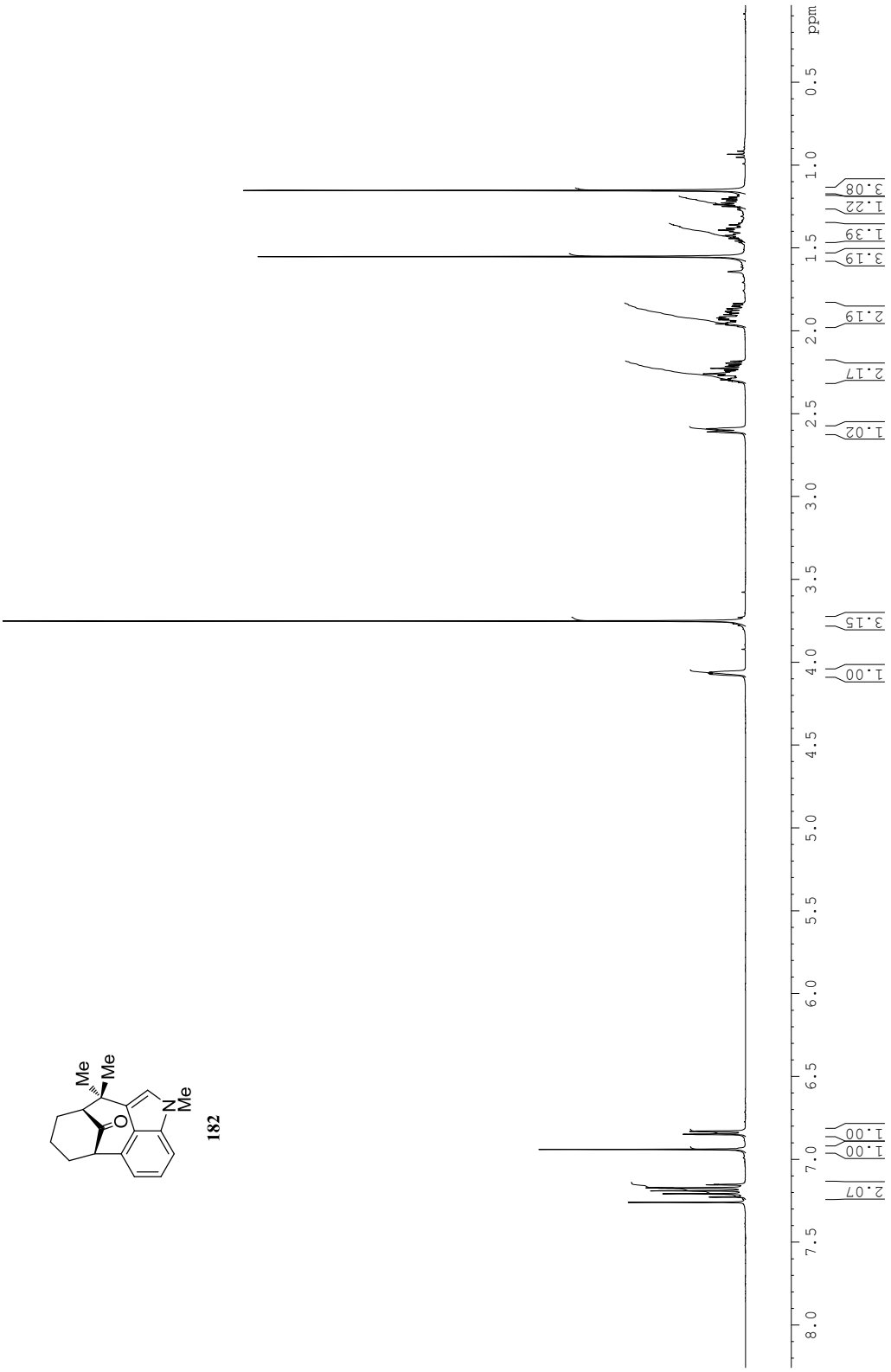
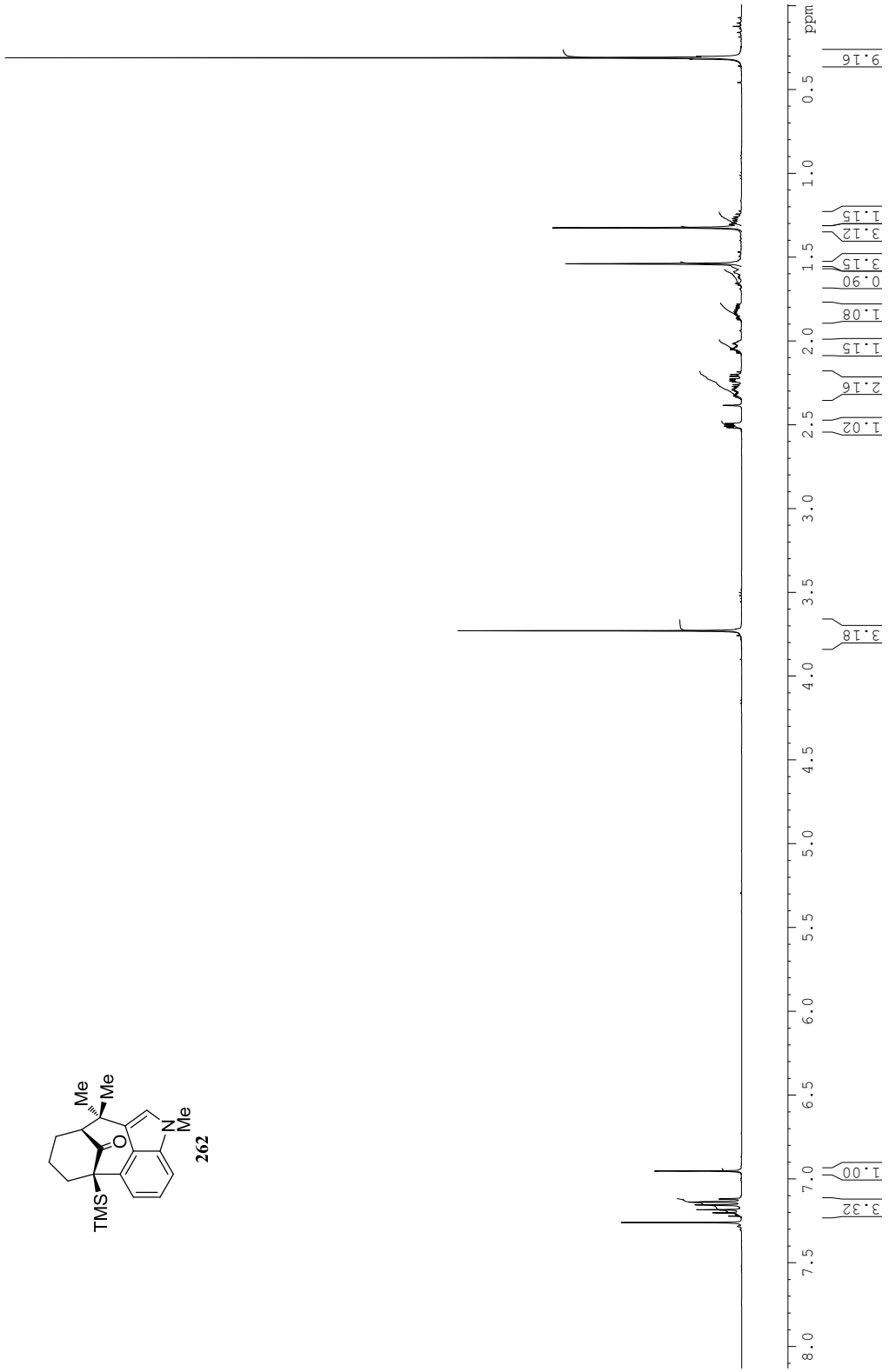
Appendix

