The Total Synthesis of Concavine

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Abstract

Concavine, a diterpene natural product was isolated from a strain of *Clitocybe concava* in 2005 and was the first diterpene alkaloid to be isolated from a mushroom. Chapter 1 presents the unprecedented core structure of this novel alkaloid consisting of a bicyclo[3.2.1]octane system linked with a oxazepane ring. Our retrosynthetic analysis highlighting the challenges for the synthesis of concavine is presented.

Chapter 2 discusses the formation of the bicyclo[3.2.1]octane system and the installation of an oxazepane ring precursor. The different strategies used to form the five-membered ring and the regioselectivity issues surrounding the addition of the oxazepane ring precursor are discussed.

The completion of the core structure of concavine and the end game is described in Chapter 3. While the strategy to use a sulfone group as a ketone precursor was not successful, the hydrolysis of a vinyl sulfide group was key to access the desired ketone and complete the total synthesis of concavine.

In Chapter 4 the comparison between the reported data for concavine and our synthesised compound is described. The synthesis of a new epimer was undertaken to solve the mismatch in the data without success. Both the HCl and AcOH salts of the synthesised concavine were formed to investigate the impact of a protonated amine on the chemical shift compared to the free amine.

A summary of the total synthesis of concavine is presented in Chapter 5. The successful sequence for the formation of concavine from the commercially available anhydride and the work to match the data with the reported natural product is summarised.

To Claude and Jeannine

I hope you are proud of me

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Firstly, I would like to thank my supervisor Professor Nigel Simpkins for believing in me to carry out this project. He always had ideas and advice to help me with my capricious chemistry and I learnt many new skills under his supervision.

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Finally, many thanks to my beloved Charlotte, this last year was tough but your love and kindness made it easier.

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Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Bn	benzyl
Bs	*p*-bromobenzenesulfonyl
Bu	butyl
Bzl	benzoyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E	electrophile
eq.	equivalent
ES	electrospray
Et	ethyl
g	gram (s)
h	hour (s)

HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoric triamide
HRMS	high-resolution mass spectrometry
IR	infrared spectroscopy
J	coupling constant (in nuclear magnetic resonance spectroscopy)
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute
MoOPH	Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)
m.p.	melting point
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
n	normal
Nb	number
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
Np	naphthalene
Ph	phenyl
ppm	parts per million
Py	pyridine
R*f*	retardation factor
RT	room temperature

TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
UV	ultraviolet
ν	frequency

Chapter 1 Introduction

1.1. Structure and Isolation

Concavine (**1**) was extracted in 2005 in Italy by Nasini's group from a strain of *Clitocybe concava* found in the Basidiomycetes fungi.[1] The fungus was grown on a malt-peptone-glucose-agar matrix and after four weeks the crude extracts were purified by flash chromatography. High-resolution mass spectrometry combined with elemental analysis determined the molecular formula as $C_{22}H_{35}NO$. Two-dimensional NMR analysis was used to determine the structure of this novel alkaloid consisting of an oxazepane ring linked with a bicyclo[3.2.1]octane system (Figure 1.1). An *exo*-double bond and a prenyl chain are also attached to this unprecedented skeleton.

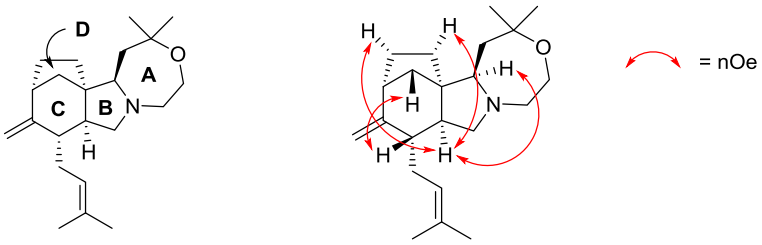


Figure 1.1 Structure of concavine

Concavine was isolated as an oil, therefore, no X-ray structure was obtained to confirm the relative and absolute configuration of the five stereocentres, four of which are contiguous. NOESY experiments determined the relative configuration of the stereogenic centres with the correlations observed in Figure 1.1.

Biological tests were performed on concavine but no antifungal (*Cladosporium cladosporioides*, *Aspergillus niger*) or antitumour (tyrosine-kinase test) activity were observed.

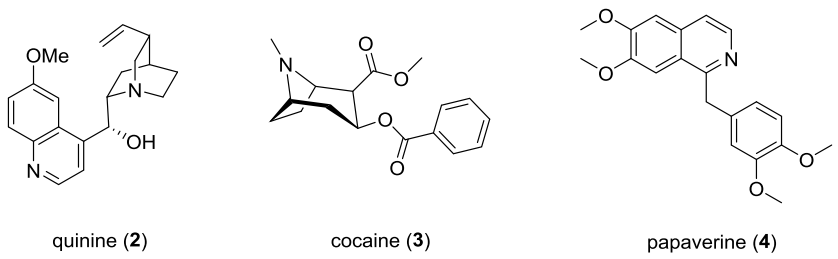
However, weak antibacterial activities against *Bacillus subtilis* and *Bacillus cereus* were found.[1]

Despite the limited biological activity, the total synthesis of concavine was undertaken due to the challenging and novel core structure including its four contiguous stereocentres.

1.2. Classification of Alkaloids and Terpenoids

1.2.1. Classification

Concavine has been characterised by Nasini as a pseudoalkaloid part of the C_{20} diterpenoid family. To understand the reasons behind this nomenclature a close look at the classification of alkaloids is needed.[1] There are three main classes of alkaloids: the true alkaloids, the protoalkaloids and the pseudoalkaloids.[2] True alkaloids come from amino acids and their nitrogen is part of a heterocyclic ring; some examples are shown in Figure 1.2.



quinine (**2**) cocaine (**3**) papaverine (**4**)

Figure 1.2 Members of the true alkaloid family

Protoalkaloids also have their nitrogen atom derived from an amino acid but it is not part of a heterocyclic ring; they represent the minority of alkaloids (Figure 1.3).

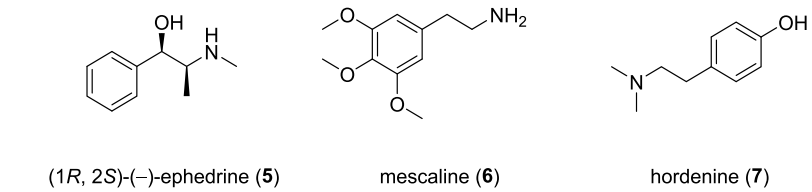


Figure 1.3 Members of the protoalkaloid family

The final class of alkaloids are the pseudoalkaloids with skeletons that do not derive from amino acids as exemplified in Figure 1.4. Their biosynthesis is still connected with the amino-acid pathway as pseudoalkaloids are derived from the precursors or postcursors of amino acids.

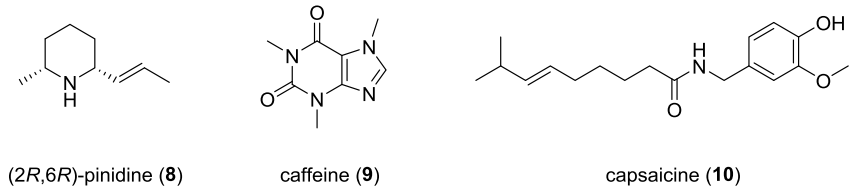


Figure 1.4 Members of the pseudoalkaloid family

Once the main class of an alkaloid has been determined, a second level of classification is assigned based on the chemical structure; nine frameworks are commonly found (Figure 1.5).

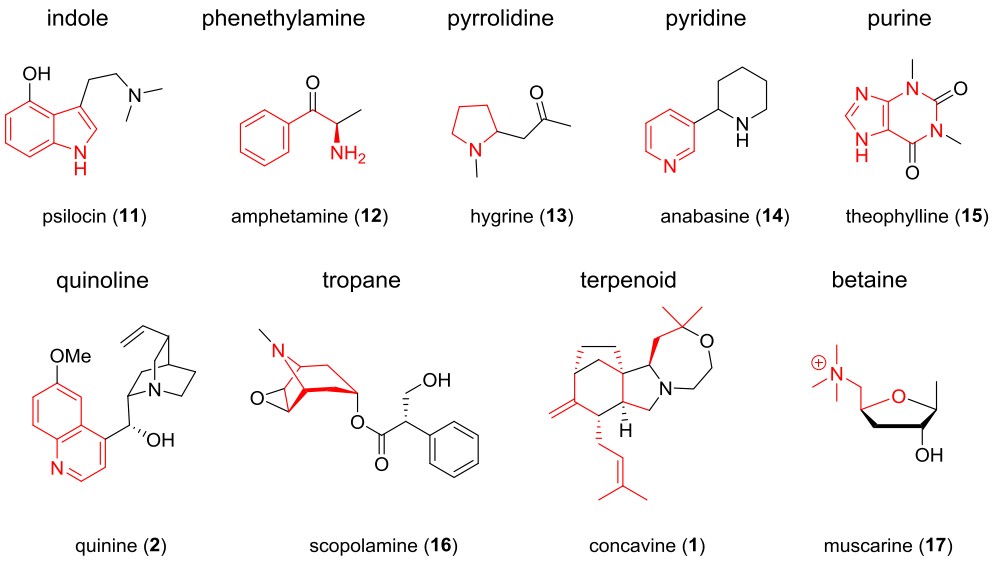
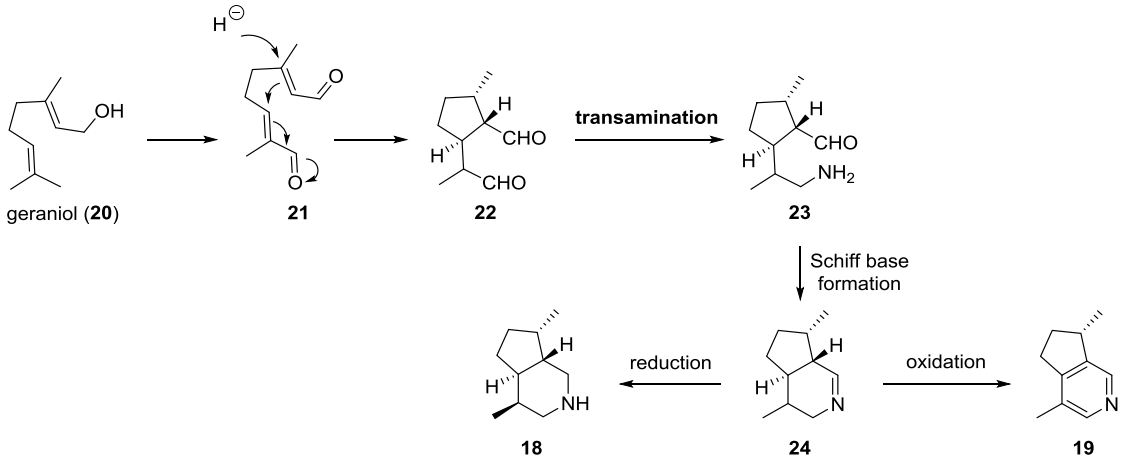


Figure 1.5 Alkaloid frameworks with examples

The terpenoids are the largest group of this classification; they are pseudoalkaloids formed by the combination of isoprene units.[3] The nitrogen atom in their skeletons does not come from an amino acid and is thought to be inserted late in the biosynthesis by an amination process like in the biosynthesis of the monoterpenoids β-skytanthine (**18**) and actinidine (**19**) (Scheme 1.1).[4] The transamination reaction takes place on iridodial (**22**) which was obtained from geraniol (**20**) after formation of dialdehyde intermediate **21**. The formation of Schiff base **24** allows then the access to β-skytanthine (**18**) and actinidine (**19**).



Scheme 1.1 Possible biosynthesis of **18** and **19**

The terpenoids can be classified by the number of isoprene units present in their skeleton (Table 1.1).

N° if isoprene units	Name
1	Hemiterpenoids
2	Monoterpenoids
3	Sesquiterpenoids
4	Diterpenoids
5	Sesterterpenoids
6	Triterpenoids
8	Tetraterpenoids
>8	Polyterpenoids

Table 1.1 Classification of terpenoids

The predominant members of this classification are the monoterpenoids and the diterpenoids. Monoterpenoids mostly come from the family *Gentianaceae* of plants whereas diterpenoids are mainly found in the *Ranunculaceae* family.

With four isoprene units present in its skeleton (see Figure 1.5), concavine belongs to the diterpenoid family, which constitutes the largest and most complicated group of terpenoid alkaloids. Diterpenoids are further divided into three classes, because of their broad structural diversity, based on their skeleton: C_{18}, C_{19} and C_{20}.

1.2.2. C_{18} diterpenoids

The C_{18} diterpenoids represent the smallest group within the diterpenoids; just over 100 compounds have been isolated from around 40 plants species from the *Aconitum* and *Delphinium* families. All C_{18} diterpenoids share the same skeleton and are divided into two types: lappaconitines and ranaconitines (Figure 1.6).[4]

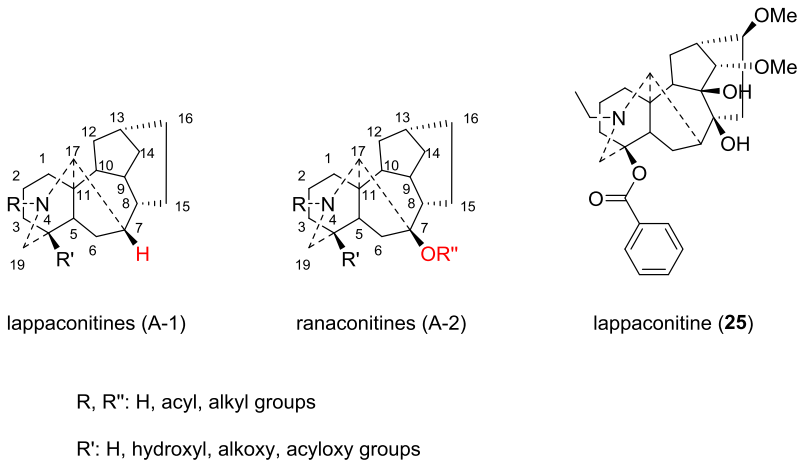


Figure 1.6 C_{18} types of diterpenoids

The lappaconitines are characterised by a lack of an oxygen functionality at the C-7 position. Lappaconitine (**25**) was the first C_{18} diterpenoid to be isolated from the plant *Aconitum septentrional* and gave its name to the family.[5]

1.2.3. C_{19} diterpenoids

The C_{19} diterpenoids are the largest class of diterpenoids with more than 700 compounds from around 315 species of plants from the genera *Aconitium* and *Delphinium*. Six types of structures are found in this class: aconitine type (B-1), lycoctonine type (B-2), pro type (B-3), lactone type (B-4), 7,17-*seco* type (B-5) and rearranged type (B-6). The order of types B-1 to B-6 is based on the descending numbers of alkaloids isolated to date (Figure 1.7).[6]

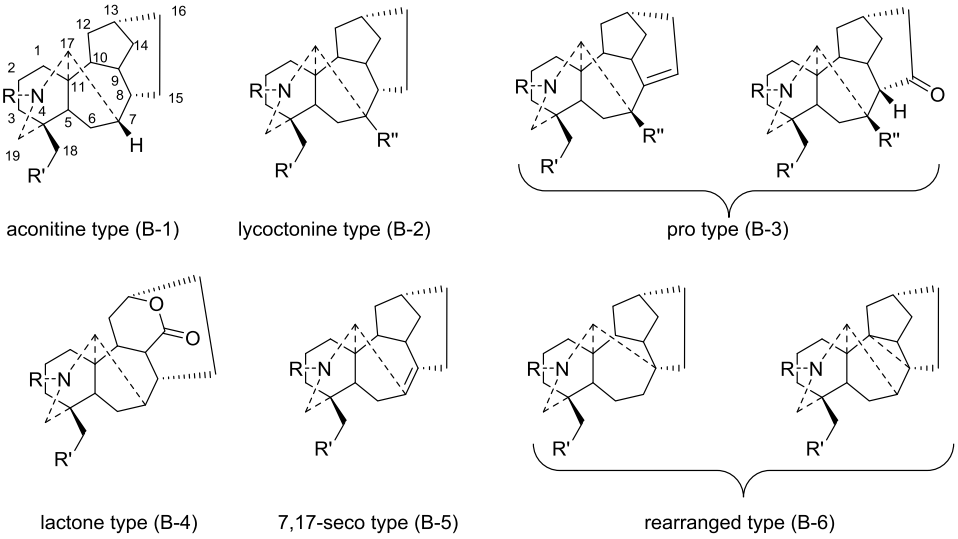


Figure 1.7 C_{19} types of diterpenoids

1.2.4. C_{20} diterpenoids

Like the two previous classes of diterpenoids, *Acotinium* and *Delphinium* genera are also the main providers of C_{20} diterpenoids. Their classification remains unclear but five different types of skeletons have been isolated (Figure 1.8).[4]

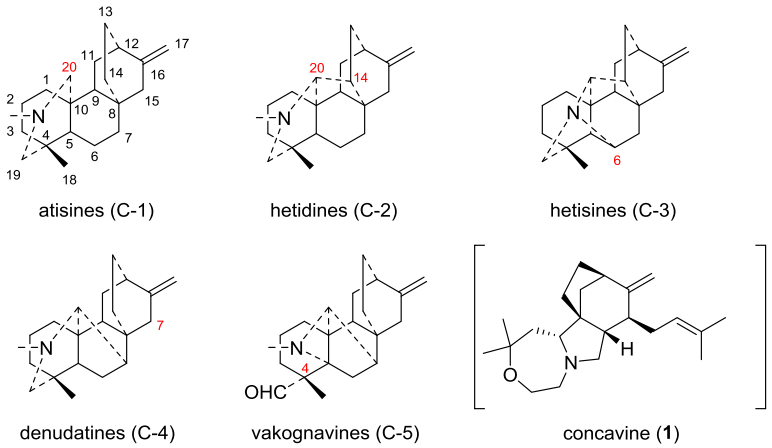


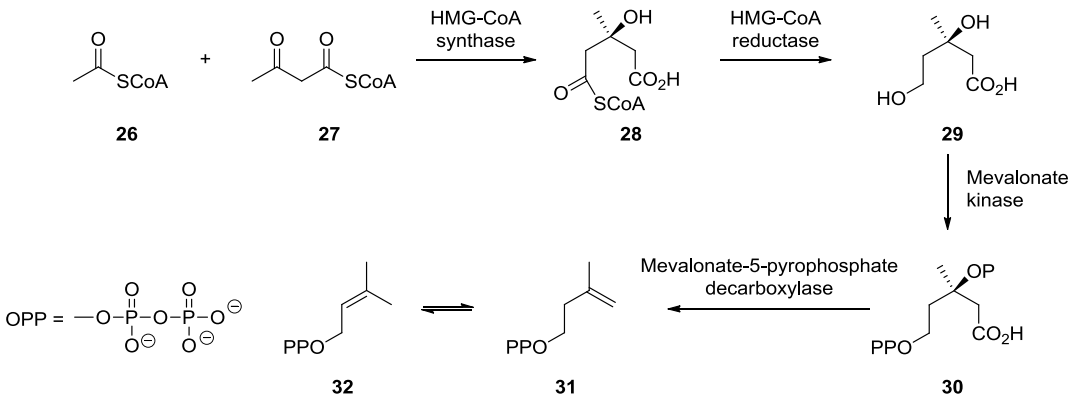
Figure 1.8 C_{20} types of diterpenoids

The atisine type is comparatively the simplest type with a pentacyclic core owing to the disubstituted nature of C-20. The hetidine type is characterised by a hexacyclic ring system

with an additional bond at C-20 – C-14. The most complex group is the hetisine one, the N-C-6 bond gives them an heptacyclic core. Denudatines, similar to the atisines, possess an extra C-20 – C-7 connection. Finally, the vakognavine type is the only one with an aldehyde moiety at C-4. Concavine is considered as a C_{20} diterpenoid because the hydroxyethyl chain attached to the nitrogen that forms the oxazepane ring does not belong to the basic skeleton of diterpenoids.[6]

1.3. Biosynthesis

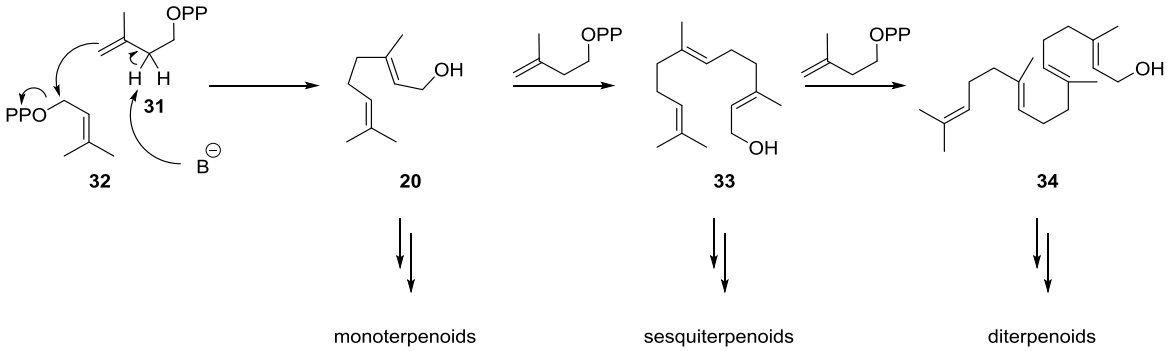
Terpenoids are made from the cyclisation of isoprene units. The formation of these building blocks starts with the condensation of acetyl-CoA (**26**) and acetoacetyl-CoA (**27**) followed by a reduction to give **29**. The pyrophosphate group is then installed and **30** is converted to isopentenyl pyrophosphate (**31**) and its isomer 3,3-dimethylallylpyrophosphate (**32**) (Scheme 1.2).[7]



Scheme 1.2 Biosynthetic formation of isopentenyl pyrophosphate

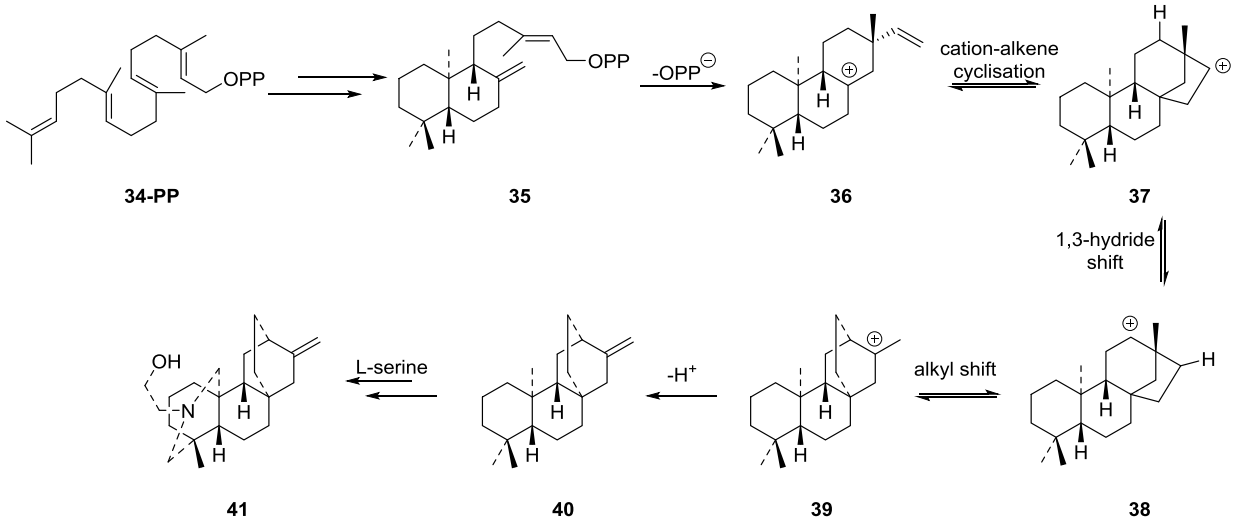
The first condensation of isopentenyl pyrophosphate (**31**) and 3,3-dimethylallyl pyrophosphate (**32**) gives geraniol (**20**) and its pyrophosphate derivative which are the precursors for the C_{10} monoterpenoids. The addition of further isopentenyl pyrophosphate (**31**) to geraniol (**20**)

furnishes farnesol **33** and then geranylgeraniol **34** (with their pyrophosphate derivatives) which are presumed to be the precursors for the C_{15} sesquiterpenoids and C_{20} diterpenoids (Scheme 1.3).



Scheme 1.3 Biosynthetic pathway to terpenoids

Due to concavine being the first diterpenoid isolated from Basidiomycetes, with a unique ring system, no biosynthesis has been reported. However, a biosynthetic pathway for a C_{20} diterpenoid type (atisane type) which contains characteristic features of concavine has been proposed. To access the skeleton of the C_{20} diterpenoids the geranylgeranyl pyrophosphate (**34-PP**) cyclises to give **35**. Another cyclisation and the loss of the pyrophosphate occurs to give primarenyl carbocation (**36**). It is generally proposed that **36** undergoes a cation-alkene cyclisation to form the beyeranyl cation (**37**). An overall 1,3-hydride shift followed by an alkyl shift and then deprotonation gives the atisane-type skeleton **39**. The aminoethanol moiety in **41** is introduced by L-serine (Scheme 1.4).[6]



Scheme 1.4 Possible biosynthesis of atisane type **41**

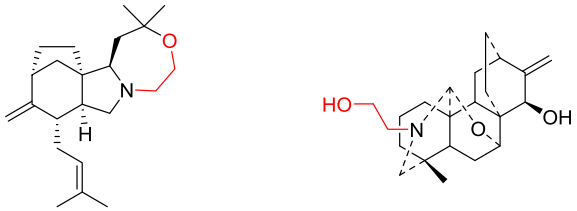
The five-membered ring, the *exo*-double bond and the hydroxyethyl chain on the nitrogen are also found in the skeleton of concavine and might be formed in a similar manner. However, the other rings present in concavine share little in common with **41** and are probably installed during the first enzymatic cyclisation of geranylgenaryl pyrophosphate (**34-PP**) *via* a different cyclisation pathway.

1.4. Similar structures

The sequence of the four isoprene units forming the skeleton of concavine is unique and no close matches are found in the common C_{20} structures listed above. Different origins can explain this lack of close diterpenoid parents, indeed, most of the diterpenoids come from *Aconitum* and *Delphinium* (plants), whereas concavine was the first diterpenoid to be isolated from Basidiomycetes (fungi).[1]

However, some diterpenoids and other natural products possess similar characteristic of concavine's framework.

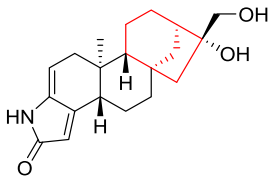
Ajaconine (**42**), isolated from *Delphinium ajacis*, has a structure similar to the denudatines type (C-4, Figure 1.8) and was the first example of a C_{20} diterpenoid bearing an internal *β*-hydroxyethyl group also found in **1** (Figure 1.9).[8]



concavine (**1**) ajaconine (**42**)

Figure 1.9 concavine and ajaconine

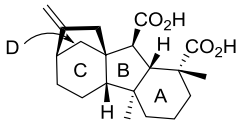
The bicyclo[3.2.1]octane structure can be found in the tricalysiamide family. These rearranged ent-kaurane diterpenoids are found in the wood of *Tricalysia dubia* in the southern parts of China and Japan (Figure 1.10).[9] The diol moiety present on the five-membered ring is shared by all members of the tricalysiamides.



tricalysiamide A (**43**)

Figure 1.10 Bicyclo[3.2.1]octane system in tricalysiamide A

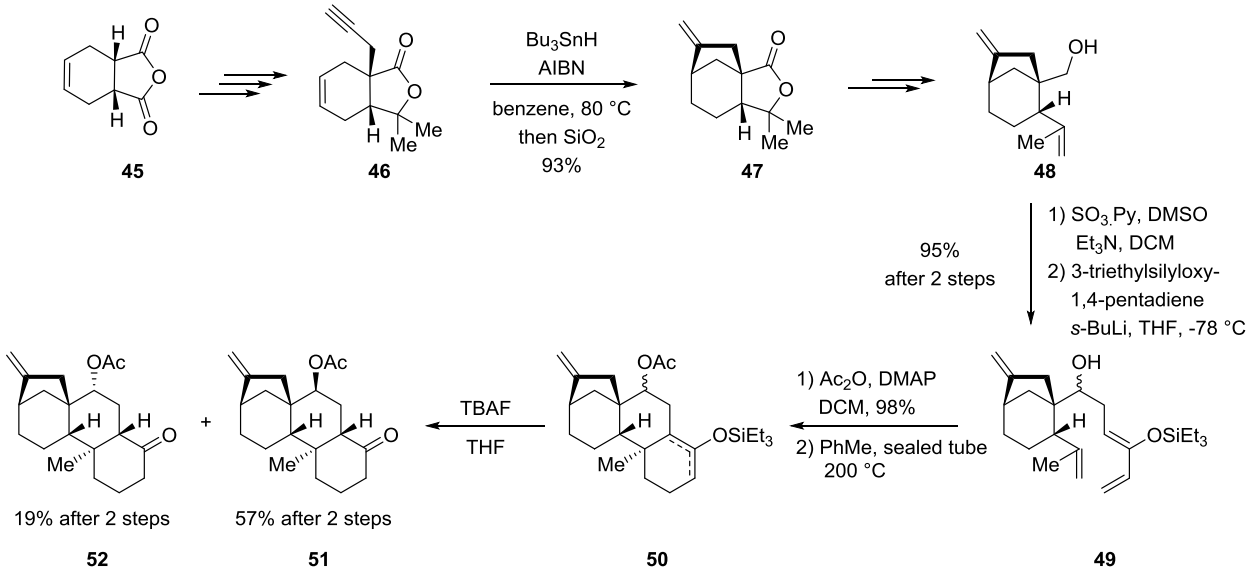
Similarities with the concavine skeleton are also found in natural products other than alkaloids. Gibberellin A_{12}, a plant-growth regulator isolated from a broth of *Gibbebrella fujikuroi*, possesses a ring arrangement close to concavine (Figure 1.11).[10]



Gibberellin A_{12} (**44**)

Figure 1.11 Gibberellin A_{12}

The total synthesis of Gibberellin A_{12} by M. Matsui and co-workers reveals how the interesting BCD ring was assembled.[10,11] Several transformations on tetrahydrophthalic anhydride **45** yielded alkyne **46** which underwent a radical cyclisation with tributyltin hydride to form the bicyclo[3.2.1]octane system **47**. Four steps were required to open the lactone. Then the alcohol on intermediate **48** was oxidised under Parikh-Doering conditions prior to alkylation with (triethylsilyloxy)pentadienyl lithium to furnish tetraene **49** in 95% yield (Scheme 1.5). An intramolecular Diels-Alder reaction in toluene at 200 °C in a sealed tube gave cyclised intermediate **50** which was treated with TBAF to yield a chromatographically separable mixture of desired **51** and **52**.



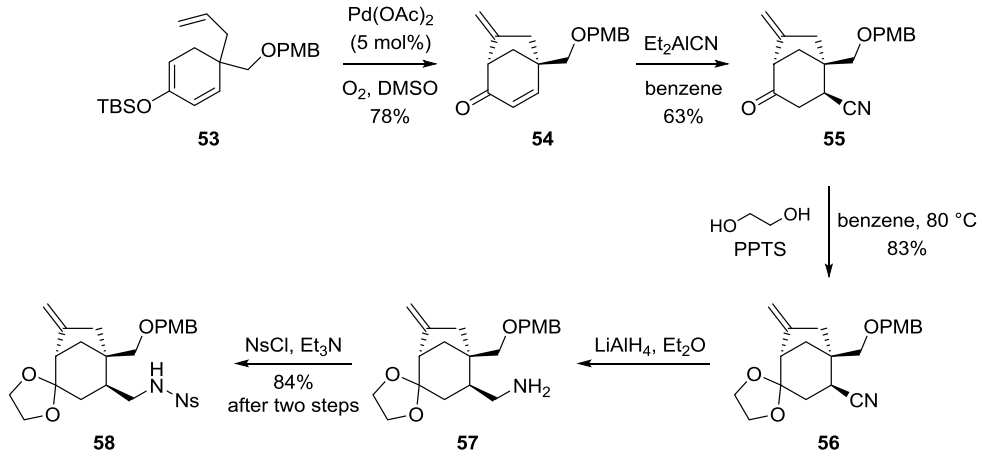
Scheme 1.5 Formation of **52** for the synthesis of Gibberellin A_{12}

The CD ring system was efficiently formed with a radical cyclisation and the B ring was constructed after contraction of the six-membered ring previously installed by a Diels-Alder reaction. This approach to form ring B seems unsuitable for concavine as a larger ring size needs to be present to perform the ring contraction.

1.5. Previous work

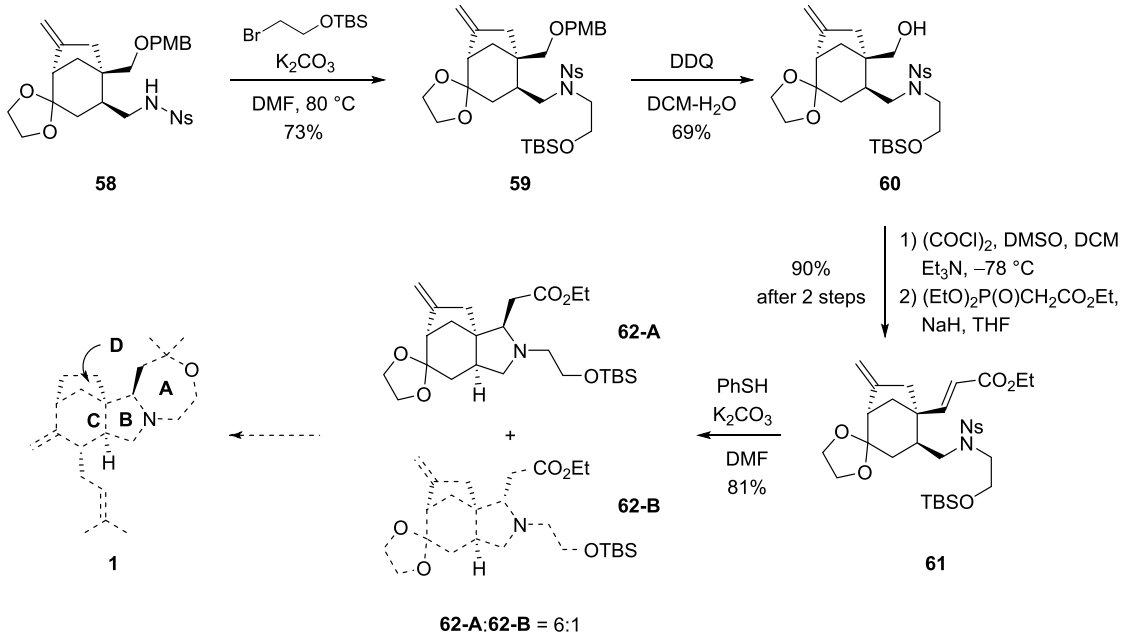
Despite the fact that no total synthesis of concavine has been published, several groups have shown interest in this novel alkaloid. In February 2016, Toyota's group published a synthesis of the BCD ring system to demonstrate the utility of their palladium-catalysed cycloalkenylation.[12]

The first target was the construction of the CD ring. This was achieved in one step by a palladium-catalysed cycloalkenylation of **53** to give the bicyclo[3.2.1]octane moiety **54** in good yield (Scheme 1.6). An hydrocyanation reaction performed on compound **54** with diethylaluminium cyanide gave **55** in 63% yield. After protection of the ketone, the cyano group was reduced to yield amine **57** which was further transformed into sulfonamide **58** in 84% yield.



Scheme 1.6 Synthesis of the BCD ring system (part 1)

A TBS-protected ethanol chain was added as a precursor for the formation of ring A (Scheme 1.7). Removal of the PMB protecting group gave alcohol **60** which was oxidised under Swern conditions to yield the corresponding aldehyde. A Horner-Wadsworth-Emmons reaction gave access to **61** in 90% yield. Formation of ring B was achieved by an intramolecular aza-Michael reaction. Thiophenol and potassium carbonate were used to cleave the nosyl group to allow the ring closure.



Scheme 1.7 Synthesis of the BCD ring system (part 2)

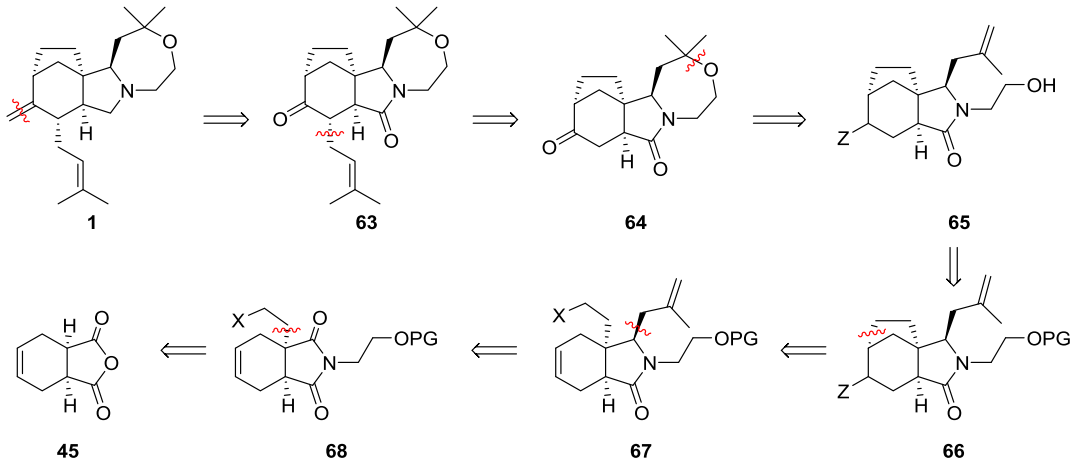
Compound **62** was formed in 81% yield and as a 6:1 mixture of diastereoisomers and the relative stereochemistry of **62** was confirmed using NOE experiments. This potential intermediate for the synthesis of concavine was synthesised in ten steps with an overall yield of 12%.

The authors have not reported any more results towards the formation of ring A or the introduction of the prenyl chain. No explanations or proposed reactions are given to describe how the undesirable *exo*-double bond present on ring D would be removed. This unfinished

synthesis highlights the difficulties of forming the core structure of concavine and to efficiently control the orientation of the stereocentres.

1.6. Retrosynthetic analysis

As seen above, the structure of concavine presents many challenges: the formation of the five-membered ring D, the *anti*-configuration between the two carbon bridge in ring D and the oxazepane ring, the construction of the oxazepane ring and the orientation of the prenyl chain. To access concavine, the retrosynthetic route below was proposed (Scheme 1.8).

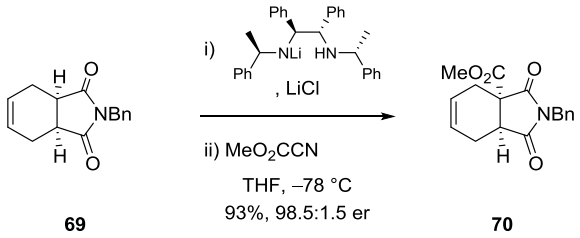


Scheme 1.8 Retrosynthetic analysis

It was planned to install the *exo*-double bond and the prenyl chain last from ketone **64** *via* a prenylation and an olefination reaction. Controlling the orientation of the prenyl chain in **63** is a key part of the synthesis. Previous work in the group suggests that the three-dimensional shape of intermediate **64** should control the approach of the prenyl group in the desired way. The tetracycle core could be assembled by a cyclisation between an alcohol and the methylallyl chain present in **65**. For the formation of the five-membered ring in **66**, a variety of functional groups X would be installed to react with the double bond. To install the methylallyl chain in

the desired orientation, a nucleophilic addition on imide **68** could be envisaged. Regioselectivity issues might occur during the formation of **67** and modification of the imide group or the reaction conditions might therefore be required. The commercially available anhydride **45** was thought to be a suitable starting material.

The use of tetrahydrophthalic anhydride **45** as starting material would also allow the chiral base methodology previously developed in the group to be applied (Scheme 1.9).[13]

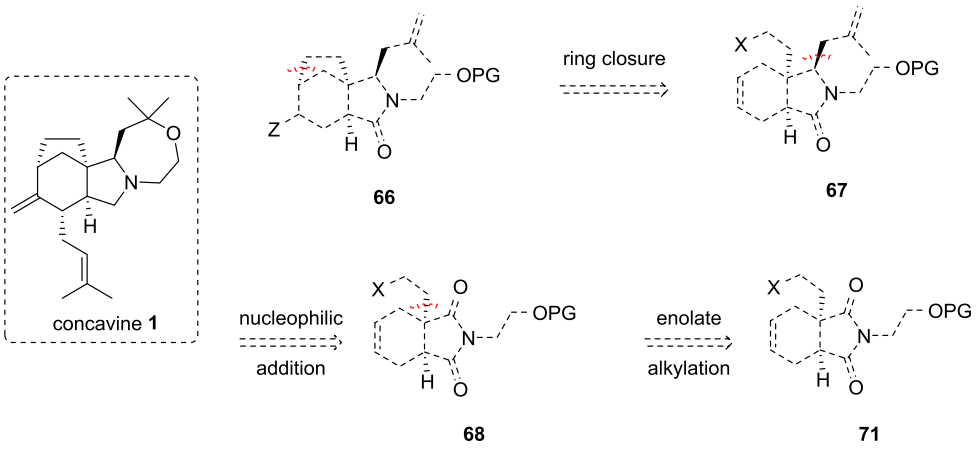


Scheme 1.9 Carboxymethylation of **69** using a chiral base

Implementing this methodology could give **68** as a single enantiomer and lead to an enantioselective synthesis of concavine.

Chapter 2 Formation of the bicyclo[3.2.1]octane system and oxazepane ring precursor

The strategy depicted in the retrosynthetic Scheme 1.8 identified compound **66** as the first key intermediate for the synthesis of concavine. This molecule possesses the bicyclo[3.2.1]octane system and a methylallyl chain in an *anti*-configuration with respect to the five-membered ring. These two key features of concavine were found to be synthetically challenging during previous work performed in the Simpkins group and their installation was investigated first (Scheme 2.1).[14]



Scheme 2.1 Retrosynthetic analysis to access key intermediate **66**

The five-membered ring in **66** could be assembled by a ring closure reaction with an appropriate functional group X, like a sulfonate or a halide, and the double bond present in **67**. A methylallyl moiety, chosen to be the precursor for the formation of the oxazepane ring, could be inserted by a nucleophilic addition on imide **68** obtained from symmetrical imide **71**.

The bicyclo[3.2.1]octane moiety is rarely found in the C_{20} diterpenoids and only the napelline and tricalysiamide families of natural products bear this characteristic in their structure (Figure

2.1).[9,15,16] The *exo*-double bond present on the five-membered ring is characteristic of the napelline family, whereas all of the tricalysiamides (A-D) have a diol moiety at this position.

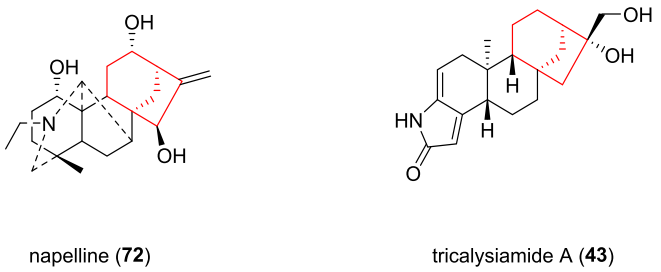
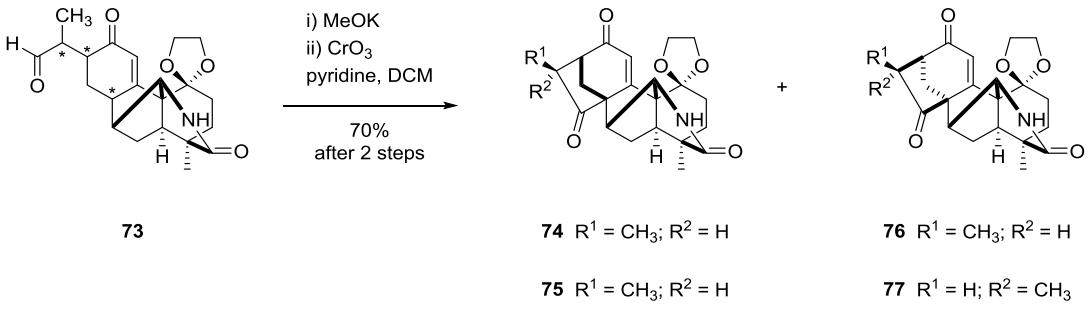


Figure 2.1 Examples of the bicyclo[3.2.1]octane system found within the tricalysiamide and napelline families of natural products

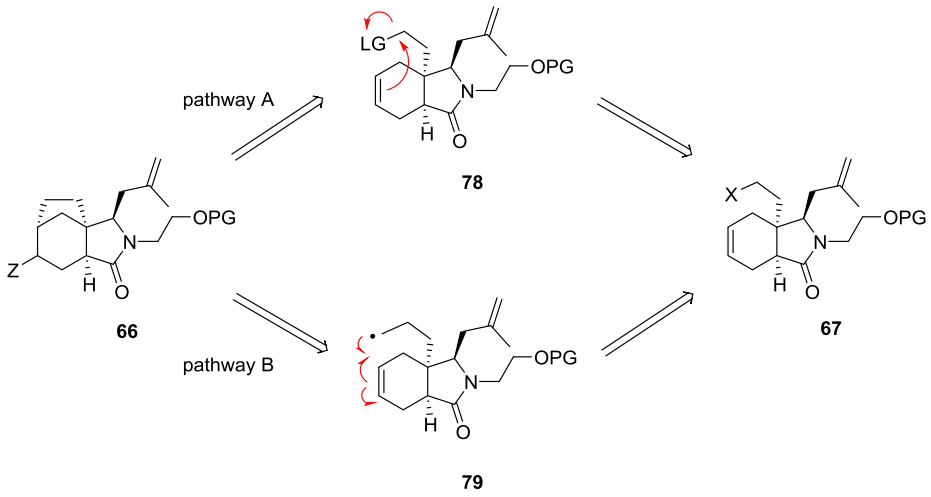
The synthesis of napelline (**72**) by Wiesner and co-workers is the only total synthesis of these types of natural products to date.[15] To access compound **75**, the authors performed a vinylogous aldol condensation on **73**, followed by an oxidation with chromium trioxide giving the desired ring in 70% yield. Unfortunately, poor control during the synthesis of **75** led to the formation of four products with a (**74**+**75**):(**76**+**77**) ratio of 6:4 (Scheme 2.2).



Scheme 2.2 Formation of the bicyclo[3.2.1]octane ring in the napelline total synthesis

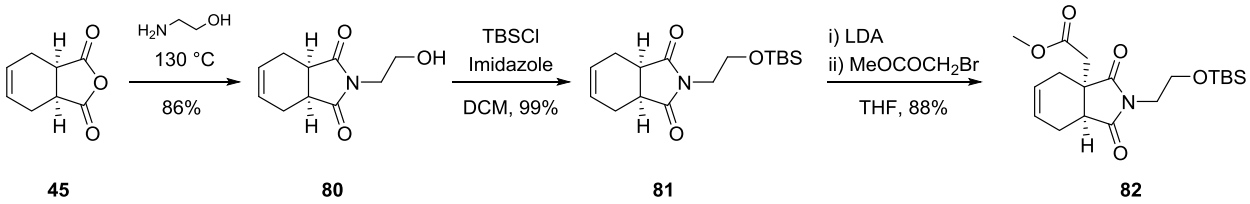
A similar route to the bicyclo[3.2.1]octane moiety following Wiesner's strategy would not be appropriate for the synthesis of concavine. The mixture of diastereoisomers is highly undesirable and the alcohol resulting from the vinylogous aldol condensation would have to be removed, requiring several steps.

Our strategy to access compound **66** was based on the reaction of a double bond with an X group under a variety of conditions (Scheme 2.3). The double bond could act as a nucleophile if X is a suitable leaving group (pathway A) or reactions utilising radical species can be employed (pathway B). In either case, trapping the carbocation or the radical formed after the formation of the five-membered ring is mandatory to introduce a new functional group Z. This new handle is needed to access the prenyl chain and the *exo*-double bond present in concavine.



Scheme 2.3 Access to key intermediate **66** *via* compounds **78** or **79**

The synthesis of intermediate **67** began with the condensation of tetrahydrophthalic anhydride **45** and ethanolamine, giving imide **80** in high yield. The alcohol in **80** was then protected with TBSCl before LDA and methyl bromoacetate were employed to provide methyl ester **82** in good yield (Scheme 2.4). The methyl ester group was chosen as a precursor to form the five-membered ring as its reduction would give the desired functionalised alkyl chain present in **67** (where X is an OH).



Scheme 2.4 Synthesis of **82** from anhydride **45**

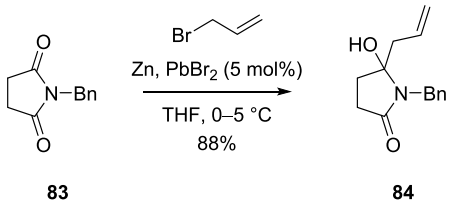
To complete the formation of **67** and introduce an oxazepane ring precursor, several conditions to install a methylallyl moiety were examined.

2.1. Nucleophilic addition to imide 82

2.1.1. Barbier allylation

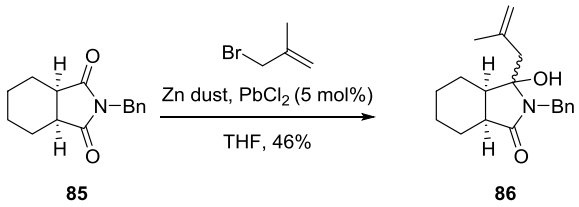
The Barbier allylation is a commonly used reaction to add an allyl chain to a carbonyl group with several advantages compared with other related methods.[17] First, a large range of inexpensive metals can be employed to form the active species, including zinc, indium, tin and aluminium.[18] In addition, the intermediate allyl metals species are less water-sensitive and so water can be used as a co-solvent. Second, formation of the nucleophile and reaction with the carbonyl group occurs in a one-pot reaction meaning that the organometallic reagent does not have to be prepared beforehand like in standard Grignard reactions.

In 2000, Kim and co-workers published a zinc-mediated Barbier-type allylation of cyclic imides.[19] Successful allylation of **83** was reported with allyl bromide, zinc dust and five mol% of lead(II) bromide in good yield (Scheme 2.5).



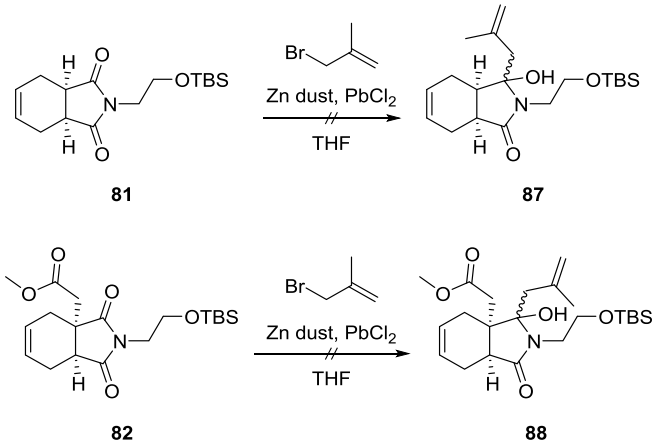
Scheme 2.5 Barbier allylation on cyclic imide **83** by Kim and co-workers

The viability of this method for our synthesis of concavine was tested on model compound **85** (Scheme 2.6). A mixture of 3-bromo-2-methylpropene, zinc dust and lead(II) chloride was employed, giving **86** in 46% yield, in addition to 50% of recovered starting material. To our disappointment, increasing the temperature, the reaction time and the amount of reagents did not afford higher yields.



Scheme 2.6 Barbier allylation on model compound **85**

The modest yield for the formation of **86** encouraged us to apply these conditions to intermediate **81** and desired compound **82**. No conversion was observed in both cases and only starting material was recovered (Scheme 2.7).

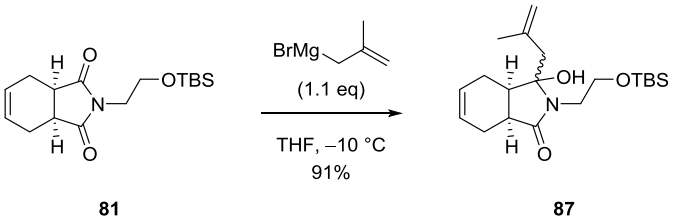


Scheme 2.7 Attempted Barbier allylations onto **81** and **82**

The inefficient formation of the organometallic reagent under the reaction conditions was one proposed reason for the modest yield obtained with model compound **84**, and the lack of reaction on **81** and **82**. To ensure a high proportion of organometallic reagent in the reaction mixture, it was instead decided to prepare it beforehand and try a Grignard reaction.

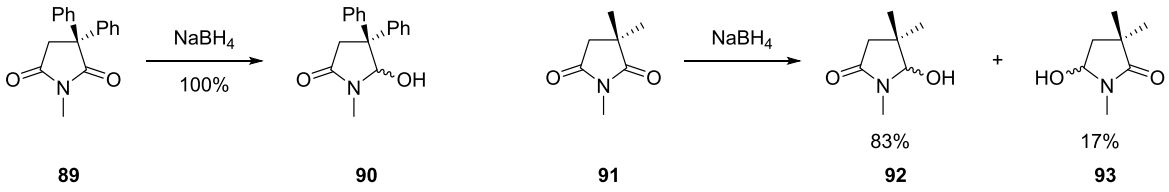
2.1.2. Grignard reaction

Like the Barbier reaction, Grignard reagents can also be employed to add an allyl group into a carbonyl group. The ease of preparation of allyl Grignard reagents, and their stability upon storage added to the advantages of this approach. A solution of 2-methylallylmagnesium bromide, prepared using 3-bromo-2-methylpropene and magnesium turnings, was added dropwise to compound **81**. Pleasingly, this gave the desired compound **87** in an excellent 91% yield following optimisation (Scheme 2.8).



Scheme 2.8 Grignard addition of 2-methylallylmagnesium bromide into imide **81**

Encouraged by these results, we then considered applying this method to compound **82**. It should be noted, however, that **82** is no longer symmetrical, and addition to either carbonyl can occur. This issue was discussed in detail by Speckamp and co-workers during their work on the regioselective reduction of *gem*-disubstituted succinimides.[20] It was observed that the steric demands of the substituents adjacent to the carbonyl can govern the regioselectivity of the reduction. Indeed, the reduction of **89** containing bulky phenyl groups gave **90** as a single isomer whereas the two methyl groups on **91** furnished a mixture of regioisomers (Scheme 2.9).



Scheme 2.9 Reduction of *gem*-disubstituted succinimides by Speckamp and co-workers

These results confirmed the authors' hypothesis that the hydride reagent approaches along a trajectory *via* the less hindered carbonyl in accord with the Bürgi-Dunitz angle (Figure 2.2). This approach favours the reduction of the more hindered carbonyl as the bulky groups R^1 and R^2 block the access to the other carbonyl.

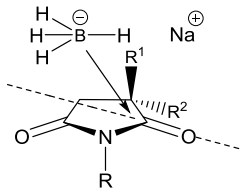
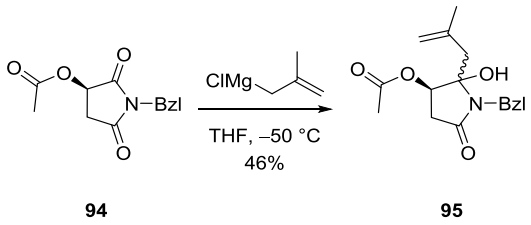


Figure 2.2 Approach of the $NaBH_4$ for the reduction of imides reported by Speckamp and co-workers

In 1990, Nozoe and co-workers used the work of Speckamp to facilitate the diastereoselective synthesis of (−)-statine.[21] Intermediate **94** was treated with a solution of 2-methylallylmagnesium chloride to furnish **95** in a modest 46% yield as a single regioisomer

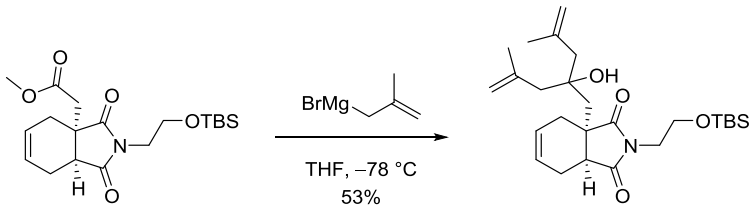
(Scheme 2.10). The Grignard addition took place on the carbonyl closer to the bulky ester and no reaction with the ester was observed.



94 **95**

Scheme 2.10 2-methylallylmagnesium chloride addition to **94** by Nozoe and co-workers

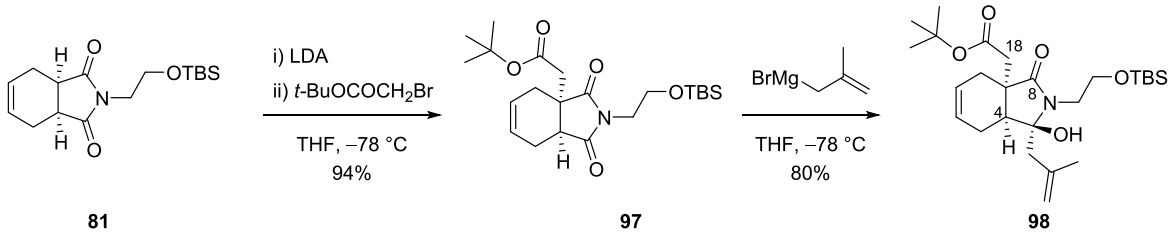
In light of these results, we proceeded with a Grignard reaction on **82**, expecting the desired addition to the carbonyl adjacent to the ester. However, when 1.1 equivalents of 2-methylallylmagensium bromide were added to imide **82**, no desired product was detected and only the product resulting from double addition of the Grignard reagent on the methyl ester was observed (Scheme 2.11).



82 **96**

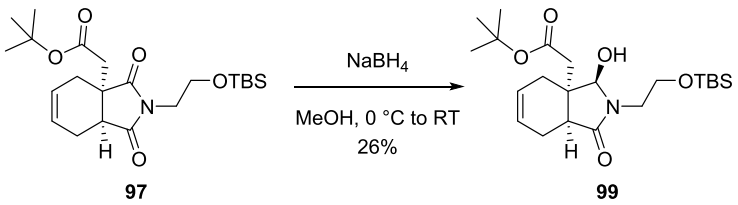
Scheme 2.11 Grignard reaction of **82** with 2-methylallylmagnesium bromide

To avoid this side reaction, a less reactive *tert*-butyl ester was introduced, in good yield, from **81**. As expected, the *tert*-butyl ester was found to be unreactive during the Grignard reaction. Surprisingly, however, the methylallyl chain was shown to have added to the carbonyl distal from the ester (Scheme 2.12). The regioselectivity of this reaction was confirmed by HMBC correlations between H-18 and C-8 and the OH and C-4.



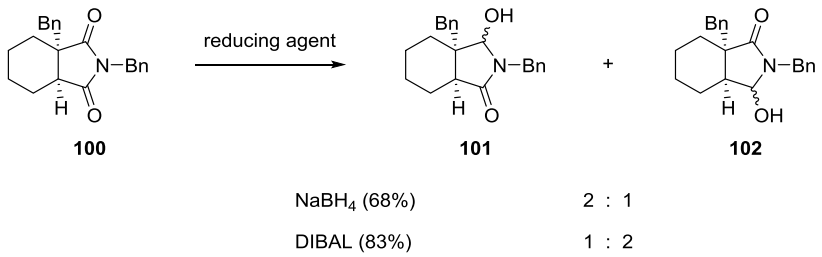
Scheme 2.12 Preparation of *tert*-butyl ester **97** and Grignard reaction on **97**

The observations made by Speckamp were not able to be repeated, and despite the good yield of the reaction, compound **98** is unfortunately not a useful intermediate for the synthesis of concavine. To test the viability of the Speckamp model on our system, the original conditions were applied to compound **97** (Scheme 2.13). The reaction proceeded with low yield but only the more hindered carbonyl was reduced in accordance with the model published.



Scheme 2.13 Reduction of *tert*-butyl ester **97** using $NaBH_4$

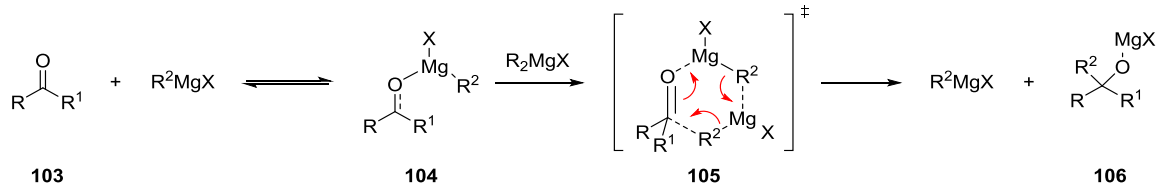
This result was in accordance with previous work published by Simpkins and co-workers on the desymmetrisation of imides in the synthesis of the alkaloid jamtine (Scheme 2.14).[22]



Scheme 2.14 Reduction of **100** with $NaBH_4$ and DIBAL by Simpkins and co-workers

The reduction of **100** with sodium borohydride showed a reduction of the more hindered carbonyl in a 2:1 ratio whereas a reduction using DIBAL yielded the other regioisomer.

The regiocomplementary results obtained with compound **97** can be explained by the different mechanisms involved in the two reactions. During the reduction reaction, the Bürgi-Dunitz trajectory between the reducing agent and the less hindered carbonyl is blocked by the bulky ester. Therefore, only the carbonyl closest to the *tert*-butyl ester is reduced (see Figure 2.2). However, the reactivity of sodium borohydride is not comparable to the reactivity of Lewis acidic organometallic compounds such as Grignard reagents for example. Indeed, during a Grignard reaction coordination of the carbonyl by the magnesium species occurs to form a six-membered transition state which is favoured on the less hindered carbonyl (Scheme 2.15).[23]

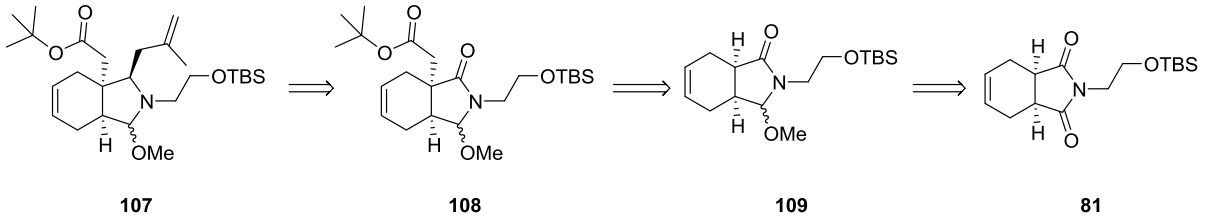


Scheme 2.15 Mechanism of Grignard addition to carbonyl **103**

The nature of the imide offered a great opportunity towards the use of Grignard reactions. However, the desired regioselectivity was disfavoured and as this issue could not be overcome, a new strategy was sought.

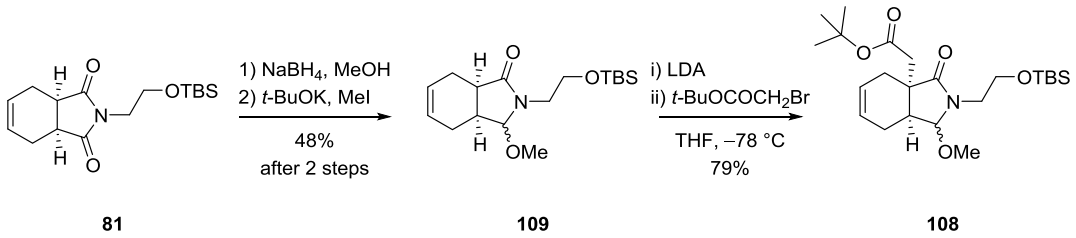
To avoid the regioselectivity problems, the synthesis of compound **108** bearing a methyl-protected hemiaminal moiety was considered. With this new strategy the formation of a lactam would avoid competition between the two carbonyls observed with the imide during the Grignard addition.

To access compound **107**, the Grignard addition could be performed on lactam **108**. Reduction of imide **81** and protection of the hemiaminal moiety to give **109** could be achieved prior to the introduction of the ester chain on **108** (Scheme 2.16).



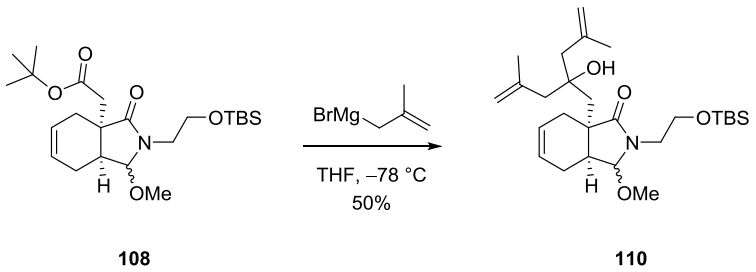
Scheme 2.16 Retrosynthetic analysis to access **107** from **81**

Imide **81** was reduced with sodium borohydride to give the hemiaminal moiety which was protected with potassium *tert*-butoxide and methyl iodide yielding compound **109** in 48% yield. LDA was employed to deprotonate at the α-position of the remaining carbonyl to install the *tert*-butyl ester (Scheme 2.17).



Scheme 2.17 Synthesis of compound **108** from imide **81**

When intermediate **108** was subjected to the Grignard conditions, no reaction on the desired carbonyl occurred and the product resulting from a double addition on the ester was isolated in 50% yield (Scheme 2.18). Replacing the imide group for a lactam had a profound effect on the reactivity of **108**. It is known that lactams are less reactive than imides as a result of the delocalisation of the nitrogen lone pair into the adjacent carbonyl, thus reducing the electrophilic nature of the carbonyl. Consequently, the bulky *tert*-butyl ester proved more reactive than the lactam to the Grignard addition.



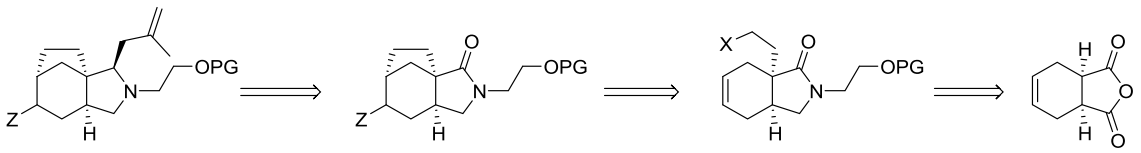
108 **110**

Scheme 2.18 Grignard reaction to **108** with 2-methylallylmagnesium bromide

The different ester side-chains which we planned to employ as precursors for the formation of the five-membered ring of the bicyclo[3.2.1]octane system were a source of many problems because of their competitive reactivity with the imide and lactam moieties. Therefore, it was decided to construct the five-membered ring prior to the addition of the methylallyl chain.

2.2. Formation of the bicyclo[3.2.1]octane system

To target the formation of the five-membered ring first, a revised retrosynthetic analysis was proposed (Scheme 2.19).

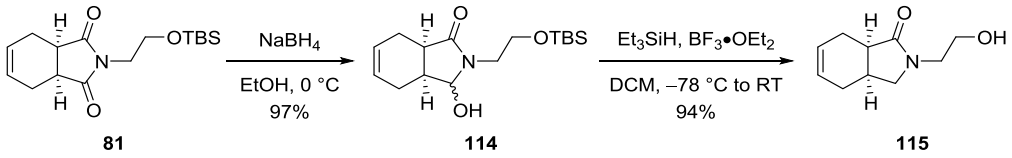


111 **112** **113** **45**

Scheme 2.19 Retrosynthetic analysis for the synthesis of **111** from **45**

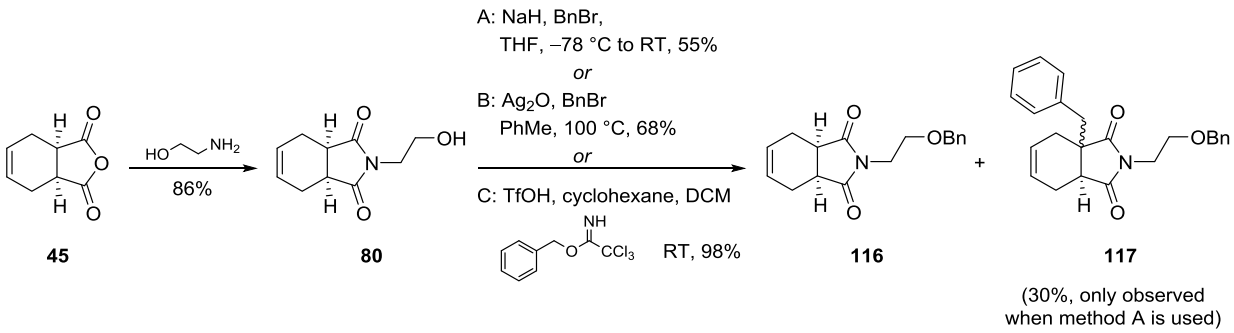
In this approach, the methylallyl group would be added in the final step, following the formation of the five-membered ring. Compound **113** with a functionalised alkyl chain could serve as an intermediate for a ring closure reaction to access **112**. The same tetrahydrophthalic anhydride could be used as starting material.

The first attempt to make intermediate **113** showed that the TBS-protecting group was cleaved when the *N*-acyliminium reduction conditions were applied to **114** (Scheme 2.20). It was found in the literature that silyl ethers can be cleaved under Lewis acid-mediated hydrolysis. In the example used by Verhoeven and co-workers, boron trifluoride diethyl etherate is utilised for this deprotection.[24]



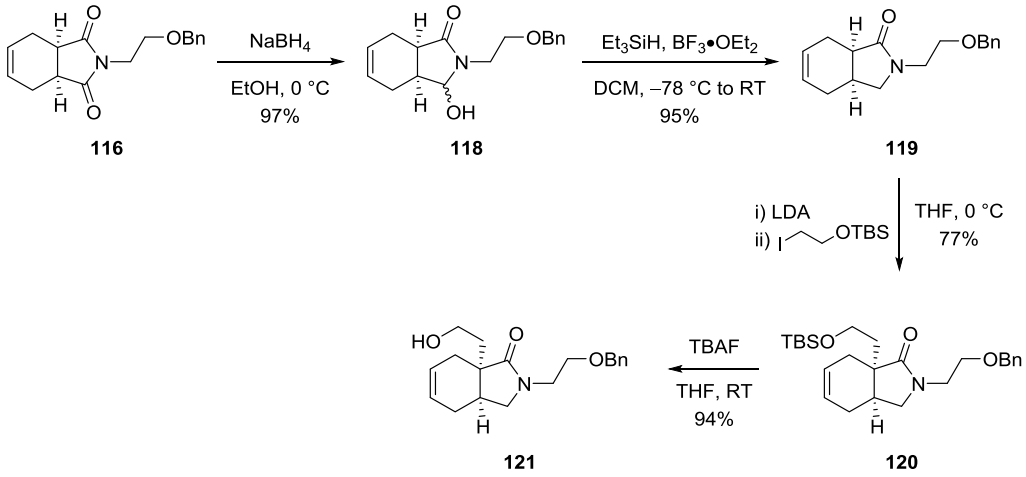
Scheme 2.20 TBS cleavage under *N*-acyliminium reduction

To avoid cleavage of the protecting group during the *N*-acyliminium reduction, the more robust benzyl protecting group was considered. Various conditions were tested to install it, first deprotonation of **80** with sodium hydride followed by addition of benzyl bromide was employed giving **116** in only 55% yield (Scheme 2.21, method A). The reason for the low yield of method A was the formation of side product **117** which could not be avoided despite optimisation of this method. The combination of silver(I) oxide and benzyl bromide provided **116** in a reasonable 68% yield (method B).[25] Finally, the use of benzyltrichloroacetimidate with a substoichiometric amount of triflic acid gave the highest yield for the preparation of **116** (method C).[26] However, the scale-up of method C revealed that purification was difficult and the acetimidate reagent was too expensive for a multi-gram scale use. Using method B, the high molecular weight of silver(I) oxide required a large amount of this reagent, this also prohibited large-scale reactions. With method A, multi-gram scale reactions were found to be easy to purify and the reagents used were fairly inexpensive.



Scheme 2.21 Protection of alcohol **80** with a benzyl group

In order to avoid the regioselectivity issue associated with the imide group, one carbonyl was reduced with sodium borohydride to give hemiaminal **118** in good yield (Scheme 2.22). This was further reduced under *N*-acyliminium conditions to form amide **119**.



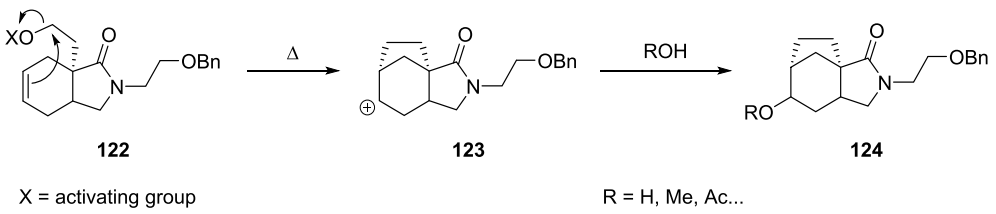
Scheme 2.22 Synthesis of compound **121**

Another notable change was the replacement of the *tert*-butyl ester for a TBS-protected alkyl alcohol as a precursor for the five-membered ring. Attempts to reduce the *tert*-butyl ester to afford the ethanol chain contained in **121** did not give satisfactory results. Therefore, deprotonation with LDA followed by addition of TBS-protected iodoethanol gave compound **120** in 77% yield. Treatment of **120** with TBAF released the free alcohol in high yield.

With compound **121** in hand, the formation of the five-membered ring was investigated. The presence of an alcohol at this stage is ideal in order to test a wide range of cyclisation conditions as alcohols can easily be transformed into different functional groups such as aldehydes, halogens and sulfonates. Moreover, the double bond offered the potential for epoxidations, nucleophilic additions and radical cyclisation.

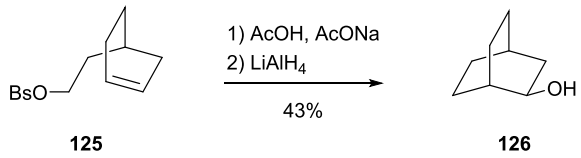
2.2.1. Five-membered ring formation with a solvolytic ring closure reaction

This type of ionic cyclisation proceeds *via* a thermally-promoted nucleophilic attack of a double bond onto an activated alcohol as proposed in Scheme 2.23. The solvent of the reaction can then trap the carbocation in **123**, formed after the cyclisation step, to introduce a new functional group.



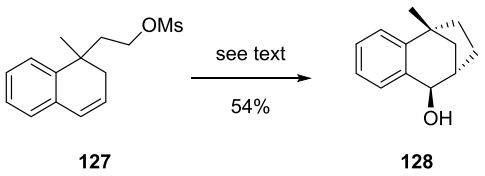
Scheme 2.23 Principle of the solvolytic ring closure reaction

The solvolytic ring closure reaction presents the advantage of being easily tuneable. A wide range of activating groups can be used to accelerate the rate of the first step and the many solvents tolerated give access to a variety of functional groups. The first example of this cyclisation was reported in 1961 by Winstein and Carter.[27] The authors demonstrated that the solvolysis of **125** in a 0.02 M acetic acid solution of sodium acetate gave alcohol **126** after reduction with lithium aluminium hydride (Scheme 2.24).



