UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

School of Chemistry

The Application of Iminium Ions to the Synthesis of Biologically Active Molecules

By

Niall J. Dickinson

Supervisor: Professor Ganesan, University of East Anglia

Thesis for the degree of Doctor of Philosophy

Submitted April 2013

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Doctor of Philosophy

The Application of Iminium Ions to the Synthesis of Bioactive Molecules

Niall J. Dickinson

In the search for new treatments for today's ailments, natural products are a commonly used starting template. While these molecules often show highly specialized activities, they are not necessarily good drugs. Medicinal chemists aim to retain and improve upon their therapeutic activities, while maximising their pharmacokinetic properties in an attempt to deliver effective bioactive molecules *in vivo*. Our research has focused largely on the synthesis of natural products or natural product like molecules in the areas of synthetic methodology, total synthesis and medicinal chemistry.

Herein is reported the use of iminium ions to the synthesis of structurally complex, biologically active molecules. Firstly, we report the use of a "reagent-free" approach for the generation of *N*-acyliminium ions *in situ*, that has been applied to α-amidoalkylation reactions; matching and improving upon established literature precedent for these reactions in both reaction yield and time when used in conjunction with μW irradiation. Secondly, we report the application of a Movassaghi-Pictet-Hubert approach to the synthesis of five naturally occurring 3*H*-pyrrolo[2,3-*c*]quinolines: marinoquinolines A, B, C, E and aplidiopsamine A. We believe our synthetic approach to be the most robust towards these compounds reported to date, since the best compromise between application scope, number of steps and overall yield is afforded. In addition, we have prepared a small library of synthetic pyrroloquinoline analogues, which have been

subjected to cell-based assays for their cytotoxicity, and evaluation against a selection of microbial pathogens. The results of these assays have revealed the interesting activity of a thieno[2,3-*c*]quinoline, which may warrant further investigation. Lastly, we have investigated the potential for a Pd(0) mediated allylative alkylation/iminium ion cyclization cascade reported by Tamaru *et al.* for the synthesis of pyrrolo[2,3-*b*]indole natural products. As a result of these investigations, we have learned both steric and electronic factors are important in the progress of this reaction, which may limit the application of this approach toward natural products in this class, despite the excellent inherent stereocontrol afforded. Despite this, these natural products remain an attractive target to synthetic chemists, and we propose alternative approaches to these molecules.

Contents

Chapter 2: Synthesis of 3*H*-pyrrolo[2,3-*c*]quinolines: *The Total Synthesis of Aplidiopsamine A, Marinoquinolines A, B, C and E and Analogues*

Chapter 3: Palladium Catalyzed Allylative Cyclizations: *Investigations Towards the Synthesis of Tryptophan Derived Natural Products*

Chapter 4: Experimental Procedures

List of Figures

Chapter 1: Reagent-Free *N*-Acyliminium Ion Chemistry: *Application to Intramolecular and Intermolecular α-Amidoalkylations*

Chapter 2: Synthesis of 3*H*-pyrrolo[2,3-*c*]quinolones: *The Total Synthesis of Aplidiopsamine A, Marinoquinolines A, B, C and E and Analogues*

Chapter 3: Palladium Catalyzed Allylative Cyclizations: *Investigations Towards the Synthesis Of Tryptophan Derived Natural Products*

List of Schemes

Chapter 1: Reagent-Free *N*-Acyliminium Ion Chemistry: *Application to Intramolecular and Intermolecular α-Amidoalkylations*

Chapter 2: Synthesis of 3*H*-pyrrolo[2,3-*c*]quinolones: *The Total Synthesis of Aplidiopsamine A, Marinoquinolines A, B, C and E and Analogues*

Chapter 3: Palladium Catalyzed Allylative Cyclizations: *Investigations Towards the Synthesis Of Tryptophan Derived Natural Products*

.

List of Tables

Chapter 1: Reagent-Free *N*-Acyliminium Ion Chemistry: *Application to Intramolecular and Intermolecular α-Amidoalkylations*

Chapter 2: Synthesis of 3*H*-pyrrolo[2,3-*c*]quinolones: *The Total Synthesis of Aplidiopsamine A, Marinoquinolines A, B, C and E and Analogues*

Chapter 3: Palladium Catalyzed Allylative Cyclizations: *Investigations Towards the Synthesis Of Tryptophan Derived Natural Products*

Declaration of Authorship

I, Niall John Dickinson declare that the thesis entitled “Application of Iminium Ions to the Synthesis of Biologically Active Molecules” and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

Signed:..... Date:.....

Acknowledgements

I would like to thank Ganesan for providing me the opportunity to work in his research group for three years, and for the supervision, guidance and advise he has provided me during this time. I appreciate the time he took to listen to my many synthetic problems and for his enthusiasm in suggesting alternative routes. I would also like to thank Vincent Dalla for his co-supervision on the *N*-acyliminium ion chemistry conducted both in Southampton and Le Havre. I spent an enjoyable three months working in his research group and thank him for his work in making my transition into life in France so successful (despite my failings with the language), and his insight into good French food and wine. I am yet to find mussels to match those of Le Havre!

To my Mum and Dad, whose love and support during my upbringing and beyond made this work, and much more, possible.

To the rest of my family, I thank you for all you have done for me. I hope I have contributed as much to you, as you have to me.

Thanks go to my former PhD colleagues at Southampton, Le Havre and Norwich, who all made life inside and outside the lab very entertaining.

Thanks to Dr's Neil Wells and Colin McDonald for running the NMR facilities at the Universities of Southampton and East Anglia respectively.

Thanks to Dr's Jenni Herrmann and Rolf Muller for their work with the biological testing of the pyrroloquinoline analogues.

Thanks to Ke Liu, who as the MS super user, ran all my MS analysis while at UEA. Thanks to Dr John Langley and Ms Julie Herniman for running the MS facilities at Southampton.

Finally, thanks again to Ganesan for his proofreading of this thesis, and to Dr Kate Bowman, Dr Michael Barwood and Dr Samuel Golten for proofreading parts of this thesis.

°	degree(s)
[α]	specific rotation
Δ	reflux
$\Delta G^{\dagger}$	activation energy
µW	microwave
4A-MS	4-angstrom molecular sieves
Ac	acyl
ACh	acetylcholine
AChE	acetylcholine esterase
AChEI	acetylcholine esterase inhibitor
ACT	artemisinin combination therapy
Aq.	aqueous
Ar	aryl
atm	atmosmhere(s)
ATP	adenosine triphosphate
BINOL	1,1'-bi-2-napthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BPO	benzoyl peroxide
BSA	bis(trimethylsilyl)acetamide
Bz	benzoyl
c	concentration
ca.	approximately
calcd.	calculated
cAMP	cyclic adenosine monophosphate
CBZ	carboxybenzyl
CIPE	complex induced proximity effect
cod	1,5-cyclooctadiene
COPD	chronic obstructive pulmonary disease
Cy	cyclohexyl
d	day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCC	dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
decomp.	decomposed
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropyl carbodiimide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide

DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppf	1,1'-bis(diphenylphosphino}ferrocene
dr	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl bipyridine
ee	enantiomeric excess
ESI	electrospray ionisation
eq.	equivalents
FT-IR	Fourier transform infrared spectroscopy
H-Trp-OMe	tryptophan methyl ester
H-Val-OMe	valine methyl ester
h	hour(s)
HCA	hexachloroacetone
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HRMS	high-resolution mass spectrometry
i	*iso*
IC_{50}	half maximal inhibitory concentration
i.e.	illustrative example
IUPAC	International Union of Pure and Applied Chemistry
LogP	partition coefficient
LRMS	low-resolution mess spectrometry
Lut	lutidine
M	molar
m	meta
m/z	mass to charge ratio
MHz	megahertz
min	minute(s)
mol.	mole(s)
MP	melting point
mRNA	messenger ribonucleic acid
Ms	methanesulfonyl
NAG	*N*-acetylglucosamine
NAM	*N*-acetylmuramic acid
NBS	*N*-bromosuccinimide
n.d.	not determined
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
n.r.	not recovered
Ns	4-nitrobenzenesulfonyl
Nu	nucleophile
p	para
p.a.	per annum
Pd/C	palladium on activated carbon
PDE	phosphodiesterase

PG	protecting group
Ph	phenyl
Pin	pinacol
Piv	pivaloyl
PMB	4-methoxybenzene
Ppm	parts per million
PyBOP	benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate
Pyr	pyridine
RCM	ring-closing metathesis
RNA	ribonucleic acid
rt	room temperature
SAR	structure-activity relationships
sat.	saturated
SER	single electron reduction
soln.	solution
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	tertiary
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilane
TLC	thin-layer chromatography
TMS	trimethylsilyl
TosMIC	toluenesulfonylmethyl isocyanide
Trp	tryptophan
Ts	tosyl
v	wavenumbers
vol.	volume
vs.	*versus*
W	watts
WHO	World Health Organization
XPhos	2-dicyclohexylphosphino-2',4',6'-tritriisopropylbiphenyl

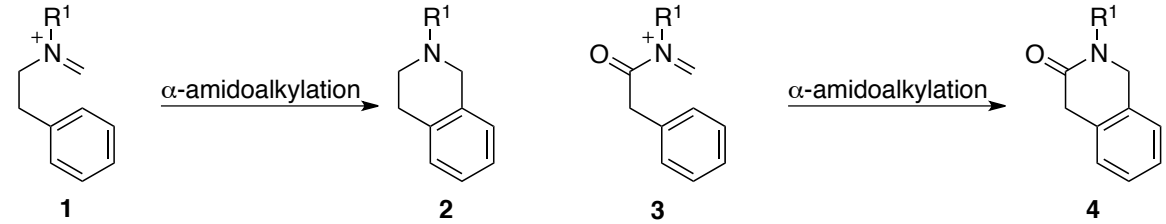
Chapter 1

REAGENT-FREE *N*-ACYLIMINIUM ION CHEMISTRY

Application to Intramolecular and Intermolecular α-Amidoalkylations

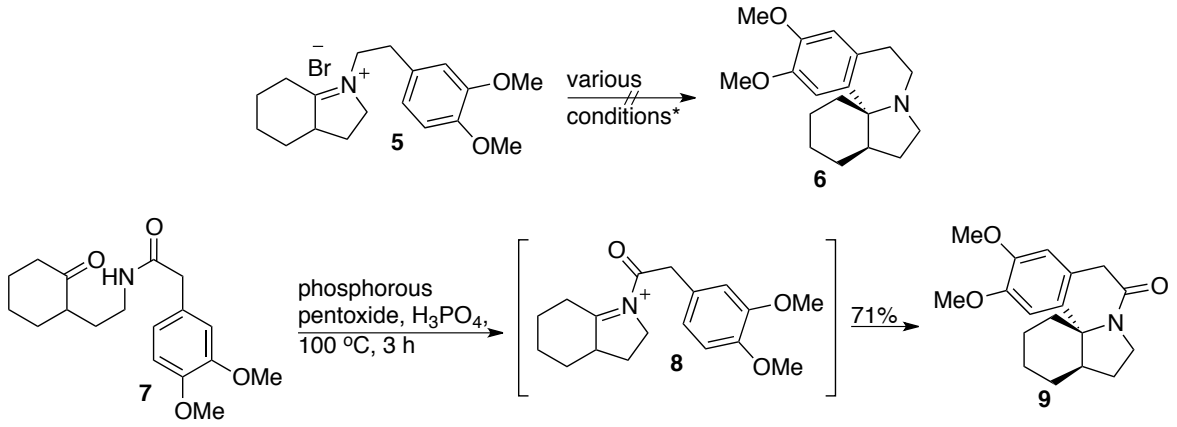
1. Introduction

N-Alkyliminium (iminium) ion chemistry has, for over 100 years, been used very successfully in carbon-carbon bond forming reactions and remains important in organic chemistry. Of course, reactions involving iminium ions have undergone significant developments since Pictet, Spengler and Mannich first described their respective reactions.[1,2] One such development was first noted in the 1950's.[3] It was found that an *N*-acylated iminium ion – the so-called *N*-acyliminium ion – in which the acyl group withdraws electron density from the iminium bond and renders the carbon centre even more electrophilic and consequently, more reactive than the equivalent iminium ion.[4] As a consequence of this increased electrophilicity, it has been shown that nucleophiles failing to trap an iminium ion can successfully react with an *N*-acyliminium ion[5] in so called α-amidoalkylation reactions.



Scheme 1. Comparison of α-amidoalkylation cyclizations from iminium and *N*-acyliminium ions.

A key example of the enhanced reactivity of the *N*-acyliminium ion against the iminium ion can be seen in Belleau's hexahydroapoerysotrine synthesis, where an α-amidoalkylation approach involving an *N*-acyliminium ion intermediate succeeded where an iminium Pictet-Spengler approach failed (Scheme 2).[4] Belleau reasoned the failure of the Pictet-Spengler approach was due to the sensitivity of this reaction to steric crowding at the carbocationic centre. Perhaps this is due to the relative electronic stability of 3° cations compared with 1° and 2° ones. Conversely, the carbocationic resonance structure of **8** is even less stable given the presence of the carbonyl, which explains the increased reactivity.[4] Nevertheless, we cannot rule out the conformational effects, which may contribute to the success in cyclization of **7** to **9**.



Scheme 2. The fate of intramolecular α-amidoalkylation of iminium **6** and *N*-acyliminium **8**. *Although the author claims "various conditions" were performed, no such conditions are reported in the paper.

There have been many excellent reviews of *N*-acyliminium ion chemistry reported in the literature.[5–12] We are interested generally in the application of *N*-acyliminium ions in organic synthesis. One of the key areas of their application is in the synthesis of alkaloids such as tetrahydroisoquinoline derivatives. Here, we will introduce this family of alkaloids, offer a broad coverage of both the methods of forming *N*-acyliminium ion precursors and their subsequent application to α-amidoalkylations and describe alternative approaches to these alkaloids. Additionally, we will touch upon the exciting new area of "reagent-free" chemistry and the possible application of this concept to α-amidoalkylations via *N*-acyliminium ion intermediates for the first time.

1.1. Tetrahydroisoquinoline and β-Carboline Alkaloids

Many alkaloids belonging to this subset of isoquinoline alkaloids have been isolated, some examples of which are provided in figure 1. Due to the huge number of available targets and their interesting biological properties, they are a source of focus of many total synthesis and medicinal chemistry groups. To date, there are currently more than 50 isolated members of the superfamily of tetrahydroisoquinolines from natural sources,[13] many of which offer biological activity which collectively spans a broad spectrum of human ailments.

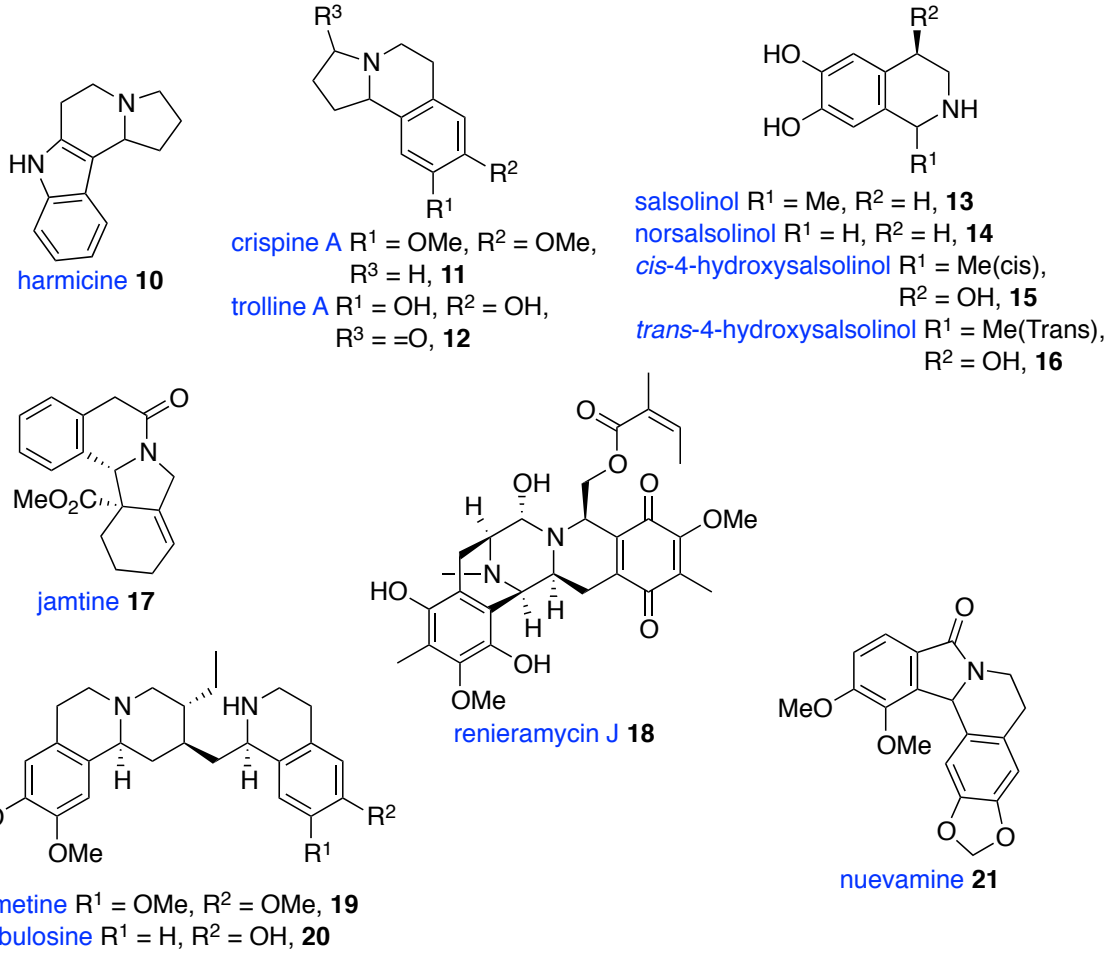
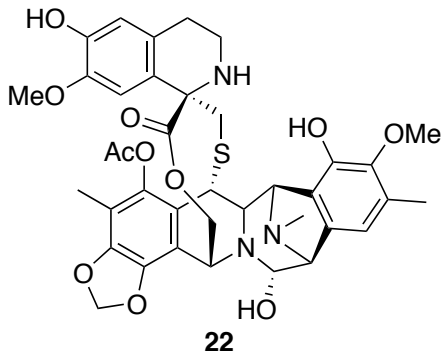


Figure 1. Some tetrahydroisoquinoline and β-carboline alkaloids.

1.1.1. Biological Importance

Currently, there is only one commercially marketed tetrahydroquinoline alkaloid – trabectedin; which is used for the treatment of soft-tissue carcinoma, having shown greater potency than taxol, and is currently in Phase II/III trials for use in other cancers (figure 2).[14]

Of the known thetrahydroisoquinolines, lemonomycin (*Streptomyces candidus*), isolated from a fermentation broth in 1964 has broad-spectrum antimicrobial activity.[15] Crispine A (*Carduus crispus*), has been reported to have cytotoxic activity, while the β-carboline harmicine (*Kophia griffithii*) has shown potent activity against leishmaniasis.[16,17] Meanwhile, jamtine has been found to exhibit notable antihyperglycaemic activity.[18]



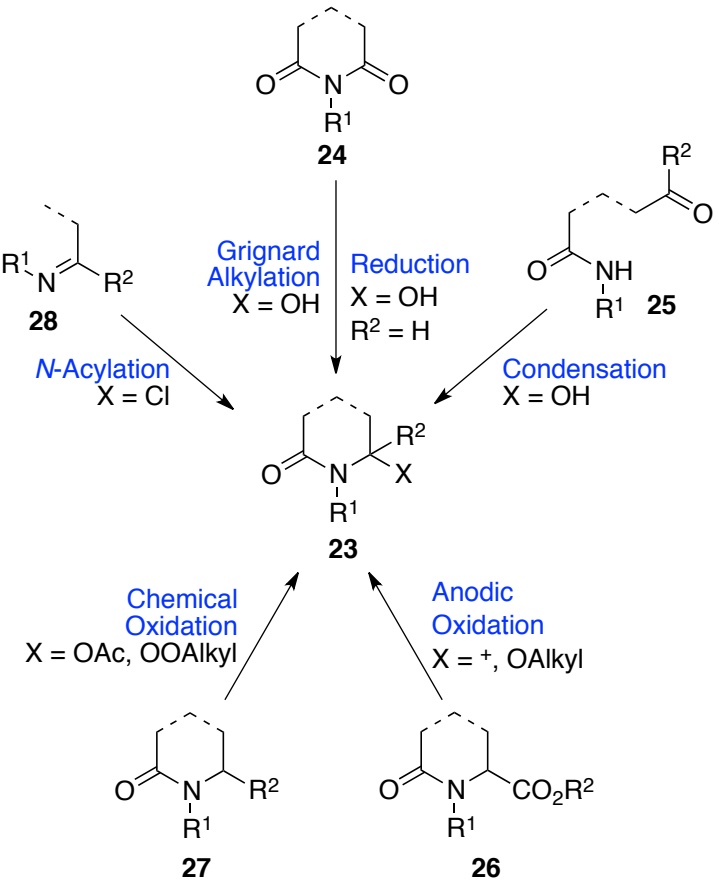
22

Figure 2. Trabectedin

1.2. *N*-Acyliminium Ion Chemistry

1.2.1. Methods of Preparation: Approaches Towards Cyclic *N*-Acyliminium Ion Precursors

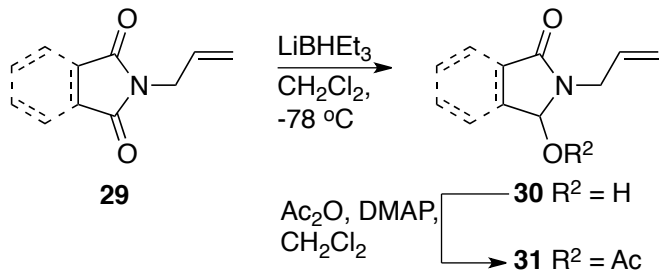
There are several approaches towards the preparation of *N*-acyliminium ions reported in the literature. A description and literature example of the most important examples are provided *vide infra*, and in scheme 3. It should be noted that all methods of *N*-acyliminium ion generation involve acidic conditions.



Scheme 3. General approaches to *N*-acyliminium ion precursors.

1.2.1.1. Reduction of Cyclic Imides

The reduction of cyclic imides is a common approach, particularly in methodology studies of *N*-acyliminium ion chemistry because of the low cost of starting materials. *N*-Alkylated phthalimide, succinimide and maleimide can be readily reduced to their corresponding hydroxy lactams, and further converted to the corresponding *N*,*O*-acetoxy lactams if desired (scheme 4).[19,20]

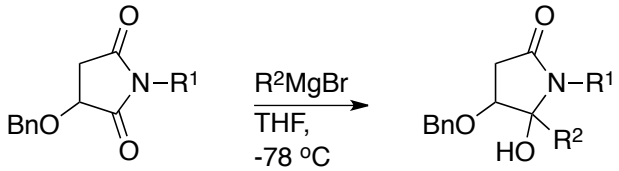


29

Scheme 4. *N*-acyliminium ion precursor from the reduction of cyclic imides.

1.2.1.2. Alkylation of Cyclic Imides

In addition to the reduction of cyclic imides, the use of Grignard reagents and organolithium salts have been used to form *N*-acyliminium ion precursors. Again, the use of phthalimide, succinimide and maleimide are a convenient source of the required imide functionality. Interestingly, the more sterically hindered carbonyl is substituted in such conditions as Huang showed (Scheme 5).[21] This is attributed by the authors to a so-called complex induced proximity effect (CIPE)[22] and Speckamp's reasoning of least-hindered approach upon observing the same phenomenon in $NaBH_4$ reduction of gem-disubstituted succinimides.[23]



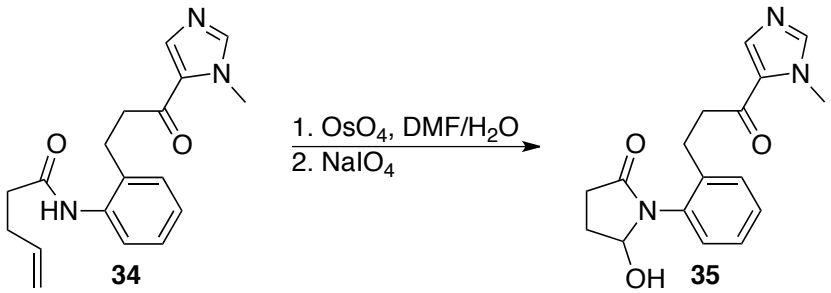
32 **33**

Scheme 5. *N*-acyliminium ion precursor from the alkylation of cyclic imides.

1.2.1.3. Condensation of Amides onto Aldehydes and Ketones

Intramolecular condensation of amides with aldehydes/ketones is an efficient approach to α-hydroxy lactams. Condensation of amides onto ketones requires acidic activation, and it is often convenient to prepare these precursors *in situ* and subsequently perform α-amidoalkylations

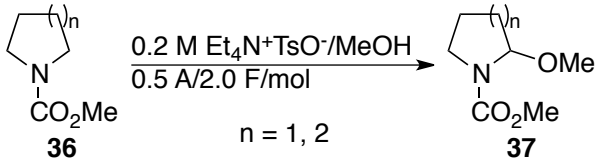
directly.[4,5,24] Condensation of amides onto aldehydes can proceed under neutral conditions, and the intermediate hydroxy lactam often can be isolated, as in Woodward's synthesis of isolongistrobine (scheme 6).[25]



Scheme 6. *N*-acyliminium ion precursor from the intramolecular condensation of amides onto aldehydes.

1.2.1.4. Anodic Oxidation of Pyrrolidine and Piperidine *N*-Carbamates

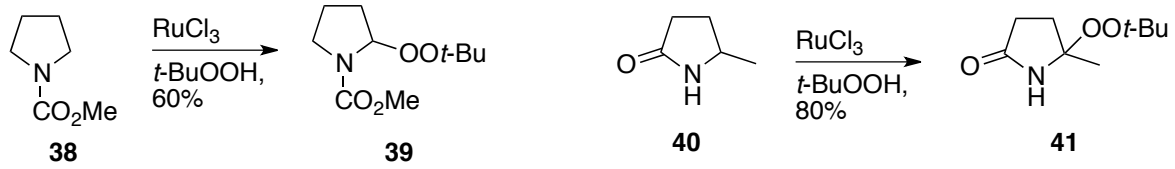
Shono reported the first electrochemical α-oxidations of pyrrolidine and piperidine *N*-carbamates.[26–28] The direct oxidation product of this approach is the corresponding *N*-acyliminium ion, which is conveniently trapped by MeOH as the solvent to afford the α-alkoxy carbamate as the *N*-acyliminium ion precursor (scheme 7). This area has recently been further explored and will be discussed in greater detail *vide infra*.



Scheme 7. *N*-acyliminium ion precursor from electrochemical oxidation of pyrrolidine and piperidine *N*-carbamates.

1.2.1.5. Chemical Oxidation of Saturated *N*-Acyl Heterocycles

Murahashi has shown ruthenium-catalyzed reaction of alkyl peroxides to efficiently oxidise carbamates of type **38** and lactams of type **40** to their corresponding α-peroxy analogues **39** and **41** respectively (scheme 8).[29]

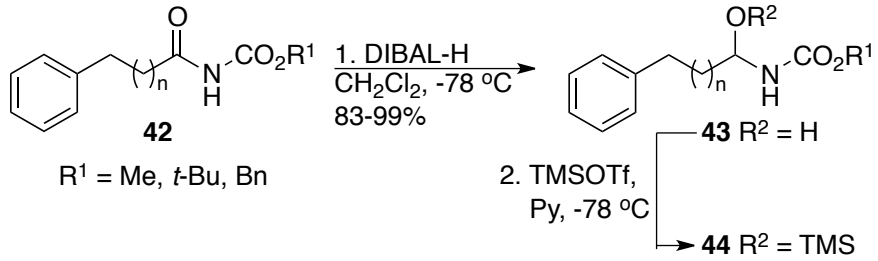


Scheme 8. *N*-acyliminium ion precursor from the ruthenium-catalysed chemical oxidation of carbamates.

1.2.2. Methods of Preparation: Approaches Towards Acyclic *N*-Acyliminium Ion Precursors

1.2.2.1. Reduction of Acyclic Imides

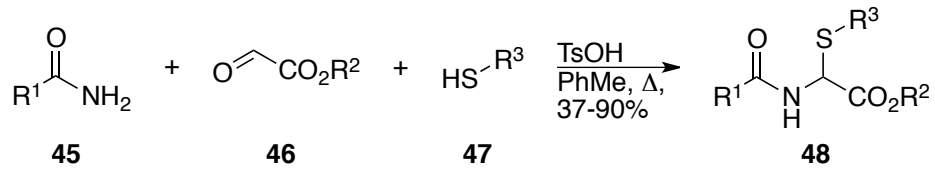
It is interesting to note, despite the success of $NaBH_4$ in the reduction of cyclic imides, only more reactive hydride sources, such as DIBAL-H are suitable for the desired partial reduction of acyclic imides.[30,31] The resulting α-hydroxy carbamates are surprisingly stable and can be stored at rt for months.[30] If so desired, the α-hydroxy carbamates can be trapped as the corresponding *N,O*-acetal silyl ethers which are amenable to flash column chromatography (scheme 9).[31]



Scheme 9. *N*-acyliminium ion precursor from the reduction of acyclic imides.

1.2.2.2. Condensation of Amides upon Aldehydes

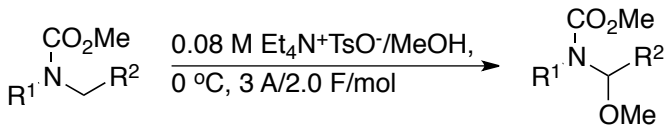
One approach towards α-hydroxy amides is the condensation of primary amides onto aldehydes. In affording more stable *N*-acyliminium ion precursors, these reactions can be performed in the presence of benzenesulfinic acid to afford α-sulfonyl amides and carbamates,[32,33] benzotriazole to afford α-benzotriazole amides and carbamates[34] and thiols to afford α-alkylthio amides and carbamates.[35,36] Scheme 10 depicts the latter.



Scheme 10. *N*-acyliminium precursor from the condensation of primary amides with aldehydes.

1.2.2.3. Anodic Oxidation of Acyclic Carbamates

Shono, in addition to the oxidations of cyclic carbamates discussed in section 1.2.1.4, also had success in acyclic systems (scheme 11).

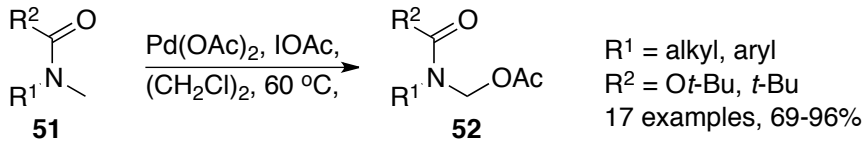


49 **50**

Scheme 11. *N*-acyliminium ion precursor from electrochemical oxidation of acyclic carbamates.

1.2.2.4. Chemical Oxidation of Amides and Carbamates

There has been a great deal of work reported on the chemical oxidation of amines to their α-oxy amines due to the interest in biomimetic oxidations.[37–39] Recently, this work has been extended to the α-oxidation of amides and carbamates with IOAc, mediated by catalytic palladium to afford *N*-acyliminium ion precursors in excellent yield.[40] One such example is provided in scheme 12, where substrates of type **51** can undergo oxidation in the presence of catalytic amounts of Pd(II) salts via a C-H insertion mechanism.

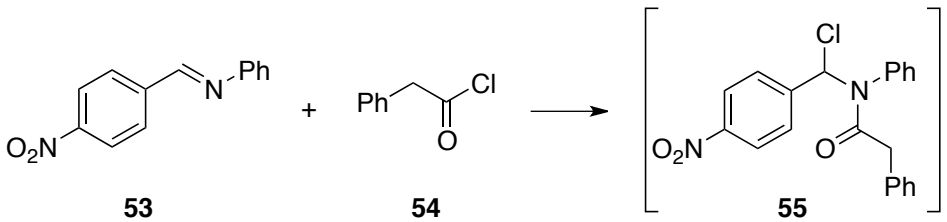


51 **52**

Scheme 12. *N*-acyliminium ion precursor from palladium-catalyzed α-oxidation of amides and carbamates.

1.2.2.5. *N*-Acylation of Imines

The *N*-acylation of imines with acyl chlorides affords the corresponding α-chloro amide as an *N*-acyliminium ion precursor. Scheme 13 depicts one such imine acylation, to afford the α-chloro amide *in situ* for subsequent α-amidoalkylation.[41]



53 **54** **55**

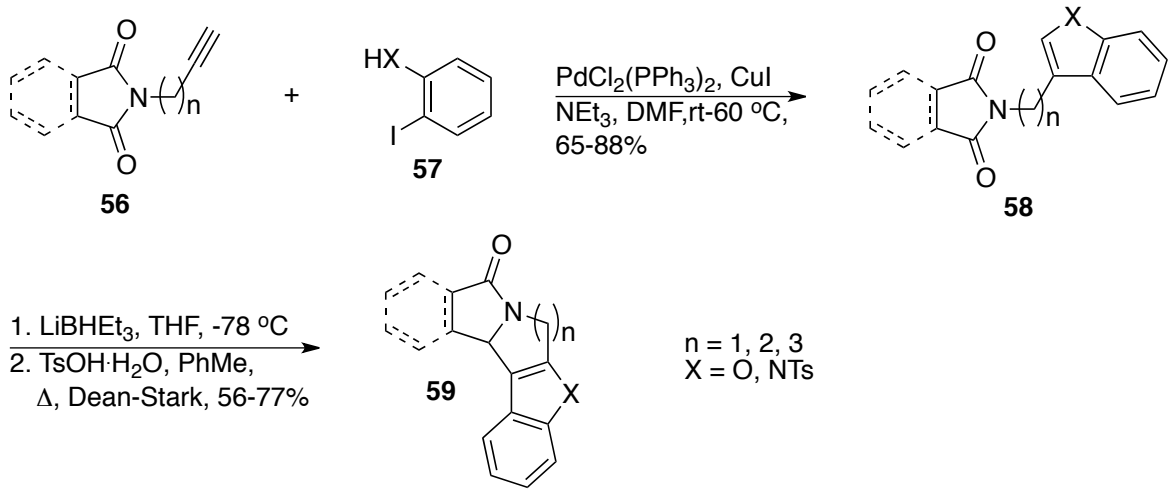
Scheme 13. *N*-acyliminium ion precursor from *N*-acylation of imines with acyl chlorides.

1.2.3. Scope and Application of *N*-Acyliminium Ion Chemistry: Intramolecular α-Amidoalkylations

Perhaps one of the most powerful applications of *N*-acyliminium ion chemistry is its application to intramolecular cyclizations for the construction of fused heterocyclic systems. These reactions are particularly useful, given they can be directly employed to access the abundance of natural products containing nitrogen heterocycles, such as isoquinolines and β-carbolines. Here, recent applications of *N*-acyliminium ions will be discussed from 2005-present.

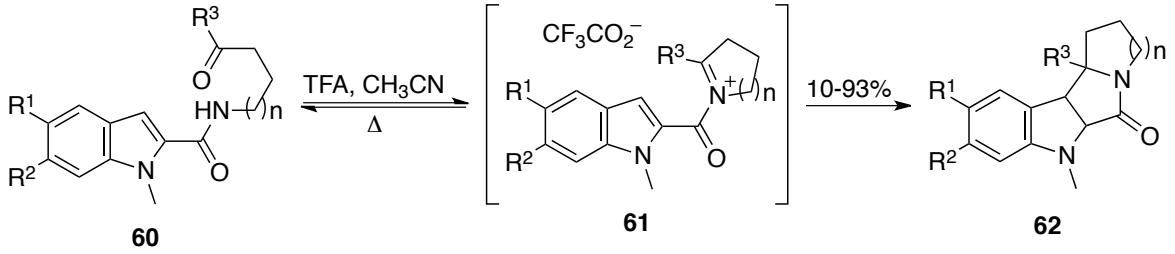
1.2.3.1. Brønsted Acid Promotion

Grigg *et al.* utilised Sonogashira mediated indole/benzofuran synthesis via a Larock-type annulation, followed by TsOH promoted *N*-acyliminium ion cyclizations between various hydroxy lactams and indole/benzofuran trapping agents to afford a series of tetra and pentacyclic systems, with the *N*-acyliminium ion step yielding 57-77% (see scheme 14).[42]



Scheme 14. Intramolecular α-amidoalkylations with hydroxy lactams and indole/benzofurans.

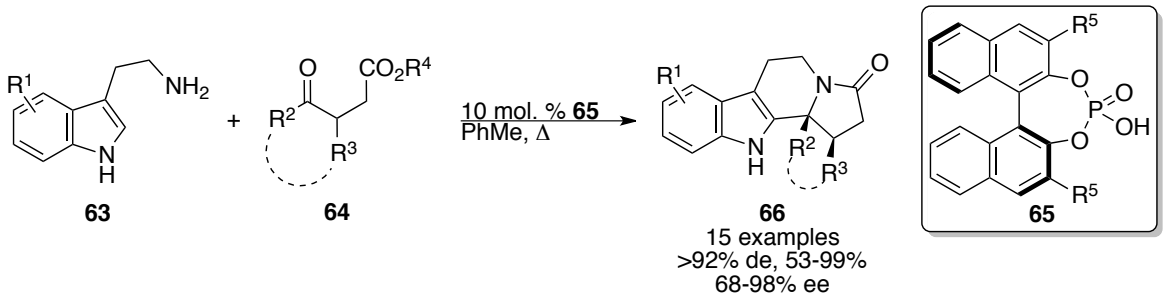
Cincinelli *et al.* unintentionally discovered a route towards tetracyclic pyrrolizinoindolones when investigating Friedel-Crafts reactions to afford β-carbolinones. An intramolecular *N*-acyliminium ion formation, followed by an intramolecular trapping with the indole afforded the tetracycle.[43] The more impressive reactions were seen with a larger ring size (n>1) and an electron-donating group at R_3 (scheme 15).



R^1 = H, OMe
R^2 = R^1
R^3 = H, CH_3, 4-CH_3O-Ph
n = 1, 2, 3

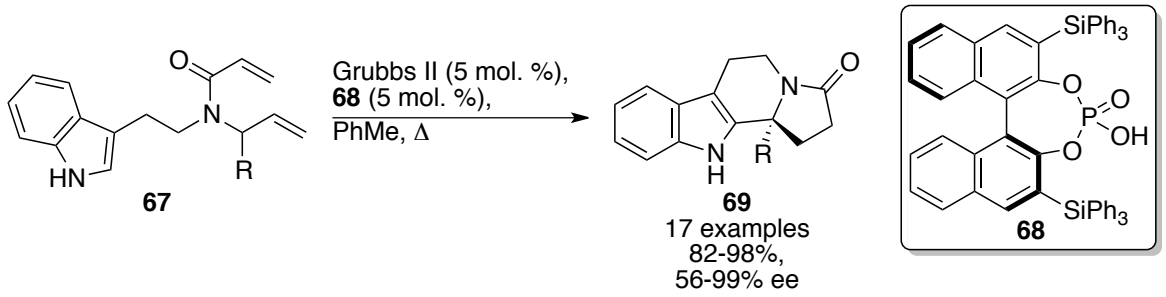
Scheme 15. *N*-acyliminium ion formation and ring closure by the intramolecular condensation of an amide and ketone and trapping with indole.

Dixon *et al*. used BINOL-derived phosphoric acids to induce enantio and diastereoselectivities in an *N*-acyliminium ion mediated α-amidoalkylation.[44] Excellent de, moderate to excellent chemical yield and good to excellent ee were possible in a diverse selection of 15 examples, as depicted in scheme 16.



Scheme 16. BINOL derived phosphoric acids catalyse asymmetric α-amidoalkylations of *N*-acyliminium ions.

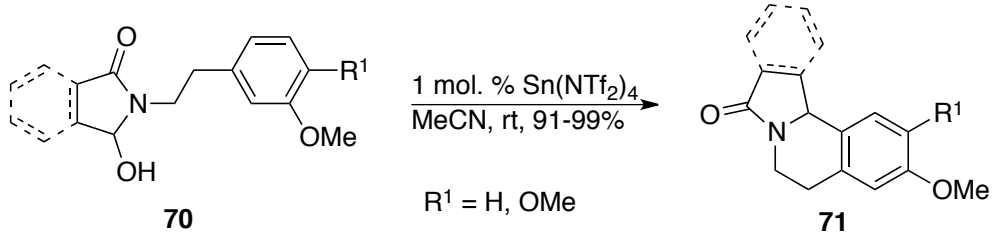
Preparing similar β-carbolines to that prepared by Dixon, an RCM/isomerization/α-amidoalkylation domino cascade was successfully applied by You *et al*. recently, utilising a similar chiral phosphoric acid to afford β-carbolines in excellent yield with moderate to excellent ee's observed.[45] The chiral acid afforded a chiral *N*-acyliminium ion pair via a series of isomerizations, and afforded the natural alkaloid harmicine (scheme 17).



Scheme 17. RCM/isomerization/α-amidoalkylation cascade to afford an enantioselective approach towards β-carbolines.

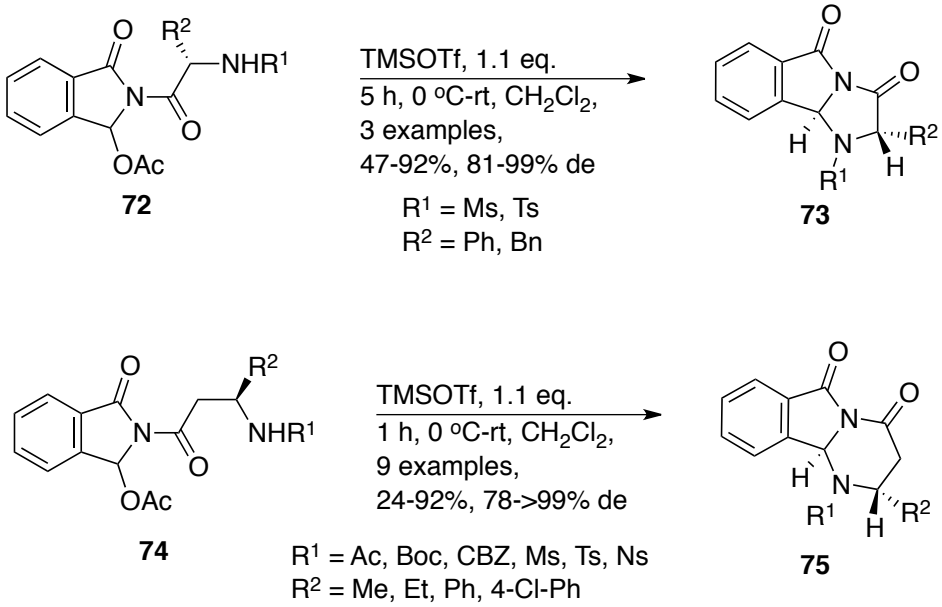
1.3.3.2. Lewis Acid Promotion

Using some of the same substrates *vide infra,* Dalla *et al.* reported the application of a "superacidic" $Sn(NTf_2)_4$ Lewis acid for the successful intramolecular *N*-acyliminium ion cyclizations of a series of phthalimide and succinimide derived α-hydroxy lactams in excellent yield (scheme 18).[46]



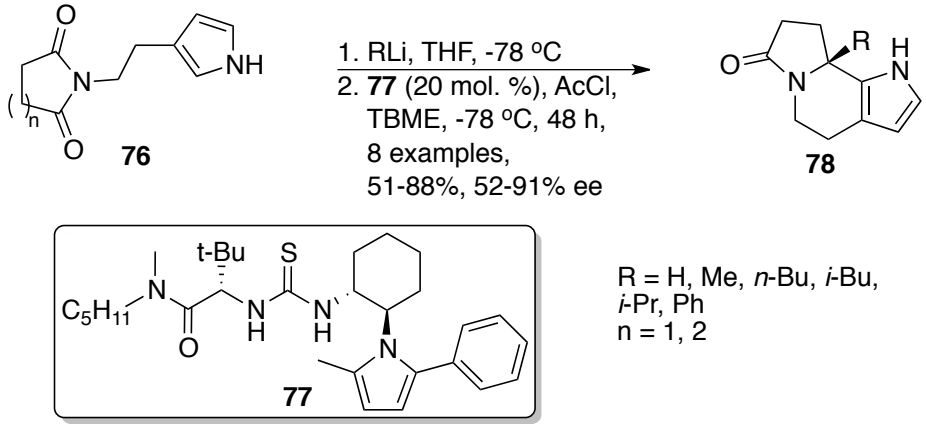
Scheme 18. Intramolecular α-amidoalkylation of *N*-acyliminium ions facilitated by $Sn(NTf_2)_4$.

Yamada *et al.* recently published their research into stereoselective *N*-acyliminium ions with impressive diastereomeric control promoted by the Lewis acid TMSOTf.[47] With the use of a chiral group on the linker between the *N*-acyliminium ion and the pendant nucleophile, de values of 83-99% for the formation of 5 membered rings and a de of 78%->99% for the formation of 6 membered rings were achieved. This is a nice example of good to excellent diastereomeric control of the newly formed chiral centre (scheme 19).



Scheme 19. Diastereoselective intramolecular *N*-acyliminium ion cyclizations facilitated by TMSOTf.

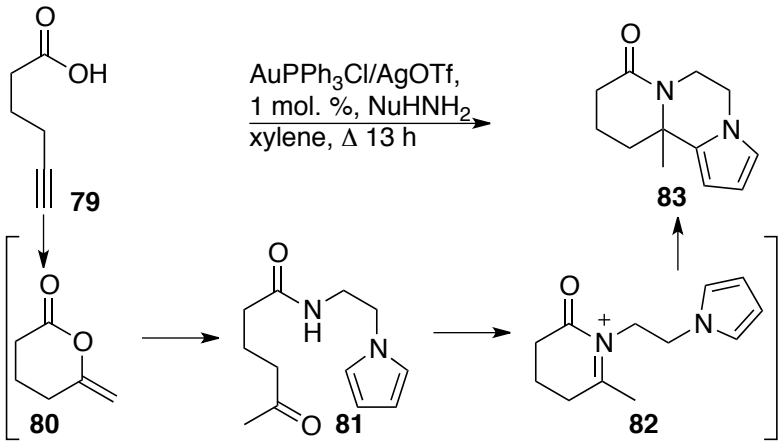
Jacobsen *et al.* have reported impressive enantioselective α-amidoalkylations of *N*-acyliminium ion intermediates with the use of AcCl or TMSCl and chiral thiourea organocatalysts.[48,49] The origin of asymmetric induction comes from the abstraction of chloride from the *in situ* generated α-chlorolactam to form the chiral ion pair. The reactions, proceeding smoothly at ≤-30 °C allow for reasonable to excellent ee's (scheme 20). This protocol was also extended to intermolecular reactions (*vide infra*).



Scheme 20. Asymmetric intramolecular α-amidoalkylations of *N*-acyliminium ions mediated by chiral thiourea organocatalysts.

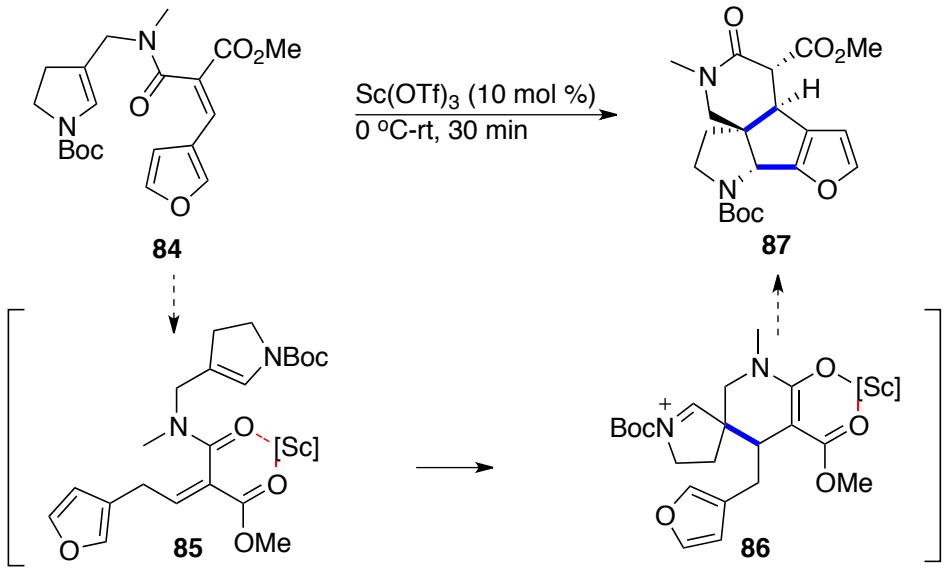
Using Au(I) salts, Dixon *et al*. reported a cascade approach to tricyclic lactams in good to excellent yield.[50] The approach involved the use of an alkyne unit as a masked ketone, which underwent

intramolecular reaction with a pendent acid to afford the corresponding lactone. This was subsequently opened with an external amine nucleophile. The resulting amide was condensed onto the ketone to afford the *N*-acyliminium ion, which was trapped by a pendent nucleophile (scheme 21).



Scheme 21. Au(I) promoted cascade reaction for the synthesis of tricyclic lactams.

Funk used $Sc(OTf)_3$ to initiate a Michael addition/*N*-acyliminium ion cyclization cascade in his strategy towards the synthesis of the core ring structure of nakadomarin A.[51] The methodology was successfully implemented to the total synthesis of the marine alkaloid, four years later.[52] The cascade involves the activation of an α,β-unsaturated 1,3-dicarbonyl to afford the intramolecular Michael adduct as an *N*-acyliminium ion. Subsequent trapping of the *N*-acyliminium ion by the pendent furan afforded the desired tetracycle in excellent yield (scheme 22).



Scheme 22. $Sc(OTf)_3$ mediated Michael addition/*N*-acyliminium ion formation/α-amidoalkylation cascade.

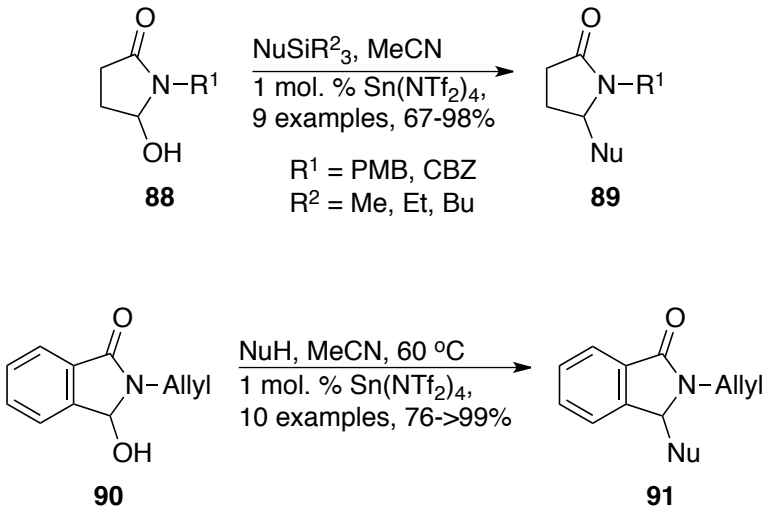
1.2.4. Scope and Application of *N*-Acyliminium Ion Chemistry: Intermolecular α-Amidoalkylations

1.2.4.1. Brønsted Acid Promotion

The application of Brønsted acids to intermolecular α-imidoalkylations is scarce, since sensitive nucleophiles such as enol ethers and alkyl silanes are readily decomposed in protic environments, where the rate of decomposition is often greater than the rate of α-amidoalkylation.

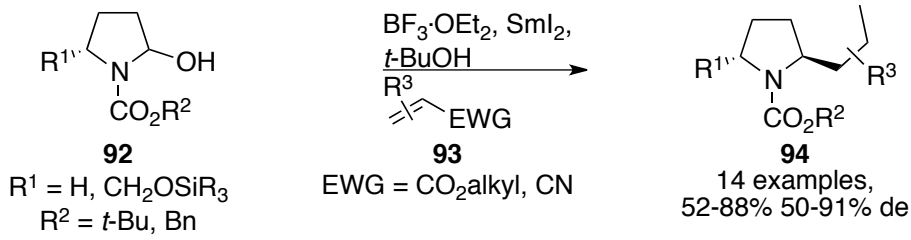
1.2.4.2. Lewis Acid Promotion

In the majority of the aforementioned publications of Dalla *et al.*; impressive activity of a "superacidic" $Sn(NTf_2)_4$ catalyst, with various *N*-acyliminium ion surrogates was seen, undergoing intermolecular *N*-acyliminium ion alkylations with allyl silanes and enol nucleophiles in 67->99% conversion with 0.1-1 mol. % $Sn(NTf_2)_4$ (scheme 23).[46]



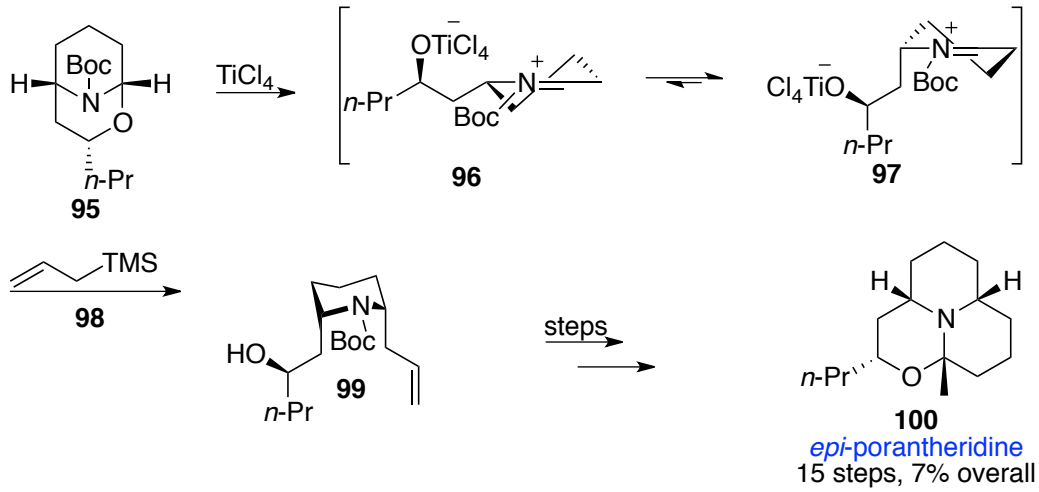
Scheme 23. Intermolecular *N*-acyliminium ion reactions with a series of π-nucleophiles and α-hydroxy amides/lactams.

Zheng and Huang used *N*-acyliminium ions prepared by activation of *N*-acyl-*N*,*O*-acetals with $BF_3{\cdot}OEt_2$ to access cross-coupled products from their reaction with α,β-unsaturated carbonyl compounds.[53] This cross-coupling was enabled by the single-electron reduction of the *N*-acyliminium ion with SmI_2 and subsequent intermolecular radical cascade (scheme 24). This methodology was further extended to the total synthesis of the pyrrolizidine alkaloid (+)-xenovenine.



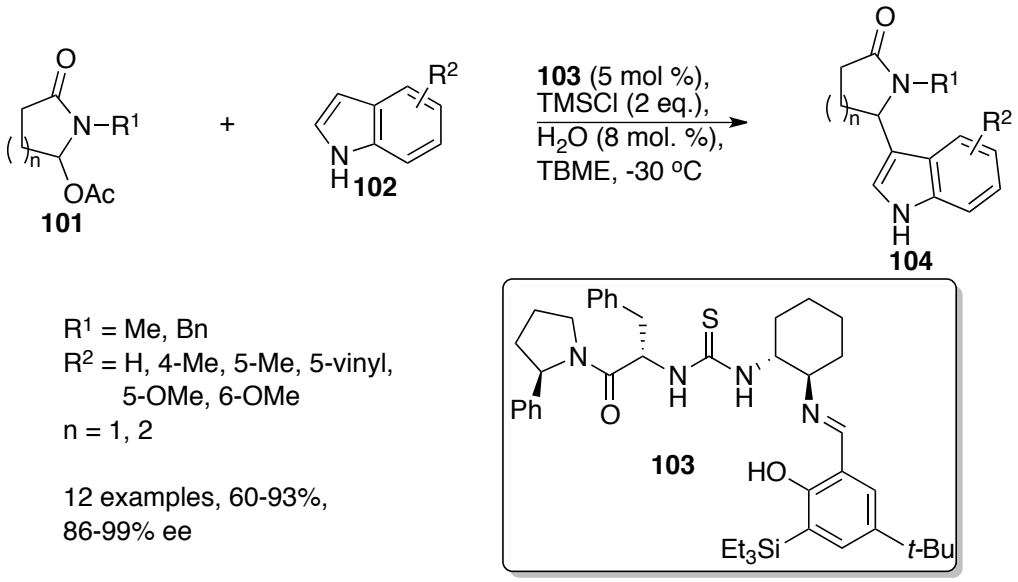
Scheme 24. SER/cross-coupling cascade via an *N*-acyliminium ion intermediate.

Bates and Lu in their 2009 publication utilised $TiCl_4$ in their total synthesis of *epi*-porantheridine, trapping the more stable conformation of the *N*-acyliminium ion with allyl trimethylsilane to afford the key piperidine **99** (scheme 25).[54]



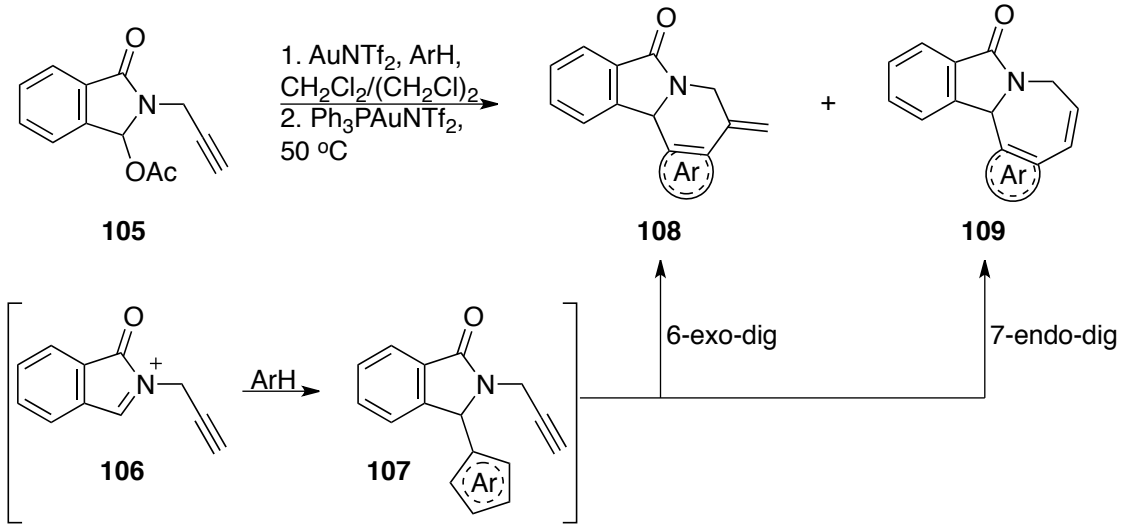
Scheme 25. Intermolecular α-amidoalkylation of an *N*-acyliminium ion towards the synthesis of *epi*-porantheridine.

Jacobsen *et al.* recently reported impressive enantioselective alkylations of *N,O*-acetals with indoles using a chiral thiourea Schiff base catalyst (scheme 26).[49]



Scheme 26. Jacobsen's enantioselective α-amidoalkylation of *N*-acyliminium ions.

Another to take advantage of the broad reactivity of Au catalysts were Dalla *et al.*, who used a one-pot Au(I)/Au(III) α-amidoalkylation/carbocyclization tandem process to access complex heterocycles in one step, as depicted in scheme 27.

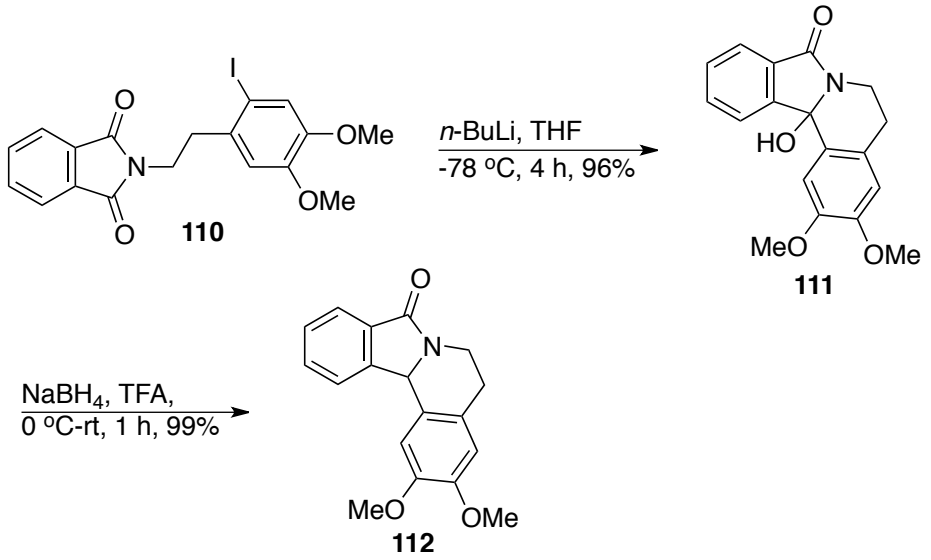


Scheme 27. Cascade α-amidoalkylation/carbacyclization involving an *N*-acyliminium ion intermediate.

1.3. Notable Alternative Approaches to Tetrahydroisoquinoline Derivatives

1.3.1. Parham Cyclization

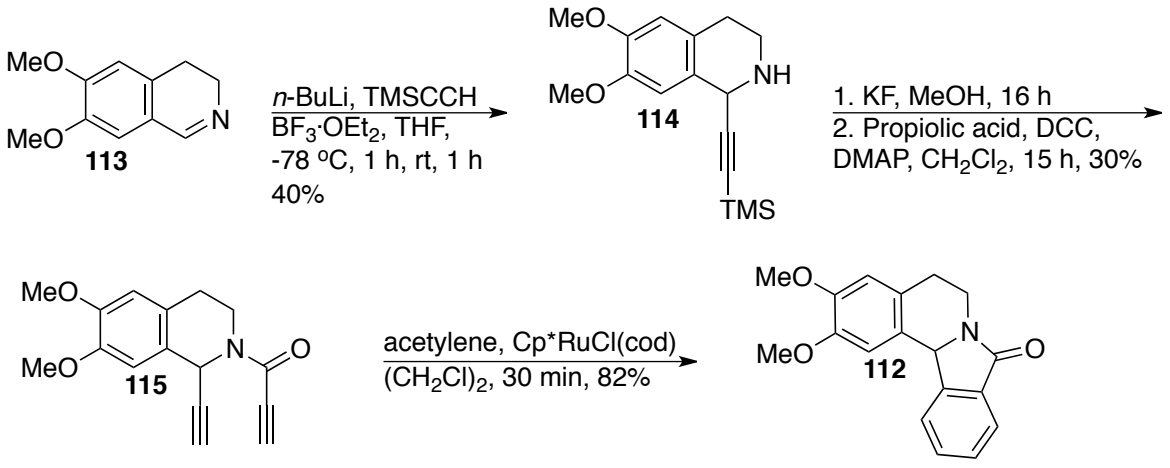
The Parham cyclization proceeds via a lithium-halogen exchange and subsequent alkylation. When applied to the preparation of isoindoloquinolinone[45] and isopyrroloquinolinone[46] alkaloids, α-hydroxylactams are afforded from the corresponding imides, as depicted in scheme 28.



Scheme 28. Parham cyclization for the preparation of isoindoloisoquinoline **112**.[55]

1.3.2. Intramolecular alkyne [2 + 2 + 2] Cyclotrimerization

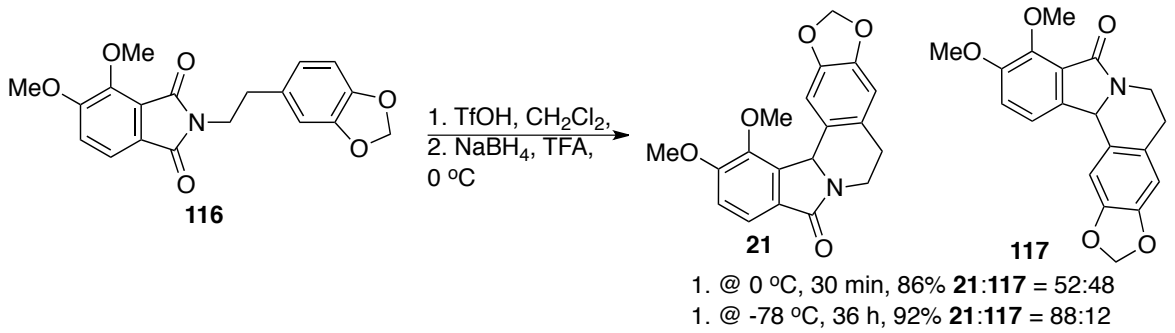
Impressive [2 + 2 + 2] reactions of α,ω-diynes and terminal alkynes for the synthesis of benzo-fused lactams and lactones have been reported. The methodology has been demonstrated by the preparation of isoindoloisoquinoline **112** (scheme 29).[56]



Scheme 29. [2 + 2 + 2] cyclotrimerization for the preparation of isoindoloisoquinoline **112**.

1.3.3. Imide Activation/Cyclization

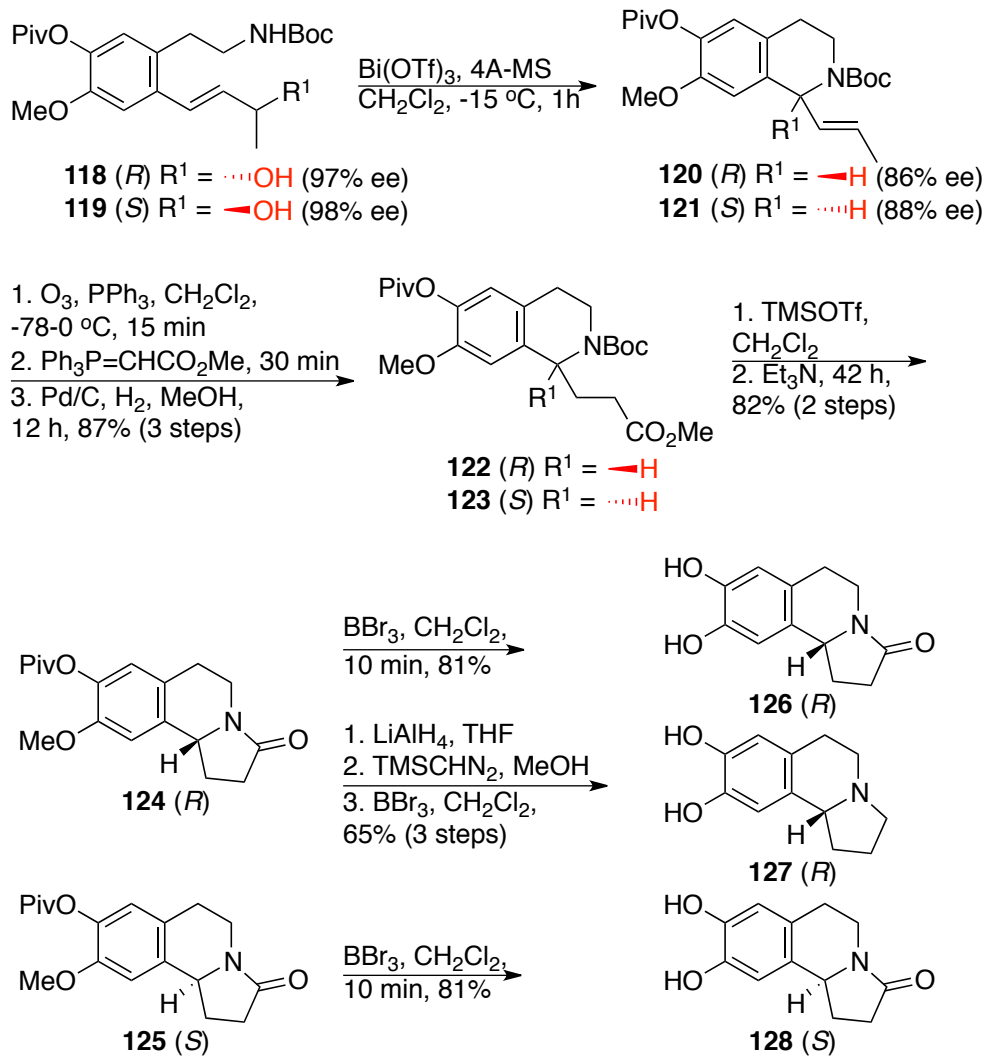
Very recently, BBr_3 and TfOH have been shown to act as Lewis and Brønsted activators of imides respectively, which has been exploited for the preparation of tetrahydroquinoline analogues.[57] The reaction outcome may be comparable to that of the Parham cyclizations and can be considered to be both atom and step economy improvements. This methodology has been successfully applied to the synthesis of nuevamine with good regioselectivity, as determined by ^1H NMR spectroscopy (scheme 30).



Scheme 30. Brønsted acid-assisted imide activation for the regioselective synthesis of nuevamine.

1.3.4. Chirality Transfer

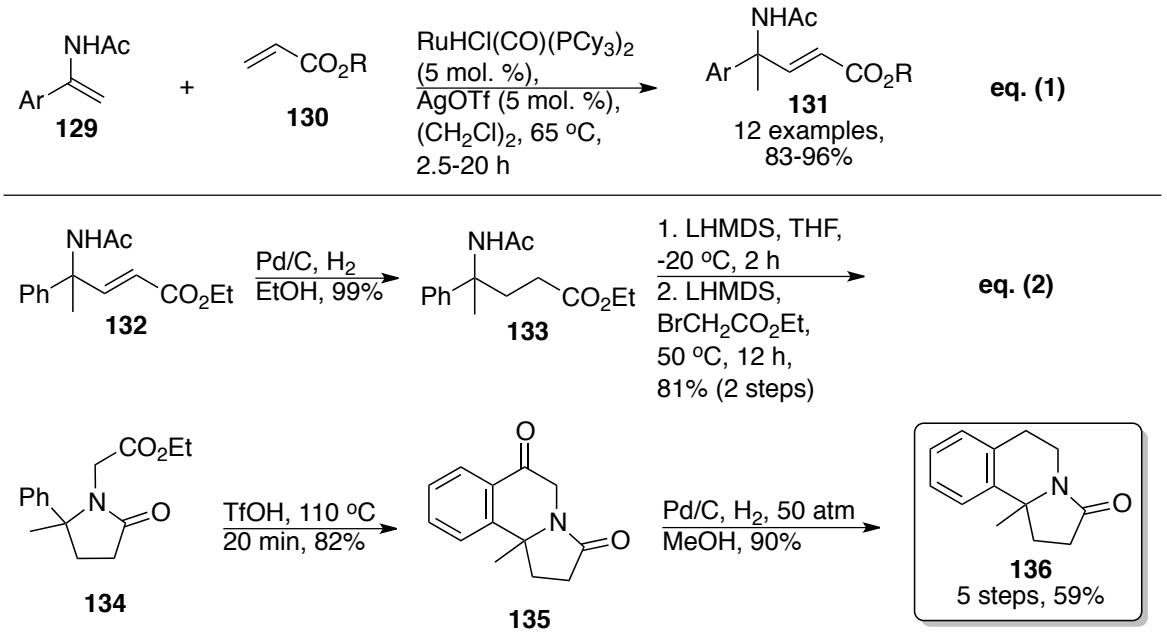
In an interesting stereoselective approach towards tetrahydroisoquinolines, Kawai used a 1,3-chirality transfer approach during a $Bi(OTf)_3$ catalyzed amination.[58,59] In demonstrating this methodology, three tetrahydroisoquinoline alkaloids were prepared in reasonably good ee.[60]



Scheme 31. Chirality transfer approach for the synthesis of tetrahydroisoquinolines.

1.3.5. Co-dimerization Approach

A recent paper has described a ruthenium-catalyzed co-dimerization of *N*-acyl α-arylenamines and acrylates, which the authors claim can be directly used to access α,β-unsaturated γ-amino esters, which are important motifs in many natural products and their synthetic precursors (scheme 32, eq. (1).[61] In addition, this methodology can also be applied to the synthesis of tetrahydroisoquinolines via a subsequent base-promoted cyclization/alkylation protocol, as depicted in scheme 32 eq. (2).

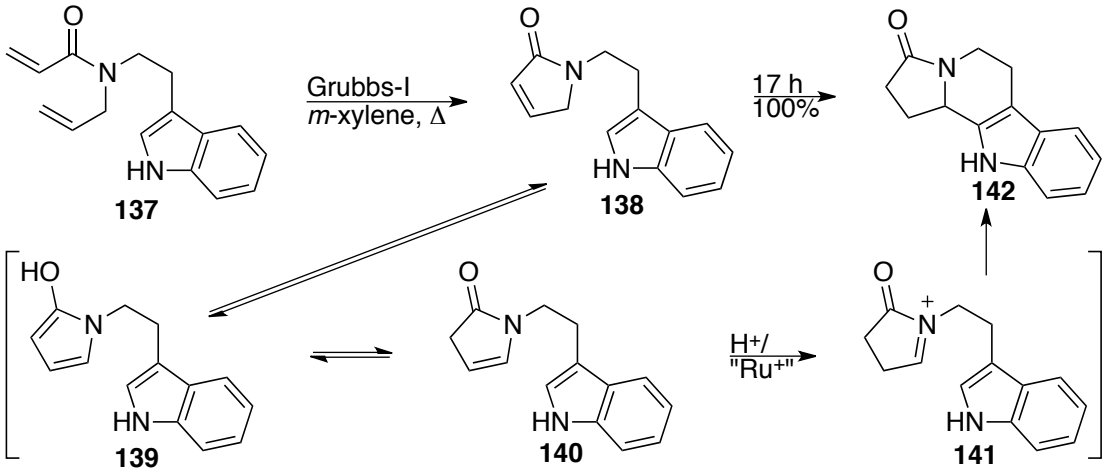


Scheme 32. Synthesis of tetrahydroisoquinolines via a ruthenium-mediated co-dimerization approach.

1.4. Reagent-Free Chemistry

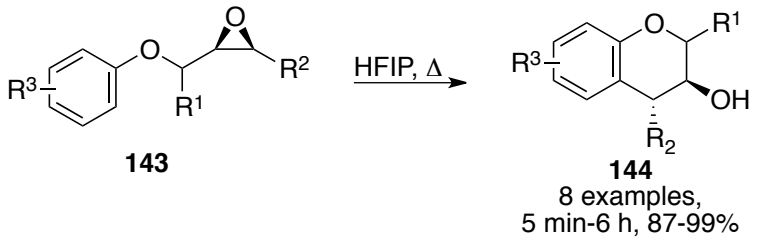
There have been recent reports in the literature of acid-mediated processes proceeding without the use of extraneous acid. Using a solvent with mild acidity and high polarizing power has been shown to mediate acid promoted reactions, without the use of an added acid reagent.[62] Additionally, the concept of one-pot tandem processes have been utilised to allow numerous steps to be performed in one reaction. This not only saves on use of reagents, but also negates the requirement for purification of reaction intermediates.

Alkene RCM and cross-metathesis are powerful synthetic transformations. The use of Grubbs catalysts have facilitated both RCM and α-amidoalkylation via the formation of an *N*-acyliminium ion intermediate, presumably (scheme 33).[63] This same approach was recently applied by You *et al*. with similar success.[45]



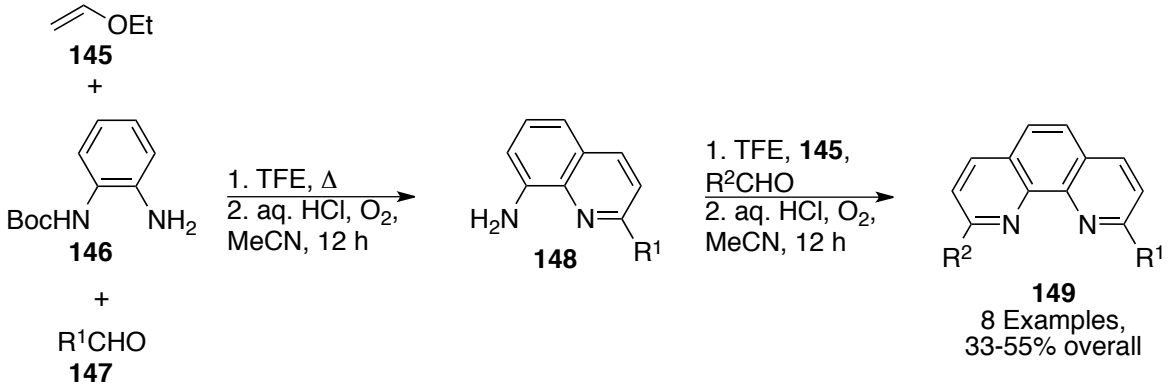
Scheme 33. Tandem RCM/α-amidoalkylation process.

Alkylations of arenes with epoxides via Friedel-Crafts type reactions have recently been reported proceeding smoothly to the desired chromanol's in excellent yield in ≤6 h (scheme 34).[64]



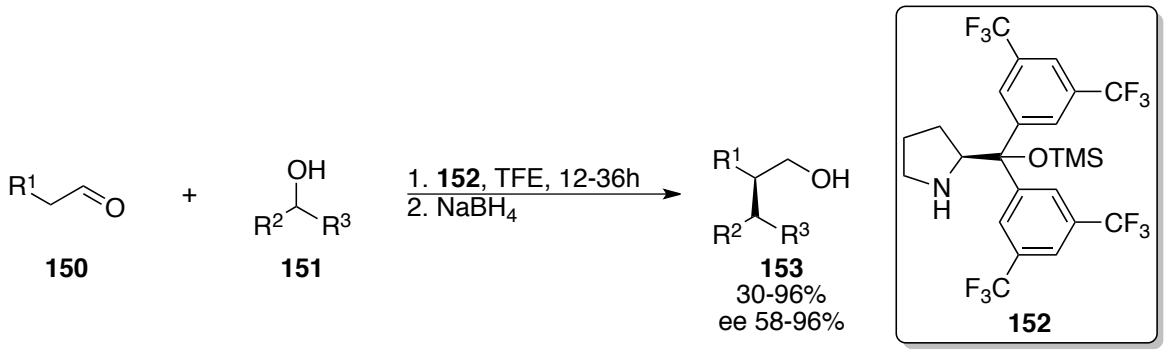
Scheme 34. HFIP mediated Friedel-Crafts type reaction of arenes and epoxides.

In a novel approach, the use of TFE and HFIP was again successful in a reagent-free context, enabling the synthesis of 8-aminoquinolines and phenanthrolines in a three-component Povarov reaction of various aldehydes, anilines and vinyl ethers (scheme 35).[65] In the latter case, access to symmetrical and unsymmetrical phenanthrolines is possible.



Scheme 35. TFE mediated aminoquinolines and phenanthroline synthesis.

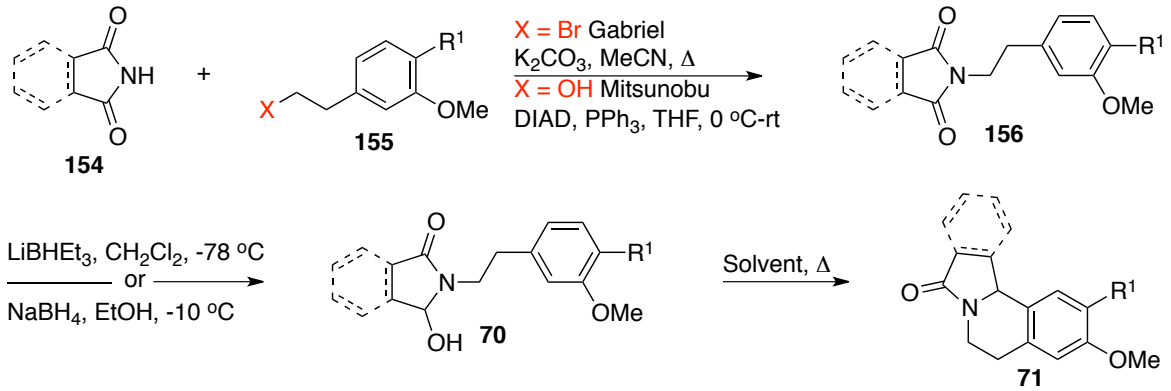
Finally, fluorinated alcohols facilitated intermolecular α-alkylation of aldehydes by an organocatalyzed reaction.[66] In an extension of the methodology, the use of chiral, proline derived organocatalysts were employed to facilitate an asymmetric protocol allowing for moderate to excellent yields and moderate to excellent ee.



Scheme 36. Organocatalyzed, TFE facilitated Mannich reactions.

1.5. Aims of the Project

The application of *N*-acyliminium ion chemistry has a rich past, and continues to be used with great success in organic chemistry. Recently, there have been several reports in the literature of acid-mediated reactions proceeding under conditions we describe as "reagent-free". That is, reactions proceeding without the addition of extraneous acid.[62,65,66] We intend to investigate the rarely explored realm of "reagent-free" *N*-acyliminium ion chemistry. We intend to use hydroxy lactams derived from phthalimide and succinimide, and will initially attempt to trap *N*-acyliminium ions with electron-rich pendent arenes in intramolecular experiments. Should we prove successful, a broader range of *N*-acyliminium ion precursors and nucleophiles will be investigated, along with intermolecular reactions. A schematic representation of our initial approach towards the chemistry is provided (scheme 37).

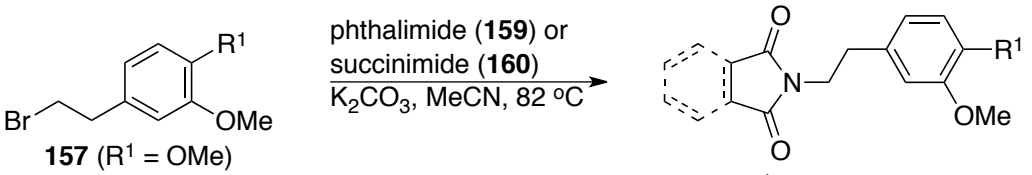


Scheme 37. Outline of the initial aims of the project.

2. Results and Discussion

2.1. Synthesis of Precursors

Using a Gabriel alkylation protocol, we prepared imides **161**-**163** (scheme 38). Due to the inherent low reactivity of phthalimide and succinimide in these conditions, the reactions required to be conducted for at least 48 h for a reasonable yield to be achieved (table 1).



157 (R^1 = OMe)
158 (R^1 = H)

161 (R^1 = OMe, phthaloyl)
162 (R^1 = H, phthaloyl)
163 (R^1 = OMe, succinyl)

Scheme 38. Gabriel reaction of phthalimide and succinimide with alkyl bromides **157** & **158**.

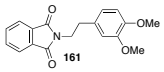
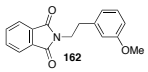
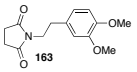
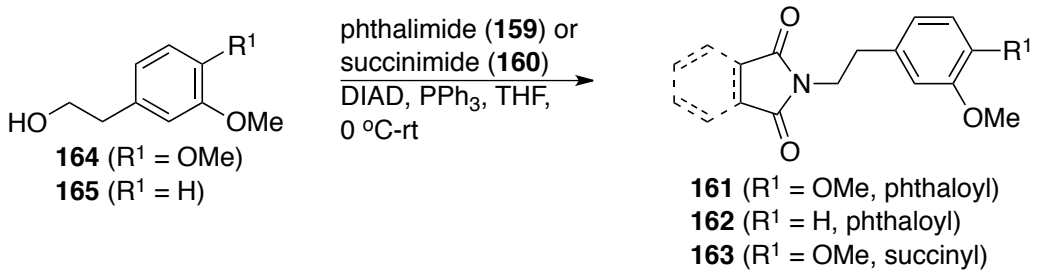
Entry	Imide (1.5 eq.)	Bromide (1.0 eq.)	Reaction conditions	Reaction product (yield)
1	Phthalimide	**157**	K_2CO_3 (1.8 eq.), MeCN, 82 °C, 48 h	 (39%)
2	Phthalimide	**158**	K_2CO_3 (1.8 eq.), MeCN, 82 °C, 48 h	 (63%)
3	Succinimide	**157**	K_2CO_3 (1.8 eq.), MeCN, 82 °C, 46 h	 (52%)

Table 1. Preparation of imides **161**-**163** using the Gabriel protocol

While workup of the Gabriel reactions was facile, we embarked upon a Mitsunobu approach (scheme 39), which was reported in the literature to be faster.[67] Our experiments confirmed this, with the Mitsunobu conditions affording the desired imides in comparable conversion to the Gabriel conditions in *ca*. 4 h, compared to 48 h for the Gabriel approach. Unfortunately, during flash column chromatography, co-elution of the hydrazine Mitsunobu by-product with our imides was seen in all cases. Attempts at re-crystallization revealed Et_2O to be a suitable solvent for the removal of most of the hydrazine, and subsequent column chromatography afforded clean imide in all cases.



Scheme 39. Mitsunobu reaction of phthalimide and succinimide with alkyl alcohols

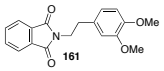
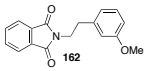
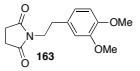
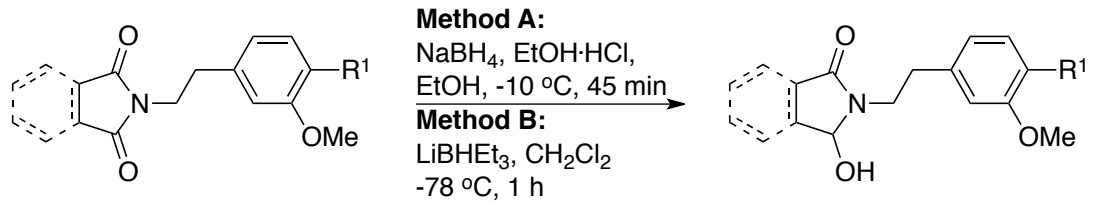
Entry	Imide (1.2 eq.)	Alcohol (1.0 eq.)	Reaction conditions	Reaction product (yield)
1	**159**	**164**	DIAD (1.2 eq.), PPh_3 (1.2 eq.), THF, 13 h	 (94%)
2	**159**	**165**	DIAD (1.2 eq.), PPh_3 (1.2 eq.), THF, 6 h	 (66%)
3	**160**	**164**	DIAD (1.2 eq.), PPh_3 (1.2 eq.), THF, 4 h	 (60%)

Table 2. Preparation of imides **161**-**163** using the Mitsunobu protocol.

With our imides in hand, we embarked upon reduction to the corresponding hydroxy lactams, the results of which are presented in scheme 40 and table 3. In applying $NaBH_4$ to the reduction, initial results indicated a ring opening and over-reduction to amide **167** was occurring (table 3, entry 1). Maintaining an acidic pH with the addition of ethanolic HCl solution prevented this, to afford the desired hydroxy lactam **164** (entry 2). We also successfully accessed hydroxy lactam **165** (entry 3), however the reduction of imide **163** appeared to be much more sluggish compared to the previous imides, presumably due to a lack of activation provided by the phenyl ring in the phthaloyl examples (entry 4). We were reluctant to raise the temperature of the reaction for fear of ring opening and over-reduction, and so we turned to $LiBHEt_3$, which furnished hydroxy lactam **166** (entry 5). With our small series of hydroxy lactams in hand, we were ready to explore "reagent-free" *N*-acyliminium ion chemistry.



161 (R^1 = OMe, phthaloyl)
162 (R^1 = H, phthaloyl)
163 (R^1 = OMe, succinyl)

164 (R^1 = OMe, phthaloyl)
165 (R^1 = H, phthaloyl)
166 (R^1 = OMe, succinyl)

Scheme 40. Reduction of imides **161**-**163** to hydroxy lactams **164**-**166**.

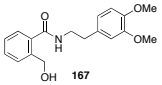
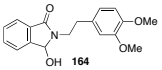
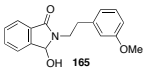
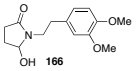
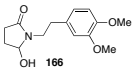
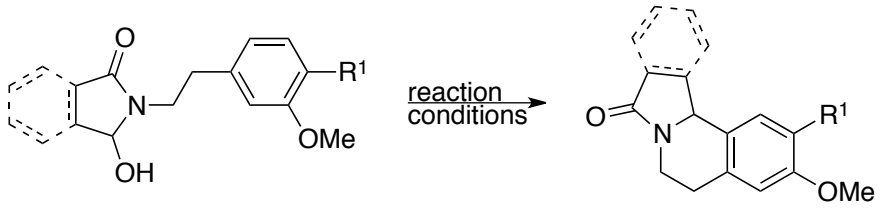
Entry	Imide (eq.)	Reaction conditions	Reaction outcome (yield)
1	**161**	$NaBH_4$ (1.5 eq.), EtOH, -10 °C, 45 min	 **167** (49%)
2	**161**	$NaBH_4$ (1.5 eq.), EtOH·HCl, EtOH, -10 °C, 45 min	 **164** (89%)
3	**162**	$NaBH_4$ (1.5 eq.), EtOH·HCl, EtOH, -10 °C, 45 min	 **165** (78%)
4	**163**	$NaBH_4$ (1.5 eq.), EtOH·HCl, EtOH, -10 °C, 45 min	 **166** (9%)
5	**163**	$LiBHEt_3$ (1.1 eq.), CH_2Cl_2, -78 °C, 1 h	 **166** (71%)

Table 3. Preparation of hydroxy lactams **164**-**166**.

2.2. Initial Results of "Reagent-Free" *N*-Acyliminium Ion Reactions

We were satisfied to observe a successful conversion of hydroxy lactam **164** to lactam **168** in a number of solvents (table 4, entries 1-4) and some failures (entries 5-6). We were especially surprised to see conversion in refluxing xylene and $(CHCl_2)_2$, and considered whether the reaction was proceeding purely from thermal initiation, as evidenced by the failures in CH_2Cl_2 and $CHCl_3$. Further to this, TFE and HFIP reactions were much slower than that of $(CHCl_2)_2$ and xylene, despite their well reported mild acidity and highly polarizing properties.[62]



164 (R^1 = OMe, phthaloyl)
165 (R^1 = H, phthaloyl)
166 (R^1 = OMe, succinyl)

168 (R^1 = OMe, phthaloyl)
169 (R^1 = H, phthaloyl)
170 (R^1 = OMe, succinyl

Scheme 41. Cyclization of hydroxy lactams **164**-**166** to lactams **168**-**170**.

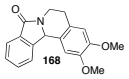
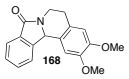
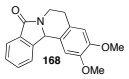
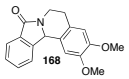
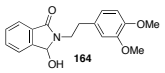
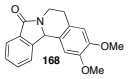
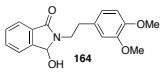
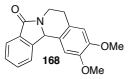
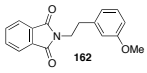
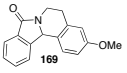
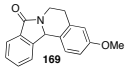
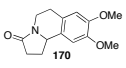
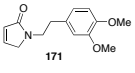
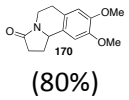
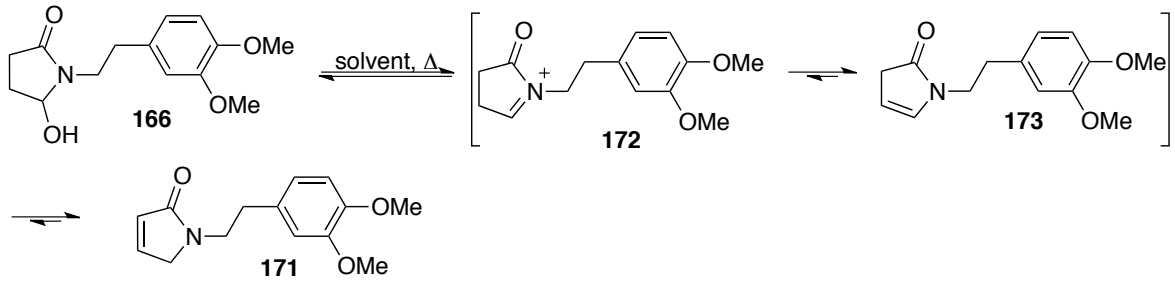
Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield)
1	**164**	Xylene, 139 °C, 105 min	 (99%)
2	**164**	$(CHCl_2)_2$, 147 °C, 45 min	 (95%)
3	**164**	TFE, 78 °C, 20 h	 (74%)
4	**164**	HFIP, 58 °C, 26 h	 (68%)
5	**164**	CH_2Cl_2, 40 °C, 2 d	 (100%)  (0%)
6	**164**	$CHCl_3$, 66 °C, 2 d	 (100%)  (0%)
7	**165**	Xylene, 139 °C, 4 h	 (89%)  (0%)
8	**165**	$(CHCl_2)_2$, 147 °C, 4 h	 (99)
9	**166**	Xylene, 139 °C, 2 h	 (0%)  (96%)
10	**166**	$(CHCl_2)_2$, 147 °C, 2 h	 (80%)

Table 4. Initial *N*-acyliminium ion transformations achieved in "reagent-free" conditions.

Successful conversions of hydroxy lactams **165** and **166** to the corresponding lactams **169** and **170** respectively was achieved in $(CHCl_2)_2$ (entry 8 and 10) however the same reactions were not successful in refluxing xylene (entry 7 and 9 respectively). In the case of hydroxy lactam **165**, the oxidised product, imide **162** was isolated (entry 7). We are not able to offer a convincing mechanistic rationale for this observation, although the presence of oxygen at high temperature would be a possible cause of the oxidation. While these reactions were conducted under nitrogen, oxygen dissolved in the solvent could be the source of oxidation. In the case of hydroxy lactam **166**, the product afforded was the corresponding α,β-unsaturated γ-lactam **171**, (entry 9), which arose, presumably via an isomerisation of the less stable β,γ-unsaturated pyrrolidinone from a dehydrative elimination (scheme 42). It was recognised this dehydrative process was not possible in the case of the phthalimide derivatives due to the quaternary centre α to the *N*-acyliminium ion, and the phthalimide derivatives would provide better substrates for this chemistry. The same dehydrative process was observed in refluxing $(CHCl_2)_2$ after periodical monitoring of the reaction progress via ^{1}H NMR spectroscopy, however presumably via another series of isomerizations to re-afford the desired *N*-acyliminium ion, preparation of lactam **170** was successfully achieved (entry 10). We propose the cationic *N*-acyliminium ion is better supported in the more polar $(CHCl_2)_2$ than xylene and therefore the subsequently lowered $\Delta G^{\ddagger}$ is achievable, allowing isomerization from the α,β-unsaturated γ-lactam back to the *N*-acyliminium ion.

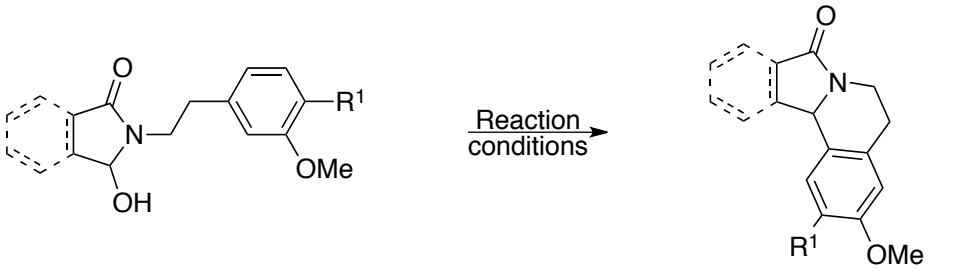


Scheme 42. Proposed dehydrative elimination/isomerization cascade to lactam **171**.

2.3 Microwave Irradiation

With impressive initial results using conventional heating techniques, μW irradiation was utilised in an attempt to improve reaction yields and times. Due to the poor dielectric constant of both toluene and xylene, rapid heating to the required temperatures was not possible, and so it was only viable to investigate $(CHCl_2)_2$ and the polyfluorinated alcohols in this case. Rapid heating to the respective boiling points is possible and in the case of TFE and HFIP, due to a favourable dielectric constant. The reactivity in these solvents using conventional heating was much lower compared to $(CHCl_2)_2$, however in the μW we were able to superheat these solvents to 120 ^{o}C. In

the case of $(CHCl_2)_2$, 2-3 fold reaction rate enhancements were seen with improvements in yield also observed when compared to thermal heating in the same solvent (table 5, entry 1, 4, 5). A remarkable rate enhancement was seen in the case of TFE (Entry 2, *ca*. 27 fold), but the conversion was still considerably inferior compared with $(CHCl_2)_2$. In the case of HFIP (entry 3), improvements were not seen, and offered significantly inferior conversion compared to TFE and $(CHCl_2)_2$.



164 R^1 = OMe, phthaloyl
165 R^1 = H, phthaloyl
166 R^1 = OMe, succinimyl

168 R^1 = OMe, phthaloyl
169 R^1 = H, phthaloyl
170 R^1 = OMe, succinimyl

Scheme 43. Comparison of thermal and μW experiments.

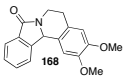
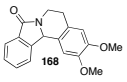
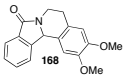
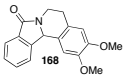
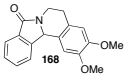
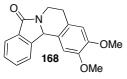
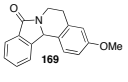
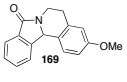
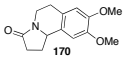
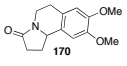
Entry	Hydroxy lactam	Reaction conditions		Reaction outcome (yield %)	
		Thermal	*μW*	*Thermal*	*μW*
1	**164**	$(CHCl_2)_2$, 147 °C, 45 min	$(CHCl_2)_2$, 147 °C, 300 W, 30 min	 (99)	 (97)
2	**164**	TFE, 78 °C, 20 h	TFE, 120 °C, 300 W, 1200 min	 (74)	 (69)
3	**164**	HFIP, 58 °C, 26 h	HFIP, 120 °C, 300 W, 1200 min	 (68)	 (33)
4	**165**	$(CHCl_2)_2$, 147 °C, 45 min	$(CHCl_2)_2$, 147 °C, 300 W, 55 min	 (76	 (>99)
5	**166**	$(CHCl_2)_2$, 147 °C, 45 min	$(CHCl_2)_2$, 147 °C, 300 W, 40 min	 (84)	 (>99)

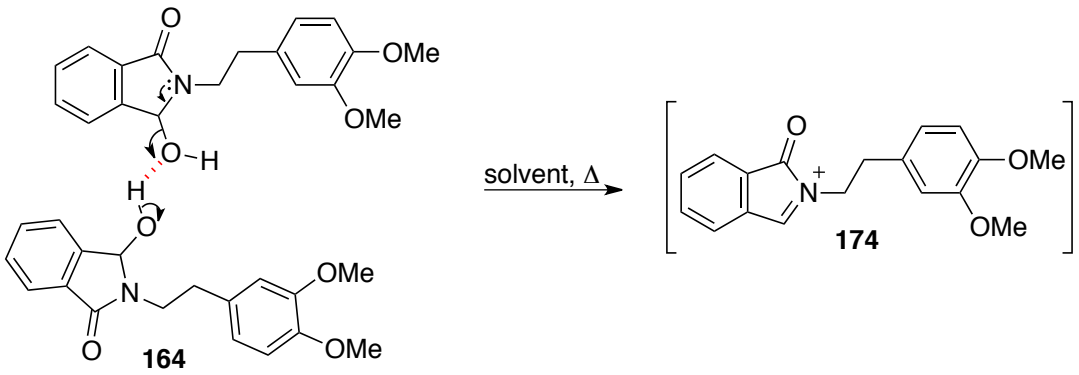
Table 5. Comparison of reaction times and yields with thermal *vs*. μW heating.

2.4 Summary of Initial Results

The initial results were pleasing, and compare equally well in terms of reaction rate and yield to those published in the literature for Lewis acid[46] and Brønsted acid[68] promoted reactions in the case of $(CHCl_2)_2$. However, it was felt investigation of the reaction mechanism was required before a more detailed analysis of the limits and possibilities of this "reagent-free" approach were to be undertaken.

2.5. Mechanistic Experiments

It was thought, due to the extremely poor leaving ability of the hydroxide anion, there must be some activation of this group for the successful progress of the reaction. Initial propositions were the possibility of a bimolecular activation whereby the combination of two hydroxy lactams facilitated the generation of the *N*-acyliminium ion (see scheme 44) and trace acid from the glassware and/or solvent was mediating the reaction.

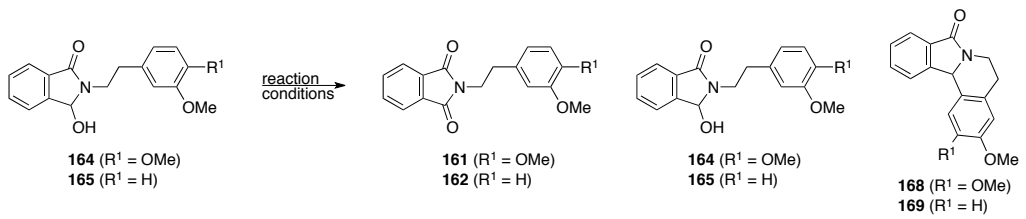


Scheme 44. Proposed bimolecular activation model.

2.5.1. Investigations into the Bimolecular Activation Model

In order to investigate the possibility of bimolecular activation, a series of experiments were designed in which reactions of hydroxy lactam **164** in xylene and **165** in $(CHCl_2)_2$ at varying concentrations were performed in parallel. Should the proposed mechanism be accurate, the experiments at more dilute concentrations should proceed more slowly due to a decrease in the effective concentration of acid (i.e. concentration of the substrate). The results of these experiments (table 6) in xylene were not consistent, with the more dilute example producing not the *N*-acyliminium product, but the synthetic precursor imide **161** (entries 1-2). The same

experiments in $(CHCl_2)_2$ with hydroxy lactam **165** did not follow the same trend, with the same conversion within experimental error (entries 3-4).



164 (R^1 = OMe)
165 (R^1 = H)

161 (R^1 = OMe)
162 (R^1 = H)

164 (R^1 = OMe)
165 (R^1 = H)

168 (R^1 = OMe)
169 (R^1 = H)

Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield %)
1	**164**	Xylene, 139 ^oC, 92 µM, 105 min	**161** (0), **164** (8), **168** (92)
2	**164**	Xylene, 139 ^oC, 9.3 µM, 105 min	**161** (97), **164** (0), **168** (3)
3	**165**	$(CHCl_2)_2$, 147 ^oC, 101 µM, 240 min	**162** (0), **165** (31), **169** (69)
4	**165**	$(CHCl_2)_2$, 147 ^oC, 10.1 µM, 240 min	**162** (0), **165** (28), **169** (72)

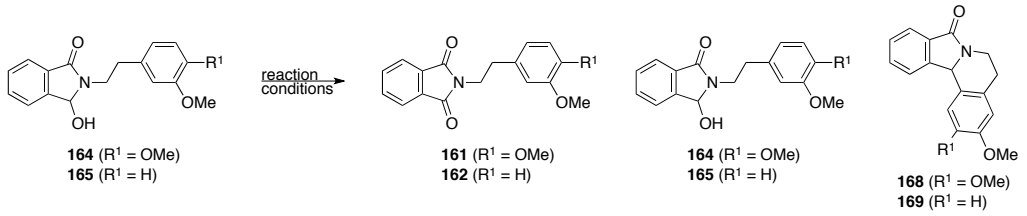
Table 6. Effect of varying the reaction concentration in the progress of α-amidoalkylations.

The disparity of results suggested different reaction mechanisms were occurring in the two different solvents. In the xylene system, the failure of the reaction seemed to indicate activation was required. This failure may be due to the proposed bimolecular activation model, or acidic sites on the glass surface, since a dilution of the reaction mixture would also dilute the effective concentration of acidic glass residues. In either case, it appeared apparent acidic activation is imperative for a successful reaction outcome.

2.5.2. Investigations into Acidic Glassware Promoting Catalysis

As previous results from the dilution experiments suggested an activation of the hydroxy lactams was required for successful reaction progress, it was thought the addition of a base would discriminate between whether trace acid or the bimolecular activation model explained the observed successful reactions. To test this hypothesis, reactions in both xylene and $(CHCl_2)_2$ in the presence of DABCO were performed, the results of which are provided in table 7. In the case of xylene, as expected a stoichiometric excess of DABCO completely inhibited the reaction progress; and actually afforded the corresponding imide **161** via a thermal oxidation (entry 1). More interestingly, 5 mol. % of DABCO also completely inhibited the reaction progress, again affording the corresponding imide (entry 2). This thermal oxidation had previously been seen when the less reactive hydroxy lactam **162** was heated under reflux in xylene (table 4, entry 7). If the reaction

was proceeding via an elimination of hydroxide without acidic activation, there should still have been 95% of hydroxy lactam available to partake in an uncompromised reaction. Similarly, if the bimolecular activation model was responsible for the successful preparation of the *N*-acyliminium ion, the presence of 5 mol. % of DABCO should not be enough to prevent the remaining 95% of hydroxy lactam proceeding in an uncompromised reaction. These results potentially confirmed our conclusions from the dilution experiments, which suggested there was some acidic activation occurring, and that 5 mol. % of DABCO was sufficient to disrupt that activity. Furthermore, the results seemed to rule out the bimolecular activation concept. Interestingly, the same experiments in $(CHCl_2)_2$ saw an acceleration in reaction rate (entries 3 and 4), which was rationalised by a reaction of DABCO with $(CHCl_2)_2$ to afford DABCO·HCl, which was then acted as a mild acid promoting the reaction.



164 (R^1 = OMe)
165 (R^1 = H)

161 (R^1 = OMe)
162 (R^1 = H)

164 (R^1 = OMe)
165 (R^1 = H)

168 (R^1 = OMe)
169 (R^1 = H)

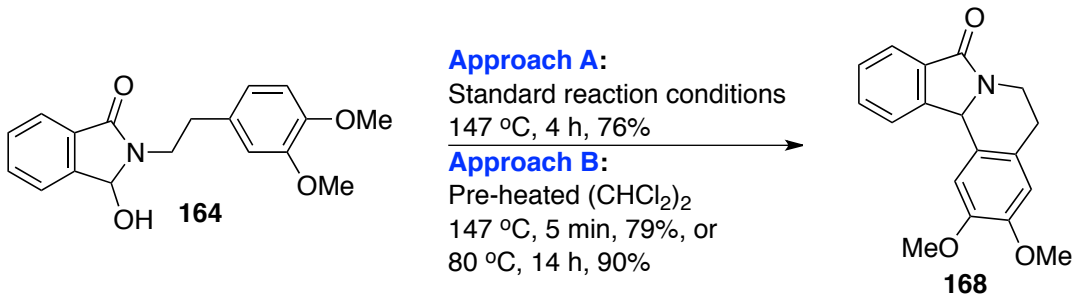
Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield)
1	**164**	Xylene, 139 °C, DABCO (1.5 eq.), 60 min	**161** (100%), **164** (0%), **168** (0%)
2	**164**	Xylene, 139 °C, DABCO (5 mol. %), 60 min	**161** (100%), **164** (0%), **168** (0%)
3	**165**	$(CHCl_2)_2$, 147 °C, DABCO (1.5 eq.), 80 min	**162** (0%), **165** (0%), **169** (100%)
4	**165**	$(CHCl_2)_2$, 147 °C, DABCO (5 mol. %), 80 min	**162** (0%), **165** (3%), **169** (97%)

Table 7. Effect of the addition of DABCO in the progress of α-amidoalkylations.

2.5.3. Investigations into *In Situ* Acid Generation

Up to this point, the mechanistic investigations suggested the $(CHCl_2)_2$ system was proceeding differently to the xylene system. Dilution of the reaction mixture in the xylene series had a profound impact upon the reaction progress, while in the $(CHCl_2)_2$ series, the effect was negligible (table 6). We began to suspect HCl may be evolved via a thermal degradation of $(CHCl_2)_2$ during the heating of the solvent. It was rationalised that if this was the case, the concentration of HCl generated would increase with increasing reaction times, and this seemed to explain why the less reactive substrates were successfully afforded in $(CHCl_2)_2$, where xylene failed. We discovered both reaction rates and scope of the chemistry increased with the use of a preheated $(CHCl_2)_2$

solvent (see table 8). It was thought the cause of this was the *in situ* preparation of dry HCl via a thermal degradation of $(CHCl_2)_2$, which then proceeded to act as an acidic initiator for the reaction.



Scheme 45. The effect of pre-heating $(CHCl_2)_2$ on α-amidoalkylations.

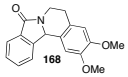
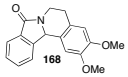
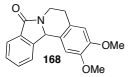
Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield)
1	**164**	$(CHCl_2)_2$, 147 °C, 240 min	 (76%)
2	**164**	Pre-heated $(CHCl_2)_2$, 147 °C, 5 min	 (79%)
3	**164**	Pre-heated $(CHCl_2)_2$, 80 °C, 14 h	 (90%)

Table 8. Results of reactions performed in "activated" $(CHCl_2)_2$ in intramolecular *N*-acyliminium ion cyclizations.[a]

2.6. Further Examples: Scope of "Reagent-Free" *N*-Acyliminium Ion Chemistry

Inspired by the recent report of polyfluorinated alcohols mediating Friedel-Crafts reactions as a result of their mild acidity and high polarizing power,[62,66] we began to investigate their application to reactions involving an *N*-acyliminium ion intermediate. Up to this point, we had found modest activity in TFE and HFIP, but had discovered $(CHCl_2)_2$ to be a remarkably good mediator of these reactions. We had performed a small number of tentative mechanistic studies in order to understand the origin of this unprecedented occurrence. The results of these mechanistic studies revealed the *in situ* generation of dry HCl via a thermal decomposition of the reaction solvent, $(CHCl_2)_2$. While not strictly a "reagent-free" approach, the protocol was providing excellent results in a small number of α-amidoalkylation reactions. We wanted to explore the scope of this chemistry and prepared a more diverse set of substrates to be probed.

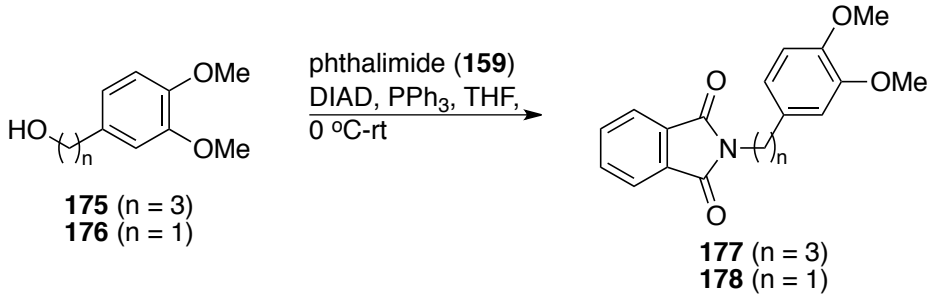
[a] The results presented in table 8 are courtesy of Dr C. Taillier, Univ. Le Havre.

2.6.1. Scope of the Linker Length

We had successfully performed intramolecular α-amidoalkylations for the synthesis of a new 6-membered ring, and it was a natural progression to question whether five and seven-membered rings were accessible via this approach.

2.6.1.1. Synthesis of Precursors

As previously, we favoured the Mitsunobu approach for the alkylation of phthalimide over the Gabriel synthesis, and used alcohols **175** and **176** to afford imides **177** and **178** respectively (see scheme 46 and table 9).



175 (n = 3)
176 (n = 1)

177 (n = 3)
178 (n = 1)

Scheme 46. Synthesis of imides **177** and **178** from alcohols **175** and **176** using a Mitsunobu protocol.

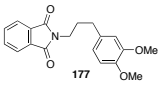
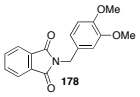
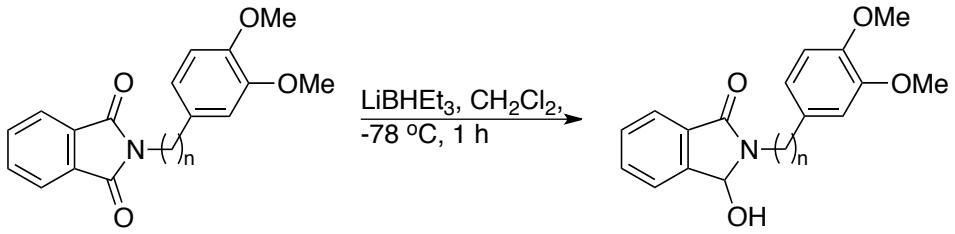
Entry	Imide (1.2 eq.)	Alcohol (1.0 eq.)	Reaction conditions	Reaction product (yield)
1	Phthalimide	**175**	DIAD (1.2 eq.), PPh_3 (1.2 eq.), THF, 24 h	 (56%)
2	Phthalimide	**176**	DIAD (1.2 eq.), PPh_3 (1.2 eq.), THF, 15 h	 (41%)

Table 9. Synthesis of imides **177** and **178**.

With the imides in hand, our $LiBHEt_3$ reduction protocol afforded hydroxy lactams **179** and **180** (scheme 47 and table 10).



177 (n = 3)
178 (n = 1)

179 (n = 3)
180 (n = 1)

Scheme 47. Synthesis of hydroxy lactams **179** and **180** from imides **177** and **178** using a $NaBH_4$ reduction protocol.

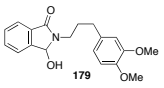
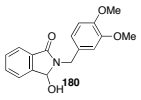
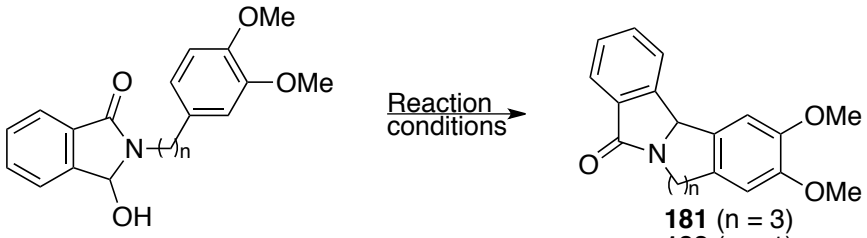
Entry	Imide (eq.)	Reaction conditions	Reaction outcome (yield)
1	**177**	$LiBHEt_3$ (1.1 eq.), CH_2Cl_2, -78 °C, 1 h	 (59%)
2	**178**	$LiBHEt_3$ (1.1 eq.), CH_2Cl_2, -78 °C, 1 h	 (61%)

Table 10. Synthesis of hydroxy lactams **179** and **180**.

2.6.1.2. α-Amidoalkylations

With the desired hydroxy lactams in hand, we subjected **179** to refluxing $(CHCl_2)_2$ which rapidly afforded us with the desired lactam **181** (table 11, entry 1). Hydroxy lactam **180** proved more troublesome and ultimately unsuccessful (entries 2-3), despite the comparative ease at which 5-membered rings are formed via other approaches. Even in a highly successful TFE/TFA protocol (*vide infra*), the reaction was not successful, and the competing reaction of TFE trapping the *N*-acyliminium ion was seen (entry 3). The building of a three-dimensional model of the *N*-acyliminium ion precursor to **182** using a modelling kit highlighted a high degree of strain for access of the aryl ring to the electrophilic centre, which appears to be inaccessible in this system.



179 (n = 3)
180 (n = 1)

181 (n = 3)
182 (n = 1)

Scheme 48. The effect of linker length on α-amidoalkylation

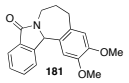
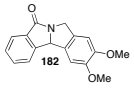
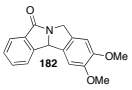
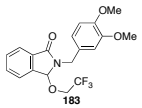
Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield)
1	**179**	$(CHCl_2)_2$, 147 °C, 105 min	 (96%)
2	**180**	$(CHCl_2)_2$, 147 °C, 8 h	 (0%)[a]
3	**180**	TFE, 5 mol. % TFA, 78 °C, 4 h	 (0%)  (100%)

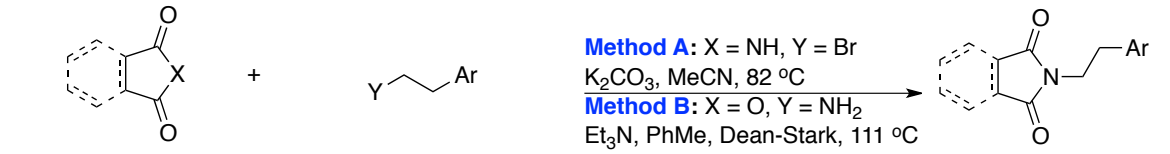
Table 11. *N*-acyliminium ion transformations achieved in "acid-free" and "catalytic acid" conditions. [a]product unidentified.

2.6.2. Scope of the Nucleophile

Up to this point, we had used 3-methoxyphenyl and 3,4-dimethoxyphenyl nucleophiles for the α-amidoalkylations of *N*-acyliminium ions in our system, and we wanted to test the scope of more nucleophiles.