^{1}H NMR of tetracycle **182**

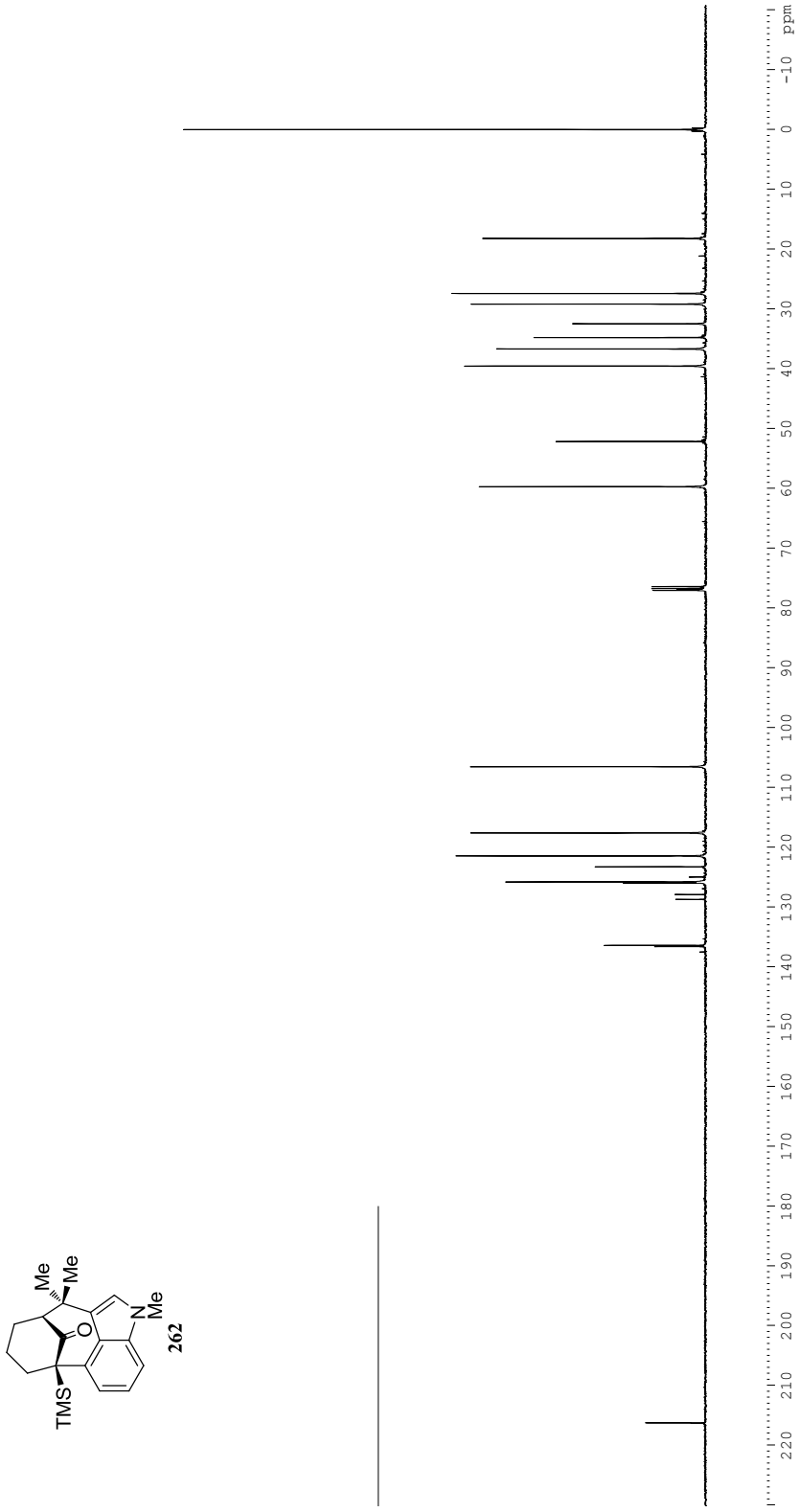


^{13}C NMR of tetracycle **182**

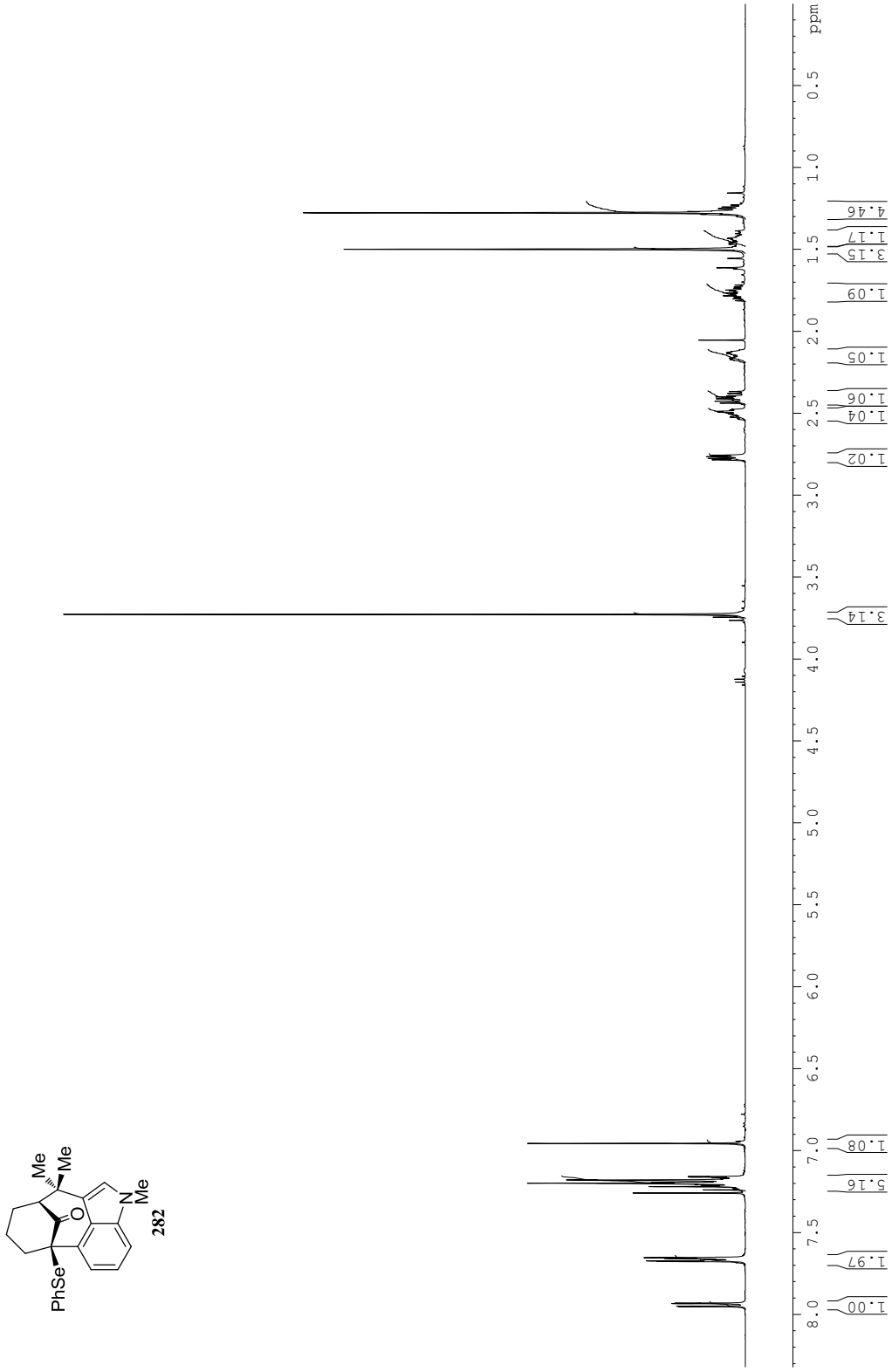
^{1}H NMR of silylated bridgehead **262**