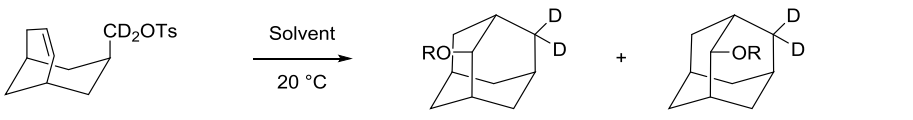
Scheme 2.24 Acetolysis of **125** by Winstein and Carter

Another example was published a year after by Herz and Caple.[28] Their attempt to purify mesylate **127** with wet benzene and petroleum ether over alumina formed cyclised compound **128**, possessing a bicyclo[3.2.1]octane moiety, in 54% yield (Scheme 2.25).



Scheme 2.25 Example of solvolytic ring closure reaction by Herz and Caple

Later, Nordlander and co-workers published the π-assisted solvolysis of *endo*-bicyclo[3.3.1]non-6-ene-3-methyl tosylate.[29] The success of this reaction, reported in several solvents, opened the scope of functional groups incorporated after the cyclisation step (Scheme 2.26).

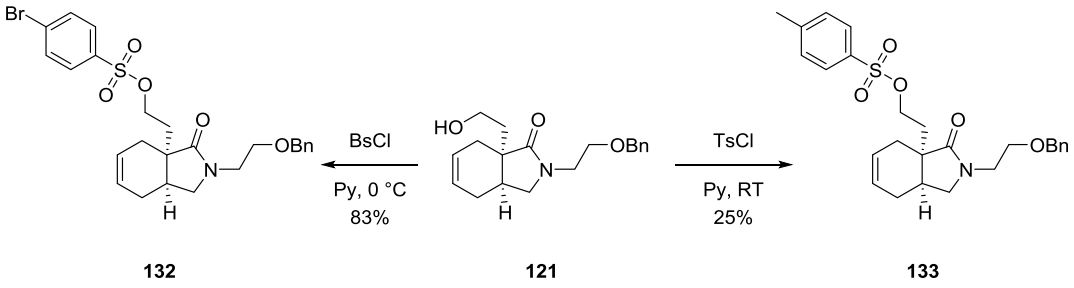


129	solvent	R	130	131	% yield
	MeOH	Me	98	2	93
	80% aq acetone	H	98	2	93
	AcOH	Ac	96	4	88
	CF_3CH_2OH	CF_3CH_2	86	14	71
	$CHCl_3$	Ts	54	46	100

Scheme 2.26 Solvent screen for solvolysis reaction

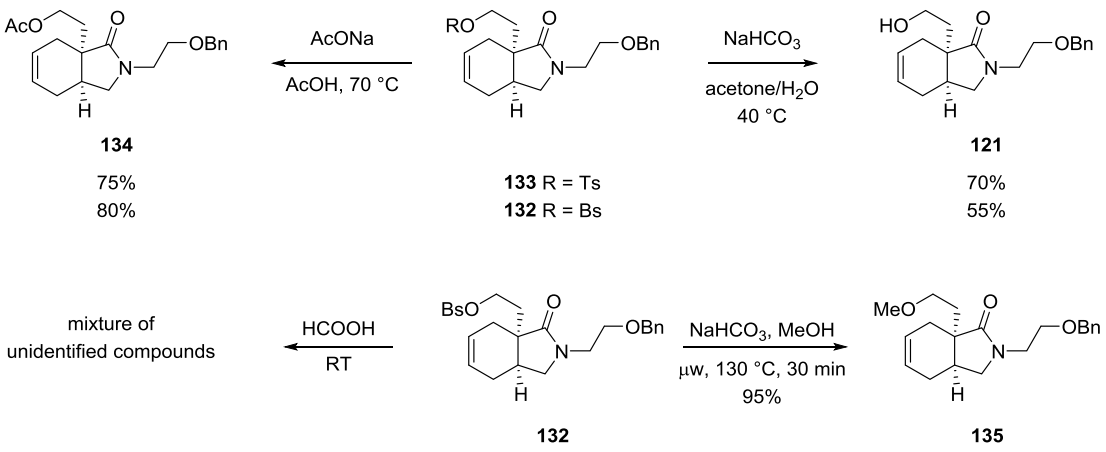
To apply these conditions to our system, two new compounds containing either a tosyl or a brosyl activating group were synthesised from alcohol **121** in 25% and 83% yield respectively

(Scheme 2.27). These two activating groups are commonly found in the literature in order to achieve this type of transformation.[27] Sufficient amounts of tosylate **133** were synthesised in order to test several solvolytic ring closure conditions and its preparation was not optimised.



Scheme 2.27 Formation of tosylate **133** and brosylate **132** from alcohol **121**

Tosylate **133** and brosylate **132** were subjected to classic solvolytic conditions, sodium acetate in acetic acid and sodium hydrogen carbonate in wet acetone, without success (Scheme 2.28).[30] In both reactions the replacement of the activating group by the solvent was observed instead. Reaction of brosylate **132** under microwave conditions with sodium bicarbonate in methanol resulted in the formation of **135** in high yield. The reaction of **132** in formic acid furnished a mixture of unidentified products.[27] Further literature conditions such as 2,6-lutidine in methanol or K_2CO_3 in aqueous THF were tested without formation of the desired five-membered ring.[29]



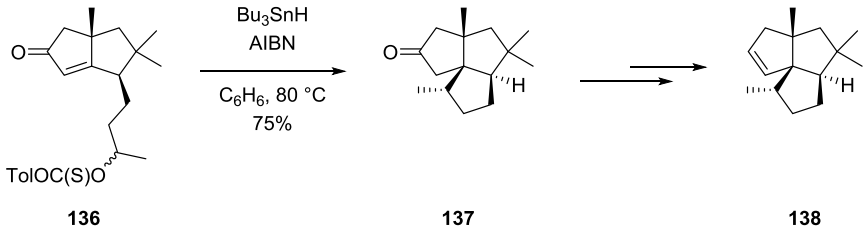
Scheme 2.28 Solvolytic ring closure of tosylate **133** and brosylate **132**

Disappointingly, none of the literature conditions applied to **132** or **133** showed evidence for the formation of the bicyclo[3.2.1]octane system. All the results indicated a substitution of the activating group by a molecule of solvent before the cyclisation step. It is clear that the bicyclic nature of brosylate **132** and tosylate **133** does not offer the same flexibility compared to the above literature examples. As a result, the competition between the intramolecular process (cyclisation) and the intermolecular process (solvent displacement) was found to favour the latter route.

With no possibility of adding more flexibility to the structure of **132** (or **133**), and no obvious options to stop the solvent displacement occurring first, alternative methods to form the five-membered ring were investigated.

2.2.2. Five-membered ring formation with a radical cyclisation

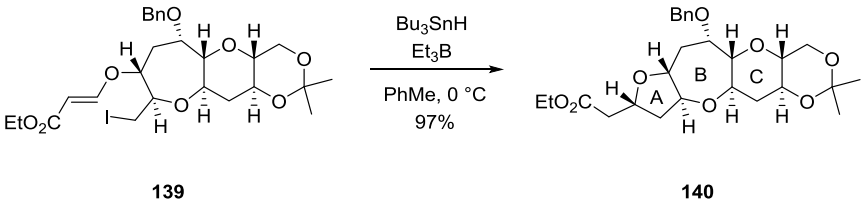
Radical cyclisation is a well-known tool to form rings of various size in total synthesis.[31] Five-membered rings are the target of choice and their formation, favoured compared to other ring sizes, has been extensively described in the literature. It was used by Nagarajan and co-workers to form the last five-membered ring of silphinene **138** with a tin hydride-promoted radical cyclisation (Scheme 2.29).[32]



Scheme 2.29 Radical cyclisation of **136** by Nagarajan and co-workers

The synthesis of the ABC ring fragment of gymnocin published by Mori and co-workers also used a radical cyclisation to form ring A.[33] The five-membered ring in **140** was closed

stereoselectively with tributyltin hydride and triethylborane used as a radical initiator (Scheme 2.30).

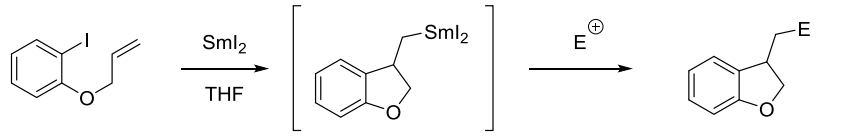


139 **140**

Scheme 2.30 Formation of ring A in **140** by Mori and co-workers

However, the conditions used by Nagarajan and Mori for their cyclisation could not be employed on our system to form the five-membered ring. The hydrogen atom transferred by the tributyltin hydride after the cyclisation step is unsuitable and would prevent the installation of a functional group required to carry on the synthesis.

Radical cyclisation promoted by metals other than tin offer better control during the termination step to add a functional group in place of a hydrogen. In 2003, Curran and co-workers published a SmI_2 radical cyclisation of *O*-allyl-2-iodophenol **141**. Various electrophiles were added after the cyclisation step to trap samarium intermediate **142** (Scheme 2.31).[34]



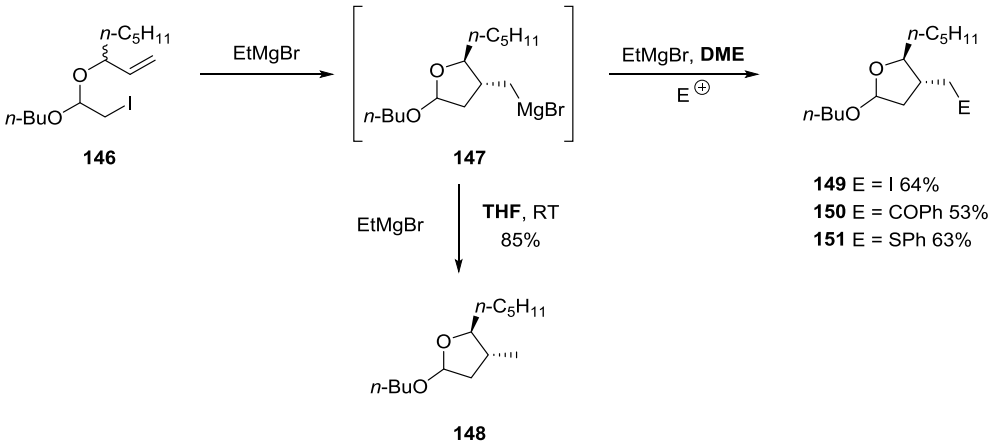
141 **142**

143 E = I 69%
144 E = SPh 65%
145 E = SePh 72%

Scheme 2.31 SmI_2 radical cyclisation of **141** by Curran

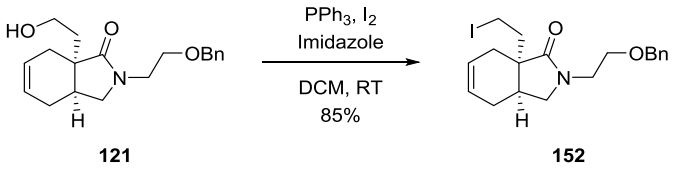
In the same manner, an EtMgBr-mediated radical cyclisation was published by Oshima and co-workers in 2000.[35] Treatment of allyl-*β*-iodoacetals with EtMgBr in THF gave the desired cyclised compound **148** in good yield. Interestingly, the use of DME (dimethoxyethane) as a

solvent allowed intermediate **147** to react with different electrophiles (Scheme 2.32).[35] The authors postulated that in THF, the Grignard intermediate **147** leads to the formation of **148** whereas in DME, various electrophiles can react with **147** to form new functionalised products in modest yields.



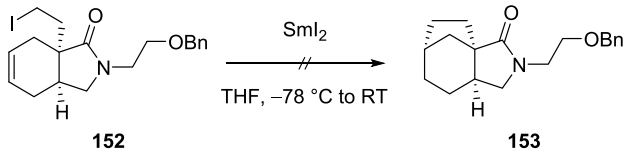
Scheme 2.32 EtMgBr radical cyclisation of **146** in THF and DME

To test the samarium and EtMgBr-mediated radical cyclisation, the alcohol of compound **121** was converted into an iodide using an Appel reaction in 85% yield (Scheme 2.33).



Scheme 2.33 Formation of Iodide **152** from alcohol **121**

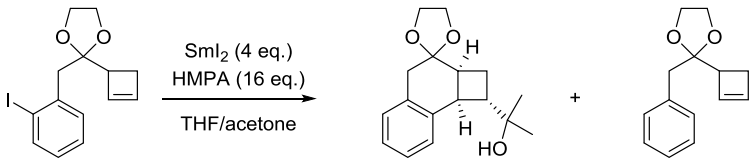
A solution of SmI_2 was prepared with samarium metal and 1,2-diiodoethane following a procedure published by Proctor.[36] Firstly, reductive conditions with no attempt at functionalisation were carried out. Disappointingly, no conversion of the starting material was recorded when up to three equivalents of SmI_2 were added to **152** (Scheme 2.34).



152 **153**

Scheme 2.34 Attempted SmI_2 radical cyclisation on **152**

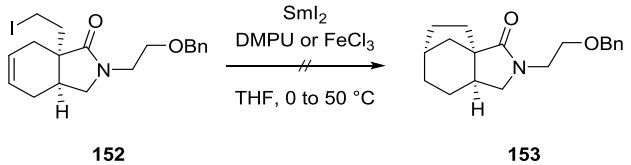
The reactivity of SmI_2 can be modified with three different types of additive: a Lewis base, an inorganic salt (to increase the reduction potential) or a proton source (to quench intermediate anions).[37] The use of a Lewis base was demonstrated by Curran and co-workers during the development of a radical/polar crossover reaction (Scheme 2.35).[38] Treatment of aryl iodide **154** with HMPA and a solution of SmI_2 in a mixture of THF and acetone successfully formed compound **155** in 60% yield along with reduced compound **156**.



154 **155** 60% **156** 19%

Scheme 2.35 radical/polar crossover reaction on **154** with SmI_2 and HMPA by Curran and co-workers

The efficiency of the Lewis base additive was tested on compound **152** and the reaction was performed with a large excess of DMPU as an alternative to the highly toxic HMPA (Scheme 2.36). The formation of **153** was not observed and the starting material was recovered. The same outcome was observed when an inorganic salt such as $FeCl_3$ was used as an additive.[39]

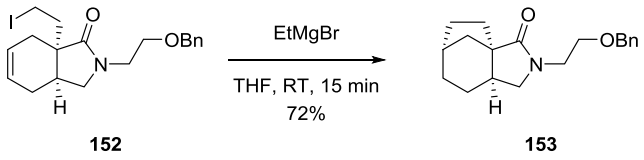


152 **153**

Scheme 2.36 Attempted SmI_2 radical cyclisation with additives on **152**

The presence of starting material at the end of these reactions was intriguing as the carbon-iodine bond is known to be unstable to radical species. No further investigations of this reaction were undertaken as success for the formation of the five-membered ring was achieved with another method.

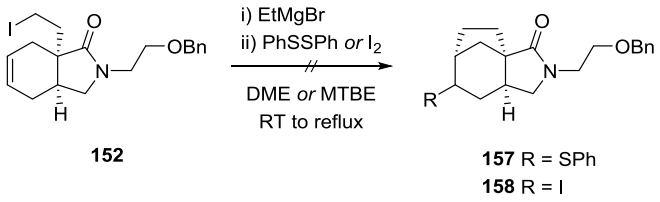
The EtMgBr-mediated radical cyclisation was also investigated using compound **152**. The reductive conditions described by Oshima and co-workers using THF as the solvent were first attempted. To our delight, addition of three equivalents of EtMgBr at room temperature to **152** furnished cyclised compound **153** in good yield (Scheme 2.37). The absence of the two resonances due to the ethylenic protons in the ^{1}H NMR spectrum and the disappearance of the resonances associated with the carbon of the C-I bond in the ^{13}C NMR spectrum confirmed the formation of the new ring.



152 **153**

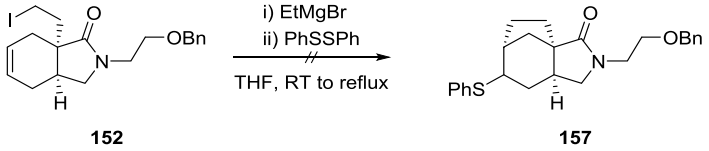
Scheme 2.37 EtMgBr mediated radical cyclisation on **152** in THF

With this first positive result, conditions to add a functional group after the cyclisation step were examined. Following Oshima's results, the reaction was carried out in DME and a solution of EtMgBr in DME was prepared. After mixing **152** with EtMgBr for 15 min, electrophiles such as PhSSPh and I_2 were added. In both cases the cyclisation did not take place and the starting material was recovered (Scheme 2.38).



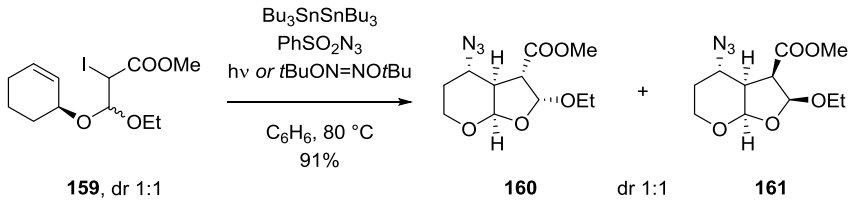
Scheme 2.38 Attempted EtMgBr radical cyclisation on **152** with electrophiles

The starting material could not be fully dissolved in DME, even with sonication, and the Grignard reagent was only partially soluble in this solvent. A different solvent (MTBE) was employed in an attempt to improve the solubility of **152** but without success. The presence of an insoluble compound was observed during the reaction which is likely to be magnesium bromide. Indeed, in DME, the Schlenk equilibrium is shifted and the EtMgBr species that exists in THF is no longer predominant.[35] The solubility issue, not mentioned in the publication, can explain the failure of the cyclisation.[35] An attempt to add PhSSPh when the reaction was conducted in THF did not yield desired compound **157** and the starting material was recovered (Scheme 2.39).



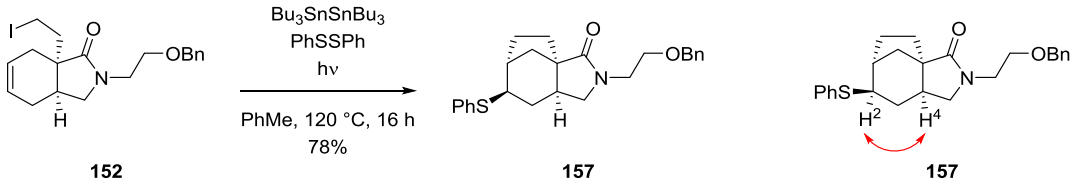
Scheme 2.39 Attempted formation of **157** in THF

Finally, an efficient method to form the five-membered ring and install a functional group simultaneously was found through the use of hexabutylditin. Unlike tributyltin hydride, this reagent provides non-reducing conditions allowing the radical formed after the cyclisation step to form a new carbon-carbon bond or a carbon-heteroatom bond. This property was used by Renaud for the formation of carbon-nitrogen bonds. A one-pot procedure with hexabutylditin and benzenesulfonyl azide was developed to cyclise **159** in excellent yield (Scheme 2.40).[40]



Scheme 2.40 Formation of **160** and **161** with hexabutylditin

Inspired by Renaud's methodology, a radical cyclisation reaction using hexabutylditin and diphenyl disulfide was performed on **152**. The reaction was initiated by irradiation with a sun lamp and cyclised compound **157** was obtained in 78% yield (Scheme 2.41). This reaction is the first example to date of the formation of a carbon-sulfur bond with a hexabutylditin-mediated radical cyclisation.



Scheme 2.41 Formation of **157** with hexabutylditin and phenyl disulfide

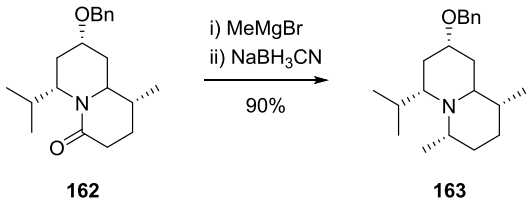
Cyclised compound **157** was obtained as a single diastereoisomer and NOE experiments showed a correlation between H-2 and H-4, thus confirming the orientation of the phenyl sulfide group.

With the five-membered ring successfully formed, the stage was now set to install the methylallyl chain as a precursor of the oxazepane ring.

2.3. Installation of an oxazepane ring precursor

2.3.1. Grignard additions on amide 157

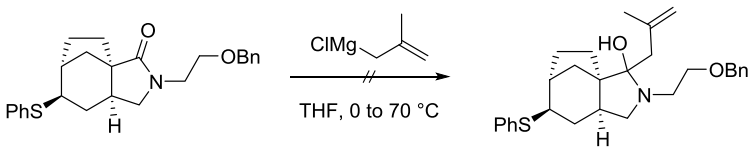
With compound **157** in hand, the problems previously reported regarding the addition of a methylallyl chain should be avoided (see Section 2.1). The absence of an ester group should avoid chemoselectivity issues during the Grignard addition, and the replacement of the imide for an amide will suppress the undesired regioselectivity observed in Scheme 2.12. In the total synthesis of the putative structure of the lupin alkaloids by Comins and co-workers, a Grignard reagent was added to amide **162** before reduction with sodium cyanoborohydride in acidic methanol to give **163** in excellent yield (Scheme 2.42).[41]



162 **163**

Scheme 2.42 MeMgBr addition on amide **162** by Comins and co-workers

The reaction of amide **157** with 2-methylallylmagnesium chloride was attempted but did not yield **164** and only the starting material was recovered. Another attempt with five equivalents of Grignard reagent at reflux also failed to furnish **164** (Scheme 2.43).

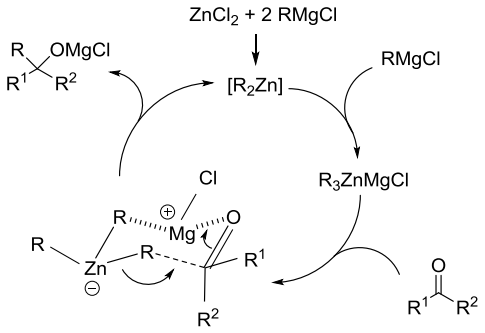


157 **164**

Scheme 2.43 Attempted 2-methylallylmagnesium chloride addition on **157**

The reactivity of Grignard reagents can be enhanced by the addition of inorganic salts. In 2006 Ishihara and co-workers showed that the presence of 10 mol% of $ZnCl_2$ increased the yield of

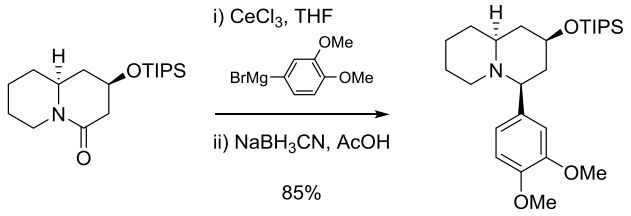
the reaction during the isopropylation of ketones.[42] According to the authors, zinc chloride reacts first with the Grignard reagent to form an active Zn(II) ate complex ($R_3ZnMgCl$) and this complex, having increased nucleophilicity compared to the original Grignard reagent, can then react with the ketone (Scheme 2.44).



Scheme 2.44 Proposed catalytic cycle for the addition of RMgCl with $ZnCl_2$ by Ishihara and co-workers

Another method to enhance the reactivity of Grignard reagents towards carbonyls and amides in particular is to use cerium(III) chloride. It was demonstrated by Imamoto and co-workers that mixing cerium(III) chloride with an amide before adding the Grignard reagent improved the yield of the reaction.[43] The strong oxophilicity of cerium(III) chloride makes it capable of activating a carbonyl group by coordination. Moreover, the *in situ* formation of the organocerium reagent also shows increased nucleophilicity compare to corresponding Grignard reagent.

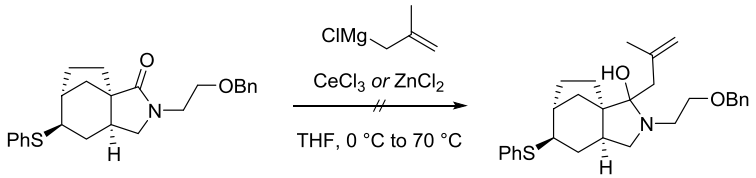
The formal synthesis of (−)-lasubine II published by Aubé in 2003 used cerium(III) chloride to improve the yield of the Grignard addition to **165** and to prevent competing elimination of the OTIPS group (Scheme 2.45).[44]



165 **166**

Scheme 2.45 Use of $CeCl_3$ and Grignard reagent on **165** by Aubé

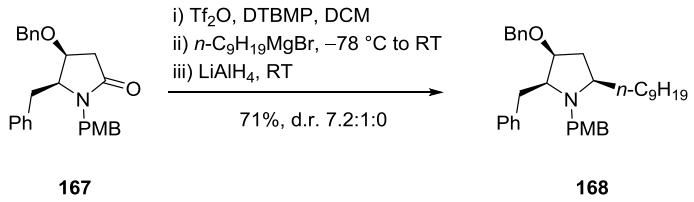
Applied to our system, amide **157** was mixed with cerium(III) chloride prior to the addition of 2-methylallylmagnesium chloride. The reaction failed to produce **164**, either at 0 °C or reflux, and the starting material was recovered. The same result was observed when either 10 mol% or one equivalent of zinc chloride was used (Scheme 2.46).



157 **164**

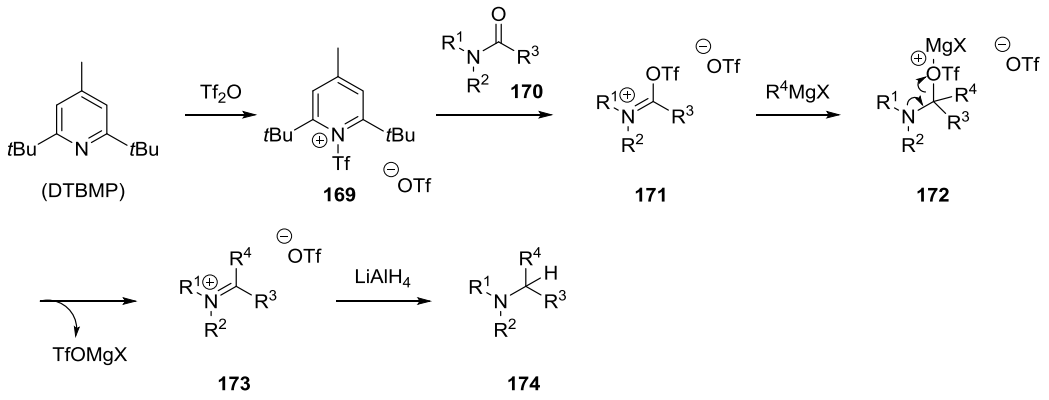
Scheme 2.46 Attempted Grignard addition on **157** with inorganic salts

Convinced that compound **157** was a suitable intermediate to install the methylallyl chain, the search for another method to increase the reactivity of the amide group was undertaken. In 2010, a versatile one-pot reductive alkylation of lactams was described by Huang and co-workers.[45] Lactam **167** was activated with triflic anhydride before addition of the Grignard reagent and reduction with lithium aluminium hydride, to afford **168** in good yield (Scheme 2.47).



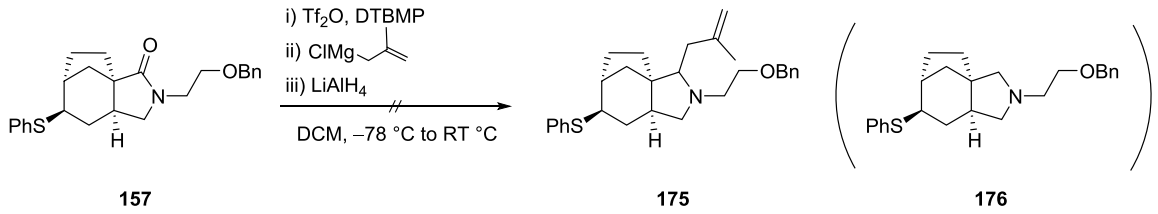
Scheme 2.47 One-pot reductive alkylation of **167** by Huang and co-workers

The authors proposed the mechanism below to explain the outcome of the reaction (Scheme 2.48).[46] Firstly, the reaction between DTBMP and triflic anhydride generates pyridinium intermediate **169**. This reacts with amide **170** to form the electrophilic iminium triflate **171**. Addition of the Grignard reagent gives hemiaminal **172** and, after elimination of the triflate group, the iminium **173** is reduced to deliver desired compound **174**.



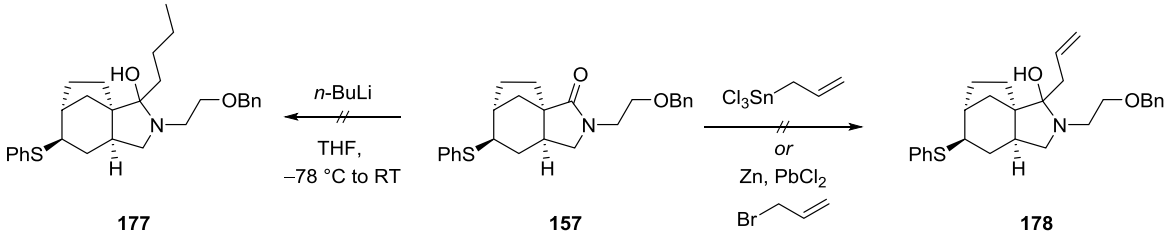
Scheme 2.48 Proposed mechanism by Huang and co-workers for the one-pot reductive alkylation of lactams

Despite many attempts to reproduce the work of Huang, the formation of desired compound **175** was never observed (Scheme 2.49). Furthermore, the use of increased equivalents of triflic anhydride and Grignard reagent did not help to form **175**. Instead, the formation of tertiary amine **176** was observed during the reaction suggesting that the amide is reactive towards reducing agents.



Scheme 2.49 Attempted formation of **175** with Tf_2O activation

In addition to Grignard reagents, other organometallic species were tested with amide **157**. The addition of several equivalents of *n*-BuLi to **157** did not yield desired compound **177** (Scheme 2.50). Treatment of amide **157** with allyltrichlorotin, prepared following a procedure published by Ferreira and co-workers, failed to convert **157** into **178**.[47] Finally, the Barbier conditions described in Section 2.1.1 were applied to **157**, but only starting material was recovered.



Scheme 2.50 Attempted nucleophilic additions on amide **157**

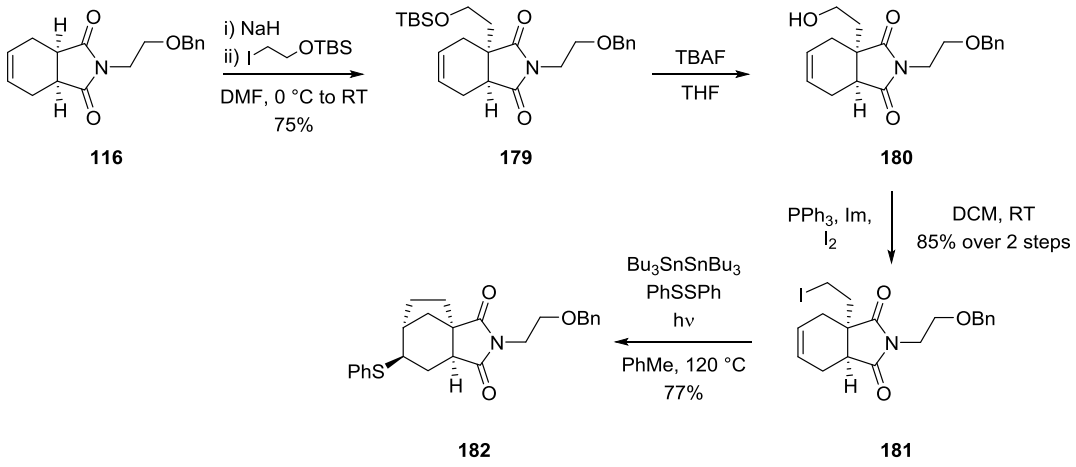
The strategy to use amide **157** to install a precursor for the oxazepane ring failed to produce the desired compound **164**. The amide group in **157** was unreactive towards the Grignard reagent and our attempts to increase the reactivity of the system failed. The use of different metals was also examined without success. The modest reactivity of amides towards nucleophilic additions combined with the steric congestion around the carbonyl is proposed to explain these results.

2.3.2. Addition of an allyl group on imide 182

To address the lack of reactivity of the amide, the use of an imide group was re-investigated. This strategy would require us to solve the regioselectivity issue observed during the Grignard

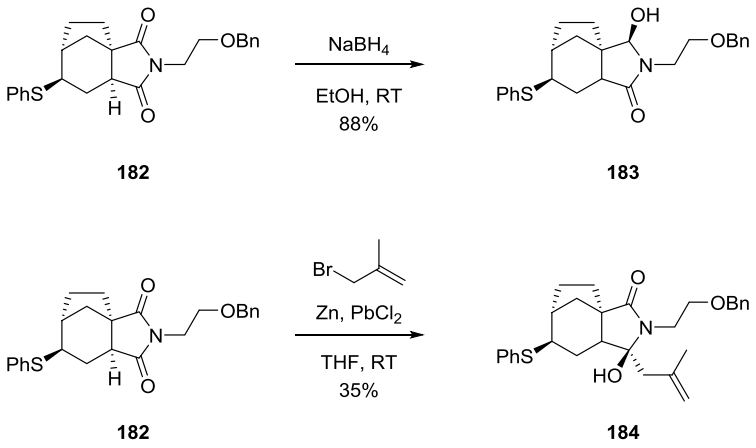
addition to **97** (see Scheme 2.12). However, the imide group has an increased reactivity towards nucleophiles and reducing agents compare to an amide moiety.

The synthesis of intermediate **182** started with a sodium hydride deprotonation on **116** followed by addition of TBS-protected iodoethanol to give **179**. Following the cleavage of the TBS group with TBAF, an Appel reaction was used to introduce an iodine in 85% yield. The same conditions previously developed were used to form the five-membered ring present in **182** in similar yield (Scheme 2.51).



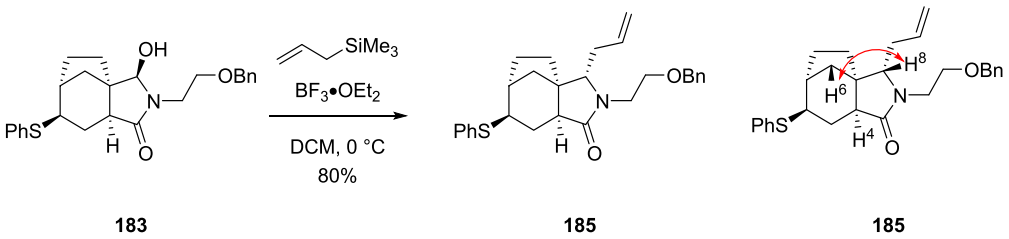
Scheme 2.51 Synthesis of imide **182** form **116**

With compound **182** in hand, the Speckamp model for sodium borohydride reduction was once again tested. Imide **182** was reduced with sodium borohydride in good yield and only reduction of the more hindered carbonyl was observed as predicted (Scheme 2.52). The behaviour of imide **182** under nucleophilic additions was examined using a Barbier allylation. Imide **182** was treated with a mixture of 3-bromo-2-methylpropene, zinc and lead(II) chloride and an addition was shown to have taken place. Unfortunately, HMBC experiments revealed the methylallyl chain was added on the less hindered carbonyl in 35% yield.



Scheme 2.52 Reduction and Barbier allylation on imide **182**

It was hoped that the five-membered ring would be less bulky than the *tert*-butyl ester side chain and would thus allow addition to the imide at the desired carbonyl during nucleophilic additions. Nevertheless, the excellent regiocontrol and yield observed during the formation of **183** allowed the possibility to add an allyl chain *via N*-acyliminium chemistry.[48] Hemiaminal **183** was mixed with boron trifluoride diethyl etherate and allyltrimethylsilane giving **185** in 80% yield (Scheme 2.53).[49] NOE analysis revealed that the allyl chain was in a *syn*-configuration with respect to the two-carbon bridge, with the lack of correlation between H-4 and H-8 and the correlation of H-8 with H-6 being key to determine the spatial orientation of the allyl chain.

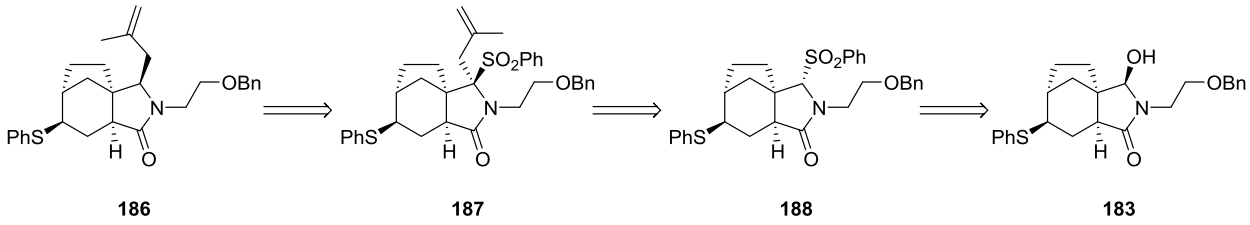


Scheme 2.53 Formation of allyl **185** and NOE correlation

This result shows an attack of the allyltrimethylsilane from the back face of the molecule (as drawn) and confirmed the hypothesis that the shape of intermediate **183** could direct the attack

of nucleophiles. Indeed, the concave shape of the molecule blocks the access of any reagent from the front face leaving only the back face available. This observation established that the order of addition of reagents is crucial to install an oxazepane ring in the desired orientation. With all the reagents approaching from the back face, the allyl chain needs to be added first. Following this, a hydride source should then be added to reverse the orientation of the allyl chain.

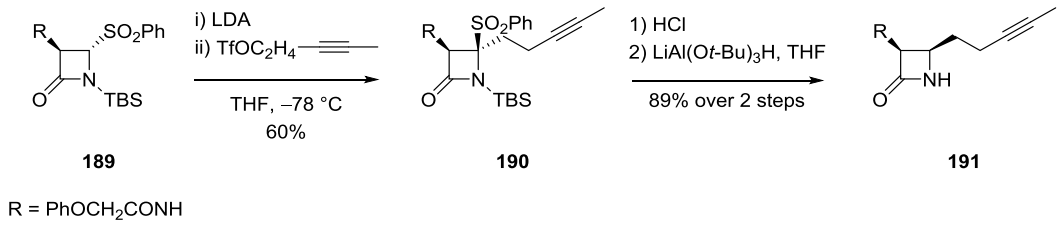
To take advantage of these results, the route below was considered (Scheme 2.54). The desired configuration of the methylallyl chain could be obtained after reductive cleavage of the sulfone in **187**. Installation of the sulfone from **183** could allow the introduction of the methylallyl chain from the back face.



186 **187** **188** **183**

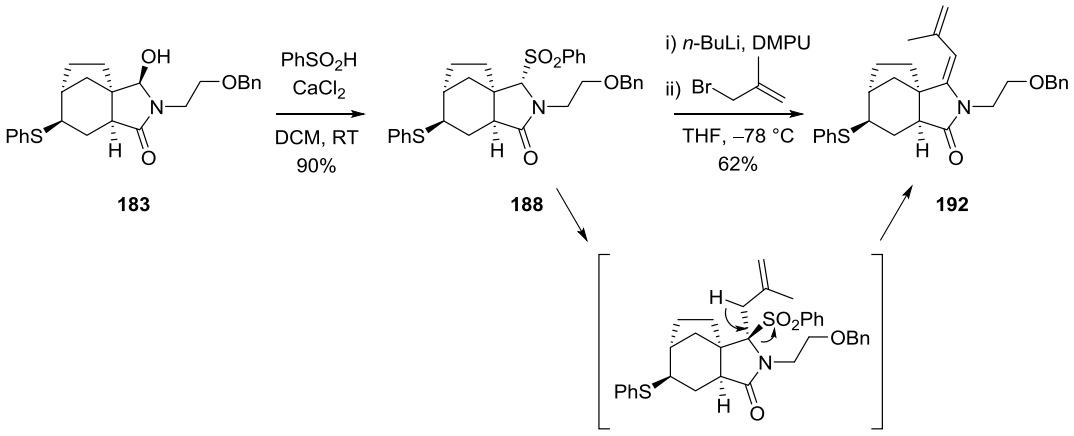
Scheme 2.54 Strategy to access the methylallyl chain in the desired configuration

The strategy of reversing the orientation of a stereocentre with an α-amido sulfone intermediate has been previously employed by Overman and co-workers for the construction of carbacephem antibiotics.[50,51] The 3-pentynyl group was installed by treatment of sulfone **189** with LDA and 3-pentynyl triflate. Then, the TBS protecting group was cleaved under acidic conditions. Removal of the sulfone with lithium tri-*tert*-butoxyaluminium hydride gave the *cis*-disubstituted β-lactam **191** in good yield (Scheme 2.55).



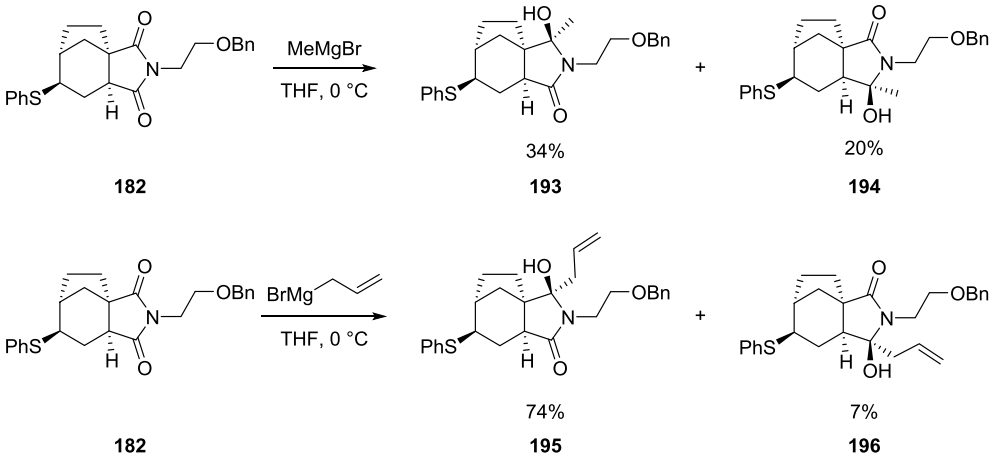
Scheme 2.55 Overman's strategy to access **191** from **189**

In order to test Overman's strategy, a sulfone group was installed by treatment of hemiaminal **183** with benzenesulfinic acid and calcium chloride. The acidic proton at the *α*-position of the sulfone was removed with *n*-BuLi and 3-bromo-2-methylpropene was added, however, the major product was not the expected sulfone, but was identified as diene **192** (Scheme 2.56). A plausible explanation for formation of **192** could be the rapid elimination of the sulfone group after installation of the methylallyl group to create a more stable conjugated system.



Scheme 2.56 Formation of sulfone **188** and attempt to add a methylallyl chain

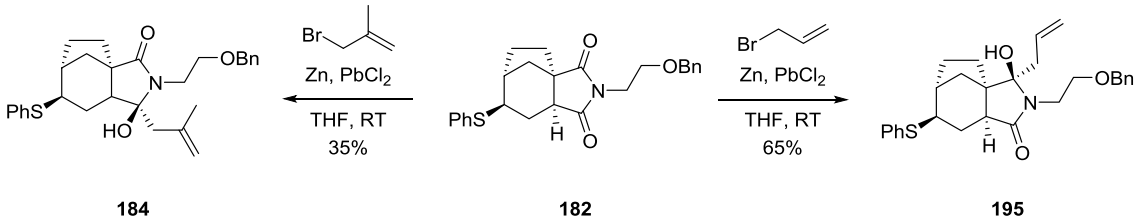
In parallel with this work some experiments to understand the regioselectivity reported during nucleophilic additions onto imide **182** were conducted (Scheme 2.57).



Scheme 2.57 Grignard additions on imide **182**

When a small Grignard reagent such as methylmagnesium bromide was added to imide **182**, the main product resulted in addition on the more hindered carbonyl. Increasing the size of the Grignard reagent to allylmagnesium bromide gave the same result, and compound **195** was isolated in 74% along with 7% of the other regioisomer.

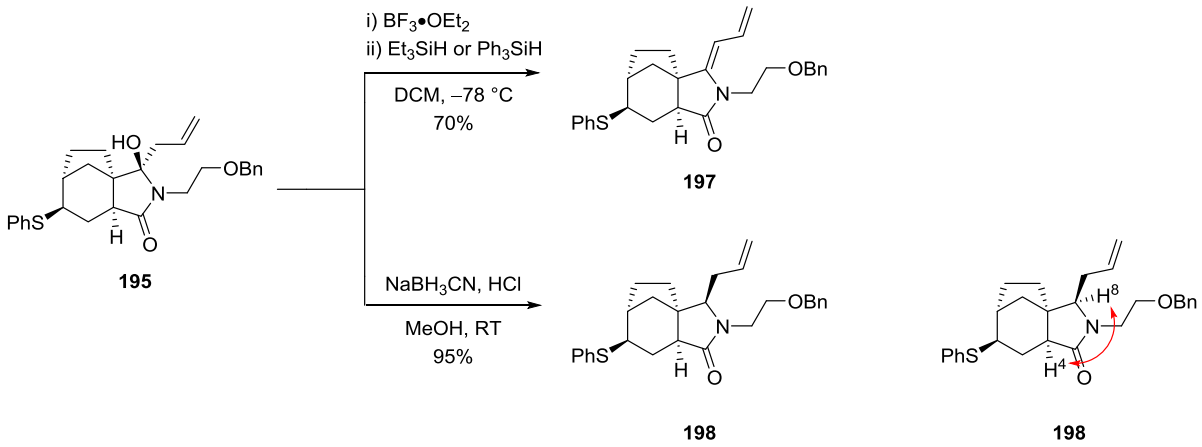
Next, a Barbier reaction with allyl bromide was performed on **182** (Scheme 2.58). The same regioselectivity as with allylmagnesium bromide was observed. This result confirmed that the only factor responsible for the regioselectivity during nucleophilic additions onto **182** is the size of the allyl group and not the nature of the organometallic reagent.



Scheme 2.58 Barbier allylation with allyl bromide on **182**

Pleased with the good yield obtained for the formation of **195**, conditions to reduce the hemiaminal moiety were tested (Scheme 2.59). Classic *N*-acyliminium conditions to remove the hydroxyl group involving boron trifluoride diethyl etherate as the Lewis acid and

triethylsilane as the hydride source were tried.[52] Compound **197** was isolated as a single isomer (geometry undetermined) with a conjugated system similar to the one observed in Scheme 2.56. To circumvent this issue, **195** was treated with sodium cyanoborohydride in the presence of HCl giving allyl lactam **198** in excellent yield.



Scheme 2.59 Reduction of hemiaminal **195**

Comparison of the ^{1}H and ^{13}C NMR spectra of **185** with **198** showed clear differences between them, indicating a change in the allyl area (Figure 2.3). The NOE experiment realised on **198** confirmed the orientation of the allyl group and so the hypothesis regarding the order of addition to get the oxazepane ring precursor in the desired configuration (Scheme 2.59).

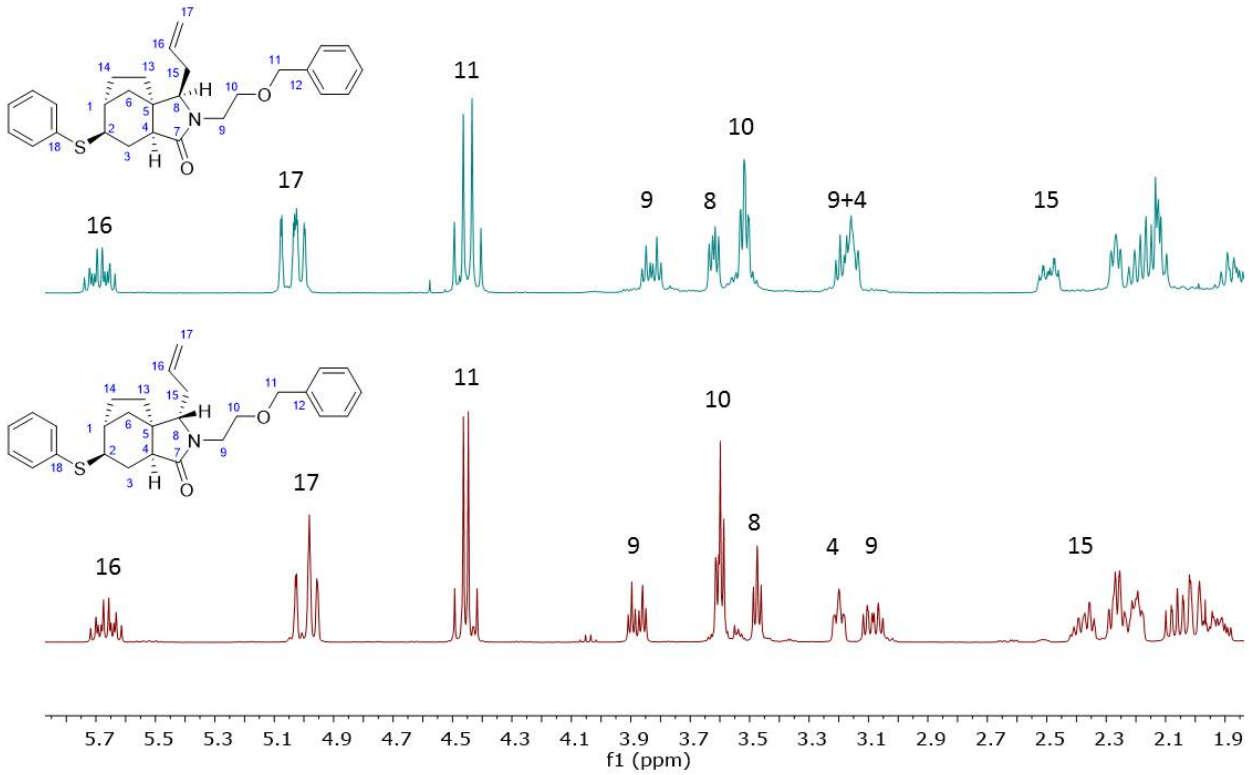


Figure 2.3 ^{1}H NMR spectra of **185** and **198**

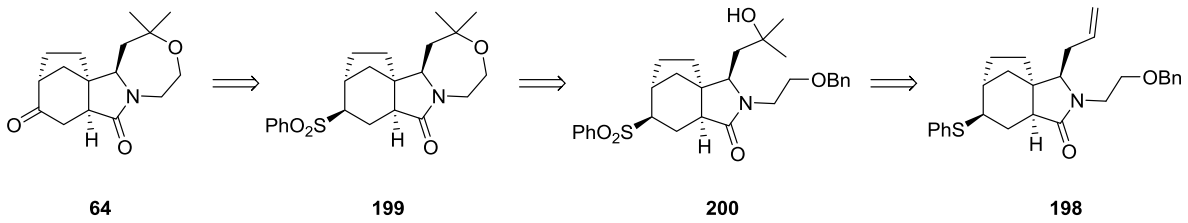
The formation of the five-membered ring combined with the introduction of an oxazepane ring precursor in the desired orientation were important successes toward the total synthesis of concavine. The following chapter will focus on the formation of the oxazepane ring to complete the core structure as well as the introduction of the *exo*-double bond and the prenyl chain.

Chapter 3 Assembly of the core structure and end game

A key step in the total synthesis of concavine was the late-stage replacement of the phenyl sulfide group, inserted after the radical cyclisation, by a ketone. This transformation is mandatory for the final stages of the synthesis as it would enable the introduction of the prenyl chain and give a quick access to the *exo*-double bond.

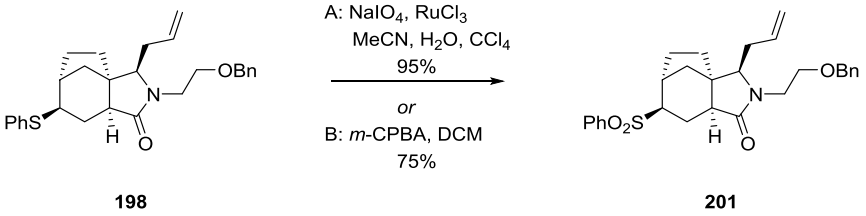
3.1. Formation of the core structure with a sulfone functional group

An oxidation of the phenyl sulfide into a sulfone was chosen as the first step to access ketone **64** and the retrosynthetic analysis below was envisaged (Scheme 3.1). The oxazepane ring in **199** could be assembled by acidic treatment after deprotection of **200**. The alcohol in **200** could result from an organometallic addition to a ketone obtained by oxidation of the alkene in **198**.



Scheme 3.1 Retrosynthetic analysis to **64**

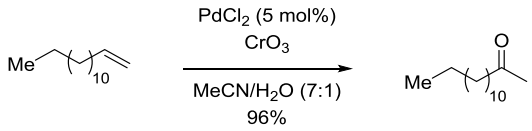
To install the sulfone, both ruthenium tetroxide and *m*-CPBA oxidations were tested.[53] Both of them gave good yields but the *m*-CPBA oxidation was found to be easier to set up and more reliable to scale-up (Scheme 3.2).



198 201

Scheme 3.2 Oxidation of the sulfur in **198** into a sulfone

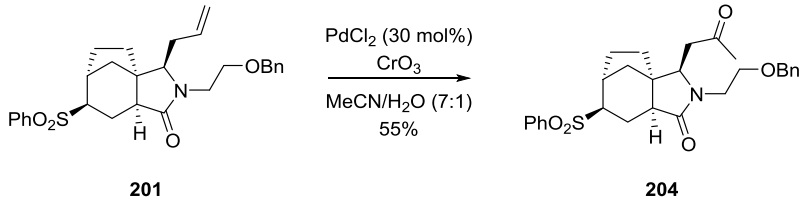
The next step to synthesise intermediate **64** was to convert the double bond into a ketone. The Wacker oxidation is the method of choice for this transformation and has been used in numerous total syntheses to form ketones from terminal olefins.[54,55] Many conditions have been published for this transformation, originally performed using palladium(II) chloride with copper(II) chloride and oxygen. Recent works describe a more operationally simple procedure.[56,57] In 2014, Bethi and Fernandes found that chromium trioxide with palladium(II) chloride in a mixture of acetonitrile and water were efficient conditions for the oxidation of 1-tetradecene (Scheme 3.3).[58]



202 203

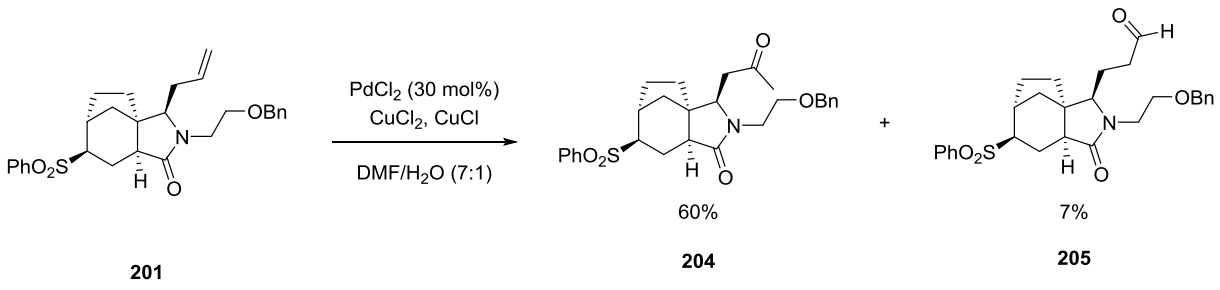
Scheme 3.3 Oxidation of 1-tetradecene

Applying these conditions to **201** gave the desired ketone in a modest 55% yield, with no starting material recovered (Scheme 3.4). With a catalyst loading of 5 mol%, the conversion was found to be very slow after 24 h and more equivalents were used to increase the rate of the reaction.



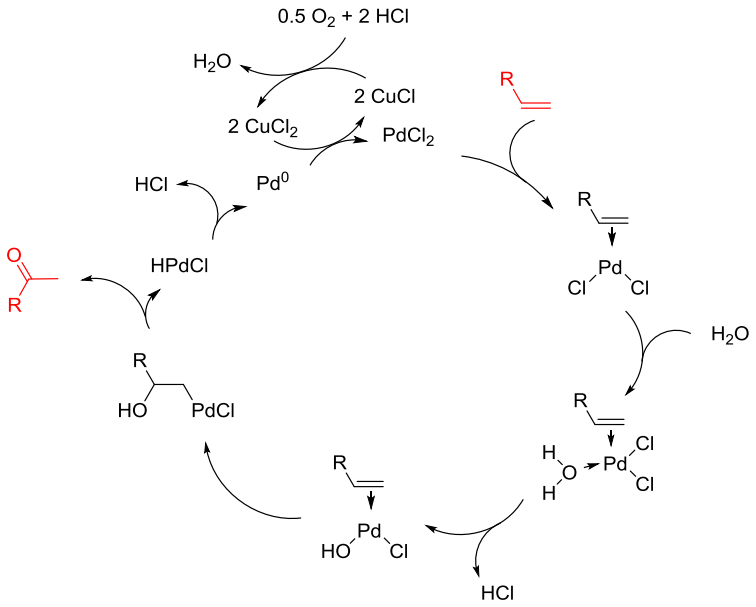
Scheme 3.4 Wacker oxidation with CrO_3 on **201**

The original conditions with palladium(II) chloride, copper(II) chloride and air as a source of oxygen gave ketone **204** along with the aldehyde **205** as a side product (Scheme 3.5).[54]



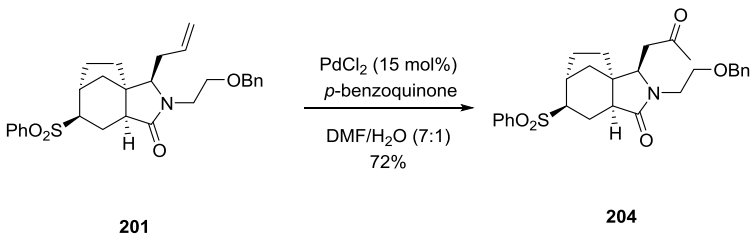
Scheme 3.5 Wacker oxidation with $CuCl_2$ and CuCl as reoxidants

The mechanism for the Wacker oxidation depicted in Scheme 3.6 shows how the ketone is formed after Markovnikov addition of the hydoxypalladium species across the double bond and how the palladium(II) is regenerated.[55,59] The formation of aldehyde **205** results from an *anti*-Markovnikov hydroxypalladation on the alkene and therefore is not favoured.



Scheme 3.6 Mechanism for the Wacker oxidation

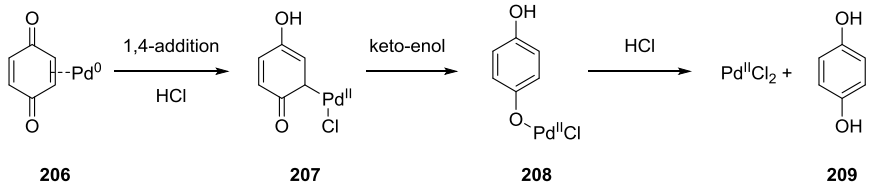
Interestingly, when the reaction was performed with *p*-benzoquinone as an oxidant, no formation of aldehyde **205** was observed (Scheme 3.7).



201 **204**

Scheme 3.7 Wacker oxidation with *p*-benzoquinone

Reoxidation of palladium(0) with *p*-benzoquinone is achieved *via* a different path than with the copper salts as shown in the scheme below (Scheme 3.8).

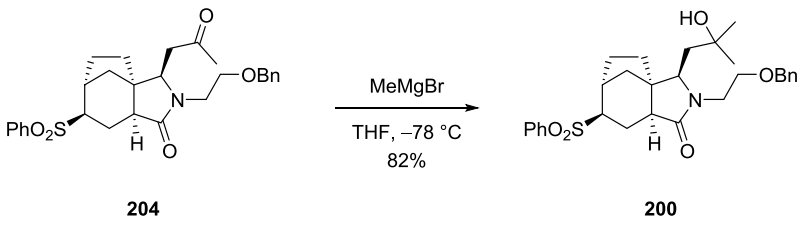


206 **207** **208** **209**

Scheme 3.8 Oxidation of palladium(0) with *p*-benzoquinone

It is hard to rationalise how the use of a different reoxidant can suppress the formation of the aldehyde, indeed, none of the literature examined gave an explanation as to the impact of the reoxidant on the aldehyde/ketone ratio. The main reasons why different reoxidants are employed are to prevent the use of oxygen needed with copper salts, to accelerate the rate of the reaction, or to reduce the loading of palladium.[55,60] However, the different temperatures used for the two reactions can explain this outcome. When the copper salts were used the reaction was performed at 60 °C while the reaction was carried out at RT with *p*-benzoquinone. This difference of energy can be responsible for the formation of the aldehyde side product.

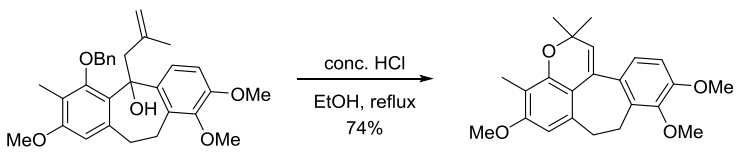
Ketone **204** was then treated with methylmagnesium bromide to provide alcohol **200** in good yield (Scheme 3.9).



204 **200**

Scheme 3.9 Methylmagnesium bromide addition on ketone **204**

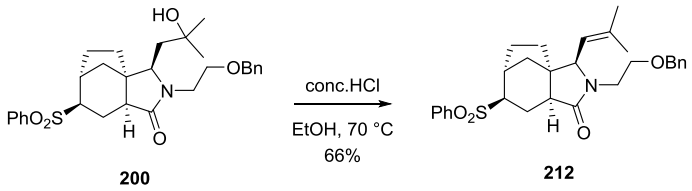
One strategy to form the oxazepane ring was to follow the work published by Rajviroongit in 2006 where a six-membered ring was formed with a benzyl-protected alcohol and a methylallyl group under acidic conditions (Scheme 3.10).[61]



210 **211**

Scheme 3.10 Cyclisation with a benzyl-protected alcohol

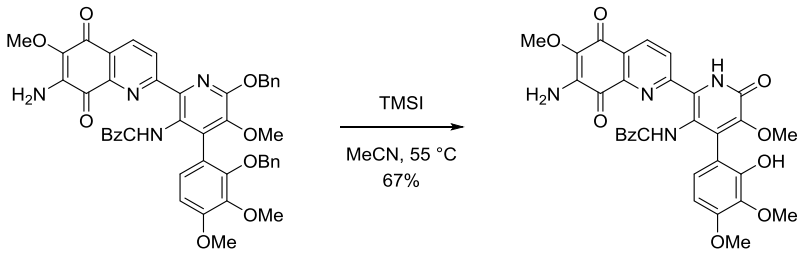
Treatment of **200** with hydrochloric acid at 70 °C did not yield the oxazepane ring and alkene **212** was formed instead (Scheme 3.11). In light of this result it was decided to remove the benzyl group prior to the cyclisation.



200 **212**

Scheme 3.11 First attempt to form the oxazepane ring

The late-stage cleavage of benzyl protecting groups in total synthesis can be difficult because the conditions need to be selective enough to not destroy other functionalities of the molecule. This issue was met by Chan and Ciufolini during the total synthesis of streptonigrone **214**.[62] Either the loss of material or reduction of the quinone moiety was observed with Pd(C)/hydrogen and BBr_3 respectively and trimethylsilyl iodide was found to be the best deprotecting agent to deliver streptonigrone **214** (Scheme 3.12).

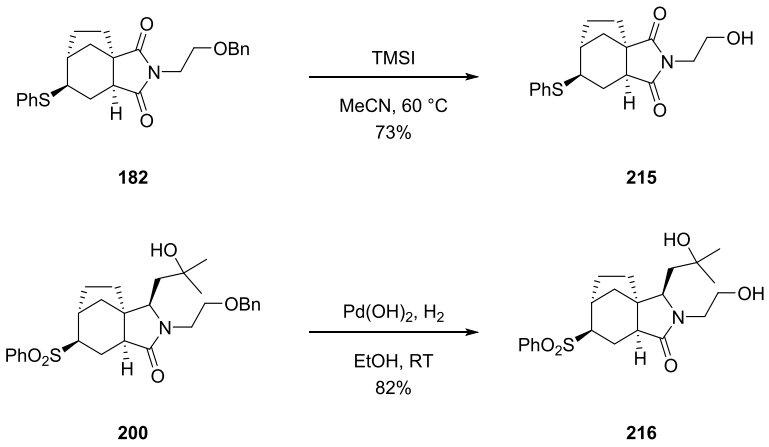


213 **214**

Scheme 3.12 Debenzylation of **213** with TMSI

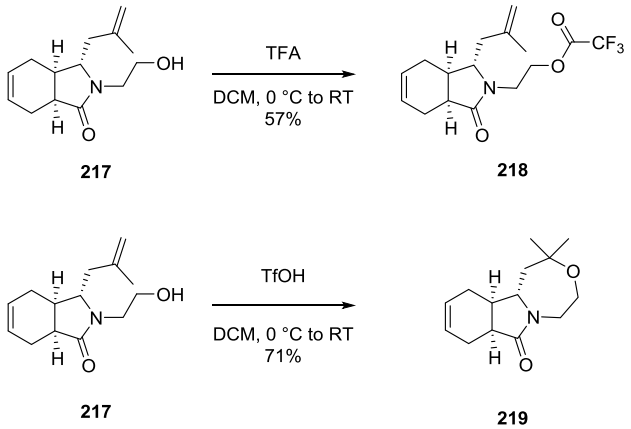
Model compound **182** was used to test the trimethylsilyl iodide deprotection and alcohol **215** was obtained in 73% yield (Scheme 3.13). However, the difficulty of following the reaction by TLC and the laborious purification required to isolate **215** prompted the investigation of another method. When palladium(II) hydroxide was used on sulfone **200** under a hydrogen atmosphere**,**

the alcohol was released in a better yield than with trimethylsilyl iodide and the reaction was easier to set up and purify.



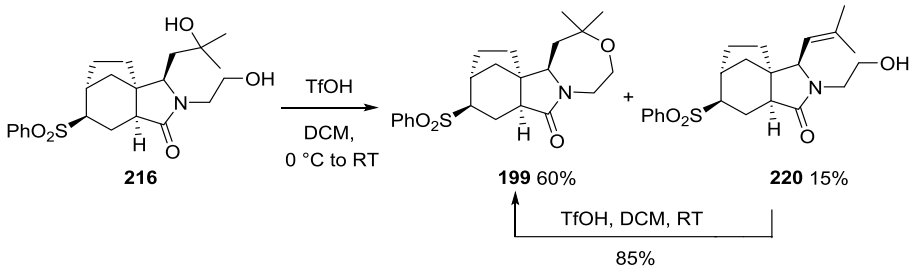
Scheme 3.13 Debenzylation of **182** with TMSI and **200** with $Pd(OH)_2/H_2$

The formation of the oxazepane ring on a model compound was previously investigated in the Simpkins group (Scheme 3.14).[14] During this work, various acidic reagents were used to form the ring. Attempts to prepare compound **219** using Amberlyst-15 and *p*-toluenesulfonic acid were unsuccessful. When trifluoroacetic acid was employed, ester **218** was isolated; however, the successful formation of the oxazepane ring was achieved using triflic acid.



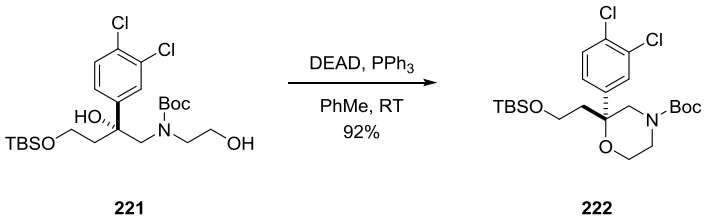
Scheme 3.14 Formation of the oxazepane ring under acidic conditions

When diol **216** was mixed with triflic acid, the oxazepane ring was formed in a 60% yield along with 15% of alkene **220**. It was found that alkene **220** could be converted into **199** with another five equivalents of triflic acid (Scheme 3.15). A longer reaction time did not avoid the formation of alkene **220**.



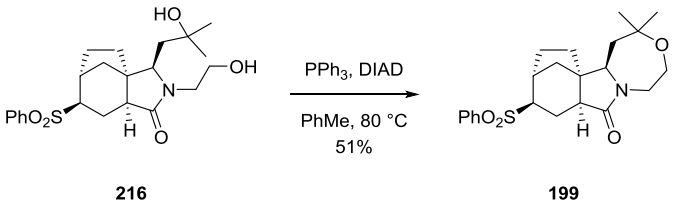
Scheme 3.15 Triflic acid cyclisation of **216**

In order to improve the yield for the formation of **199**, a Mitsunobu-type reaction was explored.[63] Nishi and co-workers used this methodology for the synthesis of four key intermediates of a tachykinin receptor antagonist.[64] Treatment of **221** with diethyl azodicarboxylate and triphenylphosphine afforded morpholine derivative **222** in 92% yield (Scheme 3.16).



Scheme 3.16 Ring closure with a Mitsunobu reaction

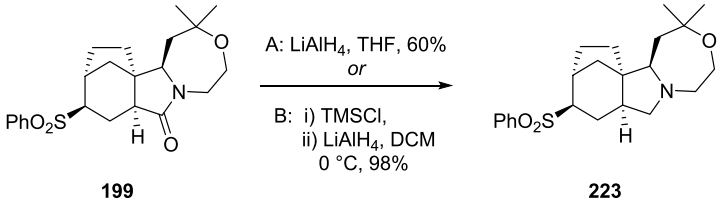
Applied to **216**, the Mitsunobu conditions furnished compound **199** in a modest 51% yield at 80 °C (Scheme 3.17). Increasing the number of equivalents of triphenylphosphine and diisopropyl azodicarboxylate did not improve the yield.



216 **199**

Scheme 3.17 Mitsunobu conditions on **216**

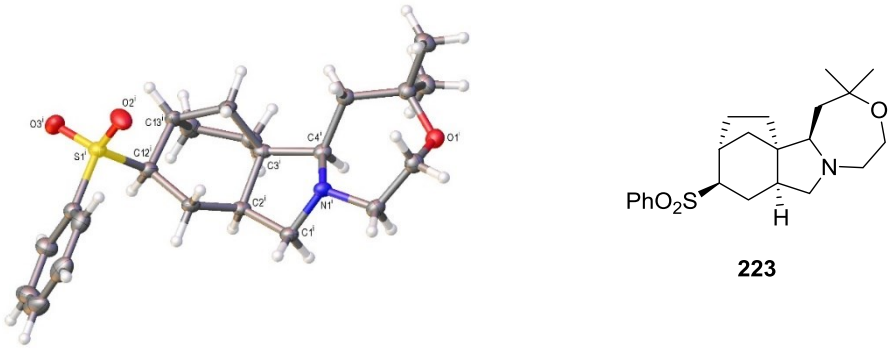
The amide moiety in **199** was then reduced to access the core structure of concavine (Scheme 3.18). A first attempt with lithium aluminium hydride in THF gave **223** in 60% yield. Activation of the amide with trimethylsilyl chloride in dichloromethane prior to the addition of lithium aluminium hydride gave the tetracycle **223** in excellent yield.[65]



199 **223**

Scheme 3.18 Reduction of amide **199** with $LiAlH_4$

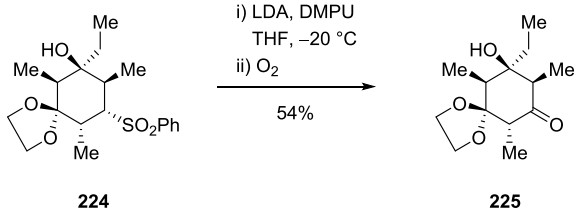
The tetracycle **223** was isolated as a white solid. Following crystallisation, an X-ray crystal structure of **223** was obtained, allowing for the determination of the relative stereochemistry (Figure 3.1). As seen in Figure 3.1, the oxazepane ring is in the desired orientation and the sulfone is axial.



223

Figure 3.1 X-ray crystal structure of **223**

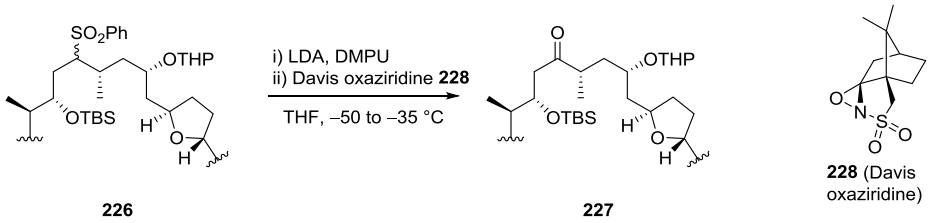
The next challenge in the synthesis of concavine was the replacement of the sulfone by a ketone with an oxidative desulfonylation. This reaction proceeds *via* the formation of a sulfone anion intermediate followed by the addition of a source of oxygen. A variety of conditions such as molecular oxygen, oxaziridine, MoOPH or bis(trimethylsilyl) peroxide have been previously reported in the litterature.[66–68] Molecular oxygen was used by Plumet and co-workers in 2001; after deprotonation at the *α*-position of sulfone **224**, oxygen was bubbled into the reaction mixture to provide ketone **225** (Scheme 3.19).[69]



224 **225**

Scheme 3.19 Transformation of sulfone **224** into **225** with O_2

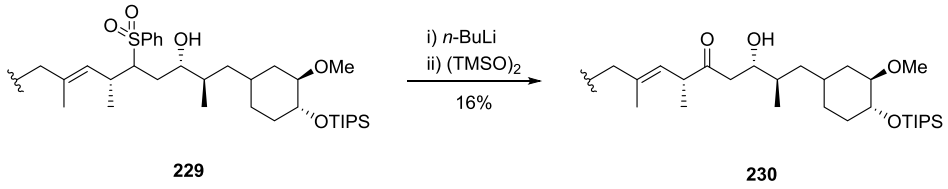
Mahapatra and Carter used the Davis oxaziridine to get the ketone **227** in 94% yield from sulfone **226** after deprotonation of the acidic position with LDA (Scheme 3.20).[70]



226 **227**

Scheme 3.20 Transformation of sulfone **226** in ketone **227** with an oxaziridine

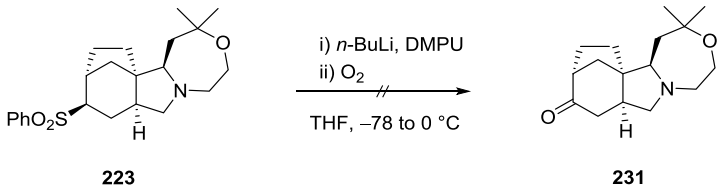
The oxidative desulfonylation can often be quite challenging and Schreiber and co-workers encountered many difficulties in converting sulfone **229** into a ketone.[71] After many attempts with various electrophilic oxygen sources, the use of *n*-BuLi and $(TMSO)_2$ gave the desired ketone albeit in a poor yield (Scheme 3.21).



229 **230**

Scheme 3.21 Transformation of sulfone **229** to ketone **230** with $(TMSO)_2$

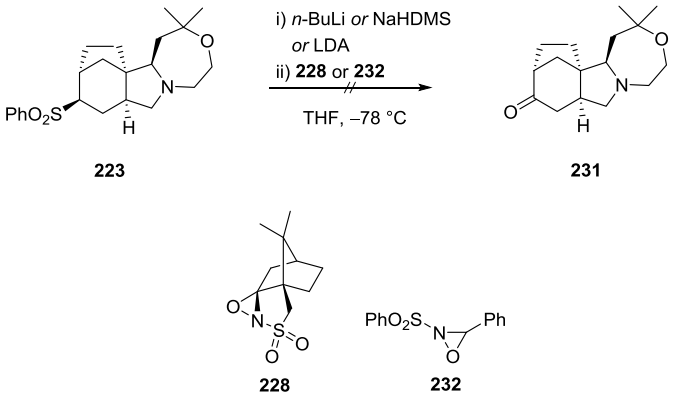
In our case, when molecular oxygen was used after deprotonation with *n*-BuLi the formation of ketone **231** was not observed and the starting material was not recovered (Scheme 3.22). Furthermore, the use of more equivalents of base and warming the reaction mixture to 0 °C did not help to form **231**.



