Multicomponent Diels-Alder Sequences of 1-Aminodendralenes

A thesis submitted for the degree of

Doctor of Philosophy

Siu Min (Margaret) Tan

Research School of Chemistry

The Australian National University

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Declaration

Except where specific acknowledgements of others are made, the work described in this thesis was carried out by the author during the period of April 2011 to November 2017 in the Research School of Chemistry of the Australian National University, Australia, under the supervision of Professor Mick Sherburn. The material presented has not been submitted for any other degree and is less than 100,000 words in length.

Siu Min (Margaret) Tan

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Finally, I am grateful to my mum and dad for giving me the freedom to pursue my dreams and for their constant encouragement and support.

Publications and Presentations

The following list details the publications and presentations that have resulted from the author's research during her candidature for the degree of Doctor of Philosophy.

Publication

Tan, S. M.; Willis, A. C.; Paddon-Row M. N.; Sherburn M. S. Multicomponent Diene-Transmissive Diels-Alder Sequences Featuring Aminodendralenes, *Angew. Chem. Int. Ed.* **2016** *55* (9) 3081-5.

Presentations

Tan, S. M. and Sherburn M. S. *Rapid Access to Heterocyclic Frameworks Through Novel Multiple Component Reactions.* Oral presentation: Southern Highlands Conference on Heterocyclic Chemistry in Bowral, Australia, 31 August-2 September 2014.

Tan, S. M. and Sherburn M. S. *Multi-Component Reactions Involving Cross-Conjugated Trienamines.* Poster Presentation: RACI NSW Organic Chemistry Group 34th Annual One Day Symposium, Canberra, Australia, 4 December 2013.

Tan, S. M. and Sherburn M. S. *Multi-Component Reactions Involving Cross-Conjugated Trienamines.* Poster Presentation: 21st International Symposium: Synthesis in Organic Chemistry, Oxford, United Kingdom, 22-25 July 2013.

Tan, S. M. and Sherburn M. S. *Cross-Conjugated Trienamines.* Poster Presentation: 19th International Conference on Organic Chemistry/The 24th Royal Australian Chemical Institute Organic Conference (ICOS19/RACI24), Melbourne, Australia, 1-6 July 2012.

Abbreviations

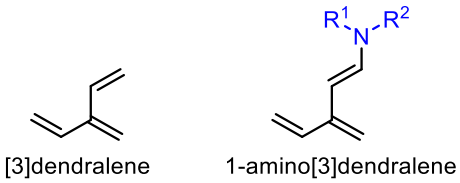
%	percentage yield
°C	degrees Celsius
Ac	acetyl
aq	aqueous
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
br	broad
Bu	butyl
ca	*circa* (approximately)
cm^{-1}	wave number
COSY	correlated spectroscopy
δ	chemical shift
d	day/s or doublet/s
DA	Diels–Alder
DFT	density functional theory
dm	decametre
DMP	Dess-Martin periodinane
DIBAL	diisobutylaluminium hydride
DMSO	dimethylsulfoxide
dr	diastereomer ratio
EDG	electron donating group
er	enantiomer ratio
EI	electron impact
equiv	equivalent/s
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
eV	electron Volts
FMO	frontier molecular orbital
GC	gas chromatography
h	hour/s
HMBC	heteronuclear multiple bond coherence
LDA	lithium diisopropylamide
HSQC	heteronuclear single quantum coherence
HOMO	highest occupied molecular orbital

HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IMDA	intramolecular Diels–Alder
i-Pr	isopropyl
IR	infrared
J	coupling constant
LRMS	low resolution mass spectometry
LUMO	lowest unoccupied molecular orbital
M	molar
M^+	molecular ion
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
min	minute/s
MHz	megahertz
mm Hg	millimetres of mercury
mol	mole or molar
mp	melting point
MS	mass spectroscopy
m/z	mass to charge ratio
ν	absorption maxima (IR)
n-BuLi	*n*-butyl lithium
n-Pr	*n*-propyl
NMM	*N*-methylmaleimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
NPM	*N*-phenylmaleimide
Ph	phenyl
ppm	parts per million
q	quartet
rt	room temperature
sat	saturated
SOI	secondary orbital interaction
t	time
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TMS	trimethylsilyl

temp	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TS	transition state

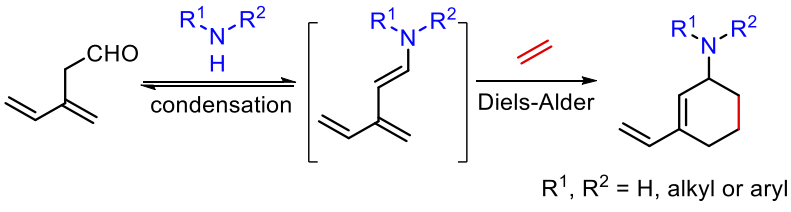
Abstract

This thesis explores the use of *in situ* generated acyclic 1-aminodendralenes in multicomponent diene-transmissive Diels-Alder (DTDA) reaction sequences. Dendralenes have previously been shown to generate polycyclic frameworks in a step-economic manner. The 1-amino substituent is shown to promote very high levels of site selectivity in these processes.

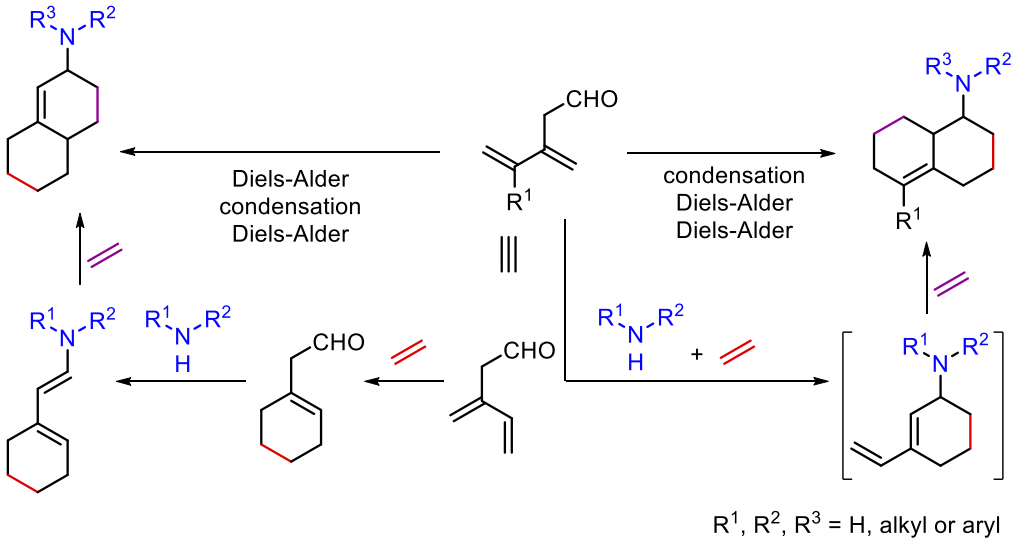


Chapter 1 reviews the Diels-Alder reactions of 1-amino-1,3-butadienes and is divided into three sections. The first two sections cover the Diels-Alder reactions of 1-amino-1,3-butadienes and 1-amino-3-siloxy-1,3-butadienes (Rawal's dienes) generated with a stoichiometric amount of amine. The third section covers enantioselective Diels-Alder reactions involving 1-amino-1,3-butadienes generated *in situ* with a catalytic amount of a chiral amine. While there have been many reports of Diels-Alder reactions of 1-amino-1,3-butadienes and 1-amino-3-siloxy-1,3-butadienes, there has been only one involving a semi-cyclic 1-amino[3]dendralene. There have been few examples which combine these Diels-Alder reactions with other transformations in multicomponent reactions to generate polycyclic frameworks.

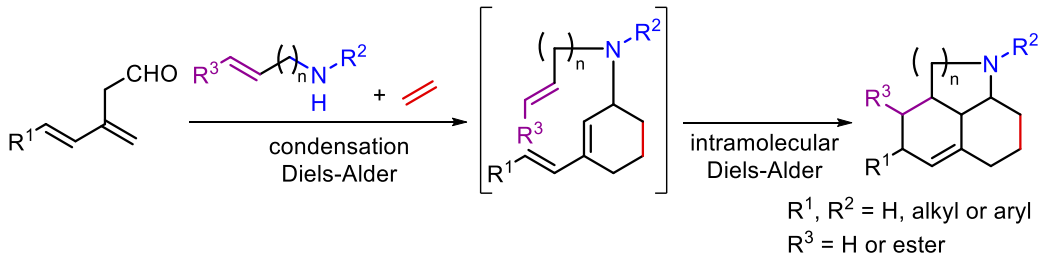
Chapter 2 describes the use of acyclic 1-amino[3]dendralenes in multicomponent reactions to generate a diverse range of heterocyclic structures. The condensation/Diels-Alder reaction sequence was tolerant of a variety of amines as well as carbon and hereoatom-based dienophiles. The Diels-Alder reactions of 1-amino[3]dendralenes were highly site-selective, taking place exclusively at the amine substituted 1,3-butadiene unit.



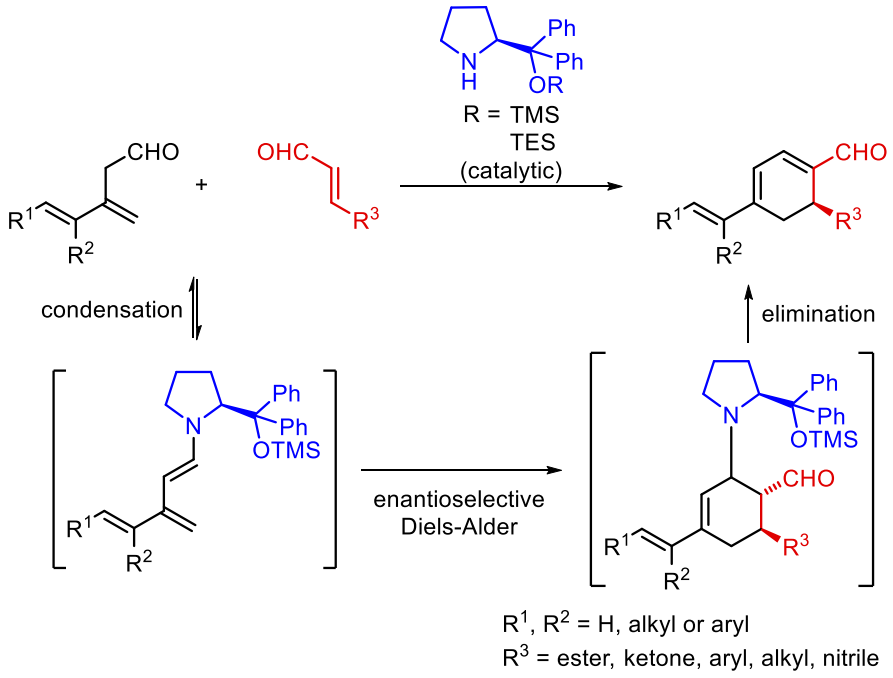
The sequence was extended to a one-pot four-component reaction by including an additional dienophile for a Diels-Alder reaction to take place at the newly generated semi-cyclic diene. These condensation/Diels-Alder/Diels-Alder cycloadducts were generated with high diastereoselectivity, the origins of which were investigated and explained with the use of density functional theory calculations (carried out by Prof Paddon-Row). By reversing the order of events, that is performing a Diels-Alder reaction on the skipped dienal precursor before the condensation/Diels-Alder reaction sequence, constitutional isomers were accessed.



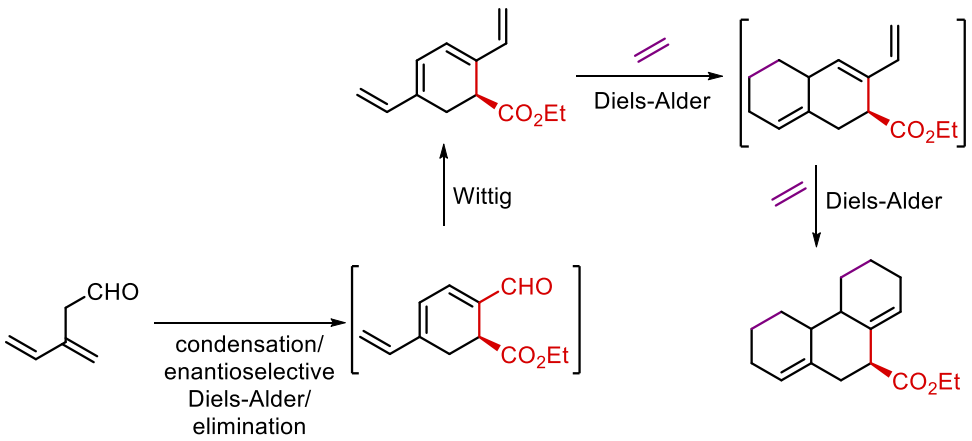
The second Diels-Alder reaction could be performed intramolecularly when an amine bearing an alkenyl substituent was used. This condensation/Diels-Alder/intramolecular Diels-Alder reaction sequence furnished a variety of tricyclic and tetracyclic heterocycles.



Chapter 3 describes the use of acyclic 1-aminodendralenes bearing chiral amines in organocatalytic, enantioselective Diels-Alder reactions to deliver enantioenriched cycloadducts. The enantioselective Diels-Alder reaction between 1-amino[3]dendralenes, the condensation product of skipped dienals and chiral amines, and various dienophiles followed by elimination of the amine generated trienal cycloadducts in good yield and high enantioselectivity. The reaction tolerates substitution on the skipped dienal as well as dienophiles possessing an aldehyde substituent at the α position.



Extension of this methodology by performing Wittig and Diels-Alder reactions on the trienal cycloadducts enabled access to enantioenriched polycyclic products.



By using a diene-dialdehyde as the starting precursor, it is anticipated that the Horeau principle would operate in the twofold condensation/Diels-Alder/elimination reaction sequence would furnish the cycloadduct in high enantioselectivity. A preliminary attempt successfully generated the desired cycloadduct as the major product.

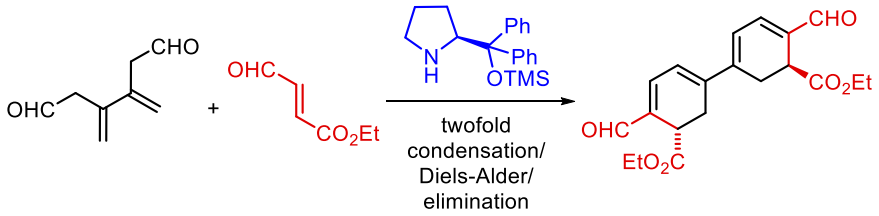
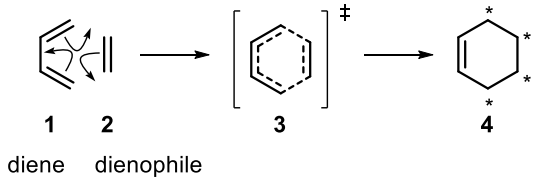


Table of Contents

1 Diels-Alder Reactions of 1-Amino-1,3-Butadienes

1.1 Introduction

The Diels-Alder reaction is a concerted [4+2] cycloaddition between a diene **1** and a dienophile **2** which generates a cyclohexene **4** through a cyclic transition state **3**. This process breaks three π bonds while forming two σ bonds and one π bond. In the prototypical reaction shown in Scheme 1.1, cyclohexene **4** does not bear any stereocentres. The Diels-Alder reaction can generate up to four stereocentres, at the positions marked by asterisks in cyclohexene **4**, depending on the presence of substituents on the diene and dienophile.



Scheme 1.1 The prototypical Diels-Alder reaction

Based on the Frontier Molecular Orbital (FMO) theory, a normal electron demand Diels-Alder reaction occurs through interaction of the highest occupied molecular orbital (HOMO) of the 1,3-butadiene with the lowest unoccupied molecular orbital (LUMO) of the dienophile (Figure 1.1a).[1,2] The reaction is made more favourable by

placing an electron-donating substituent such as an amine on the 1,3-butadiene. This raises the HOMO of the 1,3-butadiene, leading to a smaller HOMO-LUMO gap and thus a lower activation energy required for the reaction to take place (Figure 1.1b).

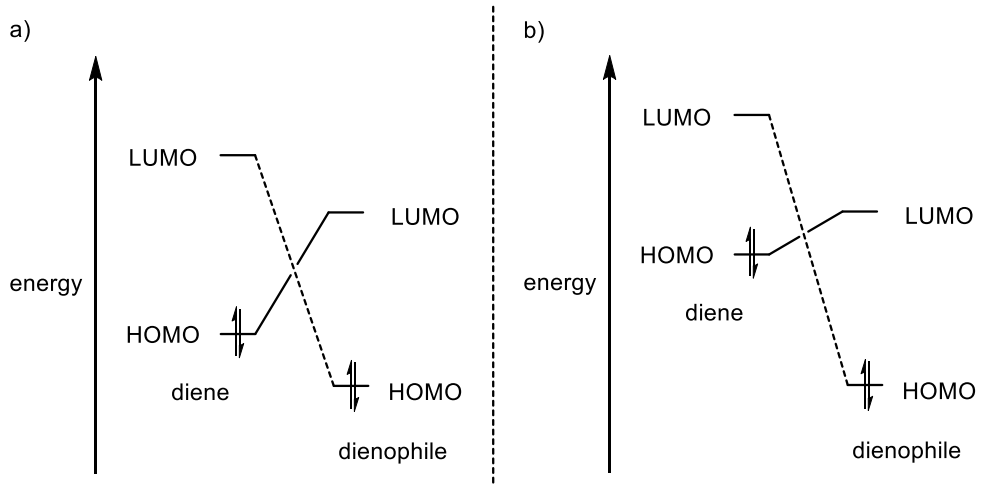


Figure 1.1 Orbital energy diagrams of a normal electron demand Diels-Alder reaction with: a) an unsubstituted 1,3-butadiene b) an amine-substituted 1,3-butadiene

An amine substituent can be placed on the C1 (1-amino-1,3-butadiene **5**) or the C2 (2-amino-1,3-butadiene **6**) position on a simple 1,3-butadiene unit (Figure 1.2). While the synthesis and Diels-Alder reactivity of 2-amino-1,3-butadienes have been reported,[3,4] they are not the focus of this thesis and will not be discussed.

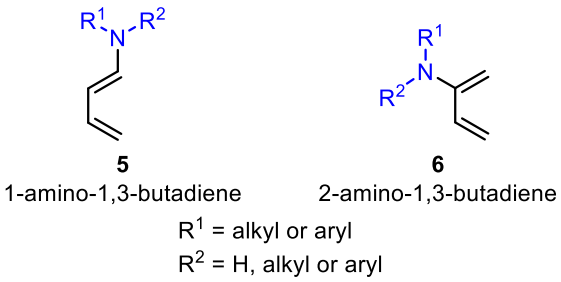


Figure 1.2 Structures of 1-amino-1,3-butadiene **5** and 2-amino-1,3-butadiene **6**

This chapter covers the literature up to December 2015. The Diels-Alder reactions of 1-amino-1,3-butadienes will be discussed, focusing on the types of structures which have been accessed as well as the *endo*/*exo*, regio-, enantio- and diastereoselectivity of these reactions. The discussion will be limited to acyclic (structure **7**) and semi-cyclic 1-amino-1,3-butadienes (structures **8** and **9**) which bear alkyl, aryl or alkenyl substituents and 1-amino-3-siloxy-1,3-butadienes **10**, which are related in terms of chemical

reactivity to 1-amino[3]dendralenes (Figure 1.2a). 1-Amino-1,3-butadienes which are cyclic, such as structures **12** and **13**, or part of aromatic heterocycles such as structures **14** and **15**, and 1-amido-1,3-butadienes **16** are not included as they are structurally different from the 1-amino[3]dendralenes **11** described in this thesis (Figure 1.2b).

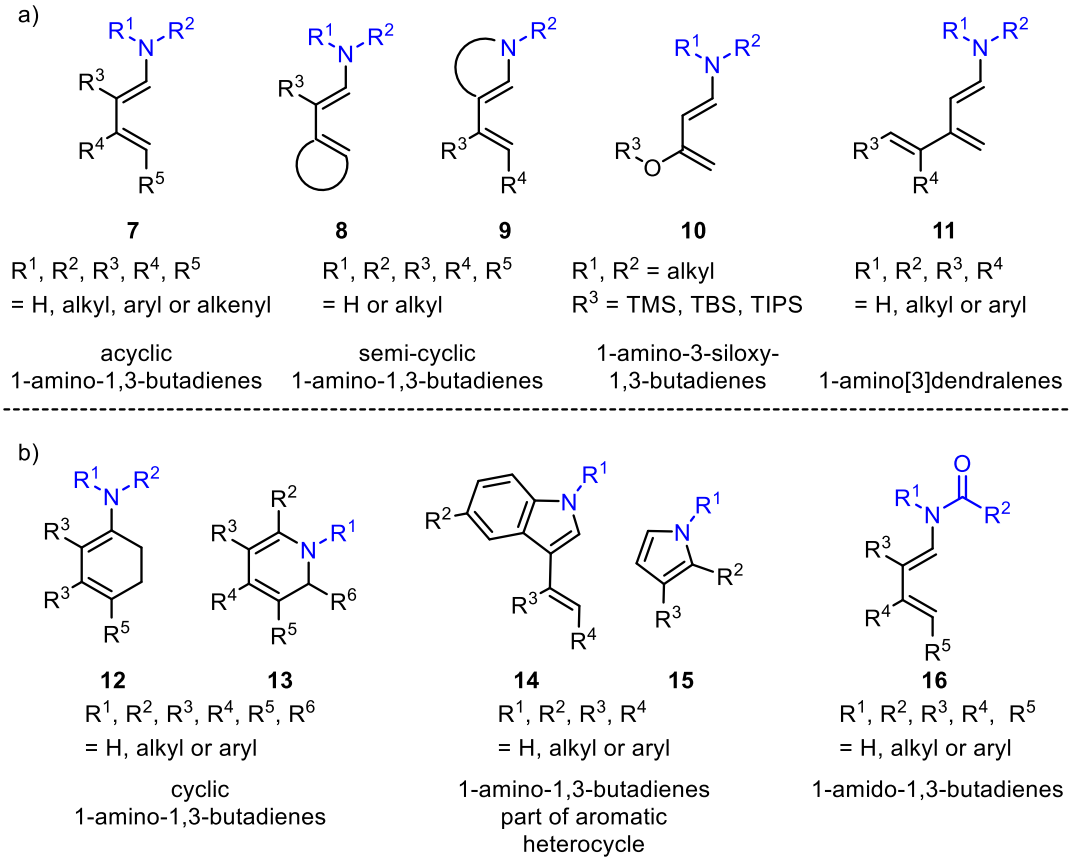
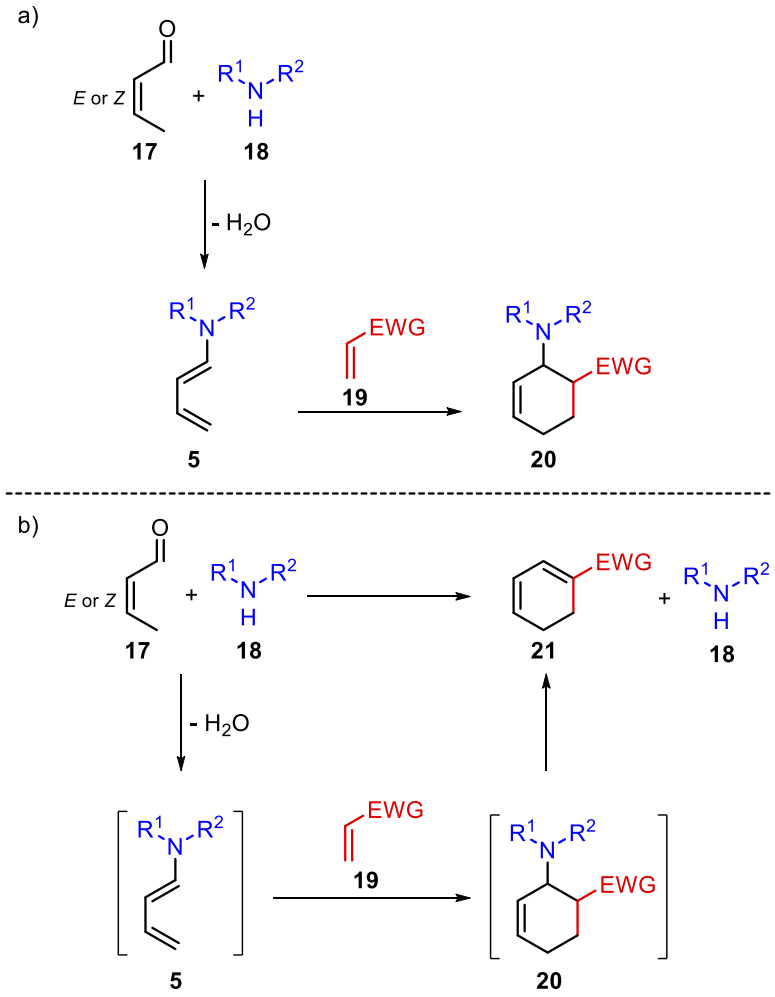


Figure 1.3 a) Types of 1-amino-1,3-butadienes discussed in this chapter and b) examples of types of 1-amino-1,3-butadienes not discussed in this chapter

The chapter is divided into two main sections, categorised by whether a stoichiometric or catalytic amount of amine is used in the reaction. The term stoichiometric is used to refer to reactions in which the amine is incorporated into the product. The term catalytic is used to refer to reactions in which the amine is incorporated into an intermediate but is regenerated at the end of the reaction sequence and is not incorporated into the product. In both cases, aldehyde **17** and amine **18** undergo a condensation reaction to form 1-amino-1,3-butadiene **5**, which participates in a Diels-Alder reaction. When a stoichiometric amount of amine is used, the reaction terminates at this point and the amine is incorporated into the product **20** (Scheme 1.2a). In Diels-Alder reactions where a catalytic amount of amine **18** is used, the Diels-Alder product **20** undergoes

elimination to produce the final product **21** and release amine catalyst **18**, which can participate in another catalytic cycle. Besides the example shown, there are other modes of reactivity through which 1-amino-1,3-butadienes undergo aminocatalytic Diels-Alder reactions and these are described in Sections 1.41 – 1.44.



Scheme 1.2 Examples of Diels-Alder reactions of a) stoichiometrically generated 1-amino-1,3-butadienes and b) catalytically *in situ* generated 1-amino-1,3-butadienes

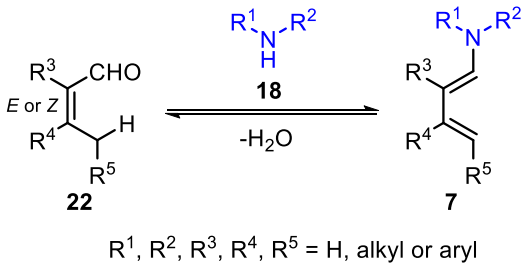
The first section (Chapter 1.2, page 5) focuses on the Diels-Alder reactions of 1-amino-1,3-butadienes generated using a stoichiometric amount of amine. Two reviews in the early 1980s cover the relevant literature of 1-amino-1,3-butadienes up to 1982 in their discussion,[5,6] so only selected examples from before 1982 will be used to illustrate the general reactivity and selectivity of 1-amino-1,3-butadienes in Diels-Alder reactions. The second section (Chapter 1.3, page 17) focuses on the Diels-Alder reactions of 1-amino-3-siloxy-1,3-butadienes. The third section (Chapter 1.4, page 24) covers Diels-Alder reactions of 1-amino-1,3-butadienes which are generated with a catalytic amount of amine and is limited to examples of enantioselective reactions, as they are relevant to

the work described in this thesis. There are numerous reviews on enantioselective amine catalysed Diels-Alder reactions but these are often brief in their coverage of reactions involving 1-amino-1,3-butadienes.[4,7-12] This third section will comprehensively discuss these examples.

1.2 Diels-Alder reactions of 1-amino-1,3-butadienes using stoichiometric amounts of amine

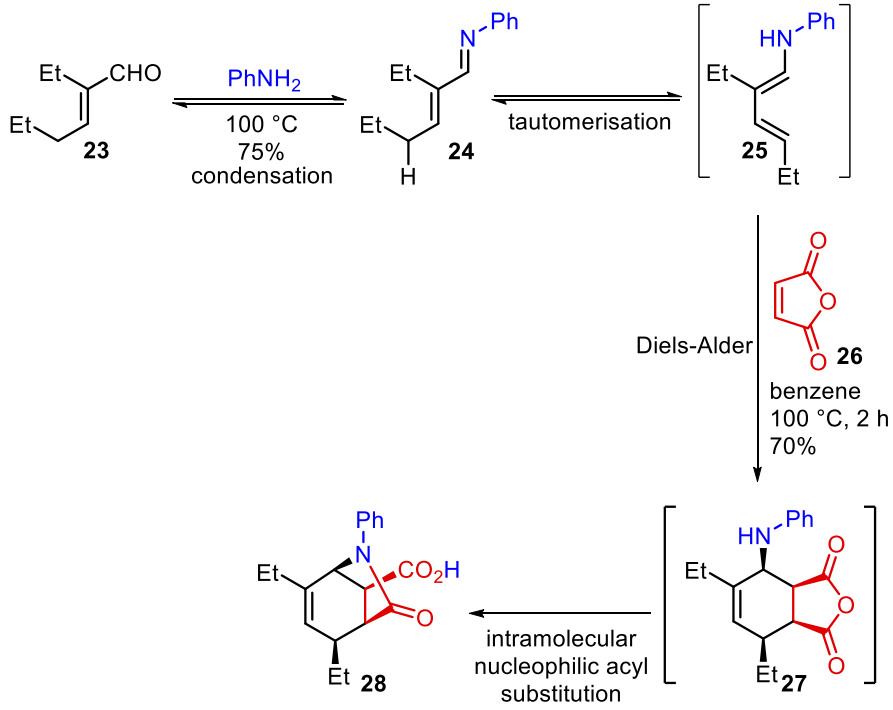
1.2.1 Intermolecular Diels-Alder reactions with acyclic 1-amino-1,3-butadienes

1-Amino-1,3-butadienes **7** are generally prepared by condensation of an enolisable α,β-unsaturated aldehyde **22** with a primary or secondary amine **18** and sometimes include the use of an acid catalyst or a dessicant such as potassium carbonate (Scheme 1.3).[13-15]



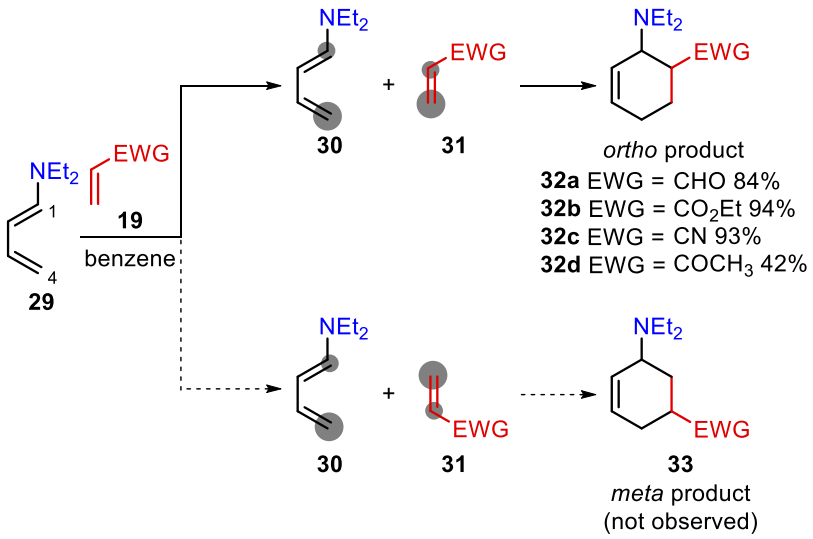
Scheme 1.3 General method of synthesising 1-amino-1,3-butadienes

The use of a 1-amino-1,3-butadiene in a Diels-Alder reaction was first reported in 1939 (Scheme 1.4).[16] Aniline and 2-ethylhex-2-enal **23** were reacted at 100 °C to generate imine **24**. Based on their understanding of tautomerisation of simple imines to enamines, the authors proposed a similar transformation of imine **24** to 1-amino-1,3-butadiene **25**. 1-Amino-1,3-butadiene **25** underwent Diels-Alder reaction with maleic anhydride **26**, generating bicycle **27**, which upon intramolecular nucleophilic acyl substitution led to the formation of bridged bicycle **28**. The stereochemistry of adducts **27** and **28** was not defined in the original paper, presumably due to a lack of suitable analytical methods at that time and there have not been any follow-up papers which address this point. The predicted stereochemistry is shown. Adduct **27** is the result of *endo* addition of maleic anhydride **26** to 1-amino-1,3-butadiene **25** (*endo*/*exo* selectivity is further explained on page 7). The stereochemistry of adduct **27** is retained in the intramolecular substitution product **28**.



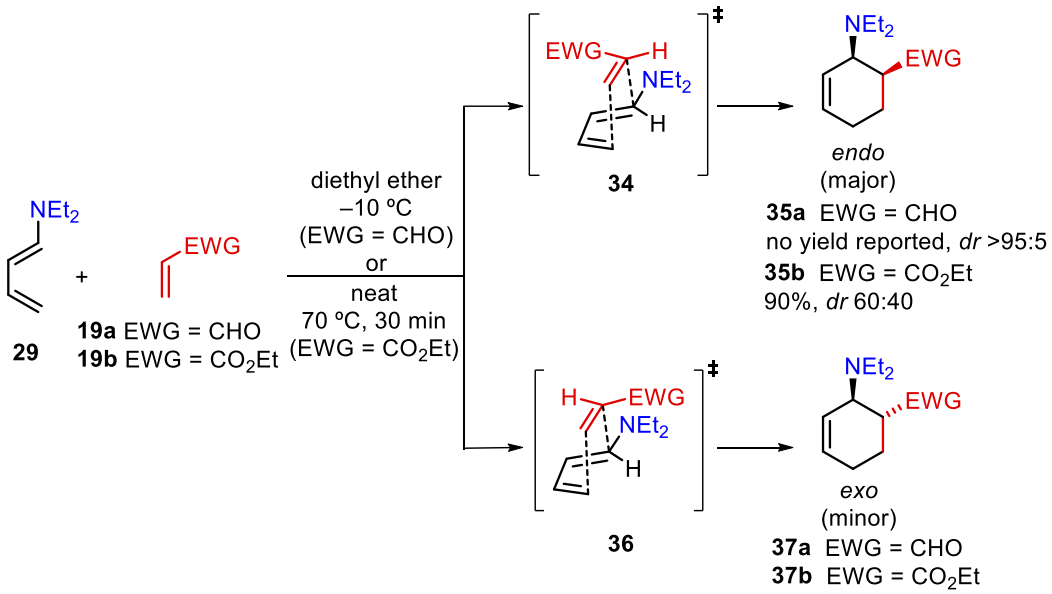
Scheme 1.4 First reported Diels-Alder reaction of a 1-amino-1,3-butadiene

Initial studies into Diels-Alder reactions between 1-amino-1,3-dienes and unsymmetrical dienophiles, namely acrolein, ethyl acrylate, acrylonitrile and methyl vinyl ketone, revealed their highly regioselective nature (Scheme 1.6).[17,18] Only the *ortho* product **32** was formed, whereas the *meta* product **33** was not observed. This can be rationalised using frontier molecular orbital (FMO) theory. [1,2] The presence of substituents causes the orbital coefficients (depicted by the shading in structures **30** and **31**, Scheme 1.5) of the diene and dienophile to be different. The conjugating, electron-withdrawing substituent on dienophile **31** results in a larger LUMO orbital coefficient on its unsubstituted end. The electron-donating amine substituent at the C1 position of diene **30** results in the largest HOMO orbital coefficient to be on C4. The orientation of the diene with respect to the dienophile, which maximises overlap between the HOMO and the LUMO orbitals leads to the favoured formation of *ortho* product **32**.



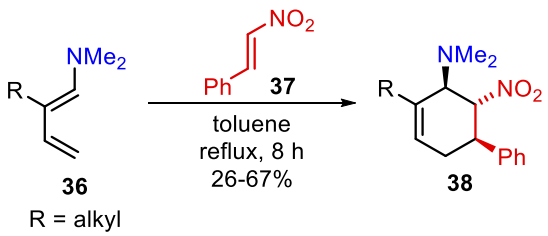
Scheme 1.6 Diels-Alder reaction between 1-amino-1,3-butadiene **29** and unsymmetrical dienophiles acrolein, ethyl acrylate, acrylonitrile and methyl vinyl ketone

The stereochemical outcome of Diels-Alder reactions between 1-amino-1,3-butadiene **29** and acrolein was established in later studies, which revealed the exclusive formation of the *cis* stereoisomer **35a**.[19] The reaction with ethyl acrylate was shown to produce a mixture of the *cis* stereoisomer **35b** and *trans* stereoisomer **37b** in the ratio 60:40.[20] The major diastereomer **35** is the result of *endo* addition of the dienophile. This preferential formation of *endo* over *exo* products is often attributed to secondary electronic interactions (SOIs).[21] Specifically, such interactions refer to overlap between the orbitals of unsaturated substituents of the dienophile with the newly forming alkene on the 1,3-butadiene to maximise orbital overlap.[22] The existence of SOIs, however, has not been proven and the preferential formation of *endo* products has also been attributed to other factors.[23]



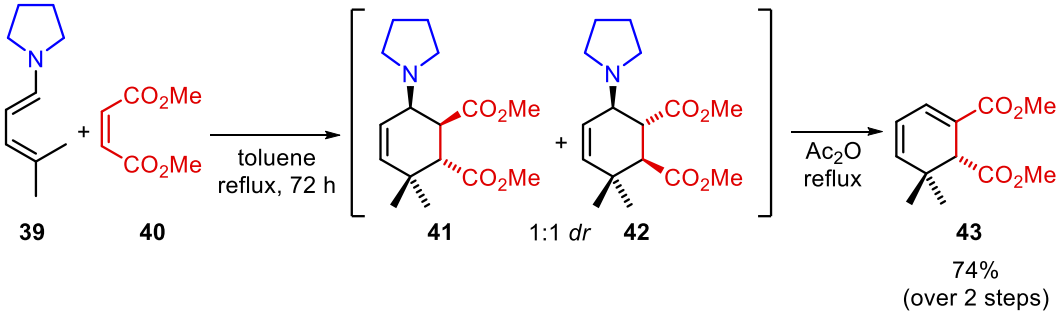
Scheme 1.7 Diels-Alder reactions of 1-amino-1,3-butadiene **29** with acrolein and ethyl acrylate

Potthoff and Breitmaier reported the *exo*-selective Diels-Alder reaction between alkyl substituted 1-dimethylamino-1,3-butadiene **36** and β-nitrostyrene (**37**) to form cyclohexene **38** (Scheme 1.8).[15,24] The reaction is suprafacial with respect to both the 1,3-butadiene and the dienophile.[2] The stereospecificity of a concerted Diels-Alder reaction results in the retention of stereochemistry of both the 1,3-butadiene and dienophile in the Diels-Alder product,[25] thus an *E*-configured dienophile such as β-nitrostyrene (**37**) generates products in which the $–NO_2$ and phenyl groups are in a *trans* relative configuration. Under kinetic control, the observed *exo* selectivity of the reaction between nitrostyrene (**37**) (with respect to the $–NO_2$ group) and electron-rich 1-amino-1,3-butadiene **36** was proposed to be the result of electrostatic repulsion between the electron rich amino and $–NO_2$ groups in the transition state.[26-28]



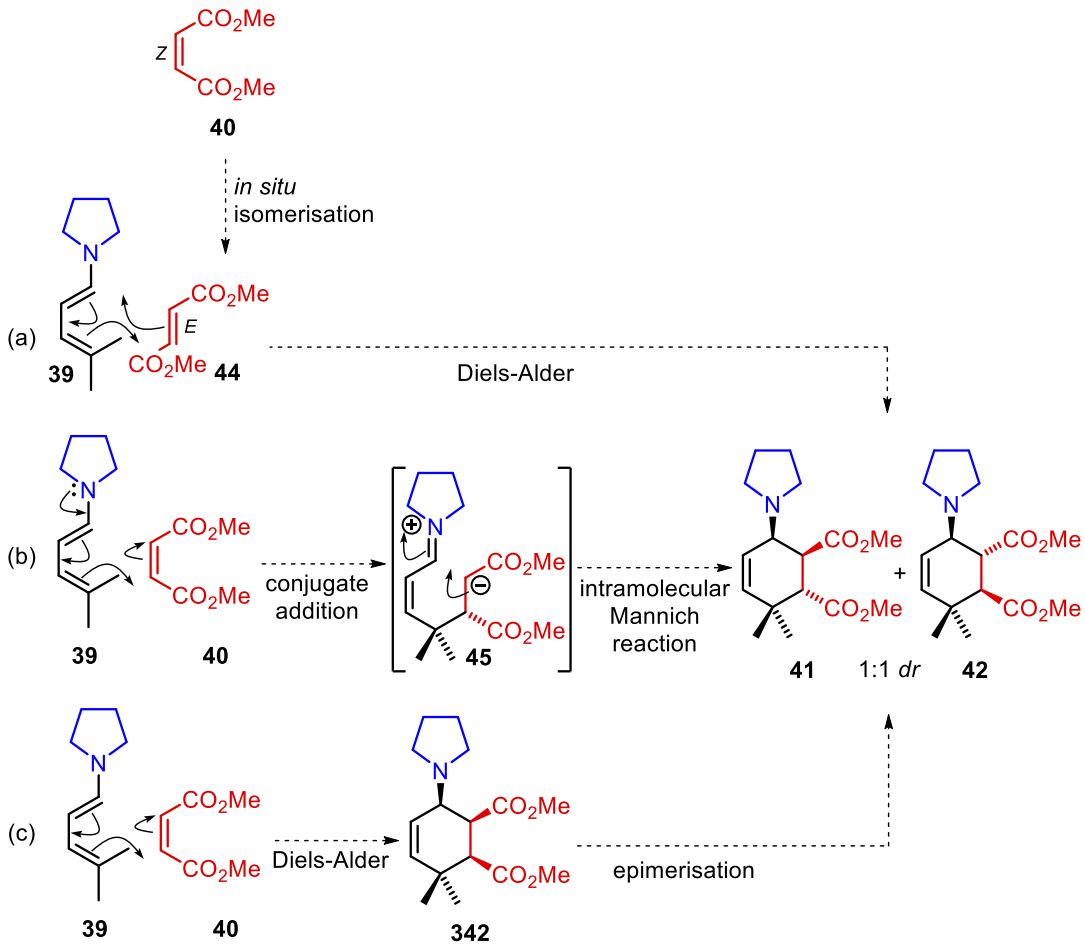
Scheme 1.8 Diels-Alder reaction between 1-dimethylamino-1,3-butadiene **36** and β-nitrostyrene (**37**)

When 1-amino-1,3-butadiene **39** was reacted with dimethyl maleate (**40**) then heated to reflux with acetic anhydride, 1,3-cyclohexadiene **43** was obtained (Scheme 1.9a).[15] It was proposed that 1-amino-1,3-butadiene **39** underwent a Diels-Alder reaction with dimethyl maleate (**40**) to generate two diastereomeric products **41** and **42**, which, upon elimination, produced the observed product, 1,3-cyclohexadiene **43**. Unlike the previous example, the stereochemistry of the dienophile was not retained in the product. The *Z*-configuration of dimethyl maleate **40** generated products **41** and **42**, in which the –CO_2Me groups are in the *trans* rather than the expected *cis* relative configuration.



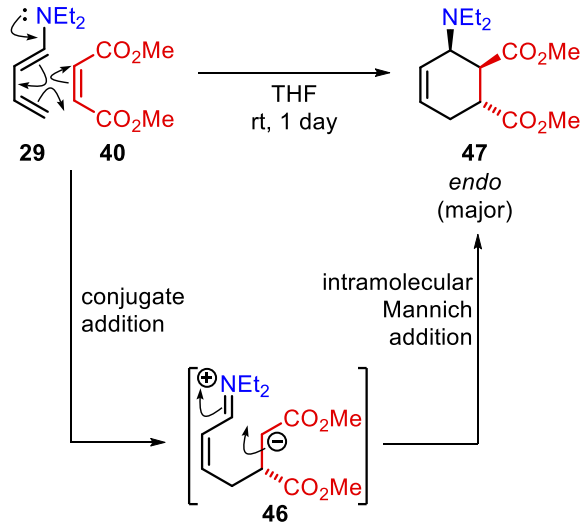
Scheme 1.9 Diels-Alder reaction of 1-amino-1,3-butadiene **169** with dimethyl maleate (**40**)

The authors proposed *in situ* isomerisation of dimethyl maleate (**40**) to dimethyl fumarate (**44**), which reacts as the dienophile, to account for the observed products (Scheme 1.10a). It was not shown whether this isomerisation could have taken place under the reaction conditions. Another possibility is a step-wise mechanism, involving firstly a conjugate addition of 1-amino-1,3-butadiene **39** to dimethyl maleate (**40**) then a Mannich-type ring closure of the resulting intermediate **45** (Scheme 1.10b). It is also possible for the Diels-Alder reaction between 1-amino-1,3-butadiene **39** and dimethyl maleate (**40**) to occur, before epimerisation of cyclohexene **342** to generate the observed products, cyclohexenes **41** and **42** (Scheme 1.10c).



Scheme 1.10 Proposed mechanisms for the reaction of 1-amino-1,3-butadiene **39** with dimethyl maleate (**40**)

In a similar example, the Diels-Alder reaction of 1-diethylamino-1,3-butadiene **29** with dimethyl maleate (**40**) generated cyclohexene **47** as the major product, in which the –CO_2Me groups are also *trans* to one another (Scheme 1.11).[29] After ruling out amine catalysed isomerisation of dimethyl maleate (**40**) the authors proposed a stepwise conjugate addition then Mannich-type ring closure process *via* intermediate **46**.

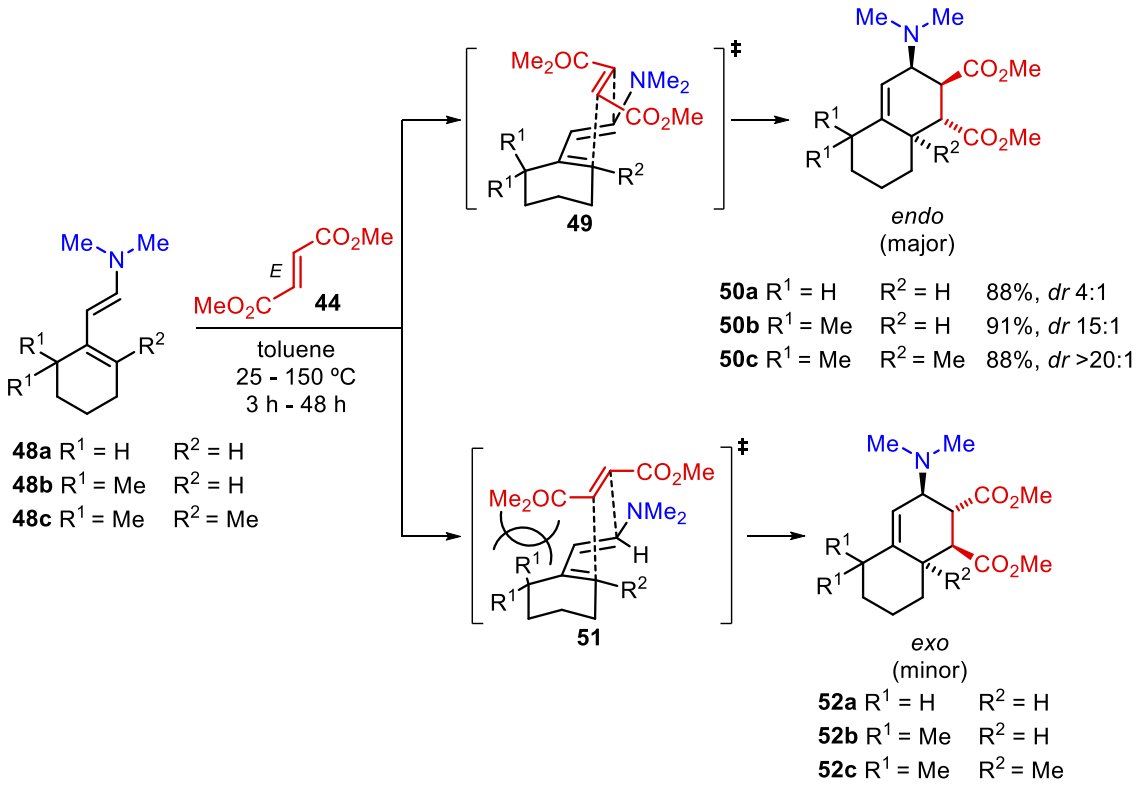


Scheme 1.11 Formal Diels-Alder reaction of 1-diethylamino-1,3-butadiene **29** with dimethyl maleate (**40**)

Diels-Alder reactions typically involve either an electron rich diene or an electron poor dienophile and these are usually concerted cycloadditions. Reactions between two highly polar reactants, an electron rich substituted diene with an electron poor dienophile, can also proceed by a step-wise ionic mechanism involving a zwitterionic intermediate.[30,31] Whether a reaction is concerted or step-wise depends on the types of substituents present on the reactants and mechanistic pathways may be elucidated with the help of computational calculations.[32]

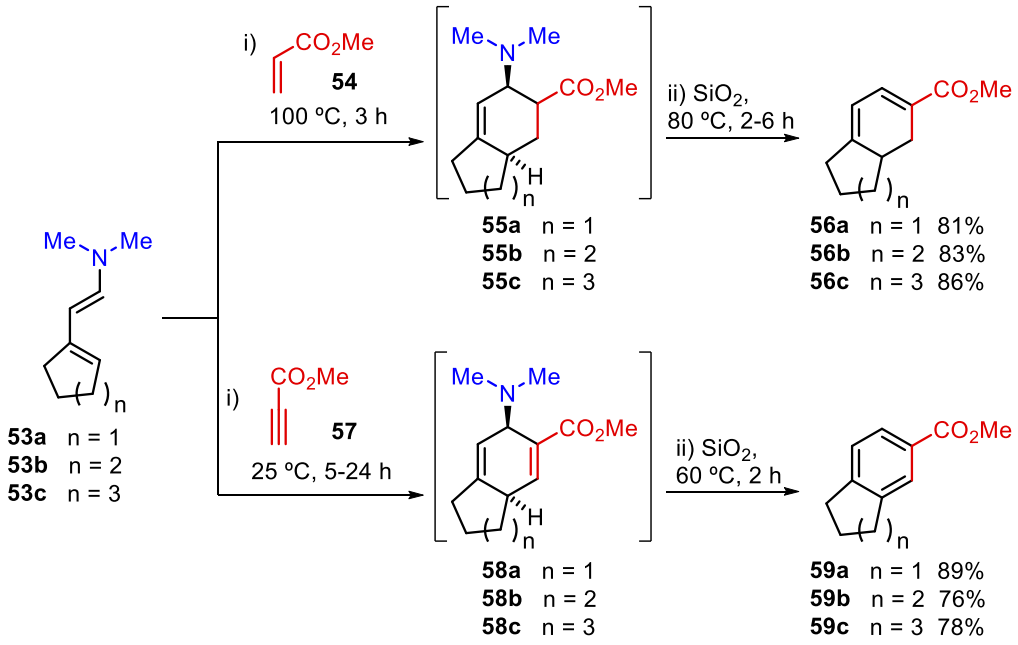
1.2.2 Intermolecular Diels-Alder reactions with semi-cyclic 1-amino-1,3-butadienes

When semi-cyclic 1-amino-1,3-butadienes **48** were reacted with dimethyl fumarate (**44**), mixtures of *endo* **50** and *exo* **52** diastereomers were generated (Scheme 1.12).[33] The Diels-Alder reaction showed increasing diastereoselectivity as the number of methyl groups present on the starting 1-amino-1,3-butadiene increased. Unfavourable steric interactions in the *exo* transition state **51** between the R^1 methyl substituents of 1-amino-1,3-butadienes **48b** and **48c** and the $-CO_2Me$ substituents of the dienophile resulted in the formation of cycloadduct **52b** and **52c** being less favoured.



Scheme 1.12 Diels-Alder reaction between semi-cyclic 1-amino-1,3-butadienes **48** and dimethyl fumarate (**44**)

The Diels-Alder reactions of semi-cyclic 1-amino-1,3-butadienes **53** with methyl acrylate (**54**)[34] and methyl propiolate (**57**)[35] as dienophiles followed by treatment with silica gel generated bicyclic adducts **56** and **59** respectively, which were suggested to arise by dimethylamine elimination from the intermediate Diels-Alder adducts **55** and **58** (Scheme 1.13). The authors proposed, based on ^{1}H NMR spectroscopic data, that adducts **55** were formed as a mixture of *endo* and *exo* diastereomers (ratios not specified). These reactions proceeded with complete orientational regioselectivity to produce adducts in which the amino– and –CO_2Me groups are adjacent to one another.

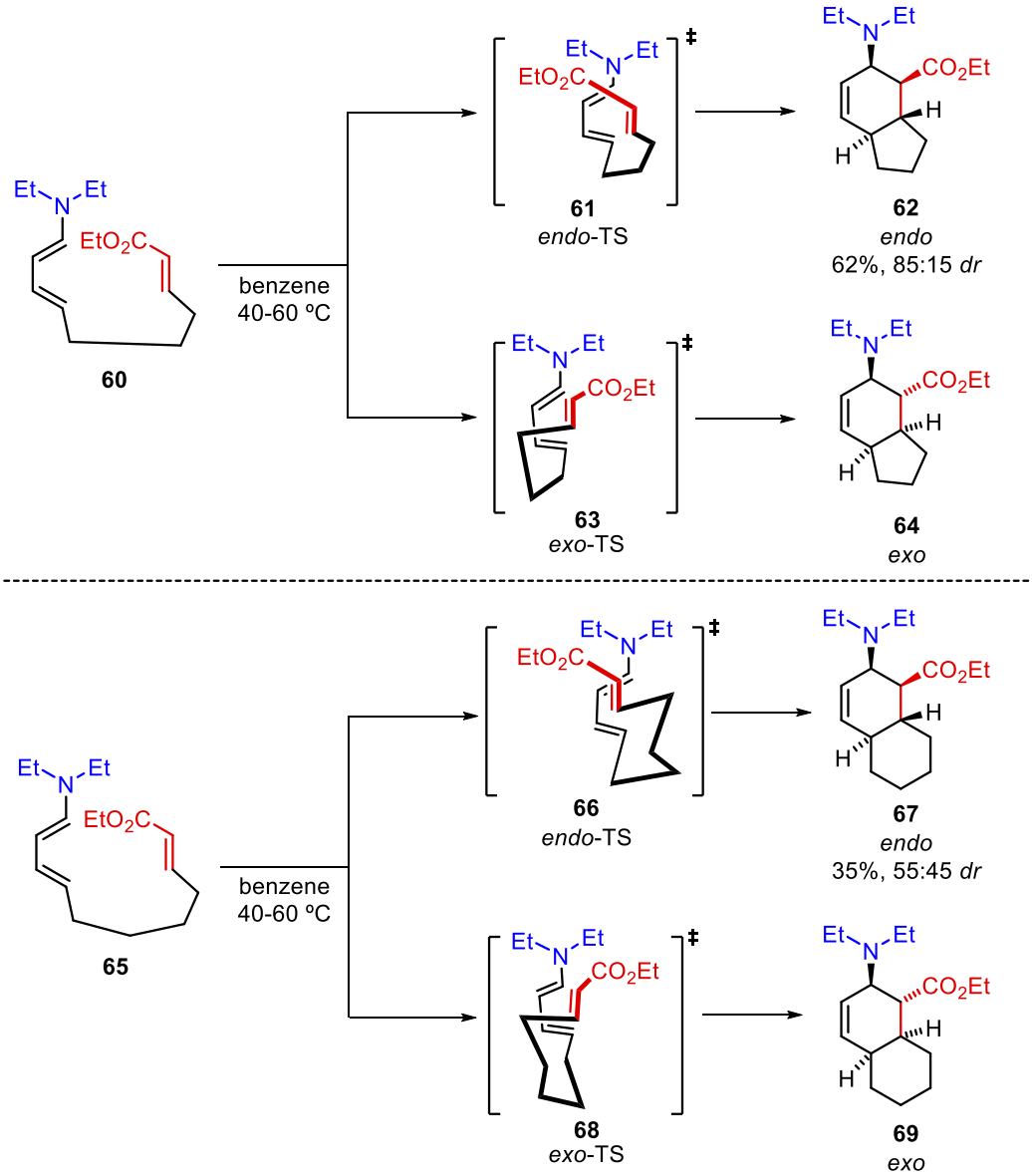


Scheme 1.13 Diels-Alder reactions of 1-dimethylamino-1,3-butadienes **53** with methyl acrylate **54** and methyl propiolate **57** followed by dimethylamine elimination

1.2.3 Intramolecular Diels-Alder reactions with acyclic 1-amino-1,3-butadienes

By tethering a 1-amino-1,3-butadiene to a dienophile, an intramolecular Diels-Alder (IMDA) reaction can be performed. The IMDA reaction is a powerful transformation which forms two new rings and up to four new stereocentres in one step.[36,37] 1-Amino-1,3-butadienes **60** and **65**, which are tethered to alkenes bearing terminal –CO_2Et activating groups, underwent intramolecular Diels-Alder (IMDA) reactions when heated (Scheme 1.14).[38] With 1-amino-1,3-butadiene **60**, *trans*-fused cycloadduct **62** and *cis*-fused cycloadduct **64**, which are products of an *endo* **61** and *exo* **63** Diels-Alder reaction respectively, were generated in an 85:15 ratio. The high *endo* selectivity was proposed to be the result of greater steric hindrance between the 1-amino-1,3-butadiene and the –CO_2Et group of the dienophile in the *exo* transition state **63** than the *endo* transition state **61** as the molecule twists to relieve strain in the developing cyclopentane ring.[39] For decatriene **65**, *endo* cycloadduct **67** and *exo* cycloadduct **69** were formed in almost equal amounts (55:45 *dr*). This is likely to be a result of minimal strain in the developing chair-like cyclohexane rings in both the *endo* transition state **66** and *exo* transition state **68**, so there is no major preference for the formation of either the *endo* or *exo* product.[39] The *endo* rule predicts preferential formation of *endo* over *exo* products in intermolecular Diels-Alder reactions due to

favourable secondary orbital interactions between the diene and the dienophile and may account for the slight preference for *endo* adduct **62**. It has a smaller impact in intramolecular reactions as other factors such as tether conformational preferences play a bigger role on the stereochemical outcome.[40]

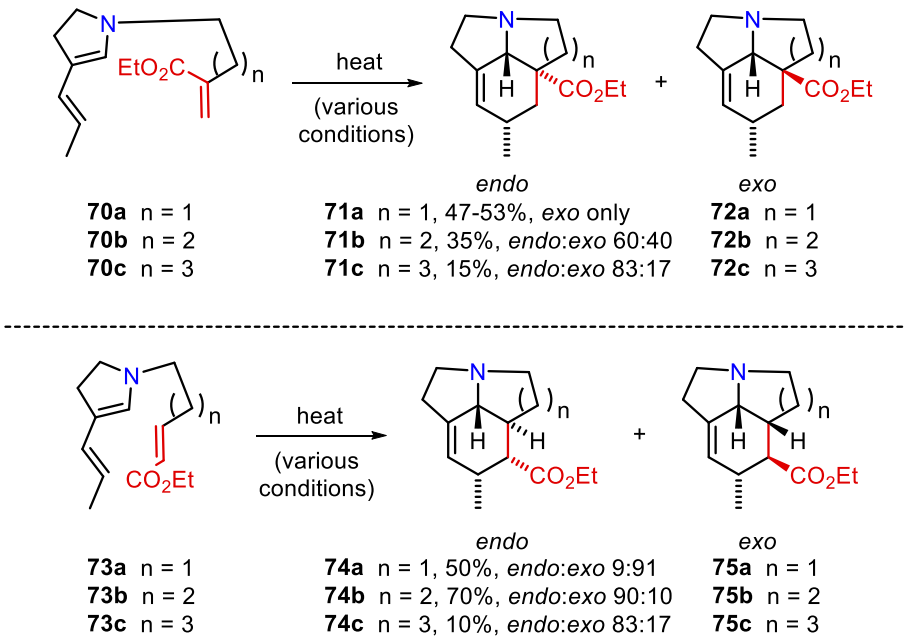


Scheme 1.14 Intramolecular Diels-Alder (IMDA) reactions of 1-amino-1,3-butadienes **60** and **65**

1.2.4 Intramolecular Diels-Alder reactions with semi-cyclic 1-amino-1,3-butadienes

A semi-cyclic 1-amino-1,3-butadiene undergoes an IMDA reaction to produce a fused tricyclic structure. 1-Amino-1,3-butadienes **70**, which bear an internal $-CO_2Et$ activating group, underwent IMDA reactions when heated to produce a mixture of

diastereomeric tricycles **71** and **72**, which arise from *endo* and *exo* cycloaddition respectively (Scheme 1.15).[41] IMDA reactions performed with 1-amino-1,3-butadienes **73**, which possess a terminal –CO_2Et activating substituent, provided mixtures of *endo* **74** and *exo* **75** adducts. The authors proposed that the preferential formation of *exo* cycloadducts **72a** and **75a** from 1-amino-1,3-butadienes **70a** and **73a**, which possess shorter tethers (n=1), was due to formation of the more favourable *cis* ring junction present in these adducts. As the IMDA reaction is irreversible,[42] such a thermodynamic argument is not valid. An alternative reason is that the *cis* transition state leading to formation of the *exo* cycloadducts is more favourable. For both the internally and terminally activated precursors, the IMDA reactions of 1-amino-1,3-butadienes **70c** and **73c**, which possess longer tethers (n=3), were much lower yielding. This was attributed to the slow IMDA reaction and competing decomposition to unidentified compounds, perhaps *via* intermolecular Diels-Alder reactions, which consumed the starting material before it underwent an IMDA reaction.

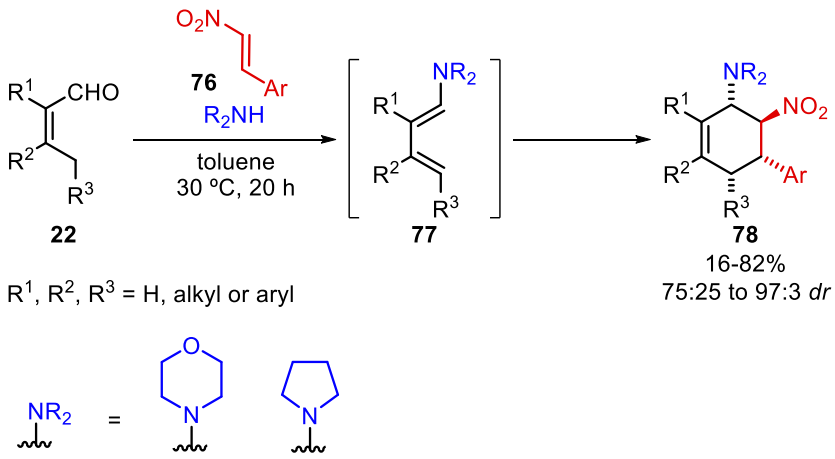


Scheme 1.15 IMDA reactions of semi-cyclic 1-amino-1,3-butadienes **70** and **73**

1.2.5 One-pot synthesis and Diels-Alder reactions of 1-amino-1,3-butadienes

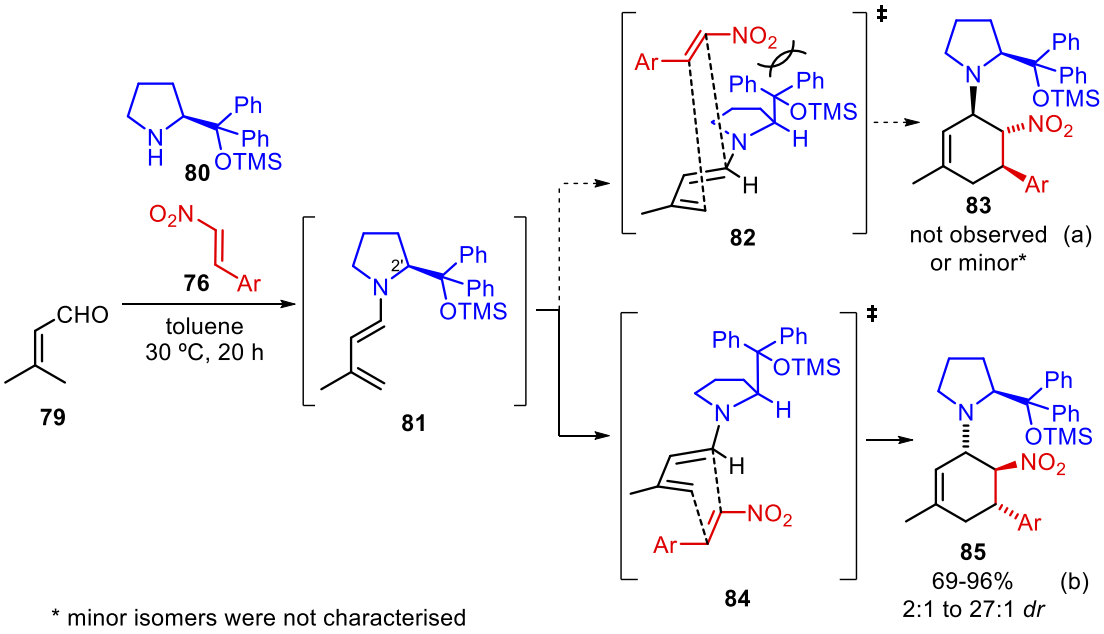
A more synthetically efficient sequence is achieved by performing both the 1-amino-1,3-butadiene formation and Diels-Alder reaction in the same pot. In 2014, the first example involving a one-pot three-component reaction between aldehydes **22**, nitroalkenes **76** and amines was reported (Scheme 1.16).[43] Initial condensation of an

amine with aldehydes **22** led to the formation of 1-amino-1,3-butadienes **77**, which underwent Diels-Alder reaction with nitroalkene dienophiles **76** to provide cycloadducts **78** in 16-82% yield and diastereomeric ratios of 3:1 to 35:1. The major diastereomer was a result of *exo* addition with respect to the $–NO_2$ group of the dienophile to the 1,3-butadiene (refer to page 8 for an explanation of the stereochemical outcome of cycloadditions of nitroalkenes to 1-amino-1,3-butadienes).



Scheme 1.16 A one-pot three-component condensation/Diels-Alder reaction between aldehydes **22**, nitroalkenes **76** and amines

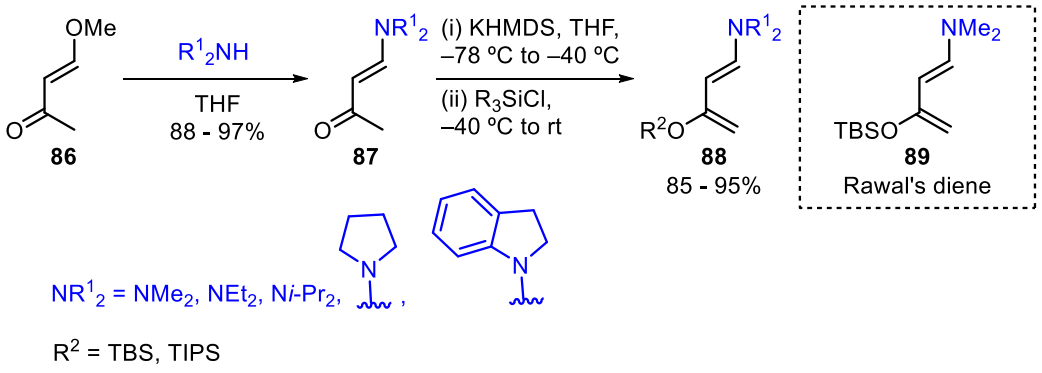
The condensation between aldehyde **79** and chiral amine **80** generates chiral 1-amino-1,3-butadiene **81**, which leads to the issue of π-diastereofacial selectivity in its Diels-Alder reactions (Scheme 1.17).[43] The conformation in which the N–C2' bond and the C1=C2 bond of 1-amino-1,3-butadiene **81** are *trans* (as shown) is favoured as it minimises steric interactions between the bulky pyrrolidine ring substituent and the diene.[12] Assuming that nitroalkene **76** only approaches the 1-amino-1,3-butadiene in an *exo* orientation, two diastereomers **83** and **85** can result from the Diels-Alder reaction, depending on whether this approach is from the same (Scheme 1.17a) or opposite face (Scheme 1.17b) as the bulky substituent on the pyrrolidine ring. The major product, cyclohexene **85**, arises from the favoured approach of dienophile **76** from the opposite face from the bulky substituent of the 1-amino-1,3-butadiene (as shown in transition structure **84**), as this minimises steric repulsion between the 1-amino-1,3-butadiene and dienophile.



Scheme 1.17 π-Diastereofacial selectivity in the Diels-Alder reaction between chiral 1-amino-1,3-butadiene **81** and nitroalkenes **76**

1.3 Diels-Alder reactions of 1-amino-3-siloxy-1,3-butadienes

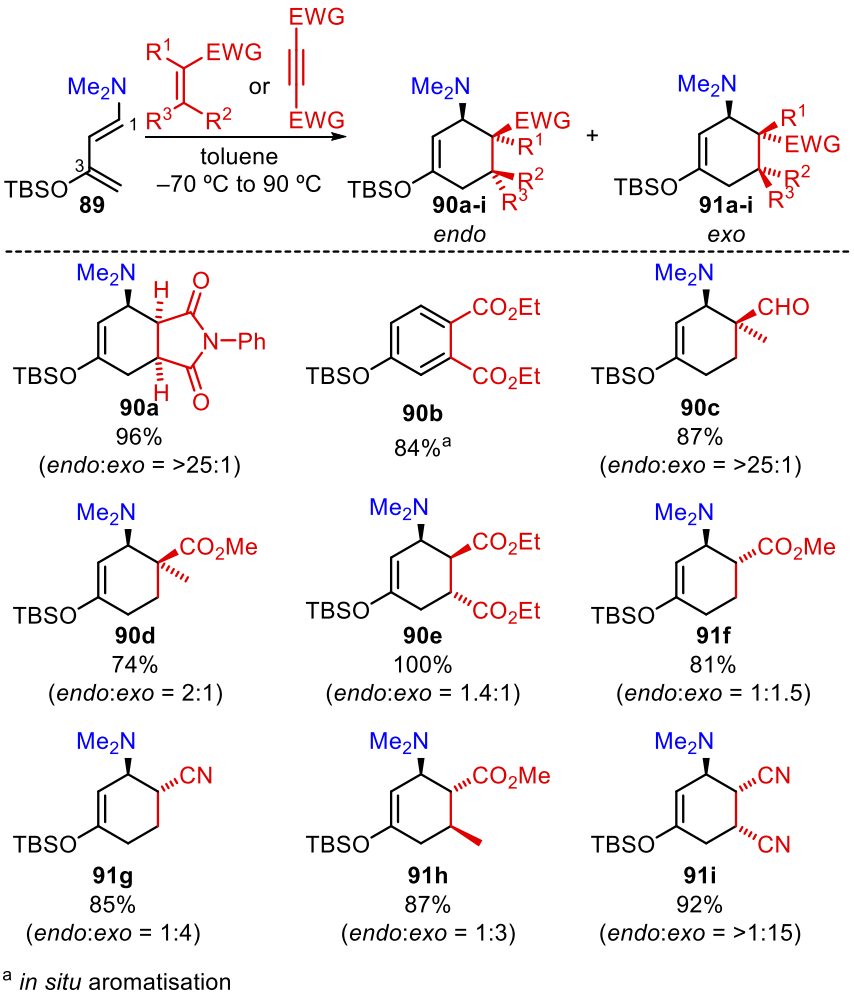
In 1997, Kozmin and Rawal reported the synthesis and Diels-Alder reactions of 1-amino-3-siloxy-1,3-butadienes **88**, which are typically prepared by a two step reaction sequence.[44] Conjugate addition-elimination between 4-methoxybut-3-en-2-one **86** and various amines delivered vinylogous amides **87**, which were transformed into 1-amino-3-siloxy-1,3-butadienes **88** *via* deprotonation and trapping of the resulting enolate with various silyl chlorides. Rawal's diene usually refers specifically to 1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene **89**.



Scheme 1.18 Synthesis of 1-amino-3-siloxy-1,3-butadienes **88**

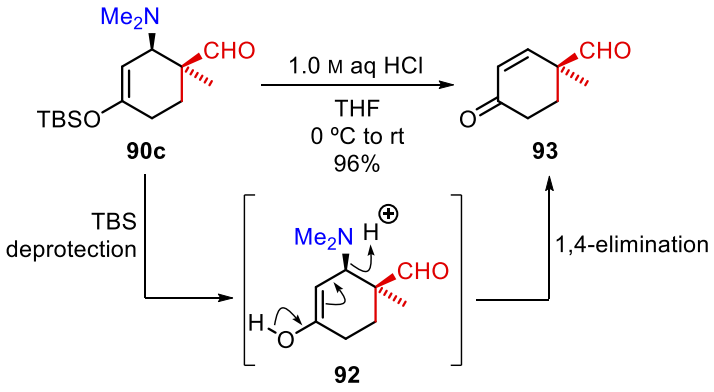
1.3.1 Intermolecular Diels-Alder reactions of 1-amino-3-siloxy-1,3-butadienes

Rawal's diene **89** is highly reactive and readily participates in Diels-Alder reactions with a variety of dienophiles under mild conditions (Scheme 1.19).[45] With reactive dienophiles such as *N*-phenylmaleimide and methacrolein, exclusive formation of *endo* products (**90a** and **90c**) was observed. The use of substituted acrylates and acrylonitriles led to the formation of *endo* and *exo* product mixtures (**90e-i**). Although Rawal's diene is highly electron rich and could undergo a step-wise, formal Diels-Alder reaction, results from kinetic studies (entropy of activation and activation energy measurements) of the reaction with methacrolein (product **90c**) were consistent with a concerted cycloaddition mechanism.[46] Computational studies showed that the high reactivity of Rawal's diene arises from the synergistic effect of the electron donating amino and enol ether substituents on the C1 and C3 positions in raising its HOMO energy level, thus reducing the activation energy for the Diels-Alder reaction to take place.[46]



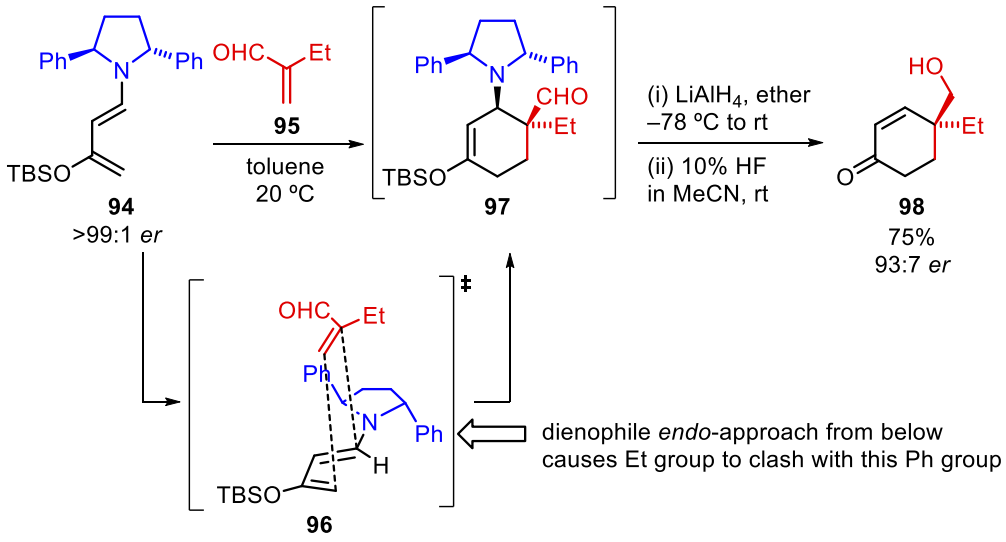
Scheme 1.19 Diels-Alder reactions of Rawal's diene **89** with various dienophiles

Diels-Alder adduct **90c** can be transformed into a useful and versatile intermediate,[47-50] cyclohexenone **93**, by acidic hydrolysis and conjugate elimination of the amine (Scheme 1.20).[44]



Scheme 1.20 Conversion of cycloadduct **90c** to cyclohexenone **93**

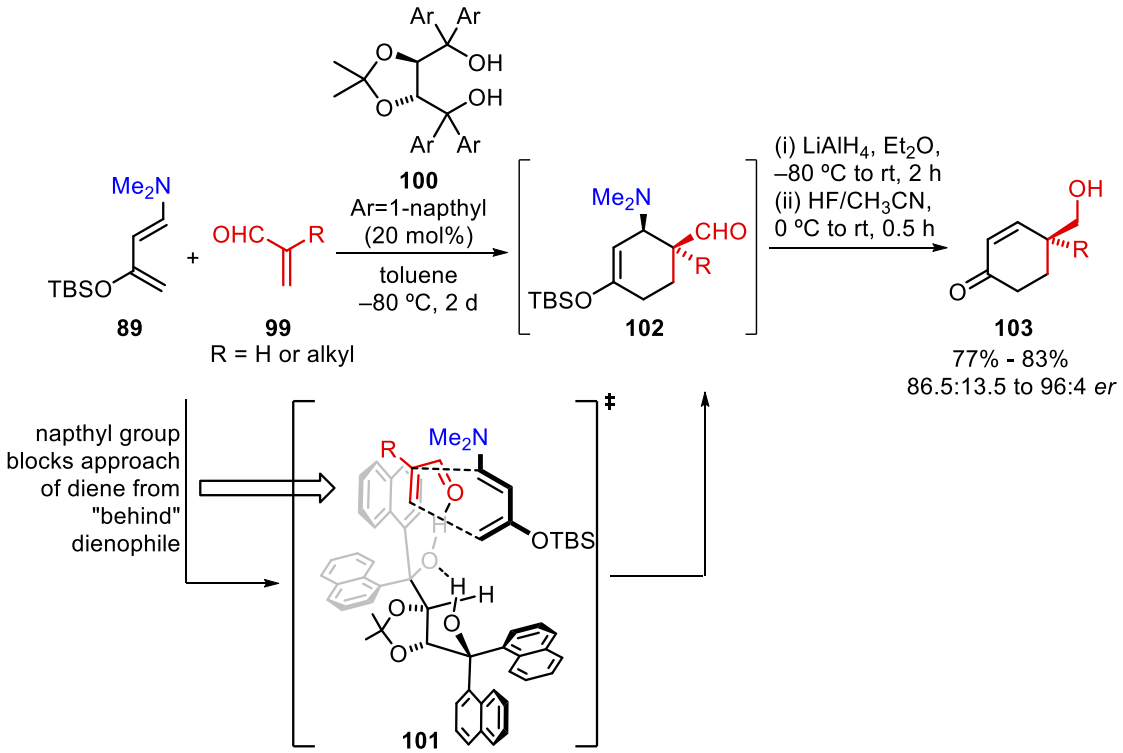
The use of chiral 1-amino-3-siloxy-1,3-butadienes allows access to enantiomerically enriched Diels-Alder adducts. The Diels-Alder reaction of 1-amino-3-siloxy-1,3-butadiene **94** (>99:1 *er*) with 2-ethylacrolein (**95**) generated intermediate **97**, which upon *in situ* reduction, acidic hydrolysis and elimination, provided cyclohexenone **98** with a high enantiomeric ratio (93:7 *er*, Scheme 1.21).[51]. Cycloadduct **97** arose from *endo* addition of 2-ethylacrolein (**95**) to 1-amino-3-siloxy-1,3-butadiene **94** from the top face to minimise steric interactions between the larger dienophile substituent i.e. the ethyl substituent and the "outside" phenyl group in the transition state **96**. The high enantioselectivity for the formation of cyclohexenone **98** observed is a result of high diastereoselectivity during the Diels-Alder reaction.



Scheme 1.21 Enantioselective Diels-Alder reaction of chiral 1-amino-3-siloxy-1,3-butadiene **94** with 2-ethylacrolein (**95**)

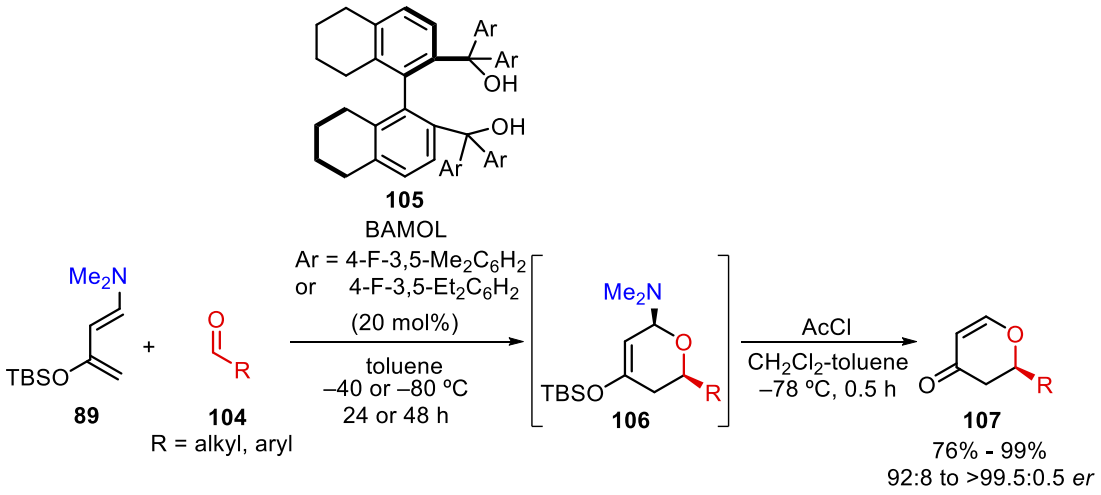
Besides using chiral amines, enantio-enriched Diels-Alder products of 1-amino-3-siloxy-1,3-butadienes have also been accessed using chiral alcohols[52,53] and a chiral metal catalyst.[54]

In 2004, Rawal and co-workers reported the use of a chiral diol, TADDOL **100**, to catalyse an enantioselective Diels-Alder reaction between Rawal's diene **89** and acrolein as well as α-substituted acroleins **99** (Scheme 1.22).[52,53] The Diels-Alder cycloadduct **102** underwent reduction, TBS deprotection and elimination to generate the isolated product **103**. The proposed transition state **101** shows interactions between TADDOL **100**, dienophile **99** and Rawal's diene **89** during the Diels-Alder reaction. The conformation of TADDOL **100** is held in place by an intramolecular hydrogen bond between the hydroxyl groups. The TADDOL hydroxyl group forms an intermolecular hydrogen bond with the carbonyl group of the dienophile, which lowers the LUMO of the dienophile. One of the napthyl groups holds the dienophile in place through π interactions with the carbonyl of the dienophile and this also blocks approach of the diene from one face, which results in an enantioselective reaction.



Scheme 1.22 Diels-Alder reaction between Rawal's diene **89** and acrolein as well as α-substituted acroleins **99** catalysed by TADDOL **100**

The enantioselective hetero-Diels-Alder reaction between Rawal's diene **89** and aldehydes **104** catalysed by an axially chiral diol, BAMOL **105**, has also been reported (Scheme 1.23).[55] BAMOL **105** is proposed to act in the same way as TADDOL **100** in which an intramolecular hydrogen bond holds the catalyst in a rigid conformation while another hydrogen bond to the aldehyde dienophile restricts approach of Rawal's diene **89** from one face. The Diels-Alder adduct **106** is converted to dihydropyranone **107** through TBS deprotection and elimination with acetyl chloride.

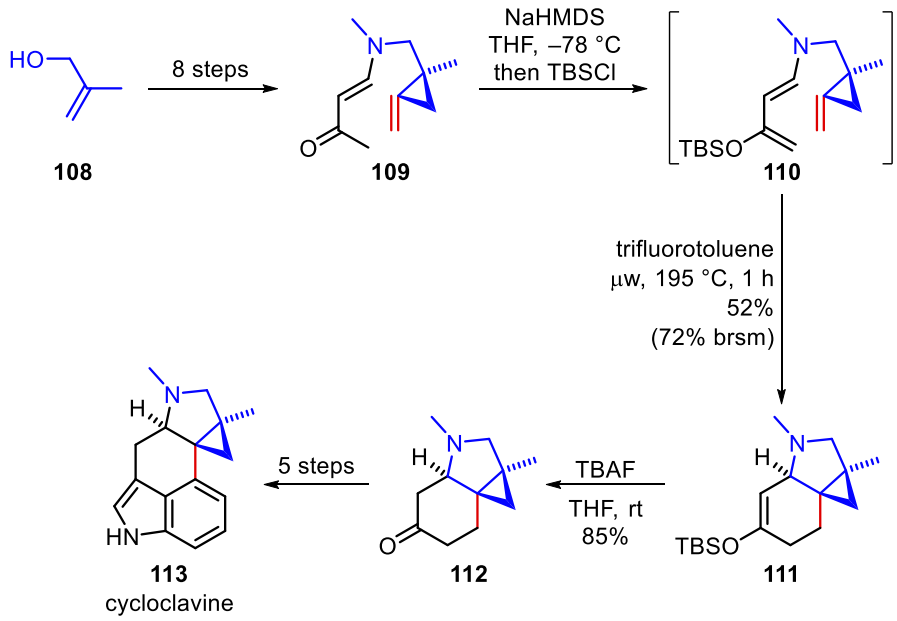


Scheme 1.23 Diels-Alder reaction between Rawal's diene **89** and aldehydes **104** catalysed by BAMOL **105**

The same hetero-Diels-Alder reaction has also been reported to be catalysed by TADDOL[52] as well as a chiral dirhodium catalyst, Rh_2(*S*-BPTPI)$_4$.[54]

1.3.2 Intramolecular Diels-Alder reaction of a 1-amino-3-siloxy-1,3-butadiene

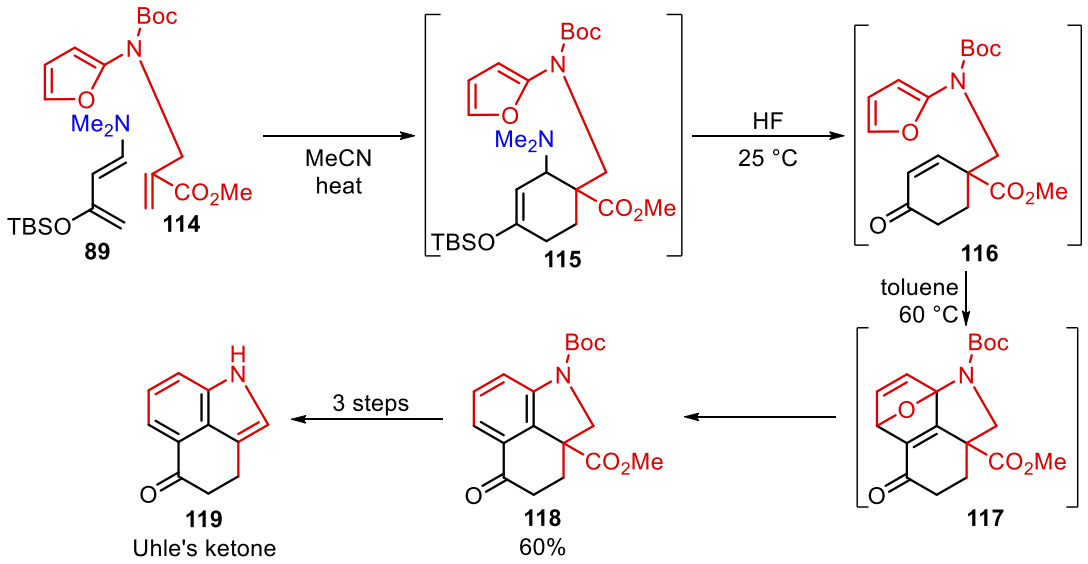
A modified Rawal's diene **109** was used in an IMDA reaction to access cycloclavine (**113**) (Scheme 1.24).[56] Vinylogous amide **109**, synthesised in eight steps from *β*-methallyl alcohol **108**, was treated with sodium bis(trimethylsilyl)amide followed by TBS trapping of the resultant enolate to generate 1-amino-3-siloxy-1,3-butadiene **110** *in situ*. Upon microwave heating, the tricyclic IMDA product **111** was delivered as a single diastereomer, in the process generating the *trans* ring junction required for the natural product. Following removal of the silyl protecting group with TBAF, enone **112** was formed. The synthesis of cycloclavine (**113**) was completed in a further five steps.



Scheme 1.24 Total synthesis of cycloclavine (**113**)

1.3.3 One-pot Diels-Alder reactions of a 1-amino-3-siloxy-1,3-butadiene

By performing more than one cycloaddition in the same sequence, polycyclic frameworks could be rapidly constructed. Bur and Padwa demonstrated the use of Rawal's diene **89** in the one-pot synthesis of tricycle **118**, which could be converted in three steps to Uhle's ketone **119**, an important intermediate in the synthesis of ergot alkaloids (Scheme 1.25).[57,58] It is proposed that a thermal Diels-Alder reaction between Rawal's diene **89** and substituted acrylate **114** led to the formation of cyclohexene **115**. Hydrolysis of the silyl enol ether followed by elimination generated cyclohexanone **116**, which acted as the dienophile in an intramolecular Diels-Alder reaction with the tethered furan. *In situ* aromatisation provided tricycle **118** in 60% yield over four steps.

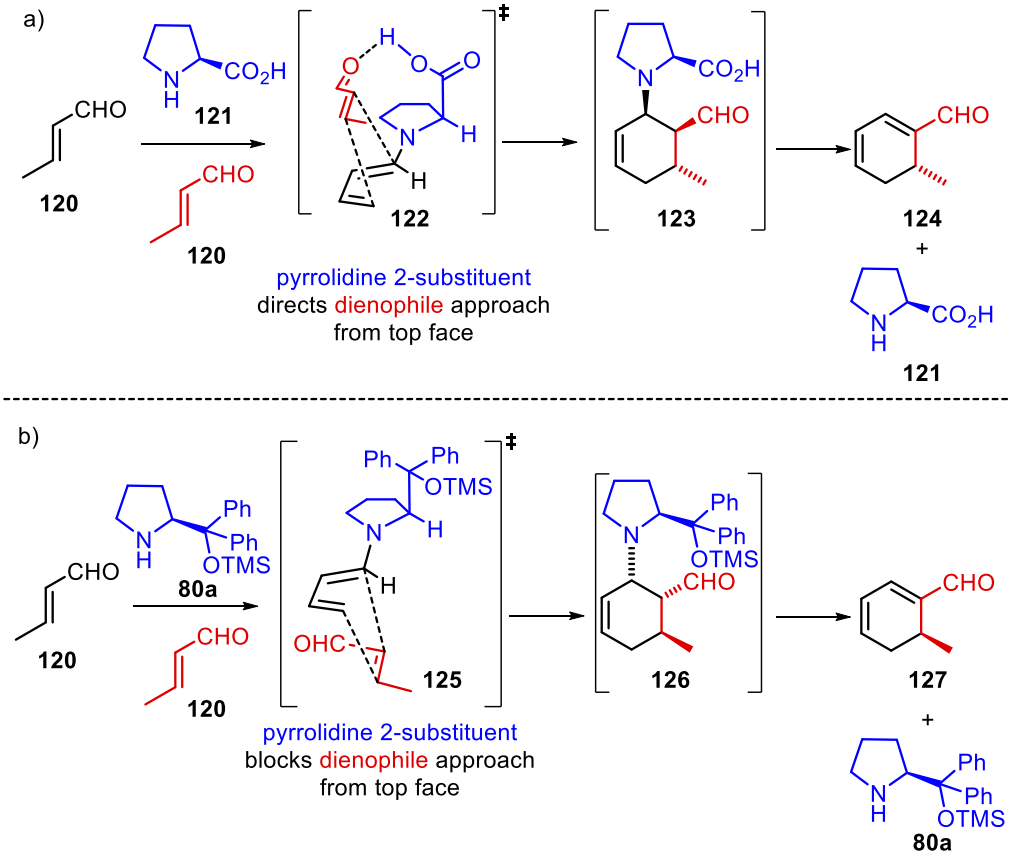


Scheme 1.25 One-pot twofold Diels-Alder reaction sequence of Rawal's diene **89** with substituted acrylate/furan diene **114**

1.4 Diels-Alder reactions of 1-amino-1,3-butadienes using catalytic amounts of chiral amine

This section focuses on the use of amine catalysts in generating 1-amino-1,3-butadienes to perform Diels-Alder reactions. The seminal reports by List on enamine catalysis[59] and MacMillan on iminium catalysis[60] in 2000 led to renewed interest in the field of organocatalysis, which has since been applied to many different reactions.[61-63] Enamine catalysis[64] has been extended[11] to dienamines (referred to as 1-amino-1,3-butadienes in this thesis),[4] trienamines[9-11,65] (referred to as 1-amino-1,3,5-trienes or 1-amino-[3]dendralene in this thesis) and tetraenamines[66] (referred to as 1-amino-1,3,5,7-tetraenes in this thesis), which participate in Diels-Alder reactions as electron-rich 1,3-butadienes to access enantioenriched cycloadducts. These are generally catalysed by chiral secondary amines, which can be broadly categorised into two groups, depending on the way they induce π-diastereofacial selectivity (Scheme 1.26). The first group, which includes L-proline (**121**), forms hydrogen bonds to carbonyl groups present in electrophilic dienophiles, thus directing their approach from the same face (Scheme 1.26a). The second group consists of diarylprolinol silyl ethers,[7,12] such as amine **80a**, which bear a large substituent consisting of two aryl groups and a silyl protected alcohol on the pyrrolidine ring. These catalysts act by blocking the approach of a dienophile from the same face as the bulky substituent (Scheme 1.26b). The amine catalysts are

regenerated from the Diels-Alder adducts, for example by an elimination reaction, to provide the final product **124** and **127**.

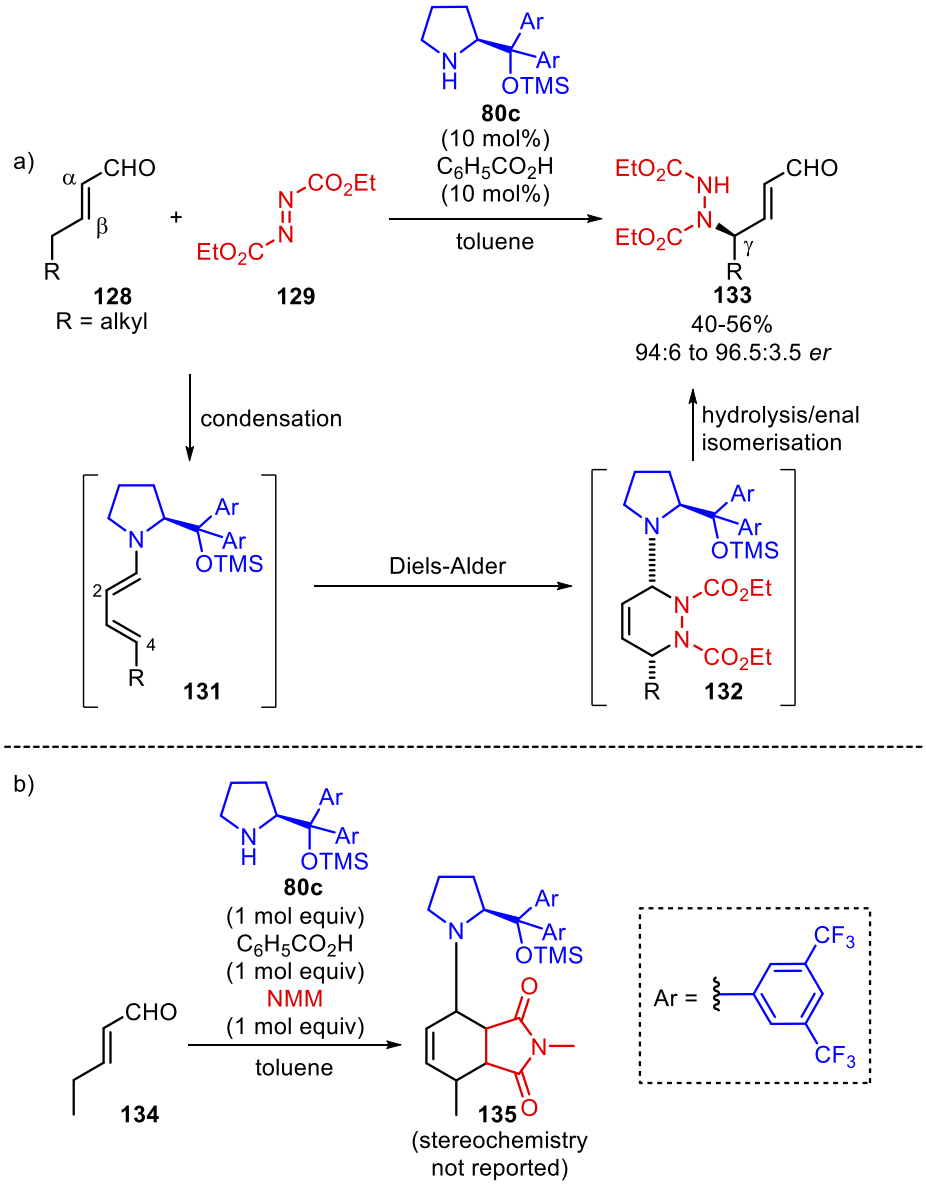


Scheme 1.26 Examples of reactions involving secondary amine catalysts which a) direct the approach of a dienophile by forming a hydrogen bond and b) block one face with towards dienophile approach with a bulky substituent

1.4.1 Intermolecular Diels-Alder reactions with acyclic 1-amino-1,3-butadienes

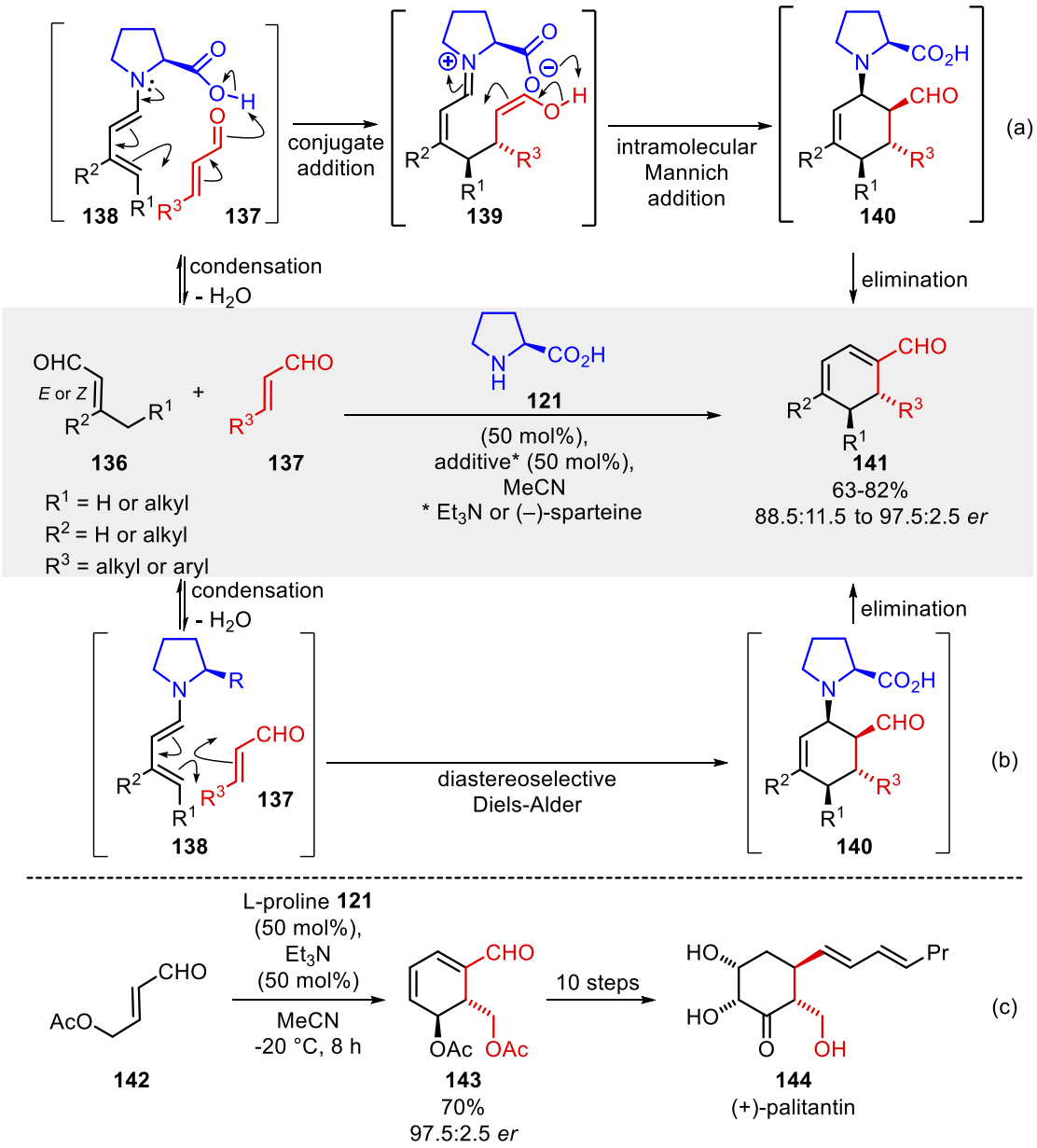
In 2006, Jørgensen reported an enantioselective HOMO-activated 1-amino-1,3-butadiene Diels-Alder reaction (Scheme 1.27a).[67] α,β-Unsaturated aldehydes **128** were reacted with diethyl azodicarboxylate (**129**) in the presence of catalytic amounts of amine **80c** and benzoic acid, which resulted in the formation of γ-substituted aldehyde **133** with high enantioselectivity. The first step of the reaction is proposed to be the condensation between aldehyde **128** and amine **80c** to form 1-amino-1,3-butadiene **131**. There are three potential nucleophilic sites in 1-amino-1,3-butadiene **131**, the N, the 2 and the 4 positions. Computational studies showed that there was no energetic preference for direct addition at either position. Instead, the reaction was suggested to

proceed *via* a [4+2] reaction to give intermediate **132** followed by hydrolysis of the aminal to generate the observed product **133**. The observed stereochemistry of enantiomer **133** is consistent with the aza dienophile approaching from the less hindered face of the 1-amino-1,3-butadiene in the Diels-Alder reaction. The proposed cycloaddition mechanism was also supported by an experiment in which the proposed 1-amino-1,3-butadiene intermediate **131** was trapped as the cycloaddition product **135** by using NMM as the dienophile (Scheme 1.27b).



Scheme 1.27 a) γ-Amination of aldehyde **128** *via* 1-amino-1,3-butadiene **131** b) Synthesis of cycloadduct **135** from aldehyde **134**

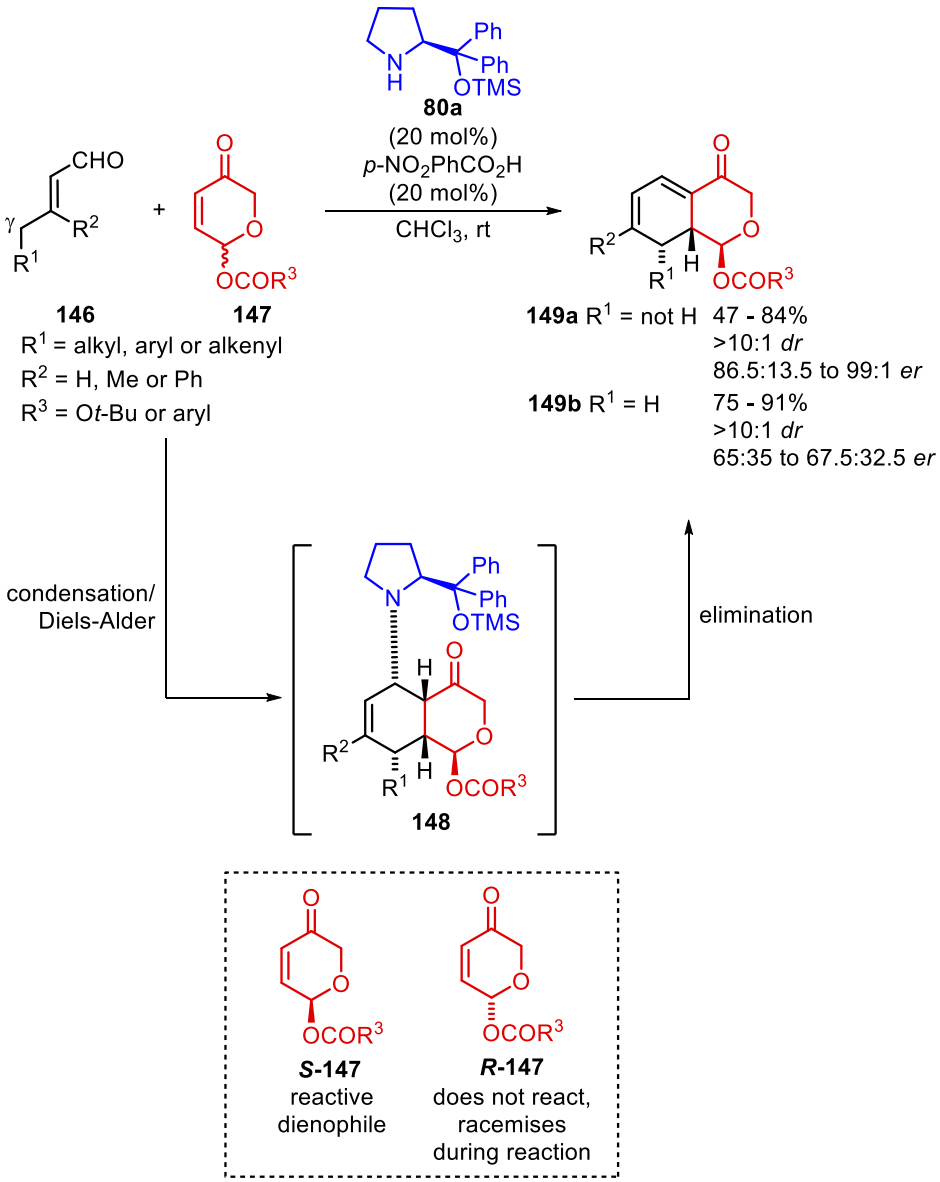
Hong and co-workers reported the reaction between aldehydes **136**, β-substituted acroleins **137** and L-proline (**121**) to generate cyclohexenes **141** (Scheme 1.28).[68] Two possible mechanisms were proposed. Condensation between aldehyde **136** and L-proline (**121**) generates 1-amino-1,3-butadiene **138** which either undergoes a step-wise, formal Diels-Alder reaction involving a conjugate addition reaction followed by an intramolecular Mannich addition (Scheme 1.28a) or a direct Diels-Alder reaction (Scheme 1.28b) to generate cyclohexene **140**. Elimination of L-proline provides 1,3-cyclohexadiene **141**. The authors favour the stepwise mechanism as reactions of (*E*)- and (*Z*)-4-acetoxycrotonaldehyde (R^1 = CH_2OAc, R^2 = H) delivered products with the same stereochemistry, indicating that the stereochemistry of the dienophile is scrambled in the reaction. The synthetic utility of the method was demonstrated by the conversion of cycloadduct **143** to (+)-palitantin (**144**) in 10 steps (Scheme 1.28c).



Scheme 1.28 a) Proposed condensation/step-wise addition/elimination reaction mechanism b) Proposed condensation/Diels-Alder/elimination mechanism c) Synthesis of (+)-palitantin (**144**) from aldehyde **142** *via* adduct **143**

A similar reaction was performed using cyclic dienophiles such as pyranones **147** with amine **80a** and *p*-nitrobenzoic acid (Scheme 1.29).[69] Only one of the enantiomers ***S*-147** is reactive in the Diels-Alder reaction whereas the non-reactive enantiomer ***R*-147** undergoes racemisation over the course of the reaction, which generates more of the reactive enantiomer ***S*-147**. This dynamic kinetic resolution resulted in the intermediate Diels-Alder adducts **148** being produced, which upon elimination generated the bicycles

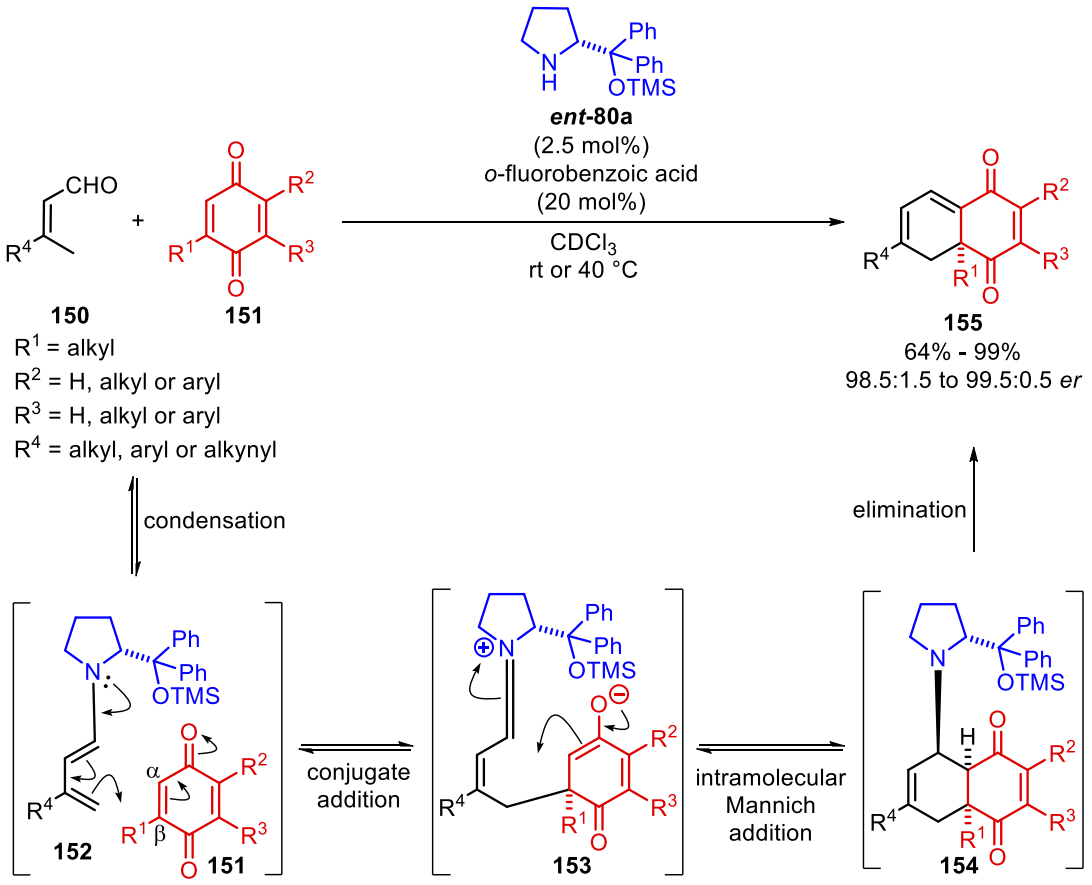
149. In the case of α,β-unsaturated aldehydes without γ substituents (i.e. R^1 = H), lower enantioselectivities of 65:35 to 67.5:32.5 *er* were observed.



Scheme 1.29 Condensation/Diels-Alder/elimination reaction of aldehydes **146**, amine **80a** and pyranones **147**

In a similar example, Jørgensen et al. reported the reaction between aldehydes **150**, substituted 1,4-quinones **151**, amine *ent*-**80a** and an acid co-catalyst to generate bicyclic adducts **155** with high regio- and enantioselectivity (Scheme 1.30).[70] In this case, computational studies suggested the mechanism to be a stepwise conjugate addition then intramolecular Mannich addition rather than a concerted Diels-Alder reaction to form bicycle **154**. The site selectivity is determined in the conjugate addition step where

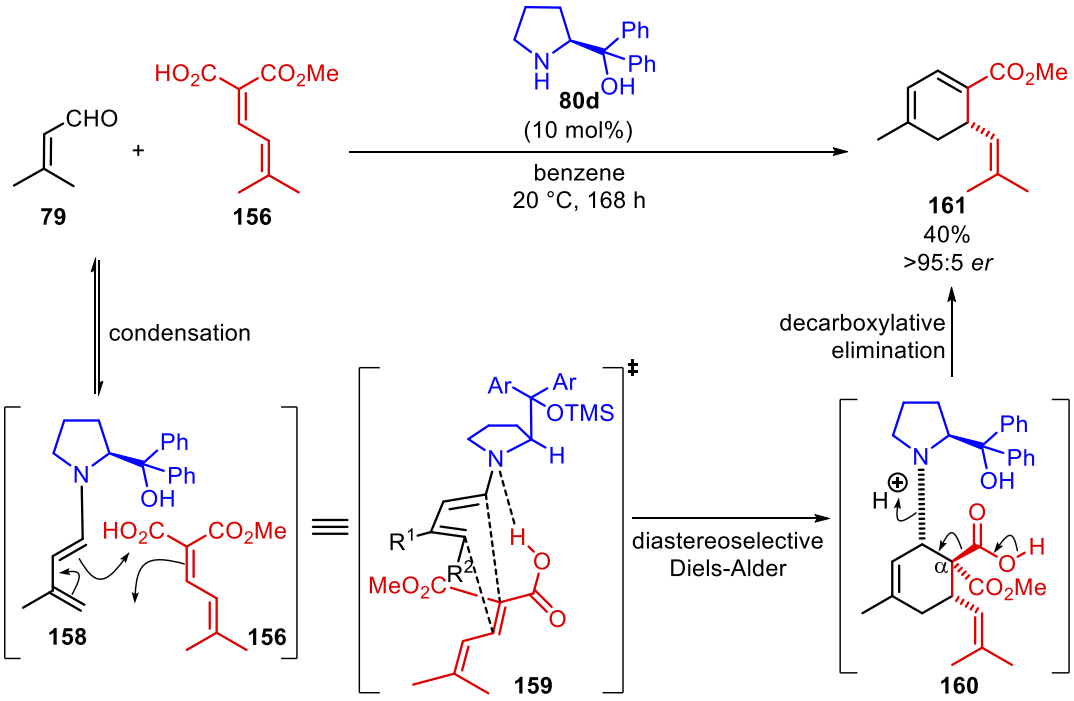
reaction at the substituted β carbon was calculated to be slightly more favourable than at the unsubstituted α carbon. Bicycle **154** is also the most thermodynamically favoured product in this reversible reaction. The observed enantiomer **155** was a result of addition of quinone **151** to 1-amino-1,3-butadiene **152** from the face opposite to the bulky pyrrolidine substituent in a "stacked" transition state, which was proposed to be preferred due to favourable electrostatic attraction between amine and quinone.



Scheme 1.30 Condensation/conjugate addition/intramolecular Mannich addition/elimination reaction between aldehydes **150**, substituted quinones **151** and amine *ent*-**80a**

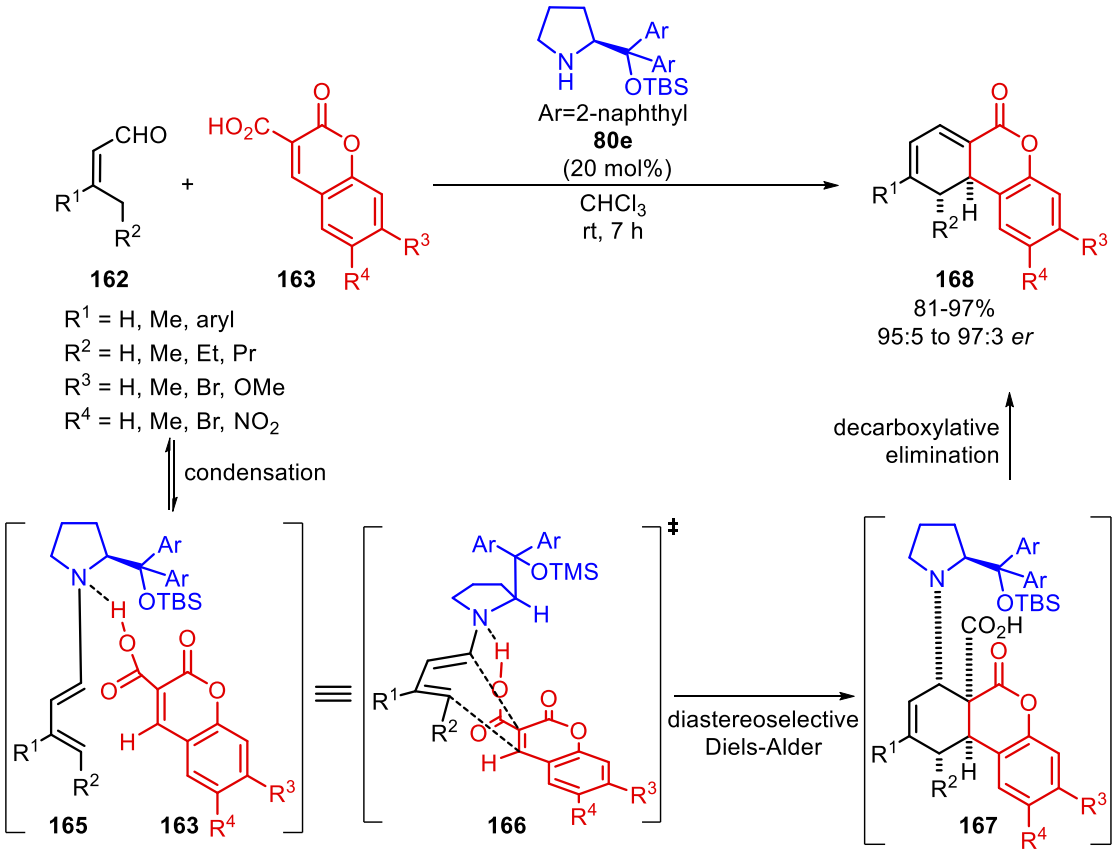
Serebryakov reported the reaction between aldehyde **79**, malonate **156** and amine **80d** (Scheme 1.31).[71] The reaction is proposed to start with a condensation between aldehyde **79** and amine **80d** to form 1-amino-1,3-butadiene **158** followed by a Diels-Alder reaction with malonate **156** *via* transition state **159** to generate cycloadduct **160**, which lacks a proton on the α carbon necessary for regeneration of the amine catalyst by elimination. In this case, the carboxylic acid substituent on the dienophile is essential in freeing the amine catalyst through a decarboxylative elimination sequence.

1,3-Cyclohexadiene **161** was obtained in 40% yield and a reported 100:0 *er*, which was determined using a chiral shift agent and ^{1}H NMR spectroscopy. Due to the limits of detection of 300 MHz ^{1}H NMR spectroscopy, it would be more accurate for the enantiomeric ratio to be reported as >95:5.[72]



Scheme 1.31 Condensation/Diels-Alder/decarboxylative elimination reaction between aldehyde **79**, malonate **156** and amine **80d**

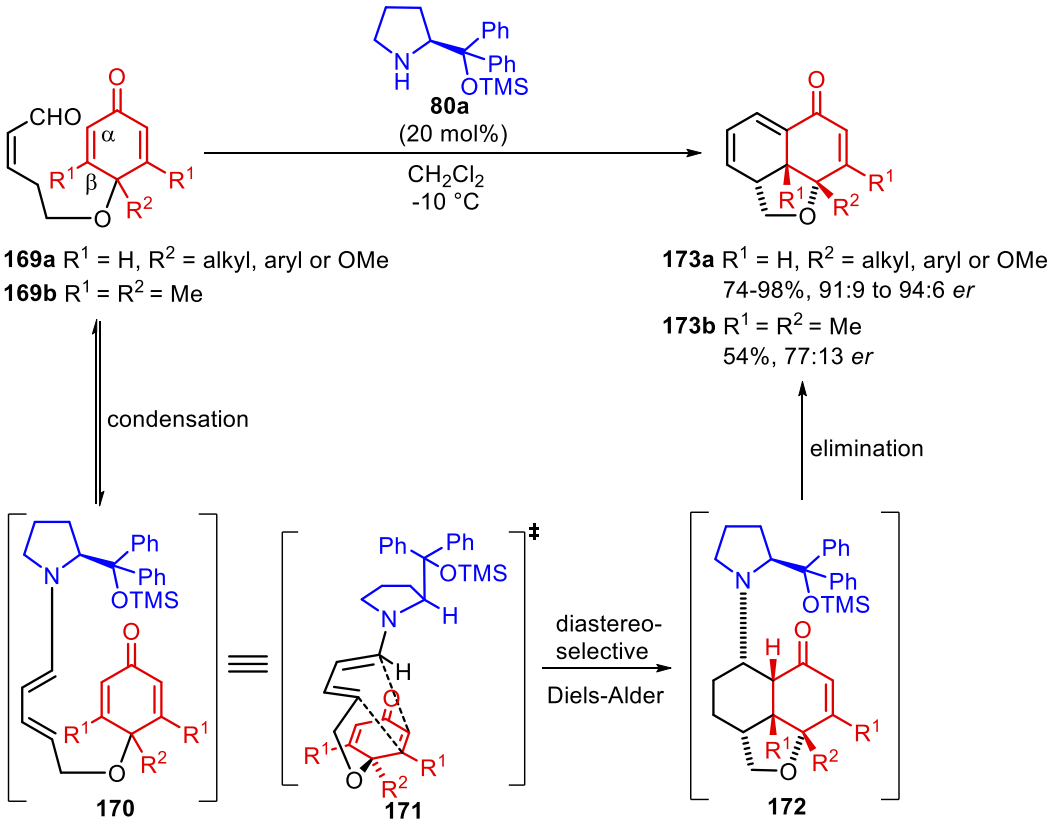
More recently, Wang and co-workers performed a similar reaction sequence using coumarin-3-carboxylic acids **163** as dienophiles to access tricyclic Diels-Alder adducts **168** (Scheme 1.32).[73] The observed stereochemical outcome is a result of *endo*-selective (with respect to the carboxylic acid) Diels-Alder reaction between 1-amino-1,3-butadiene **165** and dienophile **163**. The dienophile approaches 1-amino-1,3-butadiene **165** from the bottom face as shown in transition structure **166** to generate cycloadduct **167**, which undergoes decarboxylative elimination to afford tricycle **168**.



Scheme 1.32 Condensation/Diels-Alder/decarboxylative elimination reaction between aldehydes **162**, dienophiles **163** and amine **80e**

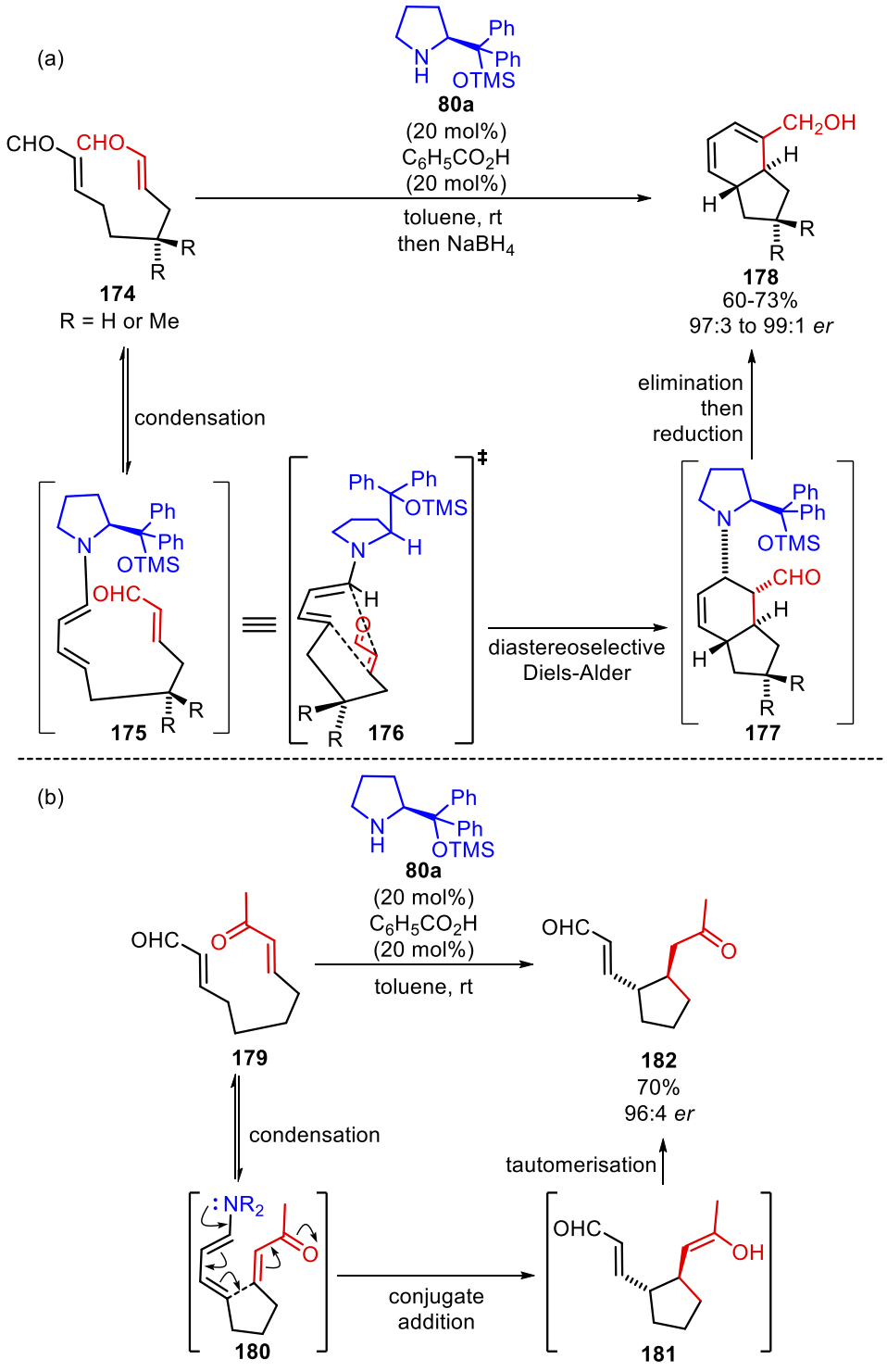
1.4.2 Intramolecular Diels-Alder reactions with acyclic 1-amino-1,3-butadienes

Aldehydes **169**, which are tethered to a cyclic dienophile, were converted into fused tricycles **173** in the presence of amine **80a** (Scheme 1.33).[74] It is proposed that condensation between aldehydes **169** and amine **80a** led to the formation of 1-amino-1,3-butadienes **170**, which reacted in an IMDA reaction to generate cycloadducts **172**. Elimination of amine **80** delivered tricycles **173**. The stereochemical outcome of the reaction is a result of *endo* approach of the dienophile from the face opposite to the bulky pyrrolidine ring substituent in the Diels-Alder reaction. Aldehyde **169b** bears substituents at the β-positions of the dienophile (i.e. R^1 is not hydrogen) and underwent the same reaction to form tricycle **173b** with lower enantioselectivity.



Scheme 1.33 Condensation/IMDA/elimination reaction reactions of aldehydes **169a** and **169b** with amine **80a**

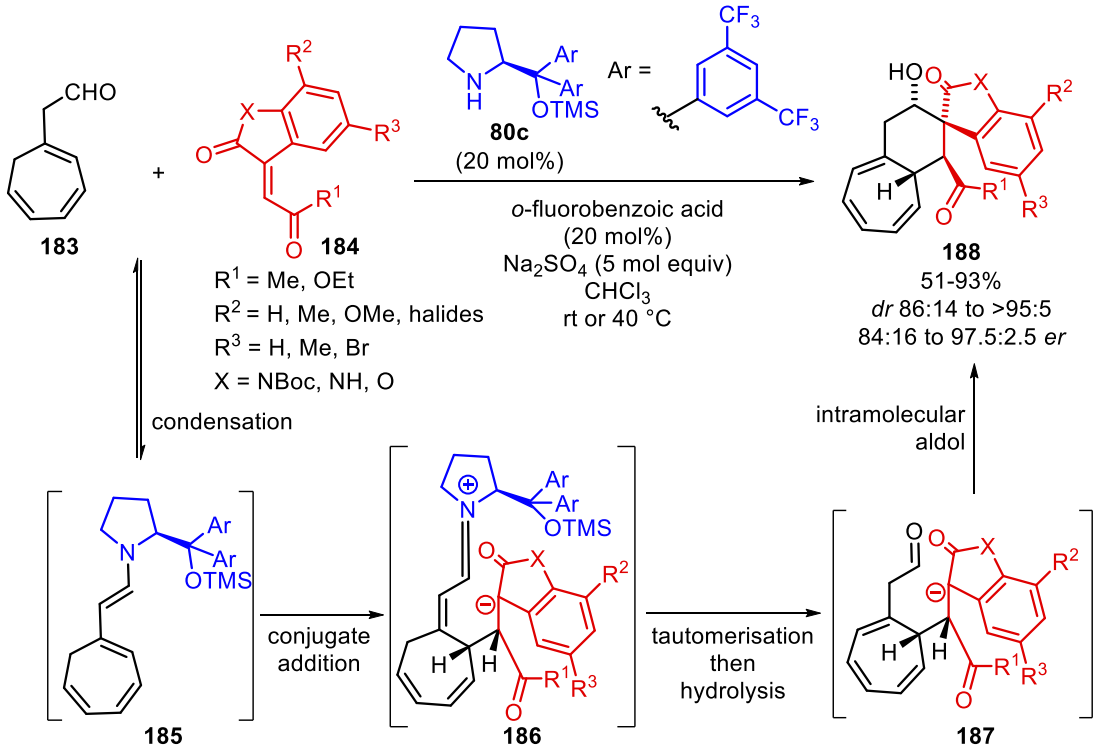
A similar condensation/IMDA/elimination reaction sequence between dialdehydes **174** and amine **80a** produced bicyclic cycloadducts **177** *via* 1-amino-1,3-butadiene **175** **(**Scheme 1.34a).[75] The cycloadducts were reduced *in situ* and isolated as alcohols **178**. The stereochemical outcome of the reaction is a result of *endo* approach of the dienophile from the face opposite to the bulky pyrrolidine ring substituent in the Diels-Alder reaction. With precursor **179**, where one of the aldehydes was replaced with a ketone, the expected cycloaddition did not occur. Cyclopentane **182**, a product of intramolecular γ addition of 1-amino-1,3-butadiene **180** to the α,β-unsaturated ketone, was obtained instead (Scheme 1.34b).



Scheme 1.34 a) Condensation/IMDA/elimination reactions of dialdehydes **174** b) intramolecular γ addition of 1-amino-1,3-butadiene **180**

1.4.3 Intermolecular formal Diels-Alder reactions with semi-cyclic 1-amino-1,3-butadienes

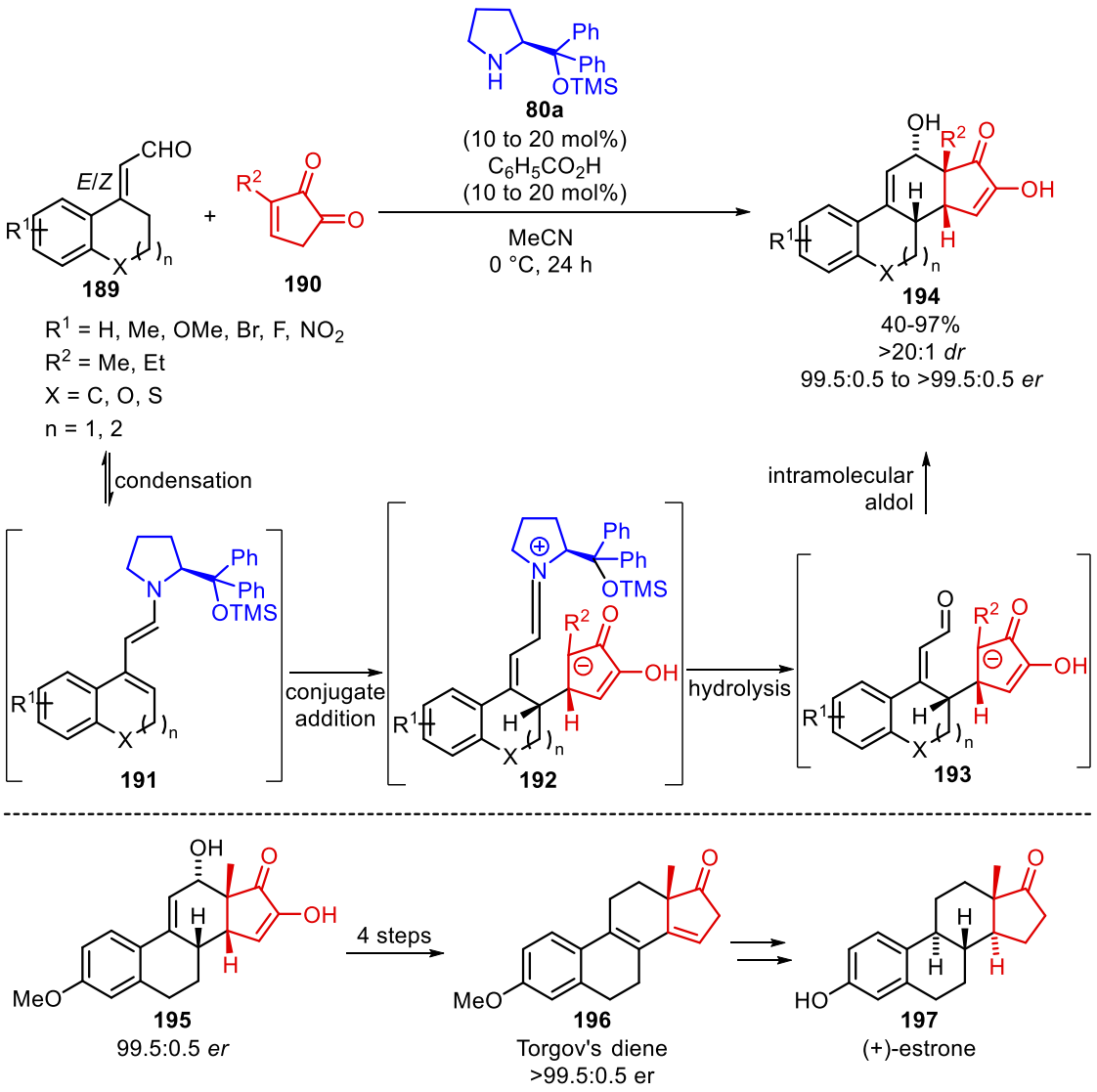
1-Amino-1,3,5,7-tetraenes have been reported to undergo formal Diels-Alder reactions *via* a stepwise mechanism (Scheme 1.35).[66] 1-Amino-1,3,5,7-tetraene **185**, a product of condensation between aldehyde **183** and amine **80c**, reacted with oxindoles **184** to generate tetracycles **188**. 1-Amino-1,3,5,7-tetraene **185** was proposed to undergo conjugate addition to form zwitterions **186** followed by iminium tautomerisation and hydrolysis to generate aldehydes **187**. Intramolecular aldol reaction of aldehyde **187** provided tetracycles **188**. This reaction is both highly enantio- and diastereoselective. The steric bulk of amine catalyst **80c** directs the conjugate addition to occur from the opposite face to the bulky pyrrolidine substituent while in the intramolecular addition, the oxindole fragment orientates to minimise the steric clash with the seven membered ring.



Scheme 1.35 Condensation/conjugate addition/intramolecular aldol reaction between aldehyde **183**, oxindoles **184** and amine **80c**

In 2014, Jørgensen and co-workers reported the use of semi-cyclic 1-amino-1,3-butadienes **191** to access highly enantio-enriched steroidal frameworks **194** (Scheme

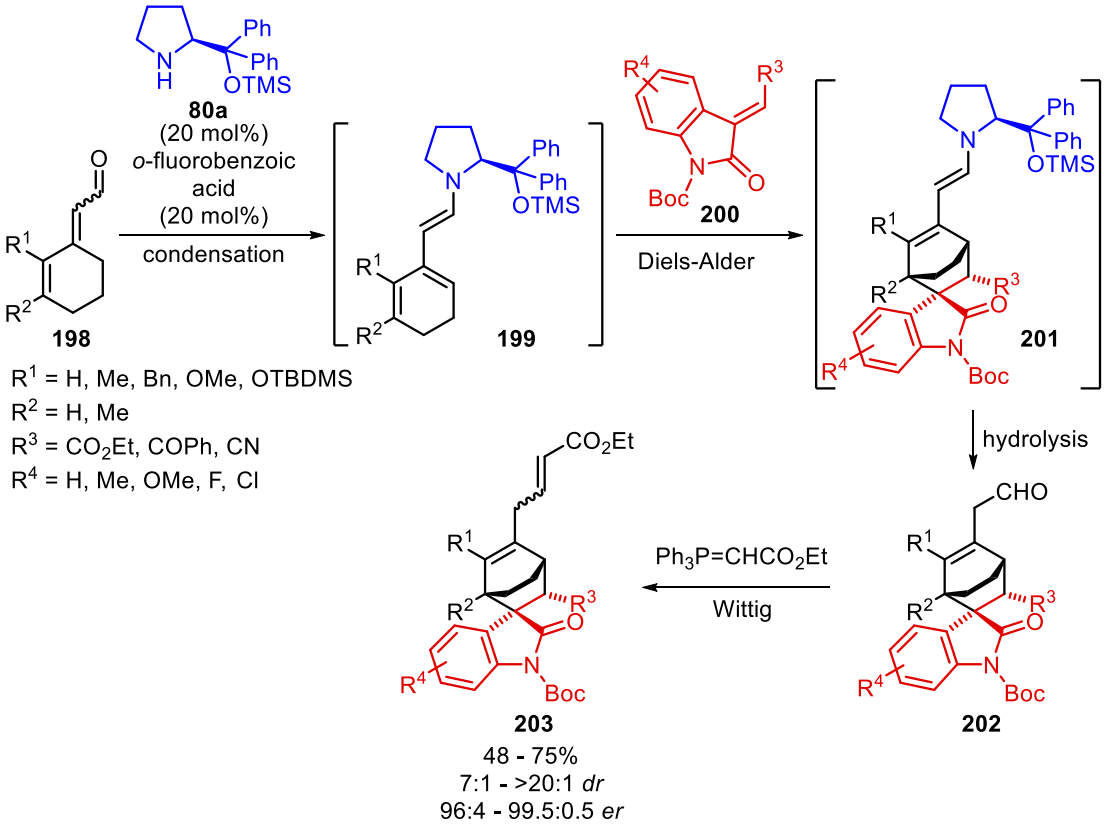
1.36).[76] Condensation between aldehydes **189** and amine catalyst **80a** resulted in the formation of 1-amino-1,3-butadienes **191**. The mechanism for subsequent transformations leading to tetracycle **194** was not described but may be similar to the mechanism proposed for the conversion of 1-amino-1,3,5,7-tetraene **185** to tetracycle **188** in **Scheme 1.35**. Tetracycle **195** was converted to Torgov's diene **196** in four steps, which constituted a formal total synthesis of (+)-estrone (**197**).



Scheme 1.36 Synthesis of tetracyclic steroidal framework **194** and Torgov's diene **196**

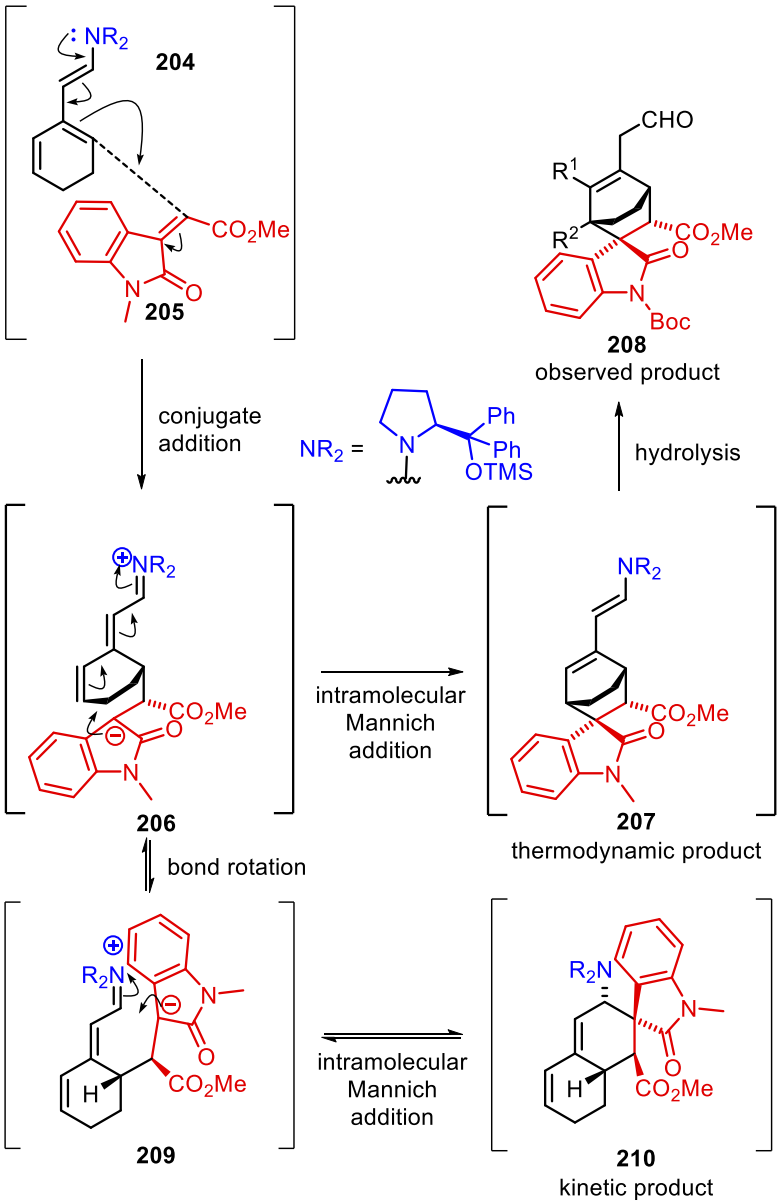
Jørgensen et al. reported an enantioselective Diels-Alder reaction involving semi-cyclic cross-conjugated 1-amino-[3]dendralenes **199**, derived from aldehydes **198** and chiral amine **80a**, and dienophiles **200** (Scheme 1.37).[77] While the reaction can take place at two possible 1,3-butadiene sites, only the cycloaddition product arising from reaction at

the cyclic 1,3-butadiene unit distant to the amine substituent was observed. Hydrolysis and Wittig olefination of cycloadducts **201** provided spirocycles **203**.



Scheme 1.37 Condensation/Diels-Alder/hydrolysis reaction sequence between aldehydes **198**, amine **80a** and dienophiles **200** followed by hydrolysis and Wittig reaction to generate spirocycles **203**

Further computational studies by Houk and co-workers showed that the formation of spirocycles **201** from 1-amino-[3]dendralenes **199** in Scheme 1.37 is a result of two step-wise addition reactions rather than a concerted cycloaddition as previously proposed (Scheme 1.38).[78] The regioselectivity is attributed to the reversible formation of the kinetically favoured 1,2-addition product **210**, which could readily equilibrate to zwitterionic intermediate **209** *via* ring-opening. Intermediate **209** then undergoes bond rotation and 1,6-addition to afford the thermodynamic product **207**, which is irreversible.

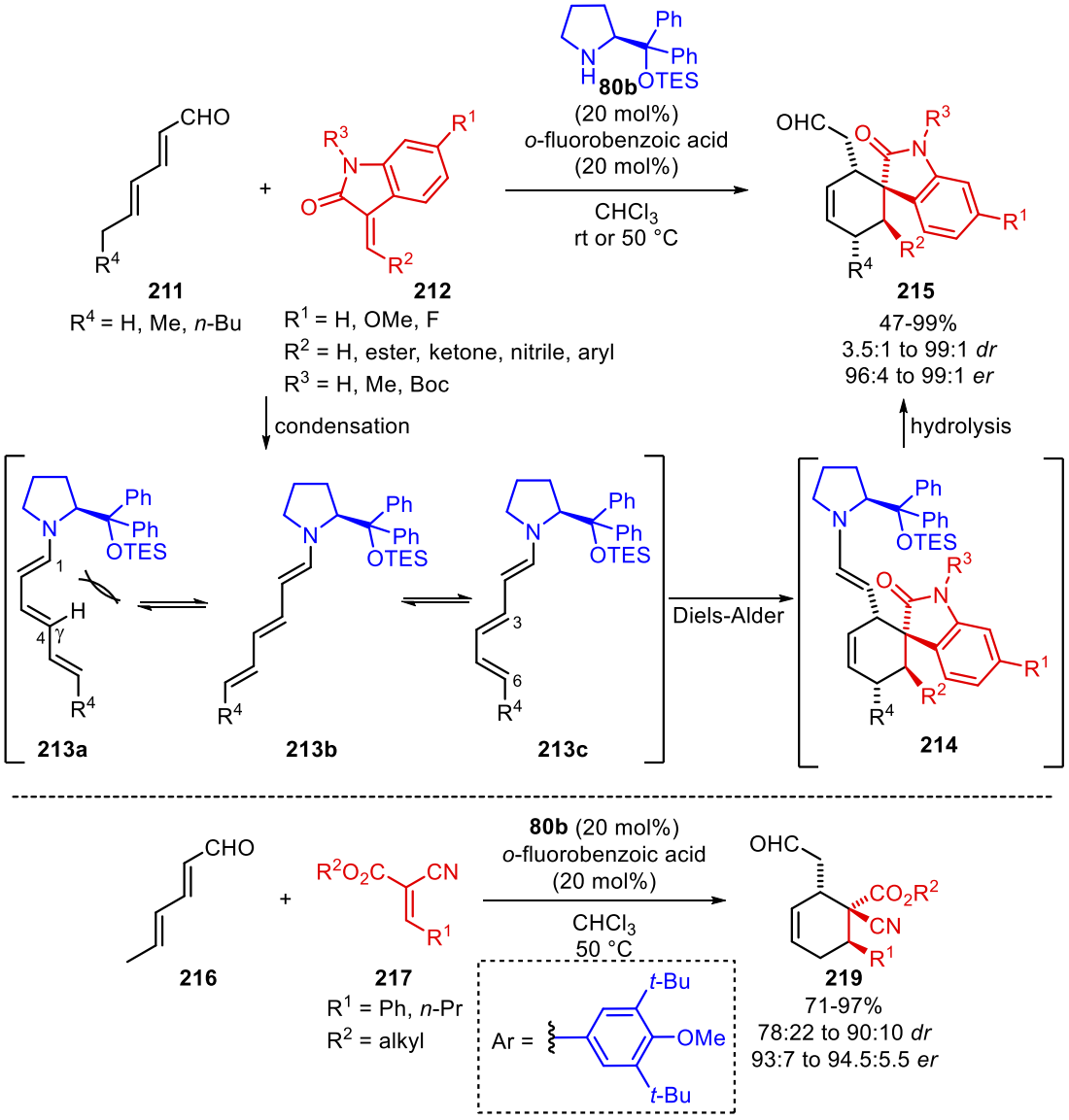


Scheme 1.38 Proposed mechanism and selectivity of the reaction between cross-conjugated 1-amino-[3]dendralene **204** and oxindole **205**

1.4.4 Intermolecular Diels-Alder reactions with acyclic 1-amino-1,3-butadienes that are part of an extended linear conjugated system

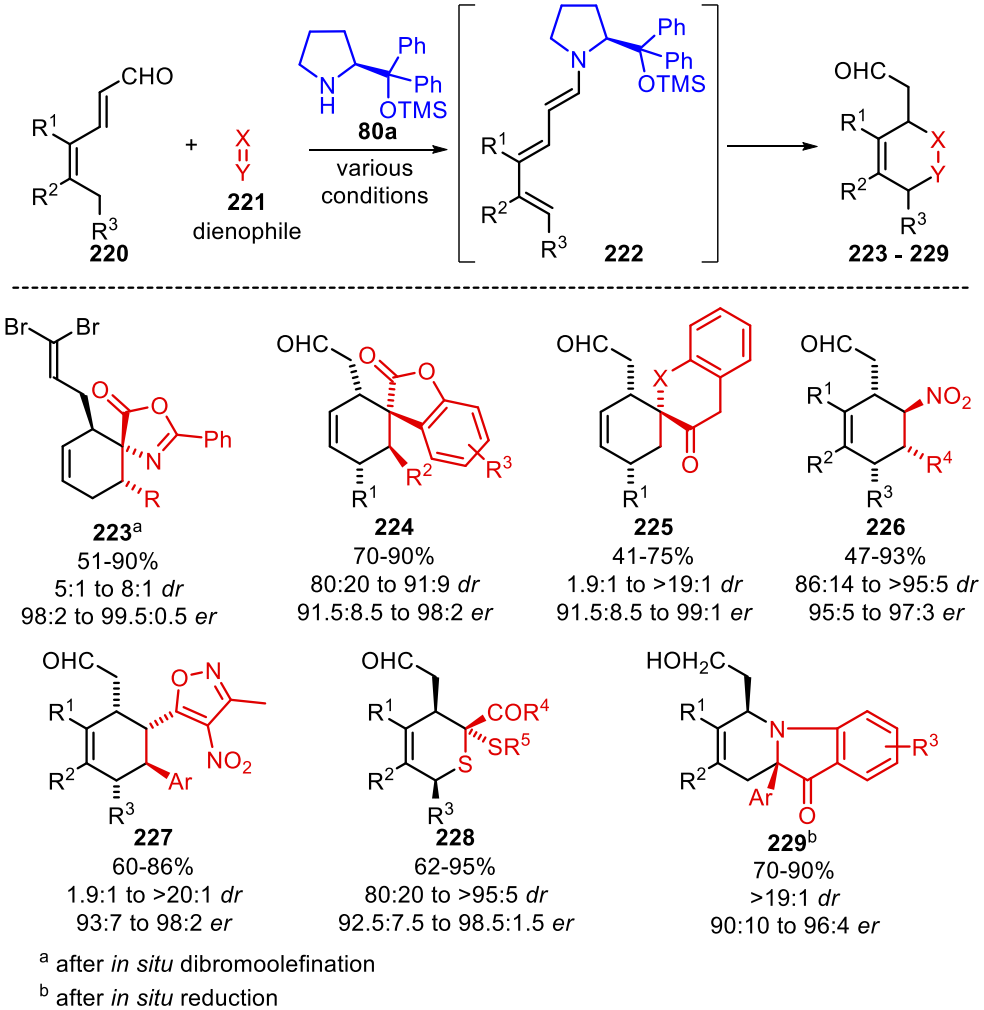
In 2011, the first example of a Diels-Alder reaction *via* a linear 1-amino-1,3,5-triene intermediate **213** was jointly reported by the groups of Jørgensen and Chen (Scheme 1.39).[79] Using 3-alkenic oxindoles **212** as the dienophile, aldehydes **211** derived 1-amino-1,3,5-trienes **213** underwent a highly regio-, diastereo- and enantioselective Diel-Alder reaction to generate spirocyclic adducts **214**. Upon hydrolysis, amine **80b** was regenerated to provide spirocycles **215**. Computational studies suggested that the

observed regioselectivity is due to a combination of steric and electronic factors. There is a smaller energy barrier to access conformer **213c** than conformer **213a** from conformer **213b** by bond rotation. This was proposed to be due to steric clash between the γ hydrogen and the pyrrolidine substituent present in conformer **213a**. Calculated orbital coefficients also indicated that 1-amino-1,3-butadiene **213c** is more reactive as the HOMO energy level of the terminal C3=C4-C5=C6 1,3-butadiene is higher than that of the C1=C2-C3=C4 1,3-butadiene. The Diels-Alder cycloadducts **214** resulted from *endo* approach of the oxindoles dienophile **212** from the less sterically hindered face of 1-amino-1,3,5-triene **213c**. Alkenic cyanoacetates **217** were also suitable dienophiles for the reaction, generating cyclohexenes **219**.