2.6.2.1. Synthesis of Precursors

In our inventory of chemicals, we had phenethyl bromide **186** and thiopheneethyl amine **187** which we proposed we could utilise to further test the scope of our protocol. **168** was reacted with phthalimide and **187** was reacted with phthalic anhydride (**184**) and succinic anhydride (**185**) to afford imides **188**-**190** (see scheme 47 and table 12).



159 (X = NH, phthaloyl)
184 (X = O, phthaloyl)
185 (X = O, succinyl)

186 (Y = Br, Ar = Ph)
187 (Y = NH_2, Ar = 2-thiophene

188 (Ar = Ph, phthaloyl)
189 (Ar = 2-thiophene, phthaloyl)
190 (Ar = 2-thiophene, succinyl)

Scheme 49. The synthesis of imides **188**-**190** using Gabriel and anhydride condensation approaches.

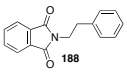
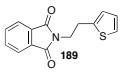
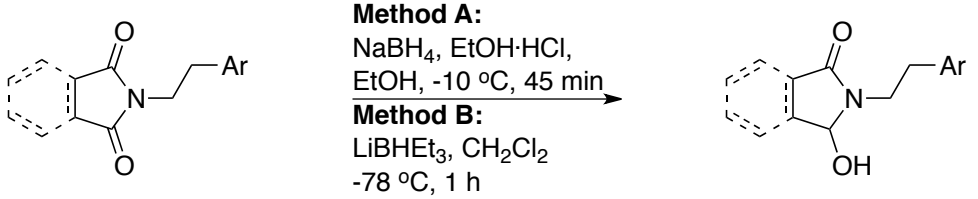
Entry	Dicarbonyl	Aryl	Reaction conditions	Reaction outcome (yield)
1	Phthalimide **159** (1.5 eq.)	**186** (1.0 eq.)	K_2CO_3 (1.8 eq.), MeCN, 82 °C, 45 h	 (66%)
2	Phthalic anhydride **184** (1.0 eq.)	**187** (1.2 eq.)	Et_3N, (0.2 eq.) PhMe, Dean-Stark, 111 °C, 16 h	 (68%)
3	Succinic anhydride **185** (1.0 eq.)	**187** (1.2 eq.)	Et_3N (0.2 eq.), PhMe, Dean-Stark, 111 °C, 18 h	 (61%)

Table 12. The synthesis of imides **188**-**190**.

With our imides in hand, we were able to access the desired hydroxy lactams with a combination of our $NaBH_4$ and $LiBHEt_3$ protocols, since we saw poor reactivity in the succinimide series as before (table 3, entry 4) for the synthesis of hydroxylactam **146** (see scheme 48 and table 13).



188 (Ar = Ph, phthaloyl)
189 (Ar = 2-thiophene, phthaloyl)
190 (Ar = 2-thiophene, succinimyl)

191 (Ar = Ph, phthaloyl)
192 (Ar = 2-thiophene, phthaloyl)
193 (Ar = 2-thiophene, succinimyl)

Scheme 50. The synthesis of hydroxy lactams **191**-**193** from imides **188**-**190**.

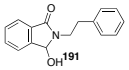
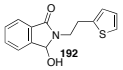
Entry	Imide (1.0 eq.)	Reaction conditions	Reaction outcome (yield)
1	**188**	$NaBH_4$ (1.5 eq.), EtOH·HCl, EtOH, -10 °C, 1 h	 (94%)
2	**189**	$NaBH_4$ (1.5 eq.), EtOH·HCl, EtOH, -10 °C, 1 h	 (82%)
3	**190**	$LiBHEt_3$ (1.1 eq.), CH_2Cl_2, -78 °C, 1 h	 (63%)

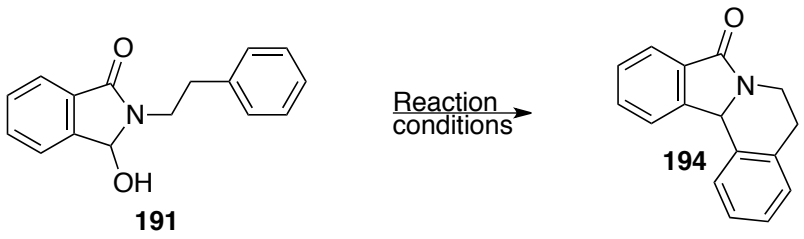
Table 13. The synthesis of hydroxy lactams **191**-**193**.

2.6.2.2. α-Amidoalkylations

Up to this point, the only successful reactions achieved were those with methoxy activated phenyl rings, and we sought to investigate the scope of other nucleophiles.

Phenyl Nucleophile

We questioned whether an unactivated arene such as phenyl would be capable of reacting in α-amidoalkylations using our conditions. There is precedent of a successful $Bi(OTf)_3$ promoted reaction of phenethyl hydroxy lactam **191** reported in the literature.[69] We were disappointed to see a failure in our previously successful thermal $(CHCl_2)_2$ conditions towards the corresponding lactam **194**, despite a prolonged reaction time (table 14, entry 1). We isolated the starting material, hydroxy lactam **191** as the sole product of the reaction. It was proposed the H_2O evolved in the generation of the *N*-acyliminium ion (the formation of which was surely not affected by the electronics of the pendant aryl group) was more nucleophilic than the aromatic (and more so than the $HO\text{-}Bi(OTf)_3^-$ from the literature example), which could explain the failure of this reaction. We considered whether a dehydrating additive, such as Na_2SO_4 (which is negligibly acidic) could remove water from the reaction mixture and hence prevent this process of the leaving group quenching the *N*-acyliminium before the phenyl group can. Unfortunately, the addition of Na_2SO_4 also failed to facilitate access to lactam **194** (entry 2).



Scheme 51. The attempted synthesis of lactam **194** from hydroxy lactam **191**.

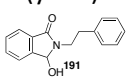
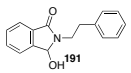
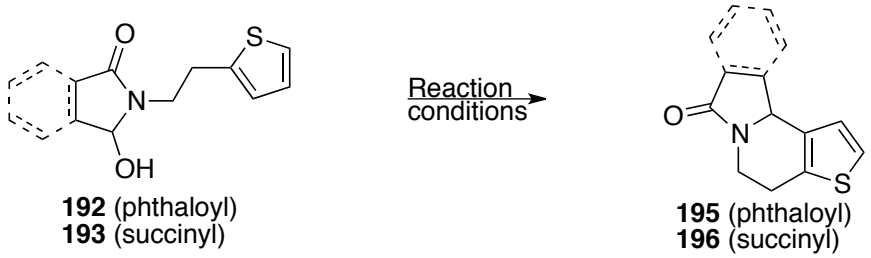
Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield)
1	**191**	$(CHCl_2)_2$, 147 °C, 6 h	 (>99%)
2	**191**	$(CHCl_2)_2$, Na_2SO_4, 147 °C, 12 h	 (>99%)

Table 14. Attempts toward the synthesis of lactam **194**.

Thiophene Nucleophile

Using a pendent thiophene nucleophile, we successfully converted hydroxy lactam **192** to its corresponding lactam **195** in refluxing $(CHCl_2)_2$ and xylene (table 15, entry 2 and 3 respectively). As before, a thermal dehydrogenation was observed in the reaction of succinimide derived hydroxy lactam **193** in refluxing xylene (entry 5) however, successful conversion to lactam **196** was possible in $(CHCl_2)_2$ (entry 4).



192 (phthaloyl)
193 (succinyl)

195 (phthaloyl)
196 (succinyl)

Scheme 52. The synthesis of lactams **195** and **196** from hydroxy lactams **192** and **193**.

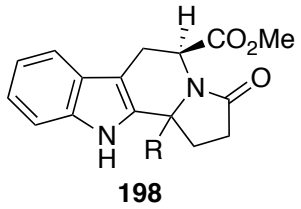
Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield)
1	**192**	TFE, TFA (0.25 eq.), 78 ^{o}C, 2 h	 (>99%)
2	**192**	$(CHCl_2)_2$, 147 ^{o}C, 1 h	 (>99%)
3	**192**	Xylene, 139 ^{o}C, 6 h	 (90%)
4	**193**	$(CHCl_2)_2$, 147 ^{o}C, 3.5 h	 (92%)
5	**193**	Xylene, 139 ^{o}C, 6 h	 (92%)

Table 15. Examples of *N*-acyliminium ion cyclizations with pendant thiophene nucleophiles.

2.6.3. Scope of the Electrophile – Diastereoselective Examples

Stereoselective *N*-acyliminium ion chemistry has proven difficult to achieve, as a consequence of the destruction of any chirality at the reaction centre due to the trigonal planar geometry of the *N*-acyliminium ion. As a result, successful enantioselective approaches are rare. One such successful example of Jacobsen's, was described in section 1.3.3.2. Existing chirality elsewhere in the molecule has been successfully exploited to afford diastereoselective approaches with

moderate to excellent dr. For example Irikawa *et al*.[70] reported their synthesis of trichotonum and its derivatives, the de of the products varying between a preference for *cis* vs. *trans* of 54->99% (see figure 3). Meanwhile, as discussed in section 1.3.3.2., Yamada *et al.* achieved up to >99% de for their diastereoselective cyclization towards tricyclic carbamate systems (scheme 19).

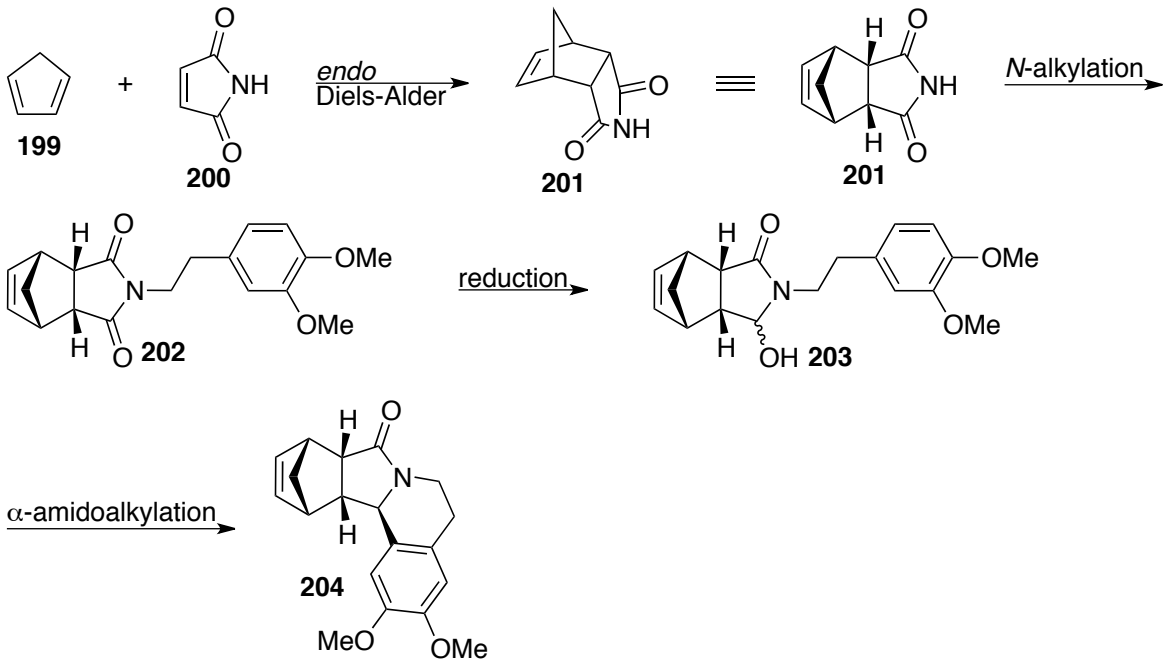


198

Compound	*Trans*:*Cis*
R=CO_2Me	10:90
R=H	>99:<1
R=Me	19:81
R=Et	35:65
R=*n*-Pr	30:70
R=C_6H_5	46:54
R=*i*-Pr	100:0
R=*t*-Bu	100:0

Figure 3. The effect of the nature of R on the diastereoselectivity of *N*-acyliminium ion reactions towards analogues of trichotonum.

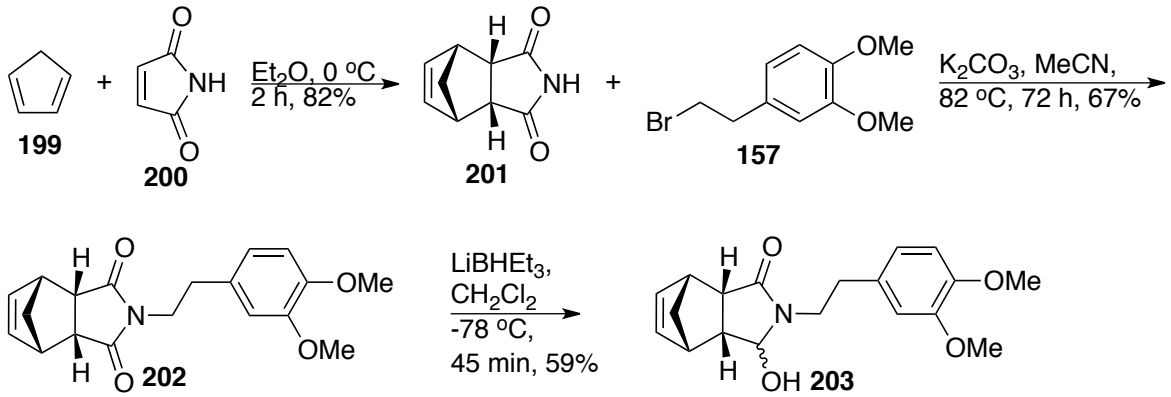
We proposed an *endo* Diels-Alder reaction of cyclopentadiene and maleimide would afford a precursor to a *N*-acyliminium ion with inequivalent faces, which would afford an approach towards facial selectivity in the cyclization step (scheme 51).



Scheme 53. Outline of our diastereoselective approach in intramolecular α-amidoalkylations.

2.6.3.1. Synthesis of Precursors

We proposed a three-step synthetic plan for the synthesis of hydroxy lactam **203** (scheme 52). Using freshly cracked cyclopentadiene **199**, an *endo* Diels-Alder reaction afforded us with imide **201**. Using the Gabriel alkylation protocol and subsequent $LiBHEt_3$ reduction, we were afforded with hydroxy lactam **203**.



Scheme 54. Synthesis of hydroxy lactam **203**.

2.6.3.2. α-Amidoalkylations

Application of hydroxy lactam **203** to our reaction conditions provided us with quantitative access to lactam **204** with >99% de (as determined by the absence of a second diastereoisomer in the ^1H NMR spectrum) (table 16, entry 1). Unfortunately, a successful reaction was not achieved in refluxing xylene (entry 2) as we had seen in the succinyl series of experiments.

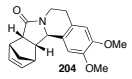
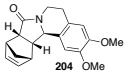
Entry	Hydroxy lactam	Reaction conditions	Reaction outcome (yield)
1	**203**	$(CHCl_2)_2$, 147 °C, 1 h	 (>99%) de = >99%[a]
2	**203**	Xylene, 139 °C, 16 h	 (0%)

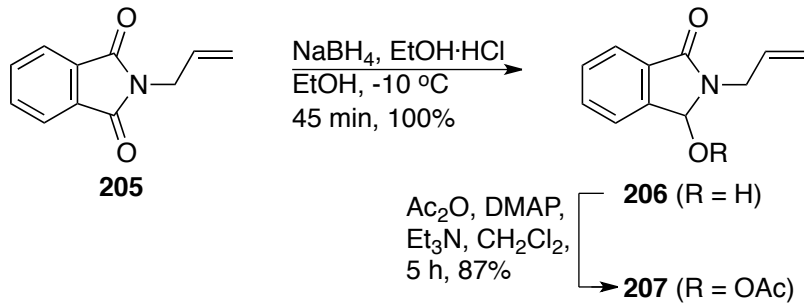
Table 16. Diastereoselective *N*-acyliminium ion cyclizations. [a]de determined by ^1H NMR spectrometry.

2.6.4. Intermolecular Reactions

Up to this point, only intramolecular reactions had been explored in this "reagent-free" approach, and it was desirable to demonstrate success with the use of other π-nucleophiles in intermolecular reactions. Due to their stability and broad range, enols and keto-enols (NuH) derived from ketones and 1,3-dicarbonyls respectively were chosen as the test agents.

2.6.4.1. Synthesis of Precursors

We were provided with imide **205** from our collaborators[b] which we reduced using our $NaBH_4$ protocol to access hydroxy lactam **206**. The requirement for a more reactive *N*-acyliminium ion source (*vide infra*) was achieved with the acylation of **206** to *N*,*O*-acetoxy lactam **207**. These reactions are described in scheme 53.

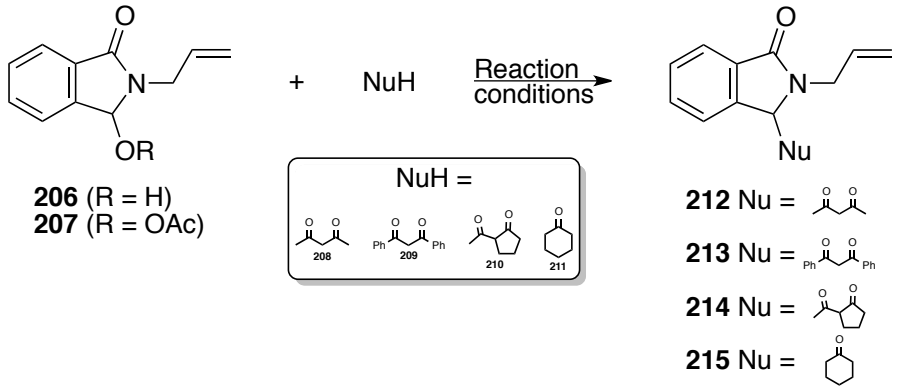


Scheme 55. Reduction of imide **205** to hydroxy lactam **206** and acylation to *N*,*O*-acetoxy lactam **207**.

2.6.4.2. α-Amidoalkylations

In applying our protocol to intermolecular α-amidoalkylations, we were disappointed to see no conversion using hydroxy lactam **206**. We questioned whether a more reactive *N*-acyliminium ion precursor would facilitate these reactions, and acylation of the parent hydroxy lactam to *N*,*O*-acetoxy lactam **207** did enable successful reaction with various enol and keto enol nucleophiles (scheme 54 and table 17). This success may be due to the increased acidity of the system, due to the generation *in situ* of 1 eq. of AcOH during the progress of *N*-acyliminium ion formation, or the decreased nucleophilicity of AcOH vs. H_2O in quenching the *N*-acyliminium ion.

[b] Imide **205** provided by Vincent Dalla, University of Le Havre. November 2009.



206 (R = H)
207 (R = OAc)

Scheme 56. Intermolecular α-amidoalkylations.

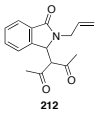
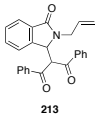
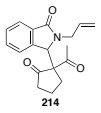
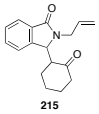
Entry	*N*,*O*-Acetoxy lactam	NuH	Reaction conditions	Reaction outcome (yield)
1	**207**	**208** (1.5 eq.)	$(CHCl_2)_2$, 147 °C, 7.5 h	 (100%)
2	**207**	**209** (1.5 eq.)	$(CHCl_2)_2$, 147 °C, 14.5 h	 (77%)
3	**207**	**210** (1.5 eq.)	$(CHCl_2)_2$, 147 °C, 8 h	 (87%)
4	**207**	**211** (3.0 eq.)	$(CHCl_2)_2$, 147 °C, 14 h	 (65%)

Table 17. Results of the intermolecular *N*-acyliminium ion chemistry of acetoxy lactam **207** and a range of carbonyl and 1,3-dicarbonyl compounds.[c]

2.6.4.2. A Successful Return of Hydroxy Lactams

With the discovery of a thermal degradation of $(CHCl_2)_2$ and the observation that preheated $(CHCl_2)_2$ improves the efficiency of this chemistry (table 8), pre-heated $(CHCl_2)_2$ was utilised in the reaction of hydroxy lactam **206** and a series of NuH compounds – the substrates which previously had failed in our standard $(CHCl_2)_2$ conditions. We chose the most reactive nucleophile – acetylacetone (**208**) and the least reactive nucleophile – cyclohexanone (**211**) to test the scope of this system. We were pleased to observe the corresponding products on this occasion (table 18,

[c] Results courtesy of Dr C. Tallier, University of Le Havre.

entries 1-2). Having seen rate enhancements in the intramolecular series of reactions, we again employed μW irradiation in an attempt to further improve the efficiency of these reactions, and chose the same nucleophiles, **208** and **211** (entries 3-4).

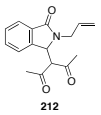
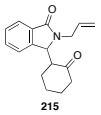
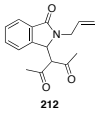
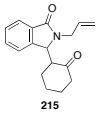
Entry	Hydroxy lactam	NuH	Reaction conditions	Reaction outcome (yield)
1[d]	**206**	**208** (1.5 eq.)	Pre-heated $(CHCl_2)_2$, 147 °C, 6 h	 **212** (87%)
2[d]	**206**	**211** (3.0 eq.)	Pre-heated $(CHCl_2)_2$, 147 °C, 14 h	 **215** (74%)
3	**206**	**208** (1.5 eq.)	μW, $(CHCl_2)_2$, 147 °C, 300 W, 30 min	 **212** (>99%)
4	**206**	**211** (3.0 eq.)	μW, $(CHCl_2)_2$, 147 °C, 300 W, 60 min	 **215** (>99%)

Table 18. Comparison of thermal vs. μW heating in intermolecular *N*-acyliminium ion reactions.

As can be seen from the results presented in table 18, an impressive enhancement in the preparation of substrates **212** and **215** was observed using μW irradiation. A 12 and 14 fold rate enhancement for the synthesis of **212** and **215** respectively and an improvement in yield compared to our pre-heated conditions was observed. This is far beyond the observed rate enhancements for μW irradiated intramolecular α-amidoalkylations in $(CHCl_2)_2$, and is an exciting observation. In comparison to literature precedent, the use of 1 mol. % of $Sn(NTf_2)_4$ yielded lactam **212** in >99% yield after 4 h at 60 °C[46] and this demonstrates once again that this "reagent-free" approach under μW irradiation can match and, arguably improve upon procedures using highly active Lewis acids.

2.7. Further μW Examples

As the initial series of intramolecular reactions and the subsequent intermolecular reactions showed impressive rate enhancements with μW irradiation compared to traditional heating, we

[d] Results courtesy of Dr C. Taillier, University of Le Havre.

decided to apply μW irradiation to some more intramolecular α-amidoalkylation reactions (table 19). In line with previous observations, a definite trend in both yield and reaction rate enhancements can be seen by the results presented.

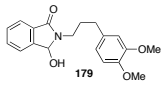
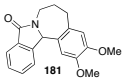
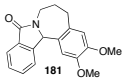
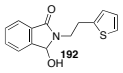
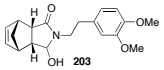
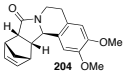
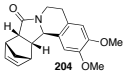
Entry	Hydroxy lactam	Reaction conditions		Reaction outcome (yield %)	
		Thermal	*μW*	*Thermal*	*μW*
1	 179	$(CHCl_2)_2$, 147 °C, 105 min	$(CHCl_2)_2$, 147 °C, 300 W, 60 min	 181 (96%)	 181 (97)
2	 192	$(CHCl_2)_2$, 147 °C, 60 min	$(CHCl_2)_2$, 147 °C, 300 W, 38 min	 195 (>99%)	 195 (>99%)
3	 203	$(CHCl_2)_2$, 147 °C, 60 min	$(CHCl_2)_2$, 147 °C, 300 W, 38 min	 204 (90%)	 204 (>99%)

Table 19. Comparison of reaction times and yields with thermal vs. μW heating.

3. Conclusion

To summarise, we report the discovery of *N*-acyliminium ion chemistry proceeding without the addition of an external acid source, with activity seen in 4 solvents of a small solvent screen – xylene, TFE, HFIP and $(CHCl_2)_2$. The most impressive results in terms of reaction yield and time have been afforded from reflux in $(CHCl_2)_2$, and improved upon further with μW irradiation. Tentative mechanistic investigations have revealed the reactions involving $(CHCl_2)_2$ are catalysed by the *in situ* generation of HCl via a thermal degradation of the solvent. Evidence for this conclusion can be found in the successful cyclization of hydroxy lactam **165** in significantly reduced reaction time and temperature using pre-heated $(CHCl_2)_2$ (table 8). The explanation of the, albeit less successful xylene protocol, has been rationalised by acidic glassware residues acting as a catalytic reaction activator. Evidence for this conclusion can be found in the failure of cyclization of hydroxy lactam **164** under standard conditions in the presence of sub-stoichiometric quantities of DABCO (table 7). Further investigation has identified there most certainly is activation of the leaving group to facilitate the formation of the *N*-acyliminium ion and has ruled out the possibility of a bimolecular activation pathway. The results of this $(CHCl_2)_2$ protocol approach those reported in the literature for acid promoted reactions in some instances. Upon μW irradiation, these activities match and improve upon established literature utilising acidic activation in both % conversion and reaction time.

Finally, Dalla *et al.* reported recently phthalimide derived *N*-acyliminium ions are poorly reactive under catalytic acidic activation, even with the use of the new "superacidic" Lewis acids such as $Sn(NTf_2)_4$.[71] Given the most impressive results of the chemistry reported here involves the phthalimide derived *N*-acyliminium ions, this "reagent-free" approach may have further application given the impressive yields and short reaction times (particularly upon μW irradiation) observed.

Chapter 2

THE TOTAL SYNTHESIS OF PYRROLOQUINOLINE NATURAL PRODUCTS

Marinoquinolines, Aplidiopsamine A and SAR Investigations

1. Introduction

A great deal of research, dating as far back as the mid-20th century has been undertaken in the field of pyrroloquinoline syntheses, given their great prevalence in nature as bioactive alkaloids. This research has continued at a pace, with several recent publications in the fields of synthesis[72,73] and isolation[74,75] of related molecules. Our interest in the synthesis of 3*H*-pyrrolo[2,3-*c*]quinolines specifically, was prompted by the isolation of aplidiopsamine A[74] and marinoquinolines A-F[75] from natural sources – the only reported natural products of this type (figure 4). Marinoquinoline A was first isolated from the marine gliding bacteria *Rapidithrix thailandica* TISTR 1742 by Plubrukarn *et al.* in 2008.[76] The authors report the compound to have interesting inhibitory activity upon acetylcholinesterase – important in the termination of neural synaptic transmissions (IC_{50} = 4.9 µM *vs. Torpedo californica*). Therapeutically, acetylcholinesterase (AChE) is an important target for the treatment of glaucoma (for example, by the alkaloid physostigmine) and Alzheimer's disease (for example, by the synthetic drug donepazil).[77] Shortly after the isolation of marinoquinoline A, aplidiopsamine A was isolated from the Australian ascidian *Aplidiopsis confluata*, and bears the 3*H*-pyrrolo[2,3-*c*]quinoline heterocycle attached to adenine via a methylene linker (see figure 4). Initial screening revealed interesting and selective cytotoxic activity against *Plasmodium falciparum* comparative to human cells – an interesting discovery, given the emergence of strains resistant to chloroquine.[74] Shortly after this discovery, Müller *et al.* reported the isolation of marinoquinolines A-F from the bacterium *Ohtaekwangia kribbensis*. These 3*H*-pyrrolo[2,3-*c*]quinolone natural products were substituted by aliphatic, aromatic and heteroaromatic groups in position 4 of a heterocyclic skeleton, and in addition to activity against *Plasmodium falciparum*, showed interesting cytotoxic activity and weak antibacterial and antifungal activity.

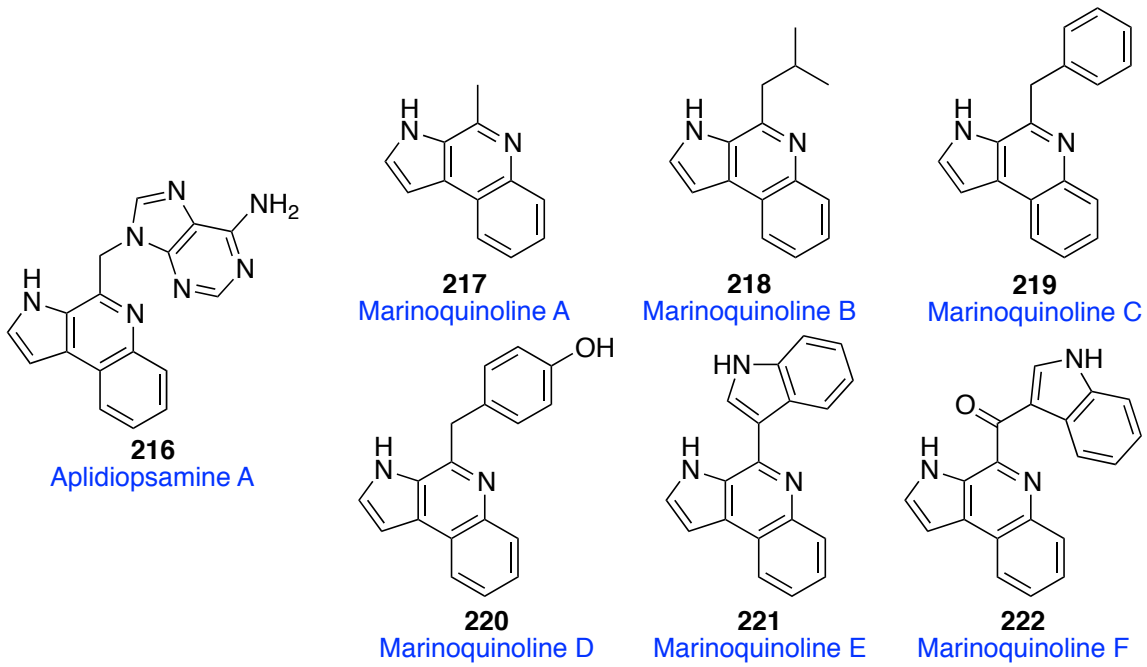
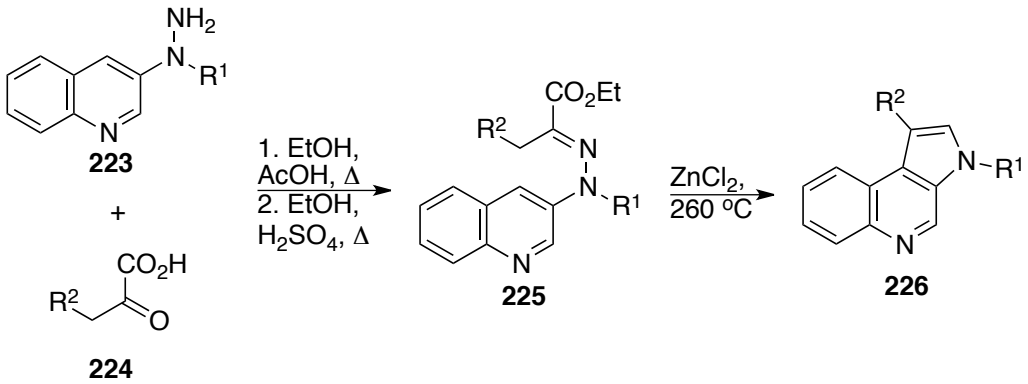


Figure 4. The structure of aplidiopsamine A and marinoquinolines A-F.

Given the recent discoveries of natural products of this class, we began exploring synthetic routes to access them, and a small library of analogues.

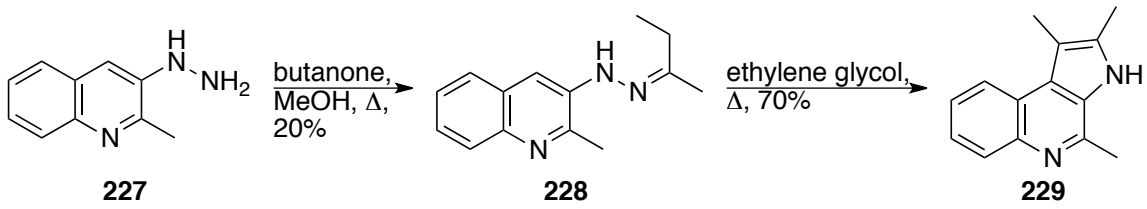
1.1 Examples from the Literature for the Preparation of 3*H*-pyrrolo[2,3-*c*]quinolines

In 1961, Govindachari *et al.* reported the preparation of a series of 3*H*-pyrrolo[2,3-*c*]quinolines and indolo[2,3-*c*]quinolines via a Fischer indole synthesis.[78] Despite the success of this approach, very high temperatures (>200 °C) and 8 eq. of $ZnCl_2$ were required, with widely varying degrees of success (yields of 7-77%) (scheme 55).



Scheme 55. Govindachari's approach to 3*H*-pyrrolo[2,3-*c*]quinolines.

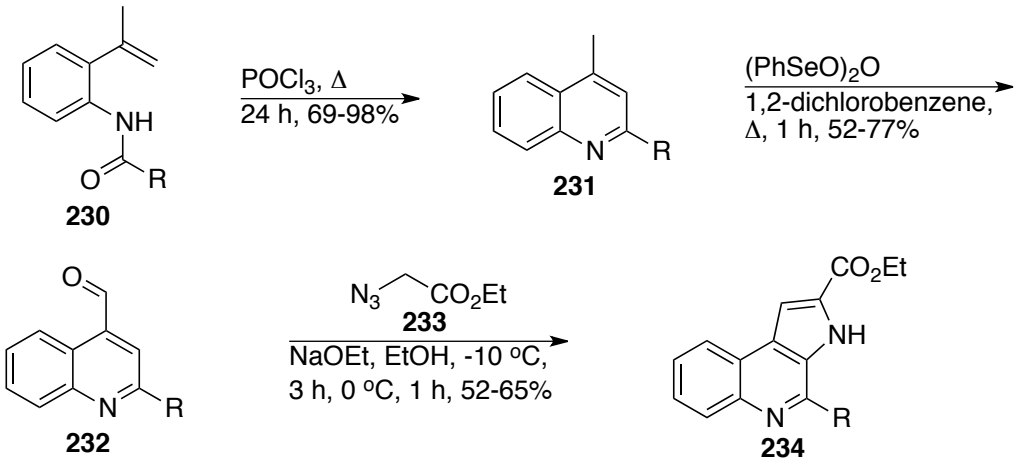
In 1976, Parrick *et al.* described their approaches to pyrrolo[3,2-*b*]-, pyrrolo[3,2-*c*]-, and pyrrolo[2,3-*c*]quinolines involving the acid mediated pyrrole formation from 3-amino-2-methylquinoline and triethyl orthoformate.[79] This procedure appears to be an improvement on Govindachari's, with reactions in saturated ethanolic HCl affording 1*H*-pyrrolo[3,2-*b*]quinolines and 1*H*-pyrrolo[3,2-*c*]quinolines in good yield. 3*H*-Pyrrolo[2,3-*c*]quinolines were prepared in the same fashion affording the corresponding products in 70-75% yield (scheme 56).



227 **228** **229**

Scheme 56. Parrick's approach to 3*H*-pyrrolo[2,3-*c*]quinolones.

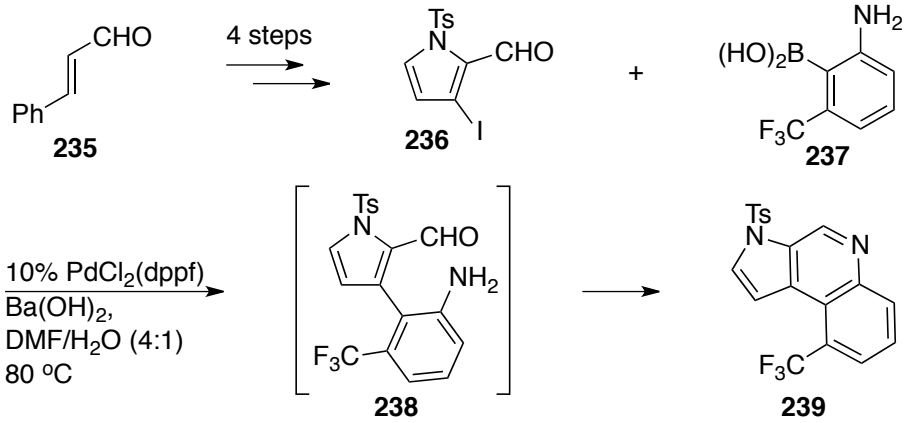
In 1993, Molina *et al.* prepared a small selection of 3*H*-pyrrolo[2,3-*c*]quinolines via a Morgan-Walls reaction, followed by benzylic oxidation and Paal-Knorr pyrrole synthesis (scheme 57).[80]



230 **231** **232** **234**

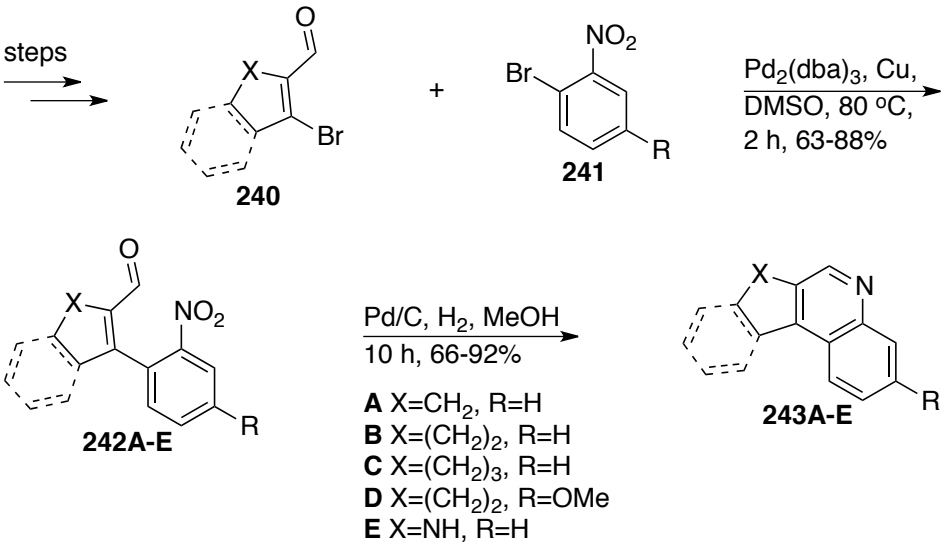
Scheme 57. Molina's approach to 3*H*-pyrrolo[2,3-*c*]quinolines.

Touillaux applied a Suzuki-Miyaura cross-coupling reaction of boronic acids to synthetically prepared pyrroles followed by an intramolecular reductive cyclization (scheme 58).[81]



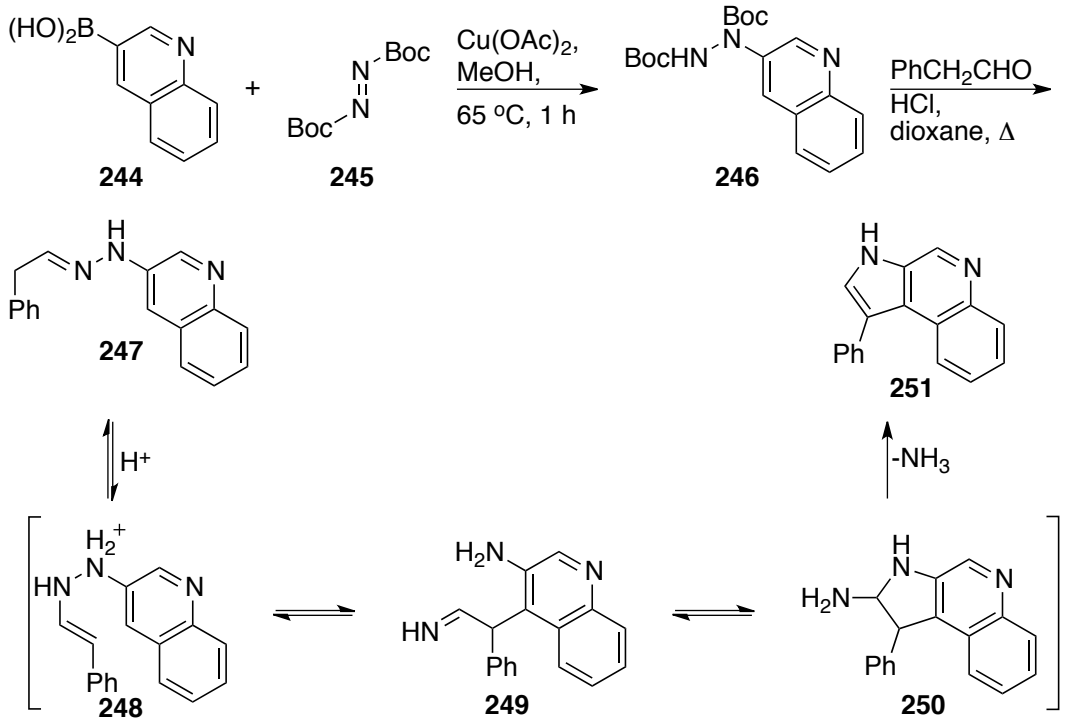
Scheme 58. Touillaux's approach to 3*H*-pyrrolo[2,3-*c*]quinolines.

Banwell *et al.*, in their recent syntheses of quinolines prepared related quinoline compounds via Ullmann cross-coupling reaction followed by a reductive condensation/cyclization, much like that of Touillaux (scheme 59).[82]



Scheme 59. Banwell's approach to 3*H*-pyrrolo[2,3-*c*]quinolines.

Very recently, Beveridge *et al.* report their very diverse approach towards pyrrolo-fused heterocycles, including pyrroloquinolines via a copper-catalyzed chemistry (scheme 60).[83] The Fischer reaction is the same approach as that of Govindachari *et al.* 41 years previously.



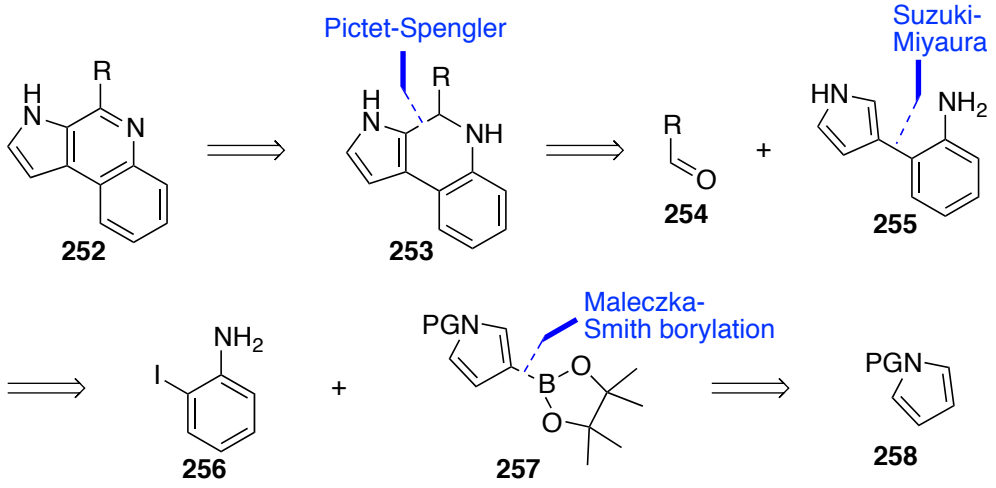
Scheme 60. Beveridge's approach to 3*H*-pyrrolo[2,3-c]quinolines

1.2. Our Synthetic Approach

Retrosynthetic analysis of the pyrroloquinoline heterocycle and analysis of the literature highlighted several potential routes towards the desired targets. Of the recent literature, Molina's approach[80] was interesting, as it clearly showed substitution of the desired position of the pyrroloquinoline was possible, but the authors described some incompatibilities in the benzylic oxidation and we would have to develop a method remove the ethyl ester from the pyrrole. The condensation/cyclizations of Toulliaux[81] and Banwell[82] were appealing, but we were concerned since there were no examples of such reactions proceeding with ketones (instead of aldehydes), which would be required for the desired substitution at position 4 of the quinoline.

We were not entirely satisfied with the literature procedures towards the 3*H*-pyrrolo[2,3-*c*]quinolines we were interested in preparing. During retrosynthetic analysis of the targets, we envisioned a potential Pictet-Spengler disconnection (scheme 61). In exploring this possibility, we discovered the isolation of pyrroloaniline **255** by Plubrukarn *et al.* during their attempts to isolate marinoquinoline A from the marine gliding bacteria *Rapidithrix thailandica* (figure 5).[76] They also report the isolation of dihydroquinoline **259**, which they report to be an artifact of the extraction process via a Pictet-Spengler reaction with acetone, since a repeated extraction in the absence of

acetone failed to provide **259**. This observation is interesting, since it indicates the synthesis of a related pyrroloquinoline from pyrroloaniline **255** via a presumed Pictet-Spengler reaction. We proposed the use of the corresponding aldehydes would provide access to the desired pyrroloquinolines via their dihydroquinoline counterparts using a Pictet-Spengler cyclization and subsequent oxidation. Furthermore, we reasoned a Pictet-Spengler approach would be very amenable to the synthesis of a diverse library of compounds for SAR investigations. Preparation of pyrroloaniline **255** had been reported in the literature via a Suzuki-Miyaura cross-coupling reaction of the corresponding protected pyrroloboronate ester and iodoaniline.[84] We were confident this would be a rapid route towards 3*H*-pyrrolo[2,3-*c*]quinolines, and if suitable, would provide us with a general approach to build a small library of molecules for investigation of SAR.



Scheme 61. Retrosynthetic analysis of 3*H*-pyrrolo[2,3-*c*]quinoline heterocycle.

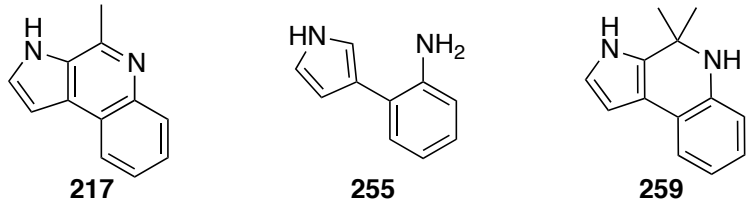
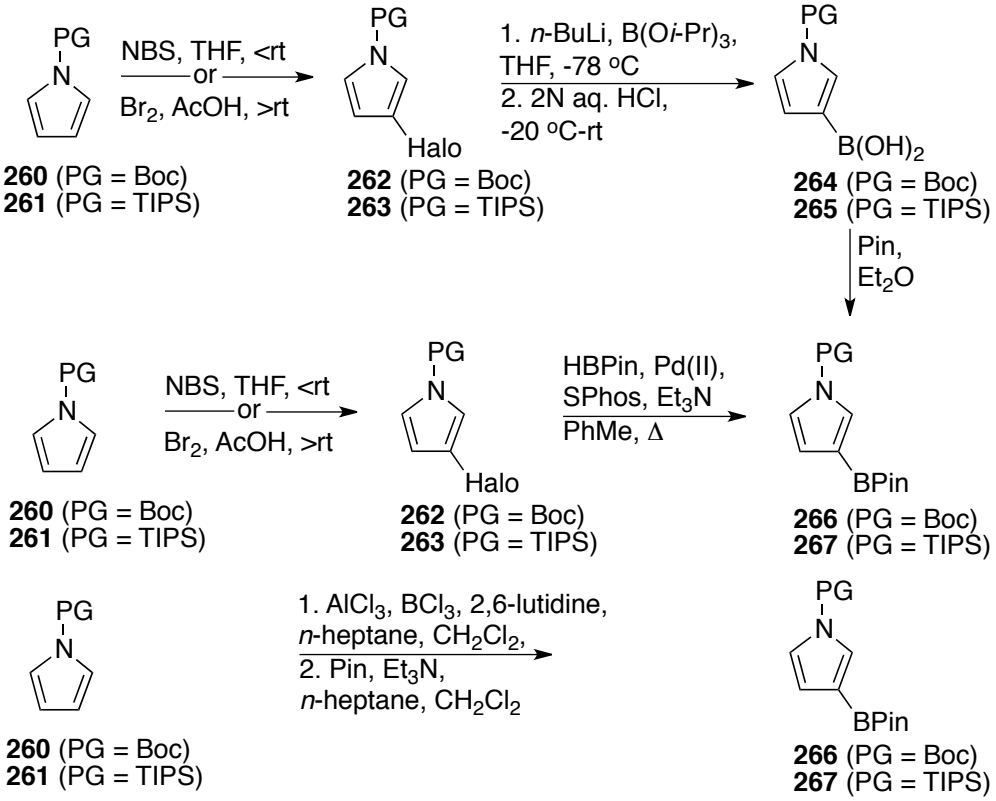


Figure 5. Plubrukarn *et al.*, in isolating marinoquinoline A and pyrroloaniline **255**, also isolated dihydroquinoline **259**, via a presumed Pictet-Spengler reaction of **255** and acetone.

1.3. Suzuki Reactions of Heterocycles

Our initial synthetic concept involved the use of a Suzuki-Miyaura cross-coupling reaction to afford pyrroloaniline **255**, and subsequent Pictet-Spengler reaction to afford the desired pyrroloquinoline architecture **252** via its dihydroquinoline counterpart **253** (scheme 61). Several

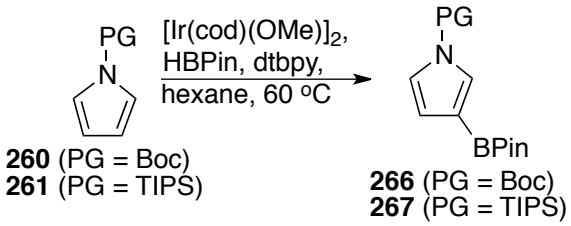
approaches toward the coupling of aryl substrates using Suzuki reactions have been reported in the literature, and involve the use of a halo-aryl and aryl boronic acid/boronate esters. In the case of heterocycles such as thiophene, furan and pyrrole, there are only successful reports of reactions proceeding where the heterocycle bears the boronic acid/boronate ester moiety. While there has been great synthetic endeavour in the area of boronic acid preparation, the preparation of heterocycles of type **264** and **265** remains challenging, since several steps and air/water sensitive reactions are required (scheme 62).



Scheme 62. Different approaches to the borylation of heterocycles, and subsequent Suzuki-Miyaura cross-coupling reactions.

The discovery of direct C-H activation for borylation was first reported independently by Hartwig and Smith at the turn of the millennia, using rhenium and iridium catalysts respectively to isolate terminal pinnacolborane functionalized alkanes in excellent yield.[85–87] This result is of note since it is a one step approach to boronate esters and avoids the use of sensitive substrates. These initial findings were followed by the work of Marder[88] and Smith,[89,90] who utilised rhodium and iridium catalysts respectively to achieve pinnacolborane functionalization of aromatics. The latter results included activated and deactivated aromatic systems in excellent yield. Since these early observations, there has been a huge amount of work performed in this area in methodology,[91–95] total synthesis[84] and in the mechanistic determination of these reactions.[96–98] Key to our interest

is the observation of C3 specific borylations of *N*-Boc and *N*-TIPS pyrrole, accessed selectively in excellent yields thanks to the directing effects of these sterically demanding protecting groups.[94,99] This approach provides a more efficient route to heteroaryl boronic acids in terms of the number of steps compared to more traditional routes discussed in scheme 62 (scheme 63). Suzuki-Miyaura cross-coupling reaction between the boronate **266**/**267** and 2-haloaniline would, in our case afford the key pyrroloaniline intermediate[84] for a prospective Pictet-Spengler cyclization.

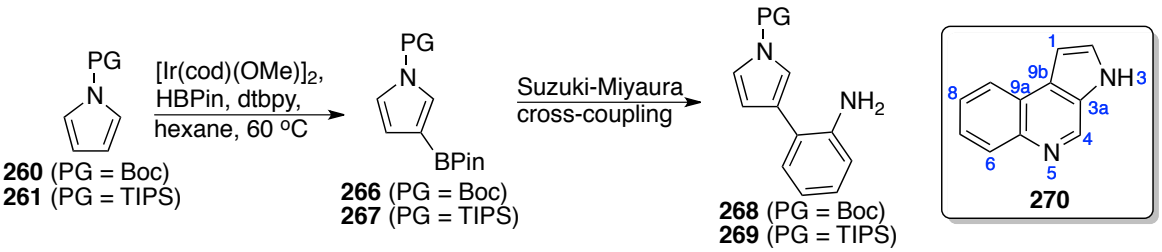


Scheme 63. Regioselective C-H activation for the borylation of pyrroles.

2. Results and Discussion

2.1. Maleczka-Smith Borylation Reaction

Our synthetic strategy required for the synthesis of pyrroloboronate esters from *N*-protected pyrroles, which would in turn undergo Suzuki-Miyaura cross-coupling reactions to form the C9a-C9b bond of the pyrroloquinolines (scheme 64). The C3 selective borylation of pyrroles has been widely reported where bulky protecting groups, such as Boc and TIPS have been employed.[94,100] In the absence of bulky protecting groups, C2 becomes the more substituted position.[100] Maleczka *et al*. report the pre-forming of the active catalyst in a glove box, before conducting the reaction in a Schlenk flask. Our attempts to repeat their results (table 20 entry 1) without a glove box failed (entry 2). We were able to modify their procedure to enable a successful borylation of *N*-protected pyrroles by forming the active catalyst in the reaction, instead of pre-forming the active catalyst and adding it to the reaction later (entries 3-4). Some remarks in the literature indicate this to significantly compromise the reaction, however fortunately this was not the case in our system.[101] Our procedure compared well to that reported in the literature, with boronate esters **266** and **267** afforded in 98% and 87% compared to 98%[95] and 79%[100] for the literature, respectively.



Scheme 64. Proposed route to pyrroloanilines **268** and **269**.

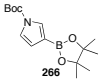
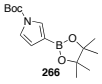
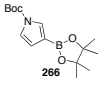
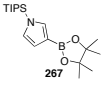
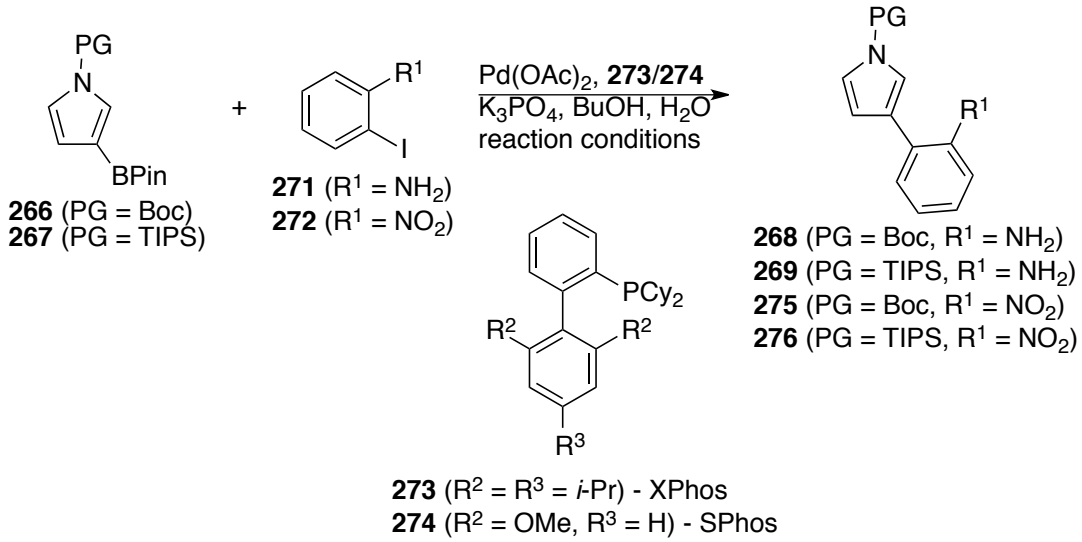
Entry	Pyrrole (1.0 eq.)	Reaction conditions	Reaction outcome (yield)
1[a]	**260**	$[Ir(cod)(OMe)]_2$ (0.015 eq.), dtbpy (0.030 eq.), HBPin (1.25 eq.), hexane, 55 °C, 13 h	 (90%)
2	**260**	$[Ir(cod)(OMe)]_2$ (0.015 eq.), dtbpy (0.030 eq.), HBPin (1.25 eq.), hexane, 55 °C, 16 h	 (0%)
3	**260**	$[Ir(cod)(OMe)]_2$ (0.015 eq.), dtbpy (0.030 eq.), HBPin (2.0 eq.), hexane, 60 °C, 12 h	 (98%)
4	**261**	$[Ir(cod)(OMe)]_2$ (0.015 eq.), dtbpy (0.030 eq.), HBPin (2.0 eq.), hexane, 60 °C, 8 h	 (87%)

Table 20. Maleczka-Smith borylation chemistry. [a]conditions and result from Maleczka *et al*.[94]

2.2. Suzuki-Miyaura Cross-Coupling Reaction

Boronate ester **267** has been previously applied by Gaunt *et al*. to the synthesis of pyrroloaniline **269** to great success (table 21, entry 1).[84] Our attempts at matching this result failed (scheme 65 and table 21 entries 2-5). Meanwhile, attempts to access pyrroloaniline from boronate ester **266** in the Boc series also failed (entries 6-7). Up to this point, the best results we had achieved for pyrroloanilines **268** and **269** was 23% yield in both cases. We are unable to explain why our system failed in comparison to that reported in the literature, but the disappointment of these setbacks was arrested by the knowledge the corresponding transformation with 1-iodo-2-nitrobenzene would be more favourable due to the weakening of the C-I bond as a result of the electronic induction of the nitro group. Indeed, the corresponding nitro products **275** and **276** were afforded from 1-iodo-2-nitrobenzene in the cases of both boronate esters **266** and **267** in excellent yield (89 and 93% respectively, entries 8-9). It can be considered a combination of the electron donating effects of the aniline strengthening the Ar-I bond and a stable coordination of the NH_2 to [Pd] once inserted into the Ar-I bond was responsible for the disappointing conversions observed in the 2-iodoaniline series of experiments. With a free choice of protecting groups on the pyrrole, we initially elected for *N*-Boc protection due to the expected ease of deprotection, and potential for concomitant cleavage during Pictet-Spengler annulation, or Suzuki-Miyaura cross-coupling.



Scheme 65. Suzuki-Miyaura cross-coupling reactions of boronate esters **266** and **267**.

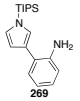
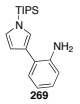
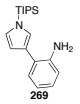
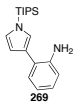
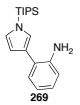
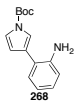
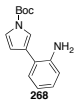
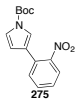
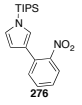
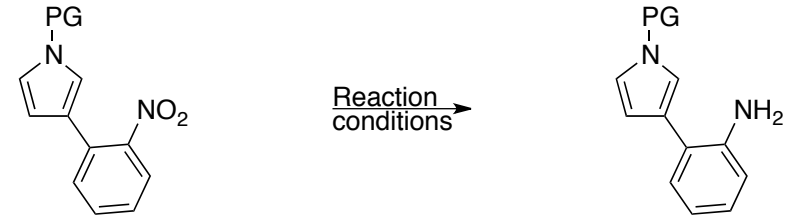
Entry	Boronate ester (1.2 eq.)	Iodo-aryl (1.0 eq.)	Ligand (0.1 eq.)	Reaction conditions	Reaction outcome (yield)
1[a]	**267**	**271**	**274**	100 °C, 2 h	 **269** (82%)
2	**267**	**271**	**273**	100 °C, 4 h	 **269** (0%)
3	**267**	**271**	**273**	35 °C, 20 h	 **269** (0%)
4	**267**	**271**	**273**	60 °C, 16 h	 **269** (15%)
5	**267**	**271**	**274**	60 °C, 12 h	 **269** (23%)
6	**266**	**271**	**273**	100 °C, 2 h	 **268** (0%)
7	**266**	**271**	**274**	60 °C, 20 h	 **268** (23%)
8	**266**	**272**	**274**	60 °C, 12 h	 **275** (93%)
9	**267**	**272**	**274**	60 °C, 12 h	 **276** (89%)

Table 21. Method development of Suzuki-Miyaura reaction. [a]Conditions and result from Gaunt *et al*.[84]

2.3. Nitro Reduction

With a reliable Suzuki protocol in hand, attempts at reduction of the nitro group highlighted the instability of both the pyrrolonitro **275**-**276** and pyrroloaniline compounds **268-269**. Exposing nitro **275** to MeOH, aq. NH_4Cl and Fe at reflux and rt; and MeOH, aq. NH_4Cl and Zn at rt all resulted in degradation (table 22, entries 1-3). We were pleased to observe quantitative conversion using H_2, Pd/C conditions in EtOH after optimisation of the Pd loading (entries 4-5), but were frustrated to discover thermal instability during *in vacuo* concentration. Surprisingly, degradation at temperatures as low as 10 ^oC during *in vacuo* concentration was seen. In an attempt to circumvent this outcome, hydrogenation reduction conditions in EtOAc were successful in protecting the nitro and aniline compounds from degradation, but the reduction was significantly slower (entry 6).



275 (PG = Boc)
276 (PG = TIPS)

268 (PG = Boc)
269 (PG = TIPS)

Scheme 66. Synthesis of pyrroloanilines **275**-**276** from nitro **275**-**276**.

In the interest of time, since the aniline was not deemed stable enough for storage after large-scale preparation, we used EtOH as the solvent and an aqueous extraction in basic conditions afforded access to anilines **268**-**269** in good yield without degradation. Now in possession of a reliable and robust approach towards the desired anilines, we embarked upon Pictet-Spengler method development.

2.4. Pictet-Spengler Reaction

Given the observed sensitivity of pyrrolonitro and pyrroloaniline compounds to mild acidic conditions and temperatures >rt in the reduction and subsequent work-up, we wanted to employ the Pictet-Spengler reactions under very mild conditions. With this in mind, we decided to preserve the protection of the pyrrole, and looked to Lewis acids to mediate these reactions.

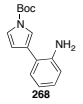
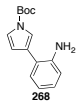
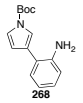
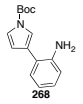
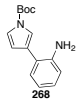
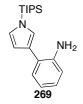
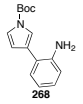
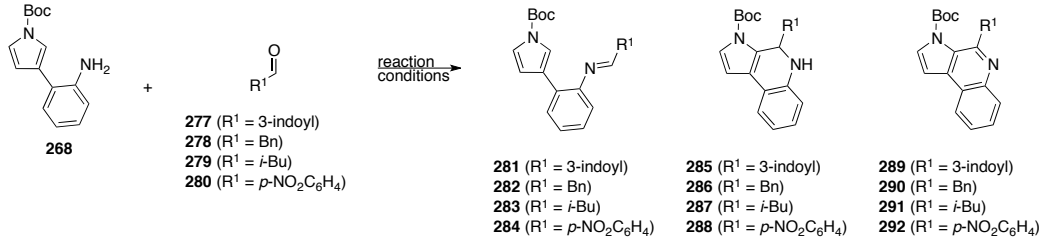
Entry	Nitro	Reaction conditions	Reaction outcome (yield)
1	**275**	Fe (5 eq.), NH_4Cl (5 eq.), MeOH, H_2O, 90 ^oC, 2 h	 (12%)
2	**275**	Fe (5 eq.), NH_4Cl (5 eq.), MeOH, H_2O, 2 h	 (n.d.)
3	**275**	Zn, NH_4Cl, MeOH, H_2O, 2 h	 (n.d.)
4	**275**	Pd/C (20%), H_2, EtOH, 1 h	 (47%)
5	**275**	Pd/C (2%), H_2, EtOH, 45 min	 (quant.)
6	**276**	Pd/C (2%), H_2, EtOH, 45 min	 (quant.)
7	**275**	Pd/C (2 %), H_2, EtOAc, 16 h	 (quant.)

Table 22. Nitro reduction method development. n.d. = not determined, quant. = quantitative (purification not required).

2.4.1. *N*-Boc-Protected Pictet-Spengler Reaction

In a series of test reactions, pyrroloaniline **268** and indole-3-carboxaldehyde (**277**) were subjected to classical imine bond forming conditions (CH_2Cl_2, $MgSO_4$, rt), which failed to provide any imine according to ^1H NMR spectroscopy, due to the inherent low reactivity of this particular aniline and/or aldehyde (table 23, entry 1). This information was useful in our initial selection of Lewis acids, since we would require a 'neutral' Lewis acid – that is one capable of activating both aldehydes and aldimines for both phases of the Pictet-Spengler. We were keen to form the imine and perform the cyclization in one step, since we assumed acidic conditions promoted degradation of pyrroloaniline **268**. The selectivity of various metals for aldehydes *vs.* aldimines was investigated by Kobayashi.[102] Meanwhile, previous research in the group[103] identified the highly successful application of a series of transition metal triflate Lewis acids to the Pictet-

Spengler reaction of tryptamine and tryptophan methyl ester and a series of aldehydes. In particular, $Yb(OTf)_3$, $Y(OTf)_3$ and $Sc(OTf)_3$, were highly active at ~10 mol. % quantities in refluxing CH_2Cl_2. These reactions also allowed for excellent conversion, albeit at a slower reaction rate at rt, and so would be suitable in this case. In method development, pyrroloaniline **268** and various aldehydes were submitted to Pictet-Spengler reactions, the results of which are provided in table 23.



Entry	Aldehyde (1.0 eq.)	Additive	Reaction conditions	Reaction outcome (yield %)
1	**277**	$MgSO_4$	CH_2Cl_2, MeOH, 24 h	-
2	**277**	$Sn(OTf)_2$, (10 mol. %)	THF, 0 ^oC-rt, 2 h	**281** (17), **285** (0), **289** (0)
3	**277**	$Sn(OTf)_2$, (10 mol. %)	MeOH, 20 h	**281** (21), **285** (0), **289** (0)
4	**277**	$Y(OTf)_3$, (20 mol. %)	THF, 16 h	**281** (16), **285** (0), **289** (20)
5	**277**	$Y(OTf)_3$, (20 mol. %)	CH_2Cl_2, 40 ^oC, 1 h	n.r.
6	**278**	$Y(OTf)_3$, (20 mol. %)	CH_2Cl_2, 40 ^oC, 1 h	n.r.
7	**279**	$Y(OTf)_3$, (20 mol. %)	CH_2Cl_2, 40 ^oC, 1 h	**283** (0), **287** (0), **291** (12)
8	**279**	$Y(OTf)_3$, (20 mol. %)	CH_2Cl_2, 0 ^oC-rt, 4 h	**283** (0), **287** (0), **291** (15)
9	**280**	$Y(OTf)_3$, (20 mol. %)	MeCN, 1 h	**284** (11), **288** (51), **292** (0)
10	**279**	$Y(OTf)_3$, (20 mol. %)	MeCN, 1 h	**283** (0), **287** (0), **291** (23)

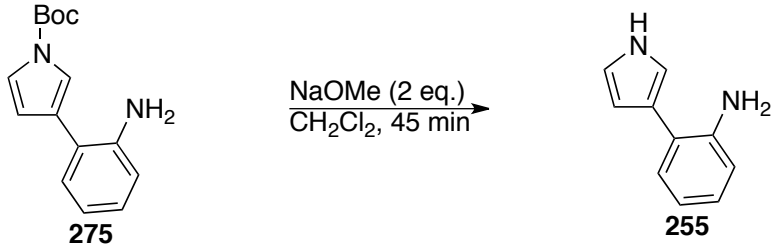
Table 23. Pictet-Spengler method development. n.r. = not recovered

Based upon the results of Kobayashi, we initially applied $Sn(OTf)_2$ as the Lewis acid, due to its activating potential for both aldehydes and aldimines. We were, however only able to isolate the imine in disappointing yields (entries 2-3). Led by our previous experience in Lewis acid catalysed Pictet-Spengler reactions, we were satisfied to observe conversion to the desired pyrroloquinoline **289** with the application of $Y(OTf)_3$ in 20% yield (entry 4). In an attempt to improve the conversion, we applied mild heating of the reaction, which unfortunately promoted significant degradation, as evidenced by TLC analysis in attempts towards marinoquinoline E and C (entries 5-6). Mild heating gave the marinoquinoline B precursor in 12%, which was improved to 15% by reaction at rt (entries 7-8). The use of the highly reactive *p*-nitrobenzaldehyde in MeCN afforded an unoxidized pyrroloquinoline **288** in a pleasing 51% yield (entry 9), but these conditions only

afforded the oxidised pyrroloquinoline **291** in 23% when using aldehyde **279** (entry 10). It was decided the reactivity of the pyrrole with Boc protection in place was not sufficient for the Pictet-Spengler reaction, and so we decided to proceed with a deprotected pyrroloquinoline.

2.4.2. Deprotected Pictet-Spengler Reaction

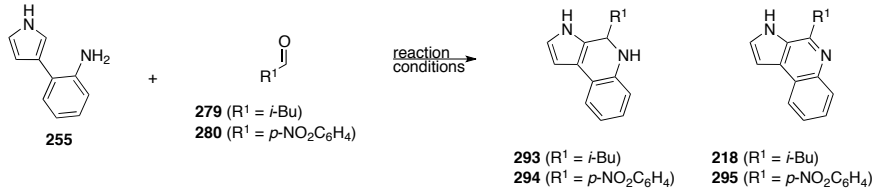
After the failure of the Pictet-Spengler reactions with Boc protection, it was thought removal of the Boc group would increase the reactivity of the system. Subsequently, we accessed pyrroloaniline **255** by Boc removal with NaOMe in quantitative yield (scheme 67). Initially, we attempted to prepare the corresponding imine by stirring **255** and *p*-nitrobenzaldehyde (**280**) in CH_2Cl_2 in the presence of $MgSO_4$. Crude NMR analysis actually indicated Pictet-Spengler cyclization as a mixture of pyrroloquinolines **294** and **295** (table 24, entry 1). Purification of the reaction mixture afforded the products in a modest 37% and 14% yield respectively. Using isovaleraldehyde (**279**), we accessed marinoquinoline B in 31% yield for the Pictet-Spengler reaction, and did not observe the corresponding unoxidized dihydropyrroloquinoline (entry 2). Given the modest yields afforded by Pictet-Spengler reaction, we looked to Lewis acids again to improve the efficiency of the reaction. We subsequently added varying amounts of $Y(OTf)_3$ to the reaction, but saw extensive degradation as evidenced by TLC analysis (e.g. entries 3-4).



275 **255**

Scheme 67. Boc deprotection of pyrroloaniline **268** for the synthesis of **255**.

Our Pictet-Spengler system was not affording acceptable conversion, and we subsequently reassessed our synthetic plan. We decided to move from a Pictet-Spengler approach to a Pictet-Hubert approach.

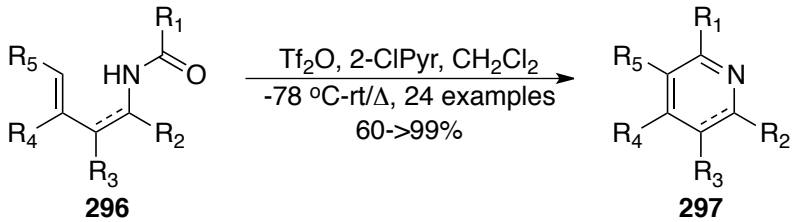


Entry	Aldehyde (1.0 eq.)	Additive	Reaction conditions	Reaction outcome (yield %)
1	**280**	$MgSO_4$	CH_2Cl_2, 12 h	**294** (37), **295** (14)
2	**279**	$MgSO_4$	CH_2Cl_2, 12 h	**293** (0), **218** (31)
3	**280**	$Y(OTf)_3$, (20 mol. %)	CH_2Cl_2, 6 h	n.d.
4	**279**	$Y(OTf)_3$, 20 mol. %)	CH_2Cl_2, 6 h	n.d.

Table 24. Pictet-Spengler cyclizations of pyrroloaniline **255** and various aldehydes. n.d. = not determined

2.5. Movassaghi-Pictet-Hubert Approach

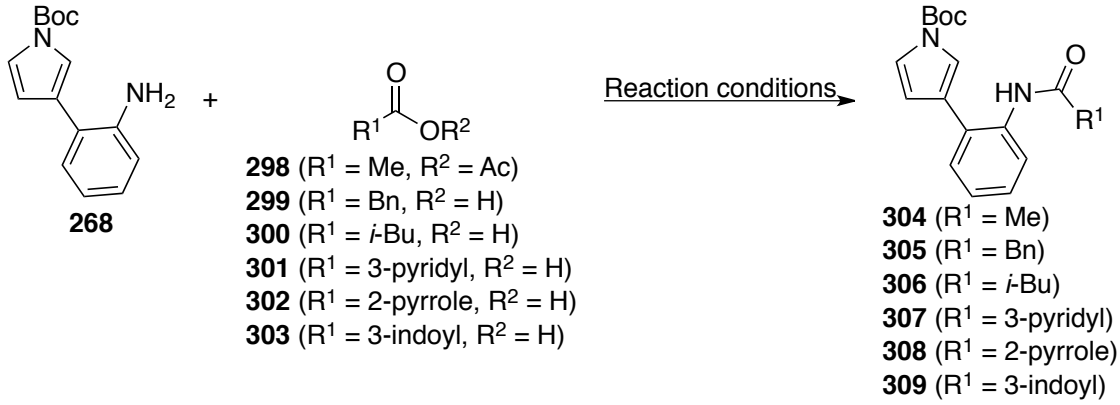
Following the disappointing results of the Pictet-Spengler reactions, we proposed a change of direction in search of improved yields, with a Pictet-Hubert approach. This reaction has undergone great development since its first report in the late 19th century in the thermal dehydrative cyclizations of amides with $ZnCl_2$.[104] Firstly, Morgan and Walls repeated the same reactions as Pictet and Hubert using $POCl_3$ in place of $ZnCl_2$ and lower temperatures to affect successful dehydrative cyclizations via an imidoyl chloride/nitrilium ion intermediate.[105] While this improvement is notable, we were concerned the high temperatures and strongly acidic reaction conditions would not be compatible with our pyrrole moiety. Recently, Movassaghi in his investigations into Bischler-Napieralski and Pictet-Hubert reactions has successfully employed Tf_2O as a dehydrative agent, active at ≤rt in neutral conditions.[106] In these investigations, he reports the synthesis of a diverse array of quinolines and β-carbolines, resembling that of our system (scheme 68). Indeed, closely related to our system, successful cyclizations with thiophene and indole nucleophiles were observed, in excellent yield. Key to our interest in these conditions was the neutral/basic pH and low temperatures at which these reactions were performed.



Scheme 68. Movassaghi Tf_2O promoted Bischler-Napieralski and Pictet-Hubert reactions.

2.5.1. Amide Formations

In order to access marinoquinoline A, we were required to synthesise amide **304**, which we achieved using acetic anhydride (table 25, entry 1). For the synthesis of the remaining amides, we proposed the use of the coupling agent PyBOP as the activating agent for amide bond formation and the corresponding acids. However, in the case of acid **299** after 6 h, there was no evidence of conversion and 100% aniline **268** was recovered (entry 2). We had previously seen the low reactivity of this aniline, when attempting to prepare imines as precursors for subsequent Pictet-Spengler reactions (table 23, entry 1). We decided upon utilisation of acyl chlorides for this transformation. $SOCl_2$ and $(COCl)_2$ were successful in converting the corresponding acids to their acyl chlorides and we observed successful conversions in all cases (e.g. entries 3-4). We were not however satisfied with the overall yields for the transformation to the amides. We assumed the acidity of the reaction conditions in forming the acid chlorides was degrading the aniline, or the acid chlorides themselves were not preserved in the reaction conditions. It has been reported in the literature, poor conversions to amides from acid chlorides has been observed despite the apparent simplicity of this reaction.[107] In some of these cases, the Appel reaction has been successfully implemented to afford acyl chlorides from their corresponding acids without *in situ* generation of HCl. Indeed, Villeneuve *et al.* report the utilisation of hexachloroacetone (HCA) for the preparation of acid chlorides via a chlorophosphonium salt, and report a significant improvement in yield of the amide *vs.* acid chloride prepared using $SOCl_2$ in their system[108] We were pleased to observe a similar outcome in our case (entries 5-6). However we were still not entirely satisfied with our results since in some cases, poor yields were still a cause for concern (entries 7-8). We next tried carbodiimides as the coupling agent, and to our surprise given the previous failure of PyBOP, this approach gratifyingly afforded amides in very good yield using DIC with no observable degradation (entries 9-13).



Scheme 69. General scheme for the synthesis of amides **304**-**309**.

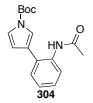
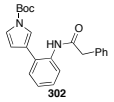
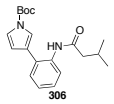
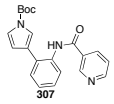
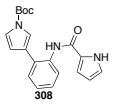
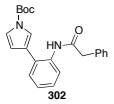
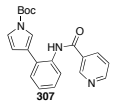
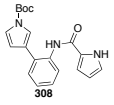
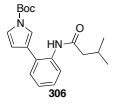
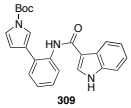
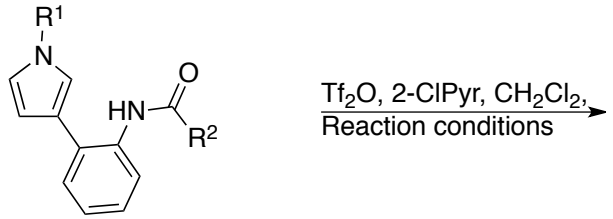
Entry	Aniline (1 eq.)	Acid/ anhydride	Reaction conditions	Reaction outcome (yield)
1	**268**	**298** (1.2 eq.)	Et_3N (2 eq.), DMAP (0.05 eq.), CH_2Cl_2, 12 h	 **304** (83%)
2	**268**	**299** (1.2 eq.)	PyBop (1.2 eq.), EtN(*i*-Pr)$_2$ (1.2 eq.), CH_2Cl_2, 6 h	 **302** (0%)
3	**268**	**299** (2.0 eq.)	$SOCl_2$ (2.5 eq.), Et_3N (5 eq.), CH_2Cl_2, 1 h	**302** (57%)
4	**268**	**299** (2.0 eq.)	$(COCl)_2$ (2.5 eq.), Et_3N (5 eq.), cat. DMF, CH_2Cl_2, 1 h	**302** (69%)
5	**268**	**299** (3.0 eq.)	HCA (1.5 eq.), PPh_3 (3 eq.) Et_3N (1.5 eq.), CH_2Cl_2, -78 ^oC-rt, 1 h	**302** (81%)
6	**268**	**300** (3.0 eq.)	HCA (1.5 eq.), PPh_3 (3 eq.) Et_3N (1.5 eq.), CH_2Cl_2, -78 ^oC-rt, 1 h	 **306** (64%)
7	**268**	**301** (3.0 eq.)	HCA (1.5 eq.), PPh_3 (3 eq.) Et_3N (1.5 eq.), CH_2Cl_2, -78 ^oC-rt, 1 h	 **307** (27%)
8	**268**	**302** (3.0 eq.)	HCA (1.5 eq.), PPh_3 (3 eq.) Et_3N (1.5 eq.), CH_2Cl_2, -78 ^oC-rt, 1 h	 **308** (14%)
9	**268**	**299** (1.0 eq.)	DIC (1.2 eq.), DMAP (0.05 eq.), CH_2Cl_2, 12 h	 **302** (89%)
10	**268**	**301** (1.0 eq.)	DIC (1.2 eq.), DMAP (0.05 eq.), CH_2Cl_2, 16 h	 **307** (92%)
11	**268**	**302** (1.0 eq.)	DIC (1.2 eq.), DMAP (0.05 eq.), CH_2Cl_2, 12 h	 **308** (72%)
12	**268**	**300** (1.0 eq.)	DIC (1.2 eq.), DMAP (0.05 eq.), CH_2Cl_2, 12 h	 **306** (96%)
13	**268**	**303** (1.0 eq.)	DIC (1.2 eq.), DMAP (0.05 eq.), CH_2Cl_2, 12 h	 **309** (81%)

Table 25. Method development of amide bond formations.

2.5.2. Movassaghi-Pictet-Hubert Method Development

Satisfied with our procedure towards the desired amides, we set about investigating the application of Movassaghi's Pictet-Hubert conditions towards successful cyclizations with pyrrole nucleophiles (scheme 70).



304 (R^1 = Boc, R^2 = Me)
305 (R^1 = Boc, R^2 = Bn)
306 (R^1 = Boc, R^2 = *i*-Bu)
309 (R^1 = Boc, R^2 = 3-indoyl)
310 (R^1 = TIPS, R^2 = Bn
311 (R^1 = TIPS, R^2 = Me

312 (R^1 = TIPS, R^2 = Bn
313 (R^1 = TIPS, R^2 = Me
314 (R^1 = Boc, R^2 = Bn)
315 (R^1 = Boc, R^2 = Me)
316 (R^1 = Boc, R^2 = *i*-Bu)
317 (R^1 = Boc, R^2 = 3-indoyl)

Scheme 70. The synthesis of pyrroloquinolines **312**-**317** from amides **304**-**311**.

Movassaghi had developed his conditions using pendent π-nucleophiles such as aryl, alkenyl, thiophene and indole, with the dehydrative cyclizations occurring initially at -78 ^{o}C before warming to rt or above. Given the greater general reactivity of pyrroles compared to these nucleophiles, we initially decided to follow this approach, but ensure careful monitoring of the reaction by TLC. As can be seen in table 26, initially application of pyrroloamide **310** to Movassaghi-Pictet-Hubert reaction conditions afforded both the corresponding deprotected pyrroloamide (**318**) and the deprotected cyclized product – marinoquinoline C (table 25, entry 1). Attempts to access marinoquinoline A from pyrroloamide **311** using the same conditions failed, with significant degradation observed by TLC analysis (entry 2). It appeared the deprotection was occurring faster than the cyclization, so we moved to the Boc protected pyrroloquinolines, in the hope these pyrroloamides would be more stable in the reaction conditions, and chose amide **305** as our test system. Using pyrroloamide **305**, no deprotection at any point in the reaction was observed, while pyrroloquinoline **312** was identified in a modest 14% isolated yield (entry 3) with significant degradation observed by TLC analysis. We subsequently decided to maintain the reaction temperature at -78 ^{o}C for the entirety of the reaction, though it appeared the addition of Et_3N to quench the triflate salts promoted degradation with a strong red colour observed (entry 4). Dilution of Et_3N to a 20% v/v solution in CH_2Cl_2 did not improve the outcome (entry 5) while

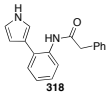
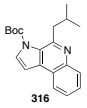
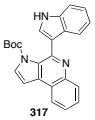
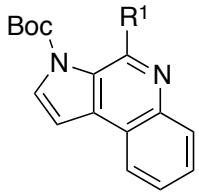
Entry	Amide (1 eq.)	Reaction conditions	Quench conditions	Reaction outcome (yield %)
1	**310**	Tf_2O (1.1 eq.), 2-ClPyr (1.2 eq.), -78 °C-rt, 200 mM, 20 min	Et_3N	 312 (0%)  219 (9%)  318 (36%)
2	**311**	Tf_2O (1.1 eq.), 2-ClPyr (1.2 eq.), -78 °C-rt, 200 mM, 35 min	Et_3N	n.d.
3	**305**	Tf_2O (1.1 eq.), 2-ClPyr (1.2 eq.), -78 °C-rt, 200 mM, 1 h	Et_3N	 314 (14%)
4	**305**	Tf_2O (1.1 eq.), 2-ClPyr (1.2 eq.), -78 °C, 200 mM, 1 h	Et_3N	 314 (12%)
5	**305**	Tf_2O (1.1 eq.), 2-ClPyr (1.2 eq.), -78 °C, 200 mM, 1 h	20% Et_3N in CH_2Cl_2	 314 (17%)
6	**305**	Tf_2O (1.1 eq.), 2-ClPyr (2.0 eq.), -78 °C, 200 mM, 1 h	20% Et_3N in CH_2Cl_2	n.d.
7	**305**	Tf_2O (1.1 eq.), 2-ClPyr (2.0 eq.), -78 °C, 28 mM, 1 h	20% Et_3N in CH_2Cl_2	 314 (45%)
8	**305**	Tf_2O (1.1 eq.), 2-ClPyr (2.0 eq.), -78 °C-rt, 28 mM, 1 h	sat. aq. $NaHCO_3$	 314 (63%)
9	**305**	Tf_2O (2.0 eq.), 2-ClPyr (4.0 eq.), -78 °C-rt, 28 mM, 1 h	sat. aq. $NaHCO_3$	 314 (86%)
10	**304**	Tf_2O (2.0 eq.), 2-ClPyr (4.0 eq.), -78 °C-rt, 28 mM, 1 h	sat. aq. $NaHCO_3$	 315 (83%)
11	**306**	Tf_2O (2.0 eq.), 2-ClPyr (4.0 eq.), -78 °C-rt, 28 mM, 1 h	sat. aq. $NaHCO_3$	 316 (79%)
12	**309**	Tf_2O (2.0 eq.), 2-ClPyr (4.0 eq.), -78 °C-rt, 28 mM, 4 h	sat. aq. $NaHCO_3$	 317 (89%)

Table 26. Results of Movassaghi-Pictet-Hubert pyrroloquinoline reactions. n.d. = not determined.

increasing the equivalents of 2-ClPyr also failed to halt degradation (entry 6). Finally, significant dilution of the reaction mixture did avoid the degradation issues that had impeded us, but complete conversion was not possible (entry 7). In an effort to promote full conversion, we returned to rt reaction conditions, and changed the quench protocol, which improved the reaction outcome only slightly (entry 8). Increasing the equivalents ratio from 1.0:1.2:1.4 to 1.0:2.0:4.0 for amide, Tf_2O and 2-ClPyr respectively did achieve full consumption of amide according to TLC and we were pleased to observe a yield of 86% of pyrroloquinoline **312** after flash column chromatography (entry 9). With a successful protocol to the synthesis of 3*H*-pyrrolo[2,3*c*]quinolines in hand, we subjected amides **304**, **306** and **309** for the synthesis of marinoquinolines A, B and E. We were pleased to see the general applicability of our Movassaghi-Pictet-Hubert protocol to these substrates, and accessed *N*-Boc-protected precursors of marinoquinolines A, B, C and E in 79-89% chemical yield upon purification (entries 9-12). With the *N*-Boc-protected pyrroloquinolines in hand, we were confident of rapidly accessing the marinoquinolines, and aplidiopsamine A.

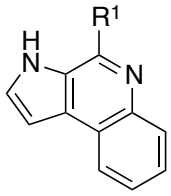
2.6. Completion of the Synthesis of the Marinoquinoline Alkaloids

Having optimised the Movassaghi-Pictet-Hubert reaction conditions, we set about completing the total synthesis of the marinoquinolines by implementing a Boc-deprotection protocol. Through synthetic investigation, we found the use of NaOMe to provide superior results to that afforded by the acidic deprotection in 4M HCl in dioxane. This protocol afforded us marinoquinolines A, B, C and E (scheme 71). A disappointing yield of 46% for marinoquinoline E was achieved, but otherwise yields of 92-97% for marinoquinolines A-C were satisfying.



314 (R^1 = Bn)
315 (R^1 = Me)
316 (R^1 = *i*-Bu)
317 (R^1 = 3-indoyl)

NaOMe, CH_2Cl_2 or THF
-78 °C-rt, 45 min-1 h

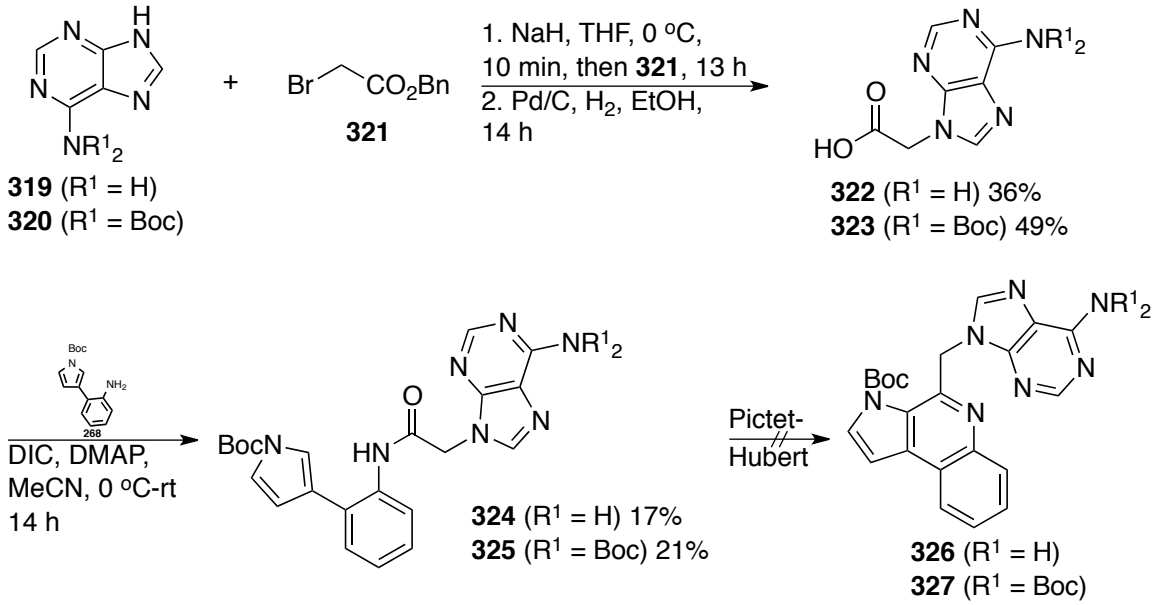


217 (R^1 = Me) 94%
marinoquinoline A
218 (R^1 = *i*-Bu) 92%
marinoquinoline B
219 (R^1 = Bn) 97%
marinoquinoline C
221 (R^1 = 3-indoyl) 46%
marinoquinoline E

Scheme 71. Completion of the synthesis of marimoquinolines A, B, C and E.

2.7. Total Synthesis of Aplidiopsamine A

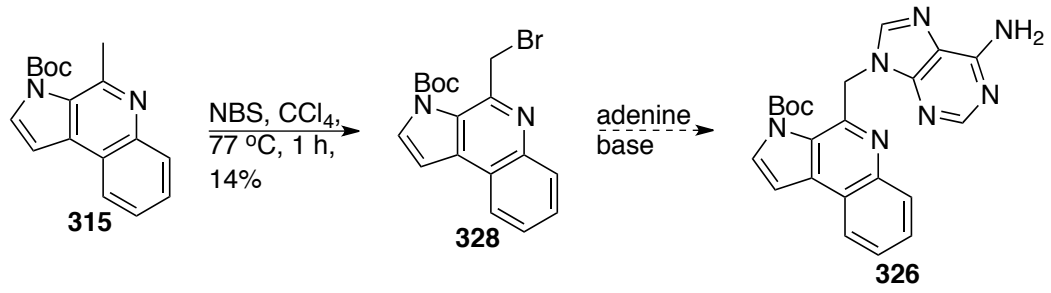
With four of the six marinoquinolines prepared, focus turned to aplidiopsamine A. We proposed a similar synthetic protocol towards the target as for the marinoquinolines, with Pictet-Hubert cyclization of the relevant amide (scheme 72).



Scheme 72. Approach towards aplidiopsamine A.

N^9 alkylation of adenine (**319**) with benzyl-2-bromoacetate (**321**) and subsequent hydrogenolysis afforded acid **322** in 36% yield. The low yield is explained by the poor solubility of the adenine in the reaction mixture. Successful amide coupling to pyrroloaniline **268** provided us with key intermediate amide **324** in an unoptimized 17% yield. Disappointingly, we did not observe conversion to the desired pyrroloquinoline **326** using our optimized Movassaghi-Pictet-Hubert conditions. Concerned free N^6 was compromising our cyclization, global *N*-Boc-protection of adenine, followed by selective N^9 deprotection[109] and subsequent alkylation with benzyl-2-bromoacetate and hydrogenolysis afforded acid **323**, which was successfully coupled to pyrroloaniline **268** to afford amide **325** in 21% yield. On this occasion, the conversion was far superior to the isolated yield, which was compromised due to co-elution with the urea by-product of the DIC coupling after flash column chromatography. As before, a subsequent Movassaghi-Pictet-Hubert reaction was unsuccessful in affording the desired pyrroloquinoline, and due to a complicated reaction mixture, we were unable to determine the outcome of the reaction. We determined the presence of an adenine unit was compromising the cyclization step, and considered approaches to introduce this moiety post-cyclization. Since we had access to

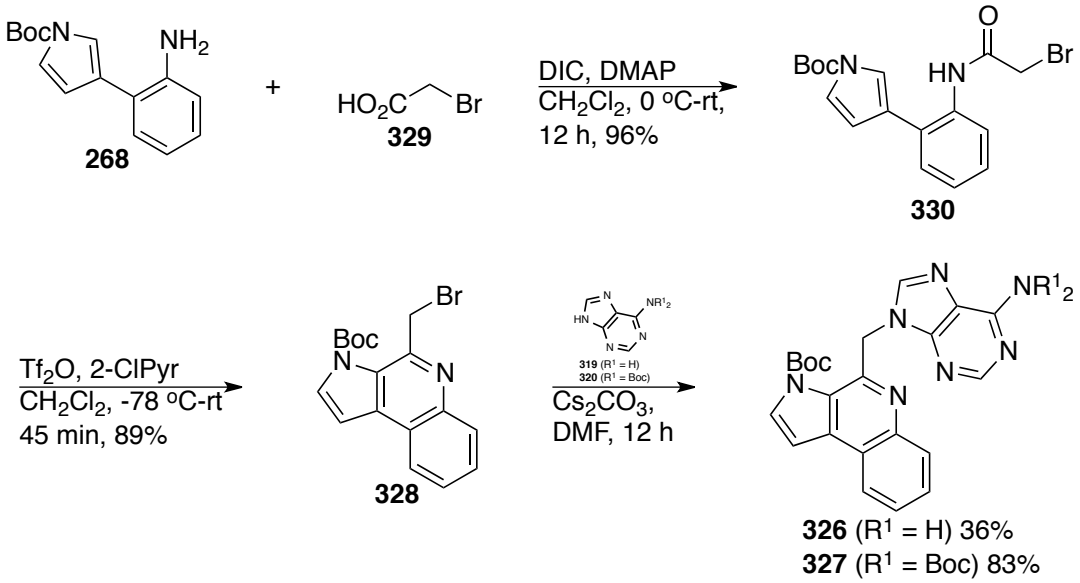
pyrroloquinoline **315**, we proposed a radical benzylic bromination, followed by an S_N2 reaction with adenine could provide us with access to pyrroloquinoline **326** (scheme 73).



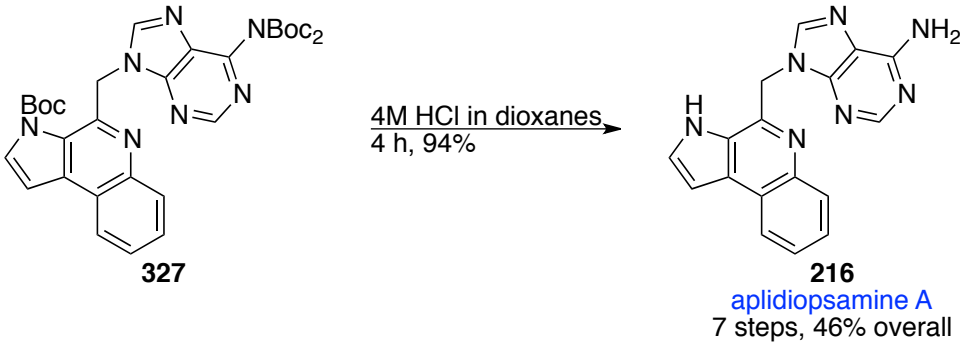
Scheme 73. Attempts toward aplidiopsamine A via a benzylic bromination of pyrroloquinoline **315**.

While the radical bromination did furnish the desired bromo compound, the overall yield was very low, with various other products isolated, including non-specific bromination of the pyrrole, and significant starting material – pyrroloquinoline **315**. As a result, we did not explore the alkylation step to access **326** at this point as we only isolated 12 mg of pyrroloquinoline **328**. In response to the poor results for the benzylic bromination, instead of attempting to optimize these bromination conditions, we questioned whether our Movassaghi-Pictet-Hubert conditions would facilitate the cyclization of α-bromo amide **330** to provide us with pyrroloquinoline **328** (scheme 74). Amide **330** was afforded using our DIC coupling protocol in 96% yield, and we were gratified our Movassaghi-Pictet-Hubert conditions proceeded very smoothly, to afford the desired bromo pyrroloquinoline **328** in 89% yield. We found Cs_2CO_3 provided us with a better alkylation protocol than that previously achieved with NaH (scheme 72) yet we still only accessed **326** in 36% yield using adenine. Bis-Boc adenine **320** provided a much more gratifying 83% of **327** for the alkylation, which we attribute again to greater solubility than adenine (**319**). Since we already required *N*-Boc deprotection of the pyrrole moiety, the presence of two further Boc groups does not affect the synthetic approach in terms of the number of linear steps.

We were surprised to see the failure of our NaOMe protocol during attempts towards Boc removal, but this was successfully achieved in good yield using anhydrous 4M HCl in dioxanes (94%) to afford aplidiopsamine A in 7 linear steps, and an overall yield of 46% (scheme 75).



Scheme 74. Attempts toward aplidiopsamine A via α-bromo amide **330**.



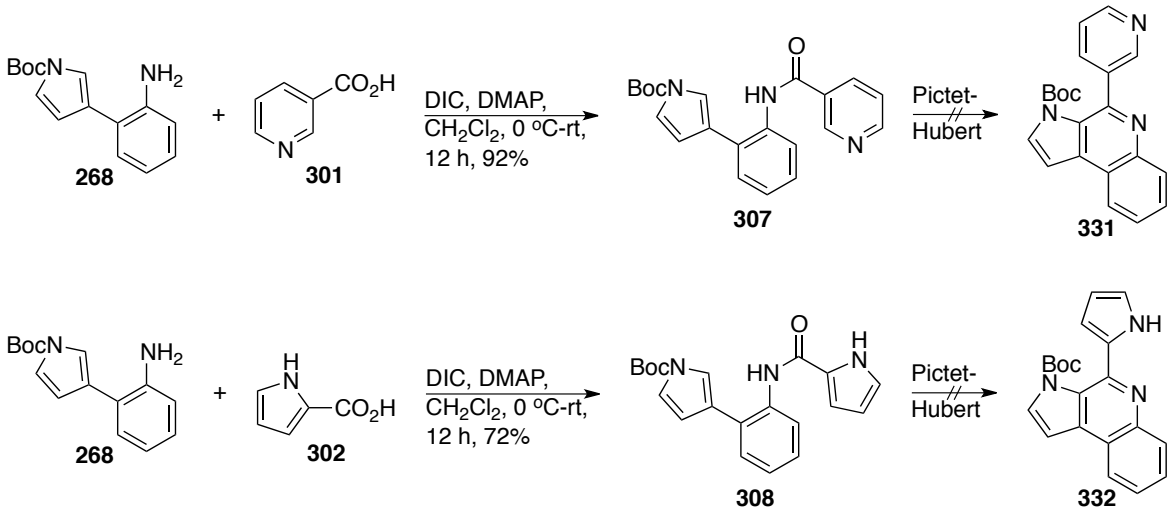
Scheme 75. Synthesis of aplidiopsamine A

2.8. Construction of a Small Library of Analogues

With marinoquinolines A, B, C, E and aplidiopsamine A in hand, we embarked upon the preparation of a series of analogues for biological evaluation. Given that the IC_{50} values were very similar for each marinoquinoline for each of the assays, we decided to focus on modifications of the substituent in position 4 in the first round of SAR. We proposed this would be facile chemistry since we had access to pyrroloquinoline **328**. We proposed introducing polar groups to decrease the LogP of the analogues compared to the natural products in order to improve their pharmacokinetic profile. We did however decide to replace the pyrrole for a thiophene and synthesize a thienoquinoline, as this would provide us with knowledge of the importance of potential hydrogen bond interactions with the corresponding pyrrolo moiety in the natural products. We also wanted to truncate the linker to access direct aryl-aryl substitution of position 4, as in the case of marinoquinoline E.

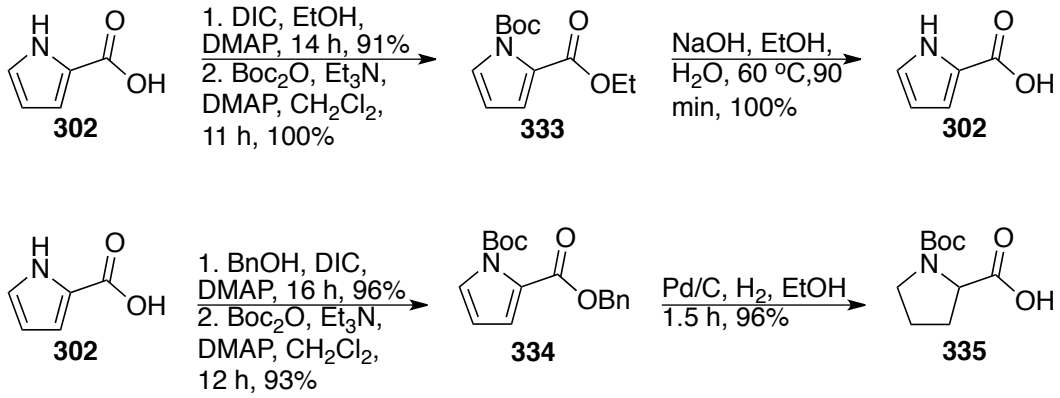
2.8.1. Pyridinyl and Pyrrolyl Analogues

We had access to nicotinic acid (**301**) and pyrrole-2-carboxylic acid (**302**) and envisioned rapid access to the corresponding pyrroloquinolines via their amides using our Movassaghi-Pictet-Hubert protocol to access some truncated analogues (scheme 76).



Scheme 76. Synthetic approach towards the synthesis of pyrroloquinolines **331** and **332**.

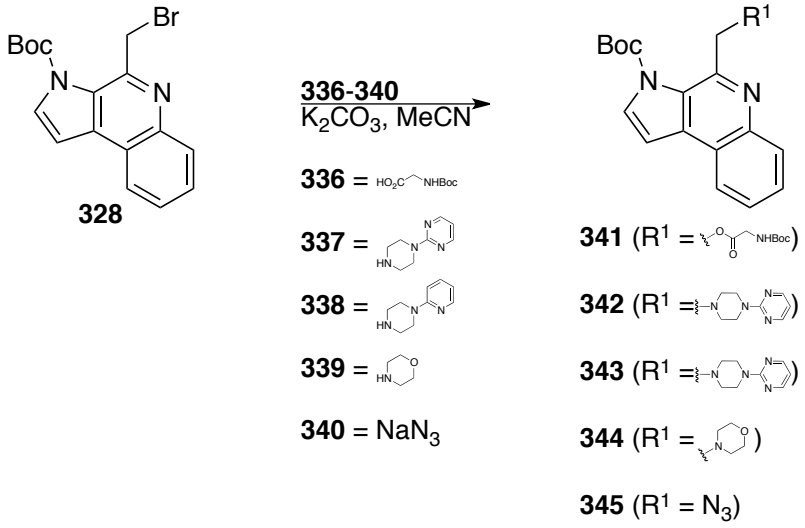
While the amides were successfully prepared using our DIC coupling method, we were unable to access the desired cyclized products using our optimised conditions. The failure to cyclize amide **307** appears to follow the observations in attempting to access aplidiopsamine A via the Movassaghi-Pictet-Hubert approach with the adenine unit in place (scheme 72). In this case, after repeated attempts, starting materials were recovered from the reaction. In the case of amide **308**, we observed a complicated reaction mixture, which we did not attempt to investigate. Since we had observed the failures of the Pictet-Hubert reaction of *N*-TIPS pyrroloamide **310** presumably due to the deprotection of the pyrrole and subsequent uncontrolled reactions (table 26, entry 1), this was perhaps not surprising. Unfortunately, approaches towards Boc-protection were fruitless (scheme 77) and at this point we abandoned our work on these analogues.



Scheme 77. Failed approaches towards the *N*-Boc-protection of acid **302**.

2.8.2. Analogues from the Alkylation of pyrroloquinoline **328**

Our synthetic protocol towards aplidiopsamine A involved pyrroloquinoline **328** from a Movassaghi-Pictet-Hubert cyclization of the corresponding α-bromo amide **330**. This was a useful synthetic intermediate, as numerous nucleophiles could be reacted with it to access a large number of analogues rapidly. The only disadvantage of this approach was the inability to access aryl-aryl systems, analogous to that of marinoquinoline E. Nevertheless, we were able to change the nature of substitution greatly via this approach (scheme 78, table 27).



Scheme 78. Synthesis of pyrroloquinolines **341**-**345** from pyrroloquinoline **328**.

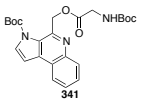
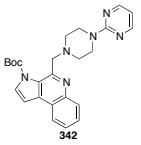
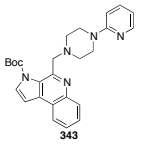
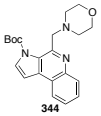
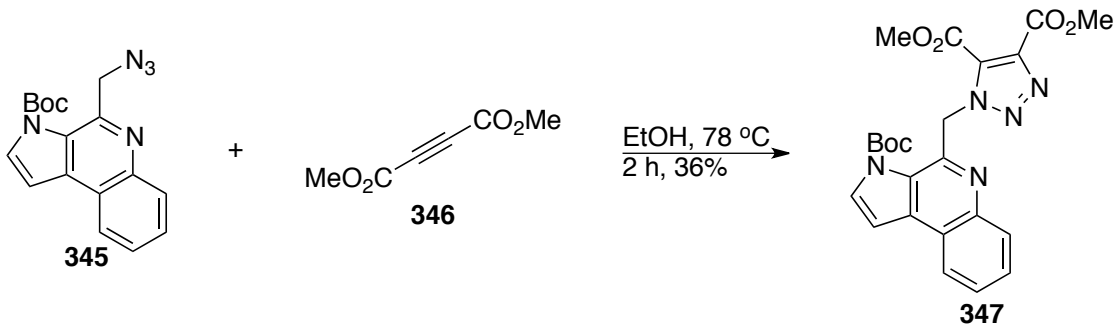
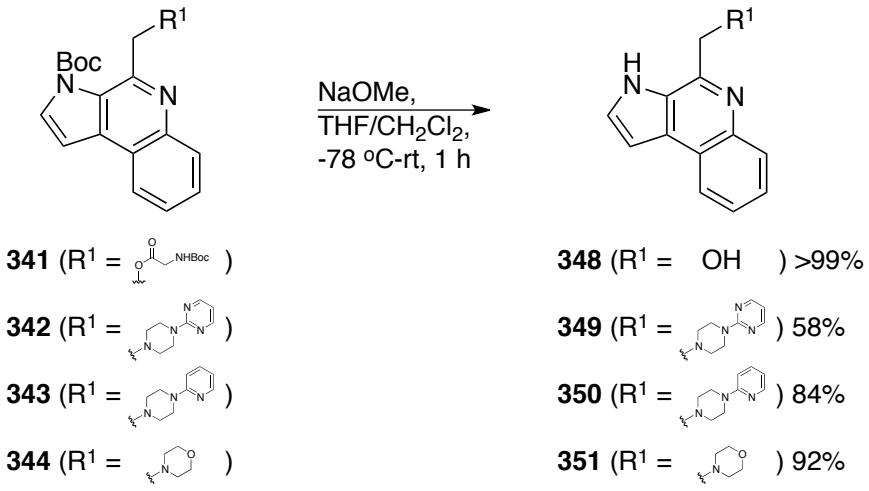
Entry	Nucleophile	Reaction conditions	Reaction outcome (yield)
1	 336 (1.0 eq.)	K_2CO_3 (3.3 eq.), MeCN, 82 ^{o}C, 48 h	 341 (87%)
2	 337 (1.5 eq.)	K_2CO_3 (1.5 eq.), MeCN, 12 h	 342 (>99%)
3	 338 (1.5 eq.)	K_2CO_3 (1.5 eq.), MeCN, 12 h	 343 (88%)
4	 339 (1.5 eq.)	K_2CO_3 (1.5 eq.), MeCN, 12 h	 344 (100%)
5	**340** (2.0 eq.)	EtOH, 22 h	 345 (100%)

Table 27. Reaction of various nucleophiles with **330** to afford pyrroloquinolines **341**-**345**.

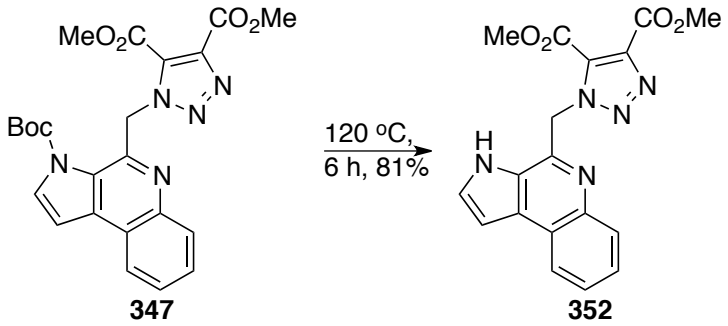
Azide **345** was subjected to a Huisgen 1,3-dipolar cycloaddition to afford triazole **347** (scheme 79). Our NaOMe conditions for the removal of the Boc group provided us with four pyrroloquinoline analogues (scheme 80). In the case of pyrroloquinoline **341**, the conditions for the removal of the Boc groups also hydrolysed the ester to afford the corresponding alcohol **348**. The same was true of pyrroloquinoline **347**, but a thermal deprotection preserved the methyl ester functionality of the triazole to afford pyrroloquinoline **352** (scheme 81).



Scheme 79. Huisgen 1,3-dipolar cycloaddition of azide **345** and **346** for the synthesis of azide **347**.



Scheme 80. Boc deprotection of pyrroloquinolines **341**-**344** for the synthesis of **348**-**351**.

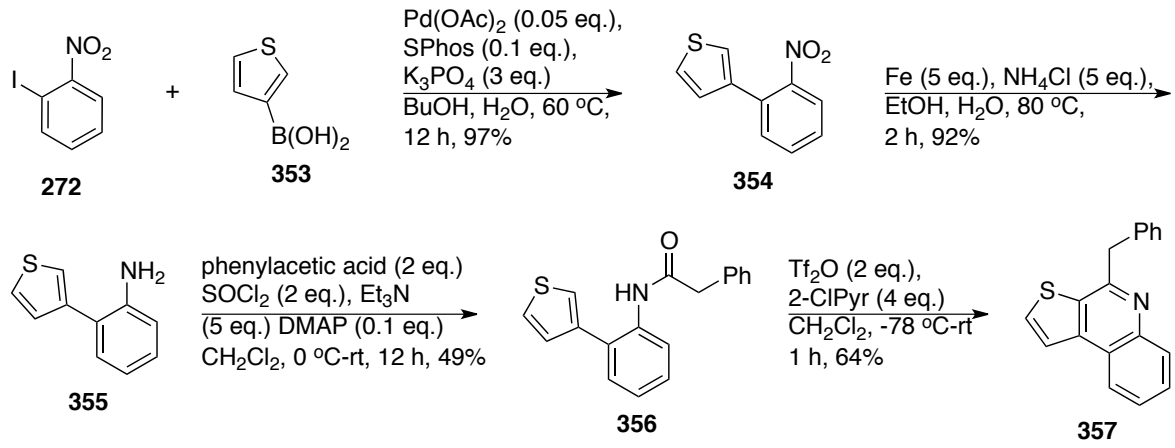


Scheme 81. Thermal Boc deprotection of **347** for the synthesis of pyrroloquinoline **352**.

2.8.3. Thieno[2,3-*c*]quinolone

We proposed changing the pyrrolo moiety for the corresponding thiophene would be an interesting modification. We suggest this change would modify the electronic properties of the heterocyclic framework, induce greater lipophilicity and remove one hydrogen bond donor functionality. We proposed its incorporation into a substrate bearing the same substitution as one of the marinoquinolines would provide robust SAR information for this modification, and the benzyl substitution was chosen. The commercially available boronic acid **353** was successfully coupled to **272** using our optimized Suzuki-Miyaura conditions to afford nitro **354** (scheme 82). We changed our approach to reduction of the nitro from the previously used Pd/C hydrogenation conditions due to the potential of thiophene coordinating to the palladium catalyst and preventing reaction progress. Using Fe in acidic conditions, we were pleased to see no degradation as we had previously encountered in the pyrrole series, to afford aniline **355** in 92% yield. We were able to access amide **356** via an *in situ* generated acyl chloride from phenylacetic

acid, and finally accessed thienoquinoline **357** using our optimised Movassaghi-Pictet-Hubert conditions.



272 **353** **354** **355** **356** **357**

Scheme 82. The synthesis of thieno[2,3-*c*]quinoline **257**.

2.8.4. Summary of the Library of Analogues

We accessed a small library of compounds via various approaches for analogue preparation (figure 6). In addition to the alkylation of pyrroloquinoline **328** with various nucleophiles, we also utilised a Huisgen 1,3-dipolar cycloaddition for the synthesis of the novel triazole **352**. By retaining the Boc protection in **314**, and replacing the pyrrolo moiety with thieno moiety in **357**, we would be able to directly compare these analogues with marinoquinoline C, which would tell us the importance of the hydrogen bond donor group of the pyrrole in **219**. Piperazines **349** and **350** and morpholine **351** represent analogues with basic, H-bond acceptor functionality. Alcohol **348** conversely, represents an analogue with H-bond donor functionality. Overall, with the exception of **314** and **357**, the analogues possess significantly lower LogP values compared with the marinoquinolines.

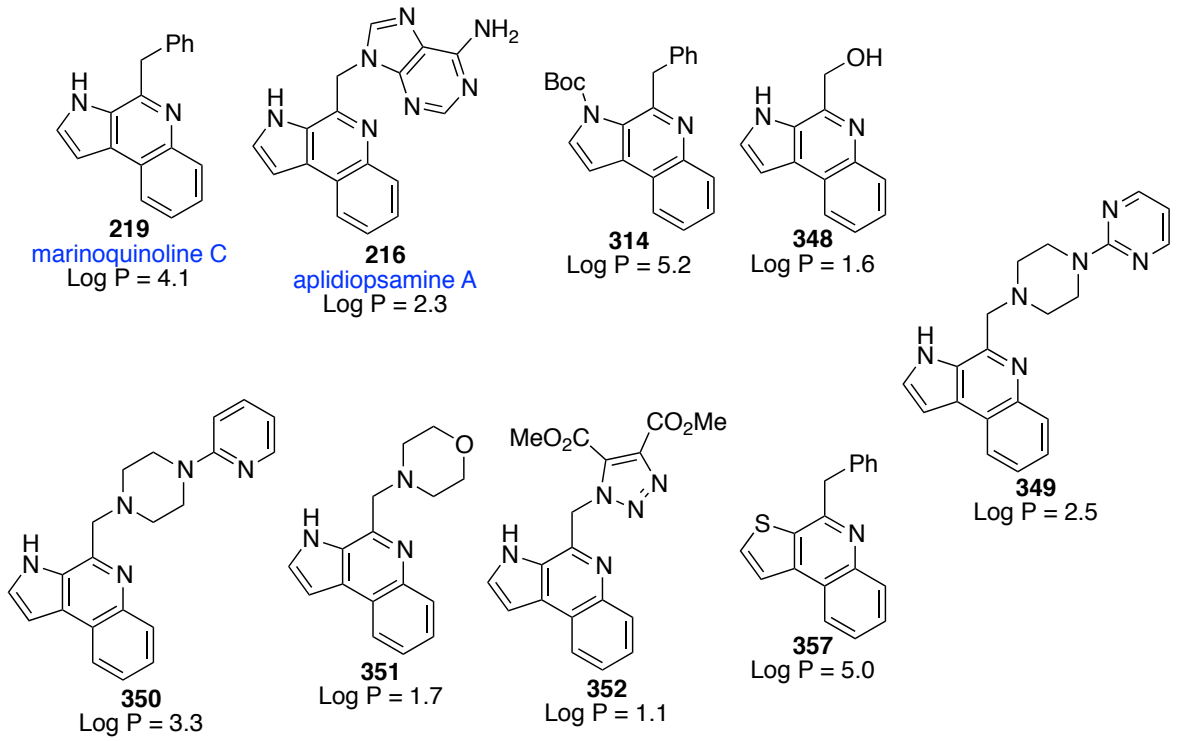


Figure 6. Pyrroloquinolines to be tested.[e]

[e] Log P values calculated using CambridgeSoft ChemDraw Ultra 12.0.3.

3. Biological Studies

3.1. Cytotoxicity Studies[f]

Cytotoxicity assays were performed on HCT-116 cells (table 28). Generally, activity in these assays was lower than that of marinoquinoline C; only results from piperazine **350** (entry 6) were comparable.

Compound	IC_{50} [μg/ml] Cell Line HCT-116 (human colon carcinoma)
aplidiopsamine A (**216**)	26.9 ± 7.6
marinoquinoline C (**219**)	7.4 ± 0.6
314	12.0 ± 4.2
348	17.5 ± 1.7
349	15.4 ± 1.5
350	7.1 ± 1.3
351	45.8 ± 8.2
352	w.a.
357	15.3 ± 0.6

w.a.: weak activity

Table 28. Results of cell bioassay into the toxicity of **216**, **219** and pyrroloquinoline analogues.