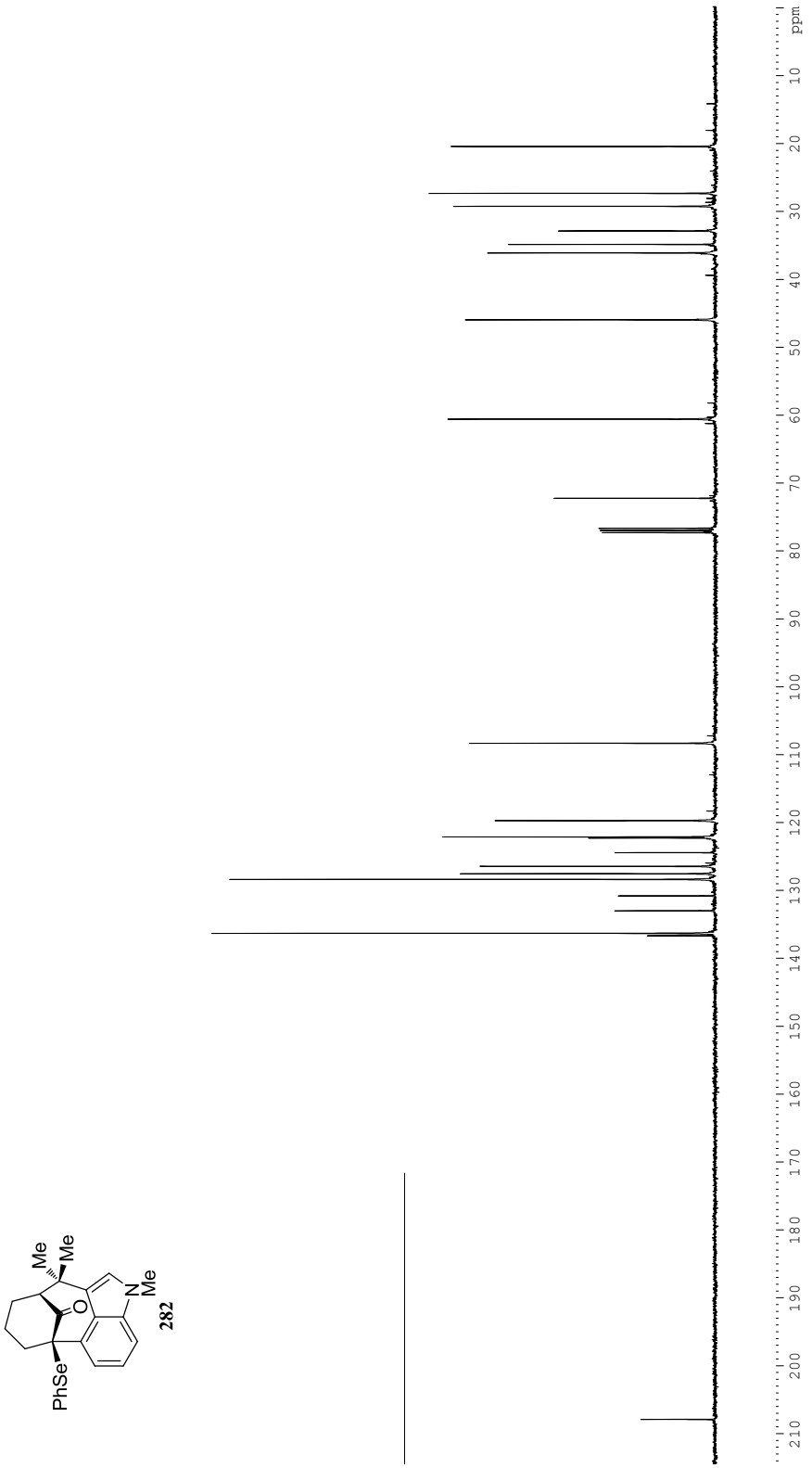
^{13}C NMR of silylated bridgehead **262**