Scheme 1.39 Diels-Alder reactions of 1-amino-1,3,5-trienes **213** with 3-alkenic oxindoles **212** and alkenic cyanoacetates **217**

Since then, 1-amino-1,3,5-trienes have been reported to undergo enantioselective Diels-Alder reactions under similar conditions with other highly reactive dienophiles to furnish diverse structures (Scheme 1.40). Spirocycles bearing α,α-disubstituted amino acid **223**,[80] benzofuranone **224**[81] and benzohexanone **225** substituents as well as cyclohexenes with nitro **226**[28] and 4-nitro-isoxazole **227**[82] groups can be accessed. Heteroatoms such as sulfur[83] and nitrogen[84] can also be incorporated into the frameworks by using heterodienophiles, generating cycloadducts **228** and **229** respectively. In all of these reactions, the dienophile selectively reacts at the 1,3-butadiene unit farther from the amine substituent of the 1-amino-1,3,5-triene intermediate **222**.

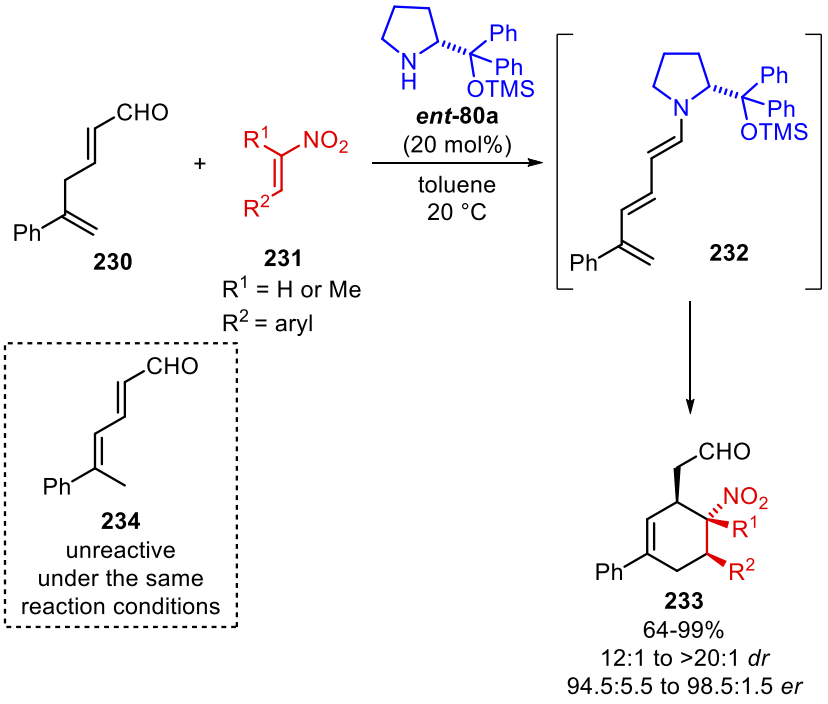


[a] after *in situ* dibromoolefination
[b] after *in situ* reduction

Scheme 1.40 Structures accessible *via* Diels-Alder reactions of 1-amino-1,3,5-trienes **222**

Aldehyde **230**, which possesses skipped conjugation, underwent condensation with amine ***ent*-80a** to generate 1-amino-1,3,5-trienes **232** more readily than the

corresponding conjugated aldehyde **234**, which was unreactive under the same reaction conditions (Scheme 1.41).[85]



Scheme 1.41 Diels-Alder reaction of 1-amino-1,3,5-triene **232** with nitroalkenes **231**

1.5 Summary and Conclusions

1-amino-1,3-butadienes and 1-amino-3-siloxy-1,3-butadienes undergo inter- or intramolecular Diels-Alder reactions to generate a structurally diverse range of cycloadducts (Figure 1.4). Almost all the examples feature pre-formed alkyl substituted 1-amino-1,3-butadienes or 1-amino-3-siloxy-1,3-butadienes undergoing single Diels-Alder reactions.

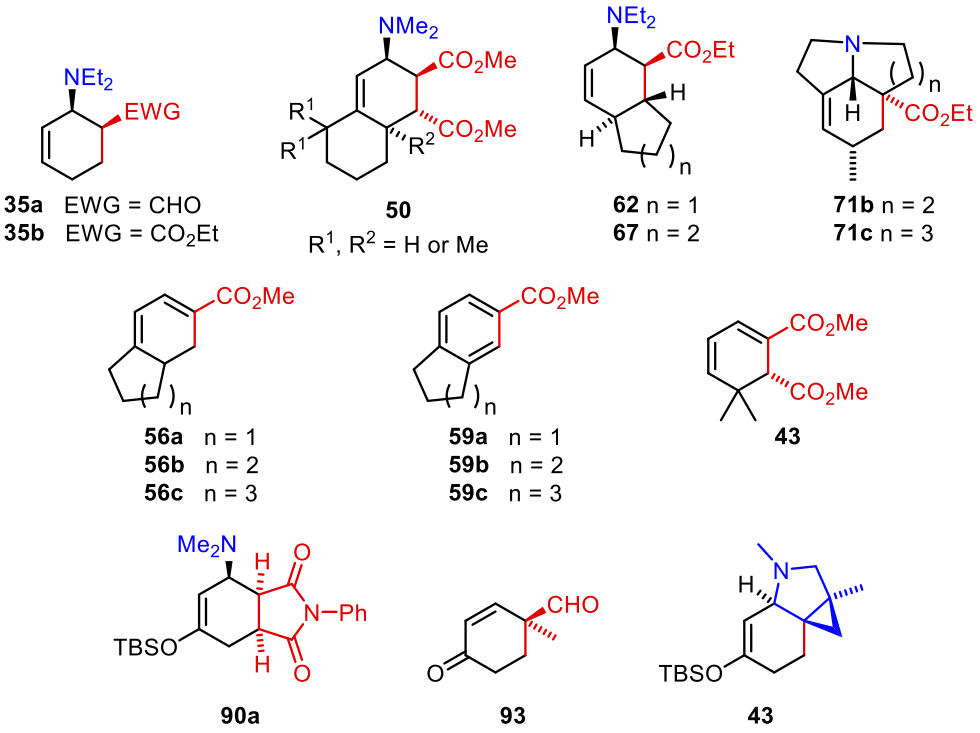
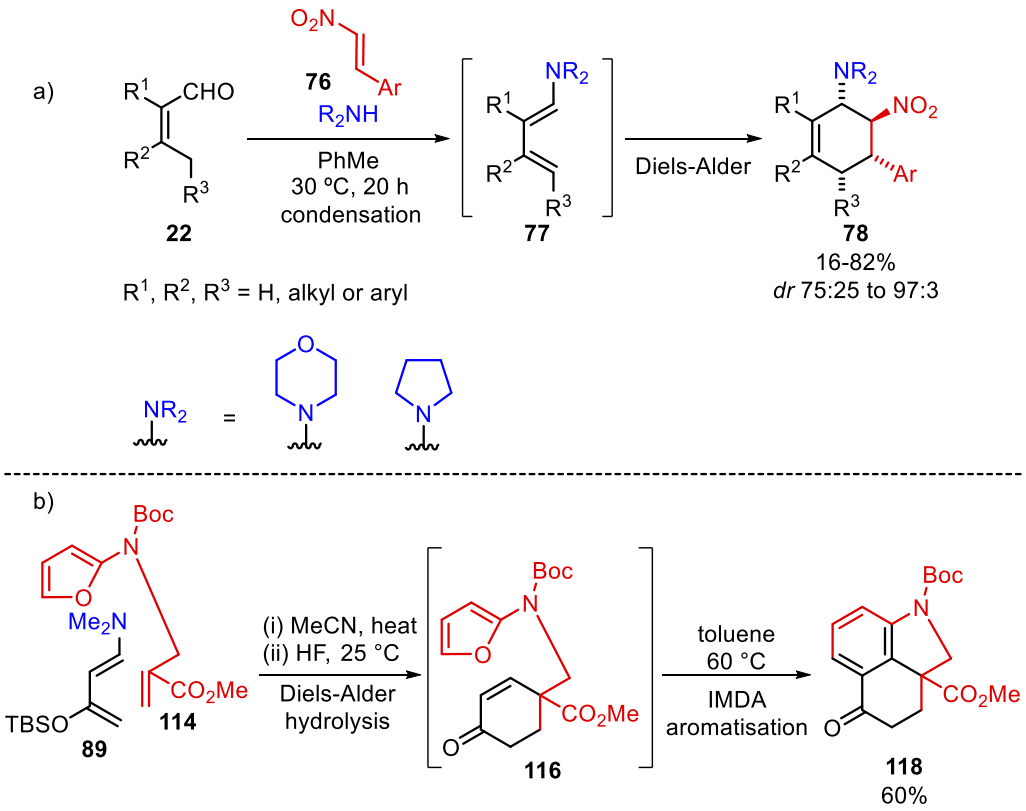


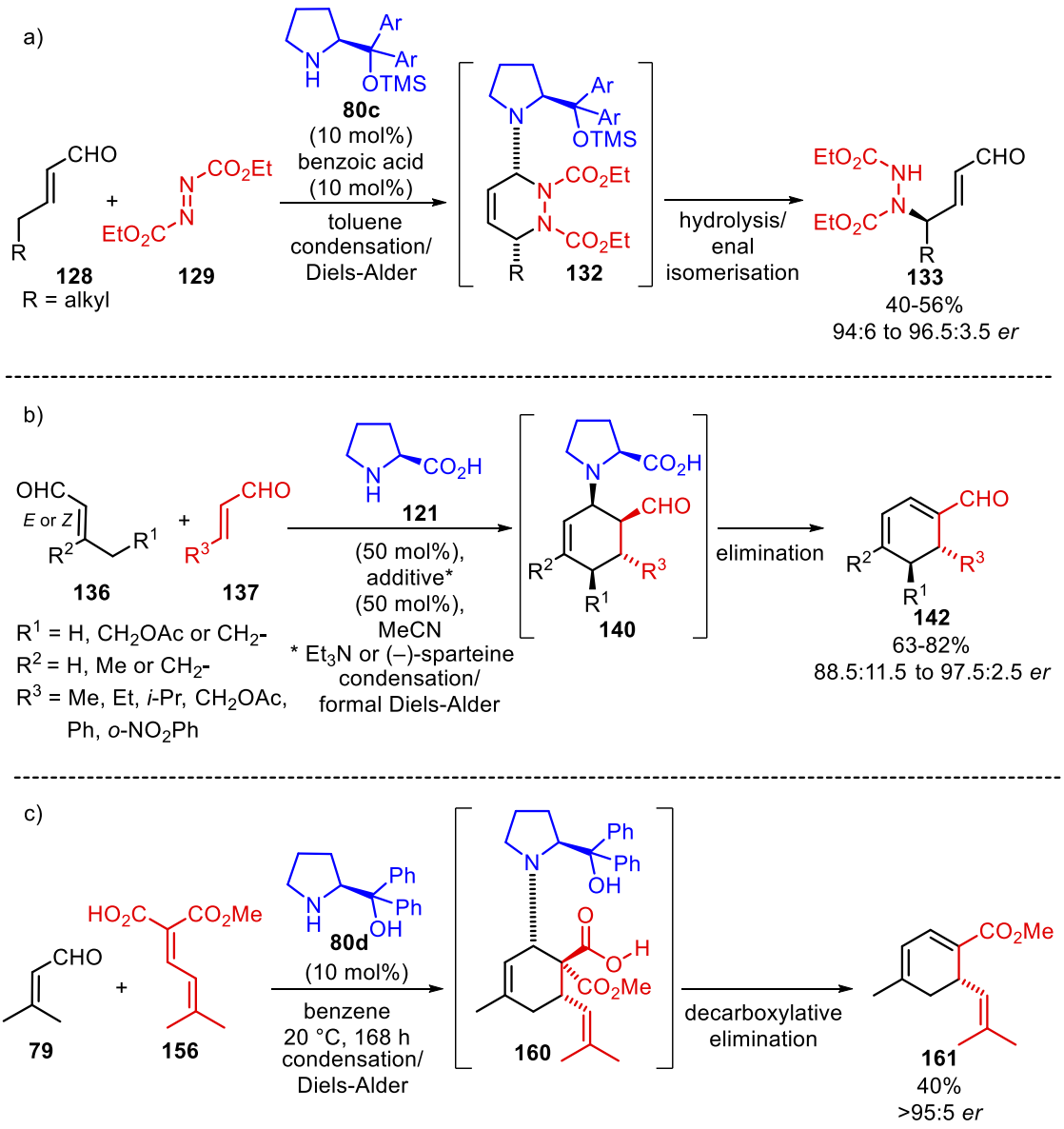
Figure 1.4 Cycloadducts obtained from Diels-Alder reactions of 1-amino-1,3-butadienes and 1-amino-3-siloxy-1,3-butadienes

By combining multiple transformations in one pot, more efficient routes to polycyclic structures are possible. There are two examples in which the Diels-Alder reaction of 1-amino-1,3-butadienes or 1-amino-3-siloxy-1,3-butadienes is combined with other transformations in one synthetic operation. The synthesis and Diels-Alder reactions of 1-amino-1,3-butadiene **77** were performed in one-pot to provide cyclohexenes **78** (Scheme 1.42a).[43] 1-Amino-3-siloxy-1,3-butadiene **89** underwent a Diels-Alder/hydrolysis/IMDA/aromatisation reaction sequence to generate tricycle **118** in one step (Scheme 1.42b).[57] The development of new methodology combining different reactions with the Diels-Alder reaction or with other functionalised 1-amino-1,3-butadienes will enable access to a larger variety of complex polycyclic frameworks.



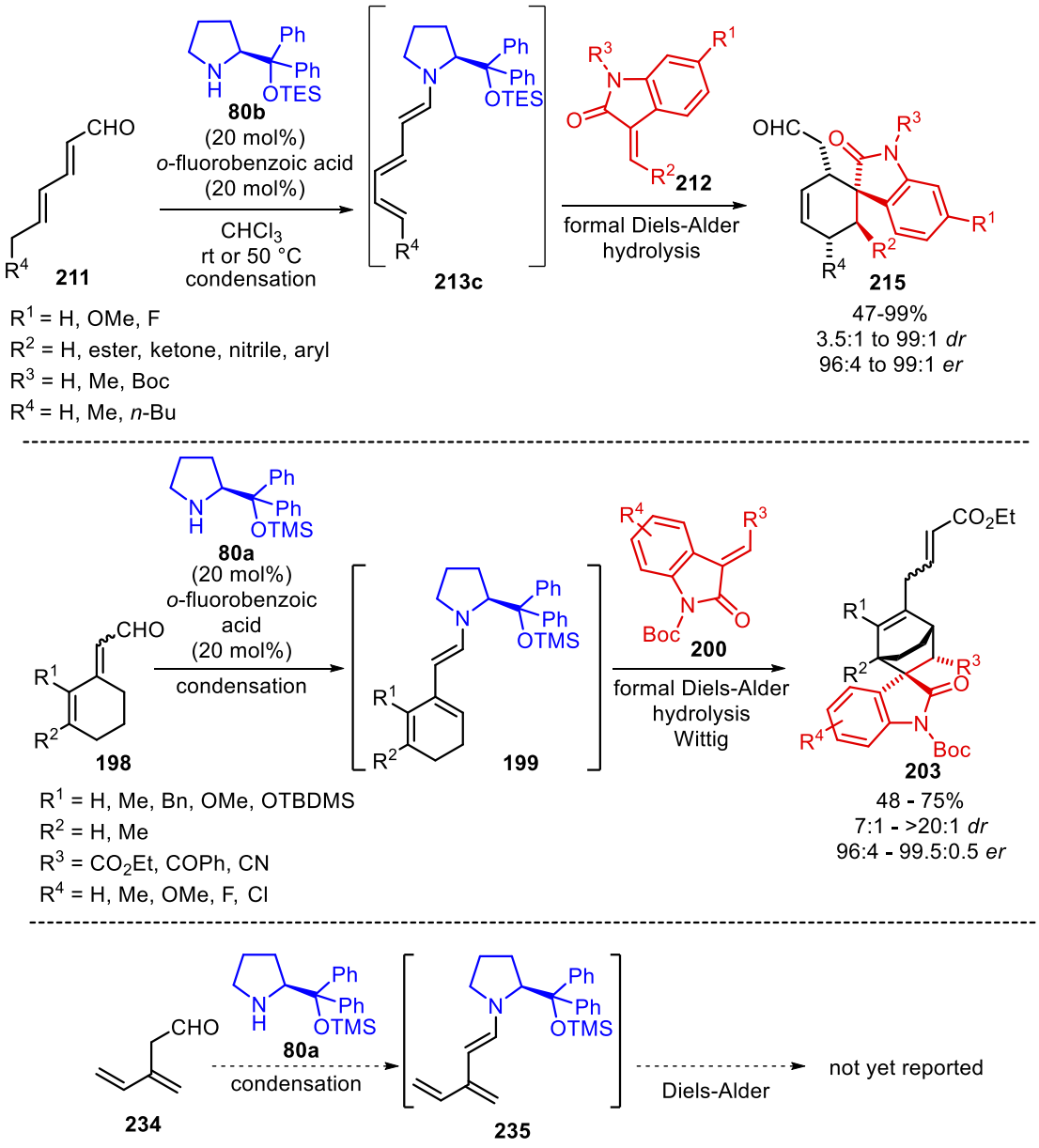
Scheme 1.42 a) One pot condensation/Diels-Alder reaction between aldehydes **22**, nitroalkenes **76** and amines b) One-pot Diels-Alder/hydrolysis/IMDA/aromatisation reaction of 1-amino-3-siloxy-1,3-butadiene **116**

The use of chiral amines to generate the corresponding 1-amino-1,3-butadienes has allowed access to enantioenriched condensation/Diels-Alder products. Different methods, such as hydrolysis, elimination and decarboxylative elimination, have been used to release the amine catalyst from the condensation/Diels-Alder product, so as to complete the catalytic cycle (Scheme 1.43).



Scheme 1.43 Catalytic enantioselective reaction sequences involving condensation/Diels-Alder reactions followed by a) hydrolysis, b) elimination and c) decarboxylative elimination

The reactivity of different types of substituted 1-amino-1,3-butadienes such as 1-amino-1,3,5-trienes **213c** and semi-cyclic 1-amino-[3]dendralenes **199** in aminocatalytic reactions has also been explored (Scheme 1.44). The use of acyclic 1-amino-[3]dendralenes **235**, which have the potential to undergo multiple Diels-Alder reactions, has not been reported.

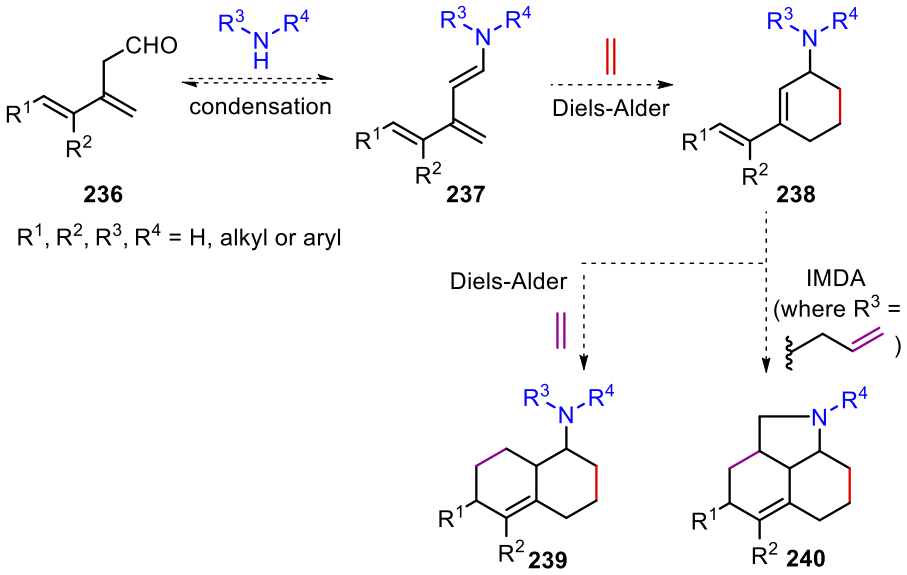


Scheme 1.44 Catalytic enantioselective condensation/formal Diels-Alder reaction sequences of a) 1-amino-1,3,5-trienes **213c**, b) semi-cyclic 1-amino-[3]dendralenes **199** and c) acyclic 1-amino-[3]dendralenes **235**

1.6 Aims

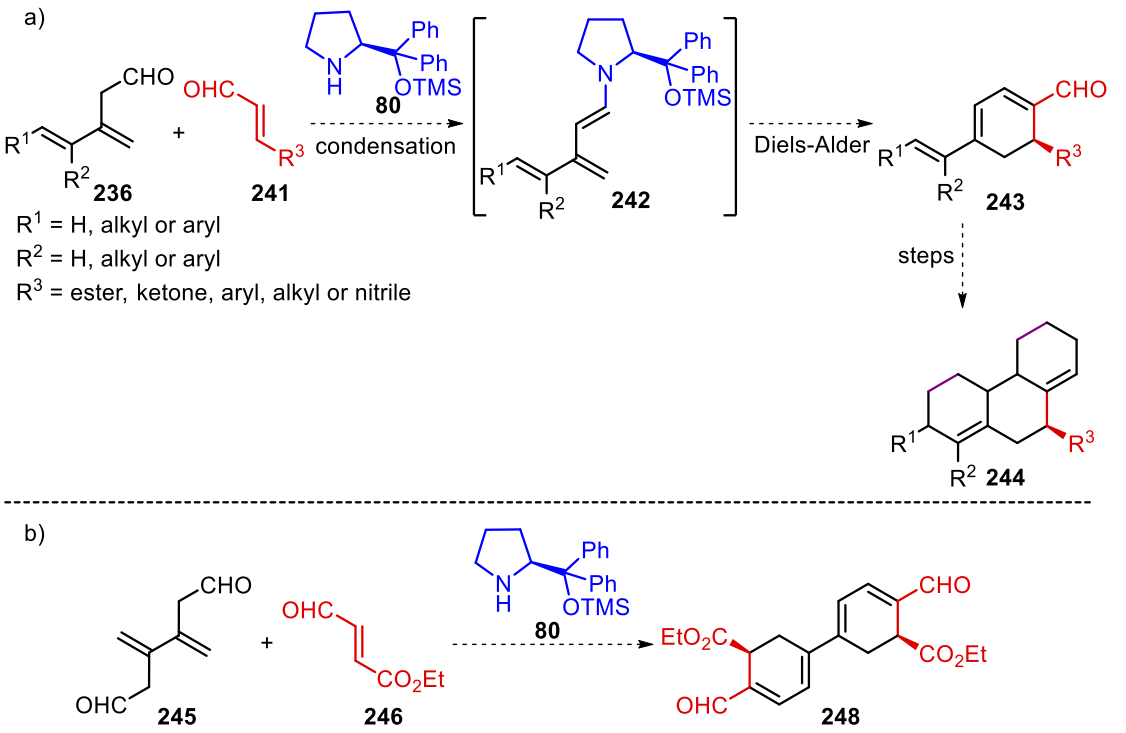
Dendralenes have been shown to undergo diene-transmissive Diels-Alder reaction sequences[86,87] to generate complex structures in step-economic[88-91] transformations. It was anticipated that 1-amino-[3]dendralenes will be useful for rapidly accessing heterocyclic frameworks closely related to alkaloids and medicinal compounds as well as enantioenriched polycyclic structures. This thesis explores the synthesis and use of acyclic 1-amino-[3]dendralenes in highly efficient and selective domino Diels-Alder

sequences. Chapter 2 describes the development of new methodology involving the synthesis of 1-amino-[3]dendralenes **237** and their double Diels-Alder reactions (Scheme 1.45). The initial focus was on investigating the reactivity and scope of the condensation/single Diels-Alder reaction sequence (aldehyde **236** to mono-adduct **238**) using various amines and dienophiles. The sequence was then extended to include a second inter- or intramolecular Diels-Alder reaction to generate polycyclic nitrogen-containing frameworks such as bicycle **239** and tricycle **240**.



Scheme 1.45 Proposed one-pot synthesis of 1-amino-[3]dendralenes **237** and their double Diels-Alder reactions

Chapter 3 describes the development of enantioselective Diels-Alder reactions involving chiral 1-amino[3]dendralenes. The first aim of this chapter was to develop and optimise the enantioselective Diels-Alder reaction between aldehyde **236**, amine **80a** and β-substituted acroleins **241** (Scheme 1.46). The second aim was to extend the reaction to include multiple Diels-Alder reactions to access polycyclic enantioenriched products such as tricycle **244**. The final objective was to briefly explore the twofold condensation/Diels-Alder/elimination reaction sequence of diene-dialdehyde **245**.



Scheme 1.46 a) Proposed Diels-Alder reactions of 1-amino[3]dendralene **242** and b) proposed condensation/Diels-Alder/elimination reaction sequence of diene-dialdehyde **245**

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2 Multicomponent Diene-Transmissive Diels-Alder Sequences Featuring Aminodendralenes

2.1 Context

Dendralenes have previously been shown to generate polycyclic frameworks in a step-economic manner through diene-transmissive Diels-Alder reaction sequences. As described in the previous chapter, the Diels-Alder reactions of 1-amino-1,3-butadienes and 1-amino-3-siloxy-1,3-butadienes have been reported. In contrast, there has been only one report involving a semi-cyclic 1-amino[3]dendralene. This chapter describes the first use of acyclic 1-amino[3]dendralenes in highly selective multicomponent reactions through *in situ* formation and diene-transmissive Diels-Alder cycloaddition sequences to generate a variety of heterocyclic structures. The mechanism of the reaction and origins of the observed π-diastereofacial selectivity are explained with the help of density functional theory calculations, which were performed by Prof Michael N. Paddon-Row. As briefly mentioned on page 11, the Diels-Alder reaction between a highly electron-rich diene such as 1-amino[3]dendralene and a highly electron-poor dienophile may proceed through a concerted or stepwise (i.e. conjugate addition followed by intramolecular Mannich) reaction mechanism. More specifically, a concerted Diels-Alder reaction may be synchronous (i.e. bonds form and break to the same extent in the transition state) or asynchronous (i.e. some bonds form or break to a greater extent than others in the transition state). The DFT calculations showed that the

Diels-Alder reaction between 1-amino[3]dendralenes and N-methyl maleimide (NMM) occurred through a concerted and asychronous mechanism.

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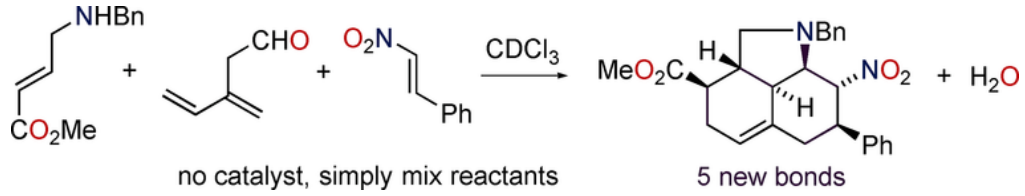
TOC Graphic



2.2 Publication

GDCh Communications Angewandte International Edition Chemie

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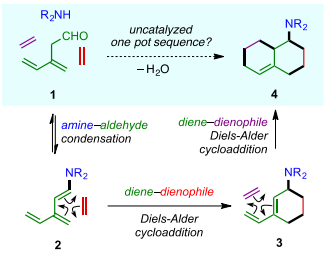
Multicomponent Diene-Transmissive Diels–Alder Sequences Featuring Aminodendralenes

Siu Min Tan, Anthony C. Willis, Michael N. Paddon-Row, and Michael S. Sherburn**

Abstract: *1-Aminodecalins were prepared from acyclic precursors by combining the powerful twofold diene-transmissive Diels–Alder chemistry of [3]dendralenes with the simplicity of enamine formation. On mixing at ambient temperature, a simple dienal condenses with a primary or secondary amine to generate the enamine, a 1-amino-[3]dendralene in situ, and this participates as a double diene in a sequence of two Diels–Alder events with separate dienophiles. Overall, four C–C bonds and one C–N bond are formed. Mechanistic insights into these reactions are provided by means of density functional theory calculations.*

Step-economic synthesis necessitates the invention of new methods for converting simple and readily accessible precursors into more complex products.[1,2] The rapid generation of structural complexity is inexorably linked with processes that form several new covalent bonds. Such multiple single-bond-forming transformations[1] have several subclassifications, with those involving successive reactions at sequentially generated functional groups featuring strongly in current research endeavors.[3] In addition to maximizing useful structural complexity gains, a new synthetic method should ideally be atom-economic,[4] operationally simple, and robust.[5]

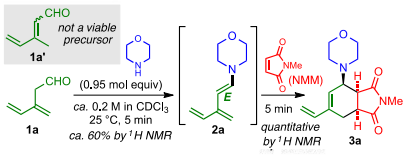
Dendralenes[6] are cross-conjugated olefins of significant value in the step-economic synthesis of complex molecules owing to their multiple-1,3-butadiene character, which permits their participation in diene-transmissive[7] Diels–Alder (DA) cycloaddition sequences.[8] Such sequences, which are amongst the most powerful of all multiple single-bond-forming processes,[9] are now finding application in step-economic total synthesis.[10] The dendralenes are invariably made first and then used separately in a cycloaddition sequence.[6] If it were possible to unite the preparation of dendralenes with their cycloaddition sequences in a single, simple synthetic operation, we reasoned that significant efficiency dividends would result. Herein, we report the successful realization of this proposition. The conceptualized



Scheme 1. Schematic representation of the four-component sequence.

sequence is depicted in stripped-back form in Scheme 1, and shows that skipped dienal **1** would condense reversibly with an amine to generate 1-amino-[3]dendralene **2**.[11] Steric effects notwithstanding, this species would be expected to react with an electron-poor dienophile at the more strongly activated 1,3-disubstituted 1,3-butadiene unit[12] to produce "transmitted" semicyclic diene **3**, which would in turn react with a second dienophile to deliver aminodecalin[13] system **4**. Significant structural complexity would thus be generated from four simple precursors through three consecutive reactions.

E-Configured trienamine **2a** was generated in $CDCl_3$ solution at ambient temperature within 5 minutes, simply by mixing methylene-skipped dienal **1a** with morpholine (Scheme 2).[14] The new dendralene **2a** readily decomposed upon attempted isolation or standing in solution, thereby resulting in complex mixtures of products including the two geometrical isomers of isomeric conjugated dienal **1a′**. Addition of the electron-poor dienophile *N*-methylmaleimide (NMM) to a preformed solution of trienamine **2a** delivered *endo*-cycloadduct **3a** very cleanly.[12] Conjugated dienal **1a′** was not converted into trienamine **2a**, instead yielding the products of aza-Michael additions upon exposure to morpholine and NMM.[14,15]



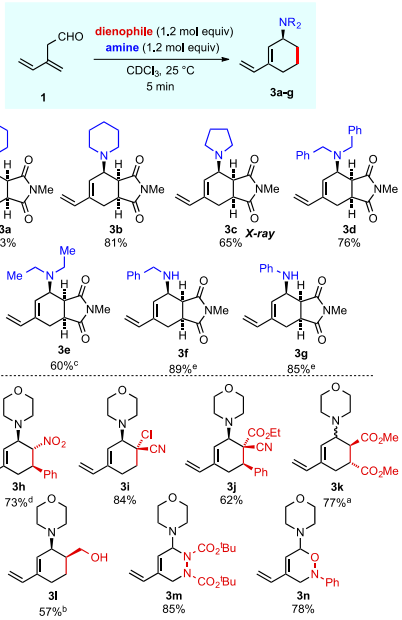
Scheme 2. Generation and Diels–Alder reaction of trienamine **2a**.

[*] S. M. Tan, Dr. A. C. Willis, Prof. M. S. Sherburn
Research School of Chemistry, Australian National University
Canberra, ACT 0200 (Australia)
E-mail: michael.sherburn@anu.edu.au
Prof. M. N. Paddon-Row
School of Chemistry, The University of New South Wales
Sydney, NSW 2052 (Australia)
E-mail: m.paddonrow@unsw.edu.au

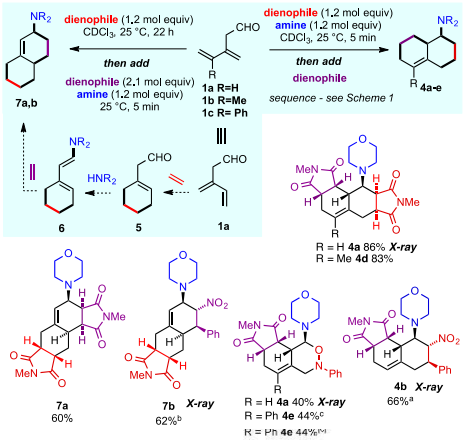
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201510925.

The formation of cycloadduct **3a** confirmed our expectation that 1-amino-[3]dendralene **2a** would undergo a highly site-selective addition of a dienophile to the more substituted 1,3-butadiene residue. The sequential addition of the dienophile to the preformed trienamine was not necessary, since optimal yields of products **3a**–**n** were obtained by premixing skipped dienal **1a** and the dienophile, then adding the amine last. Presumably, it is better to generate the reactive trienamine in low concentration and trap it quickly with a dienophile, rather than allow it to increase in concentration. This one-pot, three-component sequence has a broad scope with respect to both the amine and dienophile, as demonstrated by the fourteen examples depicted in Scheme 3. Primary and secondary, cyclic and acyclic, and alkyl- and aryl- amines are tolerated, as are carbo- and hetero-dienophiles with a variety of activating groups and other substituents. As might be anticipated,[16] the products of *endo*-cycloadditions were generally formed. This broad substrate tolerance is consistent with both a very favorable condensation and a trienamine that is highly reactive towards dienophiles, presumably due to its Rawal-type diene[17] character.

This sequence was extended to a one-pot, four-component reaction through the implementation of an in situ Diels–Alder addition of a dienophile to the semicyclic diene segment of mono-adduct **3** (Scheme 4). Compounds **4a**–**c** were produced through a highly diastereoselective *endo* addition of the dienophile to the face of the semicyclic diene intermediate **3** lacking the amine substituent. The diene component of skipped dienal **1a** is also amenable to direct Diels–Alder addition by a dienophile, producing skipped enal **5** (Scheme 4), which upon addition of a second dienophile and amine gives rise to aminotetralins **7a** and **7b**, presumably through the intermediacy of 1-amino-1,3-butadiene **6**. Simply changing the order of addition of the dienophiles and amine to dienal **1** thus results in the formation of constitutional isomers **4** and **7**, each of which carries five new covalent bonds and two new rings. Substitution on the precursor is also tolerated, as demonstrated by the formation of derivatives **4d** and **4e** from substituted skipped dienals **1b** and **1c**.



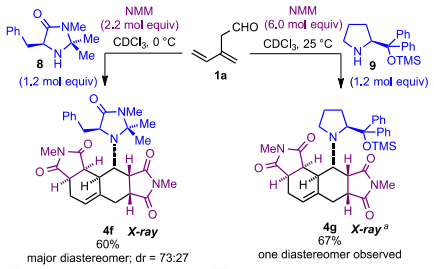
Scheme 3. Scope of the condensation–cycloaddition sequence with dienal **1a**. Major stereoisomer depicted, d.r. > 95:5 unless indicated otherwise. [a] isolated as a 1:1 diastereomeric mixture. [b] 2.5 mol equiv of amine and dienophile used, acrolein as dienophile, yield of isolated product after $NaBH_4$ reduction. [c] 0.83 mol equiv amine used. [d] d.r. = 89:11. [e] 30 minute reaction time.



Scheme 4. One-pot, four-component sequences with dienal **1**. Major stereoisomer depicted, d.r. > 95:5 unless indicated otherwise. [a] d.r. = 91:9. [b] d.r. = 71:29. [c] C_6D_6 solvent used. [d] 6.0 mol equiv NMM used.

In the presence of an excess of the dienophile NMM, dienal **1a** reacted with a stoichiometric amount of first-generation MacMillan organocatalyst[18] **8** to deliver pentacycle **4f** as the major diastereomeric product (d.r. = 73:27; Scheme 5). In a similar manner, Jørgensen–Hayashi organocatalyst[19] **9** generated four component product **4g** as a single diastereomer, within the limits of NMR detection. Enamines derived from amine **8** are known to be very poor nucleophiles,[20] so Diels–Alder trapping of the HOMO-activated trienamine derivative of oxazolidinone **8** with a dienophile is interesting.

Density functional theory calculations, using B3LYP/6-31G(d) model chemistry,[14] were carried out in order to gain mechanistic insights into the origin of the observed π-diastereofacial selectivity of the first cycloadditions depicted in Scheme 5.[21] It is instructive, in the first place, to analyze the two conformations associated with rotation about the



Scheme 5. Trapping trienamines of chiral amines as double DA adducts. [a] X-ray crystal structure of the tertiary alcohol product of silyl ether hydrolysis.

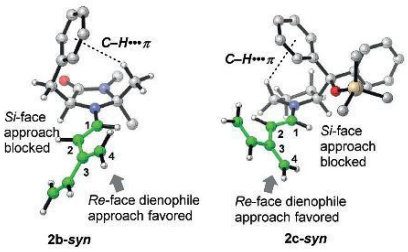


Figure 2. B3LYP/6-31G(d)-optimized structures **2b**-*syn* and **2c**-*syn*, with the favored trajectories of dienophile approach indicated. H atoms are omitted from phenyl and some methyl groups and the dendralene is colored green for clarity.

bond connecting the dendralene and the heterocycle in the two reactant aminodendralenes **2b** and **2c**. As shown in Figure 1, the two conformations are distinguished according to whether the N–C2′ or N–C5′ bond partially eclipses the dendralene C1–C2 bond. The *syn*/*anti* notation refers to the disposition of the N–C5′ bond, that is, the bond involving the less substituted C5′ atom, with respect to the C1=C2 bond. As might be expected from the small dihedral angles between C1=C2 and the partially eclipsing N–C bond in both the *syn* and *anti* conformations of **2b** and **2c** (Figure 1), the *syn* conformer should be more stable than the *anti* conformer because of diminished adverse steric interactions between the dendralene C2–H group and the less substituted C5′ center of the heterocycle.[22] Indeed, the B3LYP calculations predict the *syn* form to be more stable than the *anti* form in both **2b** and **2c**, by 9.4 and 12.2 kJ mol^{-1}, respectively.

In both *syn* and *anti* conformers of **2c**, one of the OTMS methyl groups lies substantially over the *Si* face of the dendralene C1C2C3C4 diene component of the former and over the *Re* face of this diene component in the latter (Figure 2). Stabilizing CH···π interactions between a phenyl ring and the proximal methyl group in both **2b**[9,23] and **2c**[22] results in the aromatic ring partially obscuring the *Si* and *Re* faces of the diene component in the *syn* and *anti* forms, respectively (Figure 2).

The above analysis leads to a reactant-based explanation of the observed π-diastereofacial selectivity of the DA reactions of **2b** and **2c**, namely that the dienophile preferentially approaches the more exposed *Re* faces of the *syn* conformers of **2b** and **2c** and the more exposed *Si* faces of the *anti* conformers of these molecules. Because the *syn* conformer is more stable than the *anti* form in both **2b** and **2c**, which is greater for **2c**, it is concluded that *Re* facial selectivity prevails in these reactions and that it should be more pronounced when using **2c** as the diene reagent than with **2b**. A more rigorous approach is to compare the relative energies of the transition structures (TSs) for *Re* and *Si* addition modes. The results with B3LYP optimized TSs for *endo* addition of NMM to **2b** and **2c** are presented in Table 1.

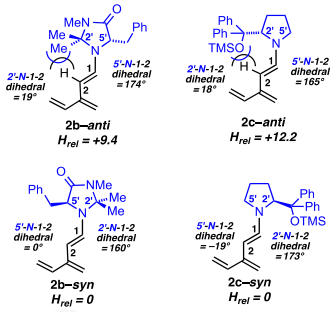


Figure 1. Schematic of the two trienamine conformations for **2b** and **2c** with respect to rotation about the C1–N bond, together with the B3LYP/6-31G(d) dihedral angles between the dendralene and N–C bonds of the heterocycle, and their relative enthalpies, H_{rel} (298 K, kJ mol^{-1}). Note the similar steric clash in the higher-energy *anti* conformations.

Table 1: Energies of B3LYP-optimized TSs for *endo* addition of NMM to **2b** and **2c.**

Cycloaddition mode[a]	**2c** $H^{\ddagger}_{rel}$ $G^{\ddagger}_{rel}$	**2b** $H^{\ddagger}_{rel}$ $G^{\ddagger}_{rel}$
Re/*syn*	0 0	0 0
Si/*syn*	25.2 24.3	6.2 4.7
Re/*anti*	19.9 21.2	16.5 14.7
Si/*anti*	10.8 11.0	5.6 5.1

[a] See Figures 1 and 2 for definitions.

The results of these calculations clearly predict a strong preference for *Re*-face addition to the *syn* conformations of the two aminodendralenes and indicate that *Re* addition on the *anti* conformations is an unimportant pathway to *Re*-based product formation. The *Si*/*anti* channel is the near exclusive source of *Si*-based product from **2c**, whereas both *Si*/*anti* and *Si*/*syn* channels are contributors to the *Si*-based product in the case of **2b**. The relative free energy data in Table 1 indicate that π-diastereofacial selectivity in the DA reaction with NMM is stronger for aminodendralene **2c** than

for **2b**. In fact, a Boltzmann distribution calculation gives a total *Re*-based product/*Si*-based product ratio of 99:1 and 76:24 for **2c** and **2b**, respectively. These ratios are in reasonable accord with the experimental values of >95:5 and 73:27, respectively (Scheme 5).

The main structural features of the reactant aminodendralenes, as discussed above, are essentially retained in the respective Diels–Alder transition structures (TSs), as exemplified by **2c-*endo-Re-syn*-TS** and **2c-*endo-Si-anti*-TS** (Figure 3). A noteworthy feature of these TSs (and of those not shown in the Figure) is the high degree of bond-forming asynchronicity between the two developing bonds between NMM and the dendralene diene component. Thus, the forming bond lengths in **2c-*endo-Re-syn*-TS** are 2.896 and 2.083 Å ($\Delta r = 0.81$ Å) and for **2c-*endo-Si-anti*-TS** they are 2.905 and 2.072 Å ($\Delta r = 0.83$ Å). The shorter forming bond involves C6 of the central double bond of the aminodendralene and this has the effect of conferring stabilizing pentadienyl radicaloid character on the dendralene component. This large degree of bond-forming asynchronicity is a general characteristic of dendralenes in their DA addition reactions.[24]

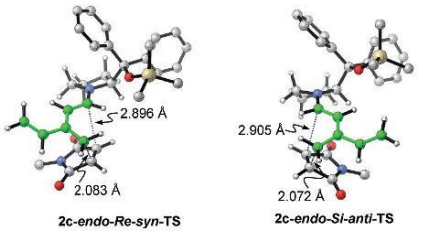
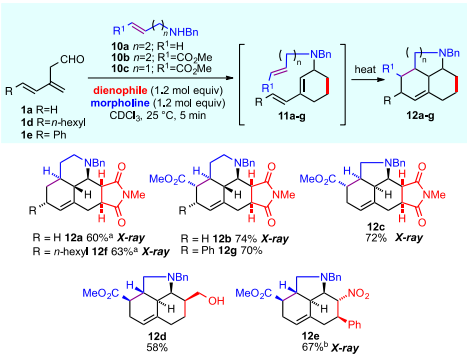


Figure 3. B3LYP/6-31G(d)-optimized TSs for the Diels–Alder cycloaddition of the NMM dienophile to aminodendralene **2c**. H atoms are omitted from phenyl and methyl groups and the dendralene is colored green for clarity.

Tethering the dienophile to the amine (as in **10a–c**) permits the second cycloaddition (**11**→**12**) to be realized in an intramolecular[25] fashion (Scheme 6). The benefits of employing this tactic include: 1) the generation of additional structural complexity with complete orientational regioselectivity, 2) attainment of products with complementary stereoselectivity to the intermolecular process,[26] and 3) the ability to deploy nonactivated dienophiles (**10a**). Substituted dienals **1d** and **1e** also participate in the tricyclization sequence, thus confirming the robust character of this new method.

In summary, the first multicomponent reaction sequences involving dendralenic intermediates have been devised. These reactions are extraordinarily easy to perform in the laboratory, in most cases involving the mixing of simple precursors. The incorporation of a 1-amino-substituent on the [3]dendralene backbone simultaneously augments both its reactivity and selectivity in diene-transmissive Diels–Alder sequences,[24] at the same time delivering highly functionalized multicyclic products akin to alkaloids and medicinal agents. This study demonstrates the diversity of multicomponent transformations with only one amine group at a specific position of the simplest possible dendralene structure. Evidently, the possibilities for step-economic synthesis with aminodendralenes are vast.



Scheme 6. Tricycle synthesis through one-pot, three-component sequences featuring an intramolecular Diels–Alder (IMDA) reaction. Major stereoisomer depicted, d.r. >95:5 unless indicated otherwise. [a] mono-adducts **11a** and **11f** were isolated before being subjected to intramolecular cycloaddition. [b] 2.5 mol equiv of amine and dienophile used, acrolein as dienophile, yield of isolated product after $NaBH_4$ reduction. [c] d.r. = 93:7.

Acknowledgements

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Keywords: density functional calculations · Diels–Alder reactions · domino reactions · multicomponent reactions · polycycles

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[26] The dienophile is constrained to approach the semicyclic diene from the same face as the amine with the shorter tether, as seen in the products **12c**, **d**, and **e**. Cycloadducts **12d** and **12e** are the result of an *endo*-selective IMDA reaction; we presume that the NMM-derived succinimide ring blocks *endo* approach of the -CO_2Me group, thereby resulting in the formation of *exo*-adduct **12c**. We suspect that similar steric influences cause an approach of the dienophile to the convex face of the semicyclic diene during the IMDA reaction of the longer tethered substrates, giving rise to adducts **12a**, **12b**, **12f**, and **12g**.
[27] CCDC nos. 1429160 – 1429173 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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2.3 Supporting Information

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Supporting Information

Multicomponent Diene-Transmissive Diels–Alder Sequences Featuring Aminodendralenes

Siu Min Tan, Anthony C. Willis, Michael N. Paddon-Row, and Michael S. Sherburn**

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Contents

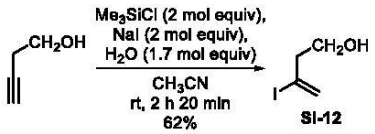
General methods

^{1}H NMR spectra were recorded under standard conditions at 800 MHz, 400 MHz or 300 MHz using a *Bruker AVANCE 800*, *Bruker AVANCE 400,* V*arian MR400* or *Varian Mercury 300* spectrometer. Residual chloroform (δ 7.26 ppm) was used as an internal reference for ^{1}H NMR spectra recorded in this solvent. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignment of proton signals was assisted by COSY and HSQC experiments where necessary. ^{13}C NMR spectra were recorded at 100 or 75 MHz on a *Bruker AVANCE 400*, V*arian MR400* or *Varian Mercury 300* spectrometer. Chloroform (δ 77.10 ppm) was used as an internal reference for ^{13}C NMR spectra recorded in this solvent. For other solvents, residual solvents were referenced according to Fulmer and co-workers.[1] Assignment of carbon signals was assisted by HSQC and/or HMBC experiments. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer as neat films on sodium chloride plates for oils, potassium bromide discs for solid products with only selected peaks being reported as characteristic. Low resolution electron impact (EI) mass spectra were recorded on an Agilent HP 6890 series gas GC/MS with a 7683 series injector. High resolution EI mass spectra were recorded on a Waters AutoSpec Premier spectrometer magnetic sector instrument, operating at 70 eV. Low resolution electrospray ionization (ESI) mass spectra were recorded on a ZMD Micromass spectrometer with Waters Alliance 2690 HPLC. High resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. Positive ionization was employed unless otherwise indicated. Melting points were measured on a Reichert melting point stage or Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Preparative HPLC was performed using a Waters 600E instrument. Analytical TLC was performed using Merck silica gel plates, pre-coated with silica gel 60 F243 (0.2 mm). Compounds on TLC were visualized by exposure to UV light and/or by dipping the plates in solutions of potassium permanganate followed by heating. Flash chromatography was carried out using Merck Kiesegel 60 (230 – 400 mesh) silica gel.
Reactions were conducted open to air unless otherwise indicated. Reaction conditions invoking microwave irradiation were carried out in a CEM Discover and Explorer SP microwave synthesis system. Solvents were dried using a solvent purification system based on that described by Pangborn and co-workers,[2] or dried using standard laboratory methods.[3] Deuterated chloroform was passed through basic silica prior to use. All chemicals were purchased from Sigma Aldrich, Alfa Aesar, Merck or Strem and used without further purification.

Experimental Section

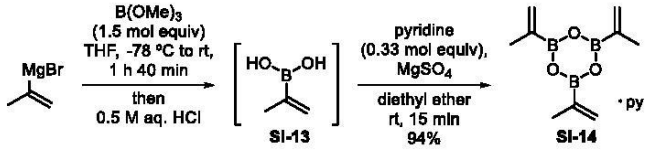
Synthesis of precursors

Iodide SI-12



The *title compound* was prepared using a modified literature procedure.[4] Chlorotrimethylsilane (17.9 mL, 142 mmol, 2 mol equiv) and water (2.1 mL, 119 mmol, 1.67 mol equiv) were added successively to a solution of sodium iodide (21.3 g, 142 mmol, 2 mol equiv) in acetonitrile (140 mL). The creamy yellow reaction mixture was stirred for 10 min before 3-butyn-1-ol (5.4 mL, 71.3 mmol) was added in portions. The reaction mixture was stirred at rt for 2 h 20 min then added to water/Et_2O. The aqueous layer was extracted with Et_2O twice, combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude reaction mixture was subjected to vacuum distillation (1.5 mBar, 75 – 85 ºC). The first fraction was further purified by flash column chromatography on silica gel eluting with petrol/EtOAc (80:20 to 60:40) to provide a clean fraction of iodide **SI-12** (4.1 g) and an impure fraction. Further purification by vacuum distillation of the combined impure fractions provided another sample of clean iodide (4.7 g). The *title compound* (8.8 g in total, 44.4 mmol, 62%) was obtained as a brown oil. The ^1H NMR spectroscopic data matched those previously reported.[5]

Boroxine SI-14

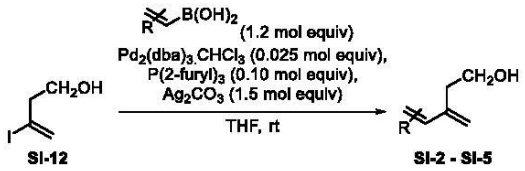


The *title compound* was prepared using a modified literature procedure.[6] Isopropenylmagnesium bromide in THF (50 mL of a 0.71 M THF solution, 36 mmol) was added dropwise to a solution of trimethyl borate (6.0 mL, 54 mol, 1.5 mol equiv) in THF (50

mL) at – 78 °C under nitrogen. The resulting mixture was warmed to rt and stirred for 1 h 40 min before being poured into 0.5 M aqueous HCl and diethyl ether. The organic layer was collected while the aqueous layer was re-extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure until about 50 mL of solution remained. Pyridine (0.96 mL, 12 mmol, 0.34 mol equiv) and magnesium sulfate were added to the solution, which was then stirred at rt for 15 min before being concentrated under reduced pressure to provide the *title compound* as a viscous yellow oil (3.18 g, 11.2 mmol, 94%). The ^{1}H NMR spectroscopic data matched those previously reported.[6b]

(i) Alcohols

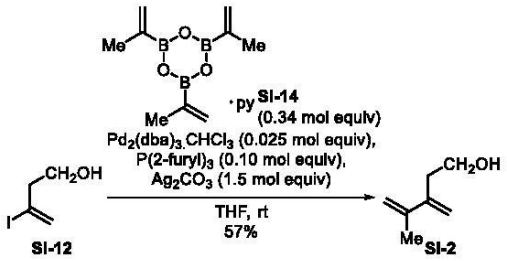
General procedure A:



SI-12 **SI-2 - SI-5**

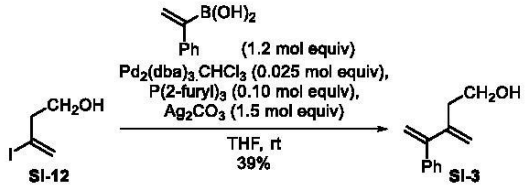
A mixture of $Pd_2(dba)_3.CHCl_3$ (0.025 mol equiv), tri(2-furyl)phosphine (0.10 mol equiv), silver carbonate (1.5 mol equiv) and boronic acid (1.2 mol equiv) were placed in a round-bottom flask. The flask was purged with vacuum and back-filled with argon three times. A solution of iodide **SI-12**[4] in freshly degassed THF (0.1 M) was cannulated into the mixture and stirred at rt in an aluminium foil covered flask until the iodide was completely consumed. The reaction mixture was diluted with CH_2Cl_2 and saturated aqueous sodium bicarbonate solution and filtered through Celite. The organic layer was collected while the aqueous layer was re-extracted with CH_2Cl_2 three times. The combined organic layers were dried over potassium carbonate and concentrated under reduced pressure. The crude material was then purified by flash column chromatography on silica gel to provide the product.

Alcohol SI-2



Prepared according to general procedure A using $Pd_2(dba)_3.CHCl_3$ (287 mg, 0.287 mmol, 0.025 mol equiv), tri(2-furyl)phosphine (258 mg, 1.11 mmol, 0.10 mol equiv), silver carbonate (4.59 g, 16.7 mmol, 1.5 mol equiv), boroxine **SI-14** (1.07 g, 3.78 mmol, 0.340 mol equiv) and iodide **SI-12** (2.20 g, 11.1 mmol). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (70:30:1 then 60:40:1) provided the *title compound* (715 mg, 6.37 mmol, 57%) as a yellow oil: R_f 0.22 petrol/EtOAc (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (s, 1H), 5.09 (s, 1H), 5.03 (s, 1H), 5.00 (s, 1H), 3.72 (t, J = 6.5 Hz, 2H), 2.56 (t, J = 6.5 Hz, 2H), 1.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1 (C), 142.2 (C), 114.4 (CH_2), 113.3 (CH_2), 61.6 (CH_2), 37.0 (CH_2), 21.1 (CH_3) ppm; IR (KBr disc): ν_{max} = 3339, 3093, 2950, 1597 cm^{-1}; MS (70 eV, EI): *m/z* (%): 112 (40) $[M]^+$, 97 (100), 95 (30); HRMS: calc for $C_7H_{12}O$ $[M]^+$: 112.0888; found 112.0884.

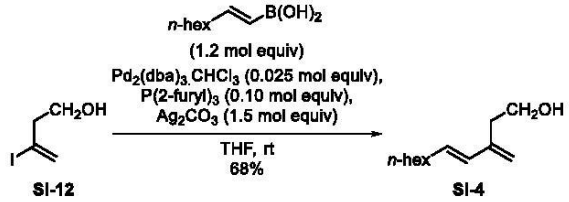
Alcohol SI-3



Prepared according to general procedure A using $Pd_2(dba)_3.CHCl_3$ (261 mg, 0.253 mmol, 0.025 mol equiv), tri(2-furyl)phosphine (234 mg, 1.01 mmol, 0.10 mol equiv), silver carbonate (4.18 g, 15.2 mmol, 1.5 mol equiv), boronic acid (1.80 g, 12.2 mmol, 1.2 mol equiv) and iodide **SI-12** (2.00 g, 10.1 mmol). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (80:20:1 then 70:30:1) provided the *title compound* (682

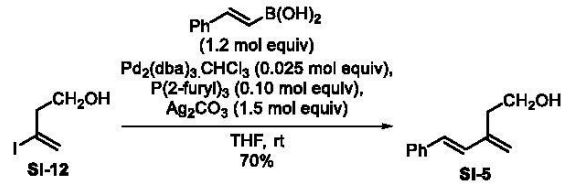
mg, 3.91 mmol, 39%) as a yellow oil. The ^{1}H NMR spectroscopic data matched those previously reported.[7]

Alcohol SI-4



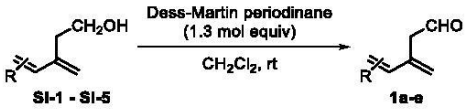
Prepared according to general procedure A using $Pd_2(dba)_3.CHCl_3$ (225 mg, 0.218 mmol, 0.025 mol equiv), tri(2-furyl)phosphine (202 mg, 0.871 mmol, 0.10 mol equiv), silver carbonate (3.60 g, 13.1 mmol, 1.5 mol equiv), boronic acid (1.63 g, 10.4 mmol, 1.2 mol equiv) and iodide **SI-12** (1.72 g, 8.71 mmol). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (90:10:1) provided the *title compound* (1.09 g, 5.98 mmol, 68%) as a yellow oil: R_f 0.16 petrol/EtOAc (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (d, J = 15.9 Hz, 1H), 5.73 (dt, J = 15.2, 6.9 Hz, 1H), 5.01 (s, 1H), 4.93 (s, 1H), 3.73 (t, J = 6.4 Hz, 2H), 2.49 (t, J = 6.4 Hz, 2H), 2.10 (dd, J = 7.2 Hz, 2H), 1.44 – 1.22 (m, 8H), 0.88 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6 (C), 131.4 (CH), 131.4 (CH), 115.3 (CH_2), 61.2 (CH_2), 35.7 (CH_2), 32.9 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3) ppm; IR (thin film): ν_{max} = 3341, 2957, 2925, 2872, 2856 cm^{-1}; MS (70 eV, EI): *m/z* (%): 182 (100) $[M]^+$, 151 (25), 97 (85); HRMS: calc for $C_{12}H_{22}O$ $[M]^+$: 182.1671; found 182.1672.

Alcohol SI-5



Prepared according to general procedure A using $Pd_2(dba)_3.CHCl_3$ (73 mg, 0.0703 mmol, 0.025 mol equiv), tri(2-furyl)phosphine (65 mg, 0.281 mmol, 0.10 mol equiv), silver carbonate (1.16 g, 4.22 mmol, 1.5 mol equiv), boronic acid **SI-12** (500 mg, 3.38 mmol, 1.2 mol equiv) and iodide **SI-12** (556 mg, 2.81 mmol). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (80:20:1) provided the *title compound* (343 mg, 1.97 mmol, 70%) as a yellow oil. The ^1H NMR spectroscopic data matched those previously reported.[7]

(ii) Aldehydes



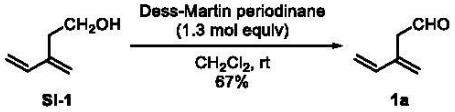
General procedure B:

To an ice-cooled suspension of Dess-Martin periodinane (1.3 mol equiv) in CH_2Cl_2 (0.5 M) was added a solution of alcohol in CH_2Cl_2 (0.8 M). The reaction mixture was stirred at rt until complete consumption of the alcohol as indicated by TLC. The reaction mixture was washed twice with a solution of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$ (1:1), water then brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide the aldehyde, which was used without further purification.

General procedure C:

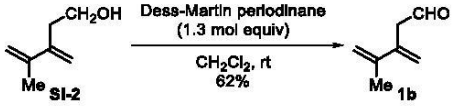
To a solution of the alcohol in CH_2Cl_2 (0.03 M) was added $NaHCO_3$ (5.0 mol equiv) then Dess-Martin periodinane (1.3 mol equiv) in portions. The reaction mixture was stirred at rt until complete consumption of the alcohol as indicated by TLC. The reaction mixture was diluted with diethyl ether and washed with a solution of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3/H_2O$ (1:1:1). The organic layer was collected while the aqueous layer was re-extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to provide the aldehyde, which was used without further purification.

Aldehyde 1a



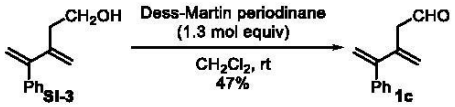
The *title compound* was prepared using a modified literature procedure.[8] Prepared using general procedure B with alcohol **SI-1**[9] (2.40 g, 24.4 mmol) and Dess-Martin periodinane (11.4 g, 31.7 mmol, 1.3 mol equiv). The *title compound* was obtained as a yellow oil (1.57 g, 16.3 mmol, 67%). The ^{1}H NMR spectroscopic data matched those previously reported.[10]

Aldehyde 1b



Prepared using general procedure B with alcohol **SI-2** (100 mg, 0.892 mmol) and Dess-Martin periodinane (492 mg, 1.16 mmol, 1.3 mol equiv). The *title compound* was obtained as a yellow oil (62 mg, 0.549 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (t, 1H), 5.37 (s, 1H), 5.15 (s, 1H), 5.05 (s, 1H), 4.97 (s, 1H), 3.30 (d, J = 2.7 Hz, 2H), 1.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8 (CH), 142.3 (C), 139.2 (C), 117.5 (CH_2), 114.8 (CH_2), 49.2 (CH_2), 20.7 (CH_3) ppm; IR (ATR): ν_{max} = 2919, 2851, 1723 cm^{-1}; MS (70 eV, EI): *m/z* (%): 110 (22) [M]$^{+}$, 95 (61), 67 (100) ; HRMS: calc for $C_7H_{10}O$ [*M*]$^{+}$: 110.0732; found 110.0733.

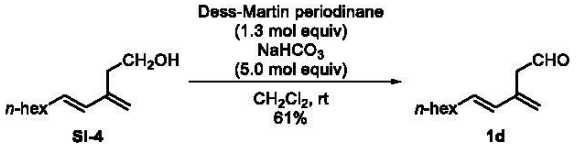
Aldehyde 1c



Prepared using general procedure B with alcohol **SI-3** (658 mg, 3.78 mmol) and Dess-Martin periodinane (2.08 g, 4.91 mmol, 1.3 mol equiv). The *title compound* was obtained as a yellow oil (307 mg, 1.76 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (t, J = 2.6 Hz, 1H), 7.37

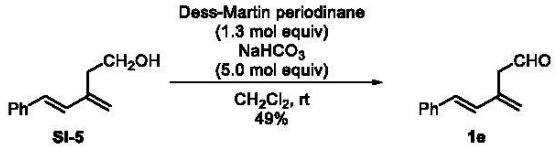
– 7.27 (m, 5H), 5.29 – 5.22 (m, 4H), 3.35 (d, J = 2.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1 (CH), 149.8 (C), 140.5 (C), 139.7 (C), 128.5 (CH), 128.2 (CH), 127.7 (CH), 120.9 (CH_2), 115.5 (CH_2), 49.3 (CH_2) ppm; IR (thin film): ν_{max} = 3081, 3057, 2925, 2822, 2721, 1725 cm^{-1}; MS (70 eV, EI): m/z (%): 172 [M]$^+$ (9), 143 (90), 129 (100); HRMS: calc for $C_{12}H_{12}O$ [M]$^+$: 172.0888; found 172.0891.

Aldehyde 1d



Prepared using general procedure C with alcohol **SI-4** (540 mg, 2.96 mmol), $NaHCO_3$ (1.26 g, 15.0 mmol, 5.0 mol equiv) and Dess-Martin periodinane (1.65 g, 3.89 mmol, 1.3 mol equiv). The *title compound* was obtained as a yellow oil (324 mg, 1.80 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (t, J = 2.5 Hz, 1H), 6.17 (d, J = 15.9 Hz, 1H), 5.62 (dt, J = 15.8, 6.9 Hz, 1H), 5.18 (s, 1H), 5.03 (s, 1H), 3.23 (d, J = 2.4 Hz, 2H), 2.10 (q, J = 6.9 Hz, 2H), 1.44 – 1.22 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5 (CH), 137.7 (C), 133.0 (CH), 131.4 (CH), 118.0 (CH_2), 47.8 (CH_2), 32.9 (CH_2), 31.8 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 22.7 (CH_2), 14.2 (CH_3) ppm; IR (ATR): ν_{max} = 2956, 2925, 2855, 1725 cm^{-1}; MS (70 eV, EI): m/z (%): 180 (13) [M]$^+$, 95 (100); HRMS: calc for $C_{12}H_{20}O$ [M]$^+$: 180.1514; found 180.1514.

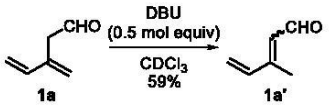
Aldehyde 1e



Prepared using general procedure C with alcohol **SI-5** (520 mg, 2.98 mmol), $NaHCO_3$ (1.25 g, 14.9 mmol, 5.0 mol equiv) and Dess-Martin periodinane (1.65 g, 3.88 mmol, 1.3 mol equiv). The *title compound* was obtained as a yellow oil (253 mg, 1.47 mmol, 49%). ^{1}H NMR (400

MHz, $CDCl_3$): δ 9.66 (t, J = 2.5 Hz, 1H), 7.42 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 16.3 Hz, 1H), 6.49 (d, J = 16.3 Hz, 1H), 5.44 (s, 1H), 5.24 (s, 1H), 3.39 (d, J = 2.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1 (CH), 137.6 (C), 136.7 (C), 130.2 (CH), 130.0 (CH), 128.8 (CH), 128.1 (CH), 126.7 (CH), 120.9 (CH_2), 47.6 (CH_2) ppm; IR (thin film): ν_{max} = 3026, 2822, 2722, 1721 cm^{-1}; MS (70 eV, EI): m/z (%): 172 (40) [M]$^+$, 129 (100); HRMS: calc for $C_{12}H_{12}O$ [M]$^+$: 172.0888; found 172.0888.

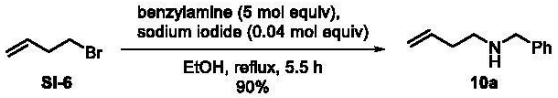
Aldehyde 1a'



DBU (40 μL, 0.26 mmol, 0.5 mol equiv) was added to a solution of aldehyde **1a** (50 mg, 0.52 mmol) in $CDCl_3$ (0.50 mL). The solution was left at rt for 1 h then diluted with $CDCl_3$ and washed with water. The organic layer was extracted once with $CDCl_3$. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to provide the *title compound* (30 mg, 0.31 mmol, 59%, E:Z = 68:32). The ^{1}H NMR spectroscopic data of the Z isomer matched those previously reported.[11]

(iii) Amines

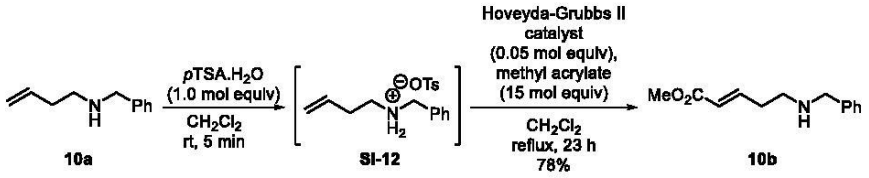
Amine 10a



The *title compound* was prepared using a literature procedure.[12] To a solution of bromide **SI-6** (1.44 mL, 14.2 mmol) in ethanol (20 mL) was added benzylamine (7.71 mL, 70.6 mmol, 5 mol equiv) then sodium iodide (80 mg, 0.53 mmol, 0.04 mol equiv). The reaction mixture was then heated to reflux for 5.5 h. After cooling to rt, CH_2Cl_2 and 1M aqueous KOH solution were added to the reaction mixture. The aqueous layer was separated and extracted three times with CH_2Cl_2. The combined organic laters were dried over potassium carbonate and concentrated under reduced pressure. The residue was purified by flash column

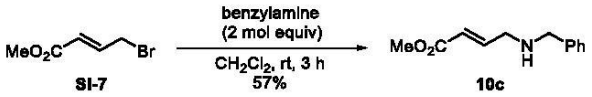
chromatography on silica gel eluting with petrol/EtOAc/Et_3N (50:50:1) to provide the *title compound* (2.06 g, 12.8 mmol, 90%) as a pale yellow oil. The ^1H NMR spectroscopic data matched those previously reported.[12]

Amine 10b



The *title compound* was prepared using a modified literature procedure.[13] To a solution of amine **10a** (600 mg, 3.72 mmol) in CH_2Cl_2 (12 mL) was added *p*TSA.H_2O (708 mg, 3.72 mmol, 1 mol equiv). The resulting solution was stirred at rt for 5 minutes then concentrated under reduced pressure to provide **SI-12** as a white solid, which was used without further purification. To a solution of ammonium salt **SI-12** (467 mg, 1.31 mmol) in CH_2Cl_2 (6 mL) was added methyl acrylate (1.80 mL, 19.7 mmol, 15 mol equiv) and Hoveyda-Grubbs II catalyst (40 mg, 0.06 mmol, 0.05 mol equiv). The resulting dark green solution was stirred under reflux for 23 h then cooled to rt and poured into a mixture of CH_2Cl_2 and 1M aqueous KOH solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over potassium carbonate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petrol/Et_2O/Et_3N (50:50:1 then 0:100:1) to provide the *title compound* (225 mg, 1.03 mmol, 78%) as a brown oil. R_f 0.30 Et_2O/Et_3N (100:1). The ^1H NMR spectroscopic data matched those previously reported.[14]

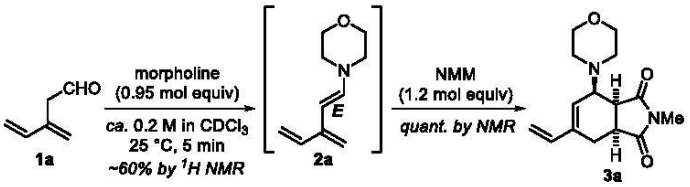
Amine 10c



The *title compound* was prepared using a literature procedure.[15] To a solution of bromide **SI-7** (358 mg, 2 mmol) in CH_2Cl_2 (5.0 mL) was added benzylamine (0.46 mL, 4.0 mmol, 2.0

mol equiv). The resulting mixture was stirred at rt for 3 h then poured into a solution of saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petrol/Et_2O (50:50 then 20:80) to provide the *title compound* (232 mg, 1.13 mmol, 57%) as a brown oil. R_f 0.28 petrol/Et_2O (20:80). The ^1H NMR spectroscopic data matched those previously reported.[15]

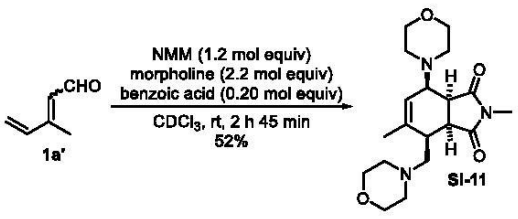
Trienamine synthesis and Diels-Alder reaction



A solution of aldehyde **1a** (11 mg, 0.12 mmol) in $CDCl_3$ (0.6 mL) was added to morpholine (19 mg, 0.11 mmol, 0.95 mol equiv). Trienamine **2a** was formed in solution with a yield of ~60% (estimated by ^1H NMR with residual $CHCl_3$ as internal standard): ^1H NMR (400 MHz, $CDCl_3$): δ 6.41 (dd, *J*=17.2, 10.4 Hz, 1 H), 6.31 (d, *J*=13.9 Hz, 1 H), 5.37 (d, *J*=17.4 Hz, 1 H), 5.17 (d, *J*=13.4 Hz, 2 H), 5.08 (d, *J*=10.8 Hz, 1 H), 4.89 (s, 1 H), 4.77 (s, 1 H), 3.69 - 3.76 (m, 4 H), 2.93 - 2.99 (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0 (C), 140.7 (CH), 137.9 (CH), 114.7 (CH_2), 109.1 (CH_2), 99.5 (CH), 66.4 (CH_2), 48.9 (CH_2) ppm.

Addition of NMM (15 mg, 0.13 mmol, 1.2 mol equiv) provided mono-adduct **3a** in quantitative yield (from trienamine **2a**, estimated by ^1H NMR with residual $CHCl_3$ as internal standard). The ^1H NMR spectroscopic data matched those reported on page 8.

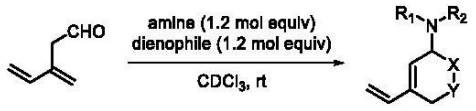
Reaction between aldehyde 1a', morpholine and NMM



To a solution of aldehyde **1a'**[16] (18 mg, 0.19 mmol) in $CDCl_3$ (0.8 mL) was added NMM (25 mg, 0.23 mmol, 1.2 mol equiv), benzoic acid (4.5 mg, 0.037 mmol, 0.2 mol equiv). The resulting solution was then added to morpholine (36 mg, 0.41 mmol, 2.2 mol equiv) and transferred to an NMR tube. Upon complete consumption of aldehyde **1a'**, as observed by ^{1}H NMR spectroscopy, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH/Et_3N (1:99:1) followed by re-purification on silica gel eluting with THF/hex (50:50) provided adduct **SI-11** (36 mg, 0.0990 mmol, 52%) as a yellow oil; R_f 0.17 CH_2Cl_2/MeOH (4:96); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (s, 1H), 3.91 – 3.64 (m, 8H), 3.48 – 3.34 (m, 2H), 3.15 (dd, J=12.9, 8.9 Hz, 1H), 2.96 – 2.71 (m, 7H), 2.66 – 2.43 (m, 7H), 1.73 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7 (C), 175.9 (C), 139.0 (C), 124.6 CH), 67.3 (CH_2), 66.9 (CH_2), 63.9 (CH), 56.7 (CH_2), 54.0 (CH_2), 53.1 (CH_2), 42.7 (CH), 41.3 (CH), 36.0 (CH), 24.8 (CH_3), 19.0 (CH_3) ppm; IR (ATR): ν_{max} = 2956, 2854, 2807, 1694 cm^{-1}; MS (70 eV, EI): m/z (%): 363 (2) $[M]^+$, 276 (43), 166 (33), 100 (100); HRMS: calc for $C_{19}H_{29}N_3O_4$ $[M]^+$: 363.2158; found 363.2158.

Synthesis of mono-adducts 3a – 3n

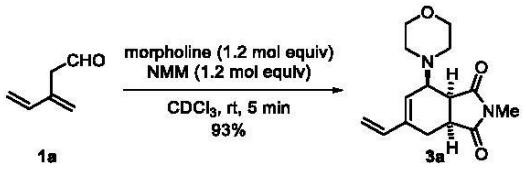
General Procedure D:



1a **3a-n**

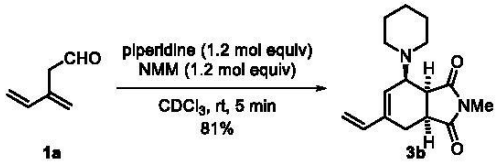
To a solution of aldehyde **1a** in $CDCl_3$ was added the dienophile (1.2 mol equiv). The resulting solution was then added to the amine (1.2 mol equiv), shaken briefly then checked by ^{1}H NMR spectroscopy to ensure complete consumption of aldehyde **1a**. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography to provide the mono-adducts **3a-n**.

Mono-adduct 3a



Prepared using general procedure D with aldehyde **1a** (73 mg, 0.76 mmol), NMM (100 mg, 0.91 mmol, 1.2 mol equiv) and morpholine (79 mg, 0.91 mmol, 1.2 mol equiv) in $CDCl_3$ (2.0 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (60:40:1) provided the *title compound* (195 mg, 0.71 mmol, 93%) as a yellow solid: R_f 0.25 petrol/EtOAc/Et_3N (60:40:1); mp 81-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27 (dd, J = 17.5, 10.7 Hz, 1 H), 5.83 (br. s, 1 H), 5.29 (d, J = 17.6 Hz, 1 H), 5.06 (d, J = 10.9 Hz, 1 H), 3.68 - 3.84 (m, 4 H), 3.42 (dd, J = 8.8, 6.5 Hz, 1 H), 3.14 - 3.26 (m, 1 H), 2.94 - 3.10 (m, 2 H), 2.88 (s, 3 H), 2.72 - 2.84 (m, 2 H), 2.52 - 2.62 (m, 2 H), 2.18 (dd, J = 15.6, 7.3 Hz, 1 H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7 (C), 176.1 (C), 137.7 (CH), 136.1 (CH), 128.2 (CH_2), 113.9 (CH_2), 66.8 (CH_2), 62.7 (CH), 52.6 (CH_2), 41.2 (CH), 39.7 (CH), 24.8 (CH_3), 22.2 (CH_2) ppm; IR (KBr disc): ν_{max} = 2955, 2855, 1700 cm^{-1}; MS (70 eV, EI): *m/z* (%): 276 (100) $[M]^+$, 105 (71), 86 (55); HRMS: calc for $C_{15}H_{20}N_2O_3$ $[M]^+$: 276.1474; found 276.1472.

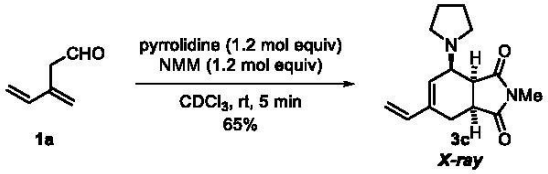
Mono-adduct 3b



Prepared using general procedure D with aldehyde **1a** (67 mg, 0.70 mmol), NMM (93 mg, 0.84 mmol, 1.2 mol equiv) and piperidine (71 mg, 0.84 mmol, 1.2 mol equiv) in $CDCl_3$ (2.0 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (80:20:1) provided the *title compound* (156 mg, 0.57 mmol, 81%) as a yellow solid: R_f 0.31 petrol/EtOAc/Et_3N (80:20:1); mp 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (dd, J=17.6, 10.9 Hz, 1 H), 5.87 (br. s, 1 H), 5.29 (d, J=17.6 Hz, 1 H), 5.05 (d, J=10.9 Hz, 1 H), 3.43 (dd, J=8.8, 6.5 Hz, 1 H), 3.10 - 3.22 (m, 1 H), 2.97 - 3.10 (m, 2 H),

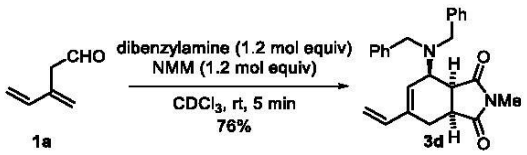
2.90 (s, 3 H), 2.61 - 2.77 (m, 2 H), 2.42 - 2.56 (m, 2 H), 2.22 (dd, *J*=16.7, 7.0 Hz, 1 H), 1.55 - 1.71 (m, 4 H), 1.38 - 1.50 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C), 176.6 (C), 137.1 (C), 136.5 (CH), 129.6 (CH), 113.4 (CH_2), 62.8 (CH), 53.5 (CH_2), 41.8 (CH), 39.4 (CH), 26.3 (CH_2), 24.9 (CH_3), 24.4 (CH_2), 22.0 (CH_2) ppm; IR (KBr disc): ν_{max} = 2933, 2757, 1697 cm^{-1}; MS (70 eV, EI): *m/z* (%): 274.2 (100) $[M]^+$, 105 (52), 84 (88); HRMS: calc for $C_{16}H_{22}N_2O_2$ $[M]^+$:274.1681; found 274.1683.

Mono-adduct 3c



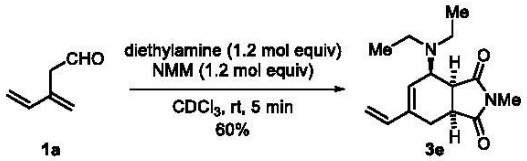
Prepared using general procedure D with aldehyde **1a** (59 mg, 0.62 mmol), NMM (82 mg, 0.74 mmol, 1.2 mol equiv) and pyrrolidine (52 mg, 0.74 mmol, 1.2 mol equiv) in $CDCl_3$ (2.0 mL). Purification by flash column chromatography on triethylamine washed silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) provided the *title compound* (105 mg, 0.40 mmol, 65%) as a yellow solid. R_f 0.15 petrol/EtOAc/Et_3N (70:30:1). Recrystallisation from ethyl acetate gave yellow needles: mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (dd, *J*=17.3, 10.8 Hz, 1 H), 5.90 (br. s., 1 H), 5.31 (d, *J*=17.3 Hz, 1 H), 5.06 (d, *J*=10.8 Hz, 1 H), 3.26 - 3.43 (m, *J*=8.7, 6.9 Hz, 1 H), 3.14 - 3.22 (m, 1 H), 3.06 - 3.14 (m, 1 H), 2.92 - 2.98 (m, 1 H), 2.88 (s, 3 H), 2.77 - 2.86 (m, 2 H), 2.62 - 2.72 (m, 2 H), 2.13 (dd, *J*=15.1, 5.7 Hz, 1 H), 1.79 - 1.92 ppm (m, 4 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (C), 176.2 (C), 136.8 (C), 136.3 (CH), 130.0 (CH), 113.7 (CH_2), 63.1 (CH), 53.6 (CH_2), 43.3 (CH), 40.0 (CH), 25.0 (CH_3), 23.4 (CH_2), 22.3 (CH_2) ppm; IR (KBr disc): ν_{max} = 2949, 2768, 1696 cm^{-1}; MS (70 eV, EI): *m/z* (%): 260 (100) $[M]^+$,105 (39), 70 (76); HRMS: calc for $C_{15}H_{20}N_2O_2$ $[M]^+$: 260.1525; found 260.1526; Elemental analysis: calc for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 69.21; H, 7.94; N, 10.73. The structure and stereochemistry of mono-adduct **3c** were confirmed through single crystal X-ray analysis.

Mono-adduct 3d



Prepared using general procedure D with aldehyde **1a** (59 mg, 0.62 mmol), NMM (82 mg, 0.74 mmol, 1.2 mol equiv) and dibenzylamine (147 mg, 0.74 mmol, 1.2 mol equiv) in $CDCl_3$ (2.0 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc (70:30) provided the *title compound* (183 mg, 0.47 mmol, 76%) as a yellow solid: R_f 0.41 petrol/EtOAc (70:30); mp 64-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J*=7.3 Hz, 2 H), 7.32 (t, *J*=7.3 Hz, 2 H), 7.23 (t, *J*=7.3 Hz, 1 H), 6.32 (dd, *J*=17.3, 10.9 Hz, 1 H), 5.96 (br. s., 1 H), 5.31 (d, *J*=17.3 Hz, 1 H), 5.08 (d, *J*=10.9 Hz, 1 H), 3.96 (d, *J*=14.7 Hz, 2 H), 3.80 (d, *J*=14.7 Hz, 3 H), 3.33 - 3.43 (m, 1 H), 3.07 - 3.14 (m, 1 H), 3.01 (d, *J*=15.8 Hz, 1 H), 2.92 (s, 3 H), 2.03 (dd, *J*=15.7, 7.2 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1(C), 177.9 (C), 139.8 (C), 137.9 (C), 136.8 (CH), 128.4 (2 x CH), 127.9 (CH), 127.1 (CH), 113.6 (CH_2), 56.1 (CH), 55.4 (CH_2), 42.3 (CH), 39.7 (CH), 25.1 (CH_3), 21.5 (CH_2) ppm; IR (KBr disc): ν_{max} = 3026, 2922, 2849, 1700 cm^{-1}; MS (70 eV, EI): *m/z* (%): 386 (93) $[M]^+$, 295 (100), 196 (28); HRMS: calc for $C_{25}H_{26}N_2O_2$ $[M]^+$:386.1994; found 386.1996.

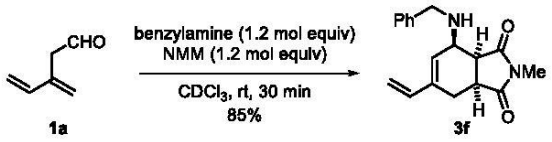
Mono-adduct 3e



Prepared using general procedure D with aldehyde **1a** (48 mg, 0.50 mmol, 1.2 mol equiv), NMM (55 mg, 0.50 mmol, 1.2 mol equiv) and diethylamine (30 mg, 0.41 mmol) in $CDCl_3$ (1.5 mL). Purification by flash column chromatography on triethylamine washed silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) provided the *title compound* (78 mg, 0.30 mmol, 60%) as a yellow oil: R_f 0.30 petrol/EtOAc/Et_3N (70:30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.31 (dd, *J*=17.6, 10.9 Hz, 1 H), 5.85 (br. s, 1 H), 5.29 (d, *J*=17.6 Hz, 1 H), 5.06 (d, *J*=10.9 Hz, 1 H), 3.62 - 3.69 (m, 1 H), 3.26 - 3.33 (m, *J*=9.0, 7.2 Hz, 1 H), 3.11 - 3.25 (m, 1 H), 3.00 (dd, *J*=16.7, 2.9 Hz, 1 H), 2.90 (s, 3 H), 2.59 - 2.77 (m, 4 H), 2.21 (dd, *J*=16.0, 7.8 Hz, 1 H),

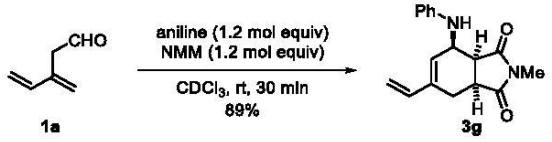
0.99 (t, *J*=7.0 Hz, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2 (C), 177.4 (C), 137.3 (C), 137.0 (CH), 128.8 (CH), 113.3 (CH_2), 58.0 (CH), 44.5 (CH_2), 43.0 (CH), 39.5 (CH), 24.9 (CH_3), 21.4 (CH_2), 12.7 (CH_3) ppm; IR (thin film): ν_{max} = 2963, 2858, 1596 cm^{-1}; MS (70 eV, EI): *m/z* (%): 262.2 (100) $[M]^+$, 105 (70), 72 (48); HRMS: calc for $C_{15}H_{22}N_2O_2$ $[M]^+$:262.1681; found 262.1679.

Mono-adduct 3f



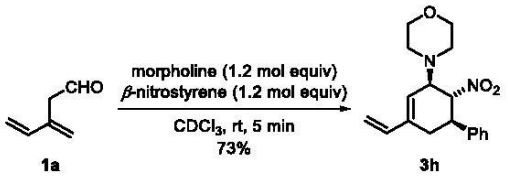
Prepared using general procedure D with aldehyde **1a** (23 mg, 0.23 mmol), NMM (31 mg, 0.28 mmol, 1.2 mol equiv) and benzylamine (30 mg, 0.28 mmol, 1.2 mol equiv) in $CDCl_3$ (1.0 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) provided the *title compound* (59 mg, 0.20 mmol, 85%) as a yellow oil: R_f 0.25 petrol/EtOAc/Et_3N (70:30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 - 7.33 (m, 2 H), 7.24 (m, 2 H), 7.14 - 7.20 (m, 1 H), 6.19 (dd, *J*=17.6, 10.9 Hz, 1 H), 5.75 (br. s., 1 H), 5.20 (d, *J*=17.6 Hz, 1 H), 4.96 (d, *J*=10.9 Hz, 1 H), 3.95 (d, *J*=13.2 Hz, 1 H), 3.81 (d, *J*=13.2 Hz, 1 H), 3.43 - 3.49 (m, 1 H), 3.27 (dd, *J*=8.8, 6.5 Hz, 1 H), 3.03 - 3.10 (m, 1 H), 2.88 - 2.96 (m, 1 H), 2.81 (s, 3 H), 2.01 (dd, *J*=15.3, 7.3 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (C), 178.0 (C), 139.7 (C), 136.9 (C), 136.3 (CH), 131.6 (CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 113.5 (CH_2), 54.1 (CH), 51.4 (CH_2), 41.8 (CH), 39.2 (CH), 24.7 (CH_3), 22.5 (CH_2) ppm; IR (thin film): ν_{max} = 2950, 2850, 1697 cm^{-1}; MS (70 eV, EI): *m/z* (%): 296 (50) $[M]^+$, 205 (38), 106 (99), 91 (100); HRMS: calc for $C_{18}H_{20}N_2O_2$ $[M]^+$: 296.1525; found 296.1522.

Mono-adduct 3g



Prepared using general procedure D with aldehyde **1a** (23 mg, 0.23 mmol), NMM (31 mg, 0.28 mmol, 1.2 mol equiv) and aniline (26 mg, 0.28 mmol, 1.2 mol equiv) in $CDCl_3$ (1.0 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) provided the *title compound* (59 mg, 0.21 mmol, 89%) as a yellow solid: R_f 0.27 petrol/EtOAc/Et_3N (70:30:1); mp 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 - 7.24 (m, *J*=1.0, 1.0 Hz, 3 H), 6.72 - 6.78 (m, 1 H), 6.67 (dd, *J*=8.5, 0.9 Hz, 2 H), 6.26 (dd, *J*=17.5, 10.7 Hz, 2 H), 5.79 (br. s., 1 H), 5.51 (d, *J*=9.7 Hz, 1 H), 5.32 (d, *J*=17.6 Hz, 2 H), 5.08 (d, *J*=10.9 Hz, 1 H), 4.23 (br. s., 1 H), 3.36 (t, *J*=8.8 Hz, 1 H), 3.26 (t, *J*=8.1 Hz, 1 H), 3.14 (d, *J*=15.3 Hz, 1 H), 2.92 (s, 3 H), 2.20 (dd, *J*=15.1, 7.2 Hz, 0 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (C), 178.6 (C), 146.5 (C), 137.4 (C), 136.0 (CH), 131.5 (CH), 129.4 (CH), 118.1 (CH), 113.9 (CH_2), 113.7 (CH), 50.3 (CH), 42.2 (CH), 39.0 (CH), 25.0 (CH_3), 22.7 (CH_2) ppm; IR (KBr disc): ν_{max} = 3027, 2950, 2850, 1697 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 282 (100) $[M]^+$, 105 (63); HRMS: calc for $C_{17}H_{18}N_2O_2$ $[M]^+$: 282.1368; found 282.1372.

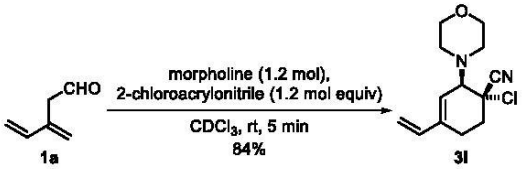
Mono-adduct 3h



Prepared using general procedure D with aldehyde **1a** (45 mg, 0.47 mmol), β-nitrostyrene (84 mg, 0.56 mmol, 1.2 mol equiv) and morpholine (49 mg, 0.56 mmol, 1.2 mol equiv) in $CDCl_3$ (1.2 mL). Two diasteoreomeric isomers were formed in the ratio 89:11. Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/ Et_3N (90:10:1) provided the *title compound* (89:11 mixture of two diastereomers, 108 mg, 0.34 mmol, 73%) as a pale yellow solid. Repeated rinsing of the pale yellow solid with methanol provided a pure sample of the major isomer as a white solid: R_f 0.24 petrol/EtOAc (90:10); mp 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 - 7.37 (m, 5 H), 6.40 (dd, *J*=17.6, 11.0 Hz, 1 H), 5.82 (s, 1 H), 5.11 (d, *J*=17.6 Hz, 1 H), 5.12 (d, *J*=11.0 Hz, 1 H), 4.97 (dd, *J*=11.7, 10.2 Hz, 1 H), 4.13 (d, *J*=10.2 Hz, 1 H), 3.59 - 3.73 (m, 5 H), 3.48 (td, *J*=11.7, 5.5 Hz, 1 H), 2.75 - 2.82 (m, 2 H), 2.66 - 2.74 (m, 1 H), 2.53 - 2.59 (m, 2 H), 2.37 - 2.49 ppm (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9 (C), 137.9 (C), 137.2 (CH), 129.0 (CH), 128.1 (CH), 127.3 (CH), 124.6

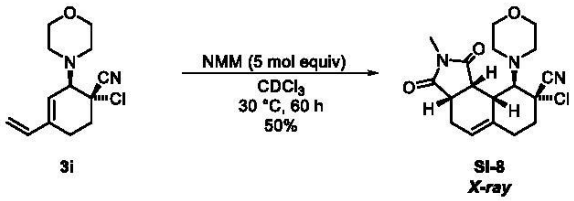
(CH), 114.1 (CH_2), 88.9 (CH), 67.4 (CH_2), 66.0 (CH), 48.9 (CH_2), 45.0 (CH), 32.7 (CH_2) ppm; IR (KBr disc): ν_{max} = 2955, 2913, 2856, 2828, 1551 cm^{-1}; MS (70 eV, EI): *m/z* (%): 314 (20) $[M]^+$, 165 (100); HRMS: calc for $C_{18}H_{22}N_2O_3$ $[M]^+$: 314.1630; found 314.1631.

Mono-adduct 3i



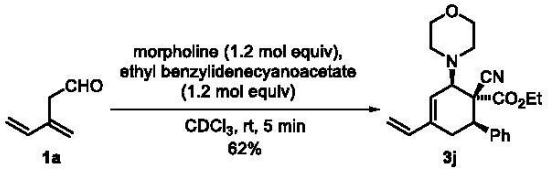
Prepared using general procedure D with aldehyde **1a** (24 mg, 0.25 mmol), 2-chloroacrylonitrile (26 mg, 0.30 mmol, 1.2 mol equiv) and morpholine (26 mg, 0.30 mmol, 1.2 mol equiv) in $CDCl_3$ (0.6 mL). The residue was purified by flash column chromatography on silica gel eluting with petrol/EtOAc/ Et_3N (80:20:1) to provide the *title compound* (53 mg, 0.21 mmol, 84%) as a yellow oil: R_f 0.35 petrol/EtOAc (80:20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 6.35 (dd, *J*=17.6, 10.9 Hz, 1 H), 5.60 - 5.72 (m, 1 H), 5.23 (d, *J*=17.6 Hz, 1 H), 5.13 (d, *J*=10.6 Hz, 1 H), 3.62 - 3.78 (m, 4 H), 3.49 - 3.55 (m, 1 H), 2.82 - 2.88 (m, 4 H), 2.37 - 2.47 (m, 3 H), 2.26 - 2.34 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1 (C), 137.4 (CH), 122.0 (CH), 119.0 (C), 114.4 (CH_2), 68.6 (CH), 67.7 (CH_2), 60.2 (C), 52.4 (CH_2), 32.8 (CH_2), 21.1 (CH_2) ppm; IR (KBr disc): ν_{max} = 2958, 2854, 2821, 2243 cm^{-1}; MS (70 eV, EI): *m/z* (%): 252 (71) $[M]^+$, 217 (71), 165 (100); HRMS: calc for $C_{19}H_{21}{}^{35}ClN_2O$ $[M]^+$: 252.1029; found 252.1029; calc for $C_{19}H_{21}{}^{37}ClN_2O$ $[M]^+$: 254.1000; found 254.1000.

Bis-adduct SI-8



To a solution of mono-adduct **3i** (76mg, 0.30 mmol) in $CDCl_3$ (0.6mL) was added NMM (170 mg, 1.50 mmol, 5.0 mol equiv) and stirred at 30 ºC until complete consumption of the mono-adduct was observed by ^1H NMR spectroscopy (60 h). The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with hexane/EtOAc/Et_3N (50:50:1) to provide the title compound (55 mg, 0.75 mmol, 50%) as a yellow solid. R_f 0.31 hexane/EtOAc/Et_3N (50:50:1). Recrystallisation from methanol gave colourless crystals: mp 160 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 5.65 (br. s, 1 H), 4.40 (d, *J*=11.1 Hz, 1 H), 3.62 - 3.75 (m, 4 H), 3.52 - 3.58 (m, 1 H), 3.32 (br. s., 2 H), 3.16 (t, *J*=8.2 Hz, 1 H), 3.10 (br. s, 2 H), 2.93 (s, 3 H), 2.50 - 2.67 (m, 4 H), 2.36 - 2.42 (m, 1 H), 2.16 - 2.25 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (C), 179.0 (C), 135.6 (C), 122.8 (CH), 118.2 (C), 68.4 (CH), 68.2 (CH_2), 61.1 (C), 50.3 (CH_2), 41.2 (CH), 39.4 (CH_2), 39.3 (CH), 39.2 (CH), 27.7 (CH_2), 25.2 (CH_3), 25.0 (CH_2) ppm; IR (KBr disc): ν_{max} = 2953, 2891, 2851, 2252, 1772, 1694 cm^{-1}; MS (70 eV, EI): *m/z* (%): 363 (72) $[M]^+$, 328 (49), 276 (100), 138 (11); HRMS: calc for $C_{18}H_{22}N_3O_3{}^{35}Cl$ $[M]^+$: 363.1350; found 363.1349; calc for $C_{18}H_{22}N_3O_3{}^{37}Cl$ $[M]^+$: 365.1320; found 365.1325. The structure and stereochemistry of bis-adduct **SI-8** were confirmed through single crystal X-ray analysis.

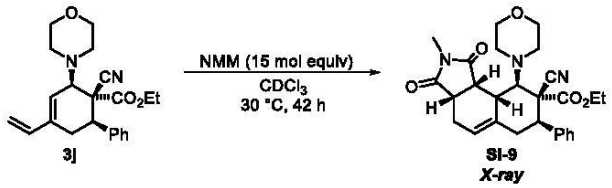
Mono-adduct 3j



Prepared using general procedure D with aldehyde **1a** (40 mg, 0.40 mmol), ethyl benzylidenecyanoacetate (95 mg, 0.48 mmol, 1.2 mol equiv) and morpholine (42 mg, 0.48

mmol, 1.2 mol equiv) in $CDCl_3$ (2 mL). The residue was purified by flash column chromatography on silica gel eluting with petrol/EtOAc (90:10 then 80:20) to provide the *title compound* (91 mg, 0.25 mmol, 62%) as an orange wax: R_f 0.32 petrol/EtOAc (70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.44 (m, 2 H), 7.27 - 7.37 (m, 3 H), 6.44 (dd, *J*=17.6, 10.9 Hz, 1 H), 5.89 (br. s, 1 H), 5.20 (d, *J*=17.6 Hz, 1 H), 5.12 (d, *J*=10.9 Hz, 1 H), 4.19 (br. s., 1 H), 3.86 - 4.01 (m, 2 H), 3.58 - 3.71 (m, 4 H), 3.34 (dd, *J*=12.3, 5.0 Hz, 1 H), 2.99 - 3.07 (m, 2 H), 2.83 - 2.95 (m, 1 H), 2.64 - 2.72 (m, 2 H), 2.59 (dd, *J*=17.6, 5.0 Hz, 1 H), 0.91 (t, *J*=7.6 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (C), 138.1 (C), 138.0 (C), 137.5 (CH), 128.7 (CH), 128.3 (2 x CH), 124.3 (CH), 117.9 (C), 113.9 (CH_2), 68.7 (CH), 67.8 (CH_2), 62.4 (CH_2), 56.5 (C), 51.3 (CH_2), 46.9 (CH), 29.3 (CH_2), 13.8 (CH_3) ppm; IR (KBr disc): ν_{max} = 3033, 2919, 2852, 2243, 1737 cm^{-1}; MS (70 eV, EI): *m/z* (%): 366.2 (32) $[M]^+$, 165.1 (100); HRMS: calc for $C_{22}H_{26}N_2O_3$ $[M]^+$:366.1943; found 366.1949.

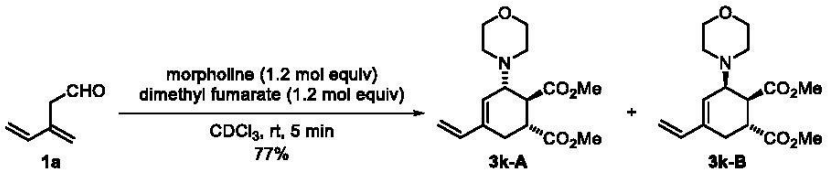
Bis-adduct SI-9



To a solution of mono-adduct **3j** (33 mg, 0.090 mmol) in $CDCl_3$ (1 mL) was added NMM (150 mg, 1.4 mmol, 15 mol equiv) and stirred at 30 ºC until complete consumption of the mono-adduct was observed by ^{1}H NMR spectroscopy (42 h). The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with hexane/EtOAc/Et_3N (50:50:1) to provide the title compound (35 mg, 0.073 mmol, 85%) as a yellow solid. R_f 0.31 hexane/EtOAc/Et_3N (50:50:1). Recrystallisation from ethyl acetate gave colourless crystals: mp 226 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 - 7.37 (m, 5 H), 5.68 (br. s, 1 H), 4.88 (d, *J*=11.4 Hz, 1 H), 3.99 (q, *J*=7.2 Hz, 2 H), 3.54 - 3.65 (m, 4 H), 3.38 (dd, *J*=8.8, 5.0 Hz, 1 H), 3.18 - 3.28 (m, 2 H), 3.03 - 3.10 (m, 2 H), 2.97 (s, 3 H), 2.87 - 2.95 (m, 4 H), 2.61 - 2.71 (m, 2 H), 2.24 - 2.35 (m, 1 H), 0.98 (t, *J*=7.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (C), 178.9 (C), 167.3 (C), 138.2 (C), 136.4 (C), 128.6 (CH), 128.1 (CH), 128.1 (CH), 122.8 (CH), 118.1 (C), 68.1 (CH_2), 65.9 (CH), 62.3 (CH_2), 57.5 (C), 50.7 (CH_2), 47.2 (CH), 41.4 (CH), 39.6 (CH), 36.1 (CH), 33.9 (CH_2), 25.0 (CH_3),

25.0 (CH_2), 13.8 (CH_3) ppm; IR (KBr disc): ν_{max} = 2956, 2909, 2851, 1772, 1739, 1695 cm^{-1}; MS (70 eV, EI): *m/z* (%): 477 (12) $[M]^+$, 276 (100), 165 (13); HRMS: calc for $C_{27}H_{31}N_3O_5$ $[M]^+$: 477.2264; found 477.2261. The structure and stereochemistry of mono-adduct **SI-9** were confirmed through single crystal X-ray analysis.

Mono-adduct 3k



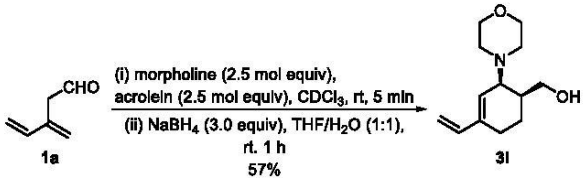
Prepared using general procedure D with aldehyde **1a** (40 mg, 0.41 mmol), dimethyl fumarate (71 mg, 0.49 mmol, 1.2 mol equiv) and morpholine (43 mg, 0.49 mmol, 1.2 mol equiv) in $CDCl_3$ (2.0 mL). Two diasteoreomeric isomers were formed in the ratio 1:1. Purification by flash column chromatography on silica gel eluting with petrol/Et_2O/Et_3N (60:40:1) provided the *title compound* (1:1 mixture of two diastereomers, 99 mg, 0.32 mmol, 77%) as a yellow oil; R_f 0.21 petrol/Et_2O/Et_3N (60:40:1). Analytical samples of each diastereomer were obtained by preparative HPLC (Waters Xbridge C18 5 µm column, 150 mm x 19 mm, 50:50:0.1 MeOH:H_2O:TFA):

mono-adduct **3k-A**: t_r = 14.5 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (dd, *J*=17.4, 10.8 Hz, 1 H), 5.79 (br. s, 4 H), 5.14 (d, *J*=17.4 Hz, 1 H), 5.06 (d, *J*=10.8 Hz, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.60 - 3.65 (m, 5 H), 2.94 - 3.05 (m, 1 H), 2.80 - 2.89 (m, 1 H), 2.57 - 2.75 (m, 3 H), 2.42 - 2.51 (m, 2 H), 2.21 - 2.34 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1 (C), 174.0 (C), 137.8 (CH), 136.6 (C), 127.1 (CH), 113.1 (CH_2), 67.7 (CH_2), 64.5 (CH), 52.2 (CH_3), 51.9 (CH_3), 48.9 (CH_2), 45.1 (CH), 42.5 (CH), 27.2 (CH_2) ppm; IR (thin film): ν_{max} = 2952, 2851, 1736, 1643, 1607 cm^{-1}; MS (70 eV, EI): *m/z* (%): 309 (100) $[M]^+$, 250 (70), 165 (60); HRMS: calc for $C_{16}H_{23}NO_5$ $[M]^+$:309.1576; found 309.1570.

mono-adduct **3k-B**: t_r = 16.5 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (dd, *J*=17.6, 11.0 Hz, 1 H), 5.85 (br. s, 1 H), 5.20 (d, *J*=17.6 Hz, 1 H), 5.10 (d, *J*=11.0 Hz, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.53 - 3.65 (m, 5 H), 2.96 - 3.15 (m, 2 H), 2.63 - 2.78 (m, 3 H), 2.47 - 2.56 (m, 2 H), 1.96 - 2.09 (m, 1 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.8 (C), 173.0 (C), 138.0 (CH), 137.4 (C), 124.7 (CH), 113.4 (CH_2), 67.9 (CH_2), 59.3 (CH), 52.2 (CH_3), 51.9 (CH_3), 51.7

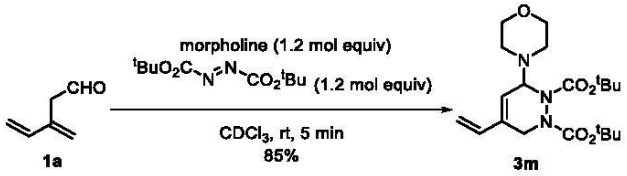
(CH_2), 47.8 (CH), 38.4 (CH), 27.2 (CH_2) ppm; IR (thin film): ν_{max} = 2952, 2851, 1736, 1643, 1607 cm^{-1}; MS (70 eV, EI): *m/z* (%): 309 (100) $[M]^+$, 250 (70), 165 (60); HRMS: calc for $C_{16}H_{23}NO_5$ $[M]^+$:309.1576; found 309.1570.

Mono-adduct 3l



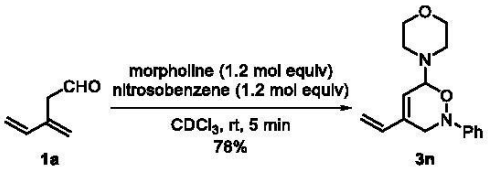
Prepared using general procedure D with aldehyde **1a** (58 mg, 0.61 mmol), acrolein (85 mg, 1.50 mmol, 2.5 mol equiv) and morpholine (132 mg, 1.51 mmol, 2.5 mol equiv) in $CDCl_3$ (2 mL). Upon complete consumption of aldehyde **1a**, as observed by ^1H NMR, a solution of sodium borohydride (69 mg, 1.81 mmol, 3.0 mol equiv) in THF/H_2O (1:1, 2mL) was added and the resulting mixture was stirred at rt for 1h. The mixture was then poured into CH_2Cl_2/H_2O (1:1, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x10 mL) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with petrol/EtOAc (60:40) provided the *title compound* (77 mg, 0.34 mmol, 57%) as a yellow oil: R_f 0.24 petrol/EtOAc (60:40); ^1H NMR (400 MHz, $CDCl_3$): δ 6.37 (dd, *J*=17.5, 10.7 Hz, 1 H), 5.85 (br. s, 1 H), 5.19 (d, *J*=17.6 Hz, 1 H), 5.03 (d, *J*=10.9 Hz, 1 H), 3.86 (dd, *J*=11.4, 3.8 Hz, 1 H), 3.75 (dd, *J*=11.3, 6.7 Hz, 1 H), 3.69 (t, *J*=4.7 Hz, 4 H), 3.30 (br. s., 1 H), 2.72 - 2.82 (m, 2 H), 2.63 - 2.71 (m, 2 H), 2.28 - 2.37 (m, 1 H), 2.01 - 2.13 (m, 1 H), 1.88 - 1.98 (m, 1 H), 1.62 - 1.80 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8 (C), 139.1 (CH), 124.8 (CH), 112.6 (CH_2), 67.4 (CH_2), 65.8 (CH_2), 62.8 (CH), 52.7 (CH_2), 38.5 (CH), 23.2 (CH_2), 22.8 (CH_2) ppm; IR (thin film): ν_{max} = 3416, 2921, 2851, 1639, 1604 cm^{-1}; MS (70 eV, EI): *m/z* (%): 223 (100) $[M]^+$, 165 (94), 165 (94); HRMS: calc for $C_{13}H_{21}NO_2$ $[M]^+$: 223.1572; found 223.1574.

Mono-adduct 3m



Prepared using general procedure D with aldehyde **1a** (32 mg, 0.33 mmol), di-*tert*-butyl azodicarboxylate (91 mg, 0.40 mmol, 1.2 mol equiv) and morpholine (35 mg, 0.40 mmol, 1.2 mol equiv) in $CDCl_3$ (1.5 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) provided the *title compound* (110 mg, 0.28 mmol, 85%) as a white solid: R_f 0.33 petrol/EtOAc/Et_3N (70:30:1); mp 91 °C; ^{1}H NMR (300 MHz, toluene-d_8, 100 ºC): δ 6.08 (dd, J=17.6, 11.0 Hz, 1 H), 5.45 (br. s., 1 H), 5.27 (br. s., 1 H), 4.98 (d, J=17.6 Hz, 1 H), 4.83 (d, J=11.0 Hz, 1 H), 4.70 (d, J=16.7 Hz, 1 H), 3.64 (d, J=16.7 Hz, 1 H), 3.47 - 3.57 (m, 4 H), 2.56 - 2.85 (m, 4 H), 1.51 (s, 7 H), 1.34 - 1.42 (m, 9 H) ppm; ^{13}C NMR (75 MHz, toluene-d_8, 100 ºC): δ 155.4 (C), 153.9 (C), 136.1 (CH), 131.4 (C), 125.3 (CH_2), 113.9 (CH_2), 81.4 (C), 81.0 (C), 73.4 (CH), 68.0 (CH_2), 49.5 (CH_2), 41.9 (CH_2), 29.0 (CH_3), 28.7 (CH_3) ppm; IR (KBr disc): ν_{max} = 2971, 2861, 1700 cm^{-1}; MS (70 eV, EI): *m/z* (%): 395 (20) $[M]^+$, 309 (33), 165 (100); HRMS: calc for $C_{20}H_{33}N_3O_5$ $[M]^+$:395.2420; found 395.2420.

Mono-adduct 3n

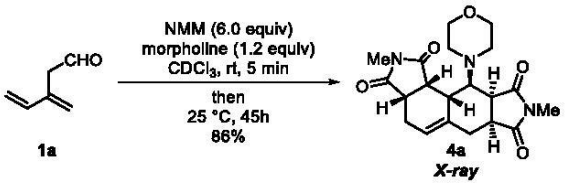


Prepared using general procedure D with aldehyde **1a** (43 mg, 0.44 mmol), nitrosobenzene (57 mg, 0.53 mmol, 1.2 mol equiv) and morpholine (46 mg, 0.53 mmol, 1.2 mol equiv) in $CDCl_3$ (2.0 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) provided the *title compound* (94 mg, 0.35 mmol, 78%) as a brown solid: R_f 0.35 petrol/EtOAc/Et_3N (70:30:1); mp 73-75 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.31 - 7.36 (m, 2 H), 7.14 - 7.21 (m, 2 H), 6.96 - 7.04 (m, 1 H), 6.47 (dd, *J*=17.8, 11.0 Hz, 1 H), 5.81 (br. s, 1 H), 5.27 (d, *J*=17.9 Hz, 1 H), 5.17 (d, *J*=11.2 Hz, 1 H), 5.14 (d, *J*=1.8 Hz, 1 H), 3.91 (s, 2 H), 3.63 - 3.74 (m, 4 H), 3.01 - 3.11 (m, 2 H), 2.81 - 2.90 ppm (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3 (C), 137.5 (C), 135.6 (CH), 129.0 (CH), 126.7 (CH), 122.2 (CH), 115.6 (CH), 113.4 (CH_2), 91.4 (CH), 67.5 (CH_2), 51.0 (CH_2), 48.6 (CH_2) ppm; IR (KBr disc): ν_{max} = 2963, 2858, 2830 cm^{-1}; MS (70 eV, EI): *m/z* (%): 272 (30) $[M]^+$, 165 (100); HRMS: calc for $C_{16}H_{20}N_2O_2$ $[M]^+$: 272.1525; found 272.1520.

Synthesis of bis-adducts 4a – 4g, 7a and 7b

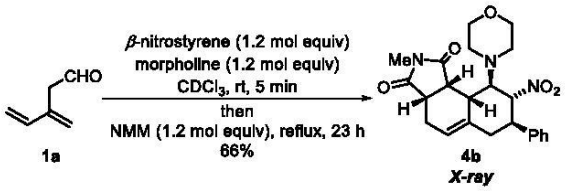
Bis-adduct 4a



To a solution of aldehyde **1a** (23 mg, 0.23 mmol) in $CDCl_3$ (1.0 mL) was added NMM (160 mg, 1.4 mmol, 6.0 mol equiv). The resulting solution was added to morpholine (24 mg, 0.28 mmol, 1.2 mol equiv) and stirred at 25 ºC for 45 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (20:80:1) to provide the *title compound* (78 mg, 0.20 mmol, 86%) as a yellow solid. R_f 0.33 petrol/EtOAc/Et_3N (20:80:1). Recrystallisation from CH_2Cl_2/ethyl acetate gave yellow crystals: mp 197-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.63 (br. s, 1 H), 4.00 - 4.07 (m, 1 H), 3.72 - 3.79 (m, 2 H), 3.62 - 3.70 (m, 2 H), 3.41 (ddd, *J*=12.8, 8.7, 4.3 Hz, 2 H), 3.11 - 3.17 (m, 1 H), 3.06 (t, *J*=8.1 Hz, 1 H), 2.95 - 3.02 (m, 1 H), 2.89 (s, 3 H), 2.87 (s, 3 H), 2.81 - 2.85 (m, 1 H), 2.61 (dd, *J*=15.6, 7.3 Hz, 1 H), 2.38 - 2.54 (m, 2 H), 2.29 (dd, *J*=12.9, 2.1 Hz, 1 H), 1.99 - 2.10 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (C), 179.3 (C), 177.7 (C), 177.6 (C), 137.0 (C), 123.4 (CH), 67.4 (CH_2), 59.2 (CH), 50.4 (CH_2), 41.2 (CH), 40.6 (CH), 40.4 (CH), 39.9 (CH), 36.4 (CH), 29.1 (CH_2), 25.4 (CH_2), 25.0 (CH_3), 24.9 (CH_3) ppm; IR (KBr disc): ν_{max} = 2962, 2949, 2851, 1689 cm^{-1}; MS (70 eV, EI): *m/z* (%): 387 (100) $[M]^+$, 276 (65), 86 (95); HRMS: calc for $C_{20}H_{25}N_3O_5$ $[M]^+$:387.1794; found 387.1799; Elemental analysis: calc for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50;

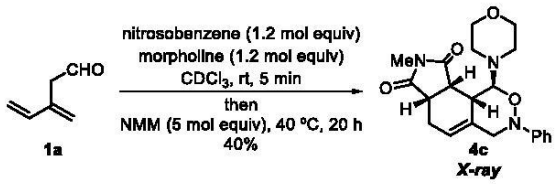
N, 10.85. Found: C, 61.65; H, 6.59; N, 10.56. The structure and stereochemistry of bis-adduct **4a** were confirmed through single crystal X-ray analysis.

Bis-adduct 4b



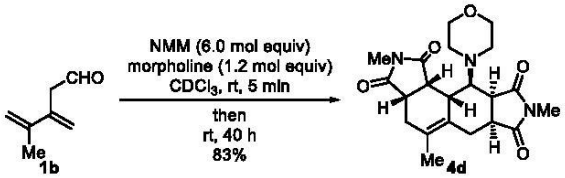
To a solution of aldehyde **1a** (42 mg, 0.43 mmol) in $CDCl_3$ (2.0 mL) was added *β*-nitrostyrene (78 mg, 0.52 mmol, 1.2 mol equiv). The resulting solution was added to morpholine (46 mg, 0.52 mmol, 1.2 mol equiv) and stirred briefly. Upon complete consumption of aldehyde **1a**, as indicated by ^{1}H NMR spectroscopy, NMM (58 mg, 0.52 mmol, 1.2 mol equiv) was added and and the mixture was stirred under reflux for 23 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with petrol/EtOAc (20:80) to provide the *title compound* (91:9 mixture of two diastereomers, 120 mg, 0.29 mmol, 66%) as a pale yellow solid: R_f 0.27 petrol/EtOAc (20:80). Recrystallisation from CH_2Cl_2/diethyl ether gave pale yellow crystals: mp 188-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 - 7.34 (m, 3 H), 7.14 - 7.19 (m, 2 H), 5.65 (br. s, 1 H), 4.82 - 4.93 (m, 2 H), 3.60 - 3.67 (m, 4 H), 3.51 (dd, *J*=8.6, 5.5 Hz, 1 H), 3.38 - 3.46 (m, 1 H), 3.20 (td, *J*=8.6, 1.6 Hz, 1 H), 3.00 (s, 3 H), 2.92 - 2.99 (m, 2 H), 2.84 (dt, *J*=11.2, 4.4 Hz, 2 H), 2.72 - 2.80 (m, 1 H), 2.67 (ddd, *J*=15.8, 6.8, 1.6 Hz, 1 H), 2.51 - 2.60 (m, 1 H), 2.39 - 2.50 (m, 1 H), 2.19 - 2.30 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5 (C), 178.4 (C), 140.2 (C), 137.1 (C), 128.9 (CH), 127.7 (CH), 127.0 (CH), 121.8 (CH), 91.8 (CH), 67.9 (CH_2), 62.7 (CH), 48.8 (CH), 44.8 (CH), 41.2 (CH), 39.7 (CH), 37.6 (CH), 36.3 (CH_2), 25.1 (CH_3), 25.0 (CH_2) ppm; IR (KBr disc): ν_{max} = 2952, 2921, 2855, 1704 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 425 (20) $[M]^+$, 379 (60), 276 (60), 202 (100); HRMS: calc for $C_{23}H_{27}N_3O_5$ $[M]^+$:425.1951; found 425.1960. The structure and stereochemistry of bis-adduct **4b** were confirmed through single crystal X-ray analysis.

Bis-adduct 4c



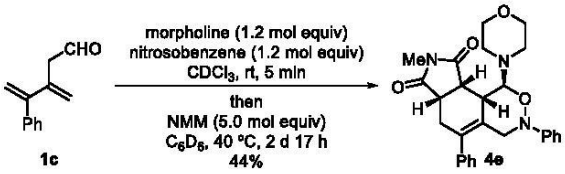
To a solution of aldehyde **1a** (42 mg, 0.43 mmol) in $CDCl_3$ (2 mL) was added nitrosobenzene (55 mg, 0.52 mmol, 1.2 mol equiv). The resulting solution was added to morpholine (46 mg, 0.52 mmol, 1.2 mol equiv) and stirred briefly. Upon complete consumption of aldehyde **1a**, as indicated by ^1H NMR spectroscopy, NMM (241 mg, 2.17 mmol, 5.0 mol equiv) was added and the mixture was stirred at 40 ºC for 20 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (50:50:1) to provide the *title compound* (67 mg, 0.18 mmol, 40%) as a yellow solid. R_f 0.23 petrol/EtOAc/Et_3N (50:50:1). Recrystallisation from CH_2Cl_2/diethyl ether gave colourless crystals: mp 169-171 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 - 7.29 (m, 2 H), 7.01 - 7.06 (m, 2 H), 6.91 - 6.97 (m, 1 H), 5.67 - 5.73 (br. s, 1 H), 5.65 (d, *J*=9.7 Hz, 1 H), 4.11 (d, *J*=14.7 Hz, 1 H), 3.59 - 3.79 (m, 5 H), 3.31 (dd, *J*=9.0, 6.6 Hz, 1 H), 3.08 - 3.21 (m, 3 H), 2.91 (s, 3 H), 2.86 - 2.97 (m, 2 H), 2.63 - 2.80 (m, 2 H), 2.14 - 2.19 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (C), 177.5 (C), 150.4 (C), 135.8 (C), 128.8 (CH), 122.1 (CH), 120.8 (CH), 115.5 (CH), 93.0 (CH), 67.6 (CH_2), 55.6 (CH_2), 48.5 (CH_2), 40.0 (CH), 39.7 (CH), 35.3 (CH), 25.0 (CH_3), 24.2 (CH_2)ppm; IR (KBr disc): ν_{max} = 2963, 2853, 1689 cm^{-1}; MS (70 eV, EI): *m/z* (%): 383 (30) $[M]^+$, 276 (100); HRMS: calc for $C_{21}H_{25}N_3O_4$ $[M]^+$:383.1845; found 383.1849. The structure and stereochemistry of bis-adduct **4c** were confirmed through single crystal X-ray analysis.

Bis-adduct 4d



To a solution of aldehyde **1b** (5 mg, 0.045 mmol) in $CDCl_3$ (0.4 mL) was added NMM (30 mg, 0.27 mmol, 6.0 mol equiv). The resulting solution was added to morpholine (5 mg, 0.0545 mmol, 1.2 mol equiv) and left at rt for 40 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (60:40:1 then 40:60:1) to provide the *title compound* (15 mg, 0.037 mmol, 83%) as a colourless wax: R_f 0.14 hex/EtOAc/Et_3N (40:60:1); ^1H NMR (400 MHz, $CDCl_3$): δ 3.99 (dd, J = 12.8, 3.8 Hz, 1H), 3.77 (ddd, J = 9.8, 6.4, 2.8 Hz, 2H), 3.67 (ddd, J = 10.4, 6.4, 2.8 Hz, 2H), 3.46 – 3.35 (m, 2H), 3.16 (t, J = 8.1 Hz, 1H), 3.08 – 2.96 (m, 3H), 2.96 – 2.81 (m, 9H), 2.51 (d, J = 14.8 Hz, 1H), 2.27 (dd, J = 12.4, 4.1 Hz, 1H), 2.17 (dd, J = 14.3, 7.2 Hz, 2H), 1.62 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (C), 179.5 (C), 177.9 (C), 177.9 (C), 131.6 (C), 127.5 (C), 68.1 (CH_2), 59.6 (CH), 50.5, 41.5 (CH), 40.6 (CH), 40.3 (CH), 39.9 (CH), 37.2 (CH), 31.9 (CH_2), 25.0 (CH_3), 24.9 (CH_3), 24.5 (CH_2), 19.1 (CH_3) ppm; IR (ATR): ν_{max} = 2949, 2852, 1770, 1694 cm^{-1}; MS (70 eV, EI): m/z (%): 401 (72) $[M]^+$, 315 (23), 290 (63), 86 (100); HRMS: calc for $C_{21}H_{27}N_3O_5$ $[M]^+$:401.1951; found 401.1947.

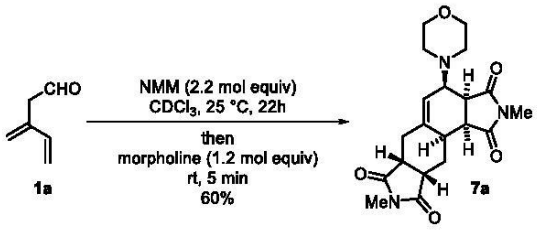
Bis-adduct 4e



To a solution of aldehyde **1c** (30 mg, 0.172 mmol) in $CDCl_3$ (0.5 mL) was added nitrosobenzene (22 mg, 0.207 mmol, 1.2 mol equiv). The resulting solution was added to morpholine (18 mg, 0.207 mmol, 1.2 mol equiv) and stirred briefly. Upon complete

consumption of aldehyde **1c**, as indicated by ^{1}H NMR spectroscopy, the mixture was concentrated under reduced pressure and redissolved in C_6D_6 (0.5 mL). NMM (96 mg, 0.860 mmol, 5.0 mol equiv) was added and the mixture was stirred at 40 ºC for 2 days and 17 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with hex/EtOAc/Et_3N (30:70:1 then 0:100:1) to provide the *title compound* (35 mg, 0.0762 mmol, 44%) as a beige solid: R_f 0.23 petrol/EtOAc/Et_3N (50:50:1); mp 130 – 138 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, J = 7.5 Hz, 2H), 7.34 – 7.22 (m, 3H), 7.13 (d, J = 8.3 Hz, 2H), 7.04 – 6.92 (m, 3H), 5.82 (d, J = 9.0 Hz, 1H), 4.12 (d, J = 15.1 Hz, 1H), 3.91 – 3.72 (m, 5H), 3.44 (dd, J = 9.1, 6.1 Hz, 1H), 3.33 (dd, J = 9.0, 7.2 Hz, 1H), 3.30 – 3.20 (m, 2H), 3.11 – 2.95 (m, 6H), 2.97 – 2.87 (m, 1H), 2.69 – 2.56 (m, 1H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (C), 177.8 (C), 150.5 (C), 139.8 (C), 133.6 (C), 130.6 (C), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.4 (CH), 122.3 (CH), 115.8 (CH), 92.8 (CH), 67.7 (CH_2), 54.5 (CH_2), 48.7 (CH_2), 40.7 (CH), 40.5 (CH), 37.0 (CH), 31.7 (CH_2), 25.2 (CH_3) ppm; IR (ATR): ν_{max} = 2983, 2971, 2957, 2855, 1771, 1695 cm^{-1}; MS (70 eV, EI): *m/z* (%): 459 (57) $[M]^+$, 352 (70), 77 (100); HRMS: calc for $C_{27}H_{29}N_3O_4$ $[M]^+$: 459.2158; found 459.2159.

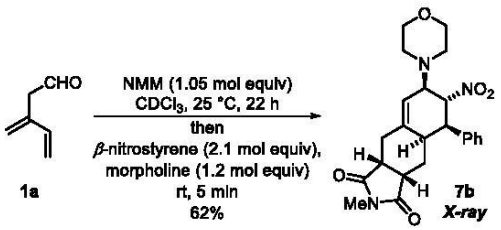
Bis-adduct 7a



To a solution of aldehyde **1a** (24 mg, 0.25 mmol) in $CDCl_3$ (1.0 mL) was added NMM (61 mg, 0.55 mmol, 2.2 mol equiv) and stirred at 25 ºC until complete consumption of aldehyde **1a**, as indicated by ^{1}H NMR spectroscopy, was observed (22 h). The reaction mixture was added to morpholine (44 mg, 0.50 mmol, 1.2 mol equiv) and shaken briefly. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with EtOAc/Et_3N (100:1) to provide the title compound (58 mg, 0.15 mmol, 60%) as a yellow solid: R_f 0.27 EtOAc/Et_3N (100:1); mp 89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (br. s, 1 H), 3.72 - 3.84 (m, 4 H), 3.37 - 3.46 (m, 1 H), 3.17 - 3.26

(m, 1 H), 3.00 - 3.13 (m, 2 H), 2.92 (s, 3 H), 2.86 (s, 3 H), 2.70 - 2.81 (m, 3 H), 2.64 - 2.69 (m, 1 H), 2.60 (dd, *J*=14.7, 1.8 Hz, 1 H), 2.48 - 2.57 (m, 2 H), 2.31 - 2.43 (m, 2 H), 2.07 - 2.16 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (C), 179.4 (C), 176.8 (C), 175.1 (C), 135.9 (C), 125.1 (CH), 66.7 (CH_2), 63.2 (CH), 52.8 (CH_2), 43.4 (CH), 41.0 (CH), 39.1 (2 x CH), 32.9 (CH), 28.8 (CH_2), 25.0 (CH_3), 25.0 (CH_3), 22.5 (CH_2) ppm; IR (KBr disc): ν_{max} = 2952, 2855, 2810, 2762, 1773, 1696 cm^{-1}; MS (70 eV, EI): *m/z* (%): 387 (3) $[M]^+$, 276 (100); HRMS: calc for $C_{20}H_{25}N_3O_5$ $[M]^+$: 387.1794; found 387.1789.

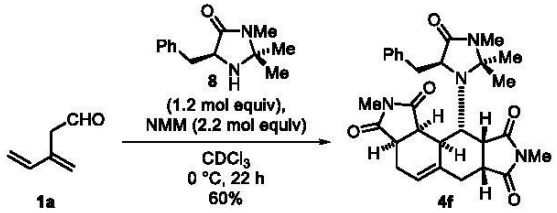
Bis-adduct 7b



To a solution of aldehyde **1a** (40 mg, 0.42 mmol) in $CDCl_3$ (1.5 mL) was added NMM (49 mg, 0.44 mmol, 1.05 mol equiv) and stirred at 25 ºC until complete consumption of aldehyde **1a**, as indicated by ^{1}H NMR spectroscopy, was observed (48 h). β-nitrostyrene (130 mg, 0.88 mmol, 2.1 mol equiv) was added to the reaction mixture. The resulting solution was added to morpholine (44 mg, 0.50 mmol, 1.2 mol equiv) and shaken briefly. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with petrol/Et_2O/Et_3N (90:10:1) to provide the title compound (71:29 mixture of diastereomers, 110 mg, 0.15 mmol, 62%) as a pale yellow solid. The mixture was further purified by flash column chromatography on silica gel eluting with petrol/THF/Et_3N (60:40:1) to provide an analytical sample of the major isomer. R_f 0.22 petrol/THF/Et_3N (60:40:1). Recrystallisation from CH_2Cl_2/diethyl ether gave yellow crystals: mp 216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 - 7.36 (m, 3 H), 7.13 (d, *J*=8.1 Hz, 2 H), 5.73 (br. s, 1 H), 5.12 (t, *J*=10.6 Hz, 1 H), 3.88 - 4.05 (m, 1 H), 3.65 - 3.75 (m, 5 H), 2.93 (s, 3 H), 2.89 - 3.02 (m, 2 H), 2.71 - 2.84 (m, 3 H), 2.50 - 2.62 (m, 2 H), 2.18 - 2.29 (m, 1 H), 2.00 - 2.13 (m, 2 H), 1.28 - 1.44 ppm (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6 (C), 177.8 (C), 139.6 (C), 136.3 (C), 129.0 (CH), 128.1 (CH), 128.0 (CH), 118.3 (CH), 84.3

(CH), 67.2 (CH_2), 65.8 (CH), 48.8 (CH_2), 47.4 (CH), 41.8 (CH), 40.0 (CH), 39.6 (CH), 35.3 (CH_2), 26.2 (CH_3), 24.9 (CH_3) ppm; IR (KBr disc): ν_{max} = 2953, 2854, 1775, 1705 cm^{-1}; MS (70 eV, EI): *m/z* (%): 426 (1) $[M]^+$, 379 (9), 276 (100), 165 (15); HRMS: calc for $C_{23}H_{27}N_3O_5$ $[M]^+$: 425.1951; found 425.1954. The structure and stereochemistry of bis-adduct **7b** were confirmed through single crystal X-ray analysis.

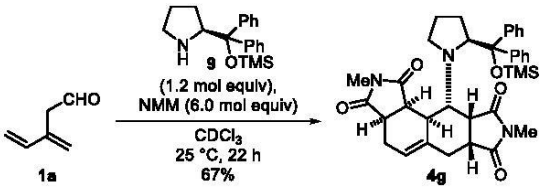
Bis-adduct 4f



To a solution of aldehyde **1a** (40 mg, 0.42 mmol) in $CDCl_3$ (2 mL) was added NMM (100 mg, 0.92 mmol, 2.2 mol equiv). The resulting solution was added to amine **8** (110 mg, 0.50 mmol, 1.2 mol equiv). The reaction mixture was stirred at 0 ºC for 22 h then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (30:70:1 then 0:100:1) provided the title compound (73:27 mixture of diastereomers, 130 mg, 0.25 mmol, 60%). R_f 0.15 EtOAc/Et_3N (100:1). Further purification by preparative HPLC (Waters Xbridge C18 5 µm column, 150 mm x 19 mm, 50:50:0.1 MeOH:H_2O:TFA) provided an analytical sample of the major diastereomer as a white powder. Recrystallisation from CH_2Cl_2/hexane gave colourless crystals: mp 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (br. s, 4 H), 7.14 - 7.22 (m, 1 H), 5.51 (br. s, 1 H), 5.13 (t, *J*=5.3 Hz, 1 H), 4.43 (d, *J*=12.9 Hz, 1 H), 3.24 - 3.43 (m, 2 H), 3.13 - 3.20 (m, 2 H), 2.92 (s, 3 H), 2.89 (s, 3 H), 2.77 (s, 3 H), 2.64 (dd, *J*=8.1, 4.0 Hz, 1 H), 2.33 - 2.51 (m, 4 H), 2.07 (d, *J*=11.7 Hz, 1 H), 1.73 - 1.85 (m, 1 H), 1.52 (s, 3 H), 1.40 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (C), 178.7 (C), 178.7 (C), 177.0 (C), 173.1 (C), 139.4 (C), 137.7 (C), 129.6 (CH), 128.3 (CH), 126.5 (CH), 124.0 (CH), 80.6 (C), 61.8 (CH), 52.3 (CH), 46.7 (CH), 41.8 (CH), 41.0 (2 x CH), 40.0 (CH), 39.7 (CH_2), 30.0 (CH_2), 28.1 (CH_3), 26.1 (CH_2), 25.8 (CH_3), 25.1 (CH_3), 24.7 (CH_3), 23.1 (CH_3) ppm; IR (KBr disc): ν_{max} = 3057, 3027, 2946, 2854, 1771, 1694 cm^{-1}; MS (ESI): *m/z* (%): 541 (100) $[M+Na]^+$; HRMS (ESI): calc for $C_{29}H_{34}N_4O_5Na$

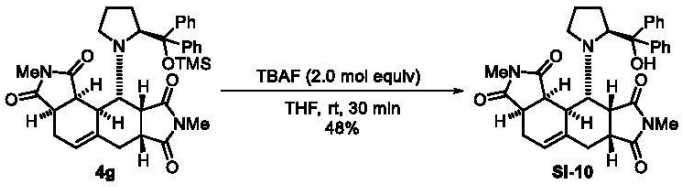
$[M+Na]^+$: 541.2427; found 541.2429. The structure and stereochemistry of bis-adduct **4f** were confirmed through single crystal X-ray analysis.

Bis-adduct 4g



To a solution of aldehyde **1a** (40 mg, 0.42 mmol) in $CDCl_3$ (2 mL) was added NMM (277 mg, 2.49 mmol, 6.0 mol equiv). The resulting solution was added to amine **9** (162 mg, 0.50 mmol, 1.2 mol equiv). The reaction mixture was stirred at 25 ºC for 22 h then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (90:10:1 then 80:20:1) provided the *title compound* (174 mg, 0.278 mmol, 67%) as a pale yellow powder: R_f 0.15 petrol/EtOAc/Et_3N (80:20:1); mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 - 7.70 (m, 4 H), 7.29 - 7.35 (m, 3 H), 7.20 (d, *J*=7.0 Hz, 1 H), 7.15 (t, *J*=7.8 Hz, 2 H), 5.51 - 5.57 (m, 1 H), 4.68 - 4.77 (m, 1 H), 4.03 - 4.14 (m, 1 H), 3.13 (dd, *J*=8.0, 2.9 Hz, 2 H), 3.01 - 3.09 (m, 1 H), 2.96 (s, 3 H), 2.94 - 3.00 (m, 1 H), 2.93 (s, 3 H), 2.56 - 2.64 (m, 1 H), 2.46 - 2.55 (m, 1 H), 2.37 - 2.45 (m, 1 H), 2.33 (s, 2 H), 2.23 - 2.29 (m, 1 H), 2.15 - 2.23 (m, 1 H), 2.04 - 2.15 (m, 1 H), 1.76 - 1.86 (m, 1 H), 1.24 - 1.35 (m, 1 H), 0.37 - 0.52 (m, 1 H), -0.21 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (2 x C), 179.7 (C), 177.6 (C), 143.9 (C), 143.3 (C), 139.1 (C), 130.0 (CH), 129.8 (CH), 127.6 (2 x CH), 126.7 (CH), 126.2 (CH), 120.7 (CH), 66.5 (CH), 54.8 (CH), 48.1 (CH_2), 42.9 (CH), 40.7 (CH), 40.5 (CH), 38.7 (CH), 37.3 (C), 29.3 (CH_2), 28.6 (CH_2), 26.1 (CH_2), 25.0 (CH_3), 24.9 (CH_3), 22.9 (CH_2), 1.8 (CH_3) ppm; IR (KBr disc): ν_{max} = 3056, 2951, 1773, 1700 cm^{-1}; MS (ESI): *m*/*z* (%): 626 (100) $[M+H]^+$; HRMS (ESI): calc for $C_{36}H_{44}N_3O_5Si$ $[M+H]^+$: 626.3050; found 626.3052.

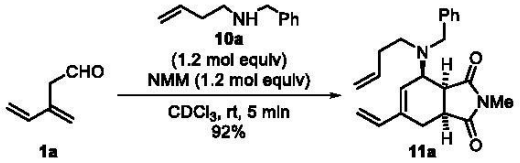
Bis-adduct SI-10



To a solution of bis-adduct **4g** (50 mg, 0.080 mmol) in THF (1.0 mL) was added TBAF (0.16 mL, 0.16 mmol of a 1.0 M THF solution, 2 mol equiv). The resulting solution was stirred at rt until complete consumption of bis-adduct **4g** as indicated by TLC (30 min). The reaction mixture was cooled to 0 ºC and added to a mixture of Et_2O and saturated aqueous $NaHCO_3$ (1:1, 10 mL). The aqueous layer was extracted with Et_2O (3x5 mL) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (80:20:1 then 50:50:1) provided the title compound (21 mg, 0.038 mmol, 48%) as a yellow solid. R_f 0.30 petrol/EtOAc/Et_3N (50:50:1). Recrystallisation from methanol/CH_2Cl_2 gave yellow crystals: mp 264 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J*=7.4 Hz, 2 H), 7.67 (d, *J*=7.4 Hz, 2 H), 7.23 - 7.30 (m, 4 H), 7.14 (t, *J*=7.4 Hz, 2 H), 5.53 (br. s, 1 H), 5.48 (br. s., 1 H), 4.44 (t, *J*=7.2 Hz, 1 H), 3.52 - 3.62 (m, 2 H), 3.43 (br. s., 1 H), 3.34 (dd, *J*=9.2, 4.1 Hz, 1 H), 3.07 (t, *J*=7.8 Hz, 1 H), 2.99 (s, 3 H), 2.95 - 3.03 (m, 1 H), 2.86 (s, 3 H), 2.62 (dd, *J*=15.5, 7.2 Hz, 1 H), 2.18 - 2.26 (m, 2 H), 2.14 (d, *J*=14.9 Hz, 1 H), 1.92 - 2.02 (m, 2 H), 1.69 - 1.91 (m, 2 H), 1.54 ppm (br. s., 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4 (C), 179.4 (C), 178.9 (C), 178.1 (C), 148.5 (C), 147.5 (C), 136.8 (C), 127.9 (2 x CH), 126.5 (CH), 126.2 (CH), 126.0 (CH), 125.4 (CH), 123.0 (CH), 76.5 (C), 66.9 (CH), 52.6 (CH), 47.7 (CH2), 41.2 (CH), 40.5 (CH), 40.1 (CH), 39.1 (CH), 38.4 (CH), 29.9 (CH_2), 28.5 (CH_2), 25.2 (CH_3), 24.8 (CH_3 and CH_2), 23.0 (CH_2) ppm; IR (KBr disc): ν_{max} = 3058, 2977, 2950, 2847, 1772, 1693 cm^{-1}; MS (ESI): *m/z* (%): 576 (15) $[M+Na]^+$; HRMS (ESI): calc for $C_{33}H_{35}N_3O_5Na$ $[M+Na]^+$: 576.2474; found 576.2475. The structure and stereochemistry of bis-adduct **SI-10** were confirmed through single crystal X-ray analysis.

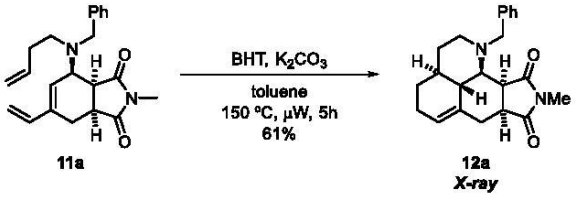
Synthesis of tricycles 12a – 12g

Mono-adduct 11a



Prepared using general procedure D with aldehyde **1a** (36 mg, 0.37 mmol), NMM (50 mg, 0.45 mmol, 1.2 mol equiv) and amine **10a** (72 mg, 0.45 mmol, 1.2 mol equiv) in $CDCl_3$ (2.0 mL). Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (80:20:1) provided the *title compound* (120 mg, 0.34 mmol, 92%) as a yellow oil: R_f 0.22 petrol/EtOAc/Et_3N (80:20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J=7.3 Hz, 2 H), 7.31 (t, J=7.3 Hz, 2 H), 7.25 (d, obs, 1 H), 6.32 (dd, J=17.5, 11.0 Hz, 1 H), 5.88 (br. s., 1 H), 5.69 - 5.83 (m, 1 H), 5.32 (d, J=17.3 Hz, 1 H), 4.94 - 5.11 (m, 3 H), 3.95 (d, J=15.3 Hz, 1 H), 3.86 (d, J=15.3 Hz, 1 H), 3.78 - 3.83 (br. s., 1 H), 3.39 (t, J=8.2 Hz, 1 H), 3.10 - 3.18 (m, 1 H), 3.00 - 3.07 (m, 1 H), 2.92 (s, 3 H), 2.68 - 2.83 (m, 2 H), 2.22 (q, J=7.2 Hz, 2 H), 2.08 (dd, J=16.0, 7.2 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C), 177.8 (C), 140.3 (C), 137.7 (C), 136.8 (CH), 136.6 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 115.8 (CH_2), 113.5 (CH_2), 57.9 (CH), 55.7 (CH_2), 51.4 (CH_2), 42.3 (CH), 39.7 (CH), 33.3 (CH_2), 25.1 (CH_3), 21.5 (CH_2) ppm; IR (thin film): ν_{max} = 3062, 3027, 3002, 2974, 2941, 2848 cm^{-1}; MS (70 eV, EI): m/z (%): 350 (23) $[M]^+$, 309 (61), 190 (52), 91 (100); HRMS: calc for $C_{22}H_{26}N_2O_2$ $[M]^+$:350.1994; found 350.1996.

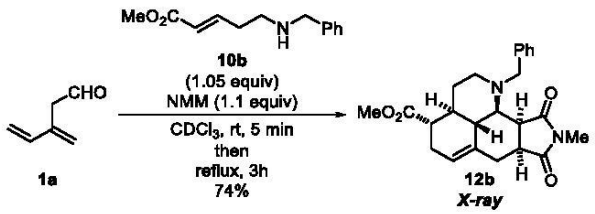
Tricycle 12a



To a solution of mono-adduct **11a** (40 mg, 0.11 mmol) in toluene (2.3 mL) was added BHT (7 mg, 0.034 mmol, 0.30 mol equiv) and K_2CO_3 (18 mg, 0.13 mmol, 1.2 mol equiv). The resulting mixture was heated in a microwave reactor at 150 °C for 5 hours, filtered through a

plug of cotton wool and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) provided the *title compound* (14 mg, 0.069 mmol, 61%) as a pale yellow solid. R_f 0.37 petrol/EtOAc/Et_3N (70:30:1). Recrystallisation from CH_2Cl_2/diethyl ether gave yellow crystals: mp 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J*=7.3 Hz, 2 H), 7.34 (t, *J*=7.3 Hz, 2 H), 7.26 (t, *J*=7.3 Hz, 0 H), 5.42 - 5.48 (m, 1 H), 4.71 (d, *J*=12.0 Hz, 1 H), 3.76 (dd, *J*=9.4, 6.5 Hz, 1 H), 3.08 - 3.13 (m, 1 H), 3.06 (d, *J*=12.0 Hz, 4 H), 3.06 (s, 4 H), 2.84 - 2.91 (m, 1 H), 2.76 (d, *J*=16.1 Hz, 1 H), 2.52 (dd, *J*=12.0, 6.5 Hz, 2 H), 1.96 - 2.19 (m, 3 H), 1.85 (t, *J*=12.0 Hz, 1 H), 1.65 (dd, *J*=12.3, 7.0 Hz, 1 H), 1.50 - 1.61 (m, 1 H), 1.37 - 1.46 (m, 1 H), 1.08 - 1.34 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (C), 176.3 (C), 138.8 (C), 132.4 (C), 129.8 (CH), 128.3 (CH), 127.0 (CH), 123.6 (CH_2), 61.1 (CH), 58.7 (CH_2), 52.1 (CH_2), 41.7 (CH), 40.6 (CH), 39.8 (CH), 38.0 (CH), 31.1 (CH_2), 29.6 (CH_2), 26.5 (CH_2), 25.1 (CH_3), 25.0 (CH_2) ppm; IR (KBr disc): ν_{max} = 2925, 2848, 2813, 1690 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 350 (81) $[M]^+$, 239 (60), 91 (100); HRMS: calc for $C_{22}H_{26}N_2O_2$ $[M]^+$: 350.1994; found 350.1994. The structure and stereochemistry of tricycle **12a** were confirmed through single crystal X-ray analysis.

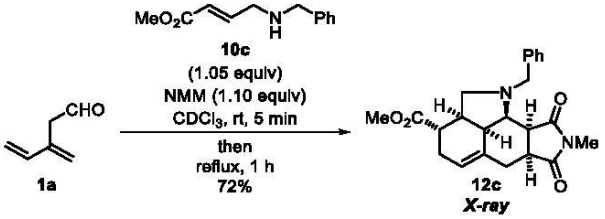
Tricycle 12b



To a solution of aldehyde **1a** (28 mg, 0.30 mmol) in $CDCl_3$ (3 mL) was added NMM (36 mg, 0.32 mmol, 1.1 mol equiv). The resulting solution was added to amine **10b** (68 mg, 0.31 mmol, 1.05 mol equiv) and stirred briefly before being heated to reflux for 3 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with CH_2Cl_2/EtOAc/Et_3N (95:5:1) to provide the title compound (90 mg, 0.22 mmol, 74%) as a beige solid. R_f 0.25 CH_2Cl_2/EtOAc/Et_3N (95:5:1). Recrystallisation from CH_2Cl_2/ethyl acetate gave colourless crystals: mp 210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=7.0 Hz, 2 H), 7.33 (t, *J*=7.0 Hz, 2 H), 7.25 (t, *J*=7.0 Hz, 1 H),

5.44 - 5.51 (m, 1 H), 4.69 (d, *J*=12.0 Hz, 1 H), 3.77 (dd, *J*=9.7, 6.5 Hz, 1 H), 3.61 (s, 3 H), 3.07 - 3.14 (m, 2 H), 3.07 (d, *J*=12.0 Hz, 1 H), 3.05 (s, 3 H), 2.86 (dt, *J*=11.7, 3.2 Hz, 1 H), 2.77 (d, *J*=15.8 Hz, 1 H), 2.55 (dd, *J*=11.9, 6.3 Hz, 2 H), 2.35 - 2.46 (m, 1 H), 2.19 - 2.35 (m, 1 H), 1.83 (td, *J*=12.0, 2.2 Hz, 1 H), 1.58 - 1.71 (m, 2 H), 1.37 - 1.53 (m, 2 H), 1.08 - 1.27 (m, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5 (C), 175.9 (C), 175.7 (C), 138.5 (C), 132.3 (C), 129.7 (CH), 128.3 (CH), 127.1 (CH), 121.9 (CH_2), 60.7 (CH), 58.4 (CH_2), 51.6 (CH_3), 51.4 (CH_2), 46.0 (CH), 40.5 (2 x CH), 39.7 (CH), 39.6 (CH), 28.6 (CH_2), 28.5 (CH_2), 26.5 (CH_2), 25.2 (CH_3) ppm; IR (KBr disc): ν_{max} = 2956, 2928, 2795, 1729, 1697 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 408 (60) $[M]^+$, 297 (41), 91 (100); HRMS: calc for $C_{24}H_{28}N_2O$ $[M]^+$: 408.2049; found 408.2046. The structure and stereochemistry of tricycle **12b** were confirmed through single crystal X-ray analysis.

