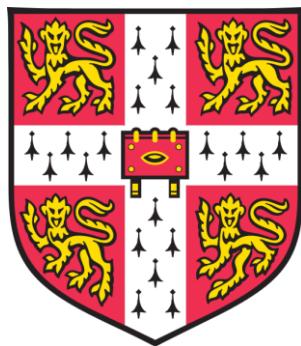


Palladium(II)-Catalysed sp³ C–H Functionalisation of Hindered Amines and its Application in Synthesis of Astemizole Analogues

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This dissertation is submitted for the degree of Doctor of Philosophy

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Declaration

This dissertation is submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy. It describes work carried out in the Department of Chemistry from October 2011 to September 2015. Unless otherwise indicated, the research is my own and not the product of collaboration.

Danny Ka Hei Ho

March 2016

Statement of Length

This dissertation does not exceed the word limit of 60 000 as set by the Degree Committee for the faculty of Physics and Chemistry.

Danny Ka Hei Ho

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Acknowledgment

I would like to express my deepest gratitude to Professor Matthew Gaunt, for his continued support and guidance throughout my PhD research. His broad vision to research has most certainly led me to the right way, especially during difficult times. I have learnt a lot from Matt for the way he approaches problems and then coming up with creative solutions.

During my time here, I have met many great people in the lab who have made the place so fun to work, as well as making it intellectually inspiring. I really appreciate the tremendous efforts that people have put into making the lab more sociable – even though I admit I haven't been to some of the social events! Special thanks go to Dr Darren Wilcox, Dr Jonas Calleja, Jamie Fox and Tim Gorman who took the time and interest to proofread this thesis thoroughly and offering their valuable suggestions.

The running of the lab would not have been so smooth if it wasn't for the technicians working tirelessly behind the scenes. This was particularly evident during our lab move. To that, I am grateful to Melvyn Oriss, Keith Parmenter, Nic Davies and Matt Pond for all your help during my four years here. I would like to thank members of the NMR service team, Duncan Howe, Peter Grice and Andrew Mason, for their help over the years. Thanks to Dr John Davies for obtaining the X-ray crystal structure reported in this thesis.

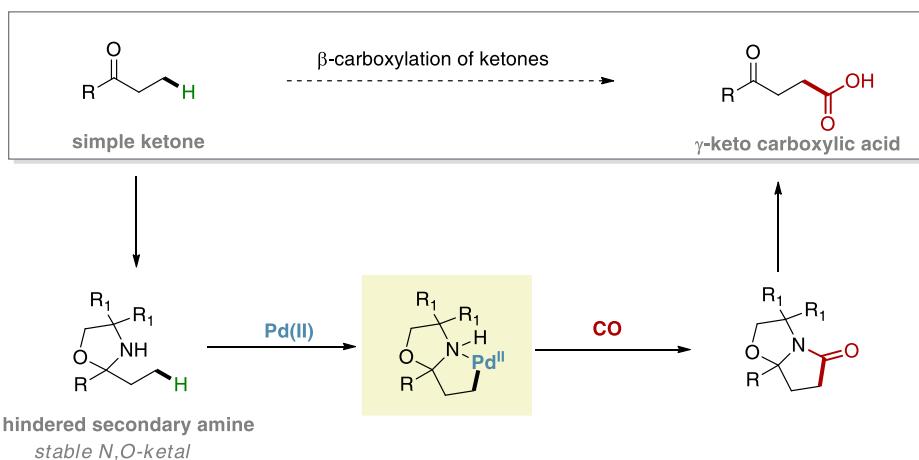
Now to you, Winnie, whom I can now call my dearest wife. You have always been here for me, during both good and difficult times. The support you have given me has allowed me to just concentrate on my work without having to worry about other things and I am looking forward to our future together. In the meantime, I am waiting for you to complete your thesis soon!

Last, but most certainly not least, my parents and sister. You have always supported me with whatever I wished to do and have always been there for me whenever I needed them. Without your unconditional support and willingness to send me to the UK for education at a very young age, I would not be where I am today.

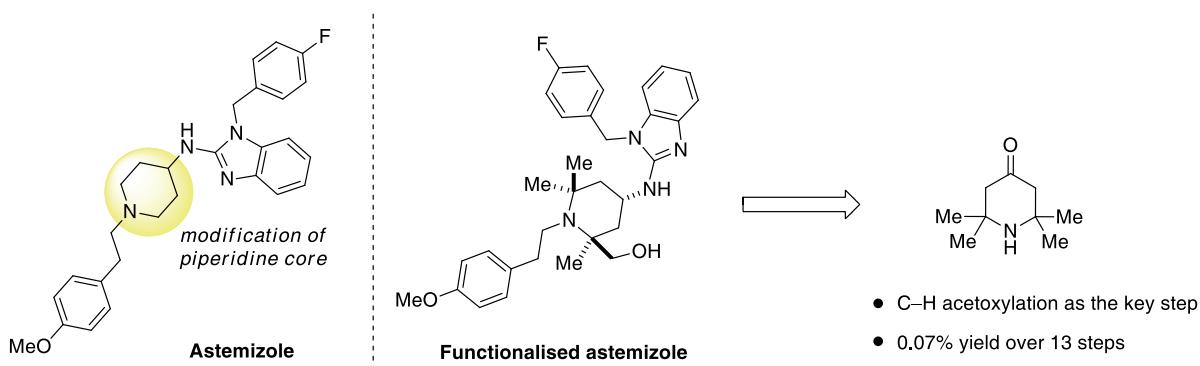
I believe God has led me through this journey, and He has helped me along the way through the hands of others. I will continue to learn to live my life for God.

Abstract

The development of a palladium-catalysed C–H carbonylation of hindered secondary amines is described. Central to this strategy is the temporary conversion of simple ketones into hindered secondary amines that facilitates a sterically promoted palladium-catalysed C–H activation. A range of functional groups are shown to be compatible with this catalytic process, and with exclusive regioselectivity for the terminal ethyl sp^3 C–H in most cases. This method allows an overall incorporation of a carboxyl group to the β -position of terminal ketones, generating 1,4-dicarbonyl moieties which are important synthetic building blocks.



The sterically promoted C–H functionalisation strategy has been employed as the key step in the synthesis of a functionalised analogue of astemizole, a pharmaceutical agent which suffers from undesired hERG activity. The increased steric bulk around the tertiary amine, coupled with introduction of a polar hydroxyl group *via* the C–H acetoxylation reaction, is proposed to reduce binding to the hERG channel. The hERG profile of this analogue is not yet established.



Abbreviations

Ac	Acetyl
Aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
br	Broad
Bz	Benzoyl
cod	1,5-Cyclooctadiene
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEMS	Diethoxymethylsilane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DPEphos	Bis-[2-(diphenylphosphino)phenyl]ether
DPPPent	1,3-Bis(diphenylphosphino)propane
°C	Degree centigrade
EDC	<i>N</i> -ethyl- <i>N'</i> -dimethylaminopropylcarbodiimide
Equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
Gly	Glycine
h	Hour
HBTU	<i>O</i> -(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HFIP	Hexafluoro-2-propanol
HOBT	Hydroxybenzotriazole
HRMS	High resolution mass spectrometry

Hz	Hertz
<i>i</i> Pr	<i>Iso</i> -propyl
IPA	<i>Iso</i> -propanol
IR	Infrared
<i>J</i>	Coupling constant
LCMS	Liquid chromatography-mass spectrometry
Leu	Leucine
m	Multiplet
M.p.	Melting point
Me	Methyl
mg	Milligram
mins	Minutes
mL	Millilitre
mM	Millimolar
mmol	Millimole
mol	Mole
MS	Molecular sieves
m/z	Mass spectrum
NBE	Norbornene
NMO	<i>N</i> -methylmorpholine
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
nOe	Nuclear overhauser effect
PA	Picolinamide
Ph	Phenyl
Phe	Phenylalanine
Phth	Phthalic
PIDA	Phenyl iodo(III)diacetate
PIFA	Phenyl iodo(III)bis(trifluoroacetate)
PMP	<i>p</i> -Methoxyphenyl
Pin	Pinacol

Ppy	2-Phenylpyridine
Py	Pyridine
<i>rac</i>	Racemic
rt	Room temperature
s	Singlet
SM	Starting material
S _N Ar	Nucleophilic aromatic substitution
t	Triplet
TBS	<i>Tert</i> -butyl silyl
<i>t</i> -amyl	<i>Tert</i> -amyl
<i>t</i> -Bu	<i>Tert</i> -butyl
<i>t</i> -Leu	<i>Tert</i> -leucine
Tf	Trifluoromethanesulfonyl
TFEol	2,2,2-Trifluoroethanol
TFA	Trifluoroacetic acid or Trifluoroacetate
THF	Tetrahydrofuran
TIPS	Tri-isopropylsilyl
TMS	Trimethylsilyl
TMP	2,2,6,6-Tetramethylpiperidine
TPAP	Tetrapropylammonium perruthenate
TLC	Thin layer chromatography
Ts	<i>p</i> -Toluenesulfonyl
Tyr	Tyrosine
Val	Valine
δ	Chemical shifts

Contents

Declaration	i
Acknowledgment.....	ii
Abstract.....	iii
Abbreviations	iv
Contents	7
1 Introduction	10
1.1 Introduction to C–H bond functionalisation.....	10
1.2 Transition metal-catalysed C–H functionalisation	11
1.3 Cyclometallation as a strategy for selective C–H functionalisation.....	13
1.4 Amines as directing groups in palladium-catalysed C–H functionalisation	18
1.4.1 Background.....	18
1.4.2 Auxiliary-directed amine C–H functionalisation <i>via</i> palladium catalysis	19
1.4.3 Unprotected amine-directed C–H functionalisation <i>via</i> palladium catalysis.....	28
2 Palladium(II)-Catalysed sp³ C–H Carbonylation of Hindered Amines.....	41
2.1 Background.....	41
2.2 Project aims	42
2.3 Results and discussion	46
2.3.1 Preliminary stoichiometric studies.....	46
2.3.2 Optimisation studies for catalytic reaction conditions.....	47
2.3.3 Substrate scope	52
2.3.4 Removal of steric tether: access to γ -keto carboxylic acids	60
2.3.5 Attempted derivitisation of the bicyclic lactam core	61
2.3.6 Palladium(II)-catalysed sp ³ C–H alkenylation – Dr Jonas Calleja	66

2.3.7	Summary	68
3	Design and Synthesis of Functionalised Astemizole Analogues <i>via</i> sp³ C–H Functionalisation of Hindered Amines	71
3.1	Background.....	71
3.2	Project aims	73
3.3	Results and discussion	75
3.3.1	Synthesis of ‘TMP-astemizole’	75
3.3.2	Proposed synthetic routes to functionalised astemizole analogues	83
3.3.3	Introduction of polar functionality: palladium(II)-catalysed acetoxylation and carbonylation	85
3.3.4	Installation of the 4-methoxyphenylethyl unit.....	88
3.3.5	Installation of primary amine <i>via</i> reductive amination	97
3.3.6	Buchwald-Hartwig amination and deprotection end-game	99
3.3.7	Summary	101
4	Conclusions and Outlook.....	102
5	Experimental.....	105
5.1	General Information:	105
5.2	C–H carbonylation: Synthesis of <i>N,O</i> -ketals.....	107
5.3	C–H carbonylation: Carbonylation products.....	134
5.4	C–H carbonylation: Access to γ -keto carboxylic acid.....	149
5.5	C–H carbonylation: <i>C</i> -Methylation of γ -lactam 185	151
5.6	C–H carbonylation: Unexpected products from ring-opening of γ -lactam 185	152
5.7	Synthesis of TMP-astemizole 287 : Literature route to astemizole	154
5.8	Synthesis of TMP-astemizole 287 : Phthalimide route	157
5.9	Synthesis of TMP-astemizole 287 : Dioxolane route	160
5.10	Synthesis of TMP-astemizole 287 : Buchwald-Hartwig amination endgame	165

5.11	Synthesis of astemizole analogue 288 :.....	167
5.12	Towards the synthesis of astemizole analogue 289/335	176
5.13	Alternative strategies to install the 4-methoxyphenylethyl unit.....	182
6	References	185
7	Appendix – ^1H and ^{13}C NMR spectra of key compounds.....	194
7.1	Palladium(II)-catalysed carbonylation: <i>N,O</i> -Ketal substrates	200
7.2	Palladium(II)-catalysed carbonylation: Carbonylation products.....	233
7.3	Palladium(II)-catalysed carbonylation: γ -Keto carboxylic acids	260
7.4	Palladium(II)-catalysed carbonylation: <i>C</i> -Methylation of γ -lactam 185	262
7.5	Synthesis of TMP-astemizole 287	263
7.6	Synthesis of astemizole analogue 288	274
7.7	Attempted synthesis of astemizole analogue 289/335	286

1 Introduction

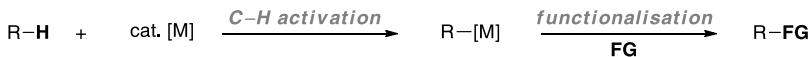
1.1 Introduction to C–H bond functionalisation

The realisation of transition-metal-catalysed functionalisation reactions has transformed organic synthesis. In particular, palladium-catalysed cross-coupling reactions are now essential tools for the construction of complex molecules. The impact of this methodology was widely recognised with the 2010 Nobel Prize being awarded to Ei-ichi Negishi,^{1–3} Richard F. Heck^{4,5} and Akira Suzuki^{6–8} for “*palladium-catalysed cross couplings in organic synthesis*”. Whilst this approach remains the benchmark for building complexity into molecules, a conceptual advance would be to exploit the ubiquitous nature of C–H bonds in organic molecules for direct C–H bond functionalisation. This advance would provide a complementary method for C–C and C–X(heteroatom) bond formation, with the potential to streamline existing syntheses of complex molecules and change the way chemists think about reactivity and plan syntheses.

Whilst the area of direct functionalisation of arenes and heteroaromatic C–H bonds have been well established, direct functionalisation of aliphatic C–H bonds remains a formidable challenge in synthetic organic chemistry.^{9,10} In general, sp³ C–H bonds are less susceptible to activation than sp² C–H bonds. The unreactive nature of aliphatic C–H bonds is attributed to (i) the low polarity of these substrates and the lack of π-orbitals that can interact with empty d-orbitals of the metal centre, (ii) the high homolytic strength of C–H bonds, with typical bond dissociation energies range from 95–105 kcal mol⁻¹,¹¹ and iii) pKa values are greater than 40, thereby rendering heterolytic cleavage by a strong base unviable.^{11,12} The ubiquitous nature of C–H bonds also poses selectivity issues, as they are often in similar electronic and spatial environments and so selective activation/functionalisation of a single C–H bond presents a significant challenge.

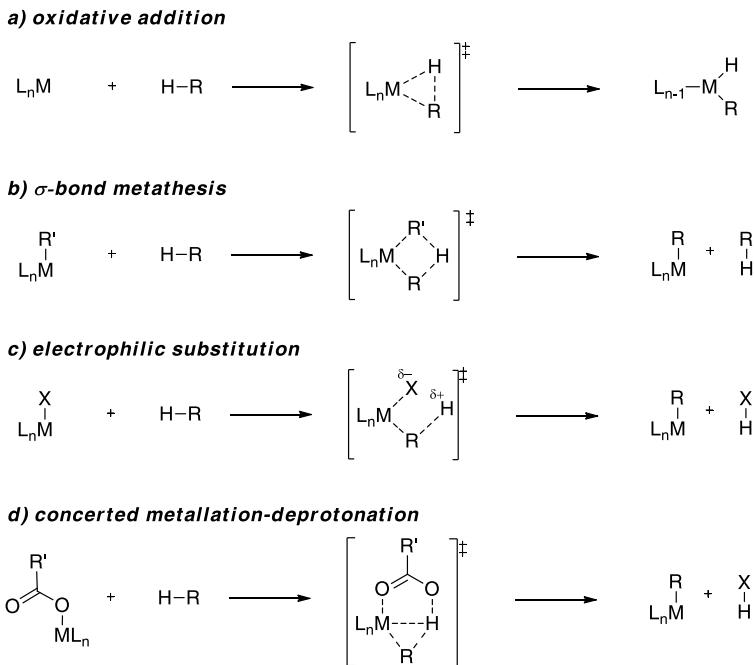
1.2 Transition metal-catalysed C–H functionalisation

Over the past 50 years, transition metals have become widely used to convert inert C–H bonds to more reactive carbon-metal (C–[M]) bonds (known as C–H activation) that can subsequently be functionalised to afford the desired product (Scheme 1). The success of this approach is in part attributed to the ease in which transition metals cycle between their available oxidation states.



Scheme 1: Concept of transition metal-catalysed C–H functionalisation

The studies into reactions of unactivated C–H bonds with transition metals have led to the identification of four main mechanistic pathways for the transformation of C–H bonds into C–[M] bonds (Scheme 2): a) oxidative addition, b) σ -bond metathesis, c) electrophilic substitution, and d) concerted metallation-deprotonation (CMD).^{13–16}

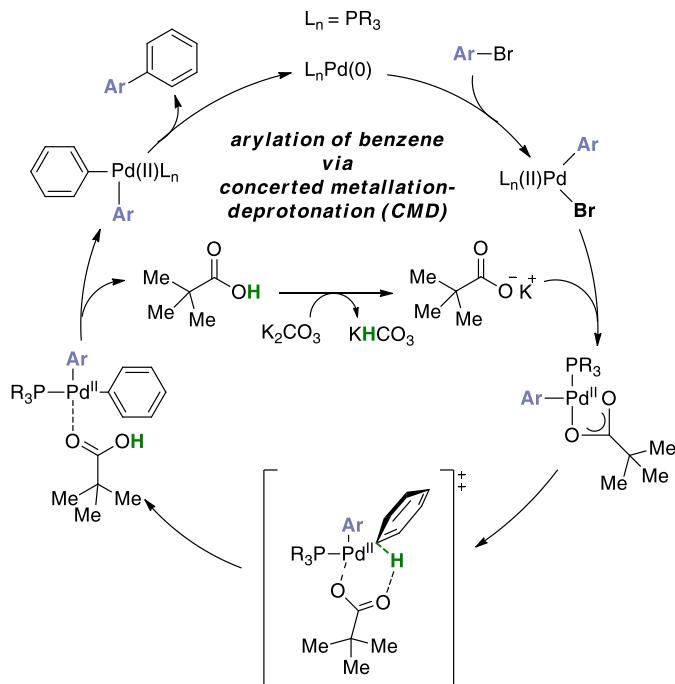


Scheme 2: Overview of the four main modes of C–H activation: a) oxidative addition, b) σ -bond metathesis, c) electrophilic substitution, d) concerted metallation-deprotonation.

Oxidative addition is a mechanism where an electron rich metal reacts with a C–H bond to form a C–[M] and [M]–H bond *via* a three-membered transition state (Scheme 2a). Studies showed that the formation of reactive 16 electron complexes prior to C–H activation was a common feature of this reaction.^{17–19} This mechanism is common for low valent transition metals such as Ru(0),

Ir(I) and Rh(I). σ -bond metathesis is a one-step reaction by which two σ -bonds are broken and two new σ -bonds are formed in a concerted manner without change of the metal oxidation state (Scheme 2b). This process is known for early d^0 transition metal complexes such as Zr(II) where a change in oxidation state is not possible.¹⁶ The electrophilic substitution mechanism effects metallation by having an electron rich π -system attacking an electropositive metal centre, followed by loss of protons to restore the π -system (Scheme 2c). This mechanism is common for late transition metals such as Pd(II) and Ni(II). A number of palladium-catalysed sp^2 C–H functionalisation reactions were shown to follow this mechanism.^{14,20,21}

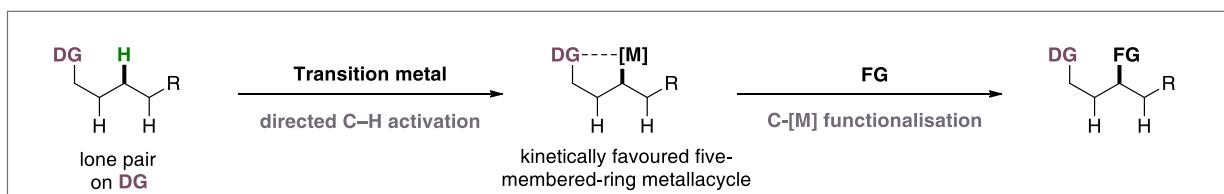
With the concerted metallation-deprotonation mechanism, a term coined by Fagnou and Echavarren, C–H bond cleavage has been proposed to occur by a simultaneous metallation and intramolecular deprotonation by an anionic ligand, typically a carboxylate ion (Scheme 2d).^{22–24} For example, the pivalate ligand has been demonstrated to facilitate the arylation of benzene (Scheme 3).²⁵ In this example, experimental and computational evidence indicated that the pivalate anion lowered the energy required for C–H bond cleavage and acted as a catalytic proton shuttle from benzene to the stoichiometric carbonate base.



Scheme 3: Fagnou's arylation of benzene *via* concerted metallation-deprotonation²⁵

1.3 Cyclometallation as a strategy for selective C–H functionalisation

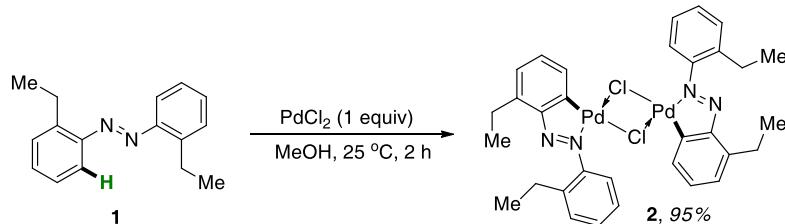
In order to achieve selective functionalisation of a single C–H bond within a complex molecule, the most common and successful strategy involves the use of substrates that contain coordinating ligands (also known as directing groups – DG). These directing groups bind to the metal catalyst and selectively deliver the catalyst to a proximal C–H bond, facilitating a directed C–H activation event (also known as cyclometallation) (Scheme 4). The resulting metallacycle can react with an external agent, which leads to an overall C–H functionalisation of a specific C–H bond. The use of directing groups to assist cyclometallation is assumed to lower both the enthalpic and entropic costs of the C–H activation event, and accounts for why kinetically favoured five-membered-ring metallacycles are preferred over metallacycles of other ring sizes.



Scheme 4: Directing group-assisted C–H bond cyclometallation strategy

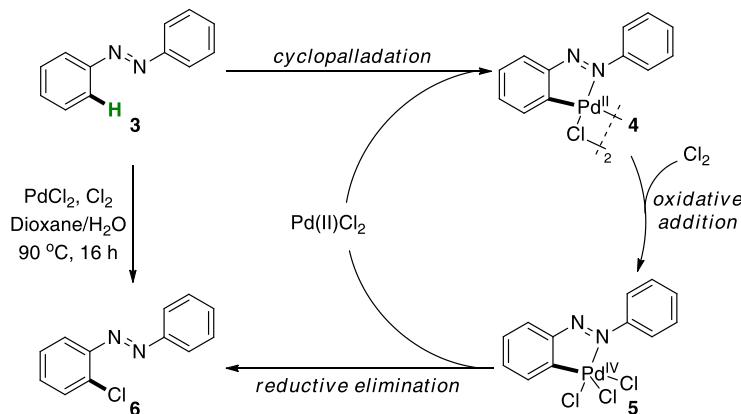
Although many different transition metals including ruthenium, rhodium and platinum have been demonstrated to undergo cyclometallation, palladium has undoubtedly been the most studied transition metal for this process and so this chapter will focus primarily on the use of palladium in cyclometallation and the subsequent functionalisations.^{26–31}

Early studies of cyclometallation with palladium (known as cyclopalladation) focused on nitrogen-based directing groups. Pioneering work by Cope and Siekman in 1965 showed that azobenzene **1** could be cyclopalladated selectively at the *ortho*-position in high yield using palladium(II) chloride (Scheme 5).²⁶ A subsequent report by Cope and Friedrich has shown that *N,N*-dimethylbenzylamine could also be cyclopalladated at the *ortho*-position.³²



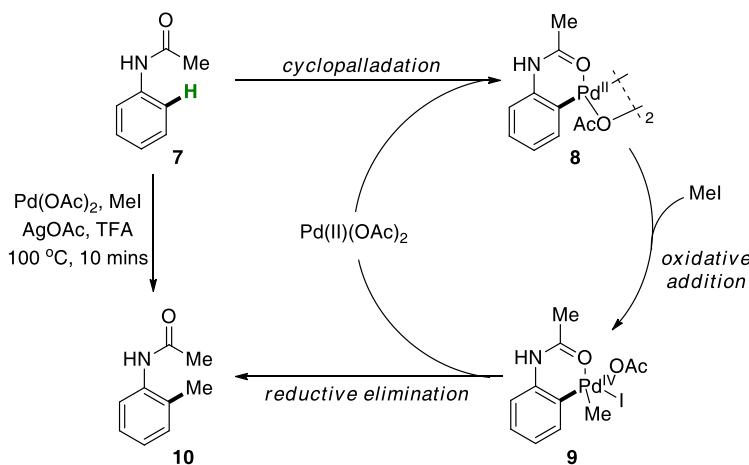
Scheme 5: Cope and Siekman's *ortho*-palladation of azobenzene²⁶

Following on from these initial reports, the first example of catalytic C–H activation came in 1970 when Fahey reported the palladium(II)-catalysed *ortho*-chlorination of azobenzene.³³ One plausible mechanistic pathway for this reaction involves the oxidation of palladacycle **4** to a palladium(IV) species **5**, followed by reductive elimination of the carbon–chlorine bond to generate the *ortho*-chlorinated product **6** and releases the palladium(II) complex back into the catalytic cycle (Scheme 6).



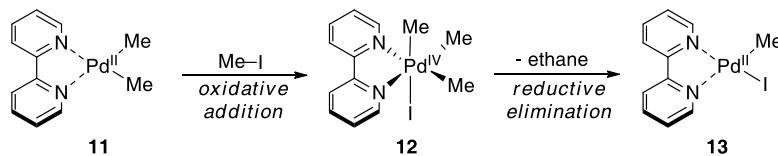
Scheme 6: Proposed palladium(II)/(IV) pathway for *ortho*-chlorination of azobenzene by Fahey³³

Another early example of palladium-catalysed C–H functionalisation was the *ortho*-methylation of acetanilide **7** reported by Tremont and Rahman (Scheme 7).³⁴ This represented the first catalytic process leading to carbon–carbon bond formation. A palladium(II)/(IV) cycle was proposed, in which the *ortho*-palladated acetanilide **8** reacted with methyl iodide to form palladium(IV) species **9**, followed by reductive elimination to form the *ortho*-methylated product **10**. Silver acetate was thought to regenerate the catalytically active palladium(II) acetate *via* ligand exchange.



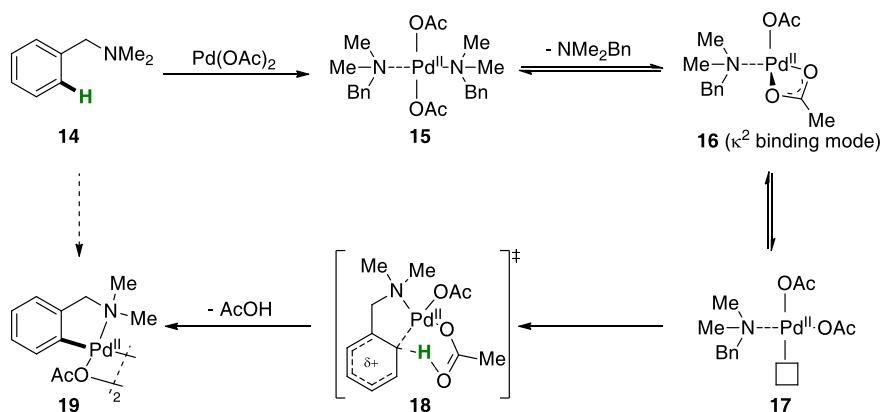
Scheme 7: Tremont and Rahman's palladium(II)-catalysed *ortho*-methylation of acetanilide³⁴

Further work by Canty and co-workers provided evidence for the proposed oxidative addition of methyl iodide to palladium(II) metallacycles. Canty reported that dimethyl(2,2'-bipyridyl)palladium(II) complex **11** could undergo oxidation addition with excess methyl iodide to generate the trimethylpalladium(IV) complex **12**, which was isolated and characterised by X-ray crystallography. Furthermore, it was observed that reductive amination of ethane to provide palladium(II) complex **13** took place upon standing at ambient temperature (Scheme 8).³⁵ Later studies by Canty have greatly enhanced our understanding of oxidative addition and reductive elimination surrounding palladium(IV) species, with a number of organo-palladium(IV) complexes isolated and characterised.³⁶



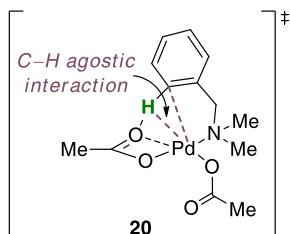
Scheme 8: Mechanistic studies of oxidative addition of methyl iodide to a palladium(II) complex by Canty and co-workers³⁵

Despite these pioneering reports, progress in palladium-catalysed C–H transformations has been slow, possibly owing to the lack of detailed mechanistic understanding on the reactivity of palladium towards C–H bonds. It wasn't until 1985 when the first in-depth kinetic and mechanistic studies were reported by Ryabov and co-workers on the *ortho*-palladation of *N,N*-dimethylbenzylamine **14**.³⁷ NMR and kinetic measurements obtained from the reaction intermediates enabled Ryabov and co-workers to propose a likely reaction pathway (Scheme 9). Treatment of amine **14** with the palladium(II) salt generates initially the stable *trans*-bis-amine complex **15**. Subsequent dissociation of an amine allows the acetate group to migrate *via* a κ^2 binding mode **16**, and generates a vacant coordination site *cis*- to the amine in mono-amine complex **17**. Kinetic isotope effect and entropy of activation calculations for mono-amine complex **17** suggested a highly ordered, compact transition state **18** whereby the leaving H atom is intramolecularly abstracted by an acetate ligand (concerted metallation-deprotonation), forming palladacycle **19**.



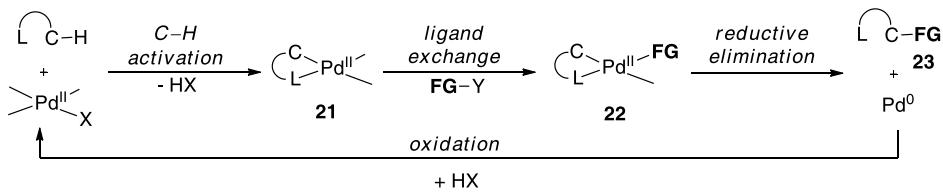
Scheme 9: Proposed reaction pathway for the stoichiometric *ortho*-palladation of *N,N*-dimethylbenzylamines by Ryabov and co-workers³⁷

The postulated reaction pathway has been supported by recent computational work undertaken by Davies and Macgregor (Scheme 10).³⁸ They suggested that an additional agostic interaction between the sp² C–H bond and palladium (in **20**) polarised the bond and formed a six-membered transition state. This rendered the C–H bond more acidic and facilitated deprotonation by the acetate base, with almost no activation barrier.



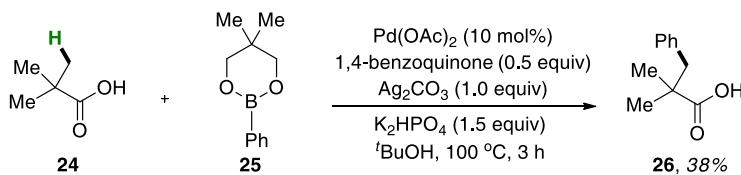
Scheme 10: Favourable C–H agostic interaction facilitates deprotonation by an acetate base³⁸

Whilst the directing group-assisted palladium-catalysed C–H functionalisations reported by Fahey and Tremont represent examples of catalytic processes which proceed *via* a palladium(II)/(IV) cycle after cyclopalladation, another common mechanistic pathway involves a palladium(II)/(0) catalytic cycle (Scheme 11). In this process, palladacycle **21**, formed after a directed C–H activation, undergoes a ligand exchange or transmetalation process to form palladium(II) species **22**, which after reductive elimination, releases the product **23** and the reduced palladium(0). An external oxidant is then required to oxidise palladium(0) back to palladium(II) to re-enter the catalytic cycle.



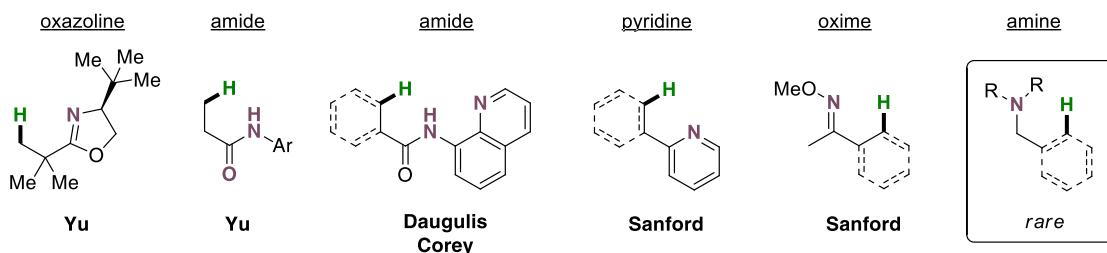
Scheme 11: Representative palladium(II)/(0) catalytic cycle for C–H functionalisation (L = directing group; FG = functional group)

One such example of palladium-catalysed C–H functionalisation reactions which follows the palladium(II)/(0) pathway is the palladium(II)-catalysed sp^3 C–H arylation of carboxylic acids with arylboronic esters reported by Yu and co-workers (Scheme 12).³⁹ Silver carbonate provided the terminal oxidant required to regenerate the catalytically active palladium(II) species. Interestingly, it was reported that other silver oxidants such as silver(I) oxide or silver(I) acetate gave <5% of the desired product **26**.



Scheme 12: Yu's palladium(II)-catalysed sp^3 C–H arylation of carboxylic acids³⁹

Apart from carboxylic acids, a number of other directing groups such as, oxazolines,^{40–42} amides,^{43–48} pyridines^{49,50} and oximes^{51,52} have been successfully employed in palladium-catalysed sp^2 and sp^3 C–H functionalisation reactions (Scheme 13). Compared to all the well-established directing groups, use of amines as directing groups has been a relatively under-researched area until recent times. The use of unprotected amines or amine-derived auxiliaries as directing groups in palladium-catalysed C–H functionalisations will form the basis of discussion in the following section.



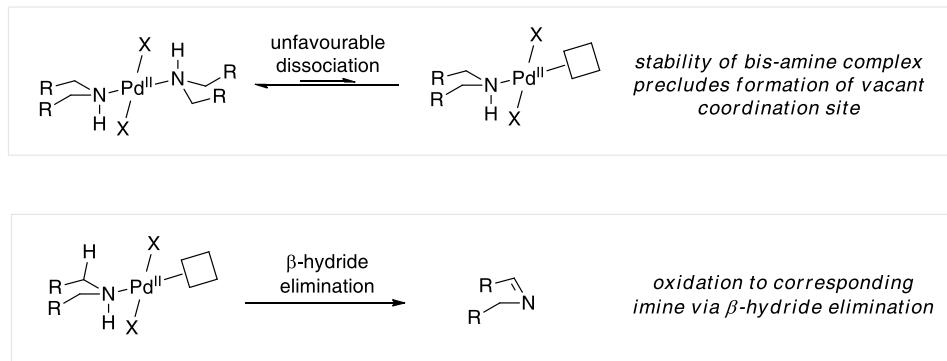
Scheme 13: Well-established directing groups in palladium-catalysed sp^2 and sp^3 C–H functionalisation reactions

1.4 Amines as directing groups in palladium-catalysed C–H functionalisation

1.4.1 Background

Despite recent advances in the field of C–H activation, the range of functional groups capable of directing C–H functionalisation still remains limited. The majority of directing groups used to facilitate C–H functionalisation processes are auxiliaries or protecting groups that need to be added and then removed from the substrate, thereby reducing the efficiency of the overall process. In recent years, significant efforts and much research have been put into employing native functionalities, such as carboxylic acids,^{39,53–56} ketones⁵⁷ and alcohols,^{58,59} to direct cyclometallation. This approach allows C–H functionalisation where site-selectivity is directed by common functional groups contained in both the reactant and the desired product. Such a process that utilises these simple moieties to direct C–H activation is desirable as it eliminates the requirement for any pre-functionalisation of starting materials, allowing for very simple, readily available material to be transformed into complex molecular architectures. The use of native directing groups also allows further manipulations to be easily carried out on the compound after the C–H functionalisation event. Considering the advantages of utilising the simple native functionalities found in common molecules as directing groups, there are clearly many benefits to be gained from developing transformations in this class.

Aliphatic amines are a broad class of molecules which have relevance to pharmaceuticals, agrochemicals, surfactants and textiles, to name but a few.⁶⁰ Despite their utility as synthetic intermediates and products, aliphatic amines have rarely been exploited in C–H functionalisation processes. There are two main reasons for this (Scheme 14). Firstly, aliphatic amines (especially primary and secondary amines) are excellent coordinating groups for palladium(II) centre and form coordinately saturated stable bis-amine complexes. The thermodynamic stability of these complexes precludes C–H activation through the lack of a vacant site at the metal centre, thereby preventing cyclometallation from taking place.^{31,32,61} Secondly, aliphatic amines with α -hydrogen atoms readily undergo degradation by β -hydride elimination to form the corresponding imines.⁶²



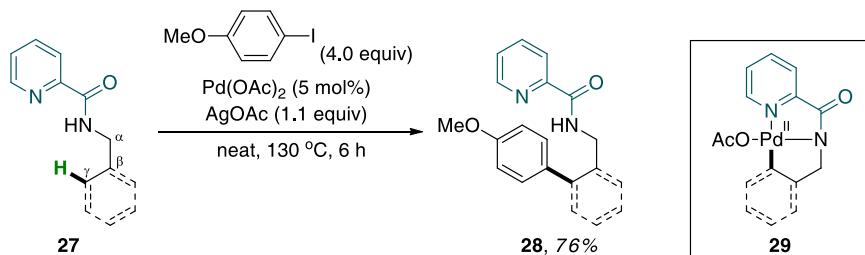
Scheme 14: Factors which disfavour the use of aliphatic amines as directing groups in C–H functionalisation

Various strategies have been developed that relied on diminishing the basicity of the nitrogen atom by adding an electron-withdrawing auxiliary. Addition of such an auxiliary also renders the N–H bond more acidic, hence allowing deprotonation to occur under mild conditions.

1.4.2 Auxiliary-directed amine C–H functionalisation *via* palladium catalysis

1.4.2.1 Picolinamides

Seminal work into the development of amine-derived auxiliary was reported by Daugulis and co-workers in 2005, where a picolinamide (PA) auxiliary was attached to primary aliphatic amines to enable sp^2 and sp^3 C–H arylation (Scheme 15).⁶³

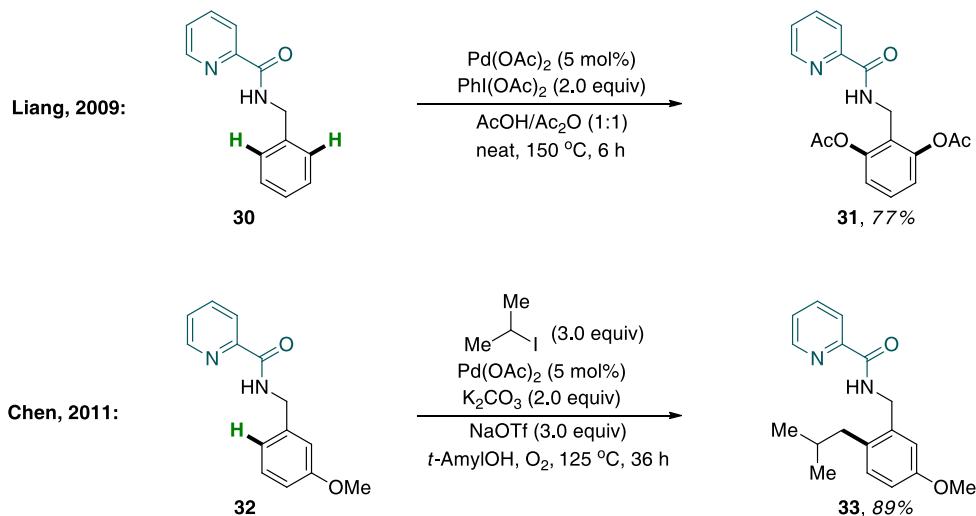


Scheme 15: Daugulis' picolinamide-directed sp^2 and sp^3 C–H arylation⁶³

The chelating pyridine-functionality is believed to facilitate both the C–H activation⁶⁴ and the subsequent oxidative addition,⁶⁵ based on the assumption that the reaction proceeded *via* a palladium(II)/(IV) pathway. In this reaction, the picolinamide-protected amine **27** could be arylated selectively in the γ -position to give **28** in good yield. Remarkably, the picolinamide group was also able to promote arylation of methylene sp^3 C–H bonds, which are known to be harder to activate than the methyl counterparts. Moreover, the *ortho*-arylation of picolinamide-

protected benzylamines were achieved in good yields. Speculative mechanistic discussion suggested that the reaction proceeded *via* an initial formation of 5,5-fused ring cyclopalladation complex **29**.

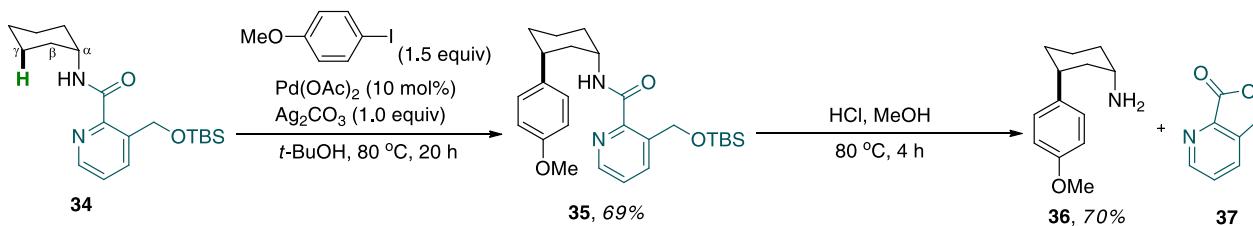
The reactivity of *N*-picolinoyl-protected benzylamines was further exploited by two different research groups. For example, Liang and co-workers have shown that *N*-picolinoyl-protected benzylamine **30** could undergo *ortho*-acetoxylation using PhI(OAc)_2 as oxidants.⁶⁶ Chen and co-workers have shown that benzylamide **32** could perform *ortho*-alkylation using simple alkyl halides to give mono-*ortho*-alkylated benzylamide **33** in excellent yields (Scheme 16).⁶⁷ In the *ortho*-alkylation, potassium carbonate and sodium triflate were found to be important in suppressing the side reaction of the nucleophilic acetate ligands reacting with alkyl halide electrophiles, causing the premature termination of the catalytic C–H alkylation. Further studies by Chen have shown that *ortho*-alkenylations and *ortho*-alkynylations are amenable to the *N*-picolinoyl-protected benzylamines system.⁶⁸ As an extension to the *ortho*-functionalisations, Chen has demonstrated that alkylation could also be performed on sp^3 C–H of *N*-picolinoyl-protected aliphatic amines.⁶⁹



Scheme 16: Picolinamide-directed *ortho*-acetoxylation (Liang)⁶⁶ and *ortho*-alkylation (Chen)⁶⁷

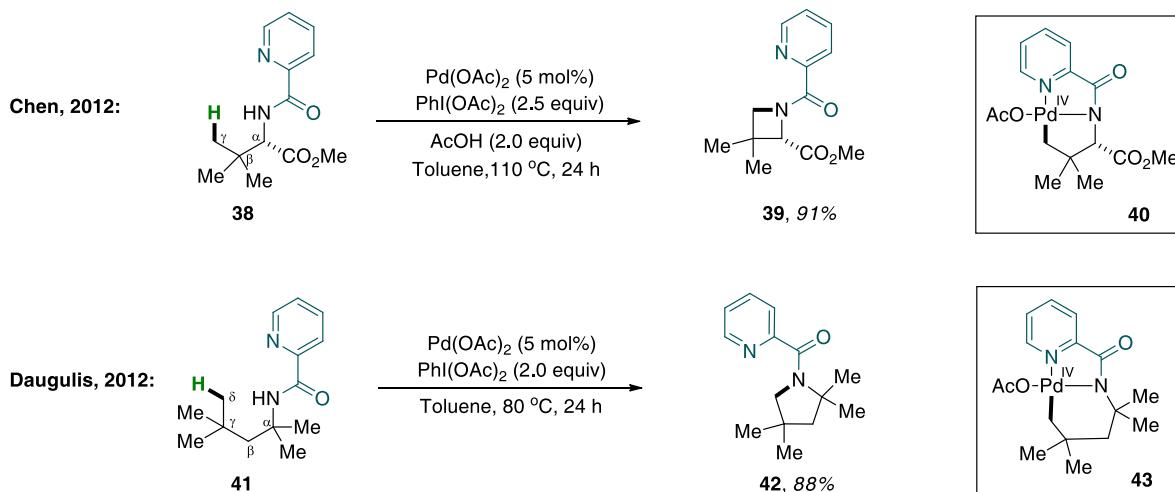
To further broaden the scope of sp^3 C–H functionalisation using this auxiliary, Chen reported a practical synthetic strategy based on the palladium-catalysed arylation and alkenylation of the remote sp^3 C–H bonds of a variety of *N*-picolinoyl-protected aliphatic amine substrates, using aryl and alkenyl halides under mild conditions.⁷⁰ Though this presented a general strategy for remote methyl and methylene sp^3 C–H functionalisation, the authors recognised that cleavage of

the picolinamide auxiliary was difficult and challenging. To overcome this issue, a more readily cleavable version of the auxiliary was developed by the group (Scheme 17). The new picolinamide auxiliary featured a methylene hydroxyl group at the *ortho*-position (in **34**). After undergoing site-selective sp^3 C–H arylation to provide arylated amide **35**, the deprotection of this new auxiliary was conducted under mild acidic conditions, driven by the formation of the five-membered γ -lactone **37**, affording the desired amine **36** in 70% yield.



Scheme 17: Chen's sp³ C–H arylation of a modified N-picolinoyl-protected amine⁷⁰

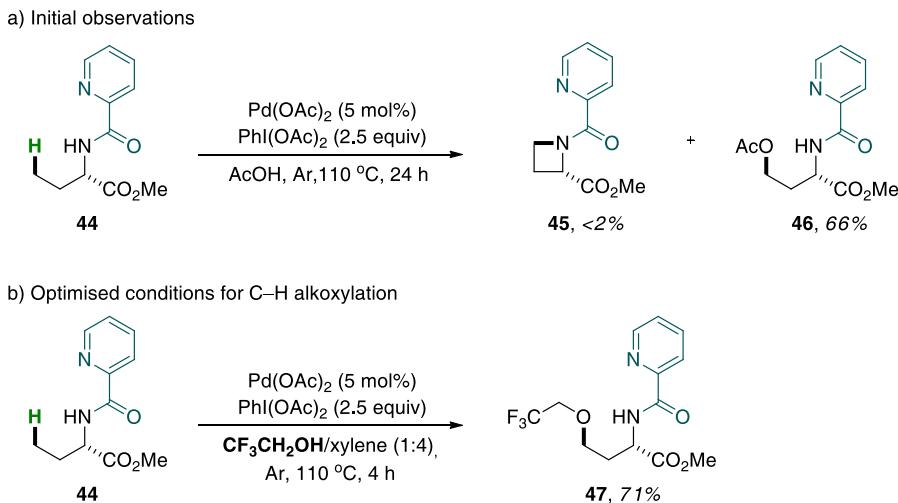
The utility of this auxiliary was further established by both Chen⁷¹ and Daugulis⁷² with the synthesis of nitrogen-containing heterocycles (such as azetidine **39** and pyrrolidine **42**) via reductive elimination of the C–N bonds from the palladium(IV) species **40** and **43**, respectively (Scheme 18). Chen has subsequently reported an improved protocol for the intramolecular amination of γ -sp²-C–H bonds to form indolines, with a much lower loading of palladium(II) acetate required (0.5 mol%).⁷³



Scheme 18: Intramolecular amination of sp^2 and sp^3 C–H Bonds at γ - and δ -positions of *N*-picolinoyl-protected aliphatic amines (Chen and Daugulis)^{71,72}

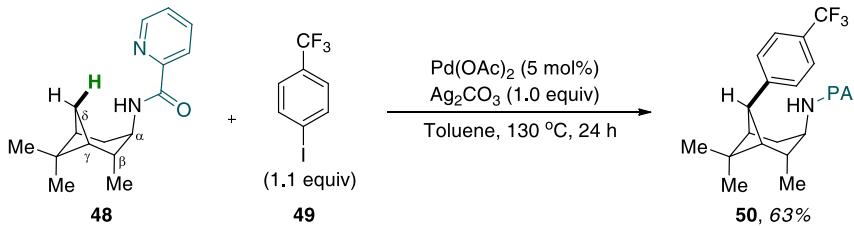
Whilst investigating the C–H intramolecular amination reaction mentioned above, Chen made the intriguing observation of the acetylated product **46** (Scheme 19a). Subsequent investigation

into the feasibility of a C–H alkoxylation reaction led to the discovery of a remote sp^3 and sp^2 C–H alkoxylation of *N*-picolinoyl-protected aliphatic amines.⁷⁴ After a brief optimisation, it was found that replacing acetic acid with alcohols/xylene (1:4) as solvents led to the formation of the corresponding alkoxylated products such as **47** in good yields (Scheme 19b).



Scheme 19: Picolinamide-directed sp^3 and sp^2 C–H alkoxylation of aliphatic amines. a) initial observations; b) optimised conditions for C–H alkoxylation⁷⁴

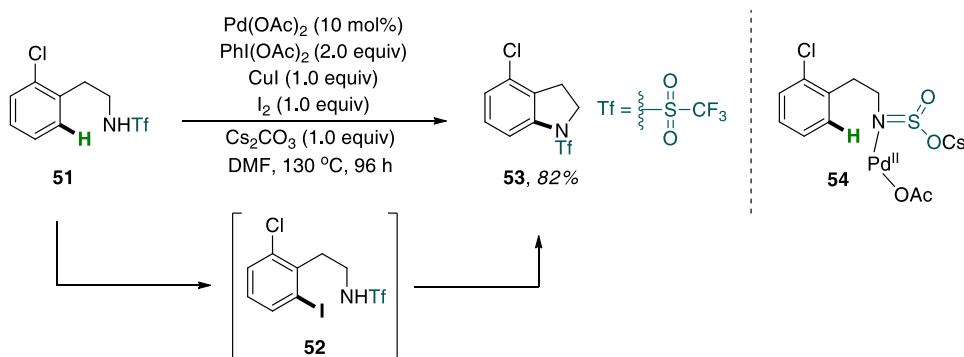
In 2014, Zhao and co-workers reported a picolinamide-directed remote sp^3 C–H arylation of 3-pinamidine **48** with aryl iodides (Scheme 20), where analogues of this amine motif had been shown to exhibit potent anti-influenza A activity.⁷⁵ Notably, arylation took place exclusively at the more hindered δ -methylene sp^3 C–H bonds, with no arylation observed at the adjacent γ -methyl sp^3 C–H bonds. The authors proposed that the remarkable selectivity stemmed from the strain-induced proximity of the δ -methylene sp^3 C–H bond to the picolinamide directing group, hence facilitating cyclopalladation. For the same reason, stereoselective arylation at the methylene C–H bond pointing to the amino group was observed. The reaction displayed a broad substrate scope with both electron-rich and electron-deficient aryl halides well tolerated in the reaction to generate a range of arylated products such as **50** in moderate to good yields.



Scheme 20: Zhao's picolinamide-directed δ -methylene sp^3 C–H arylation of 3-pinamidine⁷⁵

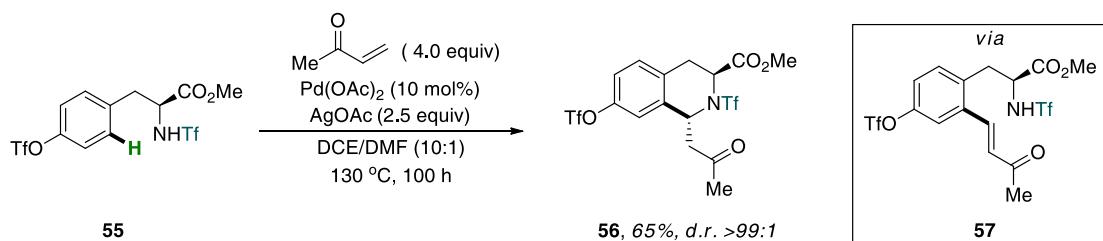
1.4.2.2 Trifluoromethanesulfonamides

An alternative strategy for functionalisation of aliphatic amines was reported by Yu and co-workers in 2008.⁷⁶ After a survey of different electron withdrawing protecting groups, it was found that trifluoromethanesulfonamide (triflamide, NHTf) derivative **51** was able to direct sp^2 C–H iodination. The resulting iodoarene **52** could subsequently undergo an Ullmann-type coupling to give indoline **53** after an intramolecular C–N bond reductive amination (Scheme 21). It was proposed that the increased acidity of the N–H bond would maintain coordination between the amine and the palladium catalyst whilst sufficient electrophilicity of the palladium(II) centre is preserved (**54**). Soon after this initial report, a ‘direct’ intramolecular amination procedure using single- or two-electrons oxidants was also reported.⁷⁷



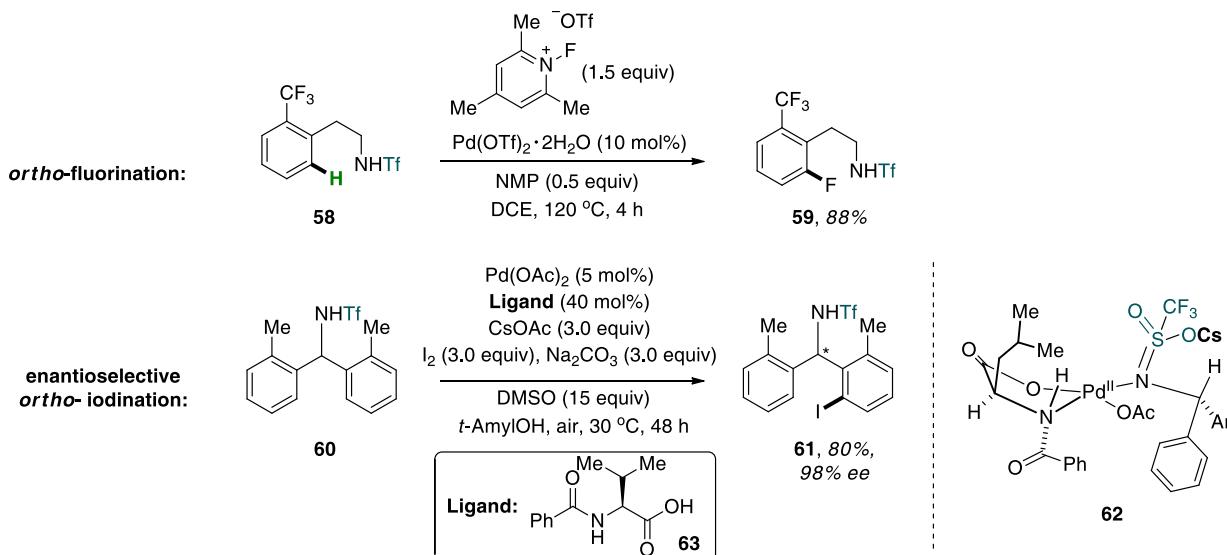
Scheme 21: Yu’s triflamide-directed tandem sp^2 C–H iodination/intramolecular amination to give indolines⁷⁶

Yu was also able to combine the triflamide-directed C–H activation with Heck coupling to generate tetrahydroisoquinoline **56**, after a tandem C–H alkenylation and aza-Michael addition process starting from *N*-triflyl-protected amino acid derivative **55** (Scheme 22).⁷⁶ It should be noted that the reactive triflate group was well-tolerated in the reaction, allowing further functionalisation.



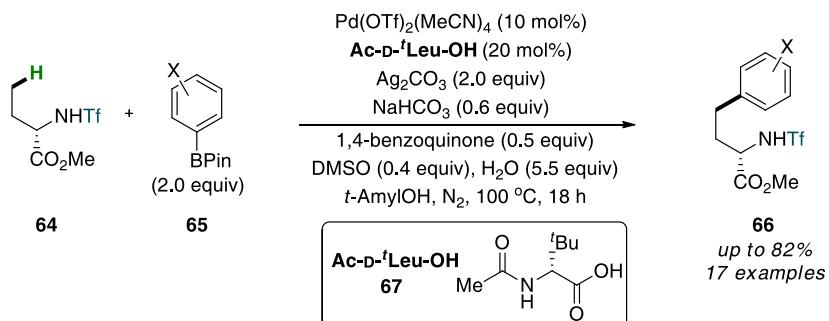
Scheme 22: Yu’s triflamide-directed tandem sp^2 C–H alkenylation/aza-Michael addition to give tetrahydroisoquinolines⁷⁶

The use of *N*-triflyl-protected amines as directing groups was further exploited in a range of C–H functionalisations, such as *ortho*-fluorination⁷⁸ and enantioselective *ortho*-iodination⁷⁹ of *N*-triflyl-protected benzylamines (Scheme 23). With the enantioselective *ortho*-iodination to synthesise chiral diarylmethylamines such as **60**, chiral mono-*N*-benzoyl-protected amino acid **63** was deployed as the ligand to impart enantioselectivity. Furthermore, it had been shown previously within the group that this type of amino acid ligand had an accelerating effects on certain C–H functionalisations.⁸⁰ Although the exact origin of the enantioselectivity was unclear, Yu hypothesised that the directing group coordinates with palladium(II) as a neutral σ-donor similar to pyridine, carbonyl and imidate, and subsequently proposed the structure of a possible intermediate **62**. This enantioselective C–H iodination has been successfully employed in kinetic resolution of chiral amines where one of the enantiomers of a racemic benzylic amine substrate undergoes faster aryl C–H activation than the other.⁸¹



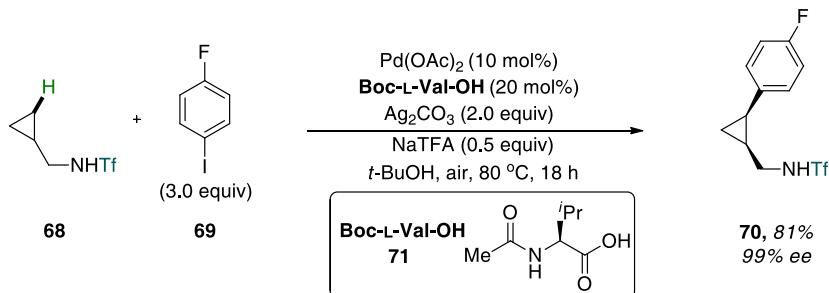
Scheme 23: Yu's triflamide-directed *ortho*-fluorination⁷⁸ and enantioselective *ortho*-iodination⁷⁹

Recently, the utility of the triflamide directing group has been extended to sp^3 C–H functionalisations. First, in 2014, Yu reported a ligand-enabled C–H arylation *via* palladium(II)/(0) catalysis, using *N*-triflyl-protected amine **64** and a range of arylboronic esters, to deliver a range of arylated products such as **66** in good yields (Scheme 24).⁸² Both electron-rich and electron-deficient arylboronic acids were well tolerated under the reactions conditions. Remarkably, no background reaction was observed in the absence of the mono-*N*-protected amino acid ligand **67**, which implied that this type of ligand could be potentially used to impart enantioselectivity in the activation of sp^3 C–H bonds.



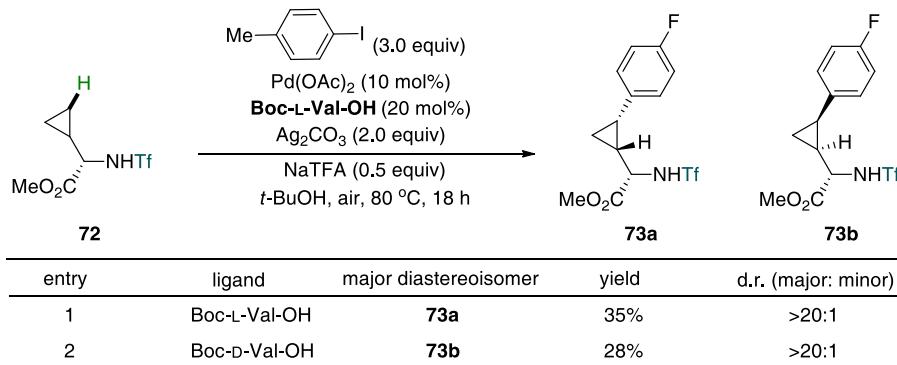
Scheme 24: Yu's sp^3 C–H arylation *via* palladium(II)/(0) catalysis⁸²

Encouraged by those findings, the first example of enantioselective C–H arylation *via* palladium(II)/(IV) catalysis was reported a year later.⁸³ *N*-triflyl-protected cyclopropylmethylamine **68** could be arylated on the cyclopropyl methylene sp^3 C–H to afford arylated sulfonamide **70** in 81% yield and 99% ee (Scheme 25).



Scheme 25: Yu's enantioselective sp^3 C–H arylation *via* palladium(II)/(IV) catalysis

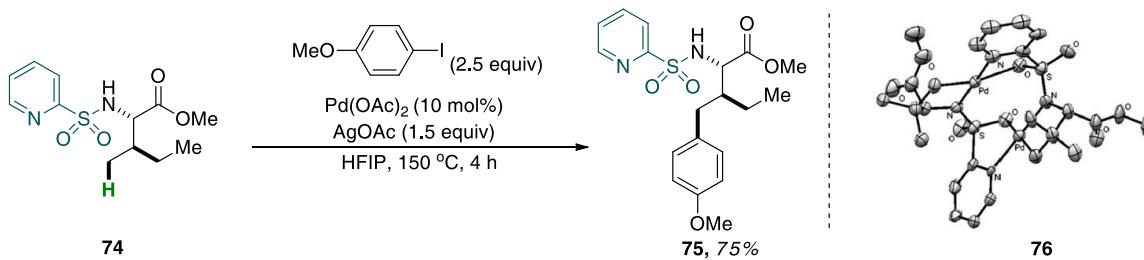
With substrate already containing a stereogenic centre, it was found that the ligand could override the inherent diastereoselectivity imparted by the substrate (Scheme 26). Treatment of cyclopropylmethyl sulfonamide **72** with either the L- or D-enantiomer of the ligand could yield the two different diastereoisomers (**73a** or **73b**) with excellent diastereocontrol, albeit in lower yields (entries 1 and 2).



Scheme 26: Overriding the diastereoselectivity with the ligand

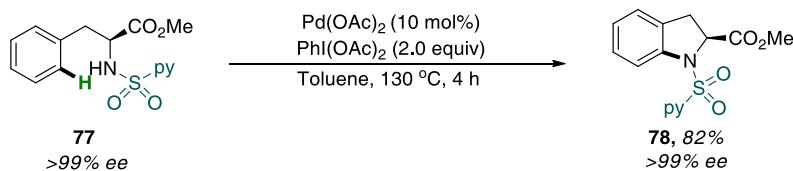
1.4.2.3 Miscellaneous auxiliaries

A modification to Yu's triflame directing group was reported by Carretero and co-workers in 2013.⁸⁴ *N*-(2-pyridyl)sulfonyl were employed to direct γ -sp³-C–H arylation in α - and β -amino acid derivatives, thereby allowing expedient synthesis of non-natural amino acids. Upon treatment of sulfonamides such **74** with an aryl iodide, the corresponding arylated product **75** was obtained in 75% yield (Scheme 27). The auxiliary could subsequently be easily removed using zinc powder under mild conditions to reveal the desired primary amine, with no loss of stereochemical integrity. Though the reaction was tolerant of electron-rich and electron-deficient aryl iodides, mixtures of mono- and di-arylated products were often obtained. Mechanistic investigation undertaken by the group has revealed the formation of a bi-metallic five-membered ring cyclopalladation complex **76**, as confirmed by X-ray crystallography, showing chelation to both the amine and the 2-pyridylsulfonyl auxiliary.



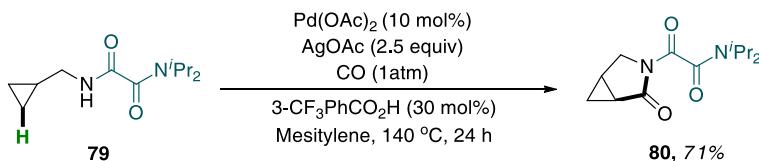
Scheme 27: Carretero's *N*-(2-pyridyl)sulfonyl-directed sp³ C–H arylation of amino acid derivatives⁸⁴

Yu has subsequently shown that this auxiliary could direct C–H intramolecular amination reaction for the synthesis of indolines,⁸⁵ and this approach was an improvement to his previous report of the same reaction using the *N*-triflyl directing group (Scheme 28)(section 1.4.2.2).⁷⁷ This reaction uses the readily available phenyl iodo(III)diacetate instead of the expensive electrophilic fluorinating reagent as an oxidant; the reactions typically reach completion within a shorter time period of 4 hours.



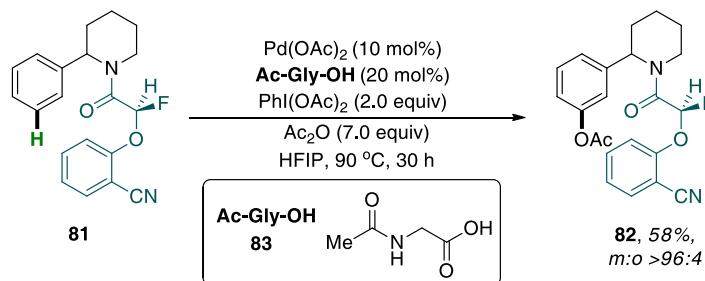
Scheme 28: Yu's sp² C–H intramolecular amination of *N*-(2-pyridyl)sulfonyl-protected phenylethylamines⁸⁵

Recently, Zhao and co-workers reported a synthesis of pyrrolidinones *via* oxallyl amide-directed γ -sp³ C–H carbonylation of aliphatic amines such as **79** (Scheme 29).⁸⁶ Both γ -methyl and cyclopropyl methylene C–H bonds were able to be activated to obtain the corresponding pyrrolidinones in moderate to excellent yields. Aliphatic, allyl and benzyl amines bearing a range of functional groups such as esters, nitriles, protected alcohols could be tolerated under the reaction conditions. Although the exact role of 3-(trifluoromethyl)benzoic acid is unclear, the authors postulate that it aids stabilisation of the palladium intermediate formed during the catalytic cycle.



Scheme 29: Zhao’s sp³ C–H carbonylation of oxallyl amide-protected aliphatic amines⁸⁶

As mentioned previously, one of the main challenges in C–H activation is site selectivity, especially in remote positions relative to the functional groups. To address this problem, Yu devised a strategy to achieve *meta*-selective sp² C–H acetoxylation of benzylamine derivatives *via* the use of a conformationally-rigid nitrile-containing template (Scheme 30).⁸⁷ Upon treatment of benzylamine derivative **81** with phenyl iodo(III)diacetate, the acetoxylated product **82** was obtained in 58% yield with high level of *meta* selectivity (*m:o* >96:4). The authors postulate that the high level of site selectivity is due to the use of the amino acid ligand **83**, which amplifies the pre-existing conformational bias in the template towards C–H insertion in the *meta* position.



Scheme 30: Yu’s template-directed *meta*-selective sp² C–H acetoxylation of benzylamines⁸⁷

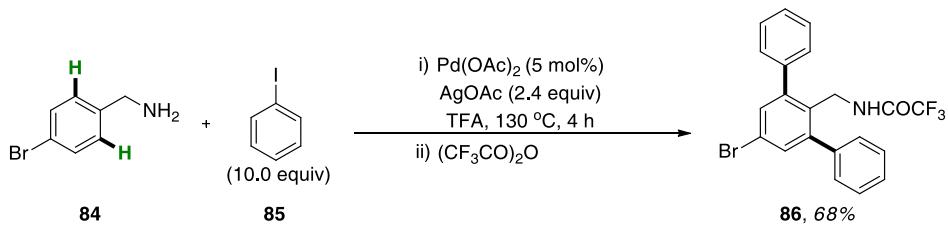
Despite the advances made in the auxiliary-directed approach to C–H functionalisation of aliphatic amines, the additional synthetic steps and the often harsh conditions required for the installation and removal of the auxiliaries still render this approach impractical. Therefore, direct

C–H functionalisation of unprotected amines are highly desirable and this is an area of extensive research in recent years. The following section documents the progress made in sp^2 and sp^3 C–H functionalisation of unprotected amines.

1.4.3 Unprotected amine-directed C–H functionalisation *via* palladium catalysis

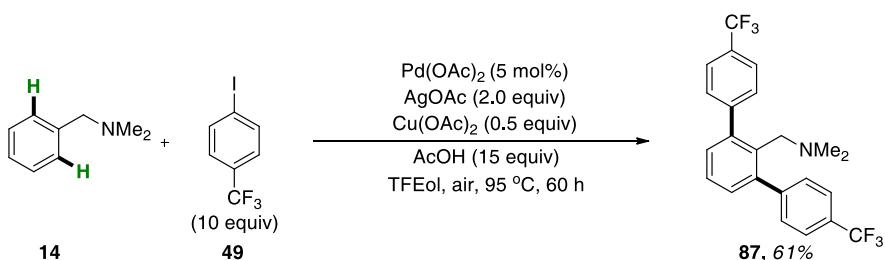
1.4.3.1 sp^2 C–H arylation of unprotected amines

An early example of catalytic sp^2 C–H activation was the direct *ortho*-arylation of benzylamines reported in 2006 by Daugulis and co-workers (Scheme 31).⁸⁸ Primary and secondary benzylamines such as **84** could be arylated to afford di-arylated products such as **86** in moderate to good yields. Di-arylation was observed in all cases except when *meta*-substituents were present, presumably owing to the steric effect. Excess aryl iodides were added to ensure di-arylation in cases where mono-arylation could not be achieved selectively. The reaction displayed a broad functional group tolerance although the reaction proceeded faster with more electron-rich benzylamines. Importantly, it was found that the amount of trifluoroacetic acid strongly influenced the results, with 5 equivalents of the acid gave the best reaction yields.



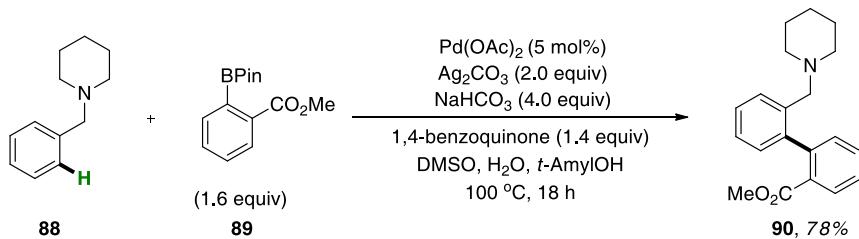
Scheme 31: Daugulis' C–H *ortho*-arylation of benzylamines⁸⁸

In 2013, Zhang and co-workers reported a copper(II)-promoted palladium-catalysed C–H *ortho*-arylation of *N,N*-dimethylbenzylamines. Upon treatment of amine substrate **14** with an aryl iodide, in the presence of the copper(II) additive, the corresponding di-arylated product **87** was obtained in 61% yield (Scheme 32).⁸⁹ Similar to Daugulis' reaction above, mono-arylation was only observed with *meta*-substituted benzylamines. Although both electron-rich and electron-deficient benzylamine and aryl iodide partners were tolerated, the main drawback of this reaction was the long reaction time required (60 hours). Copper(II) acetate monohydrate was found to be an important additive to improve the yields in this transformation. Although the role of the copper salt is not entirely clear, the authors speculate that it is acting as a Lewis acid which may serve to liberate the palladium(II) species from the palladacycle complex.



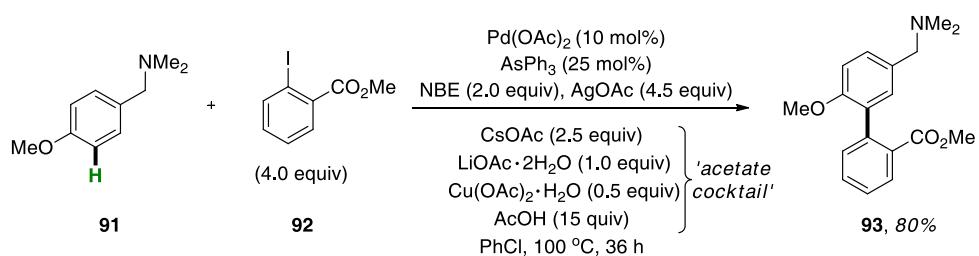
Scheme 32: Zhang's copper(II)-promoted palladium-catalysed C–H *ortho*-arylation of *N,N*-dimethylbenzylamines⁸⁹

In 2015, Dixon and co-workers demonstrated that nitrogen-containing heterocycles such as piperidines were capable of directing C–H *ortho*-arylation of benzylamines, using arylboronic acid pinacol esters.⁹⁰ Both *para*- and *meta*-arylboronic esters gave mono-arylation in good yields with piperidine substrate **88**. *Ortho*-arylboronic esters showed poor reactivity (<20% yields) except when the substituent was an ester group, which gave the desired arylated product **90** in 78% yield (Scheme 33). Heterocyclic boronic esters were found to be completely unreactive. The reaction was also compatible with other heterocycles such as pyrrolidine, morpholine and piperazine as native directing groups, but generally lower reactivity was observed.



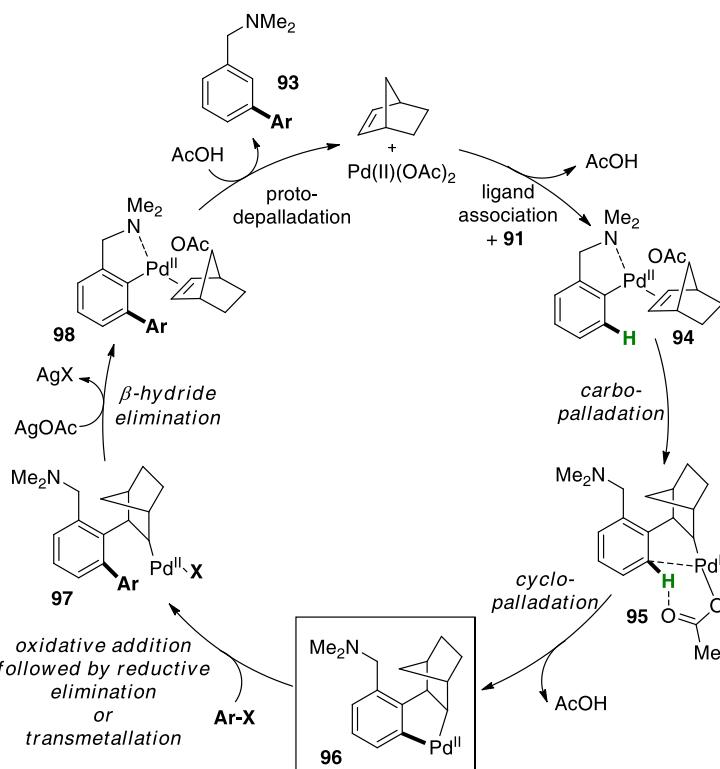
Scheme 33: Dixon's *N*-heterocycle-directed C–H *ortho*-arylation of benzylamines⁹⁰

While *ortho*-selective arene functionalisation methods have been extensively developed, *meta*-selective functionalisation of electronically unbiased arenes remains a difficult task.^{87,91} To address this problem, Dong and co-workers have recently reported a highly *meta*-selective amine-directed arylation using norbornene as a transient mediator (Scheme 34).⁹² In this study, *ortho*-substituted aryl iodides were employed as the coupling partner and a range of functionalities on the aryl iodides could be tolerated under the reaction conditions, yielding the desired *meta*-arylated benzylamines such as **93** in good yields.



Scheme 34: Dong's norbornene-mediated *meta*-arylation of *N,N*-dimethylbenzylamines⁹²

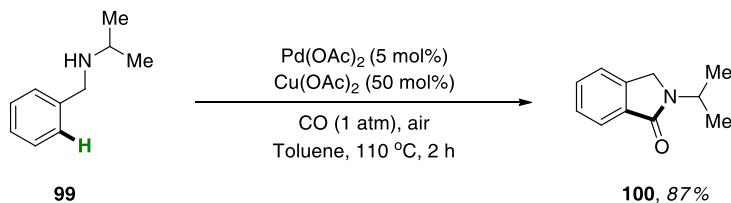
The reaction employs a palladium/norbornene catalyst system which contributes to the site selectivity of the reaction and is based on seminal works published by Catellani and latterly Lautens.^{93,94} The reaction was found to be promoted by triphenylarsenic together with an ‘acetate cocktail’, although their exact roles are not clear. The proposed mechanism for this reaction is shown in Scheme 35. Initial coordination of the palladium(II) salt with norbornene (NBE) followed by an electrophilic palladation gives the palladated species **94**. Carbopalladiation followed by cyclopalladation, in an analogous fashion to the Catellani reaction, affords the key NBE-bridged five-membered palladacycle **96**. This palladacycle is expected to react with an aryl iodide through either a palladium(IV) intermediate (oxidative addition followed by reductive elimination) or a transmetalation pathway, to generate a *meta*-arylated complex **97**. The resulting palladium(II) intermediate undergoes a β -hydride elimination to give the arylated palladated species **98**, which after proto-depalladation, furnishes the *meta*-arylated benzylamine **93** and releases palladium(II) back into the catalytic cycle.



Scheme 35: Proposed mechanism of norbornene-mediated *meta*-arylation of *N,N*-dimethylbenzylamines⁹²

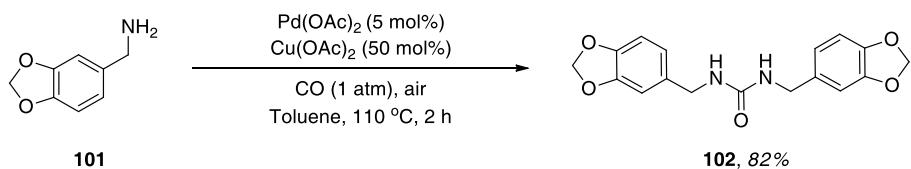
1.4.3.2 sp^2 C–H carbonylation of unprotected amines

Early examples of palladium-catalysed amine-directed sp^2 C–H carbonylation were published by Orito and co-workers.^{95,96} In 2004, they reported a C–H carbonylation procedure for the formation of 5- or 6-membered benzolactams such as **100** from *N*-alkyl- ω -arylalkylamines (Scheme 36).⁹⁵ Though benzylamines with both electron-rich and electron-deficient substituents were tolerated in the reaction, the reactions often suffered from poor regioselectivity with substituted substrates. It was observed that carbonylation of benzylamines to afford the corresponding five-membered benzolactams proceeded significantly faster than that of phenylethylamines to afford six-membered benzolactams.



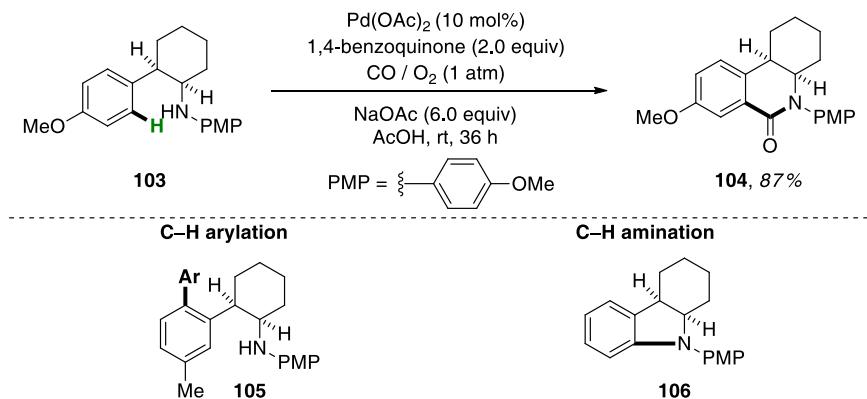
Scheme 36: Orito's amine-directed sp^2 C–H carbonylation to give benzolactams⁹⁵

Orito later found that primary aliphatic amines were shown to undergo carbonylation to give symmetrical *N,N'*-disubstituted ureas such as **102** in good yields instead of formation of benzolactams (Scheme 37).⁹⁶



Scheme 37: Orito's carbonylation of primary amines to give symmetrical N,N' -disubstituted ureas⁹⁶

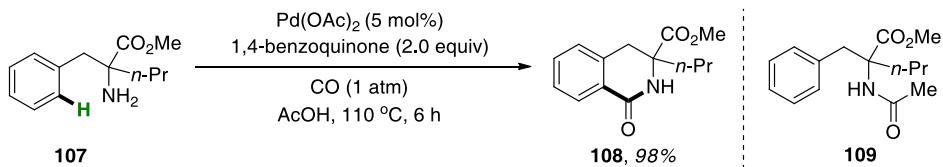
In 2011, Gaunt and co-workers reported the palladium(II)-catalysed C–H carbonylation of β -arylethylamines under ambient conditions (Scheme 38).⁹⁷ Treatment of a range of β -arylethylamines such as **103** under the optimised carbonylation conditions delivered synthetically versatile dihydro-2-quinolones **104** in good yields. It was proposed that the *p*-methoxyphenyl (PMP) group would diminish the nucleophilicity of the nitrogen atom such that it would disfavour the formation of *bis*-amino-palladium(II) complex that would have prevented cyclopalladation. Moreover, the increased acidity of the aryl N–H bond in the cyclopalladation complex may assist the deprotonation step that must accompany the C–H bond functionalisation. The β -arylethylamine scaffold could also undergo C–H arylation and amination processes, generating products such as **105** and **106** with diverse structures.



Scheme 38: Gaunt's C–H functionalisation of β -arylethylamines under ambient conditions⁹⁷

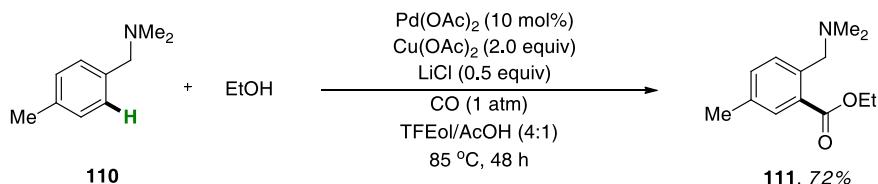
A recent report by Rodriguez and co-workers has shown that phenethylamines bearing α,α -disubstituted centres such as **107** could be carbonylated to the corresponding benzolactams **108** in excellent yields (Scheme 39).^{98,99} The α,α -disubstitution in **107** was found to be critical to the success of the reaction, either by sterically disfavouring the formation of the catalytically inactive bis-amine complex,¹⁰⁰ or through the Thorpe-Ingold effect,^{10,101} which favours cyclisation by

lowering the entropic cost of the reaction. The use of 1,4-benzoquinone as an oxidant proved important for the catalytic reaction, suppressing the formation of the *N*-acetylated amine **109**. This reaction strongly favours the formation of six-membered benzolactams over five-membered benzolactams, which is the opposite to that observed by Orito.⁹⁵



Scheme 39: Rodriguez's sp² C–H carbonylation of α,α -disubstituted phenethylamines^{98,99}

Amine-directed sp^2 C–H carbonylation is not only restricted to benzolactam formation, Shi and co-workers have shown that benzoate esters could be formed by employing alcohols as external nucleophiles.¹⁰² Upon treatment of *N,N*-dimethylbenzylamines such as **110** with carbon monoxide and an alcohol nucleophile under palladium catalysis, the corresponding benzoic esters **111** could be formed selectively at the *ortho* position in good yields (Scheme 40). The reaction conditions were based on an earlier report of an sp^2 C–H *ortho*-olefination of *N,N*-dimethylbenzylamines (section 1.4.3.3).¹⁰³ Both electron-rich and electron-deficient groups were tolerated under the reaction conditions though electron-rich substituents generally gave better yields, presumably due to the enhancement of electron density of the phenyl rings. The authors proposed that lithium chloride acts as a ligand and facilitates migratory insertion of carbon monoxide into the palladium–carbon bond.

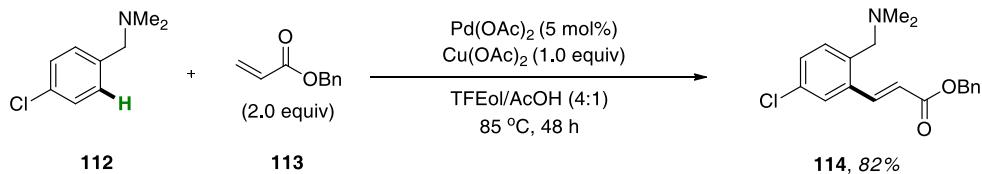


Scheme 40: Shi's sp² C–H alkoxy carbonylation of *N,N*-dimethylbenzylamines¹⁰²

1.4.3.3 Other sp^2 C–H functionalisation of unprotected amines

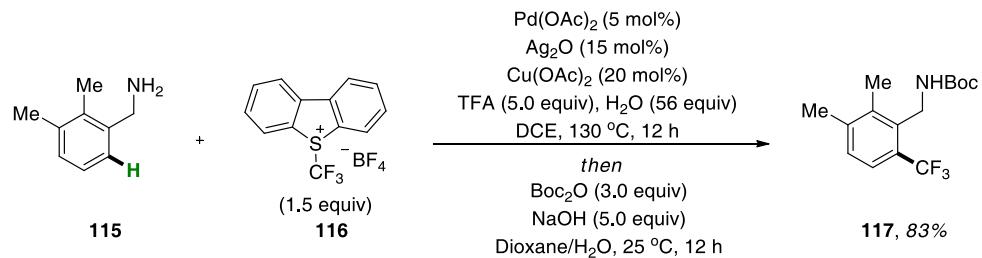
In 2007, Shi reported the *ortho*-alkenylation of *N,N*-dimethylbenzylamines with a range of acrylates, acrylamides and substituted alkenes (Scheme 41).¹⁰³ It is important to note that the aryl chloride moiety in **112** was well tolerated under the reaction conditions and the chloride could potentially be further functionalised by transition metal-catalysed cross coupling reactions.¹⁰⁴ The authors stated that the acidity of the reaction was important for ensuring good conversion to

the *ortho*-alkenylated products. This is presumably due to the fine balance between binding too strongly which would result in the formation of the catalytically inactive bis-amine complex, or binding too weakly *i.e.* when protonated, and hence unable to direct C–H activation.



Scheme 41: Shi's *ortho*-alkenylation of *N,N*-dimethylbenzylamines¹⁰³

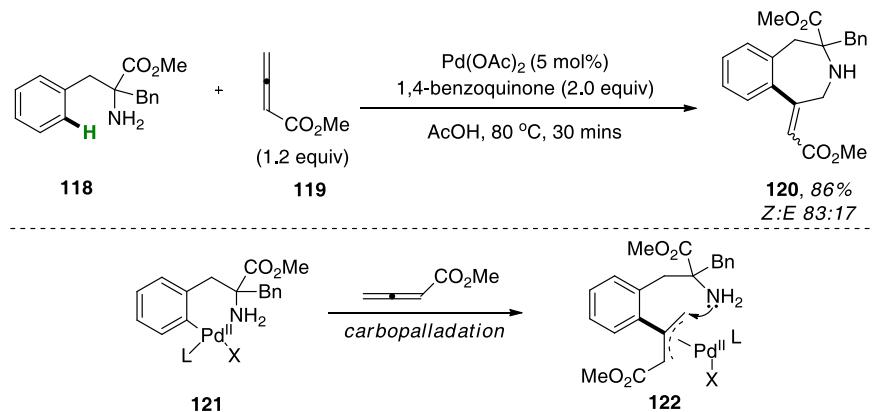
Given the utility of trifluoromethyl groups in pharmaceuticals and biologically active molecules,¹⁰⁵ there has been increasing interests in developing new methods for the installation of trifluoromethyl groups onto the aromatic scaffolds of these molecules.^{106–108} Specifically, unprotected amine-directed arene C–H trifluoromethylation would be particularly valuable given the amine functionalities could be derivatised after the reaction and thus introducing further complexity to the molecules. To address this need in medicinal chemistry, Yu and co-workers have reported a method for *ortho*-C–H trifluoromethylation of benzylamines utilising an electrophilic CF₃ reagent (Scheme 42).¹⁰⁹ In this reaction, primary and secondary benzylamines such as **115** could undergo *ortho*-C–H trifluoromethylation to generate *ortho*-trifluoromethyl benzylamines such as **117**, which are prevalent in medicinal compounds.^{110,111} The free primary amine was protected with a Boc group at the end of the reaction for ease of isolation. Although the reaction was high yielding for simple aryl and alkyl substituted benzylamines, both electron-rich and electron-deficient groups were poorly tolerated, as was substitution in the α -position of the amines.



Scheme 42: Yu's *ortho*-C–H trifluoromethylation of benzylamines¹⁰⁹

Recently, Rodriguez and co-workers reported a synthesis of tetrahydro-3-benzazepines and tetrahydroisoquinolines by annulation of phenylethylamines and benzylamines respectively with terminal allenes (Scheme 43).¹¹² Similar to their earlier reports on sp² C–H carbonylation on the

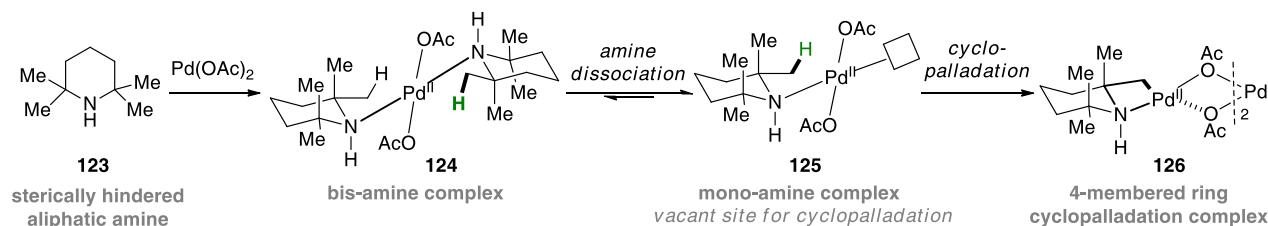
same amine system,^{98,99} the quaternary centre adjacent to the primary amine is crucial for reactivity, with the best yields obtained when one of the groups is an ester group. This catalytic C–H activation/annulation strategy was proposed to proceed *via* ring cyclisation of the π -allyl intermediates such as **122**, formed after the preceding carbopalladation step from the six-membered palladacycle **121**.



Scheme 43: Rodriguez's C–H annulation of phenylethylamines and benzylamines with allenes¹¹²

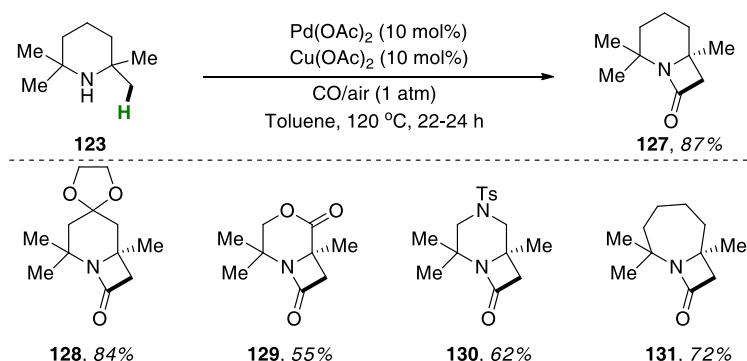
1.4.3.4 sp^3 C–H functionalisation of unprotected amines

Compared to the research on sp^2 C–H bond activation, examples of unprotected aliphatic amine-directed sp^3 C–H functionalisation have been extremely rare. Seminal work by Gaunt and co-workers in 2014 showed for the first time that unprotected aliphatic secondary amines could undergo sp^3 C–H cyclopalladation to form novel four-membered-ring cyclopalladation complexes such as **126**, which could then be functionalised to give strained nitrogen heterocycles (Scheme 44).¹¹³ It was hypothesised that the use of amines such as 2,2,6,6-tetramethylpiperidine (TMP) **123** would increase the steric bulk around the nitrogen atom and the increased steric demand would render the bis-amine complex thermodynamically unstable, promoting dissociation of one of the amine molecule to provide the vacant coordination site required for C–H activation. Moreover, the two quaternary centres adjacent to the nitrogen atom prevents β -hydride elimination from occurring.



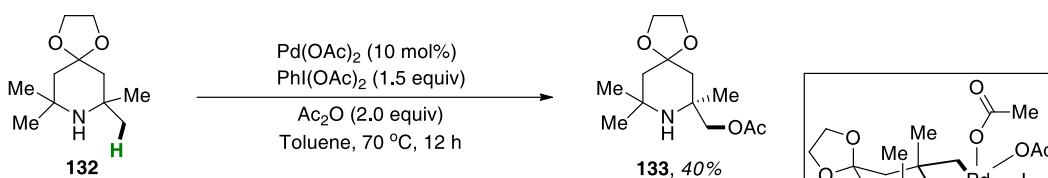
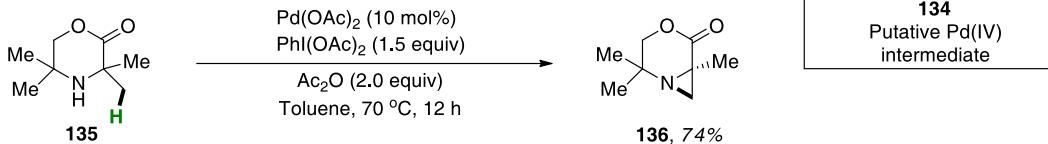
Scheme 44: Gaunt's strategy for the sp^3 C-H activation of aliphatic amines to form novel four-membered palladacycles

Treatment of palladacycle **126** with carbon monoxide furnished β -lactam **127** through a palladium(II)/(0) pathway. Subsequent development of catalytic conditions revealed that amine **123** could undergo carbonylation with 10 mol% of palladium acetate, under an atmosphere of carbon monoxide/air and copper acetate as a co-oxidant, to afford β -lactam **127** in an excellent 87% yield (Scheme 45). Commercial or readily available piperidine derivatives, as well as other heterocycles were also well tolerated under the reaction conditions to yield a variety of β -lactams (**128** to **131**) in good yields.

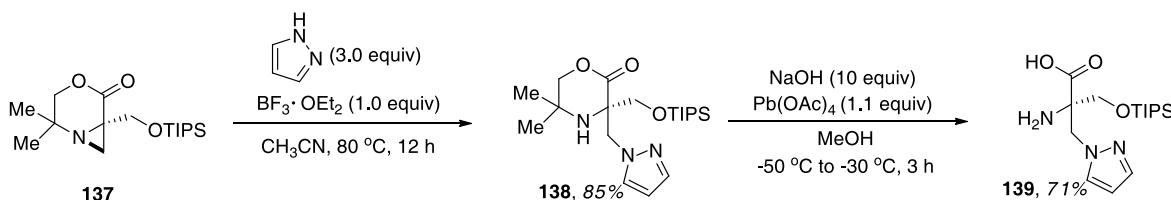


Scheme 45: Gaunt's C–H carbonylation of hindered aliphatic amines¹¹³

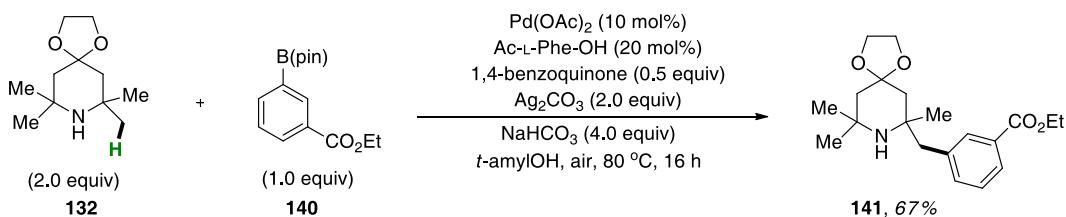
Replacing carbon monoxide with a mild oxidant, hypervalent iodine reagent PhI(OAc)_2 , resulted in an acetoxylation reaction to give acetoxylated amine **133**, proceeding *via* the putative palladium(IV) intermediate **134** (Scheme 46a). Interestingly, subjecting morpholinone derivative **135** to the same reaction conditions resulted in an azidiridination reaction to give aziridine **136** (Scheme 46b), suggesting that the carbonyl group might have played a subtle controlling role in this switch in reactivity. Further computational studies within the group has shown that the reason for this switch in reactivity lies behind the difference in energy between the C–O and C–N bond reductive elimination pathways.¹¹⁴

a) C–H acetoxylation**b) C–H aziridination****Scheme 46:** C–H acetoxylation (a) and aziridination (b) of hindered aliphatic amines¹¹³

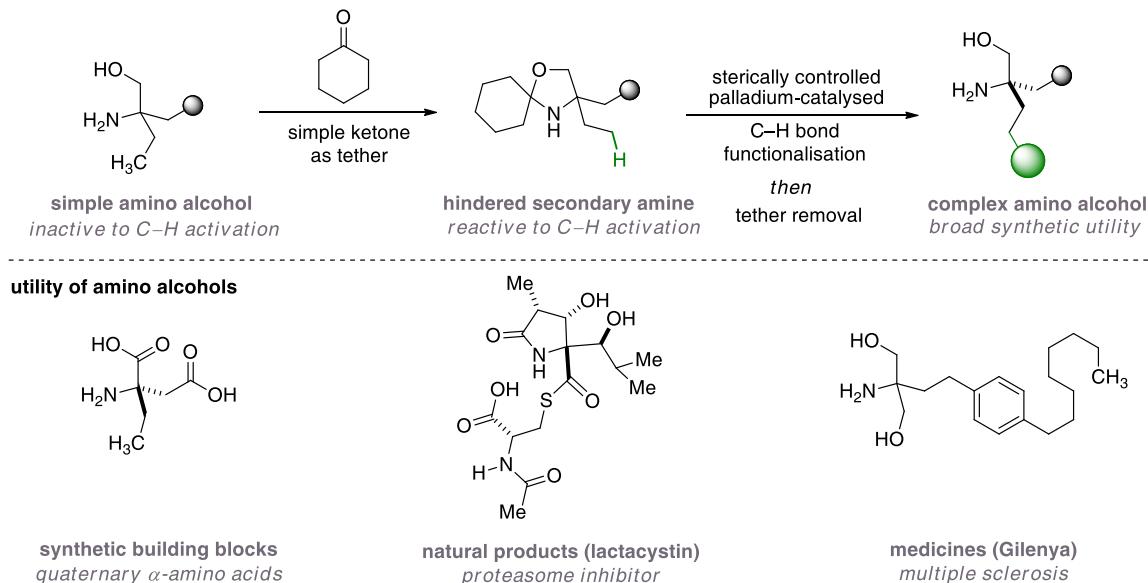
The aziridination reaction was found to be general with a broad range of substituted morpholinones, giving the desired aziridines in good to excellent yields. Aziridine **137** could be opened with nucleophiles such as pyrazole to give highly functionalised quaternary α -amino acids such as **139**, after oxidative cleavage of the cyclic framework (Scheme 47).

**Scheme 47:** Access to highly functionalised α -amino acids

Recently, the Gaunt group has demonstrated that this methodology could be applied to C–H arylation using the same four-membered-ring cyclopalladation pathway aforementioned (Scheme 48).¹¹⁵ Crucial to the success of this reaction is the employment of mono-protected amino acids as ligands for the palladium catalyst. The use of these amino acids as enabling ligands in palladium-catalysed C–H functionalisation has recently been introduced by Yu and co-workers.^{82,116,117} A range of hindered secondary amines and arylboronic esters were compatible with this process.

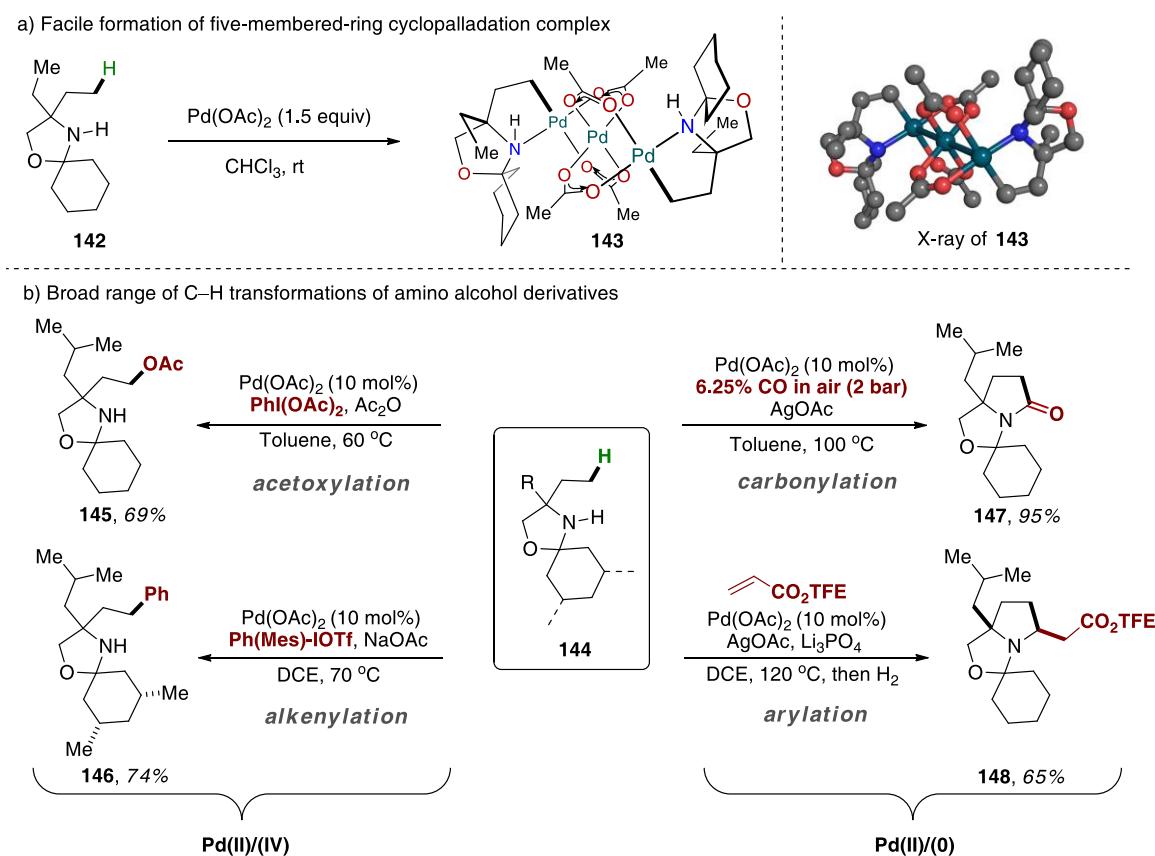
**Scheme 48:** C–H arylation of hindered aliphatic amines¹¹⁵

Inspired by these initial reports, the group has recently devised a new strategy for the functionalisation of simple primary amino alcohols by transiently converting these substrates into bulky secondary amines to facilitate C–H activation.¹¹⁸ A simple ketone acts as a tether to bridge the nitrogen and oxygen atoms of the amino alcohols, generating a hindered *N,O*-ketal which facilitates C–H activation. After the functionalisation event, the removal of the tether group reveals the structurally complex amino alcohols, which have broad synthetic applications as well as being prevalent in pharmaceuticals (Scheme 49).



Scheme 49: Aliphatic C–H functionalisation of amino alcohols *via* a sterically promoted approach¹¹⁸

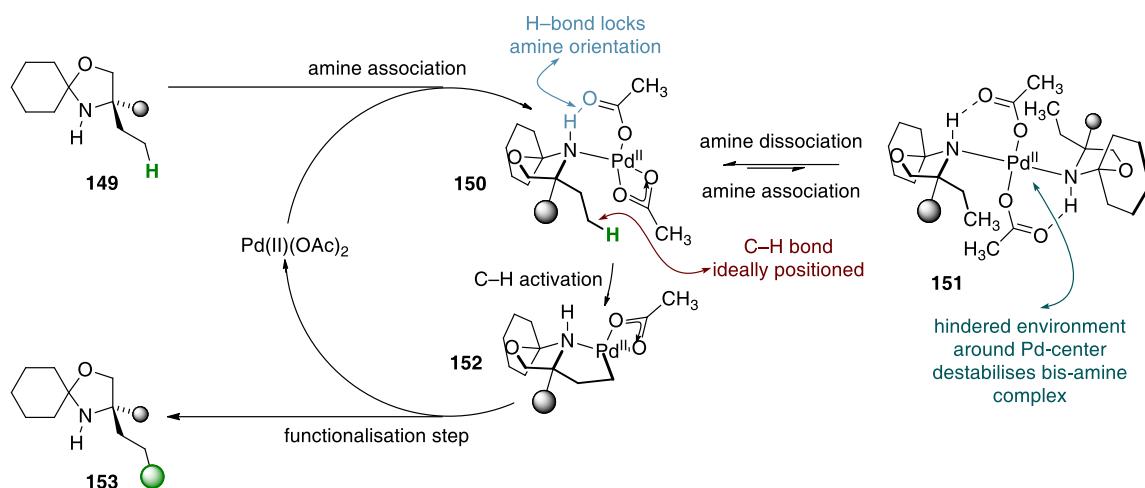
The hindered *N,O*-ketal **142** was found to undergo a facile C–H activation to form five-membered-ring cyclopalladation complex **143**, where a broad range of C–H transformations have shown to be amenable to this C–H activation strategy (Scheme 50).



Scheme 50: Summary of C–H functionalisations of amino alcohol derivatives¹¹⁸

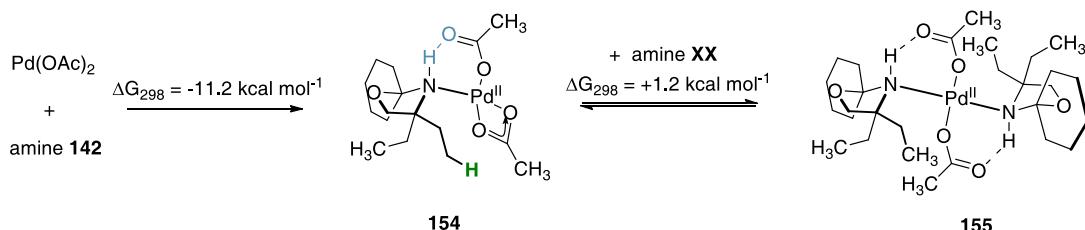
C–H acetoxylation and arylation are believed to proceed *via* a palladium(II)/(IV) pathway whilst the palladium(II)/(0) pathway is likely for C–H carbonylation and alkenylation, demonstrating the flexibility of the palladacycle intermediate **143**.

Mechanistically, it was predicted that the secondary amine **149** would bind to the palladium catalyst in such a way that the complexation would be accompanied by the formation of a hydrogen bond between the acetate ligand on the palladium and the free N–H of the amine in **150** (Scheme 51). This hydrogen bonding interaction is believed to play two important roles in the reaction: 1) to orientate the amine substituents in the bis-amine palladium(II) complex **151** in such a way that interactions between the aliphatic groups would be intensified, enabling the equilibrium to shift towards the mono-amine complex **150**; 2) to lock the conformation of the amine with respect to the palladium centre (in **150**), thereby projecting the targeted C–H bond into an optimal trajectory for activation, forming a kinetically favoured five-membered cyclopalladation complex **152**. Functionalisation of the palladium–carbon bonds in **152** with external agents would furnish functionalised products **153**.



Scheme 51: Hypothesis for C–H activation strategy for the functionalisation of amino alcohols

The hypothesis for the C–H activation event is supported by computational studies conducted within the group. Calculations performed on the basis of the proposed pathway supported the presence of the hydrogen bond between the palladium-bound amine N–H and acetate ligands, but also identified that the putative mono-amine palladium(II) complex **154** was 1.2 kcal mol⁻¹ (ΔG_{298}) lower in energy than the corresponding bis-amine palladium(II)-complex **155** (Scheme 52). This is in agreement with our hypothesis that the hindered nature of the amine means that **154** is thermodynamically and kinetically favoured over **155** and therefore leads to facile C–H activation.



Scheme 52: Molecular calculations of the mono- and bis-amine palladium(II) complexes, **154** and **155**¹¹⁸

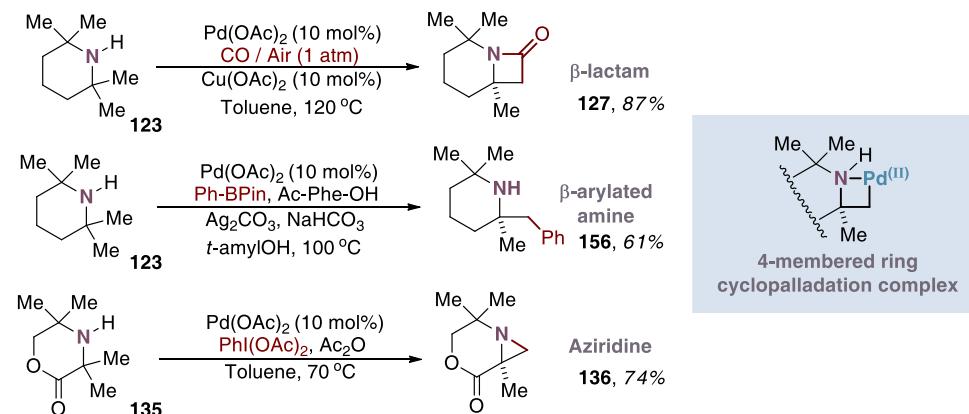
The nature of the tethering ketone was also chosen carefully. First, we reasoned that the cyclohexyl group should provide the requisite bulk to facilitate the amine dissociation step when bound to the palladium centre. Second, the methylene C–H bonds in the cyclohexyl motif are less likely to undergo C–H activation than groups with terminal C–H bonds.

2 Palladium(II)-Catalysed sp^3 C–H Carbonylation of Hindered Amines

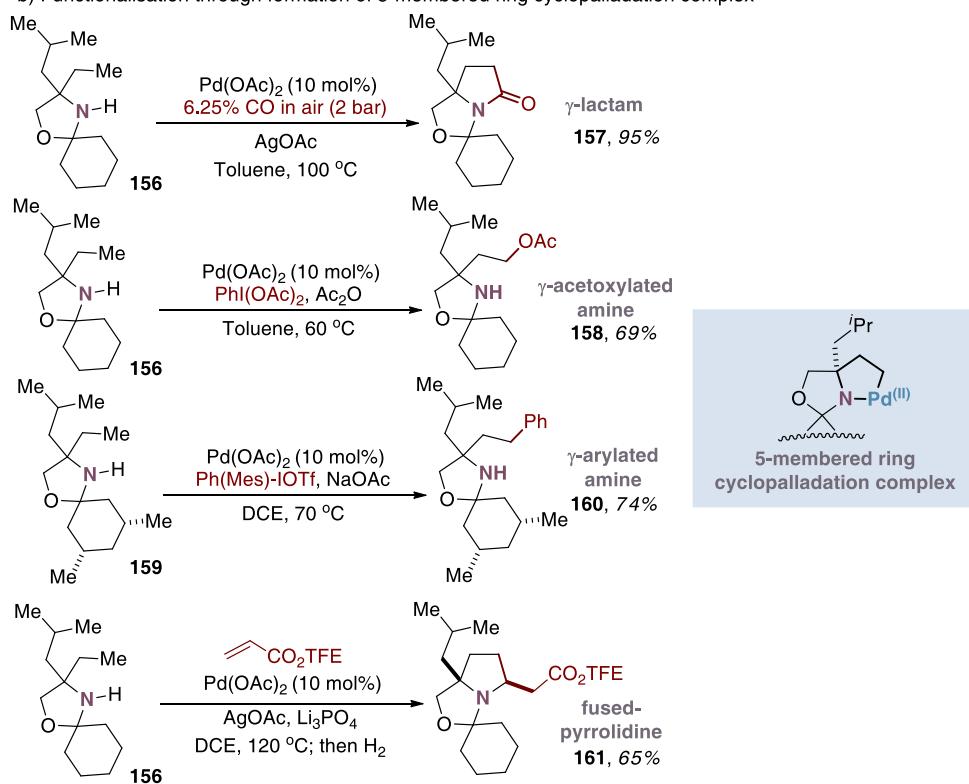
2.1 Background

As mentioned in the previous section, recent research within our group has focused on C–H functionalisation of hindered secondary aliphatic amines, *via* both the four-membered- and five-membered- ring cyclopalladation pathways (Scheme 53).^{113,115,118}

a) Functionalisation through formation of 4-membered ring cyclopalladation complex

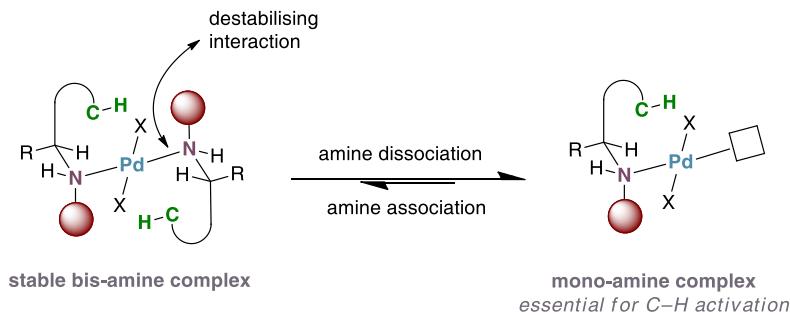


b) Functionalisation through formation of 5-membered ring cyclopalladation complex



Scheme 53: Palladium(II)-catalysed C–H functionalisation of secondary aliphatic amines developed within in our group^{113,115,118}

Key to the success of this C–H activation strategy is the steric hindrance around the secondary amine motif. We believe these interactions promote the formation of the putative mono-amine palladium(II) complex as a result of destabilising the traditionally more favourable bis-amine palladium(II) complex (Scheme 54).

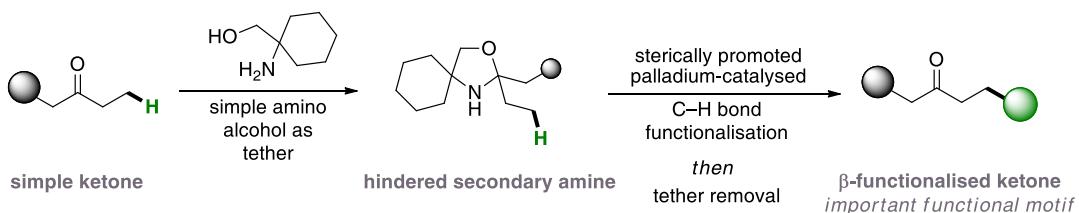


Scheme 54: Mono-amine palladium(II) complex favoured by sterically hindered amines

Given the success of our sterically promoted C–H activation approach to functionalise unprotected amines, we wondered if aliphatic C–H bonds of other useful classes of molecules could be functionalised in a similar fashion.

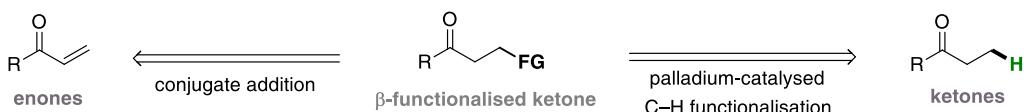
2.2 Project aims

We envisaged that the sterically promoted C–H activation approach could be utilised to functionalise the β -position of ketones, which are important functional motifs in organic chemistry. We proposed that ketones could be temporarily masked as hindered secondary amines capable of undergoing sterically promoted palladium-catalysed C–H functionalisation (Scheme 55). Subsequent removal of the tether group would reveal the β -functionalised ketones.



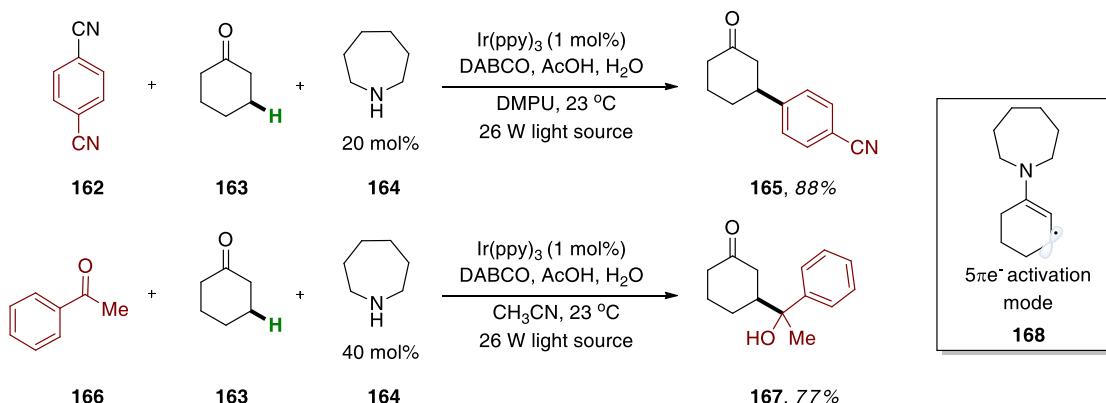
Scheme 55: Proposed aliphatic C–H functionalisation of ketones *via* a sterically promoted approach

This approach offers an attractive alternative to the traditional conjugate addition of soft nucleophiles into α,β -unsaturated ketones in synthesising β -functionalised ketones, given the wide commercial availability of ketones compared to enones (Scheme 56).



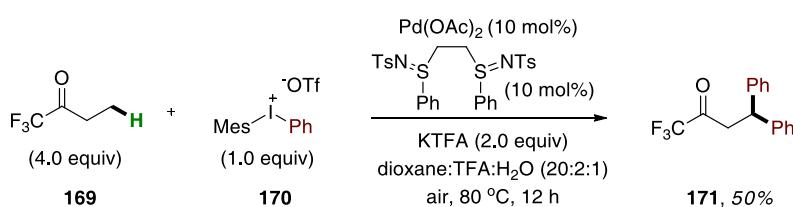
Scheme 56: Traditional conjugate addition approach to β -functionalised ketones

In 2013, Macmillan and co-workers reported a general catalytic platform for direct β -functionalisation of ketones and aldehydes, *via* merger of photocatalysis and organocatalysis (Scheme 57).^{119,120} Central to the success of this approach was the transient generation of 5π -electron β -enaminy radical such as **168** from ketones and aldehydes that rapidly coupled with cyano-substituted aryl rings¹¹⁹ or aryl ketones¹²⁰ at the carbonyl β -position. However, this catalytic reaction was only applicable to cyclic ketones and not acyclic ketones.



Scheme 57: Direct β -functionalisation of ketones *via* merger of photocatalysis and organocatalysis^{119,120}

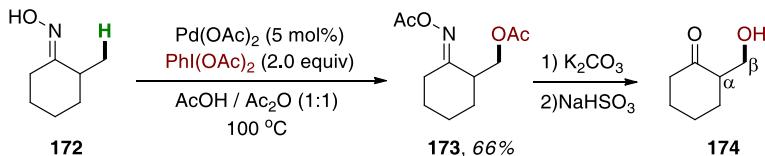
Very recently, Dong and co-workers reported a palladium(II)-catalysed direct β -arylation of ketones with diaryliodonium salts.¹²¹ Cyclic ketones with different ring-sizes were arylated in good yields. Moreover, the arylation reactions were shown to be amenable to acyclic ketones, albeit lower yields of arylated products were obtained (Scheme 58).



Scheme 58: Dong's palladium(II)-catalysed direct β -arylation of ketones with diaryliodonium salts¹²¹

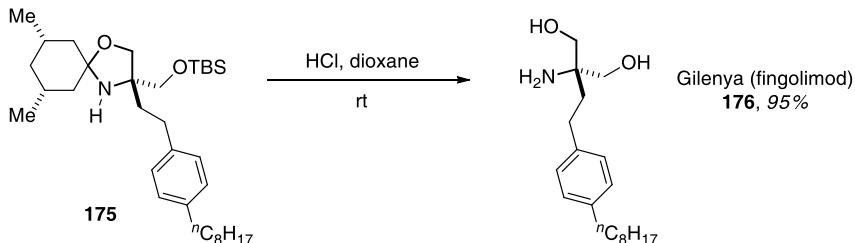
Up until the recent report by Dong, ketones were known to be ineffective directing groups in palladium-catalysed reactions because of their poor coordinating ability to palladium.^{122,123} To

overcome this challenge, Sanford and co-workers developed a palladium(II)-catalysed β -acetoxylation of *O*-acetyloximes, which masked the ketones as more coordinating oxime derivatives during C–H functionalisation before removing it to reveal the ketone functionality (Scheme 59).¹²⁴ This transformation enabled β -hydroxylation of ketones and this strategy has been successful in constructing the C–O linkage but hasn't yet been reported for C–C linkage.



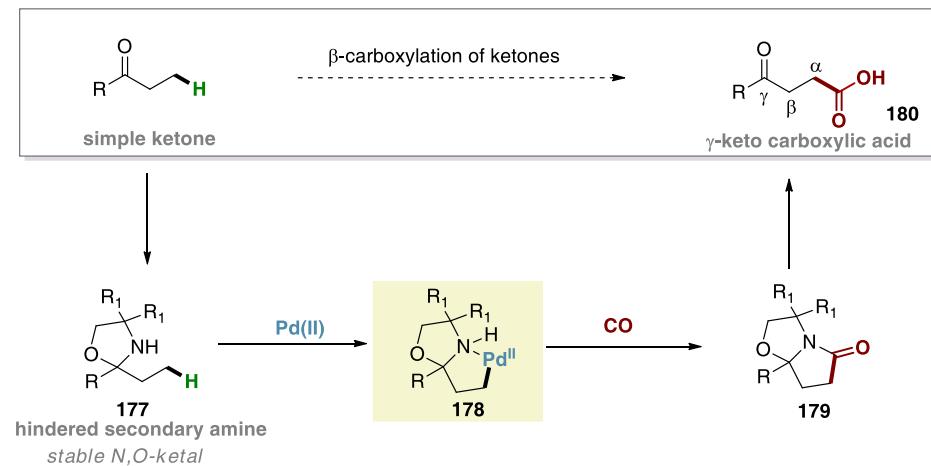
Scheme 59: Sanford's palladium(II)-catalysed β -acetoxylation of *O*-acetyloximes¹²⁴

In this investigation, we aimed to broaden the scope of aliphatic β -C–H functionalisation of ketones, through the use of our steric tethering strategy. In order for our tethering approach to become a general protocol for β -functionalisation of aliphatic ketones, two key criteria have to be met: 1) the tethering group must be easily installed and removed; 2) the tethering group must be sufficiently robust to tolerate the catalytic reaction conditions. Our previous work has shown that *N,O*-ketals can be easily hydrolysed under acidic conditions, for example, in the last step of the synthesis of a pharmaceutical agent, Gilenya™ (fingolimod) **176** (Scheme 60).¹¹⁸



Scheme 60: Hydrolysis of *N,O*-ketal **175** in the synthesis of Gilenya™

We chose to begin this investigation with a C–H carbonylation process. We anticipated that, upon treatment of a hindered *N,O*-ketal **177** with a palladium(II) source, the reaction would proceed through the formation of kinetically favourable five-membered ring palladacycle complex **178** (Scheme 61). Insertion of carbon monoxide followed by reductive amination would yield γ -lactam **179**. Subsequent hydrolysis of the *N,O*-ketal moiety would reveal γ -keto carboxylic acid **180**. These 1,4-dicarbonyls are useful synthetic building blocks in heterocycle syntheses as well as being widespread in biologically important natural products.^{125,126} This C–H carbonylation strategy represents an overall β -carboxylation of ketones.

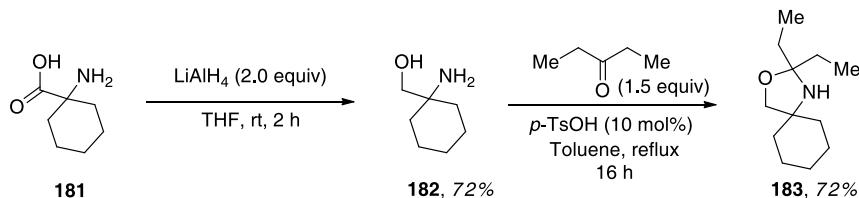


Scheme 61: Overall β -carboxylation of ketones *via* a steric-tethering strategy

2.3 Results and discussion

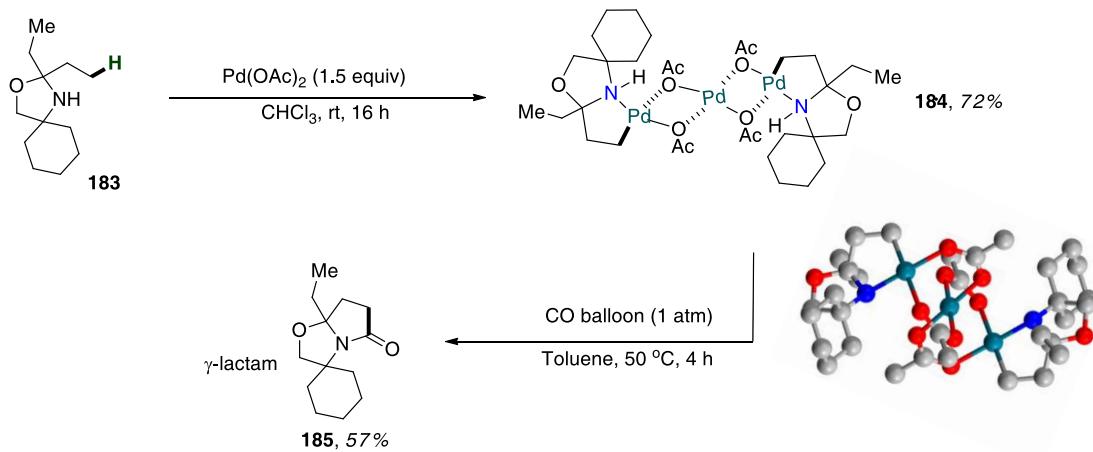
2.3.1 Preliminary stoichiometric studies

To test our hypothesis, *N,O*-ketal **183**, prepared from commercially available amino acid **181** in two synthetic steps, was chosen as the representative substrate for the preliminary stoichiometric studies (Scheme 62). The cyclohexyl group should provide the steric bulk to favour the formation of the mono-amine complex, facilitating C–H activation. Furthermore, the methylene C–H bonds in the cyclohexyl motif should be less likely to undergo to C–H activation than terminal C–H bonds.



Scheme 62: Preparation of *N,O*-ketal **183**

Our initial studies focused on the formation of palladacycle with *N,O*-ketal **183**. Upon treatment with 1.5 equivalents of palladium(II) acetate at room temperature in chloroform, a cyclopalladated complex was formed and subsequently identified as a trinuclear complex, whose structure was confirmed by X-ray crystallography following recrystallisation. Exposing the palladacycle complex **184** to an atmosphere of carbon monoxide in toluene at 50 °C furnished the desired γ -lactam **185** in 57% yield (Scheme 63).

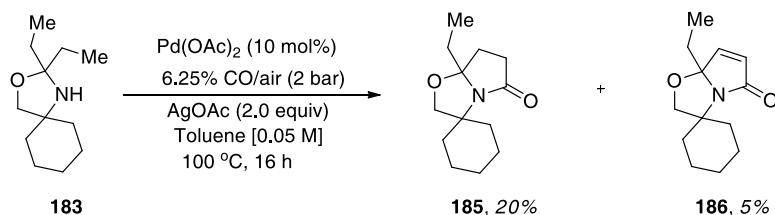


Scheme 63: Cyclopalladation and carbonylation of **183**

This promising result gave us the proof of concept and we set about investigating the development of a catalytic procedure for the conversion of *N,O*-ketal **183** into γ -lactam **185**.

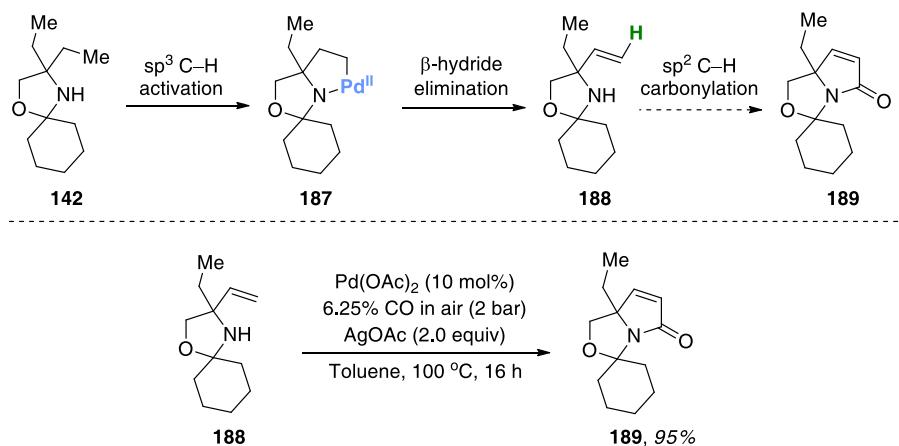
2.3.2 Optimisation studies for catalytic reaction conditions

Our initial attempts at a catalytic process for *N,O*-ketal **183** were focused on the reaction conditions employed in carbonylation of the structurally similar *N,O*-ketal **142** (see Scheme 53) that was previously developed by Dr Daniel Pla, a former postdoctoral associate within the group.¹¹⁸ Under those reaction conditions, the desired γ -lactam **185** was obtained in 20% yield, as well as the unsaturated γ -lactam **186**, which was isolated in 5% yield (Scheme 64).



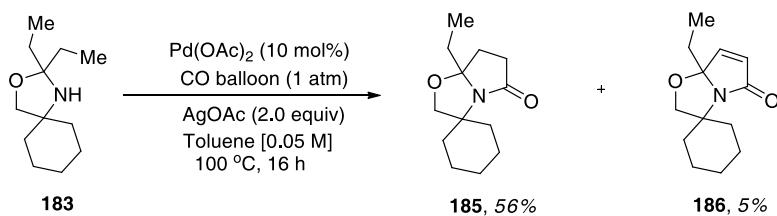
Scheme 64: Carbonylation of *N,O*-ketal **183** using previously developed catalytic conditions by Dr Pla

Our previous studies showed that unsaturated γ -lactam **189** was most likely originated from sp^2 C–H activation of an allylic amine derivative **188**, formed from β -hydride elimination of the cyclopalladation complex **187** (Scheme 65).¹¹⁸ The intermediacy of the allylic amine was confirmed by selective carbonylation of the sp^2 C–H bond (in **188**) to give the unsaturated γ -lactam **189** in excellent yields. We believe unsaturated γ -lactam **186** could be formed *via* a similar pathway.



Scheme 65: Proposed mechanism and experimental evidence for formation of unsaturated γ -lactam **189**¹¹⁸

Encouraged by these initial findings, an extensive investigation was carried out into a range of reaction parameters including CO source, nature and loadings of oxidants, additives, reaction times, concentration and solvents. As a starting point, an alternative CO source was sought given specialist equipment was required in achieving the 2 bar pressure of 6.25% of CO/air mixture. To our delight, switching the CO source to a balloon of 100% CO at approximately 1 bar *i.e.* atmospheric pressure gave a sharp increase in the yield of γ -lactam **185** to 56%, with 5% of the oxidized γ -lactam also obtained (Scheme 66). Use of $\text{Mo}(\text{CO})_6$ as a source of carbon monoxide was also explored but gave a number of unidentifiable products.



Scheme 66: Replacement of 6.25% CO (2 bar) with 100% CO (~1 bar) in the catalytic carbonylation of *N,O*-ketal **183**

Reaction times and temperature were next investigated, with the findings summarised in Table 1. Increasing the temperature to 120 °C improved the conversion of starting material to the desired product, with the highest yield obtained after heating for 16 hours (84%, entry 5), as determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Prolonged stirring at 120 °C did not lead to an improvement in yield (entry 6). There was a significant drop off in yield if the temperature was increased to 140 °C (entries 7 and 8), with no starting material observed at the end of the reactions.

Table 1: Optimisation studies on the carbonylation of *N,O*-ketal **183** - effect of reaction temperature and time

Entry	Temperature	Reaction time	Yield 185 [%] ^{a,b}	183 $\xrightarrow[\text{Temp, Reaction time}]{\text{Pd(OAc)}_2 \text{ (10 mol\%)}}$ 185	
				CO balloon(1 atm)	AgOAc (2.0 equiv)
1	100	8	35		
2	100	16	62		
3	120	4	40		
4	120	8	73		

5	120	16	84
6	120	20	84
7	140	4	25
8	140	8	0

^aYields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard; reactions performed on a 0.1 mmol scale in a sealed microwave vial attached with a balloon of carbon monoxide. ^bTraces of unsaturated γ -lactam **186** were observed in reactions where yields of γ -lactam **185** were above 40%.

The effect of terminal oxidant and additives on the carbonylation reaction was assessed and the findings from the optimisation screen are summarised in Table 2. Copper(II) acetate showed moderate reactivity, whilst 1,4-benzoquinone and oxygen showed poor reactivity, with the remaining mass balance being starting material (entries 1 to 3). Potassium persulfate yielded no product nor starting material, suggesting decomposition of the starting material and/or product (entry 4). Apart from silver(I) acetate, other silver salts such as silver(I) oxide and silver(I) carbonate showed much poorer reactivity (entries 5 and 6). This may highlight a very important role of silver(I) acetate in the catalytic cycle, beyond just being a terminal oxidant. Addition of basic additives was detrimental to the yields of the reaction (entries 8 to 10). Whilst silver(I) acetate has shown to be an effective terminal oxidant, we speculated whether addition of a second oxidant would further improve the yield of the reaction. The use of ‘mixed oxidant’ system has shown to be more effective than ‘mono oxidant’ system in various palladium(II)-catalysed transformations which utilise the palladium(II)/(0) catalytic cycle.⁴⁸ Unfortunately, lower yields were observed when 1,4-benzoquinone or TEMPO or Cu(OAc)₂ were added as a second oxidant (entries 11 to 13). Finally, increasing the loading of silver(I) acetate gave poorer yields (entries 14 and 15), though the reason for that is unclear.

Table 2: Optimisation studies on the carbonylation of N,O-ketal **183** - effect of terminal oxidant and additives

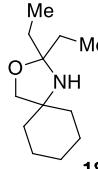
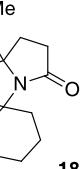
Entry	Oxidant	Additive	Yield 185 [%] ^{a,b}
1	Cu(OAc) ₂ (2.0 equiv)	-	39
2	BQ (2.0 equiv)	-	13

3	O_2^c	-	5
4	$K_2S_2O_8$ (2.0 equiv)	-	0
5	Ag_2O (2.0 equiv)	-	7
6	Ag_2CO_3 (2.0 equiv)	-	17
7	$AgOAc$ (2.0 equiv)	-	84
8	$AgOAc$ (2.0 equiv)	$NaOAc$ (5.0 equiv)	63
9	$AgOAc$ (2.0 equiv)	K_2CO_3 (5.0 equiv)	54
10	$AgOAc$ (2.0 equiv)	K_3PO_4 (5.0 equiv)	32
11	$AgOAc$ (2.0 equiv)	TEMPO (2.0 equiv)	60
12	$AgOAc$ (2.0 equiv)	BQ (1.0 equiv)	40
13	$AgOAc$ (2.0 equiv)	$Cu(OAc)_2$ (1.0 equiv)	43
14	$AgOAc$ (2.5 equiv)	-	70
15	$AgOAc$ (3.5 equiv)	-	68

^aYields determined by 1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard; reactions performed on a 0.1 mmol scale in 5 mL vials sealed with a Teflon cap and attached with a balloon of carbon monoxide. ^bTraces of unsaturated γ -lactam **186** were observed in reactions where yields of γ -lactam **185** were above 40%. ^cA balloon of oxygen was attached.

Variation of the reaction solvent had a pronounced effect on the reactivity (Table 3). Toluene as solvent gave the best yield (84%, entry 1), whilst other non-polar or polar aprotic solvents gave only moderate yields (entries 2 to 6). Polar protic solvent, such as *n*-propanol, showed no reactivity, with only decomposition observed (entry 7). An increase in concentration led to a reduction in the yield of γ -lactam **185**, while a lower concentration had little effect (entries 8 and 9).