3.2. Antimicrobial Studies[f]

The analogues, along with synthetic aplidiopsamine A and marinoquinoline C were tested against 11 microbial strains, the results of which are provided in table 29. In agreement with reports in the literature,[110] aplidiopsamine A (entry 1) had no observable activity in these assays, while results for synthetic marinoquinoline C (entry 2) were in good agreement with that reported in the literature.[75] Of the analogues, two (morpholine **351** and triazole **352**, entry 7 and 8 respectively) exhibited no activity in any of the screens, while piperazines **349** and **350** (entry 5 and 9 respectively) exhibited weak activity and were inferior to marinoquinoline C. While the scope of alcohol **348** (entry 4) was rather narrow, it did improve upon marinoquinoline C for activity against *Chromobacterium violaceum* – a strain to which all other compounds failed to show activity against. *N*-Boc marinoquinoline C (**314**, entry 3) was active in three of the screens, showing weaker activity than marinoquinoline C in two of them. The best results of the screen were afforded by thienoquinoline **357**, which exhibited a narrower activity but generally more potency compared to marinoquinoline C (entry 6).

[f] Bioassays performed by our collaborators: Jennifer Herrman & Rolf Muller; Helmholtz Institute for Pharmaceutical Research and Department of Pharmaceutical Biotechnology, Saarland University, P.O. Box 15115, 66041 Saarbrucken, Germany.
N.B. values determined as duplicates; values represent the average of 2 independent measurements ± SD

	MIC_{50} [µg/ml]										
	Indicator Strains										
Compounds	***B. subtilis***	***M. luteus***	***S. aureus Newman***	***M. diernhoferi***	***C. albicans***	***P. anomala***	***M. hiemalis***	***E.coli TolC***	***E. coli DH5alpha***	***P. aeruginosa PA14***	***C. violaceum***
216	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64
219	> 64	13.6 ± 0.4	24.1 ± 4.4	> 64	42.6 ± 2.4	20.7 ± 1.6	6.7 ± 0.8	8.6 ± 0.5	> 64	> 64	33.3 ± 9.8
314	> 64	7.5 ± 0.2	> 64	> 64	> 64	> 64	10.5 ± 0.9	15.1 ± 3.0	> 64	> 64	> 64
348	> 64	28.2 ± 10.4	> 64	> 64	> 64	> 64	25.5 ± 0.4	> 64	> 64	> 64	9.9 ± 0.6
349	> 64	40.7 ± 13.9	> 64	> 64	> 64	51.7 ± 3.3	> 64	30.2 ± 0.3	> 64	> 64	> 64
357	> 64	3.7 ± 0.3	32.8 ± 1.7	> 64	> 64	> 64	6.0 ± 0.6	3.9 ± 0.4	> 64	> 64	> 64
351	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64	> 64
352	> 64	> 64	> 64	> 64	> 64	> 64	> 64	w.a.	> 64	> 64	> 64
350	> 64	48.0 ± 17.7	w.a.	> 64	> 64	w.a.	28.2 ± 3.0	22.4 ± 2.5	> 64	> 64	> 64

w.a.: weak activity

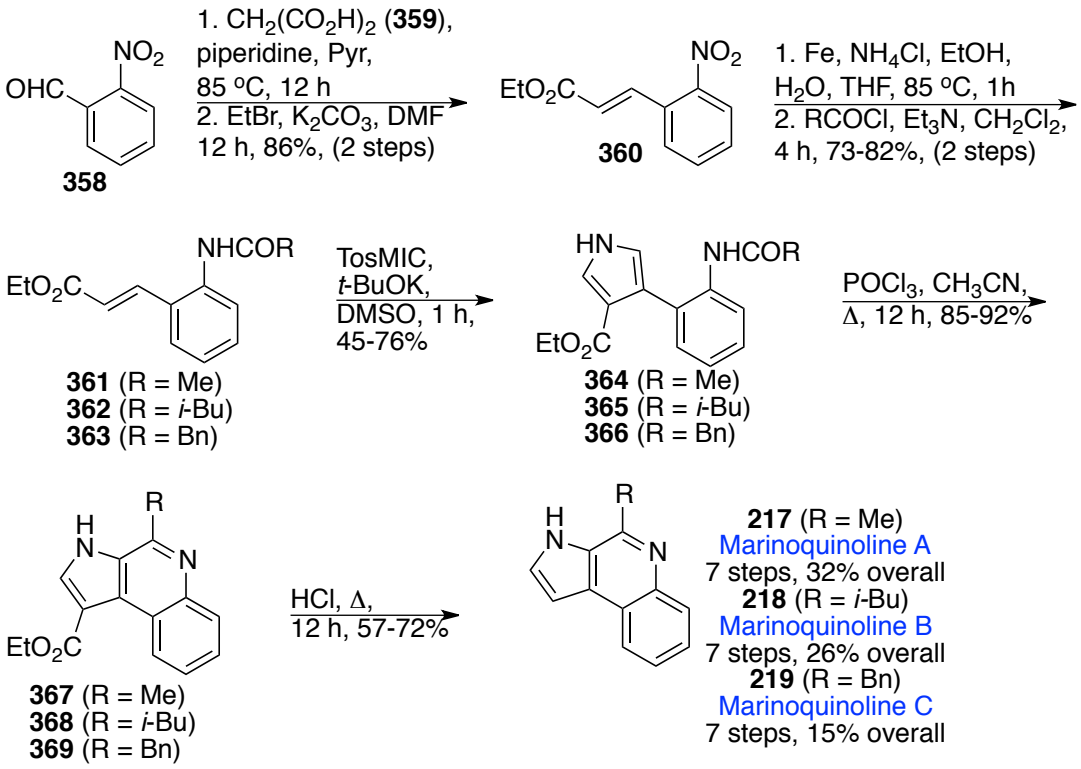
determined as duplicates; values represent the average of 2 independent measurements ± SD

Table 29. Cell bioassays on the inhibitory activity of various pyrroloquinolines against various microbial pathogens

4. Alternative Total Syntheses of the Marinoquinolines and Aplidiopsamine A

During our synthetic endeavours, there were several publications on the total syntheses of members of the marinoquinoline family of alkaloids.

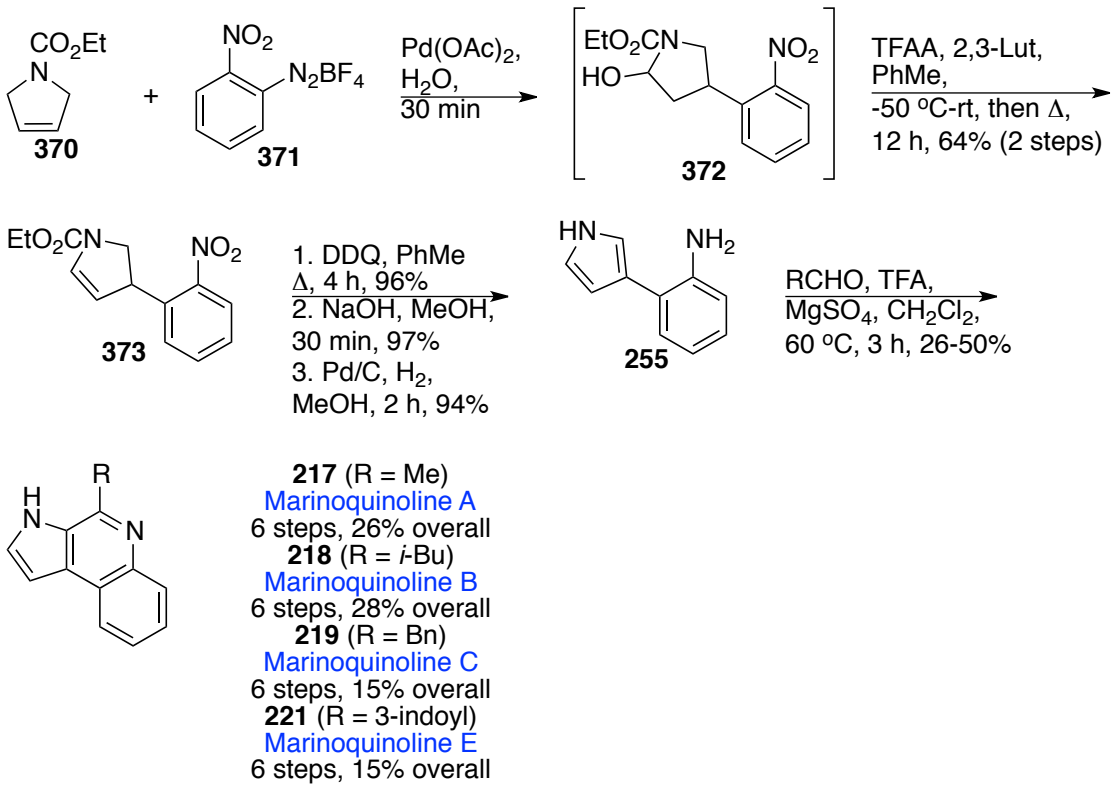
Yao *et al.* reported the first total synthesis of marinoquinolines A-C in six linear steps (scheme 83).[111] With 2-nitrobenzaldehyde as a starting material, a Doebner-Knoevenagel condensation afforded α,β-unsaturated ester **360** which subsequently underwent nitro reduction and acylation with the relevant acid chloride afforded amides **361**-**363**. Their key synthetic intermediates (**364**-**366**) were afforded from the α,β-unsaturated esters **361**-**363** by a van Leusen's pyrrole synthesis using TosMIC. Morgan-Walls-Pictet-Hubert cyclization afforded pyrroloquinolines **367**-**269**, which underwent successful decarboxylation to afford marinoquinolines A-C.



Scheme 83. Yao total synthesis of Marinoquinoline A-C.

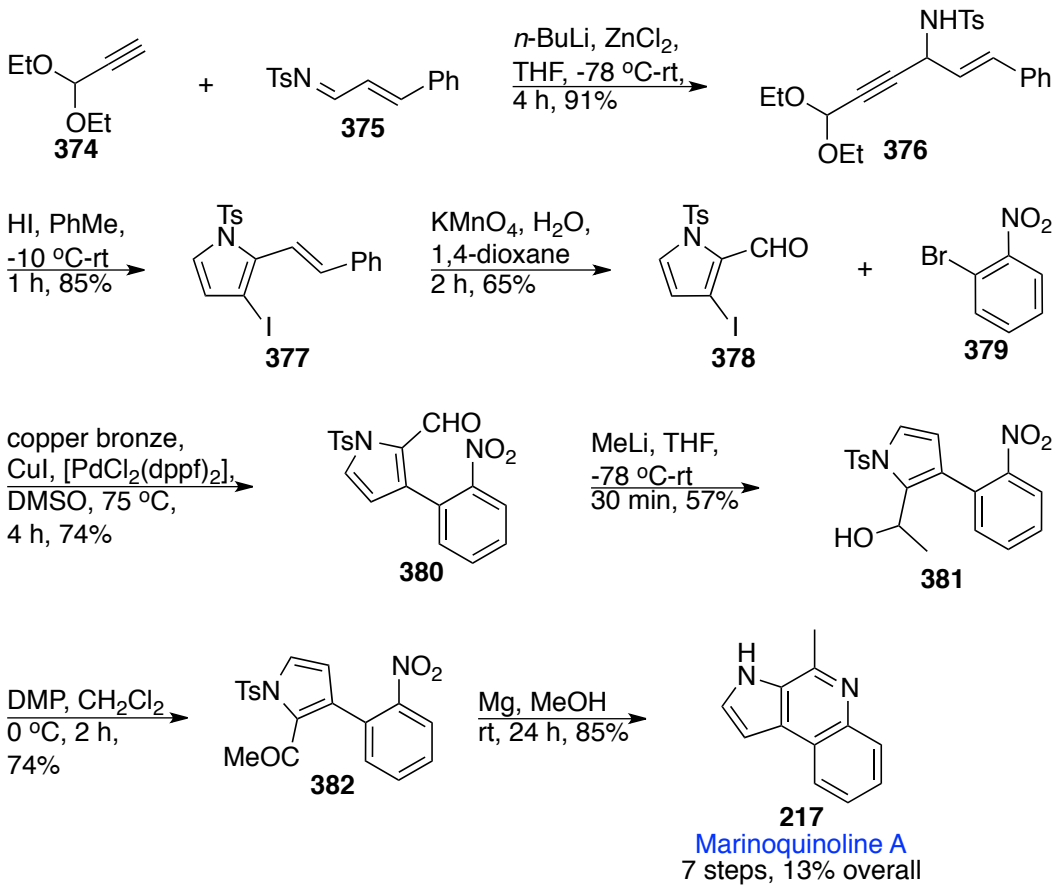
Shortly after the work of Yao, Correira *et al.* published their work on the marinoquinoline series, successfully preparing marinoquinolines A-C and E, again in six linear steps, featuring a similar Pictet-Spengler approach to our original concept (scheme 84).[112] A Heck-Matsuda arylation of pyrrole **370** with diazonium salt **371** afforded pyrrolidinol **372**, which underwent dehydration to dihydropyrrole **373** upon treatment with TFAA. Oxidation to the pyrrole, followed by

decarboxylation and nitro reduction provided pyrroloaniline **255**. Pictet-Spengler cyclization and aromatization afforded the natural products, and 9 unnatural synthetic analogues. As with our observations, the yields observed for Pictet-Spengler reactions are modest at best.



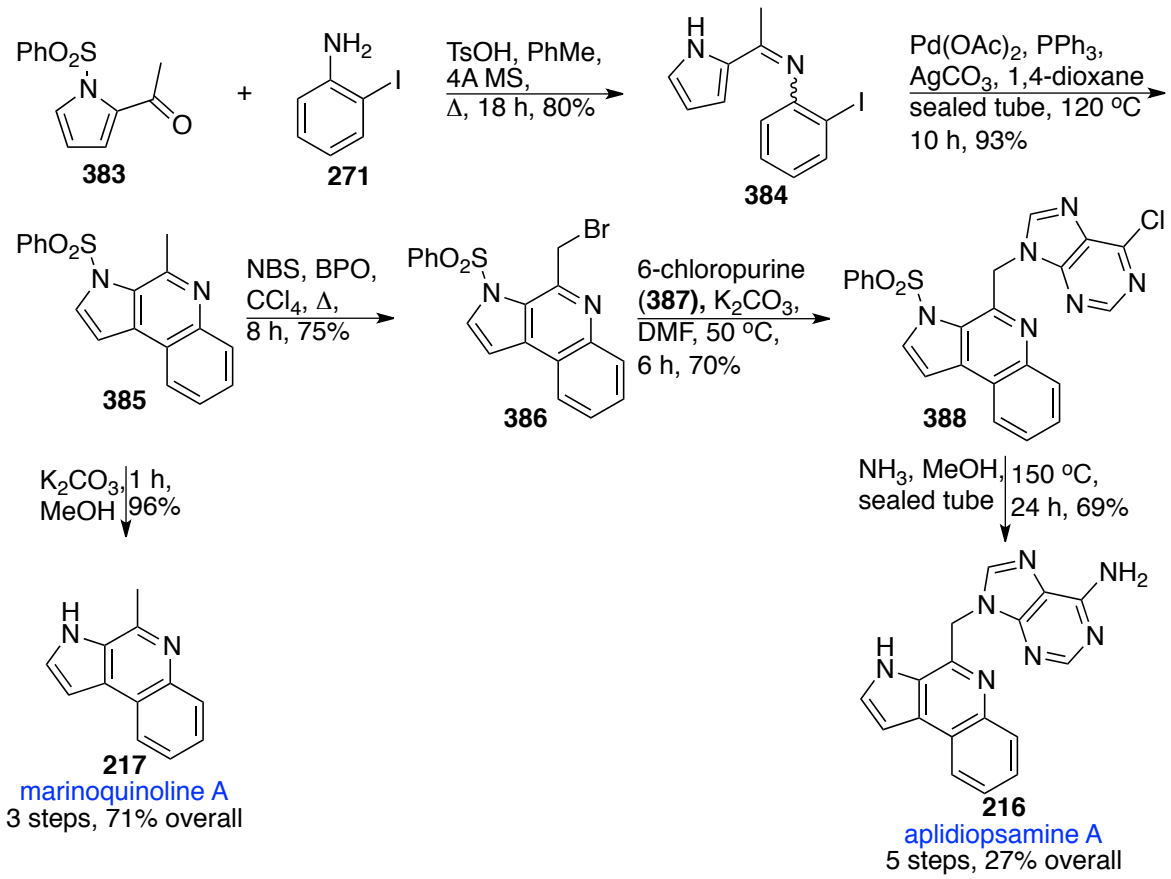
Scheme 84. Correira total synthesis of marinoquinolines A-C and E.

Banwell *et al.* were next to report their efforts toward marinoquinoline A (scheme 85).[113] Following the procedure of Masquelin and Obrecht, they prepared pyrrole **378**, which underwent Ullmann cross-coupling with 2-bromonitrobenzene (**379**). Subsequent methylation with MeLi and DMP oxidation of the resulting alcohol **381** afforded the corresponding ketone **382**. An impressive Mg/MeOH mediated nitro reduction/NTs deprotection/imine condensation cascade was successful in affording the desired heterocycle, marinoquinoline A (**217**) in seven linear steps.



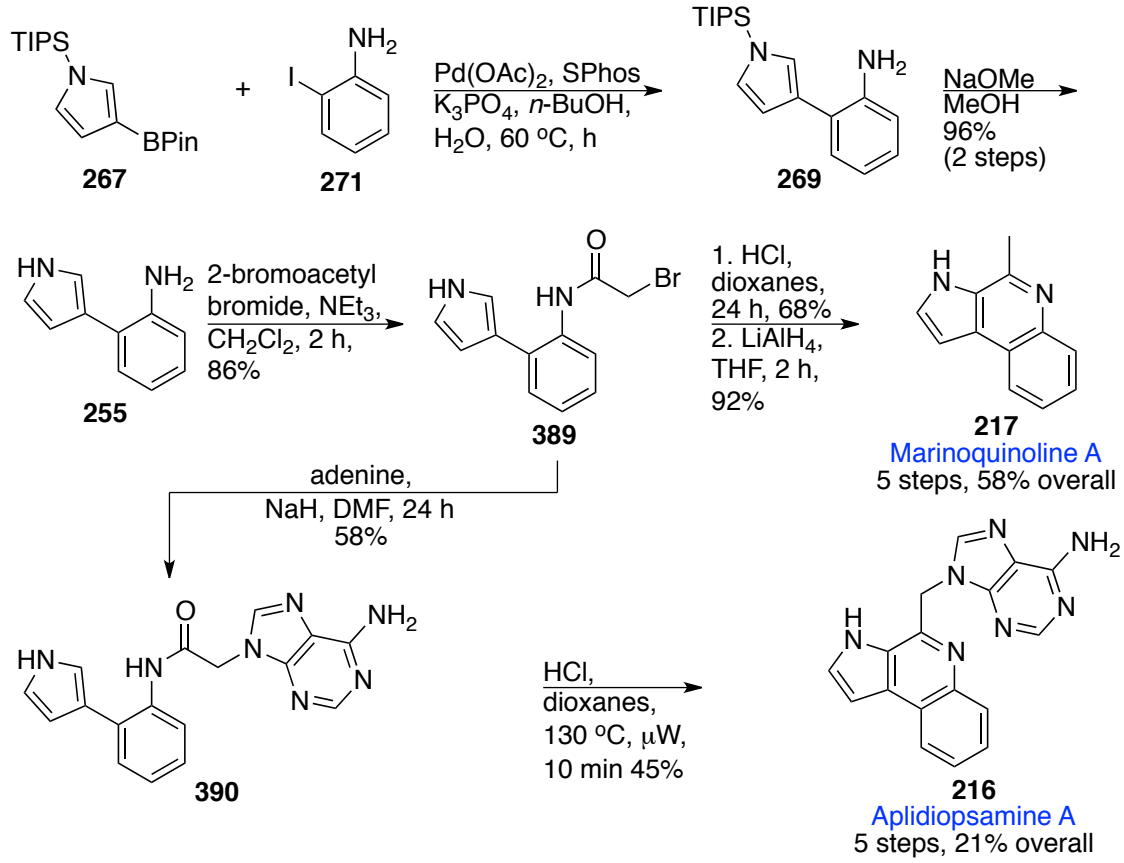
Scheme 85. Banwell total synthesis of marinoquinoline A.

Using palladium catalysed cyclization methodology, Mhaske *et al.* (scheme 86) were able to access pyrroloquinoline **385** in two steps, which was smoothly converted to marinoquinoline A (**217**) or bromo pyrroloquinoline **386** which subsequently provided aplidiopsamine A (**216**) in a further 2 steps.[114] This approach towards marinoquinoline A is the shortest and highest yielding reported to date.



Scheme 86. Mhaske total synthesis of marinoquinoline A and aplidiopsamine A.

Lindsley published his biomimetic synthesis of aplidiopsamine A and via **385**, marinoquinoline A and three 3*H*-pyrrolo[2,3-*c*]quinolone analogues. Using an approach similar to ours, they accessed aplidiopsamine A in 5 steps and 22% overall yield (scheme 87).[110] While their synthetic protocol is two steps shorter, their overall yield is inferior by more than two-fold. The biological evaluation of the compounds revealed interesting and novel phosphodiesterase (PDE) 4 activity. PDE4 is an important second messenger primarily in the mediation of the inflammatory response, and its inhibition has been shown to supress the inflammatory response *in vitro* and *in vivo*.[115]



Scheme 87. Lindsley total synthesis of marinoquinoline A and aplidiopsamine A.

5. Future Work

We have developed a highly successful and general method for the preparation of a diverse array of pyrroloquinolines and related compounds. Further to our initial analogues, scope remains for supplementary investigation into SAR of these compounds with the aim of finding more broad-acting and potent derivatives. Given the success of thienoquinoline **357**, it seems appropriate to explore further modifications of the pyrrolo moiety – perhaps furano or pyridinyl derivatives. Further method development of the Pictet-Hubert reaction to facilitate the synthesis of a more diverse series of molecules would be highly desirable. We have not managed to elucidate clear SAR's of these compounds with our small library. Our synthetic methodology should facilitate the preparation of analogues with a spacer larger than methylene, and a combination of each of the above modifications could significantly improve our knowledge of SAR in this class of compounds.

In addition, 2 of the marinoquinolines – marinoquinoline D and F remain attractive targets, since to date, no total synthesis has been reported.

6. Conclusions

In summary, we have developed a new approach to the synthesis of 3*H*-pyrrolo[2,3*c*]quinolines. Key steps include a Suzuki-Miyaura cross-coupling reaction and Movassaghi-Pictet-Hubert cyclizations. This synthetic protocol has facilitated the total synthesis of 5 natural products – marinoquinolines A-C and E, and aplidiopsamine A. We report the total synthesis of aplidiopsamine A in 46% overall yield in 7 steps and marinoquinolines A, B, C and E in 30-68% overall yield in 6 steps from readily available, cheap starting materials. In addition, a small library of compounds has been prepared for biological assays and SAR investigation.

Analysis of the results from the biological assays have not enabled a clear understanding of SAR, which given the size of library is expected. We showed a complete lack of activity in both antimicrobial and cytotoxicity assays for triazole **352**, and inactivity in microbial assays of morpholine **351**. Compared to marinoquinoline C, thienoquinoline **357** showed enhanced activity against various pathogens, though it did exhibit a narrower spectrum of activity. All other analogues were generally inferior to **357** and marinoquinoline C (**219**). We saw a trend for the more polar compounds to exhibit lower activity generally, suggesting there may be important lipophilic interactions with the target to exploit.

Chapter 3

Pd(0) CATALYZED ALLYLATIVE CYCLIZATIONS

Studies Toward the Total Synthesis of Pyrrolo[2,3-b]indole Natural Products

1. Introduction

Indole alkaloids derived from tryptophan and tryptamine, have long been at the forefront of synthetic chemistry efforts, due to the vast structural diversity and interesting biological activities. Some examples are provided in figure 7, which highlights this diversity.

In recent years, a large number of total syntheses of tryptophan derived natural products have been reported. These can vary from the monomeric alkaloids[116–120] to the directly coupled dimeric,[121,122] trimeric[123,124] and even multimeric[125,126] tryptophan or tryptamine containing alkaloids, which have been isolated and in some cases prepared synthetically. Their interesting biological activities are diverse, and include cytotoxic properties, plant growth regulation properties, vasodilatory properties and a reversal of multiple drug resistance.

Of particular interest to us are the monomeric C3-reverse prenylated pyrrolo[2,3-*b*]indoles, towards which much synthetic work has been reported, led primarily by the pioneering studies of Samuel Danishefsky in the 1990's.[127,128] Some examples of these alkaloids are provided in figure 8, and are divided into *exo* and *endo* configured alkaloids, to discriminate between the relative stereochemistry of the C2-C3 configuration of the indole.[129] While the stereochemical relationship of the H2 and C3-prenyl moieties is fundamentally *cis*, the relative configuration found in nature is for both the *exo* and *endo* enantiomers, although it appears the *exo*-enantiomers are more prolific, with more of this configuration having been isolated to date.[129] In some cases, both *exo* and *endo* configured alkaloids, such as epiamauromine (**408**) have been isolated.

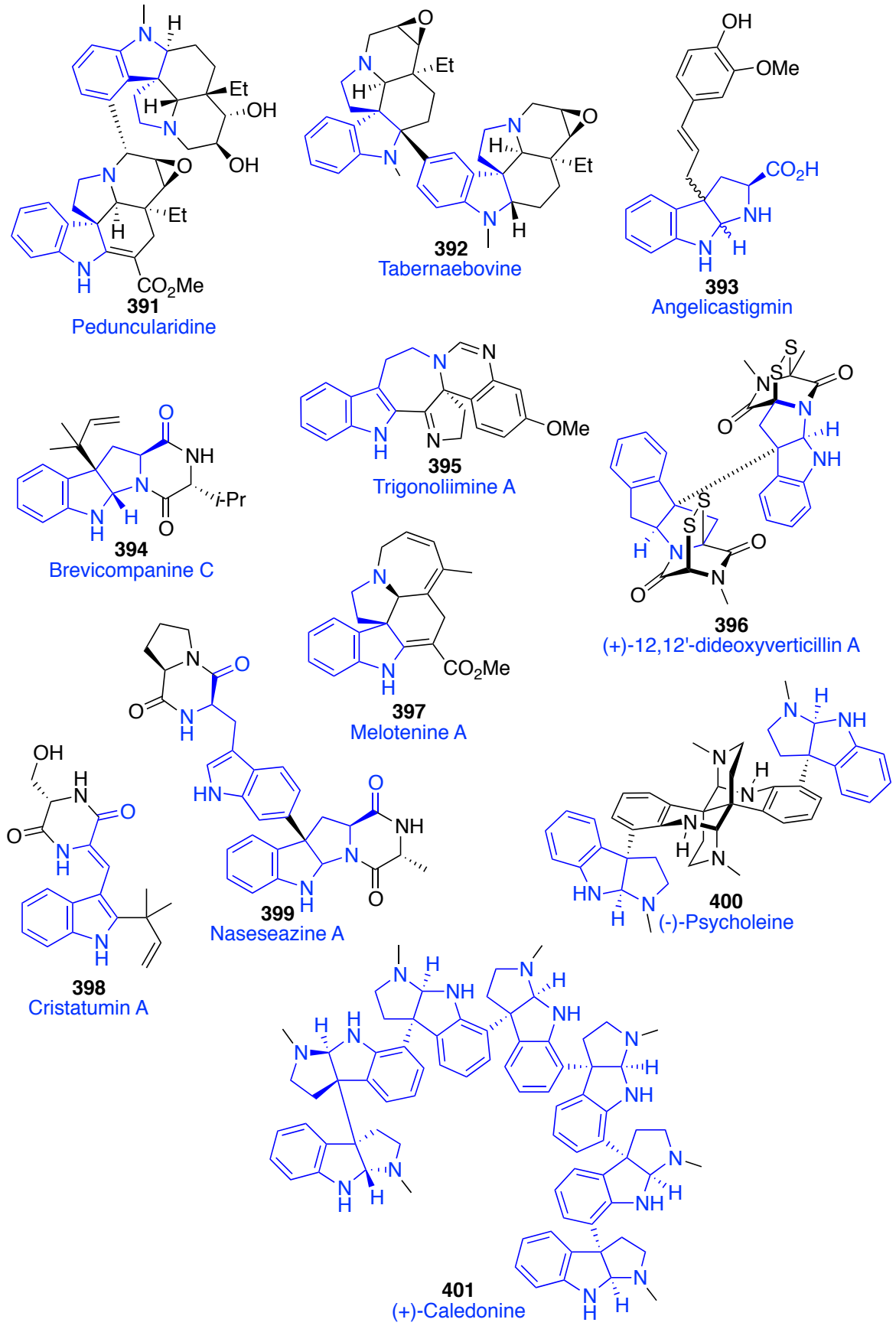


Figure 7. A selection of indole alkaloids.

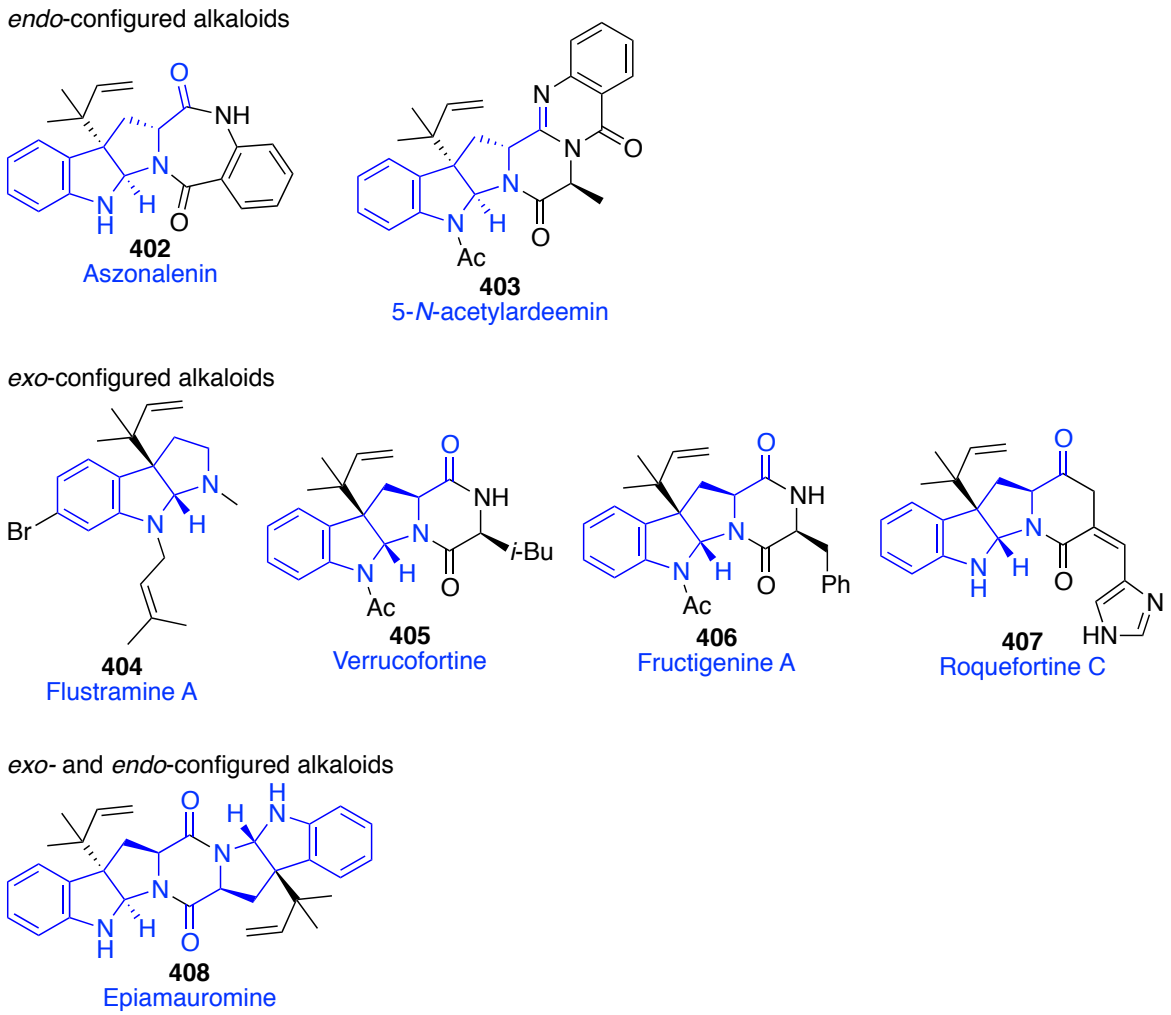
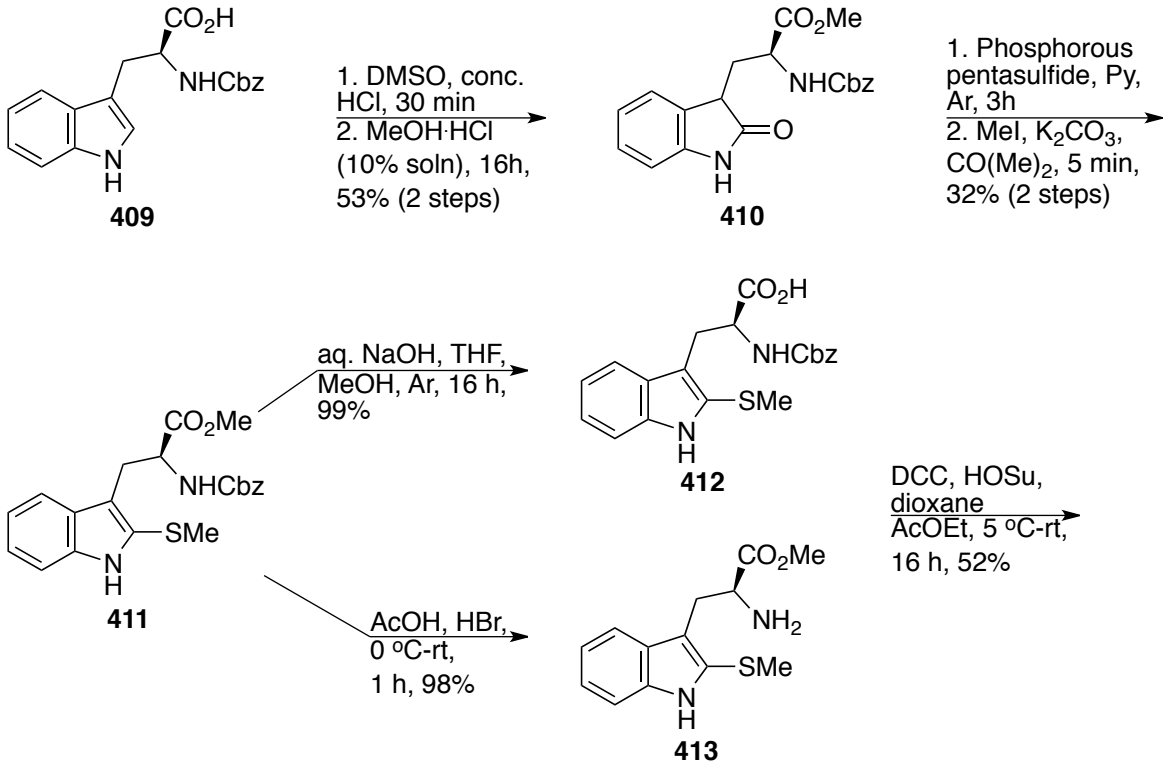


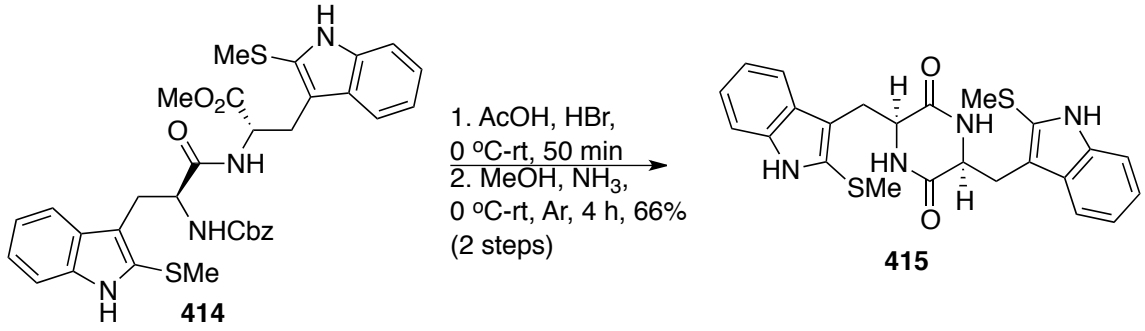
Figure 8. A selection of reverse-prenylated pyrrolo[2,3-*b*]indole alkaloids

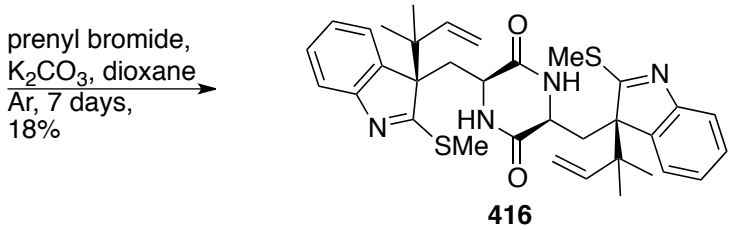
1.1. Existing Approaches for the Synthesis of Pyrrolo[2,3-*b*]indoles

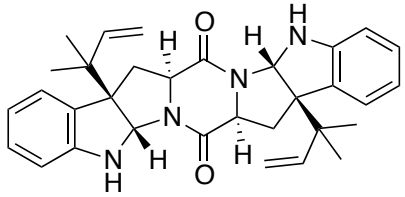
1.1.1. Thio-Claisen Rearrangement of Sulfonium Salts

Shortly after the isolation of amauromine, Takase *et al*. reported the first total synthesis, utilising the thio-Claisen rearrangement approach outlined in scheme 88. While the approach was successful, the yields for many of the steps were rather poor. Nevertheless, to our knowledge, this is the first example of its kind in the construction of reverse prenylated pyrrolo[2,3-*b*]indole architecture.







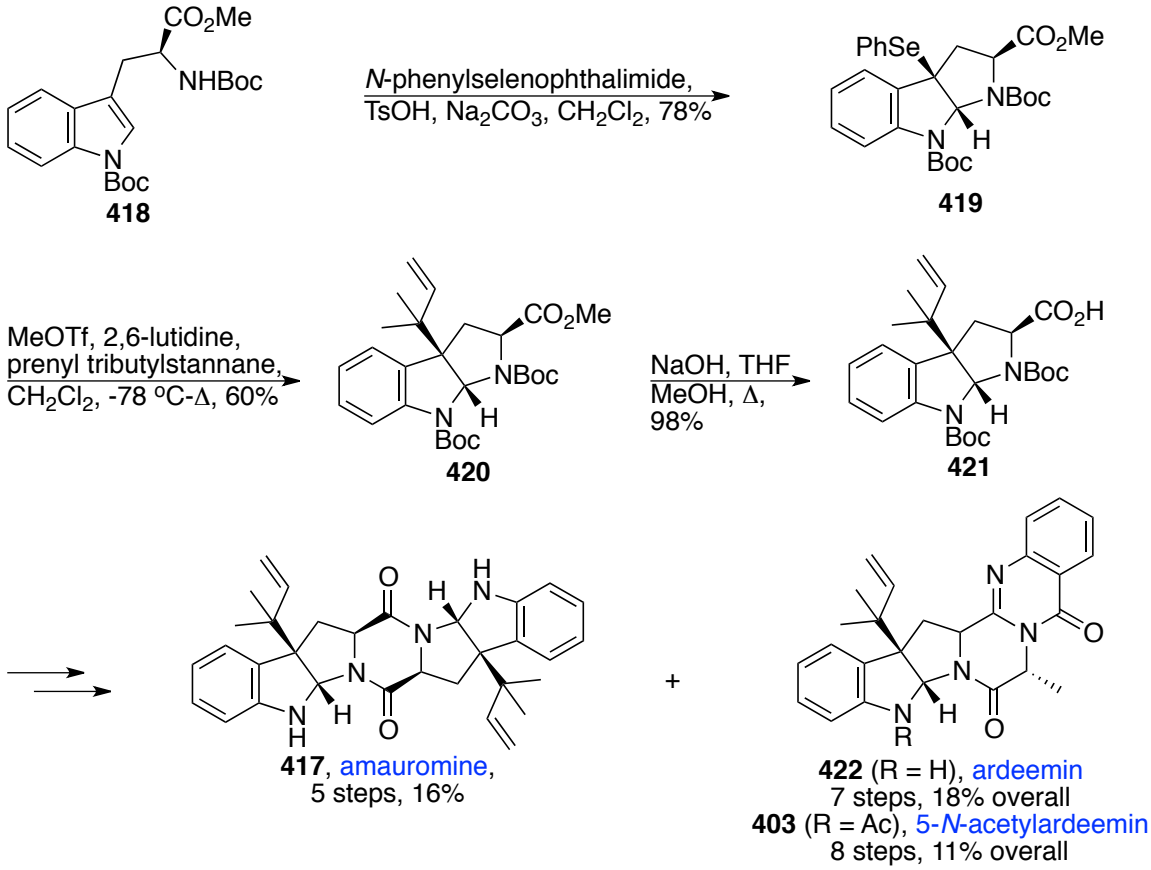


417, amauromine,
10 steps, 0.16% overall

Scheme 88. Takase approach for the preparation of amauromine using a thio-Claisen rearrangement

1.1.2. Oxidative C3 Alkylation and Cyclization of Tryptophan Derivatives

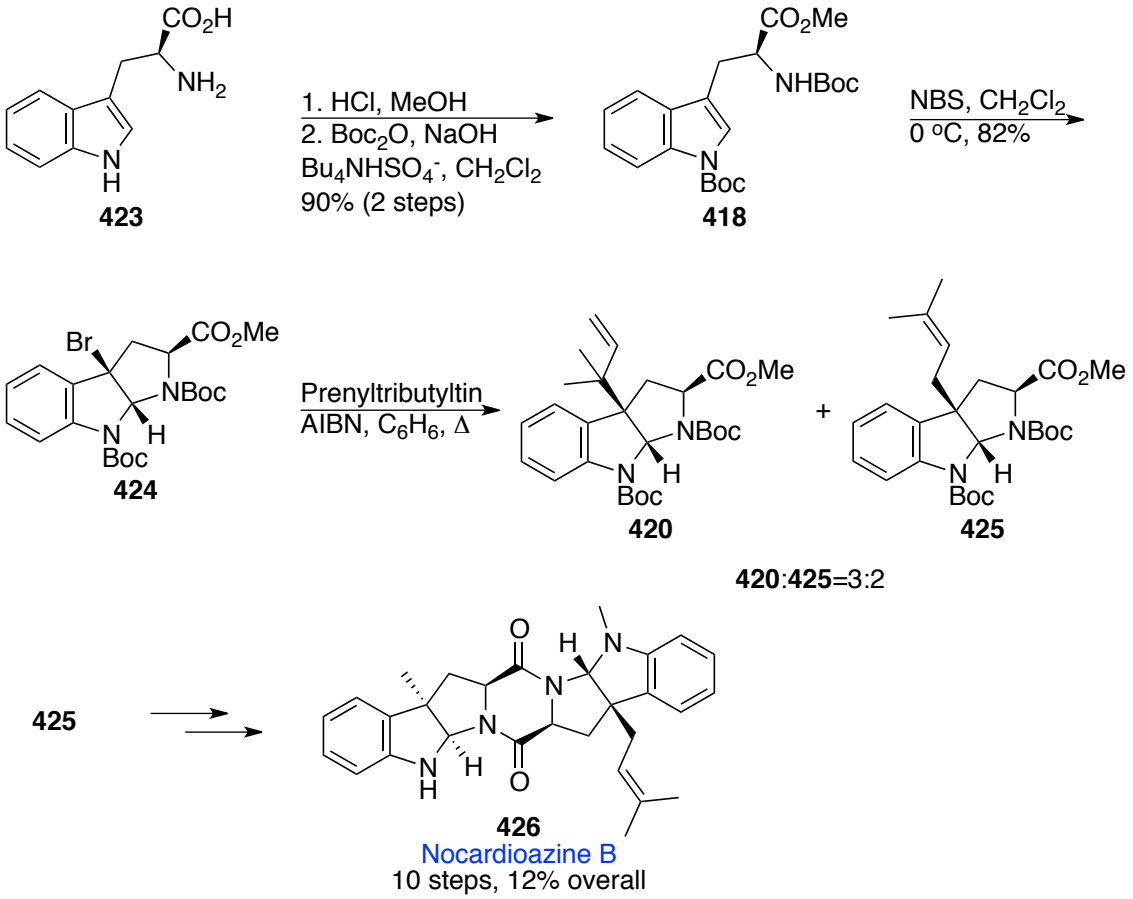
In 1994, Danishefsky reported his C3 oxidative alkylation and spontaneous iminium cyclization towards the total synthesis of amauromine (**417**) and ardeemins **403** and **422**.[127] By exposing *bis*-Boc protected tryptophan **418** to *N*-phenylselenophthalimide and catalytic TsOH, it was possible to access in one step the corresponding selenopyrrolidine **419** as a 9:1 mixture of diastereoisomers. Reaction with prenyl tributylstannane in the presence of a Lewis acid, afforded the reverse prenylated pyrroloindole **420** with retention of stereochemistry. This afforded the key synthetic intermediate, which enabled access to amauromine, ardeemin and 5-*N*-acetylardeemin (scheme 89). As can be seen, amauromine was afforded in 16% overall yield in just 5 steps from Boc-Trp(Boc)-OMe, which compares very favourably with the synthesis of Takase. Further development of this chemistry[128] made it the gold standard for reactions of this kind, until very recently, as discussed *vide infra*.



Scheme 89. Danishefsky selenocyclization and stannyl coupling approach towards reverse prenylated pyrrolo[2,3-*b*]indoles.

1.1.3. Bromocyclizations and Subsequent C3 Modification

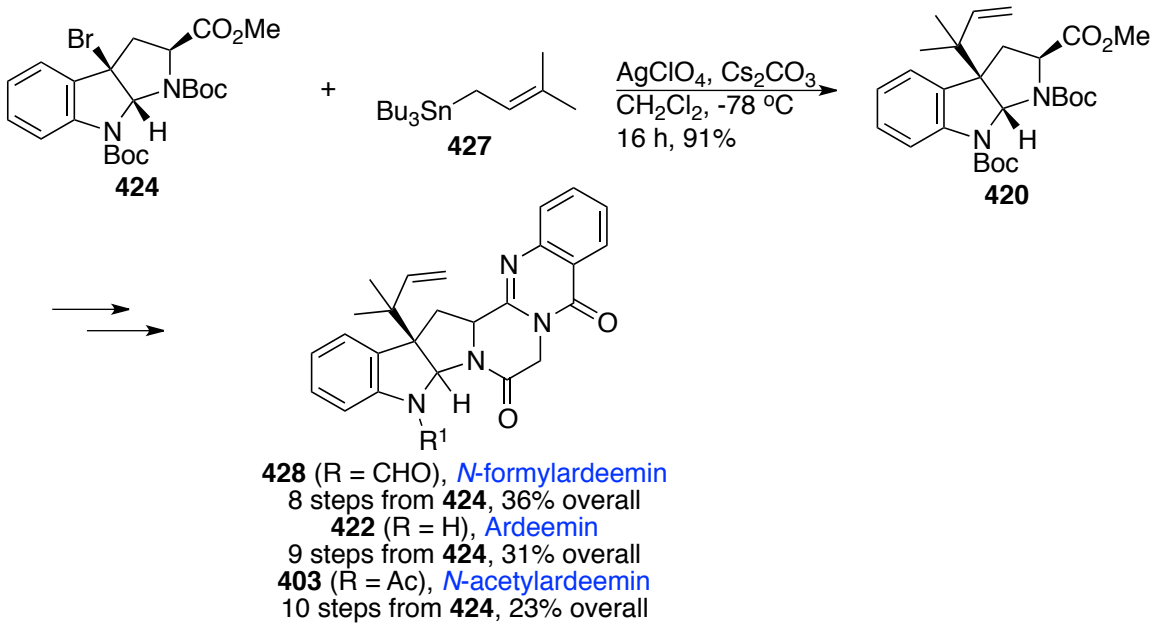
The use of NBS and bromine as electrophilic activators for the bromination/cyclization cascade to access hexahydropyrrolo[2,3-*b*]indoles from tryptophan derivatives was first reported in 2008 independently by de Lino[130] and Movassaghi[131] respectively. Since then, it has been developed further by Movassaghi[132–135] and Stevenson[136] and has become one of the most effective and widely-applied approach to access the pyrrolo[2,3-*b*]indole skeleton with good yield and stereoselectivity. Not only is this approach useful for the preparation of the numerous C3 reverse prenylated alkaloids, but also the polymeric alkaloids such as psychotetramine,[125] for which its application is more widely used. Scheme 90 depicts Xu and Ye's total synthesis of nocardioazine B, using electrophilic bromine reagents to mediate the cyclization. The prenyl group was installed using a radical approach, and it can be seen a mixture of the desired prenyl and undesired reverse prenyl were afforded in this case.



Scheme 90. Bromocyclization and radical coupling approach towards nocardioazine B.

Qin also utilised this bromocyclization methodology and, inspired by Danishefsky and Movassaghi, mediated a Friedel-Crafts reaction catalysed by silver Lewis acids to allow exclusive access to

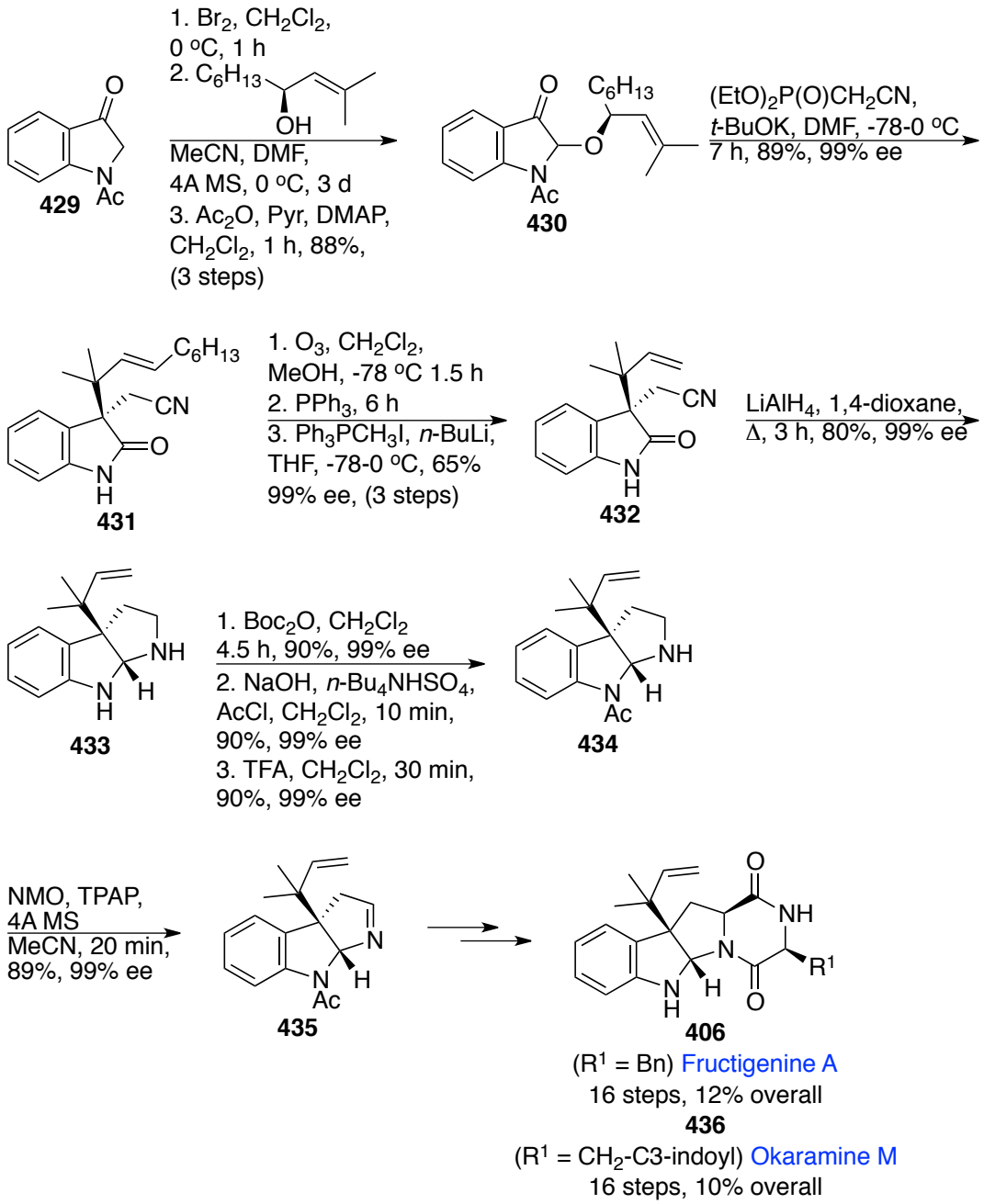
reverse-prenylated pyrrolo[2,3-*b*]indole alkaloids such as ardeemin and *N*-acetylardeemin (scheme 91).[137]



Scheme 91. Bromocyclization and Friedel-Crafts reaction for the synthesis of pyrrolo[2,3-*b*]indoles.

1.1.4. Reductive Cyclizations

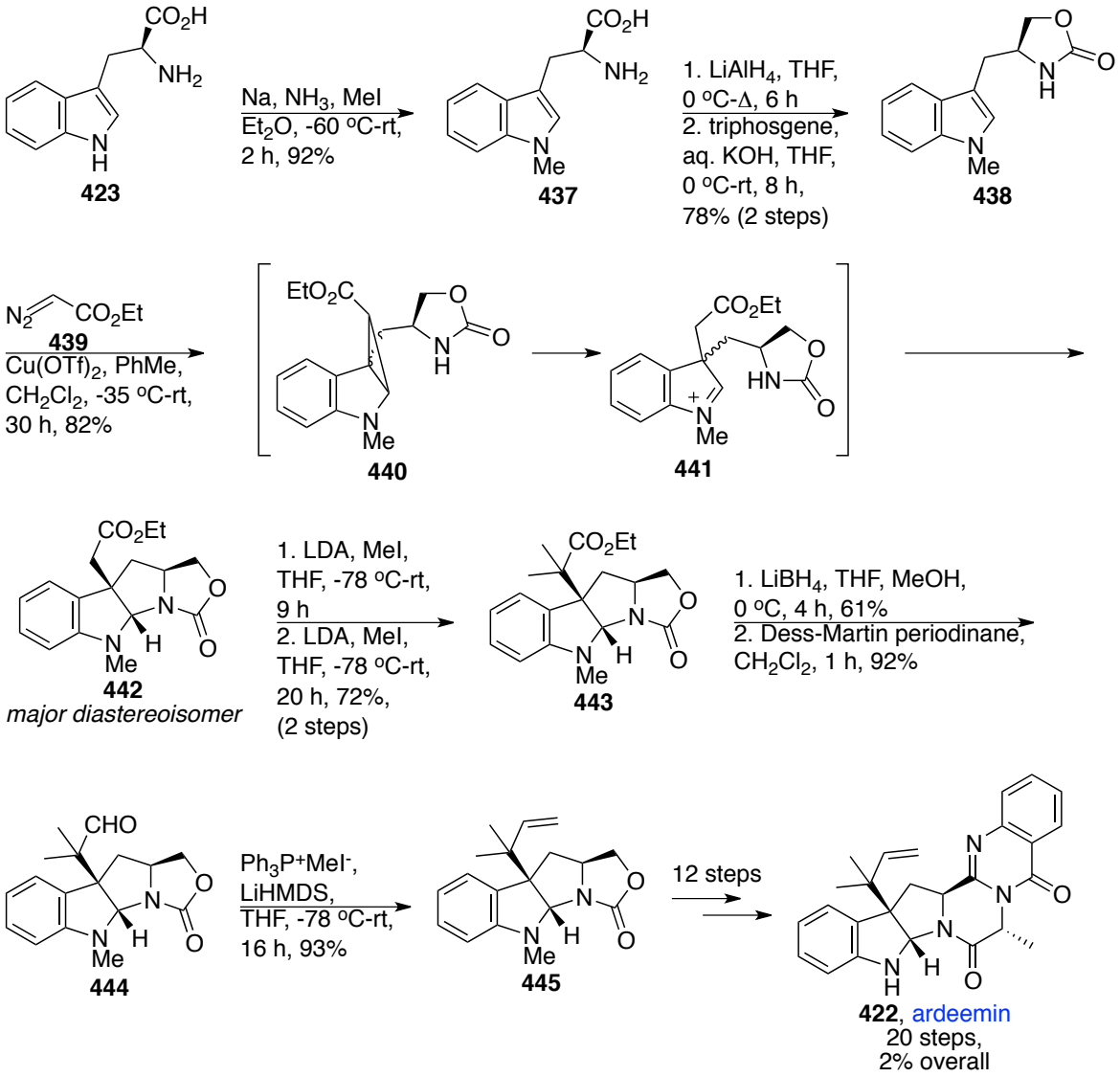
Kawasaki *et al.* have reported an enantioselective olefination/isomerization/Claisen rearrangement cascade for the synthesis of C3-di-substituted indolinone **431** from indolinone **429** in good yield.[138,139] Subsequent transformations allow access to pyrrolo[2,3-*b*]indoles through a reductive cyclization, which has enabled the first total syntheses of fructeginine A and okaramine M, both in 16 steps (scheme 92).



Scheme 92. Kawasaki reductive cyclization approach towards pyrrolo[2,3-*b*]indole natural products.

1.1.5. Cyclopropanation Reactions

Qin *et al.* have utilized Cu(II)-catalyzed cyclopropanations of indoles with activated diazo compounds for the diastereoselective synthesis of ardeemin (scheme 93).[140] The approach is general and could, in principle be applied to the total synthesis of many reverse-prenylated pyrrolo[2,3-*b*]indoles.

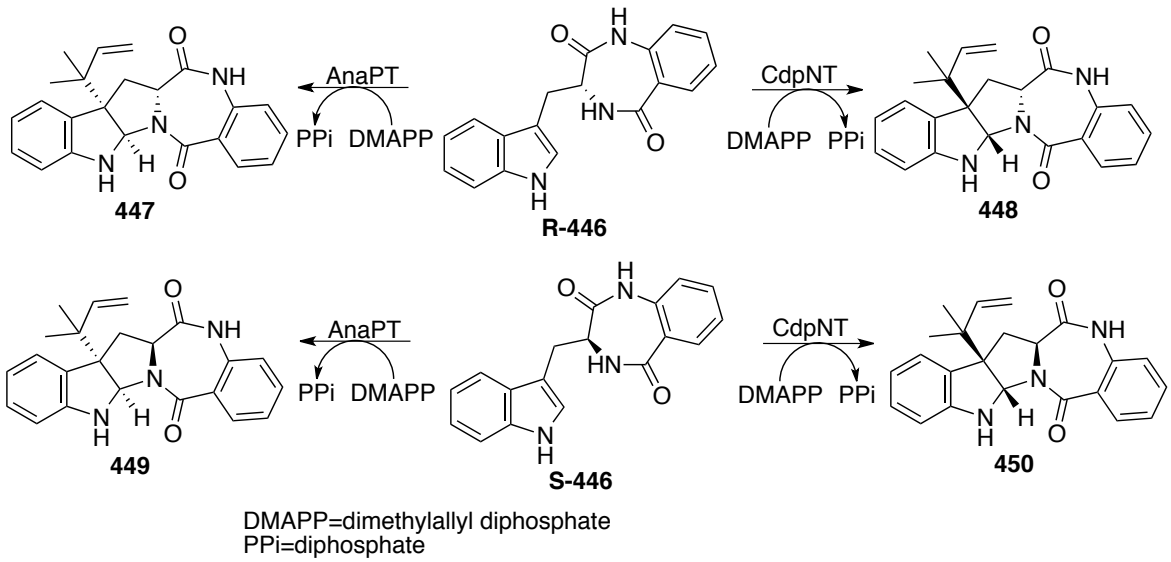


Scheme 93. Qin cyclopropanation approach towards ardeemin.

1.1.6. Use of Recombinant Prenyltransferases for C3 Alkylations

The use of enzymes to carry out synthetic transformations in organic chemistry is an ever-increasing field of research, particularly in asymmetric synthesis.[141,142] Recently, Li *et al.* have utilised this approach in the synthesis of C3-reverse prenylated pyrrolo[2,3-*b*]indoles, which has led to the synthesis of several of these alkaloids. By cloning and overexpressing a gene cluster identified by gene mining as a prenyltransferase, they were able to access synthetically useful amounts of prenyltransferases AnaPT and CdpNPT, which they found to readily catalyse the stereoselective C3-reverse prenylation and cyclization of benzodiazepinones.[143] In fact, AnaPT and CdpNPT introduce the reverse prenyl moiety on opposite faces of the benzodiazapinones,

facilitating access to *exo*- and *endo*-configured products in excellent chemical yield (scheme 94).[129,144]



Scheme 94. Use of recombinant enzyme approach towards the synthesis of reverse prenylated hexahydropyrrolo[2,3-*b*]indoles.

1.2. Project Aims and Our Synthetic Approach

C3-reverse prenylated pyrrolo[2,3-*b*]indoles are abundant in nature as bioactive alkaloids. While many total syntheses have been reported, many of these natural products remain unsynthesized by the organic chemist. One such alkaloid is brevicompanine C, isolated from *Penicillium brevi-compactum* in 2005 (figure 9).[119] The natural product belongs to the diketopiperazine family of pyrrolo[2,3-*b*]indoles, and has reported plant growth regulatory properties, which as a result makes it a compound of significant interest in an agricultural setting as the world's food demand increases exponentially.

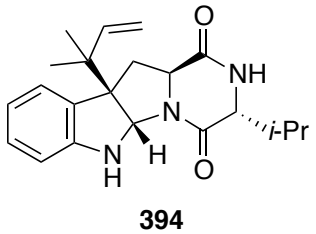
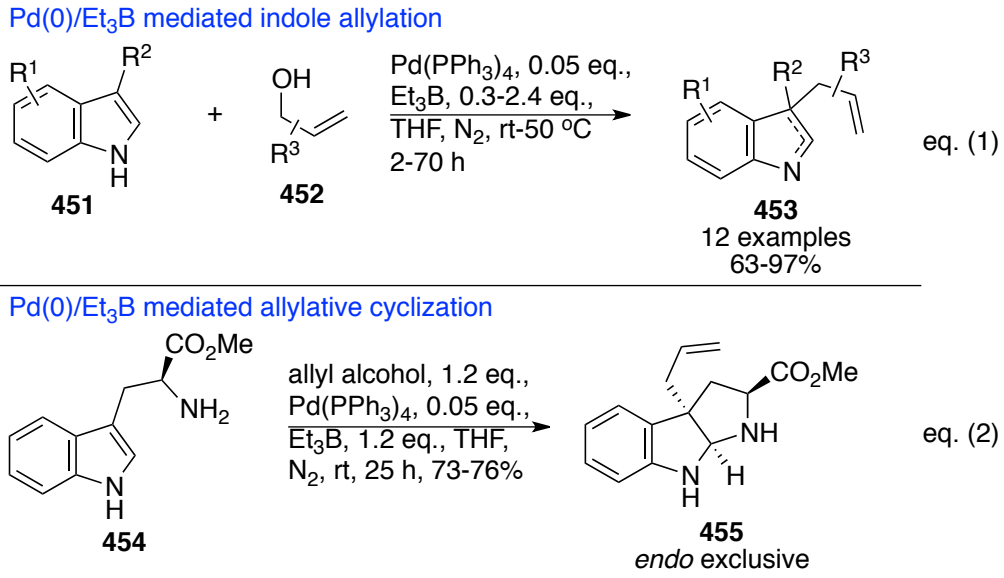


Figure 9. Brevicompanine C.

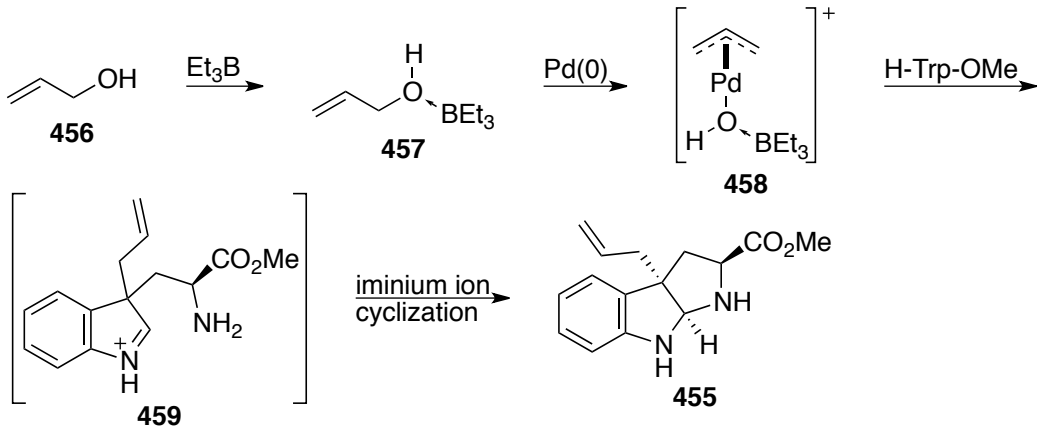
In 2005, Tamaru reported a novel approach towards C3 functionalization of indolyl compounds using trialkylborane and Pd(0) chemistry (eq. (1) scheme 95).[145] In addition to this, he also

reported the synthesis of pyrrolo[2,3-*b*]indoles from tryptophan methyl ester (H-Trp-OMe) functionalized at C3 with an allyl group (eq. (2) scheme 95). The chemistry proceeds by the generation of an allyl cation, which is captured by the indole at the most nucleophilic C3 position, promoting spontaneous iminium cyclization onto the indole with the pendant amine function to access the pyrrolo[2,3-*b*]indole skeleton.



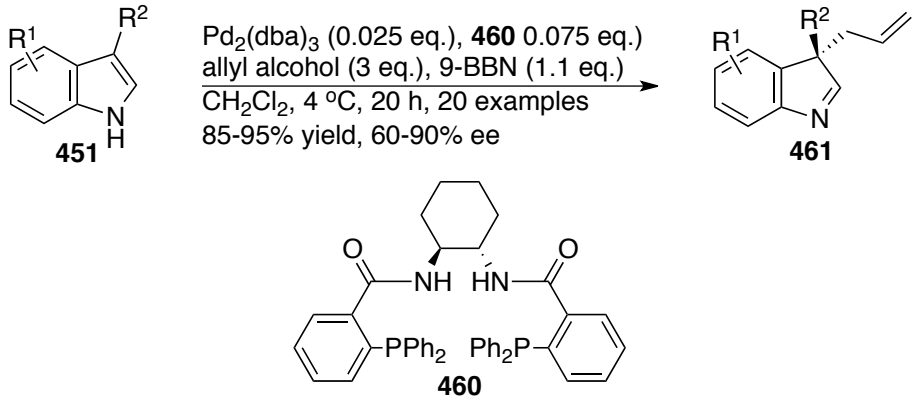
Scheme 95. Tamaru allylation of indoles and allylative cyclization of tryptophan.

These reactions proceed with the generation of an allyl cation. In the case of the H-Trp-OMe cyclizations, the amino group traps the iminium ion to form the new pyrrole ring (scheme 96).

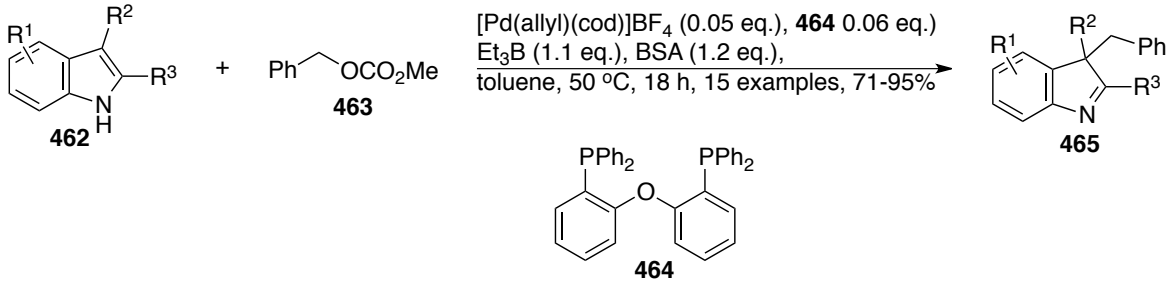


Scheme 96. Proposed reaction mechanism for the Pd catalyzed, Et_3B mediated allylative cyclizations.

Inspired by these transformations, Trost[146] developed an enantioselective approach to the C3 alkylation of indoles (scheme 97) and very recently Rawal[147] reported the suitability of benzyl methyl carbamates to the benzylation of indoles (scheme 98).



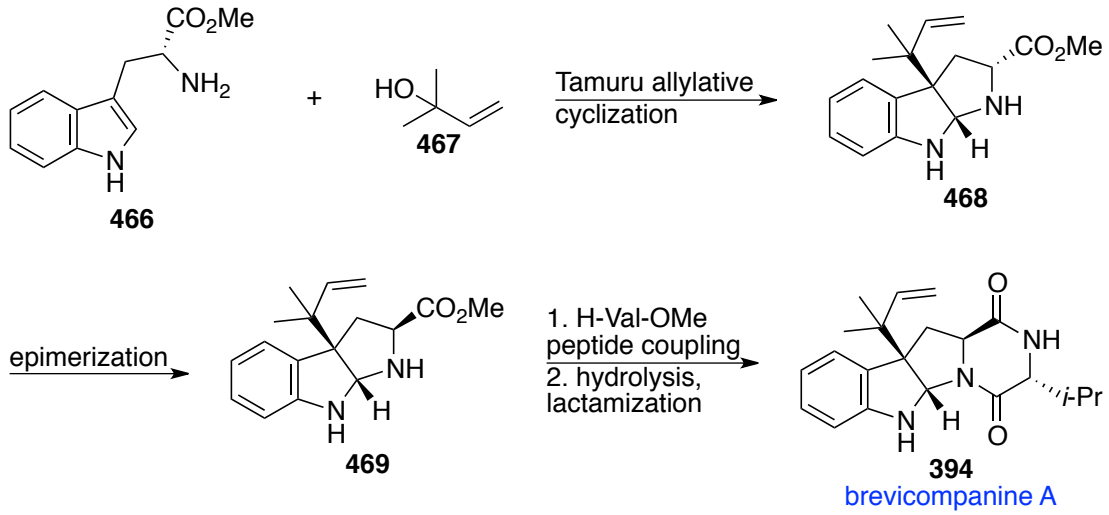
Scheme 97. Trost Pd catalyzed enantioselective indole allylation.



Scheme 98. Rawal Pd catalyzed indole benzylation.

We proposed by following Tamuru's approach, subsequent transformations should enable access to brevicompanine C (Scheme 99). Unfortunately for us, the *endo* isomer of the hexahydropyrrolo[2,3-*c*]indole skeleton is favoured using the Tamaru approach, while the configuration of brevicompanine C is *exo*. We reasoned the use of D-tryptophan and subsequent epimerization of the amino stereocenter would allow us to access the desired configuration of brevicompanine C. We propose this to be a more direct route compared to traditional electrophilic activations since no amino protecting groups were required. With this in mind we also claim it to be a greener approach, since halogen, selenium or tin containing reagents are not required, and is irrefutably better in terms of step economy and atom-economy. Since the authors only reported the allylative cyclization with allyl alcohol, we would have to explore the possibility of prenylative cyclization, which raises the potential issues of diminished reactivity due to the increased steric demand at the reaction centre, and regioselectivity, due to the non-symmetry of the carbocation generated *in situ*. Because of the abundance of C3 functionalized

pyrrolo[2,3-*b*]indole alkaloids, we were not overtly concerned, since if the reverse prenyl derivatives were not accessible, we were confident of accessing other, less sterically hindered substrates, or standard prenyl substituted alkaloids in the case of regioselectivity issues. In any case, the desired regioselectivity was achieved in the prenylation of indole in one of the examples of the type **453** (scheme 95), and as such we were reasonably confident of success when applied to the tryptophan cyclization case.

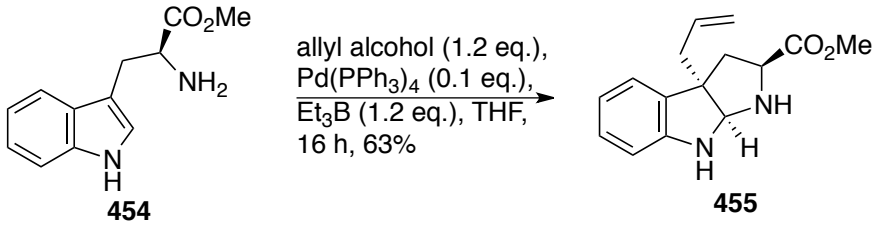


Scheme 99. Our proposed synthetic route to brevicompanine C.

2. Results and Discussion

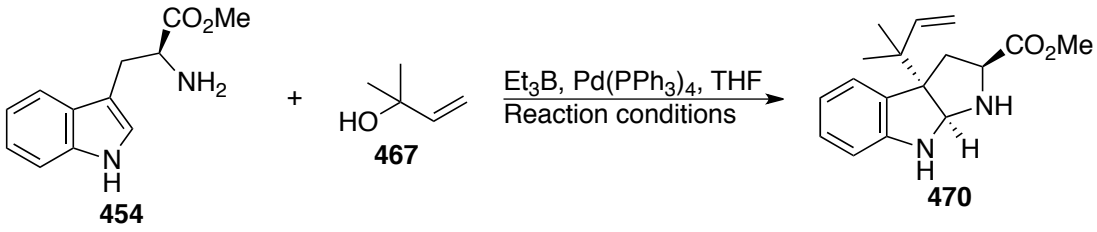
2.1. Allylative Cyclizations Towards the Synthesis of Brevicompanine C

Before we embarked upon the allylative cyclization to afford C3-reverse-prenylated pyrroloindole architecture, we first concentrated upon repeating the allylative cyclization of Tamaru with allyl alcohol. This was successfully achieved, affording the desired allyl hexahydropyrrolo[2,3-*b*]indole (**455**) in 63% yield, comparable with that reported in the literature by Tamaru (scheme 100).[145] We did however fail to access this substrate free from triphenylphosphine oxide contamination, and the yield is based upon the mass of the product, corrected corresponding to ^{1}H NMR integrations. At this point, we did not overtly concern ourselves since it likely subsequent reactions would enable the removal of phosphine oxide by chromatography, should this be a continuing problem.



Scheme 100. Allylative cyclization of H-Trp-OMe with allyl alcohol.

Having successfully reproduced Tamaru's allylative cyclization with allyl alcohol, we moved to alcohol **467** and at this stage, continued with L-tryptophan methyl ester during the method development stage for the synthesis of brevicompanine C (scheme 101). Despite our success in the case of allyl alcohol, we were disappointed to observe no conversion to the desired pyrroloindole **470**, recovering starting materials in quantitative amounts (table 30, entry 1). Subsequently, we repeated the reaction at elevated temperature, but again these reactions failed at 30 ^{o}C, 40 ^{o}C and reflux (entries 2-4). There have been successful 'reverse-prenylations' reported by Tamaru (scheme 102), but never with H-Trp-OMe.[145] Given we had seen success with allyl alcohol, Tamaru had reported the 'reverse-prenylation' of indole, and the recovery of starting materials rather than side products during our experiments towards **470** (scheme 101), we propose access to pyrroloindole **470** is not possible using this approach, due to steric factors.



Scheme 101. Proposed application of Tamaru's allylative cyclization for the synthesis of pyrroloindole **470**.

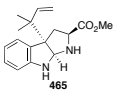
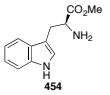
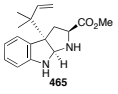
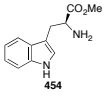
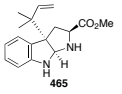
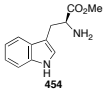
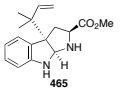
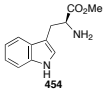
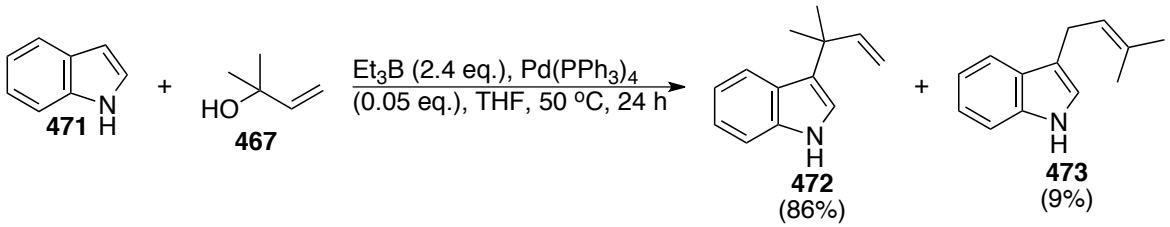
Entry	Reaction conditions	Reaction outcome (yield)	
1	**467** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 12 h	 **465** (0%)	 **454** (100%)
2	**467** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 30 °C, 12 h	 **465** (0%)	 **454** (100%)
3	**467** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 40 °C, 12 h	 **465** (0%)	 **454** (100%)
4	**467** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 66 °C, 12 h	 **465** (0%)	 **454** (100%)

Table 30. Attempts to access reverse-prenyl pyrrolo[2,3-*b*]indoles using the Tamaru allylative cyclization approach.



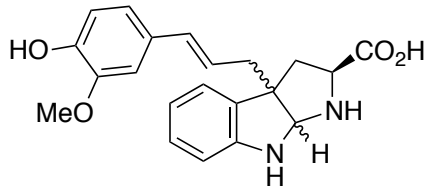
Scheme 102. Tamaru's 'reverse-prenylation' of indole.

Although the failure of this reaction was disappointing, we anticipated problems since the chemistry has been well reported, but there has been no discussion of 'reverse-prenylation' of H-Trp-OMe, despite the abundance of natural products available to synthesize. Although we had the option to further explore routes to access reverse-prenyl pyrrolo[2,3-*b*]indoles using the allylative cyclization methodology (*vide infra*) we instead decided to abandon this stream of the

project, and instead target a natural product which we thought would prove to be more amenable to this approach. A search of the literature led us to angelicastigmin.

2.2. Allylative Cyclizations Towards the Synthesis of Angelicastigmin

Angelicastigmin (**393**) is a hexahydropyrrolo[2,3-*b*]indole substituted at C3 by a coniferyl group (figure 10), and was isolated from *Angelica polymorpha Maxim* and reported in 2000.[118] We proposed the corresponding coniferyl cation would be less sterically encumbered compared to that of the prenyl cation, which may facilitate the desired alkylation/cyclization cascade. Further to this, determination by the authors of the relative stereochemistry of angelicastigmin was not possible despite NOE ^{1}H NMR experiments being conducted. Should our synthetic endeavours be successful, we proposed in addition to the first total synthesis of angelicastigmin, we would be able to synthesize enough material to enable analysis by X-ray crystallography for determination of the relative stereochemistry of the natural product.

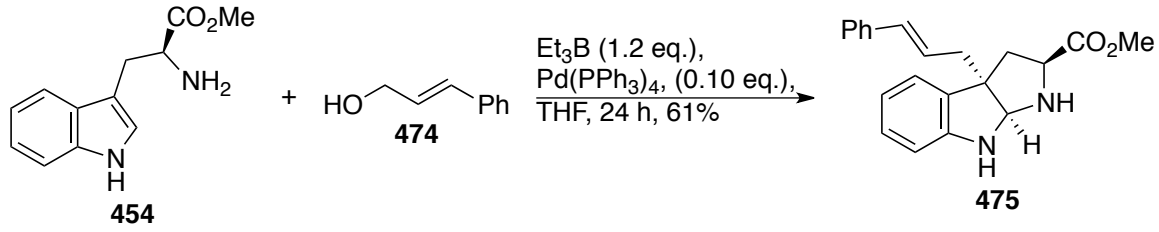


393
Angelicastigmin

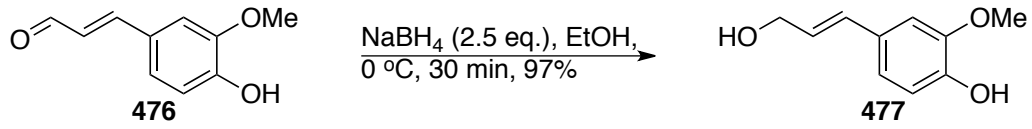
Figure 10. Angelicastigmin

2.2.1. Allylative Cyclization of Cinnamyl Alcohol: A Test System

Before embarking upon the synthesis of angelicastigmin, we proposed a test system using cinnamyl alcohol (**474**) in the allylative cyclization would provide us a simpler system to test the applicability of such a cation for the cyclization conditions (scheme 103). We were pleased to observe success in the alkylation/cyclization of H-Trp-OMe and cinnamyl alcohol to afford the corresponding hexahydropyrrolo[2,3-*b*]indole product **475** in 61% yield after 24 h. This result adds credence to our rationalization of the failure of the corresponding cyclizations with prenyl alcohol was due to steric factors. With this positive result in hand, we embarked initially upon the application of coniferyl alcohol (**477**), accessed from the commercially available coniferyl aldehyde (**476**) (scheme 104). The stereochemical outcome is assigned based upon the determination of Tamaru for his allylative cyclization for the synthesis of pyrroloindole **455**.



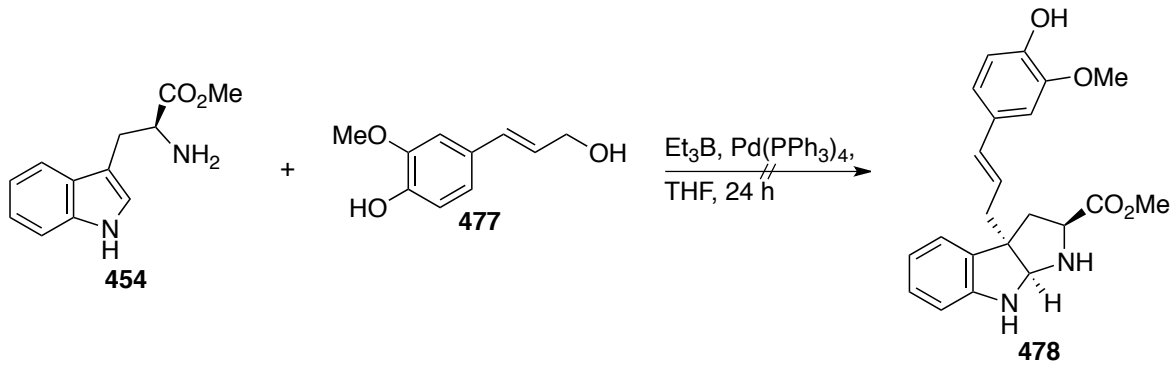
Scheme 103. Allylative cyclization of H-Trp-OMe with cinnamyl alcohol.



Scheme 104. Synthesis of alcohol **477** from aldehyde **476**.

2.2.2. Allylative Cyclization of Coniferyl Alcohol for the Synthesis of Angelicastigmin

Subjecting alcohol **477** to the allylative cyclization conditions used previously, failed to afford the desired product (scheme 105, table 31 entry 1). The reaction was conducted at rt for *ca*. 24 h, with TLC indicating no reaction. We subsequently began heating, and 12 h at 60 °C provided us with a new product as indicated by TLC analysis. Purification of the reaction mixture afforded the product with moderate contamination of phosphine oxide. We were however disappointed the NMR and MS spectra did not match that expected of the cyclized product, and we were unable to identify the structure of this product (entry 2). We subsequently decided upon protection of the free phenol moiety as a TBS ether (scheme 106).



Scheme 105. Attempts towards the synthesis of pyrroloindole **478**.

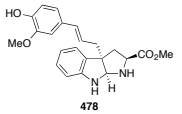
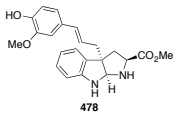
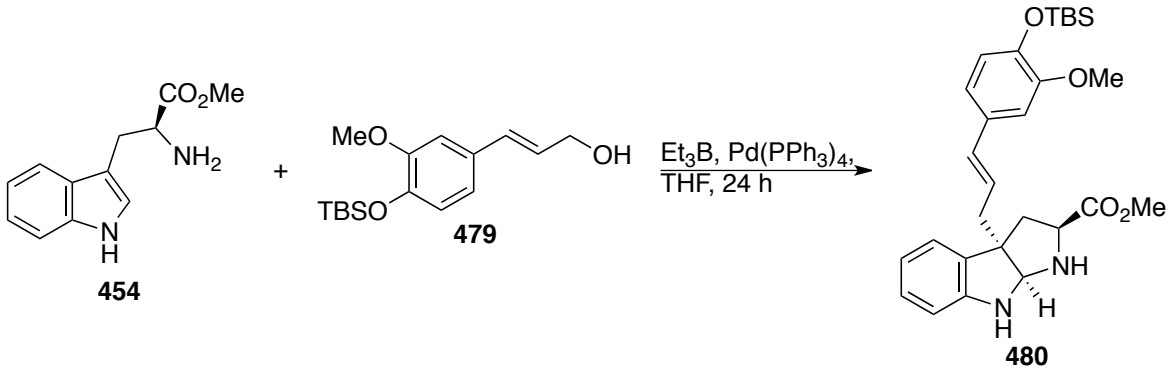
Entry	Reaction conditions	Reaction outcome (yield)
1	**477** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 24 h	 **478** (0%)
2	**477** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 60 ^{o}C, 12 h	 **478** (0%)

Table 31. Attempts towards the synthesis of pyrroloindole **478**.



Scheme 106. Allylative cyclization protocol towards angelicastigmin.

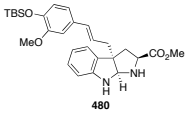
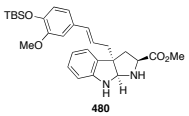
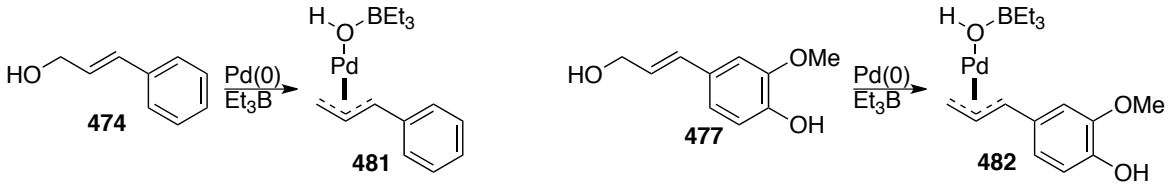
Entry	Reaction conditions	Reaction outcome (yield %)
1	**479** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 12 h	 **480** (11%)
2	**479** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 40 ^{o}C, 12 h	 **480** (0%)

Table 32. Attempts towards the synthesis of pyrroloindole **480**.

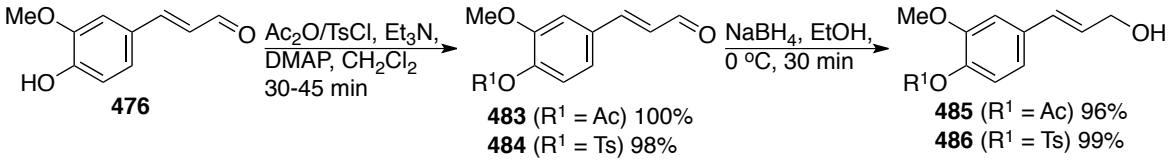
We were pleased to observe pyrroloindole **480** from the reaction of alcohol **479** to the original reaction conditions, however a disappointing 11% yield, with recovery of 64% alcohol **479** was seen (table 32, entry 1). The relative failure of the coniferyl series was surprising given the success of the cinnamyl series, however given the alcohol was recovered, we repeated the reaction, with heating at 40 ^{o}C. This afforded consumption of the alcohol, but as before, NMR and MS analysis indicated the desired product had not been formed and we were again unable to

determine the structure of the isolated product (entry 2). It appeared heating the reaction was resulting in undesired side reactions, so we considered alternatives to increase the productivity of the reaction. Comparing the relative electron richness of the coniferyl and cinnamyl systems, we realised the coniferyl system was significantly more electron rich. While this should not significantly affect the reactivity of the alcohol since conjugation of the OH to the coniferyl system is not present, the corresponding allyl cation would be in conjugation with the coniferyl system, and so its reactivity could be significantly affected by the electronics of the aromatic system (scheme 107).



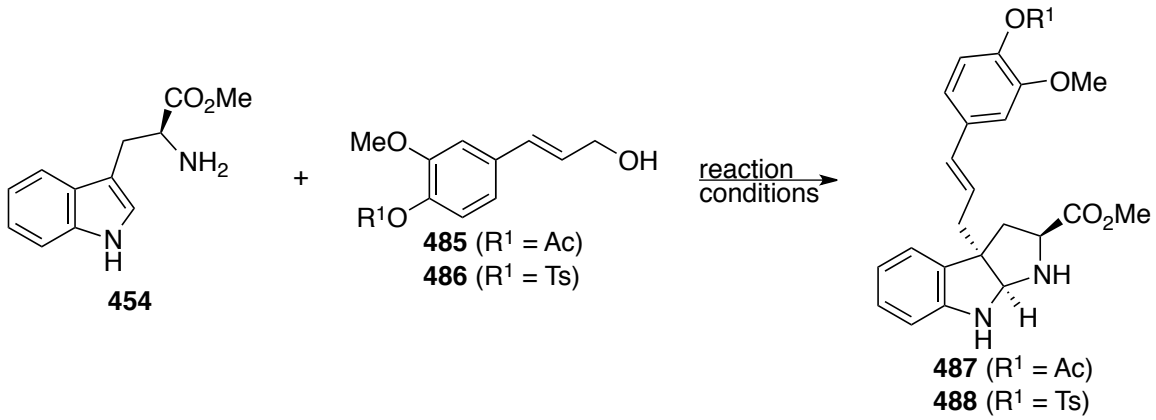
Scheme 107. Allyl cations **481** and **482** from their corresponding allyl alcohols.

To investigate this theory, we proposed the use of electron withdrawing protecting groups on the phenol. To this end, TBS was replaced with Ac and Ts as the phenol protecting group, and should deactivate the aromatic system by varying degrees (scheme 108). If our theory is correct and greater electron density in the aromatic system is stabilising the allyl cation, consequently making the system less reactive, the incorporation of an electron withdrawing group should encourage the reaction to proceed as desired.



Scheme 108. Preparation of alcohols **485** and **486** from aldehyde **476**.

We first applied alcohol **485** to the allylative cyclization protocol, but as with our previous attempts, a disappointing conversion (as confirmed by TLC analysis) was observed (scheme 109, table 33 entry 1). Undeterred, we continued along this theme, and applied alcohol **486** bearing the more deactivating protecting group, Ts. To our surprise, the reaction fared worse that that of the reactions with TBS and Ac protected alcohols, with no conversion observed with TLC analysis (entry 2). With this observation, and due to a lack of time, research was halted at this point.



Scheme 109. Attempts towards the allylative cyclization of H-Trp-OMe and various coniferyl alcohols.

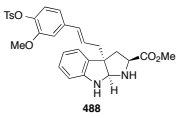
Entry	Reaction conditions	Reaction outcome (yield)
1	**485** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 12 h	n.d.
2	**486** (1.2 eq.), $Pd(PPh_3)_4$ (0.10 eq.), Et_3B (1.2 eq.), THF, 40 °C, 12 h	 **488** (0%)

Table 33. Attempts to access cinnamyl pyrrolo[2,3-*b*]indoles using the Tamaru allylative cyclization approach.

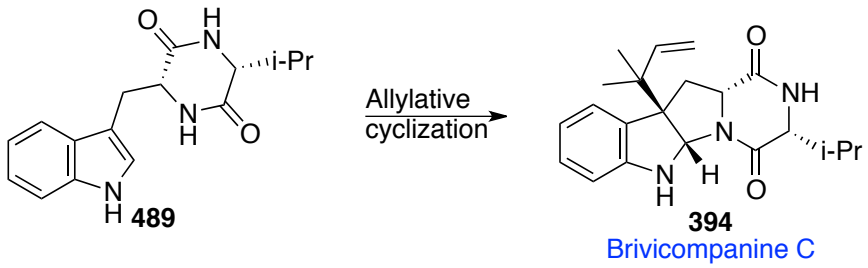
3. Conclusions and Future Work

While we were disappointed to observe the failure of the alkylation/cyclization cascade in the prenyl series, it was anticipated the congestion of the allyl cation and C3 of H-Trp-OMe might prevent this allylative cyclization methodology from being successfully applied in these cases. Further to this, we were both surprised and disappointed at the failure to afford the angelicastigmin via the allylative cyclization methodology, particularly having shown feasibility in the application of cinnamyl alcohol for success in the test system. Unfortunately, time constraints prevented us from exploring further possibilities in both cases. There are alternative approaches which could be applied in the search of the first total syntheses of brevicompanine C and angelicastigmin. The use of the allylative cyclization methodology of Tamaru, other established approaches to pyrrolo[2,3-*b*]indole alkaloids, or other, novel approaches, of which some will be further discussed *vide infra*.

3.1. Modifications to Facilitate the Successful Use of Tamaru Allylative Cyclization Methodology

3.1.1 Synthesis of Brevicompanine C

Unfortunately, we were not able to explore further modifications to the Tamaru approach towards the synthesis of brevicompanine C, where we failed to promote an allylative cyclization process using a prenyl alcohol. One possibility we did not explore is to alter the order of reactions so the diketopiperazine moiety is prepared before the subsequent allylative cyclization (scheme 110). It is speculative as to whether this would enable the cyclization, and with the required use of H-D-Trp-OMe, a subsequent epimerization may also scramble the stereocenter bearing the isopropyl group.



489 **394**
Brivicompanine C

Scheme 110. Allylative cyclization of indole diketopiperazine **489**.

3.1.2. Synthesis of Angelicastigmin

Despite a successful test system, where an allylative cyclization process involving cinnamyl alcohol afforded the desired C3-substituted pyrrolo[2,3-*b*]indole, we failed to repeat these results using coniferyl alcohol. Rational inspection of the likely reaction process led us to postulate the use of an electron rich allyl cation may prohibit allylative cyclization. By modulating the electronics of the coniferyl alcohol by the use of different protecting groups for the phenol moiety, we appear to have ruled out this hypothesis, since tentative investigations with the use of a tosylate protecting group were inferior to that of Ac and TBS.

3.2. Established Methodology for the Preparation of Hexahydropyrrolo[2,3-*b*]indoles and their Application to the Synthesis of C3-substituted Pyrrolo[2,3-*b*]indoles

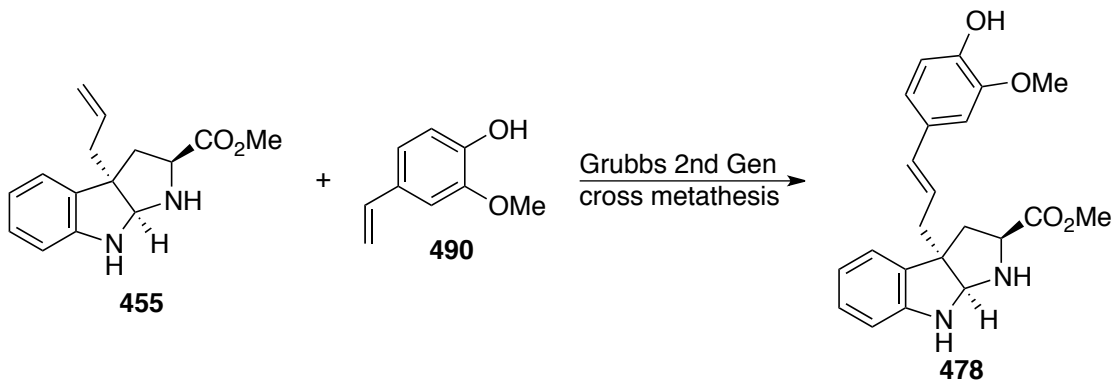
As discussed in section 1.1, there are several reported routes to C3-substituted pyrrolo[2,3-*b*]indoles and one of these established methodologies could be used to access brevicompanine C and angelicastigmin.

3.3. Novel Approaches for the Preparation of Pyrrolo[2,3-*b*]indoles

3.3.1. Synthesis of Angelicastigmin

3.3.1.1 Cross-Metathesis of Hexahydropyrrolo[2,3-*b*]indole **455**

Given we had successfully repeated Tamuro's allylation of H-Trp-OMe to afford pyrroloindole **455**, we propose a cross metathesis reaction with the alkene accessed from vanillin via a Wittig reaction may be an applicable route to angelicastigmin (see scheme 111).



455 + **490** → **478**

Scheme 111. Cross metathesis approach towards the synthesis of angelicastigmin

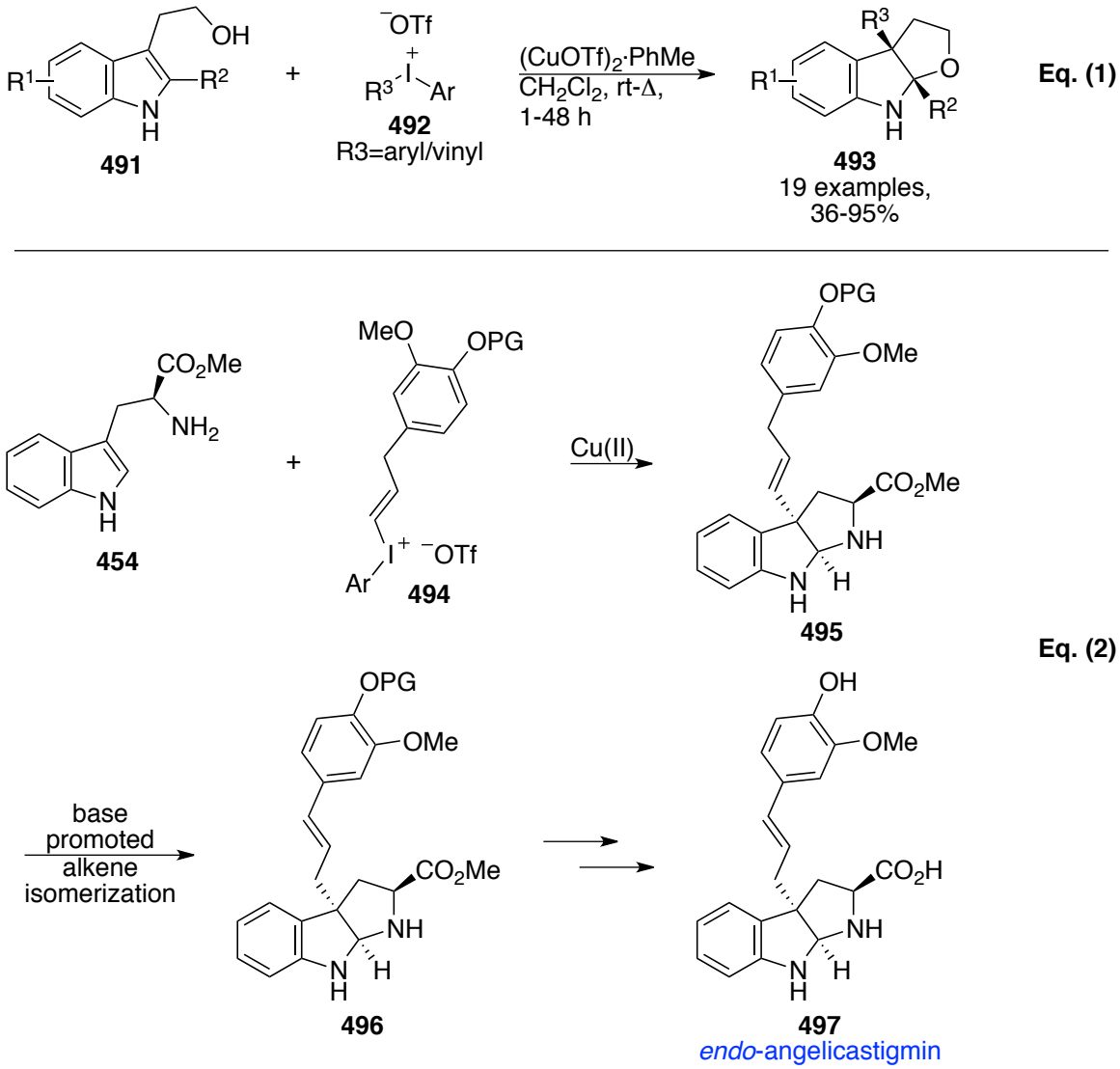
3.3.1.2. Stereoselective Tryptophan Vinylation with Iodonium Salts

In the last ten years, a great deal of work involving the use of diaryliodonium salts in α-arylation of carbonyl compounds,[148–150] Cu(II)[148,151–153] and Pd(0)[154–160] catalyzed cross-couplings, and heteroatom arylations have been reported and reviewed.[161,162] It has been reported replacement of an aryl halide or triflate as used in for example Suzuki-Miyaura, Sonogashira, Buchwald-Hartwig reactions with I(III) diaryliodonium salts can enhance the application of C-C coupling reactions in the aspect of reaction rate, time, yield and scope.[162] While having not been applied to the synthesis of pyrrolo[2,3-*b*]indoles, the use of diaryliodonium salts for the arylation of the C3 position of indoles at C3 has been reported.[163] Further to this, C3 arylation and vinylation of tryptophols and intramolecular trapping of the evolved iminium ion has been reported (eq. (1) scheme 112).[164] We propose the use of H-Trp-OMe (**454**) in place of tryptophol **491** would facilitate access to the corresponding hexahydropyrrolo[2,3-*b*]indole **495**. It is reasonable to propose, a base of sufficient strength should isomerize the alkene into conjugation with the aromatic system to access angelicastigmin (eq. (2) scheme 112).

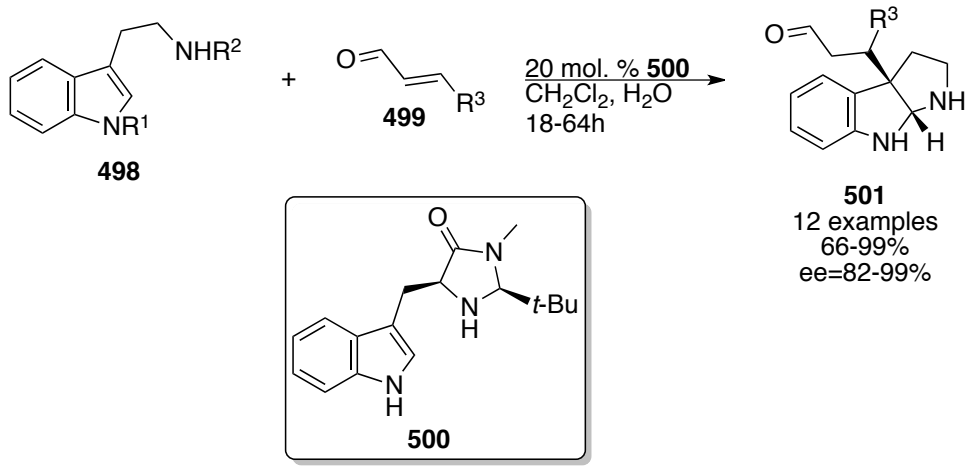
3.3.2. Novel Approaches to the General Synthesis of C3-substituted Pyrrolo[2,3-*b*]indoles

3.3.2.1 Asymmetric Tryptophan Michael Addition and Iminium Cyclization

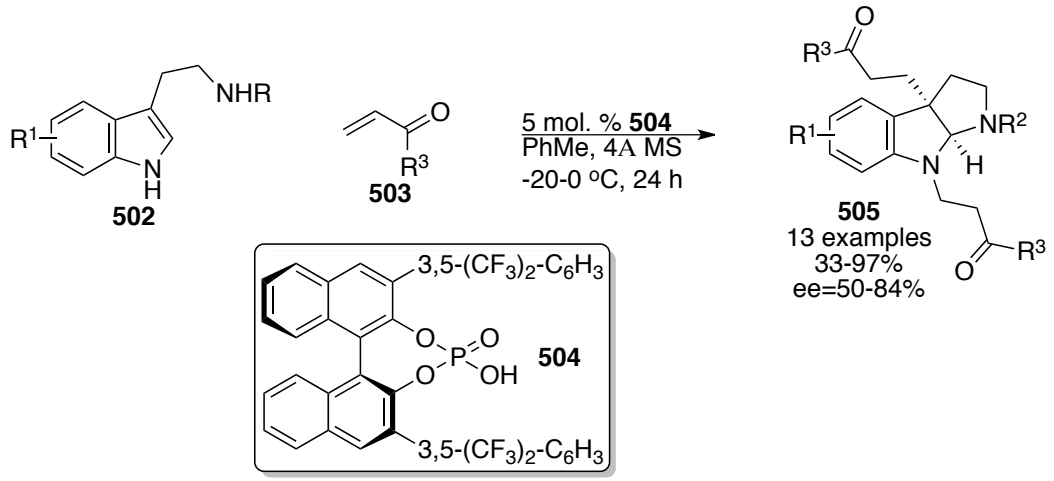
There are examples in the literature of the application of Michael additions to C3 of tryptamine with the use of asymmetric organocatalysis to access the corresponding hexahydropyrrolo[2,3-*b*]indoles in good yield and stereocontrol using Mannich[165] and Brønsted acid[166] activation (scheme 113, eq. (1) & (2) respectively). We propose the inherent diastereocontrol afforded by the presence of chirality in H-Trp-OMe could be exploited by using a similar approach to access both brevicompanine C and angelicastigmin in a diastereoselective manner, as was the case in the Tamaru allylative cyclization of H-Trp-OMe (scheme 113, eq. (3)).



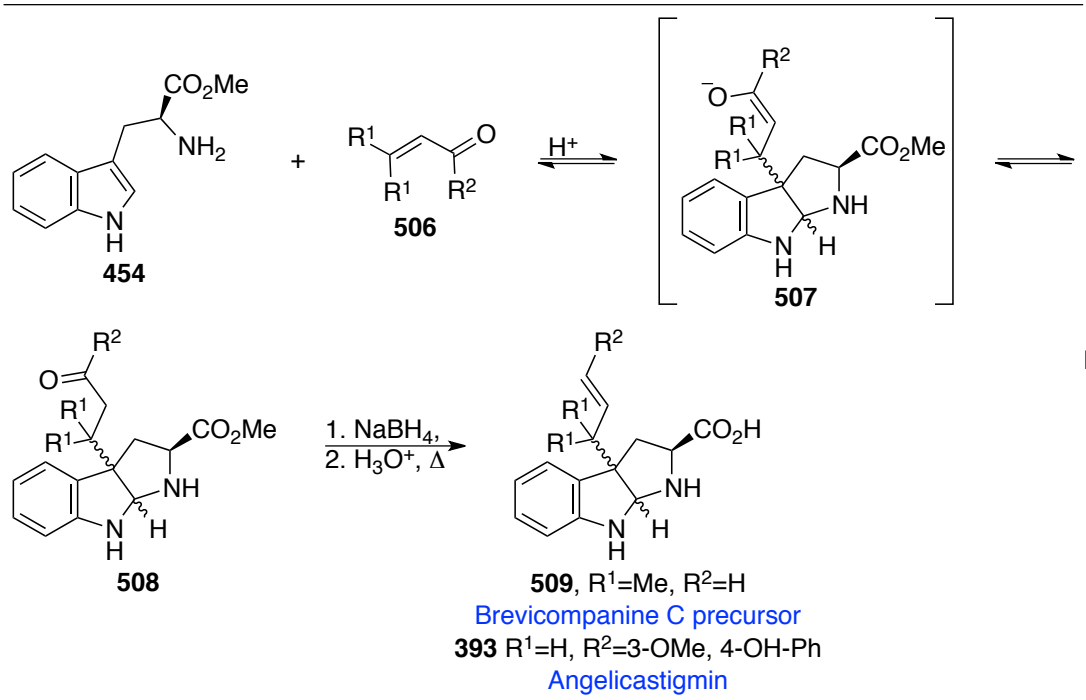
Scheme 112. Cu(II) catalyzed C3 arylation and vinylation and iminium ion cyclization of tryptophols (eq. (1)) and its proposed application to the synthesis of angelicastigmin (eq. (2)).



Eq. (1)



Eq. (2)



Eq. (3)

Scheme 113. Organocatalyzed enantioselective Michael addition/iminium cyclization of tryptamines and its possible application to the synthesis of brevicompanine C and angelicastigmin.

Chapter 4

CONCLUSIONS AND PERSPECTIVES

The research presented in this thesis has highlighted the diverse applications to which iminium ions can be implemented in synthetic organic chemistry. The area is well established, but we have shown there is scope for further development; as evidenced by our $(CHCl_2)_2$ conditions. The method we have developed for the intermolecular and intramolecular α-amidoalkylation of α-hydroxy lactams compares favourably with the leading literature in this area. We would have liked to have showcased this chemistry with the synthesis of the marinoquinoline series of natural products using the Pictet-Spengler approach detailed in chapter 2. Unfortunately, due to the sensitivity of the pyrroloaniline to high temperature, this was not possible,

We were able to synthesize marinoquinolines A, B, C, E and aplidiopsamine A using a Movassaghi-Pictet-Hubert approach in excellent yields in all cases. Our attempts using a Pictet-Spengler approach did provide us with the desired pyrroloquinoline products in some cases, but the yields for the cyclization were very low. During our efforts towards these natural products, several other groups published their successful approaches. While we were unable to deliver the first total synthesis of these natural products, we believe our approach affords the best compromise between reaction yields, number of steps and broad scope. In addition to the total syntheses, we have also produced a small library of analogues for biological testing. The results of this work have failed to provide a strong insight into SAR, but we have revealed some interesting and more active compounds in both cytotoxicity and antimicrobial assays. The details of this work are currently being transcribed into manuscript form for publication.

A very short proportion of the PhD research was conducted on the total synthesis of angelicastigmin, which ultimately was fruitless. We feel further research into the total synthesis is warranted – either using a Tamaru-inspired allylative cyclization approach as detailed in chapter 3, or one of the alternative approaches also discussed in the future work section. Our research group remains engaged in this area.

Chapter 5

EXPERIMENTAL PROCEDURES

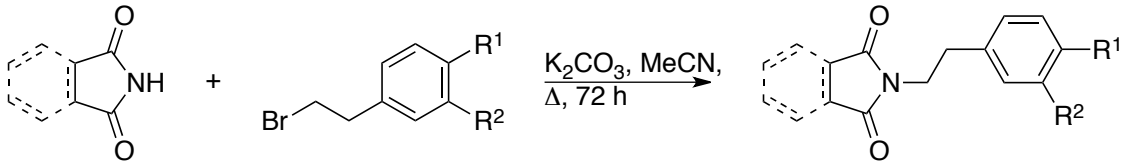
1. Experimental Procedures for Chapter 1

1.1 General

All reagents were used directly as received from commercial suppliers unless otherwise stated. When dry solvents were required, CH_2Cl_2 was distilled from CaH; anhydrous THF, DMF and MeCN were purchased from Sigma-Aldrich. Reactions were conducted at rt unless otherwise stated, and monitored by thin layer chromatography using pre-coated aluminium backed sheets of silica and visualised with UV light and a potassium permanganate or cerium sulfate stain. Column chromatography was carried out using MN Kieselgel 60, 0.04-0.063 mm 230-400 mesh ASTM silica gel. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded using a Thermo Nicolet 380 FT-IR spectrometer with a Smart Orbit Golden Gate attachment. Absorptions are reported in wavenumbers (cm^{-1}). NMR spectra were recorded on Bruker DPX-400 or Bruker AV-300 spectrometers in the solvents indicated at 298 K. Chemical shifts for proton and carbon spectra are reported on the δ scale in ppm and were referenced to residual solvent references. Multiplicities are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; spt, septet; m, multiplet; apt., apparent; r, roofing and br, broad. Electrospray mass spectra were recorded using a Thermoquest Trace MS and Micromass Platform II single quadrupole mass spectrometer. High-resolution mass spectra were recorded by the School of Chemistry Mass spectrometry Service at the University of Southampton using a Bruker Apex III FT-ICR MS coupled to an Appollo electrospray ionization source; and from the EPSRC NMSSC, University of Swansea, using a Thermofisher LTQ Orbitrap XL coupled to an Advion TriVersa NanoMate electrospray source.

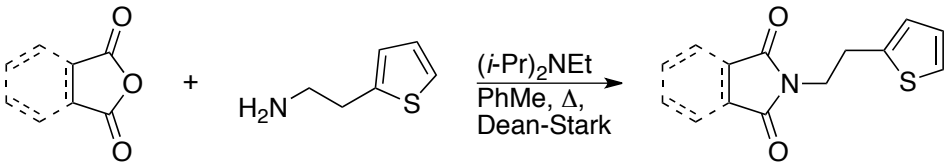
1.2. General Procedures

General Procedure 1 – *Gabriel Reaction*



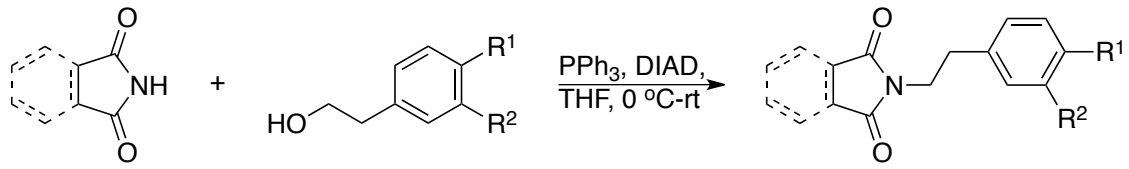
A round-bottomed flask was charged with a magnetic stirrer bar, imide (1.0 eq.), methoxyphenethyl bromide (1.2 eq.), K_2CO_3 (1.5 eq.) and anhydrous CH_3CN (4 mL/mmol imide) and the system purged with N_2/Ar. The reaction mixture was heated to reflux for the specified time and concentrated *in vacuo*. The resulting solid was dissolved in a mixture of EtOAc and NaOH (1M), the mixture transferred to a separatory funnel, the aqueous layer washed with EtOAc as required, the organic layers combined, dried over $MgSO_4$, and concentrated *in vacuo*. Purification on silica gel (petrol/EtOAc) afforded the desired imides as solids.

General Procedure 2 – *Condensation of Anhydride and Amine*



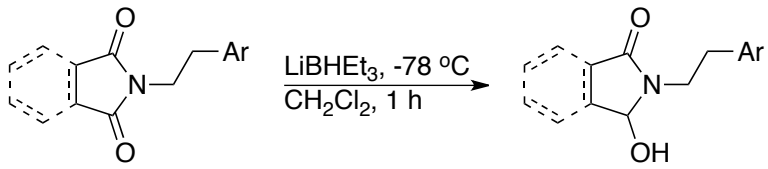
A round-bottomed flask was charged with a magnetic stirrer bar, anhydride (1.0 eq.), anhydrous PhMe (5 mL/mmol anhydride), 2-thiopheneethylamine (1.0 eq.) and $(i\text{-Pr})_2NEt$ (0.20 eq.). A Dean-Stark reflux adapter was fitted, the system purged with Ar and the mixture heated to reflux for the specified time. The reaction mixture was either concentrated *in vacuo* and purified on silica gel (petrol/EtOAc) or washed with sat. aq. NH_4Cl solution, the organic layer dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired imides as yellow solids.

General Procedure 3 – *Mitsunobu Reaction*



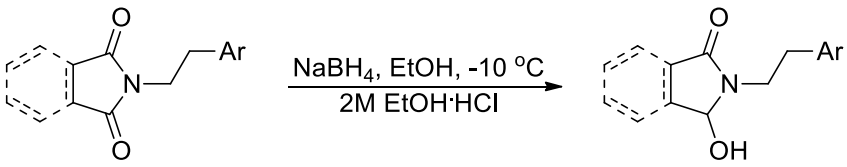
A round-bottomed flask was charged with a magnetic stirrer bar, imide (1.2 eq.), triphenylphosphine (1.2 eq.), anhydrous THF (3.5 mL/mmol alcohol) and alcohol (1.0 eq.), purged with Ar and cooled to 0 °C. Slowly, DEAD *or* DIAD (1.2 eq.) in anhydrous THF (3.5 mL/mmol alcohol) was added under a balloon of Ar, the reaction mixture brought slowly to rt and stirred for the specified time. The reaction mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2 transferred to a separatory funnel, washed with 1M NaOH, the organic layer washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallization from Et_2O and purification on silica gel (various eluent systems) afforded the desired imides as solids.