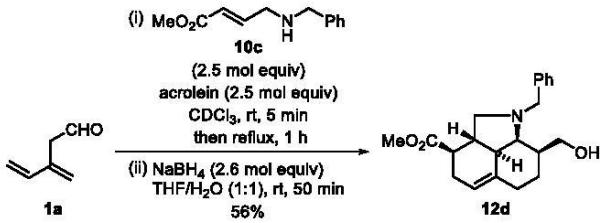
Tricycle 12c



To a solution of aldehyde **1a** (20 mg, 0.21 mmol) in $CDCl_3$ (1.0 mL) was added NMM (26 mg, 0.23 mmol, 1.1 mol equiv). The resulting solution was added to amine **10c** (46 mg, 0.22 mmol, 1.05 mol equiv) and stirred briefly before being diluted with $CDCl_3$ (1.0 mL) and heated to reflux for 1 h. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with petrol/EtOAc/Et_3N (70:30:1) to provide the title compound (60 mg, 0.15 mmol, 72%) as a yellow solid. R_f 0.20 petrol/EtOAc/Et_3N (70:30:1). Recrystallisation from methanol gave yellow crystals: mp 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J*=7.3 Hz, 2 H), 7.28 (t, *J*=7.5 Hz, 2 H), 7.20 (t, *J*=7.3 Hz, 1 H), 5.51 (br. s., 1 H), 4.15 (d, *J*=13.5 Hz, 1 H), 3.62 (d, *J*=1.0 Hz, 1 H, overlapping), 3.60 (s, 3 H), 3.44 (t, *J*=8.2 Hz, 1 H), 2.97 - 3.12 (m, 2 H), 2.79 - 2.96 (m, 2 H, overlapping), 2.87 (s, 3 H), 2.46 - 2.69 (m, 3 H), 2.25 - 2.41 (m, 2 H), 1.98 - 2.22 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4 (C), 177.3 (C), 175.9 (C), 139.2 (C), 132.0 (C), 128.5 (CH), 128.3 (CH), 126.9 (CH), 122.0 (CH), 62.3 (CH), 57.6 (CH_2), 56.2 (CH_2), 51.7 (CH_3), 42.5 (CH), 41.3

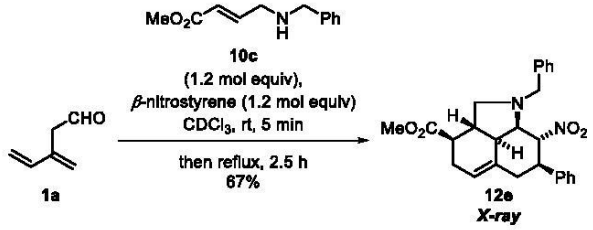
(CH), 41.2 (CH), 41.0 (CH), 37.4 (CH), 32.9 (CH_2), 26.7 (CH_2), 24.6 (CH_3) ppm; IR (KBr disc): ν_{max} = 2955, 2936, 2798, 2773, 1728, 1695 cm^{-1}; MS (70 eV, EI): *m/z* (%): 394 (84) $[M]^+$, 303 (31), 283 (40), 91 (100); HRMS: calc for $C_{23}H_{26}N_2O_4$ $[M]^+$: 394.1893; found 394.1894. The structure and stereochemistry of tricycle **12c** were confirmed through single crystal X-ray analysis.

Tricycle 12d



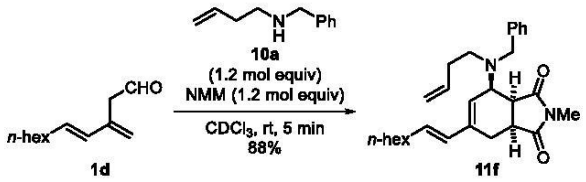
To a solution of aldehyde **1a** (22 mg, 0.23 mmol) in $CDCl_3$ (1.2 mL) was added acrolein (41 μL, 0.56 mmol, 2.5 mol equiv). The resulting solution was then added to amine **10c** (123 mg, 0.56 mmol, 2.5 mol equiv). The solution was stirred briefly before being heated to reflux for 1 h. The reaction mixture was then concentrated under reduced pressure and redissolved in THF/H_2O (1:1, 2mL). Sodium borohydride (22 mg, 0.58 mmol, 2.6 mol equiv) was added and the resulting mixture was stirred at rt for 50 min before being poured into CH_2Cl_2 and H_2O (1:1, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x10 mL) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with petrol/EtOAc (60:40 then 40:60) provided the title compound (43 mg, 0.13 mmol, 56%) as a yellow oil: R_f 0.32 petrol/EtOAc (40:60); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 - 7.34 (m, 5 H), 5.24 (br. s., 1 H), 4.05 (d, *J*=12.3 Hz, 1 H), 3.83 (t, *J*=11.4 Hz, 1 H), 3.61 (s, 3 H), 3.51 (d, *J*=12.3 Hz, 1 H), 3.46 - 3.52 (m, 1 H), 3.12 (dd, *J*=11.0, 5.1 Hz, 1 H), 2.99 - 3.04 (m, 1 H), 2.56 - 2.65 (m, 1 H), 2.39 - 2.51 (m, 3 H), 2.05 - 2.31 (m, 5 H), 1.51 - 1.59 (m, 2 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9 (C), 137.9 (C), 136.3 (C), 129.3 (CH), 128.5 (CH), 127.4 (CH), 118.6 (CH), 65.9 (CH_2), 65.6 (CH), 60.1 (CH_2), 55.8 (CH_2), 51.7 (CH_3), 45.5 (CH), 43.8 (CH), 43.8 (CH), 35.3 (CH), 29.7 (CH_2), 23.7 (CH_2), 23.7 (CH_2) ppm; IR (KBr disc): ν_{max} = 3246, 3086, 3061, 3028, 2923, 2847 cm^{-1}; MS (70 eV, EI): *m/z* (%): 341 (100), 282 (30), 91 (100); HRMS: calc for $C_{21}H_{27}NO_3$ $[M]^+$: 341.1991; found 341.1986.

Tricycle 12e



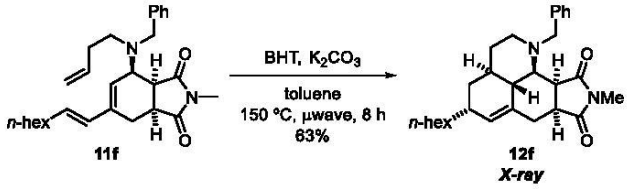
To a solution of aldehyde **1a** (20 mg, 0.21 mmol) in $CDCl_3$ (1.2 mL) was added β-nitrostyrene (37 mg, 0.25 mmol, 1.2 mol equiv). The resulting solution was then added to amine **10c** (55 mg, 0.25 mmol, 1.2 mol equiv). The solution was stirred briefly before being heated to reflux for 2.5 h. The reaction mixture was then concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with petrol/EtOAc (90:10) to provide the title compound (93:7 mixture of two diastereomers, 60 mg, 0.14 mmol, 67%) as a pale yellow solid. R_f 0.23 petrol/EtOAc (90:10). Recrystallisation from methanol/CH_2Cl_2 gave yellow needles: mp 122 - 124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 – 7.33 (m, 10 H), 5.49 (t, J=3.1 Hz, 1 H), 4.50 (t, J=11.0 Hz, 1 H), 3.90 (d, J=12.9 Hz, 1 H), 3.73 (t, J=10.2 Hz, 1 H), 3.64 (s, 3 H), 3.61 (d, J=12.9 Hz, 1 H), 3.54 (td, J=11.2, 3.5 Hz, 1 H), 2.98 - 3.08 (m, 2 H), 2.62 - 2.74 (m, 2 H), 2.50 - 2.57 (m, 2 H), 2.42 (dd, J=15.5, 3.3 Hz, 1 H), 2.17 - 2.36 (m, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8 (C), 142.6 (C), 138.7 (C), 134.2 (C), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 121.1 (CH), 96.1 (CH), 64.0 (CH), 60.8 (CH_2), 56.8 (CH_2), 51.9 (CH_3), 45.7 (CH), 44.1 (CH), 43.1 (CH), 42.6 (CH), 36.7 (CH_2), 29.9 (CH_2) ppm; IR (KBr disc): ν_{max} = 3086, 3058, 3031, 2954, 2914, 2847, 2813, 1725, 1542 cm^{-1}; MS (70 eV, EI): m/z (%): 432 (10) $[M]^+$, 386 (8), 283 (100), 91 (58); HRMS: calc for $C_{26}H_{28}N_2O_4$ $[M]^+$: 432.2049; found 432.2053. The structure and stereochemistry of tricycle **12e** were confirmed through single crystal X-ray analysis.

Mono-adduct 11f



Prepared using general procedure C with aldehyde **1d** (50 mg, 0.28 mmol), NMM (37 mg, 0.33 mmol, 1.2 mol equiv) and amine **10a** (54 mg, 0.33 mmol, 1.2 mol equiv) in $CDCl_3$ (1 mL). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (80:20:1 then 70:30:1) provided the *title compound* (106 mg, 0.244 mmol, 88%) as a yellow oil: R_f 0.26 hex/ Et_2O (60:40); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 7.3 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 6.00 (d, J = 15.7 Hz, 1H), 5.83 – 5.70 (m, 3H), 5.04 – 4.94 (m, 2H), 3.93 (d, J = 15.0 Hz, 1H), 3.85 (d, J = 15.0 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.36 (dd, J = 9.0, 7.5 Hz, 1H), 3.11 (ddd, J = 9.3, 7.5, 2.5 Hz, 1H), 2.99 (dd, J = 15.7, 2.6 Hz, 1H), 2.91 (s, 3H), 2.83 – 2.68 (m, 2H), 2.21 (q, J = 7.3 Hz, 2H), 2.15 – 2.03 (m, 3H), 1.44 – 1.22 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C), 177.9 (C), 140.4 (C), 137.5 (C), 136.6 (CH), 130.8 (CH), 130.2 (CH), 128.3 (CH), 128.1 (CH), 126.8 (CH), 125.6 (CH), 115.7 (CH_2), 57.8 (CH), 55.6 (CH_2), 51.4 (CH_2), 42.3 (CH), 39.7 (CH), 33.2 (CH_2), 32.8 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 25.0 (CH_3), 22.6 (CH_2), 22.2 (CH_2), 14.1 (CH_3) ppm; IR (thin film): ν_{max} = 2926, 2854, 1775, 1704 cm^{-1}; MS (70 eV, EI): *m/z* (%): 434 (25) $[M]^+$, 393 (32), 349 (38), 274 (35); HRMS: calc for $C_{28}H_{38}N_2O_2$ $[M]^+$: 434.2933; found 434.2938.

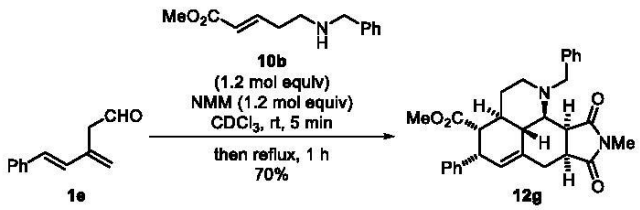
Tricycle 12f



To a solution of mono-adduct **11f** (22.5 mg, 0.052 mmol) in toluene (5 mL) was added BHT (1 crystal) and K_2CO_3 (23 mg, 0.11 mmol, 3 mol equiv). The resulting mixture was heated in

a microwave reactor at 150 ºC for 8 hours, filtered through a plug of cotton wool and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hex/EtOAc/Et_3N (90:10:1) provided the *title compound* (14 mg, 0.324 mmol, 63%) as a pale yellow solid. R_f 0.26 hex/EtOAc (80:20). Recrystallisation from Et_2O/CH_2Cl_2 gave colourless crystals: mp 154 – 156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 5.41 (br. s, 1H), 4.70 (d, J = 12.1 Hz, 1H), 3.75 (dd, J = 9.5, 6.4 Hz, 1H), 3.12 – 3.05 (m, 2H), 3.04 (s, 3H), 2.90 – 2.84 (m, 1H), 2.75 (dd, J = 16.4, 2.4 Hz, 1H), 2.56 (dt, J = 6.1, 3.1 Hz, 1H), 2.50 (dd, J = 12.1, 6.5 Hz, 1H), 2.09 (br. s, 1H), 1.85 (td, J = 11.3, 2.2 Hz, 1H), 1.56 – 1.04 (m, 16H), 0.91 – 0.84 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (C), 176.3 (C), 138.8 (C), 132.0 (C), 129.8 (CH), 128.6 (CH), 128.3 (CH), 127.0 (CH), 61.0 (CH), 58.7 (CH_2), 52.1 (CH_2), 42.3 (CH), 40.6 (CH), 39.9 (CH), 37.0 (CH), 34.7 (CH_2), 34.5 (CH_2), 33.8 (CH), 31.9 (CH_2), 31.1 (CH_2), 29.5 (CH_2), 27.6 (CH_2), 26.6 (CH_2), 25.1 (CH_3), 22.8 (CH_2), 14.2 (CH_3) ppm; IR (ATR): ν_{max} = 2952, 2919, 2855, 1767, 1684 cm^{-1}; MS (70 eV, EI): m/z (%): 434 (37) $[M]^+$, 349 (63), 323 (11), 91 (100); HRMS: calc for $C_{28}H_{38}N_2O_2$ $[M]^+$: 434.2933; found 434.2934. The structure and stereochemistry of tricycle **12f** were confirmed through single crystal X-ray analysis.

Tricycle 12g



To a solution of aldehyde **1e** (12 mg, 0.070 mmol) in $CDCl_3$ (0.5 mL) was added NMM (9 mg, 0.084 mmol, 1.2 mol equiv). The resulting solution was added to amine **10b** (18 mg, 0.084 mmol, 1.2 mol equiv) and stirred briefly before being diluted with $CDCl_3$ (0.5 mL) and heated to reflux for 1 h. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with hex/EtOAc/Et_3N (80:20:1). The impure fractions containing the product were combined, concentrated under reduced pressure and purified by flash chromatography on Et_3N washed silica gel eluting with hex/EtOAc (80:20 then 70:30) to provide the title compound (24 mg, 0.049 mmol, 70%) as a brown wax: R_f 0.43

petrol/EtOAc (60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.4 Hz, 2H), 7.27 (t, J = 7.2 Hz, 2H), 7.23 – 7.10 (m, 5H), 7.00 (d, J = 7.2 Hz, 1H), 5.45 (br. s, 1H), 4.64 (d, J = 12.2 Hz, 1H), 3.77 (dd, J = 9.7, 6.3 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.15 – 3.06 (m, 5H), 3.01 (s, 3H), 2.84 – 2.76 (m, 2H), 2.74 – 2.60 (m, 3H), 1.86 (t, J = 12.1 Hz, 1H), 1.65 – 1.52 (m, 3H), 0.95 (td, J = 12.6, 9.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4 (C), 175.9 (C), 172.2 (C), 141.3 (C), 138.4 (C), 133.3 (C), 129.8 (CH), 129.1 (CH), 128.3 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 125.4 (CH), 60.7 (CH), 58.6 (CH_2), 51.6 (CH), 51.6 (CH_2), 50.9 (CH_3), 43.0 (CH), 40.9 (CH), 40.5 (CH), 39.6 (CH), 34.9 (CH), 28.3 (CH_2), 26.7 (CH_2), 25.2 (CH_3) ppm; IR (ATR): ν_{max} = 2949, 2911, 2797, 1736, 1695 cm^{-1}; MS (70 eV, EI): *m/z* (%): 484 (82) $[M]^+$, 425 (44), 373 (40), 91 (100); HRMS: calc for $C_{30}H_{32}N_2O_4$ $[M]^+$: 484.2362; found 484.2362.

References

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Anisotropic Displacement Ellipsoid Plots for 3c, SI-8, SI-9, 4a – 4c, 7b, 4f, SI-10, 12a – 12c, 12e and 12f

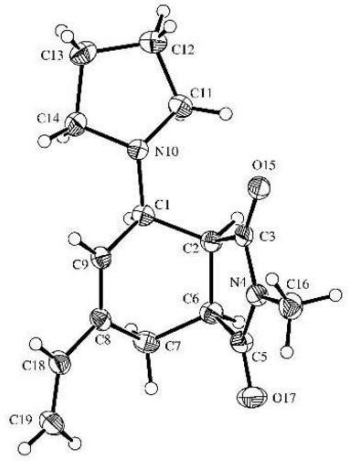


Figure S1. Anisotropic displacement ellipsoid plot of **3c** (CCDC 1429173) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

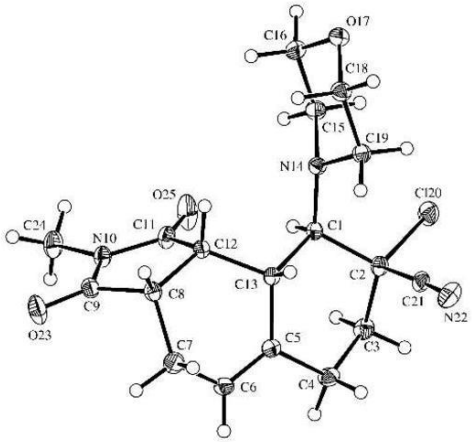


Figure S2. Anisotropic displacement ellipsoid plot of **SI-8** (CCDC 1429172) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii; the minor sites for the disordered H atoms have been omitted.

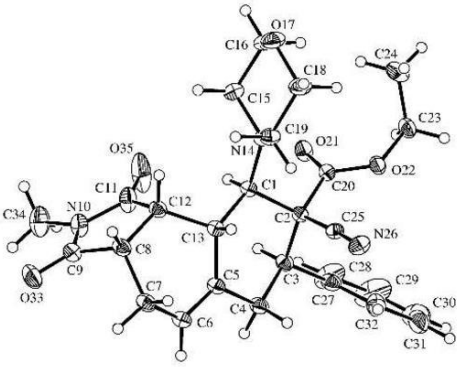


Figure S3. Anisotropic displacement ellipsoid plot of **SI-9** (CCDC 1429171) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

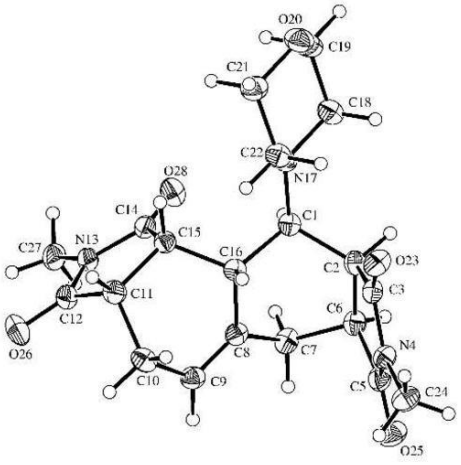


Figure S4a. Anisotropic displacement ellipsoid plot of molecule one of **4a** (CCDC 1429170) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

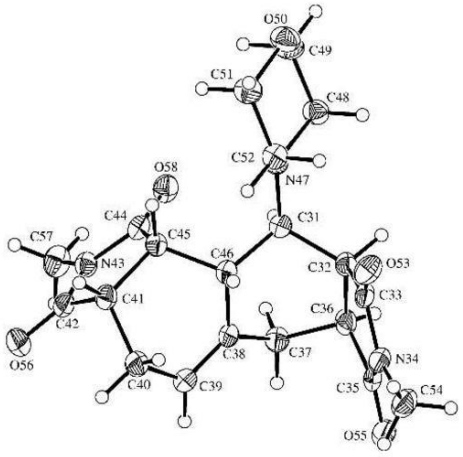


Figure S4b. Anisotropic displacement ellipsoid plot of molecule two of **4a** (CCDC 1429170) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

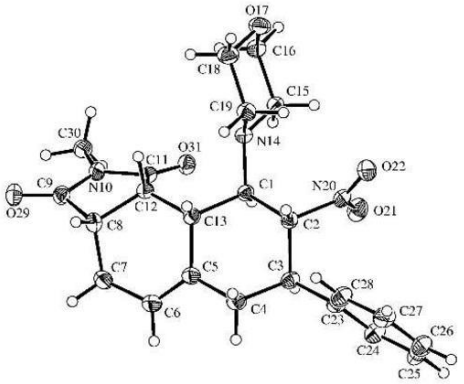


Figure S5. Anisotropic displacement ellipsoid plot of **4b** (CCDC 1429169) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

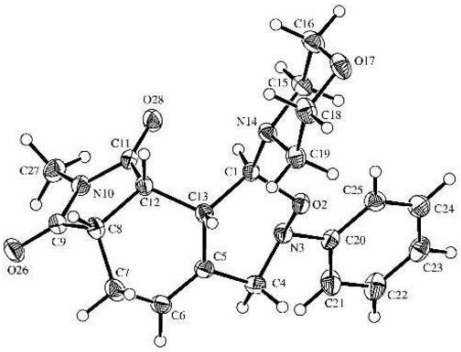


Figure S6. Anisotropic displacement ellipsoid plot of **4c** (CCDC 1429168) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

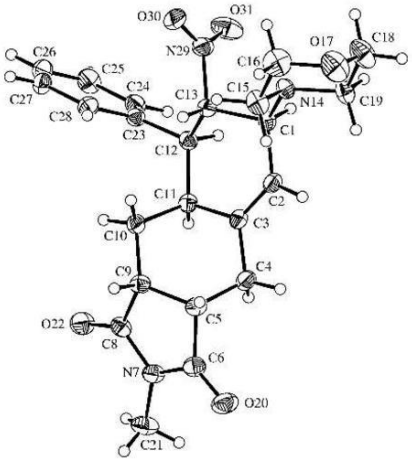


Figure S7. Anisotropic displacement ellipsoid plot of **7b** (CCDC 1429167) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

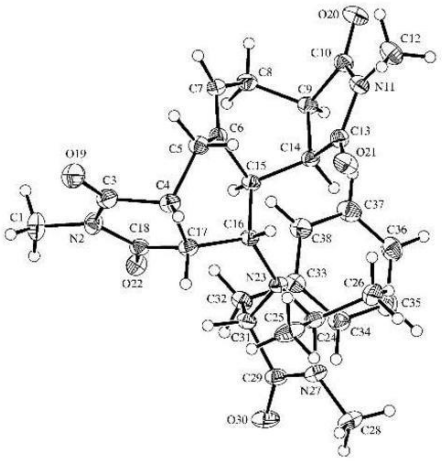


Figure S8. Anisotropic displacement ellipsoid plot of **4f** (CCDC 1429166) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

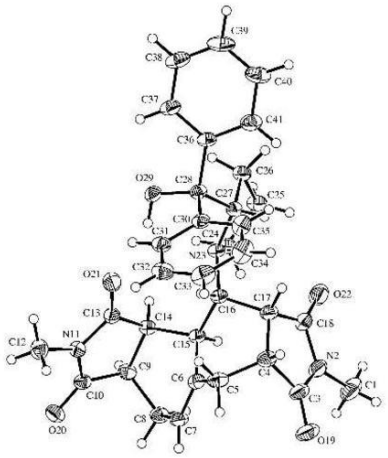


Figure S9a. Anisotropic displacement ellipsoid plot of molecule one of **SI-10** (CCDC 1429165) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

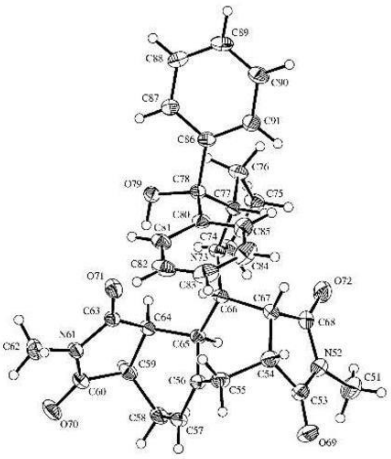


Figure S9b. Anisotropic displacement ellipsoid plot of molecule two of **SI-10** (CCDC 1429165) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

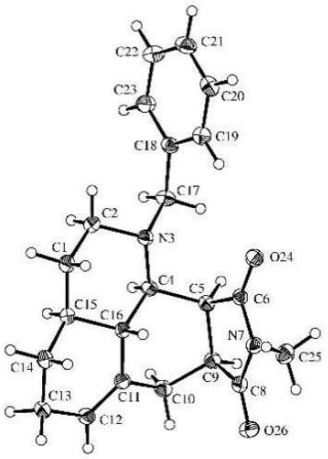


Figure S10. Anisotropic displacement ellipsoid plot of **12a** (CCDC 1429164) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

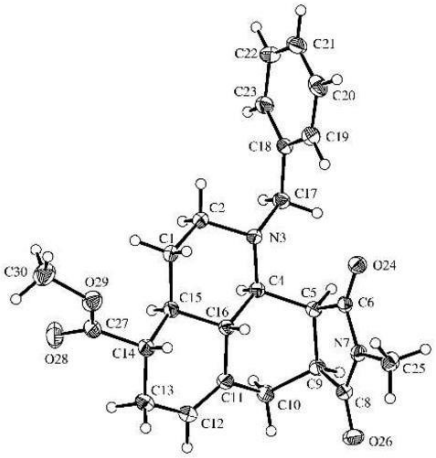


Figure S11. Anisotropic displacement ellipsoid plot of **12b** (CCDC 1429163) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

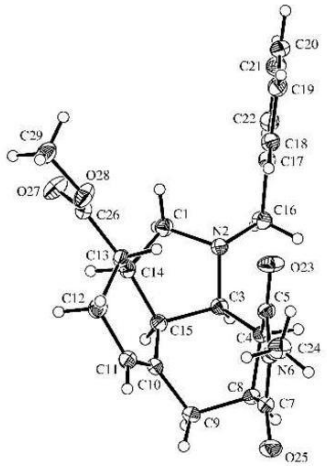


Figure S12. Anisotropic displacement ellipsoid plot of **12c** (CCDC 1429162) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

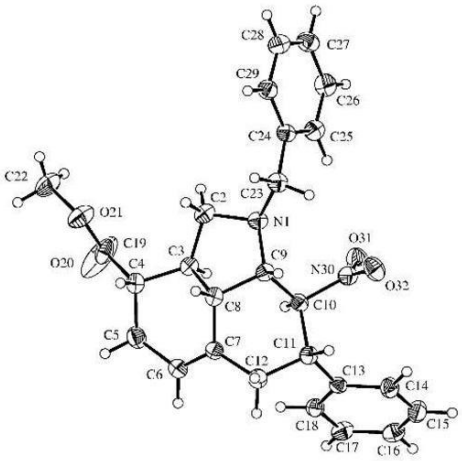


Figure S13. Anisotropic displacement ellipsoid plot of **12e** (CCDC 1429161) with labelling of selected atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

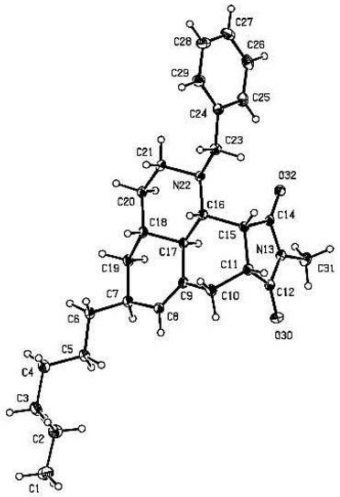


Figure S14. Anisotropic displacement ellipsoid plot of **12f** (CCDC 1429160) with labelling of selected atoms, showing only the major sites of disordered atoms. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Stereochemical assignments by NMR

Mono-adducts 3a – 3g

The stereochemistry of mono-adducts **3a**, **3b**, **3d**, **3e**, **3f** and **3g** was assigned by comparison of ^{1}H NMR spectra with that of **3c**. The stereochemical assignment of **3c** was determined by single crystal X-ray analysis.

Similarities between the ^{1}H NMR spectra of the mono-adducts are highlighted in **Figure S15**.

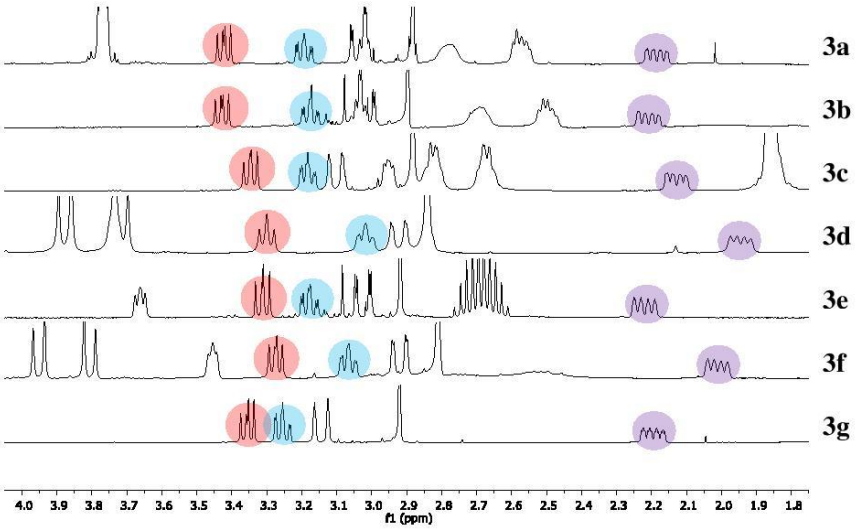
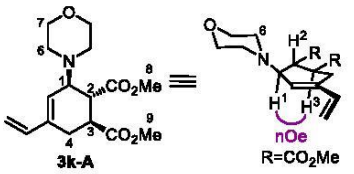


Figure S15. ^{1}H NMR spectra of mono-adducts **3a** – **3g** (400 MHz, $CDCl_3$)

Mono-adduct 3k-A

The stereochemistry of tricycle **3k-A** was assigned by 2D NMR experiments and the coupling constants between H^1, H^2 and H^3. The NOESY spectrum is shown in **Figure S16**.



The large coupling constants between H^1 and H^2 ($J_{1,2}$=10.5 Hz) and H^2 and H^3 ($J_{2,3}$=11.5 Hz) indicate that these protons are in a *trans* relationship.

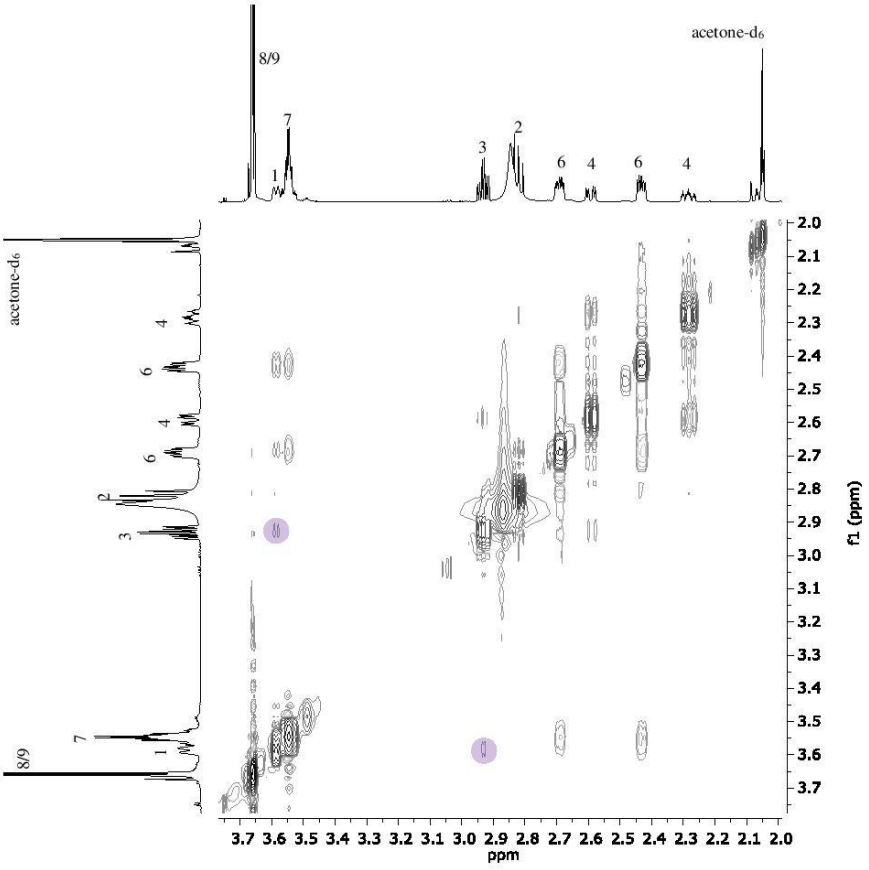


Figure S16. 2D NOESY spectrum of mono-adduct **3k-A** (800 MHz, acetone-d_6)

Bis-adduct 4d

The stereochemistry of bis-adduct **4d** was assigned by comparison of the ^{1}H NMR with that of bis-adduct **4a**.

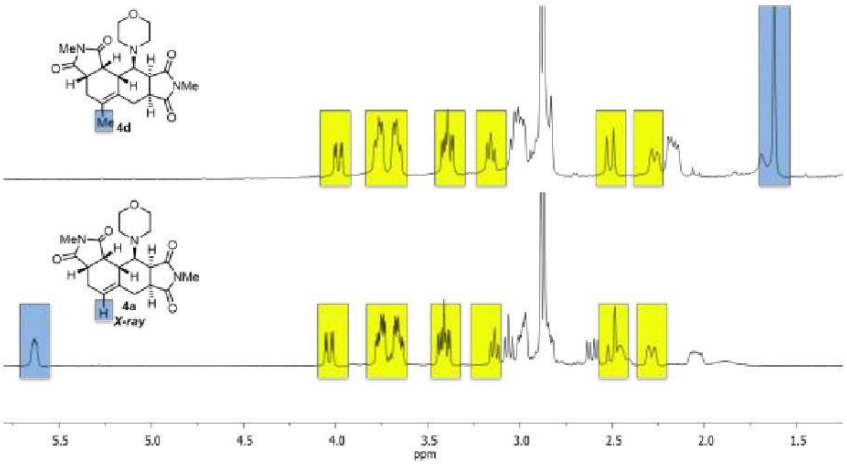


Figure S17. ^{1}H NMR comparison of bis-adducts **4a** and **4d** (400 MHz, $CDCl_3$). Differences are highlighted in blue while similarities are highlighted in yellow.

Bis-adduct 4e

The stereochemistry of bis-adduct **4e** was assigned by comparison of the ^{1}H NMR with that of bis-adduct **4c**.

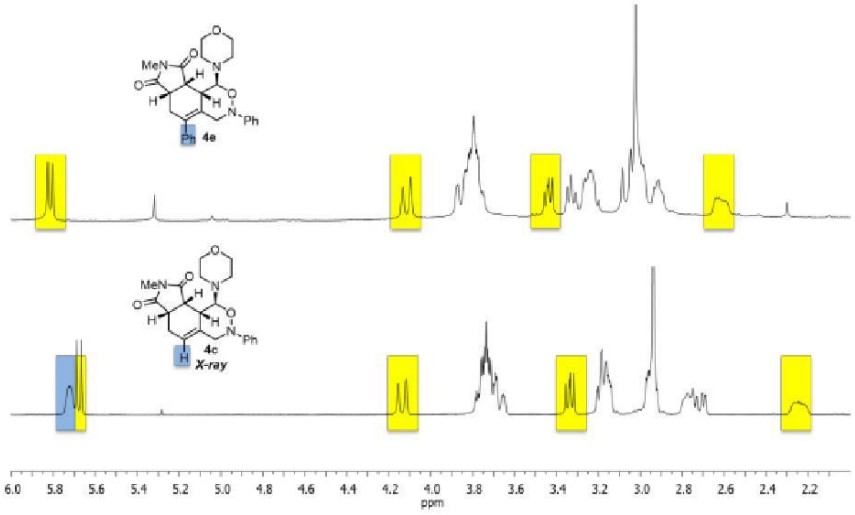


Figure S18. ^{1}H NMR comparison of bis-adducts **4c** and **4e** (400 MHz, $CDCl_3$). Differences are highlighted in blue while similarities are highlighted in yellow.

Tricycle 12d

The stereochemistry of tricycle **12d** was assigned by 2D NMR experiments. The 2D NOESY spectrum is shown in **Figure S19**.

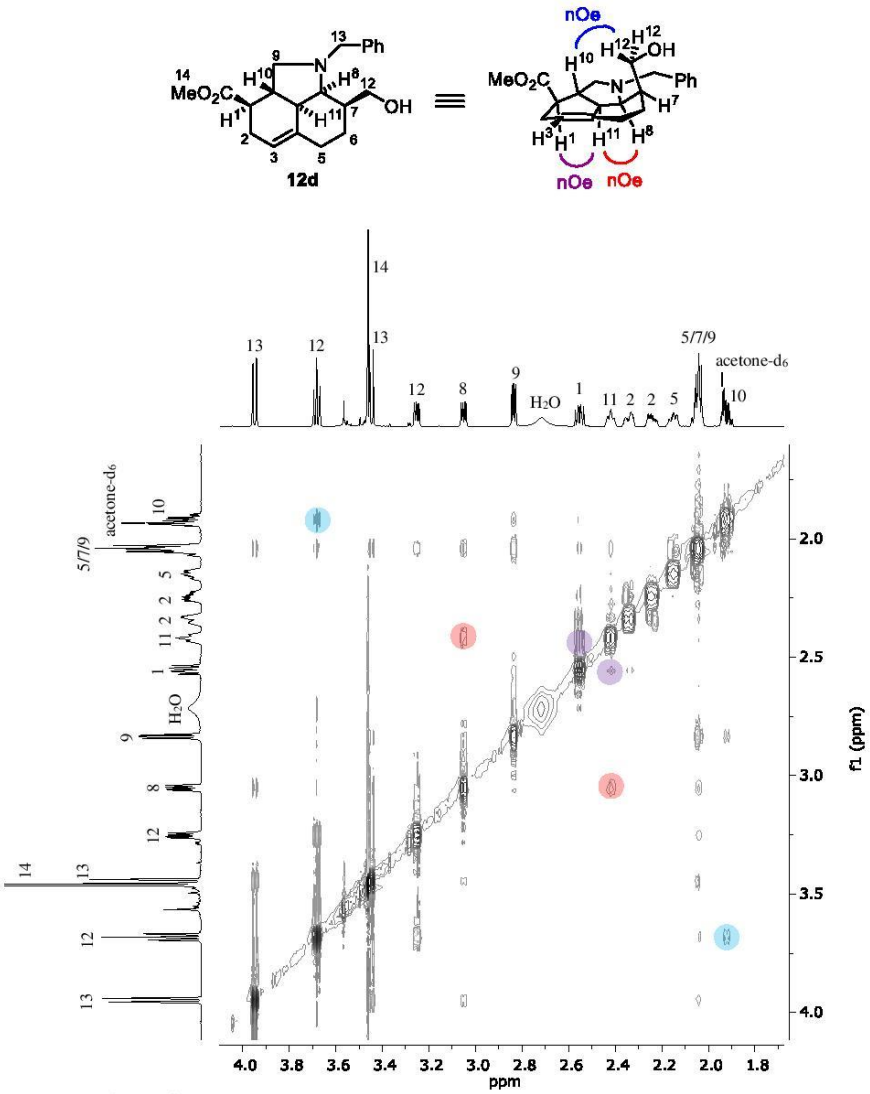


Figure S19. 2D NOESY spectrum of tricycle **12d** (800 MHz, acetone-d_6)

Tricycle 12g

The stereochemistry of tricycle **12g** was assigned by comparison of the ^{1}H NMR with that of tricycle **12b**.

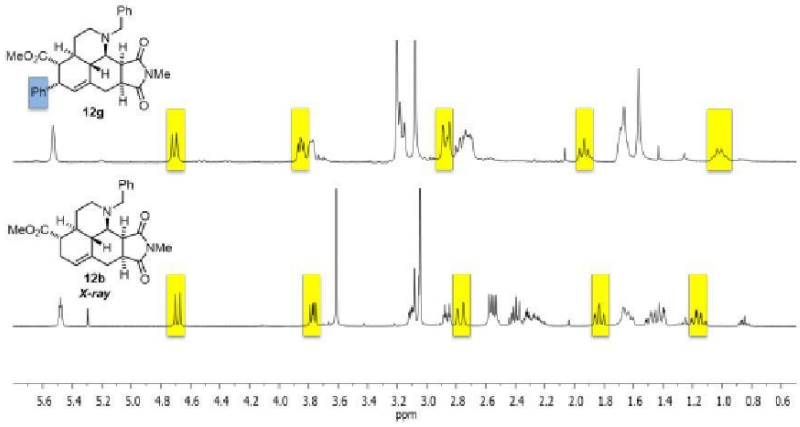
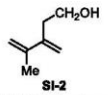
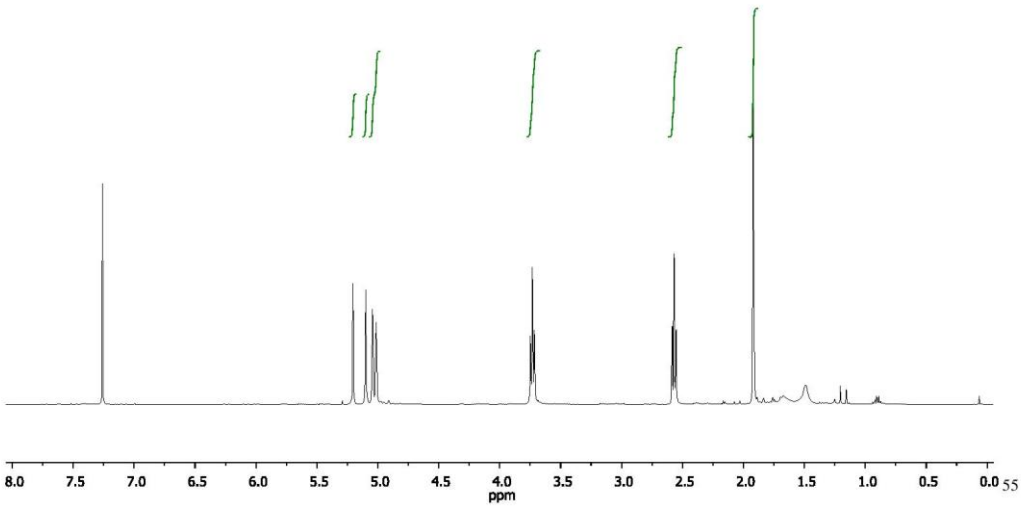


Figure S20. ^{1}H NMR comparison of bis-adducts **12b** and **12g** (400 MHz, $CDCl_3$). Differences are highlighted in blue while similarities are highlighted in yellow.

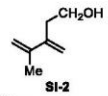


SI-2

^{1}H NMR Spectrum
400 MHz, $CDCl_3$

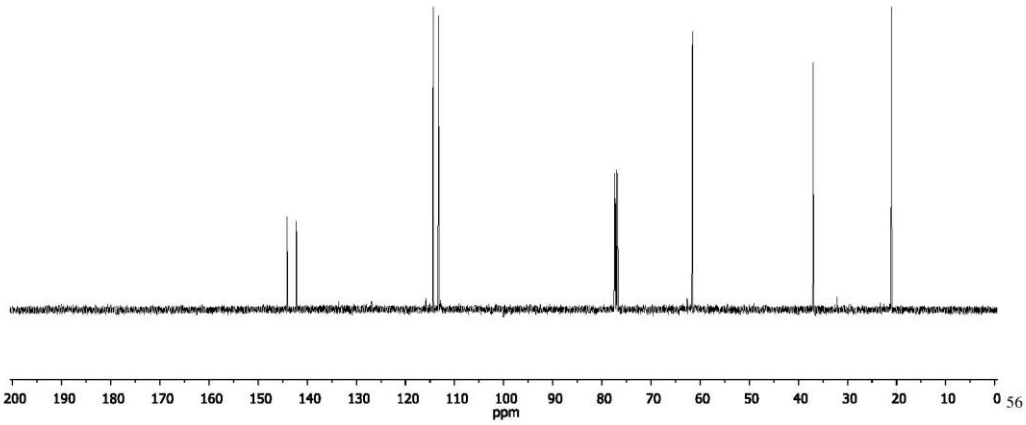


55

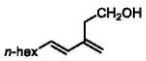


SI-2

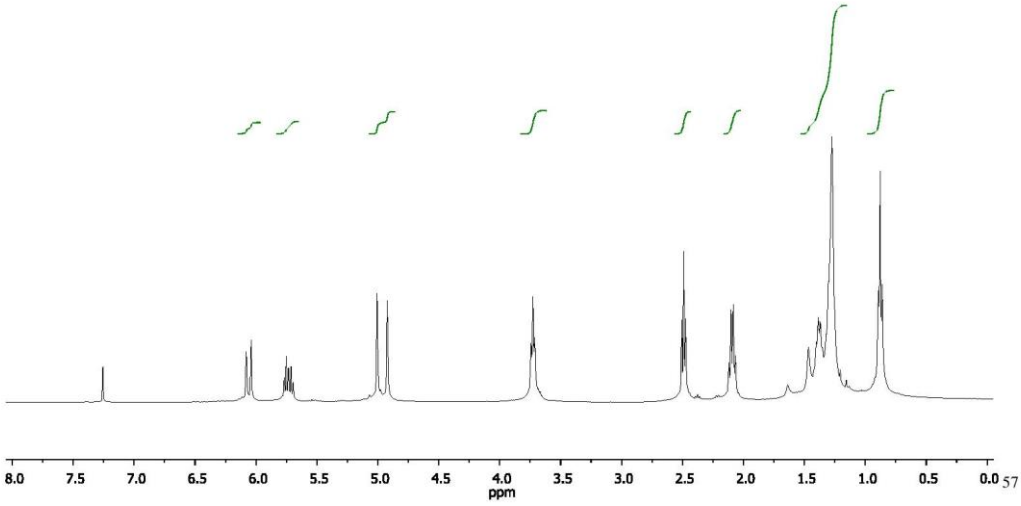
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



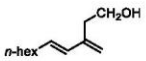
56



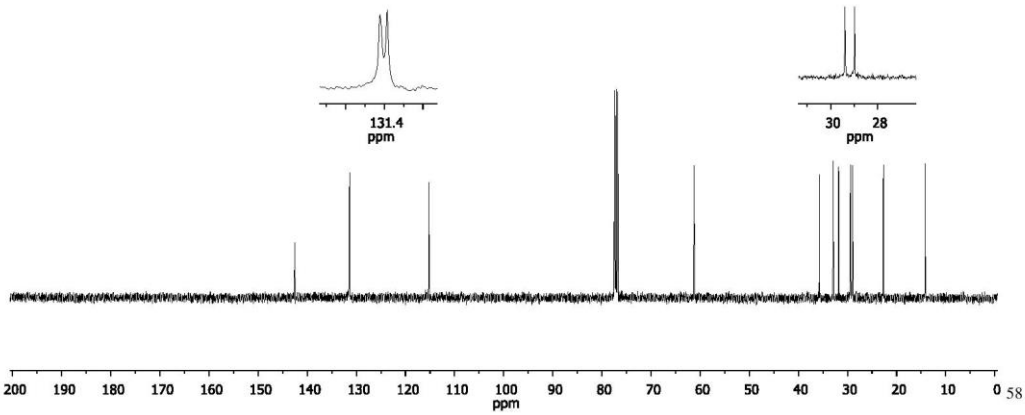
SI-4
^{1}H NMR Spectrum
400 MHz, $CDCl_3$



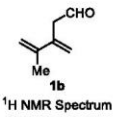
57



SI-4
^{13}C NMR Spectrum
100 MHz, $CDCl_3$

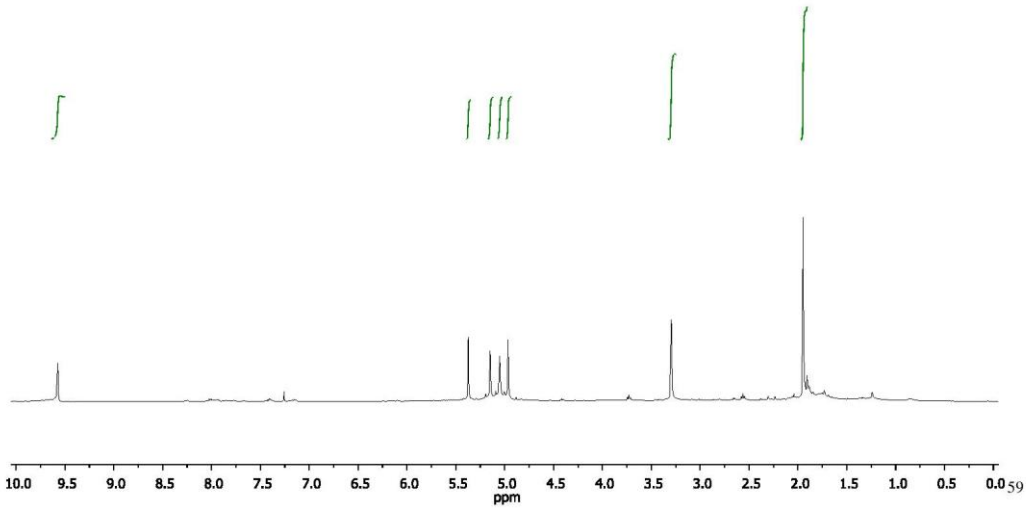


58

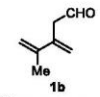


1b

^{1}H NMR Spectrum
400 MHz, $CDCl_3$

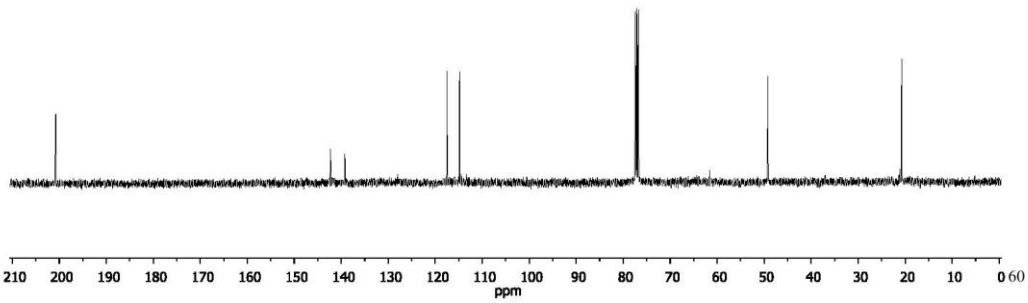


59

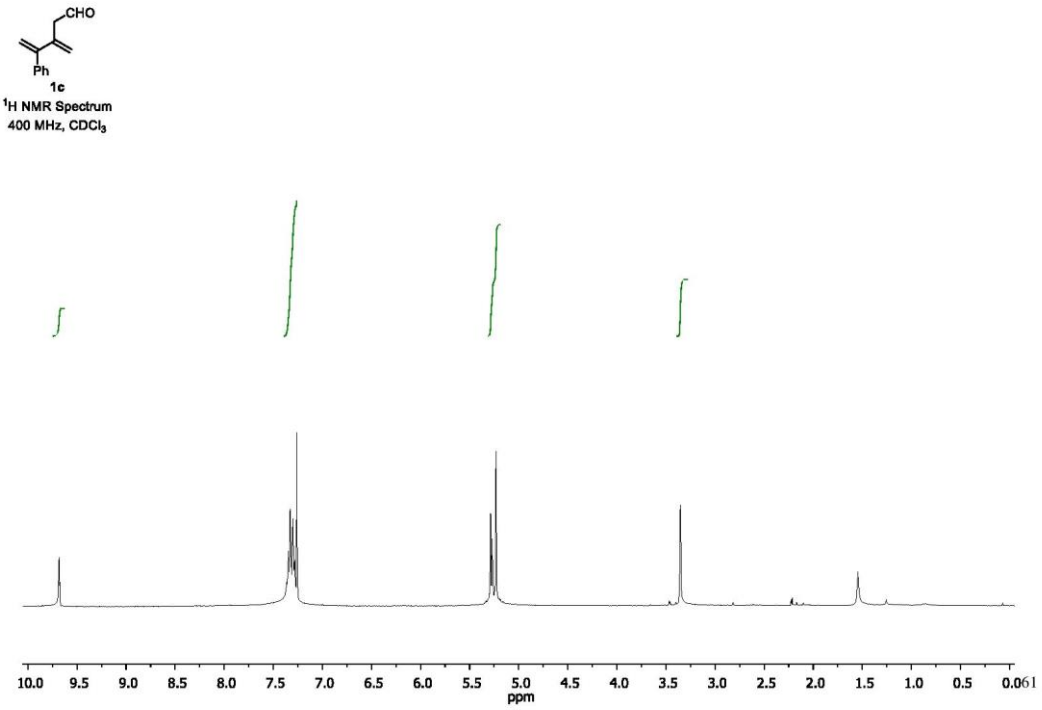


1b

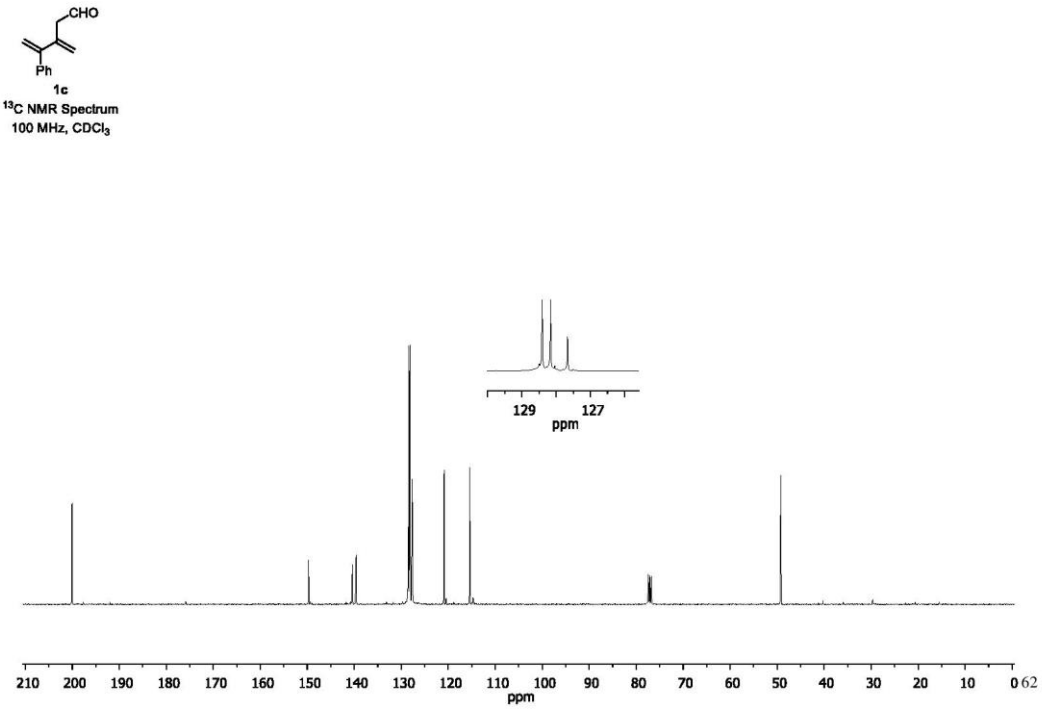
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



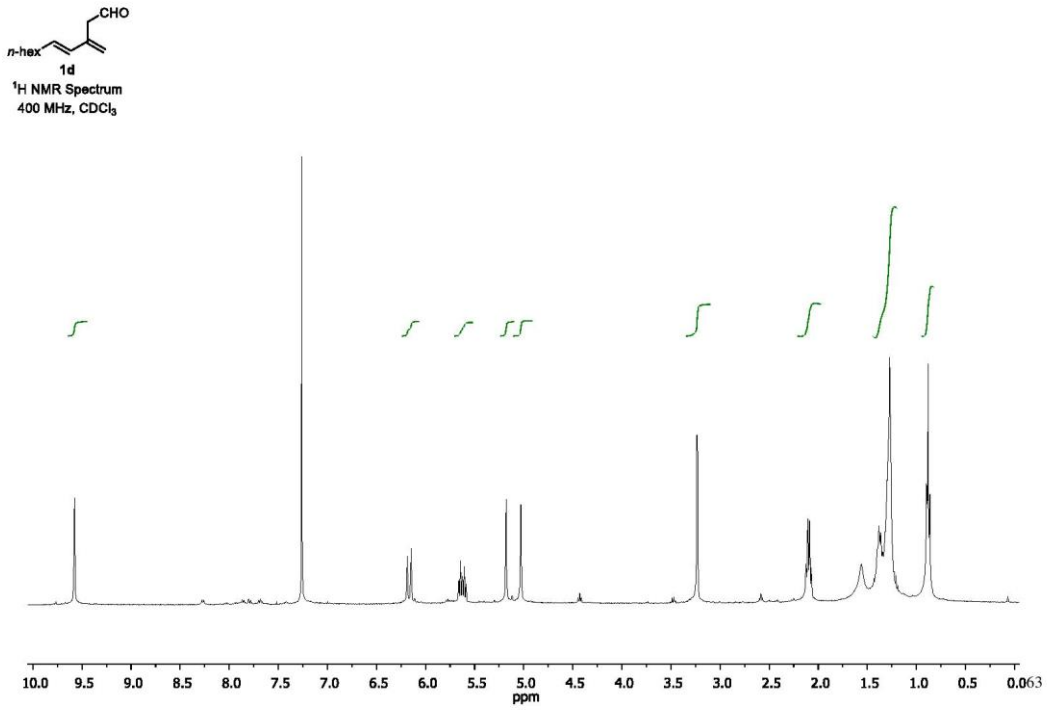
60

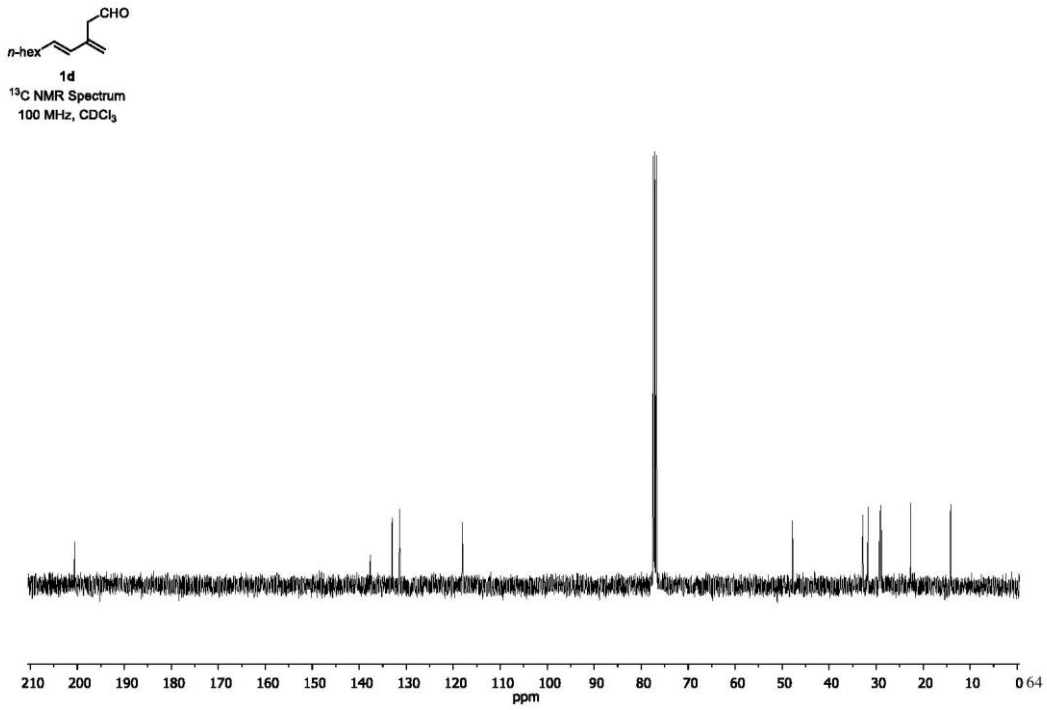

CHO
Ph
1c
1H NMR Spectrum
400 MHz, CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

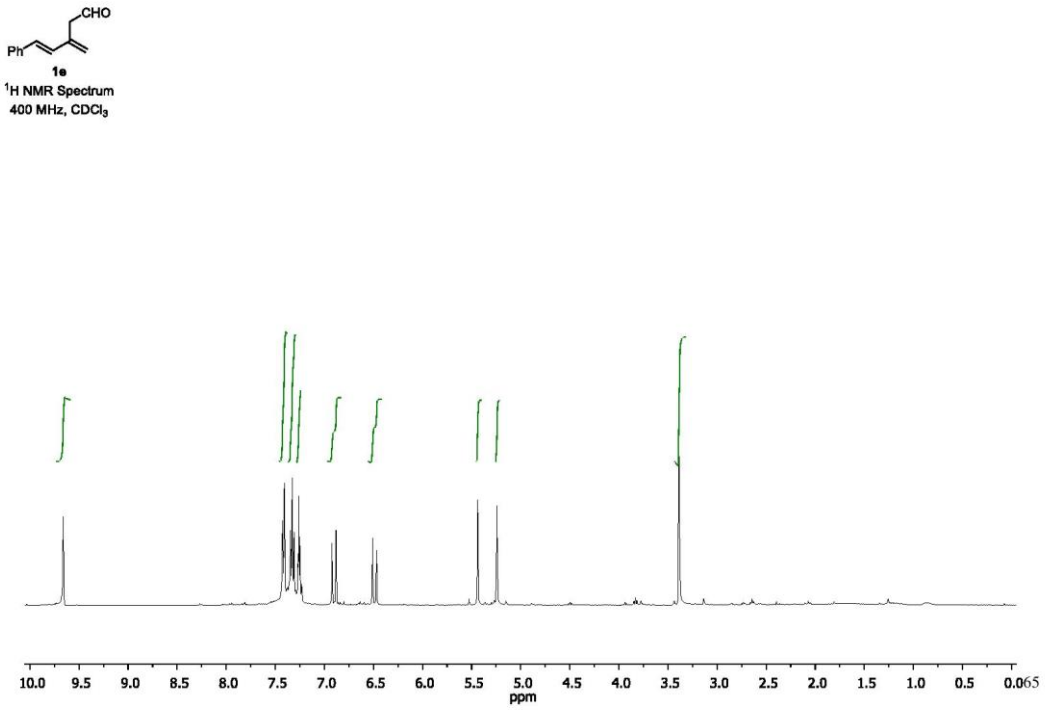
61

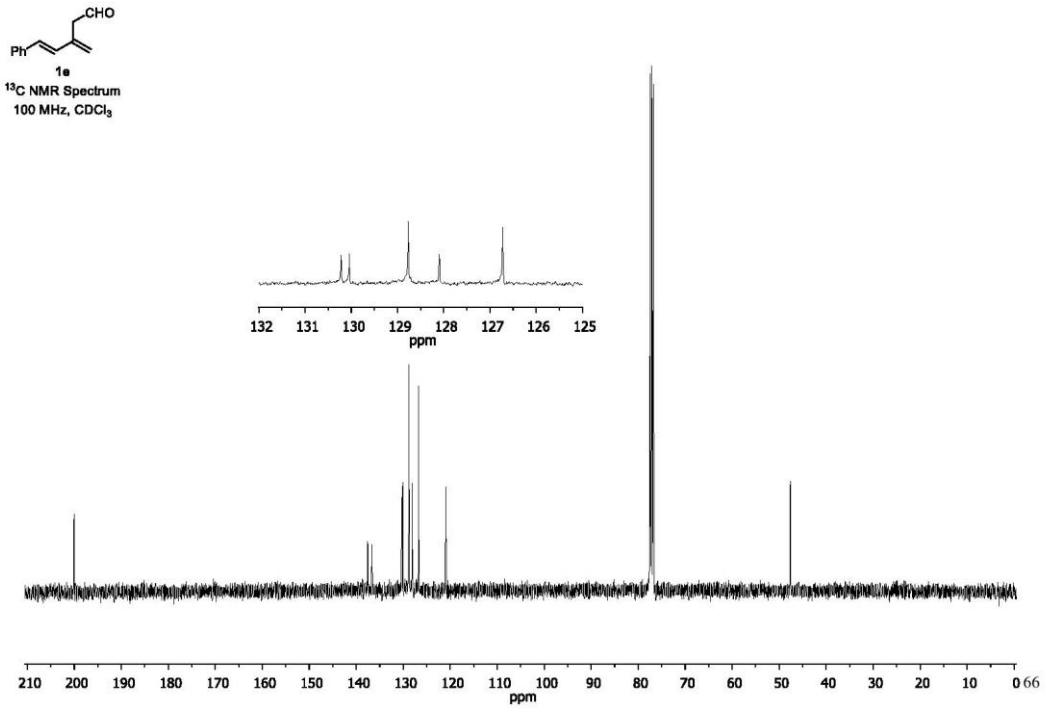

CHO
Ph
1c
13C NMR Spectrum
100 MHz, CDCl3
129 127
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

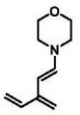
62


CHO
n-hex
1d
1H NMR Spectrum
400 MHz, CDCl3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
63


CHO
n-hex
1d
13C NMR Spectrum
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm
64

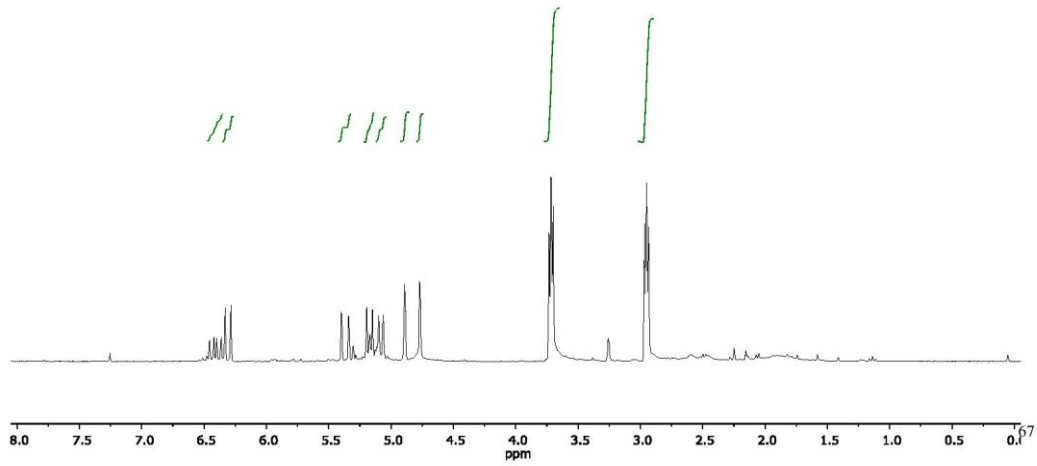

CHO
Ph
1e
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.065
ppm


CHO
Ph
1e
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
132 131 130 129 128 127 126 125
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 66
ppm

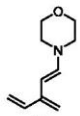


2a

^{1}H NMR Spectrum
300 MHz, $CDCl_3$

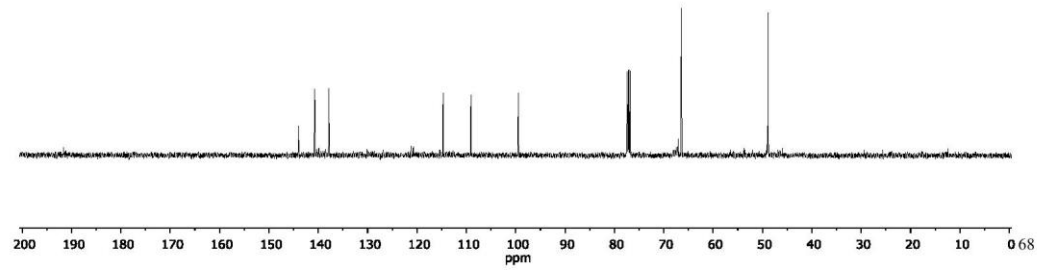


67

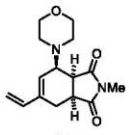


2a

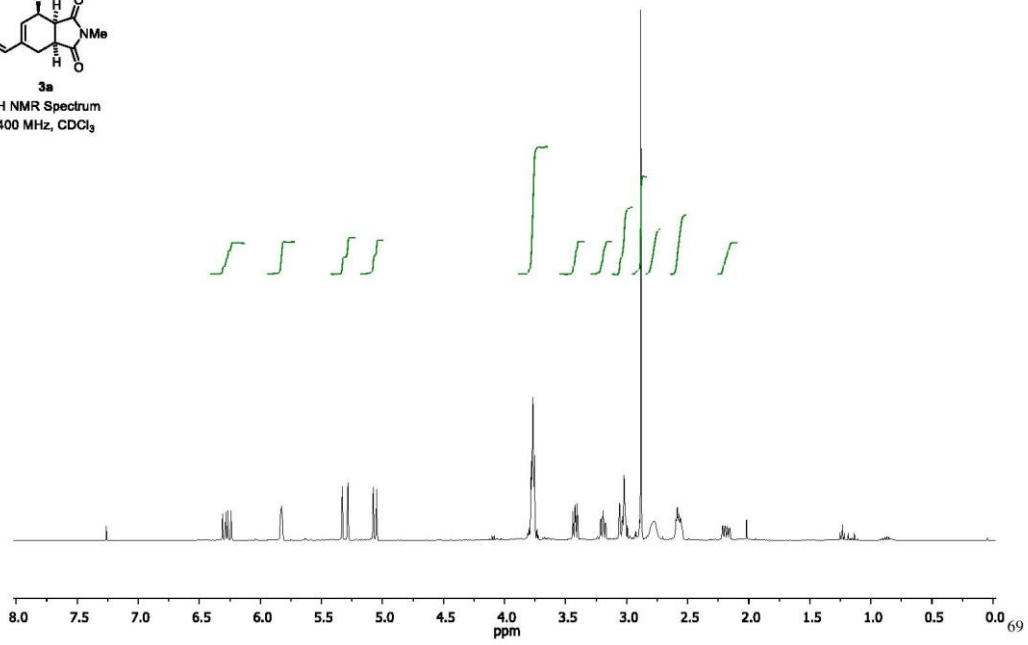
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



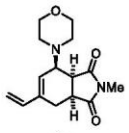
68



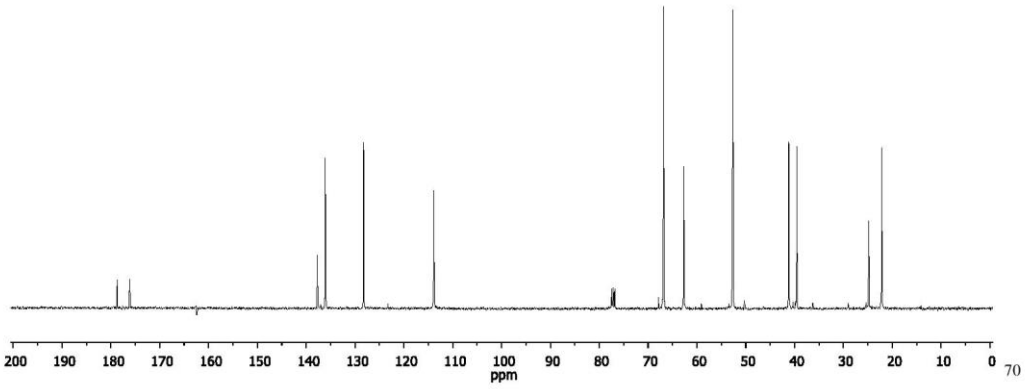
3a
^{1}H NMR Spectrum
400 MHz, $CDCl_3$



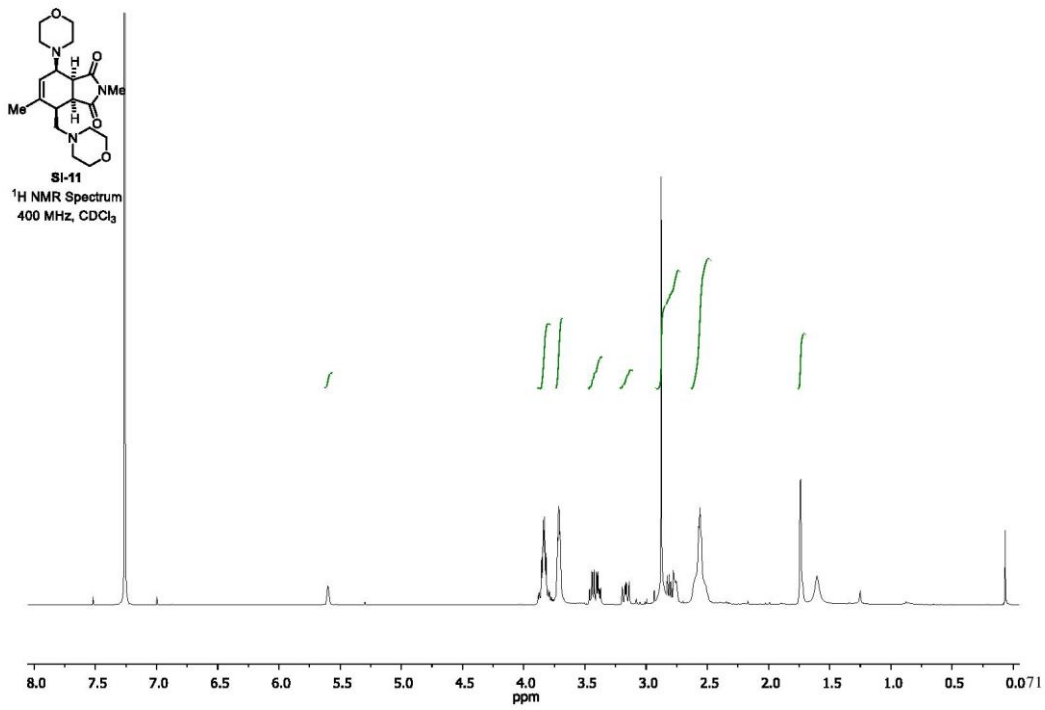
69



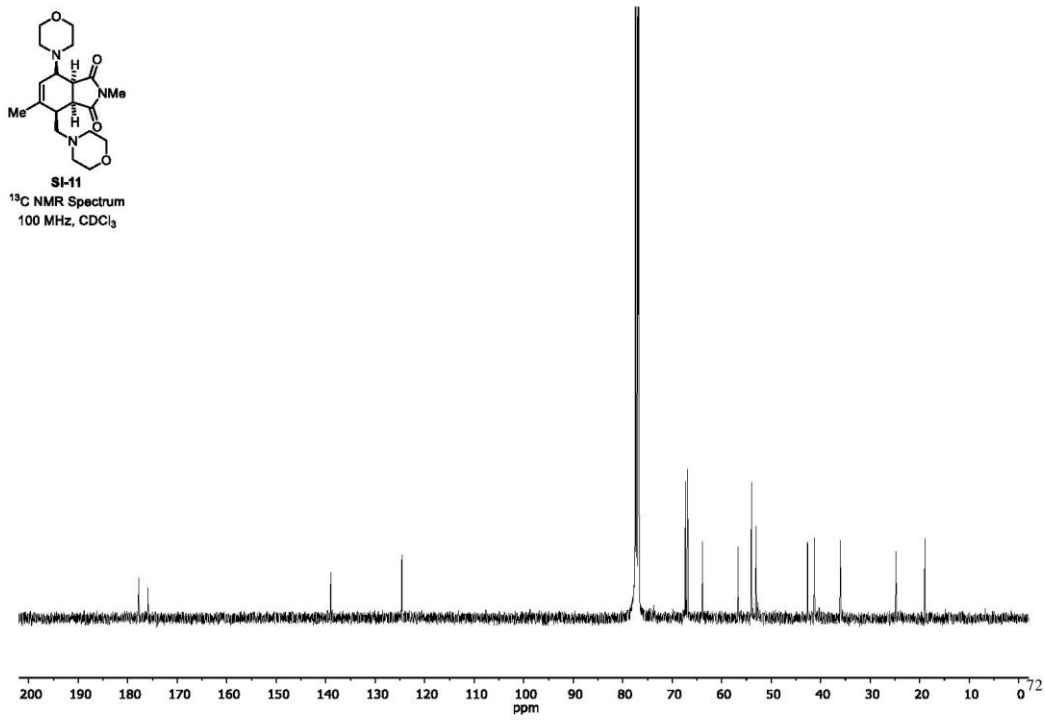
3a
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



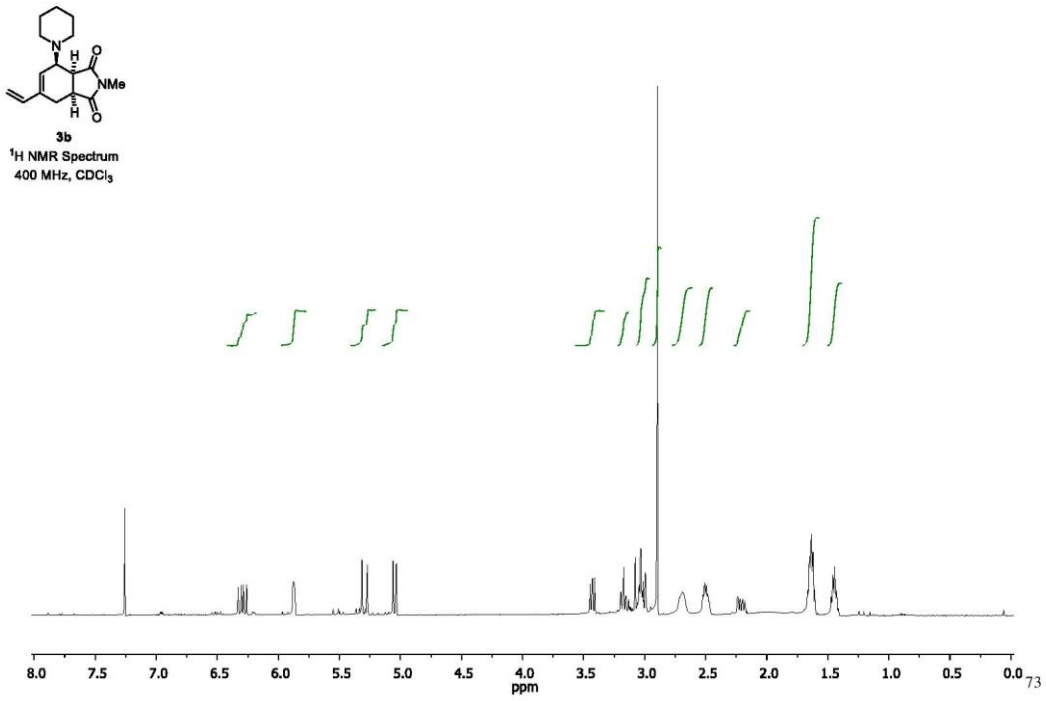
70


SI-11
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

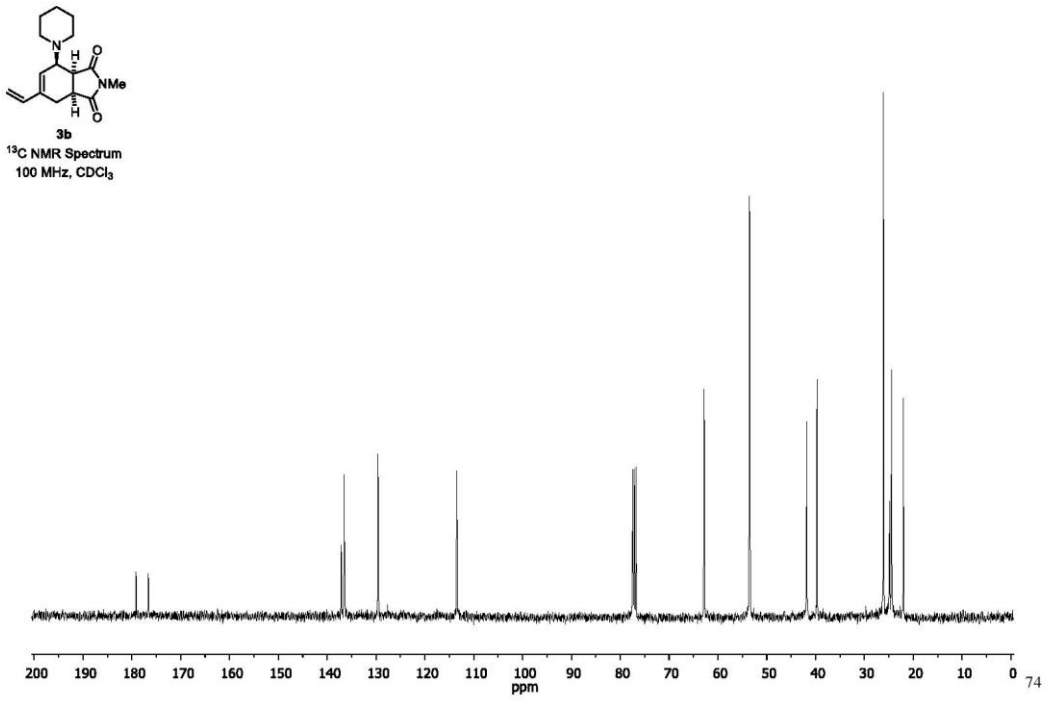
71


SI-11
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

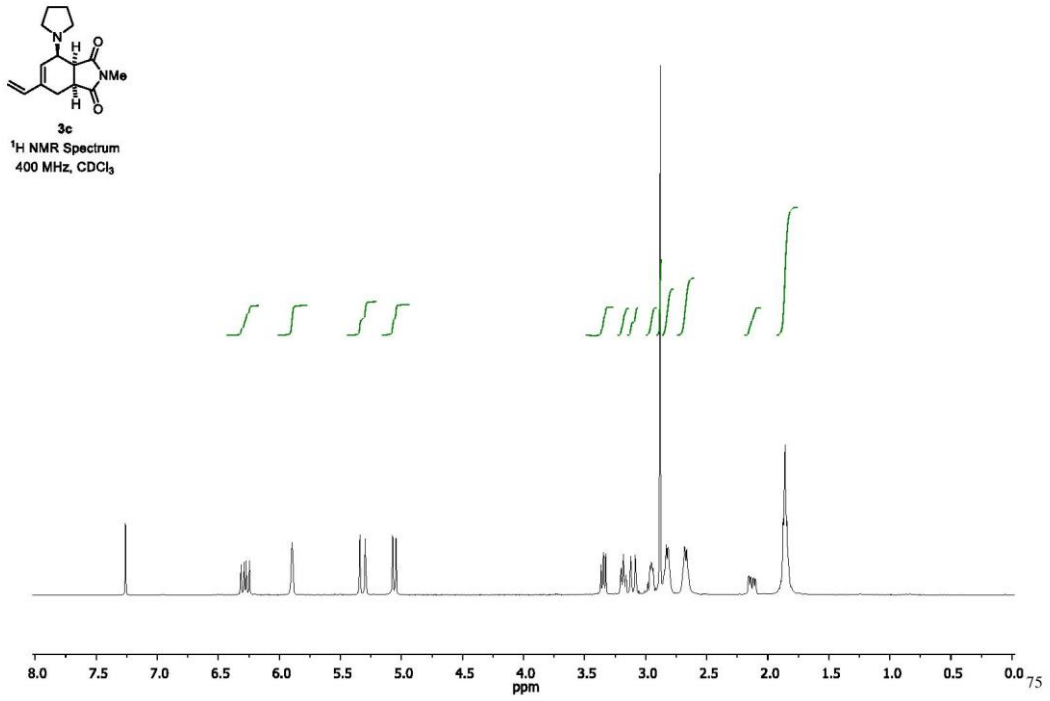
72


3b
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

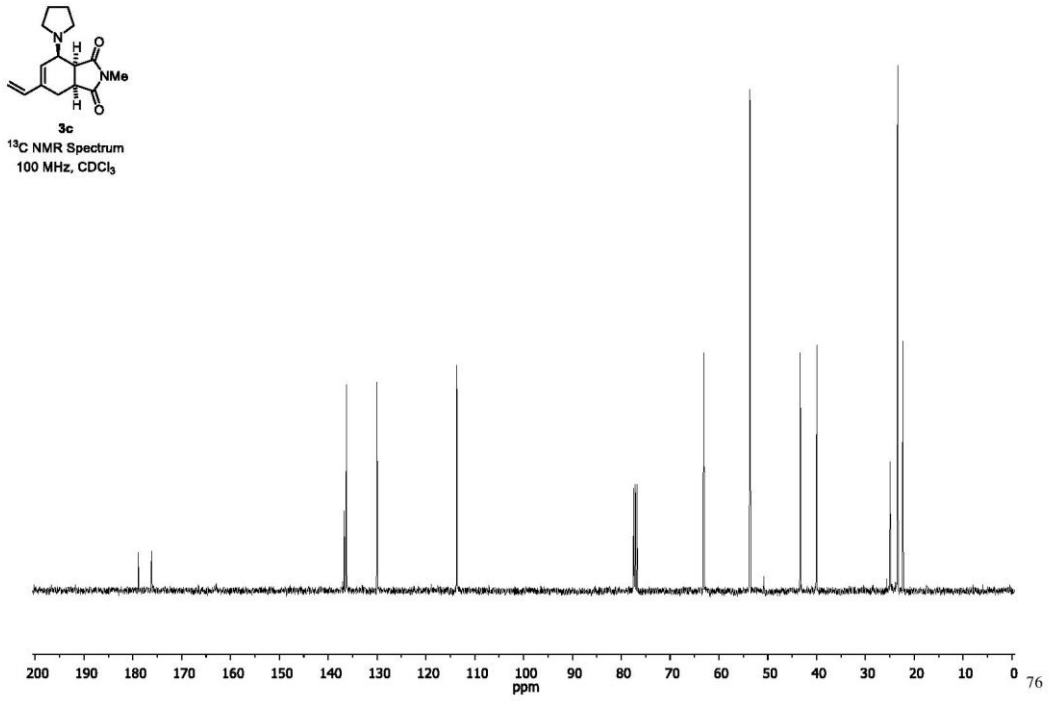
73


3b
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

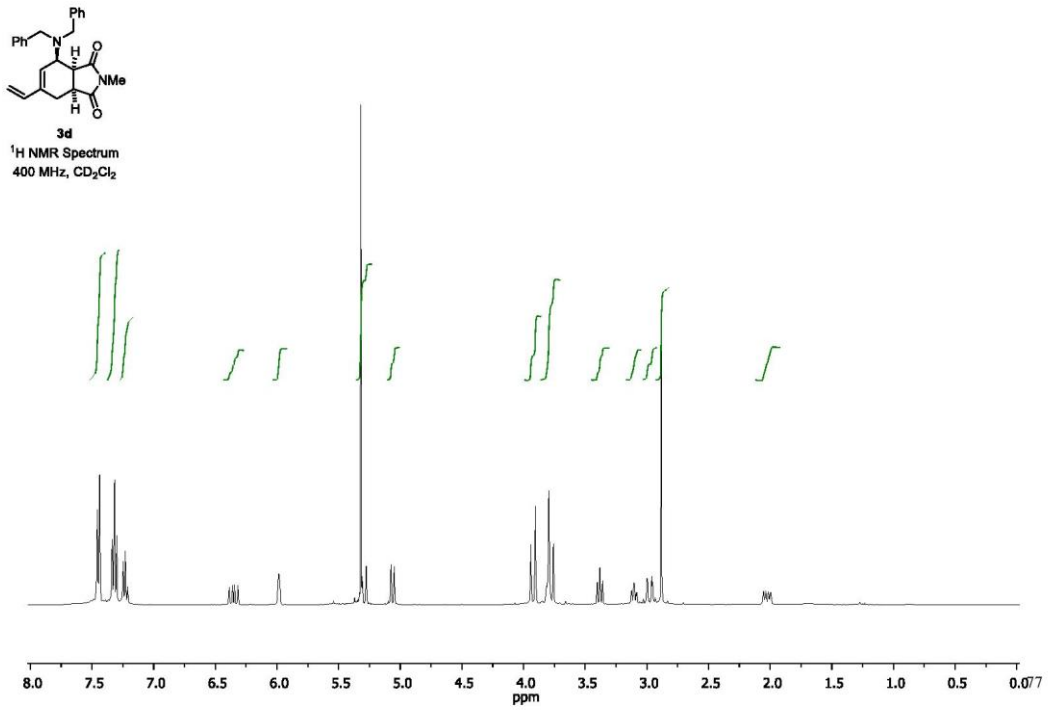
74


3c
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

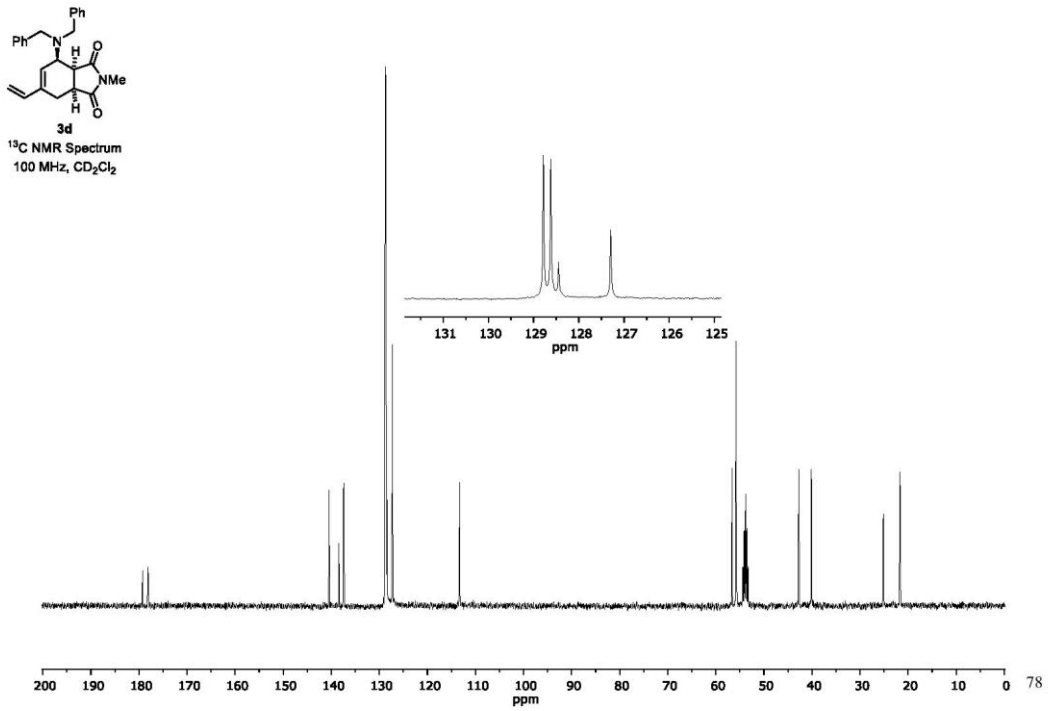
75


3c
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

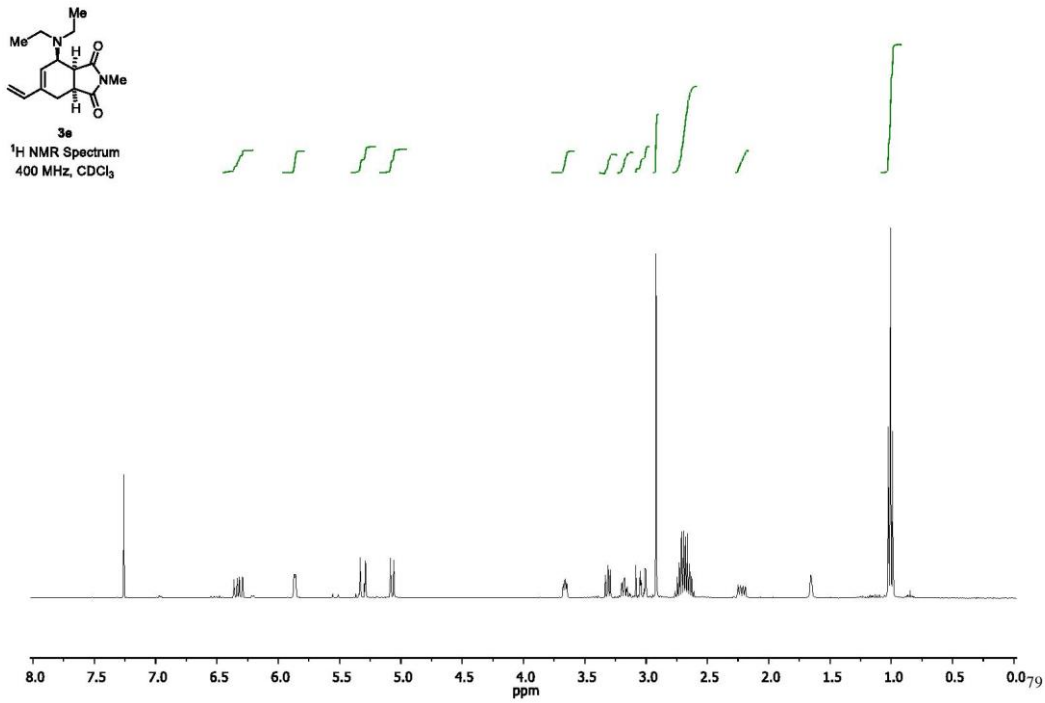
76


Ph
Ph
N
H
O
NMe
H
O
3d
1H NMR Spectrum
400 MHz, CD2Cl2
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

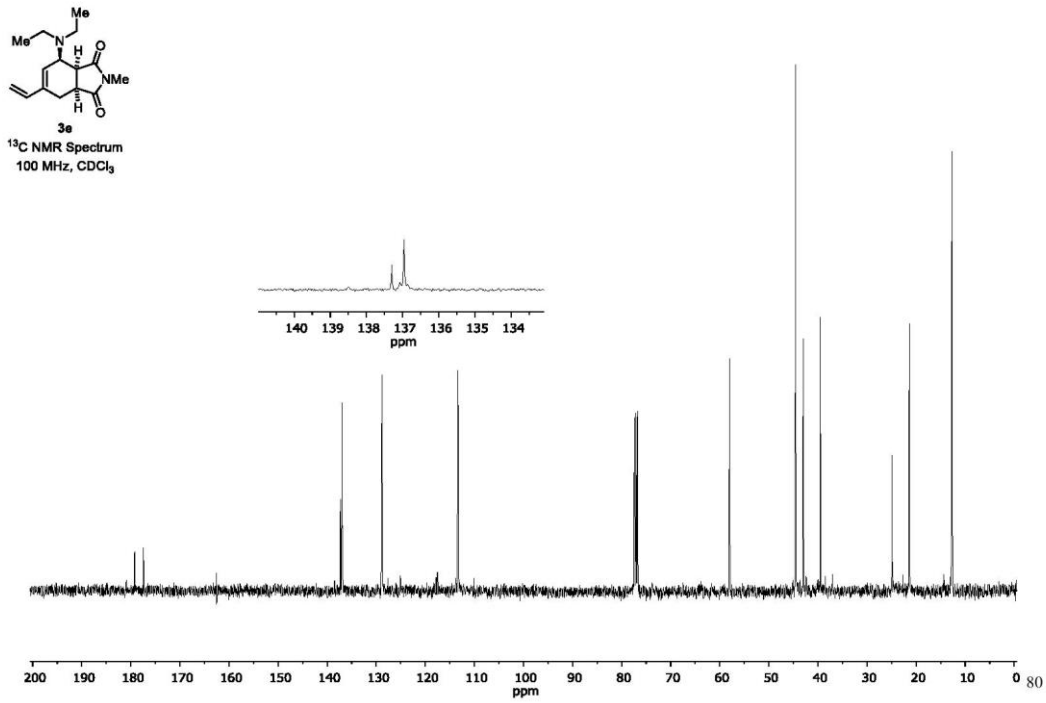
77


Ph
Ph
N
H
O
NMe
H
O
3d
13C NMR Spectrum
100 MHz, CD2Cl2
131 130 129 128 127 126 125
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

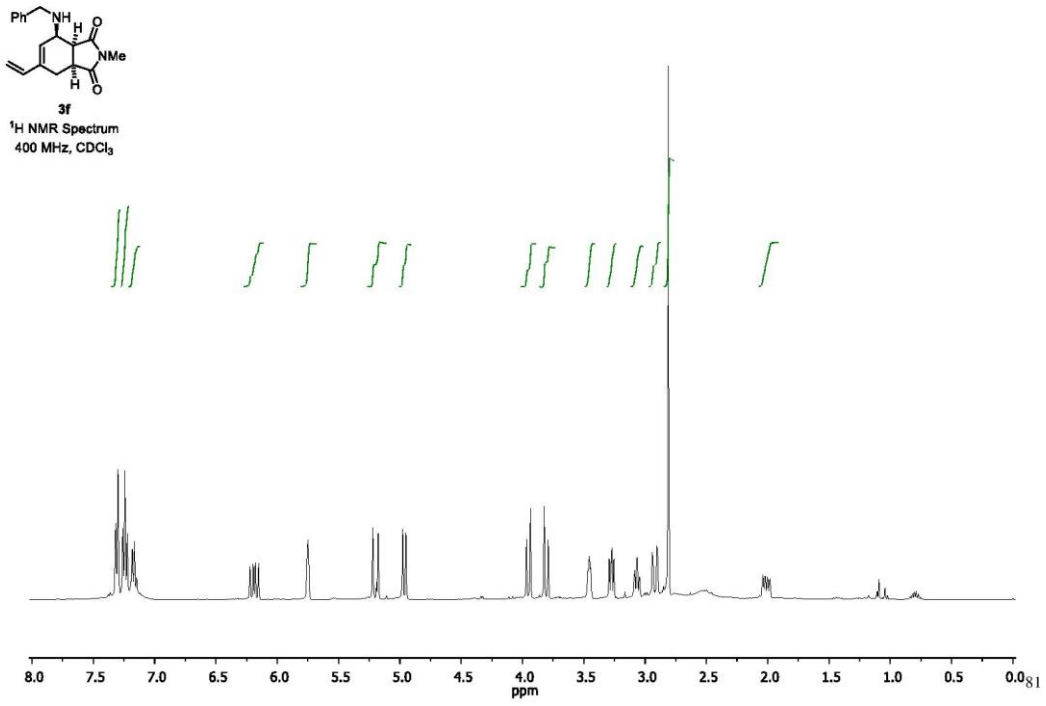
78


Me
Me
N
H
O
NMe
H
O
3e
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

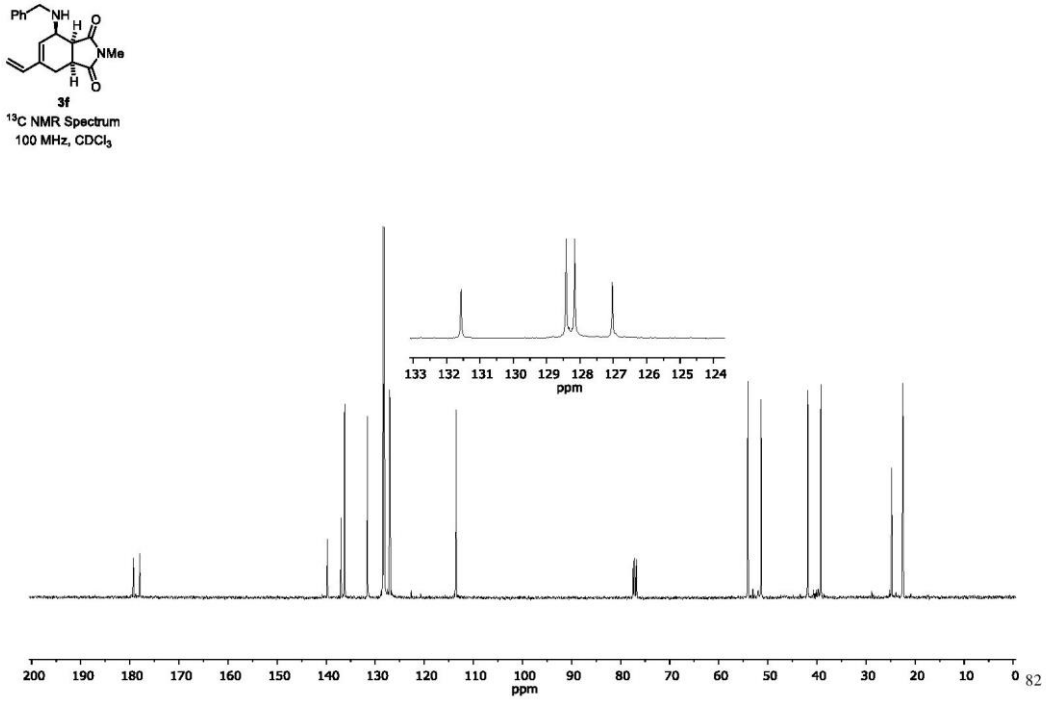
79


Me
Me
N
H
O
NMe
H
O
3e
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
140 139 138 137 136 135 134
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

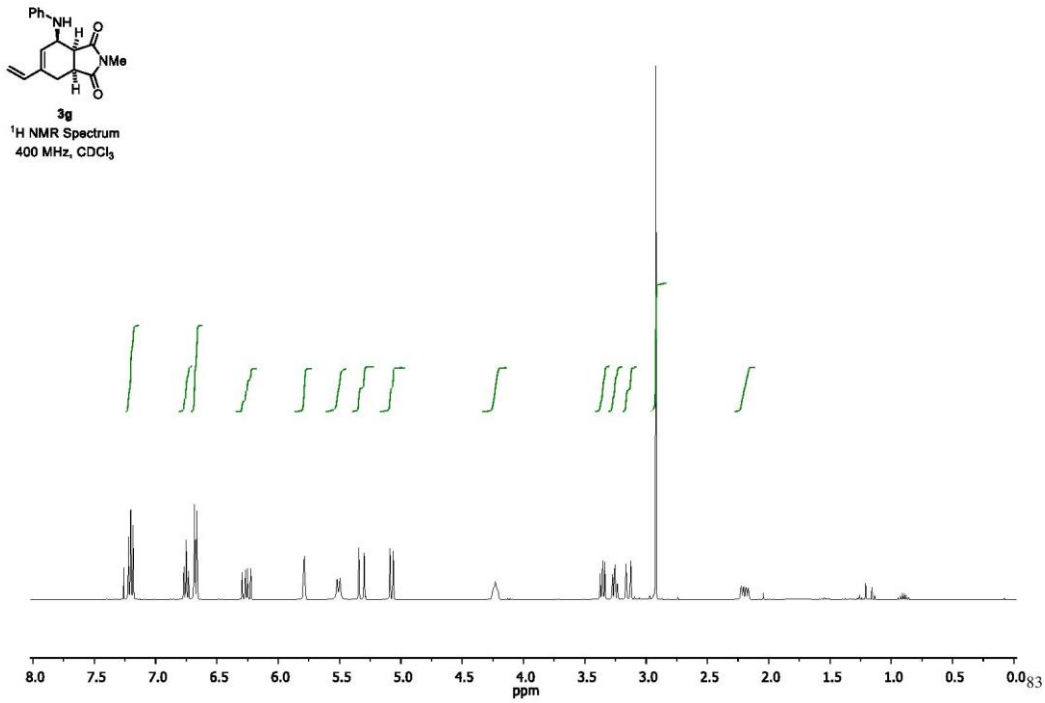
80


Ph
NH
H
O
NMe
O
H
3f
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

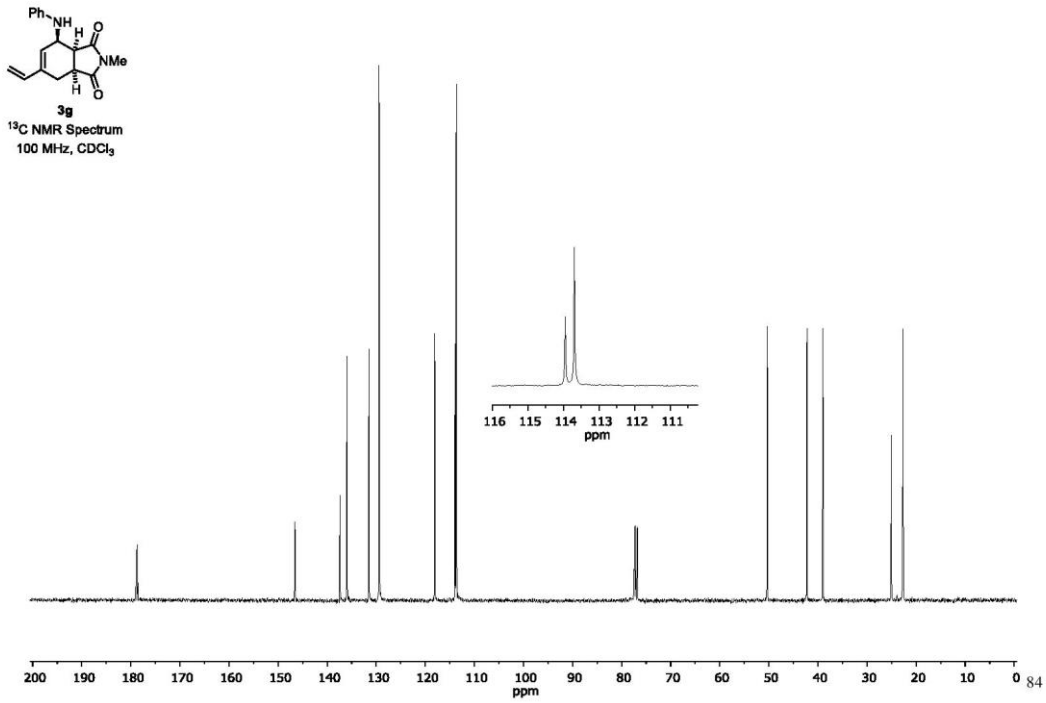
81


Ph
NH
H
O
NMe
O
H
3f
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
133 132 131 130 129 128 127 126 125 124
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

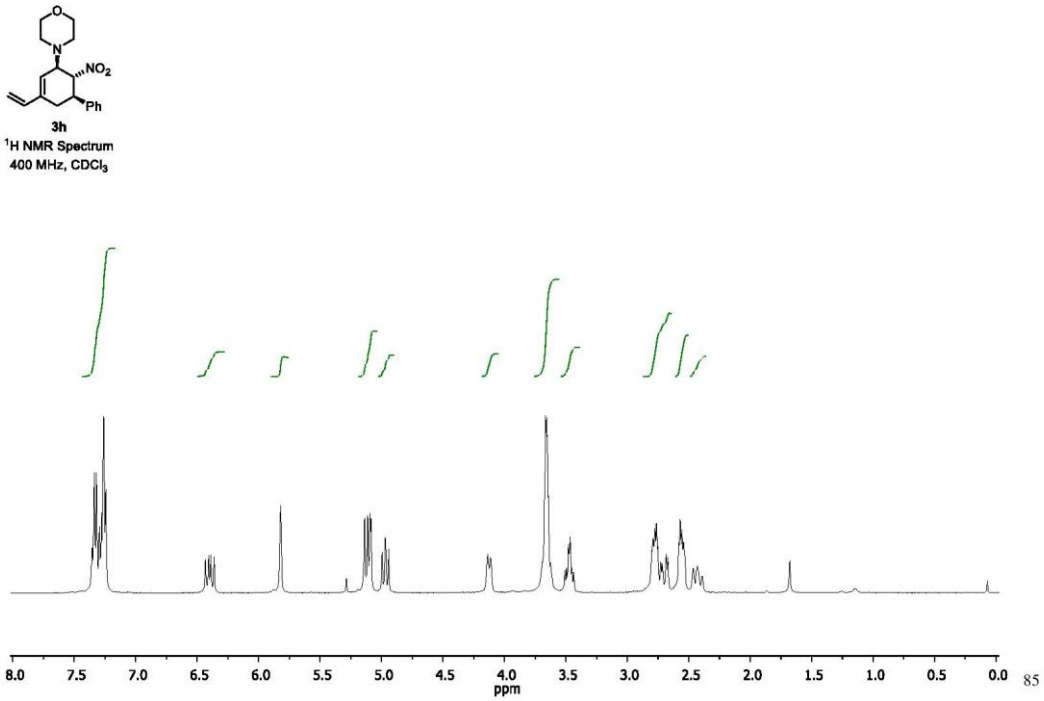
82


Ph
NH
H
O
NMe
H
O
3g
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

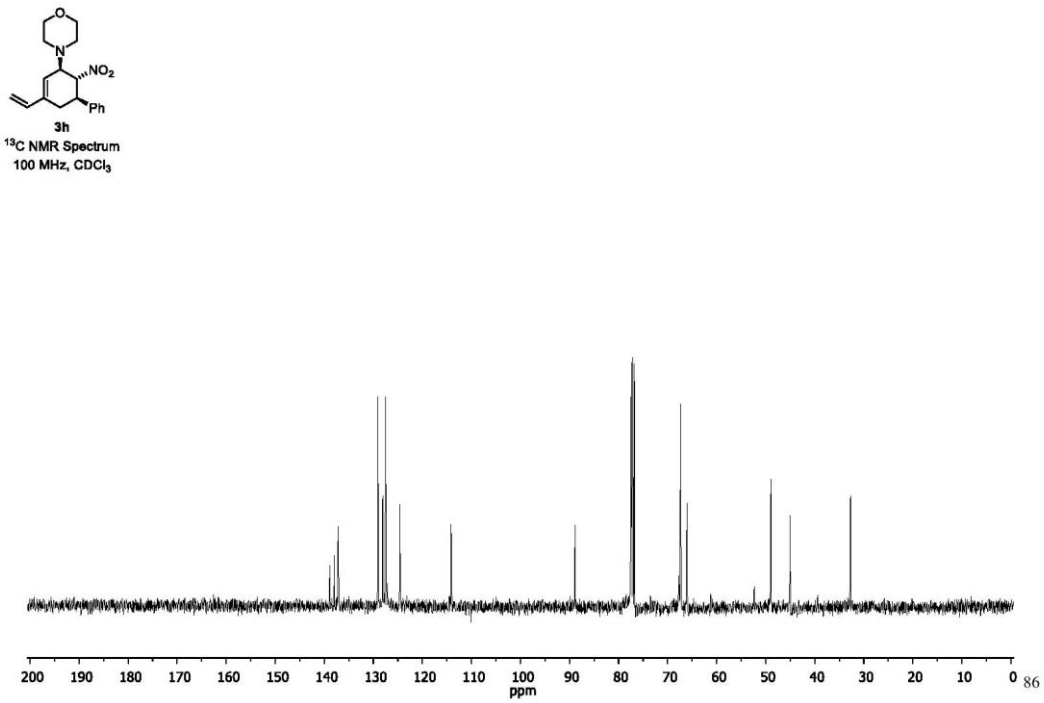
83


Ph
NH
H
O
NMe
H
O
3g
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
116 115 114 113 112 111
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

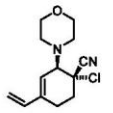
84


3h
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

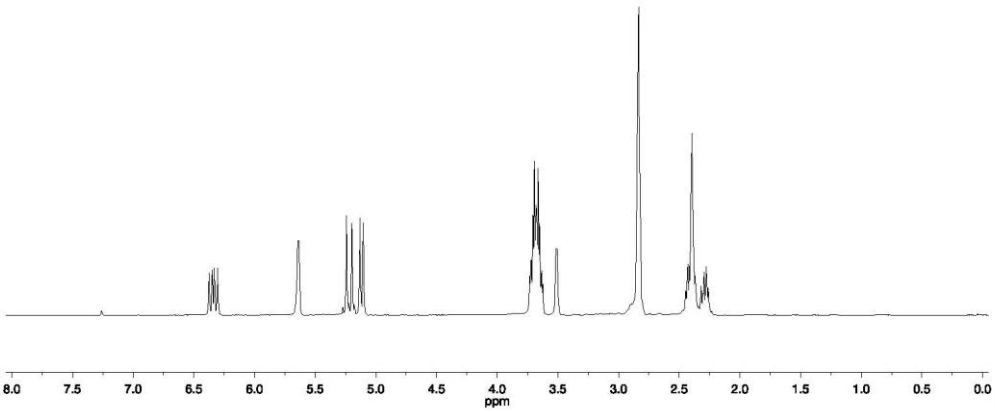
85


3h
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

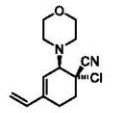
86



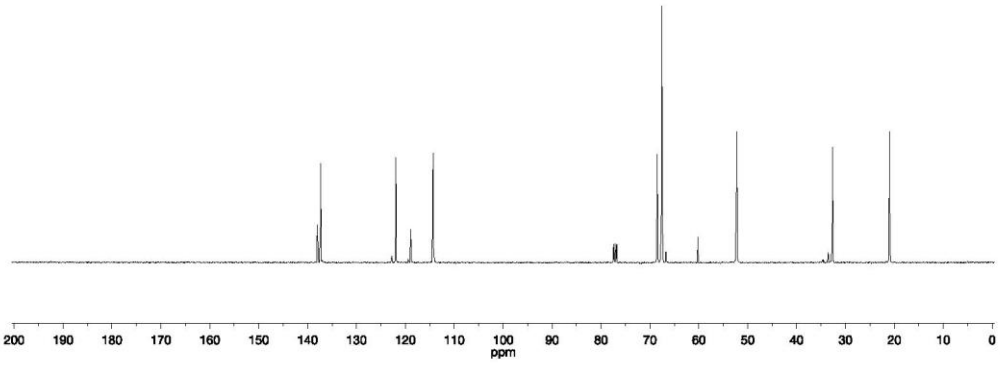
3i
^{1}H NMR Spectrum
400 MHz, $CDCl_3$



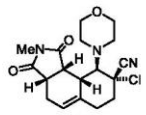
87



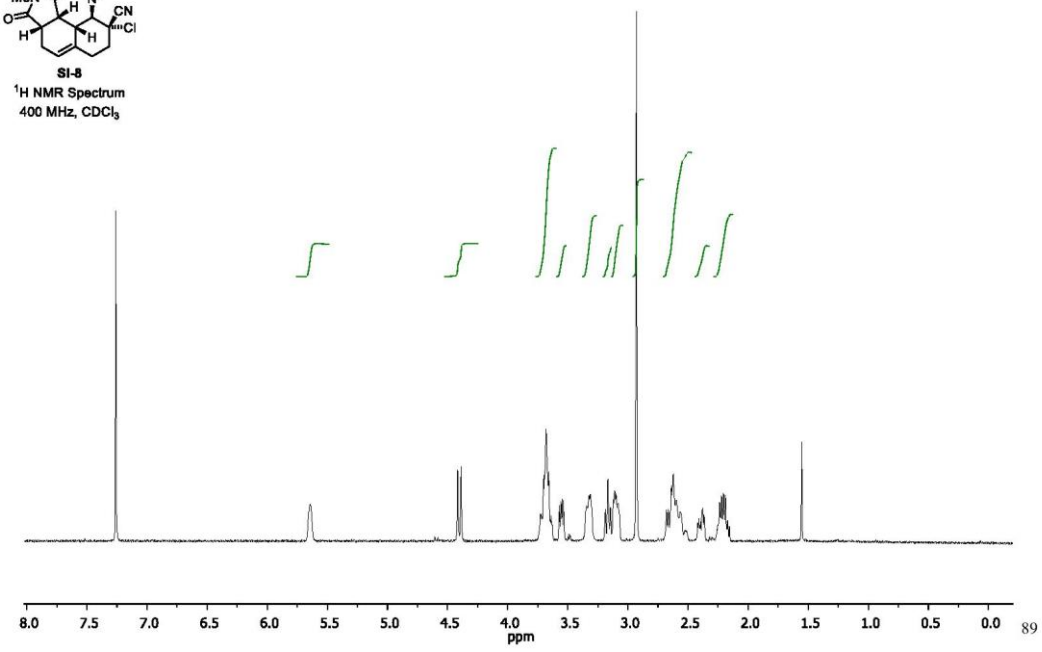
3l
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



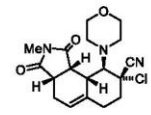
88



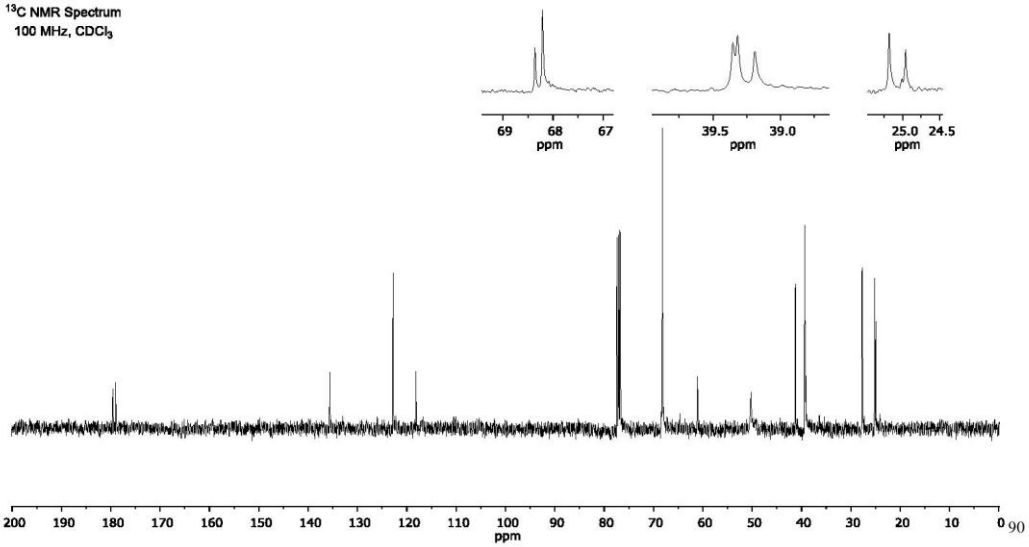
SI-8
^{1}H NMR Spectrum
400 MHz, $CDCl_3$



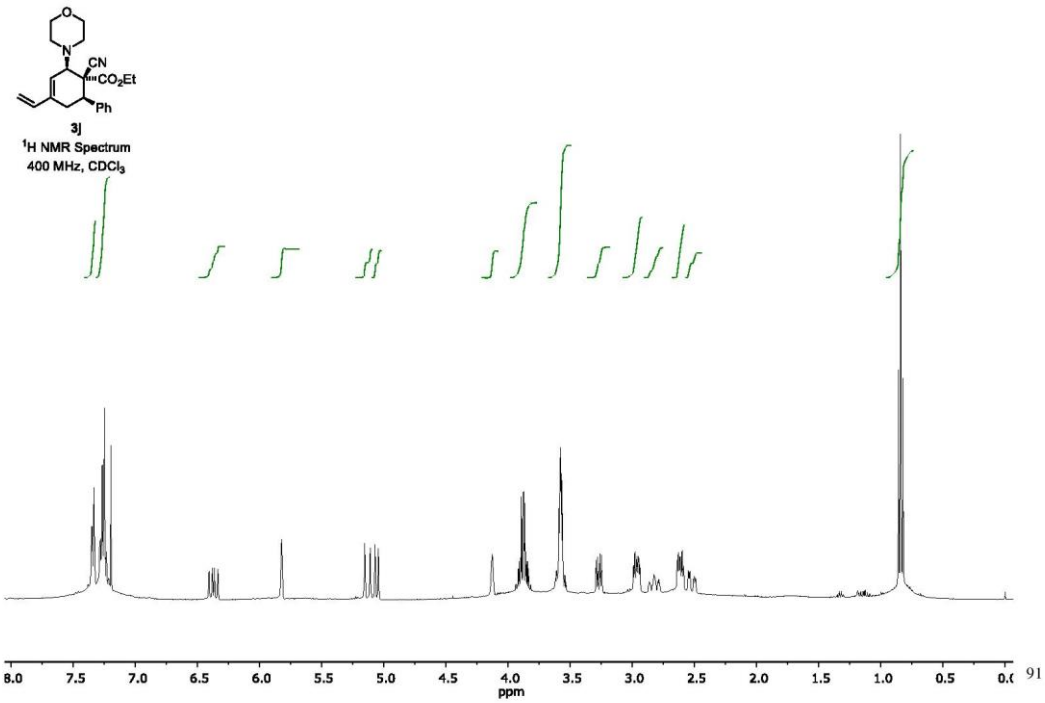
89



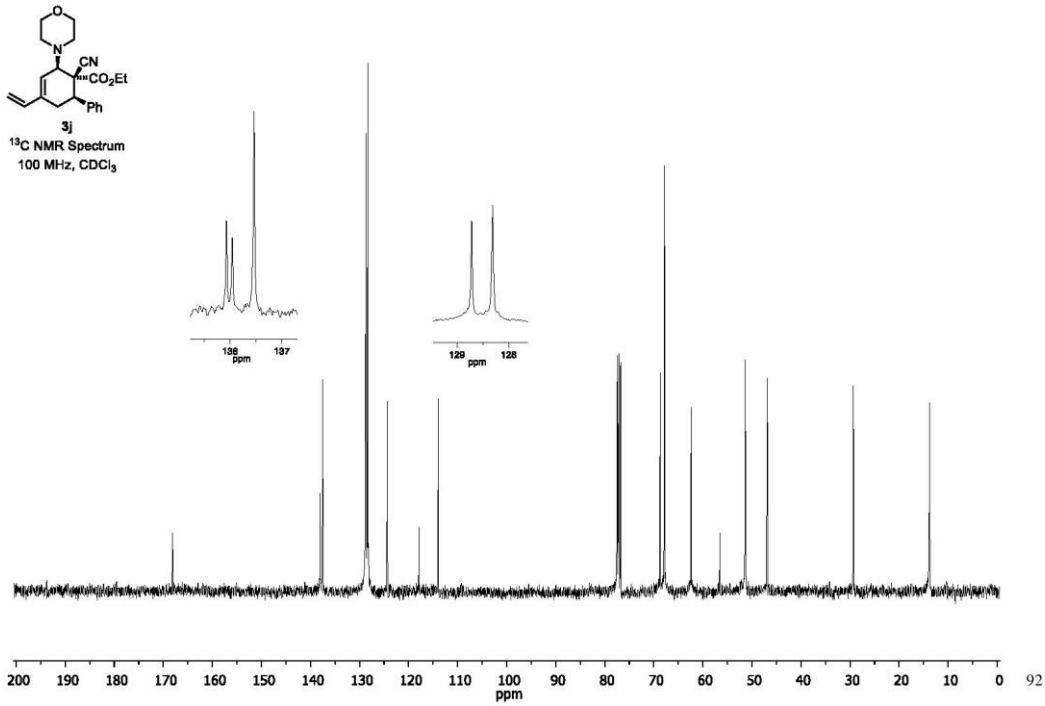
SI-8
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



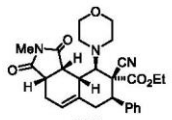
90


3j
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

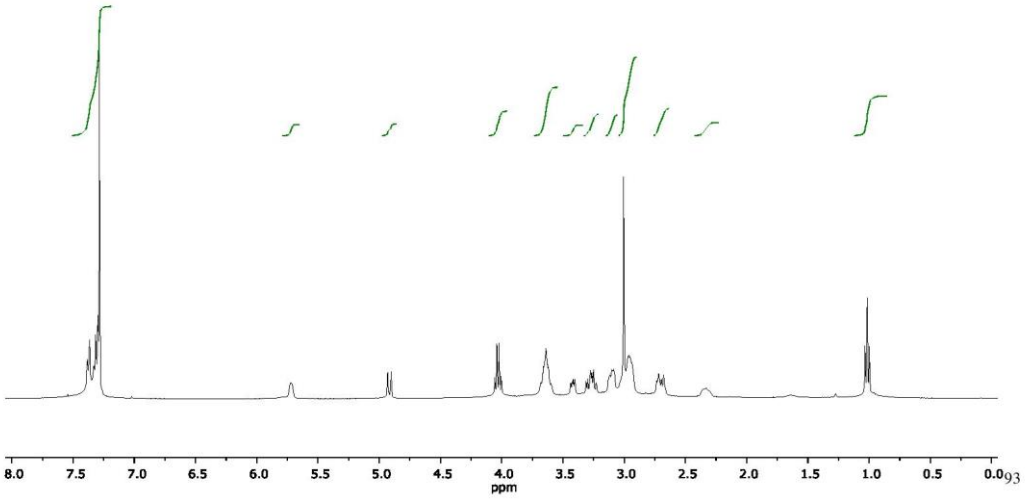
91


3j
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
138 137
129 128
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

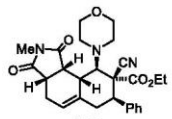
92



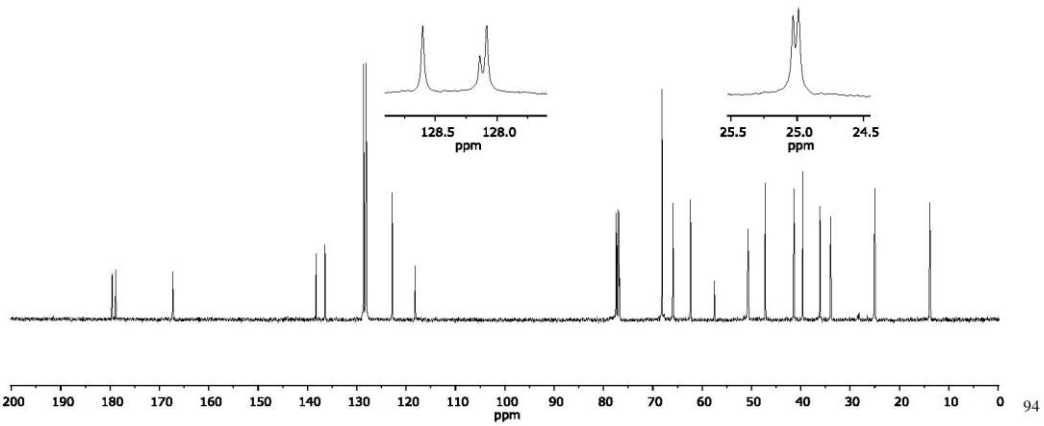
SI-9
^{1}H NMR Spectrum
400 MHz, $CDCl_3$



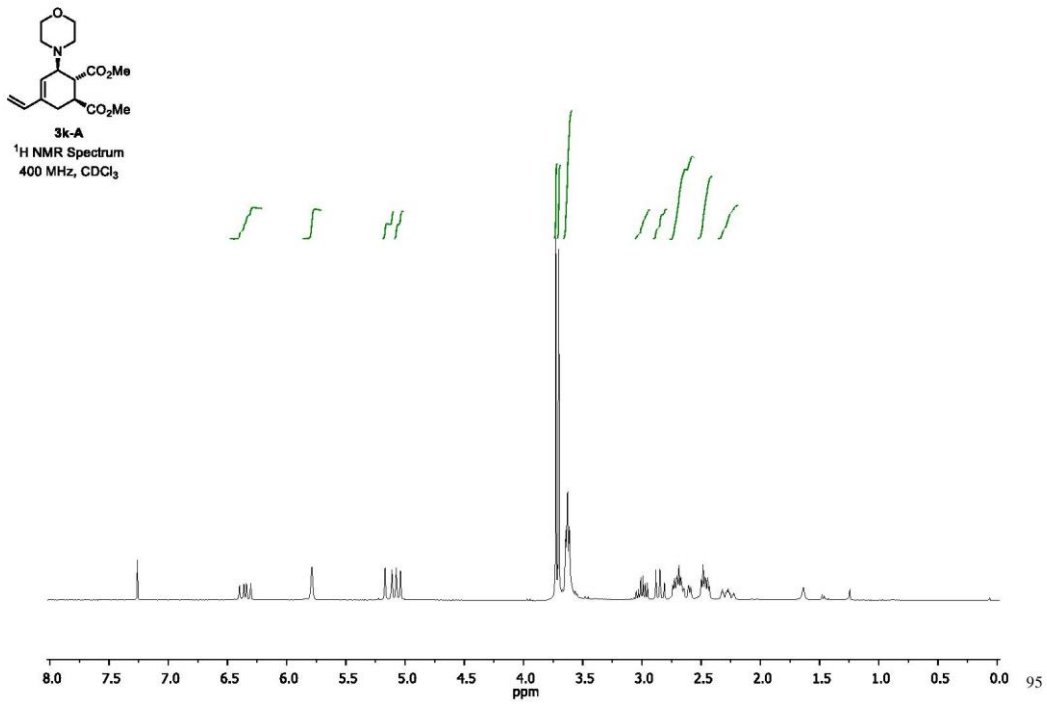
93



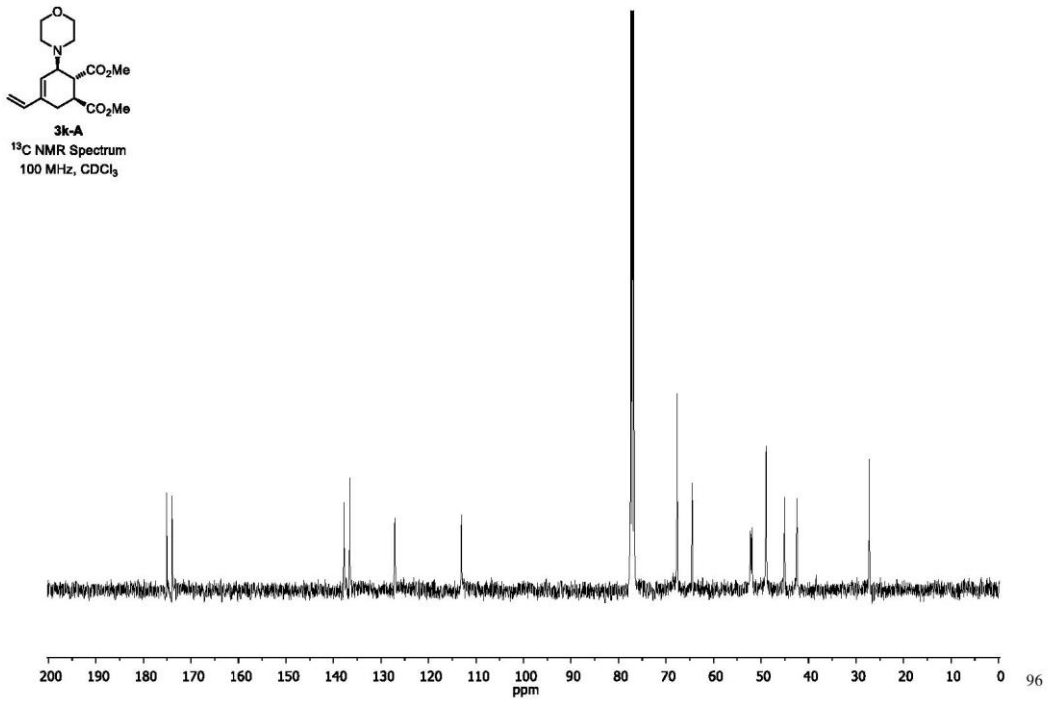
SI-9
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



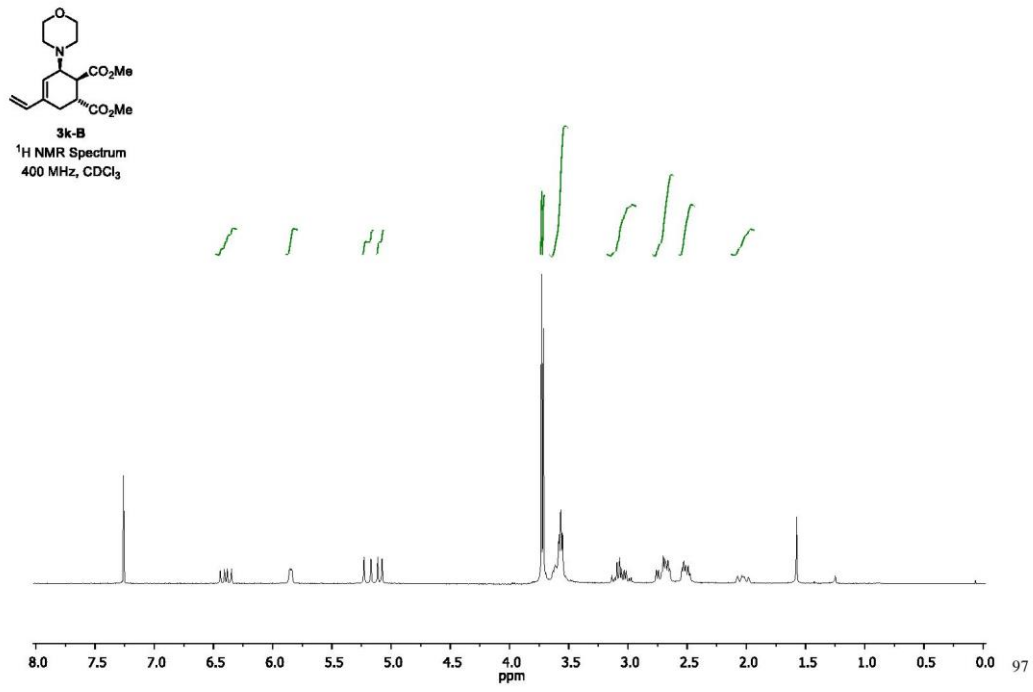
94


3k-A
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
CO$_2$Me
CO$_2$Me
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

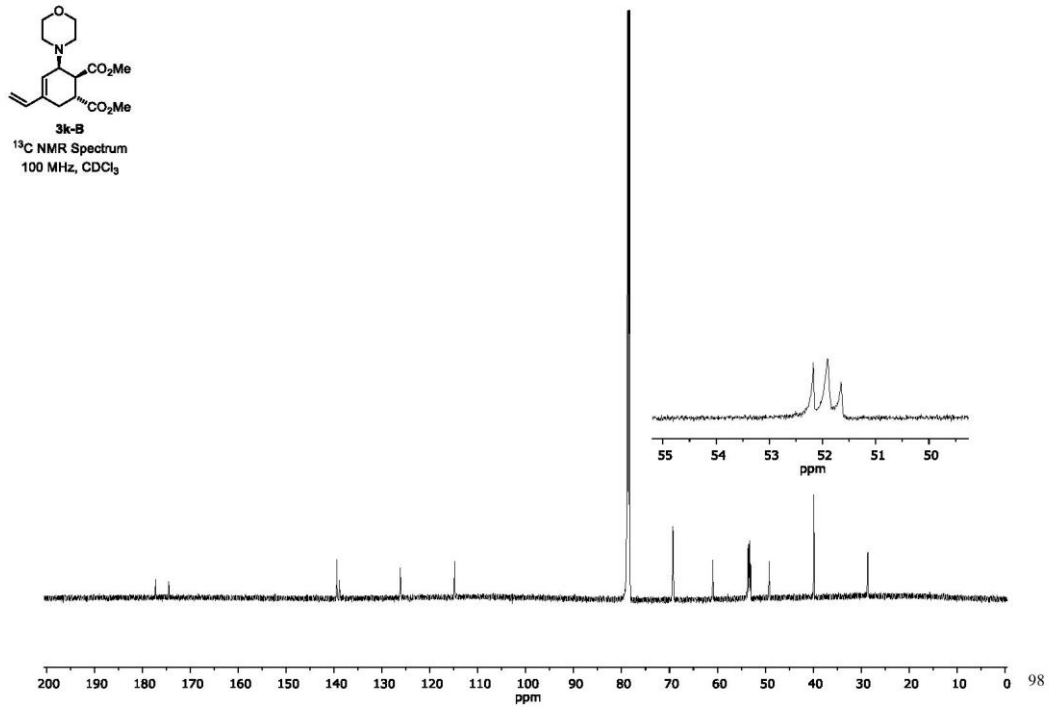
95


3k-A
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
CO$_2$Me
CO$_2$Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

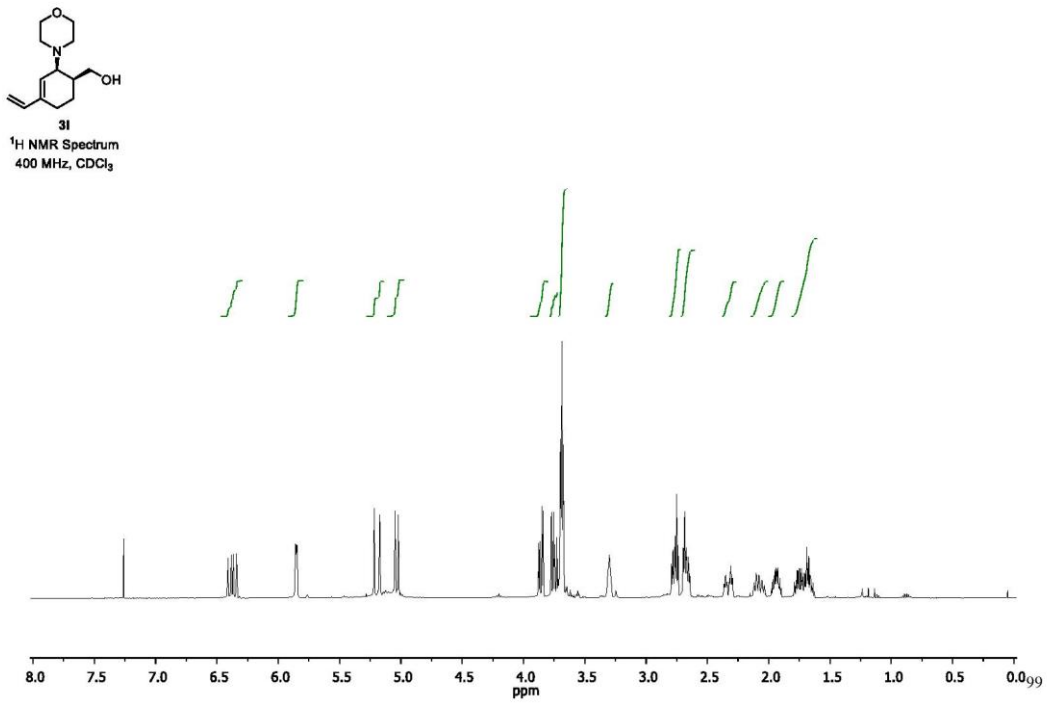
96


CO2Me
CO2Me
3k-B
1H NMR Spectrum
400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

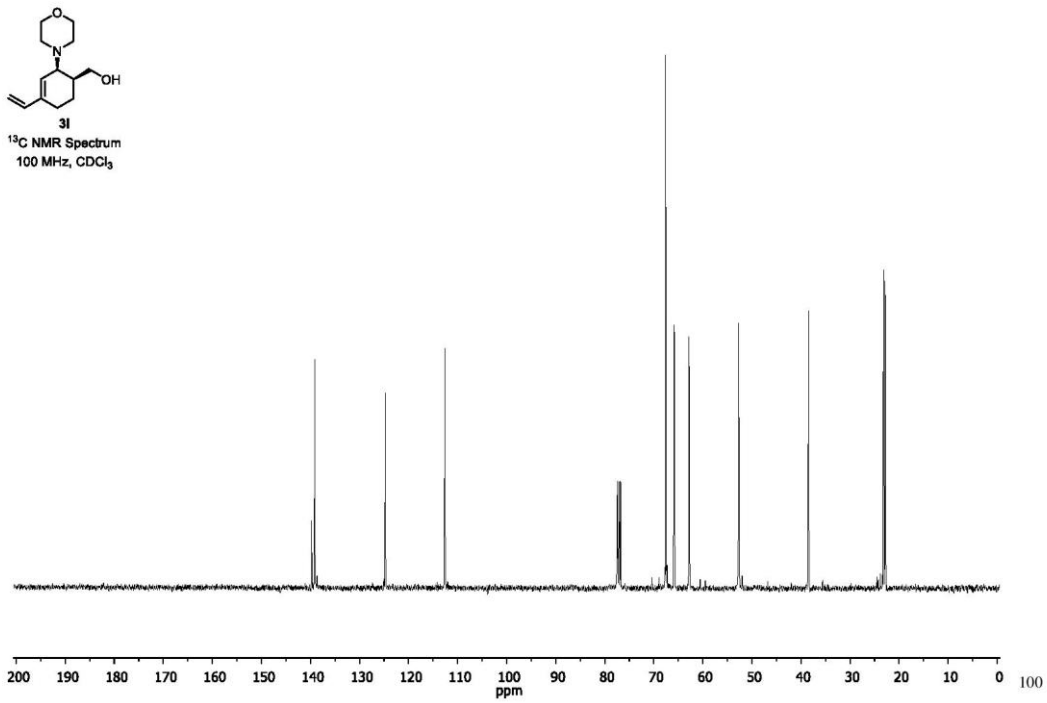
97


CO2Me
CO2Me
3k-B
13C NMR Spectrum
100 MHz, CDCl3
55 54 53 52 51 50
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

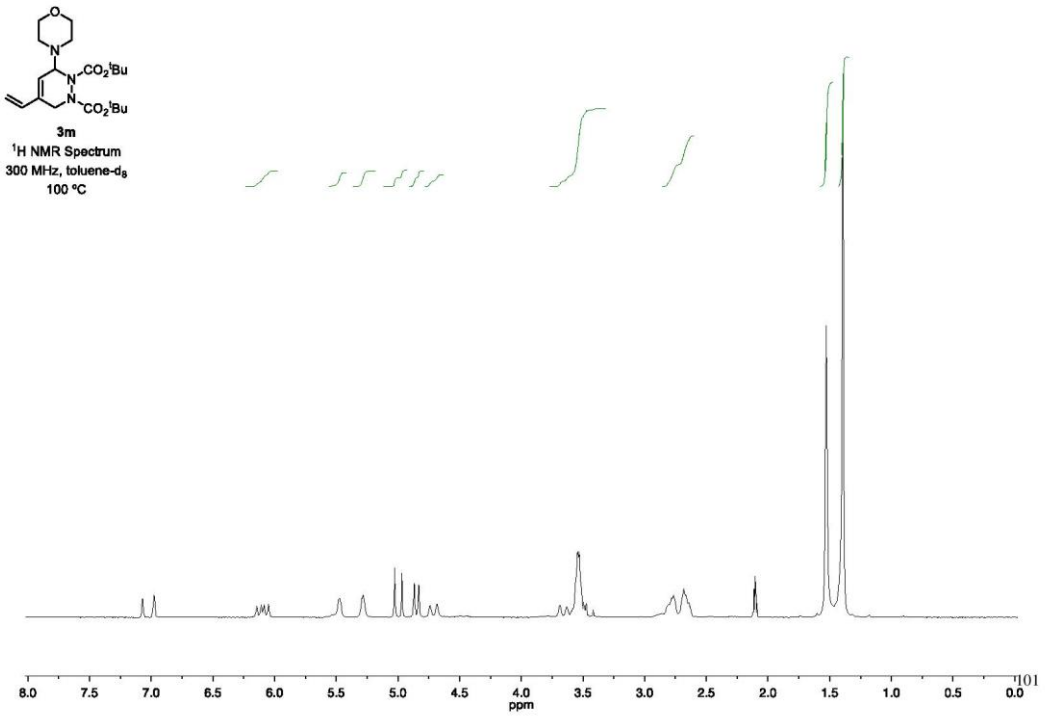
98

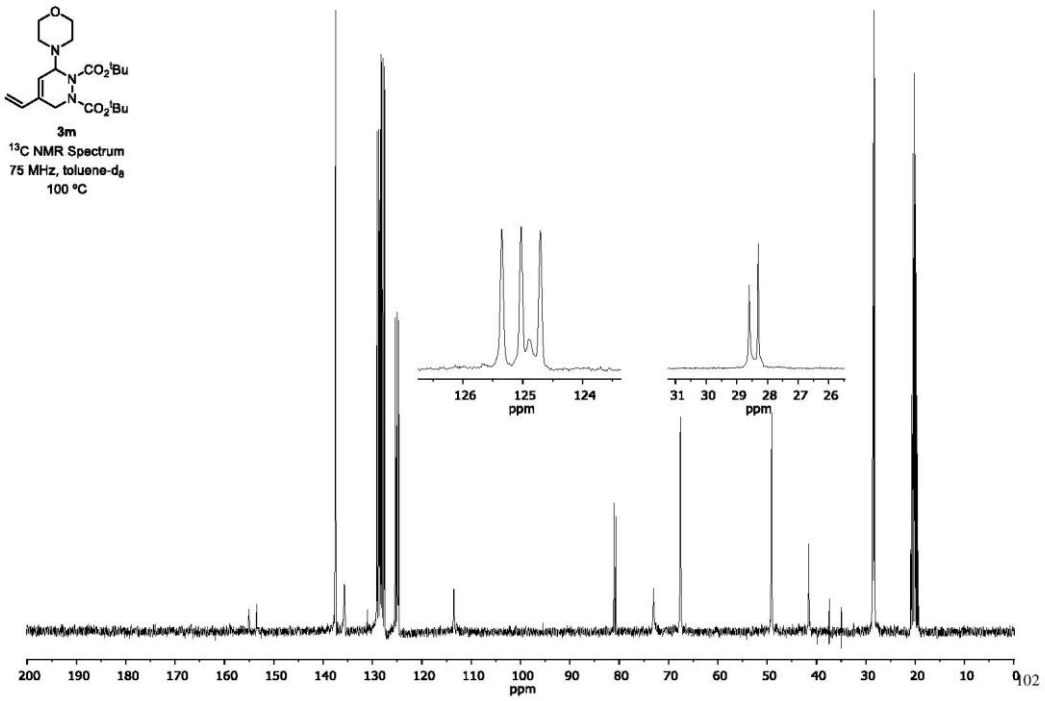

3l
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
OH
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

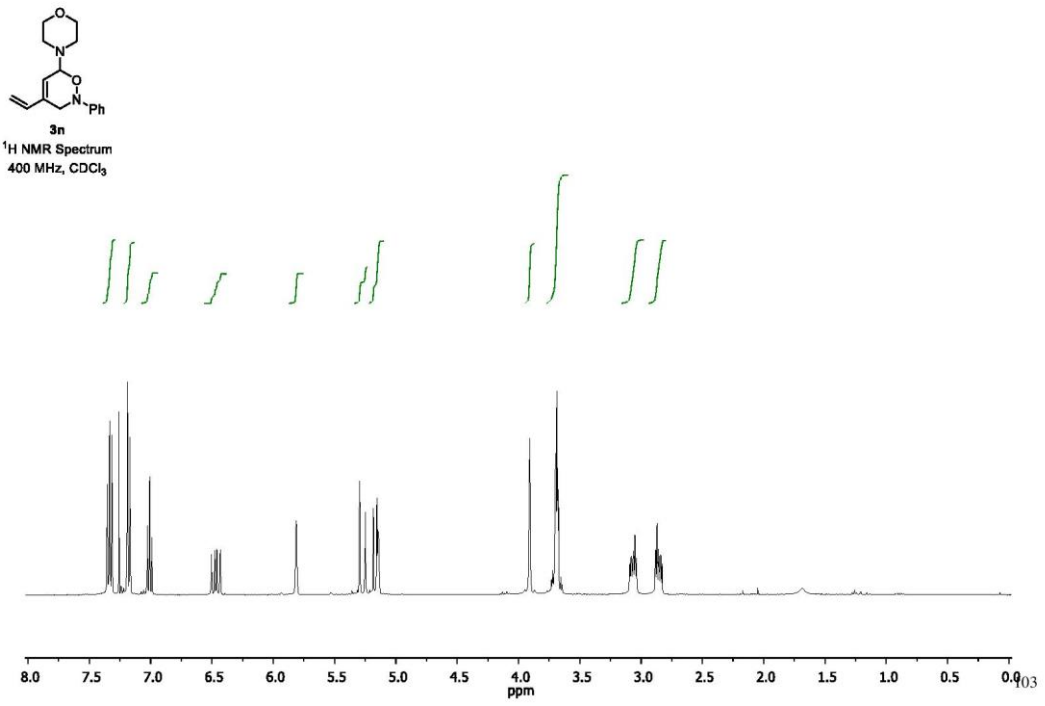
99


3l
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
OH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

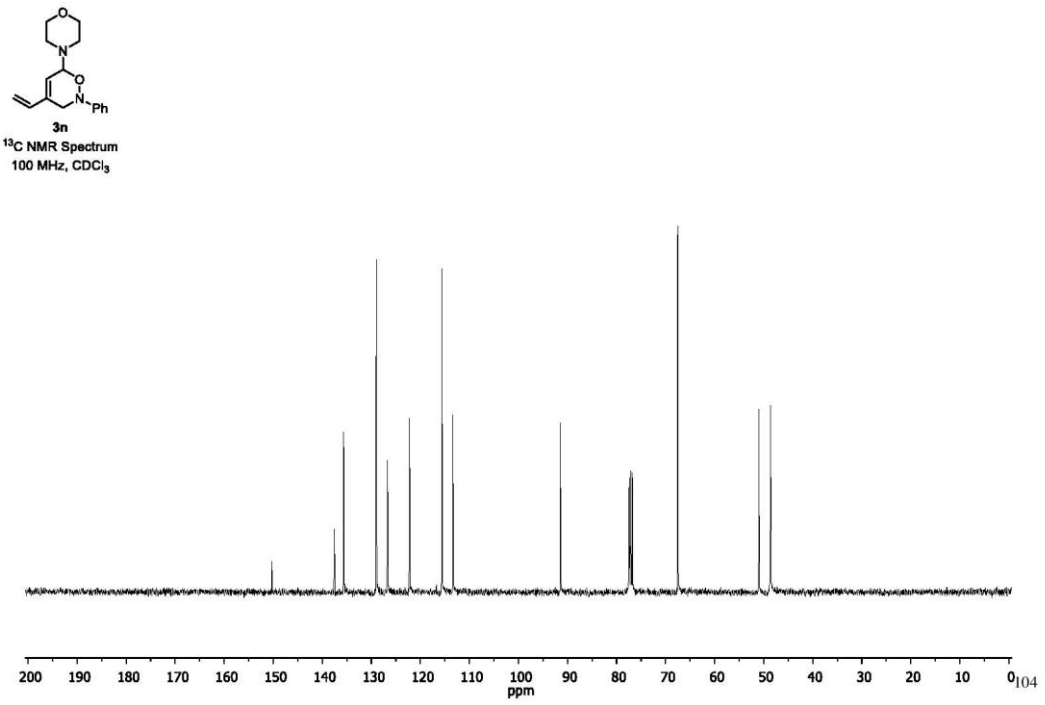
100


3m
^{1}H NMR Spectrum
300 MHz, toluene-d$_8$
100 °C
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
101

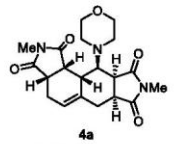

3m
^{13}C NMR Spectrum
75 MHz, toluene-d$_8$
100 °C
126 125 124
ppm
31 30 29 28 27 26
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm
102