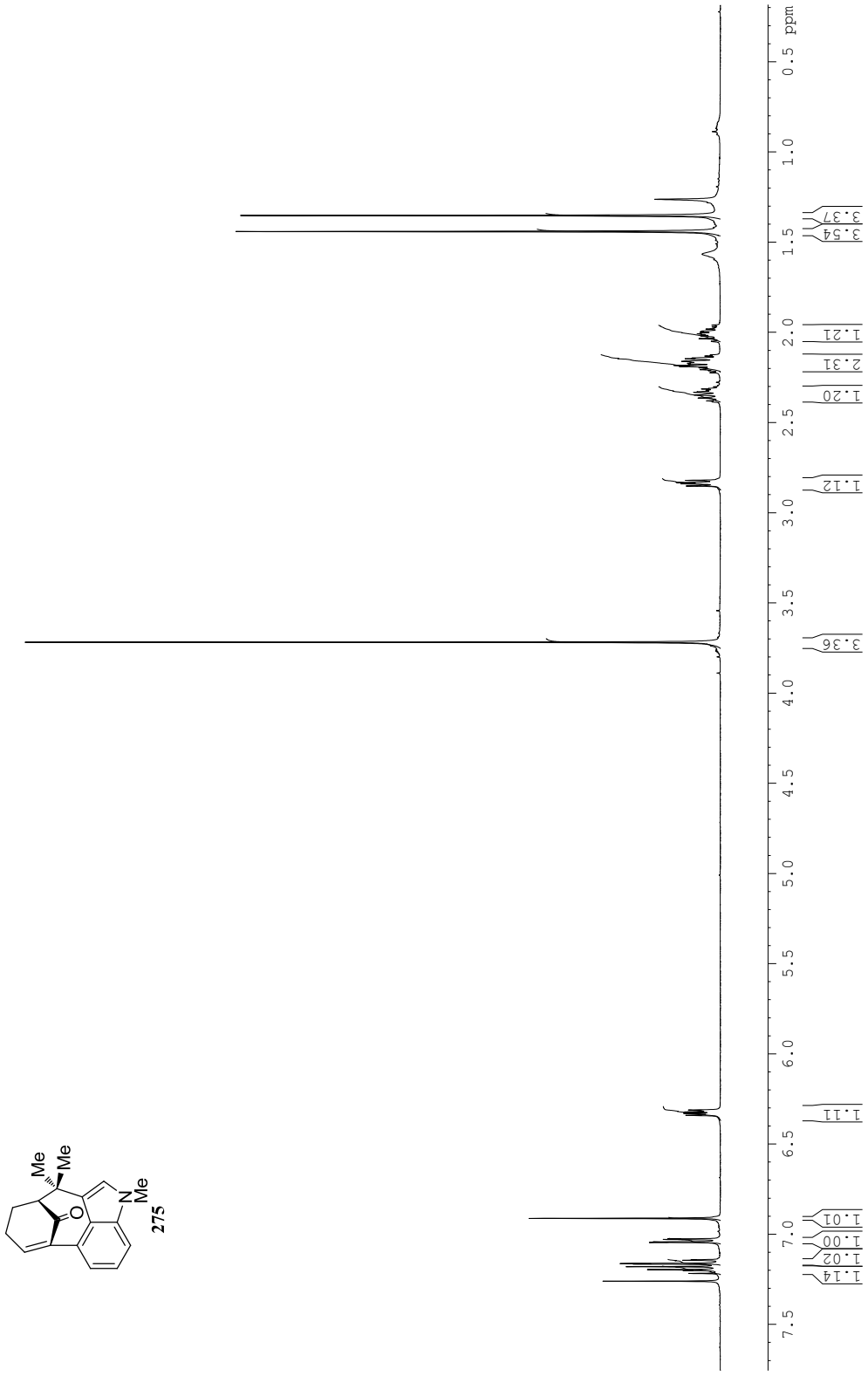
^{1}H NMR of bridgehead selenide **282**



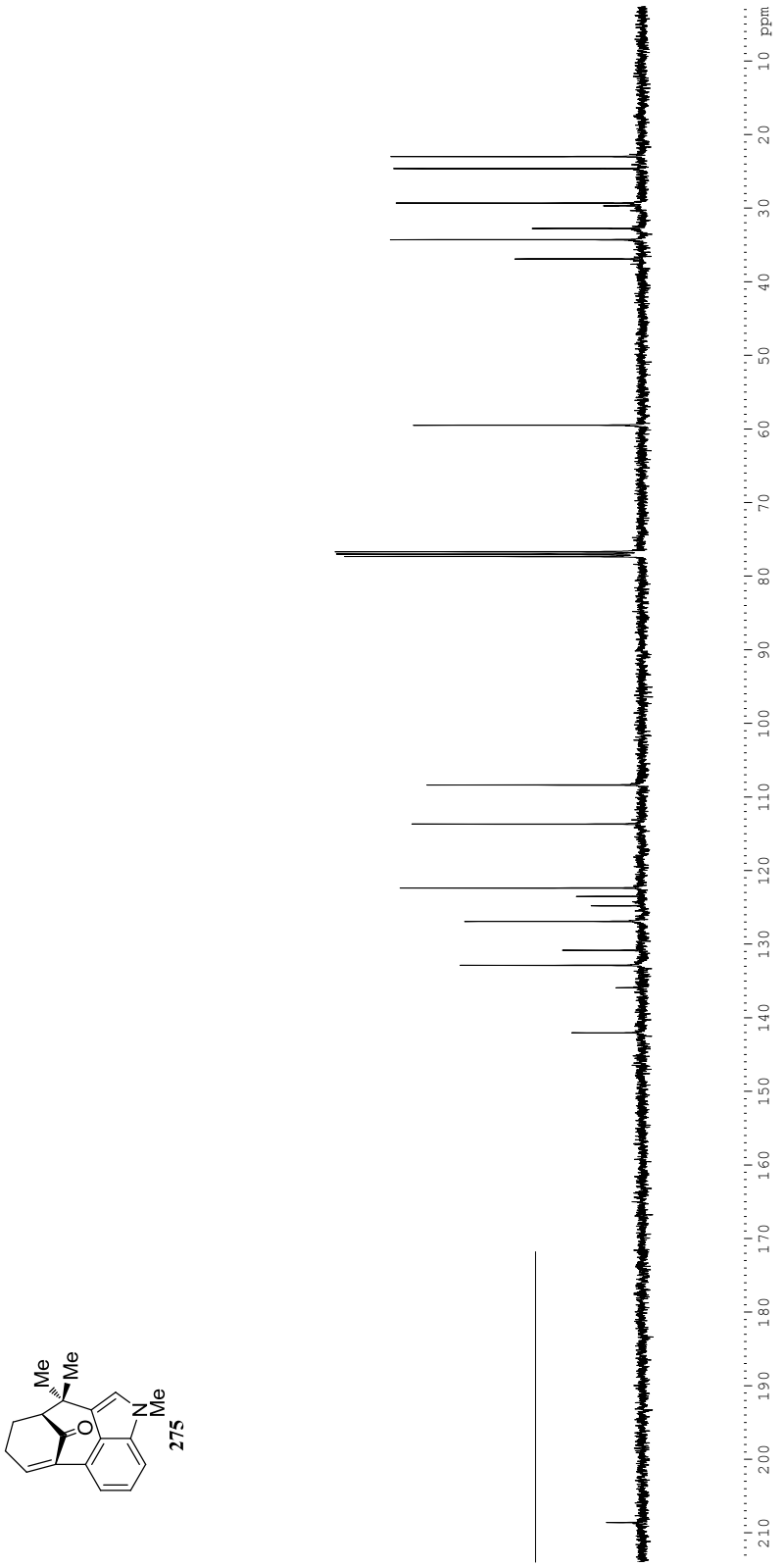
^{13}C NMR of bridgehead selenide **282**