General Procedure 4 – *$LiBHEt_3$ Reduction*



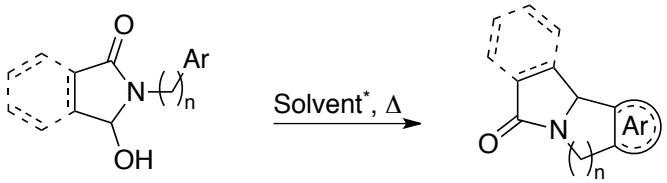
An oven-dried two-necked round-bottomed flask was purged with N_2 and charged with a magnetic stirrer bar, imide (1.0 eq.), anhydrous CH_2Cl_2 (10 mL/mmol imide) and cooled to -78 °C. $LiBHEt_3$ (1.0 eq.) was added dropwise via syringe and the reaction mixture stirred for the specified time. The reaction mixture was slowly warmed to rt and sat. $NaHCO_3$ solution (equal volume of CH_2Cl_2) was added in portions via syringe. The reaction mixture was transferred to a separatory funnel, the aqueous layer washed with CH_2Cl_2, the organic layers combined, dried over Na_2SO_4 and concentrated *in vacuo* and purified on silica gel (EtOAc/petrol). Precipitation in a stirring solution (EtOAc/petrol 1:4) afforded the desired hydroxy lactams as solids.

General Procedure 5 – *$NaBH_4$ Reduction*



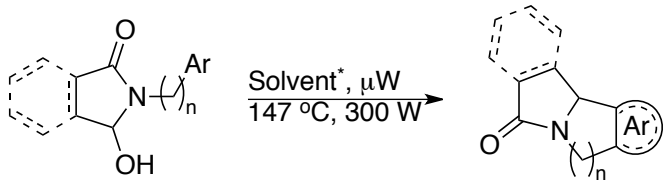
A round-bottomed flask was charged with a magnetic stirrer bar, imide (1.0 eq.) EtOH (7.5 mL/mmol imide) and CH_2Cl_2 (drops to dissolve). The reaction mixture was cooled to -10 °C and $NaBH_4$ (1.5 eq.) added. Periodically, EtOH·HCl (2M) was added dropwise and upon completion of the reaction (as indicated by TLC), the pH of the reaction mixture was adjusted to pH 5 with EtOH·HCl (2M) and quenched with H_2O (130% initial volume of EtOH). EtOH was removed *in vacuo*, and the product extracted from the aqueous mixture with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* and, if required, purified on silica gel (EtOAc/petrol). Precipitation in a stirring solution (EtOAc/petrol 1:4) afforded the desired hydroxy lactams as solids.

General Procedure 6 Intramolecular α-Amidoalkylations via Thermal Heating



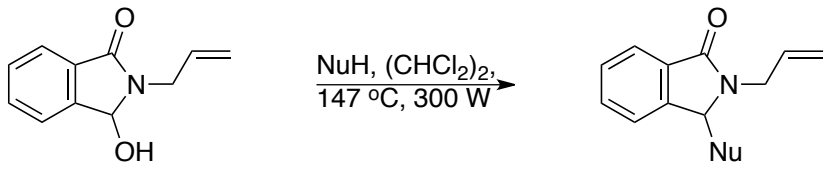
A Reacti Vial® was charged with a magnetic stirrer bar, hydroxy lactam (*ca*. 10 mg) and solvent* (0.35 mL) and placed in a heating block at the corresponding solvent reflux temperature. Upon completion (as indicated by TLC), the reaction solvent was removed either *in vacuo* or on a silica plug. Purification on silica gel (if required) afforded the desired lactams as solids. *Solvent either xylene, TFE, HFIP or $(CHCl_2)_2$.

General Procedure 7 Intramolecular α-Amidoalkylations via μW Irradiation



A microwave reaction vessel was charged with hydroxy lactam (*ca*. 10 mg) and solvent* (0.35 mL) and heated to the specified temperature at 300 W. Upon completion (as indicated by TLC), the reaction solvent was removed either *in vacuo* or on a silica plug. Purification on silica gel (if required) afforded the desired lactams as solids. *Solvent either TFE, HFIP or $(CHCl_2)_2$.

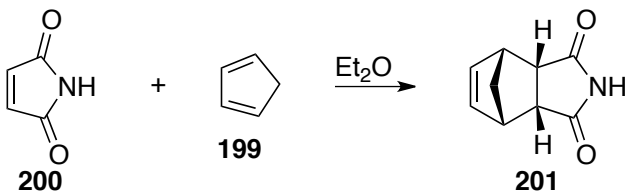
General procedure 8 Intermolecular α-Amidoalkylations via μW Irradiation



A microwave reaction vessel was charged with a magnetic stirrer bar, nucleophile, hydroxy lactam, and $(CHCl_2)_2$ (0.35 mL/10 mg hydroxy lactam) added and heated at 147 °C at 300 W. Upon completion (as indicated by TLC) the reaction mixture was concentrated *in vacuo* to afford the desired lactams as oils.

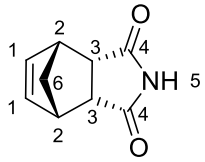
1.3. Diels-Alder Cycloadditions

1.3.1.(3aR,4S,7R,7aS)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**201**)



A round-bottomed flask was charged with a magnetic stirrer bar, maleimide (1.051 g, 10.83 mmol, 1.0 eq.), Et_2O (30 mL) and freshly cracked cyclopentadiene (1.5 mL, 17.84 mmol, 1.6 eq.) and stirred for 2 h. The white precipitate was filtered from the reaction mixture and washed with Et_2O to afford imide **201** as a white crystalline solid (1.453 g, 82%).

Spectroscopic data are consistent with that reported in the literature.[167]



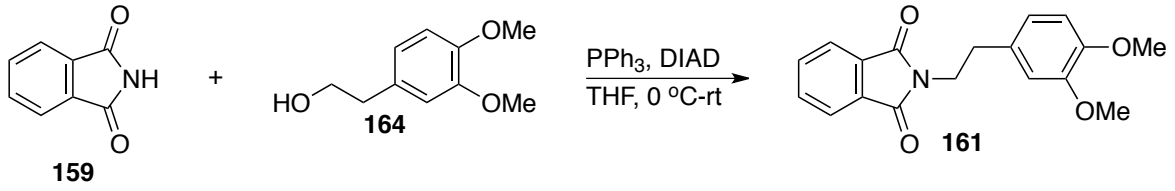
Chemical Formula: $C_9H_9NO_2$
Molecular Weight: 163.17

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.43 (1H, br s) **5**; 6.18 (2H, s) **1**; 3.37-3.29 (4H, m) **2**, **3**; 1.73 (1H, d, *J* = 8.8 Hz), 1.51 (1H, d, *J* = 8.8 Hz) **6**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 178.0, **4**; 134.6, **1**; 52.3, **6**; 47.3, **2**; 44.9, **3**.

1.4. Imide Formations

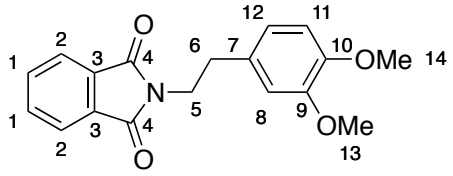
1.4.1. 2-(3,4-Dimethoxyphenethyl)isoindoline-1,3-dione (**161**)



Using general procedure 3, alcohol **164** (777 mg, 4.264 mmol, 1.0 eq.), phthalimide (757 mg, 5.145 mmol, 1.2 eq.), PPh_3 (1.34 g, 5.109 mmol, 1.2 eq.), DIAD (1.0 mL, 5.090 mmol, 1.2 eq.) and anhydrous THF (14 mL) were stirred at 0 °C-rt for 13 h. The majority of imide **161** precipitated from the reaction mixture, and was isolated by filtration and rinsed with Et_2O under vacuum filtration. The remaining imide **161** was isolated as described in

general procedure C (silica gel, EtOAc/petrol 1:3), to afford imide **161** as a white solid (1.24 g, 94%).

Spectroscopic data are consistent with that reported in the literature.[168]

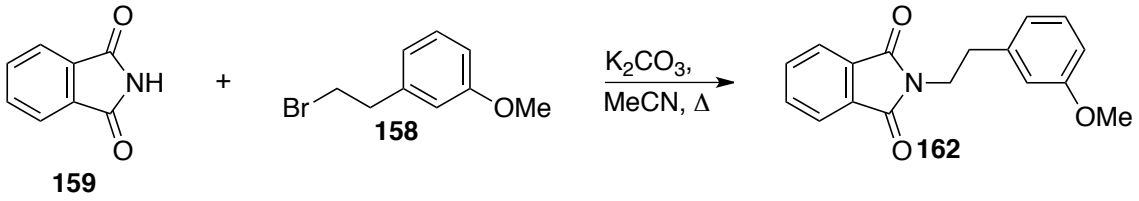


^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.85-7.69 (4H, m) **1**, **2**; 6.79-6.75 (3H, m) **8**, **11**, **12**; 3.94-3.89 (2H, m) **5**; 3.85 (3H, s), 3.82 (3H, s) **13,14**; 2.95 (2H, dd, *J*=8.4, 7.0 Hz) **6**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 168.2, **4**; 147.7, **9**, **10**; 133.9; 132.1; 130.5; 123.2; 120.9; 111.9; 111.2; 55.83, 55.78, **13,14**; 39.3, **5**; 34.1, **6**.

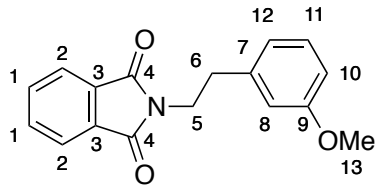
LRMS (ESI) m/z 375 $[M + Na^+ + CH_3CN]^+$.

1.4.2. 2-(3-Methoxyphenethyl)isoindoline-1,3-dione (**162**)



Using general procedure 1, phthalimide (222 mg, 1.509 mmol, 1.5 eq.), 3-methoxyphenethyl bromide **158** (0.16 mL, 1.130 mmol, 1.0 eq.), K_2CO_3 (247 mg, 1.787 mmol, 1.8 eq.) and anhydrous CH_3CN (6 mL) were stirred at reflux for 48 h. Purification of silica gel (EtOAc/petrol 1:1) afforded imide **162** as a white solid (181 mg, 63%).

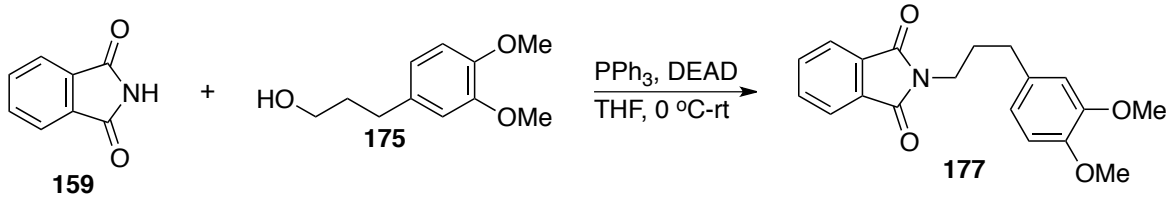
Spectroscopic data are consistent with that reported in the literature.[57]



Chemical Formula: $C_{17}H_{15}NO_3$
Molecular Weight: 281.31

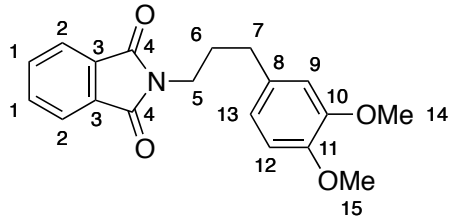
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.86-7.83 (2H, m), 7.73-7.70 (2H, m) **1, 2;** 7.21 (1H, t, *J* = 7.9 Hz) **11;** 6.87-6.76 (3H, m) **8, 10, 12;** 3.94 (2H, m) **5;** 3.78 (3H, s) **13;** 2.98 (2H, m) **6.**

1.4.3. 2-(3-(3,4-Dimethoxyphenyl)propyl)isoindoline-1,3-dione (**177**)



159 **175** **177**

Using general procedure 3, alcohol **175** (0.28 mL, 1.542 mmol, 1.0 eq.), phthalimide (273 mg, 1.856 mmol, 1.2 eq.), PPh_3 (487 mg, 1.857 mmol, 1.2 eq.), DEAD (0.38 mL, 2.422 mmol, 1.6 eq.) and anhydrous THF (6 mL) were stirred at 0 °C-rt for 24 h. Purification on silica gel (EtOAc/petrol 1:3, then CH_2Cl_2/petrol/MeOH 100:20:1) afforded imide **177** as a white solid (279 mg, 56%).



Chemical Formula: $C_{19}H_{19}NO_4$
Molecular Weight: 325.36

MP 74-80 °C.

IR (*v*, cm^{-1}) 2937, 1769, 1703, 1590, 1514.

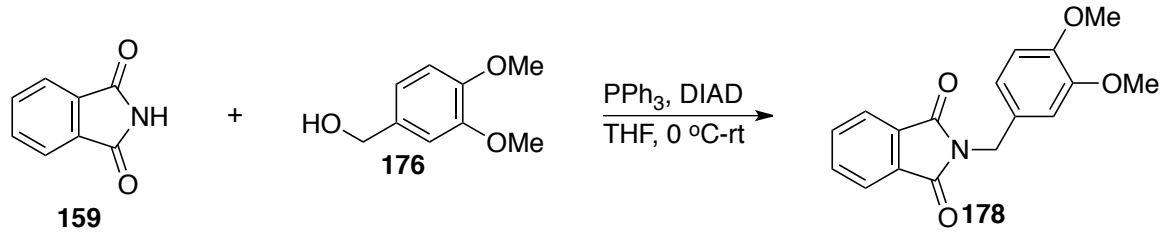
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.85-7.79 (2H, m) **2;** 7.73-7.67 (2H, m) **1;** 6.73 (3H, m) **9, 12, 13;** 3.88 (3H, s), 3.81 (3H, s)

14, **15**; 3.75 (2H, t, *J*=7.1 Hz) **5**; 2.64 (2H, t, *J*=7.7 Hz) **7**; 2.03 (2H, quin, *J*=7.3 Hz) **6**.

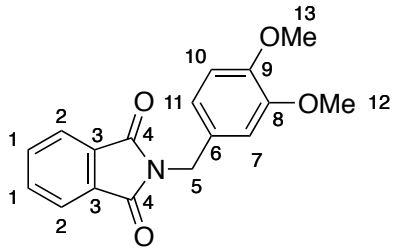
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 168.4, **4**; 148.7; 147.1; 133.8; 133.5; 132.1; 123.1; 120.0; 111.5; 111.1; 55.8, 55.7, **14**, **15**; 37.7, **5**; 32.7, **7**; 29.7, **6**.

LRMS (ESI) m/z 389 [M + CH_3CN + Na^+]$^+$; 673 [2M + Na^+]$^+$.

1.4.4. 2-(3,4-Dimethoxybenzyl)isoindoline-1,3-dione (**178**)



Using general procedure 3, alcohol **176** (0.50 mL, 3.448 mmol, 1.0 eq.), phthalimide (609 mg, 4.139 mmol, 1.2 eq.), PPh_3 (1.08 g, 4.121 mmol, 1.2 eq.), DIAD (1.0 mL, 5.094 mmol, 1.2 eq.) and anhydrous THF (14 mL) were stirred at 0 °C-rt for 15 h. Purification on silica gel (CH_2Cl_2/petrol/MeOH 60:40:1) afforded imide **178** as a white solid (423 mg, 41%).



Chemical Formula: $C_{17}H_{15}NO_4$
Molecular Weight: 297.31

MP 149-150 °C.

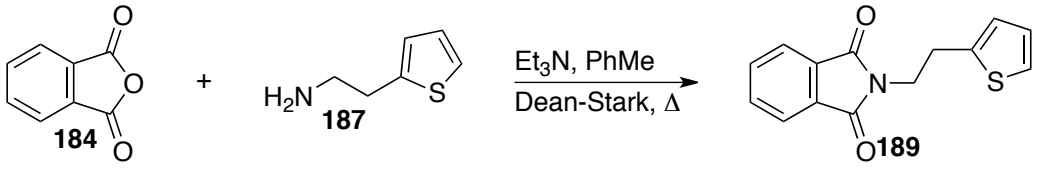
IR (*v*, cm^{-1}) 1710, 1515.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.82-7.76 (2H, m) **2**; 7.68-7.62 (2H, m) **1**; 7.01-6.97 (2H, m) **10**, **11**; 6.79-6.76 (1H, d, *J*=8.7 Hz) **7**; 4.74 (2H, s) **5**; 3.85 (3H, s), 3.81 (3H, s) **12**, **13**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.9, **4**; 148.8; 148.5; 133.8; 131.9; 128.9; 123.1; 121.1; 111.9; 110.9; 55.7, 41.3 **12**, **13**.

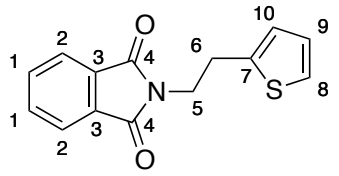
LRMS (ESI) m/z 393 $[M + Na^+ + MeOH + MeCN]^+$.

1.4.5. 2-(2-(Thiophen-2-yl)ethyl)isoindoline-1,3-dione (**189**)



Using general procedure 2, phthalic anhydride (510 mg, 3.443 mmol, 1.0 eq.), 2-thiopheneethylamine (**187**) (0.40 mL, 3.418 mmol, 1.0 eq.), Et_3N (95 µL, 0.6816 mmol, 0.20 eq.) and PhMe (18 mL) were stirred at reflux for 16 h. Aqueous work up afforded imide **189** as an orange/yellow solid (605 mg, 68%).

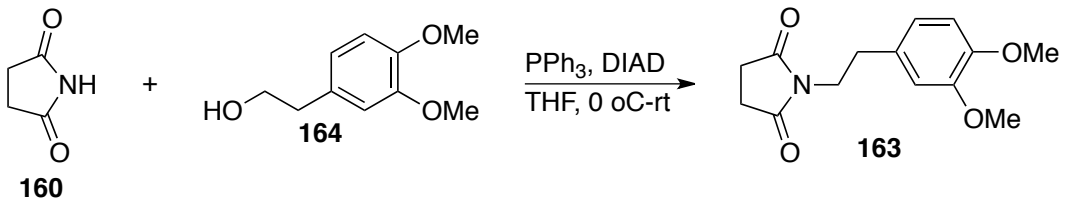
Spectroscopic data are consistent with that reported in the literature.[68]



^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.95-7.61 (4H, m) **1**, **2**; 7.15 (1H, dd, *J*=5.1, 1.1 Hz) **8**; 6.95-6.82 (2H, m) **9**, **10**; 3.98 (2H, t, *J*=7.5 Hz) **5**; 3.24 (2H, t, *J*=7.3 Hz) **6**.

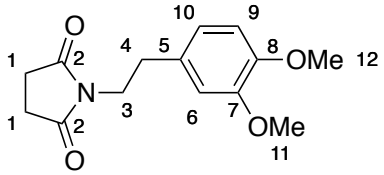
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 168.1, **4**); 140.0; 134.0; 132.0; 127.0; 125.6; 124.1; 123.3; 39.3, **5**; 28.6, **6**.

1.4.6. 1-(3,4-Dimethoxyphenethyl)pyrrolidine-2,5-dione (**163)**



Using general procedure 2, alcohol **164** (144 mg, 0.7903 mmol, 1.0 eq.), succinimide (99.0 mg, 0.9991 mmol, 1.0 eq.), PPh_3 (256 mg, 0.9760 mmol, 1 eq.), DIAD (0.19 mL, 0.9650 mmol, 1.0 eq.) and anhydrous THF (3 mL) were stirred at rt for 4 h. Purification on silica gel (EtOAc/petrol 1:1) afforded imide **163** as a white solid (125 mg, 60%).

Spectroscopic data are consistent with that reported in the literature.[169]

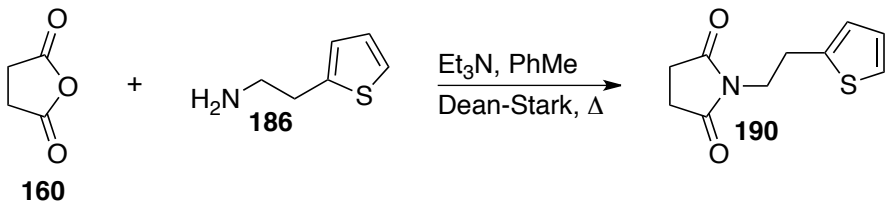


Chemical Formula: $C_{14}H_{17}NO_4$
Molecular Weight: 263.29

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.94-6.51 (3H, m) **6**, **9**, **10**; 3.83 (3H, s), 3.81 (3H, s) **11**, **12**; 3.74-3.61 (2H, m) **4**; 2.92-2.73 (2H, m) **3**; 2.61 (4H, s) **1**.

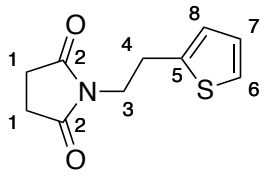
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 176.9, **2**; 148.7, 147.6, **7**, **8**; 130.1, **5**; 120.7; 111.8; 111.1; 55.7, **11**, **12**; 39.8, **3**; 32.9, **4**; 27.9, **1**.

1.4.7. 1-(2-(Thiophen-2-yl)ethyl)pyrrolidine-2,5-dione (**190)**



Using general procedure 2, succinic anhydride (289 mg, 2.888 mmol, 1.0 eq.), 2-thiopheneethylamine (**186**) (0.40 mL, 3.418 mmol, 1.2 eq.), Et_3N (80 µL, 0.5740 mmol, 0.20 eq.) and PhMe (12 mL) were stirred at reflux for 18 h. Purification on silica gel (EtOAc/petrol 1:1) afforded imide **1190** as a yellow solid (366 mg, 61%).

Spectroscopic data are consistent with that reported in the literature.[170]

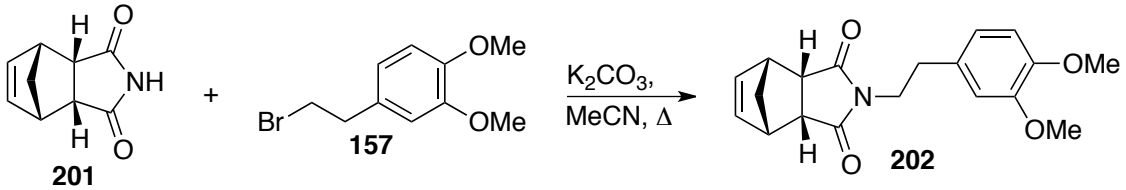


Chemical Formula: $C_{10}H_{11}NO_2S$
Molecular Weight: 209.26

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.14 (1H, dd, *J*=5.1, 1.1 Hz) **6;** 6.92 (1H, dd, *J*=5.1, 3.7 Hz), 6.84 (1H, dd, *J*=3.3, 0.7 Hz) **7, 8;** 3.78 (2H, t, *J*=7.5 Hz) **3;** 3.12 (2H, t, *J*=7.5 Hz) **4;** 2.67 (4H, apt. s) **1.**

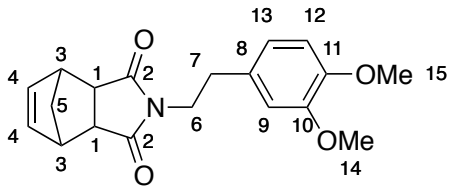
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 176.8, **2;** 139.7, **5;** 126.9, 125.6, 124.1, **6, 7, 8;** 39.9, **3;** 28.0, **1;** 27.4, **4.**

1.4.8. (3aR,4S,7R,7aS)-2-(3,4-dimethoxyphenethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**202)**



Using general procedure 1, imide **201** (490 mg, 3.003 mmol, 1.0 eq.), 3,4-dimethoxyphenethyl bromide **157** (902 mg, 3.680 mmol, 1.2 eq.), K_2CO_3 (635 mg, 4.594 mmol, 1.5 eq.) and anhydrous CH_3CN (12 mL) were stirred at reflux for 72 h. Purification on silica gel (EtOAc/petrol 1:2) afforded imide **202** as a white solid (663 mg, 67%).

Spectroscopic data are consistent with that reported in the literature.[171]



Chemical Formula: $C_{19}H_{21}NO_4$
Molecular Weight: 327.37

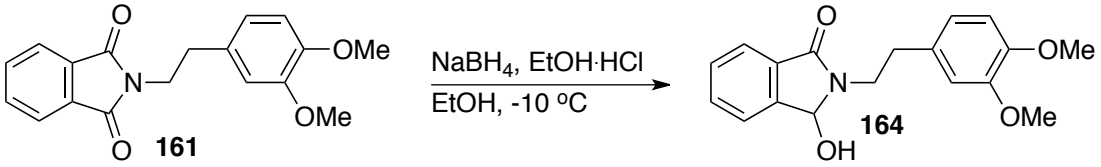
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.80-6.74 (3H, m) **9**, **12**, **13**; 5.98 (2H, apt. s) **4**; 3.88 (3H, s), 3.85 (3H, s) **14**, **15**; 3.57 (2H, t, *J*=7.7 Hz) **6**; 3.36 (2H, apt. br s) **3**; 3.22 (2H, dd, *J*=2.6, 1.5 Hz) **1**; 2.70 (2H, t, *J*=8.1 Hz) **7**; 1.71 (1H, d, *J*=9.2 Hz) **5**; 1.52 (1H, d, *J*=8.8 Hz) **5**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 177.6, **2**; 148.8, 147.7, **10**, **11**; 134.3, **4**; 130.3, **8**; 120.8, **13**; 111.9, 111.1, **9**, **12**; 55.8, **14**, **15**; 52.1, **5**; 45.7, 44.8, **1**, **3**; 39.4, **6**; 33.2, **7**.

LRMS (ESI) m/z 328 ($M + H^+$).

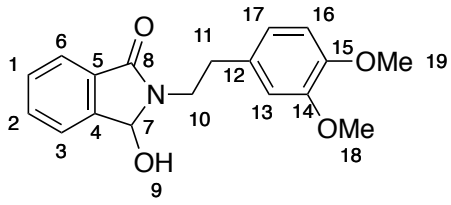
1.5. Hydroxy Lactam Formations

1.5.1. 2-(3,4-Dimethoxyphenethyl)-3-hydroxyisoindolin-1-one (**164**)



Using general procedure 5, imide **161** (620 mg, 1.991 mmol, 1.0 eq.), $NaBH_4$ (113 mg, 2.987 mmol, 1.5 eq.) and EtOH (18 mL) were stirred at -10 °C for 45 min. Purification on silica gel (EtOAc/petrol 1:3) and precipitation afforded hydroxy lactam **164** as a white solid (552 mg, 89%).

Spectroscopic data are consistent with that reported in the literature.[46]

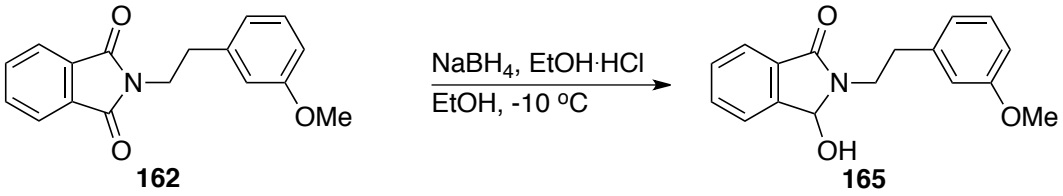


Chemical Formula: $C_{18}H_{19}NO_4$
Molecular Weight: 313.35

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.64-7.34 (4H, m) **1, 2, 3, 6;** 6.84-6.58 (3H, m) **13, 16, 17;** 5.45 (1H, d, *J*=11.7 Hz) **7;** 3.83 (3H, s, 3.75 (3H, s) **18, 19;** 3.58-3.43 (2H, m) **10;** 3.49 (1H, d, *J*=11.7 Hz) **9;** 2.87 (2H, td, *J*=7.3, 2.9 Hz) **11.**

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.4, **8;** 148.8, 147.6, **14, 15;** 143.8; 132.2; 131.4; 131.2; 129.7; 123.3, 123.1, **3, 6;** 120.6, **17;** 111.8, 111.3 **13, 16;** 82.2, **7;** 55.8, 55.7, **18, 19;** 40.8, **10;** 33.9, **11.**

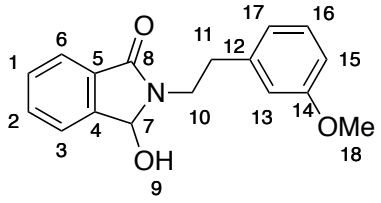
1.5.2. 3-Hydroxy-2-(3-methoxyphenethyl)isoindolin-1-one (**165**)



162 **165**

Using general procedure 5, imide **162** (281 mg, 0.9989 mmol, 1.0 eq.), $NaBH_4$ (114 mg, 3.013 mmol, 3.0 eq.) and EtOH (25 mL) were stirred at -10 °C for 45 min. Purification on silica gel (EtOAc/petrol 1:2) and precipitation afforded hydroxy lactam **165** as a white solid (220 mg, 78%).

Spectroscopic data are consistent with that reported in the literature.[46]



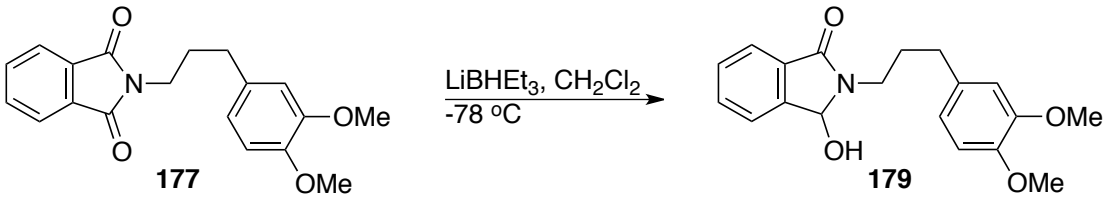
Chemical Formula: $C_{17}H_{17}NO_3$
Molecular Weight: 283.32

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.57-7.53 (3H, m), 7.43-7.37 (1H, m) **1, 2, 3, 6;** 7.16 (1H, t, *J*=7.7 Hz) **16;** 6.97-6.71 (3H, m)

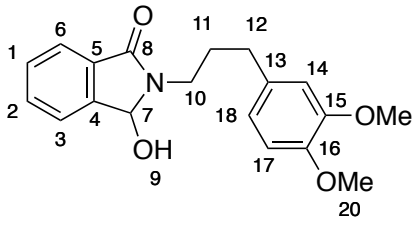
13, **15**, **17**; 5.51 (1H, d, *J*=11.0 Hz) **7**; 3.78 (1H, d, *J*=11.3 Hz) **9**; 3.74-3.64 (1H, m) **10**; 3.72 (3H, s) **18**; 3.57-3.48 (1H, m) **10**; 2.89 (2H, apt. m) **11**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.4, **8**; 159.7, **14**; 143.9, 140.3, **4**/**5**/**12**; 132.2; 131.4, **4**/**5**/**12**; 129.7; 129.5; 123.3, 123.1, **3**, **6**; 121.0; 114.2, 112.1, **13**, **15**; 82.1, **7**; 55.1, **18**; 40.6, **10**; 24.5, **11**.

1.5.3. 2-(3-(3,4-Dimethoxyphenyl)propyl)-3-hydroxyisoindolin-1-one (**179**)



Using general procedure 4, imide **177** (102 mg, 0.3135 mmol, 1.0 eq.), $LiBHEt_3$ (0.37 mL of 1M solution, 0.3700 mmol, 1.2 eq.) and anhydrous CH_2Cl_2 (3 mL) were stirred at -78 °C for 1 h. Purification on silica gel (EtOAc/petrol 1:1) and precipitation afforded hydroxy lactam **179** as a white solid (61.0 mg, 59%).



Chemical Formula: $C_{19}H_{21}NO_4$
Molecular Weight: 327.37

MP 131-133 °C.

IR (*v*, cm^{-1}) 3325, 2934, 1677, 1515.

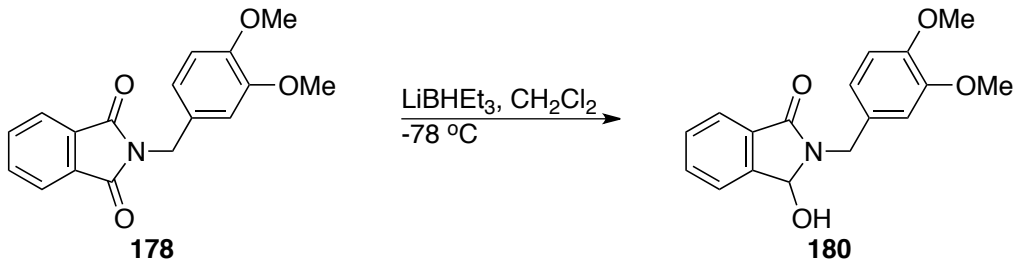
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.59-7.50 (3H, m), 7.39 (1H, apt. td, *J*=7.3, 1.2 Hz) **1**, **2**, **3**, **6**; 6.75-6.67 (3H, m) **14**, **17**, **18**; 5.70 (1H, d, *J*=11.7 Hz) **7**; 3.96 (1H, d, *J*=11.7 Hz) **9**; 3.83 (3H, s), 3.81 (3H, s) **19**, **20**; 3.44 (1H, dt, *J*=14.0, 7.6 Hz), 3.26 (1H, dt, *J*=13.8, 6.9 Hz) **10**; 2.55 (2H, t, *J*=7.7 Hz) **12**; 1.89 (2H, quin, *J*=7.7 Hz) **11**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.5, **8**; 148.7, 147.1, **15**, **16**; 143.8, **4**; 133.9, **5**/**13**; 132.1, **1**/**2**; 131.3, **5**/**13**; 129.6, **1**/**2**; 123.2, 123.0, **3**, **6**; 120.0, **18**; 111.6, 111.2 **14**, **17**; 81.6, **7**; 55.8, 55.7, **19**, **20**; 38.8, **10**; 32.8, **12**; 29.8, **11**.

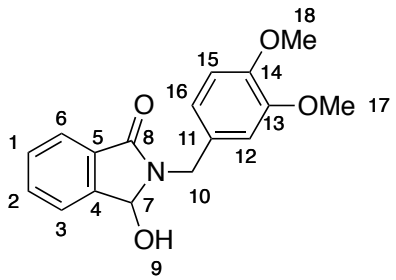
LRMS (ESI) m/z 328 $[M + H]^+$; 350 $[M + Na]^+$; 391 $[M + Na + MeCN]^+$; 677 $[2M + Na]^+$; 1005 $[3M + Na]^+$.

HRMS (ESI) m/z $C_{19}H_{21}O_4N_1Na_1$ $[M + Na]^+$ calcd. 350.1363, found 350.1369.

1.5.4. 2-(3,4-Dimethoxybenzyl)-3-hydroxyisoindolin-1-one (**180**)



Using general procedure 4, imide **178** (421 mg, 1.416 mmol, 1.0 eq.), $LiBHEt_3$ (1.7 mL of 1M solution, 1.700 mmol, 1.2 eq.) and anhydrous CH_2Cl_2 (10 mL) were stirred at -78 °C for 1 h. Purification on silica gel (EtOAc/petrol 1:3) and precipitation afforded hydroxy lactam **180** as a white solid (259 mg, 61%).



Chemical Formula: $C_{17}H_{17}NO_4$
Molecular Weight: 299.32

MP 127-130 °C.

IR (*v*, cm^{-1}) 1711, 1515.

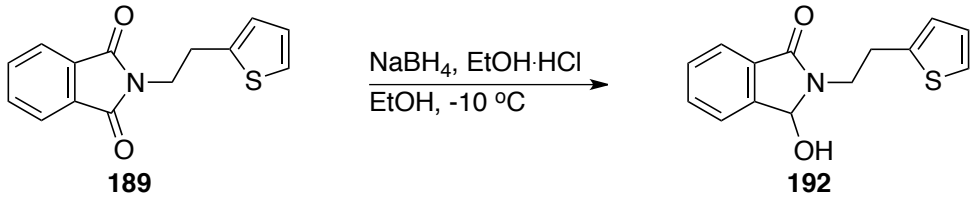
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.63 (1H, apt. d, *J*=7.3 Hz) **6**; 7.59-7.53 (2H, m) **1**, **3**; 7.45 (1H, ddd, *J*=7.4, 6.2, 2.2 Hz) **2**; 6.90-6.76 (2H, m), 6.78 (1H, d, *J*=8.0 Hz) **12**, **15**, **16**; 5.60 (1H, d,

J=11.7 Hz) **7**; 4.80 (1H, d, *J*=14.6 Hz) **9**; 4.18 (1H, d, *J*=14.3 Hz) **10**; 3.83 (3H, s), 3.82 (3H, s) **17**, **18**; 3.61 (1H, d, *J*=11.7 Hz) **10**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.2, **8**; 149.1, 148.5, **13**,**14**; 143.9, **4**; 133.9, **5**/**11**; 132.3, **1**/**2**; 131.3, **5**/**11**; 129.8, **1**/**2**; 129.4, **5**/**11**; 123.4, 123.3, **3**, **6**; 121.0, **16**; 111.8, 111.1, **12**, **15**; 80.9, **7**; 55.9, **17**, **18**; 42.5, **10**.

LRMS (ESI) 363 [M + Na^+ + CH_3CN]$^+$; 621 [2M + Na^+]$^+$; 921 [3M + Na^+]$^+$.

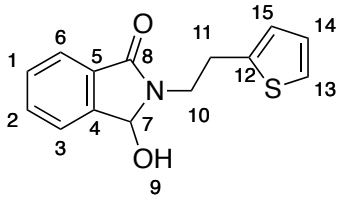
1.5.5. 3-Hydroxy-2-(2-(thiophen-2-yl)ethyl)isoindolin-1-one (**192**)



189 **192**

Using general procedure 5, imide **189** (499 mg, 1.939 mmol, 1.0 eq.), $NaBH_4$ (114 mg, 3.013 mmol, 1.5 eq.) and EtOH (18 mL) were stirred at -10 °C for 1 h. Purification on silica gel (EtOAc/petrol 1:3) and precipitation afforded hydroxy lactam **192** as a pale yellow solid (402 mg, 82%).

Spectroscopic data are consistent with that reported in the literature.[68]

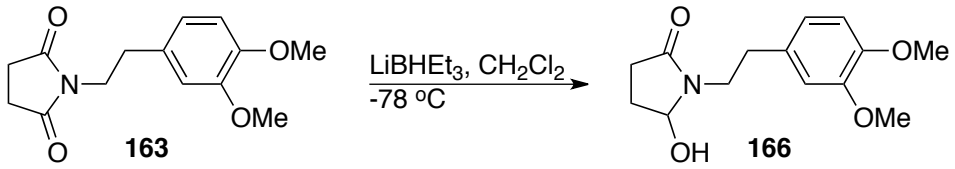


Chemical Formula: $C_{14}H_{13}NO_2S$
Molecular Weight: 259.32

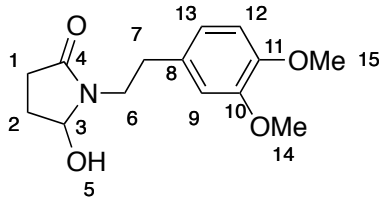
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.74-7.37 (4H, m) **1**, **2**, **3**, **6**; 7.13 (1H, dd, *J*=5.1, 1.1 Hz) **13**; 6.90 (1H, dd, *J*=5.1, 3.3 Hz), 6.82 (1H, dd, *J*=3.5, 0.9 Hz) **14**, **15**; 5.55 (1H, d, *J*=10.6 Hz) **7**; 3.83-3.67 (1H, m), 3.67-3.52 (1H, m) **10**; 3.26 (1H, d, *J*=11.0 Hz) **9**; 3.17 (2H, td, *J*=7.2, 1.6 Hz) **11**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.4, **8**; 143.8; 141.0; 132.3; 131.3; 129.8; 127.0; 125.4; 124.0; 123.3; 123.2; 82.2, **7**; 41.0, **10**; 28.6, **11**.

1.5.6. 1-(3,4-Dimethoxyphenethyl)-5-hydroxypyrrolidin-2-one (**166**)



Using general procedure 4, imide **163** (129 mg, 0.4900 mmol, 1.0 eq.), $LiBHEt_3$ (0.50 mL of 1M solution, 0.5000 mmol, 1.0 eq.) and anhydrous CH_2Cl_2 (7 mL) were stirred at -78 °C for 45 min. Purification on silica gel (CH_2Cl_2/MeOH 95:5) and precipitation afforded hydroxy lactam **166** as a white solid (92 mg, 71%).



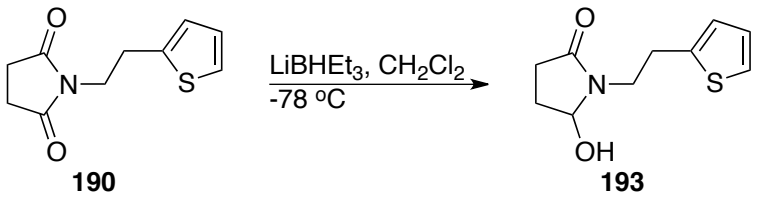
Chemical Formula: $C_{14}H_{19}NO_4$
Molecular Weight: 265.30

Spectroscopic data are consistent with that reported in the literature.[46]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.83-6.75 (3H, m) **9**, **12**, **13**; 4.98 (1H, m) **3**; 3.88 (3H, s), 3.87 (3H, s) **14**, **15**; 3.71 (1H, dt, *J*=14.0, 7.1 Hz) **6**; 3.45 (1H, dt, *J*=14.1, 7.2 Hz) **6**; 2.87 (2H, t, *J*=7.0 Hz) **7**; 2.56 (1H, m) **2**; 2.29 (2H, m) **1**; 1.82 (1H, m) **2**.

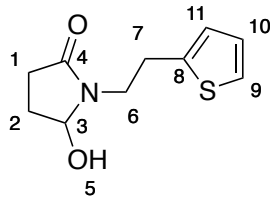
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 174.7, **4**; 148.9, 147.6, **10**, **11**; 131.4, **8**; 120.6, **13**; 111.9, 111.3, **9**, **12**; 83.7, **3**; 55.9, **14**, **15**; 41.7, **6**; 33.6, **7**; 28.8, 28.4, **1**, **2**.

1.5.7. 5-Hydroxy-1-(2-(thiophen-2-yl)ethyl)pyrrolidin-2-one (**193**)



190 **193**

Using general procedure 4, imide **190** (145 mg, 0.6929 mmol, 1.0 eq.), $LiBHEt_3$ (0.70 mL of 1M solution, 0.7000 mmol, 1.0 eq.) and anhydrous CH_2Cl_2 (7 mL) were stirred at -78 °C for 45 min. Purification on silica gel (EtOAc/petrol 1:2) and precipitation afforded hydroxy lactam **193** as a white solid (92 mg, 63%).



Chemical Formula: $C_{10}H_{13}NO_2S$
Molecular Weight: 211.28

MP 72-74 °C.

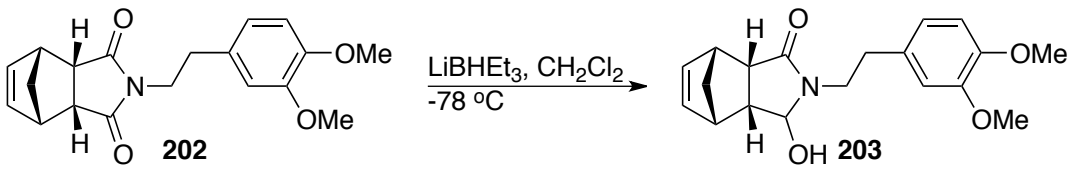
IR (*v*, cm^{-1}) 3099, 2924, 2849, 1683.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.15 (1H, dd, *J*=5.1, 1.1 Hz) **9**; 6.93 (1H, dd, *J*=5.0, 3.5 Hz) **10**; 6.84 (1H, d, *J*=3.0 Hz) **11**; 5.02 (1H, td, *J*=7.0, 1.8 Hz) **3**; 3.72 (1H, tt, *J*=10.5, 6.9 Hz) **6**; 3.64 (1H, d, *J*=8.0 Hz) **5**; 3.45 (1H, tt, *J*=10.5, 6.9 Hz) **6**; 3.19-3.03 (2H, m, **7**); 2.52 (1H, m) **2**; 2.27 (2H, m) **2**, **3**/**5**; 1.88 (1H, m) **3**/**5**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 175.0, **4**; 141.2, **8**; 127.0, 125.3, 123.9, **10**, **11**, **12**; 83.7, **3**; 41.9, **6**; 28.8, 28.3, 28.2, **1**, **2**, **7**.

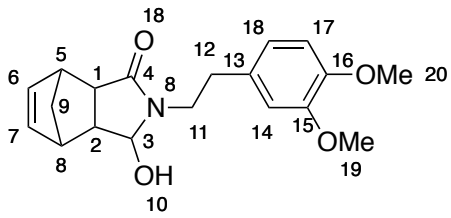
HRMS (ESI) *m/z* Calcd. for $C_{10}H_{11}NOS$ $[M + Na]^+$: 216.0459. Found: 216.0459.

1.5.8. (3S,3aR,4S,7R,7aS)-2-(3,4-dimethoxyphenethyl)-3-hydroxy-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindol-1-one (**203**)



202 **203**

Using general procedure 4, imide **202** (297 mg, 0.9072 mmol, 1.0 eq.), $LiBHEt_3$ (0.92 mL of 1M solution, 0.9200 mmol, 1.0 eq.) and anhydrous CH_2Cl_2 (6 mL) were stirred at -78 °C for 45 min. Purification on silica gel (EtOAc/petrol 2:1) and precipitation afforded hydroxy lactam **203** as a white solid (175 mg, 59%).



Chemical Formula: $C_{19}H_{23}NO_4$
Molecular Weight: 329.39

MP 172-174 °C.

IR (*v*, cm^{-1}) 3272, 2938, 2360, 2340, 1650, 1515.

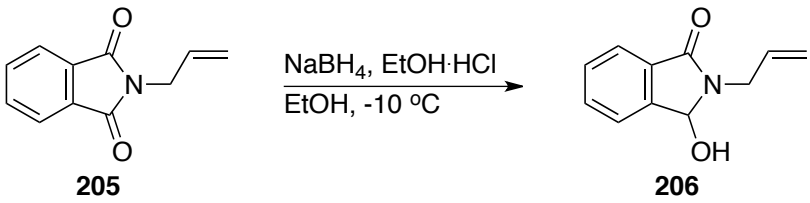
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.79-6.72 (3H, m) **14**, **17**, **18**; 6.14 (2H, apt. t, *J*=1.8 Hz) **6**, **7**; 4.96 (1H, dd, *J*=10.0, 7.5 Hz) **3**; 3.86 (3H, s), 3.85 (3H, s) **19**, **20**; 3.50-3.43 (1H, m) **11**; 3.39-3.32 (1H, m) **11**; 3.27 (1H, br dt, *J*=2.8, 1.6 Hz) **5**/**8**; 3.12-3.08 (1H, m) **1**; 3.04 (1H, br dd, *J* = 3.5, 2.0 Hz) **5**/**8**; 3.00-2.95 (1H, m) **2**; 2.85 (2H, m) **12**; 2.13 (1H, d, *J*=9.8 Hz) **10**; 1.58 (1H, dt, *J*=8.5, 1.6 Hz), 1.40 (1H, d, *J*=8.3 Hz) **9**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 173.6, **4**; 148.8, 147.5, **15**, **16**; 135.8, 134.1 **6**, **7**; 131.5, **13**; 120.7, **18**; 112.0, 111.1, **14**, **17**; 82.8, **3**; 55.8, **19**, **20**; 52.1, 49.6, 45.7, 44.4, 43.1, **1**, **2**, **5**, **8**, **9**; 41.5, **11**; 33.4, **12**.

LRMS (ESI) m/z 312 $[M - OH^-]^+$; 330 $[M + H]^+$; 352 $[M + Na^+]^+$; 393 $[M + CH_3CN + Na^+]^+$; 682 $[2M + Na^+]^+$.

HRMS (ESI) m/z $C_{19}H_{23}O_4NNa$ $[M + Na]^+$ calcd. 352.1519, found 352.1528.

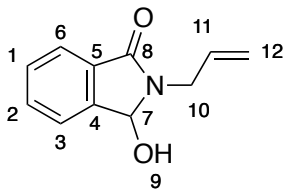
1.5.9. 2-Allyl-3-hydroxyisoindolin-1-one (**206**)



205 **206**

Using general procedure 5, *N*-allyl phthalimide (**205**) (374 mg, 1.998 mmol, 1.0 eq.), $NaBH_4$ (115 mg, 3.040 mmol, 1.5 eq.) and EtOH (15 mL) were stirred at -10 °C for 45 min. Concentration *in vacuo* afforded hydroxy lactam **206** as colourless crystals (378 mg, 100%).

Spectroscopic data are consistent with that reported in the literature.[19]



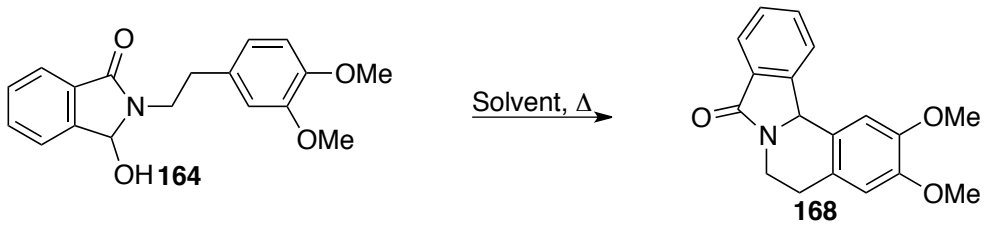
Chemical Formula: $C_{11}H_{11}NO_2$
Molecular Weight: 189.21

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.71-7.31 (4H, m) **1, 2, 3, 6;** 5.89-5.51 (2H, m) **7, 11;** 5.29-4.98 (2H, m) **12;** 4.88-4.57 (1H, m) **9;** 4.02 (1H, dd, *J*=15.4, 4.8 Hz) **10;** 3.68 (1H, dd, *J*=15.7, 7.3 Hz) **10.**

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.3, **8;** 144.0, **4;** 132.3, 132.2, **2, 11;** 131.0, **5;** 129.4, **1;** 123.3, 123.0, **3, 6;** 117.8, **12;** 81.0, **7;** 41.2, **10.**

1.6. Thermally-Promoted Intramolecular α-Amidoalkylations

1.6.1. 2,3-Dimethoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (**1.154A**)

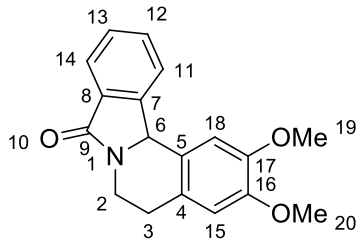


164 **168**

1.6.1.1. 2,3-Dimethoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (**168**) in $(CHCl_2)_2$

Using general procedure 6, hydroxy lactam **164** (10.1 mg, 32.23 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 45 min. Concentration *in vacuo* and purification on silica gel (1% MeOH in CH_2Cl_2) afforded lactam **168** as a white solid (9.0 mg, 95%).

Spectroscopic data are consistent with that reported in the literature.[46]



Chemical Formula: $C_{18}H_{17}NO_3$
Molecular Weight: 295.33

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.89 (1H, d, *J*=7.3 Hz), 7.84 (1H, d, *J*=7.7 Hz) **11**, **14**; 7.62 (1H, t, *J*=7.5 Hz), 7.50 (1H, t, *J*=7.3 Hz) **12**, **13**; 7.13 (1H, s), 6.67 (1H, s) **15**, **18**; 5.64 (1H, s) **6**; 4.50 (1H, ddd, *J*=13.2, 3.3, 2.2 Hz) **2**; 3.94 (3H, s), 3.86 (3H, s) **19**, **20**); 3.49-3.34 (1H, m) **2**; 3.11-2.90 (1H, m), 2.78 (1H, dt, *J*=15.7, 3.8 Hz) **3**.

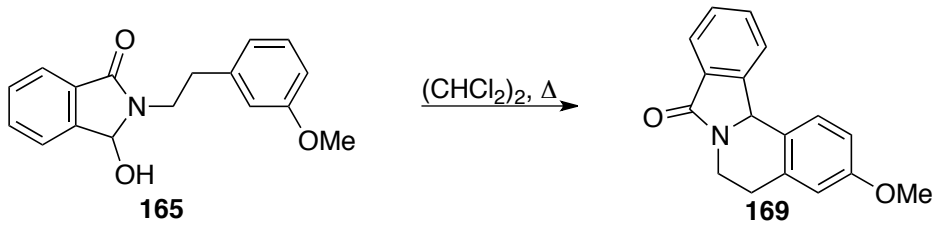
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.9, **9**; 148.4, 147.9, **16**, **17**; 144.6, **7**; 132.8, **8**; 131.6, 128.4, **12**, **13**; 126.9, 126.0, **4**, **5**; 124.0, 123.0, **11**, **14**; 112.0, 108.7, **15**, **18**; 59.0, **6**; 56.2, 55.9, **19**, **20**; 38.2, **2**; 29.1, **3**.

1.6.1.2. 2,3-Dimethoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (**168**) in xylene

Using general procedure 6, hydroxy lactam **164** (9.3 mg, 31.49 µmol) and xylene (0.35 mL) were stirred at 139 °C for 105 min. Concentration *in vacuo* afforded lactam **168** as a white solid (9.2 mg, 99%).

Spectroscopic data as for 1.6.1.1

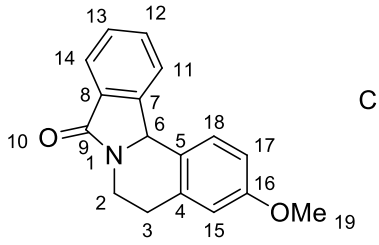
1.6.2. 2,3-Dimethoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (**169**)



165 **169**

Using general procedure 6, hydroxy lactam **165** (10.0 mg, 35.30 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 4 h. Concentration *in vacuo* afforded lactam **169** as a white solid (9.3 mg, >99%).

Spectroscopic data are consistent with that reported in the literature.[46]

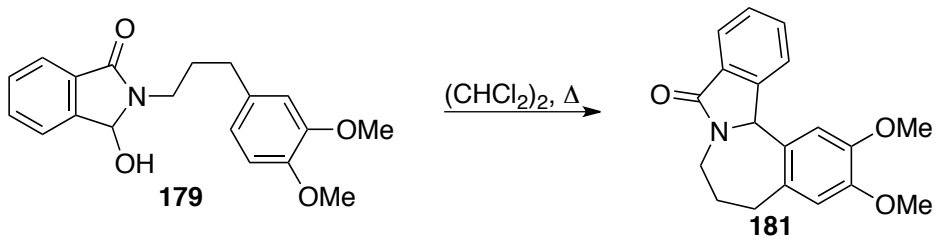


Chemical Formula: $C_{17}H_{15}NO_2$
Molecular Weight: 265.31

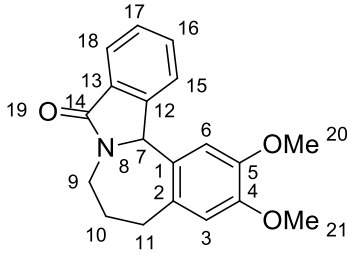
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.95-7.77 (2H, m) **11**, **14**; 7.63-7.47 (3H, m) **12**, **13**, **18** 6.84 (1H, dd, *J*=8.6, 2.7 Hz) **17**; 6.73 (1H, d, *J*=2.6 Hz) **15**; 5.63 (1H, s) **6**; 4.44 (1H, ddd, *J*=12.8, 5.9, 4.4 Hz) **2**; 3.79 (3H, s) **19**; 3.48 (1H, ddd, *J*=13.2, 9.5, 4.8 Hz) **2**; 3.06 (1H, ddd, *J*=15.4, 9.1, 5.5 Hz), 2.86 (1H, dt, *J*=15.7, 4.8 Hz) **3**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.9, **9**; 158.7, **16**; 144.5, 136.1, 132.7, **4**, **7**, **8**; 131.5, 128.4, **12**, **13**; 126.5, **18**; 126.2, **17**; 123.8, 123.3, **11**, **14**; 114.0, 112.8, **15**, **17**; 58.8, **6**; 55.3, **19**; 38.1, **2**; 29.7, **3**.

1.6.3. 2,3-Dimethoxy-6,7-dihydro-5H-benzo[3,4]azepino[2,1-a]isoindol-9(13bH)-one (**181**)



Using general procedure 6, hydroxy lactam **179** (10.4 mg, 31.77 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 105 min. Concentration *in vacuo* and purification on silica gel afforded lactam **181** as a white solid (9.4 mg, 96%).



Chemical Formula: $C_{19}H_{19}NO_3$
Molecular Weight: 309.36

MP 97-99 °C

IR (*v*, cm^{-1}) 2938, 1687, 1610.

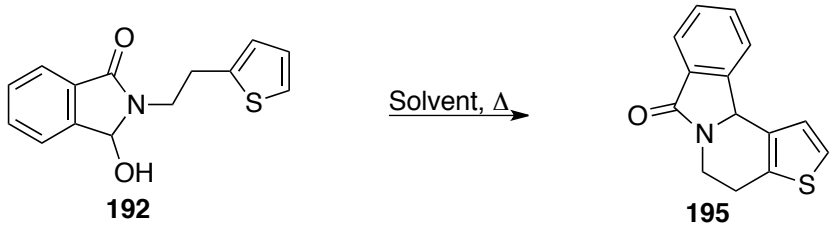
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.91 (1H, d, *J*=7.5 Hz) **18**; 7.69-7.40 (3H, m) **15**, **16**, **17**; 6.82 (1H, s), 6.65 (1H, s) **3**, **6**; 5.69 (1H, s) **7**; 4.35 (1H, ddd, *J*=13.9, 6.4, 2.6 Hz) **9**; 3.87 (3H, s), 3.85 (3H, s) **20**, **21**; 3.36 (1H, ddd, *J*=14.3, 10.5, 6.0 Hz) **9**; 2.68 (2H, dd, *J*=7.2, 5.7 Hz) **11**; 2.27-2.07 (1H, m) **10**; 1.91 (1H, dqd, *J*=13.6, 6.9, 6.9, 6.9, 2.6 Hz) **10**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 168.9 **14**; 148.4, 147.4 **4**, **5**; 144.3, **12**; 132.5, 132.3, **1**, **13**; 131.4, 128.4, **16**, **17**; 126.7, **2**; 123.9, 123.1, **15**, **18**; 113.9, 111.4, **3**, **6**; 65.5, **7**; 56.2, 55.9, **20**, **21**; 41.0, **9**; 31.1, **11**; 25.6, **10**.

LRMS (ESI) m/z 310 $[M + H]^+$; 373 $[M + CH_3CN + Na^+]^+$; 641 $[2M + Na^+]^+$; 951 $[3M + Na^+]^+$.

HRMS (ESI) m/z $C_{19}H_{19}NO_3Na$ $[M + Na]^+$ calcd. 332.1263, found 332.1268.

1.6.4. 4,5-Dihydrothieno[3',2':3,4]pyrido[2,1-a]isoindol-7(11bH)-one (**195**)



192 **195**

1.6.4.1. 4,5-Dihydrothieno[3',2':3,4]pyrido[2,1-a]isoindol-7(11bH)-one (**195**) in $(CHCl_2)_2$

Using general procedure 6, hydroxy lactam **192** (10.2 mg, 39.33 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 1 h. Concentration *in vacuo* afforded lactam **195** as an off white solid (9.6 mg >99%).

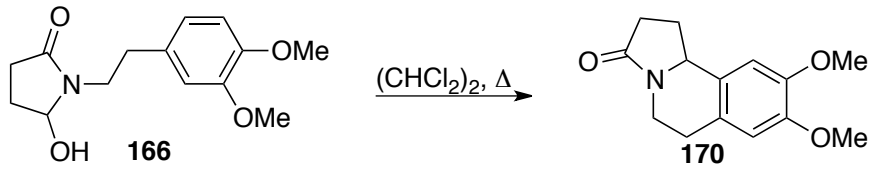
Spectroscopic data as for 1.7.4

1.6.4.2. 4,5-Dihydrothieno[3',2':3,4]pyrido[2,1-a]isoindol-7(11bH)-one (**195**) in xylene

Using general procedure 6, hydroxy lactam **192** (10.4 mg, 40.10 µmol) and xylene (0.35 mL) were stirred at 139 °C for 6 h. Concentration *in vacuo* and purification on silica gel afforded lactam **195** as an off white solid (8.7 mg, 90%)

Spectroscopic data as for 1.7.4.

1.6.5. 8,9-Dimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-a]isoquinolin-3(10bH)-one (**170**)

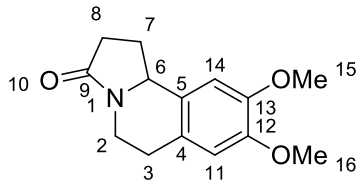


166 **170**

Using general procedure 6, hydroxy lactam **166** (40.3 mg, 0.151.9 µmol) and $(CHCl_2)_2$ (0.20 mL) were stirred at 147 °C for 2 h.

Concentration *in vacuo* and purification on silica gel afforded lactam **170** as a white solid (30.1 mg, 80%).

Spectroscopic data are consistent with that reported in the literature.[46]

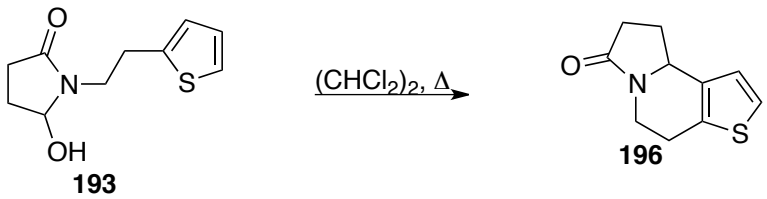


^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.62 (1H, s), 6.57 (1H, s) **11, 14;** 4.73 (1H, t, *J*=7.7 Hz) **6;** 4.37-4.25 (1H, m) **2;** 3.87 (3H, s), 3.86 (3H, s) **15, 16;** 3.10-2.80 (2H, m) **2, 8;** 2.74-2.39 (4H, m, **3, 7, 8**); 1.93-1.72 (1H, m) **7.**

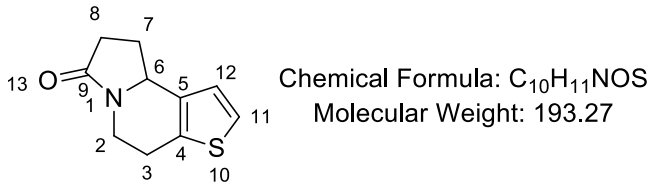
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ = 173.3, **9;** 148.1, 147.9, **12, 13;** 129.3, 125.5, **4, 5;** 111.6, 107.6, **11, 14;** 56.3, 56.0, 55.9, **6, 15, 16;** 37.0, **2;** 31.7, **8;** 28.0, 27.7, **3, 7.**

LRMS (ESI) m/z 270; $[M + Na^+]^+$.

1.6.6. 4,5,9,9a-Tetrahydrothieno[2,3-g]indolizin-7(8H)-one (**196**)



Using general procedure 6, hydroxy lactam **193** (9.7 mg, 50.19 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 3.5 h. Concentration *in vacuo* and purification on silica gel afforded lactam **196** as a pale yellow solid (8.9 mg, 92%).



MP 72-74 °C

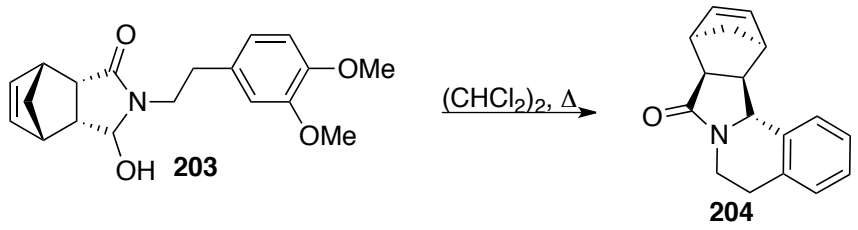
IR (ν cm^{-1}) 3099, 2924, 2849, 1683.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.19 (1H, d, *J*=5.1 Hz) **11**; 6.82 (1H, d, *J*=5.1 Hz) **12**; 4.74 (1H, t, *J*=7.5 Hz) **6**; 4.49 (1H, td, *J*=6.7, 4.3 Hz)) **2**; 3.13-2.76 (3H, m) **2**, **3**; 2.73-2.38 (3H, m) **7**, **8**; 1.93-1.68 (1H, m) **7**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 173.6, **9**; 135.9, 133.0, **8**, **12**; 124.1, 123.4, **10**, **11**; 56.3, **6**; 37.2, **2**; 31.6, **8**; 26.7, **7**; 24.6, **3**.

HRMS (ESI) m/z $C_{10}H_{11}NOSNa$ $[M + Na]^+$ calcd. 216.0459, found 216.0455.

1.6.7. (8aR,9S,12R,12aS,12bR)-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methanoisoindolo[1,2-a]isoquinolin-8(12bH)-one (**204**)

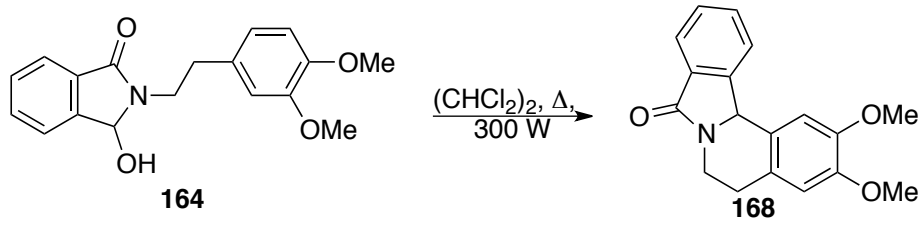


Using general procedure 6, hydroxy lactam **203** (10.0 mg, 30.37 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 1 h. Concentration *in vacuo* and purification on silica gel afforded lactam **204** as a white solid (8.5 mg, 90%).

Spectroscopic data as for 1.7.6.

1.7. µW-Promoted Intramolecular α-Amidoalkylations

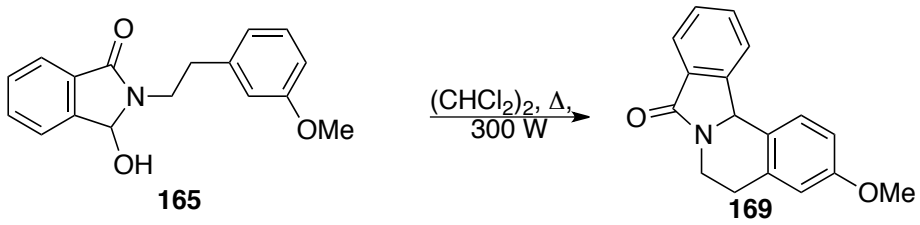
1.7.1. 2,3-Dimethoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (**168**)



Using general procedure 7, hydroxy lactam **164** (25.1 mg, 84.65 µmol) and $(CHCl_2)_2$ (0.70 mL) were stirred at 147 °C for 30 min. Concentration *in vacuo* afforded lactam **168** as a white solid (24.2 mg, 97%).

Spectroscopic data as for 1.6.1.1

1.7.2. 3-Methoxy-5,6-dihydroisoindolo[1,2-a]isoquinolin-8(12bH)-one (**169**)

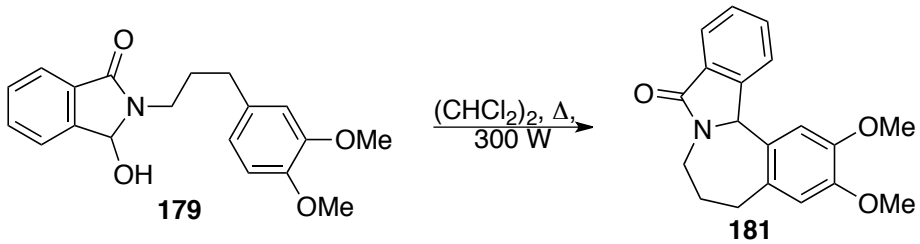


165 **169**

Using general procedure 7, hydroxy lactam **165** (23.0 mg, 82.59 µmol) and $(CHCl_2)_2$ (0.70 mL) were stirred at 147 °C for 55 min. Concentration *in vacuo* afforded lactam **169** as a white solid (21.9 mg, >99%).

Spectroscopic data as for 1.6.2

1.7.3. 2,3-Dimethoxy-6,7-dihydro-5H-benzo[3,4]azepino[2,1-a]isoindol-9(13bH)-one (**181**)

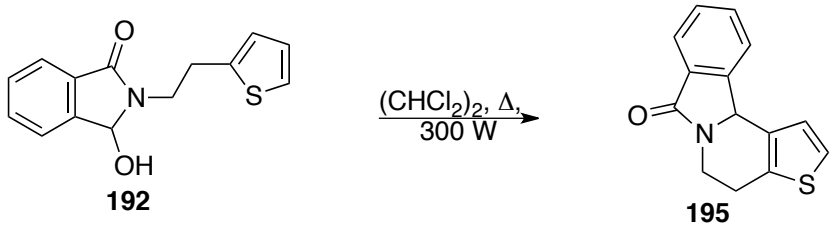


179 **181**

Using general procedure 7, hydroxy lactam **179** (19.7 mg, 60.18 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 60 min. Concentration *in vacuo* afforded lactam **181** as an oil (18.1 mg, 97%).

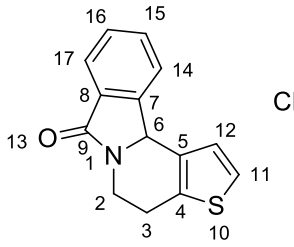
Spectroscopic data as for 5.6.3.

1.7.4. 4,5-Dihydrothieno[3',2':3,4]pyrido[2,1-a]isoindol-7(11bH)-one (**195**)



Using general procedure 7, hydroxy lactam **192** (10.2 mg, 39.33 µmol) and $(CHCl_2)_2$ (0.35 mL) were stirred at 147 °C for 38 min. Concentration *in vacuo* afforded lactam **195** as an oil (9.5 mg, >99%).

Spectroscopic data are consistent with that reported in the literature.[68]

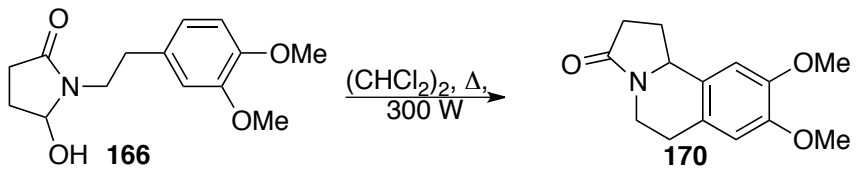


Chemical Formula: $C_{14}H_{11}NOS$
Molecular Weight: 241.31

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.87 (1H, d, *J*=7.7 Hz), 7.76 (1H, d, *J*=7.3 Hz) **14**, **17**; 7.60 (1H, td, *J*=7.5, 1.1 Hz), 7.48 (1H, t, *J*=7.3 Hz) **15**, **16**; 7.25 (1H, d, *J*=5.1 Hz), 7.21 (1H, d, *J*=5.1 Hz, **11**, **12**); 5.65 (1H, s) **6**; 4.82 (1H, ddd, *J*=13.2, 5.9, 1.1 Hz), 3.36 (1H, ddd, *J*=13.3, 11.1, 4.9 Hz) **2**; 3.13-2.78 (2H, m) **3**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 167.9, **9**; 144.2, **7**; 134.2, 132.3, 132.2, **4**, **5**, **8**; 131.8, 128.4, 124.1, 123.9, 123.9, 122.8, **11**, **12**, **14**, **15**, **16**, **17**; 58.7, **6**; 37.7, **2**; 25.3, **3**.

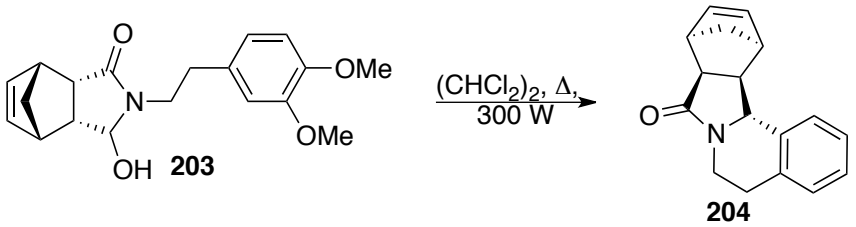
1.7.5. 8,9-Dimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-a]isoquinolin-3(10bH)-one (**170**)



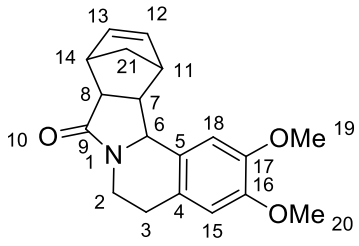
Using general procedure 7, hydroxy lactam **166** (19 mg, 71.62 µmol) and $(CHCl_2)_2$ (0.70 mL) were stirred at 147 °C for 40 min. Concentration *in vacuo* afforded lactam **170** as a white solid (17.7 mg, >99%).

Spectroscopic data as for 1.6.5

1.7.6. (8aR,9S,12R,12aS,12bR)-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methanoisoindolo[1,2-a]isoquinolin-8(12bH)-one (**204**)



Using general procedure 7, hydroxy lactam **203** (21.3 mg, 68.41 µmol) and $(CHCl_2)_2$ (0.70 mL) were stirred at 147 °C for 38 min. Concentration *in vacuo* afforded lactam **204** as a white solid (21.7 mg, >99%).



Chemical Formula: $C_{19}H_{21}NO_3$
Molecular Weight: 311.37

MP decomp. 127 °C

IR (ν, cm^{-1}) 2963, 1669, 1516.

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.67 (1H, s); 6.56 (1H, s) **15, 18**; 6.33 (1H, dd, *J*=5.7, 3.1 Hz), 6.26 (1H, dd, *J*=5.5, 2.6 Hz) **12, 13**; 4.23 (1H, d, *J*=7.0 Hz) **2**; 4.05 (1H, d, *J*=2.9 Hz) **6**; 3.91 (3H, s), 3.85 (3H, s) **19, 20**; 3.30 (2H, br. s) **11, 14**; 3.13 (1H, dd, *J*=9.5, 4.4 Hz) **8**; 2.75-2.99 (3H, m) **2, 3, 7**; 2.54 (1H, d, *J*=11.7 Hz) **3**; 1.70 (1H, apt. d, *J*=8.4 Hz), 1.49 (1H, apt. d, *J*=8.4 Hz) **21**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 173.1, **9**; 148.0, 147.9, **16, 17**; 137.0, 134.2, **12, 13**; 130.3, 125.7, **4, 5**; 111.7, 107.7, **15, 18**; 59.5, **6**; 56.1, 55.9, **19, 20**; 51.4, 51.2, 46.5, 45.8, 44.5, **7, 8, 11, 14, 21**; 37.2, **11**; 27.7, **12**.

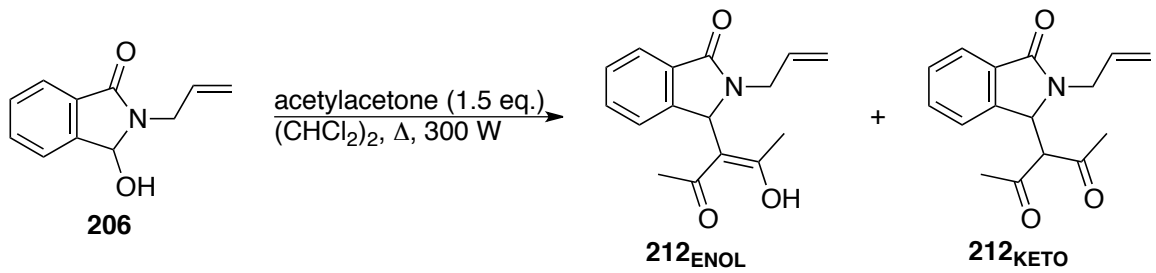
LRMS (ESI) m/z 312 $[M + H]^+$; 375 $[M + CH_3CN + Na^+]^+$; 645 $[2M + Na^+]^+$; 957 $[2M + Na^+]^+$.

HRMS (ESI) m/z for $C_{19}H_{21}NO_3$ $[M + Na]^+$: Calcd. 334.1414, Found 334.1428.

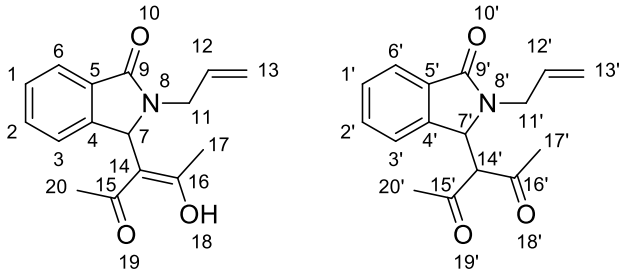
1.8. μW-Promoted Intermolecular α-Amidoalkylations

1.8.1 3-(2-Allyl-3-oxoisoindolin-1-yl)pentane-2,4-dione (**212**)

Using general procedure 8, hydroxy lactam **206** (21.5 mg, 113.6 μmol, 1.0 eq.), acetylacetone solution (0.25 mL of 0.5M solution in Et_2O, 125.0 μmol, 1.1 eq.) and $(CHCl_2)_2$ (0.70 mL) were stirred at 147 °C for 30 min. Concentration *in vacuo* afforded lactam **212** as a mixture of keto-enol tautomers as a pale yellow oil (33.1 mg, >99%).



Spectroscopic data are consistent with that reported in the literature for **1.161A**, with the exception of the enol-keto tautomer ratio of 4:1 (this work) *vs*. 1:0.[46]



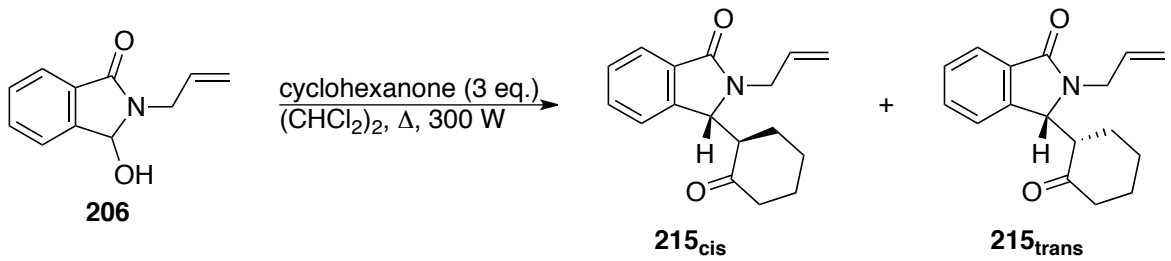
Chemical Formula: $C_{16}H_{17}NO_3$
Molecular Weight: 271.31

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm *Major tautomer* ***1.161A$_{ENOL}$*** 7.90 (1H, d, *J*=7.2 Hz) **3**; 7.63-7.40 (2H, m) **1**, **2**; 7.37-7.29 (1H, m) **6**; 5.97-5.76 (1H, m) **12**; 5.50 (1H, s) **7**; 5.30-5.17 (2H, m) **13**; 4.65 (1H, dt, *J*=15.4, 1.9 Hz) **11**; 3.56 (1H, dd, *J*=15.4, 7.5 Hz) **11**; 2.37 (3H, s) **20**; 1.38 (3H, s) **17**. *Minor tautomer* ***1.161A$_{KETO}$*** 7.84 (1H, d, *J*=7.2 Hz) **3′**; 7.63-7.40 (3H, m) **1′**, **2′**, **6′**; 5.97-5.76 (1H, m) **12′**; 5.35 (1H, d, *J*=3.0 Hz) **7′**; 5.14 (1H, d, *J*=1.1 Hz) **13′**; 4.65 (1H, dt, *J*=15.4, 1.9 Hz) **11′**; 4.29 (1H, d, *J*=3.0 Hz) **14′**; 3.76 (1H, dd, *J*=15.8, 7.2 Hz) **11′**; 2.12 (1H, s) **17′/20′**; 1.92 (1H, s) **17′/20′**.

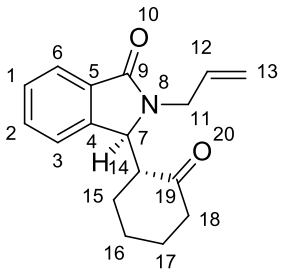
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm Major and minor tautomers 202.3; 202.1; 197.6; 189.8; 168.4; 167.8; 145.0; 142.6; 133.3; 132.7; 132.2; 132.1; 132.1 131.9; 128.9; 128.7; 124.0; 123.9; 122.1; 118.3; 118.0; 105.1; 67.1; 57.9; 57.0; 43.5; 42.4; 31.1; 30.8; 24.2; 22.8.

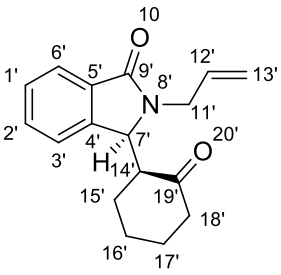
1.8.2. 2-Allyl-3-(2-oxocyclohexyl)isoindolin-1-one (**215**)

Using general procedure 8, hydroxy lactam **206** (21.1 mg, 111.5 µmol, 1.0 eq.), cyclohexanone solution (0.35 mL of 1M solution in CH_2Cl_2, 350 µmol, 3.0 eq.) and $(CHCl_2)_2$ (0.70 mL) were stirred at 147 °C at 300 W for 60 min. Concentration *in vacuo* afforded lactam **215** as an inseparable mixture of diastereoisomers as an oil (30.1 mg, >99%).



Spectroscopic data are consistent with that reported in the literature for **19B**. dr ratio 2:1.[46]





Chemical Formula: $C_{17}H_{19}NO_2$
Molecular Weight: 269.34

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm *Major diastereoisomer* 7.93-7.77 (1H, m); 7.59-7.38 (3H, m); 6.02-5.75 (1H, m); 5.32 (1H, d, *J*=2.6 Hz); 5.29-5.13 (2H, m); 4.55 (1H, dd, *J*=15.4, 5.3 Hz); 3.79 (1H, dd, *J*=15.6, 7.0 Hz); 3.00 (1H, ddd, *J*=12.7, 5.2, 2.4 Hz); 2.67-2.49 (1H, m); 2.44-2.32 (1H, m); 2.18-1.95 (1H, m); 1.89-1.18 (5H, m). *Minor diastereoisomer* 7.59-7.38 (2H, m); 7.33 (1H, d, *J*=7.5 Hz); 6.02-5.75 (1H, m); 5.45 (1H, s); 5.29-5.13 (2H, m); 4.44 (1H, dd, *J*=15.4, 6.4 Hz); 3.70 (1H, dd, *J*=15.3, 5.5 Hz); 2.82 (1H, dd, *J*=11.7, 6.8 Hz); 2.67-2.49 (1H, m); 2.44-2.32 (1H, m); 2.18-1.95 (1H, m); 1.89-1.18 (5H, m).

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm major and minor diastereoisomers 210.6; 209.4; 168.6; 143.6; 133.1; 133.0; 132.7; 131.7; 131.5; 128.2; 128.1; 124.5; 123.6; 123.5; 123.3; 121.3; 118.0; 117.7; 58.6; 57.1; 53.8; 50.1; 44.4; 43.1 42.1 41.7 26.4; 26.0 25.2 24.5; 24.4 24.2.

2. Experimental Procedures for Chapter 2

2.1. General Procedures

General Procedure 1 – *N-Boc Protection*

A round-bottomed flask was charged with a magnetic stirrer bar, nitrogen heterocycle (1.0 eq.), solvent (1 mL/mmol heterocycle), Boc_2O (1.2 eq.) and DMAP (0.15 eq.). The mixture was stirred at rt for the specified time and purified on silica gel (EtOAc in petrol) to afford the desired products.

General Procedure 2 – *Ester formation*

A round-bottomed flask was charged with a magnetic stirrer bar, acid (1.0 eq.), DMAP (0.050 eq.), alcohol (2.0 eq.) and CH_2Cl_2 (5 mL/mmol). Dropwise at 0 °C, DIC (1.2 eq.) was added and the mixture stirred for the specified time. The reaction mixtures were concentrated *in vacuo*, dissolved in Et_2O, the urea precipitate removed by filtration, the mixture concentrated *in vacuo* and purified on silica gel (EtOAc in petrol) to afford the desired products.

General procedure 3 – *Adapted Maleczka-Smith Borylation*

A three-necked round-bottomed flask was charged with a magnetic stirrer bar, pyrrole (1.0 eq.), $[Ir(OMe)(1,5\text{-cod})]_2$ (0.015 eq.) and dtbpy (0.030 eq.), equipped with a reflux condenser, and purged with Ar *in vacuo*. Hexane (2 mL/mmol pyrrole) and HBPin (2.0 eq.) were added by syringe, the reaction mixture stirred at 60 °C for the specified time, cooled to rt, filtered through Celite® and purified on silica gel (EtOAc/petrol) to afford the desired products.

General procedure 4 – *Suzuki-Miyaura Reaction*

A three-necked round-bottomed flask was charged with a magnetic stirrer bar, iodo phenyl (1.0 eq.), boronate ester/boronic acid (1.2 eq.), K_3PO_4 (2.0 eq.), $Pd(OAc)_2$ (0.050 eq.), SPhos (0.10 eq.), degassed BuOH (1 mL/mmol iodophenyl) and degassed H_2O (0.4 mL/mmol iodophenyl). The reaction flask was equipped with a reflux condenser, purged with Ar *in vacuo* and the reaction mixture stirred at 60 °C for the specified time. The reaction mixture was cooled to rt, filtered through silica gel (EtOAc) and purified on silica gel (Et_2O/EtOAc in petrol) to afford the desired products.

General procedure 5A – *Aryl Nitro Reduction*

A round-bottomed flask was charged with a magnetic stirrer bar, heteroaryl nitrophenyl (1.0 eq.), 10% Pd on activated carbon (0.050 eq. Pd) and EtOH (20 mL/mmol nitrophenyl), the flask purged with H_2 and the mixture stirred at rt for the specified time. The reaction mixture was filtered through Celite®, diluted with Et_2O, the organic washed with sat. aq. Na_2CO_3 solution and concentrated *in vacuo* at 20 °C to afford the desired products, which were used directly without further purification.

General procedure 5B – *Aryl Nitro Reduction*

A round-bottomed flask was charged with a magnetic stirrer bar, nitro (1.0 eq.), iron filings (5.0 eq.), NH_4Cl (5.0 eq.), EtOH (6 mL/mmol nitro), water (3 mL/mmol nitro) and the mixture stirred at reflux for the specified time. The mixture was cooled to rt, filtered through Celite® and extracted with CH_2Cl_2, dried (K_2CO_3) and concentrated *in vacuo* to afford the desired products, which were used directly without further purification.

General procedure 6 – *Pictet-Spengler Reaction*

A round-bottomed flask was charged with a magnetic stirrer bar, pyrroloaniline (1.0 eq.) aldehyde (1.2 eq.), Lewis acid (10-20 mol. %), solvent and purged with Ar. The reaction mixture was stirred for the specified time. Upon completion, the reaction mixture was filtered through Celite®, concentrated *in vacuo* and purified on deactivated silica gel to afford the desired products.

General procedure 7A – *Amide Bond Formations*

A round-bottomed flask was charged with a magnetic stirrer bar, acid (2.0 eq.), (CH_2Cl_2 (15 mL/mmol acid) $SOCl_2$ (5.0 eq.), DMF (2 drops), the reaction mixture purged with Ar and stirred for the specified time. The reaction mixture was concentrated *in vacuo* and aniline (1.0 eq.), Et_3N (2.0 eq.), DMAP (0.15 eq.) and CH_2Cl_2 (15 mL/mmol acid) were added, the reaction purged with Ar and stirred for the specified time. The reaction mixture was transferred to a separatory funnel, washed with water, the organics dried ($MgSO_4$), concentrated *in vacuo* and purified on silica gel (EtOAc in petrol) to afford the desired products.

General procedure 7B – *Amide Bond Formations*

Round-bottomed flask A was charged with a magnetic stirrer bar, acid (3.0 eq.) and under Ar, anhydrous THF (10 mL/mmol acid), HCA (1.5 eq.), and dropwise, PPh_3 (3.0 eq. in THF) and stirred for 20 min at rt. Round-bottomed flask B was charged with a magnetic stirrer bar, aniline and under an atmosphere of Ar, THF (10 mL/mmol aniline), dropwise, the contents of round-bottomed flask A and a Et_3N (1.5 eq.). The reaction mixture was stirred for the specified time. The reaction mixture was concentrated, dissolved in a mixture of CH_2Cl_2 and sat. aq. NH_4Cl and transferred to a separatory funnel, the organics dried (K_2CO_3), concentrated *in vacuo* and purified on silica gel (EtOAc in petrol) to afford the desired products.

General procedure 7C – *Amide Bond Formations*

A round-bottomed flask was charged with a magnetic stirrer bar, acid (1.0 eq.), DMAP (0.050 eq.), and CH_2Cl_2 (*ca*. 5 mL/mmol). Dropwise at 0 °C, DIC (1.2 eq.) was added, followed by the addition of aniline (1.0 eq. in CH_2Cl_2 (1 mL)) and the mixture stirred at rt for the specified time. The reaction mixtures were concentrated *in vacuo*, dissolved in Et_2O, the urea precipitate removed by filtration, the mixture concentrated *in vacuo* and purified on silica gel (EtOAc in petrol) to afford the desired products.

General procedure 8 – *Movassaghi-Pictet-Hubert Reaction*

A round-bottomed flask was charged with a magnetic stirrer bar, amide (1.0 eq.), 2-ClPyr (2.0 eq.) and CH_2Cl_2 (5 mL/mmol amide) and purged with Ar. At -78 °C, Tf_2O (4.0 eq.) was added dropwise. Upon completion of the addition, the reaction mixture was brought slowly to rt and stirred for the specified time. Upon completion of the reaction, sat. aq. $NaHCO_3$ solution (equal vol. of CH_2Cl_2) was added, the organics combined, dried ($MgSO_4$), concentrated *in vacuo* and purified on deactivated silica gel (EtOAc in petrol) to afforded the desired products.

General procedure 9 – *N-Alkylations*

A round-bottomed flask was charged with a magnetic stirrer bar, bromide (1.0 eq.), amine (1.2 eq.), K_2CO_3/Cs_2C0_3 (1.2 – 1.5 eq.) and MeCN (*ca*. 5 mL/mmol) and stirred for the specified time. The reaction mixture was diluted with water and transferred to a separatory funnel, the aqueous phase extracted with EtOAc, the organics combined, dried ($MgSO_4$), concentrated *in vacuo* and purified on silica gel as required to afford the desired products.

General procedure 10A – *N-Boc Deprotection*

A round-bottomed flask was charged with a magnetic stirrer bar, pyrroloquinoline (1.0 eq.), anhydrous THF (*ca*. 5 mL/mmol pyrroloquinoline) and, NaOMe (2.0 eq. of 25% soln. in MeOH) was added dropwise and the reaction mixture stirred for the specified time. Upon completion, H_2O was added and the mixture transferred to a separatory funnel, the aqueous phase extracted with EtOAc, the organics combined, dried ($MgSO_4$), concentrated *in vacuo* and purified on silica gel (EtOAc in petrol) to afford the desired products.

General procedure 10B – *N-Boc Deprotection*

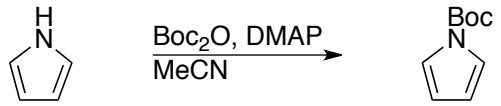
A round-bottomed flask was charged with a magnetic stirrer bar, pyrroloquinoline (1.0 eq.) and HCl in dioxane (4M, *ca*. 5 mL/mmol pyrroloquinoline) and stirred for the specified time. Upon completion, the reaction mixture was diluted with water, the pH adjusted to strongly basic (1M aq. NaOH solution) and transferred to a separatory funnel, the aqueous phase extracted with EtOAc, the organics combined, dried ($MgSO_4$), concentrated *in vacuo* and purified on silica gel to afford the desired products.

General procedure 10C – *N-Boc Deprotection*

A round-bottomed flask was charged with pyrroloquinoline and heated to 120 °C until CO_2 evolution ceased. The resulting solid was purified on silica gel to afford the desired products.

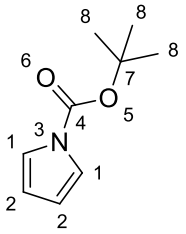
2.2. *N*-Boc Protections

2.2.1 *tert*-Butyl 1*H*-pyrrole-1-carboxylate (**260**)



Using general procedure 1, pyrrole (0.21 mL, 3.027 mmol, 1.0 eq.), CH_3CN (3 mL), Boc_2O (787 mg, 3.606 mmol, 1.2 eq.) and DMAP (53 mg, 433.8 µmol, 0.15 eq.) were stirred for 16 h and purified on silica gel (1% EtOAc in petrol) to afford pyrrole **260** as a colourless liquid (497 mg, 99%).

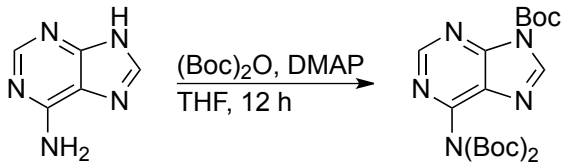
Spectroscopic data are consistent with that reported in the literature.[172]



Chemical Formula: $C_9H_{13}NO_2$
Molecular Weight: 167.21

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.25 (2H, t, *J*=2.3 Hz) **1;** 6.23 (2H, t, *J*=2.3 Hz) **2;** 1.61 (9H, s) **8.**

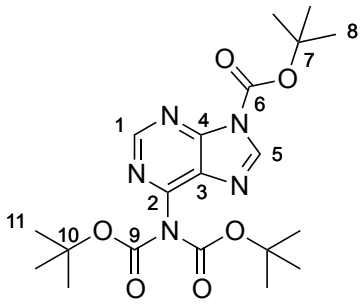
2.2.2. Tris-Boc adenine (**320**)



319 **320**

Using general procedure 1, adenine (**319**) (1.35 g, 10.00 mmol, 1.0 eq.), DMAP (123 mg, 1.000 mmol, 0.10 eq.), Boc_2O (8.86 g, 40.00 mmol, 4.0 eq.) and THF (50 mL) were stirred for 12 h and purified on silica gel (20-30% EtOAc in petrol) to afford tris-Boc-adenine **320** as a white foam (4.18 g, 96%).

Spectroscopic data are consistent with that reported in the literature.[109]



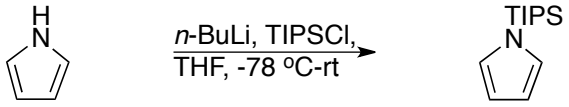
Chemical Formula: $C_{20}H_{29}N_5O_6$
Molecular Weight: 435.47

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.02 (1H, s), 8.51 (1H, s) **1**, **5**; 1.72 (9H, s) **8**; 1.44 (18H, s) **11**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 154.1; 152.5; 151.2; 150.0; 145.6; 143.2; 129.6; 87.5, **7**; 84.0, **10**; 27.9, **8**; 27.7, **11**.

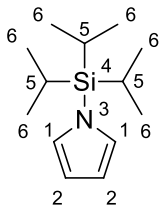
2.3. *N*-TIPS Protections

2.3.1. 1-(Triisopropylsilyl)-1*H*-pyrrole (**261**)



A two-necked round-bottomed flask was charged with a magnetic stirrer bar, pyrrole (0.21 mL, 3.026 mmol, 1.0 eq.), anhydrous THF (3 mL) and the mixture cooled to -78 °C and purged with argon. *n*-BuLi (1.32 mL of 2.5 M solution, 3.300 mmol, 1.1 eq.) was added dropwise and stirred at -78 °C for 10 min. Triisopropylsilyl chloride (0.64 mL, 2.991 mmol, 1.0 eq.) was added dropwise, the reaction mixture stirred at -78 °C for 5 min and the reaction mixture was slowly warmed to rt before concentration *in vacuo*. The residue was dissolved in Et_2O and water and transferred to a separatory funnel. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Hexane was added, the resulting black precipitate was removed by filtration and the hexane solution concentrated *in vacuo*. Purification on alumina (hexane) afforded pyrrole **261** as a clear oil (392 mg, 58%).

Spectroscopic data are consistent with that reported in the literature.[173]



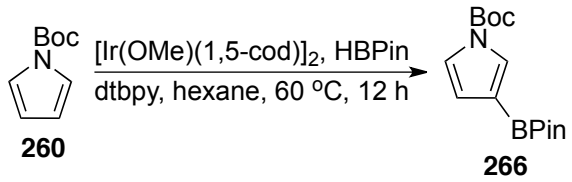
Chemical Formula: $C_{13}H_{25}NSi$
Molecular Weight: 223.43

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.82 (2H, t, *J*=2.0 Hz) **1;** 6.33 (2H, t, *J*=2.0 Hz) **2;** 1.47 (3H, spt, *J*=7.0 Hz) **5;** 1.12 (18H, d, *J*=7.3 Hz) **6.**

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 124.0, **1;** 110.0, **2;** 17.8, **6;** 11.7, **5.**

2.4. Adapted Maleczka-Smith Borylations

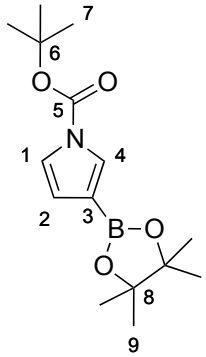
2.4.1 *tert*-Butyl 3-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1-carboxylate (**266**)



260 **266**

Using general procedure 3, *N*-Boc pyrrole (0.50 mL, 2.990 mmol, 1.0 eq.), HBPin (0.87 mL, 5.981 mmol, 2.0 eq.), hexane (6 mL), $[Ir(OMe)(1,5\text{-cod})]_2$ (30 mg, 44.85 µmol, 0.015 eq.) and dtbpy (24 mg, 89.71 µmol, 0.030 eq.) were stirred at 60 °C for 12 h and purified on silica gel (10% EtOAc in petrol) to afford boronate ester **266** as a white solid (815 mg, 98%).

Spectroscopic data are consistent with that reported in the literature.[95]

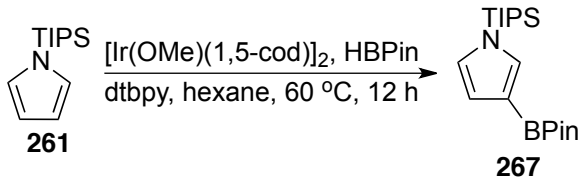


Chemical Formula: $C_{15}H_{24}BNO_4$
Molecular Weight: 293.17

^{1}H NMR (400 MHz, METHANOL-*d4*) δ ppm 7.55 (1H, t, *J*=1.7 Hz) **4;** 7.22 (1H, dd, *J*=3.1, 2.0 Hz) **1;** 6.39 (1H, dd, *J*=3.1, 1.5 Hz) **2;** 1.60 (9H, s) **7;** 1.31 (12H, s) **9.**

^{13}C NMR (100 MHz, METHANOL-*d*) δ ppm 150.0, **5;** 129.8, **4;** 121.7, **1;** 117.2, **2;** 85.2, **6;** 84.6, **8;** 28.1, **7;** 25.1, **9.**

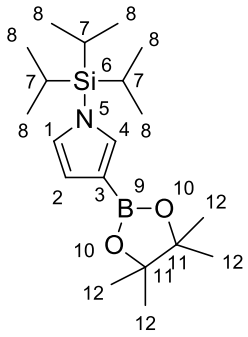
2.4.2. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (**267**)



261 **267**

Using general procedure 3, *N*-Tips pyrrole (0.25 mL, 1.012 mmol, 1.0 eq.), HBPin (0.29 mL, 2.024 mmol, 2.0 eq.), hexane (2 mL), $[Ir(OMe)(1,5\text{-cod})]_2$ (10 mg, 15.18 µmol, 0.015 eq.) and dtbpy (8 mg, 30.36 µmol, 0.030 eq.) were stirred at 60 °C for 8 h and purified on silica gel (5% EtOAc in petrol) to afford boronate ester **267** as a white solid (308 mg, 87%)

Spectroscopic data are consistent with that reported in the literature.[174]



Chemical Formula: $C_{19}H_{36}BNO_2Si$
Molecular Weight: 349.39

MP 65-67 °C

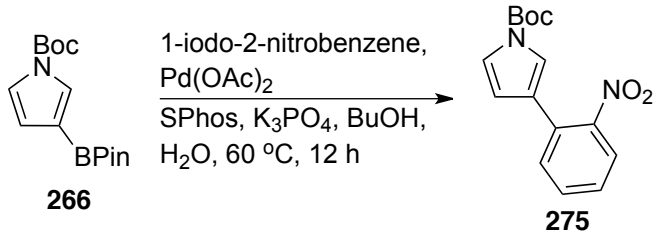
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.24 (1H, t, *J*=1.5 Hz) **4**; 6.82 (1H, t, *J*=2.3 Hz) **1**; 6.63 (1H, dd, *J*=2.6, 1.1 Hz) **2**; 1.46 (3H, spt, *J*=7.9 Hz) **7**, 1.33 (12H, s) **12**, 1.10 (18H, d, *J*=7.5 Hz) **8**.

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 133.6, **4**; 124.9, **1**; 115.6, **2**; 82.7, **11**; 24.8, **12**; 17.8, **8**; 11.6, **7**.

LRMS (ESI) m/z 350 $[M + H]^+$; 722 $[2M + Na]^+$.

2.5. Suzuki-Miyaura Reactions

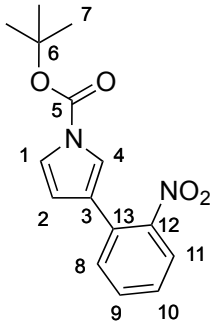
2.5.1. *tert*-Butyl 3-(2-nitrophenyl)-1H-pyrrole-1-carboxylate (**275**)



266 **275**

Using general procedure 4, boronate **266** (293 mg, 1.000 mmol, 1.2 eq.), 1-iodo-2-nitrobenzene (208 mg, 0.8333 mmol, 1.0 eq.), K_3PO_4 (354 mg, 1.667 mmol, 2.0 eq.), $Pd(OAc)_2$ (9 mg, 41.67 µmol, 0.050 eq.), SPhos (34 mg, 83.33 µmol, 0.10 eq.) BuOH (1 mL) and H_2O (0.4 mL) were stirred at 60 °C for 12 h and purified on silica gel (10-20% Et_2O in petrol) to afford nitro **275** as a pale yellow solid upon scratching (223 mg, 93%).

Spectroscopic data are consistent with that reported in the literature.[84]



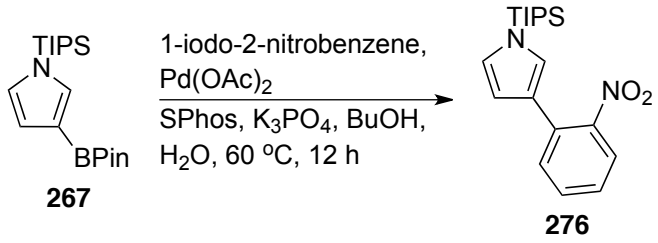
Chemical Formula: $C_{15}H_{16}N_2O_4$
Molecular Weight: 288.30

MP 62-66 °C

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.73 (1H, dd, *J*=8.1, 1.1 Hz) **11**; 7.55, (1H, td, *J*=7.5, 1.3 Hz) **9**; 7.50 (1H, dd, *J*=7.8, 1.5 Hz) **8**; 7.42-7.7.38 (2H, m) **4**, **10**; 7.28 (1H, dd, *J*=3.2, 2.2 Hz) **1**; 6.27 (1H, dd, *J*=3.3, 1.8 Hz) **2**; 1.62 (9H, s) **7**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 149.1, **12**; 148.4, **5**; 132.0, **9**; 131.2, **8**; 128.9, **13**; 127.6, **10**; 123.7, **11**; 122.7, **3**; 120.8, **1**; 118.2, **4**; 111.8, **6**; 28.0, **7**.

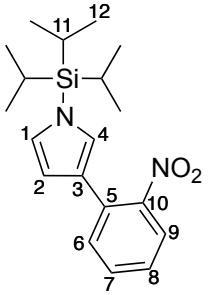
2.5.2. 3-(2-Nitrophenyl)-1-[tris(propan-2-yl)silyl]-1H-pyrrole (**276**)



267 **276**

Using general procedure 4, boronate **267** (254 mg, 0.7270 mmol, 1.2 eq.), 1-iodo-2-nitrobenzene (151 mg, 0.6058 mmol, 1.0 eq.), K_3PO_4 (257 mg, 1.212 mmol, 2.0 eq.), $Pd(OAc)_2$ (7 mg, 30.29 µmol, 0.050 eq.), SPhos (25 mg, 60.58 µmol, 0.10 eq.) BuOH (1 mL) and H_2O (0.4 mL) were stirred at 60 °C for 12 h and purified on silica gel (2.5-10% Et_2O in petrol) to afford nitro **276** as a yellow solid upon scratching (196 mg, 94%).

Spectroscopic data are consistent with that reported in the literature.[84]

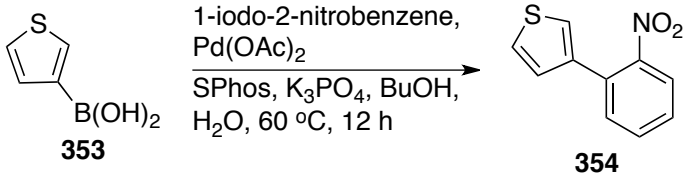


Chemical Formula: $C_{19}H_{28}N_2O_2Si$
Molecular Weight: 344.52

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.48 (1H, dd, *J*=8.0, 1.2 Hz); 7.45 (1H, dd, *J*=7.9, 1.4 Hz); 7.38 (1H, td, *J*=7.6, 1.3 Hz); 7.19-7.15 (1H, r ddd); 6.82 (1H, apt. t, *J*=1.8 Hz); 6.71 (1H, apt. t, *J*=2.4 Hz); 6.32 (1H, dd, *J*=2.7, 1.5 Hz) **2**; 1.37 (3H, spt., *J*=7.5 Hz) **11**; 1.03 (18H, d, *J*=7.6 Hz) **12**.

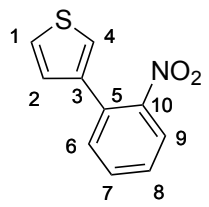
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 149.2; 131.3; 130.8; 129.9; 126.0; 125.0; 123.2; 122.9; 120.8; 110.4; 17.7; 11.6.

2.5.3. 3-(2-Nitrophenyl)thiophene (**354**)



Using general procedure 4, boronic acid **353** (401 mg, 3.133 mmol, 1.2 eq.), 1-iodo-2-nitrobenzene (600 mg, 2.410 mmol, 1.0 eq.), K_3PO_4 (1.535 g, 7.230 mmol, 2.0 eq.), $Pd(OAc)_2$ (27 mg, 0.1205 mmol, 0.050 eq.), SPhos (99 mg, 0.2410 mmol, 0.10 eq.) BuOH (2.5 mL) and H_2O (1.0 mL) were stirred at 60 °C for 16 h and purified on silica gel (5-15% EtOAc in petrol) to afford nitro **354** as an orange oil (480 mg, 97%).

Spectroscopic data are consistent with that reported in the literature.[175]



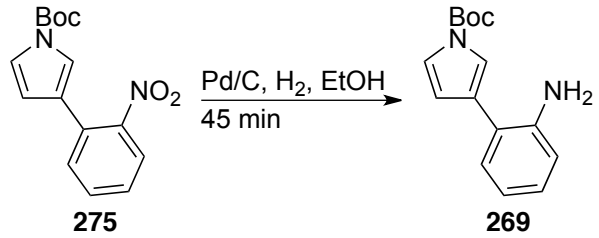
Chemical Formula: $C_{10}H_7NO_2S$
Molecular Weight: 205.23

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.80 (1H, dd, *J*=8.0, 1.2 Hz) **9**; 7.60 (1H, td, *J*=7.6, 1.3 Hz) **8**; 7.51 (1H, dd, *J*=7.7, 1.3 Hz) **6**; 7.49-7.45 (1H, r ddd) **7**; 7.40 (1H, dd, *J*=5.0, 3.0 Hz) **1**; 7.34 (1H, dd, *J*=3.0, 1.4 Hz) **4**; 7.10 (1H, dd, *J*=5.0, 1.4 Hz) **2**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 149.2, **5**; 137.0, **3**; 132.1, **8**; 131.7, **6**; 130.8, **10**; 128.1, **7**; 127.4, **2**; 126.2, **1**; 123.9, **9**; 123.5, **4**.

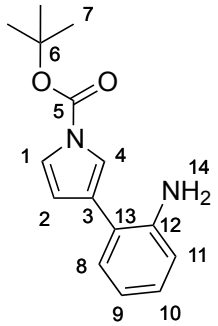
2.6. Nitro Reductions

2.6.1. *tert*-Butyl 3-(2-aminophenyl)-1H-pyrrole-1-carboxylate (**269**)



275 **269**

Using general procedure 5A, nitro **275** (50 mg, 173.4 µmol, 1.0 eq.), 10% palladium on activated carbon (3 mg) and EtOH (3.5 mL) were stirred in an atmosphere of H_2 for 45 min to afford aniline **269** as a colourless oil (43 mg, 97%), which was used directly without further purification.

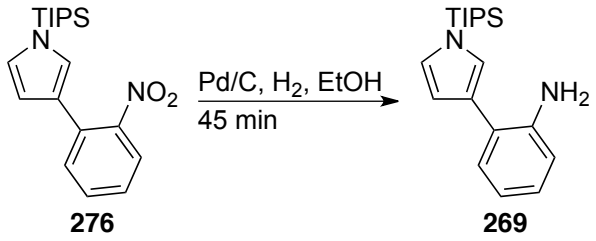


Chemical Formula: $C_{15}H_{18}N_2O_2$
Molecular Weight: 258.32

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.44 (1H, t, *J*=1.9 Hz) **4**; 7.35 (1H, dd, *J*=3.1, 2.2 Hz) **1**; 7.24 (1H, dd, *J*=7.6, 1,5 Hz) **8**; 7.12 (1H, ddd, *J*=7.9, 7.4, 1.6 Hz) **10**; 6.81 (1H, td, *J*=7.5, 1.2 Hz) **9**; 6.77 (1H, dd, *J*=8.0, 1.0 Hz) **11**; 6,48 (1H, dd, *J*3.2, 1.8 Hz) **2**; 3.93 (2H, br. s) **14**; 1.64 (9H, s) **7**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 148.7, **5**; 143.9, **12**; 129.7, **8**; 127.9, **10**; 125.1, **3**; 120.53, 120.51, **1**, **13**; 118.5, **9**; 117.5, **4**; 115.6, **11**; 112.6, **2**; 83.8, **6**; 27.9, **7**.

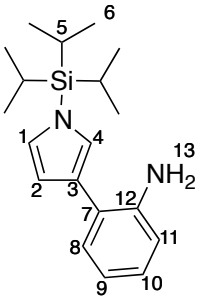
2.6.2. 2-{1-[tris(Propan-2-yl)silyl]-1H-pyrrol-3-yl}aniline (**269**)



276 **269**

Using general procedure 5A, nitro **276** (50 mg, 145.1 µmol, 1.0 eq.), 10% palladium on activated carbon (3 mg) and EtOH (3.5 mL) were stirred in an atmosphere of H_2 for 45 min to afford aniline **269** (46 mg, 100%), which was used directly without further purification.

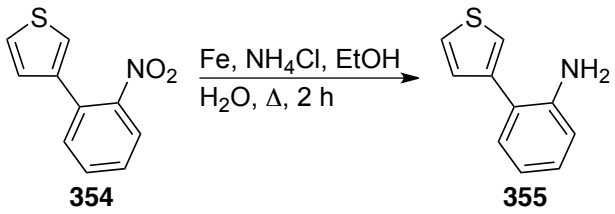
Spectroscopic data are consistent with that reported in the literature.[176]



Chemical Formula: $C_{19}H_{30}N_2Si$
Molecular Weight: 314.54

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.27 (1H, dd, *J*=7.5, 1.6 Hz); 7.07 (1H, td, *J*=7.6, 1.4 Hz); 6.97 (1H, t, *J*=1.5 Hz); 6.86 (1H, t, *J*=2.3 Hz); 6.81 (1H, dd, *J*=7.5, 0.8 Hz); 6.77 (1H, dd, *J*=7.9, 0.7 Hz); 6.53 (1H, dd, *J*=2.3, 1.4 Hz); 3.49 (2H, s) **13**; 1.50 (3H, spt., *J*=7.5 Hz) **5**; 1.14 (18H, d, *J*=7.5 Hz) **6**.

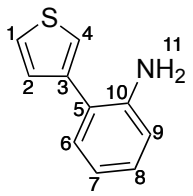
2.6.3. 2-(Thiophen-3-yl)aniline (**355**)



354 **355**

Using general procedure 5B, nitro **354** (51 mg, 248.5 µmol, 1.0 eq.), Fe filings (71 mg, 1.271 mmol, 5.1 eq.), NH_4Cl (63 mg, 1.156 mmol, 4.7 eq.), EtOH (1.4 mL) and H_2O (0.70 mL) were stirred at 80 °C for 2 h to afford aniline **355** as a yellow oil (39 mg, 92%), which was used directly without further purification.

Spectroscopic data are consistent with that reported in the literature.[175]



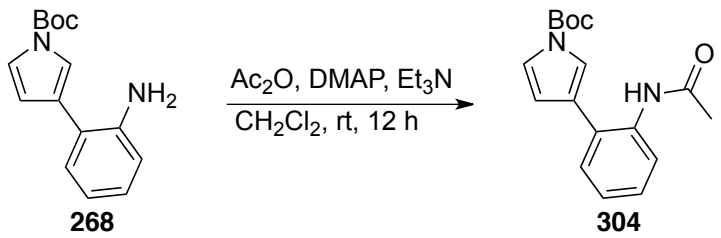
Chemical Formula: $C_{10}H_9NS$
Molecular Weight: 175.25

IR (ν (cm^{-1}) 3224, 1646, 1523, 753, 738.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.44 (1H, dd, *J*=4.9, 3.0 Hz); 7.39 (1H, dd, *J*=2.9, 1.3 Hz); 7.28 (1H, dd, *J*=4.9, 1.3 Hz); 7.23 (1H, dd, *J*=7.6, 1.5 Hz); 7.16 (1H, td, *J*=7.7, 1.6 Hz); 6.81 (1H, td, *J*=11.2, 1.2 Hz); 6.78 (1H, dd, *J*=8.0, 1.0 Hz); 3.84 (2H, br. s) **11**.

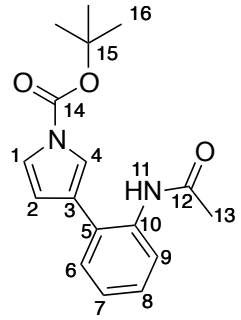
2.7. Amide Formations

2.7.1. *tert*-Butyl 3-(2-acetamidophenyl)-1*H*-pyrrole-1-carboxylate (**304**)



268 **304**

Using general procedure 7A, aniline **268** (47 mg, 173.4 µmol, 1.0 eq.), Ac_2O (20 µL, 208.1 µmol, 1.2 eq.), DMAP (1 mg, 8.670 µmol, 0.050 eq.), Et_3N (48 µL, 346.8 µmol, 2.0 eq.) and CH_2Cl_2 (1 mL) were stirred for 12 h and purified on silica gel (20-50% EtOAc in petrol) to afford amide **304** as a clear oil (43 mg, 83%).



Chemical Formula: $C_{17}H_{20}N_2O_3$
Molecular Weight: 300.35

IR (*v*, cm^{-1}) 3266, 2980, 1741, 1388, 1345, 975.

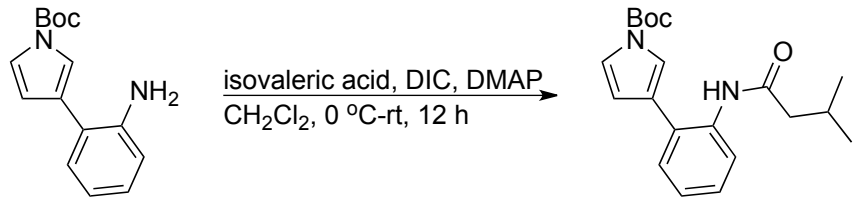
^{1}H NMR (400 MHz, ACETONE-*d*-6) δ ppm 8.41 (1H, br. s) **11**; 7.92 (1H, d, *J*=7.8 Hz) **9**; 7.45 (1H, s) **4**; 7.37 (1H, d, *J*=7.4 Hz) **6**; 7.33 (1H, dd, *J*=3.2, 2.2 Hz) **1**; 7.25 (1H, td, *J*=7.7, 1.3 Hz) **8**; 7.14 (1H, t, *J*=7.3 Hz) **7**; 6.48 (1H, apt. s) **2**; 2.08 (3H, s) **13**; 1.63 (9H, s) **16**.