3n
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

103


3n
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

104

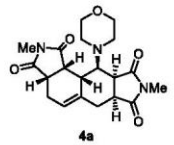


4a

^{1}H NMR Spectrum

400 MHz, $CDCl_3$

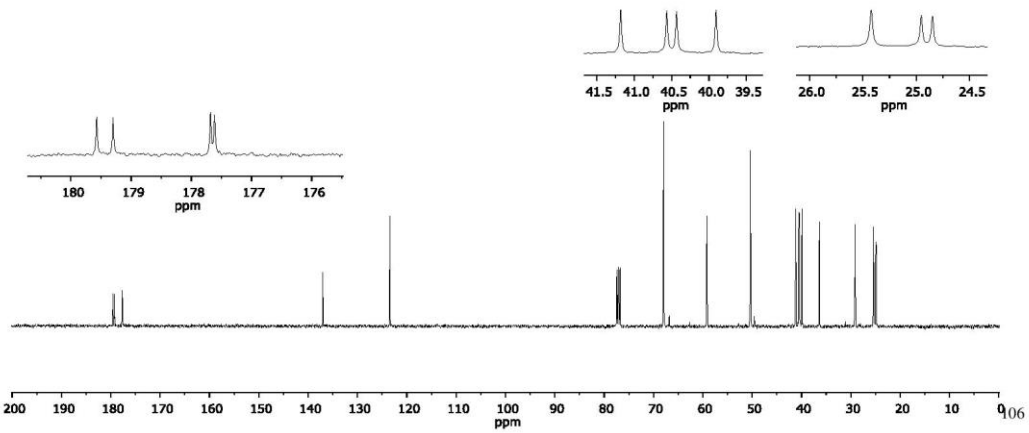
105



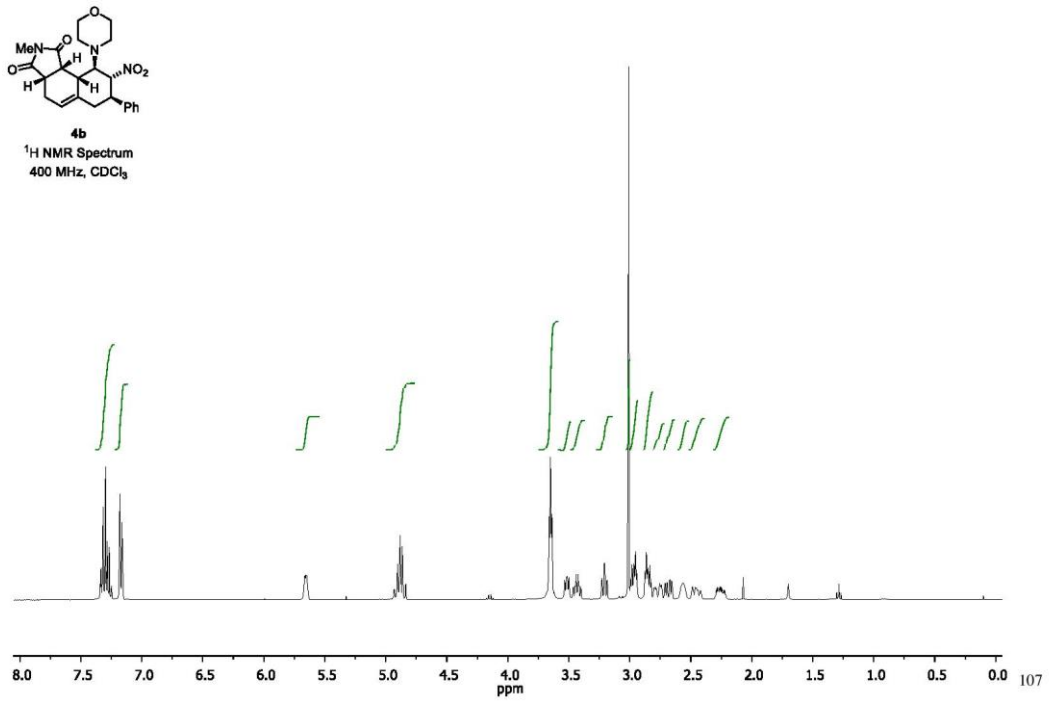
4a

^{13}C NMR Spectrum

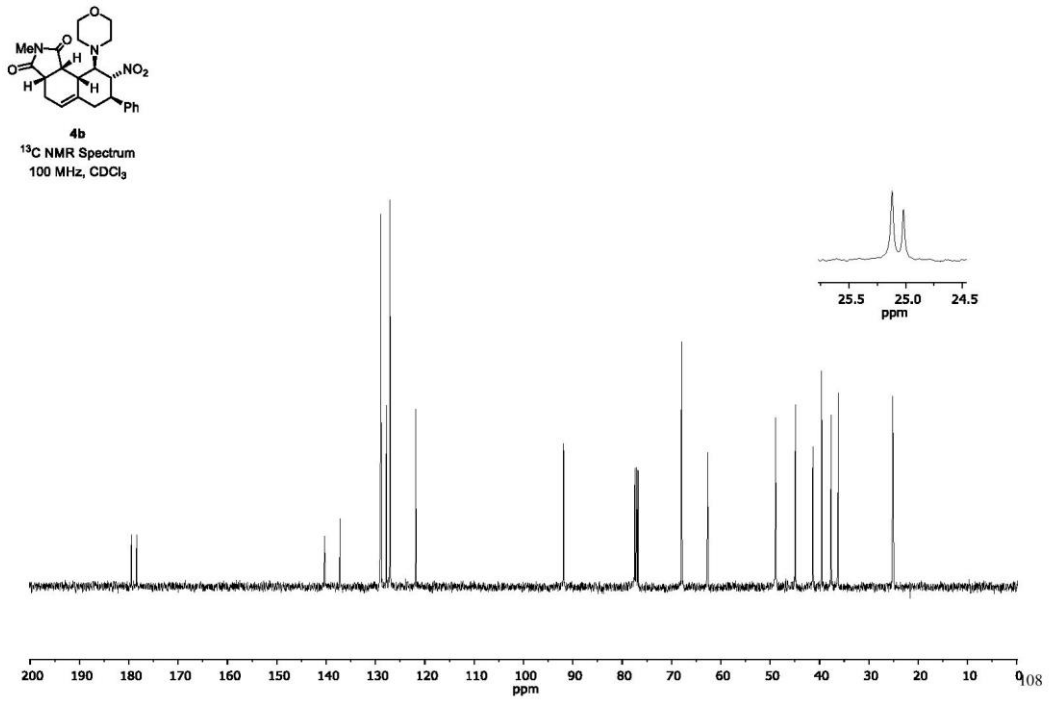
100 MHz, $CDCl_3$



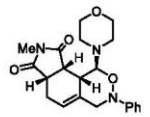
106


4b
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

107


4b
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
25.5 25.0 24.5
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

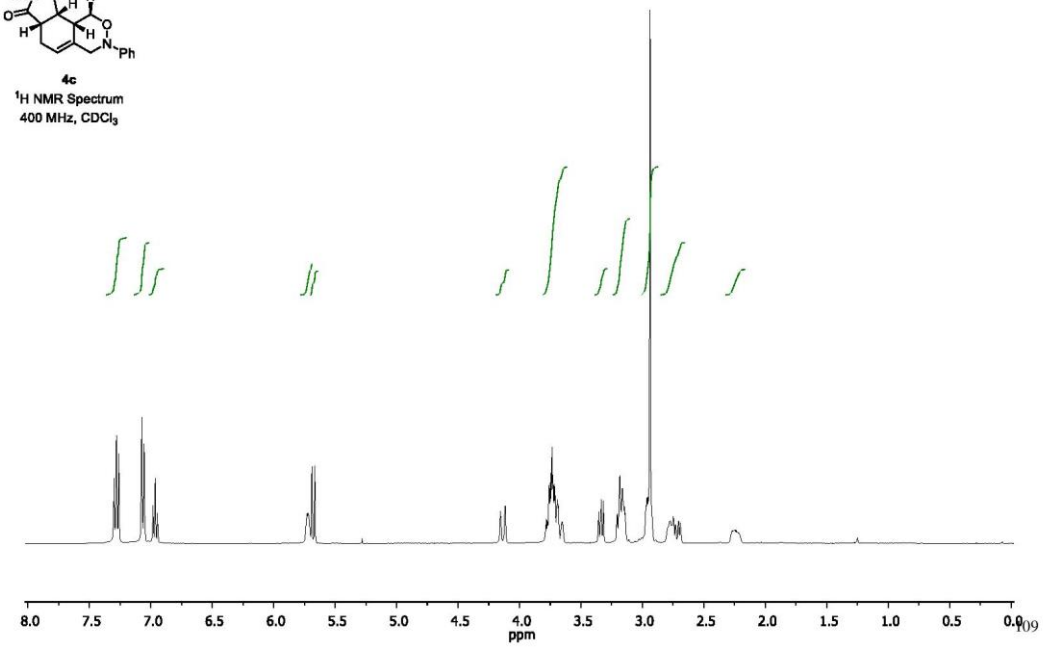
108



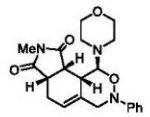
4c

^{1}H NMR Spectrum

400 MHz, $CDCl_3$



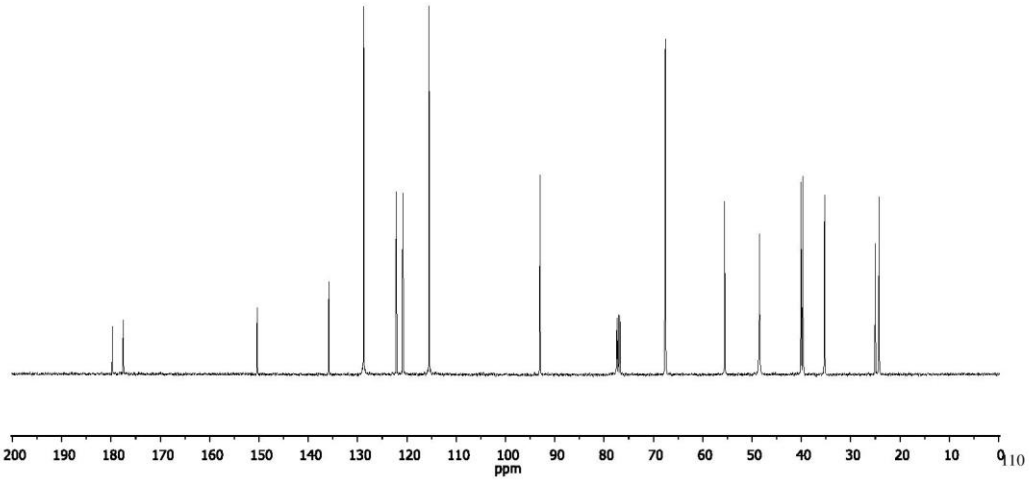
109



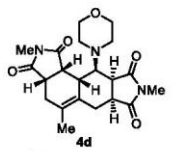
4c

^{13}C NMR Spectrum

100 MHz, $CDCl_3$

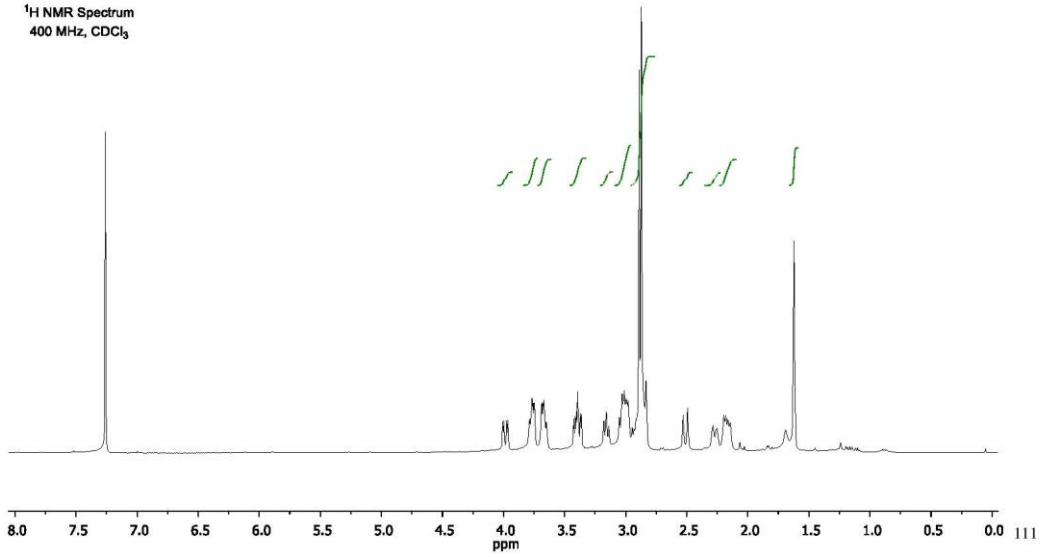


110

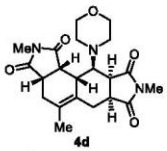


4d

^{1}H NMR Spectrum
400 MHz, $CDCl_3$

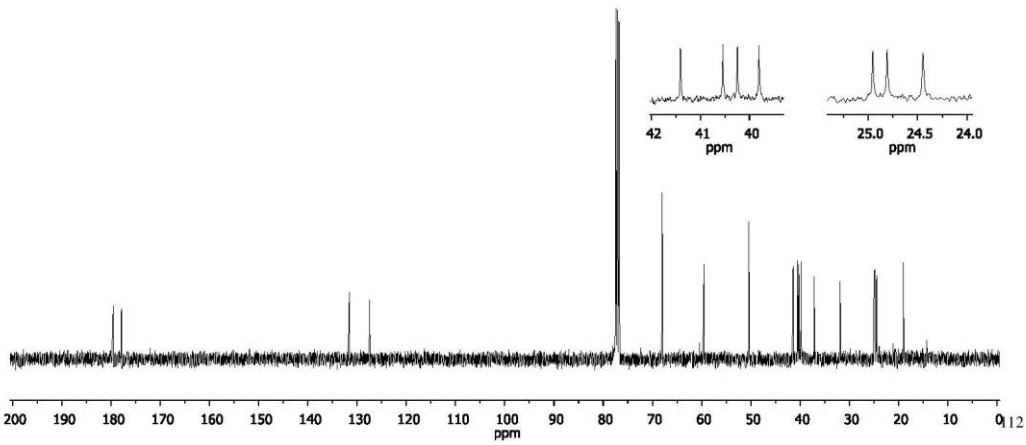


111

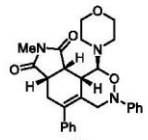


4d

^{13}C NMR Spectrum
100 MHz, $CDCl_3$

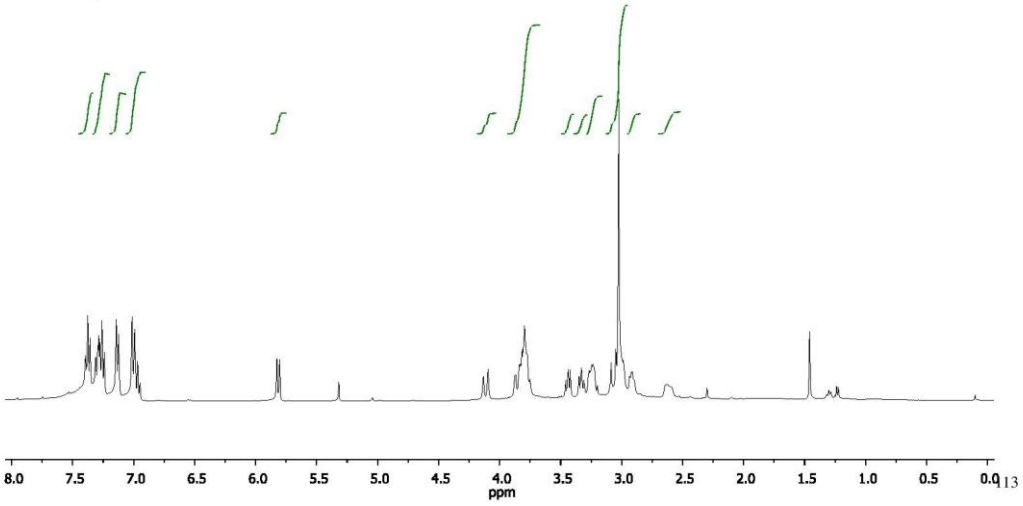


112

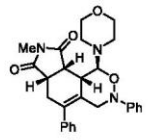


4e

^{1}H NMR Spectrum
400 MHz, $CDCl_3$

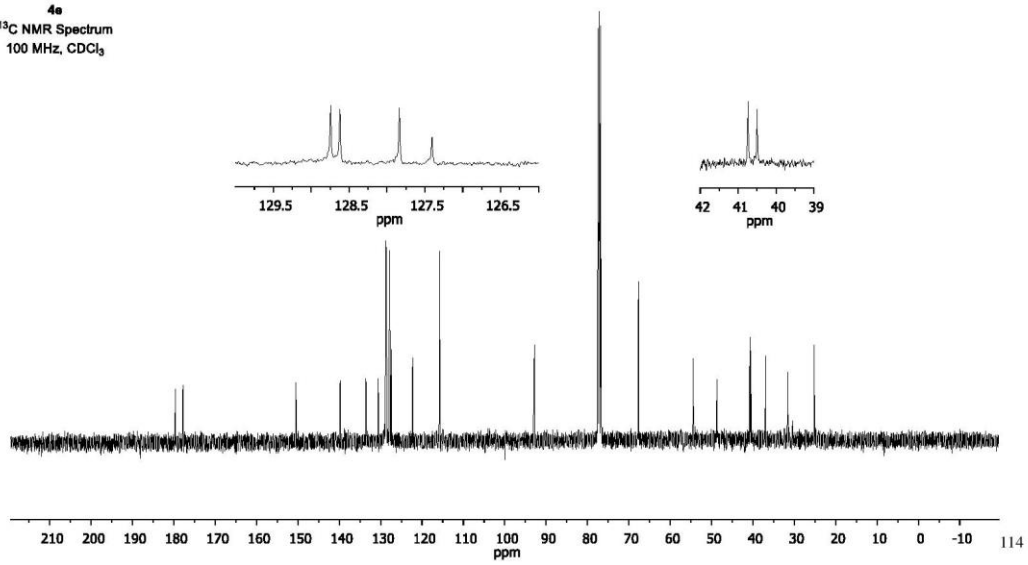


113

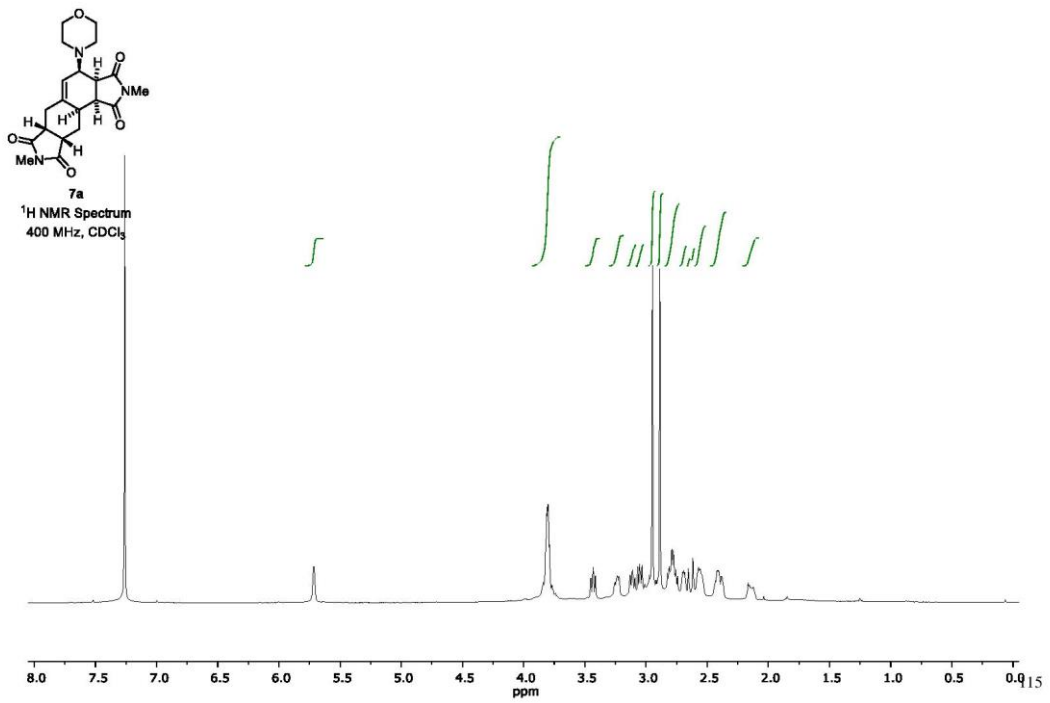


4e

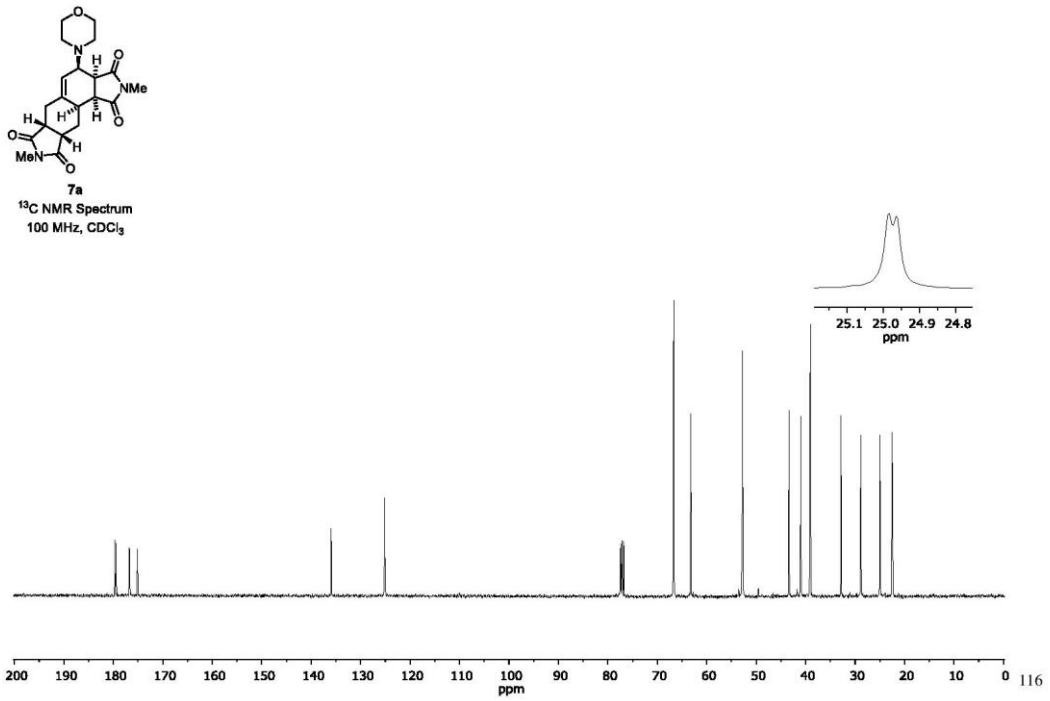
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



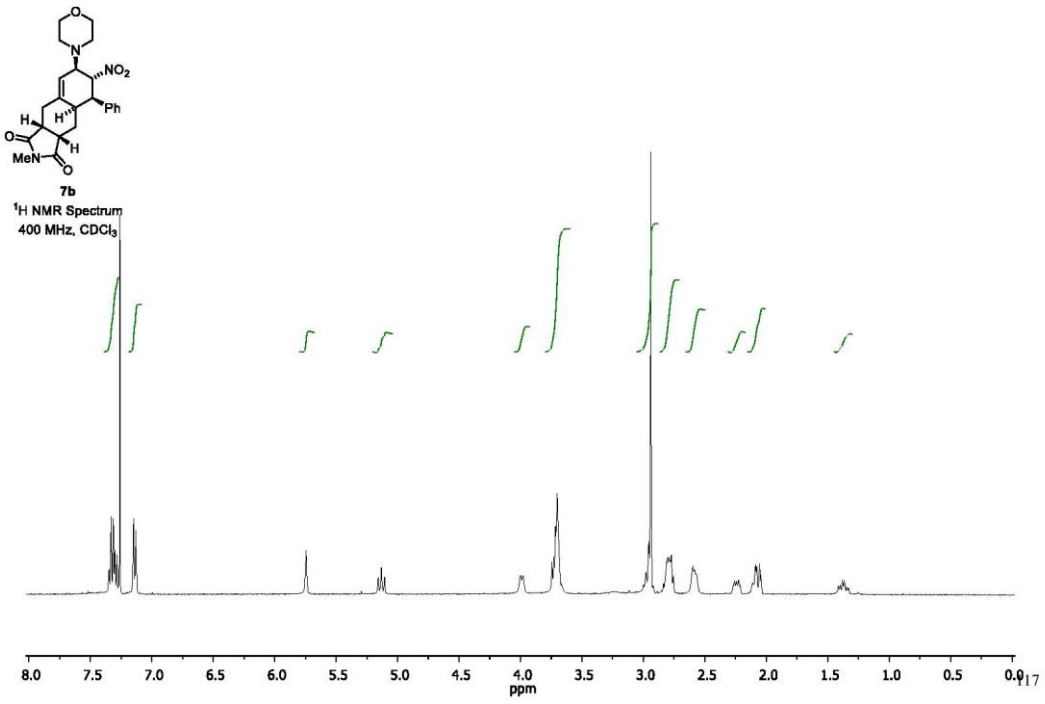
114


7a
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

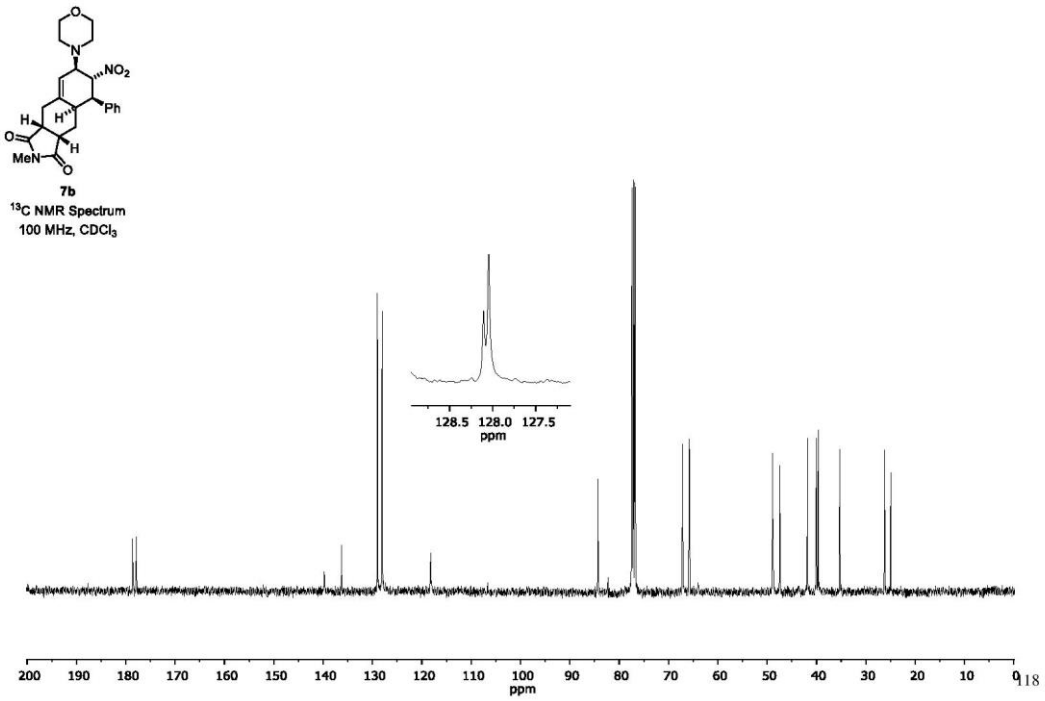
115


7a
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
25.1 25.0 24.9 24.8
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

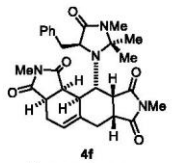
116


7b
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

117


7b
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
128.5 128.0 127.5
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

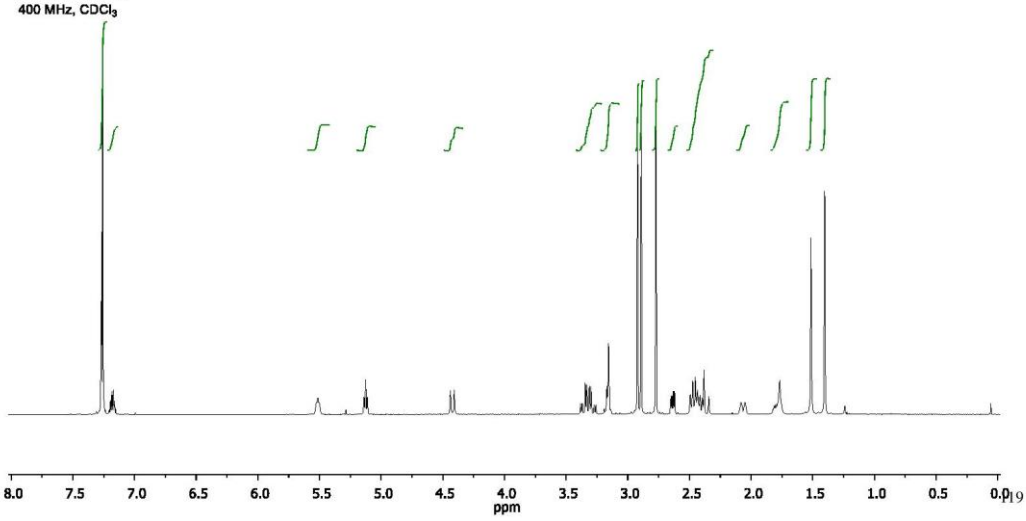
118



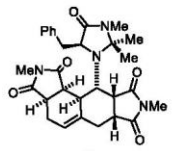
4f

^{1}H NMR Spectrum

400 MHz, $CDCl_3$



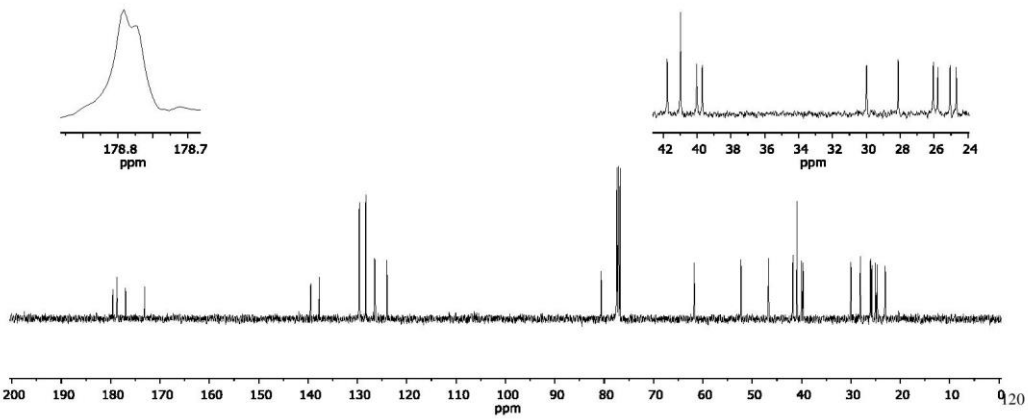
19



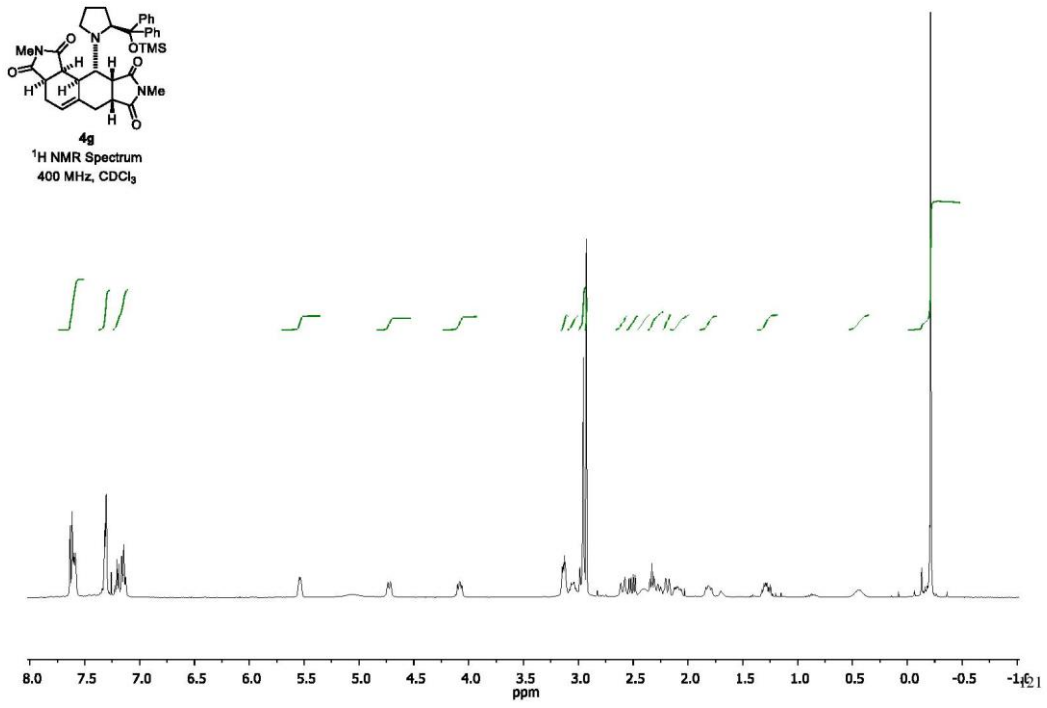
4f

^{13}C NMR Spectrum

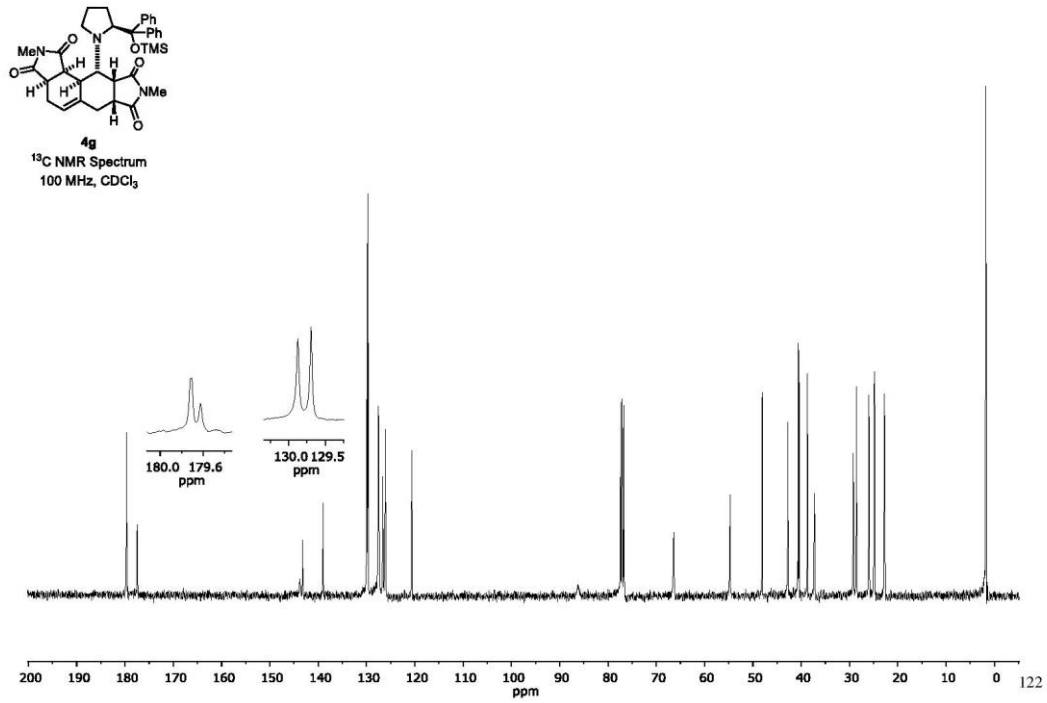
100 MHz, $CDCl_3$



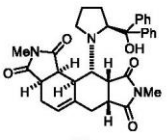
120


4g
^{1}H NMR Spectrum
400 MHz, CDCl$_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

121


4g
^{13}C NMR Spectrum
100 MHz, CDCl$_3$
180.0 179.6
ppm
130.0 129.5
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

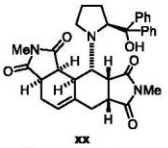
122



xx

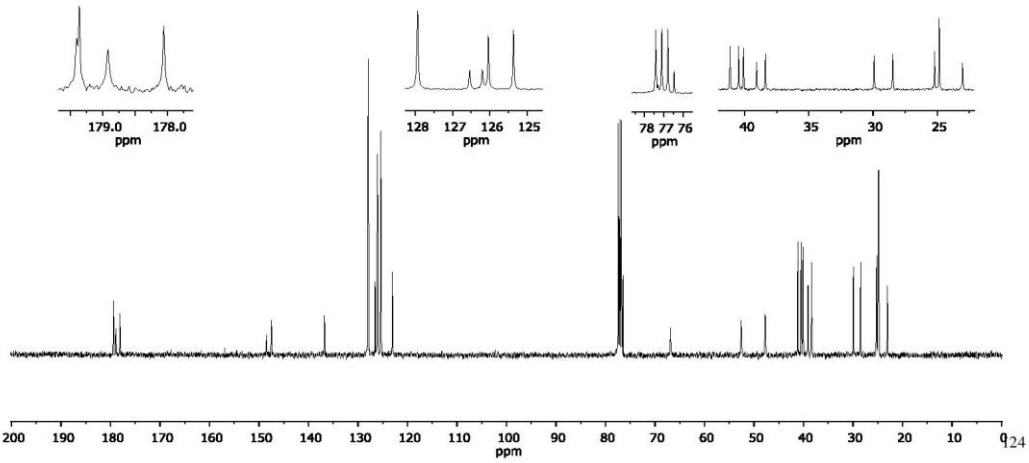
^{1}H NMR Spectrum
400 MHz, $CDCl_3$

123

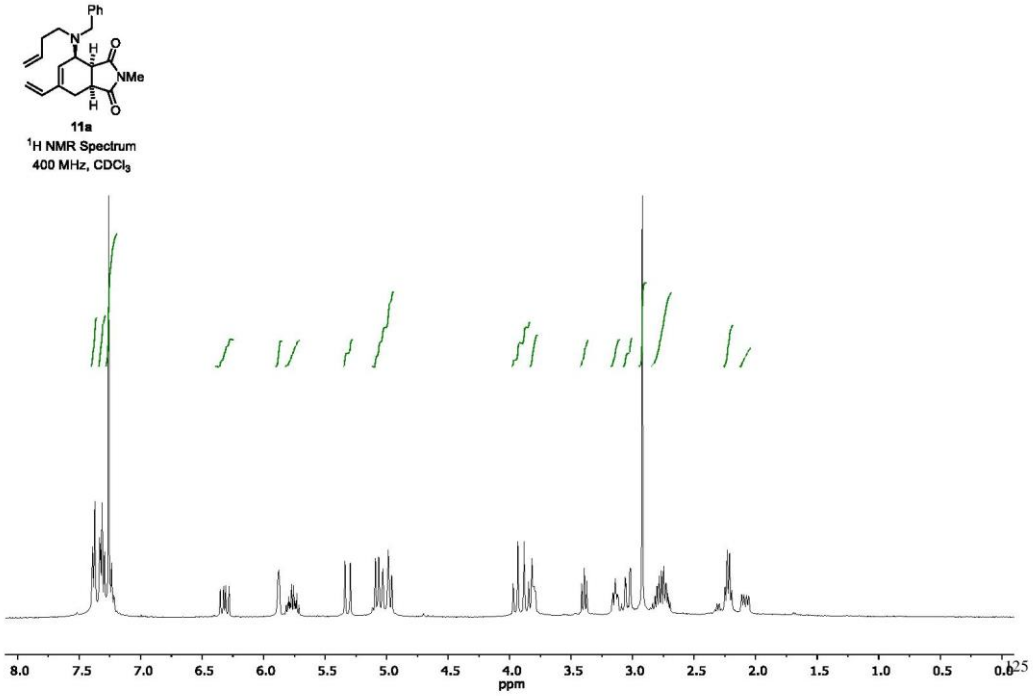


xx

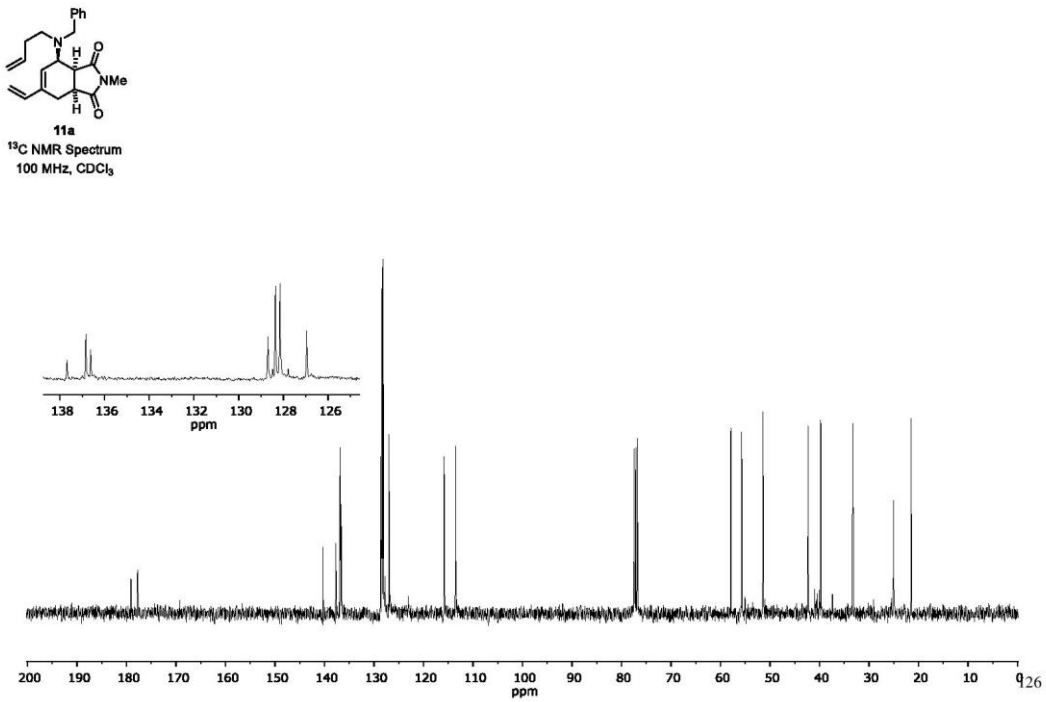
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



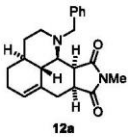
124


Ph
N
H
O
NMe
O
H
11a
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

125

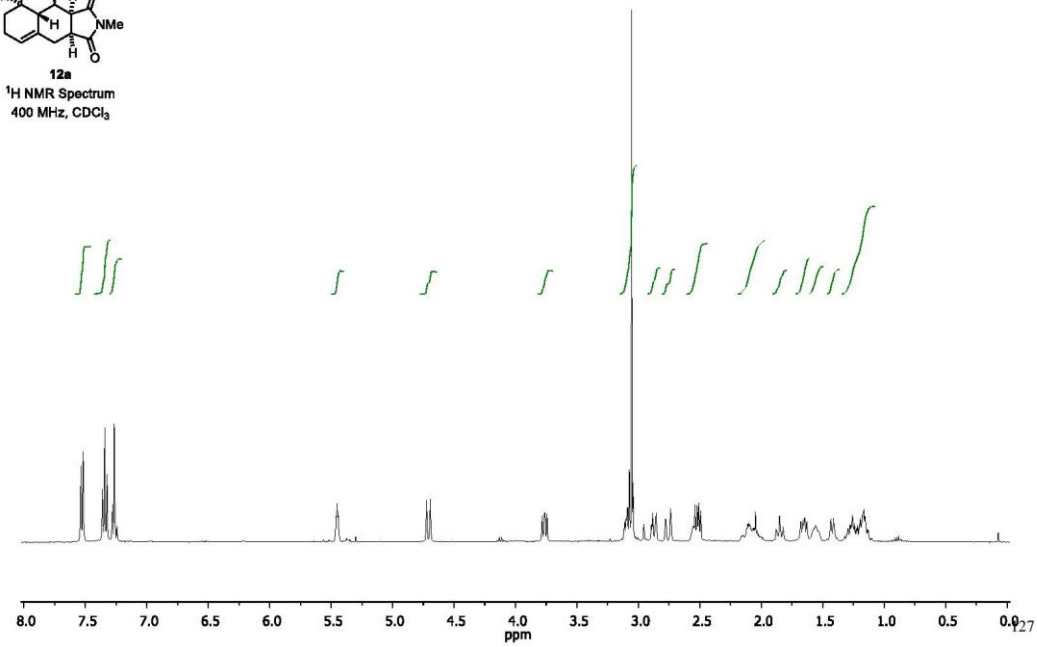

Ph
N
H
O
NMe
O
H
11a
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
138 136 134 132 130 128 126
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

126

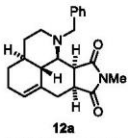


12a

^{1}H NMR Spectrum
400 MHz, $CDCl_3$

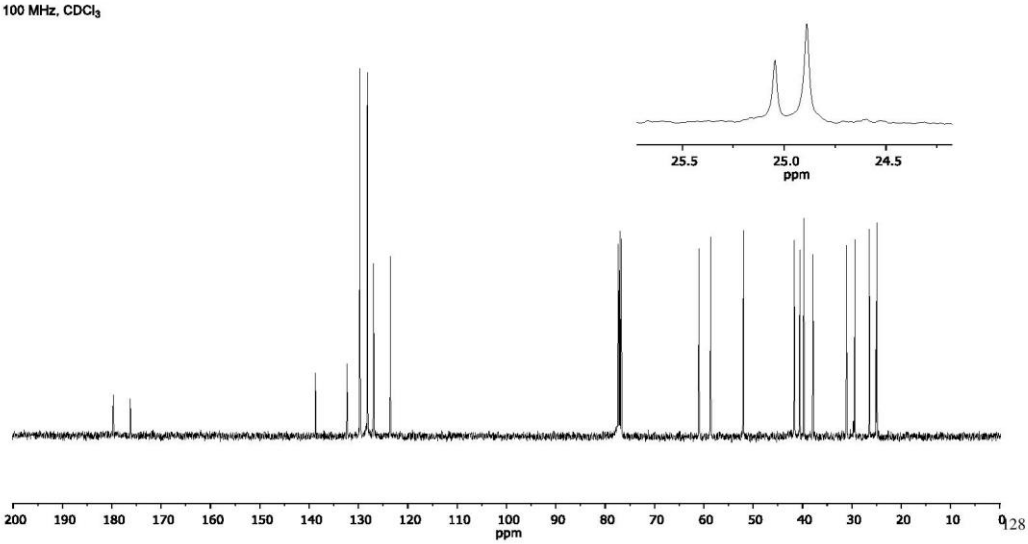


127

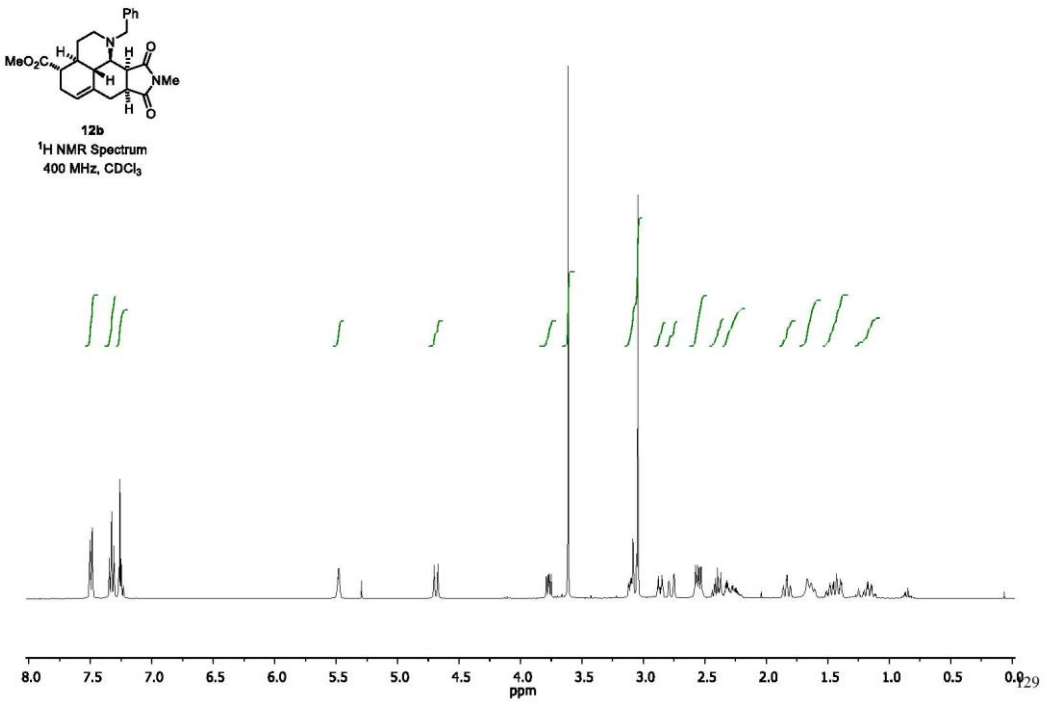


12a

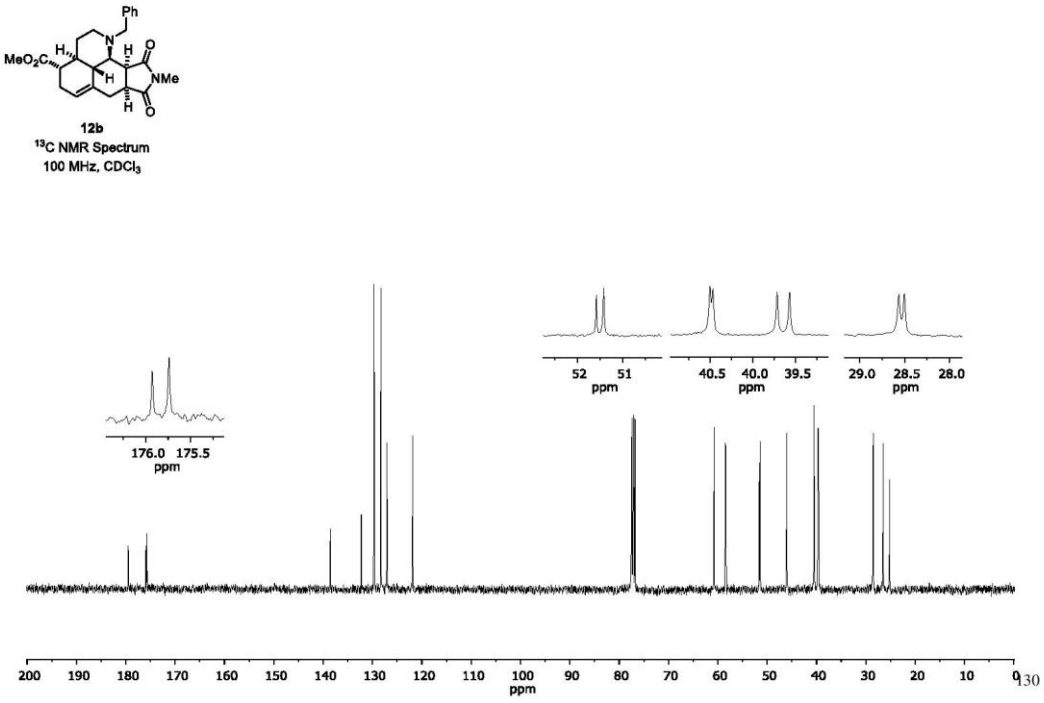
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



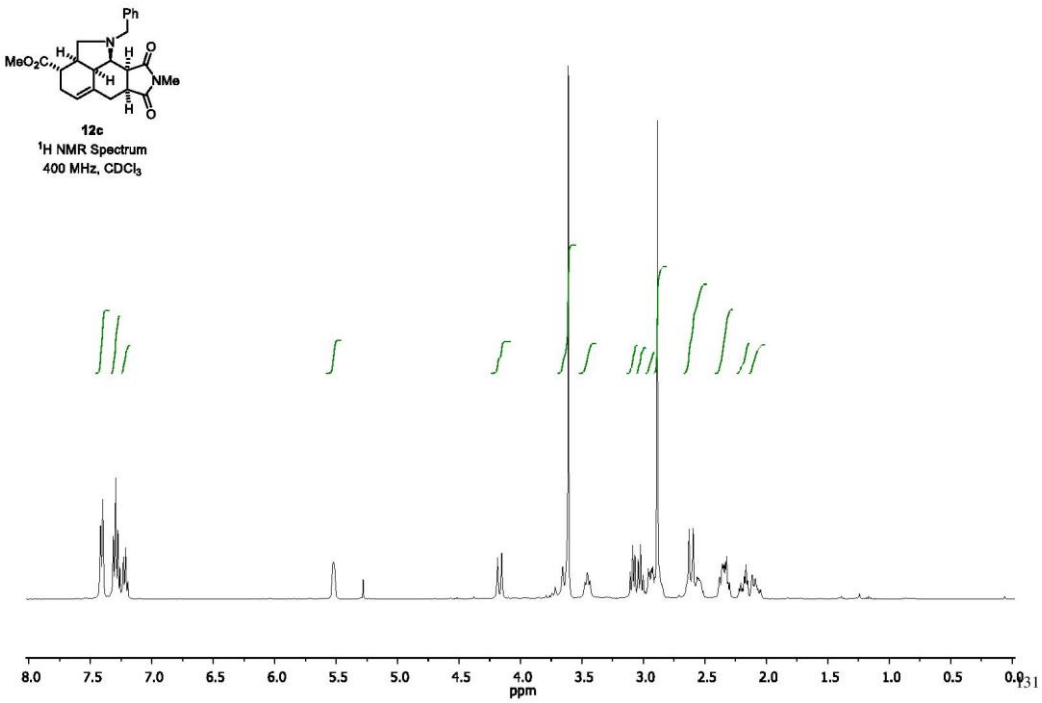
128


Ph
N
H
O
NMe
O
H
H
MeO2C
12b
1H NMR Spectrum
400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

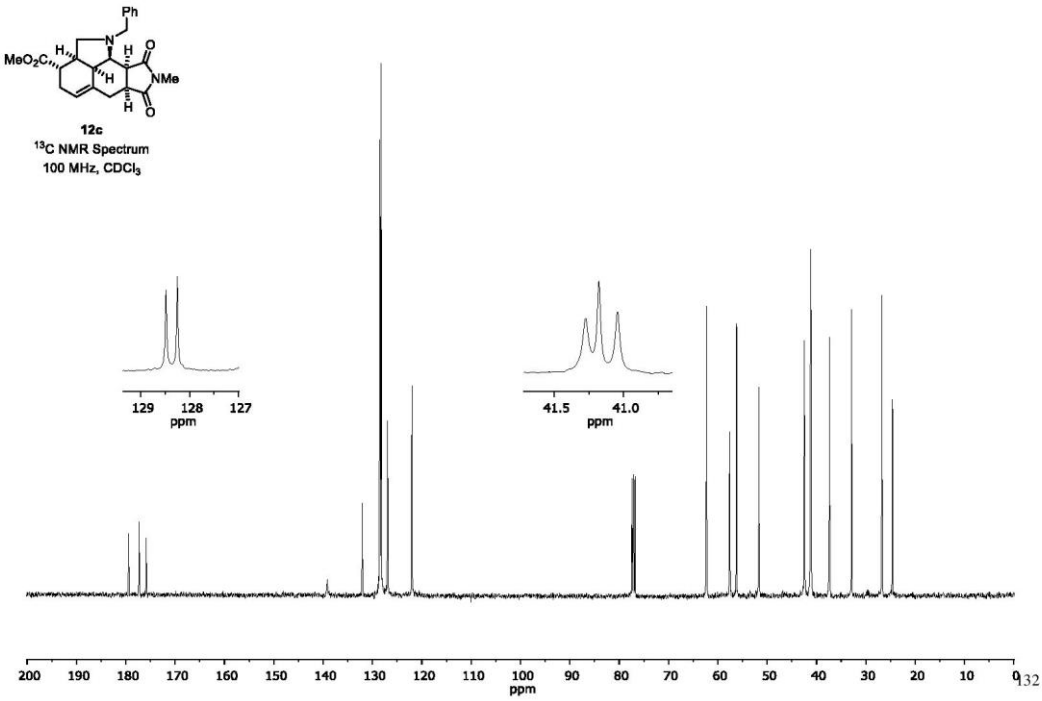
f29


Ph
N
H
O
NMe
O
H
H
MeO2C
12b
13C NMR Spectrum
100 MHz, CDCl3
176.0 175.5
ppm
52 51
ppm
40.5 40.0 39.5
ppm
29.0 28.5 28.0
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

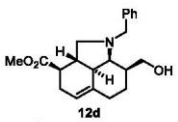
f30


Ph
N
H
O
MeO2C
H
H
NMe
H
O
12c
1H NMR Spectrum
400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

131

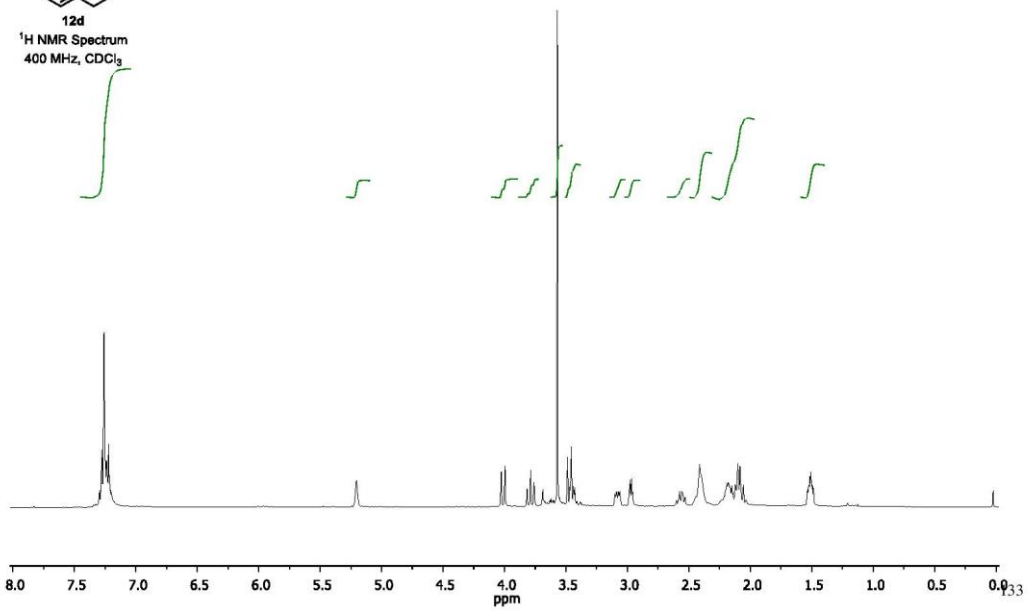

Ph
N
H
O
MeO2C
H
H
NMe
H
O
12c
13C NMR Spectrum
100 MHz, CDCl3
129 128 127
ppm
41.5 41.0
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

132

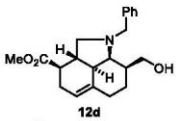


12d

^{1}H NMR Spectrum
400 MHz, $CDCl_3$

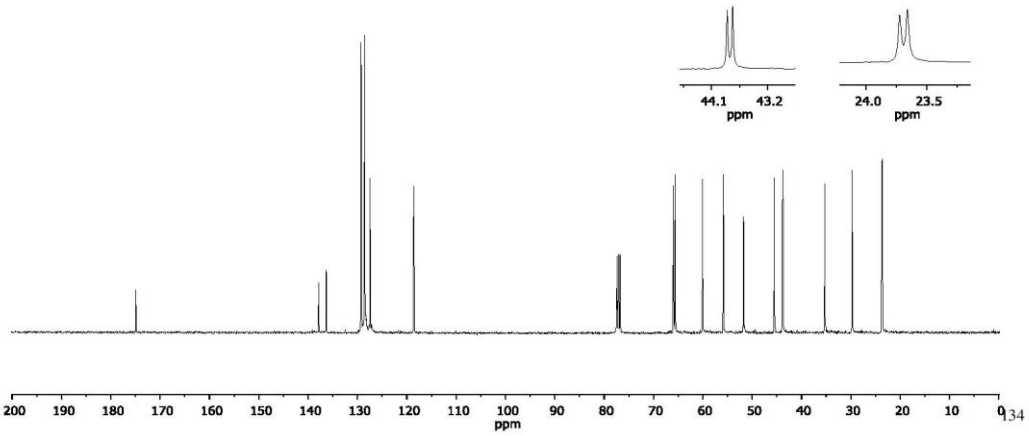


133

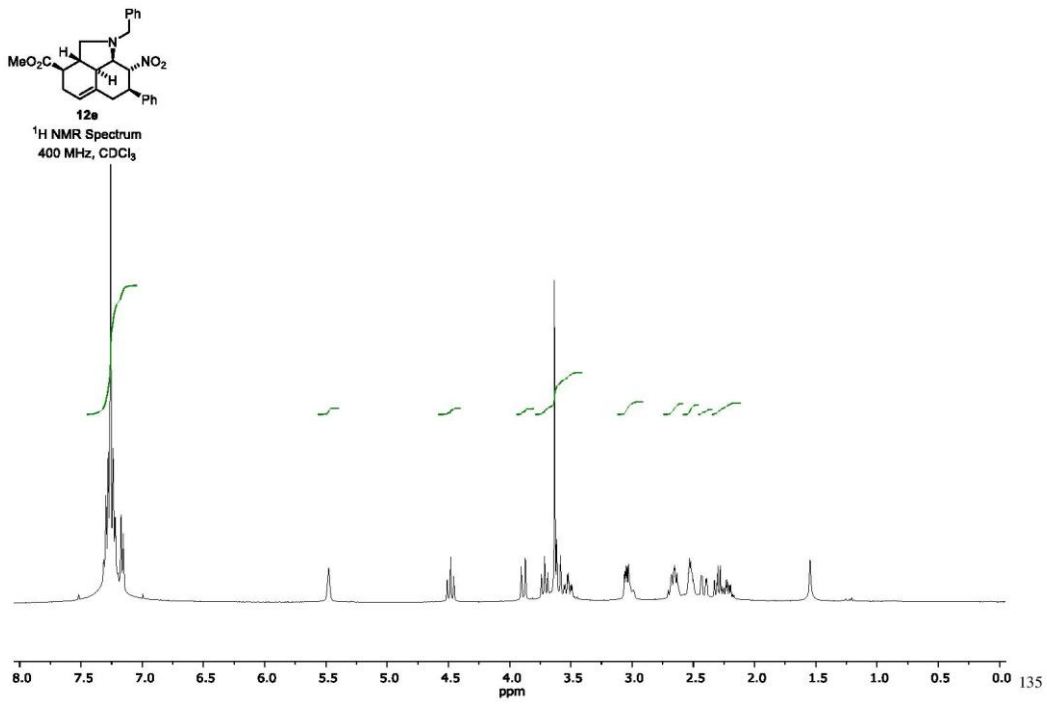


12d

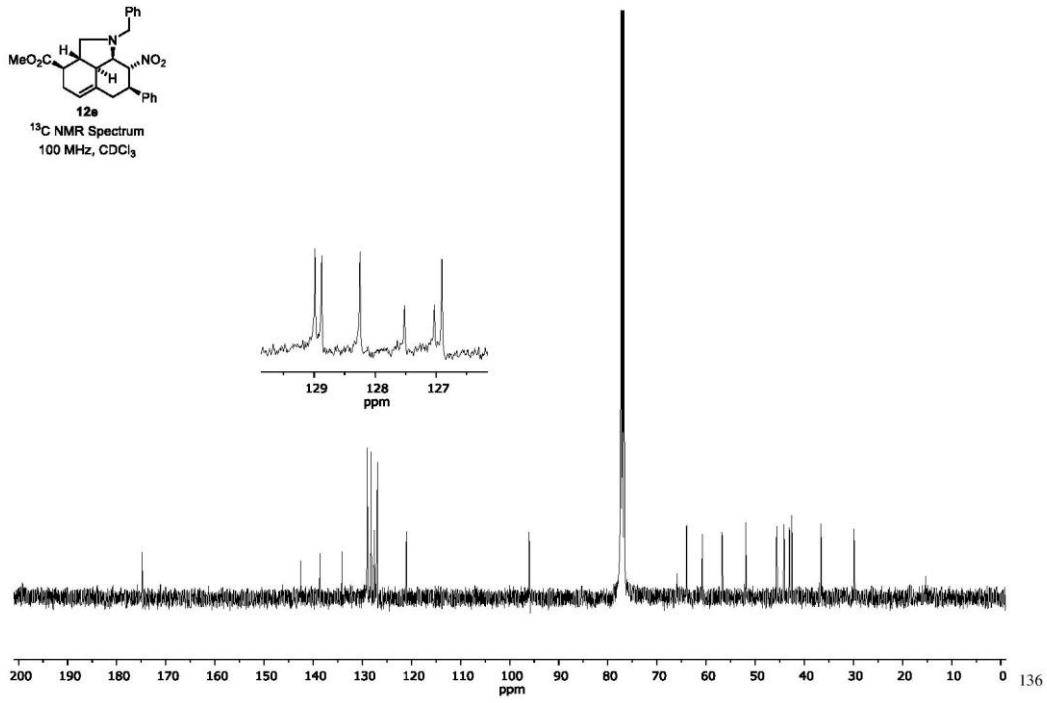
^{13}C NMR Spectrum
100 MHz, $CDCl_3$



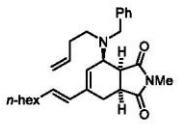
134


Ph
N
MeO2C
H
NO2
H
Ph
12e
1H NMR Spectrum
400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

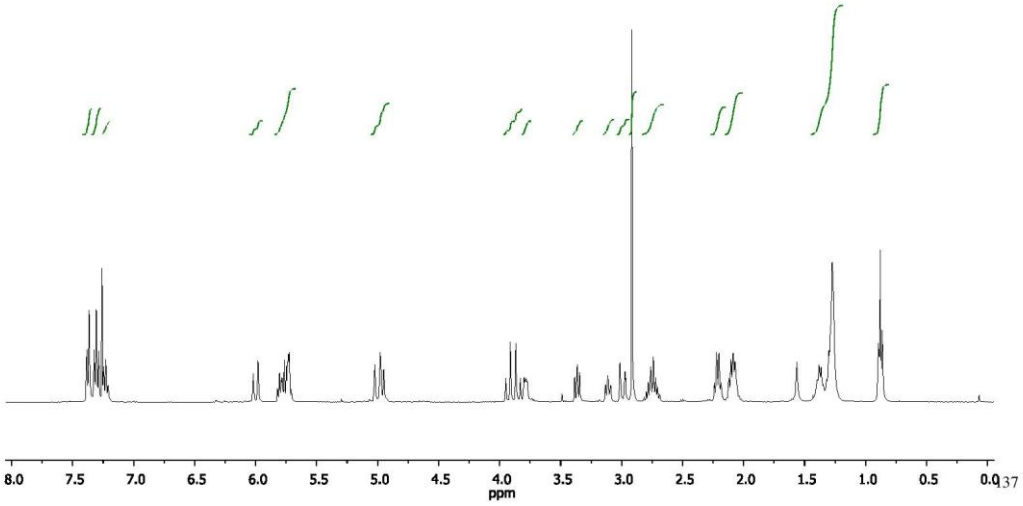
135


Ph
N
MeO2C
H
NO2
H
Ph
12e
13C NMR Spectrum
100 MHz, CDCl3
129 128 127
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

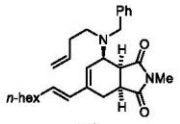
136



11f
^{1}H NMR Spectrum
400 MHz, $CDCl_3$

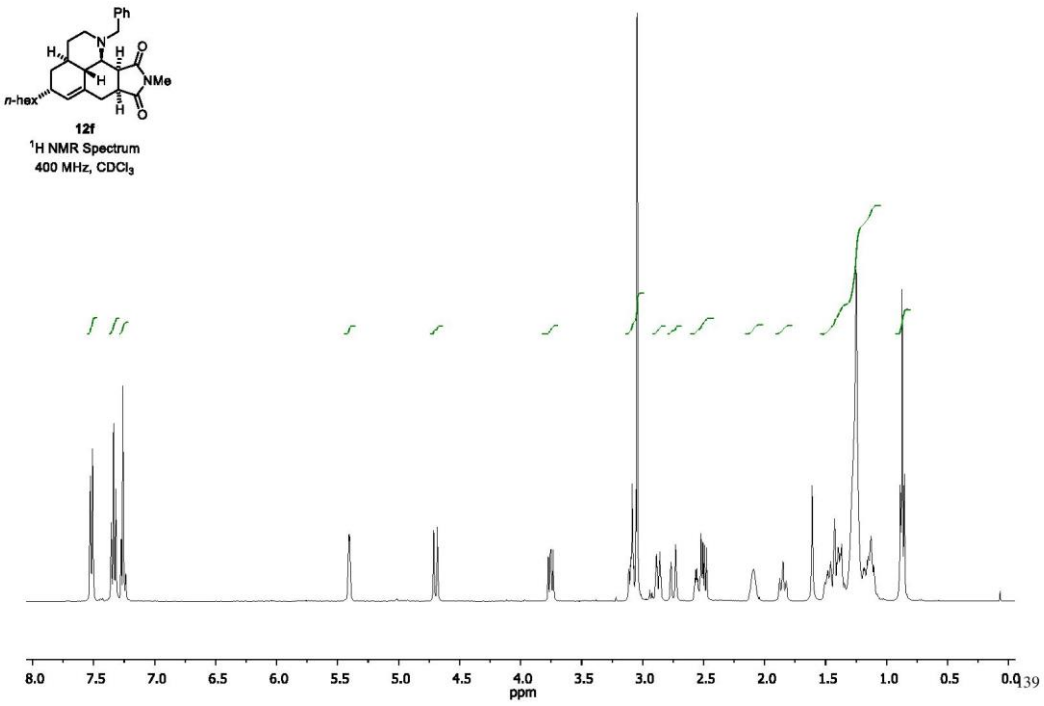


137

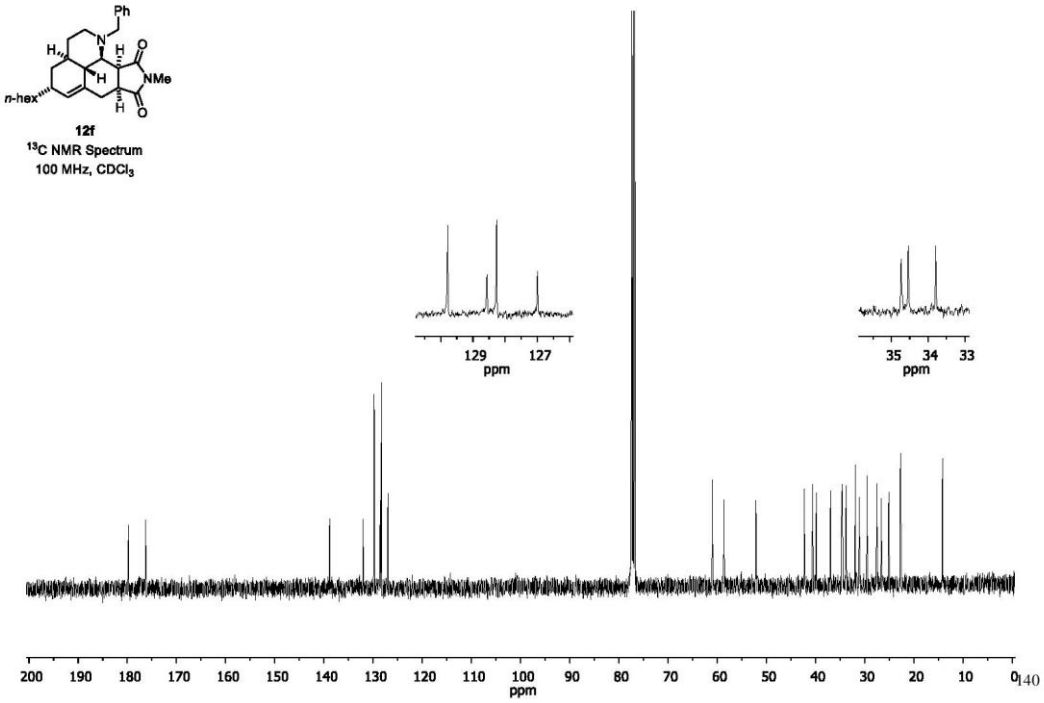


11f
^{13}C NMR Spectrum
100 MHz, $CDCl_3$

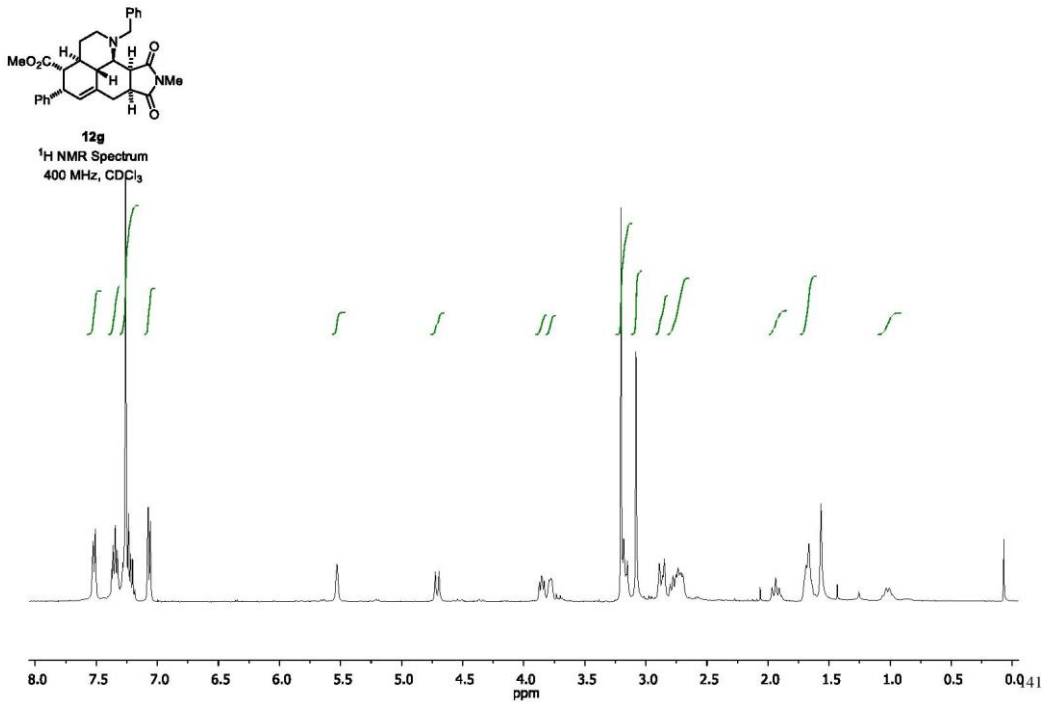
138


Ph
N
H
H
O
NMe
O
H
n-hex
12f
1H NMR Spectrum
400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

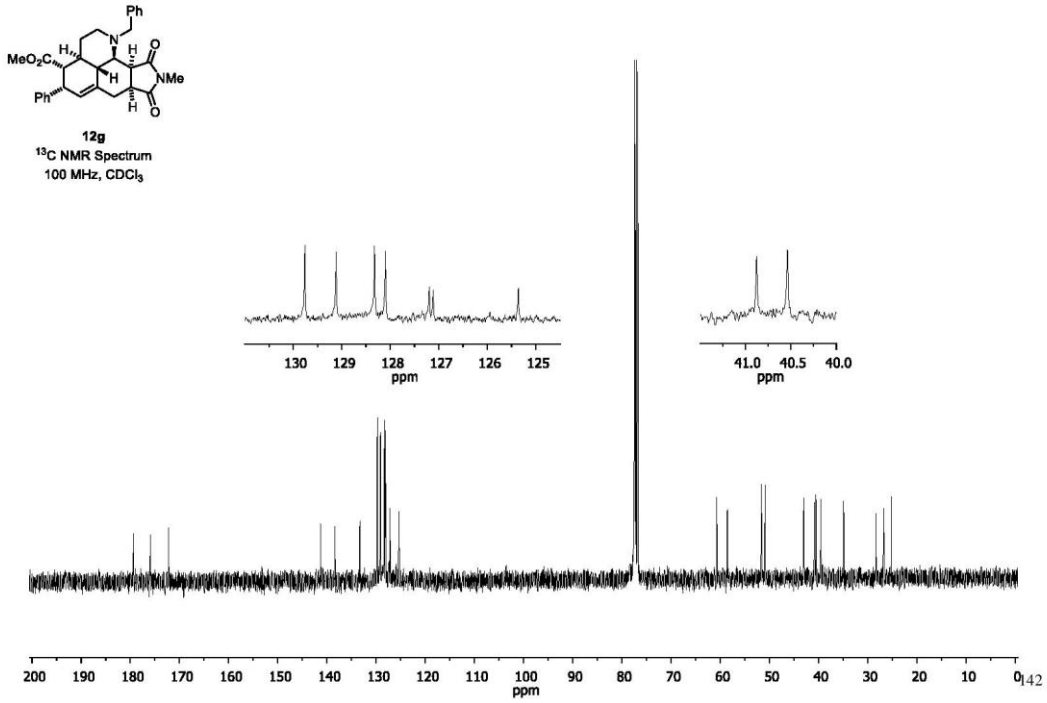
139


Ph
N
H
H
O
NMe
O
H
n-hex
12f
13C NMR Spectrum
100 MHz, CDCl3
129 127
ppm
35 34 33
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

140


12g
1H NMR Spectrum
400 MHz, CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

141


12g
13C NMR Spectrum
100 MHz, CDCl3
130 129 128 127 126 125
ppm
41.0 40.5 40.0
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

142

Computational Section

Computational methods

All calculations were carried out using the GAUSSIAN 09 software package.[1] The B3LYP[2] functional and the 6-31G(d) basis set were employed as the model chemistry (B3LYP/6-31G(d)). Gas phase geometry optimisations, vibrational harmonic frequencies, thermal corrections, characterisations of stationary points and IRC analyses were done using B3LYP/6-31G(d). Entropies were corrected using the quasi harmonic approximation as described by Truhlar and co-workers.[3]

References

[1] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision E.01: Gaussian, Inc. Wallingford, CT, USA **2009**.

[2] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785-789; For reviews of density-functional methods, see: c) R. G. Parr, W. Yang, *Density-functional Theory of Atoms and Molecules,* Oxford University Press: New York, **1989**; d) *Density Functional Methods in Chemistry,* (Eds.: J. K. Labanowski, J. W. Andzelm), Springer-Verlag: New York, **1991**; e) T. Ziegler, *Chem. Rev.* **1991**, *91*, 651-667; f) W. Koch, M. C. Holthausen, *A Chemist's Guide to Density Functional Theory,* Wiley-WCH: Weinheim, **2000**.

[3] Y. Zhao, D. G. Truhlar, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813-2818.

Cartesian coordinates and energies of molecules

***N*-Methyl maleimide**

B3LYP/6-31G(d)

Eel = -398.74426237 au; Energy(0K)) = -398.64761327 au

Enthalpy = -398.63946266 au; Gibbs energy = -398.67908594 au

C 0.648962 -1.635328 -0.000001

C -0.687108 -1.619422 0.000003

C 1.146789 -0.216105 0.000000

C -1.152765 -0.189625 -0.000001

O -2.292689 0.227376 0.000000

O 2.294046 0.180470 0.000000

H -1.386621 -2.445565 -0.000003

N 0.007507 0.591791 -0.000001

C 0.029639 2.043058 0.000000

H 0.544133 2.418626 -0.889298

H -1.006320 2.385759 -0.000029

H 0.544081 2.418628 0.889329

H 1.328210 -2.478214 -0.000003

##########

Conformations of Jørgensen-Hayashi organocatalyst-derived aminodendralene 2c, in descending order of Energy (0K); most stable first

c_syn_S_diPhTMS_pyrrolidine_1_0_t_vin

B3LYP/6-31G(d)

Eel = -1430.11529776 au; Energy(0K)) = -1429.58797217 au

Enthalpy = -1429.55637634 au; Gibbs energy = -1429.64335665 au

C	2.206563	-0.043904	-1.178081
C	3.511914	-0.185988	-0.836801
H	1.807969	0.947276	-1.371462
H	3.884310	-1.153460	-0.510599
C	4.465732	0.929794	-0.852205
C	4.407777	1.941382	-1.749971
H	5.084622	2.789656	-1.689637
H	3.684741	1.948307	-2.559587
C	5.540797	0.952364	0.157916
C	5.664075	0.132114	1.209944
H	6.295823	1.724522	0.008952
H	6.499057	0.222845	1.898894
H	4.937163	-0.645548	1.426427
N	1.274105	-1.041188	-1.294923
C	-0.146516	-0.784309	-1.531609
C	1.620584	-2.448758	-1.454896

C	-0.681007	-2.122663	-2.103099
H	-0.225108	0.025021	-2.267502
C	0.571179	-2.946522	-2.456895
H	1.563857	-2.992864	-0.500516
H	2.645208	-2.531272	-1.831850
H	-1.333440	-1.960616	-2.965081
H	-1.270697	-2.650491	-1.350005
H	0.396979	-4.025370	-2.393395
H	0.904830	-2.718453	-3.475768
C	-0.912000	-0.254401	-0.246536
C	-0.640491	-1.211479	0.929058
C	-1.439343	-2.337002	1.187828
C	0.501168	-1.021291	1.721926
C	-1.116583	-3.232850	2.209713
H	-2.336011	-2.511809	0.602051
C	0.825180	-1.915026	2.743275
H	1.146294	-0.173989	1.524362
C	0.017391	-3.025295	2.994115
H	-1.759008	-4.090614	2.391579
H	1.715283	-1.741576	3.342697
H	0.268220	-3.719505	3.791801
C	-2.412534	-0.031094	-0.533417
C	-3.351485	-0.028337	0.511506

C	-2.875005	0.297651	-1.817784
C	-4.694331	0.274918	0.283056
H	-3.030886	-0.270200	1.518643
C	-4.218019	0.595749	-2.052243
H	-2.188694	0.336728	-2.655743
C	-5.136689	0.585097	-1.003008
H	-5.394030	0.265894	1.114776
H	-4.542708	0.841946	-3.059838
H	-6.182375	0.818039	-1.184785
O	-0.295849	1.011259	0.006494
Si	-0.667242	2.434399	0.830483
C	-1.249999	2.142454	2.604891
H	-1.258357	3.097734	3.146107
H	-2.263101	1.730060	2.656001
H	-0.581887	1.461150	3.142879
C	-1.946894	3.462642	-0.102012
H	-1.638084	3.630995	-1.140354
H	-2.933681	2.988816	-0.118482
H	-2.055315	4.446010	0.374026
C	0.981586	3.344121	0.855199
H	1.368209	3.503521	-0.157833
H	0.879427	4.326802	1.332520
H	1.742520	2.780914	1.407237

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c_syn_S_diPhTMS_pyrrolidine_2_2_t_vin

B3LYP/6-31G(d)

Eel = -1430.11528187 au; Energy(0K)) = -1429.58793241 au

Enthalpy = -1429.55642950 au; Gibbs energy = -1429.64329751 au

C	2.358492	0.081846	-1.003018
C	3.652540	-0.179124	-0.687409
H	2.002603	1.108286	-0.973582
H	3.990523	-1.208314	-0.600861
C	4.644591	0.873907	-0.435932
C	4.633931	2.066590	-1.074920
H	5.340559	2.851105	-0.817135
H	3.920695	2.290054	-1.862084
C	5.707517	0.619528	0.554657
C	5.792155	-0.430121	1.382632
H	6.488883	1.378582	0.594609
H	6.621898	-0.533867	2.075927
H	5.037968	-1.211455	1.406950
N	1.400825	-0.834274	-1.352670
C	-0.008888	-0.495981	-1.563298
C	1.731606	-2.179328	-1.820074

C	-0.577110	-1.723925	-2.317870
H	-0.076934	0.389685	-2.206231
C	0.655347	-2.452239	-2.876840
H	1.692678	-2.913125	-1.001356
H	2.747445	-2.182808	-2.229677
H	-1.285012	-1.420442	-3.091909
H	-1.114630	-2.375877	-1.624143
H	0.478691	-3.520635	-3.037419
H	0.963697	-2.014376	-3.833705
C	-0.850184	-0.154053	-0.256626
C	-0.443501	1.211304	0.348481
C	-0.237571	1.408740	1.721011
C	-0.356832	2.339022	-0.488216
C	0.069268	2.671801	2.234065
H	-0.322179	0.573644	2.405693
C	-0.047984	3.600458	0.019209
H	-0.548714	2.241199	-1.551854
C	0.172958	3.772851	1.386836
H	0.226449	2.788366	3.303114
H	0.017848	4.449029	-0.656761
H	0.417870	4.753750	1.784871
C	-0.741426	-1.318925	0.741603
C	-1.820131	-2.185668	0.957485

C	0.465111	-1.590864	1.411810
C	-1.711351	-3.276826	1.823696
H	-2.749595	-2.015356	0.428221
C	0.575520	-2.682074	2.274210
H	1.325043	-0.945753	1.268857
C	-0.512984	-3.530241	2.487888
H	-2.567667	-3.929890	1.971833
H	1.518348	-2.865452	2.783283
H	-0.425195	-4.377973	3.162234
O	-2.181783	-0.055905	-0.771431
Si	-3.620535	0.711219	-0.341817
C	-3.789248	2.356048	-1.252034
H	-3.650847	2.227212	-2.332287
H	-4.791920	2.774297	-1.095476
H	-3.060607	3.094863	-0.903876
C	-3.819132	0.978111	1.515963
H	-3.682678	0.048076	2.078871
H	-3.108308	1.713039	1.906370
H	-4.831629	1.347817	1.724566
C	-4.959936	-0.459929	-0.971611
H	-4.952672	-1.419188	-0.440980
H	-5.956099	-0.018591	-0.841674
H	-4.827087	-0.671252	-2.039007

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t_syn_S_diPhTMS_pyrrolidine_1_0_c_vin

B3LYP/6-31G(d)

Eel = -1430.11449374 au; Energy(0K)) = -1429.58708410 au

Enthalpy = -1429.55560763 au; Gibbs energy = -1429.64230744 au

C	2.339114	-0.450964	-0.861719
C	3.593886	-0.797940	-0.474996
H	2.090857	0.591755	-1.031385
H	3.810582	-1.828367	-0.203267
C	4.706121	0.142263	-0.358762
C	5.876658	-0.217061	0.215945
H	6.727550	0.455375	0.239311
H	6.012167	-1.202542	0.654800
C	4.554878	1.500460	-0.936453
C	4.978998	2.635605	-0.369271
H	4.056136	1.553672	-1.905026
H	4.872635	3.594228	-0.870506
H	5.444474	2.643518	0.612883
N	1.277103	-1.297197	-1.061987
C	-0.048192	-0.815981	-1.454989
C	1.431948	-2.732199	-1.282032

C	-0.698066	-2.028869	-2.169552
H	0.089126	0.025490	-2.144631
C	0.456240	-3.012577	-2.432195
H	1.177816	-3.309372	-0.381450
H	2.470963	-2.953204	-1.545125
H	-1.211034	-1.727230	-3.086391
H	-1.444195	-2.498405	-1.524324
H	0.122652	-4.054713	-2.465700
H	0.945016	-2.784677	-3.386623
C	-0.887005	-0.230623	-0.242601
C	-0.914007	-1.268308	0.895197
C	-1.890504	-2.273563	0.981972
C	0.127338	-1.282409	1.835268
C	-1.834969	-3.250677	1.978578
H	-2.718427	-2.288058	0.280566
C	0.184679	-2.257727	2.831463
H	0.903354	-0.529335	1.773545
C	-0.796705	-3.247184	2.909324
H	-2.610192	-4.011207	2.025435
H	1.003272	-2.243835	3.546478
H	-0.753562	-4.005253	3.686898
C	-2.288001	0.230148	-0.700783
C	-3.349968	0.322714	0.213783

C	-2.520573	0.687474	-2.008149
C	-4.592187	0.836073	-0.161572
H	-3.206447	-0.013101	1.234346
C	-3.762674	1.196569	-2.389810
H	-1.728922	0.662812	-2.748311
C	-4.807025	1.273222	-1.468551
H	-5.392188	0.891340	0.572172
H	-3.909146	1.538409	-3.411066
H	-5.774095	1.670537	-1.764661
O	-0.130825	0.912584	0.168400
Si	-0.415632	2.344646	1.013853
C	-1.391060	2.100797	2.615626
H	-1.287432	2.998147	3.239647
H	-2.460330	1.942703	2.443297
H	-1.011143	1.250106	3.192066
C	-1.282152	3.615818	-0.080237
H	-0.727656	3.777219	-1.012223
H	-2.300280	3.312188	-0.344468
H	-1.343734	4.581066	0.439052
C	1.317513	2.942734	1.441907
H	1.963437	3.001232	0.559198
H	1.282042	3.939439	1.899903
H	1.806714	2.267966	2.153980

##########

t_syn_S_diPhTMS_pyrrolidine_2_2_c_vin

B3LYP/6-31G(d)

Eel = -1430.11440359 au; Energy(0K)) = -1429.58695579 au

Enthalpy = -1429.55551410 au; Gibbs energy = -1429.64204019 au

C	-2.391189	0.497020	-0.825716
C	-3.627294	0.944101	-0.480522
H	-2.184061	-0.568853	-0.822442
H	-3.811617	2.013071	-0.404693
C	-4.761172	0.078062	-0.165271
C	-5.912958	0.584657	0.330531
H	-6.779970	-0.043296	0.505649
H	-6.015986	1.644084	0.552109
C	-4.647707	-1.375632	-0.437465
C	-5.087448	-2.347774	0.368259
H	-4.160962	-1.651082	-1.373727
H	-5.002156	-3.395332	0.091707
H	-5.541186	-2.128817	1.331442
N	-1.313797	1.270218	-1.178604
C	0.013306	0.726740	-1.479608
C	-1.450372	2.671681	-1.572588

C	0.744851	1.898815	-2.178247
H	-0.085250	-0.111249	-2.180571
C	-0.375048	2.837412	-2.652178
H	-1.282673	3.348740	-0.721787
H	-2.463040	2.849194	-1.950251
H	1.380704	1.541757	-2.990905
H	1.389648	2.418223	-1.464321
H	-0.040748	3.874027	-2.762199
H	-0.773820	2.508022	-3.619096
C	0.836469	0.163375	-0.238644
C	0.230089	-1.155806	0.295633
C	0.010092	-1.405084	1.657285
C	-0.042816	-2.199259	-0.607519
C	-0.489629	-2.633709	2.097227
H	0.233145	-0.639122	2.390030
C	-0.544345	-3.425207	-0.172876
H	0.152178	-2.062802	-1.666245
C	-0.776608	-3.647379	1.185788
H	-0.652636	-2.792474	3.159936
H	-0.750674	-4.208013	-0.898218
H	-1.170861	-4.600480	1.527449
C	0.963463	1.260787	0.830967
C	2.180462	1.921176	1.043005

C	-0.153116	1.687562	1.572913
C	2.291277	2.956721	1.974609
H	3.046289	1.636241	0.458171
C	-0.044096	2.723944	2.500892
H	-1.115603	1.207852	1.434535
C	1.179638	3.362771	2.710054
H	3.250755	3.447399	2.117391
H	-0.922664	3.029210	3.063494
H	1.262707	4.167907	3.435289
O	2.110955	-0.117045	-0.825189
Si	3.421262	-1.130292	-0.506587
C	3.287045	-2.726563	-1.505737
H	3.078244	-2.515362	-2.561427
H	4.234320	-3.279511	-1.461921
H	2.498324	-3.386255	-1.130511
C	3.640404	-1.530514	1.324645
H	3.666554	-0.623962	1.939361
H	2.837091	-2.169924	1.704111
H	4.589619	-2.061772	1.473126
C	4.906745	-0.154577	-1.141519
H	5.081779	0.756002	-0.556870
H	5.820698	-0.759634	-1.092115
H	4.762864	0.145213	-2.186052

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t_syn_S_diPhTMS_pyrrolidine_1_0_t_vin

B3LYP/6-31G(d)

Eel = -1430.11372228 au; Energy(0K)) = -1429.58611908 au

Enthalpy = -1429.55464432 au; Gibbs energy = -1429.64123524 au

C	-2.380069	0.226596	-0.783081
C	-3.646391	0.535413	-0.402326
H	-2.053530	-0.805334	-0.813990
H	-3.912807	1.578896	-0.250684
C	-4.687757	-0.429170	-0.038214
C	-5.727568	-0.049005	0.742855
H	-6.518766	-0.741754	1.014528
H	-5.821161	0.968678	1.111981
C	-4.683844	-1.829184	-0.517946
C	-4.095443	-2.328240	-1.613859
H	-5.292053	-2.505991	0.082615
H	-4.217403	-3.374482	-1.880941
H	-3.512043	-1.716595	-2.294024
N	-1.390872	1.117594	-1.118016
C	-0.037248	0.695738	-1.486106
C	-1.658467	2.507410	-1.475827

C	0.531754	1.900341	-2.275931
H	-0.119967	-0.192465	-2.124388
C	-0.691866	2.758087	-2.639904
H	-1.467811	3.187659	-0.632622
H	-2.707967	2.616526	-1.767575
H	1.098213	1.576217	-3.152567
H	1.213198	2.478960	-1.647693
H	-0.442594	3.816245	-2.768432
H	-1.145359	2.403253	-3.572795
C	0.840701	0.239450	-0.246244
C	0.796257	1.338594	0.832077
C	1.699541	2.413739	0.855272
C	-0.239476	1.333025	1.778261
C	1.580638	3.437667	1.797757
H	2.520640	2.448726	0.146620
C	-0.360283	2.355064	2.720380
H	-0.962735	0.527033	1.765170
C	0.550249	3.412628	2.736810
H	2.300823	4.251862	1.796182
H	-1.173097	2.323571	3.441383
H	0.458181	4.207069	3.472700
C	2.270958	-0.148864	-0.682954
C	3.341293	-0.101868	0.225390

C	2.528513	-0.681215	-1.956899
C	4.614721	-0.552548	-0.125713
H	3.180791	0.295707	1.221072
C	3.801450	-1.126840	-2.314760
H	1.732409	-0.767434	-2.687443
C	4.853325	-1.064882	-1.400863
H	5.420281	-0.500144	0.602129
H	3.966298	-1.529434	-3.310766
H	5.844457	-1.413648	-1.677961
O	0.167442	-0.932071	0.227657
Si	0.553552	-2.282950	1.162110
C	1.416641	-1.841522	2.783952
H	1.443561	-2.724271	3.436114
H	2.450059	-1.513597	2.633214
H	0.885676	-1.046719	3.319018
C	1.600968	-3.519970	0.194817
H	1.116445	-3.797350	-0.748721
H	2.596248	-3.130141	-0.041202
H	1.730973	-4.438853	0.781439
C	-1.134002	-3.032727	1.533357
H	-1.708033	-3.209971	0.616830
H	-1.029148	-3.992212	2.055398
H	-1.734506	-2.371601	2.168916

##########

t_syn_S_diPhTMS_pyrrolidine_2_2_t_vin

B3LYP/6-31G(d)

Eel = -1430.11352276 au; Energy(0K)) = -1429.58569103 au

Enthalpy = -1429.55436996 au; Gibbs energy = -1429.64065312 au

C	2.469001	-0.315480	-0.677834
C	3.699220	-0.753353	-0.303117
H	2.221802	0.737118	-0.598312
H	3.892652	-1.823366	-0.280153
C	4.792881	0.085444	0.196762
C	5.769883	-0.457020	0.961933
H	6.598594	0.138556	1.333752
H	5.772844	-1.512610	1.219585
C	4.906508	1.524406	-0.128021
C	4.395583	2.175512	-1.181333
H	5.536839	2.087738	0.560362
H	4.596601	3.232805	-1.330884
H	3.795492	1.682062	-1.938657
N	1.439454	-1.096658	-1.141285
C	0.108399	-0.575601	-1.464076
C	1.652636	-2.450391	-1.651851

C	-0.538161	-1.703460	-2.305272
H	0.207671	0.326833	-2.079693
C	0.641468	-2.554059	-2.799262
H	1.469555	-3.208618	-0.876048
H	2.689733	-2.554947	-1.988188
H	-1.145041	-1.296227	-3.116468
H	-1.197112	-2.308168	-1.676628
H	0.355501	-3.587275	-3.020892
H	1.076242	-2.122786	-3.708947
C	-0.801507	-0.159684	-0.226634
C	-0.271595	1.113698	0.474673
C	-0.154898	1.229636	1.866733
C	0.035619	2.247773	-0.298562
C	0.275178	2.418921	2.461433
H	-0.405361	0.388748	2.502004
C	0.469420	3.434520	0.290424
H	-0.075653	2.214394	-1.377471
C	0.596156	3.525130	1.677721
H	0.357371	2.473604	3.543769
H	0.707111	4.289148	-0.337505
H	0.937117	4.447733	2.139410
C	-0.956723	-1.358318	0.724664
C	-2.168850	-2.053890	0.816980

C	0.133534	-1.834758	1.475605
C	-2.299890	-3.175819	1.639688
H	-3.013952	-1.726136	0.224287
C	0.004437	-2.957276	2.294263
H	1.089794	-1.325679	1.430240
C	-1.214008	-3.633245	2.383393
H	-3.254796	-3.692778	1.691233
H	0.862392	-3.300471	2.866758
H	-1.313045	-4.505897	3.023538
O	-2.048738	0.141624	-0.860125
Si	-3.394449	1.107806	-0.544881
C	-3.228040	2.785468	-1.395073
H	-2.957446	2.667481	-2.451304
H	-4.184769	3.322588	-1.359224
H	-2.472079	3.419459	-0.921081
C	-3.745908	1.345774	1.293826
H	-3.808176	0.388847	1.823817
H	-2.978708	1.951530	1.786121
H	-4.708558	1.858767	1.418238
C	-4.814990	0.169893	-1.359999
H	-5.001691	-0.797294	-0.878908
H	-5.745367	0.749291	-1.308984
H	-4.601662	-0.023038	-2.417814

##########

c_syn_S_diPhTMS_pyrrolidine_1_0_c_vin

B3LYP/6-31G(d)

Eel = -1430.11175566 au; Energy(0K)) = -1429.58467820 au

Enthalpy = -1429.55305473 au; Gibbs energy = -1429.64012672 au

C -2.217620 0.213472 -1.011921

C -3.500417 0.429595 -0.622884

H -1.887244 -0.800092 -1.218351

H -3.801372 1.415294 -0.274567

C -4.520692 -0.625112 -0.595087

C -4.502676 -1.713010 -1.399118

H -5.202266 -2.530796 -1.257770

H -3.782857 -1.814688 -2.205928

C -5.600317 -0.444327 0.405765

C -6.874413 -0.825653 0.258982

H -5.311360 0.071648 1.322731

H -7.606526 -0.674526 1.047692

H -7.227623 -1.294310 -0.656137

N -1.232665 1.152151 -1.166271

C 0.152980 0.805167 -1.483515

C -1.500647 2.577246 -1.327096

C	0.735701	2.101628	-2.102378
H	0.135306	-0.012416	-2.214054
C	-0.481541	2.999509	-2.393171
H	-1.356629	3.126157	-0.385023
H	-2.538199	2.718916	-1.646479
H	1.323705	1.889686	-2.999176
H	1.402088	2.598535	-1.393312
H	-0.237299	4.065796	-2.352402
H	-0.887064	2.784865	-3.388643
C	0.956945	0.236160	-0.240356
C	0.821846	1.218852	0.937563
C	1.708521	2.290574	1.131360
C	-0.277507	1.113362	1.802764
C	1.512366	3.214447	2.160195
H	2.576449	2.401038	0.489233
C	-0.475158	2.035534	2.831341
H	-0.989172	0.309950	1.656665
C	0.419613	3.090473	3.017212
H	2.221061	4.028290	2.290466
H	-1.335270	1.927999	3.487297
H	0.267218	3.806257	3.820683
C	2.420407	-0.087949	-0.613660
C	3.418308	-0.144043	0.373342

C	2.782043	-0.456805	-1.919248
C	4.722377	-0.536667	0.069018
H	3.174847	0.126198	1.394610
C	4.086216	-0.844528	-2.229695
H	2.045423	-0.457524	-2.714313
C	5.065142	-0.885844	-1.237258
H	5.469980	-0.566994	0.857415
H	4.332928	-1.119616	-3.251816
H	6.080534	-1.188614	-1.478214
O	0.273822	-0.982380	0.066281
Si	0.607566	-2.428247	0.867113
C	1.348558	-2.176326	2.588157
H	1.325713	-3.127549	3.136083
H	2.391267	-1.843503	2.556635
H	0.778671	-1.443943	3.170406
C	1.732812	-3.543929	-0.158955
H	1.319825	-3.706398	-1.161505
H	2.739842	-3.130663	-0.274471
H	1.826518	-4.526267	0.322276
C	-1.092748	-3.221003	1.028947
H	-1.576181	-3.342416	0.052979
H	-1.018601	-4.213134	1.491684
H	-1.762150	-2.612678	1.647550

##########

c_syn_S_diPhTMS_pyrrolidine_2_2_c_vin

B3LYP/6-31G(d)

Eel = -1430.11187326 au; Energy(0K)) = -1429.58437611 au

Enthalpy = -1429.55299535 au; Gibbs energy = -1429.63960634 au

C	2.338113	-0.140433	-0.899113
C	3.605719	-0.470811	-0.539637
H	2.049075	0.907258	-0.912008
H	3.869576	-1.516628	-0.398191
C	4.661301	0.518332	-0.288776
C	4.699167	1.739496	-0.867864
H	5.424101	2.487034	-0.561576
H	3.998773	2.023708	-1.647571
C	5.709632	0.104577	0.675216
C	7.001077	0.449910	0.620291
H	5.379311	-0.560831	1.474305
H	7.709059	0.121063	1.376219
H	7.393220	1.065368	-0.185478
N	1.334018	-1.005716	-1.244997
C	-0.044490	-0.585742	-1.510237
C	1.593267	-2.381143	-1.669557

C	-0.667628	-1.797575	-2.246514
H	-0.036021	0.282244	-2.180146
C	0.531608	-2.616034	-2.750044
H	1.486154	-3.088695	-0.834287
H	2.618006	-2.457334	-2.048495
H	-1.334644	-1.473947	-3.048172
H	-1.262283	-2.395208	-1.550559
H	0.292764	-3.675533	-2.887452
H	0.893226	-2.225492	-3.708770
C	-0.900387	-0.149661	-0.242008
C	-0.417904	1.201307	0.339617
C	-0.238072	1.422873	1.712141
C	-0.229343	2.296068	-0.523577
C	0.140727	2.675971	2.200939
H	-0.399327	0.614954	2.415536
C	0.151943	3.547069	-0.040278
H	-0.395724	2.180874	-1.589719
C	0.345052	3.742702	1.328431
H	0.274759	2.811926	3.270862
H	0.296498	4.369487	-0.736007
H	0.646183	4.715362	1.707624
C	-0.905103	-1.290666	0.789515
C	-2.046695	-2.076944	0.989662

C	0.258004	-1.625953	1.506352
C	-2.040731	-3.148906	1.886125
H	-2.944594	-1.860142	0.424214
C	0.265719	-2.698175	2.399141
H	1.164371	-1.045089	1.375670
C	-0.884668	-3.464413	2.597054
H	-2.943921	-3.738610	2.021020
H	1.177149	-2.931565	2.943685
H	-0.876887	-4.297466	3.294941
O	-2.204552	0.025401	-0.804409
Si	-3.601194	0.895812	-0.438513
C	-3.628264	2.528876	-1.384779
H	-3.437768	2.369068	-2.452899
H	-4.613854	3.003333	-1.293259
H	-2.880801	3.235419	-1.010717
C	-3.842685	1.212866	1.406070
H	-3.799443	0.286154	1.989069
H	-3.090550	1.898134	1.809164
H	-4.829631	1.664463	1.571502
C	-4.994922	-0.195212	-1.093815
H	-5.078399	-1.136890	-0.538697
H	-5.961300	0.318878	-1.017685
H	-4.834689	-0.446130	-2.148802

##########

c_anti_S_diPhTMS_pyrrolidine_1_0_t_vin

B3LYP/6-31G(d)

Eel = -1430.11083595 au; Energy(0K)) = -1429.58301480 au

Enthalpy = -1429.55177379 au; Gibbs energy = -1429.63786791 au

C	-2.484825	1.388662	-0.558759
C	-3.023636	0.167747	-0.343063
H	-3.132831	2.261267	-0.509697
H	-2.390155	-0.710179	-0.382128
C	-4.442181	-0.038600	-0.015906
C	-5.182308	0.838663	0.700329
H	-6.241658	0.671574	0.875802
H	-4.754144	1.740959	1.126104
C	-5.090617	-1.282008	-0.474353
C	-4.563000	-2.206126	-1.288811
H	-6.100262	-1.439749	-0.094651
H	-5.120602	-3.096941	-1.563571
H	-3.570393	-2.102303	-1.717304
N	-1.173969	1.718095	-0.847346
C	-0.199656	0.741802	-1.359395
C	-0.867778	3.054679	-1.370770

C	0.556027	1.495857	-2.492908
H	-0.768693	-0.101954	-1.764262
C	-0.261963	2.773025	-2.749080
H	-0.141684	3.561459	-0.721099
H	-1.773942	3.665874	-1.404911
H	0.659403	0.874561	-3.386004
H	1.566139	1.760738	-2.170414
H	0.349594	3.597966	-3.129189
H	-1.063704	2.581637	-3.472174
C	0.746456	0.136307	-0.241338
C	1.296787	1.294943	0.611330
C	2.466462	1.998663	0.283480
C	0.544710	1.747654	1.706006
C	2.879296	3.103264	1.033358
H	3.079611	1.677630	-0.552329
C	0.954517	2.850064	2.455693
H	-0.375148	1.233923	1.957188
C	2.125902	3.533734	2.124418
H	3.795134	3.621748	0.761299
H	0.352612	3.177378	3.299688
H	2.447541	4.390711	2.710358
C	1.835736	-0.766243	-0.862295
C	3.070119	-0.969492	-0.225167

C	1.572755	-1.521524	-2.017183
C	4.010028	-1.870143	-0.730105
H	3.304923	-0.419243	0.678976
C	2.510662	-2.418310	-2.528662
H	0.620340	-1.428026	-2.526984
C	3.737743	-2.596196	-1.889061
H	4.956842	-2.001041	-0.212544
H	2.275918	-2.983625	-3.426784
H	4.469122	-3.294867	-2.286209
O	-0.119640	-0.681955	0.550826
Si	0.082258	-1.930757	1.670139
C	1.355594	-1.527575	3.008021
H	1.334477	-2.309940	3.778102
H	2.377283	-1.482103	2.617098
H	1.142043	-0.571314	3.497150
C	0.541373	-3.557649	0.828317
H	-0.168363	-3.804290	0.030128
H	1.544102	-3.536043	0.390077
H	0.511845	-4.375730	1.560001
C	-1.623669	-2.091182	2.450956
H	-2.385727	-2.341507	1.704620
H	-1.628677	-2.881175	3.212716
H	-1.934853	-1.157927	2.933508

##########

t_anti_S_diPhTMS_pyrrolidine_1_0_c_vin

B3LYP/6-31G(d)

Eel = -1430.11074003 au; Energy(0K)) = -1429.58300819 au

Enthalpy = -1429.55165426 au; Gibbs energy = -1429.63815750 au

C	-2.611364	0.855524	-0.487373
C	-2.919309	-0.462838	-0.454774
H	-3.405795	1.585866	-0.353673
H	-2.132196	-1.200532	-0.561215
C	-4.274477	-0.980201	-0.273213
C	-4.551843	-2.293126	-0.444367
H	-5.540503	-2.694615	-0.249012
H	-3.787638	-2.994468	-0.770515
C	-5.349212	-0.046948	0.146147
C	-6.589738	-0.023965	-0.352214
H	-5.083926	0.669492	0.924836
H	-7.340886	0.664760	0.025830
H	-6.893324	-0.689996	-1.155862
N	-1.375200	1.447569	-0.672593
C	-0.248054	0.732530	-1.292265
C	-1.311849	2.871675	-1.024457

C	0.332728	1.729541	-2.338288
H	-0.661823	-0.150535	-1.788231
C	-0.696227	2.870982	-2.427890
H	-0.669331	3.410859	-0.316325
H	-2.309244	3.318039	-0.982012
H	0.503370	1.240858	-3.301029
H	1.296227	2.123333	-2.005407
H	-0.241979	3.829329	-2.700352
H	-1.469856	2.637865	-3.169048
C	0.808051	0.194381	-0.243295
C	1.204894	1.349152	0.696080
C	2.249888	2.241722	0.409308
C	0.429395	1.593395	1.839900
C	2.521055	3.329311	1.243344
H	2.877141	2.083196	-0.461775
C	0.698231	2.678839	2.673991
H	-0.397879	0.930487	2.061886
C	1.746993	3.552785	2.381074
H	3.343169	3.997627	1.000330
H	0.082036	2.842844	3.554439
H	1.958513	4.396384	3.032809
C	2.002874	-0.479730	-0.955185
C	3.267015	-0.554396	-0.348561

C	1.830269	-1.157522	-2.173399
C	4.317523	-1.259097	-0.939214
H	3.437272	-0.055326	0.598477
C	2.878531	-1.858072	-2.770443
H	0.865974	-1.158606	-2.668492
C	4.130382	-1.911780	-2.157282
H	5.283657	-1.294558	-0.442446
H	2.711019	-2.367844	-3.715620
H	4.947344	-2.458005	-2.620971
O	0.093622	-0.800452	0.493873
Si	0.488167	-2.099470	1.495839
C	1.813218	-1.690146	2.781560
H	1.854790	-2.498125	3.523925
H	2.812896	-1.595640	2.345747
H	1.588214	-0.760109	3.314501
C	1.026199	-3.601634	0.486674
H	0.266132	-3.874357	-0.254980
H	1.966903	-3.428821	-0.045999
H	1.168003	-4.467106	1.147042
C	-1.132761	-2.470066	2.380172
H	-1.949878	-2.654794	1.674338
H	-1.033199	-3.355196	3.021237
H	-1.436587	-1.630971	3.016813

##########

t_anti_S_diPhTMS_pyrrolidine_1_0_t_vin

B3LYP/6-31G(d)

Eel = -1430.10968880 au; Energy(0K)) = -1429.58186918 au

Enthalpy = -1429.55058771 au; Gibbs energy = -1429.63692992 au

C	-2.639482	0.698630	-0.773340
C	-2.887322	-0.630218	-0.698226
H	-3.471344	1.395487	-0.744043
H	-2.052900	-1.321868	-0.726635
C	-4.217949	-1.244245	-0.648122
C	-4.385786	-2.532042	-1.033869
H	-5.356982	-3.016926	-0.994259
H	-3.552831	-3.134615	-1.385830
C	-5.414168	-0.525612	-0.153443
C	-5.460539	0.497144	0.710562
H	-6.360375	-0.937553	-0.505182
H	-6.412974	0.906459	1.036391
H	-4.567642	0.933974	1.145946
N	-1.418291	1.335437	-0.897693
C	-0.210042	0.657503	-1.391956
C	-1.384423	2.751814	-1.279136

C	0.413510	1.652475	-2.415942
H	-0.536651	-0.260233	-1.890930
C	-0.650903	2.745187	-2.624263
H	-0.827054	3.334237	-0.533811
H	-2.399541	3.154914	-1.332514
H	0.683897	1.147240	-3.346835
H	1.329400	2.095957	-2.017448
H	-0.215149	3.715688	-2.883611
H	-1.347073	2.460294	-3.421937
C	0.775526	0.202324	-0.238161
C	1.006279	1.393296	0.710905
C	2.006769	2.355613	0.500947
C	0.116600	1.594681	1.777094
C	2.123063	3.470766	1.334734
H	2.719542	2.232212	-0.307890
C	0.231129	2.706877	2.611163
H	-0.677846	0.876506	1.938242
C	1.236130	3.651532	2.395116
H	2.913620	4.194262	1.152604
H	-0.471385	2.836386	3.430605
H	1.327450	4.516865	3.046291
C	2.072965	-0.401245	-0.821282
C	3.278977	-0.374928	-0.102486

C	2.057767	-1.113577	-2.031784
C	4.424354	-1.015203	-0.579218
H	3.328467	0.152142	0.843535
C	3.201034	-1.750634	-2.514737
H	1.143538	-1.191926	-2.609418
C	4.393288	-1.703219	-1.791694
H	5.341756	-0.972793	0.002205
H	3.154863	-2.290059	-3.457168
H	5.284339	-2.199433	-2.166635
O	0.058678	-0.826784	0.448164
Si	0.435706	-2.095052	1.494991
C	1.625060	-1.607434	2.881150
H	1.673444	-2.421983	3.615831
H	2.643278	-1.431591	2.520375
H	1.292037	-0.705663	3.406163
C	1.135791	-3.571343	0.548173
H	0.457045	-3.882117	-0.254836
H	2.109721	-3.353863	0.097965
H	1.261201	-4.427703	1.223562
C	-1.231977	-2.552056	2.241304
H	-1.970290	-2.796033	1.469695
H	-1.136292	-3.421750	2.903747
H	-1.642456	-1.726067	2.833554

##########

c_anti_S_diPhTMS_pyrrolidine_2_2_t_vin

B3LYP/6-31G(d)

Eel = -1430.10906872 au; Energy(0K)) = -1429.58135239 au

Enthalpy = -1429.55010339 au; Gibbs energy = -1429.63627180 au

C	2.525476	-1.434131	-0.513523
C	3.116494	-0.243368	-0.262911
H	3.132661	-2.332583	-0.424965
H	2.564597	0.683250	-0.367270
C	4.523171	-0.136467	0.156795
C	5.117164	-1.023179	0.987466
H	6.173843	-0.949178	1.230942
H	4.567048	-1.841381	1.441963
C	5.321465	0.997308	-0.345189
C	4.946775	1.883851	-1.276943
H	6.310500	1.097536	0.102249
H	5.605119	2.692664	-1.580976
H	3.982279	1.827822	-1.773312
N	1.223542	-1.714294	-0.873141
C	0.247115	-0.708590	-1.314546
C	0.908758	-3.026076	-1.458038

C	-0.581912	-1.436652	-2.412020
H	0.794574	0.131312	-1.755920
C	0.250373	-2.669509	-2.791951
H	0.210174	-3.576335	-0.812447
H	1.818889	-3.623480	-1.559934
H	-0.789033	-0.775152	-3.255965
H	-1.546559	-1.750301	-2.005225
H	-0.358757	-3.481858	-3.202291
H	1.021482	-2.413847	-3.528787
C	-0.705023	-0.102261	-0.178589
C	-0.022823	1.049226	0.596168
C	0.033804	1.128423	1.993287
C	0.486499	2.135744	-0.137694
C	0.609652	2.230375	2.632249
H	-0.382002	0.333298	2.599880
C	1.063076	3.235282	0.495151
H	0.417028	2.131163	-1.221053
C	1.134463	3.284896	1.888949
H	0.641878	2.258535	3.718282
H	1.456278	4.053868	-0.101945
H	1.587257	4.138386	2.385992
C	-1.205404	-1.249786	0.711700
C	-2.515598	-1.731206	0.601281

C	-0.336735	-1.907300	1.602185
C	-2.956349	-2.816564	1.363837
H	-3.195071	-1.262425	-0.099492
C	-0.774496	-2.991400	2.362765
H	0.688312	-1.570077	1.703124
C	-2.088500	-3.451396	2.249569
H	-3.980460	-3.165023	1.256832
H	-0.083491	-3.477429	3.046871
H	-2.428196	-4.295357	2.844111
O	-1.783784	0.461345	-0.933182
Si	-3.000473	1.601575	-0.674247
C	-2.530696	3.249079	-1.468088
H	-2.220991	3.111045	-2.511081
H	-3.393562	3.927602	-1.467968
H	-1.713843	3.746990	-0.936409
C	-3.431746	1.856567	1.145035
H	-3.675508	0.911256	1.642154
H	-2.613387	2.325852	1.700100
H	-4.309502	2.511284	1.223800
C	-4.492326	0.911143	-1.604196
H	-4.883000	-0.003604	-1.143843
H	-5.308827	1.643931	-1.623876
H	-4.233688	0.675435	-2.643115

##########

t_anti_S_diPhTMS_pyrrolidine_2_2_c_vin

B3LYP/6-31G(d)

Eel = -1430.10878762 au; Energy(0K)) = -1429.58109737 au

Enthalpy = -1429.54981987 au; Gibbs energy = -1429.63612622 au

C	-2.658691	0.880267	-0.577658
C	-3.004821	-0.415279	-0.383104
H	-3.433830	1.639893	-0.511195
H	-2.258425	-1.198413	-0.442299
C	-4.373916	-0.854263	-0.111446
C	-4.702260	-2.165565	-0.119908
H	-5.699882	-2.501786	0.142060
H	-3.969051	-2.929561	-0.365437
C	-5.401936	0.162633	0.221052
C	-6.652743	0.180392	-0.251106
H	-5.091289	0.949512	0.910064
H	-7.368028	0.935701	0.064100
H	-7.001019	-0.557316	-0.969494
N	-1.420097	1.422725	-0.848820
C	-0.256136	0.658741	-1.321132
C	-1.330323	2.819959	-1.294768

C	0.454741	1.623926	-2.314679
H	-0.622880	-0.225376	-1.853294
C	-0.577284	2.718043	-2.622465
H	-0.763516	3.420045	-0.569338
H	-2.330596	3.252718	-1.384417
H	0.801535	1.091869	-3.203260
H	1.334721	2.066102	-1.841337
H	-0.114356	3.662153	-2.928608
H	-1.265869	2.401399	-3.415191
C	0.758296	0.143548	-0.191229
C	0.295174	-1.190043	0.441111
C	0.228311	-1.417159	1.821883
C	0.020225	-2.275933	-0.409716
C	-0.132928	-2.666977	2.333029
H	0.467447	-0.620004	2.515023
C	-0.340433	-3.523935	0.095713
H	0.102198	-2.151542	-1.484881
C	-0.426123	-3.724513	1.475108
H	-0.179898	-2.808149	3.409636
H	-0.551968	-4.340181	-0.590217
H	-0.710824	-4.694658	1.873017
C	0.980158	1.274894	0.823537
C	2.168026	2.016113	0.828884

C	-0.035499	1.653117	1.720772
C	2.350336	3.087199	1.708203
H	2.954045	1.761541	0.128843
C	0.144466	2.722537	2.597859
H	-0.972406	1.107866	1.736604
C	1.339896	3.445202	2.597881
H	3.285058	3.641847	1.689719
H	-0.654715	2.990487	3.284315
H	1.478657	4.277236	3.283170
O	1.959330	-0.116774	-0.927325
Si	3.359757	-1.031847	-0.708594
C	3.231624	-2.665555	-1.645341
H	2.925191	-2.499300	-2.685151
H	4.207725	-3.167268	-1.665982
H	2.512452	-3.351196	-1.186840
C	3.788933	-1.347850	1.101454
H	3.812767	-0.418450	1.680977
H	3.076591	-2.025101	1.582899
H	4.784113	-1.806969	1.165996
C	4.712201	0.004485	-1.522825
H	4.895813	0.943420	-0.987750
H	5.659726	-0.548040	-1.552705
H	4.444190	0.258580	-2.555020

##########

c_anti_S_diPhTMS_pyrrolidine_1_0_c_vin

B3LYP/6-31G(d)

Eel = -1430.10715121 au; Energy(0K)) = -1429.57997079 au

Enthalpy = -1429.54845258 au; Gibbs energy = -1429.63526016 au

C	2.316967	-1.566495	-0.582618
C	2.948144	-0.370618	-0.537640
H	2.909053	-2.469150	-0.445853
H	2.381019	0.542155	-0.684416
C	4.389143	-0.219909	-0.287286
C	5.139540	-1.095912	0.417013
H	6.218059	-0.991424	0.478853
H	4.697799	-1.940977	0.937181
C	5.005260	0.995309	-0.875127
C	5.989646	1.715577	-0.324721
H	4.581055	1.327604	-1.824000
H	6.402103	2.588178	-0.824105
H	6.409621	1.459279	0.644634
N	0.977276	-1.837305	-0.783983
C	0.042397	-0.845214	-1.340248
C	0.576009	-3.187695	-1.199891

C	-0.787698	-1.630537	-2.397877
H	0.643826	-0.068685	-1.822863
C	-0.050976	-2.969102	-2.580364
H	-0.161197	-3.598030	-0.497435
H	1.442194	-3.854762	-1.210098
H	-0.878703	-1.068657	-3.330974
H	-1.802015	-1.813444	-2.034704
H	-0.719095	-3.781442	-2.884849
H	0.739812	-2.877222	-3.334339
C	-0.824042	-0.111236	-0.237730
C	-1.454796	-1.174988	0.681274
C	-2.688131	-1.786847	0.407394
C	-0.726994	-1.632441	1.790141
C	-3.182991	-2.810117	1.220003
H	-3.285343	-1.453233	-0.434946
C	-1.219203	-2.653757	2.602874
H	0.237028	-1.186662	2.002201
C	-2.451047	-3.248134	2.322781
H	-4.145610	-3.258735	0.988279
H	-0.634764	-2.987493	3.456585
H	-2.836108	-4.041817	2.957581
C	-1.848005	0.850134	-0.881453
C	-3.032572	1.202796	-0.214499

C	-1.569212	1.505878	-2.091819
C	-3.908912	2.153597	-0.740348
H	-3.277970	0.729669	0.729506
C	-2.445011	2.452383	-2.624556
H	-0.653330	1.295190	-2.632699
C	-3.622381	2.780959	-1.952374
H	-4.817951	2.400715	-0.198093
H	-2.199871	2.937360	-3.565822
H	-4.304807	3.518487	-2.366053
O	0.127434	0.658067	0.500829
Si	0.097475	1.997254	1.525460
C	-1.231443	1.889020	2.866615
H	-1.062951	2.681628	3.607415
H	-2.242626	2.022356	2.469047
H	-1.200298	0.928831	3.393041
C	-0.111381	3.603951	0.555259
H	0.646958	3.691679	-0.231641
H	-1.095901	3.684964	0.083503
H	0.010309	4.463757	1.227065
C	1.798543	1.965892	2.331862
H	2.599625	1.998643	1.585692
H	1.926169	2.825515	3.002030
H	1.943732	1.055813	2.925058

##########

t_anti_S_diPhTMS_pyrrolidine_2_2_t_vin

B3LYP/6-31G(d)

Eel = -1430.10778398 au; Energy(0K)) = -1429.57989921 au

Enthalpy = -1429.54866853 au; Gibbs energy = -1429.63487438 au

C	-2.702923	0.743996	-0.782041
C	-3.004356	-0.554856	-0.542713
H	-3.507470	1.472388	-0.803582
H	-2.214819	-1.297381	-0.542358
C	-4.361908	-1.089351	-0.384742
C	-4.603519	-2.401440	-0.615779
H	-5.596060	-2.826655	-0.497474
H	-3.809655	-3.083836	-0.905960
C	-5.506490	-0.259285	0.053437
C	-5.482654	0.854201	0.797969
H	-6.480666	-0.660072	-0.227734
H	-6.406317	1.342342	1.096786
H	-4.560152	1.294005	1.162841
N	-1.470416	1.316777	-1.017183
C	-0.257625	0.578852	-1.399087
C	-1.405238	2.699896	-1.508808

C	0.473453	1.535131	-2.386366
H	-0.565914	-0.335010	-1.918145
C	-0.576151	2.580025	-2.788799
H	-0.902351	3.346416	-0.776033
H	-2.413637	3.091359	-1.669224
H	0.887727	0.985997	-3.234720
H	1.310083	2.024478	-1.881771
H	-0.129347	3.529208	-3.103031
H	-1.208443	2.212194	-3.606007
C	0.714317	0.136526	-0.201803
C	0.272730	-1.197801	0.443325
C	0.141404	-1.391949	1.824406
C	0.089564	-2.316170	-0.390235
C	-0.195653	-2.642389	2.350420
H	0.310422	-0.568055	2.506890
C	-0.247145	-3.564646	0.130080
H	0.227013	-2.215757	-1.462264
C	-0.399650	-3.732854	1.508059
H	-0.294609	-2.757651	3.426595
H	-0.387547	-4.406691	-0.542788
H	-0.666329	-4.703374	1.917348
C	0.836261	1.303205	0.789221
C	1.989198	2.096379	0.831946

C	-0.240787	1.662014	1.620410
C	2.079187	3.199037	1.686257
H	2.820452	1.858391	0.180084
C	-0.152930	2.762663	2.472549
H	-1.153452	1.076935	1.604092
C	1.009083	3.536890	2.511754
H	2.988820	3.794112	1.698379
H	-0.997880	3.014871	3.108274
H	1.075992	4.393484	3.177296
O	1.961611	-0.095993	-0.866294
Si	3.391680	-0.930518	-0.545902
C	3.394730	-2.587935	-1.449770
H	3.141051	-2.459788	-2.508999
H	4.392429	-3.043177	-1.402916
H	2.682633	-3.296322	-1.015414
C	3.736062	-1.195344	1.290309
H	3.715152	-0.255055	1.852143
H	3.015058	-1.877885	1.750913
H	4.735640	-1.633225	1.411293
C	4.739088	0.151645	-1.307554
H	4.857857	1.104573	-0.778907
H	5.708598	-0.361615	-1.281133
H	4.513928	0.379924	-2.355886

##########

c_anti_S_diPhTMS_pyrrolidine_2_2_c_vin

B3LYP/6-31G(d)

Eel = -1430.10537772 au; Energy(0K)) = -1429.57808846 au

Enthalpy = -1429.54665965 au; Gibbs energy = -1429.63329944 au

C	2.409021	-1.528017	-0.616899
C	3.045702	-0.341686	-0.476010
H	2.996326	-2.436341	-0.498016
H	2.513776	0.590611	-0.628758
C	4.474791	-0.238209	-0.142059
C	5.142001	-1.142485	0.608480
H	6.219124	-1.089350	0.731730
H	4.629972	-1.960438	1.106986
C	5.174819	0.943530	-0.702052
C	6.174866	1.610555	-0.114553
H	4.806618	1.295747	-1.666818
H	6.652598	2.458421	-0.598096
H	6.542485	1.335749	0.870885
N	1.084166	-1.791518	-0.891784
C	0.108305	-0.786515	-1.338837
C	0.707031	-3.125856	-1.382216

C	-0.796288	-1.554421	-2.345912
H	0.649763	0.010596	-1.859345
C	-0.014094	-2.827695	-2.697721
H	0.031894	-3.619903	-0.669787
H	1.596048	-3.751833	-1.497166
H	-1.034884	-0.936970	-3.214559
H	-1.743696	-1.819942	-1.870240
H	-0.662707	-3.645839	-3.028242
H	0.721729	-2.633539	-3.487481
C	-0.764074	-0.091803	-0.190009
C	-0.008932	1.078210	0.482860
C	0.113677	1.236064	1.869226
C	0.501303	2.102667	-0.334824
C	0.755939	2.350510	2.416609
H	-0.300737	0.492960	2.539382
C	1.143517	3.214617	0.206448
H	0.382854	2.039899	-1.412147
C	1.281938	3.340655	1.590335
H	0.839154	2.439279	3.496636
H	1.534785	3.983608	-0.454546
H	1.786585	4.203626	2.015900
C	-1.245064	-1.175572	0.787058
C	-2.568525	-1.632471	0.764345

C	-0.348614	-1.802486	1.671917
C	-2.995003	-2.662136	1.608009
H	-3.270497	-1.189290	0.068963
C	-0.772130	-2.831131	2.513308
H	0.687027	-1.484619	1.705277
C	-2.099473	-3.265343	2.488322
H	-4.029937	-2.992328	1.568591
H	-0.059503	-3.294003	3.191255
H	-2.428001	-4.065689	3.146086
O	-1.867531	0.461122	-0.916143
Si	-3.038323	1.647902	-0.657252
C	-2.551952	3.250202	-1.529009
H	-2.290469	3.066214	-2.578108
H	-3.392293	3.956342	-1.518023
H	-1.698085	3.738713	-1.049518
C	-3.392284	1.982959	1.165610
H	-3.655578	1.066691	1.705253
H	-2.535543	2.436731	1.673643
H	-4.238984	2.676439	1.252292
C	-4.582204	0.966351	-1.504158
H	-4.971254	0.072557	-1.002936
H	-5.383496	1.715971	-1.509248
H	-4.373111	0.697967	-2.546288

##########

Conformations of MacMillan Generation 1 organocatalyst-derived aminodendralene 2b, in descending order of Energy (0K); most stable first

c_syn_imidvin_t_vin

B3LYP/6-31G(d)

Eel = -923.16863898 au; Energy(0K)) = -922.77510518 au

Enthalpy = -922.75203418 au; Gibbs energy = -922.82239057 au

C	0.355612	1.668002	-1.005723
C	0.069930	0.624336	1.190942
H	-0.678694	1.032149	1.890381
N	-0.403046	0.697882	-0.180974
N	1.393836	2.091778	-0.058115
C	2.473650	2.996106	-0.400449
H	3.062261	3.141273	0.507175
H	3.116752	2.573607	-1.180749
H	2.093668	3.966358	-0.740200
C	0.968961	0.976432	-2.235035
H	1.558761	1.681011	-2.831331
H	1.604992	0.145095	-1.921239
H	0.176712	0.583765	-2.880780
C	-0.509852	2.874241	-1.421167

H	-1.321026	2.563000	-2.085825
H	-0.947128	3.350947	-0.538588
H	0.090529	3.614991	-1.959623
C	0.458699	-0.792094	1.696222
H	0.857283	-0.645829	2.706317
H	-0.452275	-1.391013	1.787893
C	1.464755	-1.520861	0.832453
C	1.036572	-2.401607	-0.170761
C	2.842914	-1.326450	1.009274
C	1.958250	-3.068932	-0.979438
H	-0.028752	-2.565482	-0.314531
C	3.766204	-1.991740	0.201065
H	3.188031	-0.644773	1.781916
C	3.327370	-2.865122	-0.796235
H	1.606595	-3.752028	-1.748629
H	4.830362	-1.832466	0.356073
H	4.046706	-3.387876	-1.421338
C	1.275700	1.557412	1.190667
O	2.011967	1.768622	2.144114
C	-1.640572	0.244307	-0.573411
C	-2.597681	-0.315507	0.202733
H	-1.833125	0.351823	-1.638230
H	-2.463297	-0.371708	1.279274

C -3.855559 -0.849658 -0.341045

C -3.929259 -1.480572 -1.534765

H -4.881859 -1.809866 -1.941032

H -3.046273 -1.684882 -2.132456

C -5.087017 -0.694027 0.454728

C -5.224614 0.025882 1.575948

H -5.954679 -1.227910 0.067524

H -6.175400 0.075198 2.098571

H -4.405799 0.597125 2.004113

##########

t_syn_imidvin_c_vin

B3LYP/6-31G(d)

Eel = -923.16770418 au; Energy(0K)) = -922.77423278 au

Enthalpy = -922.75113416 au; Gibbs energy = -922.82159631 au

C 0.332035 1.716835 -0.812564

C 0.376577 0.614391 1.373596

H -0.188352 1.045193 2.216629

N -0.342991 0.786842 0.123194

N 1.563300 2.017480 -0.071761

C 2.635934 2.838811 -0.596872

H 3.394446 2.904069 0.185259

H	3.082111	2.390320	-1.491801
H	2.286556	3.848156	-0.842283
C	0.639149	1.024764	-2.151749
H	1.155662	1.705032	-2.837717
H	1.256741	0.138353	-1.987163
H	-0.291629	0.713320	-2.637066
C	-0.483112	3.007451	-1.030618
H	-1.426949	2.793367	-1.540743
H	-0.705852	3.483453	-0.070857
H	0.072507	3.715463	-1.654315
C	0.740478	-0.848355	1.752499
H	1.343618	-0.773975	2.664184
H	-0.178438	-1.382106	2.011760
C	1.490939	-1.613554	0.684839
C	0.799194	-2.402486	-0.245042
C	2.889455	-1.546241	0.597159
C	1.483976	-3.105246	-1.237943
H	-0.284787	-2.466473	-0.186521
C	3.576106	-2.246856	-0.395885
H	3.437350	-0.936221	1.310258
C	2.875992	-3.028922	-1.316833
H	0.930042	-3.716183	-1.946304
H	4.660465	-2.186934	-0.444986

H 3.411369 -3.579676 -2.085931

C 1.636145 1.447405 1.164499

O 2.555046 1.560304 1.963568

C -1.669567 0.457409 -0.033581

C -2.496459 -0.087873 0.892086

H -2.048357 0.644506 -1.034314

H -2.127421 -0.302534 1.891177

C -3.892654 -0.444228 0.637987

C -4.607812 -1.148616 1.542349

H -5.661967 -1.356504 1.393514

H -4.156412 -1.513036 2.461812

C -4.532641 0.024685 -0.615334

C -5.338042 -0.708367 -1.390766

H -4.317693 1.053883 -0.907070

H -5.805842 -0.290798 -2.278404

H -5.553857 -1.749406 -1.164659

##########

t_syn_imidvin_t_vin

B3LYP/6-31G(d)

Eel = -923.16698528 au; Energy(0K)) = -922.77316634 au

Enthalpy = -922.75016442 au; Gibbs energy = -922.82028478 au

C	-0.289771	1.672677	0.929025
C	-0.286733	0.739341	-1.334801
H	0.291310	1.237644	-2.130508
N	0.406360	0.816506	-0.060331
N	-1.509990	2.020923	0.190858
C	-2.593199	2.802648	0.753141
H	-3.340661	2.917197	-0.033971
H	-3.049906	2.294553	1.609988
H	-2.251461	3.794764	1.069542
C	-0.615383	0.881483	2.207334
H	-1.155733	1.503483	2.929226
H	-1.216700	0.001762	1.965035
H	0.309302	0.548246	2.689819
C	0.513727	2.947427	1.256167
H	1.448412	2.701254	1.768542
H	0.752800	3.491908	0.337628
H	-0.058516	3.606740	1.917168
C	-0.634447	-0.690349	-1.836923
H	-1.222093	-0.544398	-2.750073
H	0.291942	-1.197273	-2.121939
C	-1.398603	-1.543127	-0.848379
C	-0.718526	-2.412005	0.016671
C	-2.797902	-1.479316	-0.769409

C	-1.415102	-3.194254	0.939429
H	0.365643	-2.477006	-0.039581
C	-3.496369	-2.259737	0.153446
H	-3.337068	-0.809433	-1.433755
C	-2.807527	-3.119426	1.011501
H	-0.870443	-3.866390	1.597866
H	-4.581017	-2.200707	0.196602
H	-3.351843	-3.731677	1.725882
C	-1.554864	1.548604	-1.087059
O	-2.458118	1.719680	-1.893711
C	1.727885	0.471182	0.106434
C	2.571853	-0.008381	-0.839048
H	2.090242	0.610633	1.118897
H	2.228508	-0.085696	-1.867247
C	3.987566	-0.334451	-0.630335
C	4.841101	-0.341398	-1.680626
H	5.892549	-0.583457	-1.556947
H	4.506387	-0.120139	-2.690283
C	4.537776	-0.686520	0.697254
C	3.891141	-1.206164	1.749483
H	5.615890	-0.549652	0.781777
H	4.429275	-1.468563	2.656115
H	2.827789	-1.422643	1.736382

##########

c_syn_imidvin_c_vin

B3LYP/6-31G(d)

Eel = -923.16505946 au; Energy(0K)) = -922.77167514 au

Enthalpy = -922.74858515 au; Gibbs energy = -922.81906008 au

C	0.550486	1.761485	-0.879651
C	0.230263	0.612509	1.258161
H	-0.437121	1.064406	2.010657
N	-0.279268	0.823203	-0.086716
N	1.674778	1.986292	0.037047
C	2.839307	2.780933	-0.300449
H	3.484012	2.784558	0.580264
H	3.387286	2.347357	-1.144442
H	2.565033	3.812915	-0.547782
C	1.019155	1.104401	-2.188700
H	1.662098	1.781492	-2.761361
H	1.563679	0.181608	-1.973788
H	0.157702	0.860758	-2.818991
C	-0.185526	3.087454	-1.155920
H	-1.059168	2.922344	-1.793358
H	-0.520305	3.539095	-0.217070

H	0.470199	3.796154	-1.672657
C	0.460719	-0.868039	1.667167
H	0.893618	-0.832262	2.672977
H	-0.512595	-1.360959	1.747229
C	1.357890	-1.653261	0.735600
C	0.812908	-2.392942	-0.323490
C	2.750449	-1.653636	0.905864
C	1.635537	-3.111675	-1.192660
H	-0.265489	-2.407294	-0.462246
C	3.574769	-2.371412	0.037782
H	3.185935	-1.081177	1.720287
C	3.020447	-3.102504	-1.014760
H	1.193815	-3.684036	-2.004586
H	4.651363	-2.363756	0.188429
H	3.661988	-3.666402	-1.687022
C	1.540265	1.392350	1.257070
O	2.332472	1.453661	2.186585
C	-1.571287	0.532570	-0.454349
C	-2.561137	0.037724	0.326828
H	-1.786301	0.720077	-1.504089
H	-2.402386	-0.078353	1.396269
C	-3.891242	-0.321233	-0.187700
C	-4.107584	-0.771902	-1.442848

H -5.113154 -0.911635 -1.826669

H -3.287432 -1.005528 -2.115398

C -5.014401 -0.140254 0.763230

C -6.107044 -0.909111 0.832627

H -4.904788 0.680208 1.473792

H -6.899920 -0.703924 1.546571

H -6.240248 -1.772144 0.185171

##########

c_anti_imidvin_t_vin

B3LYP/6-31G(d)

Eel = -923.16502153 au; Energy(0K)) = -922.77160776 au

Enthalpy = -922.74845418 au; Gibbs energy = -922.81905076 au

C 0.095197 1.539695 -0.858130

C 0.695640 0.917955 1.435611

H 0.355527 1.521690 2.292800

N -0.325495 0.873996 0.396024

N 1.450161 1.989486 -0.494255

C 2.334446 2.687807 -1.406864

H 3.250614 2.902789 -0.853889

H 2.579954 2.071536 -2.279071

H 1.892272 3.629489 -1.750437

C	0.162753	0.555469	-2.040932
H	0.538900	1.058062	-2.938659
H	0.819779	-0.283084	-1.797476
H	-0.828436	0.161157	-2.276832
C	-0.793234	2.755116	-1.181688
H	-1.833021	2.453891	-1.324492
H	-0.752805	3.478108	-0.361255
H	-0.454189	3.244473	-2.100290
C	1.148674	-0.455117	1.997457
H	1.928241	-0.234229	2.735581
H	0.304902	-0.894519	2.542322
C	1.661648	-1.437456	0.966823
C	0.805081	-2.390237	0.398019
C	3.002270	-1.410404	0.553311
C	1.271933	-3.291989	-0.559998
H	-0.236900	-2.424787	0.707042
C	3.470640	-2.310213	-0.405313
H	3.675598	-0.673756	0.983070
C	2.607382	-3.254407	-0.965114
H	0.592680	-4.025998	-0.986067
H	4.513617	-2.277247	-0.709995
H	2.973898	-3.959073	-1.707073
C	1.842923	1.661899	0.767713

O 2.925125 1.909096 1.282736

C -1.602772 0.472282 0.714686

C -2.677096 0.243645 -0.077441

H -1.724787 0.305302 1.784323

H -2.595801 0.295815 -1.157734

C -3.997781 -0.105671 0.468973

C -4.477146 0.419243 1.619242

H -5.427552 0.095032 2.034809

H -3.936788 1.181864 2.171247

C -4.834751 -1.064174 -0.276004

C -4.458200 -1.792255 -1.335471

H -5.853876 -1.170971 0.095299

H -5.149811 -2.471286 -1.825542

H -3.451325 -1.748525 -1.741242

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t_anti_imidvin_c_vin

B3LYP/6-31G(d)

Eel = -923.16404428 au; Energy(0K)) = -922.77056453 au

Enthalpy = -922.74738071 au; Gibbs energy = -922.81810740 au

C -0.172242 -1.700641 -0.666224

C -0.468200 -0.583345 1.493990

H	0.025893	-0.978781	2.396163
N	0.380582	-0.744632	0.318827
N	-1.449427	-2.056847	-0.024611
C	-2.422027	-2.952998	-0.619132
H	-3.243682	-3.042392	0.093753
H	-2.809155	-2.554786	-1.563667
H	-1.994827	-3.945519	-0.800761
C	-0.428017	-1.032943	-2.029670
H	-0.875574	-1.745691	-2.730577
H	-1.098908	-0.178919	-1.907980
H	0.505886	-0.676910	-2.470277
C	0.708142	-2.958920	-0.799401
H	1.706950	-2.708671	-1.161250
H	0.807869	-3.449680	0.173576
H	0.262336	-3.666421	-1.506102
C	-0.908398	0.869771	1.813400
H	-1.544872	0.800017	2.702756
H	-0.018039	1.441120	2.101478
C	-1.640367	1.584003	0.697815
C	-0.945323	2.385080	-0.218777
C	-3.030304	1.455835	0.554788
C	-1.617153	3.041375	-1.251602
H	0.132368	2.494923	-0.123661

C	-3.704035	2.110155	-0.477532
H	-3.580909	0.833095	1.254437
C	-3.000280	2.905722	-1.384012
H	-1.059861	3.661418	-1.949140
H	-4.781866	2.002656	-0.569287
H	-3.526209	3.420129	-2.184083
C	-1.663506	-1.473877	1.186913
O	-2.642777	-1.621214	1.905718
C	1.657283	-0.229063	0.322793
C	2.615024	-0.233846	-0.637714
H	1.892233	0.253131	1.268960
H	2.441739	-0.708090	-1.598031
C	3.941413	0.359167	-0.458541
C	4.925206	0.154073	-1.361762
H	5.888879	0.643397	-1.270282
H	4.778892	-0.493527	-2.222809
C	4.182860	1.233761	0.715367
C	5.276480	1.206720	1.483796
H	3.394360	1.950264	0.950564
H	5.407922	1.902206	2.308473
H	6.073370	0.486924	1.315517

##########

t_anti_imidvin_t_vin

B3LYP/6-31G(d)

Eel = -923.16319046 au; Energy(0K)) = -922.76937602 au

Enthalpy = -922.74632435 au; Gibbs energy = -922.81669557 au

C	0.049212	1.553142	-0.866519
C	0.391246	0.737422	1.418896
H	-0.130278	1.207017	2.268539
N	-0.460848	0.706782	0.235166
N	1.290666	2.073922	-0.268265
C	2.212375	2.947522	-0.967929
H	3.030292	3.159017	-0.276852
H	2.616633	2.466017	-1.865114
H	1.733351	3.890128	-1.255917
C	0.371603	0.724314	-2.123855
H	0.794573	1.361014	-2.908348
H	1.085711	-0.065774	-1.878560
H	-0.530825	0.259162	-2.526617
C	-0.904945	2.722271	-1.178774
H	-1.879469	2.361396	-1.512657
H	-1.052206	3.333150	-0.282839
H	-0.490778	3.354498	-1.970758
C	0.917931	-0.637107	1.909956

H	1.555636	-0.420082	2.774555
H	0.065546	-1.219311	2.279433
C	1.681380	-1.440902	0.879763
C	1.028872	-2.401386	0.094346
C	3.055466	-1.236061	0.682346
C	1.726651	-3.136492	-0.865639
H	-0.035399	-2.574149	0.235108
C	3.754767	-1.968979	-0.277737
H	3.573023	-0.492259	1.281949
C	3.092978	-2.921625	-1.055170
H	1.202845	-3.879001	-1.462239
H	4.819859	-1.799203	-0.413582
H	3.638862	-3.496225	-1.798967
C	1.531114	1.657010	1.005180
O	2.493611	1.952468	1.700762
C	-1.703396	0.117046	0.304526
C	-2.646562	-0.054080	-0.654060
H	-1.905098	-0.280984	1.294611
H	-2.450211	0.257198	-1.674590
C	-3.921783	-0.757429	-0.464217
C	-4.564513	-1.288087	-1.530615
H	-5.513409	-1.805234	-1.423163
H	-4.165962	-1.204230	-2.537953

C -4.569774 -0.895323 0.859161

C -4.440813 -0.098843 1.928712

H -5.278268 -1.721156 0.923602

H -5.017553 -0.283641 2.830683

H -3.795338 0.773515 1.935053

##########

c_anti_imidvin_c_vin

B3LYP/6-31G(d)

Eel = -923.16142134 au; Energy(0K)) = -922.76827546 au

Enthalpy = -922.74503683 au; Gibbs energy = -922.81585915 au

C -0.163522 -1.556042 -0.806568

C -0.741337 -0.817686 1.458794

H -0.377360 -1.367050 2.342203

N 0.263793 -0.814506 0.402181

N -1.503473 -2.010183 -0.395722

C -2.388475 -2.774188 -1.253589

H -3.286277 -2.985740 -0.670043

H -2.670070 -2.207636 -2.148466

H -1.928183 -3.719304 -1.561798

C -0.270063 -0.640161 -2.040206

H -0.654950 -1.198349 -2.900543

H	-0.937218	0.199567	-1.830547
H	0.709145	-0.243144	-2.317521
C	0.744347	-2.769884	-1.076880
H	1.775658	-2.456093	-1.250624
H	0.729802	-3.447797	-0.217989
H	0.403533	-3.315476	-1.962630
C	-1.210763	0.575952	1.951753
H	-1.976131	0.381790	2.711934
H	-0.367713	1.058011	2.460551
C	-1.754569	1.492589	0.877620
C	-0.923137	2.429296	0.248190
C	-3.099567	1.420105	0.484088
C	-1.418064	3.270920	-0.749623
H	0.121571	2.498873	0.541803
C	-3.596026	2.259643	-0.514262
H	-3.754327	0.695890	0.961068
C	-2.757389	3.188055	-1.134624
H	-0.757796	3.993457	-1.222548
H	-4.641938	2.192215	-0.802792
H	-3.146110	3.845652	-1.907798
C	-1.884376	-1.617585	0.851138
O	-2.954498	-1.853647	1.395747
C	1.535363	-0.367377	0.674551

C 2.595245 -0.167817 -0.146558

H 1.670372 -0.129393 1.729239

H 2.495241 -0.280915 -1.221636

C 3.915029 0.254525 0.346229

C 4.393545 -0.065469 1.568756

H 5.315470 0.367170 1.944155

H 3.873303 -0.758373 2.223452

C 4.709575 1.087577 -0.588573

C 6.041976 1.067433 -0.707846

H 4.134655 1.745694 -1.241686

H 6.559045 1.722194 -1.403861

H 6.657269 0.391429 -0.119459

##########

Transition structures for the endo addition of *N*-methyl maleimide to 2b, in descending order of Energy (0K); most stable first.
Although 4 TSs are present in Table 1, there are actually eight listed here, the doubling being due to the spectator vinyl group in the dendralene adopting either a cis or trans conformation with respect to the central double bond of the dendralene.