223 **231**

Scheme 3.22 Attempted oxidative desulfonylation with O_2

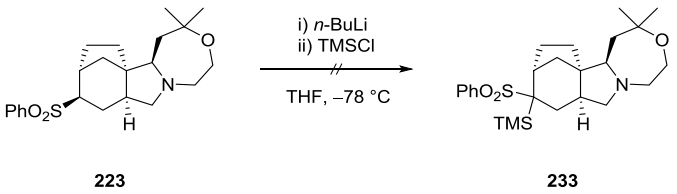
Following this result, the use of oxaziridines was investigated. The Davis oxaziridine **228** and the more simple phenylsulfonyloxaziridine **232** were tried on sulfone **223** in combination with different bases and DMPU, all without success (Scheme 3.23). In all experiments only a small fraction of the starting material was recovered and the only product observed by TLC was the oxaziridine. No side products containing the core structure fragments were isolated to understand the outcome of this reaction.



Scheme 3.23 Attempted oxidative desulfonylation with oxaziridines

Sulfone **223** was also treated with *n*-BuLi and MoOPH (a MoO_5•Py•HMPA complex) but no conversion into desired ketone **231** was observed. In addition, the preparation of $(TMSO)_2$ following a literature procedure with DABCO.$2H_2O_2$ and trimethylchlorosilane did not meet with any success. Therefore this methodology could not be tested on **223**.[72]

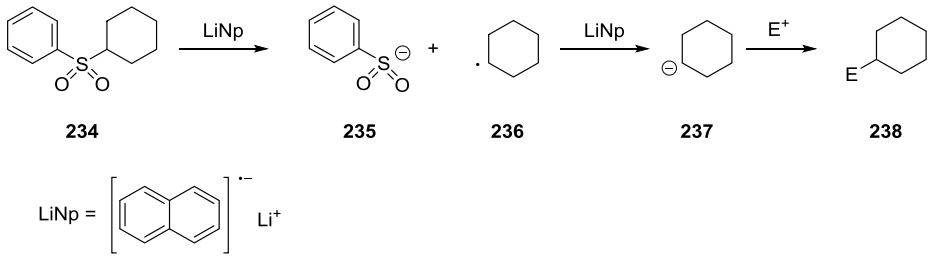
To understand why these reactions failed to produce the desired ketone, the efficiency of the deprotonation was examined (Scheme 3.24). Deprotonation with stoichiometric or excess amounts of *n*-BuLi, followed by quenching with TMSCl did not afford **233**. When the reaction was quenched with D_2O, no evidence for hydrogen-deuterium exchange was observed by ^1H NMR spectroscopy. Only small amounts of starting material were recovered during these experiments and it was concluded that **223** does not tolerate strongly basic conditions.



Scheme 3.24 Attempted TMS incorporation into **223**

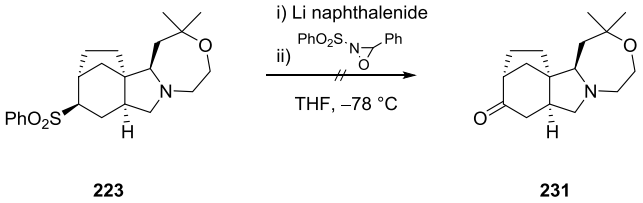
Instead of deprotonating the *α*-position of the sulfone, another methodology involving lithium naphthalenide was employed. With this reagent an electron is transferred to the sulfone to create

radical **236** and sulfonate anion **235**. The radical intermediate can react with another electron to form the anion **237** which can be added to various electrophiles to give **238** (Scheme 3.25).[73,74] The sulfur-alkyl bond is cleaved in preference to the sulfur-aryl bond due to the relative stability of the formed radical.



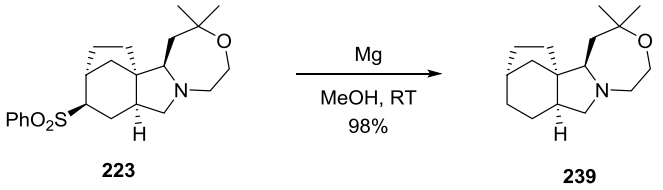
Scheme 3.25 Carbon-sulfone bond cleavage with LiNp

Sulfone **223** was treated with 2.5 equivalents of a freshly-made solution of lithium naphthalenide and after 10 min at −78 °C the oxaziridine was added. Neither ketone **231** nor compound **239** (resulting from a reductive desulfonylation, see Scheme 3.27) were isolated and the starting material was not recovered, indicating a probable decomposition (Scheme 3.26).



Scheme 3.26 Attempted oxidative desulfonylation with lithium naphthalenide

Interestingly, a reductive desulfonylation attempt on **223** with magnesium metal in anhydrous methanol furnished compound **239** in 98% yield (Scheme 3.27).[67]



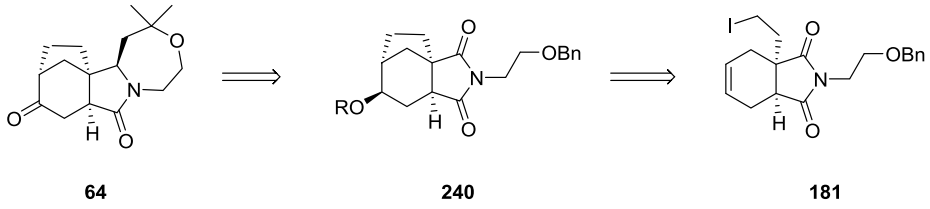
Scheme 3.27 Reductive desulfonylation with magnesium

The reasons behind our inability to access ketone **231** with an oxidative desulfonylation are unclear. The deprotonation step seems to be the source of the problem as no TMS group or deuterium atom could be incorporated into the molecule. This could indicate the absence of an anion at the *α*-position of the sulfone due to the possible decomposition of the starting material.

The strategy to use a sulfone as a ketone precursor did not work. Because there is no evidence this reaction would work at a different stage in the synthesis, another approach was considered.

3.2. Radical functionalisation with oxygen

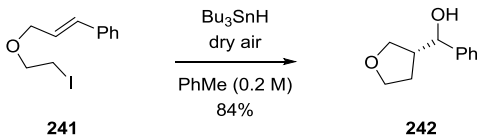
An ideal way to form ketone **64** would be the oxidation of an alcohol which could be introduced during the radical cyclisation step (Scheme 3.28).



Scheme 3.28 Retrosynthetic analysis to ketone **64**

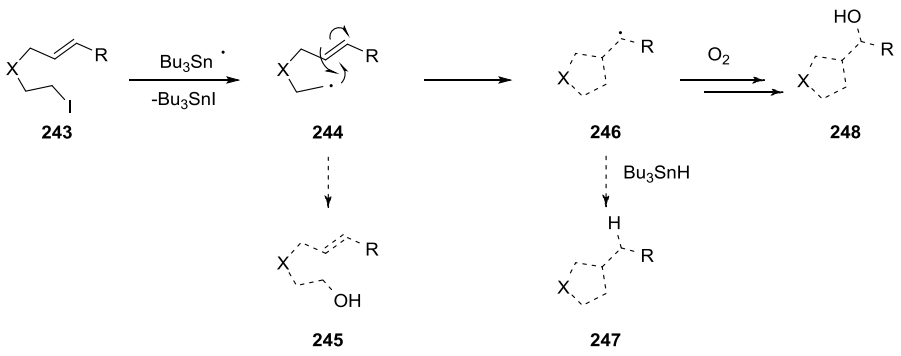
In the previous chapter, diphenyl disulfide was successfully employed to install a functional group at end of the radical cyclisation and it was thought that a source of oxygen could instead be used to access compound **240**.

The aerobic conversion of iodo compounds to alcohols was reported by Nakamura in 1991 and Prandi in 1998.[75,76] Both authors described how an oxygenative radical cyclisation can take place using tributyltin hydride, with or without AIBN, under a stream of dry air bubbled into the reaction mixture (Scheme 3.29).



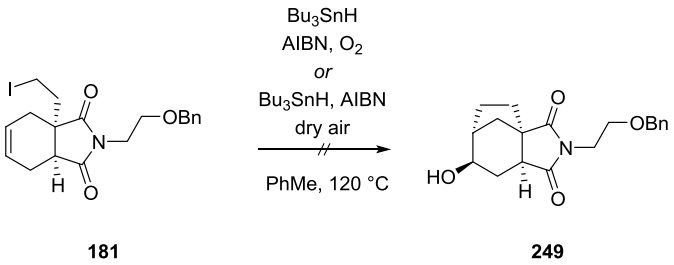
Scheme 3.29 Oxygenative radical cyclisation with dry air

It is suggested that, despite several competitive reaction pathways, the oxygenation of the radical present in **246** takes place faster than the reduction with tributyltin hydride (Scheme 3.30).



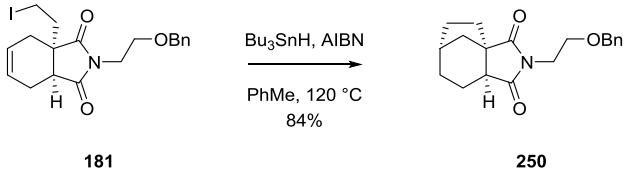
Scheme 3.30 Mechanism for the oxygenative radical cyclisation

To test these conditions, a stream of air was dried over a column of silica gel and bubbled into the reaction mixture (Scheme 3.31). The reaction failed to produce **249** and replacing the flow of dry air by an atmosphere of oxygen did not yield desired compound **249** and the starting material was recovered.



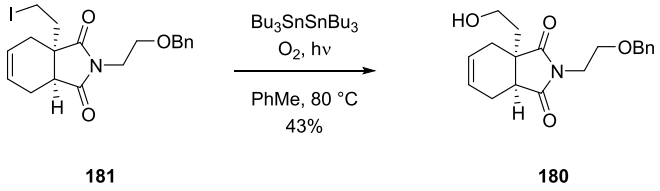
Scheme 3.31 Attempted aerobic conversion of **181**

A reaction without dry air was attempted and cyclised compound **250** was formed in good yield (Scheme 3.32).



Scheme 3.32 Reductive cyclisation of **181**

In order to reproduce the conditions previously developed to form the five-membered ring, the radical cyclisation step was performed with hexabutylditin under an oxygen atmosphere and alcohol **180** was recovered in 43% yield (Scheme 3.33).

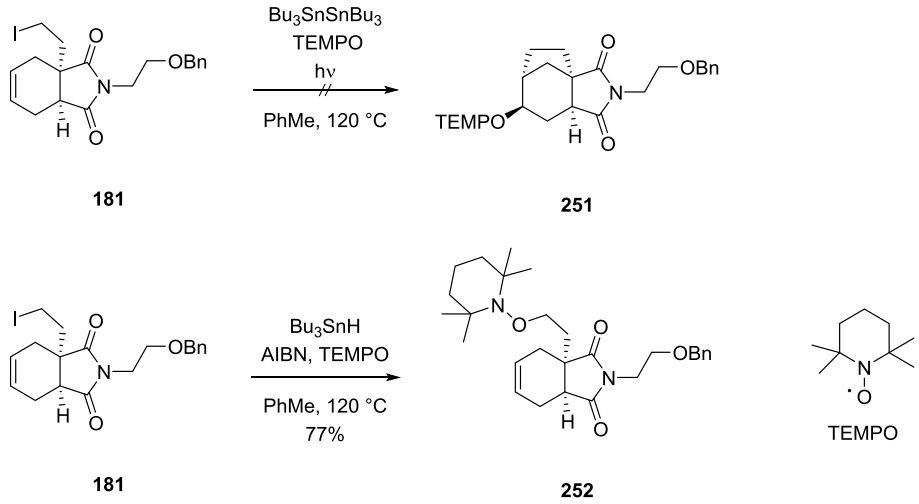


Scheme 3.33 Radical cyclisation in the presence of hexabutylditin and O_2

In an effort to avoid the large excess of molecular oxygen reacting with the radical before the cyclisation step, the reaction was performed at a higher dilution. The desired cyclised compound, however, was still not observed. The difficulty in controlling the number of

equivalents of oxygen introduced during the reaction forced the investigation of another source of oxygen.

The combination of TEMPO and hexabutylditin showed no conversion of the starting material. However, utilising tributyltin hydride and AIBN, the formation of **252** was observed in good yield (Scheme 3.34).[77]



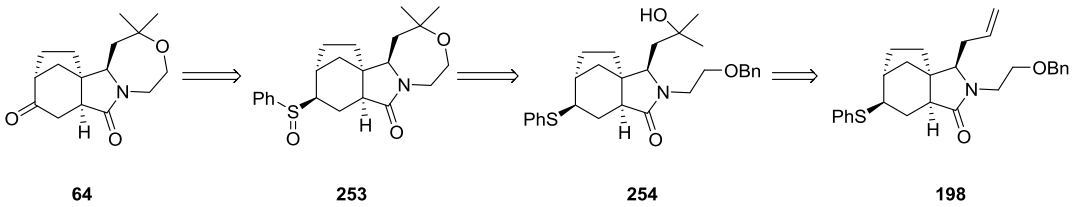
Scheme 3.34 Radical reaction with TEMPO

The good result observed for the radical cyclisation with phenyl disulfide could not be reproduced when an oxygen source was used instead. While oxygenated compound **252** was obtained in good yield the cyclisation step was not observed and this strategy to yield the ketone was abandoned.

3.3. Formation of the core structure with a sulfoxide functional group

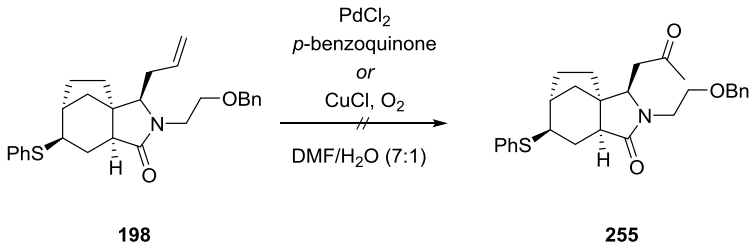
A new approach to access key compound **64** using a sulfoxide intermediate was suggested, as illustrated in the retrosynthetic analysis in Scheme 3.35. Ketone **64** could be installed by a

Pummerer rearrangement of sulfoxide **253** which could be introduced after formation of the core structure. Introducing the sulfoxide at this late stage avoids carrying a mixture of diastereoisomers, caused by the chiral sulfoxide, through the majority of the synthesis.



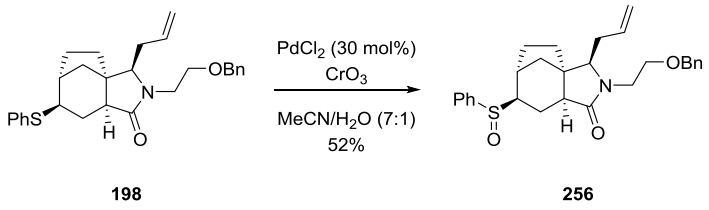
Scheme 3.35 Retrosynthetic analysis with *via* sulfoxide **253**

To prepare the oxazepane ring, the Wacker oxidation was performed on **198** (Scheme 3.36). The previously developed conditions were applied to **198** but no conversion of the starting material was recorded.



Scheme 3.36 Attempted Wacker oxidation on **198**

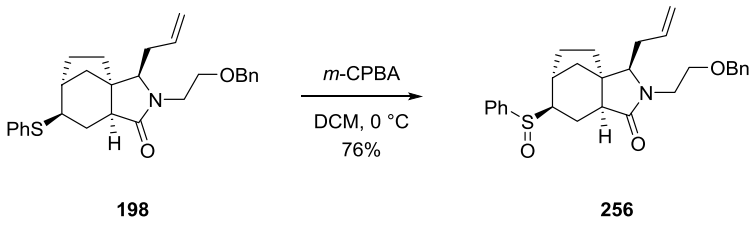
When chromium trioxide was used as a reoxidant, the sulfide was oxidised to the corresponding sulfoxide in modest yield. The double bond was not observed to react under these conditions (Scheme 3.37).



Scheme 3.37 Wacker oxidation with CrO_3 on **198**

The presence of a sulfide group in the molecule was found to be problematic for the reaction as it is known that sulfides have a strong affinity for palladium metal. The formation a Pd-S bond prevents the coordination of the palladium catalyst to the double bond.[78]

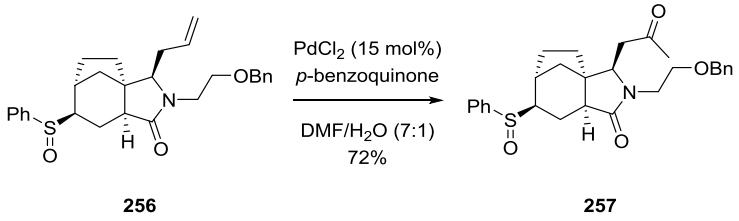
To circumvent this issue, the sulfide was oxidised into a sulfoxide with 1.1 equivalents of *m*-CPBA prior to the Wacker oxidation (Scheme 3.38). Frequent monitoring of the reaction by TLC was needed to avoid oxidation to the sulfone. Sulfoxide **256** was isolated as a mixture of diastereoisomers in a 1.0:1.3 ratio.



198 **256**

Scheme 3.38 Sulfoxide formation with *m*-CPBA

With sulfoxide **256**, the Wacker conditions delivered ketone **257** in good yield without the formation of the aldehyde side product (Scheme 3.39).

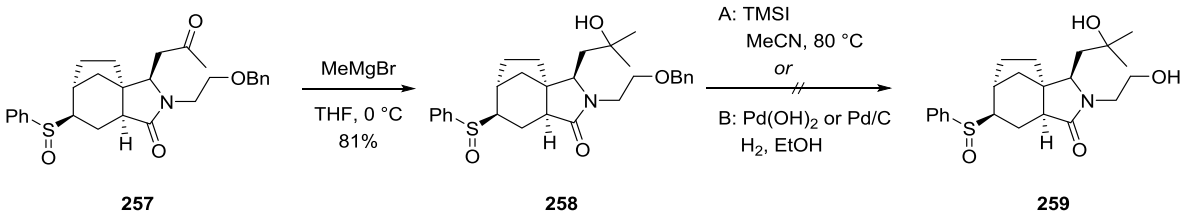


256 **257**

Scheme 3.39 Wacker oxidation on sulfoxide **256**

To continue the synthesis, compound **257** was treated with methylmagnesium bromide to furnish alcohol **258** as a 1:1 mixture of diastereoisomers in 81% yield. The conditions previously used to remove the benzyl group on **258** (TMSI and $Pd(OH)_2$ / hydrogen) failed to

give diol **259** (Scheme 3.40). It is worth noting that reduction of the sulfoxide into the sulfide was observed when TMSI was employed.[79]

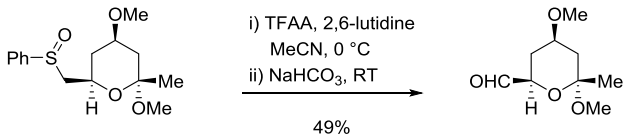


257 258 259

Scheme 3.40 Unsuccessful debenzylation of **258**

It is conceivable that the debenzylation with a palladium catalyst did not work for the same reason observed in Scheme 3.36. The sulfur is only partially oxidised, therefore it can again coordinate the palladium catalyst and prevent the cleavage of the benzyl group.

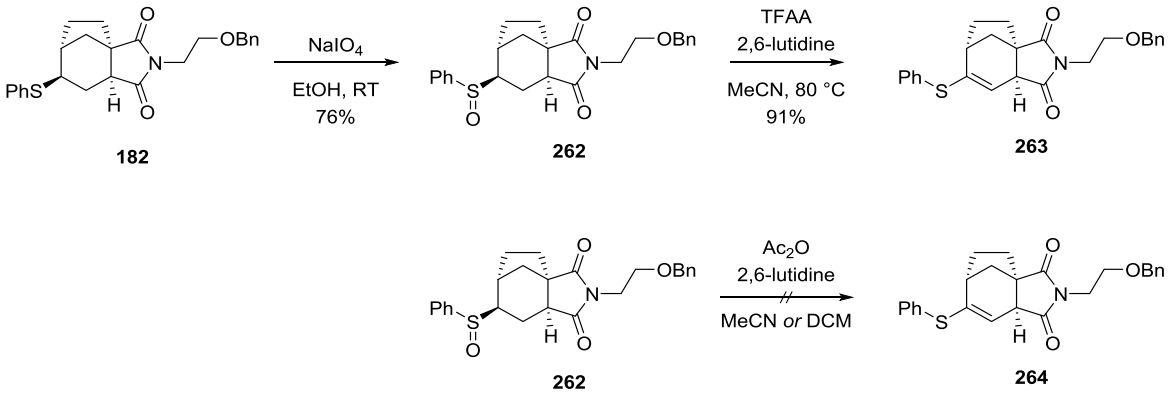
Transformation of the sulfoxide was necessary at this stage of the synthesis and the Pummerer rearrangement was investigated to yield the necessary ketone.[80] This strategy was reported by Solladié and co-workers for the asymmetric synthesis of the tetrahydropyran ring of phorboxazoles.[81] The classic Pummerer reaction conditions were applied to **260** and the aldehyde **261** was recovered in modest yield (Scheme 3.41).



260 261

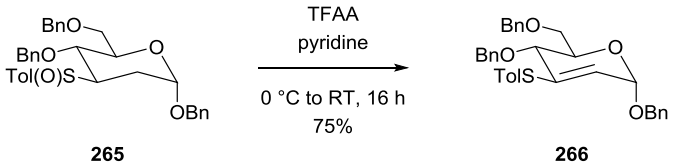
Scheme 3.41 Pummerer rearrangement of **260**

Applied to sulfoxide **262**, obtained after oxidation of the sulfide group in **182** with sodium periodate, the Pummerer conditions did not yield the desired ketone and vinyl sulfide **263** was isolated instead (Scheme 3.42). The use of acetic anhydride in acetonitrile or dichloromethane did not convert sulfoxide **262** into **264** and the starting material was recovered.



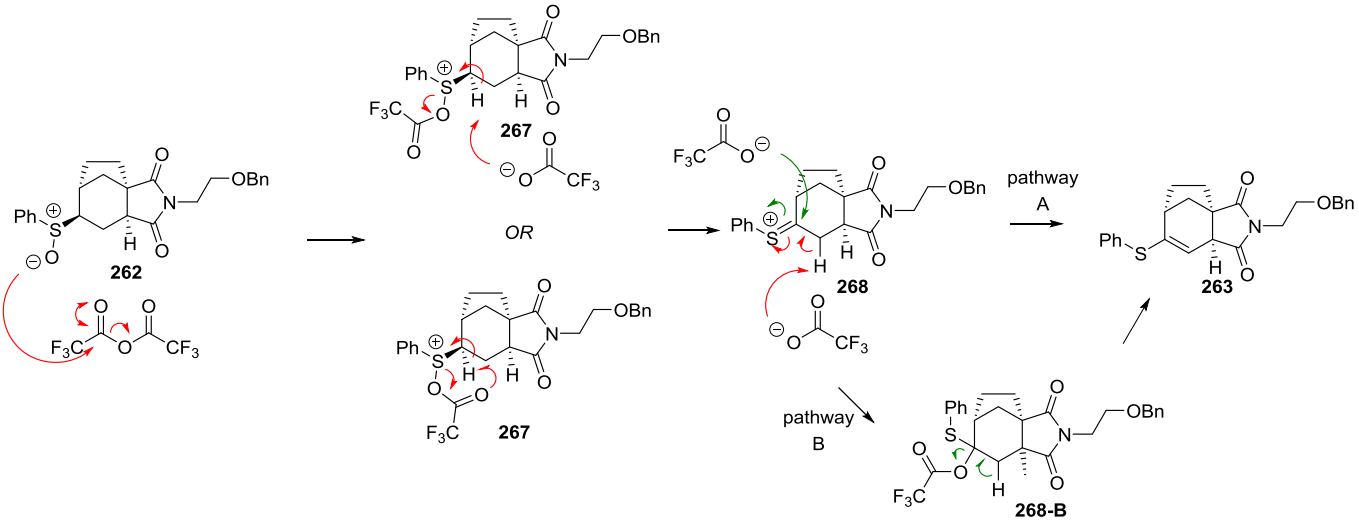
Scheme 3.42 Pummerer reaction on model compound **262**

The formation of a vinyl sulfide under Pummerer reaction conditions when the sulfoxide is linked to a disubstituted carbon is not unusual and it was described by Jayaraman in 2012.[82] Sulfoxide **265** was efficiently converted to vinyl sulfide **266** with trifluoroacetic anhydride in pyridine (Scheme 3.43).



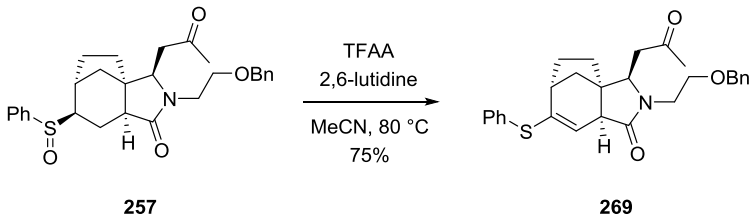
Scheme 3.43 Formation of vinyl sulfide **266**

A plausible mechanism to explain this outcome is depicted below (Scheme 3.44). The reaction begins in a classic Pummerer fashion by reaction of sulfoxide **262** with TFAA to give intermediate **267**. Following this, elimination of the trifluoroacetate group in **267** can occurs either in an intramolecular or intermolecular fashion to produce thionium **268**.[83,84] In a classic Pummerer rearrangement, the trifluoroacetate would attack the carbon at the α-position of the sulfur. In this case, however, it is plausible that the steric hindrance of this position could lead to a proton abstraction to form the stable vinyl sulfide (pathway A) or compound **263** could be form via the formation of intermediate **268-B** (pathway B).[85]



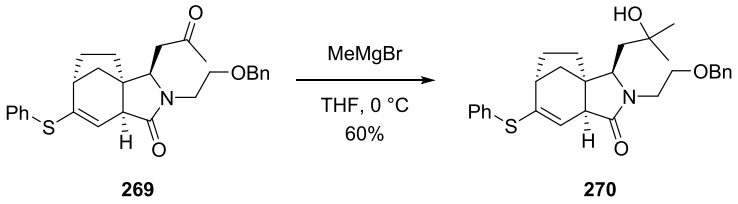
Scheme 3.44 Plausible mechanism for the Pummerer rearrangement observed on **262**

The use of trifluoroacetic anhydride and 2,6-lutidine on **257** gave the same outcome but in a slightly lower yield than on model system **262** (Scheme 3.45).



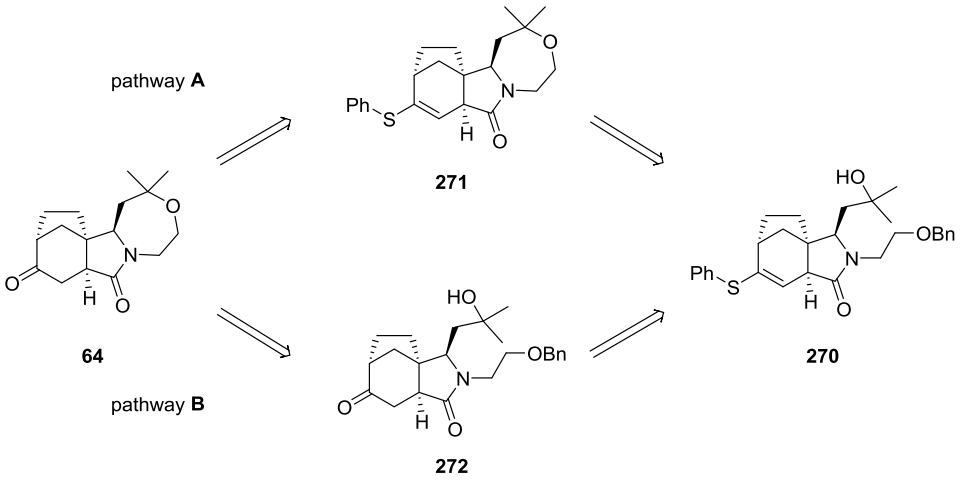
Scheme 3.45 Pummerer rearrangement on sulfoxide **257**

Examples found in the literature for the hydrolysis of vinyl sulfides to ketones convinced us to continue the synthesis and methylmagnesium bromide was added to **269** giving alcohol **270** in 60% yield (Scheme 3.46).



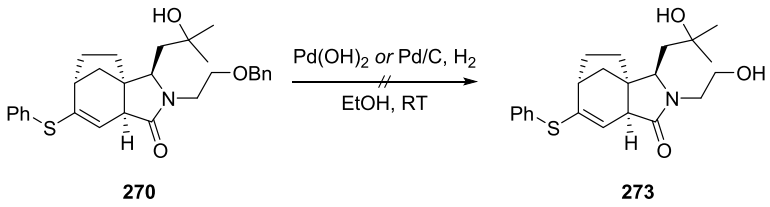
Scheme 3.46 Methylmagnesium bromide addition on **269**

At this stage, two options were available to obtain compound **64**. In pathway A, the ketone could be obtained from the hydrolysis of the vinyl sulfide group in **271** and the oxazepane ring could be closed after debenzylation of **270**. In pathway B, the core structure could be built from **272** after the hydrolysis of the vinyl sulfide (Scheme 3.47).



Scheme 3.47 Retrosynthetic analysis for the formation of **64**

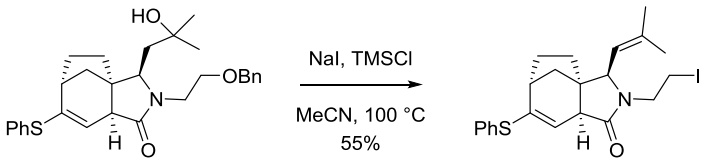
Investigating pathway A first, the debenzylation of **270** with a palladium catalyst was attempted but did not furnish diol **273** (Scheme 3.48). The presence of a non-oxidised sulfur to coordinate to the palladium catalyst may explain the failure of this reaction.



270 **273**

Scheme 3.48 Attempted debenzylation on **270** with palladium catalysts

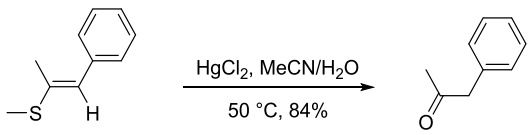
In the presence of TMSI prepared *in situ*, the protected oxygen was replaced by an iodine and elimination of the tertiary alcohol occurred to give **274** (Scheme 3.49). A slight excess of TMSCl and NaI were used to ensure sufficient formation of TMSI, which can explain how another equivalent of TMSI reacted with the alcohol intermediate formed after the debenzylation to introduce the iodine and the alkene in **274**.[86]



270 **274**

Scheme 3.49 Debenzylation of **270** with TMSI

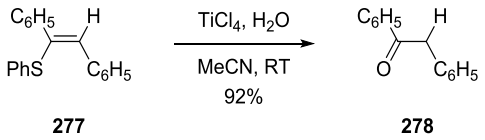
To be able to remove the benzyl group, the vinyl sulfide moiety had to be converted into a ketone (as proposed in pathway B). In one of the first examples published by Corey in 1970, vinyl sulfide **275** was hydrolysed with mercuric chloride in aqueous acetonitrile (Scheme 3.50).[87]



275 **276**

Scheme 3.50 $HgCl_2$ hydrolysis of **275**

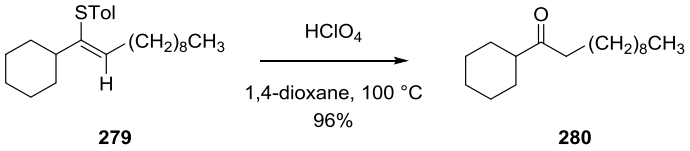
Following the success of this reaction, other sets of conditions to achieve this transformation have been published. A combination of water and titanium(IV) chloride was reported by Takei and co-workers, under these conditions ketones were obtained in good yields (Scheme 3.51).



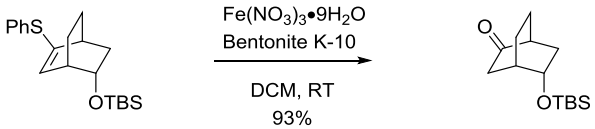
277 **278**

Scheme 3.51 Hydrolysis of vinyl sulfide with $TiCl_4$ and water

This transformation was also reported with perchloric acid or ferric nitrate adsorbed on Bentonite K-10 clay (Scheme 3.52).[88,89] Vinyl sulfides **279** and **281** were converted into their respective ketones in excellent yields.



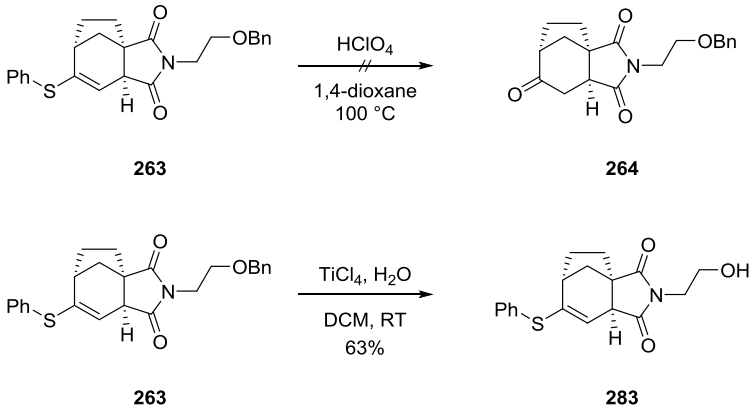
279 **280**



281 **282**

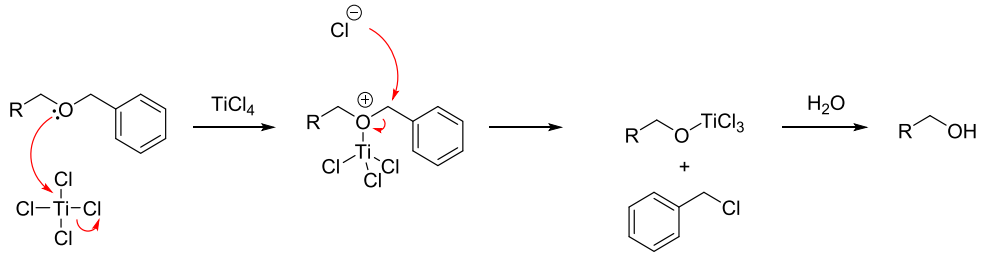
Scheme 3.52 Vinyl sulfide hydrolysis with various conditions

Compound **263** was chosen as a model system to test these vinyl sulfide hydrolysis conditions. The use of perchloric acid at RT or reflux did not yield ketone **264** and the starting material was not recovered, indicating a possible decomposition. The mixture of ferric nitrate adsorbed on Bentonite K-10 clay reacted with compound **263** but characterisation of the crude material failed to show signs of a ketone functionality. Titanium(IV) chloride and water converted vinyl sulfide **263** into a new compound which did not contain a ketone but a free alcohol resulting from a cleavage of the benzyl group (Scheme 3.53).



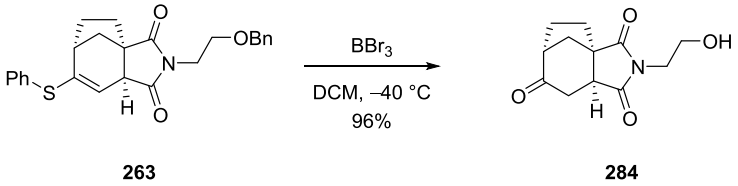
Scheme 3.53 Vinyl sulfide hydrolysis of model compound **263**

The debenzylation observed with titanium(IV) chloride is suspected to follow a similar mechanism to the known boron tribromide debenzylation (Scheme 3.54).[90]



Scheme 3.54 Mechanism for the $TiCl_4$ debenzylation

In light of this result, an attempt was made to cleave the benzyl group on compound **263** with boron tribromide (Scheme 3.55).

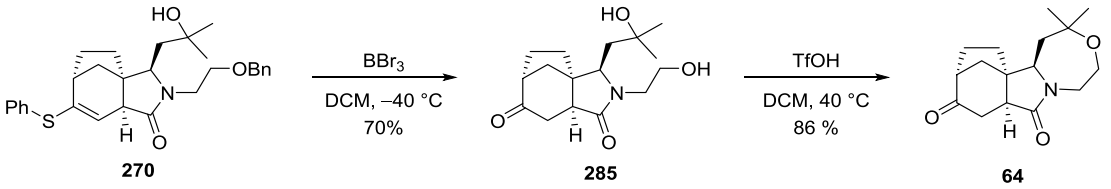


Scheme 3.55 Debenzylation and vinyl sulfide hydrolysis of **263** with BBr_3

Gratifyingly, the benzyl group was cleaved in excellent yield. However, the ^{1}H NMR spectrum did not display any aromatic protons and the ethylenic proton characteristic of the vinyl sulfide

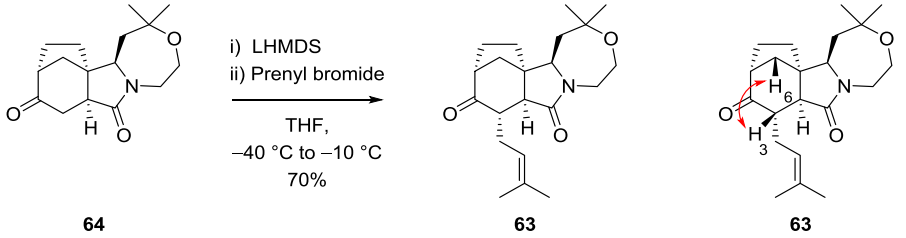
moiety was also missing. Analysis of the NMR data for **284** revealed the presence of a peak at 210.7 ppm in the ^{13}C NMR spectrum which indicated the presence of a ketone and a new methylene carbon was observed. Two-dimensional NMR and mass spectrometry experiments further confirmed the existence of a ketone in place of the vinyl sulfide.

The boron tribromide conditions were applied to **270** and the desired compound **285** was recovered in 70% yield (Scheme 3.56). The oxazepane ring was formed using the same conditions described previously. It was found that warming the reaction mixture to 40 °C avoided the formation of the alkene side product (see Scheme 3.15).



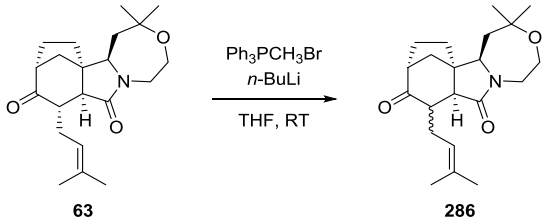
Scheme 3.56 Formation of the core structure of concavine

The prenyl chain was added by deprotonation at the *α*-position of ketone **64** with 1.15 equivalents of LHMDS followed by addition of prenyl bromide. Careful control of the temperature allowed the isolation of a single diastereoisomer (Scheme 3.57). NOE experiments showed a correlation between H-3 and H-6 indicating the equatorial position of the prenyl chain. This result was in accordance with the hypothesis that the shape of the molecule directed the addition of the prenyl chain *via* the back face of the molecule (see Chapter 2).



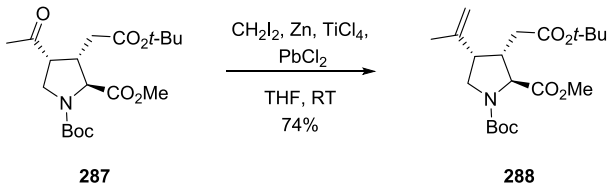
Scheme 3.57 Addition of the prenyl chain on **64**

To complete the total synthesis, the ketone was first converted into an *exo*-double bond. When the Wittig reagent was employed, the reaction failed to produce the desired product. Only partial epimerisation of the starting material was observed (Scheme 3.58).



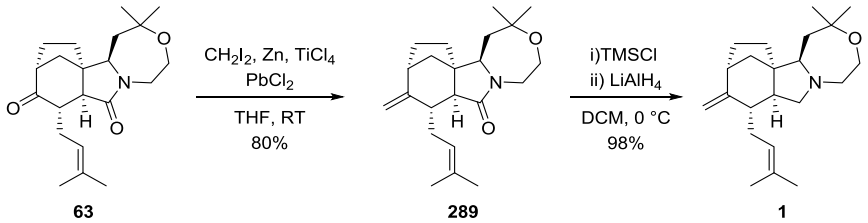
Scheme 3.58 Attempted Wittig olefination of **63**

To overcome the problematic basicity of the Wittig reagent, a Takai olefination was instead utilised.[91] Shinada and co-workers demonstrated the utility of this methodology in the total synthesis of (−)-kainic acid (Scheme 3.59).[92] The readily epimerisable ketone **287** was successfully converted into **288** without scrambling of the stereochemistry at the α-position.



Scheme 3.59 Takai olefination of ketone **287**

The same conditions were applied to ketone **63** and olefin **289** was yielded as a single product (Scheme 3.60). The reduction of the amide was performed with trimethylsilyl chloride and lithium aluminium hydride to give **1** in 98% yield.



Scheme 3.60 Olefination and amide reduction

The total synthesis of **1** was completed in seventeen steps. The structure was confirmed by ^{1}H- and ^{13}C NMR spectroscopy as well as two-dimensional NMR experiments. However, some subtle and profound differences with the reported NMR data for concavine were observed. The next chapter will highlight these differences and show the work undertaken in an attempt to explain them.

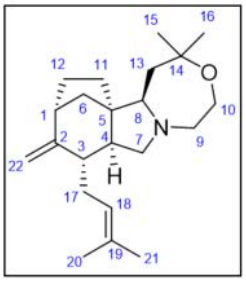
Chapter 4 Comparison between reported and synthesised concavine

The total synthesis of concavine was completed after seventeen steps featuring: a radical cyclisation, a Pummerer rearrangement, a Wacker oxidation and a Takai olefination. Extensive NMR analyses were undertaken to unambiguously confirm the structure of **1** and the relative configuration of all the stereocentres. Complete chemical shift assignments were made for **1** in acetone-d_6 and chloroform-*d* as the data for concavine were reported in these two solvents. To our surprise, the comparison between the NMR data of our synthetic concavine and the data available for the reported natural product presented many significant differences. To investigate the origin of these differences, several modifications were performed on **1** in order to match the data previously for reported concavine.

4.1. NMR data of reported and synthesised concavine

The only reported characterisation, published by Nasini and co-workers, was a tabulated array of the ^{1}H- and ^{13}C NMR data for isolated concavine in acetone-d_6 and chloroform-*d*.[1] We therefore present Table 4.1 as a comparison of the literature and our synthetic compound.

	CDCl₃			Acetone-d₆		
	Reported	Synthesised	Δ ppm	Reported	Synthesised	Δ ppm
1	2.88	2.8	0.08	2.84	2.75	0.09
2						
3	2.27	2.13	0.14	2.19	2.08	0.11
4	1.77	1.56	0.21	1.66	1.56	0.1
5						
6a	1.06	0.97	0.09	0.99	1	-0.01
6b	2.07	1.72	0.35	1.86	1.71	0.15
7a	2.78	2.52	0.26	2.63	2.42	0.21
7b	3.39	2.96	0.43	3.28	2.85	0.43
8	3.13	2.57	0.56	2.91	2.49	0.42
9a	2.63	2.34	0.29	2.51	2.2	0.31
9b	3.39	2.96	0.43	3.28	2.87	0.41
10a	3.63	3.54	0.09	3.55	3.4	0.15
10b	4.08	3.8	0.28	3.95	3.73	0.22
11a	1.41	1.26	0.15	1.32	1.24	0.08
11b	1.5	1.41	0.09	1.48	1.45	0.03
12a	1.5	1.41	0.09	1.43	1.36	0.07
12b	1.95	1.91	0.04	1.92	1.94	-0.02
13a	1.5	1.5	0	1.51	1.52	-0.01
13b	2.27	1.72	0.55	2.08	1.71	0.37
14						
15	1.26	1.2	0.06	1.15	1.11	0.04
16	1.18	1.17	0.01	1.21	1.14	0.07
17a	2.17	2.19	-0.02	2.19	2.2	-0.01
17b	2.23	2.19	0.04	2.19	2.2	-0.01
18	5.08	5.1	-0.02	5.08	5.14	-0.06
19						
20	1.61	1.61	0	1.59	1.61	-0.02
21	1.69	1.68	0.01	1.67	1.67	0
22a	4.72	4.73	-0.01	4.73	4.72	0.01
22b	4.85	4.8	0.05	4.86	4.77	0.09



0.1 - 0.3
0.3 - 0.5
> 0.5

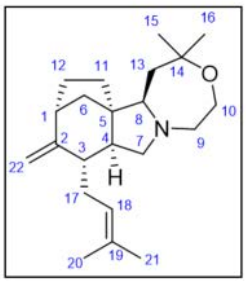
Table 4.1 ^{1}H NMR data for reported and synthesised concavine

The data in Table 4.1 may be divided into three main categories based on the difference in chemical shift between the reported and the synthesised concavine. Profound differences were observed for protons H-6, H-7, H-8, H-9 and H-13, mainly located close to the tertiary amine, with Δ ppm of more than 0.3 ppm in both the chloroform-*d* and acetone-d_6 spectra. A maximum shift of 0.56 ppm for H-8 and 0.43 ppm for H-7b compared to the original data was noted in chloroform-*d* and acetone-d_6 respectively. Small deviations of 0.14, 0.15 and 0.21 ppm, were found on the bicyclo[3.2.1]octane system for H-3, H-11a and H-4 in chloroform-*d* respectively.

Almost exact correlations (≤ 0.06 Δ ppm) were observed around the prenyl chain and for the two methyl groups on the oxazepane ring. Interestingly, almost all the chemical shifts for the reported concavine were shifted downfield compared to our synthesised compound.

The data collected for the ^{13}C NMR spectrum highlighted the same pattern observed with the ^{1}H NMR data (Table 4.2).

	$CDCl_3$			Acetone-d_6		
	Reported	Synthesised	Δ ppm	Reported	Synthesised	Δ ppm
1	41.91	41.79	0.12	41.88	41.74	0.14
2	155.52	157.1	-1.58	155.63	157.02	-1.39
3	40.93	41.52	-0.59	40.84	41.24	-0.4
4	49.3	49.63	-0.33	49.08	49.5	-0.42
5	52.99	53.45	-0.46	53.04	53.49	-0.45
6	30.28	30.36	-0.08	29.98	30.23	-0.25
7	60.46	61.52	-1.06	60.06	61.38	-1.32
8	65.9	64.82	1.08	65.47	64.52	0.95
9	57.82	58.62	-0.8	57.49	58.47	-0.98
10	60.46	61.97	-1.51	60.35	61.5	-1.15
11	33.41	33.5	-0.09	33.37	33	0.37
12	33.12	33.39	-0.27	32.98	32.95	0.03
13	39.07	41.67	-2.6	38.92	41.5	-2.58
14	74.75	74.81	-0.06	74.78	74.09	0.69
15	27.05	27.57	-0.52	27.96	27.06	0.9
16	28.37	28.76	-0.39	28.03	28.17	-0.14
17	30.28	30.01	0.27	30.14	29.91	0.23
18	122.39	123	-0.61	122.28	123.13	-0.85
19	132.42	131.8	0.62	132.15	131.09	1.06
20	17.99	17.97	0.02	17.86	17.12	0.74
21	25.8	25.28	0.52	25.67	25.04	0.63
22	108.08	107.21	0.87	107.98	106.52	1.46



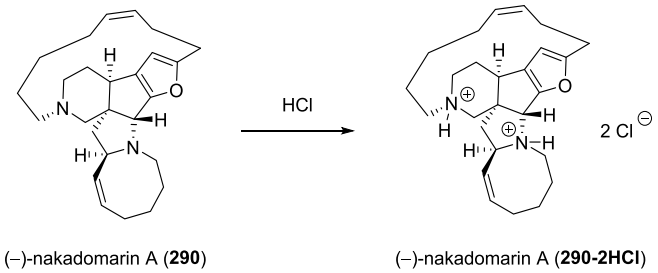
0.5 - 1.0
1.0 - 1.5
> 1.5

Table 4.2 ^{13}C NMR data for reported and synthesised concavine

In both chloroform-*d* and acetone-d_6, the carbons bound directly to the amine had an average deviation from the original data of 1.0 ppm. Substantial differences in chemical shifts were observed on the oxazepane ring for C-13 and C-10 in both solvents with a Δ ppm of up to 2.60 and 1.51 respectively. The sp^2-hybridised carbon C-2 was shifted by 1.58 ppm in chloroform-*d* and in acetone-d_6, carbons C-22 and C-19 showed significant differences to the original data.

Comparison of the ^{1}H- and ^{13}C NMR data for the reported and synthesised concavine revealed substantial differences of chemical shifts for the atoms near the tertiary amine. To rationalise these differences, it was hypothesised that concavine could have been isolated as a salt and not as a free amine. Indeed, the formation of a salt would greatly affect the chemical shifts adjacent to the tertiary amine.

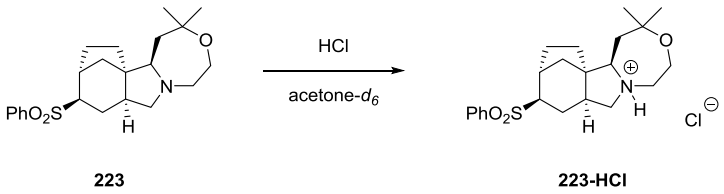
A similar issue was encountered by Nishida and co-workers during their work on the first total synthesis of nakadomarin A.[93] After the completed synthesis of nakadomarin A (**290**), the authors found that the resonances for the vinylic protons on the eight-membered ring and the protons on the carbons adjacent to the two tertiary amines were shifted downfield in the spectrum of the natural compound. Protonation of both of the tertiary amines with hydrochloric acid provided them with ^{1}H and ^{13}C spectra in accordance with the reported data (Scheme 4.1).



Scheme 4.1 Formation of the HCl salt of (−)-nakadomarin A (**290**)

The publication reporting the isolation of concavine did not specify the conditions used during the extraction of the natural product. It was envisaged that hydrochloric acid could have been used during the extraction of concavine resulting in isolation of the HCl salt.

In order to examine the effect of HCl salt formation in our system, model compound **223** was converted into its corresponding hydrochloride salt by addition of one equivalent of hydrochloric acid to a solution of **223** in acetone-d_6 (Scheme 4.2). Only 1.1 equivalents of HCl were used to avoid a possible cleavage of the ether group on the oxazepane ring.



Scheme 4.2 Formation of the HCl salt of **223**

The formation of the salt was confirmed by ^{1}H NMR spectroscopy and the most substantial changes in chemical shifts were seen near the protonated tertiary amine (Figure 4.1).

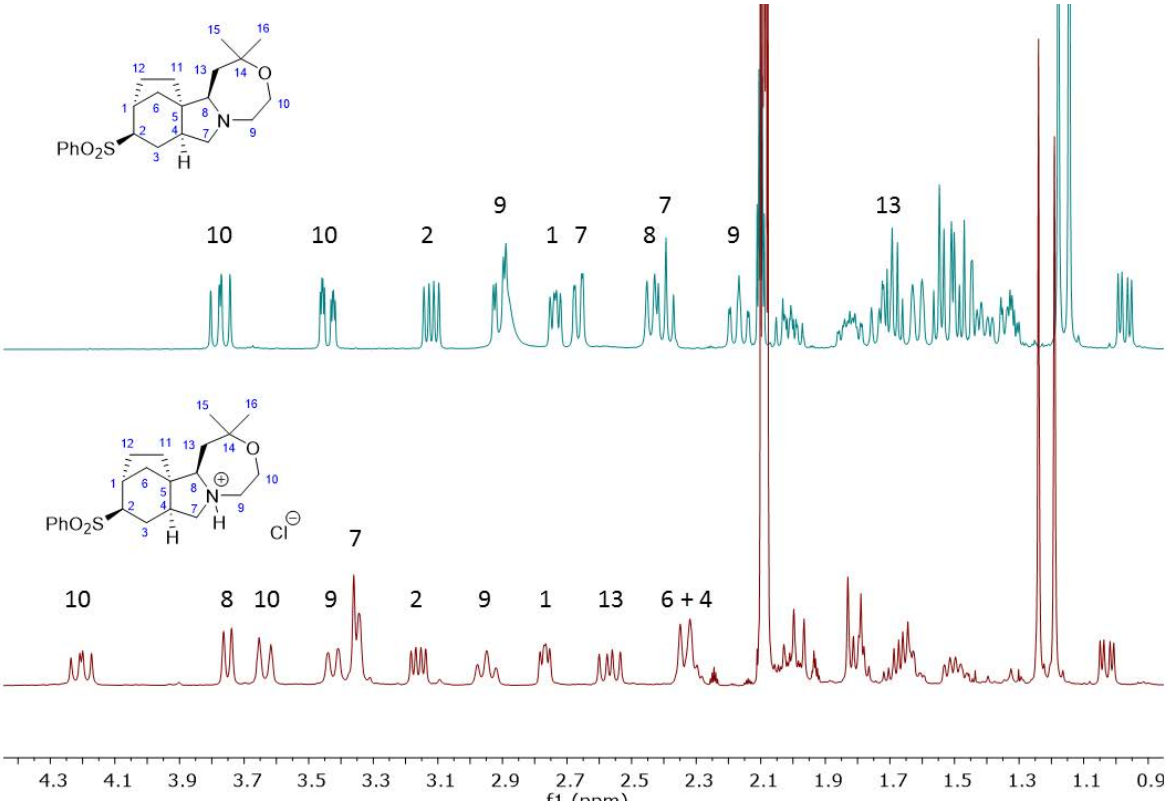
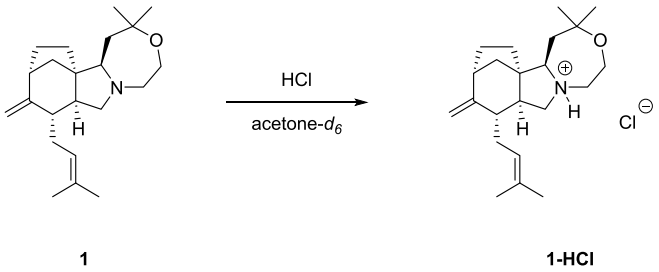


Figure 4.1 ^{1}H NMR spectra for the free amine and the HCl salt of **222**

The expected deshielding effect was particularly noticeable on protons H-13, H-10, H-9, H-8 and H-7. Protons H-8, H-7 and H-9, adjacent to the nitrogen, were shifted downfield by 1.32 ppm, 1.00 ppm and 0.70 ppm respectively.

Encouraged by this result, the HCl salt of synthesised concavine was formed in the same manner (Scheme 4.3).



Scheme 4.3 Formation of the HCl salt of concavine

The ^{1}H NMR data of **1-HCl** were collected and compared with the data reported in acetone-d_6 for concavine (Table 4.3).

	Acetone-d6		
	Reported	1-HCl	Δ ppm
1	2.84	2.83	0.01
2			
3	2.19	2.41	-0.22
4	1.66	2.05	-0.39
5			
6a	0.99	1.09	-0.1
6b	1.86	2.41	-0.55
7a	2.63	3.24	-0.61
7b	3.28	3.42	-0.14
8	2.91	3.71	-0.8
9a	2.51	2.95	-0.44
9b	3.28	3.36	-0.08
10a	3.55	3.6	-0.05
10b	3.95	4.17	-0.22
11a	1.32	1.49	-0.17
11b	1.48	1.66	-0.18
12a	1.43	1.49	-0.06
12b	1.92	1.99	-0.07
13a	1.51	1.8	-0.29
13b	2.08	2.57	-0.49
14			
15	1.15	1.17	-0.02
16	1.21	1.22	-0.01
17a	2.19	2.25	-0.06
17b	2.19	2.25	-0.06
18	5.08	5.14	-0.06
19			
20	1.59	1.63	-0.04
21	1.67	1.68	-0.01
22a	4.73	4.78	-0.05
22b	4.86	4.84	0.02

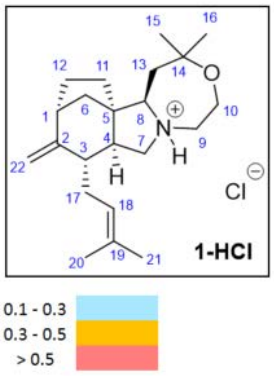


Table 4.3 ^{1}H NMR data for reported concavine and **1-HCl**

As expected, a downfield shift was observed for all proton resonances, with a stronger effect for those resonances for protons located around the tertiary amine. However, with the exception

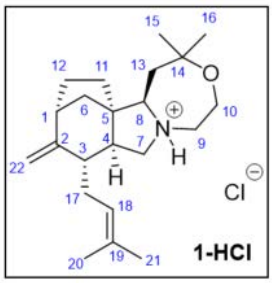
of H-9b, H-7b and H-10a, all the differences in chemical shift increased between the reported and the synthesised concavine with **1-HCl**. A threefold increase of the Δ ppm was noted for protons H-6b and H-7a and a maximum deviation of 0.80 ppm was found for H-8.

It is worth noting that the protons on the prenyl chain and the two methyl groups on the oxazepane ring were barely affected by the formation of the salt.

The ^{13}C NMR data for **1-HCl**, outlined in Table 4.4 also show increasing differences in comparison with reported concavine. The deshielding effect seen in the ^{1}H NMR spectrum was not observed on the ^{13}C NMR spectrum.

Acetone-d_6

	Reported	1-HCl	Δ ppm
1	41.88	42.04	-0.16
2	155.63	155.04	0.59
3	40.84	40.46	0.38
4	49.08	48.31	0.77
5	53.04	52.48	0.56
6	29.98	30.18	-0.2
7	60.06	58.47	1.59
8	65.47	66.29	-0.82
9	57.49	56.07	1.42
10	60.35	58.12	2.23
11	33.37	32.83	0.54
12	32.98	32.51	0.47
13	38.92	35.69	3.23
14	74.78	74.27	0.51
15	27.96	25.86	2.1
16	28.03	27.25	0.78
17	30.14	30.18	-0.04
18	122.28	122.11	0.17
19	132.15	132.28	-0.13
20	17.86	17.24	0.62
21	25.67	24.94	0.73
22	107.98	107.71	0.27



0.5 - 1.0
1.0 - 1.5
> 1.5

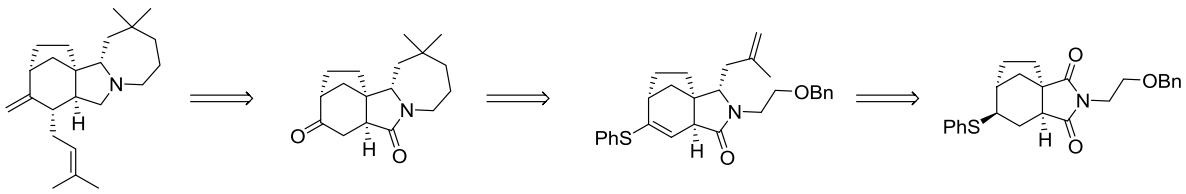
Table 4.4 ^{13}C NMR data for reported concavine and **1-HCl**

Carbons C-15, C-13 and C-10, on the oxazepane ring, and C-7 were shifted upfield by more than 1.5 ppm when compared with the reported data. A deviation of 3.23 ppm and 2.58 ppm was seen for C-13 in chloroform-*d* and acetone-d_6, respectively. In contrast, all the sp^2-hybridised carbons (C-2, C-18, C-19 and C-22) presented smaller deviations in the **1-HCl** spectrum.

In conclusion, the NMR data analysis revealed that the chemical shifts, especially for the atoms surrounding the nitrogen, did not match the original data. Converting synthesised concavine into its HCl salt had a strong effect on the chemical shifts but did not solve the issue.

4.2. Synthesis of 8-epi-concavine

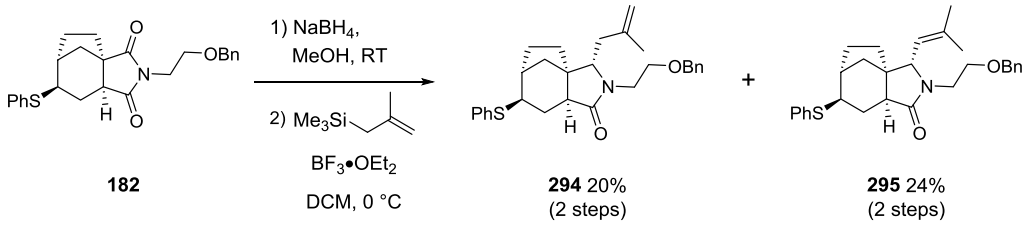
In an attempt to bring the chemical shifts of synthesised concavine closer to the reported data a modification of the structure was undertaken. It was decided to reverse the orientation of the stereocentre at the α-position of the tertiary amine following the retrosynthetic analysis depicted in Scheme 4.4. 8-Epi-concavine **291** could be accessed from intermediate **292** using the methodology previously developed while the core structure could be assembled by cyclisation of an alcohol onto a methylallyl moiety which could be introduced from imide **181**.



291 **292** **293** **182**

Scheme 4.4 Retrosynthetic analysis to access **291** from **182**

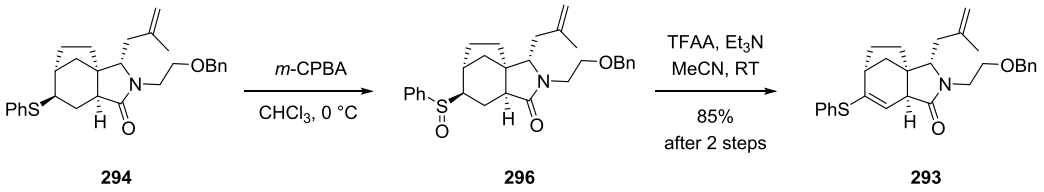
Imide **182** was reduced with sodium borohydride using the same conditions previously described in Chapter 2. The resulting hemiaminal was then treated with methallyltrimethylsilane and boron trifluoride diethyl etherate to give **294** in 20% yield along with **295** in 24% yield after two steps (Scheme 4.5).



Scheme 4.5 Formation of **294** from **182**

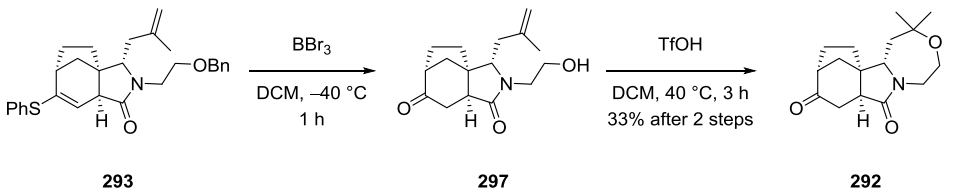
The modest combined yield of **294** and **295** could be due to the quality of the methallyltrimethylsilane which even after purification by distillation presented some impurities. Enough material of **294** was synthesised and the reaction was not optimised.

After oxidation of the sulfide with *m*-CPBA in chloroform, sulfoxide **296** was engaged in the Pummerer rearrangement to give vinyl sulfide **293** in 85% yield after two steps (Scheme 4.6).



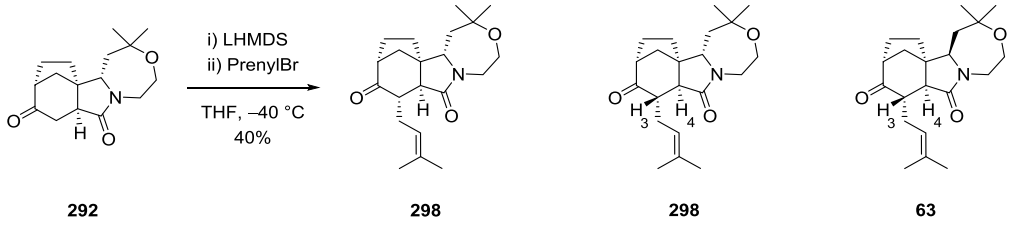
Scheme 4.6 Synthesis of vinyl sulfide **293**

Following the results described in the previous chapter, compound **293** was treated with boron tribromide to hydrolyse the vinyl sulfide moiety and cleave the benzyl group (Scheme 4.7). Exposure of alcohol **297** to triflic acid furnished the oxazepane ring in 33% yield after two steps.



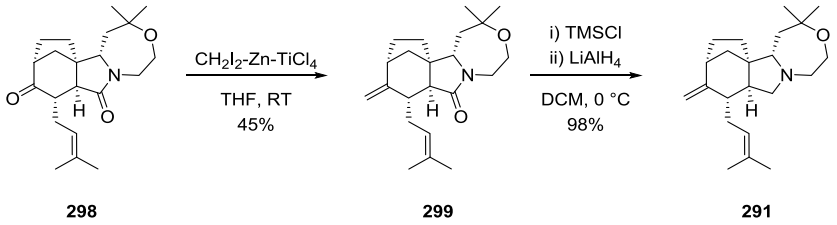
Scheme 4.7 Formation of the oxazepane ring from **292**

The prenyl chain was added after deprotonation of **292** with LHMDS to give **298** in a modest 40% yield (Scheme 4.8). Despite the back face of **292** being more hindered, due to the new orientation of the stereocentre at the α-position of the tertiary amine, compound **298** was isolated as a single diastereosiomer. This was confirmed by the coupling constant between H-3 and H-4 (J = 6.5 Hz) being identical in **298** and **63**.



Scheme 4.8 Installation of the prenyl chain from **292**

To complete the synthesis, olefination of ketone **298** was performed under Takai conditions and the amide moiety in **299** was reduced with trimethylsilyl chloride and lithium aluminium hydride to deliver 8-epi-concavine **291** (Scheme 4.9).

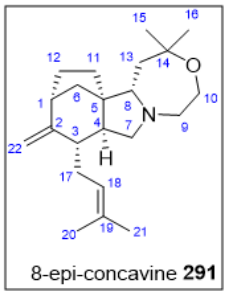


Scheme 4.9 Takai olefination on **298** and amide reduction to form 8-epi-concavine **291**

The ^{1}H- and ^{13}C NMR data of 8-epi-concavine **291** were collected and compared with the reported data for concavine (Table 4.5).

^{1}H $CDCl_3$

	Reported	8-epi-concavine **291**	Δ ppm
1	2.88	2.73	0.15
2			
3	2.27	2.1	0.17
4	1.77	1.58	0.19
5			
6a	1.06	1.16	-0.1
6b	2.07	1.49	0.58
7a	2.78	1.87	0.91
7b	3.39	3.26	0.13
8	3.13	2.49	0.64
9a	2.63	2.3	0.33
9b	3.39	3.06	0.33
10a	3.63	3.65	-0.02
10b	4.08	3.79	0.29
11a	1.41	1.34	0.07
11b	1.5	1.34	0.16
12a	1.5	1.34	0.16
12b	1.95	2.1	-0.15
13a	1.5	1.58	-0.08
13b	2.27	1.78	0.49
14			
15	1.26	1.21	0.05
16	1.18	1.18	0
17a	2.17	2.22	-0.05
17b	2.23	2.22	0.01
18	5.08	5.1	-0.02
19			
20	1.61	1.61	0
21	1.69	1.66	0.03
22a	4.72	4.68	0.04
22b	4.85	4.79	0.06



0.1 - 0.3
0.3 - 0.5
> 0.5

^{13}C $CDCl_3$

	Reported	8-epi-concavine **291**	Δ ppm
1	41.91	40.66	1.25
2	155.52	171.1	-15.58
3	40.93	39.77	1.16
4	49.3	48.3	1
5	52.99	52.28	0.71
6	30.28	35	-4.72
7	60.46	62.75	-2.29
8	65.9	65.17	0.73
9	57.82	58.35	-0.53
10	60.46	62.05	-1.59
11	33.41	33.57	-0.16
12	33.12	32.39	0.73
13	39.07	43.19	-4.12
14	74.75	74.93	-0.18
15	27.05	27.64	-0.59
16	28.37	29.1	-0.73
17	30.28	28.3	1.98
18	122.39	122.07	0.32
19	132.42	148.7	-16.28
20	17.99	18	-0.01
21	25.8	25.84	-0.04
22	108.08	105.83	2.25

0.5 - 1.0
1.0 - 1.5
> 1.5

Table 4.5 ^{1}H- and ^{13}C NMR data of 8-epi-concavine **291** compared with reported concavine

Unfortunately, inverting the configuration at the α-position of the tertiary amine did not reduce the chemical-shift differences with the reported data. The main deviations were, once again, observed around the tertiary amine. The chemical shift difference for H-7a and H-8 was more than 0.5 ppm and a 0.3 ppm deviation was observed for H-9 and H-10b.

In the ^{13}C NMR spectrum, the new stereocentre had a dramatic impact on C-2 and C-19 which resulted in shifts of more than 15 ppm. Carbons C-6 and C-13 were also greatly affected with a chemical shift difference compared to the reported data of more than 4 ppm.

The synthesis of 8-epi-concavine **291** did not solve the mismatch with the original data. Reversing the orientation of the stereocentre had a strong impact on the chemical shifts but it only increased the differences with the reported concavine.

4.3. Analysis of the original concavine extract

At this stage, contact was made with the Italian team who isolated concavine and a sample of the natural product was received. NMR analysis was performed at the University of Birmingham using chloroform-*d* as the solvent and both ^{1}H- and ^{13}C NMR spectra were in accordance with the data reported for concavine. However, the sample contained some impurities as well as DCM and purification by column chromatography with a 1:1 mixture of ethyl acetate and hexane was undertaken. To our surprise the ^{1}H NMR spectrum of the purified concavine did not match the spectrum of the crude material and formed a perfect match with the ^{1}H NMR spectrum of the concavine synthesised in Birmingham (Figure 4.2).

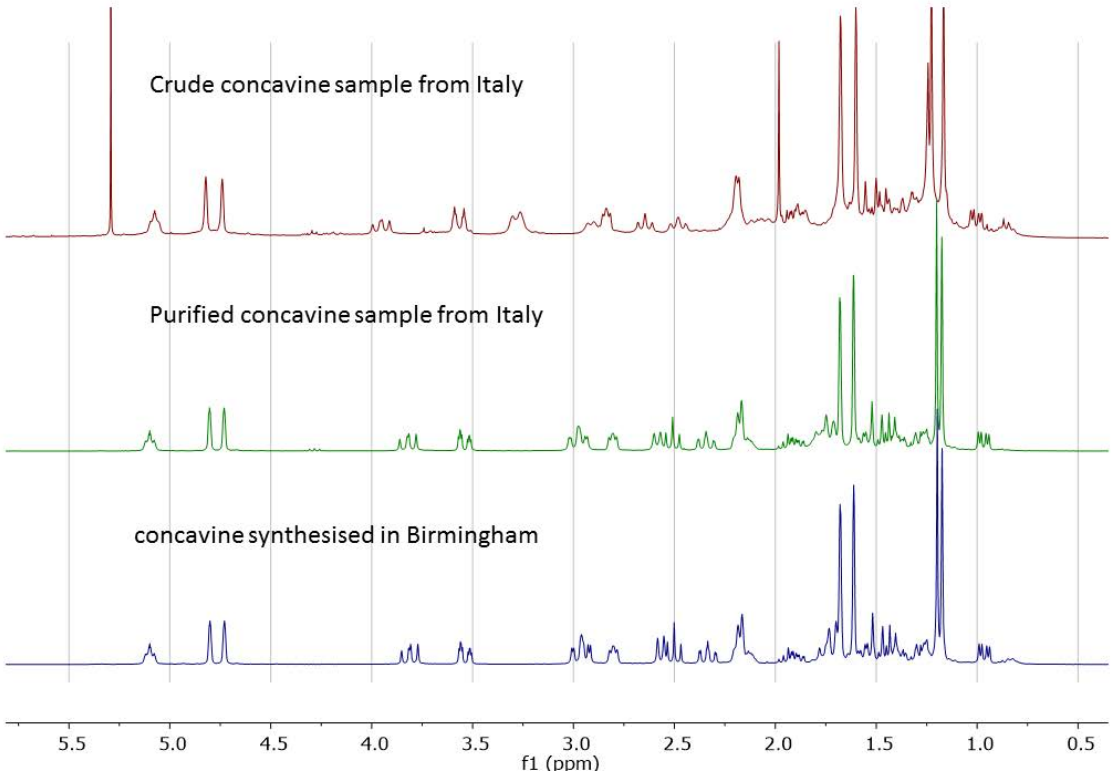
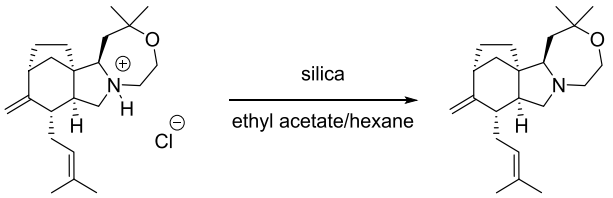


Figure 4.2 ^{1}H NMR spectra of crude, purified and synthesised concavine in chloroform-*d*

To explain this unexpected outcome, the hypothesis that concavine could have been isolated as a salt, different than HCl, was reinvestigated. To understand if a salt version of concavine could

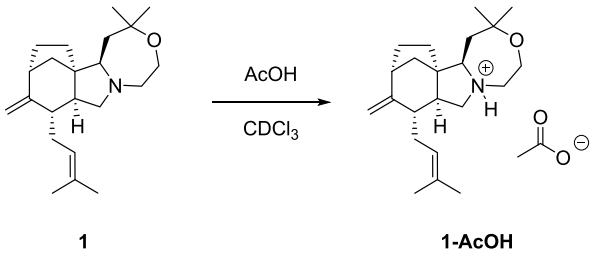
be cleaved on silica, **1-HCl** was filtered through a short column of silica and the free base **1** was collected (Scheme 4.10).



Scheme 4.10 Formation of **1** from **1-HCl**

In addition, it was found that **1-HCl** and **1** and the crude sample of concavine from Italy had the same R_f on TLC.

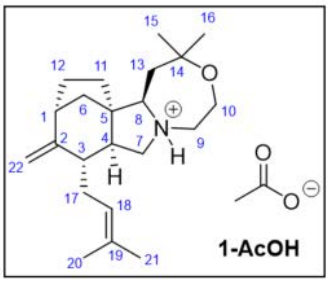
The ^{13}C NMR spectrum and ^{1}H NMR spectrum of the crude concavine sample received from Italy displayed an extra methyl resonance at 22.8 and 2.0 ppm respectively, indicating the possible presence of an acetate counter anion. To investigate this further, the AcOH salt of synthesised concavine was formed as delineated in Scheme 4.11.



Scheme 4.11 Formation of **1-AcOH**

Complete assignment for the ^{1}H- and ^{13}C NMR spectra was performed for **1-AcOH** and comparison with the original data is reported in Table 4.6.