^{13}C NMR (100 MHz, ACETONE-*d*-6) δ ppm 168.9, **12**; 149.3, **14**; 136.5, **10**; 130.1, **6**; 128.0, **8**; 125.5, 125.3, **3**,**5**; 125.1, **9**; 121.4, **1**; 119.0, **4**; 113.4, **2**; 84.7, **15**; 28.0 **16**;

LRMS (ESI) m/z 301.0 $[M + H]^+$; 323.0 $[M + Na]^+$

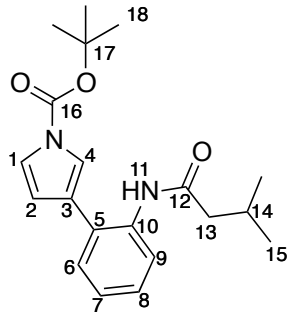
HRMS (ESI) m/z for $C_{17}H_{20}N_2O_3$ calcd. 301.1547, found 301.1551 $[M + H]^+$.

2.7.2. *tert*-Butyl 3-(2-(3-methylbutanamido)phenyl)-1*H*-pyrrole-1-carboxylate (**306**)



268 **306**

Using general procedure 7C, aniline **268** (47 mg, 173.4 µmol, 1.0 eq.), isovaleric acid (38 µL, 346.8 µmol, 2.0 eq.), DIC (68 µL, 433.5 µmol, 2.5 eq.), DMAP (1 mg, 8.670 µmol, 0.050 eq.) and CH_2Cl_2 (1 mL) were stirred for 12 h and purified on silica gel (20-50% EtOAc in petrol) to afford amide **306** as a white solid (54 mg, 91%).



Chemical Formula: $C_{20}H_{26}N_2O_3$
Molecular Weight: 342.43

MP 100-101 °C

IR (*v*, cm^{-1}) 2959, 1742, 1389, 1345, 1287.

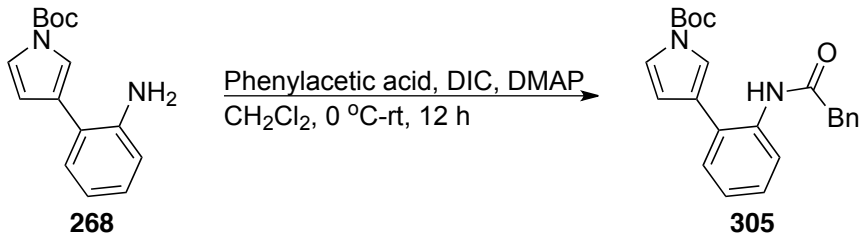
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.31 (1H, d, *J*=8.1 Hz) **9**; 7.45 (1H, br. s) **11**; 7.38 (1H, apt. t, *J*=2.6 Hz) **1**/**4**; 7.33-7.28 (3H, m) **1**/**4**, **6**, **8**; 7.12 (1H, t, *J*=7.4 Hz) **7**; 6.36 (1H, dd, *J*=3.1, 1.8 Hz) **2**; 1.63 (9H, s) **18**; 1.01 (6H, d, *J*=6.1 Hz) **15**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 170.6, **12**; 148.5, **16**; 135.2, **10**; 129.6, 128.0, **6**, **8**; 124.9, **5**; 124.0, **3**; 123.9, **7**; 121.19, 121.15, **1**/**4**, **9**; 118.2, **1**/**4**; 112.5, **2**; 84.3, **17**; 47.3, **13**; 28.0, **18**; 26.1, **14**; 22.4, **15**.

LRMS (ESI) m/z 343.1 $[M + H]^+$; 365.1 $[M + Na]^+$

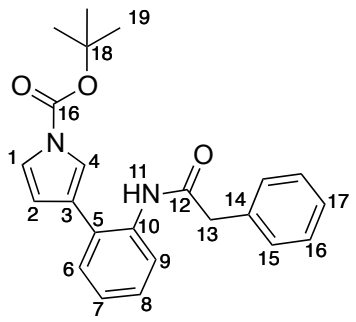
HRMS (ESI) m/z for $C_{20}H_{26}N_2O_3$ calcd. 343.2016, found 343.2015 $[M + H]^+$.

2.7.3. *tert*-Butyl 3-(2-(2-phenylacetamido)phenyl)-1*H*-pyrrole-1-carboxylate (**305**)



268 **305**

Using general procedure 7C, aniline **268** (50 mg, 173.4 µmol, 1.0 eq.), phenylacetic acid (44 µL, 346.8 µmol, 2.0 eq.), DIC (68 µL, 433.5 µmol, 2.5 eq.), DMAP (1 mg, 8.670 µmol, 0.050 eq.) and CH_2Cl_2 (1 mL) were stirred for 12 h and purified on silica gel (10-30% EtOAc in petrol) to afford amide **305** as a colourless oil (56 mg, 86%).



Chemical Formula: $C_{23}H_{24}N_2O_3$
Molecular Weight: 376.45

IR (ν, cm^{-1}) 1742, 1519, 1388, 1346, 1285, 1148, 976.

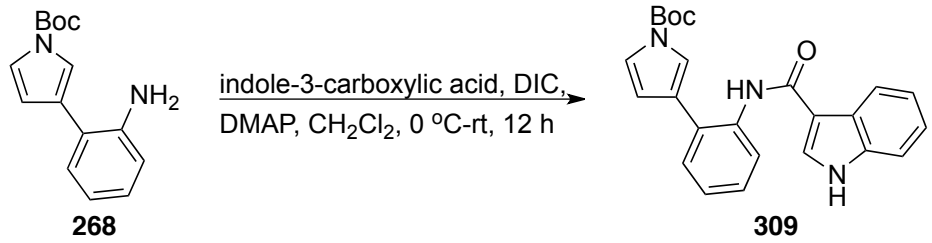
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.36 (1H, d, *J*=8.2 Hz) **9**; 7.45 (1H, br. s) **11**; 7.32-7.26 (4H, m); 7.22-7.13 (4H, m); 7.09-7.05 (2H, m); 5.93 (1H, dd, *J*=3.0, 1.7 Hz) **2**; 3.70 (2H, s) **13**; 1.67 (9H, s) **19**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 168.9; 148.4; 135.4; 134.0; 129.8; 129.5; 129.0; 128.1; 127.4; 125.0; 123.9; 123.2; 120.9; 120.3; 118.0; 112.3; 84.1; 45.2; 28.0.

LRMS (ESI) m/z 377.1 $[M + H]^+$; 399.1 $[M + Na]^+$

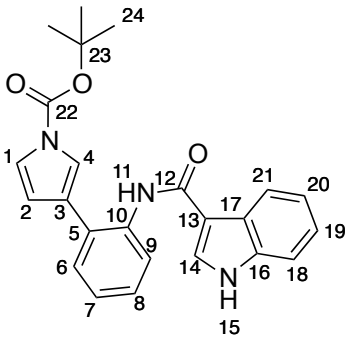
HRMS (ESI) m/z for $C_{23}H_{24}N_2O_3$ calcd. 377.1860, found 377.1863 $[M + H]^+$.

2.7.4. *tert*-Butyl 3-(2-(1*H*-indole-3-carboxamido)phenyl)-1*H*-pyrrole-1-carboxylate (**309**)



268 **309**

Using general procedure 7C, aniline **268** (47 mg, 173.4 µmol, 1.0 eq.), indole-3-carboxylic acid (56 mg, 346.8 µmol, 2.0 eq.), DIC (68 µL, 433.5 µmol, 2.5 eq.), DMAP (1 mg, 8.670 µmol, 0.050 eq.) and MeCN (1 mL) were stirred for 12 h and purified on silica gel (20-50% EtOAc in petrol) to afford amide **309** as a yellow oil (56 mg, 81%).



Chemical Formula: $C_{24}H_{23}N_3O_3$
Molecular Weight: 401.46

IR (ν, cm^{-1}) 3234, 1743, 1343, 1284, 1148.

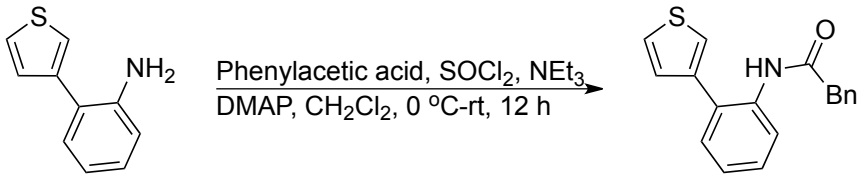
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.78 (1h, br. s) **15**; 8.52 (1H, d, *J*=8.3 Hz) **9**; 8.24 (1H, s) **11**; 7.73 (1H, d, *J*=3.2 Hz) **14**; 7.62 (1H, d, *J*=8.0 Hz) **21**; 7.43-7.61 (5H, m) **1**, **4**, **6**, **8**, **18**; 7.43-7.12 (3H, m) **7**, **19**, **20**; 6.42 (1H, apt. t, *J*=2.4 Hz) **2**; 1.56 (9H, s) **24**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 163.7, **12**; 148.5, **16**; 136.6, **10**; 135.9; 129.8, **14**; 129.0; 128.2, **5**; 125.4; 124.3; 123.9, **7**; 123.8, **19**; 122.9; 121.6; 121.3; 121.2; 119.4; 118.5, **21**; 113.0, **2**; 112.4, **17**; 112.3, **18**; 84.3, **23**; 27.9, **24**.

LRMS (ESI) m/z 402.1 $[M + H]^+$

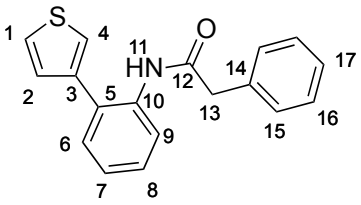
HRMS (ESI) m/z for $C_{24}H_{23}N_3O_3$ calcd. 410.1812, found 410.1810 $[M + H]^+$.

2.7.5. 2-Phenyl-*N*-(2-(thiophen-3-yl)phenyl)acetamide



355 **356**

Using general procedure 7A, aniline compound (43 mg, 243.6 µmol, 1.0 eq.), phenylacetic acid (66 mg, 487.2 µmol, 2.0 eq.), $SOCl_2$ (42 µL 584.6 µmol, 2.4 eq.), Et_3N (170 µL, 1.218 mmol, 5.0 eq.), DMAP (4 mg, 36.54 µmol, 0.15 eq.) and CH_2Cl_2 (1.2 mL) were stirred for 12 h and purified on silica gel (5-20% EtOAc in petrol) to afford amide compound as a white solid (35 mg, 49%).



Chemical Formula: $C_{18}H_{15}NOS$
Molecular Weight: 293.38

MP 114-117 °C

IR (*v*, cm^{-1}) 2968, 1736, 1499

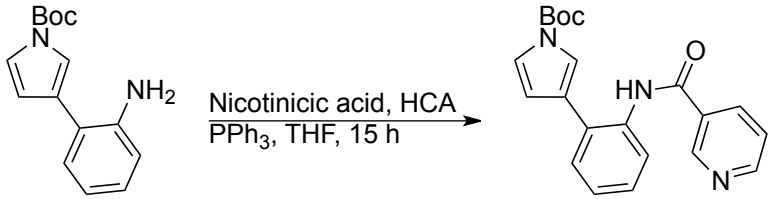
^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 8.13 (1H, br. s) **11**; 8.12 (1H, d, *J*=8.2 Hz) **9**; 7.48 (1H, dd, *J*=5.0, 2.9 Hz) **1**; 7.32-7.24 (8H, m) **4**, **6**, **8**, **15**, **16**, **17**; 7.14 (1H, t, *J*=7.5 Hz) **7**; 7.02 (1H, dd, *J*=4.9, 0.9 Hz) **2**; 3.67 (2H, s) **13**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 169.6, **12**; 139.3, **3**; 136.4, **10**; 136.2, **14**; 130.3, **6**/**8**/**17**; 130.7, **15**; 129.6, **16**; 129.2, **5**; 129.0, **4**; 128.6, 127.9, **6**/**8**/**17**; 127.4, **1**; 125.2, **7**; 124.1, **2**; 123.7, **9**; 45.3, **13**.

LRMS (ESI) m/z 293.9 $[M + H]^+$; 315.9 $[M + Na]^+$.

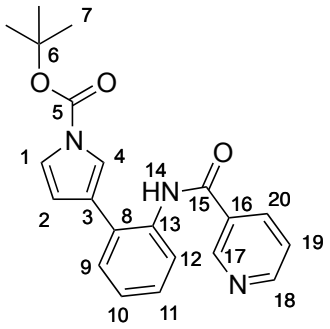
HRMS (ESI) m/z for $C_{18}H_{15}NOS$ calcd. 294.0945, found 294.0946 $[M + H]^+$.

2.7.6. *tert*-Butyl 3-(2-(nicotinamido)phenyl)-1*H*-pyrrole-1-carboxylate (**307**)



268 **307**

Using general procedure 7B, aniline **268** (45 mg, 173.4 µmol, 1.0 eq.), nicotinic acid (64 mg, 520.2 µmol, 3.0 eq.), hexachloroacetone (48 µL, 260.1 µmol, 1.5 eq.) PPh_3 (138 mg, 520.2 µmol, 3.0 eq.), Et_3N (73 µL, 520.2 µmol, 3.0 eq.) and THF (2 mL) were stirred for 15 h and purified on silica gel (10-50% EtOAc in petrol) to afford amide **307** as a white solid (29 mg, 48%).



Chemical Formula: $C_{21}H_{21}N_3O_3$
Molecular Weight: 363.41

MP 56-58 °C

IR (ν, cm^{-1}) 2978, 1739, 1655.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.97 (1H, br. s) **17**; 8.75 (1H, apt. br. s) **18**; 8.45 (1H, d, *J*=7.8 Hz) **12**; 8.34 (1H, br. s) **14**; 8.17 (1H, d, *J*=7.9 Hz) **20**; 7.44-7.35 (5H, m) **1**, **4**, **9**, **11**, **19**; 7.19 (1H, apt. t, *J*=7.5 Hz) **10**; 6.41 (1H, dd, *J*=3.0, 1.9 Hz) **2**; 1.61 (9H, s) **7**.

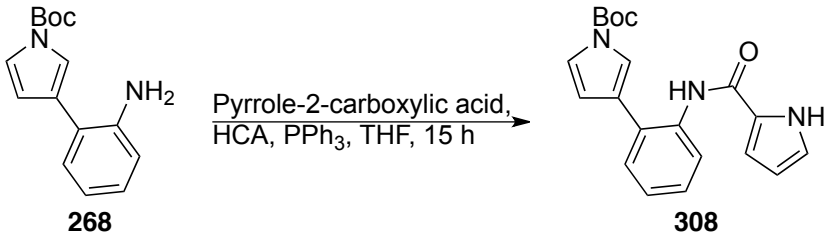
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 163.1, **15**; 152.4, **18**; 148.3, **5**; 147.7, **17**; 135.2, **20**; 134.8, **13**; 130.6, **16**; 129.8, **1**/**4**/**9**/**11**;

128.3, **1**/**4**/**9**/**11**; 125.6, **8**; 124.8, **10**; 123.7, **19**; 123.6, **3**; 121.6, **1**/**4**/**9**/**11**; 121.3, **12**; 118.4, **1**/**4**/**9**/**11**; 112.2, **2**; 84.5, **6**; 27.9, **7**.

LRMS (ESI) m/z 364.1 $[M + H]^+$; 386.1 $[M + Na]^+$.

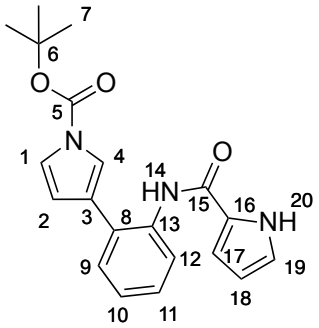
HRMS (ESI) m/z for $C_{21}H_{21}N_3O_3$ calcd. 364.1656, found 364.1655 $[M + H]^+$.

2.7.7. *tert*-Butyl 3-(2-(1*H*-pyrrole-2-carboxamido)phenyl)-1*H*-pyrrole-1-carboxylate (**308**)



268 **308**

Using general procedure 7B, aniline **268** (45 mg, 173.4 µmol, 1.0 eq.), pyrrole-2-carboxylic acid (60 mg, 520.2 µmol, 3.0 eq.), hexachloroacetone (48 µL, 260.1 µmol, 1.5 eq.) PPh_3 (136 mg, 520.2 µmol, 3.0 eq.), Et_3N (73 µL, 520.2 µmol, 3.0 eq.) and THF (2 mL) were stirred for 15 h and purified on silica gel (5-25% EtOAc in petrol) to afford amide **308** as a yellow foam (33 mg, 56%).



Chemical Formula: $C_{20}H_{21}N_3O_3$
Molecular Weight: 351.40

IR (*v*, cm^{-1}) 3250, 1736, 1651.

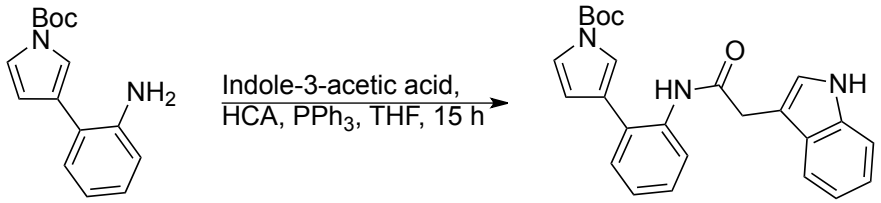
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.09 (1H, br. s) **20**; 8.45 (1H, dd, *J*=8.7, 1.2 Hz) **12**; 8.12 (1H, br. s) **14**; 7.45 (1H, dd, *J*=3.2, 2.2 Hz) **1**; 7.41 (1H, t, *J*=1.9 Hz) **4**; 7.37 (1H, d, *J*=7.7) **9**; 7.36 (1H, td, *J*=7.3, 1.6 Hz) **11**; 7.15 (1H, td, *J*=7.5, 1.3 Hz) **10**; 7.01 (1H, td, *J*=2.7, 1.3 Hz) **19**; 6.49 (1H, ddd, *J*=3.7, 2.5, 1.3 Hz)

18; 6.46 (1H, dd, *J*=3.3, 1.7 Hz) **2**; 6.26 (1H, td, *J*=3.8, 2.5 Hz) **17**; 1.64 (9H, s) **7**.

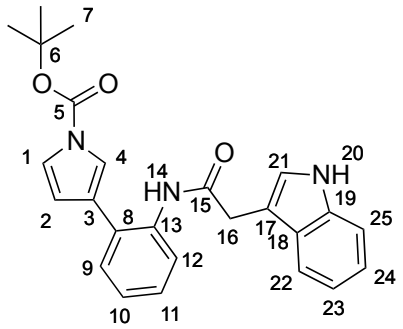
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 158.9, **15**; 148.5, **5**; 135.1 **13**; 129.5, **9**; 128.1, **11**; 126.2, **16**; 124.8, **8**; 123.8, **3**, **10**; 122.5, **19**; 121.4, **1**; 120.8, **12**; 118.3, **4**; 112.5, **2**; 110.0, **17**; 109.6, **18**; 84.4, **6**; 28.0, **7**.

LRMS (ESI) Fail.

2.7.8. *tert*-Butyl 3-(2-(2-(1*H*-indol-3-yl)acetamido)phenyl)-1*H*-pyrrole-1-carboxylate



Using general procedure 7B, aniline **268** (45 mg, 173.4 µmol, 1.0 eq.), indole-3-acetic acid (91 mg, 520.2 µmol, 3.0 eq.), hexachloroacetone (48 µL, 260.1 µmol, 1.5 eq.) PPh_3 (136 mg, 520.2 µmol, 3.0 eq.), Et_3N (73 µL, 520.2 µmol, 3.0 eq.) and THF (2 mL) were stirred for 15 h and purified on silica gel (20-50% EtOAc in petrol) to afford amide compound as an orange foam (55 mg, 82%).



Chemical Formula: $C_{25}H_{25}N_3O_3$
Molecular Weight: 415.48

IR (*v*, cm^{-1}) 3342, 1740, 1521, 1387, 1284, 1148, 975.

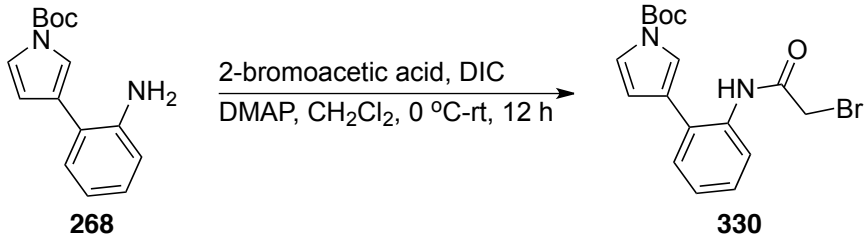
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.44 (1H, d, *J*=9.0 Hz) **12**; 8.42 (1H, br. s) **20**; 7.86 (1H, br. s) **14**; 7.50 (1H, d, *J*=8.0 Hz) **22**; 7.37 (1H, dt, *J*=8.2, 0.8 Hz) **25**; 7.32-7.28 (1H, r ddd) **11**; 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz) **24**; 7.12 (1H, td, *J*=8.1, 1.3 Hz)

9; 7.09-7.03 (3H, m) **10**, **21**, **23**; 6.92 (1H, t, *J*=1.9 Hz) **7**; 6.85 (1H, dd, *J*=3.1, 2.2 Hz) **1**; 5.54 (1H, dd, *J*=3.0, 1.7 Hz) **2**; 3.87 (2H, s) **16**; 1.66 (9H, s) **7**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 169.7, **15**; 148.5, **5**; 136.4, **19**; 135.4, **13**; 129.6, **9**; 128.1, **11**; 126.9, **18**; 124.9, **8**; 123.9, **21**; 123.8, **10**; 123.3, **3**; 122.6, **24**; 120.4, **1**; 120.3, **12**; 120.0, **23**; 118.5, **22**; 117.7, **4**; 111.5, **2**; 111.2, **25**; 108.2, **17**; 84.0, **6**; 34.7, **16**; 28.0, **7**.

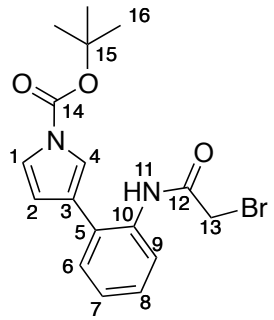
LRMS (ESI) m/z 438.1 416.1 [M + H], $[M + Na]^+$.

2.7.9. *tert*-Butyl 3-(2-(2-bromoacetamido)phenyl)-1*H*-pyrrole-1-carboxylate (**330**)



268 **330**

Using general procedure 7C, aniline **268** (47 mg, 173.4 µmol, 1.0 eq.), 2-bromoacetic acid (48 mg, 346.8 µmol, 2.0 eq.), DIC (60 µL, 381.5 µmol, 2.2 eq.), DMAP (2 mg, 17.34 µmol, 0.10 eq.) and CH_2Cl_2 (1 mL) were stirred for 12 h and purified on silica gel (5-20% EtOAc in petrol) to afford amide **330** as a yellow oil (67 mg, 96%).



Chemical Formula: $C_{17}H_{19}BrN_2O_3$
Molecular Weight: 379.25

IR (*v*, cm^{-1}) 2360, 2342, 1747, 1388, 1346, 1285, 1149.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.61 (1H, br. s) **11**; 8.28 (1H, d, *J*=8.1 Hz) **9**; 7.42-7.31 (4H, m) **1**, **4**, **6**, **8**; 7.18 (1H, td, *J*=7.5,

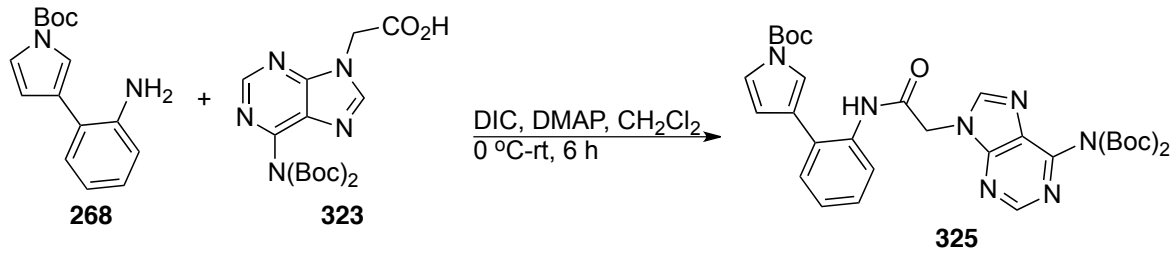
1.1 Hz) **7**; 6.39 (1H, dd, *J*=3.2, 1.8 Hz) **2**; 4.00 (2H, s) **13**; 1.63 (9H, s) **16**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 163.1, **12**; 148.4, **14**; 134.3, **10**; 129.8, 128.0, **6**, **8**; 125.6, **5**; 124.9, **7**; 123.1, **3**; 121.2, **1**/**4** 120.8, **9**; 118.5, **1**/**4**; 112.8, **2**; 84.3, **15**; 29.7, **13**; 28.9, **16**.

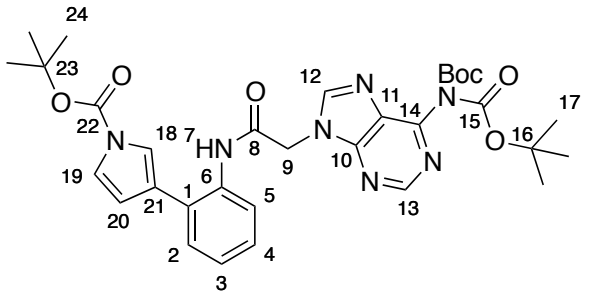
LRMS (ESI) m/z 400.9, 402.8 $[M + H]^+$; 432.9, 434.9 $[M + Na]^+$.

HRMS (ESI) m/z for $C_{17}H_{19}BrN_2O_3$ calcd. 379.0652, found 379.0655 $[M + H]^+$.

2.7.10. *tert*-Butyl 3-(2-(2-(6-((bis-*tert*-butoxycarbonyl)amino)-9*H*-purin-9-yl)acetamido)phenyl)-1*H*-pyrrole-1-carboxylate (**325**)



Using general procedure 7C, aniline **268** (200 mg, 693.6 µmol, 1.0 eq.), acid **323** (545 mg, 1.387 mmol, 2.0 eq.), DIC (272 µL, 1.734 mmol, 2.5 eq.), DMAP (4 mg, 34.68 µmol, 0.050 eq.) and CH_2Cl_2 (4 mL) were stirred for 6 h and purified on silica gel (10-50% EtOAc in petrol) to afford amide **325** as a colourless oil (92 mg, 21%). The reported yield does not account for the large amount of product contaminated with the urea by-product.



Chemical Formula: $C_{32}H_{39}N_7O_7$
Molecular Weight: 633.69

IR (*v*, cm^{-1}) 2979, 2934, 1784, 1741, 1702

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.74 (1H, s) **13**; 8.21 (1H, s) **12**; 8.14 (1H, d, *J*=8.1 Hz) **5**; 8.10 (1H, br. s) **7**; 7.36 (1H, apt.

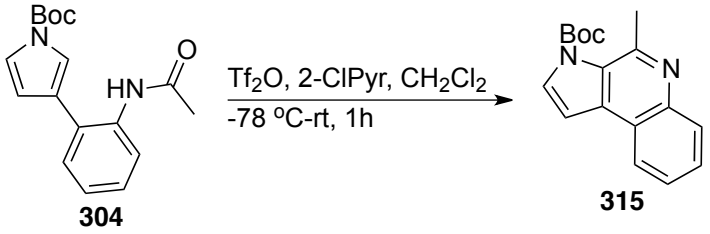
br. s) **17**; 7.32-7.25 (3H, m) **2**, **4**, **19**; 7.15 (1H, apt. t, *J*=7.5 Hz) **3**; 6.12 (1H, apt. br. s) **20**; 5.00 (2H, s) **9**; 1.66 (9H, s) **24**; 1.46 (18H, s) **17**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 163.3, **8**; 153.2, **10**; 152.1, **13**; 150.5, **14**; 150.4, **15**; 148.4, **22**; 144.9, **12**; 134.1, **6**; 129.9, **2/4**; 128.2, **11**; 128.1, **2/4**; 126.1, **1**; 125.2, **3**; 123.2, **21**; 121.6, **5**; 121.4, **19**; 118.3, **18**; 112.1, **20**; 84.5, **23**; 83.9, **16**; 47.4, **9**; 28.0, **24**; 27.7, **17**.

HRMS (ESI) m/z for $C_{32}H_{39}N_7O_7$ calcd. 634.2984, found 634.2980 $[M + H]^+$.

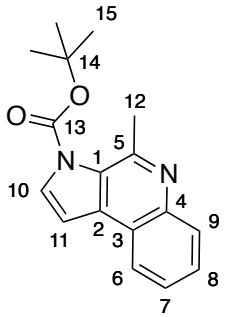
2.8. Movassaghi-Pictet-Hubert Reactions

2.8.1. *tert*-Butyl 4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**315**)



304 **315**

Using general procedure 8, amide **304** (99 mg, 329.6 µmol, 1.0 eq.), Tf_2O (111 µL, 659.2 µmol, 2.0 eq.), 2-ClPyr (125 µL, 1.318 mmol, 4.0 eq.) and CH_2Cl_2 (12 mL) were stirred at -78 °C-rt for 30 min and purified on silica gel (10-30% EtOAc/petrol) to afford pyrroloquinoline **315** as yellow solid (66 mg, 71%).



Chemical Formula: $C_{17}H_{18}N_2O_2$
Molecular Weight: 282.34

MP 95-97 °C.

IR (*v*, cm^{-1}) 1740, 1360, 1352, 1306.

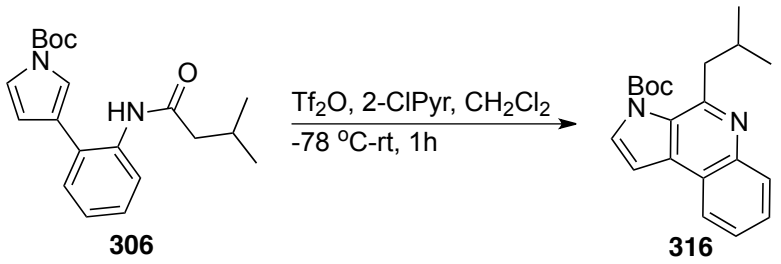
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.26 (1H, dd, *J*=8.1, 1.1 Hz) **6**; 8.02 (1H, dd, *J*=8.3, 0.6 Hz) **9**; 7.91 (1H, d, *J*=3.6 Hz) **10**; 7.64 (1H, r ddd) **8**; 7.56 (1H, r ddd) **7**; 7.28 (1H, d, *J*=3.5 Hz) **11**; 2.96 (3H, s) **12**; 1.71 (9H, s) **15**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 149.7, **13**; 148.4, **5**; 134.0, **4**; 131.2, **2**; 129.6, **10**; 128.9, **9**; 128.0, **1**; 126.5, **8**; 123.9, **7**; 122.6, **6**; 105.3, **11**; 85.6, **14**; 28.01, **15**; 26.7, **12**.

LRMS (ESI) m/z 283.0 $[M + H]^+$.

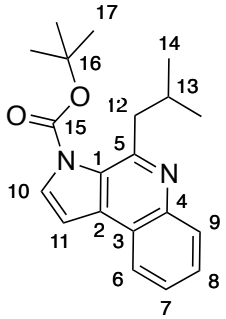
HRMS (ESI) m/z for $C_{17}H_{18}N_2O_2$ calcd. 283.1441, found 283.1437 $[M + H]^+$.

2.8.2. *tert*-Butyl 4-isobutyl-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**316**)



306 **316**

Using general procedure 8, amide **306** (17 mg, 49.65 µmol, 1.0 eq.), Tf_2O (17 µL, 99.30 µmol, 2.0 eq.), 2-ClPyr (19 µL, 198.6 µmol, 4.0 eq.) and CH_2Cl_2 (1.5 mL) were stirred at -78 °C-rt for 1 h and purified on silica gel (10-30% EtOAc in petrol) to afford pyrroloquinoline **316** as a white solid (13 mg, 79%).



Chemical Formula: $C_{20}H_{24}N_2O_2$
Molecular Weight: 324.42

IR (*v*, cm^{-1})

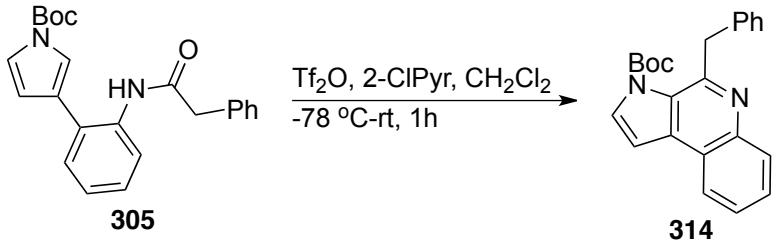
^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 8.28 (1H, dd, *J*=8.1, 1.0 Hz), **6**; 8.05 (1H, dd, *J*=8.3, 0.6 Hz) **9**; 7.92 (1H, d, *J*=3.6 Hz) **10**; 7.65 (1H, r ddd) **8**; 7.57 (1H, r ddd) **7**; 7.3 (1H, d, *J*=3.6 Hz) **11**; 3.38 (2H, d, *J*=7.2 Hz) **12**; 2.17 (1H, apt. spt., *J*=6.8 Hz) **13**; 1.72 (9H, s) **17**; 0.85 (6H, d, *J*=6.5 Hz) **14**.

^{13}C NMR (100 MHz, ACETONE-*d6*) δ ppm 151.6, **5**; 149.9, **15**; 144.4, **4**; 134.3, **2**; 131.3, **10**; 129.9, **9**; 128.4, **1**; 128.0, **8**; 126.6, **7**; 123.9, **6**; 122.7, **3**; 105.4, **11**; 85.6, **16**; 47.9, **12**; 28.7, **13**; 28.0, **17**; 22.8, **14**.

LRMS (ESI) m/z 325.1 $[M + H]^+$.

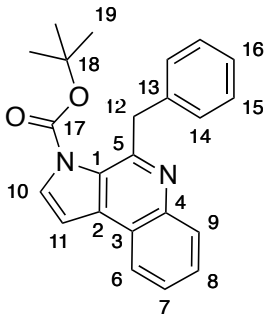
HRMS (ESI) m/z for $C_{20}H_{24}N_2O_2$ calcd. 325.1911, found 325.1914 $[M + H]^+$.

2.8.3. *tert*-Butyl 4-benzyl-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**314**)



305 **314**

Using general procedure 8, amide **305** (20 mg, 53.13 µmol, 1.0 eq.), Tf_2O (13 µL, 79.70 µmol, 2.0 eq.), 2-ClPyr (15 µL, 159.4 µmol, 4.0 eq.) and CH_2Cl_2 (1.6 mL) were stirred at -78 °C-rt for 1 h and purified on silica gel (10-30% EtOAc in petrol) to afford pyrroloquinoline **314** as a white solid (14 mg, 74%).



Chemical Formula: $C_{23}H_{22}N_2O_2$
Molecular Weight: 358.43

MP 124 °C.

IR (*v*, cm^{-1}) 1738, 1353.

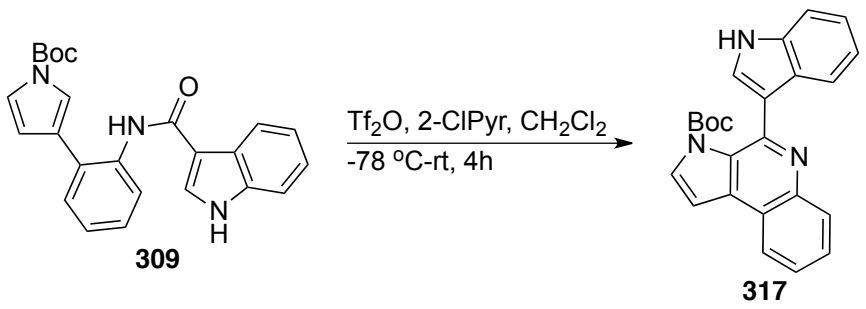
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.21 (1H, d, *J*=8.2 Hz) **9**; 8.16 (1H, d, *J*=7.9 Hz) **6**; 7.69 (1H, t, *J*=7.4 Hz) **8**; 7.63 (1H, d, *J*=3.2 Hz) **10**; 7.60 (1H, t, *J*=7.6 Hz) **7**; 5.02 (2H, s) **12**; 1.57 (9H, s) **19**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 149.8, **5**; 148.4, **17**; 143.4, **4**; 139.4, **13**; 134.2, **2**; 130.2, **10**; 129.1, **9**; 128.7, **14**; 128.1, **13**; 127.5, **8**; 126.0, **7**; 125.8, **10**; 122.8, **6**; 122.0, **3**; 104.4, **11**; 84.5, **18**; 44.7, **12**; 27.9, **19**.

LRMS (ESI) m/z 359.1 $[M + H]^+$.

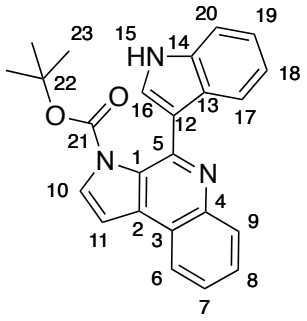
HRMS (ESI) m/z for $C_{23}H_{22}N_2O_2$ calcd. 359.1754, found 359.1757 $[M + H]^+$.

2.8.4. *tert*-Butyl 4-(1*H*-indol-3-yl)-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**317**)



Using general procedure 8, amide **309** (33 mg, 82.20 µmol, 1.0 eq.), Tf_2O (28 µL, 164.4 µmol, 2.0 eq.), 2-ClPyr (31 µL, 328.8 µmol, 4.0 eq.) and CH_2Cl_2 (3 mL) were stirred at -78 °C-rt for 4 h and

purified on silica gel (30-50% EtOAc in petrol) to afford pyrroloquinoline **317** as a yellow oil (27 mg, 86%).



Chemical Formula: $C_{24}H_{21}N_3O_2$
Molecular Weight: 383.44

IR (*v*, cm^{-1}) 1740, 1353, 1294, 1151.

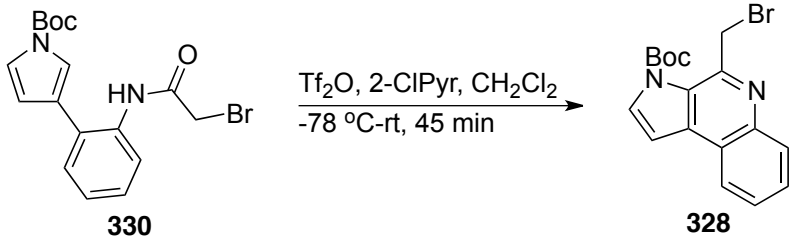
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.13 (1H, br. s) **15**; 8.22 (2H, ddd, *J*=9.9, 8.5, 1.1 Hz) **6**, **9**; 7.86 (1H, d, *J*=3.5 Hz) **10**; 7.73 (1H, d, *J*=2.6 Hz) **16**; 7.66 (2H, apt. ddd, *J*=8.3, 7.0, 1.4 Hz) **8**, **20**; 7.58 (1H, ddd, *J*=8.0, 6.9, 1.2 Hz) **7**; 7.33 (1H, dd, *J*=7.0, 1.3 Hz) **17**; 7.20 (1H, d, *J*=3.5 Hz) **11**; 7.18-7.11 (2H, m) **18**, **19**; 0.97 (9H, s) **23**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 149.0, **21**; 144.6, **5**; 144.0, **4**; 136.2, **14**; 134.5, **2**; 130.9, **10**; 129.0, **9**; 127.5, **8**; 127.0, 126.9, **1**, **13**; 125.6, **8**; 124.1, **16**; 122.9, **6**; 122.3, **17**; 121.6, **3**; 120.7, **19**; 119.9, **18**; 118.7, **12**; 111.5, **20**; 104.5, **11**; 84.6, **22**; 26.9, **23**.

LRMS (ESI) m/z 384.1 $[M + H]^+$.

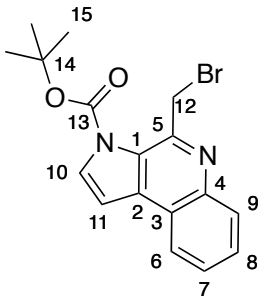
HRMS (ESI) m/z for $C_{24}H_{21}N_3O_2$ calcd. 384.1698, found 384.1702 $[M + H]^+$.

2.8.5. *tert*-Butyl 4-(bromomethyl)-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**328**)



330 **328**

Using general procedure 8, amide **330** (32 mg, 84.38 µmol, 1.0 eq.), Tf_2O (28 µL, 168.8 µmol, 2.0 eq.), 2-ClPyr (32 µL, 337.5 µmol, 4.0 eq.) and CH_2Cl_2 (3 mL) were stirred at -78 °C-rt and purified on silica gel (20% EtOAc in petrol) to afford pyrroloquinoline **328** as a pale yellow solid (27 mg, 89%).



Chemical Formula: $C_{17}H_{17}BrN_2O_2$
Molecular Weight: 361.23

MP decomp. 126 °C.

IR (*v*, cm^{-1}) 1746, 1355, 1248, 1151, 1119, 1024.

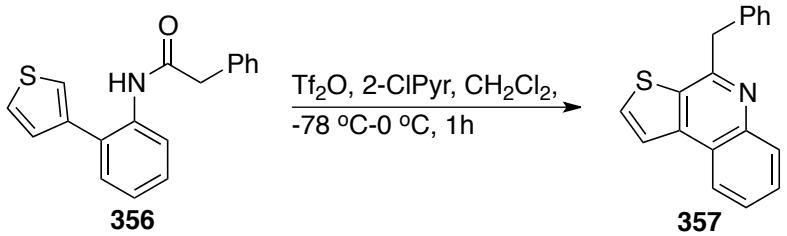
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.16 (2H, dd, *J*=8.0, 1.6 Hz) **6**, **9**; 7.81 (1H, d, *J*=3.6 Hz) **10**; 7.70-7.66 (1H, rddd) **8**; 7.64-7.60 (1H rddd) **7**; 7.12 (1H, d, *J*=3.6 Hz) **11**; 5.44 (2H, s) **12**; 1.73 (9H, s) **15**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 148.7, **13**; 145.5, **5**; 143.0, **4**; 134.7, **2**; 130.2, **10**; 129.4, **9**; 127.8, **8**; 126.9, **7**; 126.0, **1**; 122.9, **6**; 122.6, **3**; 104.5, **11**; 85.3, **14**; 37.1, **12**; 28.0, **15**.

LRMS (ESI) m/z 360.9, 363.9 $[M + H]^+$.

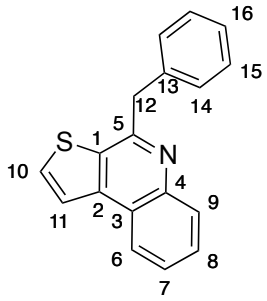
HRMS (ESI) m/z for $C_{17}H_{17}BrN_2O_2$ calcd. 361.0546, found 361.0543 $[M + H]^+$.

2.8.6. 4-Benzylthieno[2,3-*c*]quinolone (**357**)



356 **357**

Using general procedure 8, amide **356** (20 mg, 53.10 µmol, 1.0 eq.), Tf_2O (18 µL, 106.3 µmol, 2.0 eq.), 2-ClPyr (20 µL, 212.5 µmol, 4.0 eq.) and CH_2Cl_2 (2 mL) were stirred at -78 °C-rt for 1 h and purified on silica gel (20-30% EtOAc in petrol) to afford pyrroloquinoline **367** as a white solid (12 mg, 64%).



Chemical Formula: $C_{18}H_{13}NS$
Molecular Weight: 275.37

MP 61-62 °C.

IR (*v*, cm^{-1}) 1559, 1492.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.26-8.24 (2H, m) **6**, **9**; 7.95 (1H, d, *J*=5.3 Hz) **10**; 7.75 (1H, d, *J*=5.2 Hz) **11**; 7.72 (1H, ddd, *J*=8.4, 7.0, 1.4 Hz) **8**; 7.62 (1H, ddd, *J*=8.1, 7.0, 1.2 Hz) **7**; 7.45-7.43 (2H, m) **14**; 7.31-7.27 (2H, m) **15**; 7.22 (1H, tt, *J*=7.3, 1.3 Hz) **16**; 4.59 (2H, s) **12**.

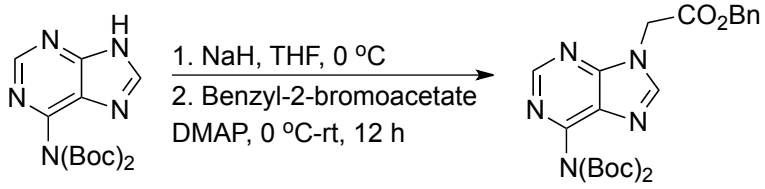
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 155.1, **5**; 144.8, **4**; 142.4, **2**; 137.7, **13**; 132.9, **1**; 131.1, **10**; 129.5, **6**/**9**; 129.3, **14**; 128.5, **15**; 128.0, **8**; 126.7, **16**; 126.3, **7**; 123.6, **3**; 123.2, **6**/**9**; 121.8, **11**; 44.9, **12**.

LRMS (ESI) m/z 276.0 $[M + H]^+$.

HRMS (ESI) m/z for $C_{18}H_{13}NS$ calcd. 276.0841, found 276.0845 $[M + H]^+$.

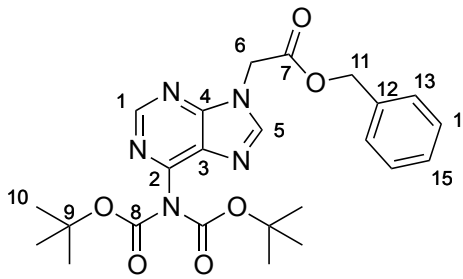
2.9. Bromide Alkylations

2.9.1 *N*-bis Boc adenine methylenebenzylacetate



A round-bottomed flask was charged with a magnetic stirrer bar, *N*-bis-Boc adenine (504 mg, 1.503 mmol, 1.0 eq.) and purged with Ar and THF (30 mL) added by Hamilton syringe. The reaction mixture was cooled to 0 °C and under a constant stream of Ar, NaH (90 mg, 2.237 mmol, 1.5 eq.) was added. Upon cessation of H_2 evolution, consecutively benzyl-2-bromoacetate (283 µL, 1.789 mmol, 1.2 eq.) dropwise and DMAP (4 mg, 29.82 µmol, 0.020 eq.) were added over Ar, the mixture slowly brought to rt and stirred for 12 h. The reaction mixture was quenched with H_2O (0.1 mL), concentrated *in vacuo*, dissolved in CH_2Cl_2, washed with H_2O, the organics dried over $MgSO_4$, concentrated *in vacuo* and purified on silica gel (40-60% EtOAc in petrol) to afford the desired product as a white foam (698 mg, 96%).

Spectroscopic data are consistent with that reported in the literature.[177]

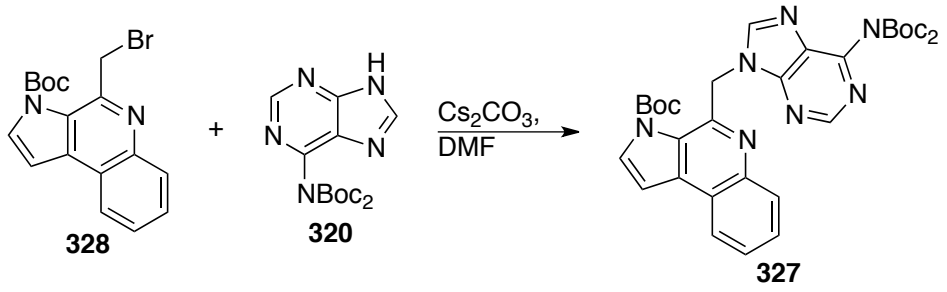


Chemical Formula: $C_{24}H_{29}N_5O_6$
Molecular Weight: 483.52

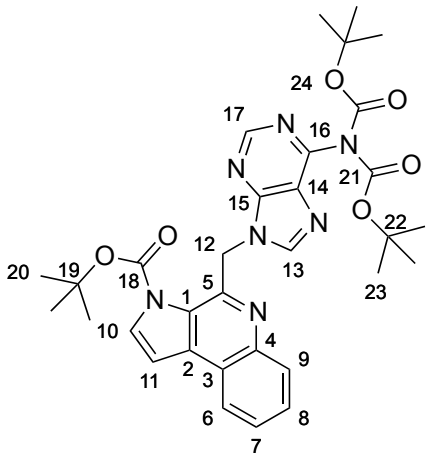
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.86 (1H, s), 8.14 (1H, s) **1**, **5**; 7.39-7.32 (5H, m) **13**, **14**, **15**; 5.24 (2H, s), 5.10 (2H, s) **6**, **11**; 1.44 (18H, s) **10**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 166.5; 153.3; 152.2; 150.4; 150.2; 144.9; 134.4; 128.7; 128.6; 128.4; 128.2; 83.6; 68.0; 44.3; 27.7.

2.9.2 *N*-tris-Boc aplidiopsamine A (**327**)



Using general procedure 9, pyrroloquinoline **328** (86 mg, 238.1 µmol, 1.2 eq.), bis-Boc adenine (**320**) (67 mg, 200.9 µmol, 1.0 eq.) and Cs_2CO_3 (72 mg, 221.0 µmol, 1.1 eq.) in anhydrous DMF (1 mL) were stirred for 12 h. Purification on silica gel (20-60% EtOAc in petrol) afforded pyrroloquinoline **327** as a yellow oil (103 mg, 83%).



Chemical Formula: $C_{32}H_{37}N_7O_6$
Molecular Weight: 615.68

MP 89-92 °C.

IR (*v*, cm^{-1}) 1791, 1743, 1147, 1124, 1101.

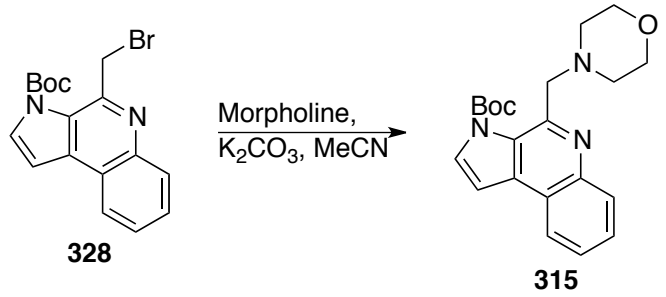
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.76 (1H, s) **17**; 8.33 (1H, s) **13**; 8.10-8.08 (1H, m) **6**; 7.81 (1H, d, *J*=3.8 Hz) **10**; 7.75-7.73 (1H, m) **9**; 7.55-7.50 (2H, m) **7**, **8**; 7.11 (1H, d, *J*=3.6 Hz) **11**; 6.29 (2H, s) **12**; 1.70 (9H, s) **20**; 1.44 (18H, s) **23**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 153.9, **15**; 151.6, **17**; 150.2, **21**; 149.8, **14**; 149.1, **18**; 147.1, **13**; 142.8, **4**; 142.2, **5**; 134.4, **2**; 130.0, **10**; 129.3, **9**; 128.6, **16**; 127.5, **8**; 126.7, **7**; 126.0, **1**; 122.7, **6**; 122.0, **3**; 105.2, **11**; 85.5, **19**; 83.3, **22**; 49.0, **12**; 27.9, **20**; 27.7, **23**.

LRMS (ESI) m/z 616.4 $[M + H]^+$.

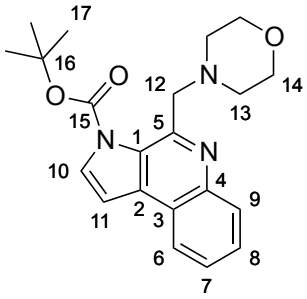
HRMS (ESI) m/z for $C_{17}H_{14}N_7$ calcd. 316.1305, found 316.1308 [M – (3 Boc) + H]$^+$.

2.9.3. *tert*-Butyl 4-(morpholinomethyl)-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**315**)



328 **315**

Using general procedure 9, pyrroloquinoline **328** (50 mg, 138.4 µmol, 1.0 eq.), morpholine (18 µL, 207.6 µmol, 1.5 eq.) and K_2CO_3 (29 mg, 207.6 µmol, 1.5 eq.) and CH_3CN (0.5 mL) were stirred for 12 h to afford pyrroloquinoline **315** as an orange oil (52 mg, 100%).



Chemical Formula: $C_{21}H_{25}N_3O_3$
Molecular Weight: 367.44

IR (ν, cm^{-1}) 1751, 1360, 1305, 1270, 1242, 1149, 1074, 1024.

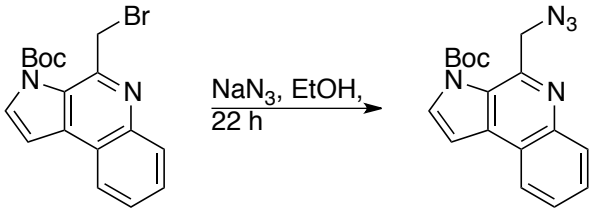
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.14 (1H, apt. t, *J*=7.4 Hz) **6, 9**; 7.70 (1H, d, *J*=3.5 Hz) **10**; 7.64 (1H, td, *J*=7.7, 1.3 Hz) **8**; 7.57 (1H, td, *J*=7.5, 1.1 Hz) **7**; 7.05 (1H, d, *J*=3.5 Hz); 4.31 (2H, s) **12**; 3.57 (4H, t, *J*=4.5 Hz) **14**; 2.31 (4H, t, *J*=4.6 Hz) **13**; 1.68 (9H, s) **17**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 148.6, **5**; 148.2, **15**; 142.9, **4**; 133.6, **2**; 130.0, **10**; 129.2, **9**; 127.3, **8**; 127.0, **1**; 126.1, **7**; 122.8, **6**; 103.8, **11**; 84.1, **16**; 67.1, **14**; 65.9, **12**; 53.2, **13**; 28.0, **17**.

LRMS (ESI) m/z 368.1 $[M + H]^+$

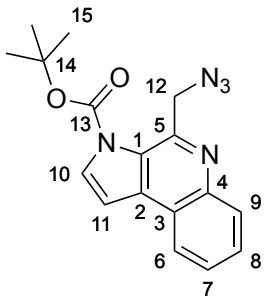
HRMS (ESI) m/z for $C_{21}H_{25}N_3O_3$ calcd. 368.1969, found 368.1971 $[M + H]^+$.

2.9.4. *tert*-Butyl α-azido 4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**345**)



328 **345**

A round-bottomed flask was charged with a magnetic stirrer bar, pyrroloquinoline **328** (200 mg, 553.7 µmol, 1.0 eq.), NaN_3 (72 mg, 1.107 mmol, 2.0 eq.) and EtOH (12 mL) and the reaction stirred for 22 h. The reaction mixture was concentrated *in vacuo*, dissolved in a mixture of water and EtOAc and transferred to a separatory funnel. The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford azide **345** as an off white solid (179 mg, 100%).



Chemical Formula: $C_{17}H_{17}N_5O_2$
Molecular Weight: 323.35

MP decomp 86 °C, 116-119 °C

IR (*v*, cm^{-1})

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.20-8.14 (2H, m) **6**, **9**; 7.80 (1H, d, *J*=3.6 Hz) **10***; 7.79 (1H, d, *J*=3.6 Hz) **10**#; 7.69 (1H, td,

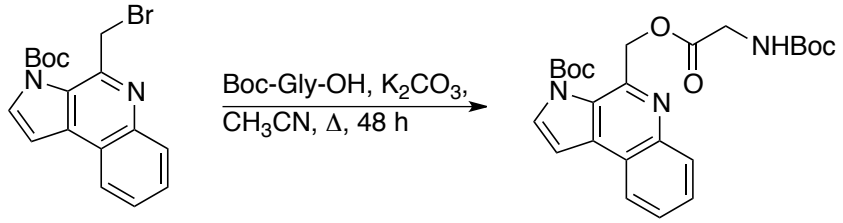
J=7.6, 1.6 Hz) **8**$^{\#}$; 7.68 (1H, td, *J*=7.7, 1.5 Hz) **8***; 7.62 (1H, r ddd, *J*=8.1, 6.9, 1.2 Hz) **7**; 7.12 (1H, d, *J*=3.4 Hz) **11**$^{\#}$; 7.11 (1H, d, *J*=3.6 Hz) **11***; 5.44 (2H, s) **12***; 5.22 (2H, s) **12**$^{\#}$; 1.73 (9H, s) **15***; 1.71 (1H, s) **15**$^{\#}$.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 148.70, **13**; 145.5, **5**; 143.0, **4**; 134.7, **2**; 130.2, **10***; 130.1, **10**$^{\#}$; 129.44, **9**$^{\#}$; 129.38, **9***; 127.8, **8**; 126.9, **7**; 126.7, **1**$^{\#}$; 126.0, **1***; 122.9, **6***; 122.6, **6**$^{\#}$; 104.8, **11**$^{\#}$; 104.5, **11***; 85.3, **14**; 57.0, **12**$^{\#}$; 37.1, **12***; 28.0, **15**.

N.B. *= major rotamer, $^{\#}$= minor rotamer

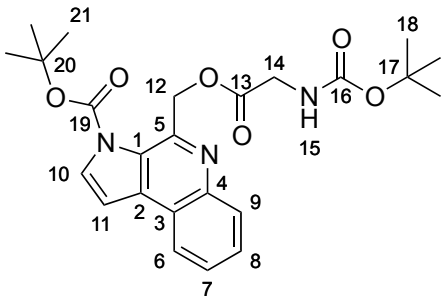
LRMS (ESI) Fail.

2.9.5. *tert*-Butyl 4-((2-((*tert*-butoxycarbonyl)amino)acetoxy)methyl)-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**341**)



328 **341**

Using general procedure 9, pyrroloquinoline **328** (99 mg, 274.1 µmol, 1.1 eq.), Boc-Gly-H (55 mg, 259.9 µmol, 1.0 eq.), K_2CO_3 (117 mg, 846.5 µmol, 3.3 eq.) and MeCN (1 mL) were stirred at reflux for 48 h and purified on silica gel (10-30% EtOAc in petrol) to afford pyrroloquinoline **341** as an oil (103 mg, 87%).



Chemical Formula: $C_{24}H_{29}N_3O_6$
Molecular Weight: 455.50

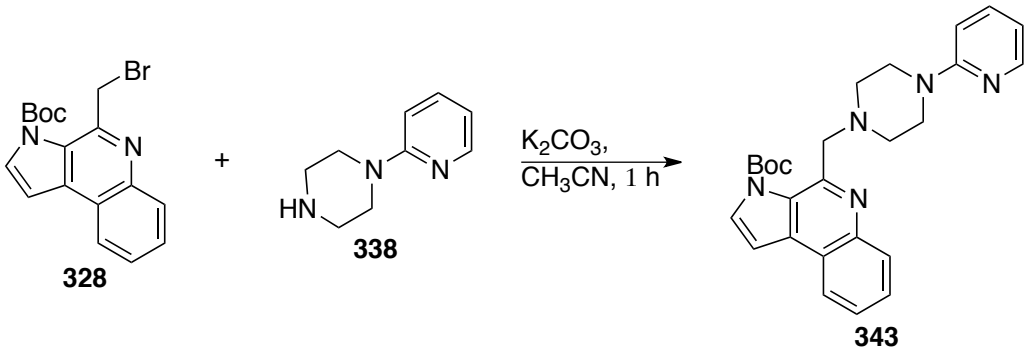
IR (*v*, cm^{-1}) 3373, 2978, 1748, 1709.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.31 (1H, m) **6**; 8.14 (1H, dd, *J*=8.1, 1.7 Hz) **9**; 7.77 (1H, d, *J*=3.6 Hz) **10**; 7.66 (1H, ddd, 8.3, 6.9, 1.5 Hz) **8**; 7.59 (1H, ddd, *J*=8.0, 7.0, 1.1 Hz) **7**; 7.10 (1H, d, *J*=3.6 Hz) **11**; 5.93 (2H, s) **12**; 5.12 (1H, br. s) **15**; 4.06 (2H, d, *J*=5.2 Hz) **14**; 1.68 (9H, s) **21**; 1.43 (9H, s) **18**.

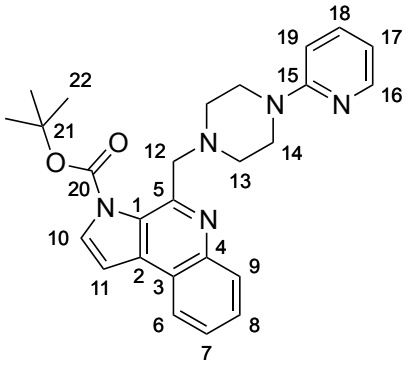
^{13}C NMR (100 MHz, ACETONE-*d*) δ ppm 170.8, **13**; 156.7, **16**; 149.7, 144.8, **5**, **19**; 143.8, **4**; 134.9, **2**; 131.4, **10**; 130.3, **9**; 128.4, **8**; 127.6, **7**; 127.0, **1**; 124.0, **6**; 123.2, **3**; 105.6, **11**; 86.1, **20**; 79.2, **17**; 69.3, **12**; 43.0, **14**; 28.5, **21**; 28.0, **18**.

LRMS (ESI) m/z 456.3 $[M + H]^+$.

2.9.6. *tert*-Butyl 4-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate



Using general procedure 9, pyrroloquinoline **328** (37 mg, 102.4 µmol, 1.0 eq.), 1-(pyridine-2-yl)piperazine (**343**) (25 µL, 166.1 µmol, 1.6 eq.), K_2CO_3 (23 mg, 166.1 µmol, 1.6 eq.) and MeCN (0.5 mL) were stirred for 1 h and purified on deactivated silica gel (10-50% EtOAc in petrol) to afford pyrroloquinoline **343** as an oil (40 mg, 88%).



Chemical Formula: $C_{26}H_{29}N_5O_2$
Molecular Weight: 443.54

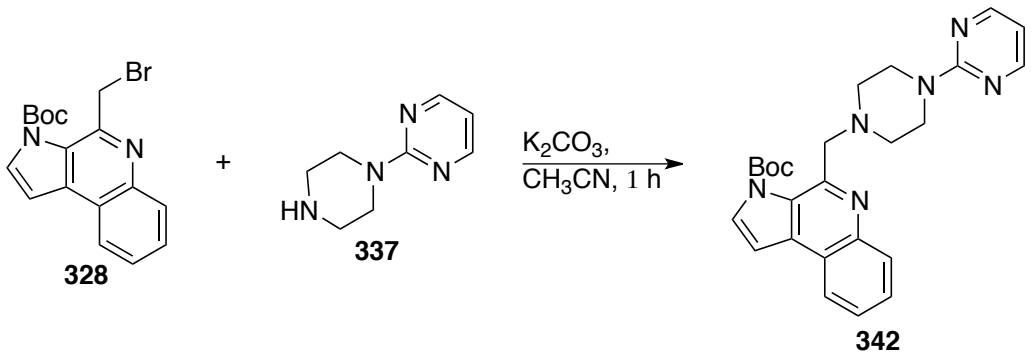
IR (*v*, cm^{-1}) 1755, 1590, 1306, 796.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.18 (3H, m) **6**, **9**, **16**; 7.71 (1H, d, *J*=3.5 Hz) **10**; 7.66 (1H, ddd, *J*=8.4, 6.9, 1.5 Hz) **8**; 7.59 (1H, ddd, *J*=8.1, 6.9, 1.2 Hz) **7**; 7.42 (1H, ddd, *J*=8.6; 7.1; 2.0 Hz) **18**; 7.07 (1H, d, *J*=3.5 Hz) **11**; 6.60-6.55 (2H, m) **17**, **19**; 4.37 (2H, s) **12**; 3.40 (4H, t, *J*=5.0 Hz) **14**; 2.43 (4H, t, *J*=5.0 Hz) **13**; 1.69 (9H, s) **22**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 159.6, **15**; 148.63, 148.56, **5**, **20**; 147.9, **16**; 143.0, **4**; 137.3, **18**; 133.7, **2**; 130.1, **10**; 129.2, **9**; 127.3, **8**; 127.1, **1**; 126.1, **7**; 122.8, **6**; 122.4, **3**; 113.1, **17**; 107.0, **19**; 103.8, **11**; 84.2, **21**; 65.6, **12**; 52.6, **13**; 45.3, **14**; 28.1, **22**.

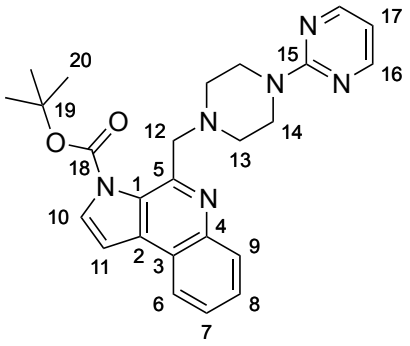
HRMS (ESI) m/z for $C_{26}H_{29}N_5O_2$ calcd. 444.2394, found 444.2392 [M + H]$^+$.

2.9.7. *tert*-Butyl 4-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (**342**)



Using general procedure 9, pyrroloquinoline **328** (40 mg, 110.7 µmol, 1.0 eq.), 2-(piperazin-1-yl)pyrimidine (**337**) (30 mg, 182.7 µmol,

1.7 eq.), K_2CO_3 (25 mg, 180.9 µmol, 1.6 eq.) and MeCN (0.5 mL) were stirred for 1 h and purified on deactivated silica gel (10-50% EtOAc in petrol) to afford pyrroloquinoline **342** as an oil (50 mg, >99%).



Chemical Formula: $C_{25}H_{28}N_6O_2$
Molecular Weight: 444.53

MP decomp. 140 °C

IR (*v*, cm^{-1}) 1752, 1583, 1546, 1477.

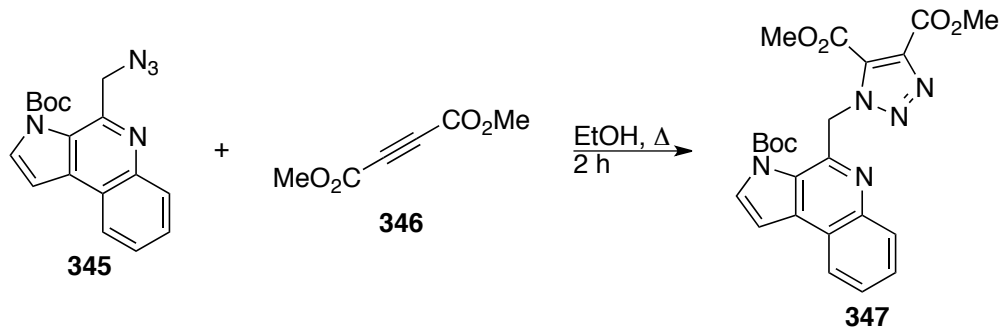
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.25 (2H, d, *J*=4.7 Hz) **16**; 8.17-8.14 (2H, m) **6**, **9**; 7.71 (1H, d, *J*=3.5 Hz) **10**; 7.65 (1H, ddd, *J*=8.4, 6.9, 1.5 Hz) **8**; 7.58 (1H, ddd, *J*=8.1, 7.0, 1.2 Hz) **7**; 7.07 (1H, d, *J*=3.6) **11**; 6.42 (1H, t, *J*=4.8 Hz) **17**; 4.35 (2H, s) **12**; 3.68 (4H, t, *J*=5.0 Hz) **14**; 2.38 (4H, t, *J*=5.1 Hz) **13**; 1.68 (9H, s) **20**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 161.7, **15**; 157.6, **16**; 148.7, 148.6, **5**, **18**; 143.0, **4**; 133.8, **2**; 130.2, **10**; 129.2, **9**; 127.4, **8**; 127.1, **1**; 126.2, **7**; 122.9, **6**; 122.4, **3**; 109.7, **17**; 103.9, **11**; 84.2, **19**; 65.7, **12**; 52.7, **13**; 43.8, **14**; 28.1, **20**.

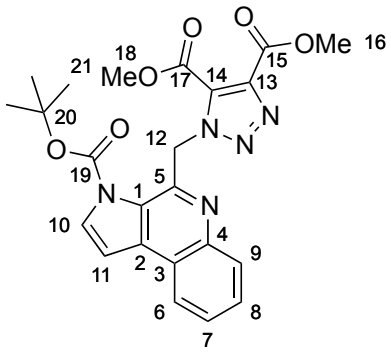
HRMS (ESI) m/z for $C_{25}H_{28}N_6O_2$ calcd. 445.2347, found 445.2348 $[M + H]^+$.

2.10. Huisgen Cycloaddition

2.10.1. Dimethyl 1-((3-(*tert*-butoxycarbonyl)-3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (**347**)



A Reacti-Vial was charged with a magnetic stirrer bar, azide **345** (35 mg, 108.2 µmol, 1.0 eq.), dimethyl acetylenedicarboxylate (**346**) (20 µL, 162.3 µmol, 1.5 eq.) and EtOH (0.5 mL) and the mixture stirred at reflux for 2 h. The reaction mixture was concentrated *in vacuo* and purified on silica gel (10-30% EtOAc in petrol) to afford pyrroloquinoline **347** as a white solid (18 mg, 36%).



Chemical Formula: $C_{23}H_{23}N_5O_6$
Molecular Weight: 465.46

MP decomp. 132 ^{o}C.

IR (ν, cm^{-1}) 1726, 1355, 1304, 1149, 1126, 1021, 747.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.11-8.08 (1H, m) **6**; 7.89-7.87 (1H, m) **9**; 7.81 (1H, d, *J*=3.6 Hz) **10**; 7.60-7.53 (2H, r ddd) **7**, **8**; 7.11 (1H, d, *J*=3.6 Hz) **11**; 6.67 (2H, s) **12**; 4.03 (3H, s), 3.81 (3H, s) **16**, **18**; 1.71 (9H, s) **21**.

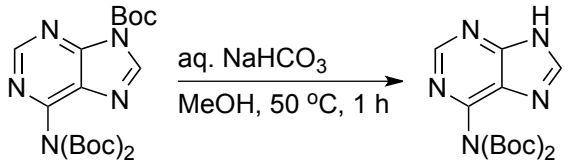
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 160.8, 159.8, **15**, **17**; 149.0 **19**; 142.6, **4**; 140.6, **5**; 138.8, **13**; 134.4, **2**; 133.4, **14**; 129.9, **10**; 129.2, **9**; 127.7, **8**; 126.8, **7**; 125.7, **1**; 122.7, **6**; 122.0, **3**; 105.2, **11**; 85.6, **20**; 55.8, **12**; 52.9, 52.5, **16**, **18**; 28.0, **21**.

LRMS (ESI) m/z 466.2 [M + H]$^{+}$.

HRMS (ESI) (ESI) m/z for $C_{23}H_{23}N_5O_6$ calcd. 466.1713, found 466.1714 $[M + H]^+$.

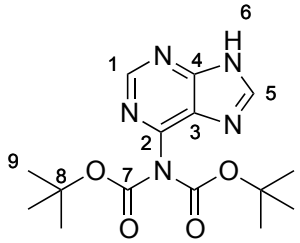
2.11. *N*-Boc Deprotections

2.11.1. Bis-Boc-adenine



A round-bottomed flask was charged with a magnetic stirrer bar, tris-Boc adenine (2.70g, 6.207 mmol, 1.0 eq.) sat. aq. $NaHCO_3$ solution (27 mL) and MeOH (60 mL) and the mixture stirred at 50 °C for 1h. MeOH was removed *in vacuo*, the aqueous transferred to a separatory funnel and extracted with CH_2Cl_2 as required, the organics dried ($MgSO_4$), concentrated *in vacuo* and purified on silica gel (EtOAc) to afford bis-Boc adenine as a white foam (1.80g, 87%).

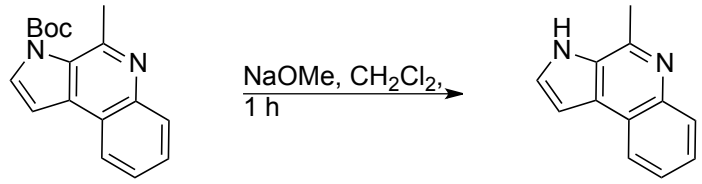
Spectroscopic data are consistent with that reported in the literature.[109]



Chemical Formula: $C_{15}H_{21}N_5O_4$
Molecular Weight: 335.36

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm (Two resonance structures) 13.30 (1H, br. s) **6**; 8.89 (1H, s) **1**; 8.54 (1H, br. s), 8.50 (1H, br. s) **5**; 1.52 (9H, s), 1.40 (9H, s) **9**.

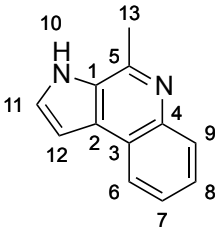
2.11.2. Marinoquinoline A (**217**)



315 **217**

Using general procedure 10A, pyrroloquinoline **315** (28 mg, 99.17 µmol, 1.0 eq.), NaOMe (25% solution in MeOH) (43 µL, 198.3 µmol, 2.0 eq.) and THF were stirred for 1 h and purified on silica gel (30-60% EtOAc in petrol) to afford marinoquinoline A (**217**) as a white solid (17 mg, 94%).

Spectroscopic data are consistent with that reported in the literature.[75]

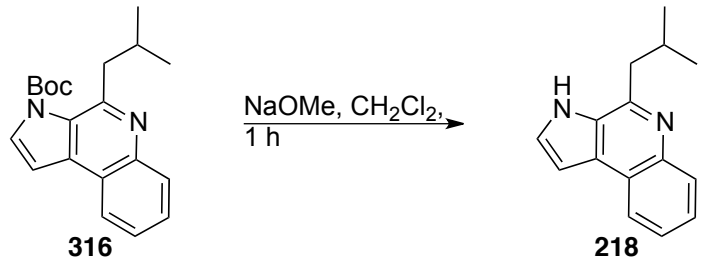


Chemical Formula: $C_{12}H_{10}N_2$
Molecular Weight: 182.22

^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 11.19 (1H, br. s) **10**; 8.24 (1H, m) **6**, 8.02-7.99 (1H, m) **9**; 7.58 (1H, d, *J*=2.9 Hz) **11**; 7.53-7.48 (2H, m) **7**, **8**; 7.12 (1H, d, *J*-3.0 Hz) **12**; 2.84 (3H, s) **13**.

^{13}C NMR (100 MHz, ACETONE-*d6*) δ ppm 146.8, **5**; 143.6, **4**; 129.8, **9**; 128.4, **1**; 127.2, **11**; 126.1, **8**; 125.7, **7**; 124.2, **3**; 123.7, **6**; 102.0, **12**; 21.2, **13**.

2.11.3. Marinoquinoline B (**218**)

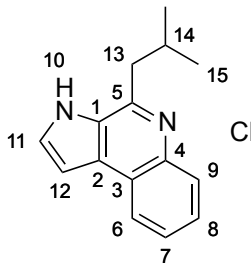


316 **218**

Using general procedure 10A, pyrroloquinoline **316** (38 mg, 117.1 µmol, 1.0 eq.), NaOMe (25% solution in MeOH) (51 µL, 234.2 µmol,

2.0 eq.) and THF were stirred for 1 h and purified on silica gel (30-60% EtOAc in petrol) to afford marinoquinoline B (**218**) as a white solid (24 mg, 92%).

Spectroscopic data are consistent with that reported in the literature.[75]

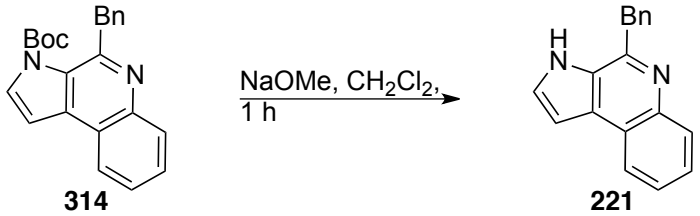


Chemical Formula: $C_{15}H_{16}N_2$
Molecular Weight: 224.30

^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 11.11 (1H, br. s) **10**; 8.24-8.21 (1H, m) **6**; 8.03-8.0 (1H, m) **9**; 7.56 (1H, apt. t, *J*=2.8 Hz) **11**; 7.54-7.47 (2H, m) **7**, **8**; 7.12 (1H, dd, *J*=2.9, 1.9 Hz) **12**; 3.06 (2H, d, *J*=7.3 Hz) **13**; 2.44 (1H, apt. spt., *J*=6.8 Hz) **14**; 1.00 (6H, d, *J*=6.6 Hz) **15**.

^{13}C NMR (100 MHz, ACETONE-*d6*) δ ppm 144.8, **5**; 130.1, **4**; 129.9, **9**; 128.6, **2**; 127.0, **11**; 126.0, **8**; 125.6, **7**; 124.1, **3**; 123.7, **6**; 101.9, **12**; 44.1, **13**; 29.0, **14**; 23.0, **15**.

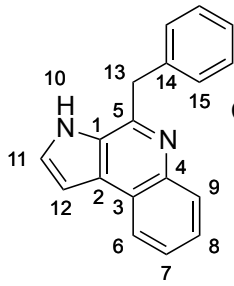
2.11.4. Marinoquinoline C (**221**)



314 **221**

Using general procedure 10A, pyrroloquinoline **314** (27 mg, 75.33 µmol, 1.0 eq.), NaOMe (25% solution in MeOH) (33 µL, 150.7 µmol, 2.0 eq.) and THF were stirred for 1 h and purified on silica gel (20-50% EtOAc in petrol) to afford marinoquinoline C (**221**) as a white solid (19 mg, 97%).

Spectroscopic data are consistent with that reported in the literature.[75]

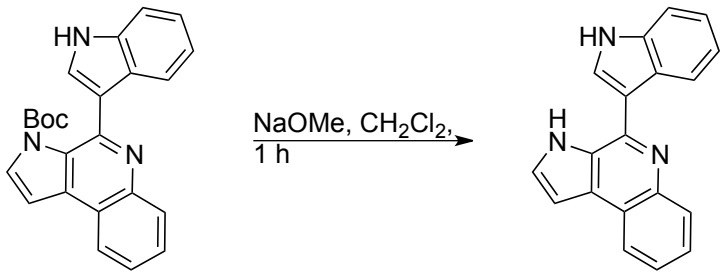


Chemical Formula: $C_{18}H_{14}N_2$
Molecular Weight: 258.32

^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 11.05 (1H, br. s) **10**; 8.25-8.23 (1H, m), 8.07-8.04 (1H, m) **6**,**9**; 7.56-7.49 (3H, m) **7**, **8**, **11**; 7.44-7.41 (2H, m) **15**; 7.26-7.22 (2H, m) **16**; 7.17-7.15 (1H, m) **17**; 7.13 (1H, dd, *J*=3.0, 1.9 Hz) **12**; 4.56 (2H, s) **13**;

^{13}C NMR (100 MHz, ACETONE-*d6*) δ ppm 148.9, 4°; 143.8, 4°; 139.9, 4°; 130.2, 3°; 129.7, **15**/**16**; 129.3, **14**; 129.2, **15**/**16**; 127.4, 3°; 127.1, 3°; 126.2, 3°; 125.9, 3°; 124.2, 4°; 123.7, 3°; 102.1, **12**; 41.6, **13**.

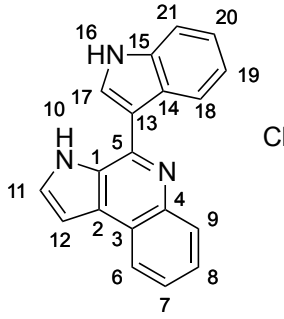
2.11.5. Marinoquinoline E (**221**)



317 **221**

Using general procedure 10A, pyrroloquinoline **317** (19 mg, 49.55 µmol, 1.0 eq.), NaOMe (25% solution in MeOH) (22 µL, 99.10 µmol, 2.0 eq.) and THF were stirred for 1 h and purified on silica gel (50-100% EtOAc in petrol) to afford marinoquinoline E (**221**) as a white solid (6 mg, 46%).

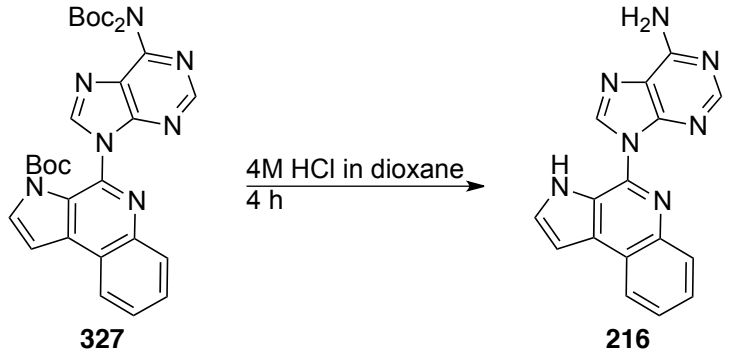
Spectroscopic data are consistent with that reported in the literature.[75]



Chemical Formula: $C_{19}H_{13}N_3$
Molecular Weight: 283.33

^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 10.98 (1H, br. s); 10.82 (1H, br. s); 8.79-8.76 (1H, m); 8.28 (1H, m); 8.26 (1H, m); 8.18-8.16 (1H, m); 7.61 (1H, t, *J*=2.6 Hz); 7.59-7.49 (3H, m); 7.27-7.19 (3H, m).

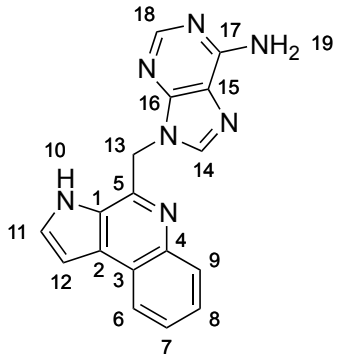
2.11.6. Aplidiopsamine A (**216**)



327 **216**

Using general procedure 10B, pyrroloquinoline **327** (25 mg, 41.55 µmol, 1.0 eq.) and 4M HCl in dioxane were stirred for 4 h and purified on silica gel (5-10% MeOH in CH_2Cl_2) to afford aplidiopsamine A (**216**) as a white solid (12 mg, 97%).

Spectroscopic data are consistent with that reported in the literature.[110]



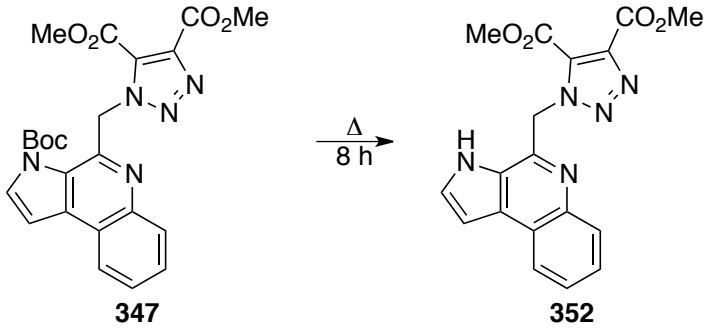
Chemical Formula: $C_{17}H_{13}N_7$
Molecular Weight: 315.33

^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 12.55, (1H, br. s) **10**; 8.73 (1H, s) **14**; 8.34-8.31 (1H, m) **6** 8.16 (1H, s) **18**; 8.05 (2H, br. s) **19**; 8.00-7.98 (1H, m) **9**; 7.88 (1H, t, *J*=2.8 Hz) **11**; 7.60 (2H, m) **7**, **8**; 7.27 (1H, dd, *J*=2.8, 1.8 Hz) **12**; 6.04 (2H, s) **13**.

^{13}C NMR (100 MHz, DMSO-*d*6) δ ppm 159.6, **17**; 152.4, **18**; 152.2, **16**; 145.7, **14**; 143.1, **5**; 140.6, **4**; 129.4, **2**; 129.1, **11**; 28.2, **9**; 126.6, **1**; 126.4, **7**; 126.2, **8**; 123.4, **6**; 123.2, **3**; 111.8, **15**; 101.8, **12**; 48.4, **13**.

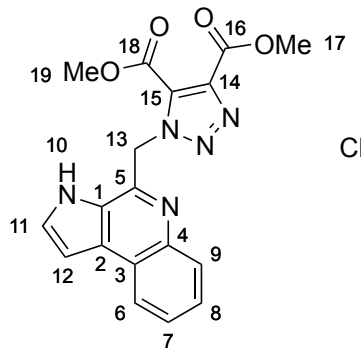
LRMS (ESI) m/z 316.1 $[M + H]^+$, 653.3 $[2M + H]^+$.

2.11.7. Dimethyl 1-((3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (**352**)



347 **352**

Using general procedure 10C, triazole **347** (14 mg, 30.08 µmol) was heated to 120 °C for 6 h. The resulting black solid was purified on silica gel (50-100% Et_2O in petrol) to afford pyrroloquinoline **352** a pale yellow solid (9 mg, 81%).



Chemical Formula: $C_{18}H_{15}N_5O_4$
Molecular Weight: 365.34

MP decomp. 159 °C.

IR (*v*, cm^{-1}) 3090, 2802, 1112, 747.

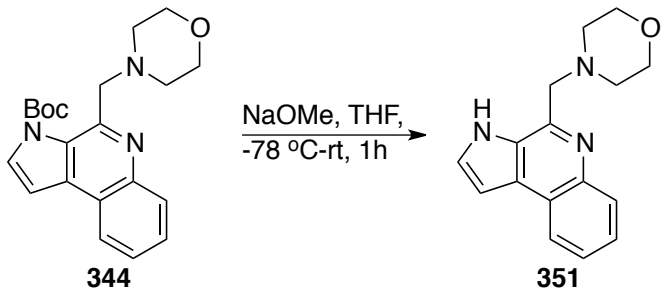
^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 11.48 (1H, br. s) **10**; 8.29-8.27 (1H, m) **6**; 7.86-7.84 (1H, m) **9**; 7.75 (1H, t, *J*=2.8 Hz) **11**; 7.58-7.51 (2H, r. ddd, *J*=) **7**, **8**; 7.23 (1H, dd, *J*=3.0, 1.9 Hz) **12**; 6.48 (2H, s) **13**; 3.93 (3H, s), 3.81 (3H, s) **17**, **19**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 161.5, 160.3, **16**, **18**; 142.8, **4**; 141.4, **5**; 140.2, **14**; 133.2, **15**; 130.1, **2**, **9**; 128.6, **11**; 127.4, **1**; 126.9, **7**; 126.7, **8**; 124.4, **3**; 123.9, **6**; 102.4, **12**; 53.5, 52.7, **17**, **19**; 52.6, **13**.

LRMS (ESI) m/z 366.0 $[M + H]^+$.

HRMS (ESI) m/z for $C_{18}H_{15}N_5O_4$ calcd. 366.1197, found 366.1201 $[M + H]^+$.

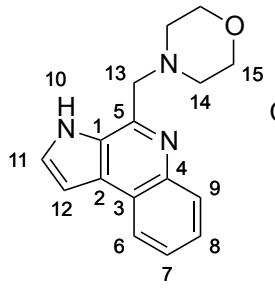
2.11.8. 4-((3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methyl)morpholine (**351**)



344 **351**

Using general procedure 10A, morpholine **344** (24 mg, 65.32 µmol 1.0 eq.), NaOMe (25% solution in MeOH) (29 µL, 130.6 µmol, 2.0 eq.)

and THF (1 mL) were stirred for 1 h to afford pyrroloquinoline **351** as an off white solid (16 mg, 92%).



Chemical Formula: $C_{16}H_{17}N_3O$
Molecular Weight: 267.33

MP decomp. 136 °C.

IR (*v*, cm^{-1}) 2801, 1112, 747.

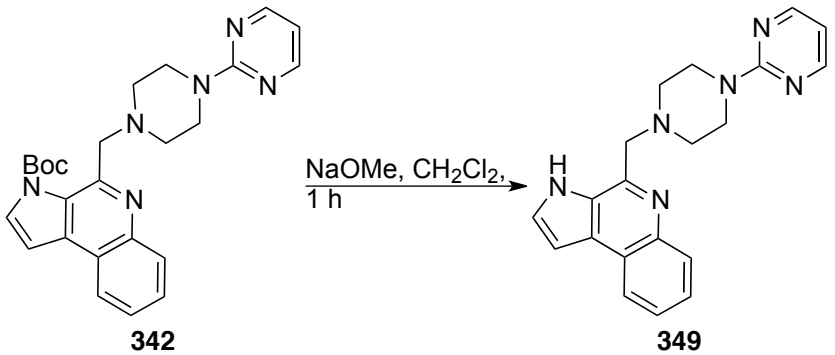
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.51 (1H br. s, 1H) **10**; 8.22-8.19 (1H, m) **6**; 8.14-8.11 (1H, m) **9**; 7.16 (2H r. ddd) **7**, **8**; 7.45 (1H, d, *J*=2.8 Hz) **11**; 7.06 (1H, d, *J*=2.8 Hz) **12**; 4.18 (2H, s) **13**; 3.8 (1H, t, *J*=4.6 Hz) **15**; 2.64 (1H, t, *J*=4.4 Hz) **14**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 145.4, **5**; 142.3, **4**; 129.0, **9**; 128.6, **2**; 128.3, **1**; 126.0, **8**; 125.7, **7**; 125.5, **11**; 123.4, **3**; 122.8, **6**; 101.3, **12**; 67.1, **15**; 65.3, **13**; 54.0, **14**.

LRMS (ESI) m/z 268.1 $[M + H]^+$

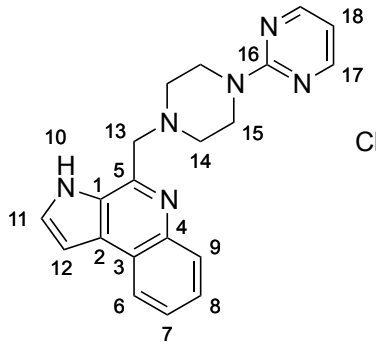
HRMS (ESI) m/z for $C_{16}H_{17}N_3O$ calcd. 268.1444, found 268.1448 $[M + H]^+$.

2.11.9. 4-((4-(Pyrimidin-2-yl)piperazin-1-yl)methyl)-3*H*-pyrrolo[2,3-*c*]quinolone (**349**)



342 **349**

Using general procedure 10A, piperazine **342** (25 mg, 55.35 µmol, 1.0 eq.), NaOMe (25% solution in MeOH) (24 µL, 110.7 µmol, 2.0 eq.) and CH_2Cl_2 (0.5 mL) were stirred for 1 h. Purification on deactivated silica gel (30-70% EtOAc in petrol) afforded pyrroloquinoline **349** (11 mg, 58%) as a white solid.



Chemical Formula: $C_{20}H_{20}N_6$
Molecular Weight: 344.41

MP decomp. 208 °C

IR (ν, cm^{-1}) 1582, 1544, 1484, 1356.

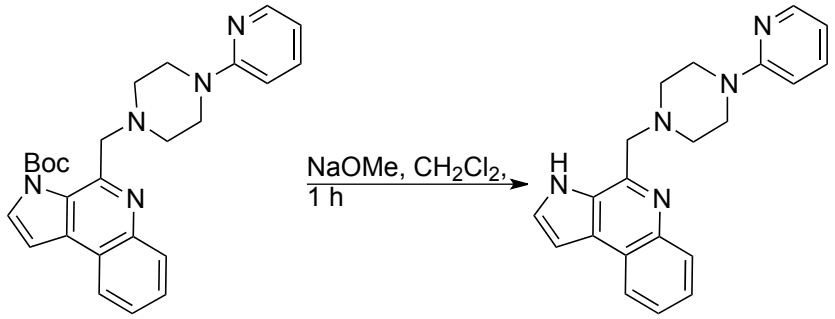
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 11.20 (1H, br. s) **10**; 8.33 (2H, d, *J*=4.8 Hz) **17**; 8.27-8.25 (1H, m) **6**; 8.04-8.02 (1H, m) **9**; 7.56-7.51 (3H, m) **7**, **8**, **11**; 7.12 (1H, dd, *J*=2.9, 2.1 Hz) **12**; 6.57 (1H, t, *J*=4.7 Hz) **18**; 4.14 (2H, s) **13**; 3.91 (4H, t, *J*=5.1 Hz) **15**; 2.63 (4H, t, *J*=5.1 Hz) **14**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 162.8, **16**; 158.6, **17**; 147.3, **5**; 143.4, **4**; 130.3, **9**; 129.2, 129.1, **1**, **2**; 127.2, **11**; 126.1, **7**, **8**; 124.6, **3**; 123.7, **6**; 110.8, **18**; 101.3, **12**; 65.4, **13**; 54.3, **14**; 44.3, **15**.

LRMS (ESI) m/z 345.1 $[M + H]^+$.

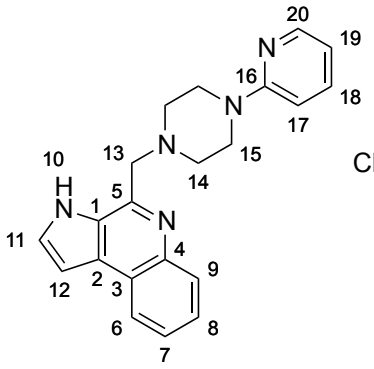
HRMS (ESI) m/z for $C_{20}H_{20}N_6$ calcd. 345.1822, found 345.1824 $[M + H]^+$.

2.11.10. 4-((4-(Pyridin-2-yl)piperazin-1-yl)methyl)-3*H*-pyrrolo[2,3-*c*]quinolone (**350**)



343 **350**

Using general procedure 10A, piperazine **343** (20 mg, 45.09 µmol, 1.0 eq.), NaOMe (25% solution in MeOH) (20 µL, 90.18 µmol, 2.0 eq.) and CH_2Cl_2 (0.5 mL) were stirred at -78 °C-rt for 1 h. Purification on deactivated silica gel (30-70% EtOAc in petrol) afforded pyrroloquinoline **350** (13 mg, 84%) as a yellow oil.



Chemical Formula: $C_{21}H_{21}N_5$
Molecular Weight: 343.42

MP decomp. 219 °C

IR (ν, cm^{-1}) 3372, 2822, 1593, 1480, 1436.

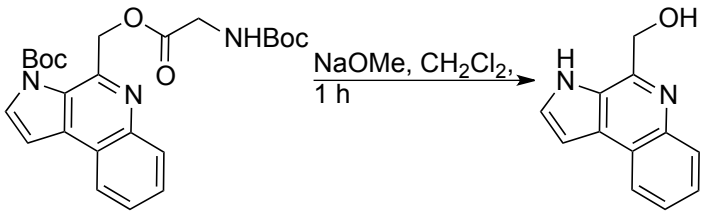
^{1}H NMR (400 MHz, ACETONE-*d*-6) δ ppm 11.17 (1H, br. s) **10**; 8.27-8.25 (1H, m) **6**; 8.12 (1H, ddd, *J*=4.9, 2.0, 0.9 Hz) **20**; 8.04-8.02 (1H, m) **9**; 7.55-7.48 (4H, m) **7**, **8**, **11**, **18**; 7.11 (1H, dd, *J*=2.9, 2.0 Hz) **12**; 6.78 (1H, apt. d, *J*=8.6 Hz) **17**; 6.61 (1H, ddd, *J*=7.1, 4.9, 0.7 Hz) **19**; 4.15 (2H, s) **13**; 3.64 (4H, t, *J*=5.2 Hz) **15**; 2.68 (4H, t, *J*=5.0 Hz) **14**.

^{13}C NMR (100 MHz, ACETONE-*d*-6) δ ppm 160.5, **16**; 148.7, **20**; 147.3, **5**; 143.4, **4**; 138.1, **18**; 130.3, **9**; 129.2, **2**; 127.2, **11**; 126.1, **7**, **8**; 124.6, **3**; 123.7, **6**; 113.8, **19**; 107.7, **17**; 101.3, **12**; 65.5, **13**; 54.2, **14**; 45.7, **15**.

LRMS (ESI) m/z 344.1 $[M + H]^+$.

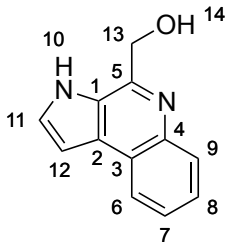
HRMS (ESI) m/z for $C_{21}H_{22}N_5$ calcd. 344.1870, found 344.1864 $[M + H]^+$.

2.11.11. (3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methanol (**348**)



341 **348**

Using general procedure 10A, ester **341** (50 mg, 109.8 µmol, 1.0 eq.), NaOMe (25% solution in MeOH) (47 µL, 219.5 µmol, 2.0 eq.) and THF (1 mL) were stirred at -78 °C-rt for 1 h. Purification on silica gel (30-80% EtOAc in petrol) afforded pyrroloquinoline **348** (22 mg, >99%) as a white solid.



Chemical Formula: $C_{12}H_{10}N_2O$
Molecular Weight: 198.22

MP decomp. 150 °C

IR (*v*, cm^{-1}) 3104, 2798.

^{1}H NMR (400 MHz, ACETONE-*d6*) δ ppm 11.10 (1H, br. s) **10**; 8.29-8.25 (1H, m) **6**; 8.05-8.01 (1H, m) **9**; 7.61 (1H, t, *J*=2.8 Hz) **11**; 7.57-7.52 (2H, r. ddd) **8**, **9**; 7.15 (1H, dd, *J*=2.9, 1.9 Hz) **12**; 5.13 (2H, s) **13**; 4.98 (1H, br. s) **14**.

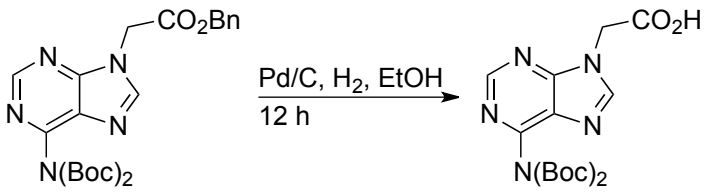
^{13}C NMR (100 MHz, ACETONE-*d6*) δ ppm 149.0, **5**; 142.7, **4**; 129.9, **9**; 129.5, **2**; 127.9, **1**; 127.7, **11**; 126.3, **8**; 126.1, **7**; 124.4, **3**; 123.8, **6**; 101.6, **12**; 64.8, **13**.

LRMS (ESI) m/z 198.9

HRMS (ESI) m/z for $C_{12}H_{10}N_2O$ calcd. 199.0866, found 199.0867 $[M + H]^+$.

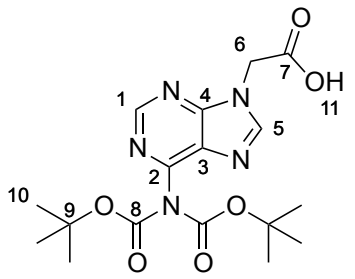
2.12. Ester Hydrogenolysis

2.12.1. Bis Boc adenine acetic acid (**323**)



Using general procedure 5A, ester (120 mg, 248.2 µmol, 1.0 eq.), 10% palladium on activated carbon (9 mg) and EtOH (7 mL) were stirred for 14 h to afford acid **323** as a white foam (89 mg, 90%).

Spectroscopic data are consistent with that reported in the literature.[177]

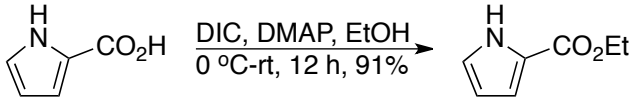


^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.63 (1H, br. s) **11;** 8.88 (1H, s) **1;** 8.45 (1H, s) **5;** 5.09 (1H, s) **6;** 1.39 (18H, s) **10.**

^{13}C NMR (400 MHz, CHLOROFORM-*d*) δ ppm 167.7, **7;** 153.2, **4;** 152.2, **1;** 150.0, **8;** 149.8, **2;** 146.5, **5;** 127.5, **3;** 84.2, **9;** 44.5, **6;** 27.7, **10.**

2.13. Miscellaneous Reactions

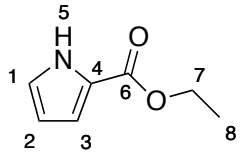
2.13.1. Ethyl 1*H*-pyrrole-2-carboxylate (**333**)



Using general procedure 2, pyrrole-2-carboxylic acid (**302**) (112 mg, 1.008 mmol, 1.0 eq.), DMAP (6 mg, 49.11 µmol, 0.050 eq.), EtOH (1.5 mL) and DIC (188 µL, 1.201 mmol, 1.2 eq.) were stirred at 0

°C-rt for 12 h and purified on silica gel (5-15% EtOAc in petrol) afforded ester as a white solid (126 mg, 91%).

Spectroscopic data are consistent with that reported in the literature.[178]

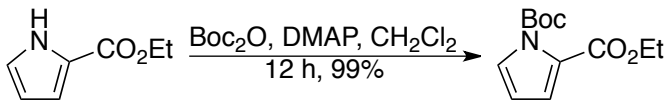


Chemical Formula: $C_7H_9NO_2$
Molecular Weight: 139.15

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.32 (1H, br. s) **5**; 6.96 (1H, td, 2.7, 1.5 Hz) **3**; 6.93 (1H, ddd, 3.8, 2.4, 1.4 Hz) **1**; 6.27 (1H, dt, 3.7, 2.6 Hz) **2**; 4.34 (2H, q, *J*=7.1 Hz) **7**; 1.37 (3H, t, *J*=7.1 Hz) **8**.

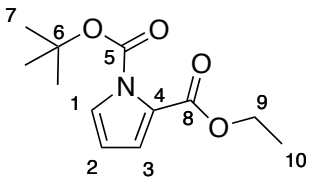
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 161.3, **6**; 123.0, **4**; 122.7, **3**; 115.1, **1**; 110.3, **2**; 60.3, **7**; 14.4, **8**.

2.13.2. 1-*tert*-Butyl 2-ethyl 1*H*-pyrrole-1,2-dicarboxylate



Using general procedure 1, pyrrole (126 mg, 0.9055 mmol, 1.0 eq.), DMAP (13 mg, 106.4 µmol, 0.10 eq.), CH_2Cl_2 (1 mL) and Boc_2O (242 mg, 1.109 mmol, 1.2 eq.) were stirred for 12 hand purified on silica gel (3% EtOAc in petrol) afforded *N*-Boc ester **333** as a colourless oil (214 mg, 99%).

Spectroscopic data are consistent with that reported in the literature.[179]

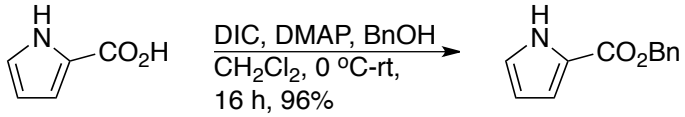


Chemical Formula: $C_{12}H_{17}NO_4$
Molecular Weight: 239.27

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.30 (1H, dd, *J*=3.1, 1.7 Hz) **1**; 6.82 (1H, dd, *J*=3.5, 1.7 Hz) **3**; 6.15 (1H, t, *J*=7.1 Hz) **2**; 4.30 (2H, q, *J*=7.1 Hz) **9**; 1.58 (9H, s) **7**; 1.34 (3H, t, *J*=7.1 Hz) **10**.

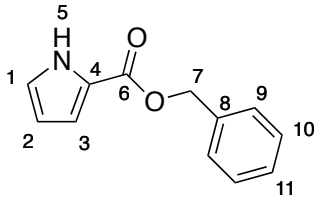
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 160.8, **8**; 148.3, **5**; 126.5, **1**; 125.5, **4**; 120.5, **3**; 110.0, **2**; 84.6, **6**; 60.7, **9**; 27.6, **7**; 14.2, **10**.

2.13.3. Benzyl 1*H*-pyrrole-2-carboxylate



Using general procedure 2, acid (**302**) (111 mg, 0.9991 mmol, 1.0 eq.), DIC (0.34 mL, 2.171 mmol, 2.2 eq.) DMAP (12 mg, 98.22 µmol, 0.10 eq.) BnOH (0.21 mL, 2.027 mmol, 2.0 eq.) and CH_2Cl_2 (5 mL) were stirred for 16 h and purified on silica gel (0-20% EtOAc in petrol) to afford the ester as a white solid (193 mg, 96%).

Spectroscopic data are consistent with that reported in the literature.[180]

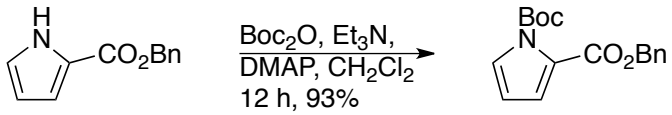


Chemical Formula: $C_{12}H_{11}NO_2$
Molecular Weight: 201.22

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.24 (1H, br. s) **5**; 7.45-7.35 (5H, m) **9-11**; 6.99 (1H, ddd, *J*=3.8, 2.4, 1.4 Hz), 6.96 (1H, td, *J*=4.1, 1.5 Hz) **1**, **3**; 6.28 (1H, td, *J*=3.7, 2.6 Hz) **2**; 5.33 (2H, s) **7**.

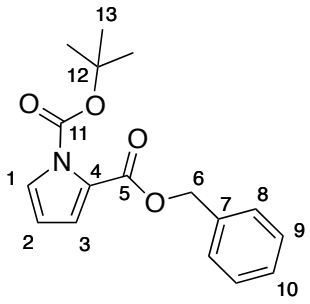
^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 160.9, **6**; 136.1, **4**; 128.6, 128.2, 128.1, **9-11**; 123.0, **1**; 122.6, **8**; 115.6, **3**; 110.5, **2**; 66.0, **7**.

2.13.4. 2-Benzyl 1-*tert*-butyl 1*H*-pyrrole-1,2-dicarboxylate



Using general procedure 1, pyrrole (186 mg, 0.9244 mmol, 1.0 eq.), Boc_2O (303 mg, 1.388 mmol, 1.5 eq.), Et_3N (102 µL, 1.388 mmol, 1.5 eq.), DMAP (6 mg, 49.11 µmol, 0.050 eq.) and CH_2Cl_2 (4 mL) were stirred for 12 h and purified on silica gel (0-20% Et_2O in petrol) to afford ester **334** as an oil (259 mg, 93%).

Spectroscopic data are consistent with that reported in the literature.[180]



Chemical Formula: $C_{17}H_{19}NO_4$
Molecular Weight: 301.34

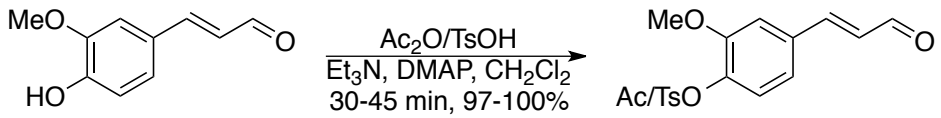
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.44-7.33 (5H, m) **8-10**; 6.90 (1H, dd, *J*=3.5, 1.8 Hz) **3**; 6.18 (1H, apt. t, *J*=3.3 Hz) **2**; 5.3 (2H, s) **6**; 1.56 (9H, s) **13**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 160.5, **5**; 148.3, **11**; 136.0, **7**; 128.5, 128.1, **8-10**; 126.9, **1**; 125.1, **4**; 121.2, **3**; 110.1, **2**; 84.8, **12**; 66.5, **6**; 27.6, **13**.

3. Experimental Procedures for Chapter 3

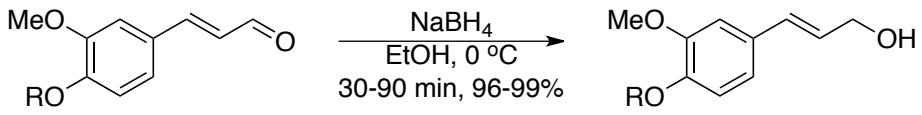
3.1. General Procedures

General Procedure 1 – *Phenol Acylation/Sulfonylation*



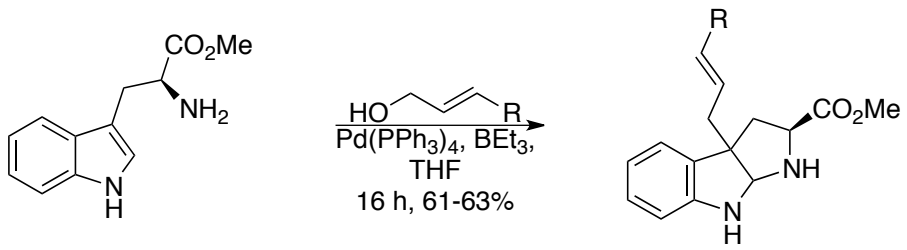
A round-bottomed flask was charged with a magnetic stirrer bar, and aldehyde (1.0 eq.), acetic anhydride/toluenesulfonyl chloride (1.2 eq.), Et_3N (1.2 eq.), DMAP (0.10 eq.) and CH_2Cl_2 (2 mL/mmol aldehyde) were stirred under Ar for the specified time. Upon completion (as indicated by TLC) the reaction mixture was concentrated *in vacuo* and purified on silica gel (EtOAc/Et_2O in petrol) to afford the desired products.

General procedure 2 – *Aldehyde Reduction*



A round-bottomed flask was charged with a magnetic stirrer bar, aldehyde (1.0 eq.), EtOH (10 mL/mmol aldehyde) and the reaction mixture cooled to 0 °C. Portion wise, $NaBH_4$ (1.0-4.0 eq.) was added and the reaction mixture stirred at 0 °C for the specified time. Upon completion (as indicated by TLC), the reaction mixture was diluted with EtOH, water, and the pH adjusted to *ca.* 5. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 as required. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting products were purified on silica gel (EtOAc/Et_2O in petrol) as required to afford the desired products.

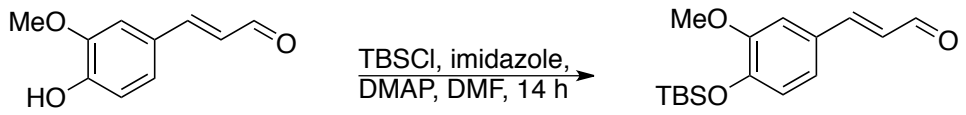
General Procedure 3 – *Allylative Cyclizations*



Using the Tamaru method,[145] an oven-dried 3-necked round-bottomed flask was charged with a magnetic stirrer bar, H-Trp-OMe (1.0 eq.), alcohol (1.2 eq.), $Pd(PPh_3)_4$ (0.050 eq.), and purged with Ar *in vacuo*. Via syringe, anhydrous THF (2.5 mL/mmol H-Trp-OMe) and slowly, Et_3B solution (1M in hexanes, 1.2 eq.) were added. The reaction mixture was stirred for the specified time, diluted with EtOAc, washed with sat. aq. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oils were purified on silica gel (EtOAc in petrol) to afford the desired products.

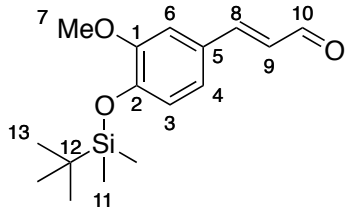
3.2. *O*-TBS Protection

3.2.1. (*E*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylaldehyde



A round-bottomed flask was charged with a magnetic stirrer bar, and aldehyde (150 mg, 0.8418 mmol, 1.0 eq.), TBSCl (254 mg, 1.684 mmol, 2.0 eq.), imidazole (115 mg, 1.684 mmol, 2.0 eq.), DMAP (10 mg, 84.18 µmol, 0.10 eq.) and DMF (1.4 mL) were stirred for 14 h. The reaction mixture was concentrated *in vacuo* and purified on silica gel (10-20% Et_2O in petrol) to afford TBS ether as a white solid (174 mg, 71%).

Spectroscopic data are consistent with that reported in the literature.[181]



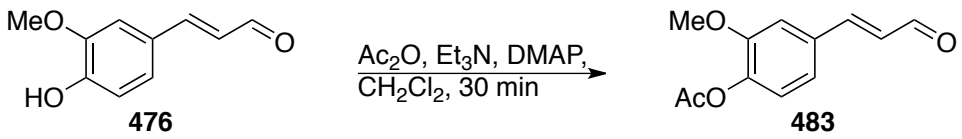
Chemical Formula: $C_{16}H_{24}O_3Si$
Molecular Weight: 292.45

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.66 (1H, d, *J*=7.8 Hz) **10**; 7.41 (1H, d, *J*=15.8 Hz) **8**; 7.08 (1H, dd, *J*=8.2, 2.1 Hz) **4**; 7.06 (1H, dd, *J*=3.1, 2.1 Hz) **6**; 6.89 (1H, d, *J*=7.9 Hz) **3**; 6.61 (1H, dd, *J*=15.8, 7.7 Hz) **9**; 3.85 (3H, s) **7**; 1.00 (9H, s) **13**; 0.19 (6H, s) **11**.

^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ ppm 193.6 **10**; 153.0 **8**; 151.4 **1**; 148.5 **2**; 127.9 **5**; 126.7 **9**; 123.1 **4**; 121.2 **3**; 111.0 **6**; 55.4 **7**; 25.6 **13**; 18.5 **12**; -4.6 **11**.

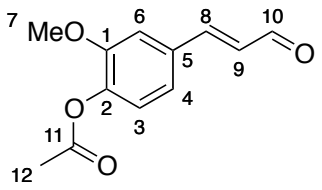
3.3. *O*-Acylation/Sulfonylation

3.3.1. (*E*)-2-methoxy-4-(3-oxoprop-1-en-1-yl)phenyl acetate (**483**)



Using general procedure 1, aldehyde **476** (199 mg, 1.117 mmol, 1.0 eq.), Ac_2O (127 µL, 1.347 mmol, 1.2 eq.), Et_3N (188 µL, 1.347 mmol, 1.2 eq.), DMAP (14 mg, 112.2 µmol, 0.10 eq.) and CH_2Cl_2 (2 mL) were stirred for 30 min and purified on silica gel (30% EtOAc in petrol) to afford acetate **483** as a white solid (246 mg, 100%).

Spectroscopic data are consistent with that reported in the literature.[182]

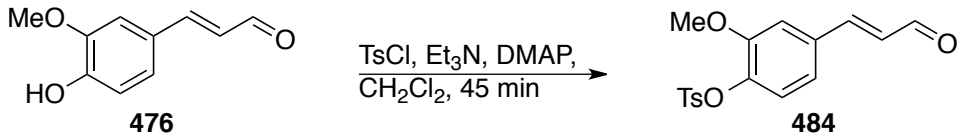


Chemical Formula: $C_{12}H_{12}O_4$
Molecular Weight: 220.22

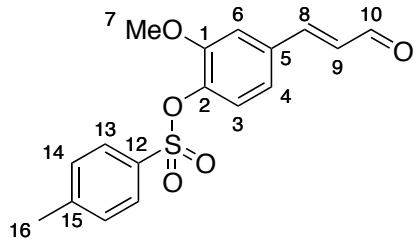
^{1}H NMR (400 MHz CHLOROFORM-*d*) δ ppm 9.70 (1H, d, *J*=7.6 Hz) **10;** 7.44 (1H, d, *J*=15.9 Hz) **8;** 7.18-7.09 (3H, m) **3**, **4**, **6;** 6.67 (1H, dd, *J*=16.0, 7.6 Hz) **9;** 3.87 (3H, s) **7;** 2.33 (3H, s) **12.**

^{13}C NMR (100 MHz CHLOROFORM-*d*) δ ppm 193.4, **10;** 168.6, **11;** 151.8, **8;** 151.5, **1;** 142.2, **2;** 132.9, **5;** 128.7, **9;** 123.4, **3;** 121.8, 111.3, **4**, **6;** 55.9, **7;** 20.6, **12.**

3.3.2. (*E*)-2-methoxy-4-(3-oxoprop-1-en-1-yl)phenyl 4-methylbenzenesulfonate (**484**)



Using general procedure 1, aldehyde **476** (200 mg, 1.122 mmol, 1.0 eq.), TsCl (257 mL, 1.346 mmol, 1.2 eq.), Et_3N (188 µL, 1.346 mmol, 1.2 eq.), DMAP (14 mg, 112.2 µmol, 0.10 eq.) and CH_2Cl_2 (2 mL) were stirred for 45 min and purified on silica gel (50-100% EtOAc in petrol) to afford tosylate **484** as a pale yellow solid (365 mg, 98%).



Chemical Formula: $C_{17}H_{16}O_5S$
Molecular Weight: 332.37

MP 106-108 °C

IR (*v*, cm $^{-1}$) 3014, 1672, 1367, 1176, 1148, 1131, 1113, 1088, 1032.

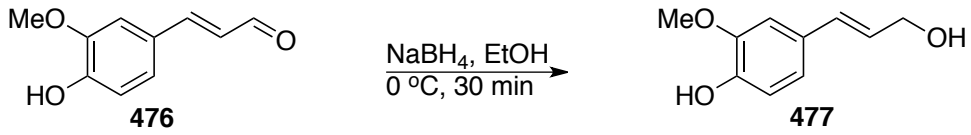
^{1}H NMR (400 MHz CHLOROFORM-*d*) δ ppm 9.70 (1H, d, *J*=7.6 Hz) **10;** 7.78 (2H, dt, *J*=8.5, 2.8 Hz) **13;** 7.41 (1H, d, *J*=15.9 Hz) **8;** 7.33 (1H, dd, *J*=8.6, 0.6 Hz) **14;** 7.22 (1H, d, *J*=8.3 Hz) **3;** 7.12 (1H, dd, *J*=8.4, 1.9 Hz) **4;** 7.02 (1H, d, *J*=1.9 Hz) **6;** 6.65 (1H, dd, *J*=16.0, 7.6 Hz) **9;** 3.63 (3H, s) **7;** 2.47 (3H, s) **16.**

^{13}C NMR (100 MHz CHLOROFORM-*d*) δ ppm 193.2, **10**; 152.3, **1**; 151.2, **8**; 145.3, **15**; 140.4, **2**; 133.8, **5**; 133.1, **12**; 129.5, **14**; 129.3, **9**; 128.6, **13**; 124.6, **3**; 121.6, **4**; 111.6, **6**; 55.7, **7**; 21.7, **16**.