N_Re_syn_pyrrole_t_vin

B3LYP/6-31G(d)

Eel = -1828.85263685 au; Energy(0K)) = -1828.22594109 au

Enthalpy = -1828.18722010 au; Gibbs energy = -1828.28808837 au

C -1.243138 0.274599 0.208112

C	-2.358396	0.815691	0.832462
C	-3.284801	0.069571	1.600231
C	-3.215341	-1.331989	1.714415
C	-3.746558	-2.111743	-0.143237
C	-2.920382	-1.647052	-1.163789
C	-5.071136	-1.402319	-0.291978
C	-3.583185	-0.552198	-1.856622
O	-3.213746	0.146456	-2.796284
O	-6.115231	-1.603843	0.306620
H	-0.892641	-0.713487	0.473345
H	-2.585307	1.862188	0.658259
H	-3.940651	-1.822496	2.358941
H	-2.248025	-1.822237	1.684351
H	-3.743410	-3.125309	0.242878
H	-1.982204	-2.064735	-1.502560
C	-4.471260	0.732136	2.164691
C	-4.615077	2.040837	2.423133
H	-5.294684	0.061533	2.405150
H	-5.534544	2.425893	2.853557
H	-3.825572	2.765905	2.242906
N	-4.865994	-0.425259	-1.251957
C	-5.859670	0.549924	-1.647010
H	-5.491170	1.044935	-2.547438

H	-6.813207	0.055000	-1.852917
H	-6.014661	1.291898	-0.855303
N	-0.435490	0.922491	-0.656499
C	0.744857	0.279201	-1.262183
C	-0.830856	2.137113	-1.385376
C	1.009390	1.109060	-2.540823
H	0.460658	-0.748361	-1.515474
C	1.967692	0.155180	-0.265179
C	-0.298660	1.874440	-2.796328
H	-0.374440	3.024173	-0.925359
H	-1.916630	2.241870	-1.366220
H	1.296878	0.470254	-3.378993
H	1.827554	1.814244	-2.374280
C	2.240983	1.530560	0.373596
C	3.197976	-0.456454	-0.969457
O	1.501404	-0.760031	0.735960
H	-0.142718	2.795037	-3.367261
H	-1.022936	1.247598	-3.324525
C	3.063001	2.492132	-0.236614
C	1.582154	1.889710	1.558546
C	4.495469	-0.212870	-0.490420
C	3.059120	-1.370903	-2.026313
Si	2.214663	-1.812978	1.850100

C	3.226461	3.761828	0.321230
H	3.602693	2.247153	-1.145422
C	1.744206	3.157757	2.117967
H	0.930755	1.170784	2.040045
C	5.607842	-0.841975	-1.051514
H	4.642619	0.481557	0.329030
C	4.169032	-1.996625	-2.594919
H	2.078373	-1.617456	-2.416973
C	3.475731	-0.962737	2.969964
C	2.994334	-3.316152	1.018722
C	0.737551	-2.376739	2.877045
C	2.567691	4.101193	1.502422
H	3.875466	4.481859	-0.170282
H	1.221548	3.407069	3.037791
C	5.450952	-1.735057	-2.111282
H	6.598199	-0.628607	-0.657964
H	4.026559	-2.694758	-3.415423
H	3.745602	-1.637935	3.792421
H	4.399757	-0.705183	2.442229
H	3.073556	-0.044168	3.410733
H	2.281611	-3.814748	0.351458
H	3.882398	-3.063067	0.431658
H	3.294200	-4.044527	1.783636

H 0.011260 -2.920438 2.261044

H 1.054905 -3.051893 3.681372

H 0.216269 -1.531140 3.340032

H 2.696156 5.087882 1.939229

H 6.315580 -2.222582 -2.553209

##########

N_Re_syn_pyrrole_c_vin

B3LYP/6-31G(d)

Eel = -1828.85172786 au; Energy(0K)) = -1828.22525010 au

Enthalpy = -1828.18639976 au; Gibbs energy = -1828.28756980 au

C 1.211768 -0.226037 0.332410

C 2.301051 -0.465018 1.157557

C 3.277864 0.501677 1.512090

C 3.251862 1.808966 1.002453

C 3.744395 1.676899 -1.063762

C 2.914369 0.795321 -1.746426

C 5.074098 0.989161 -0.891783

C 3.581087 -0.495477 -1.863772

O 3.206332 -1.551515 -2.365478

O 6.126787 1.451308 -0.482956

H 0.910094 0.787554 0.105593

H	2.465255	-1.480144	1.508598
H	3.988489	2.523434	1.355870
H	2.295719	2.253094	0.748515
H	3.723744	2.756572	-1.159610
H	1.973788	1.008590	-2.235210
C	4.401439	0.011291	2.328561
C	5.569069	0.624576	2.572835
H	4.243049	-0.976234	2.762863
H	6.323175	0.147582	3.192008
H	5.832311	1.586752	2.146584
N	4.869616	-0.323157	-1.286386
C	5.881181	-1.355799	-1.218994
H	5.433162	-2.275902	-1.598702
H	6.750375	-1.090464	-1.830151
H	6.212978	-1.495415	-0.185189
N	0.369315	-1.163719	-0.150060
C	-0.787074	-0.815556	-0.994108
C	0.714404	-2.589213	-0.257942
C	-1.075792	-2.108718	-1.792956
H	-0.470048	-0.005421	-1.660319
C	-2.006575	-0.240025	-0.165826
C	0.197555	-2.958432	-1.651321
H	0.219815	-3.163669	0.536925

H	1.794963	-2.713470	-0.171290
H	-1.321761	-1.887215	-2.834160
H	-1.929963	-2.638061	-1.363623
C	-2.330315	-1.204978	0.990745
C	-3.210693	0.055637	-1.086510
O	-1.506924	0.997662	0.359568
H	0.002399	-4.029975	-1.758737
H	0.951283	-2.660299	-2.385849
C	-3.189543	-2.305172	0.834766
C	-1.682003	-1.051618	2.225042
C	-4.520595	0.070068	-0.580236
C	-3.029980	0.441447	-2.424646
Si	-2.186500	2.436423	0.930434
C	-3.400317	-3.210933	1.876563
H	-3.720484	-2.452480	-0.099915
C	-1.892143	-1.954652	3.268009
H	-1.001954	-0.220387	2.365077
C	-5.604828	0.437243	-1.378910
H	-4.700651	-0.212512	0.450857
C	-4.111496	0.803311	-3.228350
H	-2.037245	0.475358	-2.858881
C	-3.495059	2.160363	2.263490
C	-2.898127	3.488609	-0.464630

C	-0.699992	3.322839	1.676585
C	-2.753190	-3.039638	3.099751
H	-4.077093	-4.048236	1.727729
H	-1.377176	-1.808051	4.213909
C	-5.406614	0.802040	-2.710362
H	-6.605863	0.434703	-0.955632
H	-3.936454	1.091410	-4.261453
H	-3.756864	3.123200	2.721311
H	-4.417029	1.728289	1.861185
H	-3.134083	1.499583	3.058893
H	-2.165760	3.632206	-1.267602
H	-3.798196	3.050600	-0.906836
H	-3.163515	4.482011	-0.079536
H	0.059974	3.535849	0.915432
H	-0.998916	4.281450	2.118385
H	-0.224891	2.727061	2.464202
H	-2.919147	-3.741764	3.912350
H	-6.249391	1.083875	-3.335556

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N_Si_anti_pyrrol_t_vin

B3LYP/6-31G(d)

Eel = -1828.84872308 au; Energy(0K)) = -1828.22174303 au

Enthalpy = -1828.18310794 au; Gibbs energy = -1828.28389033 au

C	1.390597	1.200770	-0.974384
C	1.817854	-0.109735	-1.115390
C	3.058122	-0.482947	-1.688328
C	4.014275	0.463850	-2.107297
C	4.820701	1.290742	-0.387298
C	3.848231	1.886698	0.414342
C	5.224885	0.007471	0.299931
C	3.470788	0.967776	1.476121
O	2.641398	1.077134	2.376808
O	6.140561	-0.748985	0.023750
H	1.918370	1.992030	-1.494456
H	1.187358	-0.888248	-0.707435
H	4.913984	0.090957	-2.590205
H	3.685998	1.428504	-2.480891
H	5.573608	1.833634	-0.948771
H	3.477305	2.901095	0.364206
C	3.478244	-1.893101	-1.692493
C	2.741218	-2.974003	-1.389565
H	4.515675	-2.050935	-1.981305
H	3.172159	-3.969062	-1.443824
H	1.697586	-2.918875	-1.094064

N	4.310939	-0.170343	1.326614
C	4.268462	-1.334499	2.184795
H	3.587914	-1.108824	3.007947
H	5.267366	-1.554783	2.572426
H	3.906120	-2.210327	1.633718
N	0.299191	1.641483	-0.303853
C	-0.396240	0.853586	0.735296
C	0.129225	3.079393	-0.036624
C	-0.600169	1.849111	1.912699
H	0.284266	0.053108	1.025401
C	-1.720161	0.166437	0.213021
C	0.108091	3.154102	1.494442
H	-0.813022	3.430162	-0.472052
H	0.947934	3.641649	-0.494626
H	-0.165366	1.442714	2.827532
H	-1.661688	2.023622	2.098722
C	-2.610158	1.227962	-0.464172
C	-2.414192	-0.600497	1.362105
O	-1.270154	-0.773644	-0.769615
H	-0.404406	4.049071	1.861006
H	1.130459	3.146853	1.880997
C	-3.514484	2.031470	0.248997
C	-2.450260	1.481390	-1.835143

C	-3.800288	-0.824201	1.357742
C	-1.663324	-1.206056	2.383545
Si	-1.928672	-2.138380	-1.520941
C	-4.236096	3.045050	-0.385608
H	-3.678521	1.858876	1.307233
C	-3.170232	2.493235	-2.471367
H	-1.745153	0.883980	-2.400121
C	-4.413429	-1.609492	2.335774
H	-4.413611	-0.379280	0.582698
C	-2.273193	-1.986623	3.365938
H	-0.587232	-1.082442	2.425475
C	-3.749597	-1.963575	-1.995742
C	-1.702944	-3.661937	-0.430270
C	-0.908708	-2.304443	-3.096717
C	-4.067663	3.281683	-1.749476
H	-4.934389	3.645411	0.191696
H	-3.026391	2.665387	-3.535006
C	-3.652737	-2.193210	3.348128
H	-5.489258	-1.760805	2.303068
H	-1.663266	-2.435986	4.145013
H	-4.016358	-2.778430	-2.681670
H	-4.418123	-2.030717	-1.132404
H	-3.951380	-1.017732	-2.509634

H -0.657024 -3.787551 -0.125785

H -2.309075 -3.603992 0.479875

H -1.999699 -4.567810 -0.974458

H 0.165743 -2.349958 -2.891031

H -1.184493 -3.217166 -3.639775

H -1.079269 -1.455759 -3.769638

H -4.631118 4.068099 -2.244427

H -4.127833 -2.801627 4.112854

##########

N_Si_anti_pyrrol_c_vin

B3LYP/6-31G(d)

Eel = -1828.84805031 au; Energy(0K)) = -1828.22129051 au

Enthalpy = -1828.18260919 au; Gibbs energy = -1828.28346234 au

C 1.335782 1.255294 -0.957782

C 1.768544 -0.049981 -1.115956

C 3.028039 -0.429196 -1.652035

C 3.999448 0.508757 -2.033289

C 4.750443 1.373691 -0.240511

C 3.738310 1.931668 0.530922

C 5.162020 0.090020 0.433588

C 3.346483 0.984531 1.564617

O	2.484701	1.059914	2.437802
O	6.110926	-0.634692	0.184175
H	1.876795	2.059519	-1.444153
H	1.119357	-0.839557	-0.757909
H	4.915055	0.155505	-2.496789
H	3.681677	1.485410	-2.382252
H	5.494009	1.932994	-0.796875
H	3.343903	2.937203	0.484347
C	3.314585	-1.874061	-1.642360
C	4.488215	-2.483374	-1.867530
H	2.454066	-2.500133	-1.405780
H	4.564925	-3.565753	-1.822472
H	5.407892	-1.943508	-2.066359
N	4.217093	-0.131092	1.423478
C	4.203578	-1.294123	2.284418
H	3.377346	-1.169333	2.986772
H	5.145940	-1.380038	2.835413
H	4.062403	-2.205308	1.694174
N	0.219560	1.674829	-0.312886
C	-0.476430	0.874755	0.718674
C	0.017794	3.109227	-0.051397
C	-0.738461	1.876438	1.879577
H	0.222773	0.099554	1.032920

C	-1.768989	0.139985	0.181644
C	-0.031057	3.185731	1.478238
H	-0.924590	3.440367	-0.502283
H	0.831685	3.687159	-0.498413
H	-0.338478	1.482247	2.815243
H	-1.808899	2.040939	2.018291
C	-2.664305	1.159557	-0.550253
C	-2.475140	-0.609299	1.334450
O	-1.273993	-0.818968	-0.760982
H	-0.555967	4.076947	1.836415
H	0.984113	3.185340	1.884087
C	-3.606003	1.962176	0.113997
C	-2.472359	1.375895	-1.923390
C	-3.854754	-0.867474	1.300464
C	-1.736865	-1.165788	2.392370
Si	-1.865923	-2.242300	-1.455435
C	-4.333039	2.938836	-0.570447
H	-3.795357	1.817531	1.172279
C	-3.197593	2.350993	-2.609160
H	-1.739307	0.777579	-2.450629
C	-4.474496	-1.638655	2.285637
H	-4.457945	-0.460729	0.496949
C	-2.353712	-1.931873	3.381685

H	-0.665508	-1.013921	2.457417
C	-3.667701	-2.137481	-2.015558
C	-1.645262	-3.704612	-0.283997
C	-0.772785	-2.462668	-2.975139
C	-4.132429	3.138823	-1.935845
H	-5.060773	3.539289	-0.030797
H	-3.028478	2.494811	-3.673288
C	-3.727045	-2.172961	3.334499
H	-5.545124	-1.817603	2.229822
H	-1.754205	-2.342847	4.189517
H	-3.888835	-2.993917	-2.666110
H	-4.371627	-2.172052	-1.178722
H	-3.865834	-1.225338	-2.588548
H	-0.608966	-3.782302	0.065454
H	-2.290033	-3.627071	0.597453
H	-1.891934	-4.641950	-0.799289
H	0.291608	-2.475278	-2.717538
H	-1.004695	-3.405639	-3.485864
H	-0.925080	-1.649828	-3.694811
H	-4.699952	3.896623	-2.469324
H	-4.207583	-2.769884	4.104869

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N_Re_anti_pyrrole_c_vin

B3LYP/6-31G(d)

Eel = -1828.84506098 au; Energy(0K)) = -1828.21775049 au

Enthalpy = -1828.17935841 au; Gibbs energy = -1828.27969737 au

C	-1.134235	1.200249	-1.572539
C	-1.603976	-0.094528	-1.698763
C	-2.960881	-0.411571	-1.981539
C	-3.943791	0.586125	-2.140642
C	-4.408238	1.389747	-0.300676
C	-3.323779	1.709799	0.519434
C	-5.044362	0.149661	0.284193
C	-3.125666	0.642946	1.483104
O	-2.289345	0.501327	2.374042
O	-6.093972	-0.387477	-0.033553
H	-1.830707	2.021438	-1.687775
H	-0.913994	-0.911988	-1.523864
H	-4.941176	0.284985	-2.443572
H	-3.638933	1.537562	-2.564245
H	-5.062196	2.125177	-0.758284
H	-2.756542	2.629109	0.553416
C	-3.303744	-1.840109	-1.974847
C	-4.523676	-2.395722	-2.061044

H	-2.446643	-2.507530	-1.885528
H	-4.638122	-3.475472	-2.036789
H	-5.437812	-1.814798	-2.122318
N	-4.177958	-0.293021	1.263853
C	-4.400290	-1.485431	2.053673
H	-3.721192	-1.449188	2.907086
H	-5.437978	-1.513985	2.398554
H	-4.203141	-2.387929	1.464586
N	0.140024	1.617610	-1.394138
C	1.350656	0.793203	-1.588251
C	0.474570	3.044208	-1.512168
C	2.350043	1.760553	-2.291708
H	1.067420	-0.033280	-2.245442
C	1.916655	0.135937	-0.261077
C	1.561325	3.050598	-2.589947
H	0.855772	3.421325	-0.556688
H	-0.416898	3.618396	-1.777764
H	2.763617	1.307635	-3.196069
H	3.193198	1.979015	-1.633903
C	1.931099	1.208532	0.845827
C	3.286509	-0.525108	-0.540647
O	0.975703	-0.890200	0.059005
H	2.190005	3.945482	-2.554237

H	1.096533	3.001553	-3.581383
C	2.989931	2.115522	1.021448
C	0.786954	1.371866	1.640482
C	4.281025	-0.613483	0.444929
C	3.524979	-1.178050	-1.761958
Si	1.018844	-2.238692	1.089663
C	2.911433	3.138709	1.969926
H	3.896516	2.021810	0.432365
C	0.706230	2.394267	2.586095
H	-0.062497	0.712199	1.521099
C	5.472788	-1.304383	0.214130
H	4.126183	-0.140393	1.407452
C	4.715685	-1.863424	-1.999380
H	2.770743	-1.172101	-2.541558
C	1.795712	-1.891030	2.775577
C	1.915446	-3.681630	0.262865
C	-0.795759	-2.661275	1.330760
C	1.768572	3.283339	2.757275
H	3.750558	3.819090	2.091780
H	-0.201047	2.481198	3.177044
C	5.699676	-1.928068	-1.011764
H	6.222818	-1.352240	0.999239
H	4.869661	-2.354098	-2.956852

H 1.655516 -2.772873 3.414866

H 2.871272 -1.695581 2.722427

H 1.317975 -1.040756 3.272911

H 1.510327 -3.882597 -0.735959

H 2.990686 -3.504788 0.158400

H 1.782134 -4.592260 0.861489

H -1.303027 -2.862349 0.380379

H -0.901957 -3.553852 1.960406

H -1.316990 -1.832175 1.821404

H 1.709326 4.078496 3.496032

H 6.627876 -2.462568 -1.194569

##########

N_Si_syn_pyrrol_t_vin

B3LYP/6-31G(d)

Eel = -1828.84338705 au; Energy(0K)) = -1828.21634341 au

Enthalpy = -1828.17760750 au; Gibbs energy = -1828.27882043 au

C 0.994550 -0.484804 -1.448005

C 2.346790 -0.749545 -1.588013

C 3.341564 0.221599 -1.876889

C 3.174916 1.601674 -1.585927

C 3.519222 1.918678 0.297315

C	2.683489	1.224239	1.191080
C	4.894612	1.290142	0.434938
C	3.385858	0.081401	1.720981
O	3.048873	-0.790950	2.518222
O	5.952567	1.682943	-0.033353
H	0.624426	0.528247	-1.555190
H	2.682803	-1.778817	-1.528119
H	3.904914	2.275586	-2.030787
H	2.166412	2.005803	-1.586815
H	3.487800	3.000893	0.193906
H	1.699127	1.509933	1.531266
C	4.658931	-0.213728	-2.347702
C	4.958894	-1.401163	-2.902666
H	5.452623	0.523443	-2.245196
H	5.971150	-1.623833	-3.226002
H	4.214595	-2.172931	-3.079458
N	4.710243	0.140402	1.170128
C	5.755303	-0.813271	1.471608
H	6.035705	-1.378480	0.575031
H	5.363129	-1.495256	2.228431
H	6.643074	-0.298442	1.851330
N	0.013618	-1.390370	-1.253923
C	-1.425683	-1.076738	-1.431921

C	0.233799	-2.840253	-1.168304
C	-2.075997	-2.452873	-1.722882
H	-1.501140	-0.411633	-2.297184
C	-2.071110	-0.292464	-0.220873
C	-0.910751	-3.415178	-2.005280
H	0.183642	-3.160881	-0.120605
H	1.216043	-3.105170	-1.560902
H	-2.780518	-2.392745	-2.555541
H	-2.635927	-2.795641	-0.850269
C	-1.743199	-1.042126	1.083861
C	-3.583438	-0.076832	-0.453875
O	-1.410255	0.982260	-0.253255
H	-1.145364	-4.450543	-1.741118
H	-0.636507	-3.391505	-3.066352
C	-2.564950	-2.058628	1.600951
C	-0.518071	-0.803467	1.721443
C	-4.452597	0.127847	0.630328
C	-4.120126	0.049010	-1.745308
Si	-1.788659	2.538660	0.298396
C	-2.179713	-2.791214	2.725912
H	-3.522681	-2.277428	1.139776
C	-0.122648	-1.540174	2.839187
H	0.150817	-0.051042	1.324600

C	-5.802502	0.423030	0.434721
H	-4.071976	0.052105	1.642423
C	-5.470317	0.338294	-1.945918
H	-3.487985	-0.065680	-2.618769
C	-2.081614	2.582784	2.161782
C	-3.242304	3.322264	-0.616580
C	-0.244576	3.528083	-0.136693
C	-0.958101	-2.535230	3.348936
H	-2.840357	-3.564272	3.110465
H	0.852878	-1.340271	3.271718
C	-6.320703	0.524420	-0.856341
H	-6.447609	0.572292	1.296503
H	-5.854154	0.423535	-2.959064
H	-2.107394	3.624068	2.508149
H	-3.031128	2.118956	2.449255
H	-1.282013	2.068416	2.705728
H	-3.100369	3.276298	-1.702586
H	-4.204853	2.858584	-0.383631
H	-3.305674	4.382958	-0.339196
H	-0.052549	3.504137	-1.216280
H	-0.371623	4.579500	0.149715
H	0.647030	3.150873	0.373095
H	-0.656529	-3.110680	4.220290

H -7.372261 0.749474 -1.011713

##########

N_Si_syn_pyrrol_c_vin

B3LYP/6-31G(d)

Eel = -1828.84198019 au; Energy(0K)) = -1828.21499802 au

Enthalpy = -1828.17631130 au; Gibbs energy = -1828.27738752 au

C -0.955493 -0.410140 1.530165

C -2.289382 -0.724157 1.723754

C -3.350969 0.210000 1.892823

C -3.238331 1.564693 1.508362

C -3.493052 1.726966 -0.464210

C -2.644369 0.938780 -1.252825

C -4.874398 1.117298 -0.585914

C -3.353048 -0.240522 -1.692684

O -3.004382 -1.194761 -2.383551

O -5.939589 1.577311 -0.203784

H -0.639415 0.625394 1.480459

H -2.562554 -1.770368 1.820516

H -4.008144 2.250401 1.850980

H -2.247435 2.008858 1.499345

H -3.431601 2.811243 -0.427710

H	-1.644948	1.173190	-1.586221
C	-4.616191	-0.353880	2.374111
C	-5.784432	0.281817	2.568386
H	-4.576749	-1.418588	2.605089
H	-6.650505	-0.261242	2.934984
H	-5.932974	1.332537	2.347239
N	-4.693109	-0.102304	-1.200550
C	-5.757519	-1.043345	-1.471453
H	-5.319466	-1.875761	-2.025296
H	-6.547814	-0.576083	-2.068671
H	-6.197983	-1.403891	-0.535825
N	0.073885	-1.282606	1.462153
C	1.494684	-0.871470	1.581577
C	-0.069381	-2.737201	1.606764
C	2.216214	-2.155173	2.064157
H	1.535945	-0.085299	2.341432
C	2.101365	-0.238066	0.265687
C	1.102709	-3.112749	2.515243
H	0.000050	-3.217120	0.622661
H	-1.036040	-2.989262	2.043695
H	2.931765	-1.936120	2.859613
H	2.774976	-2.603543	1.239917
C	1.802298	-1.178511	-0.916944

C	3.603680	0.071424	0.452460
O	1.385566	1.000048	0.126963
H	1.387005	-4.165122	2.422172
H	0.830091	-2.927371	3.560762
C	2.662746	-2.225408	-1.290588
C	0.567175	-1.082394	-1.571582
C	4.464191	0.146656	-0.654916
C	4.134571	0.409963	1.707619
Si	1.700047	2.473380	-0.650310
C	2.303287	-3.126713	-2.295202
H	3.630208	-2.336411	-0.811741
C	0.197588	-1.986343	-2.568593
H	-0.129167	-0.307173	-1.282174
C	5.802016	0.517728	-0.512331
H	4.086541	-0.090197	-1.643006
C	5.472534	0.776598	1.856119
H	3.505999	0.404527	2.591173
C	1.955317	2.256850	-2.507156
C	3.148981	3.419592	0.104565
C	0.141696	3.479523	-0.316858
C	1.070098	-3.011447	-2.937366
H	2.993258	-3.920409	-2.570768
H	-0.785042	-1.885244	-3.019381

C	6.315881	0.829184	0.746434
H	6.441194	0.561584	-1.390221
H	5.852070	1.027285	2.843107
H	2.003845	3.240429	-2.992121
H	2.886527	1.730551	-2.742109
H	1.132934	1.697569	-2.966257
H	3.034785	3.520788	1.190041
H	4.120594	2.957054	-0.089311
H	3.169292	4.432808	-0.318540
H	-0.047139	3.564447	0.760248
H	0.258469	4.497492	-0.709283
H	-0.747649	3.045545	-0.782706
H	0.789290	-3.717685	-3.714371
H	7.358142	1.114119	0.860740

##########

Transition structures for the endo addition of *N*-methyl maleimide to 2b, in descending order of energy (0K); most stable first.
Although 4 TSs are present in Table 1, there are actually eight listed here, the doubling being due to the spectator vinyl group in the dendralene adopting either cis or trans conformation with respect to the central double bond of the dendralene

N_Re_syn_benzimidaz_t_vin

B3LYP/6-31G(d)

Eel = -1321.89886048 au; Energy(0K)) = -1321.40609622 au

Enthalpy = -1321.37583023 au; Gibbs energy = -1321.46053880 au

C	0.356764	0.204203	-0.843065
C	1.115752	1.160746	-0.188405
C	2.283119	1.786004	-0.693779
C	2.930143	1.362521	-1.875374
C	3.820079	-0.401405	-1.460706
C	2.877339	-1.397035	-1.195339
C	4.487331	-0.079546	-0.139120
C	2.758856	-1.583511	0.238457
O	2.020966	-2.314849	0.894706
O	5.462271	0.623980	0.065626
H	0.537730	-0.006817	-1.890257
H	0.856077	1.396390	0.835922
H	3.774353	1.959003	-2.214349
H	2.337814	0.955650	-2.689167
H	4.431013	-0.368222	-2.357673
H	2.355049	-2.014325	-1.910639
C	2.973187	2.793683	0.123422
C	2.431844	3.544552	1.095345
H	4.023758	2.939373	-0.120831
H	3.030304	4.271644	1.635429
H	1.381521	3.486681	1.368843

N	3.739684	-0.729804	0.826091
C	3.978798	-0.622908	2.250122
H	3.332760	-1.350682	2.744588
H	5.027186	-0.838454	2.476963
H	3.745209	0.385830	2.608808
N	-0.689514	-0.464671	-0.307112
C	-1.409131	-1.541354	-1.050235
C	-1.060923	-0.407321	1.108586
N	-2.215930	-2.129975	0.024273
C	-2.295317	-0.942052	-2.155357
C	-0.439915	-2.592024	-1.616549
H	-0.180078	-0.618251	1.727898
C	-1.726994	0.905314	1.614004
C	-2.046132	-1.561814	1.249847
C	-3.134719	-3.233824	-0.178992
H	-2.830416	-1.732204	-2.692707
H	-3.018209	-0.239558	-1.734424
H	-1.676073	-0.410944	-2.885844
H	0.129794	-2.186432	-2.457633
H	0.253341	-2.923914	-0.838692
H	-1.003699	-3.448858	-1.998694
H	-2.046647	0.677799	2.636986
H	-0.974909	1.695728	1.682654

C -2.900419 1.392520 0.791837

O -2.615023 -1.878255 2.284105

H -3.625581 -3.413114 0.779024

H -3.891378 -2.986052 -0.931391

H -2.610048 -4.145404 -0.485828

C -2.715591 2.346133 -0.219053

C -4.193962 0.897965 1.017838

C -3.791129 2.791976 -0.989225

H -1.719822 2.743538 -0.402477

C -5.270418 1.340613 0.247315

H -4.351978 0.161337 1.800957

C -5.072794 2.288358 -0.759289

H -3.628211 3.535970 -1.764826

H -6.266418 0.950123 0.439823

H -5.912461 2.637521 -1.354444

##########

N_Re_syn_benzimidaz_c_vin

B3LYP/6-31G(d)

Eel = -1321.89754674 au; Energy(0K)) = -1321.40474948 au

Enthalpy = -1321.37448812 au; Gibbs energy = -1321.45923389 au

C -0.307150 0.256593 0.779445

C	-1.060359	1.169405	0.061737
C	-2.258938	1.803771	0.488091
C	-2.902663	1.475230	1.695065
C	-3.755613	-0.387790	1.451842
C	-2.789293	-1.368014	1.238523
C	-4.466145	-0.187041	0.132404
C	-2.694732	-1.653099	-0.182666
O	-1.947255	-2.406299	-0.801567
O	-5.481047	0.449775	-0.093421
H	-0.518824	0.085084	1.827927
H	-0.757220	1.378803	-0.957666
H	-3.759588	2.070542	1.995316
H	-2.301947	1.136772	2.532990
H	-4.332558	-0.283207	2.364959
H	-2.236434	-1.919553	1.983600
C	-2.870618	2.720965	-0.485301
C	-4.097209	3.263202	-0.446472
H	-2.234298	2.964284	-1.336317
H	-4.432232	3.924655	-1.239658
H	-4.816312	3.048677	0.336620
N	-3.714615	-0.874154	-0.805140
C	-4.009348	-0.900676	-2.222377
H	-3.263558	-1.540644	-2.697462

H	-5.010822	-1.304779	-2.403242
H	-3.962028	0.109079	-2.642363
N	0.767799	-0.415282	0.302917
C	1.499134	-1.427510	1.120181
C	1.155815	-0.440103	-1.109003
N	2.323865	-2.073304	0.092558
C	2.368168	-0.740042	2.186816
C	0.546684	-2.456646	1.750387
H	0.284100	-0.702082	-1.722263
C	1.808520	0.845982	-1.694581
C	2.159285	-1.586113	-1.167773
C	3.261187	-3.143648	0.375476
H	2.911412	-1.482507	2.781167
H	3.083149	-0.058434	1.720657
H	1.735865	-0.167819	2.873751
H	-0.033210	-2.008869	2.562543
H	-0.136611	-2.852503	0.993867
H	1.125263	-3.276338	2.187644
H	2.147304	0.552508	-2.694448
H	1.045788	1.617239	-1.830019
C	2.961674	1.411133	-0.893629
O	2.744432	-1.957964	-2.174296
H	3.766544	-3.373744	-0.563985

H 4.003834 -2.833457 1.118529

H 2.750673 -4.044243 0.734117

C 2.748635 2.441133 0.033210

C 4.264570 0.916278 -1.057326

C 3.805457 2.961277 0.782494

H 1.745710 2.840712 0.166471

C 5.322200 1.433177 -0.307262

H 4.445161 0.121808 -1.776414

C 5.096490 2.456767 0.615689

H 3.620535 3.763429 1.492383

H 6.325752 1.040985 -0.451063

H 5.921668 2.863281 1.194464

##########

N_Si_syn_benzimid_t_vin

B3LYP/6-31G(d)

Eel = -1321.89646183 au; Energy(0K)) = -1321.40405680 au

Enthalpy = -1321.37346859 au; Gibbs energy = -1321.45873791 au

C 0.275193 -0.500908 -0.221592

C 1.150207 -1.044656 0.701183

C 2.235343 -1.891283 0.356578

C 2.549860 -2.224495 -0.977040

C	3.348418	-0.576752	-1.886809
C	2.475423	0.510923	-1.932333
C	4.415973	-0.234159	-0.868892
C	2.830864	1.460039	-0.889892
O	2.327246	2.535360	-0.583814
O	5.439150	-0.845739	-0.610446
H	0.328121	-0.850671	-1.244709
H	1.073176	-0.750296	1.738932
H	3.360794	-2.931749	-1.131468
H	1.747744	-2.319062	-1.702643
H	3.641181	-1.157469	-2.755721
H	1.727329	0.730957	-2.682133
C	3.182884	-2.322378	1.394989
C	2.962643	-2.373960	2.717736
H	4.150787	-2.647609	1.017825
H	3.734336	-2.724603	3.395999
H	2.012716	-2.101558	3.170446
N	3.985861	0.924718	-0.247973
C	4.683996	1.570782	0.843656
H	4.238532	2.558306	0.977453
H	5.747455	1.666921	0.606599
H	4.583587	0.991523	1.768573
N	-0.735445	0.380176	-0.033271

C	-1.070519	1.106832	1.224378
C	-1.483374	0.876844	-1.190787
N	-2.098489	2.041740	0.734723
C	-1.675766	0.145129	2.263311
C	0.122803	1.897380	1.789383
H	-0.793742	1.360164	-1.898821
C	-2.307998	-0.179236	-1.969249
C	-2.374298	1.955864	-0.594316
C	-2.800669	2.977065	1.593575
H	-1.929174	0.684605	3.181782
H	-2.577333	-0.326552	1.863980
H	-0.962669	-0.639792	2.526756
H	0.868842	1.238342	2.237838
H	0.609771	2.478364	1.002750
H	-0.226940	2.569732	2.579432
H	-2.835784	0.382917	-2.747869
H	-1.615905	-0.857773	-2.482277
C	-3.287582	-0.977031	-1.134788
O	-3.199521	2.610274	-1.215872
H	-3.530872	3.491148	0.966280
H	-3.324200	2.457522	2.403395
H	-2.118456	3.717041	2.025781
C	-2.942164	-2.241894	-0.639748

C -4.558875 -0.464417 -0.833652

C -3.836108 -2.975871 0.141697

H -1.965169 -2.659806 -0.871653

C -5.454012 -1.196103 -0.051949

H -4.840901 0.513823 -1.212861

C -5.095612 -2.453324 0.439490

H -3.549666 -3.956501 0.512652

H -6.436193 -0.785404 0.167325

H -5.795646 -3.024461 1.043495

##########

N_Si_anti_benzimid_t_vin

B3LYP/6-31G(d)

Eel = -1321.89686425 au; Energy(0K)) = -1321.40395218 au

Enthalpy = -1321.37370011 au; Gibbs energy = -1321.45860698 au

C 0.529100 -1.389223 -0.261672

C 1.512406 -1.292407 0.706877

C 2.888426 -1.548891 0.472539

C 3.399402 -1.751955 -0.830610

C 3.418898 0.014017 -1.766151

C 2.185025 0.676667 -1.750901

C 4.314587 0.745097 -0.787879

C	2.184967	1.653139	-0.676636
O	1.318472	2.432398	-0.288801
O	5.509260	0.592634	-0.595880
H	0.799586	-1.721734	-1.255076
H	1.226316	-0.983686	1.706258
H	4.447860	-2.028439	-0.912270
H	2.770753	-2.241590	-1.568646
H	3.876100	-0.385196	-2.666660
H	1.374554	0.594385	-2.461597
C	3.856122	-1.450892	1.570580
C	3.593696	-1.475404	2.887906
H	4.894611	-1.370765	1.253556
H	4.397138	-1.407111	3.614690
H	2.590828	-1.590719	3.290165
N	3.485268	1.609148	-0.097948
C	3.909291	2.439255	1.010503
H	3.139131	3.196390	1.167579
H	4.866033	2.913365	0.775605
H	4.026663	1.840671	1.921412
N	-0.801679	-1.215355	-0.083698
C	-1.796976	-1.736366	-1.068049
C	-1.405145	-0.892436	1.210492
N	-2.993703	-1.831933	-0.223937

C	-1.988769	-0.755810	-2.235250
C	-1.410096	-3.135188	-1.586127
H	-0.886739	-1.448892	2.001806
C	-1.406624	0.616360	1.605304
C	-2.814991	-1.452053	1.075634
C	-4.277295	-2.306154	-0.705700
H	-2.727263	-1.139283	-2.947415
H	-2.313031	0.220534	-1.869385
H	-1.043482	-0.630616	-2.774056
H	-0.530351	-3.095930	-2.234831
H	-1.207797	-3.814182	-0.752431
H	-2.227915	-3.547976	-2.184242
H	-1.654662	0.639093	2.673013
H	-0.383698	0.991949	1.497011
C	-2.365376	1.516377	0.845383
O	-3.643199	-1.517622	1.970381
H	-4.975566	-2.221416	0.128649
H	-4.636291	-1.693662	-1.539710
H	-4.231739	-3.353921	-1.024366
C	-1.910665	2.314790	-0.214731
C	-3.719272	1.589383	1.211466
C	-2.796144	3.148707	-0.903504
H	-0.856588	2.304996	-0.479765

C -4.600709 2.421760 0.521106

H -4.083123 0.984790 2.036804

C -4.143111 3.202211 -0.542606

H -2.424288 3.767939 -1.716188

H -5.644616 2.466381 0.821561

H -4.828379 3.856425 -1.075846

##########

N_Si_anti_benzimid_c_vin

B3LYP/6-31G(d)

Eel = -1321.89641629 au; Energy(0K)) = -1321.40360420 au

Enthalpy = -1321.37334332 au; Gibbs energy = -1321.45828678 au

C 0.465014 -1.390026 -0.147517

C 1.419879 -1.273554 0.845811

C 2.811180 -1.511922 0.665187

C 3.352433 -1.801742 -0.602864

C 3.357398 -0.079552 -1.700731

C 2.135173 0.596755 -1.714064

C 4.278362 0.702072 -0.791150

C 2.163260 1.643638 -0.705744

O 1.309889 2.452642 -0.353364

O 5.475282 0.551258 -0.611578

H	0.766815	-1.721458	-1.132102
H	1.101703	-0.969912	1.838680
H	4.403159	-2.066130	-0.666205
H	2.734249	-2.339246	-1.315103
H	3.791215	-0.569020	-2.566964
H	1.315746	0.483802	-2.409978
C	3.658939	-1.308108	1.845617
C	4.999321	-1.361457	1.915931
H	3.111904	-1.084885	2.761628
H	5.507454	-1.181852	2.858571
H	5.633186	-1.553446	1.056962
N	3.473924	1.624095	-0.149867
C	3.940989	2.535912	0.873268
H	3.090926	3.150678	1.173887
H	4.741112	3.175334	0.486468
H	4.326342	1.976370	1.731719
N	-0.872744	-1.231118	-0.003047
C	-1.838950	-1.760041	-1.010564
C	-1.509965	-0.906235	1.273541
N	-3.060253	-1.846588	-0.201286
C	-1.997302	-0.789952	-2.191618
C	-1.437793	-3.163773	-1.503979
H	-1.017759	-1.466098	2.079512

C	-1.513455	0.601838	1.668620
C	-2.919247	-1.456091	1.099572
C	-4.330944	-2.318758	-0.717883
H	-2.716604	-1.179349	-2.920006
H	-2.330066	0.190087	-1.843458
H	-1.037882	-0.670240	-2.705990
H	-0.535919	-3.130833	-2.121904
H	-1.264971	-3.835691	-0.658011
H	-2.235267	-3.580781	-2.126240
H	-1.803434	0.627392	2.725581
H	-0.483182	0.967142	1.602160
C	-2.431304	1.509757	0.869560
O	-3.774961	-1.507892	1.969112
H	-5.052396	-2.229358	0.096027
H	-4.664439	-1.708112	-1.563752
H	-4.278902	-3.367651	-1.031783
C	-1.928517	2.292527	-0.180266
C	-3.795979	1.603954	1.187486
C	-2.777647	3.133215	-0.905686
H	-0.867053	2.265735	-0.413839
C	-4.640907	2.443113	0.460624
H	-4.196717	1.010347	2.003737
C	-4.135375	3.208688	-0.592157

H -2.368543 3.740099 -1.709670

H -5.693950 2.504535 0.723943

H -4.792295 3.868203 -1.153785

##########

N_Si_syn_benzimid_c_vin

B3LYP/6-31G(d)

Eel = -1321.89583032 au; Energy(0K)) = -1321.40350524 au

Enthalpy = -1321.37292946 au; Gibbs energy = -1321.45819570 au

C 0.231157 -0.468313 -0.144276

C 1.094702 -0.959664 0.816607

C 2.217982 -1.786530 0.533189

C 2.542913 -2.183924 -0.775233

C 3.287843 -0.533330 -1.808572

C 2.429008 0.563245 -1.818994

C 4.418465 -0.194639 -0.865388

C 2.855972 1.517466 -0.804403

O 2.387096 2.601734 -0.477628

O 5.456150 -0.806409 -0.673864

H 0.328312 -0.844554 -1.154767

H 0.967649 -0.658162 1.849470

H 3.366142 -2.876956 -0.914321

H	1.739131	-2.319787	-1.491603
H	3.507499	-1.148203	-2.674899
H	1.653464	0.793738	-2.536856
C	3.094546	-2.087641	1.674684
C	4.311790	-2.652351	1.650907
H	2.687970	-1.797188	2.643673
H	4.861146	-2.812844	2.573783
H	4.816250	-2.938382	0.734236
N	4.037037	0.970572	-0.224960
C	4.821976	1.625960	0.800067
H	4.288751	2.534117	1.086736
H	5.815650	1.885986	0.420741
H	4.942667	0.968614	1.667095
N	-0.821961	0.374508	-0.012110
C	-1.186045	1.172337	1.193006
C	-1.568896	0.779010	-1.205047
N	-2.234746	2.045363	0.636936
C	-1.773548	0.269707	2.293005
C	-0.013741	2.026743	1.705450
H	-0.884925	1.235052	-1.936858
C	-2.354383	-0.345967	-1.924437
C	-2.494405	1.868677	-0.686434
C	-2.971443	3.014301	1.427117

H	-2.062723	0.868569	3.162807
H	-2.650446	-0.264753	1.918611
H	-1.037587	-0.464855	2.628568
H	0.758362	1.412763	2.172892
H	0.449018	2.583146	0.887120
H	-0.375112	2.726076	2.466310
H	-2.876423	0.147270	-2.752045
H	-1.636418	-1.042948	-2.373355
C	-3.336296	-1.104237	-1.056700
O	-3.328638	2.461583	-1.355917
H	-3.696412	3.478038	0.756094
H	-3.504434	2.532349	2.253933
H	-2.311615	3.789820	1.830694
C	-2.969931	-2.311700	-0.446558
C	-4.631608	-0.610100	-0.839171
C	-3.867972	-3.007016	0.365069
H	-1.973163	-2.714790	-0.610624
C	-5.530932	-1.303411	-0.027927
H	-4.928997	0.324887	-1.305652
C	-5.152315	-2.503382	0.577750
H	-3.565182	-3.943701	0.825797
H	-6.531651	-0.907815	0.125353
H	-5.855131	-3.045296	1.205004

##########

N_Re_anti_benzimidaz_t_vin

B3LYP/6-31G(d)

Eel = -1321.89258571 au; Energy(0K)) = -1321.39997528 au

Enthalpy = -1321.36955949 au; Gibbs energy = -1321.45495111 au

C	-0.505262	-1.098055	-0.916873
C	-1.673962	-1.457128	-0.267844
C	-2.975218	-1.308645	-0.815521
C	-3.224726	-0.561198	-1.990530
C	-3.061404	1.366322	-1.529328
C	-1.817952	1.703582	-0.979859
C	-4.059844	1.410839	-0.390866
C	-1.930695	1.748851	0.465902
O	-1.091936	1.966034	1.337105
O	-5.275609	1.331078	-0.446855
H	-0.576132	-0.724167	-1.932486
H	-1.616878	-1.854745	0.736325
H	-4.239191	-0.588586	-2.381838
H	-2.469247	-0.538765	-2.770338
H	-3.396373	1.705321	-2.505367
H	-0.920022	1.994712	-1.506037

C	-4.140550	-1.793073	-0.067097
C	-4.147863	-2.705637	0.918852
H	-5.091658	-1.364922	-0.378610
H	-5.077182	-2.997852	1.397796
H	-3.250194	-3.212172	1.263656
N	-3.305773	1.514380	0.762707
C	-3.857204	1.495844	2.101407
H	-3.071119	1.823511	2.784083
H	-4.716111	2.170054	2.162988
H	-4.184407	0.485466	2.373054
N	0.781592	-1.230442	-0.512495
C	1.256503	-1.866362	0.750965
C	1.875596	-0.989768	-1.465999
N	2.706530	-1.921157	0.502586
C	0.930708	-0.991179	1.971040
C	0.732395	-3.309286	0.905895
H	1.697678	-1.571121	-2.380923
C	2.112062	0.488895	-1.885890
C	3.092608	-1.557928	-0.752992
C	3.662623	-2.418269	1.474472
H	1.232541	-1.495549	2.895102
H	1.450020	-0.033655	1.895317
H	-0.139877	-0.782797	2.030445

H	-0.341227	-3.347779	1.090756
H	0.951767	-3.890716	0.005102
H	1.226871	-3.787678	1.756682
H	2.755936	0.441088	-2.770663
H	1.151391	0.901210	-2.217474
C	2.752110	1.395019	-0.851699
O	4.217634	-1.628795	-1.222515
H	4.651675	-2.303593	1.027822
H	3.614614	-1.838689	2.401838
H	3.499968	-3.477618	1.705076
C	1.989202	2.043360	0.129226
C	4.139107	1.606231	-0.873258
C	2.600072	2.880727	1.065775
H	0.914226	1.902780	0.189058
C	4.748465	2.444681	0.060575
H	4.743663	1.099603	-1.620263
C	3.979978	3.086394	1.033842
H	1.984258	3.372998	1.813620
H	5.824014	2.598096	0.024313
H	4.453363	3.744264	1.758300

##########

N_Re_anti_benzimidaz_c_vin

B3LYP/6-31G(d)

Eel = -1321.89175961 au; Energy(0K)) = -1321.39922118 au

Enthalpy = -1321.36879580 au; Gibbs energy = -1321.45424536 au

C	-0.434302	-1.206134	-0.737162
C	-1.546753	-1.562229	0.003140
C	-2.889500	-1.525758	-0.469552
C	-3.226653	-0.980823	-1.724806
C	-3.100793	1.042254	-1.589395
C	-1.877482	1.507545	-1.100590
C	-4.109062	1.226451	-0.477231
C	-2.002031	1.770129	0.322822
O	-1.178549	2.148898	1.150935
O	-5.321714	1.104559	-0.524575
H	-0.580098	-0.895737	-1.765679
H	-1.414464	-1.886184	1.028085
H	-4.251289	-1.083673	-2.068341
H	-2.501153	-1.050778	-2.529229
H	-3.438481	1.187186	-2.610938
H	-0.990640	1.758449	-1.664741
C	-3.913868	-1.965276	0.485139
C	-5.248773	-1.924774	0.340591
H	-3.518609	-2.368042	1.417870

H	-5.898331	-2.280222	1.134784
H	-5.739977	-1.519247	-0.537049
N	-3.369848	1.533521	0.648782
C	-3.941126	1.731745	1.964158
H	-3.121412	1.977545	2.641511
H	-4.667963	2.550639	1.952390
H	-4.448905	0.821382	2.298311
N	0.879165	-1.269493	-0.402522
C	1.449468	-1.837698	0.853262
C	1.906562	-1.024572	-1.425176
N	2.882214	-1.867863	0.516024
C	1.177663	-0.919925	2.055342
C	0.975953	-3.285247	1.102506
H	1.691006	-1.631228	-2.315252
C	2.079087	0.449505	-1.889998
C	3.179157	-1.541134	-0.773233
C	3.911849	-2.300264	1.442595
H	1.562338	-1.371000	2.976076
H	1.653102	0.051207	1.901979
H	0.105751	-0.751317	2.183533
H	-0.083440	-3.343601	1.352206
H	1.159353	-3.900174	0.216087
H	1.533301	-3.711525	1.942029

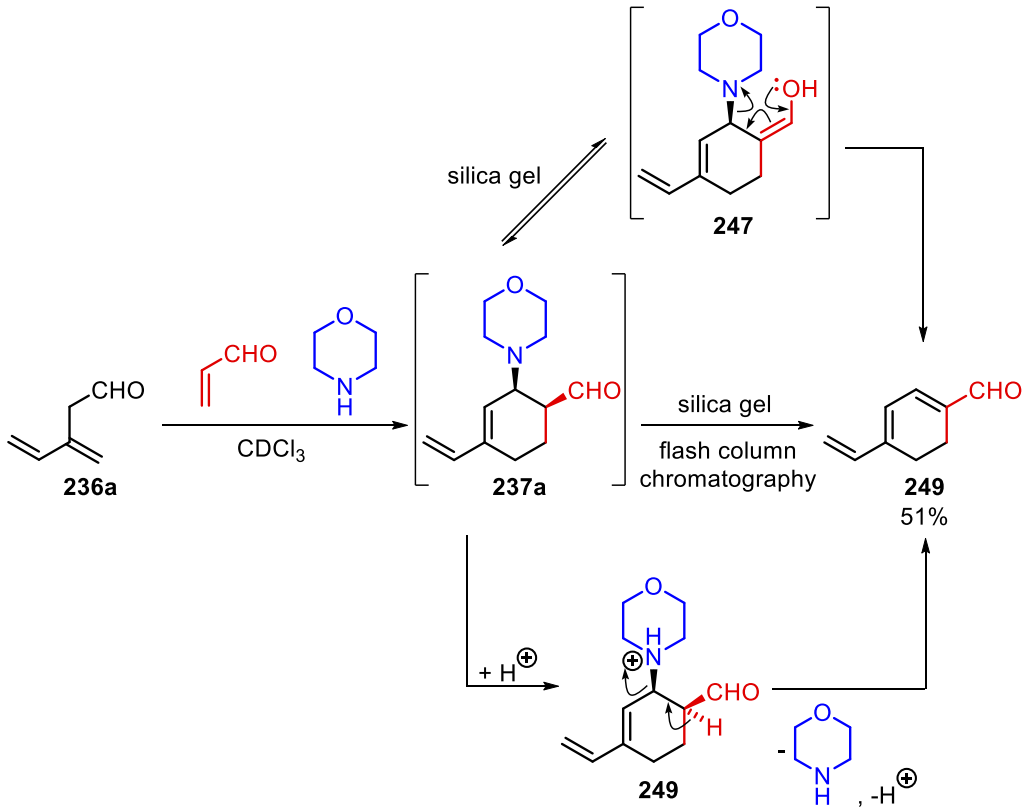
H	2.699694	0.399072	-2.791389
H	1.095789	0.819392	-2.203250
C	2.713816	1.402532	-0.895583
O	4.274741	-1.602030	-1.309740
H	4.864838	-2.196725	0.921092
H	3.920755	-1.672638	2.339609
H	3.783204	-3.347636	1.738948
C	1.943400	2.094383	0.049285
C	4.101134	1.613765	-0.917672
C	2.548050	2.972104	0.952609
H	0.866753	1.961328	0.102900
C	4.703825	2.491503	-0.016276
H	4.710273	1.076191	-1.638695
C	3.928482	3.174700	0.922933
H	1.926983	3.498774	1.672168
H	5.779576	2.643969	-0.051833
H	4.396888	3.863327	1.621635

##########

3 Enantioselective Diels-Alder Reactions of 1-Amino[3]dendralenes

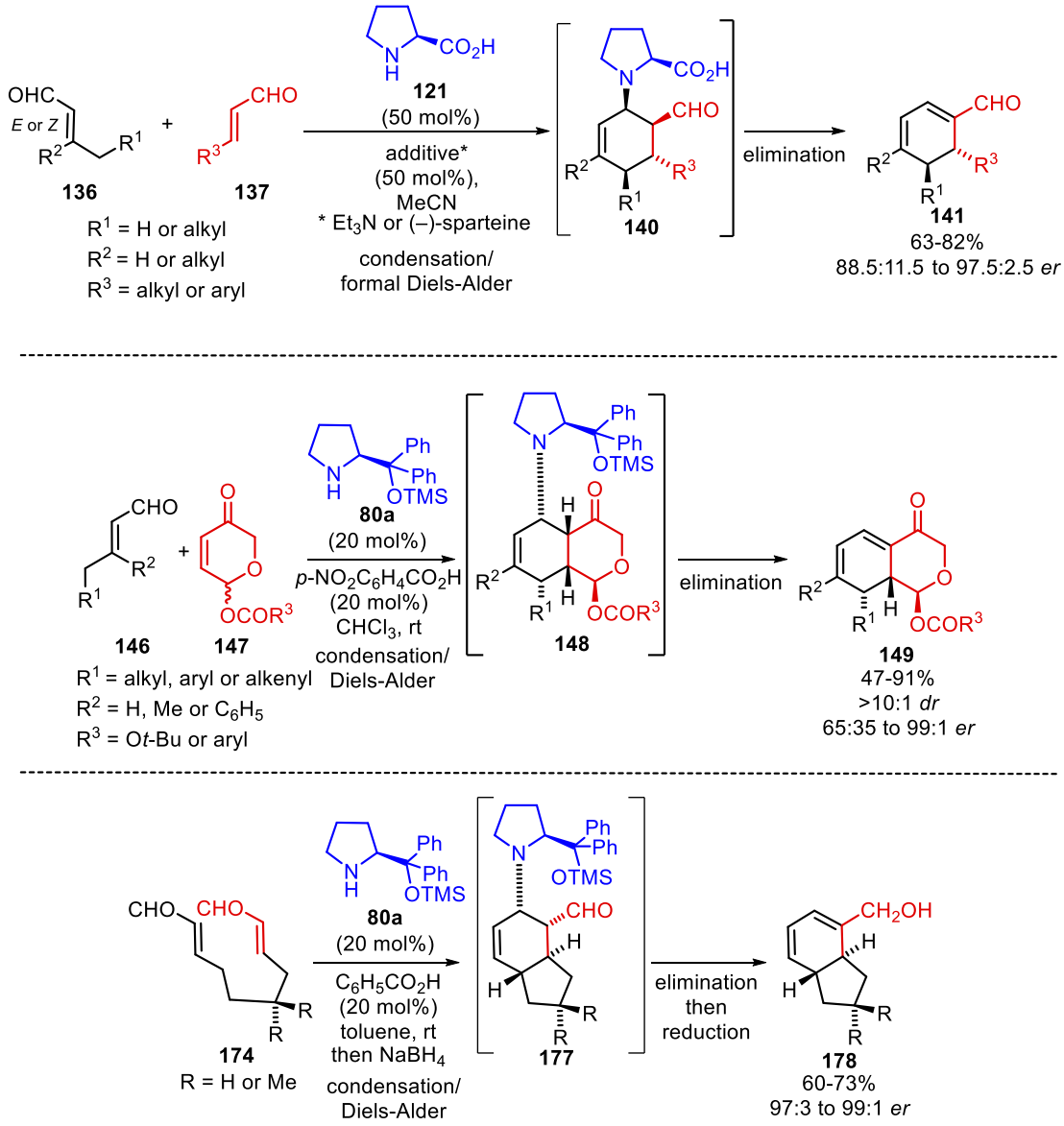
3.1 Introduction

Chapter 2 described the development of methodology where skipped dienals are reacted with stoichiometric amounts of amine to generate putative 1-amino-[3]dendralenes, which are reacted with dienophiles, providing a variety of cycloadducts. One of the examples involved a three-component condensation/Diels-Alder reaction between skipped dienal **236a**, acrolein and morpholine to generate cycloadduct **237a**, which was observed in the crude ^{1}H NMR spectrum of the reaction mixture. Purification on silica gel resulted in the isolation of trienal **249**, which was the product of elimination of morpholine from cycloadduct **237a** (Scheme 3.1). This observation led us to consider developing an enantioselective, catalytic reaction in which elimination regenerates the amine at the end of each reaction cycle.



Scheme 3.1 Condensation/Diels-Alder reaction of skipped dienal **236a**, acrolein and morpholine followed by elimination on silica gel

As described in Chapter 1, transformations involving elimination of the amine from the condensation/Diels-Alder cycloadduct as the catalyst turnover step have previously been reported in the literature. Three examples are shown in Scheme 3.2. Proline (**121**) and Jørgensen-Hayashi catalyst **80a** have been used as chiral amine catalysts and both inter- and intramolecular Diels-Alder reactions have been performed to afford the desired cycloadducts in high enantiomer ratios. The obvious advantage of extending this methodology to 1-amino[3]dendralenes is the opportunity to access enantiopure or highly enantioenriched polycyclic structures *via* domino Diels-Alder sequences.



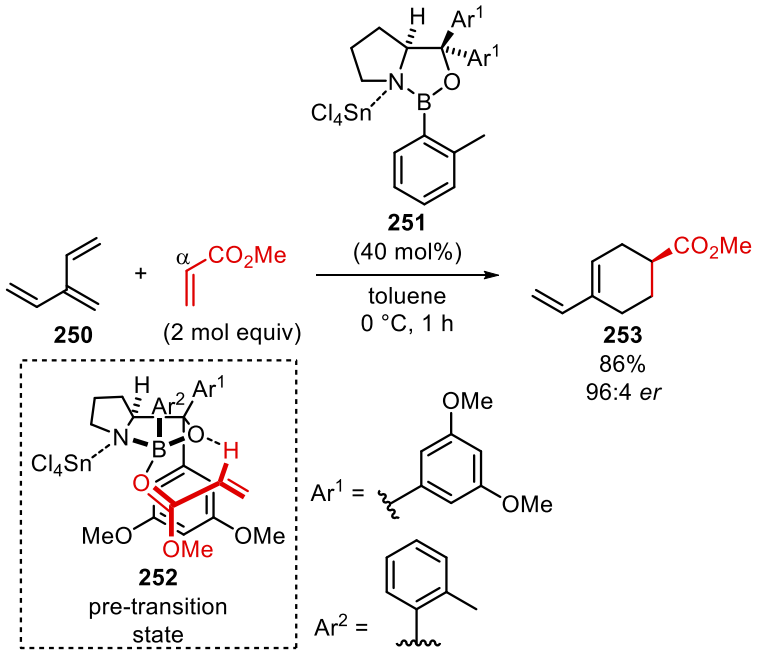
Scheme 3.2 Condensation/Diels-Alder reaction sequences followed by the regeneration of the amine catalyst by elimination

The purpose of this work is to develop enantioselective domino reaction sequences of aminodendralenes. Only a relatively small number of publications describing enantioselective Diels-Alder reactions of dendralenes have been reported and these are summarised in the following section.

3.1.1 Enantioselective Diels-Alder reactions of dendralenes

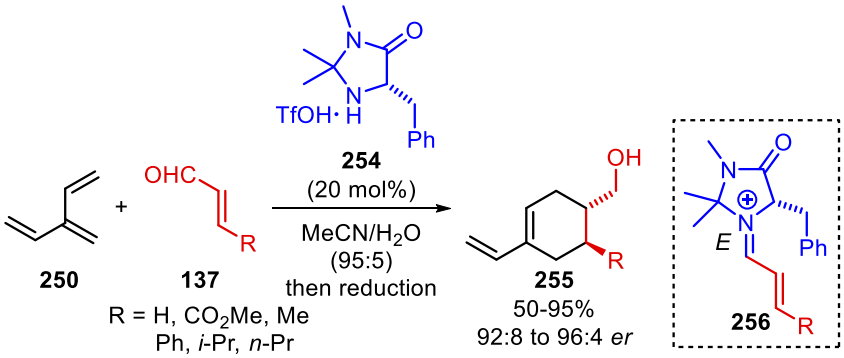
[3]Dendralene (**250**) was reported to undergo an enantioselective Diels-Alder reaction with methyl acrylate catalysed by modified Corey's catalyst **251**,[1] which acts as a chiral Lewis acid, to produce substituted cyclohexene **253** in 86% yield and 96:4 *er*

(Scheme 3.3).[2] The absolute configuration was assigned based on Corey's model[1] of the pre-transition state **252** where the carbonyl oxygen and the Lewis-acidic boron form a dative bond, while the Lewis basic oxygen participates in hydrogen bonding with α hydrogen of the methyl acrylate. This results in one of the aryl groups of catalyst **251** blocking one face of methyl acrylate. [3]Dendralene approaches methyl acrylate from the less hindered face through an *endo* transition state to generate cycloadduct **253**. This model was supported by computational modelling.[3]



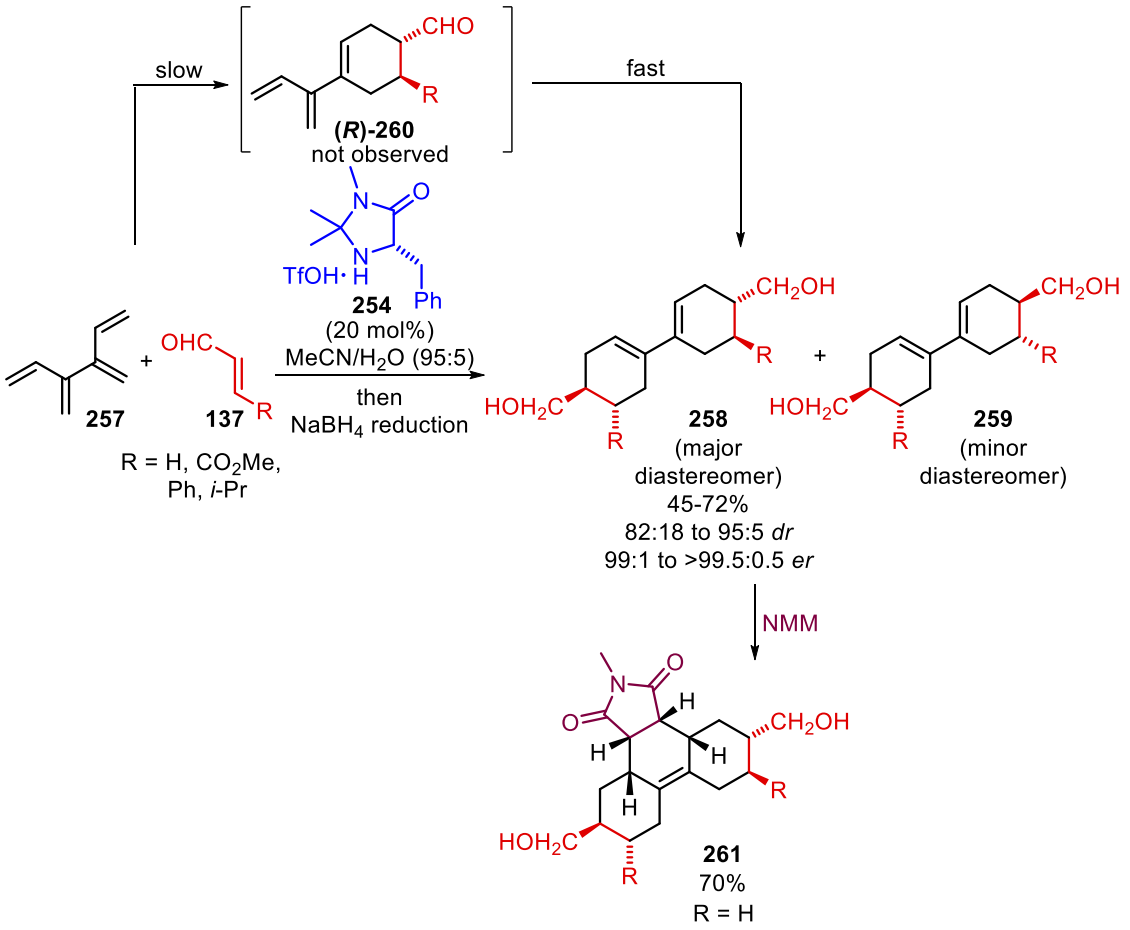
Scheme 3.3 Enantioselective Diels-Alder reaction between [3]dendralene (**250**) and methyl acrylate catalysed by modified Corey's catalyst **251**

[3]Dendralene (**250**) was also reported to undergo enantioselective Diels-Alder reactions with acrolein and β-substituted acroleins **137** in the presence of MacMillan's catalyst **254**,[4] furnishing cycloadducts **255** with high enantioselectivities (Scheme 3.4).[5] MacMillan's catalyst **254** is also a LUMO lowering catalyst. It acts by reversibly condensing with the carbonyl group on the dienophile, generating iminium **256**. Formation of the *E*-iminium isomer is favoured to minimise steric interactions between the alkene and the *gem* dimethyl substituents on the imidazolidinone. The stereochemical outcome can be rationalised by the benzyl group of iminium **256** blocking the bottom face of the dienophile and the diene (i.e. [3]dendralene) approaching from the top face, *endo* to the dienophile.



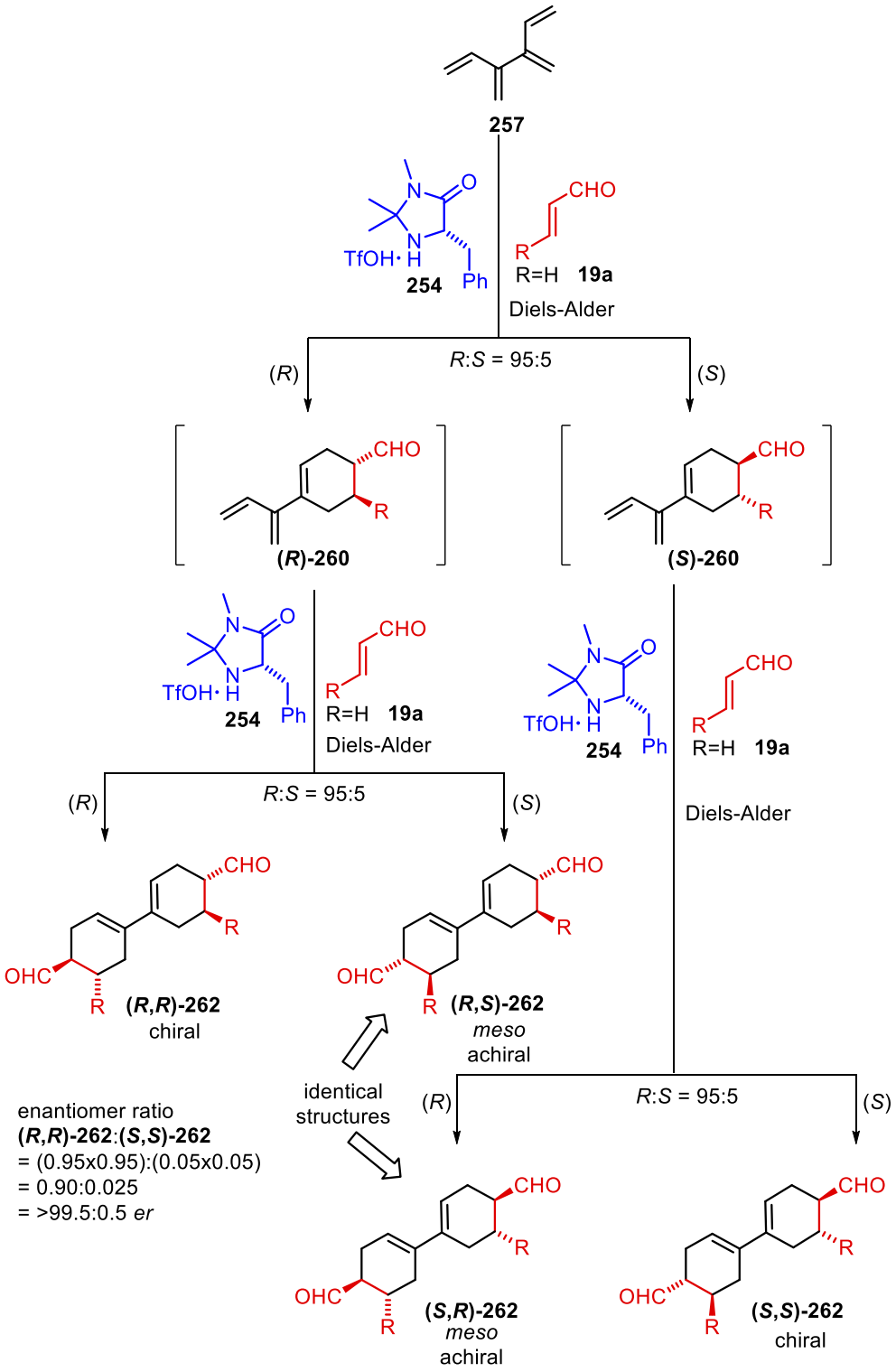
Scheme 3.4 Enantioselective Diels-Alder reaction of [3]dendralene (**250**) and β-substituted acroleins **137** with MacMillan's catalyst **254**

[4]Dendralene (**257**) was reported to undergo a double Diels-Alder reaction with β-substituted acroleins **137** in the presence of MacMillan's catalyst **254**, resulting in the formation of major diastereomers **258** with up to >99.5:0.5 *er* (Scheme 3.4).[5] Only the terminal double Diels-Alder adducts **258** and **259** were isolated while the intermediate mono-adduct **(*R*)-260** was not observed. This is due to the inherent reactivity of [4]dendralene: the first Diels-Alder reaction generates cyclo-adduct **(*R*)-260**, which is a substituted [3]dendralene and thus undergoes a faster second Diels-Alder reaction than [4]dendralene (**257**).[6] A third cycloaddition between bicycle **258** and NMM allowed access to enantioenriched polycycle **261** in two steps from an acyclic precursor, [4]dendralene (**257**).



Scheme 3.5 Double enantioselective Diels-Alder reactions between [4]dendralene (**257**) and β-substituted acroleins **137** with MacMillan's catalyst **254** followed by Diels-Alder reaction with NMM

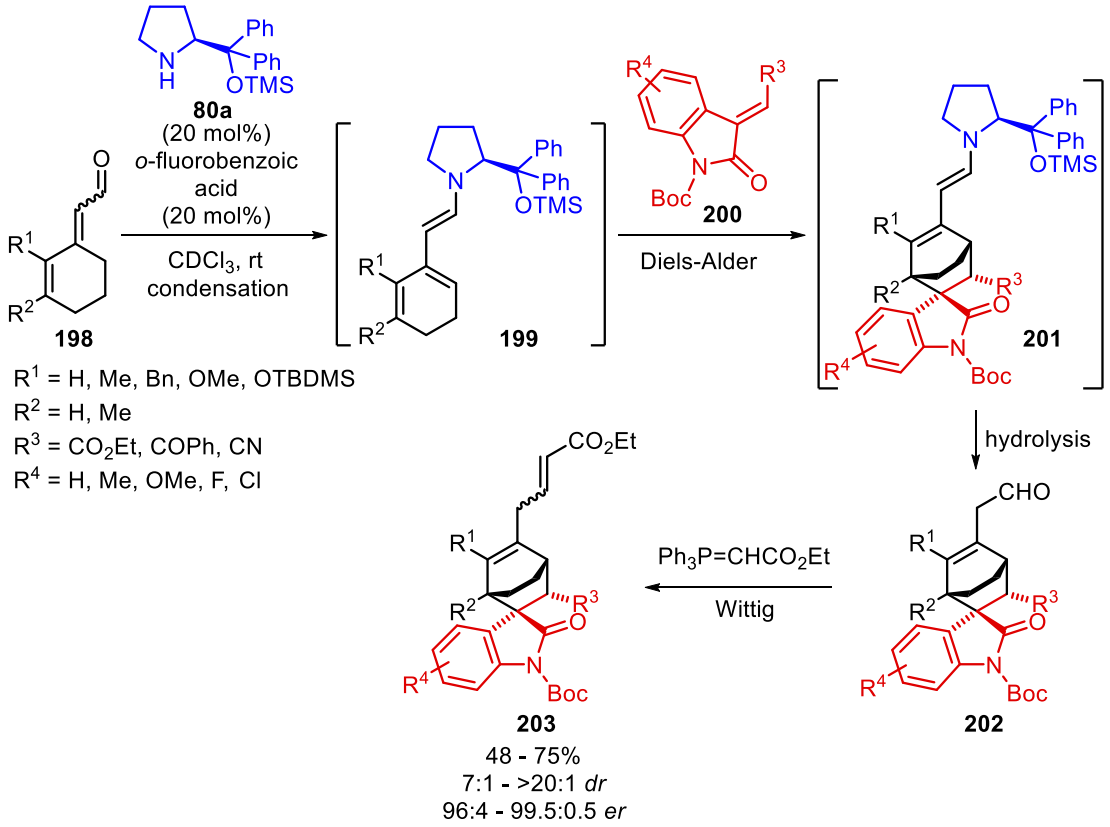
The highly enantioselective formation of chiral diastereomer **258** is a demonstration of the Horeau principle, which describes the amplification of enantiomer ratio through successive enantioselective reactions.[7] The stereochemical outcome at each step of the organocatalysed double Diels-Alder reaction between [4]dendralene (**257**) and acrolein with MacMillan's catalyst **254** is shown in Scheme 3.6. The catalyst **254** controls the enantioselectivity of both Diels-Alder reactions. The first cycloaddition generates the major enantiomer **(*R*)-260** and the minor enantiomer **(*S*)-260** in a 95:5 ratio. In the second cycloaddition, a small proportion of the major enantiomer **(*R*)-260** and a large proportion of the minor enantiomer **(*S*)-260** are converted to the *meso* diastereomer **(*R*,*S*)-262**, thus only a very small proportion of the minor enantiomer **(*S*,*S*)-262** of the chiral diastereomer is formed and the enantiomer ratio (i.e. the ratio of **(*R*,*R*)-262** to **(*S*,*S*)-262**) of the chiral diastereomer is enhanced to >99.5:0.5.



Scheme 3.6 Stereochemical outcome of the organocatalysed double Diels-Alder reaction between [4]dendralene (**257**) and acrolein with MacMillan's catalyst **254**

As described in Chapter 1 (Scheme 1.37, page 37), Jørgensen and co-workers have reported the enantioselective Diels-Alder reactions of semi-cyclic 1-amino[3]dendralenes **199**, which selectively react at the cyclic 1,3-butadiene unit distant

to the amine substituent to provide cycloadducts **202** (Scheme 3.7).[8] Products **203** are isolated following a subsequent Wittig reaction.



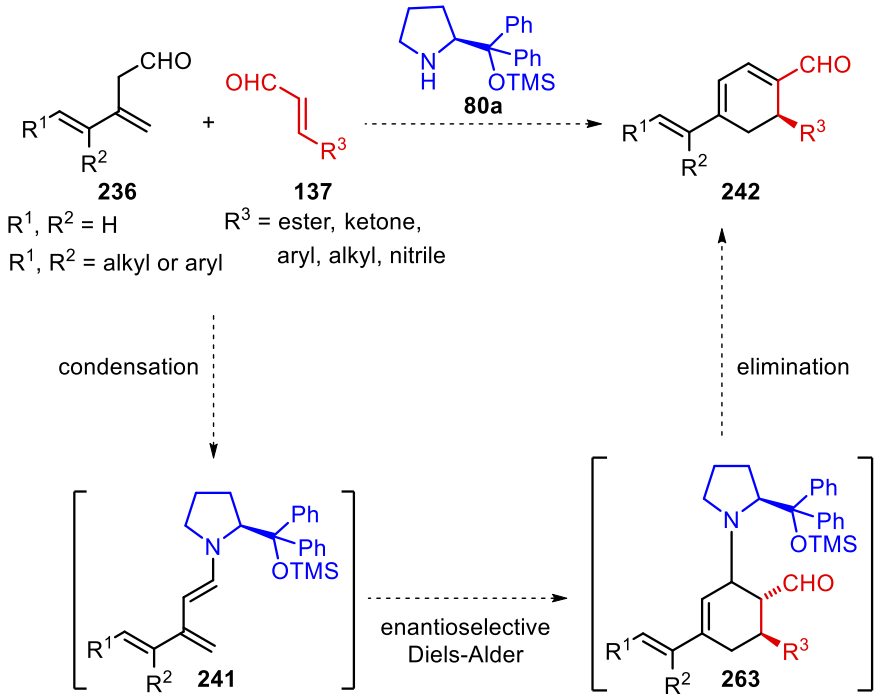
Scheme 3.7 Condensation/Diels-Alder/hydrolysis reaction sequence between dienals **198**, amine **80a** and dienophiles **200** followed by Wittig reaction to generate spirocycles **203**

In summary, dendralenes have been reported to undergo Lewis-acid catalysed[2] and iminium catalysed[5] enantioselective Diels-Alder reactions. While enantioselective Diels-Alder reactions of *in situ* generated 1-amino-1,3-butadienes have been extensively reported (Chapter 1, section 1.4), the only report of dendralenes involves single semi-cyclic 1-amino[3]dendralenes.[8] This work will extend the use of enamine catalysis to acyclic 1-amino[3]dendralenes as well as extend it to domino reaction sequences.

3.2 Aims

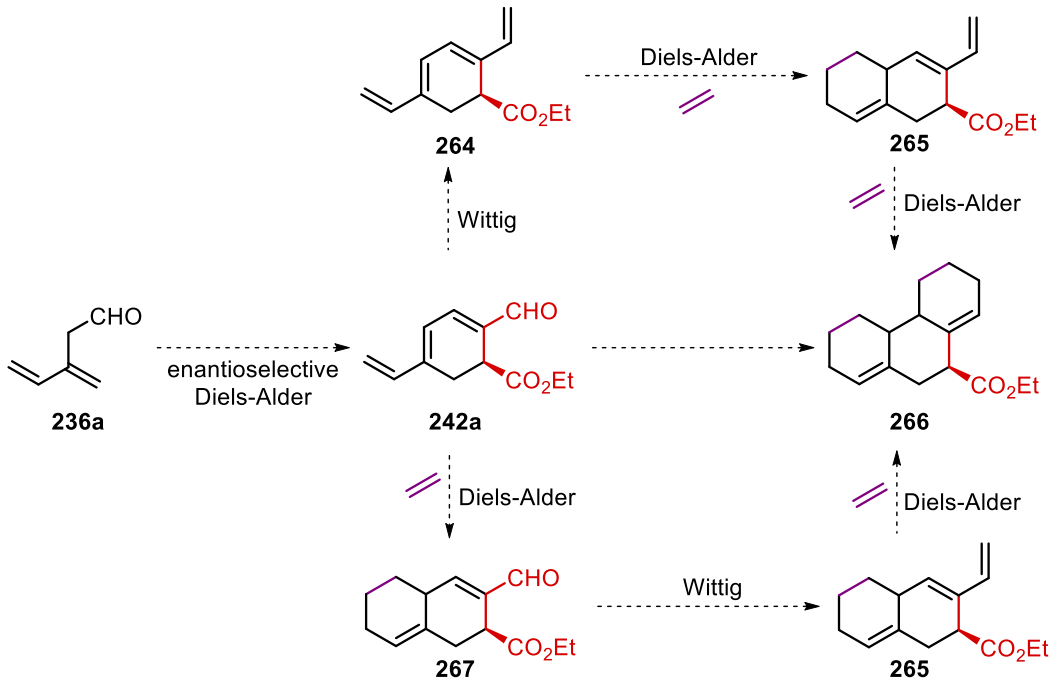
The first objective of this work is to develop and optimise the enantioselective Diels-Alder reaction between skipped dienal **236**, amine **80a** and β-substituted acroleins **137**

(Scheme 3.8). The condensation between skipped dienal **236** and amine **80a** is proposed to generate 1-amino[3]dendralene **241**, which would react with β-substituted acroleins **137** as the dienophile, leading to the formation of cycloadducts **263**. Skipped dienals bearing aryl and alkyl substituents will also be used to investigate the generality of the reaction.



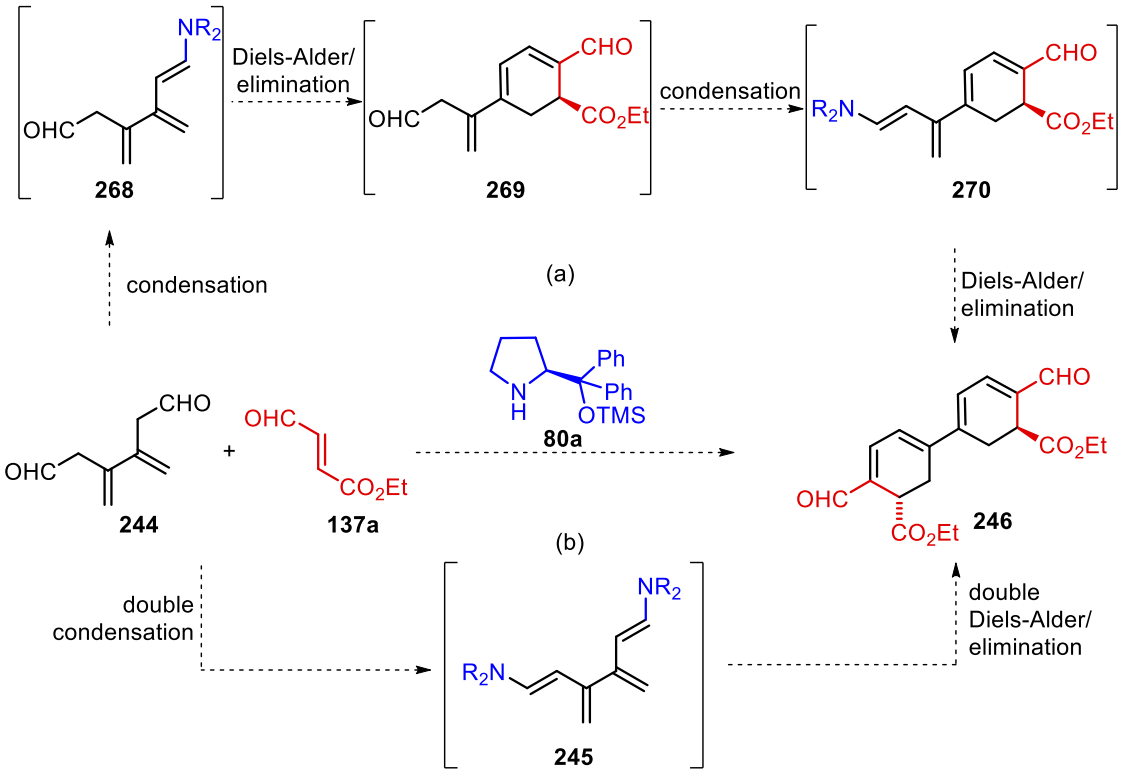
Scheme 3.8 Condensation/enantioselective Diels-Alder/elimination reaction sequences between skipped dienals **236**, dienophiles **137** and amine **80a**

The second objective is extension of this methodology to multiple Diels-Alder reactions to access polycyclic enantioenriched products such as tricycle **266** (Scheme 3.9).



Scheme 3.9 Accessing polycyclic enantioenriched products from mono-adduct **242a**

The final objective is to explore the condensation/Diels-Alder/elimination reaction sequence of diene dialdehyde **244** (Scheme 3.10). This reaction sequence may proceed through two consecutive condensation/Diels-Alder/elimination sequences (pathway (a)) or twofold condensation to form 1,6-diamino[4]dendralene **245** then successive Diels-Alder/elimination sequences (pathway (b)). It is expected that the Horeau principle (Scheme 3.6) would operate in this reaction to furnish cycloadduct **246** with high enantioselectivity.



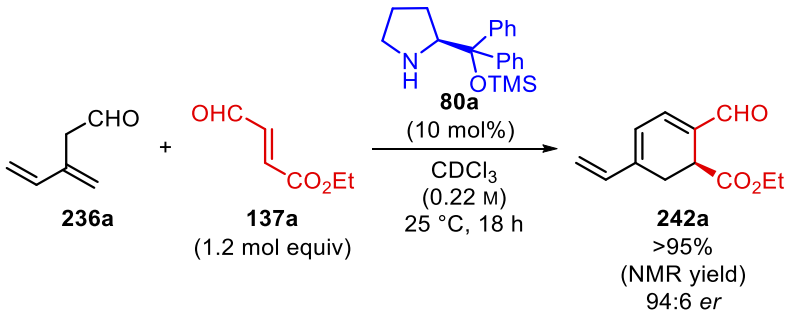
Scheme 3.10 Twofold enantioselective condensation/Diels-Alder/elimination reaction sequences between diene dialdehyde **244**, dienophile **137a** and amine **80a**

3.3 Results and Discussion

3.3.1 Condensation/Diels-Alder/elimination reaction sequence

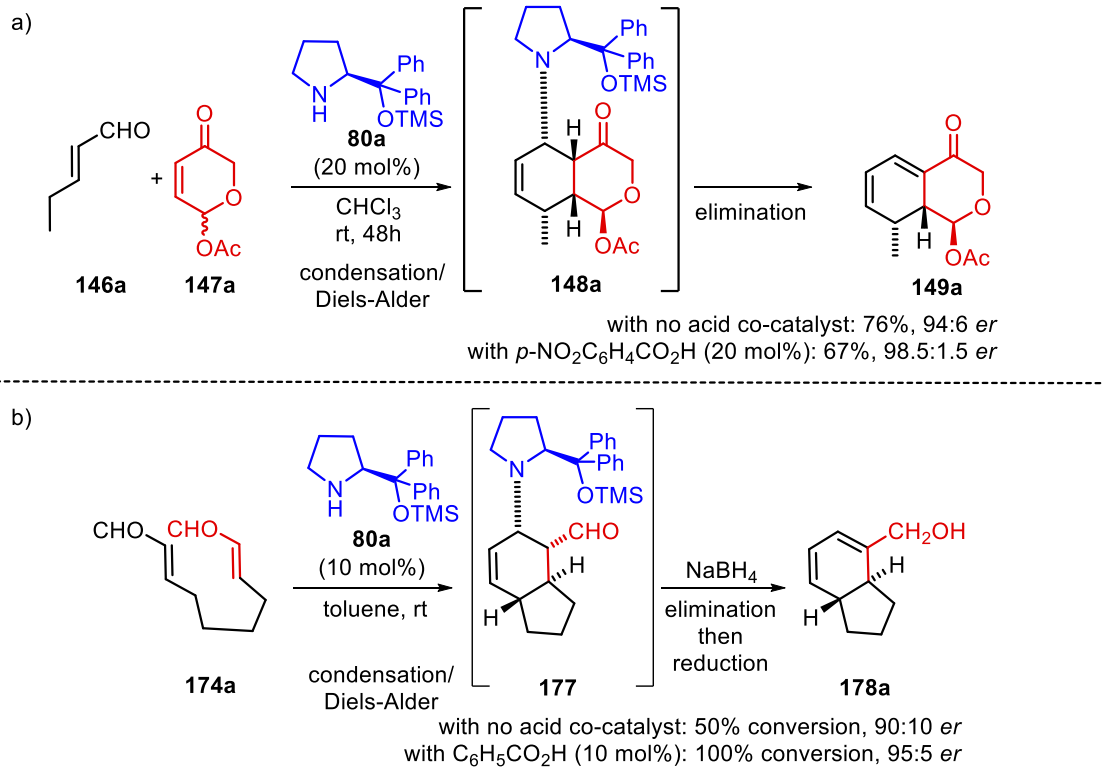
3.3.1.1 Optimisation of the reaction

The Diels-Alder reaction between skipped dienal **236a** as the diene precursor and 1.2 molar equivalents of dienophile **137a** with 10 mol% of amine **80a** as the catalyst was performed in deuterated chloroform (0.22 M) and monitored by ^{1}H NMR spectroscopy (Scheme 3.11). The target aldehyde product **242a** was formed cleanly after 18 h in >95% yield, as determined by NMR spectroscopy. To develop a method for the separation of the enantiomers of **242a** using high performance liquid chromatography (HPLC), a racemic sample was prepared with the same synthetic sequence using 20 mol% of pyrrolidine instead of 10 mol% of amine **80a**. Separation of this racemic sample was achieved by eluting with 60:40 *n*-hexane/isopropanol on a Chiralcel OJ-H column at a flow rate of 1 mL/min. The enantioenriched sample was separated with HPLC using the same conditions and the enantiomer ratio was determined to be 94:6.



Scheme 3.11 Condensation/Diels-Alder/elimination reaction between skipped denal **236a**, dienophile **137a** and amine **80a**

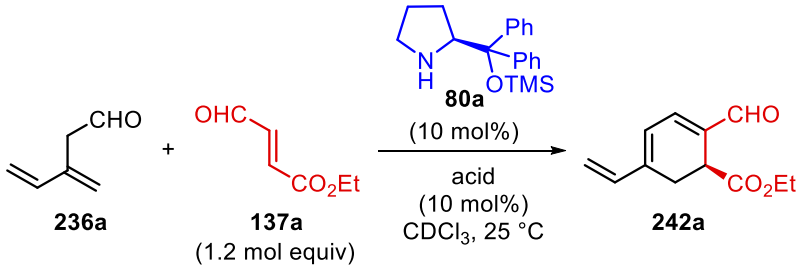
Although the enantiomer ratio was already high, we sought to increase it further by adding an acid co-catalyst. There have been reports[9,10] that the addition of an acid co-catalyst improves the enantioselectivity of condensation/Diels-Alder/elimination sequences. The enantioselectivity of the condensation/Diels-Alder/elimination reaction between α,β-unsaturated aldehyde **146a**, pyranone dienophile **147a** and amine **80a** increased from 94:6 *er* to 98.5:1.5 *er* with the addition of *p*-nitrobenzoic acid (Scheme 3.12a).[9] Similarly, the formation of bicyclic cycloadduct **178a** improved from 90:10 *er* to 95:5 *er* with the addition of benzoic acid (Scheme 3.12b).[10] An increase in the level of conversion from 50% to 100% was also observed. Based on computational studies of the intramolecular reaction shown in Scheme 3.12b, it has been proposed that benzoic acid lowers the activation energy for the formation of the 1-amino-1,3-butadiene intermediate from α,β-unsaturated aldehyde **146a** and amine **80a**, thus increasing the rate of reaction and the level of conversion of the overall reaction.[11] It was also mentioned that the energy difference between the transition states leading to the two enantiomers formed is similar with and without benzoic acid,[11] so the exact role of the acid in slightly enhancing the enantiomer ratio remains unclear. It is possible that the acid inhibits unwanted base-mediated processes, which produce a racemic mixture of the desired product and lower the enantiomer ratio.



Scheme 3.12 Literature examples of improved enantioselectivity when acid co-catalysts are used in a) intermolecular Diels-Alder[9] and b) intramolecular Diels-Alder reactions[10]

Four carboxylic acids were screened in attempts to enhance the enantioselectivity of our reaction (Table 3.1). These acids were chosen as they are most commonly used in the literature for related processes. Disappointingly, the addition of an acid additive did not have any significant effect on the reaction outcome: the addition of 10 mol% of benzoic acid, *p*-chlorobenzoic acid, acetic acid or *p*-nitrobenzoic acid did not improve the enantioselectivity of the reaction.

Table 3.1 Variation in acid co-catalyst



Entry	Acid co-catalyst	NMR yield (%)[a]	*er*[b]
1	none	>95	94:6
2	$C_6H_5CO_2H$	>95	93:7
3	*p*-$ClC_6H_4CO_2H$	95	94:6
4	CH_3CO_2H	>95	94:6
5	*p*-$NO_2C_6H_4CO_2H$	93	94:6

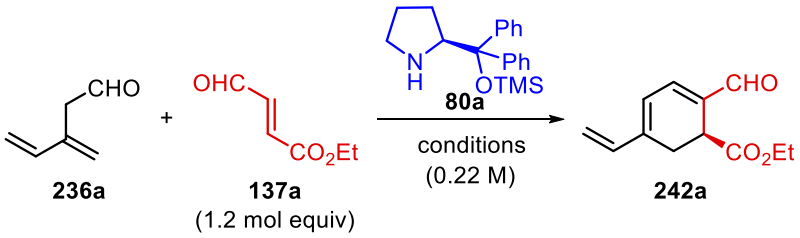
[a] 1,4-dinitrobenzene was used as the internal standard

[b] measured by HPLC on chiral stationary phases

The effect of catalyst loading and solvent on the reaction was examined next (Table 3.2). Under the initial reaction conditions, the desired product **242a** was obtained in >95% yield in 18 hours at 0.22 M concentration of skipped dienal **236a** with 10 mol% of amine **80a** as the catalyst and deuterated chloroform as the solvent (entry 1). As amine **80a** is expensive, the possibility of lowering the catalyst loading was investigated. Reducing the catalyst loading to 2 mol% did not afford the desired product **242a** being formed (entry 2). The rate of reaction is too slow at this catalyst loading. With 5 mol% of catalyst **80a**, only 19% of the cycloadduct **242a** was formed after 17 hours (entry 3). The amount of cycloadduct **242a** did not change after a further 32 hours (total reaction time of 49 hours). In both cases, over the course of the reaction, skipped dienal **236a** was consumed and other unidentified aldehyde side products were formed, presumably from self-condensation of aldehyde **236a**. The screening of various solvents for the reaction revealed chloroform as the optimal choice. Lower yields were observed when reactions were repeated in toluene, benzene and acetonitrile (entries 4-6). It is possible that hydrogen-bonding between chloroform and the carbonyl oxygen[12] of dienophile **2a** increases the reactivity of the dienophile and enhances the rate of the Diels-Alder reaction over unwanted side-reactions which consume the starting material.

With methanol, no product was formed possibly because the solvent reacted with the aldehyde functionalities of skipped dienal **236a** and dienophile **137a** to form hemi-acetals (entry 7). In DMSO, a complex mixture formed over time (entry 8). This could be due to the acceleration of other unwanted side-reactions in a highly polar solvent such as DMSO. In acetone, no product was observed possibly because acetone itself undergoes amine catalysed aldol reactions[13] (entry 9).

Table 3.2. Optimisation of the Diels-Alder reaction between aldehyde **236a** and dienophile **137a**



236a **137a** (1.2 mol equiv) **242a**

Entry	Catalyst loading (mol%)	Solvent	Temp (°C)	time	NMR yield (%)[e]	*er*[b]
1	10	$CDCl_3$	25	18 h	>95	94:6
2[a]	2	$CDCl_3$	25	48 h	0	-
3[a]	5	$CDCl_3$	25	49 h	19	90:10
4	10	toluene-d_8	25	48 h	64	92:8
5	10	benzene-d_6	25	45 h	61	93:7
6	10	acetonitrile-d_3	25	48 h	56	81:19
7	10	methanol-d_4	25	48 h	0[c]	-
8	10	DMSO-d_6	25	48 h	0[d]	-
9	10	acetone-d_6	25	48 h	0[c]	-

[a] concentration of skipped dienal: 0.26 M

[b] measured by HPLC on chiral stationary phases

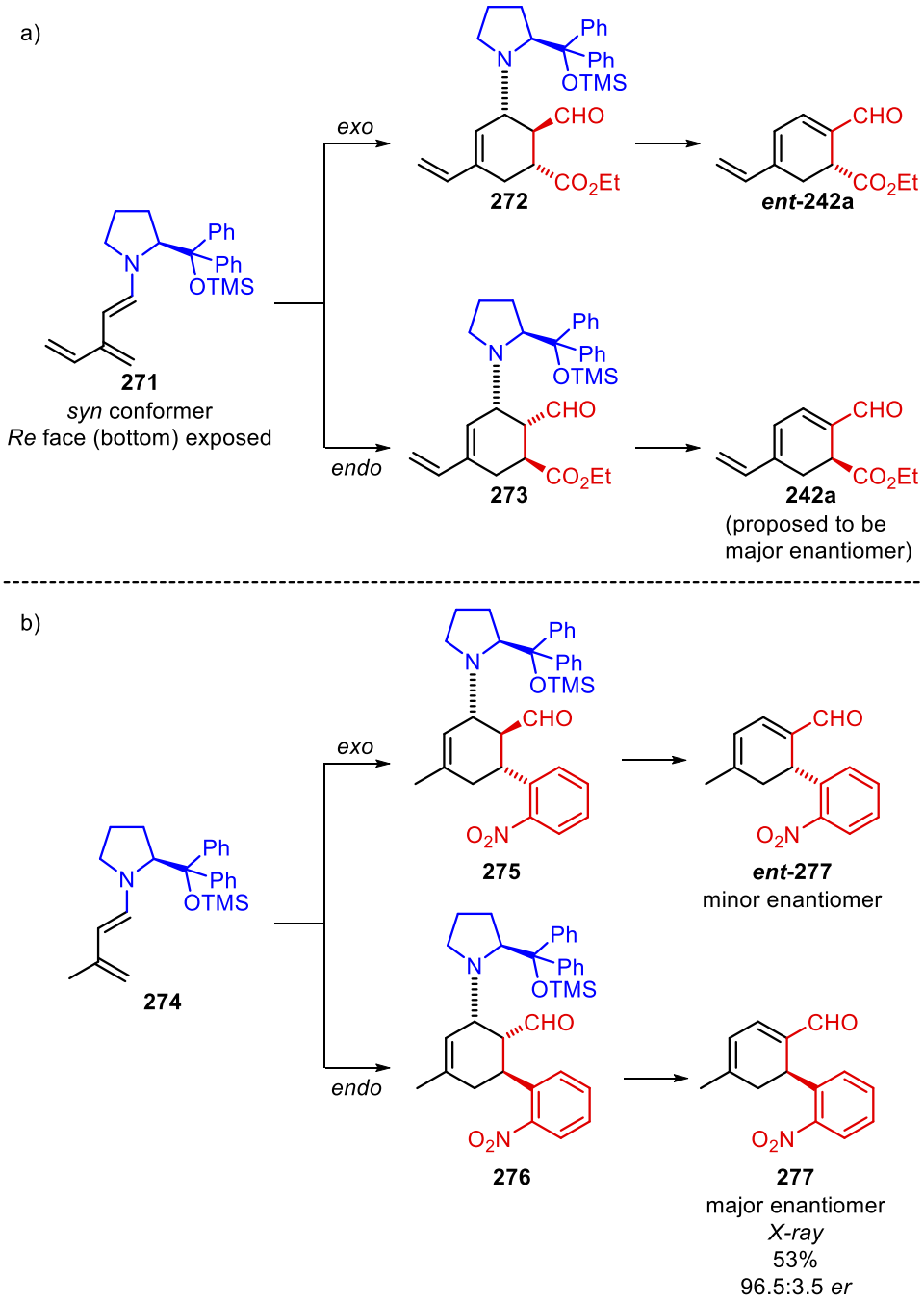
[c] no reaction

[d] complex mixture

[e] 1,4-dinitrobenzene was used as the internal standard

3.3.1.2 Absolute configuration assignment

The absolute configuration of the stereocentre in the major cycloadduct **242a** is tentatively assigned based on computational modelling and the reported absolute configuration of a literature compound (Scheme 3.13). Computational modelling described in Chapter 2 suggested that the *syn* conformer of 1-amino[3]dendralene **271** is the most stable intermediate, with the exposed bottom face of the diene undergoing a Diels-Alder reaction (Figure 2, page 55). Two diastereomers could be formed: cycloadduct **272** which arises from *exo* addition and cycloadduct **273** which arises from *endo* addition of the dienophile. Trienals *ent*-**242a** and **242** would be generated from the elimination of cycloadducts **272** and **273** respectively. Hong and co-workers have reported the absolute configuration of cyclohexadiene **277**, the condensation/Diels-Alder/elimination product of 1-amino-1,3-butadiene **274** and *o*-nitrocinnamaldehyde **137g**.[14] This was determined by single crystal X-ray analysis and arises from *endo* addition of the dienophile to the diene from the less sterically hindered diene face. If 1-amino[3]dendralene **271** reacts in the same way as 1-amino-1,3-butadiene **274**, the favoured enantiomer is expected to be trienal **242a**, which is a product of *endo* addition of dienophile **137a** to 1-amino[3]dendralene **271** from the bottom face.

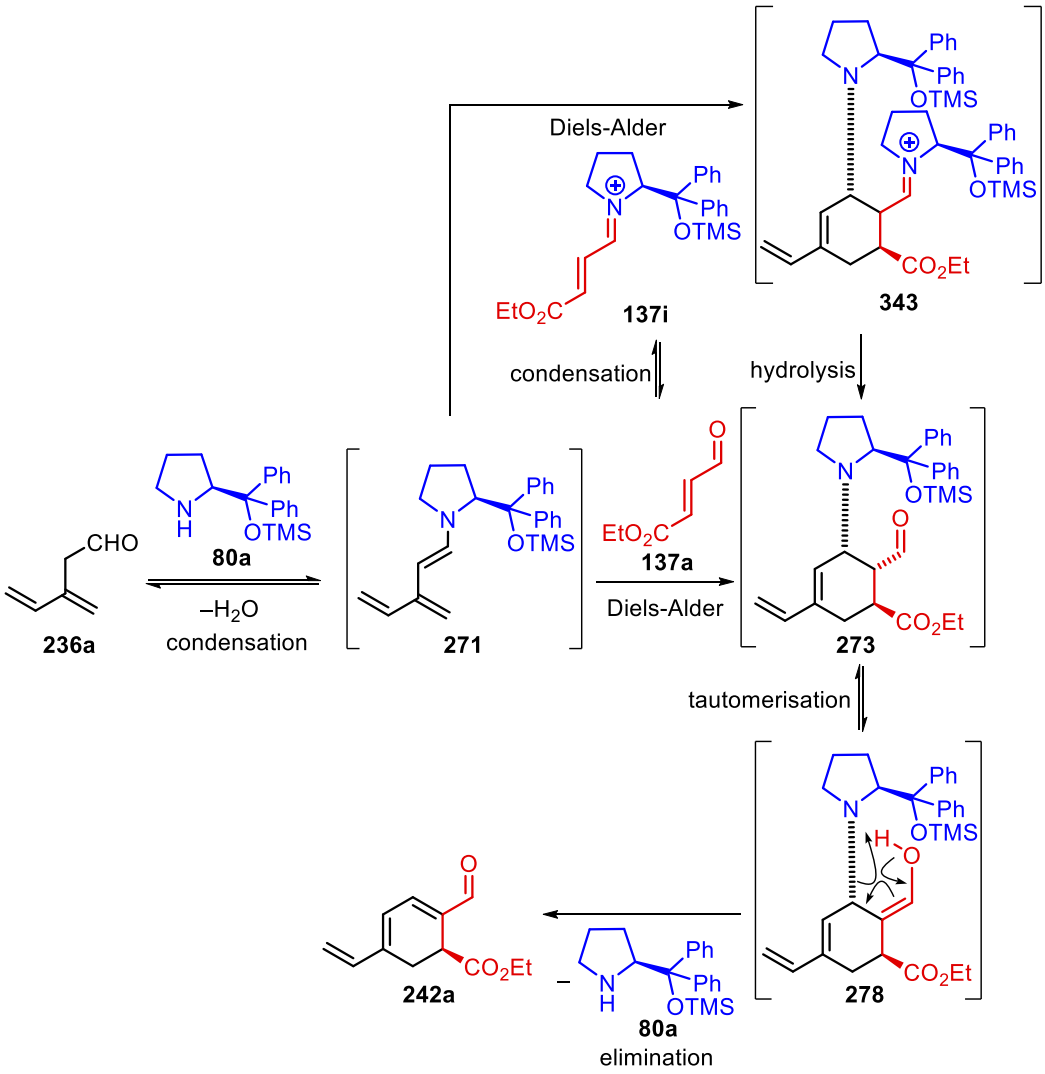


Scheme 3.13 a) Tentative assignment of the absolute configuration of cycloadduct **242a** b) Reported absolute configuration of cycloadduct **277**[14]

3.3.1.3 Proposed reaction mechanism

The proposed mechanism for the reaction is shown in Scheme 3.14. Condensation between skipped dienal **236a** and amine **137a** and subsequent tautomerisation generates 1-amino[3]dendralene **271**, which undergoes a Diels-Alder reaction with dienophile **137a** to form cycloadduct **273**. It is also possible that iminium dienophile **137i**, the product of a condensation/tautomerisation reaction between dienophile **137a** and amine

80a, reacts with 1-amino[3]dendralene **271** in a Diels-Alder reaction to generate cycloadduct **343** and upon hydrolysis, cycloadduct **273**. Tautomerisation of the aldehyde generates enol **278**, which can potentially eliminate the amine to generate the trienal product **242a**. While it is possible for the 1,3-butadiene unit present in dienal **236a** to undergo a Diels-Alder reaction with dienophile **137a** , this was never observed as the condensation reaction to form 1-amino[3]dendralene is very fast and the amine-substituted 1,3-butadiene unit is a much more reactive diene in the Diels-Alder reaction.



Scheme 3.14 Proposed reaction mechanism for the formation of cycloadduct **242a**

3.3.1.4 Synthesis of dienophiles

The scope of this catalytic enantioselective reaction was extended to different dienophiles (Figure 3.1). Dienophiles **137b** and **137c** were chosen to examine whether the size of the ester substituent has an effect on yield or enantioselectivity. To

investigate whether the reaction tolerates other types of electron-withdrawing substituents at the β position of the acrolein dienophile, the ester substituent was replaced with ketones (dienophiles **137d** and **137e**), nitrile (dienophile **137f**) and an *o*-nitrophenyl group (dienophile **137g**). To investigate whether the reaction tolerates dienophiles which do not possess an aldehyde functionality, β-nitrostyrene **137h** was included.

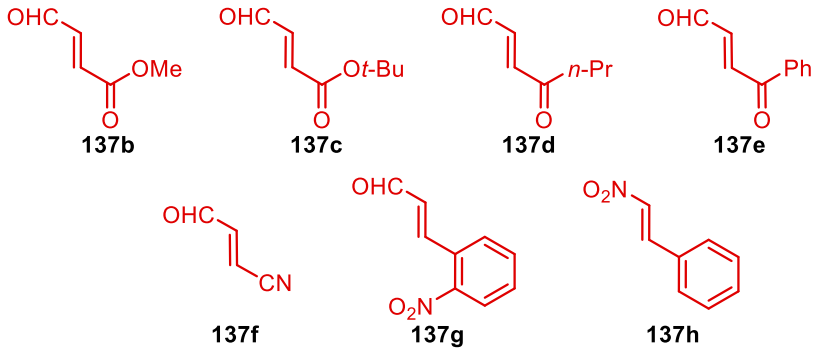
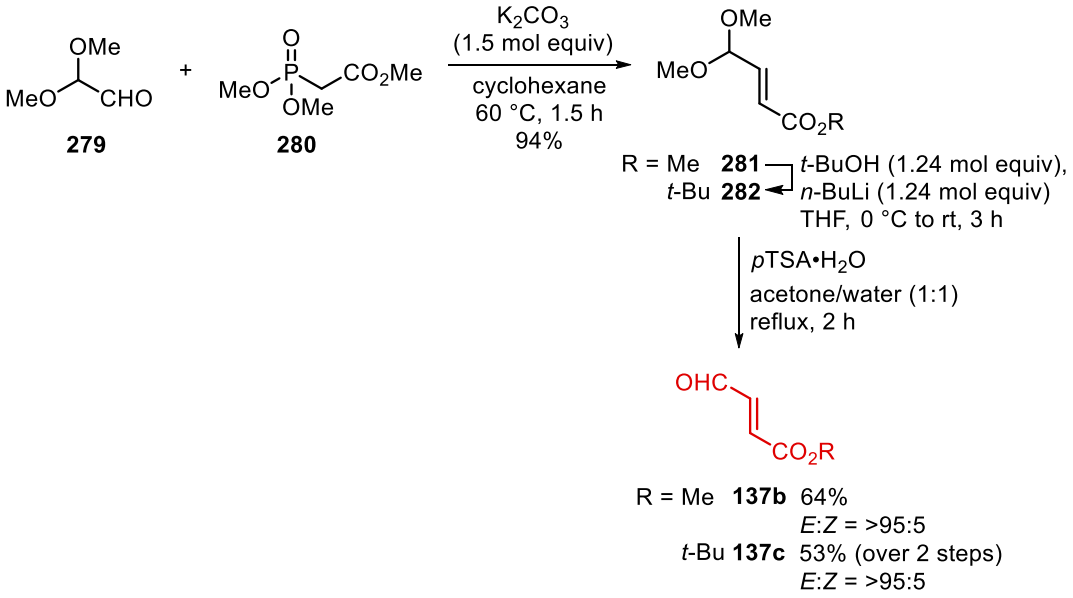


Figure 3.1 Dienophiles to be used in the Diels-Alder reaction

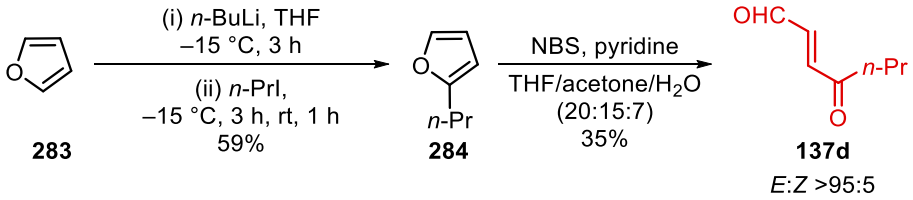
As dienophiles **137b-f** are not commercially available and dienophile **137g** was not available to us, they were synthesised according to literature procedures or modified literature procedures.

Methyl ester dienophile **137b** was synthesised following a known literature procedure.[15] Horner-Wadsworth-Emmons reaction between 2,2-dimethoxyacetaldehyde (**279**) and trimethyl phosphonoacetate **280** followed by hydrolysis of the resulting acetal **281** under acidic conditions provided methyl ester dienophile **137b** (Scheme 3.15). The *t*-butyl ester derivative **137c** was obtained by transesterification of ester **281** with lithium *t*-butoxide[16] followed by deprotection of the dimethyl acetal group. Both dienophiles **137b** and **137c** were obtained with an *E*:Z ratio >95:5 as determined by ^{1}H NMR spectroscopy.



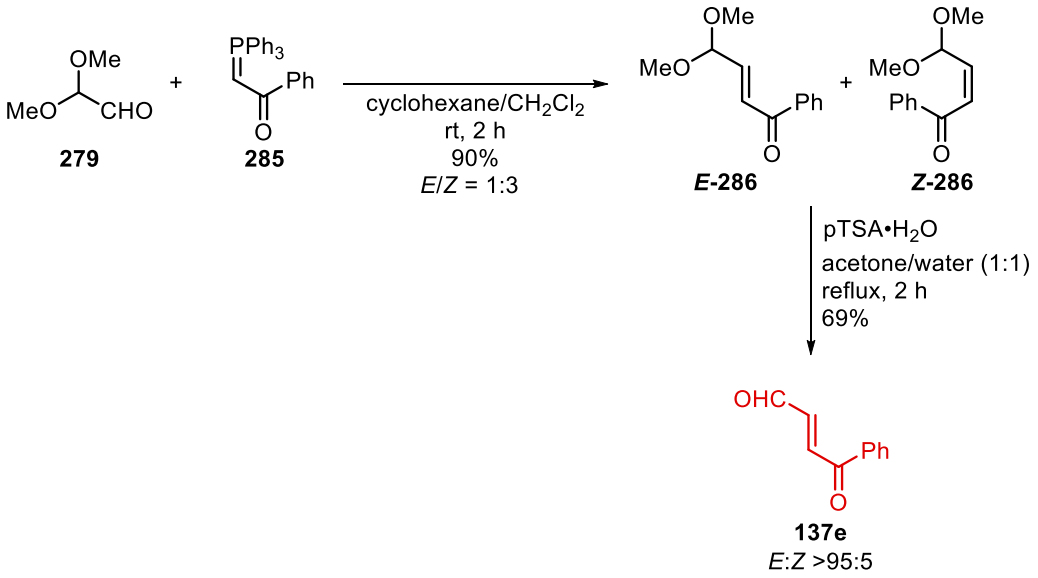
Scheme 3.15 Synthesis of dienophiles **137b** and **137c**

Dienophile **137d** was synthesised following a known literature procedure in a two-step process (Scheme 3.16).[17] Furan (**283**) was lithiated with *n*-butyllithium and subsequently alkylated with 1-iodopropane to provide substituted 2-*n*-propylfuran (**284**), which was converted to dienophile **137d** by an oxidative ring opening with *n*-bromosuccinimide in water. This dienophile, as well, was obtained with an *E*:*Z* ratio of >95:5 as determined by ^{1}H NMR spectroscopy.



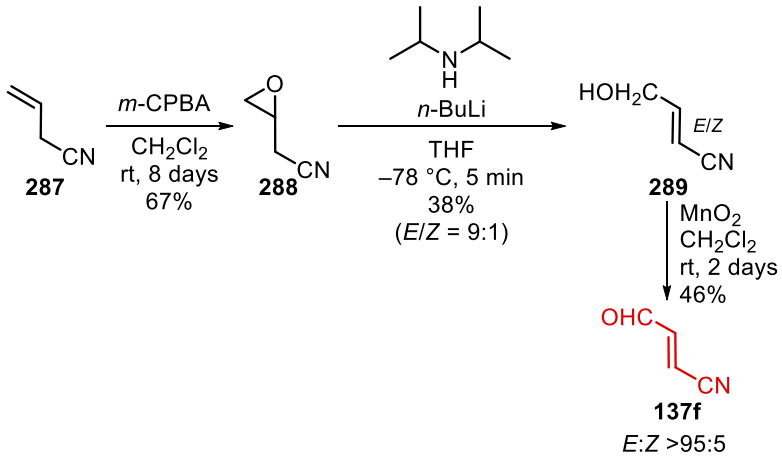
Scheme 3.16 Synthesis of dienophile **2d**

Dienophile **137e** was synthesised using a modified literature procedure involving a Wittig reaction between 2,2-dimethoxyacetaldehyde (**279**) and phosphorane **285** to produce a mixture of ketones ***E*-286** and ***Z*-286** (*E*:*Z* = 1:3) followed by deprotection of the dimethoxyacetal protecting group under acidic conditions (Scheme 3.17).[15] Acetal deprotection proceeds with alkene *Z* to *E* isomerisation. After chromatography, dienophile **137e** was obtained with an *E*:*Z* ratio of >95:5 as determined by ^{1}H NMR spectroscopy.



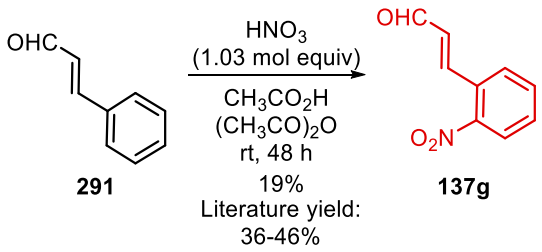
Scheme 3.17 Synthesis of dienophile **137e**

Dienophile **137f** was made in three steps from allyl nitrile (**287**) (Scheme 3.18). Alcohol **289** was prepared according to a literature procedure.[18] Epoxidation of allyl cyanide (**287**) with *m*-CPBA provided epoxynitrile (**288**), which underwent E1cb type epoxide ring-opening with lithium diisopropylamide (generated *in situ*) to furnish stereoisomeric alcohols **289** in a yield of 38% with an *E*/*Z* ratio of 9:1. The low yield is attributed to the propensity of alcohols **289** to polymerise under the reaction conditions – a thick precipitate was formed as soon as the reaction was quenched with acetic acid. Allylic alcohols **289** were oxidised to aldehyde **137f** with manganese dioxide. After chromatography, the product **137f** was isolated in 46% yield and an *E*:*Z* ratio of >95:5 as determined by ^{1}H NMR spectroscopy.



Scheme 3.18 Synthesis of dienophile **137f**

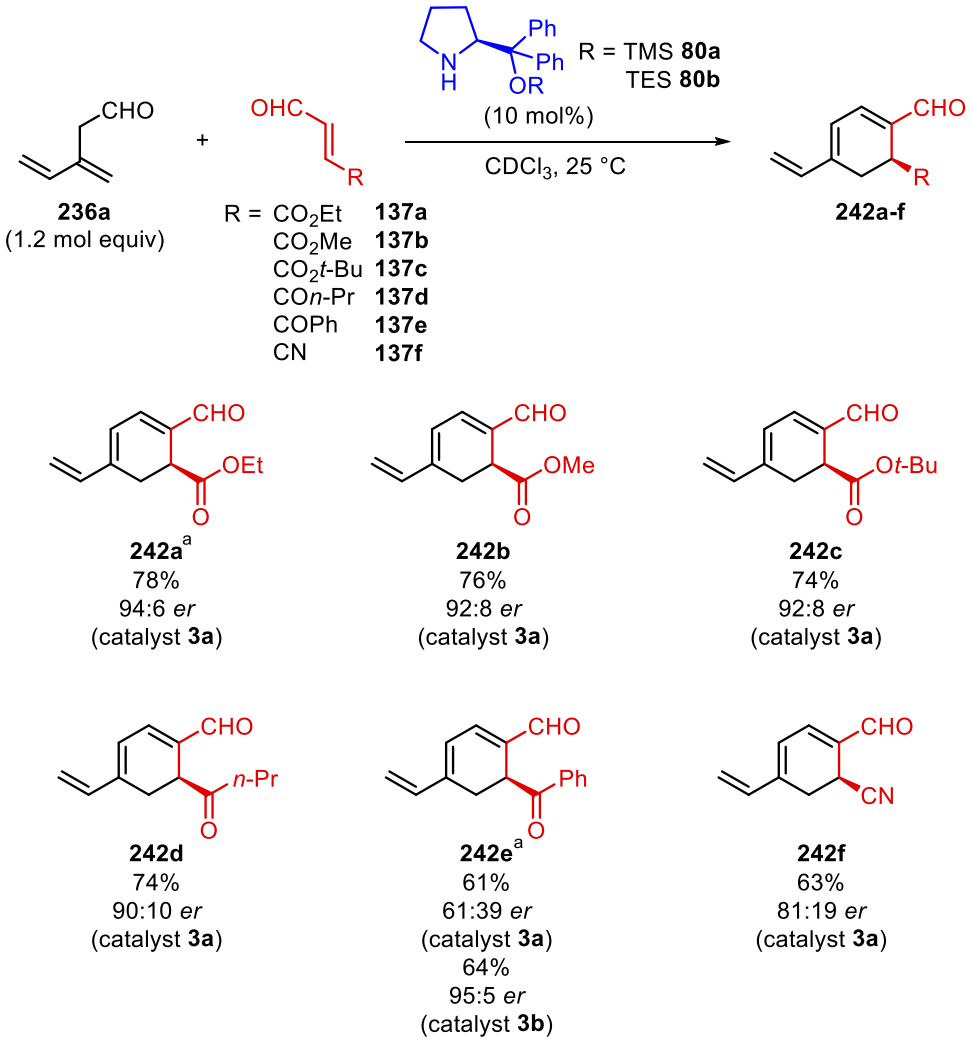
Dienophile **137g** was prepared *via ortho*-nitration of *E*-cinnamaldehyde (**291**) with nitric acid following a literature procedure[19] (Scheme 3.19).



Scheme 3.19 Synthesis of dienophile **137g**

3.3.1.5 Scope of the Diels-Alder reaction with respect to the dienophile

The condensation/Diels-Alder/elimination reaction sequence was carried out under optimised conditions between skipped dienal **236a** and dienophiles **137a-f** in the presence of amine **80a** (Scheme 3.20). Dienophiles bearing β ethyl, methyl and *t*-butyl ester substituents generated cycloadducts **242a**, **242b** and **242c** with comparable yields (74-78%) and enantioselectivities (92:8 to 94:6 *er*). The sterics of the ester substituent had no adverse impact on the enantioselectivity or reactivity. By replacing the β ester substituent with an *n*-propyl ketone, cycloadduct **242d** was generated in 74% yield and a slightly diminished *er* of 90:10. With the β phenyl ketone substituted dienophile **137e**, the Diels-Alder cycloadduct **242e** was formed in 61% yield and 61:39 *er*. Dienophile **137f**, which has a β nitrile substituent, provided Diels-Alder adduct **242f** in 63% yield and 81:19 *er*. It has been reported that the use of prolinol catalysts with bulkier silyl protecting groups result in higher enantioselectivities.[20] Repeating the reaction with dienophile **137e** using catalyst **80b**, which bears a bulkier TES protecting group than the TMS group of catalyst **80a**, afforded the Diels-Alder cycloadduct **242e** in 64% yield and a much improved enantioselectivity of 95:5 *er*. Catalyst **80b** may provide better results with the other dienophiles as well.



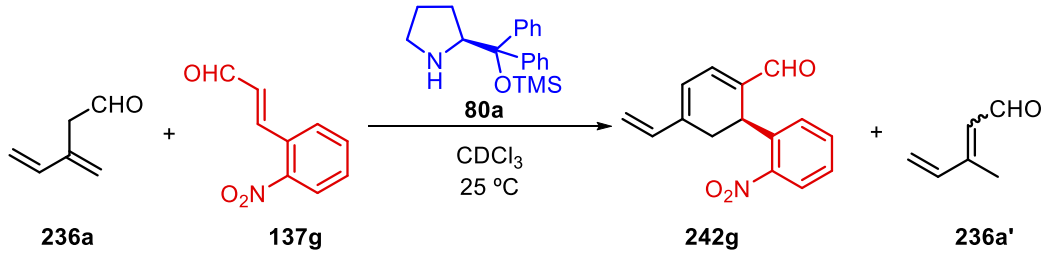
[a] skipped dienal **236a** (1.0 mol equiv) and dienophile **137** (1.2 mol equiv) used

Scheme 3.20 Diels-Alder reaction between skipped dienal **236a** and dienophiles **242a-f**

The condensation/Diels-Alder/elimination reaction sequence between skipped dienal **236a** and *o*-nitrocinnamaldehyde **137g** catalysed by amine **80a** was performed under various reaction conditions (

Table **3.3**). Under the previously optimised conditions, a poor yield (8%, determined by NMR spectroscopy) of cycloadduct **242g** was obtained. A ^{1}H NMR spectrum of the reaction mixture showed that after 19 h, skipped dienal **236a** was completely consumed, about half of the original amount of skipped dienal **236a** had been isomerised to the conjugated dienal **236a'** while only 8% of the desired product **242g** was formed. No further increase in the formation of the desired product **242g** was observed. To increase the rate of reaction, we tried doubling the amount of dienophile **242g** (entry 2), skipped dienal **236a** (entry 3) and amount of amine **80a** (entry 4). An increase in the yield of the desired product **242g** to 15% (determined by NMR spectroscopy) was observed when the amount of amine **80a** was increased. In an attempt to reduce the rate of formation of any unwanted by-products, the reaction temperature was reduced to 0 ºC, but this did not have a significant effect on the yield of cycloadduct **242g**. By doubling the reaction concentration, the yield of the desired product **242g** increased to 24%. It appears that this set of conditions improves the rate of the Diels-Alder reaction over the rate of the unwanted side-reactions. In a separate experiment, by using benzoic acid as a co-catalyst, the yield of the desired product **242g** was 24% (determined by NMR spectroscopy). It has been speculated that an acid co-catalyst may activate the dienophile towards Diels-Alder reactions.[10] Although the enantioselectivity is high (95:5 *er*), the yield of the reaction requires further optimisation.

Table 3.3 Condensation/Diels-Alder/elimination reaction sequence between skipped dienal **236a** and *o*-nitrocinnamaldehyde **137g** under various conditions



236a **137g** **242g** **236a'**

Entry	Dienal **236a** (mol equiv)	Dienophile **137g** (mol equiv)	Amine (mol %)	Dienal conc (M)	t (h)	Isomerised dienal **1a'** (%)	NMR yield (%)	*er*
1	1	1.2	10	0.2	19	52	8 [a]	-
2	1	2.4	10	0.2	19	48	11 [a]	-
3	2.2	1	10	0.2	18	57	3 [a]	-
4	1	1.2	20	0.2	19	0	15	-
5[b]	1	1.2	20	0.2	45	21	12	-
6	1	1.2	20	0.4[c]	18	0	24	-
7	1	1.2	20 [d]	0.2	18	0	24	95:5

[a] subsequent ^{1}H NMR spectra showed no further increase in the amount of product

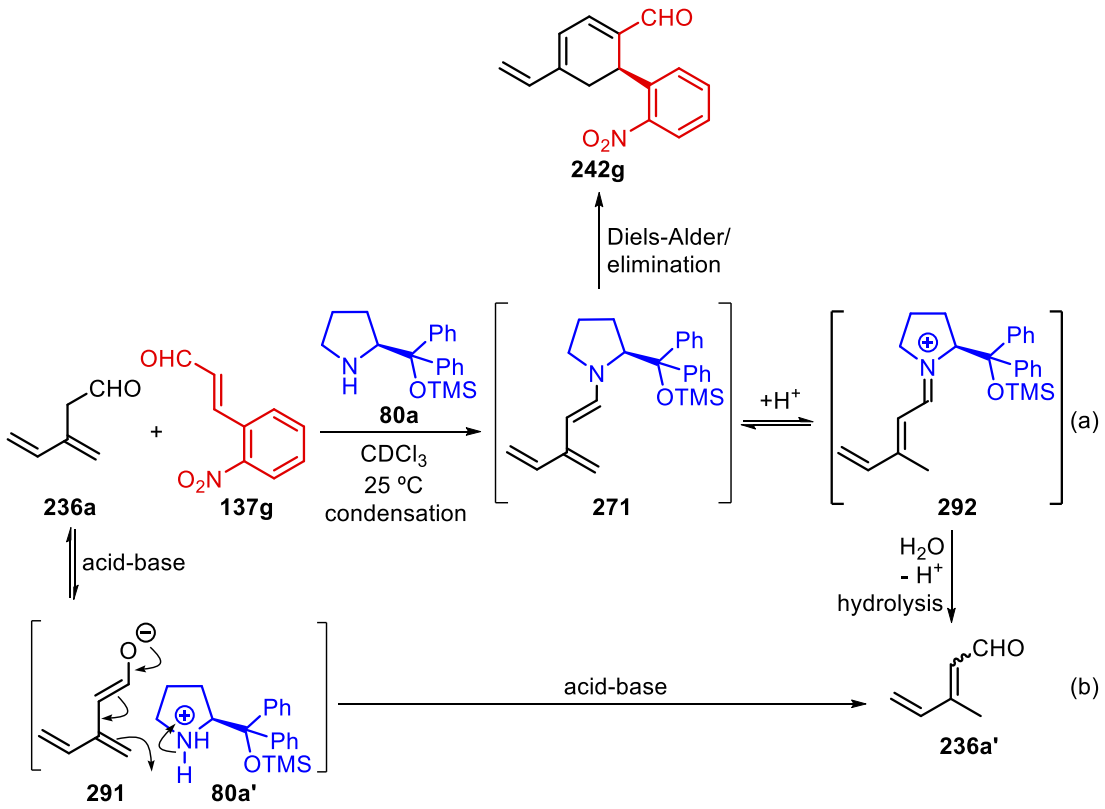
[b] reaction performed at 0 °C

[c] dienophile did not fully dissolve

[d] co-catalyst: $C_6H_5CO_2H$ (20 mol%)

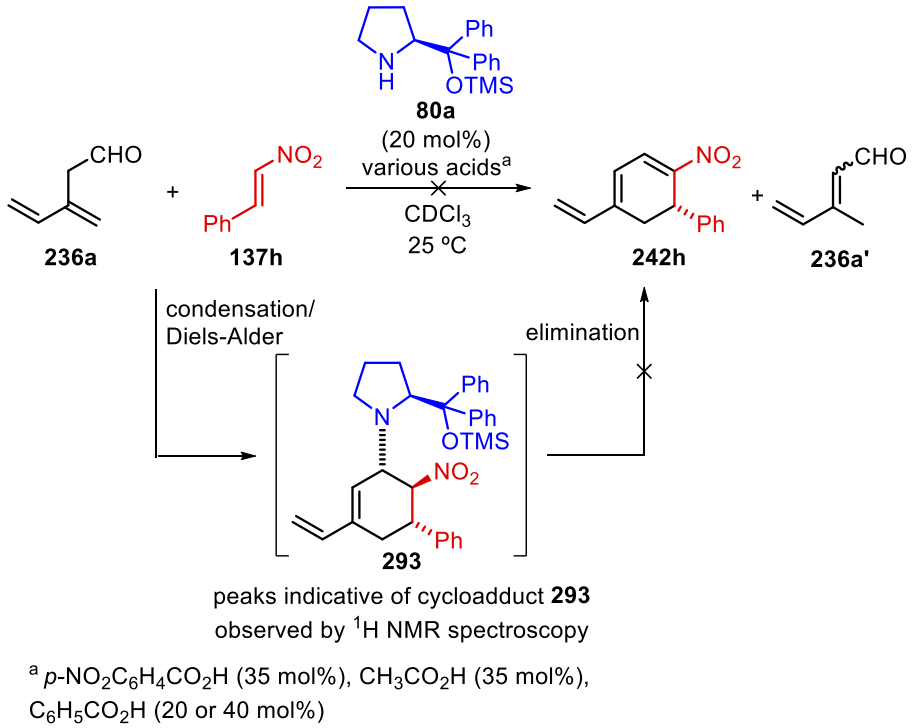
The proposed mechanism for the formation of the isomeric conjugated dienal **236a'** is shown in Scheme 3.21. Condensation between skipped dienal **236a** and amine **80a** generates 1-amino[3]dendralene **271** which undergoes protonation to form diene iminium **292** which is hydrolysed to the conjugated dienal **236a'** (Scheme 3.21a). Alternatively, amine **80a** reacts as a base to deprotonate skipped dienal **236a** to generate enolate **291**, which re-protonates to provide conjugated dienal **236a'** (Scheme 3.21b). 1-Morpholino-[3]dendralene was also observed to decompose to a complex mixture of products including conjugated dienal **236a'** upon standing in solution at room temperature (Chapter 2, page 53). As dienophile **137g** is less reactive than dienophiles

137a-f, the rate of Diels-Alder reaction between 1-amino[3]dendralene **271** and dienophile **137g** is slower and isomerisation to conjugated dienal **236a'** occurs instead.



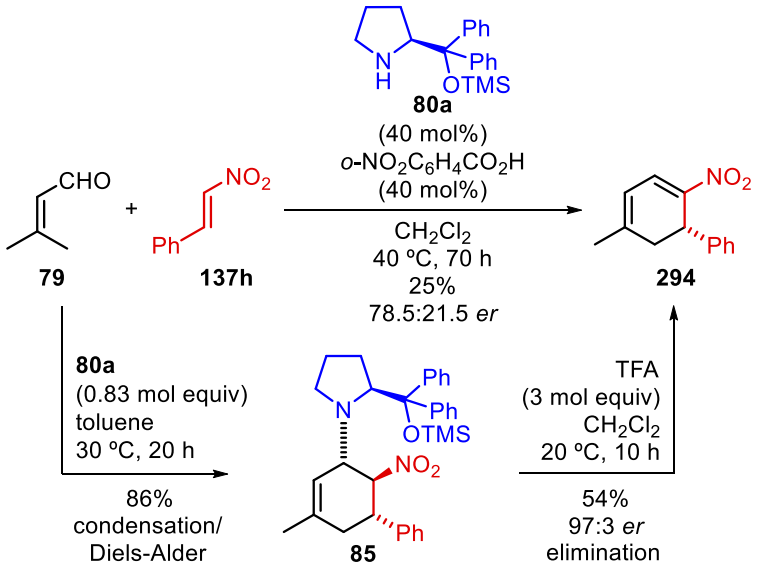
Scheme 3.21 Proposed mechanism for the formation of the isomeric conjugated dienal **236a'**

The reaction between aldehyde **236a**, β-nitrostyrene **137h**, amine **80a** and various carboxylic acids, such as benzoic acid, *p*-nitrobenzoic acid and acetic acid, did not furnish the desired cycloadduct **242h** (Scheme 3.22). ^{1}H NMR spectra of the reaction mixture showed peaks indicative of the condensation/Diels-Alder product **293** forming, however, elimination product **242h** was not observed.



Scheme 3.22 Attempted condensation/Diels-Alder/elimination reaction between skipped dienal **236a** and β-nitrostyrene **137h**

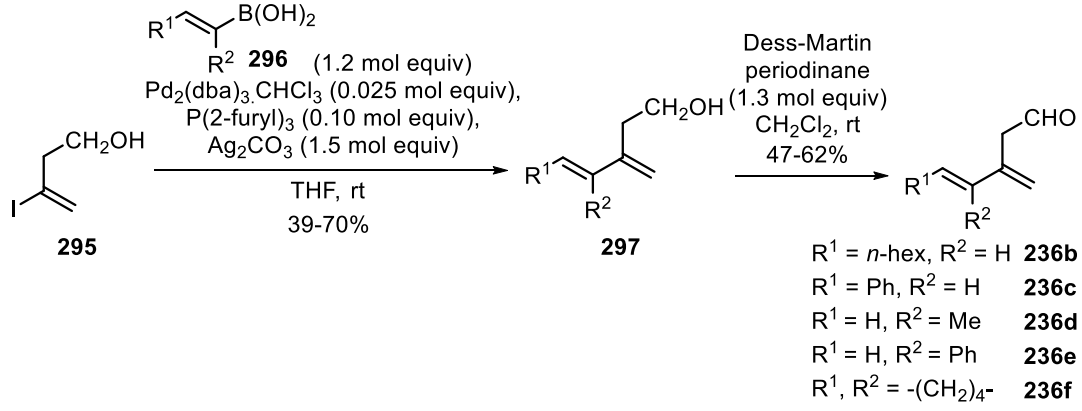
A similar reaction involving enal **79** has been reported (Scheme 3.23).[21] When the reaction was performed step-wise (i.e. the condensation/Diels-Alder reaction product cycloadduct **85** is isolated before subjecting it to elimination with trifluoroacetic acid), cyclohexadiene **294** was generated in moderate yield (46% over two steps) and an enantiomer ratio of 97:3. When the two steps were performed simultaneously, cyclohexadiene **294** was obtained with a low yield (25%) and diminished enantiomer ratio of 78.5:21.5. It is possible that the amine **3a** was desilylated[22] over the extended reaction time (70 h), resulting in the lower reaction enantioselectivity compared to the step-wise reaction. It would be useful to perform the reaction shown in Scheme 3.22 in a step-wise manner to identify which acids are capable of elimination of the amine from cycloadduct **293** before applying it to the one-pot reaction.



Scheme 3.23 Literature example of condensation/Diels-Alder/elimination reaction sequences between aldehyde **79**, β-nitrostyrene **137h**, amine **80a** and trifluoroacetic acid or *p*-nitrobenzoic acid[21]

3.3.1.6 Scope of the Diels-Alder reaction with respect to the aldehyde

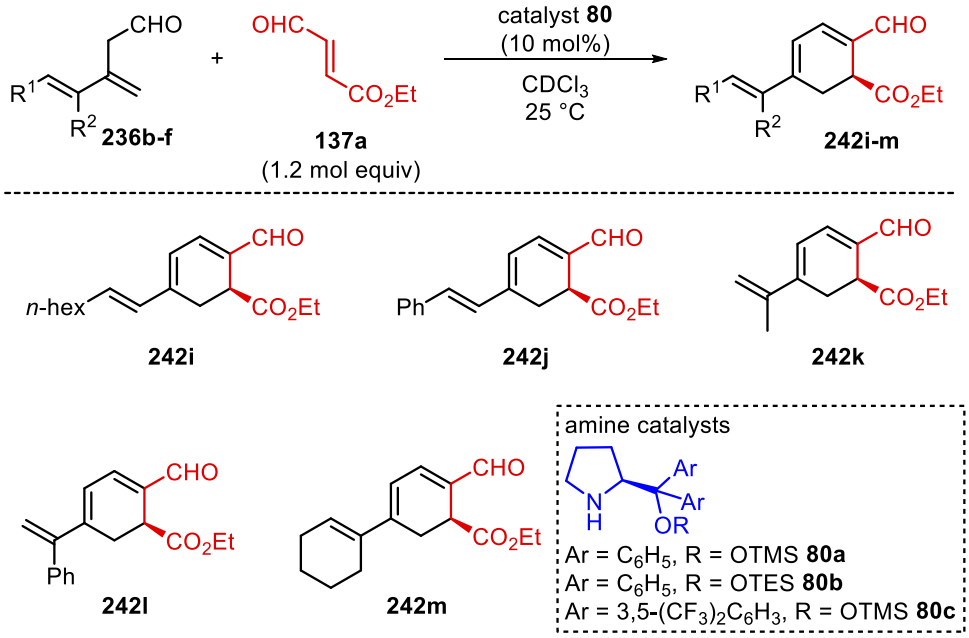
To investigate the tolerance of the reaction towards substitution on the skipped dienal starting material, skipped dienals **236b-f** bearing aliphatic and aromatic substituents on the terminal alkene were made (Scheme 3.24). They were chosen as the corresponding alcohols are readily accessible from Suzuki cross-coupling of an alkenic iodide **295** with appropriately substituted alkenyl boronic acids **296**. DMP oxidation of these alcohols delivers the desired substituted skipped dienals. Substituted skipped dienals **236b-e** have been used in stoichiometric condensation/Diels-Alder/Diels-Alder reaction sequences described in Chapter 2.



Scheme 3.24 Synthesis of substituted skipped dienals **236b-f**

Dienophile **137a** was used in the reactions as it provided the best yield and enantioselectivity out of the dienophiles that were examined. Table 3.4 summarises results from these studies. In all the cases, the substituted skipped dienals underwent the same condensation/Diels-Alder/elimination sequence as the unsubstituted skipped dienal. The substituents did not alter the course of the reaction sequence. With terminal *n*-hexyl substituted skipped dienal **236b** and internal methyl substituted skipped dienal **236d**, the respective cycloadduct products **242i** (entry 1) and **242k** (entry 4) were obtained with good enantioselectivities of 92:8 and 94:6 *er*. With the terminal phenyl (skipped dienal **236c**), internal phenyl (skipped dienal **236d**) as well as 1,2-cyclohexyl (skipped dienal **236e**) substituted skipped dienals, the corresponding cycloadducts **242j** (entry 2), **242l** (entry 5) and **242m** (entry 9) were obtained with lower enantioselectivities of 86:14 and 87:13 *er*. To improve the enantioselectivities of the reactions with substituted skipped dienals **236c**, **236d** and **236e**, a second round of optimisation was conducted using internal phenyl skipped dienal **236d** as a model substrate. By lowering the reaction temperature to 0 °C, no improvement in enantioselectivity was observed (entry 6). This is in line with Jørgensen's report that the reaction temperature does not have a substantial effect on the enantioselectivity of diarylprolinol enamine catalysed reactions.[23] As described in Chapter 1 (pages 23-24), catalyst **80** brings about enantioselective reactions by sterically shielding one face of the 1-amino-[3]dendralene intermediate so that the dienophile approaches from the opposite face thus the size of silyl protecting group and aryl substituents on the catalyst have an impact on the enantioselectivity of the reaction. Improved enantioselectivity was previously observed in the synthesis of cycloadduct **242l** when the TMS protecting group of catalyst **80a** was replaced with a bulkier TES group in catalyst **80b** (Scheme 3.20, page 297). Similarly, by using catalyst **80b** instead of catalyst **80a**, cycloadduct **242m** was obtained with an improved enantioselectivity of 96:4 *er* (entry 7). It has also been reported that the use of catalysts with sterically more demanding aryl groups give rise to higher enantioselectivities.[23] Using catalyst **80c**, which has larger 3,5-trifluoromethylphenyl groups instead of phenyl groups in catalyst **80a**, no desired product was observed (entry 8). Instead, a mixture of products was formed. Having ascertained that catalyst **80b** provides the optimal results, the reaction was repeated with skipped dienals **236c** (entry 3) and **236f** (entry 10), both of which also exhibited an increase in enantioselectivity but a slight decrease in yield.

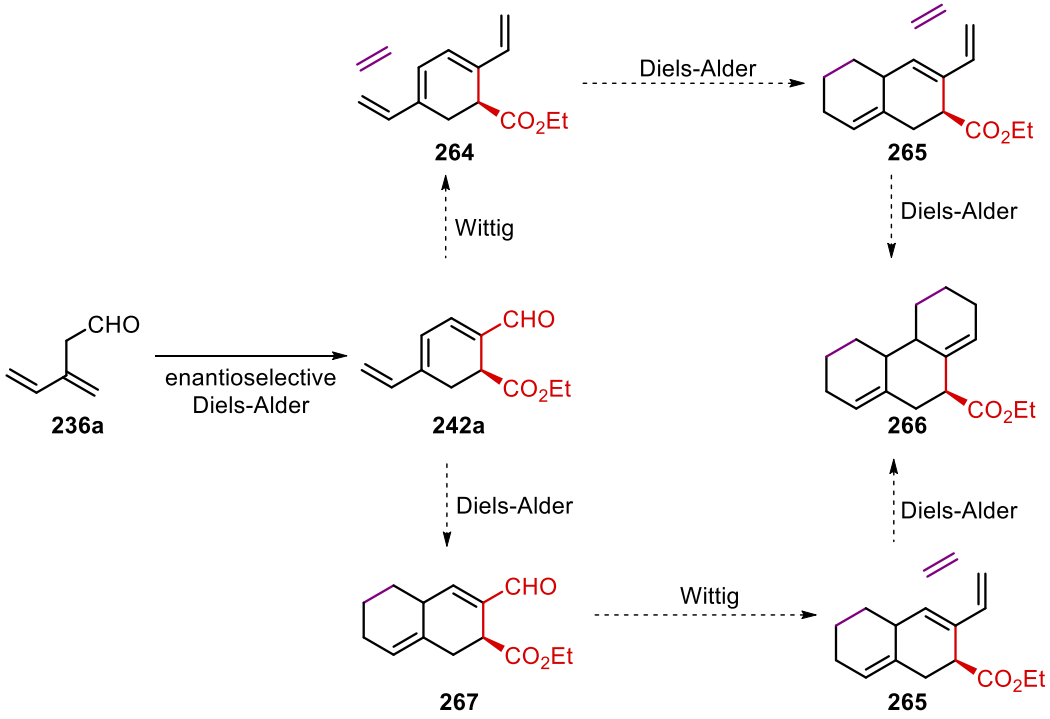
Table 3.4 Diels-Alder reactions between aldehydes **236b**–**e** and dienophile **137a**



Entry	R^1	R^2	Skipped dienal	Catalyst	Temp (ºC)	Product	Yield (%)	*er*
1	*n*-hex	H	**236b**	**80a**	25	**242i**	72	94:6
2	Ph	H	**236c**	**80a**	25	**242j**	76	86:14
3				**80b**	25		66	91:9
4	H	Me	**236d**	**80a**	25	**242k**	70	92:8
5	H	Ph	**236e**	**80a**	25	**242l**	73	87:13
6				**80a**	0		74	87:13
7				**80b**	25		67	96:4
8				**80c**	25		0	-
9	-$(CH_2)_4$-		**236f**	**80a**	25	**242m**	77	87:13
10				**80b**	25		69	96:4

3.3.2 Multiple Diels-Alder Reactions

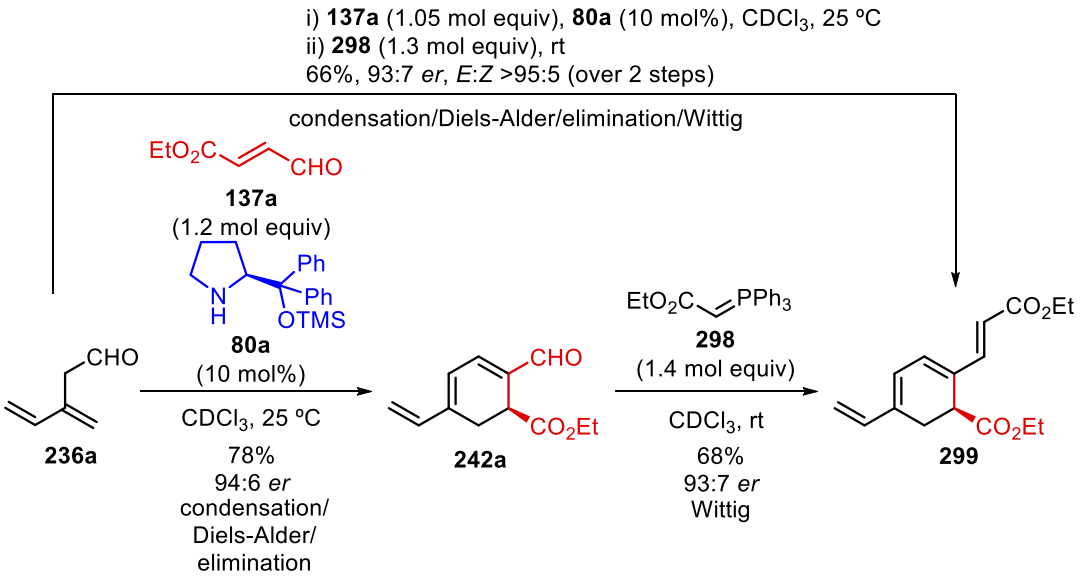
In order to access more complex structures, trienal **242a** could undergo a three step reaction sequence to generate tricycle **266** (Scheme 3.25). There are two possible pathways. Trienal **242a** could be subjected to a Wittig reaction to generate tetraene **264**, which possesses two semi-cyclic 1,3-butadiene units. A double Diels-Alder reaction of tetraene **264** with an appropriate diene generates tricycle **266**. Alternatively, trienal **242a** could undergo a Diels-Alder reaction to form bicyclic skipped dienal **267** which could be converted by a Wittig reaction to the bicyclic skipped triene **265**. A third Diels-Alder reaction would lead to the tricycle **266**.



Scheme 3.25 Proposed routes to enantioenriched polycycles

3.3.2.1 Enantioselective Diels-Alder/Wittig/Diels-Alder/Diels-Alder reaction sequence

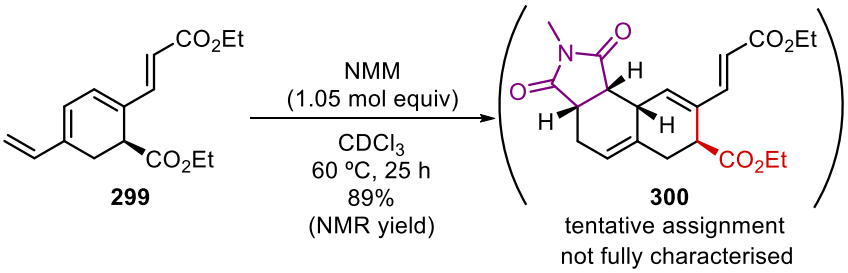
Results from the Diels-Alder/Wittig reaction sequence are summarised in Scheme 3.26. The organocatalysed Diels-Alder/elimination sequence between skipped dienal **236a**, dienophile **137a** and amine **80a** generated cycloadduct **242a**, which underwent a Wittig reaction with stablised ylide **298** to furnish tetraene **299** in 68% yield and 93:7 *er*. By performing both the Diels-Alder and Wittig reactions in one pot, an improved overall yield of 66% was obtained while maintaining high enantioselectivity – 93:7 *er*.



Scheme 3.26 Condensation/Diels-Alder/elimination/Wittig reaction sequence

With tetraene **299** in hand, its Diels-Alder reactivity was investigated with NMM (Scheme 3.27). NMM previously reacted cleanly and stereoselectively with semi-cyclic dienes in Diels-Alder reactions (see Chapter 2, page 54) thus it was chosen as the dienophile for the Diels-Alder reaction with tetraene **299**. The Diels-Alder reaction between tetraene **299** and NMM generated cycloadduct **300** (tentatively assigned as it was not fully characterised) cleanly in 89% yield, as determined by NMR spectroscopy. An attempt to isolate the product by flash column chromatography on silica gel was unsuccessful as a mixture of unidentified products was otained. The use of silica gel with eluting solvents doped with triethylamine also provided a mixture of unidentified products. It appears that cycloadduct **18** might be both acid-and base sensitive. As the reaction was clean by ^{1}H NMR spectroscopic analysis, cycloadduct **18** was characterised as a mixture with a small amount of residual NMM (0.17 mol equiv). The ^{1}H and ^{13}C NMR spectra showed the expected number of signals for cycloadduct **300** and these were assigned using HSQC and HMBC 2D NMR experiments. The ^{1}H NMR spectrum showed signals consistent with the structure of cycloadduct **300**: two doublets at 7.44 and 5.89 ppm with a *J* value of 16.0 Hz, which correspond to the two *E*-alkenic protons, two apparent singlets at 6.63 and 5.70 ppm which correspond to the two endocyclic alkenic protons, a singlet at 2.85 ppm corresponding to three protons of the *N*-methyl functionality, and two sets of signals comprising of a quartet (4.18 ppm) and a triplet (1.27 ppm) and a multiplet (4.00 – 4.10 ppm) and a triplet (1.16 ppm) which correspond to the ethyl groups of the two ethyl esters. The ^{13}C NMR spectrum showed

four signals at 167.0 – 179.6 ppm corresponding to the carbonyl carbons of the two esters and two amides present in tricycle **300**, six alkenic signals at 117.1 – 145.2 ppm and 11 aliphatic signals at 14.1 – 61.0 ppm, which is consistent with the proposed structure of cycloadduct **300**. The LRMS spectrum showed a molecular ion peak of 387.1 and HRMS of the reaction mixture showed the molecular formula to be $C_{21}H_{25}NO_6$, both of which confirmed the presence of cycloadduct **300**.