	CDCl₃		
	Reported	1-AcOH	Δ ppm
1	2.88	2.86	0.02
2			
3	2.27	2.21	0.06
4	1.77	1.75	0.02
5			
6a	1.06	1.04	0.02
6b	2.07	1.94	0.13
7a	2.78	2.72	0.06
7b	3.39	3.57	-0.18
8	3.13	3.11	0.02
9a	2.63	2.54	0.09
9b	3.39	3.51	-0.12
10a	3.63	3.57	0.06
10b	4.08	4.03	0.05
11a	1.41	1.41	0
11b	1.5	1.47	0.03
12a	1.5	1.41	0.09
12b	1.95	1.92	0.03
13a	1.5	1.54	-0.04
13b	2.27	2.31	-0.04
14			
15	1.26	1.25	0.01
16	1.18	1.17	0.01
17a	2.17	2.21	-0.04
17b	2.23	2.21	0.02
18	5.08	5.08	0
19			
20	1.61	1.6	0.01
21	1.69	1.6	0.09
22a	4.72	4.75	-0.03
22b	4.85	4.84	0.01



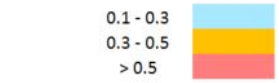
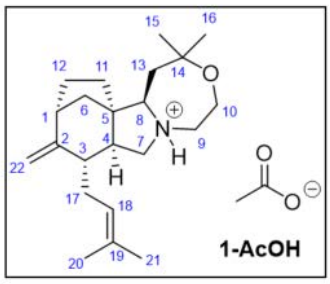


Table 4.6 ^{1}H NMR comparison between reported concavine and **1-AcOH** in $CDCl_3$

A first look at the data showed the chemical shifts for **1-AcOH** were closer to the original data compared to the free amine as no major or medium deviations were seen. The 0.5 ppm deviation observed for H-8 and H-13a in the free base spectrum was reduced to less than 0.04 ppm. Protons H-6b, H-7 and H-9 also had their chemical shift differences significantly reduced.

The ^{13}C NMR spectrum also confirmed that the data were closer to the reported concavine with the acetate salt (Table 4.7). All the chemical-shift deviations observed for synthesised concavine decreased with **1-AcOH**. Carbons C-7, C-8 and C-9, directly bound to the protonated tertiary amine, exhibited deviations reduced to less than 0.6 ppm with the original data. C-2 and C-10 also saw their deviations significantly diminished and only C-13 presented a Δ ppm higher than 0.8 ppm.

	CDCl3		
	Reported	1-AcOH	Δ ppm
1	41.91	42.01	-0.1
2	155.52	155.1	0.42
3	40.93	40.51	0.42
4	49.3	49.02	0.28
5	52.99	52.72	0.27
6	30.28	30.14	0.14
7	60.46	59.81	0.65
8	65.9	66.21	-0.31
9	57.82	57.36	0.46
10	60.46	59.7	0.76
11	33.41	33.46	-0.05
12	33.12	33	0.12
13	38.48	37.53	0.95
14	74.75	74.71	0.04
15	27.05	26.82	0.23
16	28.37	28.19	0.18
17	30.28	30.29	-0.01
18	122.39	122.1	0.29
19	132.42	132.7	-0.28
20	17.99	18	-0.01
21	25.8	25.81	-0.01
22	108.08	108.4	-0.32



0.5 - 1.0
1.0 - 1.5
> 1.5

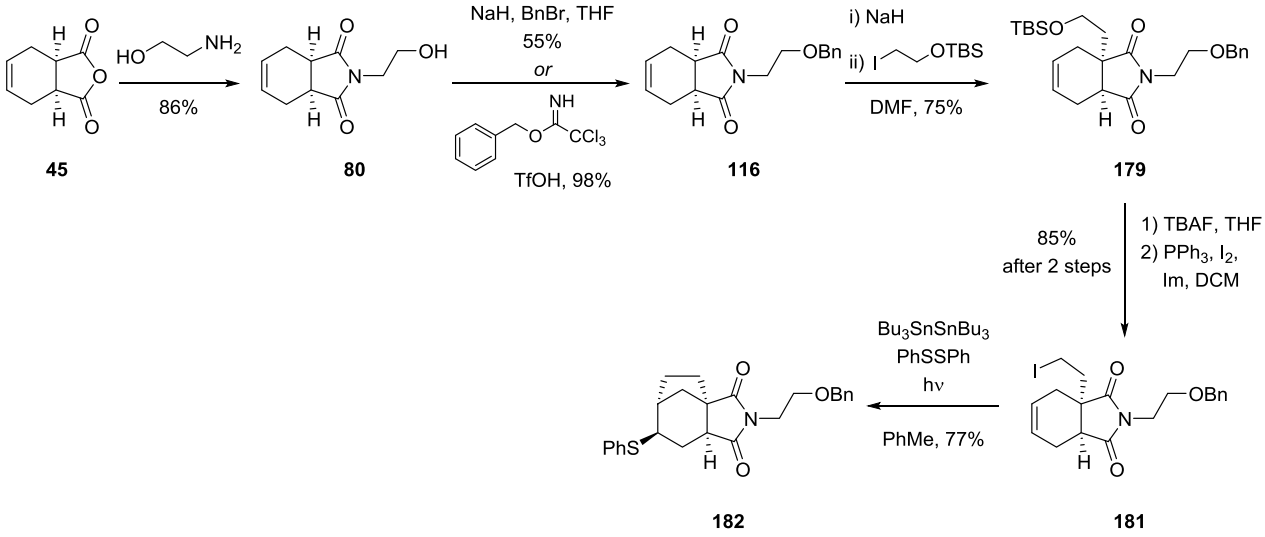
Table 4.7 ^{13}C NMR comparison between reported concavine and **1-AcOH** in $CDCl_3$

The deshielding effect, only observed in the ^{1}H NMR spectrum, created by the protonation of the tertiary amine was weaker with the acetate as a counterion compared to the chloride counterion and therefore gave a closer match with the original data.

In conclusion, it is now clear that concavine was isolated as a salt and not as a free amine. The purification of the original sample from Italy gave conclusive ^{1}H- and ^{13}C NMR spectra that matched the concavine synthesised in Birmingham. In addition, the work shown in this chapter demonstrated that a salt of concavine can be easily cleaved by filtration through silica. The two different counterions investigated had significant influence on the chemical shifts and the acetate salt gave data with minimal mismatches compared to the original data.

Chapter 5 Conclusions and Future Work

Several synthetic routes and strategies were attempted to successfully complete the first total synthesis of concavine in seventeen steps in a 3% overall yield from anhydride **45**. The first challenge in the synthesis of concavine was the formation of the five membered ring which was achieved in six steps through the installation of a functionalised alkyl chain and a radical cyclisation (Scheme 5.1).

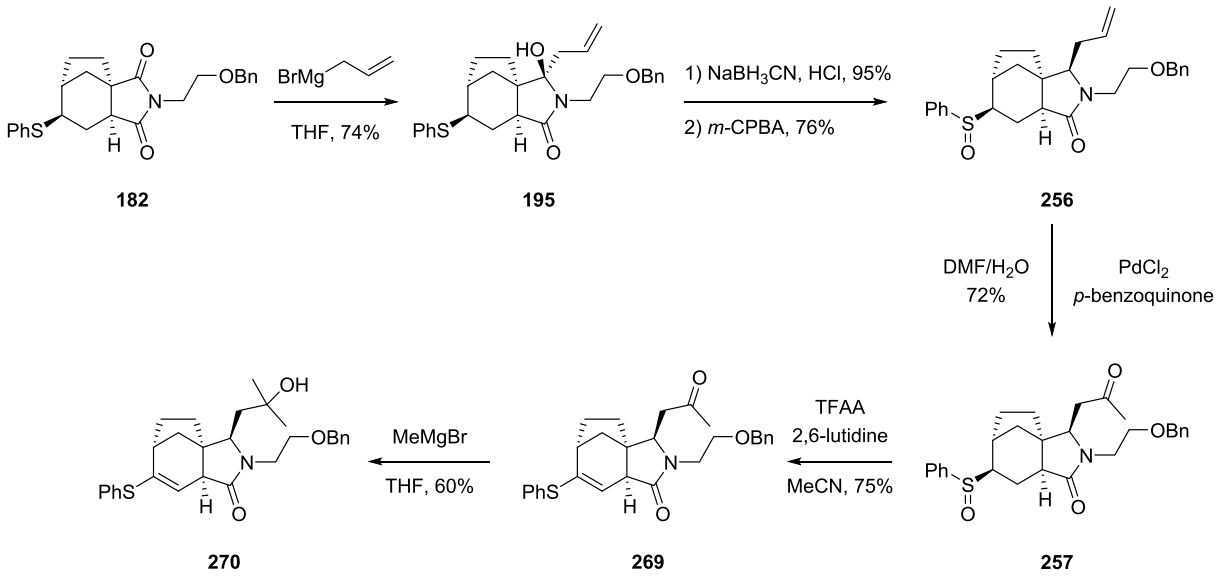


Scheme 5.1 Synthesis of intermediate **182** from **45**

The formation of compound **179** proved to be a key step as the presence of a TBS-protected alcohol allowed the synthesis of several intermediates to form the five-membered ring. Many conditions were screened to achieve this transformation and finally a radical cyclisation using hexabutylditin and phenyl disulfide was developed to deliver **182** in 77% yield.

Sodium hydride was used as a base to synthesise **179**, leading to a synthesis of racemic **1**, however chiral base methodologies previously developed in the group could be applied to this step to achieve an enantioselective synthesis.

The next major problem to solve was the installation of the oxazepane ring precursor in the desired *anti*-configuration with respect to the newly formed two-carbon bridge (Scheme 5.2).

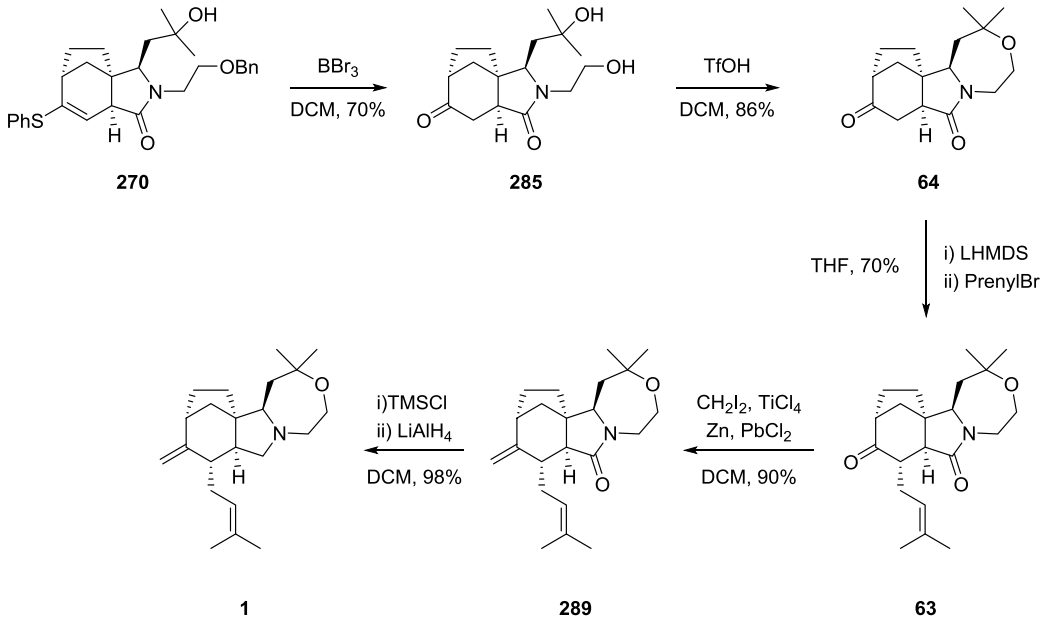


Scheme 5.2 Synthesis of intermediate **270** from **182**

The desired regioselectivity was obtained when an allyl group was added to imide **182** using a Grignard reaction to form **195** in 74% yield. Interestingly, our first attempts using a branched allyl chain showed addition to the less hindered carbonyl. The sequence to set up the allyl chain in the desired configuration was obtained after a Grignard addition to **182** followed by reduction of the resulting hemiaminal moiety. Reversing the order of addition led to the formation of the other diastereoisomer.

Oxidation of the phenyl sulfide in **195** to a sulfone allowed us to access the core structure of concavine. Unfortunately, further efforts to obtain a ketone *via* oxidative desulfonylation were unsuccessful. Alternatively, using sulfoxide **256**, a Pummerer rearrangement was attempted to obtain the corresponding ketone at this position, however vinyl sulfide **269** was isolated instead.

Many problems were encountered during the cleavage of the benzyl group present in intermediate **270** and the hydrolysis of the vinyl sulfide into a ketone (Scheme 5.3).

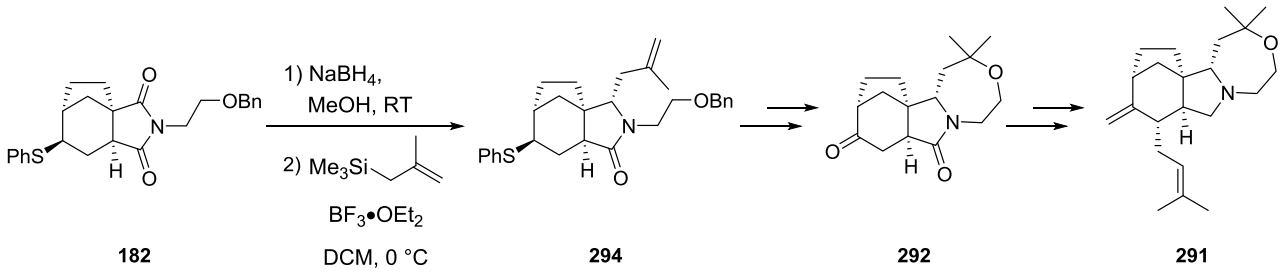


Scheme 5.3 Synthesis of concavine (**1**)

Pleasingly, it was found that boron tribromide was able to effect both transformations to furnish compound **285** in good yield. The oxazepane ring was then assembled using triflic acid to give the completed core structure of concavine in 86% yield. The last challenge in the synthesis of **1** was to introduce the prenyl chain in the desired equatorial position. As expected from previous results, the fixed three-dimensional shape of intermediate **64** allowed control of the approach of the electrophile to yield **63** as a single diastereoisomer. To complete the total synthesis, ketone **63** was treated with the Takai conditions giving the desired *exo* double bond in high yield. The amide group was then reduced with lithium aluminium hydride after activation of the carbonyl with trimethylsilyl chloride to deliver concavine (**1**).

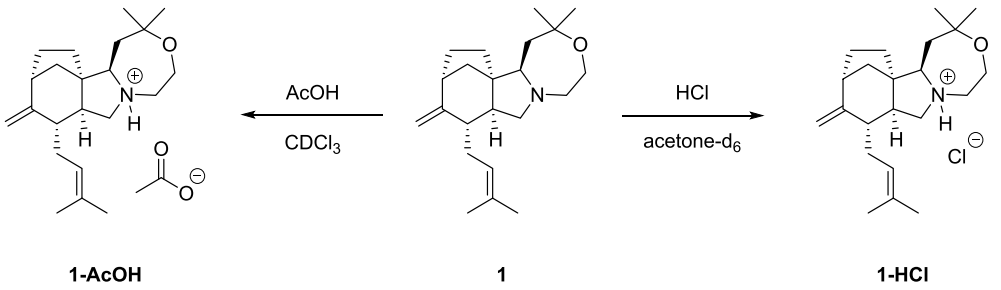
Unfortunately, the NMR data collected for **1** did not match the data reported for concavine as published by Nasini and co-workers. The synthesis of 8-epi-convavine **291**, with the

stereocentre at carbon eight inverted, was undertaken using a modification of the above route from intermediate **182**. However, the data obtained did not match that reported (Scheme 5.4).



Scheme 5.4 Synthesis of 8-epi-concavine **291** from **182**

Another idea to match the data of **1** with that reported for concavine was to investigate protonating the tertiary amine to form various salt derivatives. This was carried out using acetic acid in chloroform-d and hydrochloric acid in acetone-d_6 (Scheme 5.5).



Scheme 5.5 Formation of **1-AcOH** and **1-HCl** from **1**

The data collected for **1-AcOH** and **1-HCl** showed a deshielding effect on the chemical shift of most of the protons which was stronger in the presence of the chloride counterion compared to the acetate counterion. The data for **1-HCl** still presented some medium and major deviations compared to the original data but with **1-AcOH**, a closer match to the literature was obtained. These results make us believe that the data reported for concavine correspond to a salt version of the natural product and not the free amine. The formation of other salts could be investigated

to find the correct counterion that was in the sample of concavine isolated by Nasini and co-workers which would then perfectly match the data reported.

Chapter 6 Experimental section

Unless stated, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Anhydrous THF, MeOH, MeCN, Et_2O and DCM were collected from a PureSolv^{TM} solvent purification system. All other solvents and reagents were used as received from commercial suppliers unless otherwise stated.

NMR data were recorded on a Bruker AVIII300 (^{1}H = 300 MHz, T = 295.0 K) or AVIII400 (^{1}H = 400 MHz, ^{13}C = 101 MHz, T = 294.3 K) spectrometer. Spectra were recorded in chloroform-*d* or acetone-d_6 and calibrated on the solvent signal. For spectra in chloroform-*d*, δ_H = 7.26 ppm and δ_C = 77.16 ppm were used as references. For spectra in acetone-d_6, δ_H = 2.05 ppm and δ_C = 29.84 ppm were used as references The following abbreviations are used for multiplicity in ^{1}H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Proton-decoupled ^{13}C NMR spectra were recorded using the PENDANT pulse sequence and/or the UDEFT pulse sequence. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are shown in Hz to one decimal place.

Reaction progress was monitored by thin-layer chromatography (TLC) performed on Merck silica gel 60 F_{254} plates, which were visualised under UV light (254 nm) and potassium permanganate dip. Flash column chromatography was carried out using silica (Geduran Si 60, 40-63 µm, VWR) and the indicated solvent systems.

Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR spectrometer. Wavelengths (ν) are reported in cm^{-1}. EI mass spectra were recorded on a VG ZabSpec magnetic sector mass spectrometer and ESI mass spectra were recorded on a Micromass LCT time of flight mass spectrometer by the analytical facilities at the University of Birmingham. Melting

points were measured with a Gallenkamp melting point apparatus with an open tube and are uncorrected.

The sun lamp characteristics are “Model:SA122, ta 40C / 220-240V ~50Hz / QT-DE12 R7s MAX 500W”.

The concentration of *n*-BuLi was titrated against a solution of *N*-benzylbenzamide following a procedure published by Nielsen and co-workers.[94]

For simplicity, a different numbering scheme compared to the original numbering for concavine used by Nasini and co-workers will be followed (Figure 6.1).

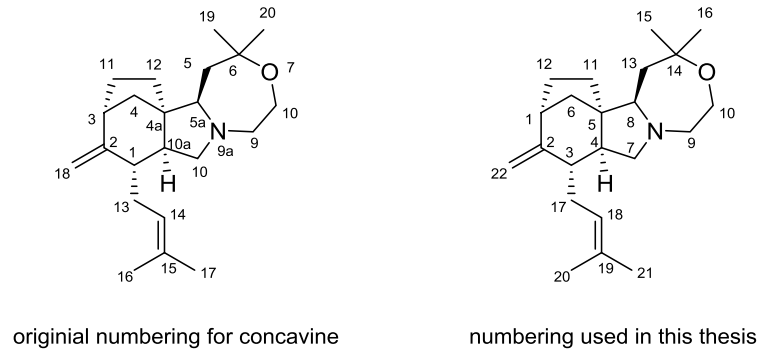
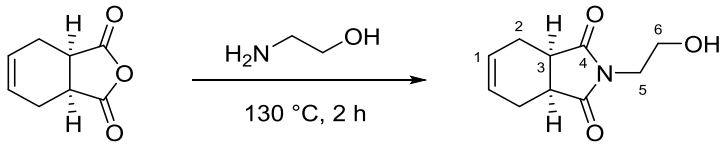


Figure 6.1 Numbering for concavine

6.1. Compounds for Chapter 2

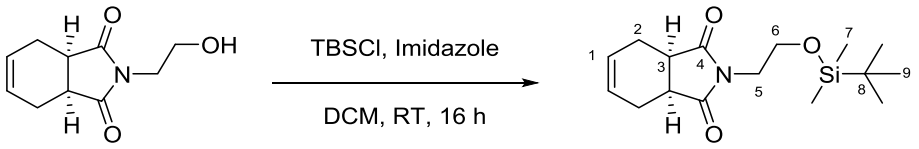
Preparation of Imide **80**[95]



45 **80**

Phthalic anhydride **45** (10.00 g, 65.00 mmol, 1.0 eq.) dissolved in ethanolamine (3.90 mL, 65.00 mmol, 1.0 eq.) was heated at 130 °C for 2 h. After being cooled to RT, the mixture was washed with an aqueous solution of HCl (1 M, 40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by recrystallisation (Et_2O) to furnish imide **80** (10.92 g, 86%) as a white powder. **m.p.** 63 – 64 °C (lit.[95] 68 – 70 °C); **IR** ν_{max}/cm^{-1} 3452, 3042, 2950, 1689, 1400, 1166, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.99 – 5.82 (m, 2H, H-1), 3.80 – 3.62 (m, 4H, H-6, H-5), 3.22 – 3.04 (m, 2H, H-3), 2.67 – 2.52 (m, 2H, H-2a), 2.33 – 2.15 (m, 2H, H-2b); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 180.9 (C=O, C-4), 127.9 (CH, C-1), 60.9 (CH_2, C-6), 42.1 (CH_2, C-5), 39.2 (CH, C-3), 23.7 (CH_2, C-2); **HRMS** (ES) found 196.0897 $[MH]^+$, requires 196.0895 for $C_{10}H_{13}NO_3$.

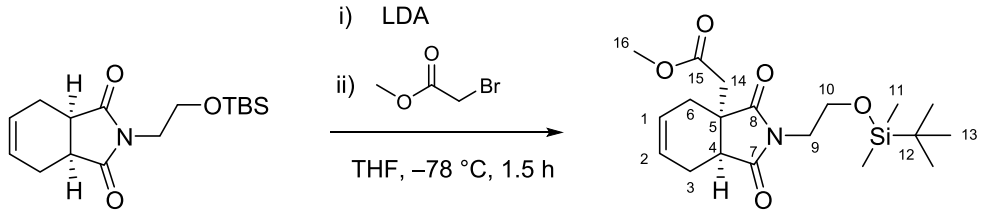
Preparation of TBS-protected alcohol **81**



80 **81**

TBSCl (2.57 mL, 7.38 mmol, 1.2 eq.) was added to a solution of **80** (1.20 g, 6.15 mmol, 1.0 eq.) and imidazole (669 mg, 9.85 mmol, 1.6 eq.) in dry DCM (5 mL) at 0 °C. The reaction mixture was stirred overnight at RT, then filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 15/1 to 12/1) to give silyl ether **81** (1.90 g, 99%) as a pale yellow oil. **IR** ν_{max} /cm^{-1} 3041, 2953, 2856, 1704, 1398, 1123, 837; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.94 – 5.83 (m, 2H, H-1), 3.79 – 3.65 (m, 2H, H-6), 3.62 – 3.57 (m, 2H, H-5), 3.08 – 3.02 (m, 2H, H-3), 2.59 – 2.53 (m, 2H, H-2a), 2.30 – 2.15 (m, 2H, H-2b), 0.88 (s, 9H, H-9), 0.04 (s, 6H, H-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.0 (C=O, C-4), 127.7 (CH, C-1), 59.2 (CH_2, C-6), 41.0 (CH_2, C-5), 39.0 (CH, C-3), 25.8 (CH_3, C-9), 23.4 (CH_2, C-2), 18.1 (C, C-8), −5.5 (CH_3, C-7); **HRMS** (ES) found 332.1760 $[MNa]^+$, requires 332.1757 for $C_{16}H_{27}NO_3NaSi$.

Preparation of methyl ester **82**

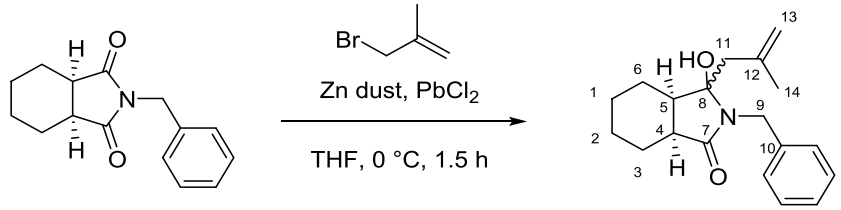


81 **82**

A solution of *n*-BuLi (1.6 M in hexanes, 1.46 mL, 2.33 mmol, 1.8 eq.) was added to a solution of diisopropylamine (0.32 mL, 2.33 mmol, 1.8 eq.) in dry THF (5 mL) at −78 °C. The mixture was stirred for 15 min at −78 °C and 15 min at 0 °C then added to a solution of imide **81** (400 mg, 1.30 mmol, 1.0 eq.) in dry THF (2 mL) at −78 °C. After 1 h, methyl bromoacetate (0.50 mL, 5.2 mmol, 4.0 eq.) was added and the reaction mixture was stirred for 1.5 h at −78 °C

before being quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 7/1 to 6/1) to give ester **82** (353 mg, 72%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3039, 2954, 2857, 1737, 1702, 1108, 837, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.94 – 5.75 (m, 2H, H-2, H-1), 3.71 – 3.56 (m, 4H, H-10, H-9), 3.63 (s, 3H, H-16), 2.95 (dd, *J* = 7.0, 2.7 Hz, 1H, H-4), 2.86 (d, *J* = 17.0 Hz, 1H, H-14a), 2.70 (d, *J* = 17.0 Hz, 1H, H-14b), 2.69 – 2.62 (m, 1H, H-3a), 2.45 – 2.40 (m, 1H, H-6a), 2.28 – 2.26 (m, 1H, H-3b), 2.04 – 1.94 (m, 1H, H-6b), 0.84 (s, 9H, H-13), 0.01 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.3 (C=O, C-8), 178.8 (C=O, C-7), 170.8 (C=O, C-15), 128.3 (CH, C-2), 126.6 (CH, C-1), 59.1 (CH_2, C-10), 51.9 (CH_3, C-16), 45.4 (C, C-5), 44.4 (CH, C-4), 41.1 (CH_2, C-9), 40.6 (CH_2, C-14), 31.0 (CH_2, C-6), 25.8 (CH_3, C-13), 23.6 (CH_2, C-3), 18.1 (C, C-12), −5.5 (CH_3, C-11); **HRMS** (ES) found 404.1967 $[MNa]^+$, requires 404.1971 for $C_{19}H_{31}NO_5NaSi$.

Preparation of methylallyl **86**

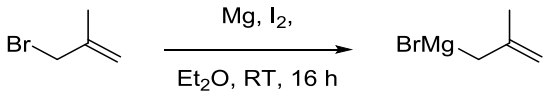


85 **86**

3-Bromo-2-methylpropene (0.82 mL, 0.82 mmol, 2.0 eq.) was added to a solution of imide **85** (100 mg, 0.41 mmol, 1.0 eq.), zinc dust (54 mg, 0.82 mmol, 2.0 eq.) and $PbCl_2$ (9 mg, 0.03 mmol, 0.07 eq.) in dry THF (0.7 mL) at 0 °C. After 1.5 h at 0 °C, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with

EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 10/1 to 5/1) to furnish hemiaminal **86** (56 mg, 46%) as a colourless oil and one major diastereoisomer[1]. **IR** ν_{max}/cm^{-1} 3327, 3068, 3031, 2950, 1664, 1443, 1416, 1081, 708; data for major stereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.14 (m, 5H, H-Ar), 4.85 – 4.80 (m, 1H, H-13a), 4.71 – 4.68 (m, 1H, H-13b), 4.58 (d, *J* = 15.0 Hz, 1H, H-9a), 4.20 (d, *J* = 15.0 Hz, 1H, H-9b) 2.60 – 2.52 (m, 1H, H-4), 2.37 (d, *J* = 15.1 Hz, 1H, H-11a), 2.22 – 2.20 (m, 1H, H-5), 2.18 (d, *J* = 15.1 Hz, 1H, H-11b), 1.76 (s, 3H, H-14), 1.72 – 1.37 (m, 4H, H-6, H-3), 1.18 – 0.78 (m, 4H, H-2, H-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2 (C=O, C-14), 141.5 (C, C-12), 139.4 (C, C-10), 128.5 (CH, C-Ar), 128.0 (CH, C-Ar), 127.1 (CH, C-Ar), 115.8 (CH_2, C-13), 92.2 (C, C-8), 44.6 (CH_2, C-11), 42.4 (CH_2, C-9), 40.9 (CH, C-4), 40.3 (CH, C-5), 23.9 (CH_3, C-14), 23.4 (CH_2, ring), 23.3 (CH_2, ring), 22.9 (CH_2, ring), 22.8 (CH_2, ring); **HRMS** (ES) found 322.1887 $[MNa]^+$, requires 322.1885 for $C_{19}H_{25}NO_2Na$.

Preparation of 2-methylallylmagnesium bromide

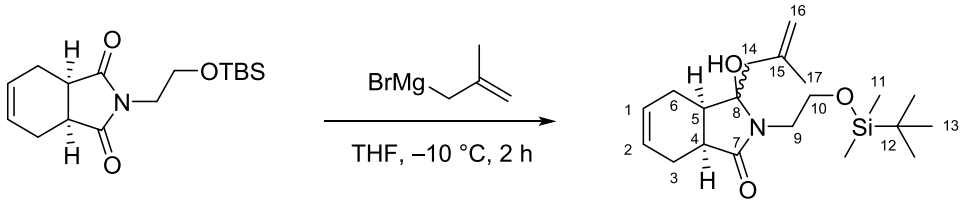


A solution of 3-bromo-2-methylpropene (0.74 mL, 7.41 mmol, 1.0 eq.) in dry Et_2O (3 mL) was added over a period of 2 h to magnesium turnings (550 mg, 22.59 mmol, 3.0 eq.) and I_2 (1 crystal) in dry Et_2O (3 mL). The reaction mixture was stirred overnight at RT. The solution

[1] Relative stereochemistry undetermined

was then transferred into a flask under inert atmosphere. Titration was achieved using menthol and 1,10-phenanthroline.

Preparation of hemiaminal **87**



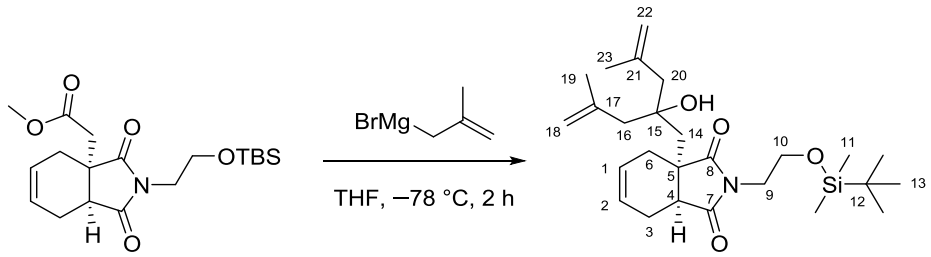
81 **87**

A solution of 2-methylallylmagnesium bromide (1.4 M in THF, 0.22 mL, 0.31 mmol, 1.1 eq.) was added to a solution of imide **81** (86 mg, 0.28 mmol, 1.0 eq.) in dry THF (0.6 mL) at −10 °C. After 2 h at −10 °C the mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 7/1 to 5/1) to furnish hemiaminal **87** (91 mg, 91%) as a colourless oil and one major diastereoisomer[2]. **IR** ν_{max}/cm^{-1} 3380, 3030, 2952, 2885; 1668, 1090, 834, 776; data for major stereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 – 5.69 (m, 2H, H-2, H-1), 4.91 – 4.88 (m, 1H, H-16a), 4.78 – 4.74 (m, 1H, H-16b), 4.61 (s, 1H, OH), 3.83 – 3.75 (m, 2H, H-10a, H-9a), 3.67 – 3.60 (m, 1H, H-9b), 3.20 – 3.08 (m, 1H, H-10b), 2.64 – 2.61 (m, 1H, H-4), 2.58 – 2.50 (m, 1H, H-5), 2.49 – 2.39 (m, 2H, H-14), 2.37 – 2.30 (m, 2H, H-6), 2.11 – 2.02 (m, 2H, H-3), 1.81 (s, 3H, H-17), 0.94 (s, 9H, H-13), 0.11 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C=O, C-7), 141.3

[2] Relative stereochemistry undetermined

(C, C-15), 126.3 (CH, C-1), 125.6 (CH, C-2), 115.6 (CH_2, C-16), 90.8 (C, C-8), 61.4 (CH_2, C-10), 46.0 (CH_2, C-14), 41.8 (CH_2, C-9), 38.7 (CH, C-4), 38.5 (CH, C-5), 25.9 (CH_3, C-13), 24.0 (CH_3, C-17), 23.3 (CH_2, C-6), 21.3 (CH_2, C-3), 18.3 (C, C-12), −5.4 (CH_3, C-11); **HRMS** (ES) found 388.2283 $[MNa]^+$, requires 388.2284 for $C_{20}H_{35}NO_3NaSi$.

Preparation of compound **96**

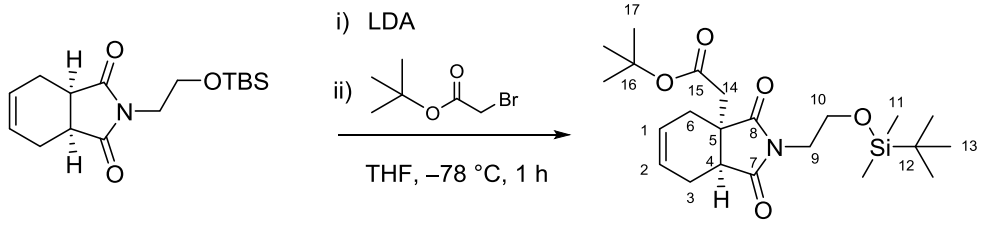


82 **96**

A solution of 2-methylallylmagnesium bromide (1.33 M in THF, 0.13 mL, 0.17 mmol, 1.1 eq.) was added to a solution of **82** (60 mg, 0.16 mmol, 1.0 eq.) in dry THF (1 mL) at −78 °C. After 2 h at −78 °C the mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 7/1 to 5/1) to furnish alcohol **96** (30 mg, 40%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3380, 3030, 2952, 2885, 1735, 1701, 1090, 834, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 – 5.78 (m, 1H, H-2), 5.69 – 5.63 (m, 1H, H-1), 4.95 (dt, *J* = 17.0, 1.8 Hz, 2H, H-22a, H-18a), 4.76 (dt, *J* = 13.5, 1.8 Hz, 2H, H-22b, H-18b), 3.70 – 3.62 (m, 2H, H-10), 3.43 – 3.29 (m, 2H, H-9), 2.78 – 2.62 (m, 2H, H-6a, H-3a), 2.56 – 2.47 (m, 2H, H-16a, H-4), 2.42 (d, *J* = 18.2 Hz, 1H, H-14a), 2.37 (d, *J* = 18.2 Hz, 1H, H-14b), 2.33 – 2.21 (m, 3H, H-20a, H-16b, H-3b), 2.17 – 2.10 (m, 1H, H-6b), 2.05 (d, *J* = 13.8

Hz, 1H, H-20b), 1.81 (s, 3H, H-19), 1.80 (s, 3H, H-23), 0.89 (s, 9H, H-13), 0.05 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.6 (C=O, C-8), 172.7 (C=O, C-7), 141.5 (C, C-17), 141.3 (C, C-21), 125.8 (CH, C-2), 123.7 (CH, C-1), 116.6 (CH_2, C-18), 116.0 (CH_2, C-22), 84.3 (C, C-15), 61.8 (CH_2, C-10), 48.4 (CH_2, C-14), 47.9 (CH_2, C-16, CH, C-4), 43.5 (CH_2, C-20), 43.3 (C, C-5), 41.7 (CH_2, C-9), 36.0 (CH_2, C-6), 27.0 (CH_2, C-3), 25.9 (CH_3, C-13), 24.5 (CH_3, C-19), 24.4 (CH_3, C-20), 18.2 (C, C-12), −5.4 (CH_3, C-11); **HRMS** (ES) found 462.2961 $[MH]^+$, requires 462.2959 for $C_{26}H_{44}NO_4Si$.

Preparation of *tert*-butyl ester **97**

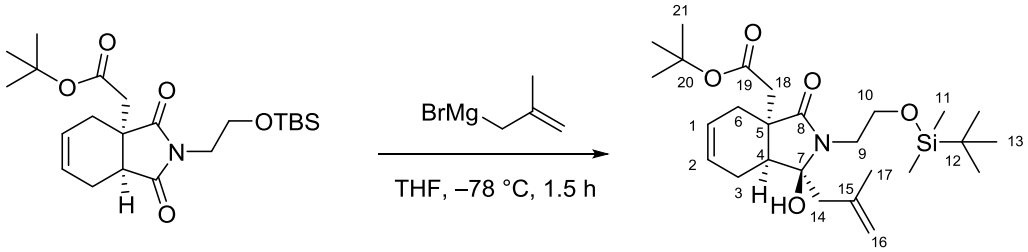


81 **97**

A solution of *n*-BuLi (1.6 M in hexanes, 1.21 mL, 1.94 mmol, 1.5 eq.) was added dropwise to a solution of diisopropylamine (0.27 mL, 1.94 mmol, 1.5 eq.) in dry THF (3 mL) at −78 °C. The mixture was stirred for 15 min at −78 °C and 15 min at 0 °C then added to a solution of imide **81** (411 mg, 1.33 mol, 1.0 eq.) in dry THF (2 mL) at −78 °C. After 1 h, *tert*-butyl bromoacetate (0.57 mL, 3.87 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 1 h at −78 °C before being quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 20/1 to 15/1) to give ester **97** (494 mg,

88%) as a white powder. **m.p.** 70 – 71 °C; **IR** ν_{max}/cm^{-1} 2955, 2856, 1731, 1705, 1153, 838, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.94 – 5.86 (m, 1H, H-2), 5.85 – 5.77 (m, 1H, H-1), 3.69 – 3.64 (m, 2H, H-10), 3.63 – 3.57 (m, 2H, H-9), 2.99 – 2.93 (m, 1H, H-4), 2.80 (d, *J* = 15.1 Hz, 1H, H-14a), 2.71 – 2.63 (m, 1H, H-3a), 2.56 (d, *J* = 15.1 Hz, 1H, H-14b), 2.50 – 2.42 (m, 1H, H-6a), 2.28 – 2.19 (m, 1H, H-3b), 2.02 – 1.95 (m, 1H, H-6b), 1.39 (s, 9H, H-17), 0.86 (s, 9H, H-13), 0.03 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.5 (C=O, C-8), 179.1 (C=O, C-7), 169.5 (C=O, C-15), 127.9 (CH, C-2), 126.9 (CH, C-1), 81.7 (C, C-16), 59.1 (CH_2, C-10), 45.7 (C, C-5), 44.4 (CH, C-4), 42.2 (CH_2, C-14), 41.4 (CH_2, C-9), 31.3 (CH_2, C-6), 28.0 (CH_3, C-17), 25.8 (CH_3, C-13), 23.8 (CH_2, C-3), 18.2 (C, C-12), −5.5 (CH_3, C-11); **HRMS** (ES) found 446.6252 $[MNa]^+$, requires 446.6250 for $C_{22}H_{37}NO_5NaSi$.

Preparation of hemiaminal **98**

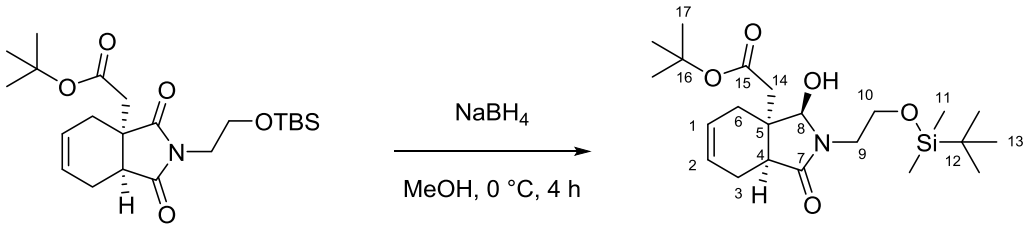


97 **98**

A solution of 2-methylallylmagnesium bromide (0.7 M in THF, 0.19 mL, 0.14 mmol, 1.3 eq.) was added to a solution of **97** (49 mg, 0.11 mmol, 1.0 eq.) in dry THF (1 mL) at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C and then quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 6/1 to

4/1) to provide hemiaminal **98** (41 mg, 80%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3366, 2988, 2904, 1677, 1393, 1251, 1066; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 – 5.73 (m, 1H, H-2), 5.70 – 5.63 (m, 1H, H-1) 4.88 – 4.74 (m, 2H, H-16), 4.60 (s, 1H, OH), 4.03 – 3.96 (m, 1H, H-9a), 3.68 – 3.80 (m, 2H, H-10), 3.17 – 3.08 (m, 1H, H-9b), 2.66 – 2.61 (m, 2H, H-18a, H-14a), 2.57 – 2.51 (m, 1H, H-4), 2.46 – 2.39 (m, 2H, H-18b, H-14b), 2.37 – 2.30 (m, 1H, H-3a), 2.30 – 2.24 (m, 1H, H-6a), 2.17 – 2.06 (m, 1H, H-3b), 2.02 – 1.95 (m, 1H, H-6b), 1.81 (s, 3H, H-17), 1.39 (s, 9H, H-21), 0.89 (s, 9H, H-13), 0.09 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.5 (C=O, C-8), 170.6 (C=O, C-19), 141.4 (C, C-15), 126.7 (CH, C-2), 123.1 (CH, C-1), 115.7 (CH_2, C-16), 89.8 (C, C-7), 80.4 (C, C-20), 62.1 (CH_2, C-10), 46.7 (CH_2, C-14), 42.6 (C, C-5), 42.0 (CH_2, C-9), 40.8 (CH_2, C-18), 39.5 (CH, C-4), 32.0 (CH_2, C-6), 28.1 (CH_3, C-21), 25.9 (CH_3, C-13), 23.7 (CH_3, C-17), 21.1 (CH_2, C-3), 18.4 (C, C-12), −5.5 (CH_3, C-11); **HRMS** (ES) found 502.7331 $[MNa]^+$, requires 502.7330 for $C_{26}H_{45}NO_5NaSi$.

Reduction of imide **97**

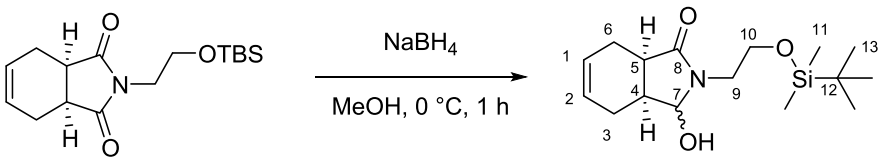


97 **99**

Sodium borohydride (19 mg, 0.50 mmol, 5.0 eq.) was slowly added to a solution of **97** (44 mg, 0.1 mmol, 1.0 eq.) in MeOH (1 mL) at 0 °C. The mixture was stirred for 4 h at 0 °C then quenched with water. The aqueous layer was extracted with EtOAc (3 × 3 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The

crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 6/1 to 3/1) to provide hemiaminal **99** (11 mg, 26%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3360, 2957, 2860, 1706, 1154, 839; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.66 – 5.57 (m, 2H, H-2, H-1), 5.09 (d, *J* = 5.3 Hz, 1H, H-8), 4.31 (d, *J* = 5.3 Hz, 1H, OH), 3.70 – 3.53 (m, 3H, H-10, H-9a), 3.27 – 3.20 (m, 1H, H-9b), 2.53 – 2.45 (m, 2H, H-4, H-3a), 2.42 (d, *J* = 14.6 Hz, 1H, H-14a), 2.27 (d, *J* = 14.6 Hz, 1H, H-14b), 2.19 – 2.10 (m, 1H, H-6a, H-3b), 1.83 – 1.75 (m, 1H, H-6b), 1.33 (s, 9H, H-17), 0.80 (s, 9H, H-13), -0.01 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.4 (C=O, C-7), 171.0 (C=O, C-15), 125.0 (CH, C-2), 124.5 (CH, C-1), 87.4 (CH, C-8), 81.2 (C, C-16), 61.8 (CH_2, C-10), 45.1 (C, C-5), 43.7 (CH, C-4), 42.8 (CH_2, C-9), 41.7 (CH_2, C-14), 28.1 (CH_3, C-17), 25.8 (CH_3, C-13), 25.7 (CH_2, C-6), 21.4 (CH_2, C-3), 18.2 (C, C-12), -5.5 (C, C-11); **HRMS** (ES) found 448.2597 $[MNa]^+$, requires 448.2595 for $C_{22}H_{39}NO_5SiNa$.

Reduction of imide **81**

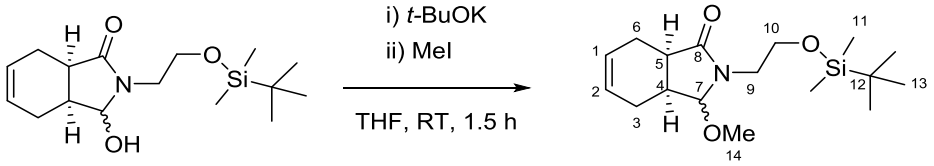


81 **114**

Sodium borohydride (200 mg, 5.29 mmol, 5.0 eq.) was added portionwise over 5 min to a solution of imide **81** (327 mg, 1.06 mmol, 1.0 eq.) in MeOH (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and quenched with water. The aqueous layer was extracted with EtOAc (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give hemiaminal **114** (324 mg, 99%) as a white powder

and one major diastereoisomer[3]. **m.p.** 53 – 55 °C; **IR** ν_{max}/cm^{-1} 3336, 3029, 2930, 2856, 1669, 1463, 1256, 1103, 837, 777; data for major stereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 – 5.69 (m, 2H, H-2, H-1), 5.07 (dd, *J* = 5.1, 3.8 Hz, 1H, H-7), 4.48 (d, *J* = 3.8 Hz, 1H, OH), 3.82 (ddd, *J* = 14.5, 3.7, 2.5 Hz, 1H, H-9a), 3.71 – 3.63 (m, 2H, H-10), 3.07 (ddd, *J* = 14.5, 8.4, 3.7 Hz, 1H, H-9b), 2.56 – 2.49 (m, 1H, H-4), 2.48 – 2.42 (m, 1H, H-5), 2.39 – 2.29 (m, 1H, H-6a), 2.25 – 2.19 (m, 1H, H-6b), 2.17 – 2.10 (m, 2H, H-3), 0.85 (s, 9H, H-13), 0.04 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.4 (C=O, C-8), 126.3 (CH, C-2), 125.0 (CH, C-1), 85.5 (CH, C-7), 62.2 (CH_2, C-10), 44.0 (CH_2, C-9), 38.2 (CH, C-5), 34.7 (CH, C-4), 25.8 (CH_3, C-13), 24.2 (CH_2, C-6), 20.7 (CH_2, C-3), 18.3 (C, C-12), −5.5 (CH_3, C-11); **HRMS** (ES) found 334.1815 $[MNa]^+$, requires 334.1814 for $C_{16}H_{29}NO_3NaSi$.

Preparation of the methyl ether **109**



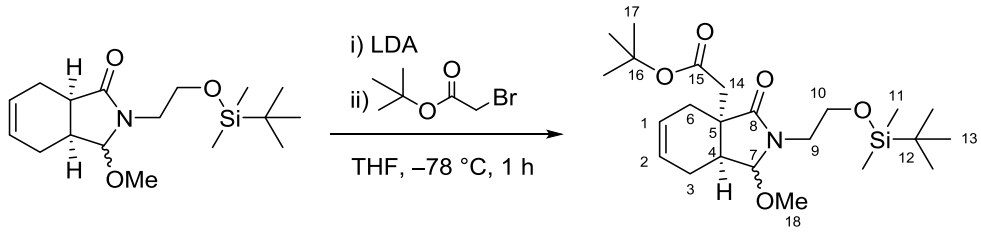
114 **109**

A solution of **114** (103 mg, 0.33 mmol, 1.0 eq.) in dry THF (0.7 mL) was added to a solution of *t*-BuOK (47 mg, 0.40 mmol, 1.2 eq.) in dry THF (0.7 mL) at 0 °C. After 40 min at 0 °C, MeI (31 μL, 0.49 mmol, 1.5 eq.) was added. The reaction mixture was warmed to RT and stirred for 1.5 h before being quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 4 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was

[3] Relative stereochemistry undetermined

purified by flash column chromatography (gradient: petrol/EtOAc = 7/1 to 6/1) to provide methyl ether **109** (55 mg, 51%) as a pale yellow oil and one major diastereoisomer[4]. **IR** ν_{max}/cm^{-1} 3029, 2952, 2857, 1706, 1438, 1254, 1100, 835, 777; data for major stereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 – 5.63 (m, 2H, H-2, H-1), 4.61 (d, *J* = 0.9 Hz, 1H, H-7), 3.75 – 3.69 (m, 2H, H-10), 3.68 – 3.63 (m, 1H, H-9a), 3.36 (s, 3H, H-14), 3.23 – 3.18 (m, 1H, H-9b), 2.87 − 2.82 (m, 1H, H-5), 2.47 – 2.44 (m, 1H, H-6a), 2.44 – 2.35 (m, 1H, H-4), 2.32 – 2.22 (m, 1H, H-6b), 2.22 – 2.13 (m, 1H, H-3a), 1.89 – 1.76 (m, 1H, H-3b), 0.88 (s, 9H, H-13), 0.03 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0 (C=O, C-8), 126.7 (CH, C-2), 124.9 (CH, C-1), 96.7 (CH, C-7), 61.8 (CH_2, C-10), 54.9 (CH_3, C-14), 43.4 (CH_2, C-9), 37.1 (CH, C-5), 34.7 (CH, C-4), 25.9 (CH_3, C-13), 25.0 (CH_2, C-3), 22.0 (CH_2, C-6), 18.2 (C, C-12), −5.5 (CH_3, C-11); **HRMS** (ES) found 348.5243 $[MNa]^+$, requires 348. 5240 for $C_{17}H_{31}NO_3NaSi$.

Preparation of *tert*-butyl ester **108**



109 **108**

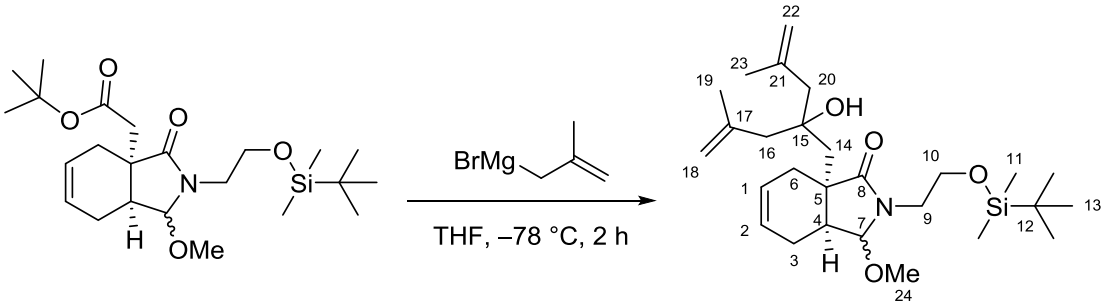
A solution of *n*-BuLi (1.6 M in hexanes, 0.82 mL, 1.31 mmol, 1.2 eq.) was added to a solution of diisopropylamine (0.19 mL, 1.37 mmol, 1.3 eq.) in dry THF (1 mL) at −78 °C. The mixture was stirred for 0.5 h at −78 °C and then transferred with a syringe into a solution of **109** (343 mg, 1.05 mmol, 1.0 eq.) in dry THF (1 mL) at −78 °C. The reaction mixture was stirred for 0.5 h at

[4] Relative stereochemistry undetermined

−78 °C before of *t*-butyl bromoacetate (0.23 mL, 1.57 mmol, 1.5 eq.) was added. After 1 h at −78 °C, the mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 8 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 8/1 to 6/1) to furnish *tert*-butyl ester **108** (363 mg, 79%) as a colourless oil and one major diastereoisomer[5]. **IR** ν_{max}/cm^{-1} 3041, 2930, 2857, 1725, 1703, 1367, 1253, 1151, 1102, 835, 777; data for major stereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 – 5.74 (m, 2H, H-2, H-1), 4.56 (d, *J* = 3.5 Hz, 1H, H-7), 3.72 – 3.62 (m, 2H, H-10), 3.61 – 3.54 (m, 1H, H-9a), 3.34 (s, 3H, H-18), 3.17 – 3.09 (m, 1H, H-9b), 2.55 – 2.53 (m, 1H, H-4), 2.52 (d, *J* = 15.1 Hz, 1H, H-14a), 2.45 (d, *J* = 15.1 Hz, 1H, H-14b), 2.31 – 2.27 (m, 1H, H-6a), 2.27 – 2.23 (m, 1H, H-3a), 2.15 – 2.07 (m, 1H, H-3b), 2.07 – 2.01 (m, 1H, H-6b), 1.40 (s, 9H, H-17), 0.83 (s, 9H, H-13), 0.00 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (C=O, C-8), 170.5 (C=O, C-15), 127.4 (CH, C-2), 126.2 (CH, C-1), 95.9 (CH, C-7), 80.8 (C, C-16), 61.3 (CH_2, C-10), 54.7 (CH_3, C-18), 45.7 (C, C-5), 42.6 (CH_2, C-9), 42.4 (CH_2, C-14), 40.6 (CH, C-4), 30.3 (CH_2, C-6), 28.1 (CH_3, C-17), 25.9 (CH_3, C-13), 25.7 (CH_2, C-3), 18.2 (C, C-12), −5.5 (CH_3, C-11); **HRMS** (ES) found 462.6682 $[MNa]^+$, requires 462.6680 for $C_{23}H_{41}NO_5NaSi$.

[5] Relative stereochemistry undetermined

Preparation of compound **110**



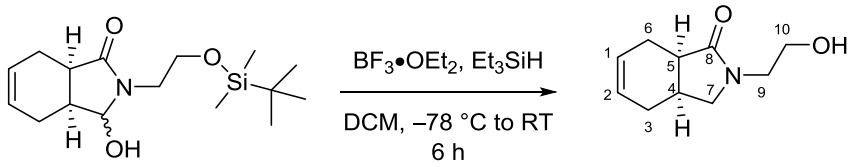
108 **110**

A solution of 2-methylallylmagnesium bromide (0.3 M in THF, 1.10 mL, 0.30 mmol, 1.2 eq.) was added to a solution of **108** (110 mg, 0.25 mmol, 1.0 eq.) in dry THF (1 mL) at −78 °C. After 2 h at −78 °C the mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 12/1 to 8/1) to furnish alcohol **110** (59 mg, 50%) as a colourless oil and one major diastereoisomer[6]. **IR** ν_{max}/cm^{-1} 3362, 2990, 2905, 1677, 1397, 1250, 1066; data for major stereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 – 5.72 (m, 2H, H-2, H-1), 4.90 – 4.85 (m, 2H, H-22a, H-18a), 4.72 – 4.66 (m, 3H, H22b, H-18b, H-7), 3.80 – 3.60 (m, 3H, H-10, H-9a), 3.42 (s, 3H, H-24), 3.24 – 3.12 (m, 1H, H-9b), 2.62 – 2.56 (m, 1H, H-4), 2.32 – 2.11 (m, 8H, H-20, H-16, H-6, H-3), 1.97 (d, *J* = 14.9 Hz, 1H, H-14a), 1.83 (s, 3H, H-23), 1.82 (s, 3H, H-19), 1.73 (d, *J* = 14.9 Hz, 1H, H-14b), 0.86 (s, 9H, H-13), 0.03 (s, 6H, H-11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.7 (C=O, C-8), 143.4 (C, C-17, C-21), 126.5 (CH, C-2), 125.6 (CH, C-1), 114.9 (CH_2, C-22), 114.8 (CH_2, C-18), 95.4 (CH, C-7), 74.2 (C, C-15), 61.0 (CH_2, C-10), 55.3 (CH_3, C-24), 50.1 (CH_2, C-14), 48.4 (CH_2, C-16), 45.6 (C, C-5), 44.2 (CH_2, C-20), 42.4 (CH_2, C-9), 41.7 (CH, C-4), 32.4 (CH_2,

[6] Relative stereochemistry undetermined

C-6), 25.9 (CH_3, C-13), 25.0 (CH_3, C-23), 24.9 (CH_3, C-19), 24.2 (CH_2, C-3), 18.2 (C, C-12), -5.5 (CH_3, C-11); **HRMS** found 500.3274 $[MNa]^+$, requires 500.3272 for $C_{27}H_{47}NO_4SiNa$

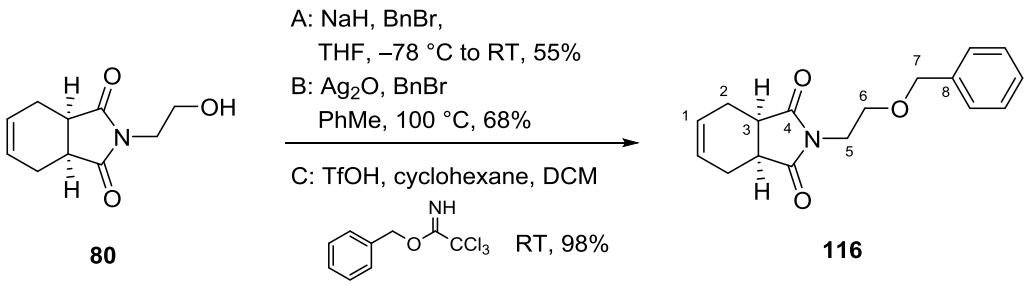
Reduction of hemiaminal **114**



114 **115**

Triethylsilane (95 µL, 0.60 mmol, 3.0 eq.) and BF_3•OEt_2 (0.12 mL, 1.00 mmol, 5.0 eq.) were successively added to a solution of **114** (62 mg, 0.20 mmol, 1.0 eq.) in dry DCM (1 mL) at −78 °C. The mixture was allowed to warm to RT and stirred for 5 h before being quenched with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to yield lactam **115** (34 mg, 94%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3382, 3027, 2905, 1662, 1488, 1437, 1064; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 – 5.67 (m, 2H, H-1, H-2), 3.79 – 3.69 (m, 2H, H-10), 3.59 (dd, *J* = 9.5, 6.1 Hz, 1H, H-7a), 3.44 – 3.39 (m, 2H, H-9), 3.39 – 3.32 (br, 1H, OH), 3.03 (dd, *J* = 9.5, 2.8 Hz, 1H, H-7b), 2.67 ("app td", *J* = 8.2, 3.1 Hz, 1H, H-5), 2.54 – 2.39 (m, 2H, H-4, H-6a), 2.32 – 2.25 (m, 1H, H-6b), 2.24 – 2.15 (m, 1H, H-3a), 1.89 – 1.81 (m, 1H, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.0 (C=O, C-8), 126.2 (CH, C-2), 125.3 (CH, C-1), 60.9 (CH_2, C-10), 54.3 (CH_2, C-7), 46.5 (CH_2, C-9), 39.8 (CH, C-5), 29.6 (CH, C-4), 26.1 (CH_2, C-6), 22.2 (CH_2, C-3); **HRMS** (ES) found 181.1102 $[MH]^+$, requires 181.1103 for $C_{10}H_{16}NO_2$.

Protection of alcohol **80**



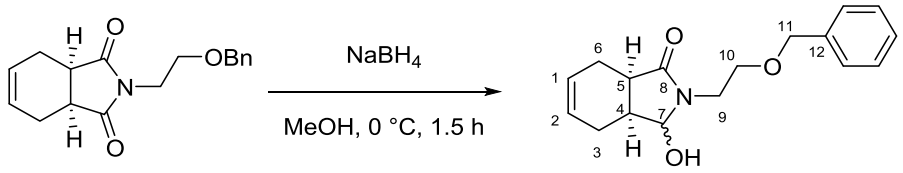
Method A: Sodium hydride (60% in mineral oil, 246 mg, 6.15 mmol, 1.2 eq.) was added to a solution of alcohol **80** (1.00 g, 5.13 mmol, 1.0 eq.) in dry THF (15 mL) at −78 °C. After 0.5 h min benzyl bromide (0.92 mL, 7.72 mmol, 1.5 eq.) was added at −78 °C. The mixture was allowed to warm to RT, stirred overnight and then quenched with water. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 3/1) to furnish benzyl ether **116** (802 mg, 55%) as a colourless oil.

Method B: Silver(I) oxide (1.54 g, 6.66 mmol, 1.3 eq.) and benzyl bromide (0.91 mL, 7.70 mmol, 1.5 eq.) were successively added to a solution of **80** (1.00 g, 5.13 mmol, 1.0 eq.) in dry PhMe (15 mL) at RT. The mixture was heated to 120 °C and stirred for 16 h. After being cooled to RT and filtered through Celite®, the crude mixture was concentrated under reduced pressure and purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to furnish benzyl ether **116** (1.00 g, 68%) as a colourless oil.

Method C: Triflic acid (27 µL, 0.31 mmol, 0.2 eq.) was added to a solution of benzyl trichloroacetimidate (0.57 mL, 3.07 mmol, 2.0 eq.) and **80** (300 mg, 1.54 mmol, 1.0 eq.) in a mixture of DCM (1 mL) and cyclohexane (2 mL) at 0 °C. After 0.5 h the reaction mixture was

warmed to RT and stirred for 2 h before being quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 2/1) to give benzyl ether **116** (1.43 g, 98%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3039, 2949, 2855, 1698, 1399; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 5H, H-Ar), 5.90 – 5.80 (m, 2H, H-1), 4.52 (s, 2H, H-7), 3.78 – 3.71 (m, 2H, H-5), 3.65 – 3.60 (m, 2H, H-6), 3.10 – 3.05 (m, 2H, H-3), 2.61 – 2.57 (m, 2H, H-2a), 2.29 – 2.20 (m, 2H, H-2b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.0 (C=O, C-4), 138.0 (C, C-8), 130.9 (CH, C-Ar), 128.4 (CH, C-Ar), 128.3 (CH, C-Ar), 127.7 (CH, C-1), 72.6 (CH_2, C-7), 66.2 (CH_2, C-6), 39.0 (CH, C-3), 38.3 (CH_2, C-5), 23.5 (CH_2, C-2); **HRMS** (ES) found 308.1270 $[MNa]^+$, requires 308.1263 for $C_{17}H_{19}NO_3Na$.

Preparation hemiaminal **118**

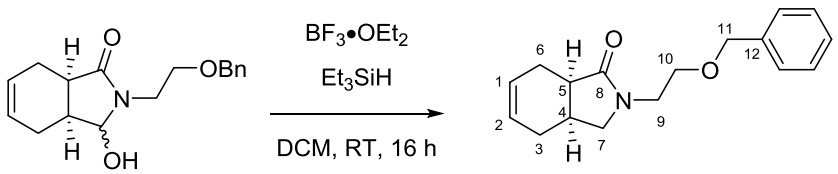


116 **118**

Sodium borohydride (311 mg, 8.24 mmol, 5.0 eq.) was added to a solution of **116** (470 mg, 1.65 mmol, 1.0 eq.) in MeOH (5 mL) at 0 °C. The mixture was stirred for 1.5 h at 0 °C and then quenched with water. The aqueous layer was extracted with DCM (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 1/1 to

0/1) to furnish hemiaminal **118** (450 mg, 95%) as a colourless oil and one major diastereoisomer[7]. **IR** ν_{max}/cm^{-1} 3355, 3029, 2928, 1667, 1454, 1095; data for major stereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.22 (m, 5H, H-Ar), 5.85 – 5.76 (m, 2H, H-2, H-1), 5.01 (dd, *J* = 5.3, 4.0 Hz, 1H, H-7), 4.51 (d, *J* = 11.8 Hz, 1H, H-11a), 4.45 (d, *J* = 11.8 Hz, 1H, H-11b), 4.21 (d, *J* = 4.0 Hz, 1H, OH), 3.81 (ddd, *J* = 14.8, 4.3, 2.4 Hz, 1H, H-9a), 3.71 – 3.52 (m, 2H, H-10), 3.22 (ddd, *J* = 14.8, 9.1, 2.4 Hz, 1H, H-9b), 2.80 – 2.64 (m, 1H, H-5), 2.54 – 2.41 (m, 2H, H-6a, H-4), 2.38 – 2.29 (m, 1H, H-3a), 2.21 – 2.09 (m, 2H, H-6b, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.6 (C=O, C-8), 136.8 (C, C-12), 128.7 (CH, C-Ar), 128.2 (CH, C-Ar), 128.0 (CH, C-Ar), 126.3 (CH, C-2), 125.0 (CH, C-1), 85.6 (CH, C-7), 73.6 (CH_2, C-11), 68.7 (CH_2, C-10), 41.6 (CH_2, C-9), 38.0 (CH, C-5), 34.6 (CH, C-4), 24.3 (CH_2, C-3), 20.7 (CH_2, C-6); **HRMS** (ES) found 310.1413 $[MNa]^+$, requires 310.1419 for $C_{17}H_{21}NO_3Na$.

Reduction of hemiaminal **118**



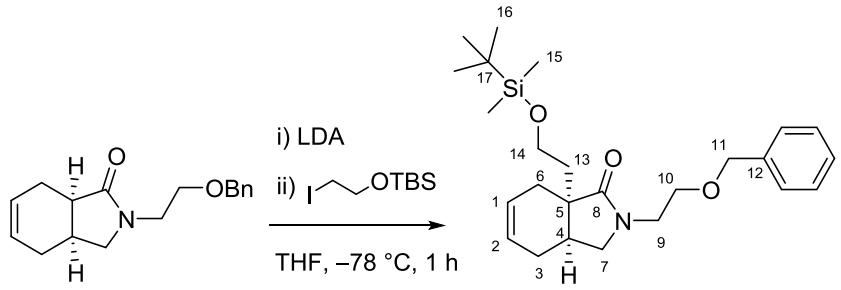
118 **119**

BF_3•OEt_2 (0.78 mL, 6.37 mmol, 3.0 eq.) and triethylsilane (1.68 mL, 10.6 mmol, 5.0 eq.) were added to a solution of **118** (610 mg, 2.12 mmol, 1.0 eq.) in dry DCM (2 mL) at −78 °C. The mixture was allowed to warm to RT and stirred overnight before being quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 ×

[7] Relative stereochemistry undetermined

5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 1/1 to 0/1) to furnish amide **119** (560 mg, 98%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3028, 2924, 2860, 1679, 1453, 1102, 1028; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H, H-Ar), 5.82 – 5.67 (m, 2H, H-2, H-1), 4.42 (s, 2H, H-11), 3.75 – 3.44 (m, 5H, H-10, H-9, H-7a), 3.02 (dd, *J* = 9.6, 2.8 Hz, 1H, H-7b), 2.64 ("app td", *J* = 8.3, 3.1 Hz, 1H, H-5), 2.51 – 2.48 (m, 1H, H-4), 2.47 – 2.42 (m, 1H, H-6a), 2.34 – 2.24 (m, 1H, H-6b), 2.22 – 2.12 (m, 1H, H-3a), 1.82 – 1.71 (m, 1H, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6 (C=O, C-8), 138.0 (C, C-12), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 127.5 (CH, C-Ar), 126.2 (CH, C-2), 125.3 (CH, C-1), 73.0 (CH_2, C-11), 68.9 (CH_2, C-10), 54.0 (CH_2, C-7), 42.7 (CH_2, C-9), 39.6 (CH, C-5), 29.5 (CH, C-4), 26.0 (CH_2, C-3), 22.2 (CH_2, C-6); **HRMS** (ES) found 272.1653 $[MH]^+$, requires 272.1651 for $C_{17}H_{22}NO_2$.

Preparation of compound **120**

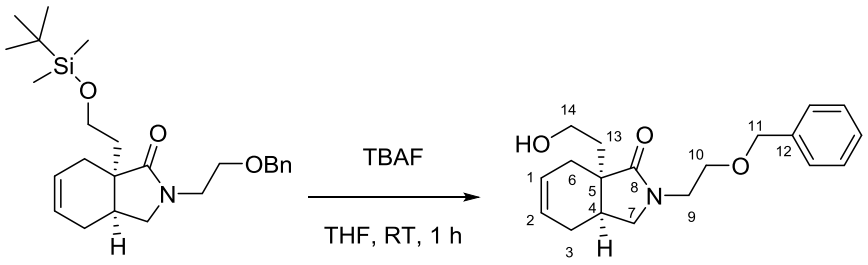


119 **120**

A solution of *n*-BuLi (1.6 M in hexanes, 1.60 mL, 2.57 mmol, 1.2 eq.) was added to a solution of diisopropylamine (0.38 mL, 2.68 mmol, 1.3 eq.) in dry THF (3 mL) at −78 °C. The solution was stirred for 15 min at −78 °C. The LDA solution was then transferred with a syringe to **119** (560 mg, 2.06 mmol, 1.0 eq.) in dry THF (2 mL) at −78 °C. The mixture was stirred for 40 min

at −78 °C before addition of TBS-protected iodoethanol (1.00 g, 3.50 mmol, 1.7 eq.). The mixture was warmed to RT and stirred for 3 h before being quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 5/1 to 1/1) to provide silyl ether **120** (680 mg, 77%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3029, 2951, 2927, 2855, 1682, 1471, 1253, 1092, 834; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H, H-Ar), 5.85 – 5.68 (m, 2H, H-2, H-1), 4.52 (s, 2H, H-11), 3.78 – 3.69 (m, 2H, H-14), 3.65 – 3.55 (m, 3H, H-10, H-9a), 3.50 – 3.37 (m, 2H, H-9b, H-7a), 3.10 (dd, *J* = 9.4, 7.9 Hz, 1H, H-7b), 2.58 – 2.50 (m, 1H, H-4), 2.38 – 2.27 (m, 1H, H-6a), 2.21 (m, 1H, H-3a), 2.01 – 1.92 (m, 2H, H-6b, H-3b), 1.91 – 1.78 (m, 2H, H-13), 0.89 (s, 9H, H-16), 0.05 (s, 6H, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.9 (C=O, C-8), 138.0 (C, C-12), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 125.9 (CH, C-2), 125.1 (CH, C-1), 73.0 (CH_2, C-11), 68.4 (CH_2, C-10), 59.9 (CH_2, C-14), 51.9 (CH_2, C-7), 44.8 (C, C-5), 42.5 (CH_2, C-9), 38.5 (CH_2, C-13), 34.4 (CH, C-4) 30.0 (CH_2, C-3), 25.9 (CH_3, C-16), 25.1 (CH_2, C-6), 18.2 (C, C-17), −5.4 (CH_3, C-15); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 452.2593 $[MNa]^+$, requires 452.2597 for $C_{25}H_{39}NO_3NaSi$.

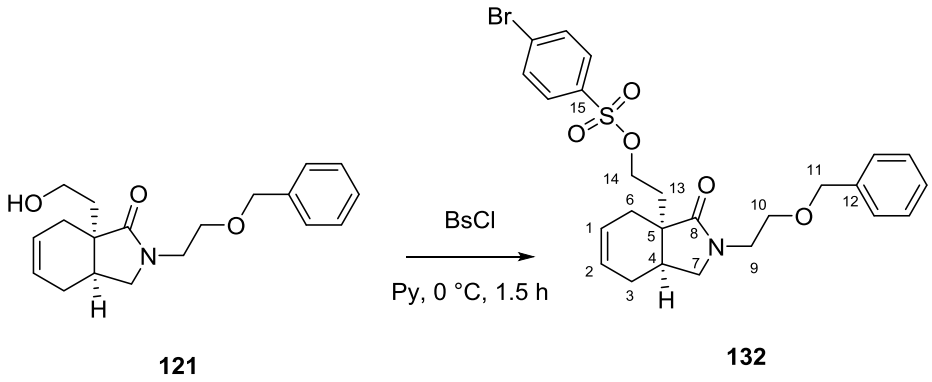
Preparation of alcohol **121**



120 **121**

A solution of TBAF (1.0 M in THF, 0.68 mL, 0.68 mmol, 2.0 eq.) was added to a solution of **120** (146 mg, 0.34 mmol, 1.0 eq.) in dry THF (1.5 mL). The reaction mixture was stirred for 1 h at RT, and then quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/2 to 0/1) to give alcohol **121** (108 mg, 99%) as a yellow oil. **IR** ν_{max}/cm^{-1} 3392, 3029, 2927, 2871, 1662, 1453, 1102, 740; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H, H-Ar), 5.77 – 5.63 (m, 2H, H-1, H-2), 4.49 (s, 2H, H-11), 3.87 – 3.80 (m, 1H, H-14a), 3.68 – 3.56 (m, 4H, H-10, H-9a, H-14b), 3.46 (dd, *J* = 9.6, 7.7 Hz, 1H, H-7a), 3.42 – 3.34 (m, 1H, H-9b), 3.22 (dd, *J* = 9.6, 2.6 Hz, 1H, H-7b), 2.40 – 2.32 (m, 1H, H-4), 2.31 – 2.21 (m, 1H, H-3a), 2.16 – 2.12 (m, 2H, H-6), 2.04 – 1.95 (m, 1H, H-3b), 1.83 – 1.76 (m, 2H, H-13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.7 (C=O, C-8), 137.9 (C, C-12), 128.5 (CH, C-Ar), 127.7 (CH, C-Ar), 124.8 (CH, C-2), 124.6 (CH, C-1), 73.0 (CH_2, C-11), 68.0 (CH_2, C-10), 58.6 (CH_2, C-14), 52.2 (CH_2, C-7), 45.1 (C, C-5), 42.7 (CH_2, C-9), 37.2 (CH_2, C-13), 36.7 (CH, C-4), 27.2 (CH_2, C-6), 23.7 (CH_2, C-3); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 338.1740 $[MNa]^+$, requires 338.1732 for $C_{19}H_{25}NO_3Na$.

Preparation of Brosylate **132**

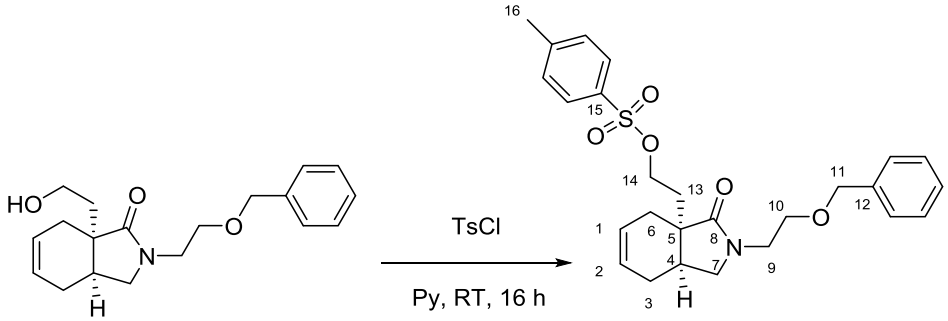


121 **132**

Brosyl chloride (255 mg, 1.00 mmol, 4.0 eq.) was added portionwise to a solution of **121** (80 mg, 0.25 mmol, 1.0 eq.) in pyridine (0.7 mL) at 0 °C. The mixture was stirred for 1.5 h at 0 °C and 1.5 h at RT then quenched with water. The aqueous layer was extracted with EtOAc (3 × 8 mL), the combined organic layers were successively washed with a solution of 1 M HCl (aq), a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 2/1 to 1/1) to furnish brosylate **132** (111 mg, 83%) as a pink oil. **IR** ν_{max}/cm^{-1} 3026, 2922, 2851, 1681, 1453, 1266, 1104; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H, H-Ar), 7.73 – 7.68 (m, 2H, H-Ar), 7.39 – 7.29 (m, 5H, H-Ar), 5.78 – 5.75 (m, 2H, H-1, H-2), 4.50 (s, 2H, H-11), 4.24 – 4.17 (m, 2H, H-14), 3.65 – 3.54 (m, 4H, H-10, H-9), 3.47 – 3.39 (m, 1H, H-7a), 3.13 (dd, *J* = 9.5, 8.5 Hz, 1H, H-7b), 2.39 – 2.36 (m, 1H, H-4), 2.34 – 2.24 (m, 1H, H-6a), 2.20 – 2.11 (m, 1H, H-3a), 2.10 – 1.85 (m, 4H, H-13, H-6b, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.8 (C=O, C-8), 146.2 (C, C-15), 138.0 (C, C-12), 132.6 (CH, C-Ar), 131.5 (C, C-Br) 129.4 (CH, C-Ar), 128.5 (CH, C-Ar), 127.7 (CH, C-Ar), 125.3 (CH, C-2), 125.0 (CH, C-1), 73.0 (CH_2, C-11), 68.3 (CH_2, C-14), 68.0 (CH_2, C-10), 51.7 (CH_2, C-7), 44.2 (C, C-5), 42.6 (CH_2, C-9), 34.8 (CH, C-4), 34.5 (CH_2, C-3), 29.4 (CH_2, C-13), 24.4 (CH_2, C-

6); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 586.0979 $[MNa]^+$, requires 586.0977 for $C_{26}H_{28}{}^{79}BrNO_6NaS$.