HRMS (ESI) m/z for $C_{17}H_{16}O_5S$ calcd. 333.0791, found 333.0794 $[M + H]^+$.

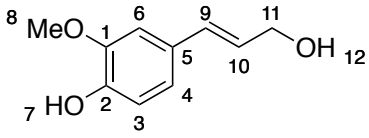
3.4. Aldehyde Reductions

3.4.1. (*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol (**477**)



Using general procedure 2, aldehyde **476** (178 mg, 1.000 mmol, 1.0 eq.), $NaBH_4$ (95 mg, 2.500 mmol, 2.5 eq.) and EtOH (10 mL) were stirred at 0 °C for 30 min and purified on silica gel (20-50% EtOAc in petrol) to afford alcohol **477** as a colourless oil (175 mg, 97%), which was used without further purification.

Spectroscopic data are consistent with that reported in the literature.[183]

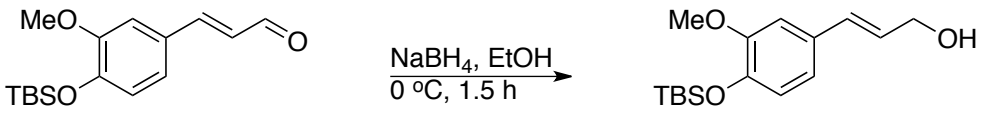


Chemical Formula: $C_{10}H_{12}O_3$
Molecular Weight: 180.20

^{1}H NMR (400 MHz ACETONE-*d*6) δ ppm 7.59 (1H, s) **7**; 7.05 (1H, d, *J*=1.9 Hz) **6**; 6.86 (1H, dd, *J*=8.1, 1.9 Hz) **4**; 6.77 (1H, d, *J*=8.1 Hz) **3**; 6.50 (1H, dt, *J*=15.9, 1.5 Hz) **9**; 6.23 (1H, dt, *J*=15.9, 5.5 Hz) **10**; 4.19 (1H, td, *J*=8.4, 1.6 Hz) **11**; 3.86 (3H, s) **8**.

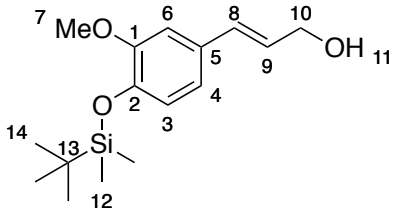
^{13}C NMR (100 MHz ACETONE-*d*6) δ ppm 148.5, **1**; 147.2, **2**; 130.4, **9**; 130.3, **5**; 128.2, **10**; 120.7, **4**; 115.8, **3**; 110.1, **6**; 63.5, **11**; 56.2, **8**.

3.4.2. (*E*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)prop-2-en-1-ol (**479**)



Using general procedure 2, aldehyde (174 mg, 0.595 mmol, 1.0 eq.), $NaBH_4$ (90 mg, 2.380 mmol, 4.0 eq.) and EtOH (6 mL) were stirred at 0 °C for 1.5 h to afford alcohol **479** as a colourless oil (170 mg, 97%), which was used without further purification.

Spectroscopic data are consistent with that reported in the literature.[181]

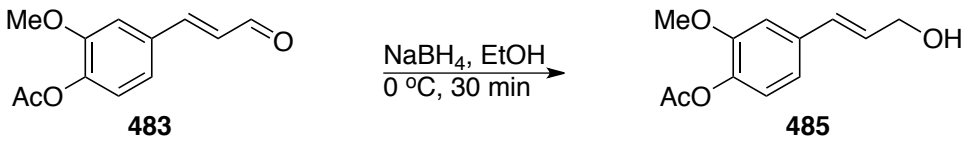


Chemical Formula: $C_{16}H_{26}O_3Si$
Molecular Weight: 294.46

^{1}H NMR (400 MHz CHLOROFORM-*d*) δ ppm 6.91 (1H, d, *J*=2.0 Hz) **6**; 6.85 (1H, dd, *J*=8.1, 1.9 Hz) **4**; 6.80 (1H, d, *J*=8.1 Hz) **3**; 6.54 (1H, td, *J*=15.8, 1.4 Hz) **8**; 6.24 (1H, td, *J*=15.8, 6.0 Hz) **9**; 4.30 (2H, dd, *J*=6.0, 1.4 Hz) **10**; 3.82 (3H, s) **7**; 1.00 (9H, s) **14**; 0.16 (6H, s) **12**.

^{13}C NMR (100 MHz CHLOROFORM-*d*) δ ppm 151.0, **1**; 145.0, **2**; 131.3, **8**; 130.6, **5**; 126.5, **9**; 120.9, **3**; 119.6, **4**; 109.9, **6**; 63.8, **10**; 55.4, **7**; 25.7, **14**; 18.4, **13**; -4.7, **12**.

3.4.3. (*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenyl acetate (**485**)

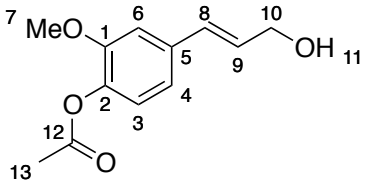


483 **485**

Using general procedure 2, aldehyde **483** (576 mg, 2.616 mmol, 1.0 eq.), $NaBH_4$ (247 mg, 6.540 mmol, 2.5 eq.) and EtOH (6 mL) were

stirred at 0 °C for 30 min and purified on silica gel (50-100% Et_2O in petrol) to afford alcohol **485** as a colourless oil (558 mg, 96%) which was used without further purification.

Spectroscopic data are consistent with that reported in the literature.[184]

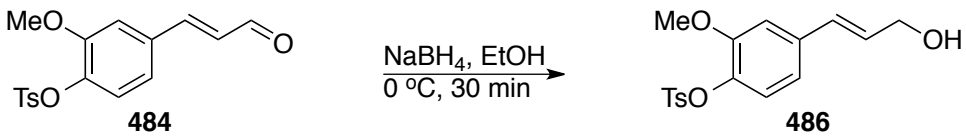


Chemical Formula: $C_{12}H_{14}O_4$
Molecular Weight: 222.24

^{1}H NMR (400 MHz) δ ppm 7.00-6.94 (3H, m) **3**, **4**, **6**; 6.58 (1H, dt, *J*=15.9, 1.5 Hz) **8**; 6.31 (1H, dt, *J*=15.9, 8.5 Hz) **9**; 4.32 (2H, d, *J*=5.2 Hz) **10**; 3.85 (3H, s) **7**; 2.32 (3H, s) **13**.

^{13}C NMR (100 MHz) δ ppm 169.1, **12**; 151.1, **1**; 139.3, **2**; 135.8, **5**; 130.4, **8**; 128.9, **9**; 122.8, **3**; 119.1, 110.1, **4**,**6**; 63.5, **10**; 55.8, **7**; 20.6, **13**.

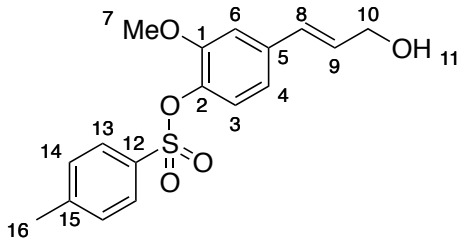
3.4.4 (*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenyl 4-methylbenzenesulfonate (**486**)



484 **486**

Using general procedure 2, aldehyde **484** (298 mg, 0.8966 mmol, 1.0 eq.), $NaBH_4$ (34 mg, 0.9026 mmol, 1.0 eq.) and EtOH (3 mL) were stirred at 0 °C for 1.5 h and purified on silica gel (60% EtOAc in petrol) to afford alcohol **486** as a colourless oil (297 mg, 99%) which was used without further purification.

Spectroscopic data are consistent with that reported in the literature.[185]



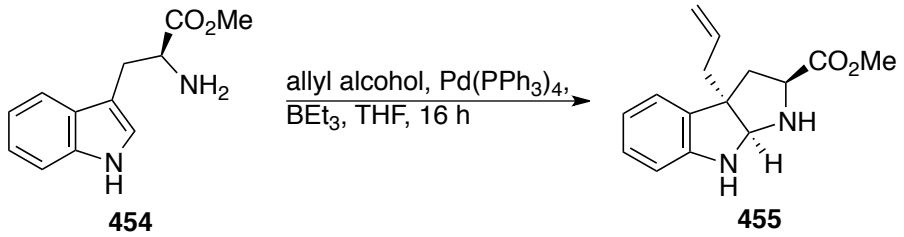
Chemical Formula: $C_{17}H_{18}O_5S$
Molecular Weight: 334.39

^{1}H NMR (400 MHz CHLOROFORM-*d*) δ ppm 7.75 (2H, dt, 8.5, 1.8 Hz) **13;** 7.30 (2H, d, *J*=8.0 Hz) **14;** 7.09 (1H, d, *J*=8.3 Hz) **3;** 6.89 (1H, dd, *J*=8.3, 2.0 Hz) **4;** 6.84 (1H, d, *J*=1.9 Hz) **6;** 6.55 (1H, dt, *J*=15.9, 1.4 Hz) **8;** 6.30 (1H, dt, *J*=15.9, 8.3 Hz) **9;** 4.32 (2H, dd, *J*=5.5, 1.5 Hz) **10;** 3.57 (3H, s) **7;** 2.45 (3H, s) **16;** 1.62 (1H, br. s) **11.**

^{13}C NMR (100 MHz CHLOROFORM-*d*) δ ppm 151.8, **1;** 145.0, **15;** 137.8, **2;** 136.8, **5;** 133.2, **12;** 129.9, **8;** 129.7, **9;** 129.3, **14;** 128.6, **13;** 124.0, **3;** 118.9, **4;** 110.3, **6;** 63.4, **10;** 55.5, **7;** 21.6, **16.**

3.5. Allylative Cyclizations

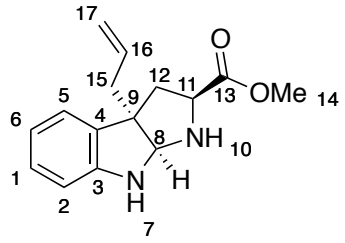
3.5.1. (2*S*)-methyl 3a-allyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (**455**)



454 **455**

Using general procedure 3, H-Trp-OMe·HCl (316 mg, 1.241 mmol, 1.0 eq.), allyl alcohol (101 µL, 1.489 mmol, 1.2 eq.), $Pd(PPh_3)_4$ (143 mg, 0.1237 mmol, 0.10 eq.), BEt_3 (1M sol. in hexane) (1.5 mL, 1.500 mmol, 1.2 eq.) and anhydrous THF (2.5 mL) were stirred for 16 h and purified on silica gel (20-100% EtOAc in petrol) to afford pyrroloindole **455** and triphenylphosphine oxide as an inseparable mixture as a yellow oil (202 mg, 63% (corrected for phosphine oxide contamination based upon ^{1}H NMR integrations)).

Spectroscopic data are consistent with that reported in the literature.[145]

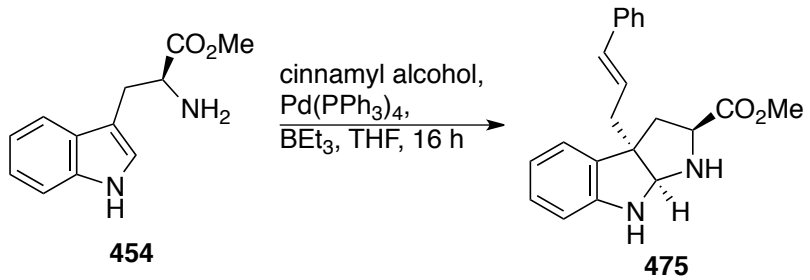


Chemical Formula: $C_{15}H_{18}N_2O_2$
Molecular Weight: 258.32

^{1}H NMR (400 MHz CHLOROFORM-*d*) δ ppm 7.02-6.98 (2H, m) **1, 6;** 6.69 (1H, td, *J*=7.42, 1.0 Hz) **2;** 6.54 (1H, dd, *J*=8.1, 0.8 Hz) **5;** 5.69 (1H, dddd, *J*=16.9, 10.2, 8.0, 6.6 Hz) **16;** 5.09 (2H, m) **15;** 4.84 (1H, s) **8;** 3.87 (1H, dd, *J*=7.8, 3.5 Hz) **11;** 3.32 (3H, s) **14;** 2.51 (1H, ddt, *J*=6.8, 1.4 Hz) **15;** 2.47 (1H, dd, *J*=12.7, 3.3 Hz) **12;** 2.41 (1H, apt. dd, *J*=13.8, 8.0 Hz) **15′;** 2.34 (1H, dd, *J*=12.7, 7.8 Hz) **12′.**

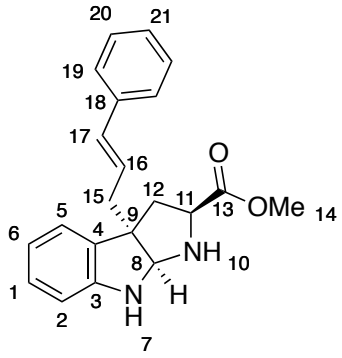
LRMS (ESI) 259.1 $[M + H]^+$

3.5.2. (2*S*)-methyl 3a-cinnamyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (**475**)



454 **475**

Using general procedure 3, H-Trp-OMe.HCl (71 mg, 0.2795 mmol, 1.0 eq.), cinnamyl alcohol (45 mg, 0.3354 mmol, 1.2 eq.), $Pd(PPh_3)_4$ (16 mg, 13.98 µmol, 0.10 eq.), BEt_3 (1M sol. in hexane) (0.34 mL, 0.3400 mmol, 1.2 eq.) and anhydrous THF (0.7 mL) were stirred for 16 h and purified on silica gel (50-100% EtOAc in petrol) to afford pyrroloindole **475** as a yellow oil (57 mg, 61% (corrected for phosphine oxide contamination based upon ^{1}H NMR integrations)).



Chemical Formula: $C_{21}H_{22}N_2O_2$
Molecular Weight: 334.41

IR (*v*, cm^{-1}) 3362, 2948, 1731, 1607, 1483, 1466, 1434.

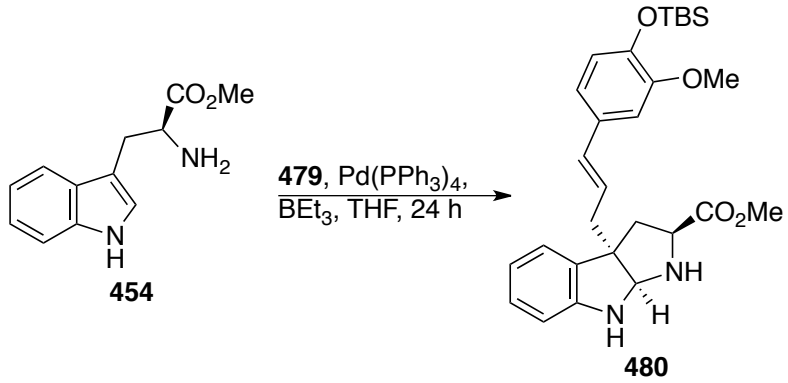
^{1}H NMR (400 MHz CHLOROFORM-*d*) δ ppm 7.23-7.10 (6H, m), 6.98-6.94 (2H, m) **1, 6, 7, 19, 20, 21;** 6.64 (1H, td, *J*=7.4, 0.9 Hz) **2;** 6.49 (1H, dd, *J*=8.2, 0.9 Hz) **5;** 6.36 (1H, d, *J*=15.7 Hz) **17;** 6.05 (1H, ddd, *J*=15.5, 8.4, 6.9 Hz) **16;** 4.82 (1H, s) **8;** 3.82 (1H, dd, *J*=7.5, 3.2 Hz) **11;** 3.26 (3H, s) **14;** 2.58 (1H, ddd, *J*=13.9, 6.6, 1.4 Hz) **15;** 2.53-2.32 (4H, m) **10, 12, 12′, 15′**

^{13}C NMR (100 MHz CHLOROFORM-*d*) δ ppm 174.3; 149.5; 137.2; 133.1; 132.7; 128.50; 128.46; 128.4; 128.3; 127.2; 126.1; 125.8; 123.9; 118.8; 109.5; 82.4; 60.0; 57.4; 51.8; 41.9; 41.3.

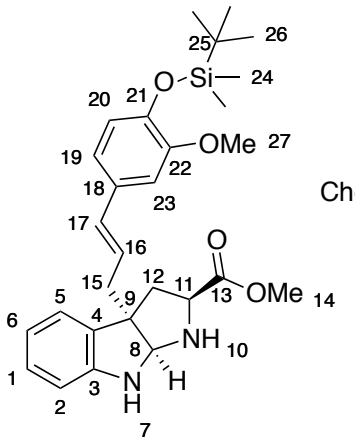
LRMS (ESI) 335.1 $[M + H]^+$ 357.0 $[M + Na]^+$.

HRMS (ESI) m/z for $C_{21}H_{22}N_2O_2$ calcd. 335.1754, found 335.1758 $[M + H]^+$.

3.5.3. (2*S*)-methyl 3a-((*E*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)allyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (**480**)



Using general procedure 3, H-Trp-OMe.HCl (39 mg, 152.8 µmol, 1.0 eq.), alcohol **479** (54 mg, 183.4 µmol, 1.2 eq.), $Pd(PPh_3)_4$ (9 mg, 76.12 µmol, 0.10 eq.), BEt_3 (1M sol. in hexane) (0.31 mL, 310.0 µmol, 1.2 eq.) and anhydrous THF (0.4 mL) were stirred for 16 h and purified on silica gel (20-100% EtOAc in petrol) to afford pyrroloindole **480** as an oil (13 mg, 11% (corrected for phosphine oxide contamination based upon ^{1}H NMR integrations)).



Chemical Formula: $C_{28}H_{38}N_2O_4Si$
Molecular Weight: 494.70

IR (ν, cm^{-1}) 3341, 2991, 1728, 1616.

^{1}H NMR (400 MHz) δ ppm 7.06-7.02 (2H, m), 6.80-6.77 (3H, m), 6.73 (1H, td, *J*=7.4, 0.9 Hz), 6.58 (1H, apt. d, *J*=7.6 Hz) **1**, **2**, **5**, **6**, **19**, **20**, **23**; 6.37 (1H, apt. d, *J*-15.5 Hz) **17**; 5.98 (1H, ddd, *J*=15.5, 8.3, 7.0 Hz) **16**; 4.91 (1H, s) **8**; 3.91 (1H, dd, *J*=7.7, 3.5 Hz) **11**; 3.8 (3H, d, *J*=12.3 Hz) **27**; 3.35 (3H, s) **14**; 2.64 (1H, ddd, *J*=13.9, 6.7, 1.2 Hz), 2.59-2.41 (4H, m) **12**, **15**; 0.99 (9H, s) **26**; 0.15 (6H, s) **24**.

^{13}C NMR (100 MHz) δ ppm 174.2; 150.9; 149.5; 144.6; 133.0; 132.9; 131.3; 123.9; 123.7; 120.9; 119.0; 119.0; 118.8; 110.0; 109.6; 82.4; 60.0; 57.5; 55.5; 51.9; 41.9; 41.2; 25.7; 18.4; 0.97.

HRMS (ESI) m/z for $C_{28}H_{38}N_2O_4Si$ calcd. 495.2674, found 495.2678 $[M + H]^+$.

References

(1) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030–2036.

(2) Mannich, C.; Krösche, W. *Archiv der Pharmazie* **1912**, *250*, 647–667.

(3) Hellmann, H. *Angew. Chem.* **1957**, *69*, 463–471.

(4) Belleau, B. *Can. J. Chem.* **1957**, *35*, 651–662.

(5) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. *Chem. Rev.* **2004**, *104*, 1431–1628.

(6) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416.

(7) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.

(8) Marson, C. *Arkivoc* **2001**, *(i)*, 1–16.

(9) Yazici, A.; Pyne, S. *Synthesis* **2009**, *2009*, 339–368.

(10) Yazici, A.; Pyne, S. *Synthesis* **2009**, *2009*, 513–541.

(11) González-López, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164–189.

(12) Le Quement, S. T.; Petersen, R.; Meldal, M.; Nielsen, T. E. *Biopolymers* **2010**, *94*, 242–256.

(13) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.

(14) Magnus, P.; Matthews, K. S. *Tetrahedron* **2012**, *68*, 6343–6360.

(15) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476–12477.

(16) Chiou, W.-H.; Lin, G.-H.; Hsu, C.-C.; Chaterpaul, S. J.; Ojima, I. *Org. Lett.* **2009**, *11*, 2659–2662.

(17) Saha, S.; Venkata Ramana Reddy, C.; Patro, B. *Tetrahedron Lett.* **2011**, *52*, 4014–4016.

(18) Badole, S.; Bodhankar, S.; Jain, B.; Bhardwaj, S. *Indian J. Pharmacol.* **2006**, *38*, 49–53.

(19) Othman, R. Ben; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825–2828.

(20) Othman, R. Ben; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335–5337.

(21) Huang, P. Q.; Wang, S. L.; Ye, J. L.; Ruan, Y. P.; Huang, Y. Q.; Zheng, H.; Gao, J. X. *Tetrahedron* **1998**, *54*, 12547–12560.

(22) Beak, P.; Meyers, a. I. *Acc. Chem. Rev.* **1986**, *19*, 356–363.

(23) Wunberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179–187.

(24) Maryanoff, B. E.; Mccomsey, D. F.; Duhl-Emswiller, B. A. *J. Org. Chem.* **1983**, *48*, 5062–5074.

(25) Wuonola, M. A.; Woodward, R. B. *Tetrahedron* **1976**, *32*, 1085–1095.

(26) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264–4268.

(27) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176.

(28) Shono, T. *Tetrahedron* **1984**, *40*, 811–850.

(29) Murahashi, S.-I. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 2443–2465.

(30) DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988–6893.

(31) Suh, Y.; Shin, D.; Jung, J.; Kim, S. *Chem. Commun.* **2002**, 1064–1065.

(32) Mecozzi, T.; Petrini, M.; Chimiche, S. *J. Org. Chem.* **1999**, *64*, 8970–8972.

(33) Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem.* **2006**, *4*, 278–290.

(34) Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Org. Chem.* **1990**, *55*, 2206–2214.

(35) Yaouanq, L.; Rene, L.; Dau, M. T. H.; Badet, B. *J. Org. Chem.* **2002**, *67*, 5408–5411.

(36) Bock, M. G.; DiPardo, R. M.; Freidinger, R. M. *J. Org. Chem.* **1986**, *51*, 3718–3720.

(37) Murahashi, S.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313.

(38) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811.

(39) Bond, C. C.; Bond, C.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2005**, *4*, 3672–3673.

(40) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387–3390.

(41) Venkov, A. P.; Mollov, N. M. *Synthesis* **1982**, 216–217.

(42) Grigg, R.; Sridharan, V.; Sykes, D. a. *Tetrahedron* **2008**, *64*, 8952–8962.

(43) Cincinelli, R.; Dallavalle, S.; Merlini, L.; Nannei, R.; Scaglioni, L. *Tetrahedron* **2009**, *65*, 3465–3472.

(44) Holloway, C. a; Muratore, M. E.; Storer, R. L.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720–4723.

(45) Cai, Q.; Liang, X.-W.; Wang, S.-G.; Zhang, J.-W.; Zhang, X.; You, S.-L. *Org. Lett.* **2012**, *14*, 5022–5025.

(46) Ben Othman, R.; Affani, R.; Tranchant, M.-J.; Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem. Int. Ed. Eng.* **2010**, *49*, 776–780.

(47) Yamada, S.; Takahashi, Y. *Tetrahedron Lett.* **2009**, *50*, 5395–5398.

(48) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577–1580.

(49) Peterson, E. a; Jacobsen, E. N. *Angew. Chem. Int. Ed. Eng.* **2009**, *48*, 6328–6331.

(50) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071.

(51) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833–3836.

(52) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912–4915.

(53) Xiang, Y.-G.; Wang, X.-W.; Zheng, X.; Ruan, Y.-P.; Huang, P.-Q. *Chem. Commun.* **2009**, *10*, 7045–7047.

(54) Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460–9465.

(55) Osante, I.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2004**, *45*, 1253–1256.

(56) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Nishiyama, H.; Itoh, K. *Org. Biomol. Chem.* **2004**, *2*, 1287–1294.

(57) Selvakumar, J.; Ramanathan, C. R. *Org. Biomol. Chem.* **2011**, *9*, 7643–7646.

(58) Kawai, N.; Abe, R.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 6580–6583.

(59) Kawai, N.; Abe, R.; Matsuda, M.; Uenishi, J. *J. Org. Chem.* **2011**, *76*, 2102–2114.

(60) Kawai, N.; Matsuda, M.; Uenishi, J. *Tetrahedron* **2011**, *67*, 8648–8653.

(61) Wang, Q.-S.; Xie, J.-H.; Guo, L.-C.; Zhou, Q.-L. *Org. Biomol. Chem.* **2012**, *10*, 43–45.

(62) Vuluga, D.; Legros, J.; Crousse, B.; Slawin, A. M. Z.; Laurence, C.; Nicolet, P.; Bonnet-Delpon, D. *J. Org. Chem.* **2011**, *76*, 1126–1133.

(63) Ascic, E.; Jensen, J. F.; Nielsen, T. E. *Angew. Chem. Int. Ed. Eng.* **2011**, *50*, 5188–5191.

(64) Li, G.-X.; Qu, J. *Chem. Commun.* **2010**, *46*, 2653–2655.

(65) De, K.; Legros, J.; Crousse, B.; Chandrasekaran, S.; Bonnet-Delpon, D. *Org. Biomol. Chem.* **2011**, *9*, 347–350.

(66) Xiao, J.; Zhao, K.; Loh, T.-P. *Chem. Commun.* **2012**, *48*, 3548–3550.

(67) Hagiya, K.; Muramoto, N.; Misaki, T.; Sugimura, T. *Tetrahedron* **2009**, *65*, 6109–6114.

(68) Othman, M.; Pigeon, P.; Decroix, B. *Tetrahedron* **1997**, *53*, 2495–2504.

(69) Pin, F.; Comesse, S.; Garrigues, B.; Marchalín, S.; Daïch, A. *J. Org. Chem.* **2007**, *72*, 1181–1191.

(70) Irikawa, H.; Toyoda, Y.; Kumagai, H.; Okumura, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 880–887.

(71) Devineau, A.; Pousse, G.; Taillier, C.; Blanchet, J.; Rouden, J.; Dalla, V. *Adv. Synth. Catal.* **2010**, *352*, 2881–2886.

(72) Kafka, S.; Klásek, A.; Polis, J.; Rosenbreierová, V.; Palík, C.; Mrkvička, V.; Košmrlj, J. *Tetrahedron* **2008**, *64*, 4387–4402.

(73) Van Baelen, G.; Hostyn, S.; Dhooghe, L.; Tapolcsányi, P.; Mátyus, P.; Lemière, G.; Dommisse, R.; Kaiser, M.; Brun, R.; Cos, P.; Maes, L.; Hajós, G.; Riedl, Z.; Nagy, I.; Maes, B. U. W.; Pieters, L. *Bioorg. Med. Chem.* **2009**, *17*, 7209–7217.

(74) Carroll, A. R.; Duffy, S.; Avery, V. M. *J. Org. Chem.* **2010**, *75*, 8291–8294.

(75) Okanya, P. W.; Mohr, K. I.; Gerth, K.; Jansen, R.; Rolf, M. *J. Nat. Prod.* **2011**, *74*, 603–608.

(76) Sangnoi, Y.; Sakulkeo, O.; Yuenyongsawad, S.; Kanjana-opas, A.; Ingkaninan, K.; Plubrukarn, A.; Suwanborirux, K. *Mar. Drugs* **2008**, *6*, 578–586.

(77) 4.11 Drugs for dementia http://www.medicinescomplete.com/mc/bnf/current/PHP3236-drugs-for-dementia.htm (accessed Nov 28, 2012).

(78) Govindachari, T. R.; Rajappa, S.; Sudarsanam, V. *Tetrahedron* **1973**, *16*, 1–4.

(79) Parrick, J.; Wilcox, R. *J. Chem. Soc. Perkin. Trans. 1* **1976**, 2121–2125.

(80) Molina, P.; Alajarin, M.; Sanchez-Andrada, P. *Synthesis* **1993**, *1993*, 225–228.

(81) Ghosez, L.; Franc, C.; Denonne, F.; Cuisinier, C.; Touillaux, R. *Can. J. Chem.* **2001**, *79*, 1827–1839.

(82) Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. *Org. Lett.* **2004**, *6*, 2741–2744.

(83) Beveridge, R. E.; Gerstenberger, B. S. *Tetrahedron Lett.* **2012**, *53*, 564–569.

(84) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem. Int. Ed. Eng.* **2008**, *47*, 3004–3007.

(85) Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed. Eng.* **1999**, *38*, 3391–3393.

(86) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995–1997.

(87) Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 7696–7697.

(88) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem. Int. Ed. Eng.* **2001**, *40*, 2168–2171.

(89) Cho, J.-Y.; Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 12868–12869.

(90) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305–308.

(91) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391.

(92) Yotphan, S.; Bergman, R. G.; Ellman, J. a *J. Am. Chem. Soc.* **2008**, *130*, 2452–2453.

(93) Chotana, G. a.; Kallepalli, V. a.; Maleczka, R. E.; Smith, M. R. *Tetrahedron* **2008**, *64*, 6103–6114.

(94) Kallepalli, V. a.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199–9201.

(95) Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586–3589.

(96) Vanchura, B. a; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. a; Staples, R. J.; Maleczka, R. E.; Singleton, D. a; Smith, M. R. *Chem. Commun.* **2010**, *46*, 7724–7726.

(97) Sawyer, K. R.; Cahoon, J. F.; Shanoski, J. E.; Glascoe, E. a; Kling, M. F.; Schlegel, J. P.; Zoerb, M. C.; Hapke, M.; Hartwig, J. F.; Webster, C. E.; Harris, C. B. *J. Am. Chem. Soc.* **2010**, *132*, 1848–1859.

(98) Roosen, P. C.; Kallepalli, V.; Chattopadhyay, B.; Singleton, D.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2012**, *134*, 11350–11353.

(99) Tse, M. K.; Cho, J. Y.; Smith, M. R. *Org. Lett.* **2001**, *3*, 2831–2833.

(100) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651.

(101) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278.

(102) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491–3494.

(103) Srinivasan, N.; Ganesan, A. *Chem. Commun.* **2003**, *7*, 916–917.

(104) Pictet, A.; Hubert, A. *Chem. Ber.* **1896**, *29*, 1182–1189.

(105) Morgan, G. T.; Walls, L. P. *J. Chem. Soc.* **1931**, 2447–2456.

(106) Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485–3488.

(107) Montalbetti, C. a. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852.

(108) Villeneuve, G. B.; Chan, T. H. *Tetrahedron Lett.* **1997**, *38*, 6489–6492.

(109) Dey, S.; Garner, P. *J. Org. Chem.* **2000**, *65*, 7697–7699.

(110) Panarese, J. D.; Lindsley, C. W. *Org. Lett.* **2012**, *14*, 5808–5810.

(111) Ni, L.; Li, Z.; Wu, F.; Xu, J.; Wu, X.; Kong, L.; Yao, H. *Tetrahedron Lett.* **2012**, *53*, 1271–1274.

(112) Schwalm, C. S.; Correia, C. R. D. *Tetrahedron Lett.* **2012**, *53*, 4836–4840.

(113) Ma, X.; Vo, Y.; Banwell, M. G.; Willis, A. C. *Asian J. Org. Chem.* **2012**, *1*, 160–165.

(114) Mahajan, J. P.; Suryawanshi, Y. R.; Mhaske, S. B. *Org. Lett.* **2012**, *14*, 5804–5807.

(115) Lipworth, B. J. *Lancet* **2005**, *365*, 167–175.

(116) Zeches-Hanrot, M.; Nuzillard, J.-M.; Richard, B.; Schaller, H.; Hadi, H. A.; Sevenet, T.; Le Men-Olivier, L. *Phytochem.* **1995**, *40*, 587–591.

(117) Lien, T. P.; Kamperdick, C.; Van Sung, T.; Adam, G.; Ripperger, H. *Phytochem.* **1998**, *49*, 1797–1799.

(118) Pachaly, P.; Kroll-Horstmann, A.; Sin, K. S. *Pharmazie* **2000**, *55*, 777–778.

(119) Kimura, Y.; Sawada, A.; Kuramata, M.; Kusano, M.; Fujioka, S.; Kawano, T. *J. Nat. Prod.* **2005**, *68*, 237–239.

(120) Feng, T.; Li, Y.; Liu, Y.-P.; Cai, X.-H.; Wang, Y.-Y.; Luo, X.-D. *Org. Lett.* **2010**, *12*, 968–971.

(121) Raju, R.; Piggott, A. M.; Conte, M.; Aalbersberg, W. G. L.; Feussner, K.; Capon, R. J.; Biol, C. *Org. Lett.* **2009**, *11*, 3862–3865.

(122) Li, L.; Li, D.; Luan, Y.; Gu, Q.; Zhu, T. *J. Nat. Prod.* **2012**, *75*, 920–927.

(123) Anet, E. F. L. J.; Hughes, G. K.; Ritchie, E. *Aust. J. Chem.* **1961**, *14*, 173–174.

(124) Duke, R. K.; Allan, R. D.; Johnston, G. A. R. *J. Nat. Prod.* **1995**, *58*, 1200–1208.

(125) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem. Int. Ed. Eng.* **2011**, *50*, 2716–2719.

(126) Jannic, V.; Gueritte, F.; Laprevote, O.; Serani, L.; Martin, M.-T.; Sevenet, T.; Potier, P. *J. Nat. Prod.* **1999**, *62*, 838–843.

(127) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143–11144.

(128) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963.

(129) Yin, W.-B.; Yu, X.; Xie, X.-L.; Li, S.-M. *Org. Biomol. Chem.* **2010**, *8*, 2430–2438.

(130) Lopez, C. S.; Perez-Balado, C.; Rodriguez-Grana, P.; De Lera, A. R. *Org. Lett.* **2008**, *10*, 77–80.

(131) Movassaghi, M.; Schmidt, M. a; Ashenhurst, J. a *Angew. Chem. Int. Ed. Eng.* **2008**, *47*, 1485–1487.

(132) Kim, J.; Ashenhurst, J. a; Movassaghi, M. *Science* **2009**, *324*, 238–241.

(133) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2010**, *132*, 14376–14378.

(134) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940–14943.

(135) Boyer, N.; Movassaghi, M. *Chem. Sci.* **2012**, *3*, 1798–1803.

(136) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem. Int. Ed. Eng.* **2011**, *50*, 9655–9659.

(137) Wang, Y.; Kong, C.; Du, Y.; Song, H.; Zhang, D.; Qin, Y. *Org. Biomol. Chem.* **2012**, *10*, 2793–2797.

(138) Takiguchi, S.; Iizuka, T.; Kumakura, Y.; Murasaki, K.; Ban, N.; Higuchi, K.; Kawasaki, T. *J. Org. Chem.* **2010**, *75*, 1126–1131.

(139) Iizuka, T.; Takiguchi, S.; Kumakura, Y.; Tsukioka, N.; Higuchi, K.; Kawasaki, T. *Tetrahedron Lett.* **2010**, *51*, 6003–6005.

(140) He, B.; Song, H.; Du, Y.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 298–304.

(141) Koeller, K. M.; Wong, C. H. *Nature* **2001**, *409*, 232–240.

(142) Hult, K.; Berglund, P. *Curr. Opin. Biotechnol.* **2003**, *14*, 395–400.

(143) Yin, W.-B.; Cheng, J.; Li, S.-M. *Org. Biomol. Chem.* **2009**, *7*, 2202–2207.

(144) Yin, W.-B.; Xie, X.-L.; Matuschek, M.; Li, S.-M. *Org. Biomol. Chem.* **2010**, *8*, 1133–1141.

(145) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592–4593.

(146) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315.

(147) Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111–114.

(148) Duong, H. a; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed. Eng.* **2011**, *50*, 463–466.

(149) Allen, A. E.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260–4263.

(150) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782–13785.

(151) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174.

(152) Phipps, R. J.; Mcmurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773–10776.

(153) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem. Int. Ed. Eng.* **2011**, *50*, 458–462.

(154) Uchiyama, M.; Suzuki, T.; Yamazaki, Y. *Nippon Kagaku Kaishi* **1982**, *1982*, 236–241.

(155) Stang, P. J.; Surber, B. W.; Chen, Z. C.; Roberts, K. a.; Anderson, A. G. *J. Am. Chem. Soc.* **1987**, *109*, 228–235.

(156) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095–4112.

(157) Grushin, V. V; Alper, H. *J. Org. Chem.* **1993**, *58*, 4794–4795.

(158) Zhou, T.; Chen, Z.-C. *J. Chem. Res.* **2000**, *2000*, 474–475.

(159) Al-Qahtani, M. H.; Pike, V. W. *J. Chem. Soc. Perkin. Trans. 1* **2000**, 1033–1036.

(160) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241.

(161) Merritt, E. a; Olofsson, B. *Angew. Chem. Int. Ed. Eng.* **2009**, *48*, 9052–9070.

(162) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924–1935.

(163) Eastman, K.; Baran, P. S. *Tetrahedron* **2009**, *65*, 3149–3154.

(164) Liu, C.; Zhang, W.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2012**, *14*, 4525–4527.

(165) Austin, J. F.; Kim, S.; Sinz, C. J.; Xiao, W.; Macmillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482–5487.

(166) Cai, Q.; Liu, C.; Liang, X.; You, S. *Org. Lett.* **2012**, *14*, 4588–4590.

(167) Michaelis, S.; Blechert, S. *Chem. Eur. J.* **2007**, *13*, 2358–2368.

(168) Selvakumar, J.; Makriyannis, A.; Ramanathan, C. R. *Org. Biomol. Chem.* **2010**, *8*, 4056–4058.

(169) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080–2092.

(170) Kobayashi, M.; Kitazawa, M.; Saito, T.; Yamamoto, R.; Harada, H. *Yakugaku Zasshi* **1984**, *104*, 652–658.

(171) Manteca, I.; Etxarri, B.; Ardeo, A.; Arrasate, S.; Osante, I.; Sotomayor, N.; Lete, E. *Tetrahedron* **1998**, *54*, 12361–12378.

(172) Taylor, J. E.; Jones, M. D.; Williams, J. M. J.; Bull, S. D. *Org. Lett.* **2010**, *12*, 5740–5743.

(173) John, E. a; Pollet, P.; Gelbaum, L.; Kubanek, J. *J. Nat. Prod.* **2004**, *67*, 1929–1931.

(174) Stockmann, V.; Eriksen, K. L.; Fiksdahl, A. *Tetrahedron* **2008**, *64*, 11180–11184.

(175) Barton, J. W.; Lapham, D. J.; Rowe, D. J. *J. Chem. Soc. Perkin. Trans. 1* **1985**, *1985*, 131–133.

(176) Morrison, M. D.; Hanthorn, J. J.; Pratt, D. *Org. Lett.* **2009**, *11*, 1051–1054.

(177) Porcheddu, A.; Giacomelli, G.; Piredda, I.; Carta, M.; Nieddu, G. *Eur. J. Org. Chem.* **2008**, *2008*, 5786–5797.

(178) Cheng, G.; Wang, X.; Bao, H.; Cheng, C.; Liu, N.; Hu, Y. *Org. Lett.* **2012**, *14*, 1062–1065.

(179) Donohoe, T. J.; Chiu, J. Y. K.; Thomas, R. E. *Org. Lett.* **2007**, *9*, 421–424.

(180) Nativi, C.; Cacciarini, M.; Francesconi, O.; Vacca, A.; Moneti, G.; Ienco, A.; Roelens, S. *J. Am. Chem. Soc.* **2007**, *129*, 4377–4385.

(181) Zhao, Y.; Sinnott, M. L. *Bioorg. Med. Chem.* **2000**, *8*, 917–924.

(182) Iliefski, T.; Li, S.; Lundquist, K. *Acta Chem. Scand.* **1998**, *52*, 1177–1182.

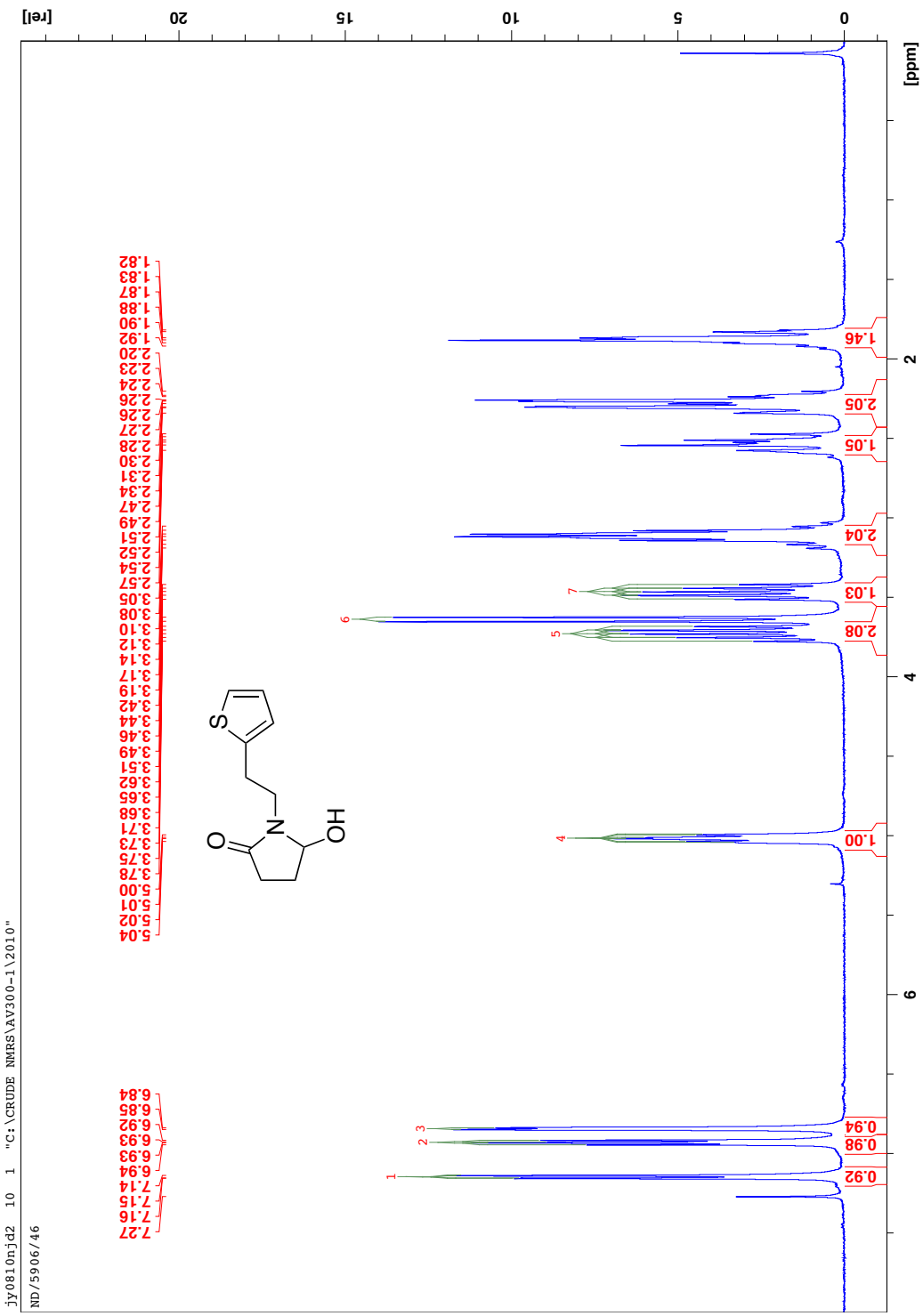
(183) Miyazawa, M.; Hishama, M. *J. Agric. Food Chem.* **2003**, *51*, 6413–6422.

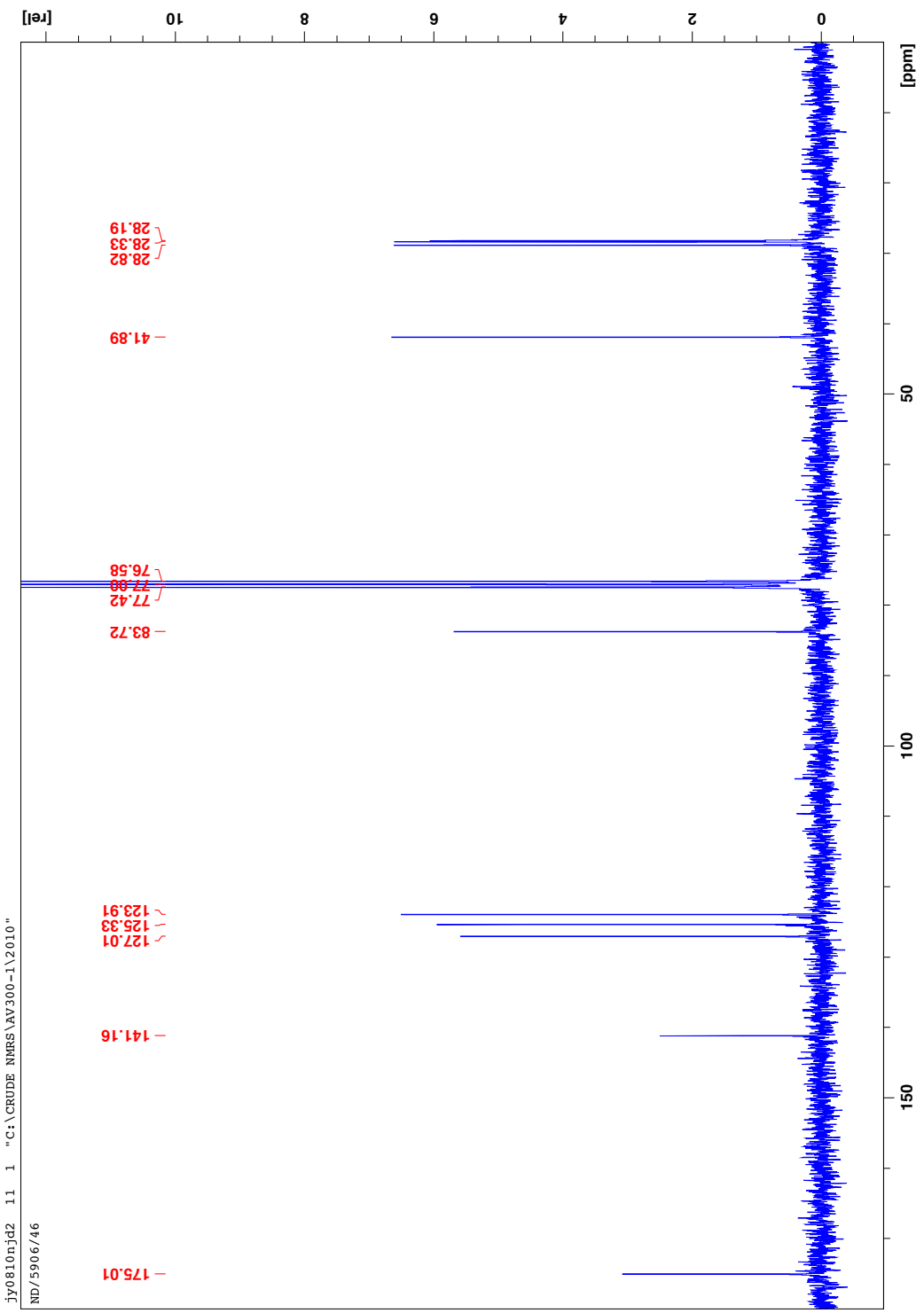
(184) Daubresse, N.; Francesch, C.; Mhamdi, F.; Rolando, C. *Synthesis* **1994**, *1994*, 369–371.

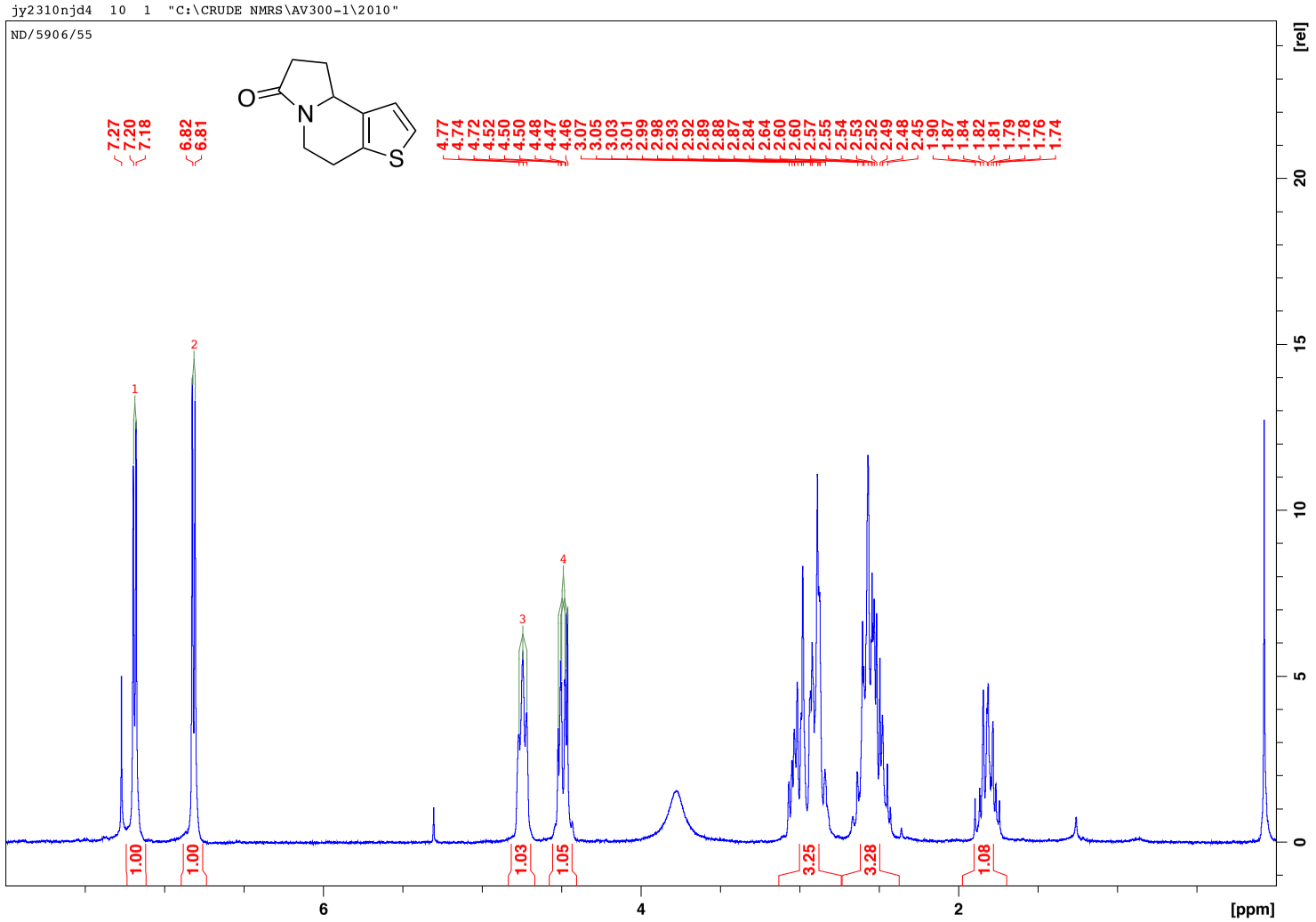
(185) Yadav, J. S.; Pandurangam, T.; Reddy, V. V. B.; Reddy, B. V. S. *Synthesis* **2010**, *2010*, 4300–4306.

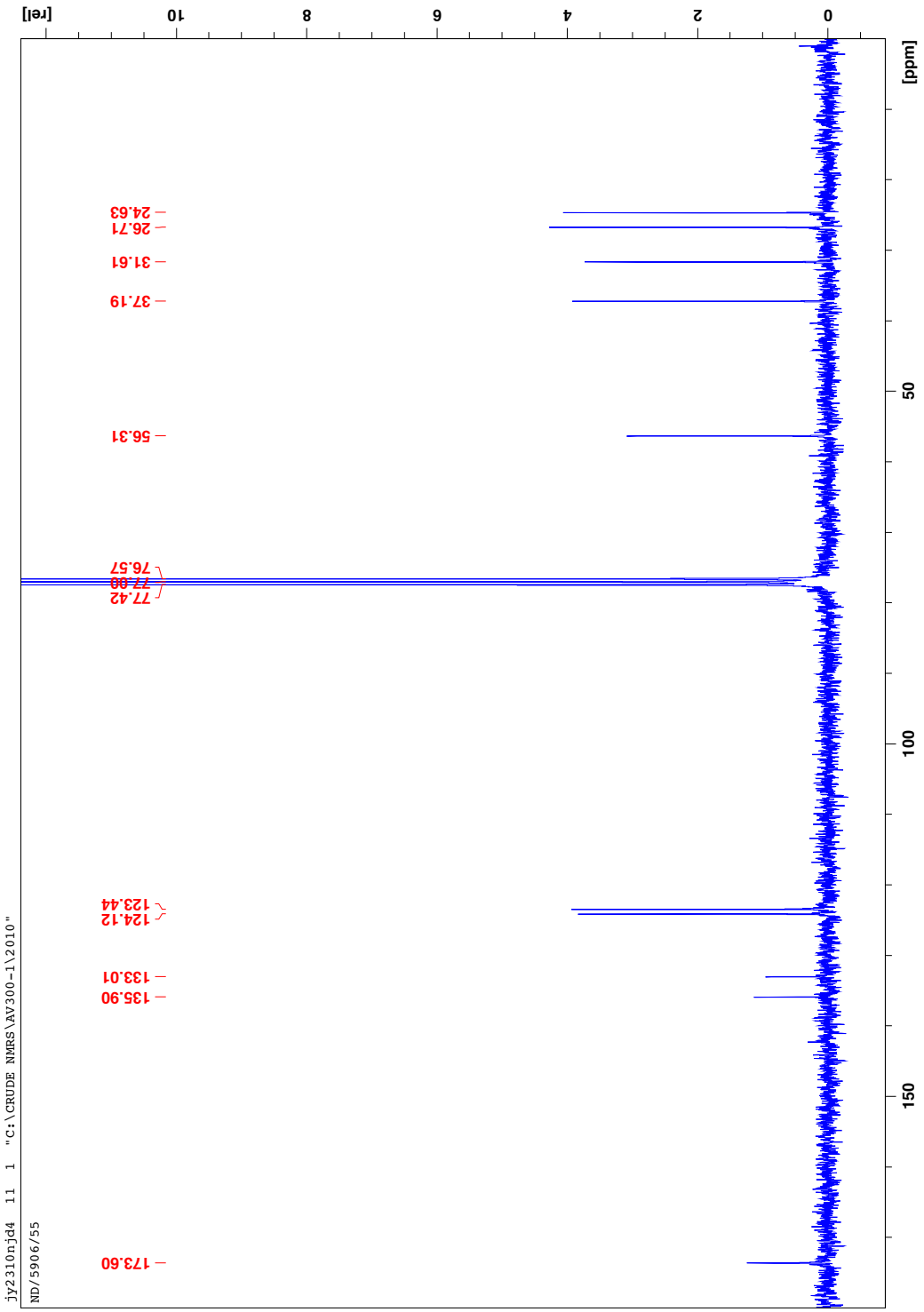
APPENDIX

^{1}H & ^{13}C NMR Spectra of Novel Compounds




jy0810njd2 11 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/46
[rel]
0
2
4
6
8
10
[ppm]
50
100
150
175.01
141.16
127.01
125.33
123.91
83.72
77.42
77.08
76.58
41.89
28.82
28.33
28.19

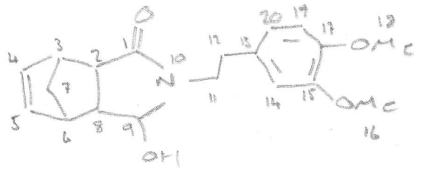

jy2310njd4 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/55
O
N
S
7.27
7.20
7.18
6.82
6.81
4.77
4.74
4.72
4.52
4.50
4.50
4.48
4.47
4.46
3.07
3.05
3.03
3.01
2.99
2.98
2.93
2.92
2.89
2.88
2.87
2.84
2.64
2.60
2.60
2.57
2.55
2.54
2.53
2.52
2.49
2.48
2.45
1.90
1.87
1.84
1.82
1.81
1.79
1.78
1.76
1.74
1
2
3
4
1.00
1.00
1.03
1.05
3.25
3.28
1.08
6
4
2
[ppm]
[rel]
0
5
10
15
20

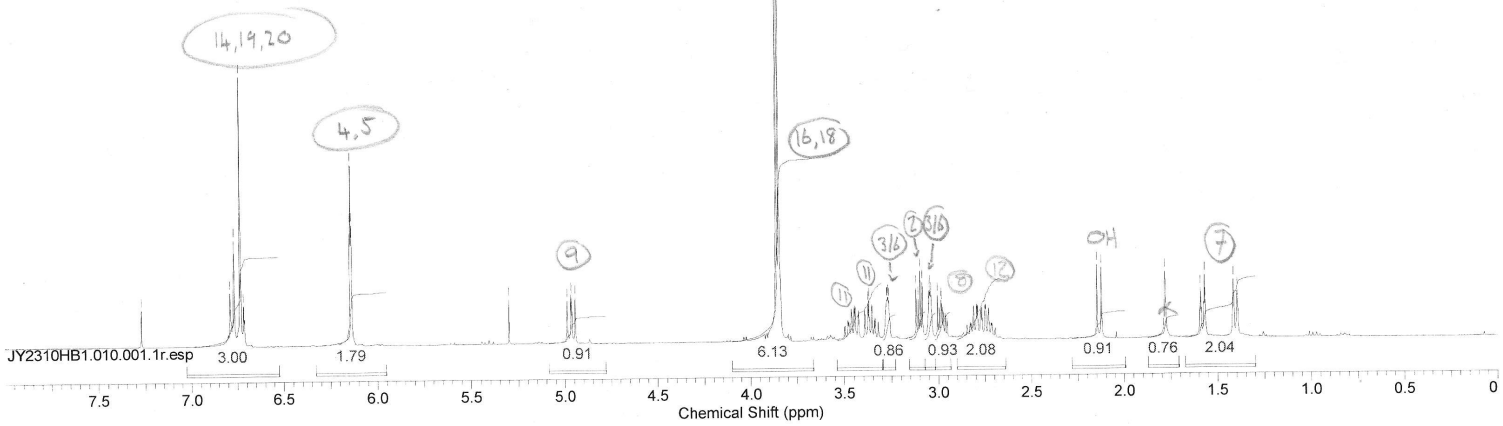

jy2310njd4 11 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/55
[rel]
0
2
4
6
8
10
[ppm]
50
100
150
173.60
135.90
133.01
124.12
123.44
77.42
77.00
76.57
56.31
37.19
31.61
26.71
24.63

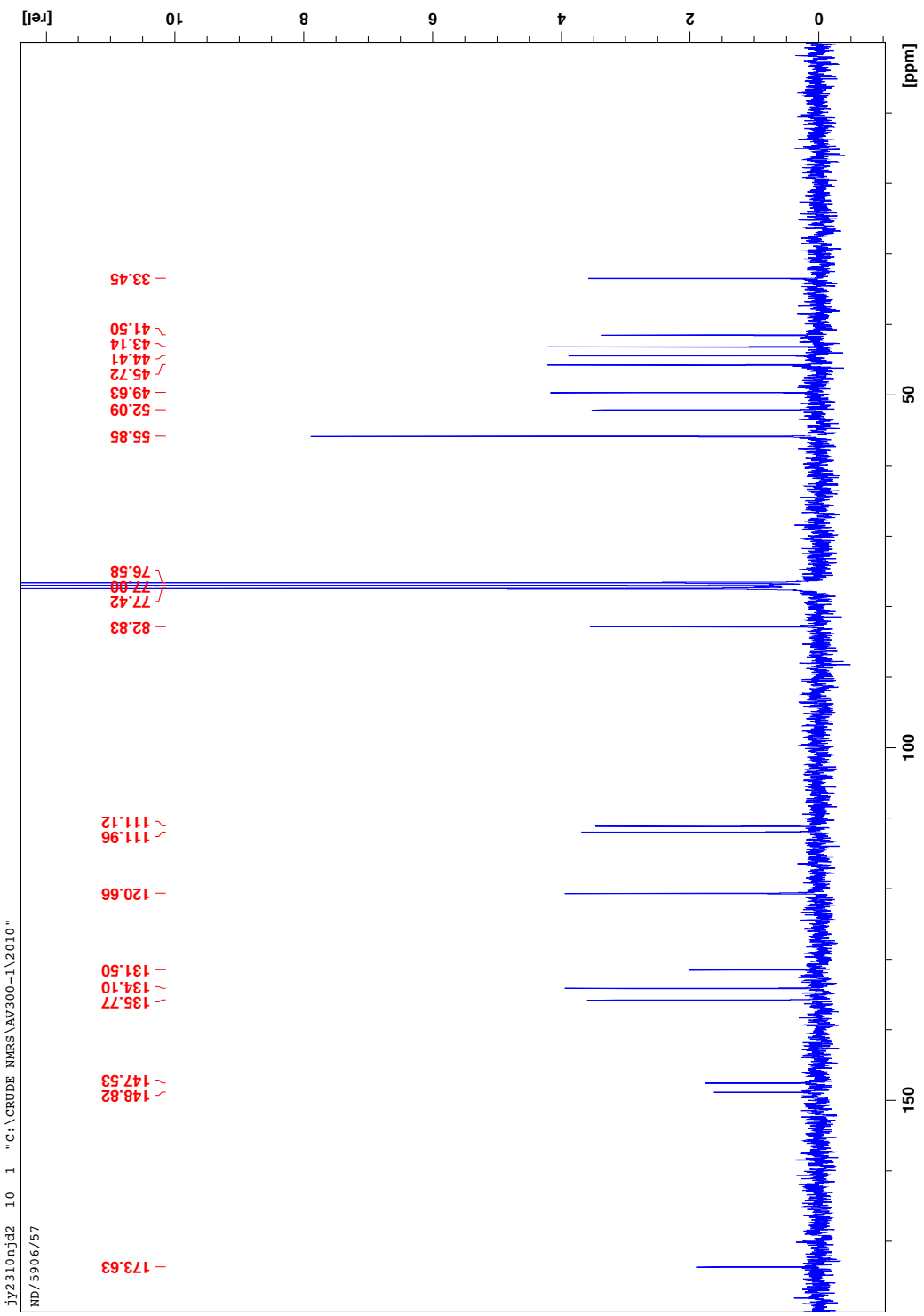
26/07/2010 13:11:44

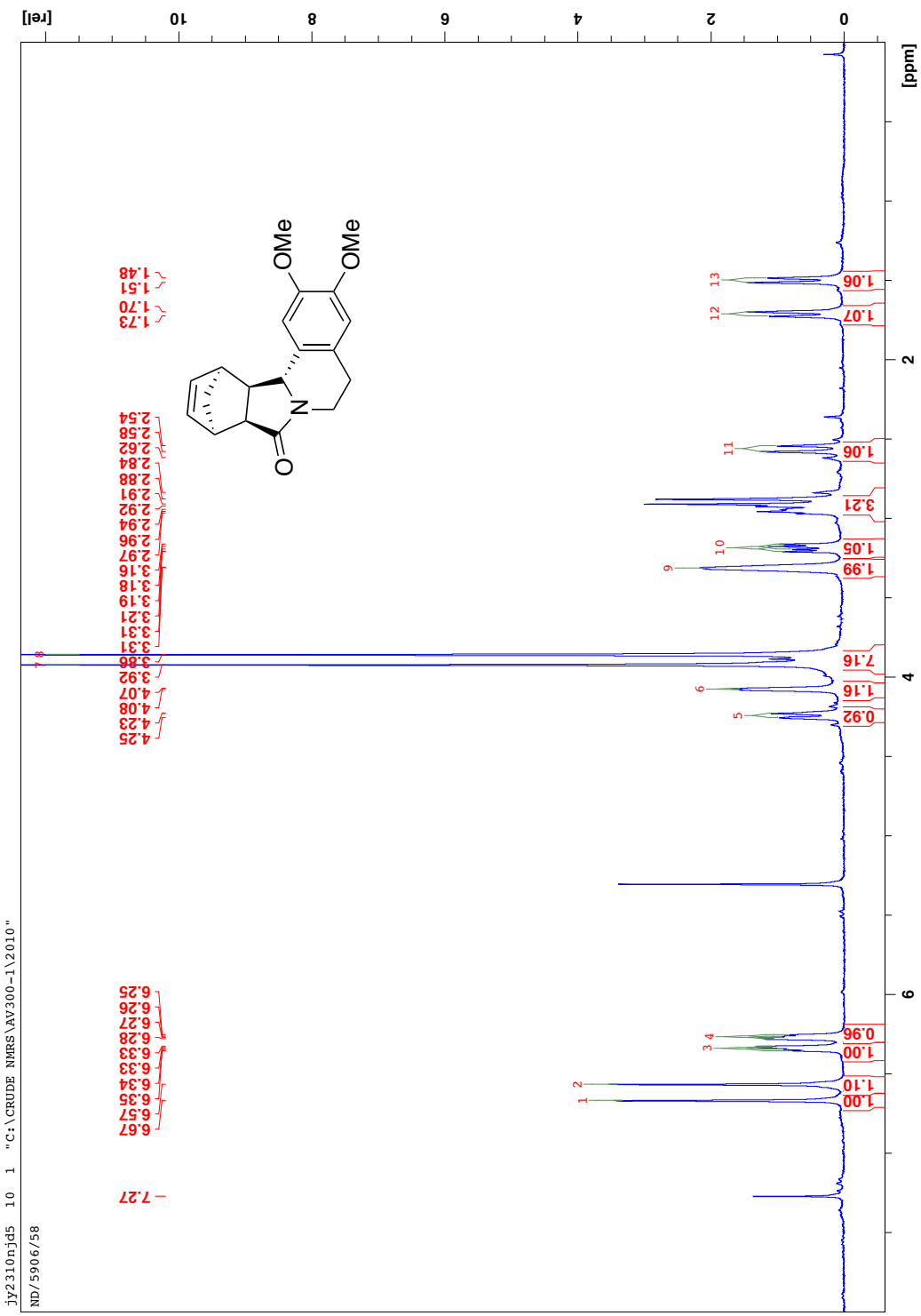
Acquisition Time (sec)	1.9923	*Comment*	ND/5906/57	*Date*	23 Jul 2010 16:53:20			*Date Stamp*	23 Jul 2010 16:53:20
File Name	\\NMR400\NMR400Z\GAN\NMR\JY2310HB1\10\PDATA\1\1r					*Frequency (MHz)*	400.13	*Nucleus*	1H
Number of Transients	16	*Origin*	spect	*Original Points Count*	16384	*Owner*	jms	*Points Count*	16384
Pulse Sequence	zg30	*Receiver Gain*	228.10	*SW(cyclical) (Hz)*	8223.68	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	2453.9424	*Spectrum Type*	STANDARD	*Sweep Width (Hz)*	8223.18	*Temperature (degree C)*	27.000		

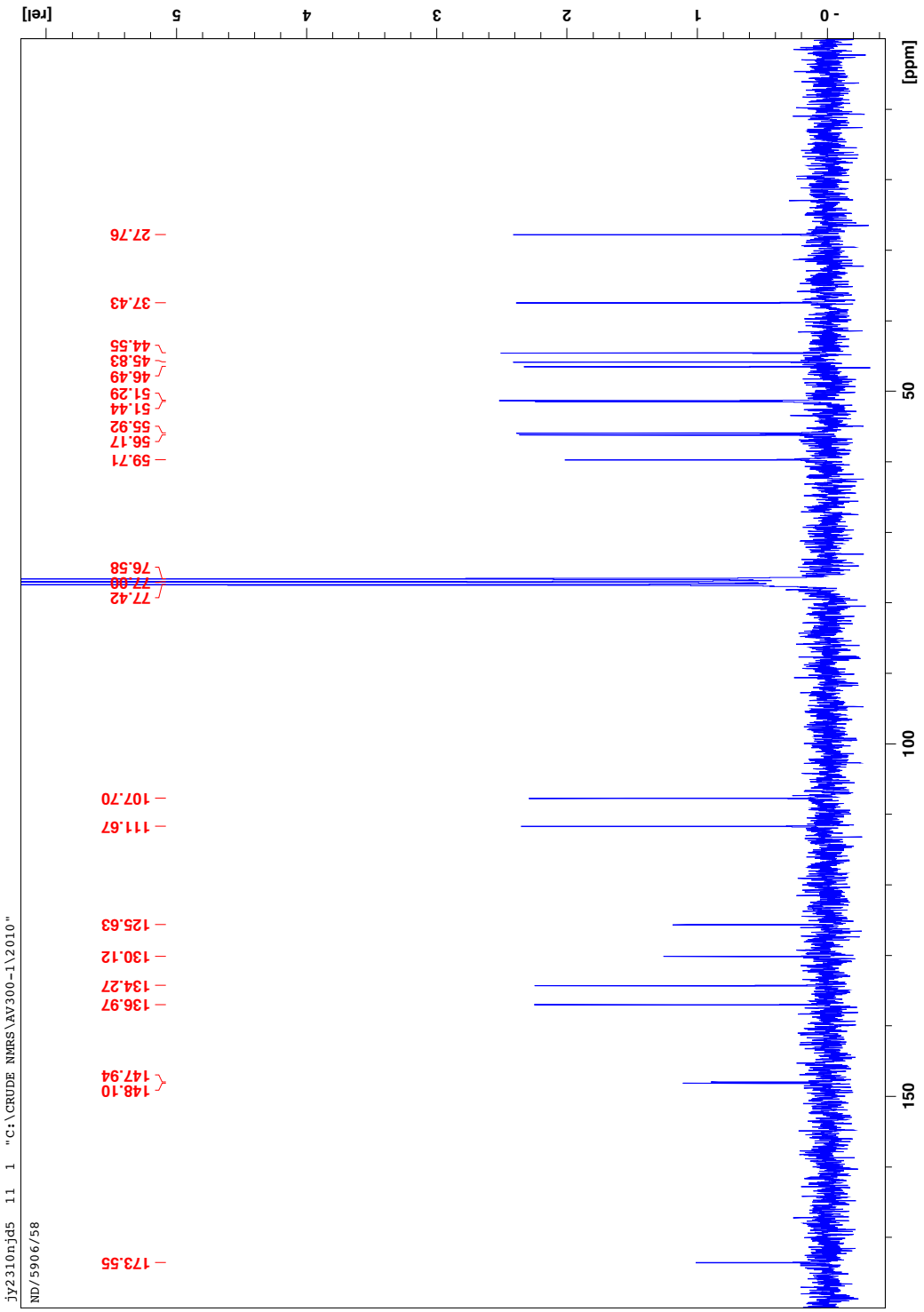
7.27 | 6.79 6.77 6.74 6.72 | 6.14 6.14 6.14 | 5.30 | 4.99 4.97 4.96 4.94 | 3.86 3.85 | 3.37 3.27 3.27 3.27 3.12 3.10 3.08 3.05 3.04 3.04 3.00 | 2.15 2.12 | 1.78 1.59 1.57 1.56 1.41 1.39

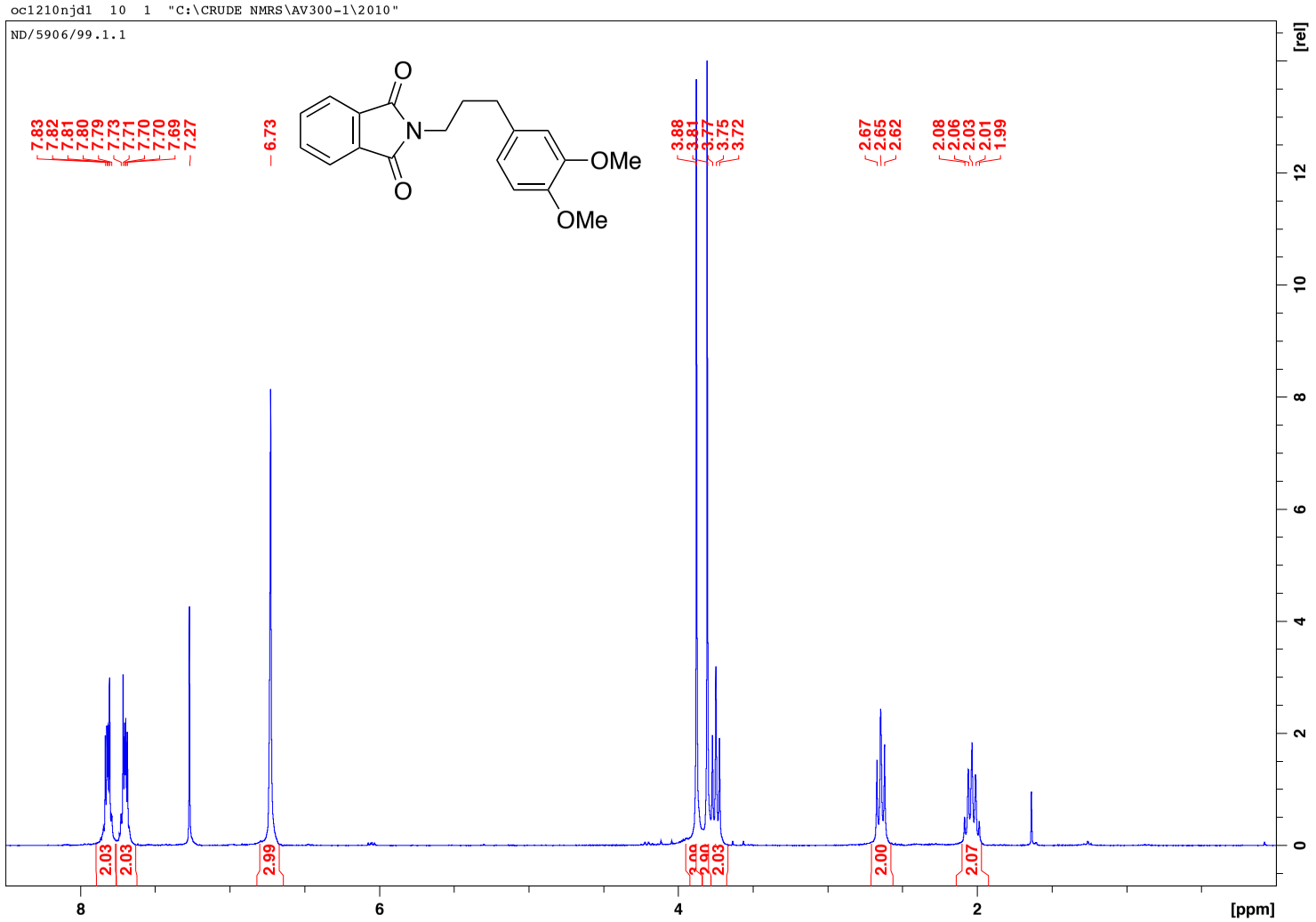


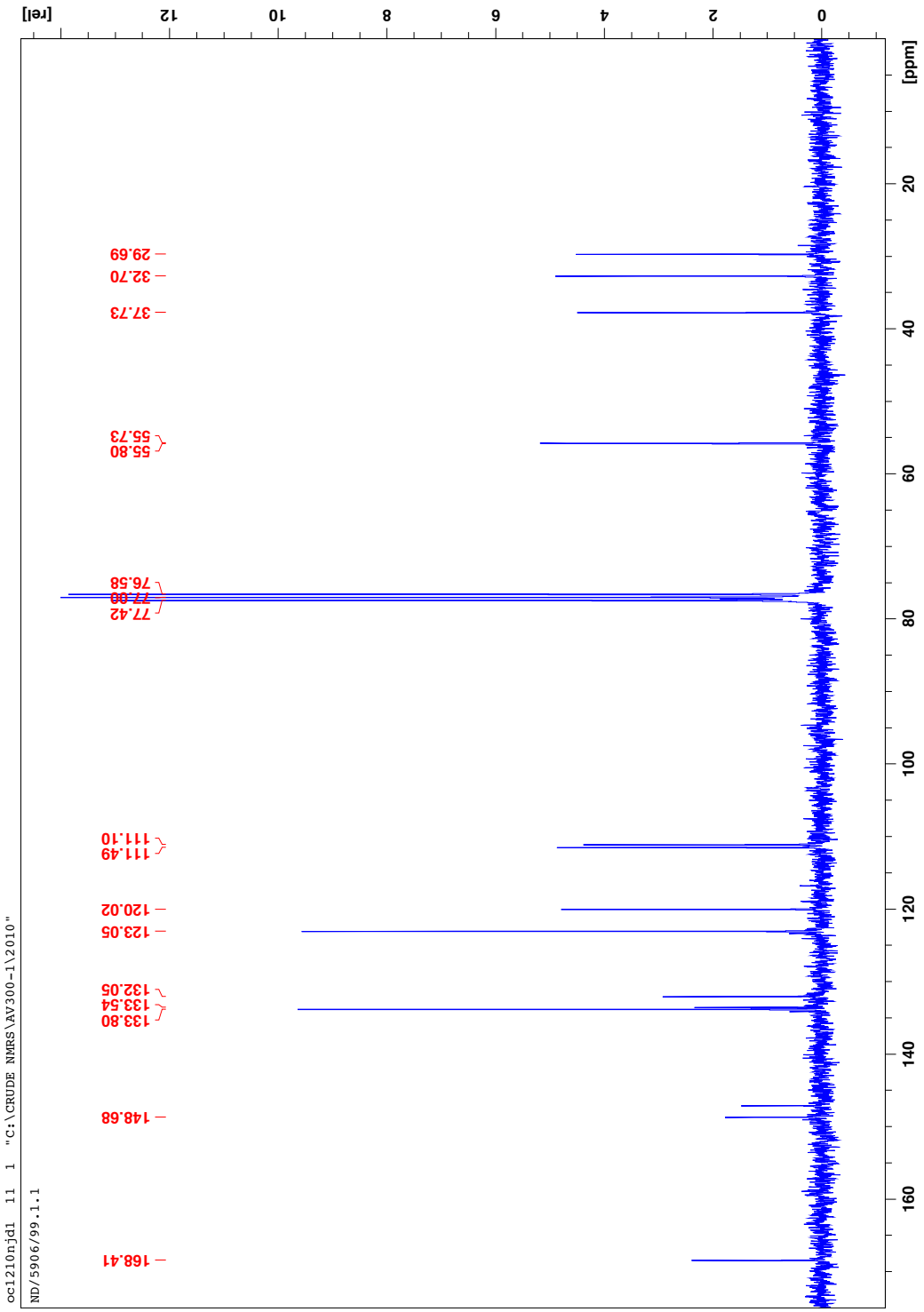


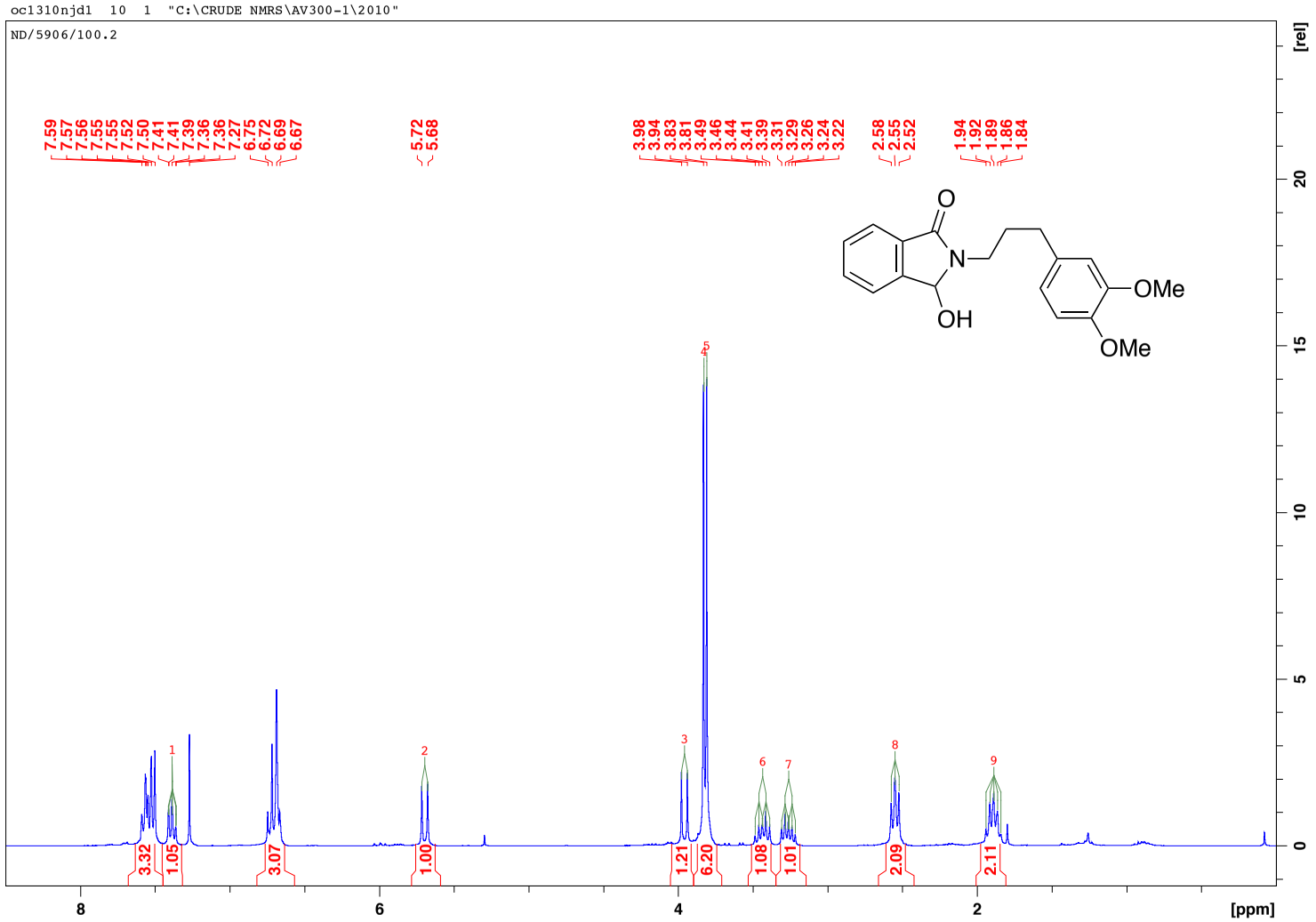

jy2310njd2 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/57
[rel]
0
2
4
6
8
10
[ppm]
50
100
150
173.63
148.82
147.53
135.77
134.10
131.50
120.66
111.96
111.12
82.83
77.42
77.08
76.58
55.85
52.09
49.63
45.72
44.41
43.14
41.50
33.45

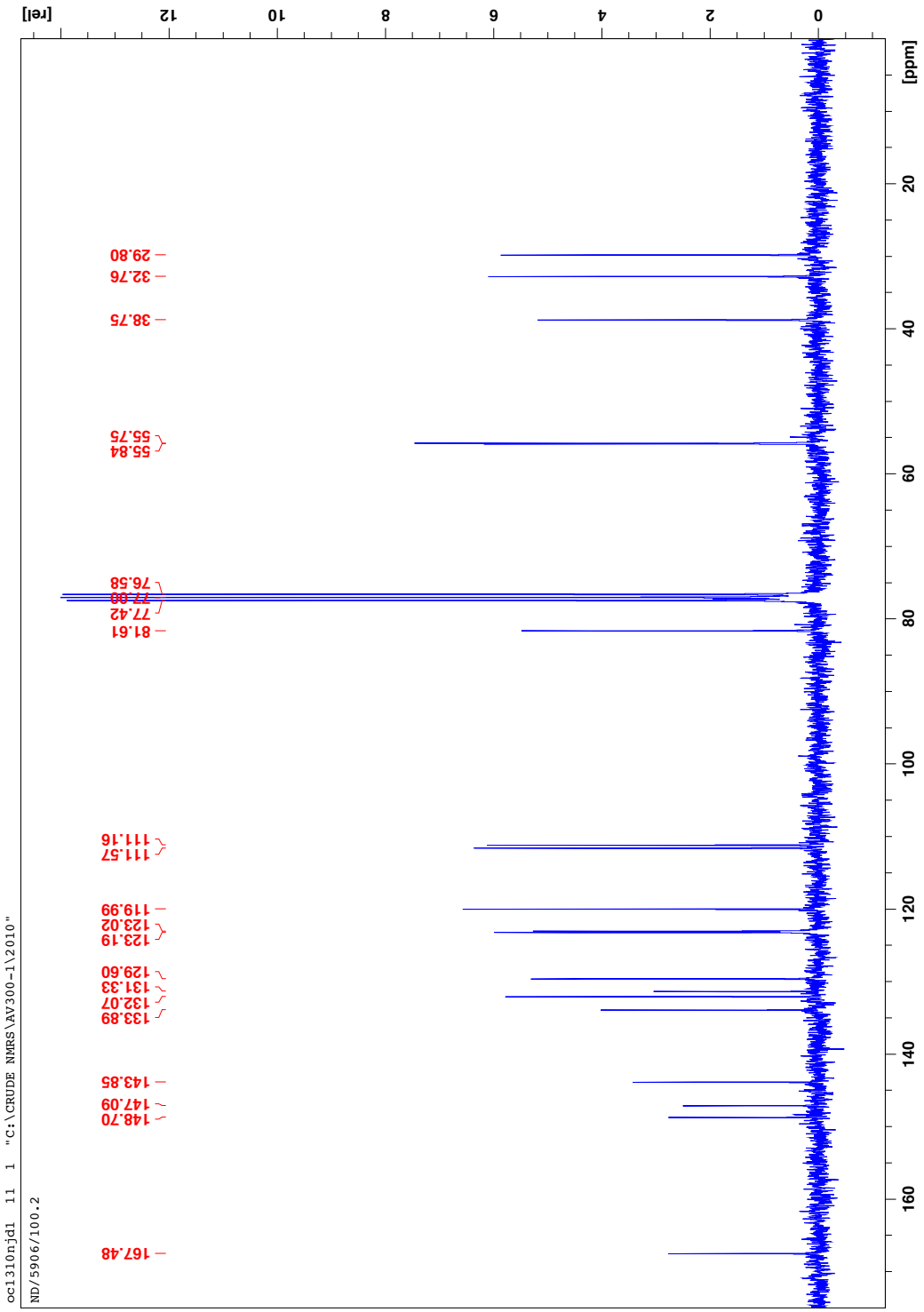

jy2310mjd5 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/59906/58
OMe
OMe
N
O
[ppm]
[rel]

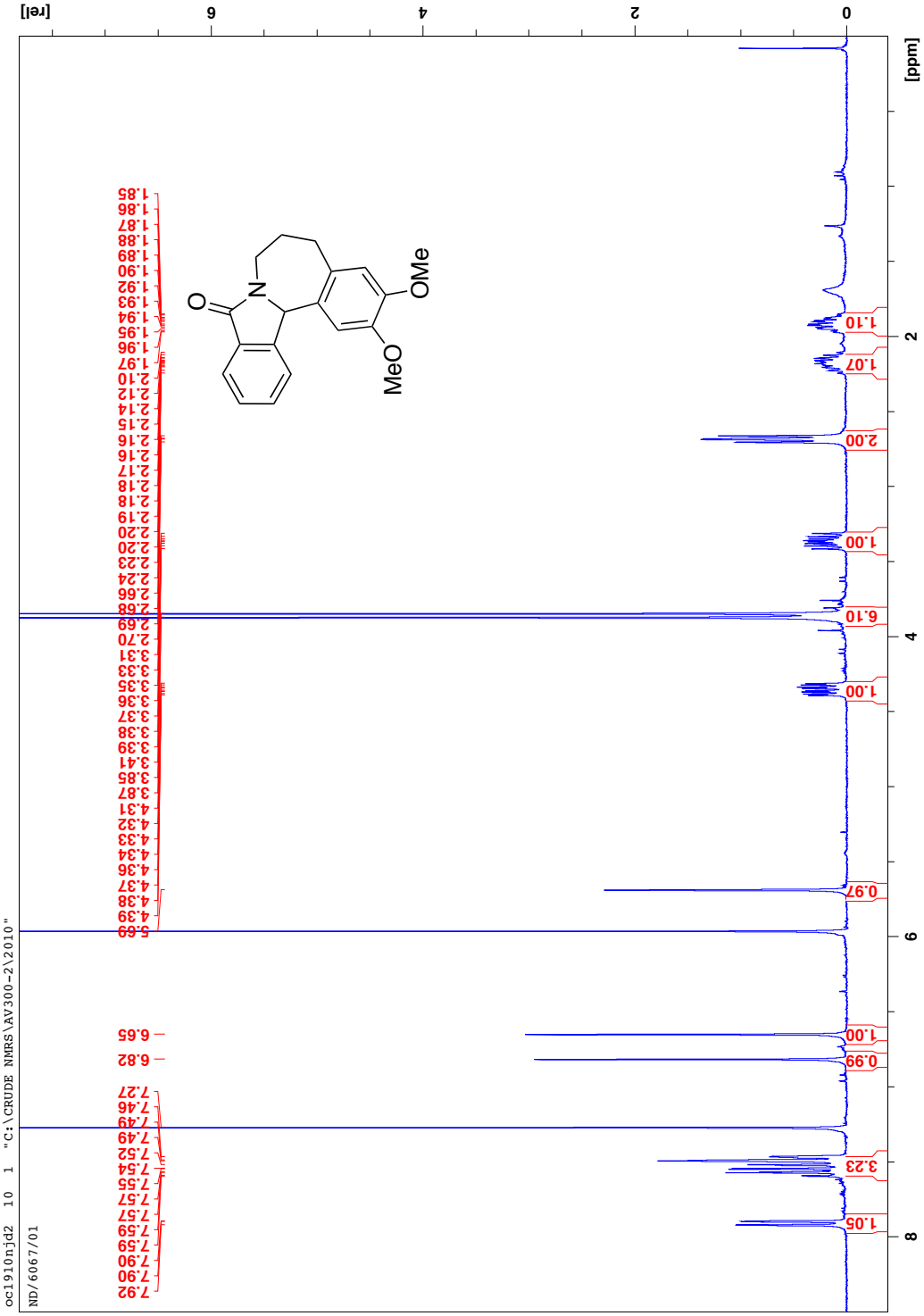

jy2310njd5 11 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/58
[rel]
0
1
2
3
4
5
[ppm]
50
100
150
173.55
148.10
147.94
136.97
134.27
130.12
125.63
111.67
107.70
77.42
77.08
76.58
59.71
56.17
55.92
51.44
51.29
46.49
45.83
44.55
37.43
27.76

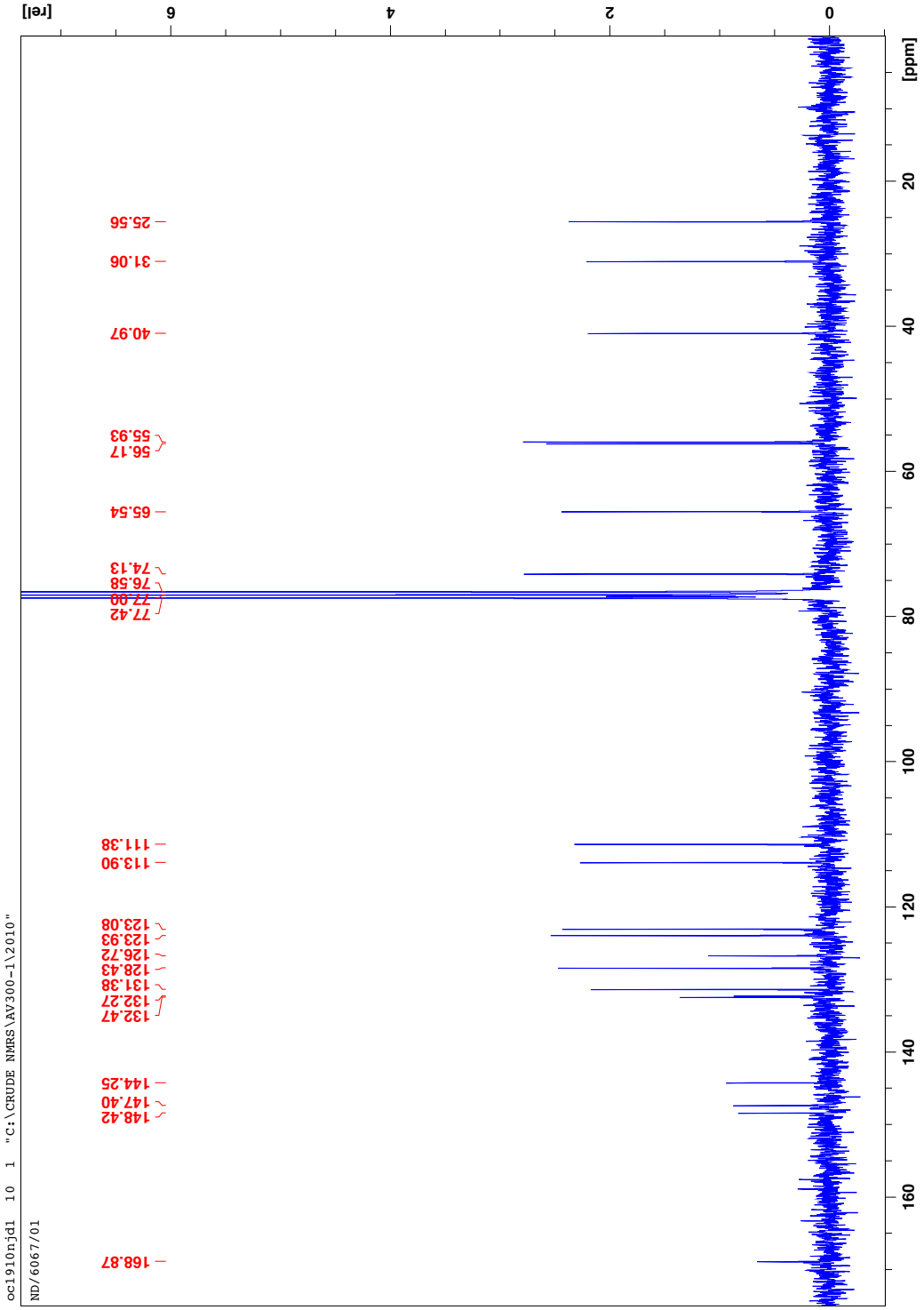

oc1210njd1 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/99.1.1
7.83
7.82
7.81
7.80
7.79
7.73
7.71
7.70
7.70
7.69
7.27
6.73
3.88
3.81
3.77
3.75
3.72
2.67
2.65
2.62
2.08
2.06
2.03
2.01
1.99
O
N
O
OMe
OMe
2.03
2.03
2.99
2.00
2.07
[rel]
[ppm]

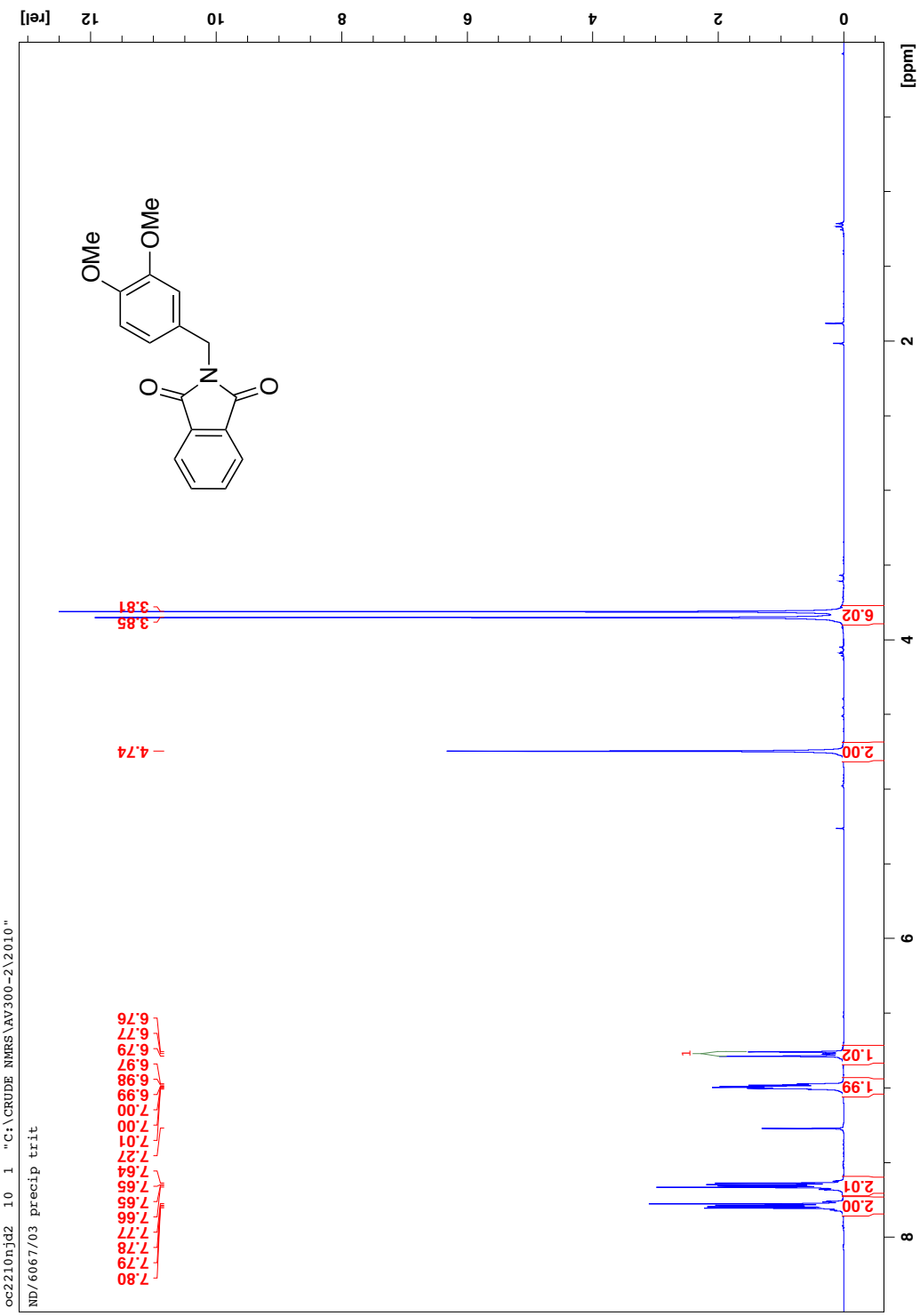

oc1210njd1 11 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/99.1.1
168.41
148.68
133.80
133.54
132.05
123.05
120.02
111.49
111.10
77.42
77.00
76.58
55.80
55.73
37.73
32.70
29.69
[ppm]
[rel]

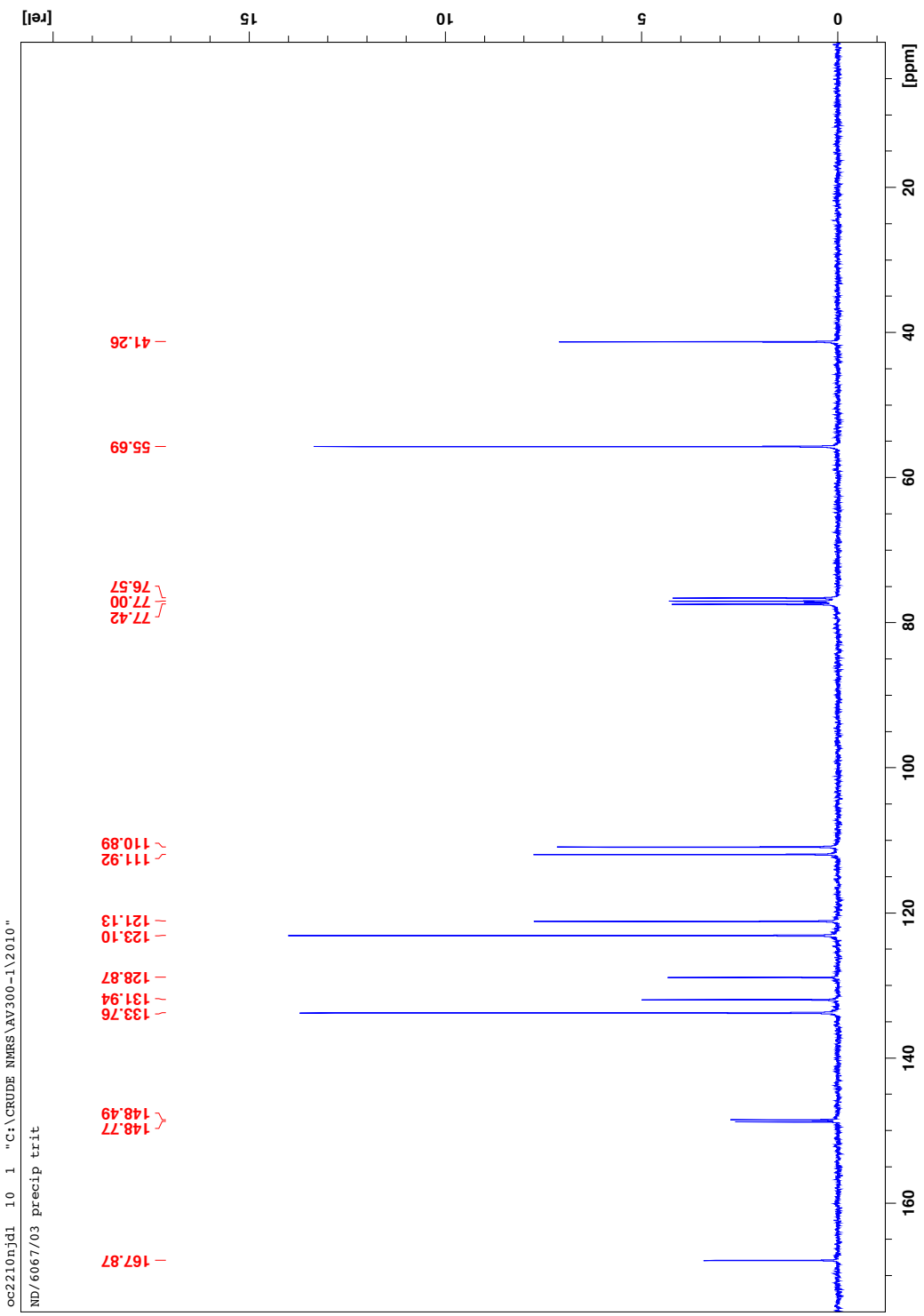

oc1310njd1 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/100.2
7.59 7.57 7.56 7.55 7.52 7.50 7.41 7.41 7.39 7.36 7.36 7.27 6.75 6.72 6.69 6.67
5.72 5.68
3.98 3.94 3.83 3.81 3.49 3.46 3.44 3.41 3.39 3.31 3.29 3.26 3.24 3.22
2.58 2.55 2.52
1.94 1.92 1.89 1.86 1.84
O
N
OH
OMe
OMe
3.32 1.05 3.07 1.00 1.21 6.20 1.08 1.01 2.09 2.11
8 6 4 2 [ppm]
0 5 10 15 20 [rel]

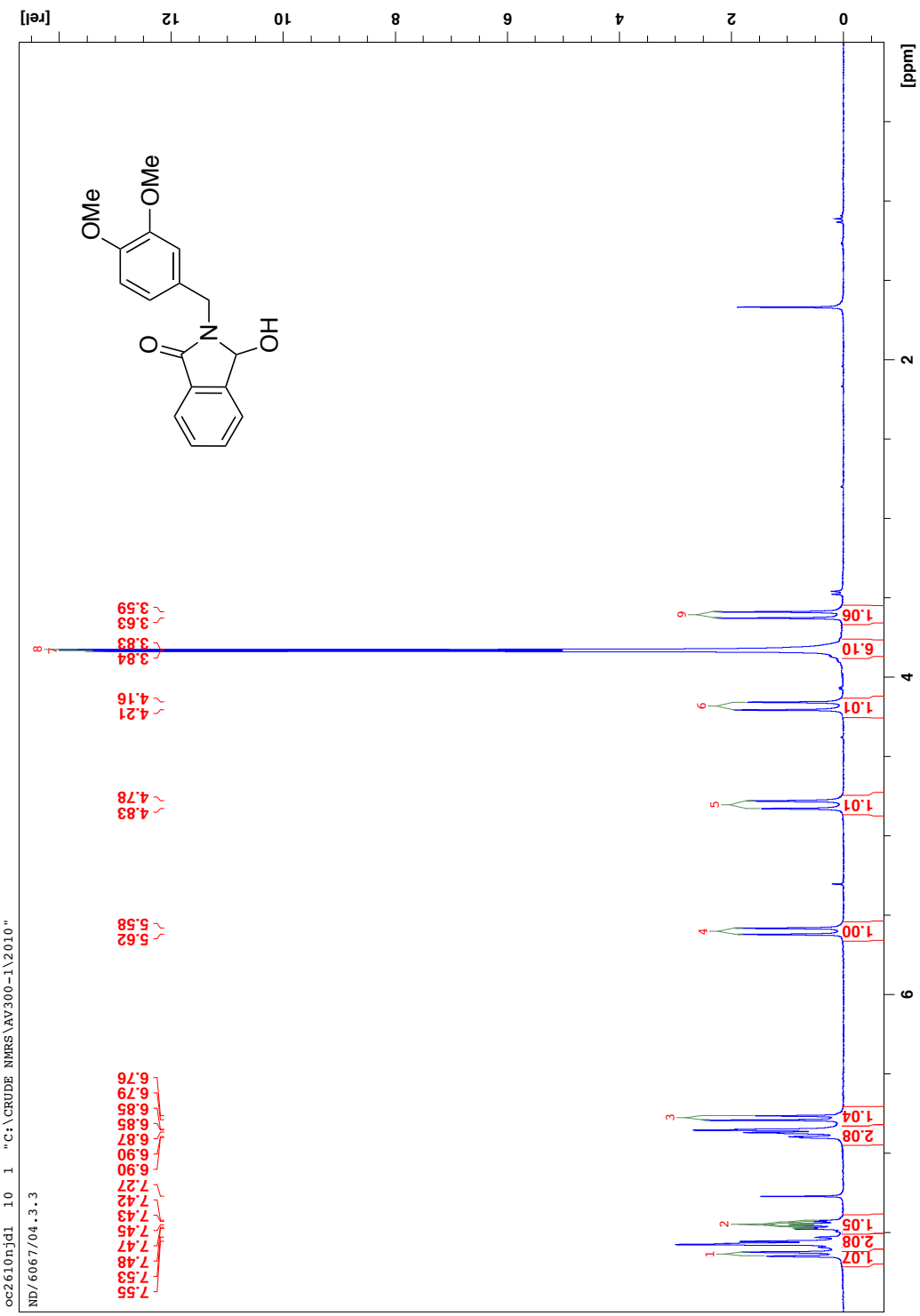

oc1310njd1 11 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/5906/100.2
[rel]
[ppm]
167.48
148.70
147.09
143.85
133.89
132.07
131.33
129.60
123.19
123.02
119.99
111.57
111.16
81.61
77.42
77.00
76.58
55.84
55.75
38.75
32.76
29.80

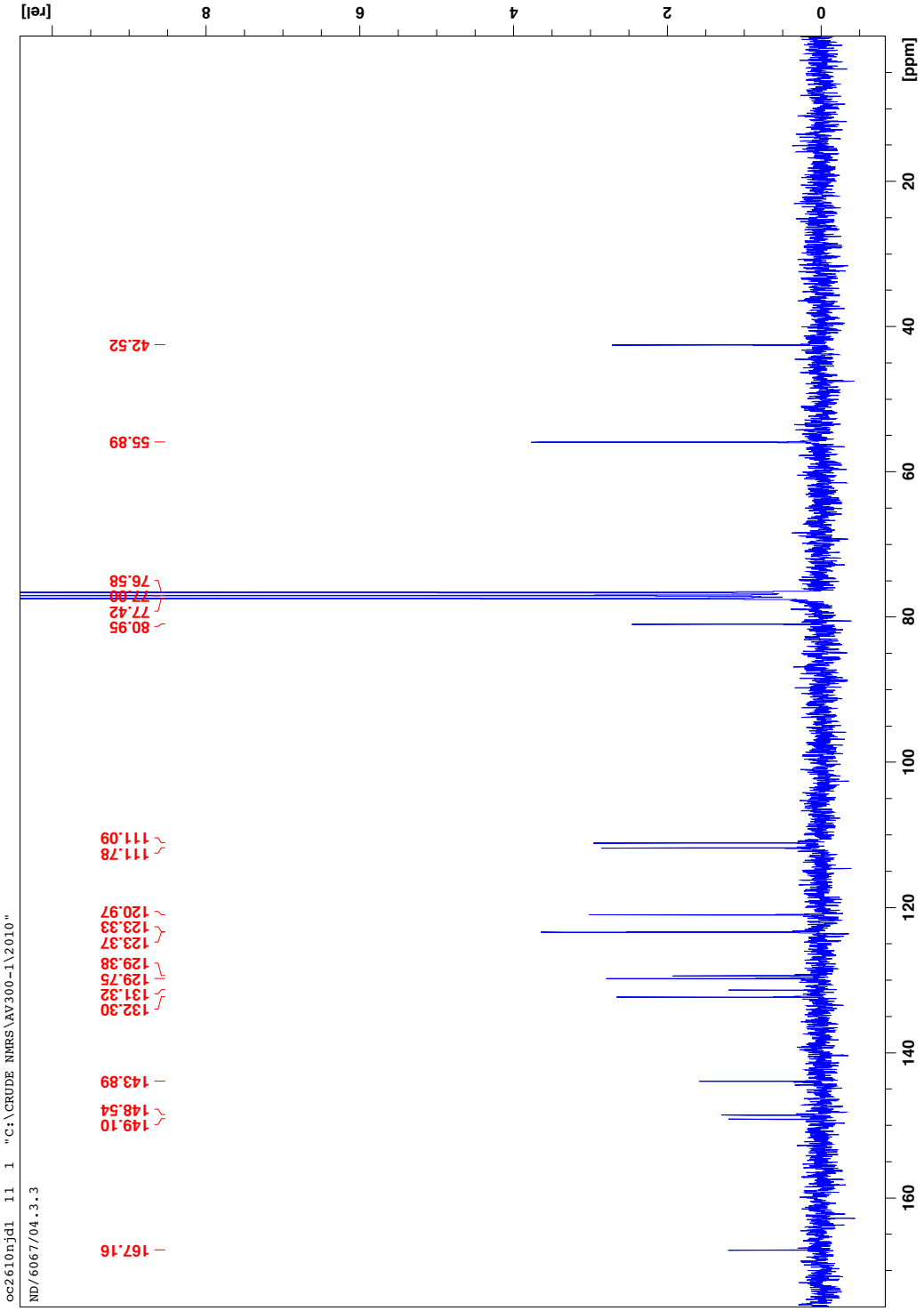

oc1910mjd2 10 1 "C:\CRUDE NMRS\AV300-2\2010"
ND/6067/01
[rel]
[ppm]
OMe
MeO
O
N

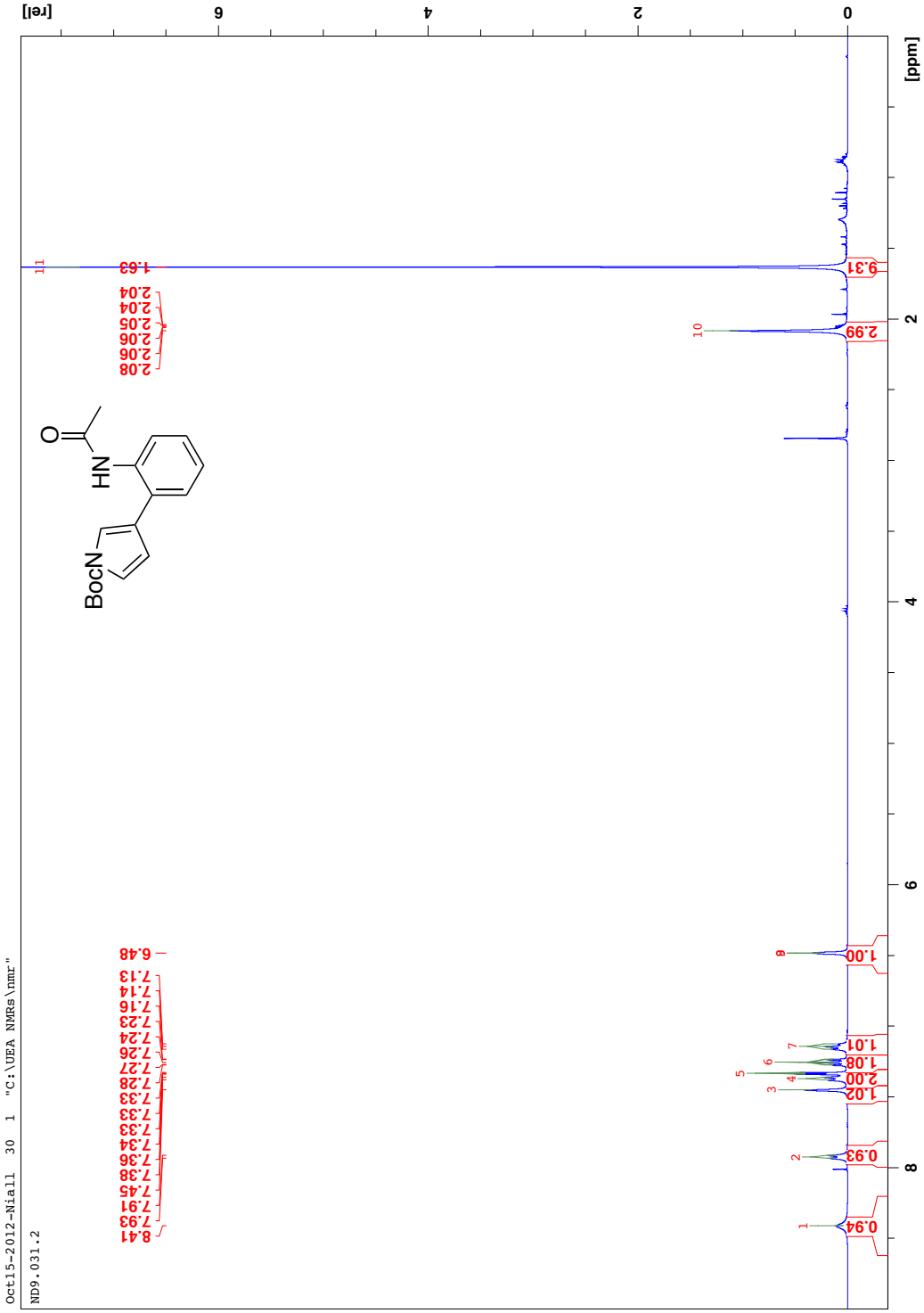

oc1910njd1 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/6067/01
168.87
148.42
147.40
144.25
132.47
132.27
131.38
128.43
126.72
123.93
123.08
113.90
111.38
77.42
77.00
76.58
74.13
65.54
56.17
55.93
40.97
31.06
25.56
[ppm]
[rel]