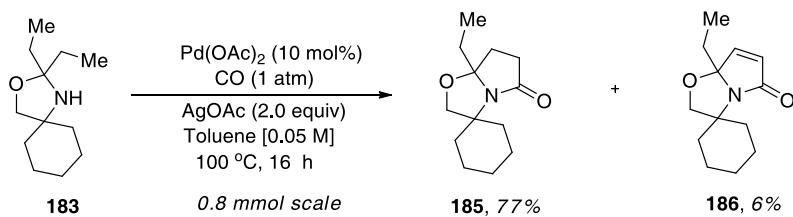
Table 3: Optimisation studies on the carbonylation of *N,O*-ketal **183** - effect of reaction solvent and concentration

	Pd(OAc) ₂ (10 mol%) CO balloon (1 atm) $AgOAc$ (2.0 equiv) Solvent, [x M] 120 °C, 16 h		
Entry	Solvent	Concentration	Yield 185 [%] ^{a,b}
1	PhMe	0.05 M	84
2	Xylene	0.05 M	49

3	1,4-Dioxane	0.05 M	32
4	PhCl	0.05 M	52
5	PhCF ₃	0.05 M	50
6	DMF	0.05 M	44
7	<i>n</i> -PrOH	0.05 M	0
8	PhMe	0.1 M	74
9	PhMe	0.002	83

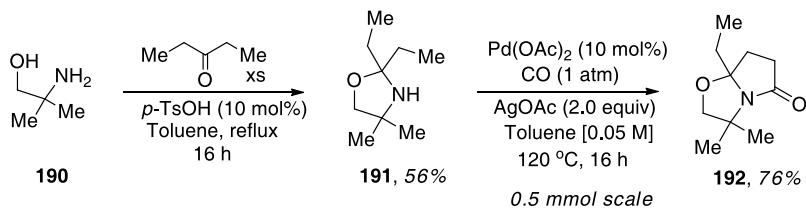
^aYields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard; reactions performed on a 0.1 mmol scale in a sealed microwave vial attached with a balloon of carbon monoxide. ^bTraces of unsaturated γ -lactam **186** were observed in reactions where yields of γ -lactam **185** were above 40%.

Gratifyingly, the optimised reaction conditions could be transferred from a sealed vial system to a round bottom flask – condenser set-up. On 0.8 mmol scale, the reaction yielded γ -lactam **185** and the unsaturated γ -lactam **186** in 77% and 6%, respectively (Scheme 67).



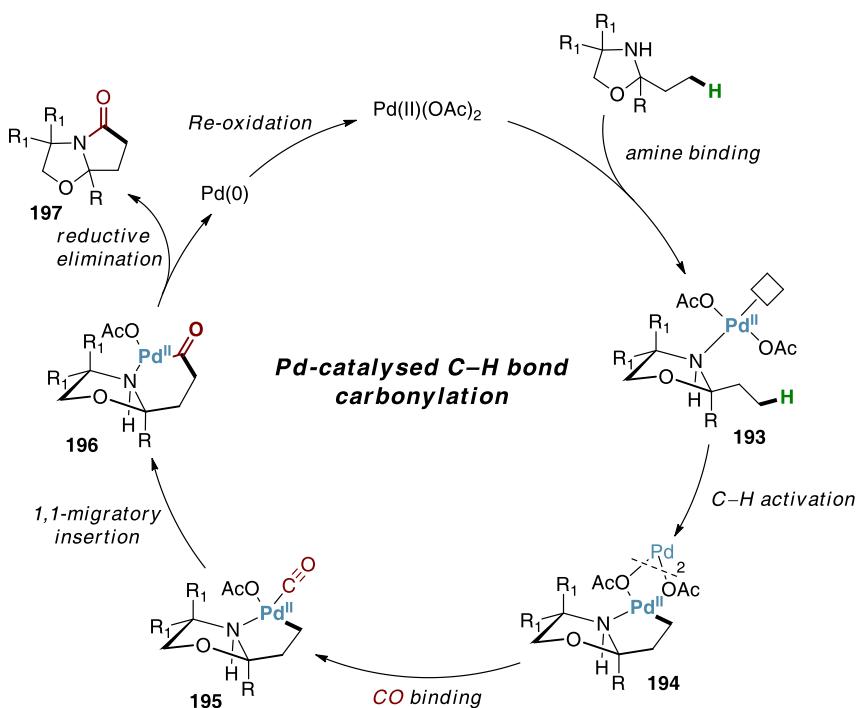
Scheme 67: Carbonylation of *N,O*-ketal **183** with a round bottom flask – condenser set-up

We were pleased to find that the carbonylation was tolerant to changes in the 4-position of the *N,O*-ketal. Replacement of cyclohexyl with a *gem*-dimethyl group gave the desired carbonylation product **192** in 76% isolated yield on 0.5 mmol scale (Scheme 68). This modification is attractive because *gem*-dimethyl amino alcohol **190** is readily available commercially.



Scheme 68: Carbonylation of *gem*-dimethyl *N,O*-ketal **191**

The carbonylation is likely to proceed *via* a palladium(II)/(0) catalytic cycle and a proposed mechanism for the palladium(II)-catalysed carbonylation is outlined in Scheme 69.



Scheme 69: Proposed mechanism for the palladium(II)-catalysed carbonylation of hindered *N,O*-ketals

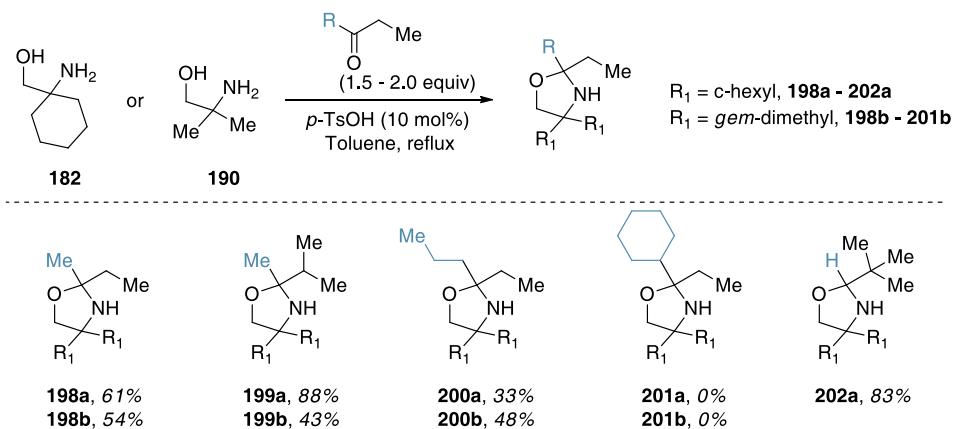
The proposed catalytic cycle begins with the binding of the palladium(II) centre by the amine substrate to form the mono-amine palladium complex **193**. The empty coordination site allows sp^3 C–H activation to occur to form the five-membered palladacycle **194**. Binding of a carbon monoxide ligand is likely to form monomeric palladacycle **195**, which undergoes 1,1-migratory insertion to form a six-membered palladacycle **196**. Reductive elimination and deprotonation provide γ -lactam **197** and releases palladium(0) into the catalytic cycle; a terminal oxidant is then required to regenerate the catalytically active palladium(II) species.

2.3.3 Substrate scope

With the optimised set of reaction conditions in hand, the focus was switched to investigating the reaction scope with respect to functional groups and structural features at the 2-position of the *N,O*-ketal, for both the *gem*-dimethyl and the cyclohexyl analogues.

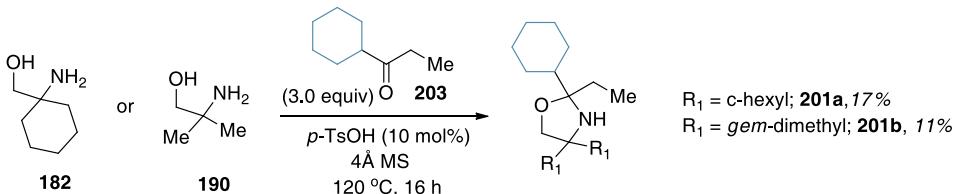
2.3.3.1 Substrates with simple alkyl substituents

The initial scope was focused on preparation of substrates with simple alkyl substituents. They were prepared from condensation of commercially available ketones with 1,2-amino alcohols **182** or **190** under Dean-Stark conditions (Scheme 70).



Scheme 70: Preparation of N,O -ketal substrates for carbonylation

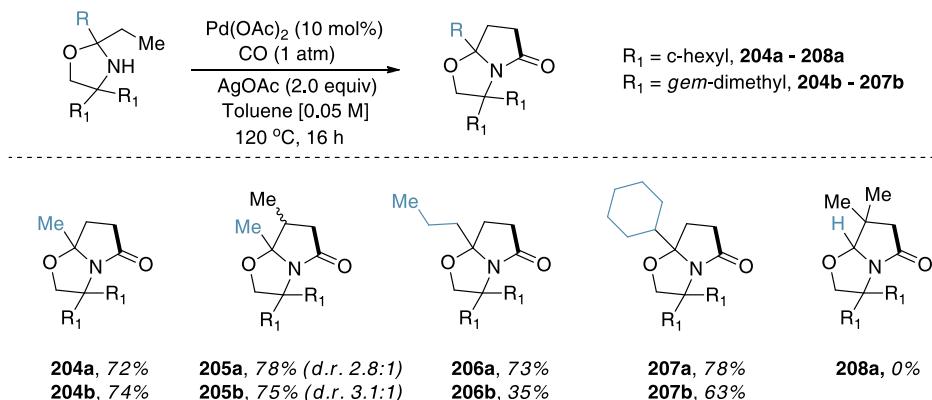
Unfortunately, N,O -ketal **201a** and **201b** could not be obtained under the standard Dean-Stark conditions. After surveying a variety of reaction conditions, N,O -ketal **201a** and **201b** were synthesised, albeit still with very poor yields, when cyclohexylethyl ketone **203** was employed as a solvent as well as present in excess (Scheme 71).



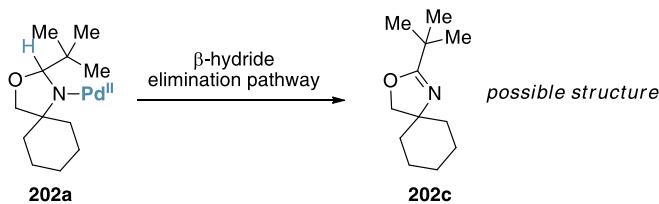
Scheme 71: Preparation of N,O -ketal **201a** and **201b** using cyclohexylethyl ketone as solvent

The substrates were then subjected to the optimised C–H carbonylation conditions and the results are summarised in Scheme 72. This initial substrate scope revealed that simple alkyl groups are well tolerated, except in the case of **206b**, where the yield was much lower than **206a**, the cyclohexyl counterpart. It is unclear why that is the case, although more side products were observed under the carbonylation conditions with substrate **200b**. With the isopropyl substituent where diastereoisomeric mixture could be formed, **205a** and **205b** were formed with moderate diastereoselectivity. The reaction was incompatible with mono-substituted N,O -ketal in the 2-position (**208a**). In this case, we observed an absence of a proton signal in the region of δ 4–5

ppm where the hydrogen in the 2-position was expected, suggesting β -hydride elimination of **202a** to give possibly oxazoline **202c** (Scheme 73). It should be noted that all substrates showed exclusive regioselectivity for the terminal position of the ethyl C–H.



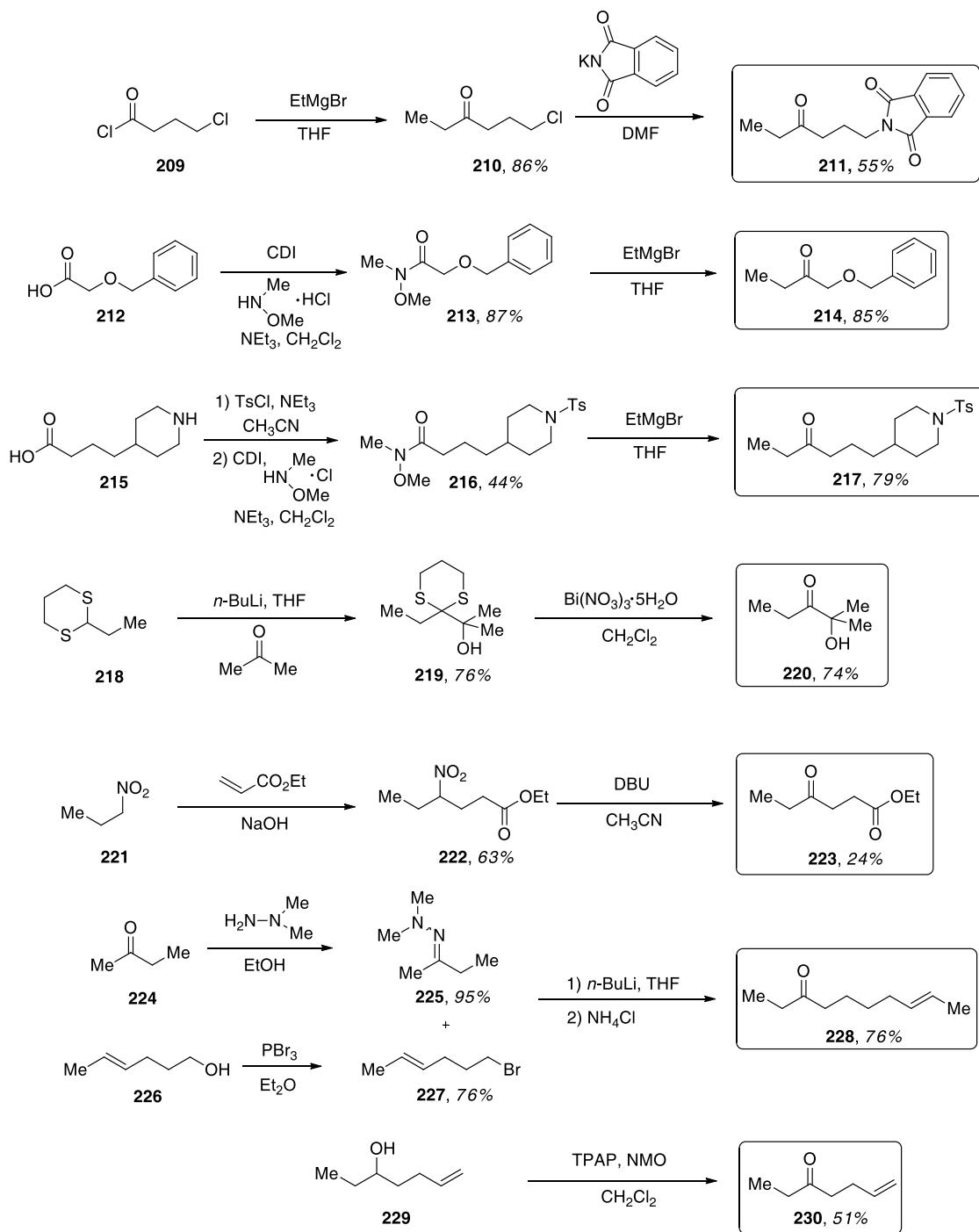
Scheme 72: Initial substrate scope for the palladium(II)-catalysed sp^3 C–H carbonylation



Scheme 73: Possible β -hydride elimination pathway for **202a**

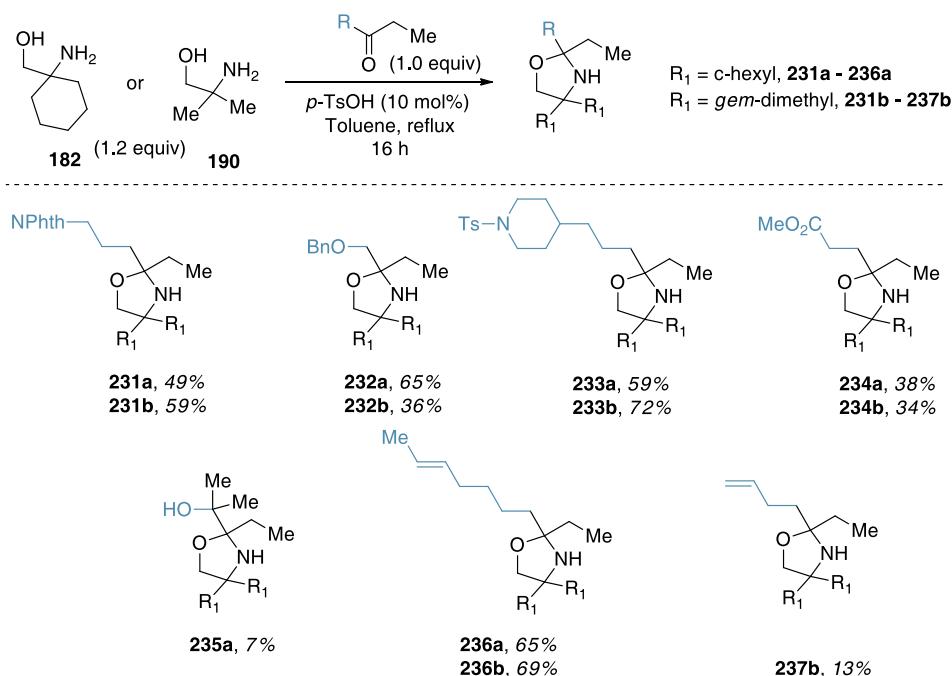
2.3.3.2 Substrates with various functional groups

Substrates which bear various different functionalities were next assessed for their reactivity and tolerability. With these substrates, the precursor ketones had to be prepared, most of which required multi-step syntheses. The synthetic routes to these functionalised ketones are shown in Scheme 74.



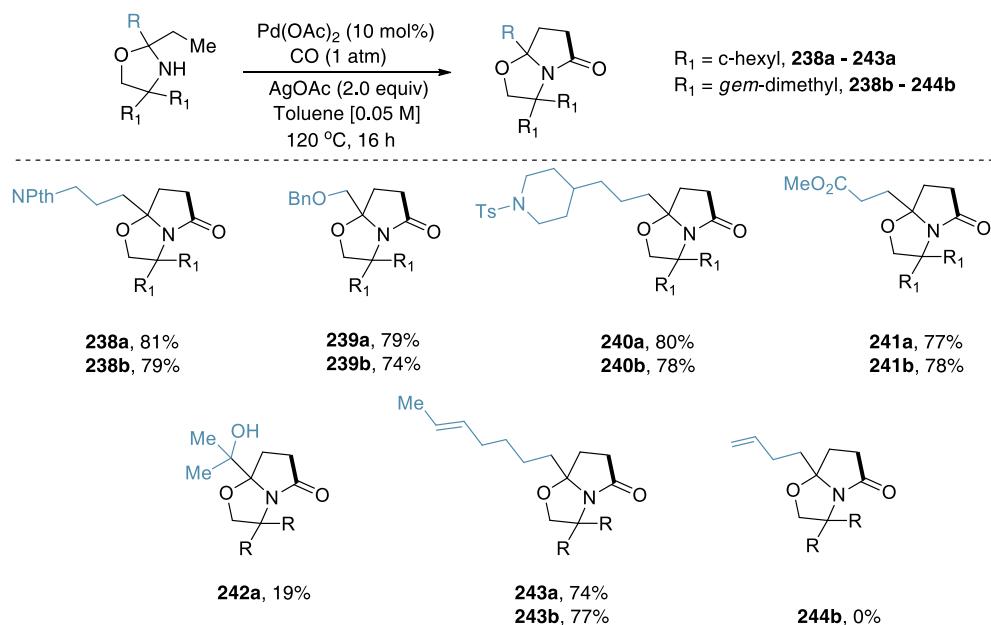
Scheme 74: Access to functionalised ketones

The ketones were then subjected to the condensation conditions described earlier to yield the various functionalised *N,O*-ketals (Scheme 75).



Scheme 75: Preparation of more functionalised N,O -ketal substrates for sp^3 C–H carbonylation

These N,O -ketals were then subjected to the optimised C–H carbonylation conditions and the results are summarised in Scheme 76.

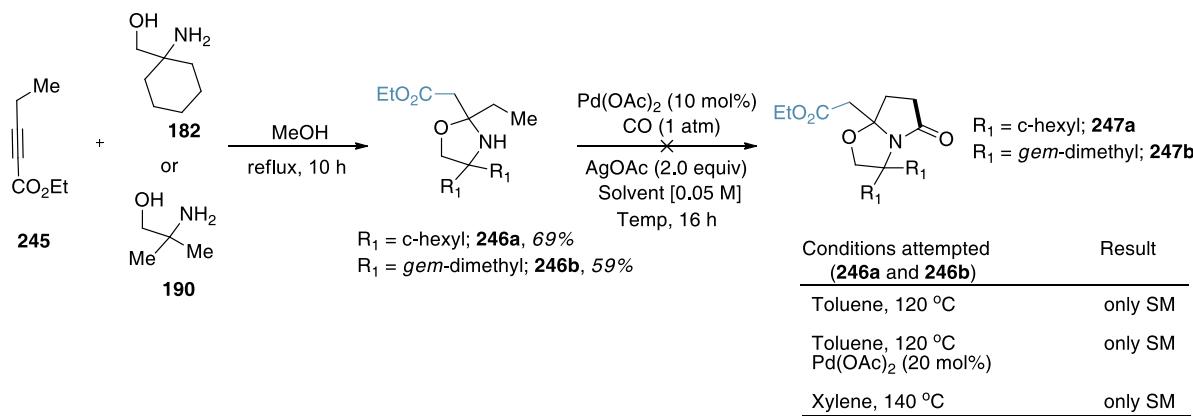


Scheme 76: Extended substrate scope for the palladium(II)-catalysed sp^3 C–H carbonylation

Gratifyingly, a range of functional groups were well-tolerated under the carbonylation conditions (for both cyclohexyl and *gem*-dimethyl analogues), with two notable exceptions. In the presence

of an unprotected alcohol, the desired carbonylation product was only obtained in 19% yield (**242a**), with the remaining mass balance being the starting material *N,O*-ketal **235a**. This is attributed to the coordination of the OH group to palladium(II) which might have partially poisoned the catalyst, reducing its catalytic efficiency. Also, the steric impediment caused by the *gem*-dimethyl group might have reduced the likelihood of the initial coordination of the nitrogen to palladium(II). This steric hindrance also explains why no sign of carbonylation on the other terminal methyls was observed. With substrate containing a terminal olefin, no desired product nor starting material were detected (0%, **244b**). The disappearance of the diagnostic terminal olefin ^1H chemical shifts suggests possible coordination of the olefin to palladium(II) followed by possibly intramolecular nucleophilic attack by the amine nitrogen atom (*5-exo*-trig or *6-endo*-trig), leading to mixture of side products.

Although the presence of ester functionality was well tolerated under the carbonylation reaction conditions, as exemplified by the formation of lactam **241a** and **241b** in 77% and 78% respectively, it was found that the reaction completely ceased if the ester group was closer to the *N,O*-ketal nitrogen atom. *N,O*-ketals **246a** and **246b**, which were prepared by a double conjugate addition of alkyne **245** with the corresponding 1,2-amino alcohols, showed no reactivity under the carbonylation reaction conditions, even at elevated temperature with xylene as the solvent or with increased palladium catalyst loadings (Scheme 77).



Scheme 77: Synthesis and attempted sp^3 C–H carbonylation of *N,O*-ketals **246a** and **246b**

This was a rather surprising result given **246a/b** is only one methylene unit less than **234a/b** between the ester group and the *N,O*-ketal nitrogen atom. One possible explanation for this could be the formation of a six-membered ring intramolecular hydrogen bonding network between the

N–H and the ester carbonyl group, and hence preventing the molecule from adopting the required conformation for C–H activation (Figure 1).

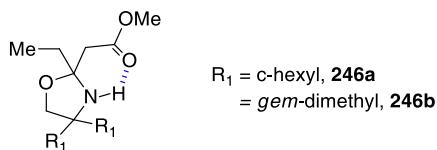
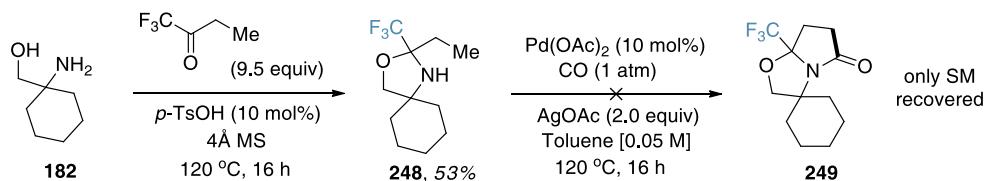


Figure 1: Possible intramolecular hydrogen bonding network in **246a** and **246b**

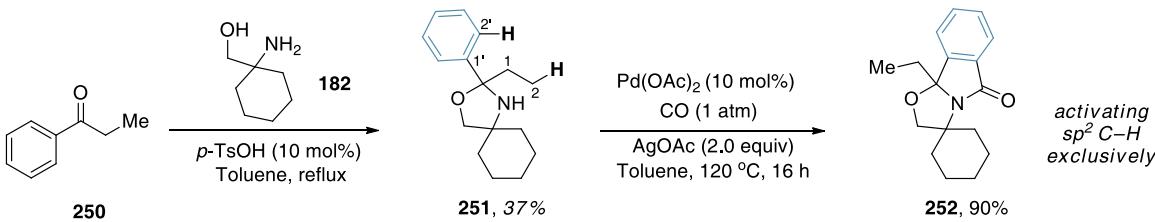
In the presence of a trifluoromethyl group in close proximity to the *N,O*-ketal nitrogen atom, no carbonylation took place, with only starting material recovered (Scheme 78). This is presumably as a result of reduced nucleophilicity of the amine caused by the electron-withdrawing effect of the trifluoromethyl group.



Scheme 78: Synthesis and attempted sp^3 C–H carbonylation of *N,O*-ketal **248**

2.3.3.3 Substrates with potentially competing C–H activation pathway

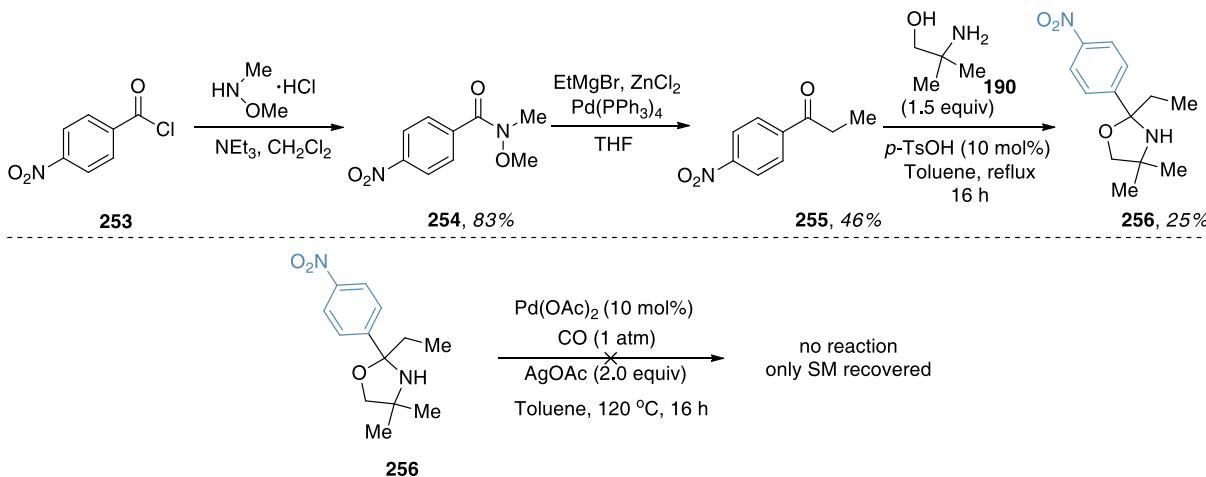
We next sought to explore substrates with possible sp^2 and sp^3 C–H activation pathways. When the phenyl group is directly attached to the *N,O*-ketal (**251**), the inherently more facile sp^2 C–H carbonylation became the predominant pathway under the carbonylation reaction conditions, generating γ -lactam **252** exclusively and in excellent yields (Scheme 79). It should be noted that activation of the phenyl *ortho* sp^2 C–H also proceeds through a kinetically favoured five-membered cyclopalladated complex.



Scheme 79: Synthesis and sp^2 C–H carbonylation of *N,O*-ketal **251**

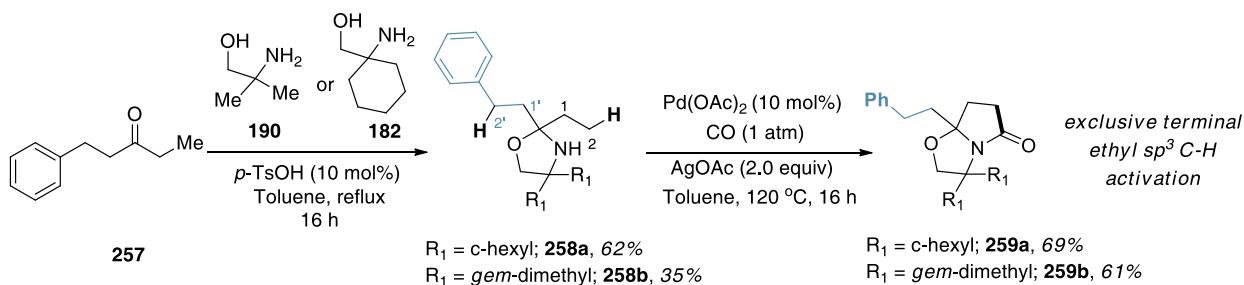
We then investigated if the presence of electron withdrawing group on the phenyl ring would disfavor sp^2 C–H activation by reducing the coordinating ability of the phenyl π -system and

hence would ‘switch’ the reactivity back to the desired sp^3 C–H activation. To test this hypothesis, *N,O*-ketal **256**, prepared in three synthetic steps from the commercially available acid chloride **253**, was subjected to the carbonylation reaction conditions (Scheme 80). Whilst the presence of the nitro group did prevent sp^2 C–H carbonylation, it did not lead to the desired sp^3 C–H carbonylation, presumably due to the reduced nucleophilicity at the nitrogen atom, preventing the initial coordination of the amine to the palladium(II) centre.



Scheme 80: Synthesis and attempted C–H carbonylation of *N,O*-ketal **256**

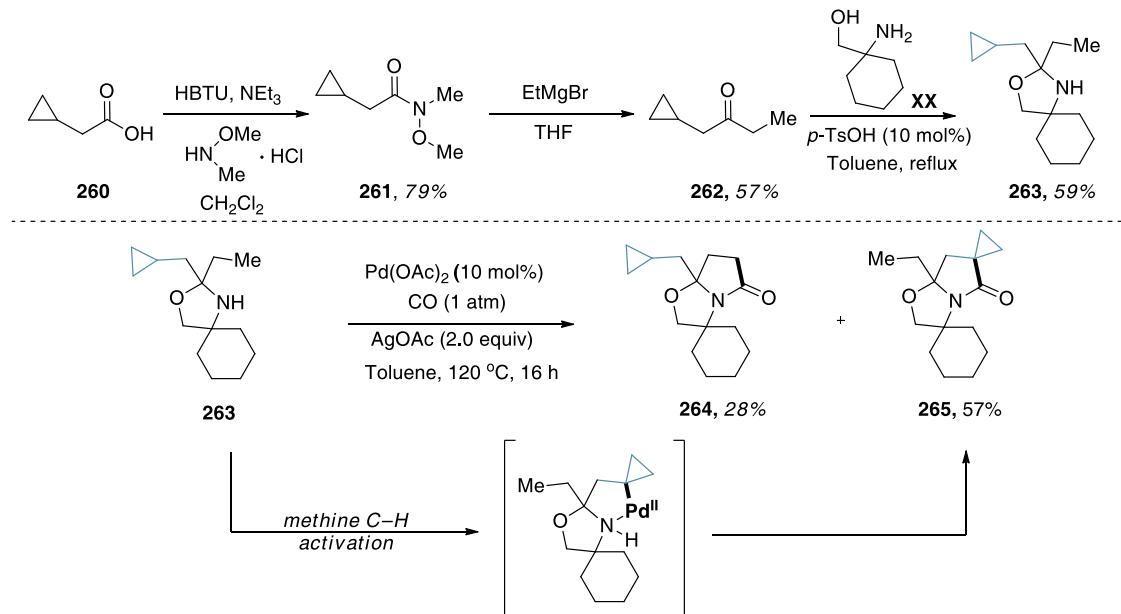
Next, *N,O*-ketals **258a** and **258b** were prepared to investigate the selectivity between terminal ethyl and benzylic methylene sp^3 C–Hs given the latter position is known to be highly activated for C–H insertion by palladium.¹²⁷ In this case, exclusive selectivity for the terminal ethyl sp^3 C–H was observed, for both the cyclohexyl and *gem*-dimethyl analogues (Scheme 81).



Scheme 81: Selectivity between terminal ethyl and benzylic sp^3 C–H in palladium(II)-catalysed carbonylation

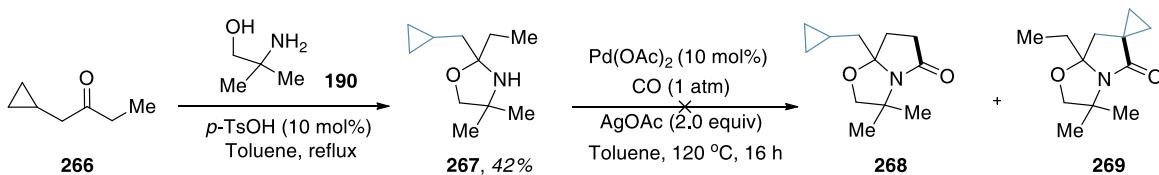
We were also interested to see if the cyclopropyl group could be activated in this system. *N,O*-ketal **263** was prepared *via* standard protocol and subjected to the carbonylation reaction conditions (Scheme 82). Interestingly, this reaction yielded a mixture of two products:

spirocyclopropyl γ -lactam **265** (57% - major product), originating from activation of the methine C–H of the cyclopropyl unit, and the expected γ -lactam **264** (28% - minor product). Although methine C–H functionalisation is known under palladium catalysis, it is still relatively rare compared to the methyl and methylene counterparts.^{128,129} This methodology represents a rare example of methine C–H being activated preferentially over methyl C–H.



Scheme 82: Preparation and carbonylation of cyclopropyl substrate **263**

Surprisingly, subjecting the corresponding gem-dimethyl analogue **267** to the optimised reaction conditions gave no signs of either **268** or **269**, with no starting material remaining at the end of the reaction (Scheme 83).



Scheme 83: Failed carbonylation of cyclopropyl substrate **267**

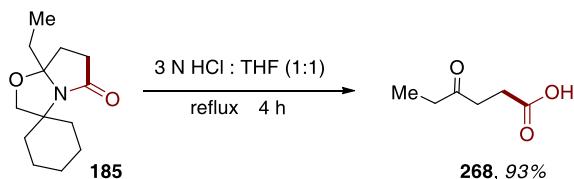
2.3.4 Removal of steric tether: access to γ -keto carboxylic acids

Having established a protocol for carbonylation which tolerates a wide range of functionalities, we next investigated the deprotection/hydrolysis step which would yield the corresponding γ -keto carboxylic acids (Scheme 84).



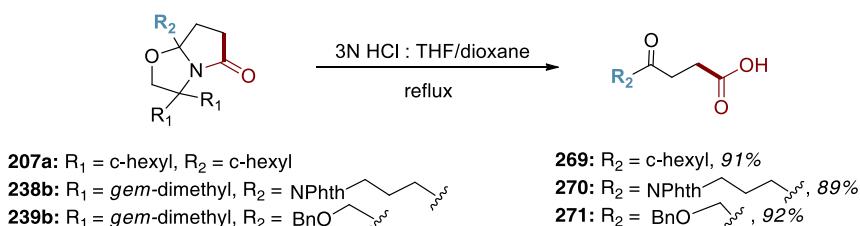
Scheme 84: Hydrolysis of fused-*N,O*-ketal-lactam allows access to γ -keto carboxylic acid

After a brief survey of hydrolysis conditions, it was found that on treatment of γ -lactam **185** with 3 N HCl:THF (1:1) at reflux for 4 hours, the desired carboxylic acid **268** was obtained in 93% yield (Scheme 85).



Scheme 85: Hydrolysis of γ -lactam **185** to give carboxylic acid **268**

To demonstrate the practicality of this transformation as a route to access γ -keto carboxylic acids, a range of γ -lactams were subjected to the acidic ring-opening conditions to obtain the desired γ -keto carboxylic acids in excellent yields, ranging from 89% to 92% (Scheme 86).



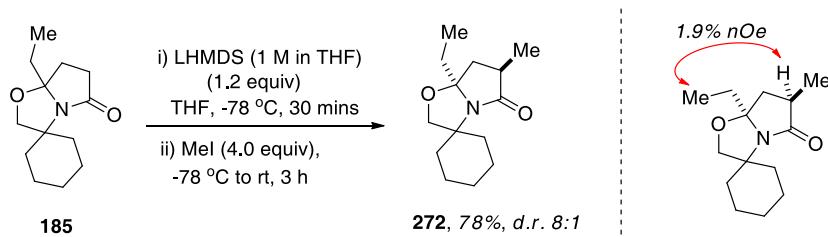
Scheme 86: Hydrolysis of γ -lactams **207a**, **238b** and **239b**

Considering the wide scope of substrates that are compatible with the C–H carbonylation reaction, coupled with the ease in which the 1,4-dicarbonyl functionality could be revealed, we believe this methodology offers a complimentary method to access these important classes of building blocks.

2.3.5 Attempted derivitisation of the bicyclic lactam core

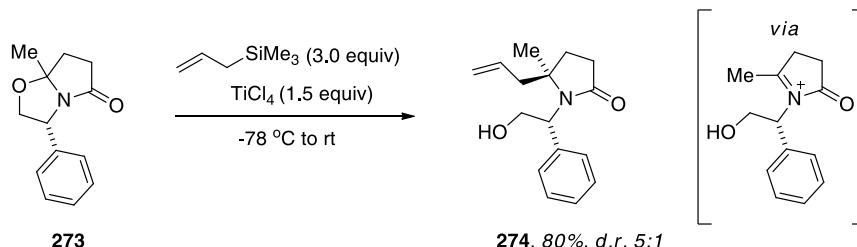
In addition to performing deprotection of the bicyclic lactams to enable entry to γ -keto carboxylic acids, we also looked to explore the intrinsic functionality of these molecules to gain access to other structurally diverse amine products. We were pleased to find that enolate methylation of **185** at the α -position to the carbonyl proceeded smoothly to give **272** in good yield and

diastereoselectivity, with the structure of the major diastereoisomer confirmed by nOe analysis (Scheme 87).



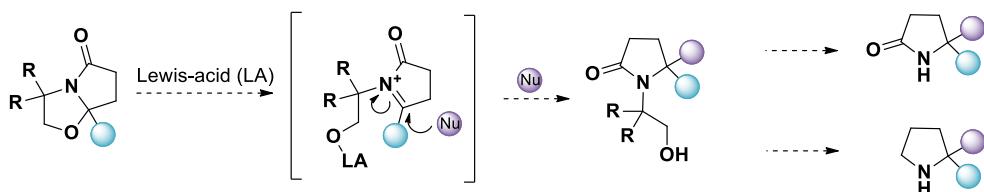
Scheme 87: α -Methylation of **185**

Meyers has shown that chiral bicyclic lactams such as **273** can undergo a Lewis acid-assisted cleavage of cyclic *N,O*-ketal, followed by trapping of the resulting *N*-acyliminium ion with allyl silane as an external nucleophile, yielding 2,2-disubstituted pyrrolidinone **274** (Scheme 88).¹³⁰



Scheme 88: Meyers' Lewis acid-assisted cyclic *N,O*-ketal ring opening of chiral bicyclic lactams¹³⁰

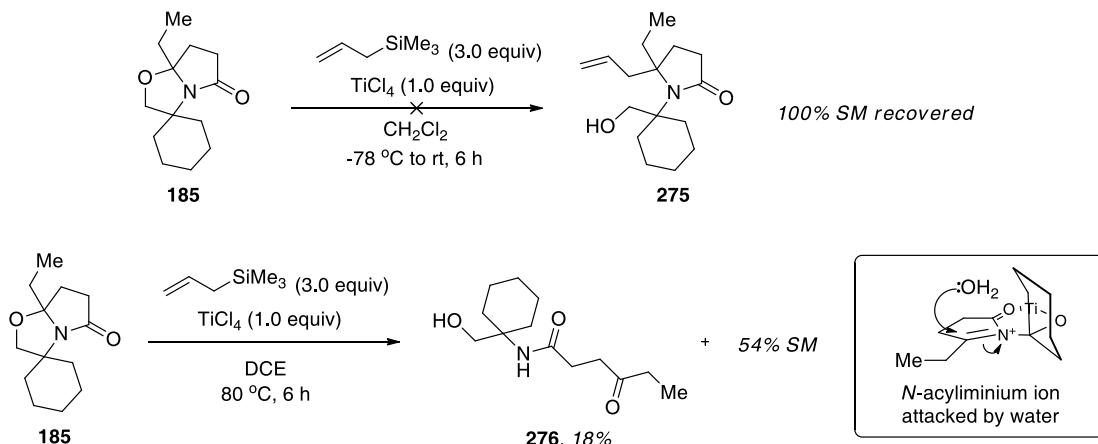
We envisaged that this process should be applicable to our lactam scaffold although it was anticipated that there would be additional steric hindrance in our system given the carbon atom in the α -position to the nitrogen is disubstituted. Subsequent cleavage of the C–N linkage would enable access to 2,2-disubstituted pyrrolidinones, or further reduced to 2,2-disubstituted pyrrolidines (Scheme 89).



Scheme 89: Proposed Lewis acid-assisted ring opening of γ -lactams to 2,2-disubstituted pyrrolidinones and pyrrolidines

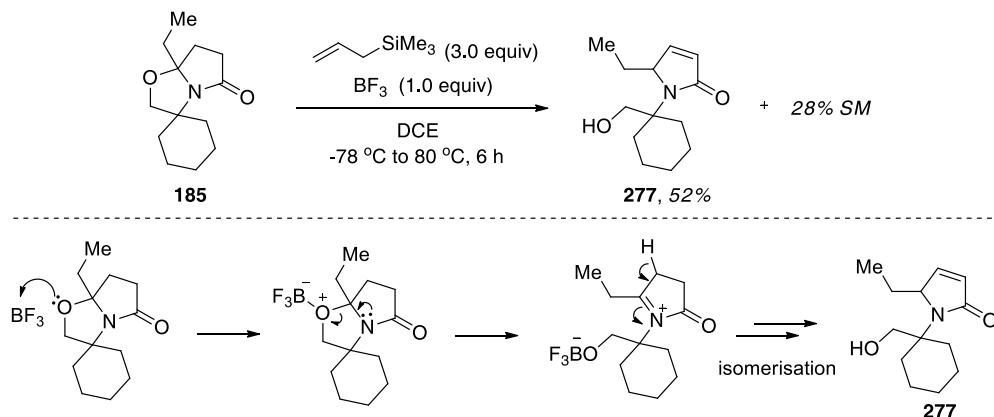
We began our investigation using **185** and allyl silane (Scheme 90). Disappointingly, employing the conditions reported by Meyers gave no reaction, with only starting material recovered. Replacement of dichloromethane with a higher boiling 1,2-dichloroethane and heating the

reaction mixture to 80 °C resulted in 54% of starting material being recovered, but encouragingly, amide **276** was also formed in 18% yield. This product is presumed to be formed from nucleophilic attack of the desired transient *N*-acyliminium species by advantageous water. Although no desired product was observed, this finding at least showed that nucleophile attack is possible on the hindered electrophile.



Scheme 90: Attempted ring-opening of **185** with allyl silane

We next attempted the same reaction using boron trifluoride etherate complex as the Lewis acid (Scheme 91). Again, no reactivity was observed at room temperature. However, when the reaction mixture was heated to 80 °C, α,β -unsaturated lactam **277** was formed in 52% yield, along with 28% of starting material recovered. This compound is likely to have been formed *via* tautomerisation of the transient *N*-acyliminium species.



Scheme 91: Attempted ring-opening of **185** using BF_3 as Lewis acid and proposed mechanism for formation of **277**

With these encouraging findings thus far, we next screened a broad range of Lewis and protic acids for their reactivities and the results are summarised in Table 4. Unfortunately, none of the

Lewis or protic acids had yielded any positive results, with only starting material recovered in majority of the cases (entries 1 to 6). With zinc(II) triflate, 28% of **277** was also observed (entry 3). Use of triflic acid only resulted in a complex mixture which was difficult to analyse (entry 7).

Table 4: Screening of Lewis and protic acids for ring-opening of **185**

Entry	Lewis acids	Temperature	Result ^a
1	TIPSOTf	rt to 80 °C	95% SM
2	AgTFA	rt to 80 °C	92% SM
3	Zn(OTf) ₂	rt to 80 °C	67% SM, 28% 277
4	Sc(OTf) ₃	rt to 80 °C	92% SM
5	AlCl ₃	rt to 80 °C	85% SM
6	HCl (in dioxane)	rt to 80 °C	96% SM
7	TfOH	0 °C to RT	Complex mixture

^aYields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard

We next sought to explore different carbon nucleophiles (Table 5). Silyl ketals such as **278** and **279** were investigated but showed no desired reactivity under a number of Lewis and protic acidic conditions (entries 1 to 7). Adding an additional activator to generate a more reactive enolate failed to improve the reaction (entries 6 and 7). Diketone **280** also showed no reactivity.

Table 5: Screening of carbon nucleophiles and Lewis/protic acids for ring-opening of **185**

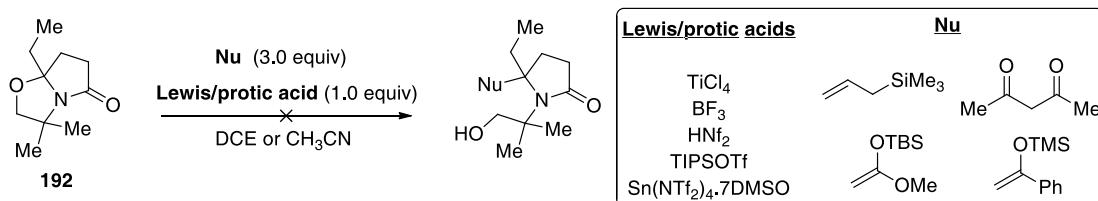
Entry	Nu	Lewis acids	Result ^a
1	278	TiCl ₄	Only SM
2	278	BF ₃	71% SM and 16% 277

3	278	TIPSOTf	Only SM
4	278	HNTf ₂	Only SM
5	279	Sn(NTf ₂) ₄ .7DMSO ^b	Only SM
6	279	MeLi, then Sn(NTf ₂) ₄ .7DMSO ^b	Only SM
7	279	KF, Sn(NTf ₂) ₄ .7DMSO ^b	Only SM
8	280	HNTf ₂	Only SM
9	280	Sn(NTf ₂) ₄ .7DMSO	Only SM

^aYields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

^bReaction performed using acetonitrile as the solvent instead of DCE.

We also tested γ -lactam **192** to see if replacement of the cyclohexyl group with gem-dimethyl would lead to better reactivity (Scheme 92). Unfortunately, repeating the different conditions aforementioned on **185** did not lead to any successful outcome.



Scheme 92: Survey of nucleophiles and Lewis/protic acids for ring-opening of **192**

Given no success had been achieved thus far with a range of latent carbon nucleophiles, it was decided to explore organometallics as nucleophiles as we hoped the increased nucleophilicity would lead to better reactivity (Table 6). The methyl group was chosen as the transferring group for this study due to its small size and hence would provide the least steric impediment. Whilst methylolithium appeared to be too reactive and gave a complex mixture with no recovery of starting material (entry 1), all the other organometallics investigated had shown no reactivity (entries 2 to 8). Given this investigation had yielded very little success, it wasn't pursued further at this point.

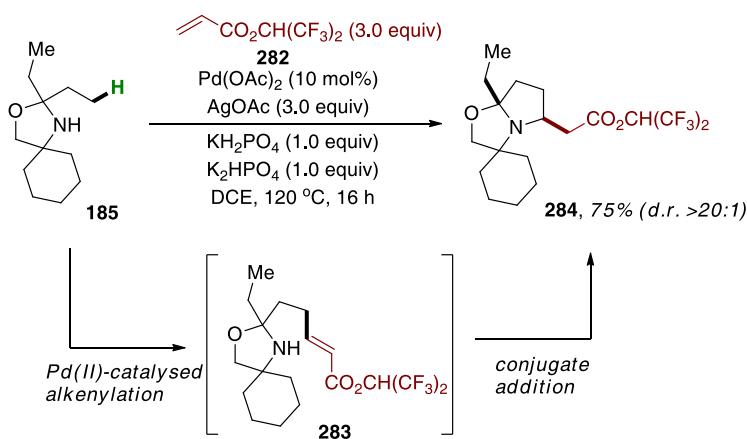
Table 6: Screening of Lewis and protic acids for ring-opening of **185**

Entry	Me-M	Lewis acids	solvent	Temperature	Result
1	MeLi	-	THF	0 °C to rt	Complex mixture
2	MeMgBr	-	THF	0 °C to 60 °C	Only SM
3	MeMgBr	TiCl ₄	DCE	0 °C to 60 °C	Only SM
4	MeMgBr	BF ₃	THF	0 °C to 60 °C	Only SM
5	AlMe ₃	-	DCE	rt to 80 °C	Only SM
6	AlMe ₃	TiCl ₄	DCE	rt to 80 °C	Only SM
7	Me ₂ CuLi ^a	TiCl ₄	THF	0 °C to 60 °C	Only SM
8	Me ₂ CuLi ^a	BF ₃	THF	0 °C to 60 °C	Only SM

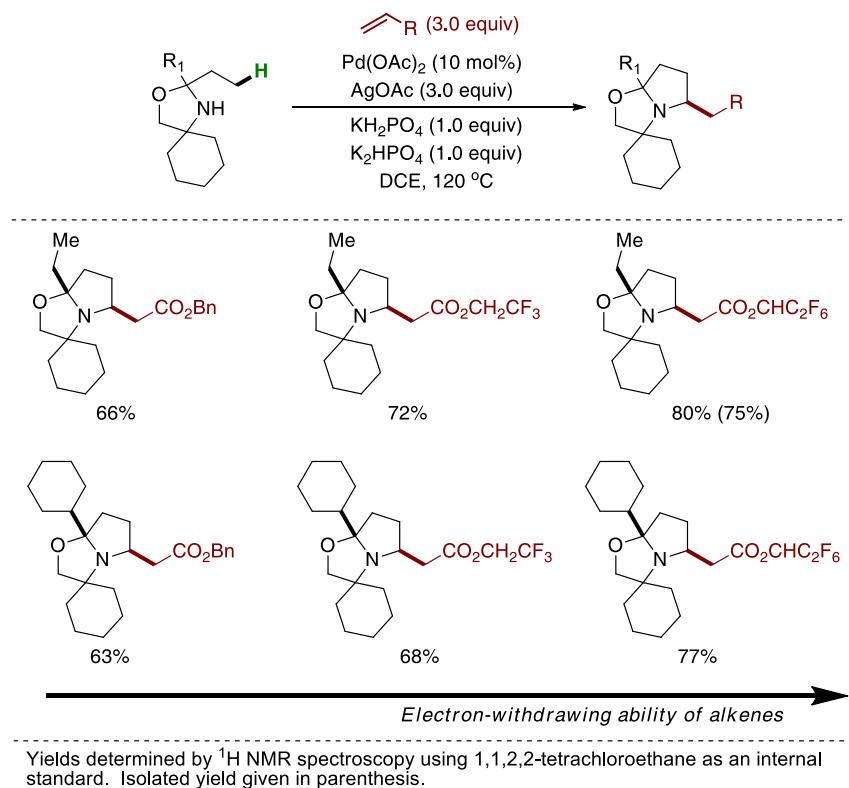
^aPrepared from 2 equivalents of methylolithium and 1 equivalent of copper(I) iodide in THF.

2.3.6 Palladium(II)-catalysed sp^3 C–H alkenylation – Dr Jonas Calleja

To broaden the scope of this methodology, different transformations were explored with this *N,O*-ketal scaffold. Dr Jonas Calleja, a postdoctoral research associate within the group, has discovered and optimised a Pd(II)-catalysed sp^3 C–H alkenylation on *N,O*-ketal **185** (Scheme 93).


Scheme 93: Palladium(II)-catalysed sp^3 C–H alkenylation on **185** - discovered and optimised by Dr Calleja

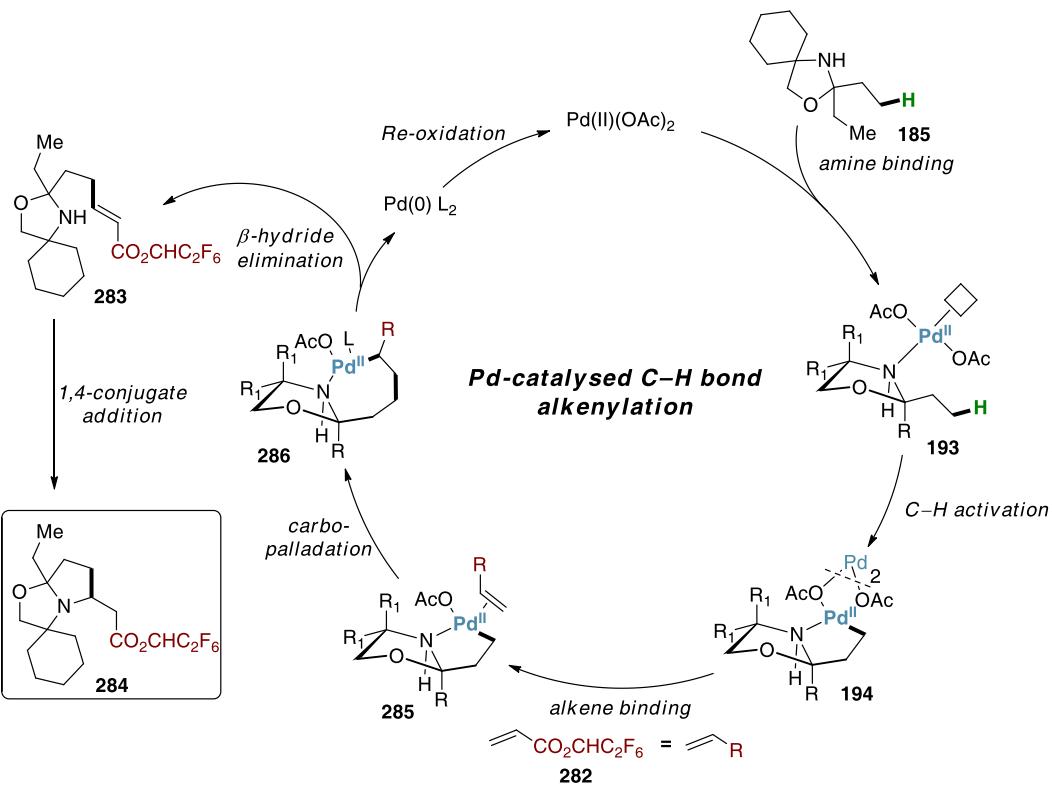
Treatment of **185** under the optimised reaction conditions with hexafluoroisopropyl acrylate **282** generated initially the alkenylated alkene **283**, which underwent a facile 1,4-conjugate addition to yield fused-pyrrolidine **284** in 75% yield, and as a single diastereoisomer. He also found that the reaction was influenced by the electronic properties of the alkene, whereby the yields of the reaction increase with the electron-withdrawing ability of the alkenes (Scheme 94). This trend is consistent for other substituents at the 2-position of the *N,O*-ketal.



Scheme 94: Influence of electronic properties of alkenes on the C–H alkenylation – Dr Calleja

This reaction is likely to proceed *via* a palladium(II)/(0) pathway, in an analogous fashion to the carbonylation. The proposed mechanism for the palladium(II)-catalysed alkenylation is shown in Scheme 95. The proposed catalytic cycle begins with the binding of the palladium(II) centre by amine **185** to form a mono-amine complex which undergoes C–H activation to form a five-membered palladacycle **194**. Binding of acrylate **282** ligand is likely to form a monomeric palladacycle **285**, which undergoes carbopalladation to form a seven-membered palladacycle **286**. β -hydride elimination provides alkenylated amine **283** and simultaneously cyclises *via* a 1,4-conjugate addition to generate fused-pyrrolidine **284**. The β -hydride elimination step releases

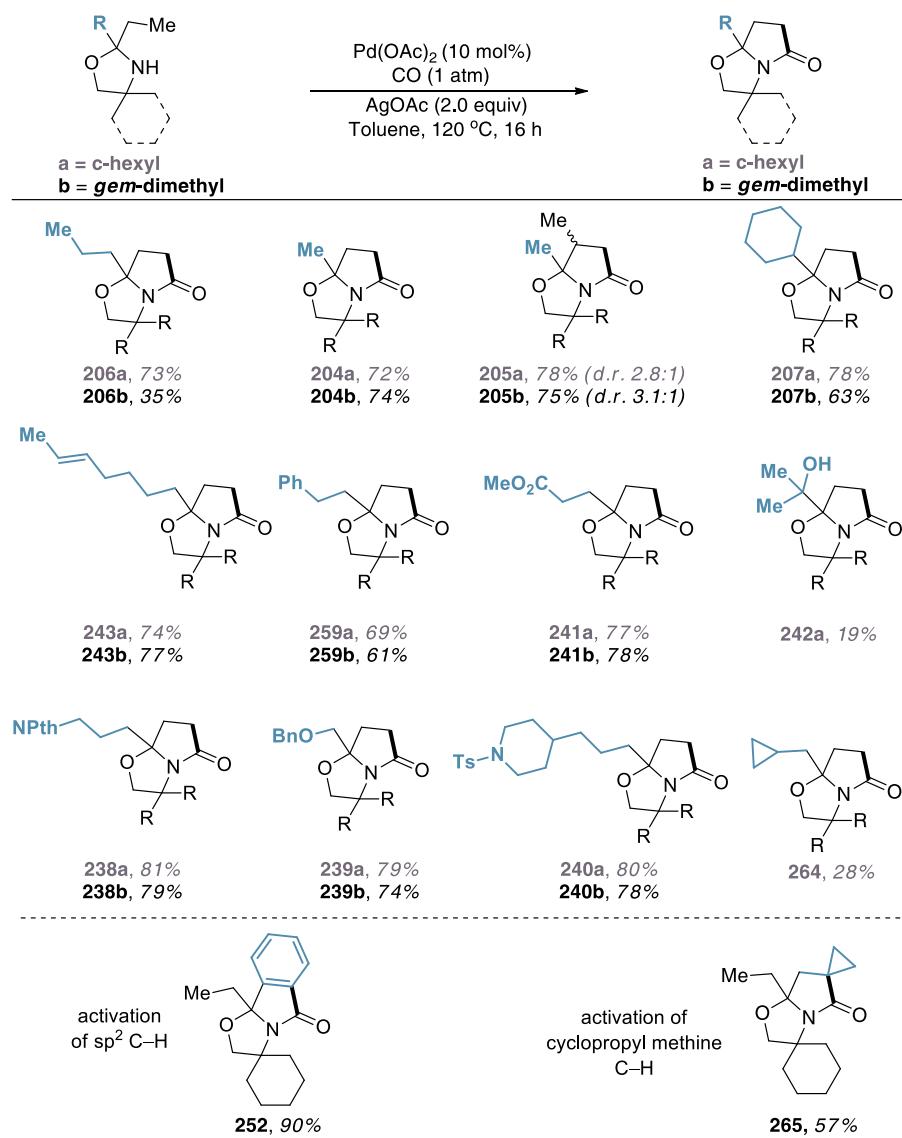
palladium(0) into the catalytic cycle and a terminal oxidant is then required to regenerate the catalytically active palladium(II) species.



Scheme 95: Proposed mechanism for palladium(II)-catalysed sp^3 C–H alkenylation (substituents abbreviated as R or R₁ for clarity)

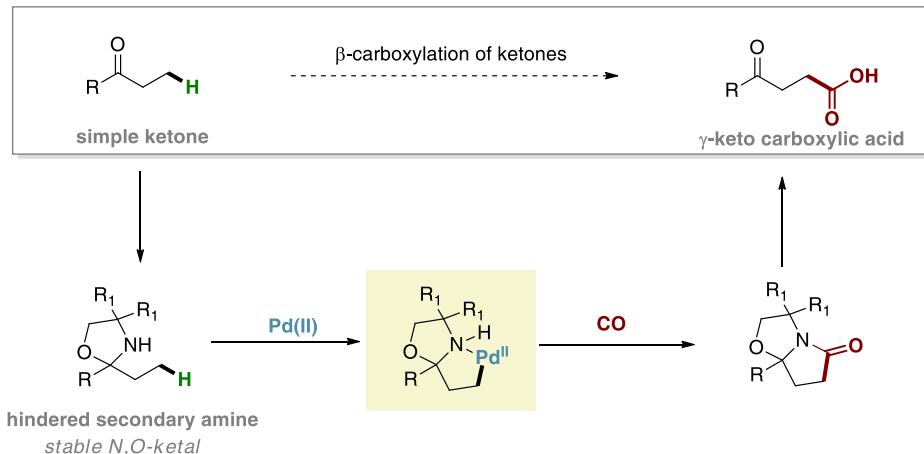
2.3.7 Summary

Chapter 2 described the development of a palladium(II)-catalysed sp^3 C–H carbonylation of hindered *N,O*-ketals which was shown to have a broad substrate scope, leading to a range of γ -lactams in good yields (Scheme 96). Most substrates showed exclusive regioselectivity for the terminal ethyl sp^3 C–H (section 2.3.3.1 and 2.3.3.2). With substrates which have potentially competing C–H activation pathways, structurally attractive products such as **252** and **265** were obtained (section 2.3.3.3). The carbonylation is believed to proceed through a palladium(II)/(0) catalytic cycle.



Scheme 96: Overall substrate scope of the palladium(II)-catalysed carbonylation

Upon ring opening of the γ -lactams, a range of γ -keto carboxylic acids could be obtained, thus providing an alternative entry to these important classes of building blocks. The palladium(II)-catalysed carbonylation served as the key step in allowing an overall β -carboxylation of ethyl ketones (Scheme 97).



Scheme 97: Overall β -carboxylation of ethyl ketones

Early studies by Dr Calleja showed that the N,O -acetals could undergo C–H alkenylation to yield structurally complex fused pyrrolidines as single diastereoisomers (section 2.3.6).

The manuscript for this work is in preparation.

3 Design and Synthesis of Functionalised Astemizole Analogues via sp³ C–H Functionalisation of Hindered Amines

3.1 Background

Astemizole, marketed under the brand name Hismanal, is a second-generation antihistamine drug originally developed by Janssen Pharmaceutica in 1977 and was approved for the treatment of allergic diseases.¹³¹ It is a non-sedative, potent, long-lasting and selective H₁-antagonist. However, it has been withdrawn from the market in most countries because of the cardiac arrhythmia side effect that is attributed to inhibition of the hERG channel.

Human ether-a-go-go related gene (hERG) potassium (K⁺) channels play a critical role in cardiac action potential repolarisation. Inhibition of the hERG channel causes QT interval prolongation resulting in potentially fatal ventricular tachyarrhythmia called *Torsade de Pointes*. This potentially fatal side effect is a major pharmacological safety concern for the pharmaceutical industry and the health regulatory authorities.¹³² As a result, a number of blockbuster drugs have been withdrawn from the market because of reports of sudden cardiac death and several others were forced to carry “black box” warning labels.¹³³ The hERG channel is unusually susceptible to blockage by drugs in comparison with other potassium channels, suggesting that it has a unique binding site. Site-directed mutagenesis studies into hERG channels identified two aromatic amino acid residues, Tyr 652 and Phe 656, located in the S6 domain and predicted to face the central cavity of the channel that are critical for high affinity binding of drugs containing tertiary amines (Figure 2a).¹³⁴ Further mutagenesis identified potent blockage of hERG channel by terfenadine required an aromatic residue in position 652, suggesting the possible importance of a cation-π interaction between the positively charged nitrogen atom of the drug and the π-electrons of Tyr 652 (Figure 2b).¹³⁵ A strongly hydrophobic attraction with Phe656 was also identified for the same drug.

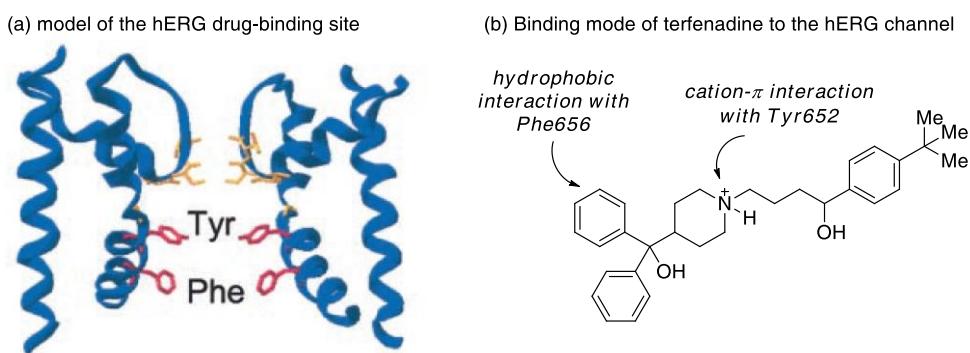


Figure 2: a) Model of the hERG drug-binding site, and b) binding mode of terfenadine to the hERG channel^{134,135}

Early detection of compounds with this undesirable side effect is consequently an important objective in assessing preclinical risks of new drug candidates. As a result, *in silico* approaches are now widely used to predict hERG channel blockade. These computational models are based on the now generally accepted hERG pharmacophore model for what molecular features are likely to give rise to hERG inhibition. The most important features are found to be the presence of a basic nitrogen atom, attaching to hydrophobic groups in at least two of the three vectors (Figure 3a).^{133,136} Examples of known hERG inhibitors are shown in Figure 3b.

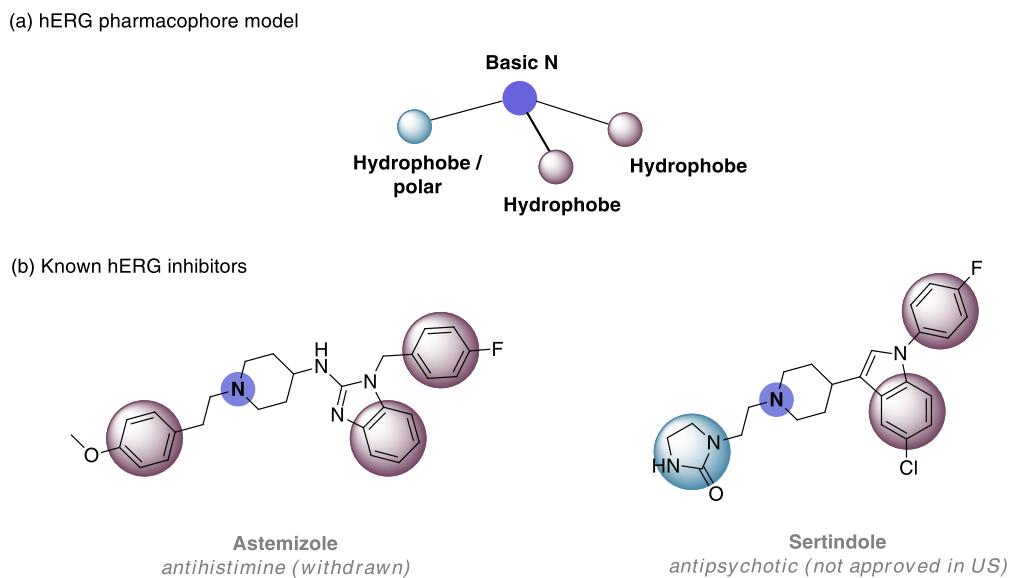
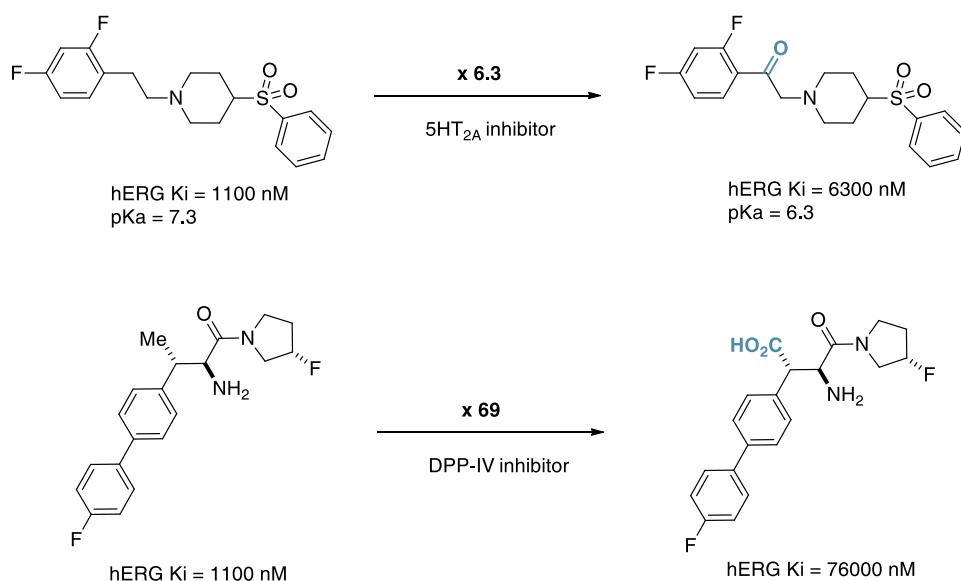


Figure 3: a) hERG pharmacophore model, and b) known hERG inhibitors

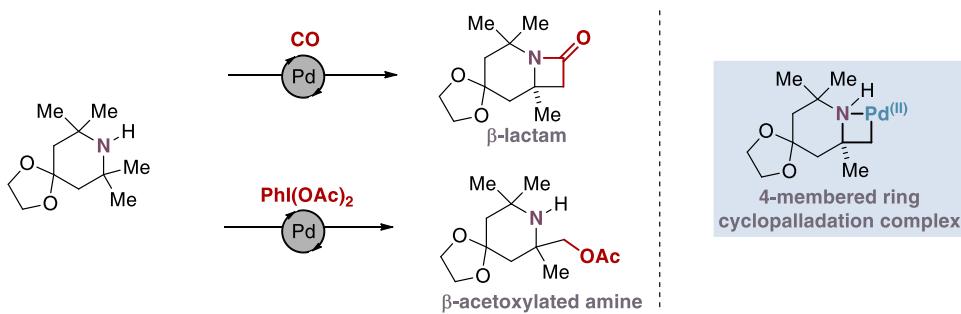
One of the commonly employed strategies in medicinal chemistry to reduce hERG inhibition is to reduce the basicity *i.e.* pKa of the amine. This is often achieved by incorporation of electronegative atoms in close proximity to the basic nitrogen atom (Scheme 98).^{137,138}



Scheme 98: Reducing pKa of amine nitrogen improves hERG profile^{137,138}

3.2 Project aims

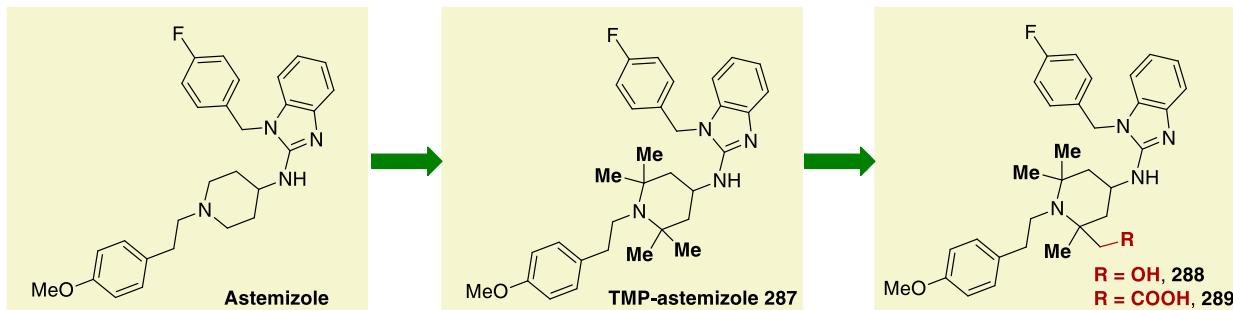
As mentioned in the introduction (see section 1.4.3.4), we have recently developed a palladium(II)-catalysed C–H activation strategy for functionalisation of hindered aliphatic amines *via* a novel four-membered ring cyclopalladation pathway (Scheme 99).¹¹³ This approach has enabled entry to previously inaccessible amines.



Scheme 99: C–H functionalisation of hindered aliphatic amines *via* a novel four-membered cyclopalladation pathway¹¹³

We envisaged that we could exploit this C–H activation strategy to access analogues of astemizole which have the potential to reduce the level of hERG inhibition (Scheme 100). Our hypothesis was that by increasing the steric bulk around the piperidine nitrogen atom, we could reduce the basicity of the nitrogen by virtue of steric hindrance and therefore reduce hERG binding. Although the additional methyl groups would bring an undesirable increase in the logP value in such derivative (**287**), it could be compensated by the introduction of polar groups (**288**)

and **289**). Moreover, the newly installed polar functional handles could offer opportunities for further derivitisation to fine-tune the physicochemical properties of these derivatives.



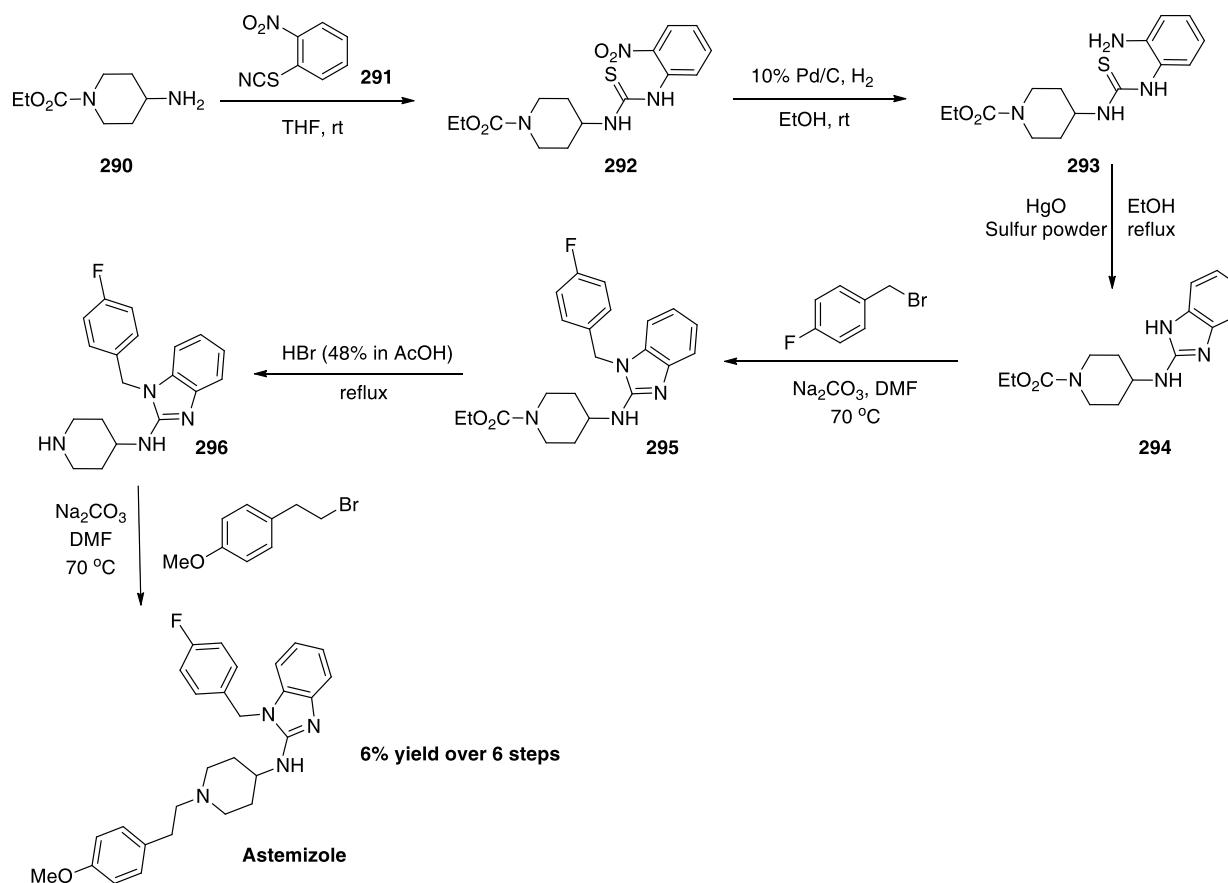
Scheme 100: Synthetically-driven design of astemizole analogues

The initial aim of the project was to establish the synthetic route for the synthesis of TMP-astemizole **287** and to subsequently employ the C–H functionalisation chemistry to further obtain the OH and COOH derivatives (**288** and **289**) in order to test their hERG activities.

3.3 Results and discussion

3.3.1 Synthesis of ‘TMP-astemizole’

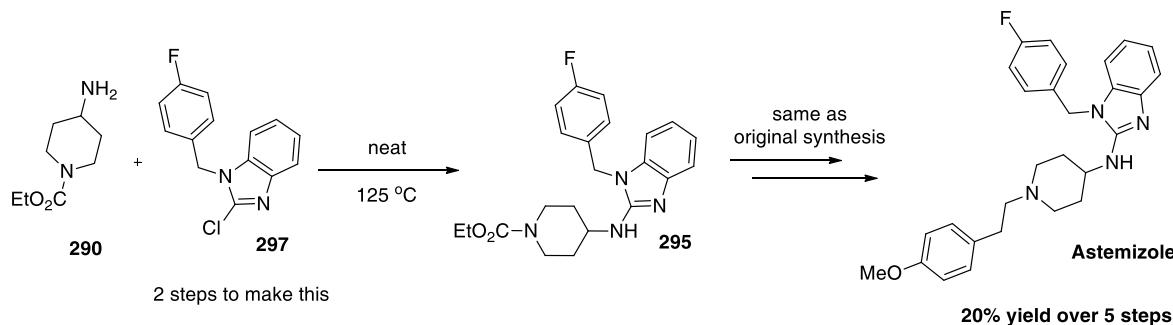
The original discovery synthesis of astemizole by Janssen Pharmaceutica,¹³¹ outlined in Scheme 101, was completed in six linear synthetic steps, starting from ethyl, 4-aminopiperidine carboxylate **290**.



Scheme 101: Discovery synthesis of astemizole by Janssen Pharmaceutica¹³¹

In this synthesis, treatment of ethyl, 4-aminopiperidine carboxylate **290** with *ortho*-nitrophenylisothiocyanate **291** afforded thiourea **292**. Catalytic hydrogenation of nitro to amino group furnished aniline **293** which underwent cyclodesulfurisation in the presence of mercury(II) oxide and sulfur powder to yield benzimidazole **294**. Subsequent *N*-alkylation of the benzimidazole followed by carbamate deprotection gave piperidine **296**, which after *N*-alkylation with 4-methoxyphenylethyl bromide, furnished astemizole, with a 6% yield over six steps.

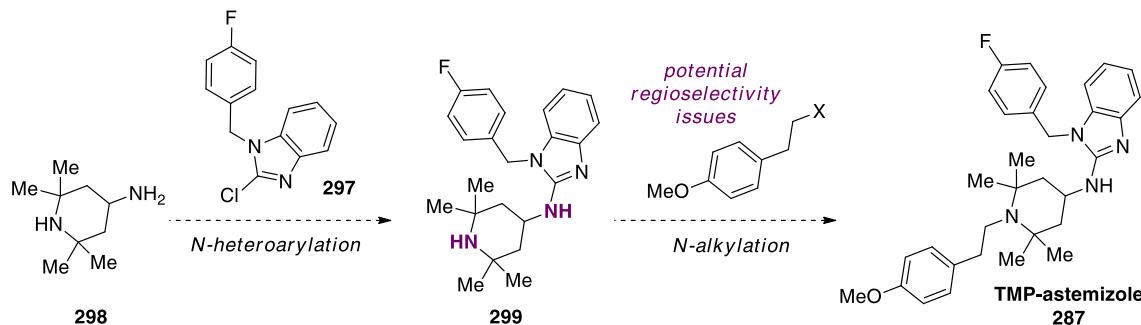
Sandoval-Ramirez and coworkers¹³⁹ later reported an improved synthesis of astemizole, which allowed a more convergent synthesis *via* a nucleophilic aromatic substitution (S_NAr) reaction of ethyl, 4-aminopiperidine carboxylate **290** with 2-chloro-1-(4-fluorobenzyl)benzimidazole **297**, which required two steps to synthesise though it is now commercially available (Scheme 102). The subsequent steps were identical to the original synthesis and an overall 20% yield was achieved.



Scheme 102: Improved synthesis of astemizole by Sandoval-Ramirez¹³⁹

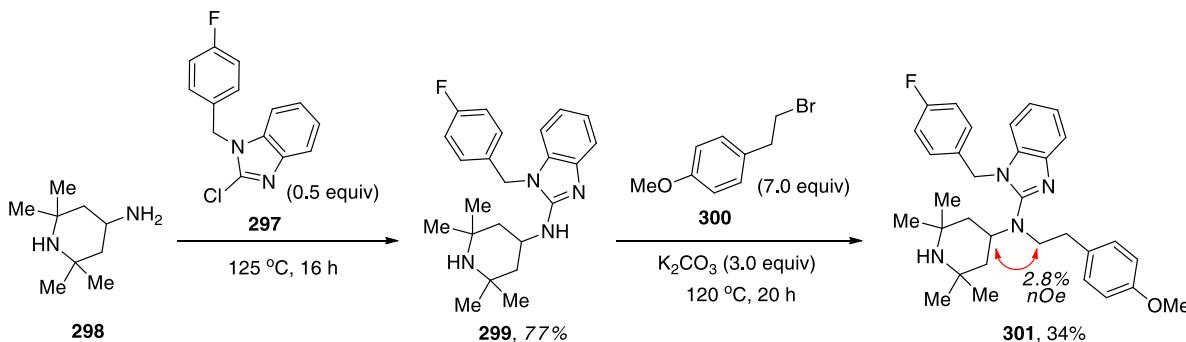
3.3.1.1 Original route

Based on the established synthetic route to astemizole, it was proposed that TMP-astemizole **287** could be synthesised in a similar fashion, starting from 2,2,6,6-tetramethylpiperidin-4-amine **298** (Scheme 103). It was anticipated that the *N*-heteroarylation reaction could be carried out without the need to protect the TMP nitrogen atom as it is sterically hindered and hence rendering it unreactive. Although this route is short, we anticipated that the subsequent *N*-alkylation on piperidine **299** could give rise to regioselectivity issues with two free amines in the molecule (highlighted in purple). This route was investigated nevertheless given the brevity of the synthetic route.



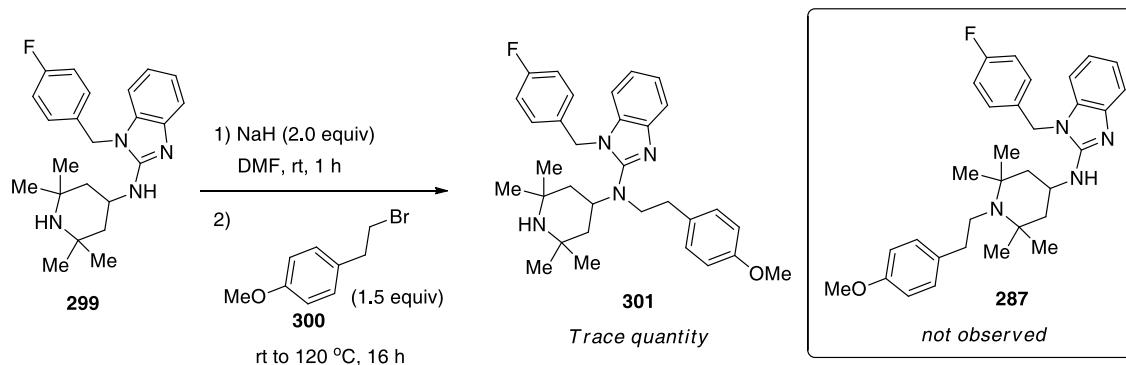
Scheme 103: Proposed synthetic route to TMP-astemizole **287**

The *N*-heteroarylation reaction proceeded efficiently between 2,2,6,6-tetramethylpiperidin-4-amine **298** and 2-chloro-1-(4-fluorobenzyl)benzimidazole **297**, yielding the desired amine **299** in 77% yield. However, the subsequent alkylation with 4-methoxyphenylethyl bromide **300** gave exclusively the undesired regioisomer **301**, in 34% yield (Scheme 104). The regiochemistry was confirmed by *n*Oe analysis.



Scheme 104: Initial attempts to synthesize TMP-astemizole **287**

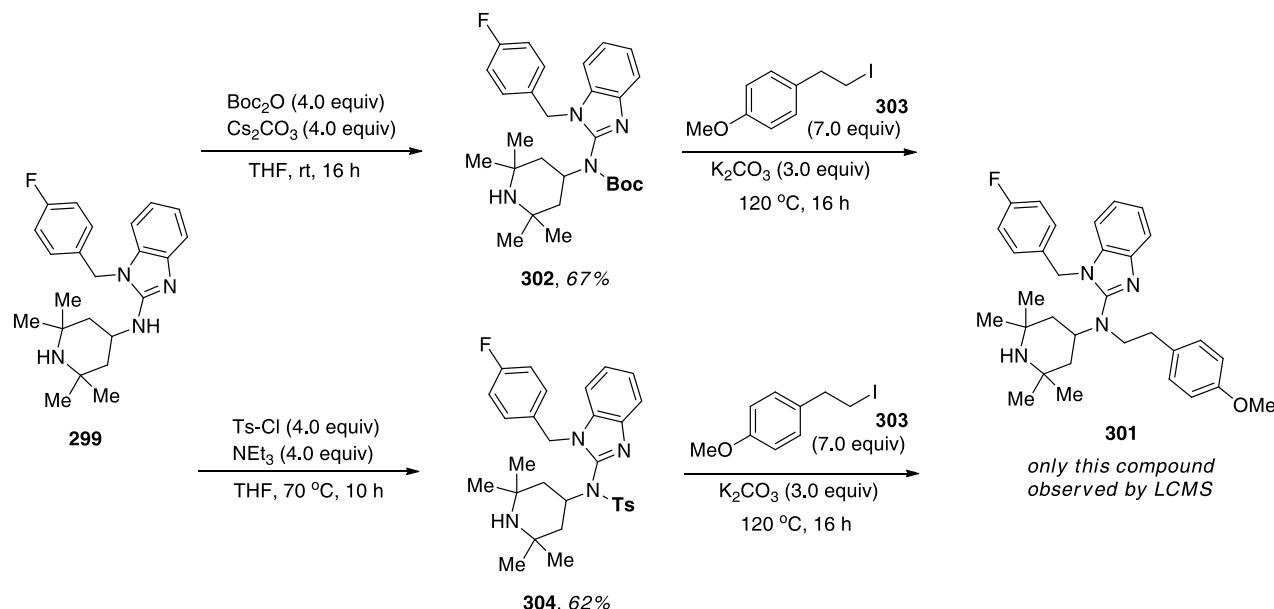
Given the pKa of the amino-benzimidazole NH is likely to be lower than that of the TMP NH, a double deprotonation strategy was attempted (Scheme 105). Unfortunately, treatment of amine **299** with 2 equivalents of sodium hydride, followed by addition of bromide **300**, gave no desired product **287** and only trace amount of the undesired regioisomer **301** was observed by ¹H NMR and LCMS analyses.



Scheme 105: Double deprotonation strategy

The next approach attempted was protection of the more reactive amino-benzimidazole nitrogen atom followed by alkylation. The Boc-protected amino-benzimidazole **302** and Ts-protected amino-benzimidazole **304** were prepared and subjected to the *N*-alkylation conditions, this time with the more reactive alkylating agent 4-methoxyphenylethyl iodide **303** (Scheme 106). Unfortunately, the protecting groups were proved too labile and the *N*-alkylation again took place

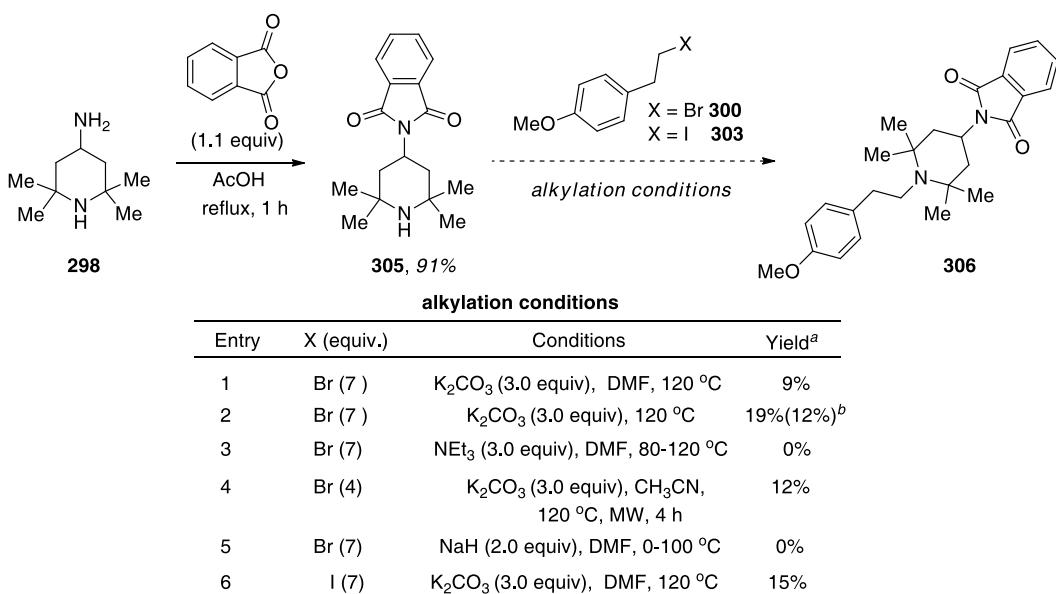
on the amino-benzimidazole nitrogen atom. As this synthetic route was met with little success, different strategies were sought.



Scheme 106: Blocking the amino-benzimidazole NH with protecting groups

3.3.1.2 Phthalimide route

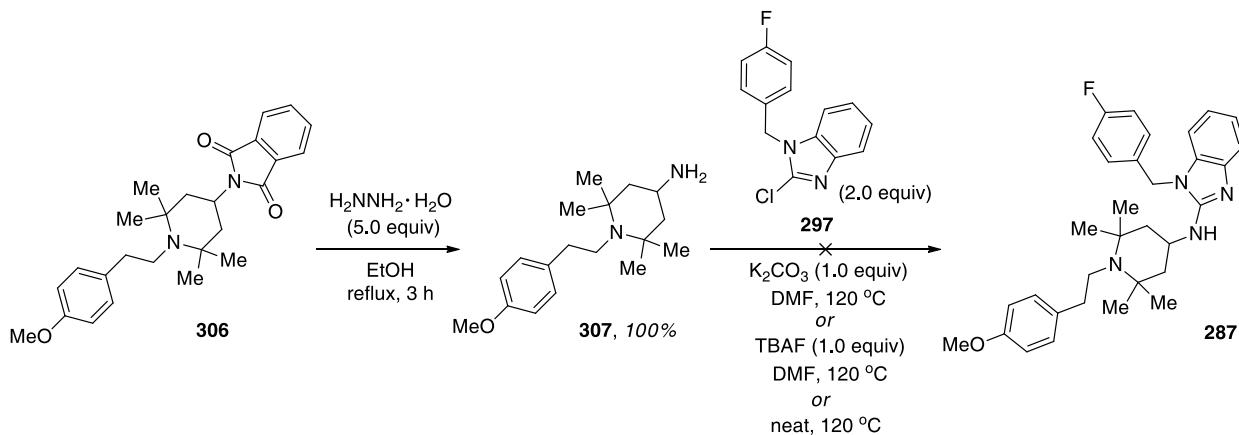
It was thought the order of the *N*-heteroarylation and *N*-alkylation steps could be reversed as this would avoid the regioselectivity issue encountered with the first route. To this end, amine **305** was prepared from 2,2,6,6-tetramethylpiperidin-4-amine **298** and a brief survey of alkylation conditions were carried out (Scheme 107). The alkylations were found to be sluggish, with mainly starting amine recovered as well as methoxy-styrene resulting from elimination of halides **300** and **303**. Nevertheless, the desired product **306** could be obtained on treatment of amine **305** with potassium carbonate as base in neat 4-methoxyphenylethyl bromide **300** at 120°C , albeit in only a poor 12% isolated yield (entry 2). Weak organic bases such as triethylamine and strong bases such as sodium hydride resulted in no conversion (entries 3 and 5). Alkylation with microwave irradiation, as well as using the more reactive iodide **303**, showed similar conversion to that obtained from the neat reaction (entries 4 and 6).



^a Yields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard; ^b Isolated yield in parentheses

Scheme 107: Preparation and attempted alkylation of amine **305**

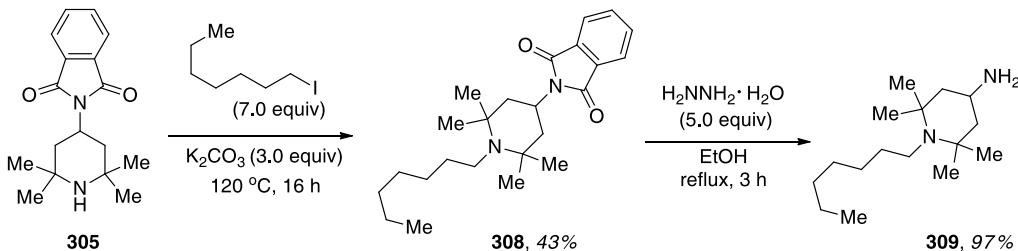
The next step was removal of the phthalimide group, which proceeded smoothly to give primary amine **307** in quantitative yield (Scheme 108). Unfortunately, the subsequent *N*-heteroarylation reaction was unsuccessful under a number of reaction conditions investigated, with only starting material observed at the end of the reaction.



Scheme 108: Removal of phthalimide group and attempted *N*-heteroarylation reaction on **307**

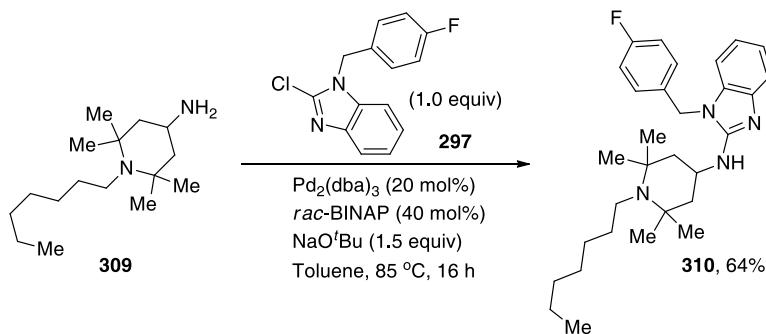
Another precedented approach to install the benzimidazole unit to 4-aminopiperidine is the Buchwald-Hartwig amination.¹⁴⁰ However, due to the irreproducible and unreliable *N*-alkylation step, it was found to be rather problematic to produce an appreciable quantity of amine **307** using the current route. At this point, we investigated making a test substrate which would hopefully

allow quick access to an analogue of amine **307** to trial the amination. To this end, amine **309** was prepared, which bore a heptyl unit on the hindered nitrogen atom instead of the 4-methoxyphenylethyl group (Scheme 109). The alkylation with heptyl iodide proved to be more robust, giving the alkylated amine **308** in a moderate 43% yield. Subsequent removal of the phthalimide group furnished amine **309**, an analogue of amine **307**, in 97% yield.



Scheme 109: Preparation of test substrate **309**

Gratifying, the Buchwald-Hartwig amination with amine **309** and 2-chloro-1-(4-fluorobenzyl)benzimidazole **297** proceeded smoothly under the reported amination conditions,¹⁴⁰ yielding the desired compound **310** in 64% yield (Scheme 110).



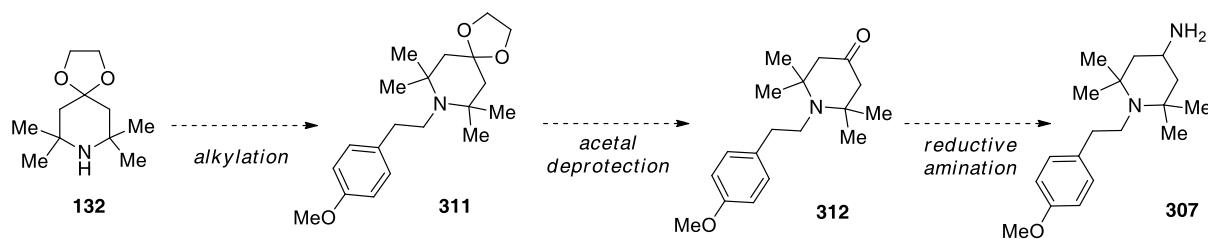
Scheme 110: Buchwald-Hartwig amination on test substrate **309**

With the method to the install the benzimidazole unit established, the focus was switched to an alternative approach to synthesise amine **307**, the precursor to TMP-astemizole **287**.

3.3.1.3 Dioxolane route

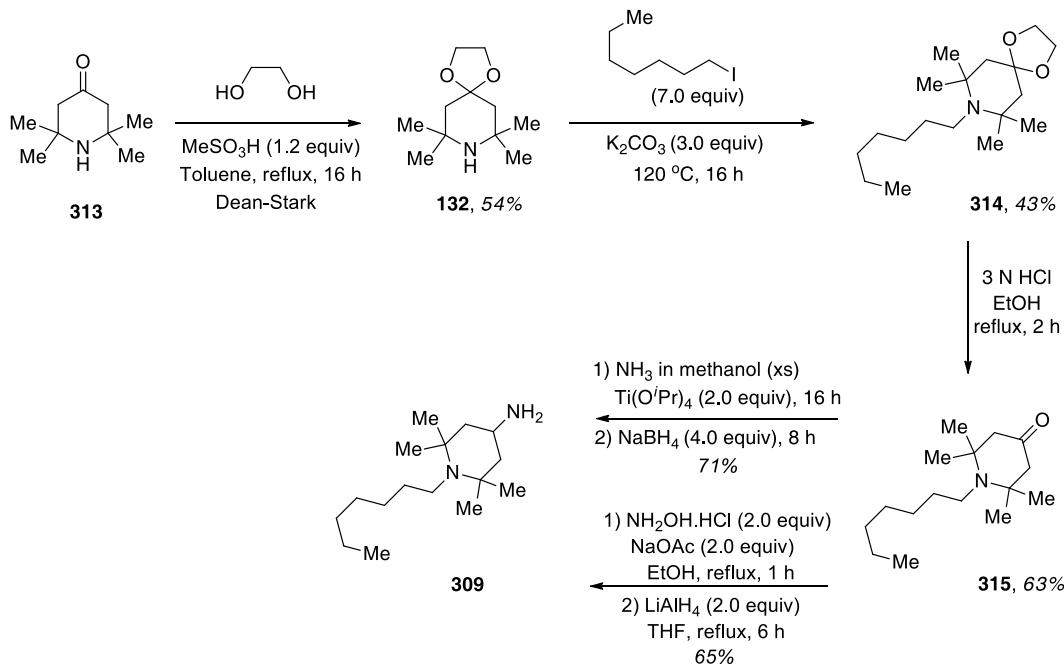
We next sought to attempt alkylation on acetal-protected tetramethylpiperidine-4-one **132** and proposed an alternative route to synthesise amine **307** starting from **132** (Scheme 111). Alkylation would be followed by an acetal deprotection. Reductive amination of the resulting ketone would install the primary amine functionality. Starting the synthesis with **132** would also

be ideal as the palladium-catalysed functionalisation has been shown to work effectively on this exact system.¹¹³



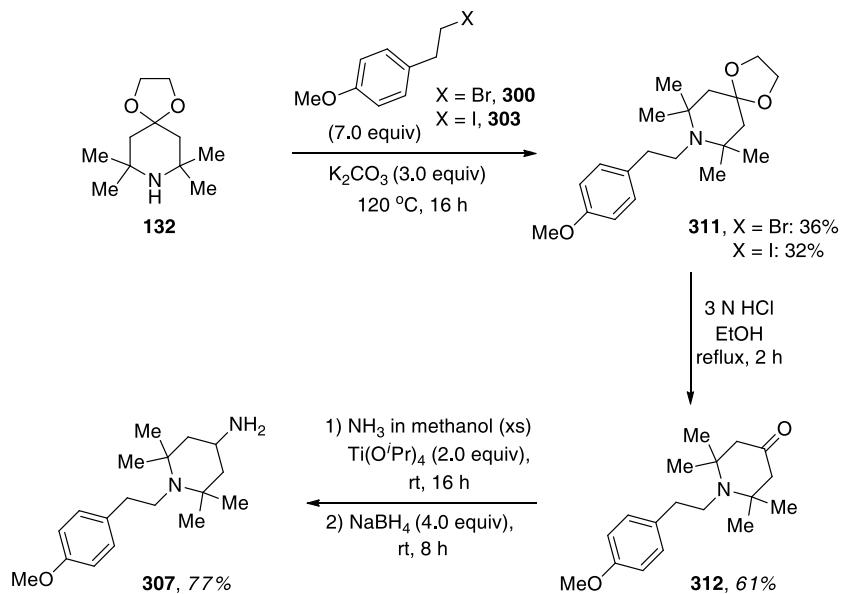
Scheme 111: Proposed synthetic route starting from dioxolane **132**

It was anticipated that alkylation with 4-methoxyphenylethyl bromide **300** would be poor. Therefore, as with the phthalimide route, it was decided to trial this route using a test substrate (Scheme 112). To this end, primary amine **309** was prepared, starting from ketone **313**. Protection of **313** with ethylene glycol gave dioxolane **132** in 54% yield. *N*-alkylation with heptyl iodide proceeded to give 43% of tertiary amine **314**. Subsequent acetal deprotection under acidic conditions furnished ketone **315** in 63% yield. Two different reductive amination conditions were attempted and it was found that treatment of **315** with 7 N ammonia in methanol and titanium(IV) isopropoxide, followed by reduction of the transient hemiaminal species with sodium borohydride, gave the best yield of the desired primary amine **309**, in 71% yield. The two step reduction *via* oxime returned **309** in a marginally lower 65% yield.



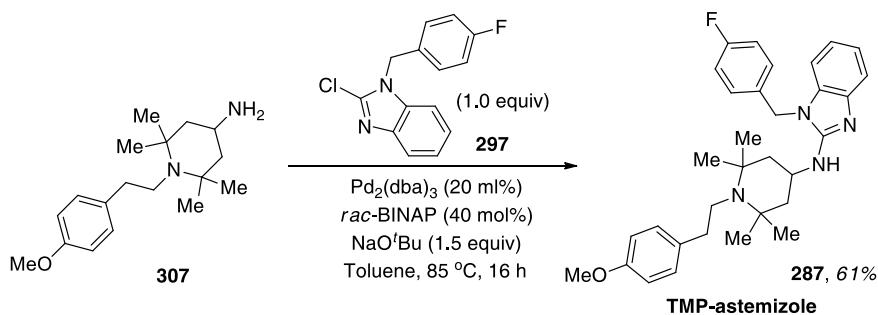
Scheme 112: Preparation of test substrate **309** *via* the dioxolane route

With the synthetic route and conditions established, attempts were made to synthesise TMP-astemizole **287** (Scheme 113). *N*-alkylation of **132** with 4-methoxyphenylethyl bromide **300** or iodide **303** was found to be a more reliable reaction, affording 36% of the desired tertiary amine **311** with bromide **300**. Ketone **312** was obtained in 61% yield following an acidic acetal deprotection. Subsequent reductive amination, following the conditions established for ketone **315**, enabled primary amine **307** to be obtained in 77% yield.



Scheme 113: Preparation of **307** via the dioxolane route

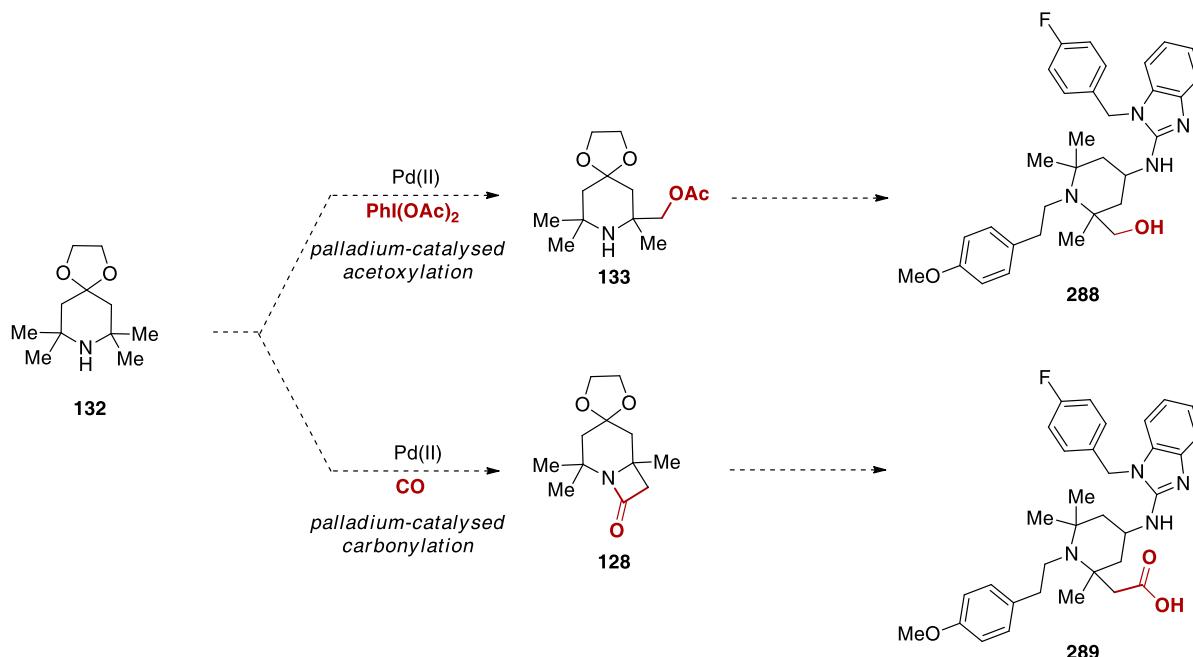
Finally, subjecting **307** to the validated Buchwald-Hartwig amination conditions furnished the desired TMP-astemizole **287** in 61% yield (Scheme 114).



Scheme 114: Access to TMP-astemizole **287** via Buchwald-Hartwig amination

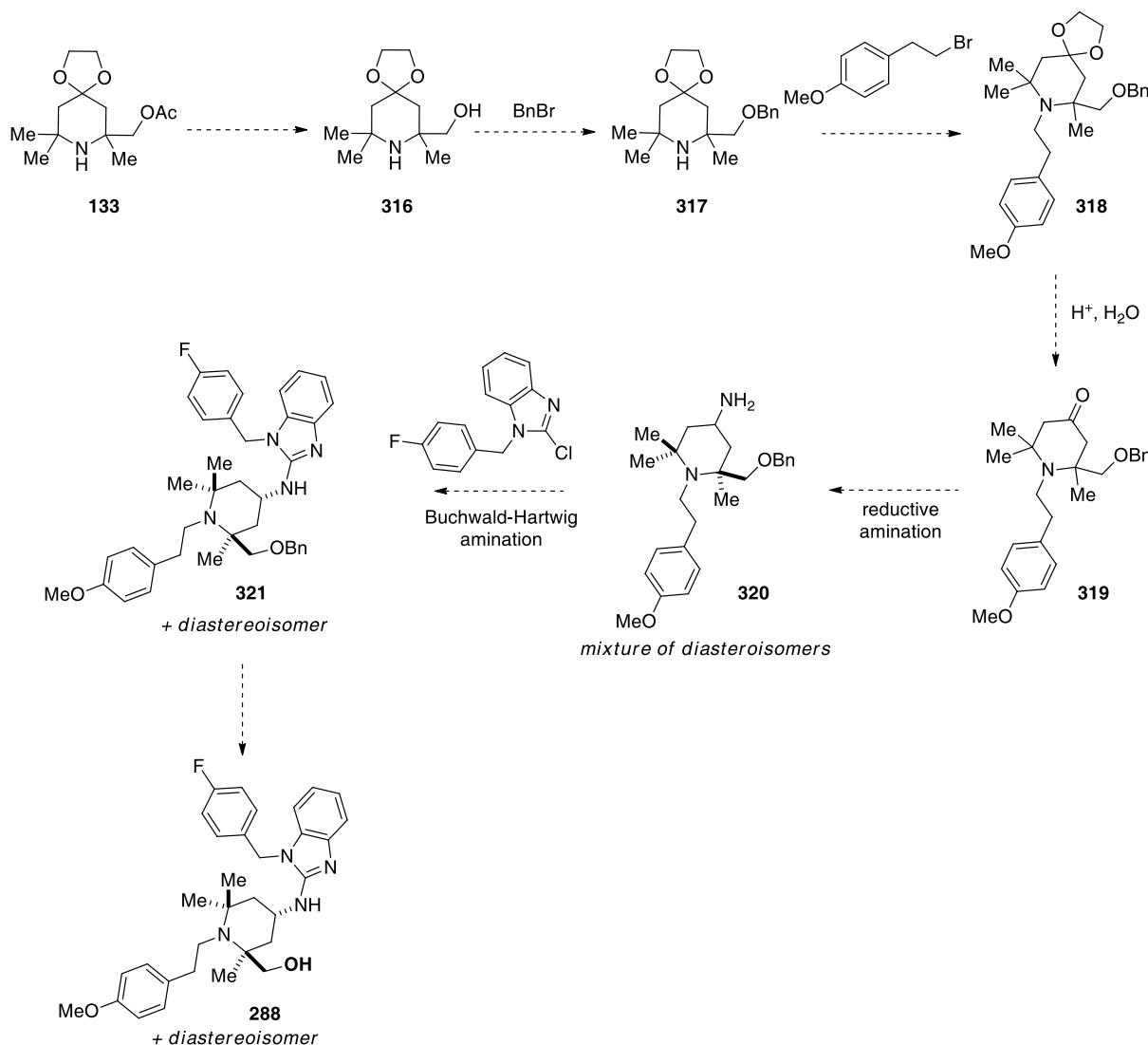
3.3.2 Proposed synthetic routes to functionalised astemizole analogues

Having established a synthetic route for synthesis of TMP-astemizole, we next set out to synthesise astemizole analogues **288** and **289**, based on the palladium-catalysed acetoxylation and carbonylation, respectively, starting from **132** (Scheme 115).



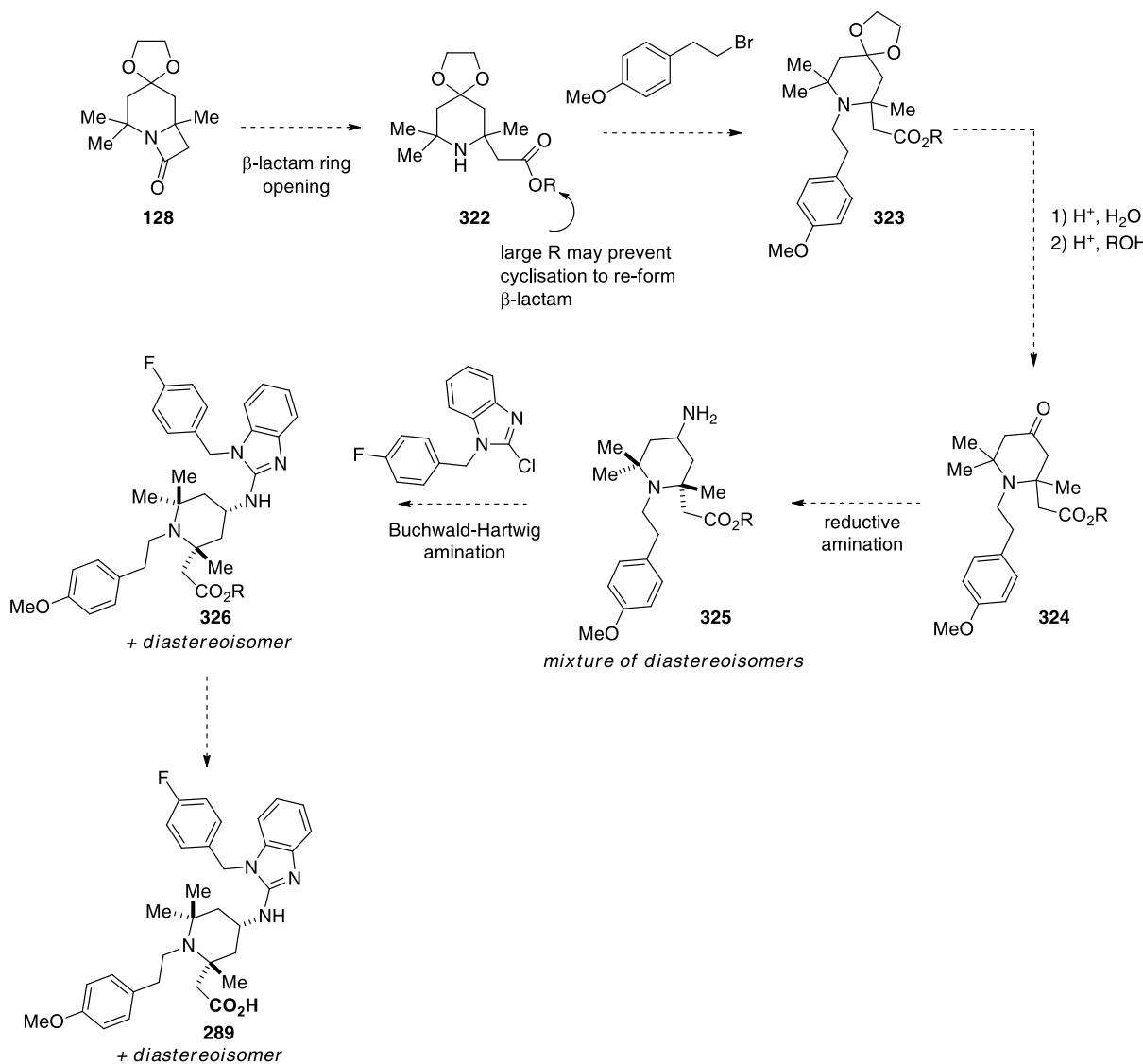
Scheme 115: Palladium-catalysed functionalisation approach to **288** and **289**

The proposed synthesis to **288**, starting from **133**, is shown in Scheme 116. Protection of the newly installed hydroxyl group was deemed necessary to avoid regioselective issues in the subsequent displacement reaction. However, it was envisaged that the installed acetyl group would be too labile to carry through the synthetic sequence. As such, the acetyl group would first be removed and replaced with a more robust protecting group, such as benzyl. Displacement with 4-methoxybenzyl bromide, followed by acetal deprotection would yield ketone **319**. The primary amine group could subsequently be introduced *via* reductive amination to yield a mixture of diastereoisomers **320**. If possible, the diastereoisomers would be separated before the subsequent Buchwald-Hartwig amination and benzyl deprotection, yielding functionalised astemizole analogue **288**.



Scheme 116: Proposed synthetic route to functionalised astemizole analogue **288**

The proposed synthesis of **289**, starting from **128**, is shown in Scheme 117. We envisaged ring-opening of the β -lactam ring with a bulky alcohol group such as *iso*-propanol would enhance the stability of the resulting ester from re-formation of the β -lactam ring in the subsequent alkylation. At this point, selective deprotection of acetal **323** to ketone **324** in the presence of the ester functionality would be explored. Should the ester group hydrolysed during acetal deprotection, it should be easily reinstated *via* a Fisher esterification. The ensuing reductive amination followed by Buchwald-Hartwig amination steps would yield ester **326**. Final hydrolysis of ester **326** (and the other diastereoisomer) would furnish functionalised astemizole analogue **289**.

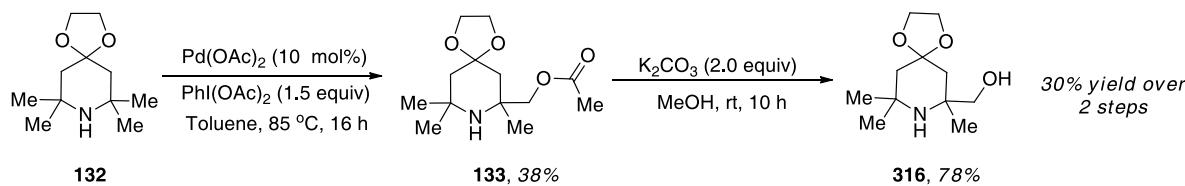


Scheme 117: Proposed synthetic route to functionalised astemizole analogue **289**

3.3.3 Introduction of polar functionality: palladium(II)-catalysed acetoxylation and carbonylation

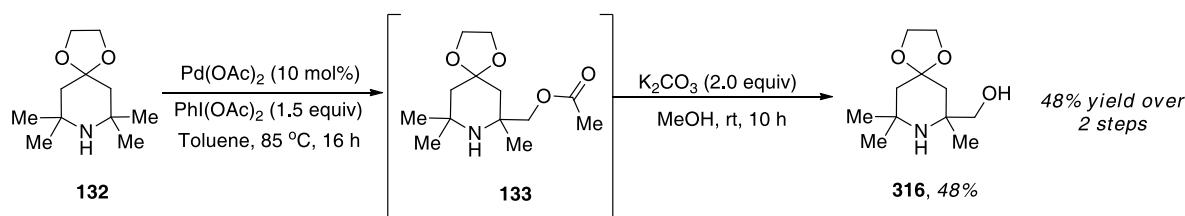
3.3.3.1 Palladium(II)-catalysed acetoxylation

We began our synthesis of **288** with the precedented palladium-catalysed acetoxylation of **132** (Scheme 118).¹¹³ Subjecting **132** to the acetoxylation condition yielded the acetoxylated amine **133** in 38% yield after purification. The subsequent acetate hydrolysis proceeded without note and delivered alcohol **316** in 78% yield.



Scheme 118: Palladium(II)-catalysed acetoxylation followed by hydrolysis

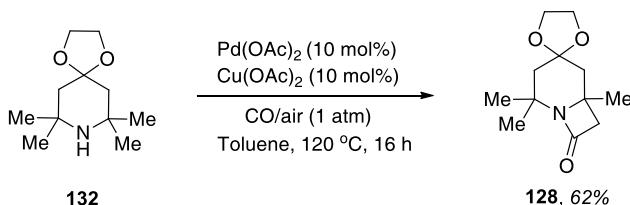
Due to difficult and time-consuming purification of **133**, we attempted telescoping the crude material of **133** directly into the acetate hydrolysis step (Scheme 119). Gratifyingly, this telescoped process proved more efficient both in terms of time and yield of **316** as the chromatographic purification was significantly easier. Overall, 48% yield was achieved over 2 steps.



Scheme 119: Telescoped palladium-catalysed acetoxylation/hydrolysis sequence

3.3.3.2 Palladium(II)-catalysed carbonylation

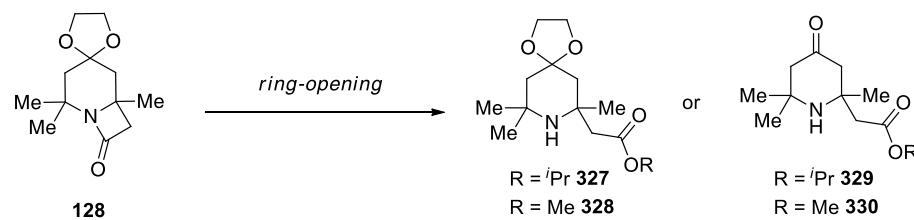
In an analogous fashion, we began our synthesis of **289** with the precedented palladium-catalysed carbonylation of **132**, which proceeded smoothly to give **128** in 62% yield (Scheme 120).¹¹³



Scheme 120: Palladium(II)-catalysed carbonylation of **132**

We next investigated ring opening of the β -lactam ring with the intention of forming β -amino ester **327** or **328** (Table 7). Ring-opening of **128** with different metal isopropoxides showed no conversion to the desired amino ester **327** whilst using the smaller methoxide nucleophile gave no reaction either (entries 1 to 4). Under protic or Lewis acidic conditions, the reaction gave complex mixtures with no sign of **327** or **329** observed (entries 7 and 8).

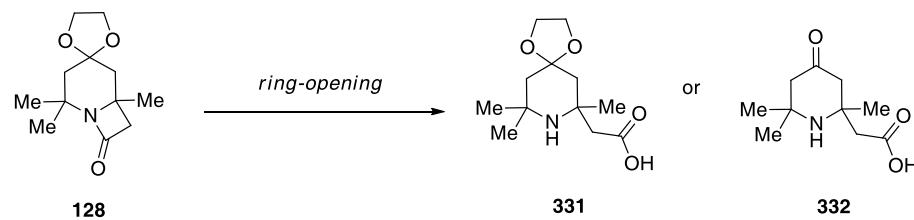
Table 7: Screening of β -lactam ring-opening conditions



Entry	Reaction conditions	Result
1	LiO <i>i</i> Pr (5.0 equiv), IPA, reflux, 16 h	Only SM
2	NaO <i>i</i> Pr (5.0 equiv), IPA, reflux, 16 h	SM and an unknown compound
3	KO <i>i</i> Pr (5.0 equiv), IPA, reflux, 16 h	SM and an unknown compound
4	NaOMe (5.0 equiv), MeOH, reflux 16 h	Only SM
5	4 N HCl in dioxane (2.0 equiv), IPA, reflux, 2 h	No SM, complex mixture
6	3 N HCl, IPA, reflux, 2 h	No SM, complex mixture
7	BF ₃ (2.0 equiv), IPA, reflux, 2 h	No SM, complex mixture
8	TMSCl (2.0 equiv), IPA, reflux, 2 h	No SM, complex mixture

Given the lack of success in the ring-opening to give β -amino ester directly, we next explored a two-step procedure involving hydrolysis then esterification (Table 8). Treatment of **128** with metal hydroxides succeeded in producing the desired β -amino acid **331**, but the conversion was very poor, despite prolonged heating (entries 1 and 2). Acidic ring-opening condition again gave a complex reaction mixture (entry 3).

Table 8: Screening of β -lactam ring-opening conditions

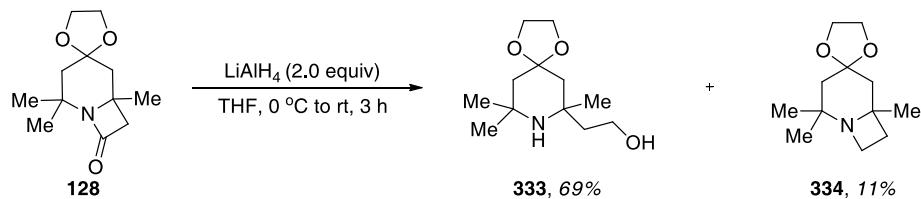


Entry	Reaction conditions	Yield ^a
1	KOH (10 equiv), THF/water(1:1), reflux, 5 days	22% 331 ; 20% SM
2	LiOH (10 equiv), THF/water(1:1), reflux, 5 days	7% 331 ; 85% SM
3	3 N HCl, THF/water, reflux, 3 h	No SM, complex mixture

^aYields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

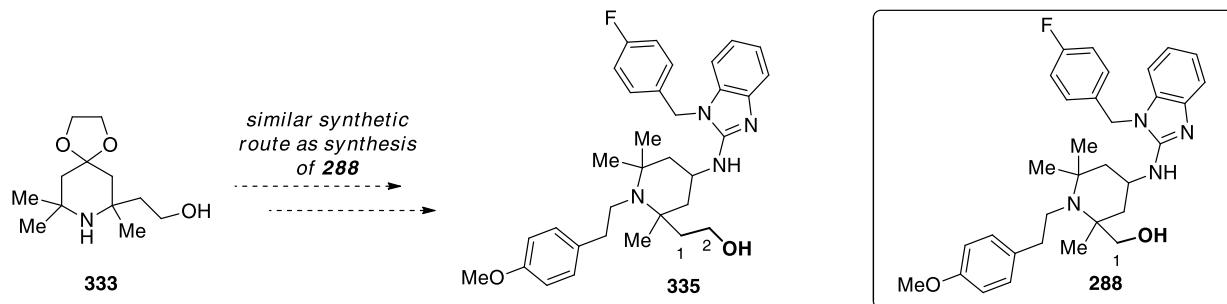
Whilst β -lactam ring-opening with oxygen nucleophiles was met with little success, we questioned whether using stronger nucleophiles would improve the ring-opening reaction. We

were pleased to find that, on treatment with the stronger nucleophile lithium aluminium hydride, reduction of β -lactam **128** proceeded efficiently to give amino alcohol **333** in 69% yield, along with 11% of azetidine **334** (Scheme 121).



Scheme 121: Reduction of **128** to β -amino alcohol **333**

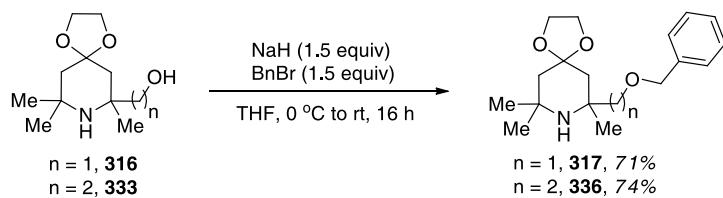
We envisaged that that amino alcohol **333** could lead to astemizole analogue **335** by following a synthetic route similar to that proposed for the synthesis of **288** (Scheme 122).



Scheme 122: Proposed synthesis of **335** - homologated analogue of **288**

3.3.4 Installation of the 4-methoxyphenylethyl unit

With the successful introduction of polar OH groups *via* palladium-catalysed acetoxylation and carbonylation, the focus was switched to the incorporation of the 4-methoxyphenylethyl unit onto the hindered nitrogen. Alcohols **316** and **333** were first protected with benzyl groups (Scheme 123).



Scheme 123: Benzylation of alcohols **316** and **333**

The alkylation reaction of **317** and **336** with 4-methoxyphenylethyl bromide/iodides were next explored (Table 9).

Table 9: Screening of alkylation conditions on **317** and **336**

Entry	n	Reaction conditions	Yield ^a
1	1	Bromide (7.0 equiv), K ₂ CO ₃ (3.0 equiv), 120 °C, 16 h	7% (3%) ^b
2	1	Bromide (7.0 equiv), K ₃ PO ₄ (3.0 equiv), 120 °C, 16 h	Traces of product (<5%)
3	1	Iodide (7.0 equiv), K ₂ CO ₃ (3.0 equiv), 120 °C, 16 h	Traces of product (<5%)
4	1	NaH (2.0 equiv), bromide (3.0 equiv), DMF, rt to 100 °C, 16 h	0%
5	1	Bromide (3.0 equiv), K ₂ CO ₃ (3.0 equiv), CH ₃ CN, 150 °C, MW, 4 h	0%
6	2	Bromide (7.0 equiv), K ₂ CO ₃ (3.0 equiv), 120 °C, 16 h	Traces of product (<5%)
7	2	NaH (2.0 equiv), bromide (3.0 equiv), DMF, rt to 100 °C, 16 h	0%
8	2	Bromide (3.0 equiv), K ₂ CO ₃ (3.0 equiv), CH ₃ CN, 150 °C, MW, 4 h	6%

^aYields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Poor conversion was observed when potassium carbonate was employed as base and gave a mere 3% isolated yield of **317**, with mostly starting material remaining (entry 1). Stronger bases, such as tribasic potassium phosphate and sodium hydride did not lead to any improvements (entries 2, 4 and 7). Employing the more reactive iodide **303** gave only traces of product whilst stirring under microwave irradiation at 150 °C gave no conversion (entries 3 and 5). The low reactivity of **316** in alkylation could be attributed to the reduced nucleophilicity of the nitrogen atom due to the β-heteroatom effect. It was also speculated that the possible formation of a stable intramolecular hydrogen bonding network might also diminish the nucleophilicity of the nitrogen atom (Figure 4).

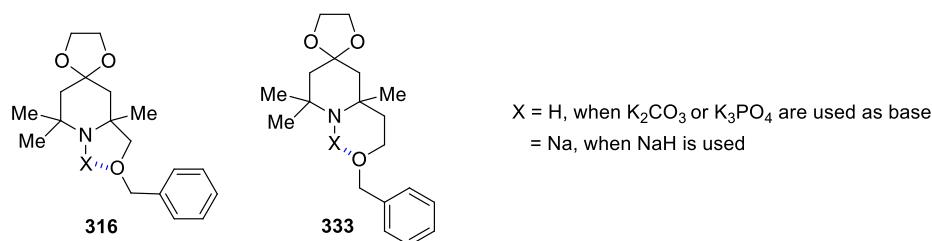
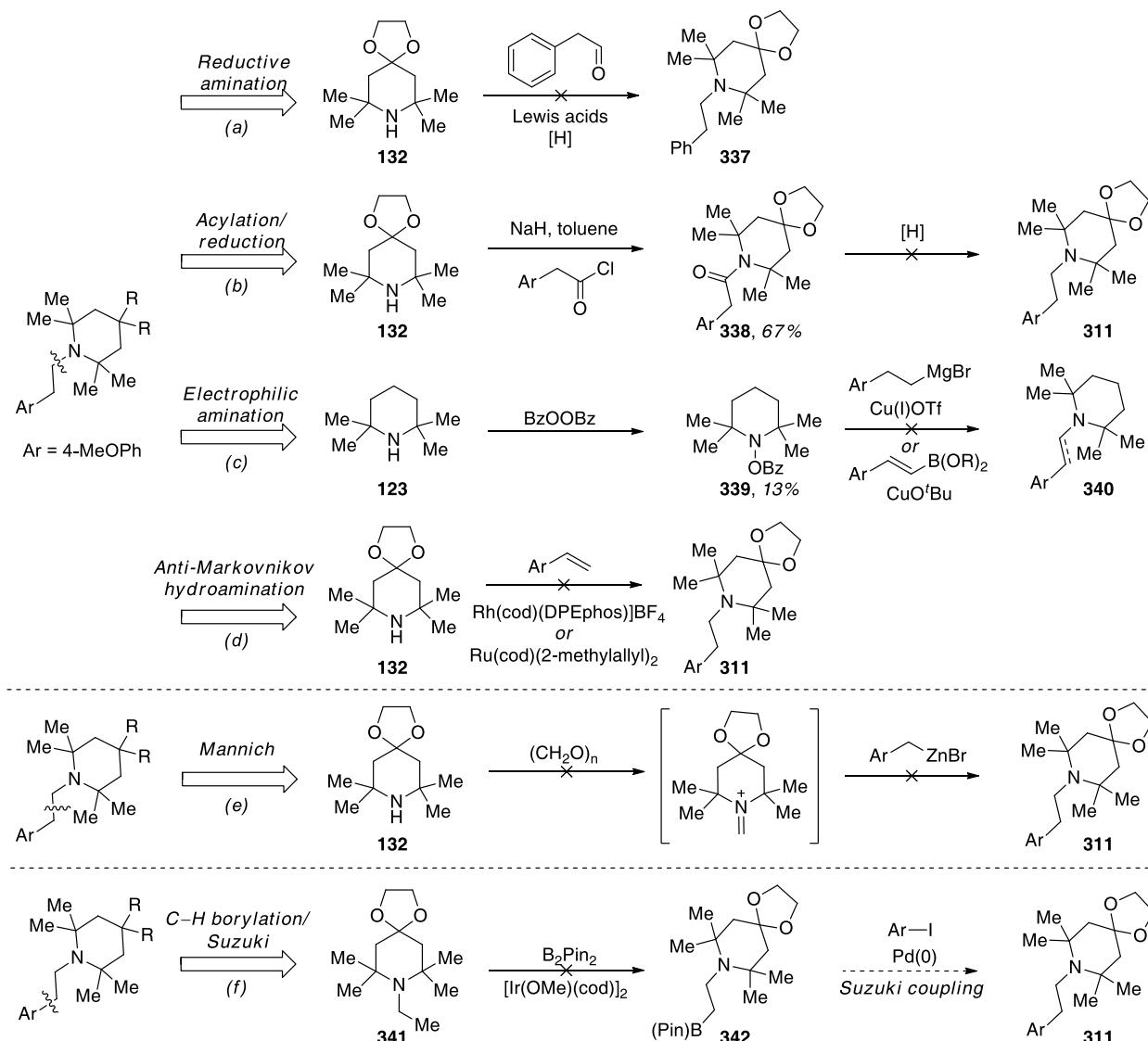


Figure 4: Possible intramolecular hydrogen bonding network in **316** and **333**

As the displacement reactions with **316** and **333** were met with little success, different approaches to install the 4-methoxyphenylethyl unit were examined. A summary of the alternative strategies investigated is shown in **Scheme 124**.



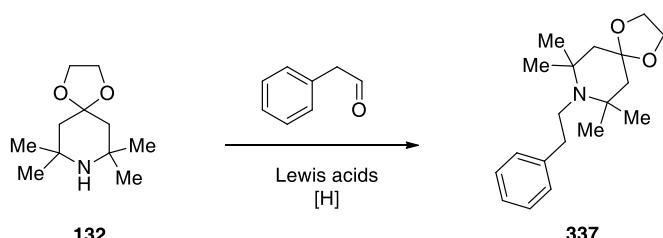
Scheme 124: Summary of the alternative strategies attempted to install the 4-methoxyphenylethyl group

Reductive amination (Scheme 124a):

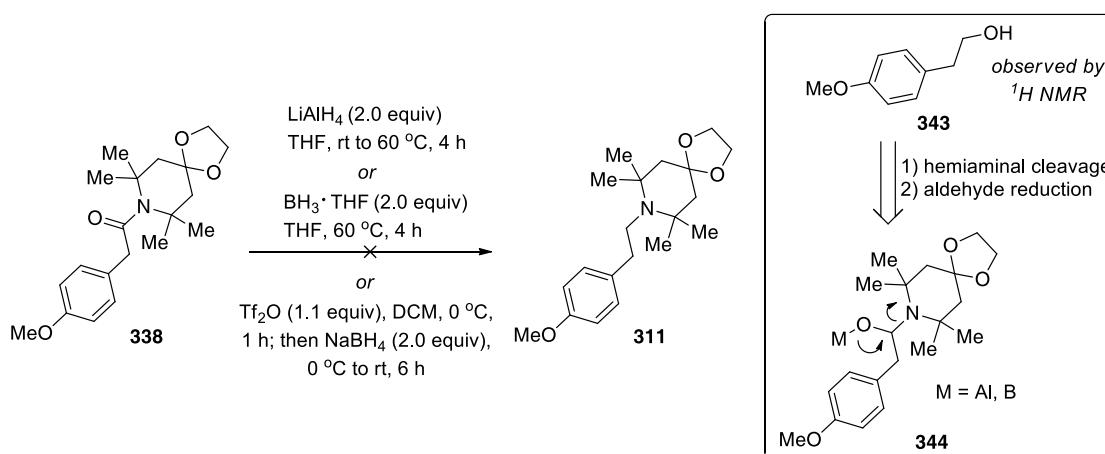
A number of standard reductive amination procedures were attempted using phenyl acetaldehyde as the model aldehyde. Disappointingly, none led to formation of the desired product **337**, with only starting material and alcohol stemming from reduction of the aldehyde recovered (Table 10). Attempts to isolate the enamine that would be formed after the initial condensation also failed, presumably owing the poor reactivity of the sterically hindered amine.

Table 10: Screening of reductive amination conditions.

Entry	Reaction conditions	Result
1	Aldehyde (2.0 equiv), AcOH (~0.1 equiv), rt to 50 °C; then NaBH(OAc) ₃ (2.0 equiv), 50 °C, 16 h	Only SM and reduction of aldehyde
2	Aldehyde (2.0 equiv), Ti(O <i>i</i> Pr) ₄ (2.0 equiv), MeOH, rt, 6 h; then NaBH ₄ (2.0 equiv), rt, 10 h	Only SM and reduction of aldehyde
3	Aldehyde (2.0 equiv), Ti(O <i>i</i> Pr) ₄ (5.0 equiv), rt, 16 h; then NaBH ₄ (4.0 equiv), rt, 6 h	Only SM and reduction of aldehyde

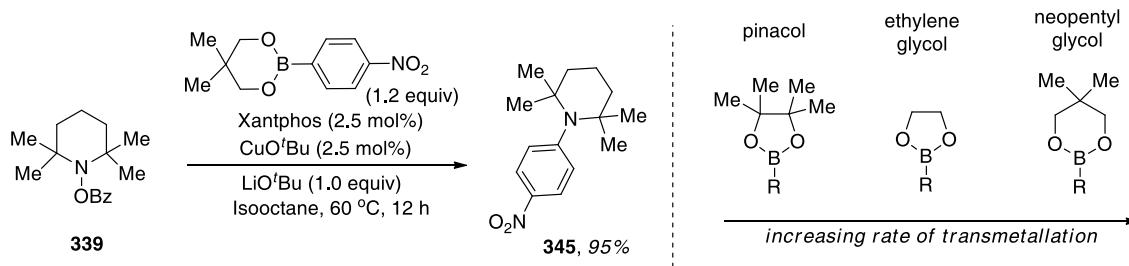
**Acylation/reduction (Scheme 124b):**

Pleasingly, acylation of **132** proceeded efficiently to give amide **338** in 67% yield. However, the ensuing amide reduction proved more challenging. Standard hydride reducing agents such as lithium aluminium hydride and borane gave no desired product with only alcohol **343** observed by ¹H NMR (Scheme 125). Alcohol **343** was presumably formed from cleavage of the hemiaminal intermediate **344** followed by reduction of the resulting aldehyde. Attempts to activate the amide with triflic anhydride followed by reduction with sodium borohydride was also unsuccessful, with either product or starting material recovered after the reaction. We next explored the possibility of using silanes as reducing agents under transition-metal catalysis.^{141–145} Unfortunately, this approach was also met with little success and so it was not pursued further.