Preparation of tosylate **133**

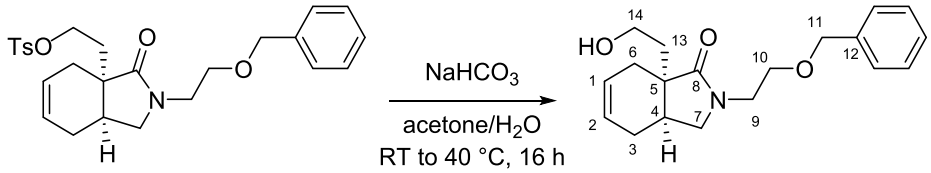


121 **133**

Tosyl chloride (182 mg, 0.98 mmol, 2.0 eq.) was added portionwise to a solution of **121** (150 mg, 0.48 mmol, 1.0 eq.) in pyridine (1.5 mL) at 0 °C. After 16 h at RT, the reaction mixture was quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed successively with a solution of 1 M HCl (aq), a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 2/1 to 1/1) to give tosylate **133** (65 mg, 29%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3034, 2930, 1709, 1180, 1130, 1011; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H, H-Ar), 7.42 – 7.22 (m, 7H, H-Ar), 5.73 – 5.70 (m, 2H, H-1, H-2), 4.47 (s, 2H, H-11), 4.16 – 4.11 (m, 2H, H-14), 3.57 – 3.54 (m, 3H, H-10, H-9a), 3.45 – 3.30 (m, 2H, H-9b, H-7a), 3.10 (dd, *J* = 9.5, 8.5 Hz, 1H, H-7b), 2.44 (s, 3H, H-16), 2.38 – 2.34 (m, 1H, H-4), 2.33 – 2.20 (m, 1H, H-6a), 2.20 – 2.08 (m, 1H, H-3a), 2.06 – 1.79 (m, 4H, H-13, H-6b, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.7 (C=O, C-8), 145.5 (C, C-15), 140.2 (CH, C-Ar), 138.3 (C, C-12), 130.4 (CH,

C-Ar), 128.6 (CH, C-Ar), 128.1 (CH, C-Ar), 127.2 (CH, C-Ar), 126.9 (CH, C-2), 126.3 (CH, C-1), 74.4 (CH_2, C-11), 68.4 (CH_2, C-10), 64.7 (CH_2, C-14), 52.1 (CH_2, C-7), 47.9 (C, C-5), 432.9 (CH, C-4), 34.9 (CH_2, C-13), 32.9 (CH_2, C-3), 24.9 (CH_2, C-6), 25.1 (CH_3, C-16); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 492.1925 $[MNa]^+$, requires 492.1923 for $C_{26}H_{31}NO_5NaS$.

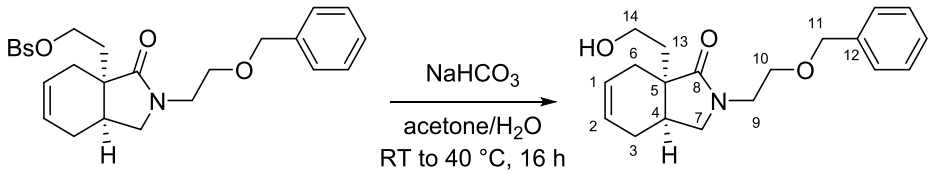
Solvolytic ring closure on tosyl **133**



133 **121**

$NaHCO_3$ (8 mg, 0.1 mmol, 2.0 eq.) was added to a solution of **133** (23 mg, 0.05 mmol, 1.0 eq.) in a mixture of acetone (1.2 mL) and H_2O (0.3 mL) at RT. The mixture was stirred for 1 h at RT, warmed to 40 °C and stirred for 16 h. The solution was diluted with water and the aqueous layer was extracted with DCM (3 × 4 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to furnish alcohol **121** (15 mg, 70%) as a colourless oil. See preparation of **121** for **IR**, **^{1}H NMR**, **^{13}C NMR** and **HRMS** (p.124).

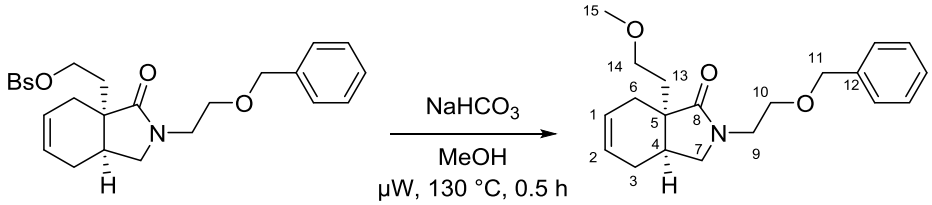
Solvolytic ring closure on brosyl **132**



132 **121**

$NaHCO_3$ (8 mg, 0.094 mmol, 2.0 eq.) was added to a solution of **132** (25 mg, 0.047 mmol, 1.0 eq.) in a mixture of acetone (1.2 mL) and H_2O (0.3 mL) at RT. The mixture was stirred for 1 h at RT, warmed to 40 °C and stirred for 16 h. The solution was diluted with water and the aqueous layer was extracted with DCM (3 × 4 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to furnish alcohol **121** (8 mg, 55%) as a colourless oil. See preparation of **121** for **IR**, **^{1}H NMR**, **^{13}C NMR** and **HRMS** (p.124).

Solvolytic ring closure on brosyl **132**

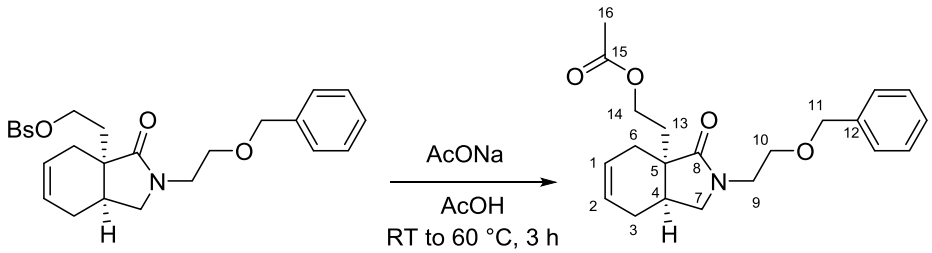


132 **135**

$NaHCO_3$ (8 mg, 0.11 mmol, 3.0 eq.) was added to a solution of **132** (20 mg, 0.037 mmol, 1.0 eq.) in MeOH (2 mL) in a microwave vial. After the vial was closed the reaction mixture was stirred for 10 min and the mixture was subjected to microwave irradiation for 0.5 h at

130 °C. The solution was diluted with water and the aqueous layer was extracted with DCM (3 × 4 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 3/1 to 1/1) to furnish methyl ether **135** (11 mg, 95%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3034, 2925, 1697, 1454, 1086, 741; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.05 (m, 4H, H-Ar), 5.80 – 5.69 (m, 2H, H-2, H-1), 4.49 (s, 2H, H-11), 3.61 – 3.52 (m, 3H, H-10, H-9a), 3.47 – 3.37 (m, 4H, H-14, H-9b, H-7a), 3.26 (s, 3H, H-15), 3.09 (dd, *J* = 9.5, 7.9 Hz, 1H, H-7b), 2.49 – 2.41 (m, 1H, H-4), 2.35 – 2.16 (m, 2H, H-6a, H-3a), 2.00 – 1.87 (m, 3H, H-13a, H-6b, H-3b), 1.86 – 1.75 (m, 1H, H-13b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.8 (C=O, C-8), 138.0 (C, C-12), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 125.9 (CH, C-2), 125.2 (CH, C-1), 73.0 (CH_2, C-11), 69.5 (CH_2, C-14), 68.3 (CH_2, C-10), 58.5 (CH_3, C-15), 51.9 (CH_2, C-7), 44.8 (C, C-5), 42.5 (CH_2, C-9), 35.4 (CH_2, C-13), 34.5 (CH, C-4), 30.0 (CH_2, C-6), 25.1 (CH_2, C-3); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 352.1991 $[MNa]^+$, requires 352.1993 for $C_{20}H_{27}NO_3Na$.

Solvolytic ring closure on brosyl **132**

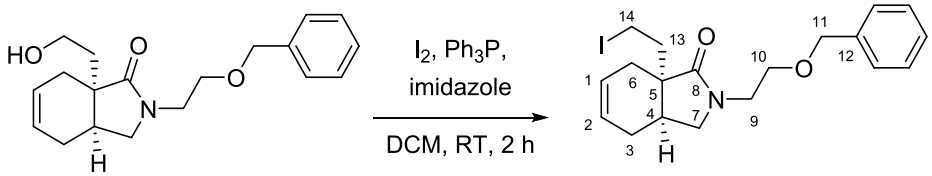


132 **134**

Sodium acetate (10 mg, 0.13 mmol, 6.0 eq.) was added to a solution of **132** (11 mg, 0.021 mmol, 1.0 eq.) in AcOH (1 mL) at RT. The mixture was stirred for 1 h at RT, 2 h at 60 °C and quenched

with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 4 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 3/1 to 1/1) to furnish acetate **134** (6 mg, 80%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3029, 2956, 2864, 1738, 1700, 1362, 1108, 778; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H, H-Ar), 5.83 – 5.69 (m, 2H, H-2, H-1), 4.49 (s, 2H, H-11), 4.20 – 4.07 (m, 2H, H-14), 3.63 – 3.54 (m, 3H, H-10, H-9a), 3.51 – 3.37 (m, 2H, H-9b, H-7a), 3.16 – 3.08 (m, 1H, H-7b), 2.46 – 2.39 (m, 1H, H-4), 2.33 – 2.15 (m, 2H, H-6a, H-3a), 2.09 (s, 3H, H-16), 2.04 – 1.94 (m, 3H, H13a, H-6b, H-3b), 1.92 – 1.84 (m, 1H, H-13b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.5 (C=O, C-8), 176.2 (C=O, C-15), 137.9 (C, C-12), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 125.7 (CH, C-2), 125.0 (CH, C-1), 73.0 (CH_2, C-11), 68.2 (CH_2, C-10), 61.3 (CH_2, C-14), 51.8 (CH_2, C-7), 44.3 (C, C-5), 42.6 (CH_2, C-9), 34.4 (CH_2, C-13), 34.2 (CH, C-4), 29.8 (CH_2, C-6), 24.8 (CH_2, C-3), 20.7 (CH_3, C-16); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 380.1940 $[MNa]^+$, requires 380.1937 for $C_{21}H_{27}NO_4Na$.

Preparation of iodide **152**

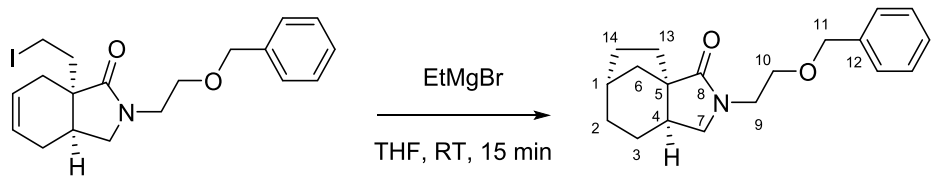


121 **152**

Iodine (433 mg, 1.71 mmol, 1.35 eq.) was added to a solution of PPh_3 (400 mg, 1.52 mmol, 1.25 eq.) and imidazole (129 mg, 1.90 mmol, 1.50 eq.) in dry DCM (3 mL) at RT. The mixture was stirred for 10 min then a solution of alcohol **121** (400 mg, 1.27 mmol, 1.00 eq.) in dry DCM

(3 mL), was added. The mixture was stirred for 2 h at RT, and then concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 2/1 to 1/1) to furnish iodide **152** (496 mg, 92%) as an orange oil. **IR** ν_{max}/cm^{-1} 3036, 2860, 1680, 1435, 1397, 1187, 1102, 738; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, H-Ar), 5.84 – 5.71 (m, 2H, H-1, H-2), 4.51 (s, 2H, H-11), 3.62 – 3.60 (m, 2H, H-10), 3.53 – 3.50 (m, 2H, H-9), 3.49 – 3.43 (m, 1H, H-7a), 3.29 – 3.21 (m, 1H, H-14a), 3.17 – 3.15 (m, 1H, H-14b), 3.13 – 3.08 (m, 1H, H-7b), 2.40 – 2.38 (m, 1H, H-4), 2.33 – 2.17 (m, 4H, H-13, H-6a, H-3a), 1.99 – 1.97 (m, 2H, H-6b, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.1 (C=O, C-8), 131.0 (C, C-12), 129.0 (CH, C-Ar), 128.2 (CH, C-Ar), 126.3 (CH, C-2), 125.8 (CH, C-1), 73.5 (CH_2, C-11), 68.6 (CH_2, C-10), 52.4 (CH_2, C-7), 48.4 (C, C-5), 43.0 (CH_2, C-9), 42.0 (CH_2, C-13), 34.8 (CH, C-4), 29.7 (CH_2, C-6), 25.7 (CH_2, C-3), 0.0 (CH_2, C-14); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 426.0932 $[MH]^+$, requires 426.0930 for $C_{19}H_{25}NO_2I$.

Preparation of bicyclo[3.2.1]octane system **153**

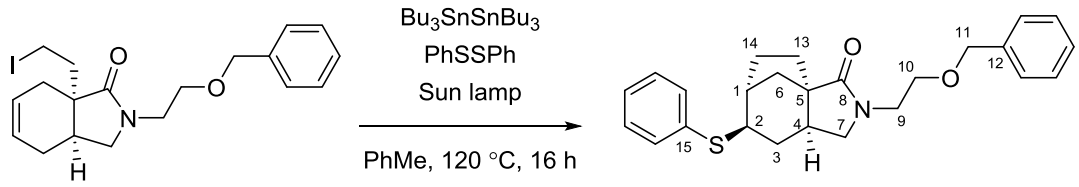


152 **153**

A solution of EtMgBr (2.0 M in THF, 0.10 mL, 0.21 mmol, 3.0 eq.) was added to a solution of **152** (30 mg, 0.07 mmol, 1.0 eq.) in dry THF (0.7 mL) at RT. The mixture was stirred for 15 min at RT and then quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced

pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 1/1 to 0/1) to give bicyclic compound **153** (15 mg, 72%) as a colourless oil. **IR** ν_{max}/cm^{-1} 2924, 2864, 1683, 1493, 1453, 1175, 1105; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H, H-Ar), 4.54 (s, 2H, H-11), 3.66 – 3.62 (m, 2H, H-10), 3.59 – 3.56 (m, 1H, H-9a), 3.52 –3.49 (m, 2H, H-9b, H-7a), 3.13 (dd, *J* = 9.4, 2.4 Hz, 1H, H-7b), 2.26 – 2.19 (m, 1H, H-1), 2.12 – 2.06 (m, 1H, H-13a), 2.04 – 1.97 (m, 1H, H-4), 1.93 – 1.81 (m, 1H, H-14a), 1.77 – 1.61 (m, 2H, H-3a, H-2a), 1.49 – 1.43 (m, 1H, H-6a), 1.41 – 1.30 (m, 3H, H-14b, H-13b, H-6b), 1.27 – 1,14 (m, 2H, H-3b, H-2b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.6 (C=O, C-8), 141.4 (C, C-12), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 72.9 (CH_2, C-11), 68.5 (CH_2, C-10), 52.6 (CH_2, C-7), 50.9 (C, C-5), 42.6 (CH_2, C-9), 41.0 (CH, C-4), 34.0 (CH_2, C-6), 33.5 (CH_2, C-13), 32.6 (CH, C-1), 30.4 (CH_2, C-14), 30.1 (CH_2, C-2), 20.6 (CH_2, C-3); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 300.1960 $[MH]^+$, requires 300.1964 for $C_{19}H_{26}NO_2$.

Preparation of phenyl sulfide **157**

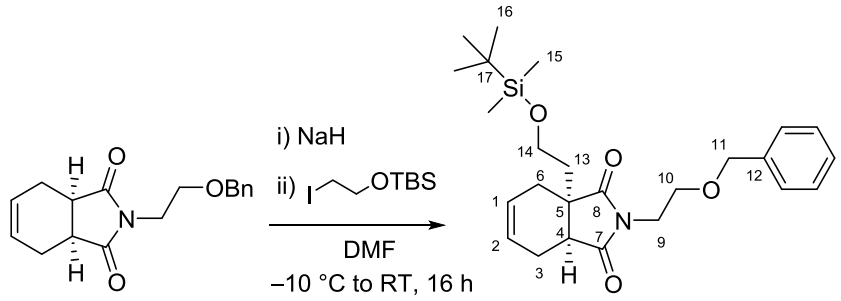


152 **157**

Hexabutylditin (1.50 mL, 2.97 mmol, 1.5 eq.) was added to a solution of phenyl disulfide (0.65 g, 2.97 mmol, 1.5 eq.) and **152** (842 mg, 1.98 mmol, 1.0 eq.) in dry PhMe (10 mL) at RT. The mixture was irradiated with a sun lamp for 2 h and heated to reflux. After 16 h, the reaction mixture was concentrated under reduced pressure. The crude mixture was purified by flash

column chromatography (gradient: hexane/EtOAc = 4/1 to 2/1) to give phenyl sulfide **157** (577 mg, 73%) as a colourless oil. **IR** ν_{max}/cm^{-1} 2940, 2868, 1682, 1493, 1438, 1259, 1104; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.20 (m, 10H, H-Ar), 4.54 (s, 2H, H-11), 3.67 – 3.58 (m, 4H, H-10, H-9a, H-7a), 3.56 – 3.53 (m, 1H, H-9b), 3.22 – 3.13 (m, 2H, H-7b, H-2), 2.43 (dd, *J* = 6.8, 4.8 Hz, 1H, H-4), 2.22 – 2.20 (m, 1H, H-3a), 2.18 – 2.13 (m, 1H, H-6a), 2.13 – 2.04 (m, 2H, H-14a, H-1), 1.84 (d, *J* = 11.7 Hz, 1H, H-13a), 1.52 – 1.50 (m, 1H, H-14b), 1.47 – 1.39 (m, 2H, H-3b, H-13b), 1.34 – 1.25 (m, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0 (C=O, C-8), 138.1 (C, C-12), 135.5 (C, C-15), 131.0 (CH, C-Ar) 129.0 (CH, C-Ar), 128.5 (CH, C-Ar), 127.7 (CH, C-Ar), 127.6 (CH, C-Ar), 127.0 (CH, C-Ar), 73.0 (CH_2, C-11), 68.5 (CH_2, C-10), 53.5 (CH_2, C-7), 50.7 (C, C-5), 49.3 (CH, C-2), 42.7 (CH_2, C-9), 40.3 (CH, C-4), 39.7 (CH, C-1), 34.8 (CH_2, C-6), 31.5 (CH_2, C-14), 31.1 (CH_2, C-13), 29.2 (CH_2, C-3); **HRMS** (ES) found 408.1986 $[MH]^+$, requires 408.1997 for $C_{25}H_{30}NO_2S$.

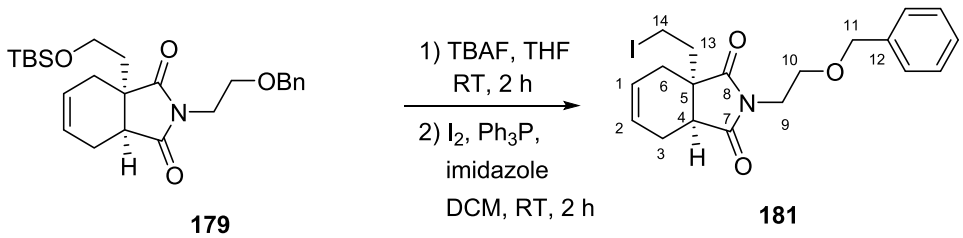
Preparation of TBS-protected alcohol **179**



NaH (60% in mineral oil, 326 mg, 8.15 mmol, 1.4 eq.) was added to a solution of **116** (1.66 g, 5.82 mmol, 1.0 eq.) in dry DMF (15 mL) at –10 °C. The mixture was stirred for 20 min at −10 °C then TBS-protected iodoethanol (5.00 g, 17.46 mmol, 3.0 eq.) was added. The solution was allowed to warm to RT and stirred overnight before being quenched with a saturated

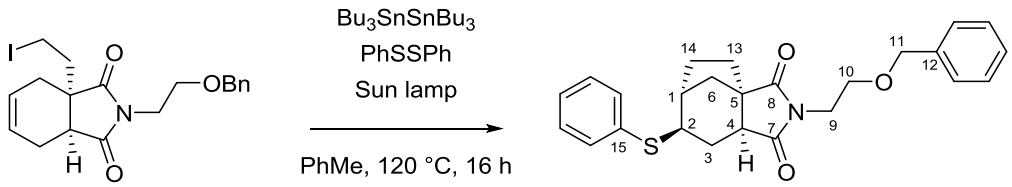
aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic layers were washed with water (4 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 10/1 to 7/1) to furnish TBS-protected alcohol **179** (2.01 g, 78%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3030, 2952, 2929, 2856, 1774, 1699, 1398, 1337, 1255, 1104, 835; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H, H-Ar), 5.88 – 5.76 (m, 2H, H-2, H-1), 4.49 (s, 2H, H-11), 3.78 – 3.67 (m, 4H, H-14, H-10), 3.60 – 3.55 (m, 2H, H-9), 3.19 (dd, *J* = 7.3, 2.4 Hz, 1H, H-4), 2.66 (ddd, *J* = 15.6, 6.0, 2.4 Hz, 1H, H-3a), 2.50 (dd, *J* = 15.1, 6.0 Hz, 1H, H-6a), 2.21 (ddd, *J* = 15.6, 7.3, 2.6 Hz, 1H, H-3b), 2.05 – 1.96 (m, 2H, H-13a, H-6b), 1.87 (ddd, *J* = 14.2, 6.5, 5.4 Hz, 1H, H-13b), 0.86 (s, 9H, H-16), 0.01 (s, 3H, H-15), 0.00 (s, 3H, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.3 (C=O, C-7), 179.7 (C=O, C-8), 138.0 (C, C-12), 128.3 (CH, C-Ar), 127.9 (CH, C-Ar), 127.5 (CH, C-2), 127.3 (CH, C-1), 72.6 (CH_2, C-11), 66.3 (CH_2, C-10), 59.6 (CH_2, C-14), 47.2 (C, C-5), 44.4 (CH, C-4), 39.1 (CH_2, C-13), 38.2 (CH_2, C-9), 31.4 (CH_2, C-6), 25.9 (CH_3, C-16), 24.0 (CH_2, C-3), 18.2 (C, C-17), -5.6 (CH_3, C-15); 1 signal in the C-H aromatic region was not observed due to overlap; **HRMS** (ES) found 444.2576 $[MH]^+$, requires 444.2570 for $C_{25}H_{38}NO_4Si$.

Preparation of iodide **181**



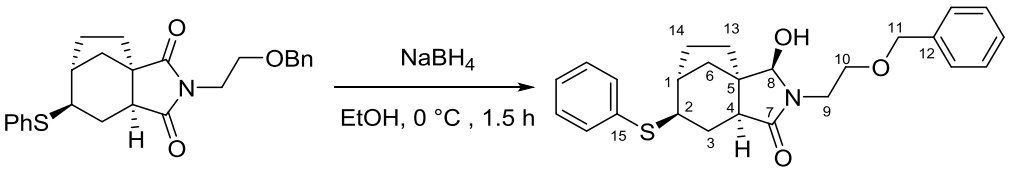
A solution of TBAF (1.0 M in THF, 13.50 mL, 13.50 mmol, 1.5 eq.) was added to a solution of **179** (3.98 g, 8.98 mmol, 1.0 eq.) in dry THF (20 mL). The reaction mixture was stirred for 2 h at RT, then quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was dissolved in dry DCM (20 mL) and added to solution of iodine (3.07 g, 12.15 mmol, 1.35 eq.), PPh_3 (2.83 g, 10.81 mmol, 1.25 eq.) and imidazole (918 mg, 13.5 mmol, 1.50 eq.) in dry DCM (20 mL) at RT. The mixture was stirred for 2 h at RT then concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: petrol/EtOAc = 4/1 to 2/1) to furnish iodide **181** (3.33 g, 85% after 2 steps) as a pale orange oil. **IR** ν_{max}/cm^{-1} 3037, 2954, 2861, 1774, 1695, 1433, 1397, 1337, 1186, 1103, 1041; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H, H-Ar), 5.90 – 5.76 (m, 2H, H-2, H-1), 4.47 (s, 2H, H-11), 3.79 – 3.67 (m, 2H, H-9), 3.65 – 3.55 (m, 2H, H-10), 3.07 (m, 2H, H-14), 2.80 (dd, *J* = 7.2, 2.4 Hz, 1H, H-4), 2.73 – 2.63 (m, 1H, H-3a), 2.56 (dd, *J* = 15.5, 6.3 Hz, 1H, H-6a), 2.38 (ddd, *J* = 13.9, 12.1, 5.2 Hz, 1H, H-13a), 2.29 – 2.21 (m, 1H, H-13b), 2.21 – 2.14 (m, 1H, H-3b), 1.94 (dd, *J* = 15.5, 2.6 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.7 (C=O, C-7), 178.6 (C=O, C-8), 137.8 (C, C-12), 128.4 (CH, C-Ar), 128.0 (CH, C-2), 127.7 (CH, C-1), 127.6 (CH, C-Ar), 127.3 (CH, C-Ar), 72.7 (CH_2, C-11), 66.0 (CH_2, C-10), 49.9 (C, C-5), 44.2 (CH, C-4), 42.3 (CH_2, C-13), 38.4 (CH_2, C-9), 30.5 (CH_2, C-6), 23.9 (CH_2, C-3), -3.4 (CH_2, C-14); **HRMS** (ES) found 440.0714 $[MH]^+$, requires 440.0723 for $C_{19}H_{23}NO_3I$.

Preparation of phenyl sulfide **182**



Hexabutylditin (2.43 mL, 4.83 mmol, 1.5 eq.) was added to a solution of **181** (1.40 g, 3.22 mmol, 1.0 eq.) and diphenyl disulfide (1.35 g, 4.83 mmol, 1.5 eq.) in dry PhMe (16 mL). The reaction mixture was irradiated with a sun lamp for 2 h then heated to 120 °C and stirred for 16 h. The solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 8/1 to 4/1) to give phenyl sulfide **182** (935 mg, 77%) as a colourless oil. **IR** ν_{max}/cm^{-1} 2954, 2872, 1771, 1700, 1392, 1101, 738; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.10 (m, 10H, H-Ar), 4.41 (s, 2H, H-11), 3.73 – 3.63 (m, 2H, H-9), 3.59 – 3.51 (m, 2H, H-10), 3.06 (dd, *J* = 11.5, 6.6 Hz, 1H, H-4), 2.39 – 2.30 (m, 2H, H-2, H-1), 2.27 – 2.18 (m, 1H, H-3a), 2.16 – 2.06 (m, 2H, H-6a, H-14a), 1.65 (dd, *J* = 11.9, 3.5 Hz, 1H, H-13a), 1.55 – 1.47 (m, 2H, H-13b, H-14b), 1.47 – 1.36 (m, 1H, H-6b), 1.31 – 1.20 (m, 1H, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.1 (C=O, C-8), 177.9 (C=O, C-7), 137.9 (C, C-12), 134.6 (C, C-15), 131.5 (CH, C-Ar), 129.1 (CH, C-Ar), 128.5 (CH, C-Ar), 127.8 (CH, C-Ar), 127.7 (CH, C-Ar), 127.1 (CH, C-Ar), 72.6 (CH_2, C-11), 66.0 (CH_2, C-10), 50.0 (C, C-5), 49.7 (CH, C-4), 47.3 (CH, C-2), 40.2 (CH, C-1), 38.1 (CH_2, C-9), 33.9 (CH_2, C-14), 33.4 (CH_2, C-13), 32.0 (CH_2, C-6), 25.1 (CH_2, C-3); **HRMS** (ES) found 444.1601 $[MNa]^+$, requires 444.1609 for $C_{25}H_{27}NO_3NaS$.

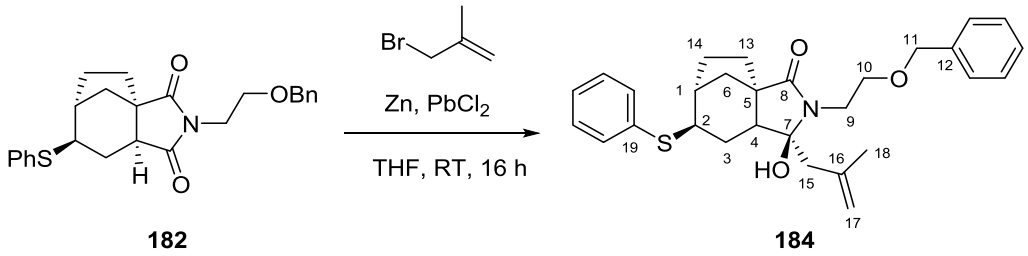
Preparation of hemiaminal **183**



182 **183**

Sodium borohydride (277 mg, 7.36 mmol, 5.0 eq.) was added portionwise to a solution of **182** (620 mg, 1.47 mmol, 1.0 eq.) in ethanol (12 mL) at 0 °C. The mixture was stirred for 1.5 h at 0 °C then quenched with water. The aqueous layer was extracted with DCM (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield hemiaminal **183** (543 mg, 88%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3358, 2940, 2868, 1667, 1583, 1453, 1102, 1026, 739; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.17 (m, 10H, H-Ar), 4.74 (s, 1H, H-8), 4.61 (d, *J* = 11.6 Hz, 1H, H-11a), 4.52 (d, *J* = 11.6 Hz, 1H, H-11b), 4.11 – 4.03 (m, 1H, H-9a), 3.67 – 3.55 (m, 2H, H-10), 3.28 – 3.23 (m, 1H, H-4), 3.13 (ddd, *J* = 14.9, 10.1, 2.8 Hz, 1H, H-9b), 2.56 – 2.49 (m, 1H, H-2), 2.37 – 2.31 (m, 1H, H-1), 2.23 – 2.14 (m, 1H, H-3a), 2.03 – 1.94 (m, 1H, H-14a), 1.89 (dd, *J* = 12.8, 5.7 Hz, 1H, H-13a), 1.79 (d, *J* = 11.6 Hz, 1H, H-6a), 1.75 – 1.59 (m, 2H, H-13b, H-3b), 1.58 – 1.46 (m, 1H, H-14b), 1.20 (dd, *J* = 11.6, 5.1 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C=O, C-7), 136.5 (C, C-12), 135.4 (C, C-15), 131.6 (CH, C-Ar), 128.9 (CH, C-Ar), 128.3 (CH, C-Ar), 128.7 (CH, C-Ar), 128.0 (CH, C-Ar), 126.7 (CH, C-Ar), 88.7 (CH, C-8), 73.7 (CH_2, C-11), 69.0 (CH_2, C-10), 49.5 (C, C-5), 49.3 (CH, C-4), 46.2 (CH, C-2), 43.0 (CH_2, C-9), 39.0 (CH, C-1), 33.4 (CH_2, C-6), 30.6 (CH_2, C-13), 30.4 (CH_2, C-14), 23.8 (CH_2, C-3); **HRMS** (ES) found 424.1948 $[MH]^+$, requires 424.1946 for $C_{25}H_{30}NO_3S$.

Preparation of methylallyl **184**

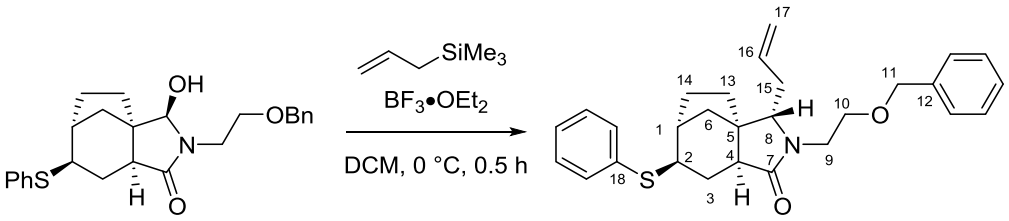


182 **184**

3-Bromo-2-methylpropene (115 µL, 1.20 mmol, 10.0 eq.) was added to a mixture of **182** (50 mg, 0.12 mmol, 1.0 eq.), zinc (116 mg, 1.78 mmol, 15.0 eq.) and lead(II) chloride (3 mg, 0.012 mmol, 0.10 eq.) in dry THF (1 mL) at RT. The mixture was stirred for 16 h at RT then quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 3/1) to give methylallyl **184** (20 mg, 35%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3375, 3077, 2946, 2871, 1686, 1666, 1437, 1092, 739; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.18 (m, 10H, H-Ar), 4.95 (s, 1H, OH), 4.90 – 4.68 (m, 2H, H-17), 4.62 (d, *J* = 11.5 Hz, 1H, H-11a), 4.57 (d, *J* = 11.5 Hz, 1H, H-11b), 3.98 (“app dt”, *J* = 15.2, 2.3 Hz, 1H, H-9a), 3.77 – 3.70 (m, 1H, H-10a), 3.65 – 3.57 (m, 1H, H-10b), 3.32 – 3.21 (m, 1H, H-9b), 3.16 – 3.09 (m, 1H, H-2), 2.58 (d, *J* = 14.1 Hz, 1H, H-15a), 2.47 – 2.40 (m, 1H, H-1), 2.34 (d, *J* = 14.1 Hz, 1H, H-15b), 2.24 – 2.13 (m, 1H, H-13a), 2.09 – 2.00 (m, 2H, H-4, H-14a), 1.88 (d, *J* = 11.6 Hz, 1H, H-6a), 1.82 – 1.76 (m, 2H, H-3), 1.69 (s, 3H, H-18), 1.53 – 1.34 (m, 3H, H-13b, H-14b, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.2 (C=O, C-8), 141.3 (C, C-16), 136.4 (C, C-19), 136.1 (C, C-12), 130.5 (CH, C-Ar), 128.8 (CH, C-Ar), 128.7 (CH, C-Ar), 128.3 (CH, C-Ar), 128.1 (CH, C-Ar), 126.2 (CH, C-Ar), 115.2 (CH_2, C-17), 88.7 (C, C-7), 73.7 (CH_2, C-11), 68.4 (CH_2, C-10), 49.7 (CH, C-2), 49.4 (C, C-5), 48.3 (CH, C-4), 47.3 (CH_2, C-15), 41.8 (CH, C-1), 39.8 (CH_2, C-9), 35.9 (CH_2, C-13), 32.7 (CH_2, C-6), 32.2 (CH_2, C-14),

23.6 (CH_3, C-18), 23.1 (CH_2, C-3); **HRMS** (ES) found 500.2233 $[MNa]^+$, requires 500.2235 for $C_{29}H_{35}NO_3NaS$.

Preparation of allyl **185**

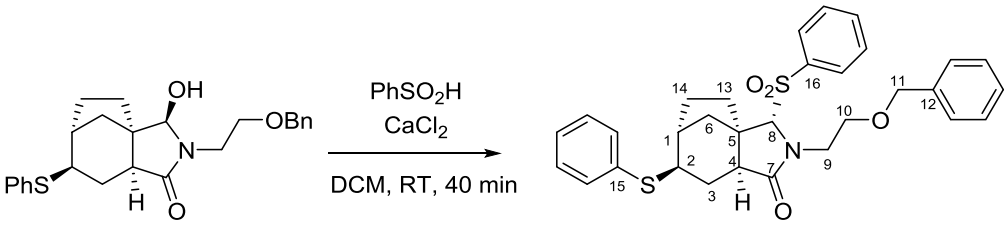


183 **185**

BF_3•OEt_2 (46 µL, 0.37 mmol, 4.0 eq.) and allyltrimethylsilyl (28 µL, 0.18 mmol, 2.0 eq.) were successively added to a solution of **183** (39 mg, 0.092 mmol, 1.0 eq.) in dry DCM (0.4 mL) at 0 °C. After stirring for 0.5 h at 0 °C the reaction mixture was quenched with water. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 5/1 to 4/1) to give allyl **185** (33 mg, 80%) as a colourless oil. **IR** ν_{max}/cm^{-1} 2935, 2865, 1680, 1583, 1438, 1275, 1099, 739; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.09 (m, 10H, H-Ar), 5.72 – 5.60 (m, 1H, H-16), 5.05 – 4.94 (m, 2H, H-17), 4.48 (d, *J* = 11.8 Hz, 1H, H-11a), 4.44 (d, *J* = 11.8 Hz, 1H, H-11b), 3.88 (dt, *J* = 14.5, 4.7 Hz, 1H, H-9a), 3.63 – 3.58 (m, 2H, H-10), 3.48 (t, *J* = 5.2 Hz, 1H, H-8), 3.25 – 3.16 (m, 1H, H-4), 3.13 – 3.04 (m, 1H, H-9b), 2.43 – 2.33 (m, 1H, H-15a), 2.30 – 2.23 (m, 2H, H-15b, H-2), 2.23 – 2.17 (m, 1H, H-1), 2.11 – 1.88 (m, 3H, H-3a, H-6a,H-13a), 1.82 – 1.73 (m, 1H, H-3b), 1.67 – 1.57 (m, 2H, H-14), 1.51 – 1.42 (m, 1H, H-13b), 1.04 (dd, *J* = 11.9, 5.3 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4 (C=O, C-7), 138.1 (C, C-12), 135.7 (C, C-18), 134.6

(CH, C-16), 131.2 (CH, C-Ar), 128.9 (CH, C-Ar), 128.4 (CH, C-Ar), 127.8 (CH, C-Ar), 127.6 (CH, C-Ar), 126.7 (CH, C-Ar), 118.2 (CH_2, C-17), 73.2 (CH_2, C-11), 68.7 (CH_2, C-10), 64.4 (CH, C-8), 49.2 (CH, C-4), 48.7 (C, C-5), 46.6 (CH, C-2), 41.2 (CH_2, C-9), 37.8 (CH, C-1), 35.9 (CH_2, C-6), 34.7 (CH_2, C-15), 30.7 (CH_2, C-13), 30.0 (CH_2, C-14), 23.4 (CH_2, C-3); **HRMS** (ES) found 470.2124 $[MNa]^+$, requires 470.2130 $C_{28}H_{33}NO_2NaS$.

Preparation of sulfone **188**

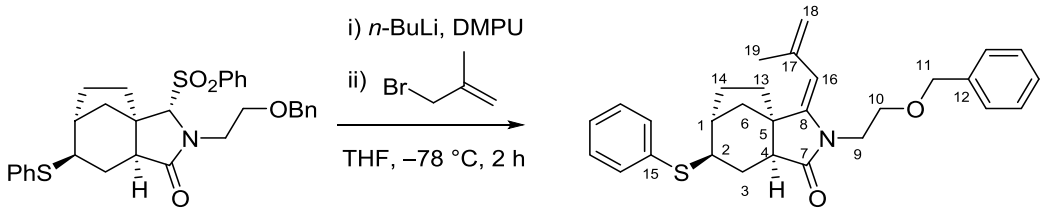


183 **188**

Benzenesulfinic acid (122 mg, 0.86 mmol, 3.0 eq.) (obtained by dissolving the sodium salt in water, acidifying with conc. H_2SO_4 to pH = 1, extraction of the aqueous layer with DCM, drying the organic layers with $MgSO_4$ and concentrated under reduced pressure) and $CaCl_2$ (96 mg, 0.86 mmol, 3.0 eq.) were added to a solution of **183** (122 mg, 0.28 mmol, 1.0 eq.) in dry DCM (2 mL) at RT. After stirring for 40 min the reaction mixture was quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to furnish sulfone **188** (140 mg, 90%) as a white powder. **m.p.** 110 – 112 °C; **IR** ν_{max}/cm^{-1} 3062, 2946, 2874, 1710, 1447, 1307, 1143, 1079; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 2H, H-Ar), 7.77 – 7.70 (m, 1H, H-Ar), 7.63 – 7.56 (m, 2H, H-Ar), 7.43 – 7.21 (m, 10H, H-Ar), 4.75 (s, 1H, H-8), 4.54

(d, *J* = 11.8 Hz, 1H, H-11a), 4.40 (d, *J* = 11.8 Hz, 1H, H-11b), 3.84 (ddd, *J* = 14.8, 4.0, 2.7 Hz, 1H, H-9a), 3.72 – 3.65 (m, 1H, H-10a), 3.50 (ddd, *J* = 10.3, 4.0, 2.7 Hz, 1H, H-10b), 3.35 – 3.30 (m, 1H, H-4), 2.65 – 2.57 (m, 2H, H-9b, H-2), 2.32 – 2.24 (m, 1H, H-1), 2.25 – 2.17 (m, 2H, H-13a, H-6a), 2.11 – 2.00 (m, 3H, H-13b, H-3), 1.71 – 1.59 (m, 1H, H-14a), 1.32 – 1.26 (m, 1H, H-14b), 1.21 (dd, *J* = 12.0, 5.7 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.9 (C=O, C-7), 138.4 (C, C-16), 137.6 (C, C-12), 135.2 (C, C-15), 134.5 (CH, C-Ar), 132.3 (CH, C-Ar), 129.6 (CH, C-Ar), 129.3 (CH, C-Ar), 128.9 (CH, C-Ar), 128.4 (CH, C-Ar), 127.8 (CH, C-Ar), 127.1 (CH, C-Ar), 126.5 (CH, C-Ar), 85.0 (CH, C-8), 73.2 (CH_2, C-11), 68.9 (CH_2, C-10), 50.0 (C, C-5), 48.6 (CH, C-4), 44.3 (CH, C-2), 42.5 (CH_2, C-9), 36.8 (CH_2, C-6), 36.1 (CH, C-1), 29.7 (CH_2, C-13), 29.1 (CH_2, C-14), 21.7 (CH_2, C-3); **HRMS** (ES) found 570.1747 $[MNa]^+$, requires 570.1749 for $C_{31}H_{33}NO_4NaS_2$.

Preparation of diene **192**

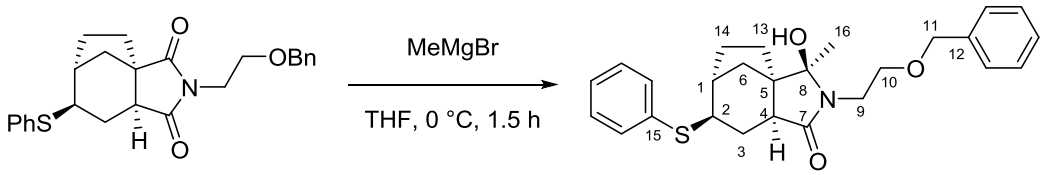


188 **192**

A solution of *n*-BuLi (2.0 M in hexanes, 0.39 mL, 0.78 mmol, 1.3 eq.) was added to a solution of **188** (328 mg, 0.60 mmol, 1.0 eq.) and DMPU (0.36 mL, 3.00 mmol, 5.0 eq.) in dry THF (4 mL) at −78 °C. The mixture was stirred for 45 min then 3-bromo-2-methylpropene (0.27 mL, 3.00 mmol, 5.0 eq.) was added at −78 °C. After 2 h at −78 °C and 1 h at 0 °C the reaction mixture was quenched with water. The aqueous layer was extracted with EtOAc (3 × 8 mL),

the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 3/1) to furnish diene **192** (156 mg, 56%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3065, 3029, 2955, 2871, 1692, 1661, 1438, 1087, 1026, 740; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.19 (m, 10H, H-Ar), 5.35 (s, 1H, H-16), 4.98 – 4.79 (m, 2H, H-18), 4.57 (d, *J* = 11.8 Hz, 1H, H-11a), 4.53 (d, *J* = 11.8 Hz, 1H, H-11b), 3.83 – 3.74 (m, 2H, H-9), 3.70 – 3.62 (m, 2H, H-10), 3.25 – 3.16 (m, 1H, H-4), 2.40 – 2.23 (m, 4H, H-1, H-2, H-3a, H-14a), 2.19 – 2.04 (m, 1H, H-13a), 1.94 (d, *J* = 11.9 Hz, 1H, H-6a), 1.80 (s, 3H, H-19), 1.68 (dd, *J* = 11.9, 5.1 Hz, 1H, H-6b), 1.51 – 1.43 (m, 2H, H-13b, H-14b), 1.43 – 1.37 (m, 1H, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (C=O, C-7), 142.9 (C, C-17), 140.4 (C, C-8), 138.1 (C, C-12), 135.2 (C, C-15), 132.2 (CH, C-Ar), 128.9 (CH, C-Ar), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 127.6 (CH, C-Ar), 126.7 (CH, C-Ar), 115.0 (CH_2, C-18), 106.3 (CH, C-16), 72.9 (CH_2, C-11), 66.2 (CH_2, C-10), 49.5 (CH, C-4), 49.2 (CH, C-2), 48.1 (C, C-5), 39.8 (CH_2, C-9), 38.9 (CH, C-1), 36.0 (CH_2, C-6), 34.9 (CH_2, C-13), 31.8 (CH_2, C-14), 25.6 (CH_2, C-3), 24.8 (CH_3, C-19); **HRMS** found 460.2320 $[MH]^+$, requires 460.2310 for $C_{29}H_{34}NO_2S$.

Preparation of hemiaminal **193**

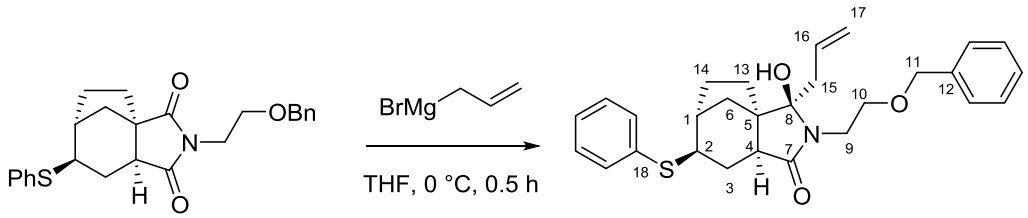


182 **193**

A solution of MeMgBr (2.1 M in Et_2O, 0.10 mL, 0.22 mmol, 1.3 eq.) was added to a solution of **182** (70 mg, 0.16 mmol, 1.0 eq.) in dry THF (2 mL) at 0 °C. The reaction mixture was stirred

for 1.5 h then quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to give hemiaminal **193** (25 mg, 34%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3034, 2953, 2871, 1701, 1393, 1330, 1101, 738; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.11 (m, 10H, H-Ar), 4.52 (d, *J* = 11.7 Hz, 1H, H-11a), 4.50 (d, *J* = 11.7 Hz, 1H, H-11b), 4.04 (s, 1H, OH), 3.75 (ddd, *J* = 11.5, 9.3, 2.3 Hz, 1H, H-10a), 3.66 (app dt, *J* = 14.4, 2.3 Hz, 1H, H-9a), 3.51 (ddd, *J* = 9.3, 3.5, 2.3 Hz, 1H, H-10b), 3.25 – 3.21 (m, 1H, H-4), 3.17 (ddd, *J* = 14.4, 11.5, 3.5 Hz, 1H, H-9b), 2.28 – 2.24 (m, 1H, H-1), 2.23 – 2.18 (m, 1H, H-2), 2.05 (ddd, *J* = 16.0, 8.9, 7.3 Hz, 1H, H-3a), 1.93 – 1.85 (m, 2H, H-3b, H-13a), 1.74 – 1.67 (m, 1H, H-14a), 1.66 – 1.58 (m, 1H, H-14b), 1.49 – 1.37 (m, 1H, H-13b), 1.19 (s, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5 (C=O, C-7), 136.9 (C, C-12), 135.6 (C, C-15), 131.9 (CH, C-Ar), 128.9 (CH, C-Ar), 128.7 (CH, C-Ar), 128.2 (CH, C-Ar), 128.1 (CH, C-Ar), 126.8 (CH, C-Ar), 88.8 (C, C-8), 73.9 (CH_2, C-11), 67.7 (CH_2, C-10), 54.7 (C, C-5), 48.9 (CH, C-4), 47.0 (CH, C-2), 38.6 (CH_2, C-9), 37.8 (CH, C-1), 29.4 (CH_2, C-13), 29.3 (CH_2, C-14), 22.8 (CH_2, C-3), 21.4 (CH_3, C-16); **HRMS** (ES) 438.2088 $[MH]^+$, requires 438.2103 for $C_{26}H_{32}NO_3S$.

Preparation of Allyl **195**

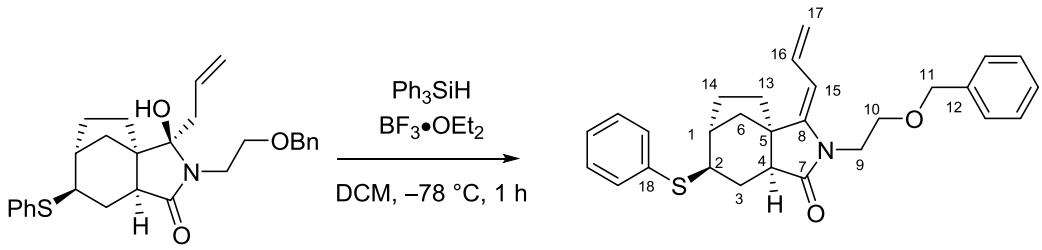


182 **195**

A solution of allylmagnesium bromide (1.0 M in Et_2O, 0.61 mL, 0.61 mmol, 1.3 eq.) was added to a solution of **182** (200 mg, 0.47 mmol, 1.0 eq.) in dry THF (4 mL) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and then quenched with water. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 3/1) to furnish allyl **195** (166 mg, 74%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3387, 2938, 1687, 1438, 1091, 743; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.09 (m, 10H, H-Ar), 5.83 – 5.69 (m, 1H, H-16), 5.04 – 4.96 (m, 2H, H-17), 4.49 (s, 2H, H-11), 4.16 (s, 1H, OH), 3.78 – 3.71 (m, 1H, H-10a), 3.71 – 3.64 (m, 1H, H-9a), 3.48 (ddd, *J* = 9.2, 3.4, 1.7 Hz, 1H, H-10b), 3.28 – 3.18 (m, 2H, H-9b, H-2), 2.38 – 2.33 (m, 2H, H-15), 2.33 – 2.26 (m, 1H, H-4), 2.25 – 2.18 (m, 1H, H-1), 2.07 – 1.97 (m, 2H, H-3), 1.96 – 1.91 (m, 1H, H-14a), 1.75 – 1.68 (m, 1H, H-13a), 1.60 (d, *J* = 11.8 Hz, 1H, H-6a), 1.54 – 1.41 (m, 2H, H-13b, H-14b), 1.20 (dd, *J* = 11.8, 5.6 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (C=O, C-7), 136.8 (C, C-12), 135.6 (C, C-18), 132.7 (CH, C-16), 132.0 (CH, C-Ar), 129.0 (CH, C-Ar), 128.8 (CH, C-Ar), 128.6 (CH, C-Ar), 128.2 (CH, C-Ar), 126.8 (CH, C-Ar), 119.2 (CH_2, C-17), 90.3 (C, C-8), 74.0 (CH_2, C-11), 67.6 (CH_2, C-10), 55.4 (C, C-5), 48.8 (CH, C-2), 46.7 (CH, C-4), 40.8 (CH_2, C-15), 39.9 (CH_2, C-9), 37.3 (CH, C-1), 30.0 (CH_2, C-6), 29.4 (CH_2, C-

14), 28.7 (CH_2, C-13), 22.6 (CH_2, C-3); **HRMS** (ES) found 486.2078 $[MNa]^+$, requires 486.2079 for $C_{28}H_{33}NO_3NaS$.

Preparation of diene **197**

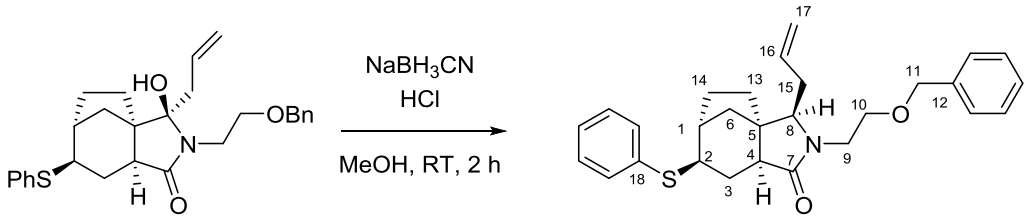


195 **197**

BF_3•OEt_2 (18 µL, 0.15 mmol, 2.0 eq.) was added to a solution of triphenylsilane (39 mg, 0.15 mmol, 2.0 eq.) and **195** (35 mg, 0.075 mmol, 1.0 eq.) in dry DCM (0.5 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C then quenched with water. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 3/1) to furnish diene **197** (23 mg, 69%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3064, 3030, 2955, 2872, 1693, 1440, 1088, 741; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.12 (m, 10H, H-Ar), 6.55 (ddd, *J* = 16.6, 11.4, 10.2 Hz, 1H, H-16), 5.55 (dd, *J* = 11.4, 1.8 Hz, 1H, H-15), 5.07 – 4.93 (m, 2H, H-17), 4.50 (s, 2H, H-11), 3.83 – 3.65 (m, 2H, H-9), 3.60 – 3.64 (m, 2H, H-10), 3.15 (dd, *J* = 11.3, 6.3 Hz, 1H, H-4), 2.39 – 2.31 (m, 1H, H-1), 2.31 – 2.20 (m, 4H, H-13a, H-6a, H-3a, H-2), 1.83 – 1.56 (m, 3H, H-14, H-6b), 1.52 – 1.42 (m, 1H, H-13b), 1.33 – 1.20 (m, 1H, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.5 (C=O, C-7), 144.4 (C, C-8), 138.0 (C, C-12), 134.9 (C, C-18), 131.3 (CH, C-Ar), 130.9 (CH, C-16), 129.0 (CH, C-Ar), 128.4 (CH, C-Ar), 127.5 (CH, C-Ar), 127.5 (CH, C-Ar), 126.8, (CH, C-Ar)

114.2 (CH_2, C-17), 104.1 (CH, C-15), 72.9 (CH_2, C-11), 66.2 (CH_2, C-10), 49.6 (CH, C-4), 49.4 (CH, C-2), 47.6 (C, C-5), 39.7 (CH_2, C-9), 39.1 (CH, C-1), 37.3 (CH_2, C-6), 33.4 (CH_2, C-14), 32.0 (CH_2, C-13), 25.8 (CH_2, C-3); **HRMS** (ES) found 468.2071 $[MNa]^+$, requires 468.2075 for $C_{28}H_{31}NO_2NaS$.

Reduction of hemiaminal **195**



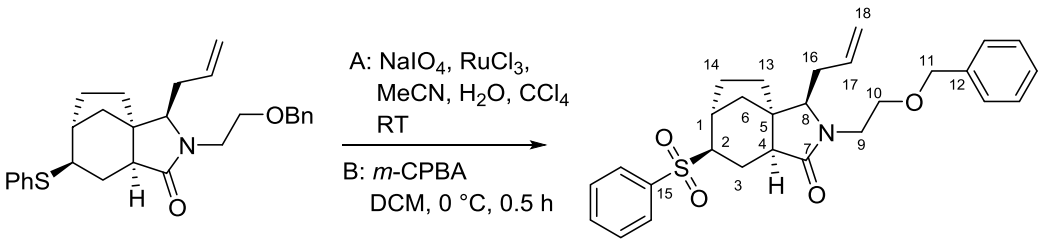
195 **198**

$NaBH_3CN$ (252 mg, 4.00 mmol, 2.0 eq.) was added to a solution of **195** (0.93 g, 2.00 mmol, 1.0 eq.) in methanol (10 mL) at 0 °C. Concentrated HCl (aq) was added until pH ≈ 3 and the reaction mixture was stirred for 1 h at 0 °C and 2 h at RT. The mixture was slowly quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give allyl **198** (950 mg, 98%) as a white oil. **IR** ν_{max}/cm^{-1} 3057, 2935, 2865, 1680, 1438, 1275, 1099, 916, 739; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.09 (m, 10H, H-Ar), 5.73 – 5.60 (m, 1H, H-16), 5.08 – 4.96 (m, 2H, H-17), 4.46 (d, *J* = 12.0 Hz, 1H, H-11a), 4.40 (d, *J* = 12.0 Hz, 1H, H-11b), 3.81 (dt, *J* = 14.5, 5.5 Hz, 1H, H-9a), 3.60 (dd, *J* = 8.1, 4.7 Hz, 1H, H-8), 3.54 – 3.44 (m, 2H, H-10), 3.20 – 3.10 (m, 2H, H-9b, H-4), 2.52 – 2.43 (m, 1H, H-15a), 2.28 – 2.22 (m, 1H, H-1), 2.21 – 2.06 (m, 3H, H-3a, H-2, H-15b), 1.90 – 1.80 (m, 1H, H-14a), 1.71 – 1.60 (m, 2H, H-13a, H-6a), 1.52 – 1.44 (m, 1H, H-3b), 1.43 – 1.33 (m, 2H, H-13b,

H-14b), 1.21 – 1.12 (m, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C=O, C-7), 138.1 (C, C-12), 135.4 (C, C-18), 134.9 (CH, C-16), 131.4 (CH, C-Ar), 128.9 (CH, C-Ar), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 126.6 (CH, C-Ar), 117.7 (CH_2, C-17), 72.9 (CH_2, C-11), 67.8 (CH_2, C-10), 60.8 (CH, C-8), 49.8 (CH, C-2), 49.2 (CH, C-4), 48.2 (C, C-5), 40.1 (CH_2, C-9), 38.7 (CH, C-1), 35.2 (CH_2, C-13), 33.7 (CH_2, C-15), 30.2 (CH_2, C-14), 27.9 (CH_2, C-6), 24.8 (CH_2, C-3); 1 signal in the CH aromatic region were not observed due to overlap; **HRMS** (ES) found 470.2134 $[MNa]^+$, requires 470.2130 for $C_{28}H_{33}NO_2NaS$.

6.2. Compounds for Chapter 3

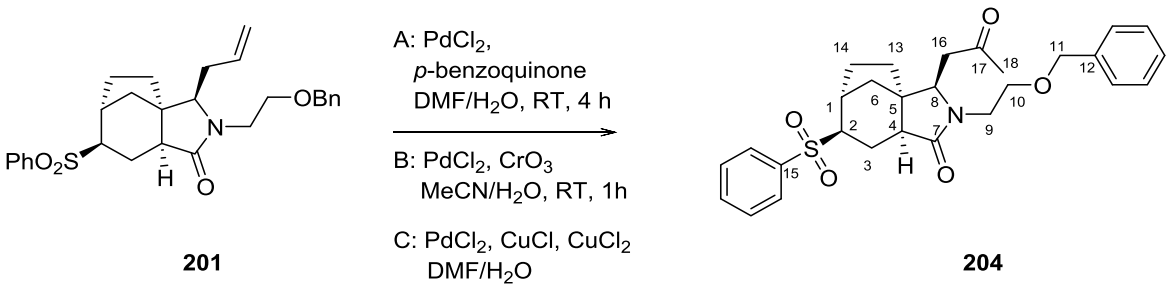
Preparation of sulfone **201**



Method A: Sodium periodate (187 mg, 0.88 mmol, 4.0 eq.) and ruthenium chloride hydrate (7 mg, 0.033 mmol, 0.15 eq.) were successively added to a solution of **198** (100 mg, 0.22 mmol, 1.0 eq.) in a mixture of MeCN (1 mL), H_2O (1 mL) and CCl_4 (3 mL) at RT. The mixture was stirred for 1.5 h then quenched with water. The aqueous layer was extracted with DCM (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered through Celite® and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to provide sulfone **201** (94 mg, 90%) as a colourless gum.

Method B: m-CPBA (77%, 437 mg, 2.54 mmol, 2.0 eq.) was added to a solution of **198** (568 mg, 1.27 mmol, 1.0 eq.) in DCM (15 mL) at 0 °C. The mixture was stirred for 0.5 h at 0 °C then quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to yield sulfone **201** (556 mg, 91%) as a colourless gum. **IR** ν_{max}/cm^{-1} 3068, 2956, 2873, 1720, 1682, 1639, 1446, 1304, 1145, 1085, 727; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.53 (m, 5H, H-Ar), 7.41 – 7.27 (m, 5H, H-Ar), 5.79 – 5.67 (m, 1H, H-17), 5.16 – 5.04 (m, 2H, H-18), 4.51 (d, *J* = 11.9 Hz, 1H, H-11a), 4.45 (d, *J* = 11.9 Hz, 1H, H-11b), 3.87 (dt, *J* = 14.4, 5.4 Hz, 1H, H-9a), 3.75 (dd, *J* = 8.5, 4.3 Hz, 1H, H-8), 3.62 – 3.55 (m, 2H, H-10), 3.23 (dt, *J* = 14.4, 5.4 Hz, 1H, H-9b), 3.08 – 3.01 (m, 1H, H-1), 2.93 (dd, *J* = 12.3, 6.5 Hz, 1H, H-2), 2.64 – 2.54 (m, 1H, H-16a), 2.29 – 2.20 (m, 1H, H-16b), 2.20 – 2.11 (m, 1H, H-4), 2.11 – 2.02 (m, 1H, H-14a), 1.92 – 1.83 (m, 1H, H-3a), 1.80 – 1.70 (m, 1H, H-13a), 1.69 – 1.60 (m, 2H, H-6a, H-3b), 1.54 – 1.46 (m, 1H, H-13b), 1.46 – 1.34 (m, 2H, H-14b, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4 (C=O, C-7), 138.0 (C, C-12), 137.6 (C, C-15), 134.4 (CH, C-17), 133.7 (CH, C-Ar), 129.3 (CH, C-Ar), 128.8 (CH, C-Ar), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 127.6 (CH, C-Ar), 118.0 (CH_2, C-18), 72.9 (CH_2, C-11), 67.7 (CH_2, C-10), 66.5 (CH, C-2), 60.8 (CH, C-8), 49.0 (CH, C-4), 47.3 (C, C-5), 40.1 (CH_2, C-9), 36.0 (CH_2, C-13), 33.8 (CH_2, C-16), 31.9 (CH, C-1), 31.5 (CH_2, C-14), 28.5 (CH_2, C-6), 19.9 (CH_2, C-3); **HRMS** (ES) found 502.2025 $[MNa]^+$, requires 502.2028 for $C_{28}H_{33}NO_4NaS$.

Preparation of ketone **204**



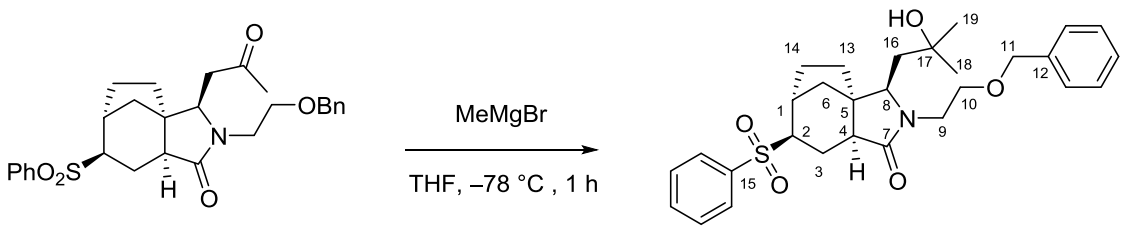
Method A: $PdCl_2$ (77 mg, 0.44 mmol, 0.15 eq.) and *p*-benzoquinone (315 mg, 2.92 mmol, 1.0 eq.) were added to a solution of sulfone **201** (1.40 g, 2.92 mmol, 1.0 eq.) in a mixture of DMF (12 mL) and H_2O (2 mL) at RT. The reaction mixture was stirred for 4 h before being quenched with a solution of 1 M HCl (aq). The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic layers were washed with water (5 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/ EtOAc = 1/2 to 1/4) to furnish ketone **204** (1.04 g, 72%) as a white powder.

Method B: Chromium trioxide (7 mg, 0.07 mmol, 2.0 eq.) was added to a solution of $PdCl_2$ (2 mg, 0.01 mmol, 0.30 eq.) and **201** (17 mg, 0.035 mmol, 1.0 eq.) in a mixture of DMF (0.6 mL) and H_2O (0.1 mL) at RT. After 1 h, the reaction mixture was quenched with a solution of 1 M HCl (aq). The aqueous layer was extracted with EtOAc (3 × 4 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/ EtOAc = 1/2 to 1/4) to furnish ketone **204** (10 mg, 55%) as a white powder.

Method C: $PdCl_2$ (8 mg, 0.05 mmol, 0.30 eq.), $CuCl_2$ (21 mg, 0.16 mmol, 1.0 eq.) and CuCl (16 mg, 0.16 mmol, 1.0 eq.) were dissolved in a mixture of DMF (1.6 mL) and H_2O (0.4 mL).

The mixture was stirred for 1 h at 60 °C. Allyl **201** (75 mg, 0.16 mmol, 1.0 eq.), dissolved in a mixture of DMF (0.8 mL) and H_2O (0.2 mL), was then added to the reaction mixture and the solution was stirred for 3 h at 60 °C before being quenched with a solution of 1 M HCl (aq). The aqueous layer was extracted with EtOAc (3 × 6 mL), the combined organic layers were washed with water (5 × 3 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/ EtOAc = 1/2 to 1/4) to furnish ketone **204** (47 mg, 60%) as a white powder. **m.p.** 48 – 50 °C; **IR** ν_{max}/cm^{-1} 3062, 3038, 2962, 2874, 1715, 1680, 1446, 1303, 1145, 1086, 724; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.53 (m, 5H, H-Ar), 7.43 – 7.25 (m, 5H, H-Ar), 4.47 (s, 2H, H-11), 4.26 ("app t", *J* = 6.3 Hz, 1H, H-8), 3.63 – 3.57 (m, 1H, H-10a), 3.57 – 3.48 (m, 2H, H-10b, H-9a), 3.32 – 3.24 (m, 1H, H-9b), 3.08 – 3.01 (m, 1H, H-1), 2.99 – 2.91 (m, 2H, H-16a, H-2), 2.44 (dd, *J* = 18.0, 6.3 Hz, 1H, H-16b), 2.21 – 2.13 (m, 1H, H-4), 2.13 – 2.05 (m, 1H, H-14a), 2.03 (s, 3H, H-18), 1.90 – 1.75 (m, 2H, H-13a, H-3a), 1.75 – 1.70 (m, 1H, H-6a), 1.69 – 1.62 (m, 1H, H-3b), 1.51 (dd, *J* = 11.2, 9.3 Hz, 1H, H-13b), 1.45 – 1.35 (m, 1H, H-14b), 1.07 (dd, *J* = 11.8, 4.8 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.8 (C=O, C-17), 175.3 (C=O, C-7), 137.8 (C, C-12), 137.6 (C, C-15), 133.8 (CH, C-Ar), 129.3 (CH, C-Ar), 128.7 (CH, C-Ar), 128.5 (CH, C-Ar), 128.0 (CH, C-Ar), 127.9 (CH, C-Ar), 73.3 (CH_2, C-11), 68.3 (CH_2, C-10), 66.5 (CH, C-2), 57.4 (CH, C-8), 48.4 (CH, C-4), 46.6 (C, C-5), 44.1 (CH_2, C-16), 41.6 (CH_2, C-9), 35.6 (CH_2, C-13), 31.6 (CH, C-1), 31.5 (CH_2, C-14), 30.2 (CH_3, C-18), 29.5 (CH_2, C-6), 20.1 (CH_2, C-3); **HRMS** (ES) found 518.1973 $[MNa]^+$, requires 518.1977 for $C_{28}H_{33}NO_5NaS$.

Preparation of alcohol **200**

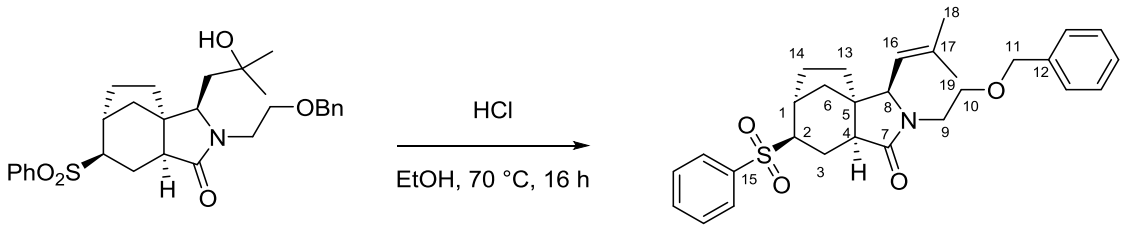


204 **200**

A solution of MeMgBr (3.0 M in Et_2O, 0.56 mL, 1.76 mmol, 2.0 eq.) was added to a solution of **204** (436 mg, 0.88 mmol, 1.0 eq.) in dry THF (6 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C before being quenched with water. The aqueous layer was extracted with EtOAc (3 × 8 mL), the combined organic layers were washed with a saturated aqueous solution of NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to furnish alcohol **200** (367 mg, 82%) as a white powder. **m.p.** = 53 – 56 °C; **IR** ν_{max}/cm^{-1} 3438, 3065, 2963, 2927, 2871, 1667, 1446, 1303, 1144; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.55 (m, 5H, H-Ar), 7.39 – 7.27 (m, 5H, H-Ar), 4.50 (d, *J* = 11.3 Hz, 1H, H-11a), 4.45 (d, *J* = 11.3 Hz, 1H, H-11b), 3.87 (dd, *J* = 5.5, 3.1 Hz, 1H, H-8), 3.80 – 3.72 (m, 2H, H-10a, H-9a), 3.70 – 3.59 (m, 2H, H-10b, H-9b), 3.28 (s, 1H, OH), 3.08 – 3.01 (m, 1H, H-1), 2.98 (dd, *J* = 11.7, 6.9 Hz, 1H, H-2), 2.15 (dd, *J* = 11.1, 7.8 Hz, 1H, H-4), 2.12 – 2.03 (m, 1H, H-13a), 1.93 – 1.84 (m, 1H, H-3a), 1.78 – 1.64 (m, 3H, H-16a, H-14a, H-3b), 1.64 – 1.55 (m, 2H, H-16b, H-6a), 1.51 – 1.40 (m, 2H, H-14b, H-13b), 1.24 (dd, *J* = 12.2, 4.8 Hz, 1H, H-6b), 1.19 (s, 3H, H-18), 1.01 (s, 3H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6 (C=O, C-7), 137.6 (C, C-12), 137.1 (C, C-15), 133.7 (CH, C-Ar), 129.3 (CH, C-Ar), 128.8 (CH, C-Ar), 128.6 (CH, C-Ar), 128.4 (CH, C-Ar), 128.2 (CH, C-Ar), 73.8 (CH_2, C-11), 69.4 (CH_2, C-10), 69.2 (C, C-17), 66.4 (CH, C-2), 59.4 (CH, C-8), 48.2 (CH, C-4), 48.2 (C, C-5), 42.2 (CH_2, C-16), 40.6 (CH_2, C-9), 33.9 (CH_2, C-

14), 32.1 (CH, C-1), 31.7 (CH_2, C-13), 31.0 (CH_3, C-18), 28.9 (CH_2, C-6), 28.7 (CH_3, C-19), 19.9 (CH_2, C-3); **HRMS** (ES) found 534.2293 $[MNa]^+$, requires 534.2290 for $C_{29}H_{37}NO_5SNa$.

Preparation of alkene **212**

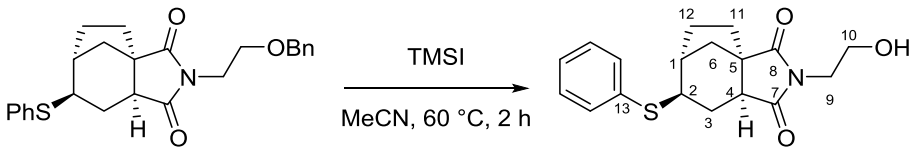


200 **212**

A solution of HCl (aq) (37%, 5 drops) was added to a solution of **200** (19 mg, 0.037 mmol, 1.0 eq.) in ethanol (2 mL) at RT. The reaction mixture was stirred for 1 h at RT and 16 h at 70 °C then carefully quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to give alkene **212** (12 mg, 66%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3068, 2933, 2873, 1670, 1446, 1304, 1144, 1085, 750; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.86 (m, 2H, H-Ar), 7.68 – 7.62 (m, 1H, H-Ar), 7.59 – 7.52 (m, 2H, H-Ar), 7.36 – 7.23 (m, 5H, H-Ar), 4.85 – 4.80 (m, 1H, H-16), 4.51 (d, *J* = 12.0 Hz, 1H, H-11a), 4.41 (d, *J* = 12.0 Hz, 1H, H-11b), 4.38 (d, *J* = 10.3 Hz, 1H, H-8), 3.71 (ddd, *J* = 14.1, 6.5, 5.0 Hz, 1H, H-9a), 3.57 – 3.43 (m, 2H, H-10), 3.07 – 2.98 (m, 2H, H-9b, H-1), 2.93 (dd, *J* = 12.2, 6.5 Hz, 1H, H-2), 2.17 (dd, *J* = 11.8, 7.4 Hz, 1H, H-4), 2.12 – 2.00 (m, 1H, H-14a), 1.91 – 1.81 (m, 1H, H-3a), 1.75 (d, *J* = 1.3 Hz, 3H, H-18), 1.67 – 1.59 (m, 2H, H-6a, H-3b), 1.57 (d, *J* = 1.4 Hz, 3H, H-19), 1.51 – 1.32 (m, 3H, H-14b, H-13), 1.08 (dd, *J* = 12.1, 4.8 Hz, 1H, H-

6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1 (C=O, C-7), 139.2 (C, C-17), 138.1 (C, C-12), 137.6 (C, C-15), 133.7 (CH, C-Ar), 129.3 (CH, C-Ar), 128.8 (CH, C-Ar), 128.4 (CH, C-Ar), 127.8 (CH, C-Ar), 127.7 (CH, C-Ar), 120.7 (CH, C-16), 72.7 (CH_2, C-11), 67.1 (CH_2, C-10), 66.9 (CH, C-2), 60.3 (CH, C-8), 48.3 (CH, C-4), 47.8 (C, C-5), 40.2 (CH_2, C-9), 35.2 (CH_2, C-13), 31.9 (CH, C-1), 31.6 (CH_2, C-14), 29.4 (CH_2, C-6), 26.2 (CH_3, C-18), 20.1 (CH_2, C-3), 18.0 (CH_3, C-19); **HRMS** (ES) found 494.2290 $[MH]^+$, requires 494.2287 for $C_{29}H_{36}NO_4S$.