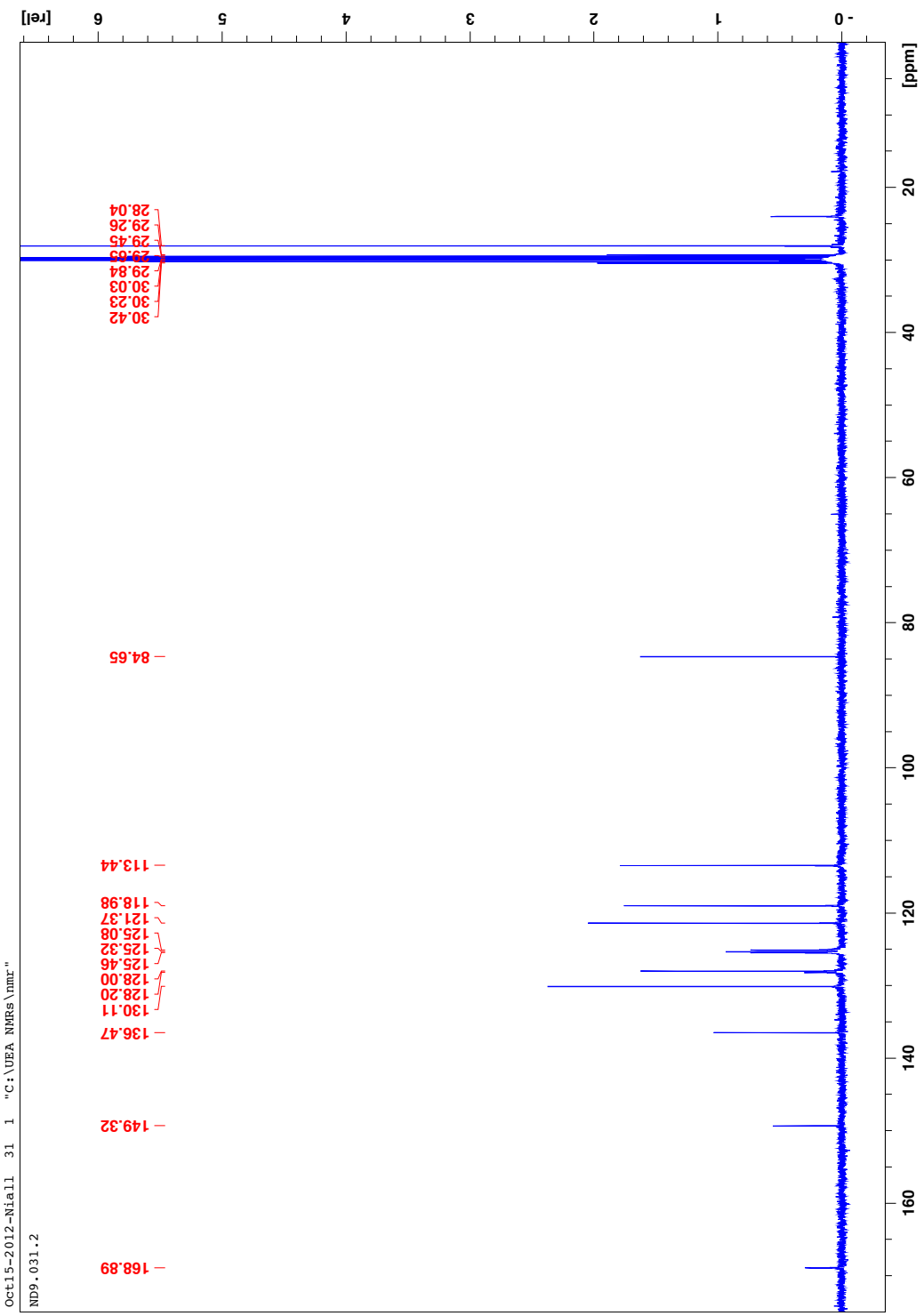

oc2210mjd2 10 1 "C:\CRUDE NMRS\AV300-2\2010"
ND/6067/03 precip trit
OMe
OMe
O
N
O
[rel]
[ppm]
0
2
4
6
8
10
12
3.85
3.81
4.74
7.80
7.79
7.78
7.77
7.66
7.65
7.65
7.64
7.27
7.01
7.00
7.00
6.99
6.98
6.97
6.79
6.77
6.76
6.02
2.00
1.02
1.99
2.01
2.00

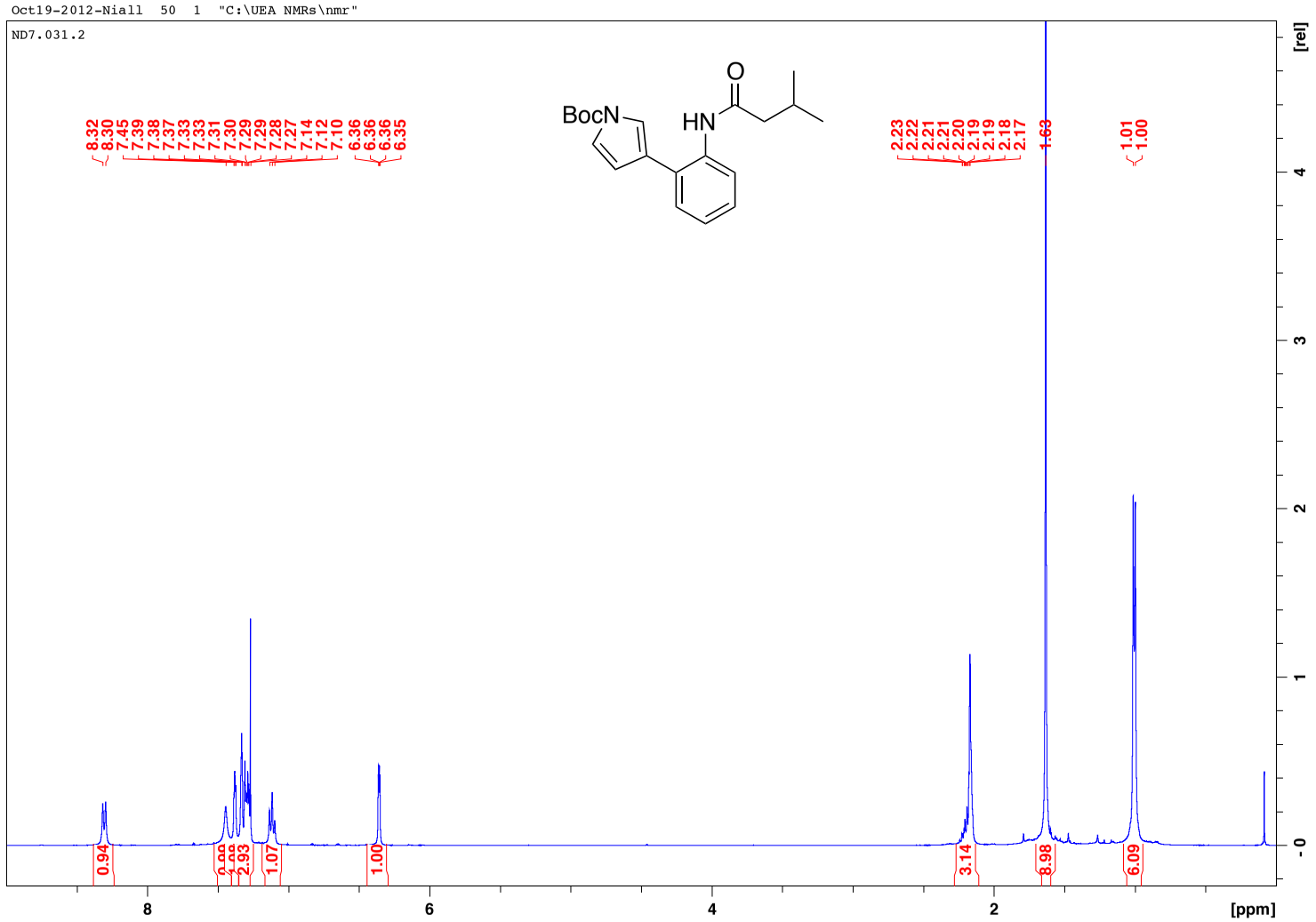

oc2210njd1 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/6067/03 precip trit
167.87
148.77
148.49
133.76
131.94
128.87
123.10
121.13
111.92
110.89
77.42
77.00
76.57
55.69
41.26
[rel]
0
5
10
15
[ppm]
20
40
60
80
100
120
140
160

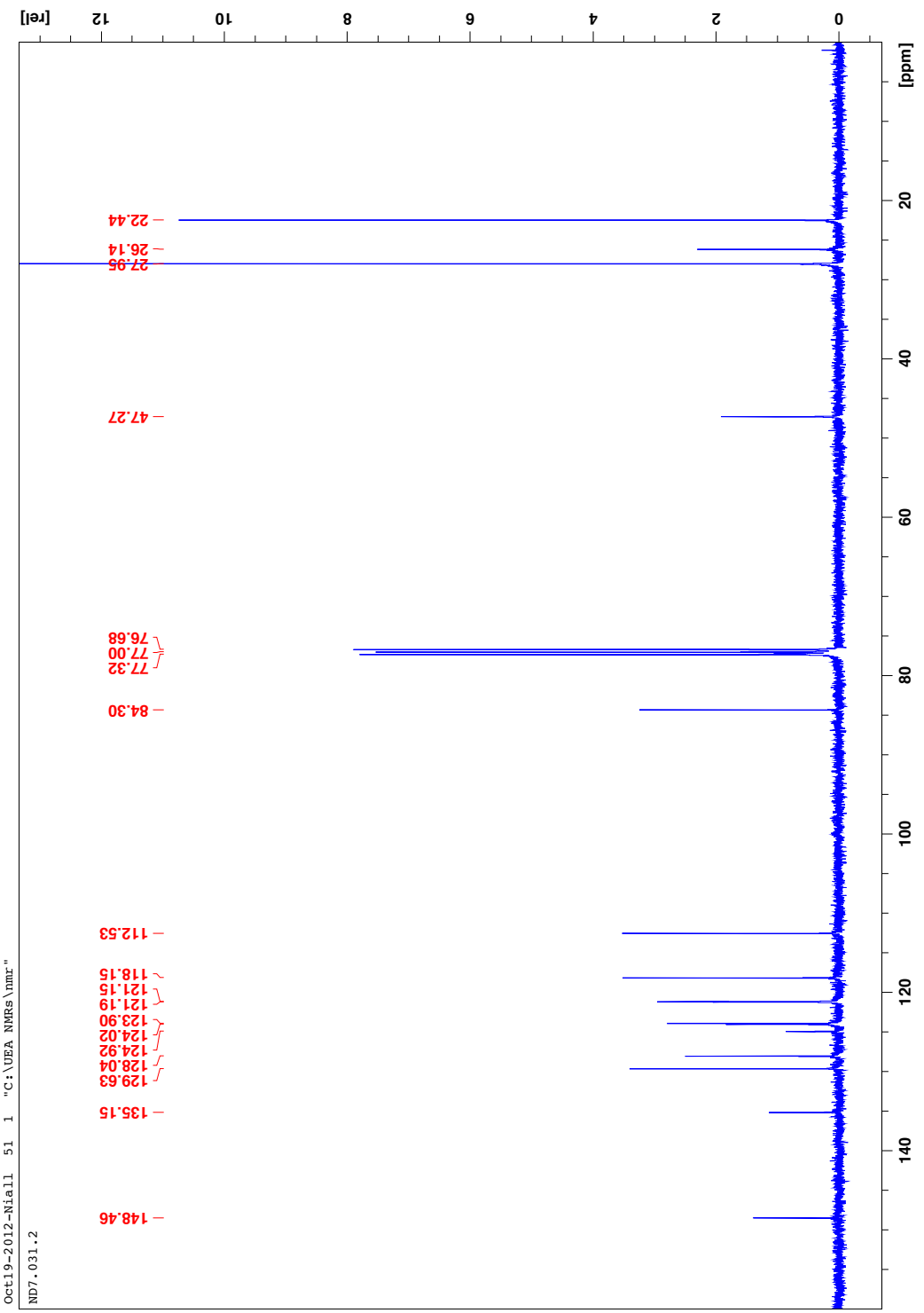

oc2610mjd1 10 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/6067/04.3.3
OMe
OMe
N
O
OH
[ppm]
[rel]

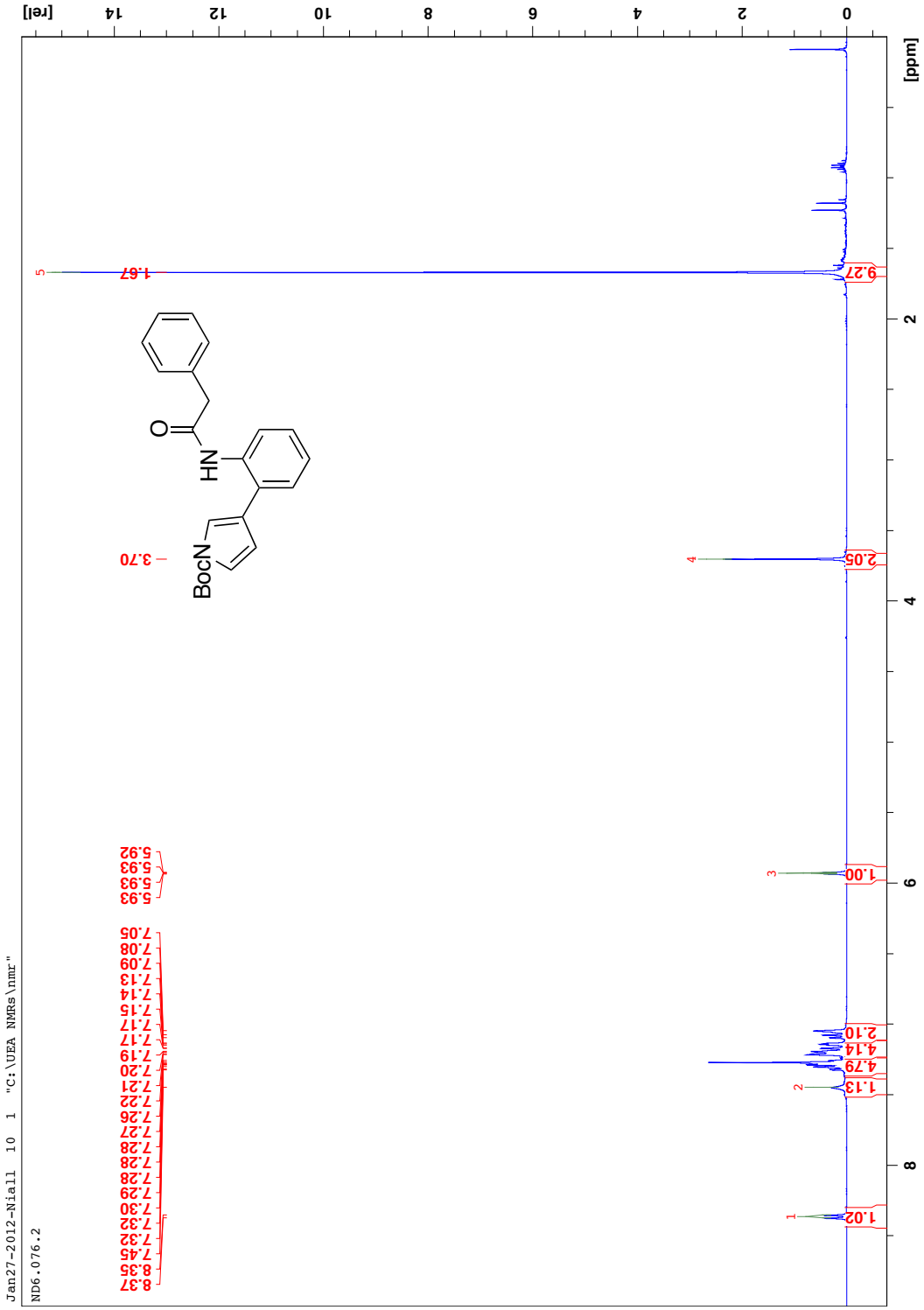

oc2610njd1 11 1 "C:\CRUDE NMRS\AV300-1\2010"
ND/6067/04.3.3
[rel]
0
2
4
6
8
[ppm]
20
40
60
80
100
120
140
160
167.16
149.10
148.54
143.89
132.30
131.32
129.75
129.38
123.37
123.33
120.97
111.78
111.09
80.95
77.42
77.00
76.58
55.89
42.52

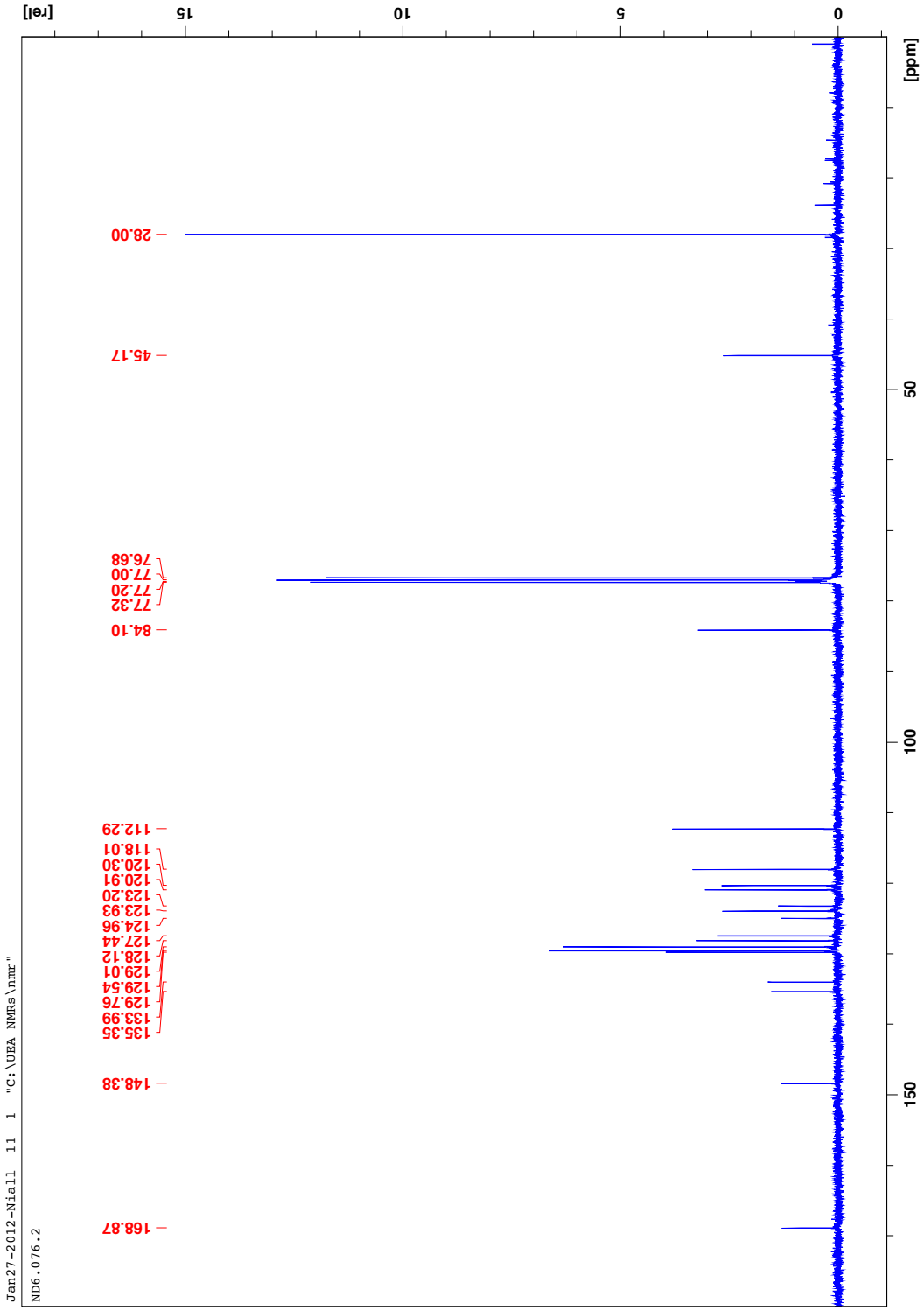

Oct15-2012-Niall 30 1 "C:\UEA NMRs\nmr"
ND9.031.2
[rel]
[ppm]
BocN
HN
O
0.94
0.93
1.02
2.00
1.08
1.01
1.00
2.99
9.31
1.63
2.08
2.06
2.06
2.05
2.04
2.04
8.41
7.93
7.91
7.45
7.38
7.36
7.34
7.33
7.33
7.33
7.28
7.27
7.26
7.24
7.23
7.16
7.14
7.13
6.48

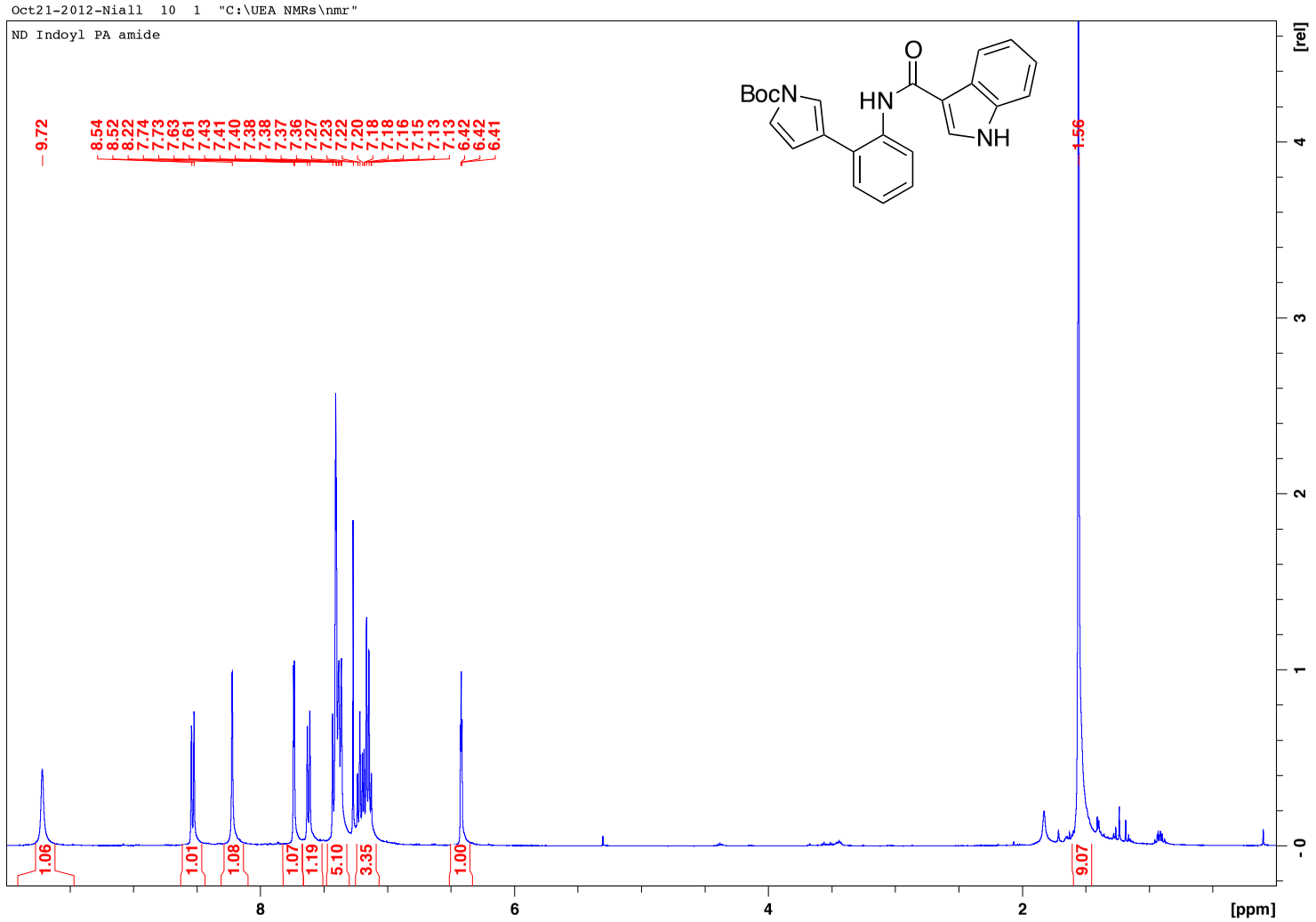

Oct15-2012-Niall 31 1 "C:\UEA NMRs\nmr"
ND9.031.2
168.89
149.32
136.47
130.11
128.20
128.00
125.46
125.32
125.08
121.37
118.98
113.44
84.65
30.42
30.23
30.03
29.84
29.63
29.45
29.26
28.04
[rel]
[ppm]


Oct19-2012-Niall 50 1 "C:\UEA NMRs\nmr"
ND7.031.2
BocN
HN
O
8.32
8.30
7.45
7.39
7.38
7.37
7.33
7.33
7.31
7.30
7.29
7.29
7.28
7.27
7.14
7.12
7.10
6.36
6.36
6.36
6.35
2.23
2.22
2.21
2.21
2.20
2.19
2.19
2.18
2.17
1.63
1.01
1.00
0.94
0.00
0.00
2.93
1.07
1.00
3.14
8.98
6.09
8
6
4
2
[ppm]
[rel]
-0
1
2
3
4

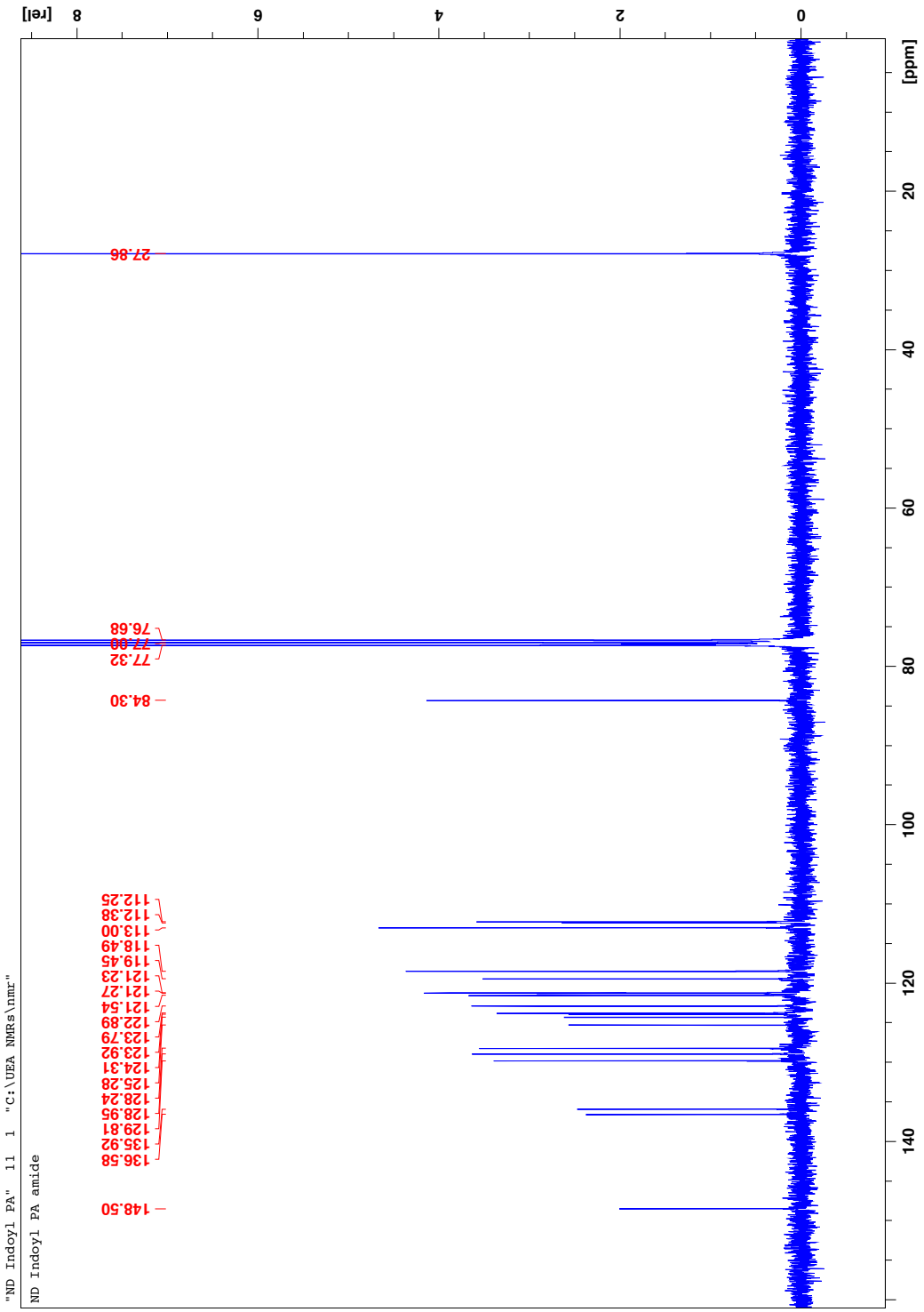

Oct19-2012-Niall 51 1 "C:\UEA NMRs\nmr"
ND7.031.2
[rel]
[ppm]
22.44
26.14
27.95
47.27
76.68
77.00
77.32
84.30
112.53
118.15
121.15
121.19
123.90
124.02
124.92
128.04
129.63
135.15
148.46

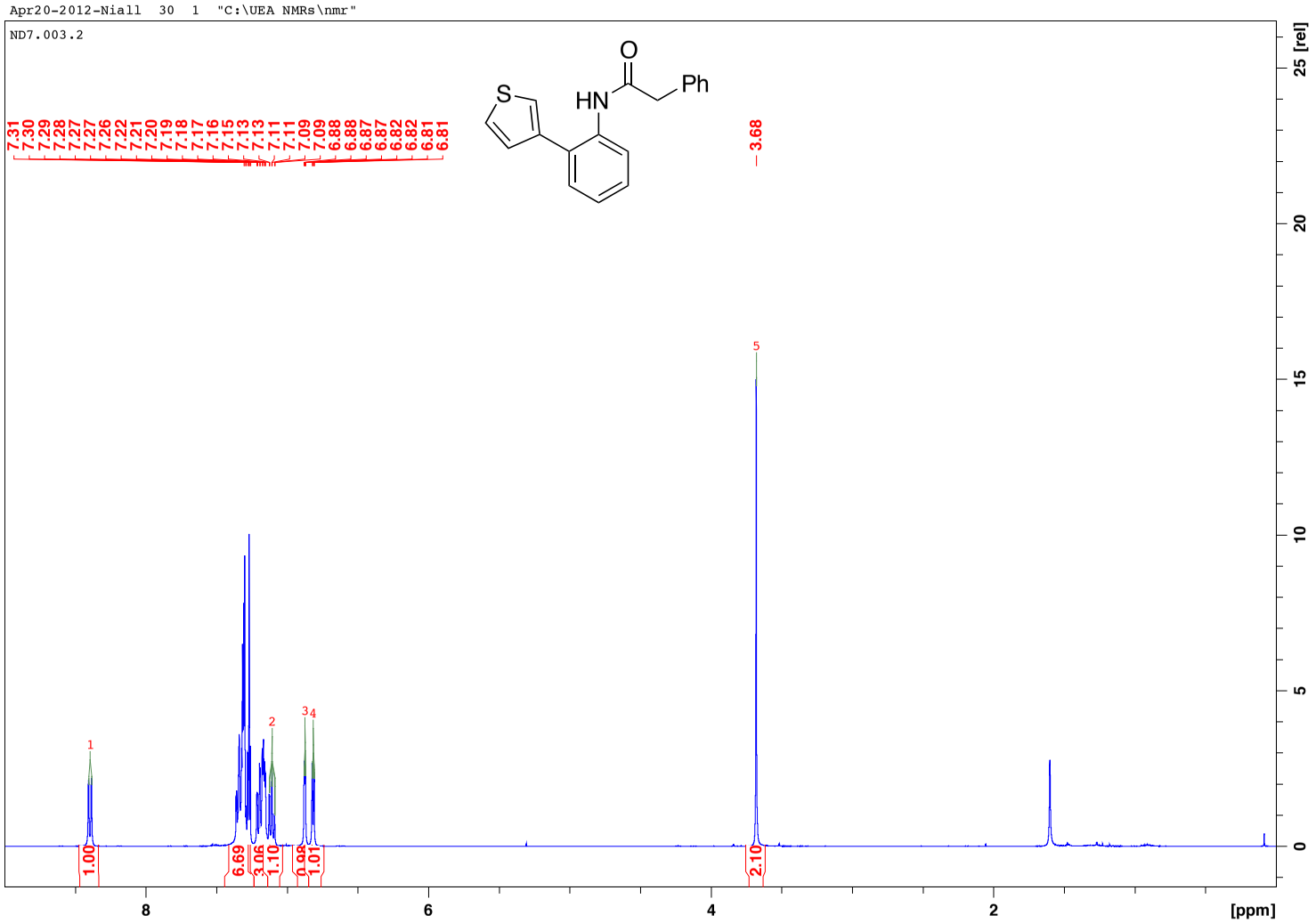

Jan27-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND6.076.2
[rel]
[ppm]
BocN
HN
O
1.67
3.70
9.27
2.05
1.00
1.02
1.13
4.79
4.14
2.10
5.93
5.93
5.92
8.37
8.35
7.45
7.32
7.32
7.30
7.29
7.28
7.28
7.28
7.27
7.26
7.22
7.21
7.20
7.19
7.17
7.17
7.15
7.14
7.13
7.09
7.08
7.05

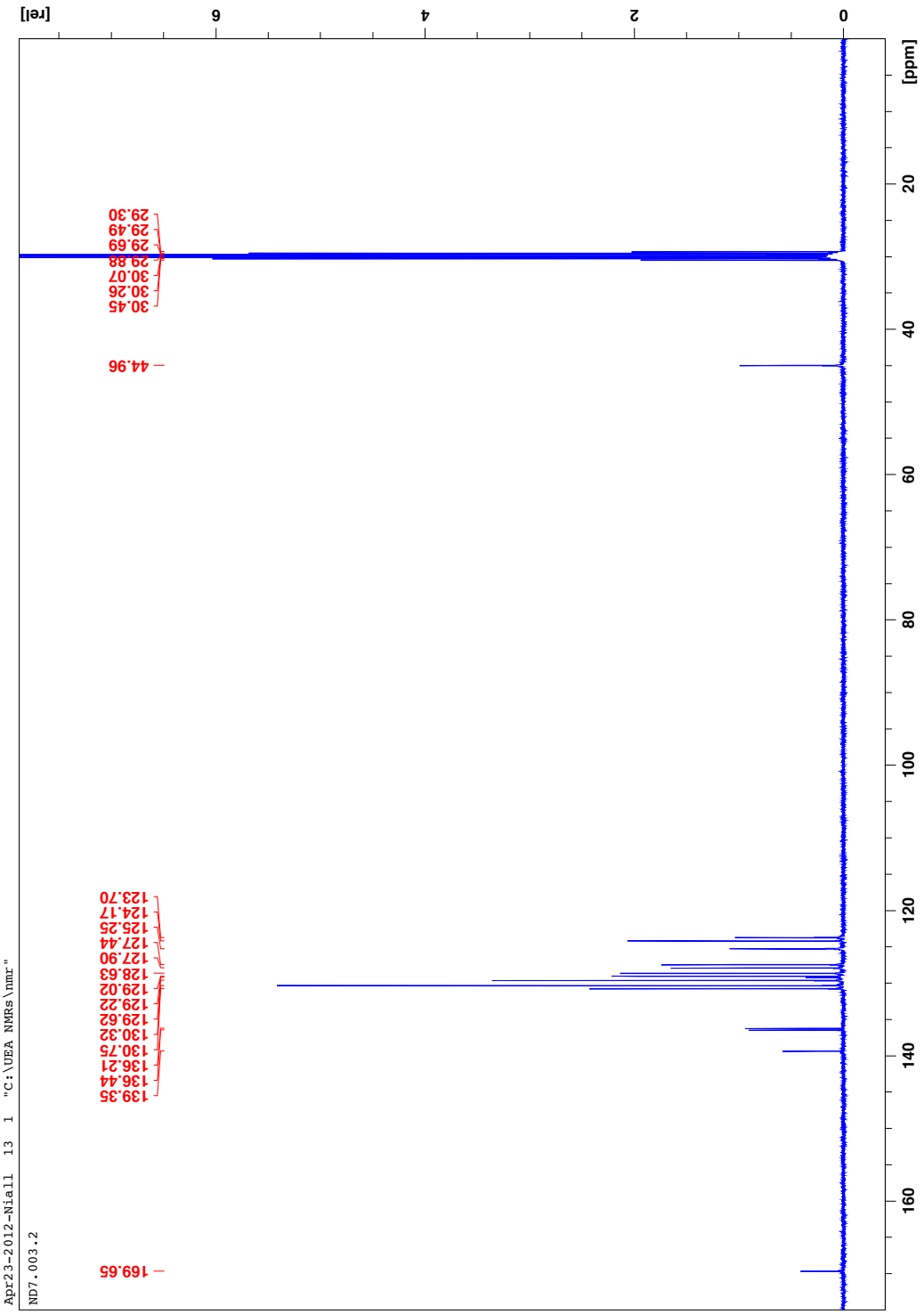

Jan27-2012-Niall 11 1 "C:\UEA NMRs\nmr"
ND6.076.2
[rel]
15
10
5
0
[ppm]
50
100
150
168.87
148.38
135.35
133.99
129.76
129.54
129.01
128.12
127.44
124.96
123.93
123.20
120.91
120.30
118.01
112.29
84.10
77.32
77.20
77.00
76.68
45.17
28.00

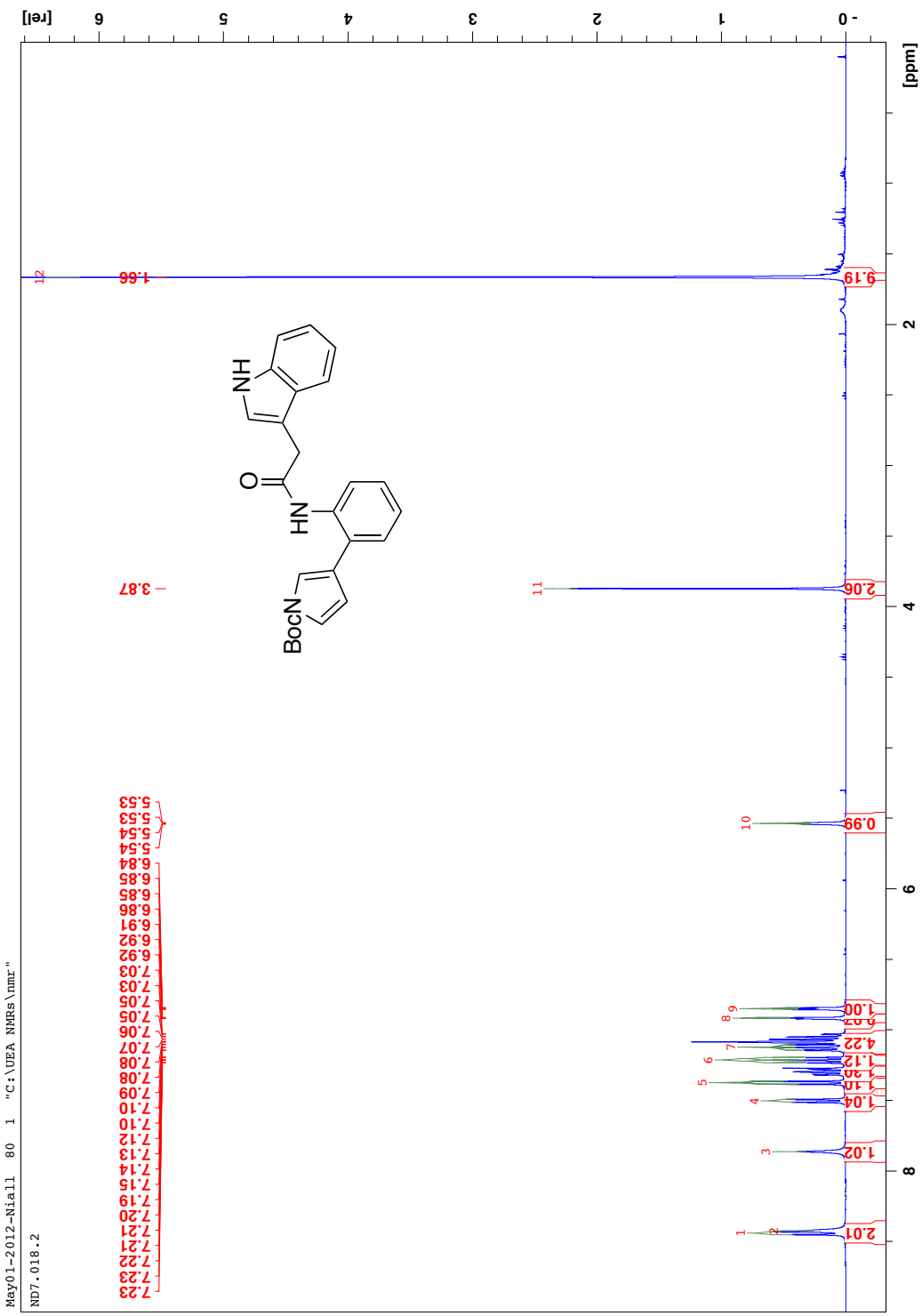

Oct21-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND Indoyl PA amide
9.72
8.54
8.52
8.22
7.74
7.73
7.63
7.61
7.43
7.41
7.40
7.38
7.38
7.37
7.36
7.27
7.23
7.22
7.20
7.18
7.16
7.15
7.13
6.42
6.42
6.41
1.56
BocN
HN
O
NH
1.06
1.01
1.08
1.07
1.19
5.10
3.35
1.00
9.07
8
6
4
2
[ppm]
[rel]
4
3
2
1
-0

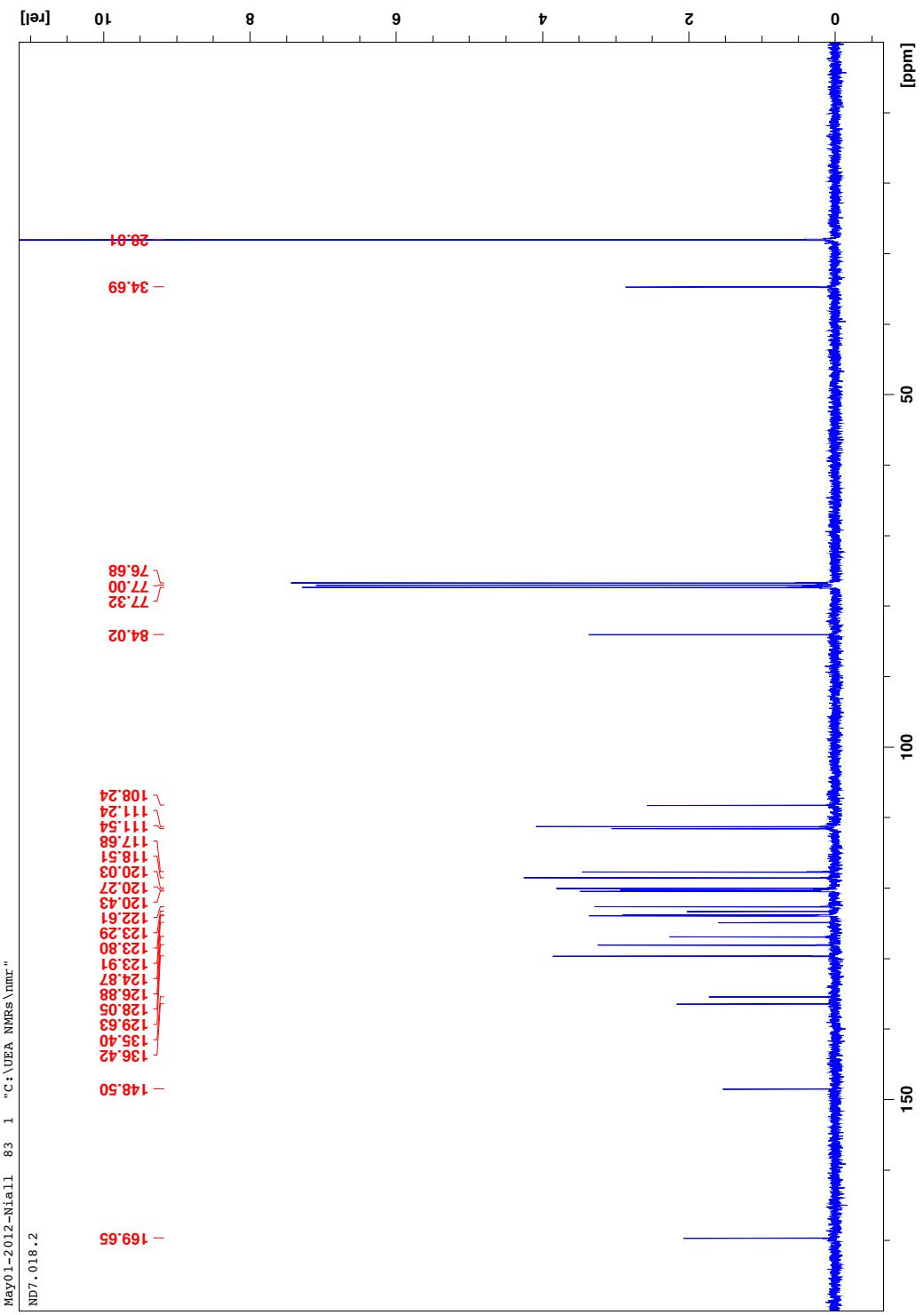
XXV

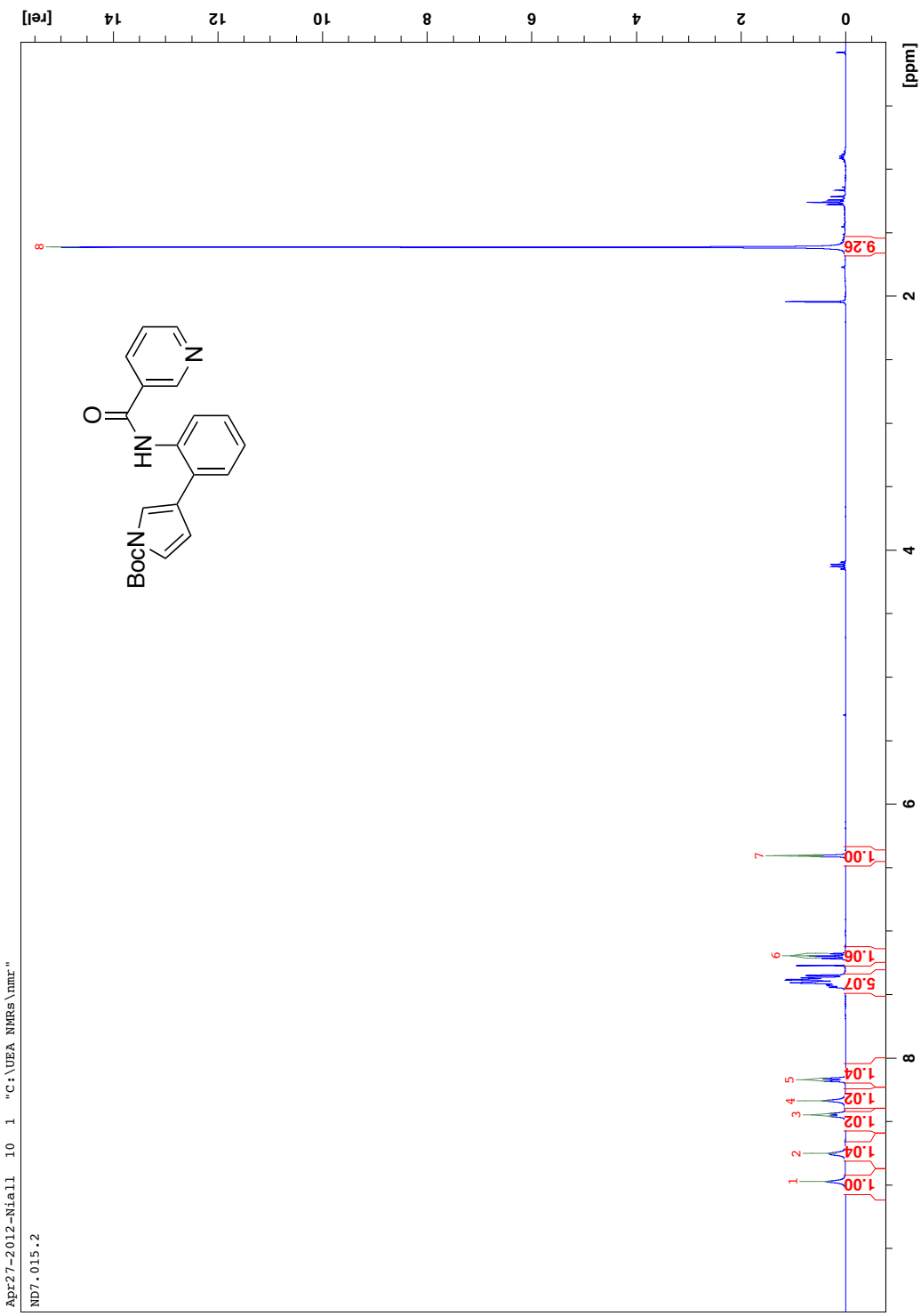

"ND Indoyl PA" 11 1 "C:\UEA NMRs\nmr"
ND Indoyl PA amide
27.86
76.68
77.08
77.32
84.30
112.25
112.38
113.00
118.49
119.45
121.23
121.27
121.54
122.89
123.79
123.92
124.31
125.28
128.24
128.95
129.81
135.92
136.58
148.50
[rel]
[ppm]

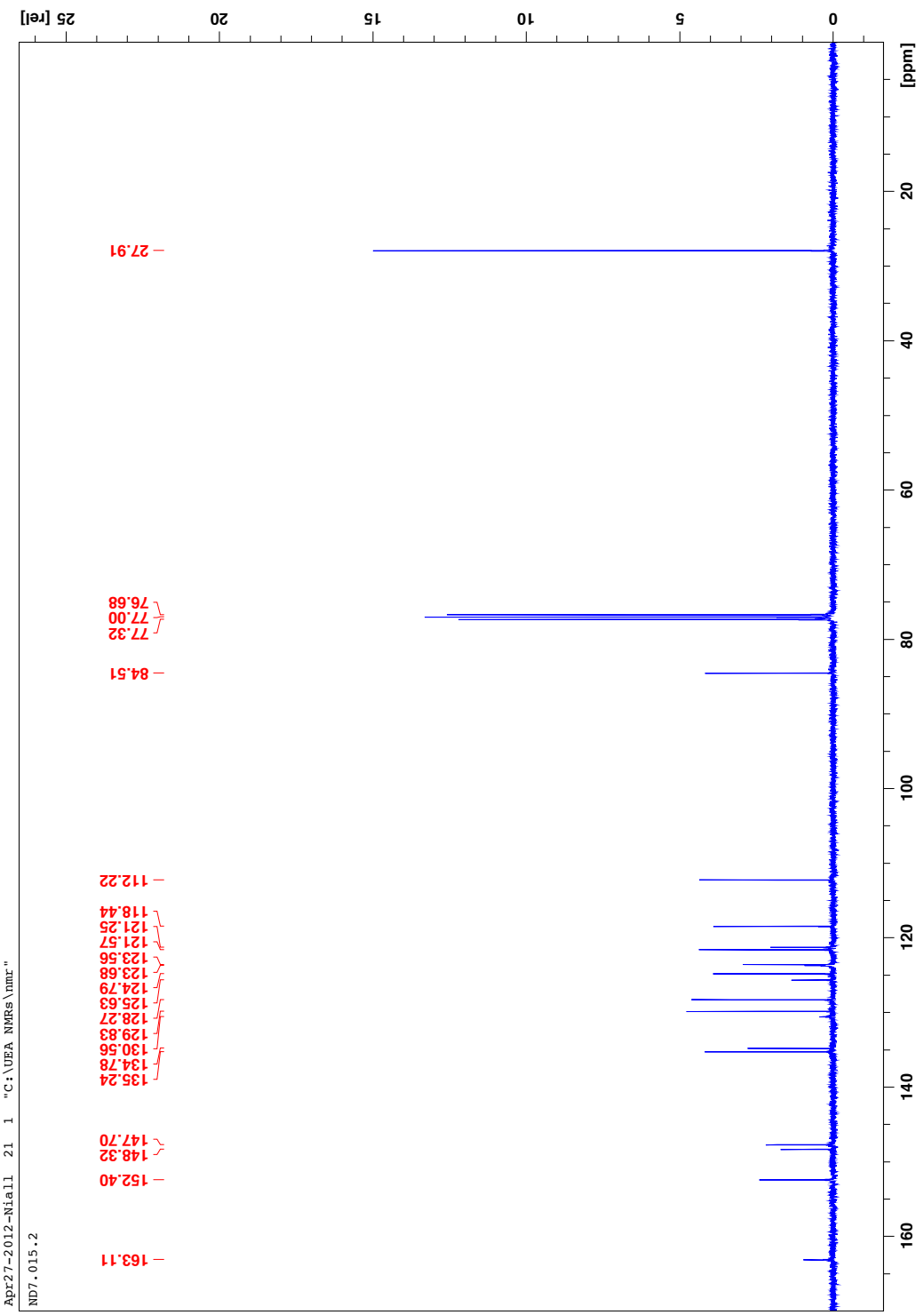

Apr20-2012-Niall 30 1 "C:\UEA NMRs\nmr"
ND7.003.2
7.31
7.30
7.29
7.28
7.27
7.26
7.22
7.21
7.20
7.19
7.18
7.17
7.16
7.15
7.13
7.13
7.11
7.11
7.09
7.09
6.88
6.88
6.87
6.87
6.82
6.82
6.81
6.81
3.68
S
HN
O
Ph
1
2
3
4
5
1.00
6.69
3.06
1.10
0.98
1.01
2.10
25 [rel]
20
15
10
5
0
8
6
4
2
[ppm]

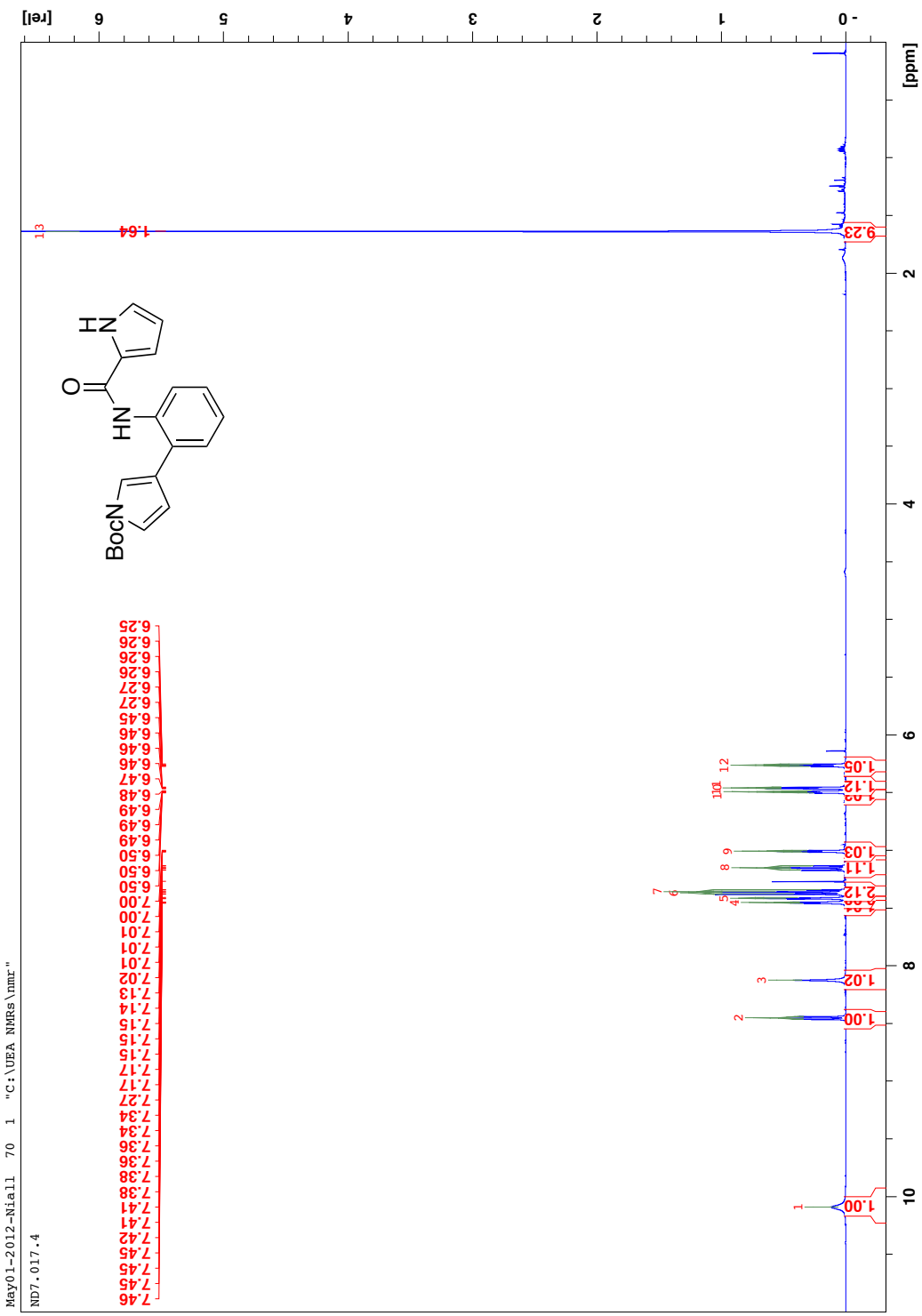

[rel]
6
4
2
0
[ppm]
20
40
60
80
100
120
140
160
169.65
139.35
136.44
136.21
130.75
130.32
129.62
129.22
129.02
128.63
127.90
127.44
125.25
124.17
123.70
44.96
30.45
30.26
30.07
29.88
29.69
29.49
29.30
Apr23-2012-Niall 13 1 "C:\UEA NMRs\nmr"
ND7.003.2


May01-2012-Niall 80 1 "C:\UEA NMRs\nmr"
ND7.018.2
[rel]
[ppm]
NH
O
HN
BocN

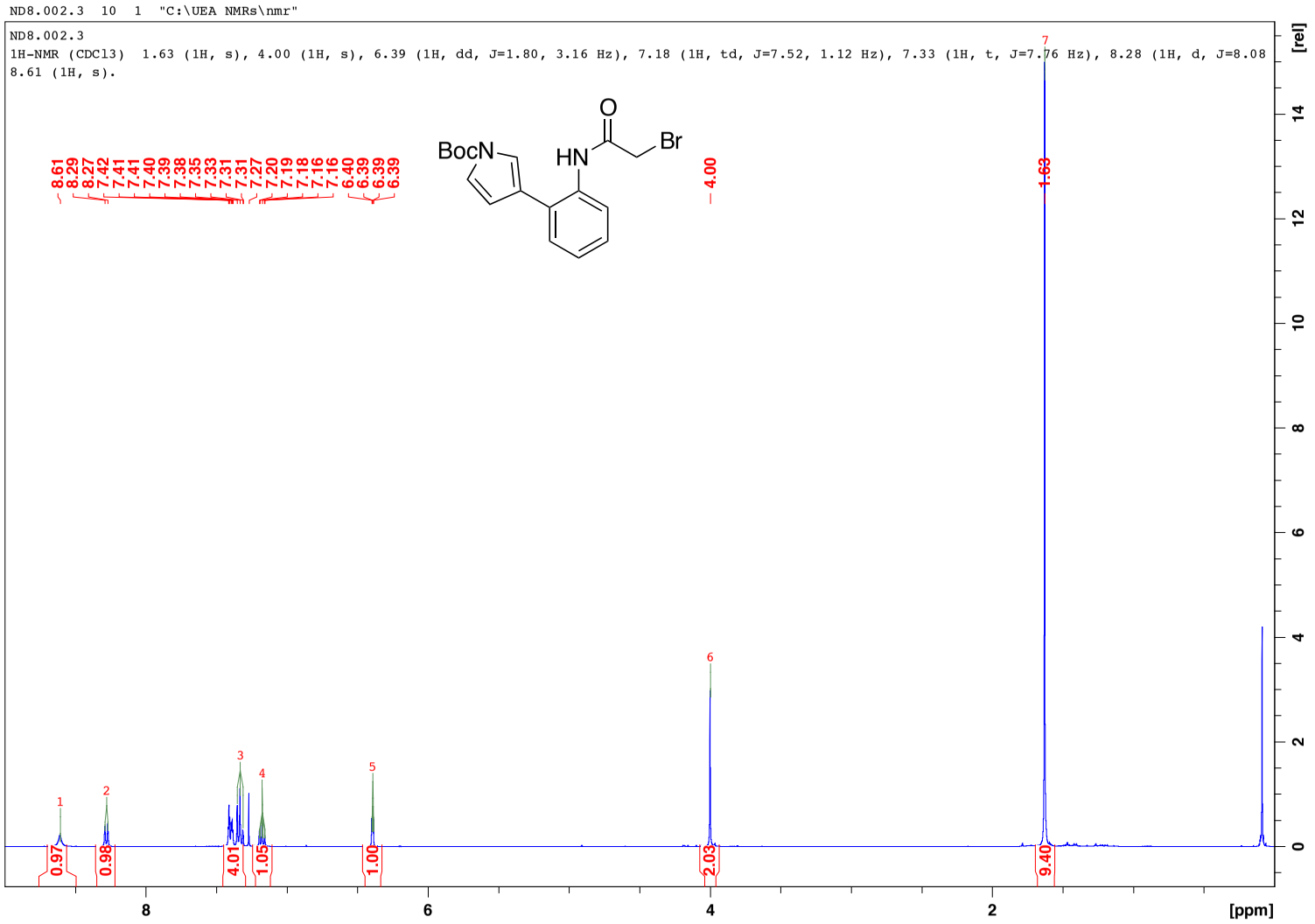

May01-2012-Niall 83 1 "C:\UEA NMRs\nmr"
ND7.018.2
[rel]
[ppm]
0
2
4
6
8
10
50
100
150
28.01
34.69
76.68
77.00
77.32
84.02
108.24
111.24
111.54
117.68
118.51
120.03
120.27
120.43
122.61
123.29
123.80
123.91
124.87
126.88
128.05
129.63
135.40
136.42
148.50
169.65

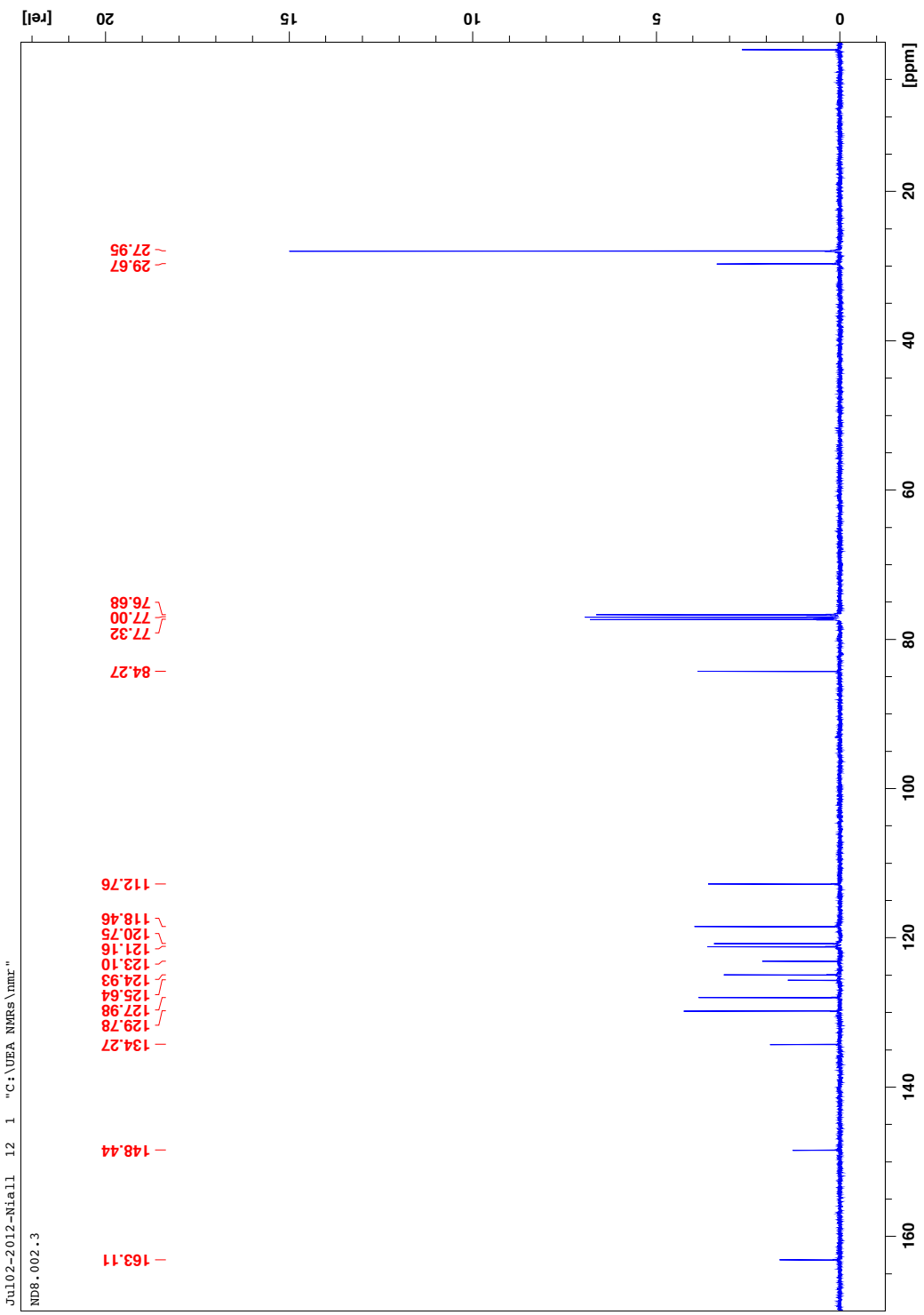

Apr27-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND7.015.2
[rel]
[ppm]
BocN
HN
O
N
1.00
1.04
1.02
1.02
1.04
5.07
1.06
1.00
9.26

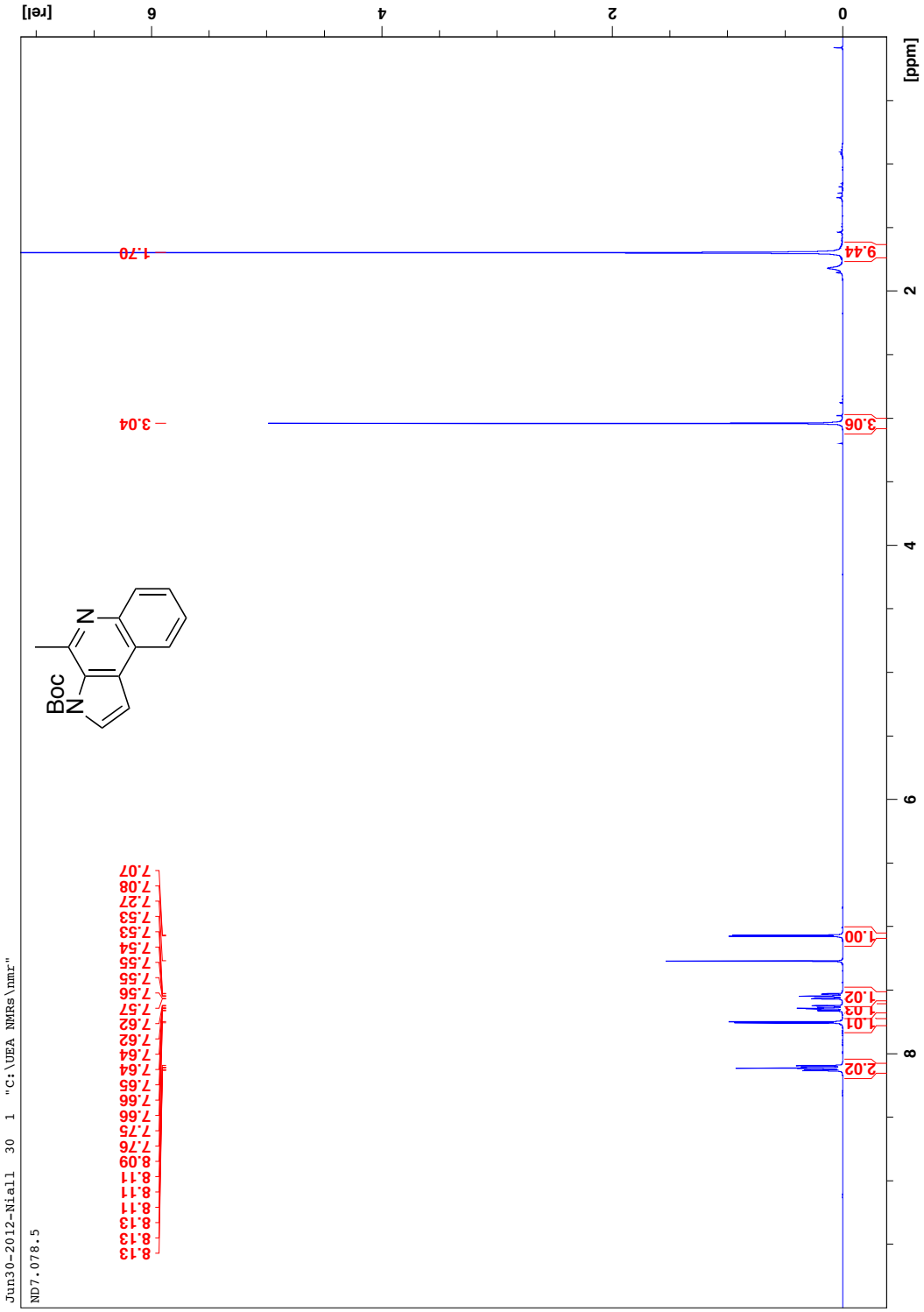

Apr27-2012-Niall 21 1 "C:\UEA NMRs\nmr"
ND7.015.2
163.11
152.40
148.32
147.70
135.24
134.78
130.56
129.83
128.27
125.63
124.79
123.68
123.56
121.57
121.25
118.44
112.22
84.51
77.32
77.00
76.68
27.91
[ppm]
[rel]

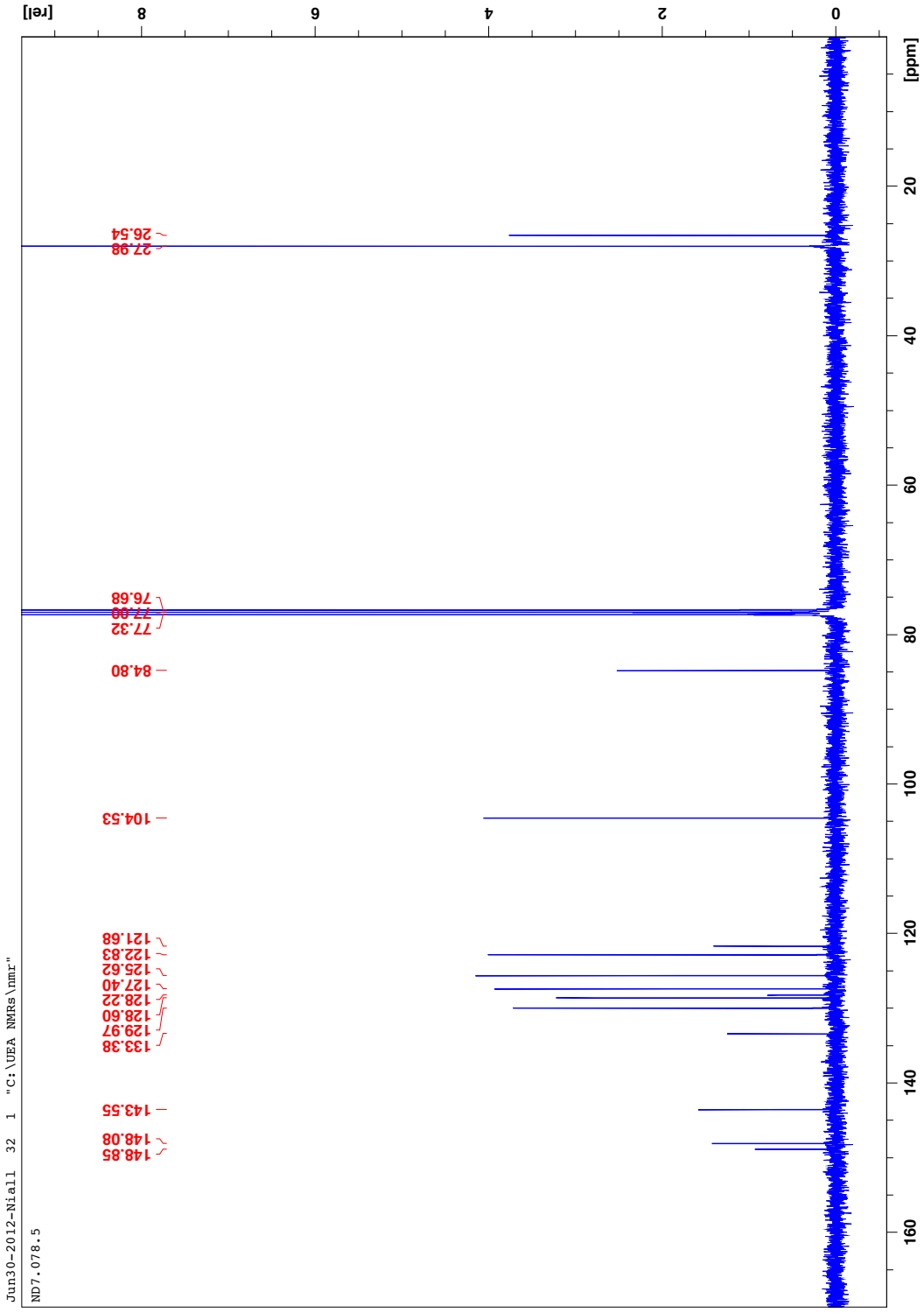

May01-2012-Niall 70 1 "C:\UEA NMRs\nmr"
ND7.017.4
[rel]
[ppm]
BocN
HN
O
NH

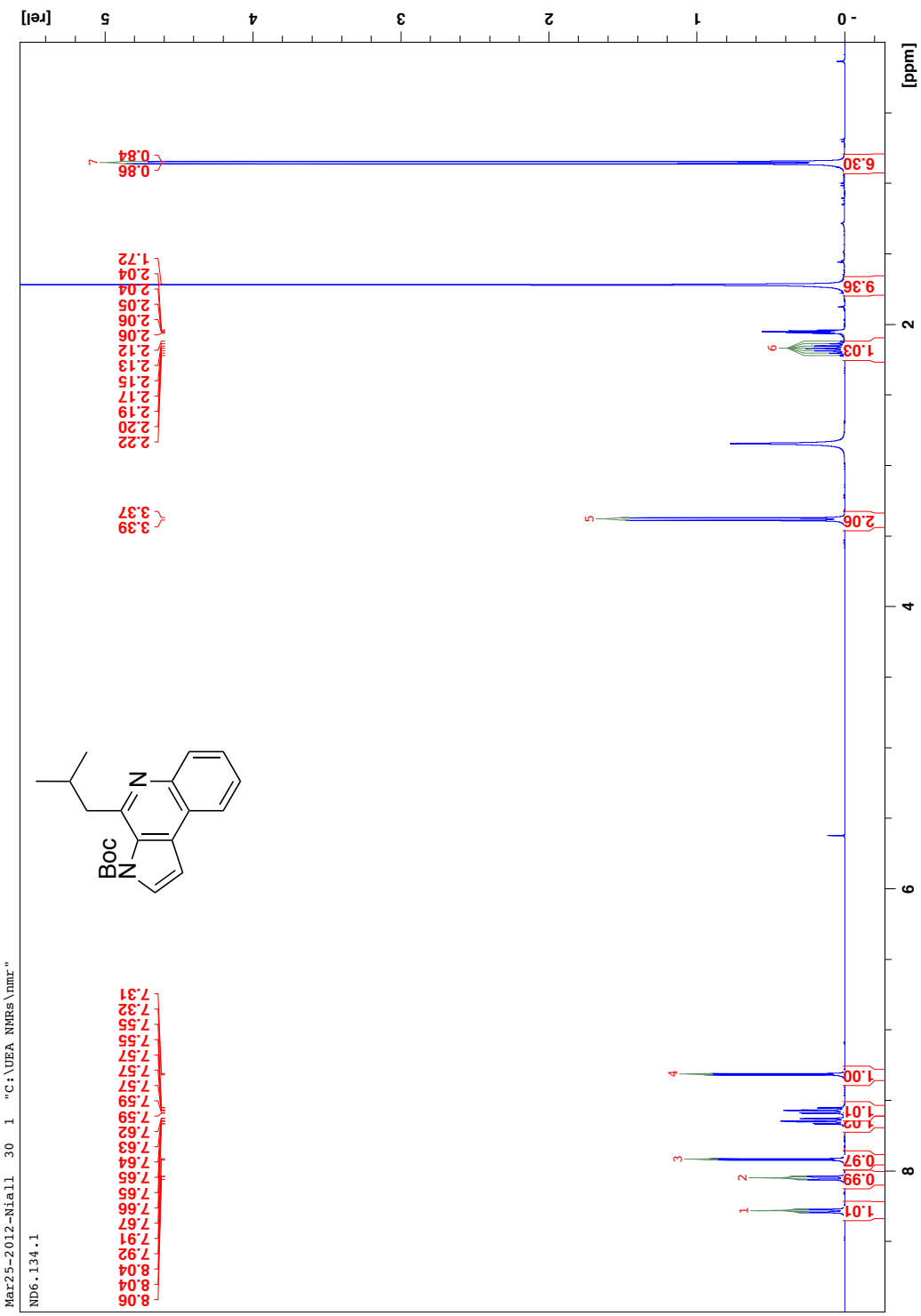
May01-2012-Niall 73 1 "C:\UEA NMRs\nmr"
ND7.017.4
[rel]
20
15
10
5
0
[ppm]
20
40
60
80
100
120
140
160
27.95
77.32
77.00
76.68
84.39
109.56
110.03
112.48
118.34
120.81
121.38
122.51
123.90
124.84
126.21
128.10
129.54
135.11
148.47
158.91

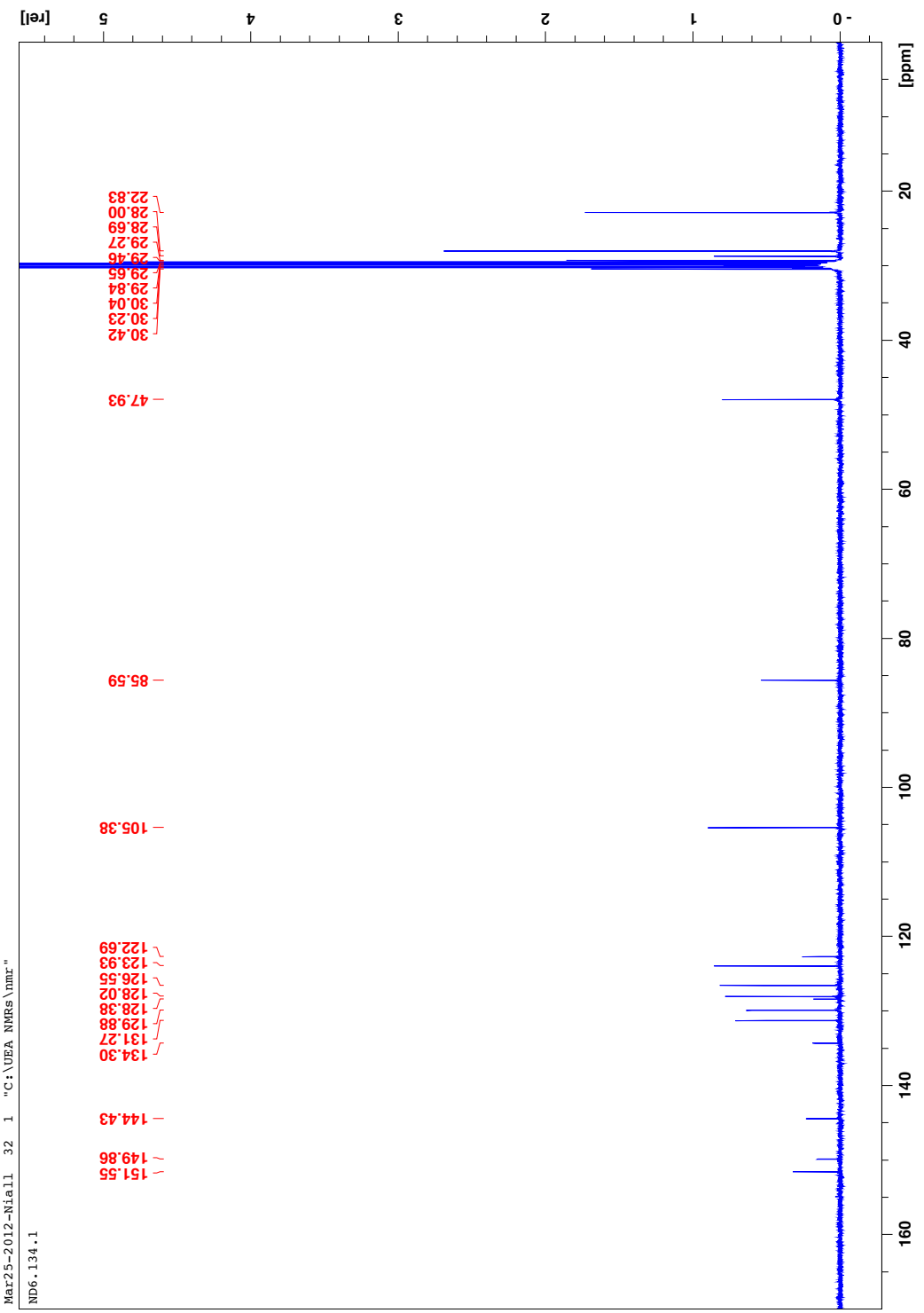

ND8.002.3 10 1 "C:\UEA NMRs\nmr"
ND8.002.3
1H-NMR (CDCl3) 1.63 (1H, s), 4.00 (1H, s), 6.39 (1H, dd, J=1.80, 3.16 Hz), 7.18 (1H, td, J=7.52, 1.12 Hz), 7.33 (1H, t, J=7.76 Hz), 8.28 (1H, d, J=8.08
8.61 (1H, s).
8.61
8.29
8.27
7.42
7.41
7.40
7.39
7.38
7.35
7.33
7.31
7.31
7.27
7.20
7.19
7.18
7.16
7.16
6.40
6.39
6.39
6.39
BocN
HN
O
Br
4.00
1.63
0.97
0.98
4.01
1.05
1.00
2.03
9.40
[rel]
[ppm]

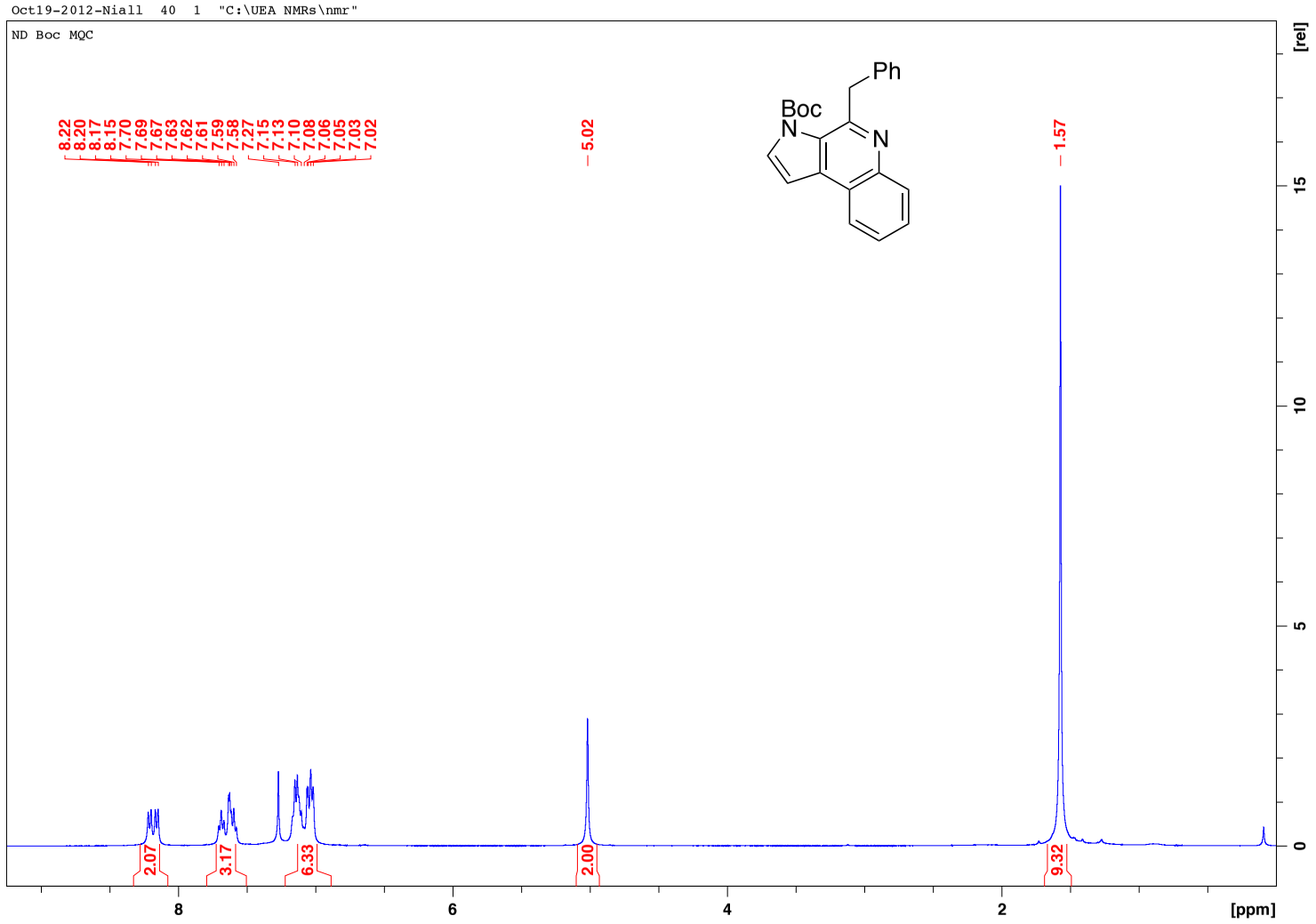

Jul02-2012-Niall 12 1 "C:\UEA NMRs\nmr"
ND8.002.3
[rel]
20
15
10
5
0
[ppm]
20
40
60
80
100
120
140
160
163.11
148.44
134.27
129.78
127.98
125.64
124.93
123.10
121.16
120.75
118.46
112.76
84.27
77.32
77.00
76.68
29.67
27.95

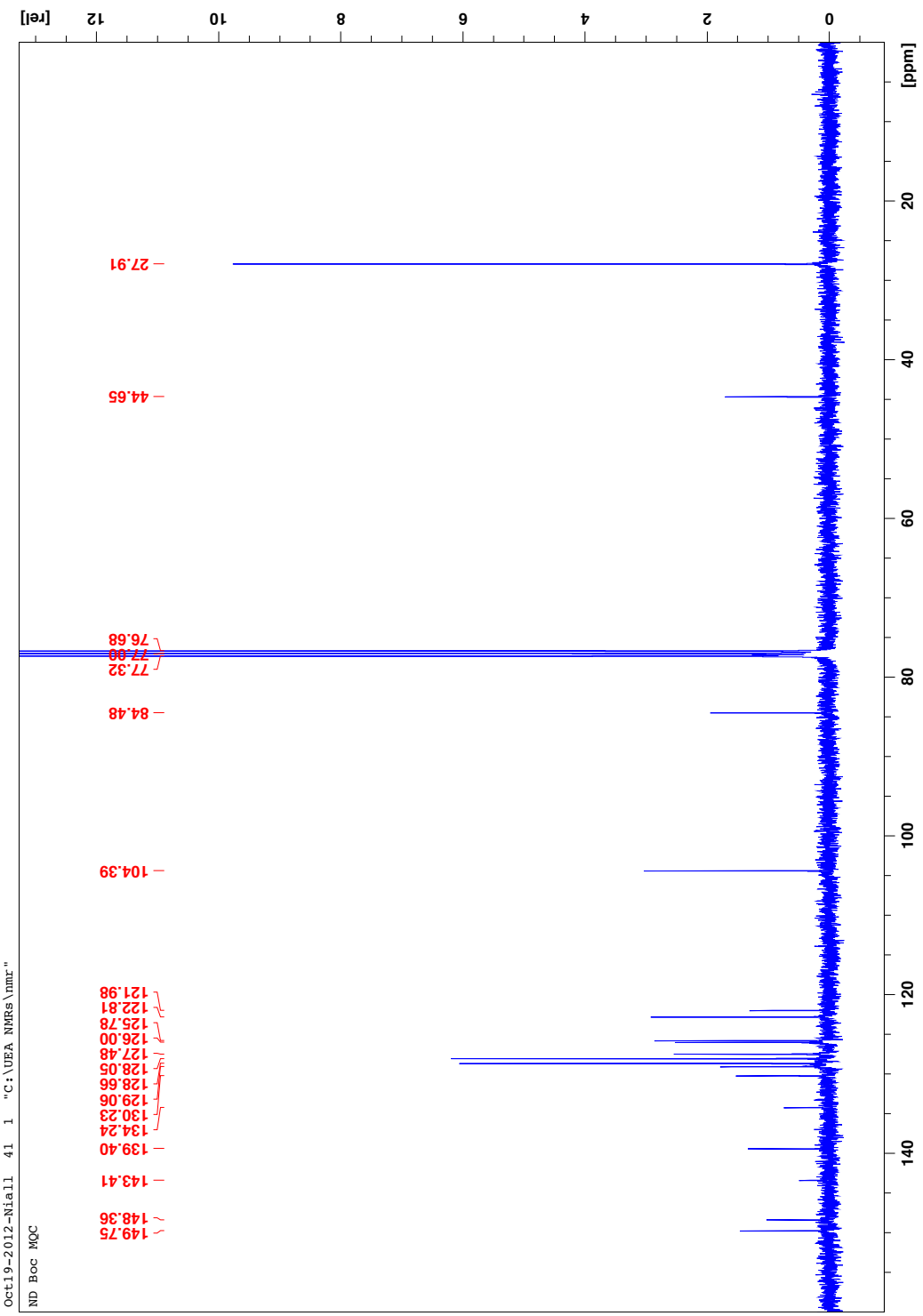

Jun30-2012-Niall 30 1 "C:\UEA NMRs\nmr"
ND7.078.5
[rel]
[ppm]
Boc
N
N
1.70
3.04
9.44
3.06
1.00
1.02
1.03
1.01
2.02
8.13
8.13
8.13
8.11
8.11
8.09
7.76
7.75
7.66
7.66
7.65
7.64
7.64
7.62
7.62
7.57
7.56
7.55
7.55
7.54
7.53
7.53
7.27
7.08
7.07

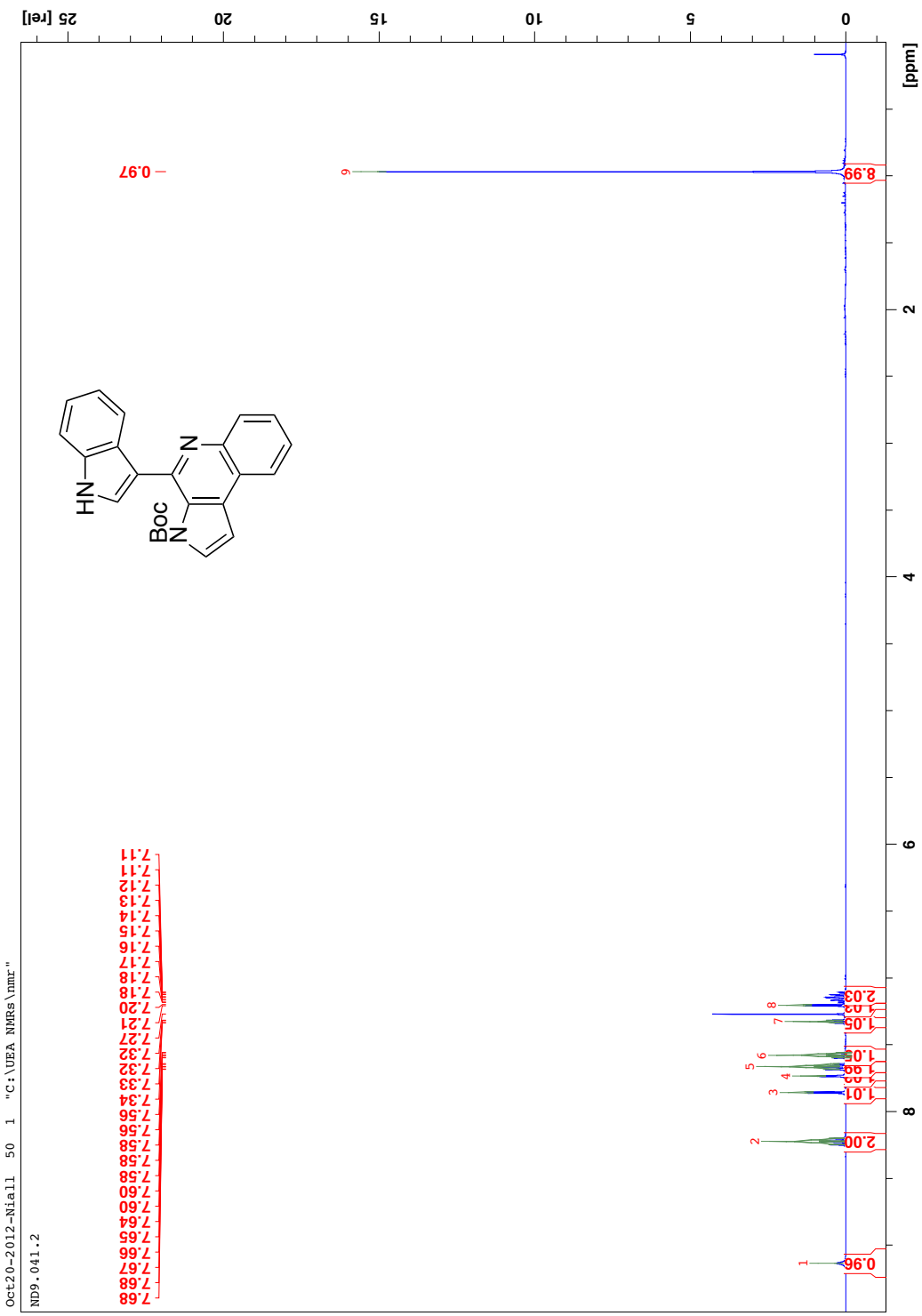

Jun30-2012-Niall 32 1 "C:\UEA NMRs\nmr"
ND7.078.5
[rel]
[ppm]
148.85
148.08
143.55
133.38
129.97
128.60
128.22
127.40
125.62
122.83
121.68
104.53
84.80
77.32
77.00
76.68
27.98
26.54

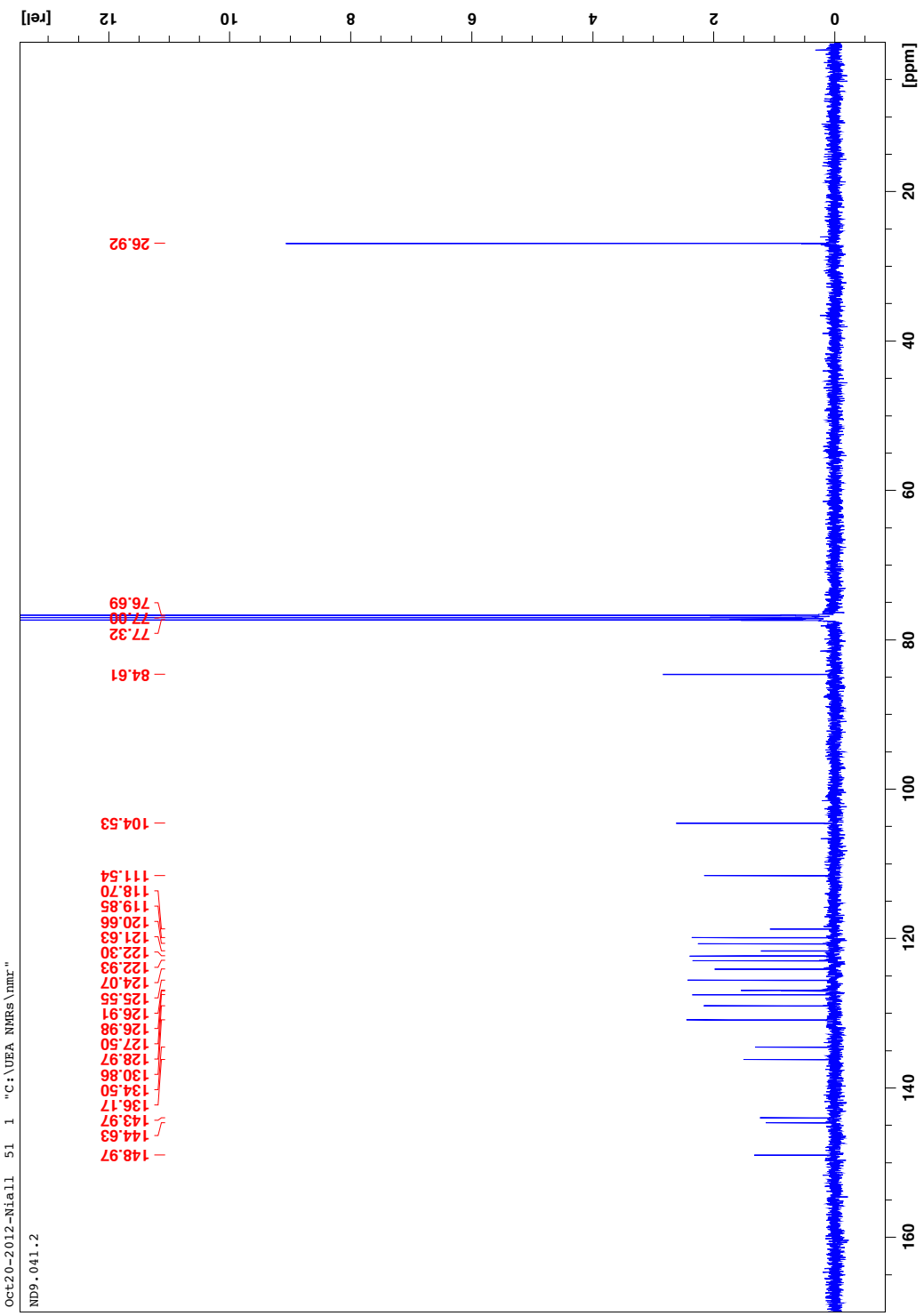

Mar25-2012-Niall 30 1 "C:\UEA NMRs\nmr"
ND6.134.1
[rel]
[ppm]
Boc
N
N
8.06
8.04
8.04
7.92
7.91
7.67
7.66
7.65
7.65
7.64
7.63
7.62
7.59
7.59
7.57
7.57
7.57
7.55
7.55
7.32
7.31
3.39
3.37
2.22
2.20
2.19
2.17
2.15
2.13
2.12
2.06
2.06
2.05
2.04
2.04
1.72
0.86
0.84
1.01
0.99
0.97
1.02
1.01
1.00
2.06
1.03
9.36
6.30

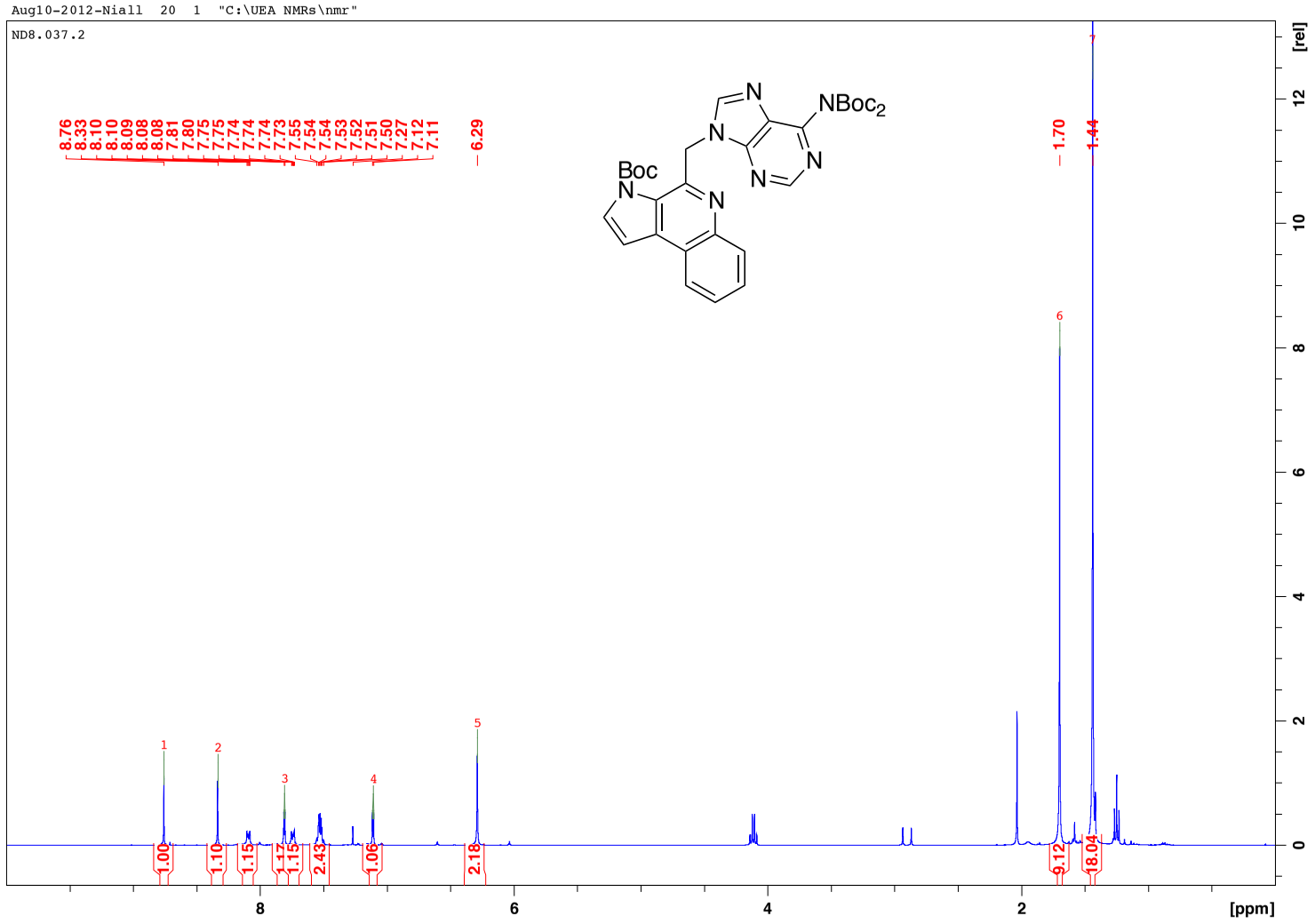

Mar25-2012-Niall 32 1 "C:\UEA NMRs\nmr"
ND6.134.1
[rel]
5
4
3
2
1
0
[ppm]
20
40
60
80
100
120
140
160
22.83
28.00
28.69
29.27
29.46
29.65
29.84
30.04
30.23
30.42
47.93
85.59
105.38
122.69
123.93
126.55
128.02
128.38
129.88
131.27
134.30
144.43
149.86
151.55


Oct19-2012-Niall 40 1 "C:\UEA NMRs\nmr"
ND Boc MQC
8.22
8.20
8.17
8.15
7.70
7.69
7.67
7.63
7.62
7.61
7.59
7.58
7.27
7.15
7.13
7.10
7.08
7.06
7.05
7.03
7.02
5.02
1.57
Ph
Boc
N
N
2.07
3.17
6.33
2.00
9.32
8
6
4
2
[ppm]
[rel]
0
5
10
15

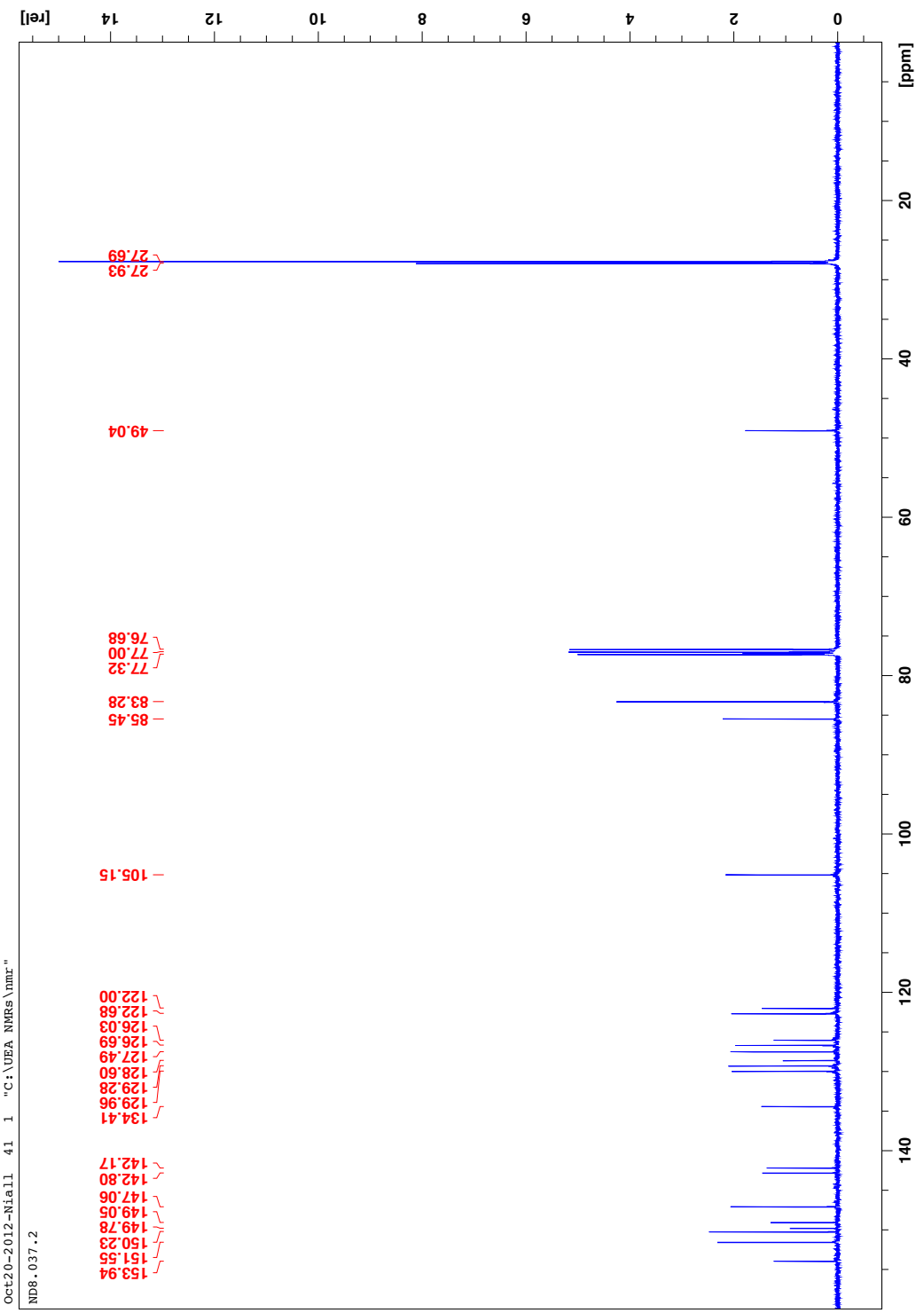

Oct19-2012-Niall 41 1 "C:\UEA NMRs\nmr"
ND Boc MQC
[rel]
[ppm]
27.91
44.65
76.68
77.08
77.32
84.48
104.39
121.98
122.81
125.78
126.00
127.48
128.05
128.66
129.06
130.23
134.24
139.40
143.41
148.36
149.75

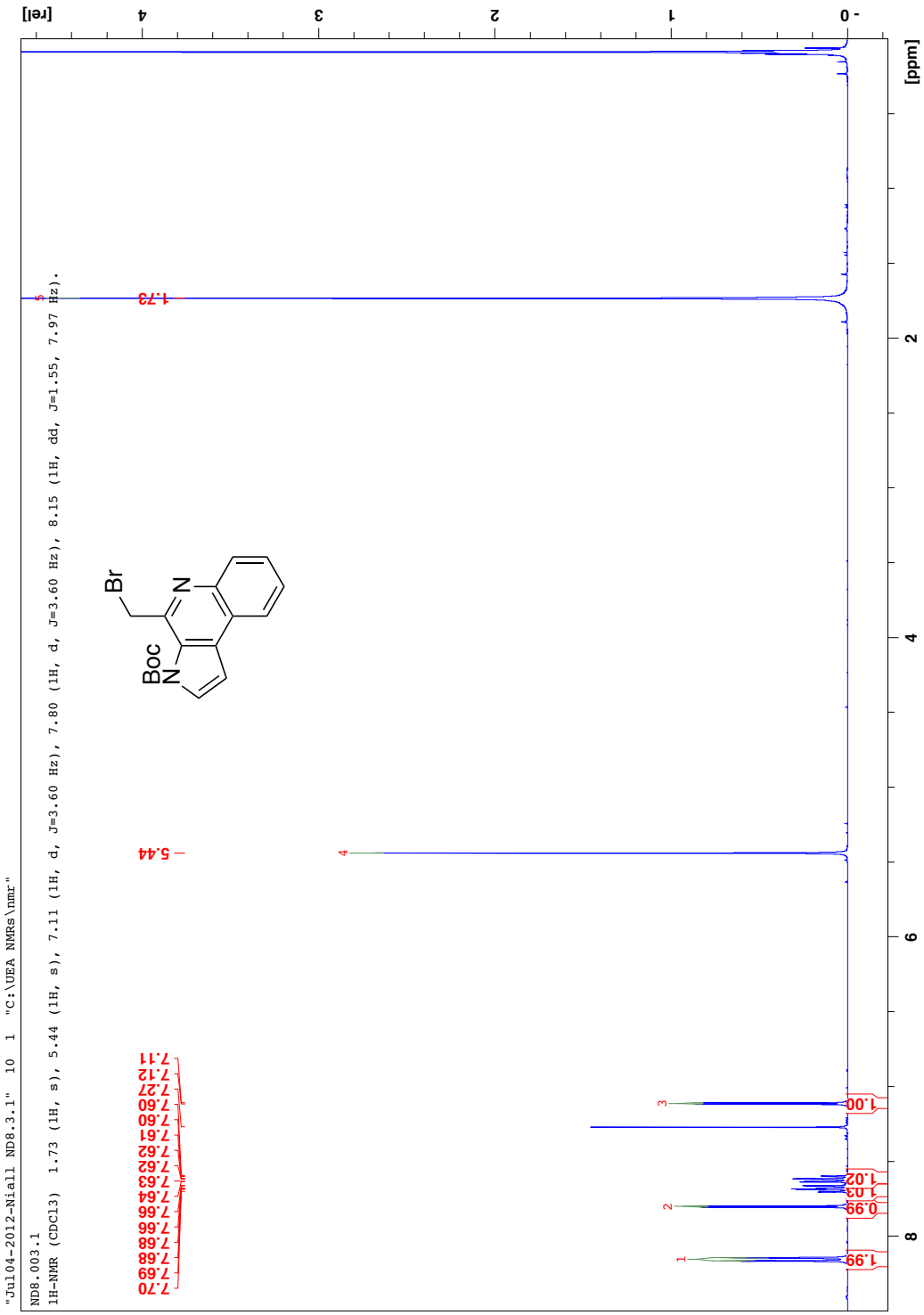

Oct20-2012-Niall 50 1 "C:\UEA NMRs\nmr"
ND9.041.2
[ppm]
[rel]
0
2
4
6
8
0.96
2.00
1.01
1.05
2.03
8.99
0.97
HN
N
Boc
N

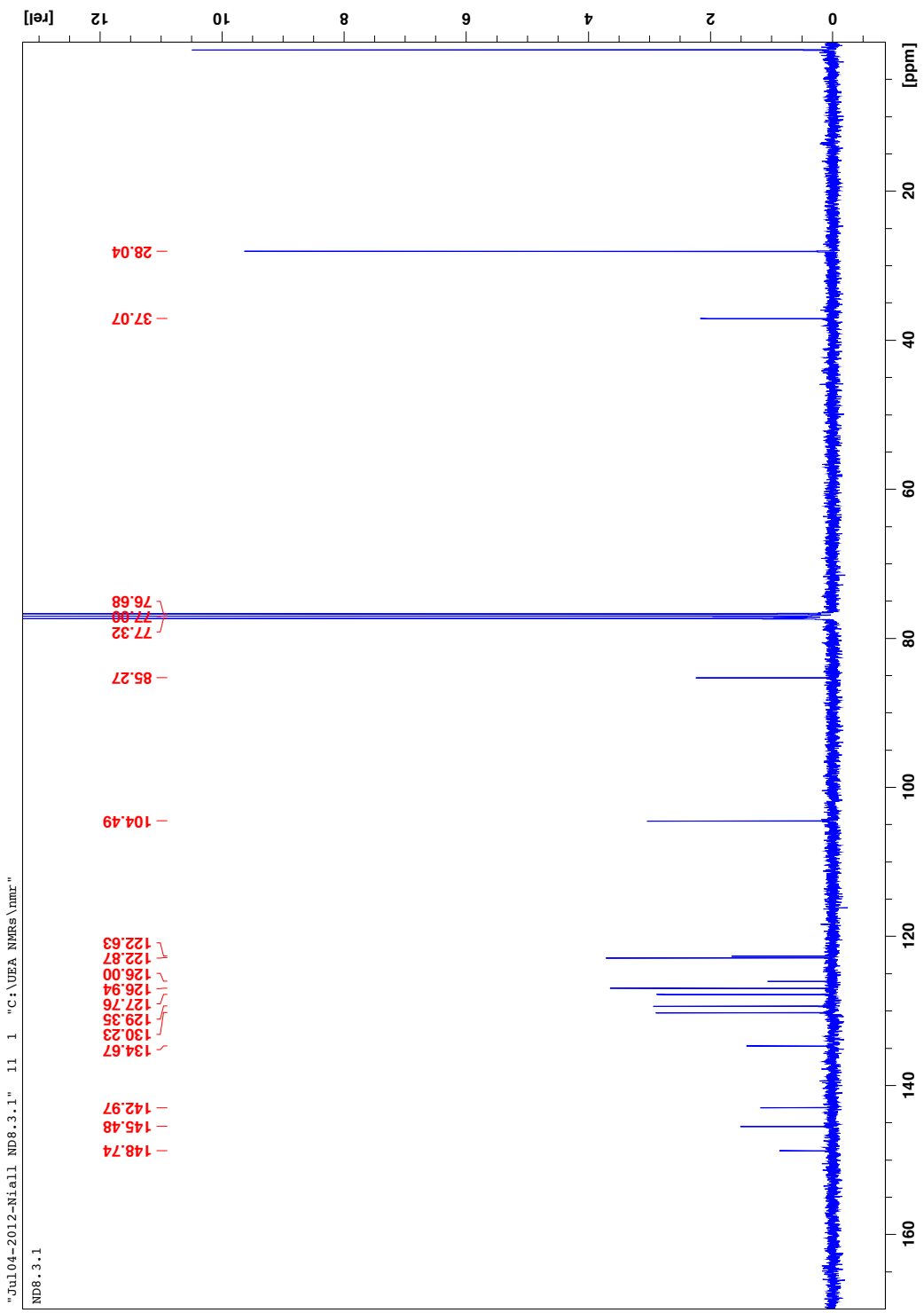

Oct20-2012-Niall 51 1 "C:\UEA NMRs\nmr"
ND9.041.2
[rel]
[ppm]
26.92
76.69
77.00
77.32
84.61
104.53
111.54
118.70
119.85
120.66
121.63
122.30
122.93
124.07
125.55
126.91
126.98
127.50
128.97
130.86
134.50
136.17
143.97
144.63
148.97

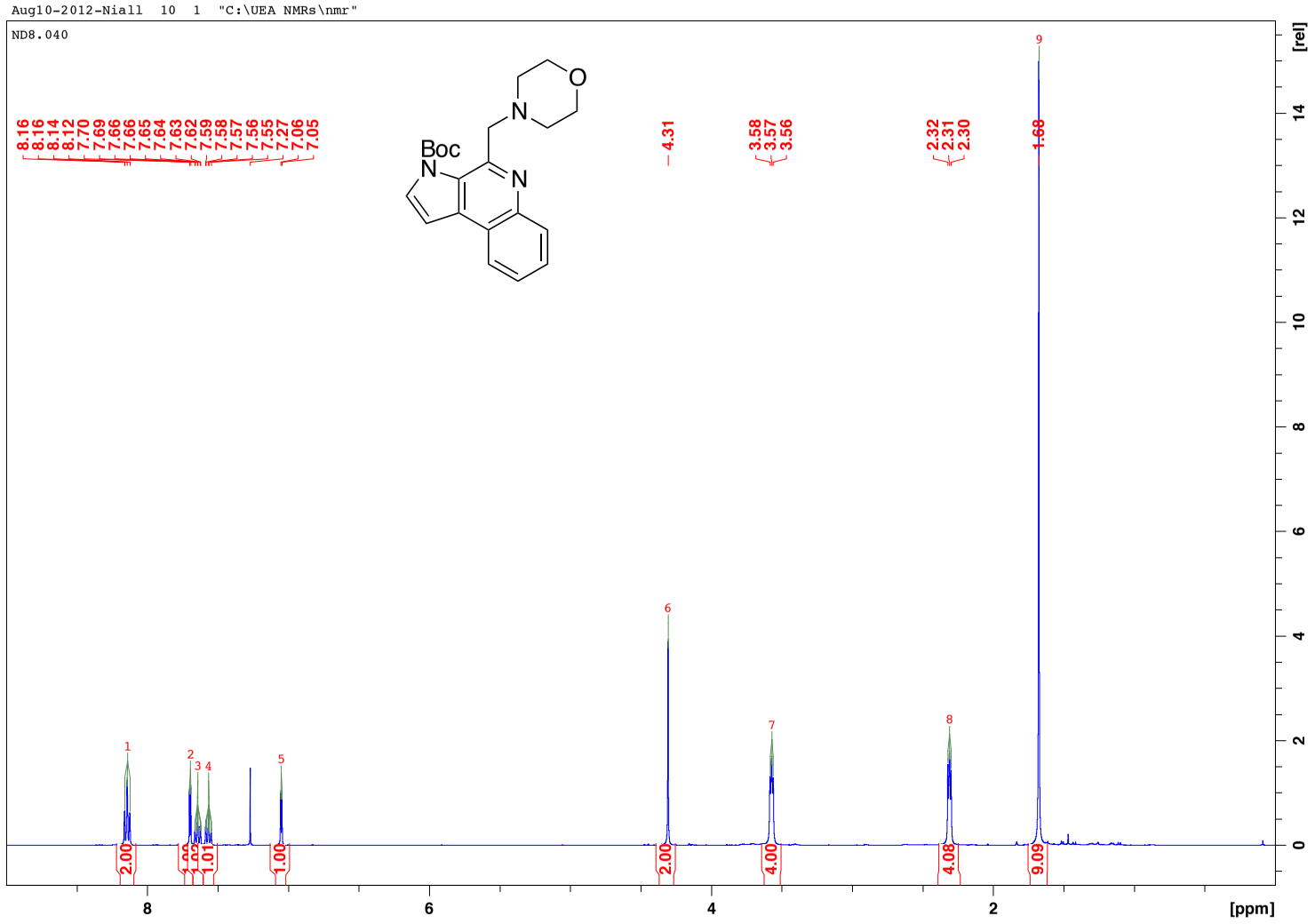

Aug10-2012-Niall 20 1 "C:\UEA NMRs\nmr"
ND8.037.2
8.76
8.33
8.10
8.10
8.09
8.08
8.08
7.81
7.80
7.75
7.75
7.74
7.74
7.74
7.73
7.55
7.54
7.54
7.53
7.52
7.51
7.50
7.27
7.12
7.11
6.29
1.70
1.44
Boc
NBoc2
1.00
1.10
1.15
1.17
1.15
2.43
1.06
2.18
9.12
18.04
[ppm]
[rel]