Scheme 3.27 Diels-Alder reaction between tetraene **299** and NMM

The cycloaddition reaction between tetraene **299** and NMM was highly site selective even though there are three possible 1,3-butadiene units in tetraene **299** which could undergo a Diels-Alder reaction – ester substituted semi-cyclic diene C1=C2–C3=C4, endocyclic diene C3=C4–C5=C6 and unsubstituted semi-cyclic diene C5=C6–C7=C8. The ^{1}H NMR spectrum of the reaction mixture showed the disappearance of a pair of doublets (H_a, H_b) and a doublet of doublets (H_c, overlapping with H_e) corresponding to the mono-substituted alkene while two doublets (H_f, H_g) corresponding to the 1,2-disubstituted alkene remained at the end of the reaction. This indicated that cycloaddition had taken place exclusively at the unsubstituted semi-cyclic diene. In a normal electron demand Diels-Alder reaction, an electron deficient dienophile such as NMM preferentially reacts with the most electron rich diene. The diene with an electron-withdrawing –CO_2Et group (C1=C2–C3=C4) is the most electron deficient and least favoured to undergo Diels-Alder reaction with NMM. The unsubstituted semi-cyclic diene (C5=C6–C7=C8) is the farthest from the conjugated ester unit and is the most electron rich diene thus it is favoured in the Diels-Alder reaction. The reacting diene unit is also the least substituted and thus sterically most accessible. Reaction between NMM and the endocyclic 1,3-butadiene unit (C3=C4–C5=C6) is presumably disfavoured as this breaks conjugation in the product. Similar selectivity was previously been observed in the Diels-Alder reaction of a linear conjugated tetraene.[24]

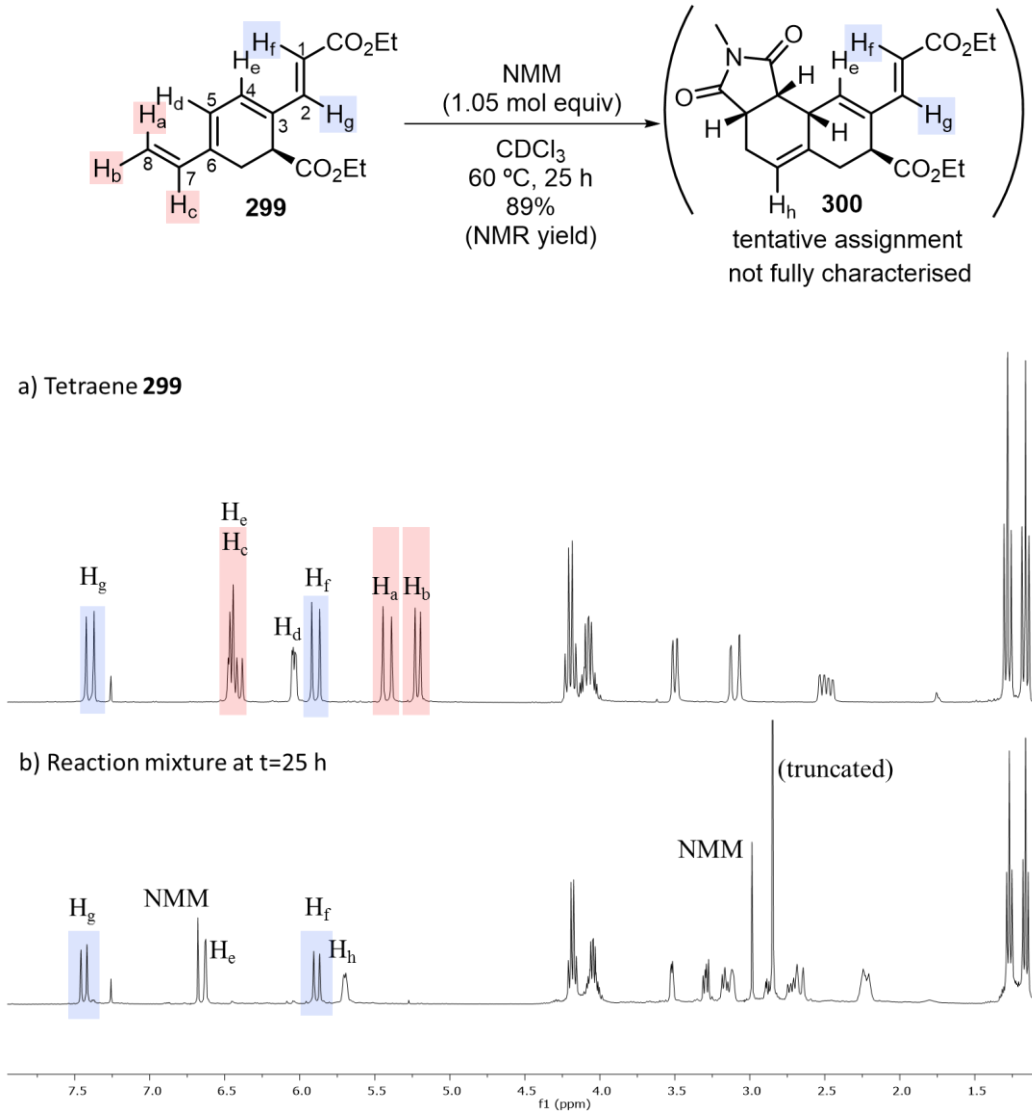
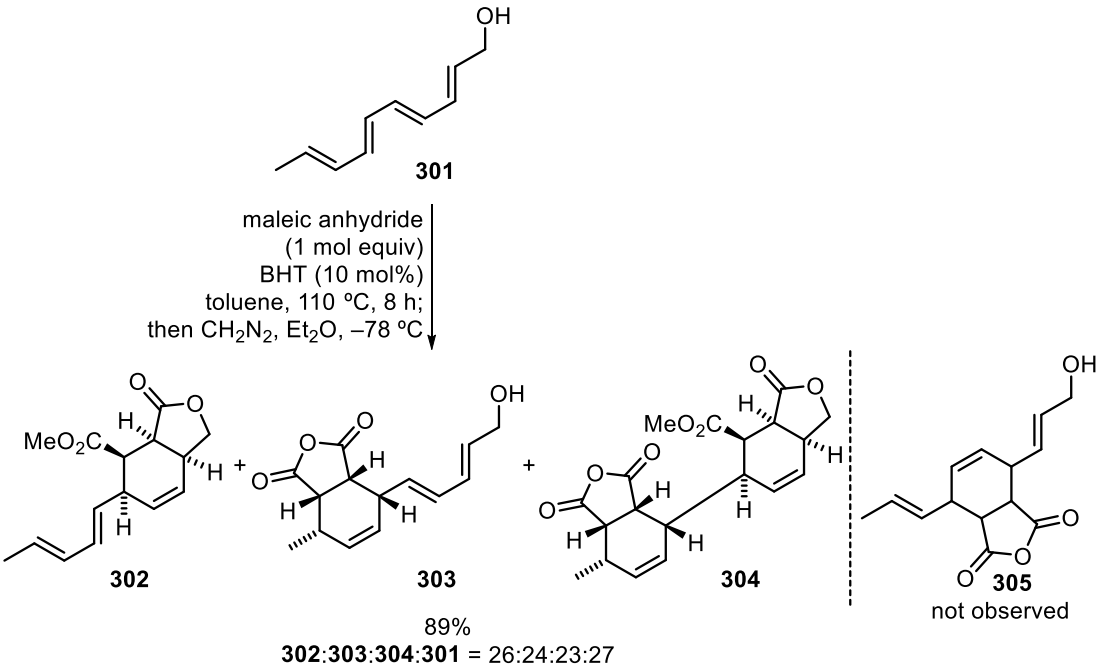


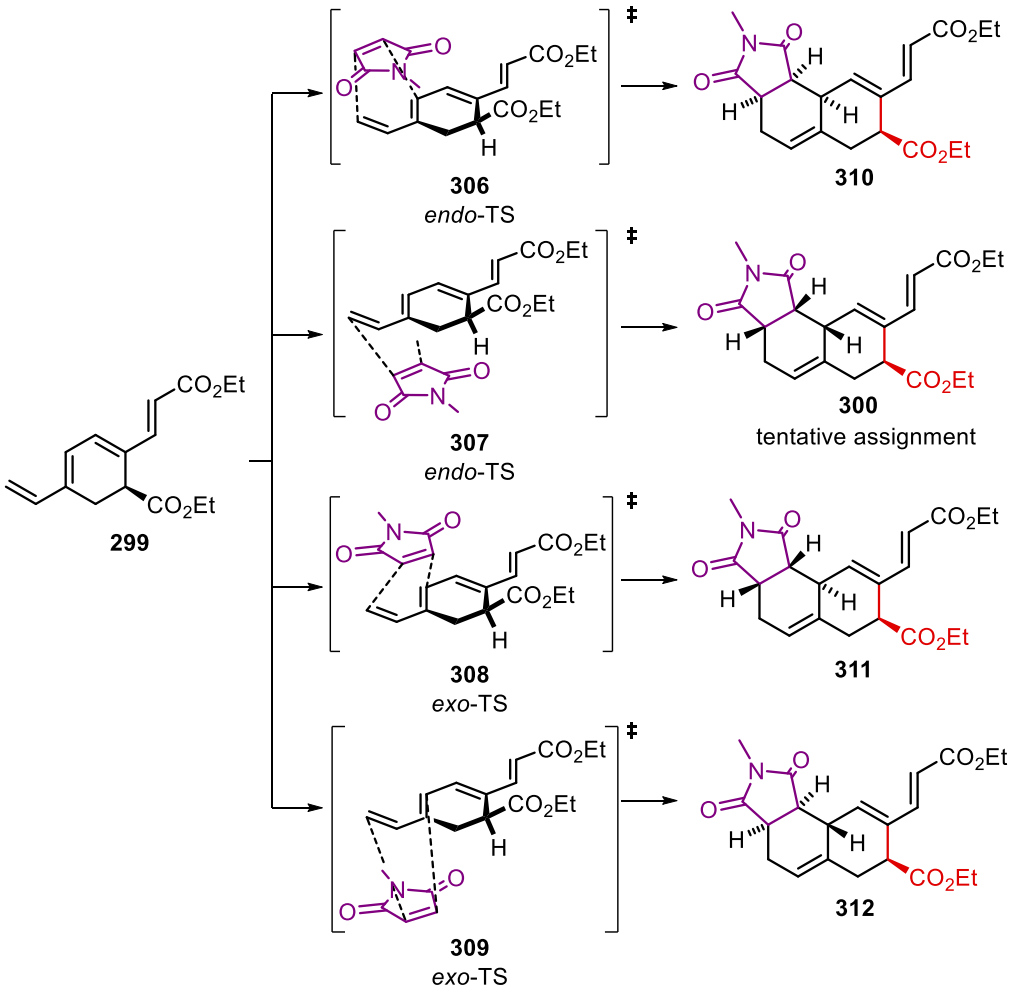
Figure 3.2 ^{1}H NMR spectra of a) tetraene **299** and b) the Diels-Alder reaction between tetraene **299** and NMM after 25 h

It has been reported that the Diels-Alder reaction of linear conjugated tetraene **301** with maleic anhydride also did not generate any product resulting from Diels-Alder reaction at the internal 1,3-butadiene unit (Scheme 3.28).[24] Only mono-adducts **302** and **303** and bis-adduct **304**, products arising from reaction at the terminal 1,3-butadiene units, were observed. Computational studies suggested that the stabilising effect of the conjugated butadienyl substituent on the transition state when reaction occurs at the terminal diene is greater than that of two vinyl substituents in the case of reaction at the internal diene.



Scheme 3.28 Literature reported Diels-Alder reaction between linear tetraene **301** and maleic anhydride

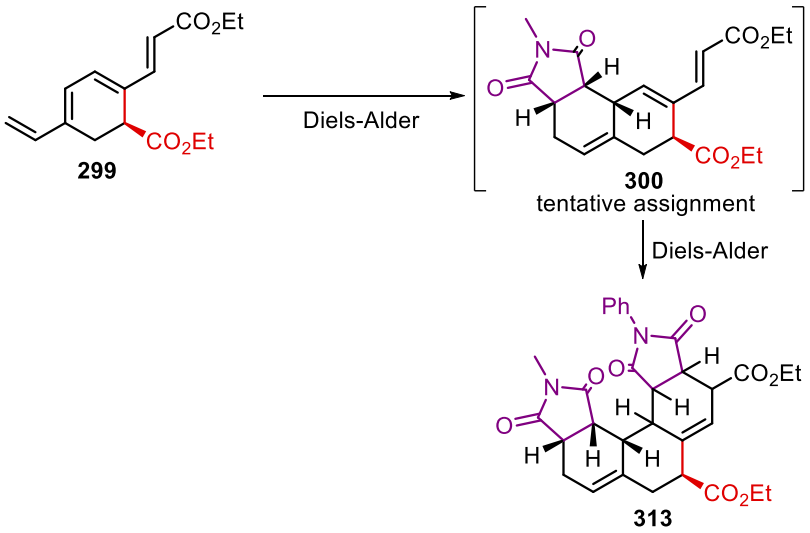
The Diels-Alder reaction between tetraene **299** and NMM (Scheme 3.27) is also highly diastereoselective, as evidenced by the ^{1}H NMR spectrum of the reaction mixture, which showed that only one diastereomer was formed in the reaction. In principle, four possible diastereomeric cycloadducts could be formed depending on whether NMM approaches the diene from the bottom or top face and whether it is an *exo* or *endo* mode of addition (Scheme 3.29). The tentative stereochemical assignment of the cycloadduct obtained is diastereomer **300**, which is the product of Diels-Alder approach of NMM from the less sterically hindered bottom face of tetraene **299** in an *endo* transition state.



Scheme 3.29 Possible stereochemical outcomes for the reaction between tetraene **299** and NMM

For the final Diels-Alder reaction on the ester substituted semi-cyclic diene of cycloadduct **300**, *N*-phenylmaleimide (NPM) was chosen as the dienophile. As cycloadduct **300** could not be isolated, both Diels-Alder reactions were performed in one pot starting from tetraene **299** (Table 3.5). The crude reaction mixture from the reaction between tetraene **299** and NMM in $CDCl_3$ was concentrated under reduced pressure, then redissolved in toluene-d_8 before NPM was added. Heating this reaction mixture to 110 ºC for 16 hours resulted in complete consumption of cycloadduct **300**. Based on the ^1H NMR spectrum of the crude reaction mixture, the cycloaddition reaction between cycloadduct **300** and NPM generated two diastereomers of pentacycle **313** in the ratio 57:43 which was subsequently isolated in a combined 45% yield (14% of a pure sample of one diastereomer and 31% of a mixture of both diastereomers). Both Diels-Alder reactions could also be conducted in the same solvent, toluene-d_8, with a slight increase in yield to 57% and no significant change in diastereomeric ratio (53:47).

Table 3.5 Two-fold Diels-Alder reaction between tetraene **299** and NMM then NPM



Entry	Conditions	Yield (over two steps)	*dr*
1	a) NMM (1.05 mol equiv), $CDCl_3$, 60 ºC, 16 h b) NPM (5.00 mol equiv), toluene-d_8, 110 ºC, 16 h	45%	57:43
2	a) NMM (1.05 mol equiv), toluene-d_8, 60 ºC, 22 h b) NPM (5.00 mol equiv), toluene-d_8, 110 ºC, 24 h	57%	53:47

Repeated purifications by flash column chromatography yielded pure samples of each diastereomer. ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, LRMS and HRMS confirmed the structure of the cycloadducts formed. The ^{1}H and ^{13}C NMR spectra of each of the diastereomers of cycloadduct **313** showed the expected number of signals and these were assigned using HSQC and HMBC 2D NMR experiments, as detailed in the following paragraphs.

The ^{1}H NMR spectrum of one of the diastereomers of pentacycle **313** showed signals consistent with the proposed structure: two multiplets at 7.33 – 7.50 ppm corresponding to five aromatic protons, two signals at 5.58 and 5.80 ppm corresponding to two alkenic protons, two sets of quartets (4.12 and 4.25 ppm) and triplets (1.23 and 1.30 ppm) corresponding to the ethyl groups of the two ethyl esters and a singlet at 2.89 ppm corresponding to three protons of the *N*-methyl functionality. The ^{13}C NMR spectrum

showed six signals at 172.3 – 179.9 ppm corresponding to four amide and two ester carbonyl carbons, four signals at 121.0, 121.2, 138.2 and 138.6 ppm corresponding to four alkenic carbons, four signals at 131.7, 129.3, 128.8 and 126.5 ppm corresponding to four non-equivalent carbons of the mono-substituted phenyl and 15 aliphatic carbons at 14.2 – 61.9 ppm, which is consistent with the proposed structure of cycloadduct **318**. The LRMS spectrum showed a molecular ion peak of 560.2 and HRMS of the reaction mixture showed the molecular formula to be $C_{31}H_{32}N_2O_8$, both of which confirmed the presence of cycloadduct **313**.

The ^{1}H NMR spectrum of the other diastereomer of pentacycle **313** also showed signals consistent with the proposed structure: a multiplet at 7.31 – 7.44 ppm corresponding five aromatic protons, two signals at 6.35 and 5.61 – 5.68 ppm corresponding to two alkenic protons, two sets of quartets (3.85 – 3.92 ppm, overlapping with a multiplet and 4.32 ppm) and triplets (1.07 and 1.33 ppm) corresponding to the ethyl groups of the two ethyl esters and a singlet at 2.93 ppm corresponding to three protons of the *N*-methyl functionality. The ^{13}C NMR spectrum showed six signals at 170.5 – 179.9 ppm corresponding to four amide and two ester carbonyl carbons, four signals at 122.3, 123.1, 137.0 and 138.1 ppm corresponding to four alkenic carbons, four signals at 126.9, 128.7, 129.0 and 131.9 ppm corresponding to four non-equivalent carbons of the mono-substituted phenyl and 15 aliphatic carbons at 14.2 – 61.5 ppm, which is consistent with the proposed structure of cycloadduct **318**. The LRMS spectrum showed a molecular ion peak of 560.2 and HRMS of the reaction mixture showed the molecular formula to be $C_{31}H_{32}N_2O_8$, both of which confirmed the presence of cycloadduct **313**.

Although both samples were solids, repeated attempts to obtain crystals suitable for single crystal X-ray analysis were unsuccessful and the relative stereochemistry of each of the cycloadducts was not determined. As was the case with cycloadduct **300**, four possible diastereomers can be formed in the Diels-Alder reaction between cycloadduct **300** and NPM, depending on the *endo*/*exo* and π diastereofacial selectivity of the reaction (Figure 3.3). More thorough analysis will be required to determine the relative stereochemistry of each of the diastereomers of the obtained adducts **313**. *Endo* adducts **314** and **315** are the most likely products based upon the known *endo*-preference of NPM and the fact that substituents hinder dienophile approach to both top and bottom faces of the diene in tricycle **300**.

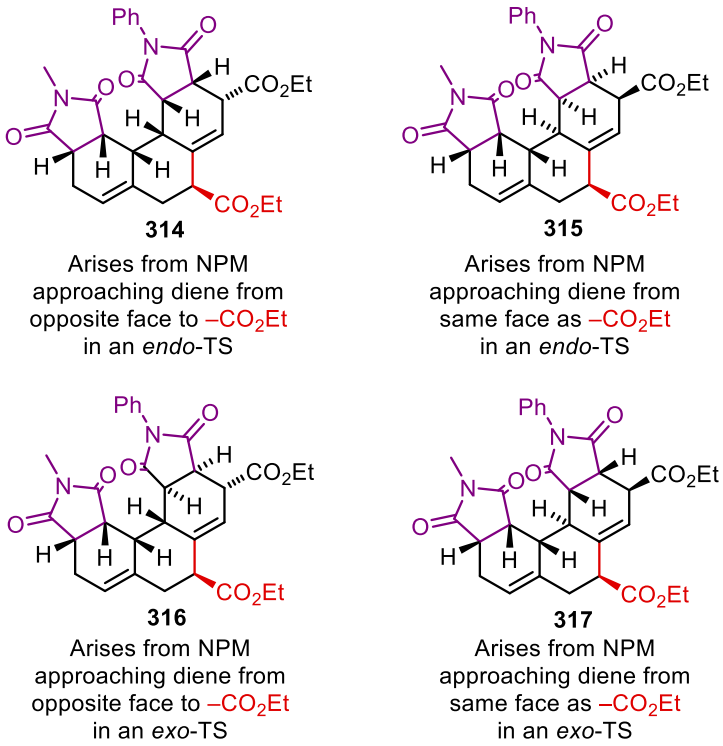
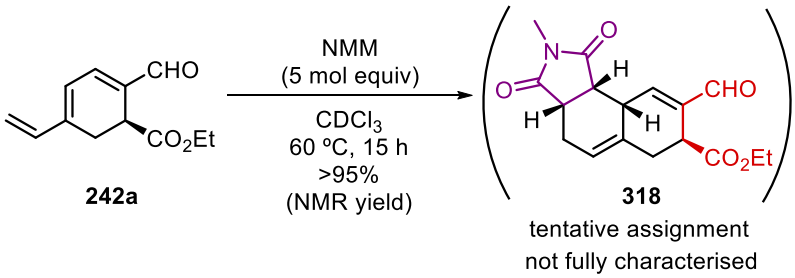


Figure 3.3 The four possible diastereomers from the two-fold Diels-Alder reaction between tetraene **299** and NMM then NPM

3.3.2.2 Enantioselective Diels-Alder/Diels-Alder/Wittig/Diels-Alder reaction sequence

The Diels-Alder reactivity of trienal **242a** was tested with NMM (Scheme 3.30). The reaction proceeded cleanly to generate tricycle **2** in >95% yield, as determined by ^{1}H NMR spectroscopy. As was the case with cycloadduct **300**, attempts to isolate the compound by flash column chromatography on silica gel with or without triethylamine additive in the eluting solvent provided a mixture of products. Tricycle **318** appears to be both acid and base sensitive. The ^{1}H and ^{13}C NMR spectra of the reaction mixture showed the expected number of peaks for cycloadduct **318** in addition to the contaminant NMM and these were assigned using HSQC and HMBC 2D NMR experiments. The ^{1}H NMR spectrum showed signals consistent with the proposed structure of cycloadduct **318**: a singlet at 9.60 ppm, which corresponds to the aldehyde proton, two apparent singlets at 7.30 and 5.76 ppm which correspond to the two endocyclic alkenic protons, a singlet at 2.88 ppm corresponding to three protons of the *N*-methyl functionality, and a quartet at 4.05 ppm and a triplet at 1.18 ppm, which correspond to the ethyl group of the ethyl ester. The ^{13}C NMR spectrum showed a signal at 191.3 ppm corresponding to the carbonyl carbon of the aldehyde, three signals at 171.8 – 179.3 ppm which corresponds to the carbonyl carbons of the two amides and an

ester, four alkenic signals at 122.2 – 150.9 ppm and 9 aliphatic signals at 14.1 – 61.1 ppm, which is also consistent with the proposed structure of cycloadduct **318**. The LRMS spectrum showed a molecular ion peak of 317.1 and HRMS of the reaction mixture showed the molecular formula to be $C_{17}H_{19}NO_5$, both of which confirmed the presence of cycloadduct **318**.



Scheme 3.30 Diels-Alder reaction between trienal **242a** and NMM

The ^{1}H NMR spectrum of the crude reaction mixture showed that the trienal reacted exclusively at the semi-cyclic diene (Figure 3.4). The disappearance of a pair of doublets (H_a, H_b), a doublet of doublets (H_c) and a broad doublet (H_d) corresponding to the semi-cyclic alkene and the appearance of a new broad singlet (H_g) corresponding to the newly formed endocyclic alkene were observed. As was discussed previously (page 306), NMM is an electron deficient dienophile which preferentially reacts in a Diels-Alder reaction with more electron rich dienes. The endocyclic diene, being directly conjugated to an aldehyde, is electron poor and less favoured to undergo a normal electron demand Diels-Alder reaction with NMM compared to the semi-cyclic diene.

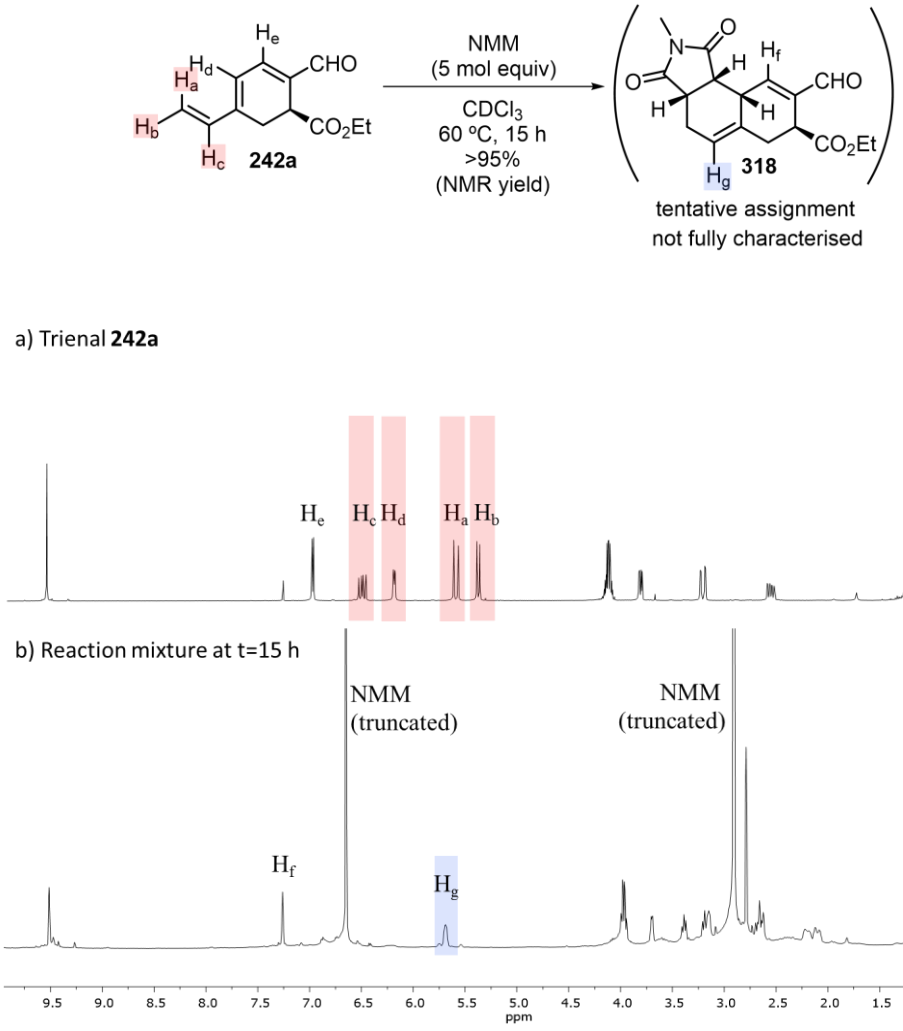
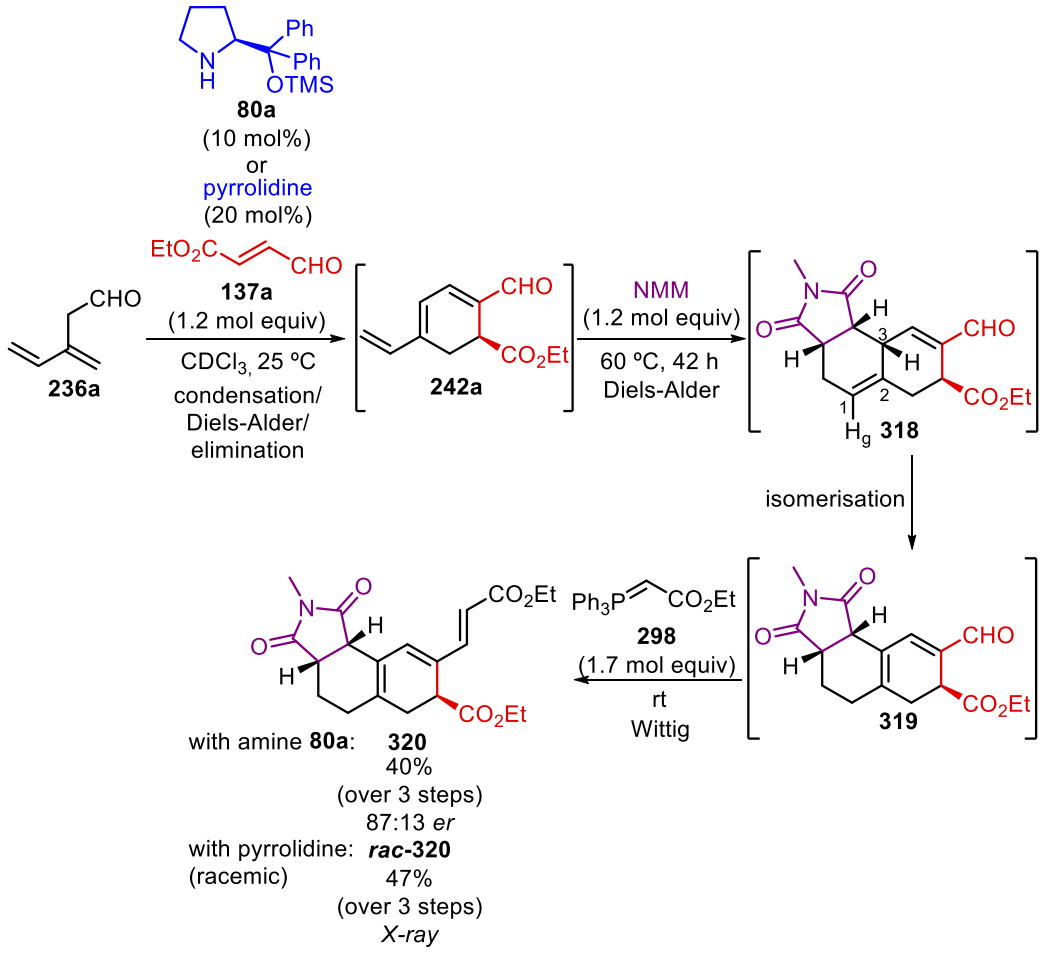


Figure 3.4 ^{1}H NMR spectrum of a) trienal **242a** and b) the Diels-Alder reaction between trienal **242a** and NMM after 15 h

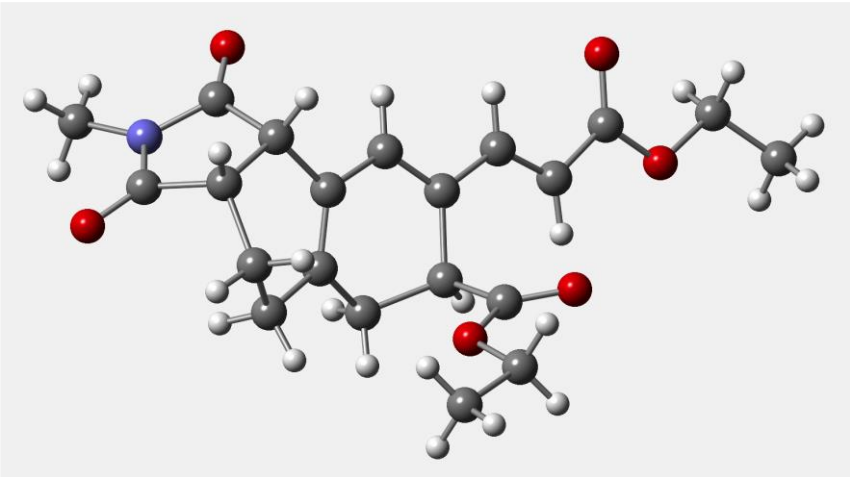
The one-pot condensation/Diels-Alder/elimination/Diels-Alder/Wittig reaction sequence was next performed (Scheme 3.31). The condensation/Diels-Alder/elimination reaction between skipped dienal **236a**, dienophile **137a** and amine **80a** generated trienal **242a**. The addition of NMM to the reaction mixture did not generate the expected Diels-Alder product, tricycle **318**. The cycloadduct produced lacked the alkenic proton corresponding to H_g thus it is postulated that the C1=C2 alkene in cycloadduct **20** had isomerised to the C2–C3 position, bringing it in conjugation with the α, β-unsaturated aldehyde. As this was only observed when the Diels-Alder reaction was conducted in the same pot as the enantioselective Diels-Alder reaction, the isomerisation may have been promoted by catalyst **80a** acting as a base. Addition of phosphorane **298** to the reaction mixture generated the Wittig product, tricycle **320**, in 40% yield from skipped

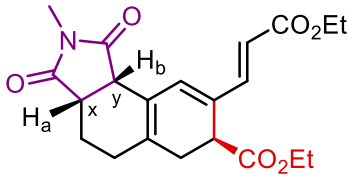
dienal **236a** in one-pot. To determine the enantiomer ratio of tricycle **320** by HPLC on chiral stationary phase, the racemic compound ***rac*-320** was synthesised by using pyrrolidine as the catalyst instead of amine **80a**. Crystals of tricycle ***rac*-320** suitable for single crystal X-ray crystallography were also obtained.



Scheme 3.31 One-pot condensation/Diels-Alder/Diels-Alder/Wittig reaction sequence

The relative stereochemistry of tricycle ***rac*-320** was confirmed by single crystal X-ray analysis of the racemic material, which showed a *syn* relationship between protons H_a/H_b and the $–CO_2Et$ group (Figure 3.5).

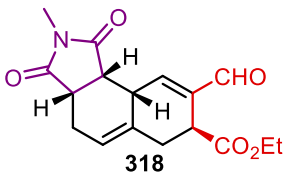




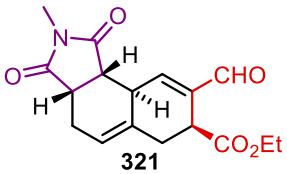
***rac*-320**

Figure 3.5 X-ray crystal structure of cycloadduct ***rac*-320**

The relative configurations at C_x and C_y of cycloadduct **320** are set during the Diels-Alder reaction between trienal **242a** and NMM. The stereochemical outcome observed could have arisen from either *endo* addition of NMM to cycloadduct **242a** from the less sterically hindered face opposite to the $-CO_2Et$ substituent (cycloadduct **318**) or *exo* addition of NMM to the more sterically hindered face (cycloadduct **321**) (Figure 3.6). As NMM is typically a highly *endo* selective dienophile, the *endo* cycloadduct **318** is more likely to be the diastereomer which formed before the isomerisation.



318
endo
anti to CO_2Et



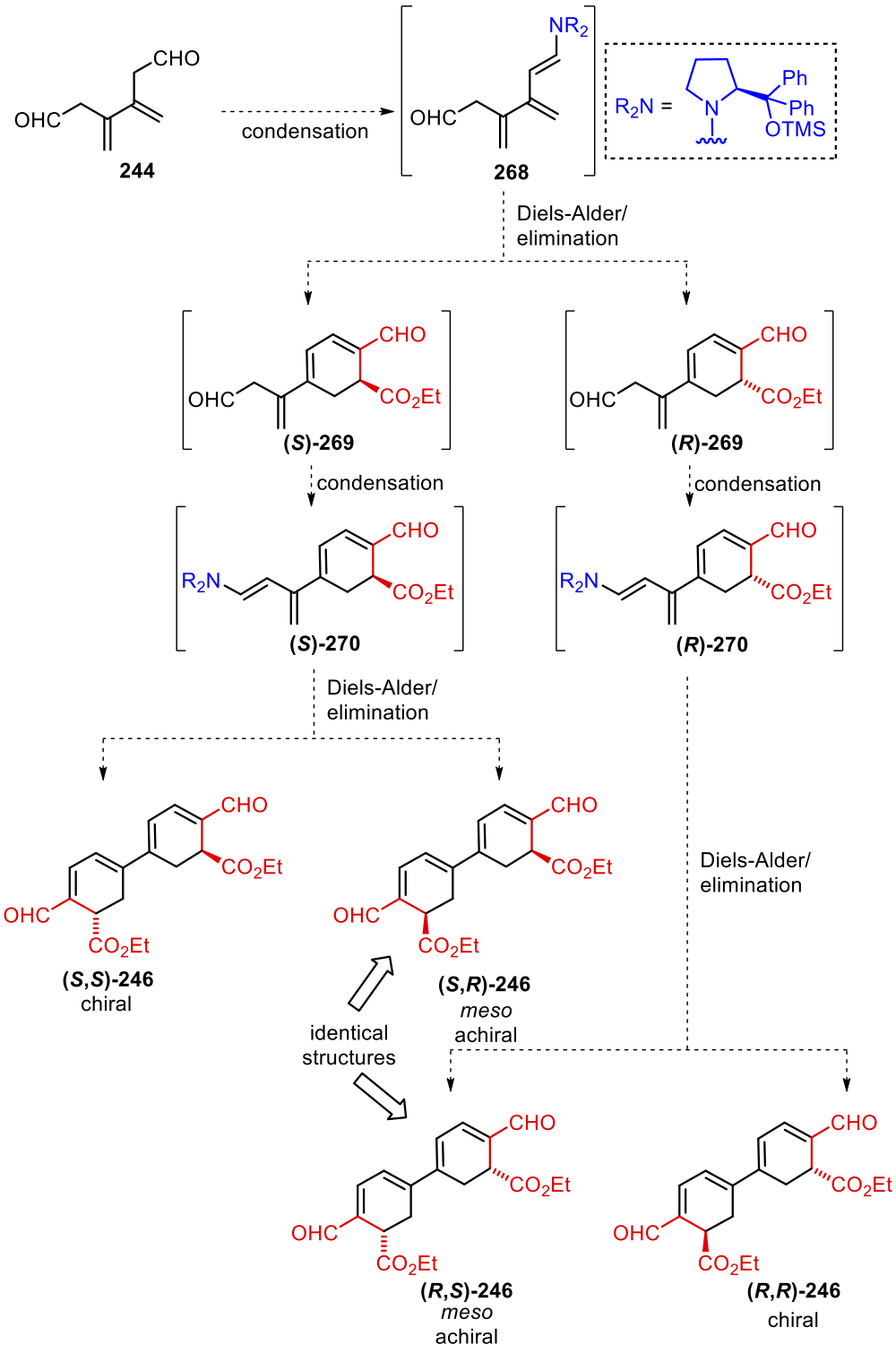
321
exo
syn to CO_2Et

Figure 3.6 Two possible diastereomers formed in the Diels-Alder reaction between cycloadduct **242a** and NMM

3.3.3 Preliminary investigation into a double enantioselective Diels-Alder reaction

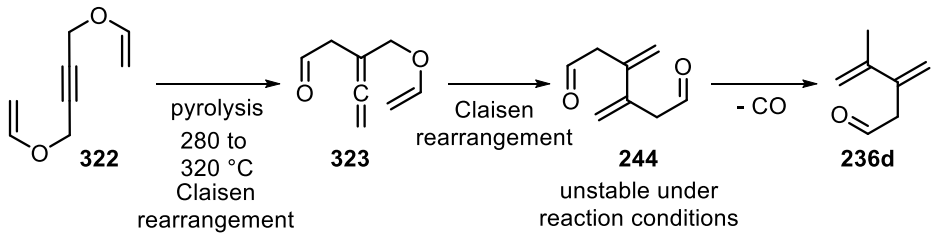
The possible stereochemical outcomes from a twofold condensation/Diels-Alder/elimination reaction sequence of diene-dialdehyde **244** are shown in Scheme

3.32. Two enantiomers (***S***)-**269** and (***R***)-**269** are expected to be generated from the inital condensation/Diels-Alder/elimination reaction sequence. These would generate four stereoisomers (***S,S***)-**246**, (***R,R***)-**246**, (***S,R***)-**246** and (***R,S***)-**246** arising from the second condensation/Diels-Alder/elimination reaction sequence. (***S,S***)-**269** and (***R,R***)-**269** are a pair of enantiomers while (***S,R***)-**246** and (***R,S***)-**246** are identical structures, representing an achiral *meso* compound. The *meso* form is diastereomeric with enantiomers (***S,S***)-**246** and (***R,R***)-**246**. With an achiral amine, it is expected that a statistical mixture will be generated from the reaction sequence, that is, equal amounts of (***S***)-**269** and (***R***)-**269** from the first condensation/Diels-Alder/elimination reaction sequence and equal amounts of (***S,S***)-**246**, (***R,R***)-**246**, (***S,R***)-**246** and (***R,S***)-**246** from the second reaction sequence i.e. a 1:1 mixture of two diastereomers, chiral (***S,S***)-**246**/(***R,R***)-**246** as a racemate and achiral *meso* (***S,R***)-**246**/(***R,S***)-**246**. With chiral amine **80a**, (***S***)-**269** and (***S,S***)-**269** are expected to be the favoured stereoisomers, based on the proposed absolute configuration assignment (Section 3.3.1.2). It is anticipated that this twofold enantioselective reaction would result in an amplification of enantioselectivity of (***S,S***)-**246** and (***R,R***)-**246**, in line with the Horeau principle, which was described earlier in Section 3.1.1 (page 281).



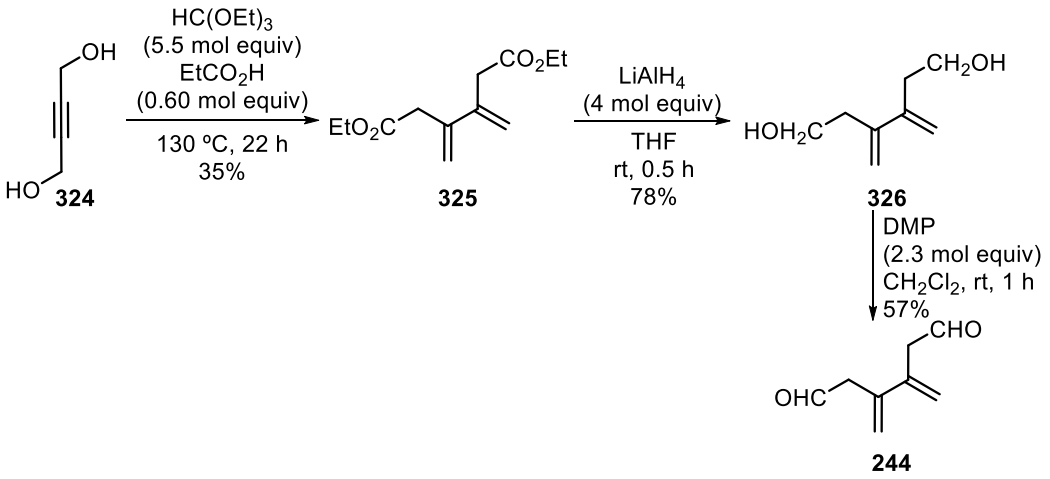
Scheme 3.32 Possible stereochemical outcomes of condensation/Diels-Alder/elimination reaction sequence of diene-dialdehyde **244**, dienophile **137a** and amine **80a**.

Diene-dialdehyde **244** has been reported in the literature (Scheme 3.33).[25] It was generated as the major product in the thermal isomerisation of 1,4-bis(vinyloxy)but-2-yne (**322**) at elevated temperatures between 280 to 320 °C through a twofold Claisen rearrangement. Diene-dialdehyde **322** was reported to undergo decomposition to methyl substituted skipped dienal **236d** under the reaction conditions.



Scheme 3.33 Hopf's and Wolff's synthesis of diene-dialdehyde **244** from 1,4-bis(vinyloxy)but-2-yne (**323**) and decomposition to methyl substituted skipped dienal **236d**

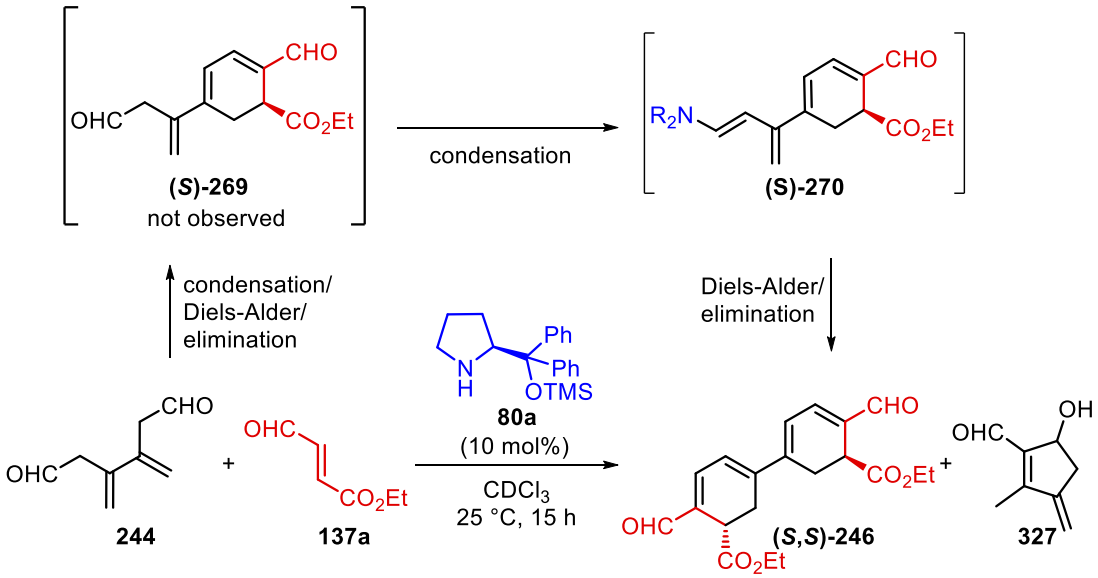
Diene-dialdehyde **244** was synthesised *via* an alternative route (Scheme 3.34), following the procedure by Roscini and co-workers. 1,4-Butynediol (**324**) was treated with triethylorthoformate and propionic acid to induce a twofold Johnson-Claisen rearrangement[26] to generate diene-diester **325**, which was reduced with lithium aluminium hydride to provide diene-diol **326**.[27] Twofold DMP oxidation of diene-diol **326** provided diene-dialdehyde **244**.



Scheme 3.34 Synthesis of diene-dialdehyde **244**

With diene-dialdehyde **244** in hand, the twofold condensation/Diels-Alder/elimination reaction sequence was performed with dienophiles **137a** and amine **80a** as the catalyst (Table 3.6). An initial attempt produced cyclopentene **327** (enantiopurity not determined) as the major product instead of the desired tetraene-dialdehyde bisadduct **246** (entry 1). Cyclopentene **327** is the product of an intramolecular reaction of diene-dialdehyde **244** catalysed by amine **80a** (the proposed mechanism is discussed later). To minimise formation of the undesired intramolecular product and favour the intermolecular Diels-Alder reaction, the amount of dienophile **137a** was increased from 2.1 to 4 molar equivalents and the concentration of the starting diene-dialdehyde **244** was increased from 0.16 M to 0.50 M. This was successful in favouring the formation of the desired tetraene-dialdehyde bisadduct **246** (ratio of **246**:**327** = 91:9), however, the low NMR and isolated yields (50% and 34%, entry 2) require further optimisation.

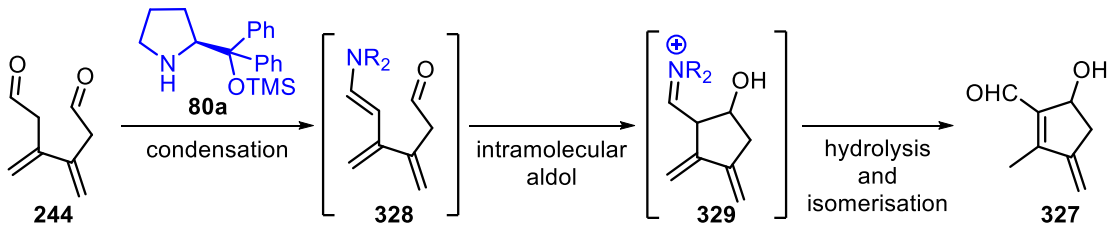
Table 3.6 Twofold condensation/Diels-Alder/elimination reaction sequence between diene-dialdehyde **244**, dienophile **137a** and amine **80a**



Entry	Dienophile **137a** (mol equiv)	Conc of diene-dialdehyde **244**	Ratio of **246**:**327**[a]	NMR yield of **246** (isolated yield)
1	2.1 mol equiv	0.16 M	40:60	11%
2	4.0 mol equiv	0.50 M	91:9	50% (34%)

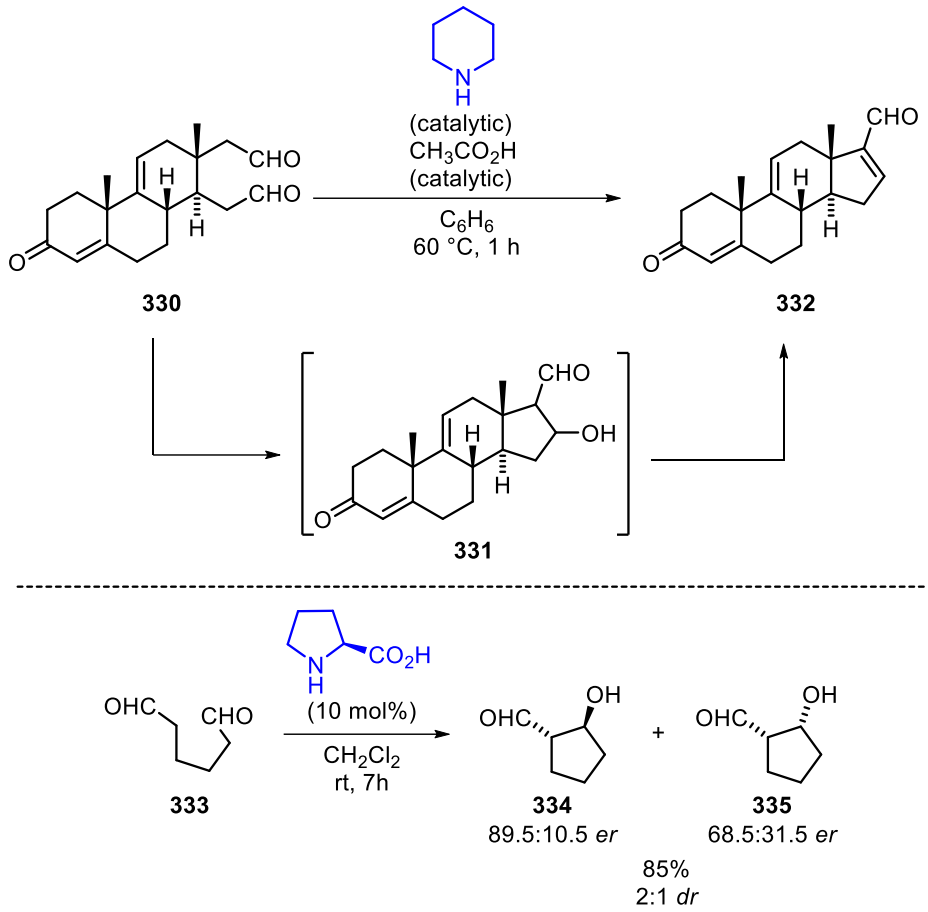
[a] determined by ^{1}H NMR spectroscopy of crude reaction mixture

The proposed mechanism for the formation of cyclopentene **327** is shown in Scheme 3.35. Condensation of amine **80a** with dialdehyde **244** generates 1-amino[3]dendralene **328**. Intramolecular 5-*exo*-trig aldol cyclisation *via* β-addition of the enamine to the aldehyde results in the formation of iminium **329**, which upon hydrolysis and isomerisation of one of the exocyclic alkenes into conjugation with the aldehyde generates the observed cyclopentene **327**.



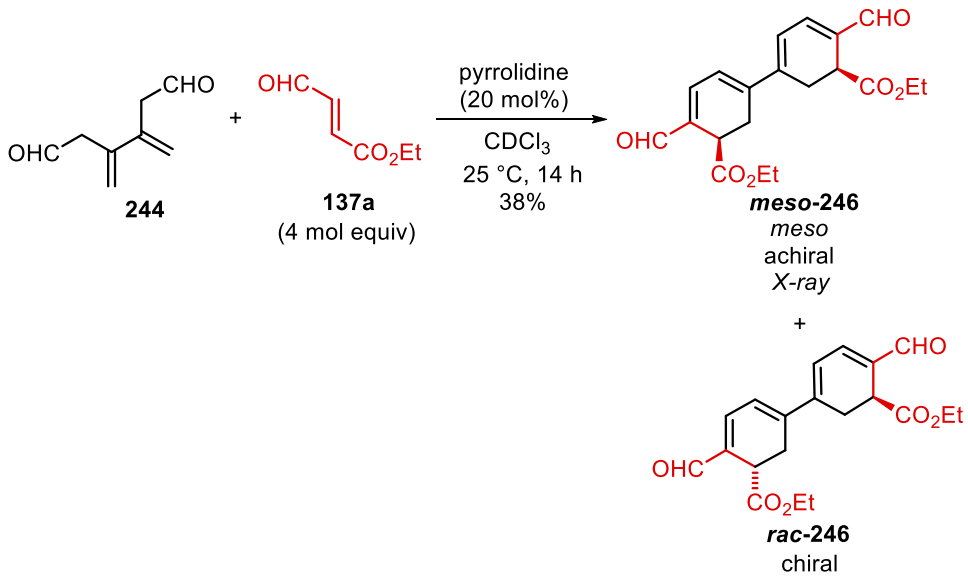
Scheme 3.35 Proposed mechanism for the intramolecular aldol condensation of dialdehyde **244**

The formation of cyclopentene **327** is not unprecedented, as amine-catalysed 5-*exo*-trig aldol cyclisations of aliphatic 1,6-dialdehydes have been reported (Scheme 3.36). Woodward reported the 5-*exo*-trig aldol cyclisation of tricyclic 1,6-dialdehyde **330** in the presence of catalytic amounts of piperidine and acetic acid to generate tetracyclic β-hydroxy aldehyde **331**, which underwent dehydration *in situ* to afford tetracyclic enal **332**.[28] An enantioselective variant of a 5-*exo*-trig aldol cyclisation was reported by List in 2003 in which an aliphatic 1,6-dialdehyde **333** was reacted with proline to provide β-hydroxycyclopentanals **334** and **335** as a mixture of diastereomers.[29]



Scheme 3.36 Literature examples of 5-*exo*-trig aldol cyclisations of aliphatic 1,6-dialdehydes **330** and **333**

To determine the enantiomer ratio of tetraene-dialdehyde bisadduct **(*S*,*S*)-246** by HPLC on chiral stationary phase, the racemic sample were synthesised by using pyrrolidine as the amine catalyst (Scheme 3.37). As expected (see pages 316-317), this reaction provided a mixture of two diastereomers (*ca.* 1:1 as determined by ^{1}H NMR spectroscopy of the crude reaction mixture). Purification by flash column chromatography provided pure samples of each diastereomer for characterisation. The relative stereochemistry of the *meso* cycloadduct ***meso*-246** was determined by single crystal X-ray analysis (**Figure 3.7**). Attempts to separate the enantiomers of ***rac*-246** by chiral HPLC was not successful thus the enantiomer ratio for cycloadduct **(*S*,*S*)-246** was not determined.



Scheme 3.37 Twofold condensation/Diels-Alder/elimination reaction sequence between diene-dialdehyde **244**, dienophiles **137a** and pyrrolidine

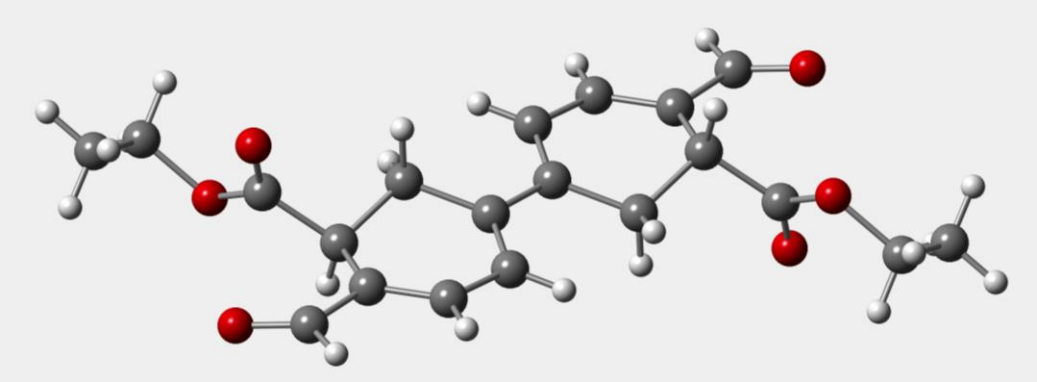
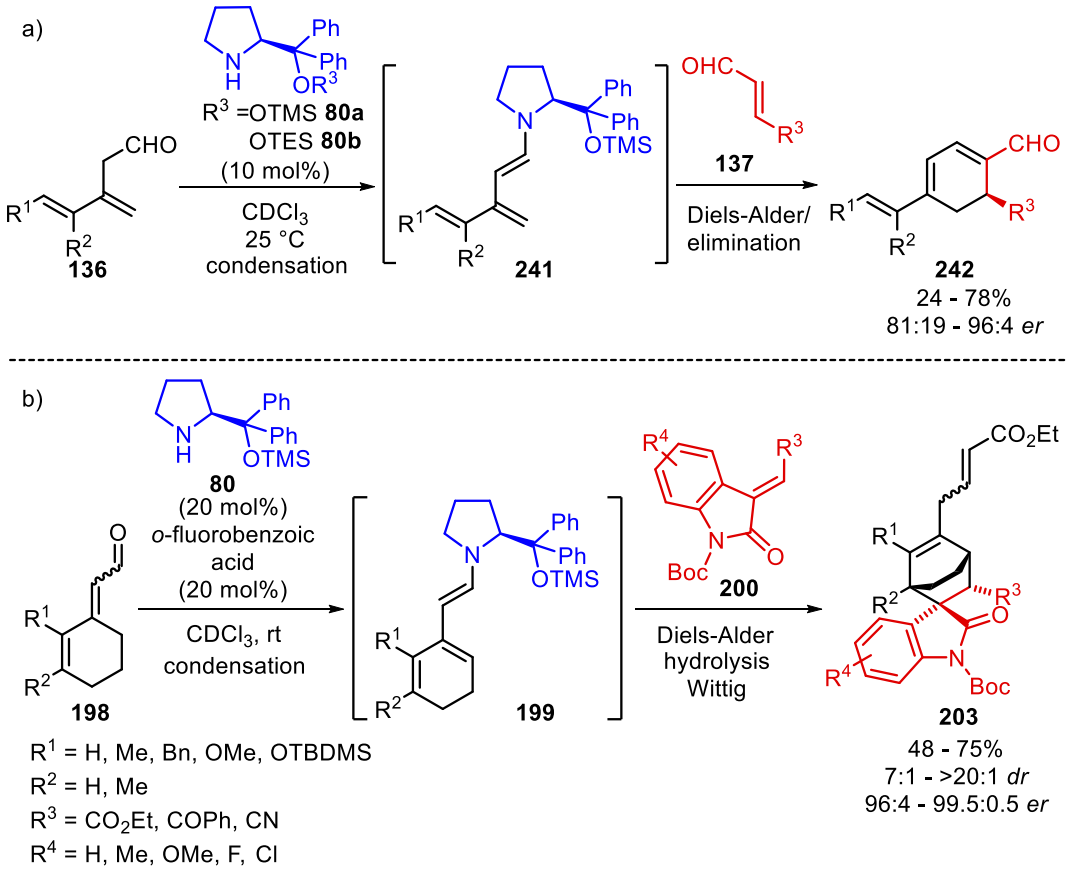


Figure 3.7 X-ray crystal structure of cycloadduct ***meso*-246**

3.4 Summary

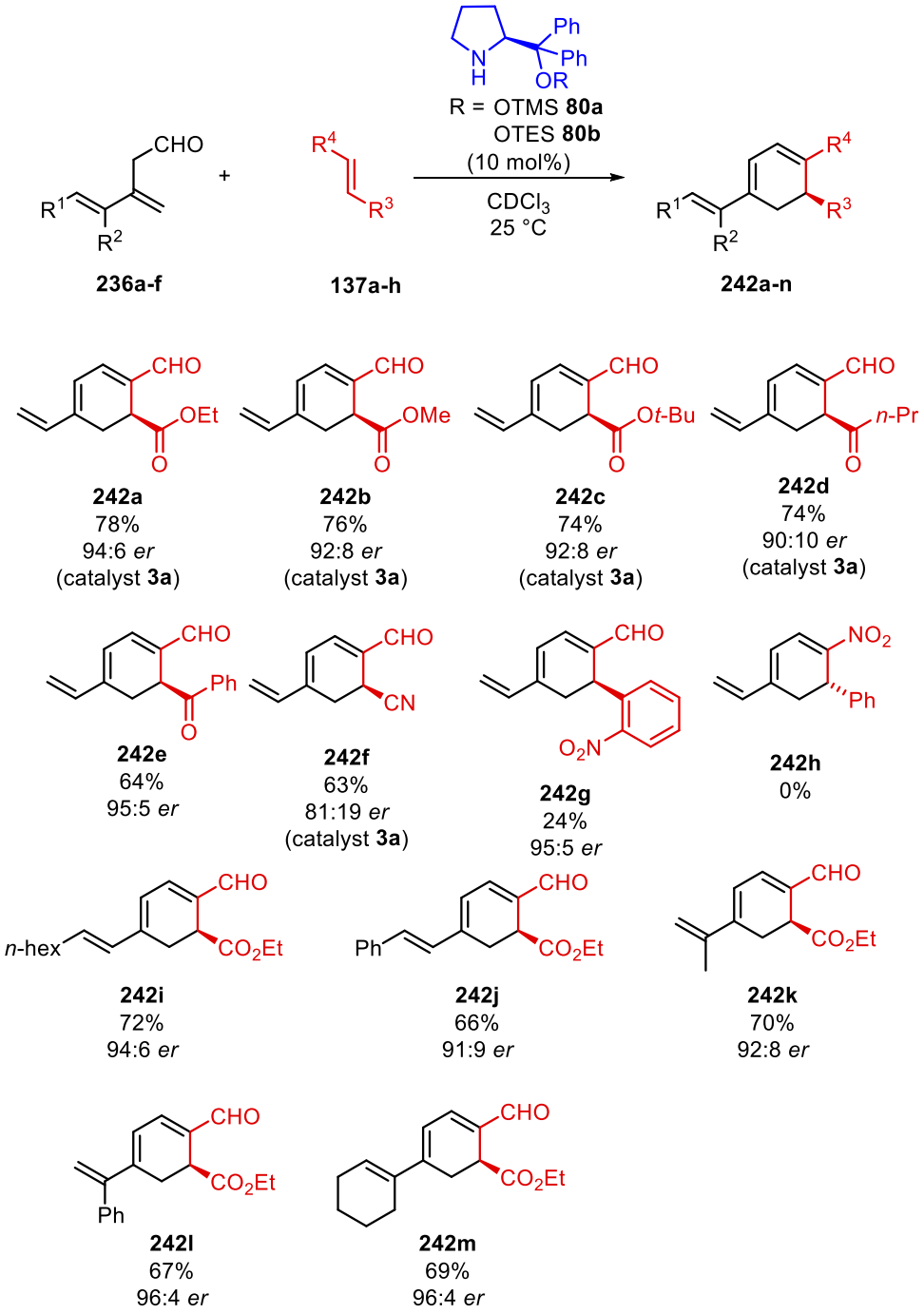
In summary, the first examples of organocatalysed enantioselective Diels-Alder reactions between acyclic 1-amino[3]dendralenes **241**, the condensation product of skipped dienals **136** and amines **80**, and various dienophiles **137** were developed. In all cases, Diels-Alder reaction occurred exclusively at the amine-substituted 1,3-butadiene unit. This is different to what was observed in the reaction between semi-cyclic 1-amino[3]dendralenes **199** and 3-alkenic oxindoles **200**, where Diels-Alder reaction at the semi-cyclic 1,3-butadiene site, more distant from the amine substituent, was observed.



Scheme 3.38 Comparison between a) our Diels-Alder/elimination reaction between acyclic 1-amino[3]dendralenes **136a-f** and β substituted acroleins **137** and b) reported[8] Diels-Alder/hydrolysis/Wittig reaction between semi-cyclic 1-amino[3]dendralenes **199** and oxindoles **200**

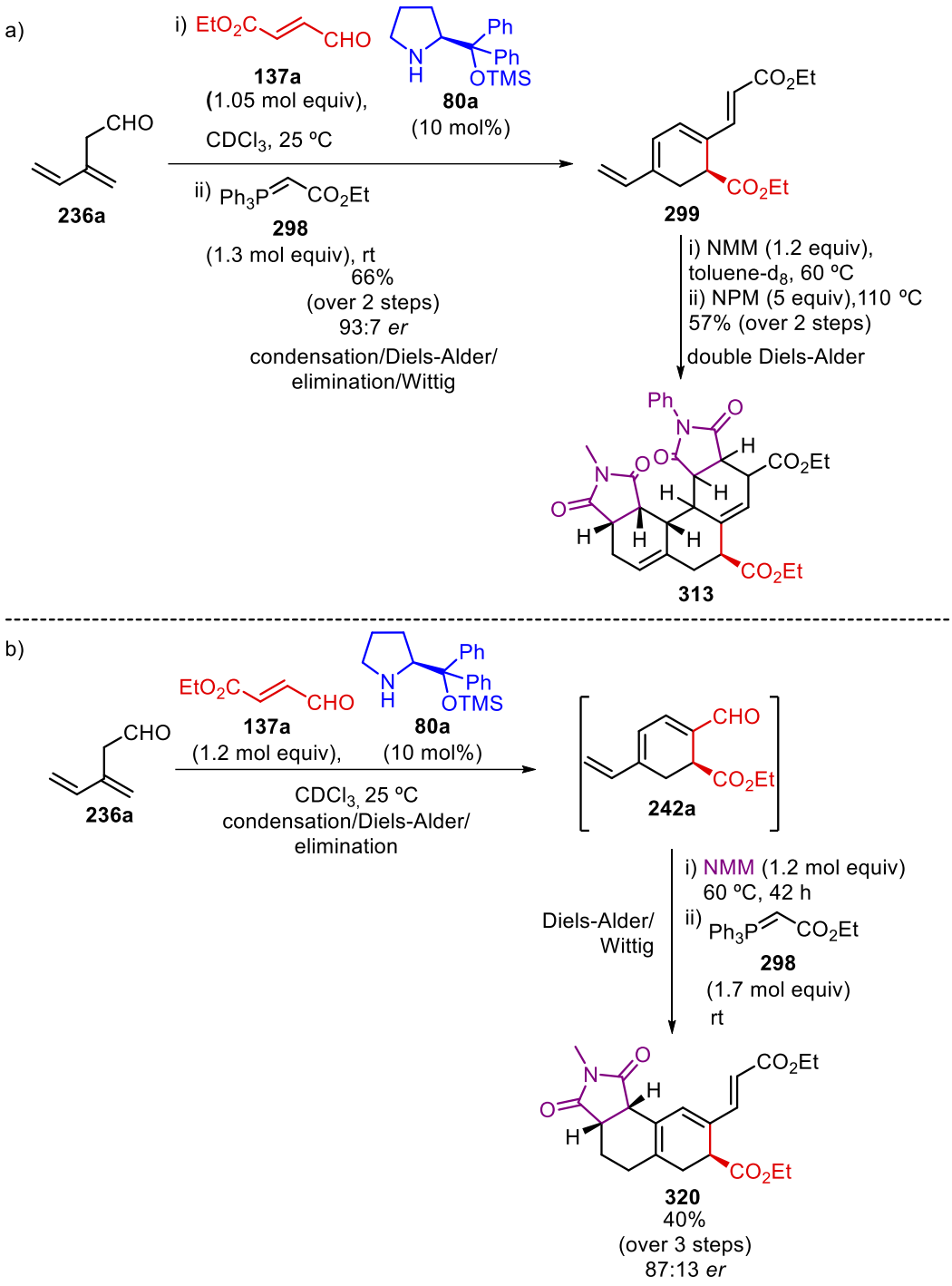
Various dienophiles and skipped dienals were prepared and examined in the reaction (Scheme 3.39). Acroleins bearing electron-withdrawing groups such as esters, ketones and nitrile at the β position generated the desired cycloadducts **242a-f** in moderate to good yield and enantioselectivity. The absence of an electron-withdrawing substituent at the β position of the dienophile reduced its reactivity in the Diels-Alder reaction step and the overall yield of the reaction was lower in these cases. *o*-Nitrocinnamaldehyde, which bears a less electron withdrawing *o*-nitrophenyl substituent at the β position, provided the corresponding cycloadduct **242g** in much lower yield. The presence of an aldehyde at the α position appears to be important for the amine catalyst to be regenerated *via* elimination (see proposed mechanism on page 293). The use of β-nitrostyrene did not generate the desired cycloadduct **242h**, likely due to difficulty at the elimination step. The reaction tolerates aryl and alkyl substituents on the terminal

alkene and these generated the corresponding cycloadducts **242i-m** in good yields and excellent enantioselectivities.



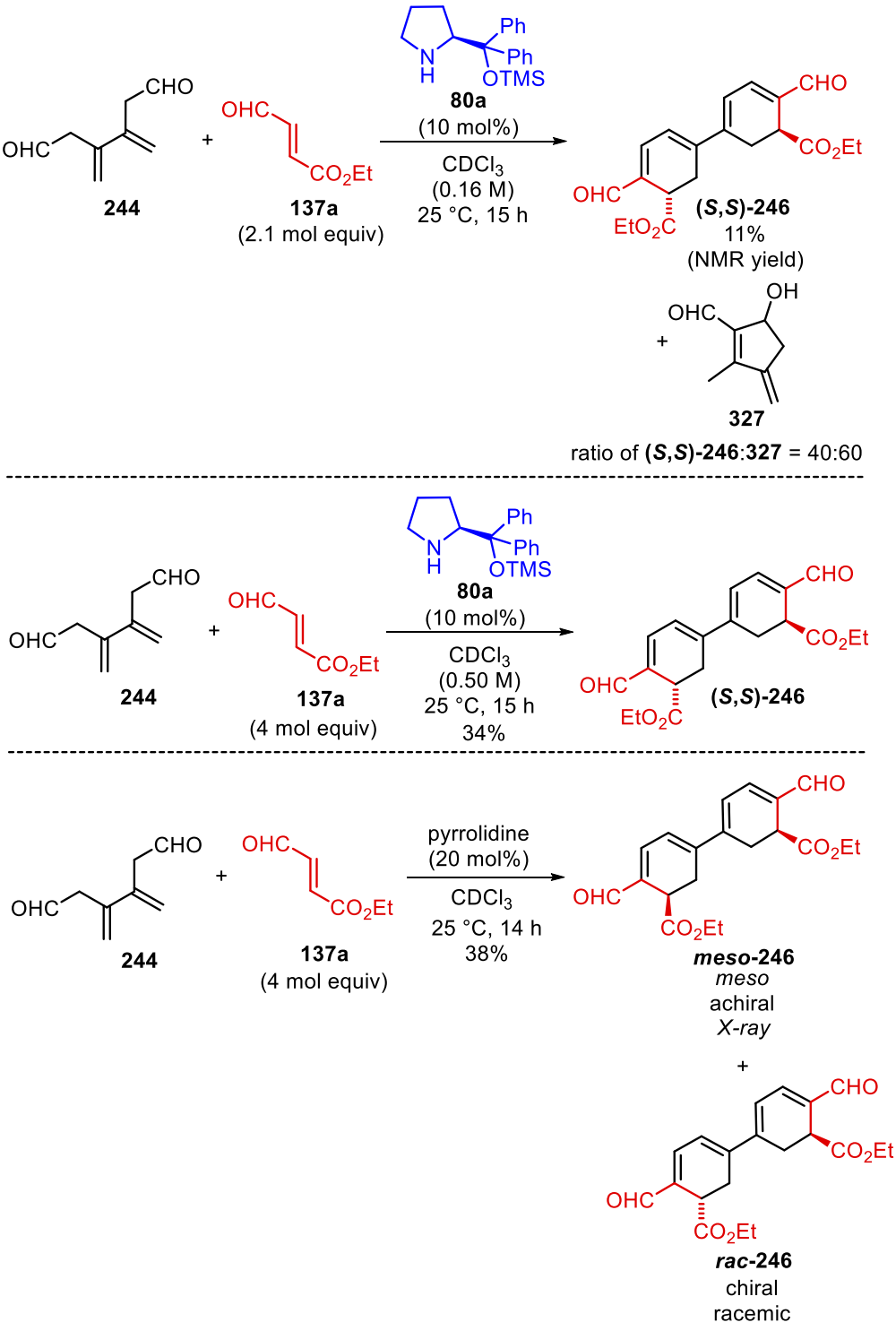
Scheme 3.39 Condensation/Diels-Alder/elimination reaction between skipped dienals **236a-f**, dienophiles **137a-h** and amines **80a-b**

The method was extended to access polycyclic compounds such as pentacycle **313** and tricycle **320** (Scheme 3.40). Further analysis is required to determine the relative configurations of pentacycle **313**.



Scheme 3.40 Synthesis of a) pentacycle **313** *via* a condensation/Diels-Alder/elimination/Wittig/double Diels-Alder reaction sequence and b) tricycle **320** *via* a condensation/Diels-Alder/elimination /Diels-Alder/Wittig reaction sequence

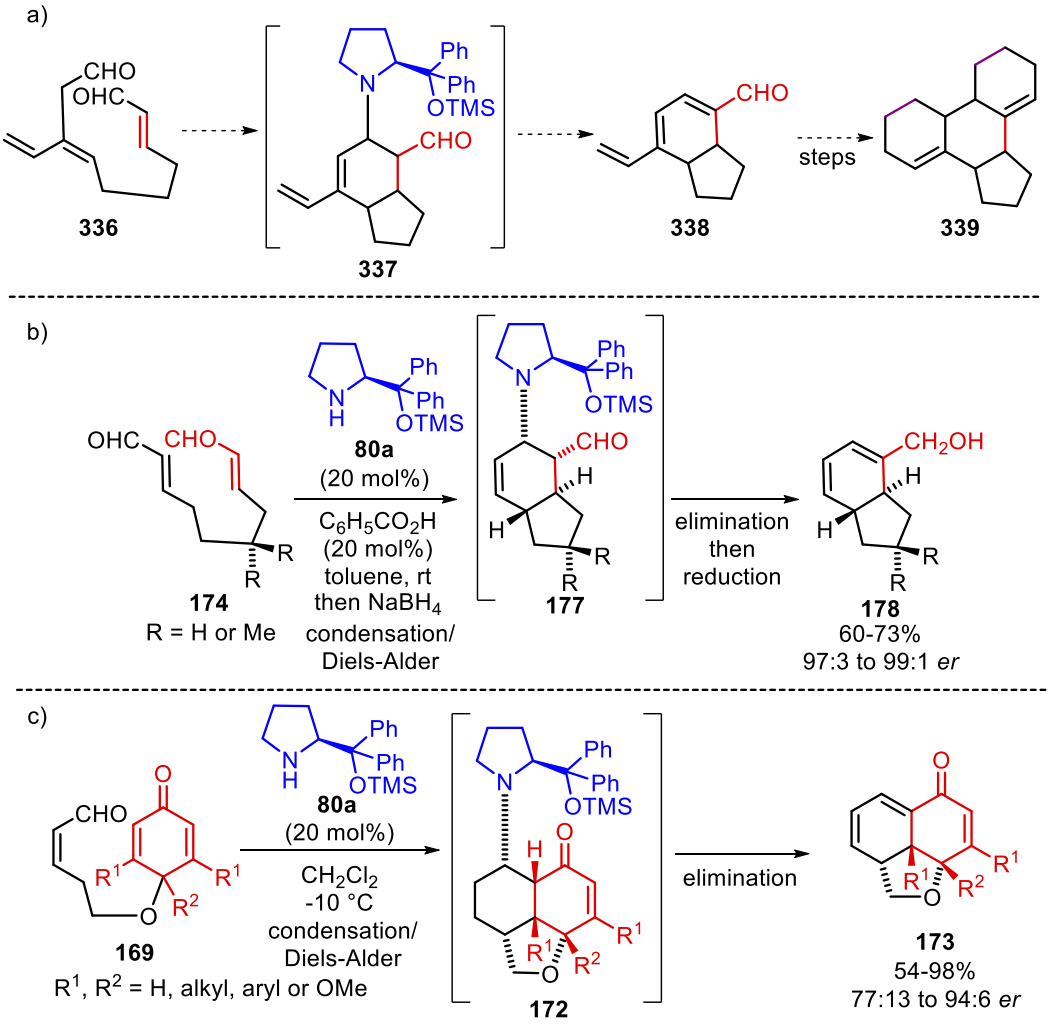
A preliminary attempt at the twofold enantioselective Diels-Alder reaction between diene-dialdehyde **244**, dienophiles **137a** and amine **80a** was successful in producing the desired bicyclic cycloadduct **(*S*,*S*)-246** but in a low yield of 11% (determined by NMR spectroscopy) (Scheme 3.41). A competing intramolecular aldol reaction of diene-dialdehyde **244** generated cyclopentene **327** as an undesired product. By increasing the concentration of the reaction and molar equivalents of dienophile, the intramolecular aldol reaction pathway was disfavoured and the desired cycloadduct was formed in an improved 50% yield (determined by NMR spectroscopy). The racemic material was synthesised with pyrrolidine as the amine catalyst. Attempts to separate the enantiomers of ***meso*-246** by HPLC on chiral stationary phase was not successful thus the enantiomer ratio for cycloadduct **(*S*,*S*)-246** was not determined.



Scheme 3.41 Synthesis of bicycle **246** *via* a twofold condensation/Diels-Alder/elimination reaction between diene-dialdehyde **244**, dienophiles **137a** and amine **80a** or pyrrolidine

3.5 Future Work

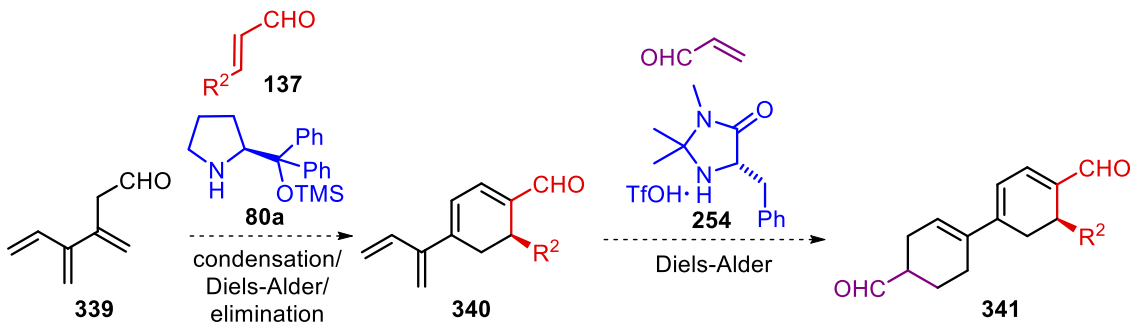
The work in this chapter has focused on intermolecular Diels-Alder reactions. An intramolecular Diels-Alder reaction may be performed with a skipped dienal that is tethered to a dienophile, such as trienal **336** (Scheme 3.42a). This could then be further transformed into polycyclic structures such as tetracycle **339** using the steps shown in Scheme 3.40a. There have been intramolecular examples of similar transformations in the literature with both acyclic[10] (Scheme 3.42b) and cyclic[30] tethered dienophiles (Scheme 3.42c).



Scheme 3.42 Reaction sequences involving intramolecular Diels-Alder reactions a) proposed as an extension of the work described in this chapter b) as reported in the literature with an acyclic dienophile[10] and c) with a cyclic dienophile[30]

Members of the Sherburn group have continued research into the twofold condensation/enantioselective Diels-Alder/elimination reaction between diene-dialdehyde **244**, amine **80a** and various dienophiles. The reactions exhibited high enantioselectivities of >99:1 in line with Horeau principle discussed in Section 3.1.1 (page 282).

It may also be interesting to combine an enamine catalysed Diels-Alder reaction, as described in this chapter, with other modes of catalysis. The condensation/Diels-Alder/elimination reaction sequence between trienal **339**, dienophile **137** and amine **80a** is expected to produce tetraene **340**, which could undergo an iminium catalysed Diels-Alder reaction with MacMillan's catalyst **254** and acrolein to generate bicyclic bis-adduct **341** (Scheme 3.43).



Scheme 3.43 An enamine catalysed Diels-Alder reaction followed by an iminium catalysed Diels-Alder reaction on skipped trienal **339**

3.6 References

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3.7 Experimental Section

3.7.1 General Methods

^{1}H NMR spectra were recorded under standard conditions at 400 MHz or 300 MHz using a *Bruker AVANCE 400*, *Varian MR400* or *Varian Mercury 300* spectrometer. Residual chloroform (δ 7.26 ppm) was used as an internal reference for ^{1}H NMR spectra recorded in this solvent. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignment of proton signals was assisted by COSY and/or HSQC experiments where necessary. ^{13}C NMR spectra were recorded at 100 MHz on a *Bruker AVANCE 400* or V*arian MR400* spectrometer. Chloroform (δ 77.10 ppm) was used as an internal reference for ^{13}C NMR spectra recorded in this solvent. For other solvents, residual solvents were referenced according to Fulmer and co-workers.[1] Assignment of carbon signals was assisted by HSQC and/or HMBC experiments. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer as neat films on sodium chloride plates for oils, potassium bromide discs for solid products or a Perkin–Elmer UATR Two spectrometer as a thin film or solid with only selected peaks being reported as characteristic. Low resolution electron impact (EI) mass spectra were recorded on an Agilent HP 6890 series gas GC/MS with a 7683 series injector. High resolution EI mass spectra were recorded on a Waters AutoSpec Premier spectrometer magnetic sector instrument, operating at 70 eV. Low resolution electrospray ionization (ESI) mass spectra were recorded on a ZMD Micromass spectrometer with Waters Alliance 2690 HPLC. High resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. Positive ionization was employed unless otherwise indicated. Melting points were measured on a Reichert melting point stage or Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Analytical HPLC was conducted using a Waters 600E pump and controller monitored by a Waters 2996 photodiode array detector, or a PDR chiral pump and autosampler monitored by a multi-wavelength detector and a laser polarimeter. Analytical TLC was performed using Merck silica gel plates, pre-coated with silica gel 60 F243 (0.2 mm). Compounds on TLC were visualized by exposure to UV light and/or by dipping the plates in solutions of potassium permanganate followed by heating. Flash chromatography was carried out using Merck Kiesegel 60 (230 – 400 mesh) silica gel. Reactions were conducted open to air unless otherwise indicated. Solvents were dried using a solvent purification system based on that described by Pangborn and co-

workers,[2] or dried using standard laboratory methods.[3] All chemicals were purchased from Sigma Aldrich, Alfa Aesar, Merck or Strem and used without further purification.

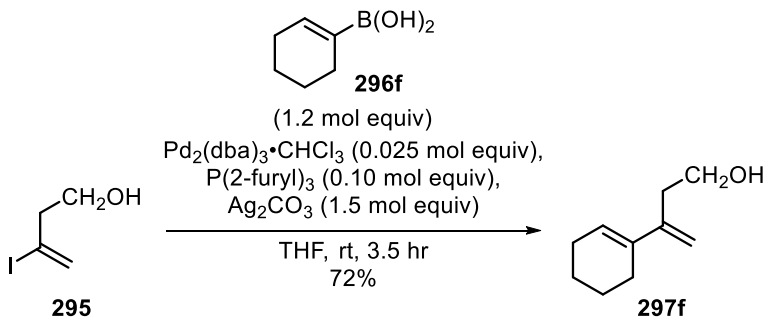
3.7.2 Experimental

3.7.2.1 Synthesis of precursors

Synthesis of skipped dienals **236a-f**

The syntheses of skipped dienals **236a-e** are described in the experimental section of Chapter 2 on pages 63-69.

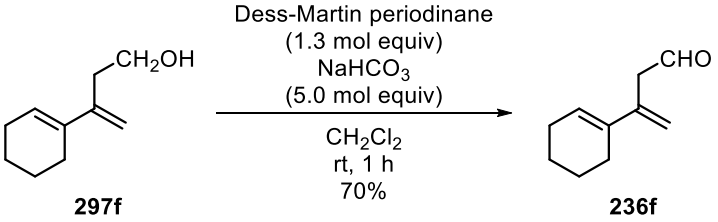
3-(Cyclohex-1-en-1-yl)but-3-en-1-ol **236f**



A mixture of $Pd_2(dba)_3$•$CHCl_3$ (84 mg, 0.81 mmol, 0.025 mol equiv), tri(2-furyl)phosphine (75 mg, 0.32 mmol, 0.10 mol equiv), silver carbonate (1.34 g, 4.86 mmol, 1.5 mol equiv) and boronic acid **296f** (490 mg, 3.89 mmol, 1.2 mol equiv) were placed in a round-bottom flask. The flask was purged under reduced pressure (0.1 mmHg) and back-filled with argon three times. A solution of iodide **297f** (642 mg, 3.24 mmol) in freshly degassed THF (32 mL) was cannulated into the mixture and stirred at rt until the iodide was completely consumed (3.5 h). The reaction mixture was diluted with CH_2Cl_2 and saturated aqueous sodium bicarbonate solution and filtered through Celite. The organic layer was collected while the aqueous layer was re-extracted with CH_2Cl_2 three times. The combined organic layers were dried over potassium carbonate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with petrol/EtOAc/Et_3N (85:15:1 to 80:20:1 to 70:30:1) provided the *title compound* (357 mg, 2.35 mmol, 72%) as a yellow oil: R_f 0.22 petrol/EtOAc/Et_3N (80:20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (s, 1H), 5.08 (s, 1H), 4.88 (s, 1H), 3.78 – 3.64 (m, 2H), 2.54 (t, J = 6.4 Hz, 2H), 2.22 – 2.10 (m, 4H), 1.72 –

1.63 (m, 2H), 1.61 – 1.54 (m, 2H), 1.47 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7 (C), 135.4 (C), 125.3 (CH), 111.2 (CH_2), 61.7 (CH_2), 37.0 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 22.9 (CH_2), 22.2 (CH_2) ppm; IR (UATR): ν_{max} = 3340 (broad), 2928, 2859, 2835 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 152 (62) $[M]^{+\bullet}$, 121 (100), 81 (60); HRMS: calc for $C_{10}H_{16}O$ $[M]^{+\bullet}$: 152.1201; found 152.1204.

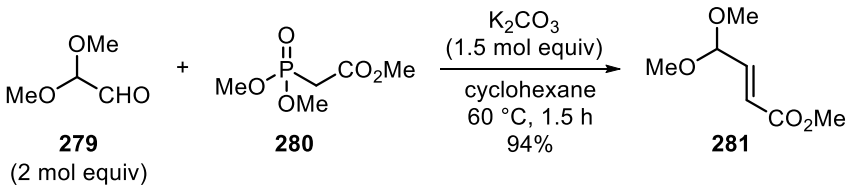
3-(Cyclohex-1-en-1-yl)but-3-enal **236f**



To a solution of dienol **297f** (325 mg, 2.13 mmol) in CH_2Cl_2 (60 mL) was added $NaHCO_3$ (895 mg, 10.6 mmol, 5.0 mol equiv) then Dess-Martin periodinane (1.17 g, 2.77 mmol, 1.3 mol equiv) in portions. The reaction mixture was stirred at rt until complete consumption of the alcohol as indicated by TLC (1 h). The reaction mixture was diluted with diethyl ether and washed with a solution of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$/H_2O (1:1:1). The organic layer was collected while the aqueous layer was re-extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to provide the *title compond* (224 mg, 1.49 mmol, 70%) as a colourless oil, which was used without further purification: R_f 0.55 petrol/EtOAc (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 – 9.52 (t, 1H), 5.77 (s, 1H), 5.24 (s, 1H), 4.98 (s, 1H), 3.25 (s, 2H), 2.27 – 2.17 (m, 2H), 2.16 – 2.08 (m, 2H), 1.71 – 1.62 (m, 2H), 1.60 – 1.51 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4 (CH), 139.6 (C), 135.7 (C), 127.0 (CH), 113.9 (CH_2), 49.3 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 22.7 (CH_2), 22.0 (CH_2) ppm; IR (thin film): ν_{max} = 2928, 2859, 2834, 1723 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 150 $[M]^{+\bullet}$ (51), 121 (100); HRMS: calc for $C_{10}H_{14}O$ $[M]^{+\bullet}$: 150.1045; found 150.1045.

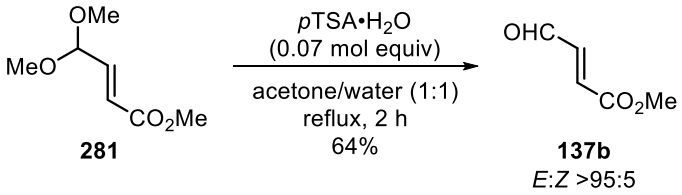
Synthesis of dienophiles **137b-h**

Methyl (*E*)-4,4-dimethoxybut-2-enoate **281**



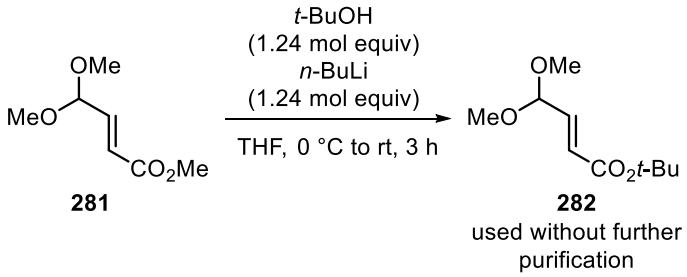
The *title compound* was prepared using a literature procedure.[4] This reaction was conducted under argon. A mixture of phosphonoacetate **280** (2.67 mL, 16.6 mmol) and potassium carbonate (3.42 g, 24.8 mmol, 1.5 mol equiv) in cyclohexane (20 mL) was heated to 60 ºC for 30 min before being cooled to rt. Dimethoxyacetaldehyde **279** (5.0 mL of a 60% mol wt in H_2O solution, 32.9 mmol, 2 mol equiv) was added and the mixture was heated to 60 ºC for 1.5 h before being cooled to rt. The reaction mixture was added to saturated aqueous ammonium chloride solution/Et_2O (1:1). The aqueous layer was extracted three times with Et_2O and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to provide the *title compound* (2.91 g, 15.4 mmol, 94%) as a colourless oil. The ^{1}H NMR spectroscopic data matched those previously reported.[4]

Methyl (*E*)-4-oxobut-2-enoate **137b**



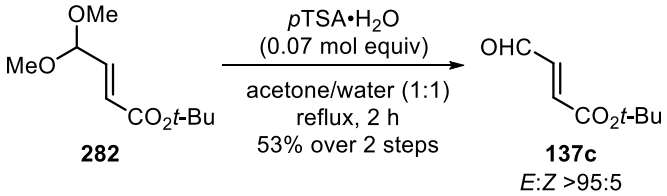
The *title compound* was prepared using a literature procedure.[4] *p*TSA•H_2O (205 mg, 1.08 mmol, 0.07 mol equiv) was added to a solution of dimethoxy methyl ester **281** (2.91 g, 15.4 mmol) in H_2O/acetone (1:1, 70 mL). The solution was heated to reflux for 2 h before being cooled to rt and poured into saturated aqueous sodium bicarbonate solution/Et_2O (1:1). The mixture was concentrated under reduced pressure and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to provide the *title compound* (1.12 g, 9.82 mmol, 64%) as a pale yellow solid. The ^{1}H NMR spectroscopic data matched those previously reported.[4]

tert-Butyl (*E*)-4,4-dimethoxybut-2-enoate **282**



The *title compound* was prepared using a modified literature procedure.[5] A solution of *t*-butanol (0.304 mL, 3.18 mmol, 1.24 mol equiv) in THF (5 mL) was cooled in an ice bath. *n*-BuLi (2.18 mL of a 1.46 M hexanes solution, 3.18 mmol, 1.24 mol equiv) was added to the solution followed by a solution of dimethoxy methyl ester **281** (482 mg, 2.56 mmol) in THF (1 mL). The reaction mixture was warmed to rt and stirred at rt for 3 h. The reaction mixture was poured into H_2O/Et_2O (1:1) and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to provide the *title compound* as a colourless oil, which was used without further purification. The ^1H NMR spectroscopic data matched those previously reported.[6]

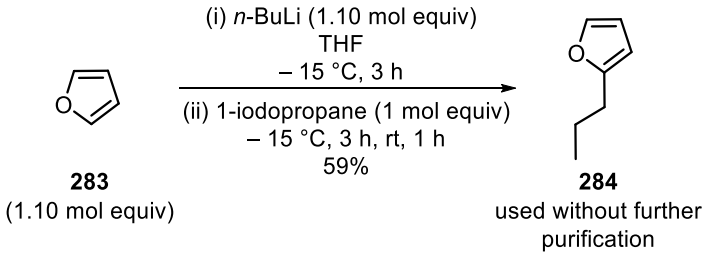
tert-Butyl (*E*)-4-oxobut-2-enoate **137c**



The *title compound* was prepared using a modified literature procedure.[4] *p*TSA•H_2O (31 mg, 0.165 mmol, 0.07 mol equiv) was added to a solution of dimethoxy *t*-butyl ester **282** (476 mg, 2.35 mmol) in H_2O/acetone (1:1, 10 mL). The solution was heated to reflux (oil bath set to 80 ºC) for 2 h before being cooled to rt and poured into saturated aqueous sodium bicarbonate solution/Et_2O (1:1). The mixture was concentrated under reduced pressure and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with

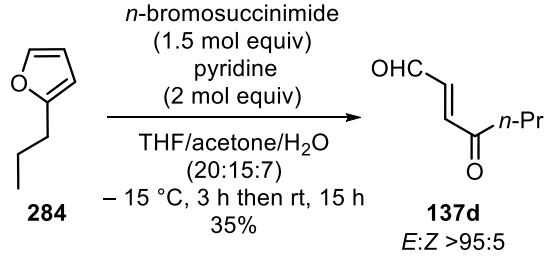
hex/Et_2O (80:20) provided the *title compound* (174 mg, 1.36 mmol, 53% over 2 steps) as a yellow oil. The ^1H NMR spectroscopic data matched those previously reported.[7]

2-*n*-Propylfuran **284**



The *title compound* was prepared using a modified literature procedure. *n*-BuLi (31.0 mL of a 1.54 M hexanes solution, 48.5 mmol, 1.10 mol equiv) was added to a solution of furan (**283**) (3.54 mL, 48.5 mmol, 1.10 mol equiv) in THF (180 mL) at – 15 ºC and the reaction mixture was stirred for 3 hours. 1-Iodopropane (4.30 mL, 44.1 mmol) was added dropwise and the mixture was stirred at at –15 ºC for 1.5 h before being warmed to rt, stirred at rt for 1 h and quenched with water. The aqueous layer was extracted three times with pentane/Et_2O (1:1). The combined organic layers were washed with aqueous 5% sodium sulfite solution, water and brine successively, dried over sodium sulfate and concentrated under reduced pressure in an ice bath. The *title compound* was obtained as a solution in THF (2.86 g of 2-*n*-propylfuran (**284**) in 0.55 mL of THF, 59%), which was used without further purification. The ^1H NMR spectroscopic data matched those previously reported.[8]

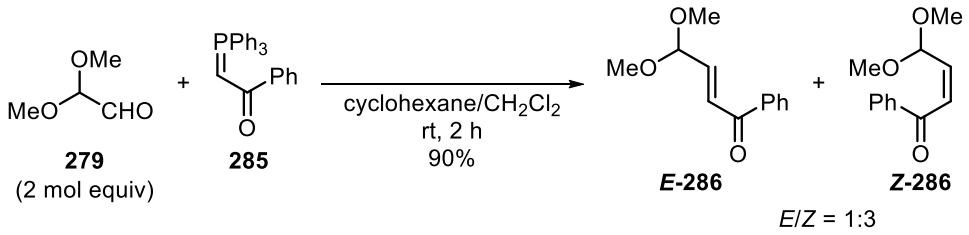
(*E*)-4-Oxohept-2-enal **137d**



The *title compound* was prepared using a literature procedure.[9] A solution of 2-*n*-propyl furan (**284**) (1.40 g, 12.7 mmol) in THF/acetone/water (42 mL, 20:15:7) was cooled to –15 ºC. *n*-Bromosuccinimide (3.40 g, 19.1 mmol, 1.5 mol equiv) was added followed by pyridine (2.05 mL, 25.4 mmol, 2 mol equiv). The reaction mixture was

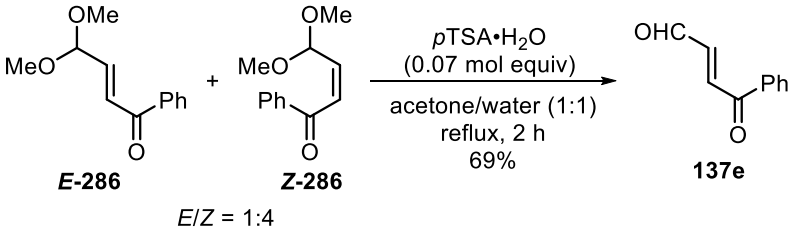
stirred at –15 ºC for 3 hours before being warmed to rt, stirred at rt for 15 h and poured into a mixture of 0.5 M aqueous HCl/Et_2O (3:2). The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with pentane/diethyl ether (70:30) provided the *title compound* (560 mg, 4.45 mmol, 35%) as a colourless oil. The ^{1}H NMR spectroscopic data matched those previously reported.[10]

4,4-Dimethoxy-1-phenylbut-2-en-1-one **286**



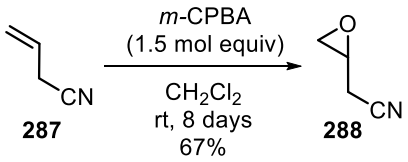
The *title compound* was prepared using a modified literature procedure.[4] This reaction was conducted under argon. A solution of phosphorane **285** (1.00 g, 2.63 mmol) and dimethoxyacetaldehyde **279** (0.79 mL of a 60% mol wt in H_2O solution, 5.26 mmol, 2 mol equiv) in cyclohexane/CH_2Cl_2 (1:1, 10 mL) was stirred at rt for 2 h. The reaction mixture was added to H_2O/Et_2O (1:1). The aqueous layer was extracted three times with Et_2O and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with hex/EtOAc (100:0 then 80:20) provided the *title compounds* as a mixture (490 mg, 2.38 mmol, 90%, ratio of *E*:*Z* = 1:4) as a yellow oil: R_f 0.51 hex/EtOAc (70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.91 (m, 8H, ***Z*-286** and ***E*-286**), 7.63 – 7.55 (m, 4H, ***Z*-286** and ***E*-286**), 7.48 (m, 8H, ***Z*-286** and ***E*-286**), 7.21 (dd, J = 15.6, 1.5 Hz, 3H, ***Z*-286**), 6.89 (dd, J = 12.1, 1.1 Hz, 1H, ***E*-286**), 6.83 (dd, J = 15.6, 3.7 Hz, 3H, ***Z*-286**), 6.16 (dd, J = 12.0, 6.9 Hz, 1H, ***E*-286**), 5.49 (dd, J = 7.0, 1.1 Hz, 1H, ***E*-286**), 5.07 (dd, J = 3.8, 1.4 Hz, 3H, ***Z*-286**), 3.38 (s, 24H, ***Z*-286** and ***E*-286**).

(*E*)-4-Oxo-4-phenylbut-2-enal **137e**



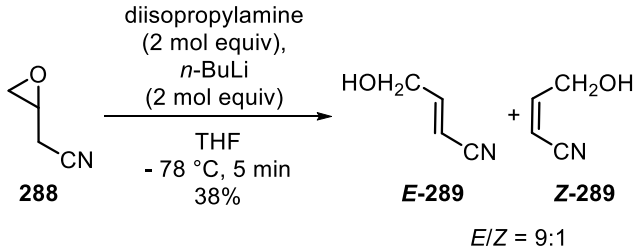
*p*TSA•H_2O (32 mg, 0.167 mmol, 0.07 mol equiv) was added to a solution of dimethoxy phenyl ***E*-286** and ***Z*-286** (490 mg, 2.38 mmol, ratio of *E*:*Z* = 1:4) in H_2O/acetone (1:1, 10 mL). The solution was heated to reflux (oil bath set to 80 ºC) for 2 h before being cooled to rt and poured into saturated aqueous sodium bicarbonate solution/Et_2O (1:1). The mixture was concentrated under reduced pressure and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with hex/Et_2O (100:0 to 60:40) provided the *title compound* (264 mg, 1.65 mmol, 69%) as an orange solid. The ^{1}H NMR spectroscopic data matched those previously reported.[11]

2-(Oxiran-2-yl)acetonitrile **288**



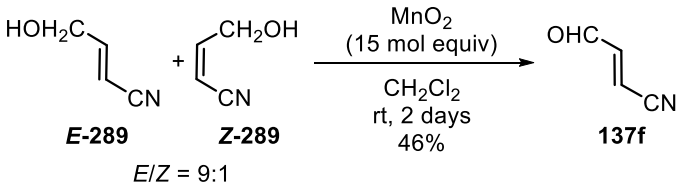
The *title compound* was prepared using a literature procedure.[12] To a solution of allylcyanide (**287**) (2.00 g, 29.8 mmol) in dichloromethane (60 mL) was added *m*CPBA (70% purity, 5.51 g, 44.8 mmol, 1.5 mol equiv) with 1/8 of the total amount (1.38 g) added each day over a period of 8 days. The reaction mixture was then cooled in ice and saturated aqueous sodium sulfite solution was added portionwise. The mixture was left to stir until 2 clear layers remained before the organic layer was separated, washed three times with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under reduced vacuum. Purification by flash column chromatography on silica gel eluting with petrol/Et_2O (80:20 then 0:100) provided the *title compound* (1.65 g, 19.9 mmol, 67%) as a colourless oil. The ^{1}H NMR spectroscopic data matched those previously reported.[13]

4-Hydroxybut-2-enenitrile **289**



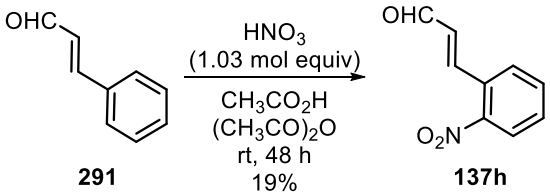
The *title compound* was prepared using a literature procedure.[12] A solution of diisopropylamine (6.20 mL, 44.3 mmol, 2.0 mol equiv) in THF (40 mL) was cooled to –78 ºC in a dry ice/acetone bath. *n*-BuLi (28.0 mL of a 1.56 M hexanes solution, 44.3 mmol, 2.0 mol equiv) was added and the solution was stirred for 10 minutes. A solution of nitrile **288** (1.84 g, 22.1 mmol) in THF (18 mL) was added to the LDA solution at –78 ºC, resulting in the formation of a thick yellow precipitate. Following the addition of acetic acid (5 mL) and ethyl acetate (60 mL), the mixture was filtered through a short pad of silica gel, which was rinsed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with petrol/ethyl acetate (70:30 then 60:40) provided the *title compound* (695 mg, 8.36 mmol, 38%, *E*:*Z* = 9:1) as a colourless oil. The ^{1}H NMR spectroscopic data matched those previously reported.[14]

(*E*)-4-oxobut-2-enenitrile **137g**



Manganese dioxide (10.9 g, 8.36 mmol, 15.0 mol equiv) was added to a solution of allylic alcohol **289** (695 mg, 8.36 mmol, *E*:*Z* = 9:1) in dichloromethane (40 mL). The mixture was stirred at rt for 2 days then filtered through Celite, concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with petrol/ether (60:40) to provide the *title compound* as a red oil (321 mg, 3.86 mmol, 46%). The ^{1}H NMR spectroscopic data matched those previously reported.[14]

(*E*)-3-(2-nitrophenyl)acrylaldehyde **137h**

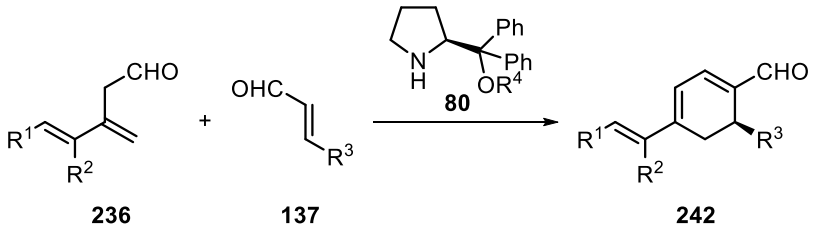


The *title compound* was prepared using a literature procedure.[15] A solution of *E*-cinnamaldehyde (**291**) (27 mL, 0.227 mol) in acetic anhydride (120 mL) was cooled in an ice-salt bath. A solution of nitric acid (9.7 mL, 0.233 mol, 1.03 mol equiv) in acetic acid (27 mL) was added dropwise while maintaining the internal temperature of the reaction mixture below 5 ºC. The reaction mixture was warmed to rt and left to stand at rt for two days after which it is cooled in an ice bath and 2 M hydrochloric acid solution (300 mL) was added in portions. The mixture was then left at rt for three days and the yellow needles formed were collected. This was repeated twice to obtain two more batches of product. The combined product was recrystallised from hot ethanol to provide the title compound (7.7 g, 0.0435 mol, 19%) as pale yellow needles. The ^{1}H NMR spectroscopic data matched those previously reported.[16]

3.7.2.2 Condensation/Diels-Alder/elimination reaction sequence

Synthesis of mono-adducts **242a-m**

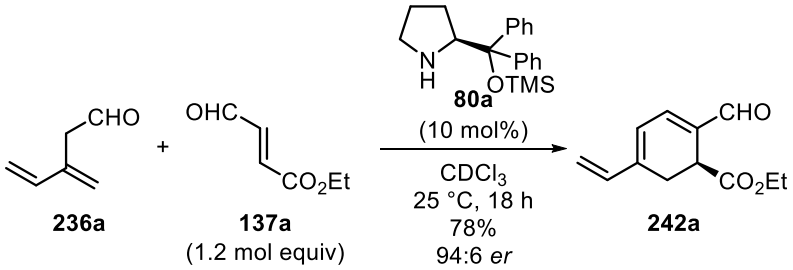
General procedure:



To a solution of skipped dienal **236** (1.0 mol equiv, unless otherwise specified) in $CDCl_3$ was added the dienophile **137** (1.2 mol equiv, unless otherwise specified) followed by the amine catalyst **80** (10 mol%, unless otherwise specified). The resulting mixture was transferred into an NMR tube, shaken briefly then held at 25 ºC until complete consumption of the skipped dienal **236** was observed by ^{1}H NMR spectroscopy. The reaction mixture was concentrated under reduced pressure then

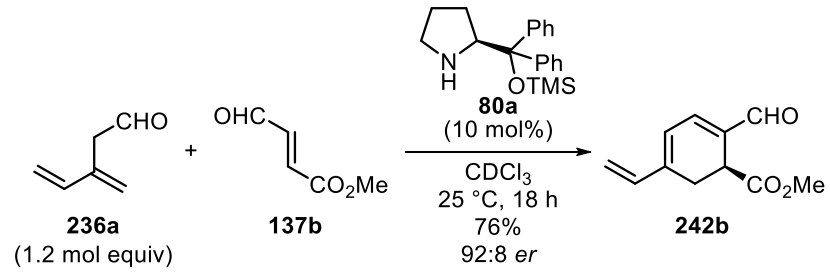
purified by flash column chromatography on silica gel (30 x crude material mass) to provide the product. Racemic material was prepared in the same manner using pyrrolidine (20 mol%) as the amine catalyst with comparable yields. (Mono-adducts **242a-m** should be concentrated under reduced pressure at a temperature of 25 ºC or lower to minimise decomposition.)

Ethyl (*S*)-2-formyl-5-vinylcyclohexa-2,4-diene-1-carboxylate **242a**



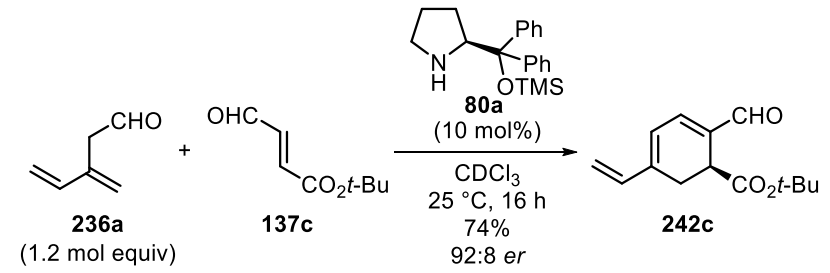
Prepared using skipped dienal **236a** (15 mg, 0.156 mmol), dienophile **137a** (24 mg, 0.187 mmol, 1.2 mol equiv) and amine **80a** (5 mg, 0.0156 mmol, 10 mol%). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (10:90:1 then 20:80:1) provided the *title compound* (25 mg, 0.121 mmol, 78%) as a yellow oil: R_f 0.12 hex/Et_2O (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1 H), 6.97 (d, J = 5.6 Hz, 1 H), 6.49 (dd, J = 17.5, 10.7 Hz, 1 H), 6.18 (dd, J = 5.6, 2.1 Hz, 1 H), 5.57 (d, J = 17.3 Hz, 1 H), 5.36 (d, J = 10.6 Hz, 1 H), 4.01 - 4.15 (m, 2 H), 3.78 (dd, J=9.4, 3.7 Hz, 1 H), 3.17 (dd, J = 17.6, 3.7 Hz, 1 H), 2.50 (dd, J = 17.6, 9.4 Hz, 1 H), 1.18 (t, J = 7.2 Hz, 3 H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1 (CH), 172.2 (C), 144.0 (C), 143.3 (CH), 137.1 (CH), 135.3 (C), 123.4 (CH), 118.1 (CH_2), 61.2(CH_2), 35.2 (CH), 25.4 (CH_2), 14.1 (CH_3) ppm; IR (thin film): ν_{max} = 2981, 2814, 2720, 1730, 1670, 1548 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 206 (9) $[M]^{+\bullet}$, 177 (86), 133 (100); HRMS: calc for $C_{12}H_{14}O_3$ $[M]^{+\bullet}$: 206.0943; found 206.0946; $[\alpha]_D$ = –215 (*c* 1.2, MeOH); e.r. 94:6, determined by chiral HPLC (Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 60:40, 1 mL/min), minor (+) enantiomer t_R = 5.7 min, major (–) enantiomer t_R = 16.0 min.

Methyl (*S*)-2-formyl-5-vinylcyclohexa-2,4-diene-1-carboxylate **242b**



Prepared using skipped dienal **236a** (23 mg, 0.24 mmol, 1.2 mol equiv), dienophile **137b** (23 mg, 0.20 mmol) and amine **80a** (6.5 mg, 0.020 mmol, 10 mol%). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (80:20:1 then 70:30:1) provided the *title compound* (29 mg, 0.15 mmol, 76%) as a yellow oil: R_f 0.14 hex/Et_2O (70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 6.99 (d, J = 5.8 Hz, 1H), 6.50 (dd, J = 17.5, 10.7 Hz, 1H), 6.19 (d, J = 5.8 Hz, 1H), 5.60 (d, J = 17.5 Hz, 1H), 5.38 (d, J = 10.7 Hz, 1H), 3.82 (dd, J = 9.4, 3.5 Hz, 1H), 3.65 (s, 3H), 3.19 (dd, J = 17.7, 3.6 Hz, 1H), 2.52 (dd, J = 17.4, 9.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1 (CH), 172.8 (C), 144.2 (C), 143.4 (CH), 137.0 (CH), 135.0 (C), 123.4 (CH), 118.3 (CH_2), 52.5 (CH_3), 35.0 (CH) , 25.3 (CH_3) ppm; IR (thin film): ν_{max} = 3007, 2952, 2819, 2722, 1733, 1670, 1548 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 192 (30) $[M]^{+\bullet}$, 133 (100), 79 (35); HRMS: calc for $C_{11}H_{12}O_3$ $[M]^{+\bullet}$: 192.0786; found 192.0788; $[\alpha]_D$ = –159 (*c* 0.93, MeOH); e.r. 8:92, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 70:30, 1 mL/min), minor (+) enantiomer t_R = 7.6 min, major (–) enantiomer t_R = 16.7 min.

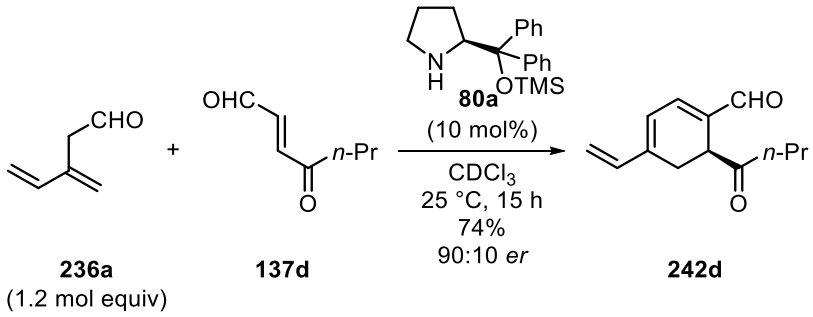
tert-Butyl (*S*)-2-formyl-5-vinylcyclohexa-2,4-diene-1-carboxylate **242c**



Prepared using skipped dienal **236a** (21 mg, 0.22 mmol, 1.2 mol equiv), dienophile **137c** (23 mg, 0.18 mmol) and amine **80a** (5.9 mg, 0.018 mmol, 10 mol%). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (90:10:1)

provided the *title compound* (31 mg, 0.13 mmol, 74%) as a yellow oil: R_f 0.13 hex/Et_2O (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 6.95 (d, J = 5.7 Hz, 1H), 6.50 (dd, J = 17.5, 10.7 Hz, 1H), 6.17 (dd, J = 6.0, 2.3 Hz, 1H), 5.58 (d, J = 17.3 Hz, 1H), 5.36 (d, J = 10.7 Hz, 1H), 3.70 (dd, J = 9.3, 3.3 Hz, 1H), 3.14 (dd, J = 17.6, 3.3 Hz, 1H), 2.45 (ddd, J = 17.7, 9.3, 2.4 Hz, 1H), 1.37 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1 (CH), 171.3 (C), 144.0 (C), 142.9 (CH), 137.2 (CH), 136.1 (C), 123.4 (CH), 117.9 (CH_2), 81.3 (C), 36.1 (CH), 27.9 (CH_3), 25.4 (CH_2) ppm; IR (thin film): ν_{max} = 2977, 2932, 2811, 2718, 1727, 1671, 1548 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 234 (10) $[M]^{+\bullet}$, 133 (42), 79 (18); HRMS: calc for $C_{14}H_{18}O_3$ $[M]^{+\bullet}$: 234.1256; found 234.1555; $[\alpha]_D$ = –328 (*c* 1.2, MeOH); e.r. 92:8, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 80:20, 1 mL/min), minor (+) enantiomer t_R = 4.7 min, major (–) enantiomer t_R = 8.4 min.

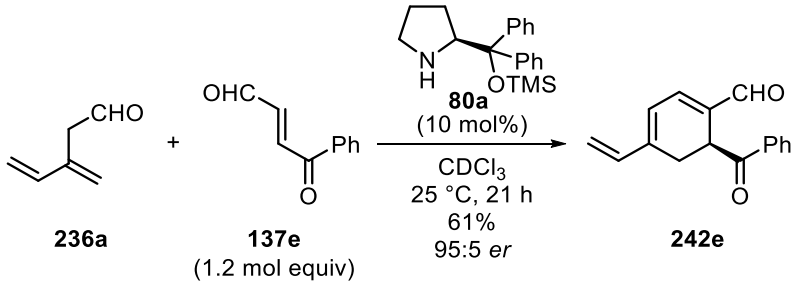
(*S*)-6-Butyryl-4-vinylcyclohexa-1,3-diene-1-carbaldehyde **242d**



Prepared using skipped dienal **236a** (46 mg, 0.476 mmol, 1.2 mol equiv), dienophile **137d** (50 mg, 0.396 mmol) and amine **80a** (13 mg, 0.040 mmol, 10 mol%). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (90:10:1 then 80:20:1) provided the *title compound* (60 mg, 0.29 mmol, 74%) as a yellow oil: R_f 0.25 petrol/Et_2O (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.00 (d, J = 5.8 Hz, 1H), 6.47 (dd, J = 17.5, 10.7 Hz, 1H), 6.13 (dd, J = 5.9, 2.3 Hz, 1H), 5.62 (d, J = 17.5 Hz, 1H), 5.38 (d, J = 10.7 Hz, 1H), 3.74 (dd, J = 9.3, 3.2 Hz, 1H), 3.14 (dd, J = 17.7, 3.2 Hz, 1H), 2.51 – 2.35 (m, 3H), 1.53 (h, J = 7.2 Hz, 2H), 0.84 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4 (CH), 191.6 (C), 145.4 (C), 145.0 (CH), 137.1 (CH), 135.8 (C), 123.2 (CH), 118.5 (CH_2), 42.2 (CH_2), 42.1 (CH), 24.5 (CH_2), 17.1 (CH_2), 13.7 (CH_3) ppm; IR (thin film): ν_{max} = 2962, 2932, 2874, 1709, 1666, 1544 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 204 (10) $[M]^{+\bullet}$, 105 (49), 79 (25), 77 (63), 71 (100); HRMS: calc for $C_{13}H_{16}O_2$ $[M]^{+\bullet}$: 204.1150; found 204.1151; $[\alpha]_D$ = –186 (*c* 0.44, MeOH); e.r. 90:10,

determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 80:20, 1 mL/min), minor (+) enantiomer t_R = 7.9 min, major (–) enantiomer t_R = 35.9 min.

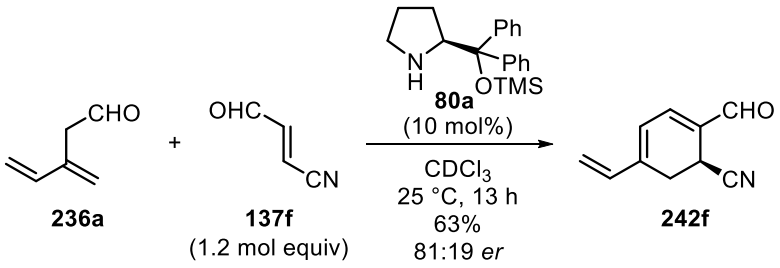
(*S*)-6-Benzoyl-4-vinylcyclohexa-1,3-diene-1-carbaldehyde **242e**



236a **137e** (1.2 mol equiv) **242e**

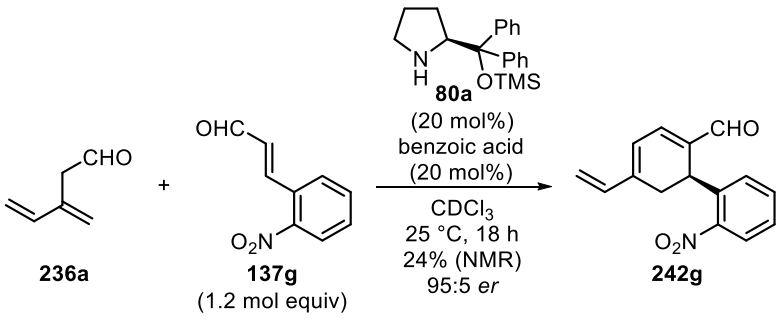
Prepared using skipped dienal **236a** (17 mg, 0.177 mmol), dienophile **137e** (34 mg, 0.212 mmol, 1.2 mol equiv) and amine **80a** (6.6 mg, 0.018 mmol, 10 mol%). Purification by flash column chromatography on silica gel eluting with hex/Et_2O (80:20) provided the *title compound* (26 mg, 0.108 mmol, 61%) as a dark yellow oil: R_f 0.10 hex/Et_2O (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.99 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.1 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.12 (d, J = 5.9 Hz, 1H), 6.47 (dd, J = 17.5, 10.7 Hz, 1H), 6.22 (d, J = 5.9 Hz, 1H), 5.35 (d, J = 17.5 Hz, 1H), 5.26 (d, J = 10.7 Hz, 1H), 4.74 (dd, J = 10.5, 5.5 Hz, 1H), 2.90 (dd, J = 18.0, 5.5 Hz, 1H), 2.80 (ddd, J = 18.4, 10.7, 2.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0 (CH), 191.1 (C), 144.8 (CH), 142.7 (C), 137.2 (CH), 136.2 (C), 135.5 (C), 133.2 (CH), 128.8 (CH), 128.8 (CH), 123.5 (CH), 117.6 (CH_2), 37.8 (CH), 26.3 (CH_2) ppm; IR (UATR): ν_{max} = 2924, 2817, 2722, 1681, 1662, 1553 cm^{-1}; MS (70 eV, EI): m/z (%): 238 (17) $[M]^{+\bullet}$, 105 (100), 77 (55); HRMS: calc for $C_{16}H_{14}O_2$ $[M]^{+\bullet}$: 238.0994; found 238.0994; $[\alpha]_D$ = –202 (*c* 0.68, MeOH); e.r. 5:95, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 30:70, 1 mL/min), minor (+) enantiomer t_R = 12.0 min, major (–) enantiomer t_R = 21.7 min.

(*S*)-2-formyl-5-vinylcyclohexa-2,4-diene-1-carbonitrile **242f**



Prepared using skipped dienal **236a** (27 mg, 0.286 mmol, 1.2 mol equiv), dienophile **137f** (19 mg, 0.238 mmol) and amine **80a** (8 mg, 0.024 mmol, 0.10 mol equiv). Purification by flash column chromatography on silica gel eluting with hex/Et_2O (80:20 to 40:60) provided the *title compound* (24 mg, 0.15 mmol, 63%) as a yellow oil: R_f 0.21 hex/Et_2O (40:60); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.10 (d, J = 5.9 Hz, 1H), 6.57 (dd, J = 17.5, 10.8 Hz, 1H), 6.34 (d, J = 5.9 Hz, 1H), 5.59 (d, J = 17.5 Hz, 1H), 5.48 (d, J = 10.8 Hz, 1H), 4.05 (d, J = 8.7 Hz, 1H), 3.03 (dt, J = 17.9, 1.6 Hz, 1H), 2.55 (dd, J = 17.8, 8.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2 (CH), 144.2 (CH), 143.3 (C), 136.5 (CH), 130.9 (C), 123.4 (CH), 119.6 (CH_2), 118.7 (C), 26.2 (CH_2), 20.8 (CH) ppm; IR (UATR): ν_{max} = 2928, 2832, 2730, 2238, 1668, 1546 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 159 (100) $[M]^{+\bullet}$, 132 (47), 130 (99); HRMS: calc for $C_{10}H_9NO$ $[M]^{+\bullet}$: 159.0684; found 159.0678; $[\alpha]_D$ = –61 (*c* 0.68, MeOH); e.r. 81:19, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 60:40, 1 mL/min), minor (+) enantiomer t_R = 10.8 min, major (–) enantiomer t_R = 12.2 min.

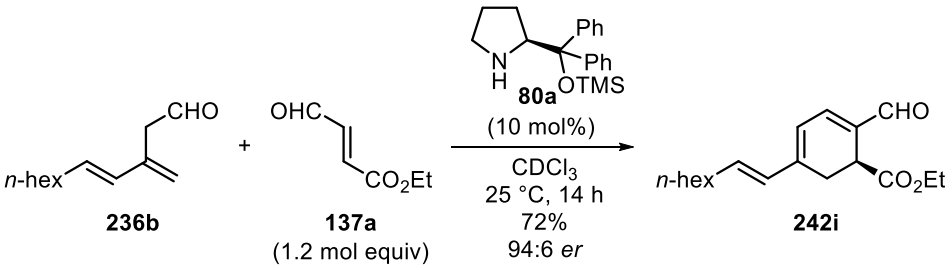
(*R*)-2'-Nitro-5-vinyl-1,6-dihydro-[1,1'-biphenyl]-2-carbaldehyde **242g**



Prepared using skipped dienal **236a** (15 mg, 0.156 mmol), dienophile **137g** (33 mg, 0.187 mmol, 1.2 mol equiv), amine **80a** (10 mg, 0.016 mmol, 20 mol%) and benzoic acid (2 mg, 0.016 mmol 20 mol%). The yield of the reaction, as estimated by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard, was 24%. Purification by

flash column chromatography on silica gel eluting with hex/Et_2O (90:10 then 80:20) provided cycloadduct **242g** as a mixture with dienophile **137g**. Further purification by flash column chromatography on silica gel eluting with hex/Et_2O (90:10) provided an analytical sample of the *title compound* as a yellow oil: R_f 0.25 hex/EtOAc (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.87 (dd, J = 8.1, 1.4 Hz, 1H), 7.41 (td, J = 7.6, 1.5 Hz, 1H), 7.32 (td, J = 8.0, 1.4 Hz, 1H), 7.22 (dd, J = 7.8, 1.5 Hz, 1H), 7.17 (d, J = 5.9 Hz, 1H), 6.49 (dd, J = 17.5, 10.7 Hz, 1H), 6.29 (dd, J = 5.9, 2.4 Hz, 1H), 5.44 (d, J = 17.4 Hz, 1H), 5.28 (d, J = 10.7 Hz, 1H), 4.72 (dd, J = 11.0, 3.4 Hz, 1H), 3.00 (ddd, J = 18.4, 11.1, 2.4 Hz, 1H), 2.90 (dd, J = 18.4, 3.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1 (CH), 148.9 (C), 144.2 (CH), 143.6 (C), 138.3 (C), 137.3 (CH), 137.0 (C), 133.0 (CH), 129.0 (CH), 127.7 (CH), 125.0 (CH), 123.1 (CH), 118.4 (CH_2), 30.1 (CH_2), 29.6 (CH) ppm; IR (UATR): ν_{max} = 2818, 2720, 1663, 1549, 1521 cm^{-1}; MS (ESI): m/z (%): 278 (100) $[M+Na]^{+\bullet}$; HRMS: calc for $C_{15}H_{13}NO_3Na$ $[M]^{+\bullet}$: 278.0793; found 278.0792; e.r. 95:5, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 90:10, 1 mL/min), minor (+) enantiomer t_R = 25.9 min, major (–) enantiomer t_R = 28.6 min.

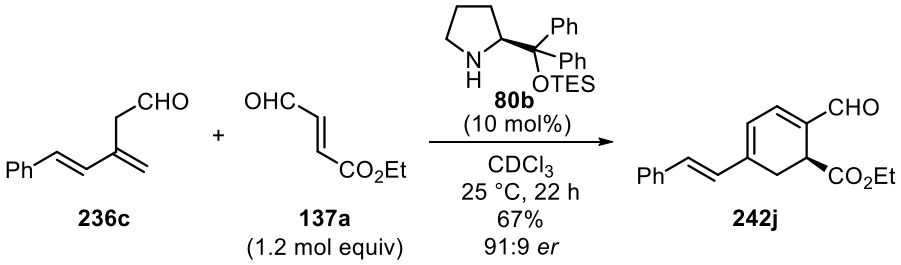
Ethyl (*S*,*E*)-2-Formyl-5-(oct-1-en-1-yl)cyclohexa-2,4-diene-1-carboxylate **242i**



Prepared using skipped dienal **236b** (24 mg, 0.133 mmol), dienophile **137a** (20 mg, 0.160 mmol, 1.2 mol equiv) and amine **80a** (4 mg, 0.013 mmol, 10 mol%) in $CDCl_3$ (0.5 mL). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (90:10:1) provided the *title compound* (28 mg, 0.096 mmol, 72%) as a yellow oil: R_f 0.07 hex/Et_2O (90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (s, 1H), 6.95 (d, J = 5.8 Hz, 1H), 6.24 – 6.02 (m, 3H), 4.15 – 4.02 (m, 2H), 3.75 (dd, J = 9.3, 3.8 Hz, 1H), 3.14 (dd, J = 17.6, 3.8 Hz, 1H), 2.49 (dd, J = 17.6, 9.3 Hz, 1H), 2.22 – 2.13 (m, 3H), 1.41 (q, J = 7.4 Hz, 2H), 1.34 – 1.22 (m, 6H), 1.17 (t, J = 7.1 Hz, 3H), 0.87 (t, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0 (CH), 172.5 (C), 144.8 (C), 144.1 (CH), 136.8 (CH), 134.1 (CH), 130.9 (CH), 121.2 (CH), 61.2 (CH2), 35.3 (CH), 33.4 (CH_2),

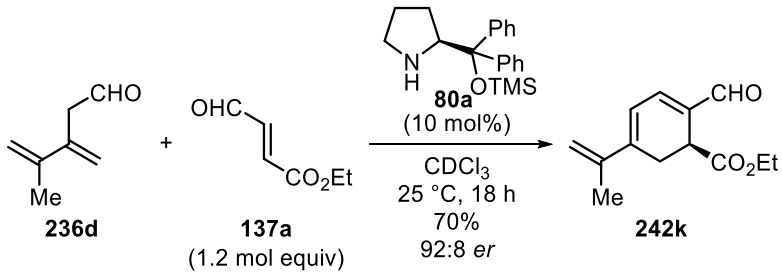
31.7 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 14.1 (CH_3) ppm; IR (thin film): ν_{max} = 2927, 2855, 2717, 1730, 1668, 1545 cm^{-1}; MS (ESI): *m*/*z* (%): 313 $[M+Na]^{+\bullet}$; HRMS: calc for $C_{18}H_{26}O_3Na$ $[M+Na]^{+\bullet}$: 313.1780; found 313.1779; $[\alpha]_D$ = –265 (*c* 0.87, MeOH); e.r. 94:6, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 70:30, 1 mL/min), minor (+) enantiomer t_R = 4.1 min, major (–) enantiomer t_R = 5.3 min.

Ethyl (*S*,*E*)-2-Formyl-5-styrylcyclohexa-2,4-diene-1-carboxylate **242j**



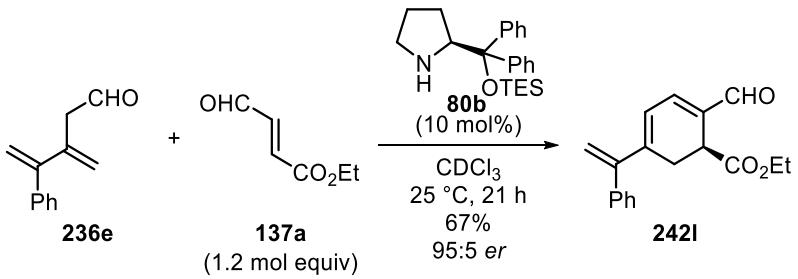
Prepared using skipped dienal **236c** (23 mg, 0.133 mmol), dienophile **137a** (20 mg, 0.160 mmol, 1.2 mol equiv) and amine **80b** (5 mg, 0.013 mmol, 10 mol%) in $CDCl_3$ (0.5 mL). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (80:20:1) provided the *title compound* (25 mg, 0.089 mmol, 67%) as a dark yellow oil: R_f 0.17 hex/Et_2O (60:40); ^1H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.47 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.1 Hz, 1H), 7.02 (d, *J* = 5.9 Hz, 1H), 6.92 (s, 2H), 6.30 (dd, *J* = 5.9, 2.3 Hz, 1H), 4.11 (qd, *J* = 7.1, 2.1 Hz, 2H), 3.84 (dd, *J* = 9.3, 3.6 Hz, 1H), 3.33 (dd, *J* = 17.5, 3.6 Hz, 1H), 2.64 (ddd, *J* = 17.4, 9.3, 2.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9 (CH), 172.3 (C), 144.3 (C), 143.5 (CH), 136.5 (C), 134.7 (C), 132.8 (CH), 128.9 (CH), 128.9 (CH), 128.7 (CH), 127.1 (CH), 123.7 (CH), 61.3 (CH_2), 35.3 (CH), 26.1 (CH_2), 14.1 (CH_3) ppm; IR (thin film): ν_{max} = 3031, 2980, 2930, 2809, 2719, 1725, 1662, 1531 cm^{-1}; MS (ESI): *m*/*z* (%): 305 $[M+Na]^{+\bullet}$; HRMS: calc for $C_{18}H_{18}O_3Na$ $[M+Na]^{+\bullet}$: 305.1154; found 305.1153; $[\alpha]_D$ = –239 (*c* 0.76, MeOH); e.r. 91:9, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 70:30, 1 mL/min), major (–) enantiomer t_R = 21.4 min, minor (+) enantiomer t_R = 24.6 min.

Ethyl (*S*)-2-formyl-5-(prop-1-en-2-yl)cyclohexa-2,4-diene-1-carboxylate **242k**



Prepared using skipped dienal **236d** (19 mg, 0.174 mmol), dienophile **137a** (27 mg, 0.209 mmol, 1.2 mol equiv) and amine **80a** (6 mg, 0.017 mmol, 0.10 mol equiv). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (90:10:1 then 80:20:1) provided the *title compound* (27 mg, 0.12 mmol, 70%) as a yellow oil: R_f 0.12 hex/Et_2O (80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.00 (d, J = 6.0 Hz, 1H), 6.29 (d, J = 6.0 Hz, 1H), 5.43 (s, 1H), 5.24 (s, 1H), 4.15 – 4.02 (m, 2H), 3.75 (dd, J = 9.3, 3.5 Hz, 1H), 3.23 (dd, J = 17.5, 3.6 Hz, 1H), 2.54 (ddd, J = 17.5, 9.3, 2.2 Hz, 1H), 1.96 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1 (CH), 172.3 (C), 145.2 (C), 143.6 (CH), 141.5 (C), 134.8 (C), 119.4 (CH), 117.3 (CH_2), 61.1 (CH_2), 35.5 (CH), 27.0 (CH_2), 20.3 (CH_3), 14.0 (CH_3) ppm; IR (thin film): ν_{max} = 2980, 2904, 2813, 2719, 1728, 1670, 1547 cm^{-1}; MS (ESI): *m*/*z* (%): 243 $[M+Na]^{+\bullet}$; HRMS: calc for $C_{13}H_{16}O_3Na$ $[M+Na]^{+\bullet}$: 243.0997; found 243.0996; $[\alpha]_D$ = –188 (*c* 0.84, MeOH); e.r. 92:8, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 70:30, 1 mL/min), minor (+) enantiomer t_R = 5.5 min, major (–) enantiomer t_R = 20.9 min.

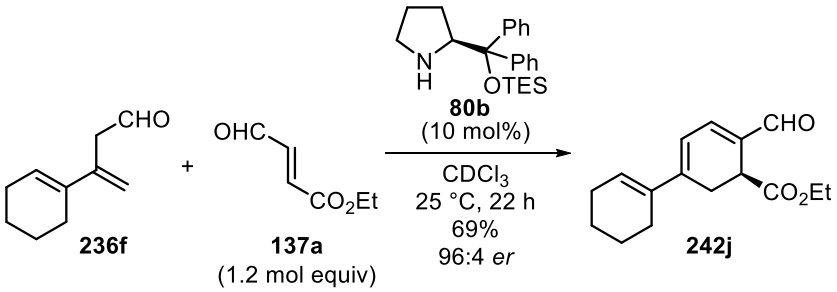
Ethyl (*S*)-2-formyl-5-(1-phenylvinyl)cyclohexa-2,4-diene-1-carboxylate **242l**



Prepared using skipped dienal **236e** (23 mg, 0.133 mmol), dienophile **137a** (20 mg, 0.160 mmol, 1.2 mol equiv) and amine **80b** (5 mg, 0.013 mmol, 10 mol%). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (90:10:1)

provided the *title compound* (25 mg, 0.089 mmol, 67%) as a yellow oil: R_f 0.14 hex/Et_2O/Et_3N (80:20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.38 – 7.31 (m, 3H), 7.25 – 7.21 (m, 2H), 6.92 (d, J = 5.9 Hz, 1H), 6.06 (dd, J = 6.0, 2.4 Hz, 1H), 5.62 (s, 1H), 5.37 (s, 1H), 4.14 (qd, J = 7.1, 2.0 Hz, 2H), 3.81 (dd, J = 9.3, 3.7 Hz, 1H), 3.24 (dd, J = 17.6, 3.7 Hz, 1H), 2.70 (ddd, J = 17.6, 9.2, 2.4 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2 (CH), 172.3 (C), 149.3 (C), 145.6 (C), 143.4 (CH), 140.3 (C), 135.0 (C), 128.8 (CH), 128.3 (CH), 127.9 (CH), 123.2 (CH), 117.5 (CH_2), 61.3 (CH_2), 35.6 (CH), 28.2 (CH_2), 14.1 (CH_3) ppm; IR (UATR): ν_{max} = 2981, 1729, 1670, 1545 cm^{-1}; MS (70 eV, EI): m/z (%): 282 (22) $[M]^{+\bullet}$, 209 (100), 179 (20), 103 (71); HRMS: calc for $C_{18}H_{18}O_3$ $[M]^{+\bullet}$: 282.1256; found 282.1257; $[\alpha]_D$ = –51 (*c* 0.89, MeOH); e.r. 95:5, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 90:10, 1 mL/min), major (–) enantiomer t_R = 14.1 min, minor (+) enantiomer t_R = 20.4 min.

Ethyl (*S*)-4-formyl-[1,1'-bi(cyclohexane)]-1',4,6-triene-3-carboxylate **242j**



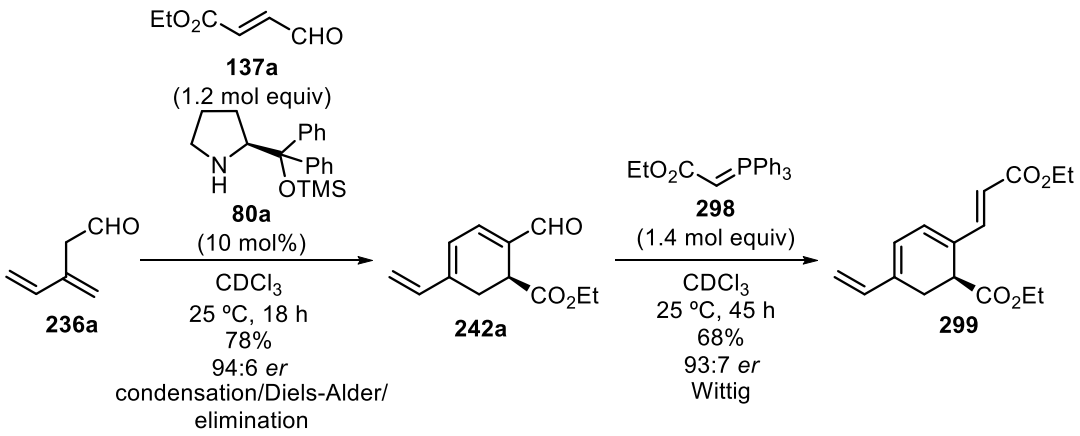
Prepared using skipped dienal **236f** (20 mg, 0.133 mmol), dienophile **137a** (20 mg, 0.160 mmol, 1.2 mol equiv) and amine **80a** (5 mg, 0.013 mmol, 10 mol%). Purification by flash column chromatography on silica gel eluting with hex/Et_2O/Et_3N (90:10:1) provided the *title compound* (24 mg, 0.092 mmol, 69%) as a yellow oil: R_f 0.24 hex/Et_2O (70:30); ^1H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 6.98 (d, J = 6.0 Hz, 1H), 6.30 (s, 1H), 6.18 (dd, J = 6.4, 2.1 Hz, 1H), 4.15 – 4.01 (m, 2H), 3.72 (dd, J = 9.1, 3.8 Hz, 1H), 3.21 (dd, J = 17.4, 3.8 Hz, 1H), 2.48 (ddd, J = 17.4, 9.1, 2.2 Hz, 1H), 2.32 – 2.11 (m, 4H), 1.79 – 1.49 (m, 4H), 1.17 (t, J = 7.1 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1 (CH), 172.6 (C), 146.5 (C), 144.4 (CH), 135.4 (C), 133.8 (C), 130.7 (CH), 116.4 (CH), 61.1 (CH_2), 35.5 (CH), 26.8 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 14.1 (CH_3) ppm; IR (thin film): ν_{max} = 2980, 2929, 1732, 1668, 1538

cm^{-1}; MS (ESI): *m*/*z* (%): 283 $[M+Na]^{+\bullet}$; HRMS: calc for $C_{16}H_{20}O_3Na$ $[M+Na]^{+\bullet}$: 283.1310; found 283.1310; $[\alpha]_D$ = –251 (*c* 0.59, MeOH); e.r. 96:4, determined by chiral HPLC (Chiralcel OJ-H column, 150 x 4.6 mm), hex/IPA 70:30, 1 mL/min), minor (+) enantiomer t_R = 5.1 min, major (–) enantiomer t_R = 7.0 min.

3.7.2.3 Diels-Alder/Wittig/Diels-Alder/Diels-Alder reaction sequence

Ethyl (*S*,*E*)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)-5-vinylcyclohexa-2,4-diene-1-carboxylate **299**

Via a two step reaction sequence:

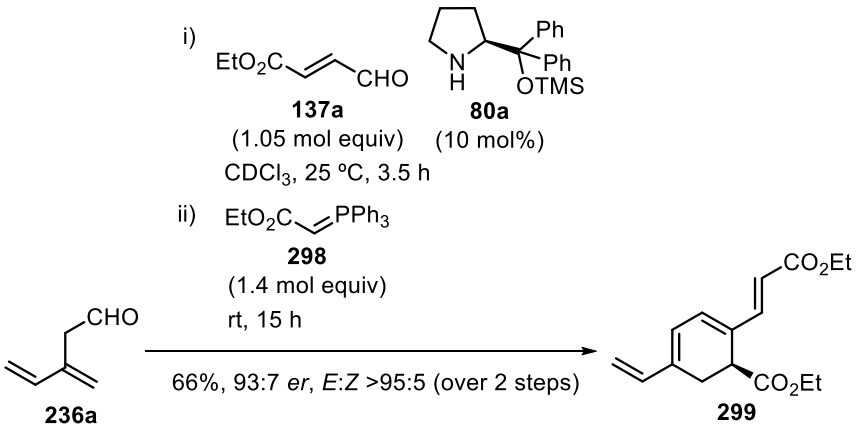


Mono-adduct **242a** was synthesised as described on page 343. To a solution of trienal **242a** (36 mg, 0.18 mmol) in $CDCl_3$ (0.5 mL) was added a solution of stabilised ylide **298** (85 mg, 0.24 mmol, 1.4 mol equiv) in $CDCl_3$ (0.2 mL) in an NMR tube. The resulting mixture was shaken briefly then held at 25 ºC for 45 h. Purification by flash column chromatography on silica gel eluting with CH_2Cl_2 (with 1 crystal of BHT per 500 mL of eluent) provided the *title compound* (70 mg, 0.12 mmol, 68%) as a yellow solid: mp 100-104 ºC; R_f 0.28 CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 15.8 Hz, 1 H), 6.43 (dd, *J* = 17.3, 10.9 Hz, 1 H), 6.45 (d, *J*=7.6 Hz, 1 H), 6.05 (dd, *J* = 5.9, 2.6 Hz, 1 H), 5.91 (d, *J* = 15.8 Hz, 1 H), 5.43 (d, *J*=17.3 Hz, 1 H), 5.23 (d, *J* = 10.9 Hz, 1 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 4.04 - 4.14 (m, 2 H), 3.51 (dd, *J* = 9.0, 1.6 Hz, 1 H), 3.11 (dd, *J* = 17.3, 1.8 Hz, 1 H), 2.46 - 2.55 (m, 1 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (C), 167.4 (C), 144.9 (CH), 139.0 (C), 137.4 (CH), 134.2 (CH), 131.8 (C), 124.6 (CH), 117.1 (CH), 115.5 (CH_2), 61.1(CH_2) , 60.4 (CH_2), 38.6 (CH), 25.6 (CH_2), 14.4 (CH_3), 14.1(CH_3) ppm; IR (KBr

disc): ν_{max} = 2981, 2937, 2904, 1709, 1627, 1610, 1593 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 276 (18) $[M]^{+\bullet}$, 203 (72), 157 (100); HRMS: calc for $C_{16}H_{20}O_4$ $[M]^{+\bullet}$: 276.1362; found 276.1360; $[\alpha]_D$ = –94 (*c* 0.60, MeOH); e.r. 94:6, determined by chiral HPLC (Phenomenex Lux Cellulose 4 column (150 x 4.6 mm), hex/IPA 85:15, 1 mL/min), minor (+) enantiomer t_R = 8.3 min, major (–) enantiomer t_R = 12.6 min.

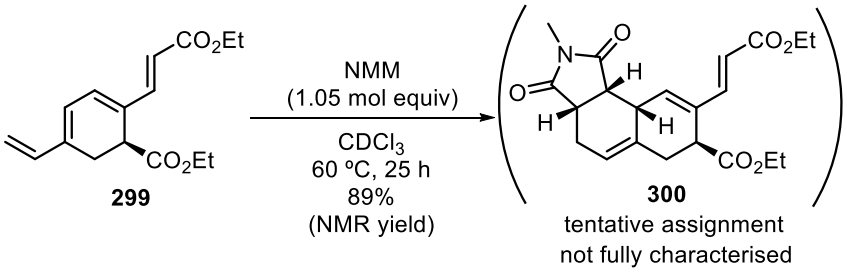
The racemic material was obtained by performing the reaction with pyrrolidine (20 mol%) instead of amine catalyst **80a**.

Via a one-pot reaction:



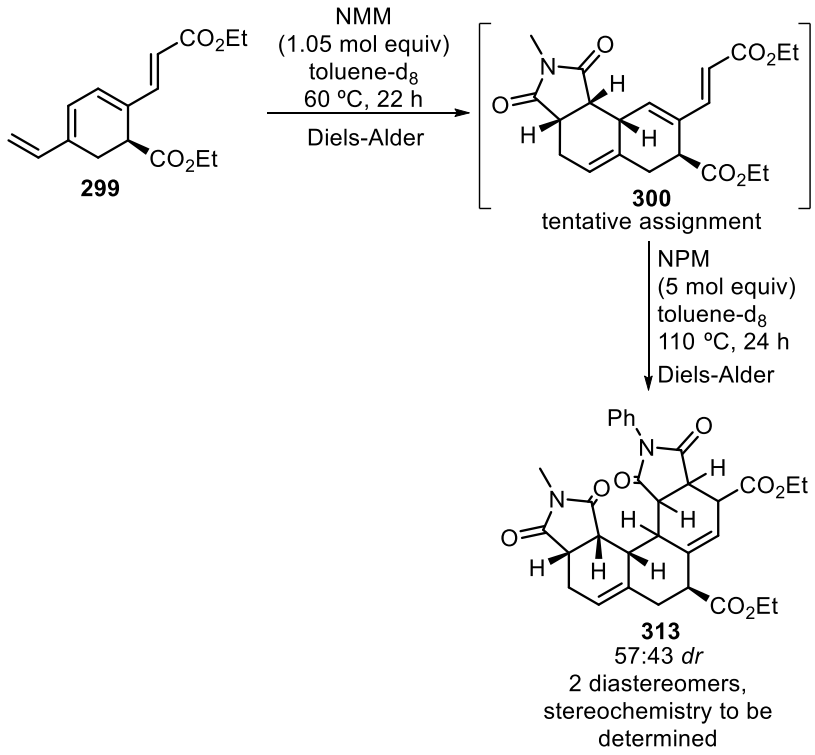
To a solution of skipped dienal **236a** (37 mg, 0.38 mmol) in $CDCl_3$ (0.4 mL) was added dienophile **137a** (52 mg, 0.40 mmol, 1.05 mol equiv) followed by amine catalyst **80a** (12 mg, 0.038 mmol, 10 mol%). The resulting mixture was transferred into an NMR tube, shaken briefly then held at 25 ºC until complete consumption of skipped dienal **236a** was observed by ^{1}H NMR spectroscopy (3.5 h). The reaction mixture was added to stabilised ylide **298** (471 mg, 135 mmol, 1.3 mol equiv) with $CDCl_3$ (0.4 mL) and stirred at rt for 15 h, after which TLC analysis indicated complete consumption of trienal **242a**. Purification by flash column chromatography on silica gel eluting with CH_2Cl_2/EtOAc (100:0 then 95:5 with 1 crystal of BHT per 500 mL of eluent) provided the *title compound* (70 mg, 0.25 mmol, 66%) as a yellow solid. The ^{1}H NMR spectroscopic data matched those reported in the above section.

Ethyl (3a*S*,7*S*,9a*S*,9b*R*)-8-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-2-methyl-1,3-dioxo-2,3,3a,4,6,7,9a,9b-octahydro-1*H*-benzo[e]isoindole-7-carboxylate **300**



Tetraene **299** (30 mg, 0.11 mmol, 1.0 mol equiv) and NMM (13 mg, 0.12 mmol, 1.05 equiv) were dissolved in $CDCl_3$ (0.5 mL) in a Young's Tap NMR tube. The reaction mixture was heated to 60 ºC for 25 h. The yield of the reaction, as estimated by ^{1}H NMR spectroscopy using durene as an internal standard, was 89%. Attempted purification with flash column chromatography on silica gel or with eluting solvents doped with triethylamine generated a mixture of unidentified products. The reaction was repeated without the internal standard and bis-adduct **300** was characterised as a mixture with a small amount of residual NMM (0.17 mol equiv). Signals tentatively assigned to bis-adduct **300** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 16.0 Hz, 1 H), 6.63 (br. s, 1 H), 5.89 (d, J = 16.0 Hz, 1 H), 5.70 (br. s, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.00-4.10 (m, 2 H), 3.52 (d, J = 3.5 Hz, 1 H), 3.29 (dd, J = 8.6, 5.9 Hz, 1 H), 3.14 – 3.20 (m, 1 H), 3.12 (br. s, 1 H), 2.85 (s, 3 H), 2.63 - 2.76 (m, 2 H), 2.19 – 2.28 (m, 2 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.16 (t, J = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (C), 177.3 (C), 172.0 (C), 167.0 (C), 145.2 (CH), 138.7 (CH), 136.3 (C), 133.6 (C), 121.3 (CH), 117.1 (CH), 61.0 (CH_2), 60.4 (CH_2), 44.3 (CH), 40.7 (CH), 40.1 (CH), 36.7 (CH), 32.1 (CH_2), 24.9 (CH_3), 24.8 (CH_2), 14.3 (CH_3), 14.1 (CH_3) ppm; IR (KBr disc): ν_{max} = 2982, 2956, 2905, 1774, 1694 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 387.1 (3) $[M]^{+\bullet}$, 342.1 (12), 314.1 (15), 268.1 (100); HRMS: calc for $C_{21}H_{25}NO_6$ $[M]^{+\bullet}$: 387.1682; found 387.1683.

Ethyl (6*S*,9a*S*,12a*R*,12b*S*)-4-((ethylperoxy)-l2-methyl)-11-methyl-1,3,10,12-tetraoxo-2-phenyl-1,2,3,3a,4,6,7,9,9a,10,11,12,12a,12b,12c,12d-hexadecahydrobenzo[2,1-e:3,4-e']diisoindole-6-carboxylate **313**



Tetraene **299** (75 mg, 0.271 mmol) and NMM (32 mg, 0.285 mmol, 1.05 mol equiv) were dissolved in toluene-d_8 (0.5 mL). The resulting reaction mixture was heated to 60 ºC overnight (22 h) in an NMR tube upon which complete consumption of tetraene **299** was observed by ^{1}H NMR spectroscopy. The reaction mixture was cooled to rt, *N*-phenylmaleimide (235 mg, 1.36 mmol, 5.0 mol equiv) and toluene-d_8 (0.3 mL) were added and the reaction mixture was heated to 110 ºC for 24 h in an NMR tube. Complete consumption of bis-adduct **300** was observed by ^{1}H NMR spectroscopy with the formation of tris-adduct **313** as a mixture of two diasteoreomers (a:b = 57:43). The reaction mixture was concentrated under reduced pressure and purified with flash column chromatography eluting with hex/Et_2O (30:70 to 10:90) to provide a mixture containing both diastereomers (63 mmol, 0.112 mmol, 41%) and pure samples of the following:

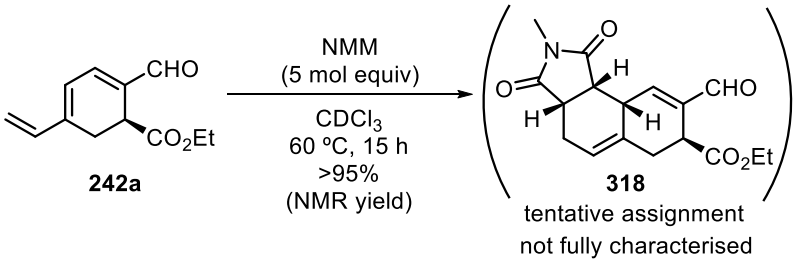
diastereomer a (10 mg, 0.0178 mmol, 7%) as a white solid: mp 96-100 ºC; R_f 0.28 Et_2O; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 - 7.50 (m, 2 H), 7.33 - 7.42 (m, 3 H), 5.80 (br. s, 1 H), 5.58 (br. s., 1 H), 4.25 (q, J = 7.2 Hz, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 3.70 - 3.79 (m,

2 H), 3.65 - 3.69 (m, 1 H), 3.40 - 3.44 (m, 1 H), 3.11 - 3.22 (m, 3 H), 2.89 (s, 3 H), 2.59 - 2.71 (m, 2 H), 2.49 - 2.55 (m, 2 H), 2.12 - 2.22 (m, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9 (C), 179.2 (C), 177.9 (C), 176.2 (C), 173.1 (C), 172.3 (C), 138.6 (C), 138.2 (C), 131.7 (C), 129.3 (CH), 128.8 (CH), 126.5 (CH), 121.2 (CH), 121.0 (CH), 61.9 (CH_2), 61.0 (CH_2), 46.5 (CH), 45.6 (CH), 42.4 (CH), 42.3 (CH), 40.6 (CH), 40.5 (CH), 40.0 (CH), 34.4 (CH), 33.3 (CH_2), 25.0 (CH_2), 24.9 (CH_3), 14.3 (CH_3), 14.2 (CH_3) ppm; IR (KBr disc): ν_{max} = 2981, 2851, 1772, 1712 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 560 (60) $[M]^{+\bullet}$, 487 (40), 376 (100), 302 (90); HRMS: calc for $C_{31}H_{32}N_2O_8$ $[M]^{+\bullet}$: 560.2159; found 560.2159; $[\alpha]_D$ = +78.5 (*c* 0.90, MeOH);

diastereomer b (14 mg, 0.0250 mmol, 9%) as a white solid: mp 110-114 ºC; R_f 0.19 Et_2O; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.31 (m, 5H), 6.35 (t, *J* = 3.2 Hz, 1H), 5.68 – 5.61 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.08 (dd, J = 9.2, 5.0 Hz, 1H), 3.92 – 3.85 (m, 3H), 3.72 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.60 – 3.53 (m, 1H), 3.48 – 3.44 (m, 1H), 3.32 – 3.23 (m, 2H), 3.20 (t, *J* = 8.1 Hz, 1H), 2.93 (s, 3H), 2.74 – 2.61 (m, 2H), 2.42 – 2.33 (m, 1H), 2.21 – 2.09 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9 (C), 179.0 (C), 176.3 (C), 176.0 (C), 172.9 (C), 170.5 (C), 138.1 (C), 137.0 (C), 131.9 (C), 129.0 (CH), 128.7 (CH), 126.9 (CH), 123.1 (CH), 122.3 (CH), 61.5 (CH_2), 60.9 (CH_2), 47.2 (CH), 43.8 (CH), 40.6 (CH), 40.5 (CH), 40.2 (CH), 40.0 (CH), 35.0 (CH_2), 34.4 (CH), 33.9 (CH), 25.0 (CH_3), 24.0 (CH_2), 14.2 (2 x CH_3) ppm; IR (UATR): ν_{max} = 2980, 2900, 1709 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 560 (57) $[M]^{+\bullet}$, 487 (42), 376 (100), 302 (88); HRMS: calc for $C_{31}H_{32}N_2O_8$ $[M]^{+\bullet}$: 560.2159; found 560.2159; $[\alpha]_D$ = +58.5 (*c* 0.68, MeOH).