Preparation of alcohol **215**

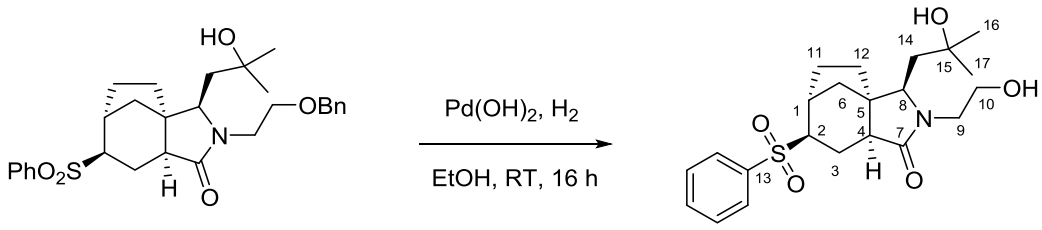


182 **215**

TMSI (20 µL, 0.136 mmol, 2.8 eq.) was added to a solution of **182** (22 mg, 0.05 mmol, 1.0 eq.) in dry MeCN (1 mL) at RT. The mixture was heated to 60 °C and stirred for 2 h before being quenched with water. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were washed with a saturated aqueous solution of NH_4Cl (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to provide alcohol **215** (12 mg, 73%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3449, 2955, 2876, 1769, 1687, 1394, 1167, 1045, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 5H, H-Ar), 3.85 – 3.70 (m, 4H, H-9, H-10), 3.19 (dd, *J* = 11.5, 6.9 Hz, 1H, H-4), 2.56 – 2.48 (m, 2H, H-1, H-2), 2.34 (dd, *J* =14.0, 6.9 Hz, 1H, H-3a), 2.33 – 2.17 (m, 2H, H-6a, H-11a), 1.86 – 1.80 (m, 1H, H-12a), 1.69 – 1.60 (m, 2H, H-11b, H-12b), 1.59 – 1.51 (m, 1H, H-6b), 1.47 – 1.36 (m, 1H, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.0 (C=O, C-8), 178.6 (C=O, C-7), 134.4 (C, C-13), 131.5 (CH, C-Ar), 129.1

(CH, C-Ar), 127.1 (CH, C-Ar), 60.8 (CH_2, C-10), 50.1 (C, C-5), 49.6 (CH, C-4), 47.4 (CH, C-2), 41.7 (CH_2, C-9), 40.2 (CH, C-1), 34.0 (CH_2, C-11), 33.6 (CH_2, C-12), 31.6 (CH_2, C-6), 25.1 (CH_2, C-3); **HRMS** (ES) found 354.1133 $[MNa]^+$, requires 354.1140 for $C_{18}H_{21}NO_3NaS$.

Preparation of diol **216**

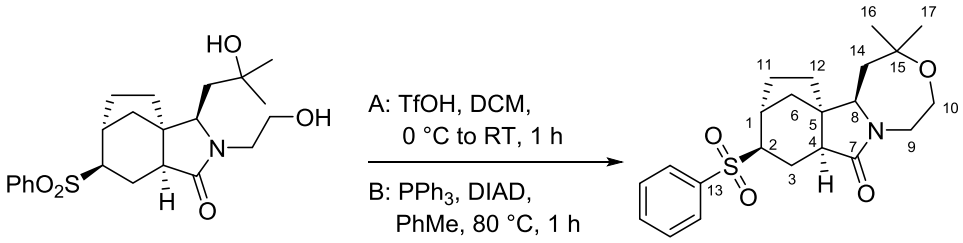


200 **216**

Compound **200** (60 mg, 0.12 mmol, 1.0 eq.) and $Pd(OH)_2$ (3.3 mg, 0.02 mmol, 0.20 eq.) were dissolved in ethanol (2 mL) and put under hydrogen pressure (balloon). The reaction mixture was stirred for 16 h at RT then filtered through Celite® and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 0/1 to 0/1 + 5% MeOH) to furnish diol **216** (367 mg, 82%) as a white powder. **m.p.** 77 – 80 °C; **IR** ν_{max}/cm^{-1} 3393, 3095, 3065, 2961, 2884, 1662, 1447, 1381, 1303, 1144, 1084, 723. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.58 (m, 5H, H-Ar), 4.01 ("app t", *J* = 4.3 Hz, 1H, H-8), 3.82 – 3.75 (m, 2H, H-10), 3.72 – 3.66 (m, 1H, H-9a), 3.54 (ddd, *J* = 14.6, 8.1, 3.5 Hz, 1H, H-9b), 3.11 – 3.04 (m, 1H, H-1), 2.99 (dd, *J* = 11.4, 7.0 Hz 1H, H-2), 2.26 (dd, *J* = 11.0, 7.9 Hz, 1H, H-4), 2.16 – 2.08 (m, 1H, H-11a), 1.93 – 1.82 (m, 1H, H-3a), 1.81 – 1.75 (m, 1H, H-12a), 1.75 – 1.68 (m, 3H, H-14, H-3b), 1.68 – 1.63 (m, 1H, H-6a), 1.56 – 1.43 (m, 2H, H-11b, H-12b), 1.35 (s, 3H, H-16), 1.31 (dd, *J* = 13.2, 5.9 Hz, 1H, H-6b), 1.27 (s, 3H, H-17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6 (C=O, C-7), 137.6 (C, C-13), 133.8 (CH, C-Ar), 129.3 (CH, C-Ar), 128.8

(CH, C-Ar), 70.0 (C, C-15), 66.4 (CH, C-2), 62.4 (CH_2, C-10), 59.5 (CH, C-8), 48.6 (CH, C-4), 48.4 (C, C-5), 43.5 (CH_2, C-9), 41.5 (CH_2, C-14), 34.2 (CH_2, C-12), 31.8 (CH, C-1), 31.6 (CH_2, C-11), 31.6 (CH_3, C-16), 29.8 (CH_3, C-17), 29.3 (CH_2, C-6), 19.9 (CH_2, C-3); **HRMS** (ES) found 444.1828 $[MNa]^+$, requires 444.1821 for $C_{22}H_{31}NO_5NaS$.

Preparation of tetracycle **199**



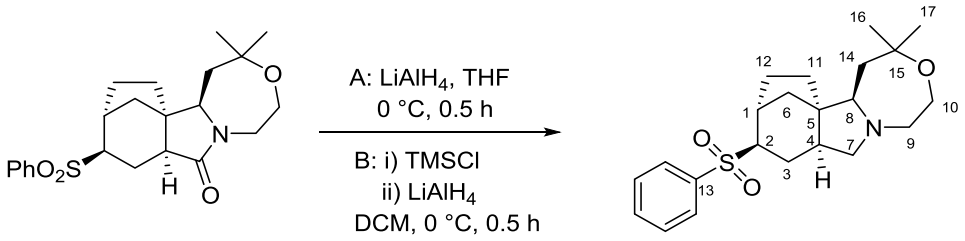
216 **199**

Method A: Triflic acid (0.30 mL, 3.36 mmol, 2.0 eq.) was added to a solution of **216** (470 mg, 1.12 mmol, 1.0 eq.) in dry DCM (5 mL) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and 0.5 h at RT before being quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to give tetracyclic compound **199** (320 mg, 71%) as a white powder.

Method B: DIAD (57 µL, 0.29 mmol, 1.3 eq.) was added to a solution of PPh_3 (77 mg, 0.29 mmol, 1.3 eq.) and **216** (95 mg, 0.23 mmol, 1.0 eq.) in dry PhMe (2 mL) at 80 °C. After 1 h, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to give tetracyclic compound **199** (46 mg, 51%) as a white powder. **m.p.** 65 – 69 °C; **IR** ν_{max}/cm^{-1} 3059, 2968, 2875, 1680, 1446,

1426, 1303, 1145, 1084, 918, 725; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H, H-Ar), 7.68 – 7.62 (m, 1H, H-Ar), 7.58 – 7.53 (m, 2H, H-Ar), 3.82 – 3.73 (m, 2H, H-8, H-9a), 3.71 – 3.64 (m, 2H, H-10), 3.22 – 3.15 (m, 1H, H-9b), 3.07 (dd, *J* = 7.4, 4.7 Hz, 1H, H-1), 2.95 (dd, *J* = 12.3, 6.6 Hz, 1H, H-2), 2.17 (dd, *J* = 11.8, 7.6 Hz, 1H, H-4), 2.11 – 2.05 (m, 1H, H-11a), 1.86 (ddd, *J* = 14.2, 7.6, 6.6 Hz, 1H, H-3a), 1.77 – 1.69 (m, 1H, H-14a), 1.66 – 1.55 (m, 4H, H-3b, H-6a, H-14b, H-12a), 1.57 – 1.50 (m, 1H, H-12b), 1.49 – 1.43 (m, 1H, H-11b), 1.23 (s, 6H, H-16, H-17), 1.08 (dd, *J* = 12.1, 4.7 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (C=O, C-7), 137.5 (C, C-13), 133.8 (CH, C-Ar), 129.4 (CH, C-Ar), 128.8 (CH, C-Ar), 74.5 (C, C-15), 66.4 (CH, C-2), 60.2 (CH_2, C-10), 58.3 (CH, C-8), 48.3 (CH, C-4), 46.6 (C, C-5), 45.8 (CH_2, C-9), 41.9 (CH_2, C-14), 34.6 (CH_2, C-12), 32.1 (CH, C-1), 31.6 (CH_2, C-11), 29.0 (CH_2, C-6), 28.4 (CH_3, C-17), 26.7 (CH_3, C-16), 20.1 (CH_2, C-3); **HRMS** (ES) found 426.1717 $[MNa]^+$, requires 426.1715 for $C_{22}H_{29}NO_4NaS$.

Preparation of amine **223**



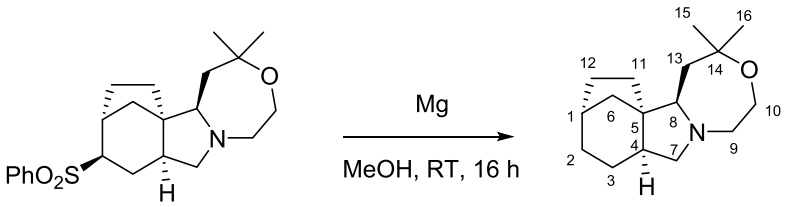
199 **223**

Method A: A solution of $LiAlH_4$ (2.4 M in THF, 33 µL, 0.08 mmol, 2.0 eq.) was added to a solution of **199** (16 mg, 0.04 mmol, 1.0 eq.), in dry THF (1.5 mL), at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C before being quenched with water. The aqueous layer was extracted with EtOAc (3 × 3 mL), the combined organic layers were dried over $MgSO_4$, filtered and

concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to give amine **223** (9 mg, 60%) as a white powder.

Method B: TMSCl (120 µL, 0.95 mmol, 1.2 eq.) was added to a solution of **199** (318 mg, 0.79 mmol, 1.0 eq.), in dry DCM (5 mL), at 0 °C. The reaction mixture was stirred for 15 min before addition of a solution of $LiAlH_4$ (2.4 M in THF, 0.60 mL, 1.42 mmol, 1.8 eq.). After 0.5 h, the reaction mixture was quenched with a solution of 2 N NaOH (aq). The aqueous layer was extracted with EtOAc (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to give amine **223** (294 mg, 96%) as a white powder. **m.p** 60 – 62 °C; **IR** ν_{max}/cm^{-1} 3066, 2937, 2868, 2800, 1446, 1304, 1143, 1085, 725; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.51 (m, 5H, H-Ar), 3.78 (dd, *J* = 13.5, 10.6 Hz, 1H, H-10a), 3.51 (ddd, *J* = 13.5, 3.2, 2.0 Hz, 1H, H-10b), 2.94 (dd, *J* = 12.5, 3.2 Hz, 1H, H-9a), 2.86 (dd, *J* = 11.6, 4.8 Hz, 1H, H-1), 2.84 – 2.79 (m, 1H, H-2), 2.70 (d, *J* = 9.3 Hz, 1H, H-7a), 2.47 (d, *J* = 9.6 Hz, 1H, H-8), 2.41 (d, *J* = 9.3 Hz, 1H, H-7b), 2.25 (ddd, *J* = 12.5, 10.6, 2.0 Hz, 1H, H-9b), 2.07 – 1.96 (m, 1H, H-12a), 1.76 – 1.63 (m, 3H, H-14a, H-6a, H-4), 1.62 – 1.53 (m, 2H, H-3), 1.47 – 1.36 (m, 2H, H-14b, H-11a), 1.31 – 1.23 (m, 2H, H-12b, H-11b), 1.18 (s, 3H, H-16), 1.15 (s, 3H, H-17), 0.91 (dd, *J* = 12.1, 4.8 Hz, 1H, H-6a); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0 (C, C-13), 133.5 (CH, C-Ar), 129.1 (CH, C-Ar), 128.8 (CH, C-Ar), 74.7 (C, C-15), 67.9 (CH, C-2), 64.3 (CH, C-8), 61.8 (CH_2, C-10), 61.4 (CH_2, C-7), 58.4 (CH_2, C-9), 52.8 (C, C-5), 43.0 (CH, C-4), 41.4 (CH_2, C-14), 33.9 (CH_2, C-11), 31.9 (CH_2, C-12), 31.6 (CH, C-1), 28.8 (CH_3, C-16), 28.6 (CH_2, C-6), 27.6 (CH_3, C-17), 25.0 (CH_2, C-3); **HRMS** (ES) found 390.2094 $[MH]^+$, requires 390.2103 for $C_{22}H_{32}NO_3S$.

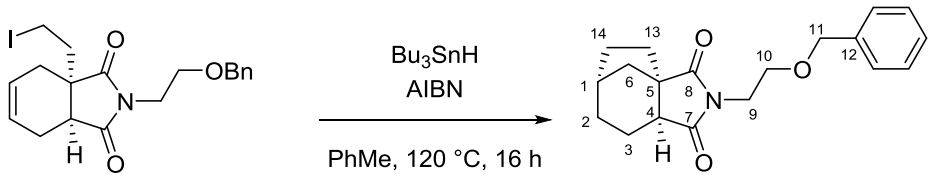
Cleavage of sulfone **223**



223 **239**

Magnesium powder (37 mg, 1.54 mmol, 20.0 eq.) was added to a solution of **223** (30 mg, 0.077 mmol, 1.0 eq.) in dry MeOH (2 mL) at RT. The mixture was stirred at RT for 16 h then quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to furnish tetracyclic compound **239** (19 mg, 98%) as a colourless oil; **IR** ν_{max}/cm^{-1} 2929, 2862, 2801, 1462, 1364, 1271, 1106, 1074, 1061, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.87 – 3.77 (m, 1H, H-10a), 3.61 – 3.50 (m, 1H, H-10b), 2.99 (dd, *J* = 12.4, 3.2 Hz, 1H, H-9a), 2.87 (dd, *J* = 9.9, 5.8 Hz, 1H, H-7a), 2.63 (d, *J* = 9.4 Hz, 1H, H-8), 2.53 – 2.41 (m, 2H, H-9b, H-7b), 2.21 – 2.13 (m, 1H, H-1), 1.90 – 1.71 (m, 4H, H-13a, H-12, H-4), 1.66 – 1.48 (m, 3H, H-13b, H-6a, H-3a), 1.45 – 1.35 (m, 2H, H-11a, H-2a), 1.35 – 1.22 (m, 3H, H-11b, H-3b, H-2b), 1.19 (s, 3H, H-15), 1.15 (s, 3H, H-16), 0.95 (dd, *J* = 11.3, 5.2 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 74.9 (C, C-14), 65.2 (CH, C-8), 62.1 (CH_2, C-10), 60.0 (CH_2, C-7), 58.3 (CH_2, C-9), 52.6 (C, C-5), 44.9 (CH, C-4), 41.1 (CH_2, C-13), 33.0 (CH_2, C-2), 31.6 (CH, C-1), 30.9 (CH_2, C-6), 30.6 (CH_2, C-12), 30.0 (CH_2, C-11), 28.8 (CH_3, C-15), 27.4 (CH_3, C-16), 22.0 (CH_2, C-3); **HRMS** (ES) found 250.2168 $[MH]^+$, requires 250.2171 for $C_{16}H_{28}NO$.

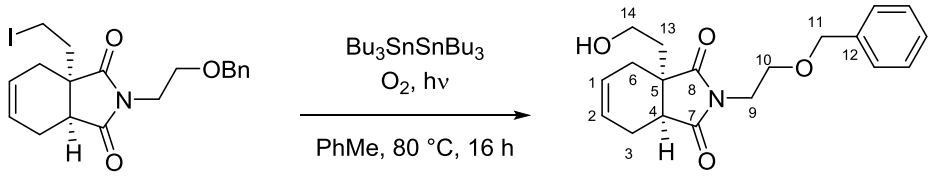
Preparation of bicyclo[3.2.1]octane system **250**



181 **250**

A solution of Bu_3SnH (86 µL, 0.32 mmol, 1.4 eq.) and AIBN (0.2 M in PhMe, 0.45 mL, 0.09 mmol, 0.40 eq.), in dry PhMe (2 mL) was added over 2 h to a solution of **181** (100 mg, 0.23 mmol, 1.0 eq.) in dry PhMe (3 mL) at 120 °C. The mixture was stirred overnight at 120 °C. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 2/1) to yield bicyclic compound **250** (60 mg, 84%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3030, 2947, 2869, 1770, 1694, 1392, 1101, 736; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.15 (m, 5H, H-Ar), 4.44 (s, 2H, H-11), 3.75 – 3.65 (m, 2H, H-9), 3.60 – 3.53 (m, 2H, H-10), 2.37 (dd, *J* = 12.0, 7.2 Hz, 1H, H-4), 2.34 – 2.28 (m, 1H, H-1), 2.16 – 2.02 (m, 2H, H-14a, H-6a), 2.02 – 1.92 (m, 1H, H-2a), 1.89 – 1.81 (m, 1H, H-3a), 1.57 – 1.45 (m, 3H, H-13, H-6b), 1.36 – 1.24 (m, 2H, H-14b, H-3b), 1.24 – 1.15 (m, 1H, H-2b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.1 (C=O, C-8), 179.1 (C=O, C-7), 138.0 (C, C-12), 128.4 (CH, C-Ar), 127.6 (CH, C-Ar), 127.0 (CH, C-Ar), 72.5 (CH_2, C-11), 66.2 (CH_2, C-10), 50.0 (C, C-5), 48.6 (CH, C-4), 37.9 (CH_2, C-9), 35.1 (CH_2, C-13), 33.6 (CH_2, C-6), 32.9 (CH_2, C-14), 32.0 (CH, C-1), 30.5 (CH_2, C-2), 17.2 (CH_2, C-3); **HRMS** (ES) found 336.1575 $[MNa]^+$, requires 336.1576 for $C_{19}H_{23}NO_3Na$.

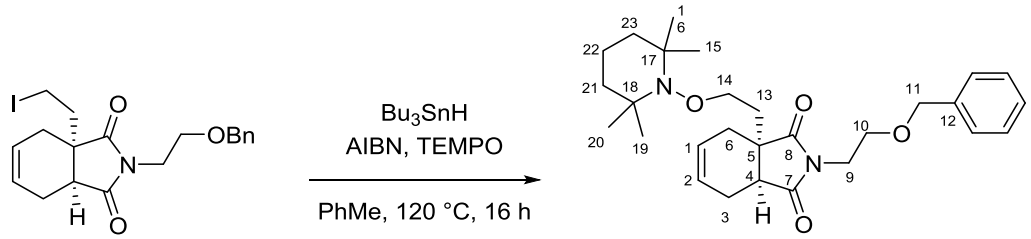
Preparation of alcohol **180**



181 **180**

Hexabutylditin (0.10 mL, 0.20 mmol, 1.5 eq.) was added to a solution of **181** (60 mg, 0.13 mmol, 1.0 eq.) in dry PhMe (1.5 mL) under an atmosphere of oxygen. The reaction mixture was irradiated with a sun lamp for 2 h then heated to 120 °C and stirred for 16 h. The solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 1/1) to give alcohol **180** (19 mg, 43%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3393, 3023, 2931, 2875, 1771, 1692, 1453, 1102, 740; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H, H-Ar), 5.90 – 5.78 (m, 2H, H-1, H-2), 4.50 (d, *J* = 8.2 Hz, 1H, H-11a), 4.48 (d, *J* = 8.2 Hz, 1H, H-11b), 3.75 – 3.69 (m, 2H, H-9), 3.68 – 3.59 (m, 4H, H-14, H-10), 3.04 (dd, *J* = 7.4, 2.3 Hz, 1H, H-4), 2.65 (ddd, *J* = 15.7, 6.3, 2.3 Hz, 1H, H-3a), 2.57 (dd, *J* = 15.1, 6.0 Hz, 1H, H-6a), 2.20 (ddd, *J* = 15.7, 7.4, 2.7 Hz, 1H, H-3b), 2.02 – 1.84 (m, 3H, H-6b, H-13); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.6 (C=O, C-8), 179.5 (C=O, C-7), 137.6 (C, C-Ar), 128.4 (CH, C-Ar), 128.0 (CH, C-Ar), 127.8 (CH, C-1, C-2), 127.5 (CH, C-Ar), 72.6 (CH_2, C-11), 66.0 (CH_2, C-10), 58.7 (CH_2, C-14), 47.2 (CH, C-5), 45.2 (CH, C-4), 39.5 (CH_2, C-13), 38.1 (CH_2, C-9), 31.5 (CH_2, C-6), 23.8 (CH_2, C-3); **HRMS** (ES) found 352.1627 [MNa]+, requires 352.1629 for $C_{19}H_{23}NO_4Na$.

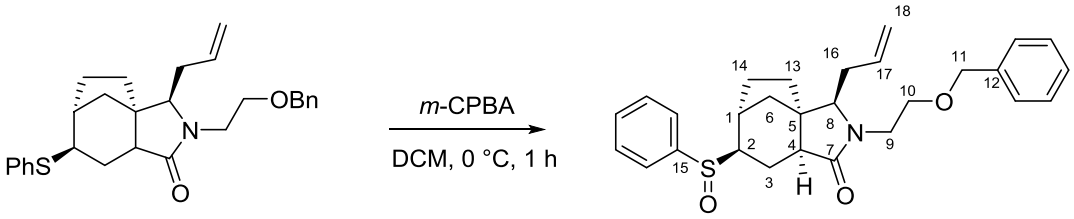
Preparation of compound **252**



181 **252**

A solution of Bu_3SnH (41 µL, 0.15 mmol, 1.4 eq.) and AIBN (0.2 M in PhMe, 0.22 mL, 0.044 mmol, 0.40 eq.), in dry PhMe (1 mL) was added over 2 h to a solution of **181** (50 mg, 0.11 mmol, 1.0 eq.) and TEMPO (52 mg, 0.33 mmol, 3.0 eq.), in dry PhMe (2 mL), at 120 °C. The mixture was stirred for 16 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 8/1 to 5/1) to give **252** (40 mg, 77%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3044, 2974, 2934, 2868, 1775, 1699, 1398, 1132, 737; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.10 (m, 5H, H-Ar), 5.80 – 5.62 (m, 2H, H-1, H-2), 4.38 (s, 2H, H-11), 3.77 – 3.69 (m, 2H, H-14), 3.64 – 3.59 (m, 2H, H-9), 3.48 – 3.43 (m, 2H, H-10), 3.00 (dd, *J* = 7.1, 2.3 Hz, 1H, H-4), 2.58 (ddd, *J* = 15.5, 6.3, 2.3 Hz, 1H, H-3a), 2.41 (dd, *J* = 15.1, 5.8 Hz, 1H, H-6a), 2.18 – 2.09 (m, 1H, H-3b), 1.97 – 1.85 (m, 2H, H-13a, H-6b), 1.84 – 1.74 (m, 1H, H-13b), 1.47 – 1.16 (m, 6H, H-21, H-22, H-23), 1.01 (s, 3H, H-15), 0.96 (s, 3H, H-16), 0.93 (s, 3H, H-19), 0.91 (s, 3H, H-20); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.2 (C=O, C-8), 179.6 (C=O, C-7), 138.0 (C, C-12), 128.4 (CH, C-Ar), 127.9 (CH, C-1), 127.8 (CH, C-2), 127.6 (CH, C-Ar), 127.5 (CH, C-Ar), 73.3 (CH_2, C-14), 72.7 (CH_2, C-11), 66.3 (CH_2, C-10), 59.7 (C, C-17), 59.6 (C, C-18), 47.2 (C, C-5), 44.6 (CH, C-4), 39.6 (CH_2, C-21), 39.5 (CH_2, C-23), 38.4 (CH_2, C-9), 36.0 (CH_2, C-13), 33.1 (CH_3, C-15), 33.0 (CH_3, C-16), 31.7 (CH_2, C-6), 24.2 (CH_2, C-3), 20.3 (CH_3, C-20), 17.0 (CH_2, C-22); **HRMS** (ES) found 469.3066 $[MH]^+$, requires 469.3067 for $C_{28}H_{41}N_2O_4$.

Preparation of sulfoxide **256**

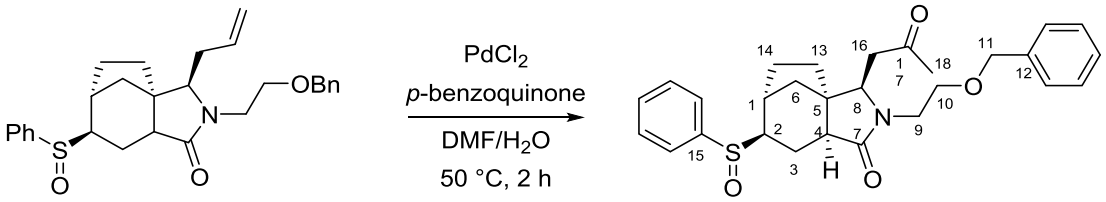


198 **256**

m-CPBA (77%, 795 mg, 3.56 mmol, 1.2 eq.) was added to a solution of **198** (1.22 g, 2.74 mmol, 1.0 eq.) in DCM (15 mL) at 0 °C. The reaction mixture was stirred for 1.5 h then quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to yield sulfoxide **256** (490 mg, 76%, 1.0:1.3 mixture of diastereoisomers) as a colourless oil. **IR** ν_{max}/cm^{-1} 3059, 2952, 2874, 1771, 1697, 1442, 1086, 1040, 748; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.14 (m, 20H, *H-Ar*, H-Ar), 5.77 – 5.55 (m, 2H, *H-17*, H-17), 5.13 – 4.94 (m, 4H, *H-18*, H-18), 4.47 – 4.36 (m, 4H, *H-11*, H-11), 3.86 – 3.70 (m, 2H, *H-9a*, H-9a), 3.66 – 3.61 (m, 2H, *H-8*, H-8), 3.53 – 3.46 (m, 4H, *H-10*, H-10), 3.20 – 3.10 (m, 2H, *H-9b*, H-9b), 2.92 – 2.87 (m, 1H, *H-1*), 2.79 – 2.74 (m, 1H, H-1), 2.53 – 2.40 (m, 4H, *H-2*, H-2, *H-16a*, H-16a), 2.26 – 2.11 (m, 2H, *H-16b*, H-16b), 2.11 – 2.02 (m, 2H, *H-4*, H-4), 2.02 –1.93 (m, 2H, *H-14a*, H-14a), 1.76 – 1.67 (m, 1H, *H-13a*), 1.67 – 1.57 (m, 4H, H-13a, *H-6a*, *H-3a*, H-3a), 1.53 – 1.45 (m, 2H, H-6a, *H-3b*), 1.45 – 1.38 (m, 3H, *H-13b*, H-13b, H-3b), 1.38 – 1.30 (m, 3H, *H-14b*, H-14b, *H-6b*), 1.28 – 1.20 (m, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (C=O, *C-7*), 175.7 (C=O, C-7), 142.7 (C, *C-15*), 141,4 (C, C-15), 138.1 (C, *C-12*), 137.4 (C, C-12), 134.7 (CH, *C-Ar*), 131.4 (CH, *C-Ar*), 130.8 (CH, C-Ar), 129.2 (CH, *C-Ar*), 129.0 (CH, C-Ar), 128.4 (CH, *C-Ar*), 127.6 (CH, *C*-Ar), 125.6 (CH, *C-Ar*), 124.4 (CH,

C-Ar), 117.8 (CH_2, *C-18*, C-18), 72.9 (CH_2, *C-11*, C-11), 67.8 (CH_2, *C-10*), 67.7 (CH_2, C-10), 65.1 (CH, *C-2*, C-2), 60.8 (CH, *C-8*), 60.6 (CH, C-8), 49.2 (CH, *C-4*), 48.7 (CH, C-4), 48.4 (C, *C-5*), 47.1 (C, C-5), 40.1 (CH_2, *C-9*, C-9), 36.2 (CH_2, *C-13*), 35.4 (CH, *C-1*), 34.4 (CH_2, C-13), 33.9 (CH_2, *C-16*), 33.5 (CH_2, C-16), 31.7 (CH, C-1), 31.6 (CH_2, *C-14*), 29.6 (CH_2, C-14), 28.7 (CH_2, *C-6*), 28.4 (CH_2, C-6), 18.0 (CH_2, *C-3*), 14.4 (CH_2, C-3); 3 signals in the CH aromatic region were not observed due to overlaps; **HRMS** (ES) found 486.2082 $[MNa]^+$, requires 486.2079 for $C_{28}H_{33}NO_3NaS$.

Preparation of ketone **257**

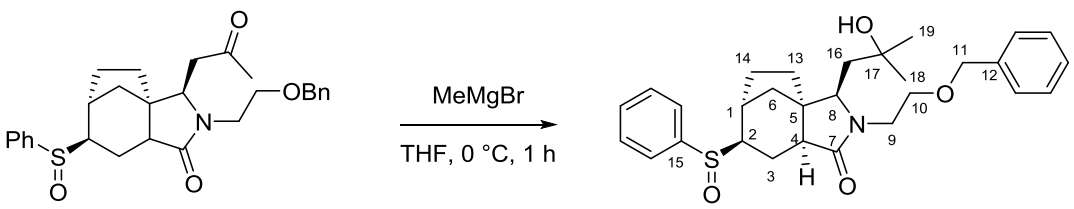


256 **257**

$PdCl_2$ (42 mg, 0.24 mmol, 0.15 eq.), *p*-benzoquinone (173 mg, 1.60 mmol, 1.0 eq.) were added to a solution of sulfoxide **256** (740 g, 1.60 mmol, 1.0 eq.) in a mixture of DMF (7 mL) and H_2O (1 mL) at RT. The reaction mixture was stirred for 2 h at 50 °C before being quenched with a solution of 1 M HCl (aq). The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with water (5 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/ EtOAc =1/1 to 0/1) to furnish ketone **257** (1.04 g, 72%, 1.0:1.5 mixture of diastereoisomers) as a colourless oil. **IR** ν_{max}/cm^{-1} 3062, 2945, 2871, 1714, 1676, 1442, 1093, 1037, 730; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.83 – 7.78 (m, 2H, H-Ar, *H-Ar*), 7.61 – 7.50 (m, 8H, H-Ar, *H-Ar*), 7.44 – 7.31 (m, 10H, H-Ar, *H-Ar*), 4.53 – 4.49 (m, 4H, H-11,

H-11), 4.30 – 4.23 (m, 2H, H-8, *H-8*), 3.68 – 3.59 (m, 2H, H-10), 3.58 – 3.50 (m, 4H, *H-10*, H-9a, *H-9a*), 3.38 – 3.27 (m, 2H, H-9b, *H-9b*), 3.05 – 2.97 (m, 3H, H-16a, *H-16a*, H-1), 2.92 (dd, *J* = 7.8, 4.8 Hz, 1H, *H-1*), 2.74 – 2.68 (m, 1H, H-2), 2.55 – 2.50 (m, 1H, *H-2*), 2.49 – 2.44 (m, 2H, H-16b, *H-16b*), 2.28 – 2.21 (m, 1H, H-4), 2.20 – 2.11 (m, 2H, *H-13a*, *H-4*), 2.09 (s, 3H, H-18), 2.05 (s, 3H, *H-18*), 1.86 – 1.67 (m, 6H, H-14a, *H-14a*, H-6a, *H-6a*, H-3a, *H-3a*), 1.64 – 1.40 (m, 7H, H-13, *H-13b*, H-14b, *H-14b*, H-3b, *H-3b*), 1.20 (dd, *J* = 11.9, 5.3 Hz, 1H, H-6b), 1.06 (dd, *J* = 11.6, 4.9 Hz, 1H, *H-6b*); **^{13}C NMR** (101 MHz, $CDCl_3$) 206.9 (C=O, C-17, *C-17*), 175.6 (C=O, C-7, *C-7*), 142.7 (C, C-15), 141.3 (C, *C-15*), 137.9 (C, C-12, *C-12*), 131.5 (CH, C-Ar), 130.8 (CH, *C-Ar*), 129.2 (CH, C-Ar), 129.1 (CH, *C-Ar*), 128.5 (CH, C-Ar), 128.0 (CH, C-Ar), 127.9 (CH, *C-Ar*), 127.8 (CH, C-Ar), 127.7 (CH, *C-Ar*), 125.6 (CH, C-Ar), 124.2 (CH, *C-Ar*), 73.4 (CH_2, C-11), 73.3 (CH_2, *C-11*), 68.4 (CH_2, C-10, *C-10*), 67.7 (CH, C-2), 65.1 (CH, *C-2*), 57.3 (CH, *C-8*), 57.0 (CH, C-8), 48.7 (CH, *C-4*), 48.1 (CH, C-4), 47.8 (C, C-5), 46.3 (C, *C-5*), 44.3 (CH_2, C-16), 43.2 (CH_2, *C-16*), 41.6 (CH_2, C-9), 41.5 (CH_2, *C-9*), 36.1 (CH_2, C-14), 35.8 (CH, *C-1*), 33.6 (CH_2, *C-14*), 31.7 (CH_2, *C-13*), 31.6 (CH, C-1), 30.2 (CH_3, C-18, *C-18*), 29.7 (CH_2, C-13), 29.5 (CH_2, C-6), 29.3 (CH_2, *C-6*), 18.1 (CH_2, C-3), 14.0 (CH_2, *C-3*); 1 signal in the CH aromatic region were not observed due to overlap; **HRMS** (ES) found 502.2023 $[MNa]^+$, requires 502.2028 for $C_{28}H_{33}NO_4SNa$.

Preparation of alcohol **258**

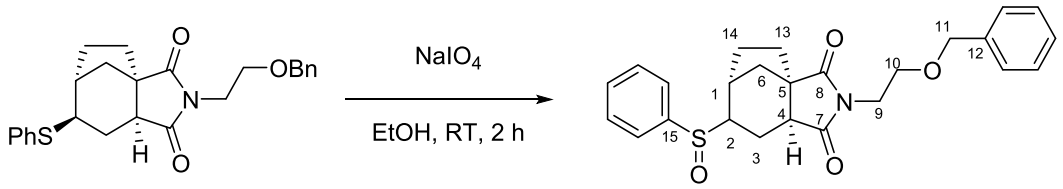


257 **258**

A solution of MeMgBr (3.0 M in Et_2O, 0.73 mL, 2.18 mmol, 2.0 eq.) was added to a solution of **257** (523 mg, 1.08 mmol, 1.0 eq.) in dry THF (6 mL) at 0 °C. After 1 h at 0 °C the mixture was quenched with water. The aqueous layer was extracted with EtOAc (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to yield alcohol **258** (433 mg, 81%, 1:1 mixture of diastereoisomers) as a colourless oil. **IR** ν_{max}/cm^{-1} 3410, 2961, 2869, 1674, 1444, 1088, 1036, 748; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H, *H-Ar*, H-Ar), 7.52 – 7.39 (m, 8H, *H-Ar*, H-Ar), 7.31 – 7.21 (m, 10H, *H-Ar*, H-Ar), 4.45 – 4.33 (m, 4H, *H-11*, H-11), 3.78 – 3.70 (m, 2H, *H-8*, H-8), 3.70 – 3.61 (m, 4H, *H-10a*, H-10a, *H-9a*, H-9a), 3.61 – 3.49 (m, 4H, *H-10b*, H-10b, *H-9b*, H-9b), 2.97 – 2.91 (m, 1H, *H-1*), 2.73 – 2.68 (m, 1H, H-1), 2.66 – 2.59 (m, 1H, *H-2*), 2.51 – 2.45 (m, 1H, H-2), 2.09 – 2.00 (m, 2H, *H-4*, H-4), 1.99 – 1.92 (m, 1H, *H-14a*), 1.81 – 1.71 (m, 1H, *H-3a*), 1.71 – 1.63 (m, 1H, *H-16a*), 1.61 – 1.57 (m, 4H, H-3, *H-6a*, H-16a), 1.55 – 1.47 (m, 8H, *H-3b*, H-14a, *H-13a*, H-13a, *H-16b*, H-16b), 1.47 – 1.34 (m, 5H, *H-14b*, H-14b, *H-13b*, H-13b, H-6a), 1.29 – 1.21 (m, 1H, *H-6b*), 1.21 – 1.16 (m, 1H, H-6b), 1.14 (s, 3H, *H-19*), 1.09 (s, 3H, H-19), 0.91 (s, 6H, *H-18*, H-18); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.0 (C=O, *C-7*), 175.9 (C=O, C-7), 141.4 (C, *C-15*, C-15), 137.0 (C, *C-12*, C-12), 131.5 (CH, *C-Ar*), 130.9 (CH, C-Ar), 129.1 (CH, *C-Ar*), 129.0 (CH, C-Ar), 128.5 (CH, *C-Ar*), 128.5 (CH, *C-Ar*), 128.4 (CH, C-Ar), 128.2 (CH, *C-Ar*), 128.1 (CH, C-Ar), 125.9 (CH, *C-Ar*), 124.5 (CH, C-Ar), 73.9 (CH_2, *C-11*), 73.8 (CH_2, C-11), 69.5 (CH_2, *C-10*), 69.4 (CH_2, C-10), 69.2 (C, *C-17*, C-17), 67.9 (CH, *C-2*), 65.4 (CH, C-2), 59.5 (CH, *C-8*), 59.4 (CH, C-8), 50.0 (C, *C-5*), 49.2 (CH, *C-4*, C-4), 48.2 (C, C-5), 42.2 (CH_2, *C-16*), 41.1 (CH_2, C-16), 40.6 (CH_2, *C-9*, C-9), 35.2 (CH, *C-1*), 34.0 (CH_2, *C-13*, C-13), 31.8 (CH, C-1), 31.6 (CH_2, *C-14*), 31.3 (CH_2, C-14), 31.1 (CH_3, *C-19*), 31.0 (CH_3, C-19), 29.2 (CH_2, *C-6*), 28.7 (CH_2, C-6), 28.6 (CH_3, *C-18*), 28.3 (CH_3, C-18),

17.0 (CH_2, *C-3*), 14.7 (CH_2, C-3); 1 signal in the CH aromatic region was not observed due to overlaps; **HRMS** (ES) founds 518.2344 $[MNa]^+$, requires 518.2341 for $C_{29}H_{37}NO_4NaS$.

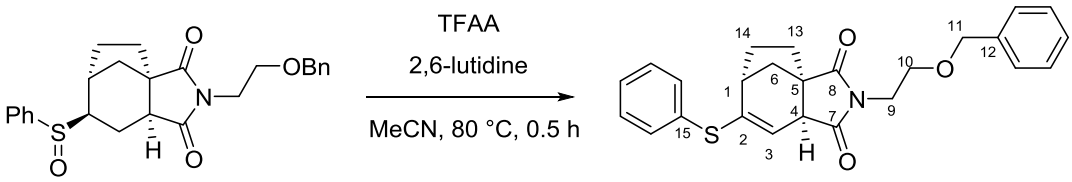
Preparation of sulfoxide **262**



A solution of sodium periodate (1.28 g, 5.98 mmol, 4.0 eq.) in water (2 mL) was added to a solution of 182 (630 mg, 1.49 mmol, 1.0 eq.) in EtOH (6 mL) at RT. The reaction mixture was stirred for 2 h at RT then quenched with water. The aqueous layer was extracted with DCM (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to yield sulfoxide **262** (490 mg, 76%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3059, 2952, 2874, 1771, 1697, 1393, 1086, 1040, 731; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 5H, H-Ar), 7.37 – 7.30 (m, 2H, H-Ar), 7.30 – 7.24 (m, 3H, H-Ar), 4.49 (s, 2H, H-11), 3.80 – 3.69 (m, 2H, H-9), 3.64 – 3.58 (m, 2H, H-10), 3.02 (dd, *J* = 7.4, 4.4 Hz, 1H, H-1), 2.53 (dd, *J* = 11.7, 7.4 Hz, 1H, H-2), 2.42 – 2.33 (m, 2H, H-14a, H-4), 2.25 – 2.17 (m, 1H, H-13a), 1.86 – 1.75 (m, 1H, H-3a), 1.75 – 1.62 (m, 2H, H-6), 1.62 – 1.47 (m, 3H, H-13b, H-14b, H-3b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.7 (C=O, C-8), 177.7 (C=O, C=7), 141.1 (C, C-15), 137.9 (C, C-12), 131.1 (CH, C-Ar), 129.2 (CH, C-Ar), 128.5 (CH, C-Ar), 127.7 (CH, C-Ar), 127.6 (CH, C-Ar), 124.2 (CH, C-Ar), 72.6 (CH_2, C-11), 66.0 (CH_2, C-10), 65.0 (CH, C-2), 49.4 (C, C-5), 46.0 (CH, C-4), 38.1 (CH_2, C-9), 36.7 (CH, C-1), 34.3 (CH_2, C-6), 33.5 (CH_2,

C-13), 32.5 (CH_2, C-14), 13.2 (CH_2, C13); **HRMS** (ES) founds 460.1567 $[MNa]^+$, requires 460.1558 for $C_{25}H_{27}NO_4NaS$

Preparation of vinyl sulfide **263**

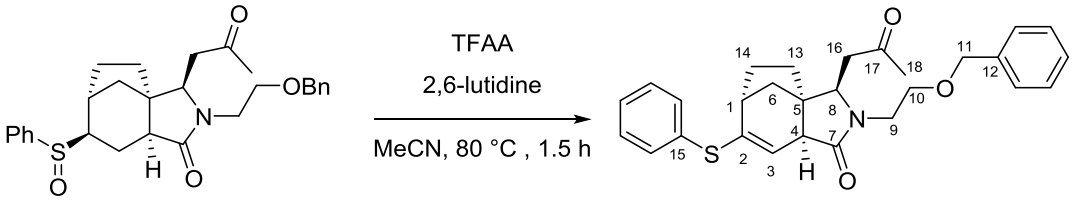


262 **263**

TFAA (101 µL, 0.73 mmol, 3.0 eq.) and 2,6-lutidine (84 µL, 0.73 mmol, 3.0 eq.) were successively added to a solution of **262** (106 mg, 0.24 mmol, 1.0 eq.) in dry MeCN (2 mL) at RT. The mixture was heated to 80 °C and stirred for 0.5 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to give vinyl sulfide **263** (92 mg, 91%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3064, 2946, 2869, 1775, 1706, 1388, 1085, 740; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 10H, H-Ar), 5.65 (d, *J* = 3.6 Hz, 1H, H-3), 4.44 (s, 2H, H-11), 3.77 – 3.63 (m, 2H, H-9), 3.63 – 3.52 (m, 2H, H-10), 2.99 (d, *J* = 3.6 Hz, 1H, H-4), 2.57 – 2.51 (m, 1H, H-1), 2.38 – 2.28 (m, 1H, H-13a), 2.11 – 2.01 (m, 1H, H-14a), 1.93 – 1.85 (m, 1H, H-14b), 1.82 (dd, *J* = 10.7, 4.6 Hz, 1H, H-6a), 1.66 – 1.57 (m, 1H, H-13b), 1.52 – 1.47 (m, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.2 (C=O, C-8), 174.6 (C=O, C-7), 147.0 (C, C-2), 137.9 (C, C-12), 132.8 (CH, C-Ar), 132.2 (C, C-15), 129.3 (CH, C-Ar), 128.4 (CH, C-Ar), 128.0 (CH, C-Ar), 127.7 (CH, C-Ar), 127.6 (CH, C-Ar), 114.7 (CH, C-3), 72.6 (CH_2, C-11), 66.2 (CH_2, C-10), 52.7 (CH, C-4), 50.7 (C, C-5), 41.8 (CH_2, C-9), 40.4 (CH, C-1), 38.0 (CH_2, C-6), 32.7 (CH_2,

C-14), 31.0 (CH_2, C-13); **HRMS** (ES) found 442.1454 $[MNa]^+$, requires 442.1453 for $C_{25}H_{25}NO_3NaS$.

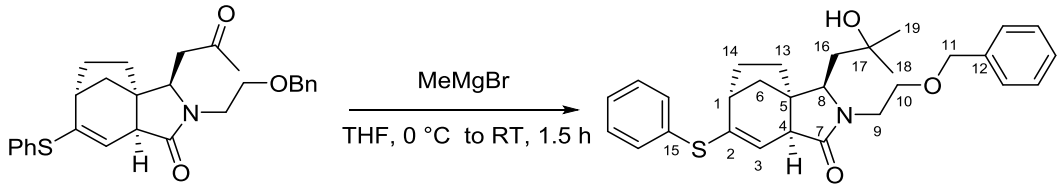
Preparation of vinyl sulfide **269**



2,6-lutidine (0.25 mL, 2.12 mmol, 3.0 eq.) and TFAA (0.30 mL, 2.12 mmol, 3.0 eq.) were successively added to a solution of **257** (340 mg, 0.71 mmol, 1.0 eq.), in dry MeCN (2 mL) at RT. The mixture was heated to 80 °C and stirred for 1.5 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 3/1 to 1/1) to give vinyl sulfide **269** (245 mg, 75%) as an orange oil. **IR** ν_{max}/cm^{-1} 3064, 3051, 2945, 2867, 1718, 1688, 1440, 1211, 1166, 745; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.22 (m, 10H, H-Ar), 5.54 (d, *J* = 3.8 Hz, 1H, H-3), 4.49 (s, 2H, H-11), 4.28 (dd, *J* = 8.2, 3.0 Hz, 1H, H-8), 3.71 – 3.50 (m, 2H, H-10), 3.46 – 3.36 (m, 2H, H-9), 3.04 (dd, *J* = 18.0, 8.2 Hz, 1H, H-16a), 2.88 (d, *J* = 3.8 Hz, 1H, H-4), 2.55 – 2.51 (m, 1H, H-1), 2.47 (dd, *J* = 18.0, 3.0 Hz, 1H, H-16b), 2.04 (s, 3H, H-18), 1.98 – 1.86 (m, 2H, H-14), 1.74 – 1.59 (m, 2H, H-13), 1.53 (d, *J* = 10.9 Hz, 1H, H-6a), 1.38 (dd, *J* = 10.9, 4.8 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.4 (C=O, C-17), 176.0 (C=O, C-7), 146.1 (C, C-2), 137.6 (C, C-12), 132.6 (CH, C-Ar), 132.3 (C, C-15), 129.2 (CH, C-Ar), 128.5 (CH, C-Ar), 128.2 (CH, C-Ar), 128.0 (CH, C-Ar), 127.9 (CH, C-Ar), 115.6 (CH, C-3), 73.5 (CH_2, C-11), 68.0 (CH_2, C-10), 56.9 (CH, C-8), 54.8 (CH, C-4), 48.6 (C, C-5), 42.3 (CH_2, C-9), 42,1 (CH_2, C-16), 39.5

(CH, C-1), 34.4 (CH_2, C-6), 32.1 (CH_2, C-14), 31.6 (CH_2, C-13), 30.0 (CH_3, C-18); **HRMS** (ES) found 484.2034 $[MNa]^+$, requires 484.2031 for $C_{28}H_{31}NO_3NaS$.

Preparation of alcohol **270**

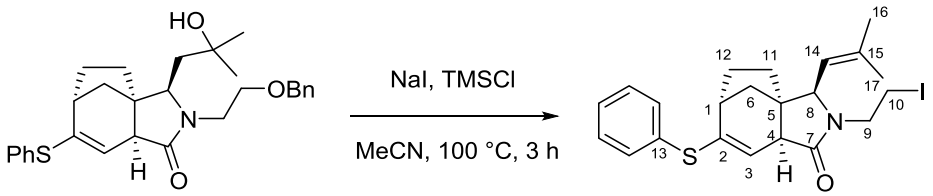


269 **270**

A solution of MeMgBr (3.0 M in Et_2O, 0.36 mL, 1.07 mmol, 1.5 eq.) was added to a solution of **269** (330 mg, 0.71 mmol, 1.0 eq.) in dry THF (5 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and 0.5 h at RT before being quenched with water. The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were washed with a saturated aqueous solution of NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to furnish alcohol **270** (200 mg, 60%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3430, 3068, 3055, 2951, 2868, 1670, 1090, 907, 726; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.12 (m, 10H, H-Ar), 5.73 (d, *J* = 4.0 Hz, 1H, H-3), 4.41 (d, *J* = 11.3 Hz, 1H, H-11a), 4.35 (d, *J* = 11.3 Hz, 1H, H-11b), 3.74 (dd, *J* = 6.5, 1.7 Hz, 1H, H-8), 3.71 – 3.64 (m, 3H, H-10a, H-9), 3.52 – 3.49 (m, 1H, H-10b), 2.56 (d, *J* = 4.0 Hz, 1H, H-4), 2.41 – 2.38 (m, 1H, H-1), 1.87 – 1.71 (m, 2H, H-14), 1.65 (dd, *J* = 15.8, 6.5 Hz, 1H, H-16a), 1.60 – 1.54 (m, 1H, H-13a), 1.54 – 1.47 (m, 1H, H-16b), 1.47 – 1.38 (m, 1H, H-13b), 1.36 – 1.29 (m, 2H, H-6), 1.12 (s, 3H, H-18), 0.88 (s, 3H, H-19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1 (C=O, C-7), 144.1 (C, C-2), 137.0 (C, C-12), 133.5 (C, C-15), 131.8 (CH, C-Ar), 129.1 (CH, C-Ar), 128.6 (CH, C-Ar), 128.5 (CH, C-Ar), 128.3 (CH,

C-Ar), 127.2 (CH, C-Ar), 120.2 (CH, C-3), 73.9 (CH_2, C-11), 69.4 (CH_2, C-10), 69.2 (C, C-17), 58.7 (CH, C-8), 55.5 (CH, C-4), 49.6 (C, C-5), 41.1 (CH_2, C-16), 40.6 (CH_2, C-9), 39.7 (CH, C-1), 33.7 (CH_2, C-6), 32.2 (CH_2, C-14), 31.3 (CH_3, C-18), 31.1 (CH_2, C-13), 28.1 (CH_3, C-19); **HRMS** (ES) found 500.2231 $[MNa]^+$, requires 500.2235 for $C_{29}H_{35}NO_3NaS$.

Preparation of alkene **274**

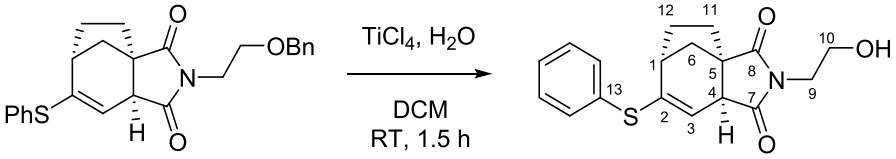


270 **274**

Trimethylsilyl chloride (114 µL, 0.94 mmol, 5.0 eq.) was added to a solution of sodium iodide (141 mg, 0.94 mmol, 5.0 eq.) and **270** (90 mg, 0.19 mmol, 1.0 eq.) in dry MeCN (3 mL) at RT. The reaction mixture was heated to 100 °C and stirred for 3 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to yield alkene **274** (50 mg, 55%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3053, 2939, 2866, 1690, 1438, 1404, 1278, 1092, 743; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.12 (m, 5H, H-Ar), 5.74 (d, *J* = 3.9 Hz, 1H, H-3), 4.95 – 4.90 (m, 1H, H-14), 4.39 (d, *J* = 10.1 Hz, 1H, H-8), 3.80 – 3.71 (m, 1H, H-9a), 3.32 – 3.16 (m, 2H, H-10a, H-9b), 3.08 – 3.00 (m, 1H, H-10b), 2.74 (d, *J* = 3.9 Hz, 1H, H-4), 2.43 – 2.36 (m, 1H, H-1), 1.87 – 1.79 (m, 1H, H-12a), 1.77 (d, *J* = 1.3 Hz, 3H, H-16), 1.70 (d, *J* = 1.4 Hz, 3H, H-17), 1.70 – 1.55 (m, 3H, H-12b, H-11), 1.50 (d, *J* = 10.7 Hz, 1H, H-6a), 1.35 (dd, *J* = 10.7, 4.7 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.2 (C=O, C-7), 143.0 (C, C-2), 139.2 (C, C-15), 132.0 (C, C-13), 130.5 (CH, C-Ar), 127.6 (CH, C-Ar), 125.8 (CH, C-Ar), 118.3 (CH, C-3), 117.4 (CH, C-14), 57.4

(CH, C-8), 53.4 (CH, C-4), 48.1 (C, C-5), 41.6 (CH_2, C-9), 38.2 (CH, C-1), 33.3 (CH_2, C-6), 30.8 (CH_2, C-11), 30.6 (CH_2, C-12), 25.0 (CH_3, C-17), 16.8 (CH_3, C-16), 0.0 (CH_2, C-10); **HRMS** (ES) found 502.1024 $[MNa]^+$, requires 502.1021 for $C_{22}H_{26}INONa$.

Preparation of alcohol **283**

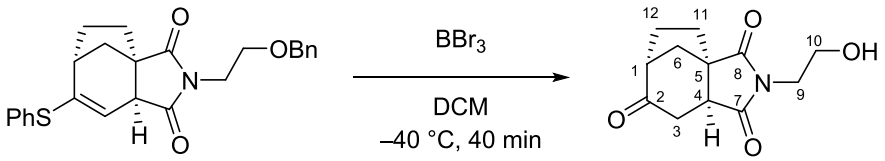


263 **283**

A solution of $TiCl_4$ (1.0 M in DCM, 0.24 mL, 0.24 mmol, 2.0 eq.) was added to a solution of **263** (52 mg, 0.12 mmol, 1.0 eq.) in dry DCM (2 mL) at RT. After 20 min, water (1 drop) was added and the mixture was stirred for 1.5 h at RT. The reaction mixture was diluted with DCM (4 mL) and the organic layer was washed with water (2 × 5 mL) dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to furnish alcohol **283** (25 mg, 63%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3403, 2945, 2870, 1776, 1705, 1389, 1085, 741; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.33 (m, 5H, H-Ar), 5.75 (d, *J* = 3.6 Hz, 1H, H-3), 3.87 – 3.78 (m, 3H, H-10, H-9a), 3.78 – 3.68 (m, 1H, H-9b), 3.19 (d, *J* = 3.6 Hz, 1H, H-4), 2.70 (dd, *J* = 6.7, 4.5 Hz, 1H, H-1), 2.46 (td, *J* = 12.4, 5.9 Hz, 1H, H-11a), 2.38 – 2.32 (br, 1H, OH), 2.26 – 2.14 (m, 1H, H-12a), 2.07 – 1.97 (m, 2H, H-12b, H-6a), 1.83 – 1.73 (m, 1H, H-11b), 1.69 (dd, *J* = 10.7, 4.5 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.0 (C=O, C-8), 175.3 (C=O, C-7), 147.3 (C, C-2), 132.9 (CH, C-Ar), 132.0 (C, C-13), 129.3 (CH, C-Ar), 128.1 (CH, C-Ar), 114.2 (CH, C-3), 60.7 (CH_2, C-10), 52.7 (CH, C-4), 50.8 (C, C-5), 41.9 (CH_2, C-6), 41.5 (CH_2, C-9), 40.4

(CH, C-1), 32.6 (CH_2, C-12), 31.1 (CH_2, C-11); **HRMS** (ES) found 352.1090 $[MNa]^+$, requires 352.1086 for $C_{18}H_{19}NO_3NaS$.

Preparation of keto-alcohol **284**



263 **284**

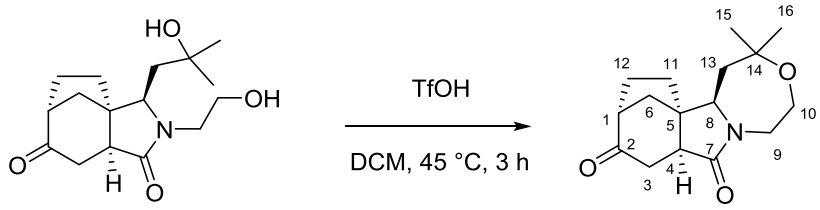
A solution of BBr_3 (1.0 M in DCM, 0.25 mL, 0.25 mmol, 2.5 eq.) was added to a solution of **263** (42 mg, 0.10 mmol, 1.0 eq.) in dry DCM (2 mL) at −40 °C. The reaction mixture was stirred at −40 °C for 40 min, before being quenched with water. The aqueous layer was extracted with EtOAc (5 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to yield ketone **284** (23 mg, 96%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3458, 2954, 2926, 2878, 1773, 1693, 1396, 1338, 1215, 1041, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 – 3.64 (m, 4H, H-10, H-9), 2.84 (dd, *J* = 8.1, 4.0 Hz, 1H, H-1), 2.76 – 2.64 (m, 2H, H-4, H-3a), 2.58 – 2.46 (m, 1H, H-3b), 2.40 – 2.31 (m, 1H, H-11a), 2.31 – 2.23 (m, 1H, H-6a), 2.07 (s, 1H, OH), 2.01 – 1.93 (m, 2H, H-12), 1.75 – 1.62 (m, 2H, H-11b, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.7 (C=O, C-2), 179.3 (C=O, C-8), 177.6 (C=O, C-7), 60.4 (CH_2, C-10), 50.4 (C, C-5), 48.6 (CH, C-1), 43.7 (CH, C-4), 41.8 (CH_2, C-9), 36.5 (CH_2, C-12), 33.7 (CH_2, C-3), 32.5 (CH_2, C-11), 27.1 (CH_2, C-6); **HRMS** (ES) found 236.0921 $[MH]^+$, requires 236.0923 for $C_{12}H_{16}NO_4$.

Preparation of keto-alcohol **285**

270 **285**

A solution of BBr_3 (1.0 M in DCM, 0.60 mL, 0.60 mmol, 2.5 eq.) was added to a solution of **270** (115 mg, 0.24 mmol, 1.0 eq.) in dry DCM (3 mL) at −40 °C. The reaction mixture was stirred at −40 °C for 40 min, before being quenched with water. The pH was adjusted to pH = 4-5 with a solution of 2 N NaOH (aq). The aqueous layer was extracted with EtOAc (5 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: EtOAc/MeOH = 1/0 to 1/0.1) to yield ketone **285** (50 mg, 70%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3391, 2963, 2875, 1713, 1666, 1417, 1067, 916, 730; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.08 (dd, *J* = 5.9, 2.4 Hz, 1H, H-8), 3.83 – 3.61 (m, 3H, H-10, H-9a), 3.59 (ddd, *J* = 15.8, 9.3, 3.9, 1H, H-9b), 2.72 – 2.64 (m, 2H, H-3a, H-1), 2.60 – 2.53 (m, 1H, H-3b), 2.51 – 2.44 (m, 1H, H-4), 2.07 – 1.98 (m, 1H, H-6a), 1.80 – 1.66 (m, 3H, H-13a, H-11a, H-6b), 1.63 – 1.49 (m, 4H, H-13b, H-12, H-11b), 1.30 (s, 3H, H-15), 1.21 (s, 3H, H-16); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.5 (C=O, C-2), 176.4 (C=O, C-7), 70.0 (C, C-14), 62.0 (CH_2, C-10), 58.6 (CH, C-8), 50.4 (C, C-5), 48.3 (CH, C-1), 46.6 (CH, C-4), 43.0 (CH_2, C-9), 40.6 (CH_2, C-13), 33.4 (CH_2, C-3), 31.9 (CH_3, C-15), 31.2 (CH_2, C-11), 30.2 (CH_2, C-12), 29.1 (CH_3, C-16), 26.4 (CH_2, C-6); **HRMS** (ES) found 318.1682 $[MNa]^+$, requires 318.1681 for $C_{16}H_{25}NO_4Na$.

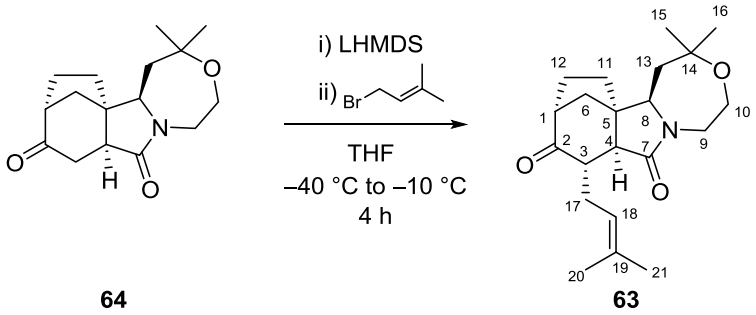
Preparation of tetracycle **64**



285 **64**

Triflic acid (60 µL, 0.67 mmol, 5.0 eq.) was added to a solution of **285** (40 mg, 0.13 mmol, 1.0 eq.) in dry DCM (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, 40 min at RT and 3 h at 45 °C. An aqueous solution of $NaHCO_3$ (4 mL) was added to quench the reaction. The aqueous layer was extracted with DCM (3 × 8 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give tetracyclic compound **64** (32 mg, 86%) as a white powder. **m.p.** 182 – 184 °C; **IR** ν_{max}/cm^{-1} 2968, 2940, 2876, 1713, 1684, 1445, 1369, 1238, 1081; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.85 (d, *J* = 10.8 Hz, 1H, H-8), 3.75 – 3.60 (m, 3H, H-10, H-9a), 3.53 – 3.26 (m, 1H, H-9b), 2.70 (dd, *J* = 8.4, 4.8 Hz, 1H, H-1), 2.58 (d, *J* = 8.5, 2H, H-3), 2.40 (t, *J* = 8.5 Hz, 1H, H-4), 2.08 – 1.98 (m, 1H, H-6a), 1.78 – 1.63 (m, 4H, H-13a, H-12a, H-11a, H-6b), 1.62 – 1.52 (m, 2H, H-13b, H-11b), 1.45 (dd, *J* = 12.3, 4.8 Hz, 1H, H-12b), 1.21 (s, 6H, H-16, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.6 (C=O, C-2), 175.2 (C=O, C-7), 74.4 (C, C-14), 60.2 (CH_2, C-10), 57,4 (CH, C-8), 48.5 (CH, C-1), 48.3 (C, C-5), 46.1 (CH, C-4), 45.9 (CH_2, C-9), 41.1 (CH_2, C-13), 34.1 (CH_2, C-3), 32.3 (CH_2, C-11), 30.4 (CH_2, C-12), 28.8 (CH_3, C-16), 26.5 (CH_2, C-6), 25.9 (CH_3, C-15); **HRMS** (ES) found 300.1575 $[MNa]^+$, requires 300.1576 for $C_{16}H_{23}NO_3Na$.

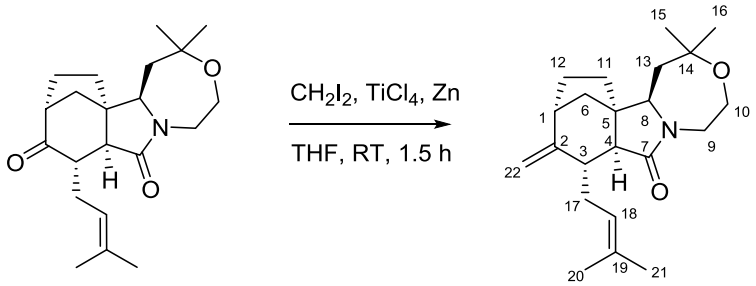
Preparation of prenylated compound **63**



A solution of LHMDS (1.0 M in THF, 0.20 mmol, 0.20 mL, 1.1 eq.) was added to a solution of **64** (50 mg, 0.18 mmol, 1.0 eq.) in dry THF (2 mL) at −40 °C. After 15 min, prenyl bromide (62 µL, 0.54 mmol, 3.0 eq.) was added. The reaction mixture was stirred for 2 h at −40 °C, then allowed to warm to −10 °C and stirred for 2 h before being quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to yield prenylated compound **63** (40 mg, 70%) as a white powder. **m.p.** 125 − 127 °C; **IR** ν_{max}/cm^{-1} 2966, 2944, 2874, 1710, 1687, 1416, 1226, 1100, 1080 ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.98 – 4.91 (m, 1H, H-18), 3.85 (d, *J* = 10.7 Hz, 1H, H-8), 3.79 – 3.67 (m, 3H, H-10, H-9a), 3.39 – 3.32 (m, 1H, H-9b), 2.78 – 2.72 (m, 2H, H-17a, H-1), 2.69 – 2.62 (m, 1H, H-3), 2.54 – 2.45 (m, 1H, H-17b), 2.12 (d, *J* = 7.6 Hz, 1H, H-4), 2.06 – 1.94 (m, 1H, H-12a), 1.81 – 1.70 (m, 2H, H-13a, H-6a), 1.70 – 1.65 (m, 4H, H-20, H-11a), 1.64 (s, 3H, H-21), 1.62 – 1.56 (m, 2H, H-13b, H-12b), 1.52 – 1.46 (m, 1H, H-11b), 1.36 (dd, *J* = 12.1, 4.5 Hz, 1H, H-6b), 1.27 (s, 6H, H-16, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 214.2 (C=O, C-2), 175.7 (C=O, C-7), 135.2 (C, C-19), 120.1 (CH, C-18), 74.4 (C, C-14), 60.2 (CH_2, C-10), 57.1 (CH, C-8), 49.6 (CH, C-4), 48.5 (C, C-5), 48.4 (CH, C-1), 45.9 (CH_2, C-9), 44.5 (CH, C-3), 41.1 (CH_2, C-13), 32.2 (CH_2, C-11), 30.0 (CH_2,

C-6), 28.9 (CH_3, C-16), 27.7 (CH_2, C-17), 26.5 (CH_2, C-12), 25.9 (CH_3, C-21, C-15), 18.2 (CH_3, C-20); **HRMS** (ES) found 368.2191 $[MNa]^+$, requires 368.2202 for $C_{21}H_{31}NO_3Na$.

Preparation of olefin **289**

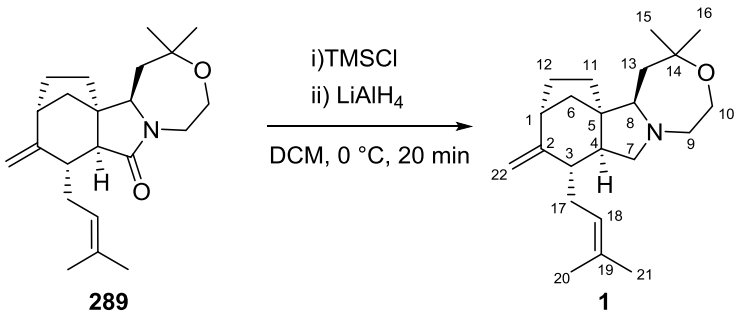


63 **289**

CH_2I_2 (0.40 mL, 5.00 mmol, 5.0 eq.) was added to a suspension of zinc (0.58 g, 9.00 mmol, 9.0 eq.) and $PbCl_2$ (15 mg, 0.05 mmol, 0.05 eq.) in dry THF (10 mL) at RT. After 0.5 h, $TiCl_4$ (1.0 M in DCM, 1 ml, 1 mmol, 1.0 eq.) was added at 0 °C and the mixture was stirred for 0.5 h at RT. A solution of [CH_2I_2, $TiCl_4$, Zn] (0.1 M in THF, 0.75 mL, 0.075 mmol, 1.3 eq.) was added to a solution of **63** (20 mg, 0.058 mmol, 1.0 eq.) at RT. After being stirred for 1.5 h, the mixture was diluted with EtOAc, the organic layer was washed with a solution of 1 M HCl (aq), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to yield olefin **289** (16 mg, 80%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3085, 2970, 2936, 2870, 1689, 1425, 1391, 1111, 1082; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.17 – 5.10 (m, 1H, H-18), 4.85 – 4.81 (m, 1H, H-22a), 4.77 – 4.75 (m, 1H, H-22b), 3.76 – 3.66 (m, 4H, H-10, H-9a, H-8), 3.38 – 3.30 (m, 1H, H-9b), 2.85 – 2.81 (m, 1H, H-1), 2.74 – 2.66 (m, 1H, H-3), 2.54 – 2.42 (m, 2H, H-17), 2.02 (d, *J* = 6.6 Hz, 1H, H-4), 1.97 – 1.88 (m, 1H, H-12a), 1.76 – 1.71 (m, 1H, H-13a), 1.70 (s, 3H, H-20), 1.64 (s, 3H, H-21), 1.62 – 1.54 (m, 3H, H-13b, H-12b, H-11a), 1.53 – 1.46 (m, 1H, H-11b),

1.40 (d, *J* = 11.4 Hz, 1H, H-6a), 1.25 (s, 6H, H-16, H-15), 1.21 (dd, *J* = 11.4, 6.3 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (C=O, C-7), 154.7 (C, C-2), 133.4 (C, C-19), 122.0 (CH, C-18), 108.4 (CH_2, C-22), 74.5 (C, C-14), 60.4 (CH_2, C-10), 57.5 (CH, C-8), 53.5 (CH, C-4), 48.7 (C, C-5), 45.8 (CH_2, C-9), 42.5 (CH, C-1), 40.8 (CH_2, C-13), 35.4 (CH, C-3), 33.2 (CH_2, C-17), 31.8 (CH_2, C-6, C-11), 31.2 (CH_2, C-12), 29.0 (CH_3, C-16), 25.8 (CH_3, C-20, C-15), 18.3 (CH_3, C-21); **HRMS** (ES) found 366.2406 $[MNa]^+$, requires 366.2409 for $C_{22}H_{33}NO_2Na$.

Preparation of concavine **1**

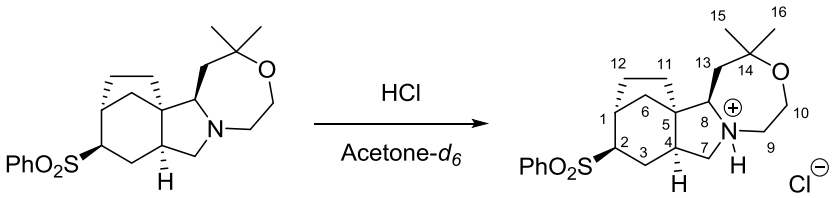


TMSCl (5 µL, 0.038 mmol, 1.2 eq.) was added to a solution of **289** (11 mg, 0.032 mmol, 1.0 eq.) in dry DCM (1 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C, then a solution of $LiAlH_4$ (2.4 M in THF, 20 µL, 0.048 mmol, 1.5 eq.) was added. After 20 min at 0 °C, the reaction mixture was quenched with 2 N solution of NaOH (aq). The aqueous layer was extracted with DCM (3 × 3 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to yield concavine **1** (10 mg, 95%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3081, 2968, 2930, 2866, 2799, 1635, 1454, 1364, 1270, 1071, 884; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.14 – 5.07 (m, 1H, H-18), 4.82 – 4.79 (m, 1H, H-22a), 4.74 –

4.72 (m, 1H, H-22b), 3.81 (dd, *J* = 13.3, 11.1 Hz, 1H, H-10a), 3.54 (ddd, *J* = 13.3, 3.2, 2.0 Hz, 1H, H-10b), 3.02 – 2.92 (m, 2H, H-9a, H-7a), 2.80 (dd, *J* = 7.0, 4.4 Hz, 1H, H-1), 2.57 (d, *J* = 9.3 Hz, 1H, H-8), 2.50 ("app t", *J* = 10.0 Hz, 1H, H-7b), 2.34 (ddd, *J* = 12.7, 10.8, 2.0 Hz, 1H, H-9b), 2.22 – 2.15 (m, 2H, H-17), 2.15 – 2.10 (m, 1H, H-3), 1.98 – 1.87 (m, 1H, H-12a), 1.79 – 1.70 (m, 2H, H-13a, H-6a), 1.68 (s, 3H, H-20), 1.61 (s, 3H, H-21), 1.57 (dd, *J* = 10.2, 3.7 Hz, 1H, H-4), 1.54 – 1.46 (m, 1H, H-13b), 1.46 – 1.36 (m, 2H, H-12b, H-11a), 1.32 – 1.24 (m, 1H, H-11b), 1.20 (s, 3H, H-16), 1.18 (s, 3H, H-15), 0.97 (dd, *J* = 11.3, 4.4 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1 (C, C-2), 131.8 (C, C-19), 123.0 (CH, C-18), 107.2 (CH_2, C-22), 74.8 (C, C-14), 64.8 (CH, C-8), 62.0 (CH_2, C-10), 61.5 (CH_2, C-7), 58.6 (CH_2, C-9), 53.4 (C, C-5), 49.6 (CH, C-4), 41.8 (CH, C-1), 41.7 (CH_2, C-13), 41.5 (CH, C-3), 33.5 (CH_2, C-11), 33.4 (CH_2, C-12), 30.4 (CH_2, C-6), 30.0 (CH_2, C-17), 28.8 (CH_3, C-16), 27.6 (CH_3, C-15), 25.8 (CH_3, C-20), 18.0 (CH_3, C-21); **HRMS** (ES) found 330.2799 $[MH]^+$, requires 330.2797 for $C_{22}H_{36}NO$.

6.3. Compounds for Chapter 4

Preparation **223-HCl**

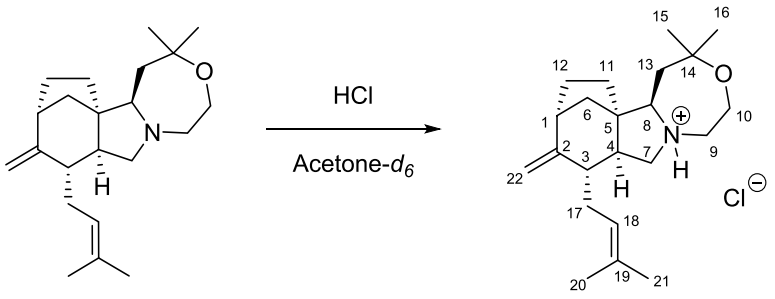


223 **223-HCl**

A solution of HCl in acetone-d_6 (0.18 M, 0.1 mL, 0.018 mmol, 1.0 eq.) was added to a solution of **223** in acetone-d_6 (7 mg, 0.018 mmol, 1.0 eq.) in a NMR tube. **^{1}H NMR** (400 MHz,

acetone-d_6) δ 7.94 – 7.90 (m, 2H, H-Ar), 7.77 – 7.63 (m, 3H, H-Ar), 4.16 (dd, *J* = 14.6, 10.8 Hz, 1H, H-10a), 3.71 (d, *J* = 9.9 Hz, 1H, H-8), 3.59 (d, *J* = 14.6 Hz, 1H, H-10b), 3.38 (d, *J* = 12.6 Hz, 1H, H-9a), 3.33 – 3.28 (m, 2H, H-7), 3.12 (dd, *J* = 12.3, 5.9 Hz, 1H, H-2), 2.95 – 2.86 (m, 1H, H-9b), 2.75 – 2.70 (m, 1H, H-1), 2.52 (dd, *J* = 16.3, 9.9 Hz, 1H, H-13a), 2.32 – 2.24 (m, 2H, H-6a, H-4), 2.01 – 1.87 (m, 2H, H-12a, H-3a), 1.81 – 1.71 (m, 2H, H-13b, H-3a), 1.67 – 1.58 (m, 2H, H-11), 1.50 – 1.41 (m, 1H, H-12b), 1.19 (s, 3H, H-15), 1.15 (s, 3H, H-16), 0.98 (dd, *J* = 12.3, 4.7 Hz, 1H, H-6); **^{13}C NMR** (101 MHz, acetone-d_6) δ 138.3 (C, C-Ar), 133.5 (CH, C-Ar), 129.3 (CH, C-Ar), 128.8 (CH, C-Ar), 74.2 (C, C-14), 66.4 (CH, C-2), 65.7 (CH, C-8), 58.2 (CH_2, C-10), 58.0 (CH_2, C-7), 56.0 (CH_2, C-9), 52.0 (C, C-5), 42.0 (CH, C-4), 35.8 (CH_2, C-13), 33.6 (CH_2, C-11), 32.6 (CH, C-1), 31.1 (CH_2, C-12), 28.2 (CH_2, C-6), 27.2 (CH_3, C-15), 25.9 (CH_3, C-16), 23.5 (CH_2, C-3).