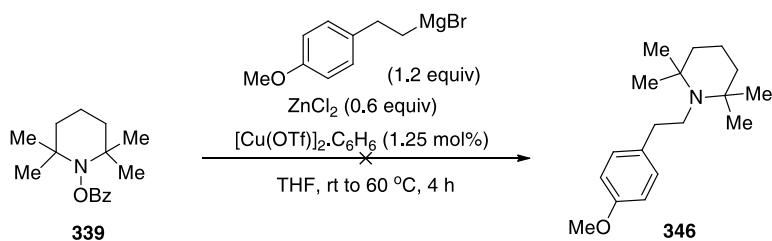
**Scheme 125:** Failed reduction of **338** with standard hydride reducing agents

Electrophilic amination (Scheme 124c):

Electrophilic amination involves the formation of a carbon–nitrogen bond through the reaction of a nucleophilic carbanion with an electrophilic source of nitrogen. In 2004, Johnson reported a mild method for the preparation of various tertiary amines through the copper-catalysed electrophilic amination of organozinc reagents with *O*-benzoylhydroxylamines.¹⁴⁶ Lalic later developed a protocol for hindered aniline synthesis *via* copper-catalysed electrophilic amination of aryl boronic esters (Scheme 126).¹⁴⁷ The use of neopentyl glycol boronic ester is important for high yields, owing to a faster transmetalation compared to the corresponding ethylene glycol or pinacol boronic esters.

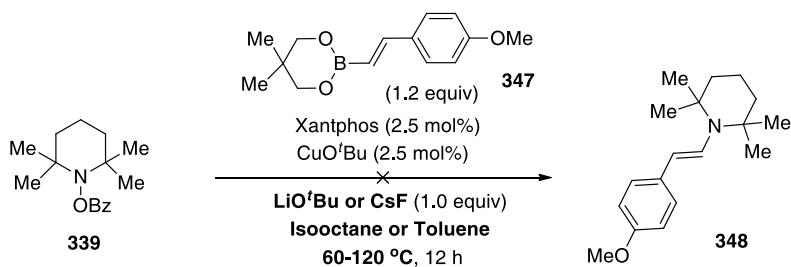
**Scheme 126:** Lalic's hindered aniline synthesis *via* copper-catalysed electrophilic amination of aryl boronic esters¹⁴⁷

Encouraged by these literature precedents, we began our initial studies based on Johnson's conditions, using **339** as our model amine electrophile (Scheme 127). Unfortunately, subjecting **339** to the reaction condition gave only unreacted starting material, even when the temperature was increased to 60 °C, indicating no copper insertion has taken place.



Scheme 127: Attempted electrophilic amination using Johnson's conditions

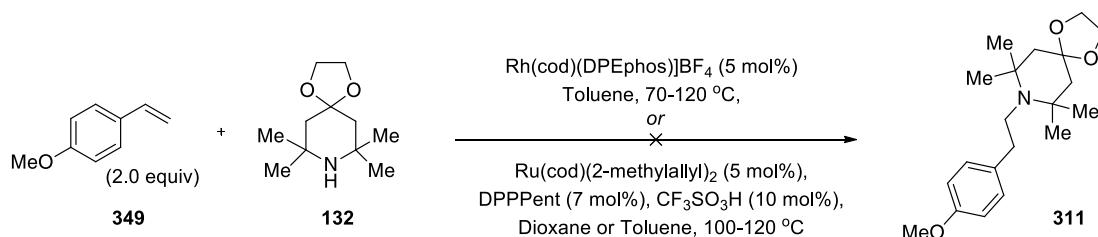
We next investigated Lalic's reaction conditions using styrenyl boronic ester 347. Disappointingly, after a brief survey of additives, solvents and temperature, only starting material could be recovered from the reactions (Scheme 128). Preformed copper(I) *tert*-butoxide/Xantphos complex was also tested in the reaction, but again, only starting material was recovered.



Scheme 128: Attempted electrophilic amination using Lalic's conditions

Anti-Markovnikov hydroamination of vinyl arenes (Scheme 124d):

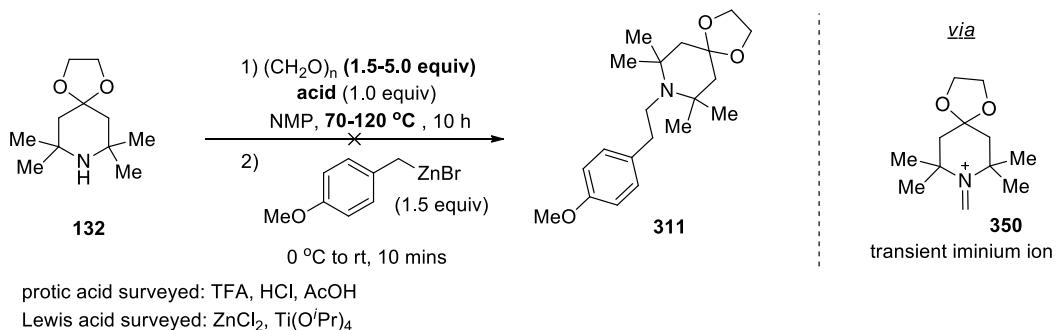
Hydroamination of vinyl arenes with a range of amines are known under both rhodium-¹⁴⁸ and ruthenium-catalysed¹⁴⁹ conditions. We investigated this approach using 132 as the model amine substrate and 4-methoxystyrene 349 as the alkene partner. Unfortunately, subjecting 132 to both the reported rhodium- and ruthenium-catalysed conditions resulted only in recovery of the starting material, even at elevated temperature (Scheme 129).



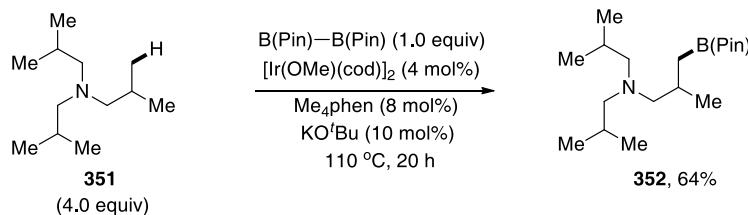
Scheme 129: Attempted anti-Markovnikov hydroamination of 4-methoxystyrene with 349

Mannich (Scheme 124d):

Ku *et. al.* reported an efficient synthesis of β -arylethylamines *via* an *in situ* formation of iminium ions, and this method was shown to be amenable to sterically hindered amines.¹⁵⁰ Encouraged by this report, we began investigation using **132** as the model substrate. Disappointingly, after a brief survey of Lewis/protic acids, equivalents of paraformaldehyde, solvent, temperature and reaction time, no conversion of the starting material to the desired product was observed (Scheme 130). The poor reactivity could be attributed to the poor conversion of the hindered amine to the transient iminium ion **350**. Given the lack of success of this approach, it was not pursued further.

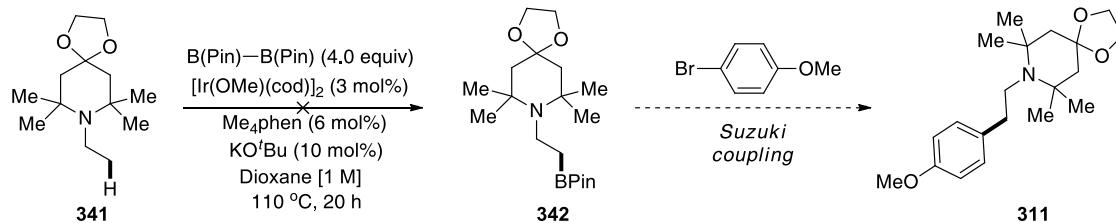
**Scheme 130:** Attempted Mannich reactions**C–H borylation/Suzuki (Scheme 124e):**

Whilst exploring other disconnection pathway to incorporate the 4-methophenylethyl unit, we became aware of an iridium-catalysed borylation of sterically hindered sp^3 C–H bonds reported by Suginome (Scheme 131).¹⁵¹ The installed boronic ester could then be converted to an aryl group *via* a traditional Suzuki cross coupling reaction.

**Scheme 131:** Suginome's iridium-catalysed borylation of sterically hindered sp^3 C–H bonds¹⁵¹

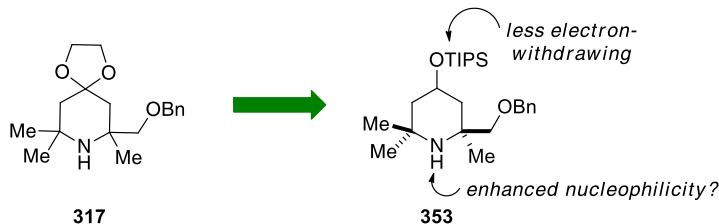
This approach was tested using **341** (Scheme 132). The iridium-catalysed borylation procedure had to be modified from the reported conditions because **341** was a solid, as opposed to liquids in all the reported examples by Suginome. Thus, a small quantity of dioxane was added (made up to 1 M concentration) to ensure efficient mixing. Also, the stoichiometry was reversed so that

341 became the limiting reagent. Disappointingly, this modified reaction conditions resulted in a complex mixture where neither desired boronic ester **342** or starting material **341** were recovered.



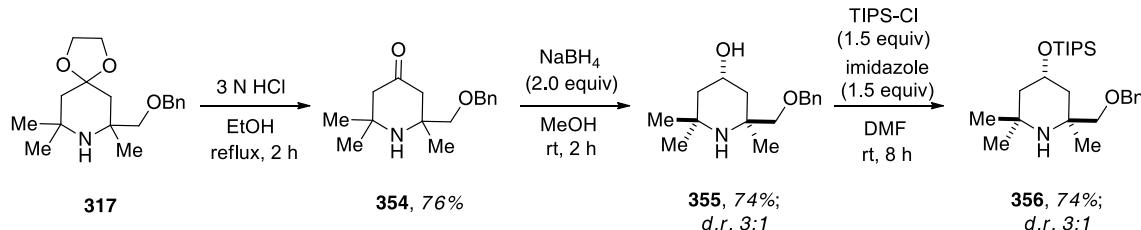
Scheme 132: Preparation and attempted iridium-catalysed $\text{sp}^3\text{C}-\text{H}$ borylation of **341**

Owing to the lack of the success of the aforementioned investigations, we next revisited the *N*-alkylation approach and focused on **317** for optimisation. We questioned whether replacing dioxolane in the 4-position of the piperidine ring with a less electron-withdrawing triisopropylsilyl-protected alcohol would enhance the nucleophilicity of the nitrogen atom and hence improve the reactivity (Scheme 133).



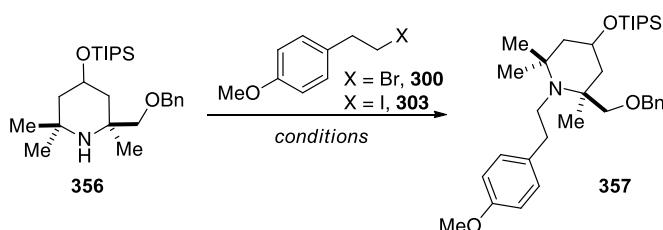
Scheme 133: Proposed hypothesis of enhancing nucleophilicity of the nitrogen atom

To test this hypothesis, **353** was prepared from **317** via three simple functional group manipulations (Scheme 134).



Scheme 134: Preparation of 356

The alkylation of **356** was then explored and the results are summarised in Table 11.

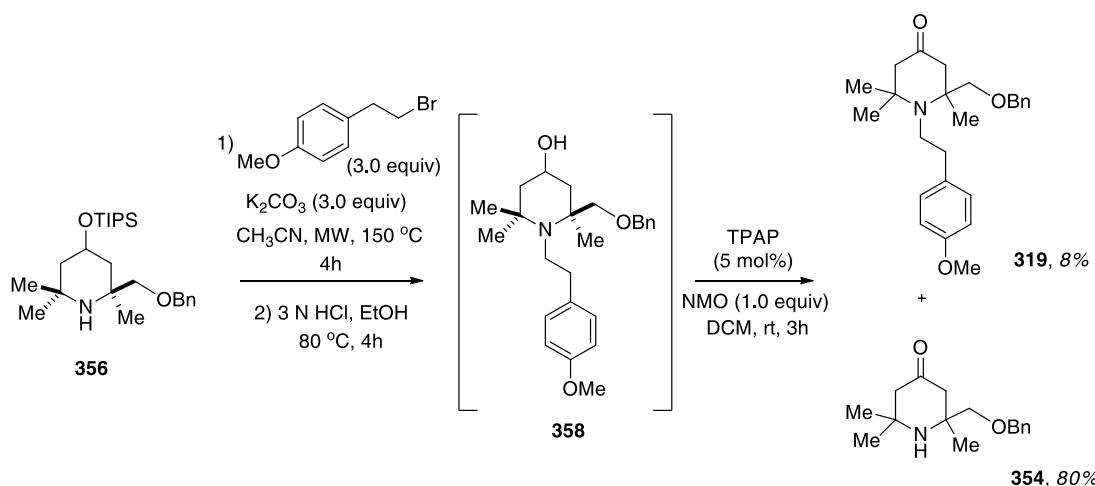
Table 11: Screening of *N*-alkylation conditions on **356**

Entry	Conditions	Yield ^a
1	Bromide (7.0 equiv), K ₂ CO ₃ (3.0 equiv), 120 °C, 16 h	15%
2	Bromide (7.0 equiv), K ₃ PO ₄ (3.0 equiv), 120 °C, 16 h	11%
3	Bromide (7.0 equiv), K ₂ CO ₃ (3.0 equiv), 18-crown-6, 120 °C, 16 h	14%
4	Iodide (7.0 equiv), K ₂ CO ₃ (3.0 equiv), 120 °C, 16 h	13%
5	NaH (2.0 equiv), bromide (3.0 equiv), DMF, rt to 100 °C, 16 h	0%
6	Bromide (3.0 equiv), K ₂ CO ₃ (3.0 equiv), CH ₃ CN, 150 °C, MW, 4 h	24%

^aYields determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

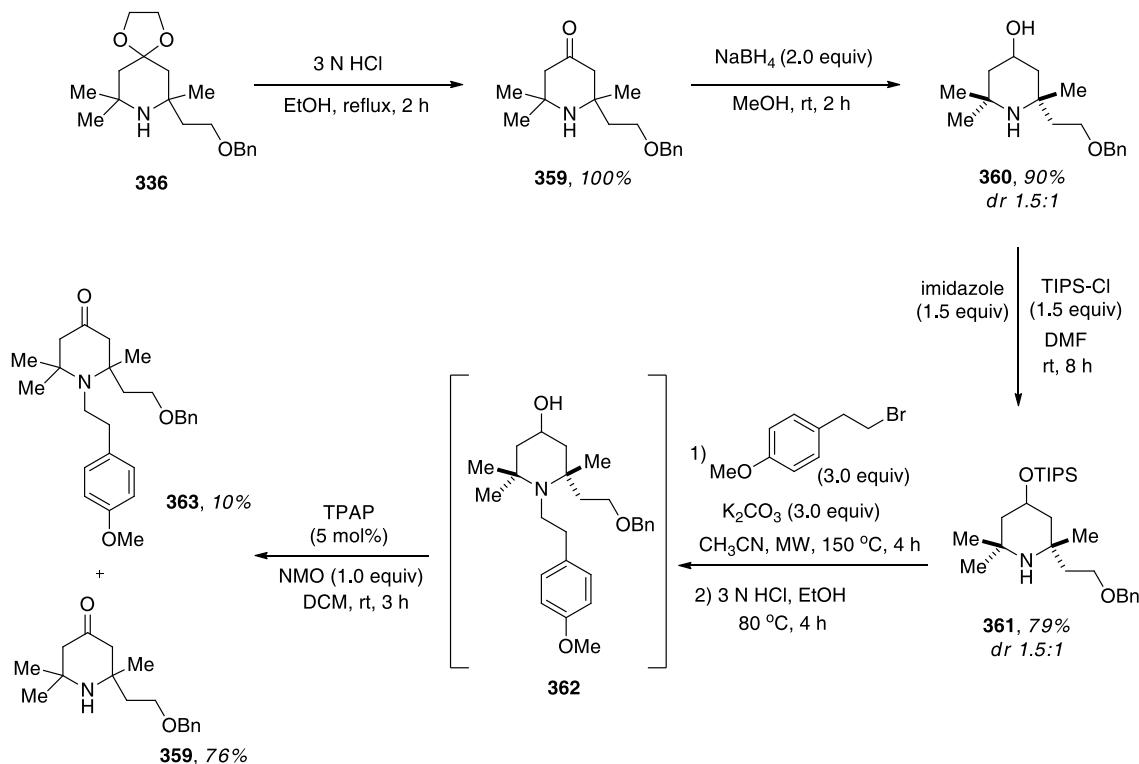
The majority of the reaction conditions attempted did show a quantifiable amount of product and using superheated acetonitrile in the microwave at 150 °C over 4 hours gave the best ¹H NMR yield of 24% (entry 6). However, isolation proved to be extremely difficult, especially as the product was present as a mixture of diastereoisomers. We envisaged purification could be made simpler if it was carried out after the subsequent triisopropylsilyl group removal, followed by an oxidation to ketone **319** to avoid the diastereoisomeric mixture isolation issue.

To this end, the reaction mixture after the alkylation step was carried straight into the deprotection step after a simple filtration and a solvent switch to ethanol. After an aqueous work up, the crude alcohol **358** was taken directly to the oxidation step, which was performed using tetrapropylammonium perruthenate. Subsequent purification by flash chromatography delivered ketone **319** in a mere 8% yield, as well as recovery of 80% of **354** (Scheme 135).



Scheme 135: Preparation of ketone **319** *via* an alkylation/deprotection/oxidation sequence

This sequence was also employed for the synthesis of astemizole analogue **289**, delivering ketone **363** in 10% yield as well as 76% of recovered **359** (Scheme 136).

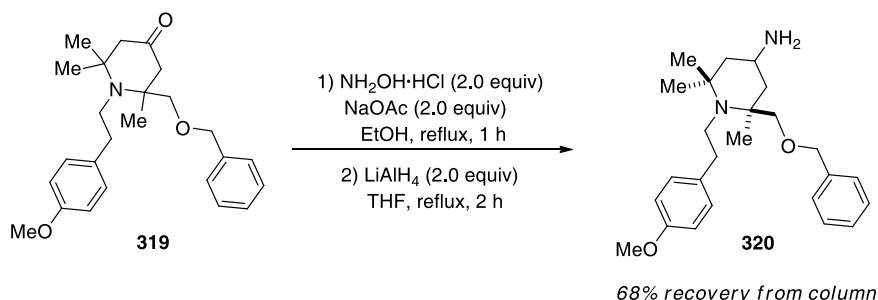


Scheme 136: Synthesis of ketone **363** *via* the optimised process

3.3.5 Installation of primary amine *via* reductive amination

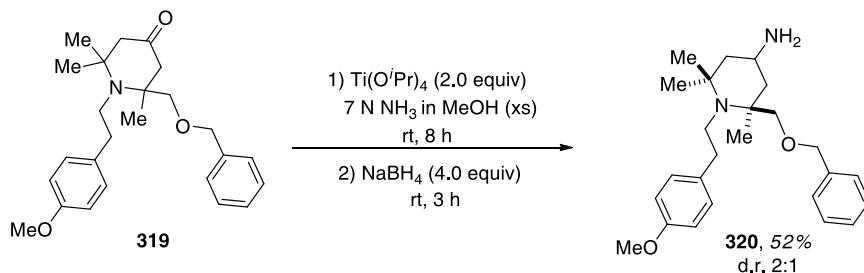
With ketones **319** and **363** in hand, the next step in the synthesis was to install the primary amine unit, *via* reductive amination. We decided to focus on **319** and proceed through the subsequent

steps to the final compound **288**. Reductive amination *via* formation of oxime followed by reduction with lithium aluminium hydride did give 68% of the desired amine **320**, as a 1.4:1 mixture of diastereoisomers. However, ¹H NMR analysis showed there were other minor aliphatic impurities which could not be removed, despite attempting the chromatography using Florisil® or basic alumina as absorbents (Scheme 137). Buchwald-Hartwig amination was also attempted on this material with the hope of better separation after the amination step, but that also proved unsuccessful. Replacing lithium aluminum hydride with the milder reducing agent lithium borohydride gave a much lower recovery (~62%) after aqueous workup as well as a more complex reaction profile.



Scheme 137: Reductive amination of **319** *via* oxime

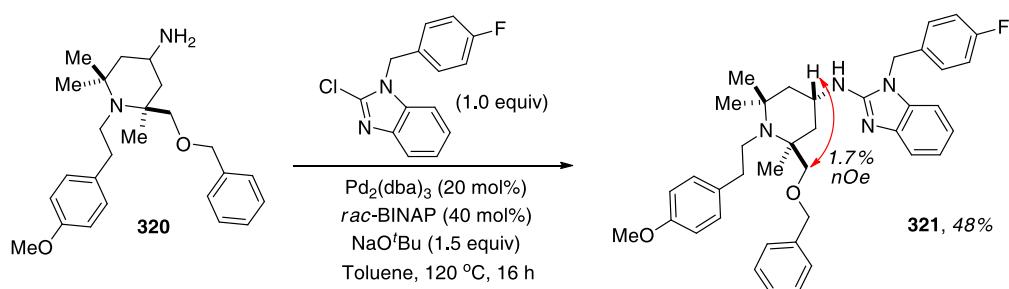
The next conditions attempted were the previously validated one-pot titanium isopropoxide-mediated reductive amination procedure (section 3.3.1.3). We were pleased to find that this procedure successfully delivered pure amine **320**, as a 2:1 mixture of diastereoisomers, in 52% yield after purification by silica gel flash chromatography (Scheme 138). The structure of the major diastereoisomer could not be definitively determined given the complex nature of the ¹H NMR.



Scheme 138: One-pot titanium isopropoxide-mediated reductive amination of **319**

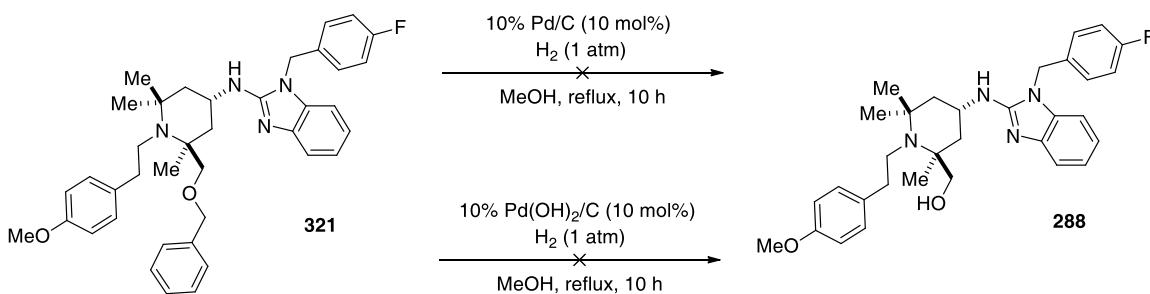
3.3.6 Buchwald-Hartwig amination and deprotection end-game

The diastereoisomeric mixture of amine **320** was next subjected to the established Buchwald-Hartwig conditions employed previously. However, only starting material could be observed by LCMS at the end of the reaction. Pleasingly, it was found that increasing the reaction temperature from 85 °C to 120 °C resulted in conversion to the desired product **321**, as indicated by LCMS. Chromatographic separation succeeded in isolation of only one of the diastereoisomers, in 48% yield, with the structure of the diastereoisomer confirmed by 1D nOe analysis (Scheme 139). LCMS and ¹H NMR analyses showed that the other diastereoisomer was present, but it could not be isolated cleanly.



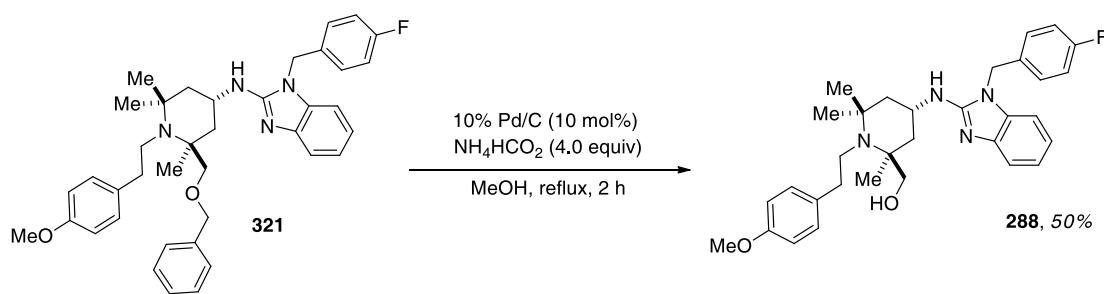
Scheme 139: Buchwald-Hartwig amination of **320**

With the framework of the functionalised astemizole complete, the final step in the synthesis was the removal of the benzyl group appended to the alcohol. Trial hydrogenation of the benzyl group with palladium on carbon in methanol at reflux showed no conversion. Replacement of palladium on carbon with the more reactive palladium hydroxide on carbon (Pearlman's catalyst) gave no success either (Scheme 140).



Scheme 140: Trial benzyl deprotection conditions

Gratifyingly, transfer hydrogenation conditions proved to be more successful. With ammonium formate as the hydrogen source and heating at reflux in methanol, desired alcohol **288** was obtained in 50% yield (Scheme 141).

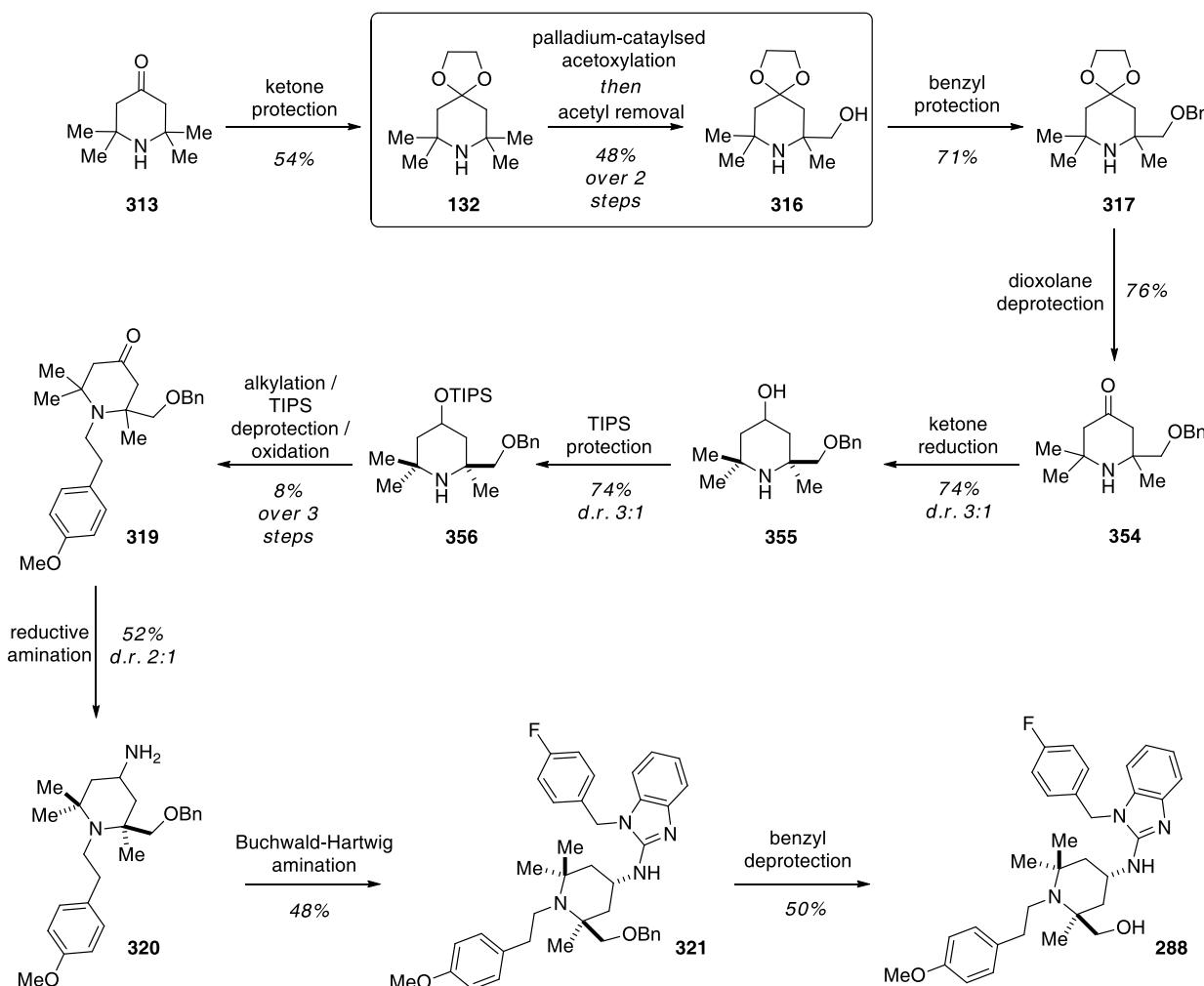


Scheme 141: Transfer-hydrogenation conditions for benzyl deprotection of **321**

Regrettably, synthesis of the other astemizole analogue **335** and hERG binding assay of **288** could not be completed in time.

3.3.7 Summary

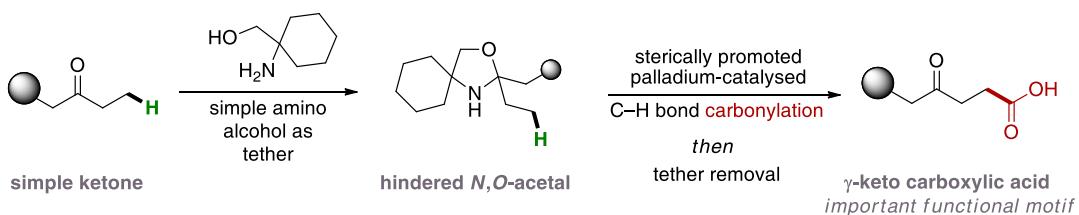
In summary, the synthesis of functionalised astemizole analogue **288** was completed in 13 steps, with an overall yield of 0.07%, from 2,2,6,6-tetramethylpiperidin-4-one **132** (Scheme 142). The key challenge of the synthesis was the installation of the 4-methoxyphenylethyl group onto the hindered nitrogen. In the end, a three-step telescoped procedure enabled access to ketone intermediate **319**, albeit in very low yield. Alternative strategies to incorporate this unit was investigated but proved unsuccessful. Regrettably, the hERG profile of this compound could not be established in time. The installed hydroxyl group nevertheless provides opportunities for further derivitisation to gain access to further analogues of **288**.



Scheme 142: Summary of the synthesis of **288**

4 Conclusions and Outlook

The first part of this thesis described the development and application of a sterically promoted C–H carbonylation strategy, enabling access to a diverse range of γ -keto carboxylic acids. Key to this strategy was the temporary conversion of simple ketones into hindered secondary amines that facilitated a sterically promoted palladium-catalysed C–H activation (Scheme 143). Directed by the nitrogen atom of the hindered *N,O*-acetals, C–H activation occurred readily to form the kinetically favoured five-membered palladacycle. Subsequent carbonylation and removal of the steric tether furnished a variety of γ -keto carboxylic acids, which are important building blocks in the synthesis of medicinally relevant heterocycles.

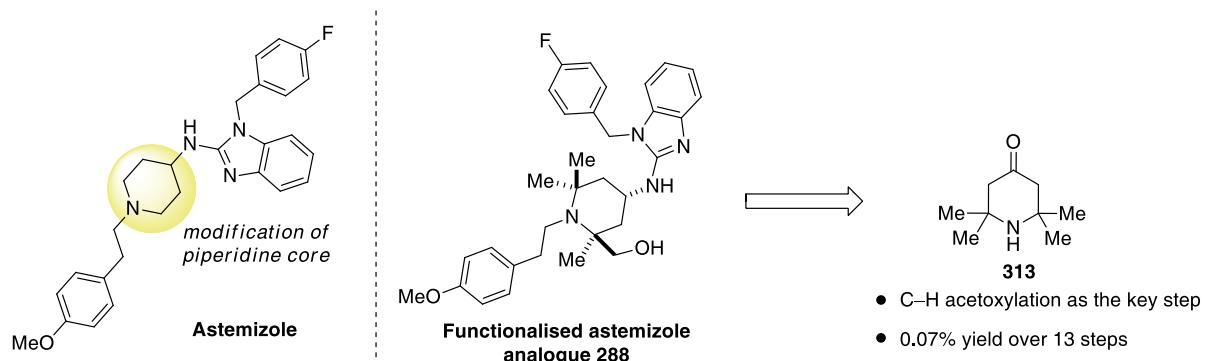


Scheme 143: Sterically promoted palladium(II)-catalysed β -C–H carbonylation of ketones

Given the stability of the palladacycle, it can be envisaged that other transformations on this palladacycle may be possible; therefore future work could involve broadening the scope of transformations using this hindered *N,O*-acetal scaffold. Early studies by Dr Calleja demonstrated that the *N,O*-acetals could undergo C–H alkenylation to yield structurally complex fused pyrrolidines as single diastereoisomers (section 2.3.6). A second key area of investigation could be functionalisation of the more challenging methylene sp^3 C–H. As well as being a logical and desirable extension to the methodology, it would also offer a unique opportunity to investigate the development of asymmetric C–H functionalisation, most likely through the use of chiral ligands. The use of mono-protected amino acids as ligands to induce chirality in C–H arylation of 2,2,6,6-tetramethylpiperidine has been the subject of investigation within the group and early results have been promising.¹¹⁵

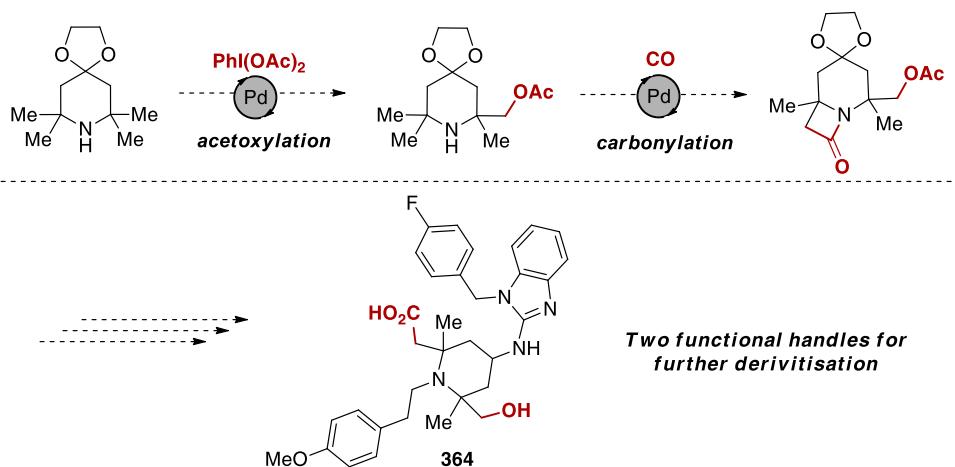
The second part of this thesis described the application of palladium-catalysed C–H functionalisations to the synthesis of astemizole analogues, with the intention of reducing hERG inhibition through increasing the steric bulk of the tertiary amine. Proceeding through four-membered palladacycles, palladium-catalysed acetoxylation and carbonylation of the 2,2,6,6-

tetramethylpiperidine core served as the key step in introduction of polar functionalities in close proximity to the nitrogen atom. Functionalised astemizole analogue **288** was synthesised in 13 linear steps, with the key C–H functionalisation being the second step of the synthesis (Scheme 144). The synthesis of **288** was an excellent example of the potential offered by novel C–H functionalisation for incorporation of functional handles into inert positions of complex molecules.



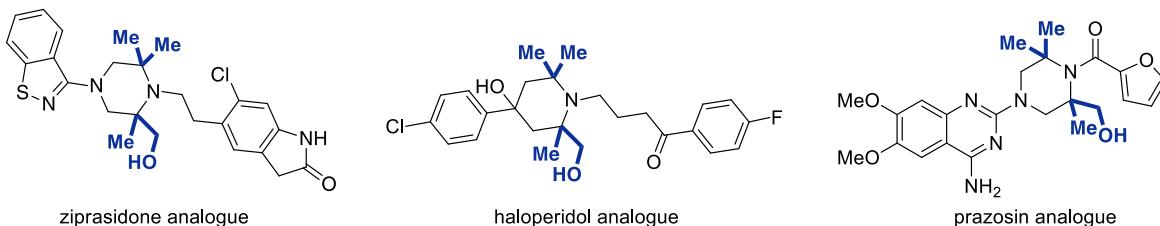
Scheme 144: Synthesis of **288** completed in 13 steps starting from **313**

To improve the utility of this methodology, a late stage functionalisation of the 2,2,6,6-tetramethylpiperidine moiety would be ideal because 1) it eliminates the need for protecting groups as the reactive functionalities are added at the end of the synthesis, and 2) it streamlines syntheses of analogues through rapid diversification of the piperidine core at a late stage. Also, it can be envisaged that iterative sp^3 C–H functionalisation of the piperidine core could be possible to generate analogues with even more complexity. For example, an iterative C–H acetoxylation/carbonylation sequence could allow access to astemizole analogues such as **364** (Scheme 145).



Scheme 145: Potential iterative C–H functionalisation strategy

This methodology can potentially be applied to synthesise analogues of other known hERG channel blockers (Scheme 146).



Scheme 146: Potential analogues of other known hERG channel blockers

Given the difficulty encountered with installation of the 4-methoxyphenylethyl unit, another area for further research could be to improve on existing methods to functionalise hindered amines, which remains a long-standing challenge in synthetic chemistry.

Palladium catalysis remains a focus of research within our group and we have shown recently that sp³ C–H carbonylation can be carried out on less hindered amines, thereby broadening the range of amines that can be functionalised. This advancement offers further opportunities to synthesise analogues of amine-containing drugs with different steric properties around the amine functionality. This would be of great benefits to medicinal chemists in expanding chemical space or to fine-tune the pharmaceutical properties of active substances.

5 Experimental

5.1 General Information:

Data Collection: ^1H NMR spectra were recorded at 400 or 500 MHz on a Bruker DPX-400 or 500 spectrometer. ^{13}C NMR spectra were recorded at 100 or 125 MHz on the same spectrometers. ^{19}F NMR spectra were recorded at 376 MHz on a Bruker DPX 400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent ($\text{CDCl}_3 - \delta_{\text{H}} = 7.26$ ppm, $\delta_{\text{C}} = 77.0$ ppm; $\text{MeOD} - \delta_{\text{H}} = 3.31$ ppm, $\delta_{\text{C}} = 49.1$ ppm; $\delta_{\text{C}} = 1.39$ ppm), and are measured to the centre of the signal except in the case of multiplets which are quoted as a range to the nearest 0.01 ppm. Coupling constants (J) are quoted in Hertz (Hz) to the nearest 0.1 Hz. DEPT-135 and 2-dimensional experiments (COSY, HMBC, HMQC) were used where appropriate to assign structures. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) and multiplet (m).

Equipment: High Resolution Mass Spectrometry (HRMS) samples were sent to the EPSRC mass spectrometry service at Swansea for analysis. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer with automatic background subtraction. Samples were prepared as neat films or run as solids, with absorptions reported in wavenumbers (cm^{-1}). Melting points (m.p.) were recorded on a Gallenkamp melting point apparatus and are reported uncorrected. Liquid Chromatography-Mass Spectrometry (LCMS) was performed on a Shimadzu UFLC-XR/LCMS 2020 system using a Shim-pack XR-ODS column (C18, 2.2 μm , 3.0 mm x 50 mm). The LCMS acetonitrile (Rathburn) was pre-treated with water (5% vol) and formic acid (12.5 mM) and the LCMS water (Rathburn) was pre-treated with formic acid (25 mM) and ammonium acetate (10 mM). Gas Chromatography-Mass Spectrometry (GCMS) was performed on a Shimadzu MDGC/GCMS-2010 system. Microwave experiments were performed in a Biotage® Initiator+ System.

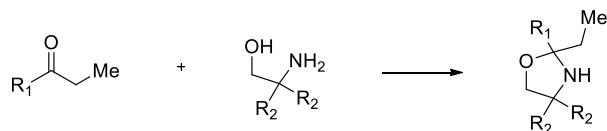
Chromatography: Flash chromatography was carried out on silica gel 60 (200-400 mesh) and activated basic alumina (~150 mesh). Thin layer chromatography (TLC) was carried out on Kieselgel 60 PF254 (Merck) 0.2 mm plates. Plates were visualised using ultraviolet light ($\lambda = 254$ nm) and by chemical staining with acidic potassium permanganate/ ceric ammonium molybdate solutions followed by heating.

Solvents: All anhydrous solvents were dried by standard techniques and freshly distilled before use. Diethyl ether and tetrahydrofuran (THF) were distilled from lithium aluminium hydride; acetonitrile, dichloromethane and toluene from calcium hydride; and triethylamine from potassium hydroxide. 1,2-Dichloroethane (DCE) and 1,4-dioxane were purchased in anhydrous form from Acros Organics. Petroleum ether is 40–60 b.p. unless otherwise stated.

Reagents: All reagents were purchased at the highest commercial quality and used without further purification. All reactions were monitored by TLC and or ^1H NMR spectra taken from reaction samples, with NMR yields determined by ^1H NMR with reference to 1,1,2,2-tetrachloroethane as an internal standard. Reactions were carried out under atmosphere of N_2 unless otherwise stated. All reagents were used as supplied without further purification unless otherwise stated.

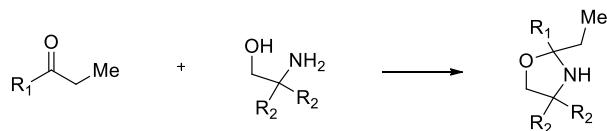
5.2 C–H carbonylation: Synthesis of *N,O*-ketals

General Procedure A for the formation of *N,O*-ketals



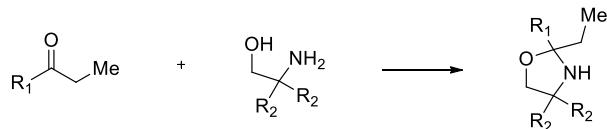
To a dry round bottom flask, equipped with a stir bar, was charged the noted amount of amino alcohol and ketone in toluene (1 M), followed by addition of *para*-toluenesulfonic acid (0.1 equiv). The flask was equipped with a Dean-Stark apparatus and the solution was heated under reflux for 16 hours. The solution was then allowed to cool to room temperature and solvent removed under reduced pressure. The crude was further purified by either bulb-to-bulb distillation or flash chromatography on silica gel to afford the desired *N,O*-ketal.

General Procedure B for the formation of *N,O*-ketals

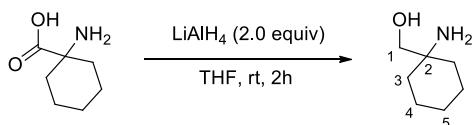


To a sealed tube was charged the noted amount of amino alcohol and ketone as the solvent, followed by addition of *para*-toluenesulfonic acid (0.1 equiv) and 4 \AA molecular sieve ($\sim 10 \text{ mg/mmol}$). The tube was sealed and heated at 120 °C for 16 hours. The solution was then allowed to cool to room temperature and solvent removed under reduced pressure. The crude was further purified by flash chromatography on silica gel to afford the desired *N,O*-ketal.

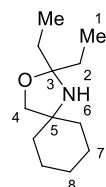
General Procedure C for the formation of *N,O*-ketals



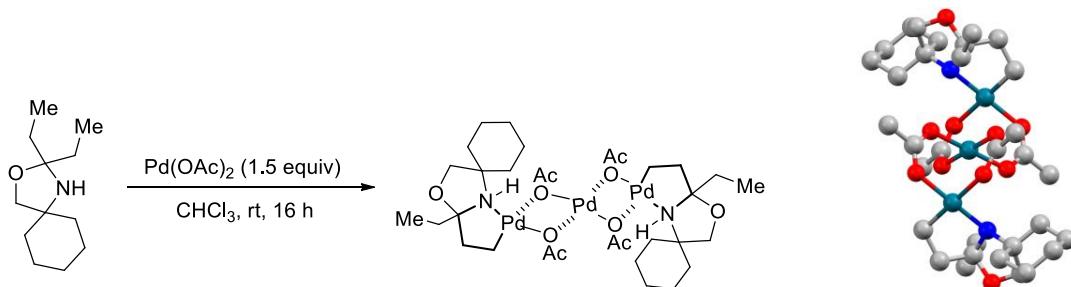
To a sealed tube was charged the noted amount of amino alcohol and ketone in toluene (3 M), followed by addition of *para*-toluenesulfonic acid (0.1 equiv) and 4 \AA molecular sieve ($\sim 10 \text{ mg/mmol}$). The tube was sealed and heated at 120 °C for 16 hours. The solution was then allowed to cool to room temperature and solvent removed under reduced pressure. The crude was further purified by flash chromatography on silica gel to afford the desired *N,O*-ketal.

(1-Aminocyclohexyl)methanol (182)

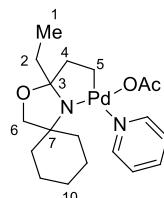
To a solution of 1-aminocyclohexanecarboxylic acid (2.00g, 14.0 mmol, 1.0 equiv) in dry tetrahydrofuran (30 mL) was added lithium aluminium hydride (1M in tetrahydrofuran, 28ml, 28.0 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 6 hours and then cooled to 0 °C in an ice bath. To the cooled mixture was added water (1.1 mL) dropwise, followed by 1 N NaOH (3.3 mL) and then water (1.1 mL). To the resulting slurry was added magnesium sulfate and the mixture was warmed to room temperature for 20 minutes. The mixture was then filtered and the filter cake was washed with diethyl ether. The filtrate was then concentrated *in vacuo* to yield the title compound as a colourless oil (1.46 g, 10.1 mmol, 72%). The crude material was used in the subsequent condensation without further purification. **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3320, 3210, 3305 (br), 3210, 2980, 1562, 1409, 1203, 1142, 987, 857, 831; **¹H NMR** (500 MHz, CDCl₃) δ 3.31 (s, 2H, H-1), 1.64 – 1.26 (m, 10H, H-3, H-4 and H-5); **¹³C NMR** (126 MHz, CDCl₃) δ 70.3, 52.0, 35.5, 26.1, 21.9. The physical data were identical in all respect to that previously reported.¹⁵²

2,2-Diethyl-3-oxa-1-azaspiro[4.5]decane (183)

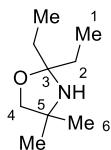
Prepared according to General Procedure A using (1-aminocyclohexyl)methanol **182** (3.13 g, 24.2 mmol, 1.0 equiv) and 3-pentanone (3.13 g, 36.3 mmol, 1.5 equiv); purification by bulb-to-bulb distillation afforded the title compound as a colourless oil (3.44 g, 17.44 mmol, 72%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2965, 2929, 2854, 1450, 1350, 1196, 1055, 920, 815, 759, 668; **¹H NMR** (500 MHz, CDCl₃) δ 3.63 (s, 2H, H-4), 1.88 – 1.18 (m, 14H, H-2, H-6, H-7 and H-8), 0.91 (t, $J = 7.5$ Hz, 6H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 98.8, 74.5, 62.0, 38.1, 30.5, 25.4, 24.0, 8.7; m/z **HRMS** (ESI) found [M+H]⁺ 198.1852, C₁₂H₂₄NO requires 198.1852.

Trinuclear *N,O*-ketal palladacycle (184)

To a solution of *2,2-diethyl-3-oxa-1-azaspiro[4.5]decane* **183** (500 mg, 2.54 mmol, 1.0 equiv) in chloroform (25 mL) was added palladium(II) acetate (853 mg, 3.81 mmol, 1.5 equiv) and the resulting brown solution was stirred at room temperature for 16 hours. The solution was filtered through a pad of Celite®, eluting with chloroform and the solvent was then removed under vacuum. The residue was redissolved in the minimum amount of toluene, and the toluene solution was added dropwise to 50 mL of petroleum ether. A solid crashed out and was filtered off, rinsed with petroleum ether and dried under vacuum to afford the palladacycle (1.79 g, 1.82 mmol, 72%) as a green solid. Crystals were grown by slow diffusion of acetone in a chloroform solution of the palladacycle at 0 °C. X-Ray crystal structure is deposited in the Cambridge Crystallographic Data Centre CCDC 997660.



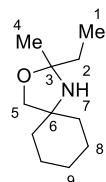
Resolved NMR spectra were obtained by treating the trinuclear *N,O*-ketal palladacycle with deuterated pyridine (2 drops added to 15 mg of palladacycle in chloroform) to generate the corresponding *N,O*-ketal palladacycle pyridine complex. **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2971, 2292, 1738, 1566, 1366, 1217, 1045, 661. **¹H NMR** (500 MHz, CDCl₃) δ 3.63 (s, 2H, H-4), 1.88 – 1.18 (m, 14H, H-2, H-6, H-7 and H-8), 0.91 (t, J = 7.5 Hz, 6H, H-1). **¹³C NMR** (126 MHz, CDCl₃) δ 98.8, 74.5, 62.0, 38.1, 30.5, 25.4, 24.0, 8.7.

2,2-Diethyl-4,4-dimethyloxazolidine (191)

Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (5.60 g, 62.8 mmol, 1.0 equiv) and 3-pentanone (8.12 g, 94.0 mmol, 1.5 equiv); purification by a silica plug, eluting with 0 to 50% diethyl ether in petroleum ether afforded the title compound as a colourless oil (4.90 g, 31.2 mmol, 56%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2967, 2939, 2879, 1460, 1381, 1364, 1198, 1056, 999, 918, 825, 757; **¹H**

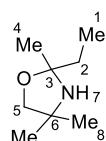
NMR (500 MHz, CDCl₃) δ 3.58 (s, 2H, H-4), 1.64 (q, 4H, *J* = 7.5 Hz, H-2), 1.26 (s, 6H, H-6), 0.92 (t, *J* = 7.5 Hz, 6H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 99.7, 76.8, 58.8, 30.4, 28.5, 8.7. The physical data were identical in all respect to that previously reported.¹⁵³

2,2-Diethyl-3-oxa-1-azaspiro[4.5]decane (198a)

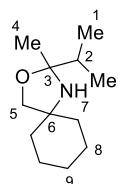


Prepared according to General Procedure A using (*1-aminocyclohexyl)methanol* **182** (4.50 g, 34.9 mmol, 1.0 equiv) and 2-butanone (3.77 g, 52.2 mmol, 1.5 equiv); purification by bulb-to-bulb distillation afforded the title compound as a colourless oil (3.9 g, 21.3 mmol, 61%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2972, 2929, 2854, 1450, 1371, 1283, 1209, 1114, 1086, 866, 810, 748; **¹H NMR** (500 MHz, CDCl₃) δ 3.66 (d, *J* = 8.3 Hz, 1H, H-5), 3.58 (d, *J* = 8.3 Hz, 1H, H-5), 1.73 – 1.40 (m, 10H, H-2, H-7 and H-8), 1.38 – 1.29 (m, 2H, H-9), 1.30 (s, 3H, H-4), 0.93 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 96.6, 74.4, 62.2, 38.1, 37.8, 33.9, 25.9, 25.4, 24.0, 23.9, 9.0; **m/z HRMS** (ESI) found [M+H]⁺ 184.1693, C₁₁H₂₁NO requires 184.1696.

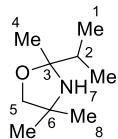
2-Ethyl-2,4,4-trimethyloxazolidine (198b)



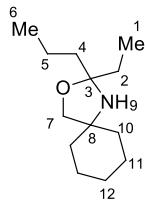
Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (4.50 g, 50.5 mmol, 1.0 equiv) and 2-butanone (5.46 g, 76.0 mmol, 1.5 equiv); purification by a silica plug, eluting with 0 to 50% diethyl ether in petroleum ether afforded the title compound as a colourless oil (3.90 g, 27.2 mmol, 54%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2967, 2931, 1463, 1372, 1201, 1057, 804; **¹H NMR** (500 MHz, CDCl₃) δ 3.61 (d, *J* = 8.1 Hz, 1H, H-5), 3.53 (d, *J* = 8.1 Hz, 1H, H-5), 1.61 (apparent septet, *J* = 6.3 Hz, 2H, H-2), 1.32 (s, 3H, H-4), 1.26 (s, 3H, H-8), 1.23 (s, 3H, H-8), 0.94 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 97.5, 76.9, 59.1, 34.0, 28.4, 28.1, 25.7, 9.0; **m/z HRMS** (ESI) found [M+H]⁺ 144.1380, C₈H₁₇NO requires 144.1383.

2-Isopropyl-2-methyl-3-oxa-1-azaspiro[4.5]decane (199a)

Prepared according to General Procedure A using (*1-aminocyclohexyl)methanol* **182** (2.90 g, 22.5 mmol, 1.0 equiv) and 3-methylbutan-2-one (2.90 g, 33.7 mmol, 1.5 equiv); purification by bulb-to-bulb distillation afforded the title compound as a colourless oil (3.90 g, 19.8 mmol, 88%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2971, 2929, 2853, 1739, 1448, 1366, 1229, 1217, 1055, 891, 860, 806, 784; **¹H NMR** (500 MHz, CDCl₃) δ 3.66 (d, J = 8.3 Hz, 1H, H-5), 3.57 (d, J = 8.3 Hz, 1H, H-5), 1.76 (septet, J = 7.0 Hz 1H, H-2), 1.72 – 1.25 (m, 10H, H-7, H-8 and H-9), 1.22 (s, 3H, H-4), 0.95 (d, J = 7.0 Hz, 3H, H-1), 0.93 (d, J = 7.0 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 98.9, 74.3, 62.1, 38.2, 37.8, 37.8, 25.4, 24.1, 23.9, 22.1, 18.1, 18.0; m/z **HRMS** (ESI) found [M+H]⁺ 198.1851, C₁₂H₂₃NO requires 198.1852.

2-Isopropyl-2,4,4-trimethyloxazolidine(199b)

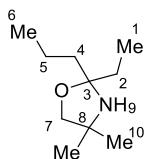
Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (5.00 g, 56.1 mmol, 1.0 equiv) and 3-methylbutan-2-one (7.25 g, 84.0 mmol, 2.0 equiv); purification by a silica plug, eluting with 0 to 50% diethyl ether in petroleum ether afforded the title compound as a colourless oil (3.80 g, 24.2 mmol, 43%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2962, 2872, 1466, 1371, 1194, 1056, 907, 856, 789; **¹H NMR** (500 MHz, CDCl₃) δ 3.62 (d, J = 8.0 Hz, 1H, H-5), 3.51 (d, J = 8.0 Hz, 1H, H-5), 1.82 (septet, J = 6.8 Hz, 1H, H-2), 1.27 (s, 3H, H-4), 1.24 (s, 3H, H-8), 1.22 (s, 3H, H-8), 0.96 (d, J = 6.8 Hz, 3H, H-1), 0.94 (d, J = 6.9 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 99.8, 76.9, 59.0, 37.9, 28.5, 28.2, 21.9, 18.1, 18.0; m/z **HRMS** (ESI) found [M+H]⁺ 158.1536, C₉H₁₉NO requires 158.1539.

2-Ethyl-2-propyl-3-oxa-1-azaspiro[4.5]decane (200a)

Prepared according to General Procedure A using (*1-aminocyclohexyl)methanol* **182** (1.00 g, 7.74 mmol, 1.0 equiv) and 3-hexanone (1.16 g, 11.6 mmol, 1.5 equiv); purification by flash chromatography on silica

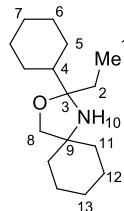
gel, eluting with 0 to 10% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (533 mg, 2.51 mmol, 33%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.21; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2929, 2854, 1450, 1376, 1251, 1192, 1175, 1055, 947, 930, 899, 817, 739; **¹H NMR** (500 MHz, CDCl₃) δ 3.61 (d, *J* = 8.4 Hz, 1H), 3.60 (d, *J* = 8.4 Hz, 1H), 1.72 – 1.41 (m, 11H, H-2, H-4, H-10, H-11 and H-12), 1.40 – 1.24 (m, 5H, H-5, H-10 and H-11), 0.91 (t, *J* = 7.3 Hz, 3H, H-6), 0.88 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 98.5, 74.4, 62.0, 40.5, 38.1, 38.1, 31.1, 25.4, 24.0, 24.0, 17.7, 14.5, 8.8; *m/z* **HRMS** (ESI) found [M+H]⁺ 212.2007, C₁₃H₂₆NO requires 212.2007.

2-Ethyl-2-propyl-3-oxa-1-azaspiro[4.5]decane (200b)



Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (500 mg, 5.61 mmol, 1.0 equiv) and 3-hexanone (843 mg, 8.41 mmol, 1.5 equiv); purification by a silica plug, eluting with 0 to 50% diethyl ether in petroleum ether afforded the title compound as a colourless oil (461 mg, 2.69 mmol, 48%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.21; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2936, 2925, 2858, 1428, 1364, 1198, 1127, 1056, 1001, 918, 825; **¹H NMR** (400 MHz, CDCl₃) δ 3.54 (s, 2H, H-7), 1.67 – 1.48 (m, 4H, H-2 and H-4), 1.34 (apparent sextet, *J* = 7.5 Hz, 2H, H-5), 1.23 (s, 3H, H-10), 1.21 (s, 3H, H-10), 0.91 (t, *J* = 7.3 Hz, 3H, H-6), 0.89 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (101 MHz, CDCl₃) δ 99.8, 77.2, 59.2, 40.7, 31.4, 28.9, 28.9, 18.1, 14.9, 9.2; *m/z* **HRMS** (ESI) found [M+H]⁺ 172.1625, C₁₀H₂₂NO requires 172.1623.

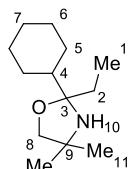
2-Cyclohexyl-2-ethyl-3-oxa-1-azaspiro[4.5]decane (201a)



Prepared according to General Procedure B using (*1*-aminocyclohexyl)methanol **182** (800 mg, 6.19 mmol, 1.0 equiv) and 1-cyclohexylpropan-1-one (2.87 mL, 18.6 mmol, 3.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (250 mg, 0.99 mmol, 17%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.31; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2923, 2851, 1450, 1319, 1116, 1058, 951, 891, 825; **¹H NMR** (500 MHz, CDCl₃) δ 3.62 (d, *J* = 8.1 Hz, 1H, H-8), 3.57 (d, *J* = 8.1 Hz, 1H, H-8), 1.86 – 1.72 (m, 4H, c-hexyl CHs),

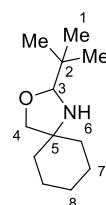
1.70 – 1.47 (m, 10H, H-4, H-2, c-hexyl CHs), 1.37 – 0.93 (m, 9H, c-hexyl CHs), 0.86 (t, $J = 7.5$ Hz, 3H, H-1); ^{13}C NMR (126 MHz, CDCl_3) δ 100.3, 74.8, 61.7, 44.2, 38.4, 38.0, 28.4, 27.8, 27.5, 26.8, 26.7, 26.5, 25.4, 24.2, 24.0, 8.3; m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 252.2324, $\text{C}_{16}\text{H}_{30}\text{NO}$ requires 252.2322.

2-Cyclohexyl-2-ethyl-4,4-dimethyloxazolidine (201b)

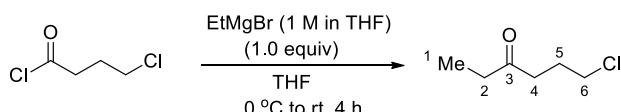


Prepared according to General Procedure B using 2-amino-2-methylpropan-1-ol (1.0 g, 11.2 mmol, 1.0 equiv) and 1-cyclohexylpropan-1-one (5.19 mL, 33.7 mmol, 3.0 equiv): purification by flash chromatography on silica gel, eluting with 0 to 30% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (261 mg, 1.23 mmol, 11%); R_f (ethyl acetate in petroleum ether, 20%): 0.21; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2963, 2924, 2852, 1975, 1451, 1381, 1364, 1191, 1057, 890, 826, 757, 672; ^1H NMR (500 MHz, CDCl_3) δ 3.59 (d, $J = 7.9$ Hz, 1H, H-8), 3.52 (d, $J = 7.9$ Hz, 1H, H-8), 1.90 – 1.73 (m, 4H, H-5 and H-6), 1.73 – 1.57 (m, 4H, H-2, H-4 and H-6), 1.26 (s, 3H, H-11), 1.24 (s, 3H, H-11), 1.23 – 1.09 (m, 3H, H-5 and H-6), 1.02 (apparent pentet, $J = 7.2$ Hz, 2H, H-7), 0.88 (t, $J = 7.5$ Hz, 3H, H-1); ^{13}C NMR (126 MHz, CDCl_3) δ 101.3, 77.0, 58.6, 44.2, 28.9, 28.6, 28.4, 27.8, 27.4, 26.8, 26.6, 26.5, 8.3; m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 212.2010, $\text{C}_{11}\text{H}_{18}\text{NO}_2$ requires 212.2009.

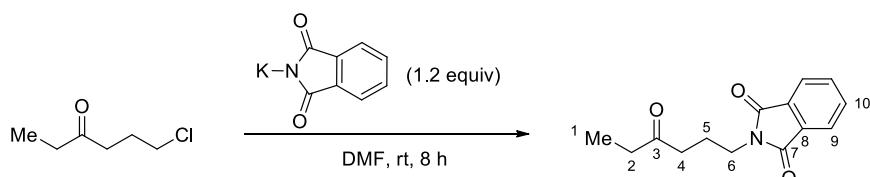
2-(*Tert*-butyl)-3-oxa-1-azaspiro[4.5]decane (202a)



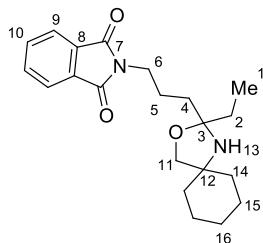
Prepared according to General Procedure A using (*1-aminocyclohexyl)methanol* **182** (1.20 g, 9.30 mmol, 1.0 equiv) and trimethylacetaldehyde (1.20 g, 14.0 mmol, 1.5 equiv); purification by bulb-to-bulb distillation afforded the title compound as a colourless oil (1.39 g, 7.07 mmol, 76%); IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2971, 2929, 2855, 1739, 1481, 1449, 1366, 1229, 1217, 1110, 1033, 910, 820, 663; ^1H NMR (500 MHz, CDCl_3) δ 4.21 (s, 1H, H-3), 3.61 (d, $J = 7.7$ Hz, 1H, H-4), 3.27 (d, $J = 7.7$ Hz, 1H, H-4), 1.98 – 1.13 (m, 10H, H-6, H-7 and H-8), 0.92 (s, 9H, H-1); ^{13}C NMR (126 MHz, CDCl_3) δ 97.6, 75.0, 62.0, 36.7, 35.0, 33.4, 25.7, 25.2, 24.2, 23.0; m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 198.1850, $\text{C}_{12}\text{H}_{23}\text{NO}$ requires 198.1852.

6-Chlorohexan-3-one (210)

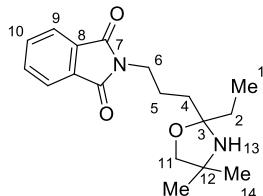
To a solution of 4-chlorobutanoyl chloride (5.00 g, 35.5 mmol, 1.0 equiv) in dry tetrahydrofuran (120 mL) at 0 °C was added ethyl magnesium bromide (1 M in tetrahydrofuran; 35.5 mL, 35.5 mmol, 1.0 equiv) dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 4 hours and then slowly quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to afford the title compound as a yellow oil (4.1 g, 30.5 mmol, 86%) which was used in the next step without further purification; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2970, 1819, 1710, 1412, 1376, 1309, 1115, 1036, 979, 867, 787, 729; **¹H NMR** (400 MHz, CDCl₃) δ 3.57 (t, *J* = 6.3 Hz, 1H), 2.61 (t, *J* = 7.0 Hz, 2H, H-6), 2.45 (q, *J* = 7.3 Hz, 2H, H-2), 2.12 – 1.99 (m, 2H, H-5), 1.07 (t, *J* = 7.3 Hz, 3H, H-1); **¹³C NMR** (101 MHz, CDCl₃) δ 210.3, 44.5, 38.8, 36.0, 26.3, 7.8. The physical data were identical in all respect to that previously reported.¹⁵⁴

2-(4-Oxohexyl)isoindoline-1,3-dione (211)

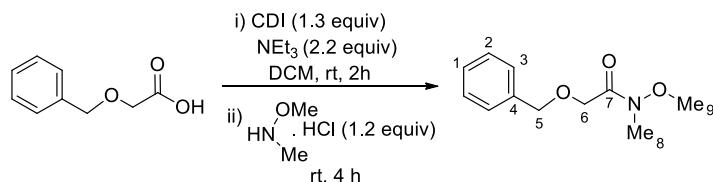
To a solution of 6-chlohexan-3-one **210** (4.1 g, 30.5 mmol, 1.0 equiv) in *N,N*-dimethylformamide (61 mL) was added potassium phthalimide (6.77 g, 36.6 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was partitioned between diethyl ether (60 mL) and water (40 mL). The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with water, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (4.1 g, 16.7 mmol, 55%); **R_f** (ethyl acetate in petroleum ether, 25%): 0.38; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2939, 1772, 1705, 1467, 1438, 1395, 1362, 1188, 1112, 1055, 1000, 888, 795, 719; **¹H NMR** (400 MHz, CDCl₃) δ 7.83 (dd, *J* = 5.4, 3.0 Hz, 2H, H-9), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H, H-10), 3.70 (t, *J* = 6.9 Hz, 2H, H-6), 2.46 (t, *J* = 7.2 Hz, 2H, H-4), 2.41 (q, *J* = 7.3 Hz, 2H, H-2), 1.96 (quint, *J* = 6.9 Hz, 2H, H-5), 1.02 (t, *J* = 7.3 Hz, 3H, H-1); **¹³C NMR** (101 MHz, CDCl₃) δ 210.1, 168.4, 133.9, 132.1, 123.2, 39.2, 37.3, 35.9, 22.7, 7.8; **m/z HRMS** (ESI) found [M+H]⁺ 246.1125, C₁₄H₁₆NO₃ requires 246.1125.

2-{3-(2-Ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propyl}isoindoline-1,3-dione (231a)

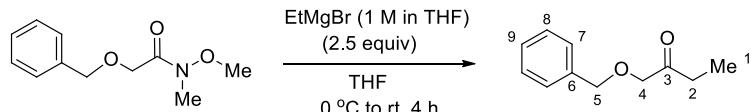
Prepared according to General Procedure A using (*1-aminocyclohexyl)methanol* **183** (316 mg, 2.45 mmol, 1.2 equiv) and *2-(4-oxohexyl)isoindoline-1,3-dione* **211** (500 mg, 2.04 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (356 mg, 1.00 mmol, 49%); **R**_f (ethyl acetate in petroleum ether, 25%): 0.36. **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2975, 2932, 1776, 1707, 1463, 1401, 1370, 1062, 885, 721; **¹H NMR** (500 MHz, CDCl₃) δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, H-9), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H, H-10), 3.72 (apparent t, *J* = 6.8 Hz, 2H, H-6), 3.61 (d, *J* = 8.2 Hz, 1H, H-11), 3.57 (d, *J* = 8.2 Hz, 1H, H-11), 1.83 – 1.67 (m, 2H, H-2 and H-5), 1.67 – 1.37 (m, 11H, H-2, H-4, H-5, H-14 and H-15), 1.36 – 1.23 (m, 3H, H-15 and H-16), 0.87 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 168.4(x2), 133.9, 132.1, 123.2, 98.1, 74.7, 62.0, 38.2, 38.2, 38.0, 35.2, 31.1, 25.4, 24.0, 23.9, 23.8, 8.6; **m/z HRMS** (ESI) found [M+H]⁺ 357.2172, C₂₁H₂₉N₂O₃ requires 357.2173.

2-{3-(2-Ethyl-4,4-dimethyloxazolidin-2-yl)propyl}isoindoline-1,3-dione (231b)

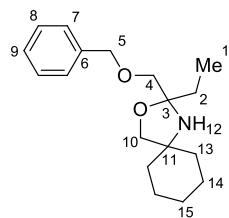
Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (273 mg, 3.06 mmol, 1.5 equiv) and *2-(4-oxohexyl)isoindoline-1,3-dione* **211** (500 mg, 2.04 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (380 mg, 1.20 mmol, 59%); **R**_f (ethyl acetate in petroleum ether, 25%): 0.28; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2966, 2769, 1709, 1617, 1396, 1361, 1260, 1189, 1056, 913, 796, 720; **¹H NMR** (500 MHz, CDCl₃) δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, H-9), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H, H-10), 3.71 (t, *J* = 6.5 Hz, 2H, H-6), 3.57 (d, *J* = 8.1 Hz, 1H, H-11), 3.53 (d, *J* = 8.1 Hz, 1H, H-11), 1.80 – 1.71 (m, 2H, H-5), 1.68 – 1.56 (m, 4H, H-4 and H-2), 1.23 (s, 3H, H-14), 1.23 (s, 3H, H-14), 0.88 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 168.4, 133.9, 132.1, 123.2, 99.0, 76.8, 58.9, 38.2, 35.1, 30.9, 28.5, 28.4, 23.8, 8.7; **m/z HRMS** (ESI) found [M+H]⁺ 317.1863, C₁₈H₂₅N₂O₃ requires 317.1865.

2-(BenzylOxy)-N-methoxy-N-methylacetamide (213)

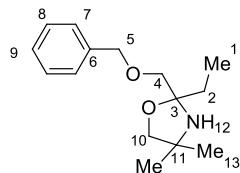
To a solution of 2-(benzyloxy)acetic acid (2.00 g, 12.04 mmol, 1.0 equiv) and triethylamine (3.69 mL, 26.5 mmol, 2.2 equiv) in dry dichloromethane (32 mL) was added *N,N*-carbonyl diimidazole (2.54 g, 15.7 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 2 hours, followed by addition of *N,O*-dimethylhydroxylamine hydrochloride (1.41 g, 14.4 mmol). The reaction mixture was stirred at this temperature for another 4 hours. Saturated ammonium chloride was added to the mixture and the layers separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (2.20 g, 10.5 mmol, 87%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.28; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2938, 2899, 1676, 1454, 1392, 1328, 1177, 1138, 1086, 991, 916, 739, 699; **1H NMR** (500 MHz, CDCl₃) δ 7.53 – 7.27 (m, 5H, Ar-H), 4.67 (s, 2H, H-5), 4.28 (s, 2H, H-6), 3.63 (s, 3H, H-8), 3.19 (s, 3H, H-9); **13C NMR** (126 MHz, CDCl₃) δ 171.0, 137.5, 128.4, 128.1, 127.8, 73.3, 67.1, 61.4, 32.3. The physical data were identical in all respect to that previously reported.¹⁵⁵

1-(BenzylOxy)butan-2-one (214)

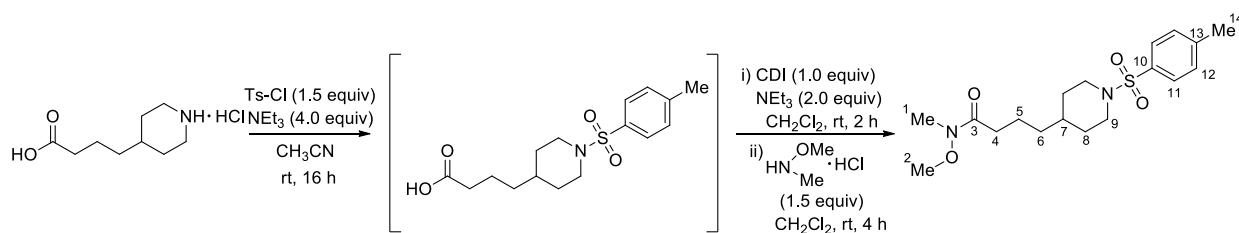
To a solution of 2-(benzyloxy)-N-methoxy-N-methylacetamide **213** (2.20 g, 10.5 mmol, 1.0 equiv) in dry tetrahydrofuran (60 mL) at 0 °C was added ethyl magnesium bromide (1 M in tetrahydrofuran; 26.3 mL, 26.3 mmol, 2.5 equiv) dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 4 hours and then slowly quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to afford the title compound as a yellow oil (1.6 g, 9.00 mmol, 85%) which was used in the next step without further purification; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2977, 2881, 1717, 1455, 1340, 1103, 1028, 96, 737, 697; **1H NMR** (500 MHz, CDCl₃) δ 7.42 – 7.28 (m, 5H, Ar-H), 4.59 (s, 2H, H-5), 4.07 (s, 2H, H-4), 2.50 (q, *J* = 7.3 Hz, 2H, H-2), 1.07 (t, *J* = 7.3 Hz, 3H, H-1); **13C NMR** (126 MHz, CDCl₃) δ 209.37, 137.25, 128.52, 128.00, 127.88, 74.80, 73.36, 32.27, 7.22. The physical data were identical in all respect to that previously reported.¹⁵⁶

2-((Benzyl)oxy)methyl-2-ethyl-3-oxa-1-azaspiro[4.5]decane (232a)

Prepared according to General Procedure A using (*1*-aminocyclohexyl)methanol **182** (435 mg, 3.37 mmol, 1.2 equiv) and *1*-(benzyloxy)butan-2-one **214** (2.87 mL, 18.6 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (530 mg, 1.83 mmol, 65%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.28; **IR** ν_{max} /cm⁻¹ (film): 2968, 2869, 1454, 1382, 1363, 1253, 1201, 1099, 1055, 914, 824, 734, 697; **¹H NMR** (500 MHz, CDCl₃) δ 7.36 – 7.31 (m, 4H, Ar-H), 7.30 – 7.25 (m, 1H, Ar-H), 4.61 (d, *J* = 12.2 Hz, 1H, H-5), 4.58 (d, *J* = 12.2 Hz, 1H, H-5), 3.65 (d, *J* = 8.1 Hz, 1H, H-10), 3.62 (d, *J* = 8.1 Hz, 1H, H-10), 3.43 (d, *J* = 10.1 Hz, 1H, H-4), 3.38 (d, *J* = 10.1 Hz, 1H, H-4), 1.70 (q, *J* = 7.5 Hz, 2H, H-2), 1.68 – 1.26 (m, 10H, H-13, H-14 and H-15), 0.88 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 138.3, 128.3, 127.6, 127.5, 97.6, 75.2, 73.4, 73.0, 62.1, 37.7, 37.6, 30.3, 28.4, 25.5, 23.9, 8.5; **m/z HRMS** (ESI) found [M+H]⁺ 290.2113, C₁₈H₂₈NO₂ requires 290.2115.

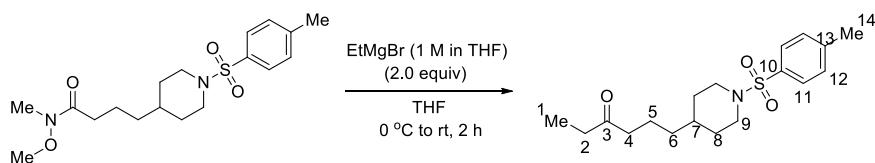
2-((Benzyl)oxy)methyl-2-ethyl-4,4-dimethyloxazolidine (232b)

Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (1.50 g, 16.8 mmol, 1.5 equiv) and *1*-(benzyloxy)butan-2-one **214** (2.00 g, 11.2 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (1.00 g, 4.01 mmol, 36%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.35; **IR** ν_{max} /cm⁻¹ (film): 2968, 2869, 1454, 1382, 1363, 1253, 1201, 1099, 1055, 914, 824, 734, 697; **¹H NMR** (500 MHz, CDCl₃) δ 7.37 – 7.26 (m, 5H, Ar-H), 4.62 (d, *J* = 12.2 Hz, 1H, H-5), 4.57 (d, *J* = 12.2 Hz, 1H, H-5), 3.60 (d, *J* = 7.8 Hz, 1H, H-10), 3.58 (d, *J* = 7.8 Hz, 1H, H-10), 3.45 (d, *J* = 10.1 Hz, 1H, H-4), 3.42 (d, *J* = 10.1 Hz, 1H, H-4), 1.72 (qd, *J* = 7.5, 1.4 Hz, 2H, H-2), 1.25 (s, 3H, H-13), 1.23 (s, 3H, H-13), 0.89 (t, *J* = 7.6 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 138.3, 128.3, 127.6, 127.5, 98.4, 77.5, 73.4, 72.9, 59.0, 30.4, 28.3, 27.8, 8.6; **m/z HRMS** (ESI) found [M+H]⁺ 250.1796, C₁₅H₂₃NO₂ requires 250.1801.

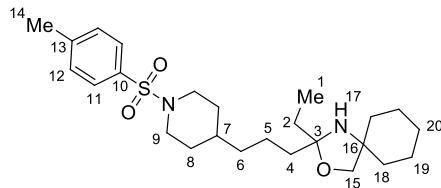
N-Methoxy-N-methyl-4-(1-tosylpiperidin-4-yl)butanamide (216)

To a solution of 4-(piperidin-4-yl)butanoic acid hydrochloride (5.00 g, 24.1 mmol, 1.0 equiv) in acetonitrile (100 mL) was added triethylamine (13.4 mL, 96.4 mmol, 4.0 equiv) and *para*-toluenesulfonyl chloride (6.9 g, 36.3 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 16 hours. Solvent was removed under reduced pressure and partitioned between 3 N HCl and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to yield 4.1 g of the crude acid which was taken on crude for the next step.

To a solution of the crude acid (4.1 g, 12.6 mmol, 1.0 equiv) and triethylamine (3.52 mL, 25.2 mmol, 2.0 equiv) in dry dichloromethane (70 mL) was added *N,N*-carbonyl diimidazole (2.04 g, 12.6 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 2 hours, followed by addition of *N,O*-dimethylhydroxylamine hydrochloride (1.84 g, 18.9 mmol, 1.5 equiv). The reaction mixture was stirred at this temperature for another 4 hours. Saturated ammonium chloride was added to the mixture and layers separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 50% ethyl acetate in petroleum ether, affording the title compound as a yellow solid (2.20 g, 10.5 mmol, 44% over 2 steps); **M.p.**: 117–119 °C; **R_f** (ethyl acetate in petroleum ether, 50%): 0.39; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2935, 1663, 1417, 1385, 1334, 1306, 1248, 1157, 1095, 1048, 989, 928, 854, 817, 724; **¹H NMR** (500 MHz, CDCl₃) δ 7.63 (d, *J* = 8.3 Hz, 2H, H-11), 7.31 (d, *J* = 7.9 Hz, 2H, H-12), 3.75 (d, *J* = 11.7 Hz, 2H, H-9), 3.65 (s, 3H, H-2), 3.15 (s, 3H, H-1), 2.43 (s, 3H, H-14), 2.37 (t, *J* = 7.4 Hz, 2H, H-4), 2.20 (td, *J* = 11.8, 2.4 Hz, 2H, H-9), 1.73 (dd, *J* = 12.8, 1.9 Hz, 2H, H-8), 1.66 – 1.51 (m, 2H, H-5), 1.40 – 1.21 (m, 4H, H-6 and H-8), 1.19 – 1.05 (m, 1H, H-7); **¹³C NMR** (126 MHz, CDCl₃) δ 174.4, 143.3, 133.2, 129.5, 127.7, 61.2, 46.4, 35.8, 35.1, 32.1, 31.8, 31.5, 21.7, 21.5; **m/z HRMS** (ESI) found [M+H]⁺ 369.1848, C₁₈H₂₉N₂O₄S requires 369.1843.

6-(1-Tosylpiperidin-4-yl)hexan-3-one (217)

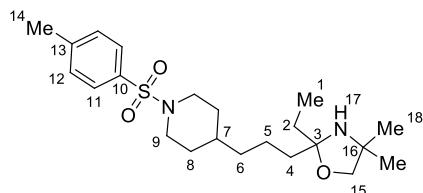
To a solution of *N*-methoxy-*N*-methyl-4-(1-tosylpiperidin-4-yl)butanamide **216** (1.60 g, 4.35 mmol, 1.0 equiv) in dry tetrahydrofuran (40 mL) at 0 °C was added ethyl magnesium bromide (1 M in tetrahydrofuran; 8.7 mL, 8.70 mmol, 2.0 equiv) dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 2 hours and then slowly quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a white solid (1.1 g, 3.26 mmol, 79%); **M.p.**: 81–83 °C; **R**_f (ethyl acetate in petroleum ether, 20%): 0.30; **IR** ν_{max} /cm⁻¹ (film): 2922, 2852, 1714, 1597, 1465, 1338, 1305, 1247, 1161, 1108, 1087, 1046, 975, 928, 849, 814, 728; **¹H NMR** (500 MHz, CDCl₃) δ 7.63 (d, *J* = 8.3 Hz, 2H, H-11), 7.31 (dd, *J* = 8.3 Hz, 2H, H-12), 3.75 (d, *J* = 11.6 Hz, 2H, H-9), 2.43 (s, 3H, H-14), 2.38 (q, *J* = 7.3 Hz, 2H, H-2), 2.35 (t, *J* = 7.3 Hz, 2H, H-4), 2.19 (td, *J* = 11.8, 2.4 Hz, 2H, H-9), 1.71 (ddd, *J* = 14.3, 11.8, 3.1 Hz, 2H, H-8), 1.57 – 1.48 (m, 2H, H-5), 1.27 (ddd, *J* = 14.3, 12.4, 4.0 Hz, 2H, H-8), 1.21 – 1.08 (m, 3H, H-6 and H-7), 1.03 (t, *J* = 7.3 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 211.5, 143.3, 133.2, 129.5, 127.7, 46.4, 42.3, 35.9, 35.6, 35.1, 31.4, 21.5, 20.9, 7.8; **m/z HRMS** (ESI) found [M+H]⁺ 338.1787, C₁₈H₂₈NO₃S requires 338.1789.

2-Ethyl-2-(3-[1-tosylpiperidin-4-yl]propyl)-3-oxa-1-azaspiro[4.5]decane (233a)

Prepared according to General Procedure A using (*1*-aminocyclohexyl)methanol **182** (138 mg, 1.07 mmol, 1.2 equiv) and *6*-(1-tosylpiperidin-4-yl)hexan-3-one **217** (300 mg, 0.89 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 30% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (232 mg, 0.52 mmol, 59%); **R**_f (ethyl acetate in petroleum ether, 50%): 0.43; **IR** ν_{max} /cm⁻¹ (film): 2925, 2850, 1598, 1449, 1339, 1251, 1163, 1094, 1049, 931, 815, 724; **¹H NMR** (400 MHz, CDCl₃) δ 7.63 (d, *J* = 8.2 Hz, 2H, H-11), 7.31 (d, *J* = 8.2 Hz, 2H, H-12), 3.75 (d, *J* = 11.6 Hz, 2H, H-9), 3.60 (d, *J* = 8.3 Hz, 1H, H-15), 3.57 (d, *J* = 8.3 Hz, 1H, H-15), 2.43 (s, 3H, H-14), 2.28 – 2.13 (m, 2H, H-9), 1.77 – 1.40 (m, 12H, H-2, H-3, H-8, H-18 and H-19), 1.39 – 1.11 (m, 11H, H-5,

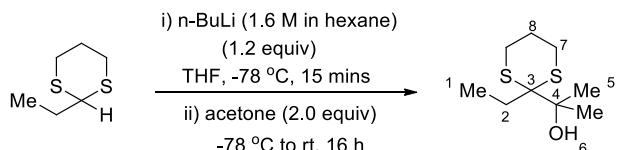
H-6, H-7, H-8, H-18 and H-19), 0.86 (t, $J = 7.5$ Hz, 3H, H-1); ^{13}C NMR (126 MHz, CDCl_3) δ 143.3, 133.2, 129.5, 127.7, 98.4, 74.5, 62.0, 46.5, 38.2, 38.1, 36.4, 35.1, 31.5, 31.0, 25.4, 24.0, 21.5, 21.5, 8.7. m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 449.2822, $\text{C}_{25}\text{H}_{41}\text{N}_2\text{O}_3\text{S}$ requires 449.2819.

2-Ethyl-4,4-dimethyl-2-(3-[1-tosylpiperidin-4-yl]propyl)oxazolidine (233b)



Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (119 mg, 1.34 mmol, 1.5 equiv) and *6-(1-tosylpiperidin-4-yl)hexan-3-one* **217** (300 mg, 0.89 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 40% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (260 mg, 0.63 mmol, 72%); \mathbf{R}_f (ethyl acetate in petroleum ether, 50%): 0.33; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2935, 2848, 1598, 1461, 1339, 1163, 1094, 1050, 931, 816, 725; ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 8.2$ Hz, 2H, H-11), 7.31 (d, $J = 8.1$ Hz, 2H, H-12), 3.75 (d, $J = 11.6$ Hz, 2H, H-9), 3.55 (d, $J = 8.1$ Hz, 1H, H-15), 3.52 (d, $J = 8.1$ Hz, 1H, H-15), 2.43 (s, 3H, H-14), 2.19 (d, $J = 11.6$, 2H, H-9), 1.71 (d, $J = 10.8$ Hz, 2H, H-8), 1.64 – 1.47 (m, 4H, H-2 and H-4), 1.36 – 1.05 (m, 7H, H-5, H-6, H-7 and H-8), 1.23 (s, 3H, H-18), 1.22 (s, 3H, H-18), 0.87 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 143.3, 133.2, 129.5, 127.7, 99.3, 76.7, 58.8, 46.5, 38.1, 36.4, 35.2, 31.5, 30.8, 28.6, 28.4, 21.5, 21.5, 8.8; m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 409.2512, $\text{C}_{22}\text{H}_{37}\text{N}_2\text{O}_3\text{S}$ requires 409.2514.

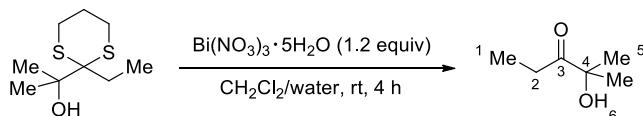
2-(2-Ethyl-1,3-dithian-2-yl)propan-2-ol (219)



To a solution of 2-ethyl-1,3-dithiane (2.92 mL, 20.2 mmol, 1.0 equiv) in dry tetrahydrofuran (50 mL) at -78°C was added *n*-butyllithium (1.6 M in hexane; 15.1 mL, 24.2 mmol, 1.2 equiv) and stirred at this temperature for 15 mins. Acetone (2.93 mL, 40.4 mL, 2.0 equiv) was added and the reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated ammonium chloride and layers separated. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 5% ethyl acetate in petroleum ether, affording the title compound as a colourless oil (3.2 g, 15.5 mmol, 76%); \mathbf{R}_f (ethyl acetate in petroleum ether, 10%): 0.33; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3463 (br), 2978, 2932, 1452, 1365, 1278, 1240, 1177, 1131, 998,

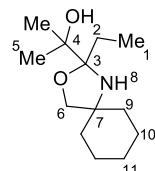
959, 907, 861, 816, 798; **¹H NMR** (400 MHz, CDCl₃) δ 2.99 – 2.87 (m, 2H, H-7), 2.86 – 2.73 (m, 2H, H-7), 2.52 (s, 1H, OH), 2.01 – 1.86 (m, 4H, H-2 and H-8), 1.41 (s, 6H, H-5), 1.18 (t, J = 7.3 Hz, 3H, H-1); **¹³C NMR** (101 MHz, CDCl₃) δ 78.8, 64.7, 30.8, 27.1, 26.2, 23.6, 11.3; m/z **HRMS** (ESI) found [M+NH₄]⁺ 224.1132, C₉H₂₂NOS₂ requires 224.1129.

2-Hydroxy-2-methylpentan-3-one (220)

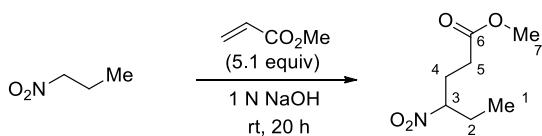


To a solution of *2-(2-Ethyl-1,3-dithian-2-yl)propan-2-ol* **219** (500 mg, 2.43 mmol, 1.0 equiv) in dichloromethane (6 mL) was added water (0.09 mL) and bismuth(III) nitrate pentahydrate (588 mg, 1.21 mmol, 1.2 equiv). [Caution: slight exotherm detected.] The reaction was vigorously stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the crude product was purified by bulb-to-bulb distillation, affording the title compound as a colourless oil (210 mg, 1.81 mmol, 74%). **IR** ν_{max}/cm⁻¹ (film): 3469 (br), 2925, 2855, 1718, 1458, 1230, 1090, 968, 863, 735; **¹H NMR** (400 MHz, CDCl₃) δ 2.60 (q, J = 7.3 Hz, 2H, H-2), 2.42 (s, 1H, OH), 1.41 (s, 6H, H-5), 1.14 (t, J = 7.3 Hz, 3H, H-1). **¹³C NMR** (400 MHz, CDCl₃) δ 215.0, 28.7, 26.6, 26.4, 7.9. The physical data were identical in all respect to that previously reported.¹⁵⁷

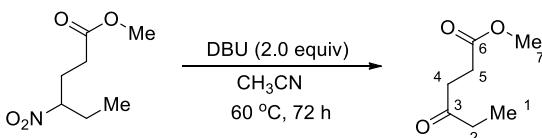
2-(2-Ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propan-2-ol (235a)



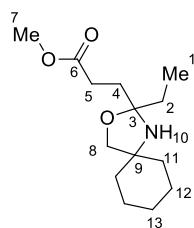
Prepared according to General Procedure B using (*1-aminocyclohexyl)methanol* **182** (500 mg, 10.7 mmol, 1.0 equiv) and *3-hydroxy-3-methylbutan-2-one* **220** (3 mL, 28.5 mmol, 2.7 equiv); purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, afforded the title compound as a pale brown oil (175 mg, 0.77 mmol, 7%); R_f (ethyl acetate in petroleum ether, 20%): 0.23; **IR** ν_{max}/cm⁻¹ (film): 3469 (br), 2928, 2855, 1450, 1367, 1164, 1049, 946, 843, 703; **¹H NMR** (500 MHz, CDCl₃) δ 3.76 (d, J = 8.1 Hz, 1H, H-6), 3.69 (d, J = 8.1 Hz, 1H, H-6), 1.77 – 1.50 (m, 8H, H-2, H-9, H-10), 1.47 – 1.29 (m, 4H, H-10 and H-11), 1.27 (s, 3H, H-5), 1.17 (s, 3H, H-5), 0.97 (t, J = 7.6 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 102.0, 74.3, 61.9, 38.4, 37.9, 28.6, 26.4, 26.1, 25.3, 24.6, 24.1, 24.0, 9.6; m/z **HRMS** (ESI) found [M+H]⁺ 228.1956, C₁₃H₂₆NO₂ requires 228.1958.

Methyl 4-nitrohexanoate (222)

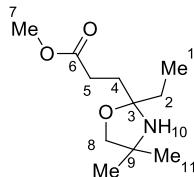
To a solution of methyl acrylate (6.65 g, 77.0 mmol, 5.1 equiv) in 1 N sodium hydroxide (31 mL) was added 1-nitropropane (15.2 g, 15.2 mmol, 1.0 equiv). The reaction mixture was stirred at RT for 20 hours. Brine was added to the mixture and extracted with diethyl ether. The combined organic extracts were dried and concentrated *in vacuo*. The crude product was purified by bulb-to-bulb distillation, affording the title compound as a colourless oil (8.50 g, 48.5 mmol, 63%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2943, 2157, 1736, 1546, 1438, 1369, 1326, 1254, 1201, 1174, 993, 864, 815; **¹H NMR** (500 MHz, CDCl₃) δ 4.54 – 4.41 (m, 1H, H-3), 3.68 (s, 3H, H-7), 2.44 – 2.26 (m, 2H, H-5), 2.26 – 2.15 (m, 1H, H-4), 2.14 – 2.04 (m, 1H, H-4), 2.03 – 1.91 (m, 1H, H-2), 1.87 – 1.74 (m, 1H, H-2), 0.96 (t, *J* = 7.4 Hz, 3H, H-1); **¹³C NMR** (101 MHz, CDCl₃) δ 172.4, 89.1, 51.9, 29.9, 28.3, 27.2, 10.1; The physical data were identical in all respect to that previously reported.¹⁵⁸

Methyl 4-oxohexanoate (223)

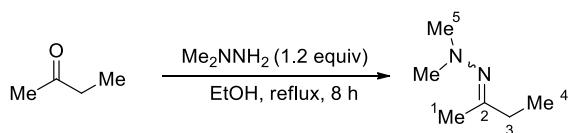
To a solution of *methyl 4-nitrohexanoate* **222** (1.00 g, 5.71 mmol, 1.0 equiv) in acetonitrile (23 mL) was added 1,8-diazabicycloundec-7-ene (1.72 mL, 11.4 mmol, 2.0 equiv). The resulting mixture was heated at 60 °C for 72 hours. The reaction mixture was cooled and partitioned between 3 N HCl and diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (200 mg, 1.39 mmol, 24%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.31; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 1915, 1736, 1714, 1550, 1438, 1359, 1263, 1206, 1170, 1115, 842, 785; **¹H NMR** (500 MHz, CDCl₃) δ 3.67 (s, 3H, H-7), 2.72 (t, *J* = 6.5 Hz, 2H, H-4), 2.59 (t, *J* = 6.6 Hz, 2H, H-5), 2.48 (q, *J* = 7.3 Hz, 2H, H-2), 1.07 (t, *J* = 7.3 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 209.4, 173.3, 51.8, 36.6, 35.9, 27.8, 7.8. The physical data were identical in all respect to that previously reported.¹⁵⁹

Methyl 3-(2-ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propanoate (234a)

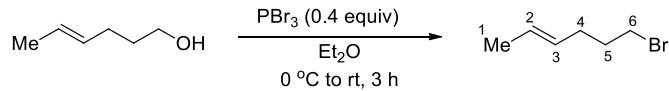
Prepared according to General Procedure A using (*1*-aminocyclohexyl)methanol **182** (161 mg, 1.25 mmol, 1.2 equiv) and *methyl 4-oxohexanoate* **223** (150 mg, 1.04 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (102 mg, 0.40 mmol, 38%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.24; **IR** ν_{max} /cm⁻¹ (film): 2929, 2859, 1737, 1437, 1258, 1168, 1101, 1053, 923, 815, 715; **¹H NMR** (500 MHz, CDCl₃) δ 3.67 (s, 3H, H-7), 3.63 (d, *J* = 8.3 Hz, 1H, H-8), 3.59 (d, *J* = 8.3 Hz, 1H, H-8), 2.41 – 2.33 (m, 2H, H-5), 1.96 – 1.88 (m, 2H, H-4), 1.70 – 1.27 (m, 12H, H-2, H-11, H-12 and H-13), 0.91 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 174.3, 97.6, 74.8, 62.0, 51.6, 38.1, 38.1, 32.9, 31.1, 29.7, 25.4, 24.0, 23.8, 8.5; m/z **HRMS** (ESI) found [M+H]⁺ 256.1910, C₁₄H₂₆NO₃ requires 256.1907.

Methyl 3-(2-ethyl-4,4-dimethyloxazolidin-2-yl)propanoate (234b)

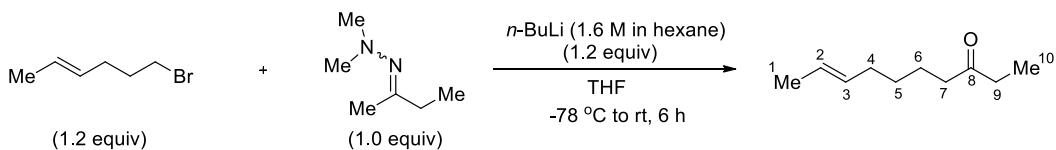
Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (185 mg, 2.08 mmol, 1.5 equiv) and *methyl 4-oxohexanoate* **223** (200 mg, 1.39 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 40% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (102 mg, 0.47 mmol, 34%); **R**_f (ethyl acetate in petroleum ether, 25%): 0.21; **IR** ν_{max} /cm⁻¹ (film): 2964, 2866, 1736, 1437, 1365, 1258, 1195, 1167, 1053, 992, 904, 834; **¹H NMR** (500 MHz, CDCl₃) δ 3.67 (s, 3H, H-7), 3.59 (d, *J* = 8.1 Hz, 1H, H-8), 3.54 (d, *J* = 8.1 Hz, 1H, H-8), 2.42 – 2.33 (m, 2H, H-5), 2.00 – 1.87 (m, 2H, H-4), 1.65 – 1.55 (q, *J* = 7.5 Hz, 2H, H-2), 1.25 (s, 3H, H-11), 1.24 (s, 3H, H-11), 0.92 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 174.3, 98.5, 76.8, 58.9, 51.6, 32.7, 31.0, 29.7, 28.5, 28.5, 8.6; m/z **HRMS** (ESI) found [M+H]⁺ 216.1593, C₁₁H₂₂NO₃ requires 216.1594.

(E)-2-(Butan-2-ylidene)-1,1-dimethylhydrazine (225)

To a solution of butanone (10.0 mL, 112 mmol, 1.0 equiv) in ethanol (30 mL) was added *N,N*-dimethylhydrazine (10 mL, 132 mmol, 1.2 equiv). The reaction mixture was heated at reflux for 8 hours and cooled to room temperature. The reaction was concentrated *in vacuo*. The crude product was purified by distillation to yield the title compound (as a mixture of isomers) as a colourless oil (12.1 g, 106 mmol, 95%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2974, 2951, 2854, 2817, 1638, 1466, 1359, 1196, 1155, 1074, 1022, 975, 947, 848, 731; **$^1\text{H NMR}$** (400 MHz, CDCl_3) δ 2.47 (q, $J = 7.7$ Hz, 2H, H-3; minor), 2.44 (s, 6H, H-5; major), 2.42 (s, 6H, H-5; minor), 2.22 (q, $J = 7.6$ Hz, 2H, H-3; major), 1.95 (s, 3H, H-1; major), 1.92 (s, 3H, H-1; minor), 1.10 (t, $J = 7.7$ Hz, 3H, H-4; minor), 1.09 (t, $J = 7.6$ Hz, 3H, H-4; major); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ 170.8 (minor), 169.2 (major), 48.0 (minor), 47.4 (major), 32.6 (major), 24.9 (minor), 22.5 (minor), 16.4 (major), 11.9 (major), 11.4 (minor). The physical data were identical in all aspect to that previously reported.¹⁶⁰

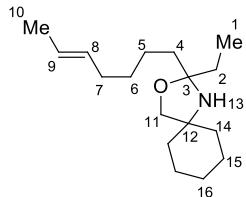
(E)-6-Bromohex-2-ene (227)

To a solution of (*E*)-hex-4-en-1-ol (5.00 g, 50.0 mmol, 1.0 equiv) and pyridine (0.50 mL) in dry diethyl ether (50 mL) at 0 °C was added phosphorous tribromide (1.83 mL, 19.3 mmol, 0.4 equiv). The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction was quenched with saturated ammonium chloride and layers separated. The organic layer was washed with brine, dried and concentrated *in vacuo* to yield the title compound as a pale brown oil (3.08 g, 19.0 mmol, 76%) which was used in the next step without further purification; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2920, 2851, 1739, 1464, 1375, 1242, 1017, 803; **$^1\text{H NMR}$** (400 MHz, CDCl_3) δ 5.59 – 5.42 (m, 1H, H-2), 5.42 – 5.30 (m, 1H, H-3), 3.40 (t, $J = 6.8$ Hz, 2H, H-6), 2.17 – 2.09 (m, 2H, H-4), 1.90 (quint, $J = 7.0$ Hz, 2H, H-5), 1.65 (ddd, $J = 6.3$, 2.6, 1.2 Hz, 3H, H-1); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ 129.2, 126.5, 33.3, 32.5, 30.9, 17.9. The physical data were identical in all respect to that previously reported.¹⁶¹

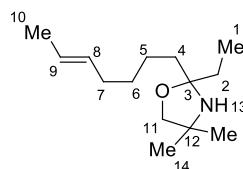
(E)-Dec-8-en-3-one (228)

To a solution of (*E*)-2-(butan-2-ylidene)-1,1-dimethylhydrazine **225** (3.00 g, 18.5 mmol, 1.0 equiv) in dry tetrahydrofuran (60 mL) at -78 °C was added *n*-butyllithium (1.6 M in hexane; 13.9 mL, 22.2 mmol, 1.2 equiv) and the mixture was stirred at this temperature for 1 hour. (*E*)-6-Bromohex-2-ene **227** (3.60 g, 22.2 mmol, 1.2 equiv) was then added and the reaction mixture allowed to warm to room temperature and stirred for 6 hours. The reaction was quenched with saturated ammonium chloride and layers separated. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the title compound as a colourless oil (2.17 g, 14.1 mmol, 76%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.32; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2935, 2856, 1714, 1454, 1413, 1376, 1111, 965, 732; **¹H NMR** (500 MHz, CDCl₃) δ 5.49 – 5.30 (m, 2H, H-2 and H-3), 2.44 – 2.36 (m, 4H, H-7 and H-9), 2.02 – 1.94 (m, 2H, H-4), 1.65 – 1.62 (m, 3H, H-1), 1.61 – 1.52 (m, 2H, H-6), 1.39 – 1.27 (m, 2H, H-5), 1.04 (t, *J* = 7.3 Hz, 3H, H-10); **¹³C NMR** (126 MHz, CDCl₃) δ 211.9, 131.0, 125.1, 42.3, 35.9, 32.3, 29.2, 23.4, 17.9, 7.8; **Elemental analysis:** Anal. Calcd. For C₁₀H₁₈O: C, 77.87; H, 11.76. Found: C, 77.84; H, 11.77.

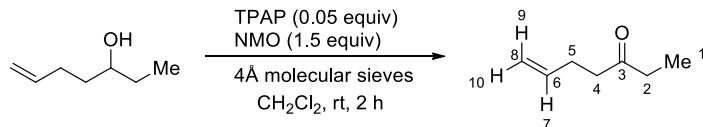
(*E*)-2-Ethyl-2-(hept-5-en-1-yl)-3-oxa-1-azaspiro[4.5]decane (236a)



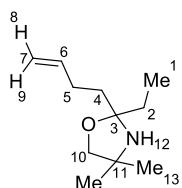
Prepared according to General Procedure A using (*1*-aminocyclohexyl)methanol **182** (314 mg, 2.43 mmol, 1.5 equiv) and (*E*)-*dec-8-en-3-one* **228** (250 mg, 1.62 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (277 mg, 1.05 mmol, 65%); **R_f** (ethyl acetate in petroleum ether, 25%): 0.41; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2928, 2853, 2191, 1450, 1195, 1114, 1055, 965, 813, 738; **¹H NMR** (500 MHz, CDCl₃) δ 5.44 – 5.37 (m, 2H, H-8 and H-9), 3.62 (d, *J* = 8.4 Hz, 1H, H-11), 3.60 (d, *J* = 8.4 Hz, 1H, H-11), 2.01 – 1.95 (m, 2H, H-7), 1.71 – 1.43 (m, 15H, H-2, H-4, H-14 and H-15), 1.39 – 1.26 (m, 6H, H-5, H-6 and H-16), 0.89 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 131.4, 124.8, 98.6, 74.4, 62.0, 38.1, 38.1, 37.9, 32.5, 31.0, 30.0, 25.4, 24.1, 24.0, 23.9, 17.9, 8.8; **m/z HRMS** (ESI) found [M+H]⁺ 266.2475, C₁₇H₃₂NO requires 266.2478.

(E)-2-Ethyl-2-(hept-5-en-1-yl)-4,4-dimethyloxazolidine (236b)

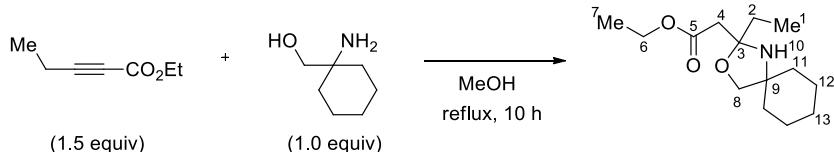
Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (217 mg, 2.43 mmol, 1.5 equiv) and (*E*)-*dec-8-en-3-one* **228** (250 mg, 1.62 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 25% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (252 mg, 1.12 mmol, 69%); **R**_f (ethyl acetate in petroleum ether, 25%): 0.31; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2963, 2933, 2856, 1460, 1381, 1364, 1199, 1056, 964, 827, 769; **1H NMR** (500 MHz, CDCl₃) δ 5.48 – 5.32 (m, 2H, H-8 and H-9), 3.56 (d, *J* = 8.3 Hz, 1H, H-11), 3.54 (d, *J* = 8.3 Hz, 1H, H-11), 2.05 – 1.92 (m, 2H, H-7), 1.65 – 1.51 (m, 7H, H-2, H-4 and H-10), 1.40 – 1.27 (m, 4H, H-5 and H-6), 1.24 (s, 3H, H-14), 1.24 (s, 3H, H-14), 0.89 (t, *J* = 7.5 Hz, 3H, H-1); **13C NMR** (126 MHz, CDCl₃) δ 131.3, 124.8, 99.5, 76.8, 58.8, 37.8, 32.5, 30.9, 29.9, 28.5, 28.4, 23.9, 17.9, 8.8; m/z **HRMS** (ESI) found [M+H]⁺ 226.2162, C₁₄H₂₈NO requires 226.2165.

Hept-6-en-3-one (230)

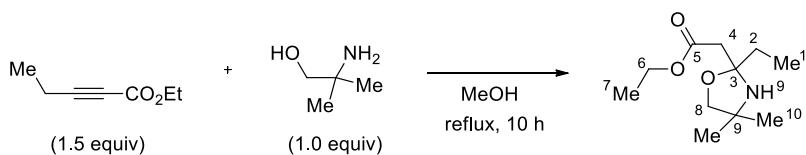
To a solution of hept-6-en-ol (1.00 g, 8.76 mmol, 1.0 equiv) in dichloromethane (18 mL) was added *N*-methylmorpholine *N*-oxide (1.54 g, 13.1 mmol, 1.5 equiv) and 4Å molecular sieve (~4 g), followed by tetrapropylammonium perruthenate (154 mg, 0.44 mmol, 0.05 equiv). [Note of caution: delayed exotherm observed after addition of the oxidant]. The mixture was stirred at room temperature for 2 hours and then filtered through a short plug of silica, eluting with dichloromethane. The filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the title compound as a colourless oil (501 mg, 4.47 mmol, 51%); **R**_f (ethyl acetate in petroleum ether, 10%): 0.29; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2971, 1936, 1716, 1658, 1407, 1272, 1177, 1114, 773; **1H NMR** (500 MHz, CDCl₃) δ 5.80 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H, H-7), 5.02 (apparent dq, *J* = 17.1, 1.7 Hz, 1H, H-9), 4.97 (apparent ddd, *J* = 10.2, 2.9, 1.7 Hz, 1H, H-10), 2.50 (t, *J* = 7.4 Hz, 2H, H-4), 2.42 (q, *J* = 7.3 Hz, 2H, H-2), 2.35 – 2.29 (m, 2H, H-5), 1.05 (t, *J* = 7.3 Hz, 3H, H-1); **13C NMR** (126 MHz, CDCl₃) δ 210.8, 137.2, 115.1, 41.4, 36.0, 27.8, 7.8. The physical data were identical in all respect to that previously reported.¹⁶²

2-(But-3-en-1-yl)-2-ethyl-4,4-dimethyloxazolidine (237b)

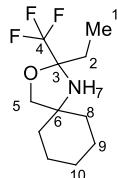
Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (2.38 g, mmol, 3.0 equiv) and *hept-6-en-3-one* **230** (1.00 g, mmol, 1.0 equiv): purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (210 mg, 1.15 mmol, 13%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.32; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2966, 2937, 2362, 1641, 1450, 1382, 1365, 1196, 1056, 907, 831, 774; **¹H NMR** (500 MHz, CDCl₃) δ 5.84 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H, H-6), 5.03 (apparent dq, *J* = 16.8, 1.7 Hz, 1H, H-9), 4.95 (apparent ddd, *J* = 10.2, 3.2, 1.7 Hz, 1H, H-8), 3.58 (d, *J* = 8.1 Hz, 1H, H-10), 3.56 (d, *J* = 8.1 Hz, 1H, H-10), 2.16 – 2.05 (m, 2H, H-5), 1.76 – 1.54 (m, 4H, H-4 and H-2), 1.25 (s, 3H, H-13), 1.25 (s, 3H, H-13), 0.91 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 138.7, 114.3, 99.2, 76.9, 58.9, 37.0, 31.0, 28.8, 28.5, 28.5, 8.7; **m/z HRMS** (ESI) found [M+H]⁺ 184.1693, C₁₁H₂₁NO requires 184.1696.

Ethyl 2-(2-ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)acetate (246a)

To a solution of (*1-aminocyclohexyl)methanol* **182** (500 mg, 3.87 mmol, 1.0 equiv) in methanol (20 mL) was added ethyl pent-2-ynoate (732 mg, 5.80 mmol, 1.5 equiv). The resulting solution was heated at reflux for 10 hours. The solvent was then removed under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, affording the title compound as a colourless oil (682 mg, 2.67 mmol, 69%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.31; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2929, 2857, 1724, 1450, 1370, 1322, 1210, 1036, 930, 819, 664; **¹H NMR** (500 MHz, CDCl₃) δ 4.14 (q, *J* = 7.1 Hz, 1H, H-6), 3.65 (d, *J* = 8.3 Hz, 1H, H-8), 3.60 (d, *J* = 8.3 Hz, 1H, H-8), 2.63 (d, *J* = 13.9 Hz, 1H, H-4), 2.59 (d, *J* = 13.9 Hz, 1H, H-4), 1.75 (qd, *J* = 7.4, 4.0 Hz, 2H, H-2), 1.69 – 1.29 (m, 10H, H-11, H-12 and H-13), 1.26 (t, *J* = 7.1 Hz, 3H, H-7), 0.94 (t, *J* = 7.5 Hz, 3H, H-1). **¹³C NMR** (126 MHz, CDCl₃) δ 170.9, 97.1, 75.2, 62.1, 60.5, 42.6, 38.0, 37.6, 32.9, 25.4, 24.0, 23.9, 14.2, 8.8; **m/z HRMS** (ESI) found [M+H]⁺ 256.1905, C₁₄H₂₆NO₃ requires 256.1907.

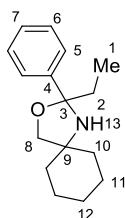
Ethyl 2-(2-ethyl-4,4-dimethyloxazolidin-2-yl)acetate (246b)

To a solution of 2-amino-2-methylpropan-1-ol (500 mg, 5.61 mmol, 1.0 equiv) in methanol (25 mL) was added ethyl pent-2-ynoate (1.06 g, 8.41 mmol, 1.5 equiv). The resulting solution was heated at reflux for 10 hours. The solvent was then removed under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a colourless oil (713 mg, 3.31 mmol, 59%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.22; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2970, 2934, 1723, 1464, 1367, 1198, 1096, 1049, 917, 815, 779; **¹H NMR** (500 MHz, CDCl₃) δ 4.14 (q, *J* = 7.1 Hz, 2H, H-6), 3.59 (d, *J* = 8.0 Hz, 1H, H-8), 3.55 (d, *J* = 8.0 Hz, 1H, H-8), 2.64 (d, *J* = 14.0 Hz, 1H, H-4), 2.61 (d, *J* = 14.0 Hz, 1H, H-4), 1.77 (tt, *J* = 7.6, 4.0 Hz, 2H, H-2), 1.27 (s, 3H, H-10), 1.27 (t, *J* = 7.1 Hz, 3H, H-7), 1.24 (s, 3H, H-10); **¹³C NMR** (126 MHz, CDCl₃) δ 170.9, 97.8, 77.3, 60.6, 59.1, 42.4, 32.9, 28.6, 27.9, 14.2, 8.8; *m/z* **HRMS** (ESI) found [M+H]⁺ 216.1588, C₁₁H₂₂NO₃ requires 216.1588.

2-Ethyl-2-(trifluoromethyl)-3-oxa-1-azaspiro[4.5]decane (248)

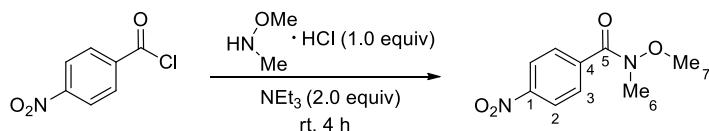
Prepared according to General Procedure B using (*1-aminocyclohexyl)methanol* **182** (100 mg, 0.77 mmol, 1.0 equiv) and 1,1,1-trifluorobutan-2-one (1 mL, 7.37 mmol, 9.5 equiv); purification by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (98 mg, 0.41 mmol, 53%); **R_f** (ethyl acetate in petroleum ether, 25%): 0.24; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2931, 2858, 1453, 1382, 1300, 1153, 1082, 1045, 945, 814, 714; **¹H NMR** (500 MHz, CDCl₃) δ 3.92 – 3.76 (m, 2H, H-5), 2.00 – 1.84 (m, 2H, H-2), 1.80 – 1.24 (m, 10H, H-8, H-9 and H-10), 1.00 (td, *J* = 7.5, 0.7 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 125.1 (q, *J* = 289.1 Hz), 95.5 (q, *J* = 28.9 Hz), 77.3, 62.3, 38.1, 37.2, 26.1, 25.1, 24.2, 23.8, 6.7; **¹⁹F NMR** (376 MHz, MeOD) δ -86.15; *m/z* **HRMS** (ESI) found [M+H]⁺ 238.1412, C₁₁H₁₉F₃NO requires 238.1411.

2-Ethyl-2-phenyl-3-oxa-1-azaspiro[4.5]decane (251)

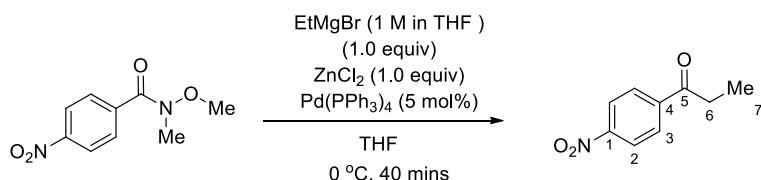


Prepared according to general procedure A using (*1-aminocyclohexyl)methanol* **182** (500 mg, 3.87 mmol, 1.0 equiv) and propiophenone (1.56 g, 11.6 mmol, 3.0 equiv); purification by flash chromatography on silica gel, eluting with toluene, afforded the title compound as a colourless oil (350 mg, 1.43 mmol, 37%); R_f (ethyl acetate in petroleum ether, 25%): 0.34; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2927, 2854, 1602, 1448, 1196, 1173, 1045, 919, 814, 757, 702; **¹H NMR** (500 MHz, CDCl₃) δ 7.56 – 7.51 (m, 2H, H-5), 7.34 – 7.27 (m, 2H, H-6), 7.25 – 7.20 (m, 1H, H-7), 3.66 (d, J = 8.0 Hz, 1H, H-8), 3.46 (d, J = 8.0 Hz, 1H, H-8), 1.92 – 1.75 (m, 2H, H-2), 1.74 – 1.49 (m, 4H, H-10, H-11), 1.45 – 1.29 (m, 3H, H-11, H-12), 1.24 – 1.04 (m, 3H, H-10, H-12), 0.81 (t, J = 7.5 Hz, 3H, H-1); **¹³C NMR** (101 MHz, CDCl₃) δ 145.17, 127.63, 126.89, 126.43, 99.24, 75.20, 62.68, 38.16, 36.96, 35.96, 25.45, 24.17, 23.39, 8.56; *m/z* **HRMS** (ESI) found [M+H]⁺ 246.1846, C₁₆H₂₄NO requires 246.1852.

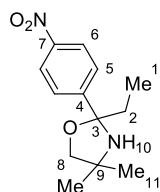
N-Methoxy-N-methyl-4-nitrobenzamide (254)



To a solution of 4-nitrobenzoyl chloride (3.00 g, 16.2 mmol, 1.0 equiv) and triethylamine (4.51 mL, 32.3 mmol, 2.0 equiv) in dry dichloromethane (32 mL) at 0 °C was added *N,O*-dimethylhydroxylamine hydrochloride (1.58 g, 16.2 mmol, 1.0 equiv). The reaction mixture was then warmed to room temperature stirred for another 2 hours. Saturated ammonium chloride was added to the mixture and layers separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to yield the title compound as a yellow solid (2.82 g, 13.4 mmol, 83%), which was taken on to the next step without further purification; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2953, 2854, 1685, 1543, 1390, 1362, 1177, 1071, 991, 914, 756; **¹H NMR** (400 MHz, CDCl₃) δ 8.26 (d, J = 8.9 Hz, 2H, H-2), 7.84 (d, J = 8.9 Hz, 2H, H-3), 3.53 (s, 3H, H-7), 3.39 (s, 3H, H-6); **¹³C NMR** (101 MHz, CDCl₃) δ 167.7, 148.9, 140.1, 129.2, 123.2, 61.4, 33.2. The physical data were identical in all respect to that previously reported.¹⁶³

1-(4-Nitrophenyl)propan-1-one (255)

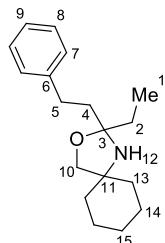
To a solution of ethyl magnesium bromide (1 M in tetrahydrofuran; 5.39 mL, 5.39 mmol, 1.0 equiv) in dry tetrahydrofuran (20 mL) at 0 °C was added zinc(II) chloride (1 M in diethyl ethyl, 4.90 mL, 4.90 mmol, 1.0 equiv). The mixture was stirred at this temperature for 10 minutes then warmed to room temperature and stirred for a further 20 minutes. The mixture was then cooled to 0 °C followed by addition of tetrakis(triphenylphosphine)palladium(0) (283 mg, 0.25 mmol, 0.05 equiv) and a solution *N*-methoxy-*N*-methyl-4-nitrobenzamide **254** (1.00 g, 5.39 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL). The reaction mixture was stirred at temperature for 40 minutes and then quenched with 3 N HCl to adjust to ~pH=1. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the title compound as a yellow solid (404 mg, 2.25 mmol, 46%); **R**_f (ethyl acetate in petroleum ether, 10%): 0.30; **IR** $\nu_{\max}/\text{cm}^{-1}$ (film): 2985, 1686, 1602, 1519, 1341, 1320, 1211, 953, 852, 804, 740, 682; **1H NMR** (400 MHz, CDCl₃) δ 8.31 (d, *J* = 9.0 Hz, 2H, H-2), 8.11 (d, *J* = 9.0 Hz, 1H, H-3), 3.06 (q, *J* = 7.2 Hz, 1H, H-6), 1.26 (t, *J* = 7.2 Hz, 2H, H-7); **13C NMR** (101 MHz, CDCl₃) δ 199.1, 150.3, 141.3, 129.0, 123.9, 32.5, 7.9. The physical data were identical in all respect to that previously reported.¹⁶⁴

2-Ethyl-4,4-dimethyl-2-(4-nitrophenyl)oxazolidine (256)

Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (120 mg, 362 mmol, 1.0 equiv) and *1-(4-nitrophenyl)propan-1-one* **255** (362 mg, 2.02 mmol, 1.5 equiv) except with the use of boron trifluoride etherate (0.02 mL, 0.14 mmol) instead of *para*-toluenesulfonic acid; purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a yellow solid (84 mg, 0.34 mmol, 25%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.27; **IR** $\nu_{\max}/\text{cm}^{-1}$ (film): 2968, 2212, 2016, 1598, 1521, 1348, 1222, 1046, 922, 854, 754, 703; **1H NMR** (500 MHz, CDCl₃) δ 8.17 (d, *J* = 8.9 Hz, 2H, H-6), 7.73 (d, *J* = 8.9 Hz, 2H, H-5), 3.59 (d, *J* = 7.9 Hz, 1H, H-8), 3.49 (d, *J* = 7.9 Hz, 1H, H-8), 1.94 – 1.69 (m, 2H, H-2), 1.31 (s, 3H, H-11), 0.85 (s, 3H, H-11), 0.82 (t,

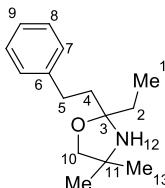
$J = 7.5$ Hz, 3H, H-1); **13C NMR** (126 MHz, CDCl₃) δ 159.2, 147.2, 127.6, 123.0, 99.4, 59.7, 35.7, 28.1, 27.5, 8.3; m/z **HRMS** (ESI) found [M+H]⁺ 251.1392, C₁₃H₁₉N₂O₃ requires 251.1390.

2-Ethyl-2-phenethyl-3-oxa-1-azaspiro[4.5]decane (258a)



Prepared according to General Procedure A using (*1-aminocyclohexyl)methanol* **182** (478 mg, 3.70 mmol, 1.2 equiv) and 1-phenylpentan-3-one (500 mg, 3.08 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil (520 mg, 1.90 mmol, 62%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.26; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2928, 2854, 1604, 1496, 1451, 1054, 814, 746, 698; **1H NMR** (500 MHz, CDCl₃) δ 7.28 (t, $J = 6.6$ Hz, 2H, H-8), 7.22 – 7.14 (m, 2H, H-7 and H-9), 3.67 (d, $J = 8.3$ Hz, 1H, H-10), 3.64 (d, $J = 8.3$ Hz, 1H, H-10), 2.77 – 2.59 (m, 2H, H-5), 1.93 – 1.84 (m, 2H, H-4), 1.74 – 1.26 (m, 13H, H-2, H-13, H-14 and H-15), 0.95 (t, $J = 7.5$ Hz, 3H, H-1); **13C NMR** (126 MHz, CDCl₃) δ 142.5, 128.4(x2), 128.3(x2), 125.7, 98.3, 74.7, 62.1, 39.9, 38.2, 38.1, 31.1, 31.0, 25.4, 24.0, 23.9, 8.7; m/z **HRMS** (ESI) found [M+H]⁺ 274.2161, C₁₈H₂₇NO requires 274.2165.

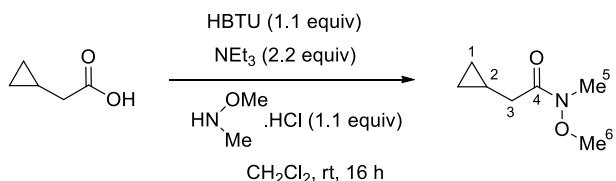
2-Ethyl-4,4-dimethyl-2-phenethyloxazolidine (258b)



Prepared according to General Procedure A using 2-amino-2-methylpropan-1-ol (412 mg, 4.62 mmol, 1.5 equiv) and 1-phenylpentan-3-one (500 mg, 3.08 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, afforded the title compound as a pale yellow oil (250 mg, 1.07 mmol, 35%); **R**_f (ethyl acetate in petroleum ether, 25%): 0.23; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2964, 2891, 1496, 1455, 1364, 1200, 1054, 900, 841, 746; **1H NMR** (500 MHz, CDCl₃) δ 7.30 – 7.26 (m, 2H, H-8), 7.22 – 7.16 (m, 3H, H-7 and H-9), 3.62 (d, $J = 8.1$ Hz, 1H, H-10), 3.60 (d, $J = 8.1$ Hz, 1H, H-10), 2.75 – 2.61 (m, 2H, H-5), 1.91 (dd, $J = 12.9, 4.8$ Hz, 2H, H-4), 1.78 – 1.65 (m, 2H, H-2), 1.27 (s, 3H, H-13), 1.26 (s, 3H, H-13), 0.97 (t, $J = 7.5$ Hz, 3H, H-1); **13C NMR** (126 MHz, CDCl₃) δ 142.5,

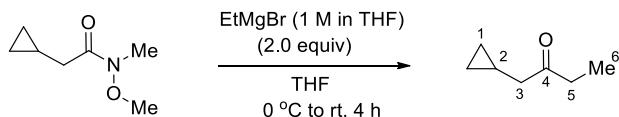
128.5, 128.4, 125.9, 99.3, 77.1, 59.1, 39.9, 31.2, 31.1, 28.7, 28.7, 8.9; m/z **HRMS** (ESI) found [M+H]⁺ 234.1846, C₁₅H₂₄NO requires 234.1851.

2-Cyclopropyl-N-methoxy-N-methylacetamide (261)



To a solution of 2-cyclopropylacetic acid (5.00 g, 49.9 mmol, 1.0 equiv) and triethylamine (54.9 mL, 109 mmol, 2.2 equiv) in dry dichloromethane (150 mL) at 0 °C was added *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (20.8 g, 54.9 mmol, 1.1 equiv) and *N,O*-dimethylhydroxylamine hydrochloride (5.35 g, 54.9 mmol, 1.1 equiv). The reaction mixture was warmed to room temperature and stirred for 16 hours. Saturated ammonium chloride was added to the mixture and layers separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (5.65 g, 39.5 mmol, 79%); **R**_f (ethyl acetate in petroleum ether, 25%): 0.27; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3003, 2942, 1659, 1463, 1414, 1367, 1176, 1008, 979, 951, 832, 805, 772, 670; **¹H NMR** (400 MHz, CDCl₃) δ 3.66 (s, 3H, H-6), 3.19 (s, 3H, H-5), 2.34 (d, *J* = 6.9 Hz, 2H, H-3), 1.16 – 0.99 (m, 1H, H-2), 0.60 – 0.49 (m, 2H, H-1), 0.20 – 0.12 (m, 2H, H-1); **¹³C NMR** (101 MHz, CDCl₃) δ 182.8, 61.5, 37.4, 32.2, 6.7, 4.4. The physical data were identical in all respect to that previously reported.¹⁶⁵

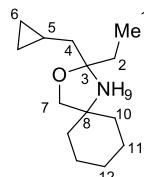
1-Cyclopropylbutan-2-one (262)



To a solution of 2-cyclopropyl-N-methoxy-N-methylacetamide **261** (4.5 g, 10.5 mmol, 1.0 equiv) in dry tetrahydrofuran (120 mL) at 0 °C was added ethyl magnesium bromide (3 M in diethyl ether; 21.0 mL, 62.9 mmol, 2.0 equiv) dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 4 hours and then slowly quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to afford the title compound as a yellow oil (2.0 g, 17.8 mmol, 57%) which was used in the next step without further purification; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2965, 2924, 1714, 1460, 1378, 1259, 1095, 1017, 954, 867, 798; **¹H NMR** (400 MHz, CDCl₃) δ 2.48 (q, *J* = 7.3

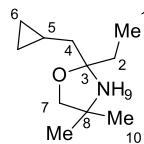
Hz, 2H, H-5), 2.28 (d, $J = 7.0$ Hz, 2H, H-3), 1.06 (t, $J = 7.3$ Hz, 3H, H-6), 1.03 – 0.93 (m, 1H, H-2), 0.62 – 0.51 (m, 2H, H-1), 0.16 – 0.07 (m, 2H, H-1); ^{13}C NMR (101 MHz, CDCl_3) δ 212.0, 48.1, 35.9, 8.1, 6.9, 4.9. The physical data were identical in all respect to that previously reported.¹⁶⁶

2-(Cyclopropylmethyl)-2-ethyl-3-oxa-1-azaspiro[4.5]decane (263)



Prepared according to General Procedure A using (*1-aminocyclohexyl)methanol* **182** (276 mg, 2.14 mmol, 1.2 equiv) and *1-cyclopropylbutan-2-one* **262** (200 mg, 1.78 mmol, 1.0 equiv); purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, afforded the title compound as a colourless oil 235 mg, 1.05 mmol, 59%; \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.34; IR ν_{max} /cm⁻¹ (film): 2927, 2853, 1450, 1261, 1176, 1112, 1052, 1017, 936, 822, 765; ^1H NMR (500 MHz, CDCl_3) δ 3.65 (d, $J = 8.2$ Hz, 1H, H-7), 3.62 (d, $J = 8.2$ Hz, 1H, H-7), 1.98 (s, 1H, NH), 1.78 – 1.25 (m, 14H, H-2, H-4, H-10, H-11 and H-12), 0.89 (t, $J = 7.5$ Hz, 3H, H-1), 0.83 – 0.70 (m, 1H, H-5), 0.55 – 0.41 (m, 2H, H-6), 0.15 – 0.03 (m, 2H, H-6); ^{13}C NMR (126 MHz, CDCl_3) δ 99.1, 74.6, 62.2, 42.2, 38.2, 38.1, 31.7, 25.4, 24.1, 23.9, 8.9, 6.2, 4.8, 3.9; m/z HRMS (ESI) found [M+H]⁺ 224.2009, $\text{C}_{14}\text{H}_{26}\text{NO}$ requires 224.2009.

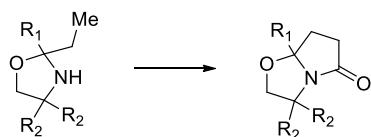
2-(Cyclopropylmethyl)-2-ethyl-4,4-dimethyloxazolidine (267)



Prepared according to General Procedure C using 2-amino-2-methylpropan-1-ol (954 mg, 10.7 mmol, 1.5 equiv) and *1-cyclopropylbutan-2-one* **262** (800 mg, 7.13 mmol, 1.0 equiv); purification by a silica plug, eluting with 0 to 50% diethyl ether in petroleum ether afforded the title compound as a colourless oil (549 mg, 3.00 mmol, 42%); IR ν_{max} /cm⁻¹ (film): 2966, 2958, 1463, 1364, 1196, 1054, 1040, 987, 824, 753; ^1H NMR (500 MHz, CDCl_3) δ 3.60 (d, $J = 8.0$ Hz, 1H, H-7), 3.57 (d, $J = 8.0$ Hz, 1H, H-7), 2.08 (s, 1H, NH), 1.80 – 1.63 (m, 3H, H-2 and H-4), 1.41 (dd, $J = 14.4, 7.6$ Hz, 1H, H-4), 1.26 (s, 3H, H-10), 1.25 (s, 3H, H-10), 0.90 (t, $J = 7.5$ Hz, 3H, H-1), 0.82 – 0.69 (m, 1H, H-5), 0.55 – 0.39 (m, 2H, H-6), 0.16 – 0.03 (m, 2H, H-6); ^{13}C NMR (126 MHz, CDCl_3) δ 100.0, 77.3, 59.0, 42.1, 31.6, 28.6, 28.5, 8.9, 6.2, 4.8, 3.9; m/z HRMS (ESI) found [M+H]⁺ 184.1696, $\text{C}_{11}\text{H}_{22}\text{NO}$ requires 184.1696.

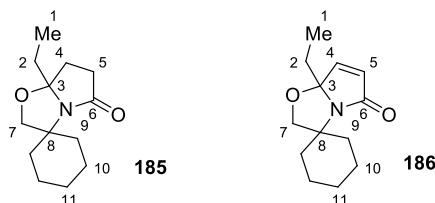
5.3 C–H carbonylation: Carbonylation products

General Procedure D for C–H carbonylation.



To a flame dried round bottom flask, equipped with a stir bar, was charged the *N,O*-ketal (0.20 mmol), palladium(II) acetate (0.02 mmol, 0.1 equiv), silver(I) acetate (0.40 mmol, 2.0 equiv) and toluene (0.05 M). The reaction flask was evacuated and back-filled with carbon monoxide (3-times, balloon). A balloon filled with carbon monoxide was fitted and then the flask was placed in a pre-heated oil bath at 120 °C and heated at this temperature for 16 hours under vigorous stirring. The reaction mixture was then cooled to room temperature and filtered through a small pad of Celite®. The filtrate was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the desired lactam.

7a'-Ethyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (**185**) and 7a'-ethyl-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(7a'H)-one (**186**)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, provided *7a'-ethyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one* **185** as a pale yellow oil (34 mg, 0.15 mmol, 76%), and *7a'-ethyl-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(7a'H)-one* **186** as a colourless oil (2 mg, 0.01 mmol, 5%).

7a'-Ethyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (**185**):

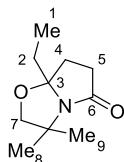
R_f (ethyl acetate in petroleum ether, 25%): 0.22; **IR** ν_{max} /cm⁻¹ (film): 2943, 1683, 1453, 1385, 1263, 131, 963, 920, 805, 657; **¹H NMR** (500 MHz, CDCl₃) δ 4.24 (d, *J* = 9.0 Hz, 1H, H-7), 3.95 (dd, *J* = 9.0, 2.0 Hz, 1H, H-7), 2.79 – 2.70 (m, 1H, H-9), 2.67 (ddd, *J* = 17.0, 9.4, 6.1 Hz), 2.50 (ddd, *J* = 17.0, 9.7, 0.9 Hz, 1H, H-5), 2.20 (ddd, *J* = 12.3, 8.1, 0.9 Hz, 1H, H-4), 2.15 – 2.02 (m, 1H, H-9), 1.95 – 1.88 (m, 1H, H-4), 1.87 – 1.78 (m, 2H, H-2 and H-10), 1.76 – 1.63 (m, 3H, H-2, H-9 and H-11), 1.61 – 1.56 (m, 1H, H-10), 1.46 (dd, *J* = 10.4, 2.6 Hz, 1H, H-9), 1.33 – 1.18 (m, 2H, H-10), 1.09 – 1.00 (m, 1H, H-11), 0.96 (t, *J* =

7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 173.0, 102.9, 77.4, 61.4, 36.8, 36.2, 32.0, 30.9, 28.8, 24.5, 24.5, 23.7, 8.3; m/z **HRMS** (ESI) found [M+H]⁺ 224.1644, C₁₃H₂₂NO₂ requires 224.1645.

7a'-Ethyl-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(7a'H)-one (186):

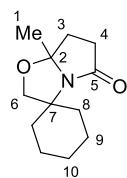
R_f (ethyl acetate in petroleum ether, 25%): 0.28; **IR** ν_{max}/cm⁻¹ (film): 2930, 2860, 1973, 1704, 1455, 1332, 1253, 958, 814, 689; **¹H NMR** (500 MHz, CDCl₃) δ 6.97 (d, *J* = 5.8 Hz, 1H, H-4), 5.99 (d, *J* = 5.8 Hz, 1H, H-5), 4.24 (d, *J* = 8.9 Hz, 1H, H-7), 4.14 (dd, *J* = 8.9, 1.7 Hz, 1H, H-9), 2.79 – 2.54 (m, 1H, H-9), 2.04 – 1.92 (m, 2H, H-2 and H-10), 1.90 – 1.80 (m, 3H, H-2, H-9 and H-10), 1.77 – 1.69 (m, 1H, H-11), 1.63 – 1.57 (m, 1H, H-10), 1.44 – 1.38 (m, 1H, H-9), 1.32 – 1.23 (m, 2H, H-9 and H-10), 1.17 – 1.05 (m, 1H, H-11), 0.88 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 174.2, 148.6, 130.9, 104.4, 79.1, 63.0, 37.6, 30.7, 28.3, 24.7, 24.3, 23.9, 8.4; m/z **HRMS** (ESI) found [M+H]⁺ 222.1486, C₁₃H₂₀NO₂ requires 222.1489.

7a-Ethyl-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (192)



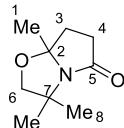
Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (28 mg, 0.15 mmol, 77%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.11; **IR** ν_{max}/cm⁻¹ (film): 2972, 2935, 1696, 1460, 1367, 1268, 1230, 1125, 1043, 1002, 961, 809, 683, 667; **¹H NMR** (500 MHz, CDCl₃) δ 3.99 (d, *J* = 8.8 Hz, 1H, H-7), 3.95 (d, *J* = 8.8 Hz, 1H, H-7), 2.65 (ddd, *J* = 17.0, 12.0, 8.2 Hz, 1H, H-5), 2.49 (ddd, *J* = 17.0, 9.7, 0.8 Hz, 1H, H-5), 2.22 (ddd, *J* = 12.4, 8.1, 0.9 Hz, 1H, H-4), 1.99 – 1.89 (m, 1H, H-4), 1.89 – 1.80 (m, 1H, H-2), 1.74 – 1.65 (m, 1H, H-2), 1.57 (s, 3H, H-8 or H-9), 1.40 (s, 3H, H-8 or H-9), 0.97 (t, *J* = 7.5 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 173.7, 103.5, 81.5, 57.9, 35.6, 32.0, 28.6, 26.6, 24.6, 8.3; m/z **HRMS** (ESI) found [M+H]⁺ 184.1331, C₁₀H₁₈NO₂ requires 184.1332.

7a'-Methyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (204a)



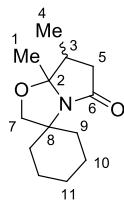
Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (30 mg, 0.14 mmol, 72%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.21; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2930, 2860, 2163, 2026, 1695, 1455, 1369, 1250, 1191, 1085, 1030, 993, 899, 841, 809, 690, 667; **¹H NMR** (500 MHz, CDCl_3) δ 4.26 (d, $J = 9.0$ Hz, 1H, H-6), 4.03 (dd, $J = 9.0, 1.9$ Hz, 1H, H-6), 2.79 – 2.62 (m, 2H, H-4 and H-8), 2.51 (ddd, $J = 16.8, 9.0, 0.9$ Hz, 1H, H-4), 2.17 – 1.99 (m, 3H, H-3, H-8 and H-9), 1.90 – 1.79 (m, 1H, H-8), 1.78 – 1.68 (m, 2H, H-3 and H-10), 1.65 – 1.54 (m, 1H, H-9), 1.48 (s, 3H, H-1), 1.46 – 1.43 (m, 1H, H-8), 1.34 – 1.18 (m, 2H, H-2 and H-9), 1.11 – 0.99 (m, 1H, H-10); **¹³C NMR** (126 MHz, CDCl_3) δ 172.5, 100.6, 77.8, 77.4, 61.5, 36.7, 36.3, 36.2, 31.0, 24.6, 23.8, 23.7; m/z **HRMS** (ESI) found [M+H]⁺ 210.1486, $\text{C}_{12}\text{H}_{20}\text{NO}_2$ requires 210.1489.