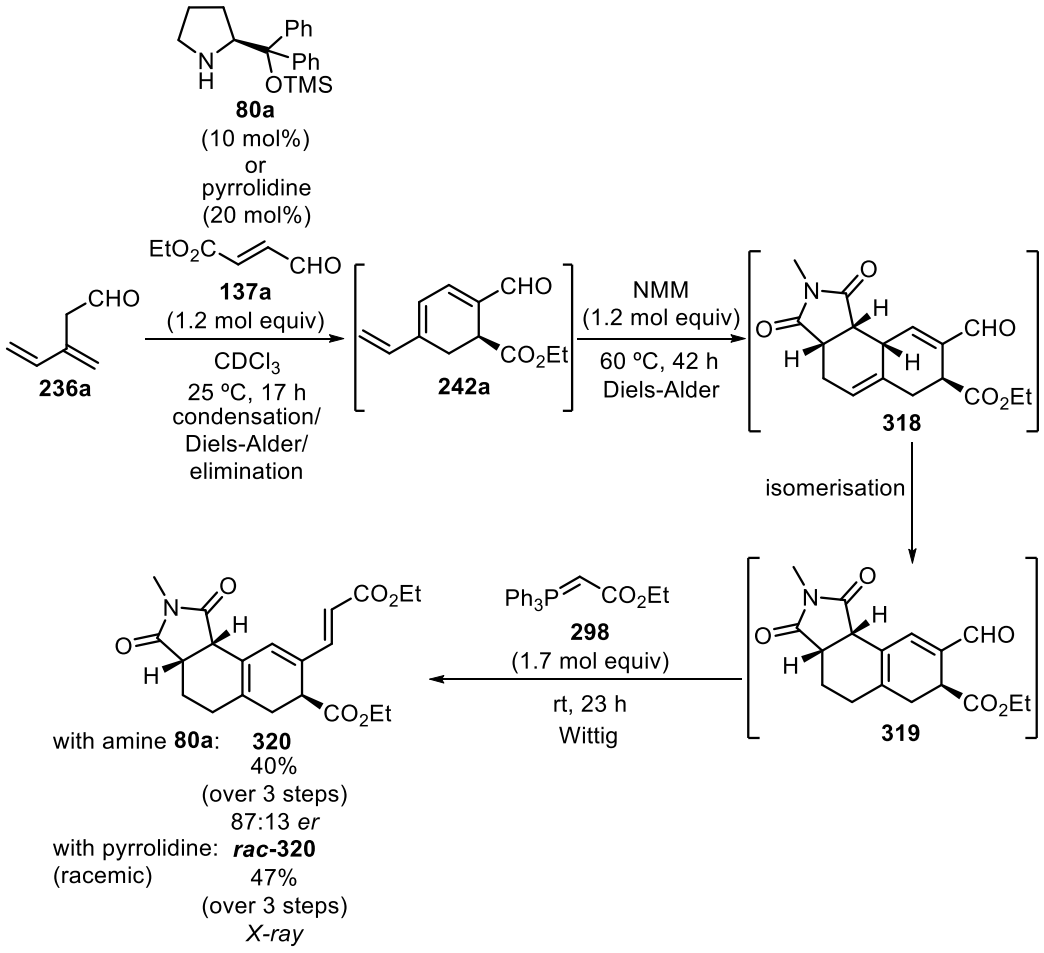
3.7.2.4 Diels-Alder/ Diels-Alder/Wittig reaction sequence

Ethyl (3a*S*,7*S*,9a*S*,9b*R*)-8-formyl-2-methyl-1,3-dioxo-2,3,3a,4,6,7,9a,9b-octahydro-1*H*-benzo[e]isoindole-7-carboxylate **318**



Trienal **242a** (20 mg, 0.096 mmol) and NMM (54 mg, 0.48 mmol, 5.0 mol equiv) were dissolved in $CDCl_3$ (0.4 mL) in a Young's Tap NMR tube. The reaction mixture was heated to 60 °C for 16 hours after which complete consumption of trienal **242a** was observed. The yield of the reaction, as estimated by ^{1}H NMR spectroscopy using 1,2-tetrachloroethane as an internal standard, was >95%. Attempted purification with flash column chromatography on silica gel or with eluting solvents doped with triethylamine generated a mixture of unidentified products. The reaction was repeated without the internal standard and bis-adduct **318** was characterised as a mixture with NMM. Signals tentatively assigned to bis-adduct **318** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1 H), 7.30 (s., 1 H), 5.76 (br. s., 1 H), 4.05 (q, J = 7.0 Hz, 2 H), 3.80 (dd, J = 5.4, 2.2 Hz, 1 H), 3.40 (dd, J = 8.7, 5.7 Hz, 1 H), 3.16 - 3.25 (m, 2 H), 2.88 (s, 3 H), 2.67 - 2.80 (m, 2 H), 2.21 - 2.31 (m, 1 H), 2.12 - 2.21 (m, 1 H), 1.18 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3 (CH), 179.3 (C), 177.3 (C), 171.8 (C), 150.9 (CH), 139.6 (C), 136.0 (C), 122.2 (CH), 61.1 (CH_2), 44.2 (CH), 40.6 (CH), 37.1 (CH), 36.8 (CH), 31.9 (CH_2), 25.0 (CH_3), 24.8 (CH_2), 14.1 (CH_3) ppm; IR (KBr disc): ν_{max} = 2981, 2952, 2905,1774, 1695, 1642 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 317.1(6) $[M]^{+\bullet}$, 243.1 (65), 214.1 (48), 129.1 (100); HRMS: calc for $C_{17}H_{19}NO_5$ $[M]^{+\bullet}$: 317.1263; found 317.1263.

Ethyl (3a*S*,7*S*,9b*S*)-8-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-2-methyl-1,3-dioxo-2,3,3a,4,5,6,7,9b-octahydro-1*H*-benzo[e]isoindole-7-carboxylate **320**



To a solution of skipped dienal **236a** (23 mg, 0.234 mmol) in $CDCl_3$ (0.5 mL) was added dienophile **137a** (36 mg, 0.281 mmol, 1.2 mol equiv) followed by amine catalyst **80a** (7.5 mg, 0.0234 mmol, 10 mol%). The resulting mixture was transferred into an NMR tube, shaken briefly then held at 25 ºC for 17 h, after which complete consumption of skipped dienal **236a** was observed by ^{1}H NMR spectroscopy. NMM (31 mg, 0.281 mmol, 1.2 mmol) was added and the mixture was heated to 60 ºC for 24 h, after which complete consumption of trienal **242a** was observed by ^{1}H NMR spectroscopy. Phosphorane **298** (117 mg, 0.337 mmol, 1.2 mol equiv) was added and the mixture was stirred at rt for 5 h, then additional phosphorane **298** (82 mg, 0.234 mmol, 0.5 mol equiv) was added and the mixture was stirred at rt for 18 h. The reaction mixture was concentrated under reduced pressure and purified with flash column chromatography eluting with petrol/EtOAc/Et_3N (90:10:1 to 60:40:1) to provide the *title compound* as a pale yellow solid (36 mg, 0.0929 mmol, 40%): R_f 0.18 petrol/EtOAc

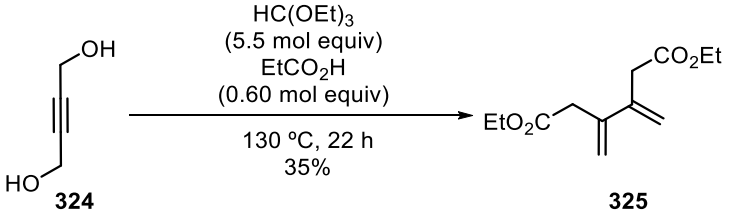
(60:40); mp 116 – 117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 15.8 Hz, 1H), 6.85 (s, 1H), 5.91 (d, J = 15.8 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.09 (p, J = 7.0 Hz, 2H), 3.43 (dt, J = 8.4, 2.2 Hz, 1H), 3.36 (dd, J = 7.9, 3.2 Hz, 1H), 3.10 (dt, J = 8.3, 5.4 Hz, 1H), 2.96 (s, 3H), 2.65 – 2.57 (m, 2H), 2.22 – 2.00 (m, 3H), 1.89 – 1.78 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0 (C), 176.8 (C), 172.1 (C), 167.2 (C), 145.0 (CH), 138.1 (C), 134.4 (CH), 130.3 (C), 121.8 (C), 117.5 (CH), 61.1 (CH_3), 60.4 (CH_3), 41.7 (CH), 39.8 (CH), 38.0 (CH), 33.0 (CH_2), 27.3 (CH_2), 24.9 (CH_3), 21.6 (CH_2), 14.4 (CH_3), 14.2 (CH_3) ppm; IR (UATR): ν_{max} = 2981, 2938, 2907, 1696, 1611 cm^{-1}; MS (70 eV, EI): m/z (%): 387 (20) $[M]^{+\bullet}$, 314 (62), 268 (100); HRMS: calc for $C_{21}H_{25}NO_6$ $[M]^{+\bullet}$: 387.1682; found 387.1681, e.r. 87:13, determined by chiral HPLC (Chiralcel OJ-H (150 x 4.6 mm), hex/IPA 70:30, 1 mL/min), minor (+) enantiomer t_R = 19.0 min, major (–) enantiomer t_R = 22.3 min; $[\alpha]_D$ = –195 (c 0.80, MeOH).

The racemic material was obtained by performing the reaction with pyrrolidine (20 mol%) instead of amine catalyst **80a**. Recrystallisation of the racemic material from CH_2Cl_2/Et_2O gave pale yellow crystals.

3.7.2.5 Twofold condensation/Diels-Alder/elimination reaction sequence

Synthesis of dialdehyde **244**

Diethyl 3,4-dimethylenehexanedioate **325**

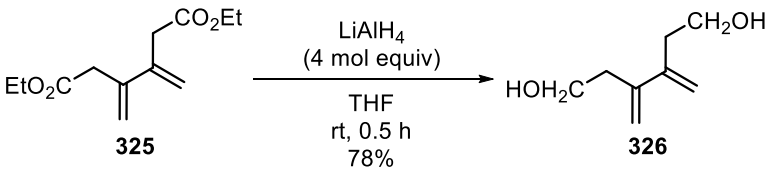


324 **325**

The *title compound* was prepared using a literature procedure.[17] Propionic acid (0.78 mL, 10.5 mmol, 0.15 mol equiv) was added to a suspension of butynediol (**324**) (6 g, 69.7 mmol) in triethylorthoacetate (70 mL, 380 mmol, 5.5 mol equiv) and the mixture was heated to 110 ºC for 30 min and 130 ºC for 1 h. An additional portion of propionic acid (0.78 mL, 10.5 mmol, 0.15 mol equiv) was added and the mixture was heated at 130 ºC for 4 h. An additional portion of propionic acid (1.60 mL, 21.5 mmol, 0.30 mol equiv) was added and the mixture was heated at 130 ºC for 17 h. The reaction mixture

was diluted with EtOAc, washed successively with 2 M HCl, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure. An attempt to purify the mixture by vacuum distillation was unsuccessful. After recombining the distillate and residue, the mixture was purified by flash column chromatography on silica gel eluting with hex/EtOAc (90:10) to provide a pure sample of the *title compound* (3.85 g, 16.7 mmol, 24%) as a colourless oil. The impure fractions containing the desired product were combined and purified by flash column chromatography on silica gel eluting with hex/EtOAc (90:10) to provide another pure sample of the *title compound* (1.75 g, 7.73 mmol, 11%). The ^{1}H NMR spectroscopic data matched those previously reported.[17]

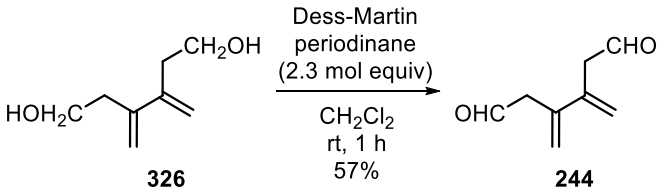
3,4-Dimethylenehexane-1,6-diol **326**



325 **326**

The *title compound* was prepared using a literature procedure.[17] A suspension of lithium aluminium hydride (335 mg, 88.4 mmol, 4 mol equiv) in THF (35 mL) was cooled in an ice bath. A solution of diene-diester **325** (500 mg, 22.1 mmol) in THF (5 mL) was added dropwise to the lithium aluminium hydride suspension. The reaction mixture was warmed to rt and stirred at rt until complete consumption of the diene-diester **325** as indicated by TLC (0.5 h). The reaction mixture was then cooled in an ice bath and water was added dropwise to the mixture until no further bubbling was observed. The mixture was filtered through Celite and the aqueous layer was extracted with ether. The combined organic layers were combined and concentrated under reduced pressure to provide the *title compound* as a colourless oil (242 mg, 17.2 mmol, 78%), which was used without further purification. The ^{1}H NMR spectroscopic data matched those previously reported.[17]

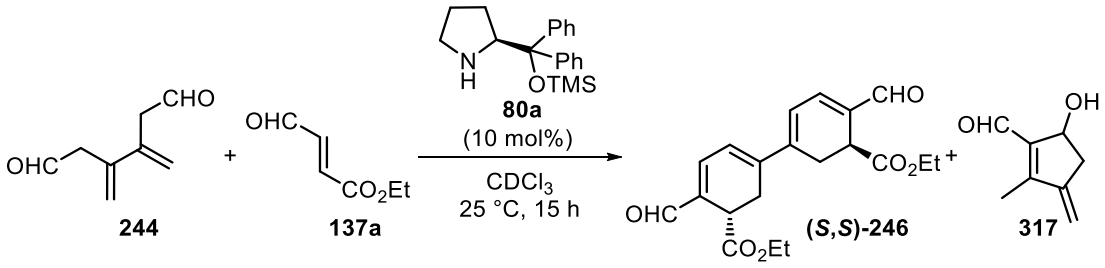
3,4-Dimethylenehexanedial **244**



To a solution of diene-diol **326** (240 mg, 1.70 mmol) in CH_2Cl_2 (7 mL) was added Dess-Martin periodinane (1.66 g, 3.91 mmol, 2.3 mol equiv). The reaction mixture was stirred at rt until complete consumption of diene-diol **326** as indicated by TLC (1 h). The reaction mixture was washed twice with a solution of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$ (1:1), water then brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to provide the *title compound* as a yellow oil (133 mg, 0.969 mmol, 57%), which was used without further purification. The ^{1}H NMR spectroscopic data matched those previously reported.[18]

Synthesis of tetraene-dialdehyde bis-adduct **246**

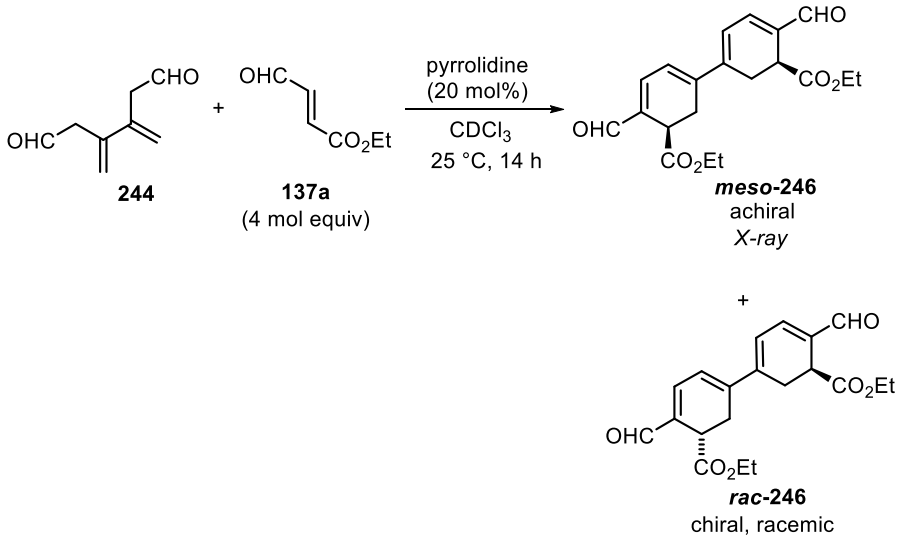
Diethyl (3*S*,3'*S*)-4,4'-diformyl-[1,1'-bi(cyclohexane)]-4,4',6,6'-tetraene-3,3'-dicarboxylate **(*S*,*S*)-246** and 5-Hydroxy-2-methyl-3-methylenecyclopent-1-ene-1-carbaldehyde **317**



To a solution of diene-dialdehyde **244** (50 mg, 0.359 mmol) in $CDCl_3$ (0.72 mL) was added dienophile **137a** (138 mg, 1.08 mmol, 4 mol equiv) followed by the amine catalyst **80a** (11 mg, 0.0359 mmol, 10 mol%). The resulting mixture was transferred into an NMR tube, shaken briefly then held at 25 ºC until complete consumption of diene-dialdehyde **244** was observed by ^{1}H NMR spectroscopy (15 h). The ^{1}H NMR spectrum of the crude reaction mixture showed that tetraene-dialdehyde bis-adduct **(*S*,*S*)-246** and cyclopentane **317** were formed in a 91:9 ratio. Purification by flash column chromatography on silica gel eluting with hex/Et_2O (20:80) provided the *title*

compound **(*S*,*S*)-246** as a dark yellow oil (43 mg, 0.12 mmol, 34%); R_f 0.40 Et_2O; ^1H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 2H), 7.04 (d, *J* = 6.0 Hz, 2H), 6.63 (dd, *J* = 6.2, 2.2 Hz, 2H), 4.08 (qd, *J* = 7.1, 4.3 Hz, 4H), 3.81 (dd, J = 9.2, 3.6 Hz, 2H), 3.27 (dd, *J* = 17.4, 3.6 Hz, 2H), 2.59 (ddd, *J* = 17.3, 9.2, 2.2 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9 (CH), 171.7 (C), 142.7 (C), 142.3 (CH), 136.3 (C), 122.5 (CH), 61.4 (CH2), 35.4 (CH), 26.9 (CH2), 14.1 (CH3) ppm; IR (UATR): ν_{max} = 2983, 2814, 1729, 1667, 1545 cm–1; MS (ESI): *m/z* (%): 381 (100) $[M+Na]^{+\bullet}$; HRMS: calc for $C_{20}H_{22}O_6Na$ $[M+Na]^{+\bullet}$: 381.1314; found 381.1315. After a second round of purification, an analytical sample of the *title compound* **317** was obtained as a yellow oil: R_f 0.38 Et_2O; ^1H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 5.46 (t, *J* = 2.5 Hz, 1H), 5.30 (t, *J* = 2.1 Hz, 1H), 5.20 – 5.13 (m, 1H), 3.05 – 2.93 (m, 1H), 2.85 (s, 1H), 2.59 – 2.40 (m, 1H), 2.19 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4 (CH), 156.6 (C), 151.7 (C), 143.5 (C), 112.0 (CH_2), 71.9 (CH), 37.6 (CH_2), 9.9 (CH_3) ppm; IR (thin film): ν_{max} = 3401, 2919, 2848, 1660 cm^{-1}; MS (70 eV, EI): *m/z* (%): 138 (15) $[M]^{+\bullet}$, 109 (100) ; HRMS: calc for $C_8H_{10}O_2$ $[M]^{+\bullet}$: 138.0681; found 138.0681.

Diethyl (3R,3'S)-4,4'-diformyl-[1,1'-bi(cyclohexane)]-4,4',6,6'-tetraene-3,3'-dicarboxylate *meso*-**246**



To a solution of diene-dialdehyde **244** (50 mg, 0.36 mmol) in $CDCl_3$ (0.72 mL) was added dienophile **137a** (140 mg, 1.1 mmol, 4 mol equiv and pyrrolidine (5 mg, 0.072 mmol, 20 mol%). The resulting mixture was transferred into an NMR tube, shaken briefly then held at 25 ºC until complete consumption of diene-dialdehyde **244** was observed by ^1H NMR spectroscopy (14 h). Purification by flash column

chromatography on silica gel eluting with hex/Et_2O (20:80) provided the *title compound* as a yellow oil (mixture of 2 diastereomers, 49 mg, 0.137 mmol, 38%). Analytical samples of each diastereomer were obtained with purification by flash column chromatography on silica gel eluting with hex/Et_2O (50:50 then 0:100):

bis-adduct ***meso*-246**: yellow solid; mp: 203 ºC; R_f 0.21 hex/EtOAc (30:70); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 2H), 7.04 (d, J = 6.0 Hz, 2H), 6.63 (dd, J = 5.9, 2.1 Hz, 2H), 4.09 (qq, J = 7.7, 3.7 Hz, 4H), 3.80 (dd, J = 9.0, 3.7 Hz, 2H), 3.26 (dd, J = 17.3, 3.7 Hz, 2H), 2.61 (ddd, J = 17.2, 9.1, 2.2 Hz, 2H), 1.18 (t, J = 7.1 Hz, 6H) ppm; 13C NMR (100 MHz, $CDCl_3$): δ 190.9 (CH), 171.9 (C), 142.8 (C), 142.2 (CH), 136.1 (C), 122.7 (CH), 61.5 (CH_2), 35.4 (CH), 26.7 (CH_2), 14.1 (CH_3) ppm; IR (UATR): ν_{max} = 2956, 2926, 2857, 1732 cm^{-1}; MS (ESI): *m/z* (%): 381 $[M+Na]^{+\bullet}$; HRMS: calc for $C_{20}H_{22}O_6Na$ $[M+Na]^{+\bullet}$: 381.1314; found 381.1318;

bis-adduct ***rac*-246**: The ^{1}H NMR spectroscopic data matched those previously reported for **(*S*,*S*)-246** on page 362.

3.7.3 References

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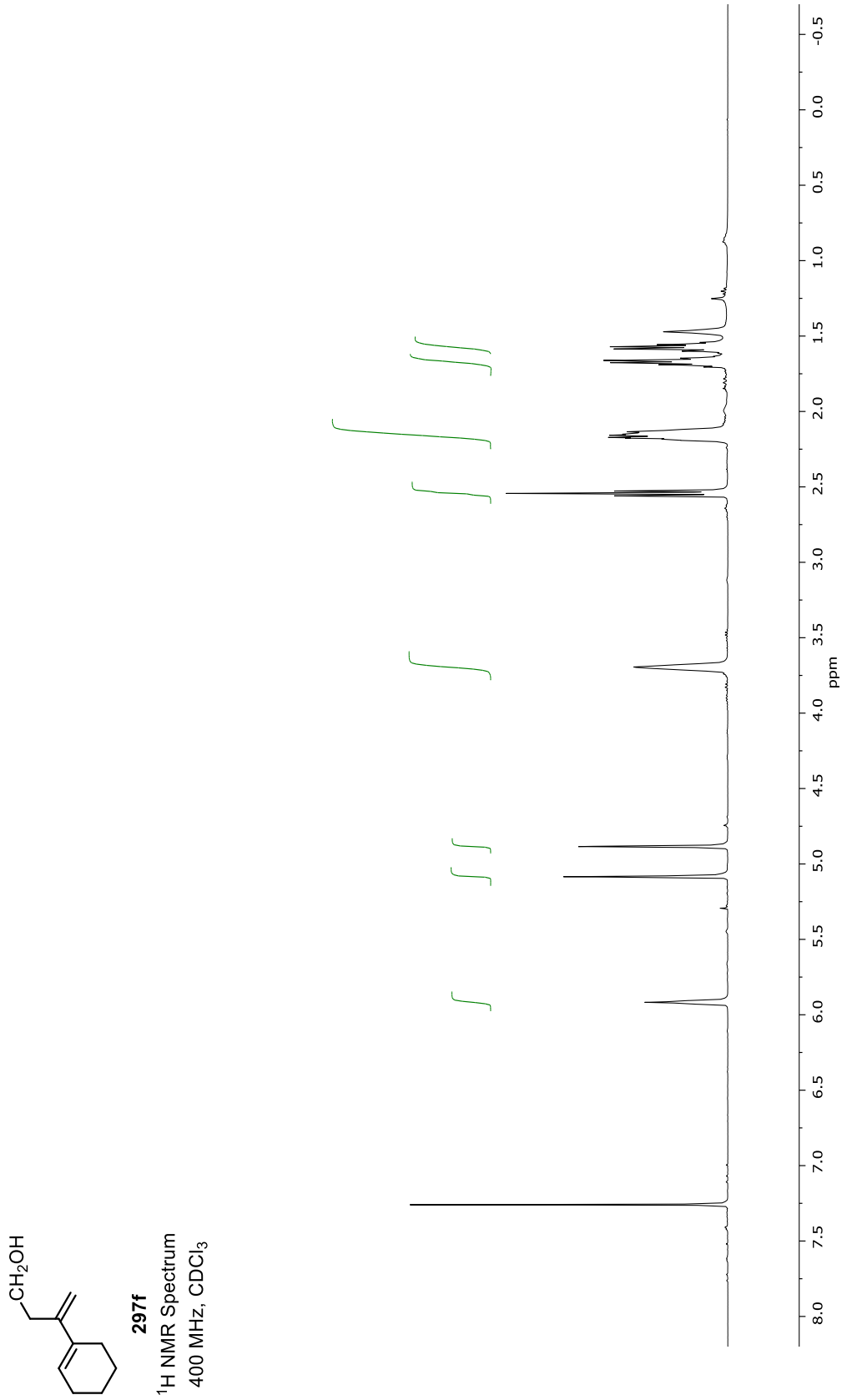
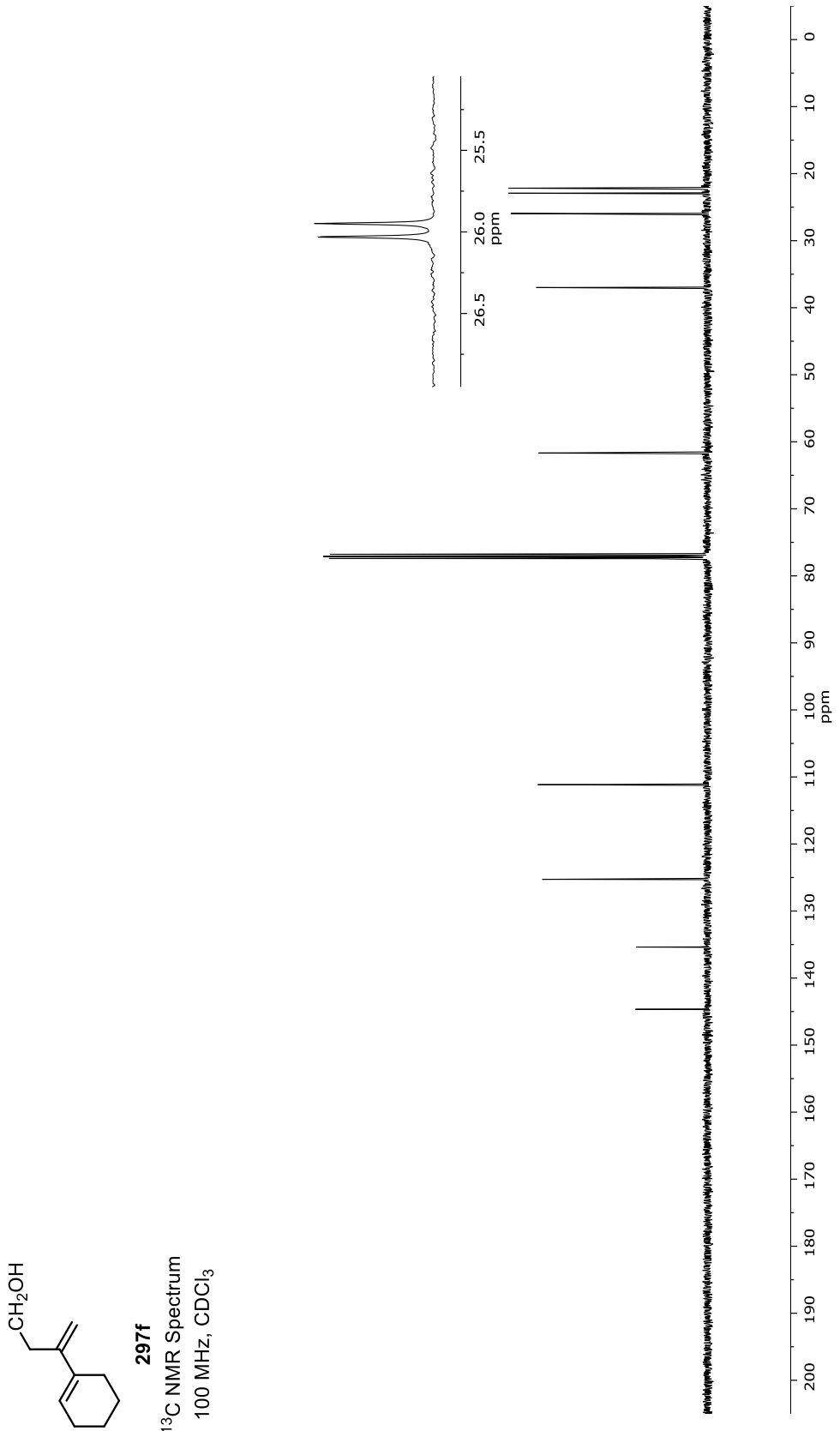
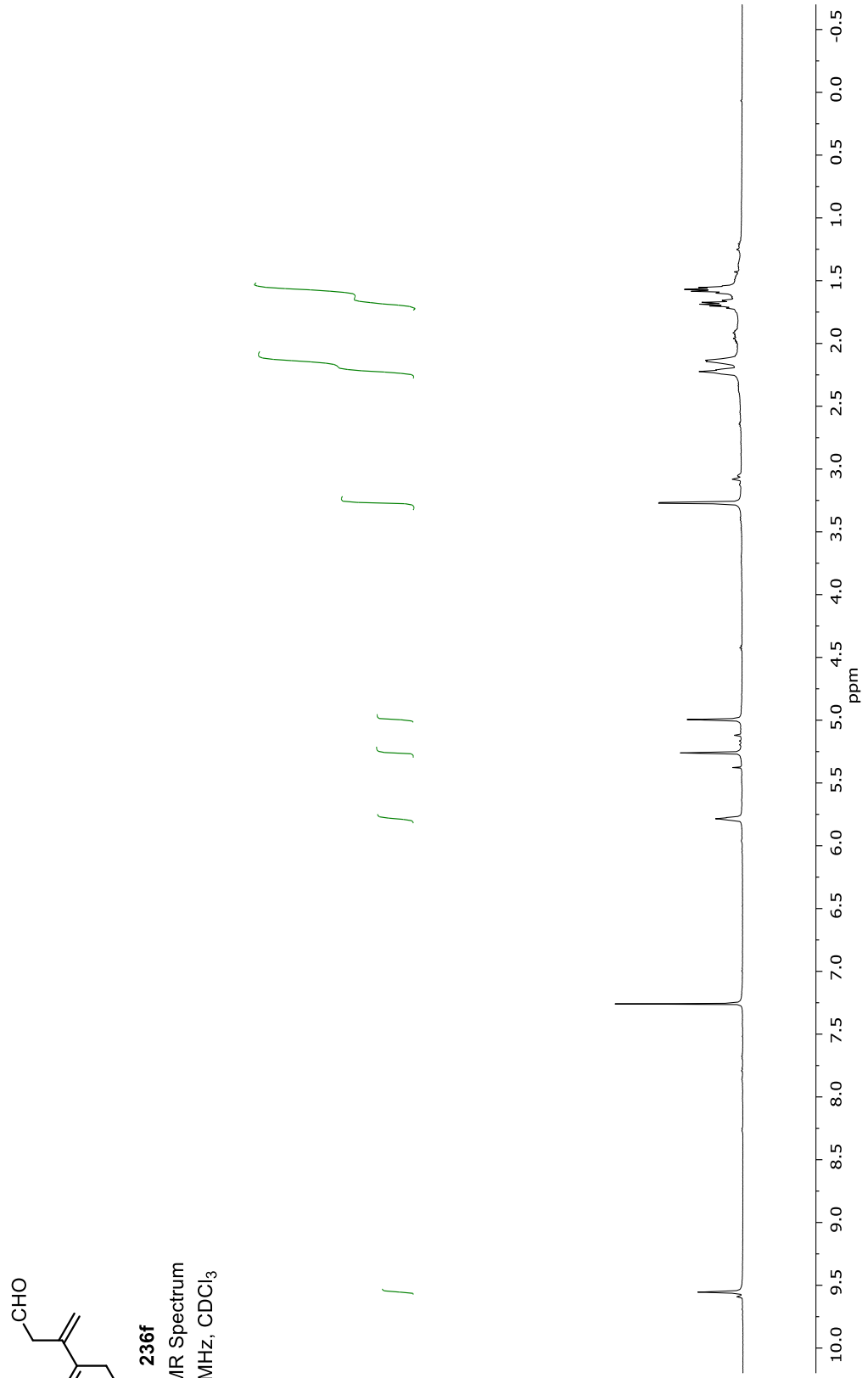
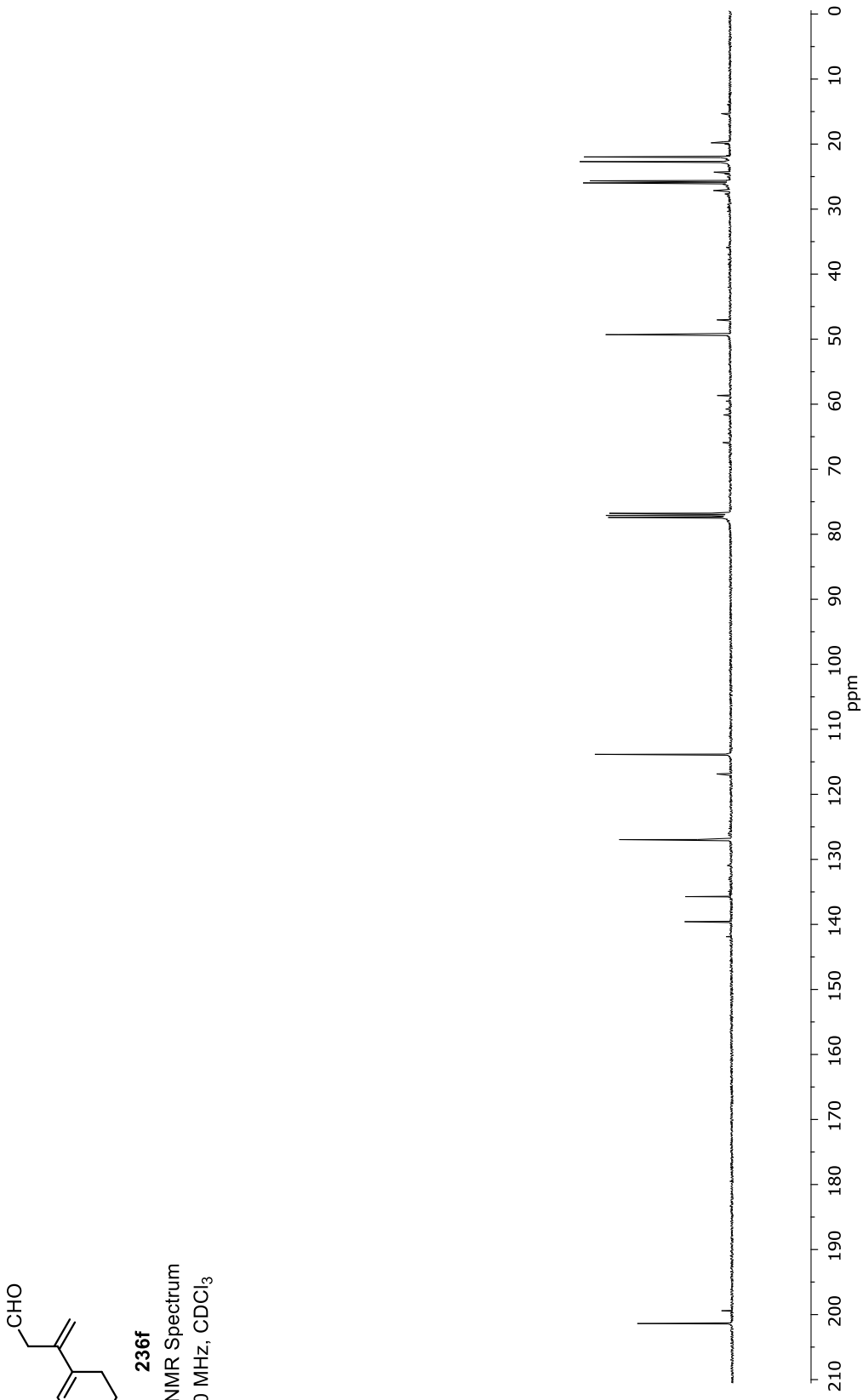
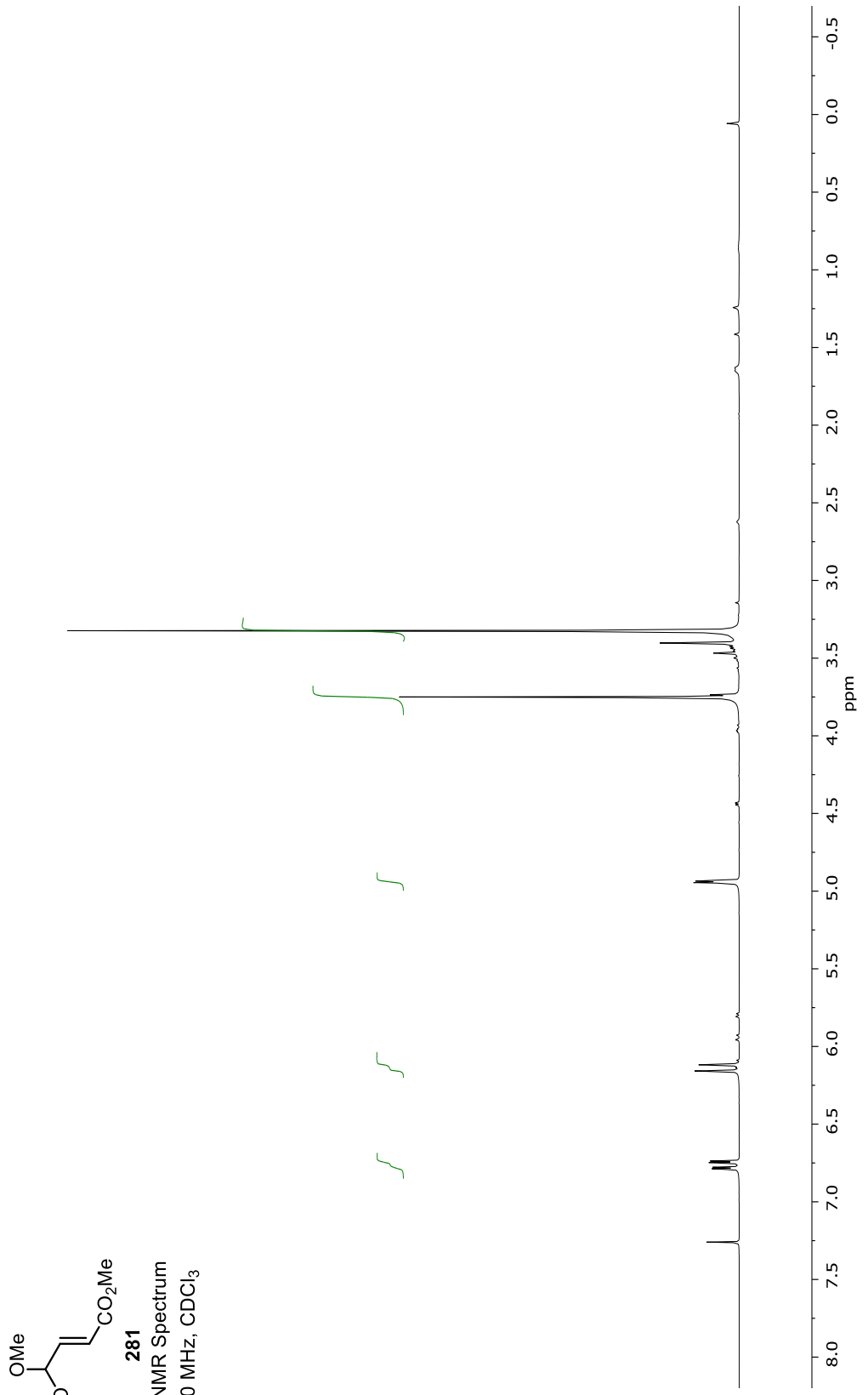
3.8 ^{1}H and ^{13}C NMR Spectra

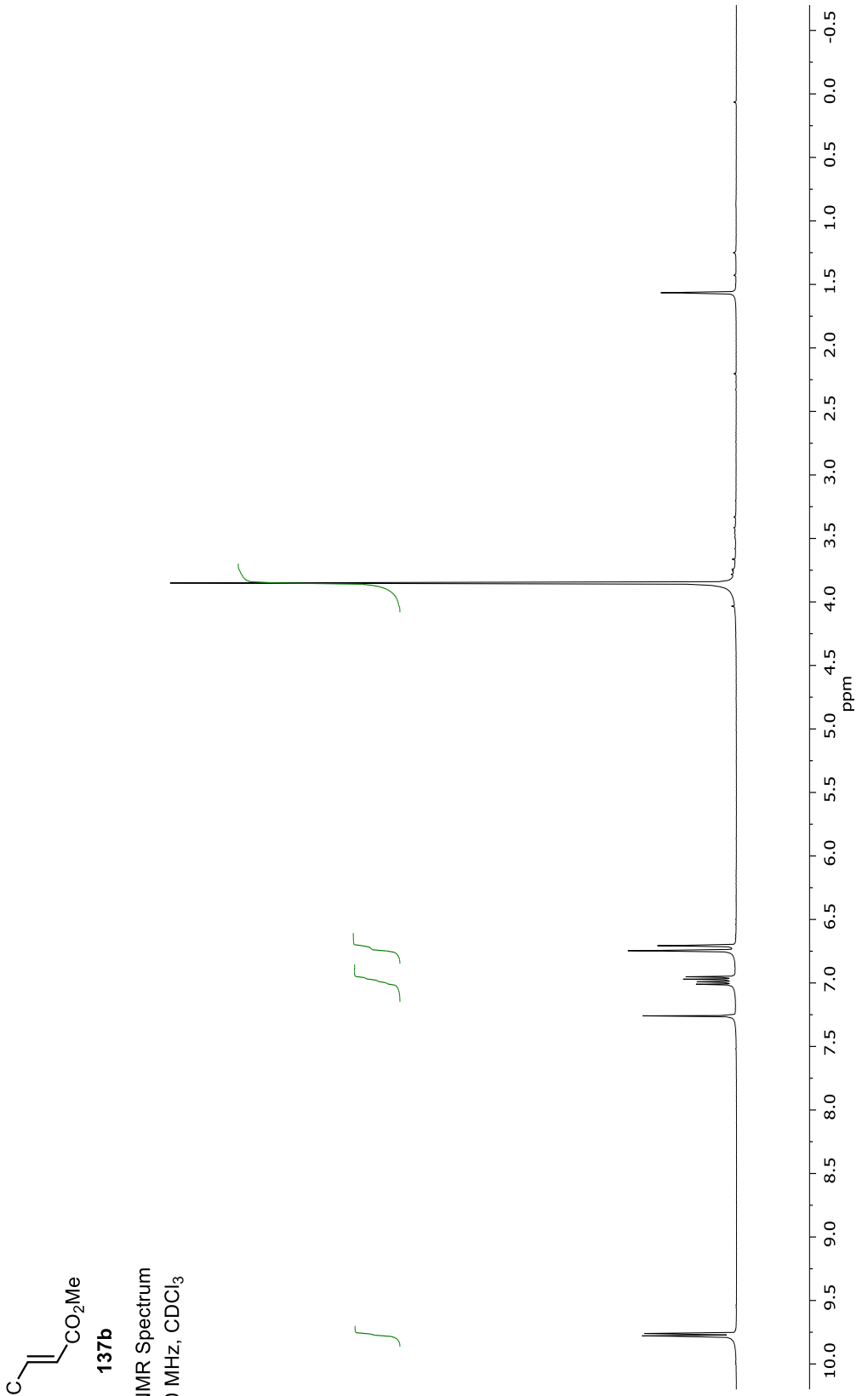


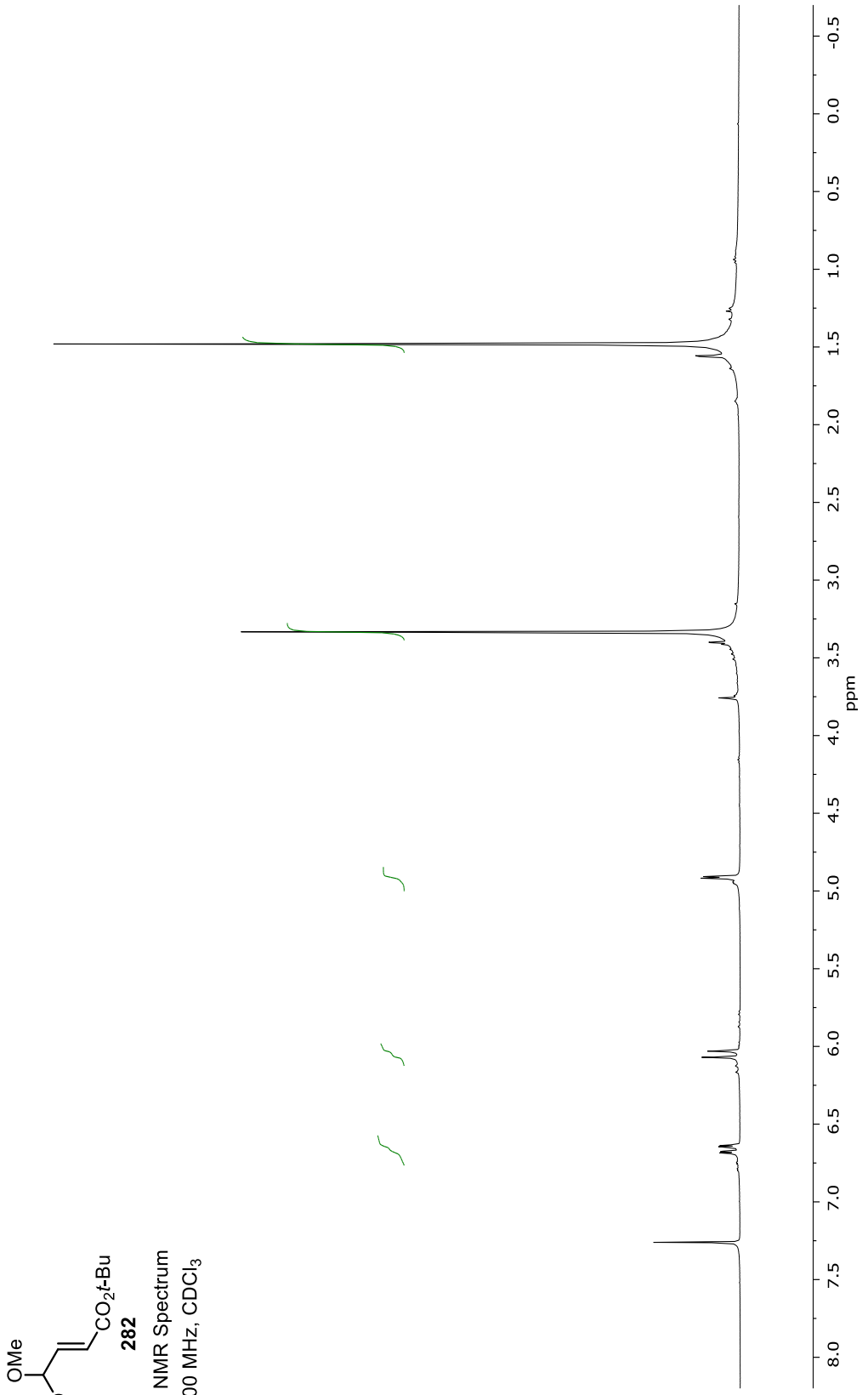

CH2OH
297f
13C NMR Spectrum
100 MHz, CDCl3
26.5
26.0
25.5
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

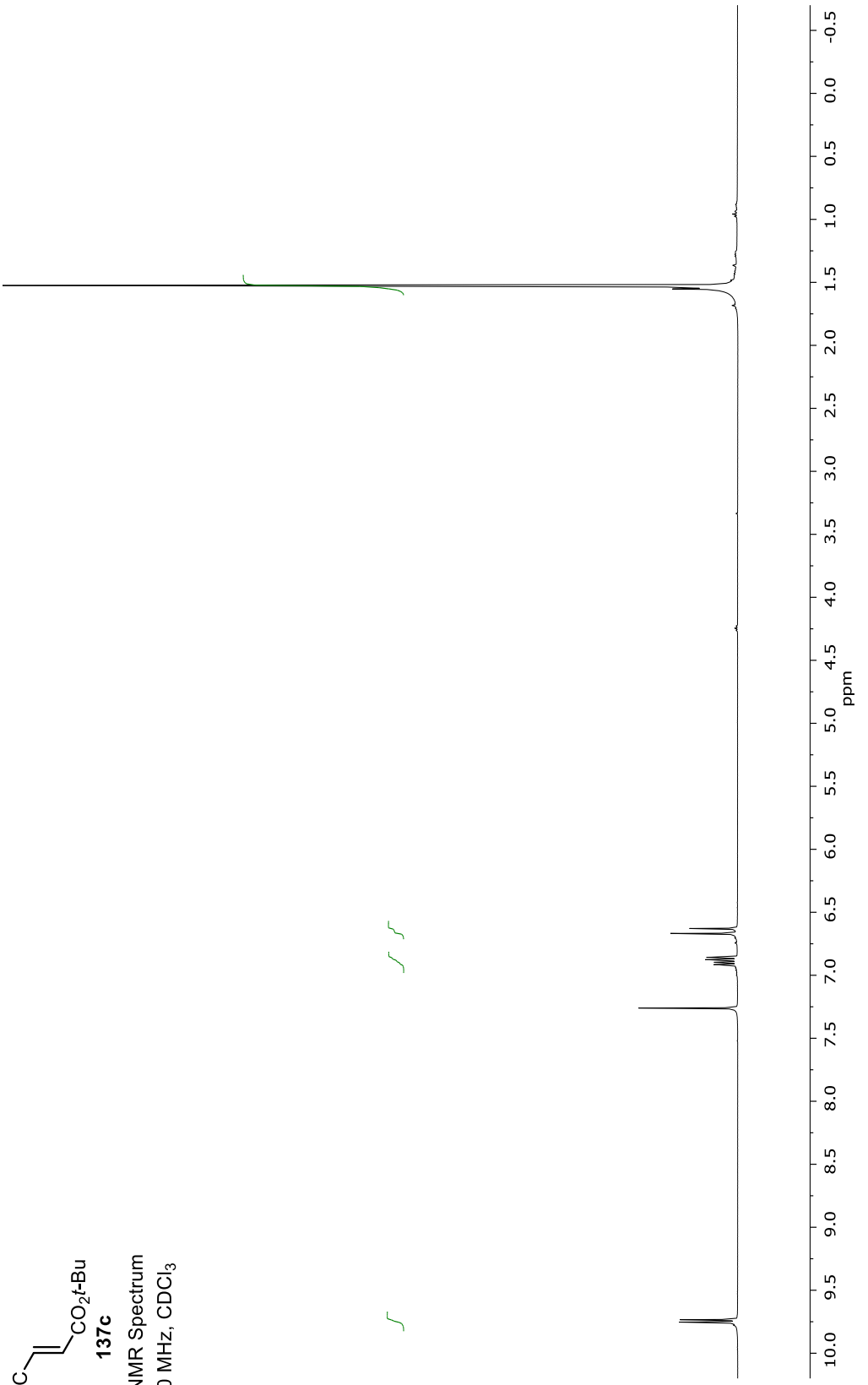

CHO
236f
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

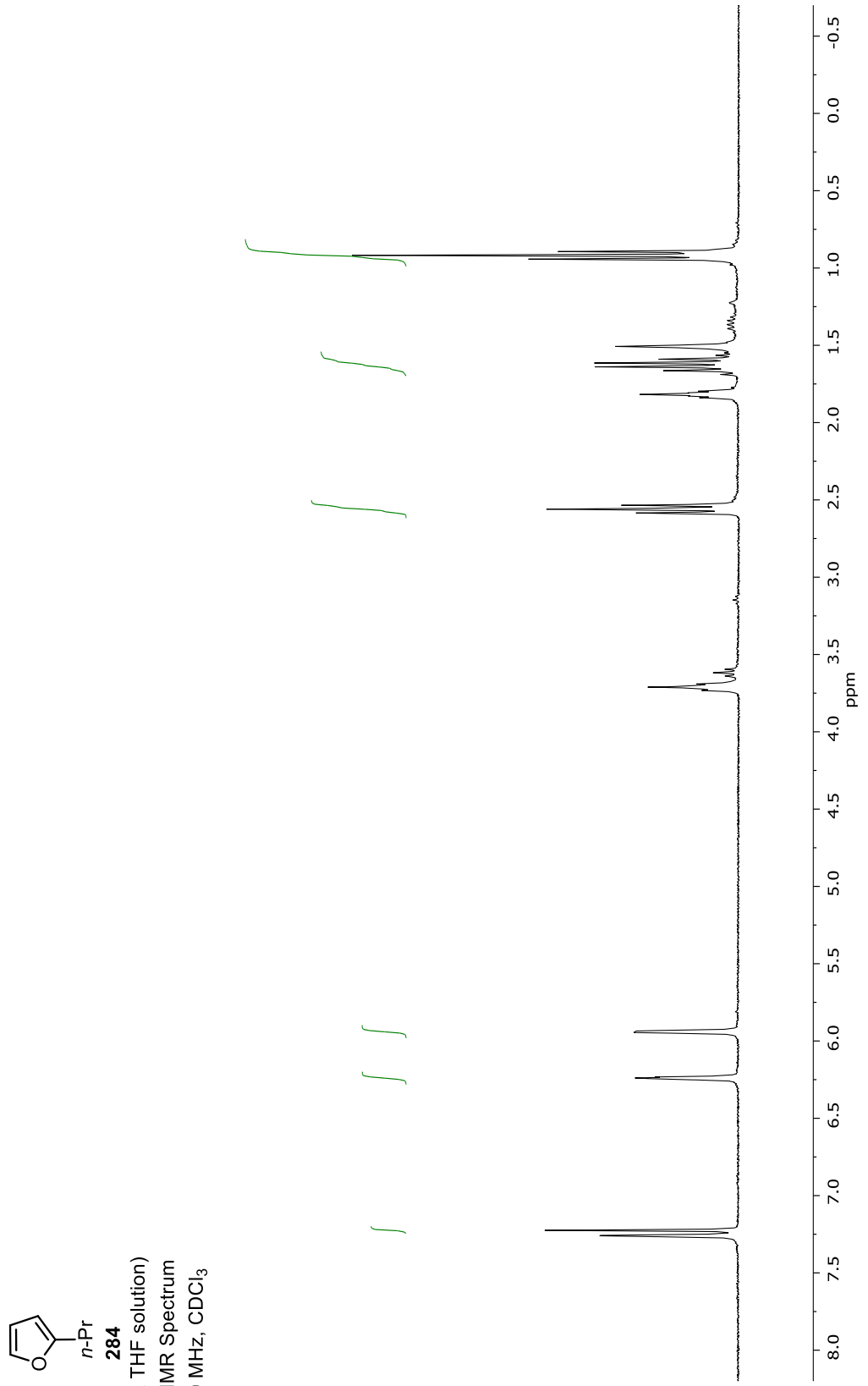

CHO
236f
13C NMR Spectrum
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

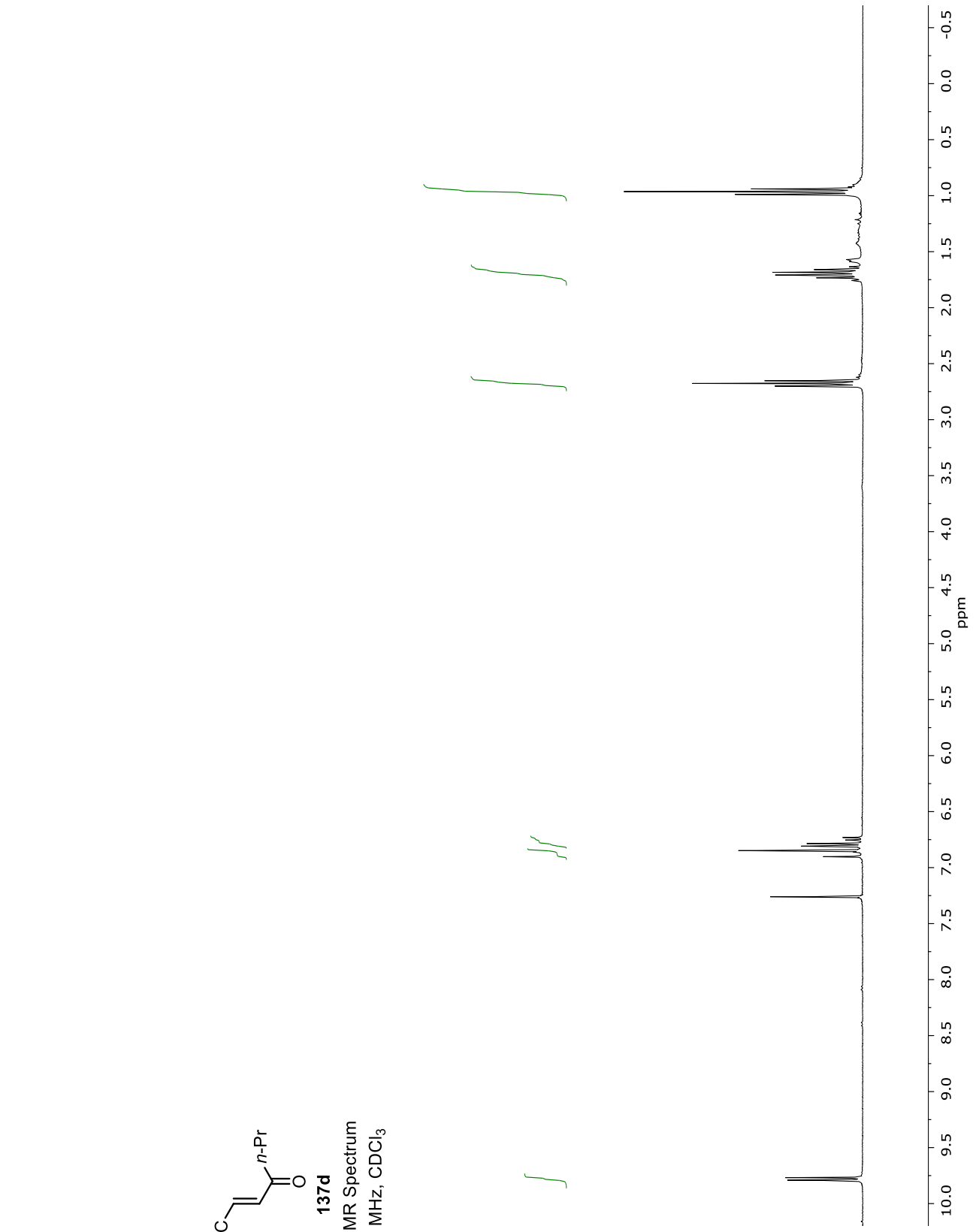

OMe
MeO
CO2Me
281
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

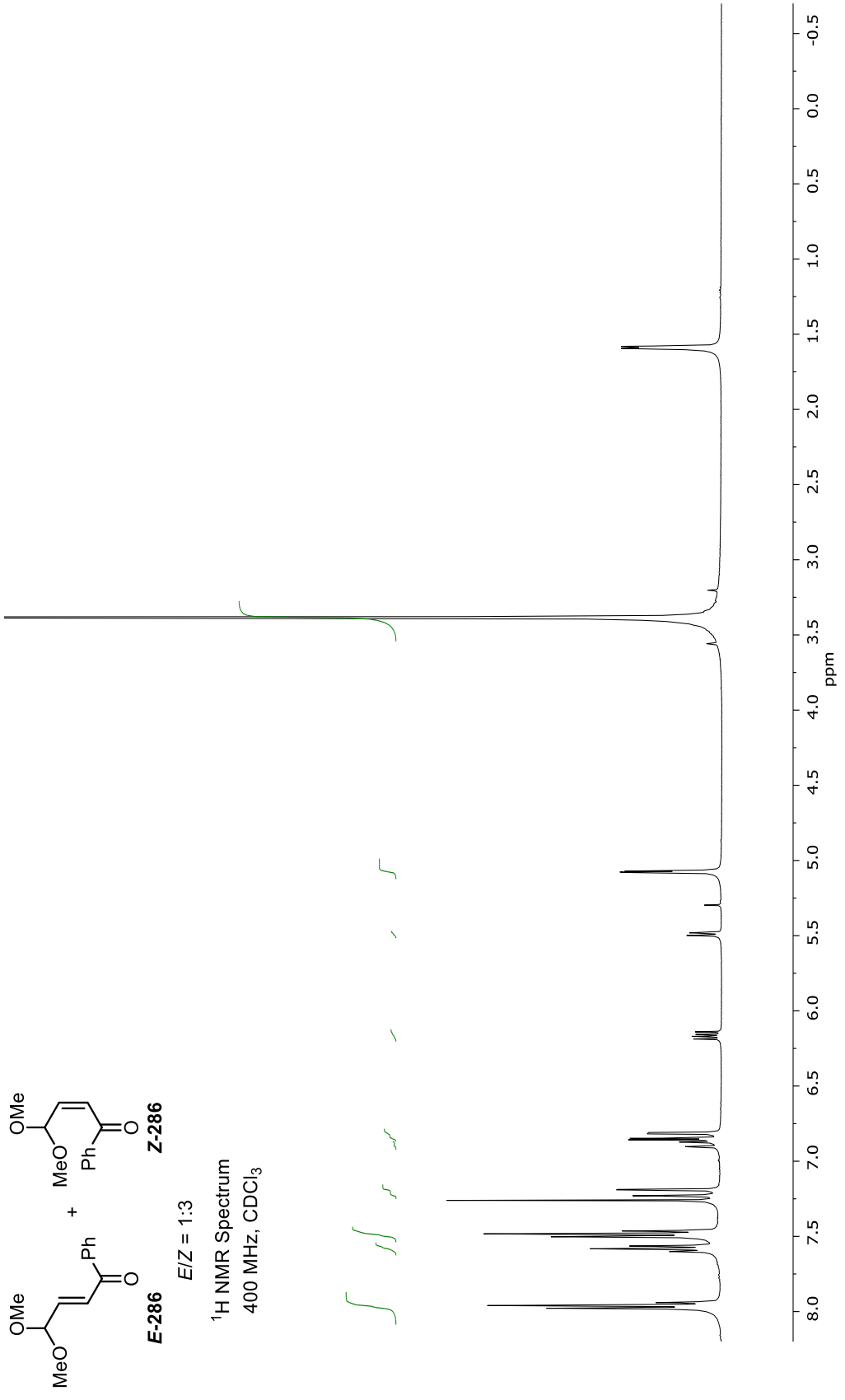

OHC
CO2Me
137b
1H NMR Spectrum
400 MHz, CDCl3
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

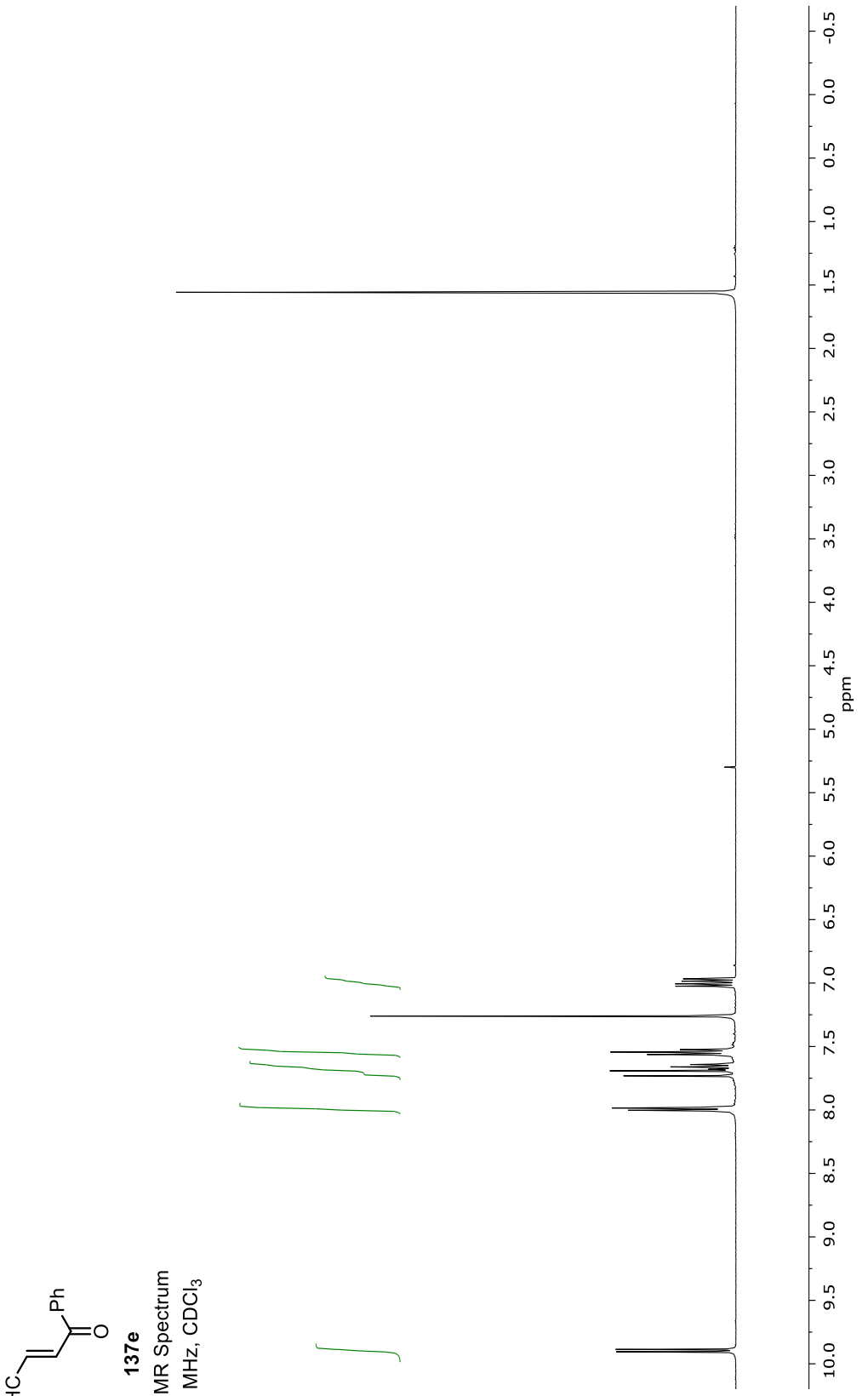

OMe
MeO
CO2t-Bu
282
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

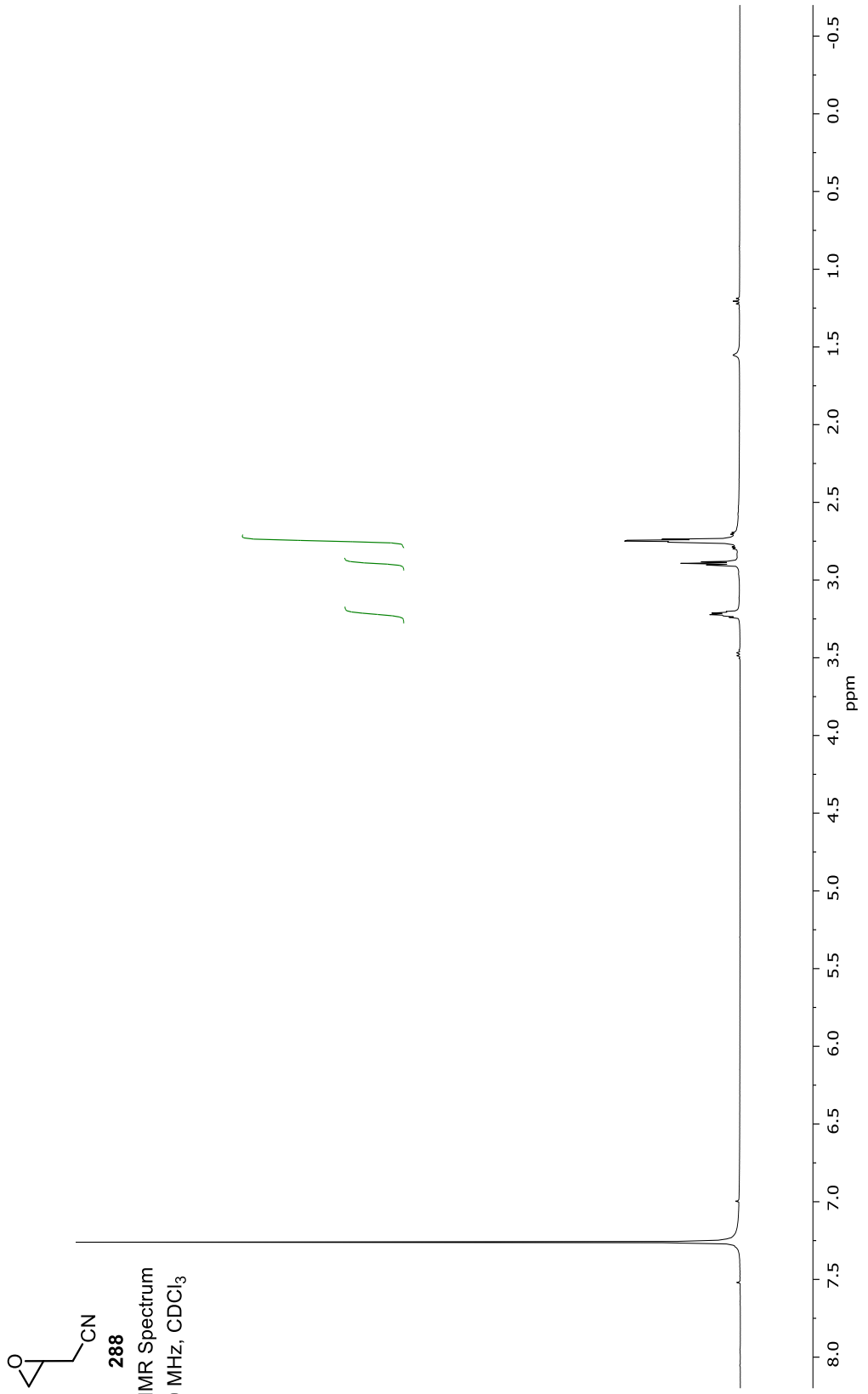

OHC
CO2t-Bu
137c
1H NMR Spectrum
400 MHz, CDCl3
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

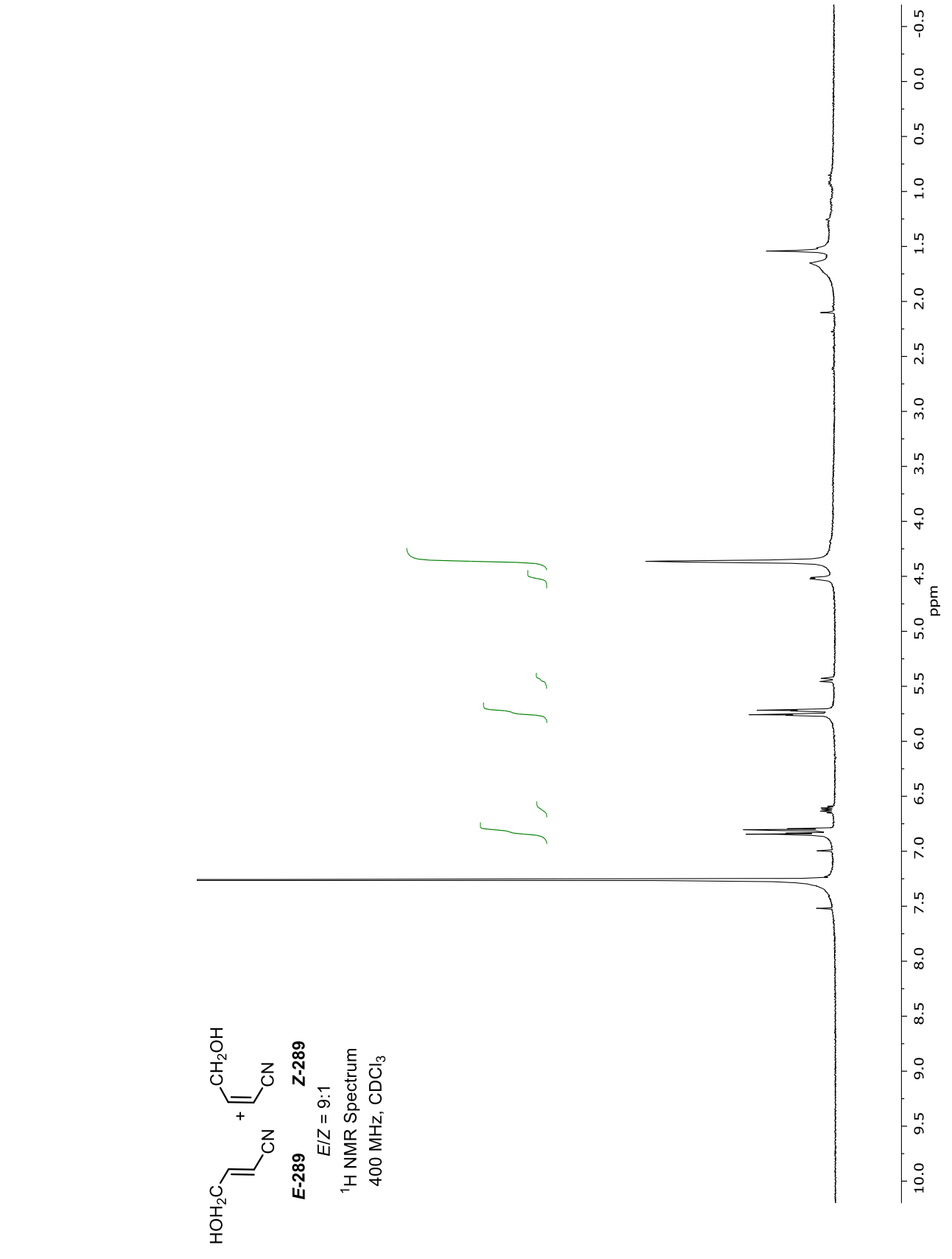

n-Pr
284
(as a THF solution)
1H NMR Spectrum
300 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

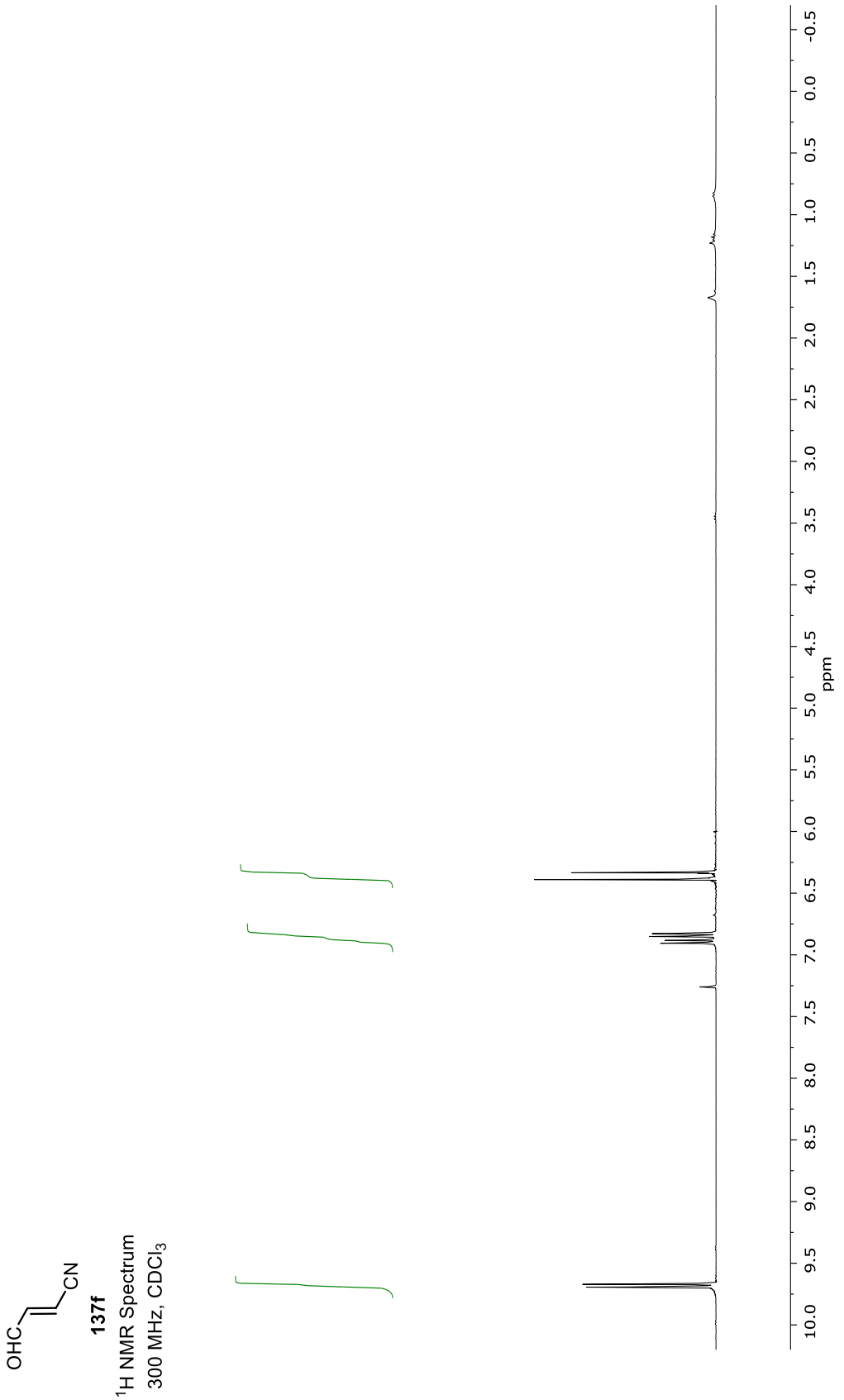

OHC
n-Pr
O
137d
1H NMR Spectrum
400 MHz, CDCl3
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

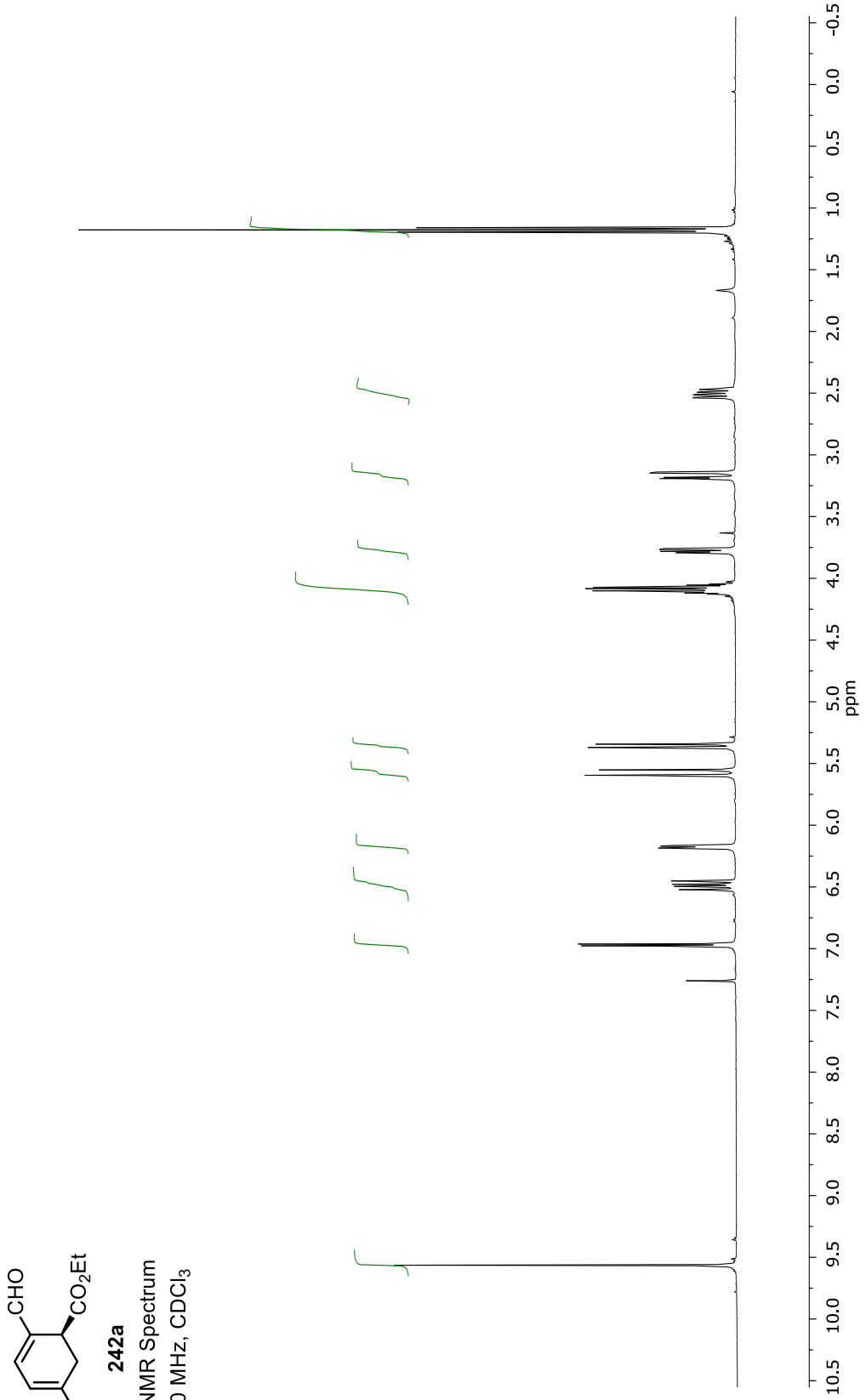

OMe
MeO
Ph
O
E-286
+
OMe
MeO
Ph
O
Z-286
E/Z = 1:3
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

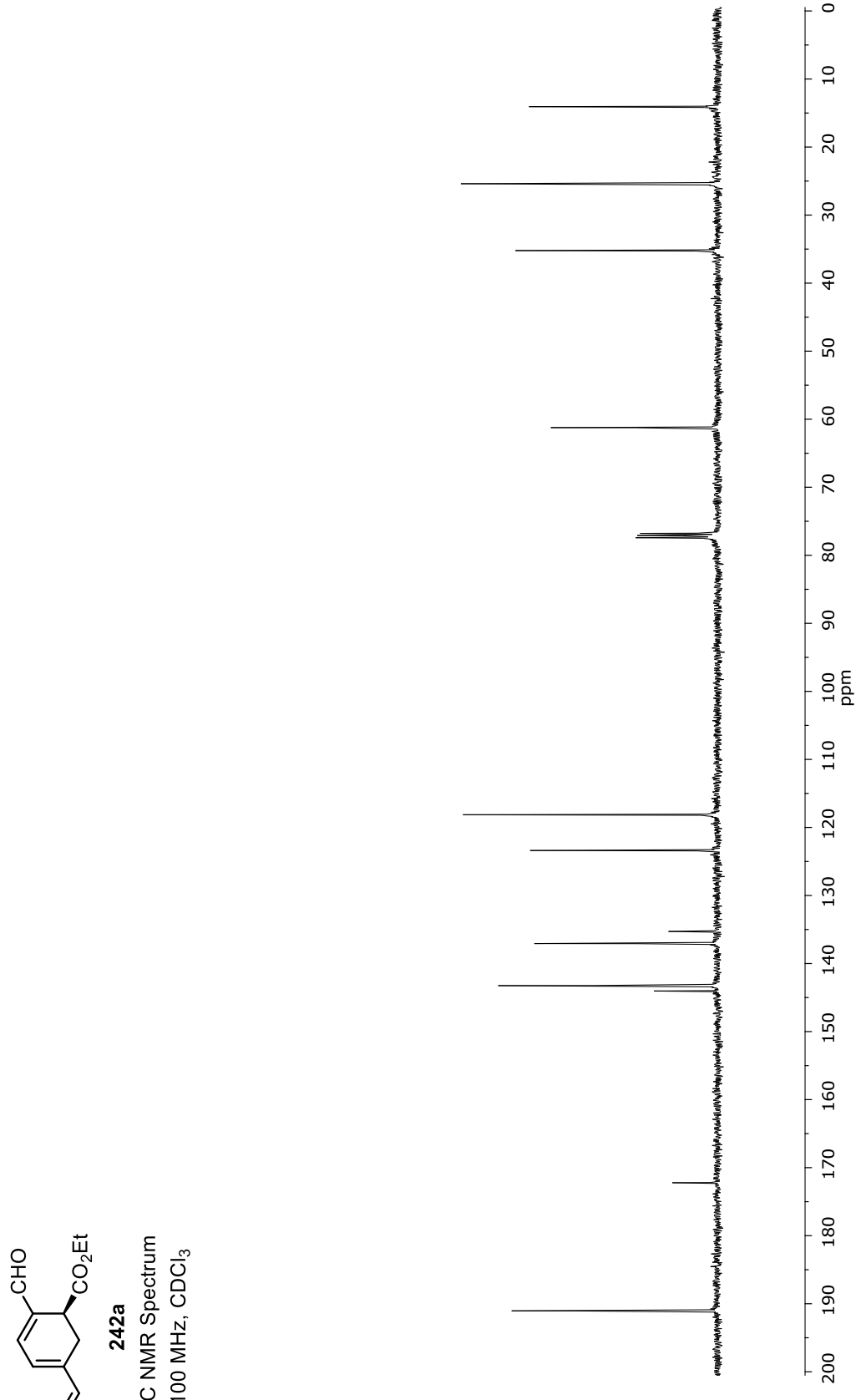

OHC
Ph
O
137e
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

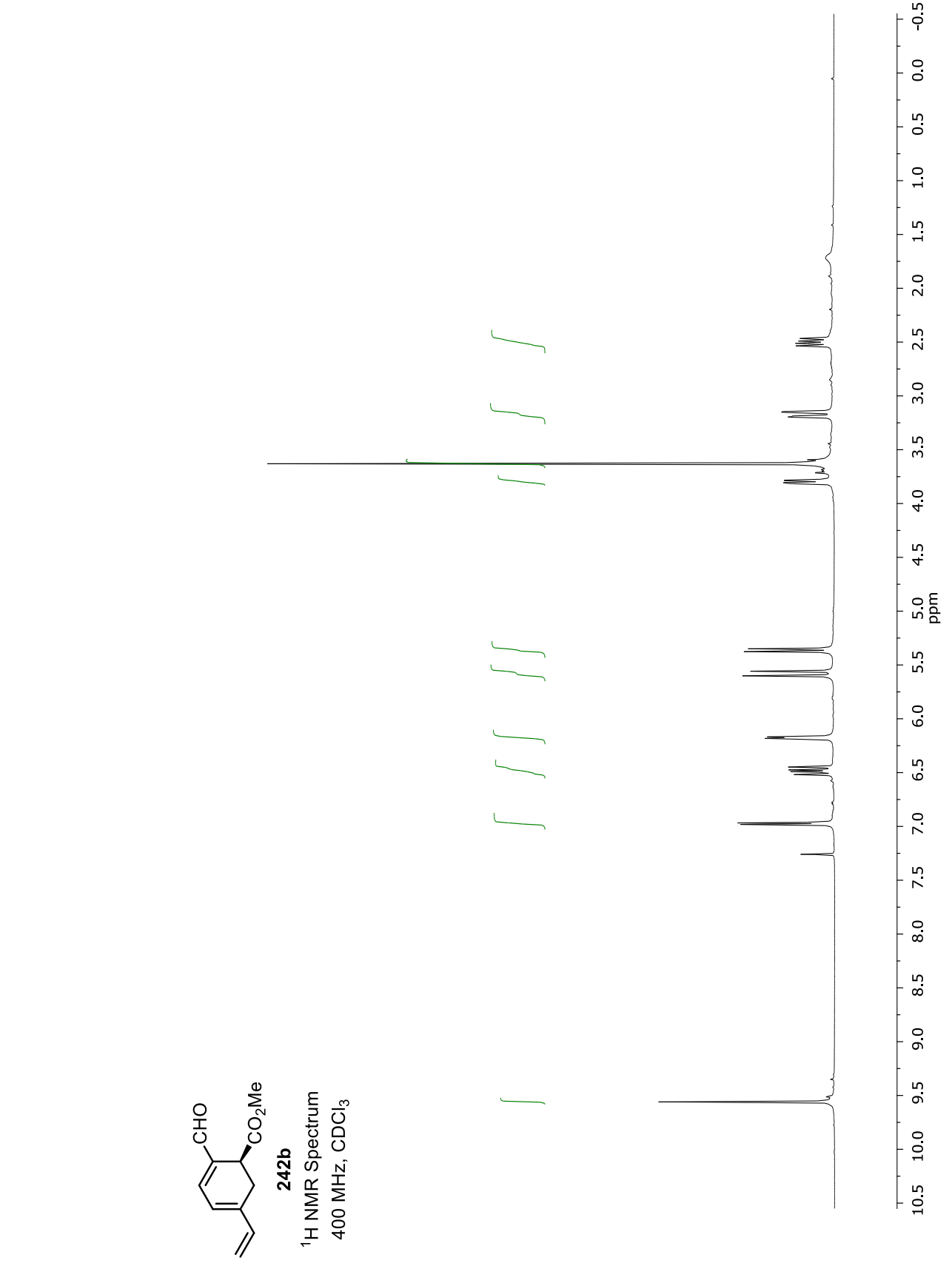

O
CN
288
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

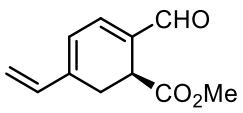

HOH2C
CN
+
CH2OH
CN
E-289
Z-289
E/Z = 9:1
1H NMR Spectrum
400 MHz, CDCl3
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm


OHC
CN
137f
^{1}H NMR Spectrum
300 MHz, $CDCl_3$
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm


CHO
CO2Et
242a
1H NMR Spectrum
400 MHz, CDCl3
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm


CHO
CO2Et
242a
13C NMR Spectrum
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

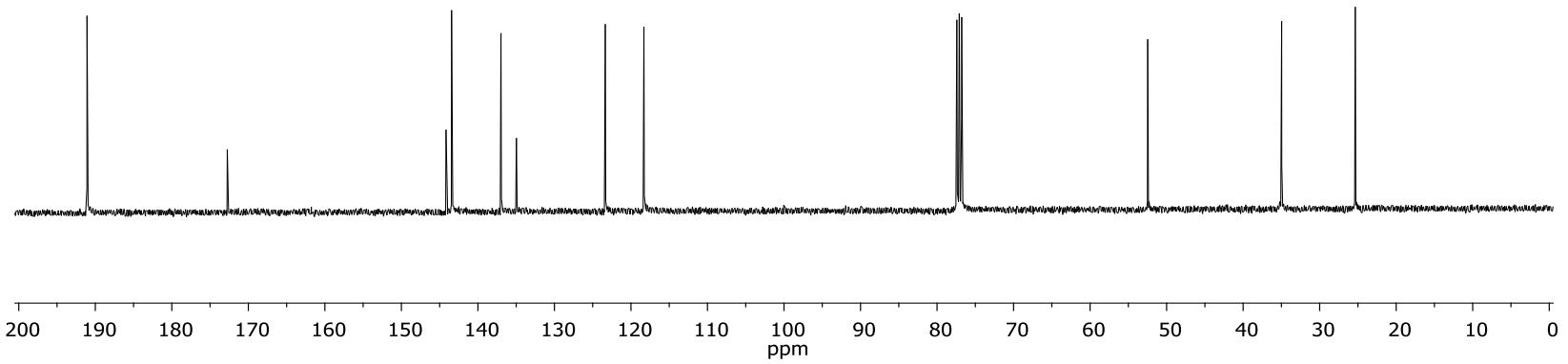

CHO
CO2Me
242b
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

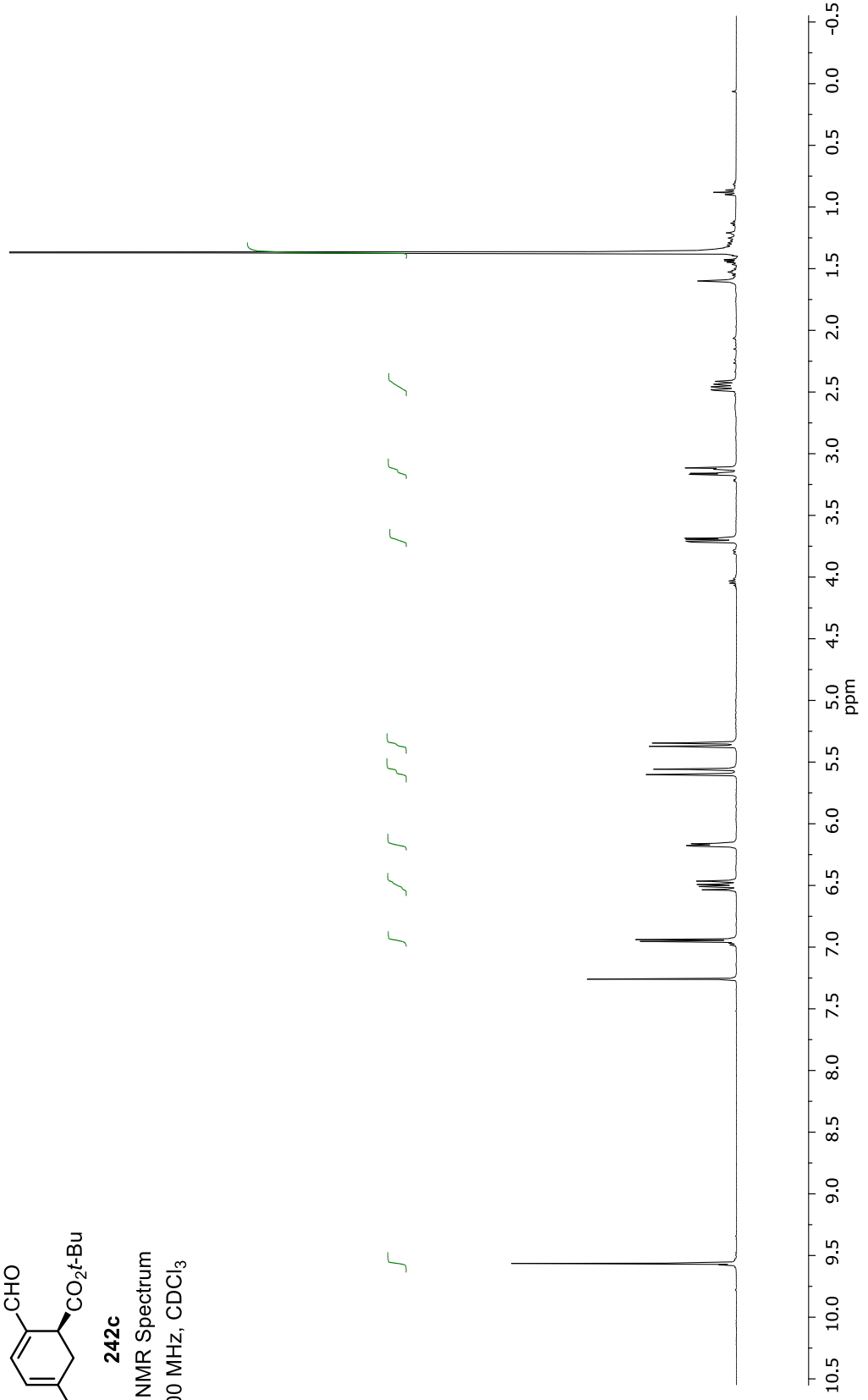


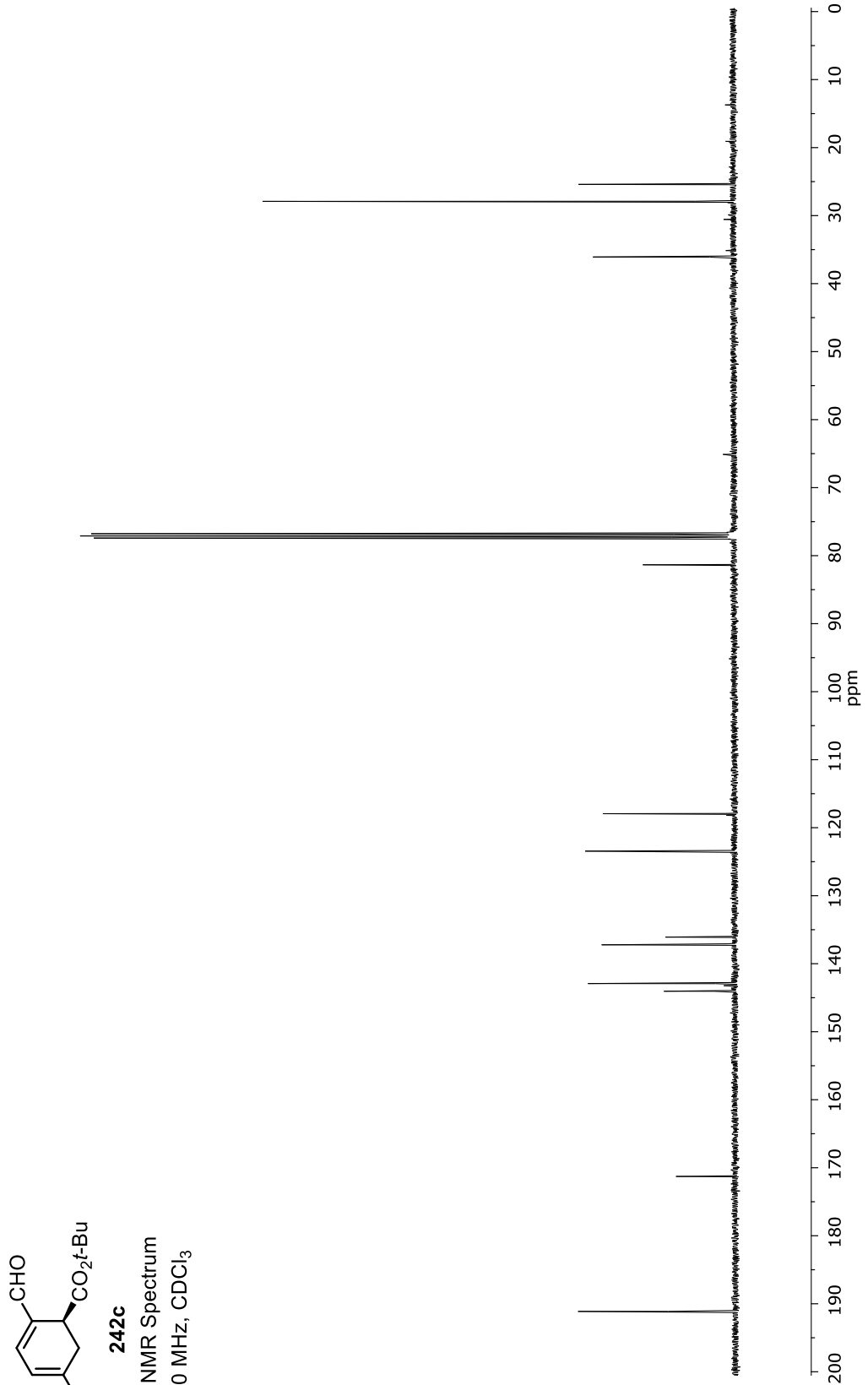
242b

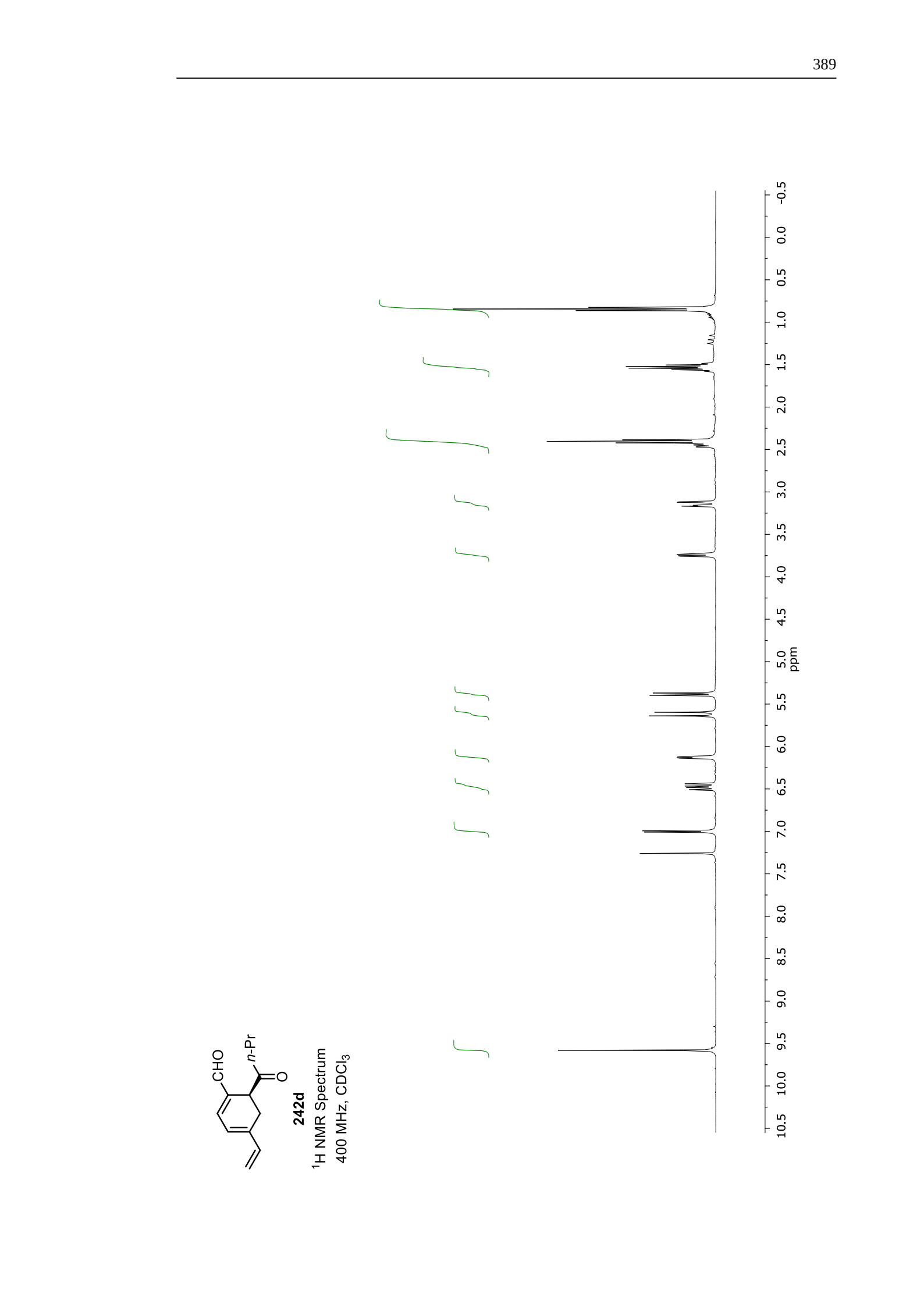
^{13}C NMR Spectrum

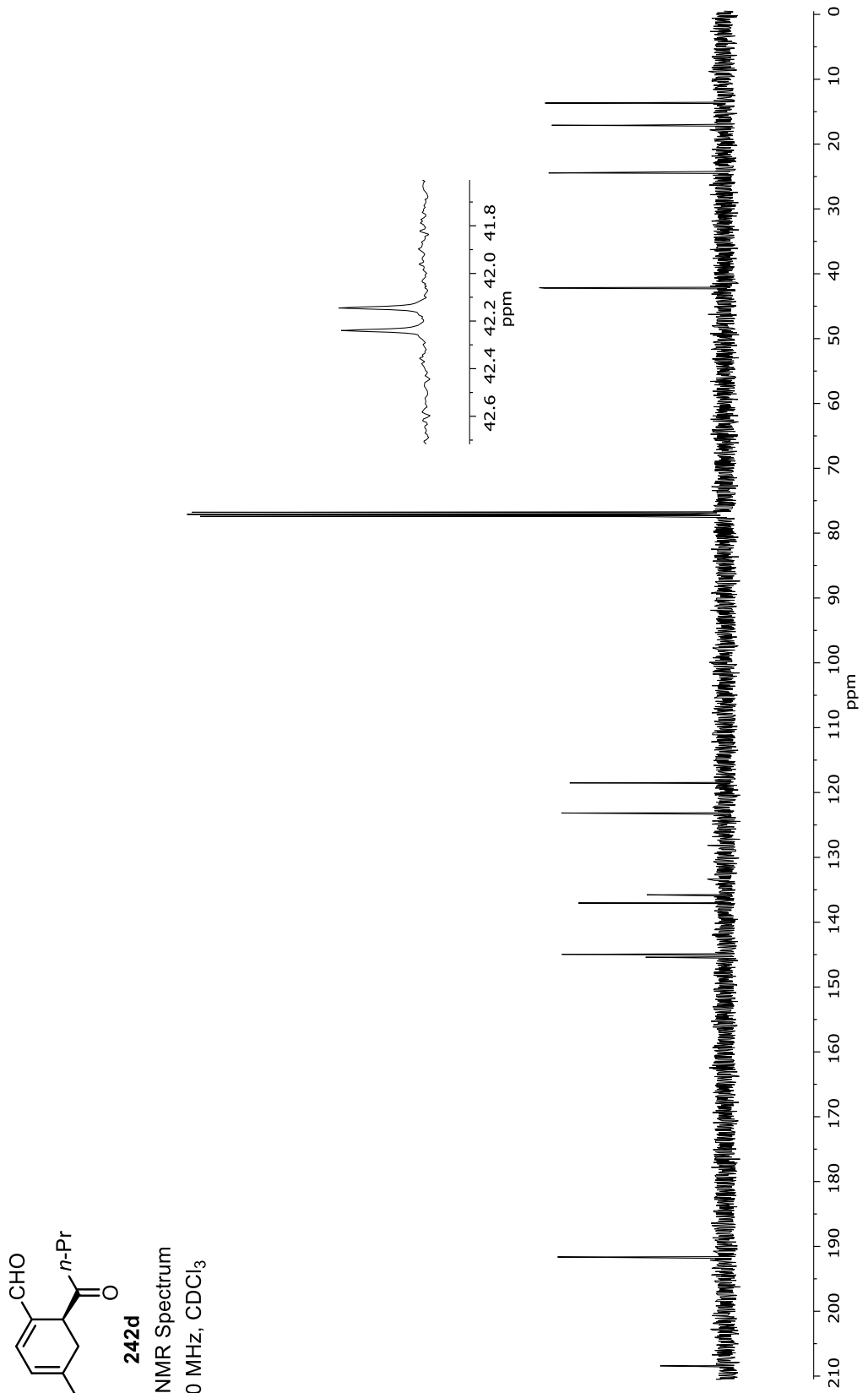
100 MHz, $CDCl_3$




CHO
CO2t-Bu
242c
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


CHO
CO2t-Bu
242c
13C NMR Spectrum
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

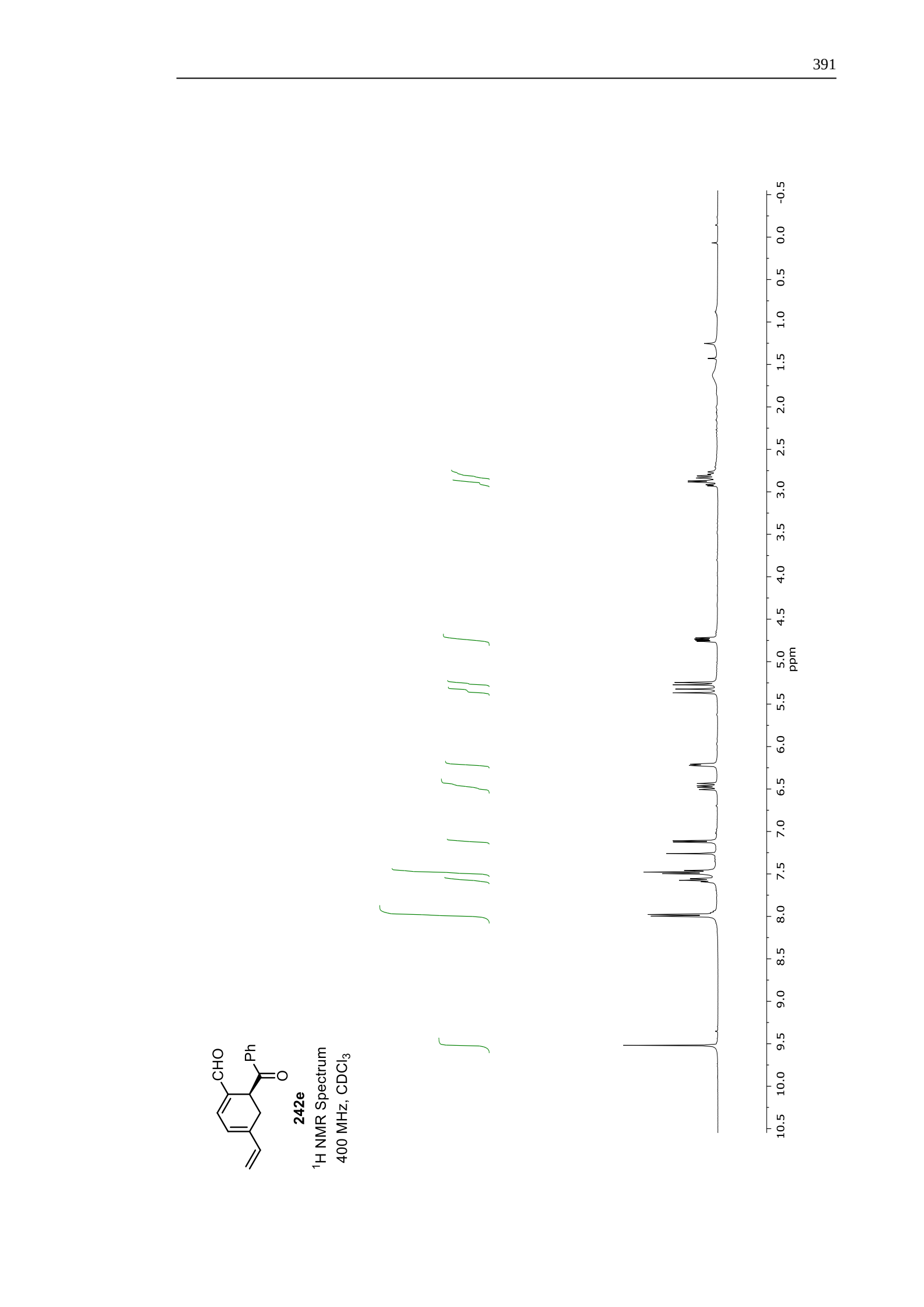

CHO
n-Pr
O
242d
1H NMR Spectrum
400 MHz, CDCl3
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

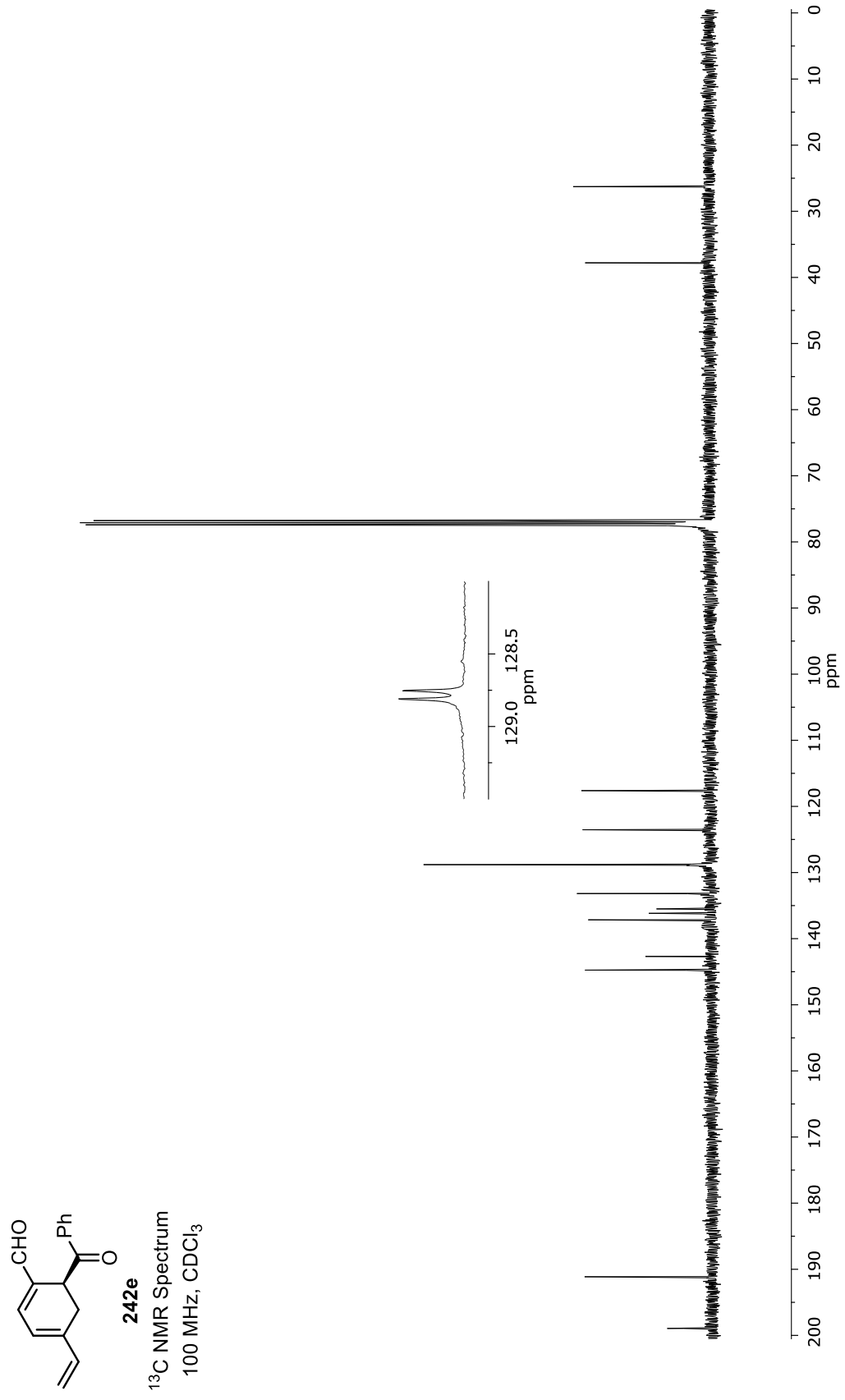


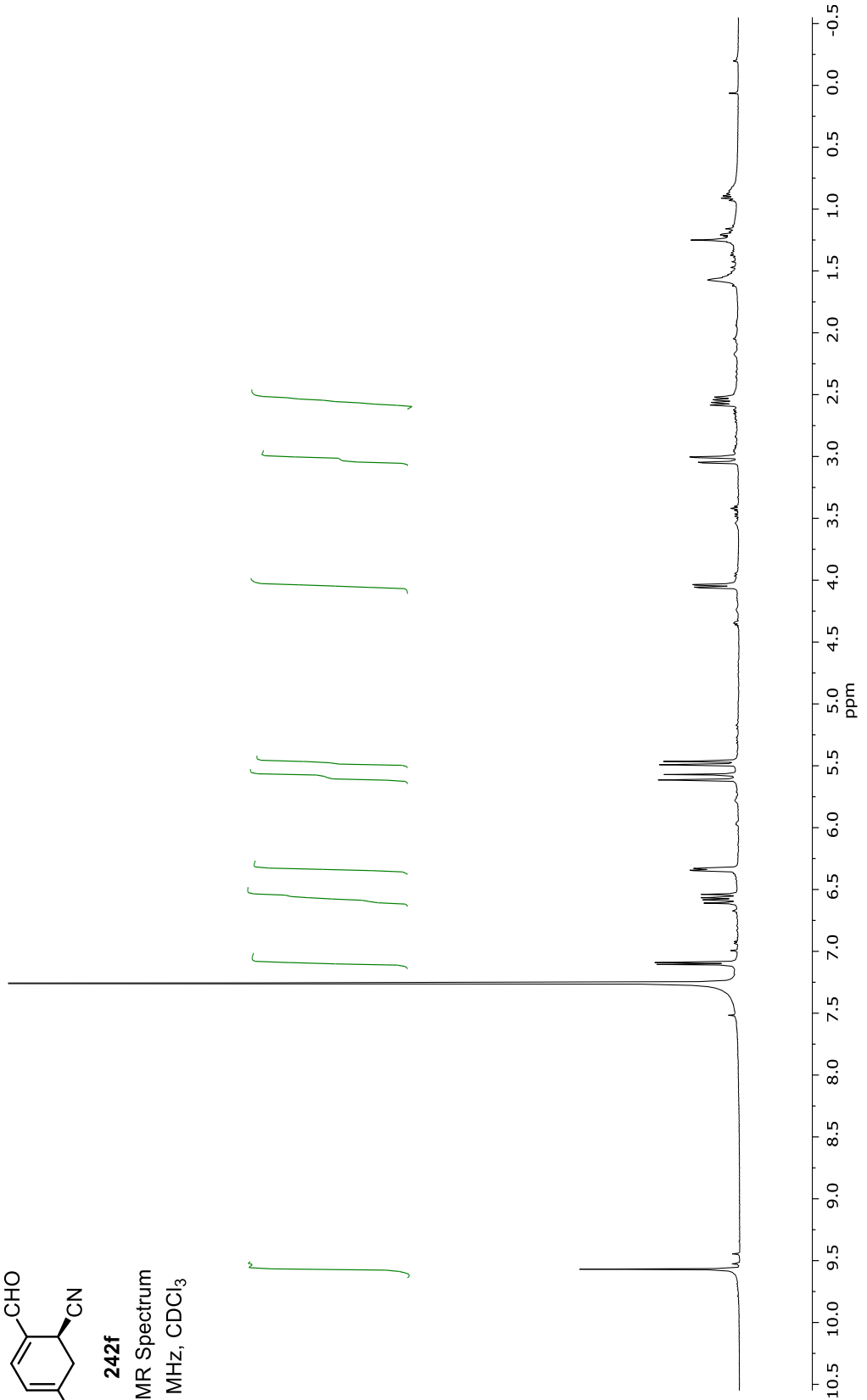
242d

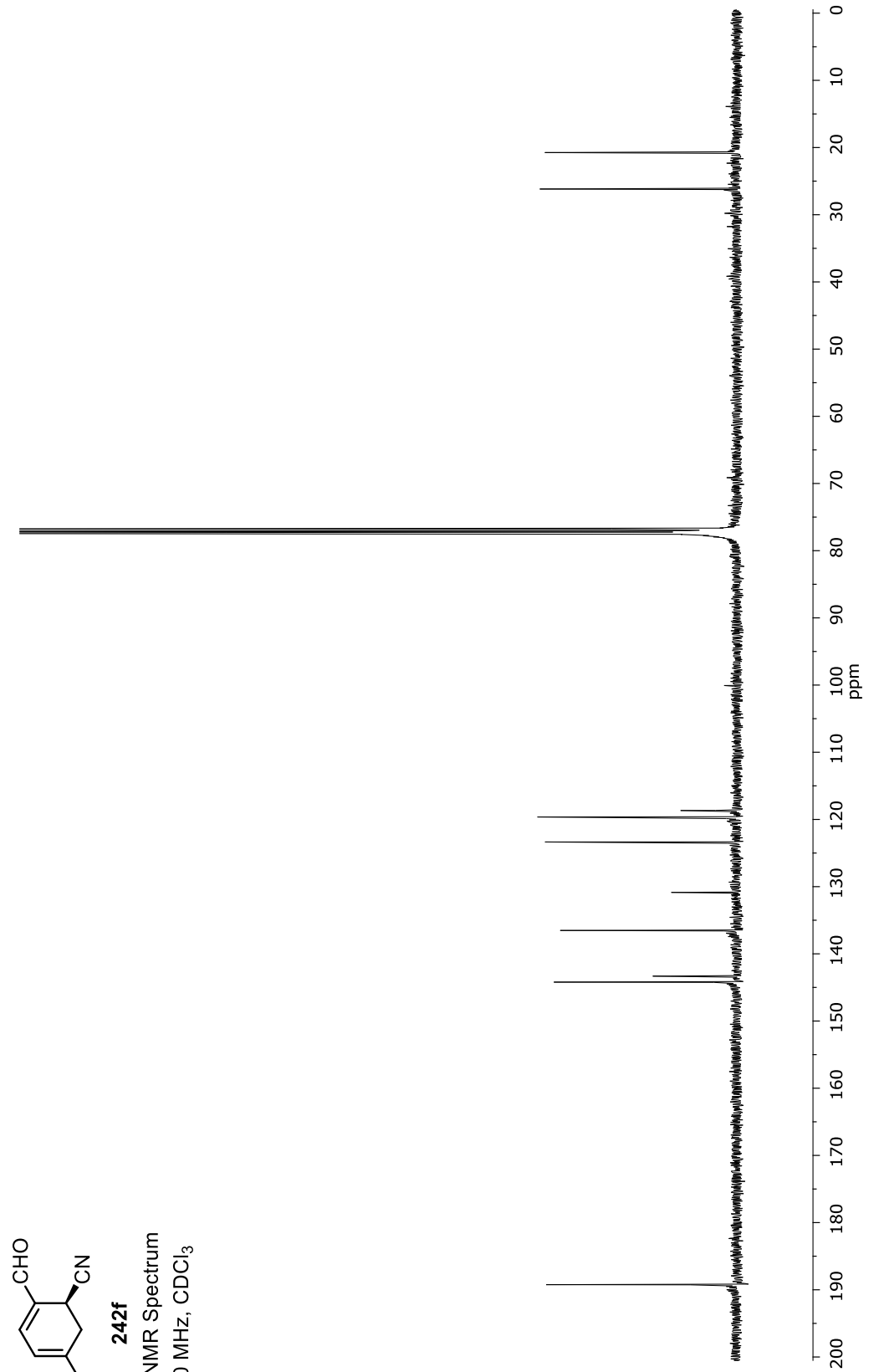
^{13}C NMR Spectrum

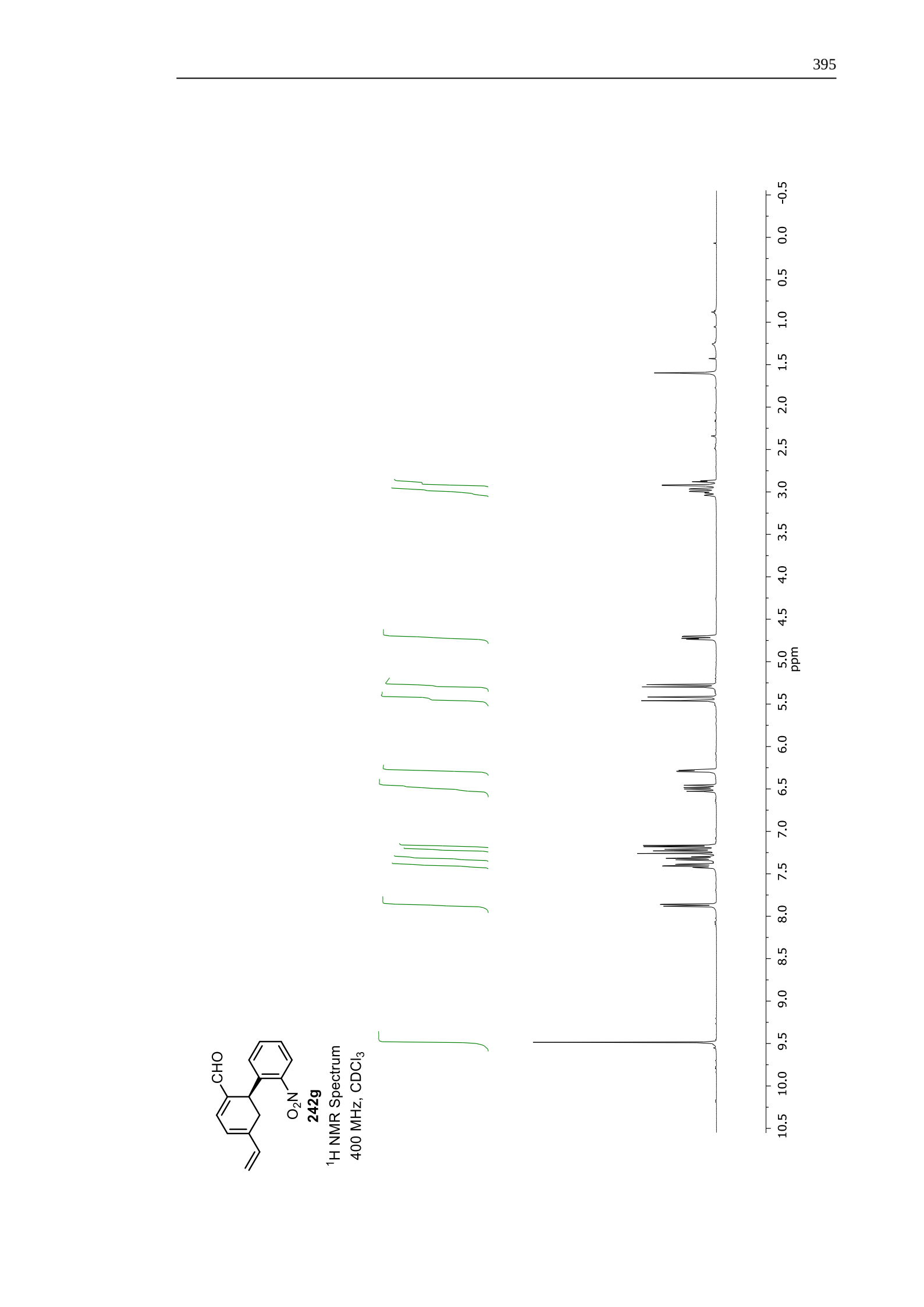
100 MHz, $CDCl_3$

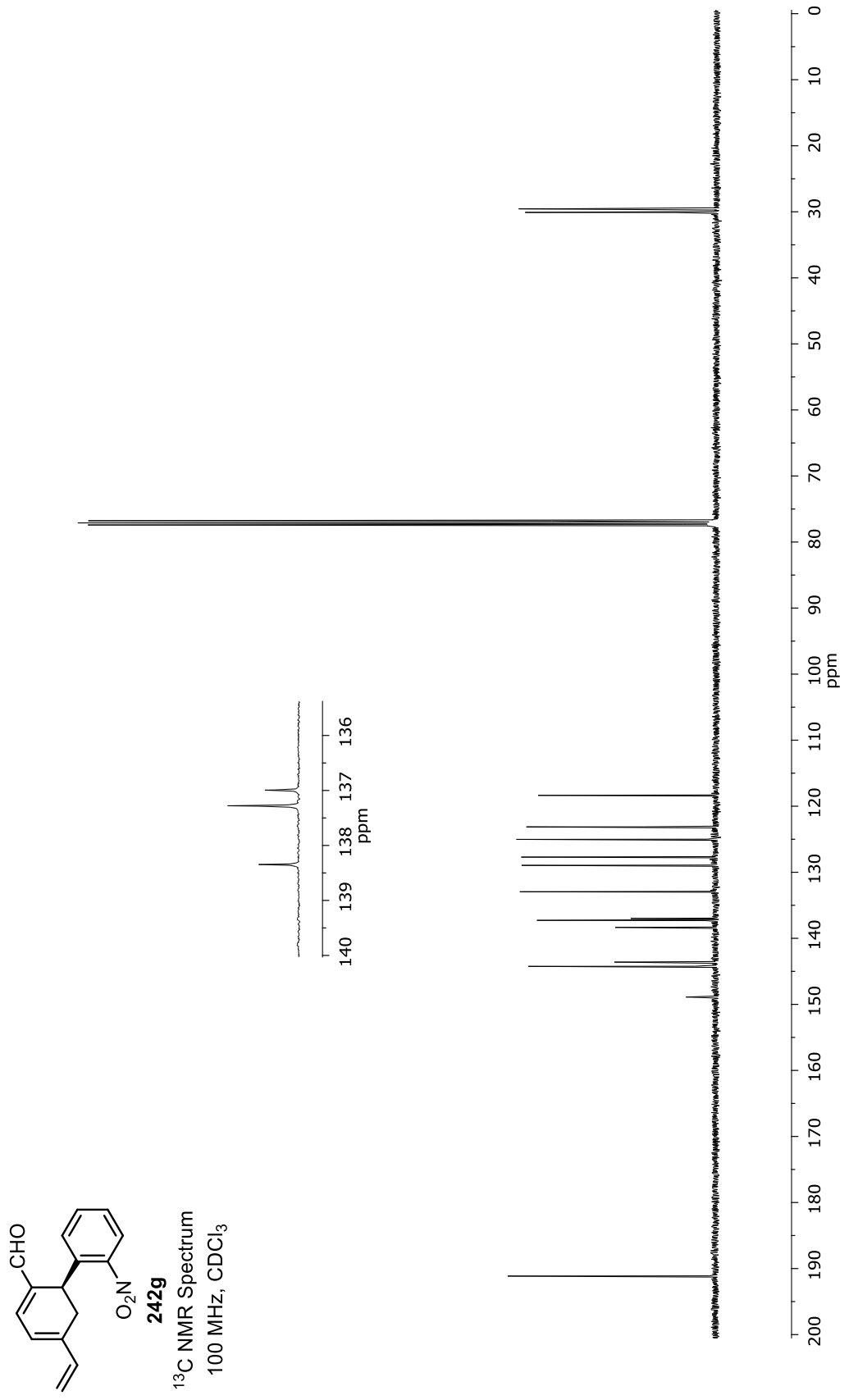

CHO
Ph
O
242e
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

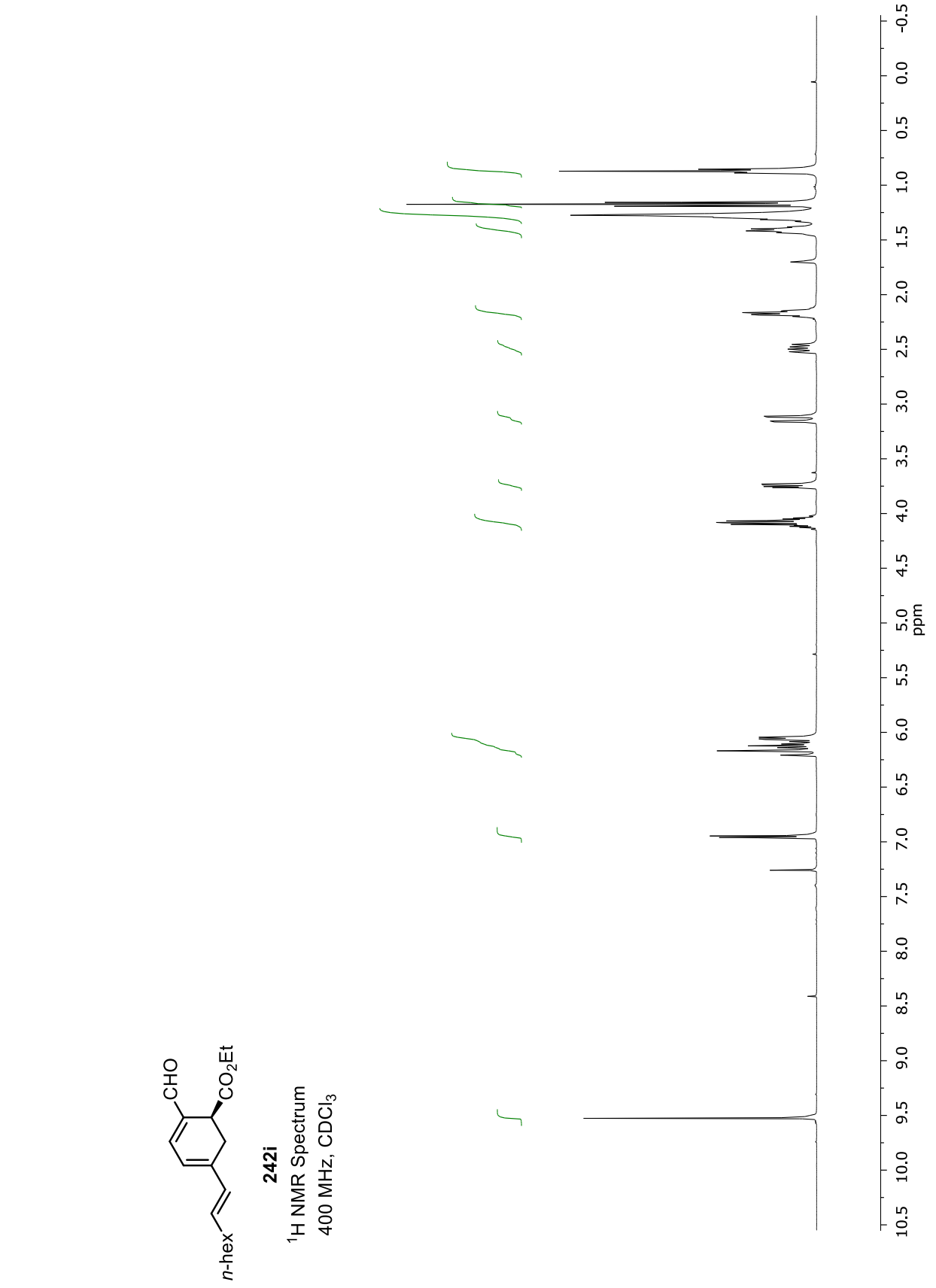

CHO
Ph
O
242e
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
129.0
128.5
ppm
ppm

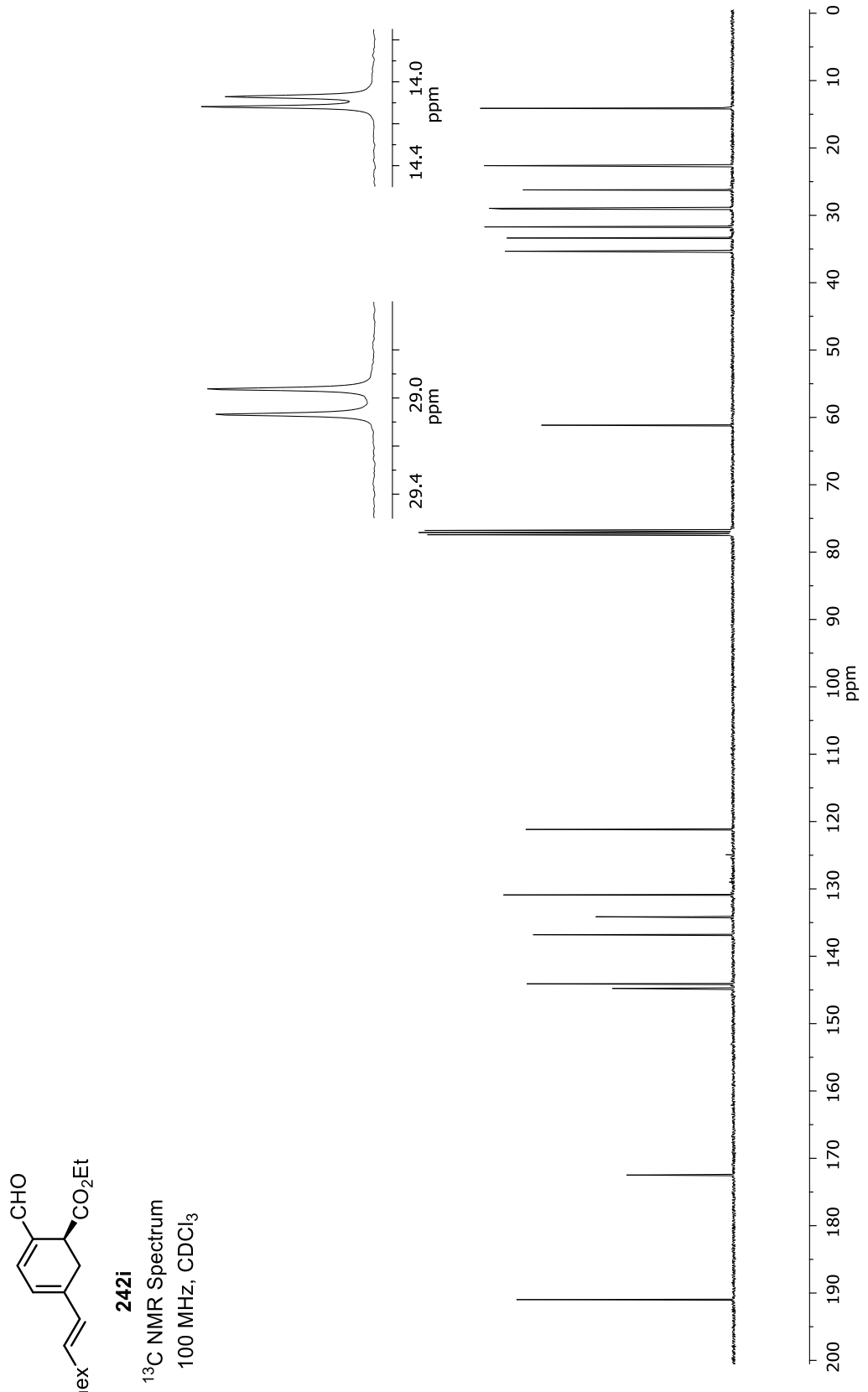

CHO
CN
242f
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

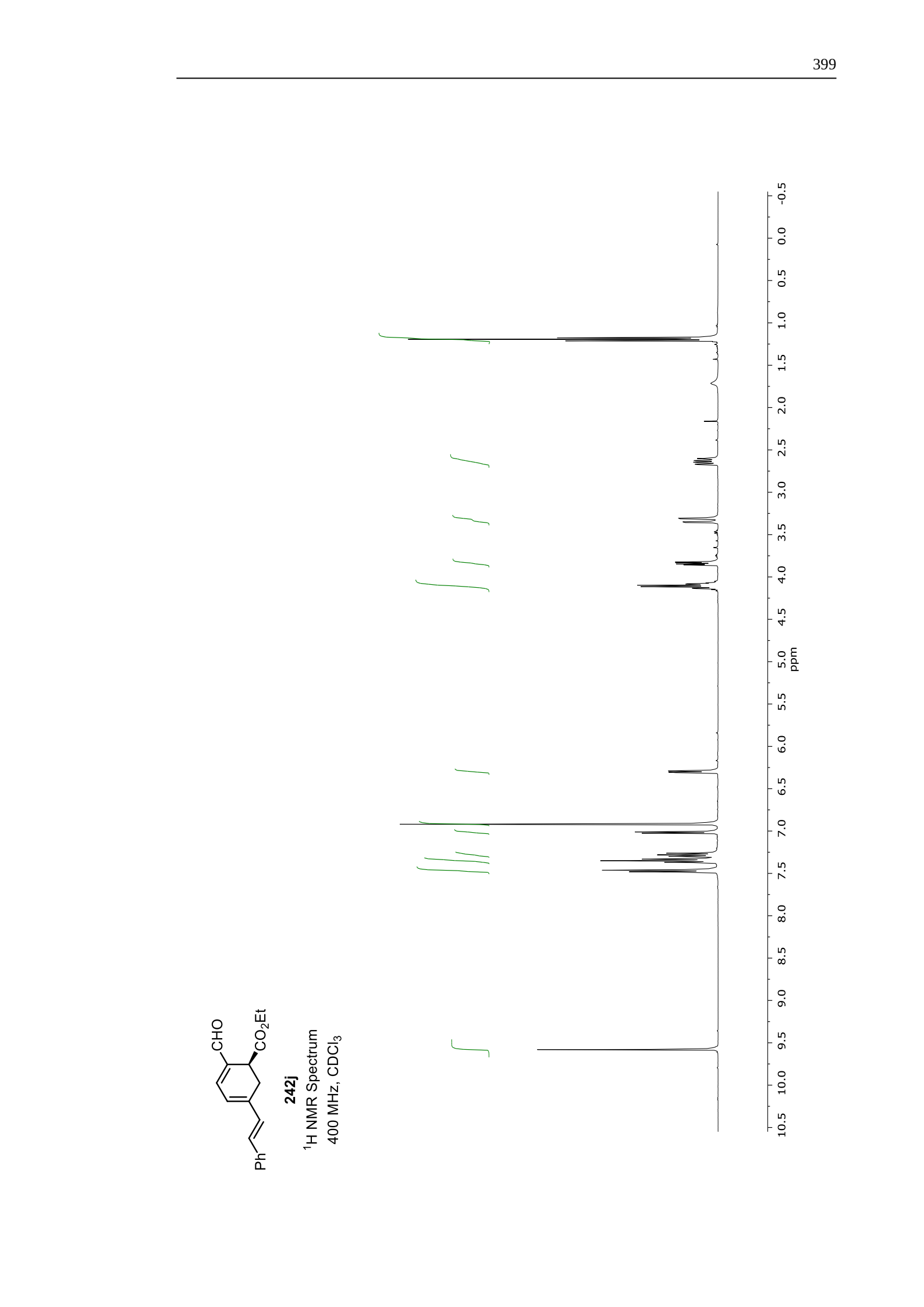

CHO
CN
242f
13C NMR Spectrum
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

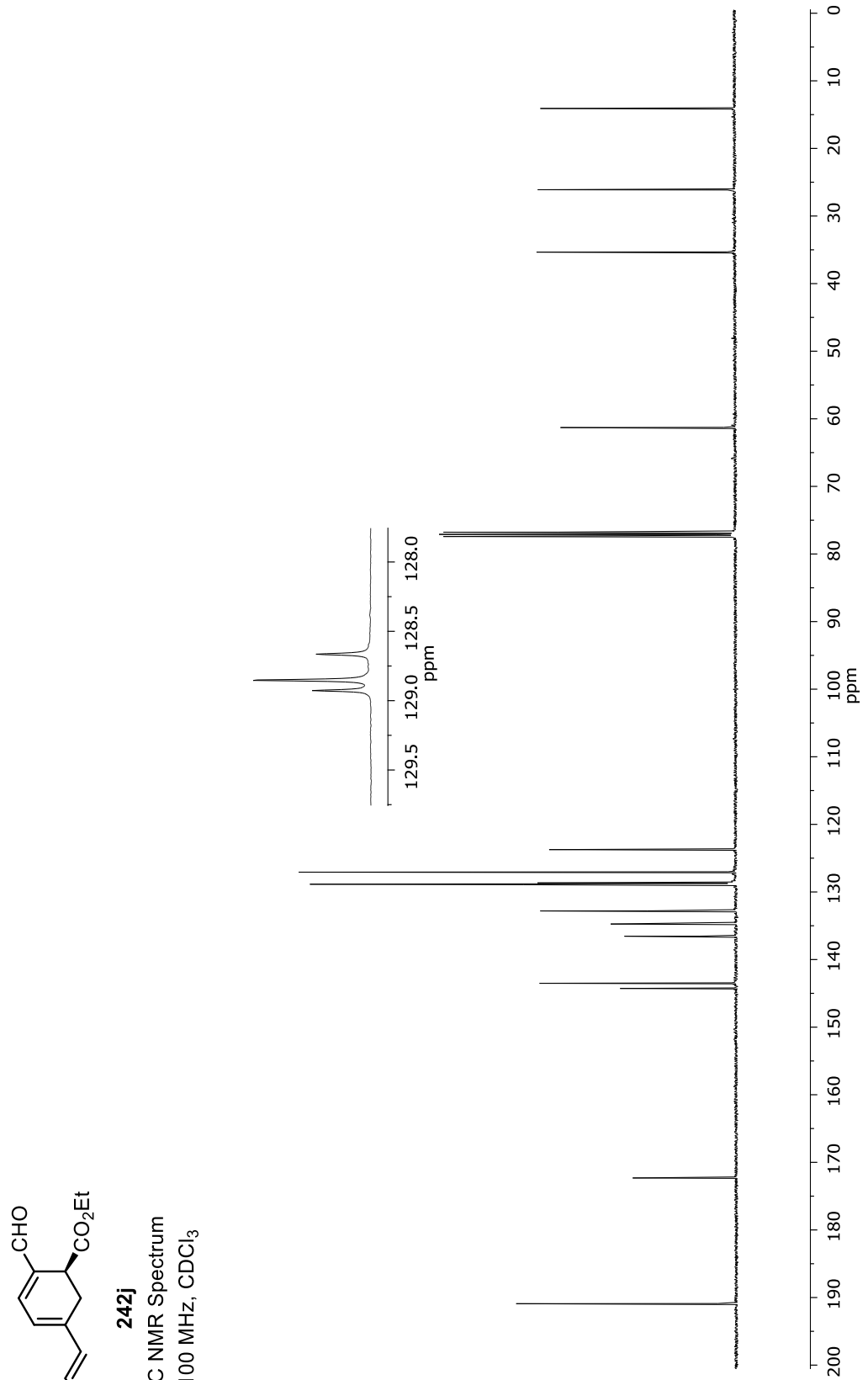

CHO
O2N
242g
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

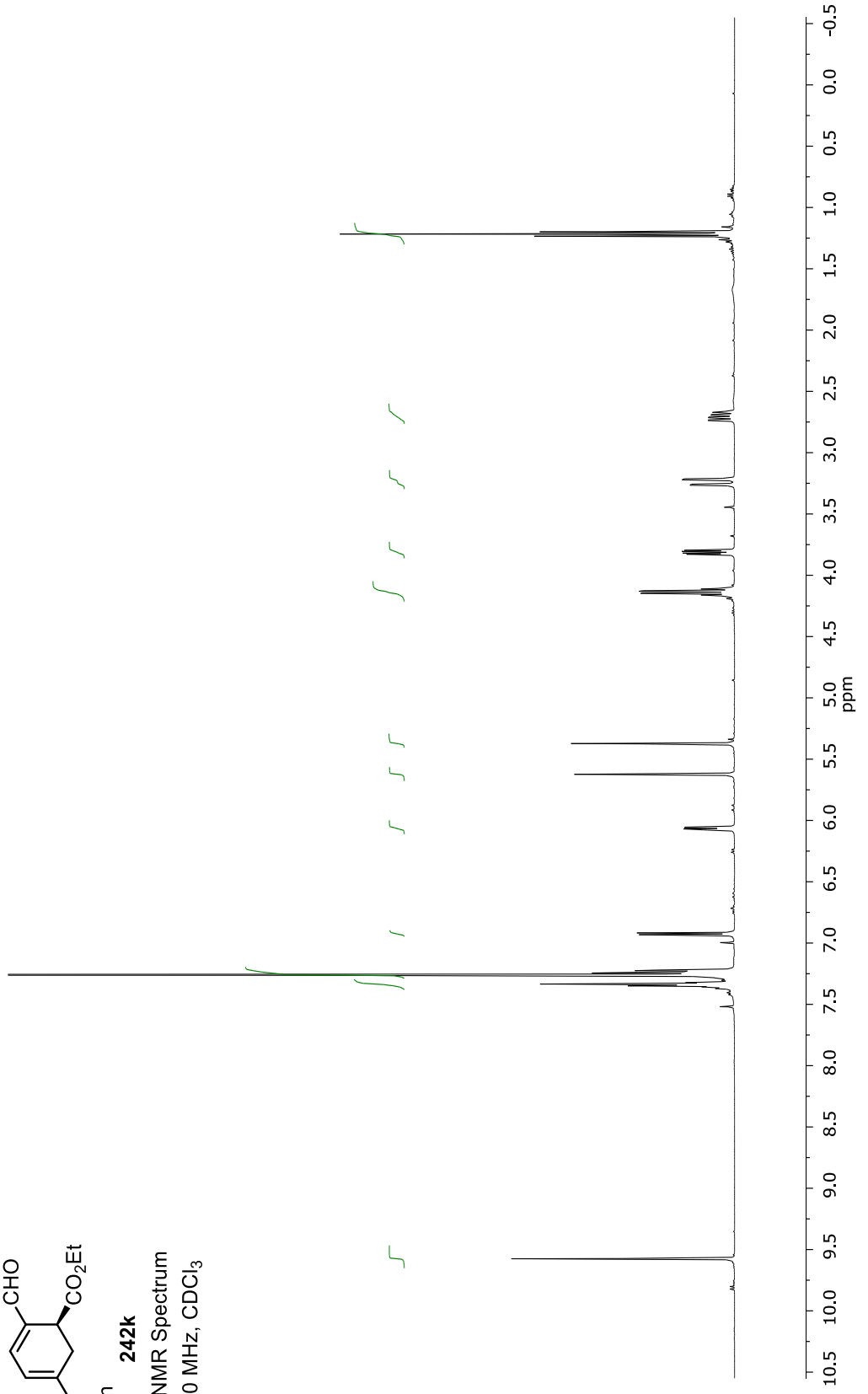

CHO
O2N
242g
13C NMR Spectrum
100 MHz, CDCl3
140 139 138 137 136
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