Preparation of **1-HCl**

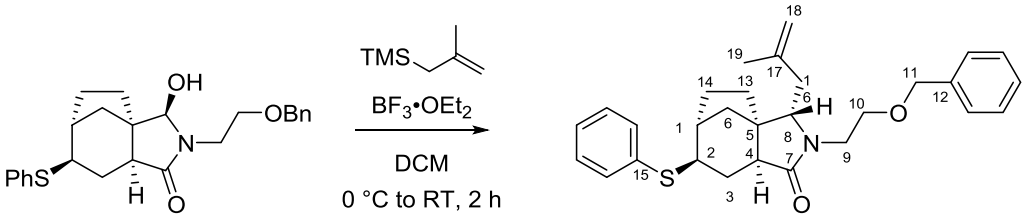


1 **1-HCl**

A solution of HCl in acetone-d_6 (0.24 M, 0.1 mL, 0.024 mmol, 1.0 eq.) was added to a solution of **1** in acetone-d_6 (8 mg, 0.024 mmol, 1.0 eq.) in a NMR tube. **^{1}H NMR** (400 MHz, acetone-d_6) δ 5.18 – 5.11 (m, 1H, H-18), 4.86 – 4.83 (m, 1H, H-22a), 4.80 – 4.77 (m, 1H, H-22b), 4.17 (ddd, *J* = 14.6, 10.7, 2.7 Hz, 1H, H-10a), 3.72 (“app t”, *J* = 9.8 Hz, 1H, H-8), 3.61 (dt, *J* = 14.6, 2.7 Hz, 1H, H-10b), 3.48 – 3.35 (m, 2H, H-9a, H-7a), 3.30 – 3.20 (m, 1H, H-7b), 3.01 – 2.92

(m, 1H, H-9b), 2.88 – 2.80 (m, 1H, H-1), 2.56 (dd, *J* = 16.3, 9.8 Hz, 1H, H-13a), 2.43 (d, *J* = 11.9 Hz, 1H, H-6a) 2.40 – 2.36 (m, 1H, H-3), 2.28 – 2.20 (m 2H, H-17), 2.03 – 1.93 (m, 2H, H-12a, H-4), 1.80 (d, *J* = 16.3 Hz, 1H, H-13b), 1.68 (s, 3H, H-20), 1.67 – 1.64 (m, 1H, H-11a), 1.63 (s, 3H, H-21), 1.56 – 1.43 (m, 2H, H-12b, H-11b), 1.22 (s, 3H, H-15), 1.17 (s, 3H, H-16), 1.09 (dd, *J* = 11.9, 4.5 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 155.1 (C, C-2), 132.3 (C, C-19), 122.2 (CH, C-18), 107.7 (CH_2, C-22), 74.2 (C, C-14), 66.3 (CH, C-8), 58.5 (CH_2, C-7), 58.2 (CH_2, C-10), 56.2 (CH_2, C-9), 48.3 (CH, C-4), 42.0 (CH, C-1), 40.4 (CH, C-3), 35.8 (CH_2, C-13), 32.8 (CH_2, C11), 32.6 (CH_2, C-12), 30.3 (CH_2, C-6), 30.2 (CH_2, C-17), 27.2 (CH_3, C-16), 25.9 (CH_2, C-15), 25.1 (CH_3, C-21), 17.2 (CH_3, C-20).

Preparation of methylallyl **301**

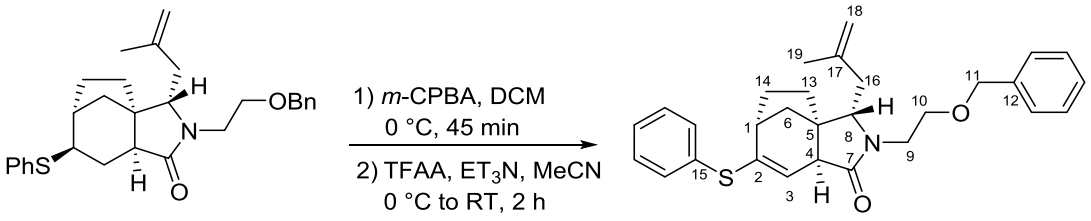


183 **294**

Methylallyltrimethylsilane (0.70 mL, 3.96 mmol, 2.0 eq.) and BF_3•OEt_2 (1.00 mL, 7.92 mmol, 4.0 eq.) were successively added to a solution of **183** (838 mg, 1.98 mmol, 1.0 eq.) in dry DCM (10 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 2 h at RT before being quenched with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 4/1 to 1/1) to yield methylallyl **294** (181 mg, 20%) as a colourless

oil. **IR** ν_{max}/cm^{-1} 3068, 2937, 2863, 1687, 1438, 1272, 1107, 899, 737; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.15 (m, 10H, H-Ar), 4.78 (dt, *J* = 17.1, 2.0 Hz, 2H, H-18), 4.57 (d, *J* = 11.8 Hz, 1H, H-11a), 4.51 (d, *J* = 11.8 Hz, 1H, H-11b), 3.96 (dt, *J* = 14.6, 4.5 Hz, 1H, H-9a), 3.72 – 3.63 (m, 3H, H-10, H-8), 3.35 – 3.29 (m, 1H, H-4), 3.15 (ddd, *J* = 14.6, 7.7, 4.5 Hz, 1H, H-9b), 2.39 (dd, *J* = 8.8, 4.3 Hz, 1H, H-2), 2.32 – 2.06 (m, 5H, H-16, H-6a, H-3a, H-1), 2.06 – 1.92 (m, 2H, H-14a, H-3b), 1.76 (s, 3H, H-19), 1.74 – 1.65 (m, 1H, H-13a), 1.65 – 1.51 (m, 2H, H-14b, H-13b), 1.13 (dd, *J* = 12.0, 5.5 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0 (C=O, C-7), 142.6, (C, C-17), 138.2 (C, C-12), 135.8 (C, C-15), 131.9 (CH, C-Ar), 128.8 (CH, C-Ar), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 127.6 (CH, C-Ar), 126.7 (CH, C-Ar), 113.5 (CH_2, C-18), 73.2 (CH_2, C-11), 69.0 (CH_2, C-10), 62.4 (CH, C-8), 49.5 (C, C-5), 49.2 (CH, C-4), 45.6 (CH, C-2), 41.6 (CH_2, C-9), 38.9 (CH_2, C-16), 37.4 (CH, C-1), 35.8 (CH_2, C-6), 30.3 (CH_2, C-13), 29.3 (CH_2, C-14), 22.6 (CH_2, C-3), 22.5 (CH_3, C-19); **HRMS** (ES) found 484.2284 $[MNa]^+$, requires 484.2286 for $C_{29}H_{35}NO_2NaS$.

Preparation of vinyl sulfide **293**:

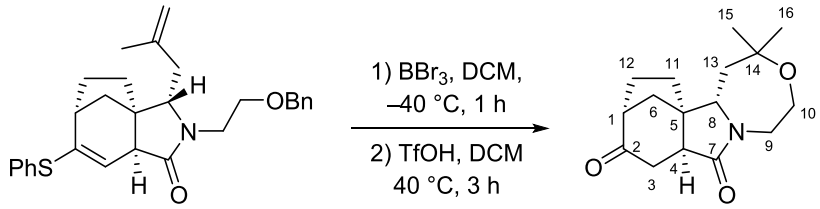


294 **293**

m-CPBA (77%, 70 mg, 0.29 mmol, 1.1 eq.) was slowly added to a solution of **294** (125 mg, 0.27 mmol, 1.0 eq.) in $CHCl_3$ (3 mL) at 0 °C. After 45 min at 0 °C the mixture was quenched with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 5 mL),

the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in dry MeCN (2 mL) then Et_3N (94 µL, 0.67 mmol, 2.5 eq.) was added at 0 °C. After 5 min, TFAA (94 µL, 0.67 mmol, 2.5 eq.) in dry MeCN (0.5 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C and 1 h at RT before being quenched with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 3/1 to 2/1) to give vinyl sulfide **293** (105 mg, 85% after 2 steps) as a colourless oil. **IR** ν_{max}/cm^{-1} 3070, 3035, 2940, 2861, 1684, 1439, 1182, 1099, 1024, 740; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.12 (m, 10H, H-Ar), 5.72 (d, *J* = 4.1 Hz, 1H, H-3), 4.72 (dt, *J* = 9.9, 1.4 Hz, 2H, H-18), 4.43 (d, *J* = 11.8 Hz, 1H, H-11a), 4.39 (d, *J* = 11.8 Hz, 1H, H-11b), 3.86 (dt, *J* = 14.5, 4.4 Hz, 1H, H-9a), 3.67 ("app t", *J* = 6.5 Hz, 1H, H-8), 3.55 – 3.50 (m, 2H, H-10), 3.05 (dt, *J* = 14.5, 5.8 Hz, 1H, H-9b), 2.83 (d, *J* = 4.1 Hz, 1H, H-4), 2.35 – 2.31 (m, 1H, H-1), 2.20 (d, *J* = 6.5 Hz, 2H, H-16), 1.85 – 1.78 (m, 2H, H-14), 1.77 – 1.73 (m, 1H, H-13a), 1.70 (s, 3H, H-19), 1.68 – 1.64 (m, 1H, H-6a), 1.60 – 1.54 (m, 1H, H-13b), 1.32 (dd, *J* = 10.8, 4.4 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1 (C=O, C-7), 143.9 (C, C-17), 138.1 (C, C-12), 133.6 (C, C-15), 131.9 (CH, C-Ar), 129.0 (CH, C-Ar), 128.4 (CH, C-Ar), 127.7 (CH, C-Ar), 127.2 (CH, C-Ar), 120.1 (CH, C-3), 114.0 (CH_2, C-18), 73.1 (CH_2, C-11), 68.9 (CH_2, C-10), 62.2 (CH, C-8), 52.1 (CH, C-4), 48.9 (C, C-5), 41.4 (CH_2, C-9), 40.9 (CH_2, C-6), 40.8 (CH_2, C-16), 39.7 (CH, C-1), 32.8 (CH_2, C-14), 30.6 (CH_2, C-13), 22.4 (CH_3, C-19); 1 signal in the CH aromatic region were not observed due to overlap; **HRMS** (ES) found 482.2123 $[MNa]^+$, requires 482.2130 for $C_{29}H_{33}NO_2SNa$.

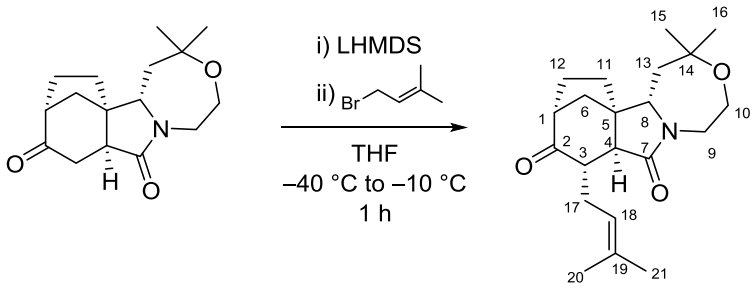
Preparation of tetracycle **292**



A solution of BBr_3 (1.0 M in DCM, 0.59 mL, 0.59 mmol, 3.0 eq.) was added to a solution of **293** (90 mg, 0.19 mmol, 1.0 eq.) in dry DCM (2 mL) at –40 °C. The mixture was stirred for 1 h at −40 °C before being quenched with water. The pH was adjusted to pH = 4-5 with a solution of 2 N NaOH (aq). The aqueous layer was extracted with EtOAc (5 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in dry DCM (3 mL) and triflic acid (138 µL, 1.57 mmol, 5.0 eq.) was added at RT. The mixture was stirred 1 h at RT and 3 h at 40 °C before being quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to give tetracyclic compound **292** (17 mg, 33% after 2 steps) as a white powder. **m.p.** 149 – 151 °C; **IR** ν_{max}/cm^{-1} 2968, 2940, 2876, 1713, 1684, 1445, 1369, 1238, 1081; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 – 4.12 (m, 1H, H-9a), 3.69 – 3.63 (m, 1H, H-10a), 3.61 – 3.53 (m, 2H, H-10b, H-8), 2.97 (ddd, *J* = 13.6, 10.5, 2.8 Hz, 1H, H-9b), 2.79 – 2.73 (m, 1H, H-1), 2.71 – 2.64 (m, 2H, H-3), 2.61 – 2.55 (m, 1H, H-4), 2.22 – 2.10 (m, 1H, H-12a), 1.96 (d, *J* = 12.3 Hz, 1H, H-6a), 1.86 (“app t”, *J* = 14.0 Hz, 2H, H-13), 1.82 – 1.70 (m, 3H, H-12b, H-11), 1.65 (dd, *J* = 12.3, 4.9 Hz, 1H, H-6b), 1.25 (s, 3H, H-16), 1.21 (s, 3H, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.8 (C=O, C-2), 173.4 (C=O, C-7), 74.7 (C, C-14), 62.5 (CH_2,

C-10), 61.1 (CH, C-8), 48.9 (CH, C-1), 48.2 (C, C-5), 44.8 (CH_2, C-13), 44.4 (CH_2, C-9), 43.9 (CH, C-4), 37.7 (CH_2, C-6), 33.6 (CH_2, C-3), 32.2 (CH_2, C-11), 28.4 (CH_3, C-16), 27.3 (CH_3, C-15), 26.4 (CH_2, C-12); **HRMS** (ES) found 300.1569 $[MNa]^+$, requires 300.1576 for $C_{16}H_{23}NO_3Na$.

Preparation of prenylated compound **298**

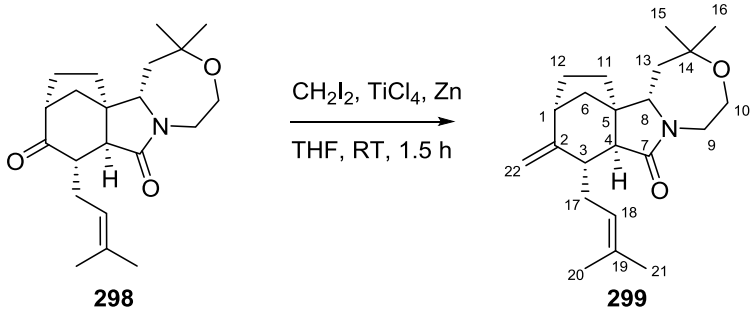


292 **298**

A solution of LHMDS (1.0 M in THF, 0.21 mmol, 0.21 mL, 1.2 eq.) was added to a solution of **292** (50 mg, 0.18 mmol, 1.0 eq.) in dry THF (2 mL) at −40 °C. After 15 min, prenyl bromide (63 µL, 0.54 mmol, 3.0 eq.) was added. The reaction mixture was stirred for 1 h at −40 °C, then allowed to warm to −10 °C and stirred for 5 h before being quenched with water. The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to yield prenylated compound **298** (28 mg, 45%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3071, 3023, 2998, 2929, 1876, 1480, 1435, 1089, 741; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.98 – 4.90 (m, 1H, H-18), 4.17 (dt, *J* = 14.0, 2.1 Hz, 1H, H-9a), 3.68 – 3.57 (m, 2H, H-10), 3.54 (d, *J* = 10.5 Hz, 1H, H-8), 2.95 (ddd, *J* = 14.0, 10.2, 3.2 Hz, 1H, H-9b), 2.74 (dd, *J* = 8.3, 4.3 Hz, 1H, H-1), 2.71 – 2.63 (m, 2H, H-17a, H-3), 2.50 – 2.40 (m, 1H, H-17b), 2.19 (d, *J* = 6.3, 1.5 Hz, 1H, H-4), 2.14 – 2.02 (m, 1H,

H-12a), 1.97 (dt, *J* = 11.9, 1.7 Hz, 1H, H-11a), 1.90 – 1.83 (m, 1H, H-13a), 1.80 – 1.69 (m, 2H, H-13b, H-6a), 1.67 (s, 3H, H-21), 1.63 (s, 3H, H-20), 1.62 – 1.58 (m, 1H, H-12b), 1.57 – 1.46 (m, 2H, H-11b, H-6b), 1.24 (s, 3H, H-16), 1.20 (s, 3H, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 213.8 (C=O, C-2), 174.2 (C=O, C-7), 135.1 (C, C-19), 120.1 (CH, C-18), 74.7 (C, C-14), 62.5 (CH_2, C-10), 61.2 (CH, C-8), 48.8 (CH, C-1), 48.3 (C, C-5), 47.6 (CH, C-4), 45.0 (CH_2, C-13), 44.7 (CH, C-3), 44.3 (CH_2, C-9), 37.2 (CH_2, C-11), 32.2 (CH_2, C-6), 28.7 (CH_2, C-17), 28.4 (CH_3, C-16), 27.2 (CH_3, C-15), 26.4 (CH_2, C-12), 25.9 (CH_3, C-21), 18.2 (CH_3, C-20); **HRMS** (ES) found 386.2204 $[MNa]^+$, requires 386.2202 for $C_{21}H_{31}NO_3Na$.

Preparation of olefin **299**

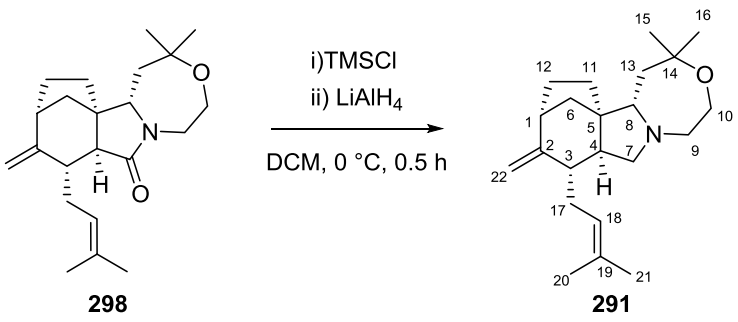


298 **299**

CH_2I_2 (0.4 mL, 5.00 mmol, 5.0 eq.) was added to a suspension of zinc (0.58 g, 9.00 mmol, 9.0 eq.) and $PbCl_2$ (15 mg, 0.05 mmol, 0.05 eq.) in dry THF (10 mL) at RT. After 0.5 h, $TiCl_4$ (1.0 M in DCM, 1.00 ml, 1.00 mmol, 1.0 eq.) was added at 0 °C and the mixture was stirred for 0.5 h at RT. A solution of [CH_2I_2, $TiCl_4$, Zn] (0.1 M in THF, 1.00 mL, 0.10 mmol, 1.3 eq.) was added to a solution of **298** (27 mg, 0.08 mmol, 1.0 eq.) at RT. After being stirred for 1.5 h, the mixture was diluted with EtOAc, the organic layer was washed with a solution of 1 M HCl (aq), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 2/1 to 1/1) to yield olefin

299 (12 mg, 45%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.19 – 5.13 (m, 1H, H-18), 4.77 – 4.74 (m, 1H, H-22a), 4.69 – 4.65 (m, 1H, H-22b), 4.15 (dt, *J* = 13.9, 2.1 Hz, 1H, H-9b), 3.67 – 3.54 (m, 2H, H-10), 3.43 (dd, *J* = 10.1, 1.5 Hz, 1H, H-8), 2.97 – 2.89 (m, 1H, H-9b), 2.82 – 2.75 (m, 2H, H-3, H-1), 2.44 – 2.30 (m, 2H, H-17), 2.16 (d, *J* = 4.2 Hz, 1H, H-4), 2.06 – 1.95 (m, 1H, H-12a), 1.87 – 1.73 (m, 2H, H-13), 1.73 (s, 3H, H-20), 1.67 – 1.52 (m, 7H, H-21, H-11, H-12b, H-6a), 1.37 (dd, *J* = 11.3, 4.9 Hz, 1H, H-6b), 1.24 (s, 3H, H-16), 1.20 (s, 3H, H-15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (C=O, C-7), 155.0 (C, C-2), 133.3 (C, C-19), 122.4 (CH, C-18), 108.3 (CH_2, C-22), 74.8 (C, C-14), 62.7 (CH_2, C-10), 61.5 (CH, C-8), 51.2 (CH, C-4), 48.4 (C, C-5), 44.1 (CH_2, C-13, C-9), 43.2 (CH, C-1), 40.5 (CH_2, C-6), 36.2 (CH_2, C-17), 35.6 (CH, C-3), 31.7 (CH_2, C-11), 30.2 (CH_2, C-12), 28.5 (CH_3, C16), 27.3 (CH_3, C-15), 25.9 (CH_3, C-21), 18.2 (CH_3, C20).

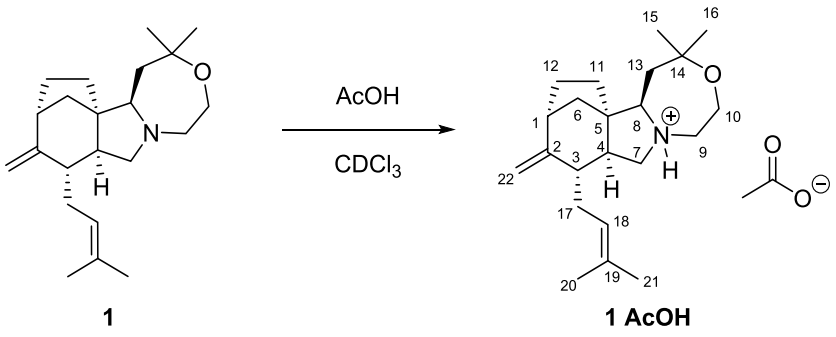
Preparation of 8-epi-concavine **291**



TMSCl (6 µL, 0.042 mmol, 1.2 eq.) was added to a solution of **298** (12 mg, 0.035 mmol, 1.0 eq.) in dry DCM (1 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then a solution of $LiAlH_4$ (2.4 M in THF, 22 µL, 0.052 mmol, 1.5 eq.) was added. After 0.5 h at 0 °C, the reaction mixture was quenched with a 2 N solution of NaOH (aq). The aqueous layer was extracted with DCM (3 × 3 mL), the combined organic layers were dried over $MgSO_4$, filtered

and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient: hexane/EtOAc = 1/1 to 0/1) to yield 8-epi-concavine **291** (10 mg, 90%) as a colourless oil. **IR** ν_{max}/cm^{-1} 3080, 2928, 2868, 2800, 1364, 1169, 1077, 882; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.14 – 5.07 (m, 1H, H-18), 4.81 – 4.77 (m, 1H, H-22a), 4.70 – 4.67 (m, 1H, H-22b), 3.85 – 3.75 (m, 1H, H-10a), 3.56 (ddd, *J* = 13.6, 3.3, 1.9 Hz, 1H, H-10b), 3.27 ("app t", *J* = 8.0 Hz, 1H, H-7a), 3.11 – 3.01 (m, 1H, H-9a), 2.72 (dd, *J* = 8.0, 4.9 Hz, 1H, H-1), 2.48 (d, *J* = 9.8 Hz, 1H, H-8), 2.36 – 2.14 (m, 3H, H-9b, H-17), 2.14 – 2.04 (m, 2H, H-12a, H-3), 1.94 – 1.71 (m, 2H, H-7b, H-13a), 1.66 (s, 3H, H-20), 1.64 –1.54 (m, 5H, H-21, H-4, H-13b), 1.49 (d, *J* = 11.3 Hz, 1H, H-6a), 1.39 – 1.30 (m, 3H, H-12b, H-11), 1.21 (s, 3H, H-15), 1.19 – 1.15 (m, 4H, H-16, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0 (C, C-2), 148.7 (C, C-19), 122.1 (CH, C-18), 105.8 (CH_2, C-22), 74.9 (C, C-14), 65.2 (CH, C-8), 62.8 (CH_2, C-7), 62.1 (CH_2, C-10), 58.4 (CH_2, C-9), 52.3 (C, C-5), 48.3 (CH, C-4), 43.2 (CH_2, C-13), 40.7 (CH, C-1), 39.8 (CH, C-3), 35.0 (CH_2, C-6), 33.6 (CH_2, C-11), 32.4 (CH_2, C-12), 29.1 (CH_3, C-16), 28.3 (CH_2, C-17), 27.6 (CH_3, C-15), 25.8 (CH_3, C-20), 18.0 (CH_3, C-21); **HRMS** (ES) found 330.2798 [MH]+, requires 330.2797 for $C_{22}H_{36}NO$.

Preparation of **1-AcOH**



1 **1 AcOH**

A solution of AcOH in $CDCl_3$ (0.18 M, 0.1 mL, 0.018 mmol, 1.0 eq.) was added to a solution of **1** (6 mg, 0.018 mmol, 1.0 eq.) in $CDCl_3$ (0.5 mL) in a NMR tube. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.10 – 5.05 (m, 1H, H-18), 4.86 – 4.82 (m, 1H, H-22a), 4.78 – 4.74 (m, 1H, H-22b), 4.03 (dd, *J* = 14.4, 10.8 Hz, 1H, H-10a), 3.58 (dt, J = 14.4, 2.5 Hz, 1H, H-10b) 3.55 – 3.47 (m, 2H, H-7a, H-9a), 3.11 (d, *J* = 9.6 Hz, 1H, H-8), 2.89 – 2.84 (m, 1H, H-1), 2.72 (“app t”, *J* = 10.9 Hz, 1H, H-7b), 2.60 – 2.51 (m, 1H, H-9b), 2.31 (dd, *J* = 16.0, 9.6 Hz, 1H, H-13a), 2.26 – 2.17 (m, 3H, H-3, H-17), 2.02 (s, 3H, AcOH), 1.98 – 1.89 (m, 2H, H-12a, H-6a), 1.78 – 1.71 (m, 1H, H-4), 1.69 (s, 3H, H-21), 1.60 (s, 3H, H-20), 1.57 – 1.51 (m, 1H, H-13b), 1.50 – 1.32 (m, 3H, H-12b, H-11), 1.25 (s, 3H, H-15), 1.17 (s, 3H, H-16), 1.04 (dd, *J* = 11.7, 4.4 Hz, 1H, H-6b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.1 (C=O, AcOH), 155.1 (C, C-2), 132.7 (C, C-19), 122.1 (CH, C-18), 108.3 (CH_2, C-22), 74.7 (C, C-14), 66.2 (CH, C-8), 59.8 (CH_2, C-7), 59.7 (CH_2, C-10), 57.4 (CH_2, C-9), 52.7 (C, C-5), 49.0 (CH, C-4), 42.0 (CH, C-1), 40.5 (CH, C-3), 37.5 (CH_2, C-13), 33.5 (CH_2, C-11), 33.0 (CH_2, C12), 30.3 (CH_2, C-17), 30.1 (CH_2, C-6), 28.2 (CH_3, C-16), 26.8 (CH_3, C-15), 25.8 (CH_3, C-20), 22.1 (CH_3, AcOH), 18.0 (CH_3, C-20).

Appendix A X-ray structure

X-ray Crystal Structure Data for Compound **223**

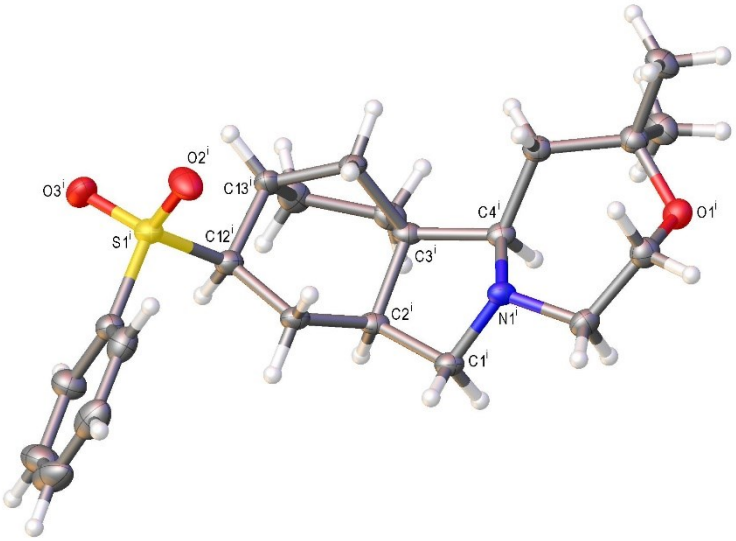


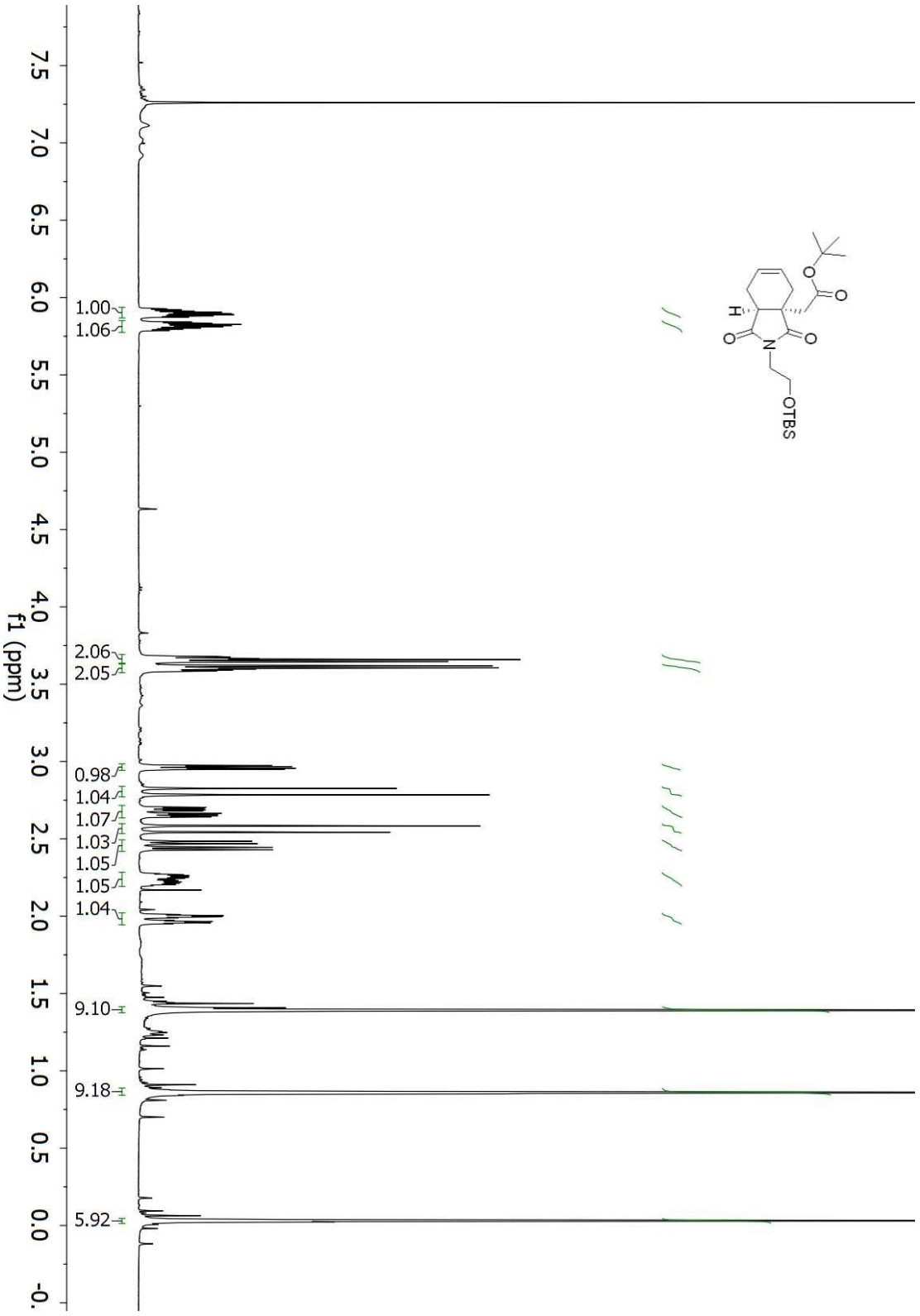
Table 1: crystal data and structure refinement

Empirical formula	$C_{22}H_{31}NO_3S$
Formula weight	389.20
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	monoclinic
Space group	I2/a
Unit cell dimensions	a = 26.9274(3)
	b = 5.87596(8)
	c = 29.0682(4)
Volume	4599.29(10) $Å^3$
Z	8
Density (calculated)	1.370 g/cm^3

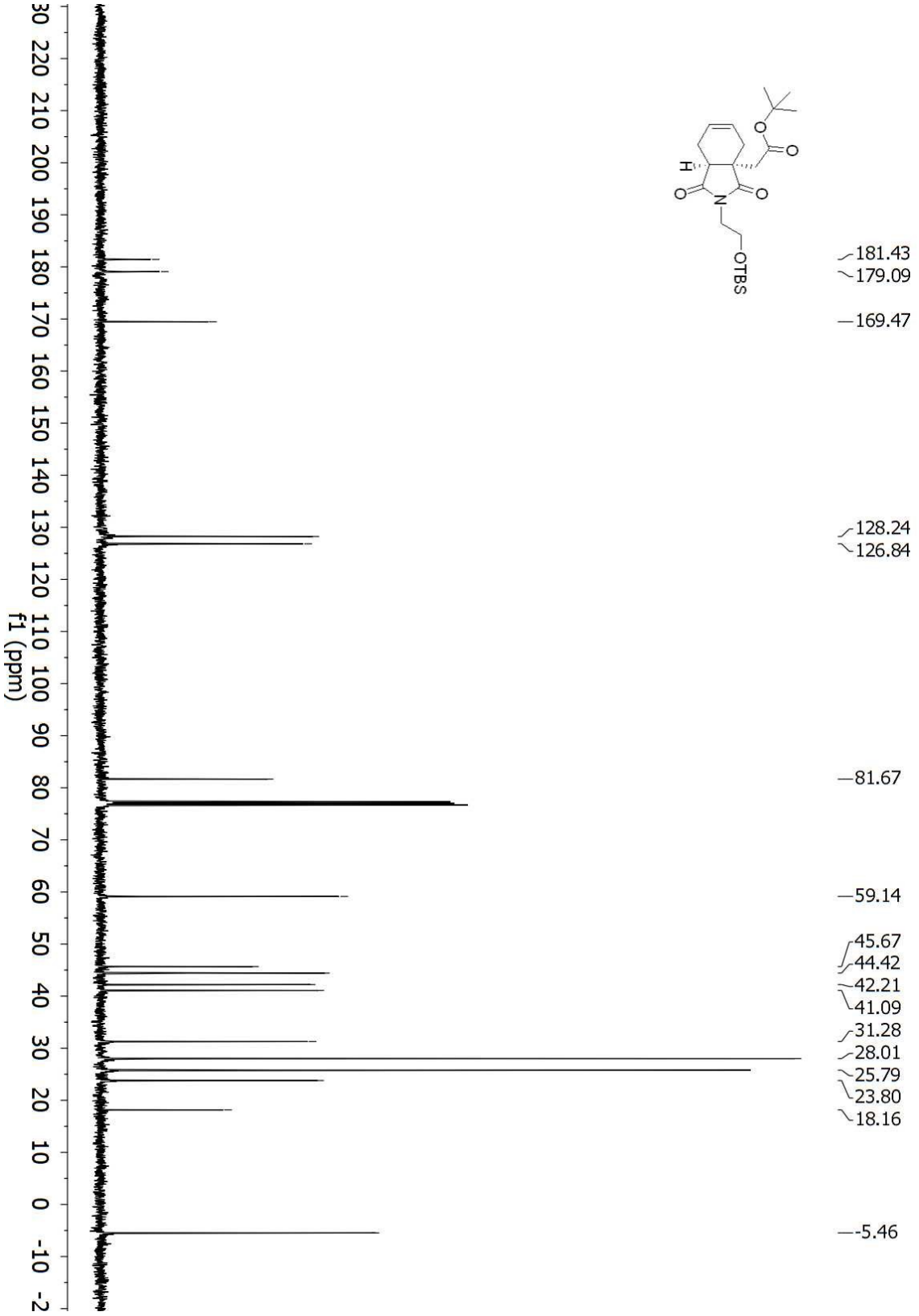
Absorption coefficient	3.587 μ/mm^{-1}
F(000)	2016.0
Crystal size	0.1388 × 0.0867 × 0.0464 mm^3
Radiations	CuKα
Theta range for data collection	6.082 to 136.468°
Index ranges	$-32 \leq h \leq 32$, $-6 \leq k \leq 7$, $-35 \leq l \leq 35$
Reflections collected	19675
Independent reflections	4194 [R_{int} = 0.0341, R_{sigma} = 0.0230]
Data/restraints/parameters	4194/0/273
Goodness-of-fit on F^2	1.090
Final R indexes [I>=2σ (I)]	R1 = 0.0754, wR2 = 0.2210
Final R indexes [all data]	R1 = 0.0791, wR2 = 0.2247
Largest diff. peak/hole	0.84/-1.13 e Å^{-3}

Appendix B Selected NMR spectra

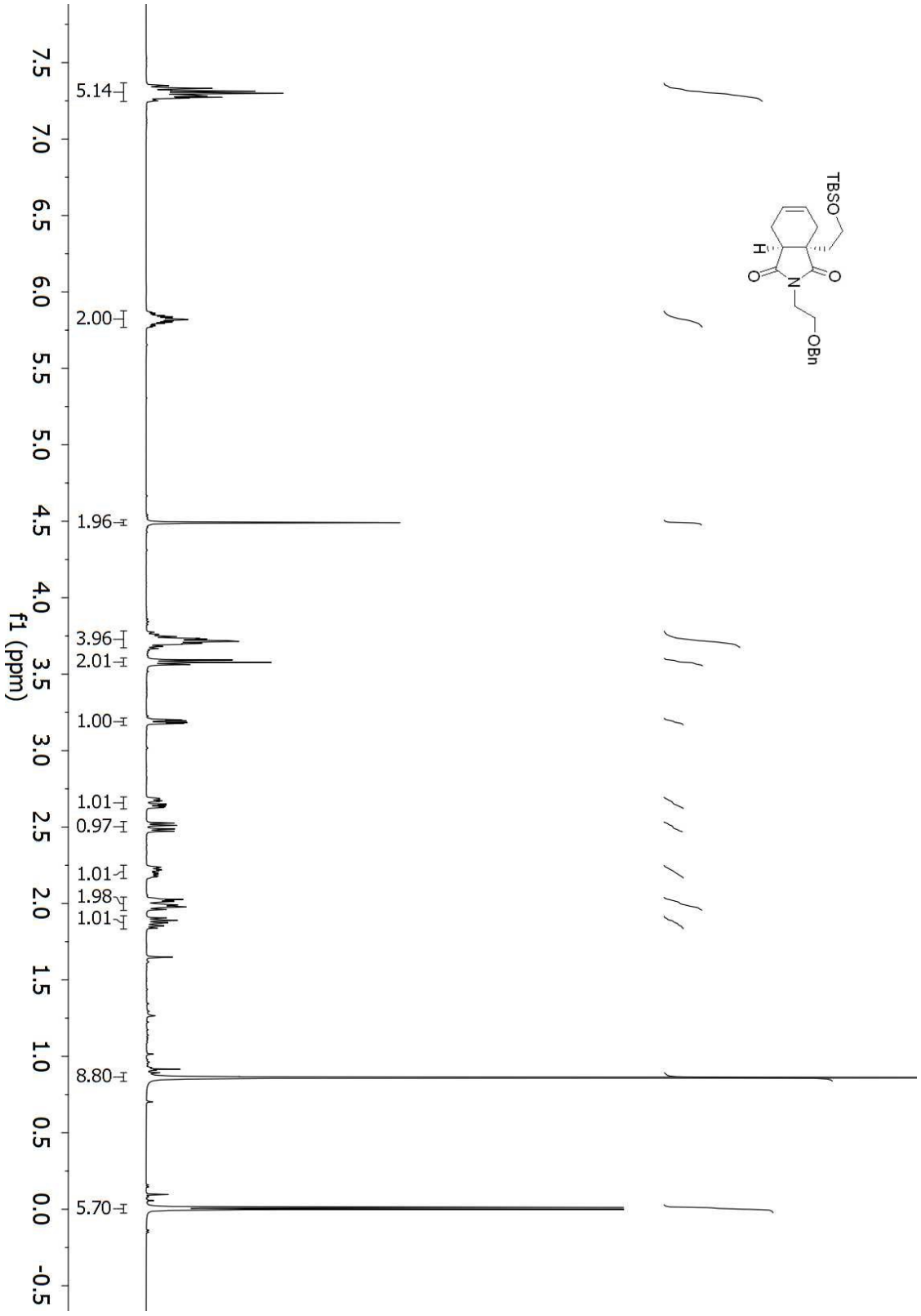
^{1}H NMR spectrum for **97** (400 MHz, $CDCl_3$)



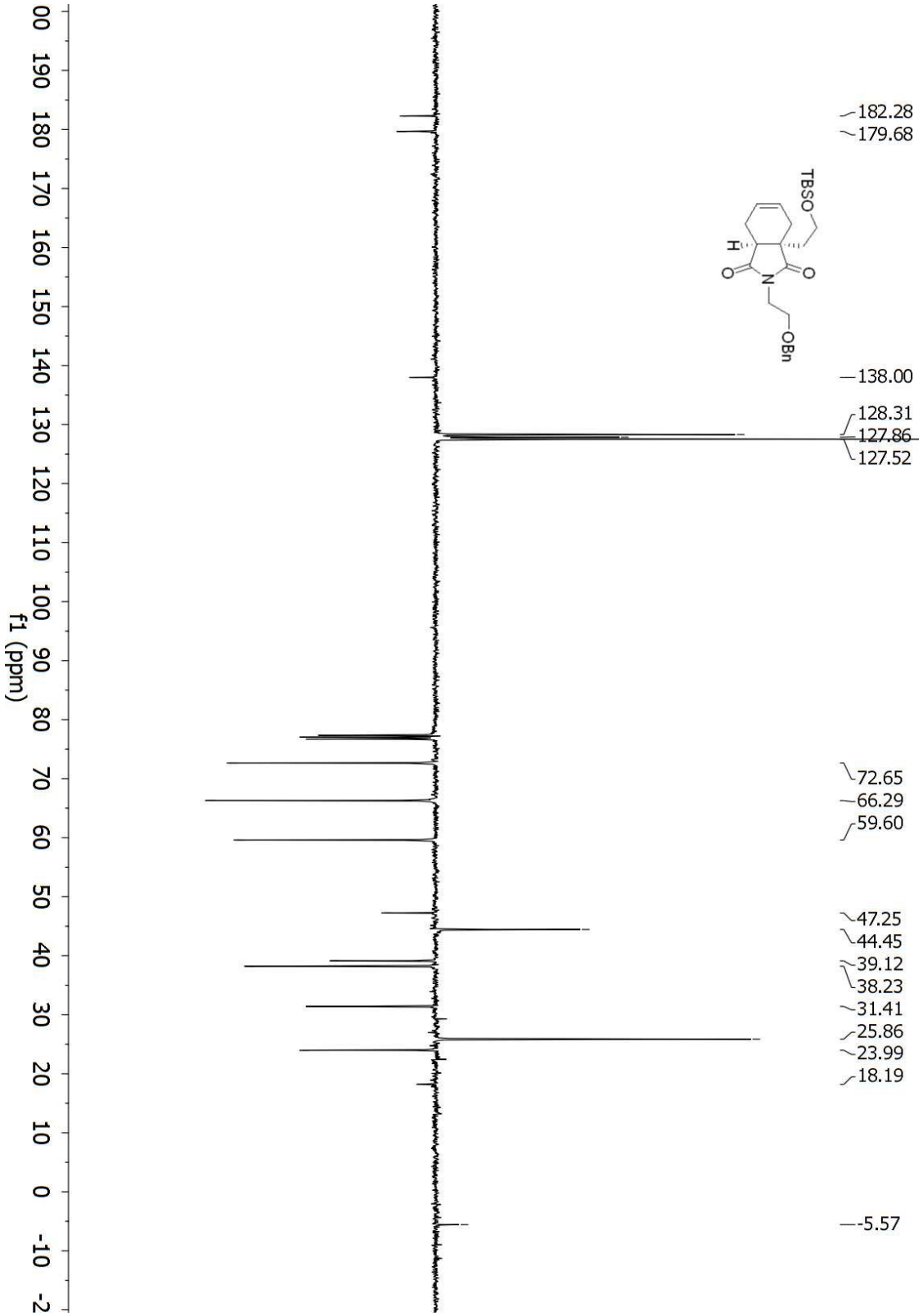
^{13}C NMR spectrum for **97** (101 MHz, $CDCl_3$)



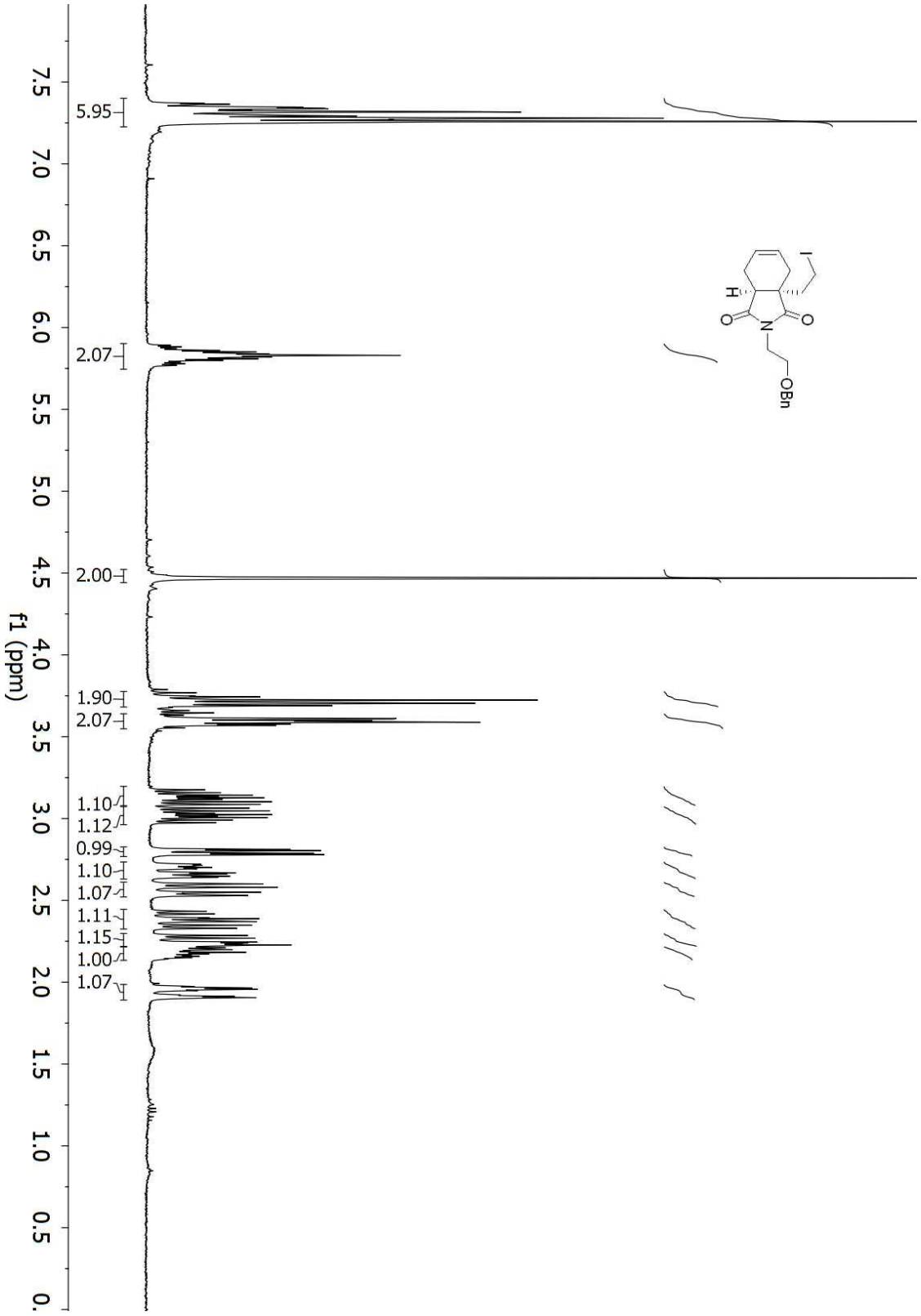
^{1}H NMR spectrum for **179** (300 MHz, $CDCl_3$)



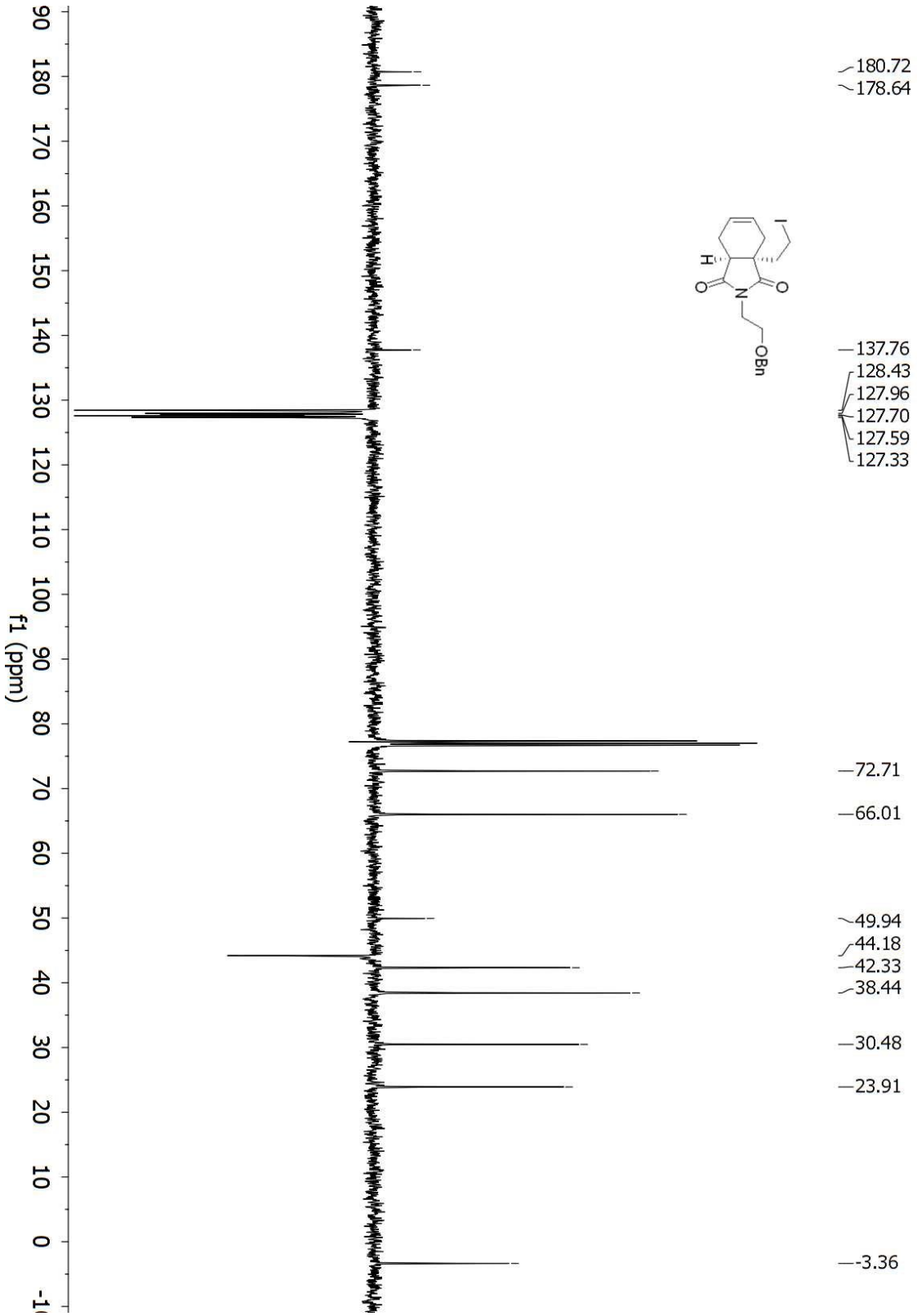
PENDANT spectrum for **179** (101 MHz, $CDCl_3$)



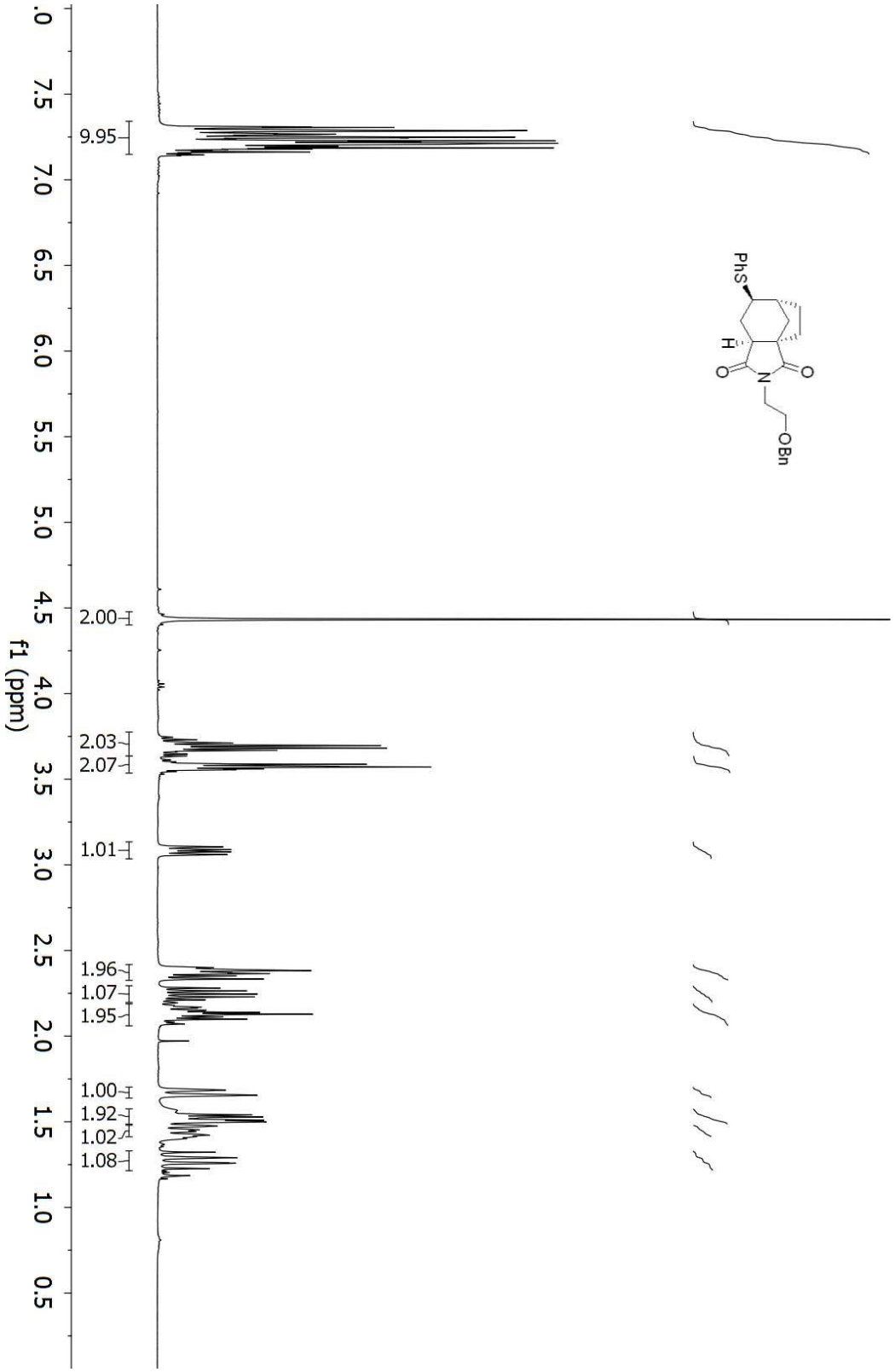
^{1}H NMR spectrum for **181** (300 MHz, $CDCl_3$)



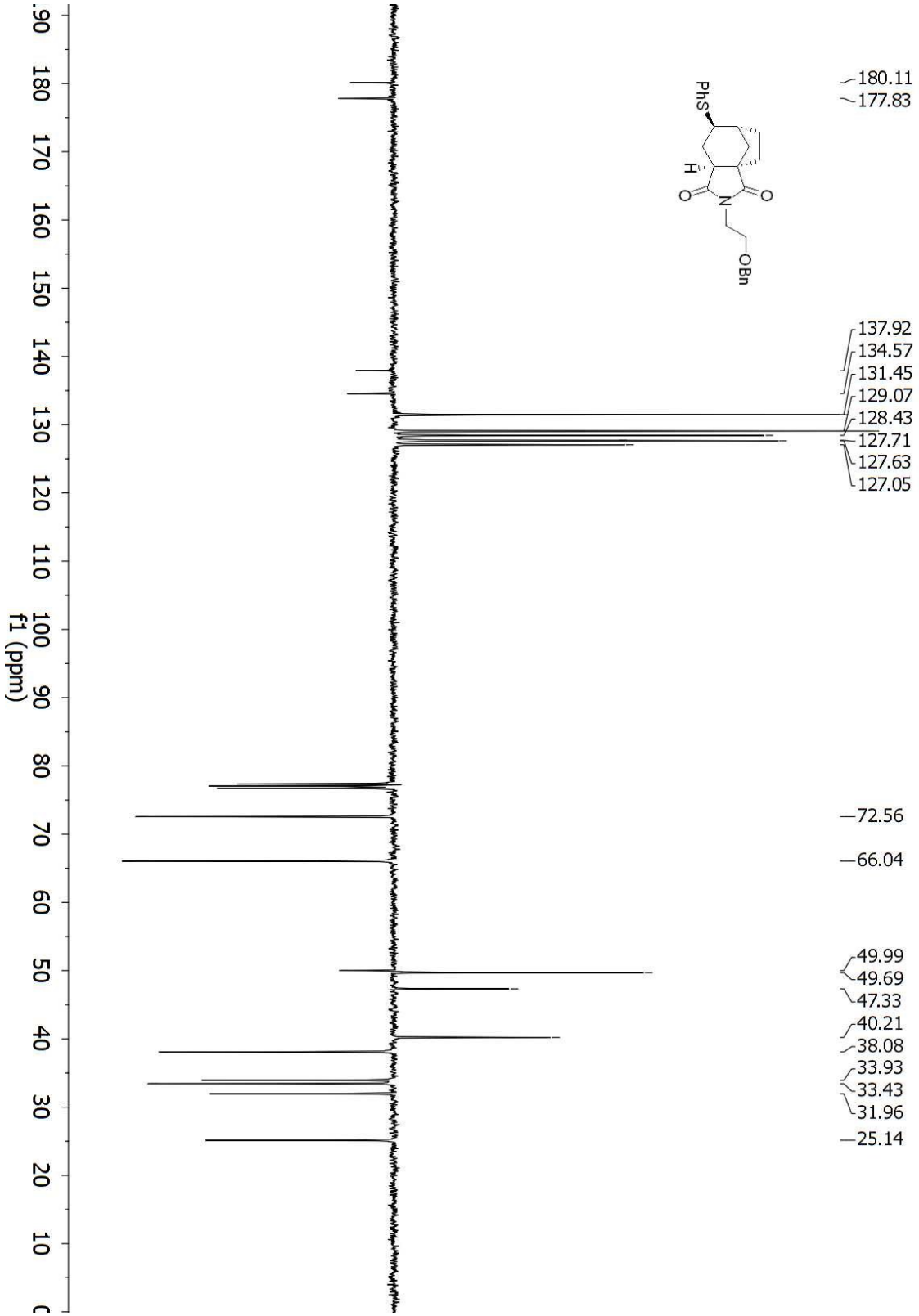
PENDANT spectrum for **181** (101 MHz, $CDCl_3$)



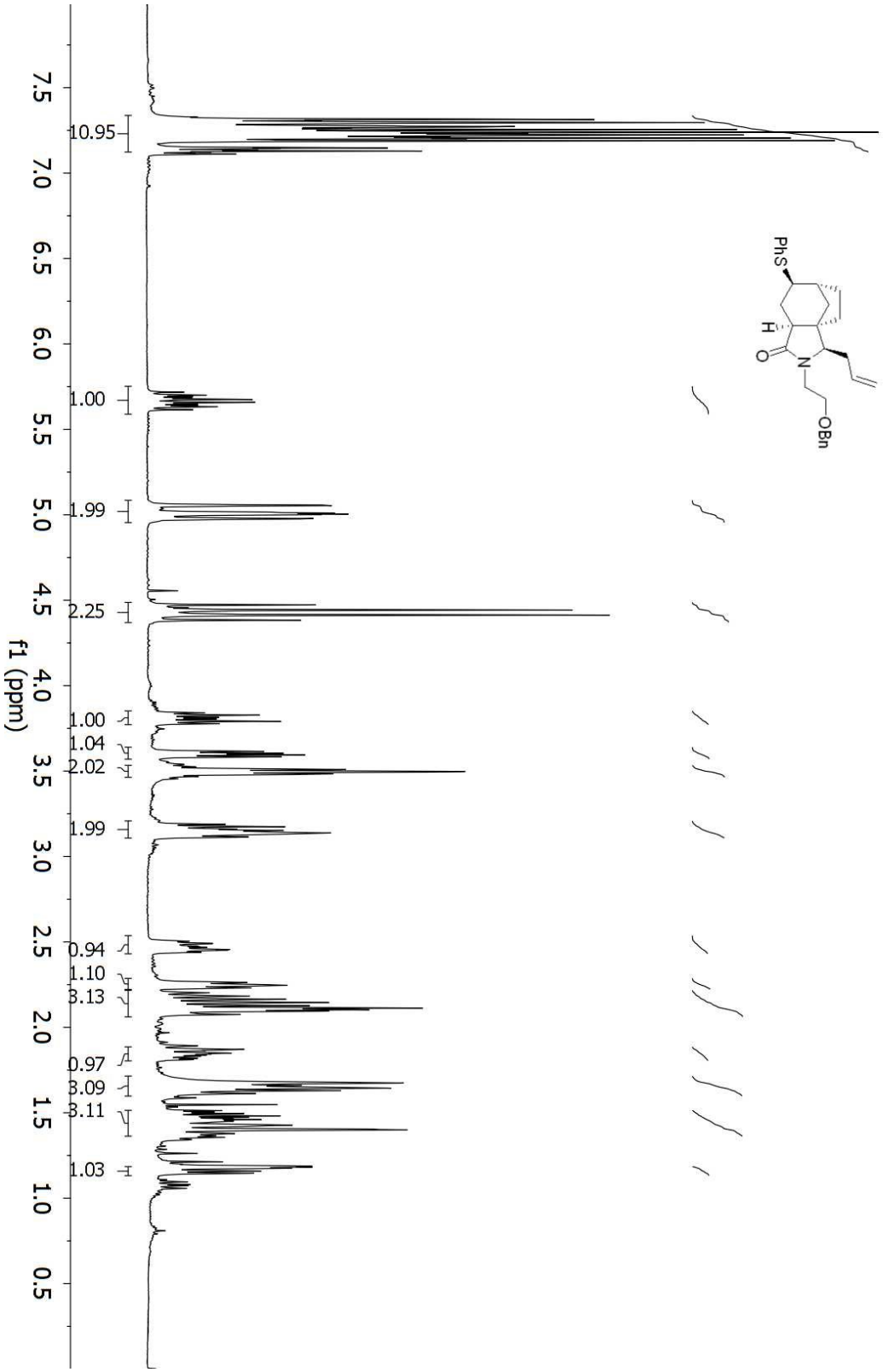
^{1}H NMR spectrum for **182** (400 MHz, $CDCl_3$)



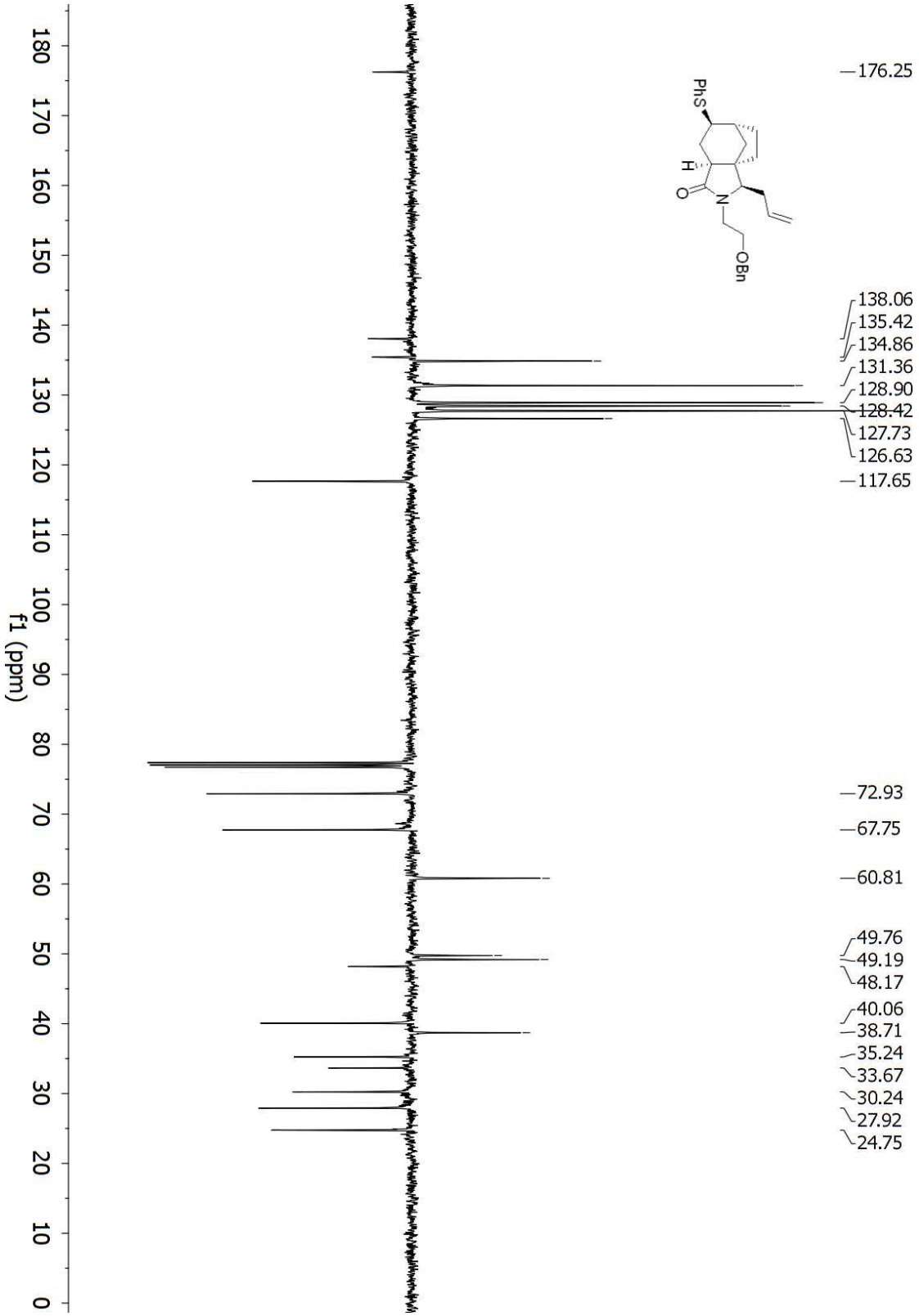
PENDANT spectrum for **182** (101 MHz, $CDCl_3$)



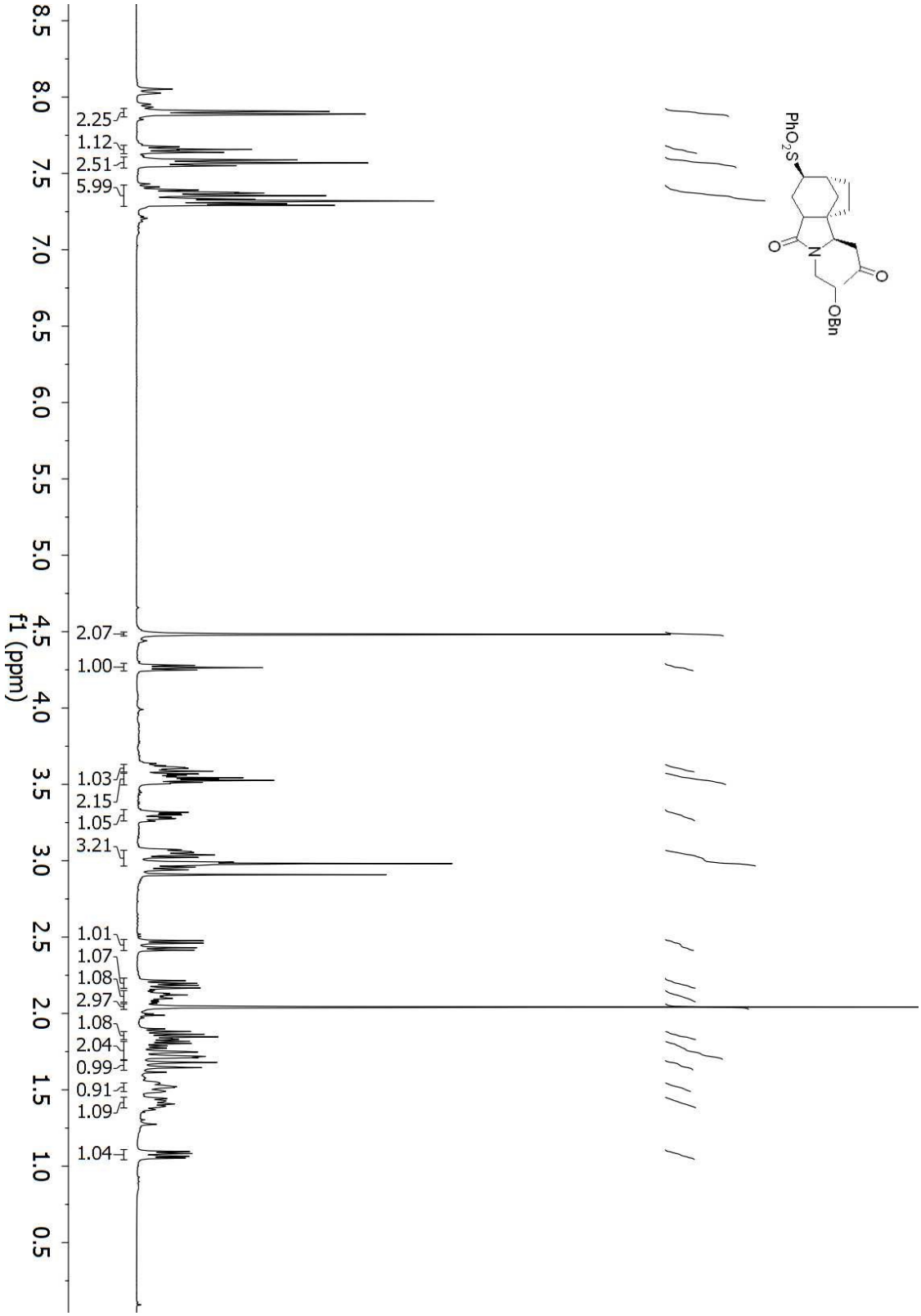
^{1}H NMR spectrum for **198** (400 MHz, $CDCl_3$)



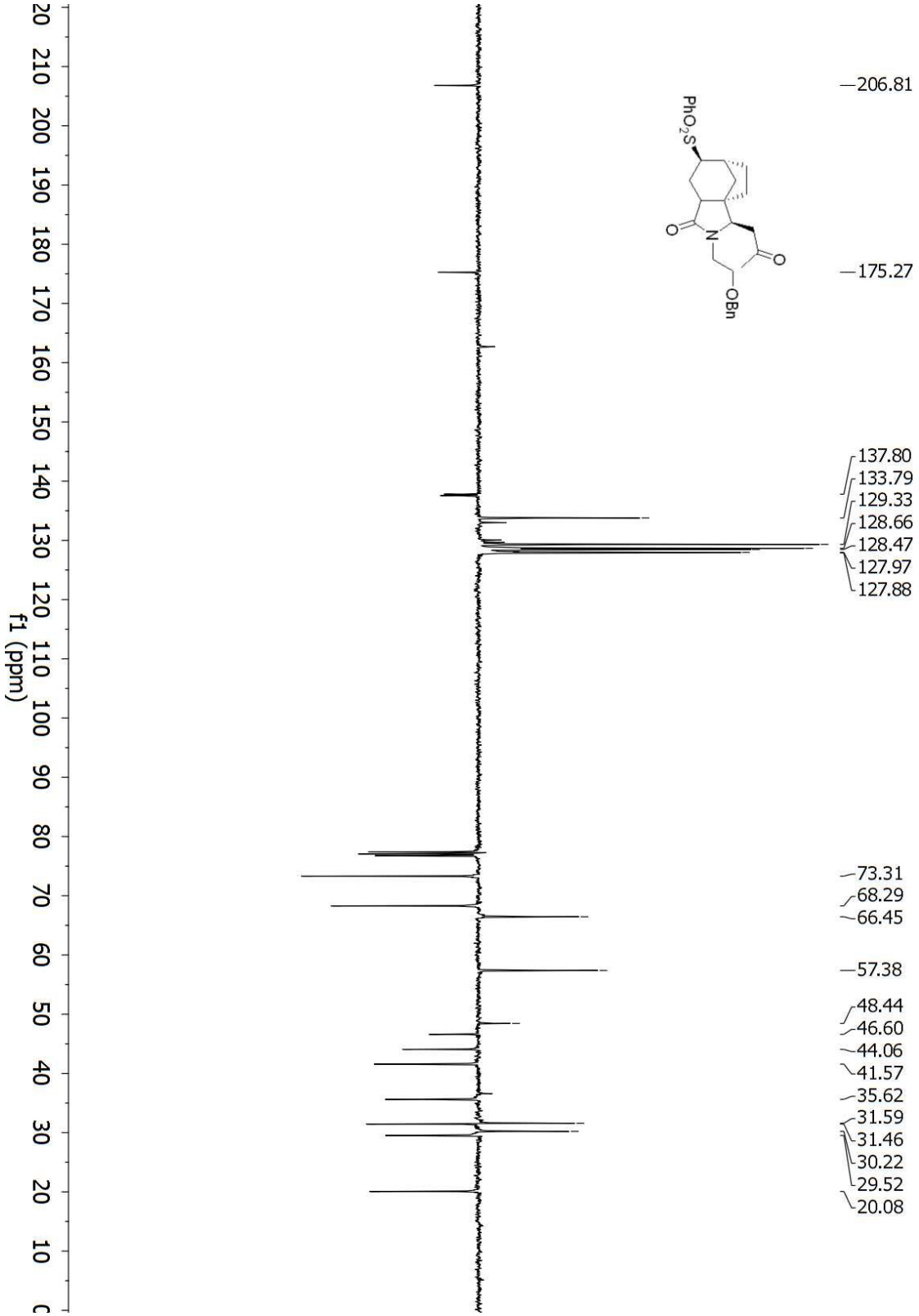
PENDANT spectrum for **198** (101 MHz, $CDCl_3$)