3,3,7a-Trimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (204b)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (25 mg, 0.15 mmol, 74%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.15; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2975, 2876, 1693, 1457, 1365, 1258, 1201, 1131, 1085, 1036, 1002, 824, 810, 672; **¹H NMR** (500 MHz, CDCl_3) δ 4.05 (dd, $J = 8.8, 0.5$ Hz, 1H, H-6), 3.97 (d, $J = 8.8$ Hz, 1H, H-6), 2.70 (ddd, $J = 16.8, 12.3, 8.0$ Hz, 1H, H-4), 2.49 (ddd, $J = 16.8, 8.8, 1.2$ Hz, 1H, H-4), 2.15 – 2.00 (m, 2H, H-3), 1.56 (s, 3H, H-1), 1.49 (s, 3H, H-8), 1.41 (s, 3H, H-8); **¹³C NMR** (126 MHz, CDCl_3) δ 173.0, 101.0, 81.7, 57.9, 36.1, 35.6, 26.5, 24.3, 23.4; m/z **HRMS** (ESI) found [M+H]⁺ 170.1175, $\text{C}_9\text{H}_{16}\text{NO}_2$ requires 170.1176.

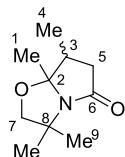
7',7a'-Dimethyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (205a) – diastereoisomeric mixture



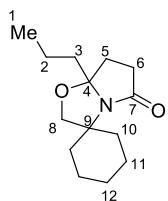
Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a 2.8:1 mixture of diastereoisomers (determined by crude NMR analysis) as a pale yellow oil (37 mg, 0.17 mmol, 83%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.21; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2928, 2860, 1693, 1453, 1368, 1214,

1190, 1031, 993, 921, 810, 689; m/z **HRMS** (ESI) found [M+H]⁺ 224.1641, C₁₃H₂₂NO₂ requires 224.1645. *Major diastereoisomer:* ¹**H NMR** (500 MHz, CDCl₃) δ 4.29 – 4.22 (m, 1H, H-7), 4.08 – 4.02 (m, 1H, H-7), 2.69 – 2.59 (m, 1H, H-9), 2.57 – 2.47 (m, 1H, H-5), 2.40 – 2.25 (m, 2H, H-3 and H-5), 2.17 – 2.03 (m, 1H, H-9), 1.87 – 1.78 (m, 1H, H-10), 1.77 – 1.68 (m, 2H, H-9 and H-11), 1.59 (ddd, *J* = 6.2, 3.3, 1.5 Hz, 1H, H-10), 1.46 – 1.43 (m, 1H, H-9), 1.31 (s, 3H, H-1), 1.30 – 1.18 (m, 2H, H-10), 1.09 – 1.00 (m, 1H, H-11), 1.05 (d, *J* = 6.7 Hz, 3H, H-4); ¹³**C NMR** (126 MHz, CDCl₃) δ 171.3, 101.70, 77.79, 61.49, 44.07, 42.69, 36.61, 30.87, 24.49, 24.45, 23.74, 18.39, 13.42. *Minor diastereoisomer:* ¹**H NMR** (500 MHz, CDCl₃) δ 4.29 – 4.22 (m, 1H, H-7), 4.08 – 4.02 (m, 1H, H-7), 2.91 (dd, *J* = 16.6, 6.8 Hz, 1H, H-5), 2.69 – 2.59 (m, 1H, H-9), 2.40 – 2.25 (m, 1H, H-3), 2.17 – 2.03 (m, 2H, H-5 and H-9), 1.87 – 1.78 (m, 1H, H-10), 1.77 – 1.68 (m, 2H, H-9 and H-11), 1.59 (ddd, *J* = 6.2, 3.3, 1.5 Hz, 1H, H-10), 1.49 (s, 3H, H-1), 1.46 – 1.43 (m, 1H, H-9), 1.30 – 1.18 (m, 2H, H-10), 1.09 – 1.00 (m, 1H, H-11), 0.97 (d, *J* = 7.0 Hz, 3H, H-4); ¹³**C NMR** (126 MHz, CDCl₃) δ 171.2, 101.2, 78.2, 60.4, 44.4, 39.3, 36.5, 30.2, 24.3, 24.3, 23.7, 18.2, 14.8.

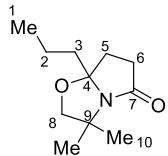
3,3,7,7a-Tetramethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (205b)



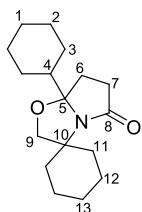
Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 30% ethyl acetate in petroleum ether, provided the title compound as a 3.1:1 mixture of diastereoisomers (determined by crude NMR analysis) as a pale yellow oil (31 mg, 0.17 mmol, 87%); R_f (ethyl acetate in petroleum ether, 25%): 0.15; **IR** ν_{max}/cm⁻¹ (film): 2972, 2875, 1694, 1458, 1366, 1263, 1170, 1052, 989, 923, 826, 664, 654; m/z **HRMS** (ESI) found [M+H]⁺ 184.1331, C₁₀H₁₈NO₂ requires 184.1332. *Major diastereoisomer:* ¹**H NMR** (500 MHz, CDCl₃) δ 4.10 – 4.03 (m, 1H, H-7), 3.99 – 3.94 (m, 1H, H-7), 2.51 (dd, *J* = 14.5, 6.5 Hz, 1H, H-5), 2.43 – 2.26 (m, 2H, H-3 and H-5), 1.54 (s, 3H, H-9), 1.41 (s, 3H, H-9), 1.33 (s, 3H, H-1), 1.07 (d, *J* = 6.5 Hz, 3H, H-4); ¹³**C NMR** (126 MHz, CDCl₃) δ 172.0, 102.3, 81.9, 58.1, 43.5, 42.7, 26.4, 24.2, 18.3, 13.5. *Minor diastereoisomer:* ¹**H NMR** (500 MHz, CDCl₃) δ 4.10 – 4.03 (m, 1H, H-7), 3.99 – 3.94 (m, 1H, H-7), 2.90 (dd, *J* = 16.6, 6.8 Hz, 1H, H-5), 2.43 – 2.26 (m, 2H, H-3 and H-5), 2.06 (d, *J* = 16.6 Hz, 1H, H-5), 1.54 (s, 3H, H-9), 1.48 (s, 3H, H-1), 1.42 (s, 3H, H-9), 0.99 (d, *J* = 7.0 Hz, 3H, H-4); ¹³**C NMR** (126 MHz, CDCl₃) δ 171.8, 101.8, 82.3, 57.0, 43.9, 39.5, 26.5, 24.2, 23.5, 14.8.

7a'-Propyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (206a)

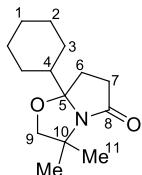
Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (34 mg, 0.14 mmol, 73%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.29; **IR** ν_{max} /cm⁻¹ (film): 2929, 2856, 1698, 1452, 1377, 1250, 1190, 1136, 1085, 1052, 995, 905, 807, 657; **¹H NMR** (500 MHz, CDCl₃) δ 4.24 (d, *J* = 9.0 Hz, 1H, H-8), 3.97 (dd, *J* = 9.0, 2.0 Hz, 1H, H-8), 2.79 – 2.69 (m, 1H, H-10), 2.64 (ddd, *J* = 16.9, 9.4, 6.1 Hz, 1H, H-6), 2.50 (ddd, *J* = 16.9, 9.7, 0.8 Hz, 1H, H-6), 2.21 (ddd, *J* = 12.3, 8.0, 0.8 Hz, 1H, H-5), 2.14 – 2.06 (m, 1H, H-10), 1.98 – 1.69 (m, 5H, H-5, H-10 and H-11 and H-12), 1.67 – 1.59 (m, 1H, H-3), 1.51 – 1.16 (m, 6H, H-2, H-10 and H-11), 1.10 – 1.00 (m, 1H, H-12), 0.97 (t, *J* = 7.4 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 172.9, 102.5, 77.4, 61.4, 38.3, 36.8, 36.1, 32.6, 30.9, 24.6, 24.5, 23.7, 17.4, 14.4; m/z **HRMS** (ESI) found [M+H]⁺ 238.1802, C₁₄H₂₄NO₂ requires 238.1802.

3,3,7a-Trimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (206b)

Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a colourless oil which solidified on standing (14 mg, 0.07 mmol, 35%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.14; **IR** ν_{max} /cm⁻¹ (film): 2952, 2915, 1665, 1459, 1368, 1281, 1232, 1125, 1043, 1014, 961, 809, 683; **¹H NMR** (500 MHz, CDCl₃) δ 4.00 (dd, *J* = 8.8, 0.6 Hz, 1H, H-8), 3.95 (d, *J* = 8.8 Hz, 1H, H-8), 2.65 (ddd, *J* = 17.0, 12.1, 8.1 Hz, 1H, H-6), 2.48 (ddd, *J* = 12.4, 9.7, 0.9 Hz, 1H, H-6), 2.23 (ddd, *J* = 12.4, 8.1, 0.9 Hz, 1H, H-5), 2.00 – 1.90 (m, 1H, H-5), 1.85 – 1.75 (m, 1H, H-3), 1.69 – 1.60 (m, 1H, H-3), 1.56 (s, 3H, H-10), 1.50 – 1.34 (m, 2H, H-2), 1.41 (s, 3H, H-10), 0.97 (t, *J* = 7.4 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 173.6, 103.1, 81.6, 57.9, 38.1, 35.6, 32.7, 26.7, 24.6, 17.4, 14.3; m/z **HRMS** (ESI) found [M+H]⁺ 198.1490, C₁₁H₂₀NO₂ requires 198.1494.

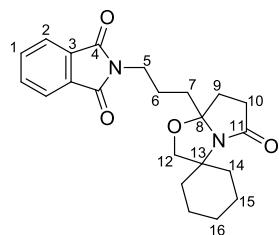
7a'-Cyclohexyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (207a)

Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (43 mg, 0.16 mmol, 78%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.24; **IR** ν_{max} /cm⁻¹ (film): 2927, 2855, 1693, 1454, 1383, 1357, 1184, 1029, 1003, 894, 729; **¹H NMR** (500 MHz, CDCl₃) δ 4.19 (d, *J* = 9.0 Hz, 1H, H-9), 3.97 (dd, *J* = 9.0, 2.0 Hz, 1H, H-9), 2.97 – 2.73 (m, 1H, H-11), 2.66 – 2.44 (m, 2H, H-7), 2.34 – 2.22 (m, 1H, H-6), 2.17 – 2.02 (m, 1H, H-11), 1.95 – 1.54 (m, 11H, H-2, H-3, H-4, H-6 and H-11), 1.48 – 1.36 (m, 1H, H-11), 1.34 – 0.91 (m, 8H, H-1, H-12 and H-13); **¹³C NMR** (126 MHz, CDCl₃) δ 174.0, 104.9, 77.0, 61.7, 43.8, 37.3, 36.7, 31.1, 28.7, 26.9, 26.9, 26.5, 26.4, 26.1, 24.7, 24.5, 23.7; **m/z HRMS** (ESI) found [M+H]⁺ 278.2117, C₁₇H₂₈NO₂ requires 278.2115.

7a-Cyclohexyl-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (207b)

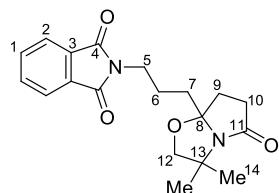
Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (30 mg, 0.13 mmol, 63%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.14; **IR** ν_{max} /cm⁻¹ (film): 2931, 2158, 1740, 1703, 1450, 1365, 1358, 1233, 1006; **¹H NMR** (500 MHz, CDCl₃) δ 4.01 (d, *J* = 8.8 Hz, 1H, H-9), 3.94 (d, *J* = 8.8 Hz, 1H, H-9), 2.63 – 2.44 (m, 2H, H-7), 2.30 (ddd, *J* = 12.9, 8.4, 1.4 Hz, 1H, H-6), 1.92 – 1.67 (m, 6H, H-1, H-2, H-3, H-4, H-6), 1.59 (s, 3H, H-11), 1.41 (s, 3H, H-11), 1.28 – 0.96 (m, 6H, H-1, H-2 and H-3); **¹³C NMR** (126 MHz, CDCl₃) δ 174.7, 105.5, 81.3, 58.1, 43.5, 36.1, 28.8, 27.2, 26.9, 26.6, 26.4, 26.1, 24.9; **m/z HRMS** (ESI) found [M+H]⁺ 238.1796, C₁₄H₂₄NO₂ requires 238.1800.

2-{3-(5'-Oxotetrahydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-7a'-yl)propyl}isoindoline-1,3-dione (238a)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (62 mg, 0.16 mmol, 81%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.31; **IR** ν_{max} /cm⁻¹ (film): 2932, 2860, 1773, 1706, 1395, 1360, 1228, 1188, 1063, 1030, 998, 914, 720; **¹H NMR** (500 MHz, CDCl₃) δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H, H-2), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H, H-1), 4.23 (d, *J* = 9.1 Hz, 1H, H-12), 3.97 (dd, *J* = 9.1, 1.9 Hz, 1H, H-12), 3.81 – 3.63 (m, 2H, H-5), 2.74 – 2.68 (m, 1H, H-14), 2.51 (ddd, *J* = 17.1, 9.8, 2.5 Hz, 1H, H-10), 2.51 (dd, *J* = 17.1, 9.5 Hz, 1H, H-10), 2.23 – 2.14 (m, 1H, H-9), 2.14 – 2.03 (m, 1H, H-14), 1.97 – 1.65 (m, 8H, H-6, H-7, H-9, H-14, H-15 and H-16), 1.64 – 1.53 (m, 1H, H-15), 1.48 – 1.38 (m, 1H, H-14), 1.32 – 1.16 (m, 2H, H-15), 1.09 – 0.96 (m, 1H, H-16); **¹³C NMR** (126 MHz, CDCl₃) δ 172.8, 168.3, 134.0, 132.0, 123.3, 102.0, 77.5, 61.6, 37.9, 36.8, 36.0, 33.2, 32.5, 30.9, 24.5, 24.4, 23.7, 23.5; **m/z HRMS** (ESI) found [M+H]⁺ 383.1969, C₂₂H₂₇N₂O₄ requires 383.1970.

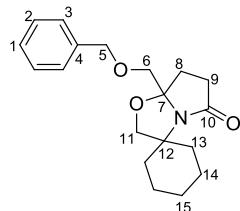
2-{3-(3,3-Dimethyl-5-oxohexahydropyrrolo[2,1-*b*]oxazol-7a-yl)propyl}isoindoline-1,3-dione (238b)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (54 mg, 0.16 mmol, 79%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.23; **IR** ν_{max} /cm⁻¹ (film): 2976, 2952, 1773, 1704, 1466, 1396, 1366, 1273, 1124, 1058, 1002, 882, 721, 667; **¹H NMR** (500 MHz, CDCl₃) δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H, H-2), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H, H-1), 4.00 (d, *J* = 9.2 Hz, 1H, H-12), 3.94 (d, *J* = 8.9 Hz, 1H, H-12), 3.81 – 3.64 (m, 2H, H-5), 2.63 (ddd, *J* = 17.0, 12.3, 8.0 Hz, 1H, H-10), 2.51 (dd, 1H, *J* = 17.0, 11.9 Hz, H-10), 2.20 (ddd, *J* = 12.3, 8.0, 0.8 Hz, 1H, H-9), 2.02 – 1.66 (m, 5H, H-6, H-7 and H-9), 1.55 (s, 3H, H-14), 1.40 (s, 3H, H-14); **¹³C NMR** (126 MHz, CDCl₃) δ 173.5, 168.3, 134.1, 132.0, 123.3,

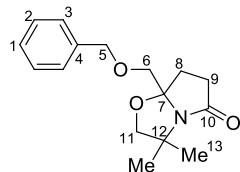
102.6, 81.6, 58.1, 37.9, 35.4, 33.0, 32.5, 26.7, 24.5, 23.5; m/z **HRMS** (ESI) found [M+H]⁺ 343.1656, C₂₀H₂₅N₂O₄ requires 343.1652.

7a'-{(BenzylOxy)methyl}dihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (239a)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (50 mg, 0.16 mmol, 79%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.31; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2928, 2858, 1695, 1453, 1367, 1272, 1108, 1028, 991, 738, 699; **¹H NMR** (500 MHz, CDCl₃) δ 7.41 – 7.27 (m, 5H, H-1, H-2 and H-3), 4.63 (d, *J* = 12.2 Hz, 1H, H-5), 4.56 (d, *J* = 12.2 Hz, 1H, H-5), 4.25 (d, *J* = 9.0 Hz, 1H, H-11), 4.00 (dd, *J* = 9.0, 1.9 Hz, 1H, H-11), 3.59 (d, *J* = 10.1 Hz, 1H, H-6), 3.46 (d, *J* = 10.1 Hz, 1H, H-6), 2.78 – 2.67 (m, 2H, H-9 and H-13), 2.52 (dd, *J* = 15.0, 8.8 Hz, 1H, H-9), 2.39 (dd, *J* = 11.9, 8.8, Hz, 2H, H-8), 2.12 – 1.99 (m, 1H, H-13), 1.92 (apparent q, *J* = 6.2, 1H, H-8), 1.88 – 1.80 (m, 1H, H-14), 1.72 – 1.56 (m, 3H, H-13, H-14 and H-15), 1.51 – 1.42 (m, 1H, H-13), 1.30 – 1.17 (m, 2H, H-14), 1.06 – 0.90 (m, 1H, H-15); **¹³C NMR** (126 MHz, CDCl₃) δ 174.0, 137.7, 128.5, 127.8, 127.7, 101.1, 78.5, 73.6, 71.1, 61.8, 36.6, 36.3, 31.9, 31.1, 24.6, 24.5, 23.7; m/z **HRMS** (ESI) found [M+H]⁺ 316.1908, C₁₉H₂₆NO₂ requires 316.1907.

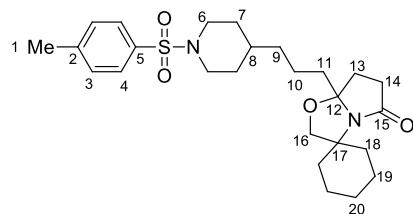
7a-{(BenzylOxy)methyl}-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (239b)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (41 mg, 0.15 mmol, 74%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.23; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2973, 2870, 1698, 1454, 1365, 1264, 1199, 1104, 1071, 1029, 1001, 738, 698, 618; **¹H NMR** (500 MHz, CDCl₃) δ 7.43 – 7.29 (m, 5H, Ar-H), 4.63 (d, *J* = 12.2 Hz, 1H, H-5), 4.56 (d, *J* = 12.2 Hz, 1H, H-5), 4.04 (d, *J* = 8.7 Hz, 1H, H-11), 3.97 (d, *J* = 8.7 Hz, 1H, H-11), 3.60 (dd, *J* = 10.1, 0.6 Hz, 1H, H-6), 3.49 (d, *J* = 10.1 Hz, 1H, H-6), 2.72 (ddd, *J* = 16.8, 12.0, 8.0 Hz, 1H, H-9), 2.51 – 2.32 (m, 2H, H-8 and H-9), 1.96 (td, *J* = 12.2,

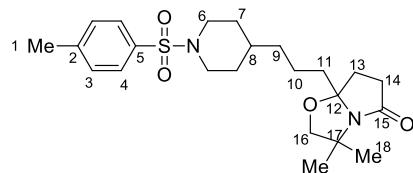
9.8 Hz, 1H, H-8), 1.57 (s, 3H, H-13), 1.36 (s, 3H, H-13); ¹³C NMR (126 MHz, CDCl₃) δ 174.6, 137.7, 128.5, 127.9, 127.7, 101.6, 82.6, 73.6, 71.2, 58.4, 35.7, 32.0, 26.5, 24.5; m/z HRMS (ESI) found [M+H]⁺ 276.1589, C₁₆H₂₂NO₃ requires 276.1593.

7a'-{3-(1-Tosylpiperidin-4-yl)propyl}dihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (240a)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 25% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (75 mg, 0.16 mmol, 80%); R_f (ethyl acetate in petroleum ether, 40%): 0.33; IR ν_{max}/cm⁻¹ (film): 2930, 1694, 1598, 1462, 1395, 1340, 1165, 1059, 986, 933, 769, 728; ¹H NMR (500 MHz, CDCl₃) δ 7.64 (d, J = 8.2 Hz, 2H, H-4), 7.32 (d, J = 8.2 Hz, 2H, H-3), 4.22 (d, J = 9.0 Hz, 1H, H-16), 3.92 (dd, J = 9.1, 1.8 Hz, 1H, H-16), 3.81 – 3.73 (m, 2H, H-6), 2.76 – 2.57 (m, 2H, H-18 and H-14), 2.49 (dd, J = 17.0, 9.1 Hz, 1H, H-14), 2.43 (s, 3H, H-1), 2.26 – 2.13 (m, 3H, H-6 and H-13), 2.10 – 2.00 (m, 1H, H-11), 1.95 – 1.80 (m, 2H, H-10 and H-13), 1.79 – 1.63 (m, 5H, H-10, H-11, H-18, H-19 and H-20), 1.48 – 1.35 (m, 2H, H-10 and H-18), 1.35 – 1.09 (m, 10H, H-7, H-8, H-9, H-18 and H-19), 1.07 – 0.94 (m, 1H, H-20); ¹³C NMR (126 MHz, CDCl₃) δ 172.8, 143.4, 133.2, 129.6, 127.7, 102.3, 61.5, 46.4, 36.8, 36.3, 36.2, 36.0, 35.2, 32.6, 31.6, 31.5, 30.9, 29.7, 24.5, 24.4, 23.7, 23.0, 21.5, 21.3; m/z HRMS (ESI) found [M+H]⁺ 475.2615, C₂₆H₃₉N₂O₄S requires 475.2612.

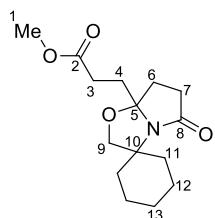
3,3-Dimethyl-7a-{3-(1-tosylpiperidin-4-yl)propyl}tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (240b)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 50% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (68 mg, 0.16 mmol, 78%); R_f (ethyl acetate in petroleum ether, 40%): 0.21; IR ν_{max}/cm⁻¹ (film): 2934, 1694, 1461, 1338, 1164, 1093, 1034, 1002, 930, 816, 729, 670; ¹H NMR (500 MHz, CDCl₃) δ 7.64 (d, J = 8.2 Hz, 2H, H-4), 7.32 (d, J = 7.9 Hz, 2H, H-3), 3.96 (d, J = 9.0 Hz, 1H, H-16), 3.93 (d, J = 9.0 Hz, 1H, H-16),

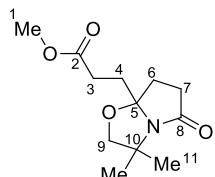
3.77 (d, $J = 11.6$ Hz, 2H, H-6), 2.61 (ddd, $J = 17.0, 12.1, 8.0$ Hz, 1H, H-14), 2.52 – 2.45 (m, 1H, H-14), 2.43 (s, 3H, H-1), 2.24 – 2.14 (m, 3H, H-6 and H-13), 1.92 (dd, $J = 17.1, 12.1$ Hz, 1H, H-13), 1.80 – 1.67 (m, 2H, H-8 and H-11), 1.63 – 1.56 (m, 2H, H-9), 1.55 (s, 3H, H-18), 1.38 (s, 3H, H-18), 1.33 – 1.12 (m, 6H, H-7, H-9 and H-11); ^{13}C NMR (126 MHz, CDCl_3) δ 173.5, 143.4, 133.2, 129.6, 127.7, 102.9, 81.5, 58.0, 46.4, 46.3, 36.3, 36.0, 35.5, 35.2, 32.6, 31.5, 26.7, 24.5, 21.5, 21.2; m/z HRMS (ESI) found [M+H]⁺ 435.2310, $\text{C}_{23}\text{H}_{35}\text{N}_2\text{O}_4\text{S}$ requires 435.2312.

Methyl 3-{5'-oxotetrahydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazo)-7a'-yl}propanoate (241a)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (43 mg, 0.15 mmol, 77%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.19; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2932, 2860, 1736, 1694, 1452, 1380, 1260, 1175, 1029, 992, 913, 666; ^1H NMR (500 MHz, CDCl_3) δ 4.26 (d, $J = 9.2$ Hz, 1H, H-9), 4.00 (dd, $J = 9.2, 2.0$ Hz, 1H, H-9), 3.72 (s, 3H, H-1), 2.77 – 2.64 (m, 2H, H-7 and H-11), 2.59 – 2.34 (m, 3H, H-7 and H-3), 2.32 – 2.23 (m, 1H, H-4), 2.22 – 2.08 (m, 2H, H-6 and H-11), 2.02 – 1.90 (m, 2H, H-4 and H-6), 1.88 – 1.71 (m, 3H, H-11, H-12 and H-13), 1.65 – 1.59 (m, 1H, H-12), 1.46 (d, $J = 12.2$ Hz, 1H, H-11), 1.35 – 1.18 (m, 2H, H-12), 1.10 – 0.99 (m, 1H, H-13); ^{13}C NMR (126 MHz, CDCl_3) δ 173.4, 172.7, 101.6, 77.6, 61.7, 51.9, 36.7, 35.9, 32.4, 30.9, 30.6, 29.3, 24.5, 24.4, 23.7; m/z HRMS (ESI) found [M+H]⁺ 282.1704, $\text{C}_{15}\text{H}_{24}\text{NO}_4$ requires 282.1700.

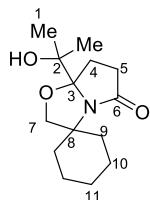
Methyl 3-(3,3-dimethyl-5-oxohexahydropyrrolo[2,1-*b*]oxazol-7a-yl)propanoate (241b)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (38 mg, 0.16 mmol, 78%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.17; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2973, 1735, 1697, 1438, 1367, 1261, 1195, 1174, 1033, 1002, 809, 670; ^1H NMR (500 MHz, CDCl_3) δ 4.02 (dd, $J = 8.9, 0.5$ Hz, 1H, H-9), 3.72 (s, 3H, H-1), 2.77 – 2.64 (m, 2H, H-7 and H-11), 2.59 – 2.34 (m, 3H, H-7 and H-3), 2.32 – 2.23 (m, 1H, H-4), 2.22 – 2.08 (m, 2H, H-6 and H-11), 2.02 – 1.90 (m, 2H, H-4 and H-6), 1.88 – 1.71 (m, 3H, H-11, H-12 and H-13), 1.65 – 1.59 (m, 1H, H-12), 1.46 (d, $J = 12.2$ Hz, 1H, H-11), 1.35 – 1.18 (m, 2H, H-12), 1.10 – 0.99 (m, 1H, H-13); ^{13}C NMR (126 MHz, CDCl_3) δ 173.4, 172.7, 101.6, 77.6, 61.7, 51.9, 36.7, 35.9, 32.4, 30.9, 30.6, 29.3, 24.5, 24.4, 23.7; m/z HRMS (ESI) found [M+H]⁺ 284.1724, $\text{C}_{16}\text{H}_{26}\text{NO}_4$ requires 284.1724.

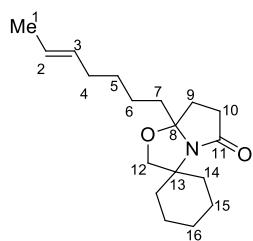
Hz, 1H, H-9), 3.94 (d, $J = 8.9$ Hz, 1H, H-9), 3.69 (s, 3H, H-1), 2.67 (ddd, $J = 17.0, 12.2, 8.0$ Hz, 1H, H-7), 2.55 – 2.34 (m, 3H, H-3 and H-7), 2.30 – 2.22 (m, 1H, H-4), 2.18 (ddd, $J = 12.4, 8.0, 0.8$ Hz, 1H, H-6), 2.00 – 1.90 (m, 2H, H-4 and H-6), 1.55 (s, 3H, H-11), 1.42 (s, 3H, H-11); ^{13}C NMR (126 MHz, CDCl_3) δ 173.4, 173.3, 102.2, 81.7, 58.2, 51.9, 35.3, 32.4, 30.4, 29.2, 26.5, 24.6; m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 242.1387, $\text{C}_{12}\text{H}_{20}\text{NO}_4$ requires 242.1387.

7a'-(2-Hydroxypropan-2-yl)dihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (242a)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 40% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (15 mg, 0.04 mmol, 19%); R_f (ethyl acetate in petroleum ether, 50%): 0.21; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3409 (br), 2932, 1705, 1456, 1358, 1168, 1019, 876, 812; ^1H NMR (500 MHz, CDCl_3) δ 4.30 (dd, $J = 8.1, 2.0$ Hz, 1H, H-7), 4.21 (d, $J = 8.1$ Hz, 1H, H-7), 2.78 – 2.70 (m, 1H, H-9), 2.69 (ddd, $J = 16.1, 11.8, 6.5$ Hz, 1H, H-5), 2.52 (ddd, $J = 16.8, 9.6, 0.9$ Hz 1H, H-5), 2.29 (ddd, $J = 13.0, 8.3, 0.9$ Hz, 1H, H-4), 2.09 – 2.02 (m, 2H, H-9), 1.95 – 1.80 (m, 2H, H-4 and H-10), 1.75 – 1.68 (m, 1H, H-11), 1.53 (s, 1H, H-10), 1.36 (s, 3H, H-1), 1.34 – 1.31 (m, 1H, H-9), 1.29 (s, 3H, H-1), 1.27 – 1.20 (m, 2H H-10), 1.02 – 0.93 (m, 1H, H-11); ^{13}C NMR (126 MHz, CDCl_3) δ 177.8, 106.3, 79.8, 64.2, 36.9, 35.1, 33.1, 32.8, 32.0, 25.9, 25.0, 24.9, 24.5, 24.1; m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 254.1751, $\text{C}_{14}\text{H}_{24}\text{NO}_3$ requires 254.1751.

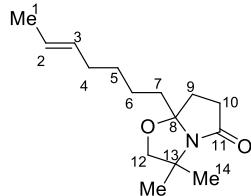
(E)-7a'-(Hept-5-en-1-yl)dihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (243a)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (45 mg, 0.15 mmol, 74%); R_f (ethyl acetate in petroleum ether, 25%): 0.35; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2929, 2858, 1694, 1454, 1378, 1087, 1030, 966, 899, 730; ^1H NMR (500 MHz, CDCl_3) δ 5.51 – 5.32 (m, 2H, H-2 and H-3),

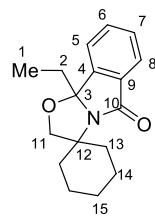
4.23 (d, $J = 9.1$ Hz, 1H, H-12), 3.95 (dd, $J = 9.1, 2.0$ Hz, 1H, H-12), 2.75 – 2.68 (m, 1H, H-14), 2.65 (ddd, $J = 16.5, 12.2, 7.4$ Hz, 1H, H-10), 2.49 (ddd, $J = 16.5, 8.0, 0.8$ Hz 1H, H-10), 2.20 (ddd, $J = 12.2, 8.0, 0.8$ Hz, 1H, H-9), 2.15 – 2.05 (m, 1H, H-14), 2.05 – 1.96 (m, 2H, H-4), 1.96 – 1.49 (m, 10H, H-1, H-7, H-9 and H-14, H-15 and H-16), 1.49 – 1.18 (m, 6H, H-5, H-6, H-14, H-15), 1.10 – 0.99 (m, 1H, H-16); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 131.0, 125.2, 102.6, 77.4, 61.4, 36.8, 36.1, 35.9, 32.6, 32.4, 30.9, 29.6, 24.5, 24.5, 23.7, 23.5, 17.9; m/z HRMS (ESI) found [M+H]⁺ 292.2274, $\text{C}_{18}\text{H}_{30}\text{NO}_2$ requires 292.2276.

(E)-7a-(Hept-5-en-1-yl)-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (243b)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (38 mg, 0.15 mmol, 77%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.27; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2934, 1698, 1457, 1366, 1270, 1230, 1041, 1002, 965, 841, 711, 666; ^1H NMR (500 MHz, CDCl_3) δ 5.57 – 5.29 (m, 2H, H-2 and H-3), 3.99 (d, $J = 8.8$ Hz, 1H, H-12), 3.95 (d, $J = 8.8$ Hz, 1H, H-12), 2.65 (ddd, $J = 17.0, 12.3, 8.1$ Hz, 1H, H-10), 2.48 (ddd, $J = 17.0, 9.7, 0.8$ Hz, 1H, H-10), 2.22 (ddd, $J = 12.3, 8.1, 0.8$ Hz, 1H, H-9), 2.05 – 1.89 (m, 3H, H-4 and H-9), 1.85 – 1.76 (m, 1H, H-7), 1.70 – 1.59 (m, 4H, H-4 and H-7), 1.56 (s, 3H, H-14), 1.41 (s, 3H, H-14), 1.47 – 1.30 (m, 4H, H-5 and H-6); ^{13}C NMR (126 MHz, CDCl_3) δ 173.6, 130.9, 125.2, 103.1, 81.6, 57.9, 35.7, 35.6, 32.6, 32.4, 29.6, 26.7, 24.6, 23.5, 17.9; m/z HRMS (ESI) found [M+H]⁺ 252.1955, $\text{C}_{15}\text{H}_{26}\text{NO}_2$ requires 252.1958.

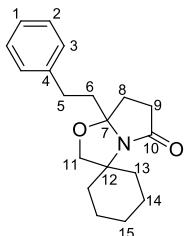
9b'-Ethyl-2'H-spiro(cyclohexane-1,3'-oxazolo[2,3-*a*]isoindol)-5'(9b'H)-one (252)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (49 mg, 0.18 mmol, 90%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.31; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2928, 2358, 1706, 1455, 1369, 1087, 1030, 662; ^1H NMR (500 MHz, CDCl_3) δ 7.74 – 7.70 (m, 1H, H-8), 7.54 (dd, $J = 7.4, 1.2$ Hz, 1H, H-6), 7.50 – 7.43 (m, 2H, H-5 and H-8), 4.37 (d, $J = 8.8$ Hz, 1H, H-11), 4.28 (dd, $J = 8.8, 1.8$ Hz, 1H, H-12).

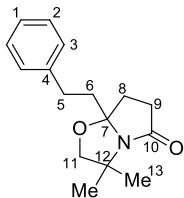
Hz, 1H, H-11), 2.94 – 2.78 (m, 1H, H-13), 2.25 – 2.04 (m, 3H, H-2 and H-13), 1.99 – 1.91 (m, 1H, H-13), 1.91 – 1.84 (m, 1H, H-14), 1.84 – 1.74 (m, 1H, H-15), 1.68 – 1.59 (m, 1H, H-14), 1.47 – 1.38 (m, 1H, H-13), 1.36 – 1.23 (m, 2H, H-14), 1.22 – 1.08 (m, 1H, H-15), 0.64 (t, $J = 7.4$ Hz, 3H, H-1); ^{13}C NMR (126 MHz, CDCl_3) δ 170.2, 145.3, 134.8, 132.4, 129.8, 123.7, 121.6, 102.6, 79.5, 63.1, 37.9, 31.1, 28.9, 24.7, 24.4, 23.9, 8.0; m/z HRMS (ESI) found [M+H]⁺ 272.1641, $\text{C}_{17}\text{H}_{22}\text{NO}_2$ requires 272.1645.

7a'-Phenethyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (259a)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (45 mg, 0.15 mmol, 74%); \mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.23; IR ν_{max} /cm⁻¹ (film): 2932, 2859, 2250, 1684, 1455, 1384, 1262, 1087, 1028, 907, 804, 729, 698; ^1H NMR (500 MHz, CDCl_3) δ 7.30 (t, $J = 7.5$ Hz, 2H, H-3), 7.24 – 7.18 (m, 3H, H-1 and H-2), 4.28 (d, $J = 9.1$ Hz, 1H, H-11), 3.99 (dd, $J = 9.1, 1.9$ Hz, 1H, H-11), 2.81 – 2.62 (m, 4H, H-5, H-9 and H-13), 2.54 (dd, $J = 17.1, 9.6$ Hz, 1H, H-9), 2.27 (dd, $J = 12.4, 7.9$ Hz, 1H, H-8), 2.19 – 2.06 (m, 2H, H-6 and H-13), 2.04 – 1.92 (m, 2H, H-6 and H-8), 1.89 – 1.80 (m, 1H, H-14), 1.79 – 1.65 (m, 2H, H-13 and H-15), 1.60 (d, $J = 11.9$ Hz, 1H, H-14), 1.47 (d, $J = 12.7$ Hz, 1H, H-13), 1.36 – 1.18 (m, 2H, H-14), 1.09 – 0.98 (m, 1H, H-15); ^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 141.2, 128.6, 128.2, 126.1, 102.2, 61.6, 37.8, 36.8, 36.1, 32.6, 30.9, 30.5, 29.7, 24.6, 24.5, 23.7; m/z HRMS (ESI) found [M+H]⁺ 300.1956, $\text{C}_{19}\text{H}_{26}\text{NO}_2$ requires 300.1958.

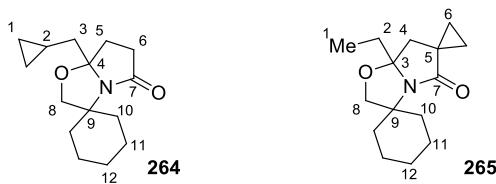
3,3-Dimethyl-7a-phenethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (259b)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, provided the title compound as a pale yellow oil (18 mg, 0.07 mmol, 35%); \mathbf{R}_f (ethyl acetate in petroleum ether, 20%): 0.14; IR ν_{max} /cm⁻¹ (film): 2949, 2156, 1698, 1455, 1374, 1367, 1230, 1030, 749, 701, 665; ^1H NMR (500 MHz, CDCl_3) δ 7.35 – 7.30 (m, 2H, Ar-H), 7.25 – 7.20 (m, 3H, Ar-H), 4.05 (d, $J = 8.9$ Hz, 1H, H-11), 4.01 (d, $J = 8.9$ Hz, 1H, H-11), 2.83 – 2.65 (m,

3H, H-5 and H-9), 2.54 (ddd, $J = 17.0, 9.7, 0.8$ Hz, 1H, H-9), 2.31 (ddd, $J = 12.5, 8.1, 0.8$ Hz, 1H, H-8), 2.21 – 2.13 (m, 1H, H-6), 2.08 – 1.95 (m, 2H, H-6 and H-8), 1.61 (s, 3H, H-13), 1.44 (s, 3H, H-13); ^{13}C NMR (126 MHz, CDCl₃) δ 173.6, 141.2, 128.6, 128.2, 126.1, 102.8, 81.6, 58.1, 37.6, 35.5, 32.6, 30.4, 26.7, 24.6; m/z HRMS (ESI) found [M+H]⁺ 260.1639, C₁₆H₂₂NO₂ requires 260.1643.

7a'-(Cyclopropylmethyl)dihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (264) and 7a'-Ethyl-6'-spirocyclopropylidihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (265)



Prepared according to General Procedure D. Purification by flash chromatography on silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, provided the title compounds 7a'-(cyclopropylmethyl)dihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one **264** as a pale yellow oil (14 mg, 0.06 mmol, 28%) and 7a'-ethyl-6'-spirocyclopropylidihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one **265** as a pale yellow oil (28 mg, 0.11 mmol, 57%).

7a'-(Cyclopropylmethyl)dihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (264):

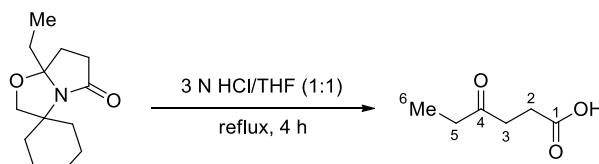
R_f (ethyl acetate in petroleum ether, 25%): 0.28; IR ν_{max}/cm⁻¹ (film): 2926, 2860, 1698, 1455, 1373, 1272, 1230, 1190, 1029, 937, 824, 703, 673; ^1H NMR (500 MHz, CDCl₃) δ 4.26 (d, $J = 9.1$ Hz, 1H, H-8), 4.00 (dd, $J = 9.1, 2.0$ Hz, 1H, H-8), 2.81 – 2.68 (m, 2H, H-6 and H-10), 2.52 (ddd, $J = 17.2, 8.6, 0.6$ Hz, 1H, H-6), 2.41 (ddd, $J = 12.2, 8.0, 0.6$ Hz, 1H, H-5), 2.17 – 2.05 (m, 1H, H-10), 2.03 – 1.89 (m, 1H, H-5), 1.88 – 1.81 (m, 1H, H-11), 1.80 – 1.67 (m, 3H, H-3, H-10 and H-12), 1.60 (dd, $J = 14.2, 7.1$ Hz, 2H, H-3 and H-11), 1.49 – 1.42 (m, 1H, H-10), 1.35 – 1.17 (m, 2H, H-11), 1.11 – 0.96 (m, 1H, H-12), 0.81 – 0.70 (m, 1H, H-2), 0.59 – 0.47 (m, 2H, H-1), 0.21 – 0.12 (m, 2H, H-1); ^{13}C NMR (126 MHz, CDCl₃) δ 173.2, 102.9, 77.6, 61.5, 40.8, 36.8, 36.4, 33.1, 31.0, 24.6, 24.5, 23.7, 6.1, 4.7, 4.4; m/z HRMS (ESI) found [M+H]⁺ 250.1803, C₁₅H₂₄NO₂ requires 250.1802.

7a'-Ethyl-6'-spirocyclopropyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one (265):

R_f (ethyl acetate in petroleum ether, 25%): 0.30; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2928, 2860, 1696, 1453, 1374, 1225, 1129, 1043, 1026, 987, 906, 845, 824, 742, 700; **¹H NMR** (500 MHz, CDCl₃) δ 4.23 (d, *J* = 9.0 Hz, 1H, H-8), 3.96 (dd, *J* = 9.0, 2.0 Hz, 1H, H-8), 2.78 – 2.62 (m, 1H, H-10), 2.29 (d, *J* = 12.4 Hz, 1H, H-4), 2.14 – 2.06 (m, 1H, H-10), 1.93 (d, *J* = 12.4 Hz, 1H, H-4), 1.88 – 1.68 (m, 5H, H-2, H-10, H-11 and H-12), 1.63 – 1.59 (m, 1H, H-11), 1.50 – 1.43 (m, 1H, H-10), 1.35 – 1.16 (m, 3H, H-6 and H-11), 1.13 – 1.01 (m, 1H, H-12), 1.01 – 0.92 (m, 4H, H-1 and H-6), 0.82 – 0.74 (m, 1H, H-6), 0.60 (ddd, *J* = 9.4, 7.0, 4.4 Hz, 1H, H-6); **¹³C NMR** (126 MHz, CDCl₃) δ 175.4, 100.6, 77.0, 61.9, 40.3, 37.2, 31.2, 29.8, 26.6, 24.7, 24.6, 23.8, 15.6, 11.2, 8.2; m/z **HRMS** (ESI) found [M+H]⁺ 250.1803, C₁₅H₂₄NO₂ requires 250.1802.

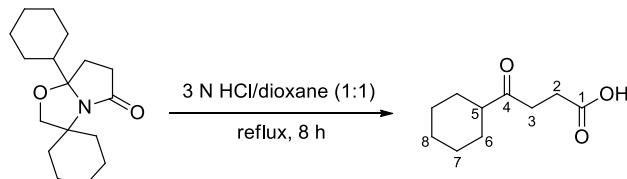
5.4 C–H carbonylation: Access to γ -keto carboxylic acid

4-Oxohexanoic acid (268)

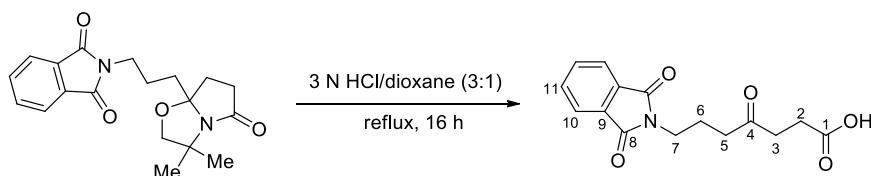


*7a'-Ethyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one* **185** (50 mg, 0.22 mmol) was heated in a 1:1 mixture of 3 N HCl and tetrahydrofuran (8 mL) at reflux for 4 hours. The reaction mixture was cooled and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 5% methanol in dichloromethane, affording the title compound as a white solid (27 mg, 0.21 mmol, 93%); **R**_f (dichloromethane in methanol, 5%): 0.15; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3200 (br), 2980, 1706, 1563, 1405, 1368, 1203, 1165, 1116, 953, 830; **¹H NMR** (400 MHz, CDCl₃) δ 2.73 (t, *J* = 9.5 Hz, 2H, H-3), 2.64 (t, *J* = 9.5 Hz, 2H, H-5), 2.48 (q, *J* = 7.3 Hz, 2H, H-2), 1.08 (t, *J* = 7.3 Hz, 3H, H-6); **¹³C NMR** (400 MHz, CDCl₃) δ 209.7, 177.9, 36.8, 36.3, 28.0, 8.1. The physical data were identical in all respect to that previously reported.¹⁶⁷

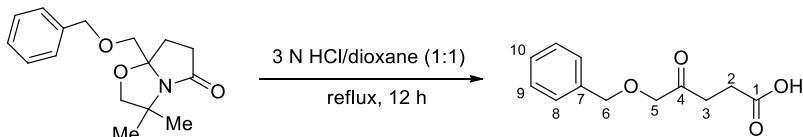
4-Cyclohexyl-4-oxobutanoic acid (269)



*7a'-Cyclohexydihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol)-5'(6'H)-one* **207a** (20 mg, 0.07 mmol) was heated in a 1:1 mixture of 3 N HCl and dioxane (2.5 mL) at reflux for 8 hours. The reaction mixture was cooled and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 5% methanol in dichloromethane, affording the title compound as a white paste (12 mg, 0.06 mmol, 91%); **R**_f (dichloromethane in methanol, 5%): 0.23; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3210-2530 (v. br), 2934, 2851, 1686, 1411, 1317, 1222, 1187, 1145, 1102, 921, 890, 801, 779; **¹H NMR** (400 MHz, CDCl₃) δ 2.75 (t, *J* = 6.4 Hz, 2H, H-3), 2.62 (t, *J* = 6.4 Hz, 2H, H-2), 2.42 – 2.30 (m, 1H, H-5), 1.95 – 1.53 (m, 4H, H-6), 1.44 – 1.12 (m, 6H, H-7 and H-8); **¹³C NMR** (101 MHz, CDCl₃) δ 211.9, 178.1, 50.7, 34.8, 28.5, 27.7, 25.8, 25.6. The physical data were identical in all respect to that previously reported.¹⁶⁸

8-(1,3-Dioxoisooindolin-2-yl)-4-oxooctanoic acid (270)

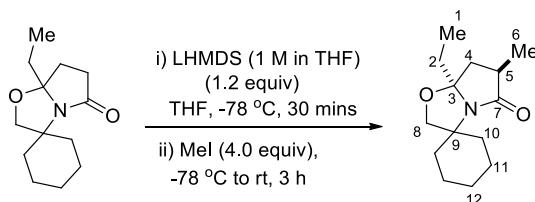
2-{3-(3,3-Dimethyl-5-oxohexahydro-1H-pyrazolo[2,1-b]oxazol-7a-yl)propyl}isoindoline-1,3-dione **238b** (15 mg, 0.05 mmol) was heated in a 3:1 mixture of 3 N HCl and dioxane (2 mL) at reflux for 16 hours. The reaction mixture was cooled and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 5% methanol in dichloromethane, affording the title compound as a white solid (12.9 mg, 0.04 mmol, 89%); **M.p.**: 73–76 °C; **R_f** (dichloromethane in methanol, 5%): 0.29; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3100-2545 (v. br), 1704, 1696, 1397, 1334, 1134, 1053, 998, 836, 719; **¹H NMR** (500 MHz, CDCl₃) δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, H-10), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H, H-11), 3.71 (t, *J* = 6.7 Hz, 2H, H-7), 2.73 (t, *J* = 6.3 Hz, 2H, H-3), 2.63 (t, *J* = 6.3 Hz, 2H, H-2), 2.53 (t, *J* = 7.1 Hz, 2H, H-5), 2.05 – 1.92 (m, 2H, H-6), 1.25 (s, 1H, OH); **¹³C NMR** (126 MHz, CDCl₃) δ 207.5, 168.5, 168.4, 134.0, 132.0, 123.3, 39.6, 37.1, 36.9, 29.7, 22.6; **m/z HRMS** (ESI) found [M-H]⁻ 290.1026, C₁₂H₁₃O₄ requires 290.1023.

5-(Benzylxy)-4-oxopentanoic acid (271)

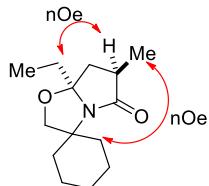
7a-((benzylxy)methyl)-3,3-dimethyltetrahydropyrazolo[2,1-b]oxazol-5(6H)-one **239b** (15 mg, 0.05 mmol) was heated in a 1:1 mixture of 3 N HCl and dioxane (2 mL) at reflux for 12 hours. The reaction mixture was cooled and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 5% methanol in dichloromethane, affording the title compound as a pale green solid (11 mg, 0.05 mmol, 92%); **M.p.**: 53–55 °C; **R_f** (dichloromethane in methanol, 5%): 0.35; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3300-2630 (v. br), 1709, 1398, 1206, 1151, 1090, 1028, 912, 740, 699; **¹H NMR** (500 MHz, MeOD) δ 7.49 – 7.22 (m, 5H, H-8, H-9 and H-10), 4.58 (s, 2H, H-6), 4.12 (s, 2H, H-5), 2.73 (t, *J* = 6.3 Hz, 2H, H-3), 2.57 (t, *J* = 6.3 Hz, 2H, H-2); **¹³C NMR** (126 MHz, MeOD) δ 209.4, 176.4, 138.9, 129.5, 129.1, 128.9, 75.8, 74.3, 34.4, 28.4; **m/z HRMS** (ESI) found [M-H]⁻ 221.0816, C₁₂H₁₃O₄ requires 221.0819.

5.5 C–H carbonylation: C-Methylation of γ -lactam 185

(6'R, 7a'S)-7a'-Ethyl-6'-methyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]oxazol]-5'(6'H)-one (\pm) (272)



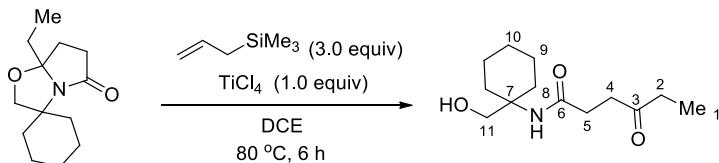
To a solution of *7a'-ethyldihydro-2'H-spiro(cyclohexane-1,3'-pyrrolo[2,1-b]oxazol)-5'(6'H)-one* **185** (50 mg, 0.22 mmol, 1.0 equiv) in dry tetrahydrofuran (2 mL) at -78 °C was added LHMDS (1 M in tetrahydrofuran; 0.26 mL, 0.26 mmol, 1.2 equiv) dropwise. The resulting solution was stirred at this temperature for 30 mins, followed by addition of methyl iodide (55 μ L, 0.88 mmol, 4.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to yield an 8:1 mixture of diastereoisomers (determined by ^1H NMR analysis). The crude product was purified by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the major diastereoisomer as a pale brown oil (41 mg, 0.17 mmol, 78%).



\mathbf{R}_f (ethyl acetate in petroleum ether, 25%): 0.35; **IR** ν_{max} /cm⁻¹ (film): 2933, 2860, 1696, 1454, 1382, 1264, 1107, 1028, 968, 900, 848, 736, 697; **^1H NMR** (500 MHz, CDCl₃) δ 4.22 (d, J = 9.0 Hz, 1H, H-8), 3.93 (dd, J = 9.0, 2.0 Hz, 1H, H-8), 2.84 – 2.67 (m, 2H, H-5 and H-10), 2.42 (dd, J = 12.1, 7.3 Hz, 1H, H-4), 2.11 (ddd, J = 15.6, 8.7, 2.8 Hz, 1H, H-10), 1.89 – 1.77 (m, 2H, H-2 and H-11), 1.76 – 1.48 (m, 5H, H-2, H-4, H-10, H-11 and H-12), 1.44 – 1.37 (m, 1H, H-10), 1.34 – 1.18 (m, 2H, H-11), 1.17 (d, J = 7.1 Hz, 3H, H-6), 1.08 – 0.99 (m, 1H, H-12), 0.96 (t, J = 7.5 Hz, 3H, H-1); **^{13}C NMR** (126 MHz, CDCl₃) δ 175.4, 100.1, 77.0, 61.4, 41.5, 41.1, 36.7, 31.0, 28.6, 24.6, 24.5, 23.7, 16.0, 8.5; **m/z HRMS** (ESI) found [M+H]⁺, 238.1801, C₁₄H₂₄NO₂ requires 238.1802.

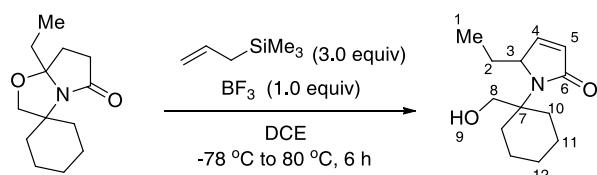
5.6 C–H carbonylation: Unexpected products from ring-opening of γ -lactam 185

N-{1-(Hydroxymethyl)cyclohexyl}-4-oxohexanamide (276)



To a solution of *7a'-ethyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'('6'H)-one* **185** (50 mg, 0.22 mmol, 1.0 equiv) in dry 1,2-dichloroethane (2 mL) was added titanium tetrachloride (1M in dichloromethane; 0.22 ml, 0.22 mmol, 1.0 equiv) followed by allyltrimethylsilane (0.10 ml, 0.66 mmol, 3.0 equiv). The resulting solution was heated at 80 °C for 6 hours. The reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a colourless oil (10 mg, 0.04 mmol, 18%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.31; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3510 (br), 2992, 2930, 1770, 1692, 1272, 1240, 1003, 998, 912, 907, 865, 792; **¹H NMR** (500 MHz, CDCl₃) δ 3.95 (s, 2H, H-11), 2.78 (t, *J* = 7.5 Hz, 2H, H-4), 2.59 (t, *J* = 7.5 Hz, 2H, H-5), 2.48 (q, *J* = 7.3 Hz, 2H, H-2), 1.84 – 1.46 (m, 7H, H-8, H-9 and H-10), 1.38 – 1.21 (m, 3H, H-8 and H-10), 1.08 (t, *J* = 7.3 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 209.6, 164.9, 70.6, 66.3, 38.2, 37.5, 36.0, 25.1, 23.0, 22.2, 7.8; **m/z HRMS** (ESI) found [M+H]⁺, 224.1674, C₁₃H₂₄NO₃ requires 242.1678.

5-Ethyl-1-{1-(hydroxymethyl)cyclohexyl}-1*H*-pyrrol-2(5*H*)-one (277)

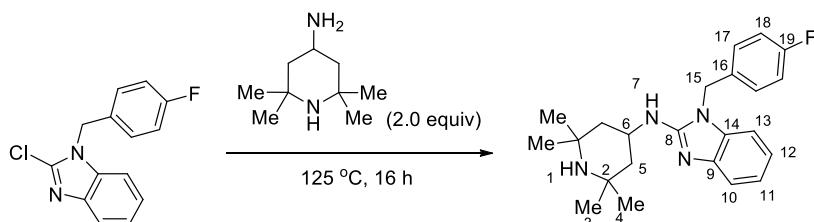


To a solution of *7a'-ethyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'('6'H)-one* **185** (50 mg, 0.22 mmol, 1.0 equiv) in dry 1,2-dichloroethane (2 mL) at -78 °C was added boron trifluoride etherate complex (27 μ L, 0.22 mmol, 1.0 equiv) followed by allyltrimethylsilane (0.10 ml, 0.66 mmol, 3.0 equiv). The resulting solution was stirred at this temperature for 30 mins, then warmed to room temperature and stirred for 30 mins, followed by further heating at 80 °C for 5 hours. The reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a pale

yellow oil (26 mg, 0.11 mmol, 52%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.22; **IR** ν_{max} /cm⁻¹ (film): 3365 (br), 2933, 2864, 1654, 1448, 1385, 1215, 1059, 910, 828, 808, 733; **¹H NMR** (500 MHz, CDCl₃) δ 6.97 (dd, *J* = 5.9, 1.9 Hz, 1H, H-4), 6.07 (dd, *J* = 5.9, 1.4 Hz, 1H, H-5), 5.49 (s, 1H, H-9), 4.38 (ddd, *J* = 6.2, 2.9, 1.4 Hz, 1H, H-3), 3.99 – 3.77 (m, 2H, H-8), 2.20 – 1.91 (m, 3H, H-2, H-10 and H-11), 1.75 – 1.48 (m, 9H, H-2, H-10 and H-11), 1.34 – 1.18 (m, 2H, H-12), 0.84 (t, *J* = 7.4 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 174.2, 148.5, 127.6, 66.9, 63.6, 62.9, 31.8, 30.5, 26.7, 25.2, 22.9, 22.6, 8.2; m/z **HRMS** (ESI) found [M+H]⁺, 224.1645, C₁₃H₂₂NO₂ requires 224.1645.

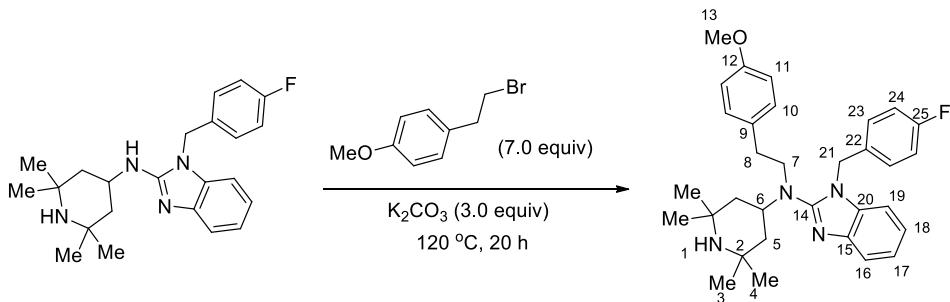
5.7 Synthesis of TMP-astemizole 287: Literature route to astemizole (299)

1-(4-Fluorobenzyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine (299)

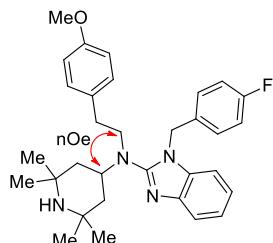


To 2-chloro-1-(4-fluorobenzyl)benzimidazole (760 mg, 2.92 mmol, 1.0 equiv) was added 2,2,6,6-tetramethylpiperidin-4-amine (1.0 mL, 5.84 mmol, 2.0 equiv) and the mixture heated at 125 °C for 16 hours. The reaction mixture was cooled and diluted with dichloromethane before washing with saturated aqueous sodium bicarbonate, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 40% methanol in dichloromethane, affording the title compound as a pale yellow oil (855 mg, 2.25 mmol, 77%); **R_f** (methanol in dichloromethane, 20%): 0.19; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2972, 1604, 1572, 1533, 1363, 1220, 1156, 1080, 1025, 953, 846, 734; **¹H NMR** (500 MHz, CDCl₃) δ 7.52 (d, *J* = 7.9 Hz, 1H, H-13), 7.17 – 7.07 (m, 3H, H-10 and H-18), 7.06 – 6.99 (m, 4H, H-11, H-12 and H-17), 5.05 (s, 2H, H-15), 4.30 (tt, *J* = 8.5, 6.0 Hz 1H, H-6), 3.60 (d, *J* = 7.4 Hz, 1H, H-7), 2.07 (dd, *J* = 12.6, 3.9 Hz, 2H, H-5eq), 1.31 (s, 6H, H-3 or H-4), 1.14 (s, 6H, H-3 or H-4), 0.86 (t, *J* = 11.6 Hz, 2H, H-5ax); **¹³C NMR** (126 MHz, CDCl₃) δ 162.4 (d, ¹J_{C-F} = 247.2 Hz), 153.3, 142.5, 134.6, 131.2, 128.1 (d, ³J_{C-F} = 8.1 Hz), 121.5, 119.8, 116.2 (d, ²J_{C-F} = 21.8 Hz), 116.1, 107.1, 51.6, 46.3, 45.8, 45.0, 34.7, 28.5; **¹⁹F NMR** (376 MHz, CDCl₃) δ -113.73; **m/z HRMS** (ESI) found [M+H]⁺ 381.2454, C₂₃H₃₀FN₄ requires 381.2454.

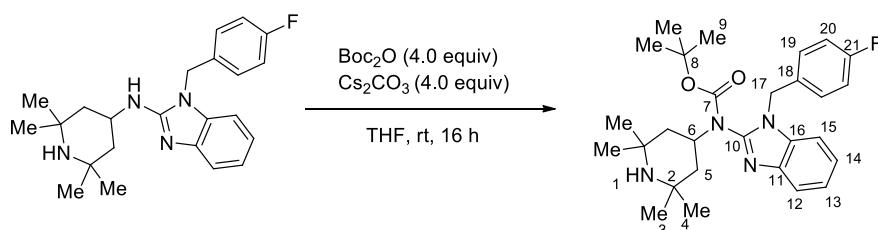
1-(4-Fluorobenzyl)-N-(4-methoxyphenethyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine (301)



A mixture of *1-(4-fluorobenzyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine* **299** (50 mg, 0.13 mmol, 1.0 equiv) and potassium carbonate (54 mg, 0.39 mmol, 3.0 equiv) were stirred in 1-(2-bromoethyl)-4-methoxybenzene (0.15 mL, 0.91 mmol, 7.0 equiv) at 120 °C for 20 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 30% methanol in dichloromethane, affording the title compound as an orange oil (23 mg, 0.04 mmol, 34%); **R_f** (methanol in dichloromethane, 20%): 0.34; **IR** ν_{max} /cm⁻¹ (film): 2916, 1656, 1611, 1511, 1499, 1363, 1247, 1225, 1157, 1036, 908, 812, 731; **¹H NMR** (500 MHz, CDCl₃) δ 7.20 (dd, *J* = 8.5, 5.3 Hz, 2H, H-23), 7.10 (d, *J* = 8.6 Hz, 2H, H-10), 7.03 (t, *J* = 8.7 Hz, 2H, H-24), 6.95 (t, *J* = 7.5 Hz, 1H, H-17), 6.87 (t, *J* = 7.5 Hz, 1H, H-18), 6.81 (d, *J* = 8.6 Hz, 2H, H-11), 6.78 (d, *J* = 7.6 Hz, 1H, H-19), 6.63 (d, *J* = 7.5 Hz, 1H, H-16), 5.04 (s, 2H, H-21) 4.20 – 4.05 (m, 2H, H-7), 4.00 – 3.86 (m, 1H, H-6), 3.78 (s, 3H, H-13), 3.04 – 2.92 (m, 2H, H-8), 1.62 (dd, *J* = 13.0, 3.3 Hz, 2H, H-5eq), 1.31 – 1.18 (m, 2H, H-5ax), 1.13 (s, 6H, H-3 or H-4), 0.98 (s, 6H, H-3 or H-4); **¹³C NMR** (126 MHz, CDCl₃) δ 162.1 (d, ¹*J*_{C-F} = 245.8 Hz), 158.3, 144.7, 133.0, 132.8, 132.5, 130.6, 129.9, 127.8 (d, ³*J*_{C-F} = 4.9 Hz), 120.8, 120.2, 115.7 (d, ²*J*_{C-F} = 21.6 Hz), 114.0, 106.1, 55.2, 51.4, 48.3, 46.6, 44.4, 34.5, 33.1, 28.2; **¹⁹F NMR** (376 MHz, CDCl₃) δ -115.16; **m/z HRMS** (ESI) found [M+H]⁺ 515.3186, C₃₂H₄₀FN₄O requires 515.3181.



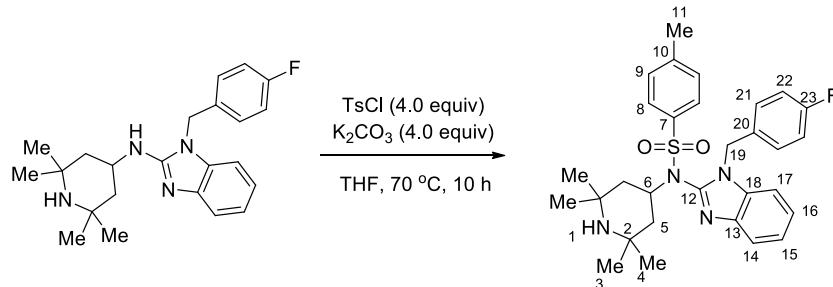
Tert-butyl (1-(4-fluorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)(2,2,6,6-tetramethylpiperidin-4-yl)carbamate (302)



To a solution of *1-(4-fluorobenzyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine* **301** (100 mg, 0.26 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) was added cesium carbonate (342 mg, 1.05 mmol, 4.0 equiv) and di-*tert*-butyl carbonate (229 mg, 1.05 mmol, 4.0 equiv). The resulting mixture was stirred at room temperature for 16 hours. Another portion of di-*tert*-butyl carbonate (342 mg, 1.05 mmol, 4.0 equiv) was added and the reaction stirred at room temperature for a further 5 hours. The

reaction mixture was partitioned between dichloromethane and water. The aqueous layer was separated and extracted with dichloromethane. The combined organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 5% methanol in dichloromethane, affording the title compound as a white solid (82 mg, 0.17 mmol, 67%); **M.p.**: 120–122 °C; **R_f** (methanol in dichloromethane, 5%): 0.28; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2940, 1733, 1670, 1603, 1488, 1342, 1246, 1219, 1149, 1082, 853, 749, 672; **¹H NMR** (400 MHz, CDCl₃) δ 7.45 (d, *J* = 7.8 Hz, 1H, H-15), 7.30 (dd, *J* = 8.6, 5.4 Hz, 2H, H-19), 7.03 – 6.93 (m, 3H, H-13 and H-20), 6.87 (t, *J* = 7.8 Hz, 1H, H-14), 6.62 (d, *J* = 7.7 Hz, 1H, H-12), 4.93 (s, 2H, H-17), 4.04 (tt, *J* = 11.5, 3.9 Hz, 1H, H-6), 2.53 (s, 1H, H-1) 1.82 (dd, *J* = 12.7, 3.8 Hz, 2H, H-5eq), 1.65 (s, 9H, H-9), 1.24 (s, 6H, H-3 or H-4), 1.13 (s, 6H, H-3 or H-4), 1.08 – 1.01 (m, 2H, H-5ax); **¹³C NMR** (126 MHz, CDCl₃) δ 162.0 (d, ¹*J*_{C-F} = 245.0 Hz), 150.2, 140.7, 134.0, 132.9, 129.2 (d, ³*J*_{C-F} = 7.5 Hz), 129.1, 124.0, 119.6, 115.3 (d, ²*J*_{C-F} = 21.4 Hz), 113.9, 106.5, 84.1, 51.0, 49.9, 46.9, 44.7, 35.1, 28.7, 28.2; **¹⁹F NMR** (376 MHz, CDCl₃) δ -115.60; **m/z HRMS** (ESI) found [M+H]⁺ 481.2975, C₂₆H₃₈FN₄O₂ requires 481.2973.

Benzyl (1-(4-fluorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)(2,2,6,6-tetramethylpiperidin-4-yl)carbamate (304)

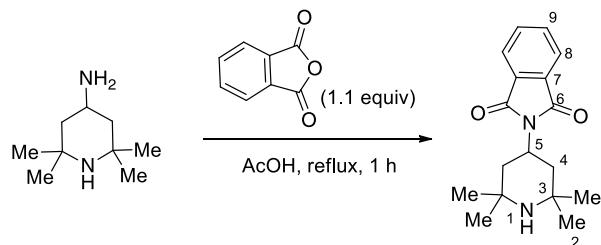


To a solution of *1-(4-fluorobenzyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine* **301** (190 mg, 0.50 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) was added potassium carbonate (276 mg, 2.00 mmol, 4.0 equiv) and 4-toluenesulfonyl chloride (380 mg, 2.00 mmol, 4.0 equiv). The resulting mixture was stirred at 70 °C for 10 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was separated and extracted with ethyl acetate. The combined organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 2% methanol in dichloromethane, affording the title compound as a brown oil (166 mg, 0.31 mmol, 62%); **R_f** (methanol in dichloromethane, 2%): 0.27; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 294058, 1675, 1583, 1423, 1300, 1289, 1226, 1082, 821, 711; **¹H NMR** (400 MHz, CDCl₃) δ 7.93 (d, *J* = 7.5 Hz, 2H, H-8), 7.67 (dd, *J* = 6.8, 2.1 Hz, 1H, H-14), 7.54 (dd, *J* = 6.9, 2.2 Hz, 1H, H-17), 7.38 (d, *J* = 7.3 Hz, 2H, H-9), 7.30 – 7.20 (m, 4H, H-15, H-16 and H-21), 6.97 (t, *J* = 7.8 Hz, 2H, H-22), 5.12 (s, 2H, H-19), 4.27 – 4.08

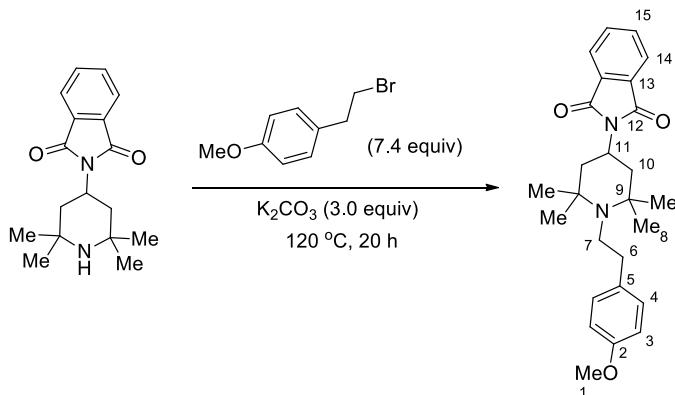
(m, 1H, H-6), 2.36 (s, 3H, H-11), 1.87 (dd, $J = 12.4, 3.1$ Hz, 2H, H-5eq), 1.50 (dd, $J = 12.4, 7.5$ Hz, 2H, H-5ax), 1.22 (s, 6H, H-3 or H-4), 1.16 (s, 6H, H-3 or H-4); ^{13}C NMR (125 MHz, CDCl₃) δ 163.0 (d, $^1J_{\text{C-F}} = 262.3$ Hz), 156.6, 142.7, 140.5, 138.6, 136.5, 131.5, 130.6 (d, $^3J_{\text{C-F}} = 6.7$ Hz), 129.8, 128.1, 122.8, 121.5, 116.1, 115.0 (d, $^2J_{\text{C-F}} = 26.7$ Hz), 111.5, 50.0, 49.9, 47.2, 42.7, 30.2, 21.1, 19.4; ^{19}F NMR (376 MHz, CDCl₃) δ -111.30; m/z HRMS (ESI) found [M+H]⁺ 535.6876, C₃₀H₃₆FN₄O₂S requires 535.6879.

5.8 Synthesis of TMP-astemizole 287: Phthalimide route

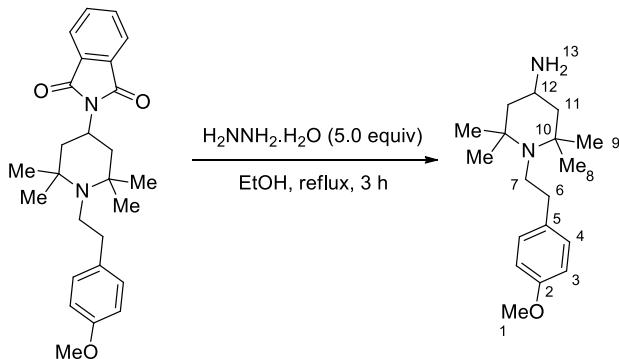
2-(2,2,6,6-Tetramethylpiperidin-4-yl)isoindoline-1,3-dione (305)



A mixture of 4-amino-2,2,6,6-tetramethylpiperidine (1.00 g, 6.40 mmol, 1.0 equiv) and phthalic anhydride (1.0 g, 6.76 mmol, 1.1 equiv) were stirred in acetic acid (5 mL) under reflux for 1 hour. The reaction mixture was cooled and acetic acid was removed by azeotrope with toluene. The residue was diluted with dichloromethane and treated with saturated aqueous sodium bicarbonate until the aqueous layer reached ~pH = 8. The aqueous phase was then extracted with dichloromethane and the combined organic phases were dried (magnesium sulfate) and concentrated *in vacuo* to give the product as a colorless crystalline solid (1.68 g, 5.83 mmol, 91% yield); **M.p.**: 104–106 °C; **IR** ν_{max} /cm⁻¹ (film): 2972, 1701, 1626, 1373, 1364, 1098, 1087, 865, 712; ^1H NMR (400 MHz, CDCl₃) δ 7.81 (dd, $J = 5.4, 3.1$ Hz, 2H, H-8), 7.69 (dd, $J = 5.4, 3.0$ Hz, 2H, H-9), 5.54 (s, 1H, H-1), 4.66 (tt, $J = 12.8, 3.5$ Hz, 1H, H-5), 2.26 (t, $J = 12.8$ Hz, 2H, H-4ax), 1.64 (dd, $J = 12.8, 3.4$ Hz, 2H, H-4eq), 1.36 (s, 6H, H-2), 1.26 (s, 6H, H-2); ^{13}C NMR (126 MHz, CDCl₃) δ 168.5, 133.9, 132.0, 123.0, 51.4, 44.8, 41.2, 34.7, 28.0. The physical data were identical in all respect to that previously reported.¹⁶⁹

2-(1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione (306)

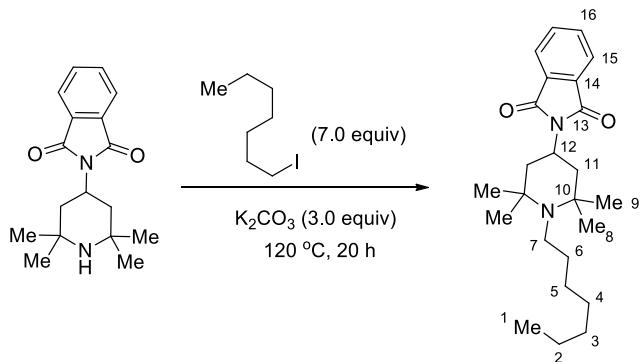
A mixture of *2-(2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione* **305** (250 mg, 0.87 mmol, 1.0 equiv) and potassium carbonate (326 mg, 2.62 mmol, 3.0 equiv) were stirred in 1-(2-bromoethyl)-4-methoxybenzene (1.0 mL, 6.4 mmol, 7.4 equiv) at 120 °C for 20 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 10% methanol in dichloromethane, affording the title compound as a brown oil (44 mg, 0.10 mmol, 12%); R_f (dichloromethane in methanol, 5%): 0.21; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2966, 1708, 1512, 1375, 1244, 1176, 1086, 1035, 912, 719; **¹H NMR** (500 MHz, CDCl₃) δ 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H, H-14), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H, H-15), 7.11 (d, *J* = 8.6 Hz, 2H, H-4), 6.85 (d, *J* = 8.6 Hz, 2H, H-3), 4.59 (ddd, *J* = 13.0, 8.3, 3.5 Hz, 1H, H-11), 2.73 – 2.62 (m, 2H, H-7), 2.60 – 2.57 (m, 2H, H-6), 2.47 (t, *J* = 12.4 Hz, 2H, H-10ax), 1.54 (dd, *J* = 12.4, 3.5 Hz, 1H, H-10eq), 1.28 (s, 6H, H-8), 1.12 (s, 6H, H-8); **¹³C NMR** (126 MHz, CDCl₃) δ 168.6, 157.9, 133.8, 133.3, 132.0, 129.4, 123.0, 113.8, 56.0, 55.3, 47.4, 44.1, 43.4, 41.3, 34.1, 21.4; *m/z* **HRMS** (ESI) found [M+H]⁺ 421.2483, C₂₆H₃₃N₂O₃ requires 421.2486.

1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-amine (307)

To a solution of *2-(1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione* **306** (44 mg, 0.10 mmol, 1.0 equiv) in ethanol (2 mL) was added hydrazine hydrate (20 μL, 1.55 mmol, 5.0

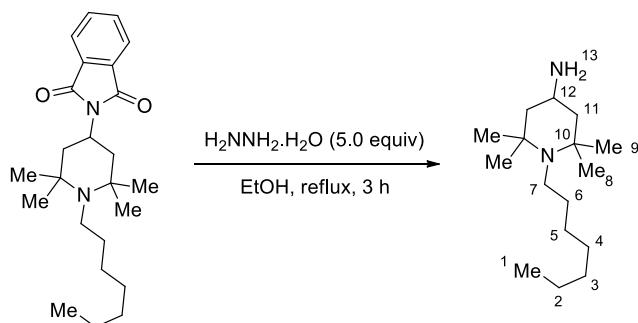
equiv). The reaction mixture was heated at reflux for 3 hours during which white precipitate was formed. The reaction mixture was concentrated *in vacuo* and suspended in dichloromethane. The white precipitate was filtered off and the filtrate was concentrated in *vacuo* to yield the title compound as a pale yellow oil (29 mg, 0.10 mmol, 100%); **IR** ν_{max} /cm⁻¹ (film): 2938, 2835, 1611, 1583, 1511, 1464, 1378, 1366, 1243, 1175, 1111, 1036, 961, 853, 821, 743; **¹H NMR** (500 MHz, CDCl₃) δ 7.10 (d, *J* = 8.6 Hz, 2H, H-4), 6.84 (d, *J* = 8.6 Hz, 2H, H-3), 3.79 (s, 3H, H-1), 3.01 (ddd, *J* = 11.7, 8.3, 3.6 Hz, 1H, H-12), 2.70 – 2.47 (m, 4H, H-6 and H-7), 1.69 (dd, *J* = 12.2, 3.1 Hz, 2H, H-11eq), 1.44 (br. s, 2H, H-13), 1.43 (s, 6H, H-8 or H-9), 1.22 (s, 6H, H-8 or H-9), 1.28 – 1.15 (m, 2H, H-11ax); **¹³C NMR** (126 MHz, CDCl₃) δ 157.9, 133.2, 129.4, 113.8, 55.7, 55.3, 51.5, 47.3, 42.5, 41.4, 34.3, 21.9; **m/z HRMS** (ESI) found [M+H]⁺ 291.2433, C₁₈H₃₀N₂O requires 291.2431.

2-(1-Heptyl-2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione (308)



A mixture of 2-(2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione **306** (500 mg, 1.74 mmol, 1.0 equiv) and potassium carbonate (720 mg, 5.22 mmol, 3.0 equiv) were stirred in 1-iodoheptane (2.0 mL, 12.2 mmol, 7.0 equiv) at 120 °C for 20 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 5% ethyl acetate in petroleum ether, affording the title compound as a colourless oil (287 mg, 0.75 mmol, 43%); **R_f** (ethyl acetate in petroleum ether, 10%): 0.36; **IR** ν_{max} /cm⁻¹ (film): 2926, 2855, 1769, 1710, 1467, 1374, 1336, 1177, 1086, 943, 869, 717; **¹H NMR** (500 MHz, CDCl₃) δ 7.83 (dd, *J* = 5.4, 3.0 Hz, 2H, H-15), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H, H-16), 4.60 (tt, *J* = 13.0, 3.5 Hz, 1H, H-12), 2.52 – 2.33 (m, 4H, H-7 and H-11ax), 1.52 (dd, *J* = 12.3, 3.5 Hz, 2H, H-11eq), 1.50 – 1.41 (m, 2H, H-6), 1.36 – 1.21 (m, 8H, H-2, H-3, H-4 and H-5), 1.17 (s, 6H, H-8 or H-9), 1.14 (s, 6H, H-8 or H-9), 0.92 (t, *J* = 6.1 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 168.6, 133.8, 132.0, 123.0, 55.8, 44.6, 44.2, 43.5, 35.7, 34.1, 32.1, 29.3, 27.5, 22.7, 21.2, 14.1; **m/z HRMS** (ESI) found [M+H]⁺ 385.2856, C₂₄H₃₇N₂O₂ requires 385.2855.

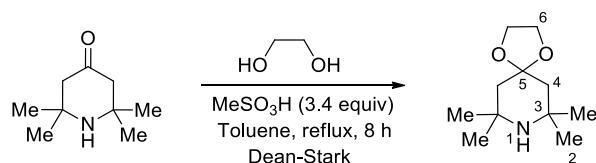
1-Heptyl-2,2,6,6-tetramethylpiperidin-4-amine (309)



To a solution of *2-(1-heptyl-2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione* **308** (120 mg, 0.31 mmol, 1.0 equiv) in ethanol (2 mL) was added hydrazine hydrate (0.05 mL, 1.55 mmol, 5.0 equiv). The reaction mixture was heated at reflux for 3 hours during which white precipitate was formed. The reaction mixture was concentrated *in vacuo* and suspended in dichloromethane. The white precipitate was filtered off and the filtrate was concentrated in vacuo to yield the title compound as a pale yellow oil (75 mg, 0.30 mmol, 97%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2920, 2872, 1577, 1464, 1378, 1330, 1260, 1214, 1187, 1112, 1013, 913, 839, 722; **¹H NMR** (400 MHz, CDCl₃) δ 3.04 – 2.91 (m, 1H, H-12), 2.40 – 2.27 (m, 2H, H-7), 1.65 (dd, *J* = 12.4, 3.7 Hz, 2H, H-11eq), 1.46 – 1.32 (m, 2H, H-6), 1.34 – 1.12 (m, 10H, H-2, H-3, H-4, H-5 and H-11ax), 1.08 (s, 6H, H-8 or H-9), 1.01 (s, 6H, H-8 or H-9), 0.88 (t, *J* = 6.8 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 55.5, 51.7, 44.6, 42.5, 35.8, 34.2, 32.0, 29.3, 27.5, 22.7, 21.7, 14.1; **m/z HRMS** (ESI) found [M+H]⁺ 255.2795, C₁₆H₃₅N₂ requires 255.2795.

5.9 Synthesis of TMP-astemizole **287**: Dioxolane route

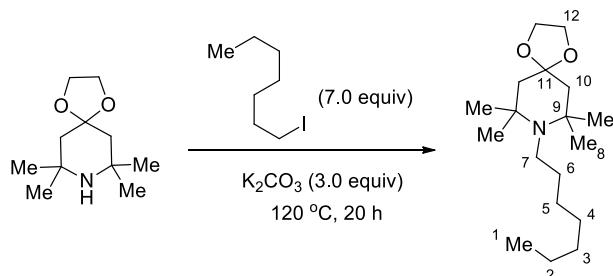
7,7,9,9-Tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (132)



To a mixture of 2,2,6,6-tetramethylpiperidin-4-one (2.00 g, 12.9 mmol, 1.0 equiv) in ethylene glycol (15 mL) and dry toluene (5 mL) was added methanesulfonic acid (2.84 mL, 44 mmol, 3.4 equiv). The reaction was heated at reflux with a Dean-Stark apparatus for eight hours, then cooled to 0 °C and basified by adding saturated aqueous sodium bicarbonate and extracted with diethyl ether. The organic extract was washed with saturated aqueous sodium bicarbonate, brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by bulb-to-bulb distillation, affording the title compound as a pale yellow oil (1.39 g, 6.97 mmol, 54%); **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2953, 1355, 1233, 1089, 959, 785; **¹H NMR** (500 MHz, CDCl₃) δ 3.91 (s, 4H, H-6), 1.50 (s, 4H, H-4), 1.19 (s, 12H, H-2); **¹³C NMR**

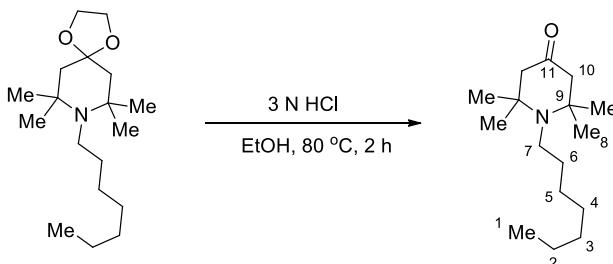
NMR (126 MHz, CDCl₃) δ 109.2, 63.9, 51.4, 45.3, 32.1; **m/z HRMS** (ESI) found [M+H]⁺ 200.1642, C₁₁H₂₂NO₂ requires 200.1645.

8-Heptyl-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (314)



A mixture of *7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **132** (2.0 g, 10.1 mmol, 1.0 equiv) and potassium carbonate (4.18 g, 30.3 mmol, 3.0 equiv) were stirred in 1-iodoheptane (11.6 mL, 70.7 mmol, 7.0 equiv) in a sealed oven-dried microwave tube at 120 °C for 20 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 5% ethyl acetate in petroleum ether, affording the title compound as a pale brown oil (1.29 g, 4.34 mmol, 43%); R_f (ethyl acetate in petroleum ether, 10% - on triethylamine-pretreated silica plate): 0.34; **IR** ν_{max}/cm⁻¹ (film): 2949, 2874, 1467, 1361, 1259, 1189, 1082, 1013, 959, 841, 798, 733, 702; **¹H NMR** (500 MHz, CDCl₃) δ 3.94 (s, 4H, H-12), 2.46 – 2.37 (m, 2H, H-7), 1.66 (s, 4H, H-10), 1.49 – 1.38 (m, 2H, H-6), 1.37 – 1.17 (m, 8H, H-2, H-3, H-4 and H-5), 1.14 (s, 12H, H-8), 0.90 (t, J = 6.9 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 107.8, 63.6, 55.7, 47.6, 44.2, 35.9, 32.0, 29.3, 27.5, 23.0, 22.7, 14.1; **m/z HRMS** (ESI) found [M+H]⁺ 334.2376, C₂₀H₃₂NO₃ requires 334.2377.

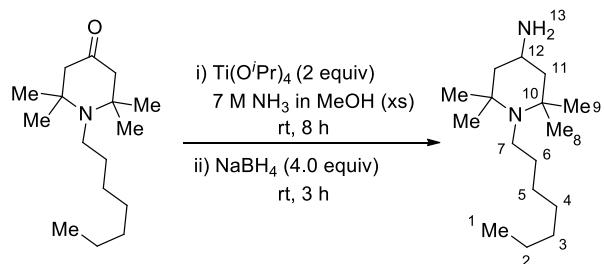
1-Heptyl-2,2,6,6-tetramethylpiperidin-4-one (315)



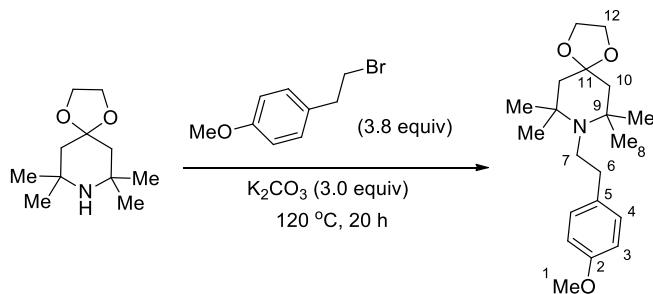
To a solution of *8-heptyl-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **314** (100 mg, 0.34 mmol) in ethanol (1 mL) was added 3 N hydrochloric acid (1 mL) and stirred at 80 °C for 2 hours. The reaction mixture was cooled and ethanol was removed under reduced pressure. The mixture was basified with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts

were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (54 mg, 0.21 mmol, 63%); **R_f** (ethyl acetate in petroleum ether, 10% - on triethylamine-pretreated silica plate): 0.29; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2957, 2926, 2854, 1675, 1615, 1444, 1378, 1359, 1219, 1112, 1032, 868, 770, 724; **¹H NMR** (500 MHz, CDCl₃) δ 2.50 (t, *J* = 10.0 Hz, 2H, H-7), 2.15 (s, 4H, H-10), 1.51 – 1.43 (m, 2H, H-6), 1.36 – 1.25 (m, 8H, H-2, H-3, H-4 and H-5), 1.15 (s, 12H, H-8), 0.89 (t, *J* = 7.0 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 200.9, 52.9, 52.4, 42.5, 31.8, 30.9, 29.3, 27.6, 27.5, 22.6, 14.1; m/z **HRMS** (ESI) found [M+H]⁺ 254.2481, C₁₆H₃₂NO requires 254.2478.

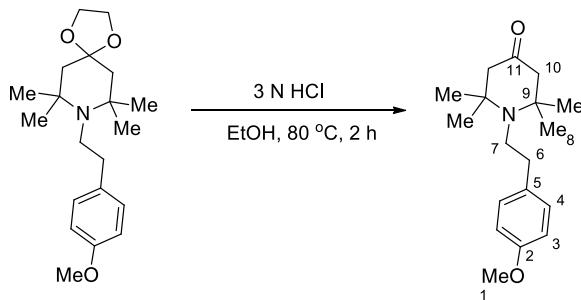
1-Heptyl-2,2,6,6-tetramethylpiperidin-4-amine (309)



To *1-heptyl-2,2,6,6-tetramethylpiperidin-4-one* **315** (50 mg, 0.20 mmol, 1.0 equiv) in 7 M ammonia in methanol (4 mL) was added titanium(IV) isopropoxide (0.12 mL, 0.40 mmol, 2.0 equiv). The mixture was stirred at room temperature for 8 hours, followed by addition of sodium borohydride (31 mg, 0.80 mmol, 4.0 equiv) and reaction mixture further stirred at this temperature for 3 hours. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate. The inorganic precipitate was filtered and the filtrate extracted with diethyl ether. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 30% ethyl acetate in petroleum ether, affording the title compound as a pale yellow oil (41 mg, 0.14 mmol, 38%); **R_f** (ethyl acetate in petroleum ether, 30% - on triethylamine-pretreated silica plate): 0.25; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2920, 2872, 1577, 1464, 1378, 1330, 1260, 1214, 1187, 1112, 1013, 913, 839, 722; **¹H NMR** (400 MHz, CDCl₃) δ 3.04 – 2.91 (m, 1H, H-12), 2.40 – 2.27 (m, 2H, H-7), 1.65 (dd, *J* = 12.4, 3.7 Hz, 2H, H-11eq), 1.46 – 1.32 (m, 2H, H-6), 1.34 – 1.12 (m, 10H, H-2, H-3, H-4, H-5 and H-11ax), 1.08 (s, 6H, H-8 or H-9), 1.01 (s, 6H, H-8 or H-9), 0.88 (t, *J* = 6.8 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 55.5, 51.7, 44.6, 42.5, 35.8, 34.2, 32.0, 29.3, 27.5, 22.7, 21.7, 14.1; m/z **HRMS** (ESI) found [M+H]⁺ 255.2795, C₁₆H₃₅N₂ requires 255.2795.

8-(4-Methoxyphenethyl)-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (311)

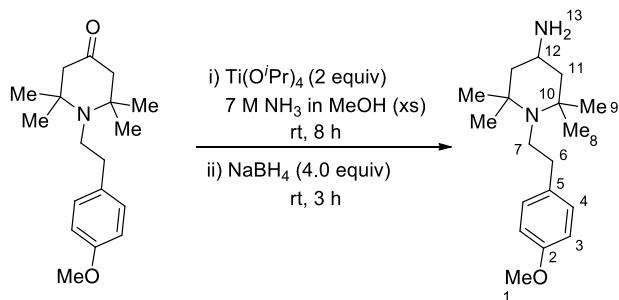
A mixture of *7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **132** (1.00 g, 5.03 mmol, 1.0 equiv) and potassium carbonate (2.08 g, 15.1 mmol, 3.0 equiv) were stirred in 1-(2-bromoethyl)-4-methoxybenzene (3 mL, 19.2 mmol, 3.8 equiv) in a sealed oven-dried microwave tube at 120 °C for 20 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the title compound as a pale brown oil (602 mg, 1.81 mmol, 36%); **R**_f (ethyl acetate in petroleum ether, 10% - on triethylamine-pretreated silica plate): 0.31; **IR** ν_{max} /cm⁻¹ (film): 2953, 2880, 1611, 1511, 1364, 1243, 1188, 1080, 1037, 1011, 959, 854, 821, 730, 572, 560; **¹H NMR** (500 MHz, CDCl₃) δ 7.10 (d, *J* = 8.7 Hz, 2H, H-4), 6.84 (d, *J* = 8.7 Hz, 2H, H-3), 3.93 (s, 4H, H-12), 3.79 (s, 3H, H-1), 2.66 – 2.62 (m, 4H, H-6 and H-7), 1.68 (s, 4H, H-10), 1.18 (s, 12H, H-8); **¹³C NMR** (126 MHz, CDCl₃) δ 157.8, 133.3, 129.4, 113.8, 107.7, 63.6, 55.9, 55.3, 47.5, 46.9, 41.4, 28.0; **m/z HRMS** (ESI) found [M+H]⁺ 334.2376, C₂₀H₃₂NO₃ requires 334.2377.

1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-one (312)

To a solution of *8-(4-methoxyphenethyl)-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **311** (100 mg, 0.30 mmol) in ethanol (1 mL) was added 3 N hydrochloric acid (1 mL) and stirred at 80 °C for 2 hours. The reaction mixture was cooled and ethanol removed under reduced pressure. The mixture was basified with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0

to 10% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (53 mg, 0.18 mmol, 61%); **R_f** (ethyl acetate in petroleum ether, 10% - on triethylamine-pretreated silica plate): 0.39; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2969, 2835, 1712, 1611, 1511, 1464, 1302, 1245, 1177, 1143, 1092, 1036, 1012, 855, 822; **¹H NMR** (500 MHz, CDCl₃) δ 7.13 (d, *J* = 8.6 Hz, 2H, H-4), 6.86 (d, *J* = 8.7 Hz, 2H, H-3), 3.81 (s, 3H, H-1), 2.78 – 2.72 (m, 2H, H-7), 2.72 – 2.66 (m, 2H, H-6), 2.39 (s, 4H, H-10), 1.20 (s, 12H, H-8); **¹³C NMR** (126 MHz, CDCl₃) δ 209.9, 158.0, 132.6, 129.4, 113.9, 60.0, 55.8, 55.3, 47.3, 41.1, 28.4; *m/z* **HRMS** (ESI) found [M+H]⁺ 290.2116, C₁₈H₂₈NO₂ requires 290.2115.

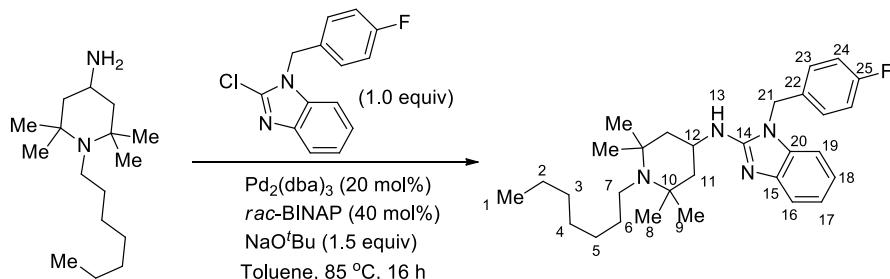
1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-amine (307)



To *1-(4-methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-one* **312** (50 mg, 0.17 mmol, 1.0 equiv) in 7 M ammonia in methanol (4 mL) was added titanium(IV) isopropoxide (0.10 mL, 0.34 mmol, 2.0 equiv). The mixture was stirred at room temperature for 8 hours, followed by addition of sodium borohydride (26 mg, 0.68 mmol, 4.0 equiv) and stirred for a further 3 hours. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate. The inorganic precipitate was filtered and the filtrate extracted with diethyl ether. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 40% ethyl acetate in petroleum ether, affording the title compound as a pale yellow oil (38 mg, 0.13 mmol, 77%); **R_f** (ethyl acetate in petroleum ether, 30% - on triethylamine-pretreated silica plate): 0.22; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2938, 2835, 1611, 1583, 1511, 1464, 1378, 1366, 1243, 1175, 1111, 1036, 961, 853, 821, 743; **¹H NMR** (500 MHz, CDCl₃) δ 7.10 (d, *J* = 8.6 Hz, 2H, H-4), 6.84 (d, *J* = 8.6 Hz, 2H, H-3), 3.79 (s, 3H, H-1), 3.05 – 2.95 (m, 1H, H-12), 2.70 – 2.47 (m, 4H, H-6 and H-7), 1.69 (dd, *J* = 12.2, 3.1 Hz, 2H, H-11eq), 1.44 (br. s, 2H, H-12), 1.43 (s, 6H, H-8 or H-9), 1.22 (s, 6H, H-8 o H-9), 1.28 – 1.15 (m, 2H, H-11ax); **¹³C NMR** (126 MHz, CDCl₃) δ 157.9, 133.2, 129.4, 113.8, 55.7, 55.3, 51.5, 47.3, 42.5, 41.4, 34.3, 21.8; *m/z* **HRMS** (ESI) found [M+H]⁺ 291.2433, C₁₈H₃₀N₂O requires 291.2431.

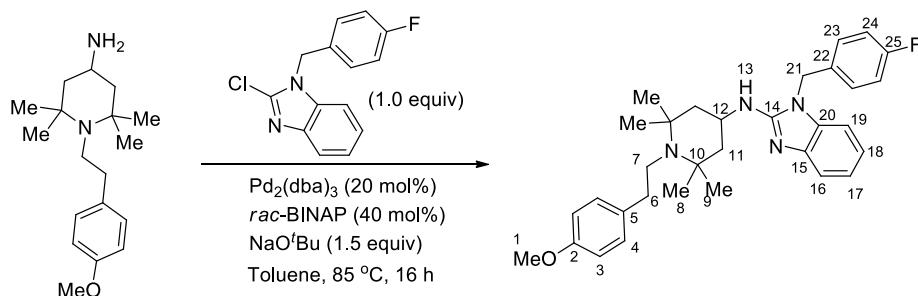
5.10 Synthesis of TMP-astemizole 287: Buchwald-Hartwig amination endgame

1-(4-Fluorobenzyl)-N-{1-(4-methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl}-1*H*-benzo[*d*]imidazol-2-amine (310)



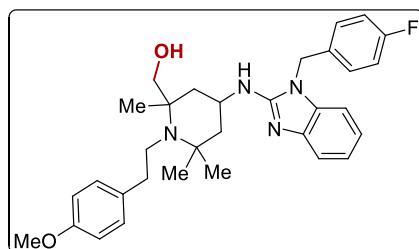
To a solution of *1-heptyl-2,2,6,6-tetramethylpiperidin-4-amine* **309** (160 mg, 0.55 mmol, 1.0 equiv) in dry toluene (5 mL) was added bis(dibenzylideneacetone)palladium(0) (63 mg, 0.11 mmol, 0.2 equiv), sodium *tert*-butoxide (80 mg, 0.83 mmol, 1.5 equiv), *rac*-BINAP (137 mg, 0.22 mmol, 0.4 equiv) and 2-chloro-1-(4-fluorobenzyl)benzimidazole (143 mg, 0.55 mmol, 1.0 equiv). The mixture was stirred at 85 °C for 16 hours in a pre-heated oil bath, after which time the mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, affording the title compound as a yellow solid (167 mg, 0.35 mmol, 64%); **M.p.**: 90–92 °C; **R_f** (ethyl acetate in petroleum ether, 15% - on triethylamine-pretreated silica plate): 0.32; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2929, 2875, 1618, 1602, 1558, 1509, 1464, 1390, 1360, 1249, 1224, 1158, 1080, 1015, 963, 846, 820, 737, 703; **¹H NMR** (500 MHz, CDCl₃) δ 7.54 (d, *J* = 7.8 Hz, 1H, H-19), 7.18 – 7.11 (m, 3H, H-18 and H-23), 7.08 – 7.02 (m, 4H, H-16, H-17 and H-24), 5.05 (s, 2H, H-21), 4.31 – 4.16 (m, 1H, H-12), 3.56 (d, *J* = 8.3 Hz, 1H, H-13), 2.45 – 2.34 (m, 2H, H-7), 1.96 (dd, *J* = 11.7, 3.2 Hz, 2H, H-11eq), 1.46 – 1.35 (m, 2H, H-6), 1.36 – 1.17 (m, 10H, H-2, H-3, H-4 and H-5, H-11 ax), 1.14 (s, 6H, H-8 or H-9), 1.10 (s, 6H, H-8 or H-9), 0.90 (t, *J* = 7.0 Hz, 3H, H-1); **¹³C NMR** (126 MHz, CDCl₃) δ 162.4 (d, ¹*J*_{C-F} = 247.2 Hz), 153.5, 142.6, 134.6, 131.2, 128.09 (d, ³*J*_{C-F} = 8.2 Hz), 121.4, 119.6, 116.8, 116.2 (d, ²*J*_{C-F} = 21.7 Hz), 107.0, 55.6, 48.1, 45.4, 45.0, 44.5, 35.8, 34.1, 32.0, 29.2, 27.4, 22.6, 21.7, 14.1; **¹⁹F NMR** (376 MHz, CDCl₃) δ -113.77; **m/z HRMS** (ESI) found [M+H]⁺ 479.3532, C₃₀H₄₄FN₄ requires 479.3531.

1-(4-Fluorobenzyl)-N-{1-(4-methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl}-1H-benzo[d]imidazol-2-amine (287)

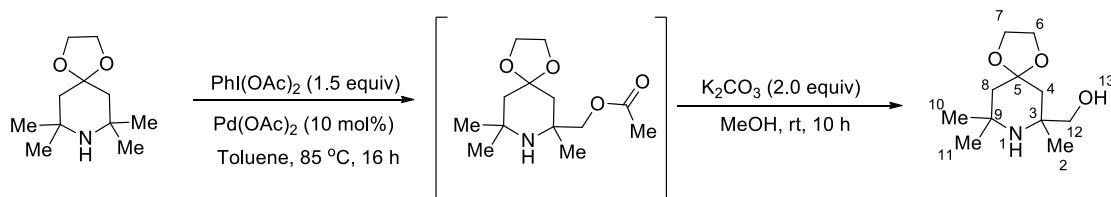


To a solution of *1-(4-methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-amine* **307** (41 mg, 0.14 mmol, 1.0 equiv) in dry toluene (1 mL) was added bis(dibenzylideneacetone)palladium(0) (16 mg, 0.03 mmol, 0.2 equiv), sodium *tert*-butoxide (20 mg, 0.21 mmol, 1.5 equiv), *rac*-BINAP (35 mg, 0.06 mmol, 0.4 equiv) and 2-chloro-1-(4-fluorobenzyl)benzimidazole (37 mg, 0.14 mmol, 1.0 equiv). The mixture was stirred at 85 °C for 16 hours in a pre-heated oil bath, after which time the mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, affording the title compound as a yellow solid (44 mg, 0.09 mmol, 61%); **M.p.**: 140–142 °C; **R_f** (ethyl acetate in petroleum ether, 20% - on triethylamine-pretreated silica plate): 0.31; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2963, 1605, 1563, 1510, 1245, 1027, 908, 821, 731; **¹H NMR** (400 MHz, CDCl₃) δ 7.52 (d, *J* = 7.8 Hz, 1H, H-19), 7.18 – 6.95 (m, 9H, H-4, H-16, H-17, H-18, H-23 and H-24), 6.84 (d, *J* = 8.6 Hz, 2H, H-3), 5.05 (s, 2H, H-21), 4.39 – 4.13 (m, 1H, H-12), 3.79 (s, 3H, H-1), 3.57 (d, *J* = 8.0 Hz, 1H, H-13), 2.62 (s, 4H, H-6 and H-7), 1.98 (dd, *J* = 12.1, 3.5 Hz, 2H, H-11eq), 1.21 (s, 6H, H-8 or H-9), 1.19 – 1.14 (m, 2H, H-11ax), 1.12 (s, 6H, H-8 or H-9); **¹³C NMR** (101 MHz, CDCl₃) δ 162.5 (d, *J*_{C-F} = 247.1 Hz), 157.9, 153.5, 142.6, 134.6, 133.0, 131.2, 129.4, 128.1 (d, *J*_{C-F} = 8.2 Hz), 121.5, 119.7, 116.8, 116.2 (d, *J*_{C-F} = 21.8 Hz), 113.9, 107.0, 55.8, 55.3, 48.0, 47.2, 45.4, 45.0, 41.3, 34.2, 21.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -113.72; **m/z HRMS** (ESI) found [M+H]⁺ 515.3168, C₃₂H₄₀ FN₄O requires 515.3167.

5.11 Synthesis of astemizole analogue 288:

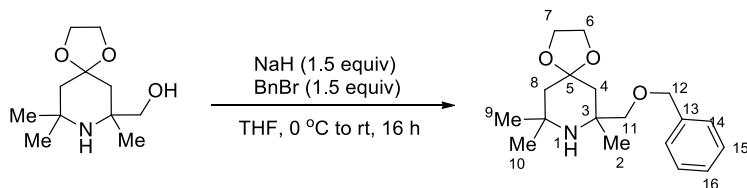


(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)methanol (316)

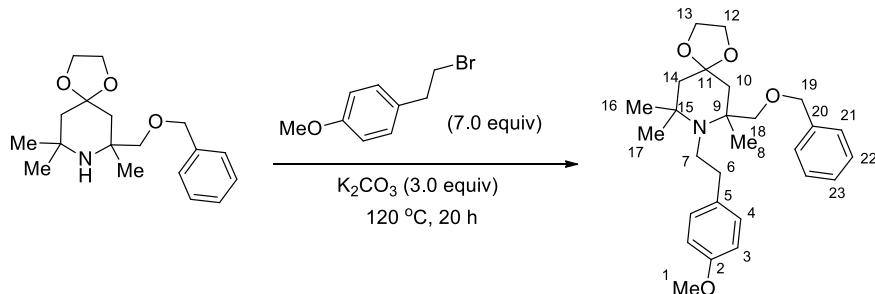


To a solution of *7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **132** (100 mg, 0.5 mmol, 1.0 equiv) in dry toluene (5 mL) was added palladium(II) acetate (11 mg, 0.05 mmol, 0.1 equiv) and iodobenzene diacetate (242 mg, 0.75 mmol, 1.5 equiv). The flask was then fitted with a balloon filled with air and placed in a pre-heated bath at 70 °C and allowed to stir at this temperature for 16 hours. The mixture was then cooled and filtered through a pad of Celite® and the filter cake was washed with ethyl acetate. The filtrate was then washed with saturated aqueous sodium bicarbonate, brine, dried (magnesium sulfate) and concentrated *in vacuo*.

To a solution of crude acetate in methanol (5 mL) was added potassium carbonate (138 mg, 1.0 mmol, 2.0 equiv based on *7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **132**). The resulting mixture was stirred at room temperature for 10 hours before filtering and concentrating *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 2% methanol in dichloromethane, affording the title compound as a beige solid (52 mg, 0.24 mmol, 48%); **M.p.**: 63–65 °C; **R_f**(methanol in dichloromethane, 5% - on triethylamine-pretreated silica plate): 0.28; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3320–3168(br), 2958, 1662, 1479, 1355, 1219, 1078, 1016, 949, 776; **¹H NMR** (500 MHz, CDCl₃) δ 4.01 – 3.84 (m, 4H, H-6 and H-7), 3.47 (d, *J* = 10.3 Hz, 1H, H-12), 3.07 (d, *J* = 10.3 Hz, 1H, H-12), 1.77 (dd, *J* = 13.8, 0.9 Hz, 1H, H-4), 1.59 (dd, *J* = 13.5, 0.9 Hz, 1H, H-8), 1.53 (dd, *J* = 13.5, 1.5 Hz, 1H, H-8), 1.44 (dd, *J* = 13.8, 1.5 Hz, 1H, H-4), 1.27 (s, 3H, H-10 or H-11), 1.19 (s, 3H, H-10 or H-11), 1.19 (s, 3H, H-2); **¹³C NMR** (126 MHz, CDCl₃) δ 108.6, 68.4, 63.9, 63.8, 54.7, 51.2, 44.8, 39.9, 32.2, 32.0, 27.7; **m/z HRMS** (ESI) found [M+H]⁺ 216.1592, C₁₁H₂₂NO₃ requires 215.1594.

7-{(Benzyl)oxy}methyl-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane (317)

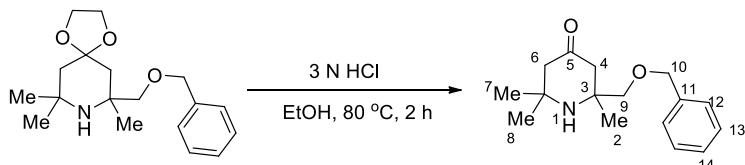
To a solution of *(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)methanol* **316** (100 mg, 0.47 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) at 0 °C was added sodium hydride (60% in mineral oil; 28 mg, 0.71 mmol, 1.5 equiv) and stirred at this temperature for 30 minutes. Benzyl bromide (0.08 mL, 0.71 mmol, 1.5 equiv) was then added and the resulting mixture was warmed to room temperature and stirred at this temperature for 16 hours. The reaction mixture was partitioned between diethyl ether and saturated aqueous sodium bicarbonate. The aqueous layer was separated and extracted with diethyl ether. The combined organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 15% ethyl acetate in petroleum ether, affording the title compound as a pale yellow oil (101 mg, 0.33 mmol, 71%); **R_f** (ethyl acetate in petroleum ether, 10% - on triethylamine-pretreated silica plate): 0.21; **IR** ν_{max} /cm⁻¹ (film): 2961, 1495, 1454, 1356, 1203, 1088, 1034, 948, 787, 736, 697; **¹H NMR** (500 MHz, CDCl₃) δ 7.42 – 7.26 (m, 5H, Ar-Hs), 4.54 (d, *J* = 12.2 Hz, 1H, H-12), 4.50 (d, *J* = 12.2 Hz, 1H, H-12), 4.03 – 3.85 (m, 4H, H-6 and H-7), 3.30 (d, *J* = 8.7 Hz, 1H, H-11), 3.27 (d, *J* = 8.7 Hz, 1H, H-11), 1.80 (d, *J* = 13.5 Hz, 1H, H-4), 1.66 (dd, *J* = 13.4, 1.7 Hz, 1H, H-8), 1.49 – 1.40 (m, 2H, H-4 and H-8), 1.26 (s, 3H, H-9 or H-10), 1.21 (s, 3H, H-9 or H-10), 1.18 (s, 3H, H-2); **¹³C NMR** (126 MHz, CDCl₃) δ 138.6, 128.3, 127.5, 127.5, 109.3, 78.4, 73.1, 64.2, 63.4, 54.2, 51.1, 45.1, 39.8, 33.4, 30.8, 26.4; **m/z HRMS** (ESI) found [M+H]⁺ 306.2064, C₁₈H₂₈NO₃ requires 306.2064.

7-{(Benzyl)oxy}methyl-8-(4-methoxyphenethyl)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane (318)

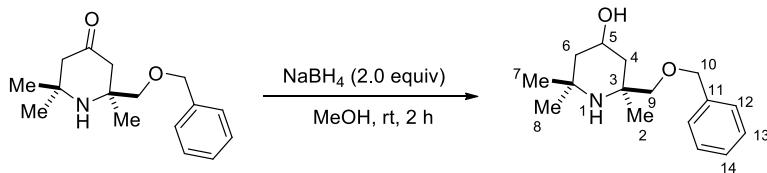
A mixture of *7-{(benzyloxy)methyl}-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane* **317** (520 mg, 1.70 mmol, 1.0 equiv) and potassium carbonate (469 mg, 3.40 mmol, 2.0 equiv) were stirred in 1-(2-bromoethyl)-4-methoxybenzene (1.86 mL, 11.9 mmol, 7.0 equiv) in a sealed oven-dried microwave tube

at 120 °C for 20 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a pale brown oil (130 mg, 0.30 mmol, 18%); **R_f** (ethyl acetate in petroleum ether, 20%): 0.25; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2951, 2880, 1611, 1511, 1365, 1244, 1177, 1079, 1037, 1037, 1011, 960, 822, 733, 699; **¹H NMR** (500 MHz, CDCl₃) δ 7.37 – 7.26 (m, 5H, H-21, H-22 and H-23), 7.02 (d, *J* = 8.6 Hz, 2H, H-4), 6.80 (d, *J* = 8.6 Hz, 2H, H-3), 4.54 (d, *J* = 12.2 Hz, 1H, H-19), 4.51 (d, *J* = 12.2 Hz, 1H, H-19), 3.99 – 3.86 (m, 4H, H-12 and H-13), 3.79 (s, 3H, H-1), 3.58 (d, *J* = 8.7 Hz, 1H, H-18), 3.33 (d, *J* = 8.7 Hz, 1H, H-18), 2.86 – 2.72 (m, 1H, H-7), 2.71 – 2.40 (m, 3H, H-6 and H-7), 1.96 (d, *J* = 13.5 Hz, 1H, H-10), 1.70 (s, 2H, H-14), 1.62 (d, *J* = 13.5 Hz, 1H, H-10), 1.24 (s, 3H, H-16 or H-17), 1.20 (s, 3H, H-16 or H-17), 1.18 (s, 3H, H-8); **¹³C NMR** (126 MHz, CDCl₃) δ 157.8, 138.8, 133.2, 129.5, 128.3, 127.5, 127.4, 113.8, 107.6, 73.4, 63.7, 63.6, 58.9, 56.0, 55.3, 47.5, 47.0, 42.5, 40.9, 29.71, 29.37, 27.56, 22.24; **m/z HRMS** (ESI) found [M+H]⁺ 440.2788, C₂₇H₃₈NO₄ requires 440.2792.

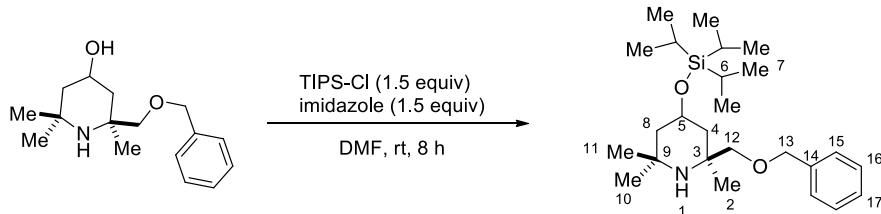
2-{(Benzylxy)methyl}-2,6,6-trimethylpiperidin-4-one (**354**)



To a solution of *7-((benzyloxy)methyl)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane* **317** (100 mg, 0.33 mmol) in ethanol (1 mL) was added 3 N hydrochloric acid (1 mL) and stirred at 80 °C for 2 hours. The reaction mixture was cooled and ethanol removed under reduced pressure. The mixture was basified with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (65 mg, 0.25 mmol, 76%); **R_f** (ethyl acetate in petroleum ether, 20% - on triethylamine-pretreated silica plate): 0.20; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2967, 2861, 1705, 1454, 1296, 1095, 1027, 737, 698; **¹H NMR** (500 MHz, CDCl₃) δ 7.39 – 7.27 (m, 5H, Ar-Hs), 4.59 (d, *J* = 12.0 Hz, 1H, H-10), 4.53 (d, *J* = 12.0 Hz, 1H, H-10), 3.33 (d, *J* = 8.9 Hz, 1H, H-9), 3.17 (d, *J* = 8.9 Hz, 1H, H-9), 2.63 (dd, *J* = 13.3, 0.6 Hz, 1H, H-4), 2.31 (dd, *J* = 13.1, 1.6 Hz, 1H, H-6), 2.22 (dd, *J* = 13.1, 0.6 Hz, 1H, H-6), 2.11 (dd, *J* = 13.3, 1.6 Hz, 1H, H-4), 1.26 (s, 3H, H-7 or H-8), 1.21 (s, 3H, H-7 or H-8), 1.14 (s, 3H, H-2); **¹³C NMR** (126 MHz, CDCl₃) δ 211.3, 137.9, 128.5, 127.8, 127.7, 77.9, 73.3, 57.9, 55.1, 54.1, 48.7, 33.3, 30.4, 26.6; **m/z HRMS** (ESI) found [M+H]⁺ 262.1797, C₁₆H₂₄NO₂ requires 262.1802.

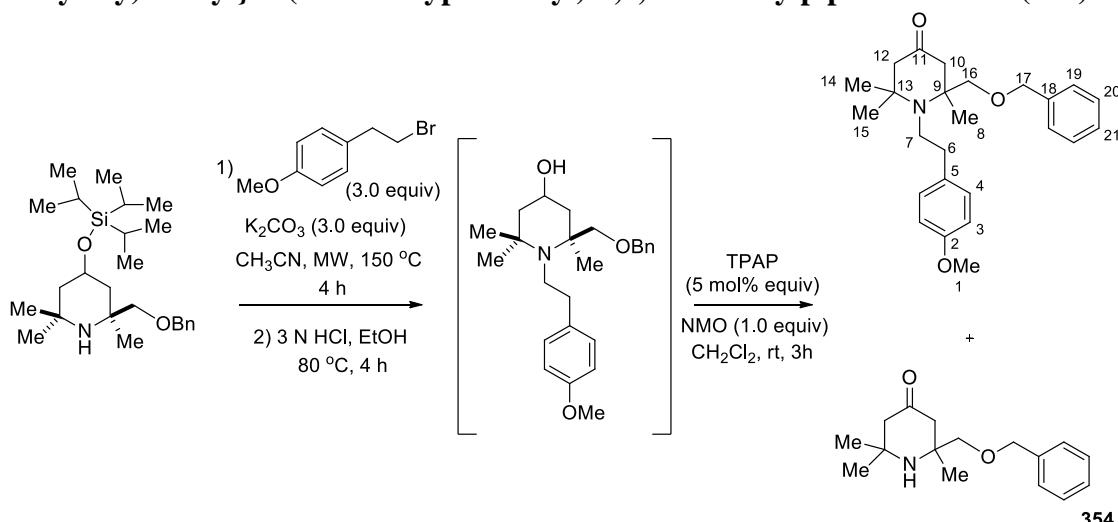
2-{(Benzylxy)methyl}-2,6,6-trimethylpiperidin-4-ol (355)

To a solution of *2-((Benzylxy)methyl)-2,6,6-trimethylpiperidin-4-one* **354** (700 mg, 2.68 mmol, 1.0 equiv) in methanol (27 mL) was added sodium borohydride (204 mg, 5.36 mmol, 2.0 equiv) and stirred at room temperature for 2 hours. The reaction mixture was quenched with water and methanol was removed *in vacuo*. The mixture was then partitioned between dichloromethane and water. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to yield the title compound as an inseparable 3:1 mixture of diastereoisomers (determined by ¹H NMR of the crude mixture) as a yellow oil (520 mg, 1.98 mmol, 74%). The crude alcohol was then taken on to the subsequent protection step without further purification. **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3319 (br.), 2958, 2858, 1454, 1366, 1191, 1098, 1075, 1051, 738, 698; **m/z HRMS** (ESI) found [M+H]⁺ 264.1957, C₁₆H₂₆NO₂ requires 264.1958. *Major diastereoisomer:* **¹H NMR** (500 MHz, CDCl₃) δ 7.41 – 7.30 (m, 5H, Ar-Hs), 4.57 (d, *J* = 12.3 Hz, 1H, H-10), 4.50 (d, *J* = 12.3 Hz, 1H, H-10), 4.01 – 3.88 (m, 1H, H-5), 3.36 (d, *J* = 8.9 Hz, 1H, H-9), 3.31 (d, *J* = 8.9 Hz, 1H, H-9), 2.04 (ddd, *J* = 12.6, 4.3, 2.0 Hz, 1H, H-4), 1.85 (ddd, *J* = 12.3, 4.1, 2.0 Hz, 1H, H-6), 1.19 (s, 3H, H-2), 1.18 (s, 3H, H-7 or H-8), 1.15 (d, *J* = 9.1 Hz, 1H, H-6), 1.14 (s, 3H, H-7 or H-8), 1.08 (dd, *J* = 12.5, 11.3 Hz, 1H, H-4); **¹³C NMR** (126 MHz, CDCl₃) δ 138.4, 128.3, 127.7, 127.5, 76.0, 73.2, 64.8, 54.4, 51.2, 47.3, 43.3, 34.9, 30.4, 29.5. *Minor diastereoisomer:* **¹H NMR** (500 MHz, CDCl₃) δ 7.46 – 7.31 (m, 5H, H-12, H-13 and H-14), 4.59 (d, *J* = 12.8 Hz, 1H, H-10), 4.55 (d, *J* = 12.8 Hz, 1H, H-10), 4.14–1.10 (m, 1H, H-5), 3.27 (d, *J* = 8.7 Hz, 1H, H-9), 3.19 (d, *J* = 8.7 Hz, 1H, H-9), 1.96 (ddd, *J* = 12.2, 4.2, 1.8 Hz, 1H, H-4), 1.74 (ddd, *J* = 12.0, 4.3, 1.8 Hz, 1H, H-6), 1.50 – 1.36 (m, 1H, H-6), 1.23 (s, 3H, H-7 or H-8), 1.19 (s, 3H, H-7 or H-8), 1.16 (s, 3H, H-2), 1.07 – 1.00 (m, 1H, H-4); **¹³C NMR** (126 MHz, CDCl₃) δ 138.3, 128.4, 127.6, 127.5, 79.6, 76.0, 64.9, 53.4, 51.5, 47.9, 42.0, 34.6, 29.1, 25.3.

2-((Benzylxy)methyl)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (356)

To a solution of *2-((benzylxy)methyl)-2,6,6-trimethylpiperidin-4-ol* **355** (520 mg, 1.98 mmol, 1.0 equiv; 3:1 mixture of diastereoisomers) in *N,N*-dimethylformamide (20 mL) at 0 °C was added imidazole (202

mg, 2.97 mmol, 1.5 equiv) and triisopropylsilyl chloride (0.64 ml, 2.97 mmol, 1.5 equiv). The resulting pale yellow solution was warmed to room temperature and stirred for 8 hours. The mixture was then partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was washed with water, brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as an inseparable 3:1 mixture of diastereoisomers as a pale yellow oil (610 mg, 1.46 mmol, 74%); **R_f** (ethyl acetate in petroleum ether, 20% - on triethylamine-pretreated silica plate): 0.29; **IR** ν_{max} /cm⁻¹ (film): 2942, 2865, 1455, 1378, 1089, 1013, 882, 766, 696; m/z **HRMS** (ESI) found [M+H]⁺ 420.3287, C₂₅H₄₆NO₂ requires 420.3292. *Major diastereoisomer:* **¹H NMR** (500 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H, Ar-Hs), 4.52 (d, *J* = 12.1 Hz, 1H, H-13), 4.48 (d, *J* = 12.1 Hz, 1H, H-13), 4.06 (tt, *J* = 10.5, 4.1 Hz, 1H, H-5), 3.31 (d, *J* = 8.9 Hz, 1H, H-12), 3.29 (d, *J* = 8.9 Hz, 1H, H-12), 1.99 (ddd, *J* = 13.0, 4.2, 1.9 Hz, 1H, H-4), 1.76 (ddd, *J* = 12.5, 4.1, 1.9 Hz, 1H, H-8), 1.23 (dd, *J* = 12.5, 10.5 Hz, 1H, H-8), 1.16 (s, 3H, H-2), 1.16 (s, 3H, H-10 or H-11), 1.15 – 1.13 (m, 1H, H-4), 1.11 (s, 3H, H-10 or H-11), 1.08 – 1.04 (m, 21H, H-6 and H-7); **¹³C NMR** (126 MHz, CDCl₃) δ 138.5, 128.3, 127.6, 127.4, 76.8, 73.2, 65.3, 54.3, 51.0, 47.8, 43.4, 34.8, 30.2, 29.9, 18.1, 12.3. *Minor diastereoisomer:* **¹H NMR** (500 MHz, CDCl₃) δ 7.36 – 7.27 (m, 5H, Ar-Hs), 4.55 (d, *J* = 12.2 Hz, 1H, H-13), 4.51 (d, *J* = 12.1 Hz, 1H, H-13), 4.21 – 4.12 (m, 1H, H-5), 3.22 (d, *J* = 8.6 Hz, 1H, H-12), 3.16 (d, *J* = 8.6 Hz, 1H, H-12), 1.86 (ddd, *J* = 12.4, 4.0, 1.7 Hz, 1H, H-4), 1.65 (ddd, *J* = 12.3, 4.2, 1.8 Hz, 1H, H-8), 1.51 – 1.42 (m, 1H, H-8), 1.18 (s, 3H, H-2), 1.15 (s, 3H, H-10 or H-11), 1.12 (s, 3H, H-10 or H-11), 1.12 – 1.09 (m, 1H, H-4), 1.08 – 1.04 (m, 21H, H-6 and H-7); **¹³C NMR** (126 MHz, CDCl₃) δ 138.5, 128.3, 127.5, 127.4, 79.8, 76.8, 65.3, 54.5, 51.3, 48.4, 42.6, 34.6, 29.2, 25.4, 17.7, 12.4.

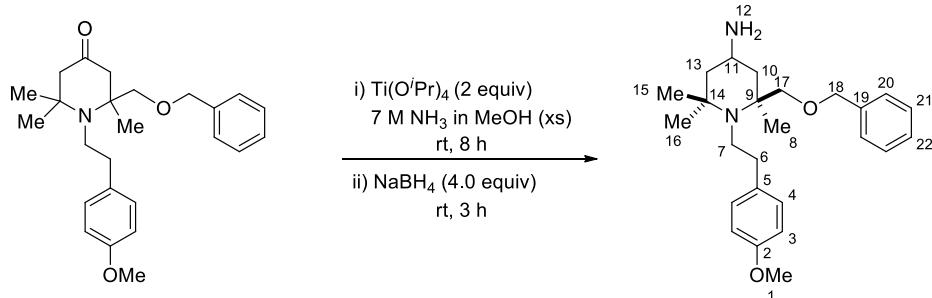
2-((Benzyl)oxy)methyl-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-one (319)

To a solution of 2-((benzyloxy)methyl)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine **356** (200 mg, 0.48 mmol, 1.0 equiv, 3:1 mixture of diastereoisomers) in acetonitrile (2 mL) in a microwave tube was added 1-(2-bromoethyl)-4-methoxybenzene (0.23 mL, 1.43 mmol, 3.0 equiv) and potassium carbonate (198 mg, 1.43 mmol, 3.0 equiv). The resulting mixture was sealed and heated at 150 °C in the microwave for 4 hours. The reaction mixture was filtered and filtrate concentrated *in vacuo*. To the crude material was added ethanol (2 mL) and 3 N hydrochloric acid (2 mL) and the mixture heated at 80 °C for 4 hours. The solution was cooled and basified to ~pH=10 with 1 N sodium hydroxide and extracted with dichloromethane. The layers are separated and the aqueous layer was further extracted with dichloromethane. The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*.

The crude alcohol was then dissolved in dichloromethane (3 mL), followed by addition of *N*-methylmorpholine *N*-oxide (56.0 mg, 0.48 mmol, 1.0 equiv – based on 2-((Benzyloxy)methyl)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine **356**) and tetrapropylammonium perruthenate (8.50 mg, 0.024 mmol, 0.05 equiv). The mixture was stirred at room temperature for 3 hours and filtered through a pad of silica gel, eluting with dichloromethane. The solvent was then recovered under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a pale yellow oil (15.2 mg, 0.038 mmol, 8%), as well as 2-((benzyloxy)methyl)-2,6,6-trimethylpiperidin-4-one **354**, which was recovered as a yellow oil (100 mg, 0.38 mmol, 80%); R_f (ethyl acetate in petroleum ether, 20%): 0.26; **IR** ν_{max}/cm^{-1} (film): 2966, 1713, 1511, 1301, 1244, 1093, 1034, 822, 737, 699; **¹H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H, H-19, H-20 and H-21), 7.05 (d, J = 8.5 Hz, 2H, H-4), 6.84 (d, J = 8.5 Hz, 2H, H-3), 4.59 (d, J = 12.1 Hz, 1H, H-17), 4.55 (d, J = 12.1 Hz, 1H, H-17), 3.82 (s, 3H, H-1), 3.45 (d, J = 9.2 Hz, 1H, H-16), 3.29 (d, J = 9.2 Hz, 1H, H-16), 2.87 – 2.67 (m, 5H, H-6, H-7 and H-10), 2.52 (d, J = 13.0 Hz, 1H, H-12), 2.36 – 2.25 (m,

2H, H-10 and H-12), 1.29 (s, 3H, H-14 or H-15), 1.18 (s, 3H, H-8), 1.17 (s, 3H, H-14 or H-15); **¹³C NMR** (126 MHz, CDCl₃) δ 210.1, 158.0, 138.1, 132.6, 129.5, 129.6, 129.4, 128.4, 127.6, 113.9, 76.8, 73.4, 62.4, 59.6, 55.5, 55.3, 51.1, 47.3, 40.3, 30.8, 26.7, 22.3; m/z **HRMS** (ESI) found [M+H]⁺ 396.2529, C₂₅H₃₄NO₃ requires 396.2533.

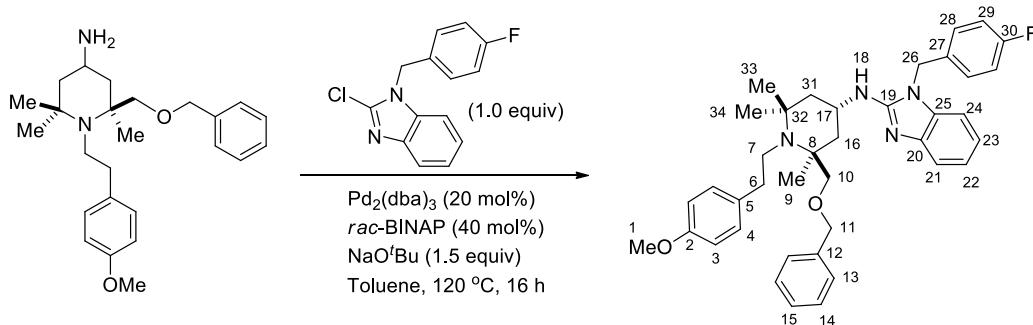
2-{(Benzyl)oxy}methyl}-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-amine (**320**)



To *2-{(benzyl)oxy}methyl}-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-one* **319** (100 mg, 0.25 mmol, 1.0 equiv) in 7 M ammonia in methanol (4 mL) was added titanium(IV) isopropoxide (0.15 mL, 0.50 mmol, 2.0 equiv). The mixture was stirred at room temperature for 8 hours, followed by addition of sodium borohydride (38 mg, 1.0 mmol, 4.0 equiv) and reaction mixture further stirred at this temperature for 3 hours. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate. The inorganic precipitate was filtered and the filtrate extracted with diethyl ether. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 5% MeOH in dichloromethane, affording the title compound as an inseparable 2:1 mixture of diastereoisomers (determined by ¹H NMR of the crude mixture), as a pale yellow oil (51 mg, 0.13 mmol, 52%); **R_f** (methanol in dichloromethane, 5% - on triethylamine-pretreated silica gel): 0.21; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3392, 3381, 2942, 1513, 1432, 1247, 1202, 1133, 1030, 835, 722; m/z **HRMS** (ESI) found [M+H]⁺ 397.2846, C₂₅H₃₇N₂O₂ requires 397.2850. *Major diastereoisomer:* **¹H NMR** (400 MHz, CDCl₃) δ 7.42 – 7.30 (m, 5H, H-20, H-21 and H-22), 7.10 (d, *J* = 8.6 Hz, 2H, H-4), 6.85 (d, *J* = 8.6 Hz, 2H, H-3), 4.52 (d, *J* = 12.2 Hz, 1H, H-18), 4.44 (d, *J* = 12.2 Hz, 1H, H-18), 3.81 (s, 3H, H-1), 3.38 (d, *J* = 8.5 Hz, 1H, H-17), 3.36 (d, *J* = 8.5 Hz, 1H, H-17), 3.19 – 3.06 (m, 1H, H-11), 2.98 – 2.79 (m, 1H, H-7), 2.73 – 2.56 (m, 3H, H-6 and H-7), 2.18 – 2.10 (m, 1H, H-10), 1.79 – 1.68 (m, 1H, H-13), 1.36 (s, 3H, H-8), 1.34 – 1.28 (m, 1H, H-13), 1.26 (s, 3H, H-15), 1.02 (t, *J* = 6.1 Hz, 1H, H-10), 0.98 (s, 3H, H-16); **¹³C NMR** (126 MHz, CDCl₃) δ 157.9, 138.8, 133.1, 129.4, 128.3, 127.7, 127.4, 113.8, 80.8, 73.3, 72.2, 58.9, 55.3, 51.0, 47.2, 46.5, 42.1, 41.4, 34.5, 28.3, 23.5. *Minor diastereoisomer:* **¹H NMR** (400 MHz, CDCl₃) δ 7.41 – 7.29 (m, 5H, H-20, H-21 and H-22), 6.99 (d, *J* = 8.6 Hz, 2H, H-4), 6.80 (d, *J* = 8.6 Hz, 2H, H-3), 4.62 (d, *J* = 12.2 Hz, 1H, H-18), 4.58 (d, *J* = 12.2 Hz, 1H, H-18), 3.80 (s, 3H, H-1), 3.48 (d, *J* = 9.1 Hz, 1H, H-

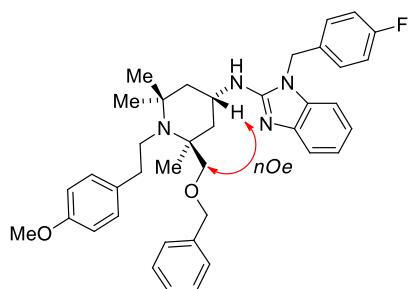
17), 3.32 (d, $J = 9.1$ Hz, 1H, H-17), 2.99 – 2.80 (m, 2H, H-7 and H-11), 2.72 – 2.54 (m, 3H, H-6 and H-7), 1.95 – 1.84 (m, 1H, H-10), 1.79 – 1.67 (m, 1H, H-13), 1.34 – 1.29 (m, 1H, H-13), 1.25 (s, 3H, H-8), 1.20 (dd, $J = 9.0, 5.7$ Hz, 1H), 1.07 (s, 3H, H-15), 1.06 (s, 3H, H-16); ^{13}C NMR (126 MHz, CDCl_3) δ 158.0, 138.5, 133.1, 129.5, 128.4, 127.5, 127.4, 113.8, 75.9, 73.5, 72.2, 58.7, 55.4, 51.1, 47.5, 46.9, 43.2, 40.5, 33.9, 22.3, 18.1.

N-{(2*R*,4*R*)-2-((Benzylxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-yl}-1-(4-fluorobenzyl)-1*H*-benzo[*d*]imidazol-2-amine (321)

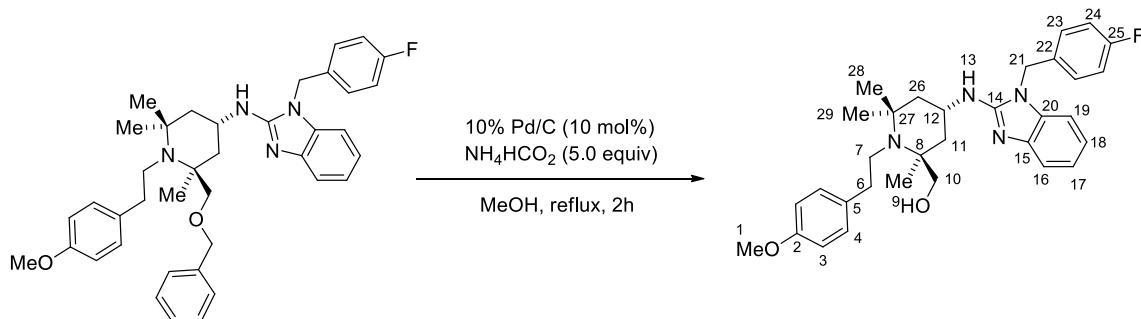


To a solution of 2-*{(benzylxy)methyl}-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-amine **320** (22 mg, 0.06 mmol, 1.0 equiv; 2:1 mixture of diastereoisomers) in dry toluene (1 mL) was added bis(dibenzylideneacetone)palladium(0) (7.0 mg, 0.01 mmol, 0.2 equiv), sodium *tert*-butoxide (9.0 mg, 0.09 mmol, 1.5 equiv), *rac*-BINAP (15 mg, mmol, 0.4 equiv) and 2-chloro-1-(4-fluorobenzyl)benzimidazole (16 mg, 0.06 mmol, 1.0 equiv). The mixture was stirred at 120 °C for 16 hours in a pre-heated oil bath, after which time the mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on basic alumina, eluting with 0 to 30% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (19 mg, 0.03 mmol, 48%) as a single diastereoisomer; **R**_f (ethyl acetate in petroleum ether, 25%): 0.23; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2924, 1604, 1563, 1510, 1368, 1245, 1175, 1077, 908, 822, 730; **1H** NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 7.8$ Hz, 1H, H-21), 7.39 – 7.19 (m, 5H, H-15, H-22, H-23, and H-29), 7.15 – 6.96 (m, 9H, H-4, H-13, H-14, H-24 and H-28), 6.82 (d, $J = 8.3$ Hz, 2H, H-3), 5.04 (s, 2H, H-26), 4.56 (d, $J = 12.0$ Hz, 1H, H-11), 4.49 (d, $J = 12.0$ Hz, 1H, H-11), 4.25 – 4.10 (m, 1H, H-17), 3.78 (s, 3H, H-1), 3.63 (d, $J = 9.2$ Hz, 1H, H-10), 3.56 (d, $J = 7.7$ Hz, 1H, NH), 3.46 (d, $J = 9.2$ Hz, 1H, H-10), 2.96 – 2.84 (m, 1H, H-7), 2.69 – 2.56 (m, 3H, H-6 and H-7), 2.35 (d, $J = 12.0$ Hz, 1H, H-16), 2.03 (d, $J = 9.4$ Hz, 1H, H-3), 1.31 (s, 3H, H-9), 1.22 (s, 3H, H-33), 1.19 – 1.12 (m, 1H, H-31), 1.10 (s, 3H, H-34), 1.04 – 0.93 (m, 1H, H-16); **13C** NMR (101 MHz, CDCl_3) δ 162.5 (d, $^1J_{\text{C-F}} = 247.1$ Hz), 157.9, 153.4, 142.6, 138.9, 134.6, 132.96, 131.2, 129.4, 128.3, 128.1 (d, $^3J_{\text{C-F}} = 8.2$ Hz), 127.4, 127.3, 121.5, 119.7, 116.8, 116.2 (d, $^2J_{\text{C-F}} = 21.7$ Hz), 113.8, 107.1, 73.5, 72.6, 59.1, 55.6, 55.3, 47.7, 47.2, 45.2,*

45.1, 43.1, 41.4, 34.4, 28.2, 23.4; **¹⁹F NMR** (376 MHz, MeOD) δ -113.75; m/z **HRMS** (ESI) found [M+H]⁺ 621.3596, C₃₉H₄₆FN₄O₂ requires 621.3599.