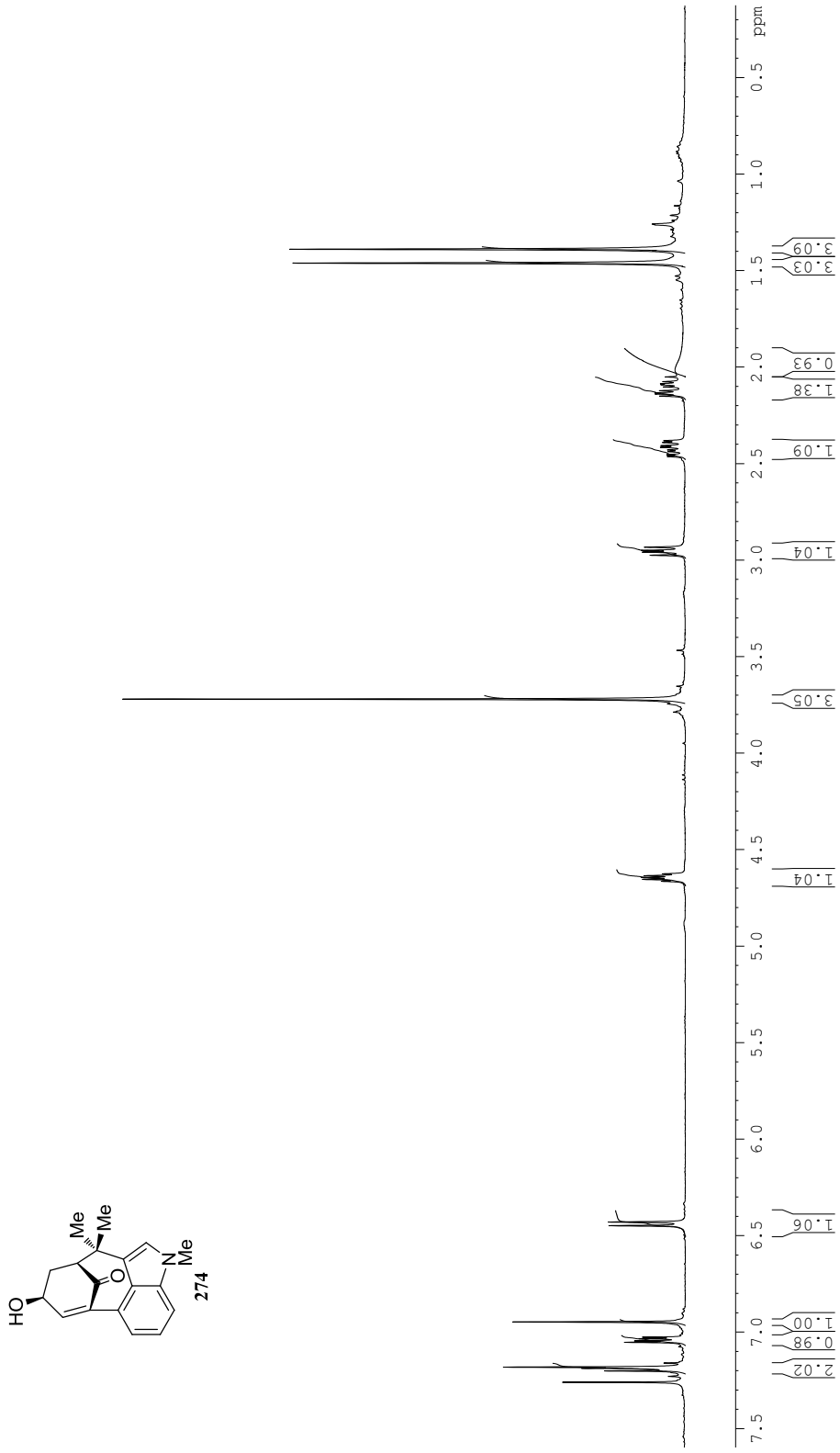
^{1}H NMR of bridgehead alkene **275**



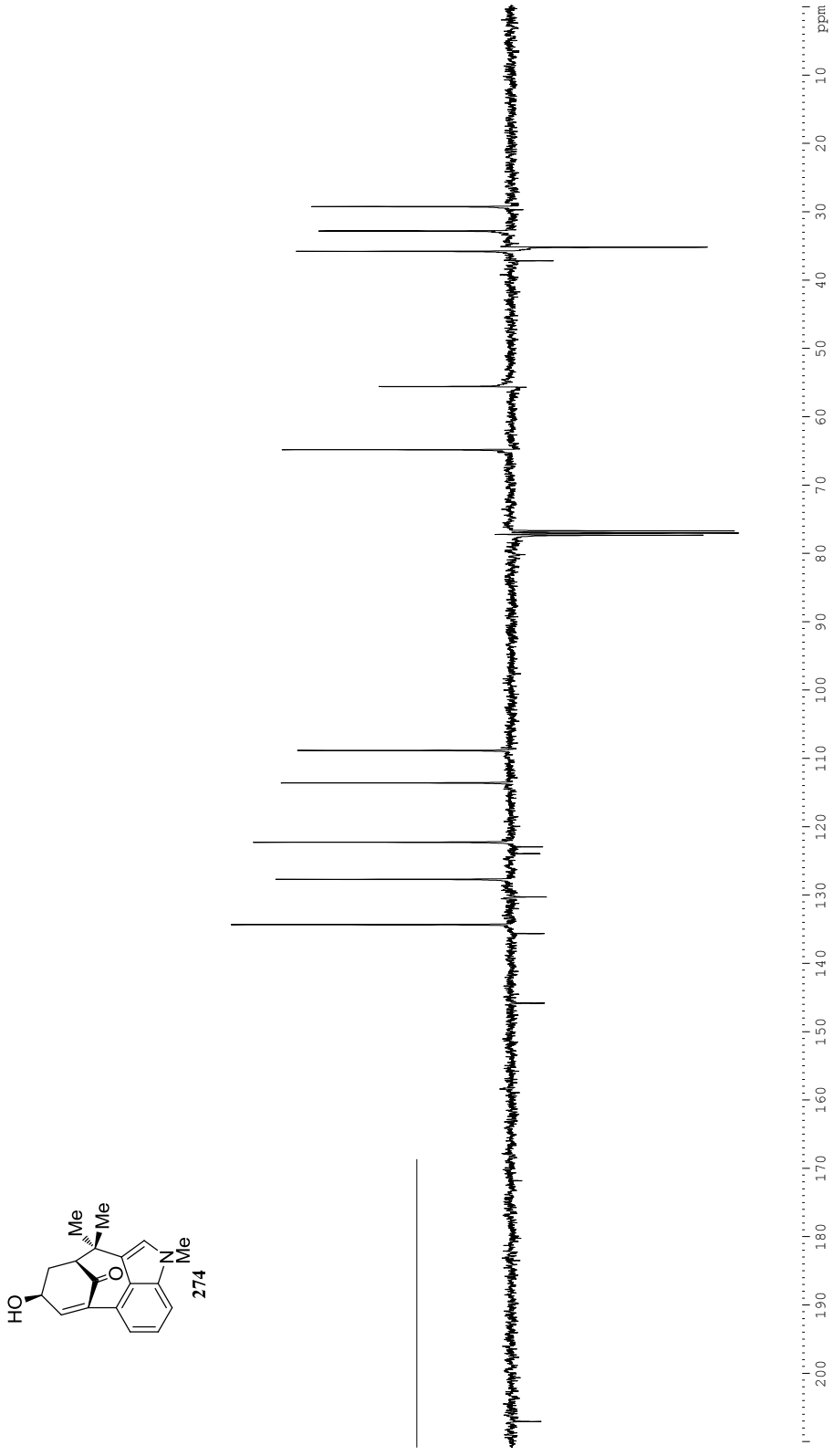
^{13}C NMR of bridgehead alkene **275**