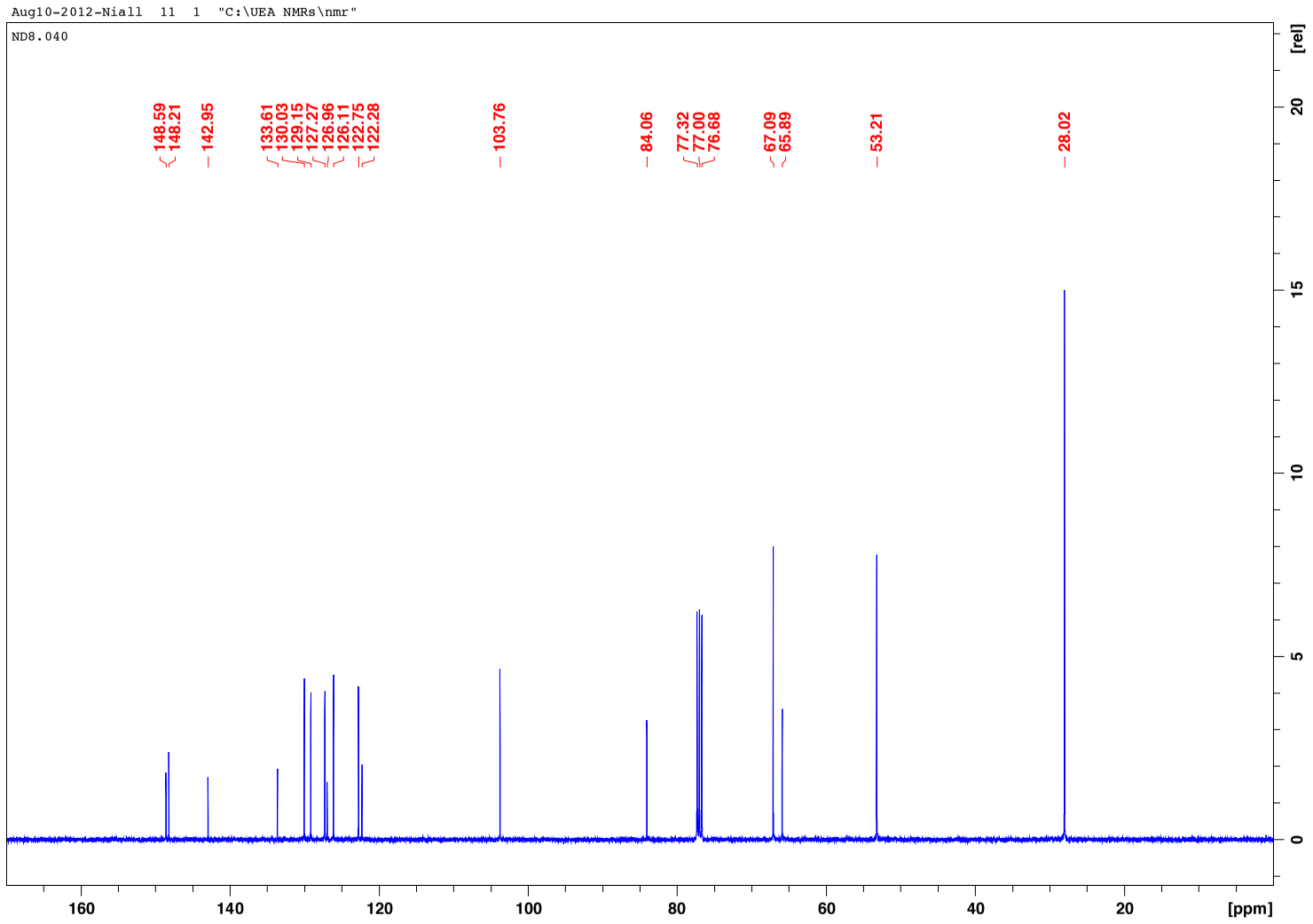
xIv

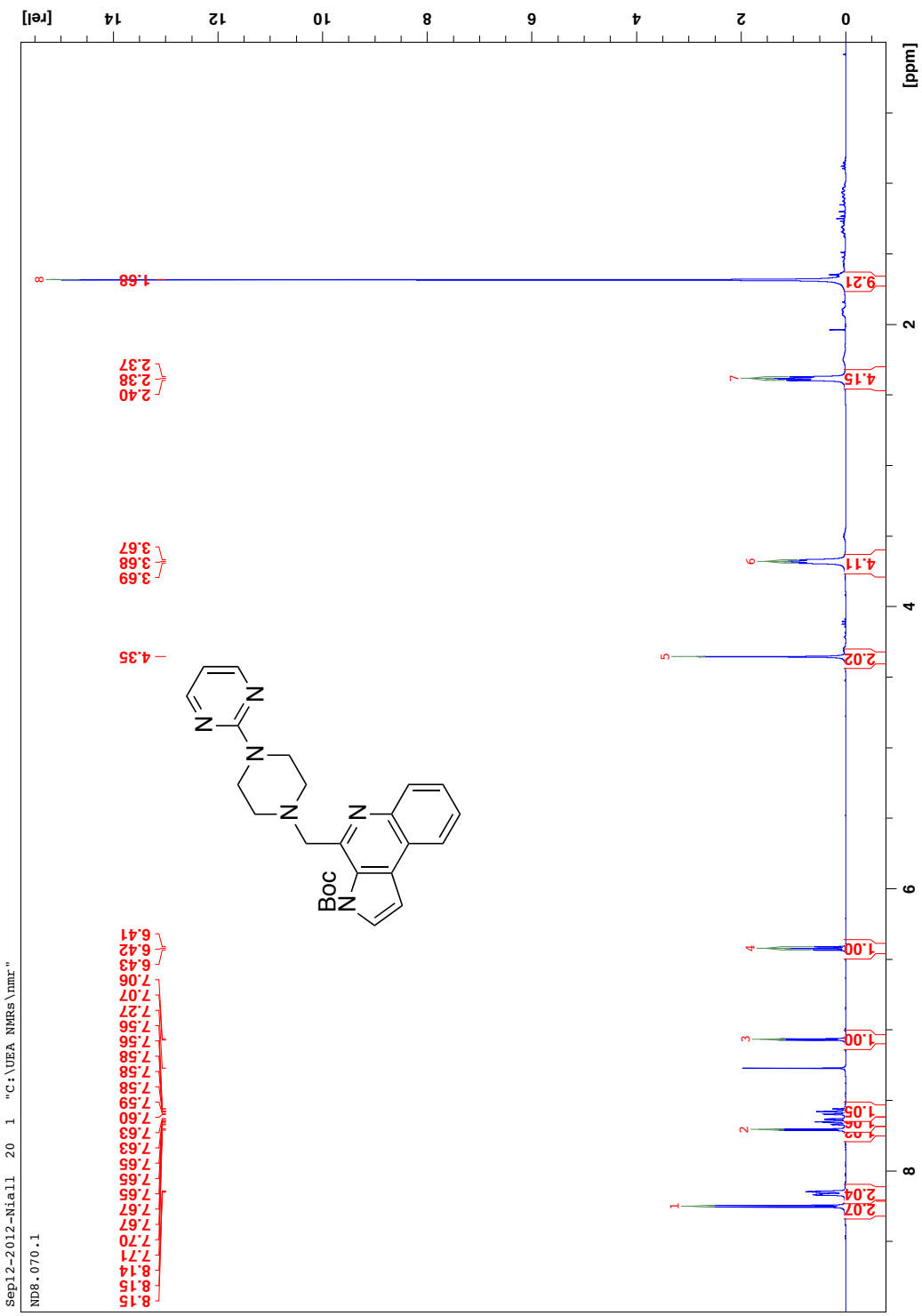

Oct20-2012-Niall 41 1 "C:\UEA NMRs\nmr"
ND8.037.2
[rel]
[ppm]
153.94
151.55
150.23
149.78
149.05
147.06
142.80
142.17
134.41
129.96
129.28
128.60
127.49
126.69
126.03
122.68
122.00
105.15
83.28
85.45
77.32
77.00
76.68
49.04
27.93
27.69

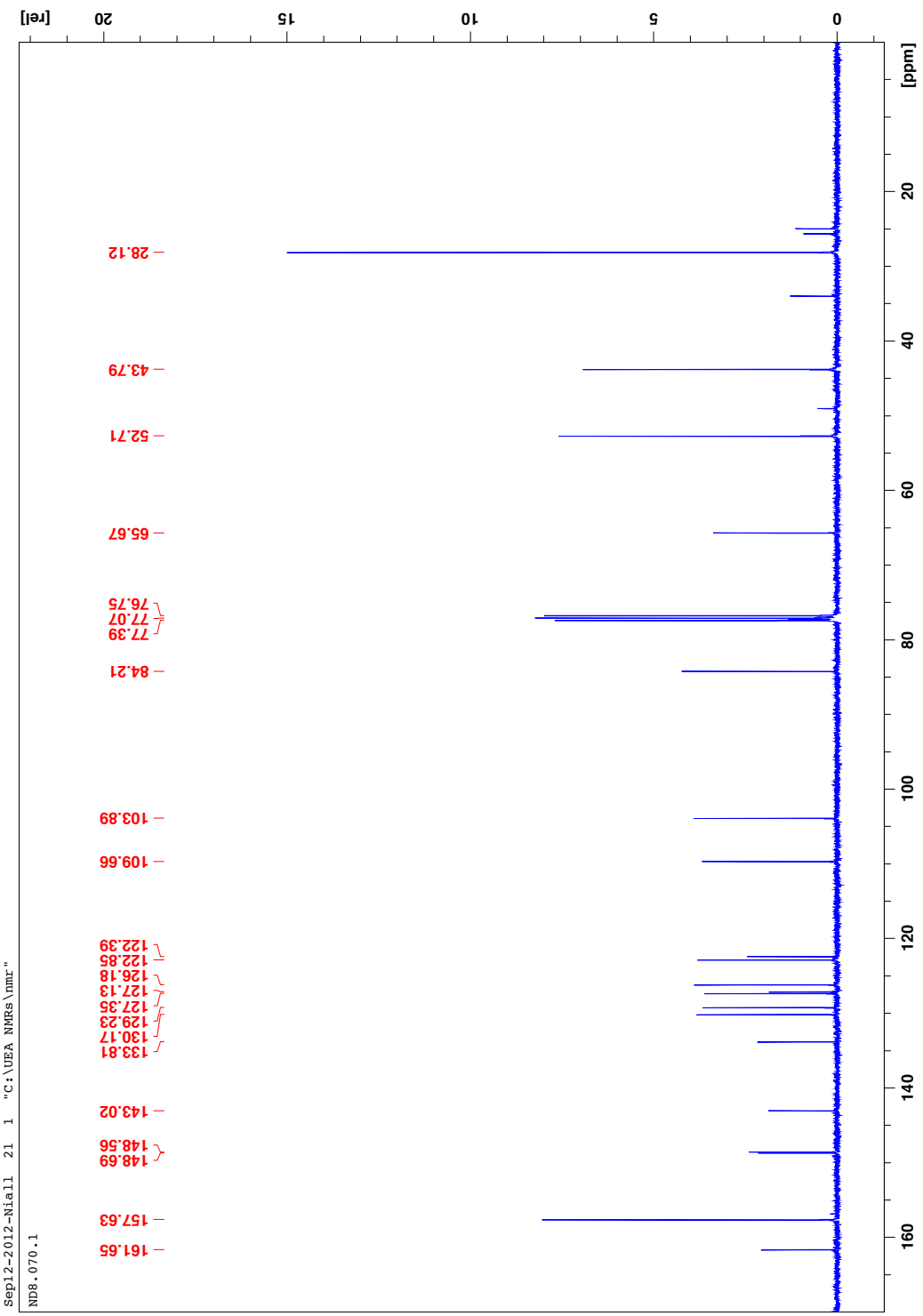

"Jul04-2012-Niall ND8.3.1" 10 1 "C:\UEA NMRs\nmr"
ND8.003.1
1H-NMR (CDCl3) 1.73 (1H, s), 5.44 (1H, s), 7.11 (1H, d, J=3.60 Hz), 7.80 (1H, d, J=3.60 Hz), 8.15 (1H, dd, J=1.55, 7.97 Hz).
Br
N
Boc
N
1.73
5.44
7.11
7.12
7.27
7.60
7.60
7.61
7.62
7.62
7.63
7.64
7.66
7.66
7.68
7.68
7.69
7.70
1.00
1.02
1.03
0.99
1.99
[rel]
[ppm]

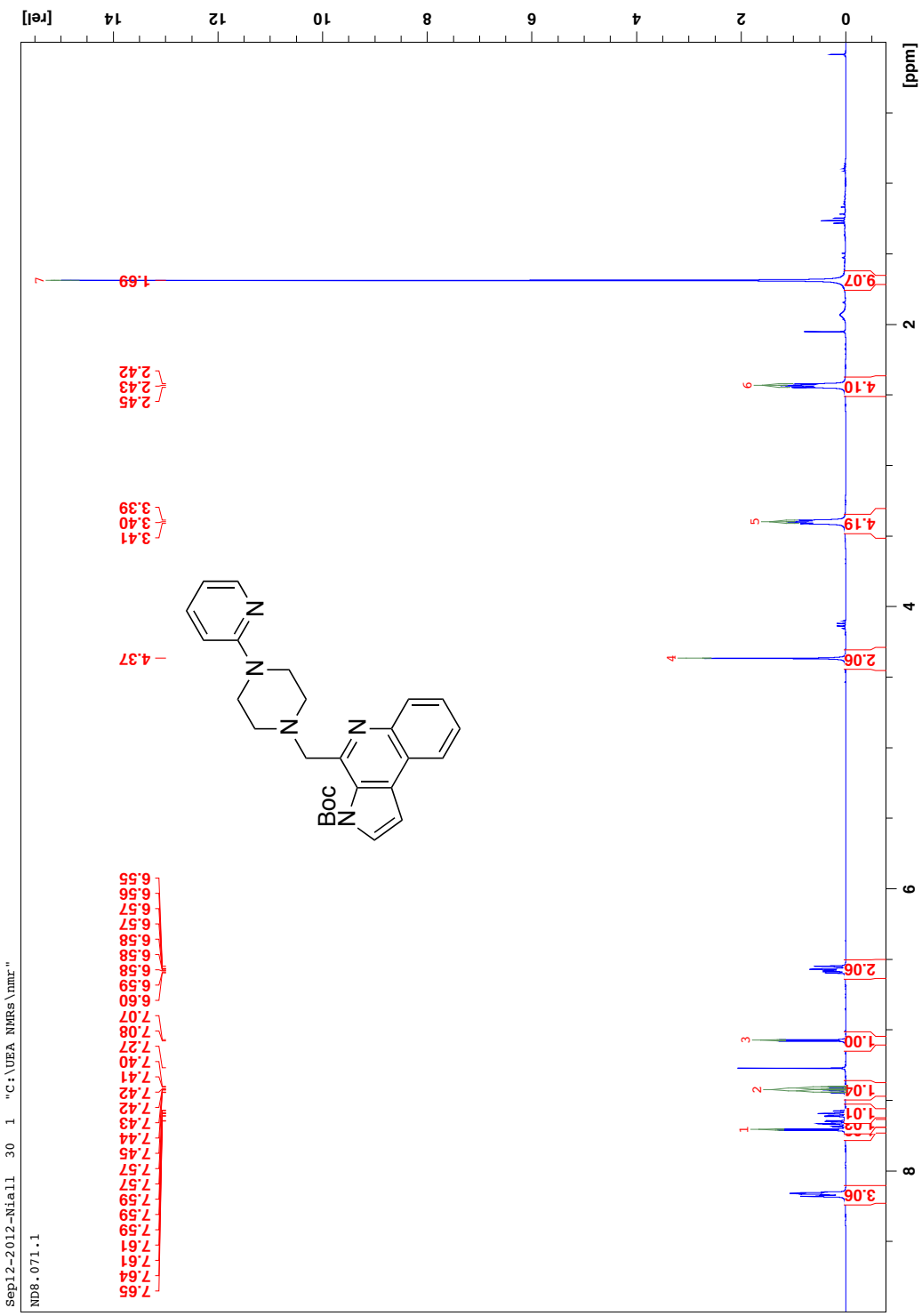

"Jul04-2012-Niall ND8.3.1" 11 1 "C:\UEA NMRs\nmr"
ND8.3.1
[rel]
[ppm]
28.04
37.07
76.68
77.00
77.32
85.27
104.49
122.63
122.87
126.00
126.94
127.76
129.35
130.23
134.67
142.97
145.48
148.74

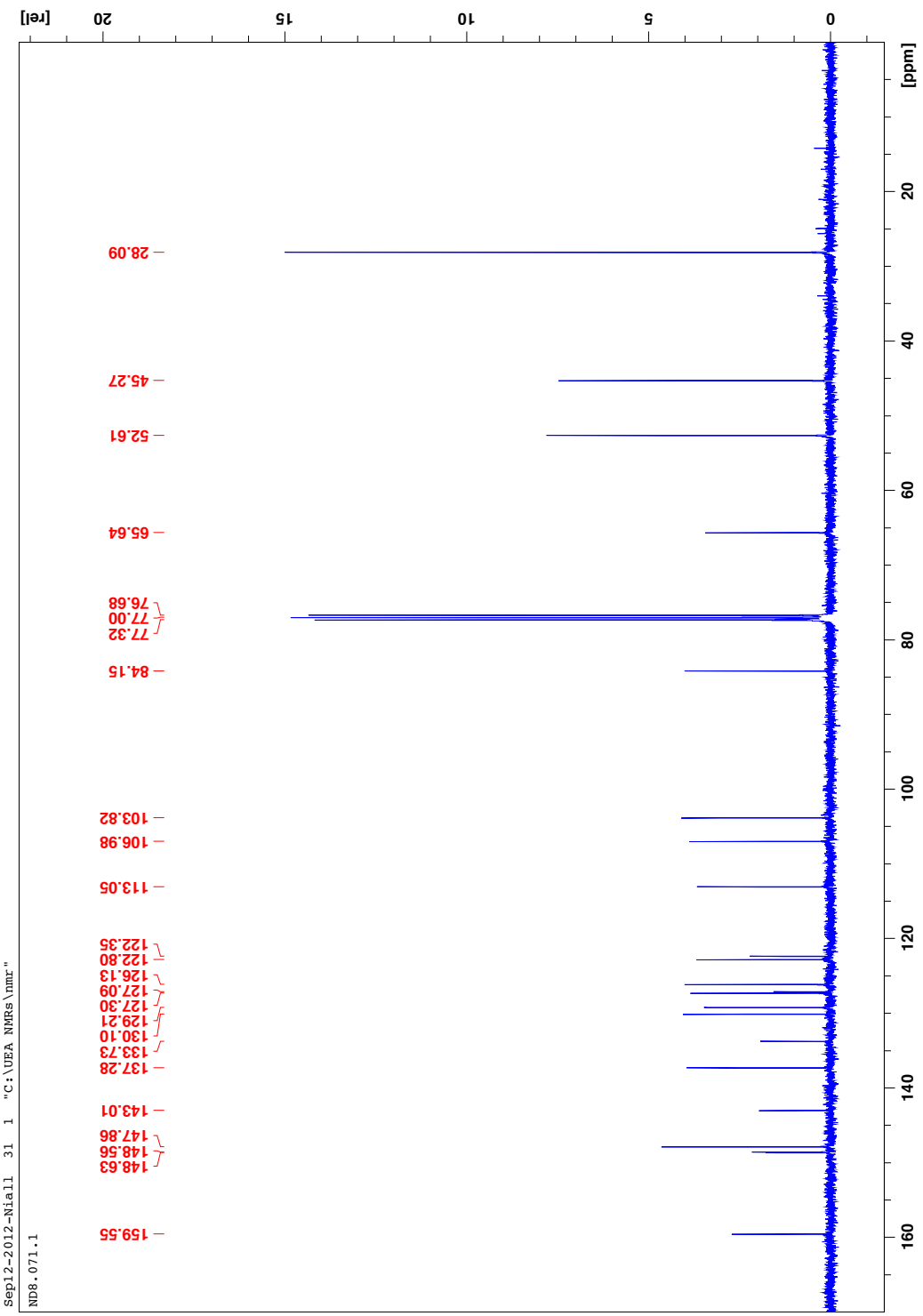

Aug10-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND8.040
8.16
8.16
8.14
8.12
7.70
7.69
7.66
7.66
7.65
7.64
7.63
7.62
7.59
7.58
7.57
7.56
7.55
7.27
7.06
7.05
4.31
3.58
3.57
3.56
2.32
2.31
2.30
1.68
Boc
N
N
O
N
1
2
3
4
5
6
7
8
9
2.00
1.01
1.00
2.00
4.00
4.08
9.09
8
6
4
2
[ppm]
[rel]
0
2
4
6
8
10
12
14

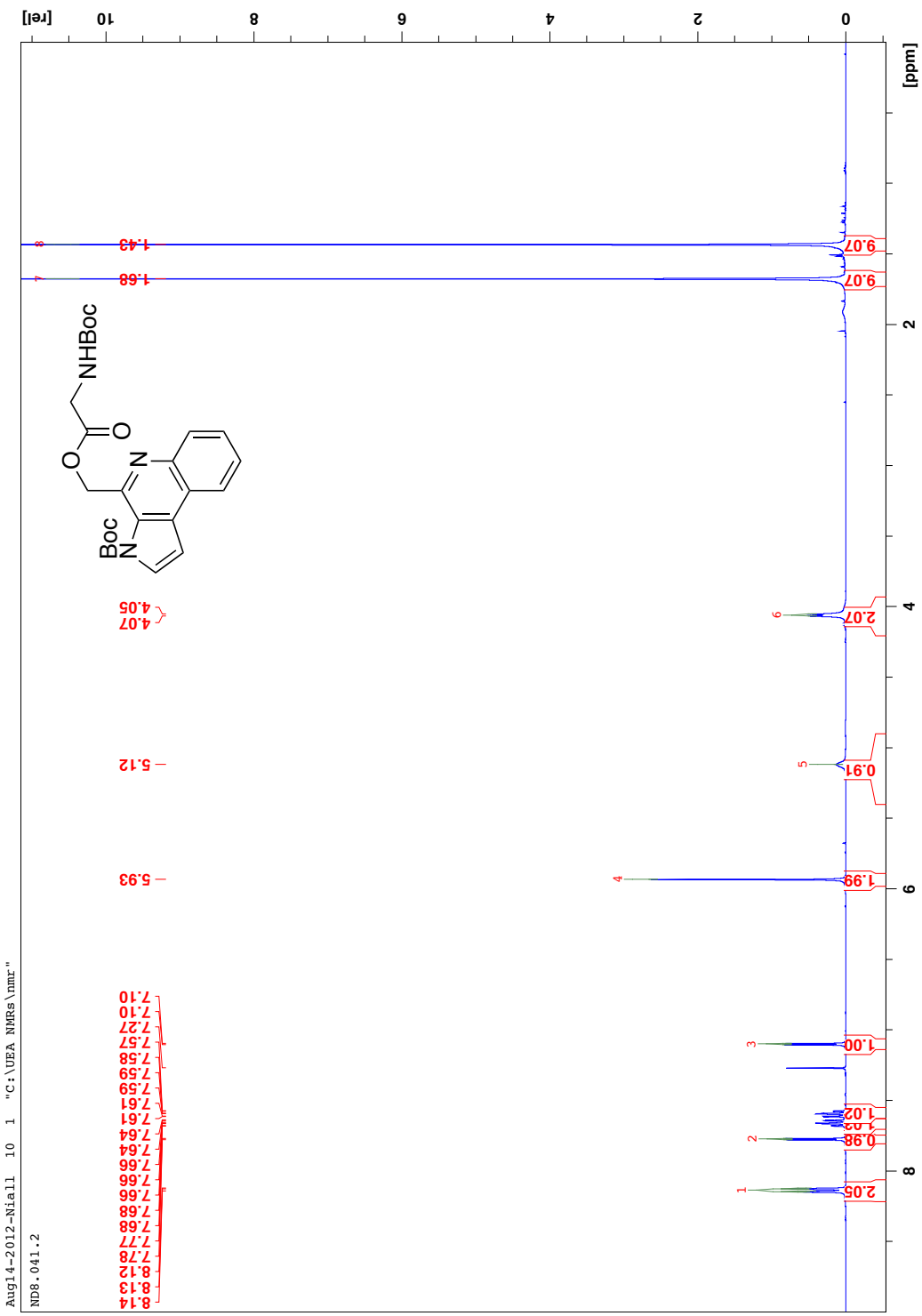

Aug10-2012-Niall 11 1 "C:\UEA NMRs\nmr"
ND8.040
148.59
148.21
142.95
133.61
130.03
129.15
127.27
126.96
126.11
122.75
122.28
103.76
84.06
77.32
77.00
76.68
67.09
65.89
53.21
28.02
[rel]
20
15
10
5
0
160
140
120
100
80
60
40
20
[ppm]

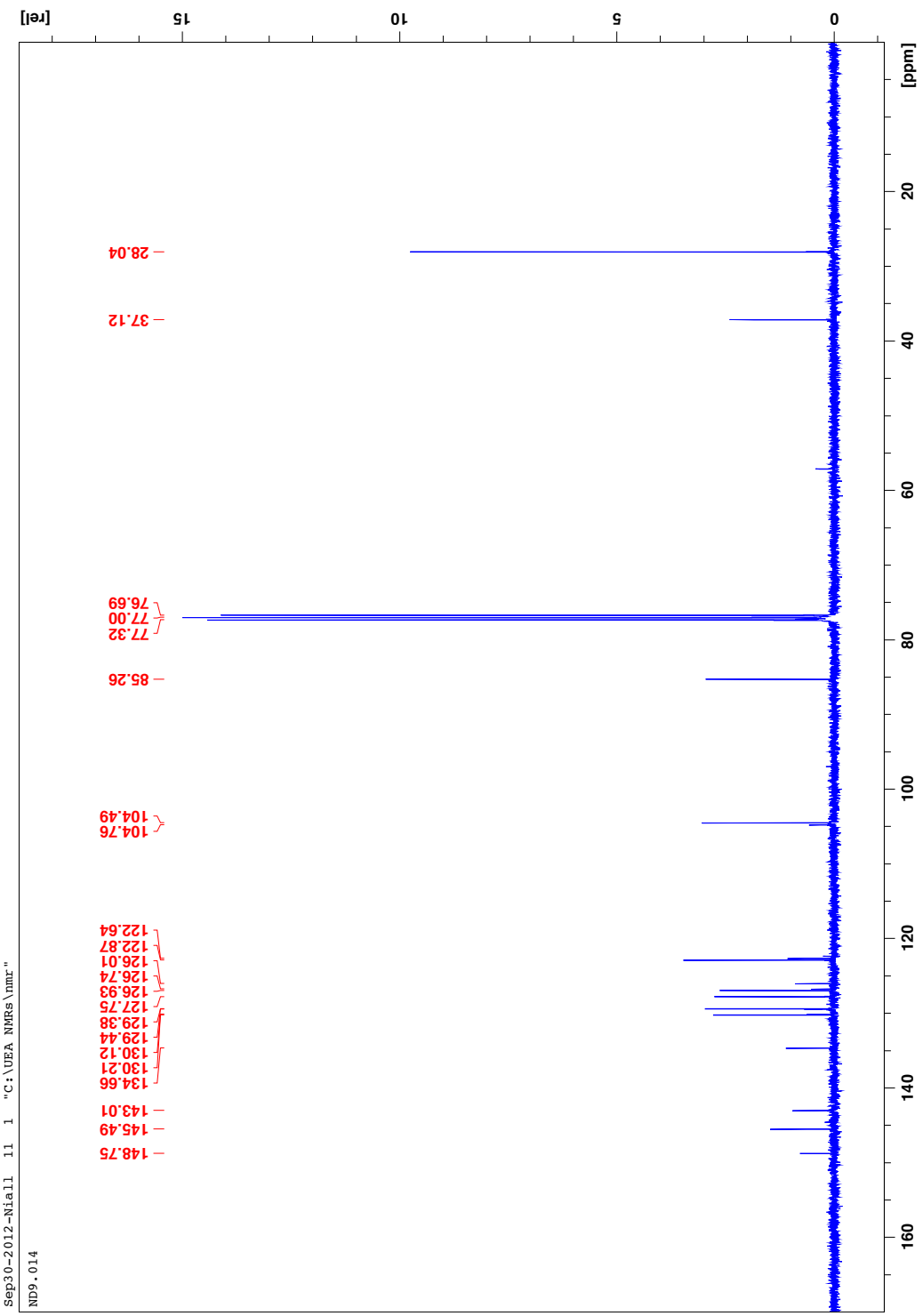

Sep12-2012-Niall 20 1 "C:\UEA NMRs\nmr"
ND8.070.1
[rel]
[ppm]
Boc
N
N
N
N
N
8.15
8.15
8.14
7.71
7.70
7.67
7.67
7.65
7.65
7.63
7.63
7.60
7.59
7.58
7.58
7.58
7.56
7.56
7.27
7.07
7.06
6.43
6.42
6.41
4.35
3.69
3.68
3.67
2.40
2.38
2.37
1.68
2.07
2.04
1.05
1.00
1.00
4.11
2.02
4.15
9.21

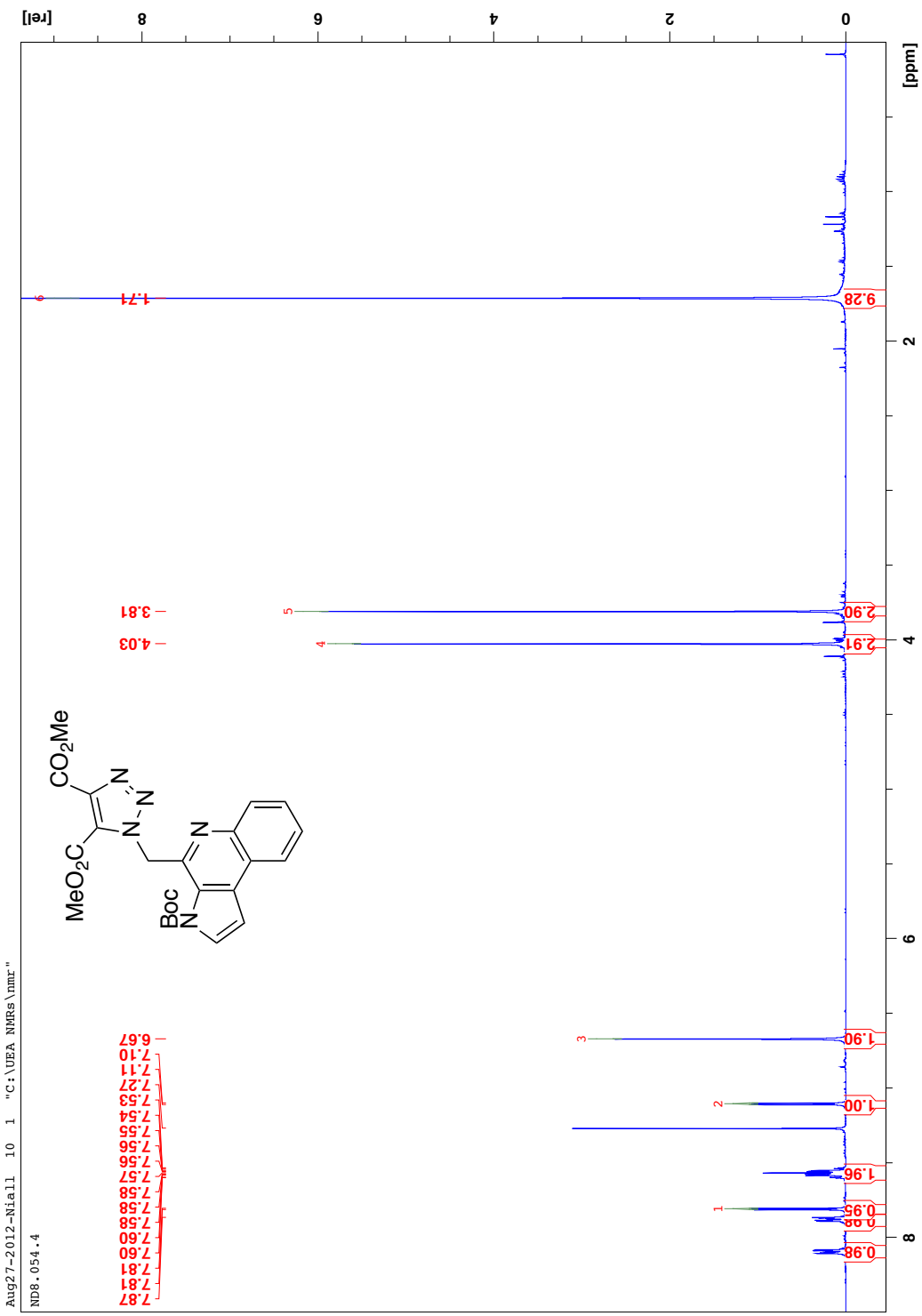

Sep12-2012-Niall 21 1 "C:\UEA NMRs\nmr"
ND8.070.1
[rel]
20
15
10
5
0
[ppm]
20
40
60
80
100
120
140
160
28.12
43.79
52.71
65.67
77.39
77.07
76.75
84.21
103.89
109.66
122.39
122.85
126.18
127.13
127.35
129.23
130.17
133.81
143.02
148.69
148.56
157.63
161.65

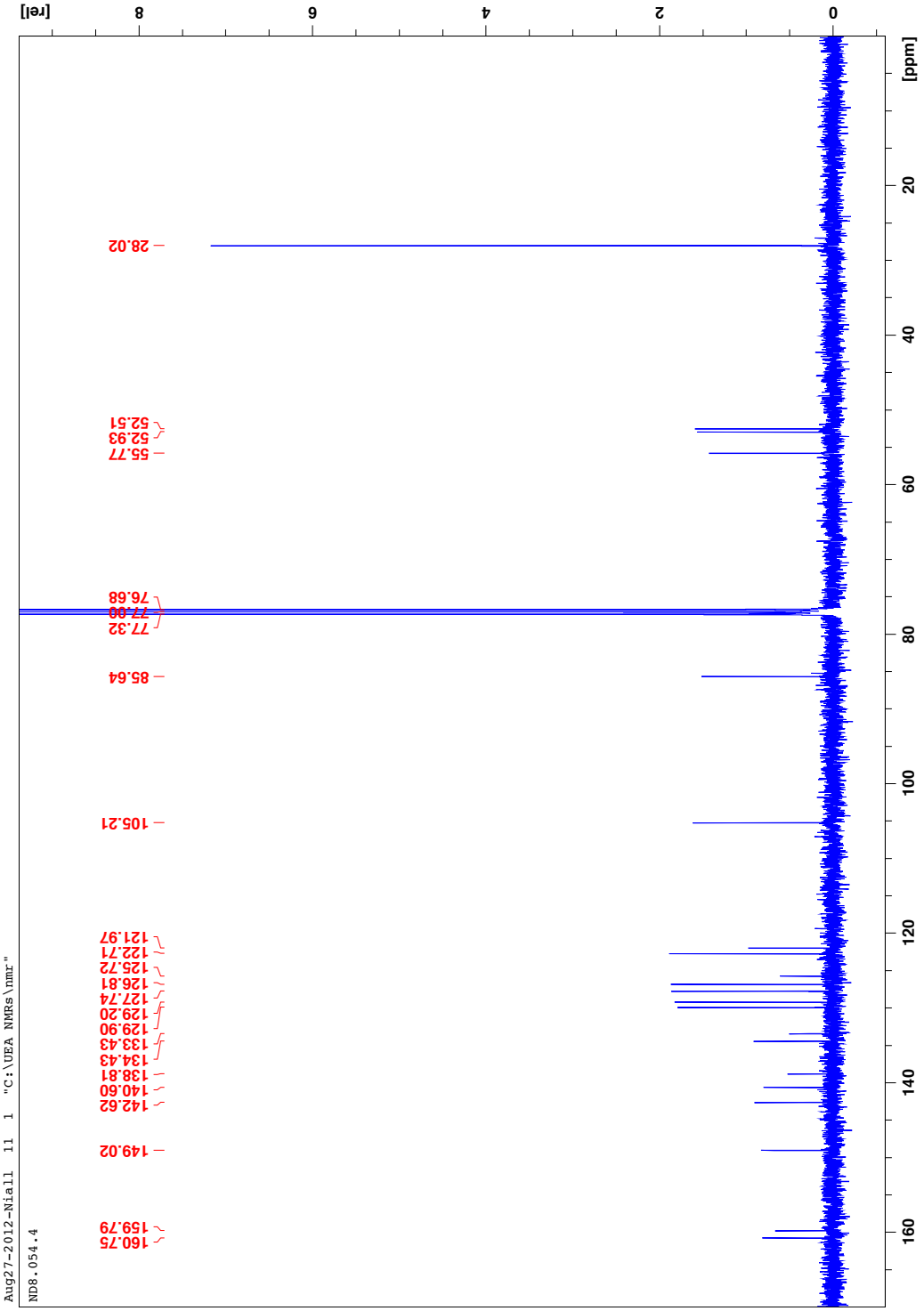

Sep12-2012-Niall 30 1 "C:\UEA NMRs\nmr"
ND8.071.1
[rel]
[ppm]
Boc
N
7.65
7.64
7.61
7.61
7.59
7.59
7.59
7.57
7.57
7.45
7.44
7.43
7.42
7.42
7.41
7.40
7.27
7.08
7.07
6.60
6.59
6.58
6.58
6.58
6.57
6.57
6.56
6.55
4.37
3.41
3.40
3.39
2.45
2.43
2.42
1.69
9.07
4.10
4.19
2.06
2.06
1.00
1.04
1.01
3.06

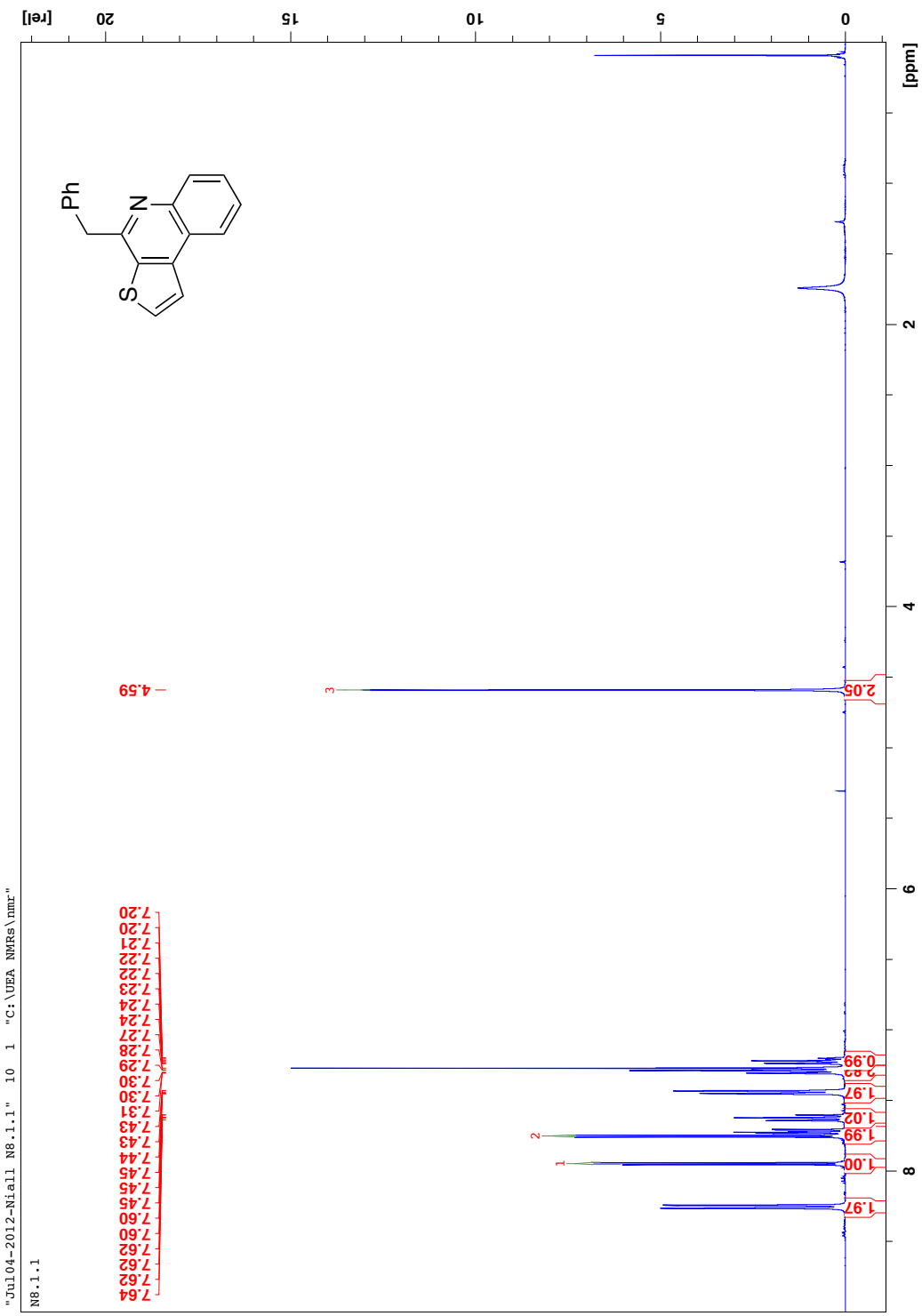

Sep12-2012-Niall 31 1 "C:\UEA NMRs\nmr"
ND8.071.1
[rel]
[ppm]
159.55
148.63
148.56
147.86
143.01
137.28
133.73
130.10
129.21
127.30
127.09
126.13
122.80
122.35
113.05
106.98
103.82
84.15
77.32
77.00
76.68
65.64
52.61
45.27
28.09

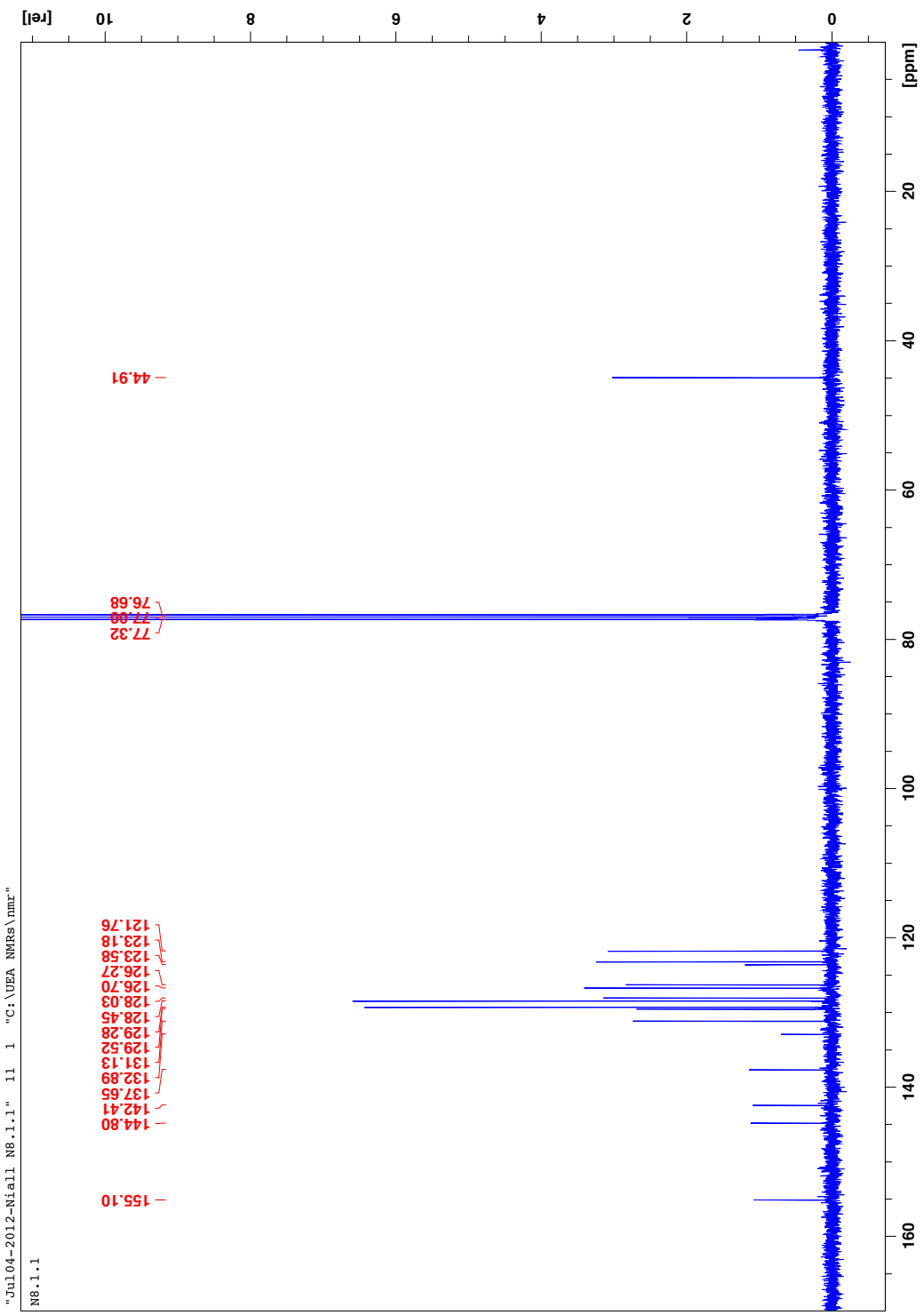

Aug14-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND8.041.2
[rel]
[ppm]
NHBoc
Boc
N
O
O
N
1.43
1.68
4.07
4.05
5.12
5.93
7.10
7.10
7.27
7.57
7.58
7.59
7.59
7.61
7.61
7.64
7.64
7.66
7.66
7.66
7.68
7.68
7.77
7.78
8.12
8.13
8.14
9.07
9.07
2.07
0.91
1.99
1.00
1.02
0.98
2.05

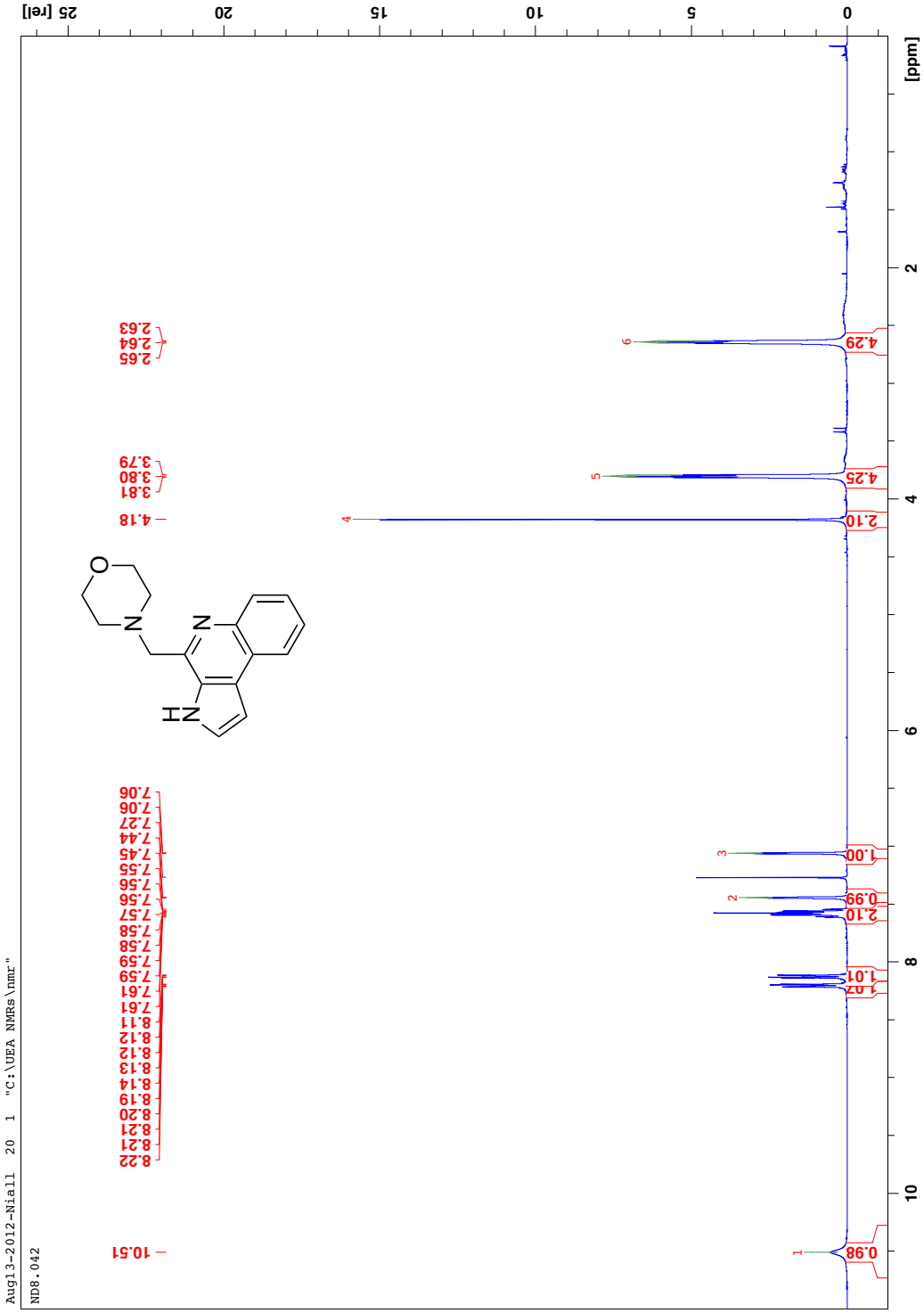

Sep30-2012-Niall 11 1 "C:\UEA NMRs\nmr"
ND9.014
[rel]
15
10
5
0
[ppm]
20
40
60
80
100
120
140
160
28.04
37.12
77.32
77.00
76.69
85.26
104.76
104.49
122.64
122.87
126.01
126.74
126.93
127.75
129.38
129.44
130.12
130.21
134.66
143.01
145.49
148.75

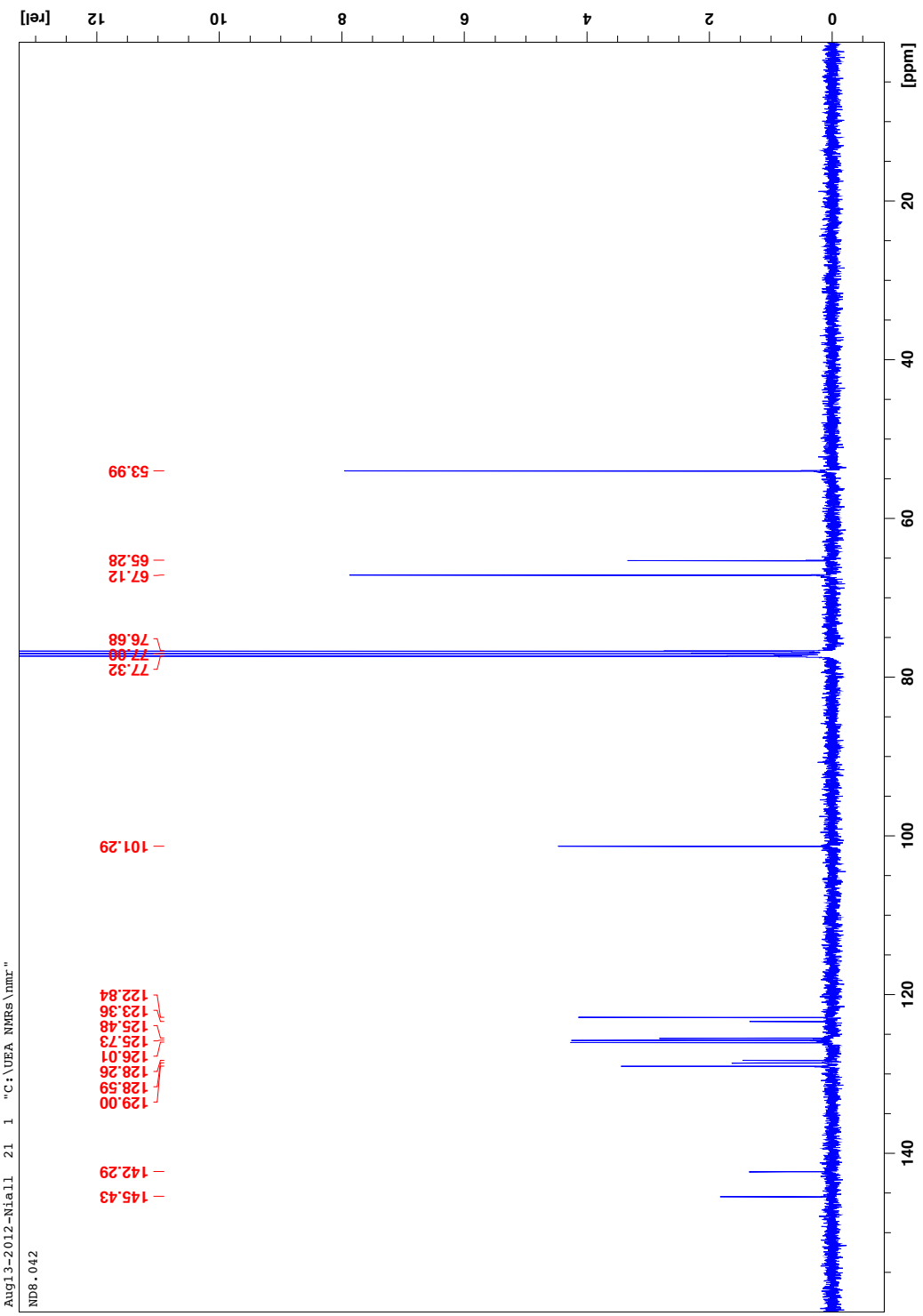

Aug27-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND8.054.4
[rel]
[ppm]
CO2Me
MeO2C
Boc
N
9.28
1.71
2.90
2.91
3.81
4.03
1.90
1.00
1.96
0.95
0.98
0.96
7.87
7.81
7.81
7.60
7.60
7.60
7.58
7.58
7.58
7.57
7.56
7.56
7.55
7.54
7.53
7.27
7.11
7.10
6.67

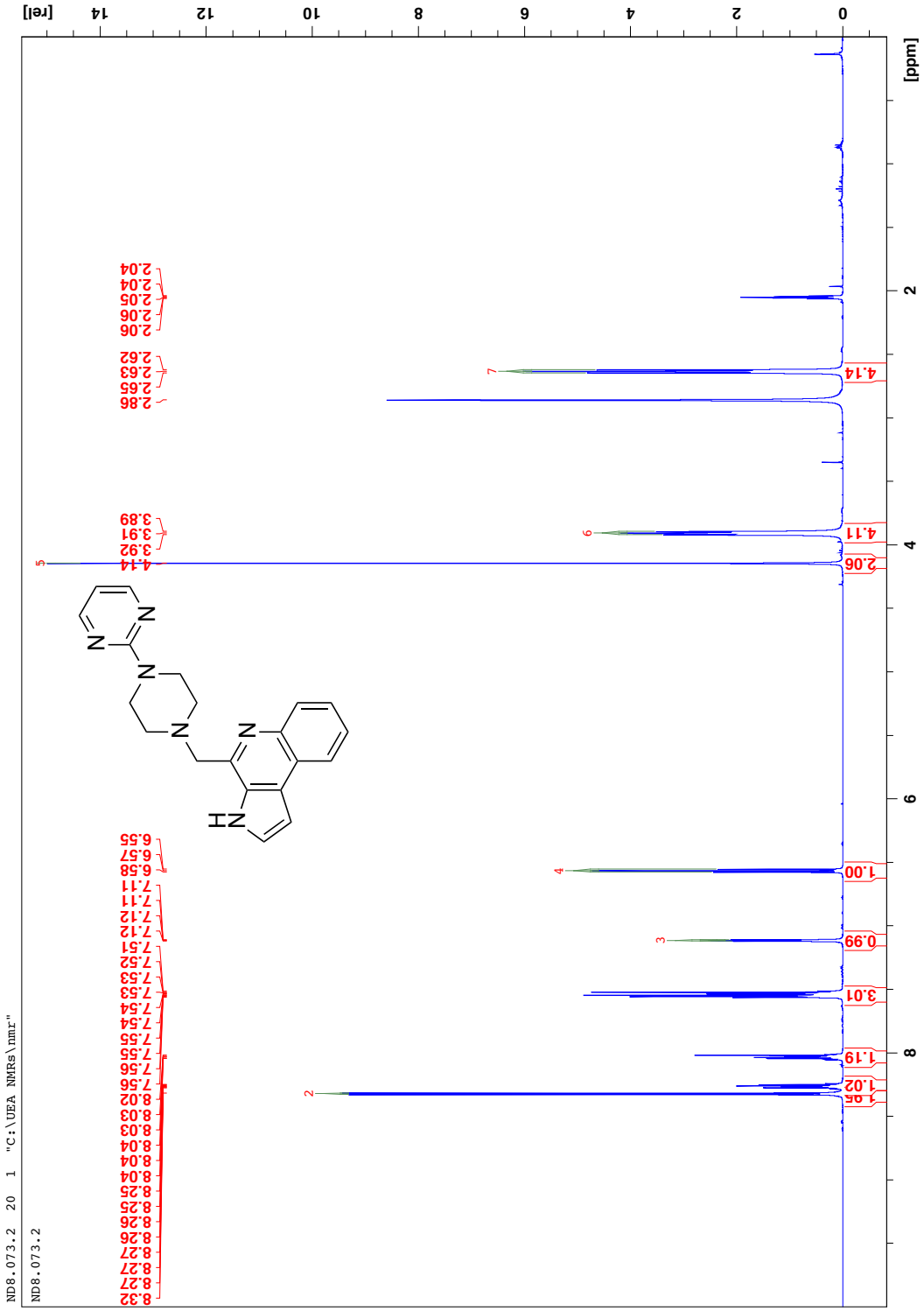

[rel]
8
6
4
2
0
[ppm]
20
40
60
80
100
120
140
160
28.02
52.51
52.93
55.77
76.68
77.00
77.32
85.64
105.21
121.97
122.71
125.72
126.81
127.74
129.20
129.90
133.43
134.43
138.81
140.60
142.62
149.02
159.79
160.75
Aug27-2012-Niall 11 1 "C:\UEA NMRs\nmr"
ND8.054.4

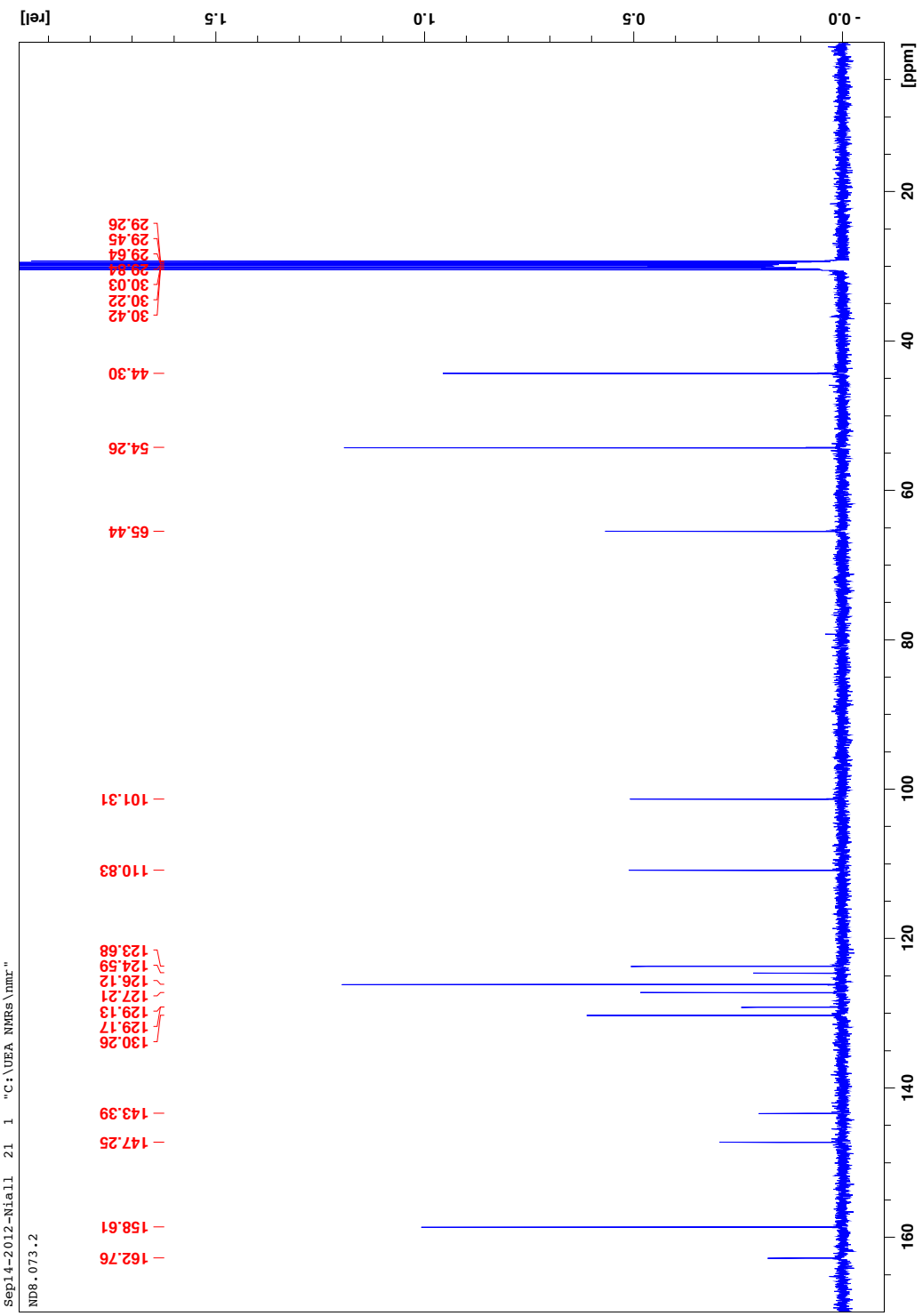

"Jul04-2012-Niall N8.1.1" 10 1 "C:\UEA NMRs\nmr"
N8.1.1
[rel]
20
15
10
5
0
[ppm]
8
6
4
2
4.59
2.05
0.99
1.97
1.02
1.99
1.00
1.97
7.64
7.62
7.62
7.62
7.60
7.60
7.45
7.45
7.45
7.44
7.43
7.43
7.31
7.30
7.30
7.29
7.28
7.27
7.24
7.24
7.23
7.22
7.22
7.21
7.20
7.20
Ph
N
S

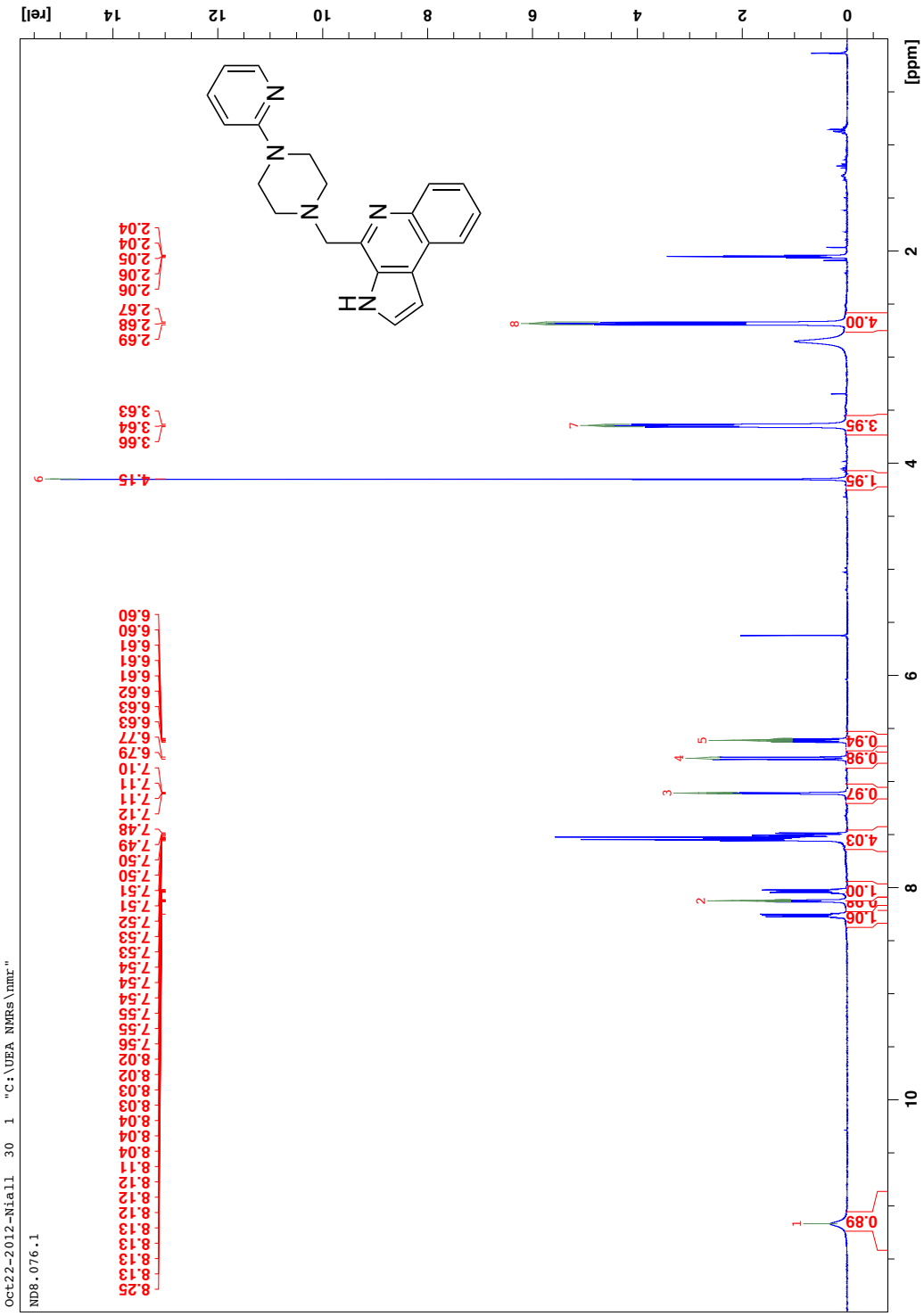

"Jul04-2012-Niall N8.1.1" 11 1 "C:\UEA NMRs\nmr"
N8.1.1
[rel]
[ppm]
155.10
144.80
142.41
137.65
132.89
131.13
129.52
129.28
128.45
128.03
126.70
126.27
123.58
123.18
121.76
77.32
77.00
76.68
44.91

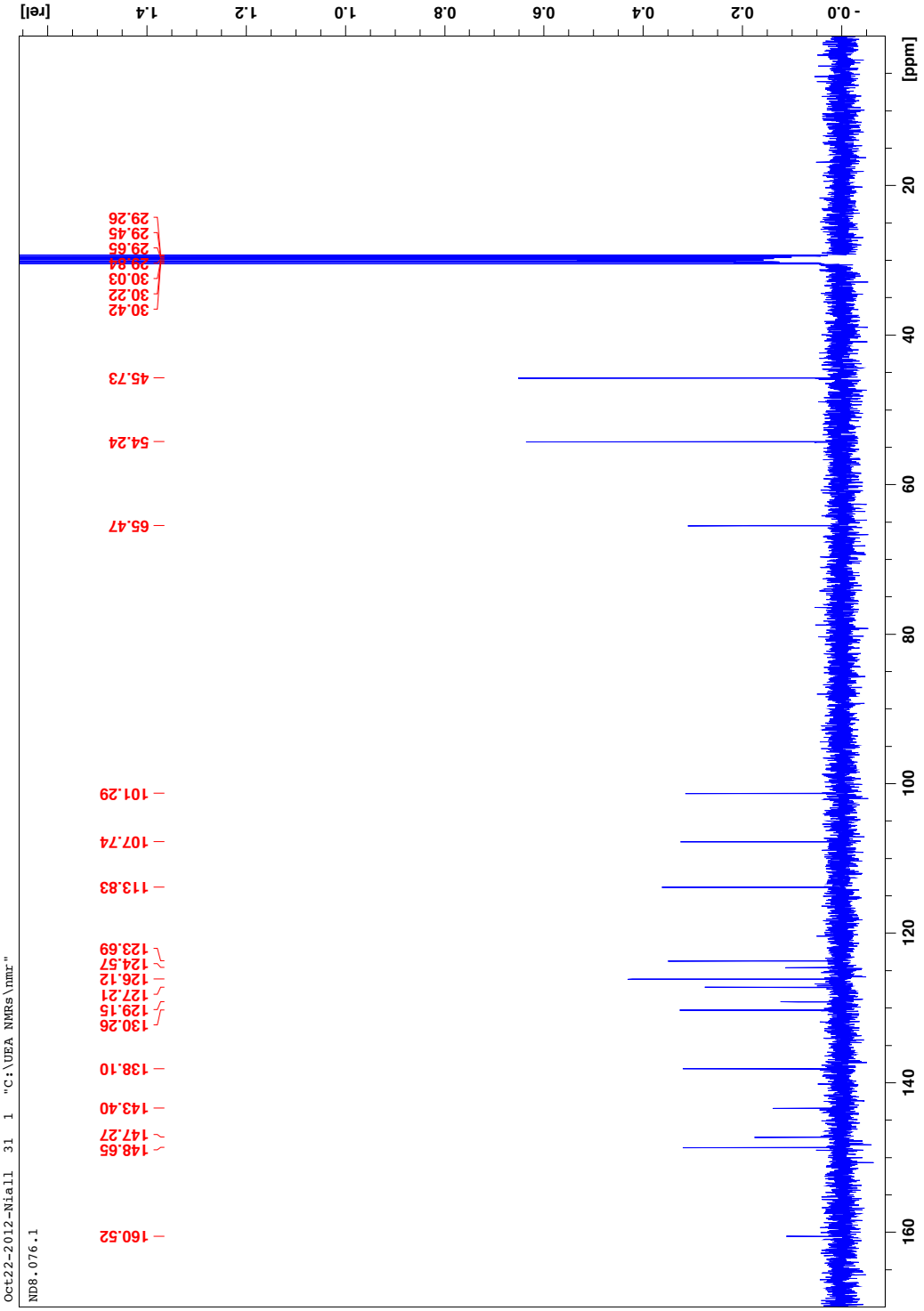

Aug13-2012-Niall 20 1 "C:\UEA NMRs\nmr"
ND8.042
[ppm]
[rel]
0
5
10
15
20
25
2
4
6
8
10
0.98
4.29
4.25
2.10
1.00
0.99
2.10
1.02
1.01
2.65
2.64
2.63
3.81
3.80
3.79
4.18
10.51
8.22
8.21
8.21
8.20
8.19
8.14
8.13
8.12
8.12
8.11
7.61
7.61
7.59
7.59
7.59
7.58
7.58
7.57
7.56
7.56
7.55
7.56
7.45
7.44
7.27
7.06
7.06
O
N
N
NH

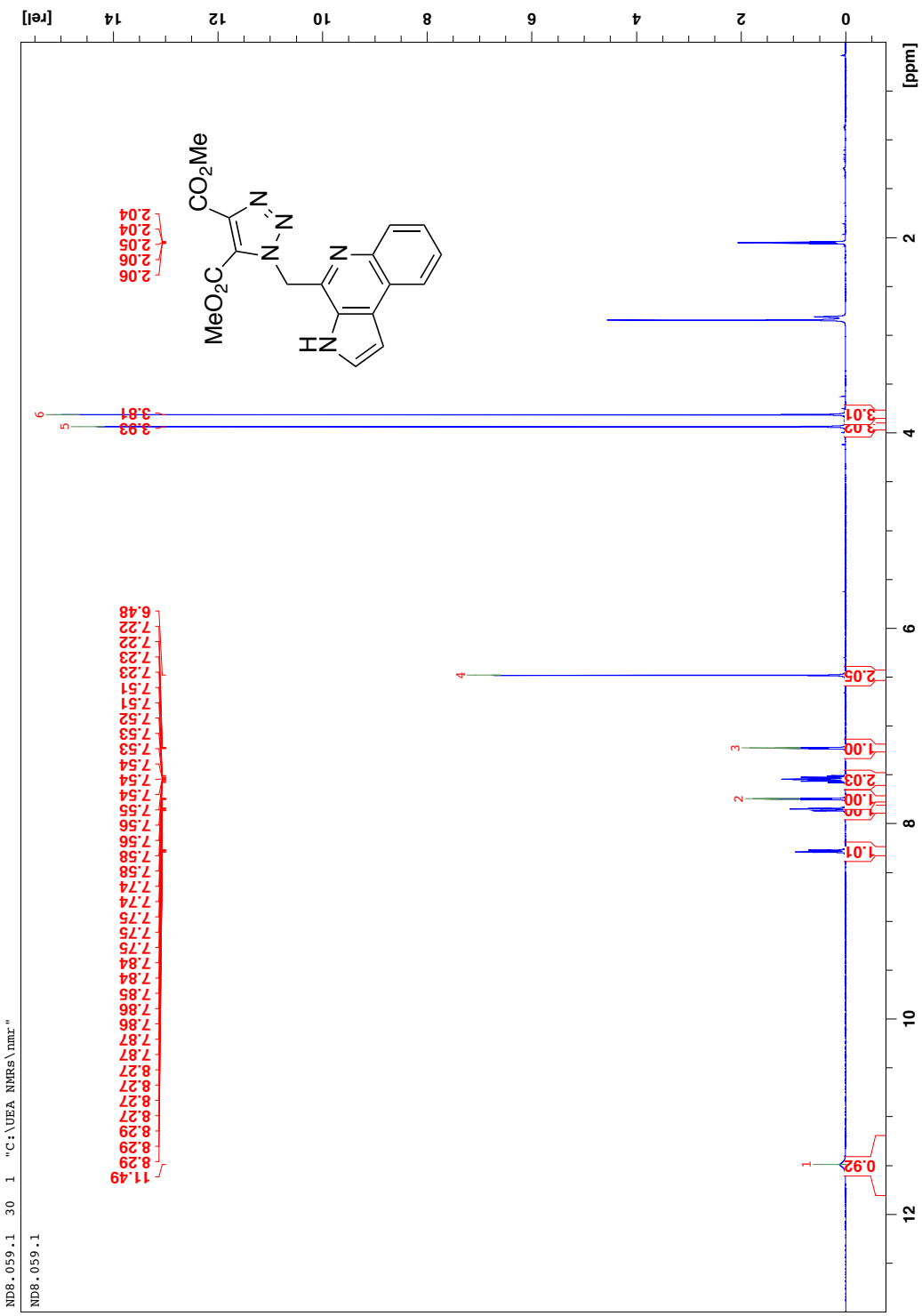

Aug13-2012-Niall 21 1 "C:\UEA NMRs\nmr"
ND8.042
[rel]
[ppm]
0
2
4
6
8
10
12
20
40
60
80
100
120
140
53.99
65.28
67.12
76.68
77.08
77.32
101.29
122.84
123.36
125.48
125.73
126.01
128.26
128.59
129.00
142.29
145.43

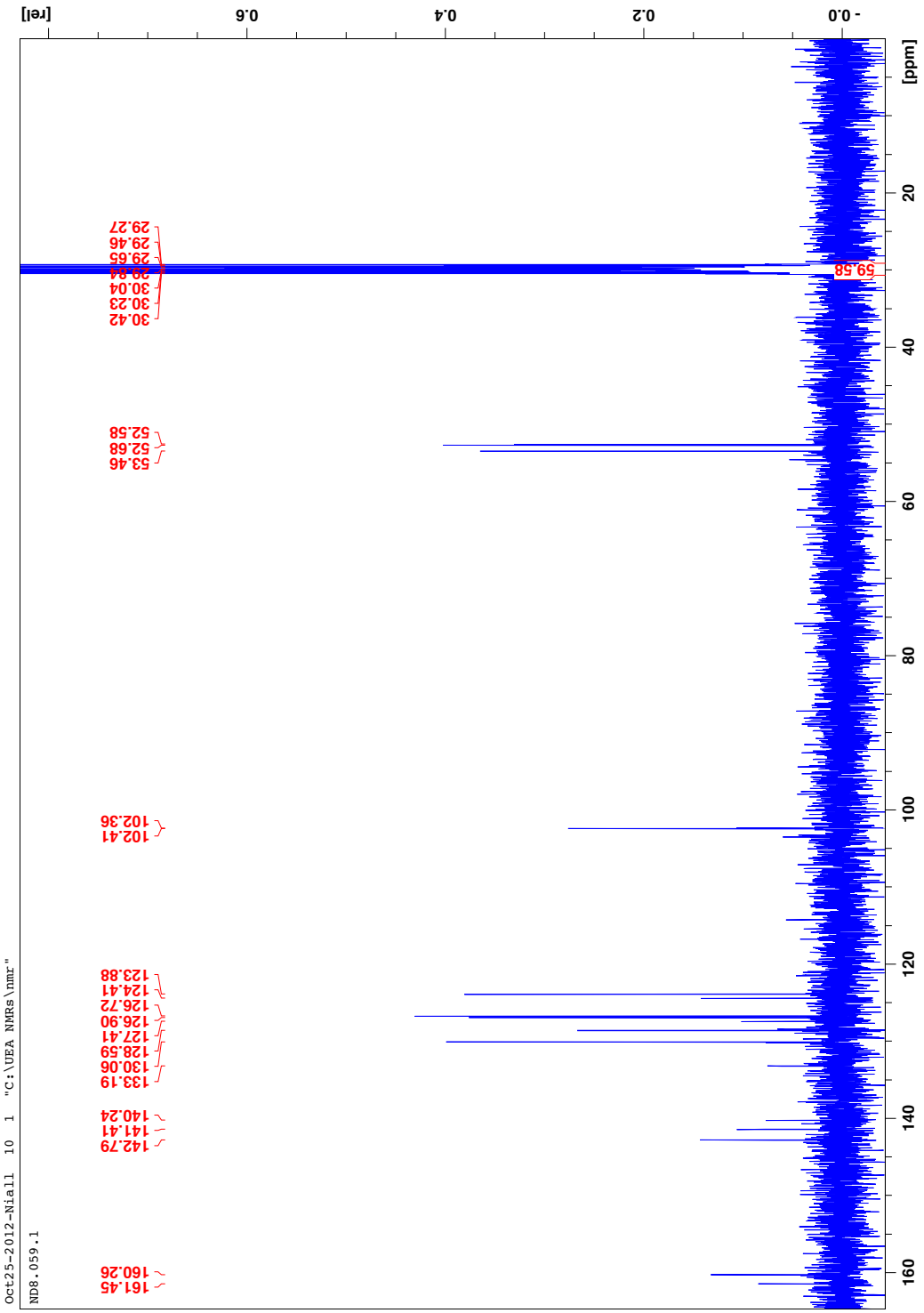

ND8.073.2 20 1 "C:\UEA NMRs\nmr"
ND8.073.2
[rel]
[ppm]
0
2
4
6
8
10
12
14
8.32
8.27
8.27
8.27
8.26
8.26
8.25
8.25
8.04
8.04
8.04
8.03
8.03
8.02
7.56
7.56
7.55
7.55
7.54
7.54
7.53
7.53
7.52
7.51
7.12
7.12
7.11
7.11
6.58
6.57
6.55
4.14
3.92
3.91
3.89
2.86
2.65
2.63
2.62
2.06
2.06
2.05
2.04
2.04
1.95
1.02
1.19
3.01
0.99
1.00
2.06
4.11
4.14
N
N
N
N
N
NH

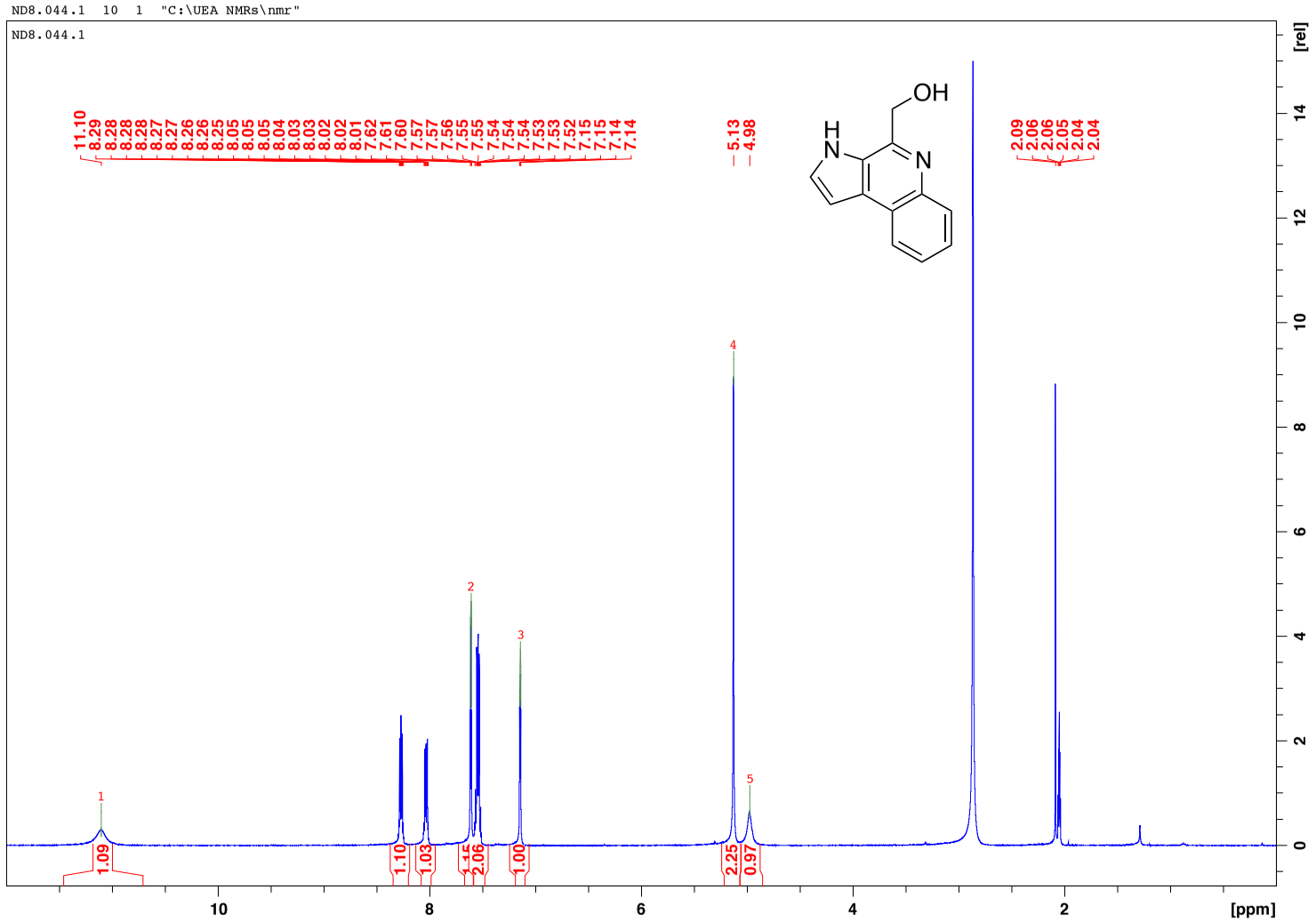

Sep14-2012-Niall 21 1 "C:\UEA NMRs\nmr"
ND8.073.2
[rel]
0.0
0.5
1.0
1.5
[ppm]
20
40
60
80
100
120
140
160
29.26
29.45
29.64
29.84
30.03
30.22
30.42
44.30
54.26
65.44
101.31
110.83
123.68
124.59
126.12
127.21
129.13
129.17
130.26
143.39
147.25
158.61
162.76

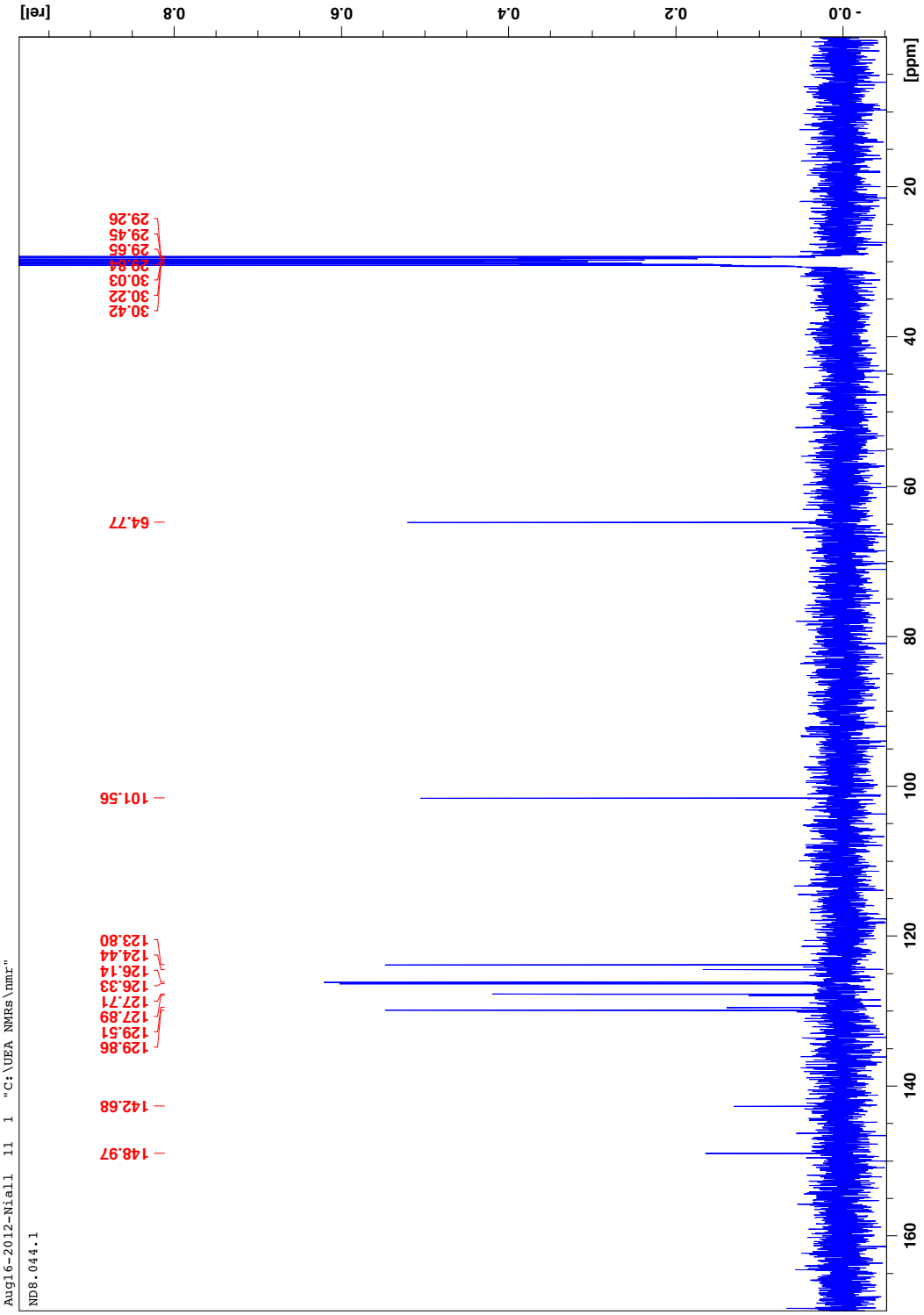

Oct22-2012-Niall 30 1 "C:\UEA NMRs\nmr"
ND8.076.1
[rel]
[ppm]
0
2
4
6
8
10
12
14
0.89
4.00
3.95
1.95
0.94
0.98
0.97
4.03
1.00
1.06
8.25
8.13
8.13
8.13
8.13
8.12
8.12
8.12
8.11
8.04
8.04
8.04
8.03
8.03
8.02
8.02
8.02
7.56
7.55
7.55
7.54
7.54
7.54
7.53
7.53
7.52
7.51
7.51
7.50
7.50
7.49
7.48
7.12
7.11
7.11
7.10
6.77
6.79
6.63
6.63
6.62
6.61
6.61
6.61
6.60
6.60
6.60
3.66
3.64
3.63
2.69
2.68
2.67
2.06
2.06
2.05
2.04
2.04

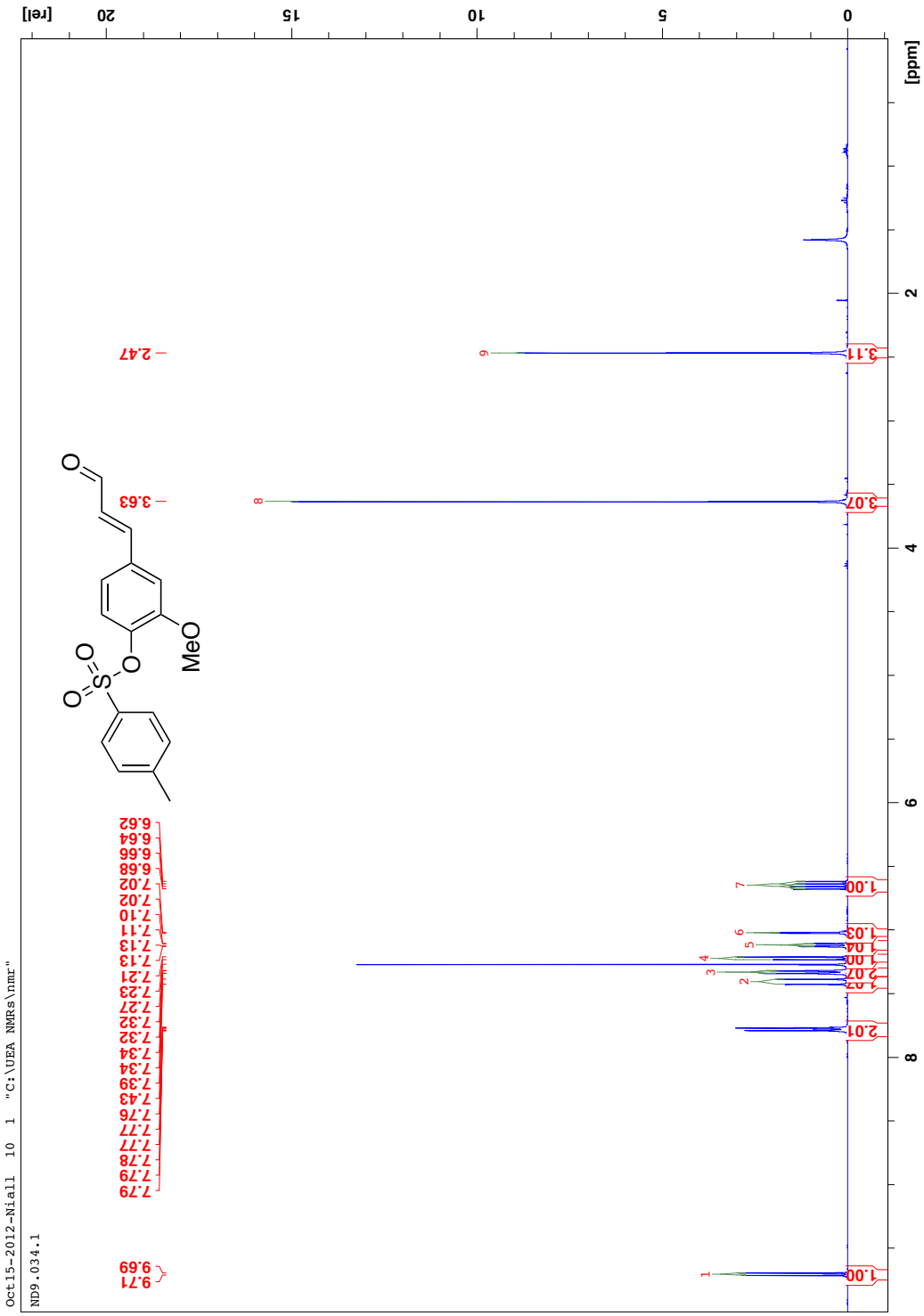

Oct22-2012-Niall 31 1 "C:\UEA NMRs\nmr"
ND8.076.1
[rel]
[ppm]
160.52
148.65
147.27
143.40
138.10
130.26
129.15
127.21
126.12
124.57
123.69
113.83
107.74
101.29
65.47
54.24
45.73
30.42
30.22
30.03
29.84
29.65
29.45
29.26

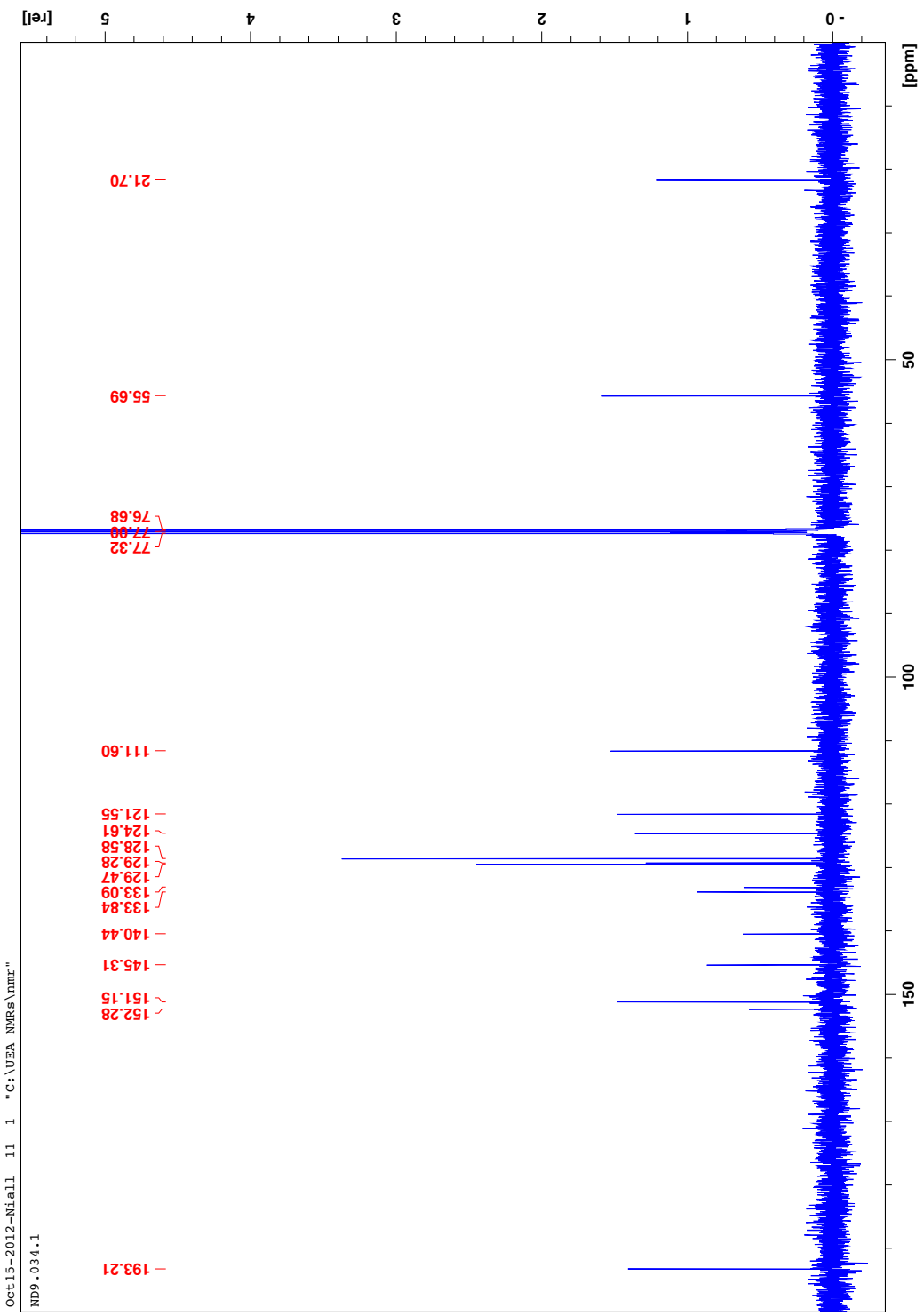

ND8.059.1 30 1 "C:\UEA NMRs\nmr"
ND8.059.1
[rel]
[ppm]
CO_2Me
MeO_2C
N
N
N
NH

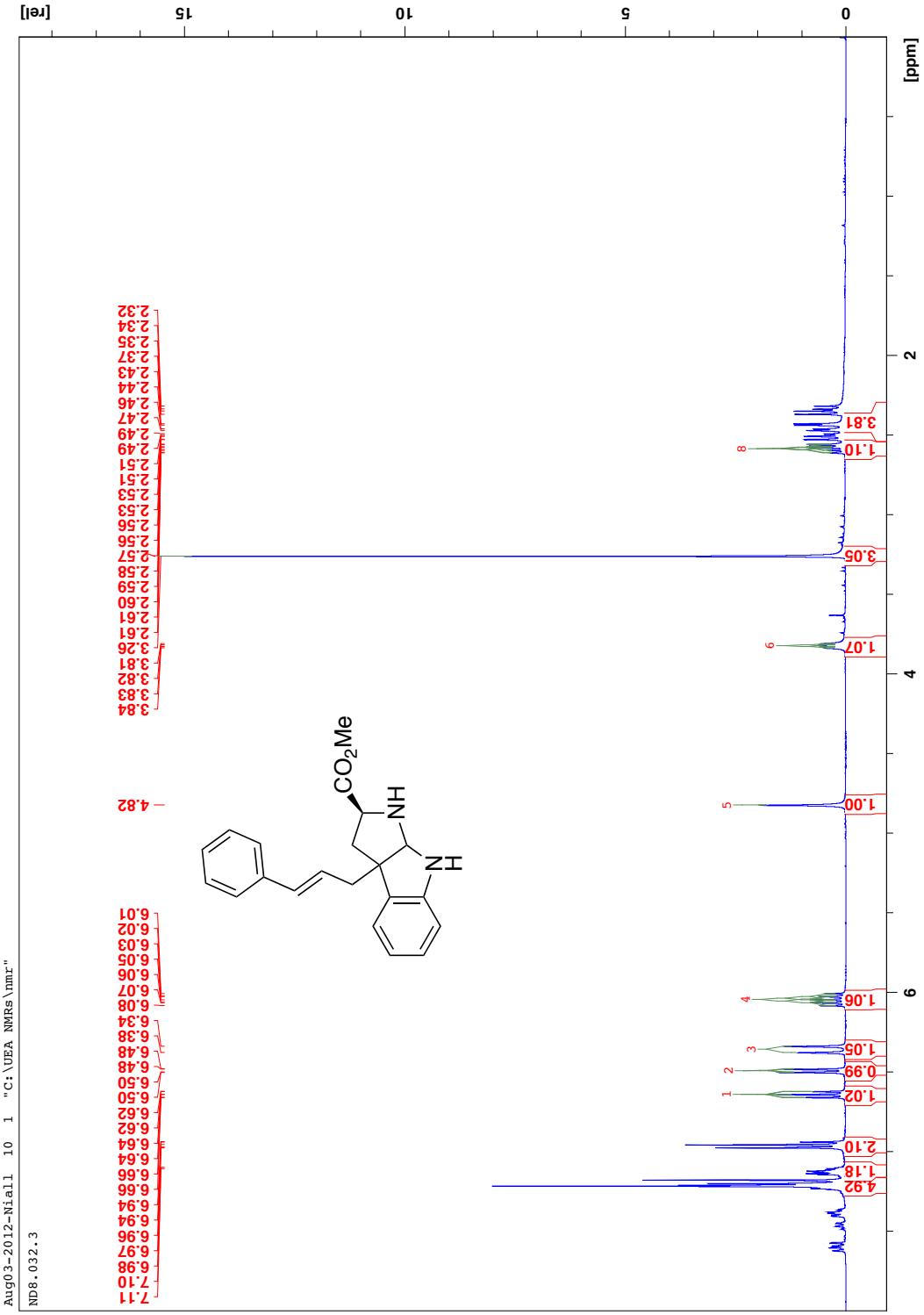

Oct25-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND8.059.1
[rel]
0.0
0.2
0.4
0.6
[ppm]
20
40
60
80
100
120
140
160
161.45
160.26
142.79
141.41
140.24
133.19
130.06
128.59
127.41
126.90
126.72
124.41
123.88
102.41
102.36
53.46
52.68
52.58
30.42
30.23
30.04
29.84
29.65
29.46
29.27
59.58

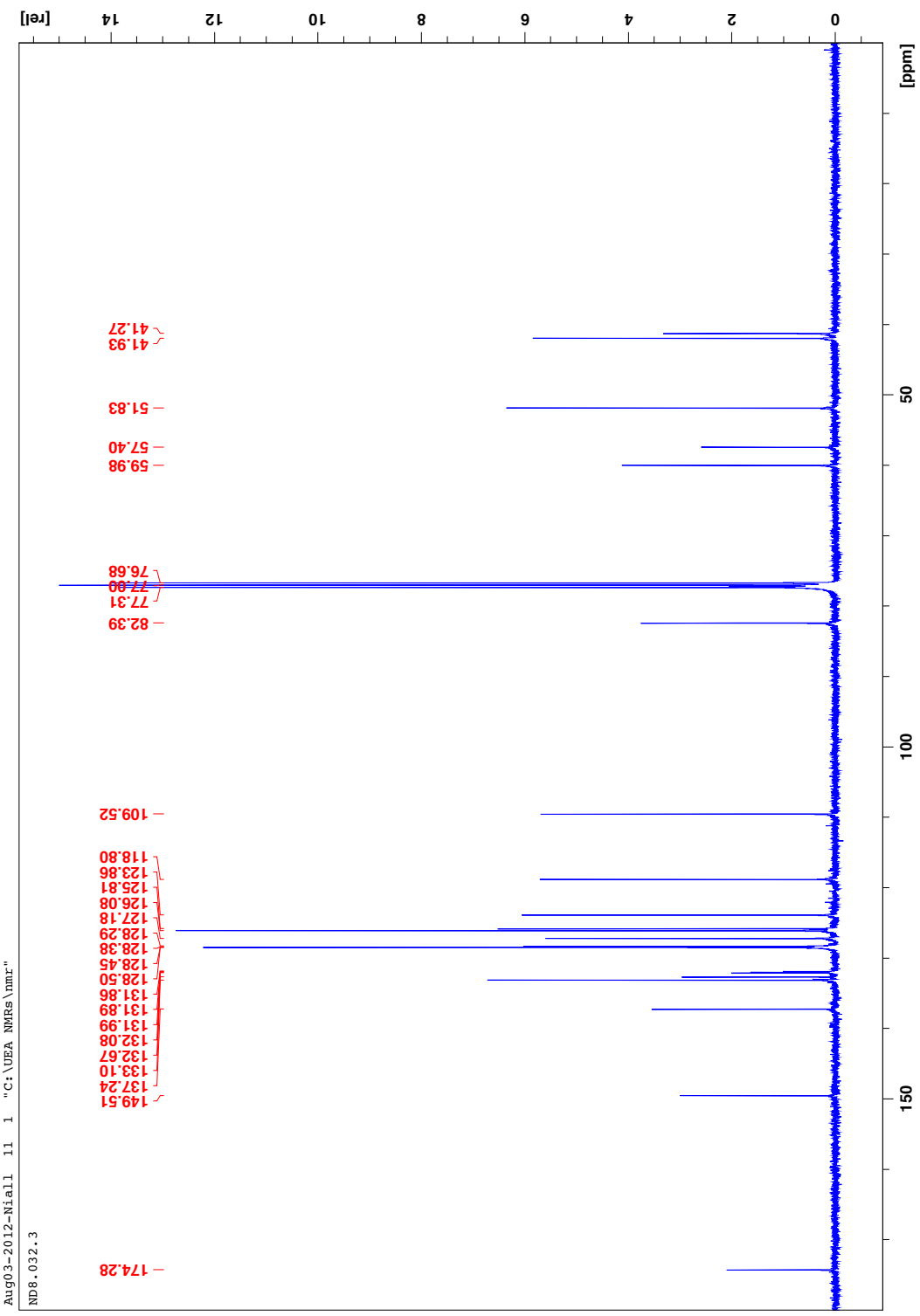

ND8.044.1 10 1 "C:\UEA NMRs\nmr"
ND8.044.1
11.10
8.29
8.28
8.28
8.28
8.27
8.27
8.26
8.26
8.25
8.05
8.05
8.04
8.03
8.03
8.02
8.02
8.01
7.62
7.61
7.60
7.57
7.57
7.56
7.55
7.55
7.54
7.54
7.54
7.53
7.53
7.52
7.15
7.15
7.14
7.14
5.13
4.98
2.09
2.06
2.06
2.05
2.04
2.04
OH
H
N
N
1
2
3
4
5
1.09
1.10
1.03
2.06
1.00
2.25
0.97
10
8
6
4
2
[ppm]
[rel]
0
2
4
6
8
10
12
14

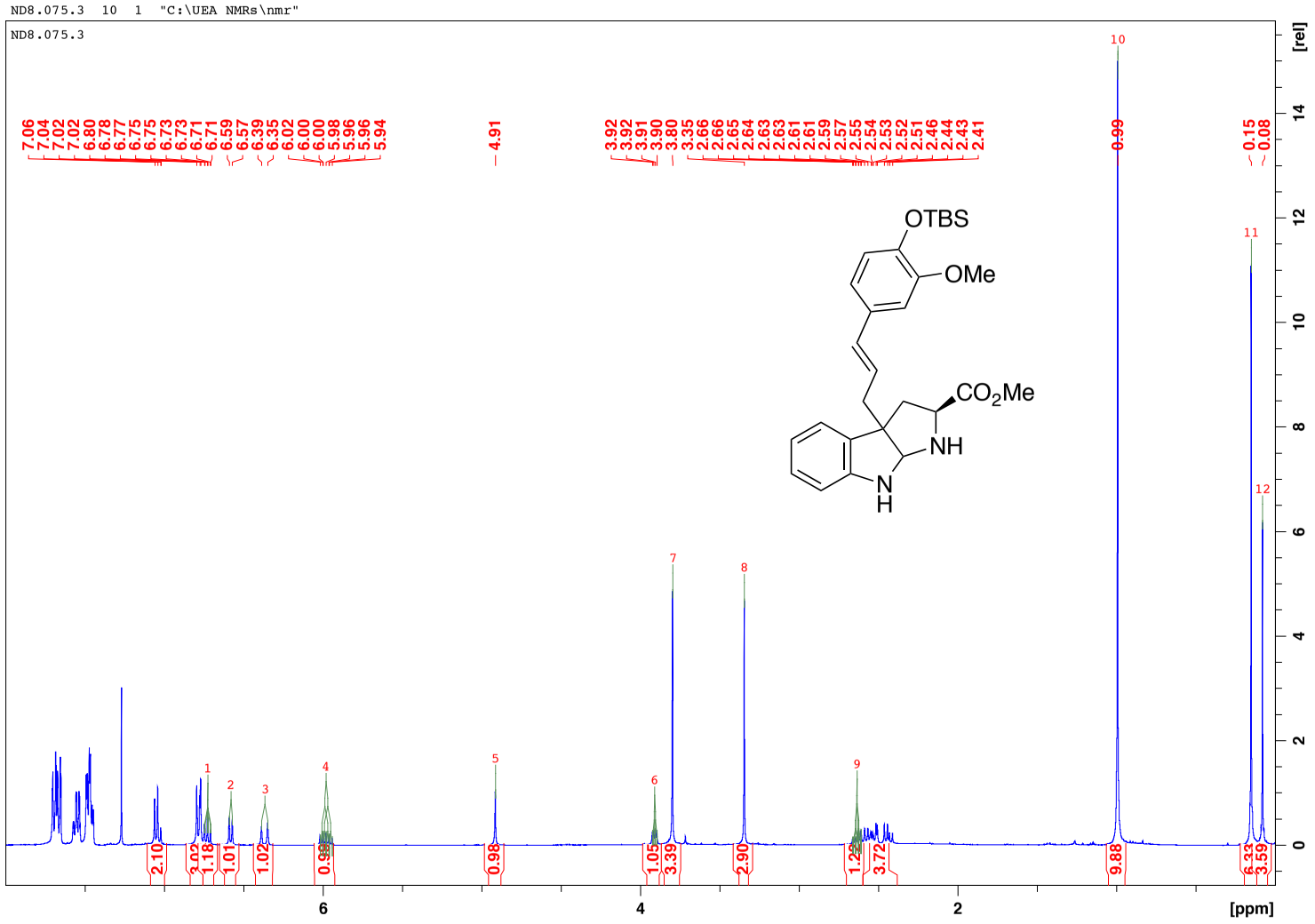

Aug16-2012-Niall 11 1 "C:\UEA NMRs\nmr"
ND8.044.1
[rel]
0.8
0.6
0.4
0.2
- 0.0
[ppm]
160
140
120
100
80
60
40
20
148.97
142.68
129.86
129.51
127.89
127.71
126.33
126.14
124.44
123.80
101.56
64.77
30.42
30.22
30.03
29.84
29.65
29.45
29.26

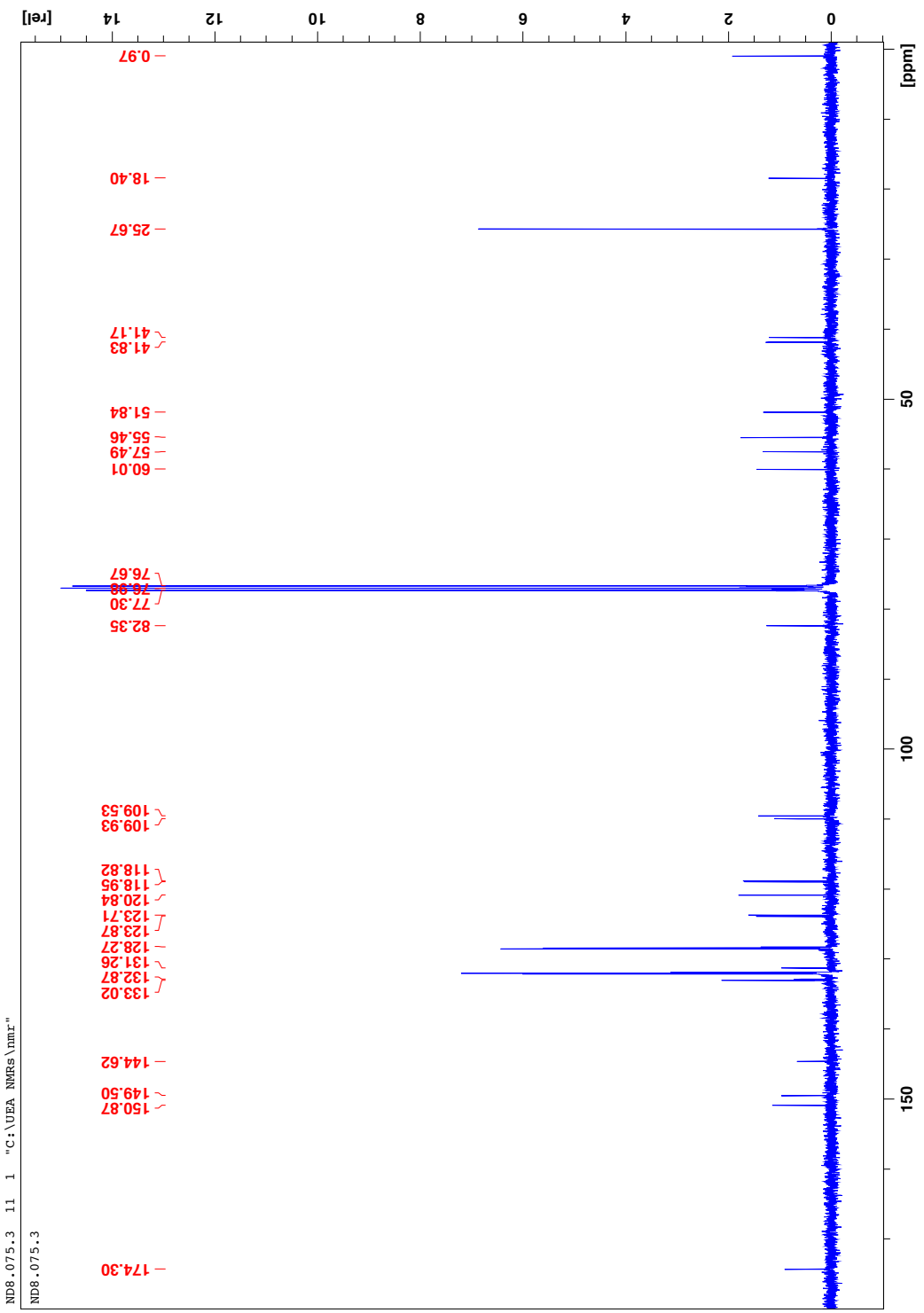

Oct15-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND9.034.1
[rel]
20
15
10
5
0
[ppm]
2
4
6
8
9.71
9.69
7.79
7.79
7.78
7.77
7.77
7.76
7.43
7.39
7.34
7.34
7.32
7.32
7.27
7.23
7.21
7.13
7.13
7.11
7.10
7.02
7.02
6.68
6.66
6.64
6.62
3.63
2.47
1.00
2.01
1.07
1.00
1.04
1.03
1.00
3.07
3.11
MeO


Oct15-2012-Niall 11 1 "C:\UEA NMRs\nmr"
ND9.034.1
193.21
152.28
151.15
145.31
140.44
133.84
133.09
129.47
129.28
128.58
124.61
121.55
111.60
77.32
77.09
76.68
55.69
21.70
[rel]
[ppm]


Aug03-2012-Niall 10 1 "C:\UEA NMRs\nmr"
ND8.032.3
[rel]
[ppm]
CO2Me
NH
NH


Aug03-2012-Niall 11 1 "C:\UEA NMRs\nmr"
ND8.032.3
[rel]
[ppm]
174.28
149.51
137.24
133.10
132.67
132.08
131.99
131.89
131.86
128.50
128.45
128.38
128.29
127.18
126.08
125.81
123.86
118.80
109.52
82.39
77.31
77.00
76.68
59.98
57.40
51.83
41.93
41.27


ND8.075.3 10 1 "C:\UEA NMRs\nmr"
ND8.075.3
7.06
7.04
7.02
7.02
6.80
6.78
6.77
6.75
6.75
6.73
6.73
6.71
6.71
6.59
6.57
6.39
6.35
6.02
6.00
6.00
5.98
5.96
5.96
5.94
4.91
3.92
3.92
3.91
3.90
3.80
3.35
2.66
2.66
2.65
2.64
2.63
2.63
2.61
2.61
2.59
2.57
2.55
2.54
2.53
2.52
2.51
2.46
2.44
2.43
2.41
0.99
0.15
0.08
OTBS
OMe
CO2Me
NH
N
H
1
2
3
4
5
6
7
8
9
10
11
12
2.10
2.02
1.18
1.01
1.02
0.98
1.05
3.39
2.90
9.88
6.33
3.59
[rel]
[ppm]


ND8.075.3 11 1 "C:\UEA NMRs\nmr"
ND8.075.3
[rel]
[ppm]
0.97
18.40
25.67
41.17
41.83
51.84
55.46
57.49
60.01
76.67
77.30
78.88
82.35
109.53
109.93
118.82
118.95
120.84
123.71
123.87
128.27
131.26
132.87
133.02
144.62
149.50
150.87
174.30