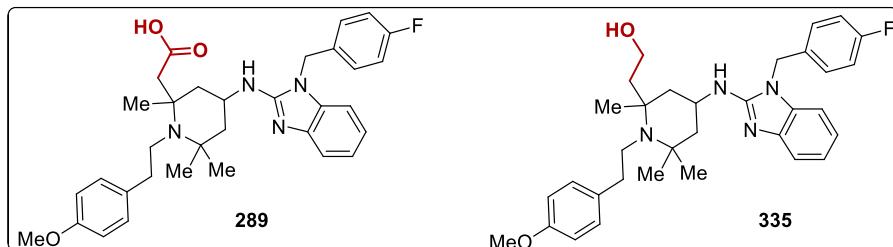
{(2*R*,4*R*)-4-((1-(4-Fluorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)amino)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-2-yl}methanol (288)



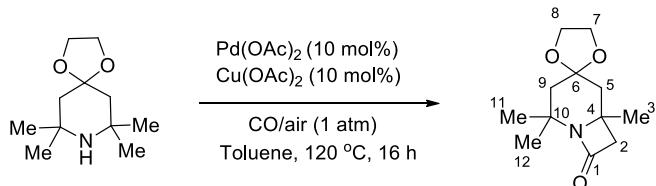
To a solution of *N*-{(2*R*,4*R*)-2-((benzyloxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-yl}-1-(4-fluorobenzyl)-1*H*-benzo[*d*]imidazol-2-amine **321** (14 mg, 0.02 mmol, 1.0 equiv) in methanol (1 mL) was added ammonium formate (5.0 mg, 0.08 mmol, 4.0 equiv) and 10% palladium on carbon (1 mg, 8 μ mol, 0.1 equiv). The resulting mixture was heated at reflux for 2 hours. The mixture was cooled to room temperature and filtered through a pad of celite and washed with methanol. The filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on basic alumina, eluting with 0 to 5% methanol in dichloromethane, affording the title compound as a pale orange solid (6 mg, 0.01 mmol, 50%); **M.p.**: 179–181 °C; **R_f** (methanol in dichloromethane, 5%): 0.26; **IR** ν_{max} /cm⁻¹ (film): 3280 (br.), 2939, 1605, 1567, 1509, 1244, 1158, 1078, 1030, 821, 737, 700; **¹H NMR** (500 MHz, MeOD) δ 7.33 (d, J = 7.6 Hz, 1H, H-16), 7.25 – 7.16 (m, 3H, H-18 and H-24), 7.12 – 7.04 (m, 5H, H-4, H-19 and H-23), 6.99 – 6.95 (m, 1H, H-17), 6.85 (d, J = 8.7 Hz, 2H, H-3), 5.28 (s, 2H, H-21), 4.23 – 4.12 (m, 1H, H-12), 3.88 (d, J = 11.4 Hz, 1H, H-10), 3.78 (s, 3H, H-1), 3.48 (d, J = 11.4 Hz, 1H, H-10), 2.95 – 2.87 (m, 1H, H-7), 2.76 – 2.62 (m, 3H, H-6 and H-7), 2.32 – 2.25 (m, 1H, H-11), 1.87 (d, J = 12.2 Hz, 1H, H-25), 1.56 – 1.48 (m, 1H, H-25), 1.31 (s, 3H, H-28), 1.31 (s, 3H, H-9), 1.22 – 1.15 (m, 1H, H-11), 1.19 (s, 3H, H-29); **¹³C NMR** (126 MHz, MeOD) δ 162.2 (d, $^1J_{\text{C-F}} = 244.4$ Hz), 158.1, 154.0, 141.4, 133.9, 132.6, 132.4, 129.0, 128.2 (d, $^3J_{\text{C-F}} = 8.2$ Hz), 121.1, 119.4, 115.0 (d, $^2J_{\text{C-F}} = 21.9$ Hz), 114.5,

113.5, 107.7, 62.3, 60.0, 55.6, 54.2, 46.8, 44.5, 43.8, 41.2, 41.0, 33.5, 26.5, 22.5, 20.1; **¹⁹F NMR** (376 MHz, MeOD) δ -117.20; m/z **HRMS** (ESI) found [M+H]⁺ 531.3126, C₃₂H₄₀FN₄O₂ requires 531.3130.

5.12 Towards the synthesis of astemizole analogue 289/335

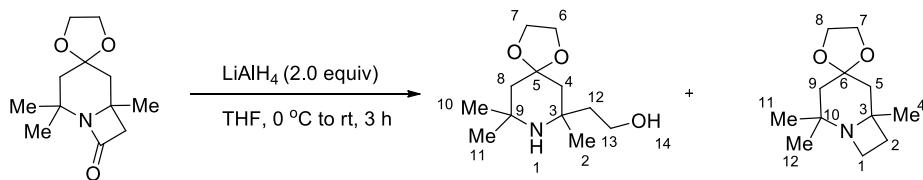


2,2,6-Trimethyl-1-azaspiro[bicyclo[4.2.0]octane-4,2'-[1,3]dioxolan]-8-one (128)



To a dried 25 mL round bottom flask was charged palladium acetate (11 mg, 0.05 mmol, 0.1 equiv), copper(II) acetate (9.0 mg, 0.05 mmol, 0.1 equiv) followed by solution of *7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **132** (100 mg, 0.5 mmol, 1.0 equiv) in dry toluene (5 mL). A reflux condenser was fitted and a balloon of carbon monoxide and a balloon of air were attached to the condenser with a septum. The flask was placed in a pre-heated oil bath at 120 °C and stirred at this temperature for 16 hours. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite®, eluting with ethyl acetate. The filtrate was washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 10% diethyl ether in dichloromethane, affording the title compound as an orange oil (70 mg, 0.03 mmol, 62%); **R_f** (diethyl ether in dichloromethane, 10%): 0.26; **IR** ν_{max} /cm⁻¹ (film): 2971, 1737, 1326, 1094, 667; **¹H NMR** (500 MHz, CDCl₃) δ 4.01 (2H, td, *J* = 6.0 Hz, 0.4 Hz, H-7 or H-8), 3.93-3.86 (2H, m, H-7 or H-8), 2.68 (2H, d, *J* = 14.4 Hz, H-2), 2.00 (1H, dd, *J* = 13.2, 1.6 Hz, H-5), 1.71-1.65 (3H, m, H-5 and H-9), 1.63 (3H, s, H-11 or H-12), 1.54 (3H, s, H-3), 1.32 (3H, s, H-11 or H-12); **¹³C NMR** (126 MHz, CDCl₃) δ 165.4, 108.1, 64.9, 63.3, 55.0, 53.3, 52.6, 46.0, 42.8, 29.2, 27.2, 25.4; m/z **HRMS** (ESI) found [M+H]⁺ 226.1437, C₁₂H₂₀NO₃ requires 226.1438.

2-(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)ethanol (333) and 2,2,6-trimethyl-1-azaspiro(bicyclo[4.2.0]octane-4,2'-[1,3]dioxolane) (334)



To a solution of *7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **128** (1.2 g, 5.33 mmol, 1.0 equiv) in dry tetrahydrofuran (50 mL) at 0 °C was added lithium aluminium hydride (4.40 mL, 10.7 mmol, 2.0 equiv; 2.4 M solution in tetrahydrofuran). The resulting solution was warmed to room temperature and stirred for 3 hours. The mixture was then cooled to 0 °C and quenched with water (0.4 mL), 1 N sodium hydroxide (1.2 mL), water (0.4 mL), followed by addition of magnesium sulfate. The resulting slurry was stirred at this temperature for 20 mins and filtered. The filter cake was washed with diethyl ether and the filtrate concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 5% MeOH in dichloromethane, affording *2-(7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)ethanol* **333** as a white solid (842 mg, 3.68 mmol, 69%) and *2,2,6-trimethyl-1-azaspiro(bicyclo[4.2.0]octane-4,2'-[1,3]dioxolane)* **334** (124 mg, 0.59 mmol, 11%) as a colourless oil.

2-(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)ethanol (333):

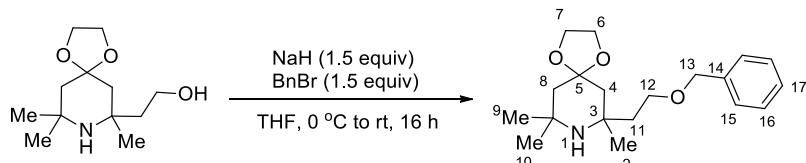
M.p.: 50–52°C; **R_f**(methanol in dichloromethane, 5% - on triethylamine-pretreated silica plate): 0.32; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3463–3170 (br), 2959, 1480, 1357, 1232, 1087, 1035, 950, 840, 790, 774; **¹H NMR** (400 MHz, CDCl₃) δ 4.00 – 3.94 (m, 2H, H-6 or H-7), 3.94 – 3.89 (m, 2H, H-6 or H-7), 3.86 (dt, *J* = 6.5, 4.3 Hz, 2H, H-13), 1.94 – 1.88 (m, 1H, H-12), 1.85 (d, *J* = 13.9 Hz, 1H, H-4), 1.67 (d, *J* = 13.8 Hz, 1H, H-5), 1.62 (dd, *J* = 13.8, 1.7 Hz, 1H, H-5), 1.58 (ddd, *J* = 10.5, 5.4, 2.1 Hz, 1H, H-12), 1.52 (dd, *J* = 13.9, 1.4 Hz, 1H, H-4), 1.40 (s, 3H, H-2), 1.32 (s, 3H, H-10 or H-11), 1.27 (s, 3H, H-10 or H-11); **¹³C NMR** (101 MHz, CDCl₃) δ 108.1, 64.3, 63.6, 59.7, 56.2, 52.6, 44.5, 42.5, 42.4, 33.1, 30.6, 28.6; **m/z HRMS** (ESI) found [M+H]⁺ 230.1752, C₁₂H₂₄NO₃ requires 230.1751.

2,2,6-Trimethyl-1-azaspiro(bicyclo[4.2.0]octane-4,2'-[1,3]dioxolane) (334):

R_f(methanol in dichloromethane, 5% - on triethylamine-pretreated silica plate): 0.40; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 1641, 1454, 1361, 1189, 1086, 1032, 895, 805, 735, 698; **¹H NMR** (500 MHz, CDCl₃) δ 4.04 – 3.95 (m, 2H, H-7 or H-8), 3.92 – 3.82 (m, 2H, H-7 or H-8), 3.22 (dt, *J* = 9.2, 6.9 Hz, 1H, H-1), 3.16 – 3.05 (m, 1H, H-1), 2.01 (dd, *J* = 17.2, 9.4 Hz, 1H, H-2), 1.92 (d, *J* = 13.7 Hz, 1H, H-5), 1.67 – 1.54 (m, 3H, H-2, H-5 and H-9), 1.42 (dd, *J* = 13.7, 2.3 Hz, 1H, H-9), 1.36 (s, 3H, H-4), 1.18 (s, 3H, H-11 or H-12), 0.96 (s, 3H,

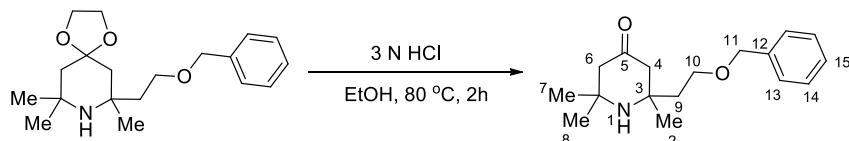
H-11 or H-12); **¹³C NMR** (126 MHz, CDCl₃) δ 108.9, 64.7, 63.5, 62.9, 53.1, 43.3, 38.7, 37.8, 32.9, 29.9, 29.2, 28.1; m/z **HRMS** (ESI) found [M+H]⁺ 212.1575, C₁₂H₂₂NO₂ requires 212.1752.

7-(2-(BenzylOxy)ethyl)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane (336)



To a solution of 2-(7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)ethanol **333** (900 mg, 3.93 mmol, 1.0 equiv) in dry tetrahydrofuran (40 mL) at 0 °C was added sodium hydride (60% in mineral oil; 314 mg, 5.90 mmol, 1.5 equiv) and stirred at this temperature for 30 minutes. Benzyl bromide (0.94 mL, 5.90 mmol, 1.5 equiv) was then added and the resulting mixture was warmed to room temperature and stirred at this temperature for 16 hours. The reaction mixture was partitioned between diethyl ether and saturated aqueous sodium bicarbonate. The aqueous layer was separated and extracted with diethyl ether. The combined organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 25% ethyl acetate in petroleum ether, affording the title compound as a pale yellow oil (927 mg, 2.91 mmol, 74%); **R_f** (ethyl acetate in petroleum ether, 10% - on triethylamine-pretreated silica plate): 0.20; **IR** ν_{max}/cm⁻¹ (film): 2953, 2877, 1454, 1358, 1228, 1090, 1034, 948, 787, 735, 698; **¹H NMR** (500 MHz, CDCl₃) δ 7.35 – 7.31 (m, 3H, H-16 and H-17), 7.30 – 7.26 (m, 2H, H-15), 4.49 (s, 2H, H-13), 3.96 – 3.86 (m, 4H, H-6 and H-7), 3.62 (t, *J* = 7.0 Hz, 2H, H-12), 1.97 (dt, *J* = 13.8, 6.8 Hz, 1H, H-11), 1.77 (dt, *J* = 13.8, 7.1 Hz, 1H, H-11), 1.65 – 1.45 (m, 4H, H-4 and H-8), 1.22 (s, 3H, H-2), 1.21 (s, 3H, H-9 or H-10), 1.16 (s, 3H, H-9 or H-10); **¹³C NMR** (126 MHz, CDCl₃) δ 138.6, 128.3, 127.6, 127.5, 109.1, 73.0, 67.2, 63.9, 63.7, 53.1, 51.1, 45.5, 44.0, 42.8, 32.4, 32.0, 29.5; m/z **HRMS** (ESI) found [M+H]⁺ 320.2221, C₁₉H₃₀NO₃ requires 320.2220.

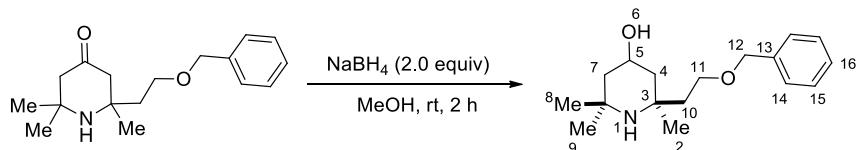
2-{(BenzylOxy)ethyl}-2,6,6-trimethylpiperidin-4-one (359)



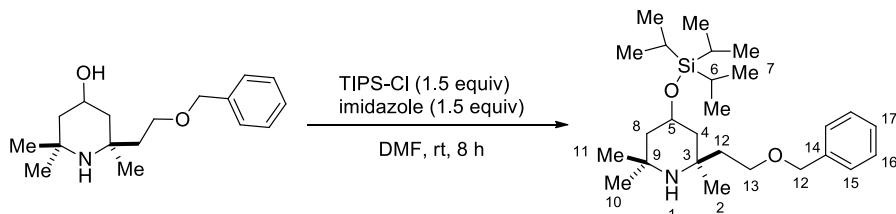
To a solution of 7-(2-(benzylOxy)ethyl)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane **336** (1.40 g, 4.39 mmol, 1.0 equiv) in ethanol (10 mL) was added 3 N hydrochloric acid (10 mL) and stirred at 80 °C for 2 hours. The reaction mixture was cooled and ethanol removed under reduced pressure. The mixture was basified with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The

crude product was purified by flash chromatography on silica gel, eluting with 0 to 50% ethyl acetate in petroleum ether, affording the title compound as a yellow oil (1.20 g, 4.39 mmol, 100%); **R_f** (ethyl acetate in petroleum ether, 50%): 0.19; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2965, 2864, 1703, 1454, 1365, 1292, 1215, 1098, 736, 697; **¹H NMR** (500 MHz, CDCl₃) δ 7.39 – 7.29 (m, 5H, Ar-Hs), 4.51 (s, 2H, H-11), 3.72 – 3.57 (m, 2H, H-10), 2.42 (d, *J* = 13.2 Hz, 1H, H-4), 2.28 (d, *J* = 13.3 Hz, 1H, H-6), 2.25 (d, *J* = 13.3 Hz, 1H, H-6), 2.21 (dd, *J* = 13.2, 1.0 Hz, 1H, H-4), 1.82 (t, *J* = 6.4 Hz, 2H, H-9), 1.23 (s, 3H, H-2), 1.22 (s, 3H, H-7 or H-8), 1.20 (s, 3H, H-7 or H-8); **¹³C NMR** (126 MHz, CDCl₃) δ 211.1, 138.2, 128.4, 127.8, 127.7, 73.2, 66.9, 57.0, 54.9, 54.2, 52.5, 43.4, 32.9, 31.5, 29.8; *m/z* **HRMS** (ESI) found [M+H]⁺ 276.1957, C₁₇H₂₆NO₂ requires 276.1958.

2-{2-(BenzylOxy)ethyl}-2,6,6-trimethylpiperidin-4-ol (360)

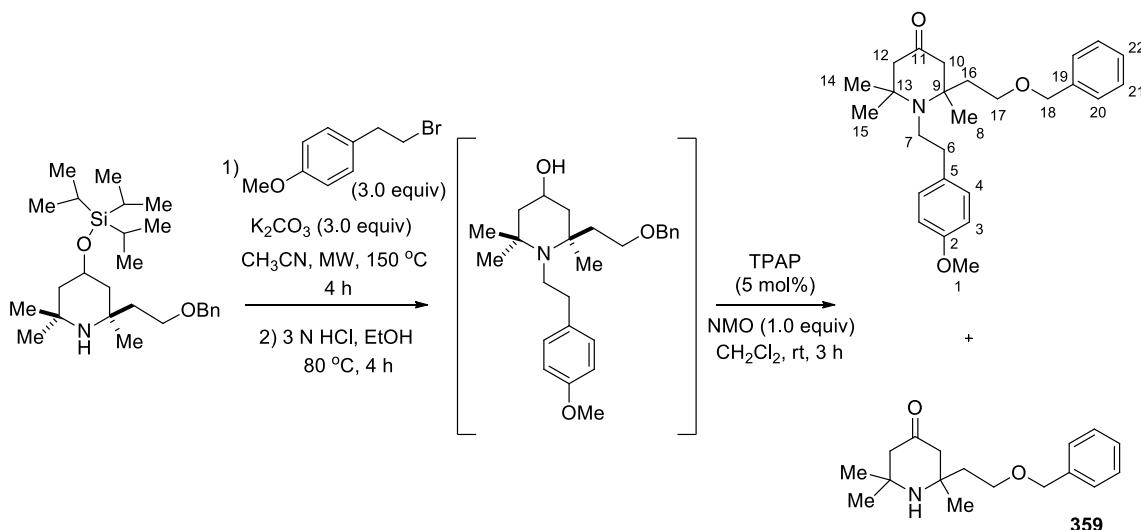


To a solution of 2-{(benzyloxy)methyl}-2,6,6-trimethylpiperidin-4-one **359** (1.20 g, 4.39 mmol, 1.0 equiv) in methanol (50 mL) was added sodium borohydride (332 mg, 8.78 mmol, 2.0 equiv) and stirred at room temperature for 2 hours. The reaction mixture was quenched with water and methanol was removed *in vacuo*. The mixture was then partitioned between dichloromethane and water. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to yield the title compound as an inseparable 1.5:1 mixture of diastereoisomers (determined by ¹H NMR of the crude material) as a yellow oil (1.1 g, 3.97 mmol, 90%). The crude alcohol was then taken on to the subsequent protection step without further purification. **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3340 (br.), 2929, 1455, 1366, 1222, 1098, 1051, 1028, 735, 697; *m/z* **HRMS** (ESI) found [M+H]⁺ 278.2115, C₁₇H₂₈NO₂ requires 278.2115. *Major diastereoisomer:* **¹H NMR** (500 MHz, CDCl₃) δ 7.38 – 7.29 (m, 5H, Ar-Hs), 4.53 (d, *J* = 11.9 Hz, 1H, H-12), 4.50 (d, *J* = 11.8 Hz, 1H, H-12), 4.15 – 4.02 (m, 1H, H-5), 3.73 – 3.56 (m, 2H, H-11), 2.06 – 1.88 (m, 3H, H-4, H-7 and H-10), 1.81 – 1.65 (m, 1H, H-10), 1.17 (s, 3H, H-8 or H-9), 1.15 (s, 3H, H-8 or H-9), 1.14 (s, 3H, H-2), 1.07 – 0.94 (m, 2H, H-4 and H-7); **¹³C NMR** (126 MHz, CDCl₃) δ 138.6, 128.4, 127.6, 127.5, 73.1, 67.6, 64.7, 53.3, 51.6, 48.2, 48.0, 39.3, 35.1, 31.7, 28.8. *Minor diastereoisomer:* **¹H NMR** (500 MHz, CDCl₃) δ 7.38 – 7.29 (m, 5H, Ar-Hs), 4.53 (d, *J* = 11.9 Hz, 1H, H-12), 4.50 (d, *J* = 11.8 Hz, 1H, H-12), 4.15 – 4.02 (m, 1H, H-5), 3.73 – 3.56 (m, 2H, H-11), 2.06 – 1.88 (m, 2H, H-7 and H-10), 1.84 (ddd, *J* = 12.0, 4.1, 1.9 Hz, 1H, H-4), 1.81 – 1.65 (m, 1H, H-10), 1.22 (s, 3H, H-8 or H-9), 1.20 (s, 3H, H-8 or H-9), 1.12 (s, 3H, H-2), 1.07 – 0.94 (m, 2H, H-4 and H-7); **¹³C NMR** (126 MHz, CDCl₃) δ 138.4, 128.4, 127.7, 127.6, 73.1, 66.7, 65.0, 53.7, 51.3, 48.1, 45.7, 39.3, 34.9, 29.5, 28.0

2-{2-(BenzylOxy)ethyl}-2,6,6-trimethyl-4-{(triisopropylsilyl)oxy}piperidine (361)

To a solution of *2-(benzyloxy)ethyl*-2,6,6-trimethylpiperidin-4-ol **360** (1.10 g, 3.96 mmol, 1.0 equiv; 1.5:1 mixture of diastereoisomers) in *N,N*-dimethylformamide (40 mL) at 0 °C was added imidazole (404 mg, 5.94 mmol, 1.5 equiv) and triisopropylsilyl chloride (1.27 ml, 5.94 mmol, 1.5 equiv). The resulting pale yellow solution was warmed to room temperature and stirred for 8 hours. The mixture was then partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was washed with water, brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as an inseparable 1.5:1 mixture of diastereoisomers as a pale yellow oil (1.31 mg, 3.13 mmol, 79%); **R_f** (ethyl acetate in petroleum ether, 20% - on triethylamine-pretreated silica plate): 0.32; **IR** ν_{max} /cm⁻¹ (film): 2938, 2865, 1455, 1363, 1223, 1089, 1014, 882, 733, 636; **m/z HRMS** (ESI) found [M+H]⁺ 434.3446, C₂₆H₄₈NO₂Si requires 434.3449. **Major diastereoisomer:** **¹H NMR** (500 MHz, CDCl₃) δ 7.38 – 7.29 (m, 5H, Ar-Hs), 4.53 (d, *J* = 12.0 Hz, 1H, H-12), 4.51 (d, *J* = 12.0 Hz, 1H, H-12), 4.14 (tt, *J* = 11.0, 4.1 Hz, 1H, H-5), 3.68 – 3.57 (m, 2H, H-13), 2.07 – 1.81 (m, 3H, H-4, H-8 and H-12), 1.75 – 1.66 (m, 1H, H-12), 1.16 (s, 3H, H-10 or H-11), 1.13 (s, 3H, H10 or H-11), 1.12 (s, 3H, H-2), 1.10 – 0.98 (m, 25H, H-4, H-6, H-7 and H-8); **¹³C NMR** (126 MHz, CDCl₃) δ 138.6, 128.4, 127.7, 127.5, 73.2, 67.6, 65.1, 53.2, 51.5, 48.8, 48.7, 39.5, 35.0, 31.8, 28.7, 18.1, 12.3. **Minor diastereoisomer:** **¹H NMR** (500 MHz, CDCl₃) δ 7.38 – 7.29 (m, 5H, Ar-Hs), 4.53 (d, *J* = 12.0 Hz, 1H, H-12), 4.51 (d, *J* = 12.0 Hz, 1H, H-12), 4.10 – 4.05 (m, 1H, H-5), 3.68 – 3.57 (m, 2H, H-13), 2.07 – 1.81 (m, 3H, H-4, H-8 and H-12), 1.75 – 1.66 (m, 1H, H-12), 1.10 – 0.98 (m, 34H, H-2, H-4, H-6, H-7, H-8, H-10 and H-11); **¹³C NMR** (126 MHz, CDCl₃) δ 138.6, 128.4, 127.7, 127.5, 73.0, 66.8, 65.4, 53.6, 51.3, 46.3, 45.7, 39.5, 35.0, 31.8, 28.1, 18.2, 12.4.

2-{2-(BenzylOxy)ethyl}-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (363)



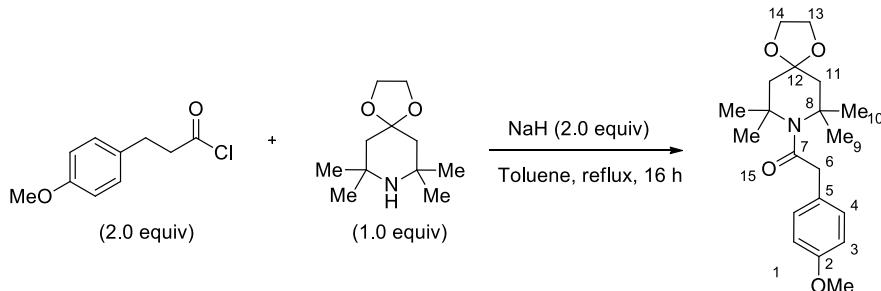
To a solution of 2-{2-(benzyloxy)ethyl}-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine **361** (200 mg, 0.46 mmol, 1.0 equiv, 2:1 mixture of diastereoisomers) in acetonitrile (2 mL) in a microwave tube was added 1-(2-bromoethyl)-4-methoxybenzene (0.22 mL, 1.38 mmol, 3.0 equiv) and potassium carbonate (191 mg, 1.38 mmol, 3.0 equiv). The resulting mixture was sealed and heated at 150 °C in the microwave for 4 hours. The reaction mixture was filtered and filtrate concentrated *in vacuo*. To the crude material was added ethanol (2 ml) and 3 N hydrochloric acid (2 ml) and the mixture heated at 80 °C for 4 hours. The solution was cooled and basified to ~pH=10 with 1 N sodium hydroxide and extracted with dichloromethane. The layers were separated and the aqueous layer was further extracted with dichloromethane. The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*.

The crude alcohol was then dissolved in dichloromethane (3 mL), followed by addition of *N*-methylmorpholine *N*-oxide (54.0 mg, 0.46 mmol, 1.0 equiv – based on 2-{2-(benzyloxy)ethyl}-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine **361**) and tetrapropylammonium perruthenate (8.1 mg, 0.023 mmol, 0.05 equiv). The mixture was stirred at room temperature for 3 hours and filtered through a pad of silica gel, eluting with dichloromethane. The solvent was then recovered under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 20% ethyl acetate in petroleum ether, affording the title compound as a pale yellow oil (18.9 mg, 0.046 mmol, 10%), as well as 2-((benzyloxy)ethyl)-2,6,6-trimethylpiperidin-4-one **359**, which was recovered as a yellow oil (95 mg, 0.35 mmol, 76%); **R**_f (ethyl acetate in petroleum ether, 20%): 0.30; **IR** ν_{max} /cm⁻¹ (film): 2966, 1714, 1611, 1511, 1364, 1245, 1176, 1094, 1034, 822, 698; **1H NMR** (500 MHz, CDCl₃) δ 7.39 – 7.29 (m, 5H, H-20, H-21 and H-22), 7.12 (d, *J* = 8.7 Hz, 2H, H-4), 6.87 (d, *J* = 8.7 Hz, 2H, H-3), 4.51 (s, 2H, H-18), 3.82 (s, 3H, H-18), 3.61 (t, *J* = 6.6 Hz, 2H, H-17), 2.78 – 2.66 (m, 4H, H-6 and H-7), 2.59 (dd, *J* = 13.0,

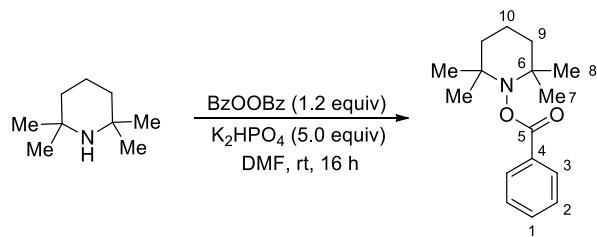
1.5 Hz, 1H, H-10), 2.42 (dd, J = 12.7, 1.5 Hz, 1H, H-12), 2.34 (dd, J = 12.7, 1.8 Hz, 1H, H-12), 2.29 (dd, J = 13.0, 1.8 Hz, 1H, H-10), 2.03 – 1.94 (m, 2H, H-16), 1.89 – 1.79 (m, 1H, H-16), 1.26 (s, 3H, H-14 or H-15), 1.20 (s, 6H, H-8, and H-14 or H-15); ^{13}C NMR (126 MHz, CDCl_3) δ 210.0, 158.0, 138.2, 132.6, 129.4, 128.4, 127.7, 127.6, 113.9, 73.1, 67.2, 61.9, 59.9, 55.7, 55.3, 52.6, 47.4, 40.5, 40.1, 30.0, 27.6, 25.6; m/z HRMS (ESI) found [M+H]⁺ 410.2692, $\text{C}_{26}\text{H}_{36}\text{NO}_3$ requires 410.2690.

5.13 Alternative strategies to install the 4-methoxyphenylethyl unit

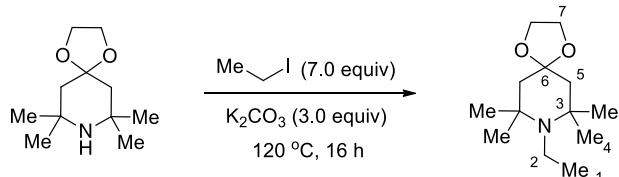
2-(4-Methoxyphenyl)-1-(7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethanone (338)



To a solution of *7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* **132** (50 mg, 0.25 mmol, 1.0 equiv) in dry toluene (0.5 mL) was added sodium hydride (20 mg, 0.50 mmol; 60% dispersion in oil, 2.0 equiv). The resulting mixture was stirred at room temperature for 10 mins followed by addition of 4-methoxyphenylacetyl chloride (0.09 mL, 0.50 mmol, 2.0 equiv). The reaction mixture was then heated at reflux for 16 hours and cooled. The mixture was then quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 30% ethyl acetate in petroleum ether, affording the title compound as a brown solid (63 mg, 0.18 mmol, 72%); **M.p.**: 48–50 °C; **R_f** (ethyl acetate in petroleum ether, 30% - on triethylamine-pretreated silica plate): 0.30; **IR** $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2962, 1728, 1666, 1516, 1251, 1164, 1144, 809, 763, 694; **¹H NMR** (500 MHz, CDCl_3) δ 7.21 (d, J = 8.8 Hz, 2H, H-4), 6.86 (d, J = 8.7 Hz, 2H, H-3), 4.34 (dd, J = 5.4, 4.3 Hz, 2H, H-13 or H-14), 3.92 – 3.83 (m, 2H, H-13 or H-14), 3.79 (s, 3H, H-1), 3.60 (s, 2H, H-6), 1.91 (s, 4H, H-11), 1.21 (s, 6H, H-9 or H-10), 1.18 (s, 6H, H-9 or H-10); **¹³C NMR** (126 MHz, CDCl_3) δ 171.9, 158.7, 151.0, 130.3, 125.9, 114.0, 102.7, 64.1, 63.1, 55.3, 40.4, 40.3, 32.8, 30.3; m/z HRMS (ESI) found [M+H]⁺ 348.2170, $\text{C}_{20}\text{H}_{30}\text{NO}_4$ requires 348.2169.

2,2,6,6-Tetramethylpiperidin-1-yl benzoate (339)

To a solution of 2,2,6,6-tetramethylpiperidine (3.00 g, 20 mmol, 1.0 equiv) in *N,N*-dimethylformamide (20 mL) was added dibenzoyl peroxide (5.80 g, 24 mmol, 1.2 equiv) and dipotassium phosphate (17.5 g, 100 mmol, 5.0 equiv). The mixture was stirred at room temperature for 16 hours and filtered. The filtrate was partitioned between water and diethyl ether. The organic layer was washed with water, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the title compound as a white solid (700 mg, 2.68 mmol, 13%); **R**_f (ethyl acetate in petroleum ether, 10%): 0.27; **IR** ν_{max} /cm⁻¹ (film): 2978, 1741, 1449, 1363, 1249, 104, 906, 717; **1H NMR** (400 MHz, CDCl₃) δ 8.10 (d, *J* = 7.1 Hz, 2H, H-3), 7.59 (t, *J* = 7.4 Hz, 1H, H-1), 7.48 (t, *J* = 7.6 Hz, 2H, H-2), 1.94 – 1.41 (m, 6H, H-9 and H-10), 1.30 (s, 6H, H-7 or H-8), 1.14 (s, 6H, H-7 or H-8); **13C NMR** (101 MHz, CDCl₃) δ 166.4, 132.8, 129.8, 129.6, 128.4, 60.4, 39.1, 32.0, 20.9, 17.0. The physical data were identical in all respect to that previously reported.¹⁴⁶

8-Ethyl-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (341)

A mixture of 7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (132) (1.0 g, 5.05 mmol, 1.0 equiv) and potassium carbonate (2.09 g, 15.2 mmol, 3.0 equiv) were stirred in iodoethane (2.8 mL, 35.4 mmol, 7.0 equiv) in a sealed oven-dried microwave tube at 120 °C for 20 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was purified by flash chromatography on triethylamine-pretreated silica gel, eluting with 0 to 10% ethyl acetate in petroleum ether, affording the title compound as a pale yellow solid (500 mg, 2.20 mmol, 44%); **M.p.**: 54–56 °C; **R**_f (ethyl acetate in petroleum ether, 10% - on triethylamine-pretreated silica plate): 0.33; **IR** ν_{max} /cm⁻¹ (film): 2969, 2884, 1478, 1356, 1185, 1086, 947, 796, 726; **1H NMR** (400 MHz, CDCl₃) δ 3.94 (s, 4H, H-7), 2.56 (q, *J* = 7.1 Hz, 2H, H-2), 1.66 (s, 4H, H-5), 1.14 (s, 12H, H-4), 1.05 (t, *J* = 7.1 Hz, 3H, H-1); **13C NMR** (101 MHz,

CDCl_3) δ 107.8, 63.6, 55.8, 47.6, 37.3, 27.9, 20.9; m/z **HRMS** (ESI) found $[\text{M}+\text{H}]^+$ 228.1956, $\text{C}_{13}\text{H}_{26}\text{NO}_2$ requires 228.1958.

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7 Appendix – 1H and ^{13}C NMR spectra of key compounds

Content of ^1H and ^{13}C spectra

7.1 Palladium(II)-catalysed carbonylation: <i>N,O</i> -Ketal substrates.....	200
2,2-Diethyl-3-oxa-1-azaspiro[4.5]decane (183).....	200
2,2-Diethyl-4,4-dimethyloxazolidine (191)	201
2,2-Diethyl-3-oxa-1-azaspiro[4.5]decane (198a).....	202
2-Ethyl-2,4,4-trimethyloxazolidine (198b).....	203
2-Isopropyl-2-methyl-3-oxa-1-azaspiro[4.5]decane (199a)	204
2-Isopropyl-2,4,4-trimethyloxazolidine (199b)	205
2-Ethyl-2-propyl-3-oxa-1-azaspiro[4.5]decane (200a).....	206
2-Ethyl-2-propyl-3-oxa-1-azaspiro[4.5]decane (200b).....	207
2-Cyclohexyl-2-ethyl-3-oxa-1-azaspiro[4.5]decane (201a)	208
2-Cyclohexyl-2-ethyl-4,4-dimethyloxazolidine (201b)	209
2-(<i>Tert</i> -butyl)-3-oxa-1-azaspiro[4.5]decane (202a).....	210
2-{3-(2-Ethyl-4,4-dimethyloxazolidin-2-yl)propyl}isoindoline-1,3-dione (231b)	212
2-((Benzyl)oxy)methyl-2-ethyl-3-oxa-1-azaspiro[4.5]decane (232a)	213
2-((Benzyl)oxy)methyl-2-ethyl-4,4-dimethyloxazolidine (232b).....	214
2-Ethyl-2-(3-[1-tosylpiperidin-4-yl]propyl)-3-oxa-1-azaspiro[4.5]decane (233a).....	215
2-Ethyl-4,4-dimethyl-2-(3-[1-tosylpiperidin-4-yl]propyl)oxazolidine (233b)	216
Methyl 3-(2-ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propanoate (234a)	217
Methyl 3-(2-ethyl-4,4-dimethyloxazolidin-2-yl)propanoate (234b).....	218
2-(2-Ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propan-2-ol (235a)	219
(<i>E</i>)-2-Ethyl-2-(hept-5-en-1-yl)-3-oxa-1-azaspiro[4.5]decane (236a)	220
(<i>E</i>)-2-Ethyl-2-(hept-5-en-1-yl)-4,4-dimethyloxazolidine (236b)	221
2-(But-3-en-1-yl)-2-ethyl-4,4-dimethyloxazolidine (237b).....	222
Ethyl 2-(2-ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)acetate (246a).....	223
Ethyl 2-(2-ethyl-4,4-dimethyloxazolidin-2-yl)acetate (246b)	224

2-Ethyl-2-(trifluoromethyl)-3-oxa-1-azaspiro[4.5]decane (248)	225
2-Ethyl-2-phenyl-3-oxa-1-azaspiro[4.5]decane (251)	227
2-Ethyl-4,4-dimethyl-2-(4-nitrophenyl)oxazolidine (256)	228
2-Ethyl-2-phenethyl-3-oxa-1-azaspiro[4.5]decane (258a)	229
2-Ethyl-4,4-dimethyl-2-phenethyloxazolidine (258b)	230
2-(Cyclopropylmethyl)-2-ethyl-3-oxa-1-azaspiro[4.5]decane (263)	231
2-(Cyclopropylmethyl)-2-ethyl-4,4-dimethyloxazolidine (267).....	232
7.2 Palladium(II)-catalysed carbonylation: Carbonylation products	233
7a'-Ethyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6'H)-one (185)	233
7a'-Ethyl-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(7a'H)-one (186).....	234
7a-Ethyl-3,3-dimethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (192).....	235
7a'-Methyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6'H)-one (204a) ..	236
3,3,7a-Trimethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (204b).....	237
7',7a'-Dimethyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6'H)-one (205a)	238
3,3,7,7a-Tetramethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (205b)	239
7a'-Propyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6'H)-one (206a) ...	240
3,3,7a-Trimethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (206b).....	241
7a'-Cyclohexyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6'H)-one (207a)	242
7a-Cyclohexyl-3,3-dimethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (207b).....	243
2-(3-(5'-Oxotetrahydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-7a'-yl)propyl)isoindoline-1,3-dione (238a)	244
2-(3-(3,3-Dimethyl-5-oxohexahydropyrrolo[2,1- <i>b</i>]oxazol-7a-yl)propyl)isoindoline-1,3-dione (238b).....	245
7a'-(Benzylxy)methyl)dihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6'H)-one (239a)	246

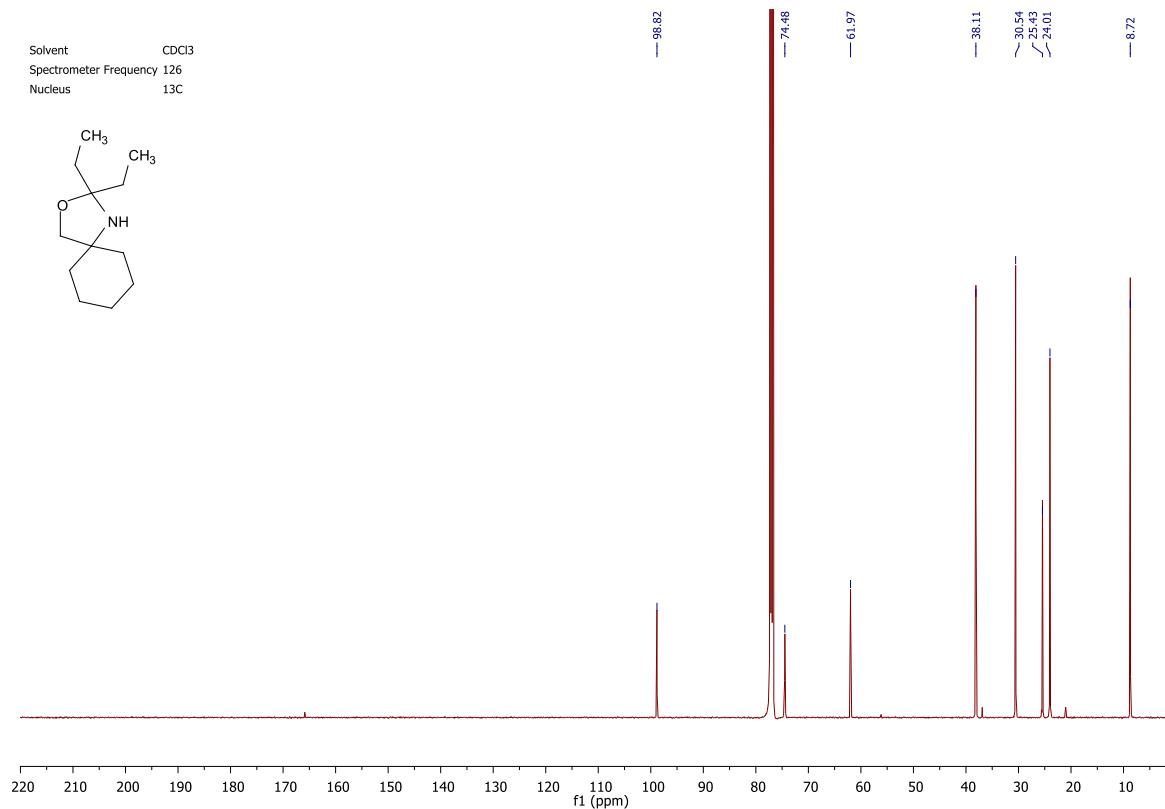
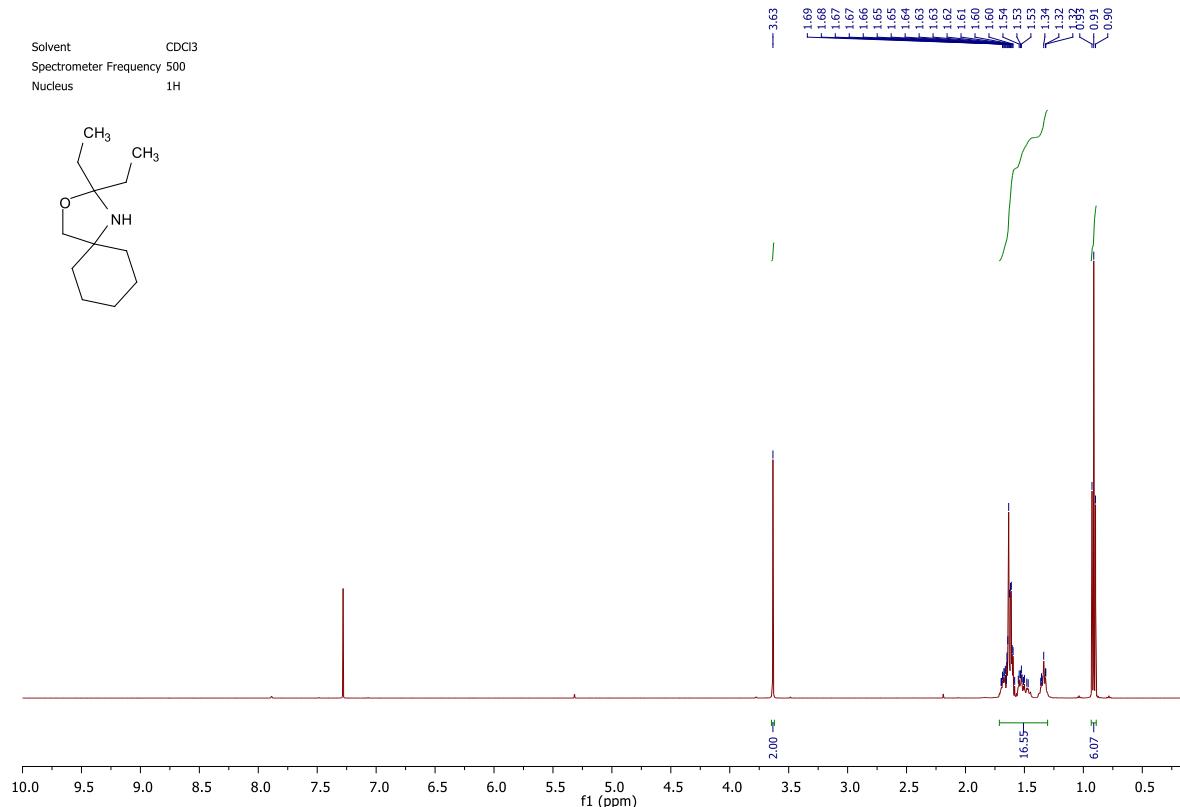
7a-((Benzylxy)methyl)-3,3-dimethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (239b) ...	247
7a'-(3-(1-Tosylpiperidin-4-yl)propyl)dihydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6' <i>H</i>)-one (240a)	248
3,3-Dimethyl-7a-(3-(1-tosylpiperidin-4-yl)propyl)tetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (240b).....	249
Methyl 3-(5'-oxotetrahydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-7a'-yl)propanoate (241a).....	250
Methyl 3-(3,3-dimethyl-5-oxohexahydropyrrolo[2,1- <i>b</i>]oxazol-7a-yl)propanoate (241b)	251
7a'-(2-Hydroxypropan-2-yl)dihydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6' <i>H</i>)-one (242a).....	252
(<i>E</i>)-7a'-(Hept-5-en-1-yl)dihydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6' <i>H</i>)-one (243a)	253
(<i>E</i>)-7a-(Hept-5-en-1-yl)-3,3-dimethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (243b)....	254
9b'-Ethyl-2' <i>H</i> -spiro[cyclohexane-1,3'-oxazolo[2,3- <i>a</i>]isoindol]-5'(9b' <i>H</i>)-one (252)	255
7a'-Phenethyldihydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6' <i>H</i>)-one (259a)	256
3,3-Dimethyl-7a-phenethyltetrahydropyrrolo[2,1- <i>b</i>]oxazol-5(6 <i>H</i>)-one (259b)	257
7a'-(Cyclopropylmethyl)dihydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6' <i>H</i>)-one (264)	258
7a'-Ethyl-6'-spirocyclopropylidihydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6' <i>H</i>)-one (265).....	259
7.3 Palladium(II)-catalysed carbonylation: γ -Keto carboxylic acids	260
8-(1,3-Dioxoisooindolin-2-yl)-4-oxooctanoic acid (270)	260
5-(Benzylxy)-4-oxopentanoic acid (271).....	261
7.4 Palladium(II)-catalysed carbonylation: <i>C</i> -Methylation of γ -lactam 185	262
(6'R, 7a'S)-7a'-Ethyl-6'-methyldihydro-2' <i>H</i> -spiro[cyclohexane-1,3'-pyrrolo[2,1- <i>b</i>]oxazol]-5'(6' <i>H</i>)-one (\pm) (272).....	262
7.5 Synthesis of TMP-astemizole 287	263

1-(4-Fluorobenzyl)- <i>N</i> -(2,2,6,6-tetramethylpiperidin-4-yl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-amine (299)	263
1-(4-Fluorobenzyl)- <i>N</i> -(4-methoxyphenethyl)- <i>N</i> -(2,2,6,6-tetramethylpiperidin-4-yl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-amine (301)	264
2-(2,2,6,6-Tetramethylpiperidin-4-yl)isoindoline-1,3-dione (305)	266
2-(1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione (306)	267
7,7,9,9-Tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (132)	268
8-(4-Methoxyphenethyl)-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (311)	269
1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-one (312)	270
1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-amine (307)	271
1-(4-Fluorobenzyl)- <i>N</i> -(1-(4-methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-amine (287)	272
 7.6 Synthesis of astemizole analogue 288	274
(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)methanol (316)	274
7-((Benzyl)oxy)methyl)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane (317)	275
7-((Benzyl)oxy)methyl)-8-(4-methoxyphenethyl)-7,9,9-trimethyl-1,4-dioxa-8 azaspiro [4.5]decane (318)	276
2-((Benzyl)oxy)methyl)-2,6,6-trimethylpiperidin-4-one (354)	277
2-((Benzyl)oxy)methyl)-2,6,6-trimethylpiperidin-4-ol (355)	278
2-((Benzyl)oxy)methyl)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (356)	279
2-((Benzyl)oxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-one (319) ..	280
2-((Benzyl)oxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-amine (320) ..	281
<i>N</i> -(2 <i>R</i> ,4 <i>R</i>)-2-((Benzyl)oxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-yl)-1-(4-fluorobenzyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-amine (321)	282
(2 <i>R</i> ,4 <i>R</i>)-4-((1-(4-Fluorobenzyl)-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)amino)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-2-yl)methanol (288)	284
 7.7 Attempted synthesis of astemizole analogue 289/335	286

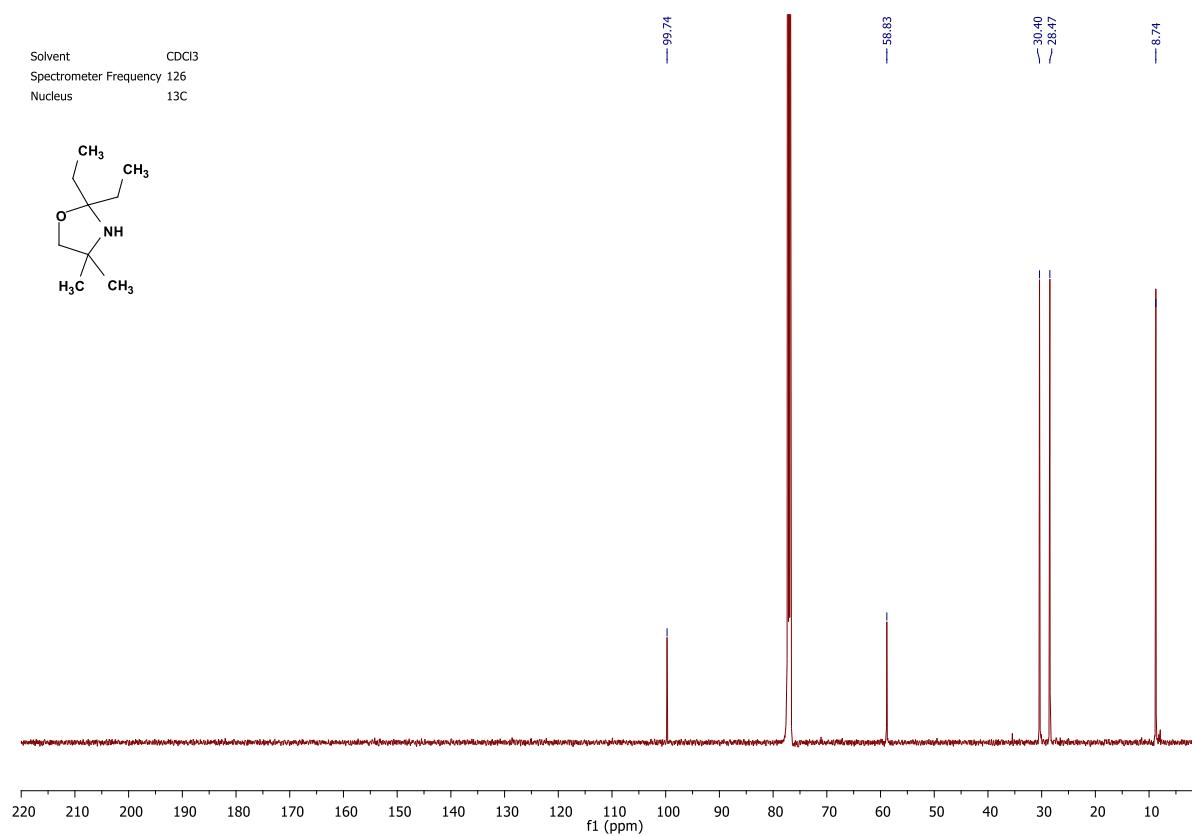
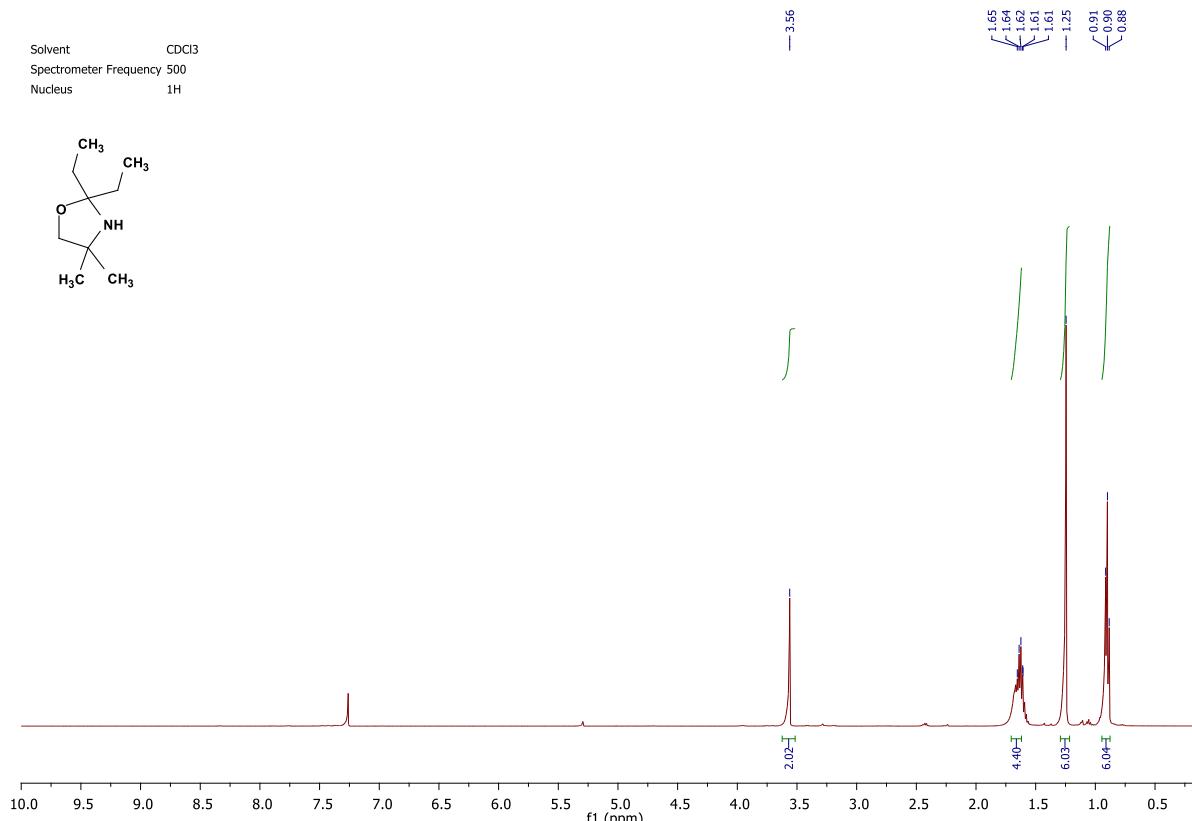
2,2,6-Trimethyl-1-azaspiro[bicyclo[4.2.0]octane-4,2'-[1,3]dioxolan]-8-one (128).....	286
2-(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)ethanol (333).....	287
7-(2-(Benzyl)ethoxy)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane (336)	288
2-((Benzyl)ethoxy)-2,6,6-trimethylpiperidin-4-one (359)	289
2-(2-(Benzyl)ethoxy)-2,6,6-trimethylpiperidin-4-ol (360)	290
2-(2-(Benzyl)ethoxy)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (361).....	291
2-(2-(Benzyl)ethoxy)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (363).....	292

7.1 Palladium(II)-catalysed carbonylation: *N,O*-Ketal substrates

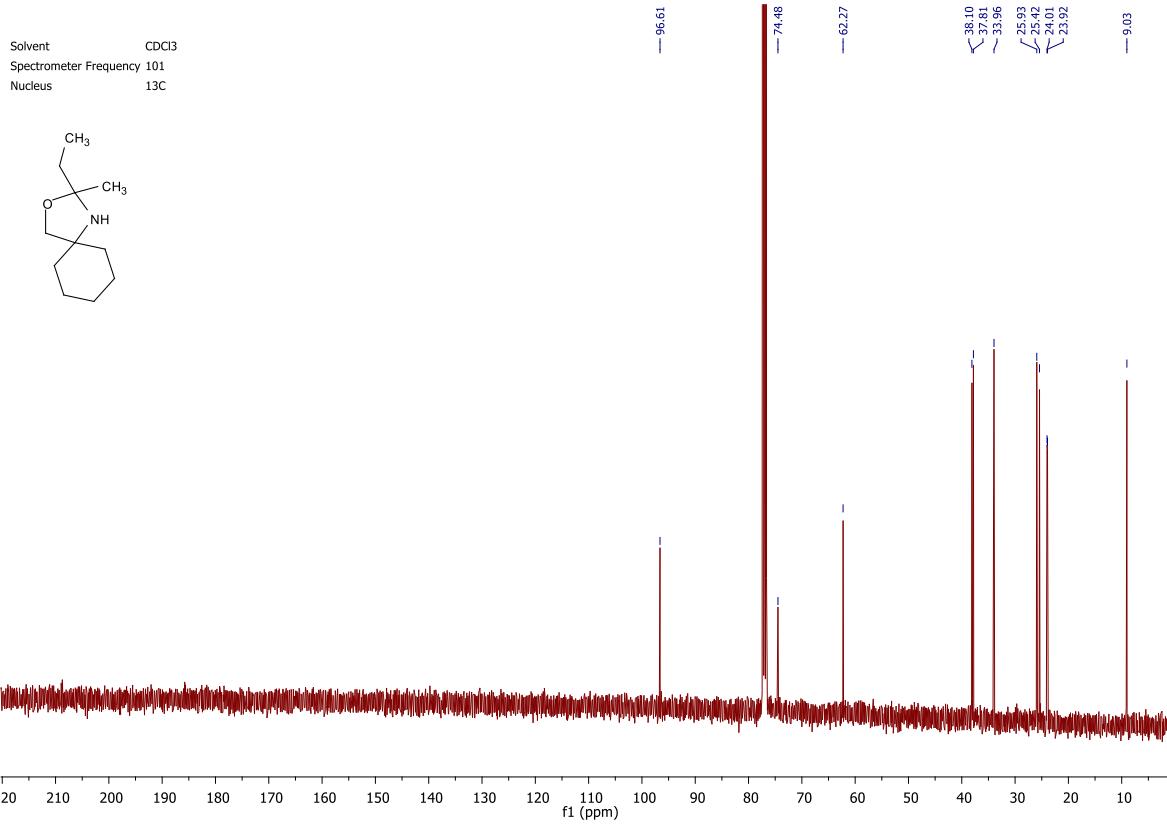
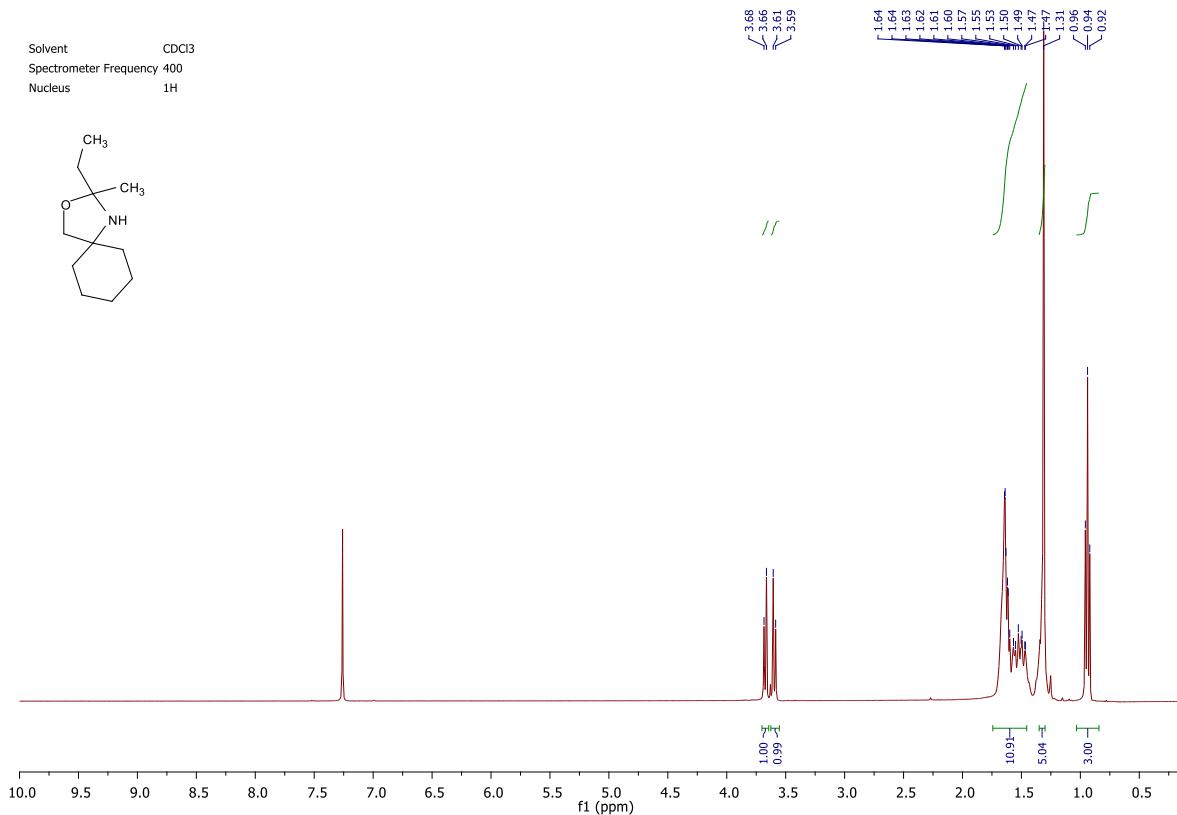
2,2-Diethyl-3-oxa-1-azaspiro[4.5]decane (183)



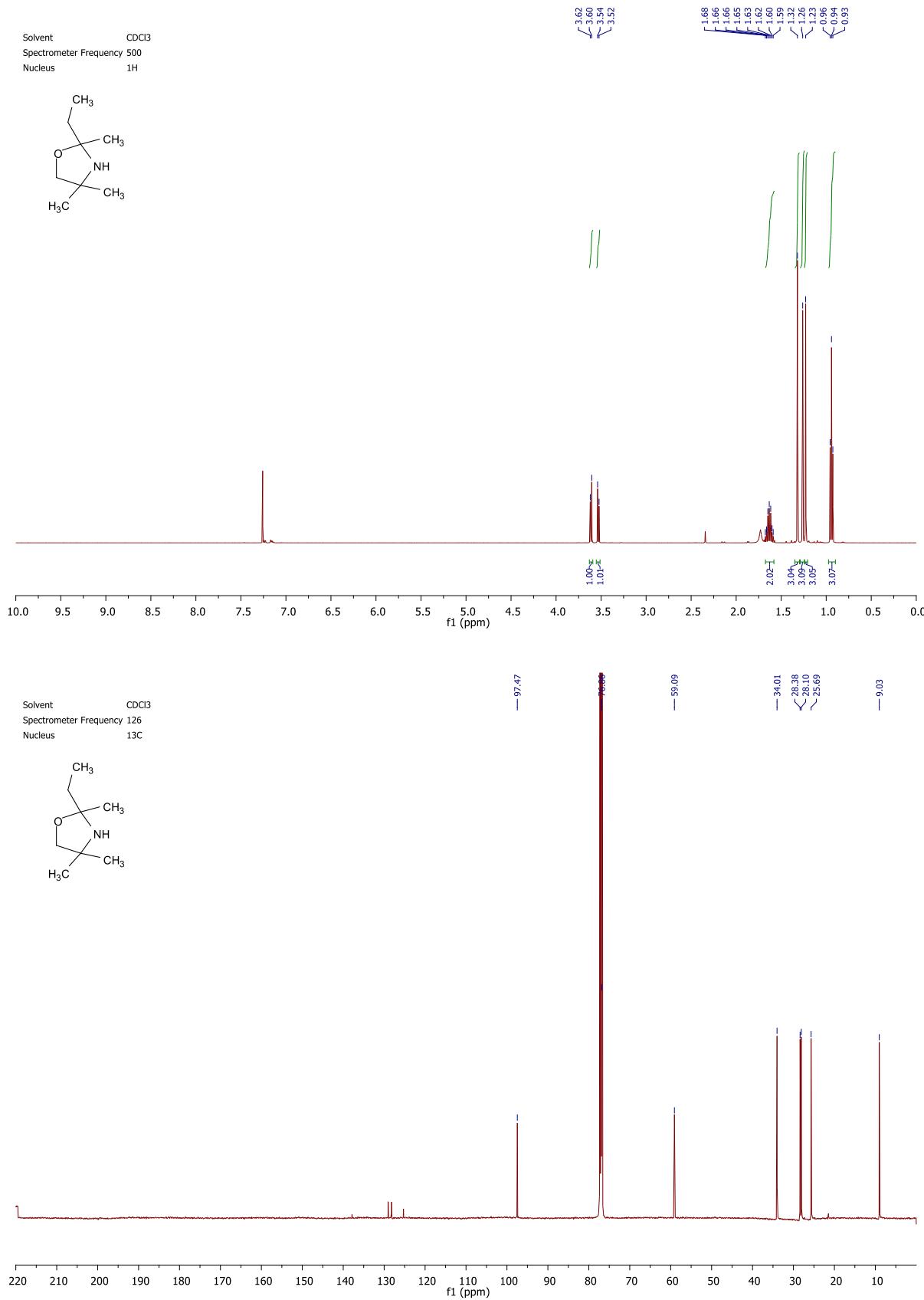
2,2-Diethyl-4,4-dimethyloxazolidine (191)



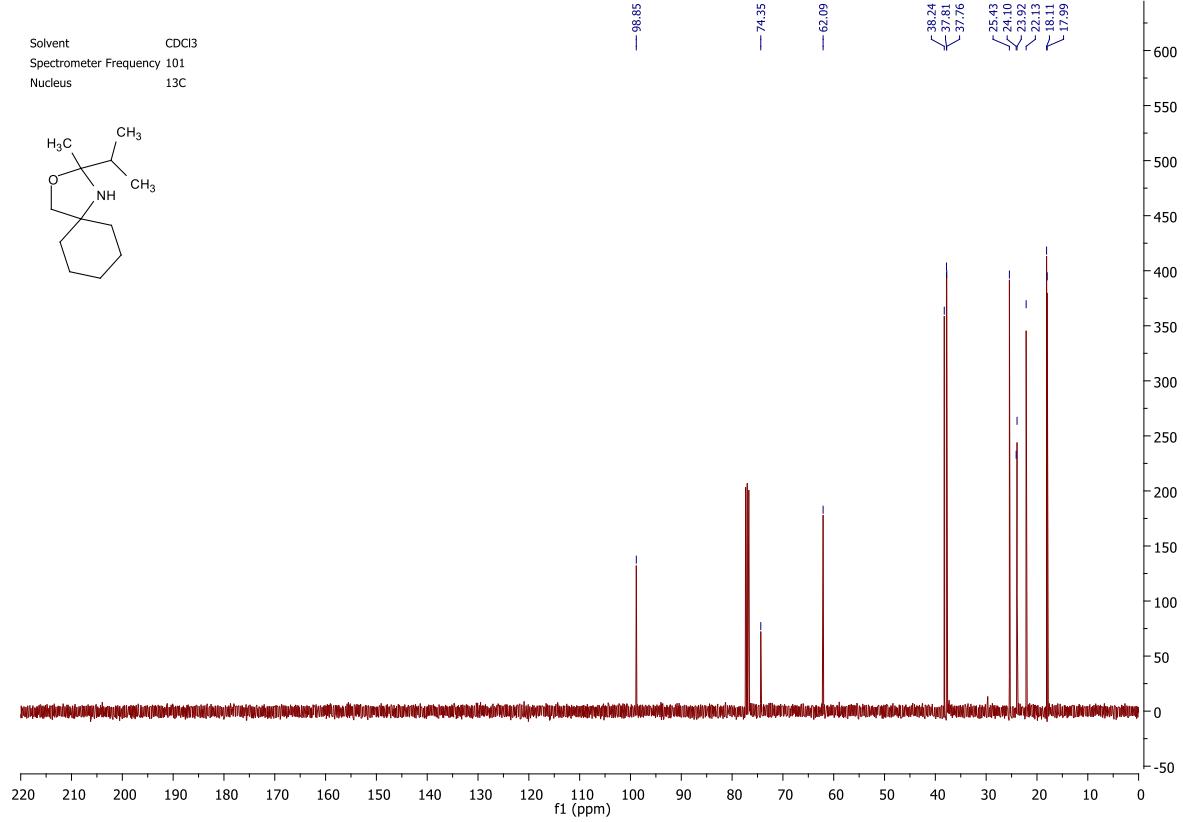
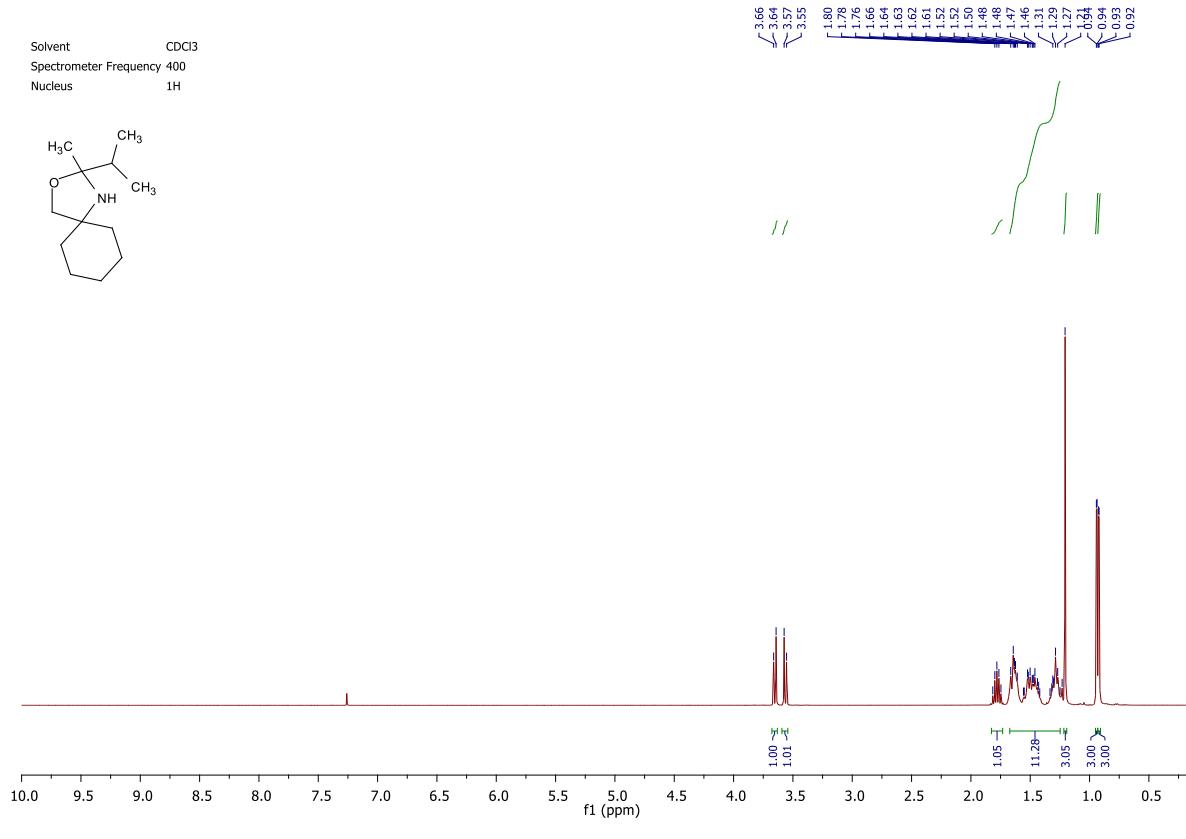
2,2-Diethyl-3-oxa-1-azaspiro[4.5]decane (198a)



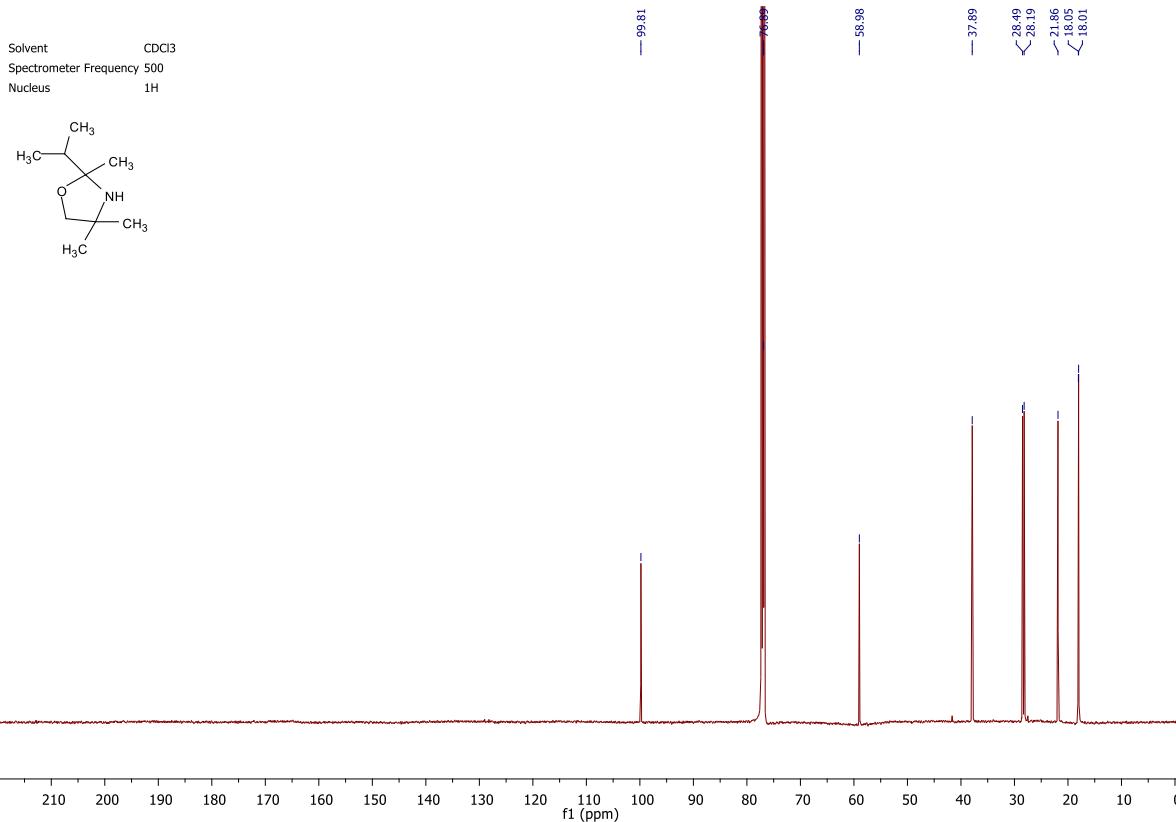
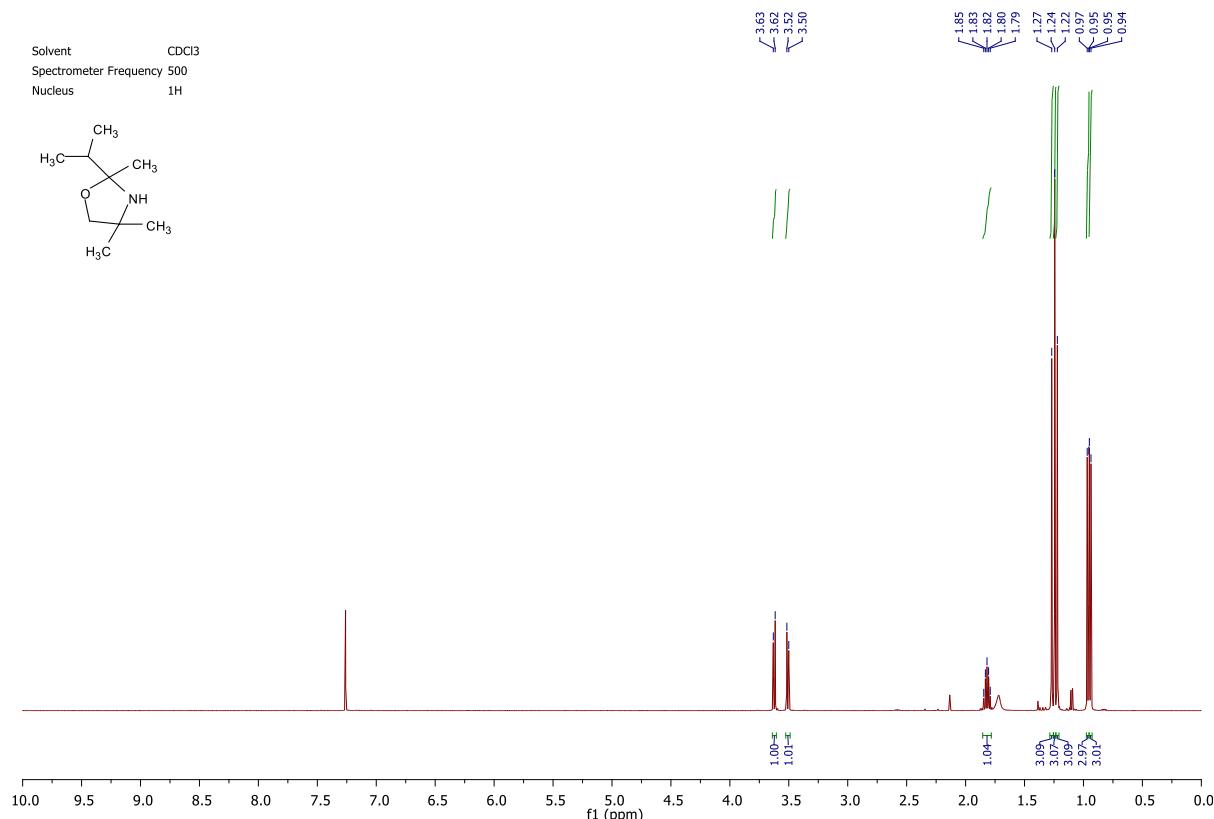
2-Ethyl-2,4,4-trimethyloxazolidine (198b)



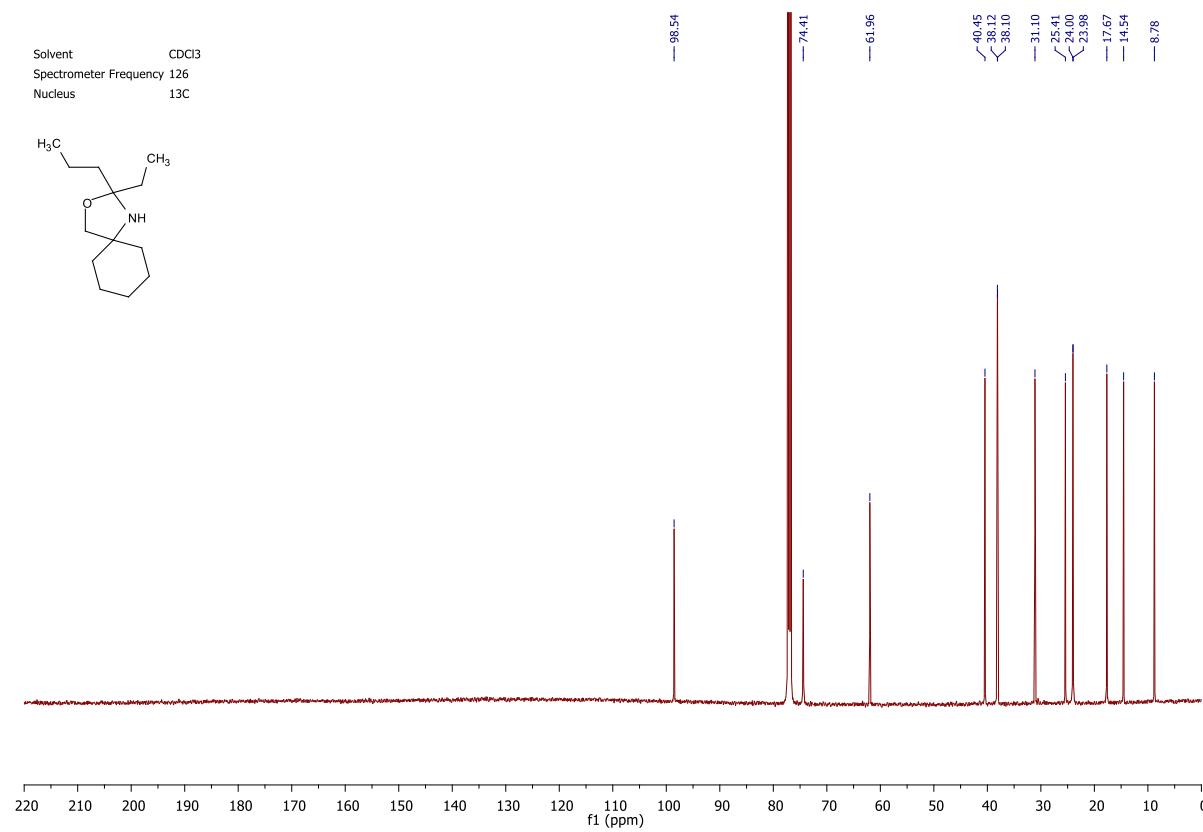
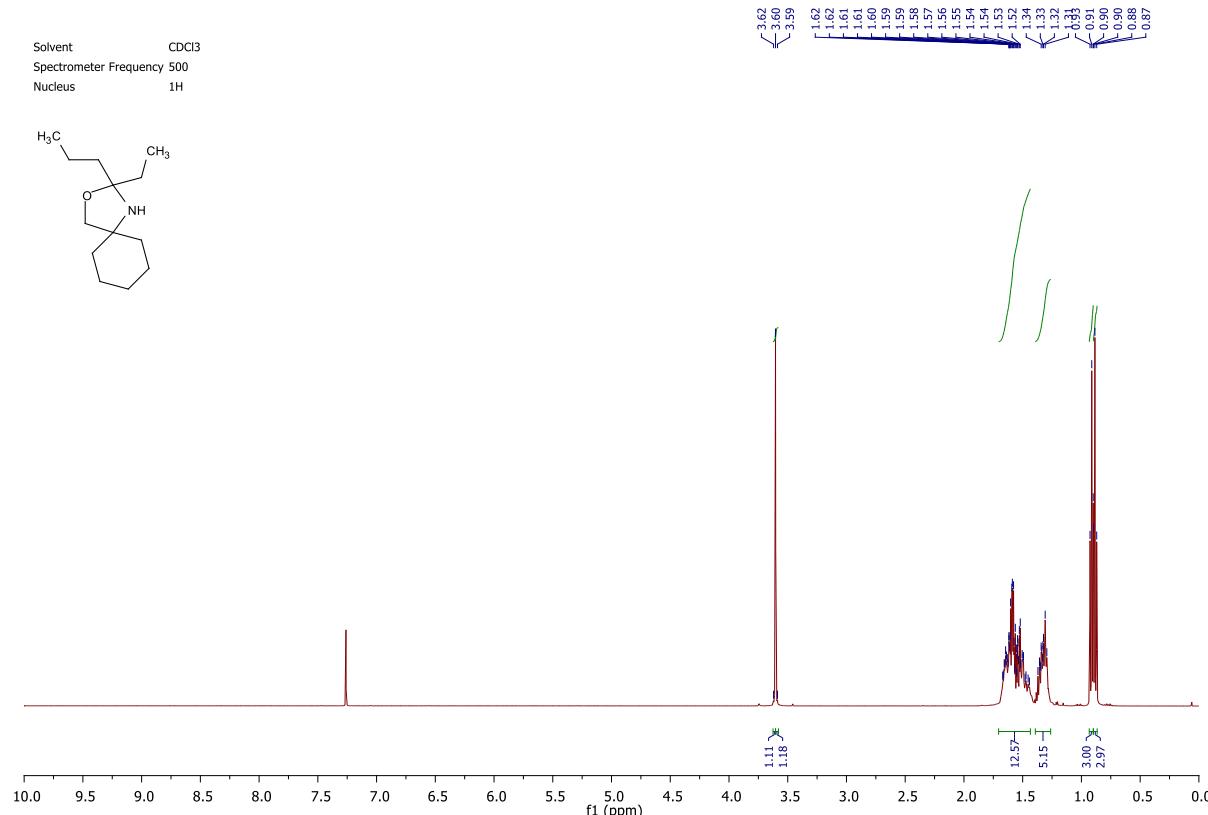
2-Isopropyl-2-methyl-3-oxa-1-azaspiro[4.5]decane (199a)



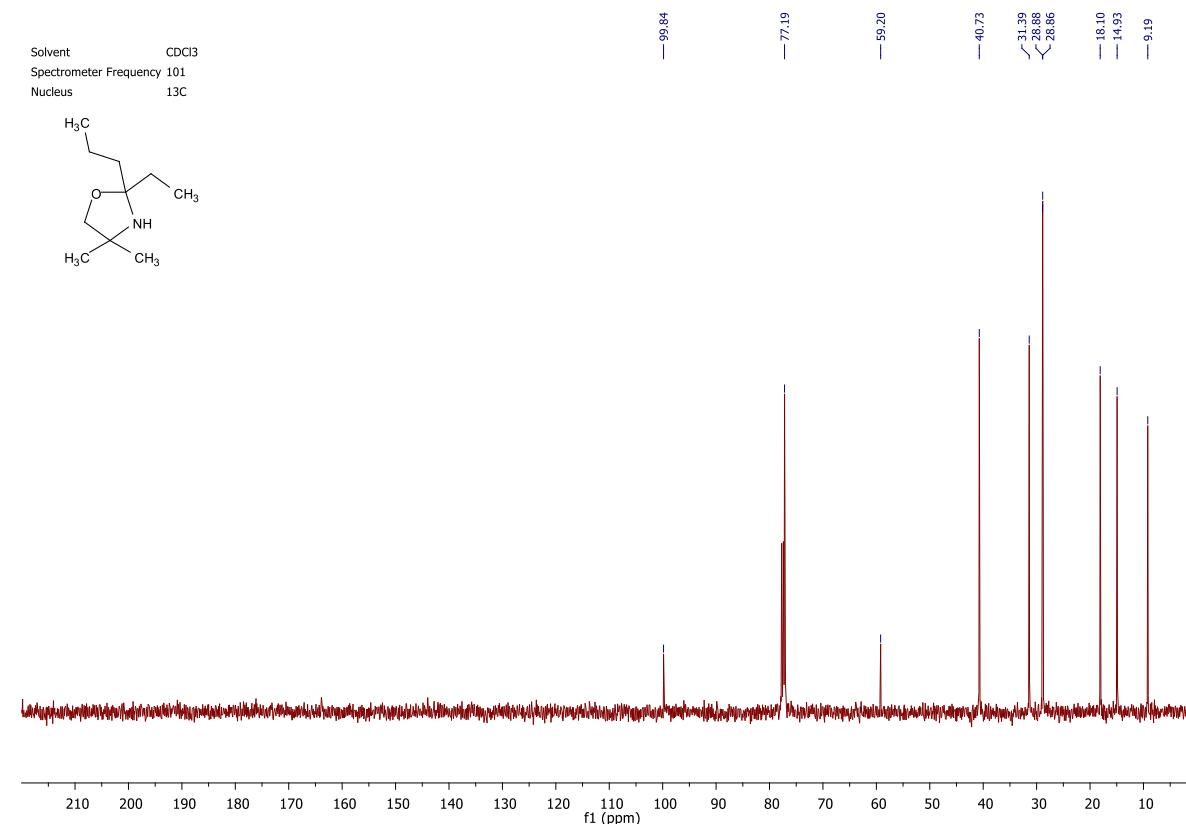
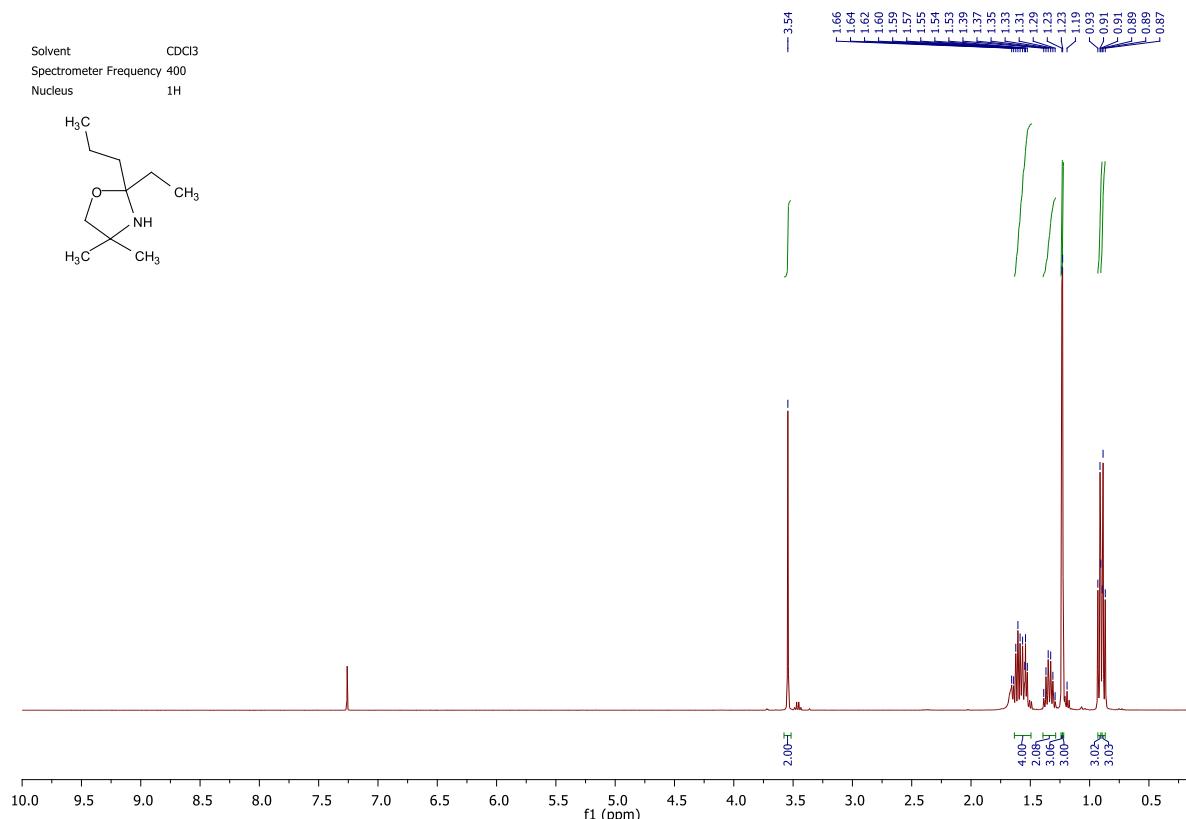
2-Isopropyl-2,4,4-trimethyloxazolidine (199b)



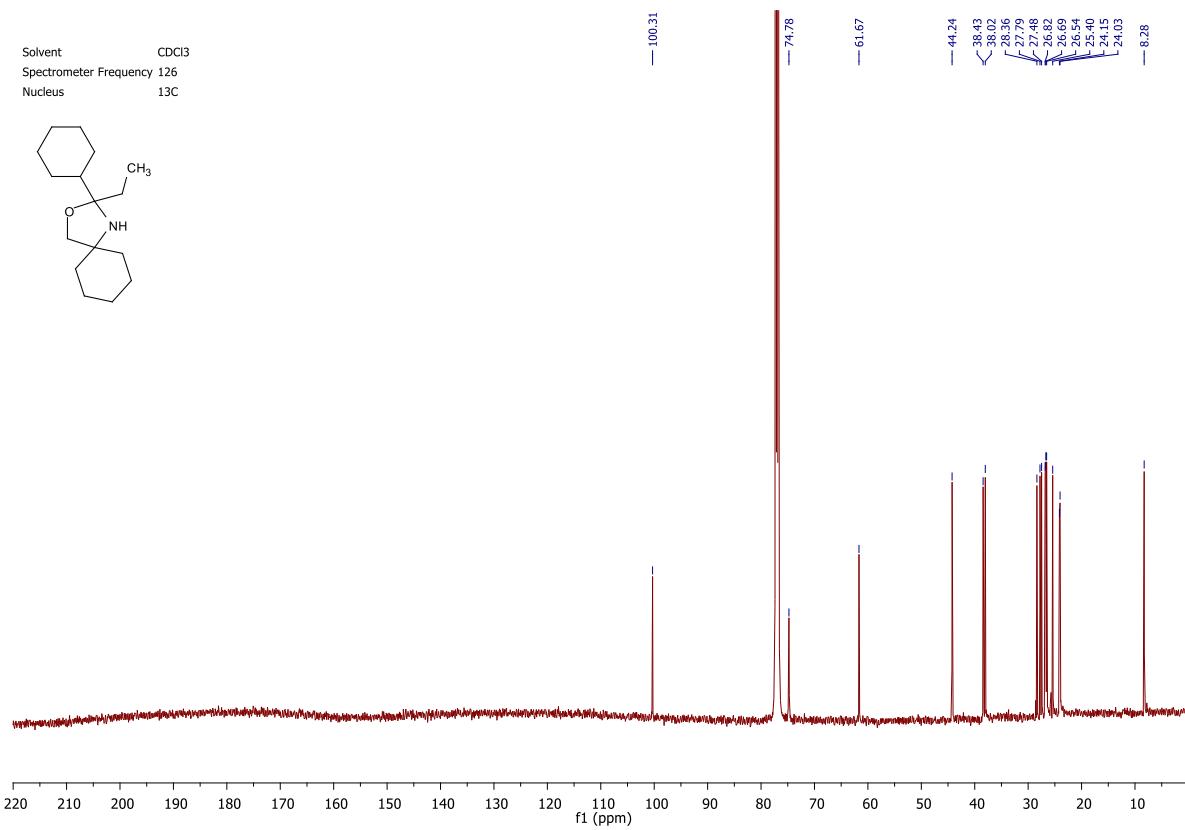
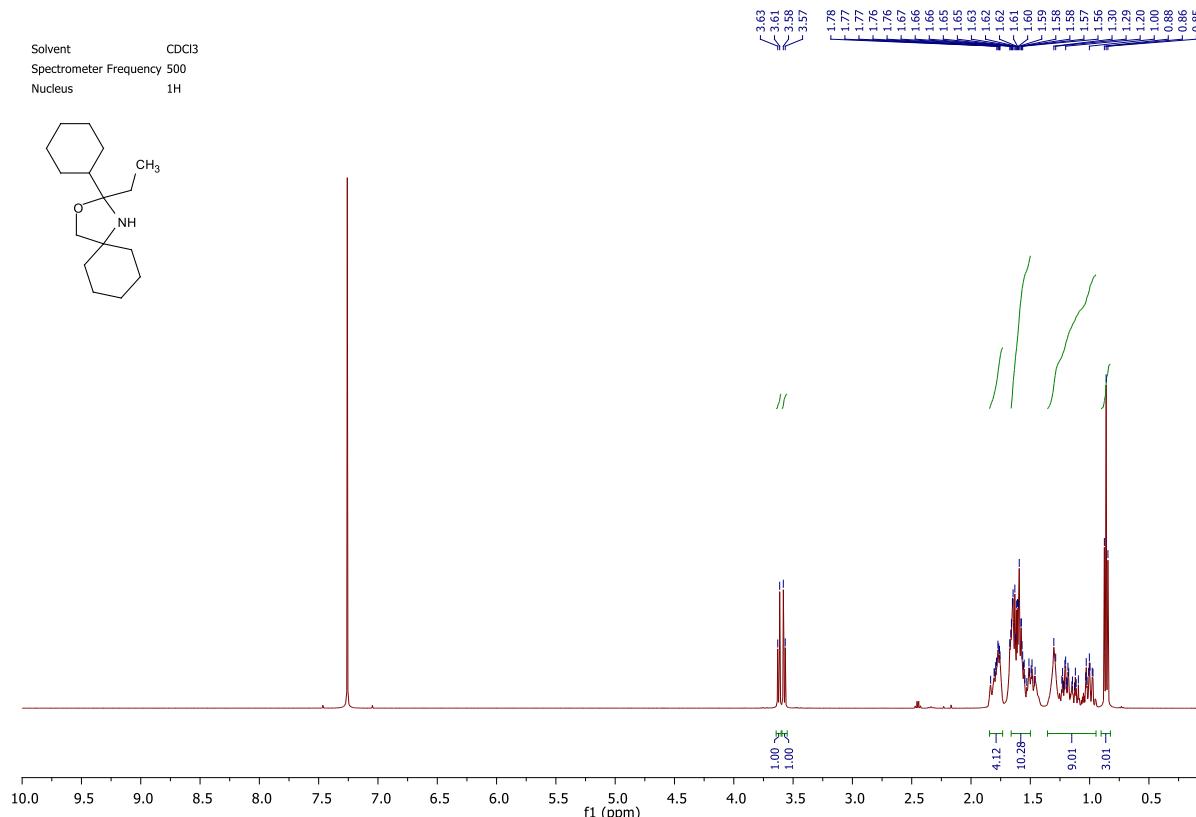
2-Ethyl-2-propyl-3-oxa-1-azaspiro[4.5]decane (200a)



2-Ethyl-2-propyl-3-oxa-1-azaspiro[4.5]decane (200b)

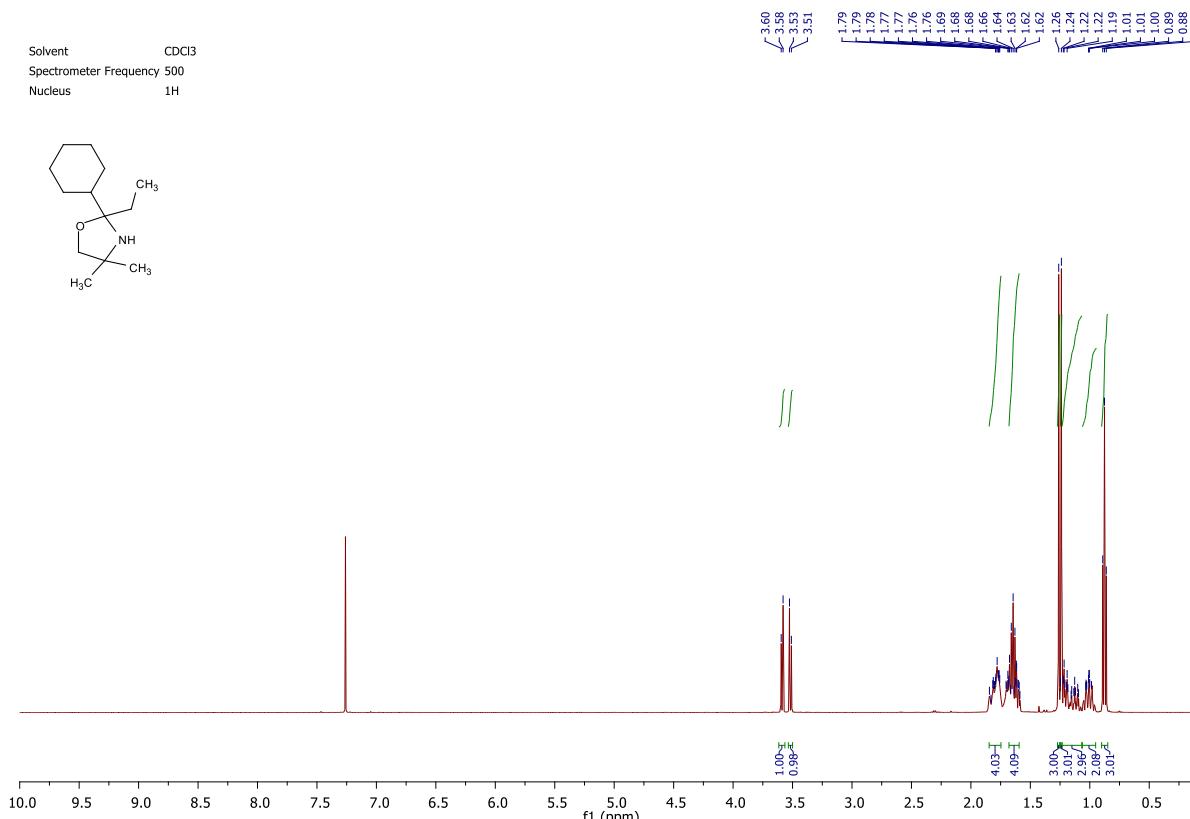
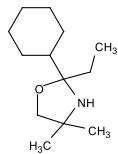


2-Cyclohexyl-2-ethyl-3-oxa-1-azaspiro[4.5]decane (201a)

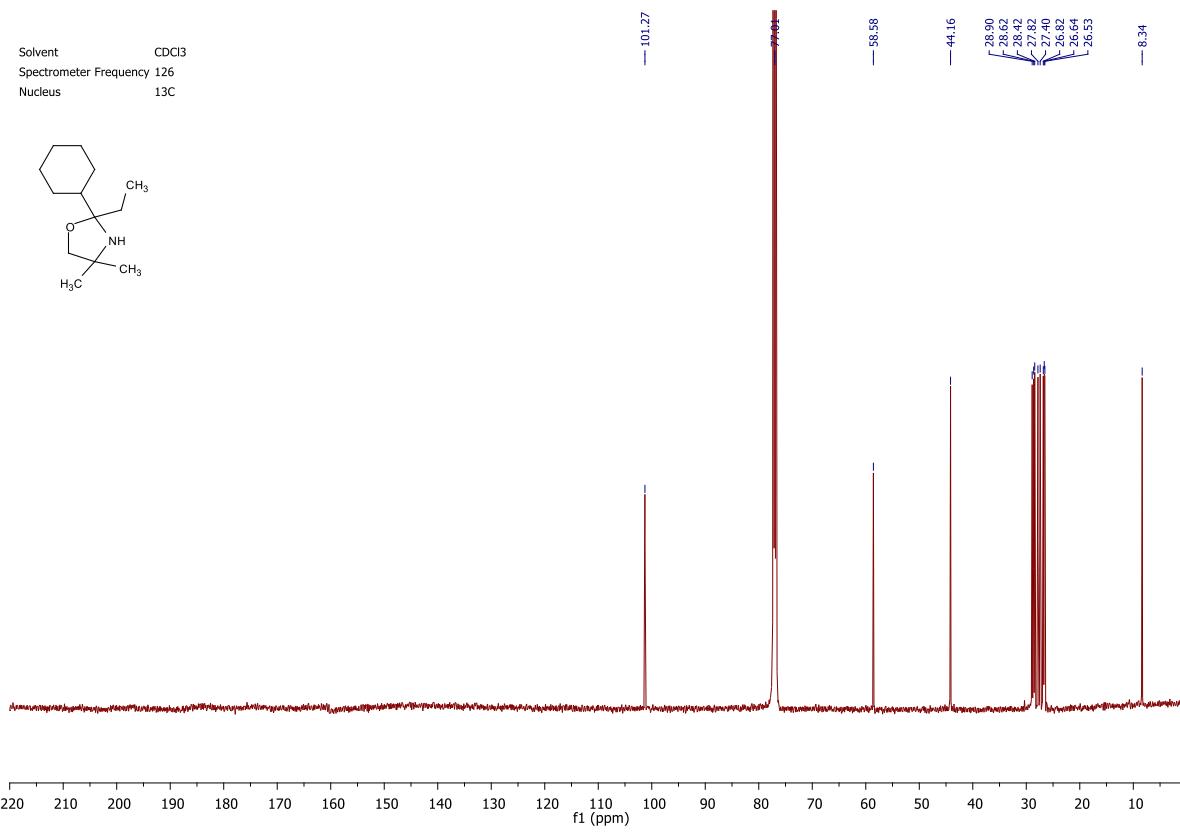
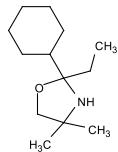


2-Cyclohexyl-2-ethyl-4,4-dimethyloxazolidine (201b)

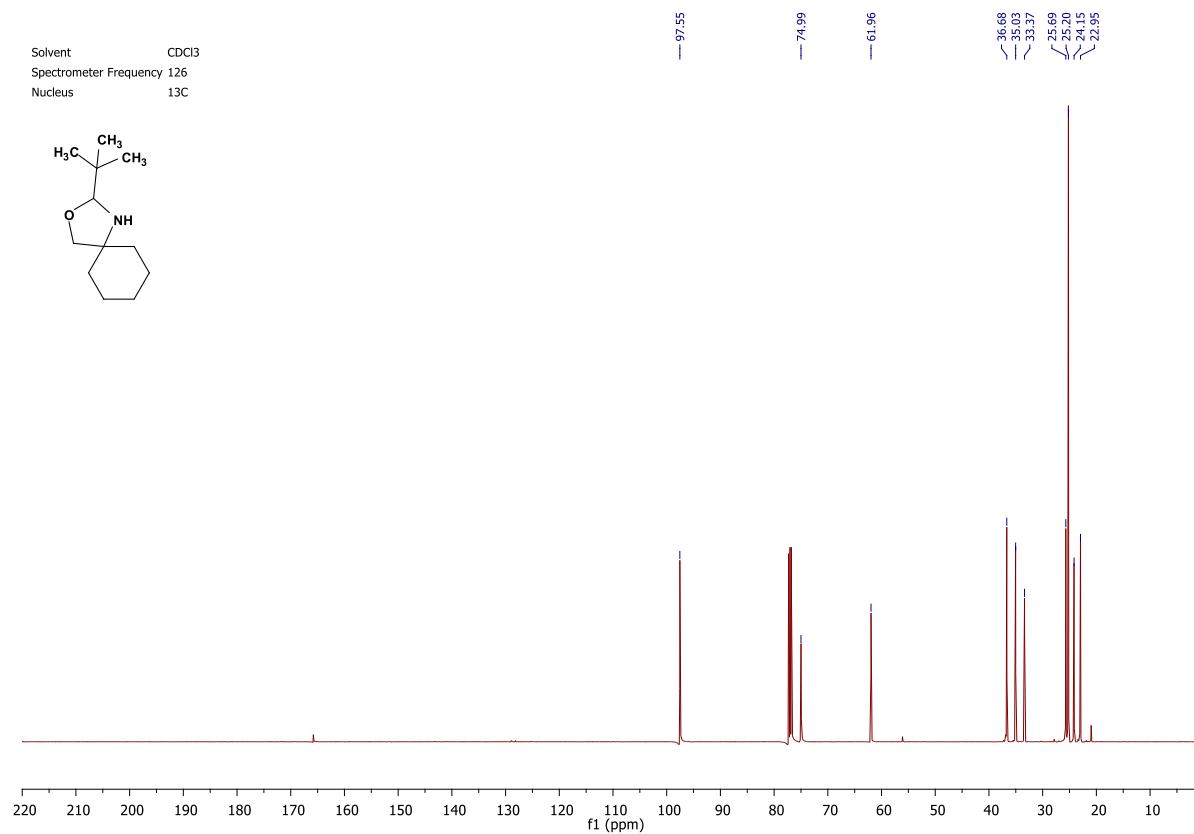
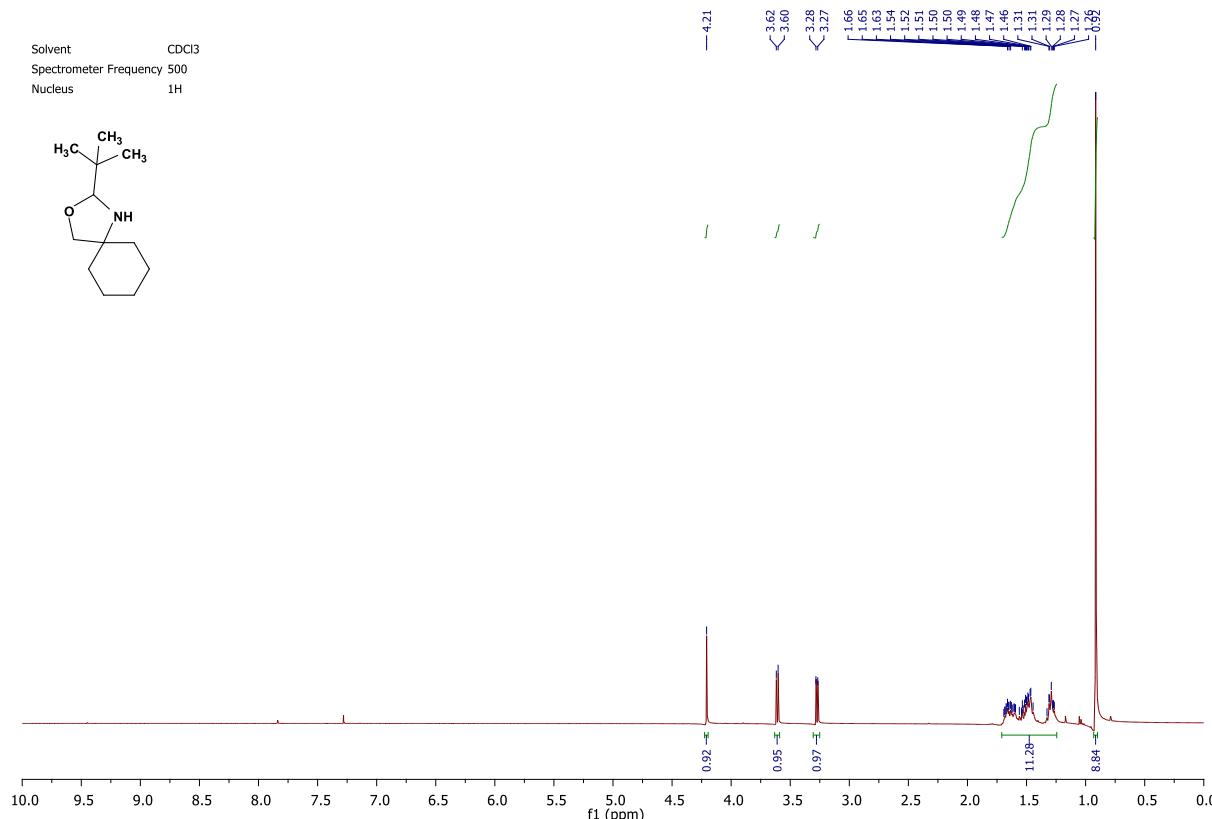
Solvent CDCl₃
Spectrometer Frequency 500
Nucleus 1H



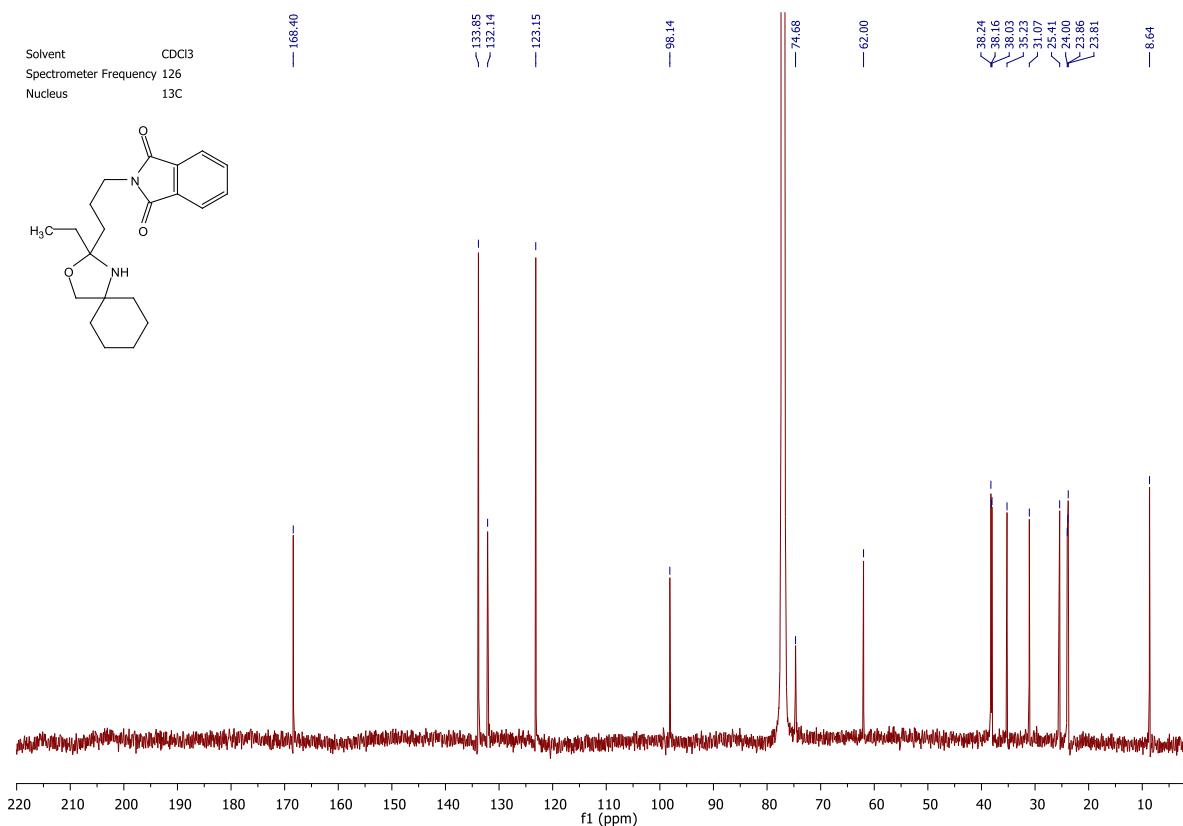
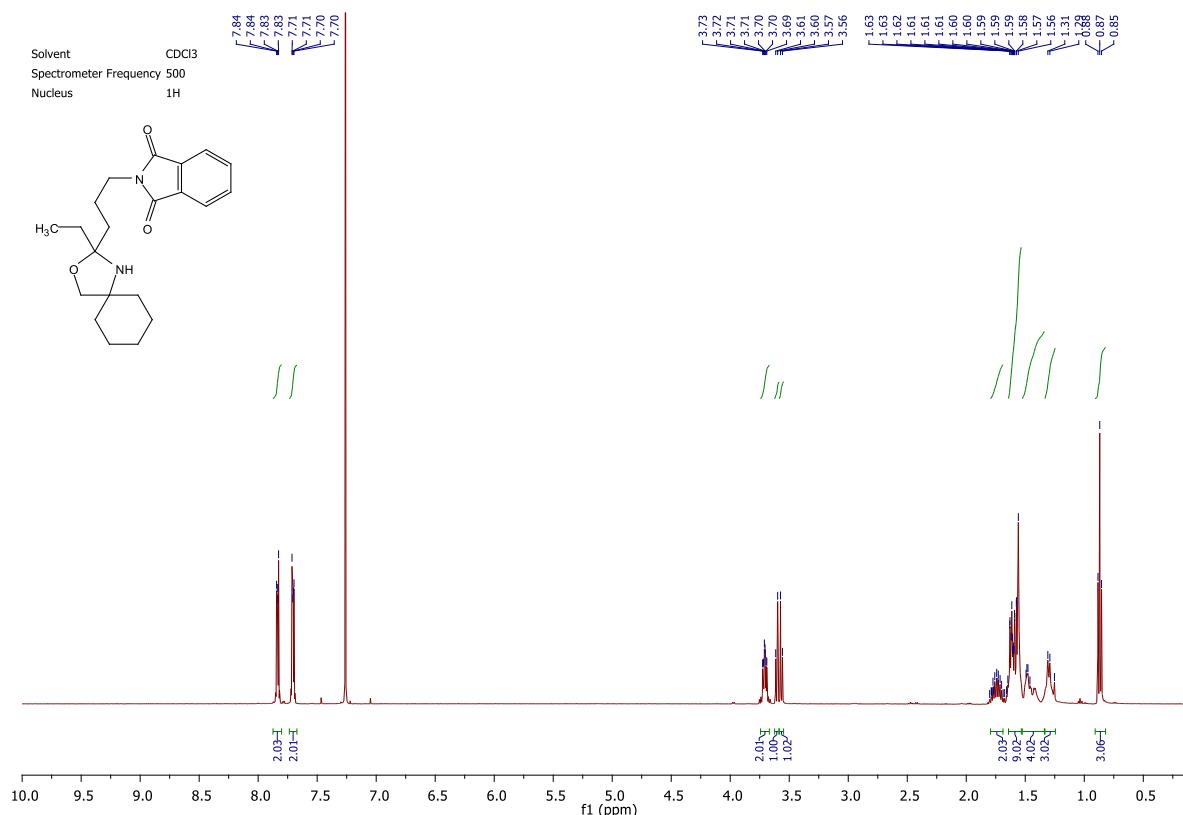
Solvent CDCl₃
Spectrometer Frequency 126
Nucleus ¹³C



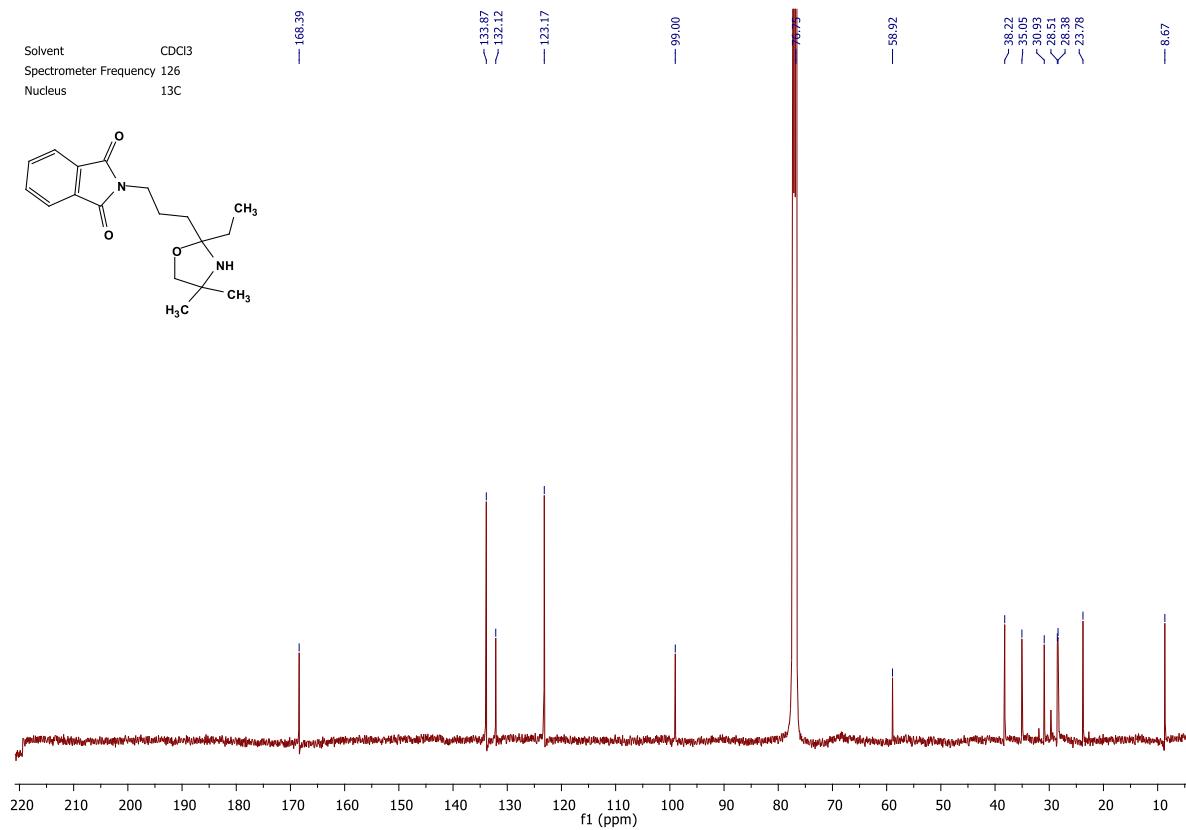
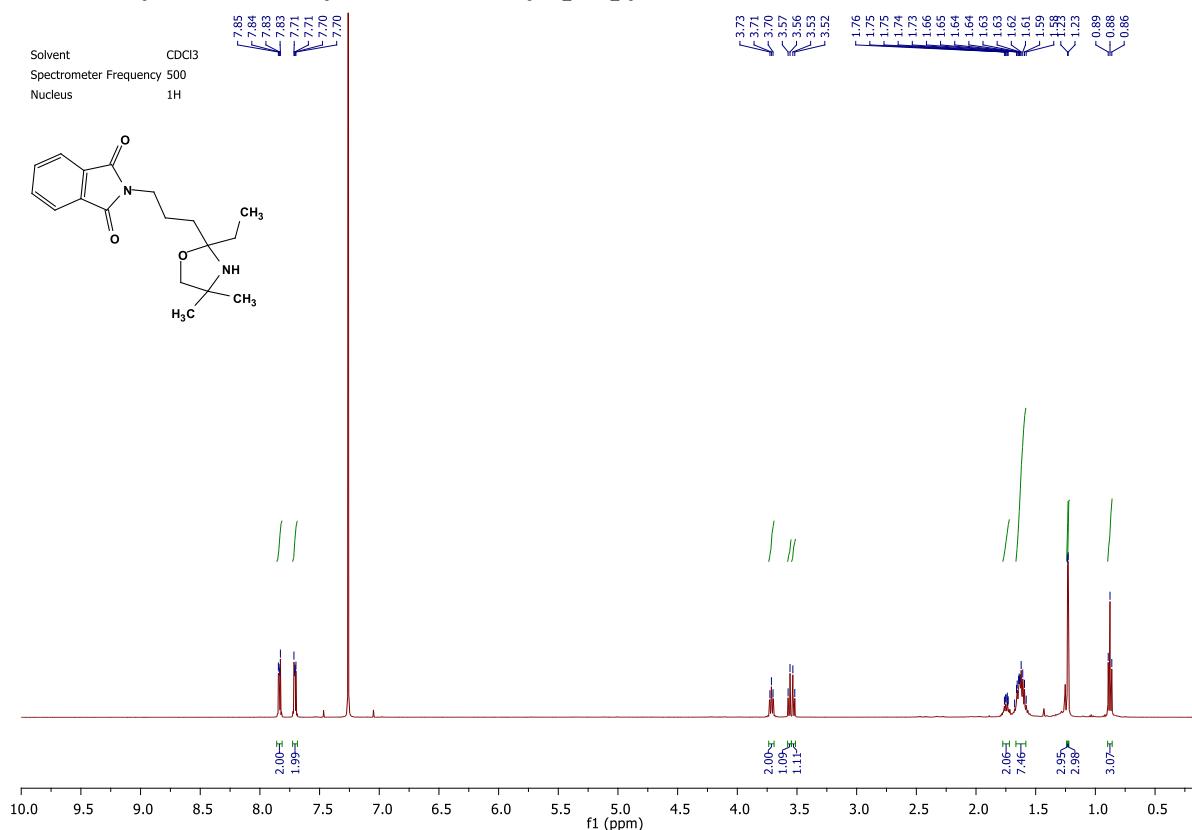
2-(*Tert*-butyl)-3-oxa-1-azaspiro[4.5]decane (202a)



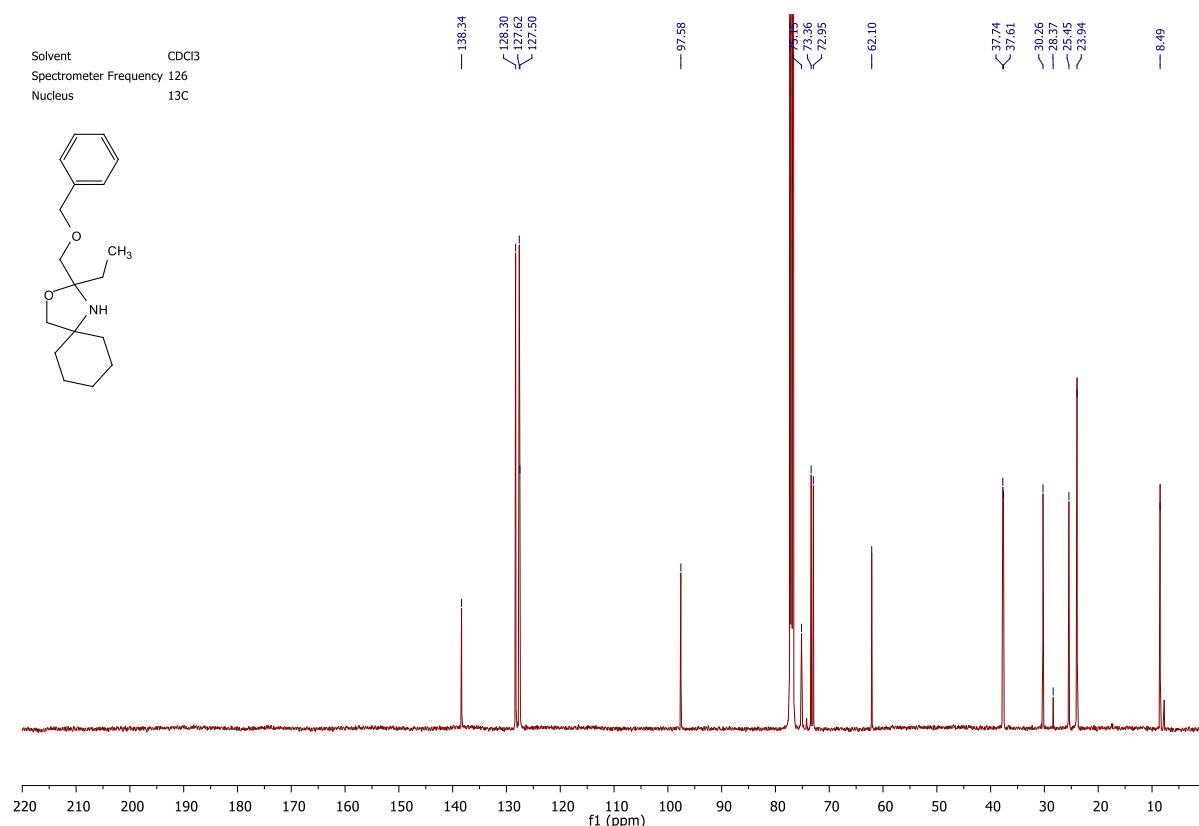
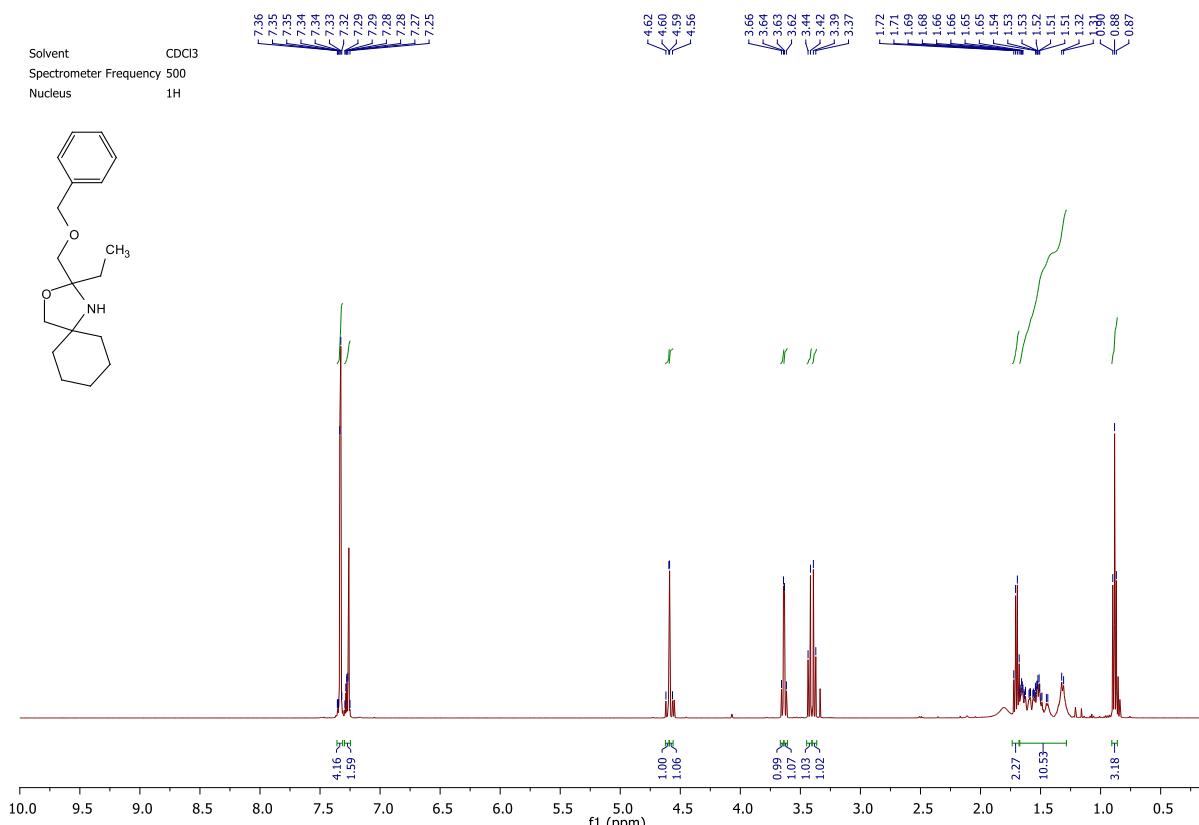
2-{3-(2-Ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propyl}isoindoline-1,3-dione (231a)



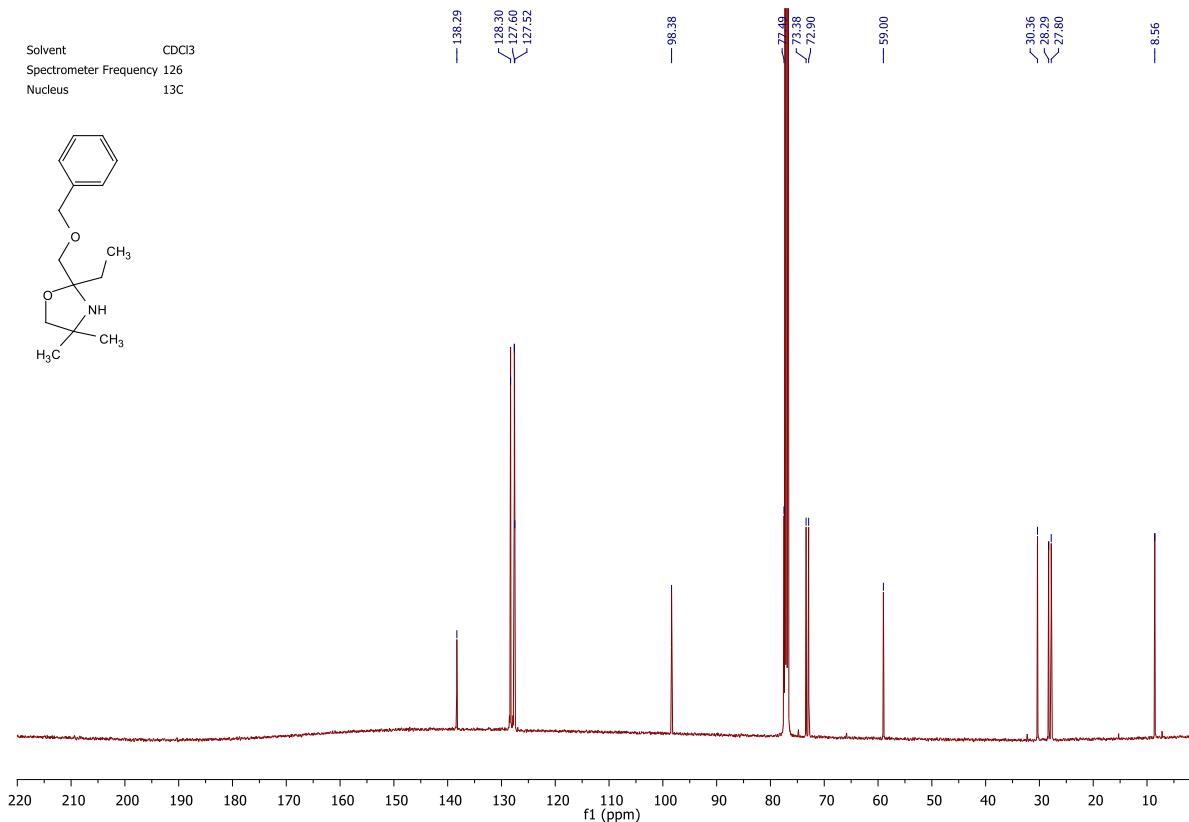
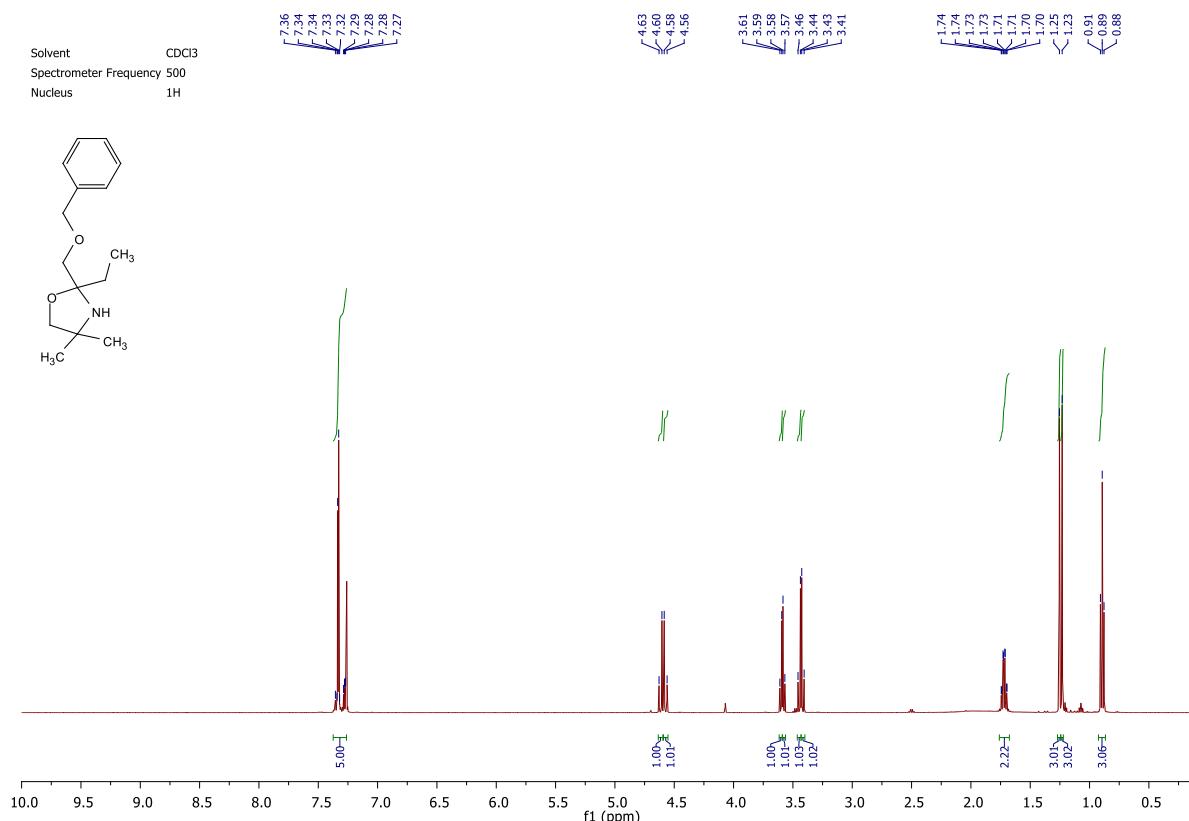
2-{3-(2-Ethyl-4,4-dimethyloxazolidin-2-yl)propyl}isoindoline-1,3-dione (231b)