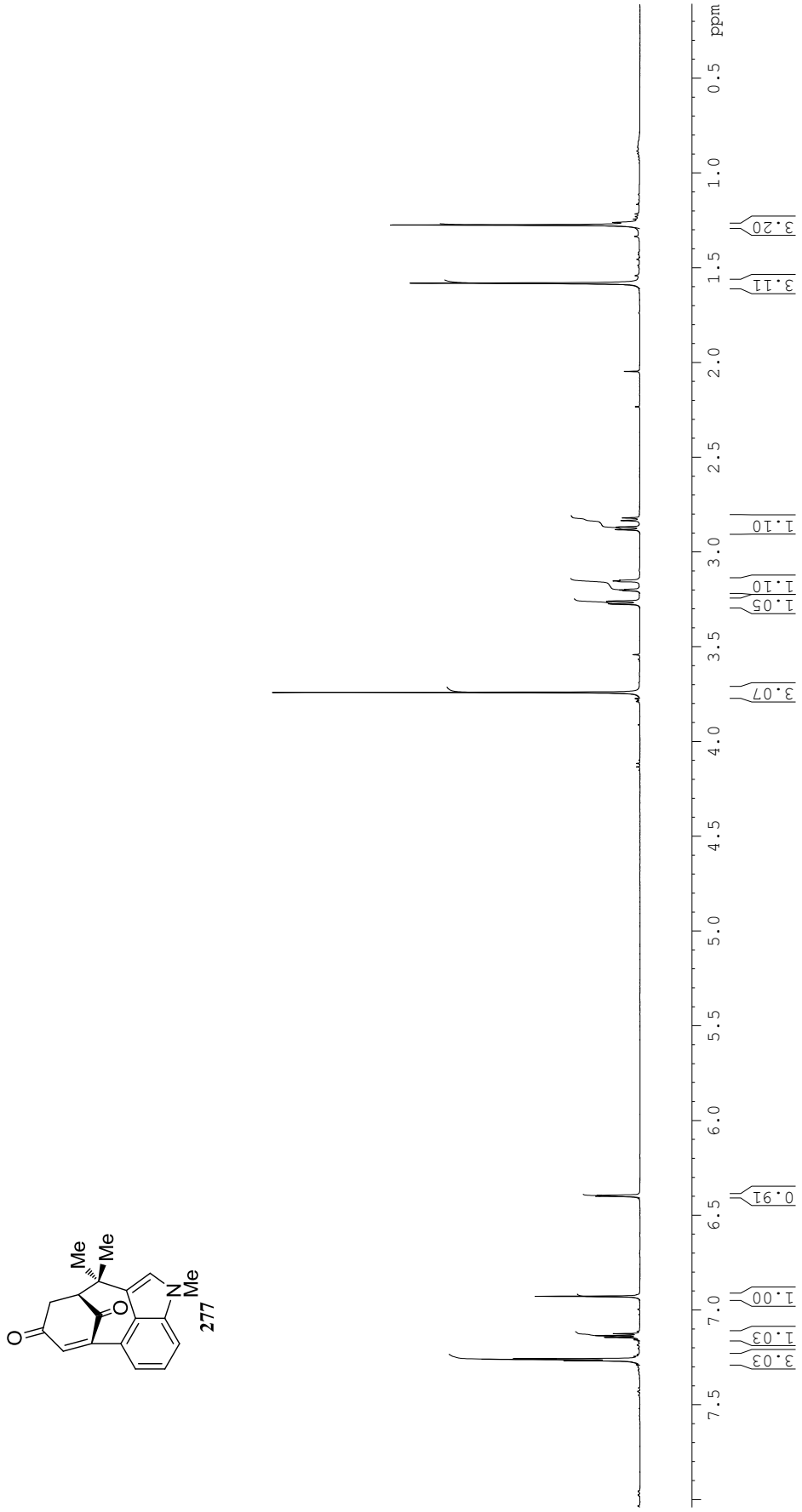
^{1}H NMR of allylic alcohol **274**



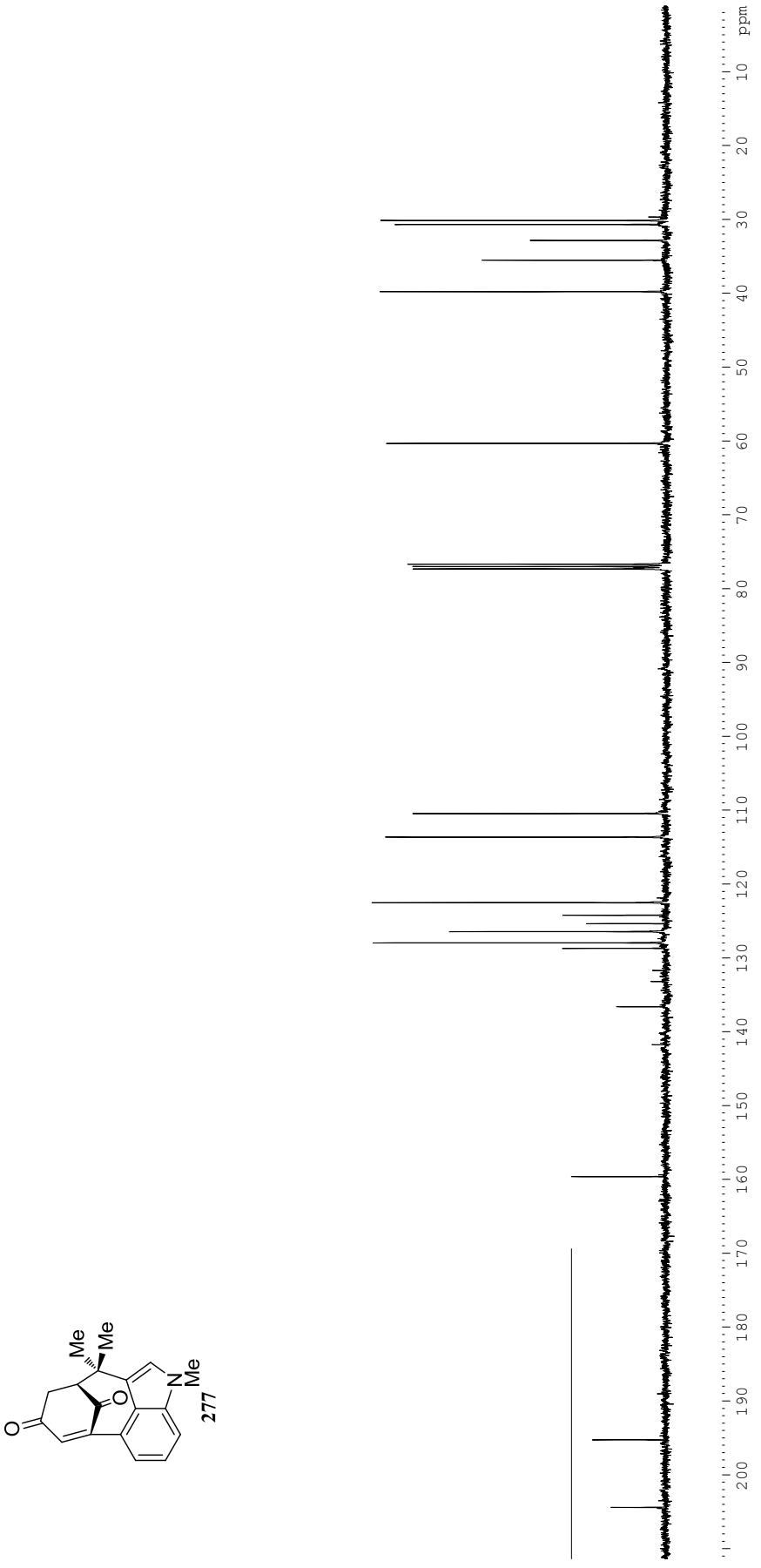
^{13}C NMR of allylic alcohol **274**