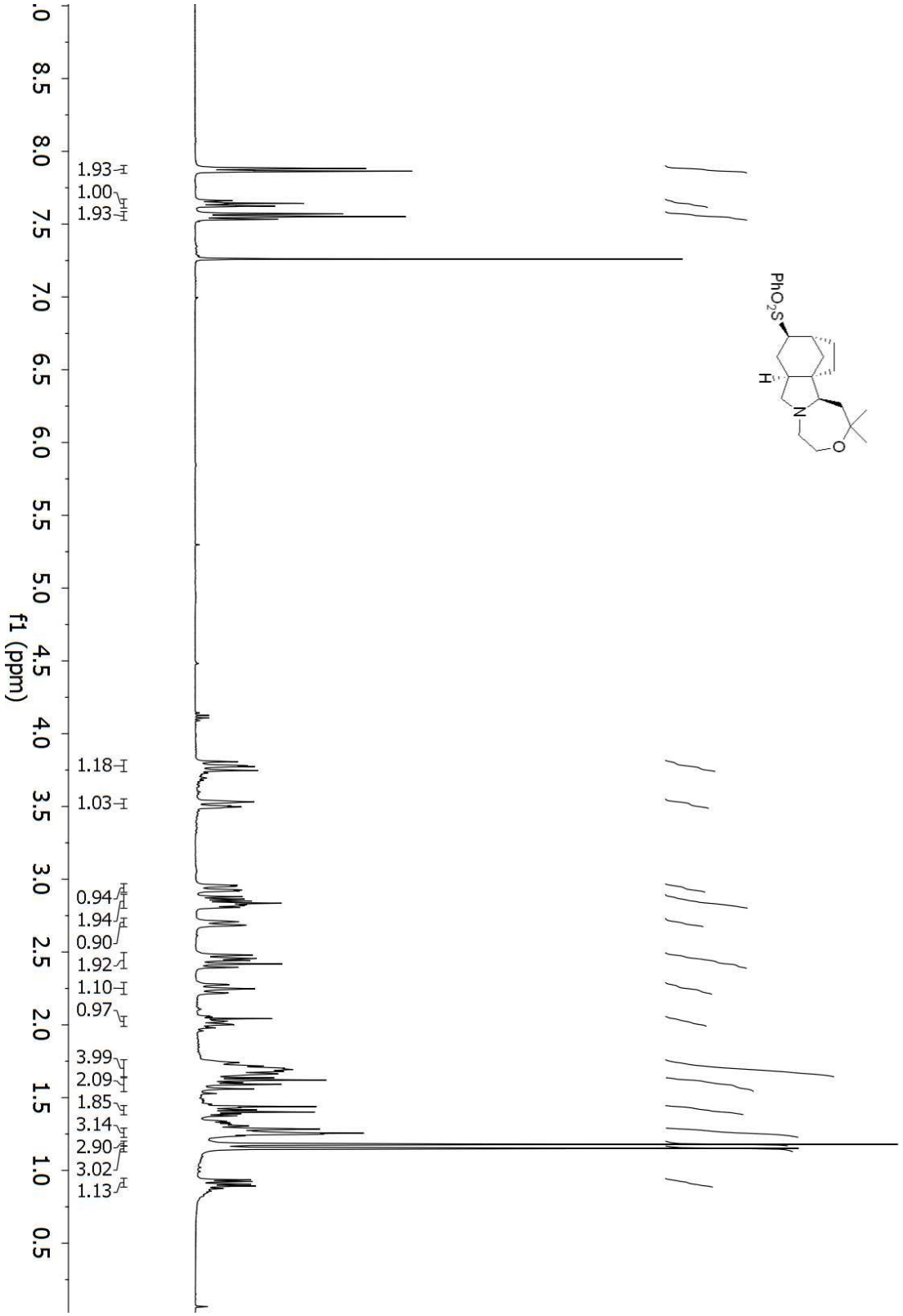
^{1}H NMR spectrum for **204** (400 MHz, $CDCl_3$)



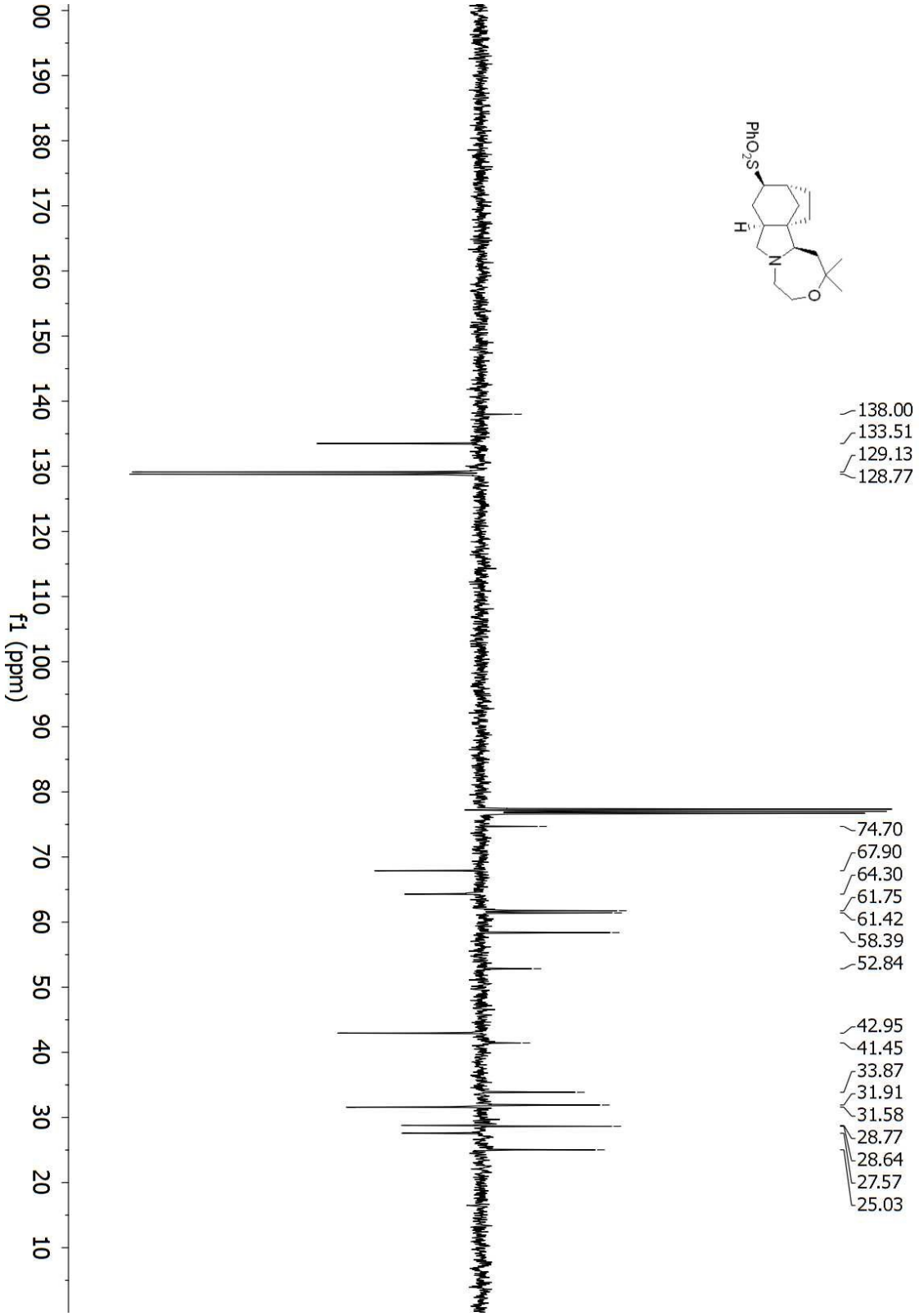
PENDANT spectrum for **204** (101 MHz, $CDCl_3$)



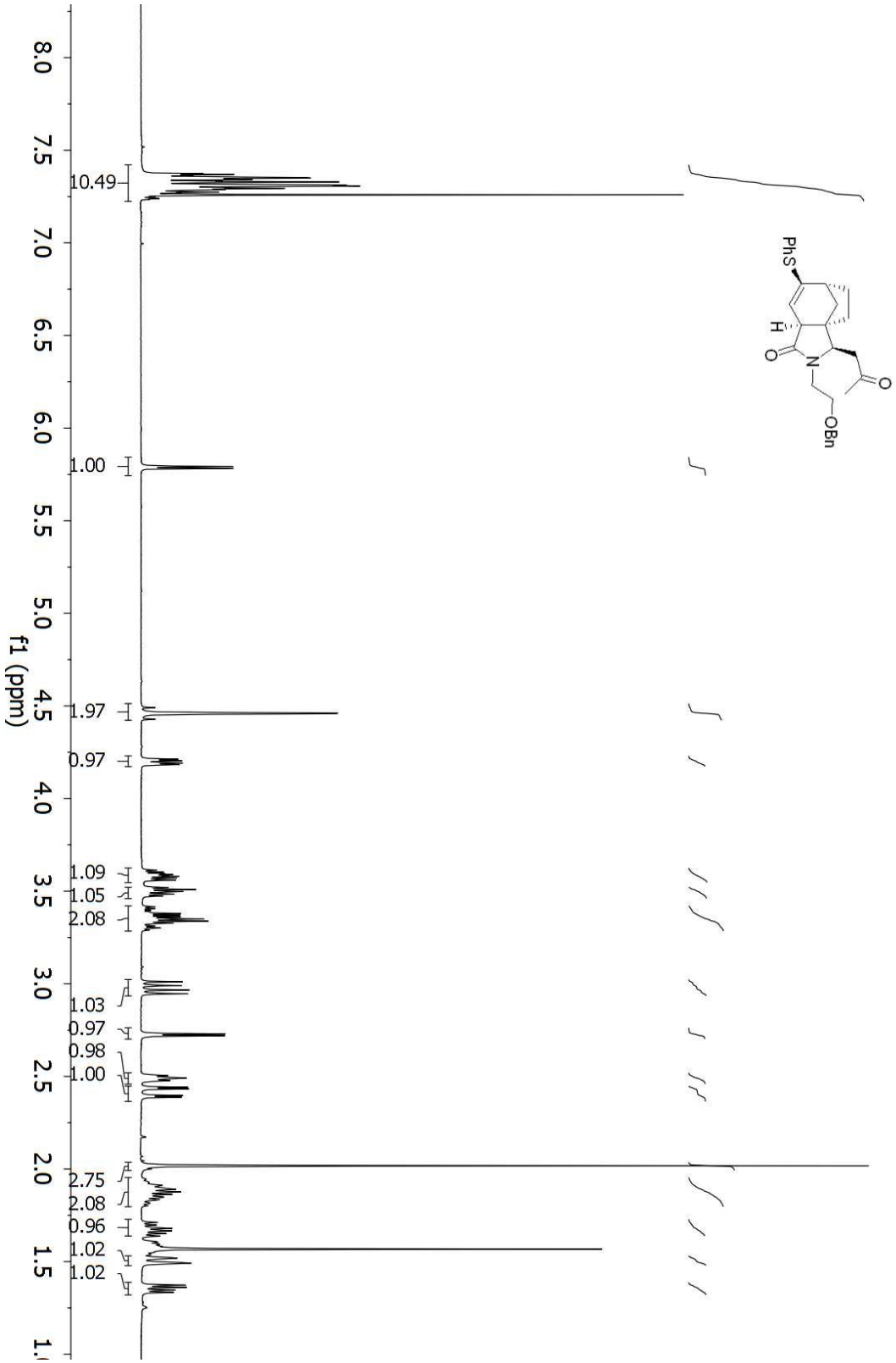
^{1}H NMR spectrum for **223** (400 MHz, $CDCl_3$)



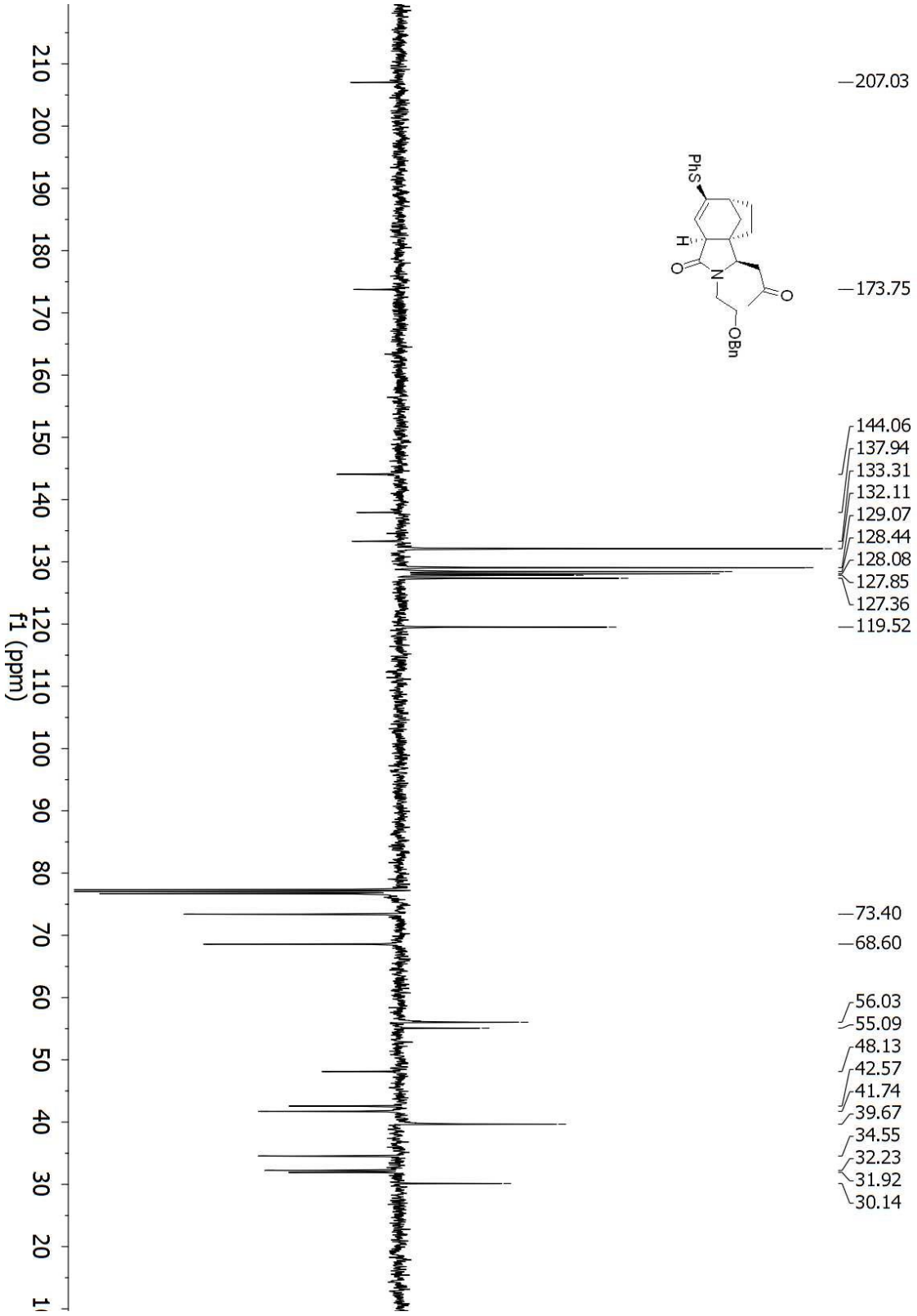
PENDANT spectrum for **223** (101 MHz, $CDCl_3$)



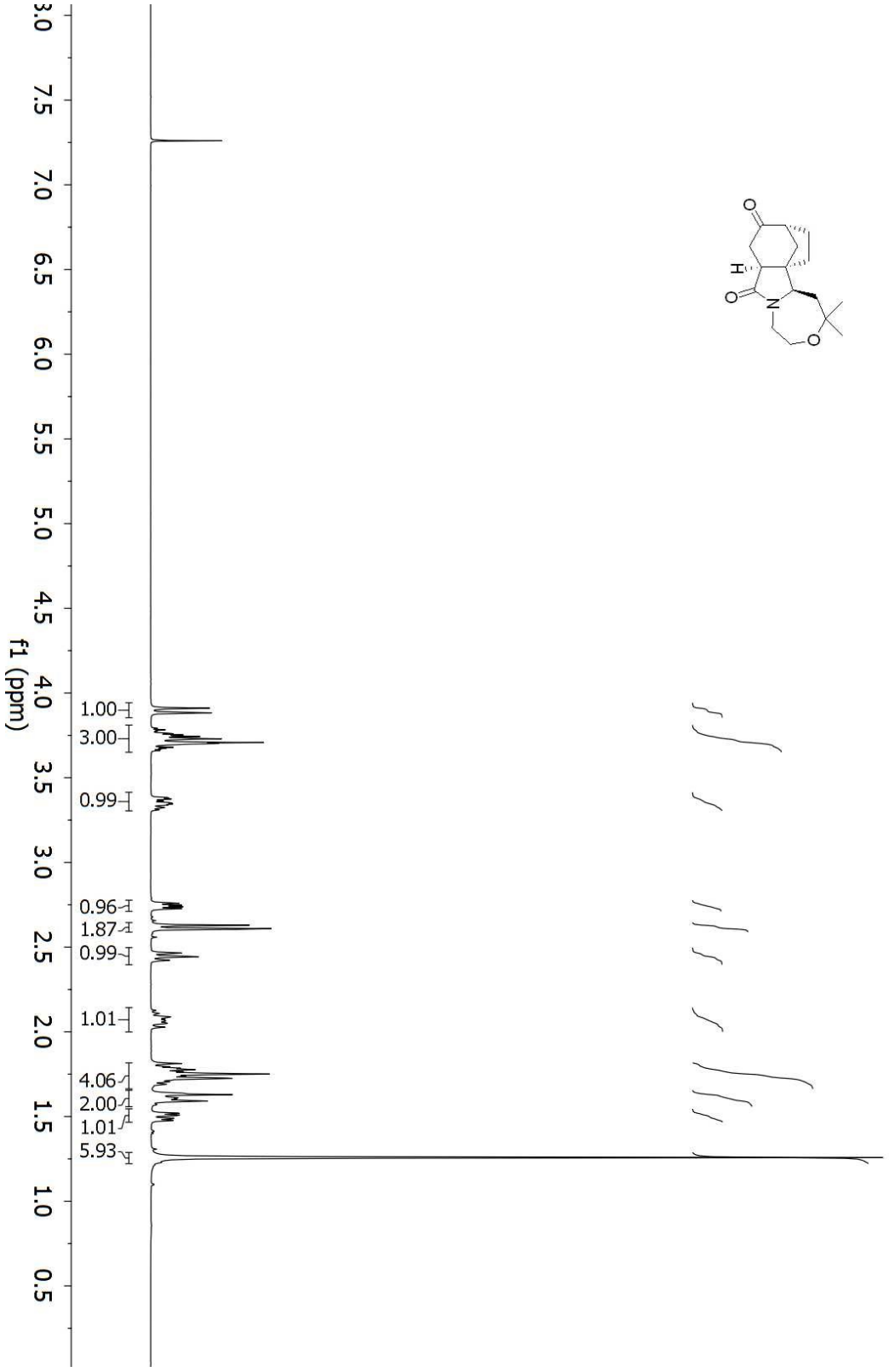
^{1}H NMR spectrum for **269** (400 MHz, $CDCl_3$)



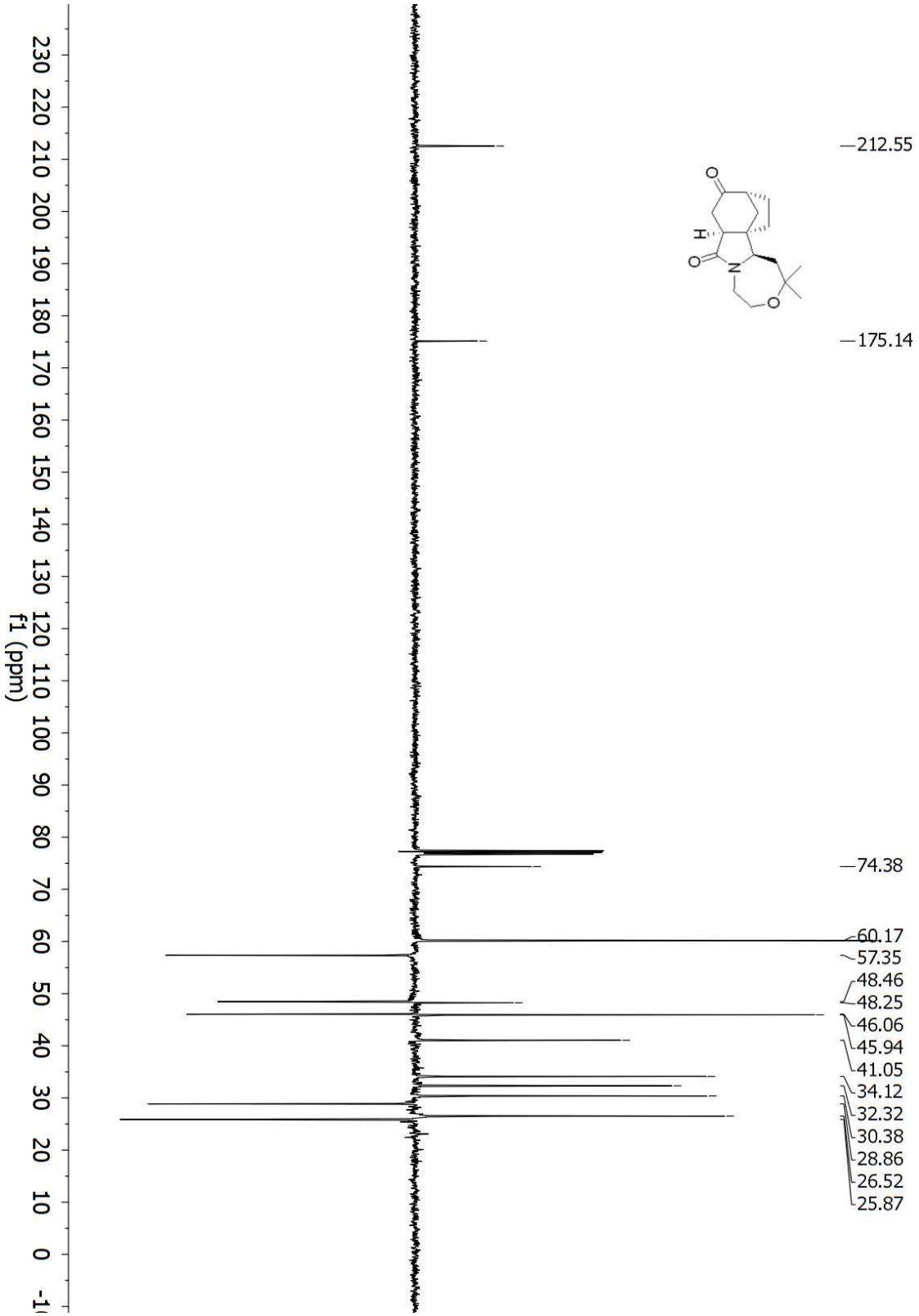
PENDANT spectrum for **269** (101 MHz, $CDCl_3$)



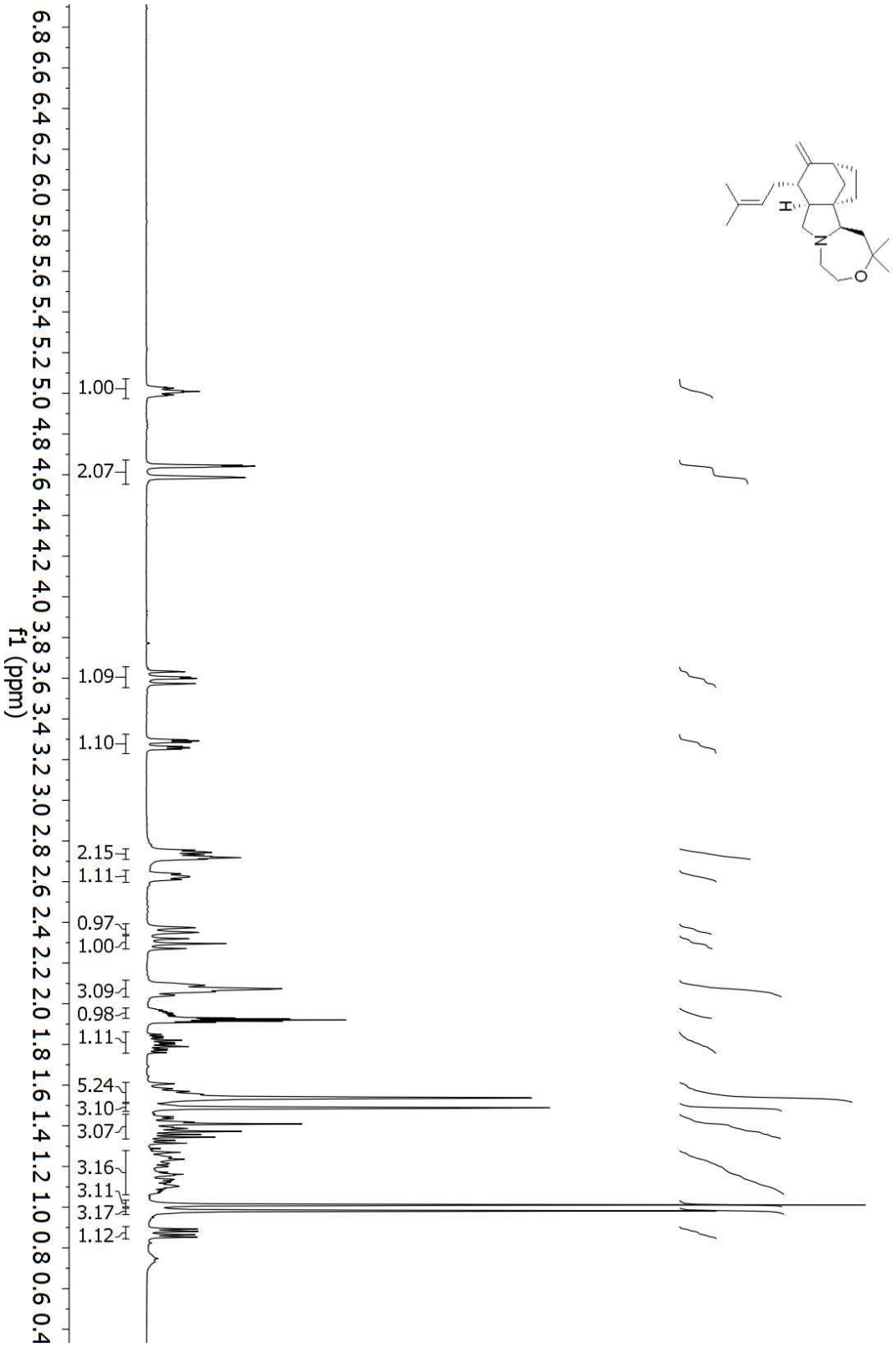
^{1}H NMR spectrum for **64** (400 MHz, $CDCl_3$)



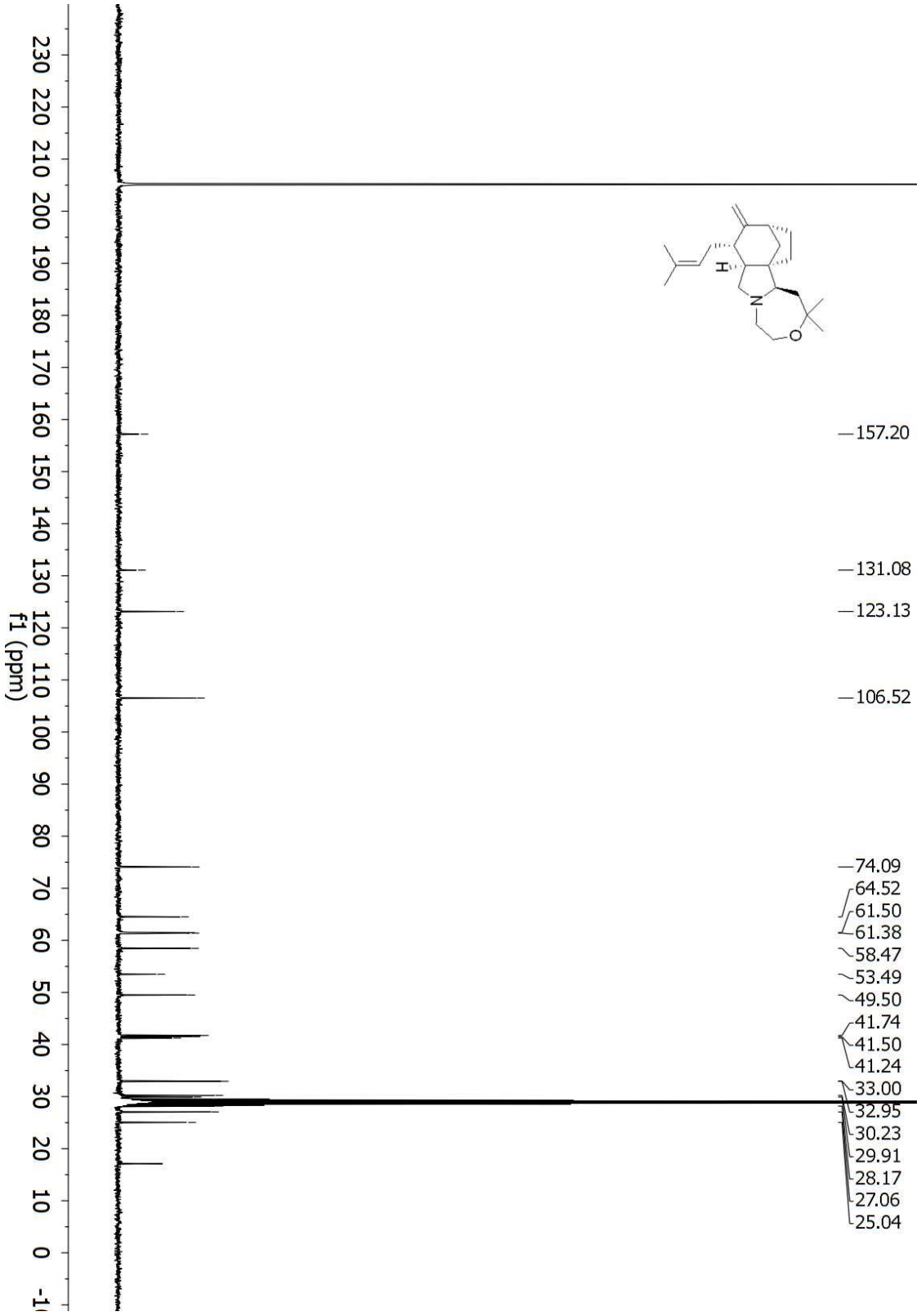
PENDANT spectrum for **64** (101 MHz, $CDCl_3$)



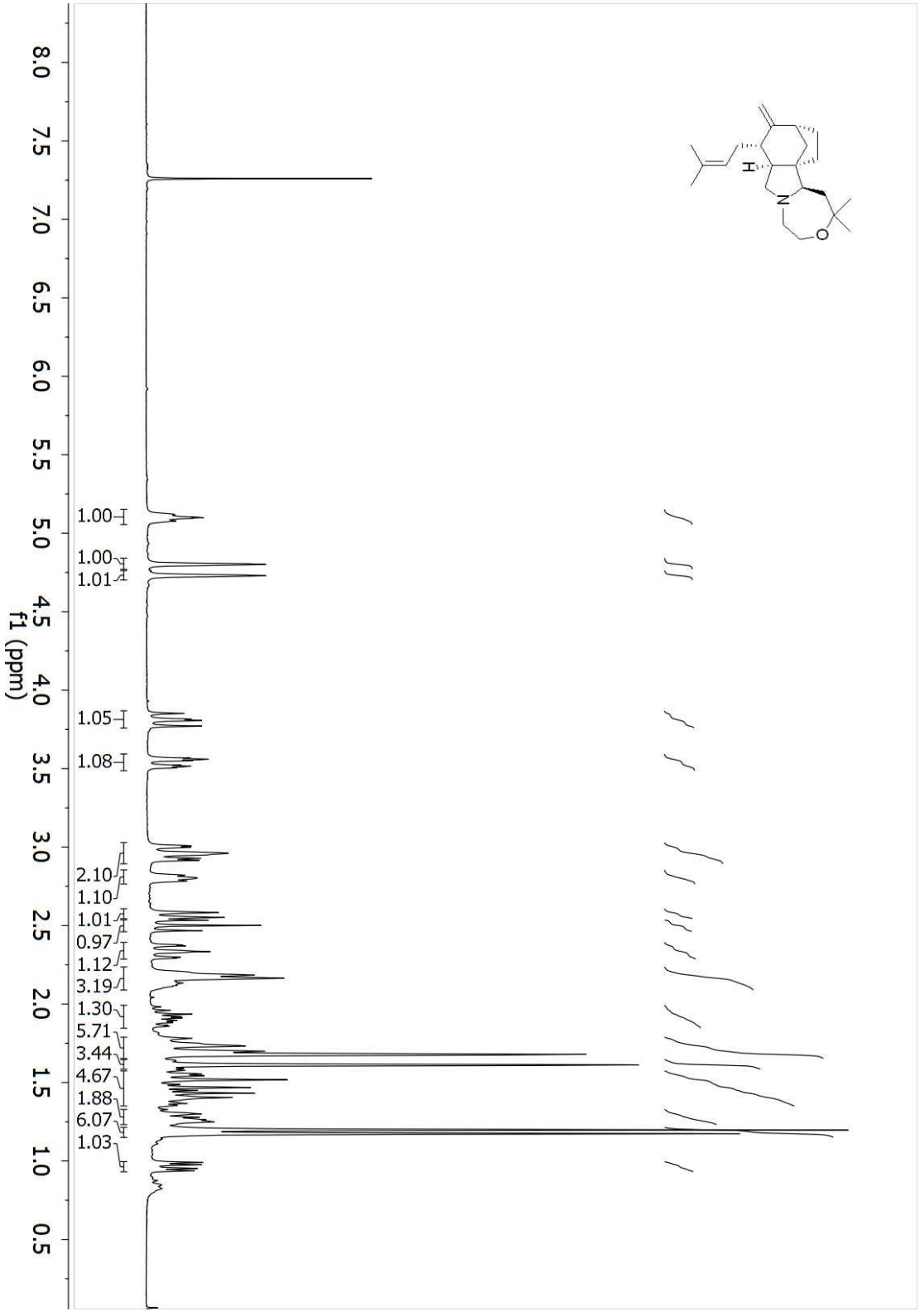
^{1}H NMR spectrum for **1** (400 MHz, acetone-d_6)



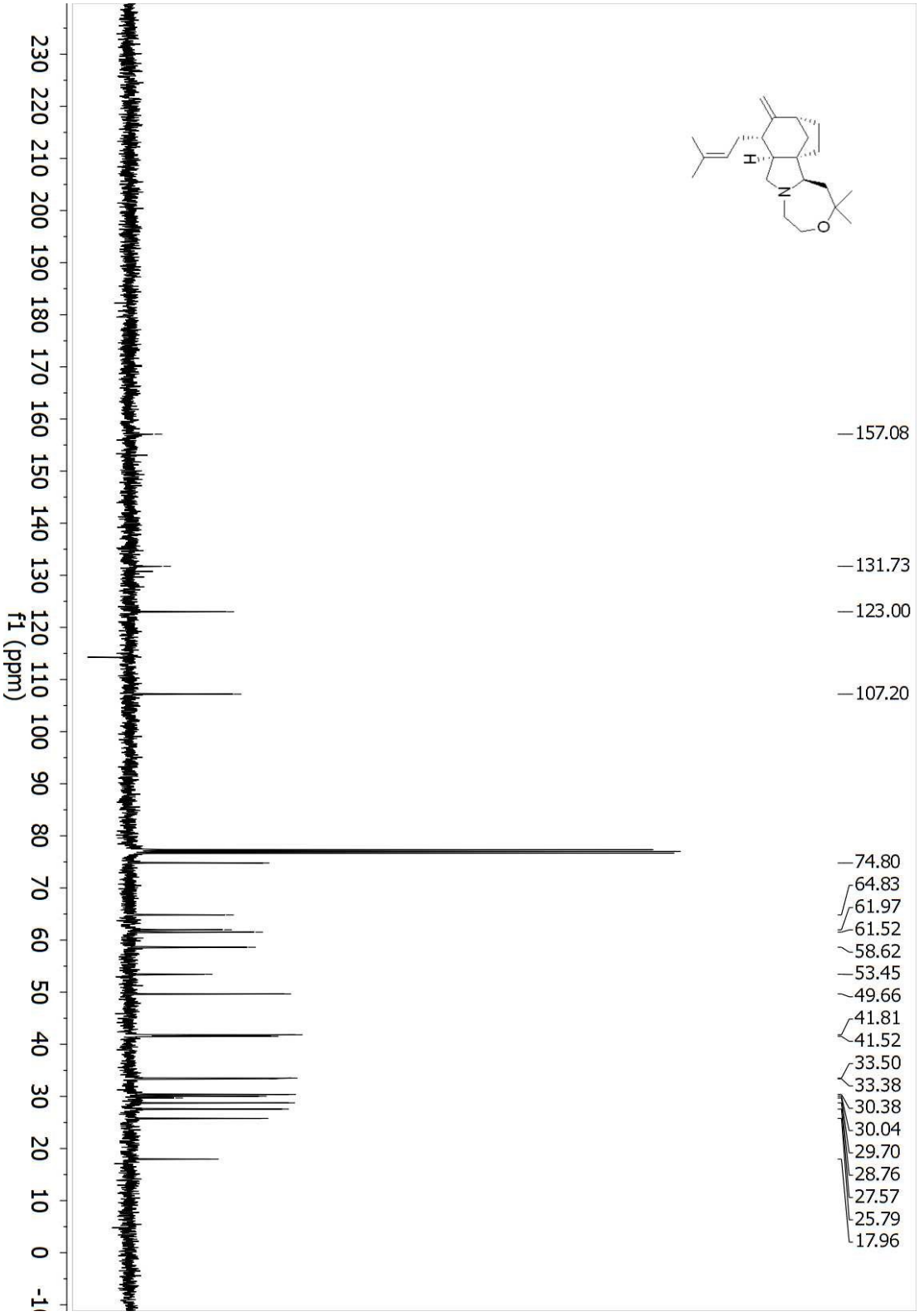
^{13}C NMR spectrum for **1** (101 MHz, acetone-d_6)



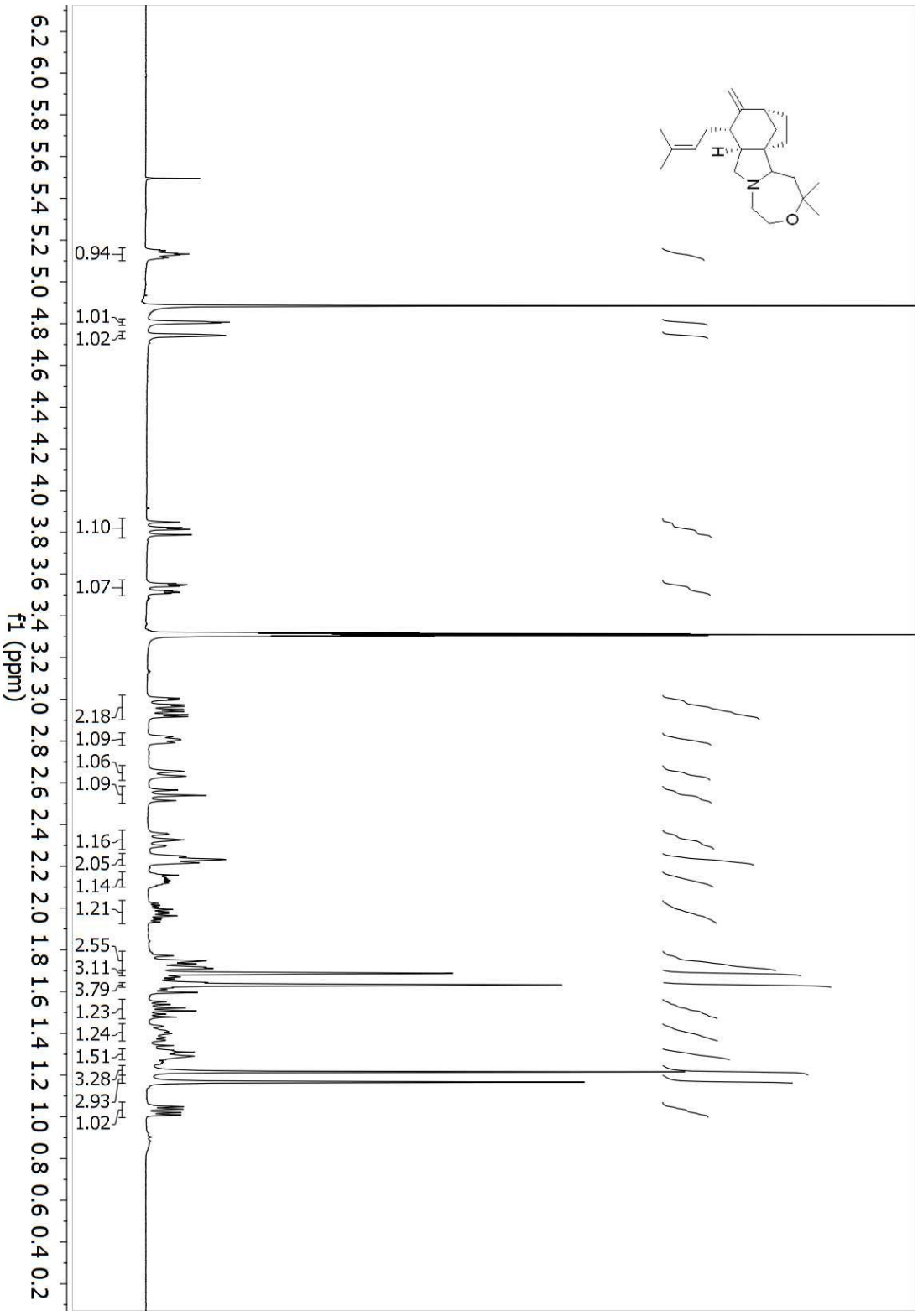
^{1}H NMR spectrum for **1** (400 MHz, $CDCl_3$)



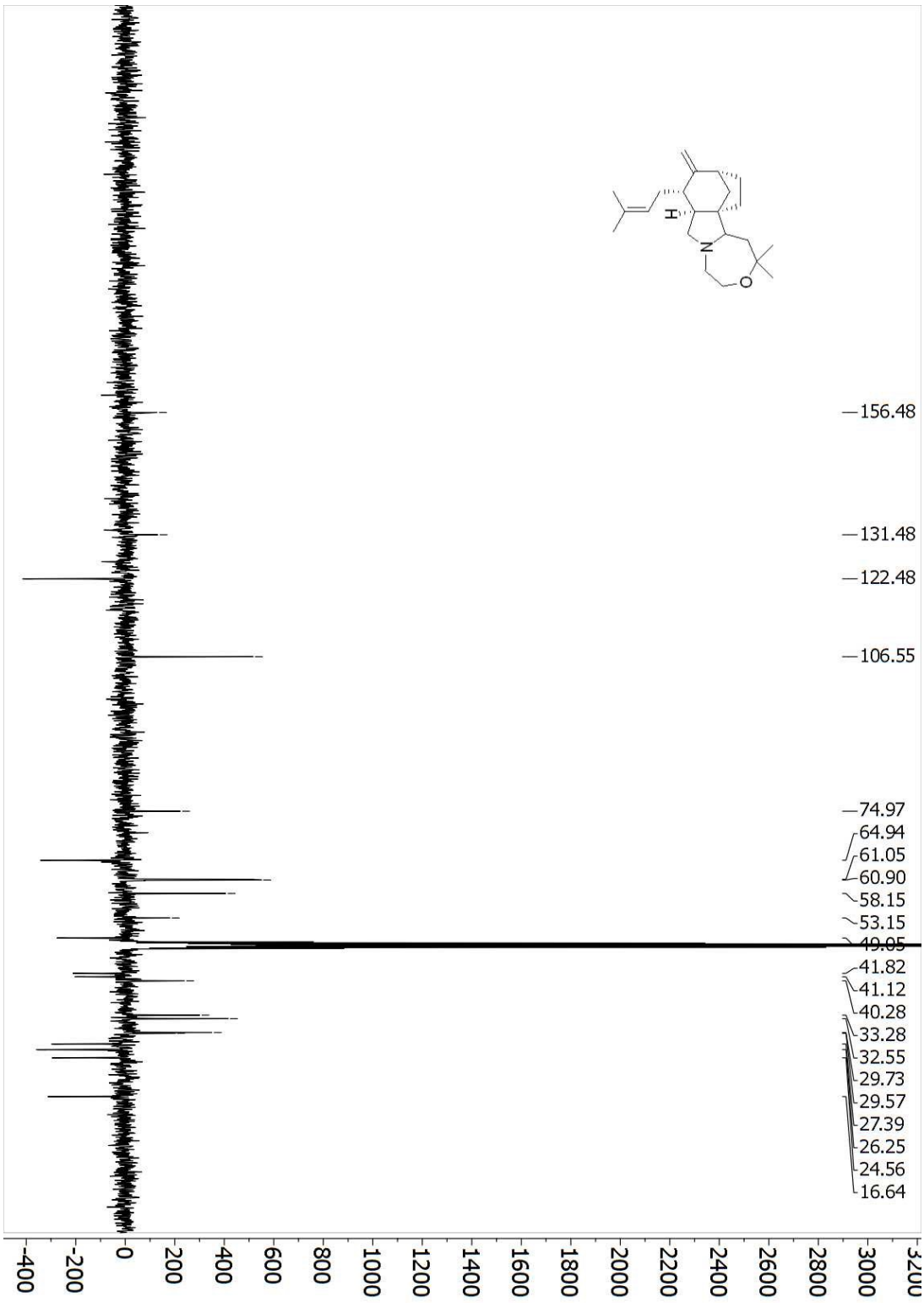
^{13}C NMR spectrum for **1** (101 MHz, $CDCl_3$)



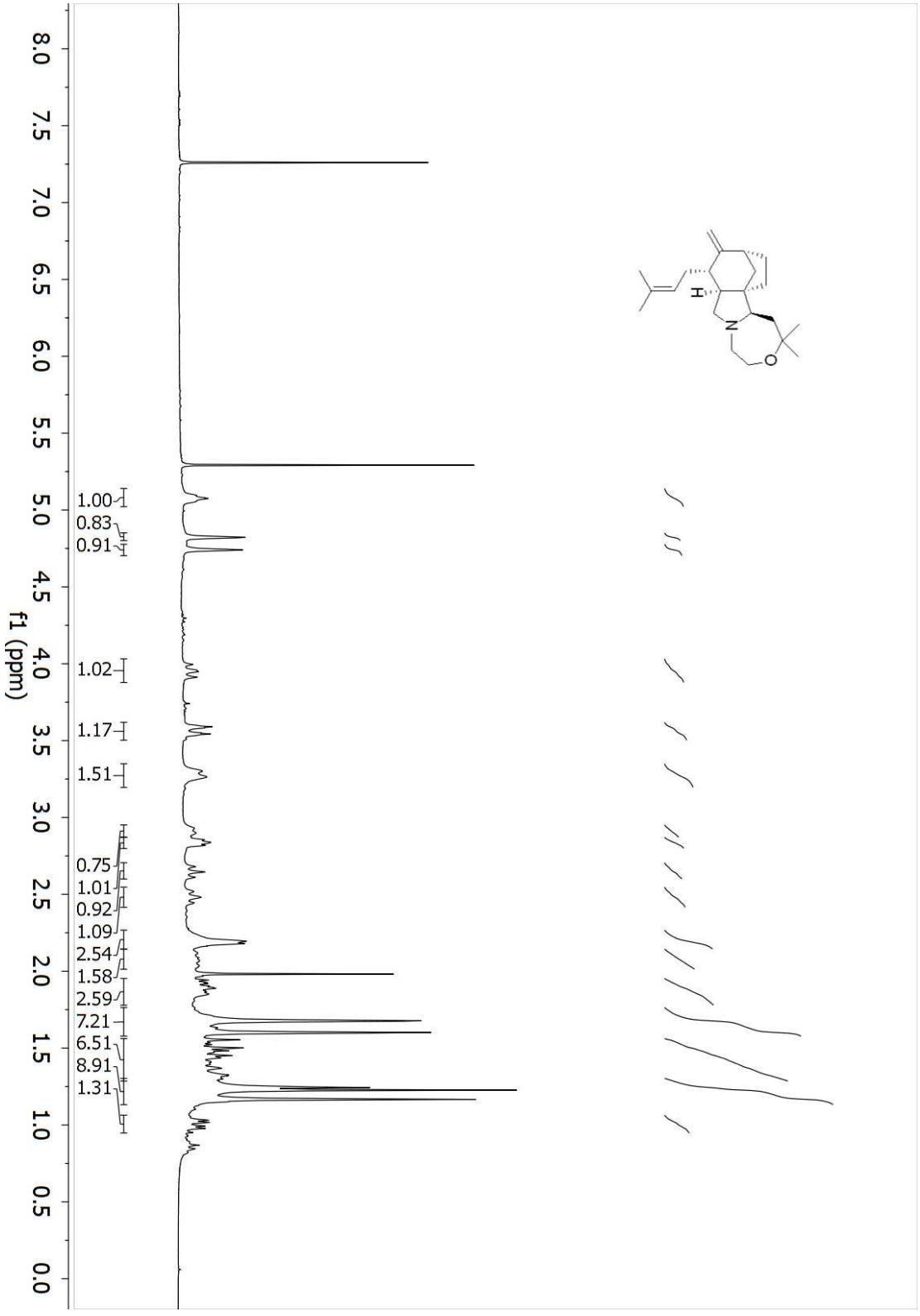
^{1}H NMR spectrum for **1** (400 MHz, MeOD)



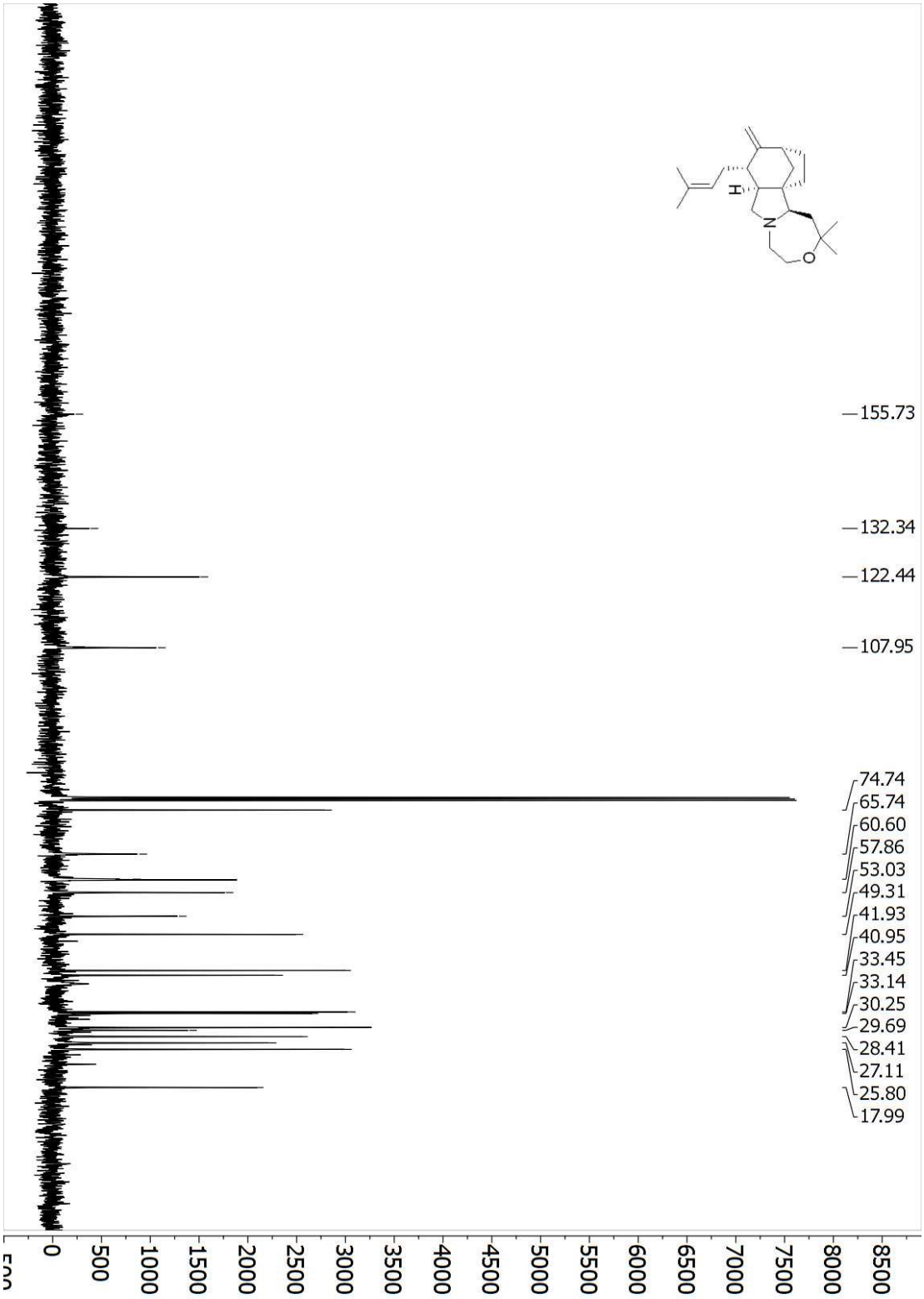
PENDANT spectrum for **1** (101 MHz, MeOD)



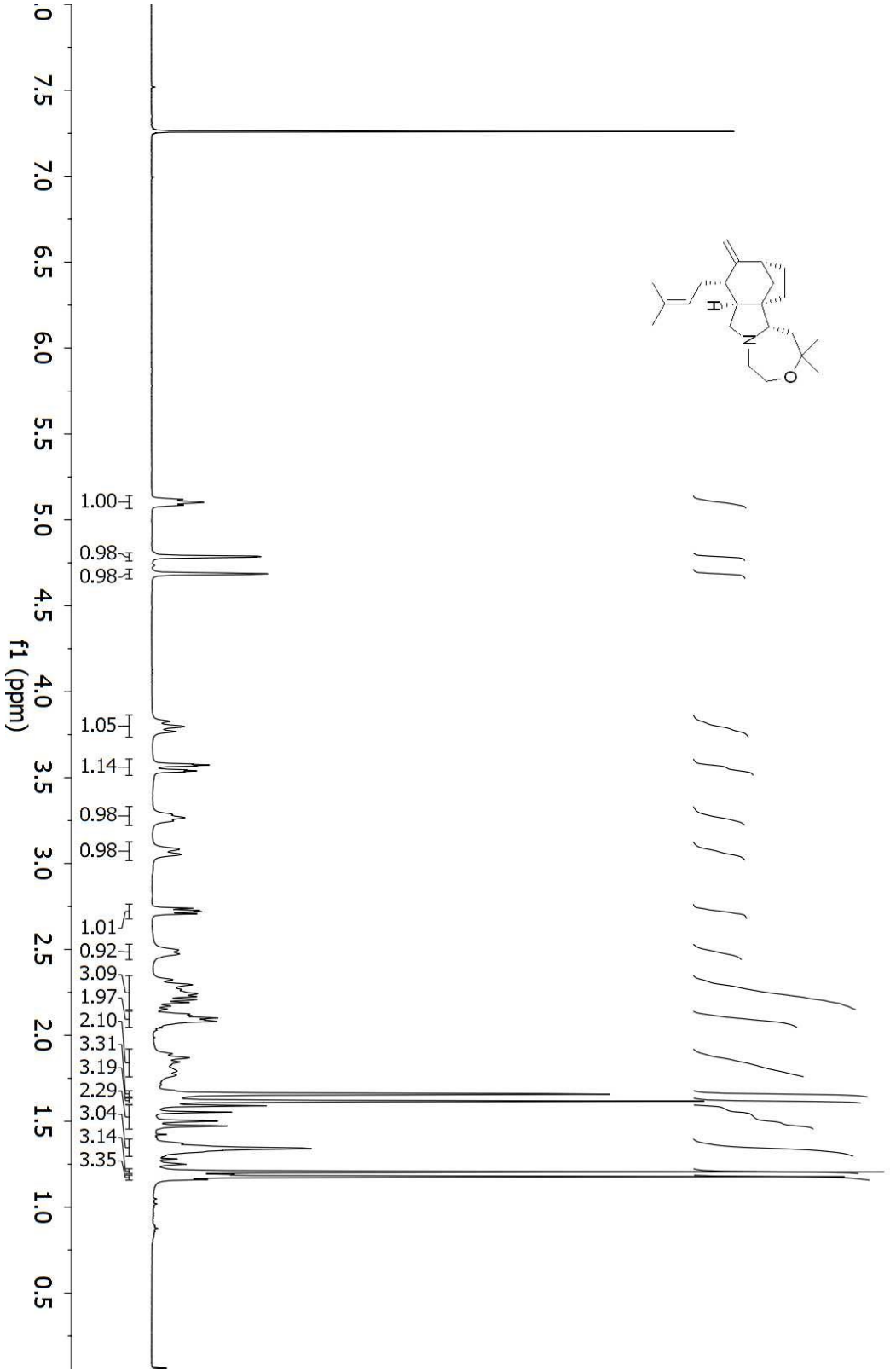
^{1}H NMR spectrum for the crude Italian sample of concavine (300 MHz, $CDCl_3$)



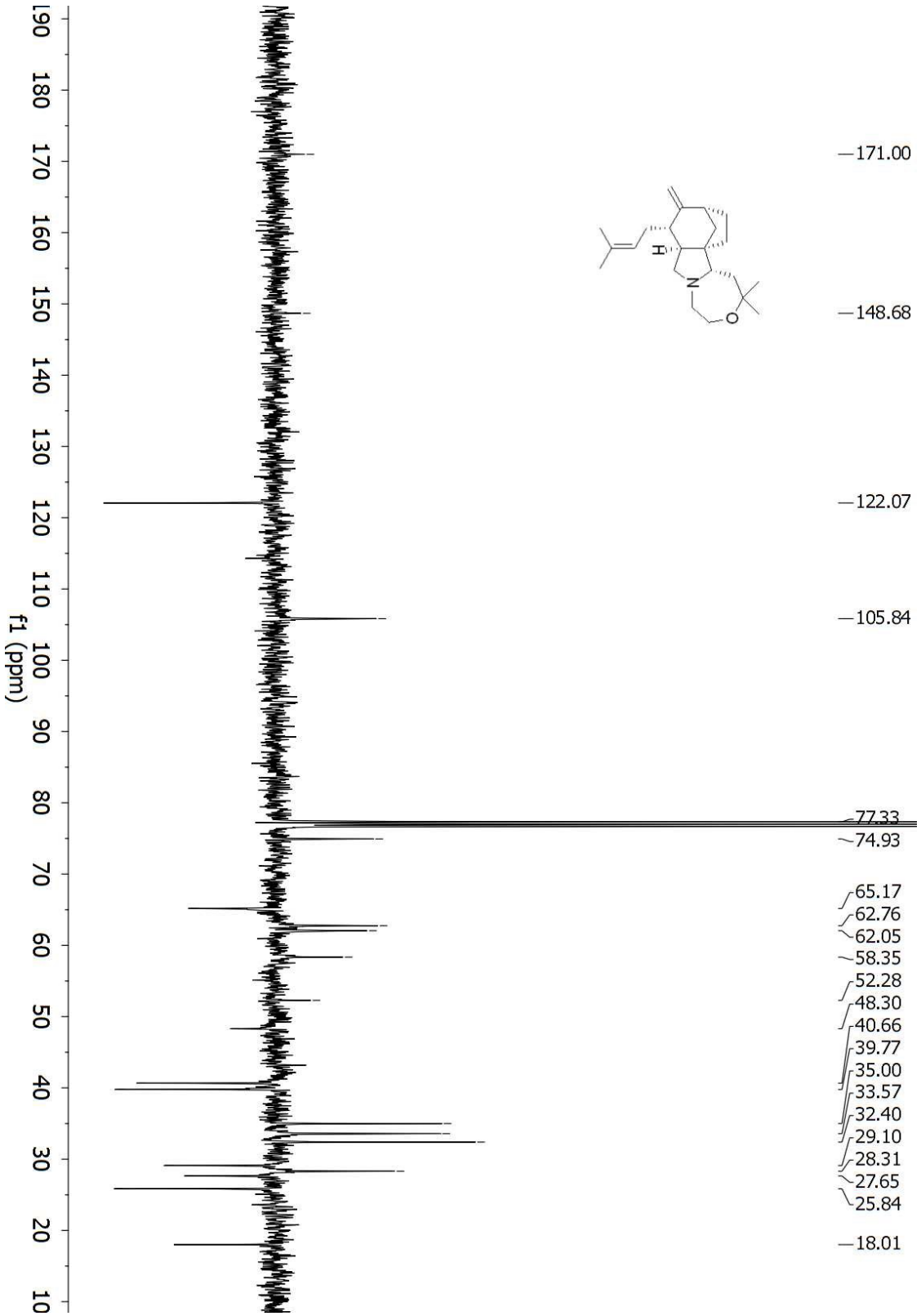
^{13}C NMR spectrum for the crude Italian sample of concavine (101 MHz, $CDCl_3$)



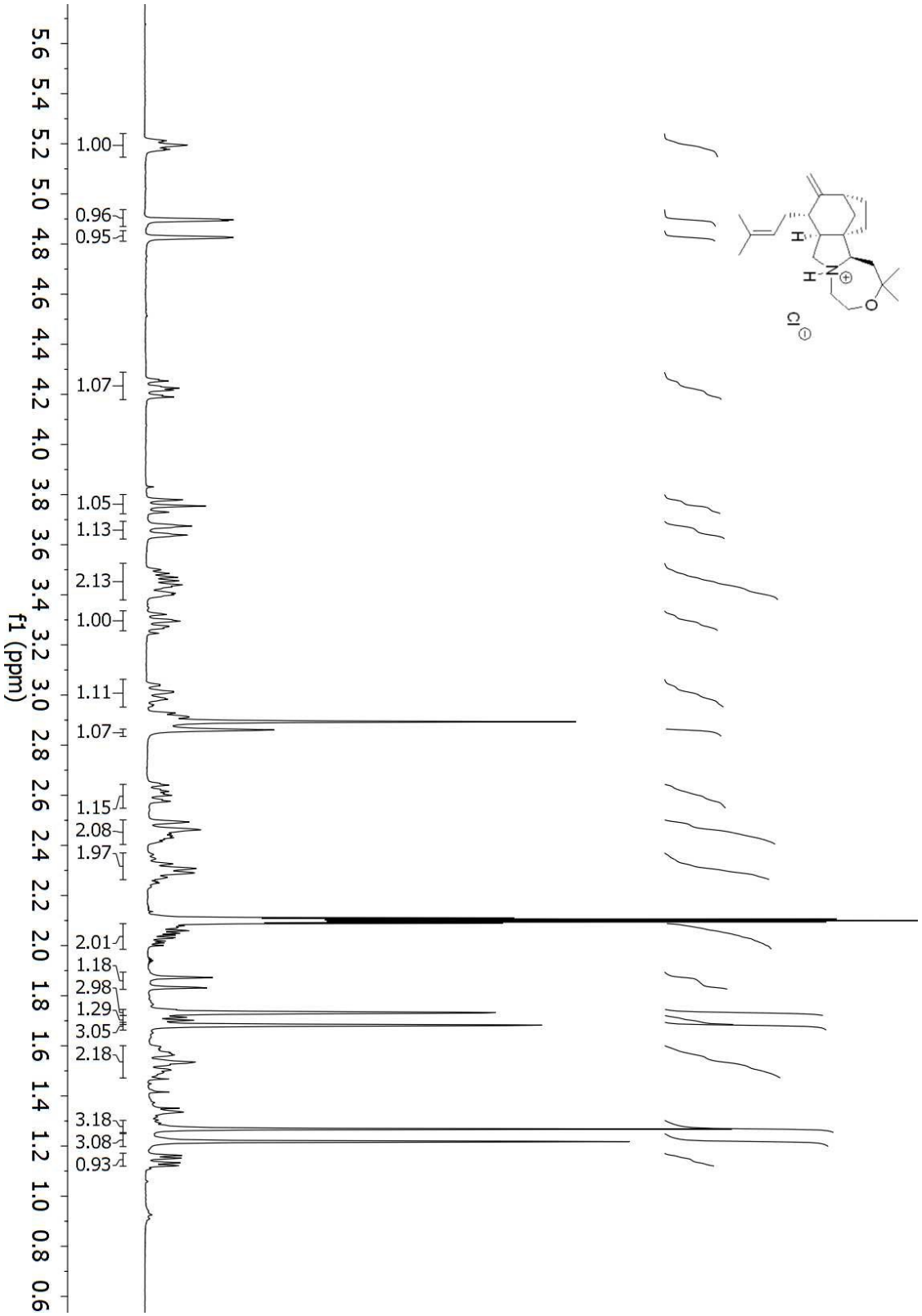
^{1}H NMR spectrum for 8-epi-concavine **298** (400 MHz, $CDCl_3$)



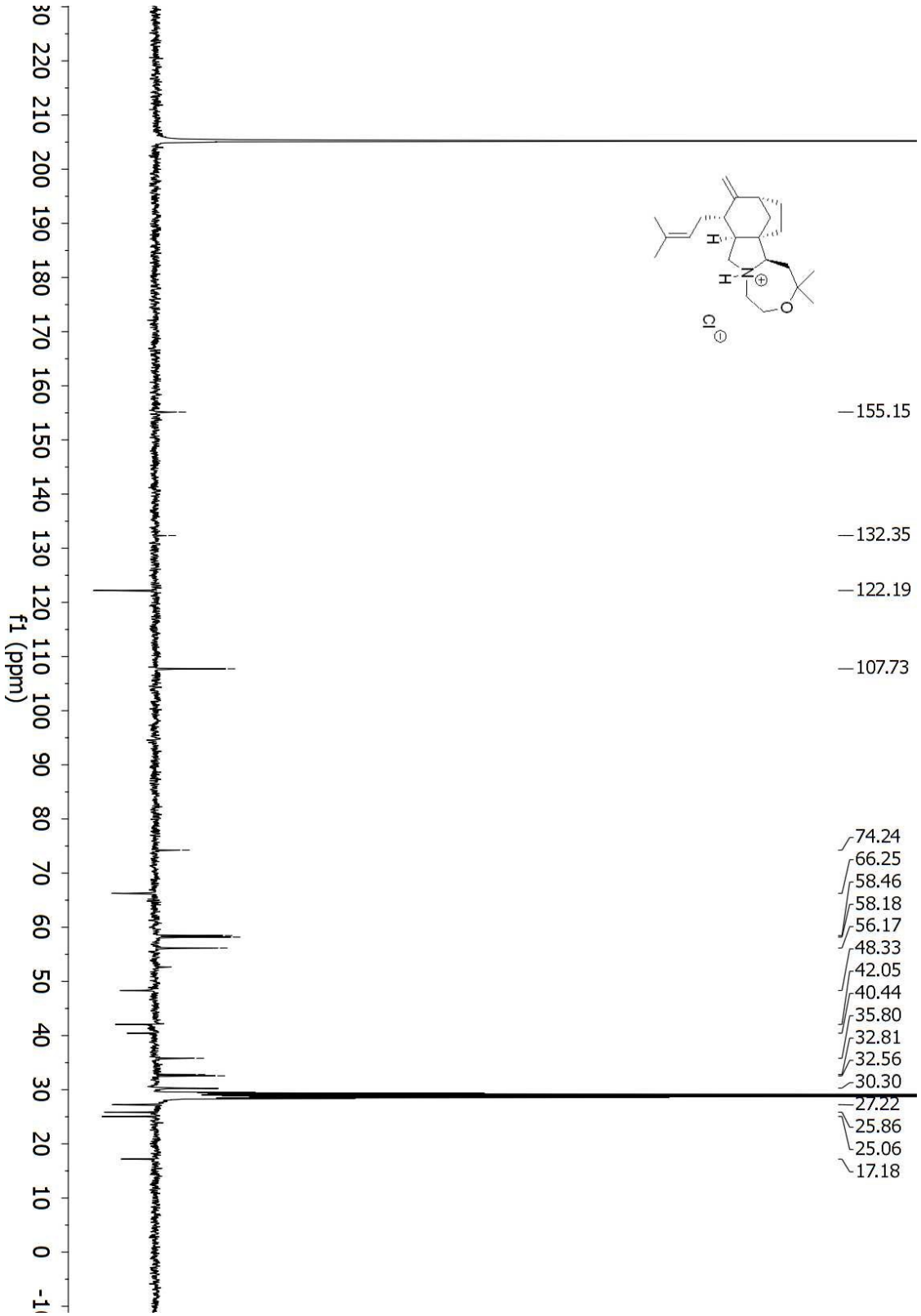
PENDANT spectrum for 8-epi-concavine **298** (101 MHz, $CDCl_3$)



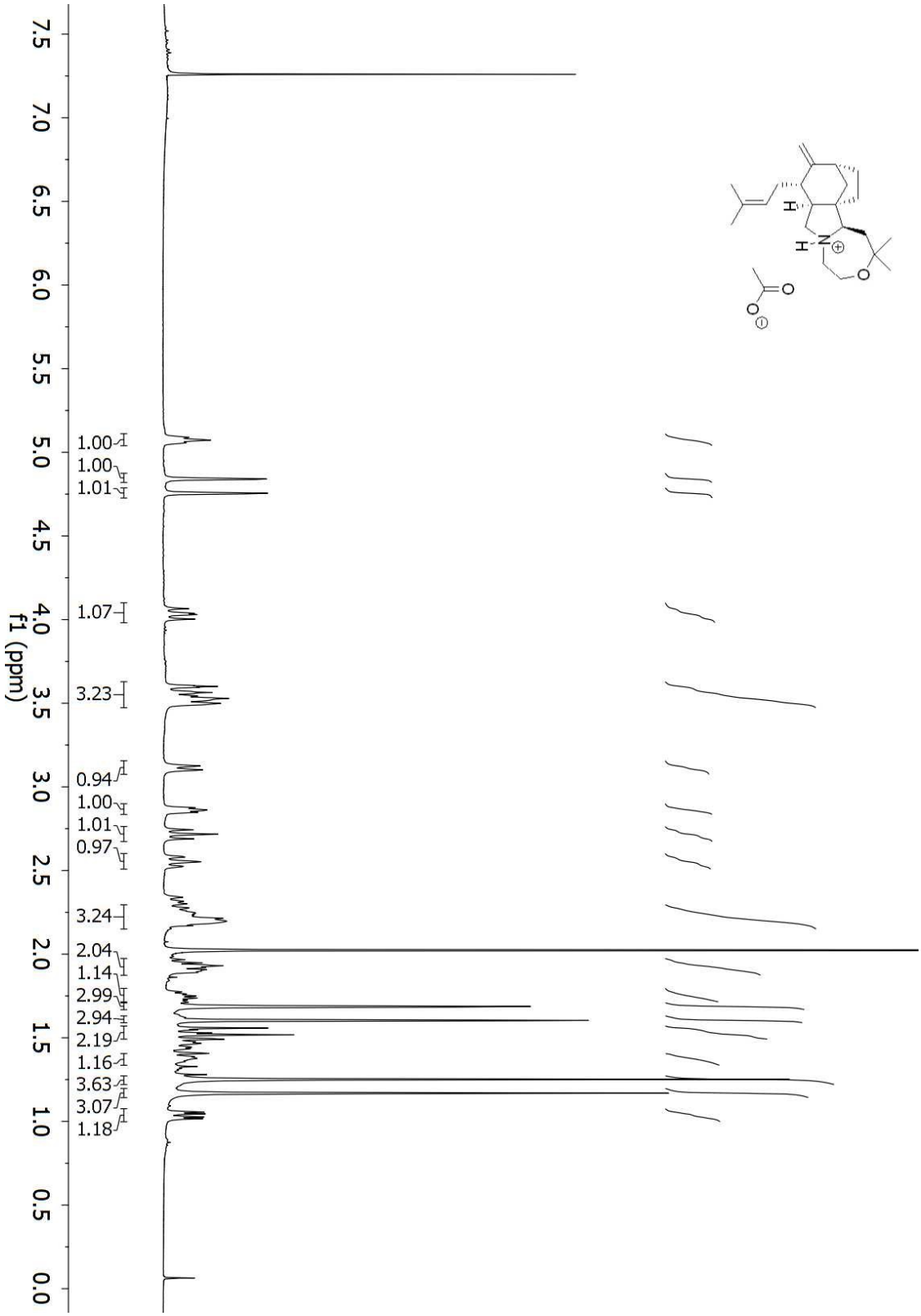
^{1}H NMR spectrum for **1-HCl** (400 MHz, acetone-d_6)



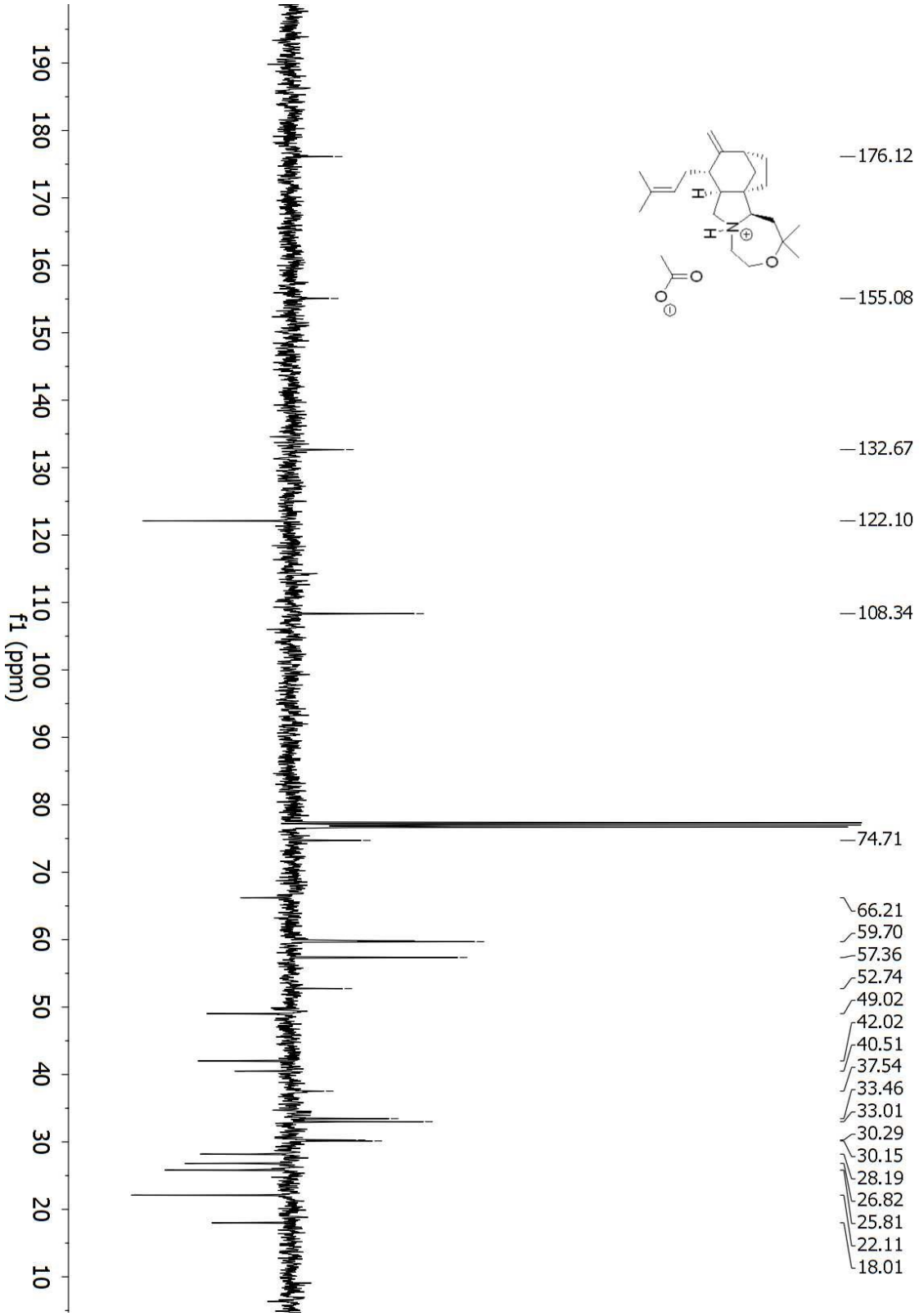
PENDANT spectrum for **1-HCl** (101 MHz, acetone-d_6)



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



PENDANT spectrum for **1-AcOH** (400 MHz, $CDCl_3$)



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