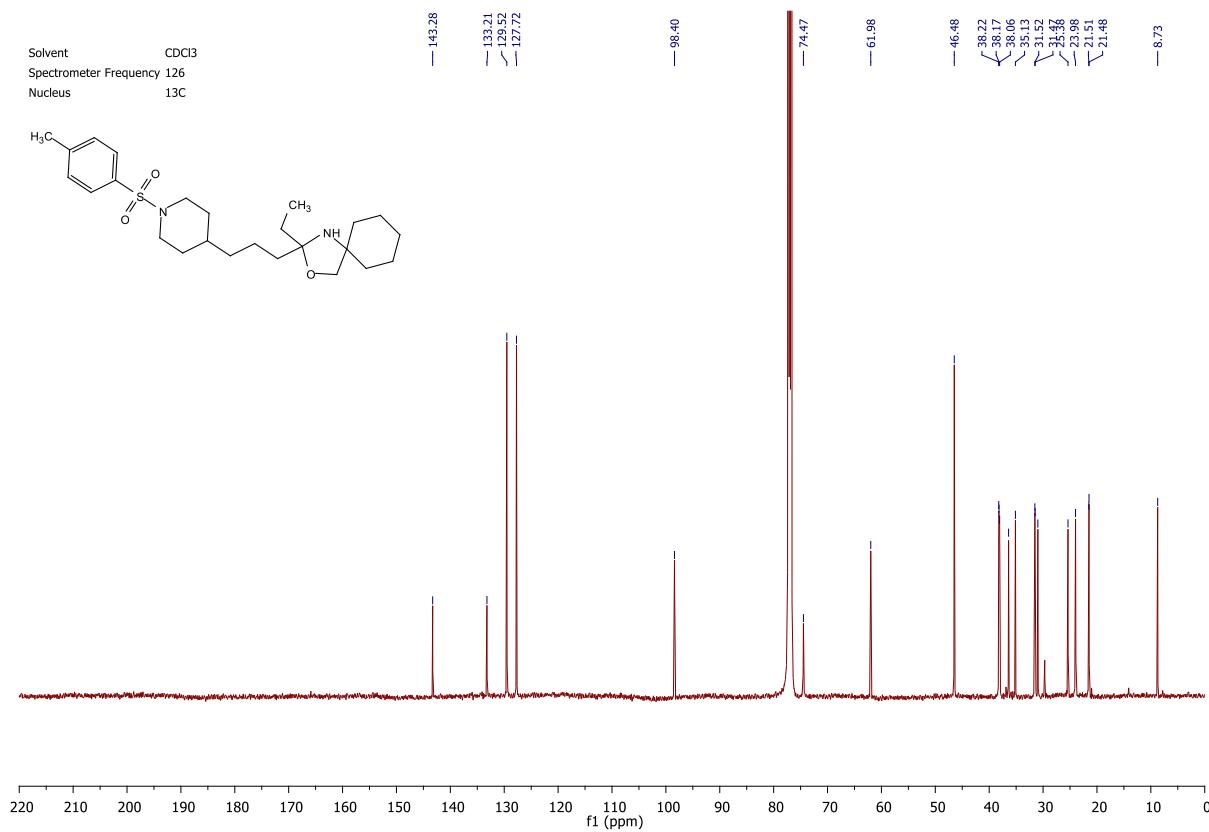
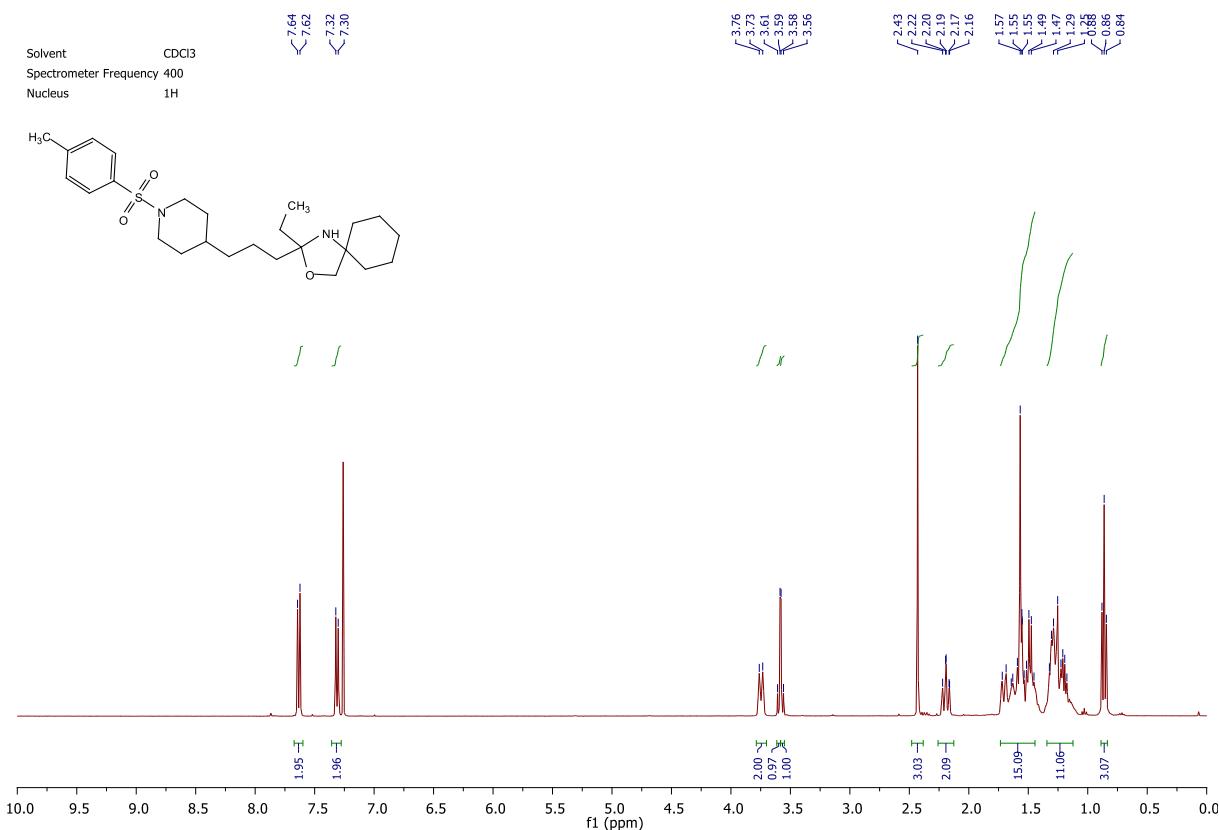
2-((Benzyl)oxy)methyl)-2-ethyl-3-oxa-1-azaspiro[4.5]decane (232a)



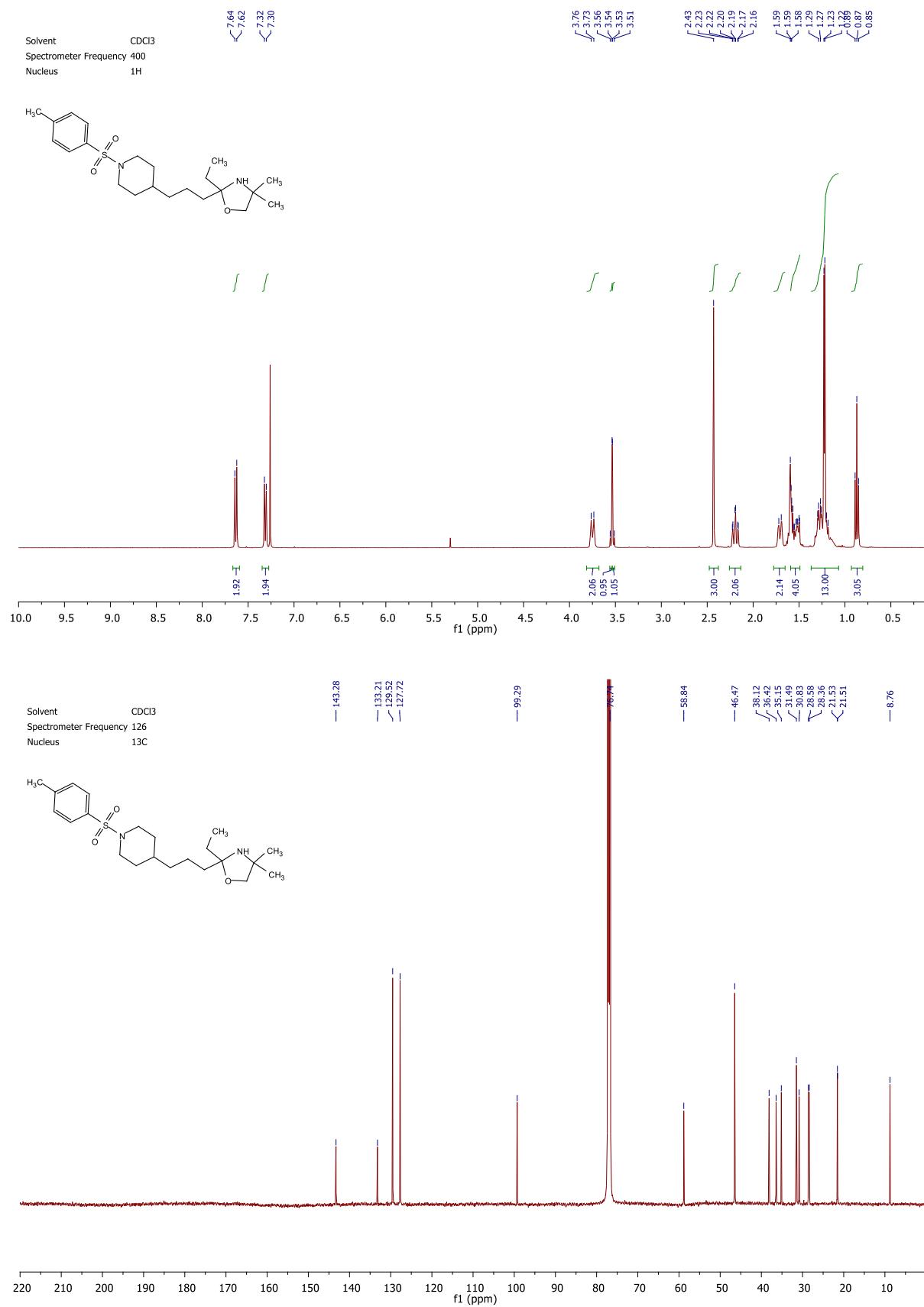
2-((Benzyl)oxy)methyl-2-ethyl-4,4-dimethyloxazolidine (232b)



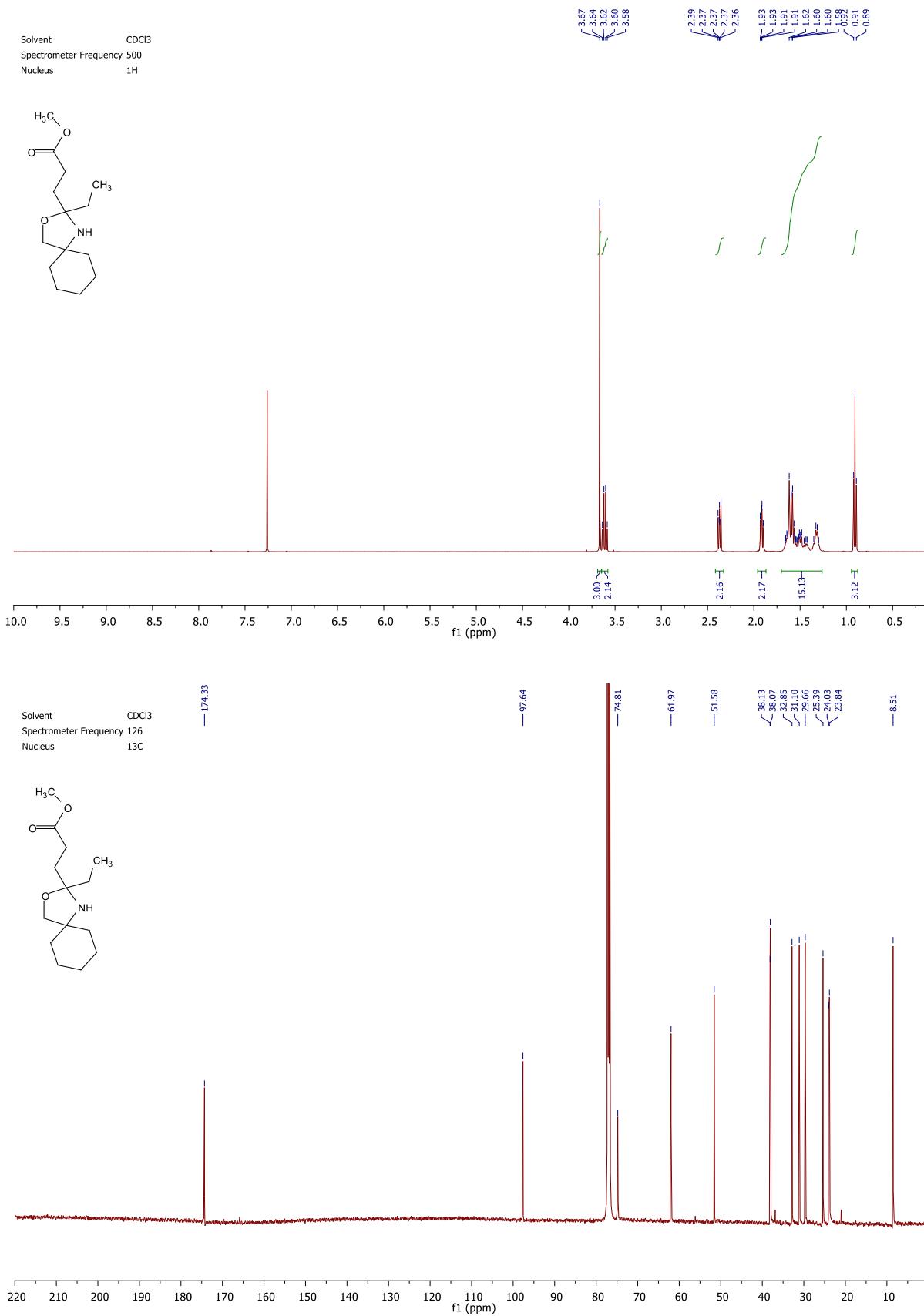
2-Ethyl-2-(3-[1-tosylpiperidin-4-yl]propyl)-3-oxa-1-azaspiro[4.5]decane (233a)



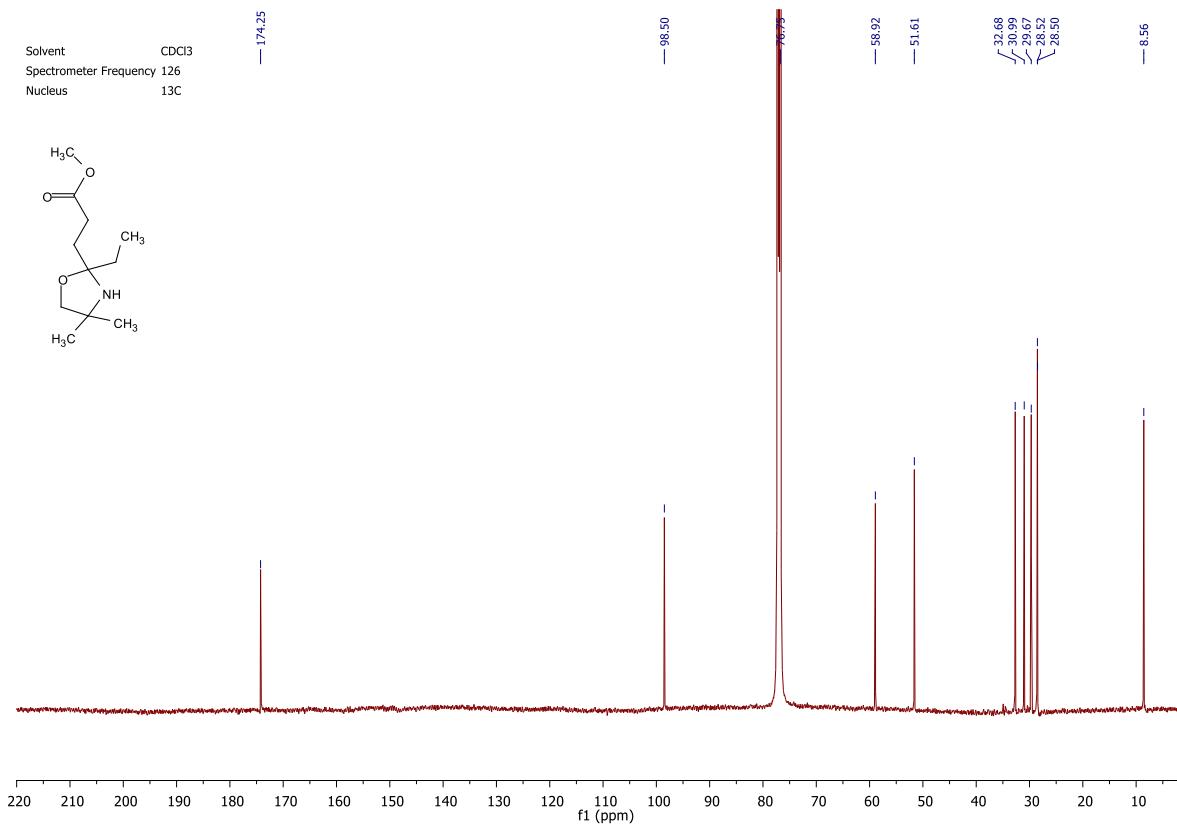
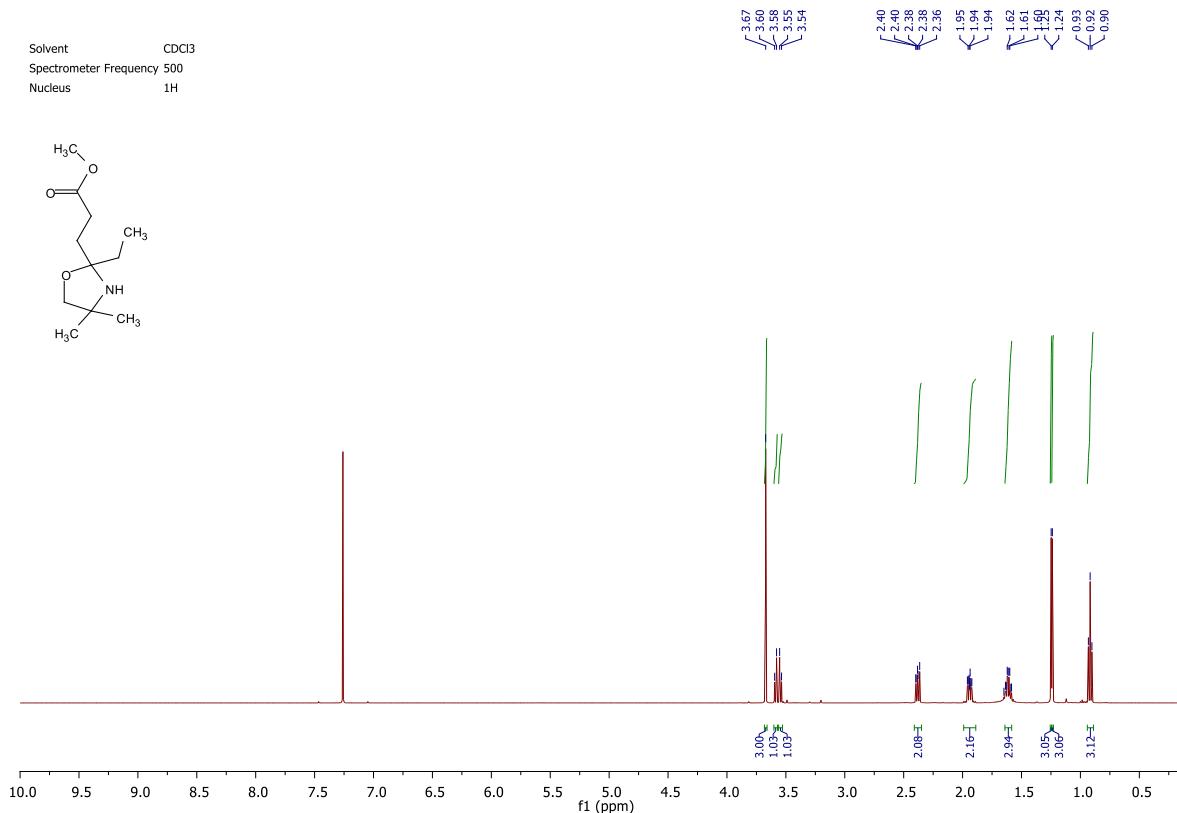
2-Ethyl-4,4-dimethyl-2-(3-[1-tosylpiperidin-4-yl]propyl)oxazolidine (233b)



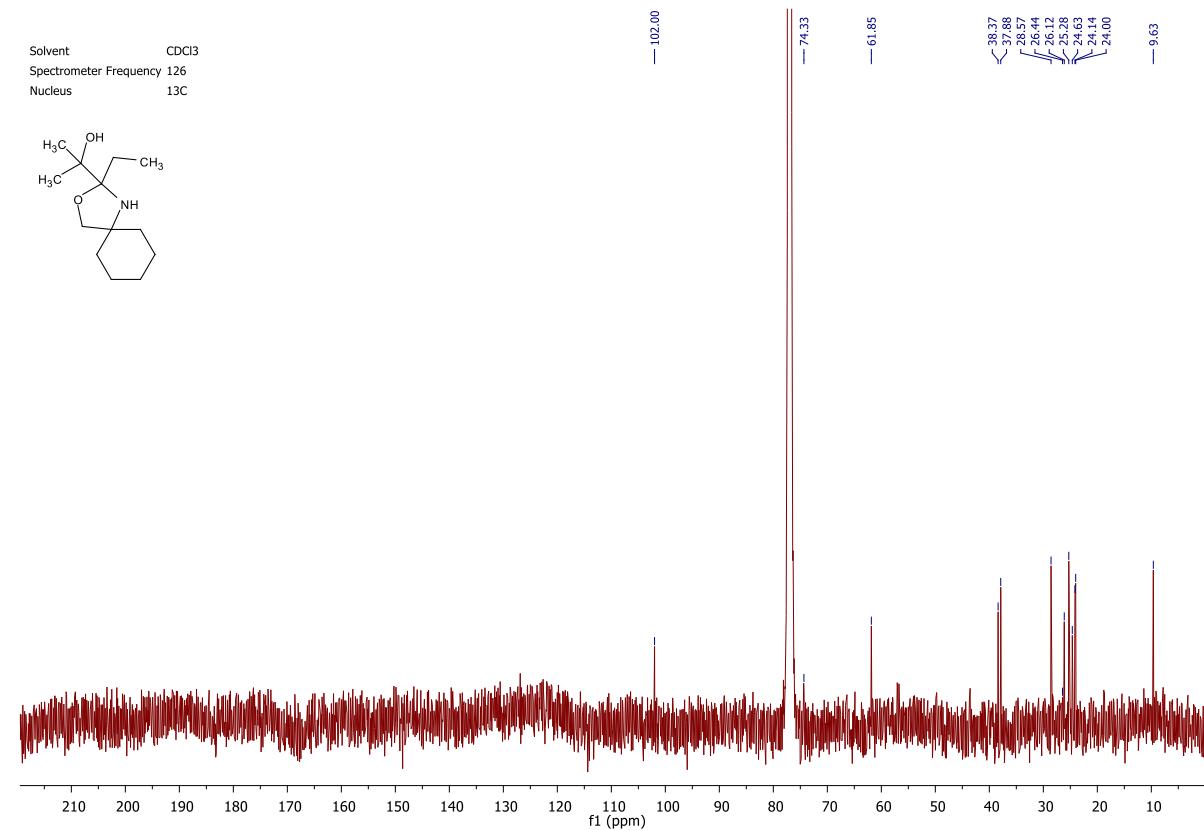
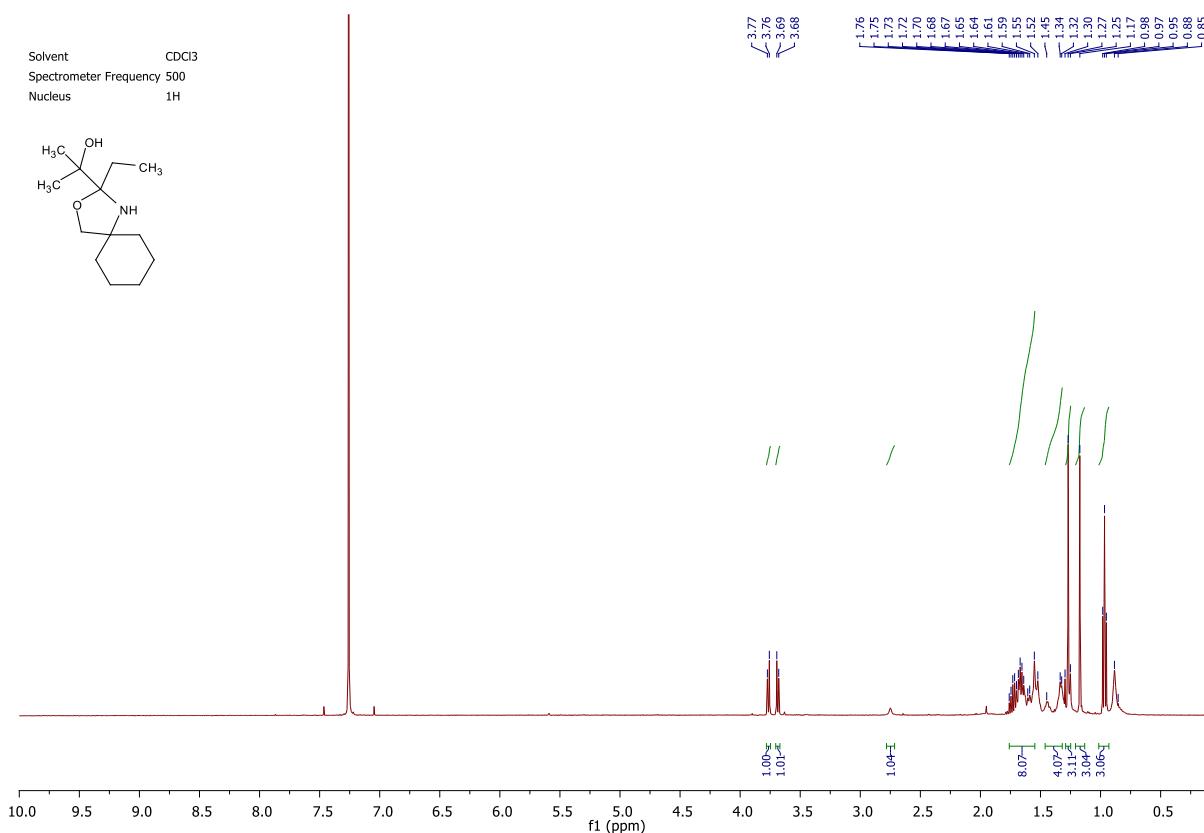
Methyl 3-(2-ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propanoate (234a)



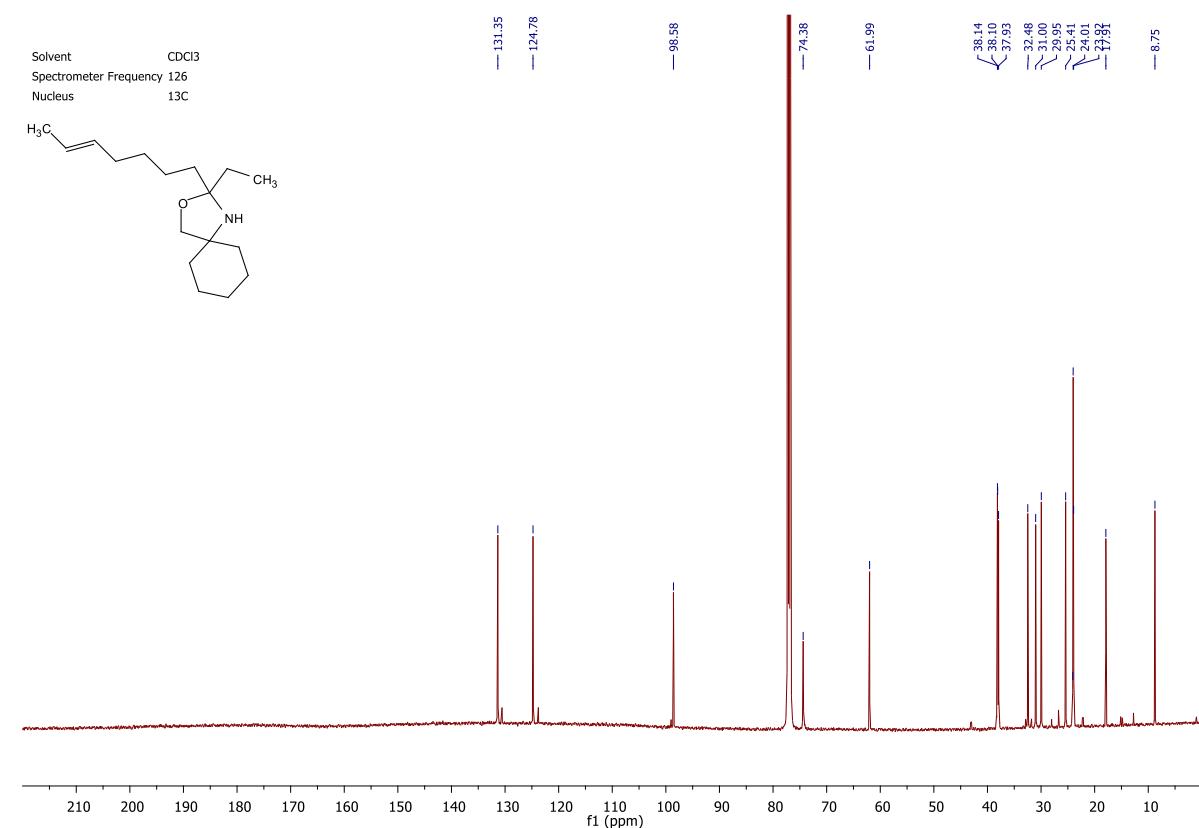
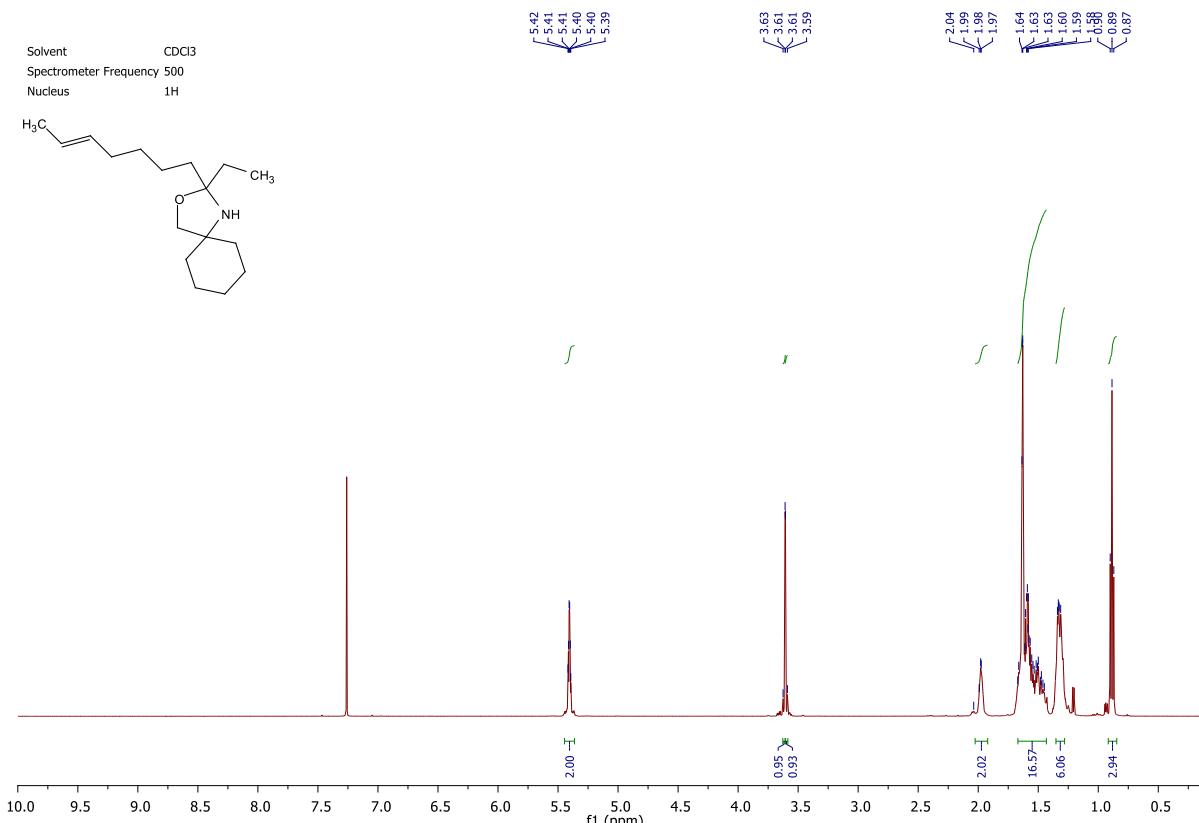
Methyl 3-(2-ethyl-4,4-dimethyloxazolidin-2-yl)propanoate (234b)



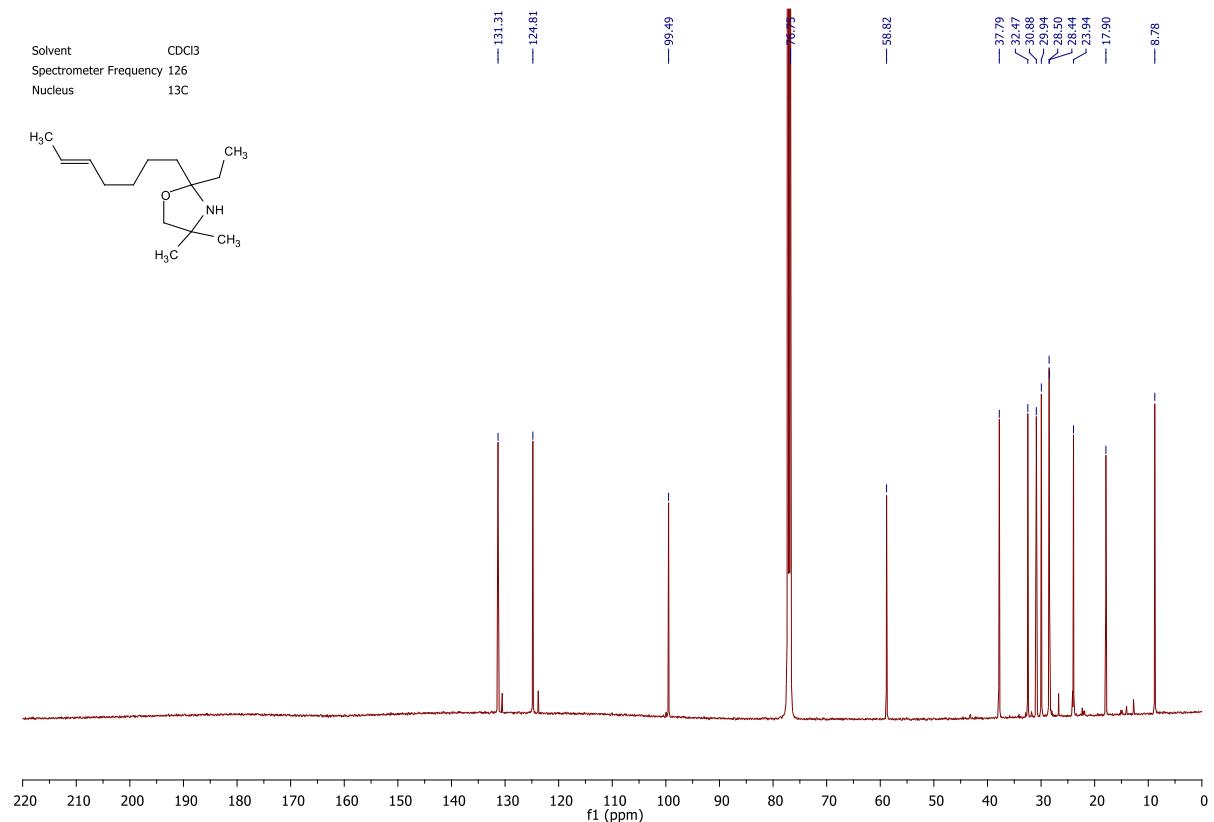
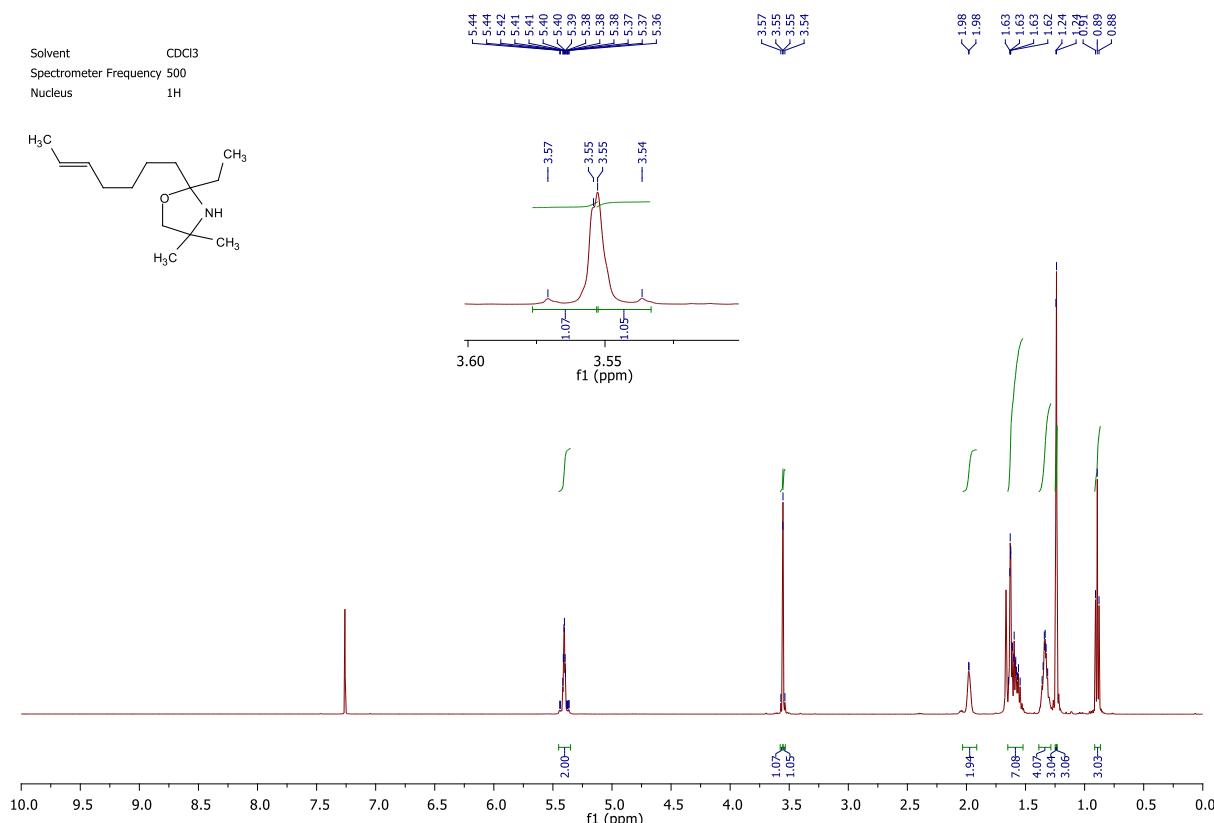
2-(2-Ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)propan-2-ol (235a)



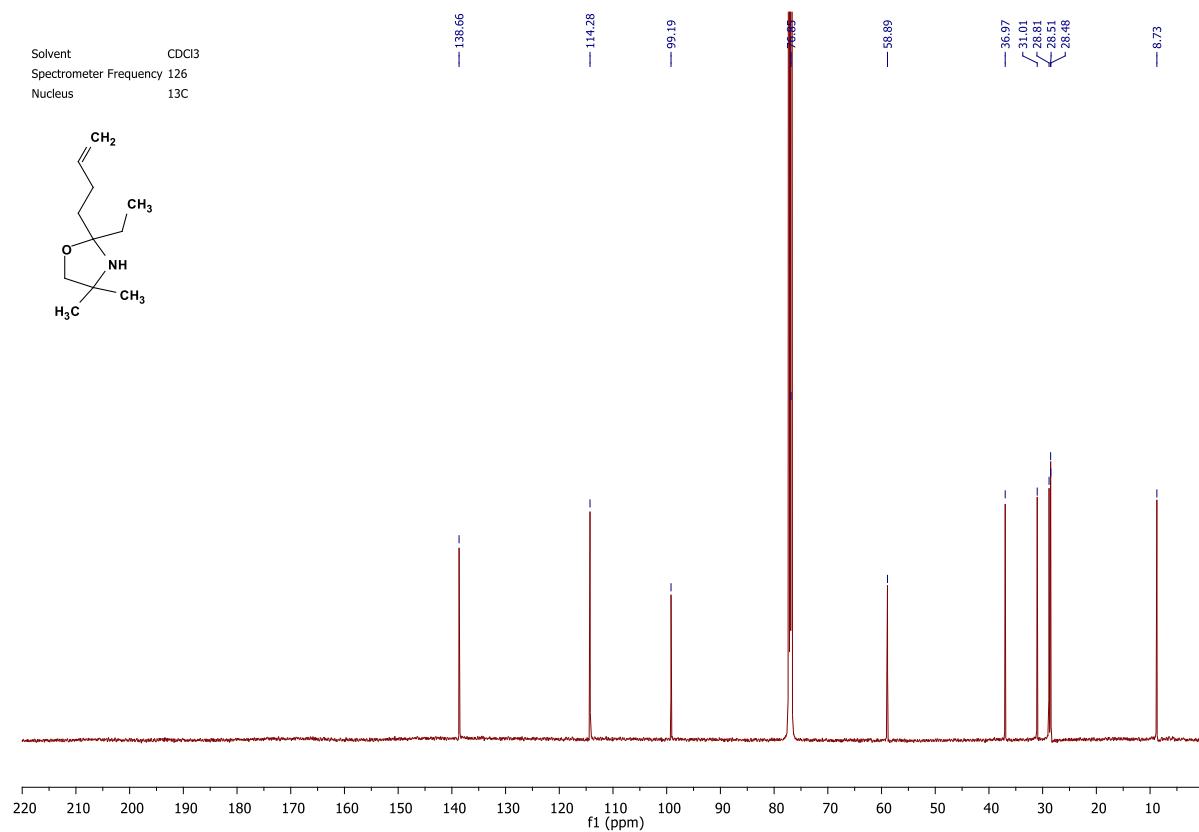
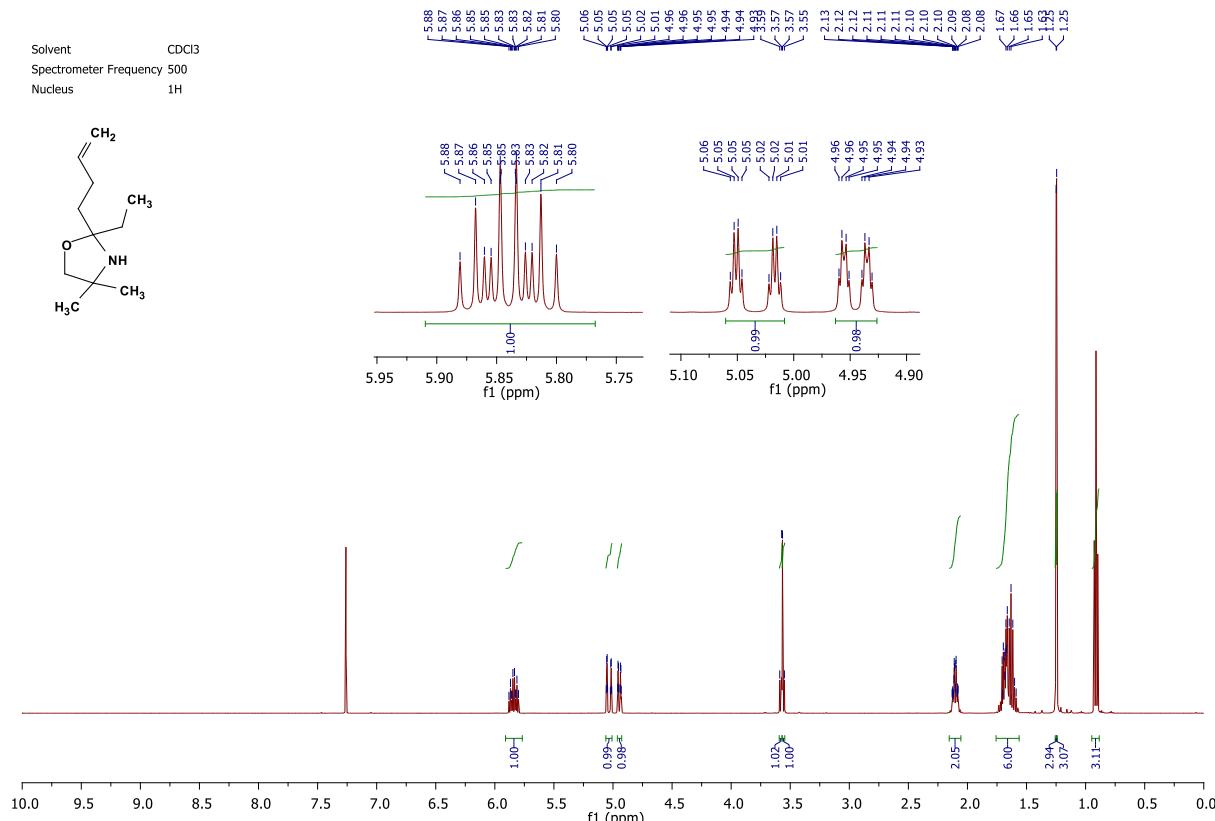
(E)-2-Ethyl-2-(hept-5-en-1-yl)-3-oxa-1-azaspiro[4.5]decane (236a)



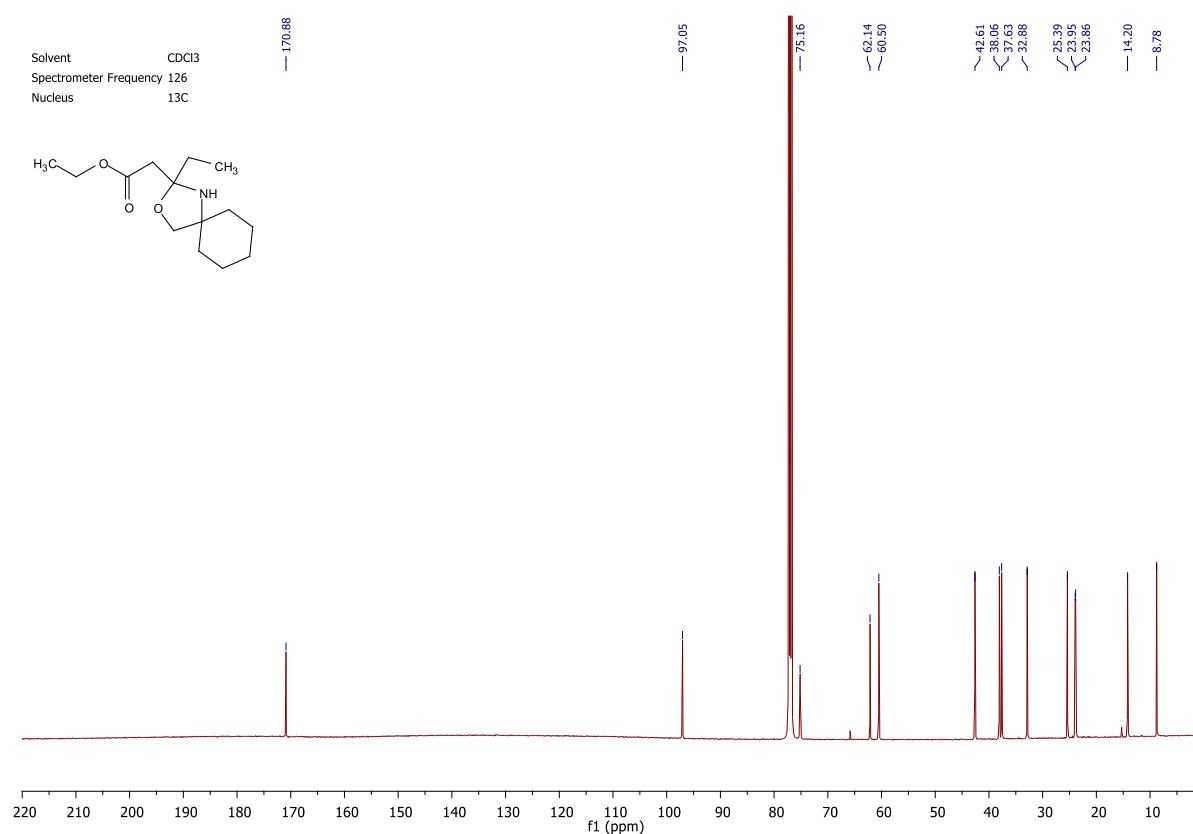
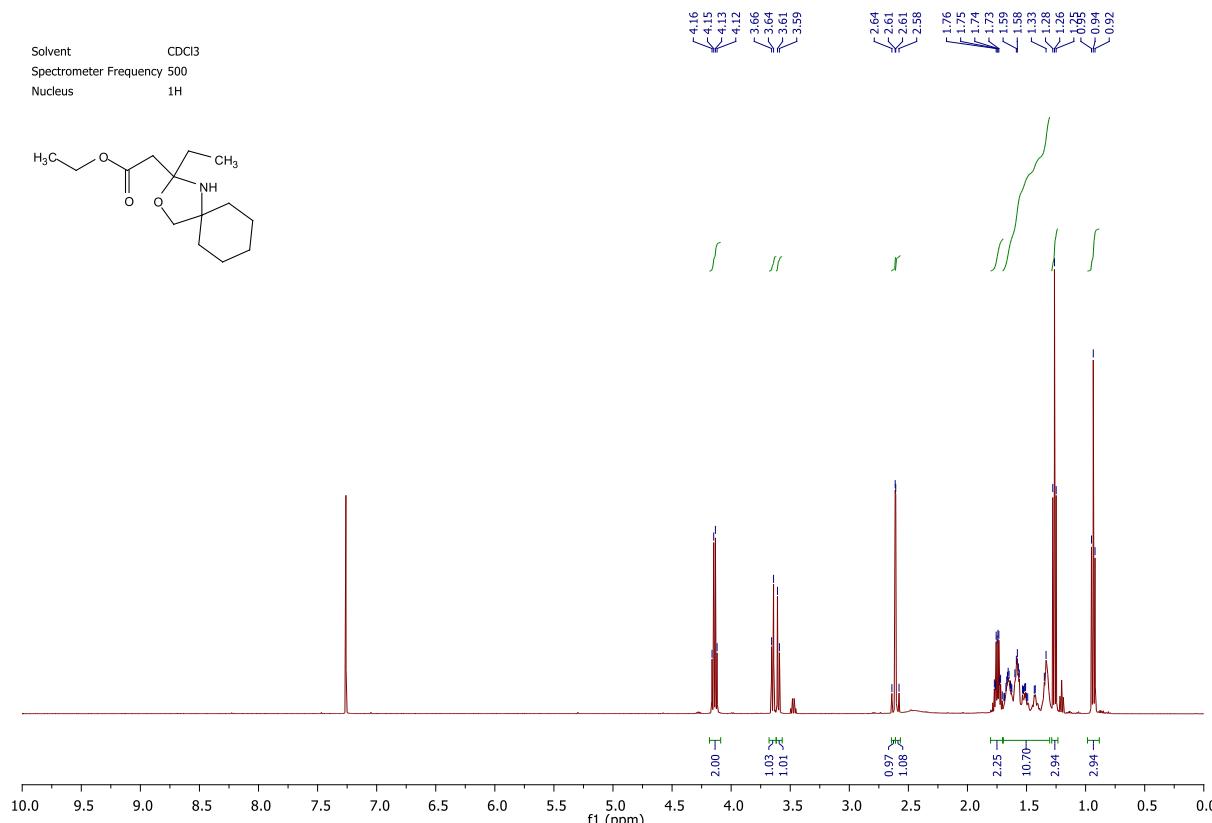
(E)-2-Ethyl-2-(hept-5-en-1-yl)-4,4-dimethyloxazolidine (236b)



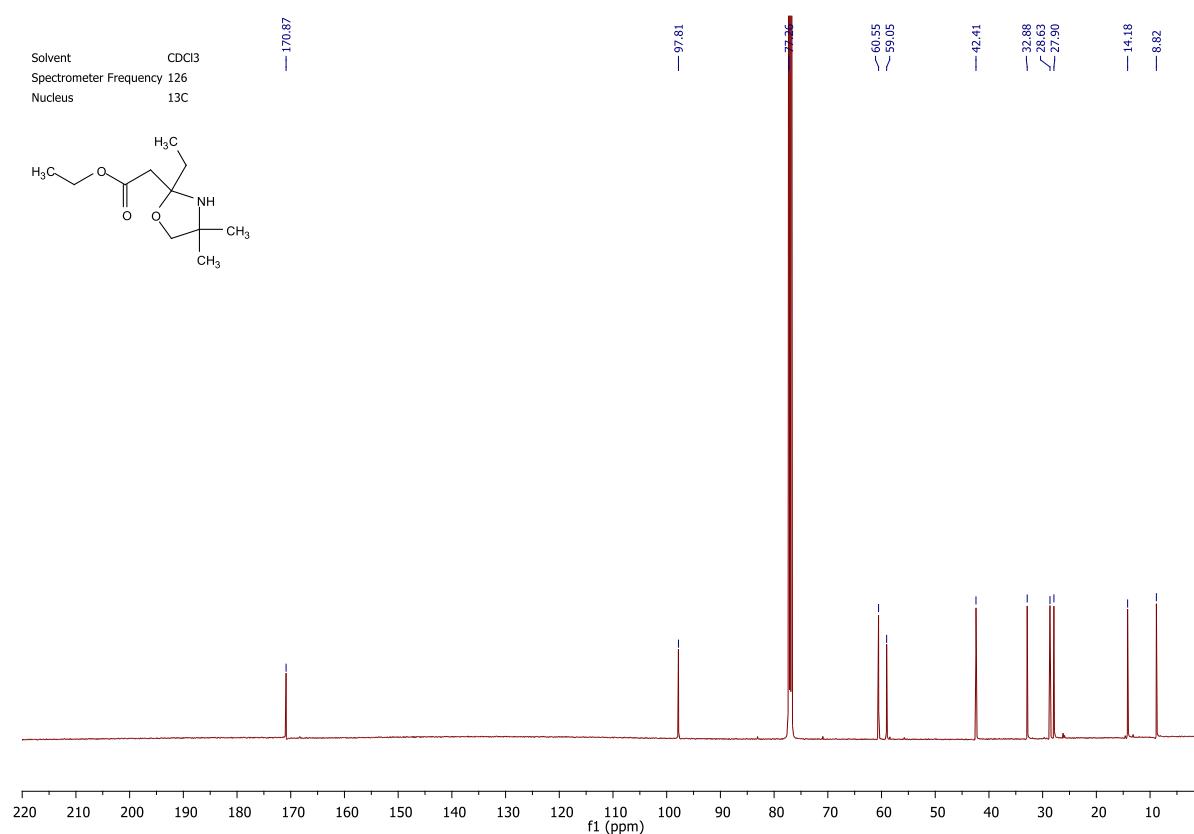
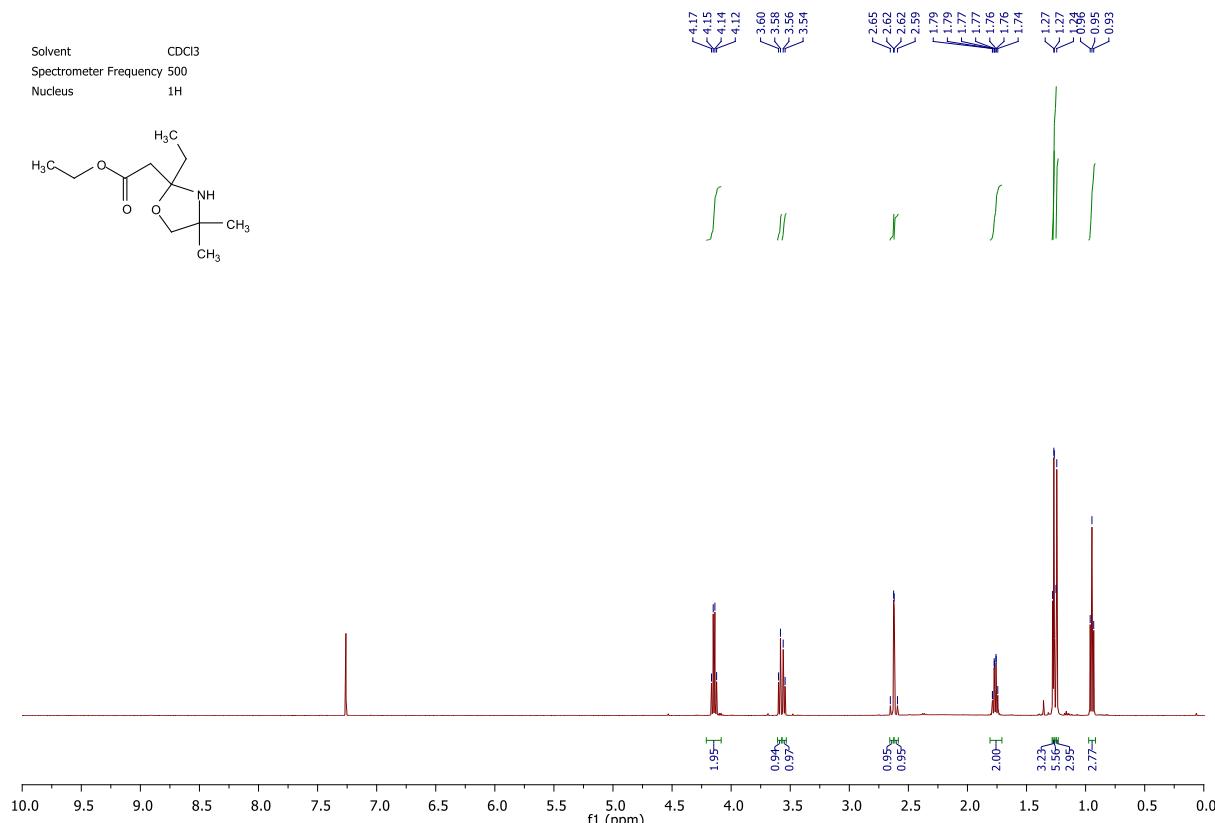
2-(But-3-en-1-yl)-2-ethyl-4,4-dimethyloxazolidine (237b)



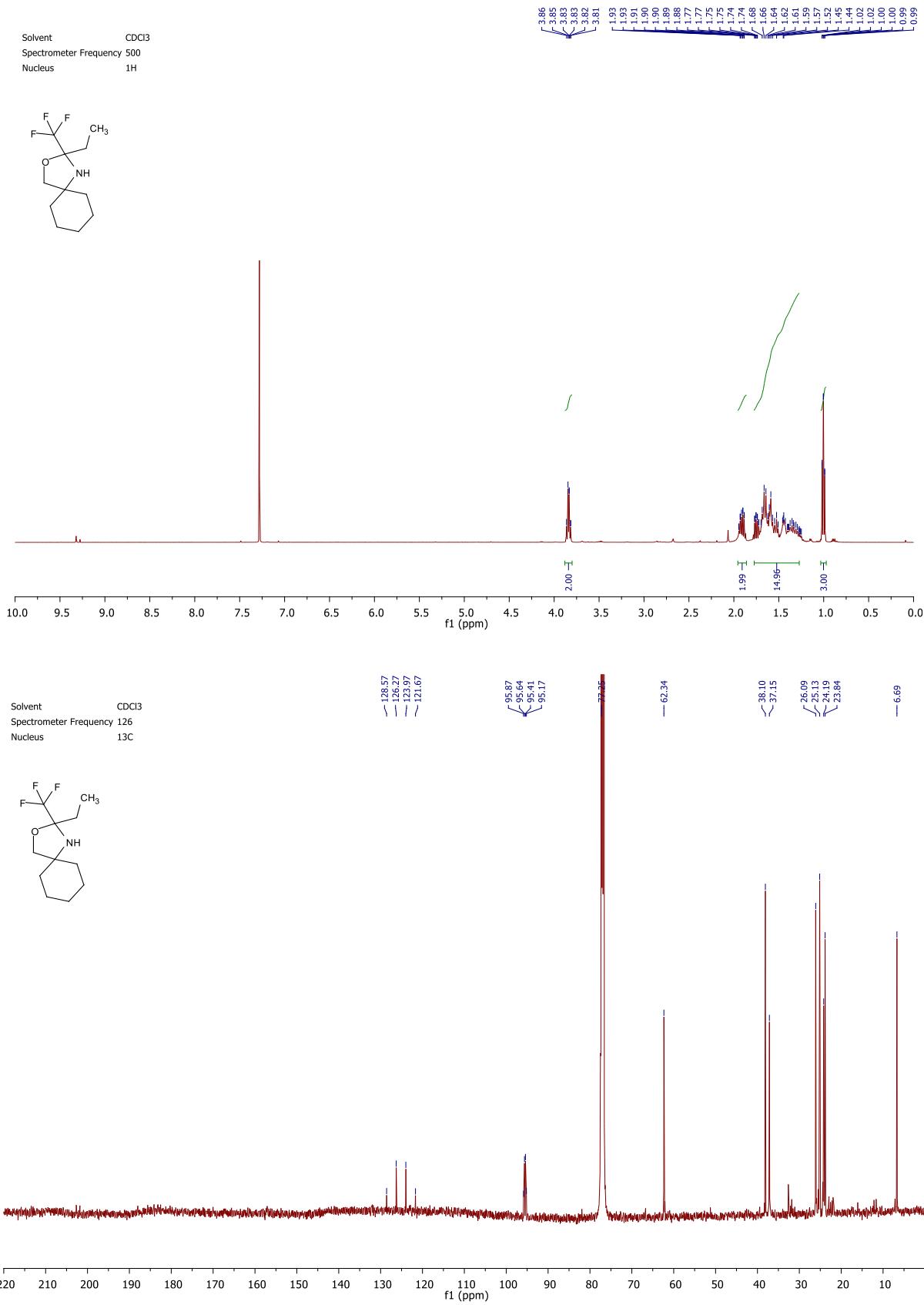
Ethyl 2-(2-ethyl-3-oxa-1-azaspiro[4.5]decan-2-yl)acetate (246a)



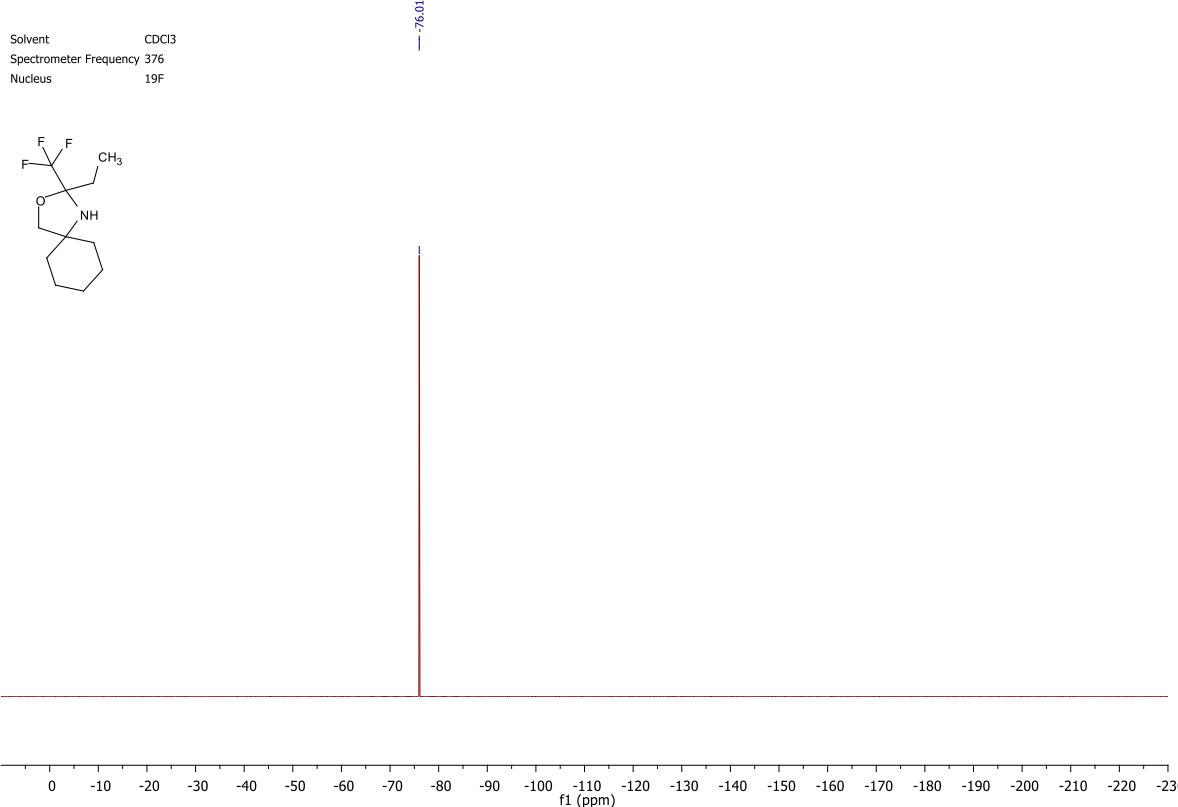
Ethyl 2-(2-ethyl-4,4-dimethyloxazolidin-2-yl)acetate (246b)



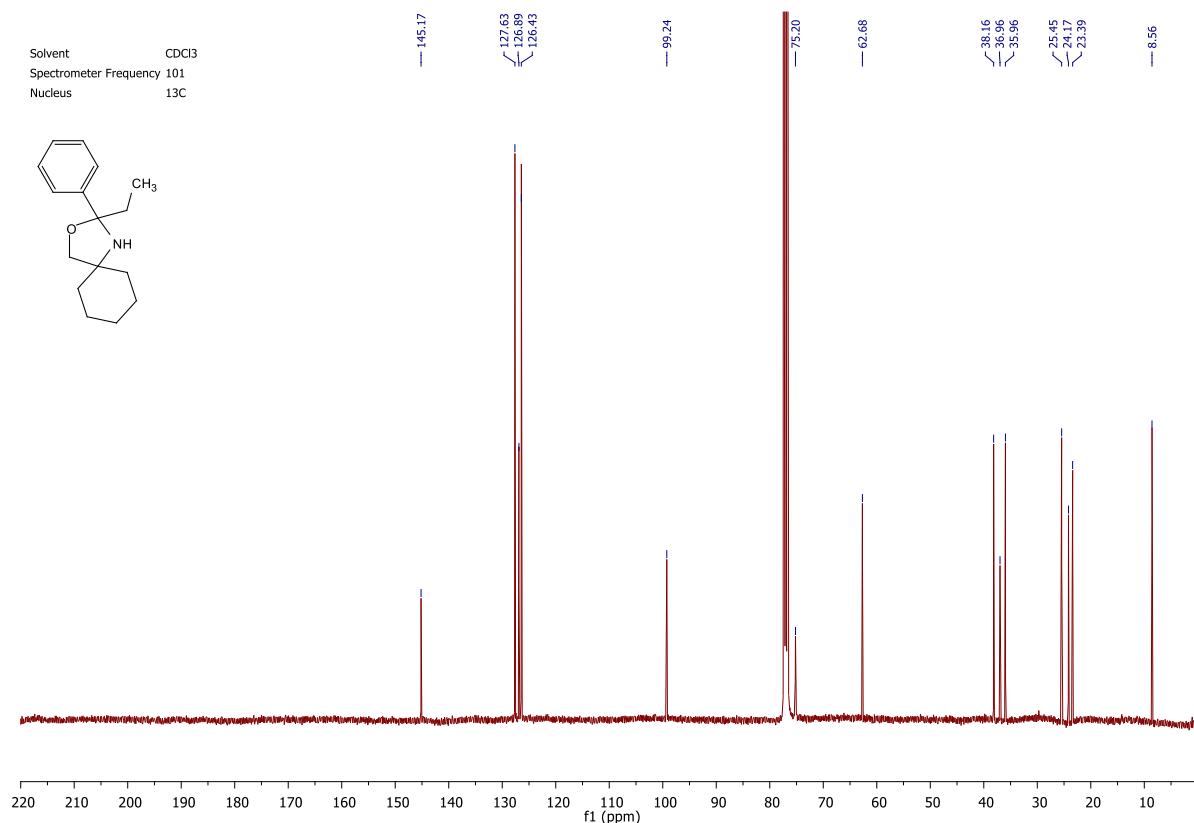
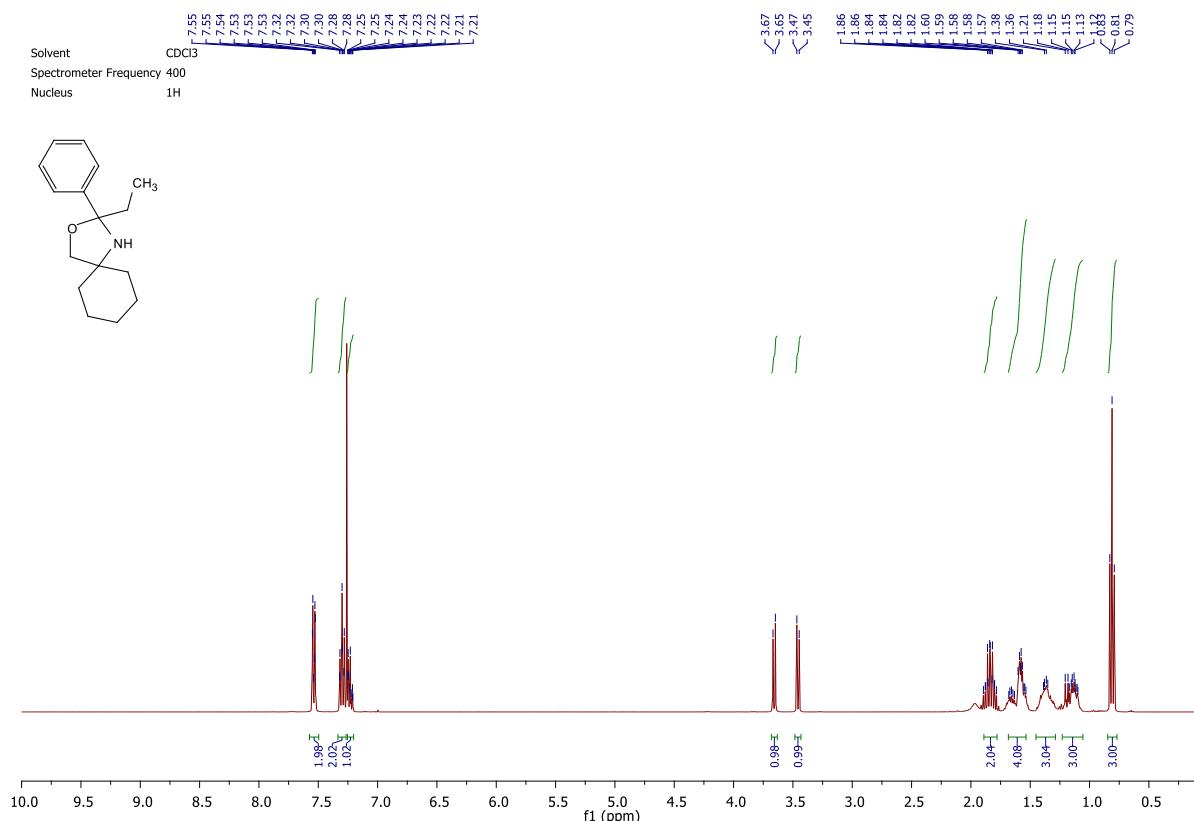
2-Ethyl-2-(trifluoromethyl)-3-oxa-1-azaspiro[4.5]decane (248)



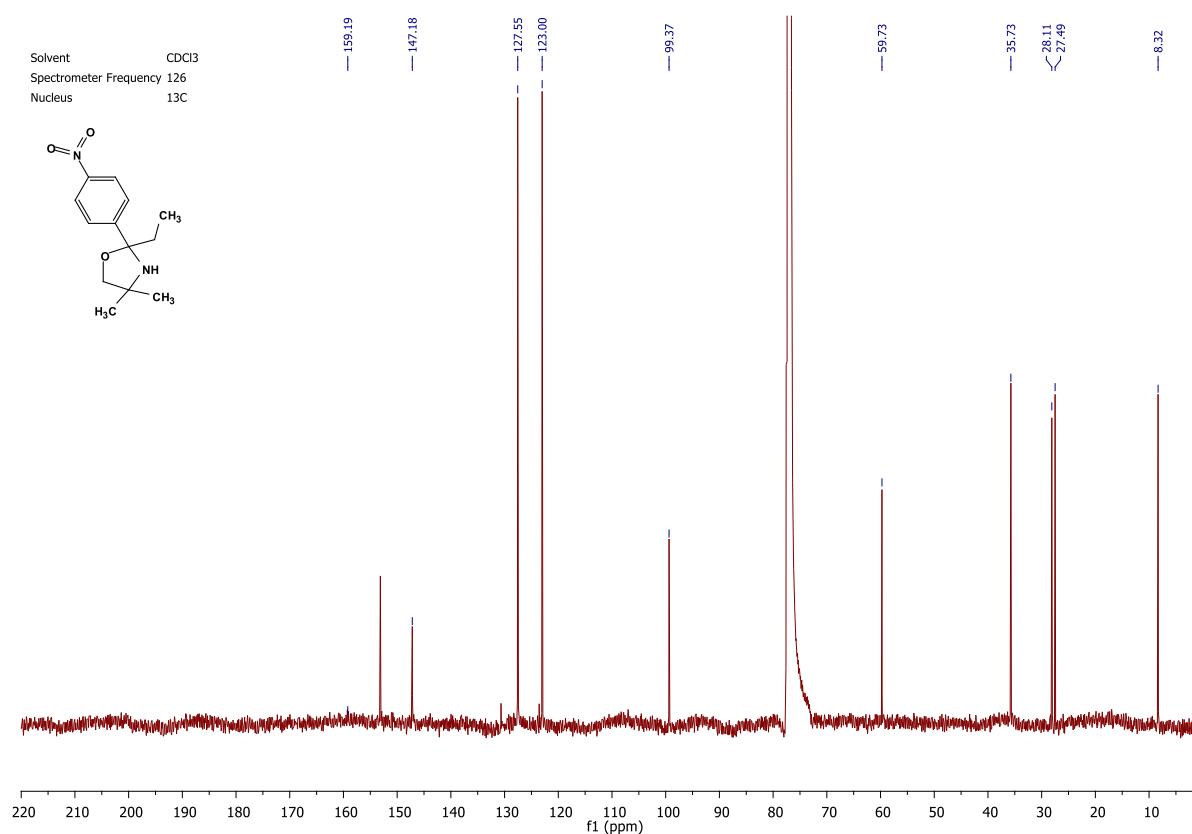
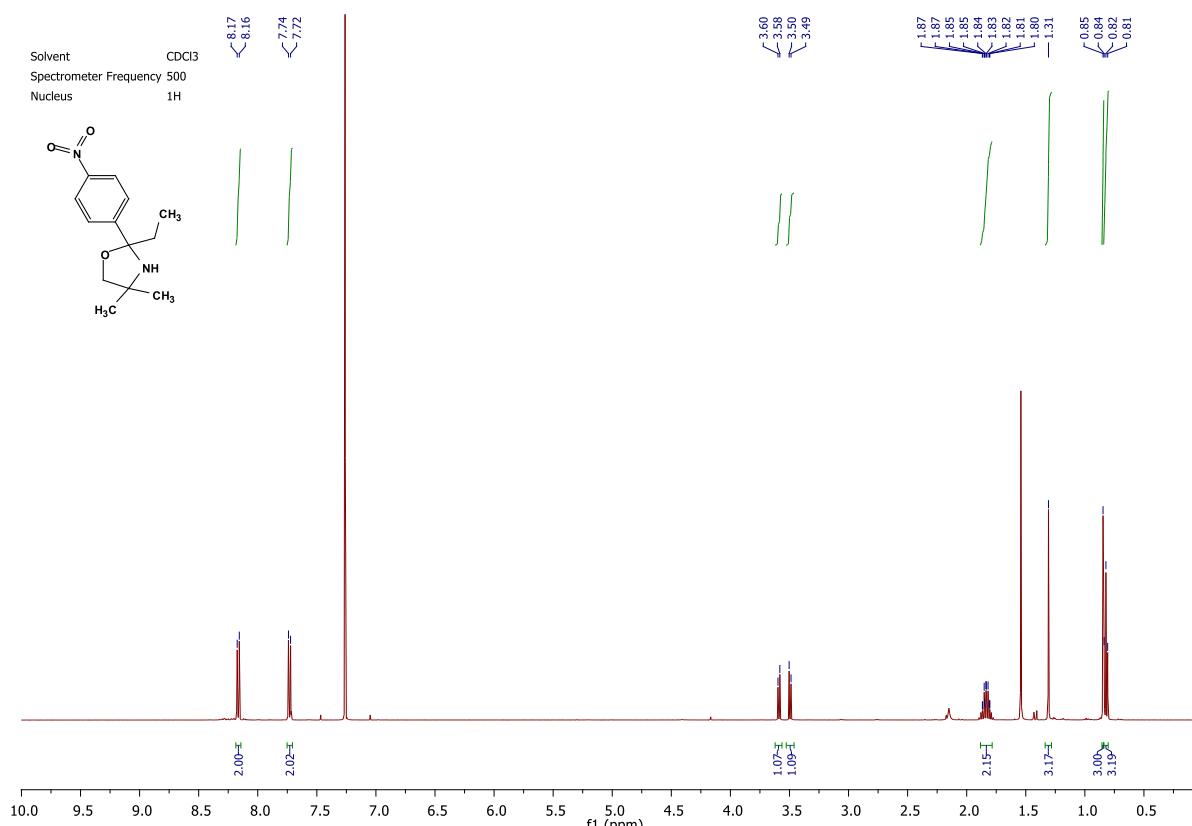
Appendix – 1H and ^{13}C NMR spectra of key compounds



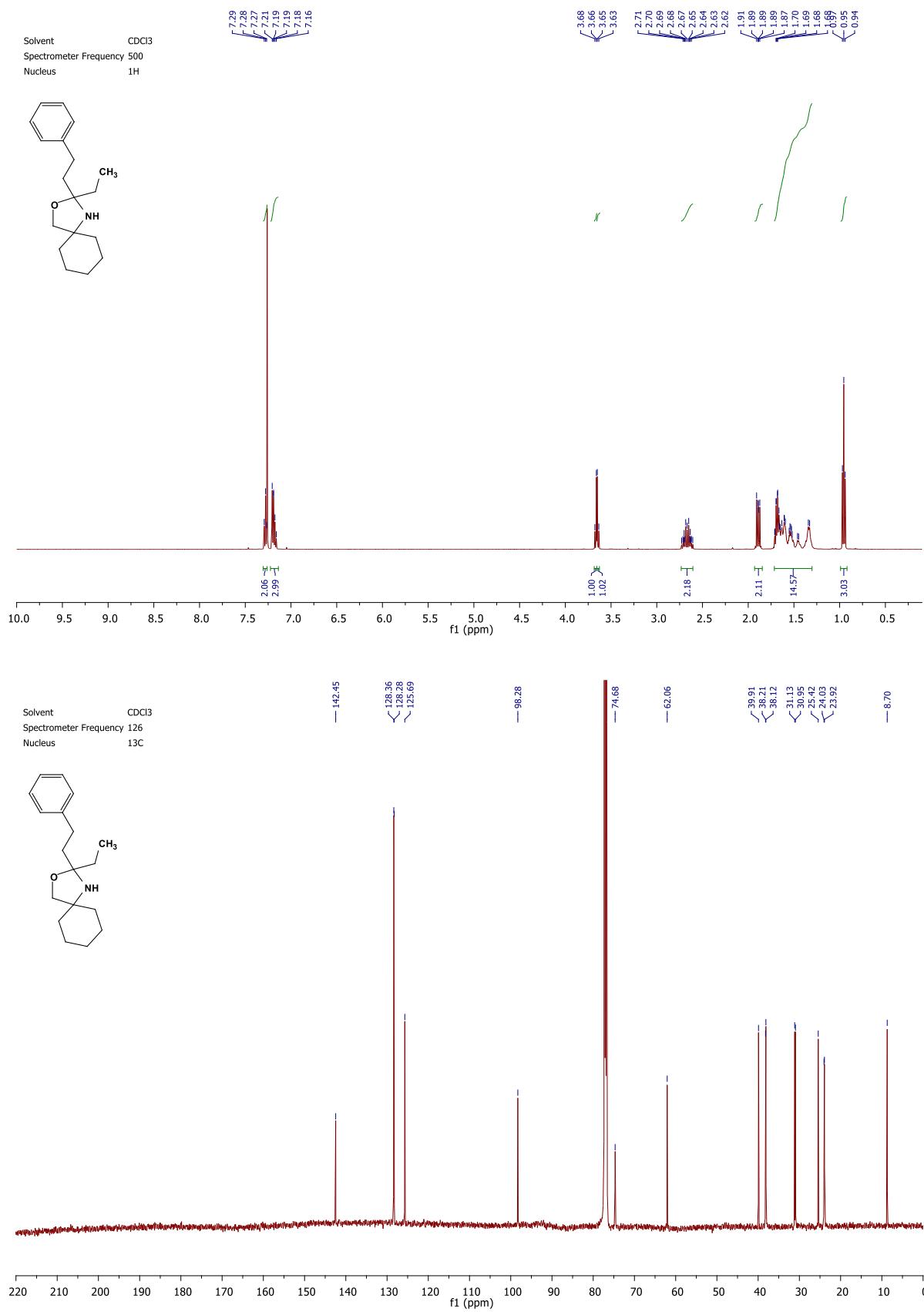
2-Ethyl-2-phenyl-3-oxa-1-azaspiro[4.5]decane (251)



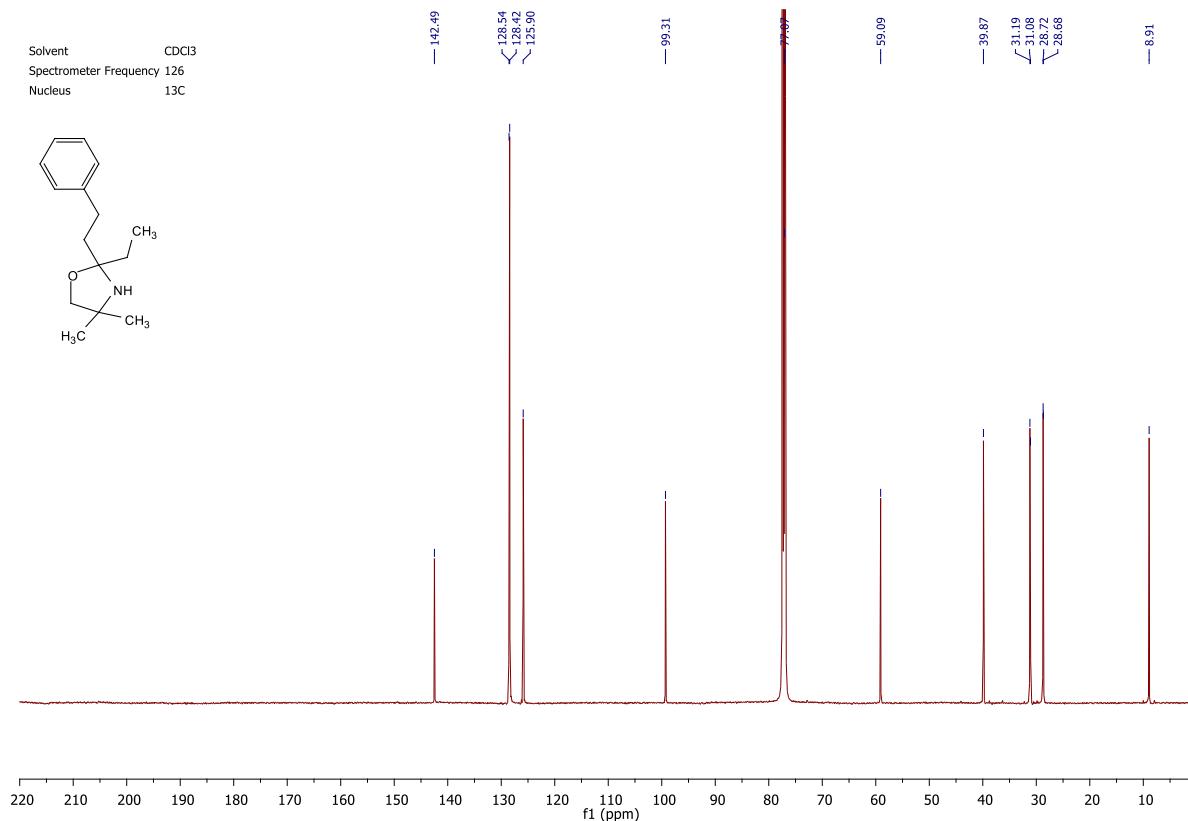
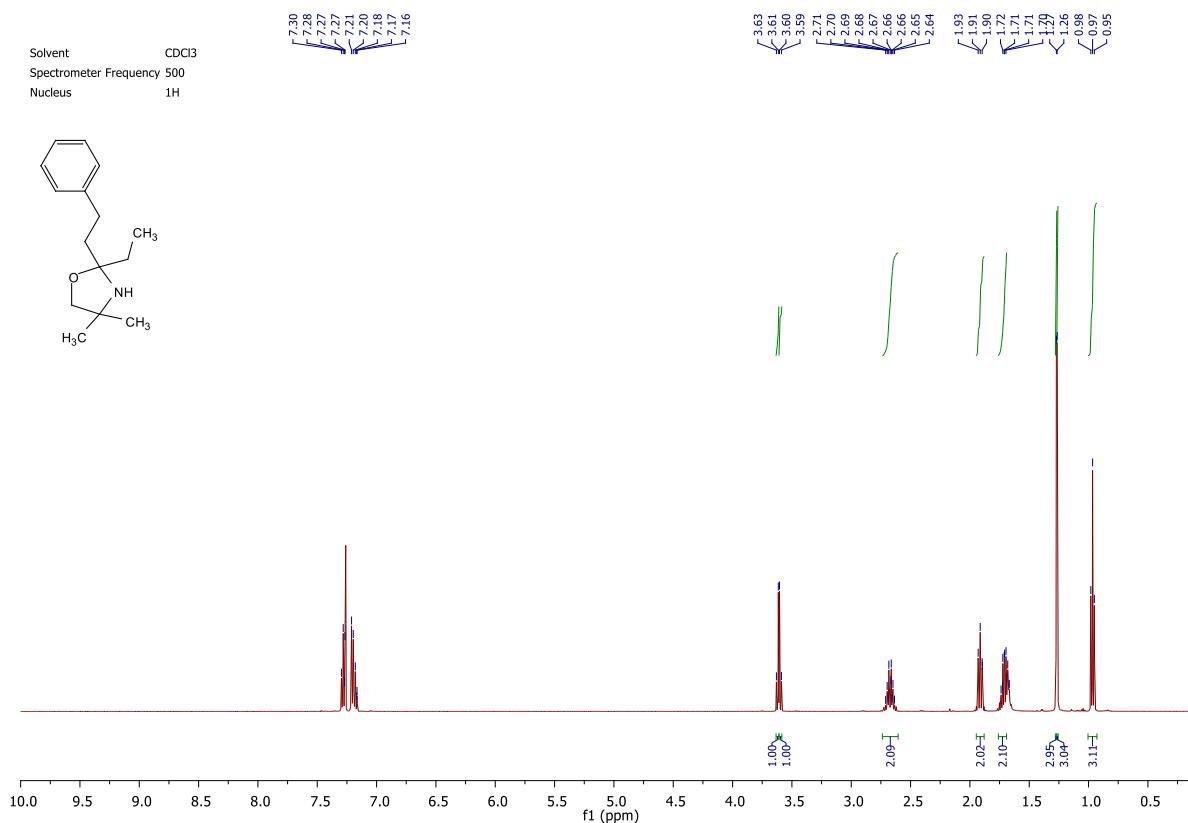
2-Ethyl-4,4-dimethyl-2-(4-nitrophenyl)oxazolidine (256)



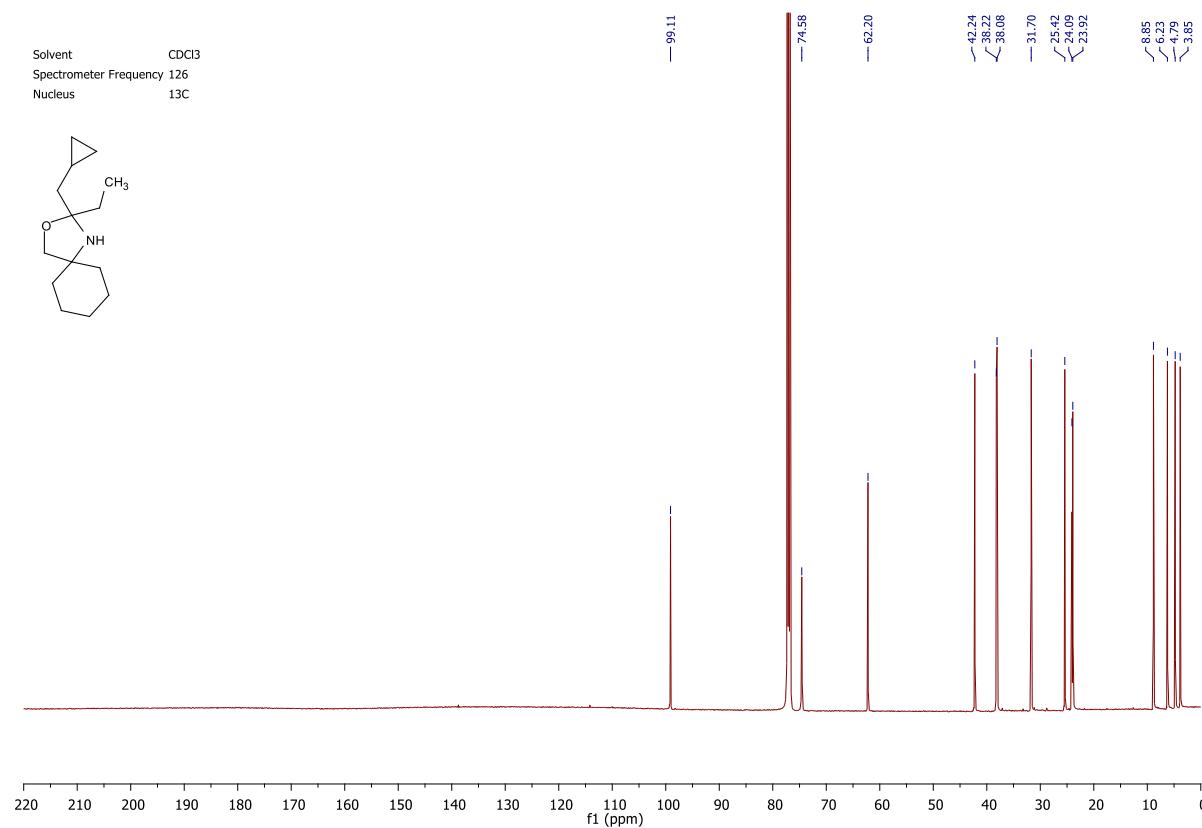
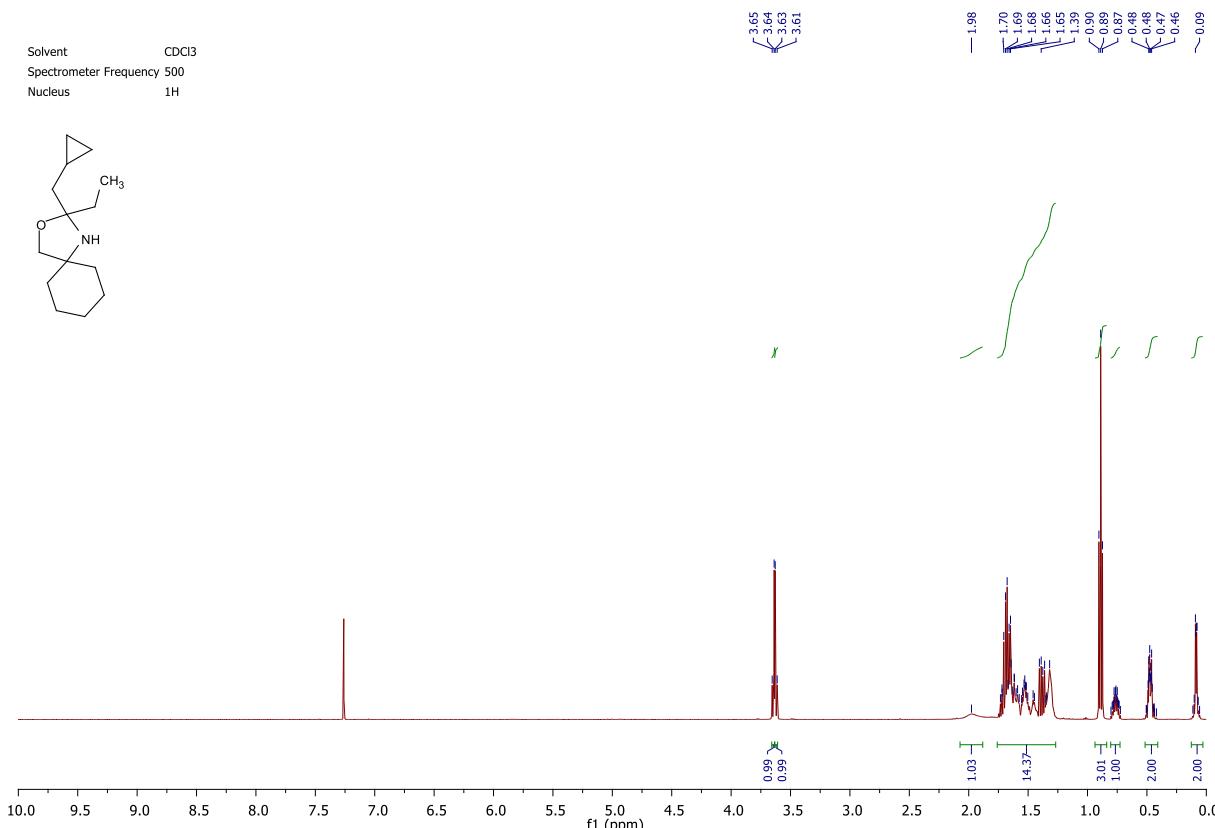
2-Ethyl-2-phenethyl-3-oxa-1-azaspiro[4.5]decane (258a)



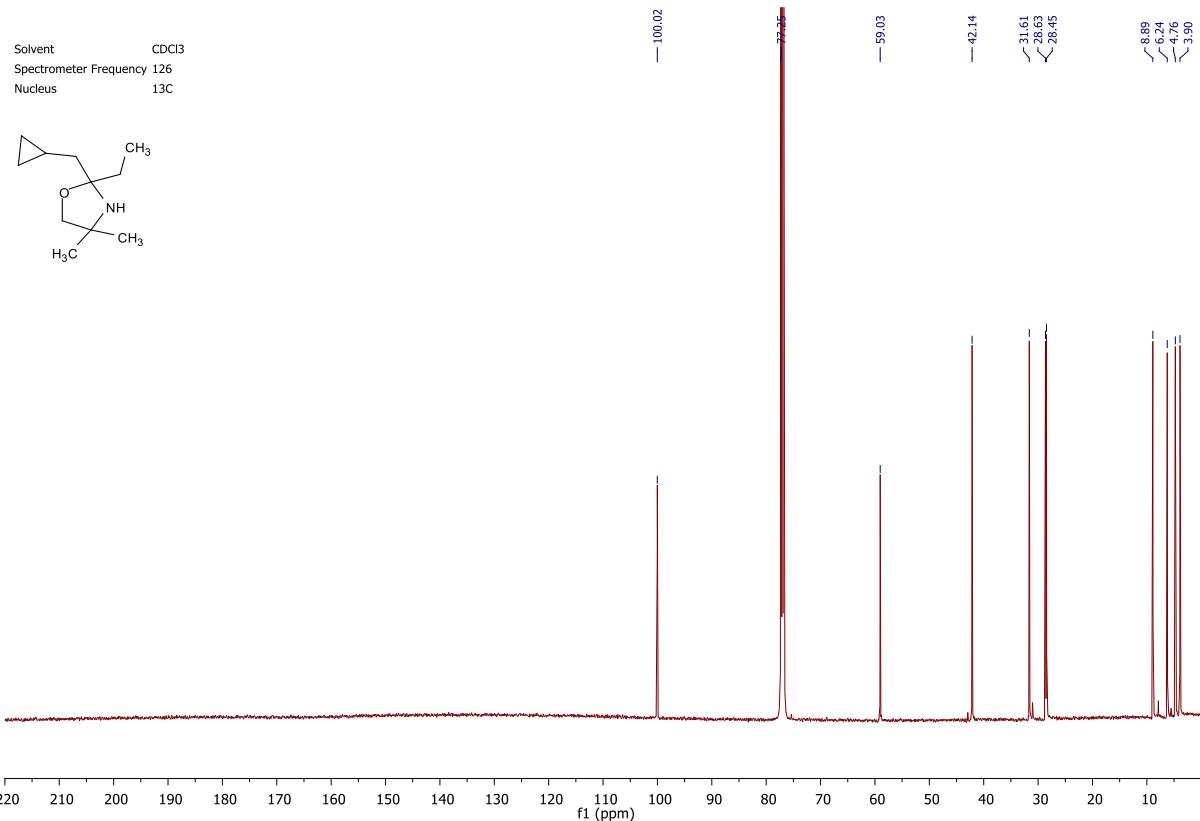
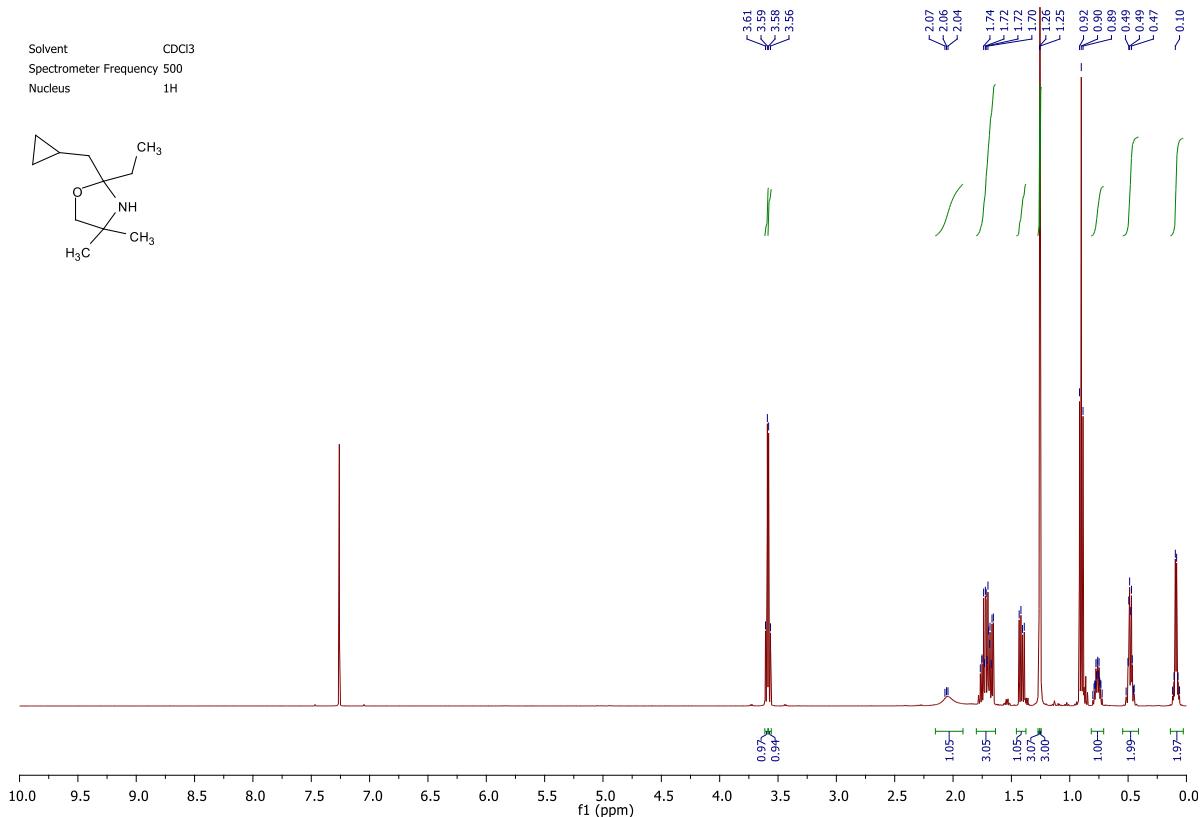
2-Ethyl-4,4-dimethyl-2-phenethyloxazolidine (258b)



2-(Cyclopropylmethyl)-2-ethyl-3-oxa-1-azaspiro[4.5]decane (263)

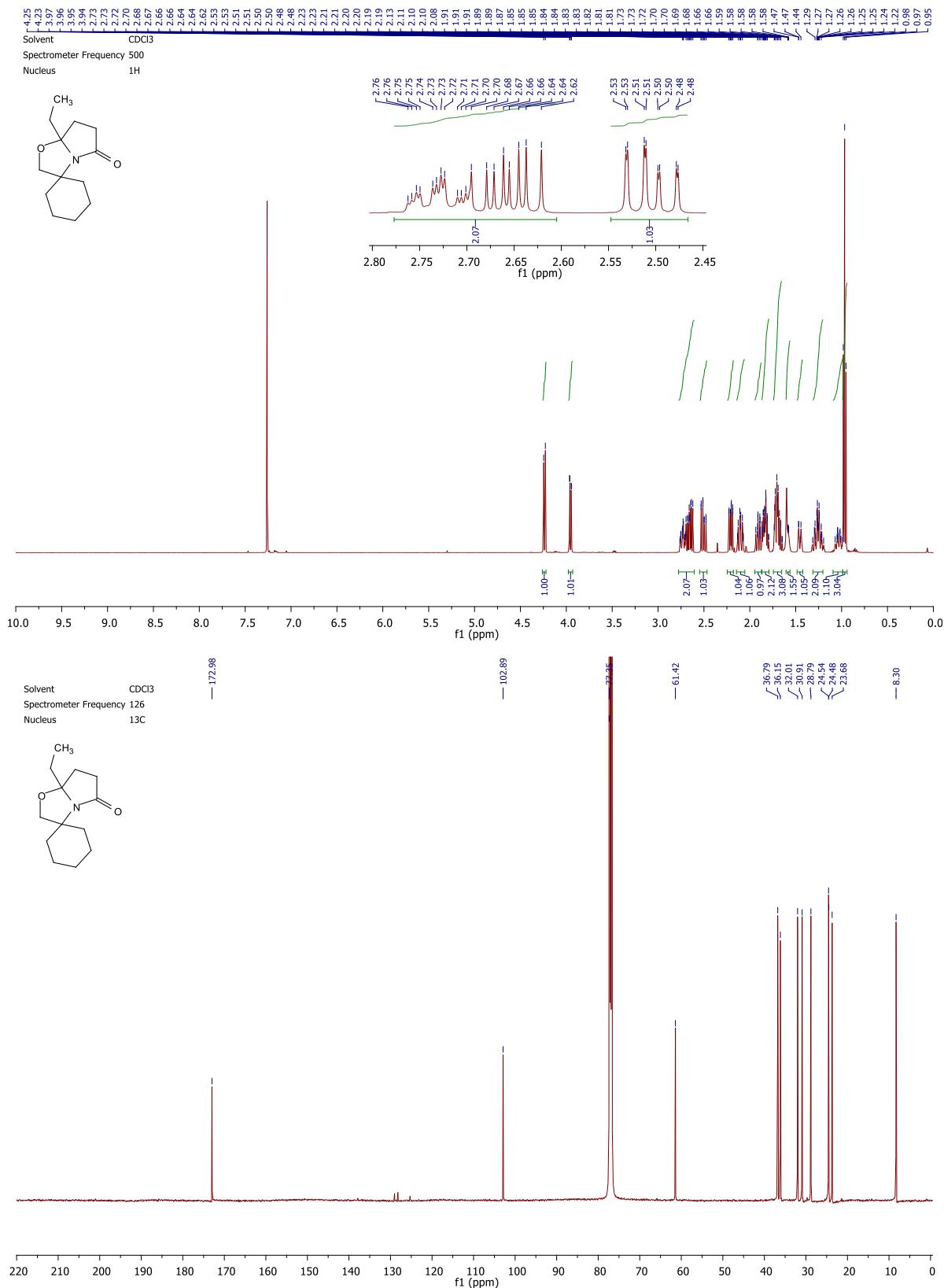


2-(Cyclopropylmethyl)-2-ethyl-4,4-dimethyloxazolidine (267)

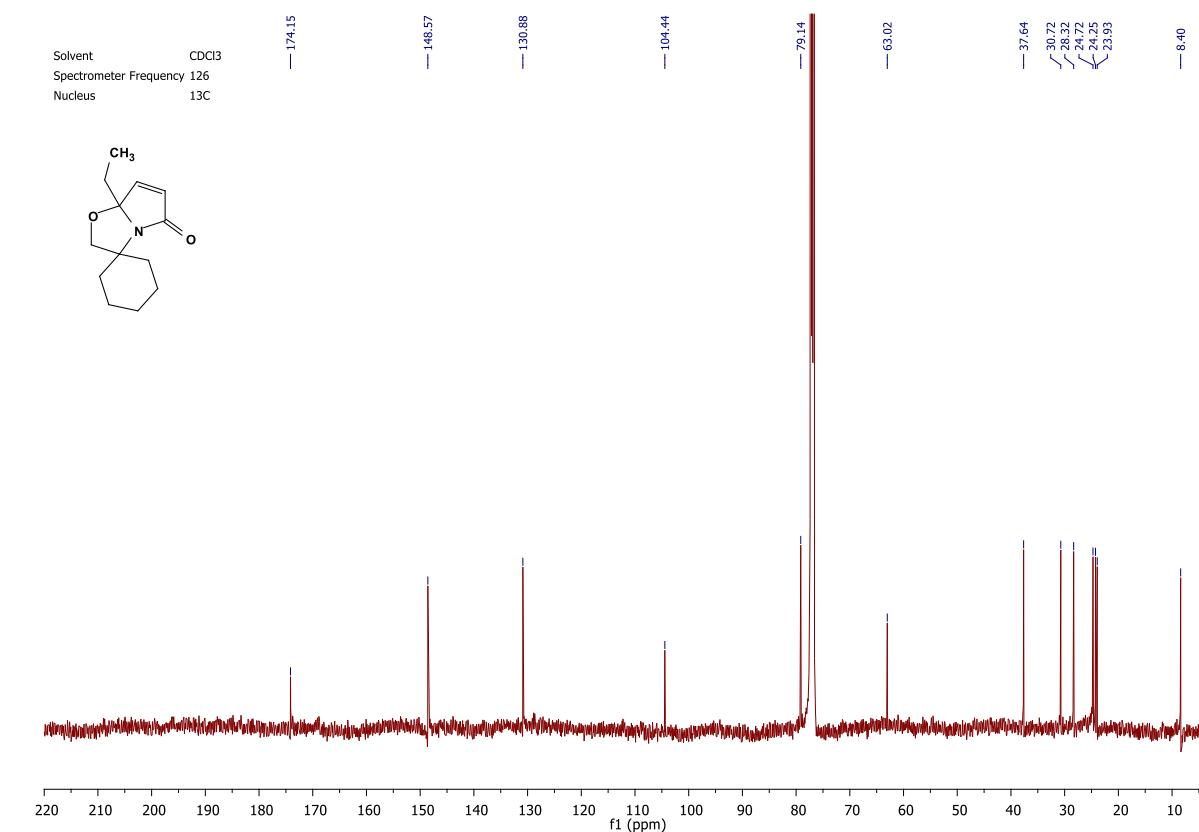
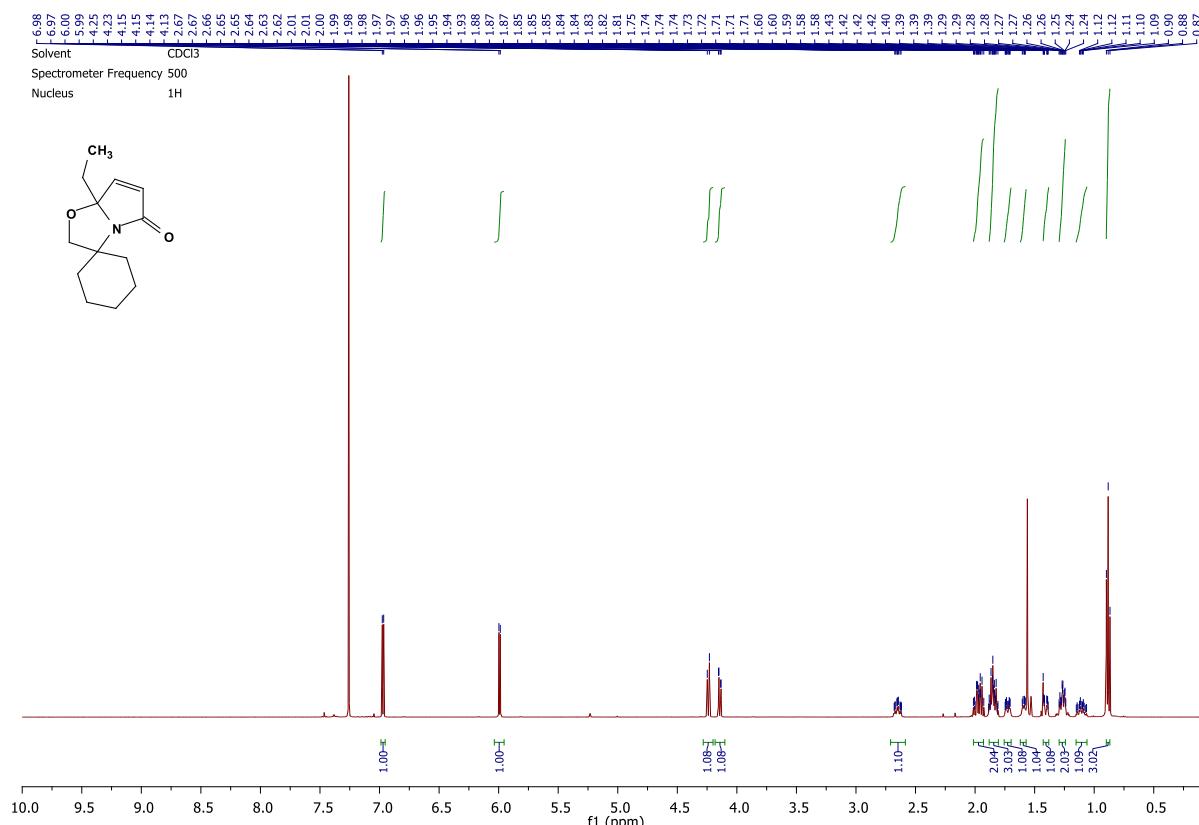


7.2 Palladium(II)-catalysed carbonylation: Carbonylation products

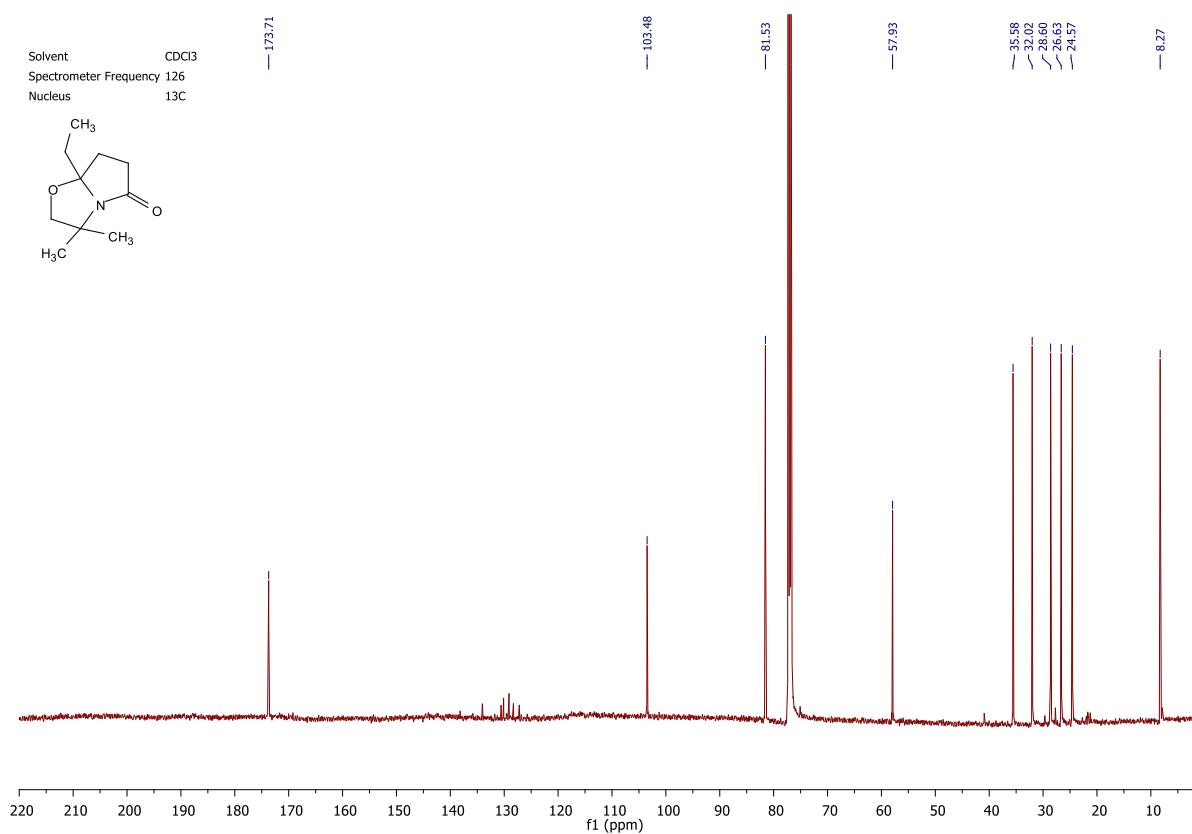
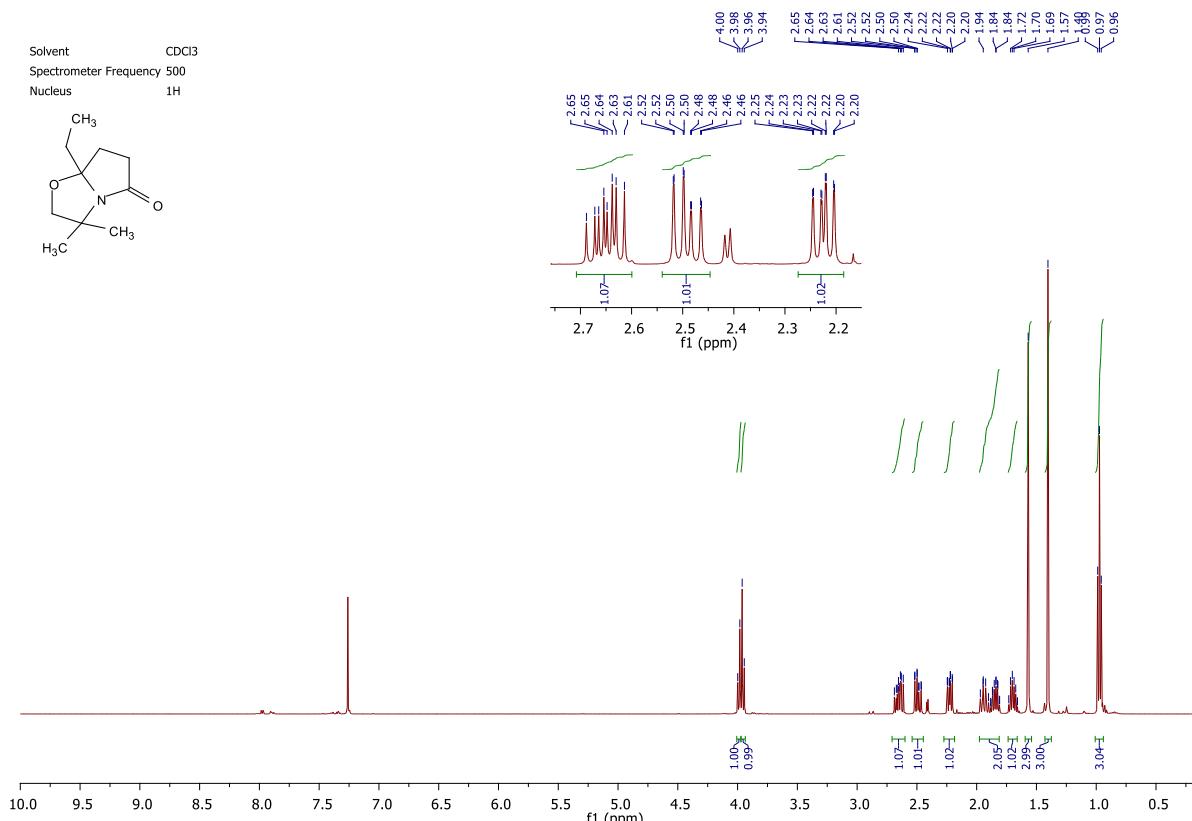
7a'-Ethylidihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(*6'*H)-one (185)

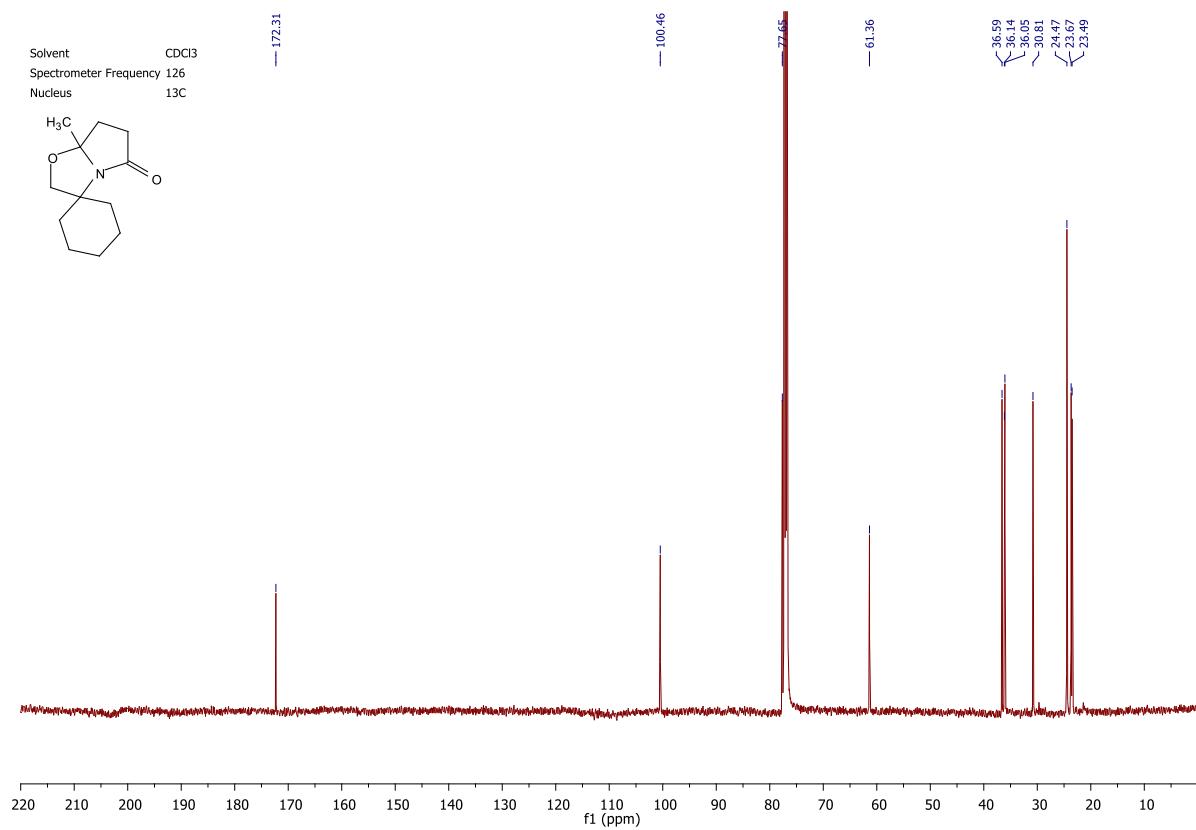
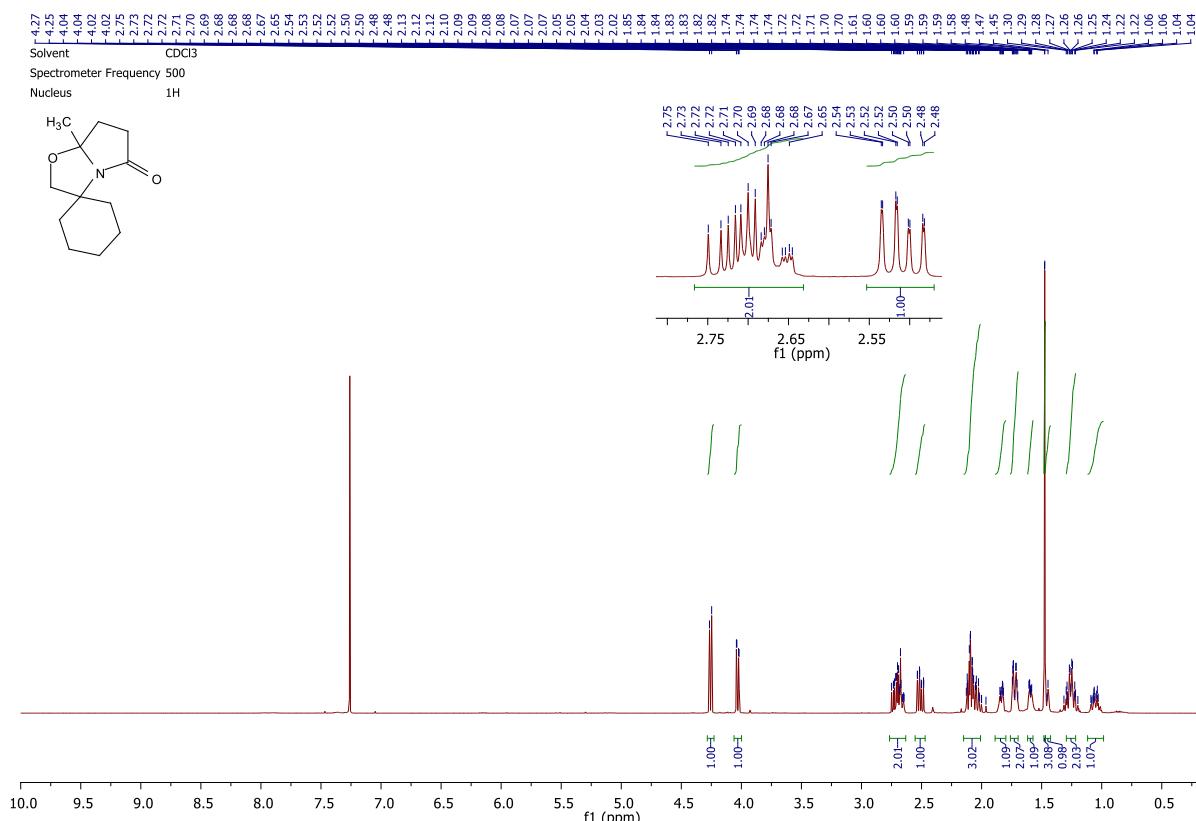


7a'-Ethyl-2' H -spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(7a' H)-one (186)

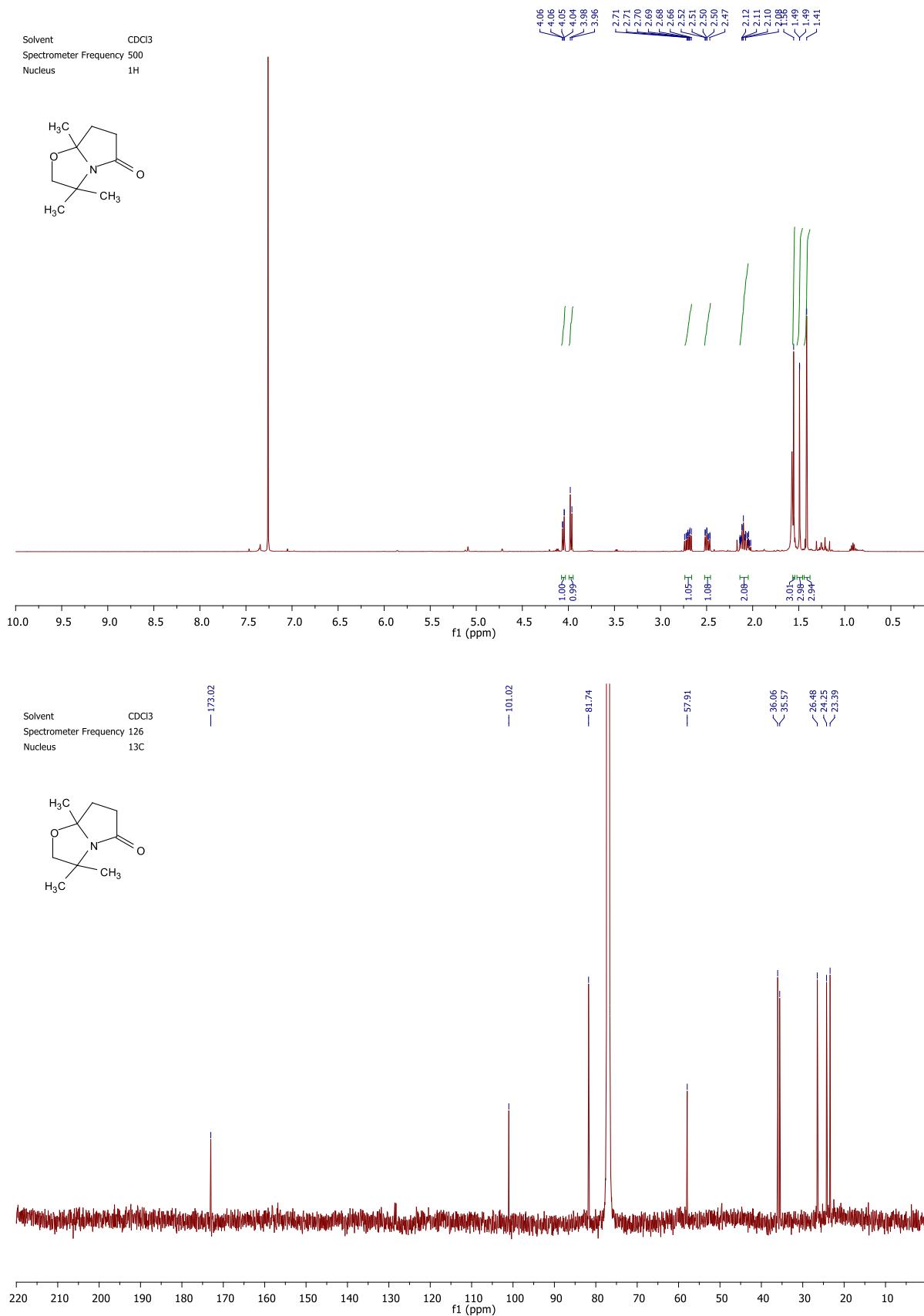


7a-Ethyl-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (192)

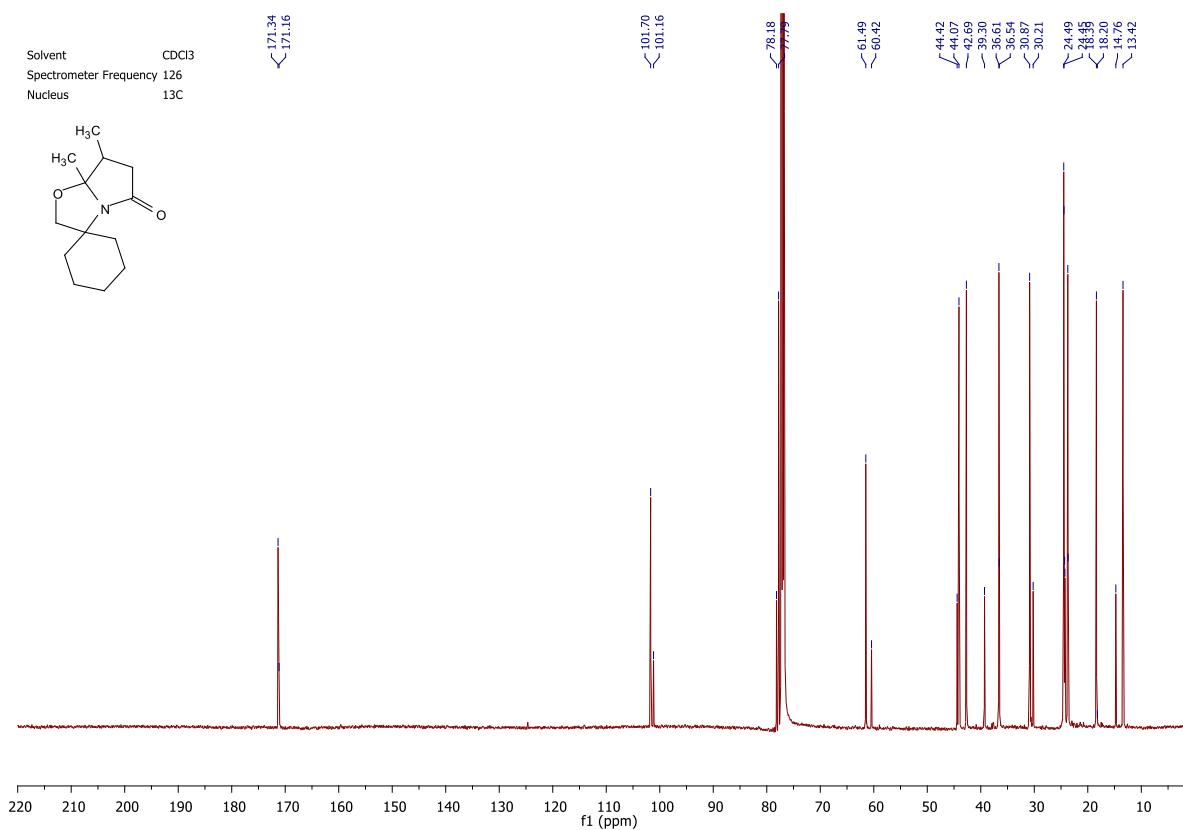
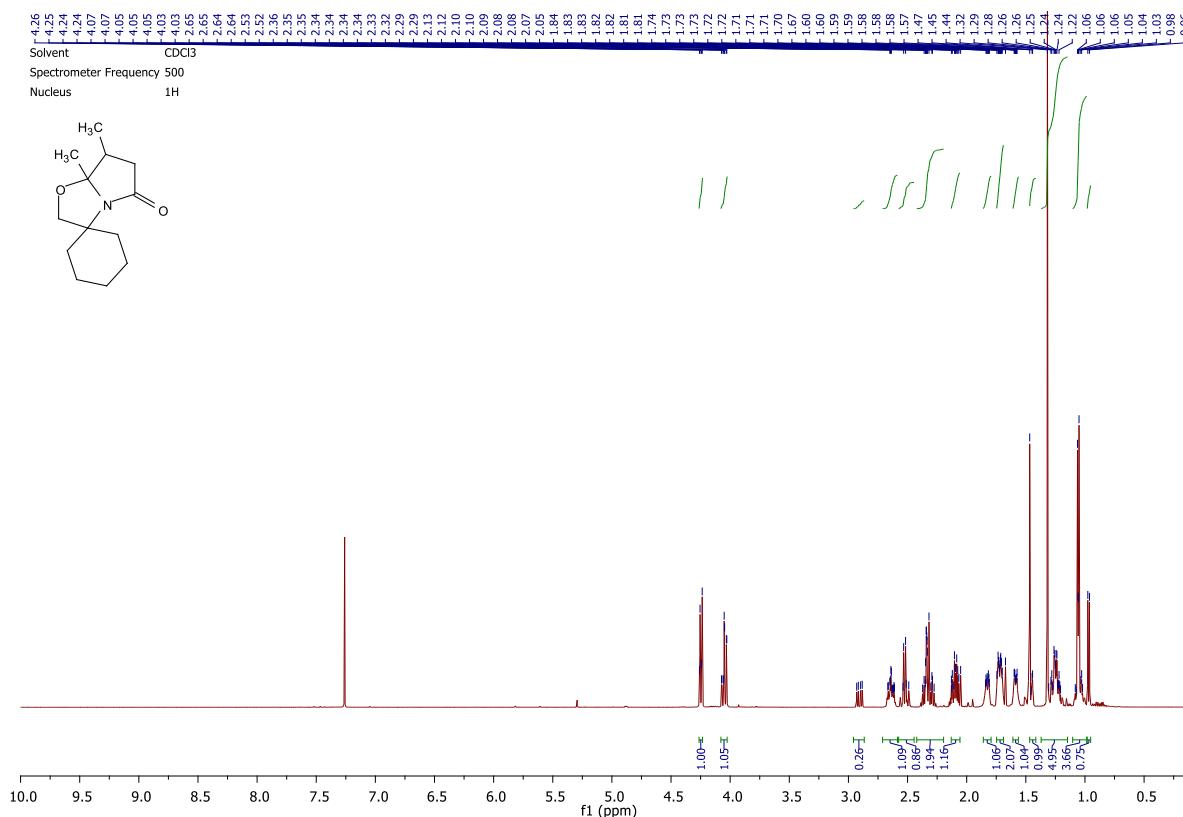


7a'-Methyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (204a)


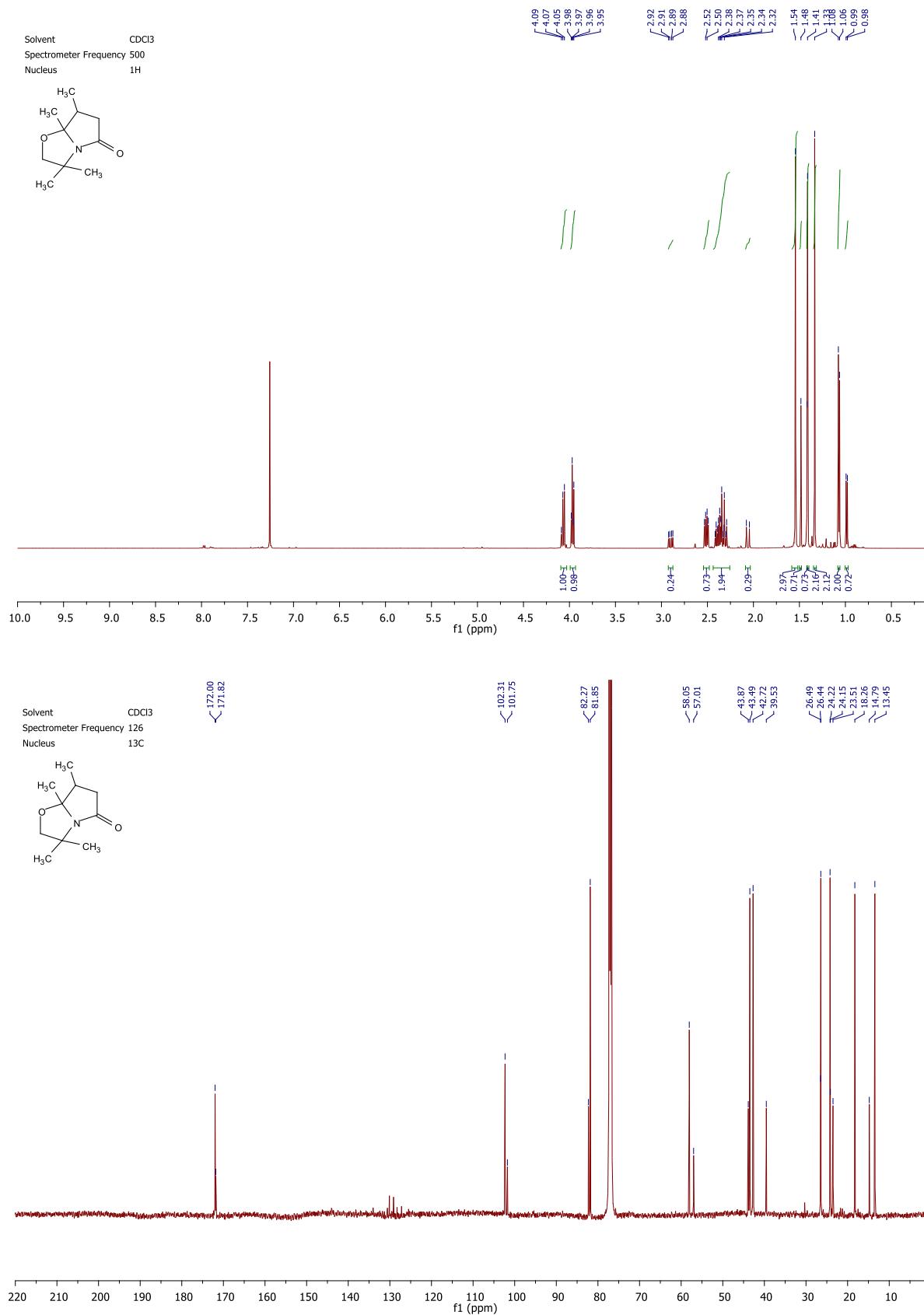
3,3,7a-Trimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (204b)