^{1}H NMR of enedione **277**

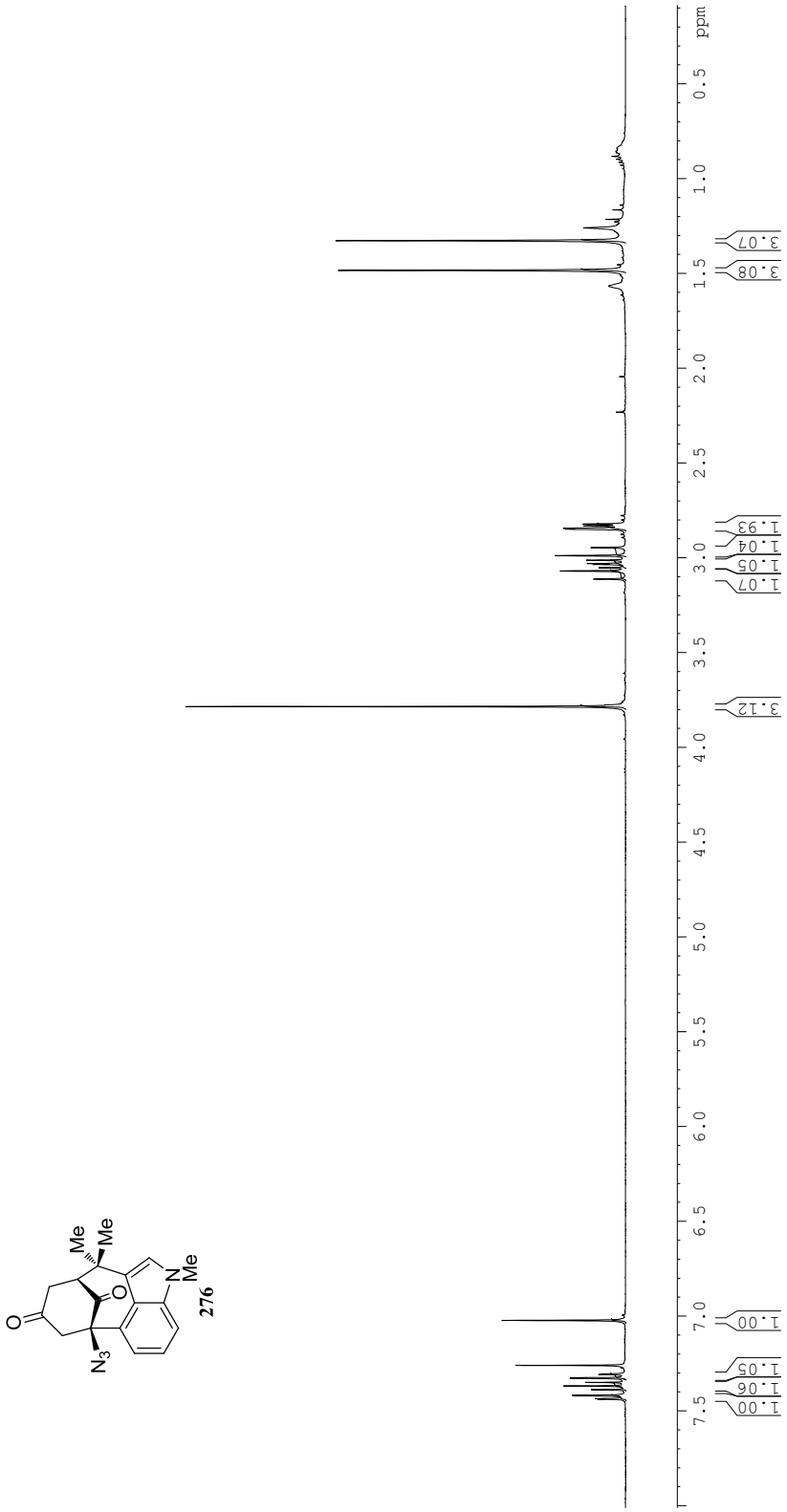


^{13}C NMR of enedione **277**

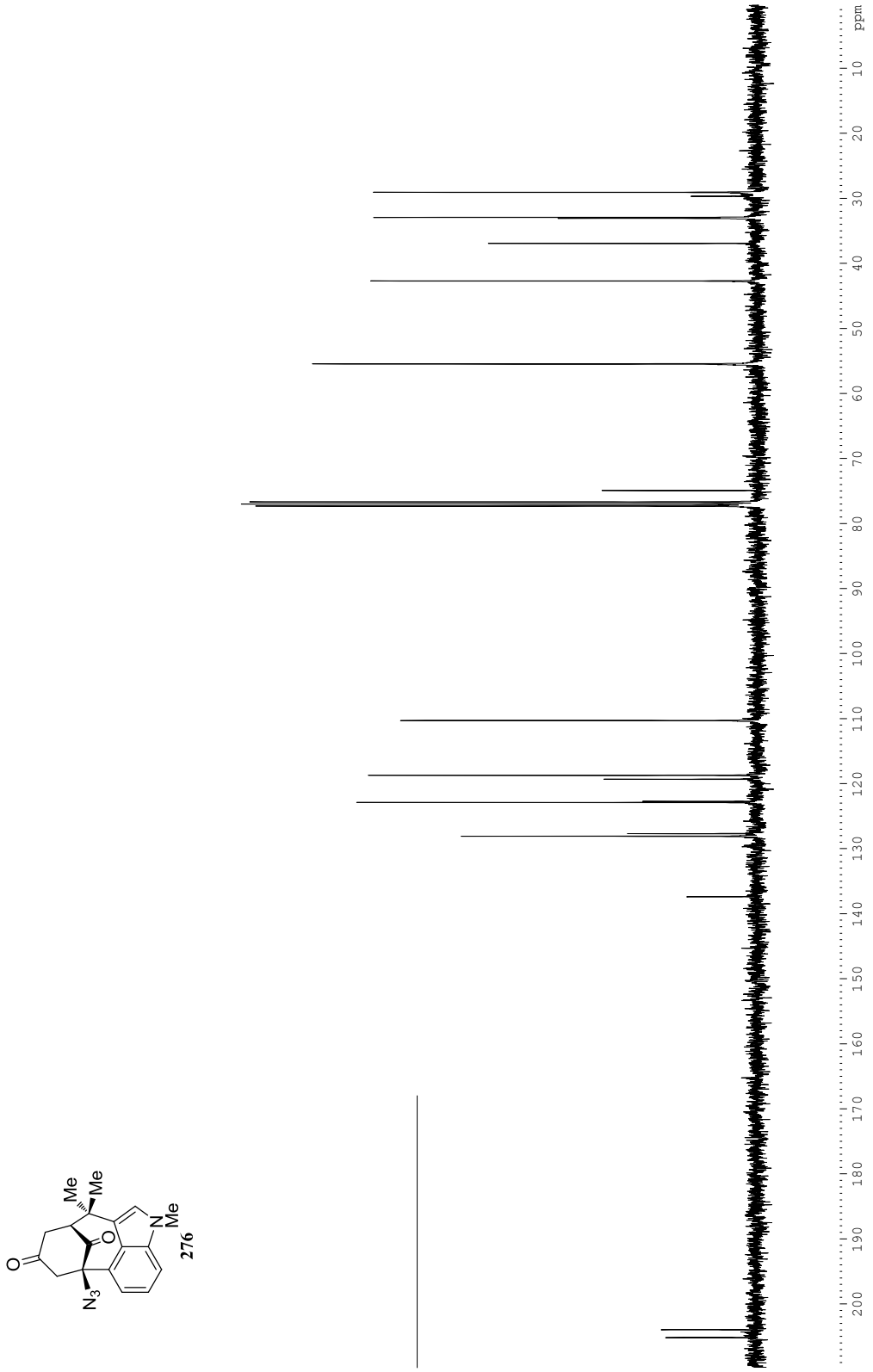


277