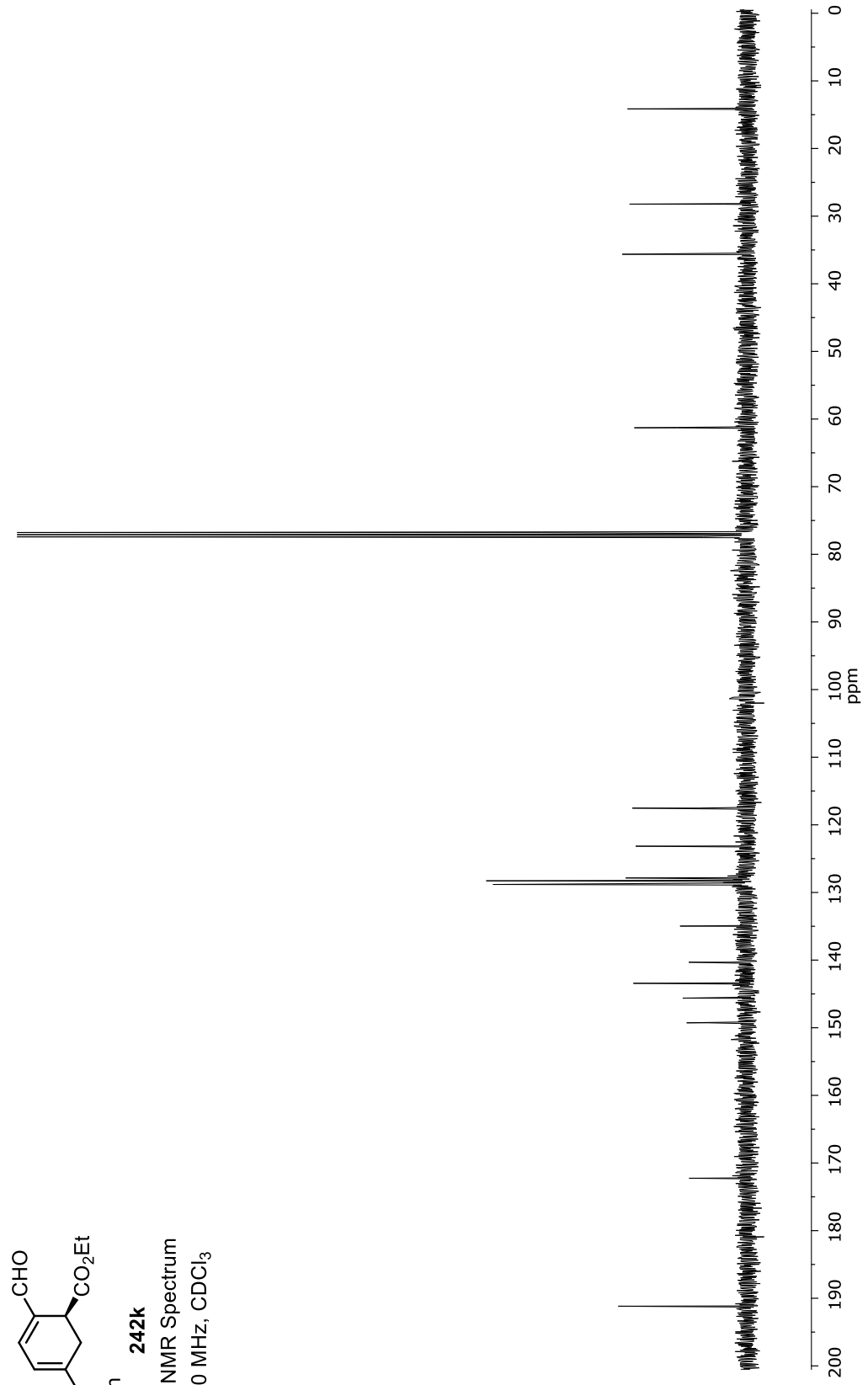

CHO
CO2Et
n-hex
242i
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

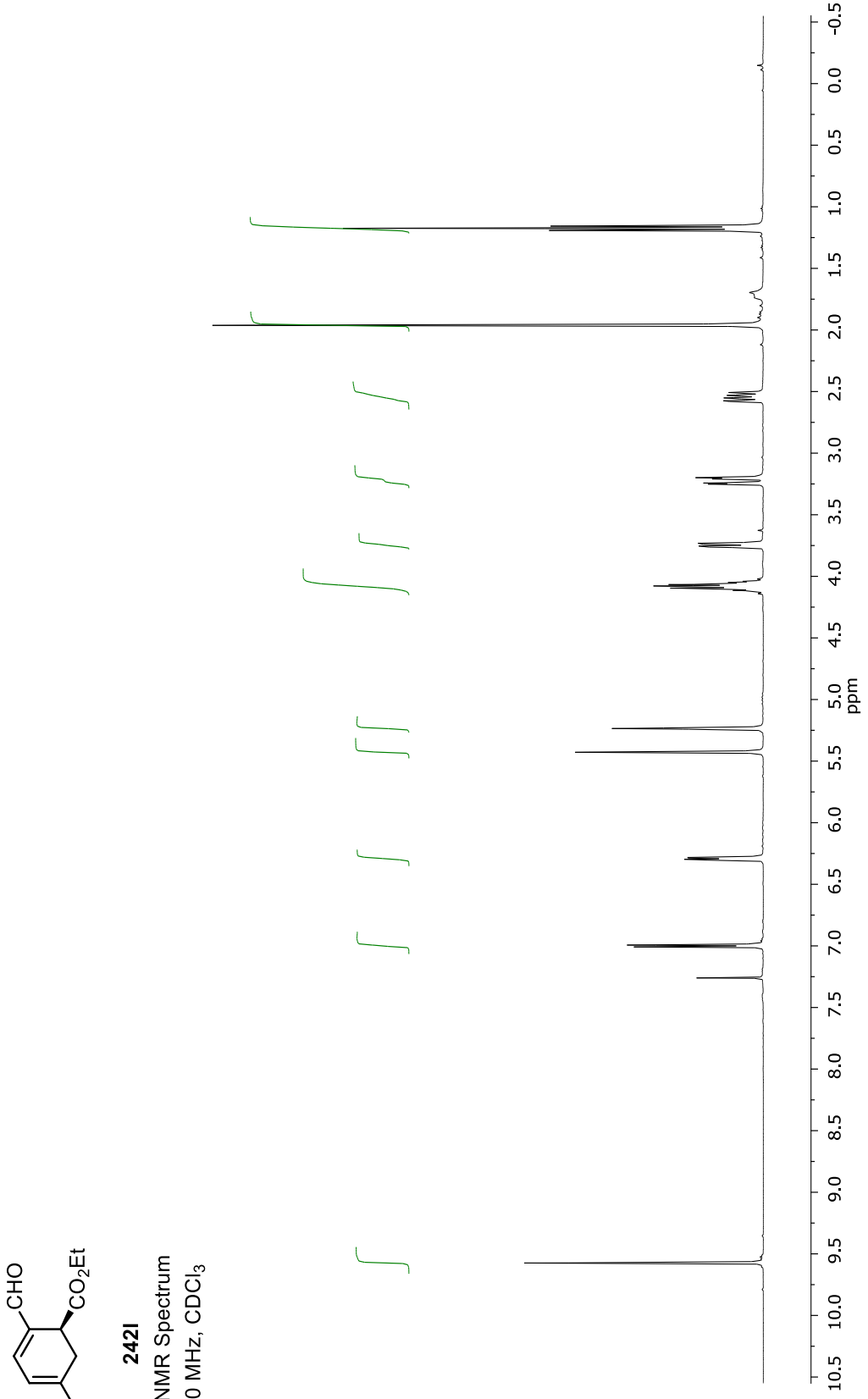

CHO
CO2Et
n-hex
242i
13C NMR Spectrum
100 MHz, CDCl3
29.4
29.0
14.4
14.0
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

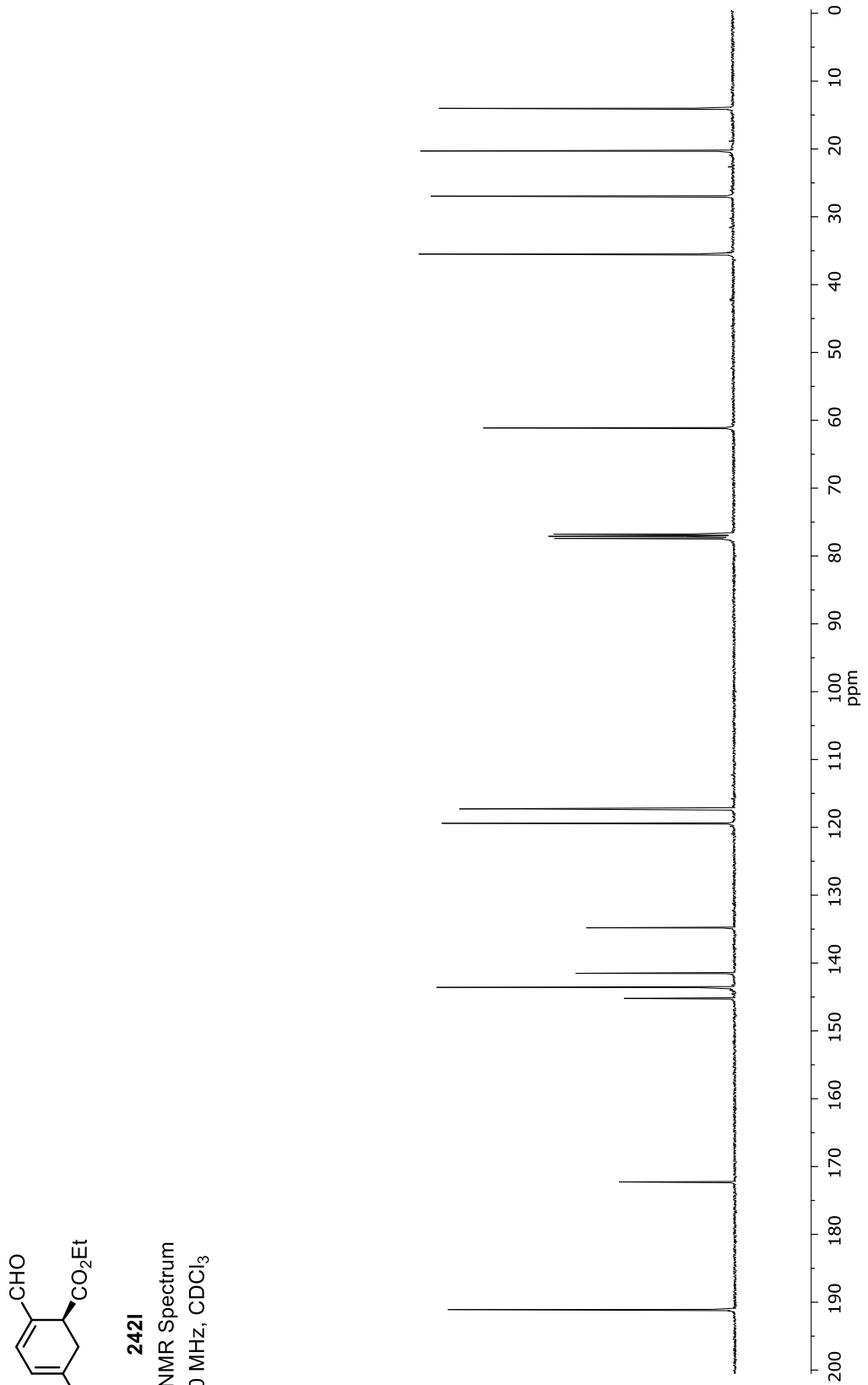

CHO
CO2Et
Ph
242j
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


CHO
CO2Et
Ph
242j
13C NMR Spectrum
100 MHz, CDCl3
129.5
129.0
128.5
128.0
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


CHO
CO2Et
Ph
242k
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

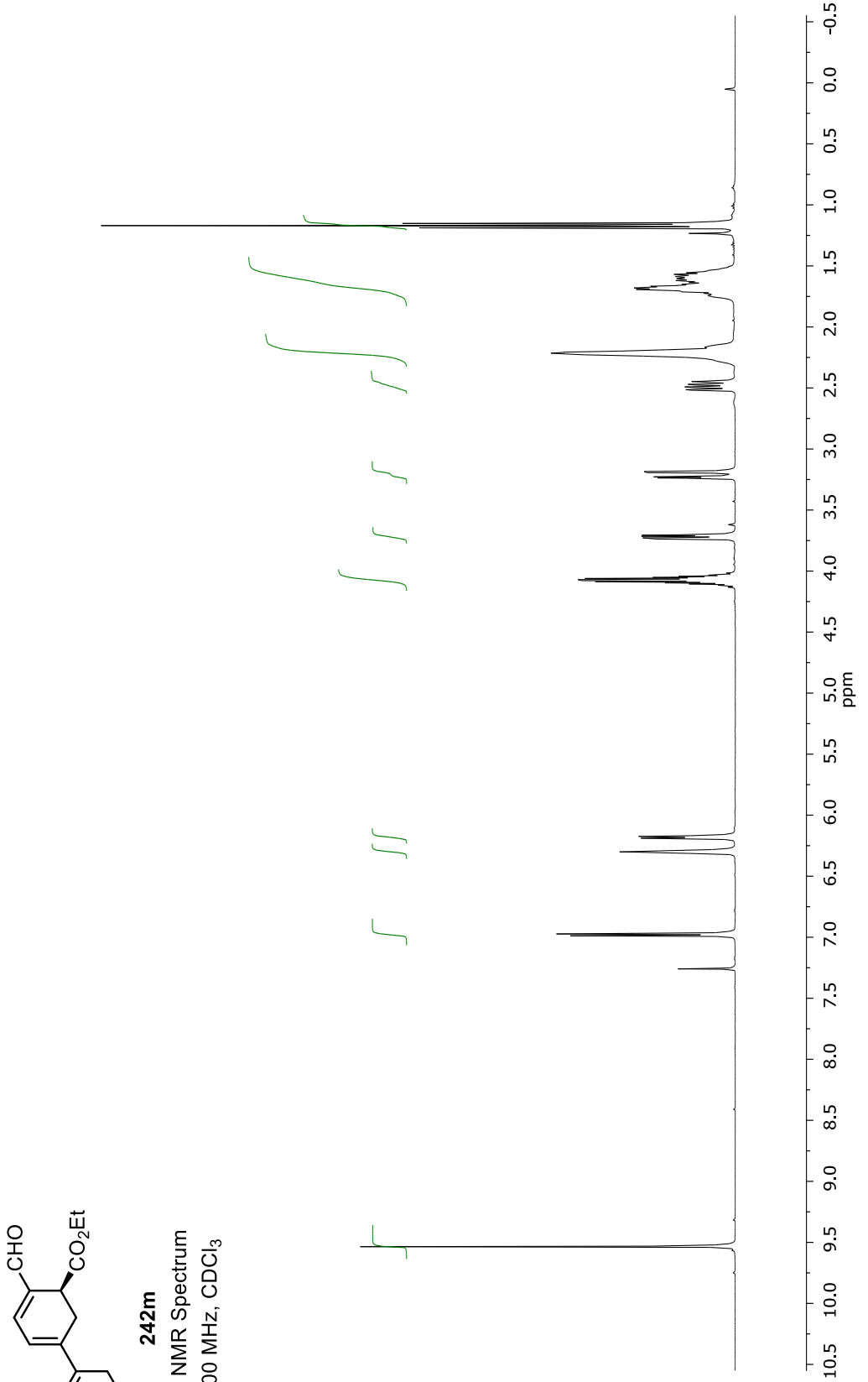

CHO
CO2Et
Ph
242k
13C NMR Spectrum
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

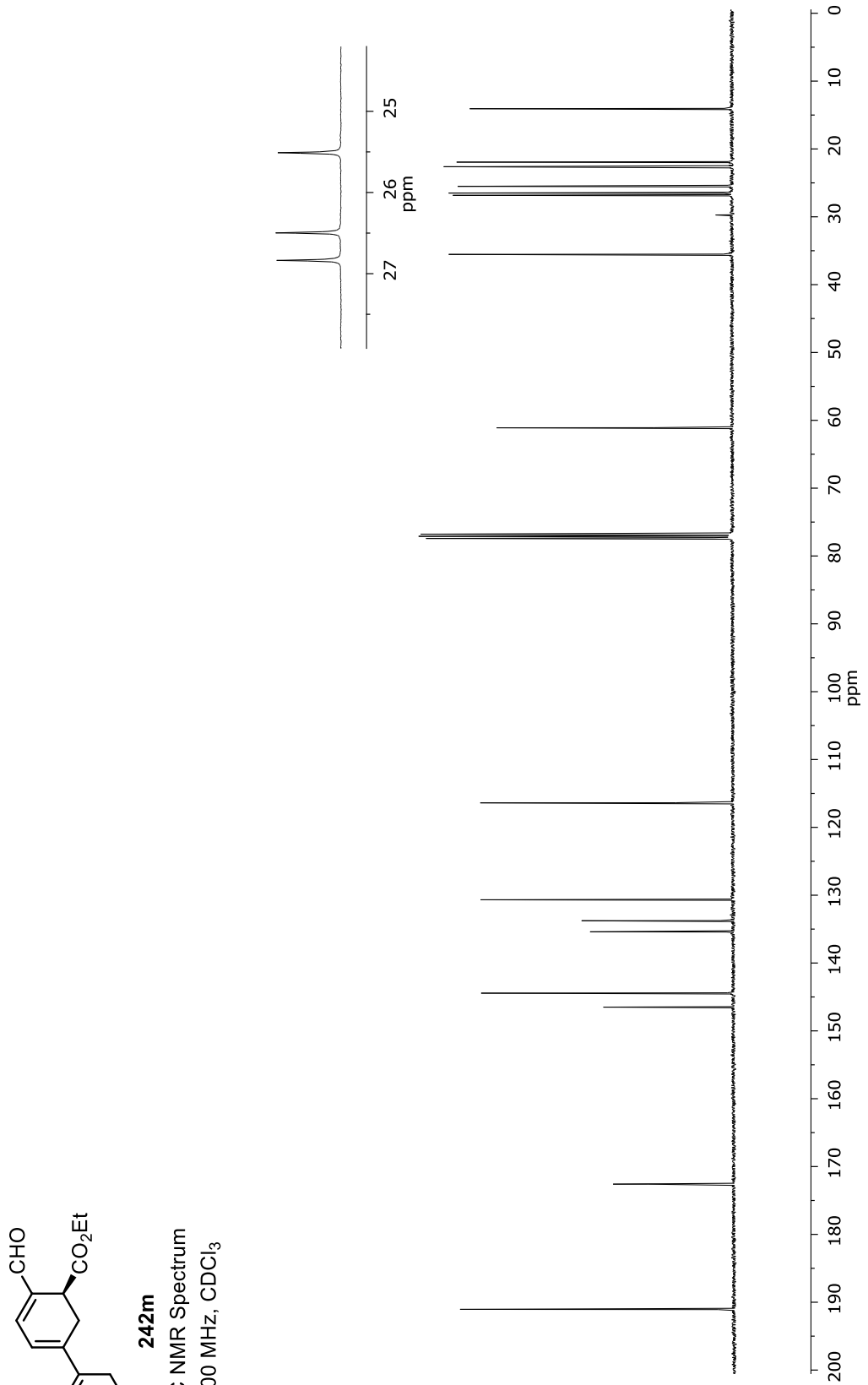

CHO
CO2Et
242l
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

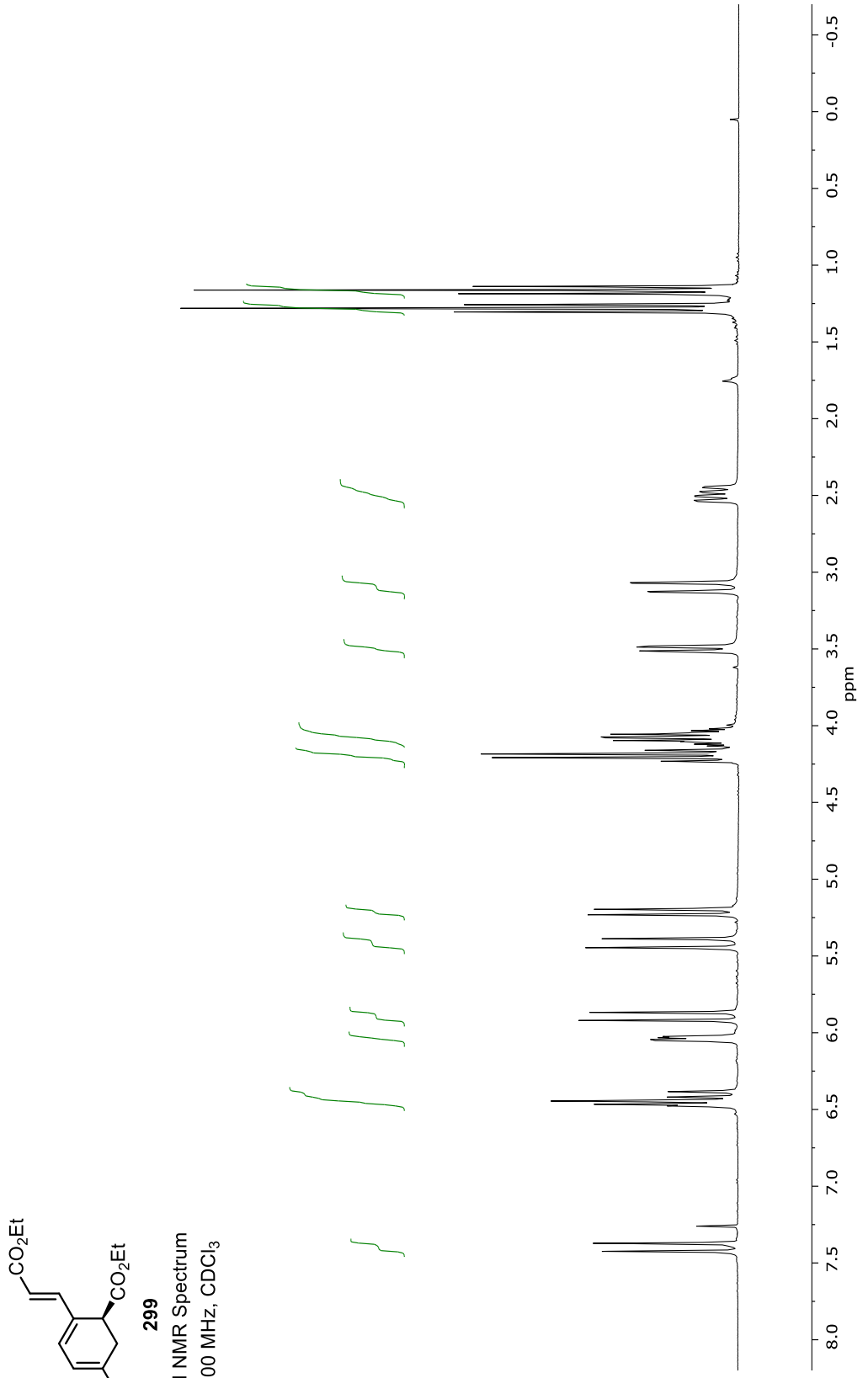


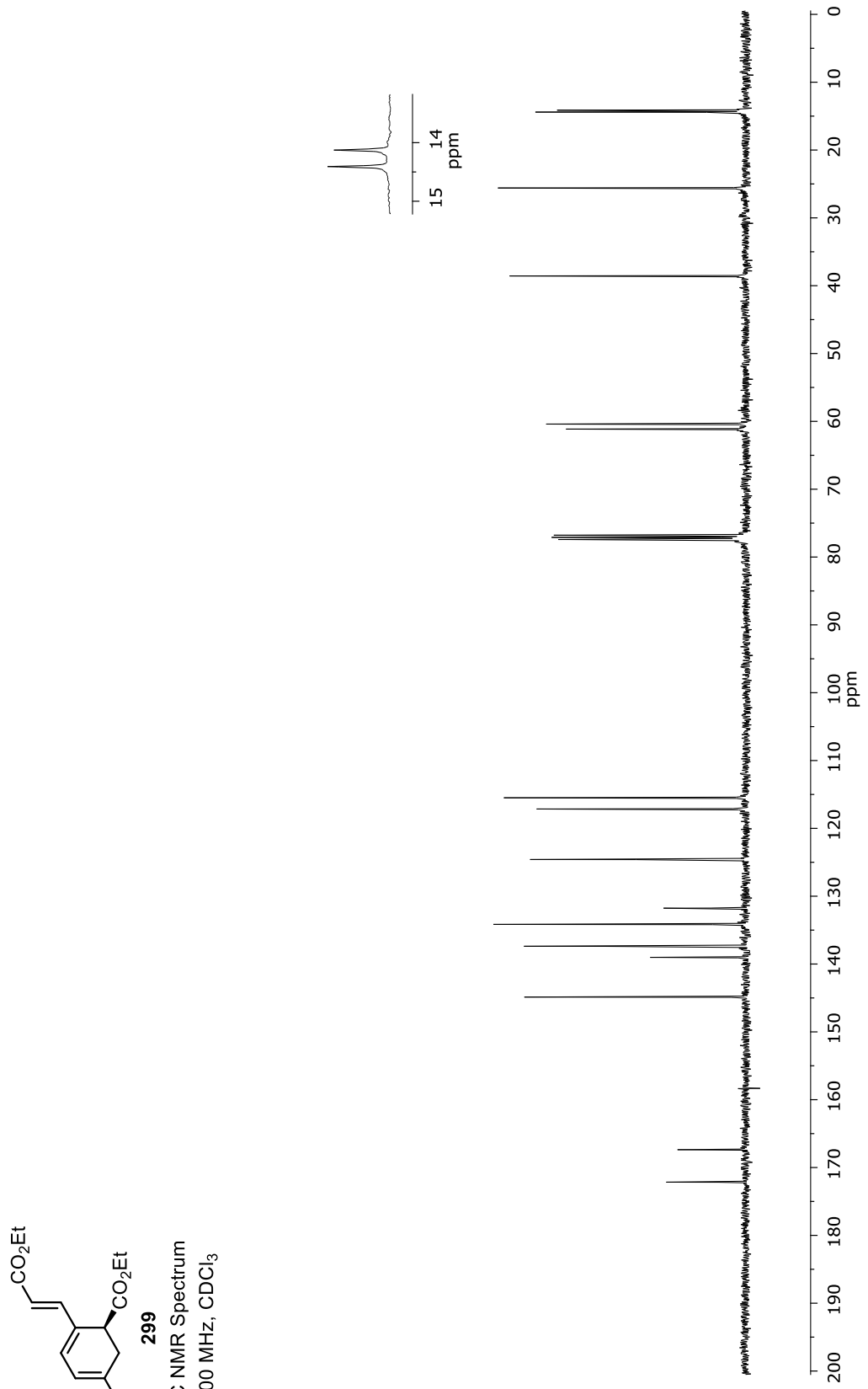
242l

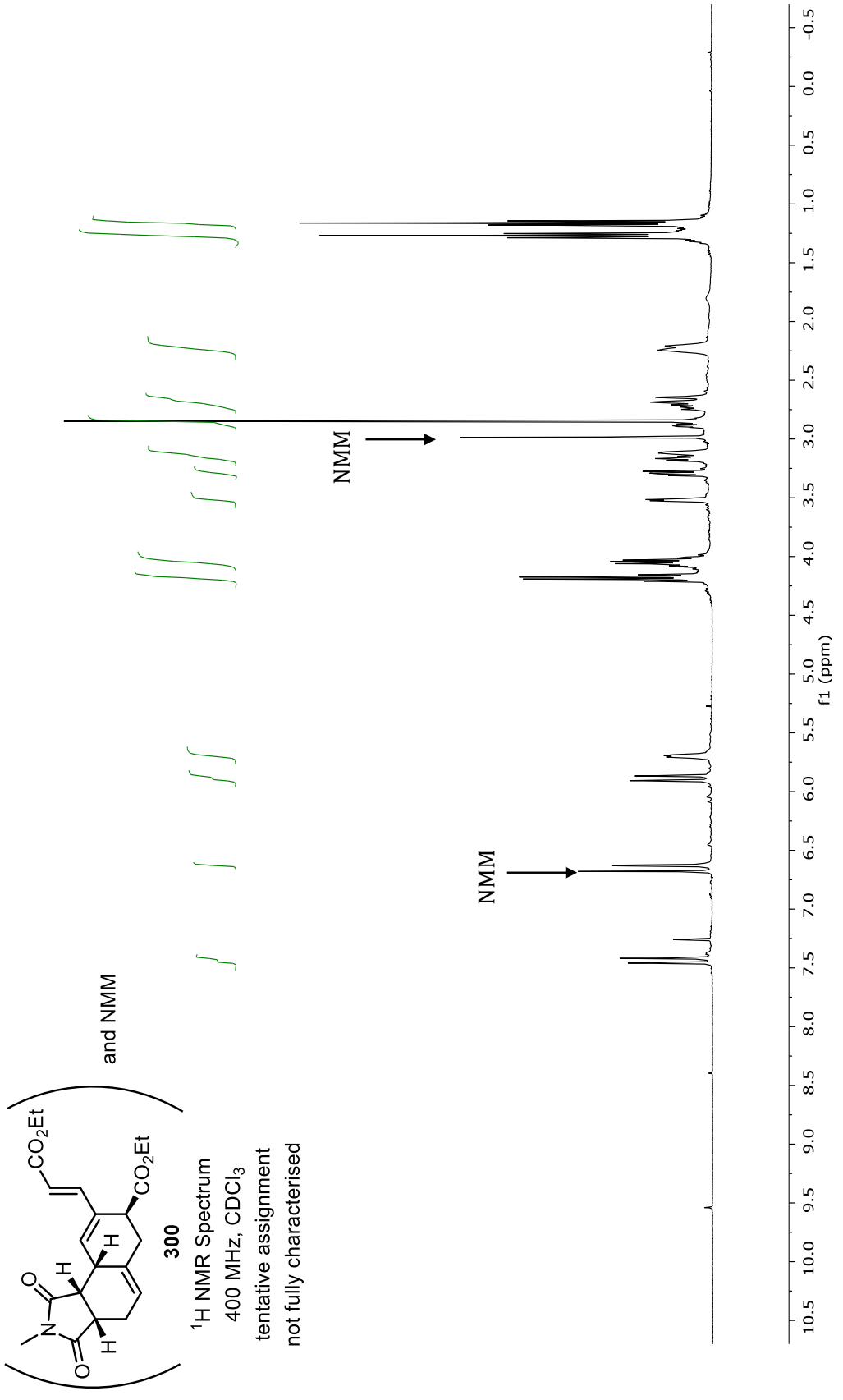
^{13}C NMR Spectrum
100 MHz, $CDCl_3$

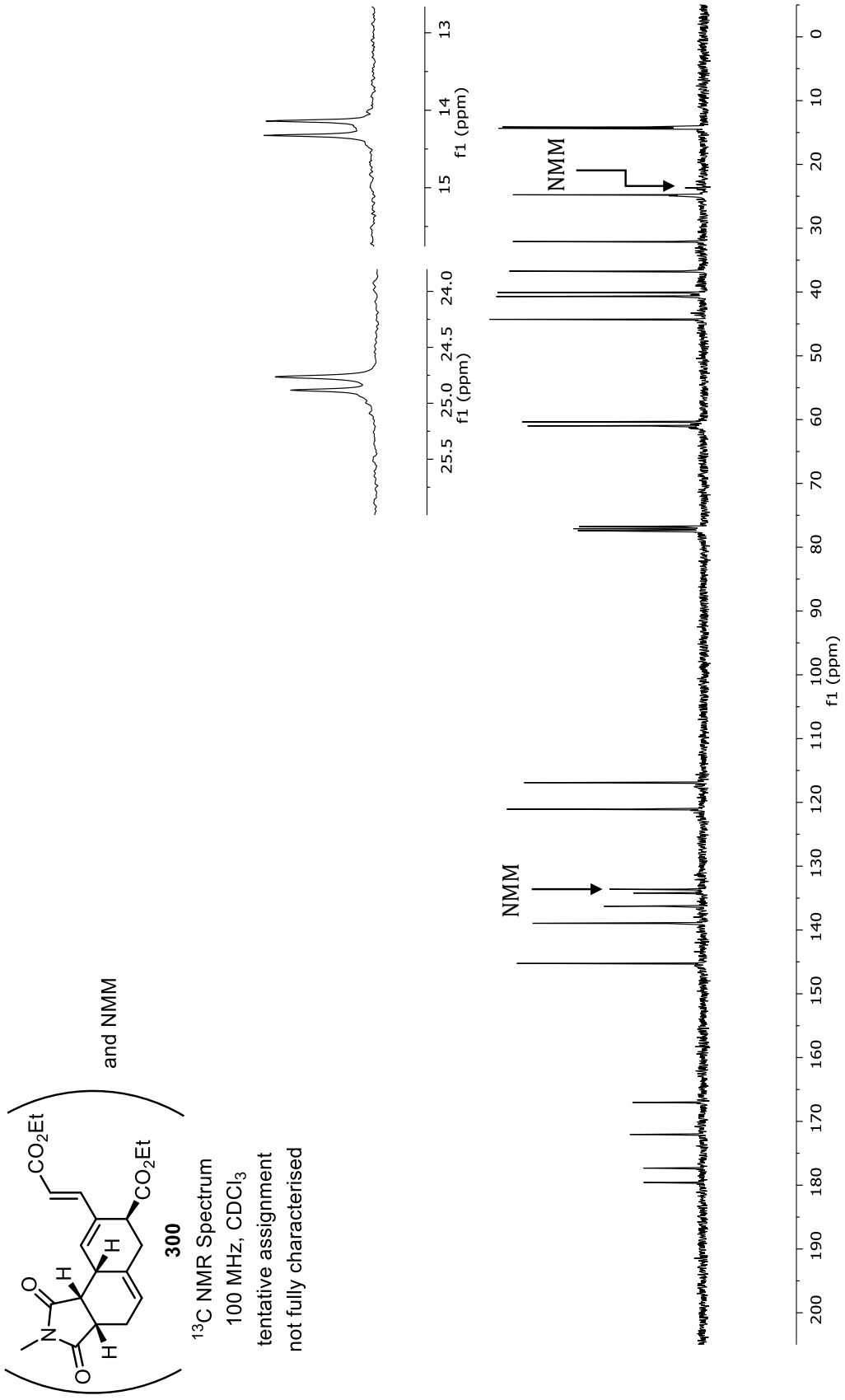

CHO
CO2Et
242m
1H NMR Spectrum
400 MHz, CDCl3
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

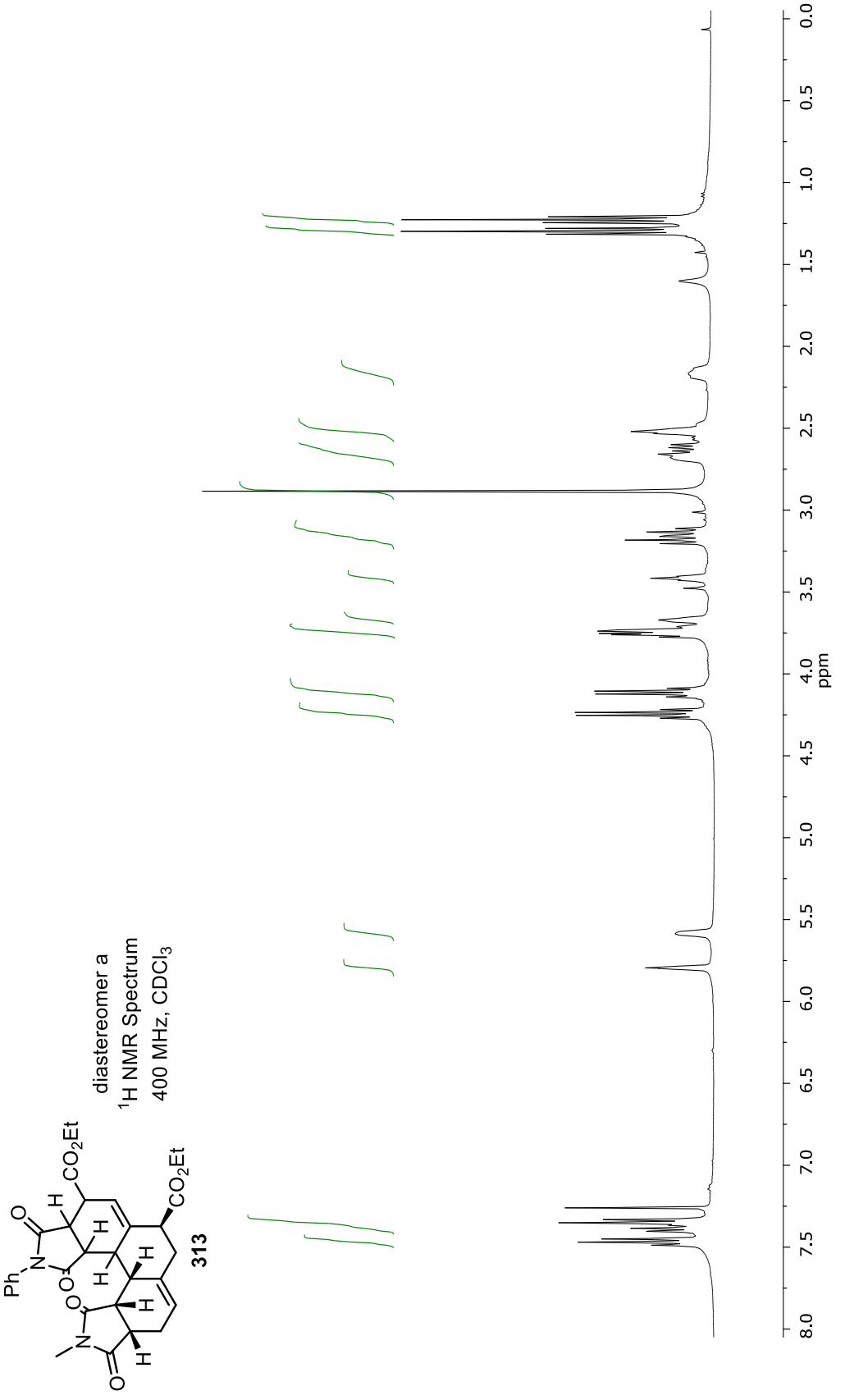

CHO
CO2Et
242m
13C NMR Spectrum
100 MHz, CDCl3
25
26
27
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
ppm

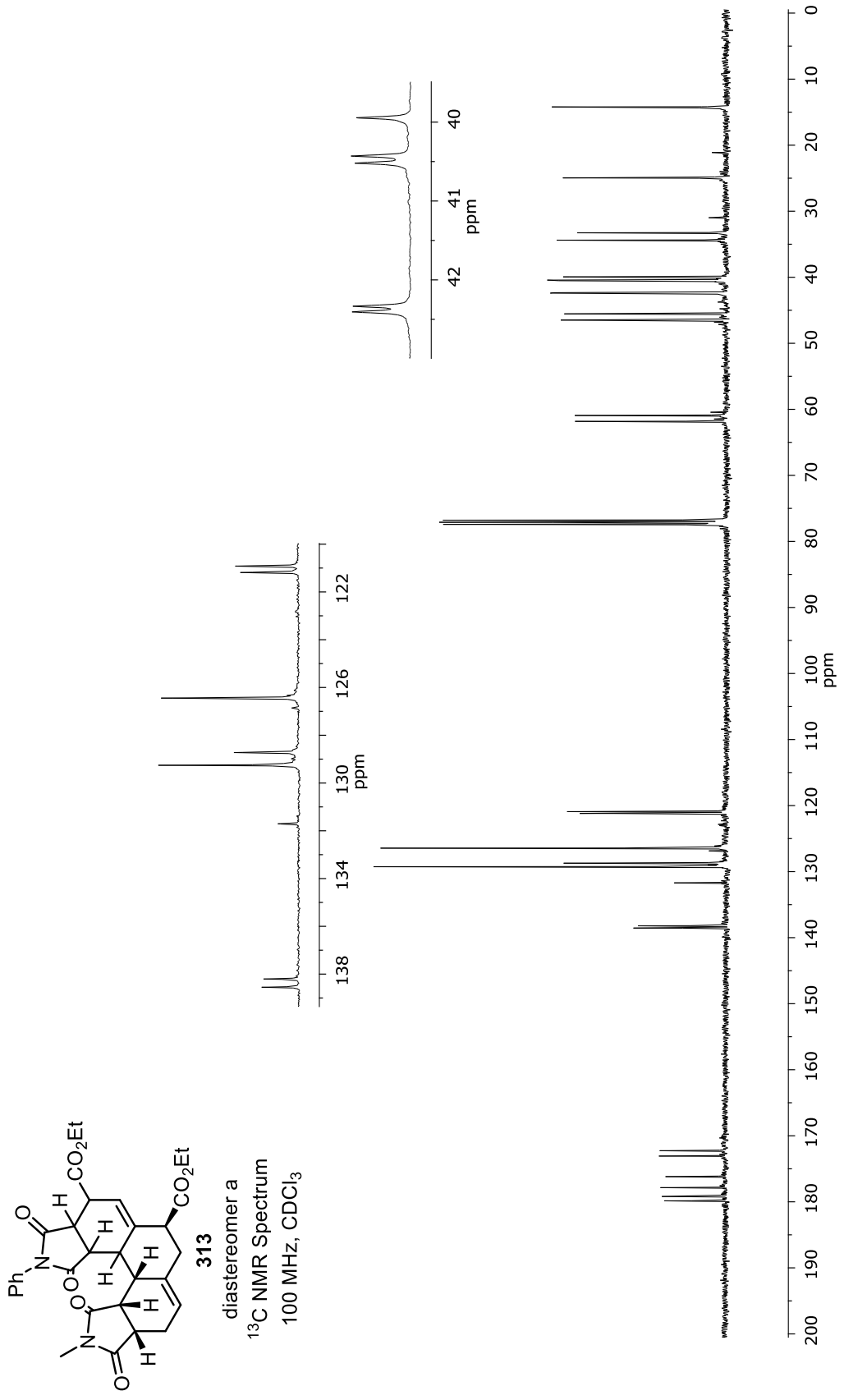

CO2Et
CO2Et
299
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

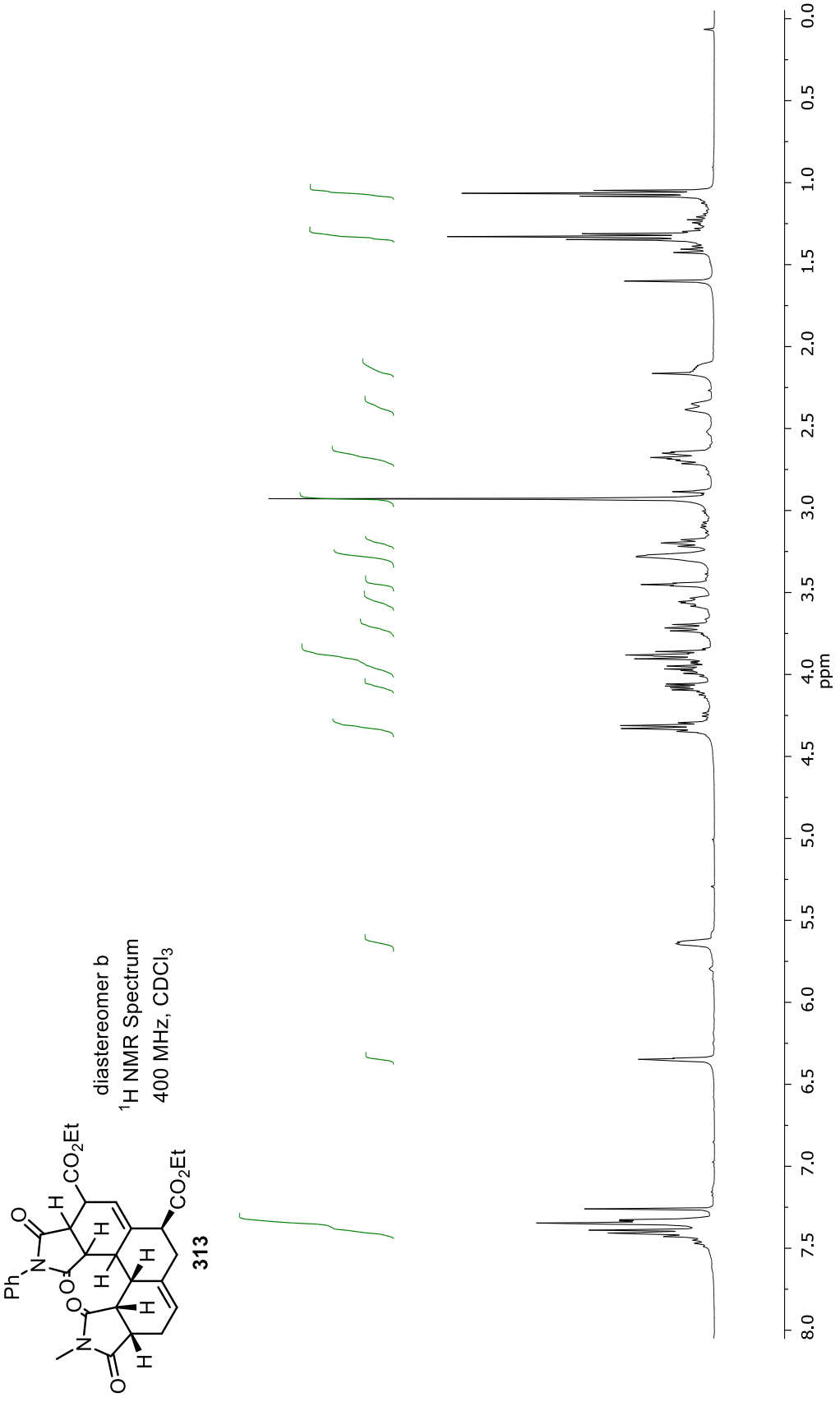

CO2Et
CO2Et
299
13C NMR Spectrum
100 MHz, CDCl3
15
14
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

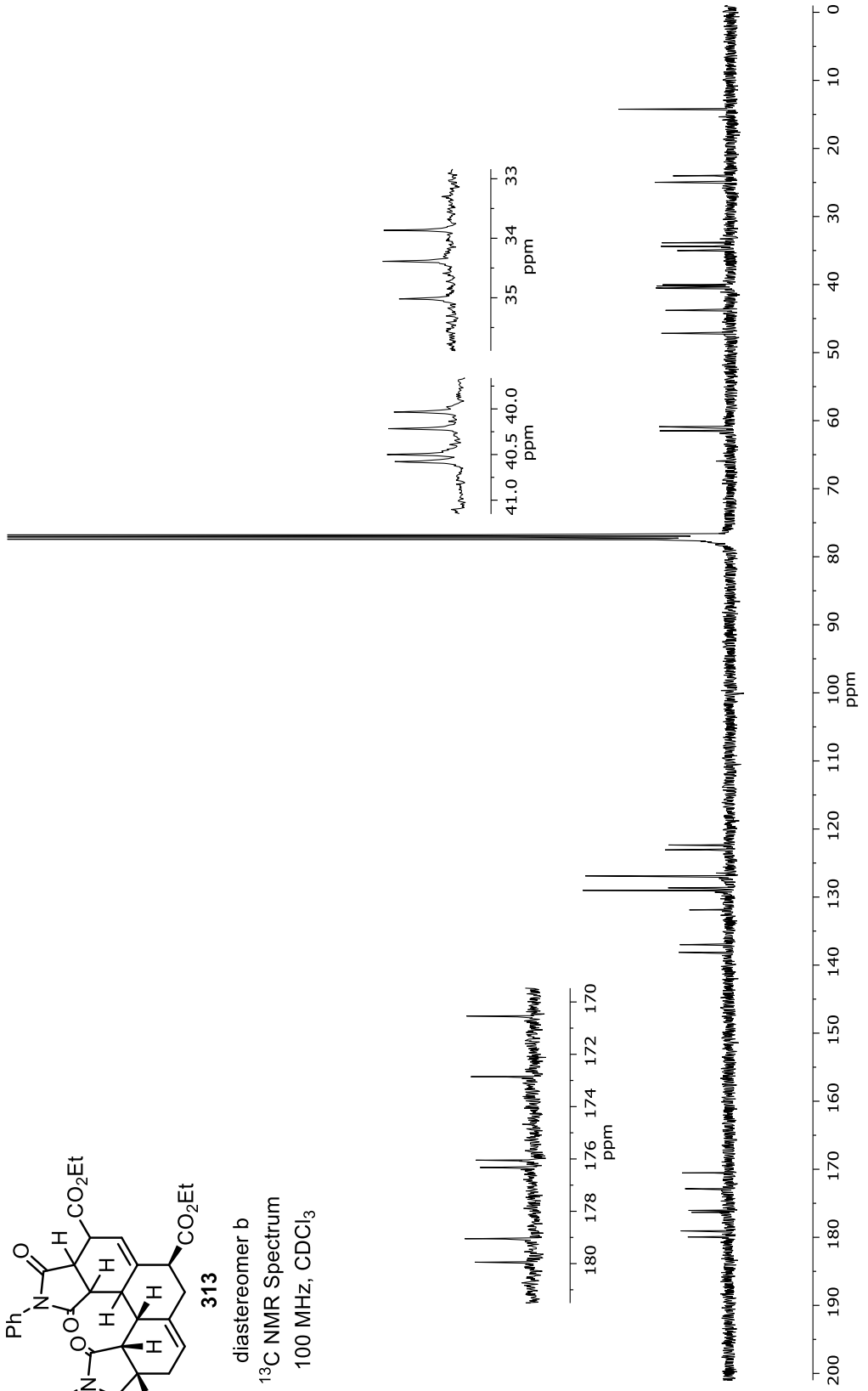

CO2Et
CO2Et
H
H
O
N
O
and NMM
300
1H NMR Spectrum
400 MHz, CDCl3
tentative assignment
not fully characterised
NMM
NMM
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

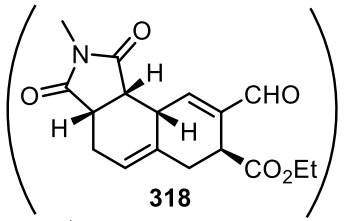

CO2Et
CO2Et
H
H
H
O
O
N
and NMM
300
13C NMR Spectrum
100 MHz, CDCl3
tentative assignment
not fully characterised
NMM
NMM
25.5
25.0
24.5
24.0
15
14
13
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


diastereomer a
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
313
CO_2Et
CO_2Et
Ph
O
N
O
H
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Ph
N
O
O
O
N
O
H
H
H
H
H
CO2Et
CO2Et
313
diastereomer a
13C NMR Spectrum
100 MHz, CDCl3
138
134
130
126
122
ppm
42
41
40
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


diastereomer b
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
313
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

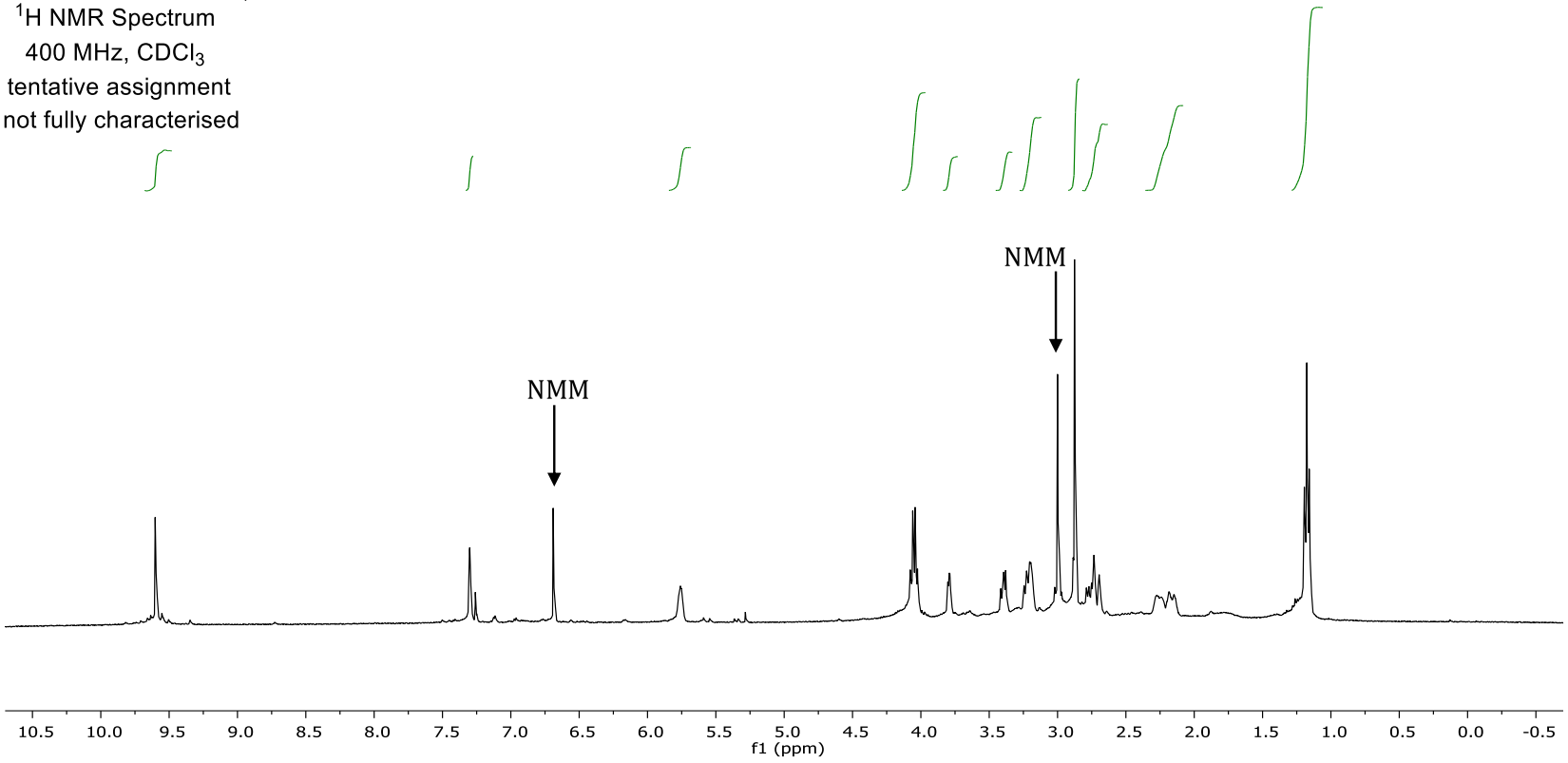

Ph
N
O
O
O
N
O
H
H
H
H
H
CO2Et
CO2Et
313
diastereomer b
13C NMR Spectrum
100 MHz, CDCl3
180 178 176 174 172 170
ppm
41.0 40.5 40.0
ppm
35 34 33
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

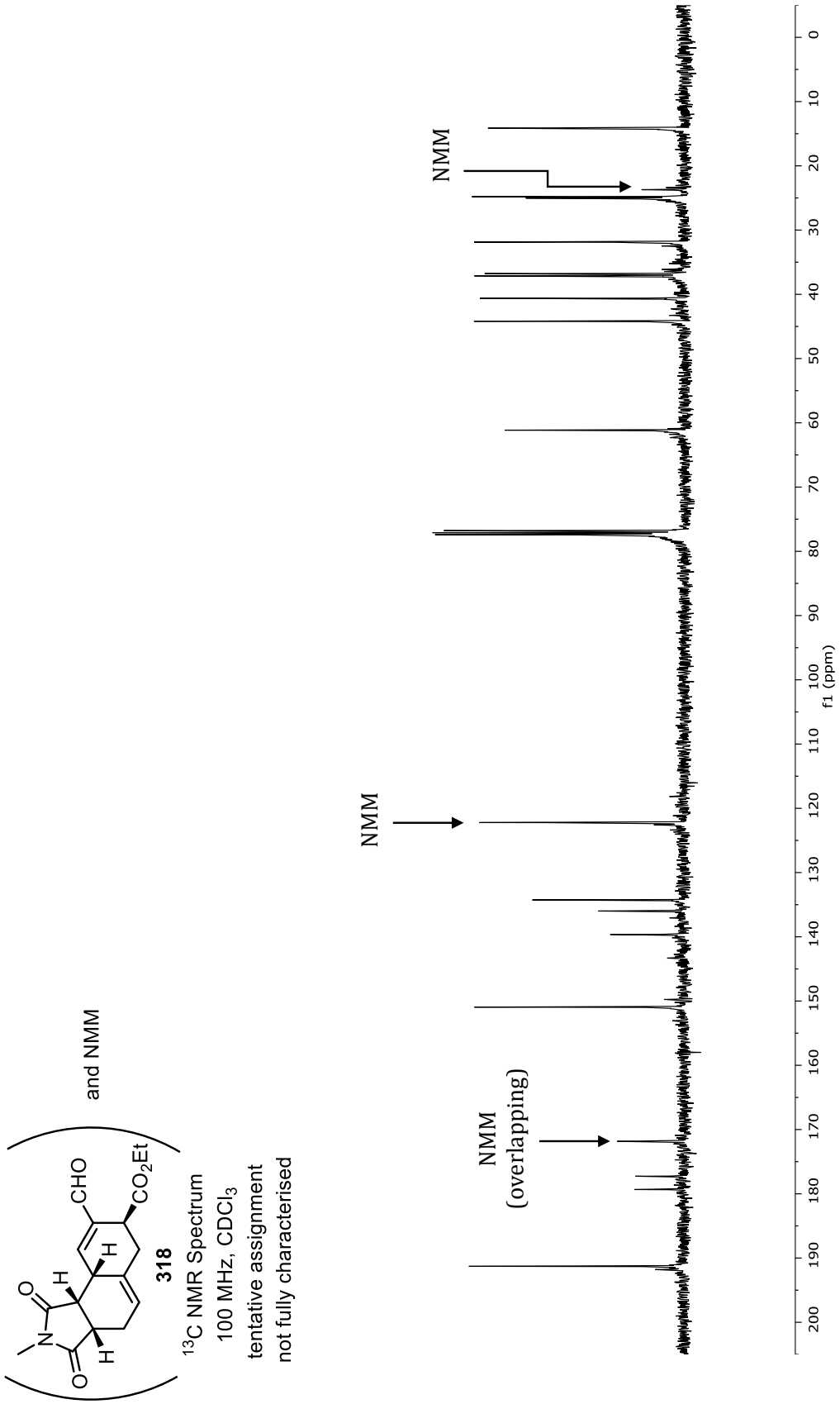


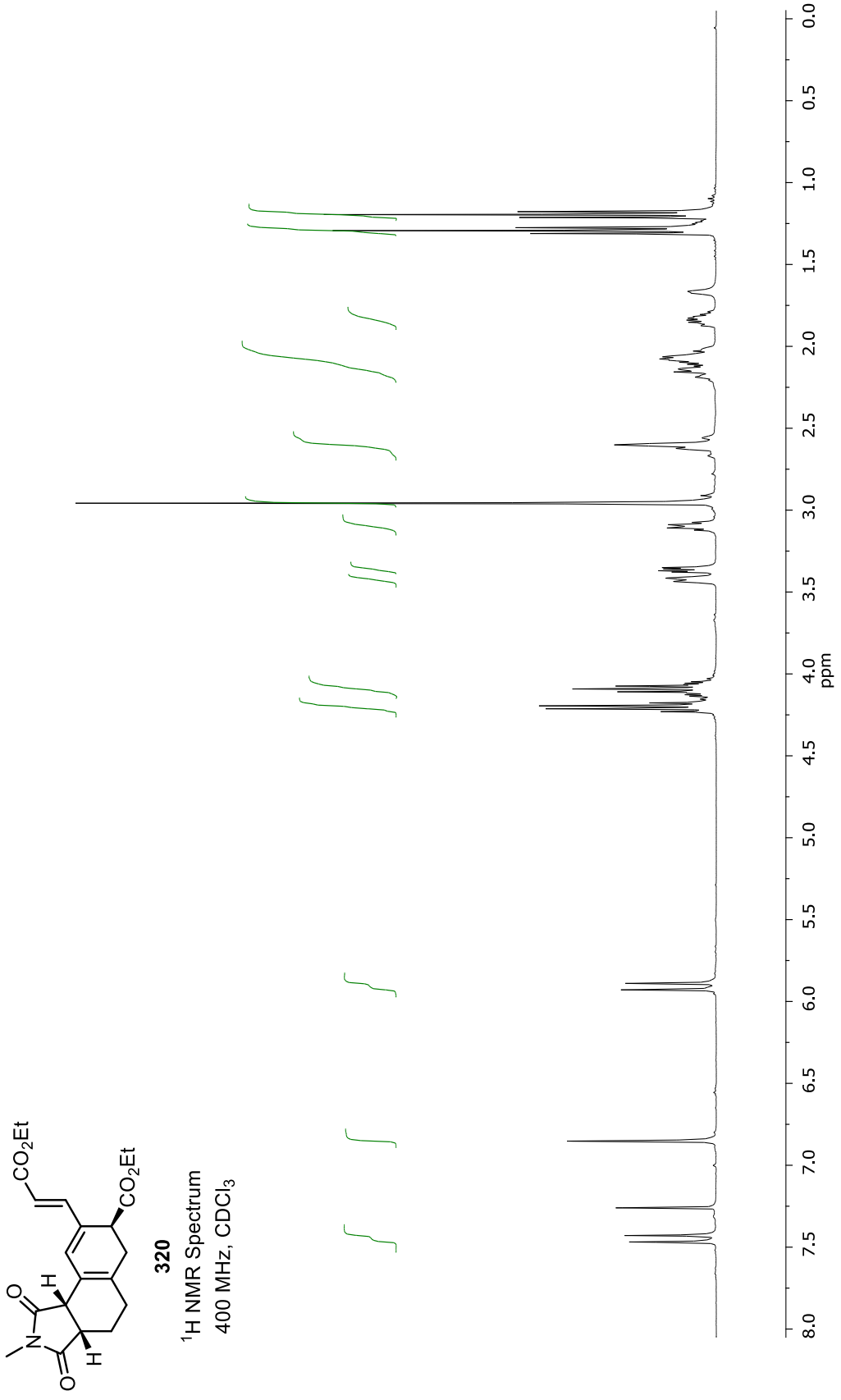
318

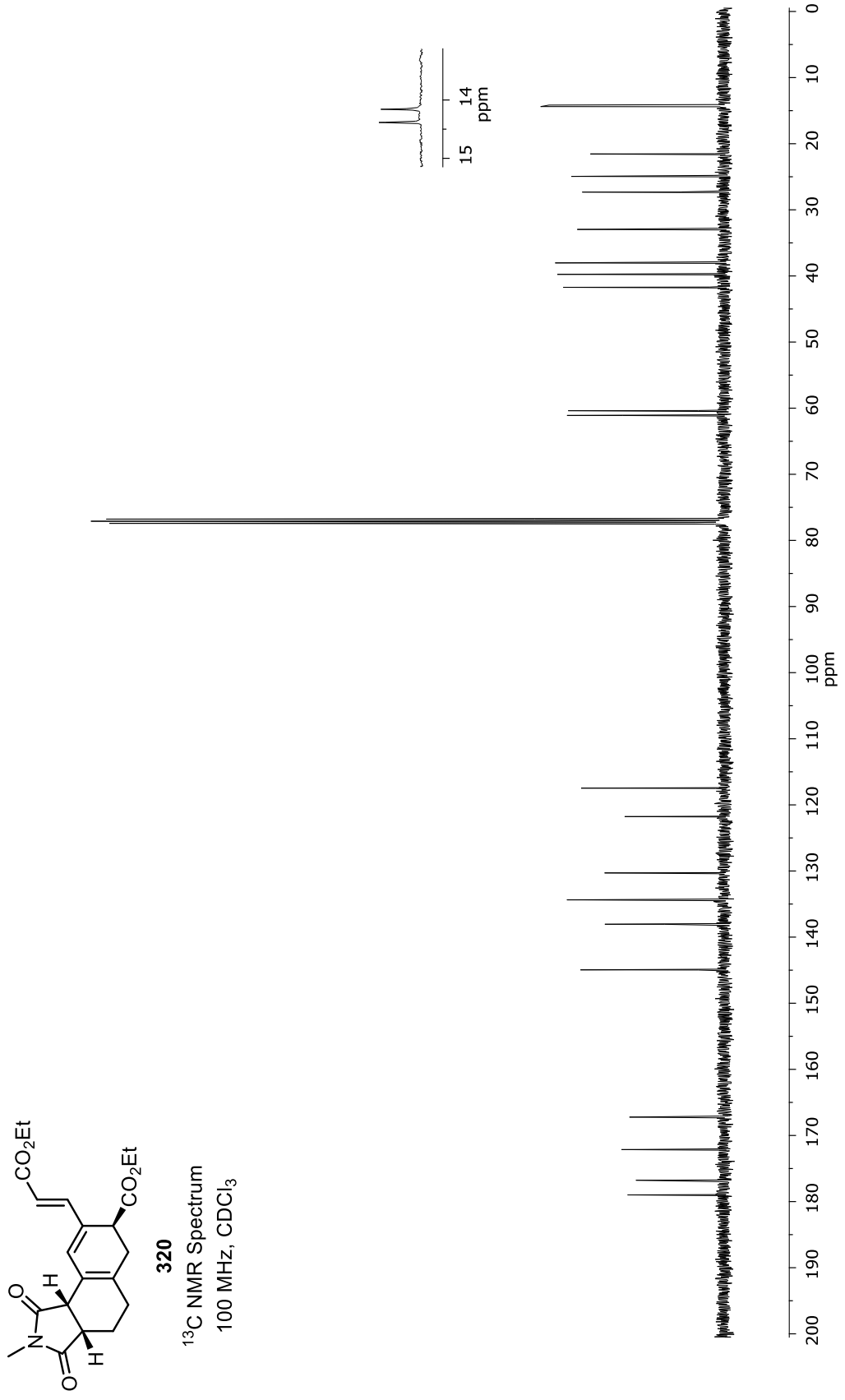
and NMM

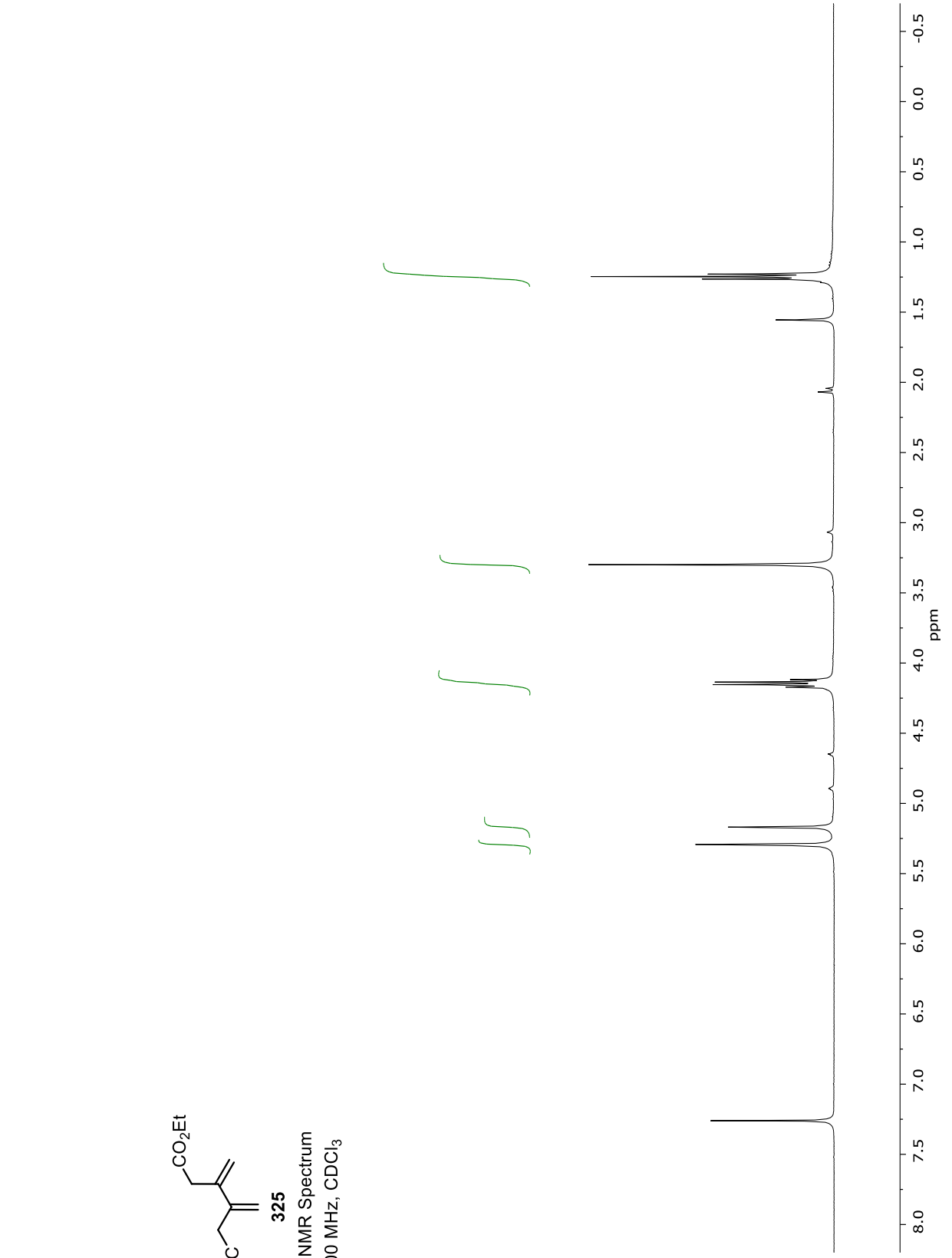
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
tentative assignment
not fully characterised

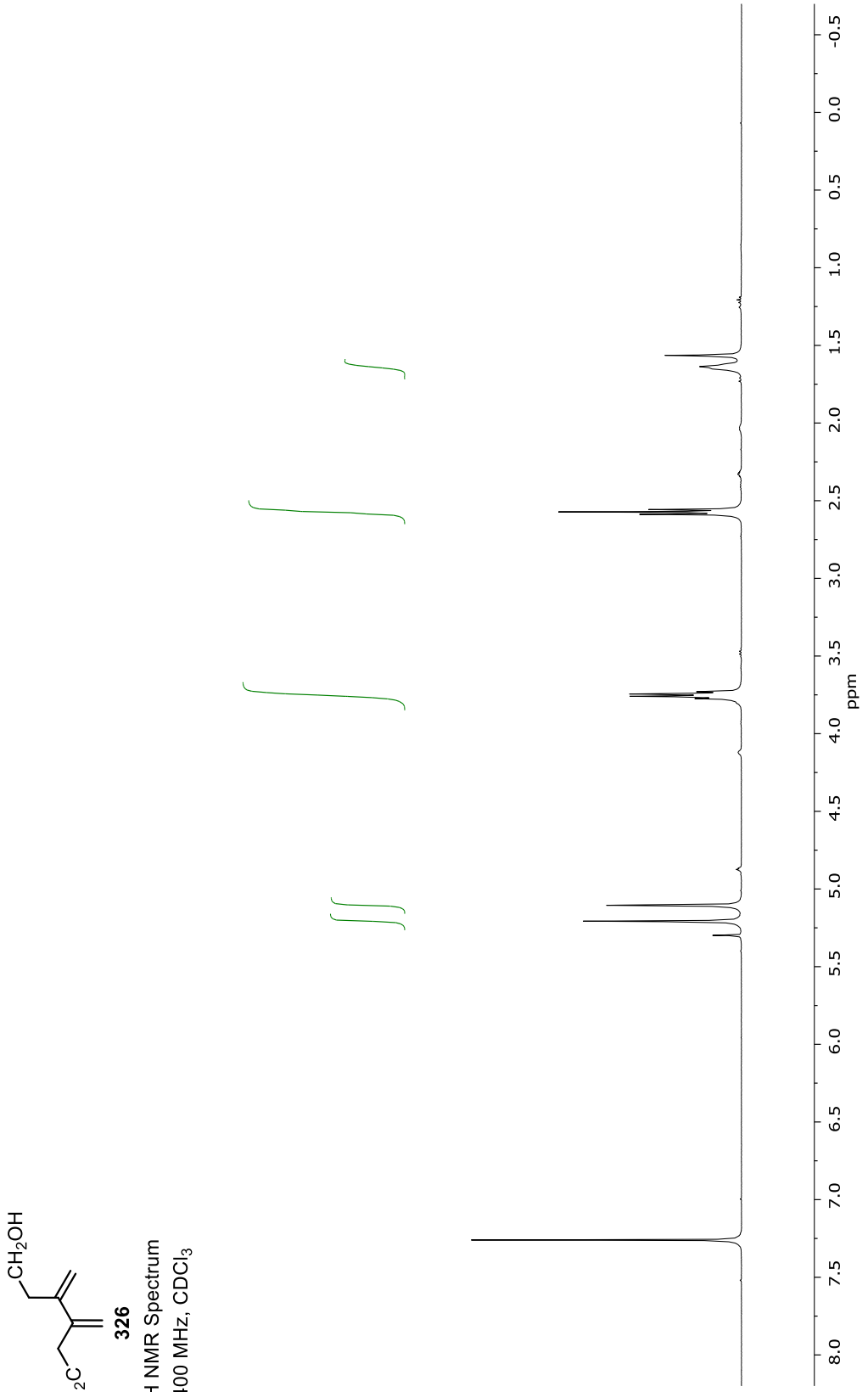


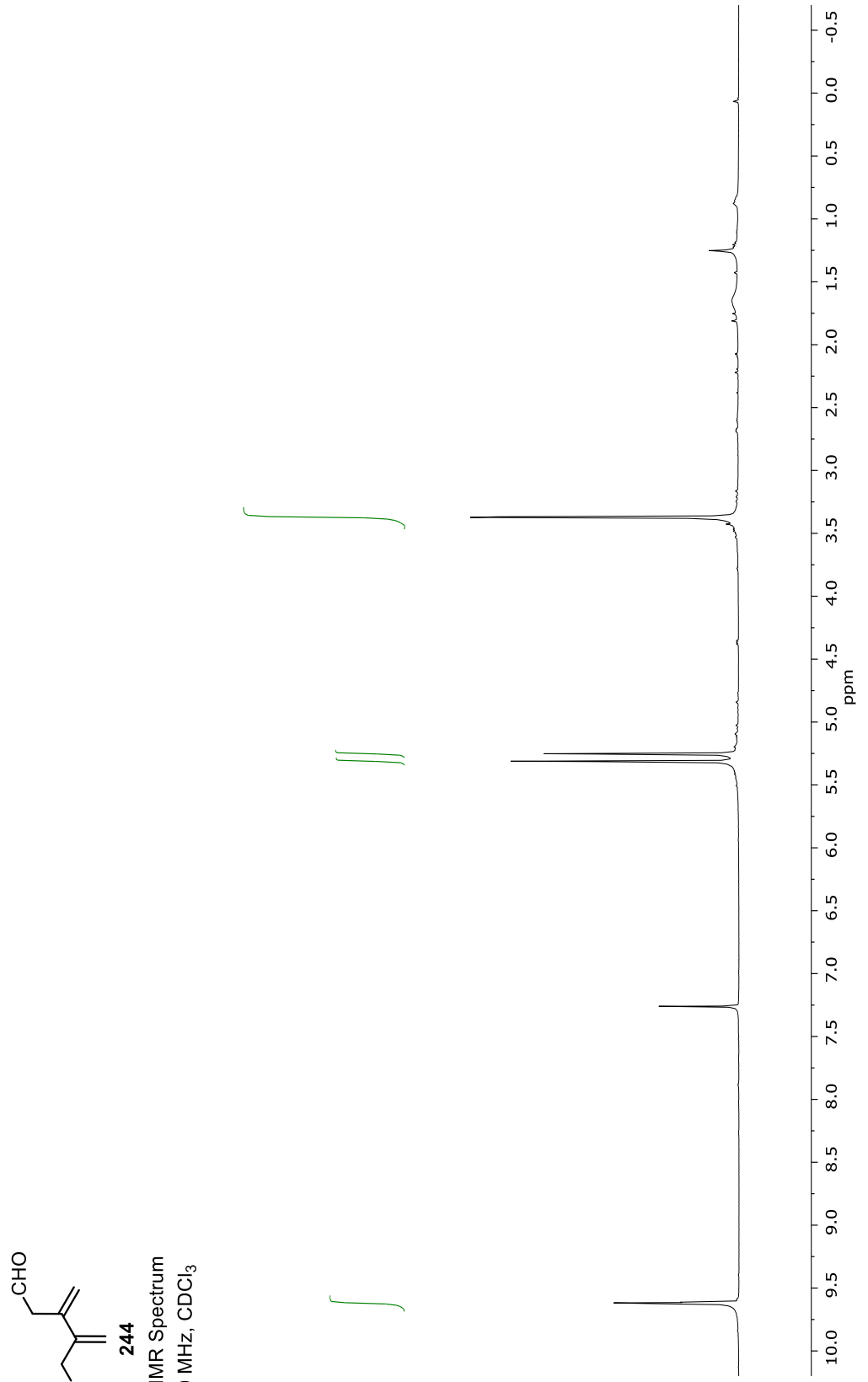

and NMM
CHO
CO2Et
H
H
H
O
O
N
318
13C NMR Spectrum
100 MHz, CDCl3
tentative assignment
not fully characterised
NMM
NMM
(overlapping)
NMM
f1 (ppm)

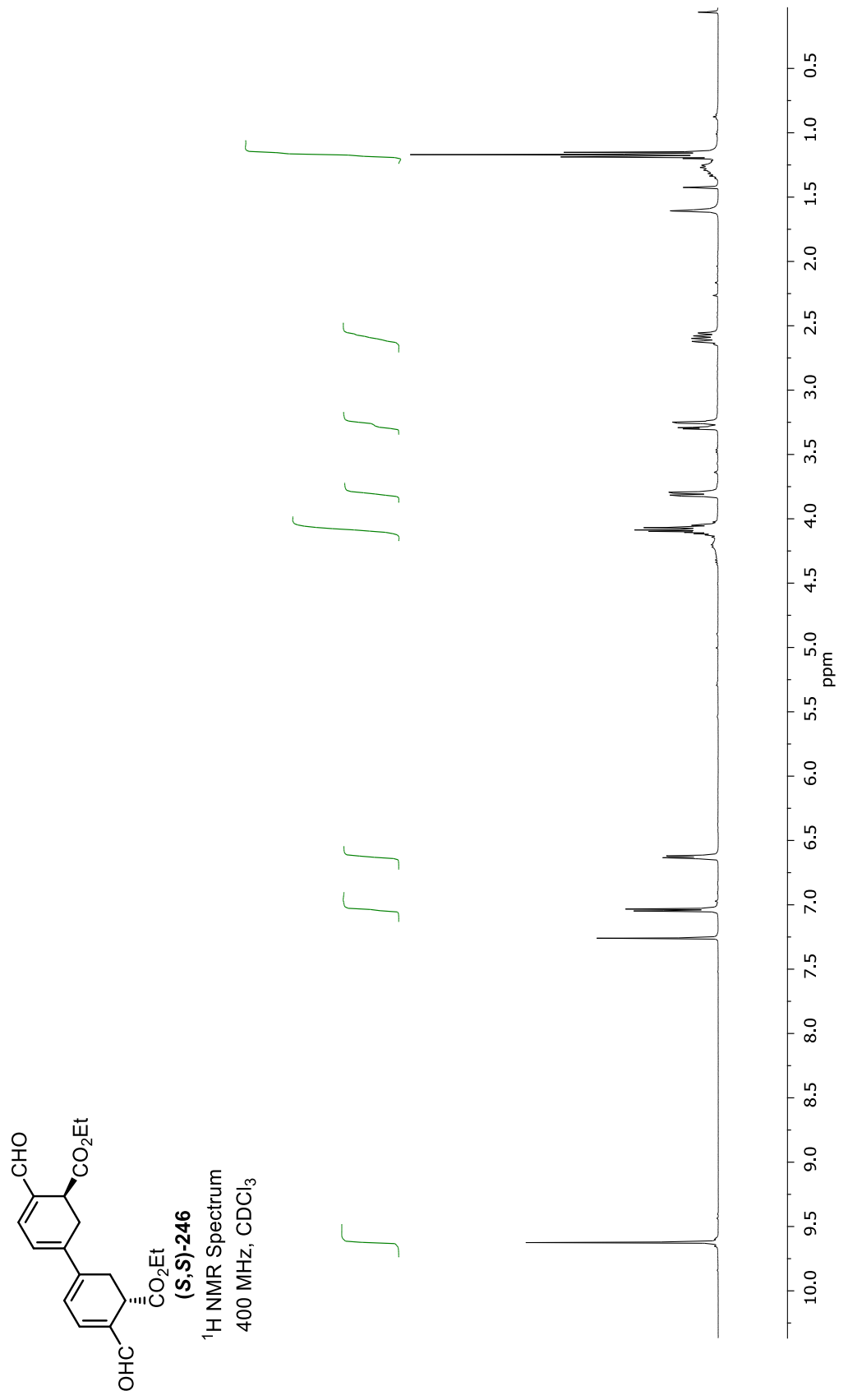

CO2Et
CO2Et
O
N
O
H
H
320
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

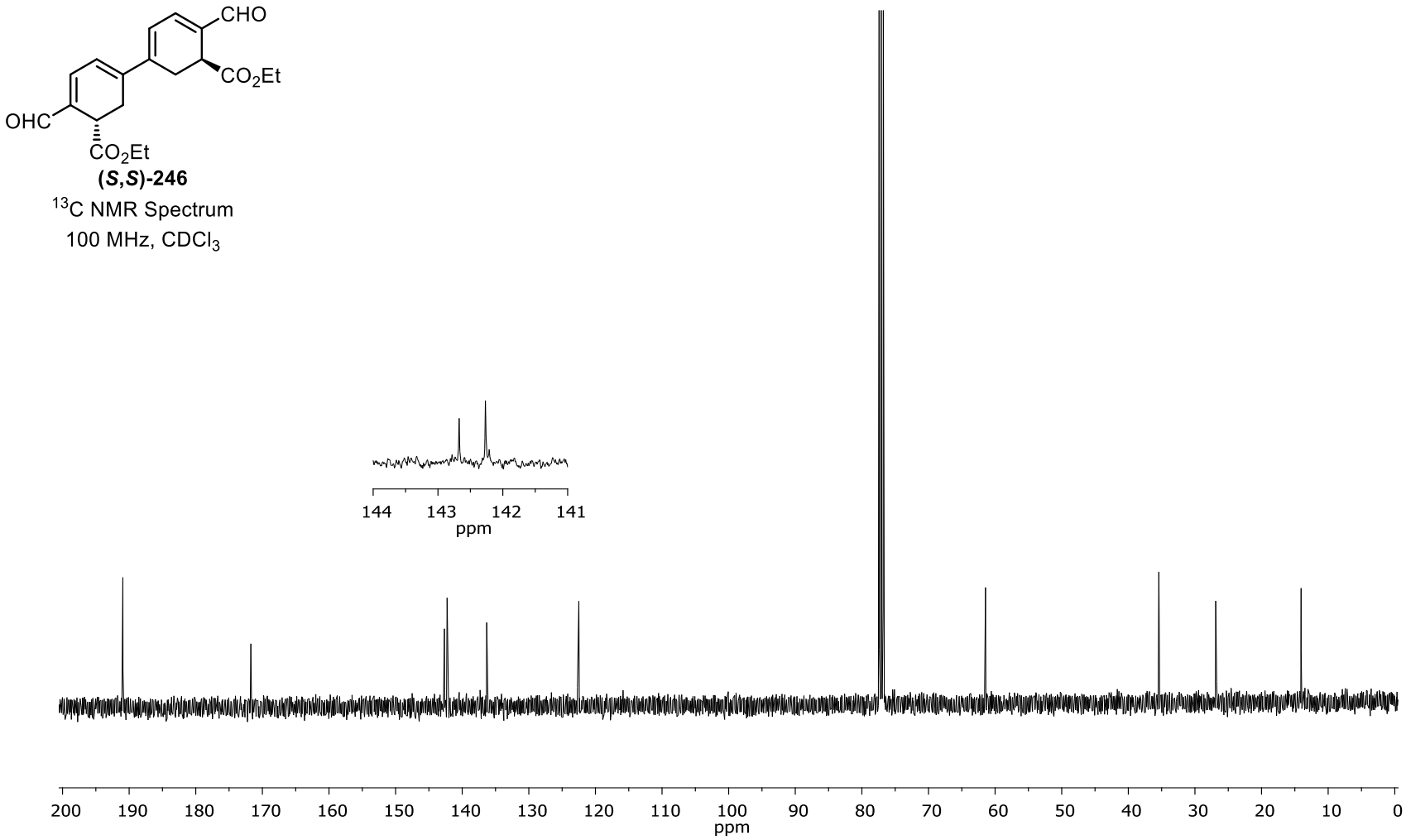

CO2Et
CO2Et
O
N
O
H
H
320
13C NMR Spectrum
100 MHz, CDCl3
15
14
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

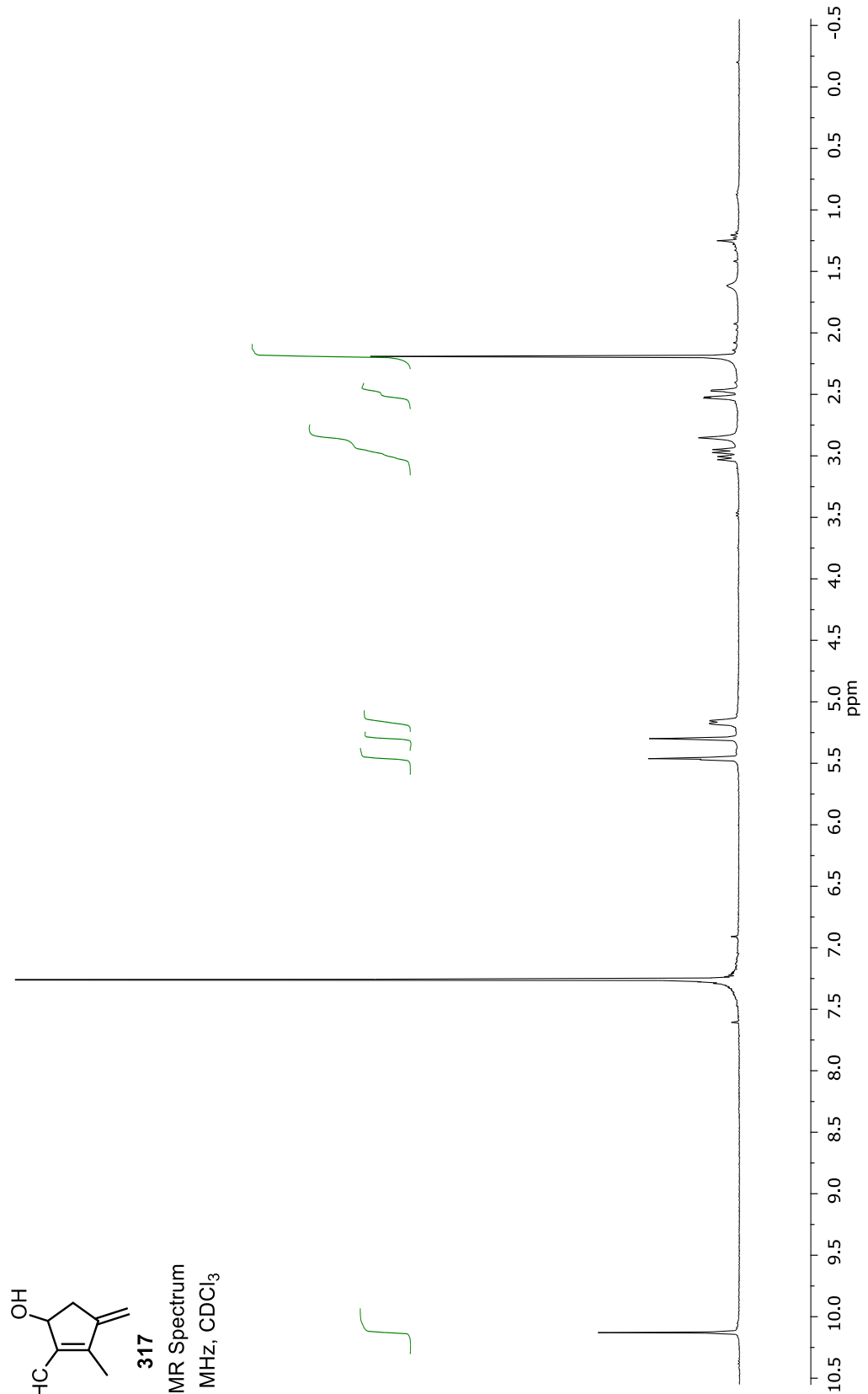

CO2Et
EtO2C
325
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

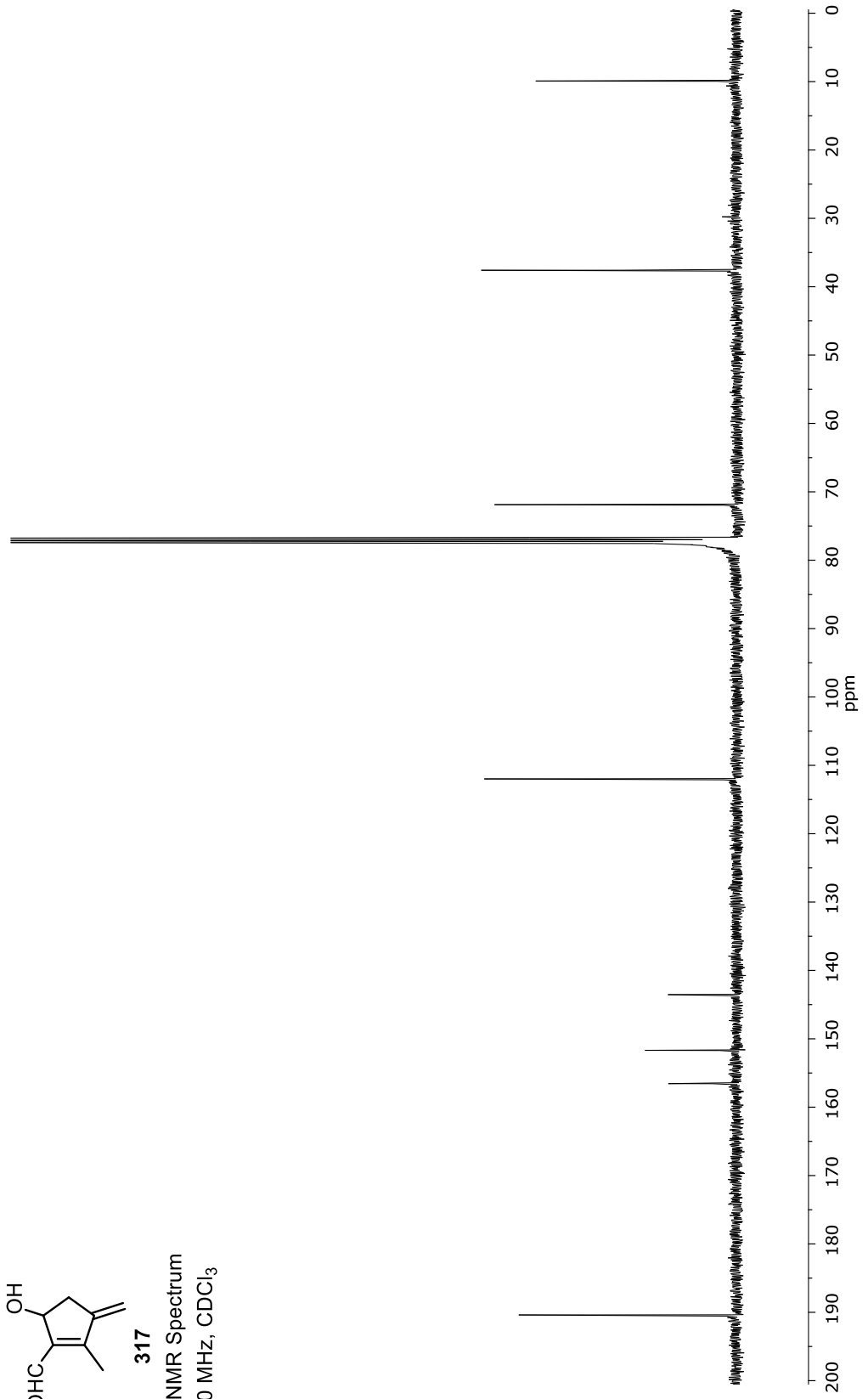

CH2OH
HOH2C
326
1H NMR Spectrum
400 MHz, CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

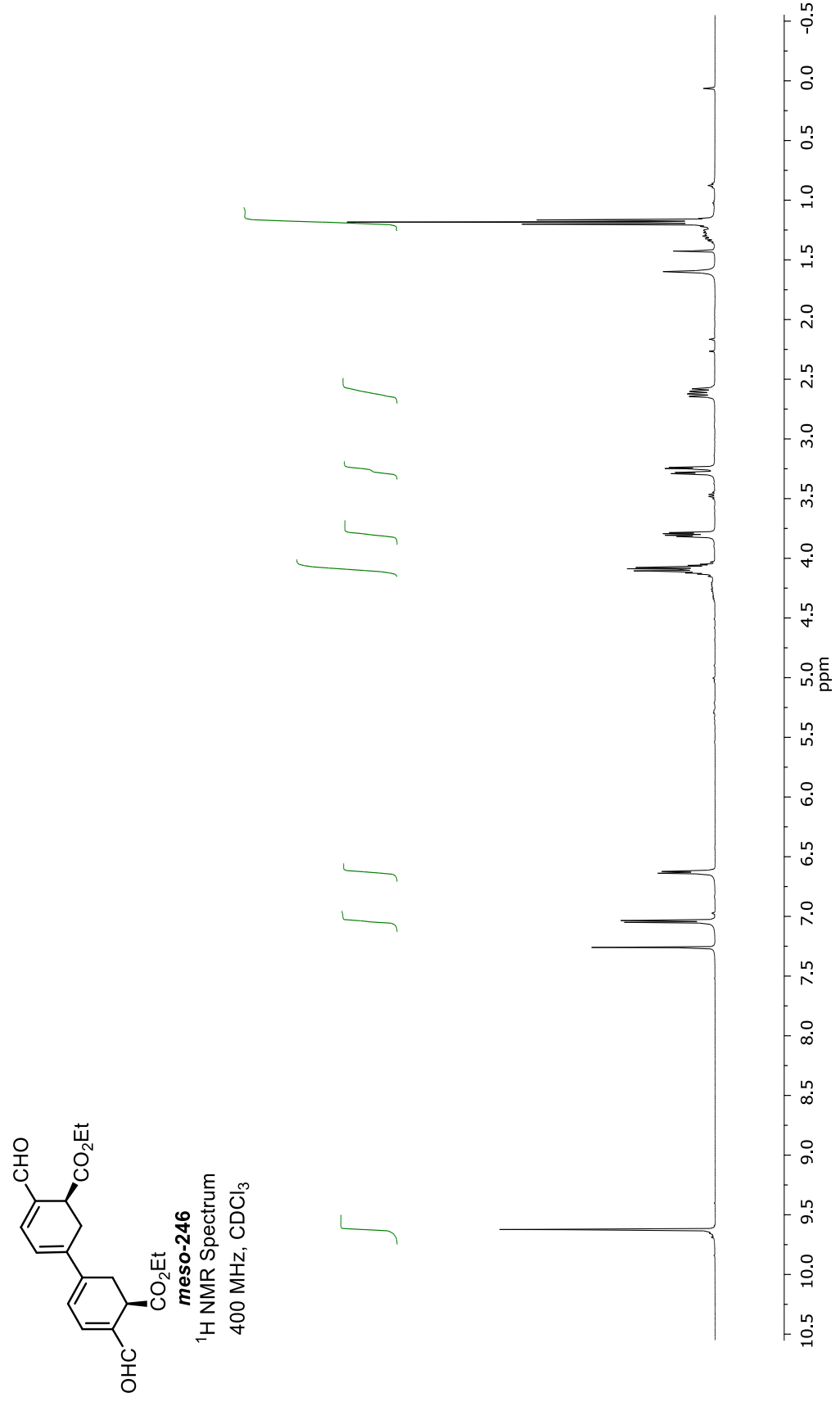

CHO
OHC
244
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

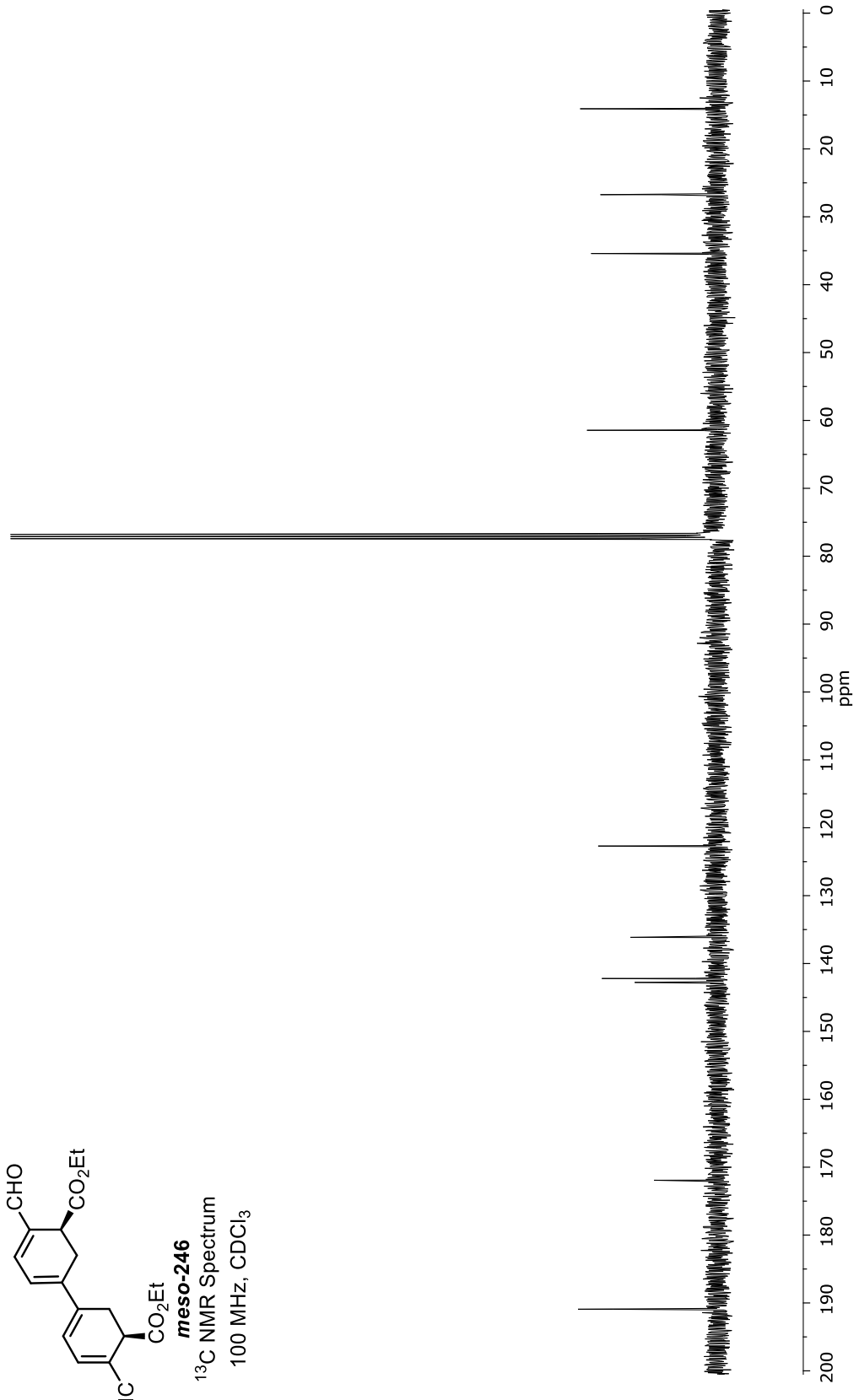

CHO
CO2Et
CO2Et
OHC
(S,S)-246
1H NMR Spectrum
400 MHz, CDCl3
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


CHO
CO2Et
OHC
CO2Et
(S,S)-246
13C NMR Spectrum
100 MHz, CDCl3
144
143
142
141
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OH
OHC
317
^{1}H NMR Spectrum
400 MHz, $CDCl_3$
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


OH
OHC
317
^{13}C NMR Spectrum
100 MHz, $CDCl_3$
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
ppm


CHO
CO2Et
CO2Et
OHC
meso-246
1H NMR Spectrum
400 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


CHO
CO2Et
CO2Et
OHC
meso-246
13C NMR Spectrum
100 MHz, CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

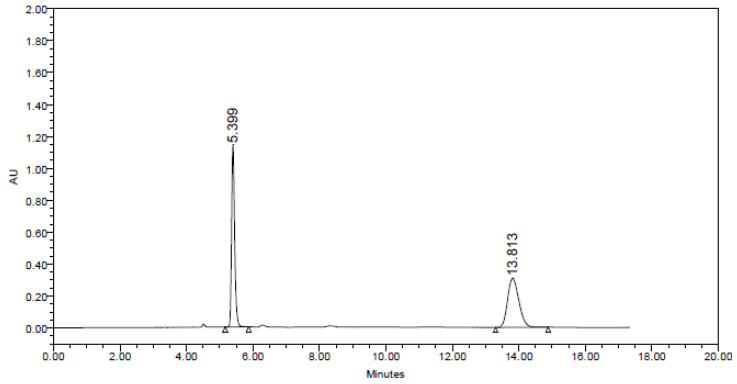
3.9 HPLC Traces

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 60:40 1 mL/min

Racemic:

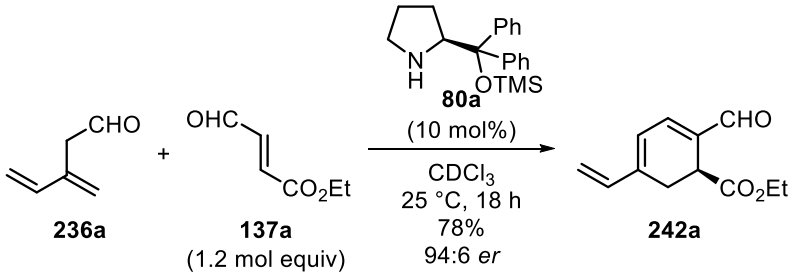
SAMPLE INFORMATION

Sample Name:	mtad180-r-run3	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	40%IPAhexane
Injection #:	1	Processing Method:	x
Injection Volume:	10.00 ul	Channel Name:	337.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 337.0 nm
Date Acquired:	7/21/2014 4:50:16 PM EST		
Date Processed:	6/30/2015 2:14:02 PM EST		



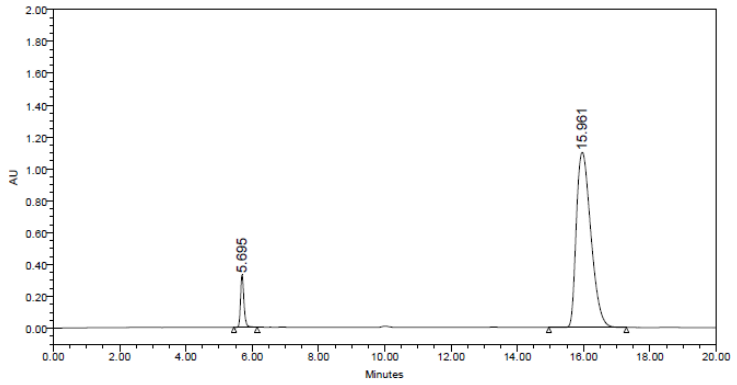
	RT	Area	% Area	Height
1	5.399	7267301	50.08	1142239
2	13.813	7244860	49.92	308188

Enantioenriched:



SAMPLE INFORMATION

Sample Name:	mtae12-a-chk	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	40%IPAhexane
Injection #:	1	Processing Method:	x
Injection Volume:	10.00 ul	Channel Name:	337.2nm
Run Time:	120.0 Minutes	Proc. Chnl. Descr.:	PDA 337.2 nm
Date Acquired:	7/23/2014 10:37:01 AM EST		
Date Processed:	6/30/2015 2:06:34 PM EST		



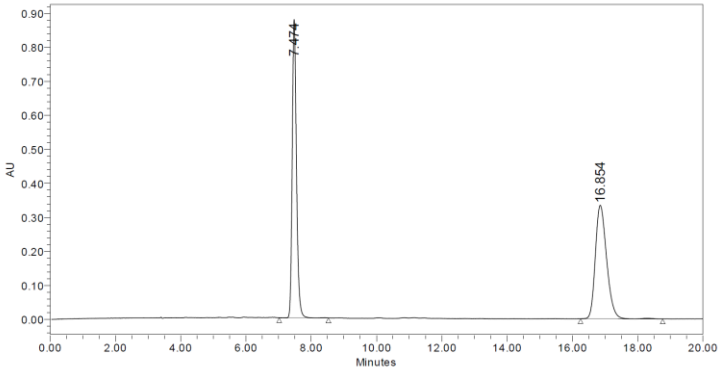
	RT	Area	% Area	Height
1	5.695	2322844	6.49	329522
2	15.961	33464643	93.51	1099308

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 70:30 1 mL/min

Racemic:

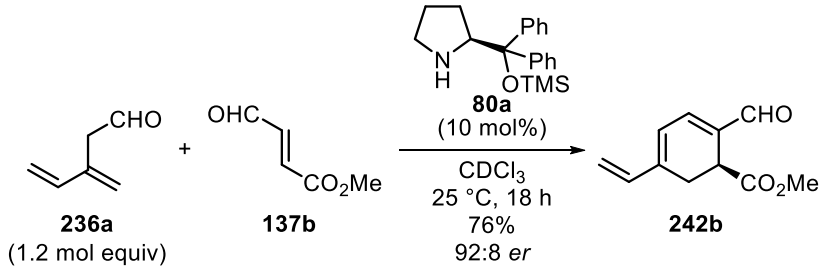
SAMPLE INFORMATION

Sample Name:	mtaf018-a-rac-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	1	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.6nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.6 nm
Date Acquired:	3/3/2015 12:29:01 PM EST		
Date Processed:	5/18/2015 7:01:55 PM EST		



	RT	Area	% Area	Height
1	7.474	7933819	49.77	876512
2	16.854	8007661	50.23	333821

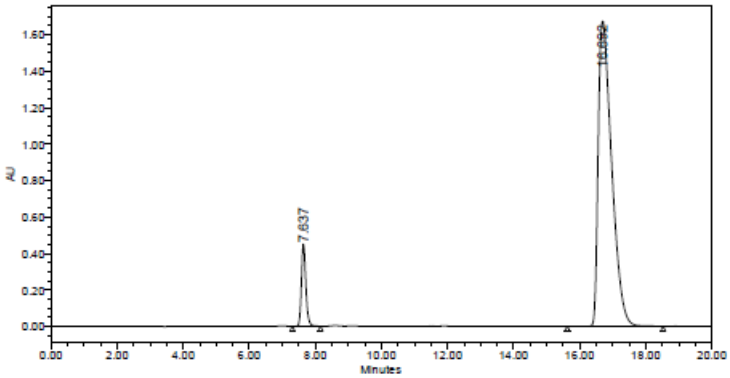
Enantioenriched:



236a (1.2 mol equiv) **137b** **242b**

SAMPLE INFORMATION

Sample Name:	mtaf018-b-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	2	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.6nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.6 nm
Date Acquired:	3/3/2015 2:00:20 PM EST		
Date Processed:	5/18/2015 7:02:24 PM EST		



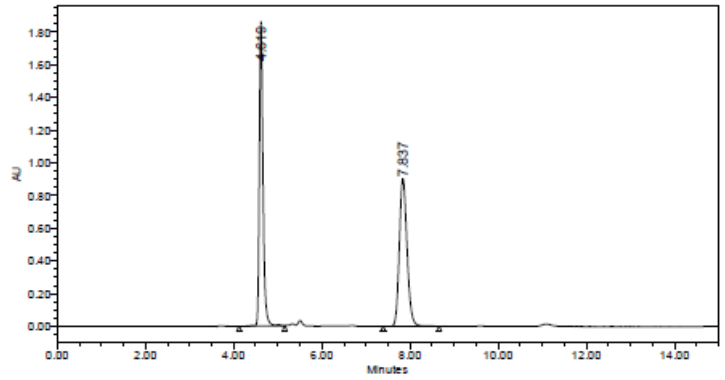
	RT	Area	% Area	Height
1	7.637	4166264	8.10	450013
2	16.692	47280646	91.90	1674336

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 80:20 1 mL/min

Racemic:

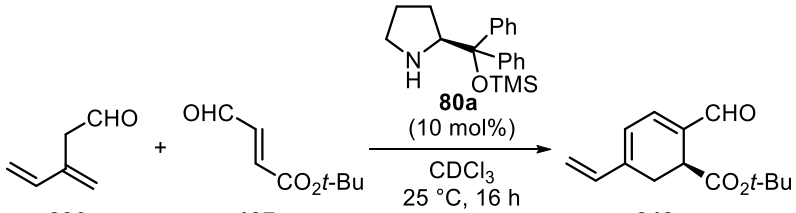
SAMPLE INFORMATION

Sample Name:	mtaf023-a-20-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 20%
Injection #:	3	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	339.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 339.0 nm
Date Acquired:	3/10/2015 11:35:22 AM EST		
Date Processed:	6/30/2015 2:26:14 PM EST		



	RT	Area	% Area	Height
1	4.619	10704343	49.51	1854668
2	7.837	10916327	50.49	903565

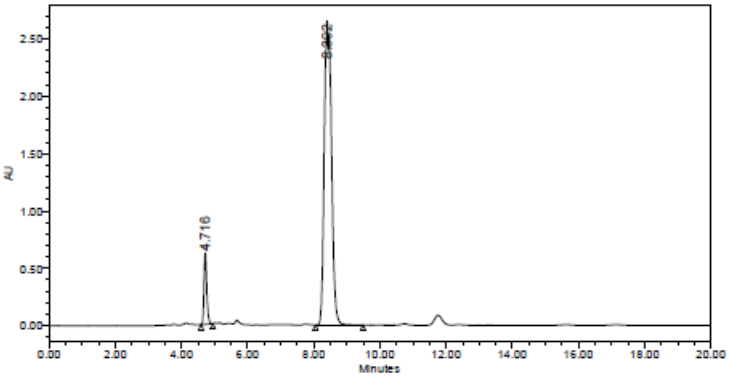
Enantioenriched:



236a (1.2 mol equiv) **137c** **242c**

SAMPLE INFORMATION

Sample Name:	mtaf023-b-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 20%
Injection #:	8	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	339.1nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 339.1 nm
Date Acquired:	3/10/2015 4:24:29 PM EST		
Date Processed:	6/30/2015 2:22:01 PM EST		



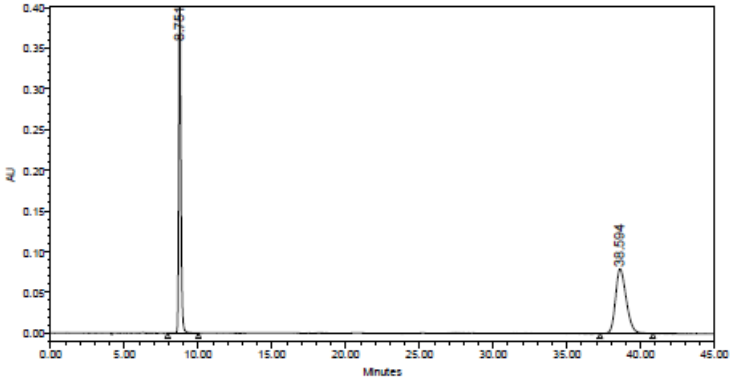
	RT	Area	% Area	Height
1	4.716	3567077	8.13	620589
2	8.392	40330762	91.87	2651566

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 80:20 1 mL/min

Racemic:

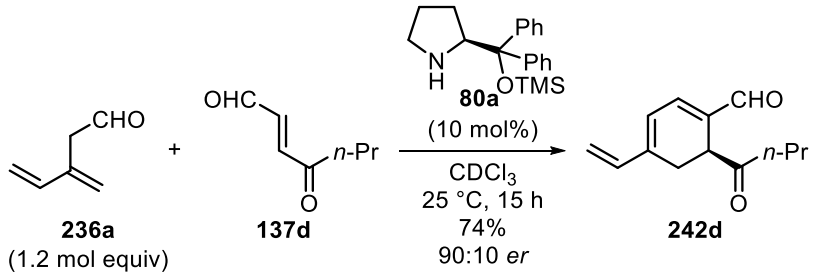
SAMPLE INFORMATION

Sample Name:	mtad193-r-run1	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	20%IPAhexane
Injection #:	6	Processing Method:	x
Injection Volume:	20.00 ul	Channel Name:	350.0nm
Run Time:	60.0 Mnutes	Proc. Chnl. Descr.:	PDA 350.0 nm
Date Acquired:	6/27/2014 12:16:46 PM EST		
Date Processed:	5/18/2015 7:33:17 PM EST		



	RT	Area	% Area	Height
1	8.751	4200825	51.33	410133
2	38.594	3983243	48.67	79189

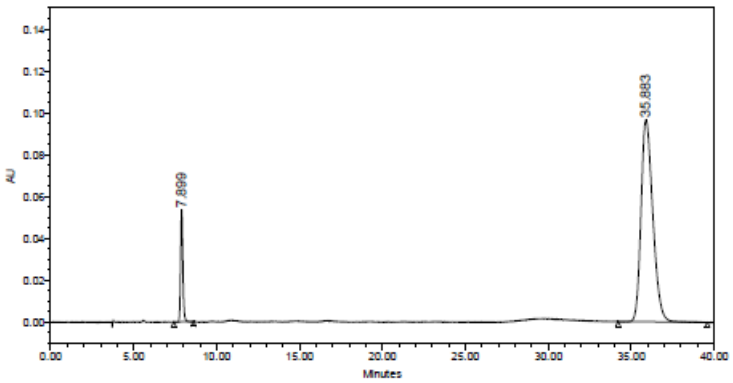
Enantioenriched:



236a (1.2 mol equiv) **137d** **242d**

SAMPLE INFORMATION

Sample Name:	mtad193-e-run1	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	20%IPAhexane
Injection #:	7	Processing Method:	x
Injection Volume:	20.00 ul	Channel Name:	349.9nm
Run Time:	60.0 Mnutes	Proc. Chnl. Descr.:	PDA 349.9 nm
Date Acquired:	6/27/2014 2:04:13 PM EST		
Date Processed:	5/18/2015 7:25:33 PM EST		



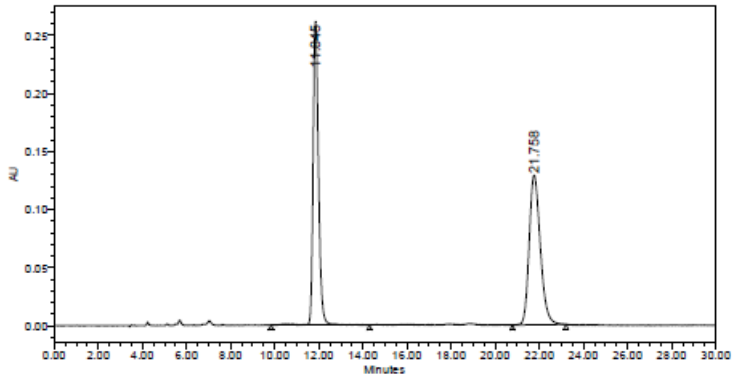
	RT	Area	% Area	Height
1	7.899	509916	9.69	53478
2	35.883	4750628	90.31	96400

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 70:30 1 mL/min

Racemic:

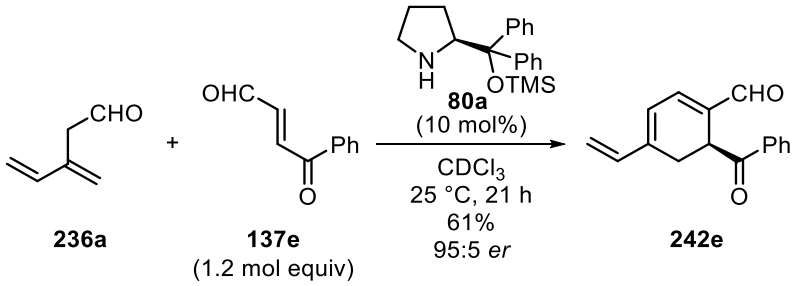
SAMPLE INFORMATION

Sample Name:	mtaf015-a-rac-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	5	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	339.7nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 339.7 nm
Date Acquired:	2/27/2015 1:52:04 PM EST		
Date Processed:	4/30/2015 11:54:52 AM EST		



	RT	Area	% Area	Height
1	11.845	4451135	49.59	261123
2	21.758	4524995	50.41	128740

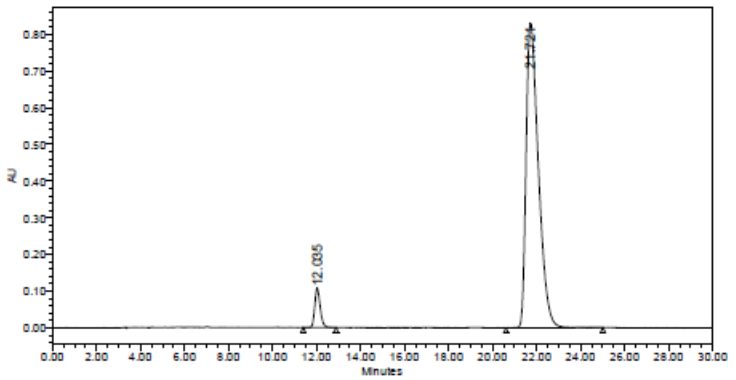
Enantioenriched:



236a **137e** (1.2 mol equiv) **242e**

SAMPLE INFORMATION

Sample Name:	mtaf069-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	8	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	337.1nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 337.1 nm
Date Acquired:	5/8/2015 12:22:12 PM EST		
Date Processed:	5/8/2015 1:56:29 PM EST		



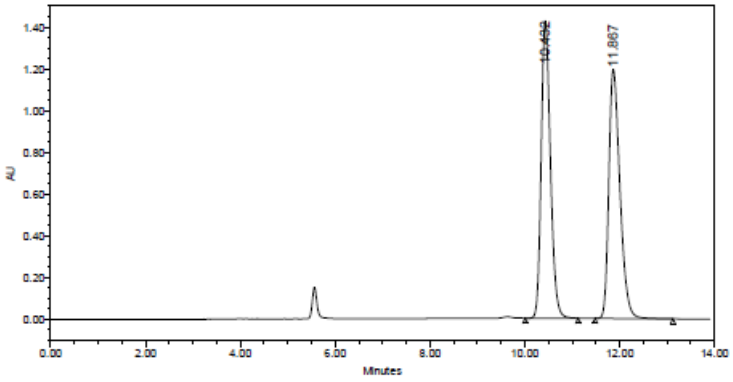
	RT	Area	% Area	Height
1	12.035	1854311	5.45	106474
2	21.721	32179756	94.55	830160

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 60:40 1 mL/min

Racemic:

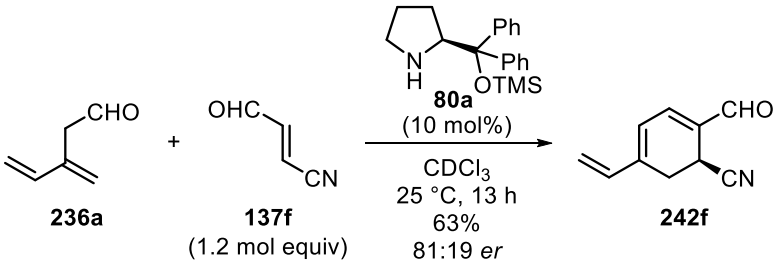
SAMPLE INFORMATION

Sample Name:	mtae18-run2	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	40%IPAhexane
Injection #:	4	Processing Method:	x
Injection Volume:	10.00 ul	Channel Name:	330.4nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.4 nm
Date Acquired:	8/14/2014 6:06:22 PM EST		
Date Processed:	5/19/2015 3:05:57 PM EST		



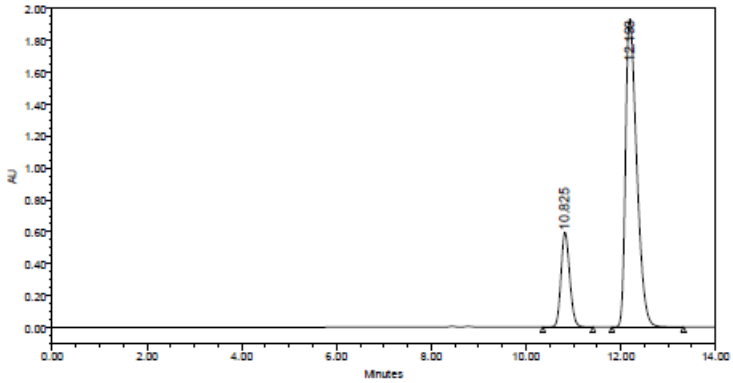
	RT	Area	% Area	Height
1	10.432	19284339	49.84	1425218
2	11.867	19405728	50.16	1193617

Enantioenriched:



SAMPLE INFORMATION

Sample Name:	mtae60-b-40-IPA-hex	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	40%IPAhexane
Injection #:	2	Processing Method:	x
Injection Volume:	10.00 ul	Channel Name:	330.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.0 nm
Date Acquired:	8/28/2014 11:34:08 AM EST		
Date Processed:	6/30/2015 1:59:41 PM EST		



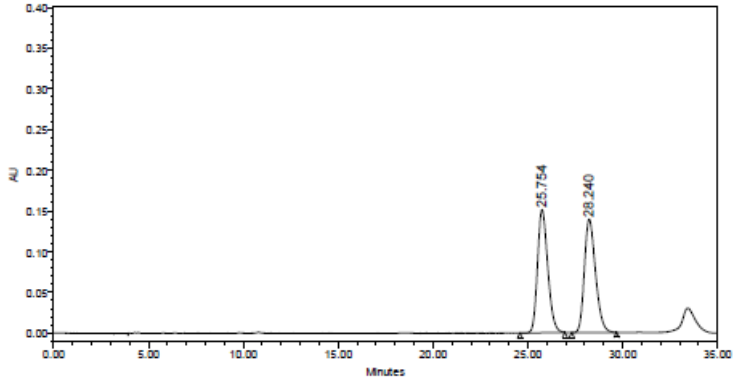
	RT	Area	% Area	Height
1	10.825	7577290	19.27	594607
2	12.193	31736410	80.73	1935909

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 90:10 1 mL/min

Racemic:

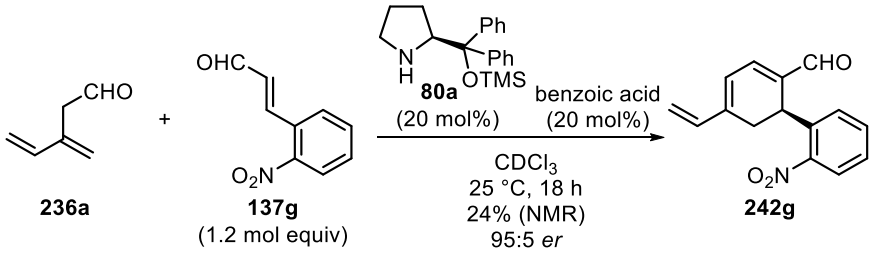
SAMPLE INFORMATION

Sample Name:	mtae189-rac-10-IPA-hex	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	10%IPAhexane
Injection #:	3	Processing Method:	x
Injection Volume:	10.00 ul	Channel Name:	339.3nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 339.3 nm
Date Acquired:	8/28/2014 1:34:01 PM EST		
Date Processed:	5/19/2015 2:56:19 PM EST		



	RT	Area	% Area	Height
1	25.754	5679731	49.99	151114
2	28.240	5682132	50.01	139219

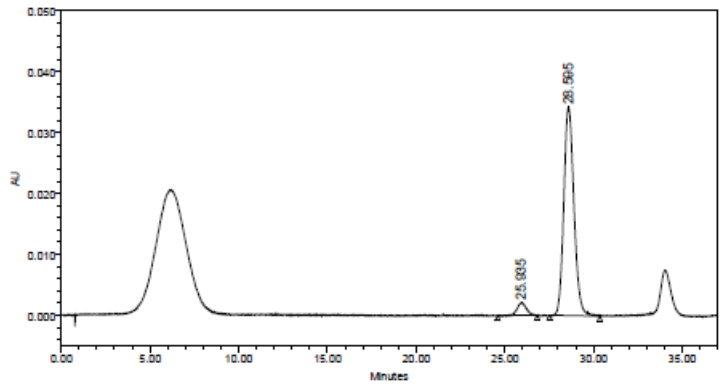
Enantioenriched:



236a + **137g** (1.2 mol equiv) → **242g**

SAMPLE INFORMATION

Sample Name:	mtad189-g-10-IPA-hex	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	10%IPAhexane
Injection #:	4	Processing Method:	x
Injection Volume:	10.00 ul	Channel Name:	340.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 340.0 nm
Date Acquired:	8/29/2014 10:16:51 AM EST		
Date Processed:	5/19/2015 3:03:40 PM EST		



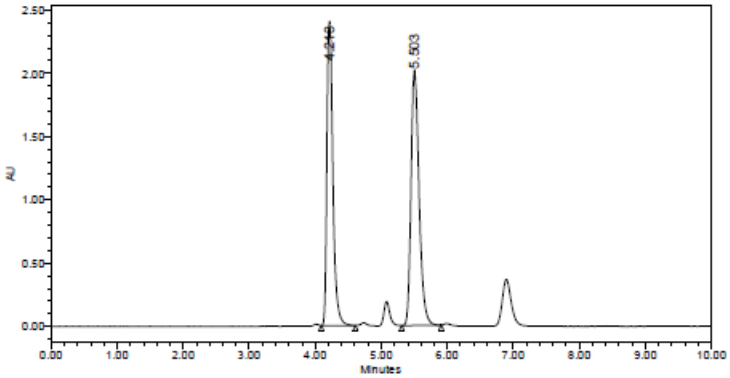
	RT	Area	% Area	Height
1	25.935	74276	5.16	2002
2	28.595	1364114	94.84	34300

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 70:30 1 mL/min

Racemic:

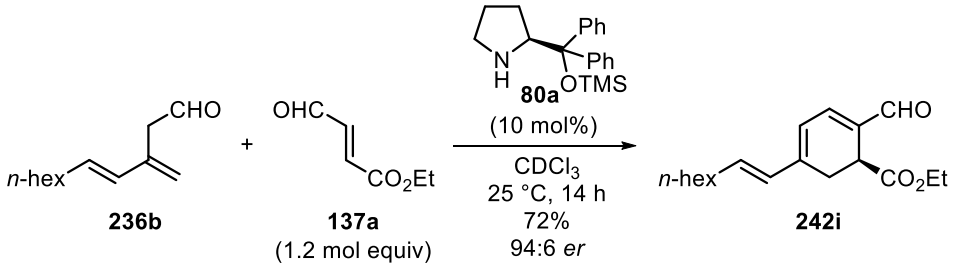
SAMPLE INFORMATION

Sample Name:	mtae196-rac-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	3	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	360.7nm
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	PDA 360.7 nm
Date Acquired:	2/23/2015 4:55:57 PM EST		
Date Processed:	5/18/2015 6:57:57 PM EST		



	RT	Area	% Area	Height
1	4.213	15162093	47.15	2379080
2	5.503	16992725	52.85	2011787

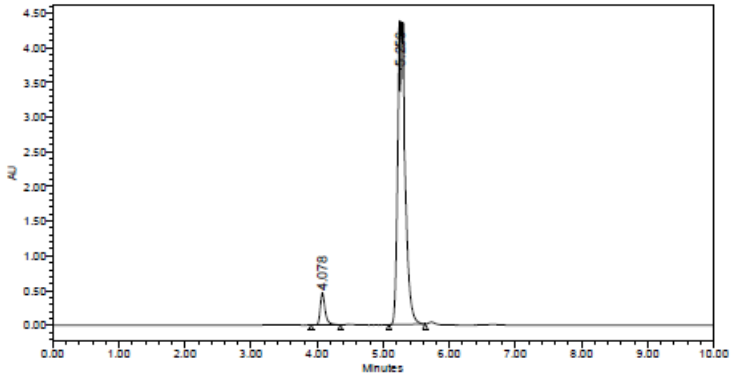
Enantioenriched:



236b **137a** (1.2 mol equiv) **242i**

SAMPLE INFORMATION

Sample Name:	mtaf028-b-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	10	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	359.8nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 359.8 nm
Date Acquired:	3/11/2015 3:22:51 PM EST		
Date Processed:	5/18/2015 6:59:32 PM EST		



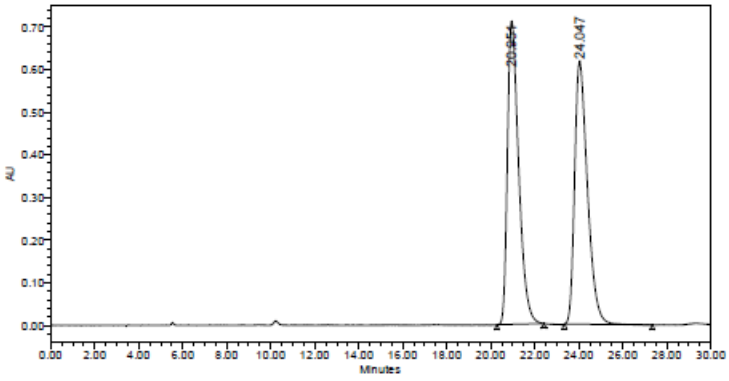
	RT	Area	% Area	Height
1	4.078	2354545	6.35	460555
2	5.256	34702229	93.65	4121324

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 70:30 1 mL/min

Racemic:

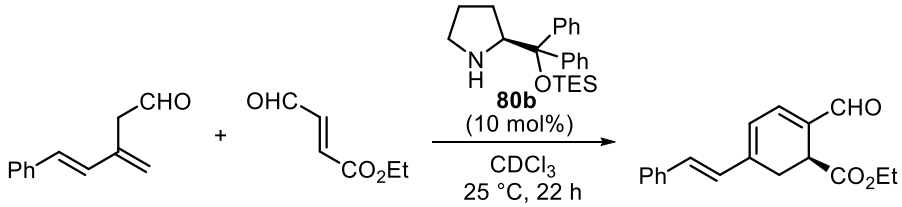
SAMPLE INFORMATION

Sample Name:	mtaf003-a-rac-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	13	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	380.9nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 380.9 nm
Date Acquired:	2/22/2015 2:50:15 PM EST		
Date Processed:	5/18/2015 6:14:28 PM EST		



	RT	Area	% Area	Height
1	20.951	25161460	50.21	711243
2	24.047	24947797	49.79	616080

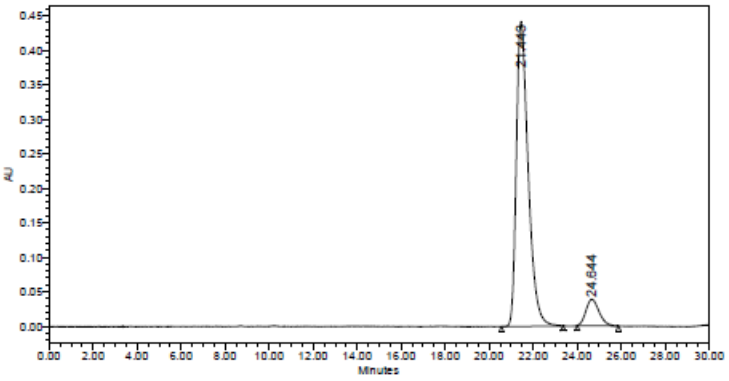
Enantioenriched:



236c + **137a** (1.2 mol equiv) → **242j**

SAMPLE INFORMATION

Sample Name:	mtaf046-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	2	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	380.2nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 380.2 nm
Date Acquired:	4/8/2015 1:44:39 PM EST		
Date Processed:	5/18/2015 6:19:11 PM EST		



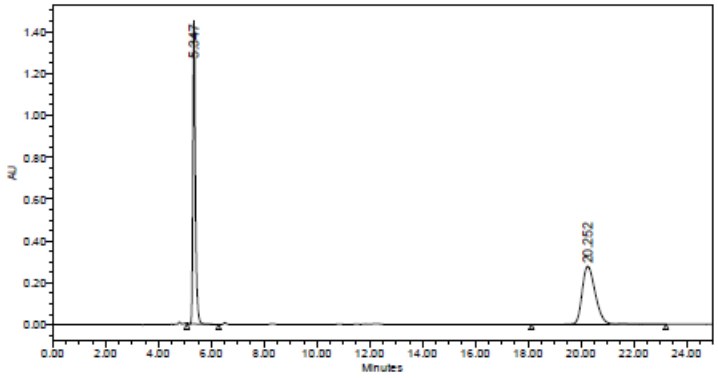
	RT	Area	% Area	Height
1	21.443	16471841	91.25	441366
2	24.644	1580167	8.75	38046

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 70:30 1 mL/min

Racemic:

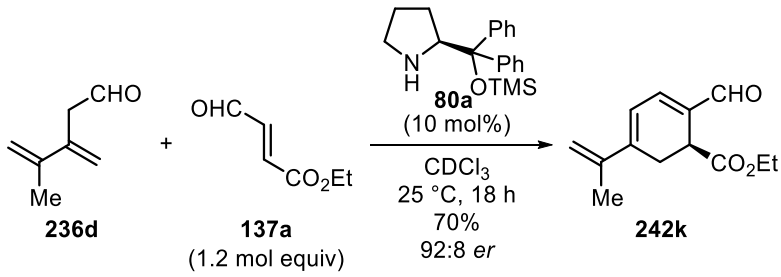
SAMPLE INFORMATION

Sample Name:	mtaf007-a-rac-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	11	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.5nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.5 nm
Date Acquired:	2/22/2015 1:47:38 PM EST		
Date Processed:	5/18/2015 6:44:36 PM EST		



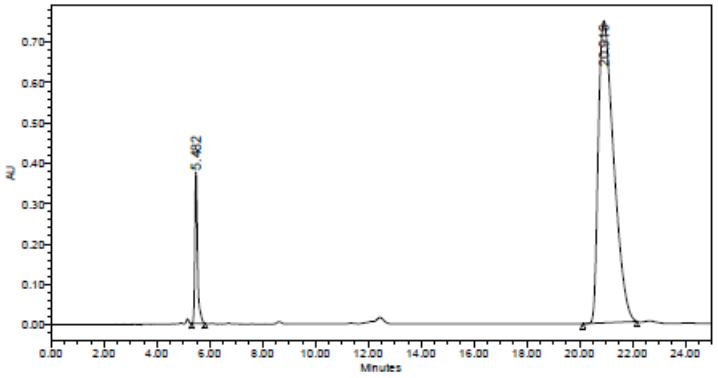
	RT	Area	% Area	Height
1	5.347	9548516	49.78	1452900
2	20.252	9633416	50.22	277648

Enantioenriched:



SAMPLE INFORMATION

Sample Name:	mtaf007-b-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	12	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.1nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.1 nm
Date Acquired:	2/22/2015 2:20:28 PM EST		
Date Processed:	5/18/2015 6:40:53 PM EST		



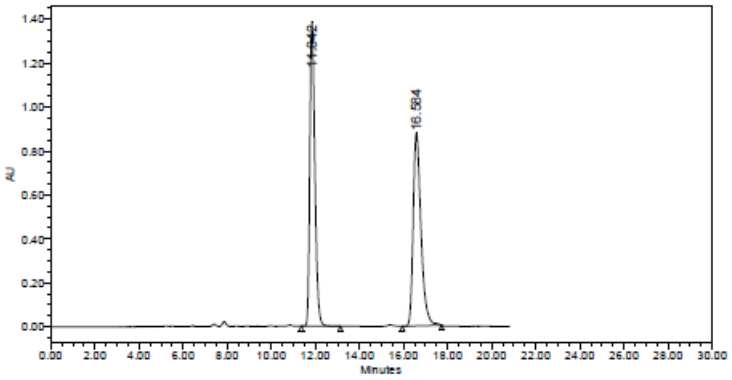
	RT	Area	% Area	Height
1	5.482	2610713	7.93	375592
2	20.919	30315741	92.07	748203

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 90:10 1 mL/min

Racemic:

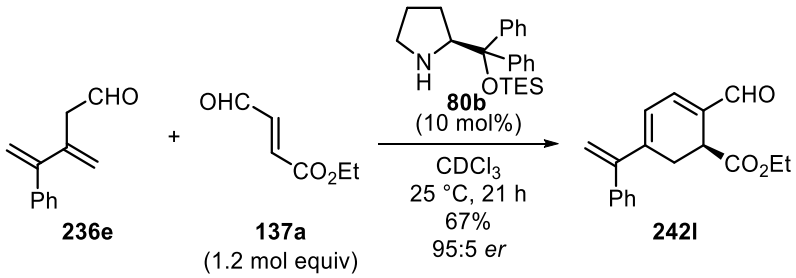
SAMPLE INFORMATION

Sample Name:	mtae185-rac-10-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 10%
Injection #:	10	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.5nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.5 nm
Date Acquired:	3/17/2015 11:48:30 AM EST		
Date Processed:	5/18/2015 6:27:28 PM EST		



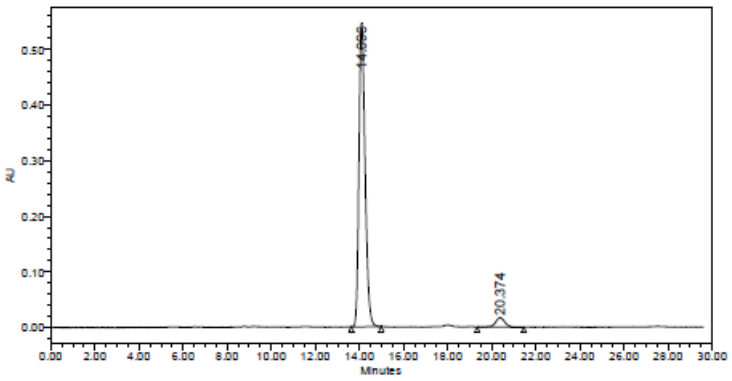
	RT	Area	% Area	Height
1	11.842	22068593	50.58	1383227
2	16.584	21558719	49.42	877186

Enantioenriched:



SAMPLE INFORMATION

Sample Name:	mtaf043-10-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 10%
Injection #:	21	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.5nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.5 nm
Date Acquired:	3/27/2015 3:06:27 PM EST		
Date Processed:	5/18/2015 6:23:33 PM EST		



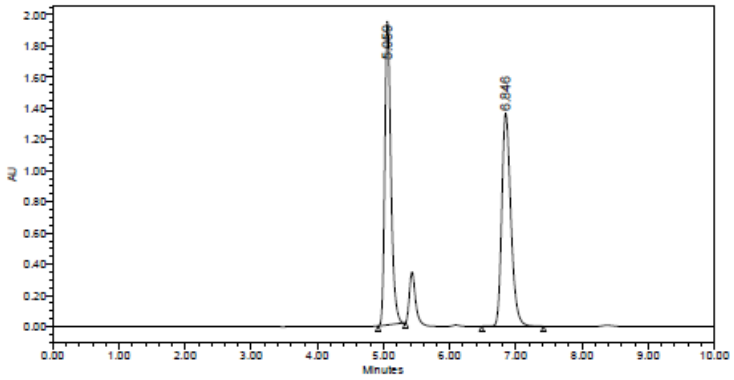
	RT	Area	% Area	Height
1	14.096	10573242	95.50	546338
2	20.374	498661	4.50	16880

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 70:30 1 mL/min

Racemic:

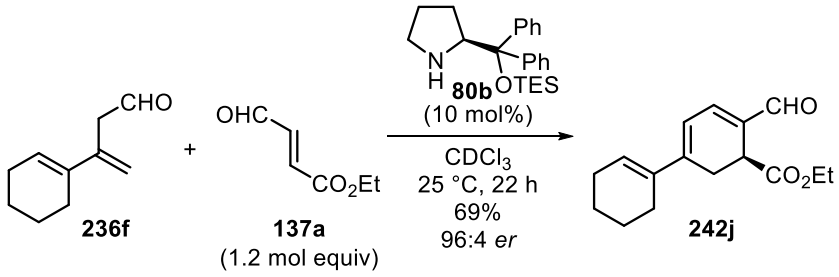
SAMPLE INFORMATION

Sample Name:	mtae197-rac-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	1	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.5nm
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	PDA 330.5 nm
Date Acquired:	2/23/2015 3:31:26 PM EST		
Date Processed:	5/18/2015 6:52:11 PM EST		



	RT	Area	% Area	Height
1	5.059	12562499	48.93	1948160
2	6.846	13110496	51.07	1368029

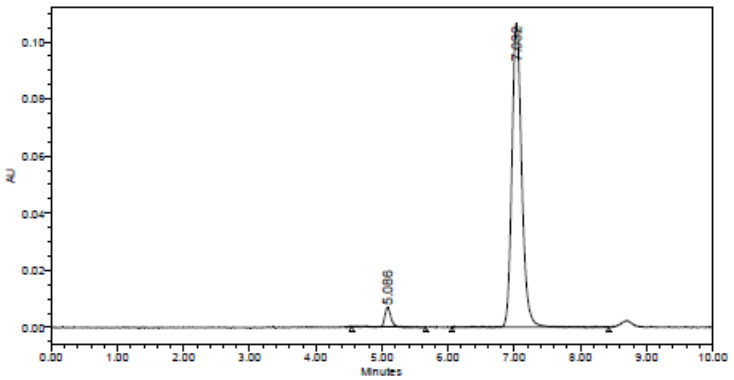
Enantioenriched:



236f + **137a** (1.2 mol equiv) → **242j**

SAMPLE INFORMATION

Sample Name:	mtaf047-30-IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	3	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	330.5nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 330.5 nm
Date Acquired:	4/8/2015 2:58:53 PM EST		
Date Processed:	5/18/2015 6:51:21 PM EST		



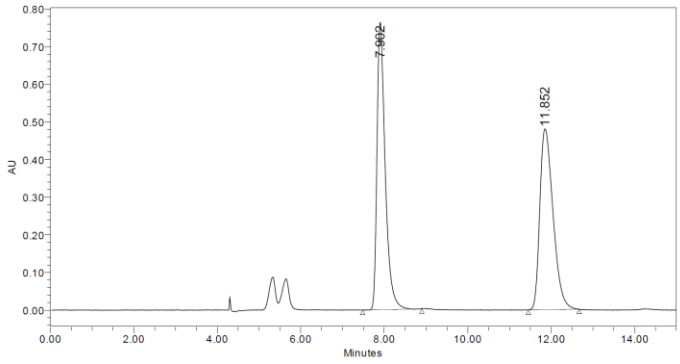
	RT	Area	% Area	Height
1	5.086	48106	4.19	6824
2	7.032	1098969	95.81	106663

Phenomenex Lux Cellulose 4 column (150 x 4.6 mm), hex/IPA 85:15, 1 mL/min

Racemic:

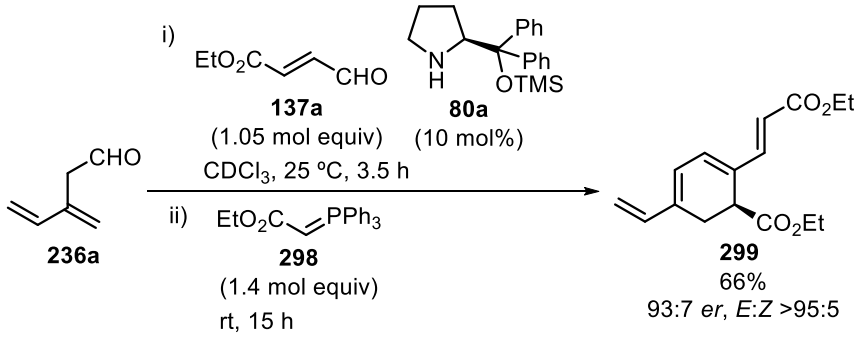
SAMPLE INFORMATION

Sample Name:	mtaf080-rac-15IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 15%
Injection #:	21	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	354.9nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 354.9 nm
Date Acquired:	7/28/2015 4:51:03 PM EST		
Date Processed:	7/28/2015 5:53:58 PM EST		



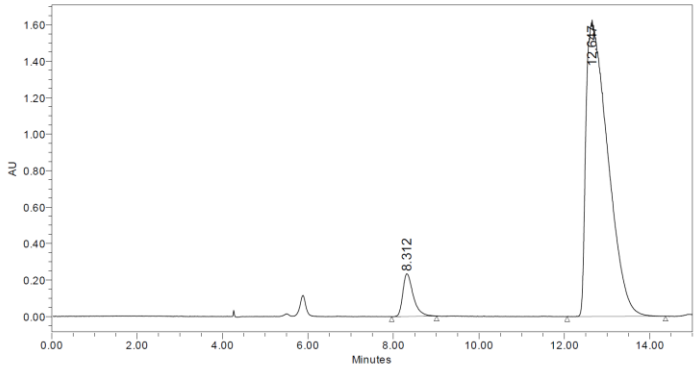
	RT	Area	% Area	Height
1	7.902	10385151	49.61	763704
2	11.852	10546886	50.39	480598

Enantioenriched:



SAMPLE INFORMATION

Sample Name:	mtaf083-b-15IPA-cell4	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 15%
Injection #:	33	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	354.9nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 354.9 nm
Date Acquired:	7/30/2015 5:10:51 PM EST		
Date Processed:	7/30/2015 5:31:35 PM EST		



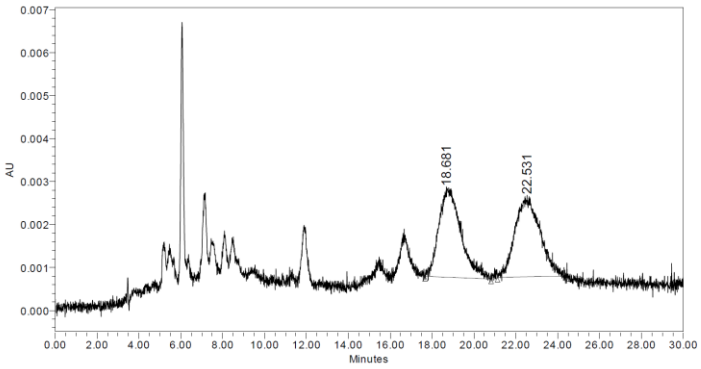
	RT	Area	% Area	Height
1	8.312	3960153	6.46	234145
2	12.647	57350923	93.54	1613287

Chiralcel OJ-H column (150 x 4.6 mm), hex/IPA 70:30 1 mL/min

Racemic:

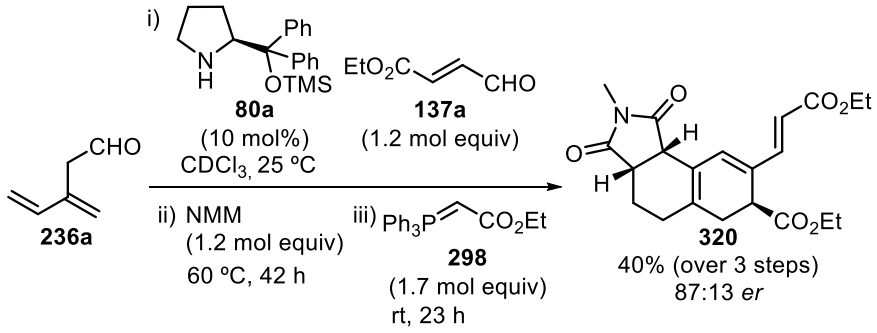
SAMPLE INFORMATION

Sample Name:	mtaf089-rac-30IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	10	Processing Method	x
Injection Volume:	10.00 ul	Channel Name:	310.1nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 310.1 nm
Date Acquired:	8/8/2015 12:13:22 PM EST		
Date Processed:	1/17/2016 2:28:57 PM EST		



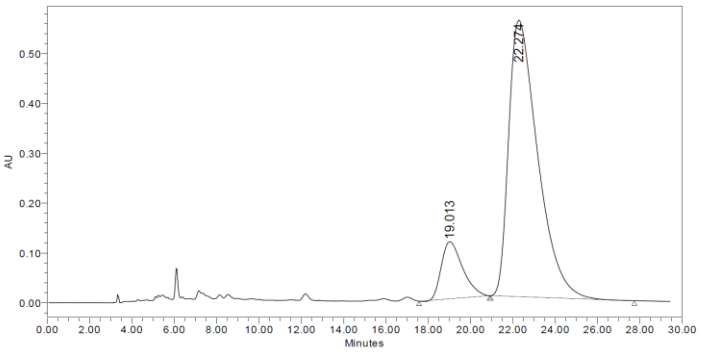
	RT	Area	% Area	Height
1	18.681	151460	49.65	1977
2	22.531	153625	50.35	1835

Enantioenriched:



SAMPLE INFORMATION

Sample Name:	mtaf084-30IPA	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	
Vial:	1	Acq. Method Set:	IPA hex 30%
Injection #:	1	Processing Method	x2
Injection Volume:	10.00 ul	Channel Name:	310.1nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 310.1 nm
Date Acquired:	8/8/2015 2:12:29 PM EST		
Date Processed:	1/17/2016 2:30:25 PM EST		



	RT	Area	% Area	Height
1	19.013	8017755	13.17	114688
2	22.274	52862424	86.83	554495