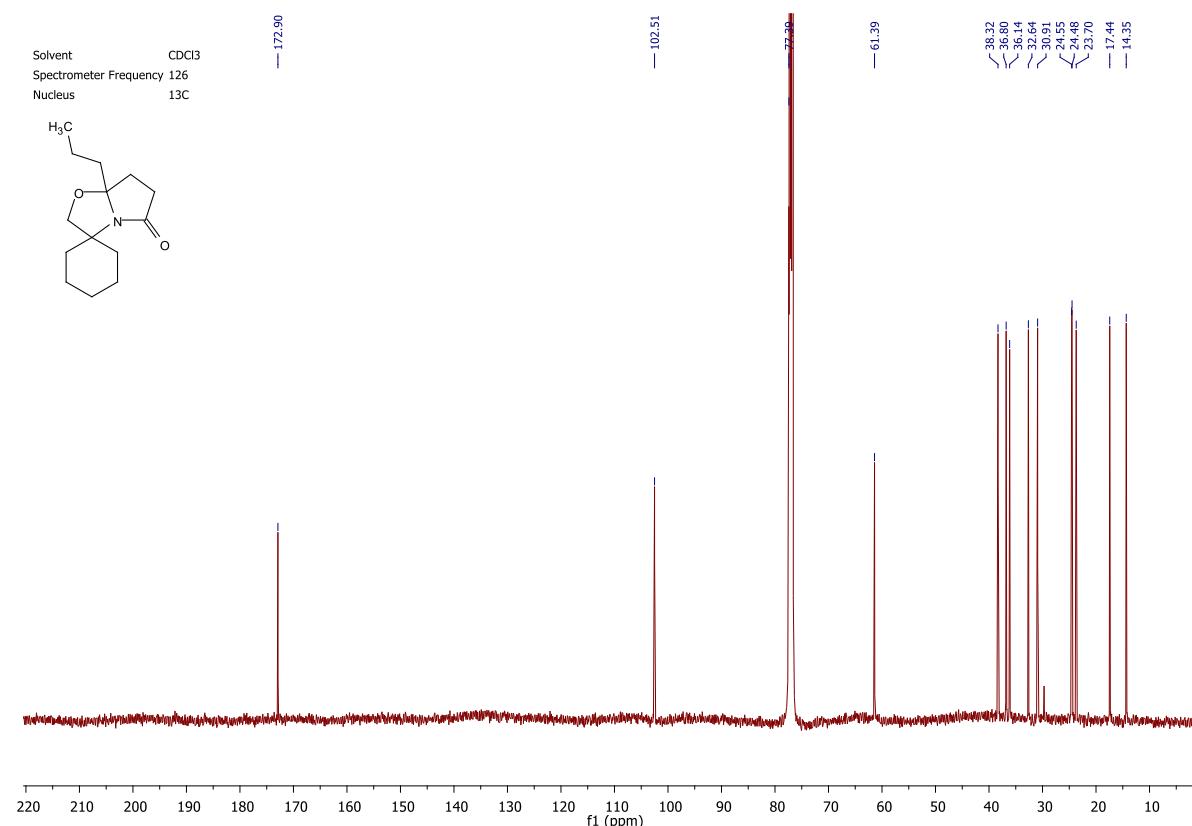
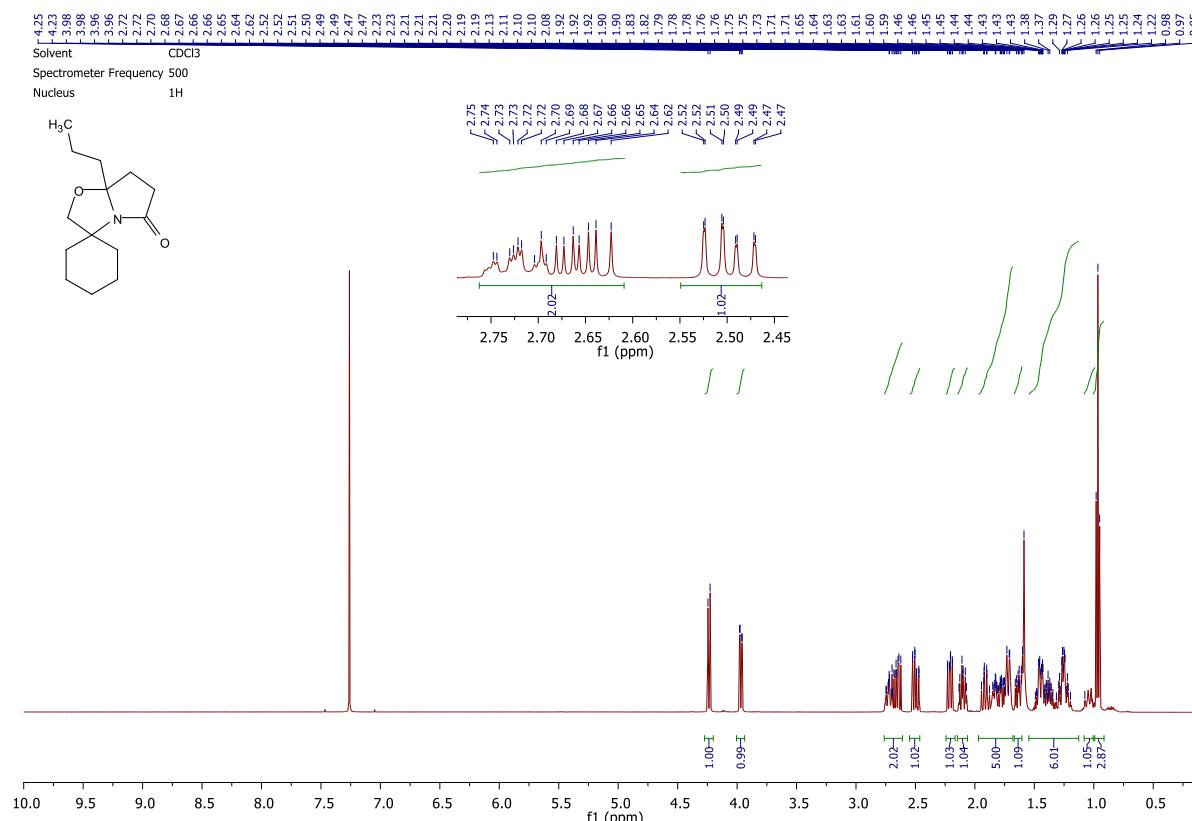
7',7a'-Dimethyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (205a)

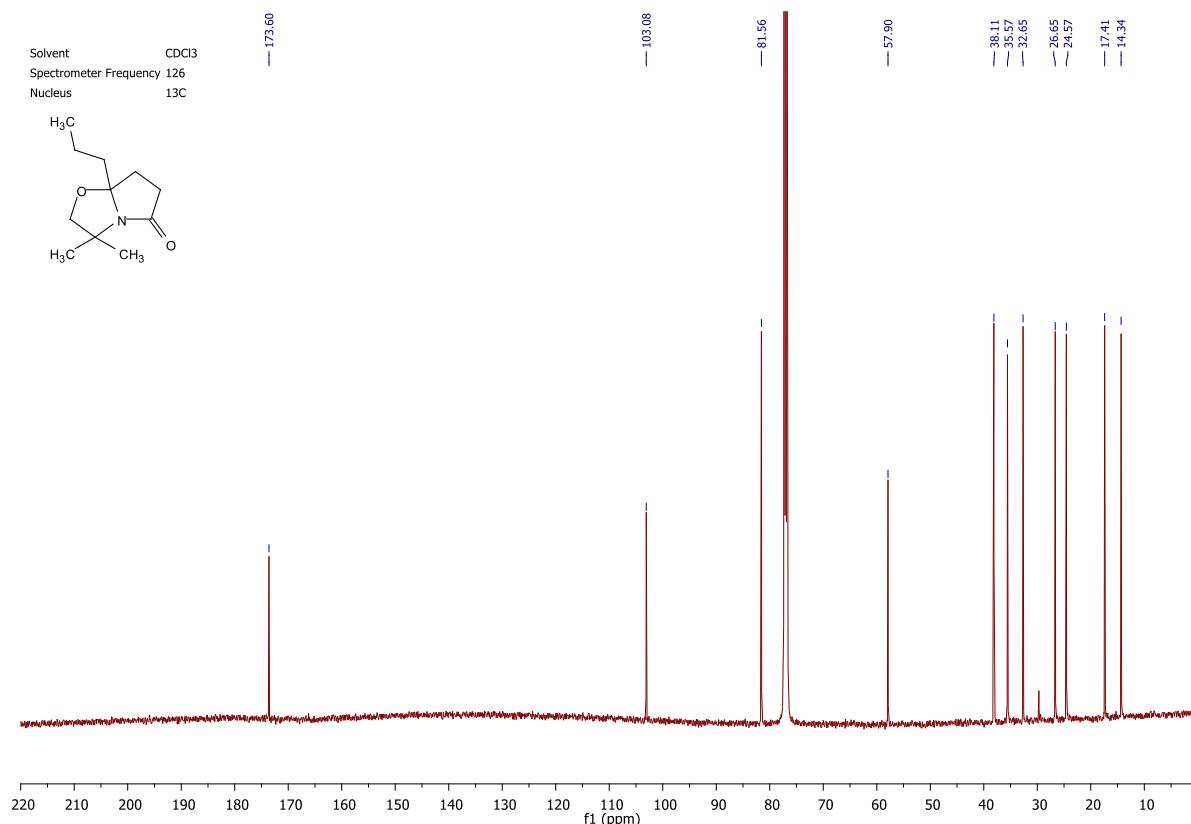
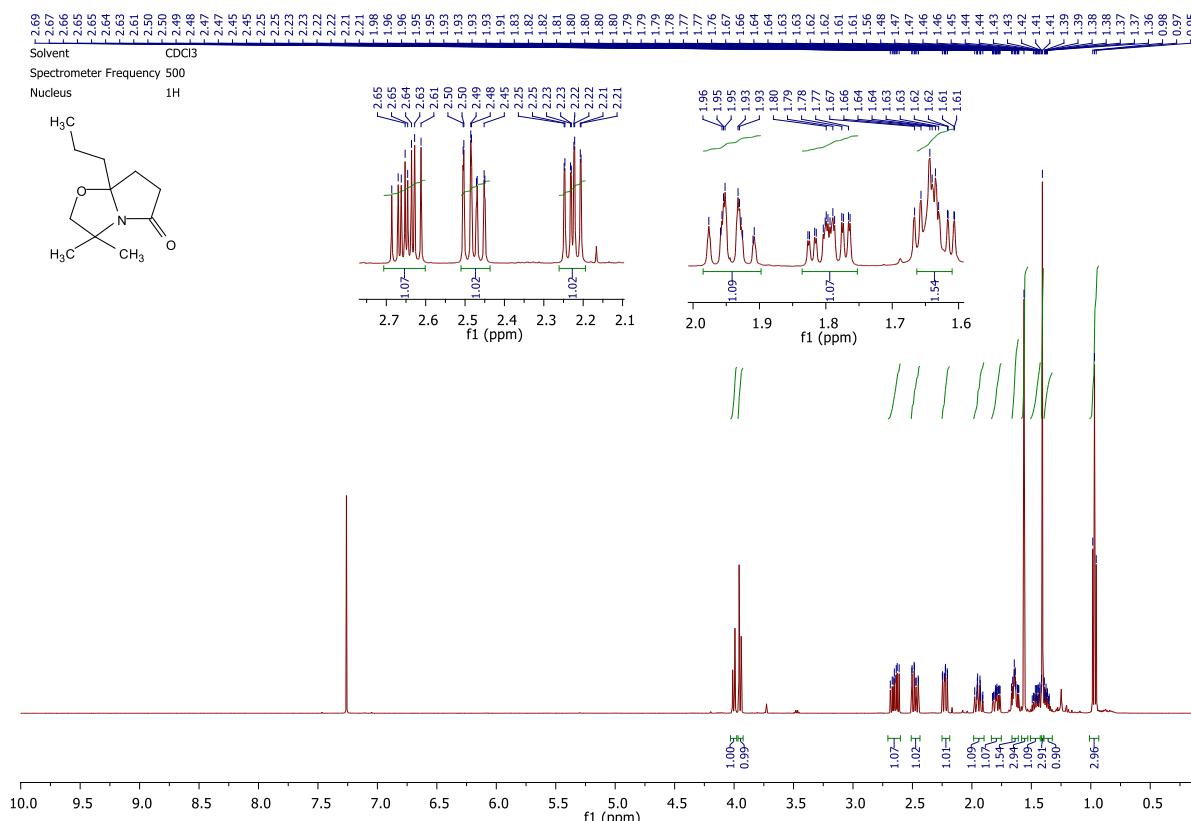


3,3,7,7a-Tetramethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (205b)

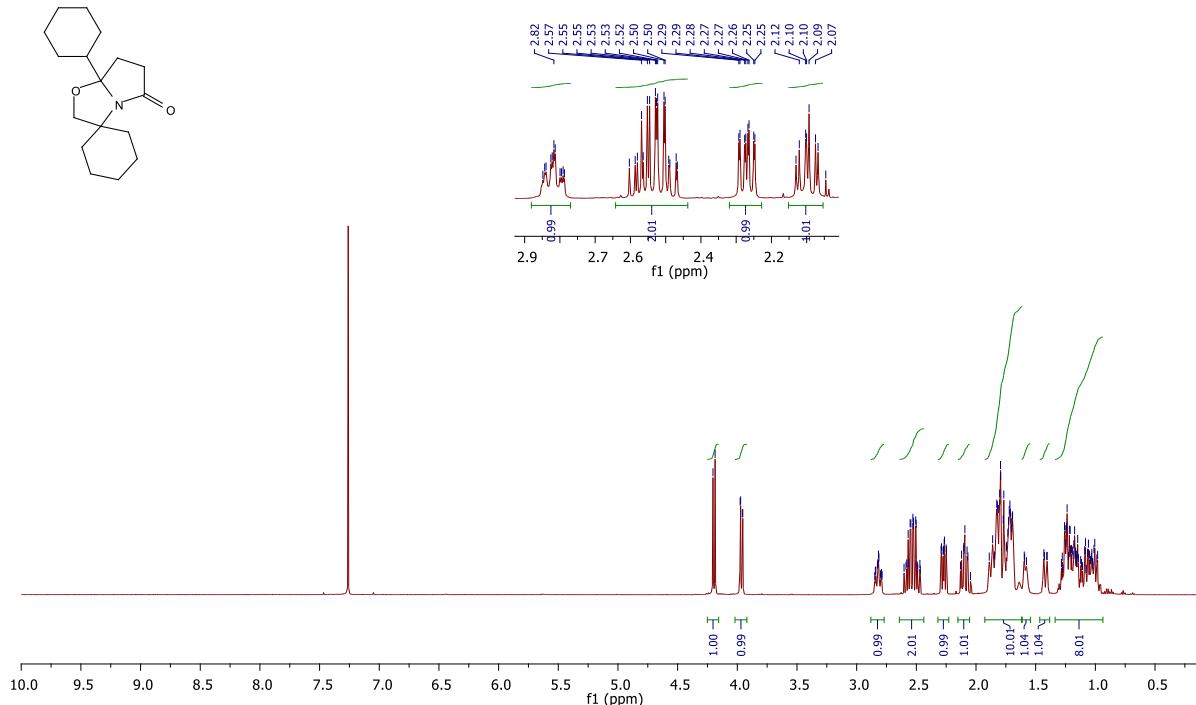
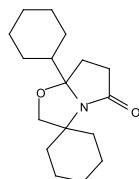


7a'-Propyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (206a)

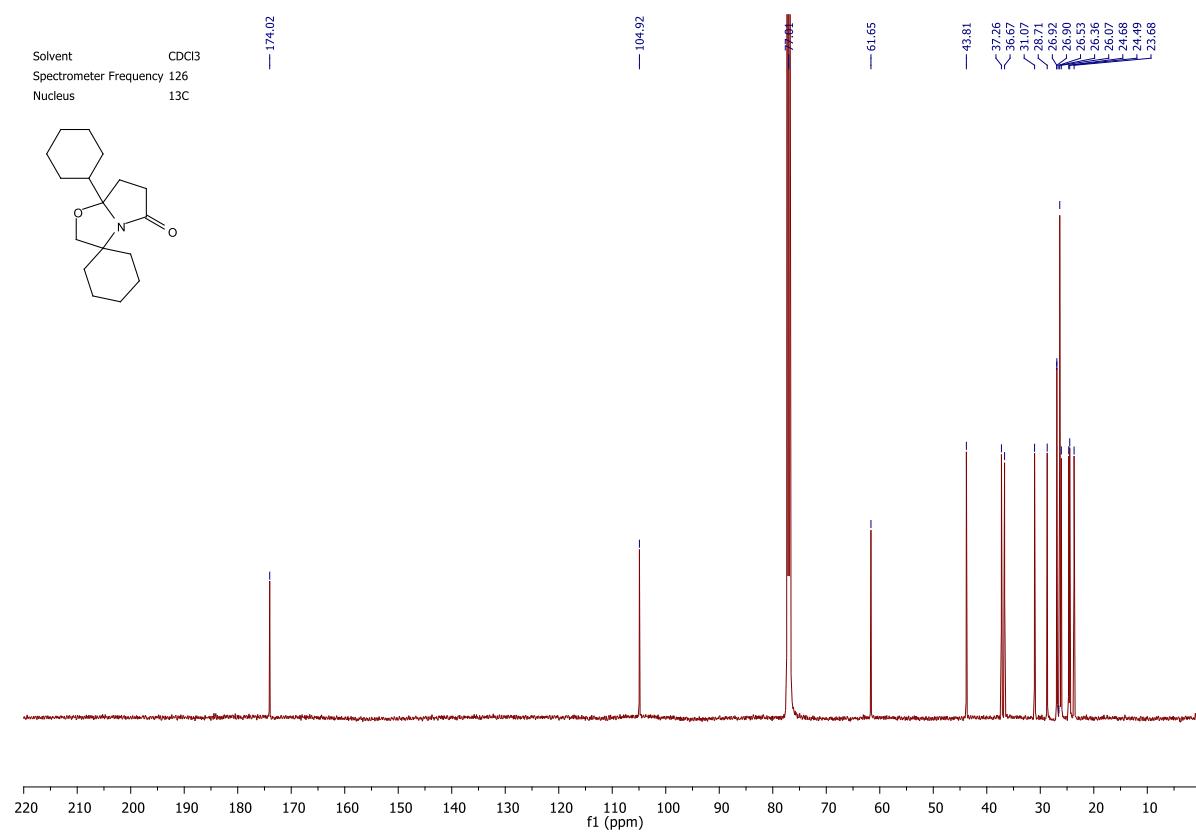
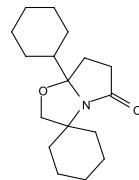


3,3,7a-Trimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (206b)


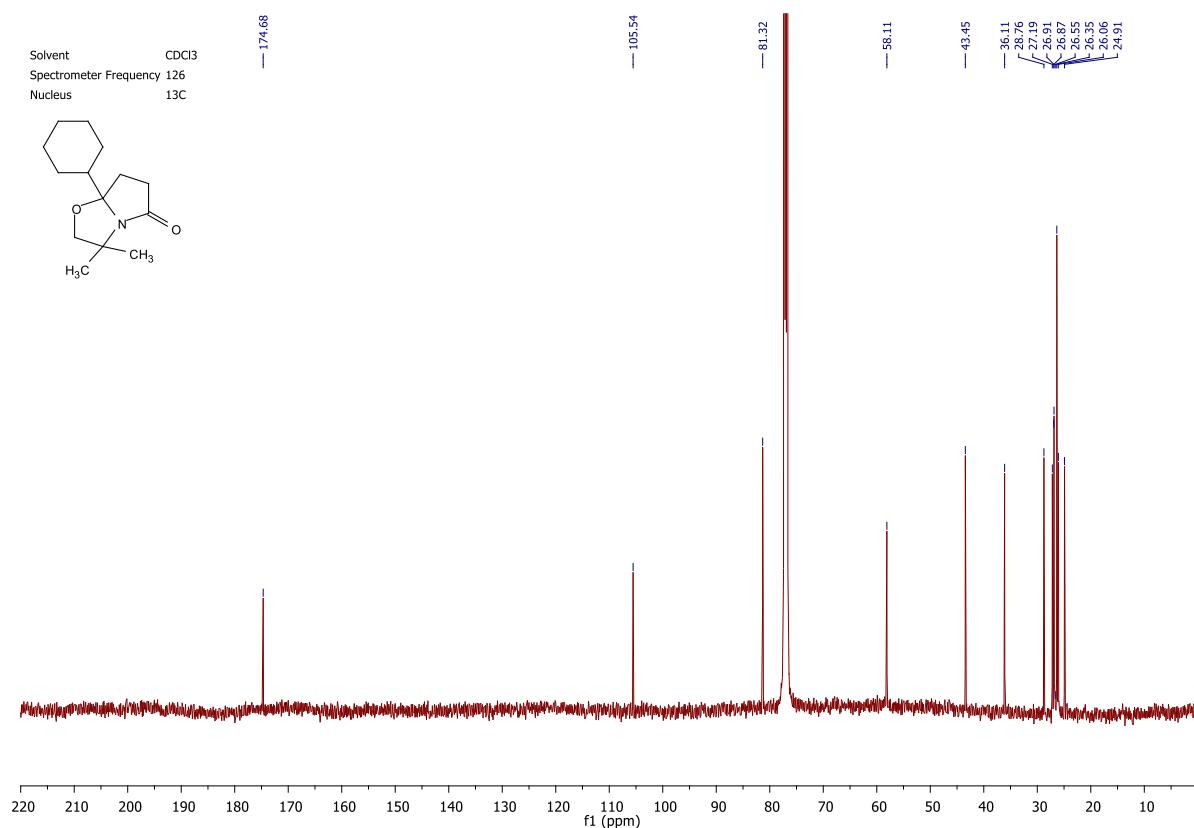
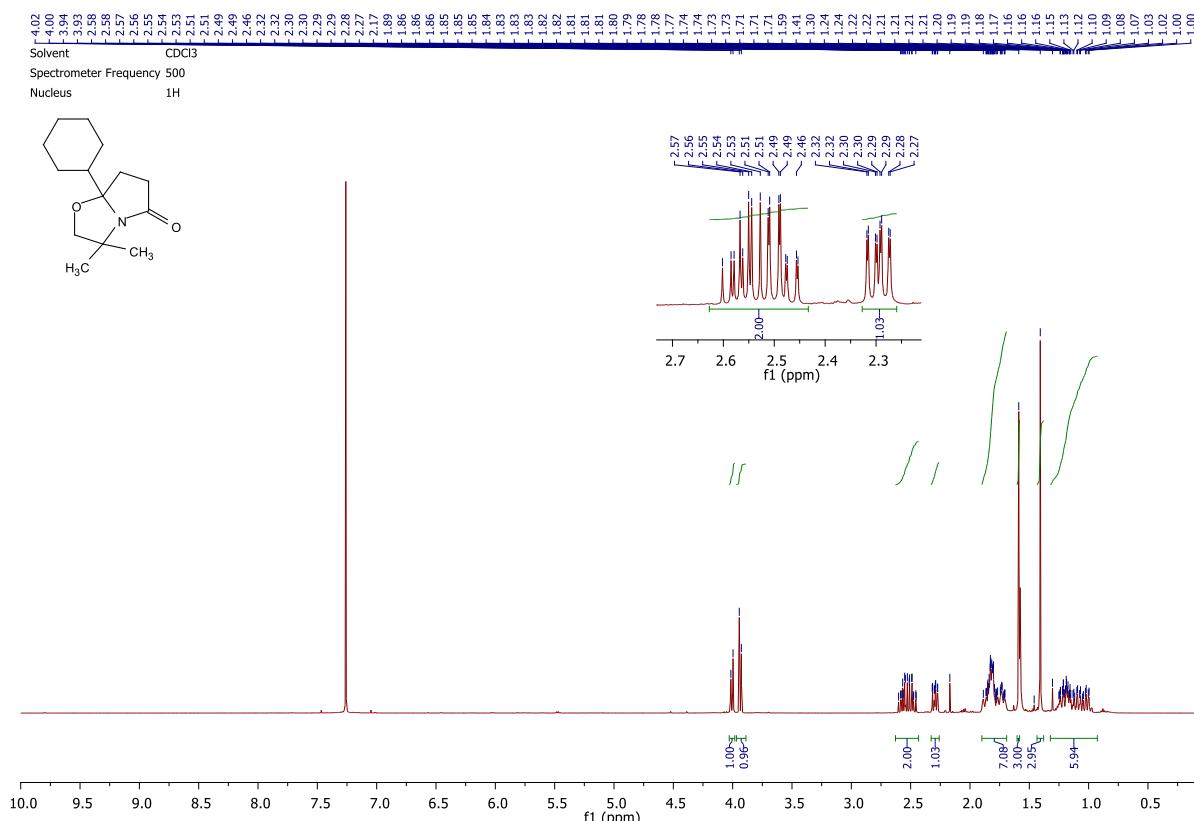
7a'-Cyclohexyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (207a)



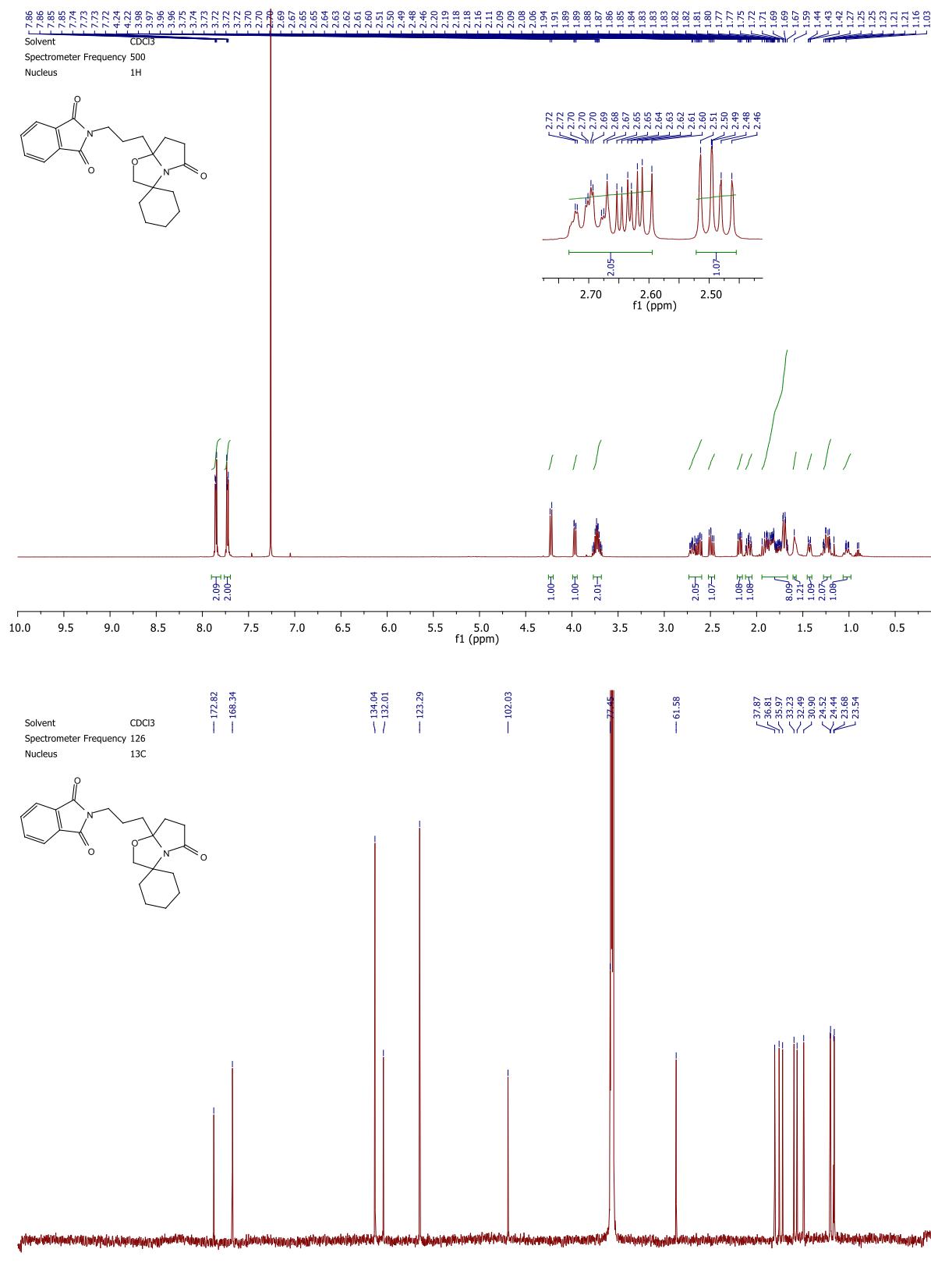
Solvent CDCl₃
 Spectrometer Frequency 126
 Nucleus ¹³C



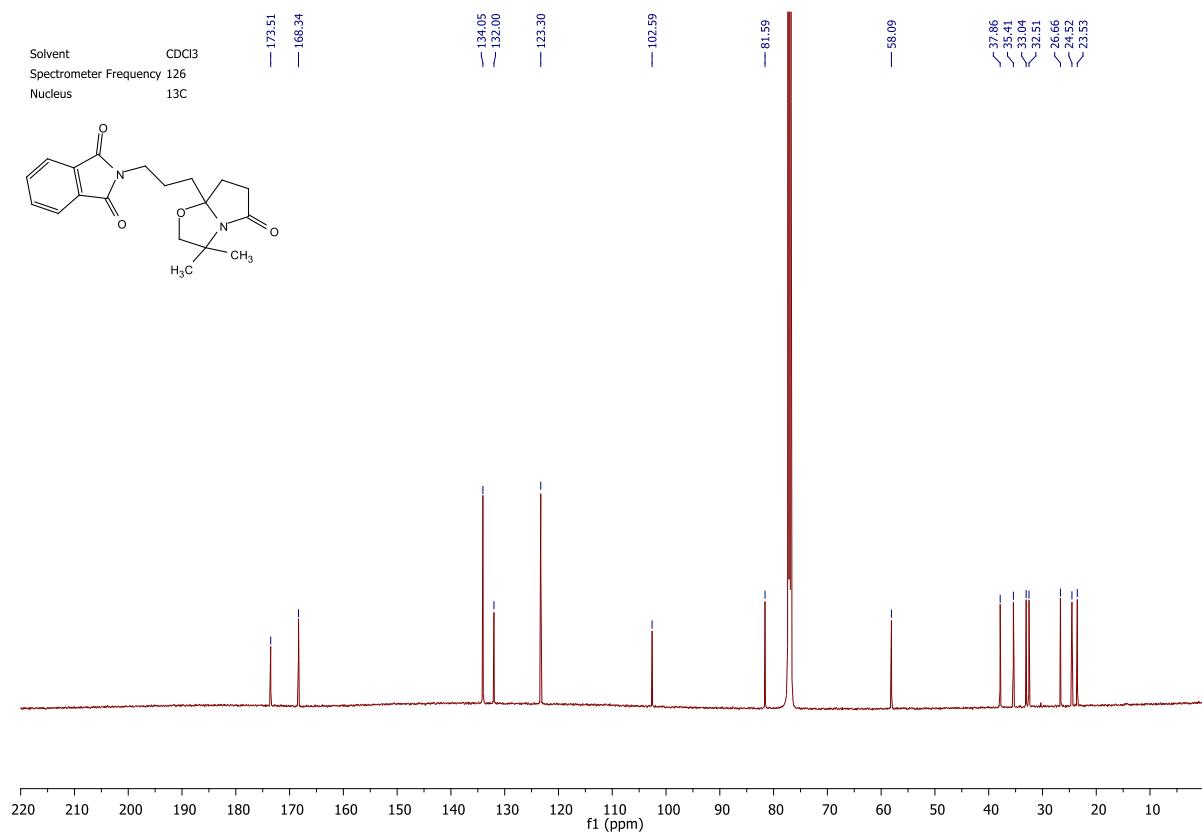
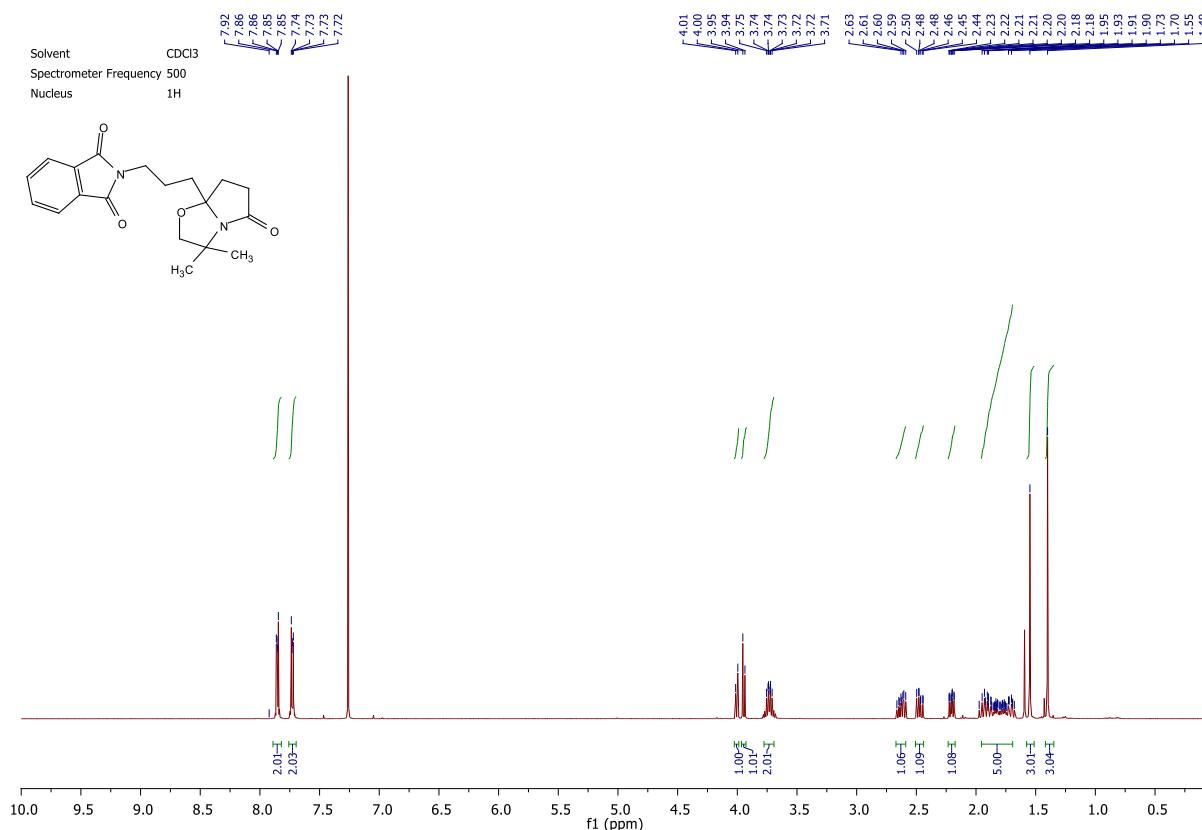
7a-Cyclohexyl-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (207b)



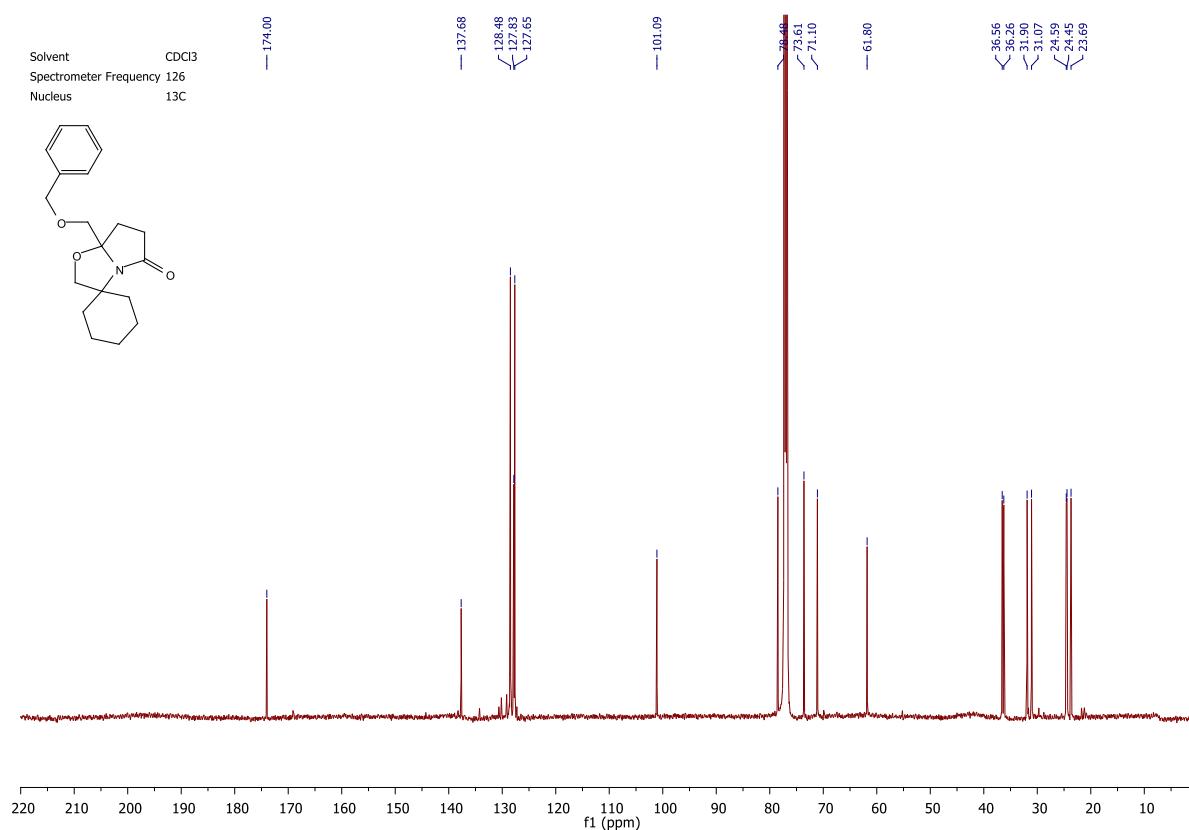
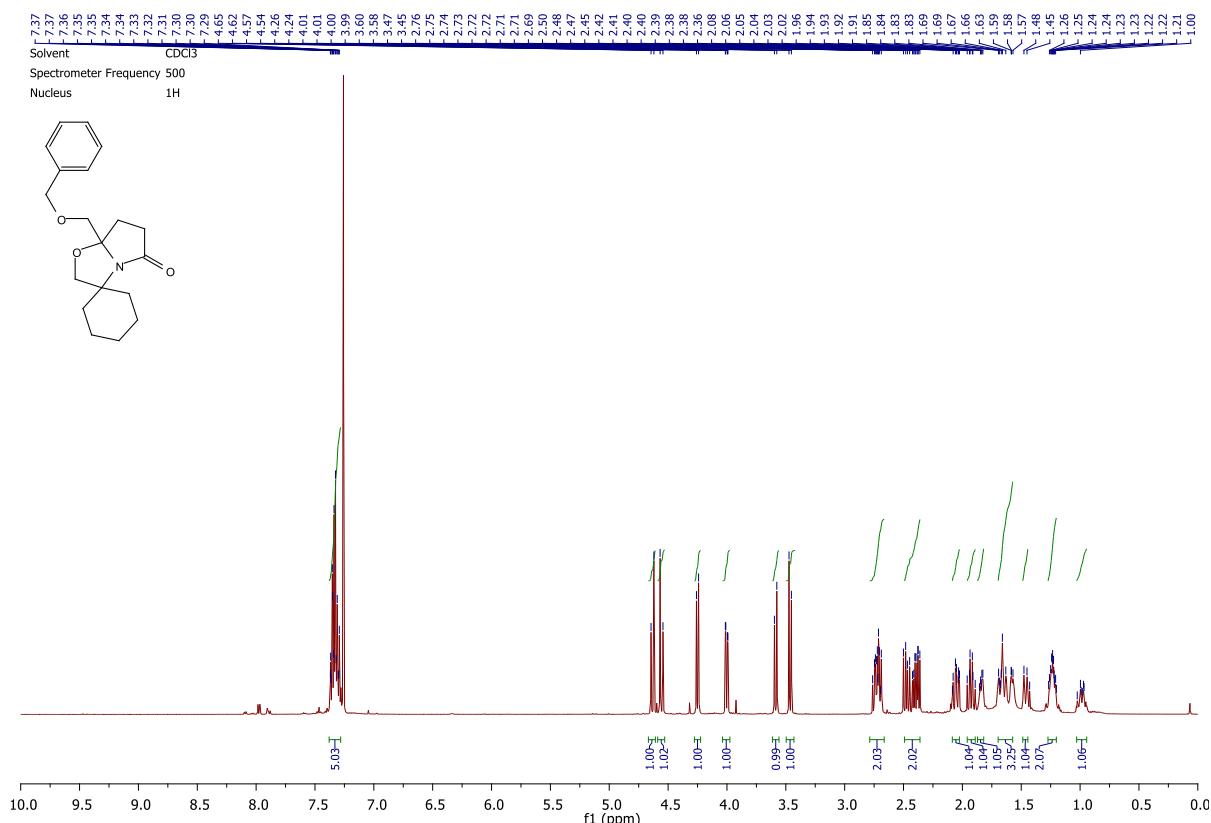
2-(3-(5'-Oxotetrahydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-7*a*-yl)propyl)isoindoline-1,3-dione (238a)



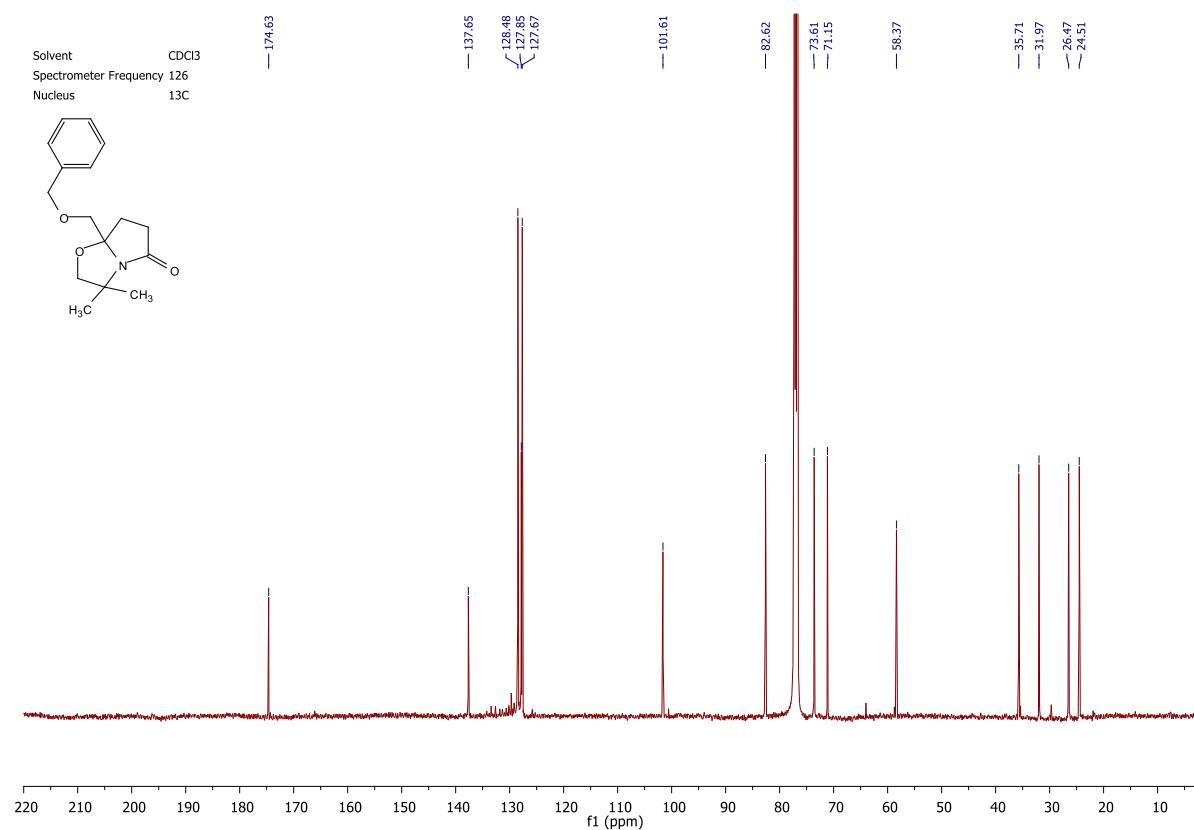
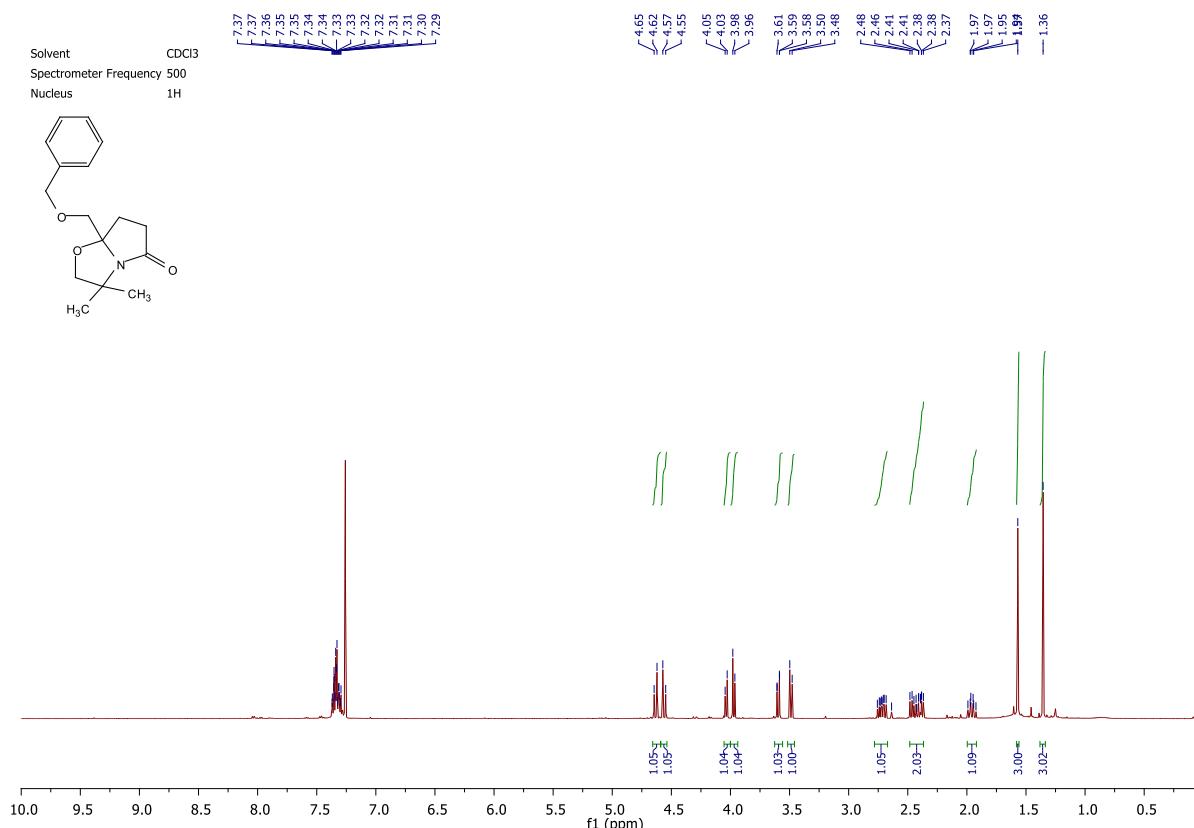
2-(3-(3,3-Dimethyl-5-oxohexahydropyrrolo[2,1-*b*]oxazol-7*a*-yl)propyl)isoindoline-1,3-dione (238b)

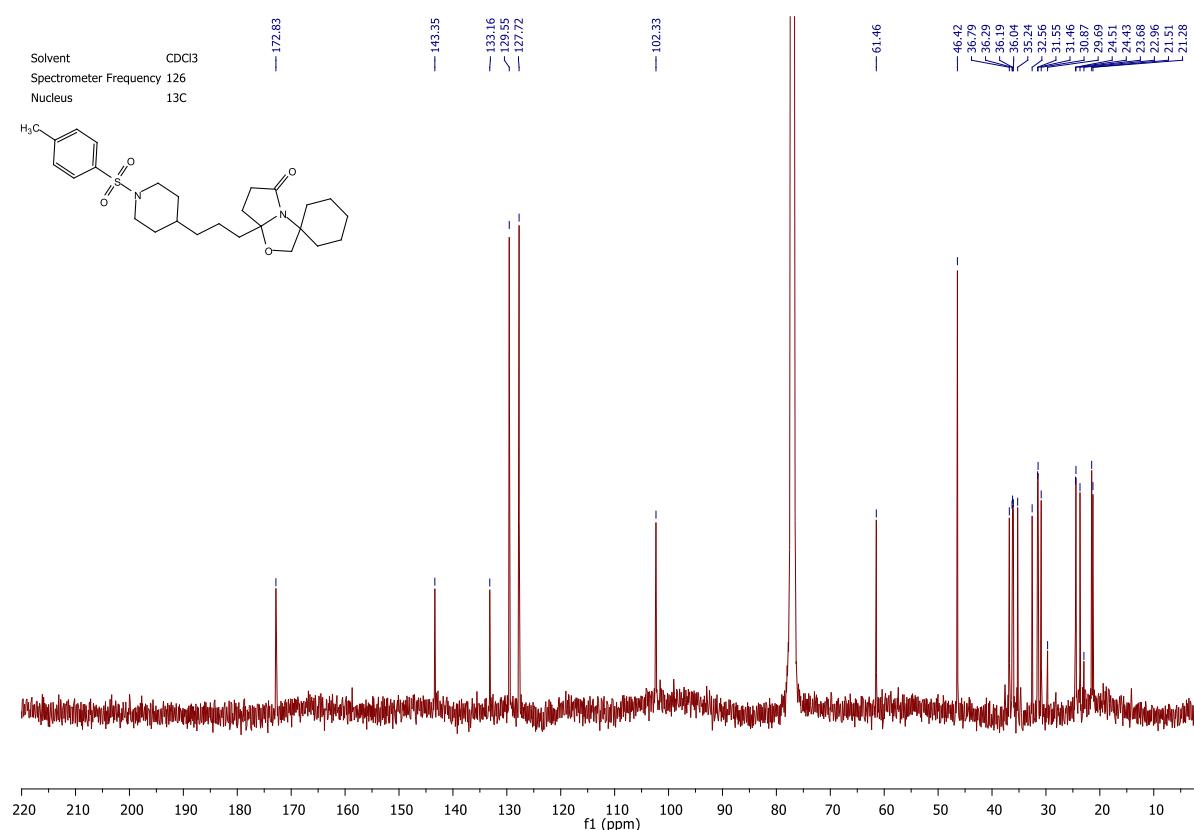
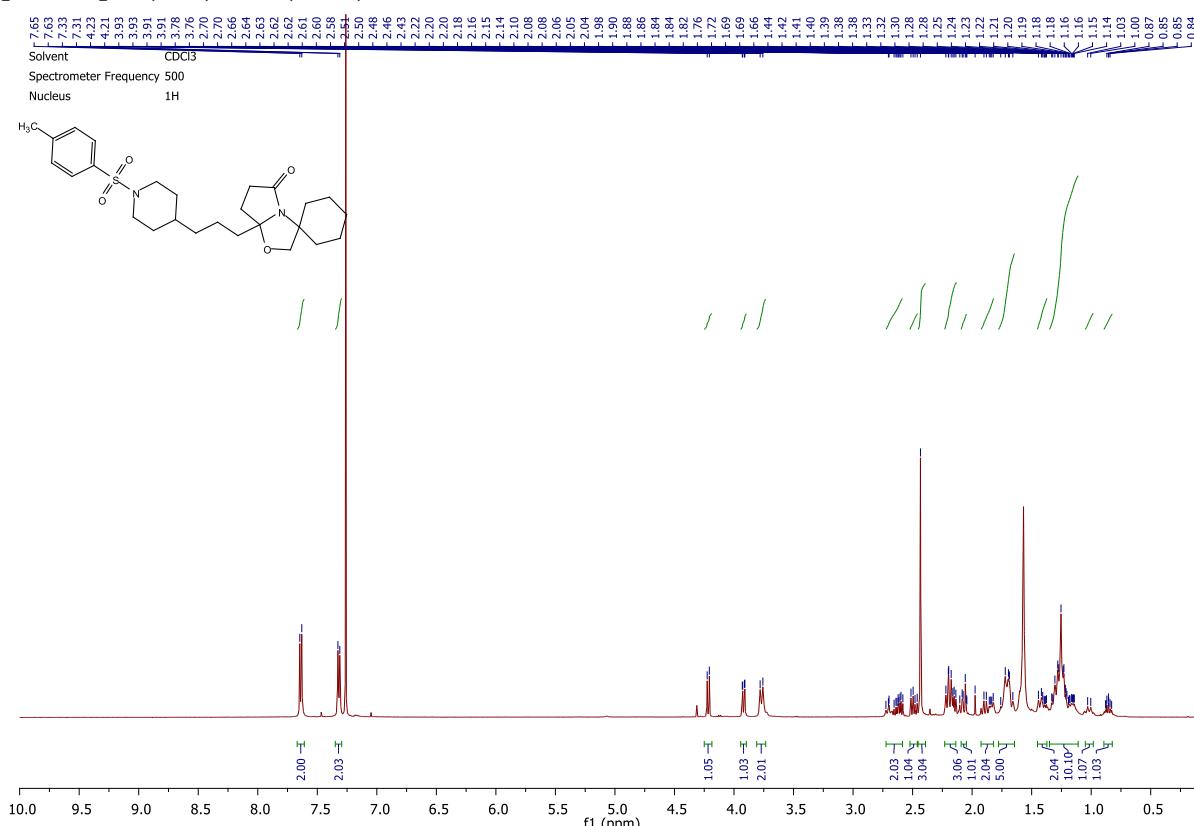


7a'-(BenzylOxy)methyl)dihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (239a)

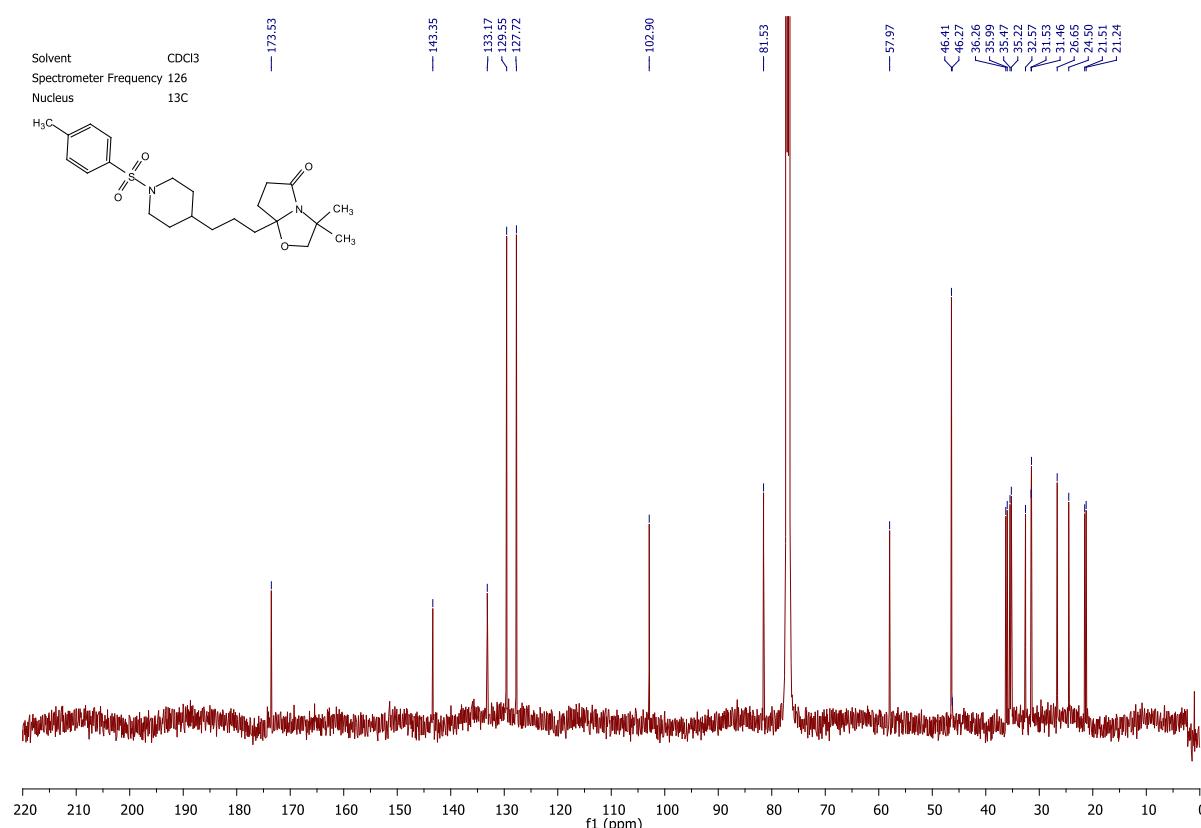
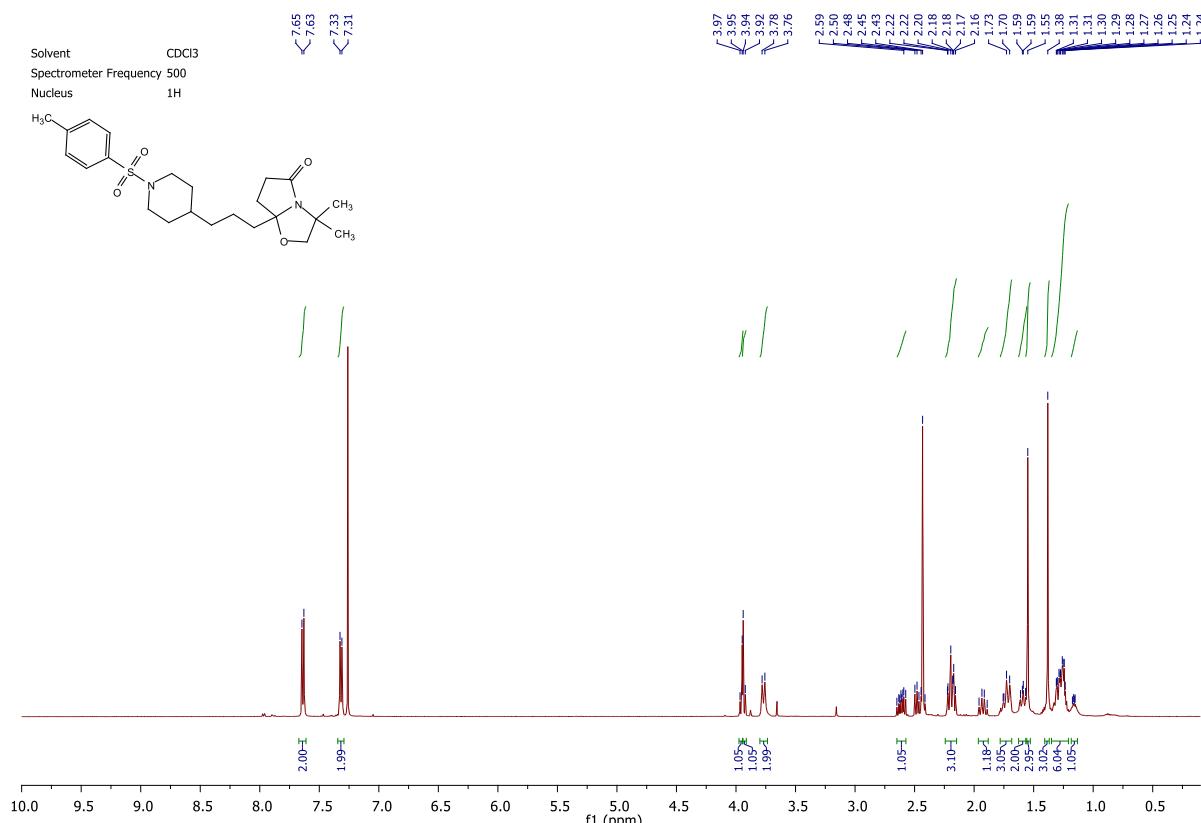


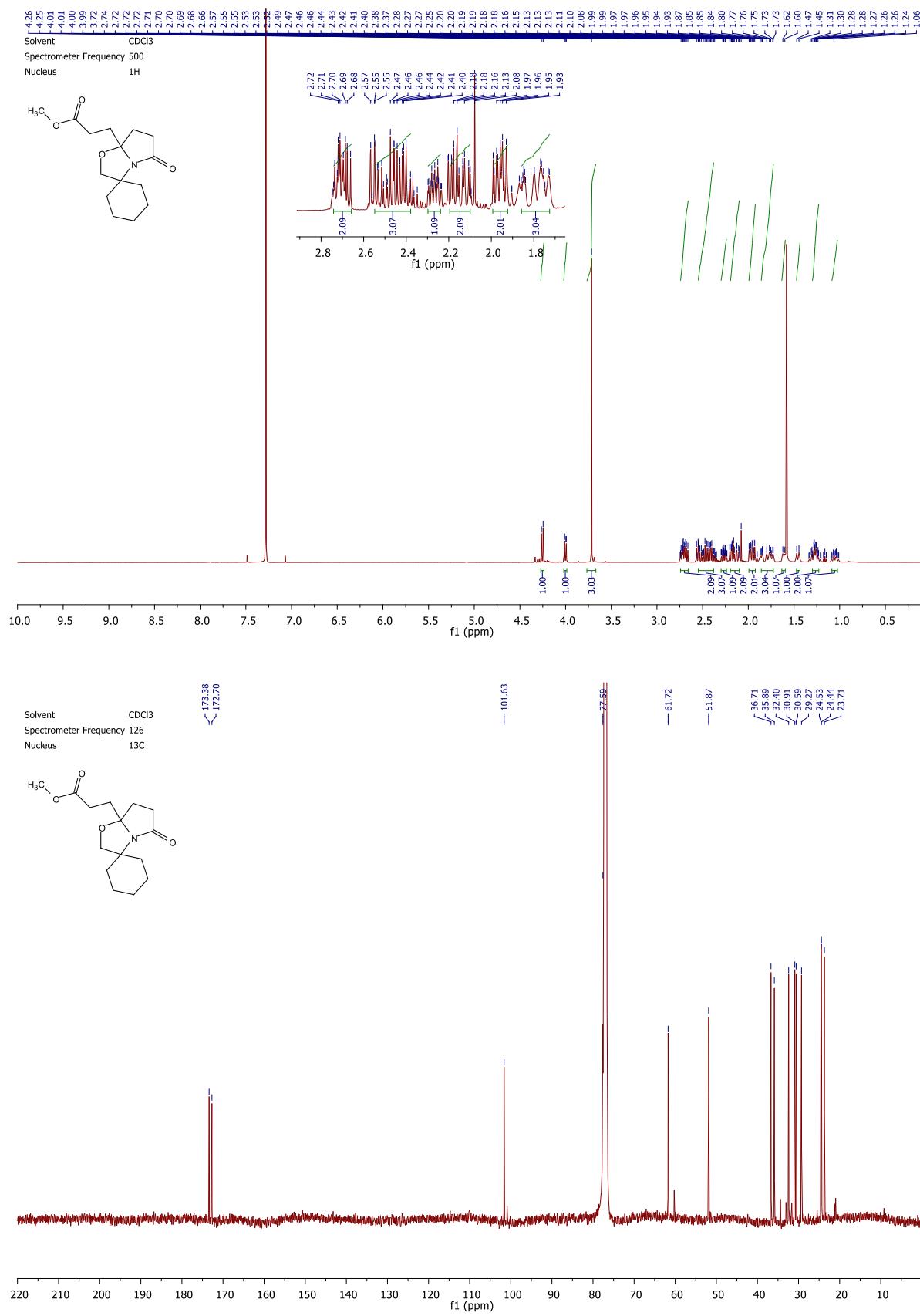
7a-((Benzyl)oxy)methyl)-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (239b)



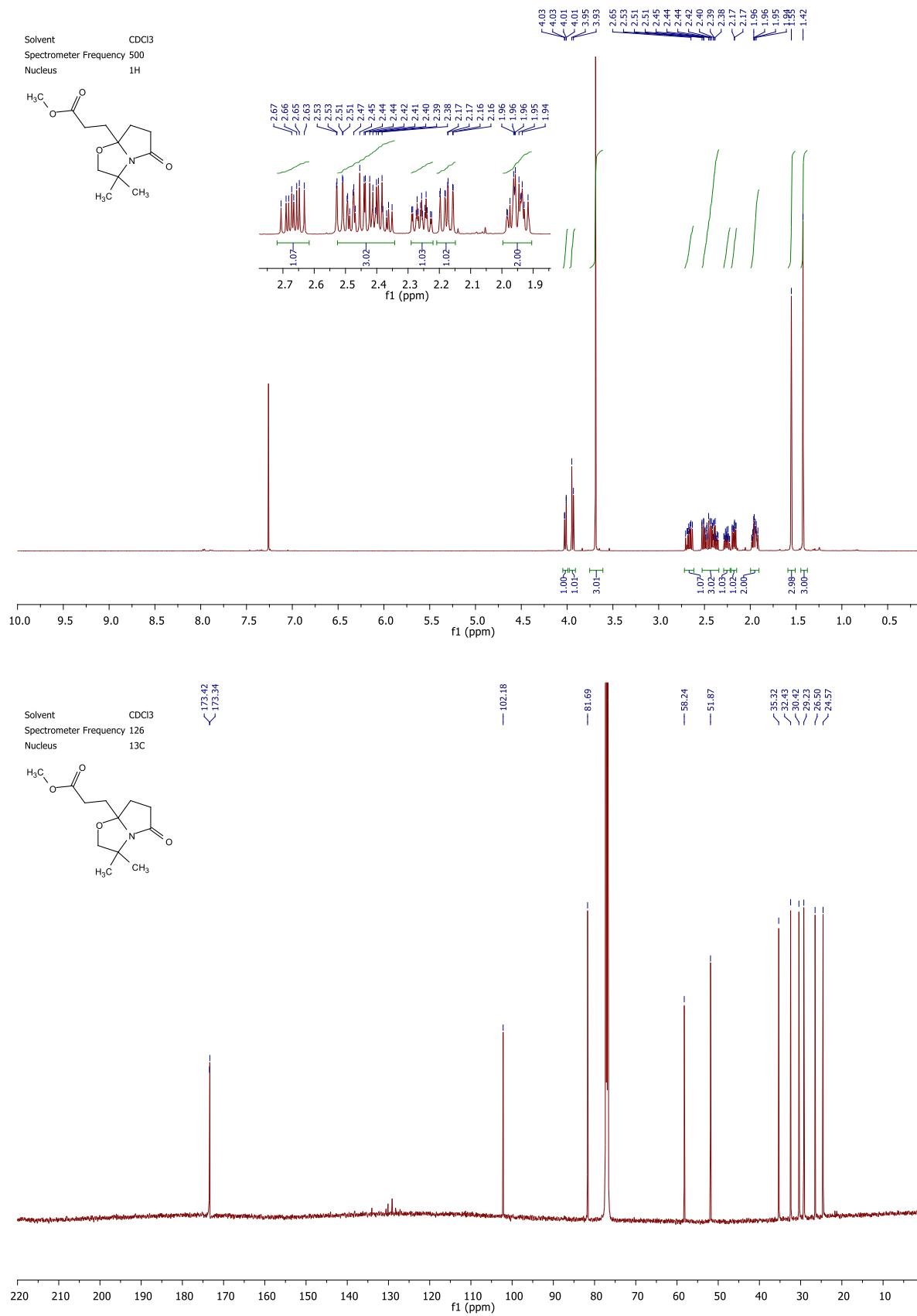
7a'-(3-(1-Tosylpiperidin-4-yl)propyl)dihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]oxazol]-5'(6'H)-one (240a)


3,3-Dimethyl-7a-(3-(1-tosylpiperidin-4-yl)propyl)tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (240b)

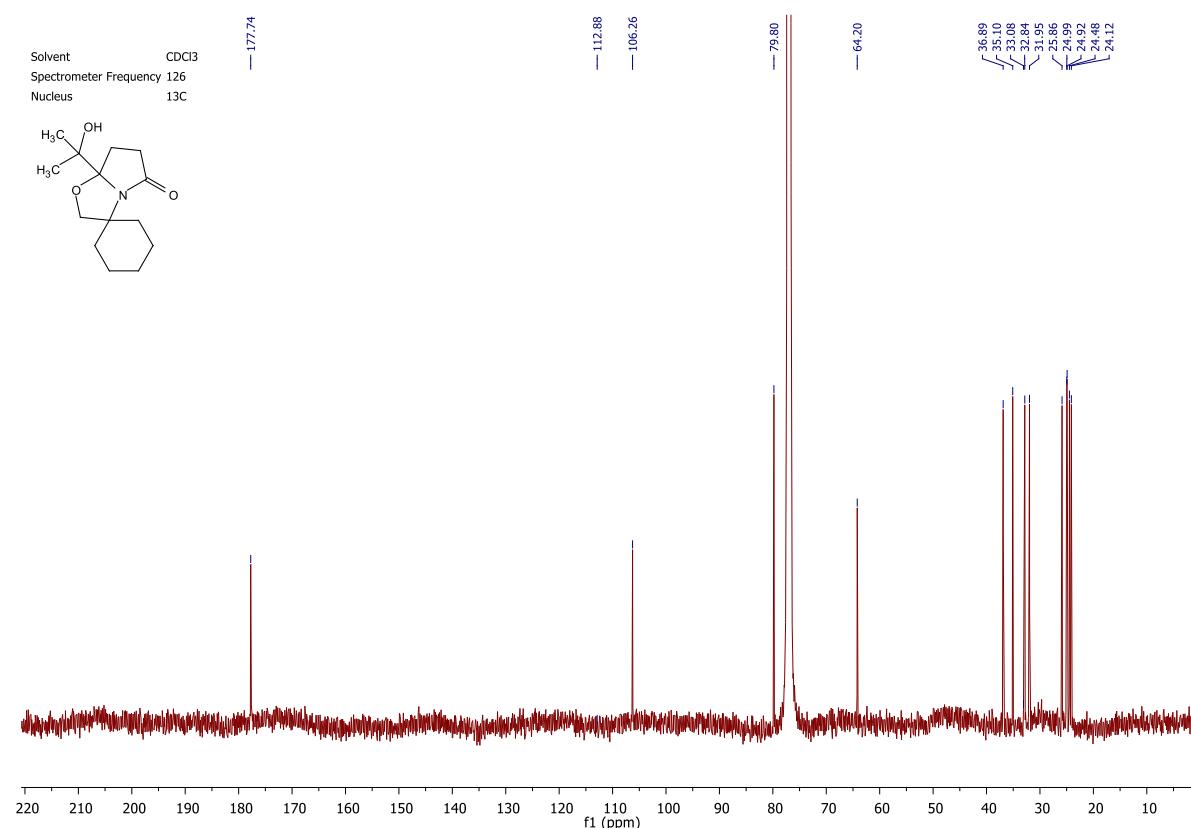
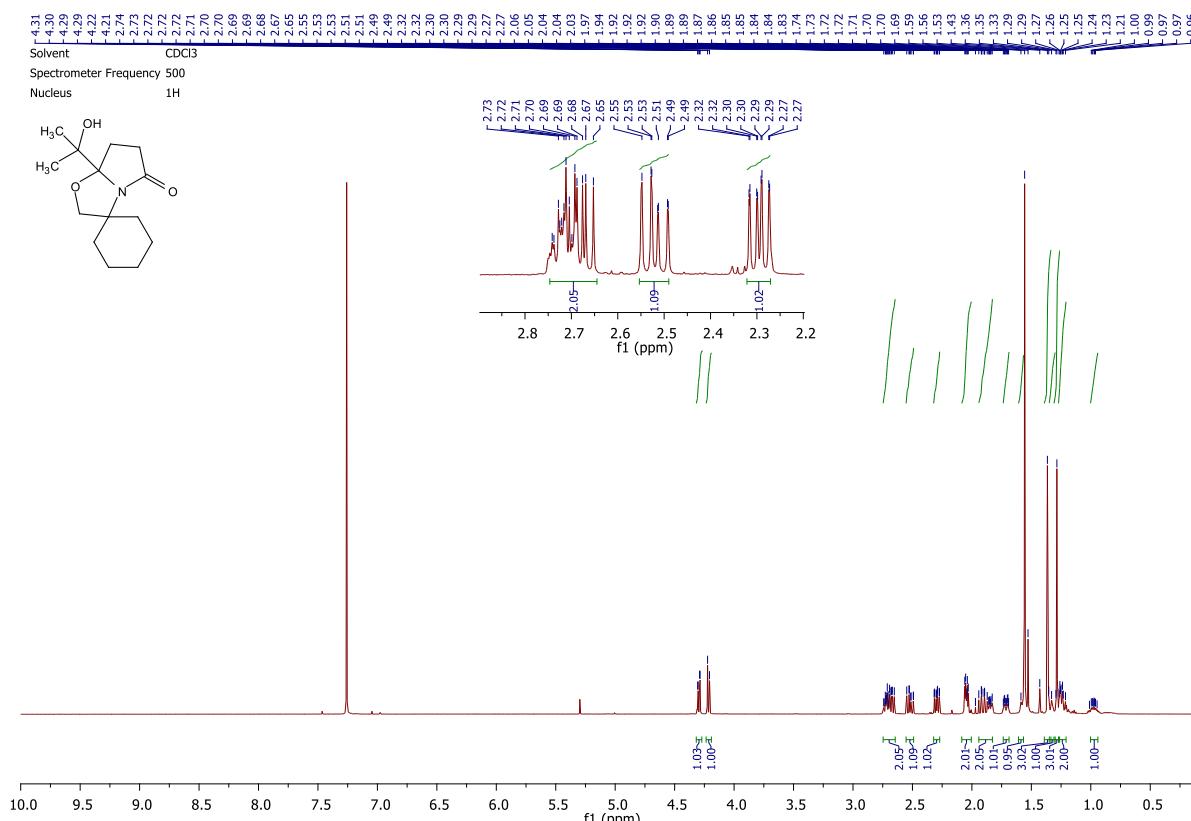


Methyl 3-(5'-oxotetrahydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-7a'-yl)propanoate (241a)


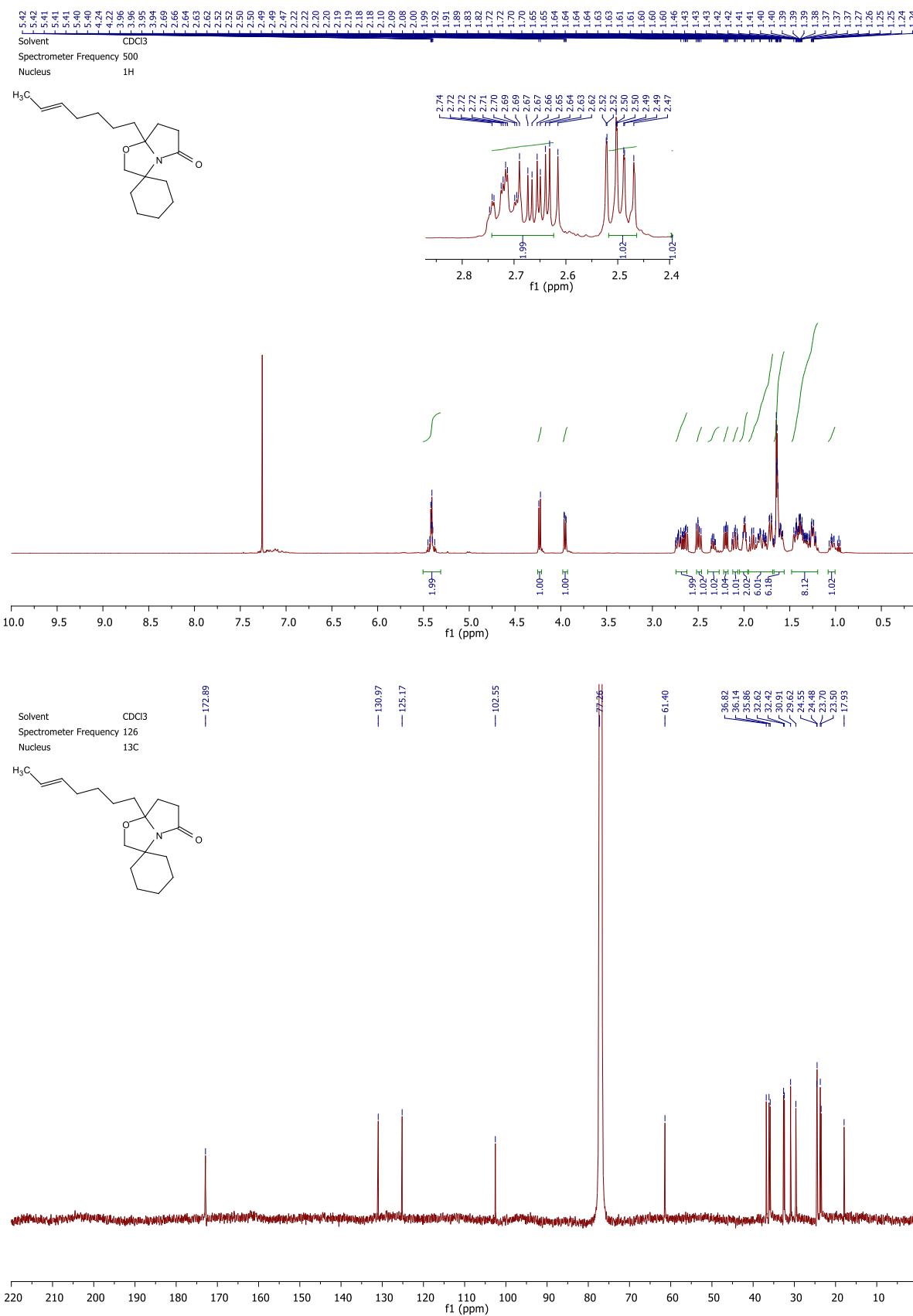
Methyl 3-(3,3-dimethyl-5-oxohexahydropyrrolo[2,1-*b*]oxazol-7a-yl)propanoate (241b)



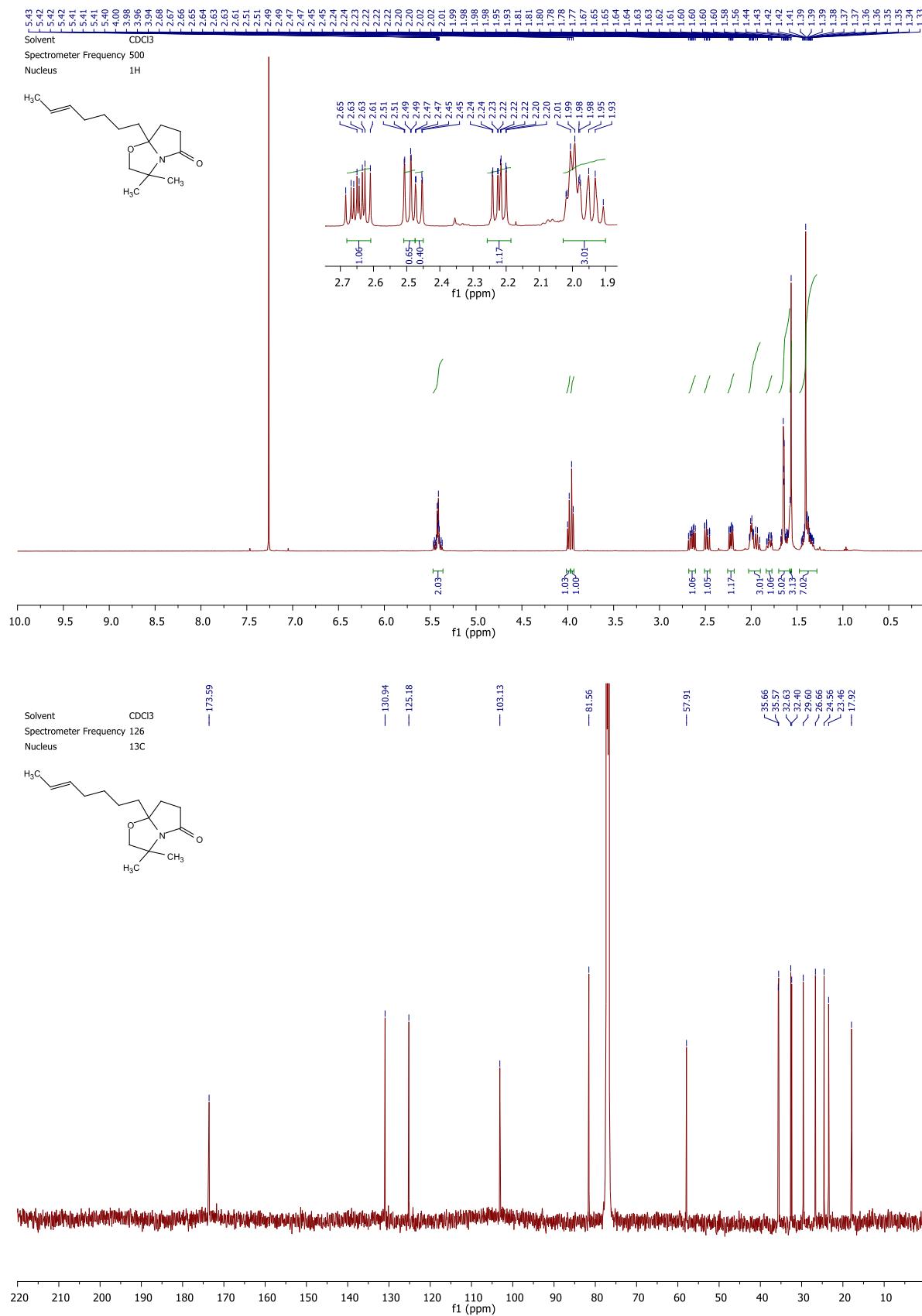
7a'-(2-Hydroxypropan-2-yl)dihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'*H*-one (242a)



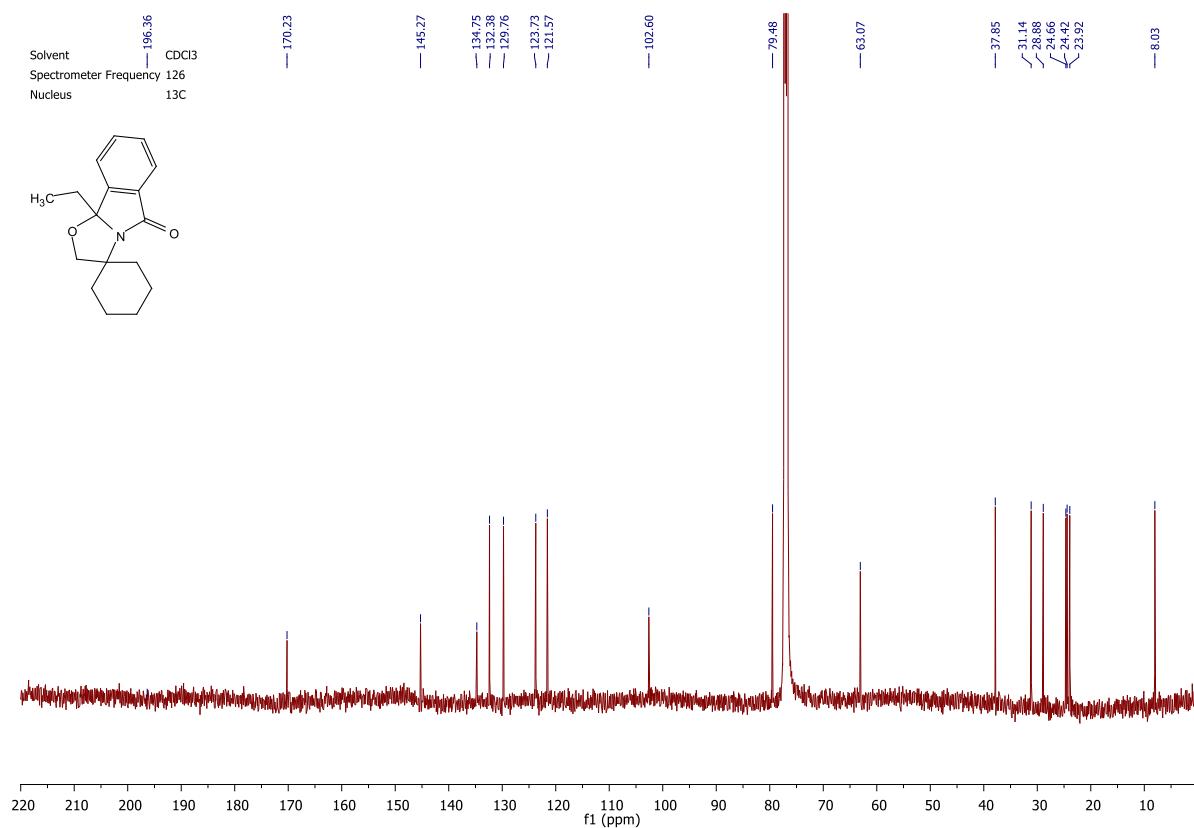
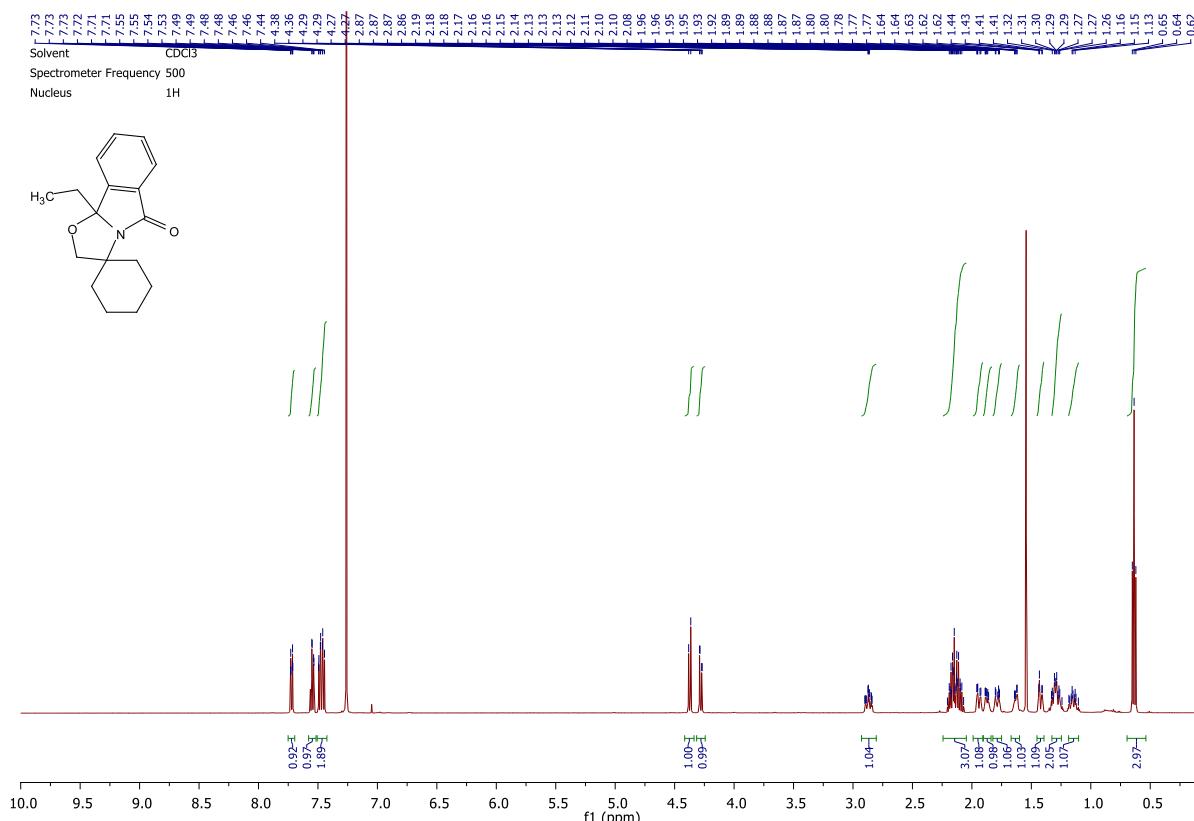
(E)-7a'-(Hept-5-en-1-yl)dihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (243a)



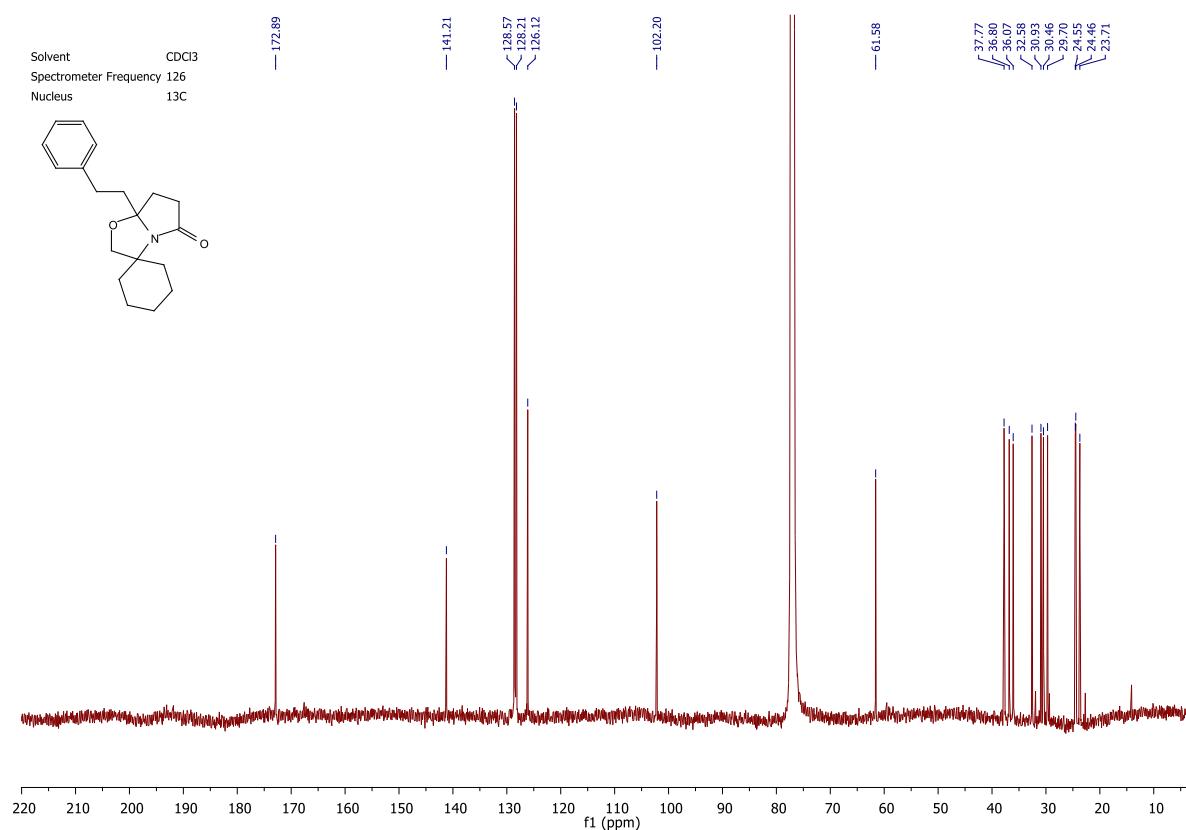
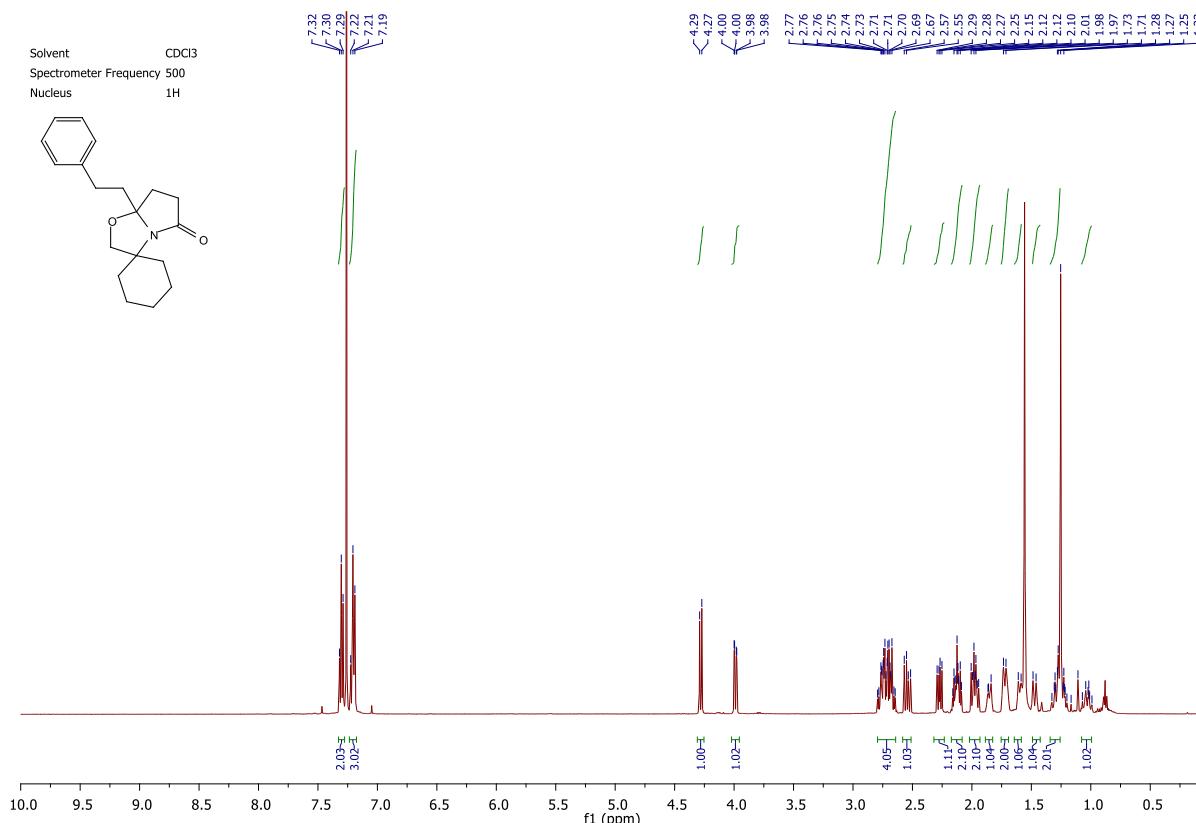
(E)-7a-(Hept-5-en-1-yl)-3,3-dimethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (243b)



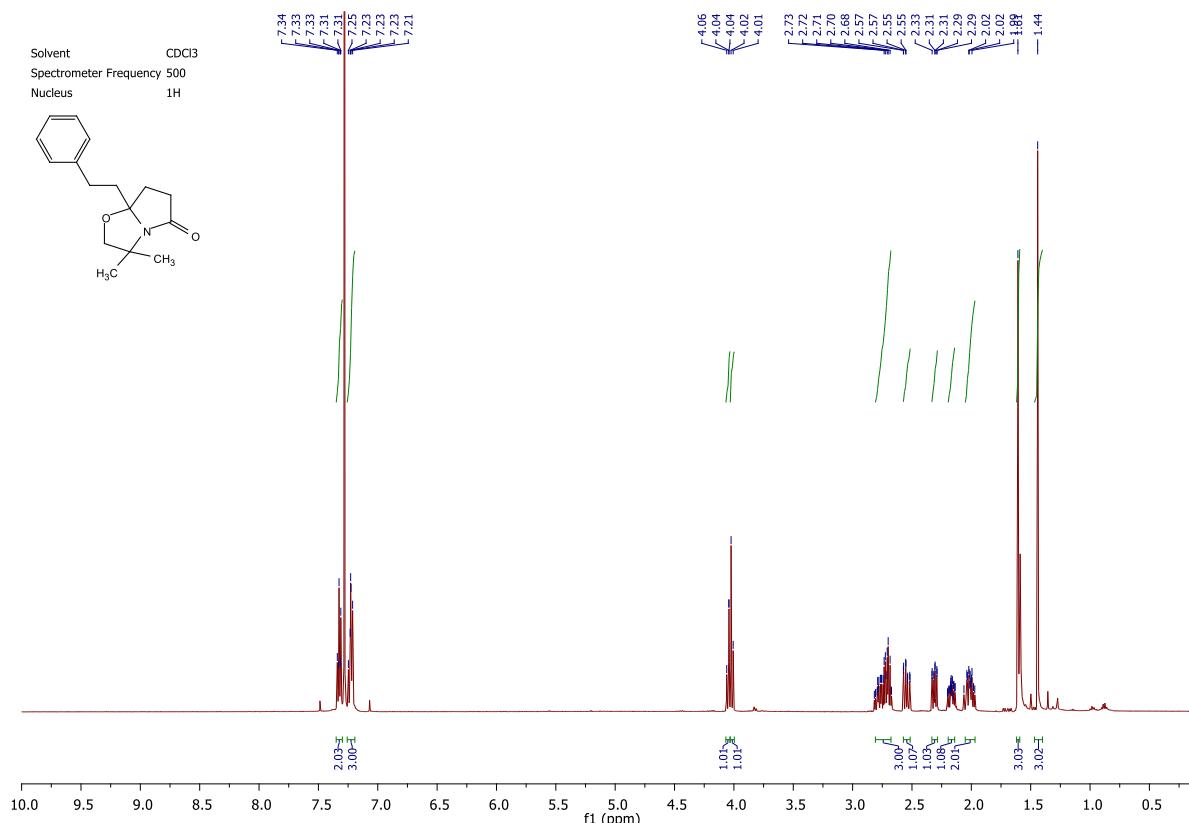
9b'-Ethyl-2'H-spiro[cyclohexane-1,3'-oxazolo[2,3-*a*]isoindol]-5'(9b'H)-one (252)



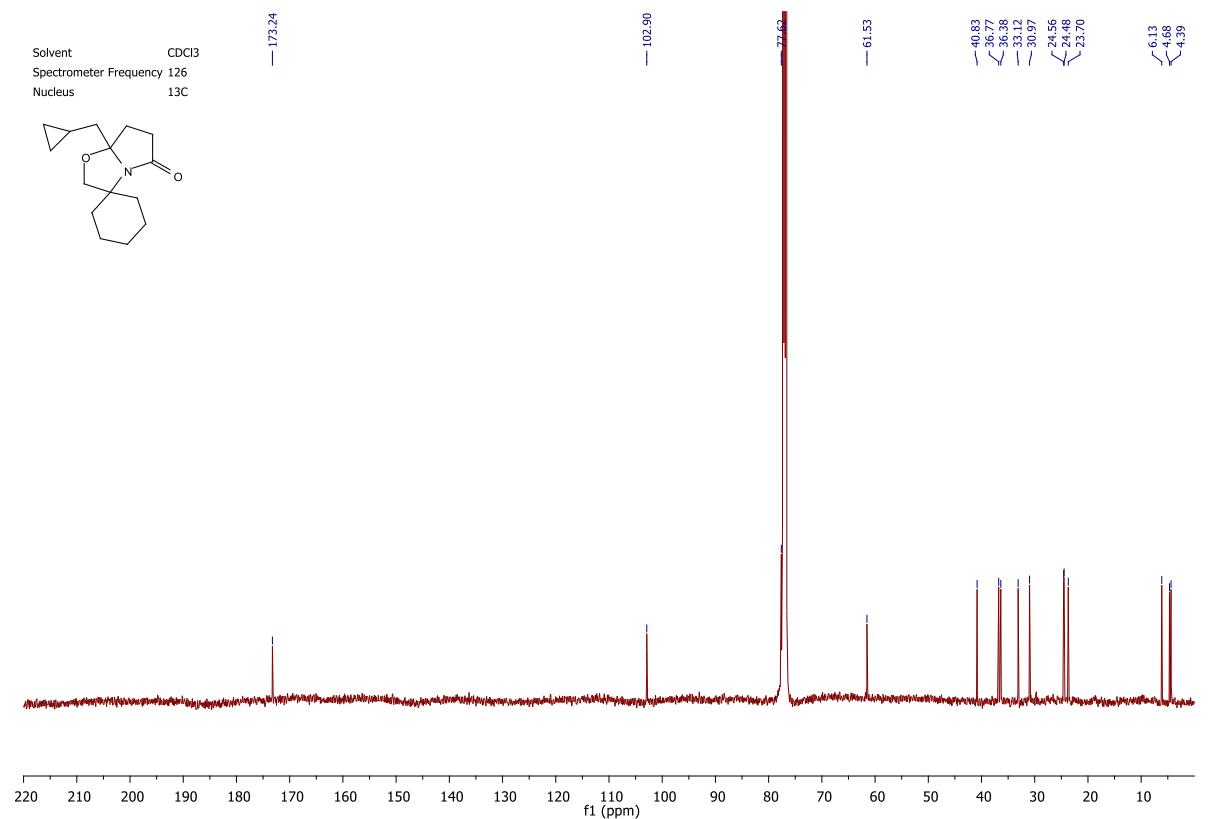
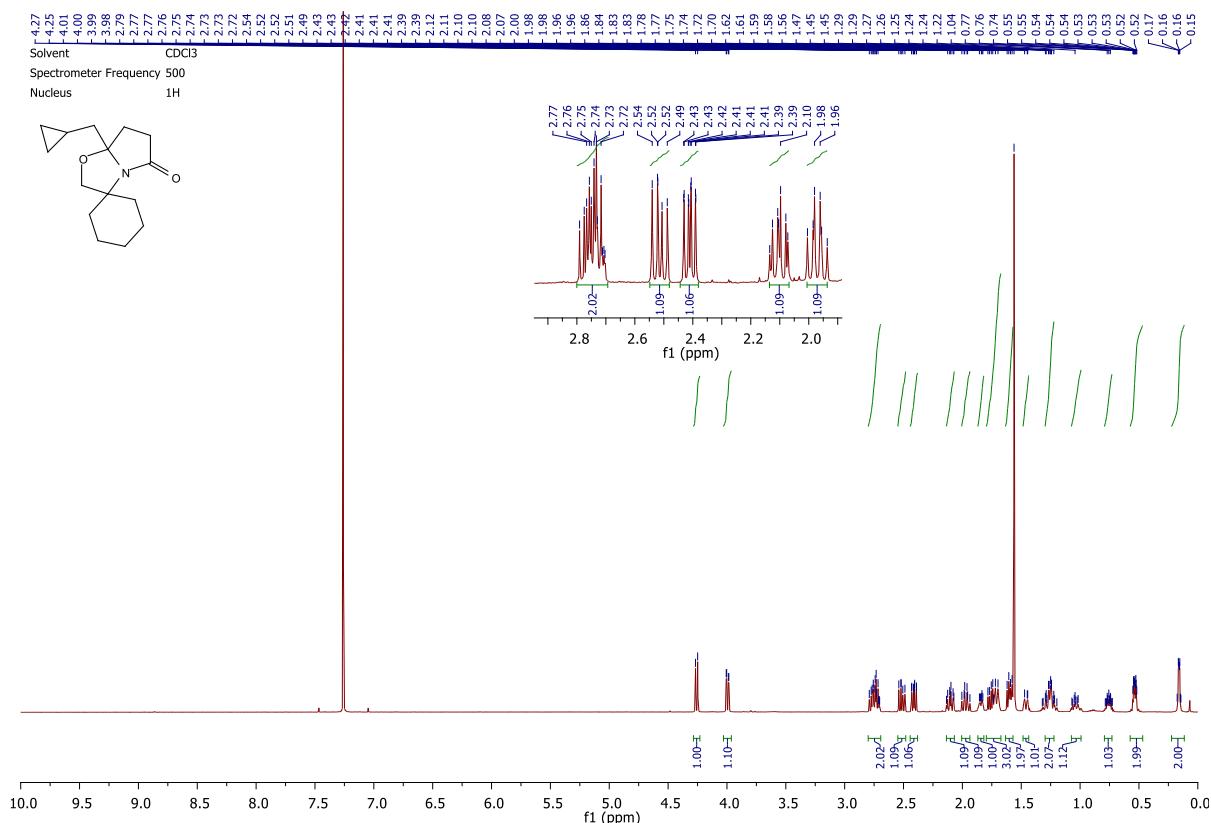
7a'-Phenethyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (259a)



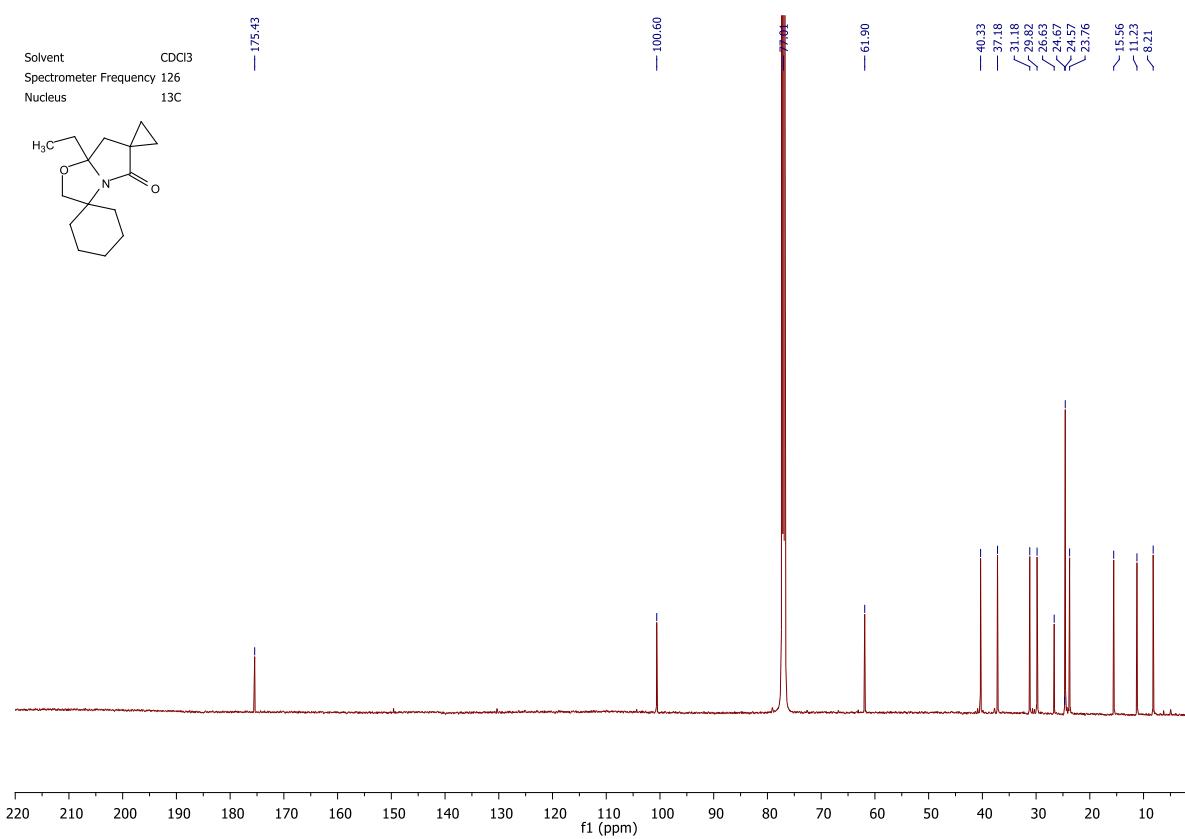
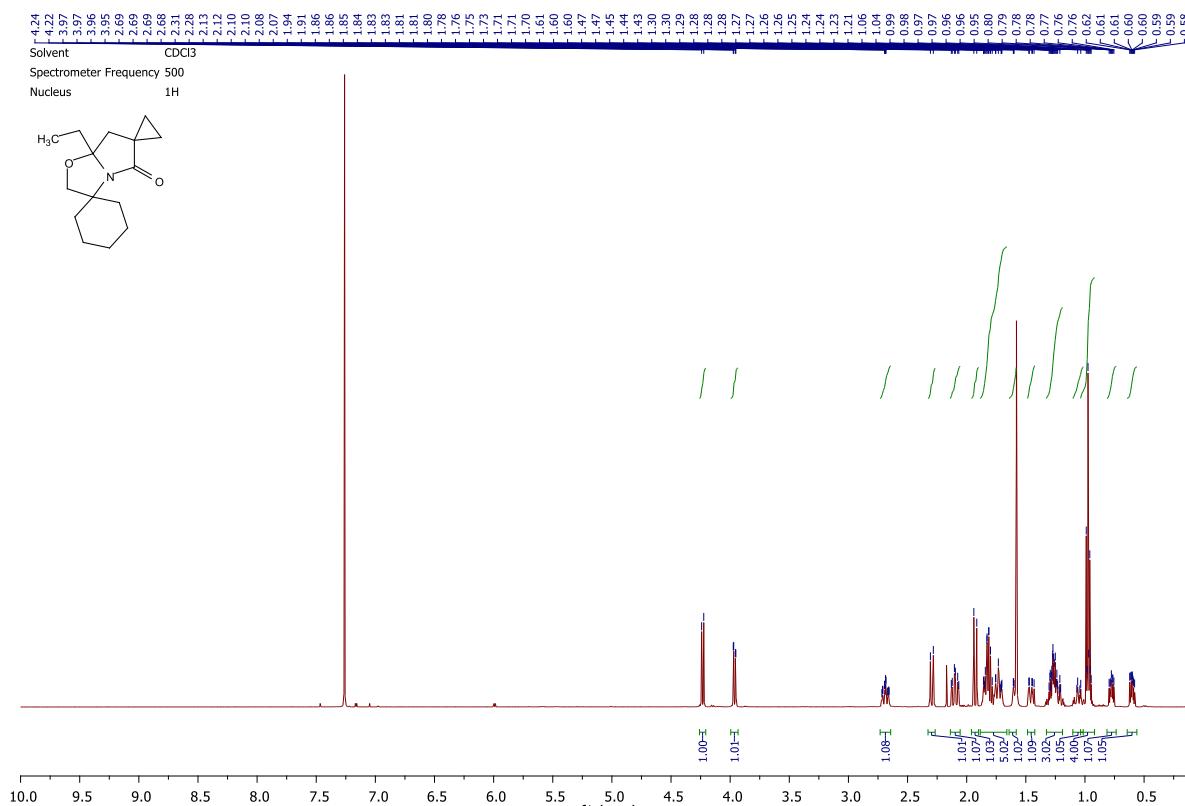
3,3-Dimethyl-7a-phenethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (259b)



7a'-(Cyclopropylmethyl)dihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (264)

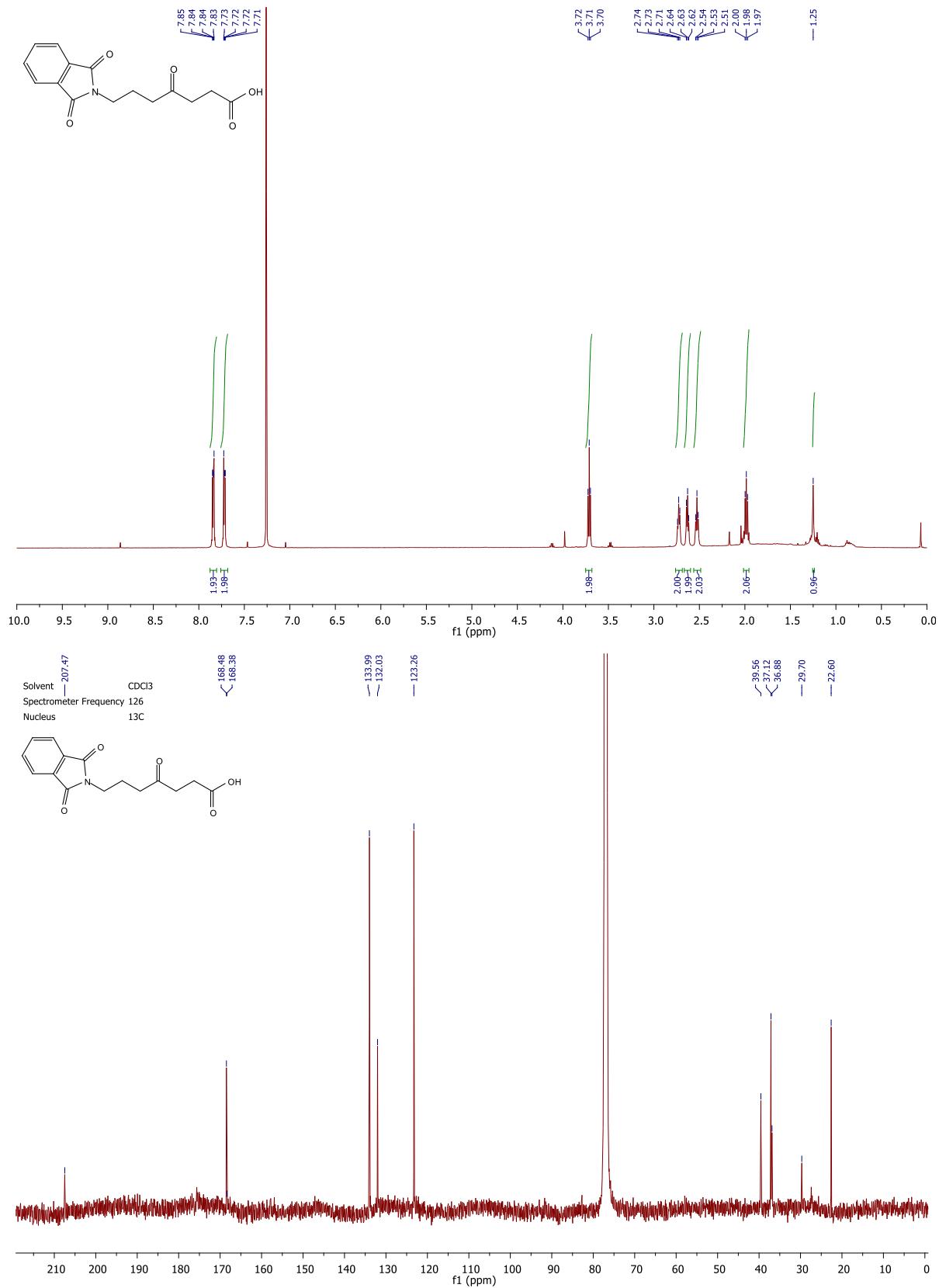


7a'-Ethyl-6'-spirocyclopropylidihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'($6'\text{H}$)-one (265)

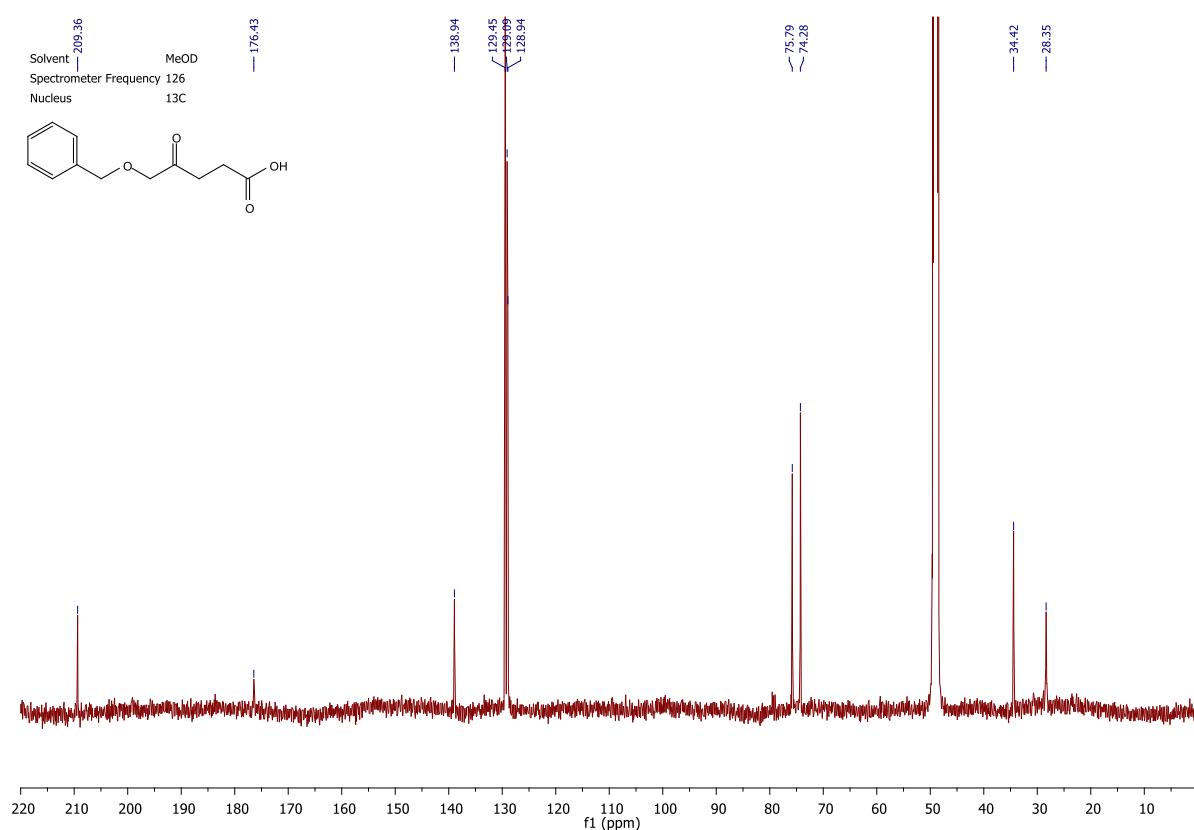
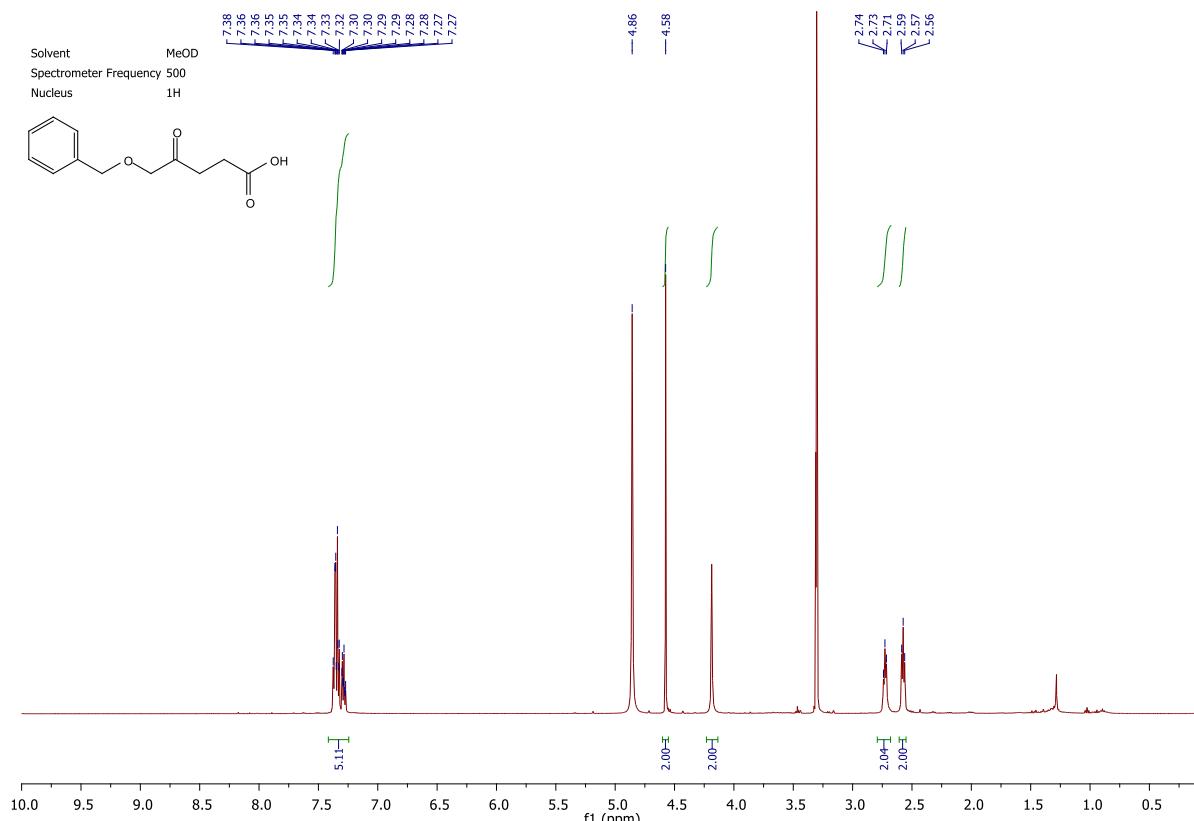


7.3 Palladium(II)-catalysed carbonylation: γ -Keto carboxylic acids

8-(1,3-Dioxoisooindolin-2-yl)-4-oxooctanoic acid (270)

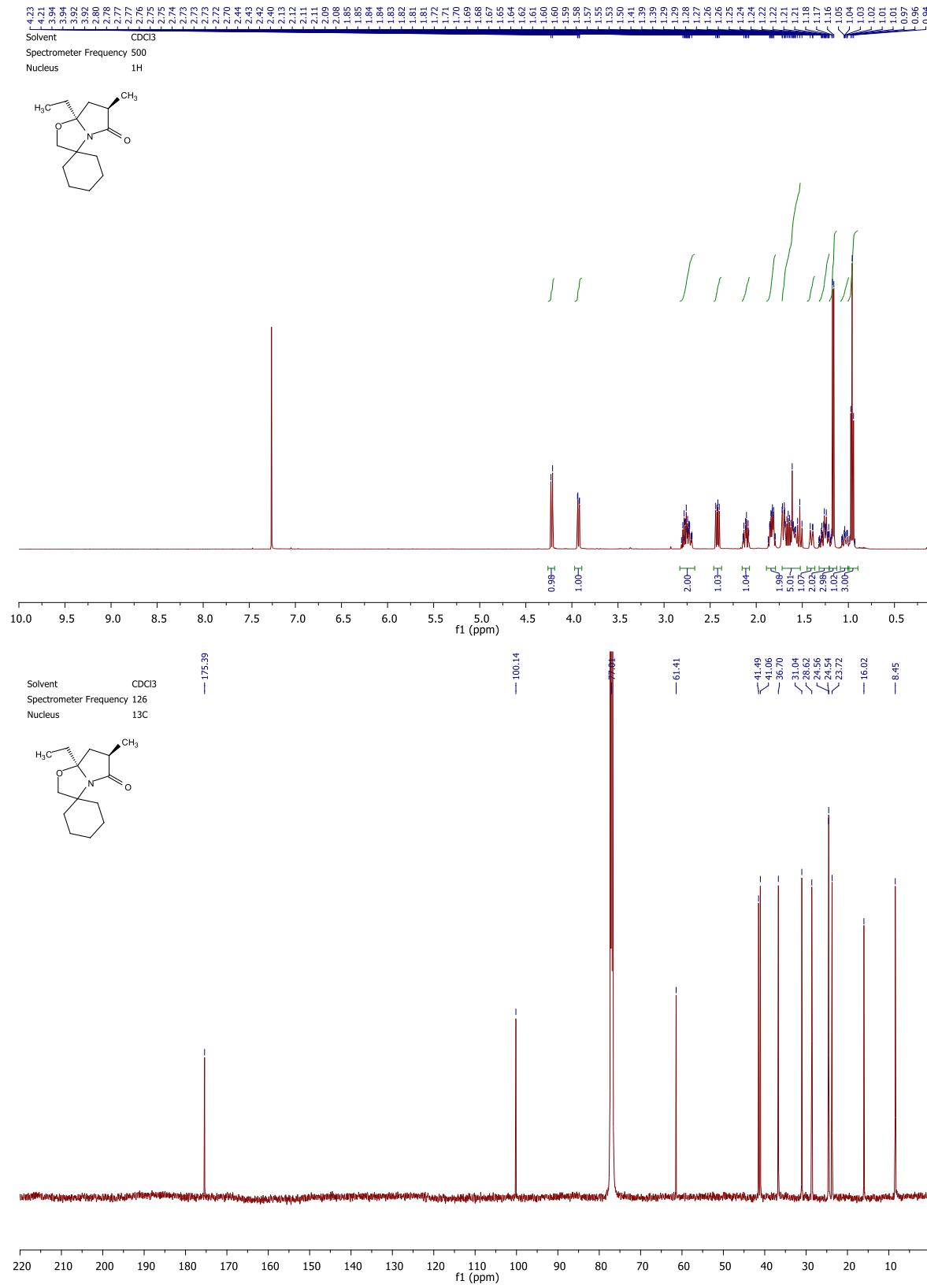


5-(Benzyl)-4-oxopentanoic acid (271)



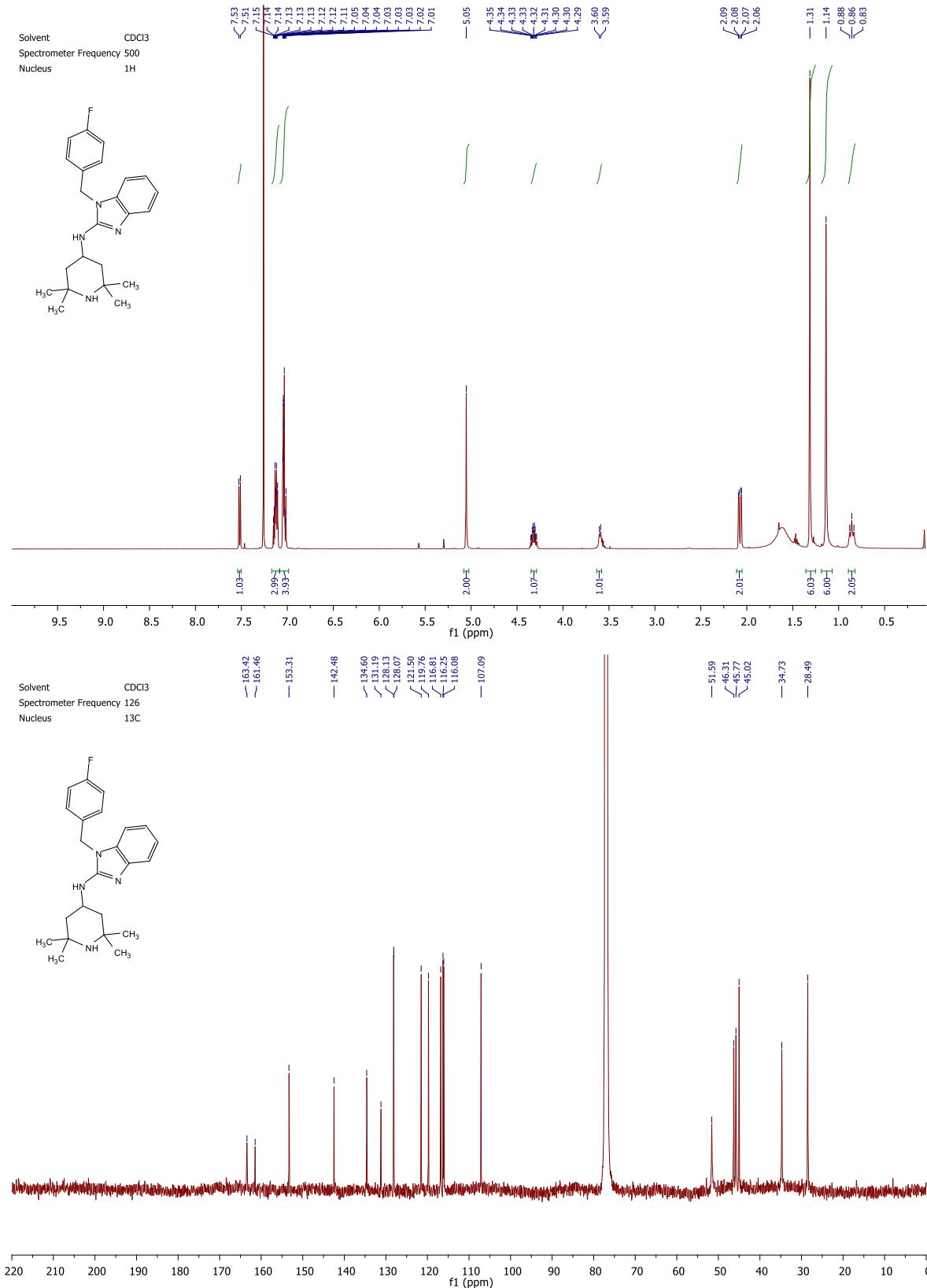
7.4 Palladium(II)-catalysed carbonylation: C-Methylation of γ -lactam 185

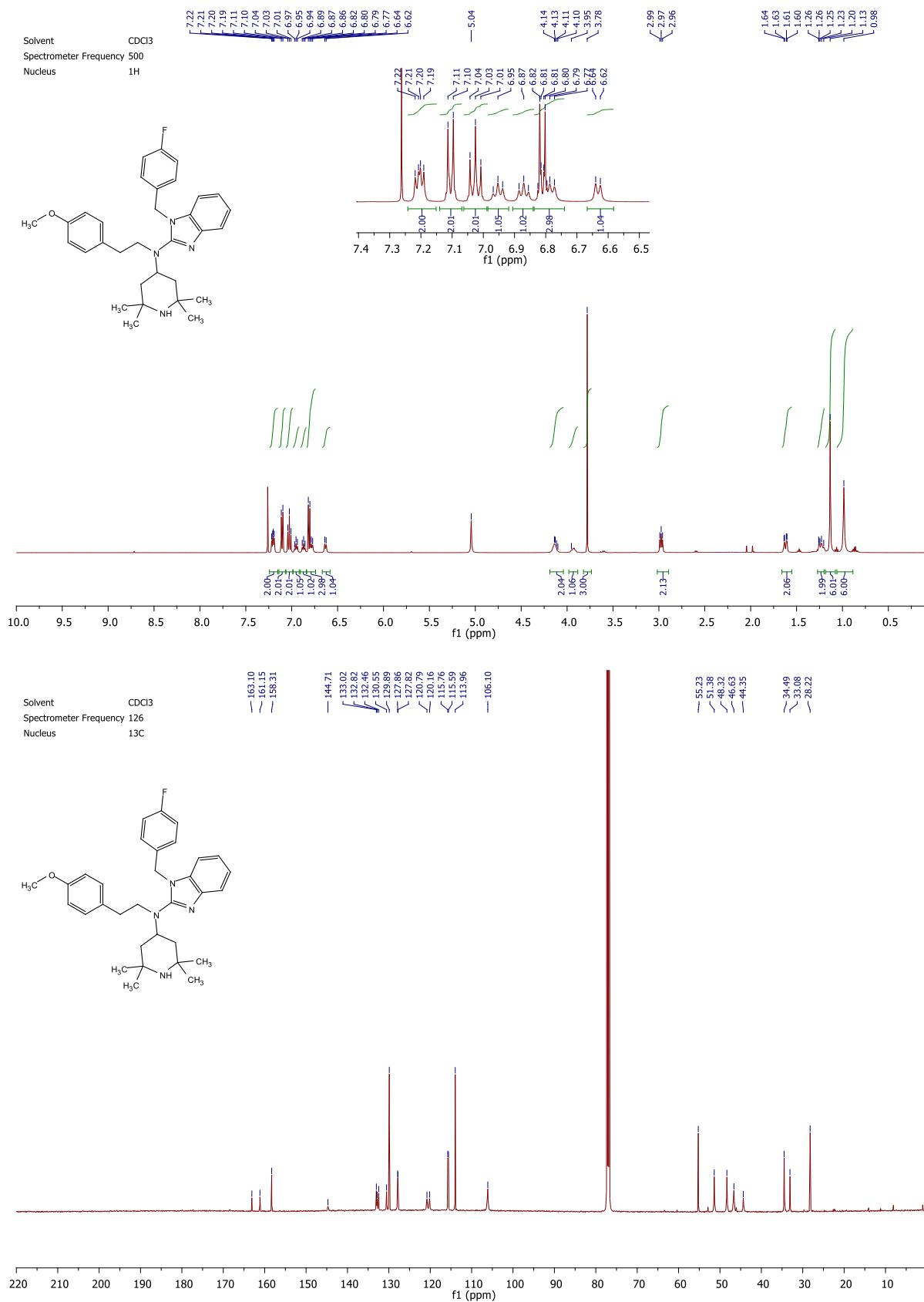
(6'R, 7a'S)-7a'-Ethyl-6'-methyldihydro-2'H-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]oxazol]-5'(6'H)-one (\pm) (272)



7.5 Synthesis of TMP-astemizole 287

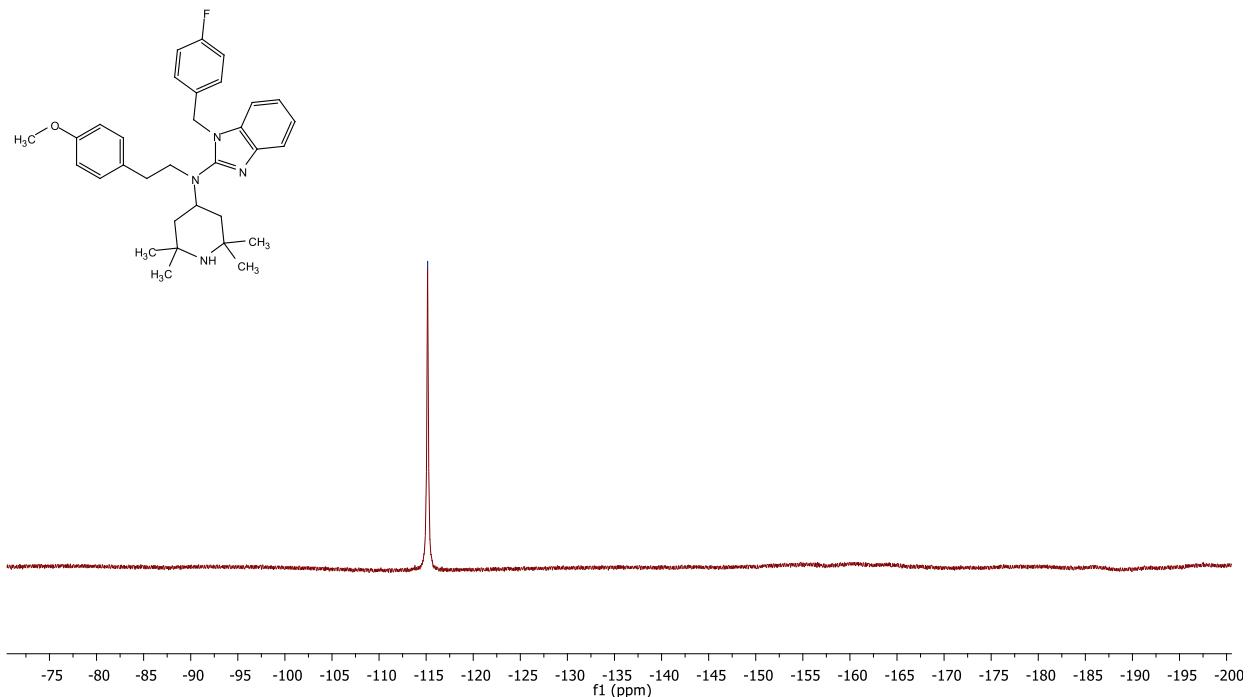
**1-(4-Fluorobenzyl)-*N*-(2,2,6,6-tetramethylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-2-amine
(299)**