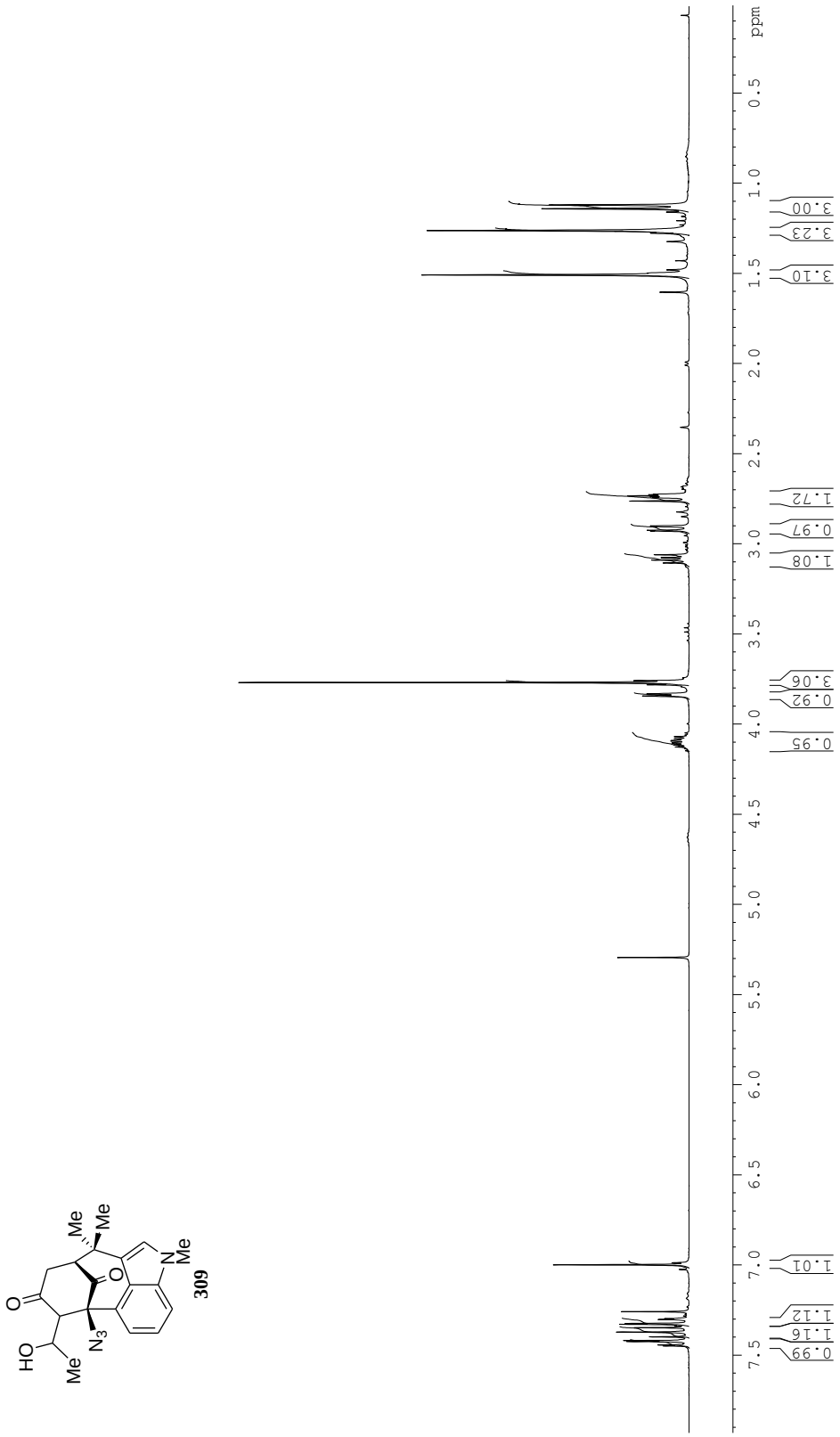
^{1}H NMR of diketoazide **276**



^{1}H NMR of diketoazide **276**



^{1}H NMR of diketoazide **309**



^{13}C NMR of diketoazide **309**