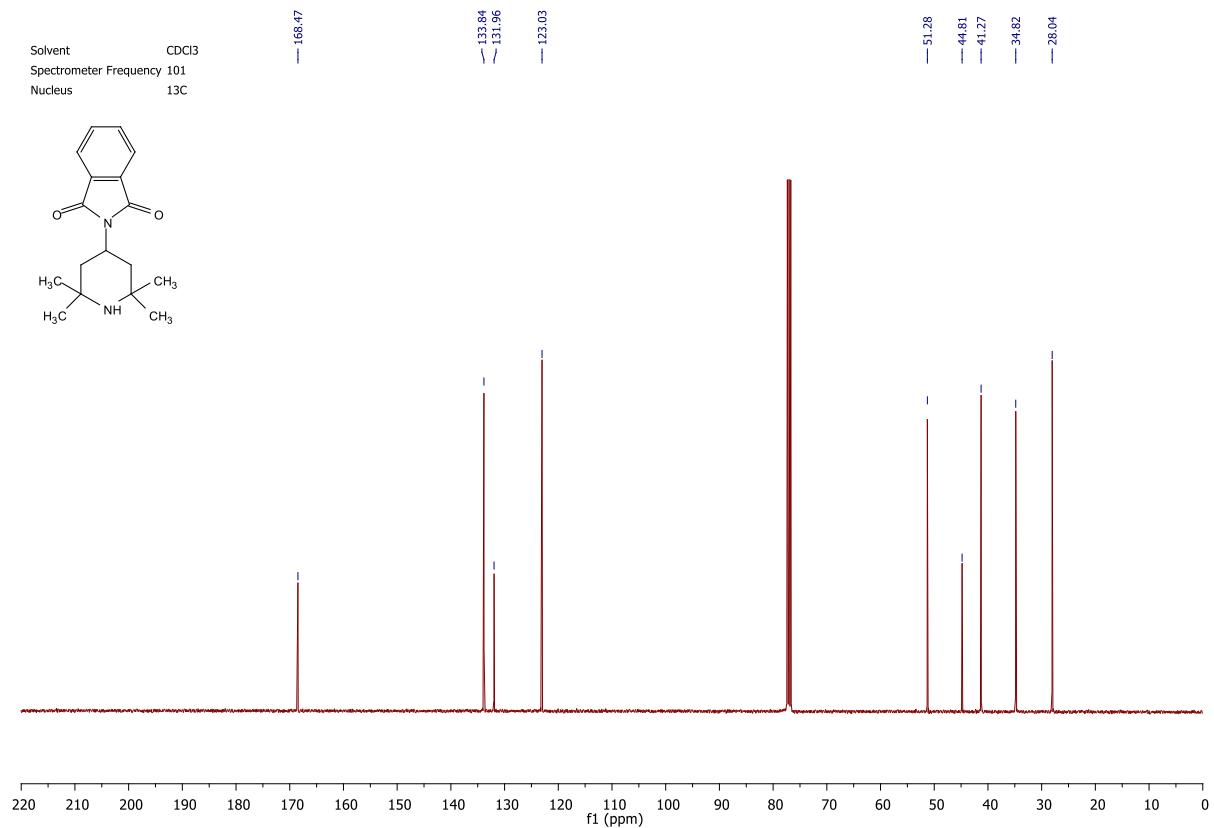
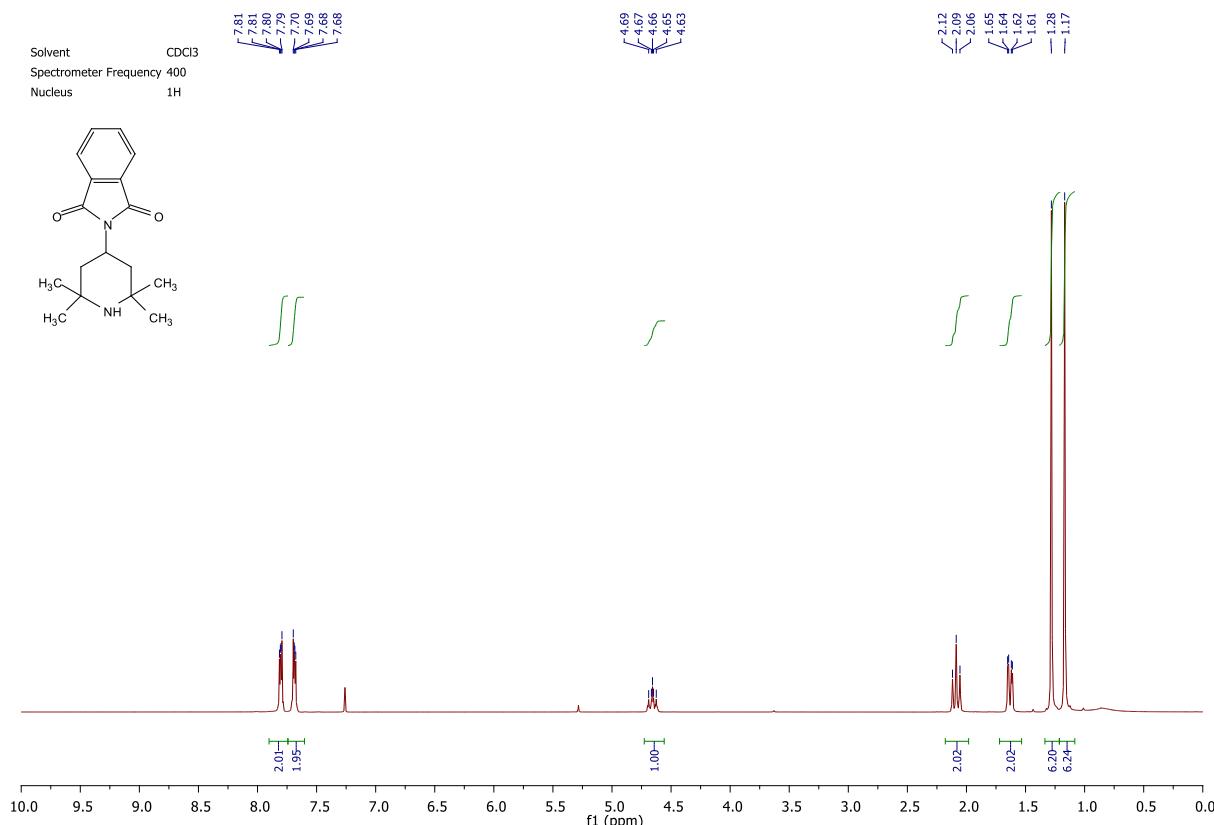
1-(4-Fluorobenzyl)-N-(4-methoxyphenethyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1*H*-benzo[d]imidazol-2-amine (301)


Appendix – ^1H and ^{13}C NMR spectra of key compounds

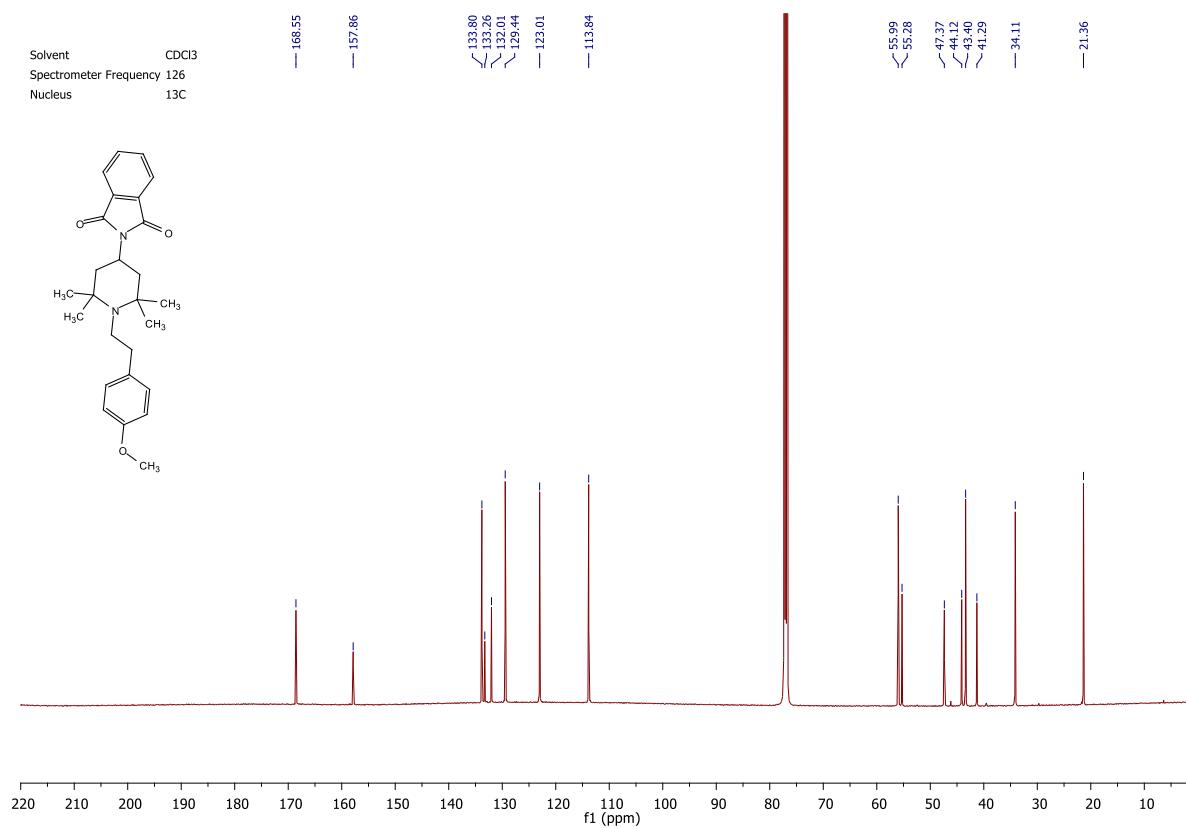
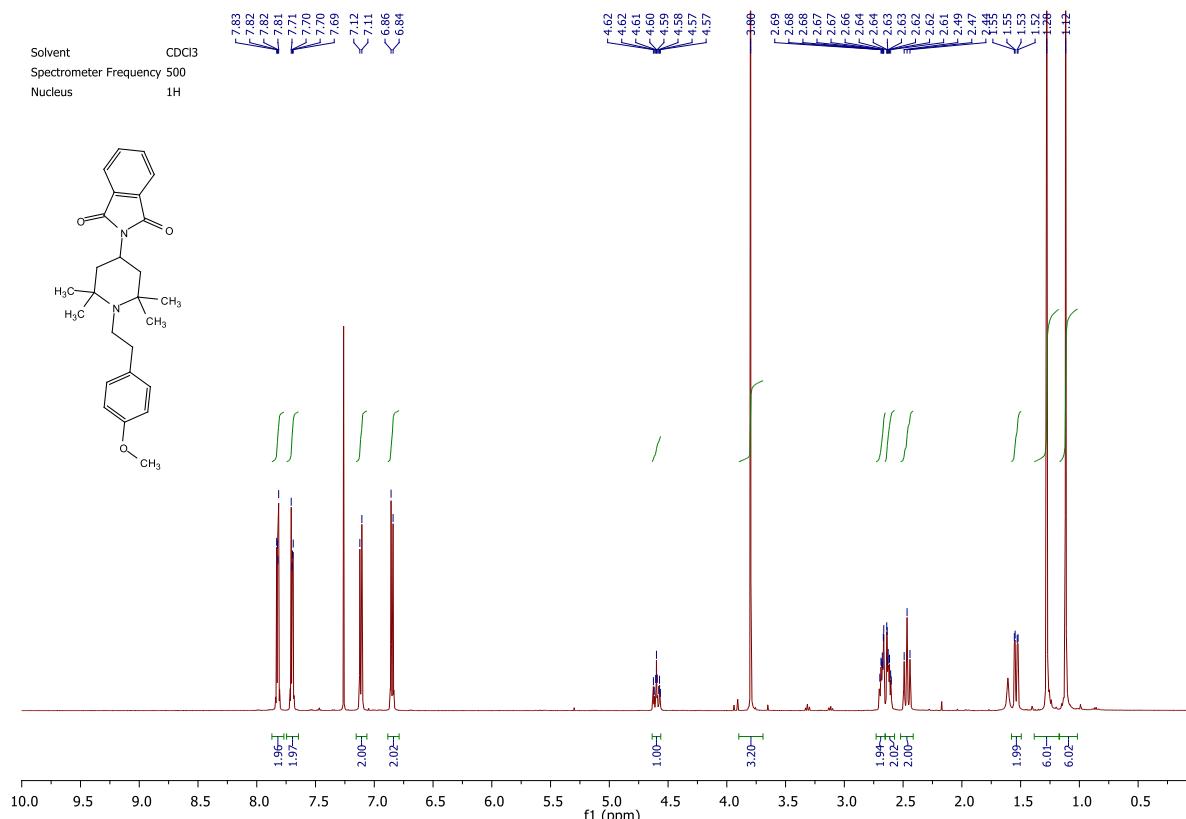
Solvent CDCl_3
Spectrometer Frequency 376
Nucleus ^{19}F



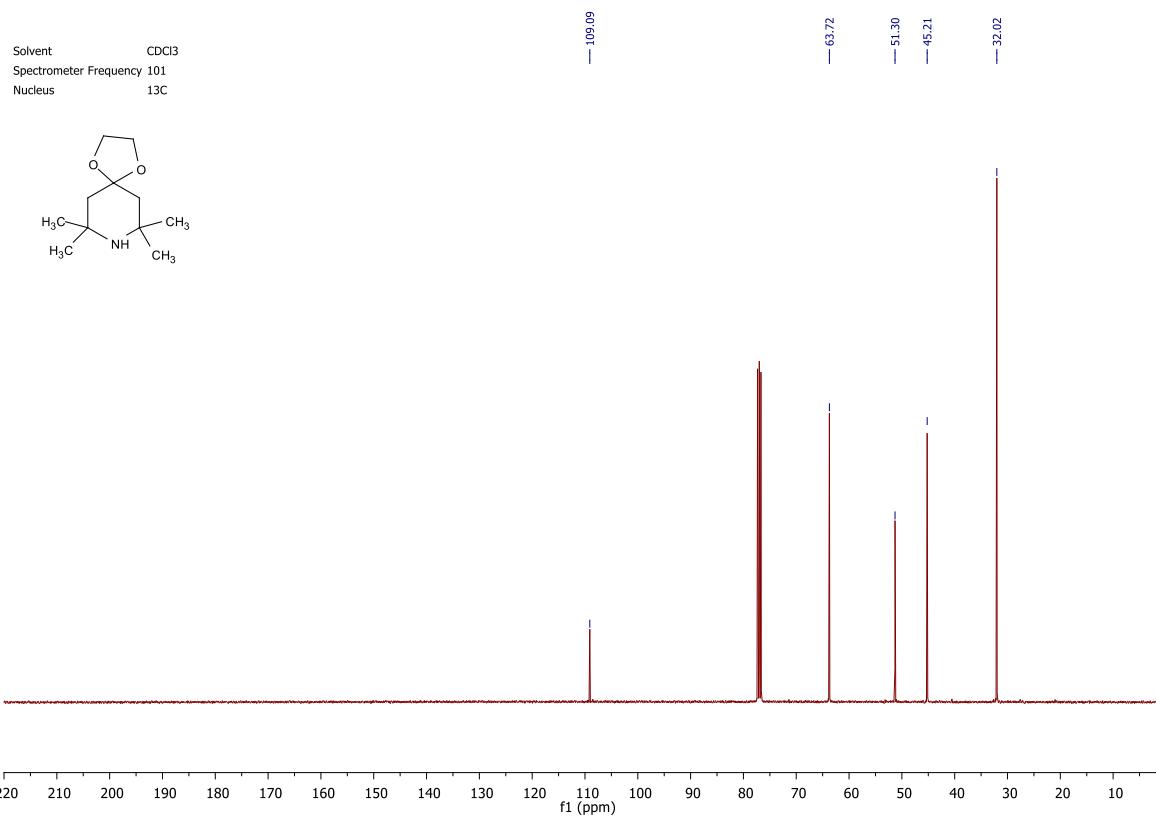
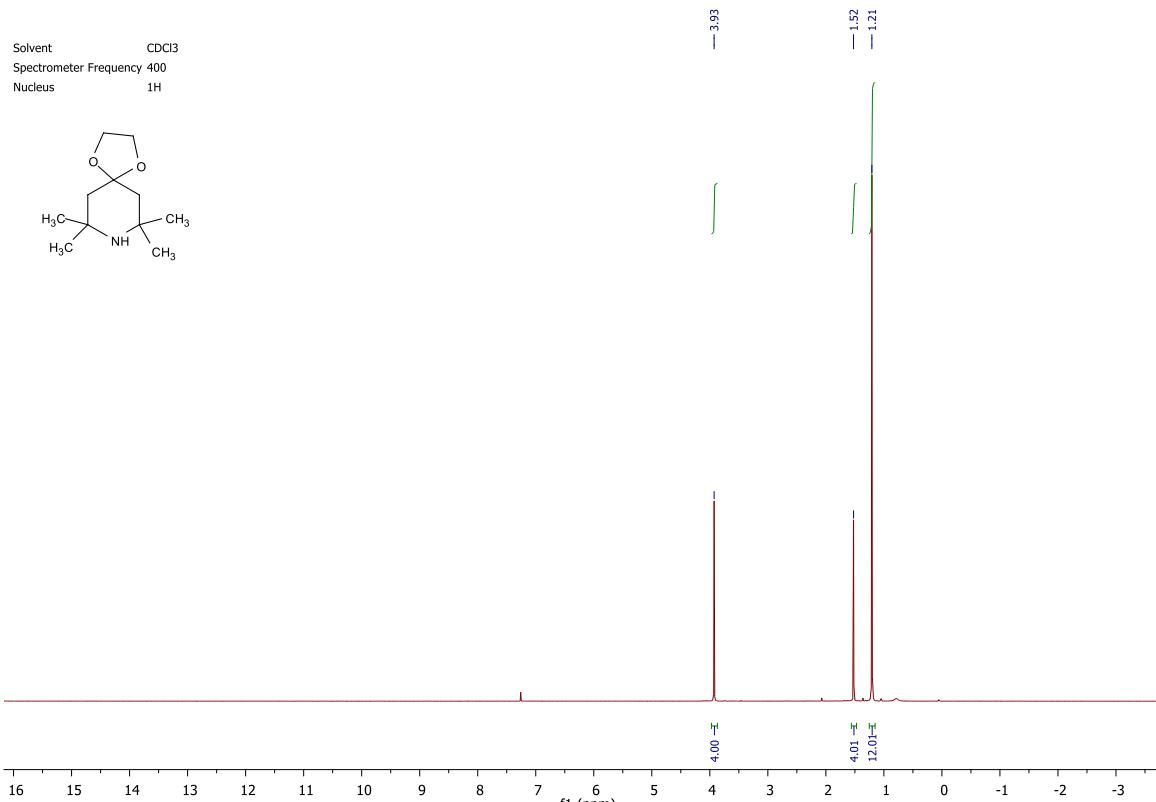
2-(2,2,6,6-Tetramethylpiperidin-4-yl)isoindoline-1,3-dione (305)



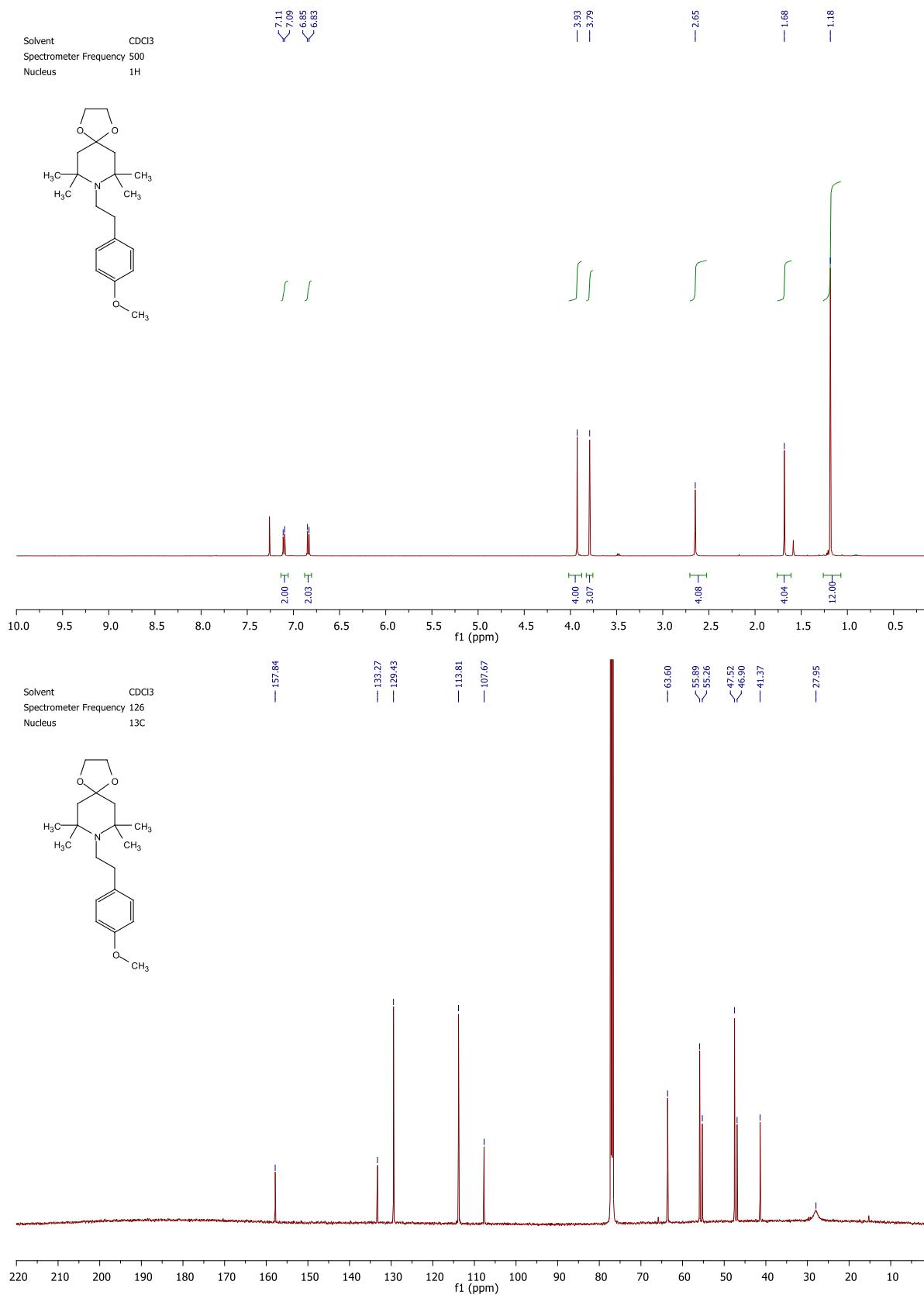
2-(1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl)isoindoline-1,3-dione (306)



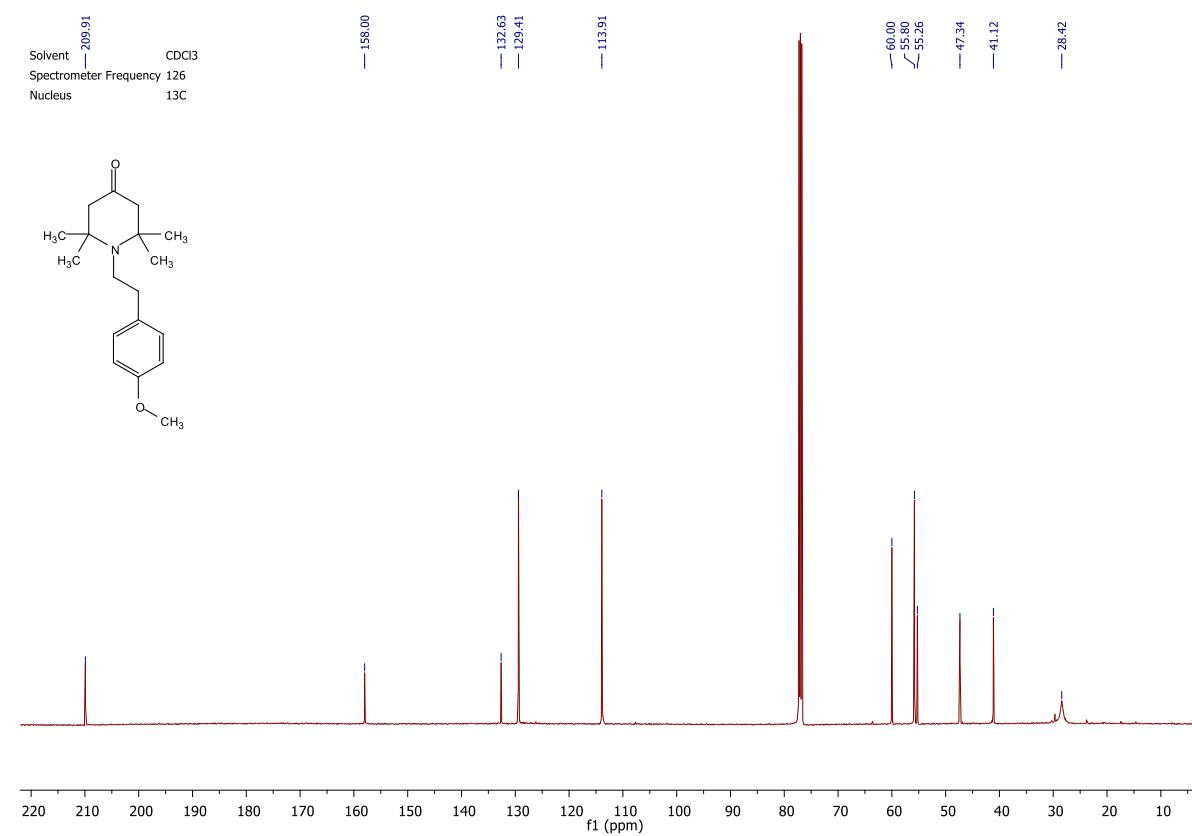
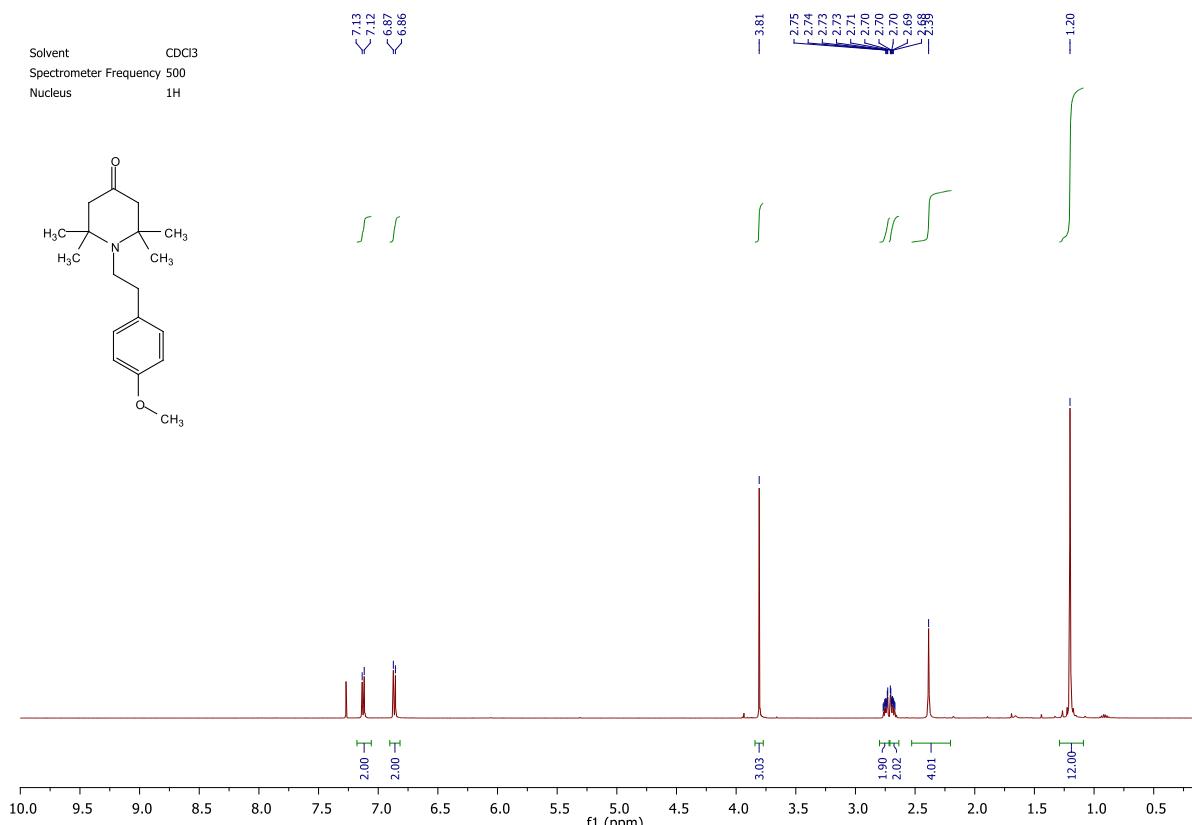
7,7,9,9-Tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (132)



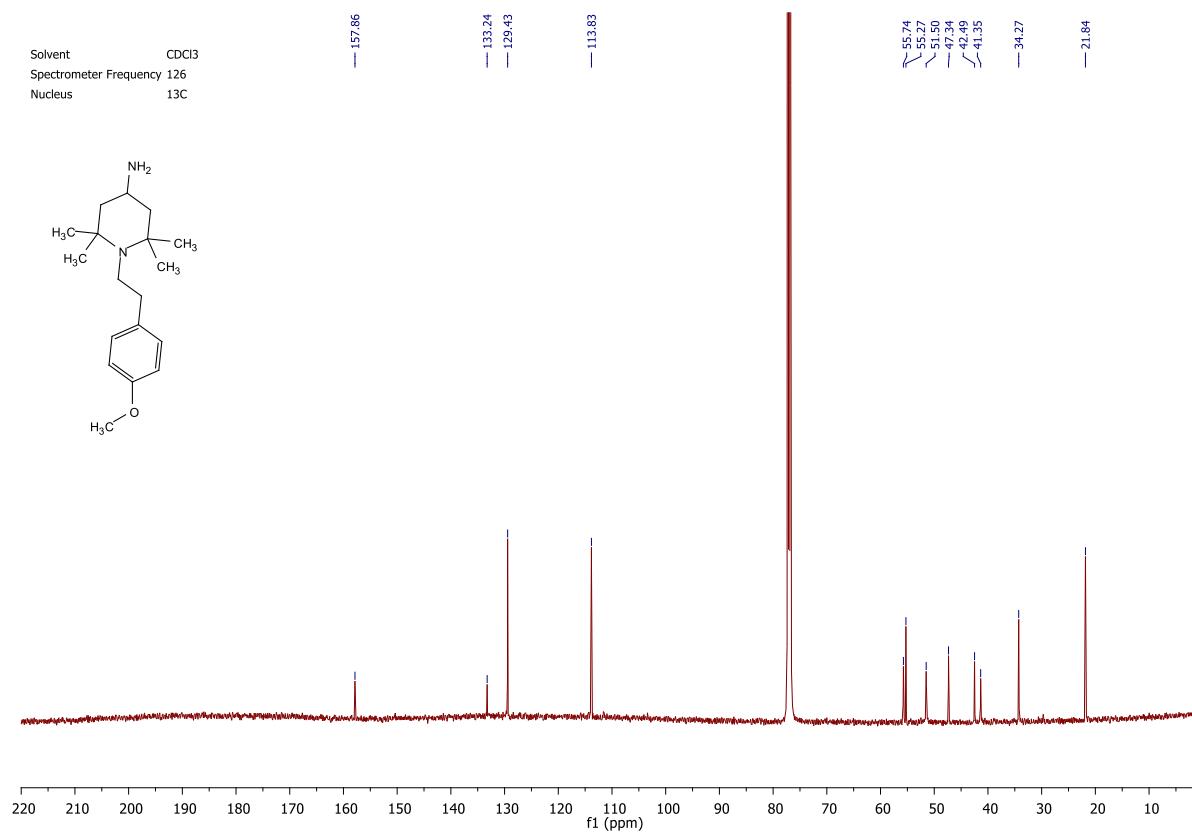
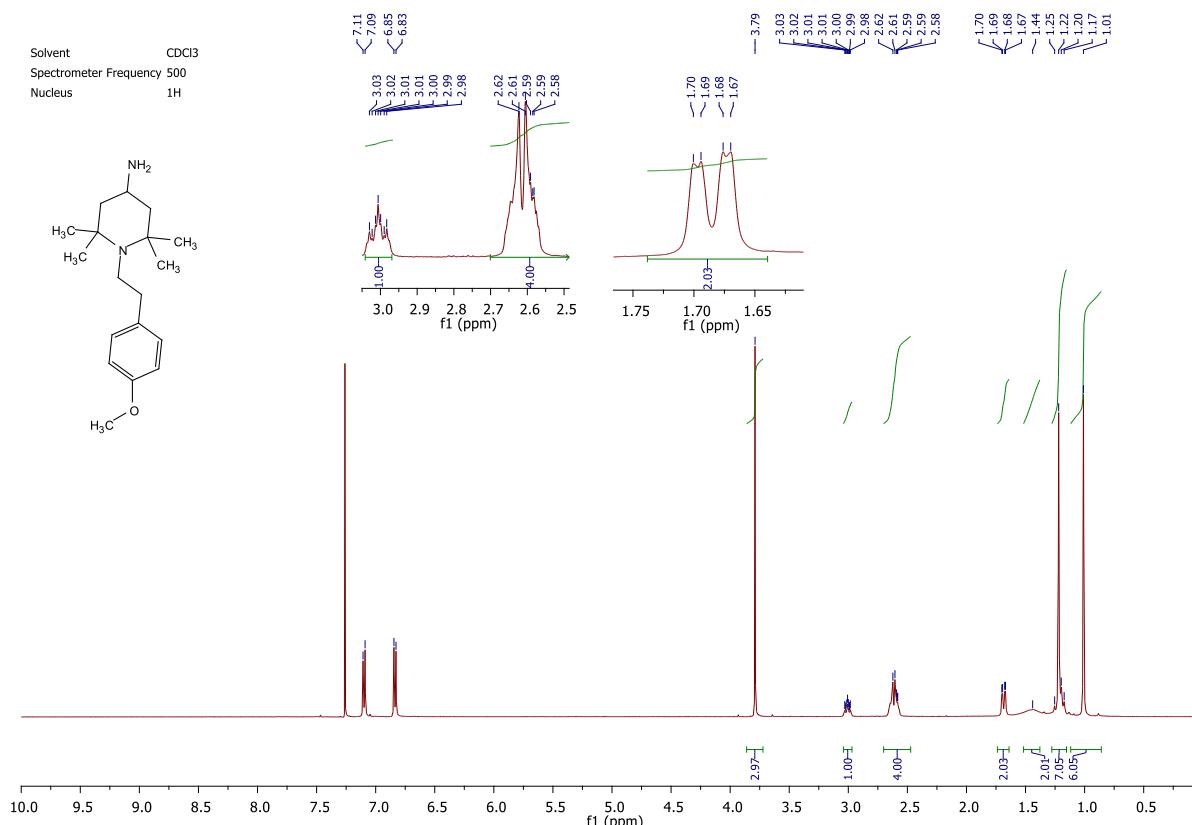
8-(4-Methoxyphenethyl)-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (311)



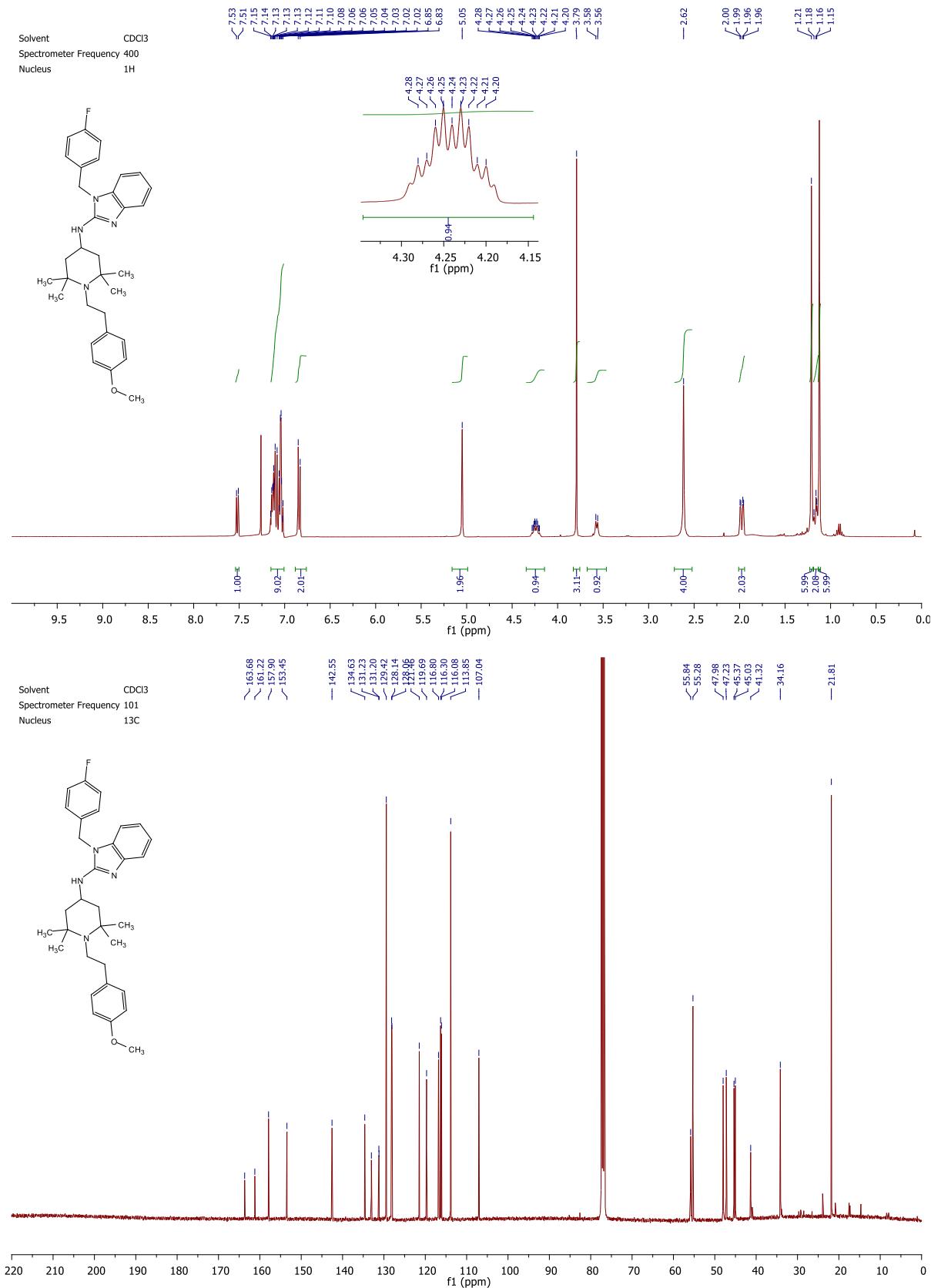
1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-one (312)



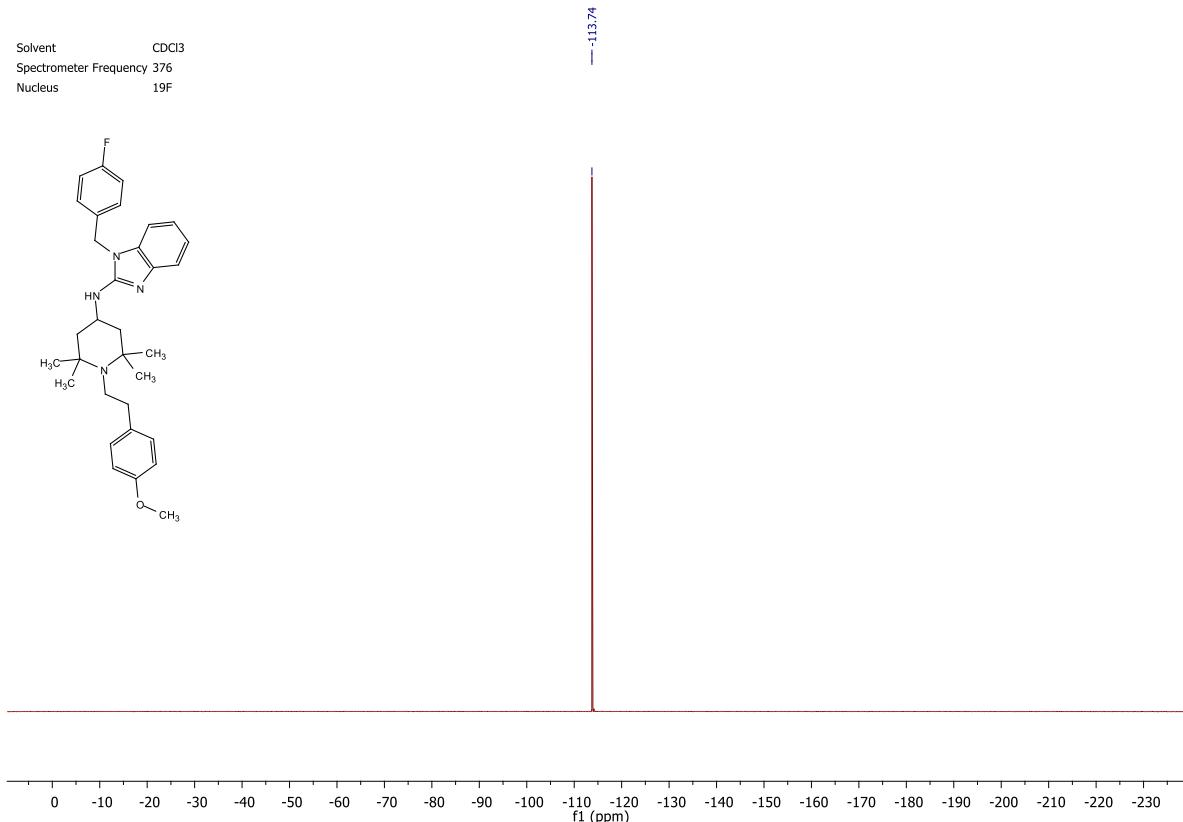
1-(4-Methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-amine (307)



1-(4-Fluorobenzyl)-N-(1-(4-methoxyphenethyl)-2,2,6,6-tetramethylpiperidin-4-yl)-1*H*-benzo[*d*]imidazol-2-amine (287)

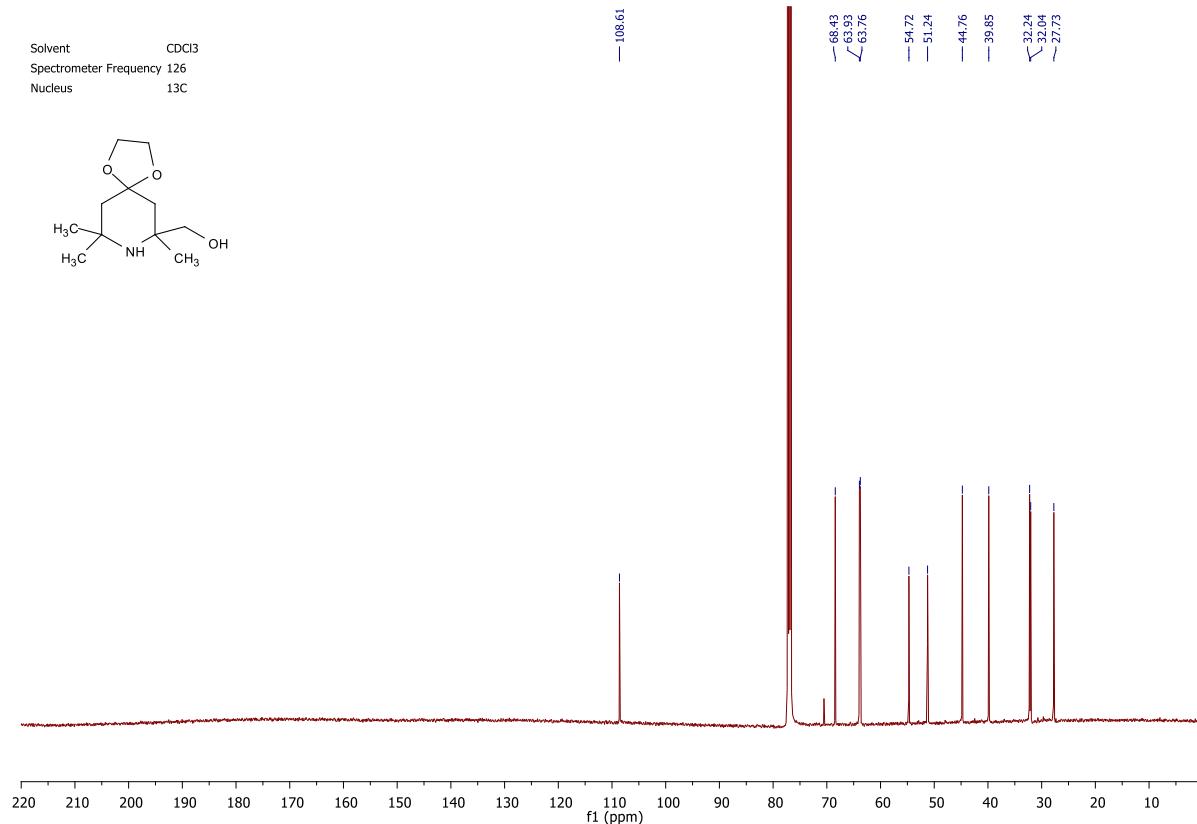
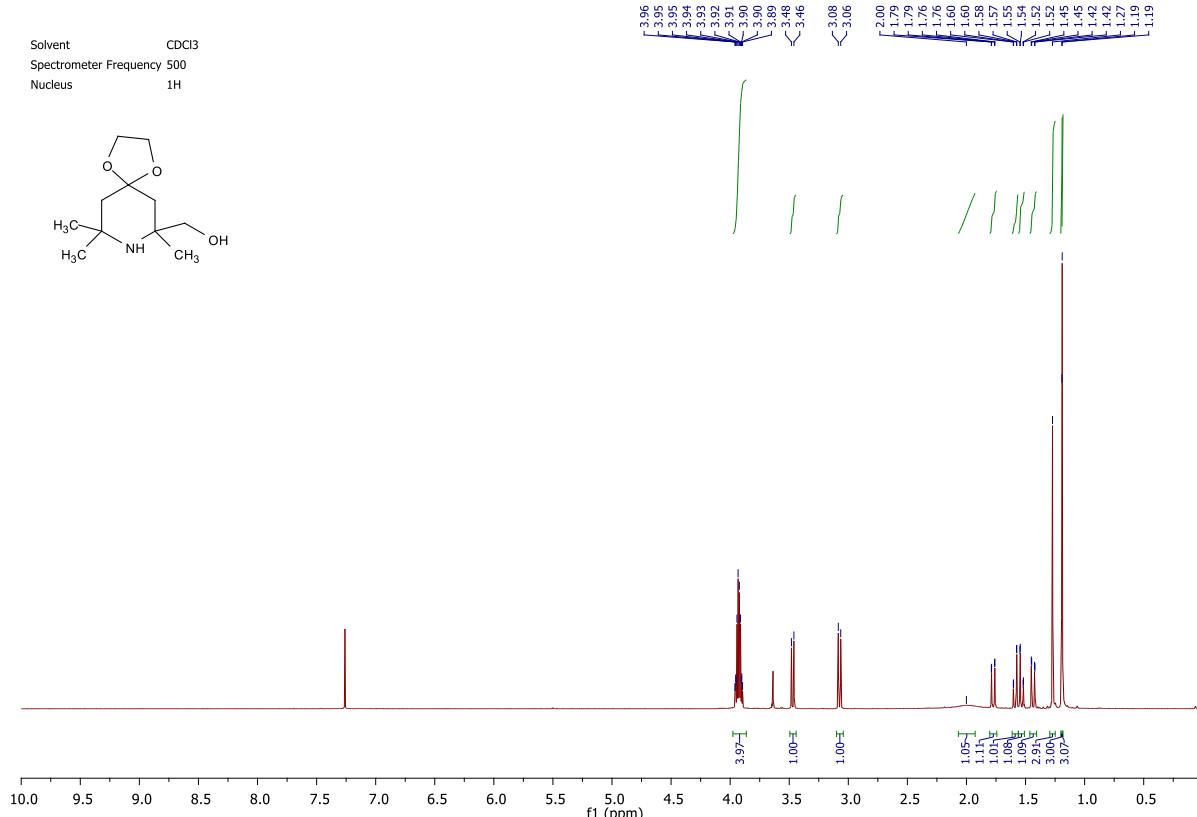


Appendix – ^1H and ^{13}C NMR spectra of key compounds



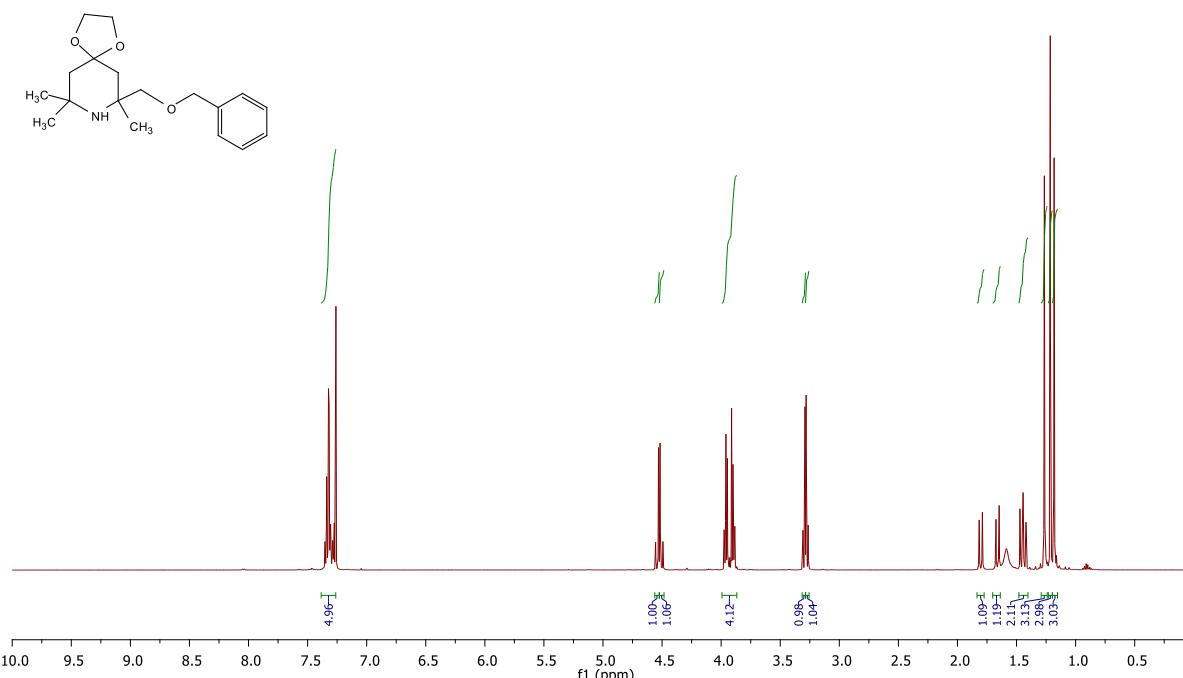
7.6 Synthesis of astemizole analogue 288

(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)methanol (316)

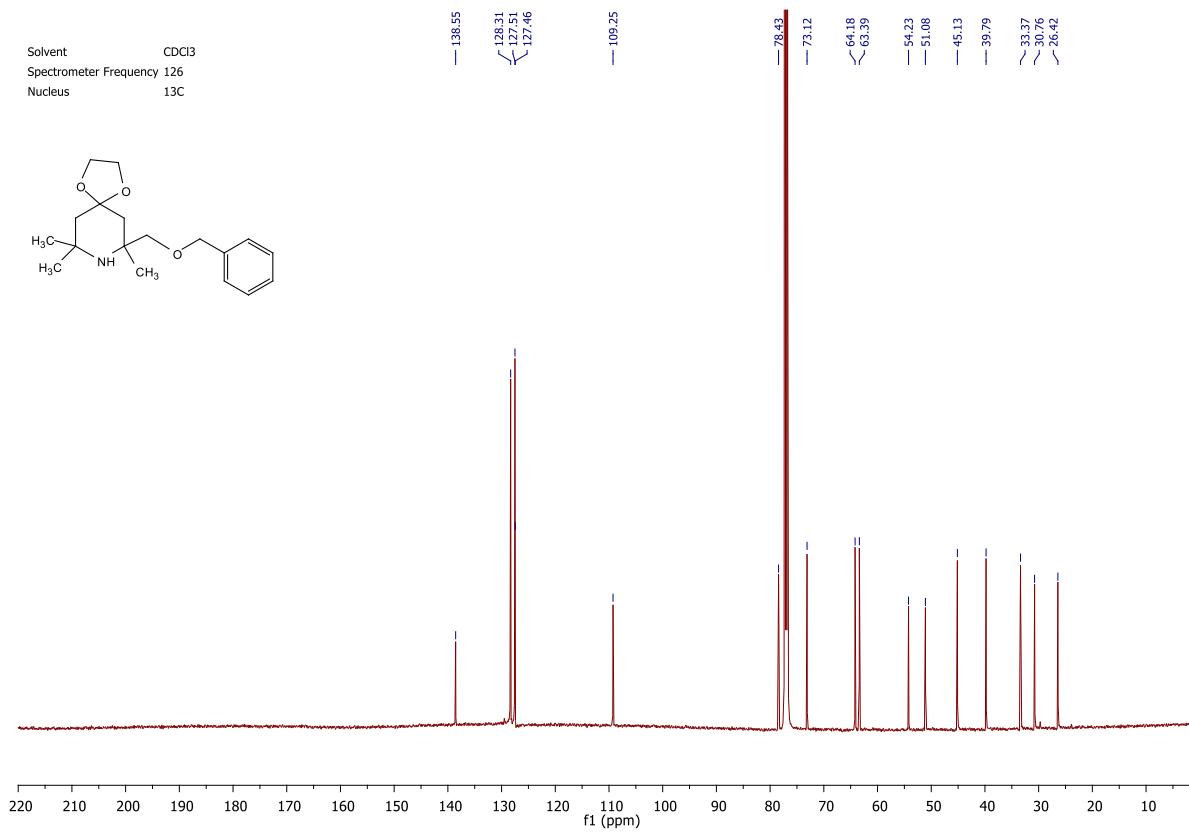
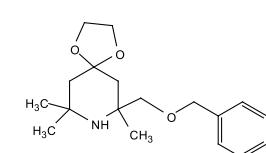


7-((Benzyl)oxy)methyl)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane (317)

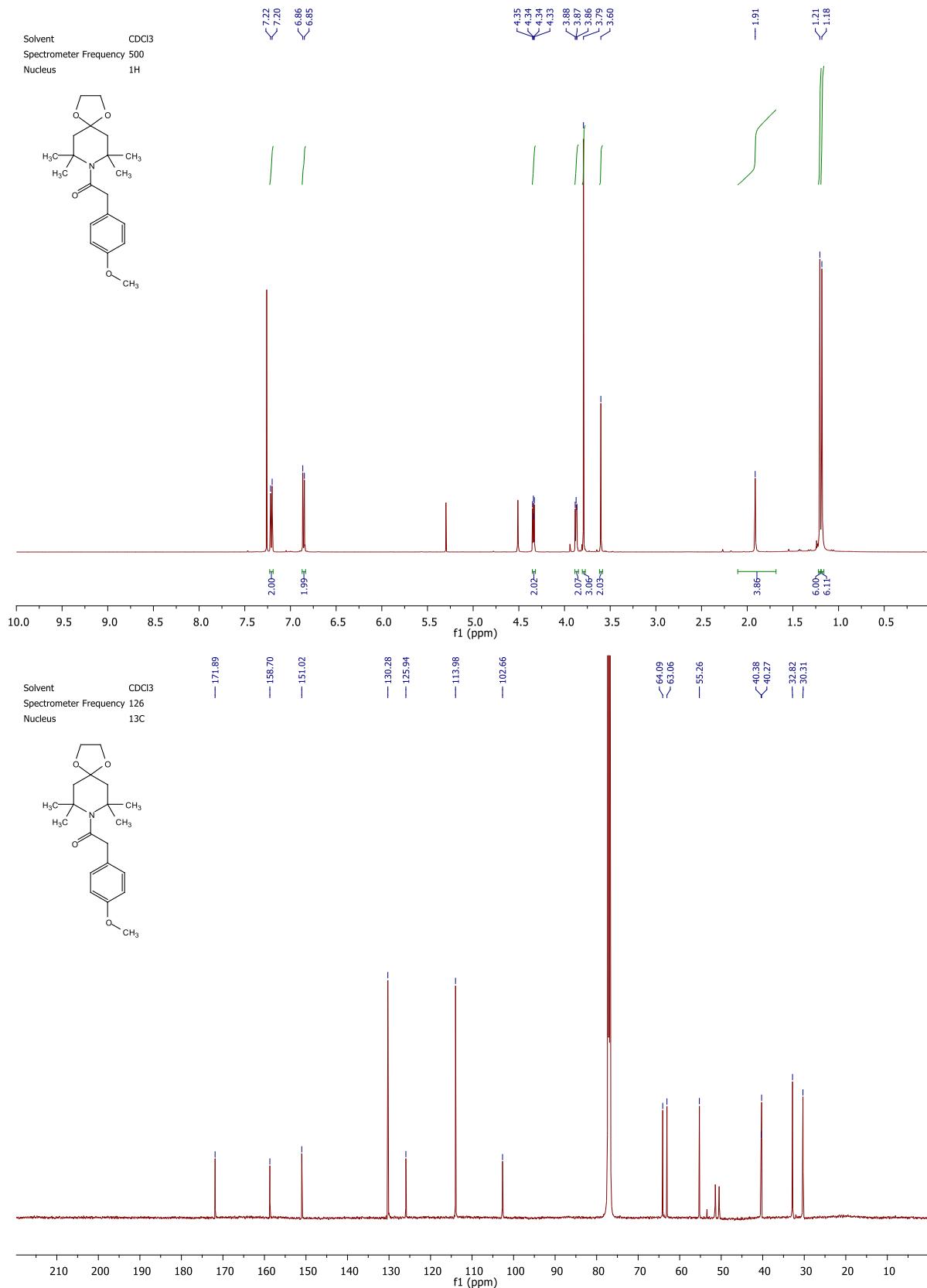
Solvent CDCl_3
 Spectrometer Frequency 500
 Nucleus ^1H



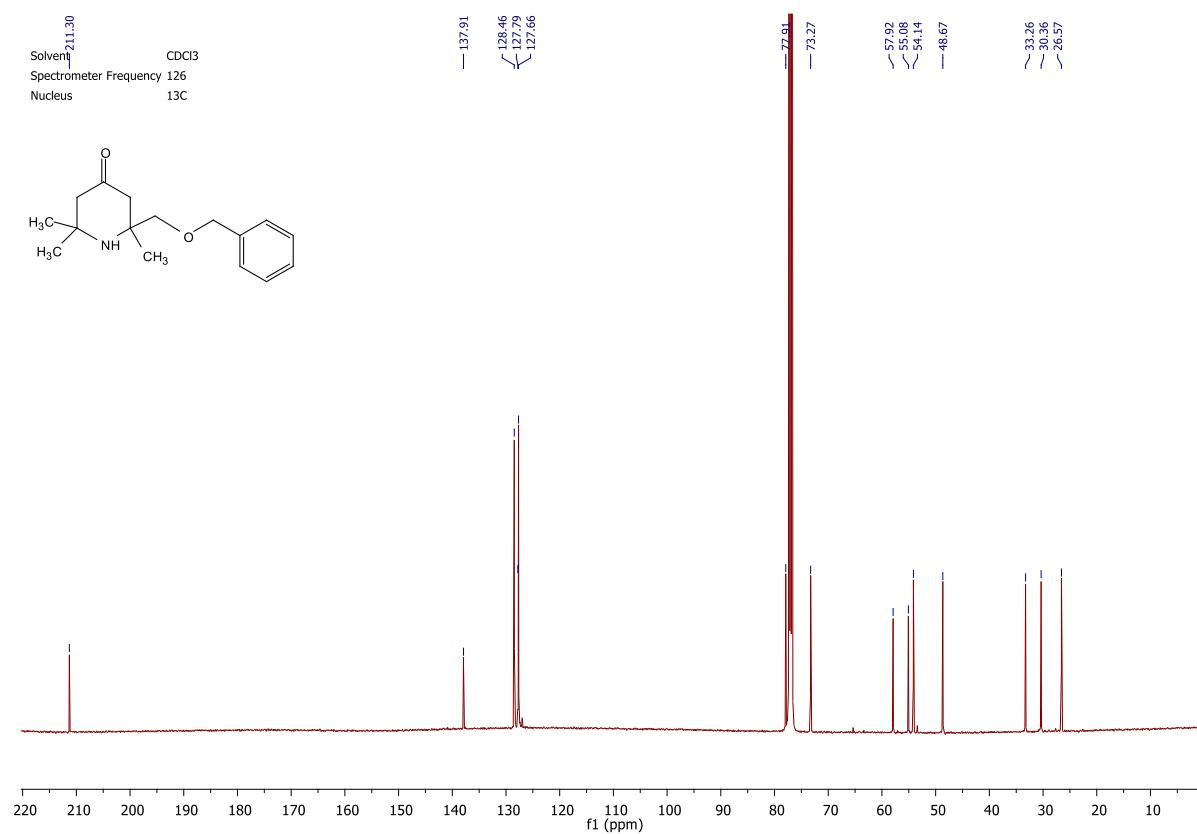
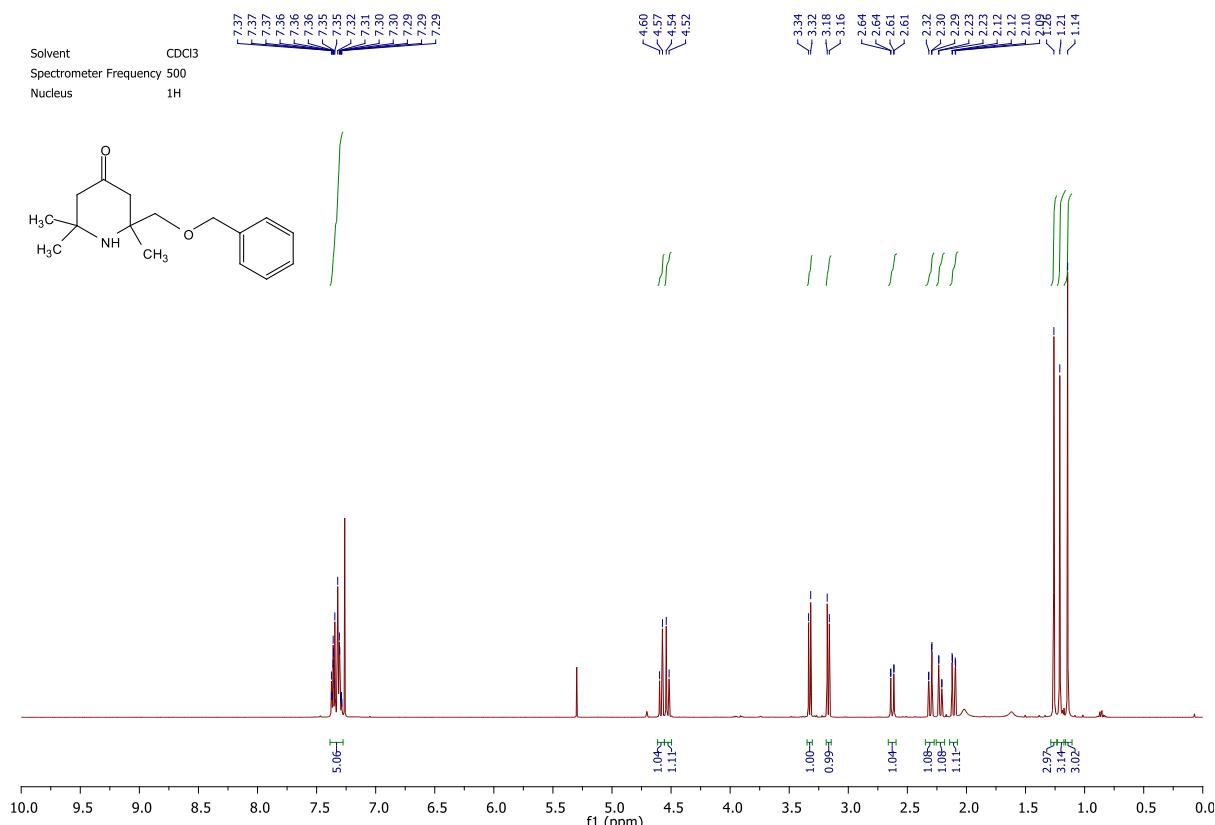
Solvent CDCl_3
 Spectrometer Frequency 126
 Nucleus ^{13}C



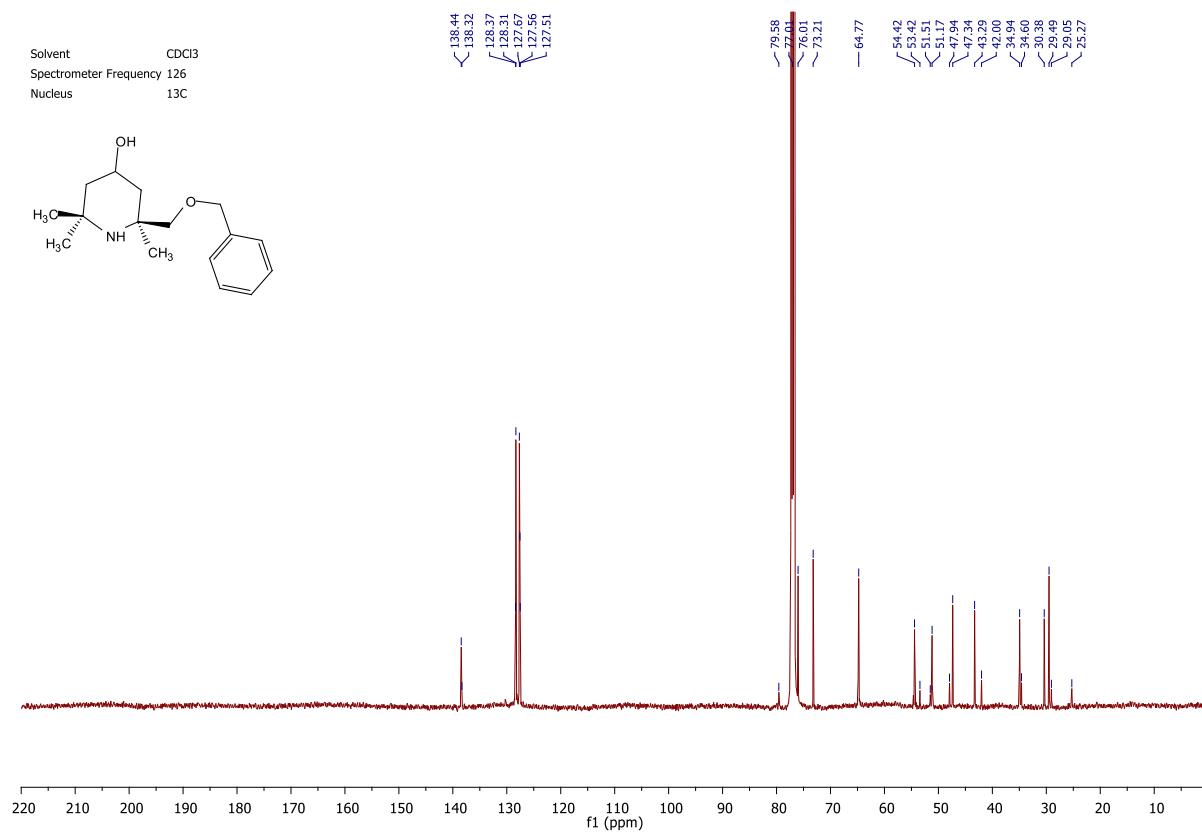
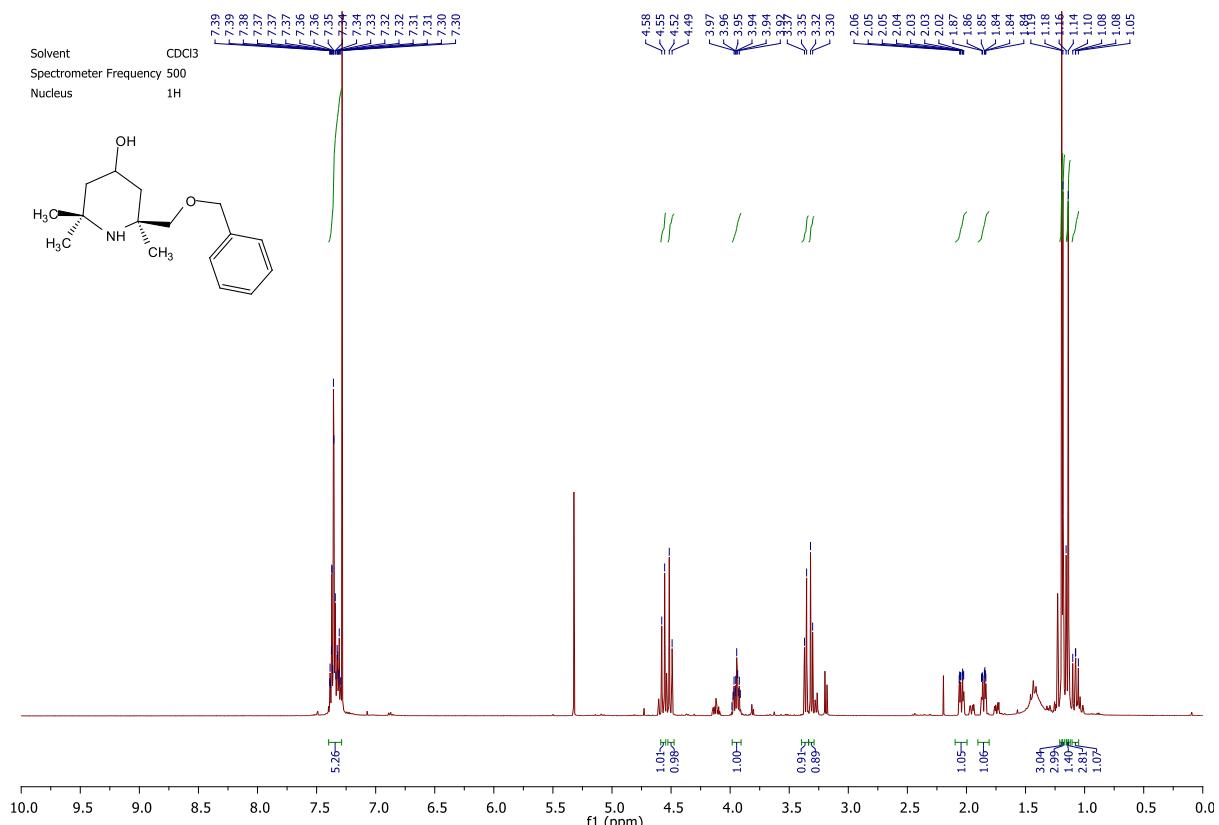
7-((BenzylOxy)methyl)-8-(4-methoxyphenethyl)-7,9,9-trimethyl-1,4-dioxa-8 azaspiro [4.5]decane (318)



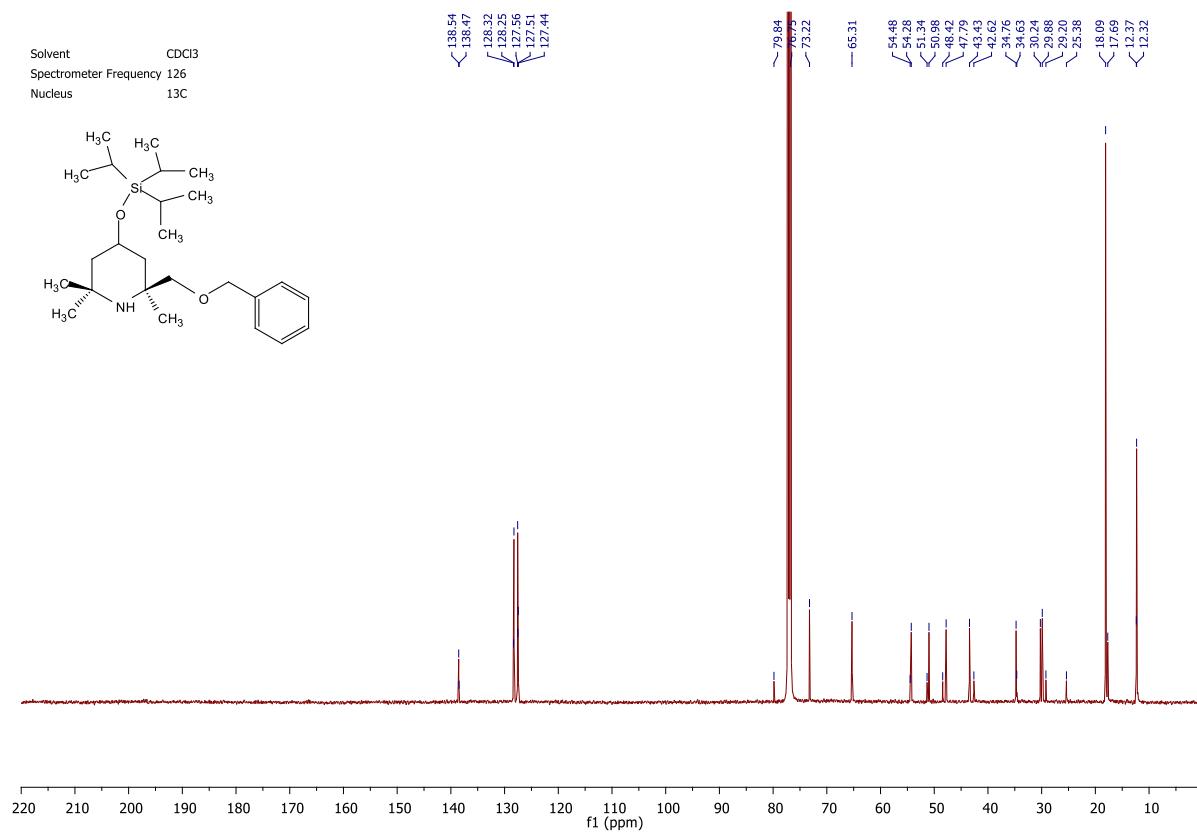
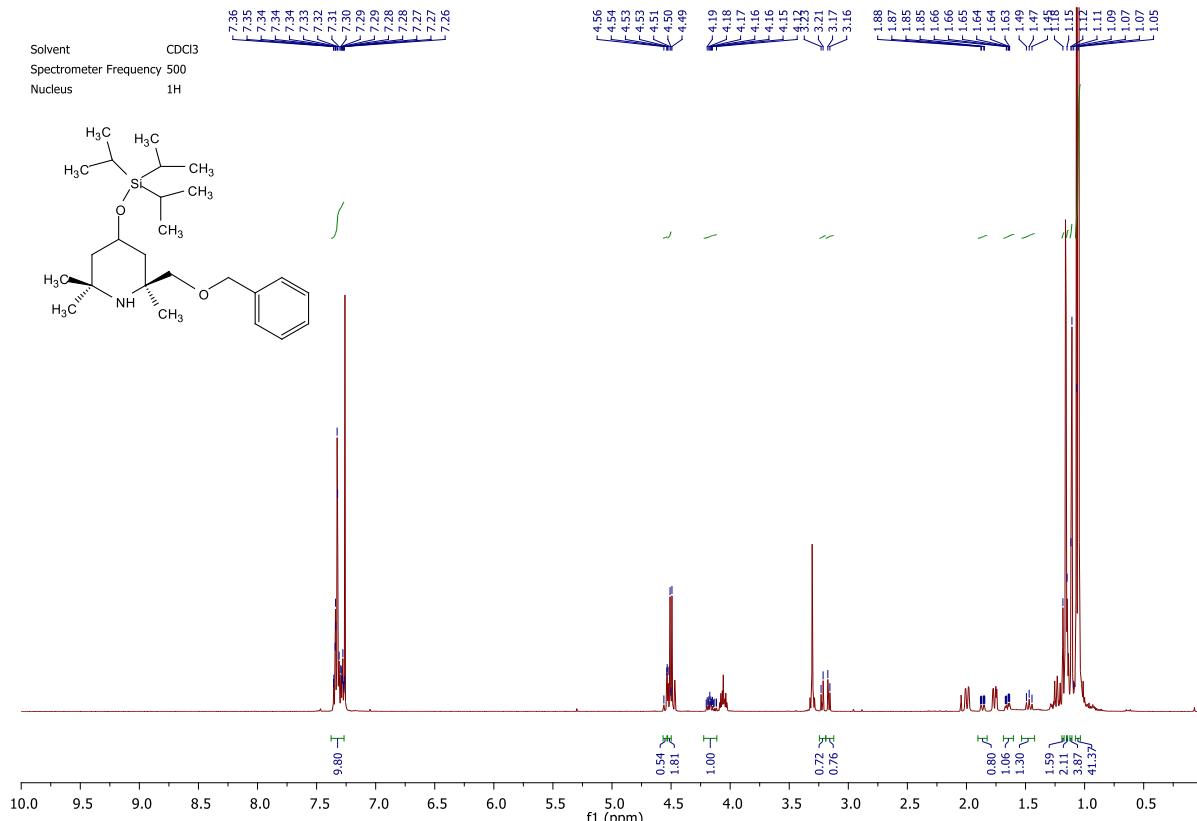
2-((BenzylOxy)methyl)-2,6,6-trimethylpiperidin-4-one (354)



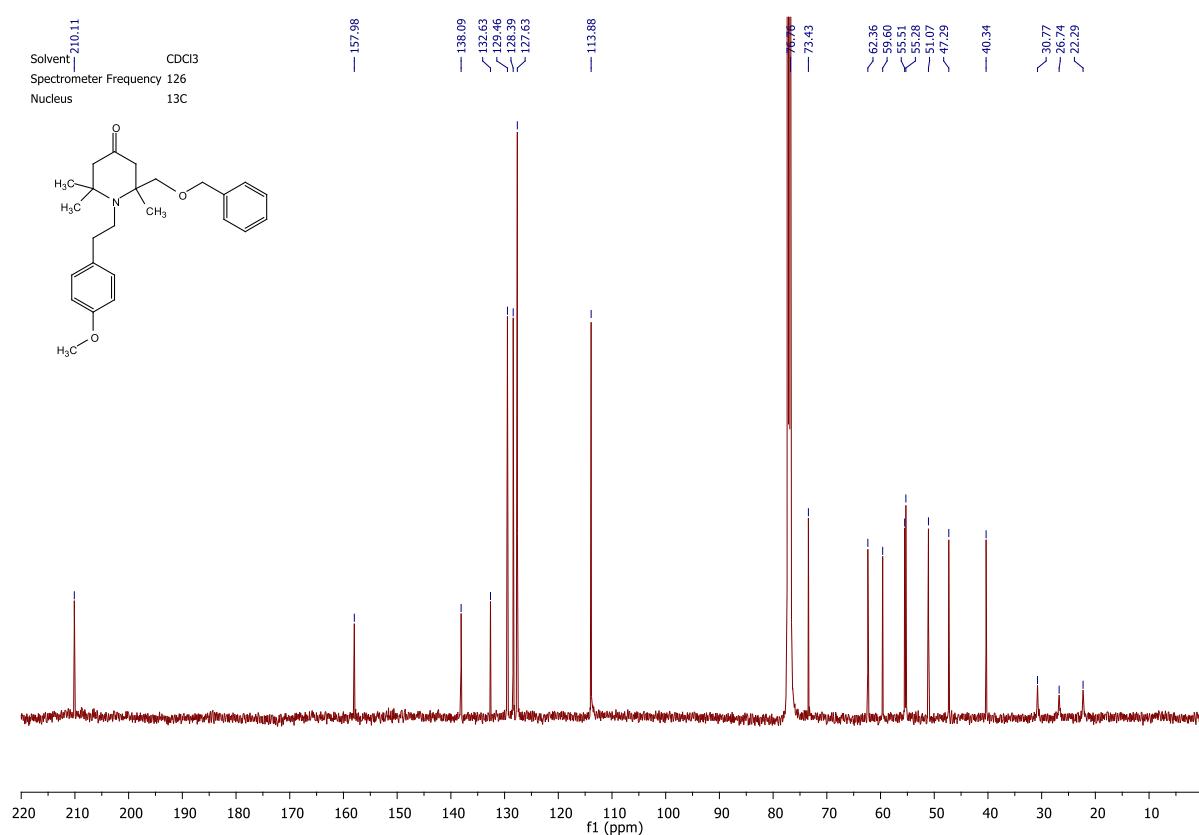
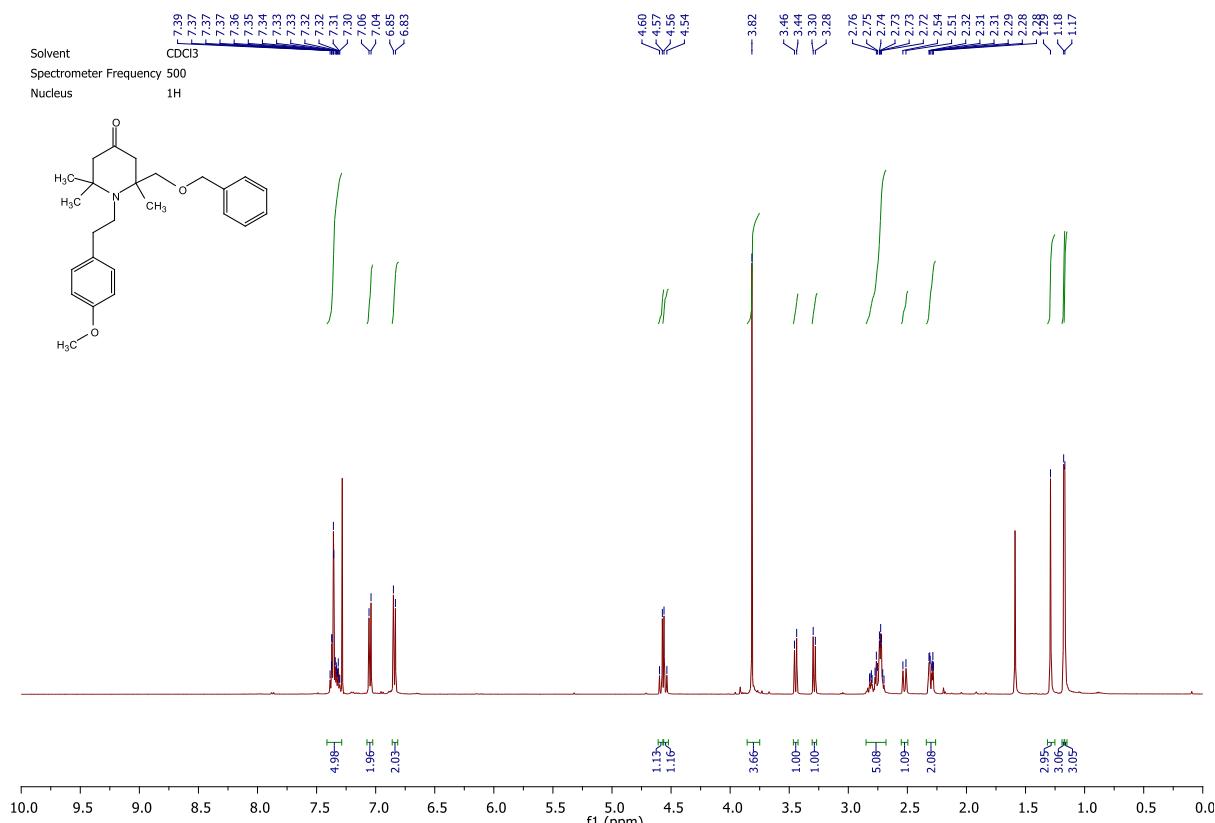
2-((BenzylOxy)methyl)-2,6,6-trimethylpiperidin-4-ol (355)



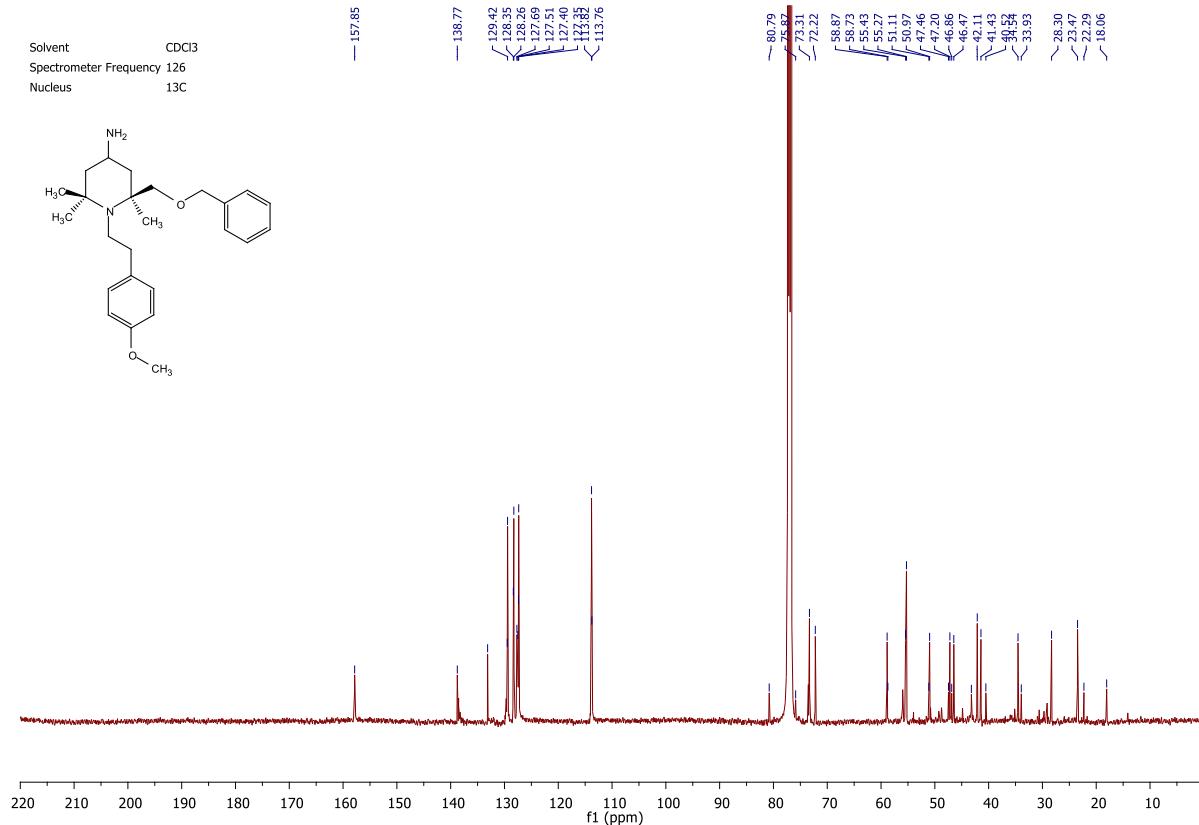
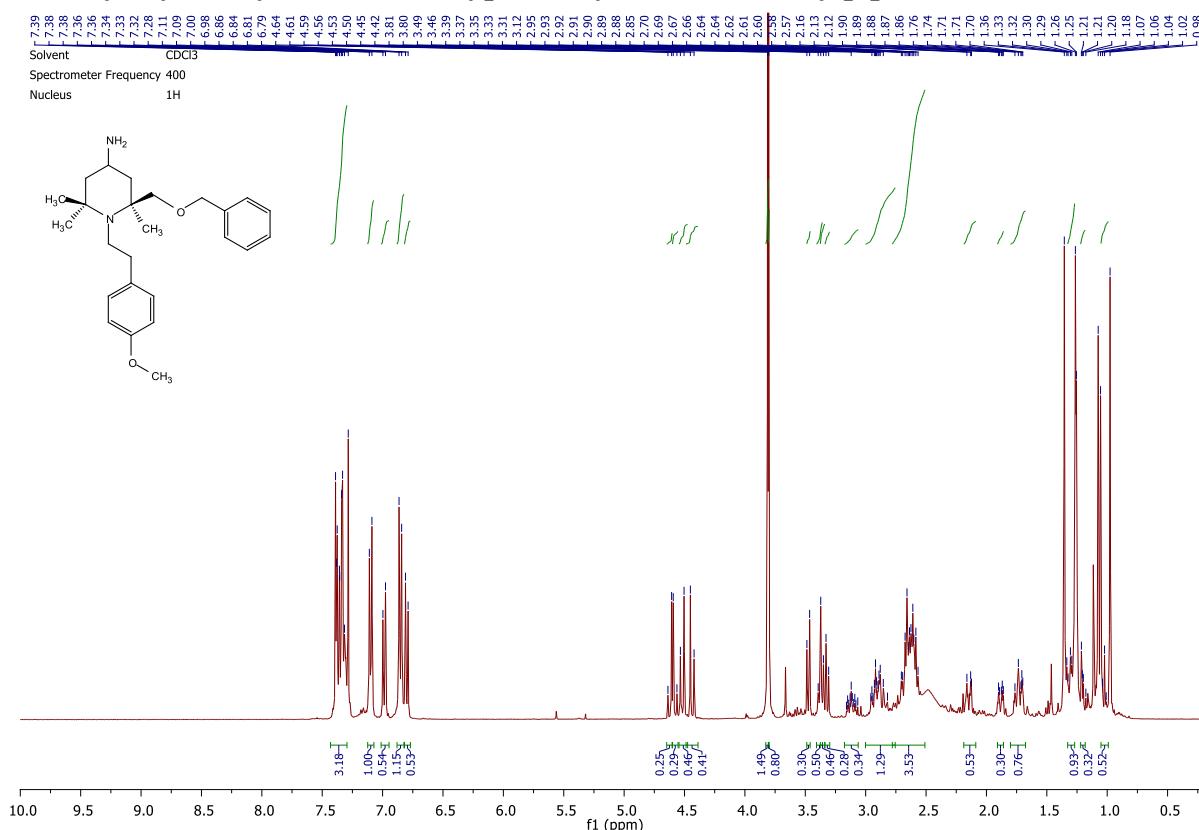
2-((Benzyl)oxy)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (356)



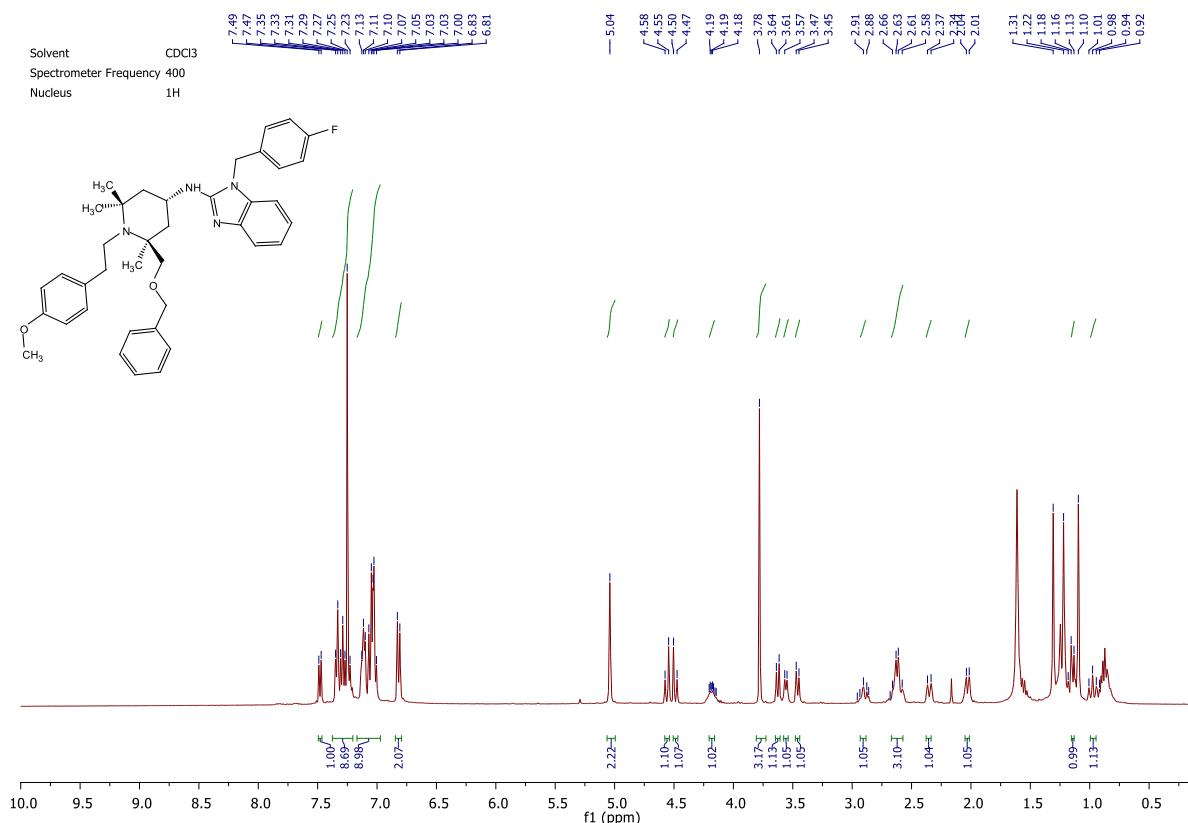
2-((Benzylxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-one (319)



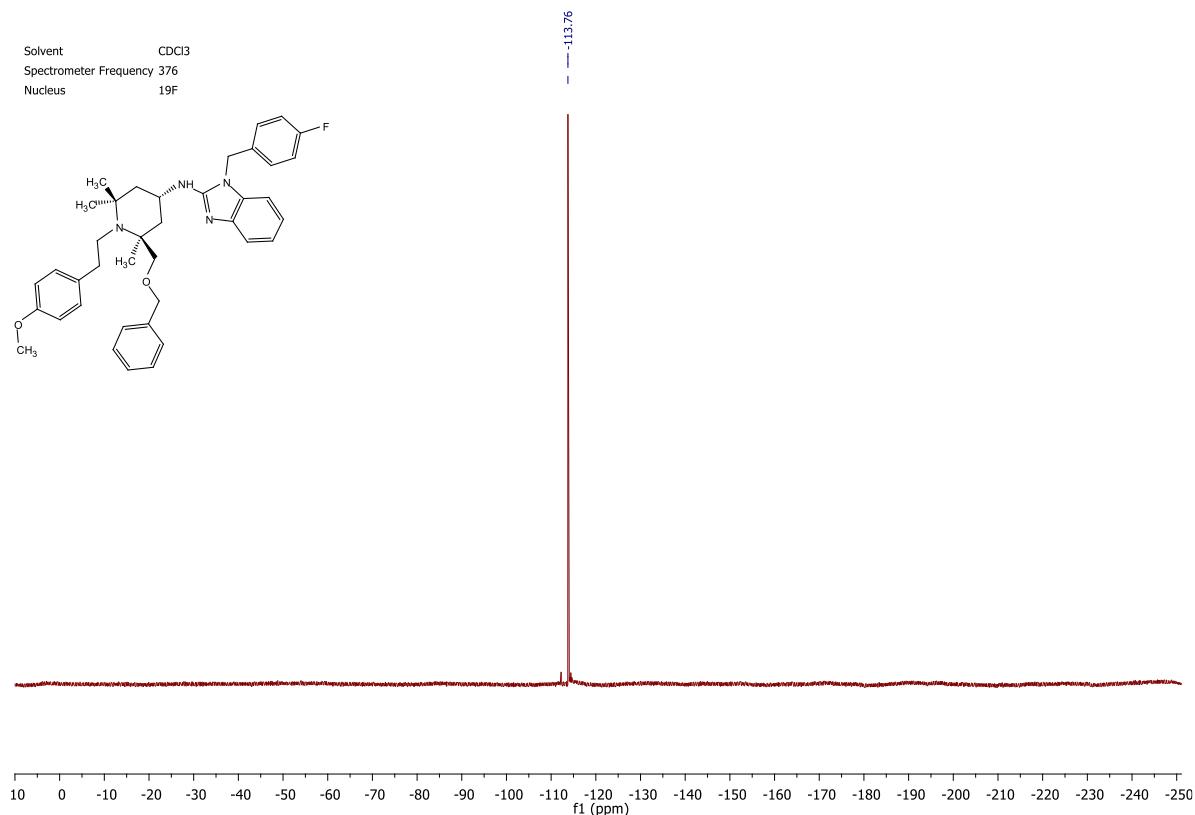
2-((Benzyl)oxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-amine (320)



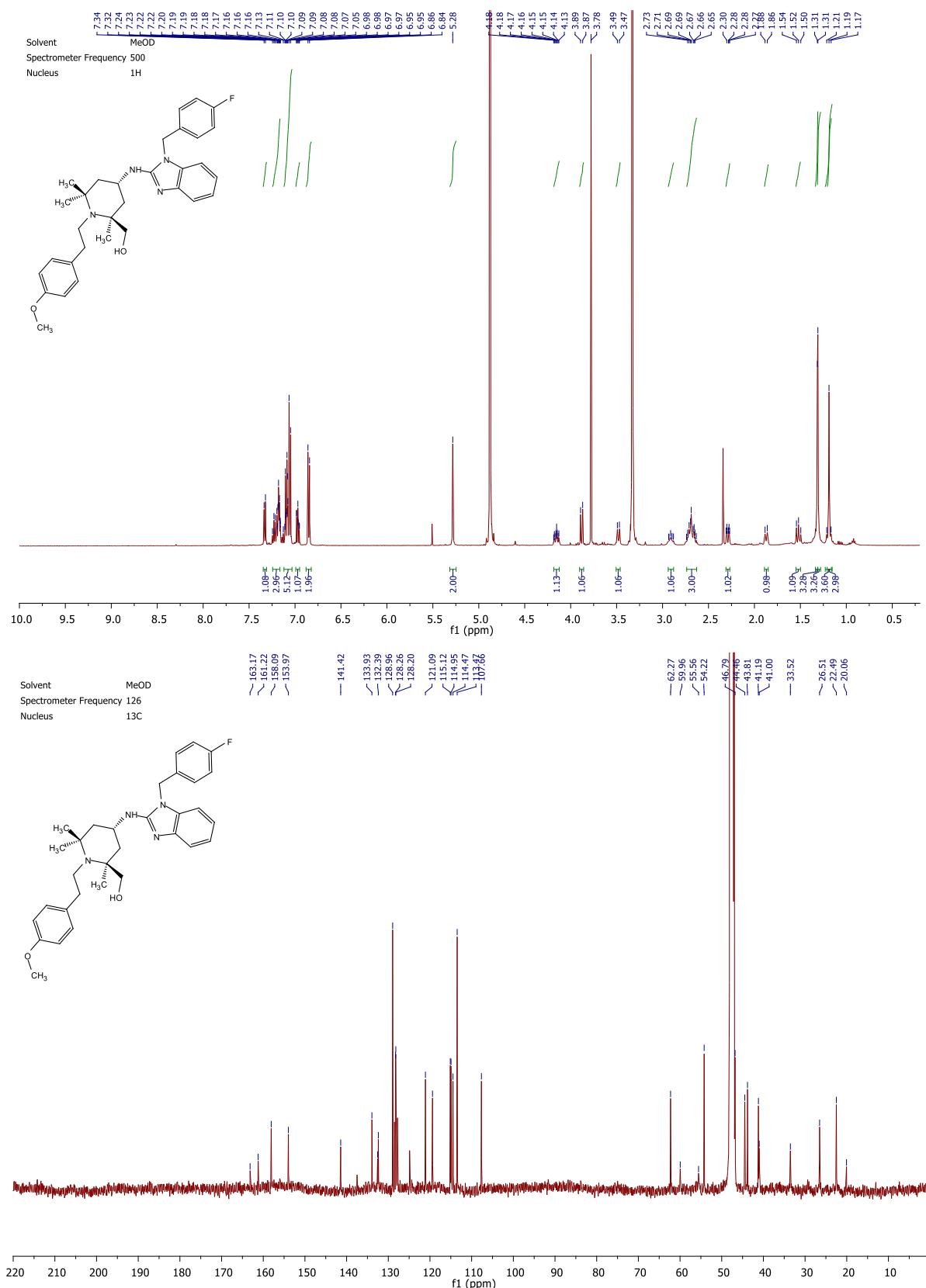
N-((2R,4R)-2-((Benzyl)oxy)methyl)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-4-yl)-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-amine (321)



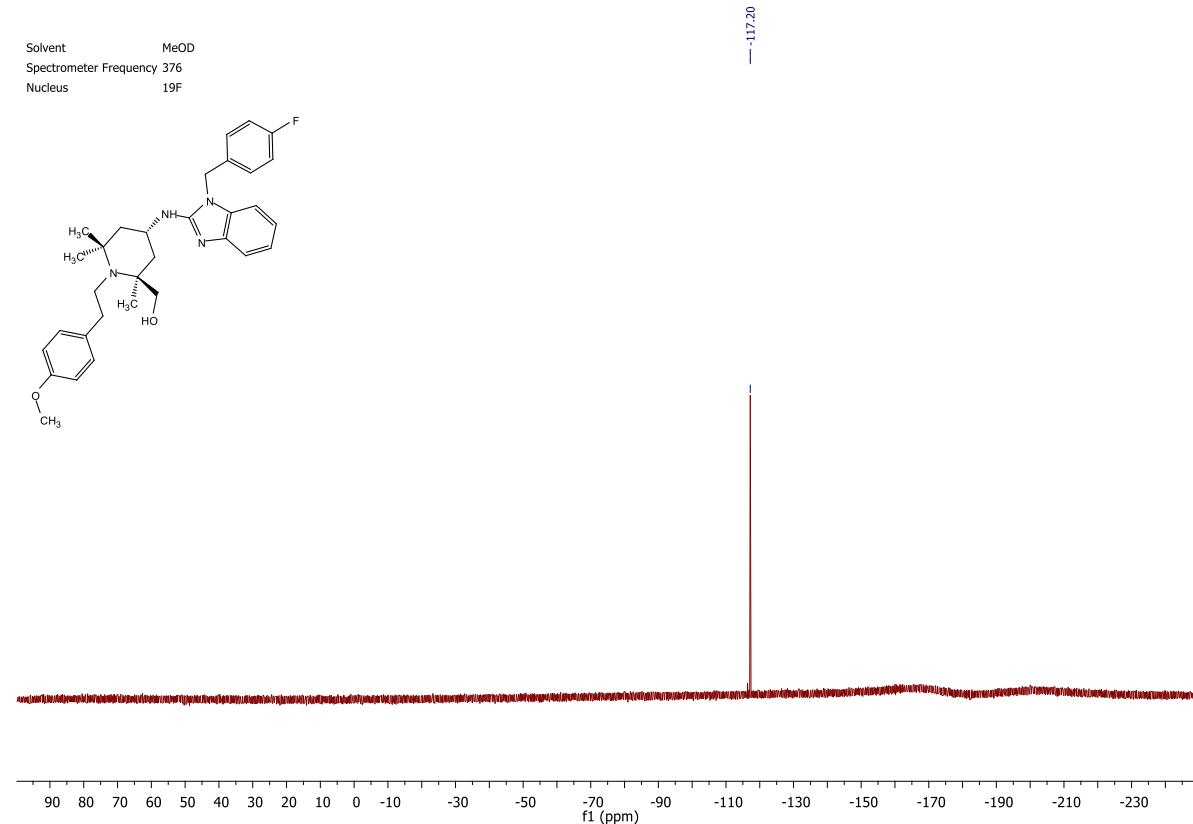
Appendix – ^1H and ^{13}C NMR spectra of key compounds



((2*R*,4*R*)-4-((1-(4-Fluorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)amino)-1-(4-methoxyphenethyl)-2,6,6-trimethylpiperidin-2-yl)methanol (288)

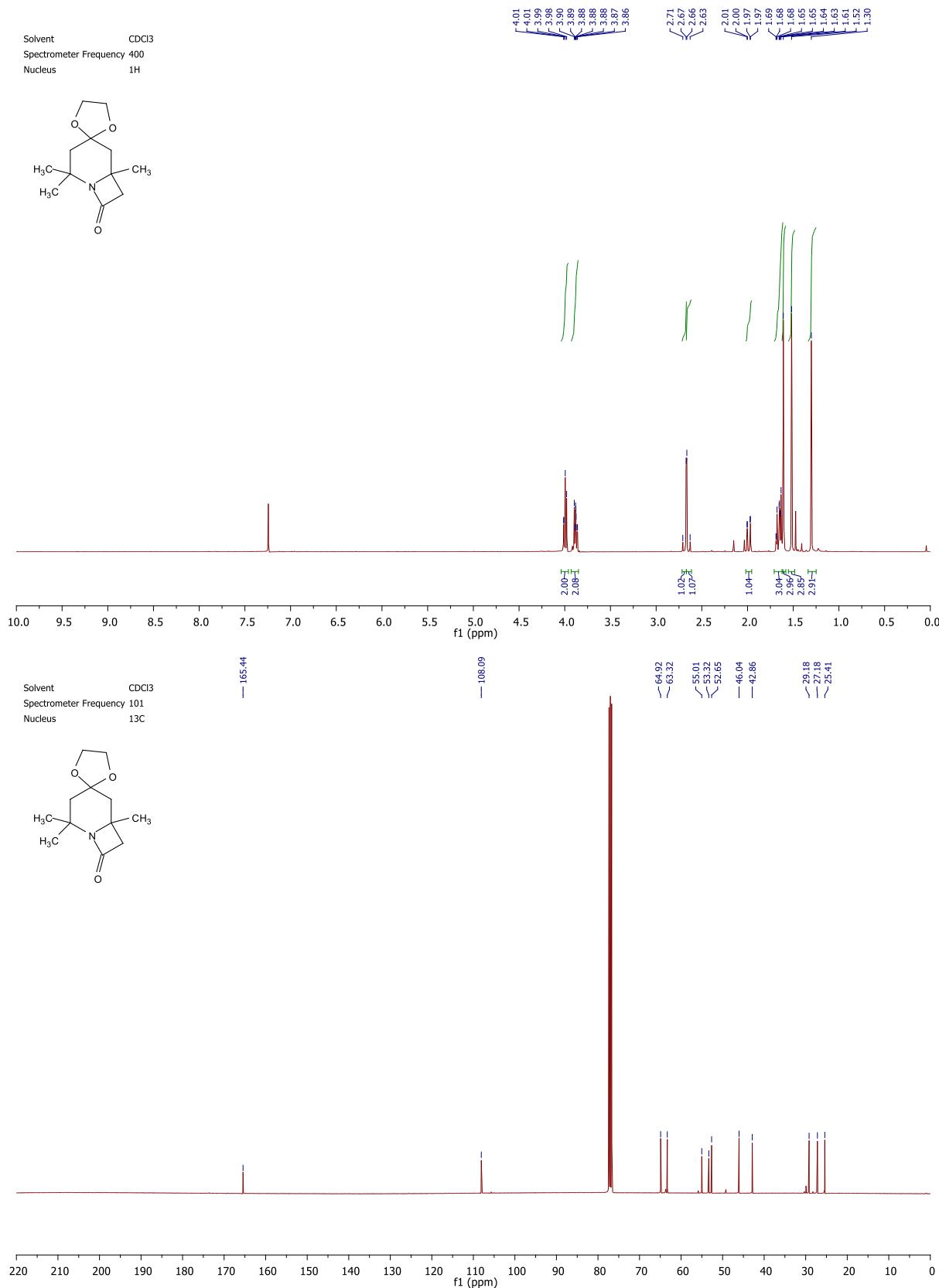


Appendix – ^1H and ^{13}C NMR spectra of key compounds

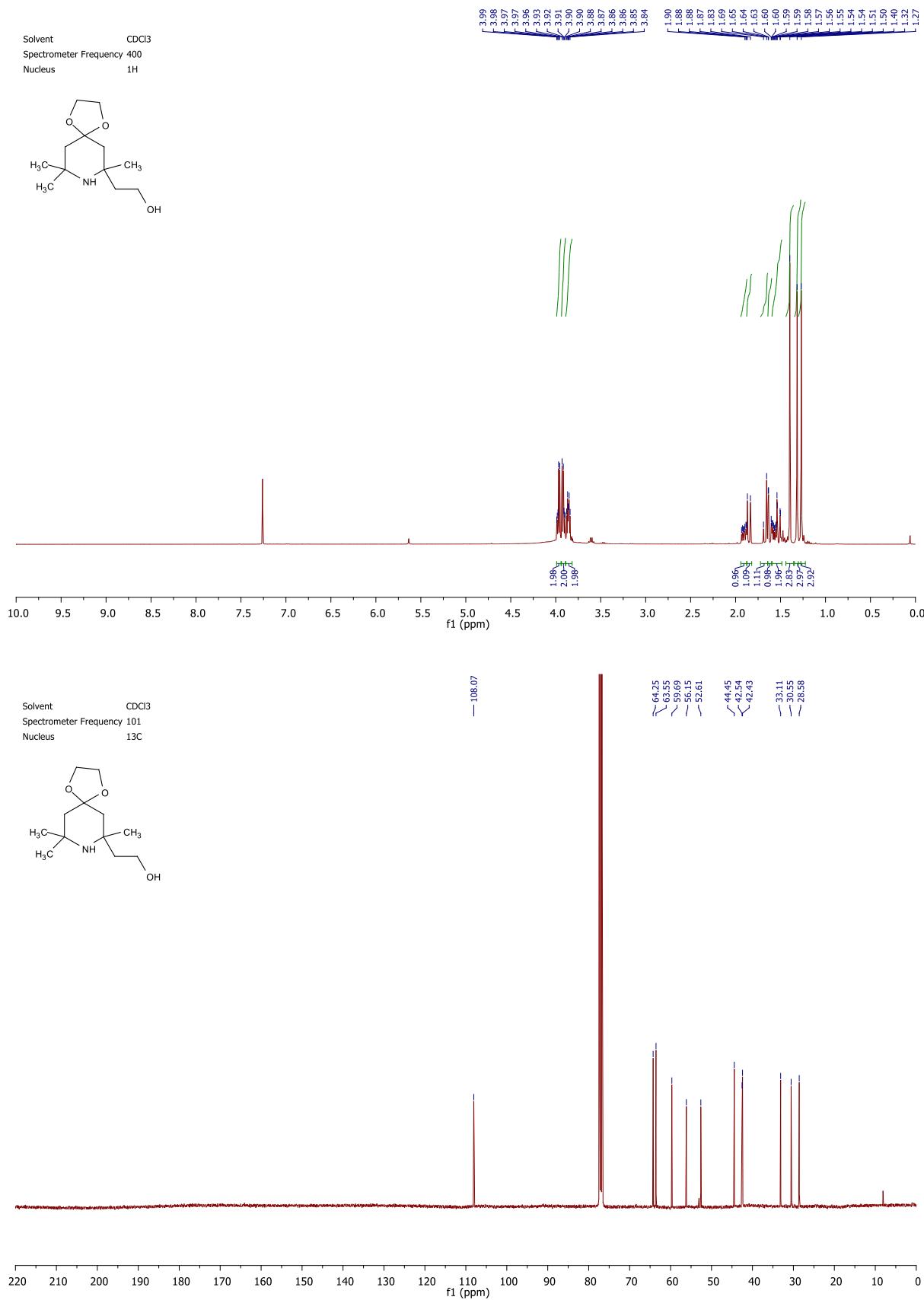


7.7 Attempted synthesis of astemizole analogue 289/335

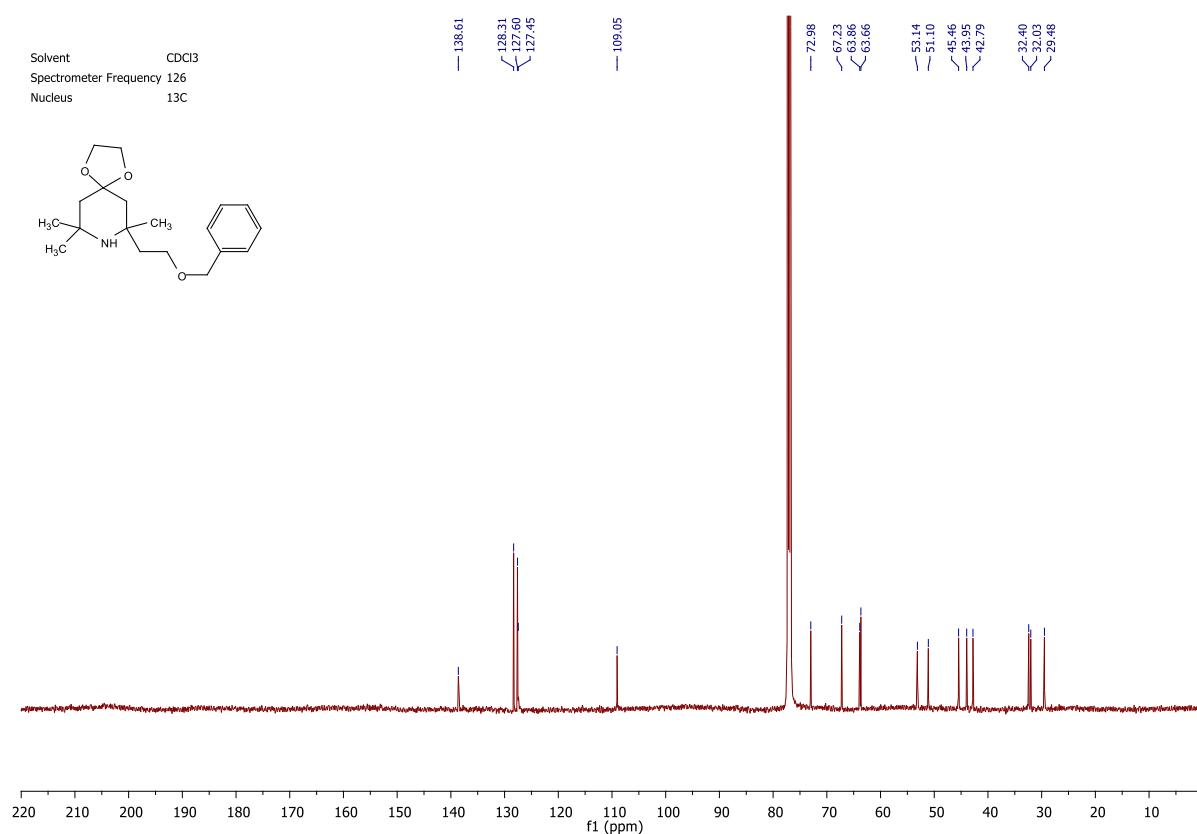
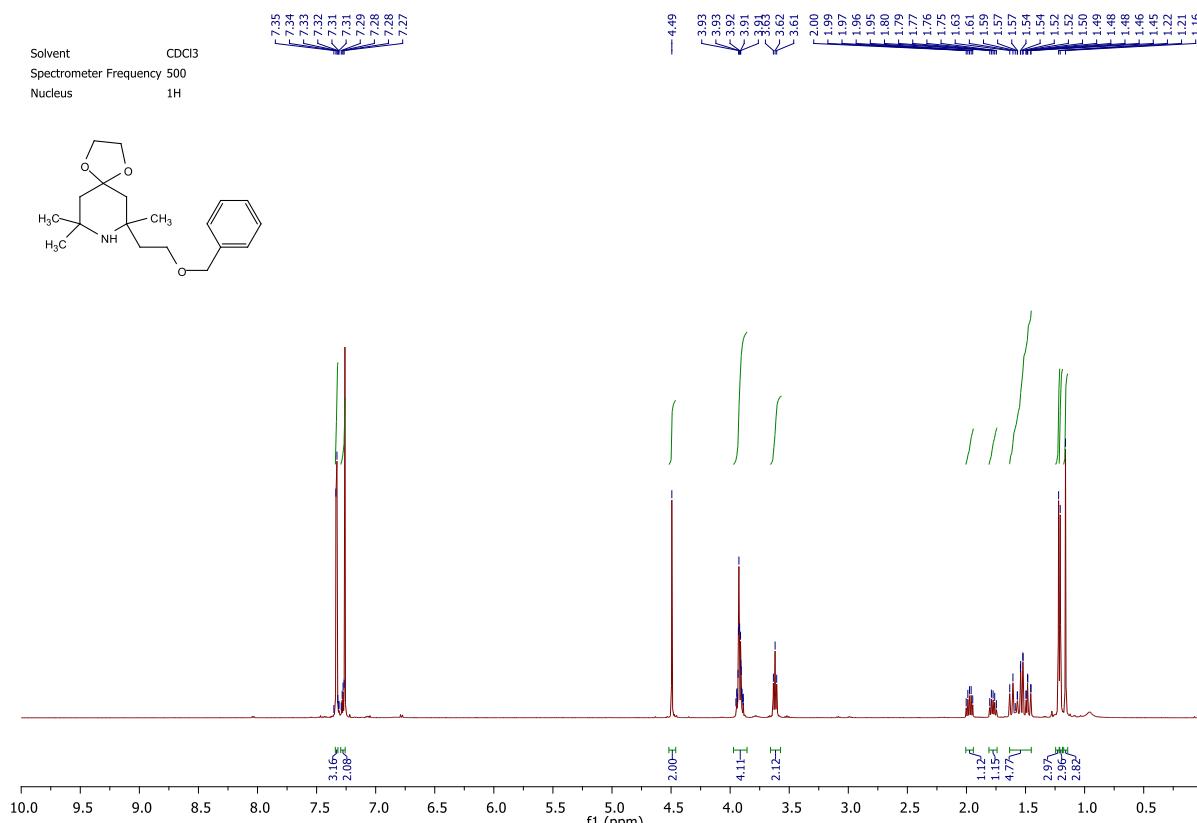
2,2,6-Trimethyl-1-azaspiro[bicyclo[4.2.0]octane-4,2'-[1,3]dioxolan]-8-one (128)



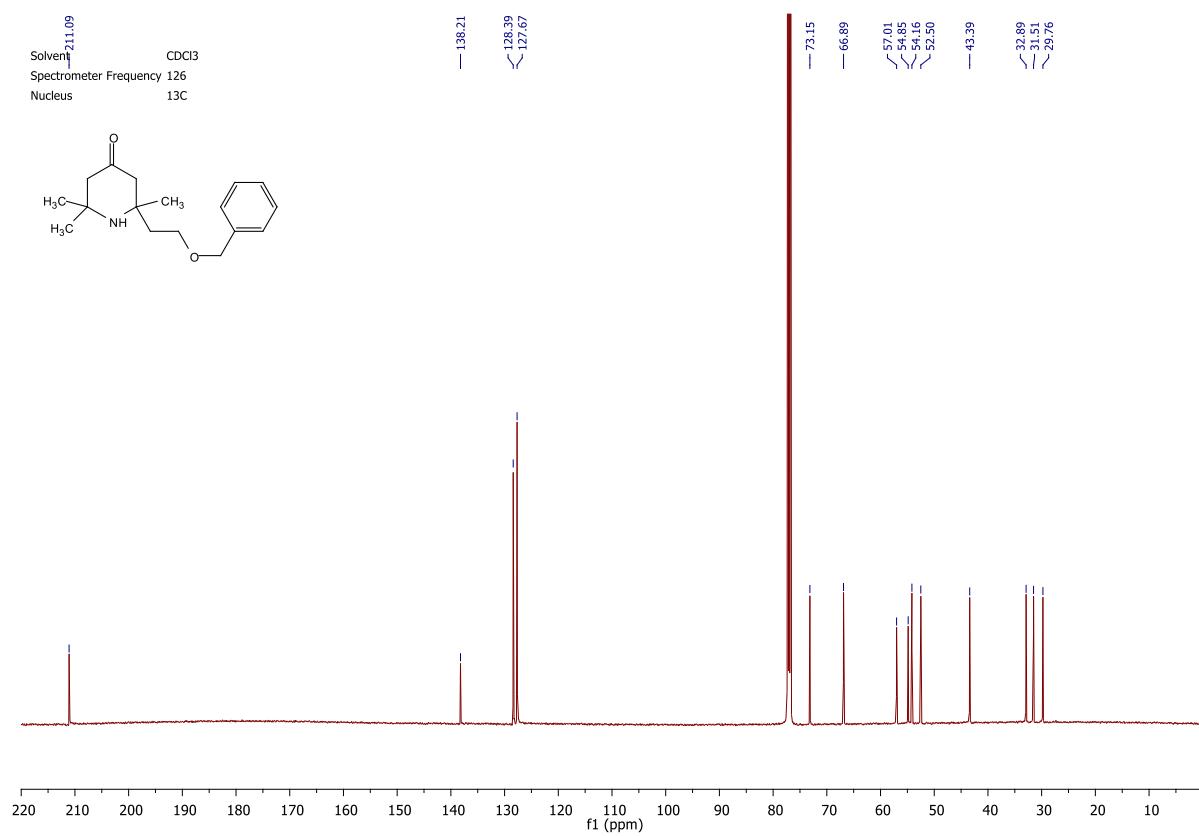
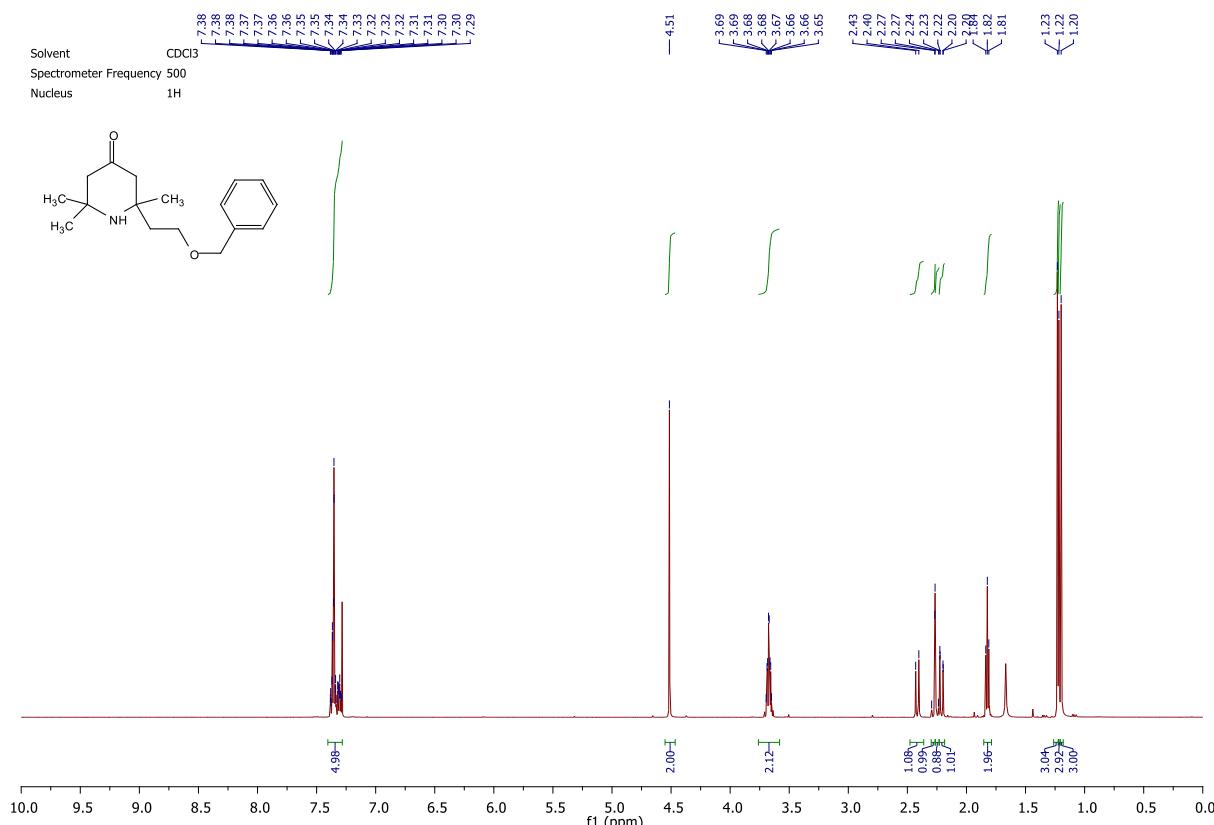
2-(7,9,9-Trimethyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)ethanol (333)



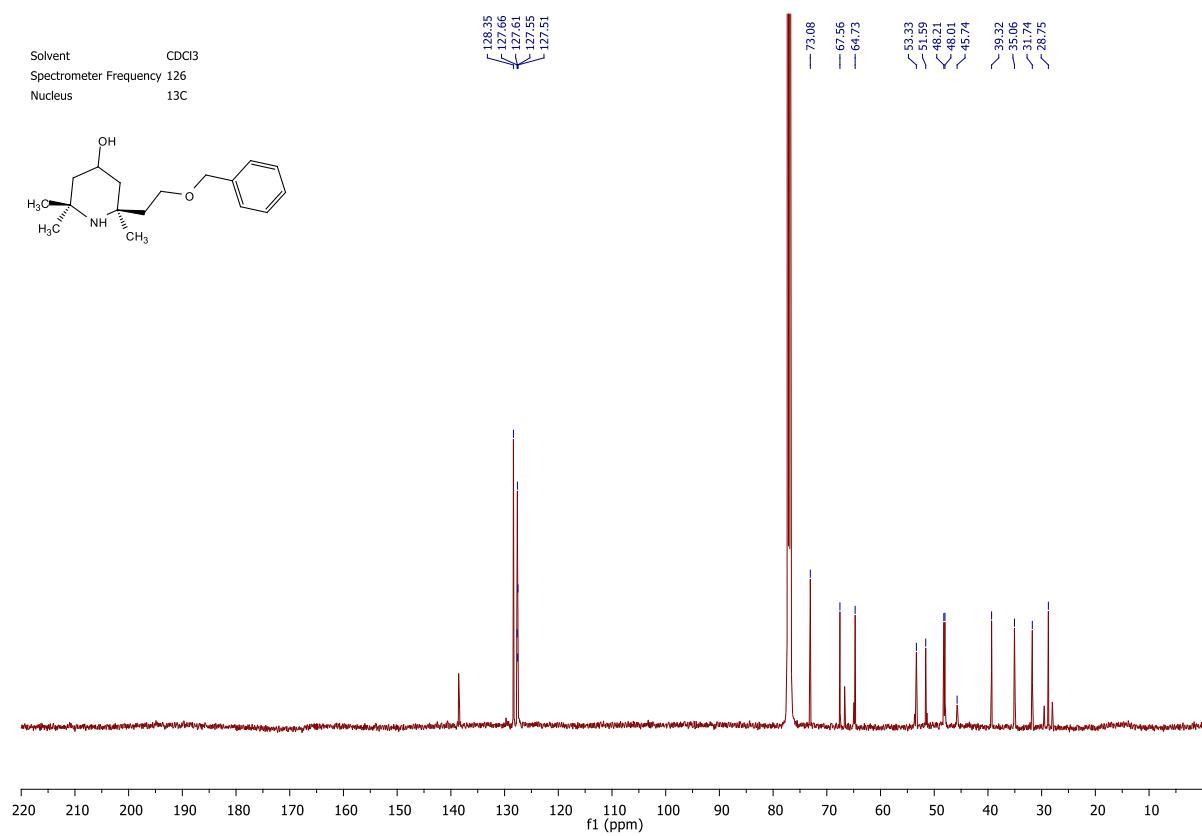
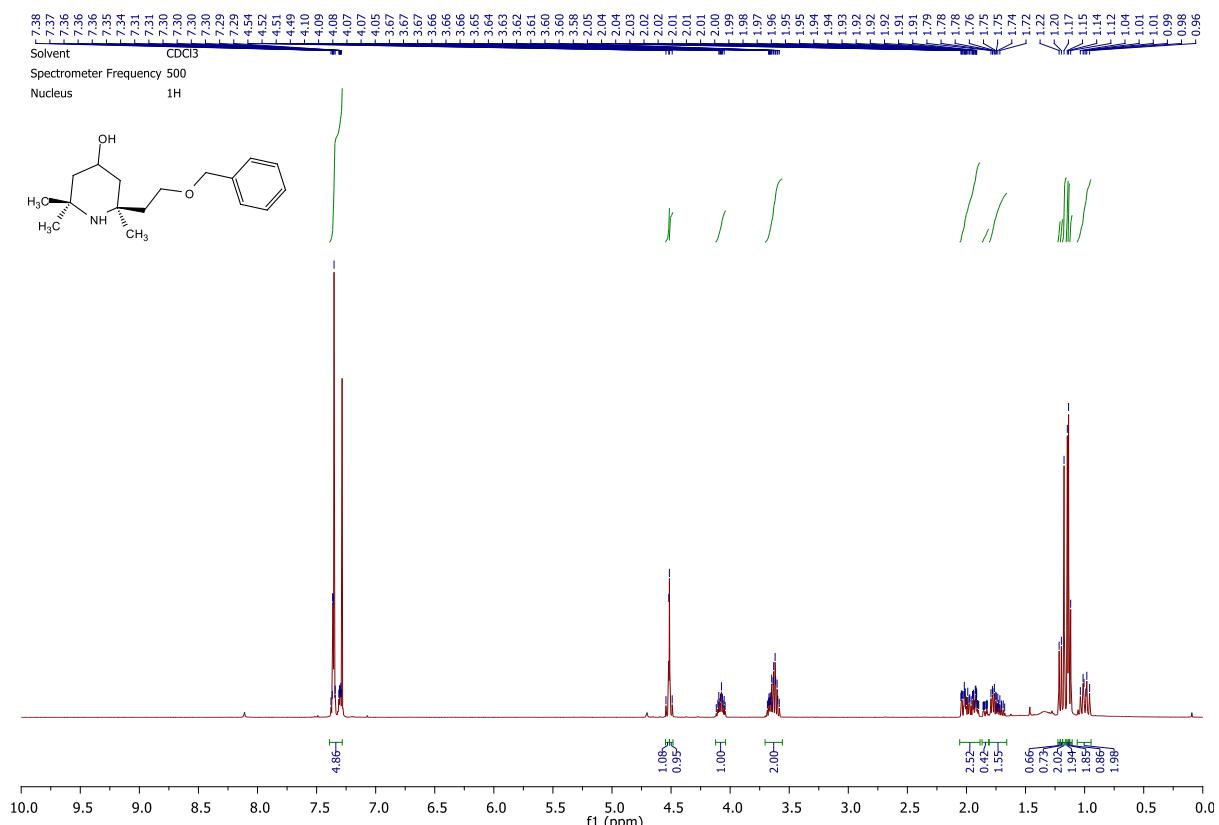
7-(2-(BenzylOxy)ethyl)-7,9,9-trimethyl-1,4-dioxa-8-azaspiro[4.5]decane (336)



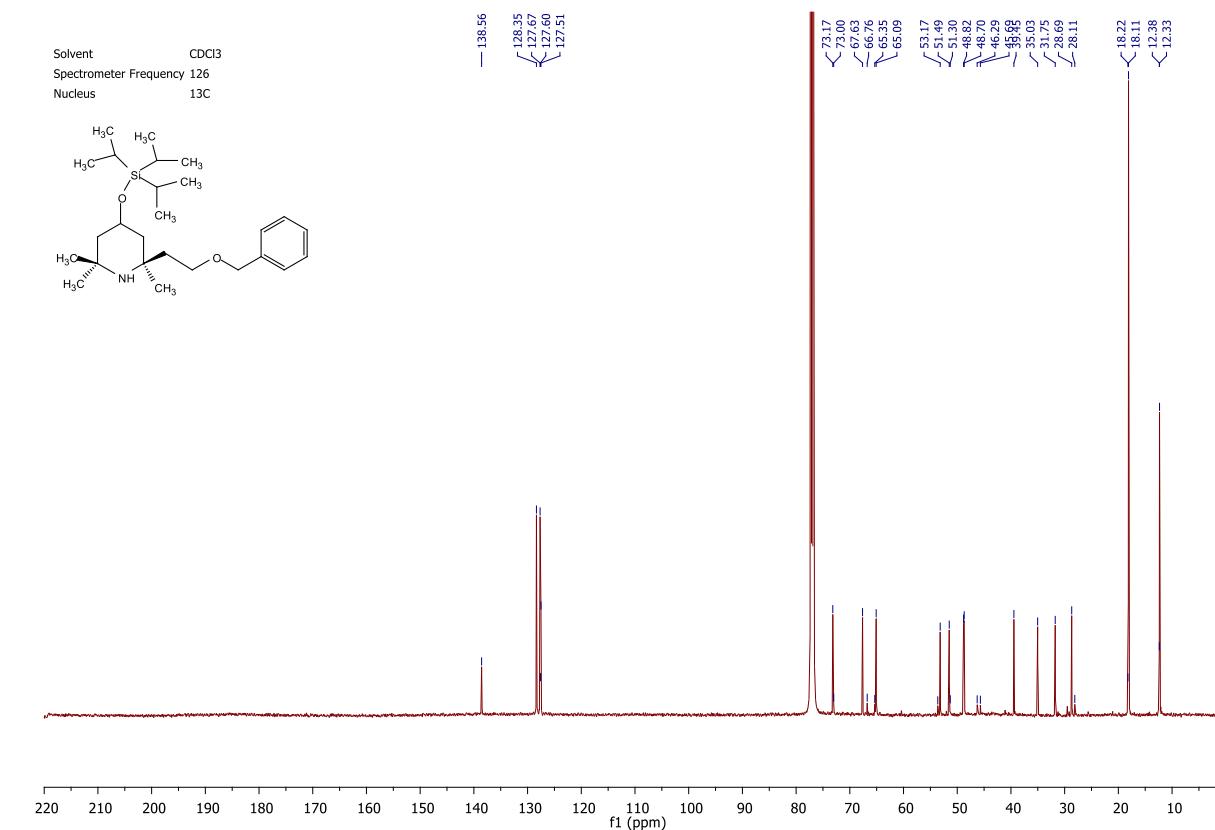
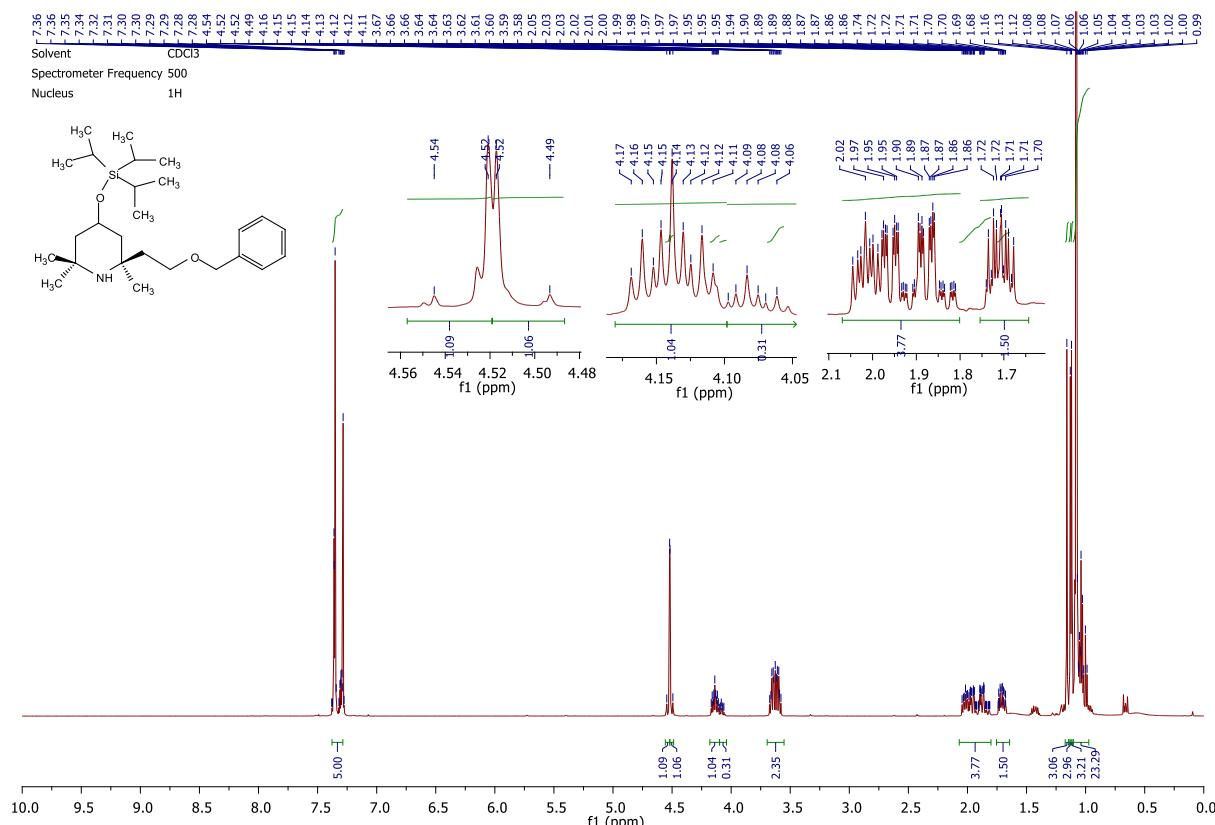
2-((Benzylxy)ethyl)-2,6,6-trimethylpiperidin-4-one (359)



2-(2-(BenzylOxy)ethyl)-2,6,6-trimethylpiperidin-4-ol (360)



2-(2-(BenzylOxy)ethyl)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (361)



2-(2-(BenzylOxy)ethyl)-2,6,6-trimethyl-4-((triisopropylsilyl)oxy)piperidine (363)

